TRANSITION METAL-CATALYZED REACTIONS OF ALLENES IN DIVERSITY-ORIENTED SYNTHESIS

by

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Transition Metal-Catalyzed Reactions of Allenes in Diversity-Oriented Synthesis

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University of Pittsburgh, 2006

Abstract

Transition metal-catalyzed cyclization reactions involving allenes were demonstrated as useful methods for the synthesis of novel heterocyclic compounds. Multiple scaffolds were accessed from pivotal allenic amino-ester intermediates by varying the reaction conditions. Rhodium(I)-catalyzed allenic Alder-ene reaction of allenynes afforded cross-conjugated trienes in high yields. Double bond selectivity in the allenic cyclocarbonylation reaction of allenynes was accomplished by utilizing either rhodium(I)-catalyzed or molybdenum-mediated conditions, thus gaining access to 4-alkylidene or α-alkylidene cyclopentenones, respectively. In addition, a detailed study of the molybdenum-mediated reaction uncovered an unexpected diastereocontrol element based on the amino acid side chain. Furthermore, replacement of the alkyne with an alkene led to discovery of a novel rhodium(I)-catalyzed cycloisomerization of ene-allenes affording tetrahydroazepines.

The novel molecular scaffolds obtained in this manner were studied in complexity generating reactions that were employed in the synthesis of libraries of compounds for biological evaluation. For example, stereoselective sequential Diels-Alder reactions of the cross-conjugated trienes allowed rapid access to polycyclic molecular skeletons. Additionally, a Stetter/Paal-Knorr reaction sequence was developed to gain access to novel tricyclic pyrroles.

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Thank you! Благодарам! Grazie!

List of Abbreviations

Ac	acetyl
AcOH	acetic acid
aq.	aqueous
Ar	aryl
ATP	adenosine triphosphate
BICPO	2,2'-*bis*(diphenylphosphino)-1,1'-dicyclopentane
BINAP	2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bu	butyl
Bz	benzoyl
Cbz	carbobenzyloxy
CN	cyano
CO	carbon monoxide
COD	1,5-cyclooctadiene
Cp	cyclopentadienyl
Cy	cyclohexyl
DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DEPT	distortionless enhancement by polarization transfer
DIBALH	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DOS	diversity-oriented synthesis
dppb	1,4-*bis*(diphenylphosphino)butane
dppe	1,2-*bis*(diphenylphosphino)ethane
dppm	*bis*(diphenylphosphino)methane
dppp	1,3- *bis*(diphenylphosphino)propane
DPS	dimethylphenylsilyl
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide·HCl
Et	ethyl
fod	*tris*(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octadienoate)
h	hours
HMAF	hydroxymethylacylfulvene
HOBt	1-hydroxybenzotriazole
HPLC	high performance liquid chromatography
i-Bu	isobutyl
i-Pr	isopropyl
IR	infrared
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisalazide

Me	methyl
min	minutes
MAPK	mitogen activated protein kinase
MKP	mitogen activated protein kinase phosphatase
μw	microwave
nbd	norbornadiene
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser effect spectroscopy
Ph	phenyl
PPTS	pyridinum *p*-toluenesulfonate
PS	polymer supported
PTSA	*p*-toluenesulfonic acid
RI	refractive index
sat'd	saturated
TBAF	tetrabutylammonium fluoride
TBS or TBDMS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFE	trifluoroethanol
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	toluene
Tos	toluenesulfonyl
UPCMLD	University of Pittsburgh Center for Chemical Methodologies and Library Development
wt.	weight

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1.0 Introduction

1.1 The Role of Diversity-Oriented Synthesis in Modern Biomedical Research

Modern drug discovery efforts are based upon a deep understanding of the cellular pathways responsible for a particular disease. The extreme complexity of the cellular circuitry has made the goal of understanding all of its aspects a formidable challenge. Significant progress in this area has been made by using modern biochemical tools such as mutagenesis, which is commonly used to irreversibly modify proteins in order to understand their cellular function. However, there are many aspects of the cell's biochemistry that remain a mystery. These include important signaling pathways based on dynamic protein-protein interactions that are particularly difficult to study.[1] Therefore, there is a tremendous need for innovative strategies to discover new cellular pathways and probe the function of various protein targets.

Small organic molecules are useful research probes for studying cellular pathways. Small molecules are capable of interacting with macromolecules such as proteins generally in a reversible manner, thereby modulating their function.[2] Observing the effects that result from such interactions in designed assays can often lead to an understanding of the role a particular target plays in the cell. Additionally, if the protein is a known therapeutically relevant target, lead compounds for drug discovery can be identified. The great number of relevant protein targets and their immense structural diversity dictates that the small molecules screened against these

targets must also be structurally and functionally diverse.[3, 4]

Nature is one of the greatest sources of diverse small molecules with a broad bioactivity profile. However, a major limitation of screening natural products is their limited availability.[5] Therefore, synthetic small molecules constitute a major portion of the modern screening palette. Advances in the field of synthetic organic chemistry have led to development of many methodologies for efficient assembly of small molecules. The field of combinatorial synthesis has evolved in the past two decades as a consequence of the demand for diverse small molecules for biomedical research.[6] The synthetic strategy that is most commonly utilized in the combinatorial approach involves appending different building blocks around a common structural core. This approach has been greatly facilitated by development of practical technologies that allow the streamlined parallel synthesis of large numbers of compounds (thousands) in a short period of time. Although this approach will undoubtedly continue to lead to identification of additional biological agents, researchers have questioned whether the level of structural diversity that is achieved is sufficient to complement the wide variety of modern biomedical targets.[7] The appendage diversity that is achieved by varying substituents around a common core is thought to limit the compounds to a narrow "chemical space". Very often, and particularly in the pharmaceutical company setting, the molecules accessed in this manner are designed to fall within defined physico-chemical parameters that increase their chances of becoming drug candidates.[8] For example, the well known Lipinski rules for drug-like molecules consider properties aimed at increasing bio-availability (molecular weight, solubility, number of hydrogen-bond donors and acceptors, etc).[9]

The need for novel, chemically diverse small molecules has been made clear in the National Institutes of Health (NIH) roadmap for medical research (http://nihroadmap.nih.gov/).

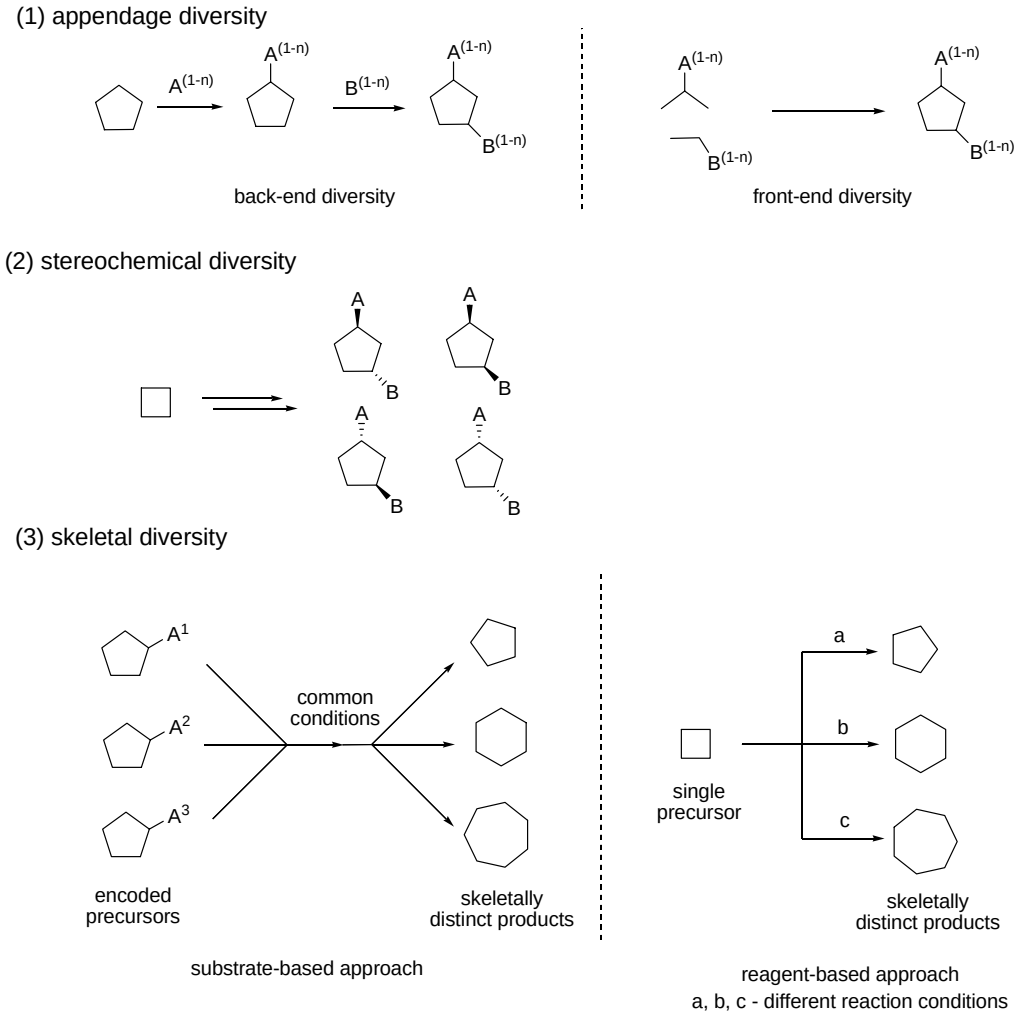
According to these guidelines, the goal of biomedical research in the future is to identify a comprehensive set of small molecules that are capable of selectively modifying the function of the majority of biological targets in the human cell. Since the number of relevant biological targets continues to grow as a result of intense research, this important goal can only be achieved by effectively integrating the development of new synthetic technologies to generate novel chemically diverse entities, with assays against a broad range of biological targets. New synthetic technologies encompass methods for more efficient synthesis of small molecules, their purification, isolation and characterization. In recent years, organic chemists have become increasingly aware of these issues and have begun addressing them by innovative combinatorial strategies and diversity-oriented synthesis (DOS).[10] Diversity-oriented synthesis aims to develop new and adapt existing synthetic methodologies for generating structurally diverse molecules specifically for biological screening. Because synthetic chemists generate novel compounds continuously, the term diversity-oriented synthesis is carefully assigned only to the designed and deliberate synthesis of collections of small molecules populating novel chemical space. Contrary to the classical combinatorial approach, modern DOS efforts put their main emphasis on the diversity of the molecular scaffolds that are accessed and not on the numbers of compounds.[11] Therefore, the synthesis of libraries of compounds is generally limited between tens to hundreds of compounds, and not thousands (or more) as in the classical combinatorial approach.[12] Moreover, the compounds are accessed in milligram quantities, which allows a thorough assessment of their biological activity in a wide variety of biological assays.[13]

Characterizing the diversity of molecular libraries is another important aspect of DOS.[14] This is commonly done by using computational methods to predict various physico-chemical properties (i.e., molecular descriptors) which are then compared to those of existing libraries.[9]

These can include more common parameters such as number of rotatable bonds, H-bond donor and acceptor groups, solvent-accessible surface area, clogP (distribution coefficient for octanol/water), but also pharmacologically related ones such as predicted affinity for serum-protein binding, intestinal permeability, metabolizable groups in the molecule, etc. Computational prediction of parameters like these allows the practicing DOS chemist to design libraries that posess a broad diversity profile.

In designing such "discovery libraries" of novel compounds, at least three forms of structural diversity have been considered and include appendage, stereochemical and skeletal diversity (Scheme 1.1). An ideal DOS strategy incorporates all three forms.

Scheme 1.1 Three forms of diversity in small molecule library synthesis.



(1) Appendage diversity is the most common form of diversity and involves decorating a common structural scaffold with different substituents or functional groups. When appendages are introduced via a coupling reaction subsequent to formation of the core scaffold, this represents *back-end* diversification. In contrast, *front-end* diversification results when bulding blocks possessing the appendage diversity elements are brought together in the key scaffold formation step (appendage diversity, Scheme 1.1).

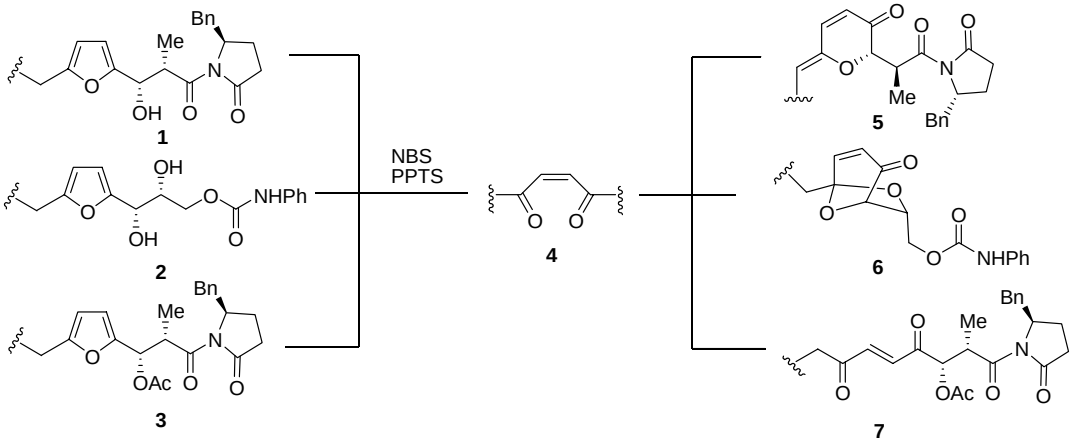
(2) Stereochemical diversity can be achieved by utilizing asymmetric synthetic methods to access both enantiomers of a compound from an achiral precursor. In addition, substrate-based

stereocontrol elements can be used to access different diastereomers from a common precursor. This form of diversity is important because it is well known that stereoisomeric compounds (enantiomers, diastereomers or atropisomers) can have different biological activity by virtue of displaying functional groups differently in three-dimensional space (stereochemical diversity, Scheme 1.1).[15]

(3) Skeletal diversity is arguably the most important but relatively difficult to achieve in an efficient manner. There are at least two conceptually distinct ways it can be accomplished:

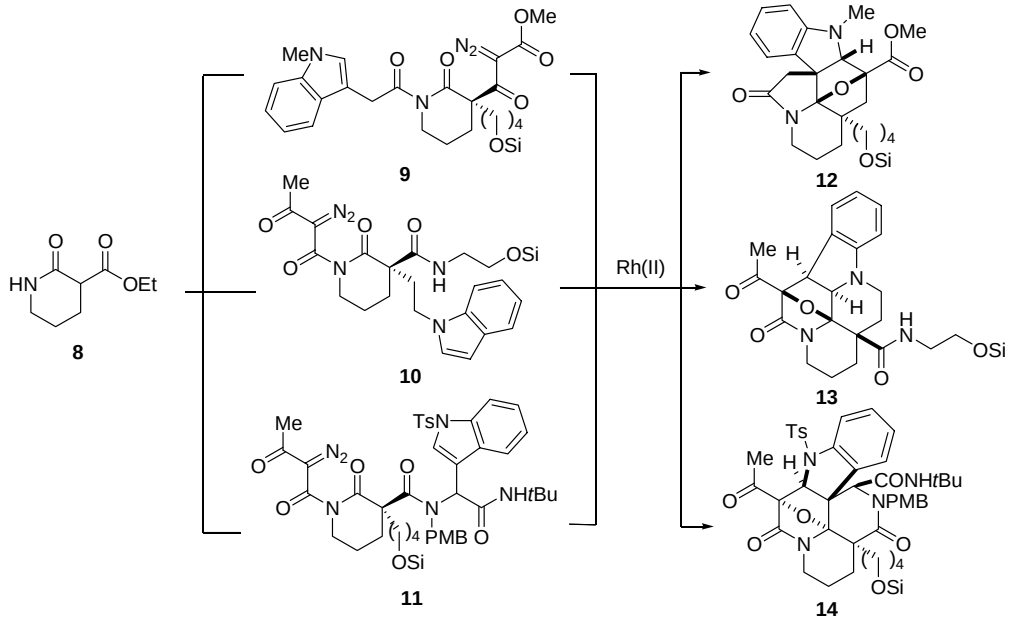
- The first one involves designing structurally similar substrates that under common reaction conditions undergo diverging transformations affording skeletally distinct products. The chemical information that leads to different products is therefore encoded in the substrates (*substrate-based control*, Scheme 1.1). This is the most commonly utilized synthetic approach to skeletal diversity.[16] For example, Schreiber demonstrated that substituted furans **1**-**3** containing one, two or no alcohols in the side chain can undergo different transformations when treated to oxidative acidic conditions (NBS and PPTS).[10c] The reaction proceeds via an oxidative opening of the furan to a *cis*-endione intermediate **4**, which then is subject to nucleophilic attack by the hydroxyl groups to give skeletally distinct products **5**-**7** (Scheme 1.2).

Scheme 1.2 Substrate-controlled skeletal diversity.



Another example from the Schreiber group involves a 1,3-dipolar cycloaddition between an indole dipolarophile and an *in situ* generated cyclic oxonium ylide to give skeletally different products by varying the placement of the reactive functional groups around a common pyridone core **8** (Scheme 1.3).[17]

Scheme 1.3 Synthesis of skeletally distinct products by substrate-design.

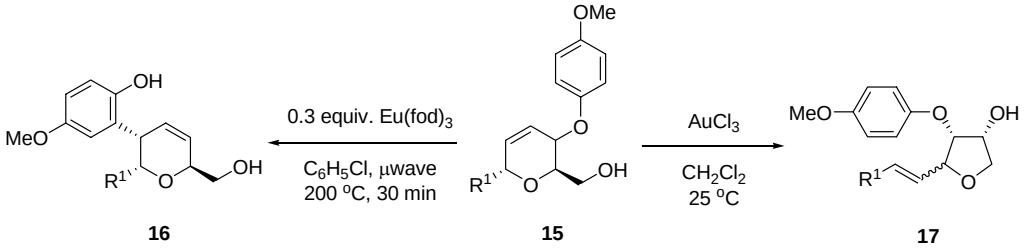


Despite the fact that a high degree of skeletal diversity can be accessed via the *substrate-based approach*, the efficiency of the overall process is compromised since all of the precursors need to be synthesized independently.

- Therefore, a more efficient approach to skeletal diversity involves subjecting a common synthetic precursor to different reaction conditions to give skeletally unique products (*reagent-based control*, Scheme 1.1). Although there are some applications of this concept, it remains the most difficult to achieve, particularly in the context of cyclic skeleton synthesis.[18] For example, Schaus and Porco have shown that aryl-ether *C*-glycoside derivative **15** unveils phenol **16** via a [3,3]-sigmatropic rearrangement under microwave irradiation, or furanyl alcohol **17** via a Au-

promoted rearrangement (Scheme 1.4).[19]

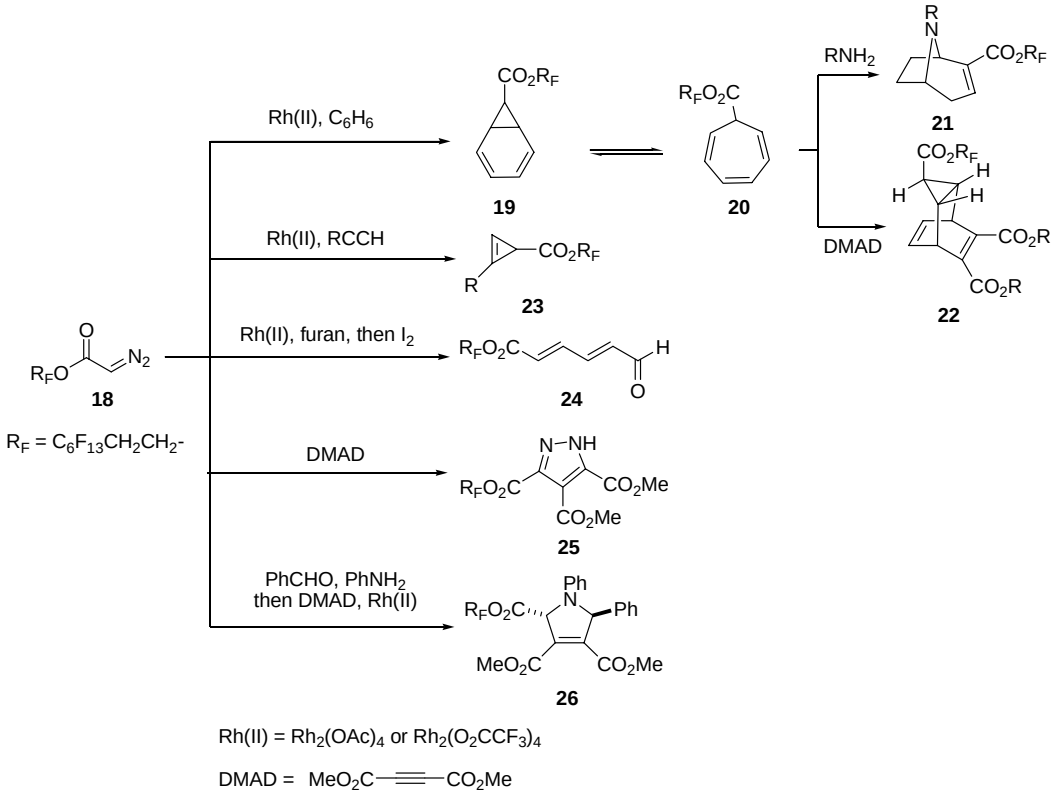
Scheme 1.4 Reagent-controlled skeletal diversity.



16 **15** **17**

Another example of the "common precursor" approach is illustrated in Scheme 1.5. Spring *et al.* have exploited the versatility of a fluorous-tagged[20] diazoacetate **18** to gain access to a broad range of skeletally distinct scaffolds by utilizing different reaction conditions.[21] Since the pivotal intermediate **18** is relatively unfunctionalized, the diversity in the product results from the nature of the second reagent used in the reaction.

Scheme 1.5 Skeletal diversity via reactions of a fluorous-tagged diazoacetate.



18 **19** **20** **21** **22** **23** **24** **25** **26**

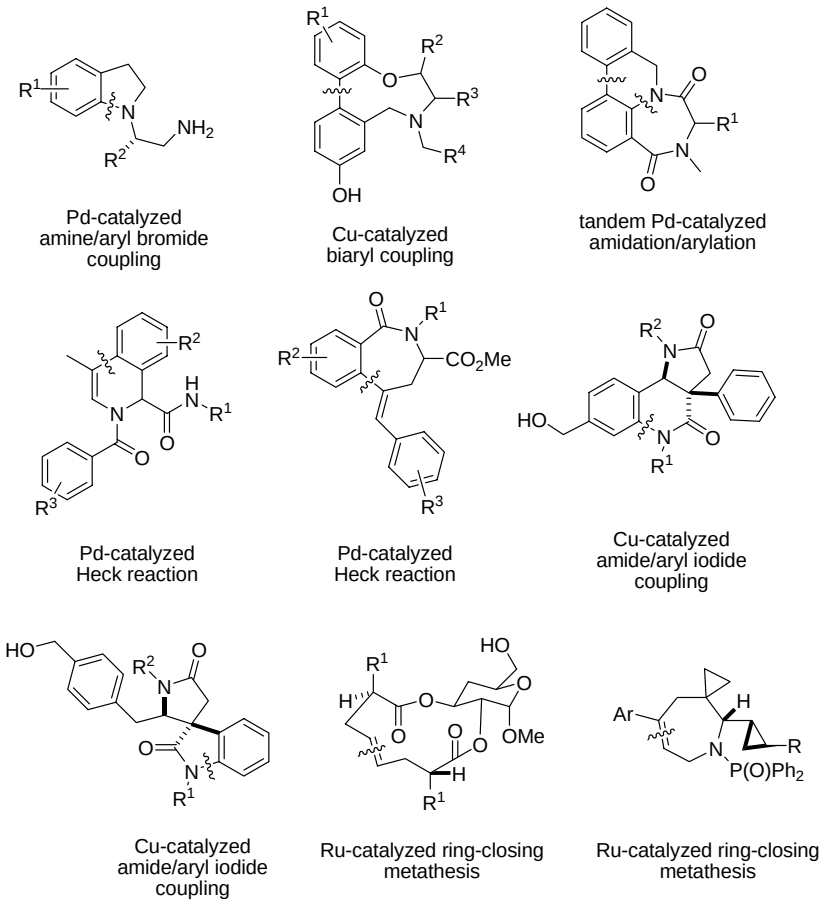
R_F = $C_6F_{13}CH_2CH_2$-

1.1.1 Transition Metal-Catalyzed Reactions in Diversity-Oriented Synthesis

Accessing all three forms of diversity requires DOS strategies with branching reaction pathways available to common synthetic precursors. In this manner, structurally distinct scaffolds can be obtained from a relatively smaller pool of reactants, thereby increasing the overall efficiency of the process. Therefore, there is a strong incentive to develop new chemical transformations and design strategies towards this goal. The development of many useful transition metal-catalyzed reactions in the last decades has opened the door for their application to DOS.[22] Transition-metal catalyzed reactions are generally environmentally benign and economic synthetic processes, proceeding with high levels of selectivity (chemo-, regio-, and/or stereoselectivity) and minimize the use of raw materials and generation of byproducts. Among these, Pd-catalyzed coupling reactions (Heck,[23] Stille,[24] Sonogashira,[25] Suzuki,[26] etc.) and allylic substitution reactions[27] are regarded as some of the most important with highest impact on the field of modern organic synthesis. Not surprisingly, these reactions have seen the most application in combinatorial and diversity-oriented synthesis. The majority of classical combinatorial strategies in the past have been largely limited to utilizing transition metal-catalyzed coupling reactions only introducing appendage diversity (for examples see Pd-catalyzed Suzuki,[28] Heck[29] and Stille[30] coupling reactions). In addition, intramolecular versions of these and related reactions have seen recent use to create skeletal diversity in the synthesis of small and medium size rings.[31] Related transformations such as the coupling of aryl boronic acids and amides recently developed by Buchwald[32] are also becoming increasingly popular in the generation of cyclic-skeletons.[33] Another very important transformation that has found wide use in combinatorial and diversity-oriented synthesis is the Ru-catalyzed ring-closing methathesis developed by Grubbs.[34] Some recent examples of diverse cyclic scaffolds generated

by using the above-mentioned classes of reactions are illustrated in Scheme 1.6.

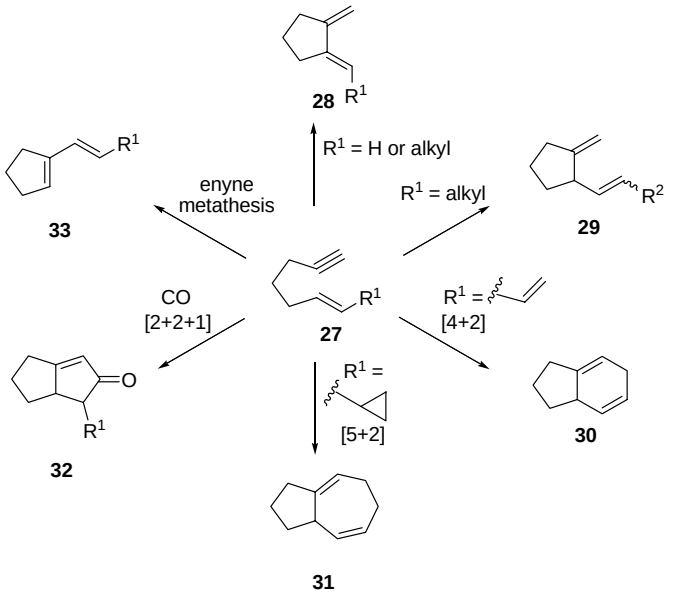
Scheme 1.6 Recent examples of diverse cyclic skeletons accessed via transition metal-catalyzed cyclization reactions.



Transition metal catalyzed reactions that transform relatively simple acyclic starting materials to cyclic (or polycyclic) products via a carbocyclization process are another important class of reactions that has received attention in the past decade.[35] Carbocyclization, in general, refers to a cyclization process that involves carbon-carbon bond formation via a carbometalation, whereas a C*-M (**C**arbon-**M**etal) species delivers the carbon and metal component across an unsaturated bond (C=C) thereby affording a C*-C-C-M species.[36] In particular, carbocyclization reactions of precursors containing unsaturated functional groups (e.g., alkenes, alkynes) have been very useful in the syntheses of carbocyclic and heterocyclic molecules.[35-37] Examples of

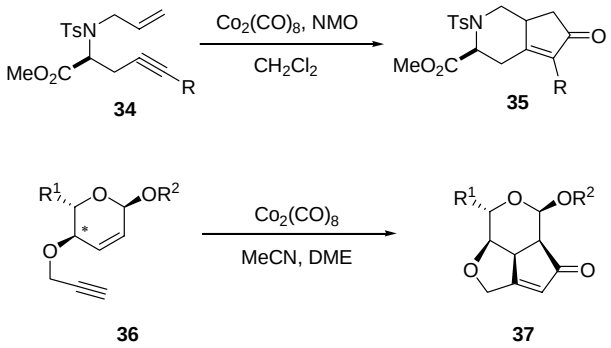
such reactions include transition metal catalyzed ene-type cycloisomerizations,[37, 38, 39] [4+2] and [5+2] cycloadditions[40] and [2+2+1] cyclocarbonylation[41] reactions of enynes (Scheme 1.7). Aside from increasing molecular complexity, an important aspect of these reactions is that metal catalysis often allows for bond formation that would be difficult or impossible under conventional methods, to readily occur under mild conditions. A typical example is the intramolecular [4+2] cycloaddition of electronically unactivated dieneynes proceeding under Rh(I) catalysis (**27** to **30**, Scheme 1.7).[42]

Scheme 1.7 Some carbocyclization reactions of 1,6-enynes.



The vast potential for increasing molecular complexity and achieving skeletal diversity via metal catalyzed carbocyclization reactions (e.g., cycloadditon, cycloisomerization, cyclocarbonylation, etc.) remains an untapped resource for DOS. One of the few examples of utilizing a Pauson-Khand cyclocarbonylation reaction in the synthesis of a library of amino-acid derived bicyclic skeletons **35** was reported by Bolton in 1997 (Scheme 1.8).[43] More recently, a cyclocarbonylation reaction was also employed to prepare a library of fused tricyclic systems **37** shown in Scheme 1.8.[44]

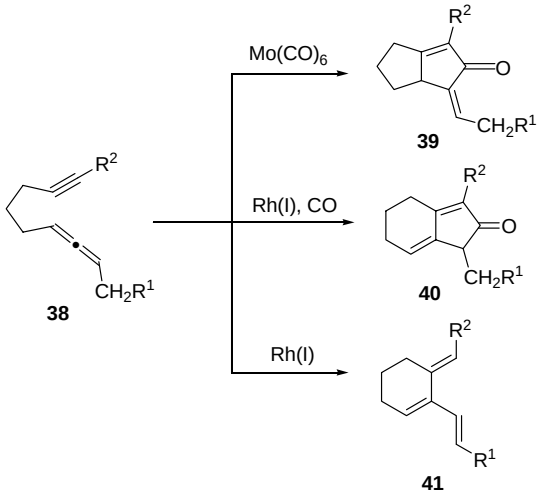
Scheme 1.8 Examples of using a cyclocarbonylation reaction in diverse skeleton synthesis.



Although olefins and acetylenes are most commonly utilized in carbocyclization reactions, use of allenes as π-components is becoming increasingly prevalent. For a relatively long time since their first synthesis,[45] allenes were considered no more than a chemical curiosity and remained underutilized.[46] Intense research in the past decades, however, has resulted in many useful synthetic methods involving allenes.[47, 48, 49] The two cumulated double bonds of the allene display high reactivity towards a range of transition metals, and have been exploited in a variety of ways. Using allenes as olefin components in transition metal-catalyzed reactions often has the advantage of increased reactivity. This is largely due to the strain associated with having two cumulated double bonds which is estimated at 10 kcal/mol.[50] Despite this fact, transition metal-catalyzed carbocyclizations of allenes (e.g., cycloaddition and cycloisomerization reactions) remain largely unexplored and underutilized in synthesis, presumably because there are no known control elements for effecting double bond selectivity other than substrate modification.[51, 52] Recent studies by Brummond and coworkers have resulted in some of the first examples of reagent-based control of olefin selectivity in the allenic cyclocarbonylation (Pauson-Khand reaction) and cycloisomerization reactions.[53] Reagent-based control of double bond-selectivity in transition metal-catalyzed carbocyclization reactions of allenes is ideally suited for application to DOS since skeletally different products can be obtained. For example, selective engagement of

the proximal olefin of allenyne **38** in a cyclocarbonylation reaction leads to an α-alkylidene cyclopentenone **39** (Scheme 1.9). Alternatively, the same transformation of the distal double bond leads to a 4-alkylidene cyclopentenone **40**. Furthermore, a cycloisomerization reaction involving the distal double bond of the allene can lead to a cross-conjugated triene **41**.

Scheme 1.9 Skeletal diversity using carbocyclization reactions of allenynes.



Each reaction results in increase of molecular complexity since relatively simple acyclic precursors are transformed to mono- or bicyclic skeletons. Furthermore, a novel reactive moiety is generated (enone, cross-conjugated triene) that can be further exploited in diversity generating transformations. Therefore, implementing a diversity-oriented synthetic strategy based on transition metal-catalyzed cyclocarbonylation and cycloisomerization reactions of allenes is of great interest. Herein, the efforts toward this goal are described. In this study, two important goals have been combined: (1) development of new synthetic methodologies for efficient assembly of complex small molecules; and (2) synthesis of collections of these compounds specifically for use as biological probes. At the initiation of the project, we envisioned employing the three reaction pathways available to a single allenyne (Scheme 1.9). It was reasoned that other reaction pathways may be available to an appropriately designed precursor.

The allenyne substrate was designed to contain an amino-ester tether (Chapter 2). The scope and limitation of the cycloisomerization reaction leading to cross-conjugated trienes was studied with this substrate class, and the results are presented in Chapter 3. In addition, the discovery of a novel cycloisomerization reaction of ene-allenes is discussed in Chapter 3. The synthesis of 4- and α-alkylidene cyclopentenones via cyclocarbonylation reaction is discussed in Chapter 4. Diversification of each of the three scaffolds was examined to increase molecular complexity and establish protocols for library synthesis (these results are discussed within the corresponding chapters).

2.0 Design and Synthesis of the Pivotal Intermediates

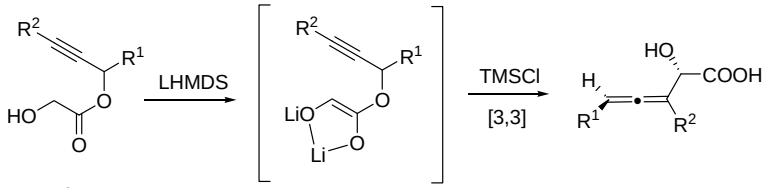
2.1 Design of the Pivotal Intermediates

In designing a pivotal allene intermediate for the planned DOS strategy, three aspects were considered: (1) incorporating higher number of N and O heteroatoms was important since compounds containing them are more likely to have a desirable pharmacological profile and exhibit interesting biological effects via specific interactions with proteins; (2) potential for diversification of the molecular scaffolds by employing both *front-end* and *back-end* appendage diversity strategies; and (3) ease of preparation and availability of the starting precursors. Incorporating nitrogen and oxygen containing functional groups in the pivotal allenes is also important because they would allow for rapid attachment of pre-functionalized alkynes and alkenes used in the carbocyclization reactions, thereby incorporating *front-end* diversity into the scaffolds. Additionally, the reactivity of nitrogen and oxygen containing functional groups can be exploited in *back-end* functionalization of the scaffolds subsequent to their formation.

With this in mind, several known methods for preparation of functionalized allenes were considered.[48a] Claisen rearrangement of propargyl ethers and esters is a versatile method for preparation of allenes.[54] In 1985, Fujusawa reported the Claisen rearrangement of α-hydroxy-propargyl ester **42** via ester-enolate **43** leading to α-hydroxy-β-allenic acid **44** (Scheme 2.1).[55] However, the scope of this transformation was limited to the rearrangement of α-unsubstituted

esters (glycolates) thereby limiting the diversity that can be introduced at this position. Moreover, it was reasoned that converting these carboxylic acids to esters will increase the likelihood of a base-promoted isomerization of the allene to a 2,4-dienoic ester.

Scheme 2.1 Ester-enolate Claisen rearrangement of propargyl glycolates.

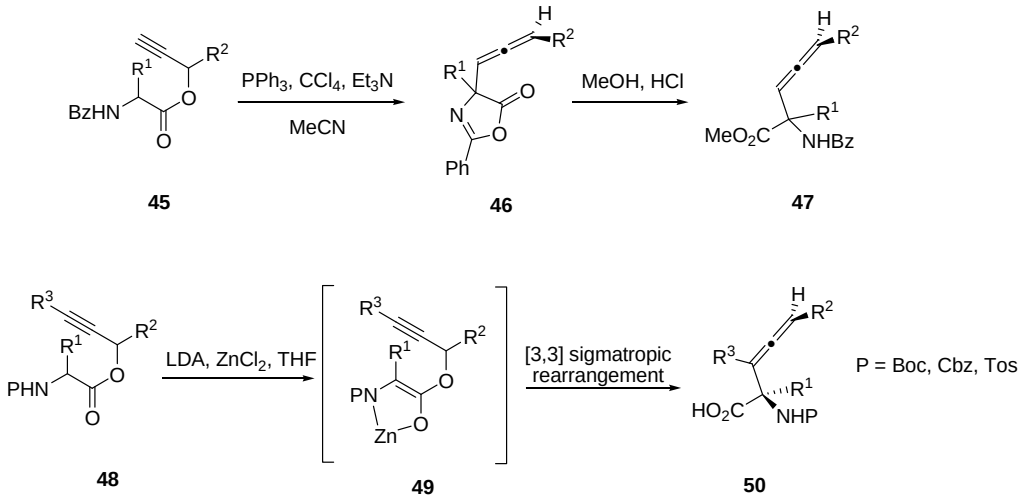


42 **43** **44**

R^1 = alkyl, H
R^2 = alkyl, TMS

The corresponding Claisen rearrangement of propargylic α-amino-esters was more attractive. Work by Castelhano and Krantz demonstrated that mild dehydrative conditions (Et_3N, CCl_4, PPh_3) effect the rearrangement of benzoyl protected amino ester **45** to 4-allenyl-5-oxazolone **46**, which is transformed to methyl ester **47** when treated with MeOH (Scheme 2.2).[56] Furthermore, Kazmaier reported an ester-enolate Claisen rearrangement of variety of propargyl amino-esters **48** using LDA/$ZnCl_2$ affording allenic amino acids **50** with diastereoselectivity greater than 93%.[57]

Scheme 2.2 Methods for preparation of allenic amino acids.



45 **46** **47**

48 **49** **50**

The allenic amino acid derivatives obtained via these two methods appeared ideal for adapting to the DOS strategy (both methods are discussed in detail in Section 2.2). Notably, the propargyl esters are easily obtained in one step by coupling of the corresponding N-protected amino acid and a propargyl alcohol, allowing for multiple points of diversity to be introduced. Therefore, the allenic amino esters obtained in this manner were elected as pivotal intermediates for development of a DOS strategy based on transition metal catalyzed cycloisomerization and cyclocarbonylation reactions of allenes.

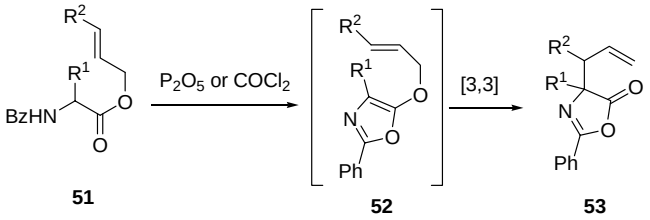
2.2 Synthesis of the Pivotal Intermediates

2.2.1 Synthesis of Allenic Amino Esters

2.2.1.1 Claisen Rearrangement via an Oxazole

The Claisen rearrangement of allyl and propargyl esters of α-amino-acids is a versatile method for preparing unsaturated amino acid derivatives. This field was pioneered by Steglich in the late 1970's by demonstrating that *N*-benzoyl protected amino esters **51**, under dehydrative conditions ($P_2O_5/CHCl_3$ or $COCl_2$/pyridine), afford 4,4-disubstituted oxazolone derivatives **53** (Scheme 2.3).[58] The reaction involves an *in situ* formation and [3,3] sigmatropic rearrangement of allyloxy-oxazole **52**.

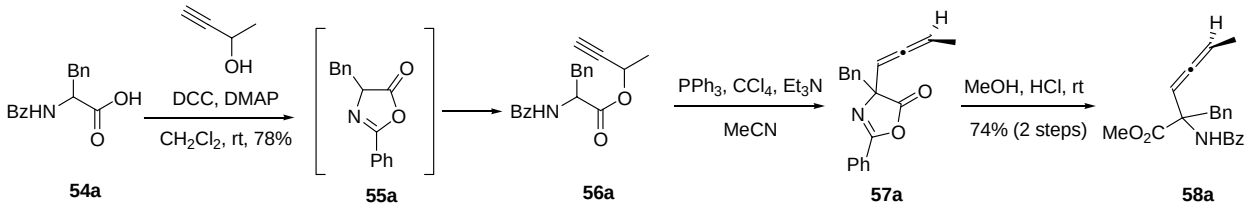
Scheme 2.3 Claisen rearrangement via an oxazole.



Interest in preparing allenic amino acid derivatives was spurred by their potential to act as specific inhibitors of vitamin B_6-linked decarboxylases.[59] Krantz and Castelhano reported that a combination of PPh_3, CCl_4 and Et_3N provides a milder and robust protocol for effecting the same transformation of propargyl esters (**45** to **47**, Scheme 2.2).[56] It was established, however, that the benzamide protecting group is essential for reaction to proceed, which is attributed to a stabilizing effect of the phenyl group on the oxazole intermediate. The use of other protecting groups including trifluoroacetamide, Boc and Cbz groups was unsuccessful.

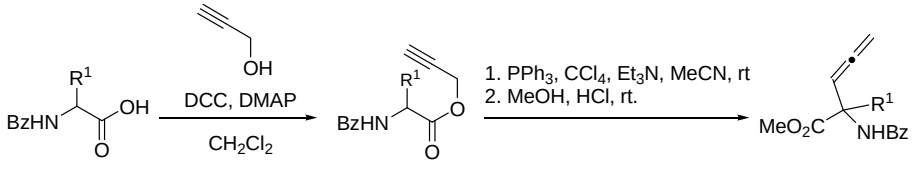
Using this protocol, the phenylalanine-derived allene **58a** was prepared as outlined in Scheme 2.4. Esterification of *N*-benzoyl phenylalanine **54a** with 3-butyne-2-ol by using DCC and DMAP gave ester **56a** in 78% yield. The reaction proceeds via the intermediacy of oxazolone **55a** which is then subject to nucleophilic attack by the alcohol. Treatment of ester **56a** with CCl_4, PPh_3 and Et_3N in acetonitrile affords the 4-allenyl-2-oxazolin-5-one **57a**, which is treated with MeOH/HCl to give allene **58a** in 74% yield as a 1.7 : 1 mixture of diastereomers (as previously reported by Krantz).[56]

Scheme 2.4 Synthesis of phenylalanine-derived allene **58a**.

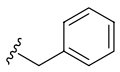
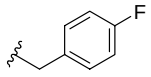
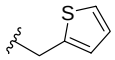
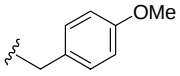
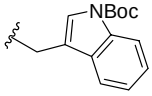


This protocol proved particularly useful for preparation of monosubstituted allenes, which are summarized in Table 2.1. These substrates were prepared in order to study the scope and limitations of the Mo-mediated and Rh-catalyzed cyclocarbonylation reaction. Phenylalanine, alanine and leucine derived allenes (**58b**, **58c** and **58d**, respectively) were prepared in yields ranging from 40 to 95% for the Claisen rearrangement step. The broad variations in yield do not reflect differences in reactivity, but rather, difficulties associated with purification of the resulting allenes from triphenylphosphineoxide (Ph_3PO), which is a byproduct in the reaction. Initial experiments were performed utilizing a procedure where an aqueous workup of the reaction mixture after the methanolysis step was followed directly by flash chromatography to separate the product from Ph_3PO. However, more polar allenes such as the alanine derived **58c** proved difficult to separate completely and thus lower yields were obtained (40%).

Table 2.1 Synthesis of monosubstituted allenes **58b-58h**.



54 **56** **58**

Entry	R^1	Ester/Yield%	Allene/Yield%	Entry	R^1	Ester/Yield%	Allene/Yield%
1		**56b**/98	**58b**/95	5		**56f**/42	**58f**/65
2		**56c**/68	**58c**/40	6		**56g**/52	**58g**/83
3		**56d**/90	**58d**/62				
4		**56e**/85	**58e**/70	7		**56h**/66	**58h**/64[a]

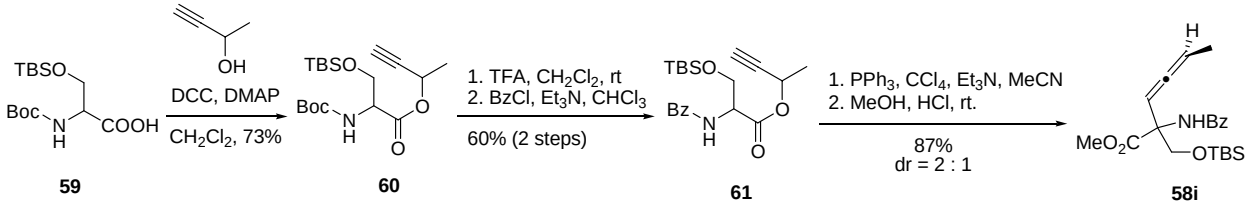
[a] Claisen rearrangement step was performed at 50 ^oC; MeOH, Et_3N was used instead of MeOH, HCl to prevent Boc-removal.

In later experiments, it proved advantageous to circumvent the aqueous work-up, and precipitate the solid Ph_3PO by addition of hexanes to a solution of the crude reaction mixture in diethyl ether. This was followed by chromatography of the filtrate after removal of the solvents under

vacuum. In this manner, yields between 60-80% were generally obtained. Using this protocol, unnatural aromatic amino acids were utilized to prepare *p*-methoxyphenyl (**58e**), *p*-fluorophenyl (**58f**), 2-thienyl (**58g**) and an *N*-Boc-indolyl (**58h**) derivatized allenes in yields ranging from 64 to 83%. The rearrangement of the *N*-Boc-indolyl derivative **56h** required heating to 50 °C to proceed which is attributed to the bulkiness of this group.

A serine derived allene **58i** was also synthesized following the route outlined in Scheme 2.5. Esterification of acid **59** with 3-butyn-2-ol in 73% yield was followed by removal of the Boc protecting group in **60** with TFA and coupling of the primary amine with benzoyl chloride to afford amido-ester **61** in 60% yield for the two steps. Claisen rearrangement of **61** afforded allene **58i** in 87% yield as a ~2 : 1 mixture of diastereomers (determined by integration of the allenic methyl group resonances in the ^{1}H NMR spectrum).

Scheme 2.5 Synthesis of serine derived allene **58i**.

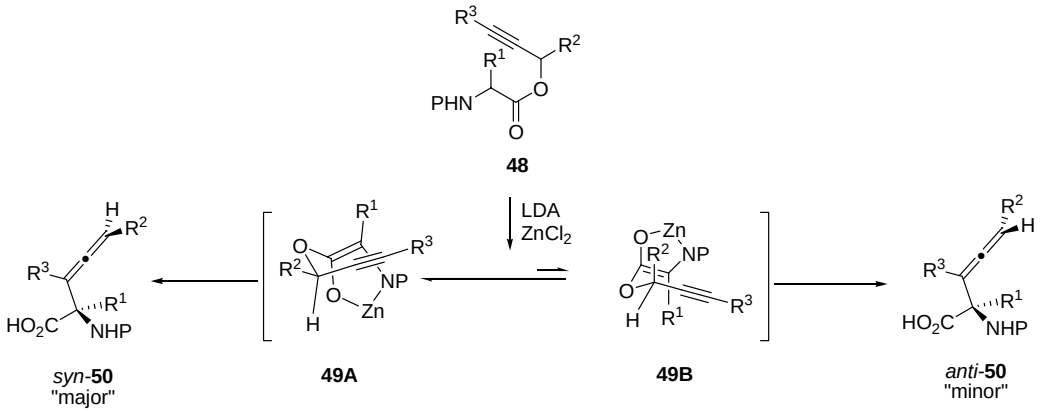


2.2.1.2 Ester-enolate Claisen Rearrangement

The ester-enolate version of the Claisen rearrangement was first introduced by Ireland[60] in 1976 and has since become a widely used method for acyclic stereocontrol.[61] Extension of the scope of the reaction to α-hydroxy and α-amino ester derivatives was reported by Bartlett and coworkers in 1982.[62] Subsequently, Kazmaier reported an ester-enolate Claisen rearrangement of α-amino acid propargylic esters to form α-allenyl amino acids with diastereoselectivity ranging between 93-98%.[57] Control of the enolate geometry was accomplished by using an equimolar amount of

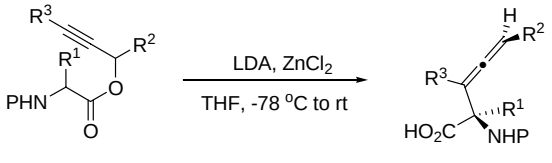
$ZnCl_2$, which results in a Zn-chelate **49** with fixed *Z*-geometry (Scheme 2.6). Rearrangement of this intermediate via a chair-like transition state **49A**, where the R^2 substituent is in a pseudoeqatorial position, leads to the major allene diastereomer *syn*-**50**. On the contrary, rearrangement via transition state **49B** where the R^2 substituent is in a pseudoaxial position, affords the minor diastereomer *anti*-**50**. The *syn/anti* notation for the allene products was introduced by Hoppe in analogy of the aldol product terminology.[63]

Scheme 2.6 Diastereocontrol in the ester-enolate Claisen rearrangement.



Notably, the reaction conditions were compatible with either carbamate (Boc, Cbz) or sulfonamide (tosyl) protecting groups. All examples in this initial report by Kazmaier involved terminally substituted alkynes in the propargylic esters (R^3 = alkyl, Table 2.2). Consequently, all of the prepared allenes contained an alkyl group at the proximal allenic position (i.e., trisubstituted allenes).

Table 2.2 Claisen rearrangement examples reported by Kazmaier.



48 **50**

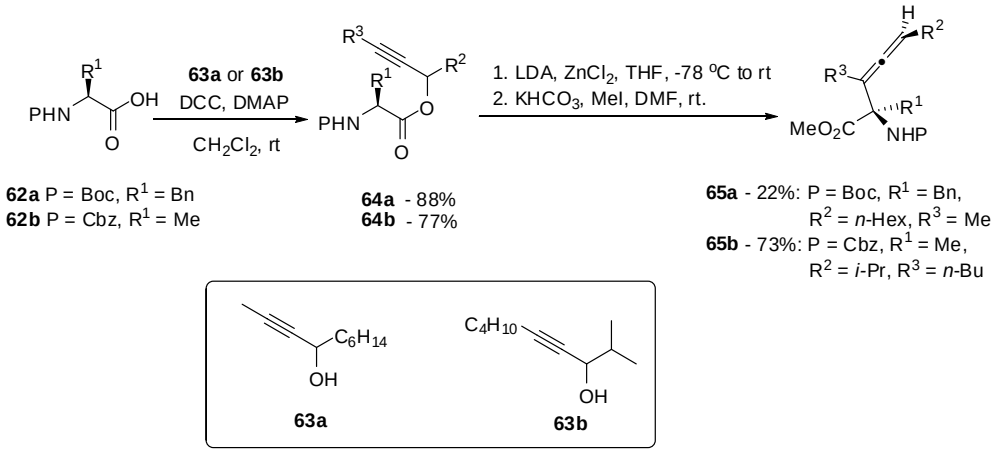
Entry	P	R^1	R^2	R^3	Yield (%)	diastereoselectivity (%)[a]
1	Boc	H	H	*t*-Bu	58	
2	Boc	H	Me	*t*-Bu	54	93
3	Cbz	H	Et	Bu	78	95
4	Cbz	Me	*i*-Pr	Pr	66	> 95
5	Boc	Bn	*i*-Pr	Pr	59	> 95
6	Tos	*i*-Bu	*i*-Pr	Pr	57	> 95

[a]diastereoselectivity was determined by ^{1}H NMR

Therefore, initial efforts were focused on reproducing Kazmaier's protocol by preparing trisubstituted allenes. Propargylic esters **64a** and **64b** were obtained by coupling of the corresponding acid **62** and alcohol **63** using DCC and DMAP in 88% and 77% yield, respectively (Scheme 2.7). Claisen rearrangement of **64a** using the reported conditions (LDA, $ZnCl_2$, THF, -78 °C to rt) proceeded to give the intermediate allenic acid, which was converted to the methyl ester **65a** by treatment with MeI and $KHCO_3$ in 22% overall yield. Since following both reactions by TLC did not reveal significant formation of any byproducts, the low yield was attributed to loss of the intermediate carboxylic acid during silica gel chromatography due to increased polarity. To circumvent this problem, in all subsequent reactions, the crude reaction mixture after Claisen rearrangement was immediately treated with MeI and $KHCO_3$ without intermediate purification.[a] Applying this strategy to the preparation of **65b** resulted in 73% yield after one final purification step.

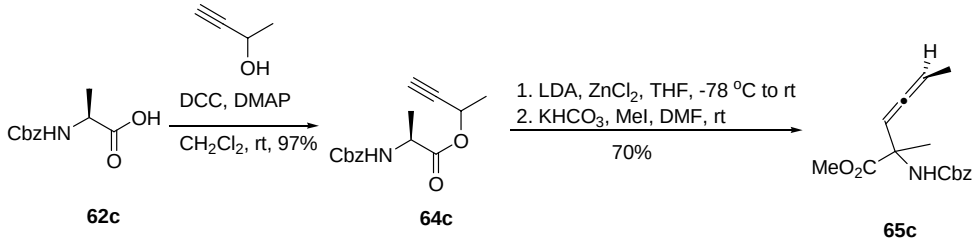
[a] Since sufficient amounts of **65a** were prepared using the unoptimized protocol this reaction was not repeated.

Scheme 2.7 Synthesis of trisubstituted allenes **65a** and **65b** using Kazmaier's protocol.



Preparing 1,3-disubstituted allenes using this protocol was also pursued. To this end, propargylic ester **64c** was prepared in 97% yield from *N*-Cbz-alanine **62c** and 3-butyn-2-ol (Scheme 2.8). Applying the two-step reaction sequence to this substrate resulted in the corresponding allenic-amino ester **65c** in 70% yield as a mixture of diastereomers in 1 : 1 ratio as determined by ^{1}H NMR. This result was disappointing since the high diastereoselectivity is considered the major advantage of utilizing Kazmaier's protocol. Since all examples of Claisen rearrangement proceeding with high diastereoselectivity reported by Kazmaier contain a terminally substituted alkyne, the lack of diastereoselectivity in the case of **64c** is attributed to the absence of this substituent. Nevertheless, the origin of this effect is not clear.

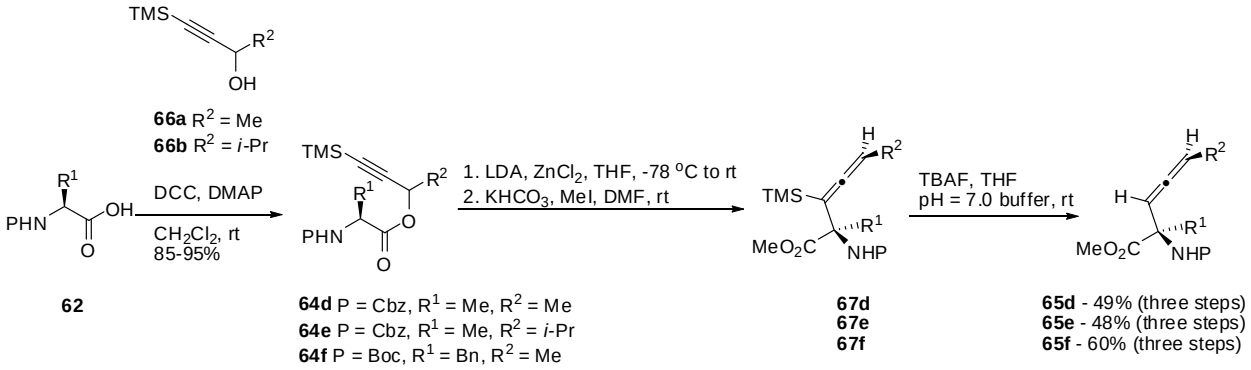
Scheme 2.8 Synthesis and Claisen rearrangement of **64c**.



To circumvent this problem, disubstituted allenes were prepared diastereoselectively by utilizing a TMS group to temporarily protect the alkyne terminus (Scheme 2.9). Following the original

protocol, a solution of **64d** in THF (kept at rt) was added to a solution of LDA at -78 °C followed by addition of $ZnCl_2$ (0.5 M in THF; kept at rt). The resulting Zn-enolate was then warmed to rt affording the intermediate carboxylic acid, which was converted to the methyl ester after aqueous work-up. Removal of the allenyl-TMS group was accomplished by treatment of **67d** with TBAF in presence of a phosphate buffer (pH = 7.0) to give the disubstituted allene **65d** in 49% yield for the three steps.[64] This yield was reproducibly obtained when the three steps are performed without purification of the carboxylic acid and allenyl-TMS intermediate.

Scheme 2.9 Synthesis of disubstituted allenes **65d-f**.



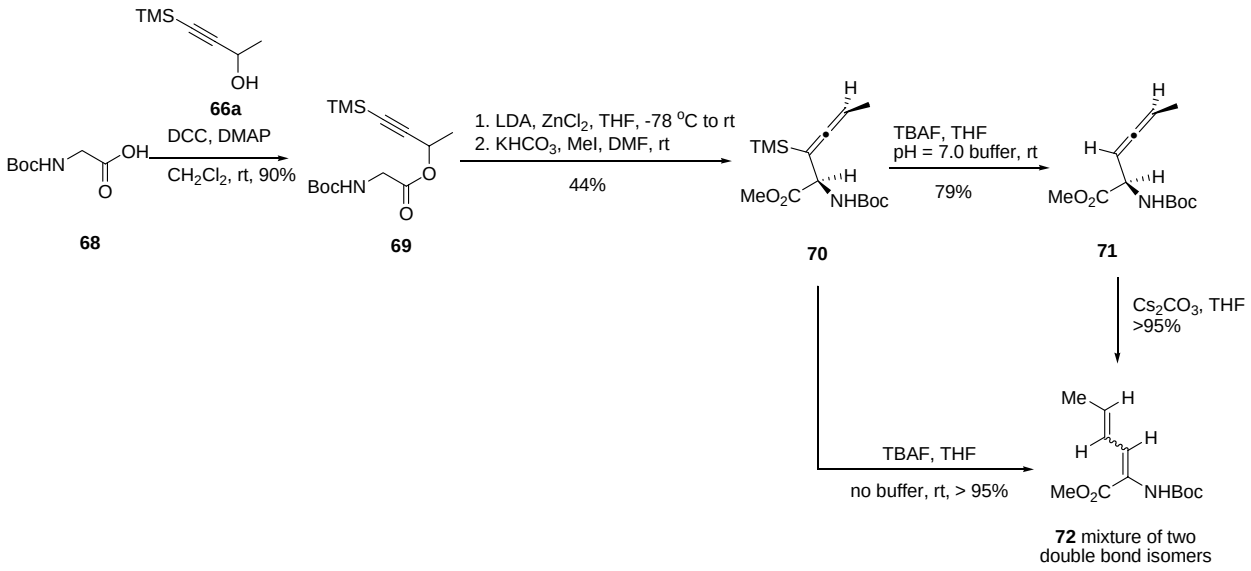
Allene **65d** was obtained as nearly a single diastereomer (diastereomer ratio of ~95 : 5 was determined by ^{1}H NMR). The relative stereochemistry of the major diastereomer was assigned as *syn*, in accordance with Kazmaier's results.[57] This route was then applied to the synthesis of one additional allene (**65e**) containing an isopropyl group at the terminal position, which was obtained in 48% yield. At later stages of the project, during the preparation of Boc-protected allenic amino-ester **65f**, additional optimization of the Claisen rearrangement protocol was performed. It was reasoned that formation of unidentified byproducts in this step can be minimized by keeping the temperature of the reaction solution stable at -78 °C during the addition of the propargyl ester **64f** to LDA. Indeed, it was found that by cooling the THF solution of **64f** to -78 °C and adding it to a solution of LDA simultaneously with $ZnCl_2$ (0.5 M in

THF), the yield was increased from ~45% to 60% for the three step sequence (the protocols for the remaining two steps were kept identical). Presumably, simultaneous addition of $ZnCl_2$ and the substrate to LDA is advantageous by immediately leading to the stabilized Zn-enolate, which minimizes side reactions resulting from exposure of the propargyl ester to excess LDA.

Thus far, all of the allenic amino-esters that were prepared utilize an α-substituted amino acid as a precursor and contain a quaternary α-stereocenter. Since the ultimate goal of the project is to prepare small molecule biological probes, being able to prepare analogues lacking an α-substituent was considered important in eventually establishing structure-activity relationships. In Kazmaier's original report, glycine propargyl esters were utilized sucessfuly to obtain the corresponding allenic amino-acids (Table 2.2, entries 1-3). However, it was reasoned that converting these acids to the methyl ester would result in increased acidity at the α-position, thereby increasing the propensity for isomerization of the allene to a more stable 1,3-diene. With this in mind, the Claisen rearrangement of glycine-ester **69** was attempted (Scheme 2.10). The rearrangement proceeded to afford the allenic carboxylic acid, which was converted to the methyl ester **70** without event in 44% yield. In an initial experiment to remove the allenyl-TMS group, a solution of **70** in THF was directly treated with TBAF. The only isolable product from this reaction was the diene **72** in quantitative yield as a mixture of isomers in a 1 : 1 ratio which was determined by integration of the olefin resonances in the ^1H NMR (the two isomers were separated by flash chromatography). It was reasoned that the mild basicity of TBAF is cause for this isomerization, so our next attempt involved adding a phosphate buffer with pH = 7.3 to TBAF prior to treating **70**. This protocol prevented the observed isomerization and allowed the isolation of **71** in 79% yield. To determine whether the formation of the diene is indeed promoted by base, a small sample of **71** in THF was treated with equimolar amount of Cs_2CO_3

and resulted in isomerization to **72** within 10 min (Cs_2CO_3 was chosen since it could be used as a base for N-alkylation of **71**).

Scheme 2.10 Synthesis of glycine-derived allenic amino-ester.

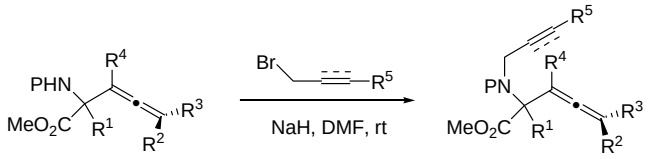


2.2.2 N-Alkylation of Allenic Amino Esters

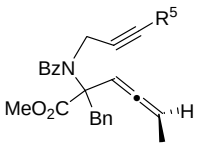
The next goal was to develop a general procedure for N-alkylation of the allenic amino-esters that would introduce the alkyne component of the precursors for transition metal-catalyzed carbocyclization reactions. It was quickly found that treatment of the amides or carbamates with NaH in DMF at rt for 2-5 min, followed by addition of the corresponding propargylic bromide results in clean N-alkylation. Using this protocol on the Bz-protected substrate **58a** and 1-bromo-2-butyne gave allenyne **73a** in 83% yield (Table 2.3). Varying the substitution pattern of the alkyne was important in order to study the scope of the carbocyclization reactions. Therefore, terminally unsubstituted alkyne was incorporated via N-alkylation with propargyl bromide affording **73b** in 73% yield, whereas alkylation with 3-phenyl-1-bromopropyne gave a phenyl substituted allenyne **73d** in 89% yield. Attempts to prepare precursor **73c** with a TMS group on

the terminus of the alkyne led to desilylation which was attributed to to presence of NaOH in the bulk NaH. This problem was circumvented by utilizing KH (in mineral oil) as a base and THF as a solvent, which gave **73c** in 75% yield. The same protocols were applied to synthesize the Cbz-protected substrates **73f-i** derived from alanine in yields ranging from 68-86%. These two sets of allenynes were envisioned to serve as main model systems for studying the transition metal-catalyzed reactions and subsequent diversification of the scaffolds. In order to examine the effect of allene substitution on the carbocyclization reactions, allenynes **73j**, **73k** and **73l** were synthesized in 73-86% yields. Allenynes possessing a terminal allene **74a-i** were synthesized in order to study the diastereoselectivity in the Mo-mediated cyclocarbonylation reaction described in Section 4.4. Yields for preparing these compounds varied from 66-94%. Allenynes **74b**, **74d** and **74e** were also prepared in larger quantities (5-10 g) for library synthesis using a modified protocol where a solution of the allenyne was slowly added to a slurry of NaH at 0 °C in order to avoid overheating from the exothermic reaction. Finally, we were also interested in preparing substrates containing an alkene instead of an alkyne (ene-allenes) in order to study the effect of this group on the cycloisomerization reaction affording cross-conjugated trienes. The yields for alkylation with allyl or crotyl bromide generally were lower, ranging from 42-71% (**75a-e**). Nevertheless, this protocol proved generally robust and performed uniformly across a broad range of substrates, which is ideal for performing these reactions in parallel for eventual library synthesis.

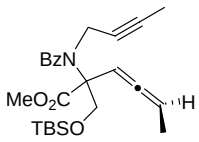
Table 2.3 Synthesis of allenynes and ene-allenes via N-alkylation.



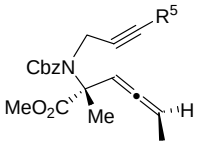
73a-l, 74a-i, 75a-e



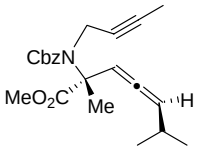
73a : R^5 = Me, 83%
73b : R^5 = H, 73%
73c : R^5 = TMS, 75%[a]
73d : R^5 = Ph, 89%



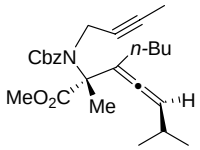
73e : 94%



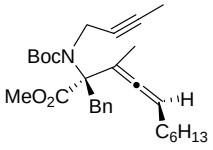
73f : R^5 = Me, 84%
73g : R^5 = H, 77%
73h : R^5 = TMS, 86%[a]
73i : R^5 = Ph, 68%



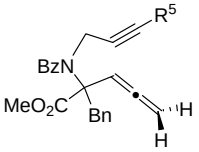
73j : 86%



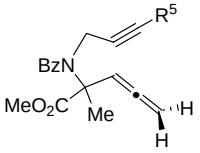
73k : 78%



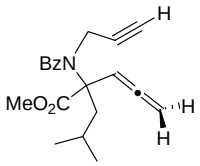
73l : 73%



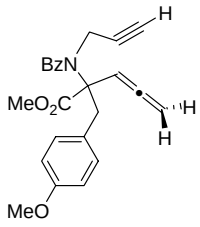
74a: R^5 = Me, 84%
74b : R^5 = H, 66%



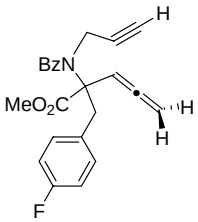
74c : R^5 = Me, 93%
74d : R^5 = H, 94%



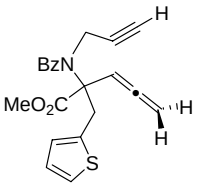
74e : 77%



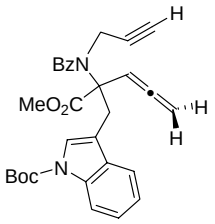
74f : 84%



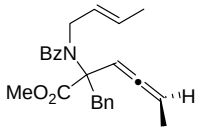
74g : 85%



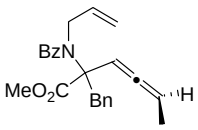
74h : 89%



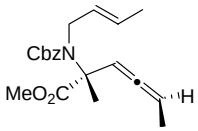
74i : 78%



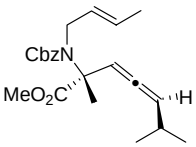
75a : 56%



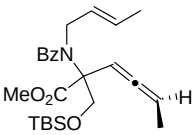
75b : 71%



75c : 66%



75d : 61%

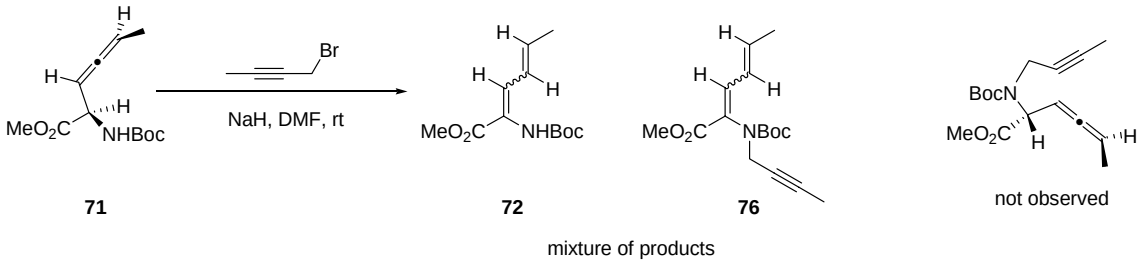


75e : 42%

[a] Conditions: KH, THF

N-Alkylation of the glycine-derived allene **71** was also attempted. Under the standard conditions (NaH, 1-bromo-2-butyne, DMF) the reaction afforded a mixture of products containing the previously characterized diene **72** and its N-alkylated derivative **76** (Scheme 2.11). This result was obtained despite quenching the reaction with pH = 7.0 buffer in an effort to prevent exposing the crude reaction mixture to aqueous base.

Scheme 2.11 Attempted alkylation of **71**.



71 **72** **76** not observed

mixture of products

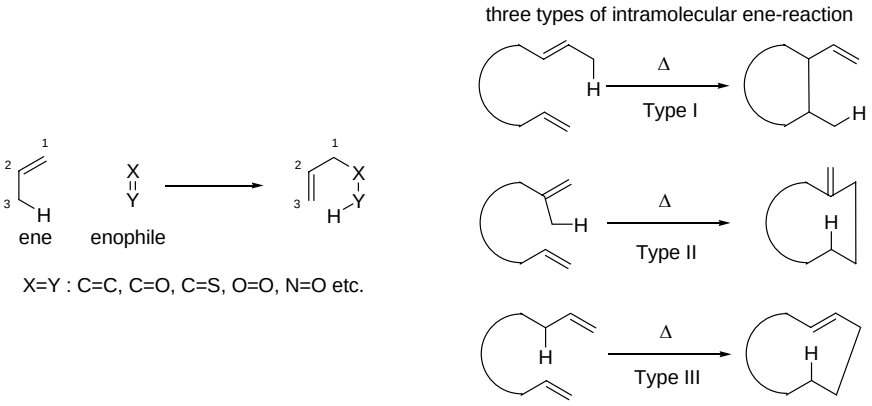
Attempting to N-alkylate **71** using milder basic conditions (Cs_2CO_3, TBAI and 1-bromo-2-butyne) led only to the diene isomer **72**, which is not surprising since it was shown that Cs_2CO_3 alone promotes this facile isomerization. Since treatment of **71** with base appeared to cause isomerization to **72**, further experiments towards preparing a glycine-derived allenyne were suspended.

3.0 Synthesis and Use of Cross-Conjugated Trienes

3.1 Transition Metal-Catalyzed Ene-type Cycloisomerization Reactions

The ene reaction is recognized as a thermal pericyclic reaction of an olefin containing an allylic hydrogen (ene) and a multiple bond (X=Y, enophile), resulting in formation of a new C-C and Y-H bond as shown in Scheme 3.1.[65] The reaction was first discovered by Alder in 1943, and is often referred to as the Alder-ene reaction.[66] Since then, intramolecular variants have been studied extensively. Depending on the placement of the ene component in the starting material, there are three types of intramolecular ene reactions: type I – connected via the olefin terminal; type II – connected via the central carbon; and type III – connected via the allylic terminal.[67]

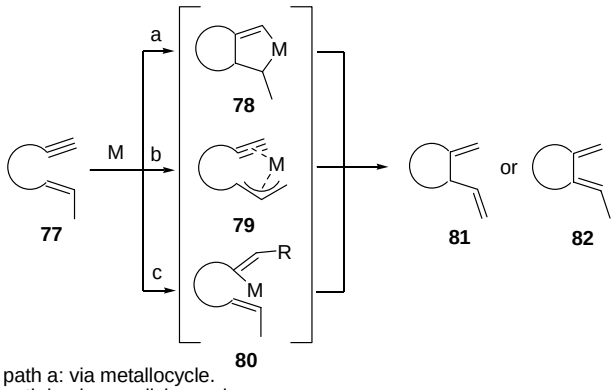
Scheme 3.1 Classification of ene reactions.



Thermal ene reactions of unactivated substrates generally require very high temperatures between 300-500 °C to proceed, which has limited their direct application in synthesis. To

circumvent this issue, variants such as the metallo-ene reaction have been developed. In this case, the transfer of hydrogen is replaced by a metal (lithium, magnesium, zinc) and requires milder conditions.[68] More recently, transition metals have been used to effect ene-type reactions. In this regard, 1,n-enynes have served as a standard substrate class for development of new methodologies.[37-39] Because an alkyne is used as an enophile component, the product of the rearrangement is generally a 1,4- or 1,3-diene (**81** or **82**) (Scheme 3.2). Transition metal catalyzed ene-reactions do not occur via the classical pericyclic mechanism, and they are often referred to as formal ene reactions or ene-type cycloisomerizations. A recent review by Malacria[39] has categorized the three mechanisms by which enyne cycloisomerization can occur: path a involves simultaneous complexation of the metal to the olefin and the alkyne, leading to oxidative addition and formation of a metallocycle **78**. This intermediate then undergoes a β-hydride elimination from one allylic position giving the product; path b occurs via a π-allyl complex **79** formed by insertion of the metal into the allylic position; and path c involves a carbo- or hydrometalation of the alkyne leading to vinyl-metal species **80**, which then undergoes carbometallation of the olefin.

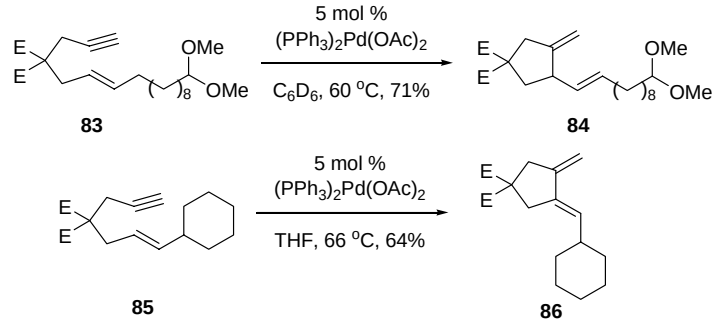
Scheme 3.2 Transition metal-catalyzed ene-type cycloisomerization of enynes.



A number of metals have been used to effect enyne cycloisomerization via these three pathways, including Pd, Ru, Fe, Ni, Rh, and Ir.[39] The metallocycle pathway is particularly intriguing since these intermediates have proven high synthetic utility otherwise. For example, metallocyclic intermediates formed from enynes have been utilized in processes such as cyclocarbonylation, [2+2], [4+2], [2+2+2] and [5+2] cycloadditions etc.[40-42]

Some of the first examples of enyne cycloisomerization were reported by Trost employing Pd(II) catalyst.[69] For example, enyne **83** rearranges to 1,4-diene **84** when treated with 5 mol % $(PPh_3)_2Pd(OAc)_2$ (Scheme 3.3).[69a] When steric bulk is introduced at the terminal allylic position by a cyclohexyl substituent **(85**), 1,3-diene **86** is obtained. The former transformation has been extensively applied by Trost to the total synthesis of several natural products.[70]

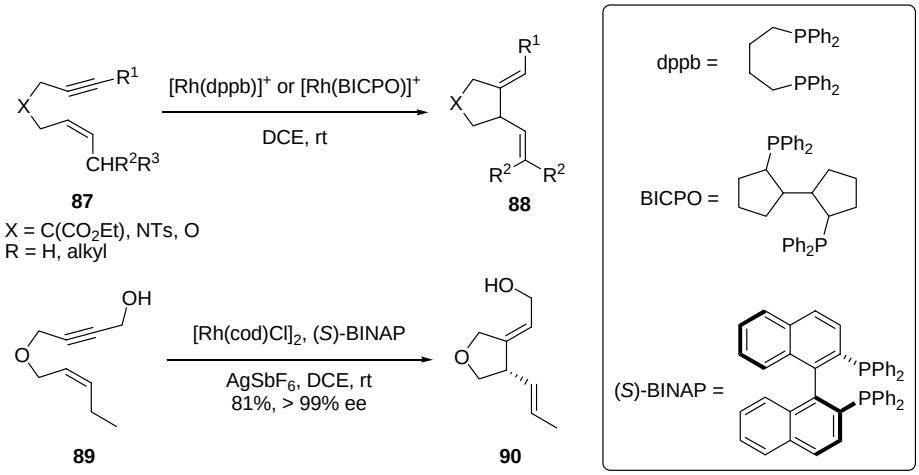
Scheme 3.3 Pd(II)-catalyzed cycloisomerization of enynes.



More recently, Zhang has successfully performed Rh(I)-catalyzed enyne cycloisomerizations exclusively affording 1,4-dienes. A cationic Rh(I) complex containing a 1,4-diphosphine ligand (either dppb or 2,2'-bisdiphenylphosphine-1,1'-dicyclopentane - BICPO[71]) was shown to catalyze the cycloisomerization of a variety of enynes **87** leading to 5-membered carbo- and heterocycles **88** (Scheme 3.4).[72] This method is limited to *cis*-alkenes, while *trans*-alkenes proved unreactive. Nevertheless, Rh(I) catalysts have proven highly advantageous, since most reactions can be performed at rt and the phosphine ligands can be readily tuned to develop an enantioselective version of the reaction. This idea was put into practice by Zhang by utilizing

BINAP as a chiral ligand to obtain various 5-membered carbo- and heterocycles with high enantiopurity (>99% ee) (**89** to **90**, Scheme 3.4).[73]

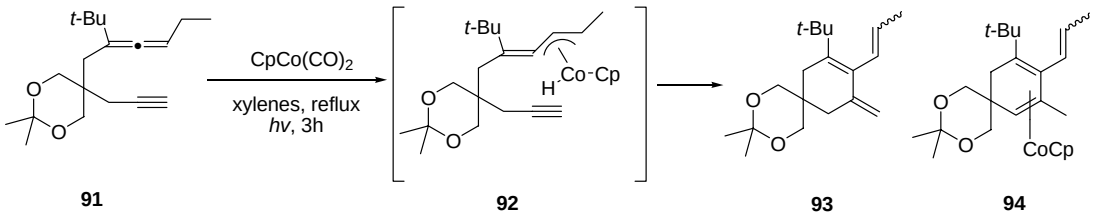
Scheme 3.4 Rh(I)-catalyzed cycloisomerization of enynes.



3.1.1 Allenic Cycloisomerization Reaction.

The first example of allenyne cycloisomerization was provided by Malacria in 1996 by transforming **91** to cross-conjugated triene **93** using stoichiometic amount of $CpCo(CO)_2$ in refluxing xylene (Scheme 3.5).[74] A mechanism involving a π-allyl Co-hydride species **92** was invoked to explain this result. Presumably, reaction with the distal double bond of the allene was directed by the sterically demanding *t*-butyl group on the proximal carbon.

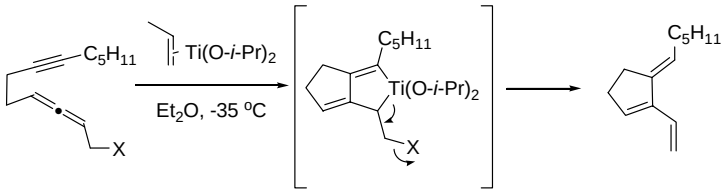
Scheme 3.5 Allenic cycloisomerization reported by Malacria.



Additionally, Sato reported the formation of 5-membered cross-conjugated trienes **97** from

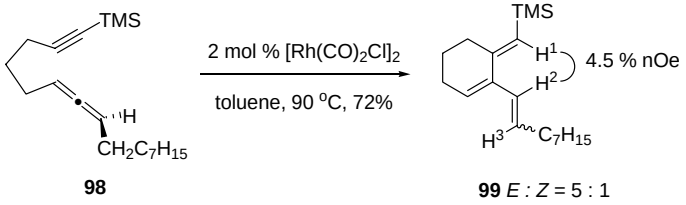
allenynol derivatives **95** proceeding via a metallocyclic intermediate **96**, by using stoichiometric (η^2-propene)Ti(*i*-PrO)$_2$ (Scheme 3.6).[75] Livinghouse and Oh have also observed cross-conjugated trienes during transition-metal catalyzed reactions of allenynes.[76]

Scheme 3.6 Allenic cycloisomerization reported by Sato.



In 2002, Brummond reported the first systematic study of the Rh(I)-catalyzed allenic Alder-ene reaction.[77] It was shown that $[Rh(CO)_2Cl]_2$ serves as a very general catalyst for converting allenynes into cross-conjugated trienes. For example, the cycloisomerization of **98** using 2 mol % catalyst, at 90 °C gives triene **99** in 72% yield (Scheme 3.7). The appending olefin is obtained as a kinetic mixture of *E : Z* isomers (5 : 1), while the exocyclic olefin is obtained as a single isomer with *E*-geometry.

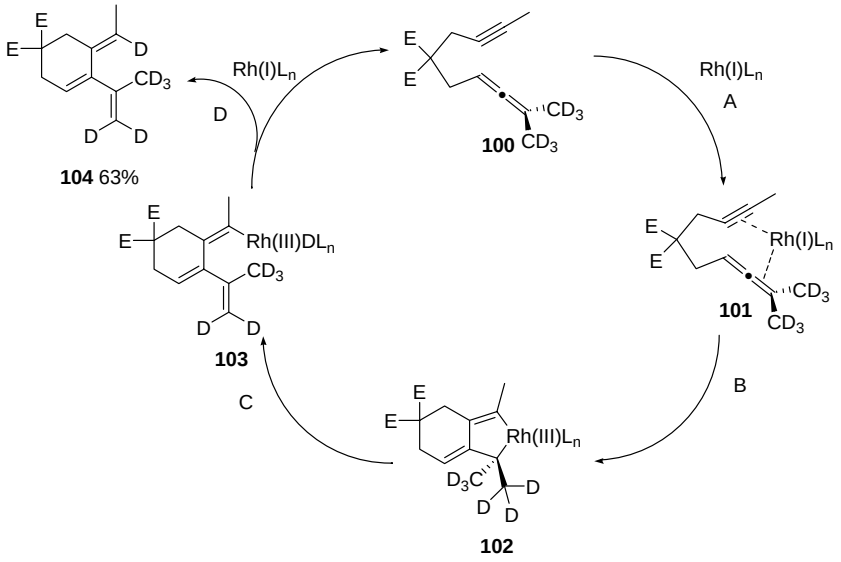
Scheme 3.7 Rh(I)-catalyzed allenic Alder-ene reaction.



A mechanism based on a deuterium labeling study has been proposed to account for these observations (Scheme 3.8). The first step is complexation of the Rh(I) to the alkyne and the distal double bond of the allene, eventually leading to a metallocyclic Rh(III) intermediate **102** via oxidative addition. The next step involves elimination of a β-deuteride (hydride) leading to a Rh(III)-deuteride species **103**, which undergoes a facile reductive elimination setting the

stereochemistry of the exocyclic olefin in the triene **104** and regenerating the active catalyst.

Scheme 3.8 Mechanism of the Rh(I)-catalyzed allenic Alder-ene reaction.

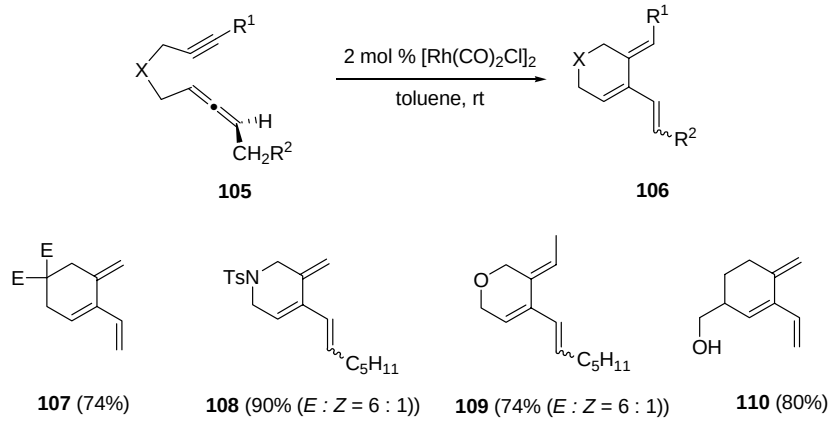


A: complexation; B: oxidative addition; C: β-deuteride elimination; D: reductive elimination.

According to the proposed mechanism, the stereochemistry of the appending olefin in the resulting triene is set during the β-hydride elimination step. Brummond and coworkers have shown that the selectivity for the *E*-isomer in the reaction of **98** (Scheme 3.7) can be drastically increased (>100 : 1) by utilizing an *in situ* generated cationic Ir(I) catalyst ($[Ir(COD)Cl]_2$, $AgBF_4$). This protocol, however, was limited to substrates containing a silicon group on the terminus of the alkyne.

The scope of the $[Rh(CO)_2Cl]_2$-catalyzed reaction has been demonstrated on carbon, nitrogen and oxygen tethered allenynes. With most substrates, the reaction proceeds at rt affording a variety of trienes in good yields (Scheme 3.9).

Scheme 3.9 Examples of Rh(I)-catalyzed allenic Alder-ene reaction.



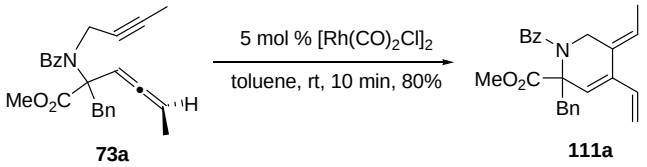
Finally, it should be noted that following the initial report by Brummond, Shibata[78] and Mukai[79] have also reported Rh(I)-catalyzed cycloisomerization of allenynes leading to cross-conjugated trienes.[80]

In summary, the Rh(I)-catalyzed cycloisomerization of allenynes allows rapid access to cyclic cross-conjugated trienes. Additional studies in the Brummond group have been aimed at extending the scope and utility of this transformation. The presence of three stereodefined olefins in the cross-conjugated trienes makes them valuable synthetic intermediates, and offers unique opportunities for exploiting these compounds in target- and diversity-oriented synthesis.

3.2 Rhodium(I)-Catalyzed Allenic Cycloisomerization Reaction of Amino-Ester Tethered Allenynes

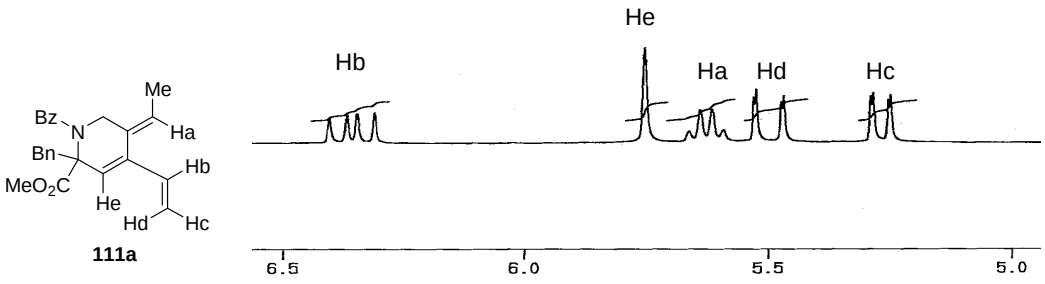
Synthetic investigations started with the Rh(I)-catalyzed allenic Alder-ene reaction. When allenyne **73a** was submitted to the optimized reaction conditions (5 mol % $[Rh(CO)_2Cl]_2$, toluene),[77] cycloisomerization proceeded at rt in less than 10 min to give the expected cross-conjugated triene **111a** in 80% yield (Scheme 3.10).[81] The structure of triene **111a** was assigned based on the characteristic olefin resonances in the ^{1}H NMR spectrum (Scheme 3.11). Triene **111a** was obtained as a single isomer of the exocyclic olefin, which is assigned *Z*-geometry in accordance with previous examples and mechanistic studies by Brummond and coworkers (*vide supra*, Schemes 3.7 to 3.9).[77]

Scheme 3.10 Allenic Alder-ene reaction of **73a**.



73a **111a**

Scheme 3.11 ^{1}H NMR of **111a** (olefin region, $CDCl_3$, rt, 300 MHz).

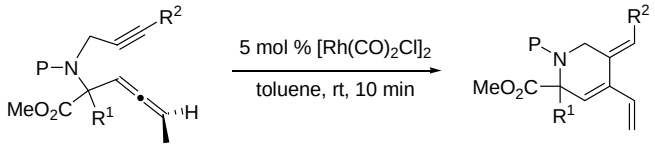


111a

assigned resonance	chemical shift (ppm)	splitting/coupling constant
Hb	6.36	dd, *J* = 17.2, 10.7 Hz
He	5.75	s
Ha	5.63	q, *J* = 7.0 Hz
Hd	5.50	dd, *J* = 17.2, 1.5 Hz
Hc	5.27	dd, *J* = 10.7, 1.5 Hz

The scope of this transformation was next examined by varying different substituents on the allenyne. First, only allenynes substituted with a methyl group on the terminal allenic position were tested to avoid formation of *E/Z* isomers of the appending olefin. In all cases, the reaction proceeded in 10 min to afford the cross-conjugated trienes **111b-111i** (Table 3.1). The reaction conditions were compatible with either a Bz- (entries 1-4) or Cbz- (entries 5-8) protected amine. Allenynes **73b** and **73g** with a terminal alkyne reacted to give **111b** and **111g** in 74% and 84% yield, respectively (entries 1 and 6). Substitution of the alkyne terminus with either a TMS (entries 2 and 7) or phenyl group (entries 3 and 8) resulted in the corresponding trienes in yields ranging between 81-95%. Finally, variations at the amino acid side chain R^1 with a methyl (entries 5-8), benzyl (entries 1-3) and silyloxymethylene (entry 4) group were also incorporated without event.

Table 3.1 Allenic Alder-ene reaction affording cross-conjugated trienes.



73b-i **111b-i**

entry	allenyne	P	R^1	R^2	triene	yield%	entry	allenyne	P	R^1	R^2	triene	yield%
1	**73b**	Bz	Bn	H	**111b**	74	5	**73f**	Cbz	Me	Me	**111f**	81
2	**73c**	Bz	Bn	TMS	**111c**	92	6	**73g**	Cbz	Me	H	**111g**	84
3	**73d**	Bz	Bn	Ph	**111d**	81	7	**73h**	Cbz	Me	TMS	**111h**	87
4	**73e**	Bz	$-CH_2OTBS$	Me	**111e**	89	8	**73i**	Cbz	Me	Ph	**111i**	95

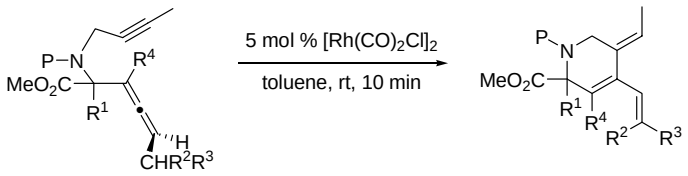
It is noteworthy to mention that Bz-protected allenynes (**73a-73e**, entries 1-4 and Scheme 3.1) were subjected to the reaction conditions as mixtures of diastereomers (~1.7 : 1, see Chapter 2) while the Cbz-protected allenynes (entries 5-8) were nearly single isomers (all compounds are racemic; see Chapter 2 for preparation of allenic amino-esters). Nevertheless, all reactions resulted in the corresponding cross-conjugated triene as a single isomer indicating that the

exocyclic olefin geometry is not related to the relative stereochemistry of the allenyne, and is a result of the last reductive elimination step in the mechanism of the reaction.[b]

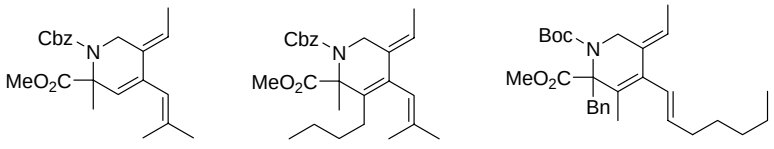
It should be noted that the rate with which the reaction of these amino-ester tethered substrates proceeded was noticeably higher compared to previous examples reported by Brummond and coworkers, some of which required up to 6 h for completion.[77] That the increased reactivity of the amino-ester substrates is likely a result of a Thorpe-Ingold effect imposed by the quaternary center adjacent to the allene.[82] In addition, the carbomethoxy group may play a directing role by reversibly coordinating to the metal center.[83]

Next, variations of the substituents on the allene moiety were tested (Scheme 3.12). Allenyne **73j**, substituted with an isopropyl group at the terminal allenic position reacted to afford triene **111j** with trisubstituted appending olefin in 95% yield. In this case, there is only one hydrogen atom that can undergo β-hydride elimination. This does not affect the rate or the yield of the reaction, since **111j** was produced in 95% yield after 10 min.

Scheme 3.12 Preparation of polysubstituted trienes **111j-111l**.



73j (P = Cbz, R^1 = Me, R^2 = R^3 = Me, R^4 = H)
73k (P = Cbz, R^1 = Me, R^2 = R^3 = Me, R^4 = *n*-Bu)
73l (P = Boc, R^1 = Bn, R^2 = H, R^3 = C_5H_{11}, R^4 = Me)

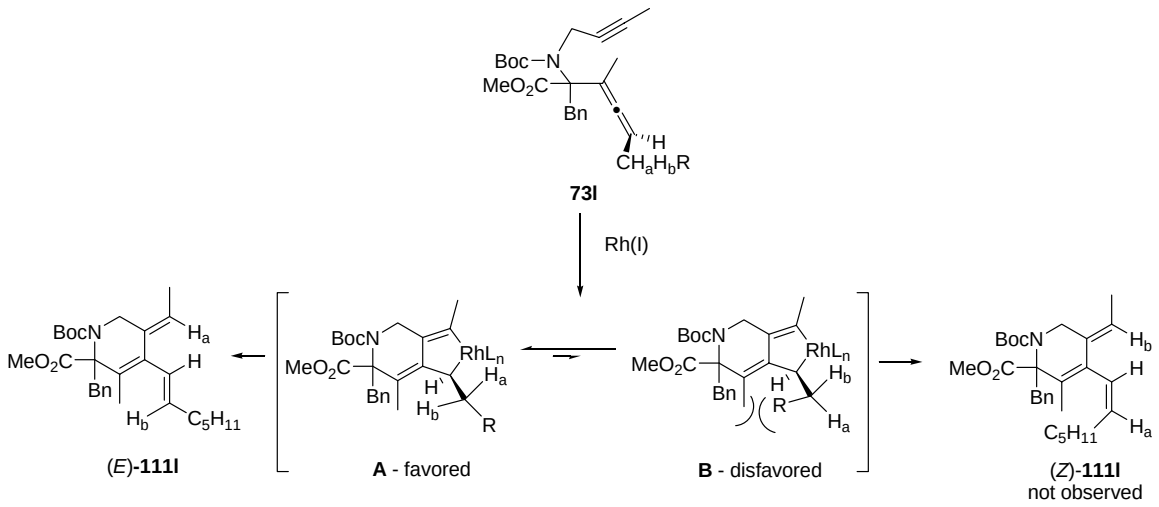


111j 95% **111k** 78% **111l** 80% (*E* isomer only)

[b] For the proposed mechanism of the reaction, see Scheme 3.8.

Additionally, trisubstituted allenes **73k** and **73l** underwent the Alder-ene reaction affording **111k** and **111l** in 78% and 80% yield, respectively. In the case of **111l**, only the *E* isomer of the appending olefin was observed, characterized by J = 16.0 Hz for the vinyl hydrogens in the ^{1}H NMR spectrum. This is in contrast to earlier examples from the Brummond group, where Rh(I)-catalyzed reaction of alkyl allenes resulted in mixture of appending olefin isomers in *E/Z* ratio in the range of 3-6 : 1.[77] The geometry of the appending olefin is determined during the β-hydride elimination step of the reaction mechanism, which requires a coplanar arrangement of the Rh-C bond and the C-H bond that is being broken. Therefore, β-hydride elimination in the formation of **111l** can occur via rotamer **A** or **B** as shown in Scheme 3.13. Rotamer **B**, which would lead to the *Z*-olefin isomer, results in an unfavorable steric interaction between the appending alkyl group and the methyl substituent in the ring and is strongly disfavored. Therefore, β-hydride elimination via rotamer **A** leads to the exclusive *E*-isomer **111l**.

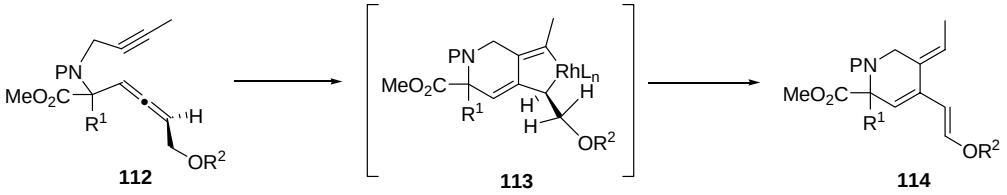
Scheme 3.13 Mechanistic rationale for the exclusive *E* geometry of **111l**.



3.2.1 Preparation of Enol-ether Trienes via an Allenic Cycloisomerization Reaction

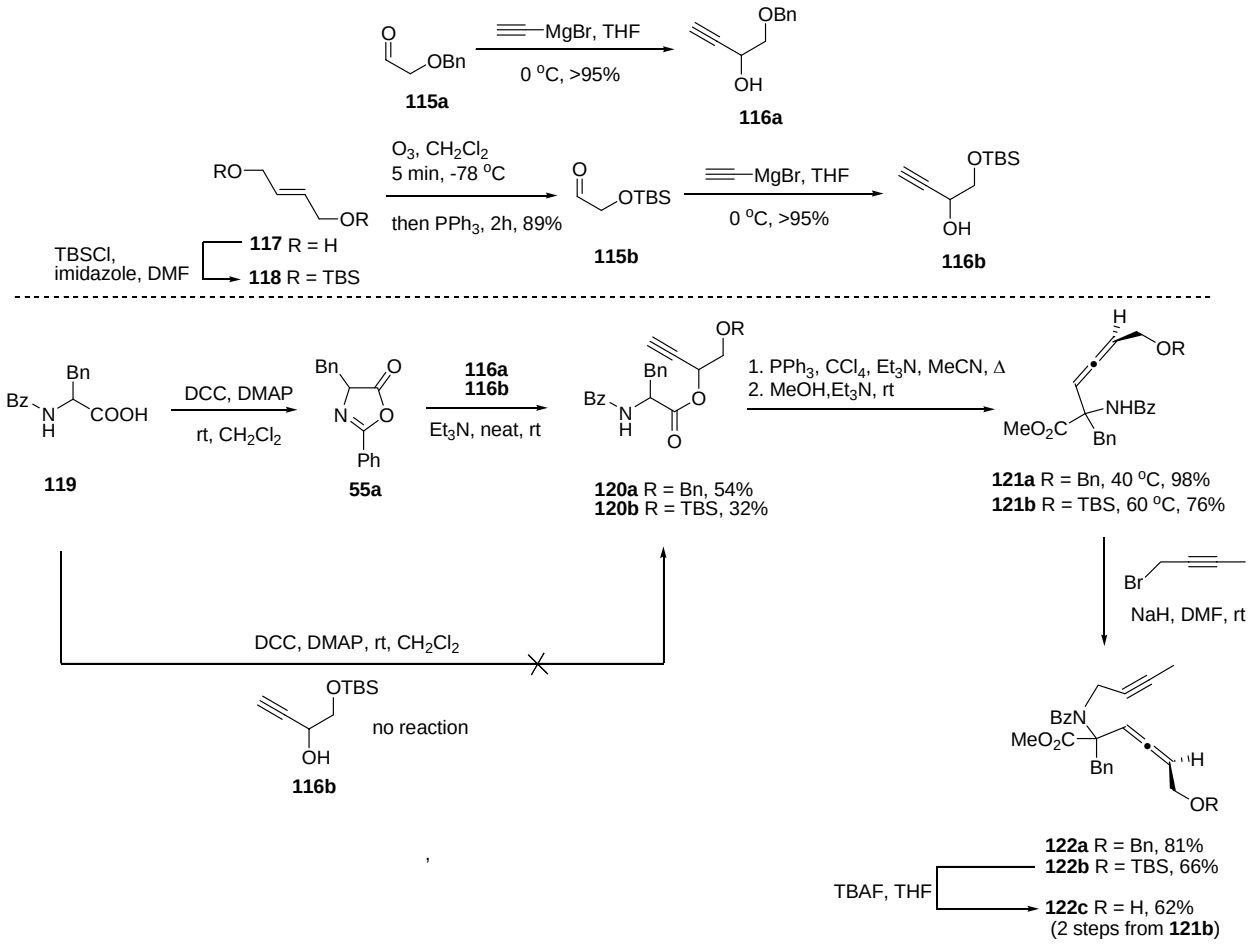
The success of the Rh(I)-catalyzed allenic cycloisomerization reaction of amino-ester tethered substrates prompted further examination of the scope of this transformation. In these and previous examples from the Brummond group, variations of the substitution pattern of the allene have been limited to introducing different alkyl groups. Consequently, the resulting trienes possess three cross-conjugated olefins with similar electronic properties, and are expected to react unselectively with various electrophilic reagents (e.g., epoxidation and dihydroxylation agents). Being able to perform selective reactions on the three olefins is important in applying these compounds to complex molecule synthesis. Therefore, we were interested in preparing trienes in which the olefins are electronically differentiated. Although a number of different strategies can be undertaken towards this goal, we became particularly interested in preparing trienes possessing an electron rich enol-ether as the appending olefin. Preparing this class of trienes was envisioned by cycloisomerization reaction of allenynes possessing a protected alcohol group at the allylic position of the allene (Scheme 3.14). According to the proposed mechanism of the reaction, β-hydride elimination in metallocycle **113** would have to occur from a carbon possessing an oxygen substituent. The feasibility of this process has been demonstrated by Trost[84] in the Ru(II)-catalyzed and Zhang[85] in the Rh(I)-catalyzed cycloisomerization of 1,5-enynes to prepare five-membered rings possessing an appending enol ether.

Scheme 3.14 Proposed cycloisomerization to form enol-ether trienes.



The requisite allenynes of general structure **112** were prepared as outlined in Scheme 3.15. The mono-benzyl protected diol **116a** was synthesized in >95% yield by addition of ethynyl-magnesium bromide to commercially available aldehyde **115a**. The corresponding mono-TBS protected diol **116b** was prepared by diprotection of 1,4-butanediol with TBSCl, followed by ozonolysis and alkynylation of the resulting aldehyde. With alcohol **116b** in hand, the DCC/DMAP mediated coupling with Bz-phenylalanine was attempted under the standard conditions (rt, in CH_2Cl_2). However, this reaction led only to formation of the oxazolone intermediate **55a**. It was reasoned that the sterically hindered nature of the secondary alcohol prevents the facile opening of **55a** under the reaction conditions. To solve this problem, **55a** was formed by separately treating benzoyl-phenylalanine with DCC and DMAP. Upon isolation, the oxazolone was treated to neat alcohol **116a** or **116b** in presence of catalytic amount of Et_3N. Under these conditions formation of esters **120a** and **120b** was observed, albeit in relatively low isolated yields (54% for the benzyl-protected and 32% for the TBS-protected alcohol). The lower yield for the TBS-protected case is attributed to increased steric influence by the silyl group. Next, the Claisen rearrangement of these propargyl esters **120a** and **120b** was attempted under dehydrative conditions reported by Krantz. Reaction of the benzyl-protected **120a** proceeded at 40 °C to give the desired allene **121a** in >95% yield after treatment with MeOH. In contrast, the reaction of the TBS-protected **120b** required heating to 60 °C and afforded the product **121b** in lower yield (76%). Notably, formation of methyl ester was accomplished by using MeOH/Et_3N instead of the standard MeOH/HCl in order to avoid potential cleavage of the TBS-ether under strong acidic conditions. As expected, allenes **121a** and **121b** were obtained as mixtures of diastereomers in ~2 : 1 ratio determined by ^1H NMR.

Scheme 3.15 Synthesis of cycloisomerization precursors **122a-c**.

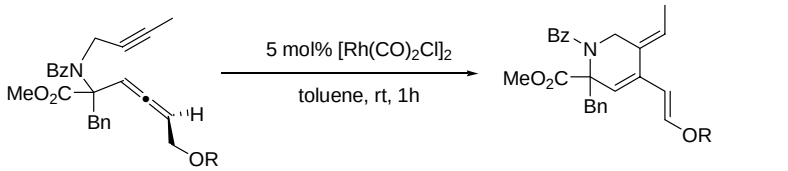


Finally, the desired cycloisomerization precursors **122a** and **122b** were prepared by alkylation with 1-bromo-2-butyne in presence of NaH. Removal of the TBS protecting group in **122b** was accomplished using TBAF, to obtain allenic alcohol **122c** in 62% yield (2 steps from **121b**).

Precursors **122a-c** were next tested in the Rh(I)-catalyzed cycloisomerization reaction. Treatment of **122a** to 5 mol% $[Rh(CO)_2Cl]_2$ led to the formation of the expected triene **123a** which was isolated in 64% yield after 1 h (Scheme 3.16). Triene **123a** was obtained as a mixture of *E* and *Z* isomers of the vinyl-ether in 8 : 1 ratio (determined by integration of the olefinic resonances in the ^{1}H NMR spectrum; the *E* isomer is characterized by a coupling constant of *J* =

12.5 Hz for the vinyl hydrogens, compared to J = 7.9 Hz for the Z-isomer). The rate of this cycloisomerization was somewhat slower than the previous examples of alkyl-substituted allenes (from Table 3.1), and took approximately 1 h for completion (following the reaction by ^{1}H NMR showed 1 : 1 ratio of product and starting material after 15 min). The TBS-protected allenyne **122b** reacted similarly, affording silyl enol ether **123b** in 60% yield and increased selectivity for the *E*-olefin (>10 : 1 ratio determined by integration of the olefin resonances in the ^{1}H NMR spectrum).

Scheme 3.16 Cycloisomerization of **122a** and **122b**.

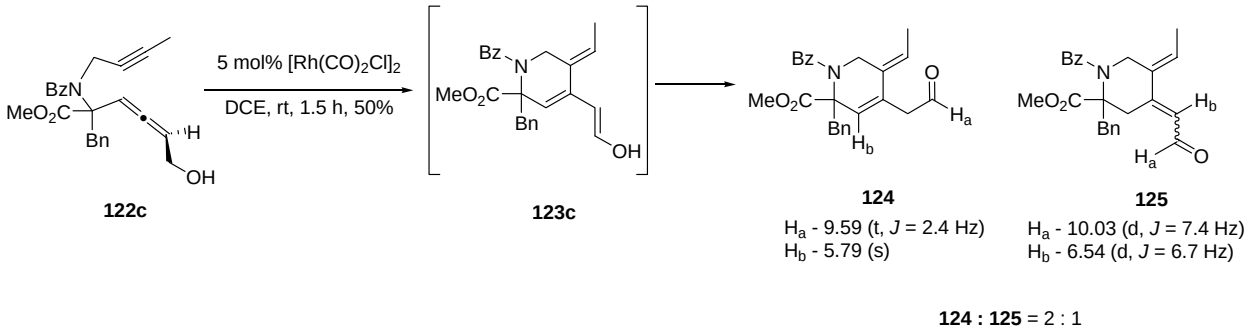


122a R = Bn
122b R = TBS

123a R = Bn, 64% *E* : *Z* = 8 : 1
123b R = TBS, 60% *E* : *Z* = 12 : 1

Finally, the cycloisomerization of the free alcohol **122c** was tested (Scheme 3.17). Upon addition of 5 mol% $[Rh(CO)_2Cl]_2$, the starting material was consumed in 1.5 h at rt, to give a mixture of two aldehydes in 2 : 1 ratio based on integration of the aldehyde proton resonances in the ^{1}H NMR spectrum (the two aldehydes were obtained in unoptimized 50% yield). Unfortunately, these aldehydes could not be separated by flash chromatography. The major isomer was assigned structure **124**, based on the presence of a triplet for the aldehyde proton H_a (J = 2.4 Hz), and a singlet for the olefinic proton H_b within the ring. The minor isomer displayed a doublet for the aldehyde proton H_a suggesting structure **125**. Presumably, the initial product of the reaction is trienol **123c**, which tautomerizes in 1,2- or 1,4-fashion to give the two aldehydes. Alternatively, aldehyde **125** could arise from **124** by isomerization of the endocyclic olefin into conjugation with the aldehyde.

Scheme 3.17 Cycloisomerization of allenic alcohol **122c**.



122c **123c** **124** **125**

124 : 125 = 2 : 1

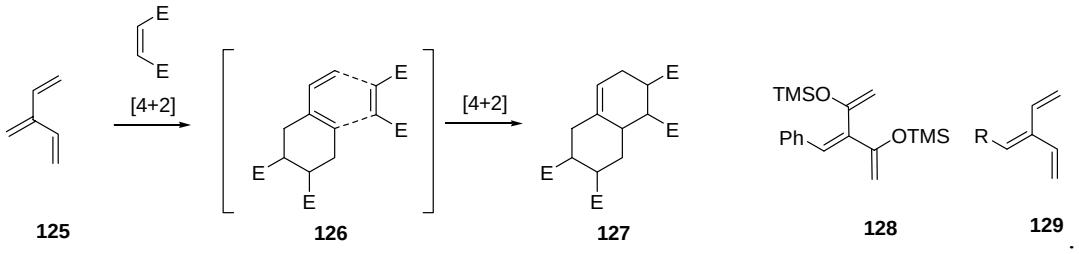
In summary, the scope and limitations of the Rh(I)-catalyzed allenic Alder-ene reaction of amino-ester tethered allenynes were explored. The reaction displays a broad scope and functional group compatibility proving it ideal for DOS. Although the triene products obtained in this manner may serve as useful biological probes, the potential reactivity of the triene moiety in biological systems was concerning. Instead, it was reasoned that this reactivity can be exploited towards the efficient assembly of more complex molecular scaffolds. These efforts are described next.

3.3 Diversification of Cross-Conjugated Trienes via Diels-Alder Reaction

3.3.1 Intermolecular Diels-Alder Approach – First Generation Triene

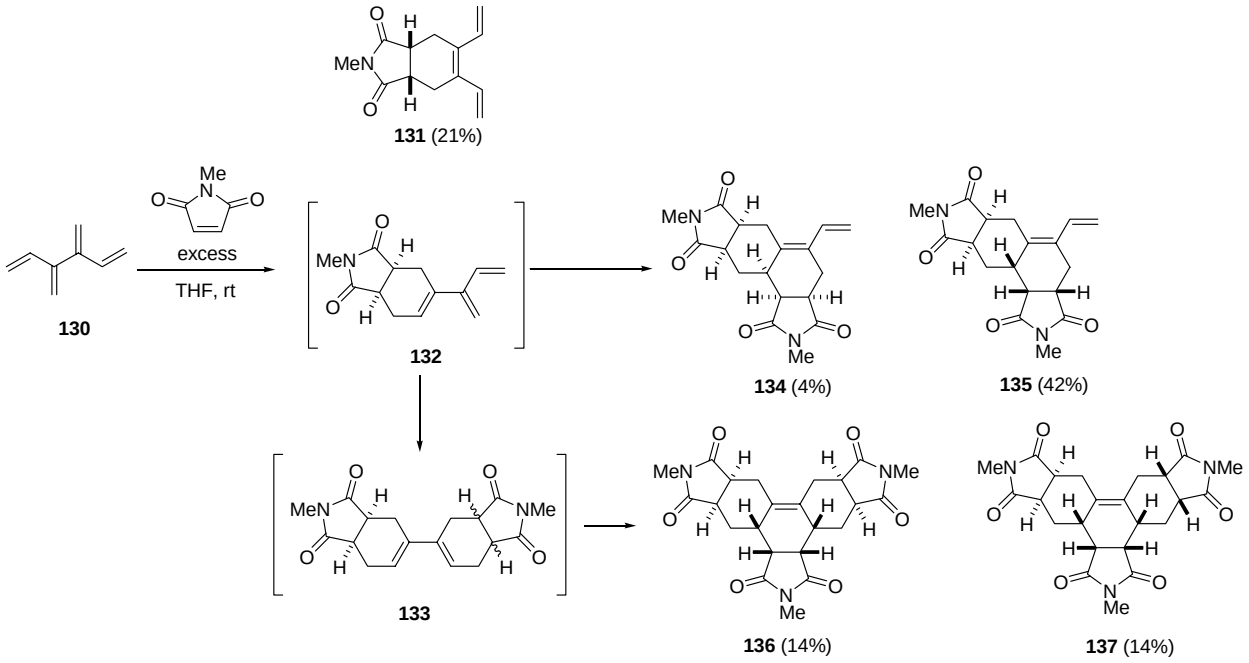
Sequential Diels-Alder reactions of the amino ester trienes can quickly lead to complex molecular scaffolds, particularly if two different dienophiles are utilized in tandem fashion. Sequential Diels-Alder reactions of acyclic cross-conjugated trienes **125** affording functionalized decalins **127** were initially studied by Tsuge,[86] who utilized *bis*-silylenolether **128**, and by Fallis, who employed monosubstituted triene **129** (Scheme 3.18).[87] However, sequential reactions of these acyclic trienes have proven difficult to control, typically affording mixtures of regioisomers. Moreover, preparation of the acyclic trienes is not trivial, in part due to their instability and tendency to polymerize.[88, 89] Therefore, these compounds have seen only limited synthetic application, despite their potential.[90]

Scheme 3.18 Tandem Diels-Alder reactions of acyclic cross-conjugated trienes.



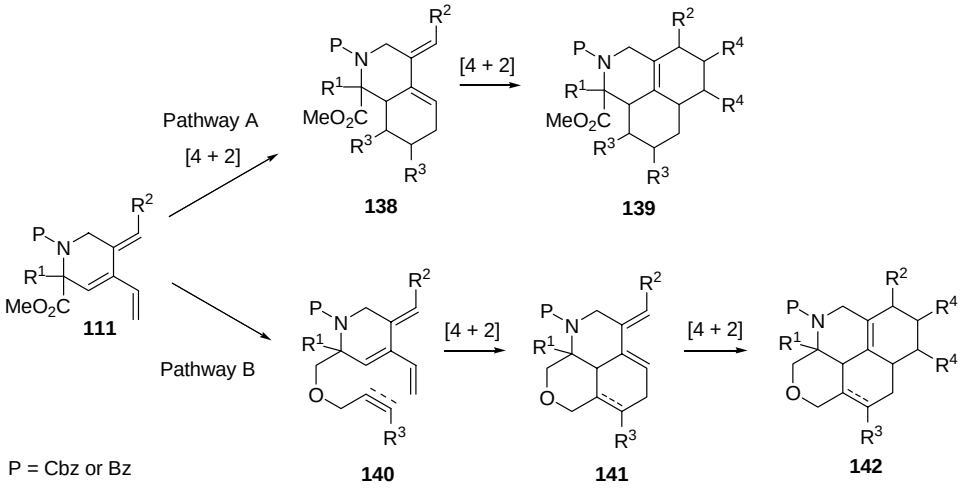
Acyclic cross-conjugated tetraene ([4]dendralene-**130**) has also been recently examined for participation in tandem Diels-Alder reactions by Willis and coworkers (Scheme 3.19).[91] For example, the reaction of **130** with excess *N*-methylmaleimide affords a mixture of mono-, di and tri-cycloaddition products. Nevertheless, this example underlines the fact that rapid increase in molecular complexity can be obtained via tandem cycloaddition reactions of cross-conjugated polyenes.

Scheme 3.19 Tandem cycloadditions of [4]-dendralene reported by Willis.



It was reasoned that the cyclic trienes obtained via an allenic Alder-ene reaction (Table 3.1) could offer a solution to the regioselectivity issues in these tandem cycloaddition reactions by locking one diene in an unreactive *s-trans* conformation. We were interested in exploring the feasibility of both cycloaddition pathways illustrated in Scheme 3.20. Pathway A involves sequential intermolecular cycloaddition reactions of triene **111** using two different dienophiles (**111**→**138**→**139**). Alternatively, pathway B, involves an intra-/intermolecular cycloaddition sequence (**111**→**140**→**141**→**142**).

Scheme 3.20 Diels-Alder reactions of triene **111**.

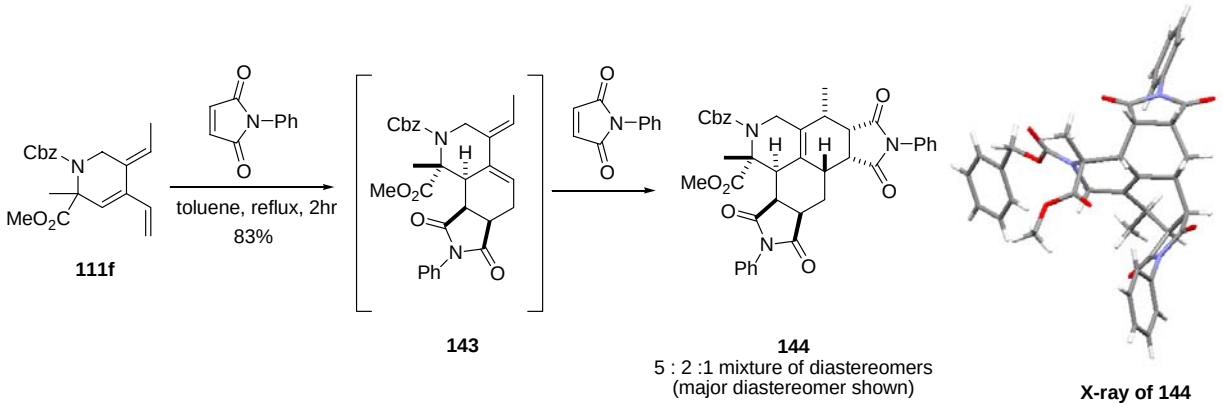


Exploring these pathways offers an opportunity to study the reactivity of cyclic cross-conjugated trienes as novel chemical entities. Furthermore, it was reasoned that these rigid and conformationally defined polycycles would serve as useful biological probes. In medicinal chemistry, conformationally defined polycyclic small molecules often exhibit higher potency and specificity of binding to biological targets compared to their acyclic analogues, since they do not have to undergo conformational changes in order to adapt to a binding site.[92]

The more direct pathway A was initially more appealing, so investigations began with the reaction of triene **111f** with *N*-phenylmaleimide (Scheme 3.21). Unfortunately, the initial Diels-Alder cycloadduct **143** was not observed, but it immediately underwent a second Diels-Alder reaction to afford **144** as a 5 : 2 : 1 mixture of diastereomers in 83% yield. The ratio of diastereomers was determined by normal phase HPLC, which allowed their complete separation.[c]

[c] The ratio was determined by integration of the peaks in the HPLC trace (refractive index detector was used).

Scheme 3.21 Intermolecular Diels-Alder reaction of **111f**.

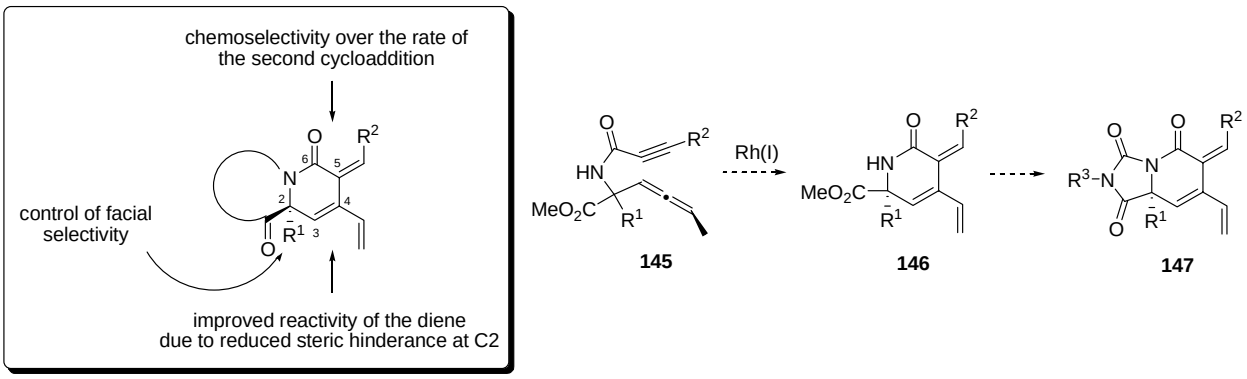


The relative stereochemistry of the major diastereomer from this mixture was assigned by X-ray crystallography, and results from *endo* selectivity in the first cycloaddition occuring from the same face of the methyl group, while the second dienophile adds from the less hindered convex face of the newly formed diene in *endo* mode (Appendix A). Attempts to obtain the cycloadduct **143**, by reaction of **111f** with equimolar amount of dienophile resulted in formation of **144** and recovered triene. This result is attributed to the higher reactivity of the second diene of **143** because it is locked in an *s-cis* conformation. Other dienophiles (maleic anhydride and 4-phenyl-[1,2,4]-triazole-3,5-dione) also reacted with **111f** to give mixtures of diastereomeric products similar to **144**. Although the cycloaddition reaction of **111f** illustrated in Scheme 3.21 affords a complex molecular scaffold in a rapid manner, obtaining the product as a mixture of diastereomers discouraged applying this reaction to library synthesis. Biological testing of mixtures of multiple compounds may complicate the interpretation of the results. Although separation of the diastereomers by HPLC was feasible it may prove costly and time consuming when preparing a larger scale library. Therefore, controlling the chemo- and diastereoselectivity of the Diels-Alder reaction of the triene was important, and a new strategy for tandem intermolecular cycloaddition was considered.

3.3.2 Intermolecular Diels-Alder Approach-Second Generation Triene

It was reasoned that tying back the appending ester in a ring would increase the reactivity of the diene in the first Diels-Alder reaction by reducing the steric bulk. Moreover, this constraint leads to a sterically biased triene, in which one face is blocked by the R^1 group. Finally, introducing an electron withdrawing carbonyl group at the C6 position would slow the second Diels-Alder reaction. The novel imidazo-pyridinone triene **147** addresses all of these issues (Scheme 3.22).

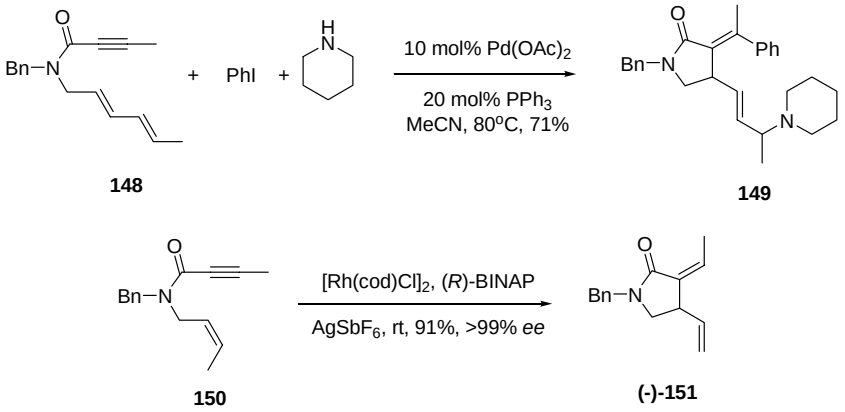
Scheme 3.22 Novel fused bicyclic Diels-Alder precursor **147**.



Putting the synthesis of **147** into practice required examination of the Rh(I)-catalyzed cycloisomerization of amide-tethered allenyne **145** to form δ-lactam triene **146**. Traditionally, lactams are synthesized via carbon-nitrogen bond formation. For example, lactams are formed via dehydration of amino-acids,[93] by cyclization of an amide onto an alkene,[94] alkyne[95] or an allene,[96] and intramolecular vinylation of amides.[97] Alternatively, lactams can be synthesized from ketones by Schmidt or Beckmann rearrangement.[98] There are very few examples of lactam syntheses via transition metal catalyzed carbon-carbon bond formation, and most involve a ring-closing metathesis.[99] Synthesis of lactams via cycloisomerization reaction appears particularly

attractive, since additional functionality is generated in the course of the reaction (a cross-conjugated triene in this case). Surprisingly, there are only few examples of lactam formation via cycloisomerization reactions, and are strictly limited to preparing γ-lactams. For example, in 1999, Lu reported a Pd(0)-catalyzed tandem cyclization/amination of dienyne **148** leading to α-alkylidene-γ-lactam **149** (Scheme 3.23).[100] More recently, Zhang reported an enantioselective Rh(I)-catalyzed cycloisomerization of amide-tethered enyne **150**, affording γ-lactam **151** with >99% *ee*.[101] Notably, both reports used a benzyl protected amide, and Zhang reported that reaction did not proceed with the unprotected amide.

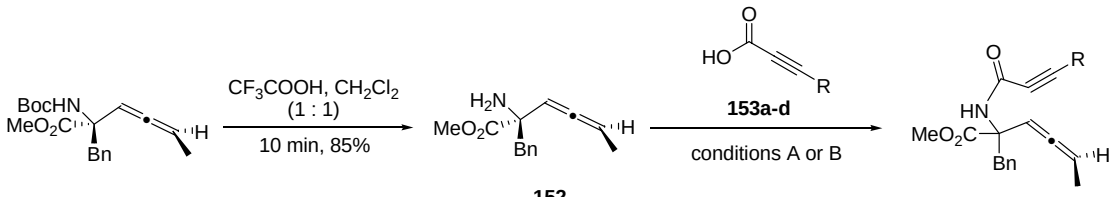
Scheme 3.23 Transition metal-catalyzed formation of γ-lactams.



To test the feasibility of a Rh(I)-catalyzed formation of δ-lactam trienes, amide-tethered allenynes **145a-145d** were synthesized by Boc-deprotection of amine **65f** to **152** followed by coupling with alkynoic acids **153a-d** (Scheme 3.24). The use of a DCC/DMAP coupling protocol (conditions A) proved useful in preparing amides **145b** and **145d** in sufficient amounts for testing the subsequent cycloisomerization reaction (~100 mg). Nevertheless, this protocol results in formation of additional byproducts including dicyclohexylurea which made the purification difficult, and the yields irreproducible. To circumvent this issue, an alternative protocol was

applied for the preparation of **145a** and **145c**.[d] Treatment of the alkynoic acid with isobutylchloroformate and *N*-methylmorpholine afforded a mixed anhydride, which was treated *in situ* with amine **152** to give the corresponding amide. This proved a robust protocol, which reproducibly gave 70-85% yield of the desired amides.

Scheme 3.24 Preparation of amide-tethered allenynes.



entry	R	conditions	product	yield
1	Me	B	**145a**	85%
2	H	A	**145b**	82%
3	TMS	B	**145c**	72%
4	Ph	A	**145d**	55%

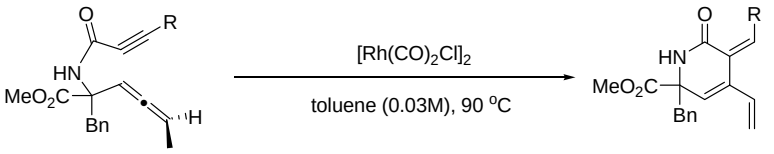
conditions A: DCC, DMAP, CH_2Cl_2, rt.
conditions B: *i*-BuOCOCl, NMM, -10 °C, then amine **152**.

With these allenynes in hand, the cycloisomerization reaction was tested (Table 3.2). When **145a** was subjected to the optimized conditions for triene formation (5 mol% $[Rh(CO)_2Cl]_2$, toluene, 0.3M), reaction did not occur at rt (entry 1). Instead, triene formation was effected by heating **145a** to 90 °C. With this information in mind, the catalyst loading was varied between 2.5 and 10 mol% (entries 2-4) to establish its effect on the efficiency and yield of the reaction at 90 °C. All reactions were performed in toluene at 0.03M concentration.[e] With, 2.5 mol% the reaction was relatively sluggish and consumption of the starting material was incomplete after 90 min, affording triene **146a** in only 18% yield (along with ~50% recovered starting material). Increasing the catalyst loading to 5 mol% resulted in shorter reaction time of 50 min and

[d] This protocol was first applied to the synthesis of related amides by Dr. Donald A. Probst.
[e] Work performed by Dr. Donald A. Probst determined that running the reaction at higher concentration (0.1-0.5M) leads to formation of an unidentified polymeric side product and lowers the yield of triene.

increased yield of the triene (47%). Further increase in catalyst loading to 10 mol% resulted in complete consumption of the starting material in less than 30 min, and 92% yield of the triene **146a** (this reaction was performed on ~1g of **145a**, demonstrating the scalability of the reaction). Next, the cycloisomerization of propynamide **145b** was tested with 10 mol% of catalyst. Consumption of the starting material occurred after 2h and resulted in **146b** isolated in only 45% yield (entry 5). Trimethylsilyl (**145c**) and phenyl (**145d**) substituted propynamides also underwent the rearrangement to afford the corresponding trienes **146c** and **146d** in 77% and 66% yield, respectively (entries 6 and 7). Notably, the reaction of the TMS-substituted alkyne required only 15 min.

Table 3.2 Synthesis of δ-lactam trienes.



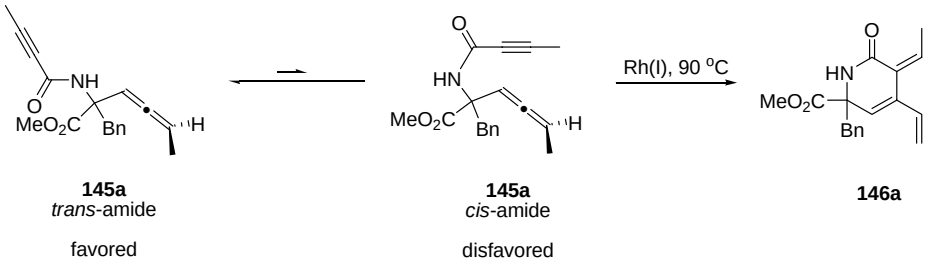
145a-d **146a-d**

entry	allenyne	R	catalyst (mol%)	time	triene	yield%
1	**145a**	Me	5		**146a**	0[a]
2	**145a**	Me	2.5	90 min	**146a**	18[b]
3	**145a**	Me	5	45 min	**146a**	47[b]
4	**145a**	Me	10	30 min	**146a**	92
5	**145b**	H	10	120 min	**146b**	45
6	**145c**	TMS	10	15 min	**146c**	77
7	**145d**	Ph	10	30 min	**146d**	66

[a] conditions: 5 mol% $[Rh(CO)_2Cl]_2$, toluene, rt;
[b] Incomplete reaction;starting material was recovered.

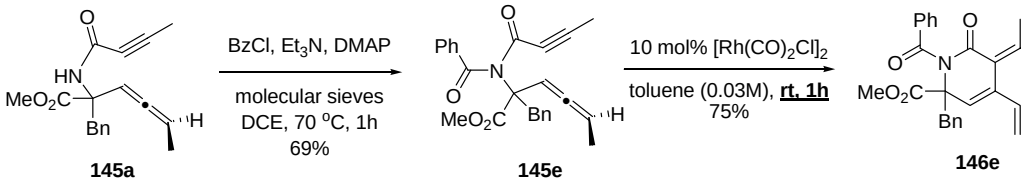
The higher temperature required to effect the cycloisomerization of these unprotected amides is attributed to a prefered *trans*-conformation of the secondary amide, placing the reactive termini away from each other (Scheme 3.25).[102]

Scheme 3.25 Amide bond rotamers of **145a**.



To confirm this, allenyne **145e** with benzamide protection on the amide nitrogen was synthesized in 69% yield by treatment of **145a** with BzCl at 70 °C (Scheme 3.26). Indeed, reaction of this precursor using 10 mol% of $[Rh(CO)_2Cl]_2$ occurred in less than 1h at rt, affording cross-conjugated triene **146e** in 75% yield.

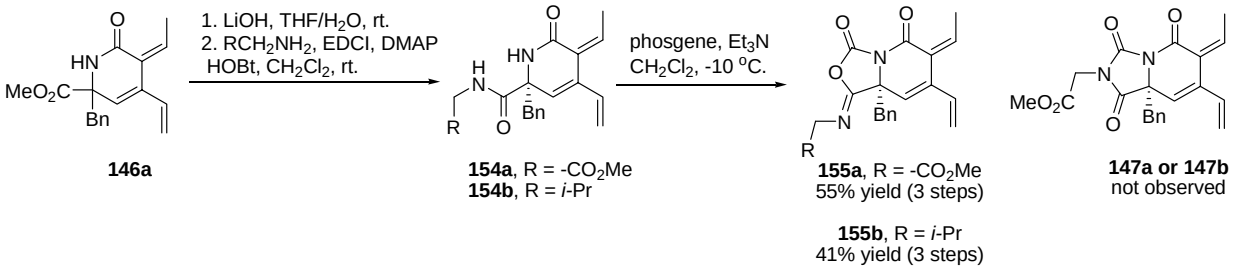
Scheme 3.26 Preparation and cycloisomerization of **145e**.



With a synthetic route to lactam triene **146a**, a facially differentiated precursor for the Diels-Alder reaction was next prepared. Saponification of the methyl ester occurred within 5 min upon treatment of **146a** with LiOH. After aqueous work-up, the acid was obtained in sufficient purity (by ^{1}H NMR) and was immediately coupled with glycine-methyl ester using EDCI, HOBt and DMAP to give diamide **154a** (Scheme 3.27). In order to complete the synthesis of hydantoin **147a**, amide **154a** was reacted with phosgene ($COCl_2$). Interestingly, the exclusive product of the reaction was the unexpected imino-oxazolidinone **155a** in 55% yield for three steps (this structural assignment was made later based on an X-ray crystal structure of the Diels-Alder product **156a**, *vide infra*). Nevertheless, imino-oxazolidinone **155a** should provide the same steric and electronic control elements as hydantoin **147a**. An additional substrate functionalized

as an isobutyl-amide **155b** was prepared using the same protocol in 41% yield over three steps. To our knowledge, oxazolidinones with this substitution pattern have not been reported.[103]

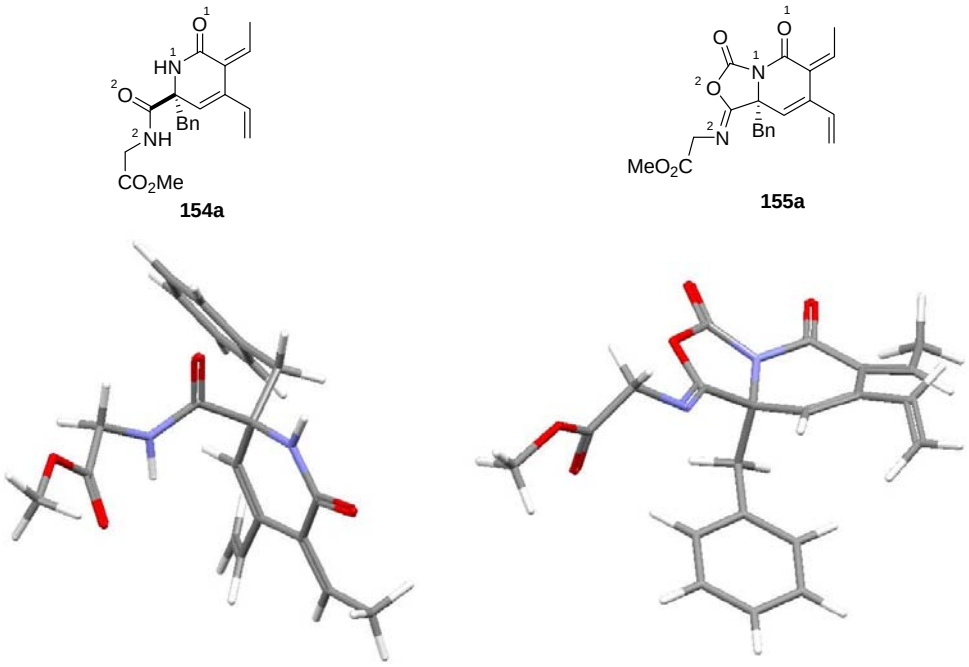
Scheme 3.27 Synthesis of novel imino-oxazolidinone trienes **155a** and **155b**.



It was rationalized that the imino-oxazolidinone **155a** resulting from *O*-acylation of the appending amide is a kinetic product of the reaction, and a consequence of the preferred conformation of the amide side chain in **154a**. To confirm this, computational modeling of **154a** was performed using Cache. The energy minimized model placed the appending amide oxygen O2 and lactam nitrogen N1 of **154a** in the same direction, confirming the observed reactivity (Figure 3.1).[f] Finally, it should be noted that the newly obtained imino-oxazolidinone ring in **155a** and **155b** proved relatively sensitive to silica gel, since prolonged chromatographing led to opening to the parent diamides **154a** and **154b**, respectively.

[f] Energy minimization was performed with Cache Worksystem Pro. version 6.1.10. First, global minimum search was performed using MM3 parameters, followed by optimization of the side chain conformation with AM1 parameters. Then, energy minimization of the sample was performed using AM1 parameters.

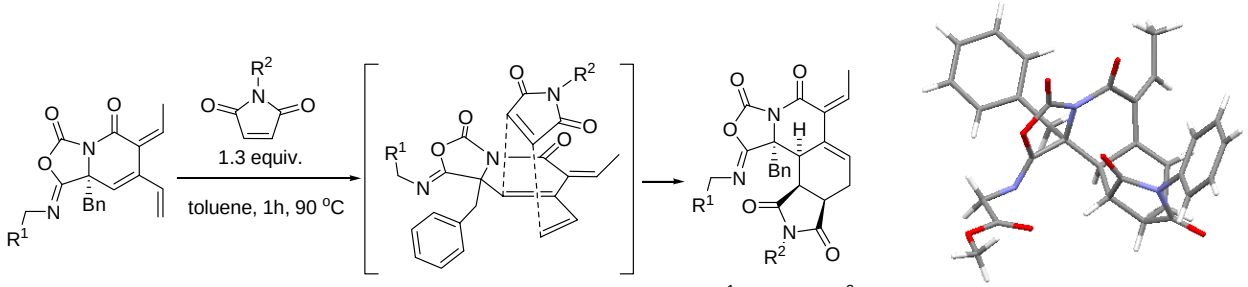
Figure 3.1 Stereoviews of the energy minimized models of **154a** and **155a**.



The newly obtained bicyclic triene **155a** was also modeled in order to visualize its three-dimensional structure. As illustrated in Figure 3.1 the fused bicyclic structure is relatively planar due to the presence of multiple sp^2-hybridized atoms and the bottom face is blocked by the benzyl substituent. Therefore, cycloaddition reaction with the diene is expected to occur selectively with the top face (the facial assignment is relative since all compounds are racemic). To test this hypothesis, triene **155a** was reacted with *N*-phenylmaleimide (1.3 equiv.). Reaction occurred in less then 1 h at 90 °C to afford the cycloadduct **156a** in 73% yield as a single diastereomer (Scheme 3.28). The relative stereochemistry of **156a** was assigned by X-ray crystallography, confirming that the cycloaddition occurred with *endo* selectivity and the diene approached from the opposite face of the benzyl group (Appendix B). Excess dienophile (2 equiv) still gave exclusive formation of **156a**, indicating a reduction in the rate of the second cycloaddition. Similarly, cycloaddition of **155b** with *N*-methylmaleimide resulted in formation of **156b** in 95% yield as a single diastereomer. Additional experimentation by Dr. Yan (Brummond

group) demonstrated that this cycloaddition is limited mainly to using maleimides.[104] Other dienophiles (diethylfumarate, *p*-benzoquinone and dimethylacetylene dicarboxylate) generally gave yields of the cycloadduct lower than 50%.

Scheme 3.28 Diels-Alder reaction of imino-oxazolidinones **155a** and **155b**.



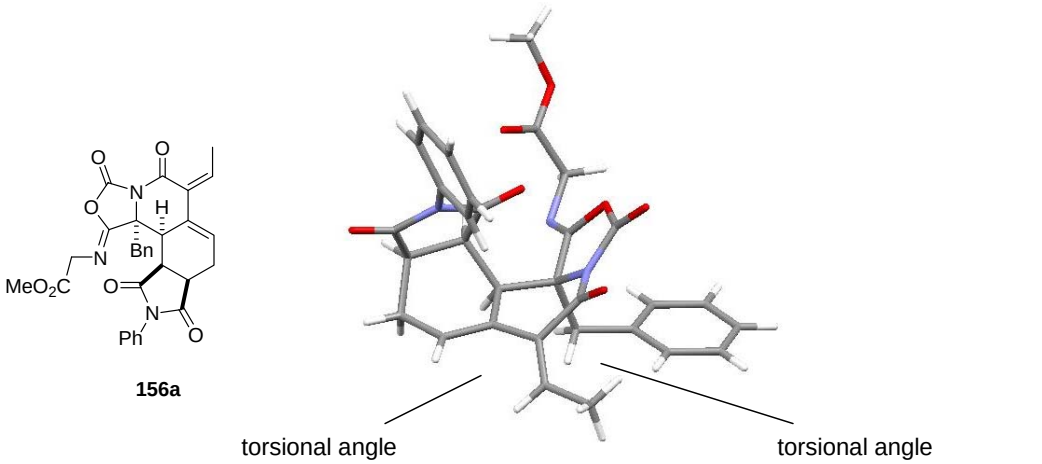
155a, R^1 = -CO_2Me
155b, R^1 = *i*-Pr

156a, R^1 = CO_2Me, R^2 = Ph, 73%
156b, R^1 = *i*-Pr, R^2 = Me, 95%

X-ray of 156a

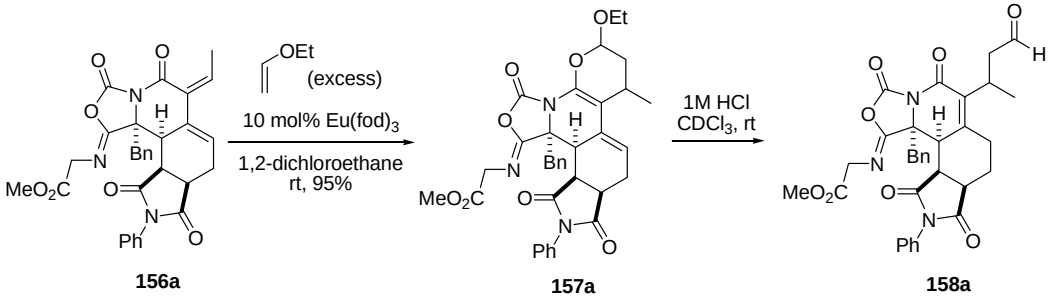
The X-ray crystal structure of **156a** reveals several interesting features. As a result of the *endo*-cycloaddition occurring from the concave face of **155a**, the product adopts a folded shape with the *N*-phenylpyrrolidinone moiety projecting directly above the new diene system (Figure 3.2). Moreover, the two double bonds of the 1,3-diene are twisted out of planarity by a 39.9° angle. In addition, the α,β-unsaturated amide is also twisted in the opposite direction by 42.4°.

Figure 3.2 Stereoview of the X-ray crystal structure of **156a** with diene and amide torsional angles.



These steric and electronic features of the new diene significantly impart its reactivity towards electron poor dienophiles. For example, the second cycloaddition of the new diene could not be effected using electron deficient dienophiles, except with diethylfumarate (demonstrated by Dr. Bingli Yan). Therefore ethyl vinyl ether was examined as a small, electron rich dienophile to better match the character of the diene. Heating **156a** in a mixture of toluene/ethylvinylether at 90 °C afforded 70% yield of pyran **157a**. This was somewhat unexpected since only a few inverse electron demand hetero-Diels-Alder reactions of α,β-unsaturated amides have been reported, and generally result in formation of an aromatic compound (e.g., indole, thiazole, pyrazole).[105] Since lanthanide Lewis acids including $Eu(fod)_3$ have been used to catalyze hetero-Diels-Alder reactions, we tested this reagent to accelerate the cycloaddition of **156a** and ethyl vinyl ether. With 10 mol% of $Eu(fod)_3$, the reaction proceeded at rt, giving **157a** in 95% yield as a single diastereomer (Scheme 3.29).[106] Exposure of **157a** to aqueous HCl afforded aldehyde **158a**, resulting from hydrolysis of the acetal moiety and isomerization of the double bond into conjugation with the amide.

Scheme 3.29 Hetero Diels-Alder reaction of **156a** with ethyl vinyl ether.

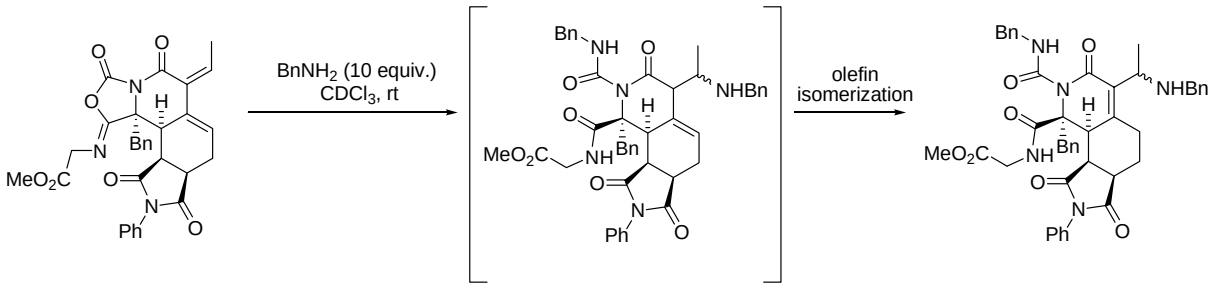


Next, hydrolysis of the oxazolidinone moiety in **156a** to the parent diamide was explored as means to introduce structural diversity in the products and increase the number of hydrogen-bond donors. It was anticipated that this transformation would increase the water solubility of these compounds, and improve their pharmacological profile.[8] When **156a** was heated to 70 °C

in 1M HCl/dioxane (1 : 1) for 1h, the hydrolysis product was not observed and the starting material was recovered in ~80% yield. The stability of the imino-oxazolidinone in this compound to acidic conditions is in sharp contrast to the bicyclic-triene **155a** which is readily hydrolyzed in presence of aqueous acid.[g] Next, an attempt was made to cleave the imino-oxazolidinone under Lewis acid conditions, by using a combination of BF_3OEt_2 and Me_2S (conditions that have been utilized previously to cleave a Cbz protecting group).[107] Unfortunately, these conditions did not effect the desired transformation either (starting material was recovered in 86% yield). On the contrary, treatment of **156a** with LiOH in THF/H_2O caused complete decomposition.[108]

Since both acidic and basic conditions failed to cleave the imino-oxazolidinone moiety in **156a**, its susceptibility to primary amines as nucleophilic reagents was next examined. To this end, a solution of **156a** in $CDCl_3$ was treated with benzylamine and the reaction was followed by ^1H NMR.

Scheme 3.30 Reaction of **156a** with benzylamine.



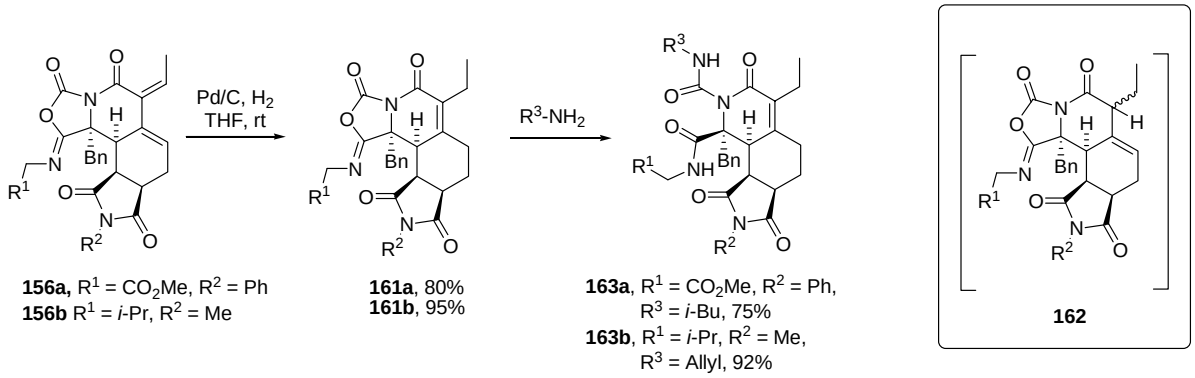
Although cleavage of the oxazolidinone moiety occured as established by the appearance of new amide and urea N-H resonances in the downfield region (8-9 ppm), a gradual disappearance of both olefinic peaks of the diene was observed. Based on these observations, it was speculated

[g] Personal communication by Dr. Bingli Yan

that the final product of the reaction is **160a** resulting from cleavage of the imino-oxazolidinone and 1,4-addition of benzyl amine to the α,β-unsaturated amide, followed by isomerization of the remaining olefin into conjugation within the δ-lactam ring (Scheme 3.30, via intermediacy of **159a**).

Since this 1,4-addition side process was not desired, reduction of the diene in **156a** and **156b** was attempted using Pd/C and H_2 (1 atm). Interestingly, complete reduction of either substrate was not observed after 4h at rt, but the α,β-unsaturated amides **161a** and **161b** were isolated in 80% and 95% yield respectively (Scheme 3.31). This result is again attributed to the steric hindrance around the diene. Presumably, reduction of the more accessible exocyclic double bond leads to intermediate **162** followed by isomerization of the remaining olefin into conjugation with the amide. Next, solutions of **161a** and **161b** in $CDCl_3$ were treated with a primary amine (isobutylamine and allylamine, respectively) which cleanly effected opening of the imino-oxazolidinone to ureas **163a** and **163b**.[h]

Scheme 3.31 Reduction and functionalization of **156a** and **156b**.



The structure of **163a** was assigned by ^1H NMR (in $CDCl_3$) based on the presence of two downfield resonances at 9.02 ppm (t, J = 5.8 Hz, 1H) assigned to the urea N-H proton and 8.46

[h] In addition to isobutylamine and allylamine shown in Scheme 3.31, benzylamine and 2-methoxyethylamine were also used to afford ring opening in >80% yield.

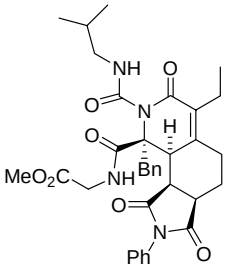
ppm (dd, J = 7.1, 4.6 Hz, 1H) assigned to the appending amide proton.[i] The presence of sharp signals for these protons instead of the normally-observed broad resonances, suggested an ordered secondary structure of the urea and amide side chains. It was speculated that this ordering is a result of intramolecular hydrogen bonding within the molecule. The chemical shifts of the amide and urea protons support this notion, since it is known that participation of N-H protons in hydrogen bonding normally results in a downfield shift.[109] To examine this computationally, **163a** was modeled using Cache.[j] The minimized model of **163a** resulted in arrangement of the side chains as shown in Figure 3.3, with two potential hydrogen bonds: (a) between the urea N-H and lactam carbonyl oxygen (distance 2.287 Å); and (b) between the appending amide N-H and the adjacent pyrrolidine-dione carbonyl oxygen (distance 2.140 Å). As a result of this secondary bonding, the two side chains are presumably held rigidly which accounts for the sharp N-H resonances in the NMR spectrum. It was reasoned that this feature may be useful in designing biological probes that project functional groups in specific three-dimensional space. For example, many potent protease inhibitors are small peptide-like molecules that posess a defined secondary structure, resulting in strong interaction with the enzyme.[110] We anticipate that the rigid amido-ureas may also prove as useful biological probes to study protein function.

---

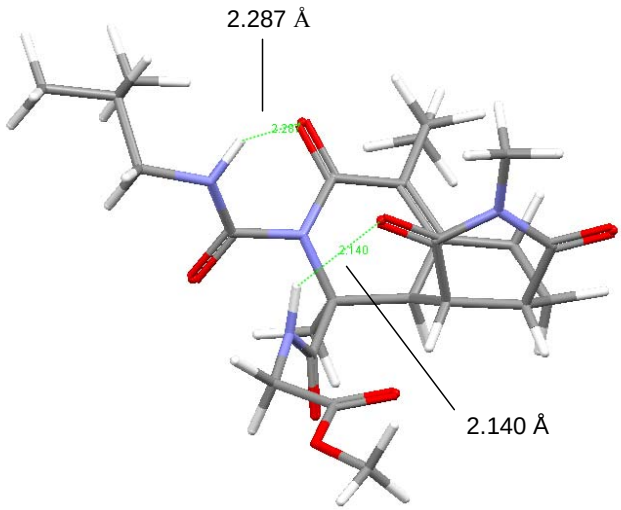
[i] To determine whether these two resonances arise from the amide and urea N-H protons, a solution of the product in $CDCl_3$ was shaken in an NMR tube in presence of excess D_2O and the primary amine used in the ring-opening reaction. The exchange was followed by ^1H NMR spectroscopy which showed disappearance of the two resonances within ~30 min. Reversed exchange from deuterium to hydrogen was also accomplished using the same protocol with H_2O.

[j] Energy minimization was performed with Cache Worksystem Pro. version 6.1.10. First, global minimum search was performed using MM3 parameters, followed by optimization of the side chain conformation with AM1 parameters. Then, energy minimization of the sample was performed using AM1 parameters.

Figure 3.3 Energy-minimized model of **163a** with potential hydrogen bonds labeled in green.



163a

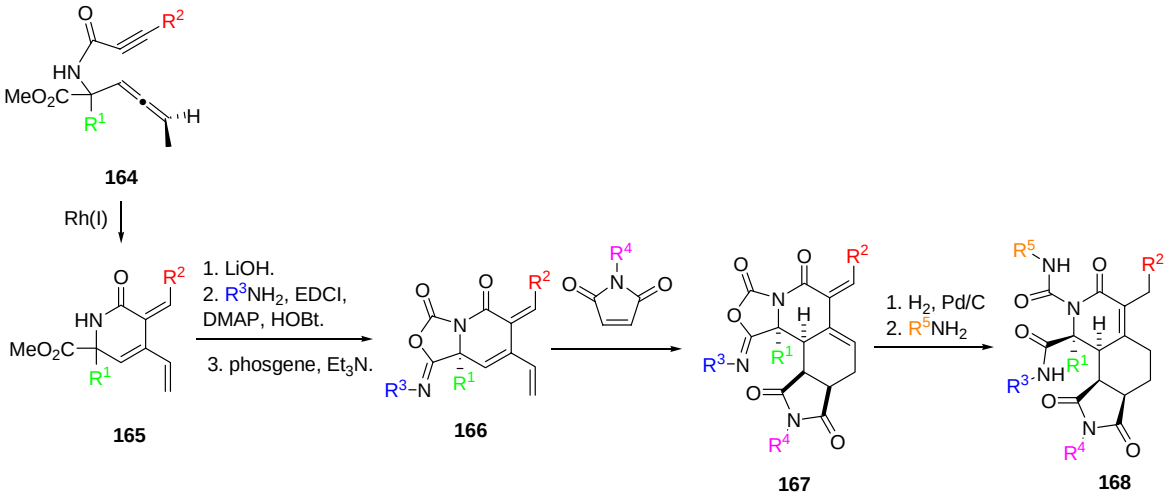


energy-minimized model of **163a**; the two phenyl groups were replaced with a methyl group for clarity purposes

Consequently, the focus shifted to designing a library of these polycyclic scaffolds using the synthetic routes that were developed. As outlined in Scheme 3.32, this synthetic pathway offers at least five points of diversity to be introduced gradually as the complexity of the scaffold increases. The imino-oxazolidinone moiety was envisioned as a crucial part of the triene precursor **166** because in enables a highly stereo- and chemoselective Diels-Alder reaction with a number of maleimides. Furthermore, this moiety is used as a key diversity element, because the transformation of **167** to **168** results in the conversion of a molecule rich in hydrogen-bond acceptors to one that contains two hydrogen-bond donor groups. This transformation is expected to bring about significant differences in the physico-chemical properties and potentially the biological activity of the compounds. Since both classes of compounds were envisioned as library members, a broad range of diversity was therefore accessed via a relatively simple set of transformations. The library synthesis was put into practice by the staff at the University of Pittsburgh Center for Chemical Methodologies and Library Development (UPCMLD,

http://ccc.chem.pitt.edu/). Using four points of diversity (allenic amino-ester, amine for oxazolidinone formation, *N*-alkyl maleimide and amine for the oxazolidinone opening reaction), the center synthesized 200 library members in quantities of 5-100 mg each.[111] These compounds have been made broadly available to biological collaborators for testing.

Scheme 3.32 Synthesis of a library of polycyclic scaffolds from cross-conjugated trienes.



164 165 166 167 168

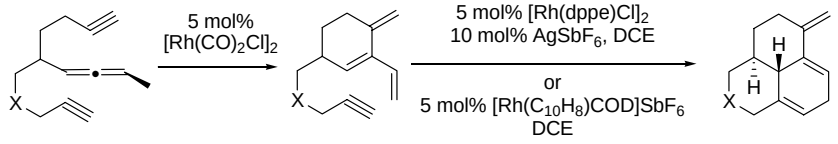
In summary, a novel Rh(I)-catalyzed cycloisomerization of allenynes was achieved, affording δ-lactam trienes. These compounds proved useful in the synthesis of structurally unique poly-heterocyclic scaffolds via a stereocontrolled Diels-Alder reaction. The sequence of reactions is amenable to library synthesis which has been recently completed by the staff at the UPCMLD.

3.3.3 *Intra*-/*Inter*molecular Diels-Alder Approach for the Synthesis of Complex Polycyclic Scaffolds

An alternative approach to elaborating the amino-ester tethered cross-conjugated trienes into complex polycyclic scaffolds involves performing a sequence of *intra*molecular and

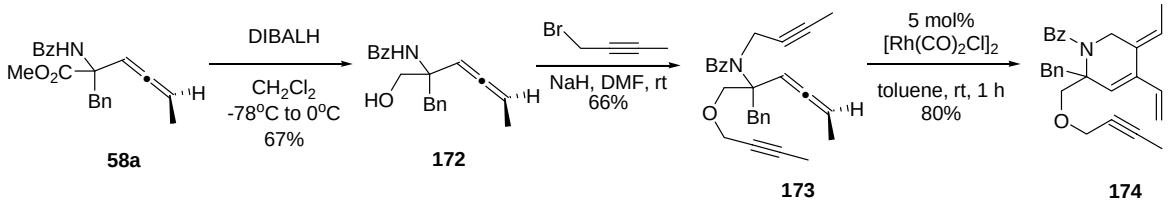
*inter*molecular cycloaddition reactions as outlined previously in Scheme 3.20 (path B). Although this approach requires some functionalization of the existing triene in order to tether a requisite dienophile, it also offers possibility for greater stereocontrol since the initial cycloaddition will be performed intramolecularly. For, example, Brummond and You have demonstrated that triene-yne systems **170**, undergo a Rh(I) catalyzed formal [4+2] cycloaddition stereoselectively affording tricyclic trienes **171** (Scheme 3.33).[112] Moreover, a one-pot protocol for tandem cycloisomerization/cycloaddition of the parent allenynes **169** was achieved and the resulting diene of **171** was used in subsequent intermolecular cycloaddition reactions.

Scheme 3.33 Rh(I)-catalyzed [4+2] cycloaddition of cross-conjugated trienes.



Applying this same strategy to the amino-acid derived substrates was enticing. To this end trieneyne **174** was prepared according to the sequence outlined in Scheme 3.34. Reduction of the methyl ester in **58a** was accomplished in 67% yield by addition of DIBALH (3 equiv.) at -78 °C and warming to 0 °C.

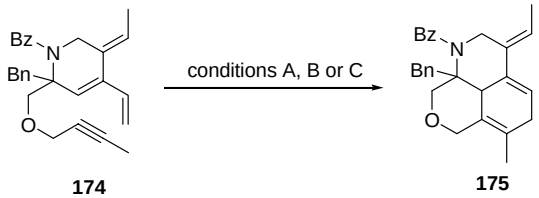
Scheme 3.34 Synthesis of trieneyne **174**.



Next, amido-alcohol **172** was *N*,*O*-dialkylated in one pot using NaH and 1-bromo-2-butyne to afford allene-diyne **173** in 66% yield (both yields are unoptimized). Subjecting **173** to 5 mol% of $[Rh(CO)_2Cl]_2$ at rt resulted in cycloisomerization to the desired trieneyne **174** in 80% yield.

Notably, exclusive cycloisomerization of the *N*-tethered allenyne system was observed despite the presence of an *O*-tethered allenyne that could also undergo the reaction to give an oxepine. This is not surprising since the rate of cycloisomerization to form a larger ring size is expected to be slower. Subjecting **174** to the conditions previously reported by Brummond and You for effecting the desired cycloaddition ($[Rh(dppe)Cl]_2$, $AgSbF_6$, 1,2-dichloroethane) led to no reaction at rt, and eventual decomposition of the starting material upon refluxing for 12h (Scheme 3.35).[113] Therefore, two other Rh(I)-catalysts were utilized. In 1999, Chung, reported $[Rh(naphthalene)(COD)]BF_4$ as an efficient catalytic system for both inter- and intramolecular cycloaddition of dieneynes at rt.[114] Unfortunately, these conditions did not result in the desired cycloaddition product either (starting material was recovered in 71%). Finally, we resorted to testing a catalytic system first reported by Livinghouse in 1990.[115] In this report, it was demonstrated that $[Rh(COE)_2Cl]_2$, in the presence of the fluorinated phosphite ligand $P[OCH(CF_3)_2]_3$ catalyzes the intramolecular cycloaddition reaction of diene-ynes (COE = cyclooctene). It was reasoned that the electron withdrawing properties of this ligand will increase the affinity of the metal toward coordination of the trienyne. However, the desired cycloaddition product was not observed in this case either (starting material was recovered in 78%).

Scheme 3.35 Attempted Rh(I)-catalyzed cycloadditions of **174**.



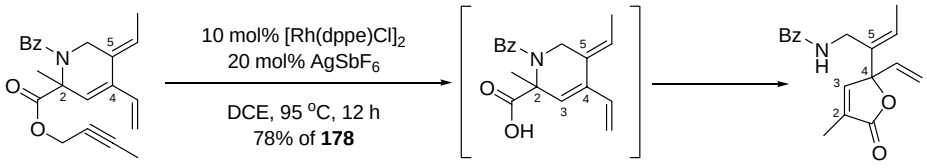
174 **175**

conditions:
A. 10 mol % $[Rh(dppe)Cl]_2$, $AgSbF_6$, DCE; decomposition over 12h at reflux.
B. 10 mol % $[Rh(naphtalene)COD]BF_4$, CH_2Cl_2, 50 ^oC; recovered starting material in 71%.
C. 10 mol % $[Rh(COE)_2Cl]_2$, $P[OCH(CF_3)_2]_3$, THF, reflux; recovered starting material in 78%.

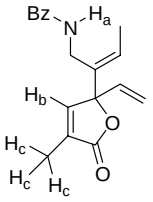
Since these three catalytic conditions failed to provide cycloadduct **175**, further study on effecting the cycloaddition of **174** was suspended. In addition, we tested the cycloaddition

reaction of butynyl-ester **176** (see experimental section for full details on the preparation of this precursor). To our knowledge there are no reports of ester-tethered dieneyne participating in a transition metal-catalyzed cycloaddition reaction, although ester-tethered enynes have been shown to participate in a cycloisomerization reaction.[116] Interestingly, prolonged heating of butynyl-ester **176** in presence of *in situ* generated catalytic Rh(I) ($[Rh(dppe)Cl]_2$, $AgSbF_6$, 1,2-dichloroethane) resulted in formation of γ-lactone **178** in 78% yield (Scheme 3.36). The structure of **178** was assigned based on the presence of a new olefinic resonance attributed to H_b in the downfield region (at 7.14 ppm) displaying allylic coupling with the methyl group protons (q, J = 1.6 Hz). In addition to this, the presence of an amide was deduced based on a resonance in the ^1H NMR as a broad singlet (at 6.39 ppm) and a broad amide stretching band for the N-H bond in the IR (at 3344 cm^{-1}). Compound **178** was rationalized to arise from Rh(I)-catalyzed depropargylation of **176**, followed by cyclization of the resulting carboxylic acid of **177** onto C4, concomitant with allylic disposition of the C2 benzamide. This represents an overall 5-*endo-trig* process known to be disfavored by Baldwin's guidelines.[117]

Scheme 3.36 Unexpected formation of γ-butenolide **178**.



176 **177** **178**



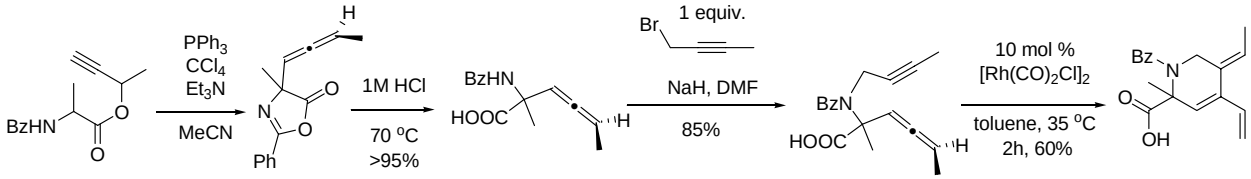
178

^1H NMR (in $CDCl_3$):
H_a 6.39 (bs, 1H)
H_b 7.14 (q, J = 1.6 Hz, 1H)
H_c 1.93 (d, J = 1.6 Hz, 3H)
IR: (N-H) 3344 cm^{-1}
HRMS: $C_{18}H_{19}NO_3$ m/z $[M]^+$ 297.1379.

Since γ-lactones (butenolides) are important both as synthetic targets and intermediates, the formation of **178** merited some further study.[118] To support the hypothesis that acid **177** is an

intermediate in the reaction we sought a method to independently prepare this compound and subject it to the same reaction conditions. Acid **177** was synthesized starting with propargylic ester **179** as outlined in Scheme 3.37.[k] Claisen rearrangement under dehydrative conditions gave allenyl oxazolone **180** which was isolated and hydrolyzed to allenic-acid **181** using 1M HCl. Then, **181** was carefully N-alkylated with 1-bromo-2-butyne to give allenyne-acid **182**. Rh(I)-catalyzed cycloisomerization of this precursor was acheved using 10 mol % of catalyst, and heating to 35 °C for 2h. The reaction time for the cycloisomerization of the free acid was considerably longer compared to the methyl ester (2h vs 10 min, see **111a**, Scheme 3.1) and resulted in relatively low yield of the triene **177** (60%).

Scheme 3.37 Synthesis of carboxylic acid **177**.

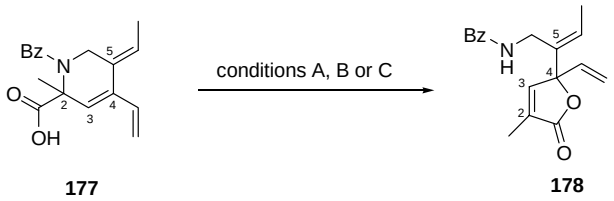


When **177** was subjected to the the catalytic Rh(I) conditions ($[Rh(dppe)Cl]_2$, $AgSbF_6$, 1,2-dichloroethane) the reaction resulted in 73% yield of **178** (Scheme 3.38). Thus, the free acid **177** is a probable intermediate in the cyclization of propargyl ester **176**. Heating **177** in presence of 20 mol% $AgSbF_6$ alone gave no reaction, indicating that the cyclization is not catalyzed by the silver salt additive.[119] Furthermore, heating **177** in 1,2-dichloroethane also gave recovered starting material. These experiments demonstrate that presence of the Rh catalyst is necessary for transforming acid **177** to **178**, however the exact mechanism is not clear. The overall

[k] Initially we attempted to prepare acid **177** by saponification of the corresponding methyl ester with LiOH in THF/H_2O (conditions utilized previously to cleave the methyl ester of lactam-triene **145a**, Scheme 3.27). However, these conditions did not cause saponification and the starting material was recovered. The resistance of this ester to saponification under basic conditions is presumably due to electronic and/or steric effects imposed by the neighboring benzoyl protecting group.

transformation can be regarded as Rh(I)-catalyzed substitution of an allylic amide. The related reaction of activated allylic amines finds precedent in recent work by Lautens.[120]

Scheme 3.38 Rh(I)-catalyzed rearrangement of acid **177**.

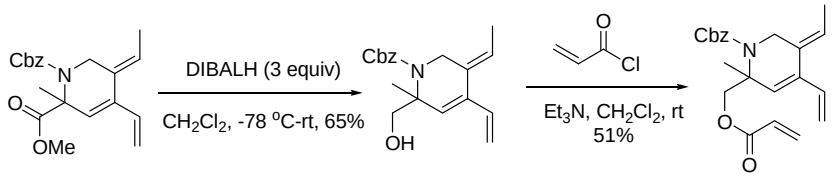


177 **178**

A. 10 mol% $[Rh(dppe)Cl]_2$, 20 mol% $AgSbF_6$, DCE, 95 ^oC, 73%
B. 20 mol % $AgSbF_6$, DCE, 95 ^oC; no reaction
C. DCE, 95 ^oC; no reaction

We finally turned our attention to examining a thermal intramolecular Diels-Alder reaction as a method for increasing molecular complexity in a diastereoselective manner. For this purpose, tetraene **184** (Scheme 3.39) was synthesized by reduction of the methyl ester of **111f** using DIBALH, followed by condensation of the resulting alcohol with acryloyl chloride (the low overall yield of 33% for this transformation is unoptimized).

Scheme 3.39 Synthesis of thermal Diels-Alder precursor **184**.

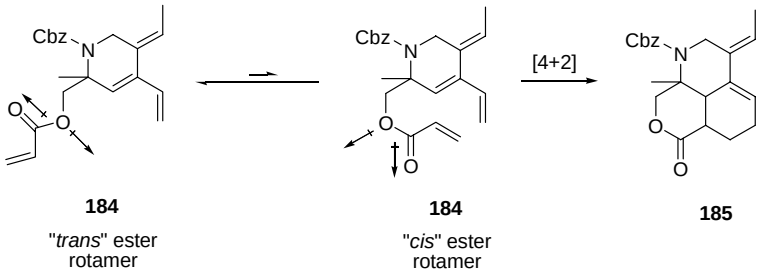


111f **183** **184**

The reactive portion of this cycloaddition precursor, a hexadienyl-acrylate, belongs to a class of substrates whose application in synthesis remains underutilized. Recently, a comprehensive study examined the effects contributing to the observed stereochemistry for thermal and Lewis acid catalyzed reactions of relatively unfunctionalized hexadienyl-acrylates.[121] In general, difficulties associated with Diels-Alder reactions of ester-tethered substrates are attributed to existence of the ester moiety in a *transoid* conformation to minimize

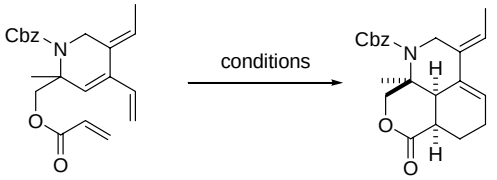
repulsive dipole interactions (Scheme 3.40). Rotation into the required *cisoid* conformation results in increase of the net dipole moment and steric repulsion between the two alkyl groups.[122]

Scheme 3.40 Ester bond rotamers of **184**.



Promoting the desired cycloaddition by heating **184** in toluene at 110 °C resulted in decomposition over a 24 h period (entry 1, Table 3.3). Attempts to catalyze this reaction with Et_2AlCl or $BF_3{\cdot}OEt_2$ gave either no reaction or decomposition, depending on the temperature (entries 2, 3 and 4, Table 3.3).[123] It is noteworthy mentioning that Taguchi recently reported that both $In(OTf)_3$ and $TfN[Al(Me)Cl]_2$ serve as efficient Lewis acid catalysts for the Diels-Alder reaction of hexadienyl-acrylates.[124]

Table 3.3 Diels-Alder reaction of tetraene **184.**



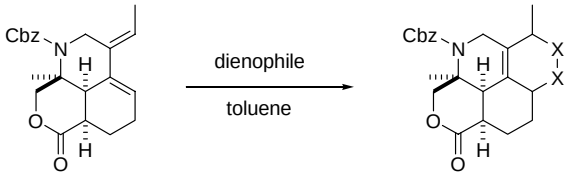
Entry	Conditions	Result / Yield%
1	toluene, 110 ^oC	decomposition
2	Et_2AlCl, toluene, -78 ^oC	no reaction
3	Et_2AlCl, toluene, 80 ^oC	decomposition
4	BF_3OEt_2, toluene, 80 ^oC	decomposition
5	acetonitrile, 90 ^oC	no reaction
6	DMSO, 80 ^oC, 8h	43%
7	DMSO / H_2O, 80 ^oC, 6h	50%

Earlier studies have unveiled a dramatic solvent effect on the ester tethered Diels-Alder

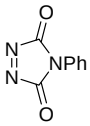
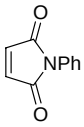
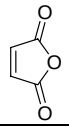
reaction.[125] Therefore, more polar solvents were examined, and the reaction was found to proceed in DMSO, at 80°C, giving 43% yield of the desired tricyclic lactone **185** as a single diastereomer. The relative stereochemistry, resulting from *endo* cycloaddition, was assigned based on the X-ray crystal structure of a later intermediate **186b** (Table 3.4, *vide infra*). The cycloaddition could be marginally accelerated by using a mixed solvent system consisting of DMSO / H_2O (2 : 1). Highest yield (50%) of the tricyclic lactone **185** was obtained when the reaction was performed at lower concentrations (0.01M), suggesting that side reactions may be responsible for the low yield.

With **185** in hand, we examined its participation in subsequent intermolecular Diels-Alder reactions (Table 3.4). Reaction with 4-phenyl-[1,2,4]-triazole-3,5-dione was complete in 5 min to afford **186a** as a single diastereomer (entry 1). *N*-Phenylmaleimide reacted at rt within 6 h to give **186b** in 95% yield and diastereoselectivity greater than 10 : 1 (entry 2). The relative stereochemistry of **186b** was established by X-ray crystallography indicating *endo* approach of the dienophile from the convex face of the fused tricycle (Appendix C). Maleic anhydride reacted similarly to give **186c** (entry 3). The relatively high reactivity of the diene towards these activated dienophiles, suggests that less active dienophiles may also undergo the reaction (e.g. acrolein, methyl vinyl ether, cyclopentenone, etc.); however further studies in that direction were not pursued.

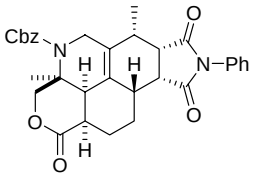
Table 3.4 Diels-Alder reactions of **185.**



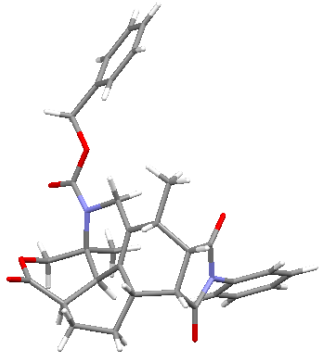
185 **186a-c**

Entry / Product	Dienophile	Temperature / Time	Yield	dr[a]
1 / **186a**[b]		rt / 5 min	95%	1 : 0
2 / **186b**[c]		rt / 6 h	95%	> 10 : 1
3 / **186c**[c]		rt / 3 h	78%	> 10 : 1

Notes: [a] diastereomer ratio; [b] 1 equiv. of dienophile was used; [c] 1.5 equiv. of dienophile was used;



186b



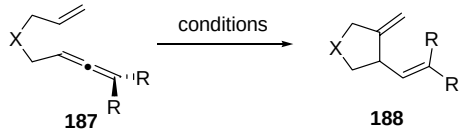
X-ray of 186b

It should be noted that compounds **186a-c** possess a steroidal-like heterocyclic skeleton, and may therefore serve as useful biological probes. The rapid manner and selectivity by which these scaffolds are assembled using this strategy make it attractive for generation of libraries of compounds. Unfortunately, the low yields obtained during the synthesis of the key tricyclic intermediate **185** from triene **111f** (~15% overall) are a limiting factor in preparing a larger scale library.

3.4 Rhodium(I)-Catalyzed Cycloisomerization of Ene-Allenes

The Rh(I)-catalyzed allenic Alder-ene reactions of amino ester tethered allenynes discussed earlier in this chapter (Section 3.2), generally proceed in 10 min to give the corresponding cross-conjugated trienes in high yield (Table 3.1). The success of this transformation prompted us to examine the effect of replacing the alkyne moiety with an alkene. It is well known that in the related Rh(I)-catalyzed cyclocarbonylation reaction of 1,n-enynes, replacing the alkyne component with an alkene completely diminishes the reactivity.[126] This can be attributed to lower propensity of the diene to undergo the first oxidative addition step forming a five-membered metallocycle, which is a presumed intermediate in the reaction. In the case of ene-allenes, however, the increased reactivity of the allene may compensate for this issue. At the time this study was initiated, there were only few examples utilizing ene-allenes in cycloisomerization reactions. For example, Trost first reported the cycloisomerization of 1,6-ene-allenes **187** to five-membered dienes **188** by using bimetallic Ni-Cr catalyst (Scheme 3.41).[127]

Scheme 3.41 Cycloisomerization of ene-allenes.



187 **188**

X = Me, -CO_2Et, NTs, O etc.

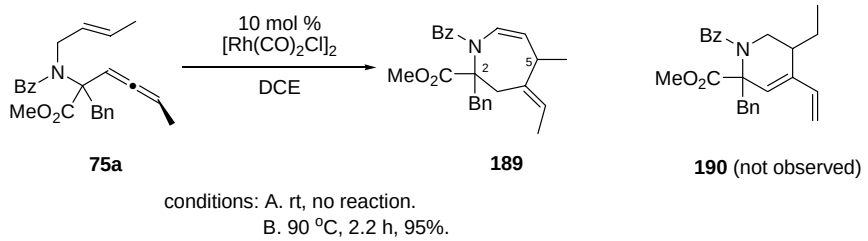
conditions: A. 10 mol% (p-diphenylphosphinopolystyrene)$NiCl_2$ and 30 mol% $CrCl_2$.
B. 5 mol% $RuClH(CO)(PPh_3)_3$.
C. 5 mol% $[RhCl(cod)]_2$, 10 mol% $P(OPh)_3$.

Subsequently, the same transformation was reported by Kang using $RuClH(CO)(PPh_3)_3$ as a catalyst,[128] and Itoh, using $[RhCl(COD)]_2$ as catalyst with a triphenylphosphite ligand.[129]

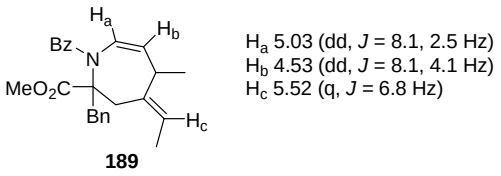
To examine the effect of replacing the alkyne with an alkene on the Rh(I)-catalyzed

allenic Alder-ene reaction, ene-allene **75a** was subjected to 10 mol% $[Rh(CO)_2Cl]_2$ in DCE; reaction did not occur at rt. However, upon heating to 90 °C, the starting material was consumed and tetrahydroazepine **189** was isolated as the sole product in 43% yield. It was determined that the low isolated yield was due to decomposition of the product during purification. Minimal exposure of the crude reaction mixture to silica gel resulted in 95% yield of **189** (Scheme 3.42). The presence of an enamide olefin in **189** is characterized with two resonances in the ^{1}H NMR spectrum (in $CDCl_3$) at 5.03 ppm (dd, J = 8.1, 2.5 Hz) and 4.53 ppm (dd, J = 8.1, 4.1 Hz) (Scheme 3.43). In addition, the exocyclic olefin displays a signal at 5.52 ppm (q, J = 6.8 Hz).

Scheme 3.42 Formation of tetrahydroazepine **189**.



Scheme 3.43 Selected data from the ^{1}H NMR spectrum of **189** in $CDCl_3$.



Furthermore, **189** was isolated from the reaction as mainly one stereoisomer[l] with respect to the C2 and C5 relative stereochemistry, and *E*-geometry of the exocyclic olefin, which is predicted based on a mechanistic hypothesis (see Scheme 3.45).[m] The relative stereochemistry of the C2 and C5 stereocenters was not determined.

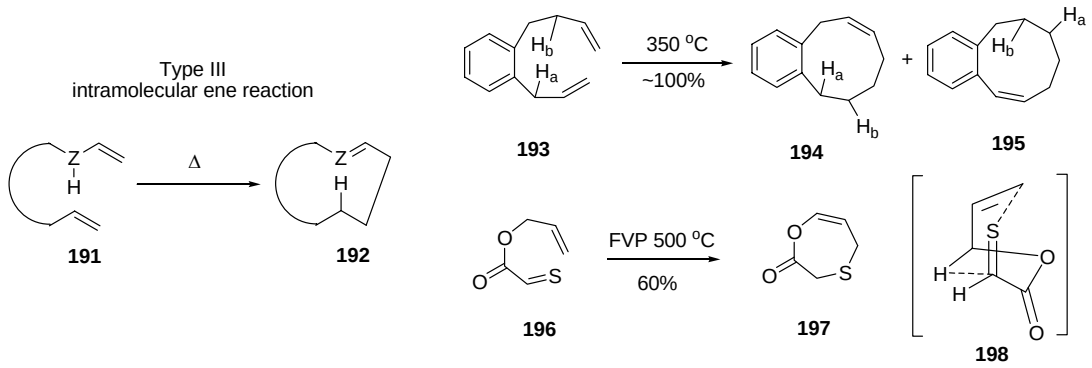
---

[l] The ^{1}H NMR spectrum of the reaction mixture after passing through a short silica gel column displayed additional peaks, which may be attributed to small amounts of a second isomer (estimated ~10%).

[m] Additional examples of azepines prepared by Dr. Hongfeng Chen were also obtained as the *E* isomer of the exocyclic olefin: Brummond, K. M.; Chen, H.; Mitasev, B. *Org. Lett.* **2004**, *6*, 2161.

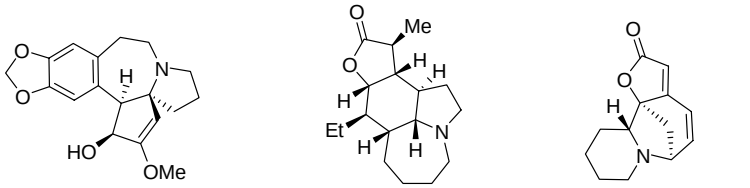
The transformation of ene-allene **75a** to tetrahydroazepine **189** represents a formal intramolecular ene-reaction of type III (Scheme 3.44).[130] This type is characterized by terminal placement of the double bond in the "ene" unit, thereby leading to formation of the largest ring possible (**191** to **192**).

Scheme 3.44 Type III intramolecular ene reaction.



There are only a few examples of type III ene reactions and these generally require very high temperatures to occur. For example, the thermal rearrangement of *ortho*-allylbutenyl benzene **193** occurs at 350 °C to give a mixture of fused benzocyclononadienes **194** and **195** in quantitative yield.[131] Similarly, thioaldehyde **196** undergoes an intramolecular ene reaction under flash vacuum pyrolysis (FVP) at 500 °C affording a thialactone **197**, in a rare example of 7-membered ring formation.[132] The high temperature required for this reaction to occur can be attributed to the strained nature of the transition state **198** required for an ene reaction. Therefore, the formation of tetrahydroazepine **189** via a Rh(I)-catalyzed cycloisomerization reaction of **75a** at 90 °C is an intriguing result. Moreover, azepines are an important synthetic target due to their presence in a variety of natural products (cephalotaxanes, *Stemona* and *Securinega* alkaloids, Figure 3.4).[133, 134]

Figure 3.4 Examples of natural products containing an azepine ring.



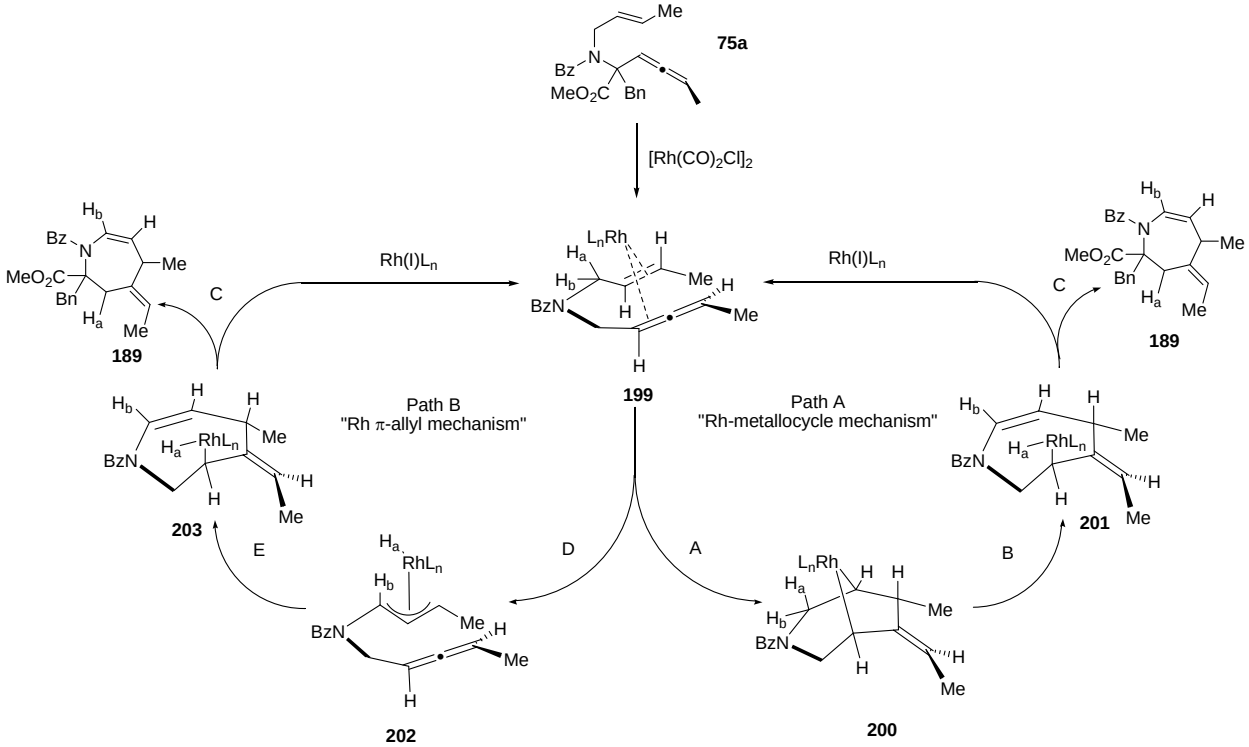
cephalotaxine
(cephalotaxane alkaloid)

stenine
(Stemona alkaloid)

securinine
(Securinega alkaloid)

At least two mechanistic pathways can be proposed for the cycloisomerization reaction of ene-allene **75a** to azepine **189** (Scheme 3.45). Path A involves oxidative insertion of Rh(I) between the alkene and the proximal double bond of the allene, in an *endo* mode, affording a Rh(III) bridging metallocycle **200**. Extraction of H_a via a β-hydride elimination would lead to Rh(III)-hydride species **201**, which then undergoes a reductive elimination to afford the observed product **189**.

Scheme 3.45 Proposed mechanisms of the Rh(I)-catalyzed cycloisomerization of ene-allene **75a**.

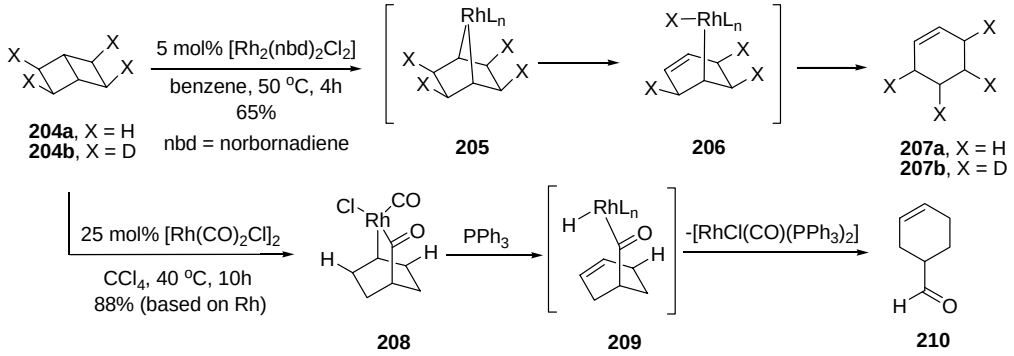


A: oxidative addition; **B**: β-hydride elimination; **C**: reductive elimination; **D**: C-H insertion; **E**: carbometallation.

Note: The 2-carbomethoxy and 2-benzyl substituents were omitted in the mechanism for clarity purposes.

Bridging rhodacycles related to **200** have been proposed as intermediates in the rearrangement of strained cycloalkanes by Halpern[135] and Gassman (Scheme 3.46).[136] For example, treatment of bicyclo[2.2.0]hexane **204a** with catalytic amount of $[Rh_2(nbd)_2Cl_2]$ leads to exclusive formation of cyclohexene (**207a**). This observation is readily accommodated by a mechanism involving oxidative insertion of Rh(I) into the strained C-C bond, to form a bridging metallocycle **205** which undergoes a β-hydride elimination and reductive elimination to give cyclohexene. The same reaction of tetradeuteriated bicyclo[2.2.0]hexane **204b** results in 3,4,5,6-tetradeuteriocyclohexene **207b** in support of this mechanism. Moreover, when **204a** is treated with 25 mol% $[Rh(CO)_2Cl]_2$, it affords an isolable acyl-rhodacycle **208** in 88% yield. Interestingly, treatment of this compound with PPh_3 initiates a sequence of β-hydride elimination and reductive elimination steps to give aldehyde **210**. These results clearly indicate that bridging rhodacycle **200** is a viable intermediate in the cycloisomerization of ene-allenes as outlined in Path A (Scheme 3.45).

Scheme 3.46 Bridged Rh(III)-metallocycles via oxidative addition of Rh(I) into strained bonds.

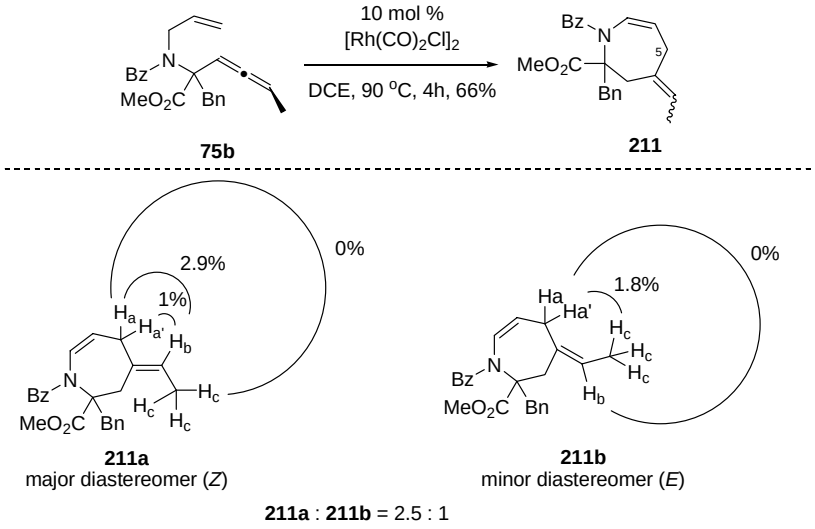


The alternative mechanistic path B involves an oxidative addition of Rh(I) into the allyl C-H bond of intermediate **199** leading to a π-allyl rhodium hydride species **202** (Scheme 3.45). Insertions of this type are common for many transition metals (e.g., Rh, Ru, Ir) and often result in isomerization of the allylic amide to an enamide.[137] Next, *endo*-carbocyclization of this

species onto the proximal double bond of the allene assembles the azepine core **203** resulting in a Rh(III)-hydride species which undergoes a reductive elimination to give the product **189**. Recently, a cyclization of a (π-allyl)-Pd-OAc species onto the internal double bond of the allene in all-carbon tethered ene-allenes leading to 5-membered ring formation has been reported.[138] In addition, Trost reported a cycloisomerization of 1,6-enynes catalyzed by $CpRu(CH_3CN)_2PF_6$, which was rationalized by a similar C-H insertion-carbocyclization mechanism.[139]

Exclusive formation of the exocyclic olefin in azepine **189** with *E* geometry can be rationalized by coordination of the crotyl moiety away from the terminal allenyl methyl group to avoid unfavorable steric interactions, as shown in intermediate **199** (Scheme 3.45). To test whether the methyl group on the alkene moiety influences the resulting stereochemistry of the exocyclic olefin, ene-allene **75b** was subjected to the Rh(I)-catalyzed reaction conditions. The reaction resulted in the formation of azepine **211** as a mixture of exocyclic olefin isomers in 2.5 : 1 ratio (Scheme 3.47), clearly indicating a decrease in selectivity.

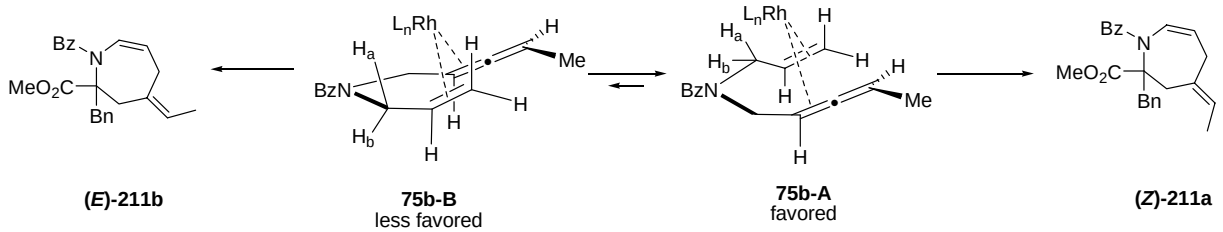
Scheme 3.47 Rh(I)-catalyzed ene reaction of **75b**.



The two isomers were separated by normal phase HPLC and the major product **211a** was assigned *Z*-geometry based on nOe data (it should be noted that the *E/Z* notation is changed from

azepine **189** due to absence of the 5-methyl group). In particular, when the exocyclic olefin resonance (H_b) of **211a** was irradiated, enhancements of 1% and 2.9% were observed for the bis-allylic methylene resonances H_a and $H_{a'}$. In contrast, no enhancement of the same resonances was observed when the methyl group signal H_c was irradiated. The minor diastereomer **211b** was assigned *E*-geometry of the exocyclic olefin by irradiating the methyl group resonance, which resulted in 1.8% enhancement for the bis-allylic methylene resonances H_a and $H_{a'}$. The formation of both *Z* and *E* isomers in this case is attributed to the less sterically demanding allyl substituent which allows reaction to occur from either face of the allene. Reaction via **75b-A** is marginally preferred over **75b-B** (Scheme 3.48) resulting in a ratio of 2.5 : 1 for the exocyclic olefin geometry.

Scheme 3.48 Rationale for the observed olefin geometry in the cycloisomerization of **75b**.

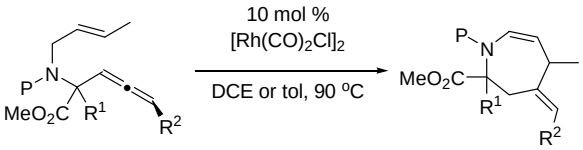


(*E*)-211b | **75b-B** less favored | **75b-A** favored | **(*Z*)-211a**

observed ratio **(*Z*)-211b** : **(*E*)-211b** = 2.5 : 1
note: substituents were removed for clarity

Three additional amino-ester tethered ene-allenes were subjected to $[Rh(CO)_2Cl]_2$ and resulted in azepine formation (Scheme 3.49). The Cbz-protected azepines **212** and **213** were obtained as single isomers in relatively low yield (63% and 51%, respectively). Finally, ene-allene **75e** containing a TBS-ether in the side chain gave 72% yield of azepine **214** as a 4 : 1 mixture of isomers, which were not separated.

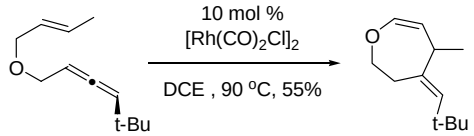
Scheme 3.49 Rh(I)-catalyzed ene reaction of **75c-e**.



75c P = Cbz, R^1 = Me, R^2 = Me	**212**, 63%
75d P = Cbz, R^1 = Me, R^2 = *i*-Pr	**213**, 51%
75e P = Bz, R^1 = CH_2OTBS, R^2 = Me	**214**, 72%

These, and additional examples from the Brummond group, demonstrate the broad scope and good functional group compatibility of the Rh(I) catalyzed reaction. It was demonstrated that highest rates of conversion and yields up to 95% can be obtained by using a bulky group on the terminus of the allene (e.g., *t*-butyl). Additionally, replacing the nitrogen tether with oxygen, leads to formation of oxepines in moderate yields (Scheme 3.50). A valuable feature of these cycloisomerizations is the generation of two stereodefined olefins, one of which is an enamide (or vinylether) and can potentially be exploited in further transformations aimed at target- or diversity-oriented synthesis.[140]

Scheme 3.50 Formation of oxepine **216** via cycloisomerization of ene-allene **215**.[n]



215 **216**

In summary, a novel Rh(I)-catalyzed cycloisomerization of ene-allenes leading to functionalized azepines was discovered. The application of these unique compounds to DOS is subject of current investigation. Finally, it should be noted that in 2004, Itoh reported a similar cycloisomerization reaction of a carbon tethered ene-allene affording a 4-alkylidenecycloheptene under Rh(I) catalysis.[141]

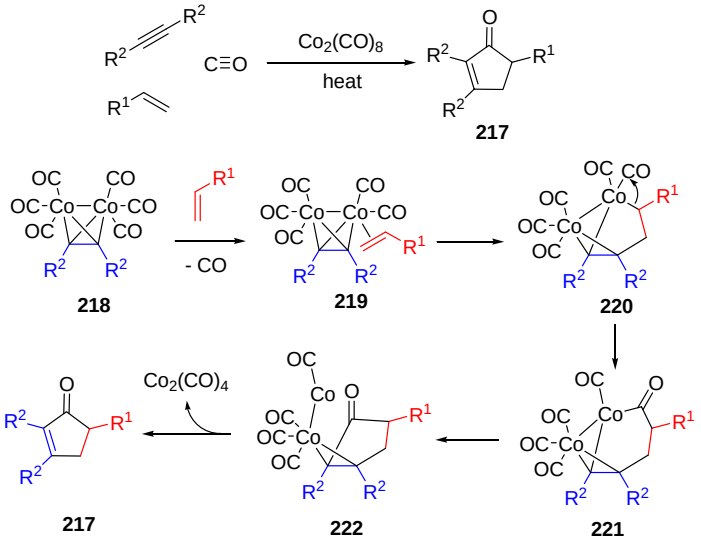
[n] Reactions performed by Dr. Hongfeng Chen (Brummond group)

4.0 Synthesis and Use of Amino-Acid Derived Cyclopentenones

4.1 Transition Metal Catalyzed Cyclocarbonylation – Pauson-Khand Reaction

The cocyclization of an alkyne, alkene and carbon monoxide to form a cyclopentenone (**217**) constitutes a formal [2+2+1] cycloaddition and was first described by Pauson and Khand in 1973 (Scheme 4.1).[142] Since then, the Pauson-Khand reaction has become one of the most convenient methods for synthesis of cyclopentenones, which are synthetically important class of molecules.[143] The initial reaction conditions utilized a stoichiometric amount of dicobaltoctacarbonyl ($Co_2(CO)_8$) to effect the intermolecular reaction of an alkyne and an alkene.

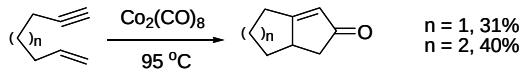
Scheme 4.1 Intermolecular $Co_2(CO)_8$-mediated Pauson-Khand reaction.



A widely accepted mechanism for this Co-mediated cyclocarbonylation reaction was proposed

by Magnus[144] and it involves the intermediacy of the cobalt complex **218**, formed by complexation of $Co_2(CO)_8$ to the alkyne, which was later firmly established by Krafft (Scheme 1.1).[145] These conditions, however, were limited to promoting the reaction of strained olefins (e.g., norbornadiene), typically with low efficiency. Furthermore, use of unsymmetrical olefins generally led to formation of regioisomers. Despite these initial disadvantages, the potential application of this transformation to complex molecule synthesis was apparent, and wealth of research in the past three decades has resulted in improved methods for effecting related Co-mediated cyclocarbonylation reactions. In the intramolecular version of the reaction, first reported by Schore in 1981, enyne **223** was converted to a fused bicyclic cyclopentenone **224** (Scheme 4.2).[146] Tethering of the alkyne and alkene gives the advantage of exclusive regioselectivity and increased reactivity.

Scheme 4.2 Intramolecular Pauson-Khand reaction of a tethered enyne.

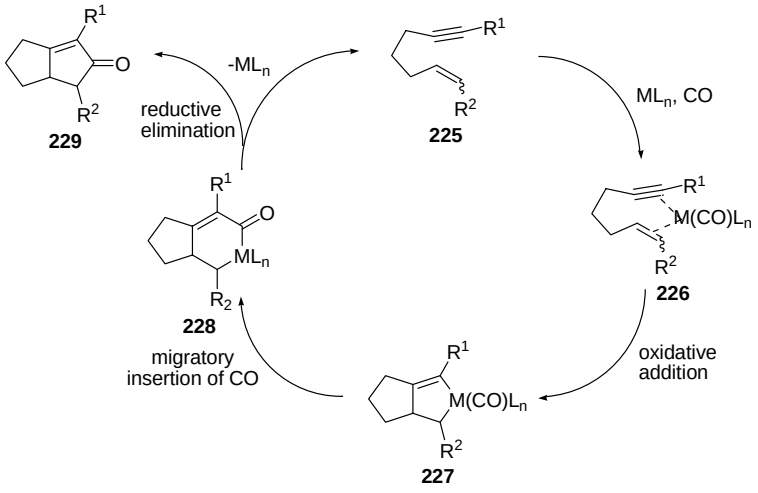


223 **224**

Extensive efforts in the past have been aimed at improving the efficiency of the Co-mediated reaction by using various additives.[147] Silica gel is believed to accelerate the reaction by acting as a polar surface to facilitate CO ligand exchange. Primary amines (e.g., cyclohexylamine) are more effective additives and are believed to act by stabilizing certain coordinatively unsaturated intermediates in the reaction pathway. Thioethers and phosphines have similar effect on accelerating the reaction. Amine oxides are another class of effective additives, which generally act by oxidizing a coordinated CO ligand to CO_2 thereby creating a vacant site on the metal. Although the use of stoichiometric amount of $Co_2(CO)_8$ to promote the Pauson-Khand reaction is still widely used today, there has been a significant progress in developing a catalytic reaction

with this metal under CO atmosphere.[148] In addition, a number of other transition metals have been demonstrated as useful mediators or catalysts for the Pauson-Khand reaction, including Mo, Ru, Rh, and Ti.[41a, 149] Currently, the name Pauson-Khand reaction is used to refer only to the initial Co-mediated transformation developed by Pauson and Khand, whereas all other related transformations are known as cyclocarbonylation reactions. The common mechanistic features of nearly all cyclocarbonylations are presented in Scheme 4.3. The reaction is initiated by coordination of the metal to the enyne, followed by the formation of a metallocycle **227** which occurs via oxidative addition of the metal into the olefin and alkyne. Then, migration of one of the metal-carbon bonds occurs into a CO ligand leading to an acyl-metallocycle **228**, which undergoes a reductive elimination to give the product **229**.

Scheme 4.3 Common mechanistic features of transition metal-catalyzed cyclocarbonylation reactions.

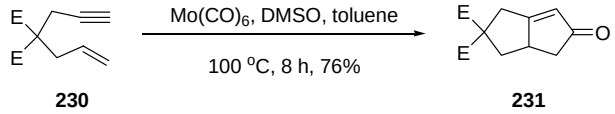


4.1.1 $Mo(CO)_6$-Mediated Cyclocarbonylation Reaction.

$Mo(CO)_6$ was reported to mediate the cyclocarbonylation reaction of 1,3-enynes by Jeong in 1993.[150] The reagent is used in a stoichiometric amount in conjunction with a promoter, which

usually is DMSO. Heating to 100 ºC is generally required for reaction to proceed (Scheme 4.4). The role of DMSO is believed to involve oxidation of one or more CO ligands to CO_2, which then leaves, opening a vacant site on the metal for coordination of the enyne. In this initial report, it was shown that 1,3-enynes with diester, ether or nitrogen in the tether can participate in the $Mo(CO)_6$-promoted cyclization to afford the corresponding [5,5]-fused bicyclic systems (**230** to **231**, Scheme 4.4). Notably, attempts to prepare [6,5]-fused systems by extending the enyne tether by one carbon were unsuccessful.

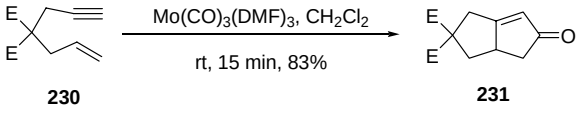
Scheme 4.4 $Mo(CO)_6$-mediated cyclocarbonylation reaction.



230 **231**

There has been only one report on a catalytic version of the Mo-mediated cyclocarbonylation reported to date, but it is limited to highly reactive substrates.[151] Recently, Carretero found that $Mo(CO)_3(DMF)_3$ serves as a milder and more efficient promoter for the intramolecular cyclization of enynes.[152] This air-sensitive complex can be synthesized from $Mo(CO)_6$ itself and allows the reaction of enynes to occur at rt with improved yields and without the necessity of promoters (Scheme 4.5).

Scheme 4.5 Improved protocol for the Mo-mediated cyclocarbonylation reaction.



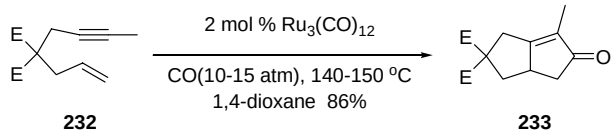
230 **231**

4.1.2 Late Transition Metal-Catalyzed Cyclocarbonylation Reaction.

Late transition metals such as Rh and Ru have been widely utilized in a variety of catalytic transformations of 1,n-enynes including [4+2] and [5+2] cycloadditions, and ene-type

cycloisomerization reactions.[40-42] Such reactions are presumed to proceed via intermediacy of metallocyclopentenes formed by oxidative addition of the metal into the enyne. It has been demonstrated that under an atmosphere of CO, these metallocyclopentene intermediates can be intercepted and subsequently lead to insertion of CO in one of the metal-carbon bonds, thereby constituting a catalytic cyclocarbonylation reaction. The first examples of late transition metal-catalyzed cyclocarbonylations appeared in the literature in the late 1990's. Initially, Murai[153] and Mitsudo[154] demonstrated the use of $Ru_3(CO)_{12}$ under CO pressure of 10-15 atm to perform the cycloaddition of diester-tethered substrate **232** upon heating to 140-150 °C (Scheme 4.6).

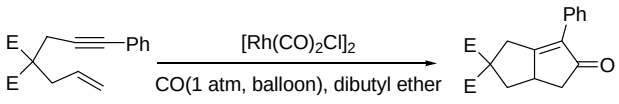
Scheme 4.6 Ru-catalyzed cyclocarbonylation reaction.



232 **233**

Subsequently, in 1998, Narasaka[155] and Jeong[156] independently reported the first examples of a Rh(I)-catalyzed cyclocarbonylation reactions. Narasaka detailed the use of the dimeric square-planar complex $[Rh(CO)_2Cl]_2$ to catalyze the reaction of a range of substrates with catalyst loading as low as 1 mol %. For example, the reaction of **234** proceeds at either 90 °C with 5 mol % of catalyst or 130 °C with 1 mol %, to give cyclopentenone **235** in high yield (Scheme 4.7).

Scheme 4.7 $[Rh(CO)_2Cl]_2$-catalyzed cyclocarbonylation reported by Narasaka.



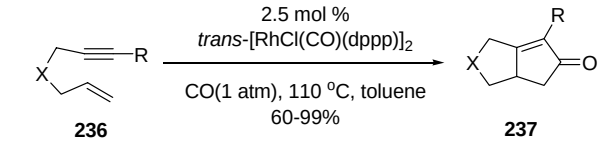
234 **235**

catalyst loading	temperature	yield
5 mol %	90 °C	97%
1 mol %	130 °C	94%

Most importantly, with this catalyst the reaction can be carried out under 1 atm of CO by simply using a balloon, which is in sharp contrast to many previous catalytic Pauson-Khand reactions

that require high pressures of CO.[148] This was further exemplified by Jeong, who utilized a number of Rh(I) complexes with phosphine ligands.[156] It was demonstrated that $RhCl(PPh_3)_3$ (Wilkinson's catalyst), *trans*-$RhCl(CO)(PPh_3)_2$ and RhCl(CO)(dppe) catalyze the cyclocarbonylation of 1,3-enynes at 110 °C when activated with an additive such as AgOH or AgOTf, while the dimeric *trans*-$[RhCl(CO)(dppp)]_2$ does not require any additive (Scheme 4.8).

Scheme 4.8 Rh(I)-catalyzed cyclocarbonylation reaction reported by Jeong.

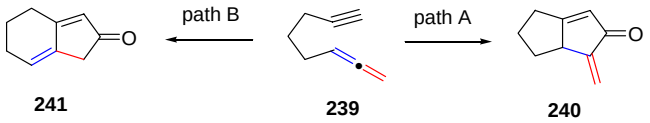


These initial discoveries have led to the first practical examples of a Rh(I)-catalyzed asymmetric cyclocarbonylation reaction by using chiral phosphine ligands.[157, 158]

4.1.3 Allenic Cyclocarbonylation Reaction.

Use of an allene as the olefin component in the cyclocarbonylation reaction is particularly intriguing, since two different products can be formed depending on which double bond reacts (Scheme 4.9). In an intramolecular process, reaction of the proximal double bond leads to an α-alkylidene cyclopentenone (path A), whereas reaction with the distal double bond forms a 4-alkylidene cyclopentenone (path B).

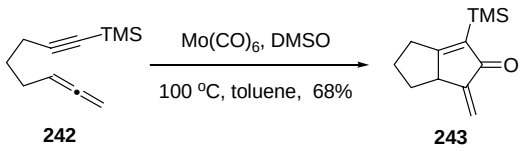
Scheme 4.9 Allenic cyclocarbonylation reaction.



In 1995, Brummond and coworkers reported the first examples of an allenic cyclocarbonylation

reaction.[159] It was shown that Jeong's $Mo(CO)_6$ conditions applied to allenyne **242** containing a terminally unsubstituted allene selectively afford the α-alkylidene cyclopentenone **243** arising from reaction with the proximal double bond of the allene (Scheme 4.10).

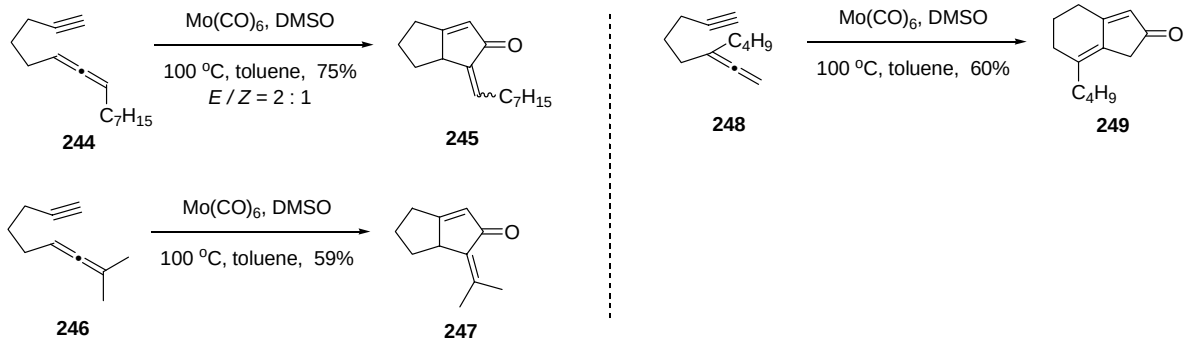
Scheme 4.10 $Mo(CO)_6$-mediated cyclocarbonylation reaction of **242**.



242 **243**

Subsequent detailed studies by Brummond established that the double bond selectivity is substrate dependent (Scheme 4.11).[160] In addition to terminally unsubstituted allenes (**242**), substrates possessing one or two substituents on the terminal allenic position were found to react selectively with the proximal double bond to give α-alkylidene cyclopentenones. In the case of terminally monosubstituted allenes, the products are obtained as mixtures of *E* and *Z* isomers of the exocyclic olefin. For example, reaction of allenyne **244** gives **245** as a 2 : 1 mixture of diastereomers. The terminally disubstituted allene in **246** also reacts to give α-alkylidene cyclopentenone **247** as a single product in 59% yield. In contrast, placing an additional substituent on the proximal carbon of the allene as in **248**, leads exclusively to formation of 4-alkylidene cyclopentenone **249**. These trends were proven general by subjecting variety of additional substrates to the reaction conditions.[160b-c]

Scheme 4.11 Mo-mediated allenic cyclocarbonylation reactions.

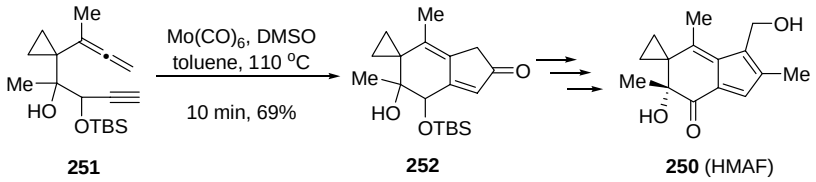


244 **245** **246** **247** **248** **249**

In contrast to the $Mo(CO)_6$-mediated cyclocarbonylation reaction, which exhibits excellent double bond selectivity, the standard Pauson-Khand promoter $Co_2(CO)_8$ proved largely unselective by giving mixtures of constitutional group isomers. Subsequently, Cazes reported low selectivity in more examples of Co-mediated allenic Pauson-Khand reaction.[161]

The substrate-controlled selectivity observed in the Mo-mediated reaction by Brummond has been exploited towards the synthesis of the potent antitumor agent hydroxymethylacylfulvene (HMAF) (**250**). Due to the presence of a methyl group at the proximal allenic position, the cyclocarbonylation reaction of allenyne **251** proceeds to give exclusively the 4-alkylidene cyclopentenone **252** desired for the synthesis of HMAF (Scheme 4.12).[162]

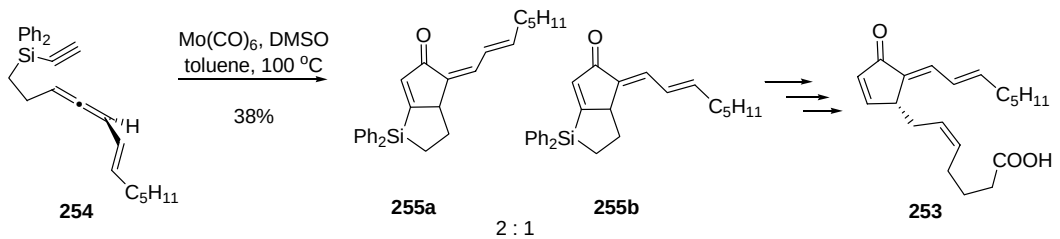
Scheme 4.12 Application of the allenic cyclocarbonylation reaction to the synthesis of HMAF.



251 **252** **250** (HMAF)

The alternative pathway, selective for the proximal double bond of the allene, was employed in the synthesis of 5-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (**253)** by utilizing a cleavable silicon tether in the allenyne **254** which gave 38 % yield of α-alkylidene cyclopentenones **255a** and **255b** (Scheme 4.13).[163]

Scheme 4.13 Application of the allenic cyclocarbonylation reaction to the synthesis of 5-deoxy-$\Delta^{12,14}$-PGJ_2 (**253**).

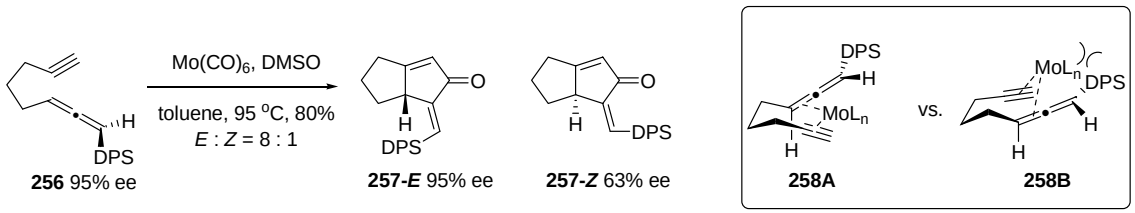


254 **255a** **255b** **253**

2 : 1

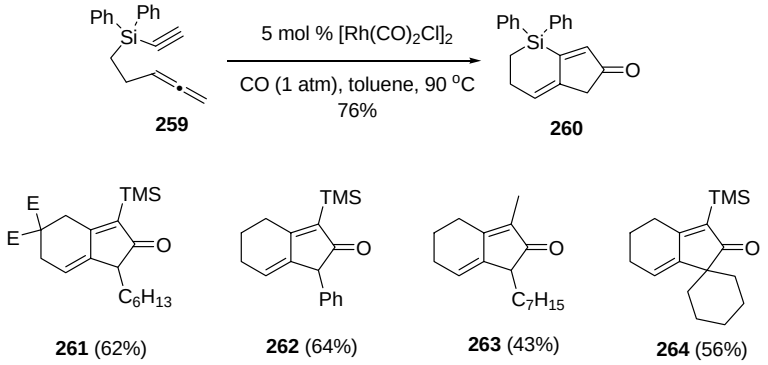
Since 1,3-disubstituted allenes inherently exhibit axial chirality, there is a potential for transfer of this chiral information to the stereocenter at the ring fusion in the α-alkylidene cyclopentenones during the cyclocarbonylation reaction. Brummond and coworkers demonstrated that this is indeed the case, by submitting enantioenriched dimethylphenylsilyl-substituted allenyne **256** to the Mo-mediated conditions, which afforded the *E*-isomer of **257** with 8 : 1 selectivity and complete retention of enantiopurity (95% ee) (Scheme 4.14).[164] The lower enantiopurity (63% ee) of the *Z*-isomer was attributed to isomerization during the purification steps. The transfer of chirality is rationalized by selective coordination of the metal to the less hindered face of the allene, minimizing the interaction between the alkyne and the bulky silyl group as shown in **258A**, which leads to the major *E*-isomer.

Scheme 4.14 Transfer of chirality in the allenic cyclocarbonylation reaction.



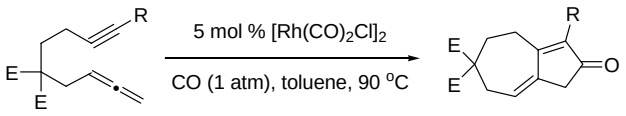
Brummond and coworkers screened other metal catalysts in order to achieve catalyst-based double bond selectivity and extend the overall utility of the allenic cyclocarbonylation reaction. It was found that the Rh(I) conditions first reported by Narasaka (5 mol % $[Rh(CO)_2Cl]_2$) effect the reaction exclusively with the distal double bond of the allene.[165] For example, reaction of the silicon tethered allenyne **259** gave 76% yield of the 4-alkylidene cyclopentenone **260** when heated to 90 °C under 1 atm (balloon pressure) of CO (Scheme 4.15). The remarkable regiochemical preference for reaction to occur with this selectivity was shown by preparing a number of other cyclopentenones, some of which are shown in Scheme 4.15.

Scheme 4.15 Rh(I)-catalyzed allenic cyclocarbonylation reaction.



Importantly, even terminally disubstituted allenes reacted exclusively with the distal double bond (**264**). The selectivity and reactivity for the distal double bond in the Rh(I)-catalyzed reaction was retained in substrates containing an additional carbon in the tether, thereby allowing the construction of seven membered rings (Scheme 4.16). Notably, formation of seven-membered rings has not been possible via the Pauson-Khand reaction of enynes, and therefore the ability to form the larger-size ring is attributed to the allenic moiety. The first example of seven membered ring formation in a Co-mediated allenic Pauson-Khand reaction was reported by Cazes; however, selectivity was accomplished with a sterically biased allene.[161] Additionally, Narasaka[166] and Mukai[167] have reported examples of a Rh(I)-catalyzed allenic cyclocarbonylation reaction affording seven membered rings (in Mukai's case, the proximal allenic position is substituted with a phenylsulfonyl group).

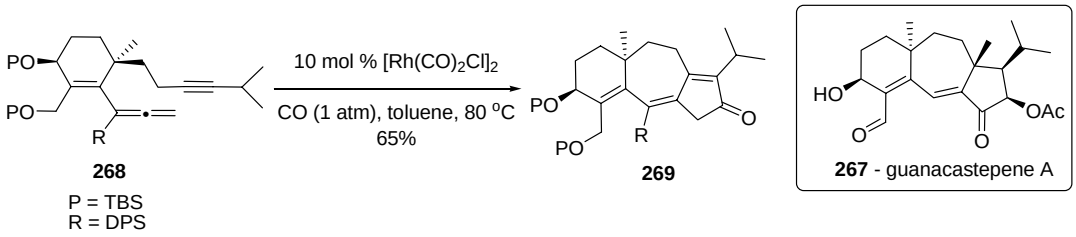
Scheme 4.16 Formation of bicyclo[5.3.0]decadienes via an allenic cyclocarbonylation reaction.



The bicyclo[5.3.0]decadiene system obtained in this manner is found in a variety of terpenoid natural products with a broad range of biological activities.[168] Brummond and coworkers have

used this reaction to craft an approach towards to naturally occurring antibiotic guanacastepene A (**267**).[169, 170] To this end, reaction of allenyne **268** with 10 mol% $[Rh(CO)_2Cl]_2$ at 80 °C affords the [6,7,5]-fused tricyclic enone **269** in 65% yield (Scheme 4.17).

Scheme 4.17 Allenic cyclocarbonylation reaction toward the synthesis of guanacastepene A.



268

P = TBS
R = DPS

269

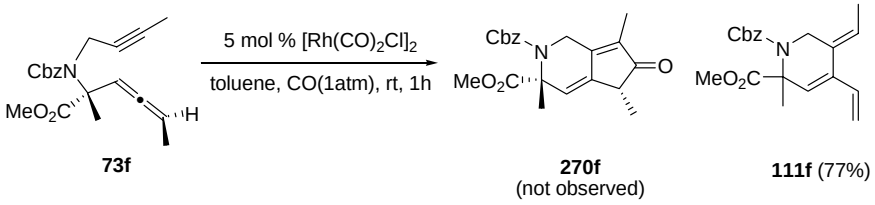
267 - guanacastepene A

In summary, the allenic cyclocarbonylation reaction has proven as a useful method for the synthesis of α- and 4-alkylidene cyclopentenones. The regioselectivity can be controlled by the choice of metal used to effect the reaction, thereby allowing for conversion of a single precursor to two structurally distinct products.

4.2 Rhodium(I)-Catalyzed Cyclocarbonylation of Amino-Ester Tethered Allenynes for Preparation of 4-Alkylidene Cyclopentenones

Our next goal was to demonstrate that the amino ester-tethered allenynes could be used in the preparation of 4-alkylidene cyclopentenones via a selective cyclocarbonylation reaction with the distal double bond of the allene. In 2002, Brummond and coworkers reported that $[Rh(CO)_2Cl]_2$ effectively catalyzes the cyclocarbonylation reaction of variety of allenynes, selectively affording 4-alkylidene cyclopentenones.[165] In all reported cases, product formation was effected under 1 atm of CO and heating to 90 °C in toluene. In sharp contrast, when allenyne **73f** was subjected to 5 mol% $[Rh(CO)_2Cl]_2$ in toluene under 1 atm of CO, reaction proceeded at rt to give only the cross-conjugated triene **111f** in 77% yield and none of the expected cyclopentenone **270f** (Scheme 4.18).

Scheme 4.18 Attempted cyclocarbonylation reaction of **73f**.



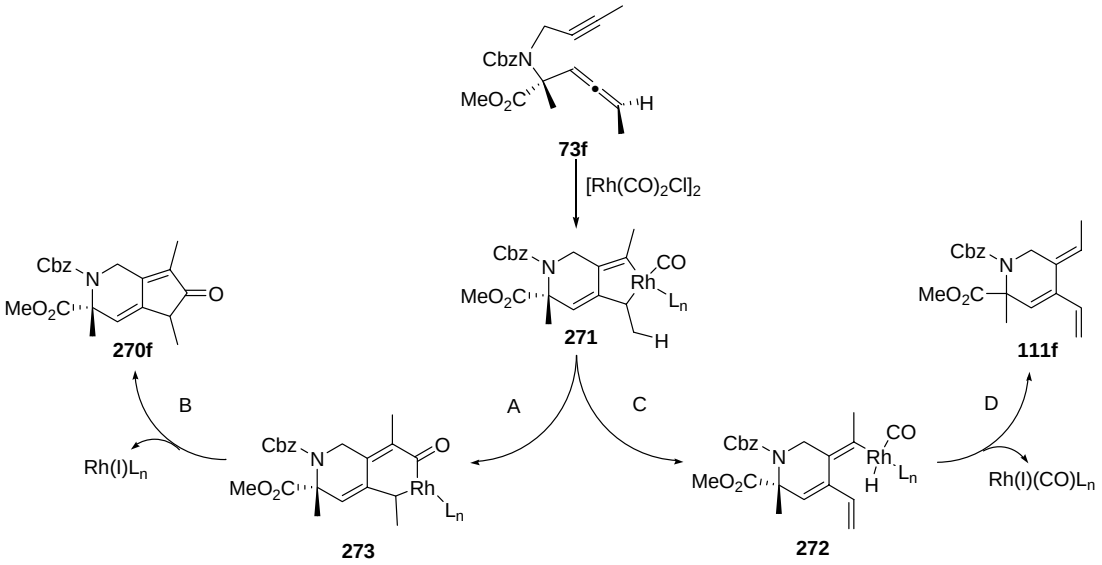
73f **270f** (not observed) **111f** (77%)

This result was somewhat anticipated since it was already established that cycloisomerization of the amino-ester tethered allenynes proceeds at an exceedingly fast rate (less than 10 min in presence of 5 mol % $[Rh(CO)_2Cl]_2$). Performing the reaction under CO atmosphere only noticeably slowed the rate of the cycloisomerization (1h vs. 10 min).

It was rationalized that both triene **111f** and cyclopentenone **270f** are formed from a common Rh(III)-metallocyclopentene intermediate **271** as shown in Scheme 4.19. The

cycloisomerization pathway involves β-hydride elimination from the adjacent methyl group to give Rh(III)-H species **272**, followed by reductive elimination. Alternatively, migratory insertion of CO in the vinyl-Rh(III) bond leads to acyl-metallocyclohexene **273**, which is transformed to cyclopentenone **270f** via a reductive elimination.

Scheme 4.19 Mechanism for the cycloisomerization and cyclocarbonylation reaction of **73f**.



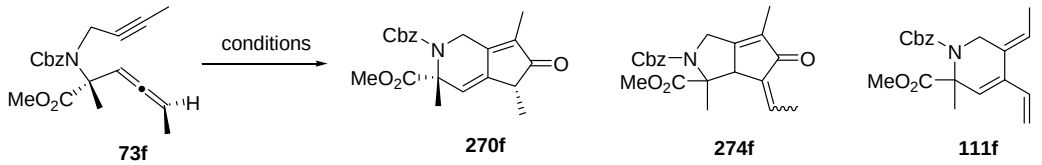
A: CO insertion; B: reductive elimination; C: β-hydride elimination; D: reductive elimination.

The reaction of **73f** in presence of $[Rh(CO)_2Cl]_2$ clearly indicated that the cycloisomerization pathway leading to **111f** is greatly favored with this catalyst. To circumvent this issue, other catalytic conditions were examined.

In 2000, Shibata reported the use of Ir(I) catalysts for the intramolecular cyclocarbonylation reaction of enynes.[171] Borrowing from this report, $[Ir(CO)_3Cl]$ was used in an attempt to effect selective formation of **270f**. Heating allenyne **73f** to 90 °C under 1 atm of CO, resulted in a mixture of all three possible products in 73% yield (entry 1, Table 4.1). Interestingly, the α-alkylidene cyclopentenone **274f (**48%) resulting from reaction with the proximal double bond of the allene was formed preferentially over **270f** (15%), along with a small amount of undesired triene **111f** (10%). This result was encouraging despite the complete

lack of double bond selectivity, since cyclocarbonylation was the predominating reaction pathway. In an effort to inhibit the formation of the triene either sterically or electronically, PPh_3 was added to the iridium catalyst. Formation of the triene **111f** was avoided by using an *in situ* prepared catalyst by addition of 20 mol % of PPh_3 to 10 mol % $[Ir(cod)Cl]_2$ (Ir : P ratio = 1 : 1). However, these conditions also gave a mixture of cyclocarbonylation products in 60 % yield with the α-alkylidene cyclopentenone **274f** preferred (entry 2, Table 4.1). Both results indicate that Ir-based catalysts may have a unique preference to promote the reaction with the proximal double bond of the allene. This was confirmed in a report by Shibata in 2003 by converting terminally disubstituted allenynes to α-alkylidene cyclopentenones using $IrCl(CO)(PPh_3)_2$.[172]

Table 4.1 Cyclocarbonylation conditions for allenyne **73f**.



73f **270f** **274f** **111f**

entry	conditions[a]	yield	ratio **270f : 274f : 111f**
1	$[Ir(CO)_3Cl]$, CO, toluene, 90 °C	73%	2 : 6.5 : 1.5
2	$[Ir(COD)Cl]_2$, PPh_3, CO, toluene, 90 °C	60%	1.5 : 8.5 : 0
3	$Rh(PPh_3)_3Cl$, CO, toluene, 90°C,	no reaction	
4	$Rh(CO)Cl(PPh_3)_2$, CO, toluene, 90°C	no reaction	
5	**$Rh(CO)Cl(PPh_3)_2$, AgOTf,[b] CO, toluene, 50°C**	**66%**	**7.5 : 2.5 : trace**

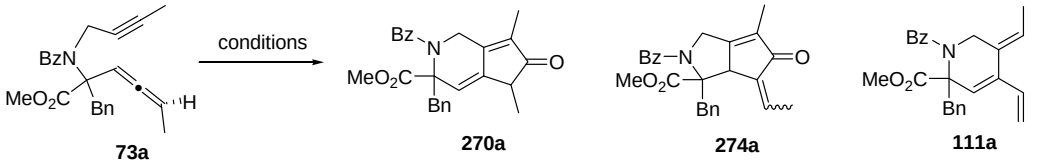
[a] 10 mol % of catalyst and 1 atm of CO was used in all cases; [b] 10 mol %

Next, the effect of ligands on the Rh(I) catalyst was examined because it was reasoned that the undesired β-hydride elimination pathway from metallocylopentene **271** could also be suppressed in presence of phosphine ligands. It is well known that a vacant site on the Rh(III)-center is required for β-hydride elimination to occur.[173, 174] Therefore, coordinatively saturated Rh(III)-metallocycle is deemed more likely to undergo CO insertion than β-hydride elimination. With this in mind, $Rh(PPh_3)_3Cl$ (Wilkinson's catalyst)[175] and *trans*-$Rh(CO)Cl(PPh_3)_2$ were tested.[176]

As shown in Table 4.1 (entries 3 and 4), reaction with **73f** did not occur upon heating to 90 °C. The unreactive nature of these two catalysts is attributed to very low π-acidity due to presence of phosphine ligands. These observations are in accord with those by Jeong, who first reported that activation of both catalysts by Ag-additives is necessary in the cyclocarbonylation reaction of enynes.[156] Addition of Ag(I) salts with non-coordinating anions (e.g., $CF_3SO_3^-$, BF_4^-, SbF_6^-, PF_6^-) to a metal-halide complex replaces the strongly coordinating halide with a weakly coordinating counterion thereby creating a vacant binding site on the metal and increasing its π-acidity. When *trans*-$Rh(CO)Cl(PPh_3)_2$ was treated with equimolar amount of AgOTf, reaction of **73f** occurred at 50 °C to give a mixture of cyclocarbonylation products **270f** and **274f** in 66% yield, with the desired 4-alkylidene cyclopentenone preferred by ca. 3 : 1 (entry 5, Table 4.1).

A similar result was obtained when N-benzoyl protected allenyne **73a** was submitted to the same reaction conditions (entry 1, Table 4.2). Changing the solvent from toluene to DCE, resulted in formation of the cyclocarbonylation product **270a** (55%) and triene **111a** in 10% yield (entry 2, Table 4.2). Based on this result DCE was retained as a solvent, and variation of the Ag-salt additive was examined. The type of the counterion is known to have an effect on the outcome of transition metal catalyzed reactions, but strict survey to our knowledge has not been performed in the context of Rh(I)-catalyzed cyclocarbonylation reactions.[177] Interestingly, when using $AgBF_4$, the only isolated product was the desired 4-alkylidene cyclopentenone **270a** in 76% yield (entry 3, Table 4.2). However, this reaction required 36 h at rt for completion, which may seriously limit its broader application.

Table 4.2 Cyclocarbonylation reaction conditions for allenyne **73a**.



73a **270a** **274a** **111a**

entry	conditions[a]	yield	ratio **270a : 274a : 111a**
1	$Rh(CO)Cl(PPh_3)_2$, AgOTf, CO, toluene, 50 ^oC	52%	4 : 1 : trace
2	$Rh(CO)Cl(PPh_3)_2$, AgOTf, CO, DCE, rt	65%	8.5 : 0 : 1.5
3	$Rh(CO)Cl(PPh_3)_2$, $AgBF_4$, CO, DCE, rt, 36h	76%	10 : 0 : 0
4	**$[Rh(CO)_2Cl]_2$, PPh_3, $AgBF_4$, CO, DCE, rt, 1h**	**76%**	**10 : 0 : 0[b]**

[a] 10 mol % of catalyst and 1 atm of CO was used in all cases; [b] 10 mol % $[Rh(CO)_2Cl]_2$, 30 mol % PPh_3, 22 mol % $AgBF_4$.

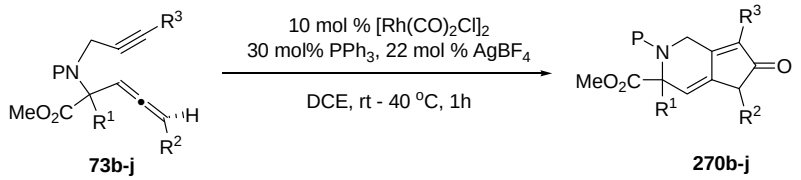
Based on observations that $RhCl(PPh_3)_3$ activated by $AgBF_4$ on average gave longer reaction times it was reasoned that reducing the amount of PPh_3 would have an effect on increasing the rate of the reaction. Therefore, an experiment was designed where the catalytic species was prepared *in situ* from 10 mol % of $[Rh(CO)_2Cl]_2$, 30 mol % PPh_3 and 22 mol % of $AgBF_4$ (P : Rh ratio = 1.5 : 1).[o] When allenyne was added under 1 atm CO, reaction occurred at rt in 1h to give 4-alkylidene cyclopentenone **270a** in 76% yield (entry 4, Table 4.2). To our knowledge, this is the first example of a Rh(I)-catalyzed cyclocarbonylation reaction occurring at rt (the initial examples by Jeong and Narasaka required heating over 100 °C).[178]

These conditions were then tested on a set of substrates to examine the scope. Variation of the alkyne terminus with a TMS group (entries 2 and 6, Table 4.3) resulted in formation of α-silyl-cyclopentenones **270c** and **270h** in high yield. This result is in contrast to Narasaka's who reported obtaining desilylated products in the reaction of trimethylsilyl-alkynes at higher

[o] PPh_3 : Rh ratio of 1.5 : 1 proved necessary since increasing the amount of PPh_3 (P : Rh = 2 : 1) led to slower reaction (as in entry 3), whereas lowering the amount of PPh_3 (P : Rh = 1 : 1) led to formation of triene **111a**.

temperatures. The reaction conditions were also tolerant of a phenyl-substituted alkyne (entries 3 and 7) giving α-phenyl-cyclopentenones **270d** and **270i** in ca. 75% yield. The reaction of serine derived allenyne **73e** proceeded to give cyclopentenone **270e** in 81% yield. In nearly all cases, filtration of the reaction mixture over a short column of silica gel and eluting with EtOAc/hexanes provides the product with satisfactory purity for characterization (the rhodium catalyst shows high affinity for silica gel and does not elute with these solvents).

Table 4.3 Preparation of 4-alkylidene cyclopentenones via a Rh(I)-catalyzed allenic cyclocarbonylation reaction.



73b-j **270b-j**

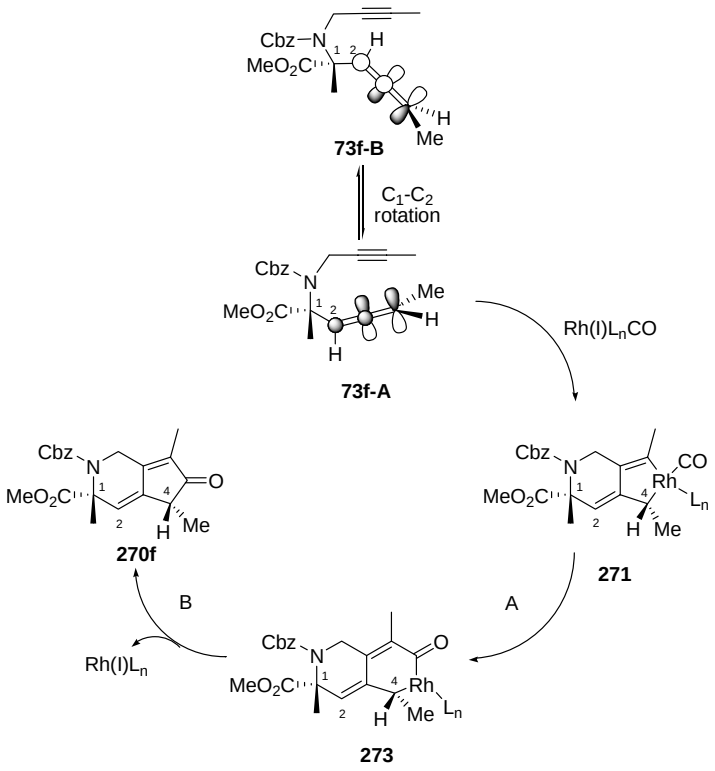
entry/allenyne	P	R^1	R^2	R^3	product	yield%	entry/allenyne	P	R^1	R^2	R^3	product	yield%
1/**73b**	Bz	Bn	Me	H	**270b**	32	5/**73f**	Cbz	Me	Me	Me	**270f**	75
2/**73c**	Bz	Bn	Me	TMS	**270c**	98	6/ **73h**	Cbz	Me	Me	TMS	**270h**	78
3/**73d**	Bz	Bn	Me	Ph	**270d**	74	7/**73i**	Cbz	Me	Me	Ph	**270i**	75
4/**73e**	Bz	-CH_2OTBS	Me	Me	**270e**	81	8/**73j**	Cbz	Me	*i*-Pr	Me	**270j**	74

Note: the products in entries 2, 3 and 4 were obtained as mixtures of diastereomers in ~1.7 : 1 ratio.

To test whether the newly developed catalytic reaction conditions are compatible with terminal alkynes, allenyne **73b** was subjected to the reaction conditions. The reaction resulted in a complex mixture of unidentified products with the desired 4-alkylidene cyclopentenone **270b** isolated in only 32% yield (entry 1). This observation is attributed to competing reaction pathways resulting from oxidative insertion of the Rh(I)-catalyst into the acetylenic C-H bond, which is well precedented.[179] Finally, reaction of **73j** with an isopropyl group on the allene terminus afforded 74% yield of the cyclopentenone **270j** demonstrating that increase in steric bulk at this position does not affect the selectivity (entry 8).

Notably, the allenic cyclocarbonylation reactions summarized in Tables 4.2 and 4.3 occurred with transfer of stereochemical information from the starting allenynes. For example, allenyne **73a** which was subjected to the reaction conditions as a mixture of diastereomers in 1.7 : 1 ratio, reacted to give the corresponding ratio of diastereomeric cyclopentenones **270a** which were separated by normal phase HPLC. Alternatively, the N-Cbz protected allenyne **73f** (entry 5, Table 4.3) was used as a nearly single diastereomer, and reacted to give cyclopentenone **270f** as a single diastereomer (diastereomer ratio of ~95 : 5 is obtained in the Claisen rearrangement, see Chapter 2).

Scheme 4.20 Transfer of stereochemical information in the reaction of **73f**.



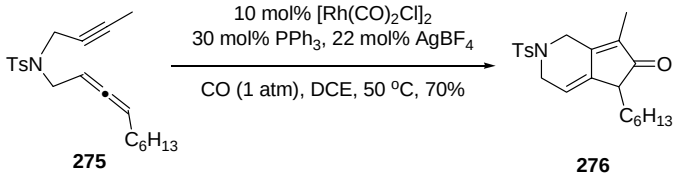
A: CO insertion; B: reductive elimination.

The transfer of stereochemical information is a result of the axial chirality of the allene which allows reaction to occur from only one diastereotopic face. As illustrated in Scheme 4.20, despite the free rotation around the C1-C2 bond, oxidative addition of Rh(I) to form a [6,5]-fused

metallocycle can occur only from rotamer **73f-A** (Scheme 4.20). The relative stereochemistry at the C4 is then retained in the course of the reaction giving a single diastereomer **270f** with the relative stereochemistry predicted as shown.[p] Previously, chirality transfer in the Mo-mediated allenic cyclocarbonylation reaction affording α-alkylidene cyclopentenones has been observed.[180]

Because the new Rh(I) catalytic conditions were optimized exclusively utilizing amino-ester tethered allenynes, in was intriguing in whether their scope extends to other, less functionalized substrates. To test this, tosyl-amide tethered allenyne was subjected to the *in situ* prepared catalyst. It was found that the reaction of this substrate required heating to 50 °C, and gave a 70% yield of the 4-alkylidene cyclopentenone **276** selectively (Scheme 4.21). This result demonstrates that the selectivity observed in the cyclocarbonylation reaction of amino-ester tethered substrates is not influenced by the quaternary center, and the conditions may be applicable to a broader set of substrates.

Scheme 4.21 Cyclocarbonylation reaction of N-tosyl tethered allenyne **275**.

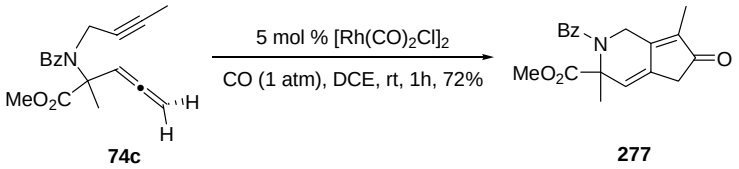


275 **276**

Finally, it should be noted that allenynes with terminally unsubstituted allenes are readily transformed to 4-alkylidene cyclopentenones by using the standard catalytic conditions (5 mol % $[Rh(CO)_2Cl]_2$, CO) because triene formation is not an option. For example, allenyne **74c** gives cyclopentenone **277** in 72% yield (Scheme 4.22).

[p] The stereochemistry of the starting allenyne is obtained in the Claisen rearrangement and is assigned in accordance with the original results reported by Kazmaier (see Chapter 2; Kazmaier, U.; Görbitz, C. H. *Synthesis* **1996**, 1489).

Scheme 4.22 Cyclocarbonylation reaction of a terminally unsubstituted allene.

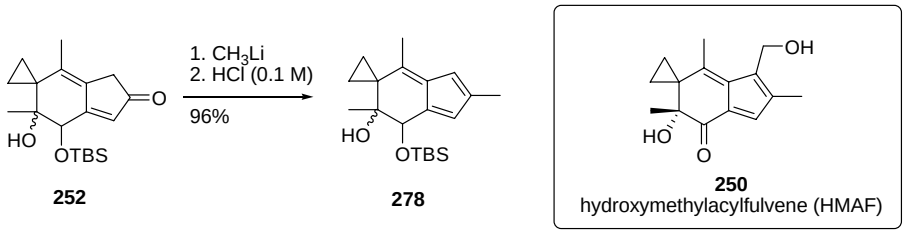


74c **277**

4.3 Diversification of 4-Alkylidene Cyclopentenones

In 2000, Brummond and Lu reported the total synthesis of hydroxymethylacylfulvene (HMAF, **250**), a potent anticancer agent.[162] HMAF has generated considerable interest because it displays anticancer activity against a number of different malignancies including breast, lung and colon carcinoma.[181] The mechanism that contributes to HMAF's proapoptotic and antiproliferative activity against cancer cells is believed to involve irreversible damage caused by covalent binding to proteins and/or nucleic acids in the cell. HMAF is structurally characterized by the presence of a unique pentafulvene moiety, rarely seen in biologically active compounds or natural products.[182] In the synthesis of HMAF reported by Brummond, formation of fulvene **278** was effected by 1,2-addition of MeLi to cyclopentenone **252** followed by acid-promoted elimination (Scheme 4.23). We became interested in applying this protocol to the amino-ester derived 4-alkylidene cyclopentenones to access novel fused pentafulvenes and examine their biological activity.

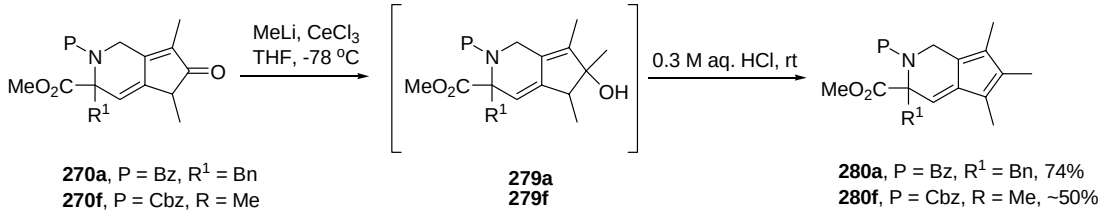
Scheme 4.23 Structure of HMAF and key fulvene synthesis step.



252 **278** **250** hydroxymethylacylfulvene (HMAF)

Therefore, cyclopentenone **270a** was treated with MeLi/$CeCl_3$ (1.5 equiv.) to afford tertiary alcohol **279a** (Scheme 4.24).[q] Immediate treatment of the crude reaction mixture with aq. HCl and warming to rt led to formation of a bright yellow solution, from which fulvene **280a** was isolated in 74% yield (pentafulvenes are generally characterized by yellow color, Lat. *fulvus* = yellow).[183]

Scheme 4.24 Synthesis of novel pentafulvenes.

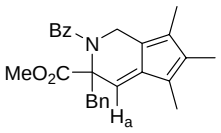


270a, P = Bz, R^1 = Bn
270f, P = Cbz, R = Me

279a
279f

280a, P = Bz, R^1 = Bn, 74%
280f, P = Cbz, R = Me, ~50%

select ^{1}H NMR signals of **280a**



three methyl group resonances

1.87 (s, 3H)
1.71 (s, 3H)
1.39 (s, 3H)

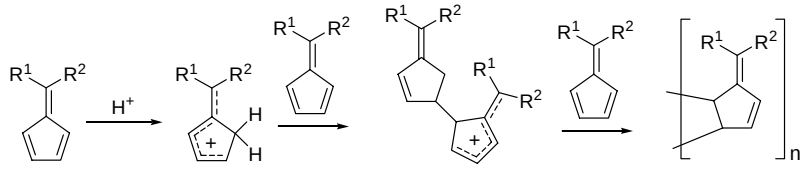
H_a 6.29 (s, 1H)

The structure of **280a** was assigned based on the presence of one olefin peak in the ^{1}H NMR spectrum at 6.29 ppm for H_a and three methyl groups (Scheme 4.24). Similarly, the N-Cbz protected cyclopentenone **270f** afforded fulvene **280f** in 50% yield. Unfortunately, the newly synthesized fulvenes proved unstable and readily decomposed when kept on the bench-top either

[q] The presumed tertiary alcohol **279** was treated *in situ* with aq. HCl and was not characterized.

neat or in solution. This decomposition was qualitatively assessed by collecting the ^{1}H NMR spectrum of **280a** at different times. A solution of **280a** in $CDCl_3$ stored at rt for 5 days resulted in appearance of additional broadened resonances in the upfield region (1.0 – 2.0 ppm). The decomposition was accelerated when **280a** was stored neat. In contrast, storing **280a** in deoxygenated frozen benzene[r] at -10 °C proved advantageous in extending its shelf life up to three months. Unfortunately, these observations rendered the newly synthesized fulvenes unsuitable for biological evaluation because the results may be compromised by the presence of impurities. The pathway of decomposition has not been determined, however it is well known that simple alkyl-pentafulvenes readily polymerize in presence of traces of acid (Scheme 4.25).[184] Additionally, polymerization of pentafulvenes has been triggered by reaction with molecular oxygen.[185]

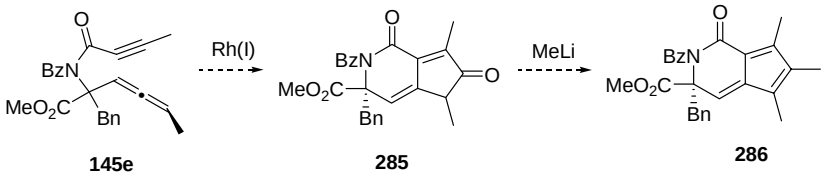
Scheme 4.25 Acid catalyzed polymerization of pentafulvenes.



The electron density of the fulvene moiety in **270a** and **270f** is likely responsible for the observed decomposition. Based on the structure of HMAF (**252**, Scheme 4.23), it was hypothesized that an acyl group may impart greater stability to these compounds by reducing the electron density of the fulvene. To examine this effect we sought to prepare fulvene **286** (Scheme 4.26). To this end, the cyclocarbonylation reaction of amide tethered allenyne **145e** was briefly examined.

[r] Benzene was deoxygenated prior to freezing by bubbling nitrogen via a needle.

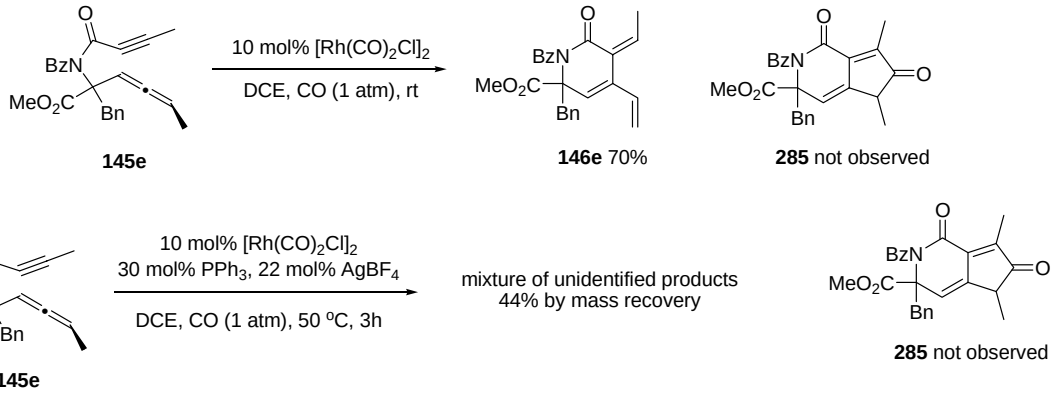
Scheme 4.26 Design of novel acyl-fulvenes.



145e **285** **286**

Subjecting **145e** to 10 mol% of $[Rh(CO)_2Cl]_2$ under CO atmosphere led to formation of the cross-conjugated triene **146e**, which was isolated in 70 % yield (Scheme 4.27). To circumvent the formation of triene, the newly developed cationic Rh(I)-conditions were applied next. Treatment of **145e** to the *in situ* prepared catalyst (10 mol% $[Rh(CO)_2Cl]_2$, 30 mol% PPh_3 and 22 mol% $AgBF_4$) at 50 °C resulted in complete consumption of the starting material in 3h and generation of a mixture of unidentified products in 44% yield by mass recovery. The major compound isolated from this mixture in 22% yield displayed a molecular ion peak in the mass spectrum same as the starting material (*m/z* = 401), indicating that it is likely a product of an isomerization reaction. Unfortunately, the desired cyclocarbonylation product **285** was not observed.

Scheme 4.27 Attempted cyclocarbonylation reactions of **145e**.



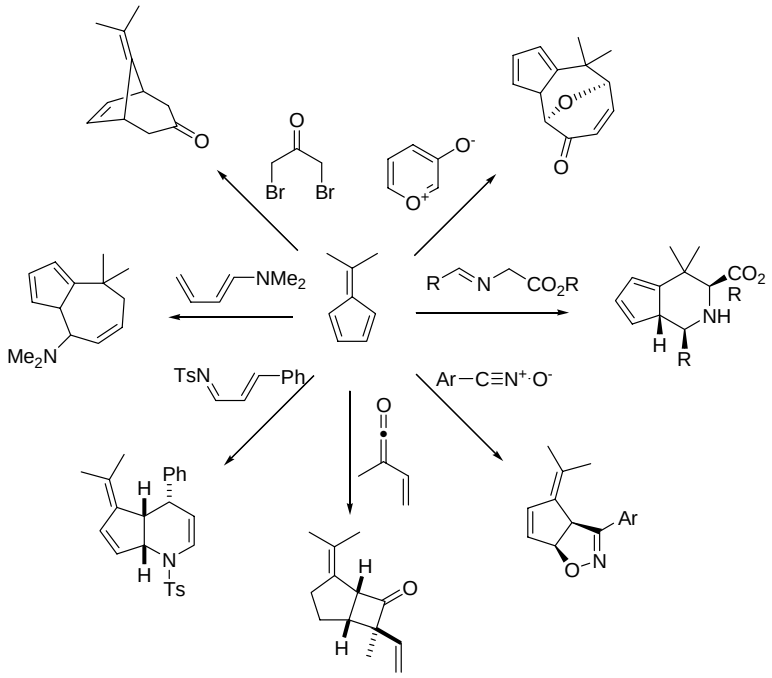
145e **146e** 70% **285** not observed

145e **285** not observed

Due to these discouraging results, further study on generating a library of amino-acid derived fulvenes was discontinued. In addition to stabilizing the fulvene moiety by installing an acyl substituent, another potential strategy for future investigation involves exploiting the reactivity of

the newly synthesized fulvenes (e.g. **280a**) in other complexity generating reactions. For example, alkyl-fulvenes have been demonstrated as useful cycloaddition partners in a variety of reactions including [4+2],[186] [6+3],[187] [2+2][188] and [3+2] cycloadditions (Scheme 4.28).[189] The vast majority of the reported examples involve symmetrical fulvenes, substituted only at the exocyclic olefin. The method of fulvene preparation that we have demonstrated allows the synthesis of polysubstituted ring-fused fulvenes whose cycloaddition reactions have not been examined.

Scheme 4.28 Selected cycloaddition reactions of fulvenes

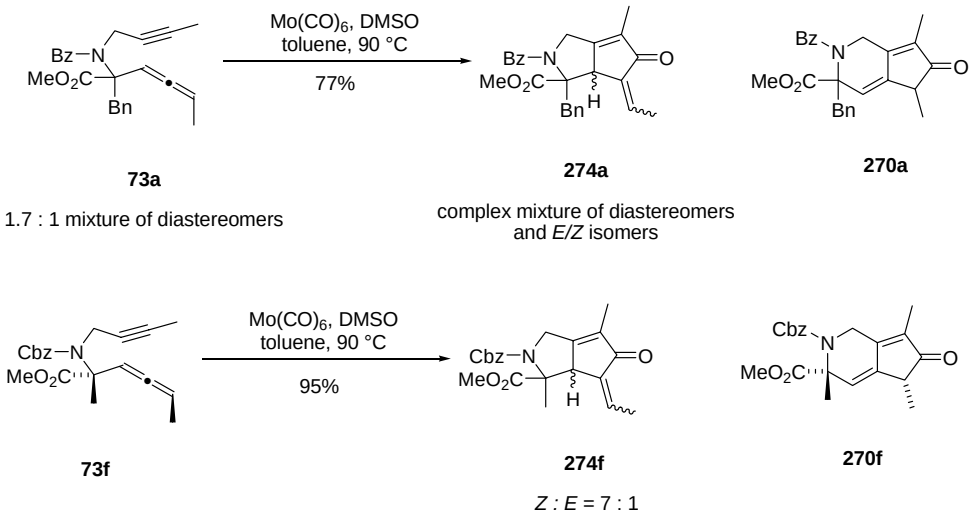


In summary, a new Rh(I)-catalytic system for the allenic cyclocarbonylation reaction was developed affording amino-ester tethered 4-alkylidene cyclopentenones in high yields and selectivity. These protocols have been applied to the preparation of a library of sixteen compounds using fluorous mixture synthesis by Dr. Sukhdev Manku in the Curran group.[190, 191] Diversification of the 4-alkylidene cyclopentenones by converting them to fulvenes did not result in useful biological probes because these compounds proved relatively unstable.

4.4 $Mo(CO)_6$-Mediated Cyclocarbonylation Reaction for Preparation of α-Alkylidene Cyclopentenones

Brummond and coworkers had previously shown that the $Mo(CO)_6$ mediated cyclocarbonylation reaction of 1,3-disubstituted allenes generally proceeds to give α-alkylidene cyclopentenones as mixtures of *E* and *Z* isomers (see Scheme 4.11).[160] A similar trend was anticipated with the amino-ester derived substrates. Indeed, subjection of allenyne **73a** containing a methyl group on the terminus of the allene to the standard reaction conditions (1.25 equiv. $Mo(CO)_6$, 10 equiv. DMSO, toluene, 90 °C) resulted in a complex mixture of cyclocarbonylation products without one particular major product according to ^{1}H NMR analysis of the crude reaction mixture (presumably diastereomers and *E/Z* isomers of **274a** and diastereomers of the minor product **270a**).

Scheme 4.29 Mo-mediated cyclocarbonylation reactions of **73a** and **73b**.



Since the starting Bz-protected allenyne **73a** was submitted to the reaction as a mixture of diastereomers in 1.7 : 1 ratio, it was reasoned that each diastereomer reacts to give the product **274a** as a mixture of diastereomers with respect to the relative stereochemistry of the two sp^3

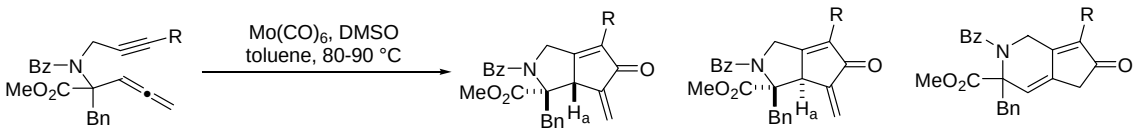
stereocenters and mixture of *E/Z* isomers of the alkylidene olefin, further complicating the characterization. Therefore the Cbz-protected allenyne **73f** as single diastereomer was tested next (Scheme 4.29). The cyclocarbonylation reaction of **73f** with $Mo(CO)_6$ provided α-alkylidene cyclopentenone **274f** with ~20 : 1 selectivity over the 4-alkylidene cyclopentenone **270f** (determined by ^{1}H NMR and HPLC/UV). Cyclopentenone **274f** was present as a mixture of mainly two isomers in ~7 : 1 ratio which were separated by normal phase HPLC. The major isomer was assigned *Z*-geometry of the alkylidene olefin based on the ^{1}H NMR signal appearing at 5.98 (q, J = 7.3 Hz, 1H) while the minor diastereomer was assigned *E*-geometry since the olefin signal appeared further downfield at 6.65 (q, J = 7.2 Hz, 1H). Nevertheless, obtaining the products as mixture of isomers was disappointing particularly since separation of the products was possible only by HPLC.

To eliminate the formation of *E* and *Z* isomers and focus on determining the diastereoselectivity of the reaction, our subsequent investigations were focused on the reaction of monosubstituted allenes. When phenylalanine derived allenynes **74a** (R = Me) and **74b** (R=H) were submitted to the standard cyclocarbonylation conditions (1.25 equiv. $Mo(CO)_6$, 10 equiv. DMSO, toluene, 90 °C), the reaction proceeded to give mixtures of products (Scheme 4.30). The major diastereomer **287a** (57%) could be easily separated by column chromatography from **288a** and **289a**. Likewise, **287b** (55%) was also chromatographed away from **288b** and **289b**. Unfortunately, **288a** and **289a** could not be separated; likewise, **288b** and **289b** also coeluted. The composition of the reaction mixture was determined by integration of the olefinic resonances in the ^{1}H NMR spectrum of the crude reaction mixture (Scheme 4.30).[s] Allenyne **74a** gave the α-alkylidene cyclopentenones **287a** and **288a** in 6.4 : 1 ratio, whereas **74b** gave **287b**

[s] These ratios are averages and showed reasonable variation in different experiments (±10%). The ratios in all subsequent reactions were determined by integration of the olefinic resonances in the ^{1}H NMR spectrum.

and **288b** in 3 : 1 ratio. Notably, both reactions resulted in ~15% of the 4-alkylidene cyclopenenone (**289a**, **289b**) resulting from reaction with the distal double bond of the allene.

Scheme 4.30 Cyclocarbonylation reaction of phenylalanine derived allenynes.



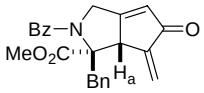
	yield			
74a R = Me	79%	**287a** 57%	**288a** 10%	**289a** 13%
74b R = H	94%	**287b** 55%	**288b** 20%	**289b** 15%

(**287a** + **288a**) : **289a** = 5.7 : 1, **287a** : **288a** = 6.4 : 1[a]
(**287b** + **288b**) : **289b** = 5 : 1, **287b** : **288b** = 3 : 1[a]

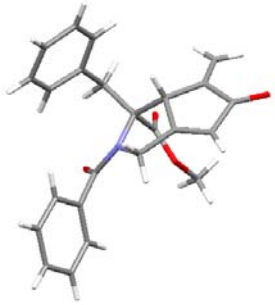
[a] The ratios were determined by integration of the olefin resonances in the ^{1}H NMR spectrum.

The relative stereochemistry of the major diastereomer **287b** was unambiguously assigned by X-ray crystallography, where the benzyl group and H_a are *syn* (Scheme 4.31) (for X-ray data see Appendix D). The same relative stereochemistry was assigned to **287a**, based on an X-ray structure of a later intermediate (**296**, in Scheme 4.41, *vide infra*).

Scheme 4.31 X-ray crystal structure of **287b**.



287b

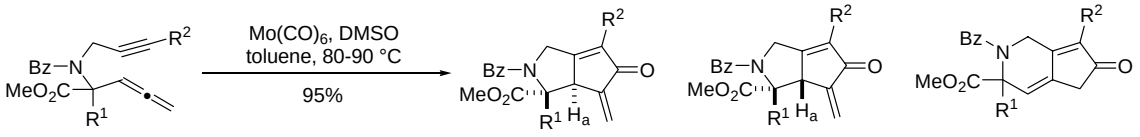


X-ray of 287b

The cyclocarbonylation reaction of allenynes **74c**, **74d** and **74e**, possessing aliphatic side chains was examined next (Scheme 4.32). The alanine-derived allenynes (R^1 = Me) **74c** and **74d** afforded α-alkylidene cyclopentenones with dramatically increased selectivity (14 : 1), and high diastereoselectivity (~10 : 1). The leucine derived allenyne **74e** also reacted selectively with the

proximal double bond to give α-alkylidene cyclopentenones in 5.4 : 1 ratio.

Scheme 4.32 Cyclocarbonylation reaction of allenynes **74c**, **74d** and **74e**.



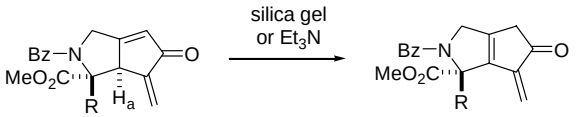
74c R^1 = Me, R^2 = Me	**287c** 81%	**288c** 8%	**289c** 6%
74d R^1 = Me, R^2 = H	**287d** 82%	**288d** 7%	**289d** 6%
74e R^1 = *i*-Bu, R^2 = H	**287e** 74%	**288e** 14%	**289e** 7%
		(**287c** + **288c**) : **289c** = 14 : 1, **287c** : **288c** = 10 : 1[a]	
		(**287d** + **288d**) : **289d**= 14 : 1, **287d** : **288d** = 11 : 1[a]	
		(**287e** + **288e**) : **289e** = 12 : 1, **287e** : **288e** = 5.4 : 1[a]	

[a] Ratios and individual compound yields were determined by integration of the olefin resonances in the ^{1}H NMR spectrum.

The relative stereochemistry of the major products **287c-287e** was initially predicted to be the same as in the phenylalanine case **287b**. However, chromatography of the product mixture from the reaction of **74e** gave a new compound characterized as dienone **290e** possessing a double bond across the ring fusion (Scheme 4.33).[t] Because there was no evidence of compound **290e** being present in the ^{1}H NMR of the crude reaction mixture prior to chromatography, it was assumed that **290e** was result of an isomerization reaction promoted by silica gel. This was later confirmed in a separate experiment by adsorbing the crude reaction mixture onto silica gel for 1 h, followed by elution and collecting the ^{1}H NMR spectrum which showed the presence of this new compound.

[t] The structure of **290e** was assigned based on ^{1}H NMR, ^{13}C NMR, DEPT135 and mass spectral data.

Scheme 4.33 Isomerization of enones **287d**, **287e** and **288b**.



287e R = *i*-Bu
287d R = Me
288b R = Bn

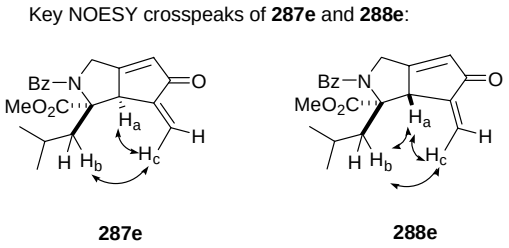
290e R = *i*-Bu
290d R = Me
290b R = Bn

Closer studies revealed that **290e** resulted exclusively from isomerization of the major diastereomer **287e**, while the minor diastereomer was considerably more stable to silica gel. To examine whether this isomerization was acid- or base-promoted, the crude reaction mixture was treated separately to minor excess of AcOH and Et_3N (~10 equiv). While the Et_3N-treated sample displayed rapid isomerization within 1h (as followed by ^1H NMR), the AcOH-treated sample was stable indefinitely. We took advantage of this observation by using 1% acetic acid in the eluting solvent during column chromatography on silica gel, which allowed for isolation of all three enones from the reaction (**287e**, **288e** and **289e**). Then, the enones were separately readsorbed onto silica gel and their spectrum was collected after 1 h. Diastereomer **287e** completely isomerized to **290e** within 1 h (Scheme 4.33), while diastereomer **288e** did not isomerize. Moreover, exposure of **287e** and **288e** to Et_3N led to rapid isomerization of **287e**, and slower isomerization of **288e**. Similarly, the alanine-derived cyclopentenone **287d** isomerizes to **290d** upon treatment with silica gel or Et_3N. It was also shown that the minor diastereomer **288b** in the phenylalanine case isomerizes to **290b**. The new enones **290d**, **290e** and **290b** proved to be highly unstable and decomposed upon storage.[192]

Since the major diasteromer **287b**, from the reaction of the phenylalanine derived allenyne **74b** did not isomerize in a manner like **287e**, we suspected that these two major products may have opposite stereochemistry. The NOESY spectrum of both diastereomers **287e** and **288e** revealed this to be true (Scheme 4.34). The major diastereomer **287e** is the one where

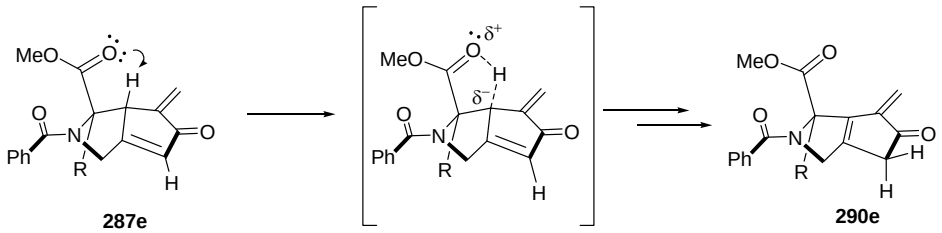
the methyl ester and H_a are *syn*.

Scheme 4.34 Assignment of the relative stereochemistry of **287e** and **288e** based on NOESY correlation spectrum.



Similar observations collected from the reaction of the alanine-derived allenyne **74d** led us to postulate that in all cases where the R^1 is aliphatic, the product with the methyl ester and H_a in *syn* orientation is obtained as the major diastereomer.[u] The facile isomerization of diastereomers **287d**, **287e** and **288b** may be a result of the methyl ester carbonyl serving as an internal Lewis base in labilizing the C-H_a bond as shown in Scheme 4.35.

Scheme 4.35 Ester assistance in the isomerization of **287e** to **290e**.



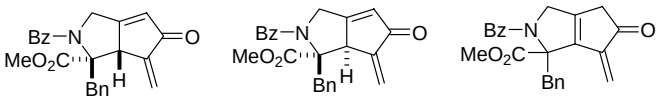
It is noteworthy to mention that the α-alkylidene cyclopentenones **287a**, **288a** and **287c**, **288c** (Schemes 4.30 and 4.32, respectively) did not isomerize under the silica gel conditions. In these cases, the olefin is already tetrasubstituted and may account for this observation.

To rationalize the isomerization of only one cyclopentenone diastereomer, *ab initio* energy calculations were performed comparing the energies of the phenylalanine-derived

[u] Another substrate derived from norvaline (R^1 = *n*-Bu) was shown to give the same diastereoselectivity as alanine and leucine (personal communication from Dr. Stefan Fischer, Curran group).

cyclopentenones **287b**, **288b** and the isomer **290b**. The calculations indicated that the transformation of **288b** to **290b** is favorable by ca. 1.9 kcal/mol, whereas **287b** and **290b** are nearly isoenergetic (Scheme 4.36).[193] Therefore, these calculations support the observed results.

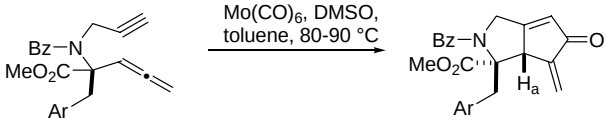
Scheme 4.36 *Ab initio* energy calculations of α-methylene cyclopentenones **287b**, **288b** and **290b**.



287b -26.0 kcal/mol **288b** -23.8 kcal/mol **290b** -25.9 kcal/mol

To determine whether the diastereoselectivity in the cyclocarbonylation reaction of allenynes with aromatic side chains could be increased, we tested four other substrates containing a *p*-OMe-phenyl (**74f**), *p*-F-phenyl (**74g**), 2-thienyl (**74h**) and 3-*N*-Boc-indolyl (**74i**) moiety. These were chosen to provide an electron donating, electron withdrawing and two heterocyclic groups respectively. Interestingly, the cyclocarbonylation reaction of all four substrates proceeded with nearly the same diastereoselectivity (2-3 : 1) as the phenylalanine case giving the product with the aromatic group and H_a in *syn* orientation as the major diastereomers (Scheme 4.37).

Scheme 4.37 Cyclocarbonylation reaction of allenynes **74f-i**.



74f
74g
74h
74i

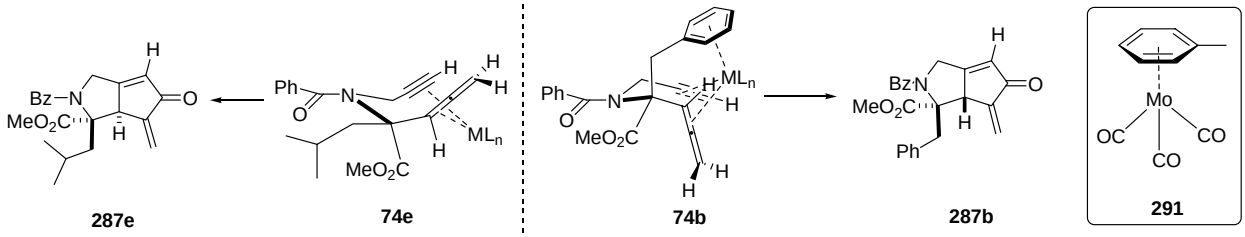
287f Ar = *p*-OMe-Ph 42% dr = 2.3 : 1[a]
287g Ar = *p*-F-Ph 40% dr = 2 : 1[b]
287h Ar = 2-thienyl 39% dr = 2 : 1[a]
287i Ar = 3-*N*-Boc-indolyl 45%, dr = 2.7 : 1[c]

[a] yield of mixture 95% [b] total yield of mixture 76%, yield of major diastereomer determined by NMR.[c] total yield of mixture 77%, yield of major diastereomer determined by NMR.

From these results, it was concluded that opposite diastereomers are favored in the cyclocarbonylation reaction of allenynes with aliphatic vs. aromatic side chains. It is speculated

that the major diastereomer in the aliphatic case (e.g. **74e** leading to **287e**) results from a transition state shown in Scheme 4.38 where the alkyl group is placed in a pseudoequatorial position. In addition, there may be an interaction between the carbonyl oxygen of the methyl ester and the oxophilic molybdenum center contributing to this transition state being favored. The origin of reversed diastereoselectivity in the presence of an aromatic residue in the side chain is subject to speculation. One potential explanation is based on coordination of the aromatic ring in the side chain with the molybdenum center as shown on **74b** (Scheme 4.38). It is well known that $Mo(CO)_6$ readily reacts with various arenes to form [$Mo(\eta^6$-arene$)(CO)_3$] "piano-stool" complexes.[194] Since the $Mo(CO)_6$-mediated cyclocarbonylation reaction takes place in toluene, formation of the octahedral complex [$Mo(\eta^6$-toluene$)(CO)_3$] (**291**) has been proposed as the initial step of the reaction.[195] A recent study has demonstrated that the arene ligands in these molybdenum complexes can be readily exchanged even at rt.[196] Thus, it is conceivable that temporary chelation of the phenyl ring in allenyne **74b** with the molybdenum center as shown in Scheme 4.38 may be responsible for the stereochemistry observed in the major diastereomer **287b**.

Scheme 4.38 Arene complexation rationale for the diastereoselectivity in the cyclocarbonylation reaction.

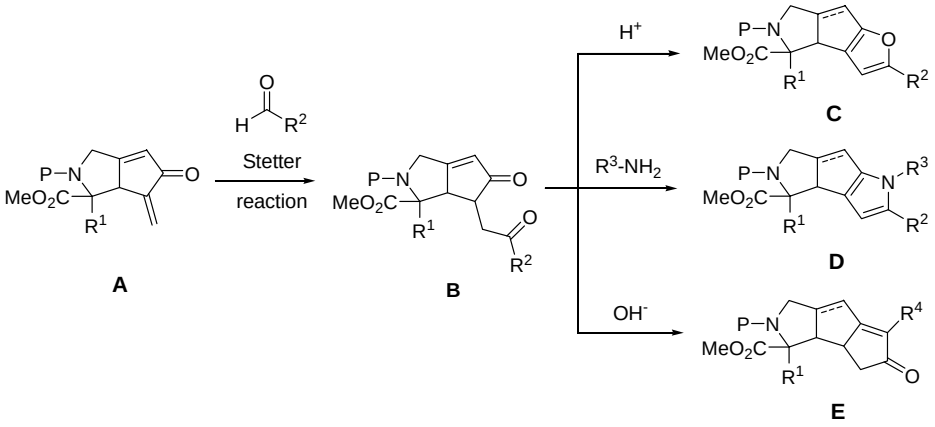


4.5 Diversification of α-Alkylidene Cyclopentenones

4.5.1 Studies Towards the Synthesis of Tricyclic Pyrroles

Although the amino-ester derived α-alkylidene cyclopentenones could potentially serve as useful tools to study biological systems, we were somewhat concerned with the reactivity of the exocyclic enone moiety towards nucleophilic reagents, which may lead to non-specific alkylation of biomolecules. It was reasoned that the reactivity of the enone could instead be utilized in various Michael-type additions to increase the molecular complexity of the newly obtained cyclopentenones.[197] More specifically, umpolung[198] addition of an aldehyde to the enone via a Stetter reaction would yield a 1,4-diketone **B** resulting in increase of molecular complexity (Scheme 4.39).[199, 200] Moreover, this 1,4-dicarbonyl moiety is synthetically versatile and could, in principle, be utilized in a Paal-Knorr reaction to afford furan **C** under acidic conditions or pyrrole **D** in presence of an amine.[201, 202] Additionally, aldol condensation was envisioned under basic conditions, affording enone **E** (Scheme 4.39).[203]

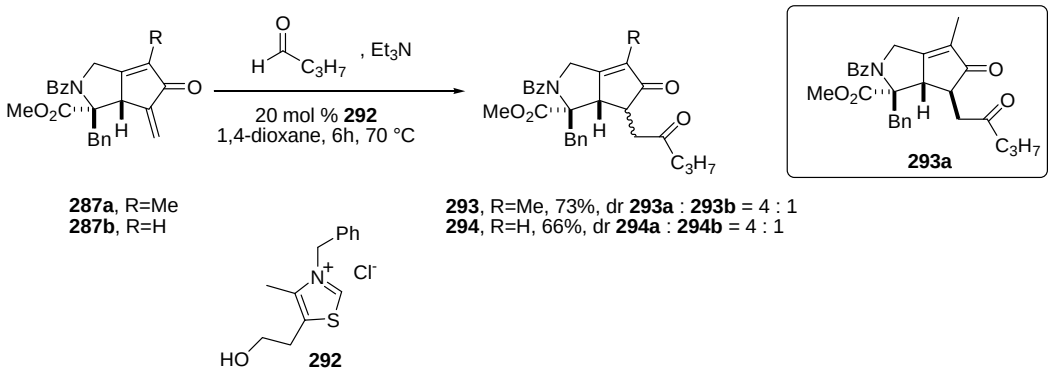
Scheme 4.39 Diversification potential of α-alkylidene cyclopentenones.



We were motivated to first examine the formation of pyrroles **D** for three reasons: (1) multicomponent processes involving a Stetter/Paal-Knorr reaction sequence have been utilized previously for the synthesis of functionalized pyrroles;[204] (2) an additional diversification site could be easily introduced by the preparation of pyrrole by using a variety of amines (R^3-NH_2); and (3) a plethora of biologically interesting compounds from natural and synthetic origin possess pyrroles as part of their substructure thus it is presumed that these compounds will be useful as potential biological probes.[205]

To this end, the conversion of **287a** and **287b** to 1,4-diketones was explored using a Stetter reaction protocol reported by Tius.[206] Diversifications were performed only with phenylalanine derived α-methylene cyclopentenones **287a** and **287b** since the major diastereomers **287d** and **287e** (from the alanine and leucine derived substrates, respectively) isomerize under basic conditions needed for the Stetter reaction.[v] Treatment of **287a** to butyraldehyde, Et_3N and thiazolium salt **292** in 1,4-dioxane for 6h at 70 °C resulted in the Stetter product **293** in 73% yield as a 4 : 1 mixture of diastereomers.

Scheme 4.40 Stetter reaction of **287a** and **287b** with butyraldehyde.



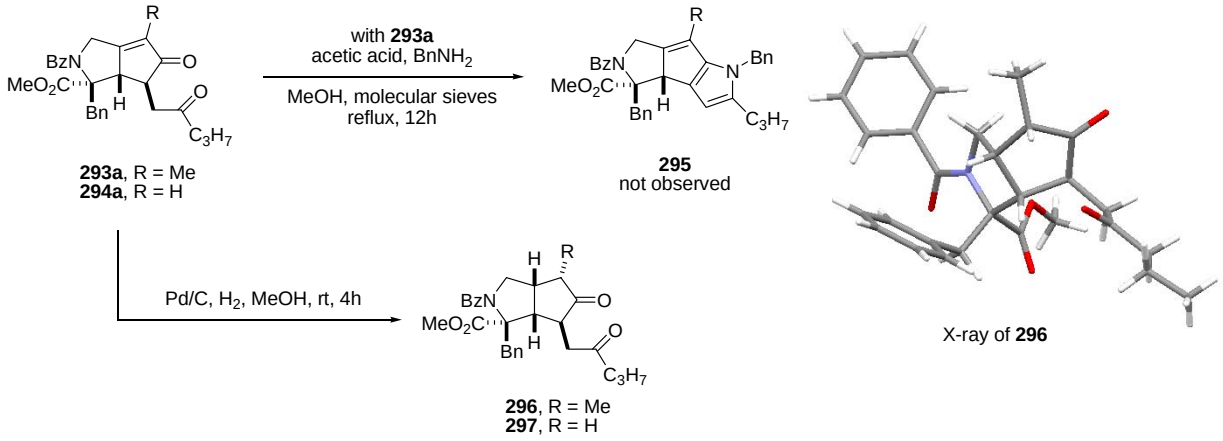
The major diastereomer **293a** selectively precipitates from an EtOAc/hexanes solution of the

[v] Treatment of **287d** and **287e** to the Stetter reaction conditions resulted mainly in decomposition and very low yields of 1,4-diketone.

crude mixture after workup and can be easily isolated in this manner. The relative stereochemistry of **293a** was subsequently assigned by X-ray crystallography of the reduced product (**296**, Scheme 4.41). Cyclopentenone **287b** was also submitted to the same reaction conditions to give a 66% yield of product **294** with identical diastereoselectivity.

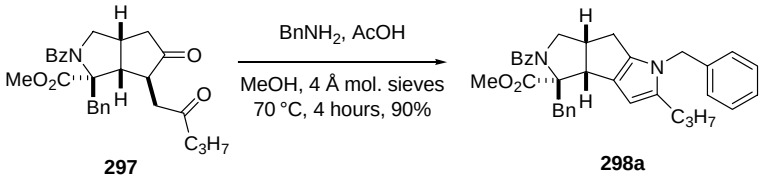
A single attempt to convert **293a** to pyrrole **295** using a Paal-Knorr protocol was unsuccessful. It was reasoned that the strained nature of the product **295** was problematic and that reduction of the double bond in **293a** would alleviate some of this strain. Reduction of cyclopentenones **293a** and **294a** to give single diastereomer of cyclopentanones **296** and **297**, respectively, was effected using Pd/C, H_2 (Scheme 4.41).[207] The structure and relative stereochemistry of **296** was assigned by X-ray crystallography, confirming that reduction occurred from the convex face to give the *cis*-fused bicycle (Appendix E).

Scheme 4.41 Attempted pyrrole synthesis and reduction of **205a** and **206a**.



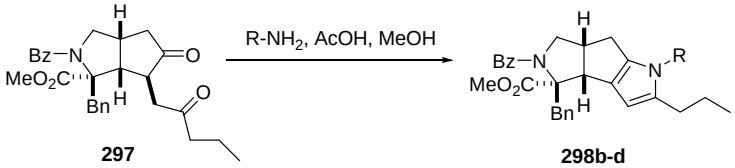
When **297** was treated with benzylamine and AcOH in methanol in the presence of molecular sieves at 70 °C, it afforded tricyclic N-benzyl pyrrole **298a** in 90% yield (Scheme 4.42).

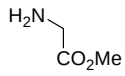
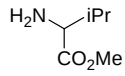
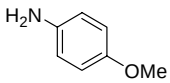
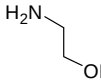
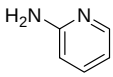
Scheme 4.42 Synthesis of pyrrole **298a**.



Other amines were tested in this pyrrole forming reaction to determine its scope and the results are shown in Table 4.4. The reaction with an amino acid derivative was first attempted, since incorporation of a second amino acid would be an interesting diversification feature. The soluble glycine-methyl ester hydrochloride participated in the reaction and gave pyrrole **298b** in 70% yield (entry 1, Table 4.4) but the more sterically hindered valine methyl ester, failed to participate under the same reaction conditions (entry 2). Next the aromatic amine, anisidine was used (entry 3) and the reaction proceeded to give **298c** in 85% yield. Similarly, ethanolamine gave **298d** in 76% yield (entry 4). Finally, 2-amino pyridine gave none of the desired product (entry 5).

Table 4.4 Preparation of tricyclic pyrroles from **297**.

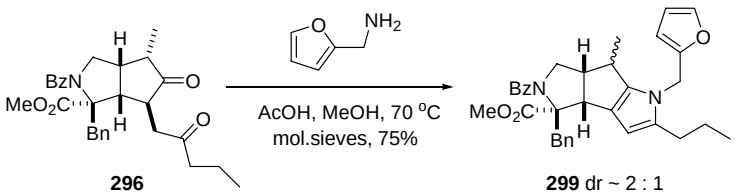


Entry	Amine	Temp.	Time(h)	Product	Yield (%)
1		70 °C	4	**298b**	70[a]
2		70 °C	4		no reaction[a]
3		60 °C	2	**298c**	85[a]
4		70 °C	1	**298d**	76[b]
5		70 °C	4		no reaction[a]

[a] R-NH_2 (5 equiv.), AcOH (5 equiv.); [b] R-NH_2 (10 equiv.), AcOH (8 equiv.).

Based upon this small sampling of amines, aliphatic amines of type H_2N-CH_2-R appear to be the best substrates for the pyrrole formation since substitution next to the amine results in complete recovery of the starting material likely due to sterics. Of the two aromatic amines tested, 2-amino-pyridine was relatively unreactive which can be attributed to the presence of second basic nitrogen in the molecule proximal to the reactive primary amine. Formation of a pyrrole from a single diastereomer of the methyl substituted diketone **296** using furfuryl amine proceeded to give the product **299** in 75% yield as a mixture of two diastereomers in 2 : 1 ratio (Scheme 4.43). The diastereomers are likely a result of epimerization of the stereocenter bearing the methyl group. The epimerization of this stereocenter in the pyrrole formation was unfortunate and deemed uncontrollable under the acidic reaction conditions.

Scheme 4.43 Formation of pyrrole **296** as a diastereomeric mixture.

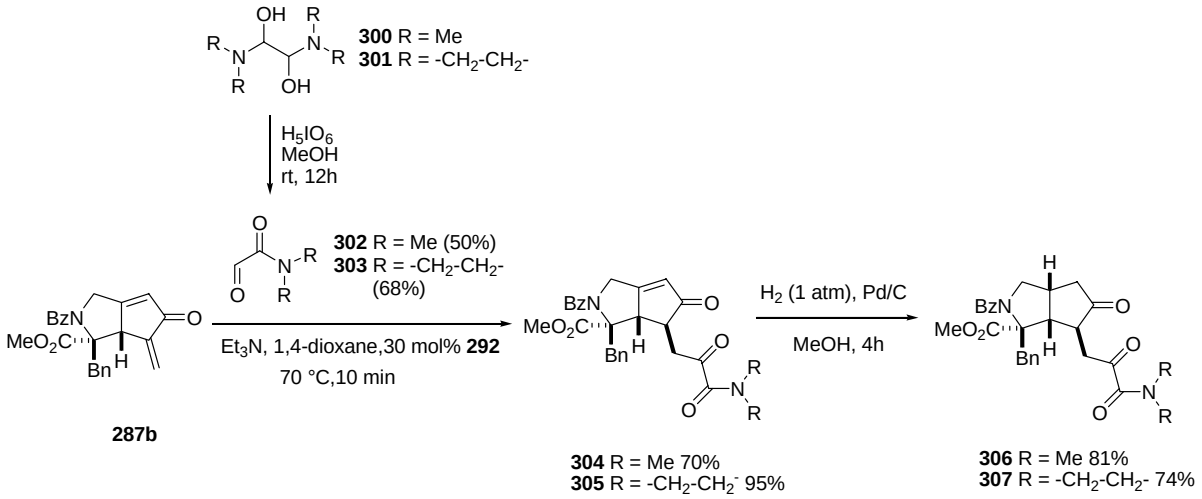


296 **299** dr ~ 2 : 1

Unfortunately, the new alkyl pyrroles **298a-d** exhibited a considerable tendency to decompose when stored neat or open to the atmosphere, rendering them less than desirable for biological assays. This decomposition was initially only qualitatively assessed and later confirmed by an NMR study performed by Dr. Stefan Fischer (Scheme 4.47, *vide infra*). Thus, stabilizing the pyrrole moiety by introducing an electron withdrawing substituent was explored. An acyl substituent attached to the 2 position of the pyrrole seemed like a plausible solution since this group could be introduced via the Stetter reaction using 1,4-addition of glyoxylamides.[208] Two glyoxylamides from dimethyl amine (**302**) and pyrrolidine (**303**) were prepared by oxidative cleavage of the corresponding tartaric acid amides **300** and **301** with

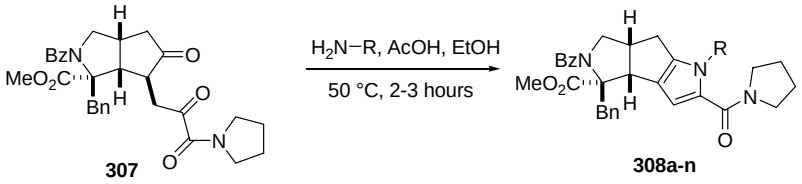
periodic acid (H_5IO_6).[209] These highly electrophilic aldehydes both participated in the Stetter reaction with **287b** when 30 mol % of the thiazolium salt catalyst **292** was used, affording the products **304** and **305**, respectively in 10 min as single diastereomers (Scheme 4.44).

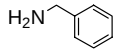
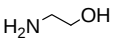
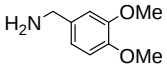
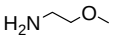
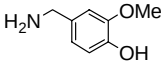
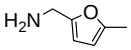
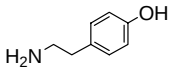
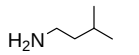
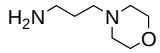
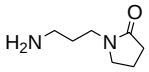
Scheme 4.44 Addition of glyoxylamides to **287b** and subsequent reduction.



It is noteworthy that subsequent to Stetter's original report in 1987, there are no additional examples in the literature that utilize this 1,4-addition of glyoxylamides. It appears that this reaction is a viable entry into the α-keto-amide moiety that is both synthetically useful,[210] and present in biologically active molecules.[211] Next, the double bond of enones **304** and **305** was reduced giving **306** and **307** in 81% and 74% yield, respectively. A slightly modified protocol for pyrrole formation was developed using 3 equivalents of the amine, excess acetic acid and ethanol as solvent. Heating of **307** at 50 °C for 2-3 hours generally gave complete conversion to pyrroles **308a-n**, which were isolated following an acidic workup and short column chromatography purification (Table 4.5). This reaction allows direct access to the pyrrole-2-carboxamide moiety which has not been previously synthesized via a Paal-Knorr synthesis.[212]

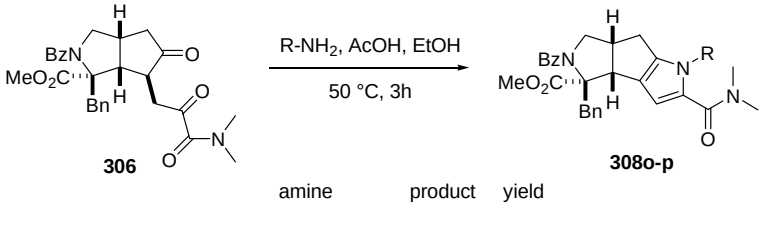
Table 4.5 Preparation of a 14-member library of acyl-pyrroles from **307**.



amine	product	yield (%)	amine	product	yield (%)
	**308a**	80%		**308h**	70%
	**308b**	88%		**308i**	93%
	**308c**	72%		**308j**	89%
	**308d**	85%		**308k**	69%
	**308e**	63%		**308l**	79%
	**308f**	39%		**308m**	95%
	**308g**	81%	NH_3	**308n**	64%

Two pyrroles were also prepared from diketone **306** using the same conditions (Scheme 4.45).

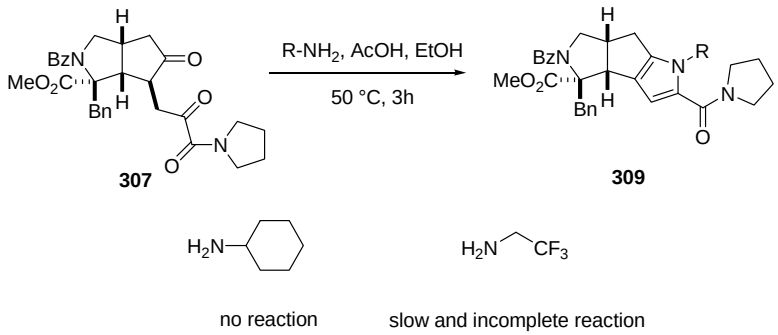
Scheme 4.45 Preparation of pyrroles from diketone **306**.



The most suitable aliphatic amines for the Paal-Knorr reaction do not have branching at the position alpha to the amine since cyclohexylamine failed to give any product (Scheme 4.46). When 2,2,2-trifluoroethylamine was used the reaction rate was significantly retarded, and the

reaction failed to go to completion, which is attributed to the electron withdrawing effect of the trfluoromethyl group. Increased heating drives the reaction further but results in impurities (Scheme 4.46).

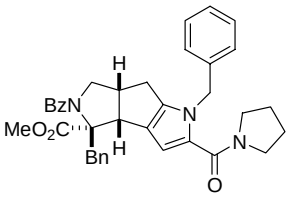
Scheme 4.46 Unsuccessful examples of pyrrole formation.

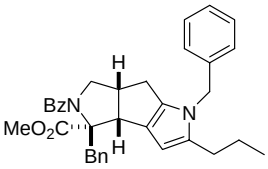


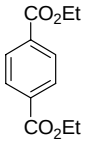
To determine whether the newly formed acyl pyrroles **308a-p** are more stable than the alkyl-pyrroles as initially hypothesized, we performed an NMR experiment where an alkyl and acyl-pyrrole of benzyl amine were placed in an NMR tube with a standard (*p*-phthalic acid ethyl ester) in d_6-DMSO.[w] The sample was kept at rt in a sealed NMR tube. Monitoring of the ^{1}H NMR of the sample over a period of 60 days, revealed that the alkyl-pyrrole **298a** had been reduced to half of its initial amount, whereas the acyl-pyrrole **308a** remained virtually unchanged (Scheme 4.47).

[w] NMR study was performed by Dr. Stefan Fischer (Prof. Curran group).

Scheme 4.47 Comparison of the stability between alkyl-pyrrole **298a** and acyl-pyrrole **308a**.





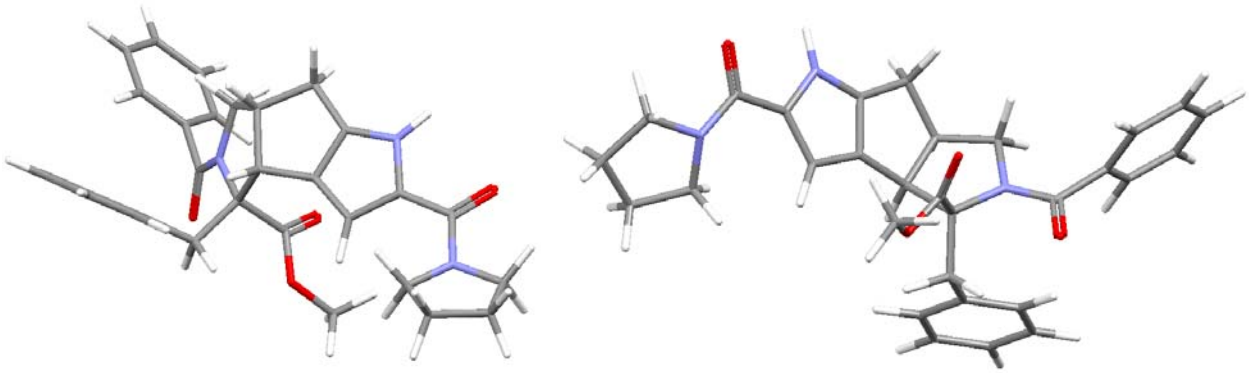


	acyl pyrrole (**308a**)	alkyl pyrrole (**298a**)	standard
initial ratio	4.9	1.9	
ratio after 60 days[a]	4.8	3.8	

[a]The ratios shown are standard / compound. The sample was kept in an NMR tube in d^6 DMSO at rt under N_2 atmosphere.

Since compounds **308a-p** represent a new class of angularly fused tricyclic pyrroles with high molecular complexity, we became interested in synthesizing a discovery library for biological evaluation. To obtain a better understanding of the three-dimensional structure of the pyrroles, energy minimization was performed on the simplest pyrrole member **308n** (Figure 4.1).[x]

Figure 4.1 Two different stereoviews (top and bottom) of the energy-minimized model of **308n**.

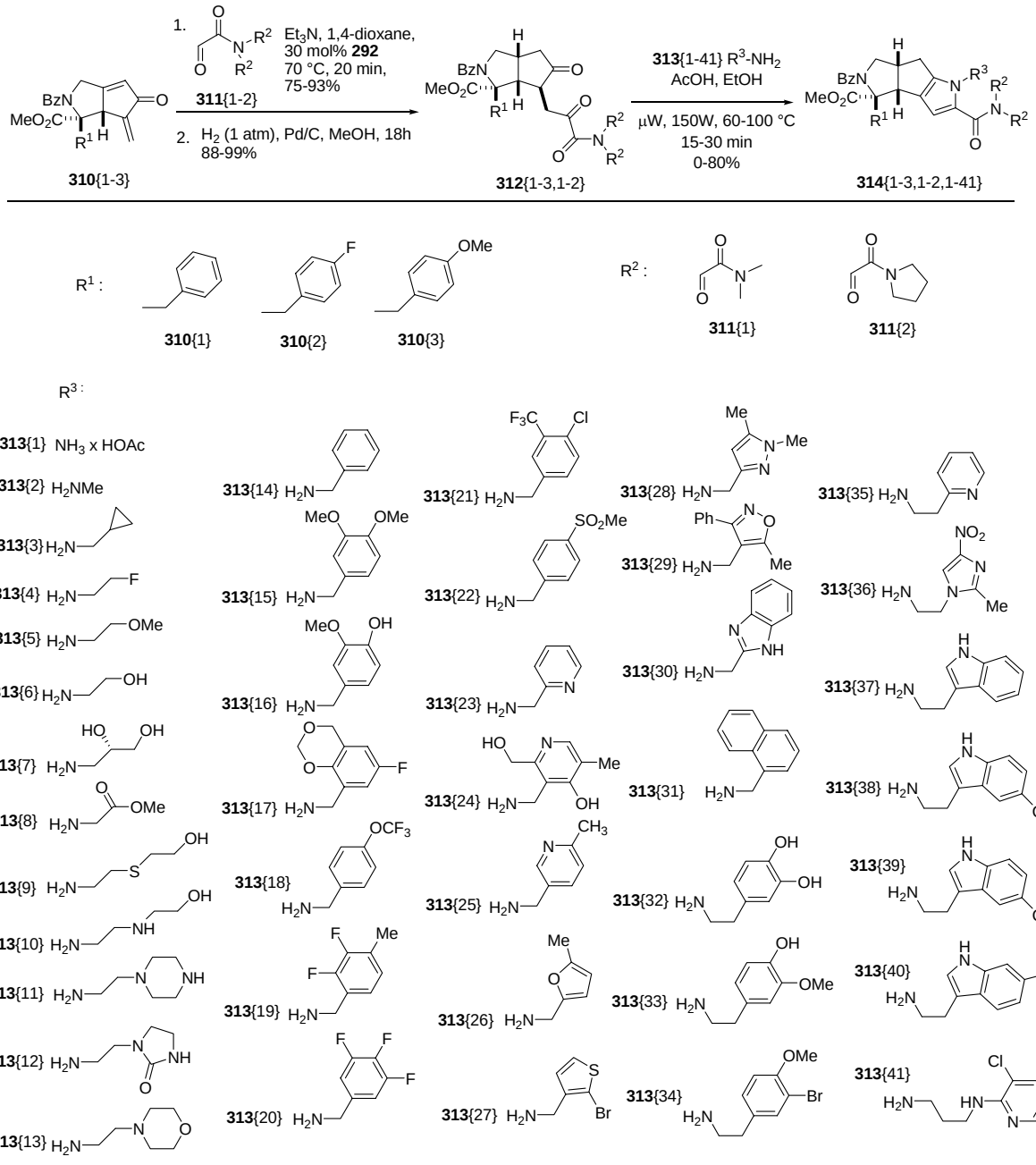


[x] Energy minimization was performed with Cache Worksystem Pro. version 6.1.10. First, global minimum search was performed using MM3 parameters, followed by energy minimization using AM1 paramaters.

4.5.2 Synthesis of a Library of Tricyclic Pyrroles

The methodology involving a cyclocarbonylation/Stetter/Paal-Knorr reaction sequence that allows the synthesis of tricyclic pyrrole-2-carboxamides **308a-p** has been applied to library synthesis within the University of Pittsburgh Center for Chemical Methodologies and Library Development (UPCMLD).[213] The library design is based on three points of diversity: (1) amino acid side chain R^1; (2) glyoxylamide used in the Stetter reaction (R^2); and (3) amine used in the pyrrole formation (R^3) (Scheme 4.48). While studying the $Mo(CO)_6$-mediated cyclocarbonylation reaction of allenynes, it was demonstrated that only amino-esters containing an aromatic group in the side chain afford a stable diastereomer in the reaction that can be taken the subsequent steps. Therefore the amino-ester building blocks were a limited source of *front-end* diversity and were chosen to contain a benzyl, *p*-fluorobenzyl and *p*-methoxybenzyl group (**310**{1-3}). Similarly, the library was designed using only two glyoxylamide building blocks (N,N-dimethyl **311**{1} and pyrolidinyl **311**{2}). Since the pyrrole formation is used as a last step in the synthesis, the choice of the amine was used as a greatest source of appendage diversity. A subset of 41 amines **313**{1-41} was selected from a larger set of 300 primary amines, based on calculating properties such as molecular weight, clogP(octanol/water) of the product, cost and diversity (a range of aliphatic, heteroatom-containing aliphatic, aromatic and heteroaromatic amines were included).

Scheme 4.48 Synthesis of a library of tricyclic pyrroles.



Using the previously discussed cyclocarbonylation protocol, α-alkylidene cyclopentenones **310**{1-3} were obtained in 40-50% yield for the diastereomer shown (all reactions subsequent to this step were performed by the staff at the UPCMLD). Next, performing six Stetter reactions in parallel using a Radley's carousel station, followed by reduction of the double bond afforded

diketones **312**{1-3,1-2} in yields ranging between 75-93% and 88-99% yields for each step, respectively. Using an optimized microwave reaction protocol for the pyrrole formation (150 W, 80 °C, 15 min),[214] the six diketones were reacted with the 41 amines outlined in Scheme 4.48. Of the possible 246 reactions, 210 were performed affording 172 pyrroles **314**{1-3,1-2,1-41} in average yield of 53% after purification. The average amount of each library member obtained was 14.7 mg, in average purity of 94% (determined by LC/MS analysis with UV detection at 210, 220, 240 nm).

Computational prediction of pharmacologically relevant physico-chemical properties of small molecule libraries is important in characterizing their potential to to serve as biological tools or drug candidates. Physico-chemical properties for the tricyclic pyrrole library have been calculated using QikProp 2.1[215] and are outlined in Table 4.6.[y] The majority of molecular descriptors listed (molecular weight, molecular volume, clogP, number of hydrogen bond donors and acceptors, number of primary metabolites, etc.) fall within the range of values for most known drugs (first column). The distribution of predicted physico-chemical properties can also be used to to characterize the diversity of the library members. As can be seen from Figure 4.2, the pyrroles display broad distribution of molecular weights (472-763 g/mol), clogP values (3.3-8.9) and number of hydrogen bond acceptors (7-13). Less distribution is seen in the number of hydrogen bond donors (0-2). The number of rotatable bonds ranges from 5-12, whereas FISA (hydrophilic component of the solvent accessible surface area) ranges between 15.4-153.1 $Å^2$.

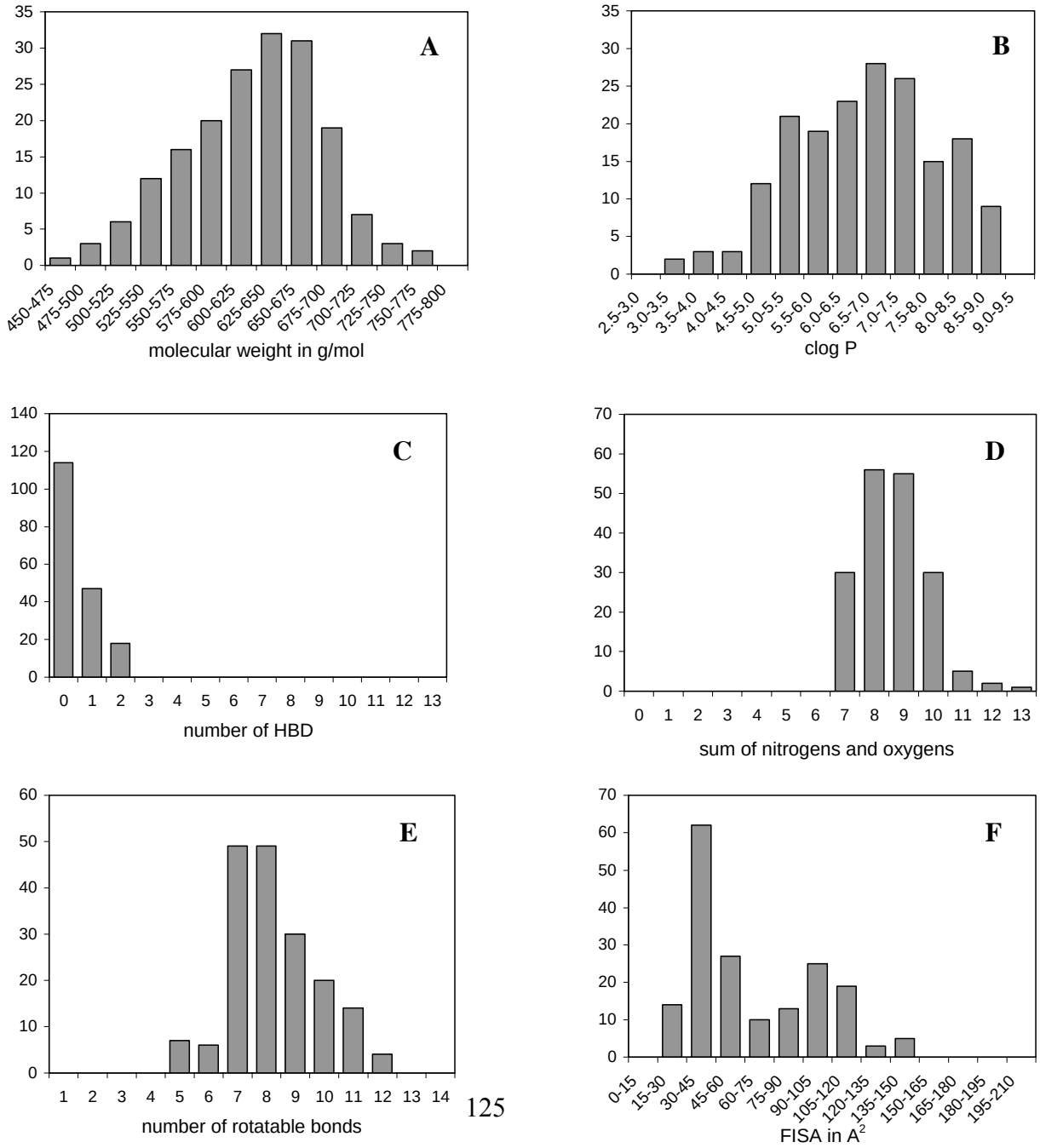
[y] Calculations were performed by Dr. Stefan Werner.

Table 4.6 Computational analysis of molecular descriptors for the pyrroles **314**{1-3,1-2,1-41} using QikProp 2.1 (table reproduced with permission from Dr. Stefan Werner).

Parameter	Range for 95% of all Drugs	Average ± Standard Deviation for 179 Pyrroles	Number of Compounds out of Range
molecular weight (g/mol)	130 to 725	620±57	5
molecular volume ($Å^3$)[a]	500 to 2000	1800±100	3
FISA ($Å^2$)[b]	7 to 330	64±33	0
number of rotatable bonds[c]	0 to 15	8.3±1.5	0
number of hydrogen bond donors[d]	0 to 6	0.5±0.7	0
number of hydrogen bond acceptors[e]	2 to 20	9.6±1.3	0
logP (octanol/water)	-2 to 6	6.6±1.3	119
logKhsa (serum protein binding)	-1.5 to 1.2	1.2±0.5	94
number of primary metabolites	1 to 8	5.0±1.3	6

[a] total solvent accessible volume, using a probe with a 1.4 Å radius. [b] hydrophilic component of the solvent accessible surface area (SASA), using a probe with a 1.4 Å radius (SASA on N, O and attached H). [c] non-trivial (not CX_3), non-hindered (not alkene, amide, small ring). [d] estimated number of hydrogen bonds that would be donated by the solute from water molecules in an aqueous solution. [e] estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution.

Figure 4.2 Distribution for physico-chemical parameters: molecular weight (A), log of the octanol/water partition coefficient (logP) (B), number of hydrogen donor bonds (HBD) (C), sum of nitrogen and oxygen atoms (D) and for the number of rotatable bonds (E) and the hydrophilic component of the solvent accessible surface area (FISA) (F); calculated for the 178 pyrroles **314**{1-3,1-2,1-41} using QikProp 2.1 (reproduced with permission from Dr. Stefan Werner)



4.5.3 Biological Evaluation of Tricyclic Pyrroles

The library of tricyclic pyrroles has been made available to a broad range of collaborators via the biological outreach program at the UPCMLD (Figure 4.3).

Figure 4.3 List of assays performed on the tricyclic pyrroles **314**{1-3,1-2,1-41}.

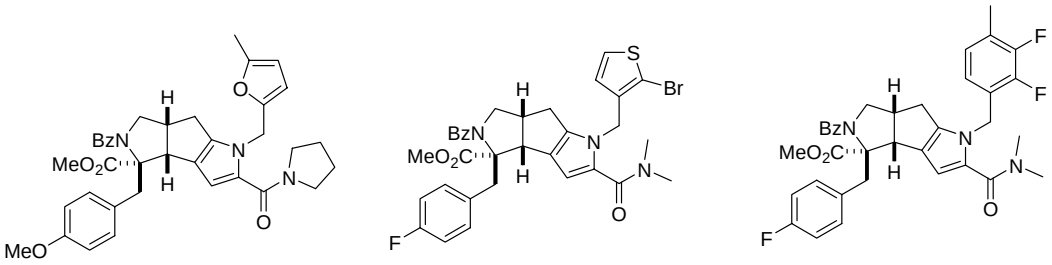
Testing facility	Assay type	Testing facility	Assay type
JMI Labs	antibacterial assays	NIH-Chemical Genomics Center	various assays:
Southern Research Institute	antiviral assays:		Prx2 sOGT P450-cyp1a2 GR-EFC
	influenza tacaribe west nile ponta toro denga yellow fever herpes-HSV, VZV, HSV-1 tuberculosis hepatitis C and B	National Cancer Institute	60 cell-line cytotoxicity assays HIV protease inhibition
		ChemBank (Broad Institute-Harvard University)	various assays:
PDSP (Phychoactive Drug Screening Program)	40-50 assays		CREB reporter assay NOX superoxide generation yeast growth modification assay

In addition, members of this library have been identified as inhibitors of cytoplasmic dynein by Prof. Day's lab (University of Pittsburgh) and as inhibitors of human mitogen-activated protein kinase phosphatase-1 (MKP-1) by Prof. Lazo's lab (University of Pittsburgh).

Cytoplasmic dynein is an ATPase motor protein involved in multiple cellular processes.[216] For example, dynein provides force for nuclear envelope breakdown, formation in the mitotic spindle and chromosomal segregation.[216d] In addition, dynein is responsible for intracellular transport of organelles, protein complexes etc. Small molecules that interfere with dynein activity can be used to study its important functions in the cell. Unfortunately, there are only a few known inhibitors of dynein, characterized with low activity and/or lack of specificity.[217] Therefore, the discovery of structurally novel inhibitors of dynein is an important area of research. Using a cell-based phenotypic assay, Day and coworkers have identified

tricyclic pyrrole **314**{3,2,26} (Figure 4.4) as an inhibitor of cytoplasmic dynein activity.[218] Concentration-dependent experiments have shown that **314**{3,2,26} uncompetitively inhibits dynein's ATPase activity with IC_{50} value of 2.0 μM.[z] These very encouraging results have prompted further studies into the mechanism of action of **314**{3,2,26}.

Figure 4.4 Structures of bioactive tricyclic pyrroles.



314{3,2,26}
dynein ATPase inhibitor
IC_{50} = 2.0 μM

314{2,1,27}
MKP-1 inhibitor
IC_{50} = 8.0 μM

314{2,1,19}
MKP-1 inhibitor
IC_{50} = 8.3 μM

Mitogen-activated protein kinases (MAPK) are important cellular proteins that act as effectors of various growth factors, stress detectors and drug sensors in the cell.[219] Their function is regulated by a number of mitogen-activated protein kinase phosphatases (MKPs). MKP-1 is a dual specificity phosphatase, meaning it is capable of dephosphorylating both phosphotyrosine and phosphothreonine residues on a same protein substrate. Furthermore, MKP-1 expression is elevated in prostate, breast, gastric and renal cancers.[220] Therefore, MKP-1 is an important target for inhibition by small molecules in order to further understand its function and potentially generate lead structures for cancer chemotherapy. However, MKP-1 has evaded inhibition by small molecules and the few known inhibitors are not potent and/or not selective.[221] Lazo and coworkers have screened 172 members of the tricyclic pyrrole library in an effort to identify novel inhibitors of MKP-1.[222] The study resulted in identification of 22 compounds with IC_{50}

[z] Biological tests were performed by Mr. Guangyu Zhu under the supervision of Professor Billy W. Day.

values lower than 30 μM.[aa] Most notable were library members **314**{2,1,27} and **314**{2,1,19} (Figure 5.4) with IC_{50} values of 8.0 μM and 8.3 μM, respectively. Both pyrroles showed high selectivity for MKP-1 over other phosphatases, including the dual-specificity phosphatase MKP-3. Importantly, the pyrroles **314**{2,1,27} and **314**{2,1,19} were identified as the most potent inhibitors of MKP-1 from a broader screen of over 65,000 compounds from the NIH repository (http://pubchem.ncbi.nlm.nih.gov/assay/assay.cgi?aid=374). These promising results have prompted further studies into the mechanism of action of **314**{2,1,27} and **314**{2,1,19} and development of more potent analogues.

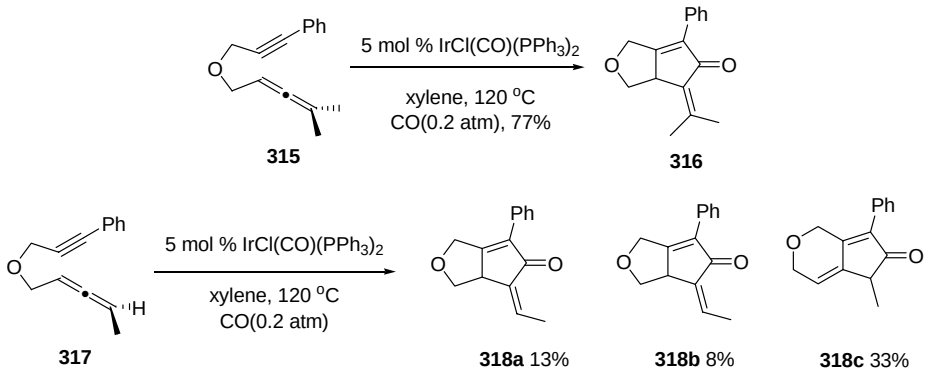
[aa] Biological tests were performed by Mr. John J. Skoko under the supervision of Professor John S. Lazo.

4.6 Synthesis of α-Alkylidene Cyclopentenones via a Rhodium(I)-Catalyzed Allenic Cyclocarbonylation Reaction

During our investigations of the $Mo(CO)_6$-mediated cyclocarbonylation reaction of amino-ester tethered allenynes, a number of issues were encountered: (1) the reaction was not entirely selective for the proximal double bond of the allene, affording up to 20% of the undesired 4-alkylidene cyclopentenone particularly in the reaction of sterically encumbered amino acids; (2) the desired α-alkylidene cyclopentenones were obtained as mixtures of diastereomers with unpredictable diastereoselectivity depending on the nature of the amino-acid side chain (Schemes 4.30 and 4.32); and (3) because $Mo(CO)_6$ is used in stoichiometric amount, purification issues were encountered upon scale-up during library synthesis. In addition, generating large amounts of unidentified molybdenum waste posed an environmental concern. However, the amino-acid derived α-alkylidene cyclopentenones obtained via this protocol proved extremely useful in the synthesis of a library of tricyclic pyrroles and can potentially be used in other DOS applications. For these reasons, we have recently begun investigating the possibility to conduct a catalytic cyclocarbonylation reaction selective for the proximal double bond of the allene.

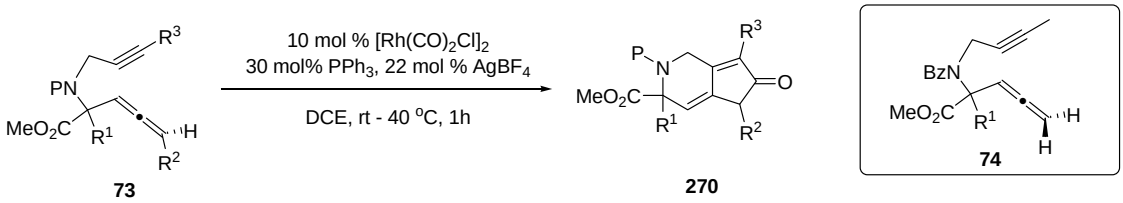
In 2003, Shibata reported that $IrCl(CO)(PPh_3)_2$ (Vaska's complex) selectively catalyzes the formation of α-alkylidene cyclopentenone **316** from trisubstituted allenyne **315**.[223] It was demonstrated that the course of the reaction with the proximal double bond of the allene is sterically influenced by the substitution pattern of the allene, since disubstituted substrate **317** gave a mixture of cyclocarbonylation products with **318c** dominating.

Scheme 4.49 Ir(I)-catalyzed cyclocarbonylation reaction by Shibata.



In the course of the study on developing conditions for preparation of 4-alkylidene cyclopentenones, a similar trend was observed when using Ir(I)-catalysts (Table 4.1, in Section 4.2). Subsequently, it was shown that an *in situ* prepared catalyst by sequential addition of PPh_3 and $AgBF_4$ to $[Rh(CO)_2Cl]_2$ exhibits remarkable reactivity in promoting the reaction with the distal double bond of the allene (Scheme 4.50, for details see Section 4.2).

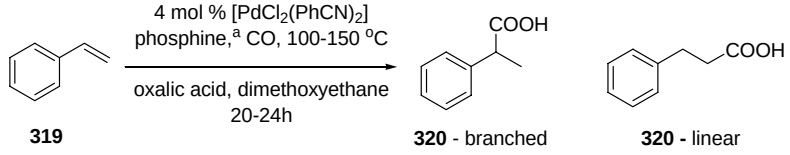
Scheme 4.50 Rh(I) catalyzed formation of 4-alkylidene cyclopentenones.



We became interested whether the double bond selectivity of this Rh(I)-catalyzed allenic cyclocarbonylation reaction can be reversed by using diphosphine ligands. It is generally accepted that diphosphine ligands can have a profound effect on various transition metal-catalyzed reactions. Most often this effect is on the rate and observed yield of the reaction, however there are some instances where ligands have affected the formation of structurally different products. Recent reviews by van Leeuwen and coworkers have summarized and related such effects to the natural bite angle of diphosphines.[224] One compelling example is the ligand effect on the Pd-catalyzed hydroxycarbonylation reaction of styrene, where formation of a

branched and linear carboxylic acid is possible. Van Leeuwen and coworkers found that use of PPh_3 leads to predominant formation of the branched product. As shown in Table 4.7, switching to bidentate phosphine ligands leads to gradual reversal of the selectivity, and with dppb (1,4-bis(diphenylphosphino)butane) the linear product is favored. In addition to the product ratios, the efficiency of the reaction was also dependent on the nature of the diphosphine ligand (see conversion column in Table 4.7). The authors associated these effects to the increasing bite angle of the diphosphine ligand.

Table 4.7 Effect of the phosphine ligand on the Pd-catalyzed hydroxycarbonylation of styrene reported by van Leeuwen.



319 **320** - branched **320 -** linear

phosphine	bite angle (deg)	% conversion	branched : linear ratio
PPh_3		96	84 : 16
dppe	78	5	47 : 53
dppp	86	28	23 : 77
BINAP	93	42	30 : 70
dppb	98	95	17 : 83

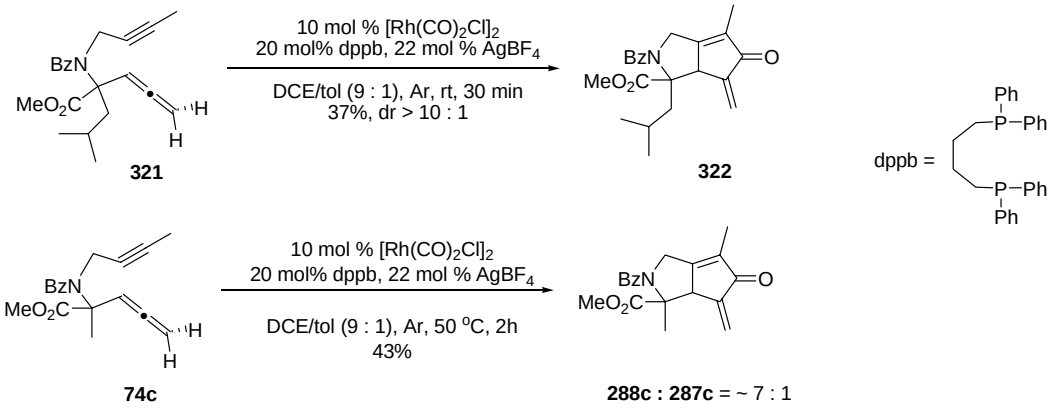
[a] P : Pd ratio = 4 : 1

To examine whether double-bond selectivity in the Rh(I)-catalyzed allenic cyclocarbonylation reaction can be influenced with diphosphine ligands, terminally unsubstituted allenes **74** (Scheme 4.50) were chosen to minimize steric bias, and avoid formation of *E* and *Z* isomers in the reaction. Preliminary results of this investigation are presented here.

A preliminary screen of common bidentate phosphine ligands (dppm, dppe, BINAP and dppb) was first preformed. It was found that the reactive species prepared by addition of dppb to 10 mol % $[Rh(CO)_2Cl]_2$ followed by $AgBF_4$ (in 2 : 1 : 2 molar ratio) effected the transformation

of **321** to **322** in 37 % yield when the reaction was performed under Ar atmosphere (Scheme 4.51).[bb] In this experiment **322** was formed with high diastereoselectivity (>10 : 1) and high regioselectivity, since only trace amounts of the 4-alkylidene cyclopentenone were observed. Similarly, the methyl-substituted allenyne **74c**, resulted in selective formation of α-alkylidene cyclopentenones in 43% yield (7 : 1 diastereomeric ratio). Since both reactions were performed under Ar atmosphere, the yield around 40% suggested that the reaction is stoichiometric in Rh(I), and the carbon monoxide incorporated in the products results from the starting catalyst (10 mol % $[Rh(CO)_2Cl]_2$ contains 40 mol % CO).

Scheme 4.51 Rh(I)-mediated formation of α-alkylidene cyclopentenones.



Although these results were encouraging, attempts to perform the reaction catalytically under CO atmosphere (1 atm, balloon pressure) gave only recovered starting material and no cyclocarbonylation products if CO atmosphere is introduced to the system prior to addition of the allenyne. Furthermore, reproducibility issues were encountered, mainly due to the multiple components required for preparation of the active Rh-species.[cc] It was also found that the

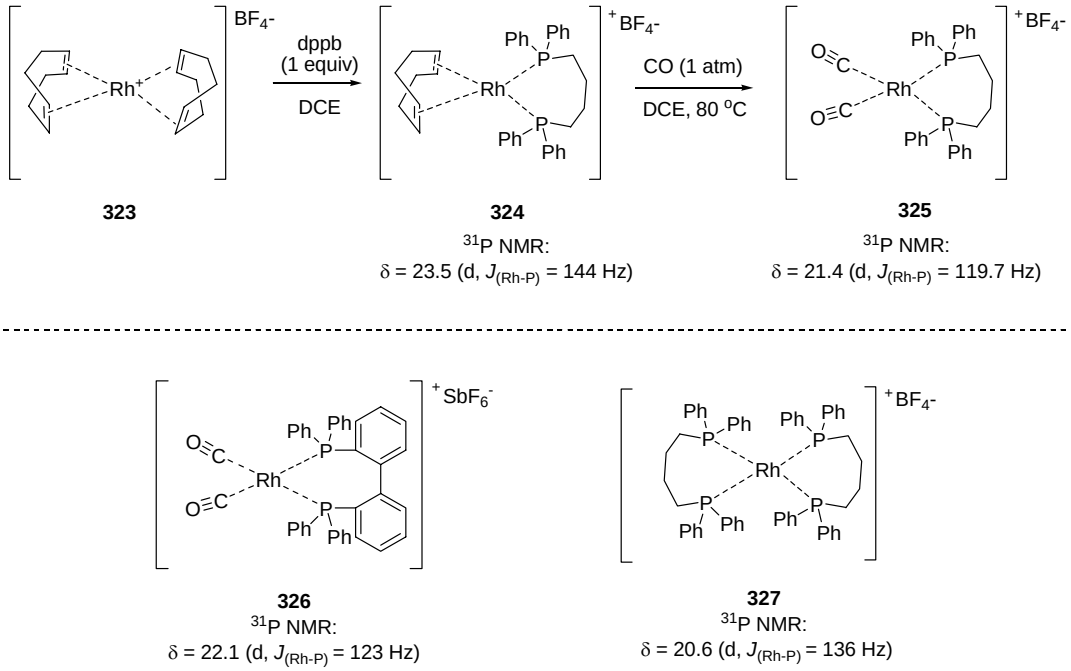
[bb] Use of dppm and dppe in the same experiment gave predominantly the 4-alkylidene cyclopentenone, while BINAP unselectively gave mixtures of products in a very sluggish reaction.

[cc] In particular, the amount of dppb relative to $[Rh(CO)_2Cl]_2$ proved critical for obtaining high regio- and diastereoselectivity. Decreasing the amount of dppb below 20 mol% led to unselective reaction with both double bonds.

reactivity of the species prepared *in situ* depends on the commercial source of $[Rh(CO)_2Cl]_2$. Based on the stoichiometry of all components in the initial experiment, it was hypothesized that the active Rh(I)-species formed *in situ* has a general formula $[Rh(CO)_2dppb]BF_4$ (**325**). To resolve the reproducibility issues, a more convenient route to prepare and identify this complex was sought (to our knowledge, this compound has not been characterized before). To this end, commercially available $[Rh(cod)_2]BF_4$ (**323**) was treated with dppb (1 equiv) in DCE presumably affording the known yellow complex $[Rh(cod)(dppb)]BF_4$ (**324**) via ligand exchange (cod = 1,5-cyclooctadiene).[225] Replacement of the remaining cyclooctadiene ligand with CO was accomplished by treatment with CO (1 atm) at 80 °C. In this manner, a bright yellow powder is obtained in 92% yield upon cooling to rt and addition of Et_2O (yield is based on the assumed formula $[Rh(CO)_2dppb]BF_4$]).[226] This compound displays a single resonance in the ^{31}P NMR spectrum (doublet, δ = 21.4 ppm, $J_{(Rh\text{-}P)}$ = 119.7 Hz) and a strong CO stretching band in the IR spectrum (ν = 2024 cm^{-1}) suggesting a square planar geometry as shown in Scheme 4.52 (the ^{31}P NMR data for three related complexes **324**,[225] **326**[227] and **327**[225] is also listed for comparison). This is indeed the most common geometry observed for d^8 Rh(I) complexes.[228] Efforts to crystalize **325** and obtain an X-ray structure were unsuccesful.[dd]

[dd] Attempts to grow crystals of this complex using a common technique by layering Et_2O onto a solution of the compound in CH_2Cl_2 have thus far proved fruitless. For an example, see reference 225.

Scheme 4.52 Synthesis and ^{31}P NMR data for $[Rh(CO)_2dppb]BF_4$ and related complexes.

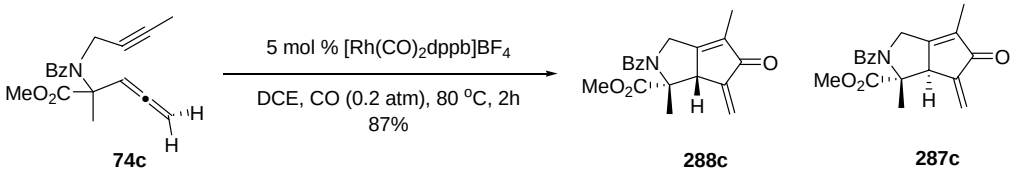


With **325** in hand, it was tested in promoting the cyclocarbonylation reaction of **74c**. As expected, reaction did not occur under full atmosphere of CO. Similar phenomenon of CO impeding the rate of the Rh(I)- or Ir(I)-catalyzed cyclocarbonylation reaction has been observed by Narasaka and Shibata, and is attributed to competitive binding of CO and the substrate to the catalyst.[223, 229] Therefore, using partial pressure of CO to catalyze the reaction was attempted. It was soon discovered that the reaction can be driven to completion under partial pressure of CO (0.2 atm), and heating to 80 °C.[ee] In this manner, using 5 mol % of catalyst resulted in 87% yield of the α-alkylidene cyclopentenone (Scheme 4.53). It was found that either the pre-isolated catalyst or a freshly prepared solution can be used without noticeable difference in reactivity and yield. The product was obtained as a mixture of diastereomers **288c** : **287c** = 2.2 : 1 ratio which were separated by semi-preparative HPLC (normal-phase, 35% EtOAc/hexanes). This is

[ee] The partial pressure of CO is approximate, and it was created by injecting a measured volume of CO from a syringe into a sealed reaction vessel containing a solution of substrate and catalyst. Reactions were most commonly performed on ~20 mg scale in a 15 mL test tube (3 mL of CO was injected).

considerably lower than the ratio of 7 : 1 obtained in the initial experiment (Scheme 4.51) and is attributed to the higher temperature required for the catalytic reaction (80 °C vs. rt). The major diastereomer **288c**, is the one where the methyl substituent and the hydrogen at the ring fusion are *syn* (interestingly, the major diastereomer is different than the one observed in the Mo-mediated cyclocarbonylation reaction of **74c**, Scheme 4.32).

Scheme 4.53 Rh(I)-catalyzed cyclocarbonylation reaction of **74c**.



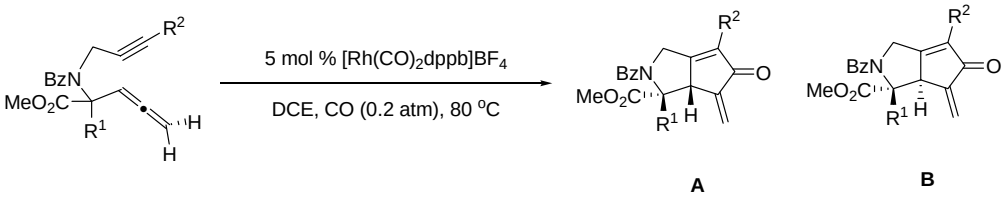
A number of other solvents (benzene, toluene, DCE, THF and TFE) were tested for the reaction in an effort to increase the diastereoselectivity; however, the initially used DCE gave the best combination of reactivity and selectivity. Interestingly, TFE resulted in a shorter reaction time of 30 min, but no diastereoselectivity (the α-alkylidene cyclopentenone was obtained as a 1 : 1 mixture of diastereomers). A similar rate increase phenomenon when using TFE for a Rh(I)-catalyzed cyclocarbonylation reaction was first reported by Wender and is attributed to the acidity of this solvent which results in activation of CO towards insertion via hydrogen bonding.[230]

Next, the scope of this Rh(I)-catalyzed cyclocarbonylation reaction to form α-alkylidene cyclopentenones was examined (Table 4.8).[ff] Allenyne **74a**, containing a methyl-substituted

[ff] All reactions in Table 4.8. (except **74c**, shown for comparison) were performed only to determine the ratio of products. The reported yields are those of crude mixtures obtained after filtration of the reaction solution over a short plug of silica gel eluting with EtOAc/hexanes. Separation of the product mixtures was not performed. The major diastereomers A in the reaction of **74a** and **74b** have been characterized previously in the Mo-mediated cyclocarbonylation reaction (Scheme 4.30). The minor diastereomer B in the reaction of **74d** has been characterized previously in the Mo-mediated cyclocarbonylation reaction (Scheme 4.32). Likewise, both diastereomers A and B in the reaction of **74e** have been characterized from the Mo-mediated cyclocarbonylation reaction (Scheme 4.32).

alkyne gave a mixture of **A** and **B** in 89% yield in 9 : 1 ratio, which is the highest obtained to date with this catalyst. When phenylalanine derived allenyne **74b** with terminally unsubstituted alkyne was subjected to the same conditions, it afforded the products with low diastereoselectivity (1.7 : 1). Allenyne **74d**, with a terminal alkyne, gave a mixture of **A** and **B** in 2.8 : 1 ratio in 92 % yield, while leucine-derived allenyne **74e** afforded α-alkylidene cyclopentenones **A** and **B** in 2.4 : 1 ratio. In these two cases, formation of additional unidentified products was observed in the crude ^{1}H NMR spectrum. Nevertheless, the compatibility of this catalyst with terminal alkynes is in contrast to our catalytic conditions for preparation of 4-alkylidene cyclopentenones ($[Rh(CO)_2Cl]_2$, PPh_3, $AgBF_4$) that were not compatible with terminal alkynes (see Table 4.3, Section 4.2).

Table 4.8 Rh(I)-catalyzed cyclocarbonylation reaction forming α-alkylidene cyclopentenones.



Entry/allenyne	R^1	R^2	Yield %[a]	Ratio of **A : B**[b]
1/**74a**	Bn	Me	89%	9 : 1
2/**74b**	Bn	H	93%	1.7 : 1
3/**74c**	Me	Me	87%	2.2 : 1
4/**74d**	Me	H	92%	2.8 : 1
5/**74e**	*i*-Bu	H	82%	2.4 : 1

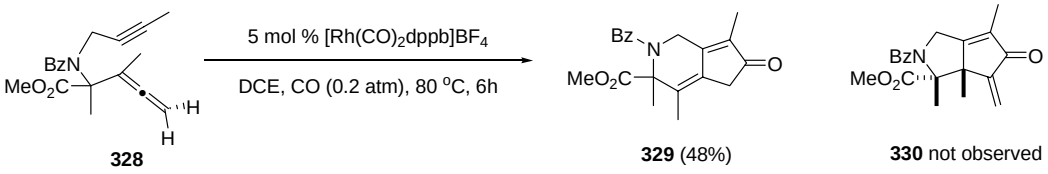
[a]Yields are of crude mixture of products; Trace amounts of the [6,5] cyclopentenone were observed in all cases. [b] ratios were determined by integration of the olefinic resonances in the ^{1}H NMR spectrum of the crude reaction mixture after filtration over a short plug of silica gel.

Notably, the reversal of diastereoselectivity between aliphatic and aromatic side chains that is unique for the $Mo(CO)_6$ mediated cyclocarbonylation reaction is not observed in this case, since either alanine, leucine and phenylalanine derived allenynes all gave the same major

diastereomer.

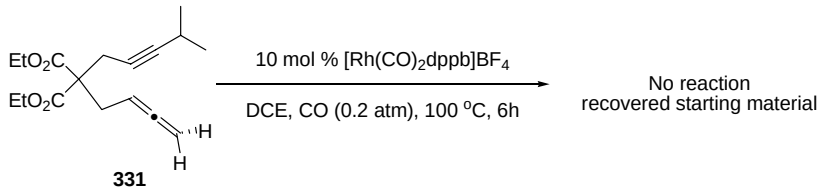
Next, allenyne **328** was subjected to the reaction conditions to test whether the double bond selectivity can be retained in the presence of a methyl group at the proximal allenic position. Unfortunately, the sluggish reaction resulted in 48% yield of the 4-alkylidene cyclopentenone **329**, while the desired **330** was not observed (Scheme 4.54).

Scheme 4.54 Attempted cyclocarbonylation reaction of **328**.



Finally, an attempt was made to extend the scope of the new catalyst to substrates other than amino-acid derived allenynes. However, when the diester-tethered allenyne **331** was subjected to 10 mol % of catalyst, cyclocarbonylation did not occur at 100 °C.

Scheme 4.55 Attempted cyclocarbonylation reaction of **331**.



In summary, we have demonstrated a novel Rh(I)-catalyzed cyclocarbonylation reaction of amino-ester tethered allenynes selective for the proximal double bond of the allene. Selectivity was accomplished under partial pressure of CO using a freshly prepared Rh(I)-catalyst containing a dppb ligand. The origin of the observed selectivity is subject to speculation, and further studies are required to asses this issue. One potential explanation is based on recent computational studies by Brummond and Bayden addressing the selectivity observed in the "normal" Rh(I)-catalyzed and Mo-mediated allenic cyclocarbonylation reactions.[231] The calculations support that the product-determining step in both reactions is the oxidative addition

of the metal into the allenyne leading to a metallocycle. The energy difference between the transition states in this step is responsible for the double bond selectivity in the respective reaction. In the Rh(I)-catalyzed reaction, the transition state leading to a [6,5]-fused metallocycle is better accommodated by the square-planar Rh(I)-center, compared to the transition state leading to a [5,5]-metallocycle. In contrast, the transition state leading to a [5,5]-metallocycle is preferred by the distorted trigonal-bipyramidal molybdenum center in the Mo-mediated reaction. These calculations show that the double bond selectivity is result of the geometry constraints imposed by the metal center in the oxidative addition step of the reaction. We are speculating that the presence of a diphosphine ligand (dppb) on the Rh(I)-center results in a transition-state geometry that can better accommodate the formation of the [5,5]-metallocycle. Further studies at supporting this hypothesis will be forthcoming.

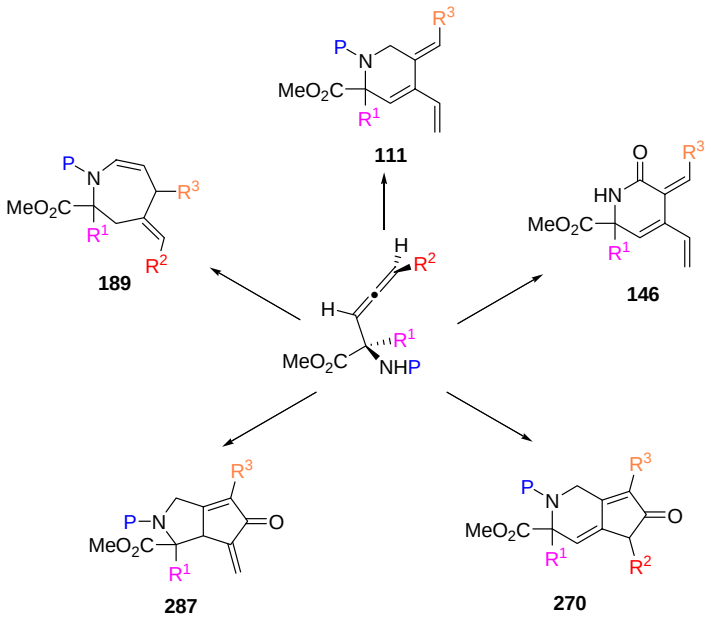
Conclusions

In summary, we have demonstrated a diversity-oriented synthetic strategy based on transition metal-catalyzed and mediated reactions of allenes (Scheme 4.56). We have gained access to a number of structurally and functionally unique products in a relatively short number of synthetic steps. Amino-acid derived allenes accessed via Claisen rearrangement were used as pivotal synthetic intermediates. The Rh(I)-catalyzed allenic Alder-ene reaction of allenynes proceeds in excellent yield affording cross conjugated trienes. These compounds were studied in sequential cycloaddition reactions, gaining access to complex polycyclic skeletons. Furthermore, a novel cycloisomerization of propiolamides was developed affording δ-lactams. Modified catalytic conditions were developed to allow the synthesis of 4-alkylidene cyclopentenones. While studying the Mo-mediated cyclocarbonylation reaction of amino-ester tethered allenynes, a novel stereocontrol element was uncovered based on the amino-acid side chain. The knowledge gained from these studies was used to design and synthesize a novel class of tricyclic pyrroles via a Stetter/Paal-Knorr reaction sequence.

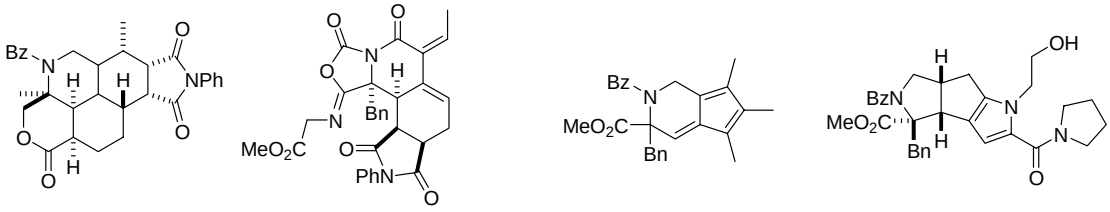
By modifying the substrate to include an alkene instead of an alkyne, a novel catalytic pathway was discovered leading to the formation of tetrahydroazepines, for which mechanistic rationale was provided. In this project we have successfully combined the goal of developing new synthetic methodologies with providing small molecule probes for biological research. The

synthetic pathways that were studied resulted in the synthesis of two distinct libraries (triene-derived polycylic compounds, tricyclic pyrroles), which have been made broadly available to biological colaborators.

Scheme 4.56 Summary of reaction pathways available to allenic amino-esters.



Complex molecular scaffolds accessed:



186 (from **111**) **156** (from **146**) **280** (from **270**) **318** (from **287**)

Experimental Section

General Methods. All commercial reagents were used without further purification unless otherwise noted. The rhodium catalyst ($[Rh(CO)_2Cl]_2$) was purchased from Aldrich Chemical Co. or Strem Chemicals and used as received. Carbon monoxide gas (99.9%) was purchased from Matheson Tri-Gas and used as received. All reactions were carried out under nitrogen atmosphere unless otherwise noted. Toluene, 1,2-dichloroethane and triethylamine (Et_3N) were all freshly distilled from CaH_2 prior to use. 1,4-Dioxane was distilled from CaH_2 and stored over 4Å molecular sieves prior to use. Tetrahydrofuran (THF), diethyl ether (Et_2O) and dichloromethane (CH_2Cl_2) were purified over alumina using the SolTek ST-002 solvent purification system. $ZnCl_2$ (0.5M solution in THF) was purchased from Aldrich Chemical Co. and stored over activated 4Å molecular sieves prior to use. TLC analyses were performed on EM Science Silica Gel 60 F_{254} plates (250 μm thickness). Purification of the compounds by flash chromatography was performed by using silica gel (32-63 μm particle size, 60 Å pore size).[gg] HPLC purification was performed on a Varian-Prostar 210 instrument using a Varian Microsorb Dynamax 100-5 Si column (5 μm packing, 250 mm x 10 mm). All ^1H NMR and ^{13}C NMR spectra were obtained on a Bruker Avance 300 or 500 MHz instrument at rt unless otherwise specified, and chemical shifts (δ) reported relative to residual solvent peak $CHCl_3$ (7.27 ppm and 77.0 ppm respectively). High-resolution mass spectra (HRMS) were obtained on a Micromass

[gg] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Autospec and are reported as *m/z* (relative intensity). Accurate masses are reported for the molecular ion $[M]^+$ for EI and [M+H] or [M+Na] for ESI or a suitable fragment ion. IR spectra were obtained using a Nicolet Avatar E.S.P. 360 FT-IR. The CIF files for **144** (CCDC 618793), **156a** (CCDC 618794) and **186b** (CCDC 618795) were deposited at the Cambridge Crystallographic Data Centre (CCDC) and are available free of charge (http://www.ccdc.cam.ac.uk/). The CIF files for compounds **287b** and **296** can be obtained from (http://pubs.acs.org/).[232] Stick model representations of the X-ray structures used in the text were generated using Mercury v.1.4.1. (http://www.ccdc.cam.ac.uk/mercury/). Compounds **56a-58a** and **56b-58b** were prepared using literature protocols and were obtained in comparable yields and spectroscopic data.

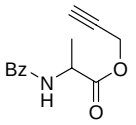
General notes:

(a) The majority of Rh(I)-catalyzed and Mo-mediated reactions were perfomed in new disposable test tubes of appropriate size in order to eliminate variables from impurities in commonly-used glassware. Magnetic stir-bars were used repeatedly and were thoroughly washed each time by first soaking into aqua regia (HCl/HNO_3) followed by extended rinsing with water and acetone (the stir-bars were then dried in an oven at ca. 100 °C prior to use).

(b) Often, preliminary purification of crude reaction mixtures was performed by first filtering over a plug of silica gel using a fritted funnel under vacuum. The amount of silica gel that was used is proportional to the reaction size (as a guideline: ca. 10 g of silica gel per 1 g of crude residue). In these cases, elution of the desired substance from the silica gel plug was performed using an appropriate solvent mixture as determined by TLC analysis (ca. $R_f = 0.5$).

(c) Molecular sieves (4Å) used for storage of solvents or to sequester water in reactions were activated by three rounds of flame-drying in a round-bottomed flask under vacuum.

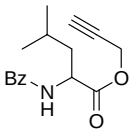
General procedure A for esterification of benzoyl protected amino acids.



56c

2-**Benzoylaminopropionic acid prop-2-ynyl ester (56c)**. To a solution of propargyl alcohol (9.7 mL, 0.17 mol) in CH_2Cl_2 (400 mL) was added DMAP (100 mg, 0.820 mmol) and DCC (22.9 g, 0.111 mol) followed by *N*-Bz-alanine (21.4 g, 0.111 mol). A white precipitate forms immediately. After stirring for 36 h at rt, hexanes (~100 mL) were added. A 150 mL fritted funnel equipped with vacuum outlet was filled with silica gel and connected to a 1 L round-bottomed flask. The reaction mixture was filtered over the plug of silica gel under vacuum eluting with hexanes : EtOAc (1 : 1). The resulting colorless solution was concentrated under vacuum and dissolved in EtOAc. Recrystallization (hexanes-EtOAc, 4 : 1, v/v) afforded **56c** (17.4 g, 68%).

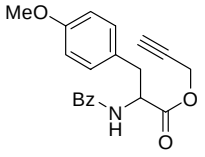
mp range 94.5-97.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78-7.76 (m, 2H), 7.75-7.35 (m, 3H), 6.98 (br d, *J* = 6.9 Hz, 1H), 4.79 (quin, *J* = 7.2 Hz, 1H), 4.76 (dd, *J* = 15.5, 2.5 Hz, 1H), 4.69 (dd, *J* = 15.5, 2.5 Hz, 1H), 2.51 (t, *J* = 2.4 Hz, 1H), 1.50 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 166.9, 133.6, 131.6, 128.4, 127.0, 76.9, 75.4, 52.7, 48.3, 18.0; IR (thin film): ν 3294, 2940, 2128, 1749, 1642, 1536, 1164 cm^{-1}; MS *m/z* (%) 231 (43), 176 (20), 148 (63), 105 (100); EI-HRMS calcd for $C_{13}H_{13}NO_3$ *m/z* $[M]^+$ 231.0895; found 231.0899.



56d

2-Benzoylamino-4-methylpentanoic acid prop-2-ynyl ester (56d). Prepared by following general procedure A with: *N*-Bz-leucine (35.0 g, 0.15 mol), propargyl alcohol (26.0 mL, 0.45

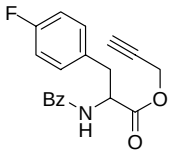
mol), DCC (30.7 g, 0.15 mol), DMAP (500 mg, 4.1 mmol). Purification of the crude residue after filtration by flash chromatography (hexanes-EtOAc, 9 : 1, v/v) afforded **56d** (36.5 g, 90%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78-7.75 (m, 2H), 7.46-7.32 (m, 3H), 6.95 (bs, 1H), 4.86-4.80 (m, 1H), 4.74 (dt, *J* = 15.6, 2.0 Hz, 1H), 4.65 (dt, *J* = 15.6, 2.0 Hz, 1H), 2.49 (t, *J* = 2.3 Hz, 1H), 1.78-1.63 (m, 3H), 0.94-0.92 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 167.2, 133.5, 131.5, 128.3, 127.0, 75.3, 52.5, 50.9, 41.0, 24.7, 22.7, 21.7; IR (thin film): ν 3298, 2958, 2131, 1750, 1642, 1355, 1159 cm^{-1}; MS *m/z* (%) 273 (40), 217 (37), 190 (55), 105 (100); EI-HRMS calcd for $C_{16}H_{19}NO_3$ *m/z* $[M]^+$ 273.1365; found 273.1361.



56e

2-Benzoylamino-3-(4-methoxyphenyl)-propionic acid prop-2-ynyl ester (56e). Prepared by following general procedure A with: *N*-Bz-*p*-methoxyphenylalanine (25 g, 0.084 mol), propargyl alcohol (14.6 mL, 0.25 mol), DCC (17.2 g, 0.084 mol), DMAP (500 mg, 4.1 mmol). Yield of **56e** (24.1 g, 85 %).

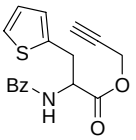
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74-7.72 (m, 2H), 7.55-7.41 (m, 3H), 7.12-7.07 (m, 2H), 6.86-6.81 (m, 2H), 6.53 (d, *J* = 7.3 Hz, 1H), 5.11 (ddd, *J* = 7.6, 5.4, 5.4 Hz, 1H), 4.84 (dd, *J* = 15.6, 2.5 Hz, 1H), 4.73 (dd, *J* = 15.5, 2.5 Hz, 1H), 3.79 (s, 3H), 3.31-3.18 (m, 2H), 2.55 (t, *J* = 2.5 Hz, 1H).



56f

2-Benzoylamino-3-(4-fluorophenyl)propionic acid prop-2-ynyl ester (56f). Prepared by following general procedure A with: *N*-Bz-*p*-fluorophenylalanine (900 mg, 3.14 mmol), propargyl alcohol (916 μL, 15.7 mmol), DCC (646 mg, 3.14 mmol), DMAP (36 mg, 0.30 mmol) The reaction was performed in THF (15 mL) instead of CH_2Cl_2. Purification of the crude residue after filtration by flash chromatography (gradient elution, hexanes-EtOAc, 20 : 1 to 3 : 1, v/v) afforded **56f** (503 mg, 42%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, *J* = 7.7 Hz, 2H), 7.54-7.40 (m, 3H), 7.17-7.12 (m, 2H), 7.00-6.95 (m, 2H), 6.65 (d, *J* = 7.2 Hz, 1H), 5.14-5.08 (m, 1H), 4.83 (dd, *J* = 15.9, 2.2 Hz, 1H), 4.71 (dd, *J* = 15.3, 2.3 Hz, 1H), 3.31 (dd, *J* = 14.0, 5.7 Hz, 1H), 3.23 (dd, *J* = 14.0, 5.4 Hz, 1H), 2.56 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 166.8, 163.7, 160.4, 133.6, 131.9, 131.2, 131.0, 130.9, 128.6, 126.9, 115.6, 115.3, 76.8, 75.7, 53.4, 52.9, 36.8; IR (thin film): ν 3298, 2933, 2129, 1749, 1644, 1510 cm^{-1}; MS *m/z* (%) 325 (53), 269 (35), 204 (30), 160 (47), 105 (100); EI-HRMS calcd for $C_{19}H_{16}NO_3F$ *m/z* $[M]^+$ 325.1114; found 325.1110.

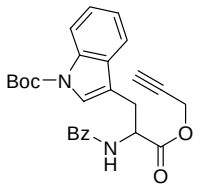


56g

2-Benzoylamino-3-thiophen-2-ylpropionic acid prop-2-ynyl ester (56g). Prepared by following general procedure A with: *N*-Bz-(2-thienyl)-alanine (843 mg, 3.07 mmol), propargyl alcohol (895 μL, 15.3 mmol), DCC (631 mg, 3.07 mmol), DMAP (36 mg, 0.30 mmol). The reaction was performed in THF (20 mL) instead of CH_2Cl_2. Purification of the crude residue after filtration by flash chromatography (gradient elution, hexanes-EtOAc, 20 : 1 to 1 : 1, v/v)

afforded **56g** (500 mg, 52%).

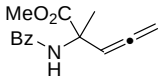
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80-7.78 (m, 2H), 7.54-7.41 (m, 3H), 7.19-7.17 (m, 1H), 6.96-6.83 (m, 3H), 5.13 (dt, *J* = 7.5, 5.0 Hz, 1H), 4.81 (dd, *J* = 15.9, 2.3 Hz, 1H), 4.74 (dd, *J* = 15.5, 2.3 Hz, 1H), 3.54 (d, *J* = 4.9 Hz, 2H), 2.55547 (t, *J* = 2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 166.8, 136.8, 133.6, 131.8, 128.5, 127.0, 125.0, 76.7, 75.8, 53.2, 53.0, 31.8; IR (thin film): ν 3291, 2932, 2853, 2129, 1748, 1645, 1531 cm^{-1}; MS *m/z* (%) 313 (7), 230 (5), 192 (53), 105 (100); EI-HRMS calcd for $C_{17}H_{15}NO_3S$ *m/z* $[M]^+$ 313.0773; found 313.0774.



56h

3-(2-Benzoylamino-2-prop-2-ynyloxycarbonylethyl)indole-1-carboxylic acid *tert*-butyl ester (56h). Prepared by following general procedure A with: *N*-Bz-(3-*N*-Boc-indolyl)-alanine (600 mg, 1.47 mmol), propargyl alcohol (429 μL, 7.35 mmol), DCC (303 mg, 1.47 mmol), DMAP (10 mg, 0.08 mmol). Purification of the crude residue after filtration by flash chromatography (gradient elution, hexanes-EtOAc, 1 : 0 to 2 : 1, v/v) afforded **56h** (430 mg, 66%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12 (d, *J* = 7.9 Hz, 1H), 7.71-7.69 (m, 2H), 7.54-7.16 (m, 7H), 6.73 (d, *J* = 7.4 Hz, 1H), 5.21 (dt, *J* = 7.4, 5.2 Hz, 1H), 4.78 (dd, *J* = 15.5, 2.4 Hz, 1H), 4.69 (dd, *J* = 15.5, 2.4 Hz, 1H), 3.50-3.37 (m, 2H), 2.56 (t, *J* = 2.3 Hz, 1H), 1.65 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 167.0, 149.5, 135.3, 133.7, 131.8, 130.5, 128.5, 127.1, 124.6, 124.5, 122.6, 118.9, 115.3, 114.6, 83.7, 76.8, 75.8, 53.0, 28.2, 24.9; IR (thin film): ν 3297, 2979, 2131, 1732, 1645, 1371 cm^{-1}; ESI-HRMS calcd for $C_{26}H_{26}N_2O_5Na$ *m/z* $[M+23]^+$ 469.1739; found 469.1749.

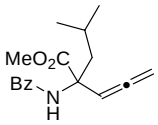


58c

2-Benzoylamino-2-methylpenta-3,4-dienoic acid methyl ester (58c). To a solution of ester **56c** (15.5 g, 67.1 mmol) in MeCN (300 mL), were added successively Et_3N (39.0 mL, 282 mmol), CCl_4 (23.0 mL, 235 mmol) and PPh_3 (54.5 g, 208 mmol) all at rt. After 2.5 h the starting material was consumed based on TLC analysis, and MeOH (1 mL) was added. The dark brown solution was poured in a 1 L Erlenmeyer flask and hexanes (300 mL) were added under vigorous stirring. During the addition, a viscous precipitate formed which was filtered over a plug of silica gel using a fritted funnel and eluted 2-3 times with hexanes/Et_2O (1 : 1). The filtrate was concentrated under vacuum and the resulting residue dissolved in MeOH (50 mL) and a sat'd solution of HCl in MeOH (10 mL) was added. After stirring for 10 min the reaction mixture was poured in Et_2O (500 mL) and the resulting solution washed with sat'd aq. $NaHCO_3$ (500 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum. Purification of the crude residue by flash chromatography (hexanes-EtOAc, 3 : 1, v/v) afforded **58c** (6.5 g, 40%) as a white solid (mp range 135.1-136.6 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79-7.77 (m, 2H), 7.52-7.35 (m, 3H), 6.91 (bs, 1H), 5.64 (t, J = 6.6 Hz, 1H), 5.04 (d, J = 6.6 Hz, 2H), 3.78 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.6, 172.8, 166.4, 134.2, 131.6, 128.5, 126.9, 94.1, 80.2, 58.0, 52.9, 23.1; IR (thin film): ν 3246, 2998, 1959, 1739, 1630, 1533 cm^{-1}; MS *m/z* (%) 245 (23), 230 (52), 186 (71), 105 (100); EI-HRMS calcd for $C_{14}H_{15}NO_3$ *m/z* $[M]^+$ 245.1052; found 245.1058.

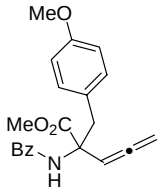
General procedure B for the Claisen rearrangement via an oxazole.



58d

2-Benzoylamino-2-isobutylpenta-3,4-dienoic acid methyl ester (58d). To a solution of propargyl ester **56d** (36.5 g, 134.0 mmol) in MeCN (500 mL), were added successively Et_3N (78 mL, 560 mmol), CCl_4 (45 mL, 470 mmol) and PPh_3 (109 g, 414 mmol) all at rt. After 2.5 h the starting material was consumed based upon TLC analysis. The solution was concentrated under vacuum to a viscous brown paste which was next dissolved in MeOH (50 mL). Then, sat'd solution of HCl in MeOH (10 mL, prepared by bubbling HCl gas through MeOH) was added and the reaction was stirred for additional 10 min. The solvents were removed using a rotary evaporator and the resulting viscous oil was dispersed in Et_2O (200 mL) and poured in a 1 L Erlenmeyer flask. Hexanes (400 mL) were added under vigorous stirring and a yellow precipitate formed. Filtration of the mixture over a plug of silica gel using a fritted funnel was followed by rinsing with hexanes/Et_2O (1 : 1). The filtrate was concentrated under vacuum and the crude residue was purified by silica gel chromatography (hexanes-EtOAc, 6 : 1 to 3 : 1, v/v) to give **58d** (23.8 g, 62%) as a white solid (mp range 68-69 °C).

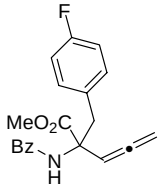
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77-7.74 (m, 2H), 7.44-7.35 (m, 3H), 7.23 (s, 1H), 5.57 (t, *J* = 6.6 Hz, 1H), 4.92 (d, *J* = 6.6 Hz, 2H), 3.75 (s, 3H), 2.47 (dd, *J* = 14.2, 5.5 Hz, 1H), 2.05 (dd, *J* = 14.2, 5.5 Hz, 1H), 1.65 (sept, *J* = 6.5 Hz, 1H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.4, 173.1, 165.9, 134.4, 131.3, 128.3, 126.7, 93.9, 79.7, 61.5, 52.6, 42.7, 24.5, 23.6, 22.6; IR (thin film): ν 3319, 2956, 1958, 1742, 1651, 1526, 1486 cm^{-1}; MS *m/z* (%) 287 (33), 228 (55), 105 (100); EI-HRMS calcd for $C_{17}H_{21}NO_3$ *m/z* $[M]^+$ 287.1521; found 287.1535.



58e

2-Benzoylamino-2-(4-methoxybenzyl)-penta-3,4-dienoic acid methyl ester (58e). Prepared by following general procedure B with: **56e** (24.1 g, 71.4 mmol), Et_3N (41.7 mL, 300.0 mmol), CCl_4 (24.1 mL, 250.0 mmol), PPh_3 (58 g, 221 mmol). Yield of **58e** (17.5 g, 70%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71-7.69 (m, 2H), 7.52-739 (m, 3H), 7.03 (d, *J* = 8.3 Hz, 2H), 6.84 (s, 1H), 6.76 (d, *J* = 8.2 Hz, 2H), 5.64 (t, *J* = 6.7 Hz, 1H), 5.00 (dd, *J* = 10.6, 6.7 Hz, 1H), 4.93 (dd, *J* = 11.1, 6.6 Hz, 1H), 3.83 (s, 3H), 3.75 (s, 3H), 3.71 (d, *J* = 13.9 Hz, 1H), 3.47 (d, *J* = 13.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.8, 172.1, 166.5, 158.5, 134.6, 131.5, 131.1, 128.5, 127.6, 126.8, 113.5, 93.0, 80.1, 62.8, 55.0, 2.9, 39.1; IR (thin film): ν 3413, 2951, 1958, 1740, 1662, 1513, 1249 cm^{-1}; MS *m/z* (%) 351 (10), 319 (7), 292 (12), 246 (27), 230 (60), 105 (100); EI-HRMS calcd for $C_{21}H_{21}NO_4$ *m/z* $[M]^+$ 351.1471; found 351.1470.

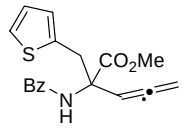


58f

2-Benzoylamino-2-(4-fluorobenzyl)-penta-3,4-dienoic acid methyl ester (58f). Prepared by following general procedure B with: **56f** (0.40 g, 1.23 mmol), Et_3N (0.72 mL, 5.17 mmol), CCl_4 (0.42 mL, 4.31 mmol), PPh_3 (0.99 g, 3.81 mmol). Yield of **58f** (270 mg, 65%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70-7.67 (m, 2H), 7.51-7.39 (m, 3H), 7.09-7.04 (m, 2H), 6.92-6.83 (m, 3H), 5.62 (t, *J* = 6.7 Hz, 1H), 5.03 (dd, *J* = 11.2, 6.6 Hz, 1H), 4.62 (dd, *J* = 11.2, 6.6 Hz, 1H), 3.83 (s, 3H), 3.75 (d, *J* = 13.7 Hz, 1H), 3.54 (d, *J* = 13.7 Hz, 1H); ^{13}C NMR (75 MHz,

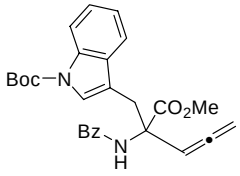
$CDCl_3$): δ 206.7, 172.0, 166.6, 163.5, 160.3, 134.4, 131.7, 131.5, 128.6, 128.6, 126.8, 115.1, 114.8, 92.9, 80.4, 62.6, 53.0, 38.8; IR (thin film): ν 3412, 2951, 1958, 1741, 1655, 1510 cm^{-1}; MS *m/z* (%) 338 (28), 230 (57), 198 (19), 105 (100); EI-HRMS calcd for $C_{20}H_{18}NO_3F$ *m/z* $[M]^+$ 339.1259; found 339.1258.



58g

2-Benzoylamino-2-thiophen-2-ylmethylpenta-3,4-dienoic acid methyl ester (58g). Prepared by following general procedure B with: **56g** (270 mg, 0.863 mmol), Et_3N (504 μL, 3.62 mmol), CCl_4 (291 μL, 3.02 mmol), PPh_3 (700 mg, 2.67 mmol). Yield of **58g** (235 mg, 83%).

^1H NMR (300 MHz, $CDCl_3$): δ 7.75-7.72 (m, 2H), 7.52-7.38 (m, 3H), 7.13-7.11 (m, 1H), 7.01 (s, 1H), 6.89-6.86 (m, 1H), 6.79-6.78 (m, 1H), 5.61 (t, *J* = 6.6 Hz, 1H), 5.04 (dd, *J* = 11.4, 6.6 Hz, 1H), 4.99 (dd, *J* = 11.3, 6.6 Hz, 1H), 4.05 (d, *J* = 14.7 Hz, 1H), 3.83 (s, 3H), 3.80 (d, *J* = 14.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.0, 171.7, 166.4, 137.1, 134.5, 131.5, 128.4, 127.4, 126.8, 126.5, 124.7, 92.6, 80.2, 62.6, 52.9, 34.2; IR (thin film): ν 3410, 2950, 1957, 1740, 1655, 1521 cm^{-1}; MS *m/z* (%) 327 (10), 230 (40), 206 (47), 147 (31), 105 (100); EI-HRMS calcd for $C_{18}H_{17}NO_3S$ *m/z* $[M]^+$ 327.0929; found 327.0937.



58h

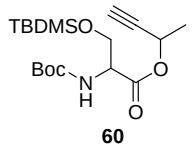
3-(2-Benzoylamino-2-methoxycarbonylpenta-3,4-dienyl)-indole-1-carboxylic acid *tert*-butyl ester (58h). Prepared by following general procedure B with these modifications: (a) the reaction mixture was heated to 50 °C for 2 h. (b) methanolysis was performed by addition of Et_3N (0.1

mL) and MeOH (10 mL) instead of sat'd solution of HCl in MeOH and stirred for 12 h (it was reasoned that addition of HCl/MeOH may result in cleavage of the Boc group). After concentrating the reaction mixture under vacuum the viscous brown paste was immediately purified by flash chromatography (hexanes/EtOAc, 9 : 1 to 4 : 1, v/v) to afford **58h**.

Starting reagents used: **56h** (239 mg, 0.535 mmol), Et_3N (312 μL, 2.25 mmol), CCl_4 (181 μL, 1.87 mmol), PPh_3 (434 mg, 1.66 mmol). Yield of **58h** (157 mg, 64%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.24-8.23 (m, 1H), 7.78-7.19 (m, 9H), 7.06 (s, 1H), 5.80 (t, *J* = 6.6 Hz, 1H), 5.11 (dd, *J* = 11.2, 6.7 Hz, 1H), 5.03 (dd, *J* = 11.2, 6.6 Hz, 1H), 4.01 (d, *J* = 14.5 Hz, 1H), 3.87 (s, 3H), 3.74 (d, *J* = 14.6 Hz, 1H), 1.65 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.1, 172.2, 166.7, 149.4, 135.0, 134.6, 131.5, 130.9, 128.5, 126.9, 125.0, 124.2, 122.4, 119.1, 115.0, 114.6, 93.1, 83.4, 80.2, 62.6, 53.0, 29.8, 28.0; IR (thin film): ν 3411, 2979, 1959, 1735, 1666, 1369 cm^{-1}; ESI-HRMS calcd for $C_{27}H_{28}N_2O_5Na$ *m/z* $[M+23]^+$ 483.1896; found 483.1893.

2-*tert*-Butoxycarbonylamino-3-(*tert*-butyldimethylsilyloxy)propionic acid (59) was prepared from *N*-Boc-serine according to a previously reported procedure.[hh]



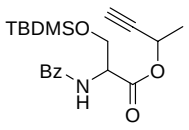
60

2-*tert*-Butoxycarbonylamino-3-(*tert*-butyldimethylsilyloxy)propionic acid 1-methylprop-2-ynyl ester (60). To a solution of 3-butyne-2-ol (53 μL, 0.72 mmol) in CH_2Cl_2 (2 mL) were added DCC (149 mg, 0.724 mmol) and DMAP (8 mg, 7 μmol) at rt. Then, a solution of carboxylic acid **59** (220 mg, 0.69 mmol) in CH_2Cl_2 (4 mL) was added via a syringe. After 1 h at rt, the reaction

[hh] Yoo, D.; Oh J. S.; Lee, D. -W.; Kim, Y. G. *J. Org. Chem.* **2003,** *68*, 2979.

mixture was filtered over a pad of silica gel using a fritted funnel, eluting with hexanes/EtOAc 2 : 1 (100 mL). The filtrate was concentrated under vacuum and the resulting pale yellow oil was purified by flash chromatography (hexanes/EtOAc, 20 : 1, v/v) to give **60** (187 mg, 73%) as a colorless oil and a 1 : 1 mixture of diastereomers.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.52-5.42 (m, 1H), 5.32 (br d, *J* = 7.4 Hz, 1H), 4.36-4.30 (m, 1H), 4.08-4.03 (m, 1H), 3.81 (dd, *J* = 10.0, 2.9 Hz, 1H), 2.45 (d, *J* = 2.1 Hz, 0.5H), 2.41 (d, *J* = 2.1 Hz, 0.5H), 1.50 (d, *J* = 6.7 Hz, 1.5H), 1.49 (d, J = 6.6 Hz, 1.5H), 1.44 (s, 9H), 1.85 (s, 4.5H), 1.85 (s, 4.5H), 0.03-0.01 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6, 155.4, 155.3, 81.6, 79.8, 73.3, 73.2, 63.6, 63.5, 61.1, 55.7, 55.6, 28.3, 25.7, 25.7, 21.3, 21.2, 18.1, -5.6; IR (thin film): ν 3451, 3314, 2932, 2122, 1750, 1720 cm^{-1}; MS *m/z* (%) 372 (11), 316 (22), 258 (51), 206 (43), 57 (100); EI-HRMS calcd for $C_{18}H_{34}NO_5Si$ *m/z* $[M+1]^+$ 372.2206; found 372.2201.

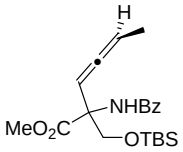


61

2-Benzoylamino-3-(*tert*-butyldimethylsilyloxy)propionic acid 1-methylprop-2-ynyl ester (61). Boc-protected amine **60** (1.48 g, 3.98 mmol) was dissolved in TFA (5 mL) and stirred for 5 min at rt, and then the excess TFA was removed under vacuum (rotary evaporator was used with a dry ice-cooled trap to collect the TFA). The brown oil was purified by flash chromatography (hexanes-EtOAc, 3 : 1, v/v then EtOAc). After evaporation of the solvents the resulting residue (1.54 g) was dissolved in $CHCl_3$ (20 mL) and Et_3N (1.65 mL, 12.0 mmol) was added followed by benzoyl chloride (444 μL, 3.84 mmol) at 0 °C under nitrogen. The reaction mixture was stirred for 1 h after which it was diluted with $CHCl_3$ (120 mL). The organic phase was washed with 5% aq. AcOH (50 mL) and then sat'd aq. $NaHCO_3$ (50 mL), dried over $MgSO_4$ and concentrated under vacuum. Purification of the crude residue by flash chromatography (gradient elution,

hexanes-EtOAc, 19 : 1 to 4 : 1, v/v) afforded **61** (900 mg, 60%, 2 steps) as a 1 : 1 mixture of diastereomers.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84-7.81 (m, 2H), 7.62-7.44 (m, 3H), 6.98 (d, *J* = 7.5 Hz, 1H), 5.61-5.44 (m, 1H), 4.97-4.86 (m, 1H), 4.23-4.17 (m, 1H), 4.00-3.96 (m, 1H), 2.49 (d, *J* = 2.1 Hz, 0.5H), 2.46 (d, *J* = 2.1 Hz, 0.5H), 1.57 (d, *J* = 5.7 Hz, 1.5H), 1.55 (d, *J* = 5.7 Hz, 1.5H), 0.89 (s, 4.5H), 0.88 (s, 4.5H), 0.07 (s, 1.5H), 0.06 (s, 1.5H), 0.04 (s, 1.5H), 0.04 (s, 1.5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 169.4, 167.0, 166.9, 134.0, 131.8, 128.7, 127.0, 81.5, 81.4, 73.6, 73.5, 63.5, 63.4, 61.5, 61.4, 54.7, 54.5, 25.8, 25.7, 21.3, 21.2, 18.2, 18.1, -5.5, -5.6; IR (thin film): ν 3442, 3310, 2930, 2121, 1747, 1665, 1109 cm^{-1}; MS *m/z* (%) 360 (42), 318 (35), 105 (100); EI HRMS calcd for $C_{20}H_{29}NO_4Si$ *m/z* $[M]^+$ 375.1866, found 375.1852.



58i

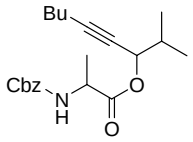
2-Benzoylamino-2-(*tert*-butyldimethylsilyloxymethyl)hexa-3,4-dienoic acid methyl ester (58i). To a solution of propargyl ester **61** (730 mg, 1.95 mmol) in MeCN (10 mL), were added in consecutive order Et_3N (758 μL, 5.45 mmol), CCl_4 (430 μL, 4.49 mmol) and PPh_3 (1.12 g, 4.29 mmol) at rt. After 3 h the starting material was consumed based upon TLC analysis. The solution was concentrated under vacuum to a viscous brown paste which was next dissolved in MeOH (10 mL). Then, Et_3N (500 μL) was added and after 3 h the solution was again concentrated under vacuum. The crude residue was diluted with EtOAc (50 mL), and the solution was poured in an Erlenmyer flask, and then hexanes (20 mL) were added under vigorous stirring. The resulting mixture was filtered through a plug of silica gel using a fritted funnel, and eluted with hexanes/Et_2O (1 : 1). The filtrate was concentrated under vacuum and the residue was purified by

flash chromatography (hexanes-EtOAc, 9 : 1, v/v) to afford **58i** (660 mg, 87%) as a mixture of diastereomers in ratio of ~ 2 : 1 determined by ^{1}H NMR).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80-7.77 (m, 2H), 7.57-7.41 (m, 3H), 7.12 (bs, 1H), 5.54 (sex, *J* = 3.2 Hz, 0.66H), 5.44 (sex, *J* = 3.1 Hz, 0.33H), 5.38-5.30 (m, 1H), 4.40 (d, *J* = 9.8 Hz, 0.33H), 4.31 (d, *J* = 9.8 Hz, 0.66H), 4.09 (d, *J* = 9.8 Hz, 1H), 3.80 (s, 1H), 3.80 (s, 2H), 1.68-1.64 (m, 3H), 0.84 (s, 9H), 0.02 (s, 1H), 0.01 (s, 2H), 0.00 (s, 2H), -0.01 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.0, 204.0, 171.1, 171.6, 166.3, 166.1, 134.8, 134.7, 131.3, 128.4, 126.8, 126.7, 90.7, 90.4, 89.9, 89.7, 64.6, 64.4, 64.1, 52.8, 52.7, 25.5, 17.9, 13.8, 13.8, -5.6, -5.7; IR (thin film): ν 3421, 3298, 2952, 1967, 1741, 1669, 1247 cm^{-1}; MS *m/z* (%) 374 (10), 332 (92), 244 (90), 105 (100); EI HRMS calcd for $C_{21}H_{31}NO_4Si$ *m/z* $[M]^+$ 389.2022, found 389.2020.

General procedure C for preparation of esters 64a-f.

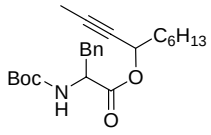
Esters **64a-f** were obtained as mixtures of diastereomers in 1 : 1 ratio as a result of using a racemic propargylic alcohol.



64b

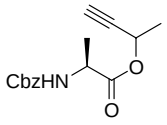
2-Benzyloxycarbonylaminopropionic acid 1-isopropylhept-2-ynyl ester (64b). To a solution of 2-methylnon-4-yn-3-ol (418 mg, 2.73 mmol) in CH_2Cl_2 (5 mL) was added DCC (562 mg, 2.73 mmol) and DMAP (17 mg, 0.14 mmol) at rt. Addition of *N*-Cbz-alanine (609 mg, 2.73 mmol) was followed by formation of a white precipitate. After 1 h the reaction mixture was filtered on a plug of silica gel using a fritted funnel eluting with hexanes-EtOAc (1 : 1). The filtrate was concentrated under vacuum and the crude residue was purified by flash chromatography (gradient elution, hexanes-EtOAc, 1 : 0 to 9 : 1, v/v) to give **64b** (750 mg, 77%)

which was immediately used in the Claisen rearrangement step.



64a

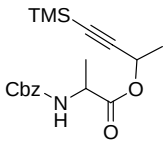
2-*tert*-Butoxycarbonylamino-3-phenylpropionic acid 1-hexylbut-2-ynyl ester (64a). Prepared by following general procedure C, using: dec-2-yn-4-ol (200 mg, 1.29 mmol), DMAP (15 mg, 0.12 mmol), DCC (267 mg, 1.29 mmol), *N*-Boc-phenylalanine (344 mg, 1.29 mmol). Yield of **64a** (458 mg, 88%).



64c

2-Benzyloxycarbonylaminopropionic acid 1-methylprop-2-ynyl ester (64c). Prepared by following general procedure C, using: 3-butyn-2-ol (165 μL, 2.24 mmol), DMAP (12 mg, 0.098 mmol), DCC (462 mg, 2.24 mmol) and *N*-Cbz-alanine **62c** (500 mg, 2.24 mmol). Yield of **64c** (600 mg, 97%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.27 m (5H), 5.53-5.45 (m, 2H), 5.11 (s, 2H), 4.45-4.35 (m, 1H), 2.50-2.45 (m, 1H), 1.53-1.48 (m, 3H), 1.43-1.39 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7, 155.4, 136.1, 128.3, 127.9, 81.3, 81.2, 73.5, 73.3, 66.7, 61.0, 49.5, 49.4, 20.9, 18.3.

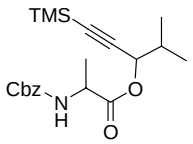


64d

2-Benzyloxycarbonylaminopropionic acid 1-methyl-3-trimethylsilylprop-2-ynyl ester (64d). Prepared by following general procedure C using: 4-trimethylsilylbut-3-yn-2-ol (600 mg, 4.22 mmol), DMAP (51 mg, 0.42 mmol), DCC (956 mg, 4.64 mmol), *N*-Cbz-alanine (988 mg, 4.43

mmol) Yield of **64d** (1.35 g, 92%).

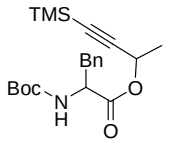
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.27 (m, 5H), 5.50 (quin, *J* = 6.8 Hz, 1H), 5.33 (bs, 1H), 5.12 (s, 2H), 4.41 (sep, *J* = 7.3 Hz, 1H), 1.52-1.41 (m, 6H), 0.18 (s, 4.5H), 0.17 (s, 4.5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8, 155.6, 136.3, 128.6, 128.2, 103.0, 102.8, 90.5, 90.2, 67.0, 62.0, 49.7, 21.4, 18.9, 18.6, -0.2; IR (thin film): ν 3341, 2960, 2178, 1727, 1251 cm^{-1}; MS *m/z* (%) 348 (5), 270 (10), 178 (13), 134 (26), 91 (100); EI-HRMS calcd for $C_{18}H_{25}NO_4Si$ *m/z* $[M]^+$ 347.1553; found 347.1541.



64e

2-Benzyloxycarbonylaminopropionic acid 1-isopropyl-3-trimethylsilylprop-2-ynyl ester (64e). Prepared by following general procedure C using: 4-methyl-1-trimethylsilylpent-1-yn-3-ol (800 mg, 4.71 mmol), DMAP (63 mg, 0.52 mmol), DCC (1.06 g, 5.15 mmol), *N*-Cbz-alanine (1.15 g, 5.17 mmol). Yield of **64e** (1.65 g, 85%).

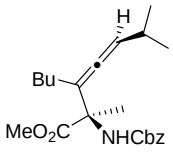
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 5.44 (m, 1H), 5.29 (d, *J* = 5.6 Hz, 0.5H), 5.25 (d, *J* = 5.7 Hz, 0.5H), 5.12 (s, 2H), 4.49-4.38 (m, 1H), 2.05-1.94 (m, 1H), 1.44 (d, *J* = 7.1 Hz, 1H), 1.03-0.98 (m, 3H), 0.18 (s, 4.5H), 0.17 (s, 4.5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 171.7, 155.5, 136.3, 128.4, 128.1, 128.0, 100.8, 100.6, 91.6, 91.4, 70.4, 70.3, 66.8, 49.8, 49.5, 32.4, 32.3, 18.8, 18.3, 18.0, 18.0, 17.4; IR (thin film): ν 3340, 2965, 2180, 1728, 1526 cm^{-1}; MS *m/z* (%) 376 (6), 375 (14), 295 (25), 280 (34), 223 (50), 91 (100); EI-HRMS calcd for $C_{20}H_{29}NO_4Si$ *m/z* $[M]^+$ 375.1866; found 375.1863.



64f

***tert*-Butyl-1-((4-(trimethylsilyl)but-3-yn-2-yloxy)carbonyl)-2-phenylethylcarbamate (64f)**. Prepared by following general procedure C using: 4-trimethylsilylbut-3-yn-2-ol (6.0 g, 4.2 mmol), DMAP (200 mg, 1.64 mmol), DCC (8.7 g, 4.2 mmol), *N*-Boc-phenylalanine (11.2 g, 4.23 mmol) Yield **64f** (16.4 g, >95%). The compound was immediately used in the next Claisen rearrangement step.

General procedure D for preparation of 65a-65c via a Claisen rearrangement.



65b

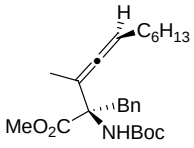
2-Benzyloxycarbonylamino-3-butyl-2,6-dimethylhepta-3,4-dienoic acid methyl ester (65b). General procedure for preparation of a THF solution of LDA: *i*-Pr_2NH (5.1 mmol) was added to a flame dried 100 mL round-bottomed flask, followed by THF (10 mL) under nitrogen atmosphere. The reaction flask was cooled to -20 °C and *n*-BuLi (5.1 mmol of 1.6 M solution in hexanes) was added dropwise over 5 min. The colorless solution was then cooled to -78 °C and held at that temperature for 30 min.

Step 1. Ester-enolate Claisen rearrangement: To a freshly prepared solution of LDA (5.1 mmol) in THF (10 mL) was added **64b** (730 mg, 2.04 mmol) in THF (10 mL) at -78 °C. After 2 min of stirring, $ZnCl_2$ (4.9 mL of a 0.5 M solution in THF, 2.4 mmol) was added at -78 °C. The reaction mixture was allowed to warm to rt over 10 h. The reaction mixture was then poured in Et_2O (100

mL) and treated with 1M HCl (50 mL). The aqueous layer was extracted with Et_2O (2 x 50 mL), and the organic layers were combined, washed with 1M HCl (50 mL), dried over $MgSO_4$, and concentrated under vacuum to afford a yellow oil.

Step 2. Methyl ester formation: The yellow oil was dissolved in DMF (5 mL). Pulverized $KHCO_3$ (515 mg, 5.09 mmol) was added at rt, followed by addition of MeI (256 μL, 4.08 mmol) via a syringe. The reaction mixture was stirred for 2 h, and then diluted with water (100 mL). The cloudy mixture was extracted with EtOAc (3 x 75 mL), the organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated under vacuum. Purification of the crude residue by flash chromatography (gradient elution; hexanes-EtOAc, 10 : 0 to 4 : 1, v/v) afforded **65b** (555 mg, 73%).

65b : ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.28 (m, 5H), 5.78 (bs, 1H), 5.49 (dt, *J* = 7.0, 3.5 Hz, 1H), 5.13 (d, *J* = 12.4 Hz, 1H), 5.07 (d, *J* = 12.3 Hz, 1H), 3.70 (s, 3H), 2.37 (sex, *J* = 6.3 Hz, 1H). 1.92-1.86 (m, 2H), 1.70 (s, 3H), 1.36-1.27 (m, 4H), 1.05 (s, 3H), 1.03 (s, 3H), 0.88 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.7, 173.5, 154.8, 137.0, 128.7, 128.2, 108.0, 105.8, 77.5, 66.7, 60.9, 52.9, 30.4, 28.9, 27.0, 22.7, 22.6, 14.2; IR (thin film): ν 3416, 2958, 1728, 1493, 1273 cm^{-1}; MS *m/z* (%) 373 (11), 314 (9), 183 (21), 91 (100); EI-HRMS calcd for $C_{22}H_{31}NO_4$ *m/z* $[M]^+$ 373.2253; found 373.2268.

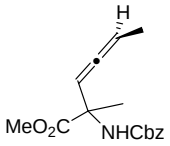


65a

2-Benzyl-2-*tert*-butoxycarbonylamino-3-methylundeca-3,4-dienoic acid methyl ester (65a). Prepared by following general procedure D, using: LDA (1.58 mmol), **64a** (265 mg, 0.661 mmol), $ZnCl_2$ (158 μL of a 0.5 M solution in THF, 0.793 mmol), $KHCO_3$ (62 mg, 0.62 mmol),

MeI (38 μL, 0.62 mmol). Yield **65a** (60 mg, 22%).

Note: The intermediate carboxylic acid after the Claisen rearrangement step was purified by silica gel flash chromatography (hexanes-EtOAc, 4 : 1 to 1 : 1, v/v) and obtained in 41% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27-7.23 (m, 3H), 7.08-7.06 (m, 2H), 5.27 (bs, 1H), 5.16 (bs, 1H), 3.78 (s, 3H), 3.55-3.43 (m, 2H), 2.04 (bs, 2H), 1.72 (d, *J* = 2.7 Hz, 3H), 1.48 (s, 9H), 1.48-1.28 (m, 8H), 0.88 (t, *J* = 6.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.6, 172.8, 153.8, 137.0, 130.3, 127.9, 126.6, 99.6, 95.7, 64.5, 52.8, 37.9, 31.8, 29.1, 28.8, 28.5, 22.7, 15.5, 14.2. MS *m/z* (%) 416 (27), 359 (25), 324 (30), 268 (100), 57 (100); EI-HRMS calcd for $C_{21}H_{29}NO_4$ *m/z* [M-57]$^+$ 359.2097; found 359.2110.



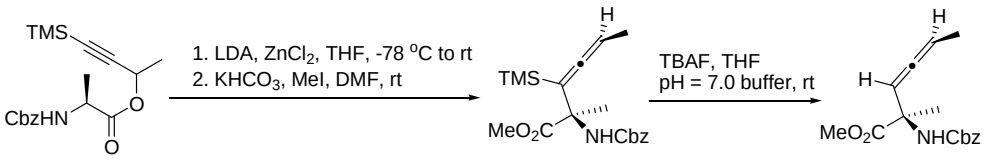
65c

2-Benzyloxycarbonylamino-2-methylhexa-3,4-dienoic acid methyl ester (65c).

Prepared by following general procedure D, using: LDA (7.15 mmol), **64c** (820 mg, 2.98 mmol), $ZnCl_2$ (7.1 mL of a 0.5 M solution in THF, 3.6 mmol), $KHCO_3$ (752 mg, 7.45 mmol), MeI (460 μL, 7.45 mmol). Purification by flash chromatography (hexanes-EtOAc, 9 : 1, v/v) afforded **65c** (618 mg, 70%) as a 1 : 1 mixture of diastereomers.

65c : ^{1}H NMR (300 MHz, C_6D_6): δ 7.21-7.02 (m, 5H), 5.39 (m, 2H), 5.09-4.98 (m, 3H), 3.32 (s, 3H), 1.74 (s, 1.5H), 1.70 (s, 1.5H), 1.37-1.32 (m, 3H).

General procedure E for the preparation of 65d-f via a three step reaction sequence.



64d **67d** **65d**

The following is a general procedure based on using 4.0 mmol of propargylic ester:

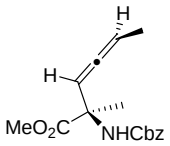
General procedure for preparation of a THF solution of LDA: *i*-Pr_2NH (10.0 mmol) was added to a flame dried 100 mL round-bottomed flask, followed by THF (10 mL) under nitrogen atmosphere. The reaction flask was cooled to -20 °C and *n*-BuLi (10.0 mmol of 1.6 M solution in hexanes) was added dropwise over 5 min. The colorless solution was then cooled to -78 °C and held at that temperature for 30 min.

Step 1. Ester-enolate Claisen rearrangement: The amino acid propargylic ester (4.0 mmol) was placed in a pear-shaped flask as a solution in benzene and the solvent was removed under vacuum. The atmosphere was subsequently replaced with nitrogen and THF (10 mL) was added. The resulting solution was added via a syringe to a freshly prepared solution of LDA (10 mmol) at -78 °C over 5 min. After 3-5 min of stirring, $ZnCl_2$ (4.8 mmol of a 0.5 M solution in THF) was added in dropwise manner over 5 min at -78 °C. The reaction mixture was allowed to warm to rt over 12 h. The reaction mixture was then poured in Et_2O (200 mL), and treated with 1M HCl (200 mL). The aqueous layer was extracted with Et_2O (2 x 100 mL), and the organic layers were combined and washed with brine. Concentration under vacuum afforded an oily residue.

Step 2. Methyl ester formation: The residue from step 1 was dissolved in DMF (10 mL). Pulverized $KHCO_3$ (10 mmol) was added at rt, followed by MeI (8 mmol). The reaction mixture was stirred for 2-4 h until complete based upon TLC analysis, and then diluted with water (100 mL). The cloudy mixture was extracted with EtOAc, the organic layers were combined, washed

with brine and concentrated under vacuum to afford a dark-yellow oil.

Step 3. TMS removal: The dark yellow oil from step 2 was dissolved in THF (20 mL), and phosphate buffer (pH = 7.0, 1 mL) was added, followed by dropwise addition of TBAF (8 mmol of a 1.0 M solution in THF) at rt. The reaction mixture was stirred for 3 h at rt and then diluted with water (100 mL) and the aqueous layer extracted with Et_2O (3 x 100 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under vacuum. Purification of the crude residue by flash chromatography (hexanes-EtOAc, 4 : 1, v/v) afforded the allenic amino-ester.

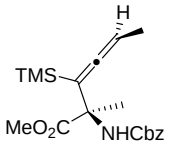


65d

2-Benzyloxycarbonylamino-2-methylhexa-3,4-dienoic acid methyl ester (65d). Prepared by the general procedure E, using:

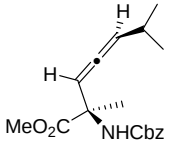
Step 1: LDA (17 mmol), **64d** (2.36 g, 6.80 mmol), $ZnCl_2$ (16.3 mL of a 0.5 M solution in THF, 8.16 mmol). Step 2: $KHCO_3$ (1.37 g, 13.6 mmol), MeI (0.67 mL, 11 mmol). Step 3: TBAF (6 mL of a 1.0 M solution in THF, 6 mmol). Yield **65d** (970 mg, 49%, 3 steps).

65d : ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.32 (m, 5H), 5.50 (bs, 1H), 5.44-5.36 (m, 2H), 5.13 (d, *J* = 12.5 Hz, 1H), 5.08 (d, *J* = 12.3 Hz, 1H), 3.74 (bs, 3H), 1.69-1.66 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.9, 173.2, 154.9, 136.5, 128.6, 128.3, 94.4, 91.9, 66.8, 58.6, 53.0, 23.6, 14.1; IR (thin film): ν 3348, 2951, 1966, 1724, 1267 cm^{-1}; MS *m/z* (%) 289 (21), 274 (10), 230 (42), 91 (100); EI-HRMS calcd for $C_{16}H_{19}NO_4$ *m/z* $[M]^+$ 289.1314; found 289.1316.



67d

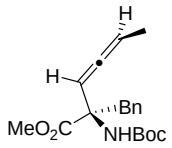
Benzyl-2-(methoxycarbonyl)-3-(trimethylsilyl)hexa-3,4-dien-2-ylcarbamate (67d): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.28 (m, 5H), 5.82 (bs, 1H), 5.18-5.04 (m, 3H), 3.71 (s, 3H), 1.73 (s, 3H), 1.73-1.68 (m, 3H), 0.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.8, 174.1, 154.7, 136.9, 128.7, 128.4, 128.3, 100.4, 85.5, 66.7, 60.8, 52.9, 24.2, 13.5, 0.2; IR (thin film): ν 3417, 2953, 1940, 1727, 1490 cm^{-1}; MS *m/z* (%) 362 (35), 361 (361 (43), 302 (45), 91 (100); EI-HRMS calcd for $C_{19}H_{27}NO_4Si$ *m/z* $[M]^+$ 361.1709; found 361.1710.



65e

2-Benzyloxycarbonylamino-2,6-dimethylhepta-3,4-dienoic acid methyl ester (65e). Prepared by following the general procedure E, using: Step 1: LDA (5.3 mmol), **64e** (800 mg, 2.13 mmol), $ZnCl_2$ (5.1 mL of a 0.5 M solution in THF, 2.6 mmol). Step 2: $KHCO_3$ (537 mg, 5.32 mmol), MeI (265 μL, 4.26 mmol). Step 3: TBAF (2.1 mL of a 1.0 M solution in THF, 2.1 mmol).Yield **65e** (325 mg, 48%, 3 steps).

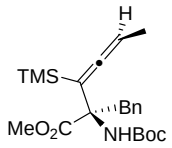
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.32 (m, 5H), 5.51-5.42 (m, 2H), 5.13 (d, *J* = 12.3 Hz, 1H), 5.07 (d, *J* = 12.2 Hz, 1H), 3.73 (bs, 3H), 2.39-2.24 (m, 1H), 1.67 (s, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.5, 173.0, 154.8, 136.4, 128.5, 128.1, 104.5, 96.0, 66.6, 58.4, 52.7, 27.9, 23.4, 22.2, 22.1; IR (thin film): ν 3353, 2960, 1965, 1728, 1264 cm^{-1}; MS *m/z* (%) 318 (22), 317 (61), 302 (44), 274 (40), 258 (51), 91 (100); EI-HRMS calcd for $C_{18}H_{23}NO_4$ *m/z* $[M]^+$ 317.1627; found 317.1626.



65f

***tert*-Butyl-2-(methoxycarbonyl)-1-phenylhexa-3,4-dien-2-ylcarbamate (65f)**. Prepared by following the general procedure E, using: Step 1: LDA (74.3 mmol), **64f** (11.6 g, 29.7 mmol), $ZnCl_2$ (71 mL of a 0.5 M solution in THF, 35.6 mmol). Step 2: $KHCO_3$ (7.4 g, 74 mmol), MeI (4.6 mL, 74 mmol). Step 3: TBAF (44.5 mL of a 1.0 M solution in THF, 44.5 mmol).Yield **65f** (5.9 g, 60%, 3 steps). Notes: Simultaneous dropwise addition of $ZnCl_2$ and **64f** to LDA was performed at -78 °C. The solution of **64f** in THF was cooled to -78 °C and added to LDA via a canula.

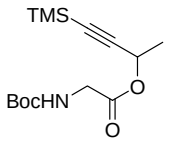
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.24 (m, 3H), 7.13-7.11 (m, 2H), 5.40 (bs, 1H), 5.28 (quin, *J* = 6.8 Hz, 1H), 5.19 (bs, 1H), 3.78 (s, 3H), 3.45 (d, *J* = 13.2 Hz, 1H), 3.42 (d, *J* = 13.2 Hz, 1H), 1.68 (dd, *J* = 6.9, 3.0 Hz, 3H), 1.48 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.1, 172.4, 154.1, 136.1, 130.3, 128.0, 126.7, 93.5, 91.3, 79.5, 62.5, 52.5, 40.6, 28.3, 13.9; IR (thin film): ν 3430, 2978, 1969, 1741, 1717, 1494 cm^{-1}; MS *m/z* (%) 332 (7), 276 (30), 184 (50), 91 (44), 57 (100); EI-HRMS calcd for $C_{19}H_{25}NO_4$ *m/z* $[M]^+$ 331.1784; found 331.1781.



67f

***tert*-Butyl-2-(methoxycarbonyl)-3-(trimethylsilyl)-1-phenylhexa-3,4-dien-2-ylcarbamate (67f)**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.36 (m, 3H), 7.21-7.18 (m, 2H), 5.65 (bs, 1H), 5.20 (q, *J* = 7.0 Hz, 1H), 3.90 (s, 3H), 3.89 (d, *J* = 13.4 Hz, 1H), 3.54 (d, *J* = 13.4 Hz, 1H), 1.91 (d, *J* = 6.9 Hz, 3H), 1.65 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.3, 173.1, 153.4, 136.8, 130.0,

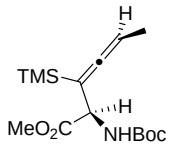
127.8, 126.5, 98.9, 84.6, 78.9, 64.0, 52.4, 40.0, 28.4, 13.3, -0.3; IR (thin film): ν 3426, 2977, 1938, 1723, 1487 cm^{-1}; MS *m/z* (%) 403 (5), 347 (7), 256 (100), 178 (49); EI-HRMS calcd for $C_{22}H_{33}NO_4Si$ *m/z* $[M]^+$ 403.2179; found 403.2196.



69

***tert*-Butoxycarbonylaminoacetic acid 1-methyl-3-trimethylsilylprop-2-ynyl ester** (**69**). To a solution of 4-trimethylsilyl-3-yn-2-ol (1.17 g, 8.27 mmol), in CH_2Cl_2 (10 mL), was added DMAP (81 mg, 0.66 mmol), DCC (1.38 g, 6.71 mmol) and *N*-Boc-Glycine **68** (954 mg, 6.71 mmol) all at rt. The reaction mixture was stirred for 1 h at rt, then filtered through a plug of silica gel eluting with hexanes/EtOAc (1 : 1), and the filtrate was concentrated under vacuum. Purification of the crude oily residue by flash chromatography (hexanes-EtOAc, 4 : 1, v/v) afforded **69** (1.92 g, 92%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.50 (q, *J* = 6.7 Hz, 1H), 5.06 (br s, 1H), 3.91 (d, *J* = 5.4 Hz, 2H), 1.48 (d, *J* = 6.7 Hz, 1H), 1.44 (s, 9H), 0.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 155.8, 102.9, 90.3, 80.1, 61.8, 42.7, 28.4, 21.6, -0.2; IR (thin film): ν 3379, 2978, 1756, 1721, 1169 cm^{-1}; MS *m/z* (%) 299 (10), 243 (100); EI-HRMS calcd for $C_{14}H_{25}NO_4Si$ *m/z* $[M]^+$ 299.1553; found 299.1547.

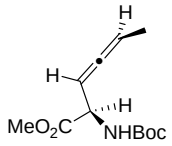


70

2-*tert*-Butoxycarbonylamino-3-trimethylsilylhexa-3,4-dienoic acid methyl ester (70). Ester-enolate Claisen rearrangement. To a freshly prepared solution of LDA[ii] (20.4 mmol) in THF (10 mL) was added **69** (1.6 g, 5.1 mmol) in THF (10 mL) at -78 °C. After 10 min of stirring $ZnCl_2$ (20 mL of a 0.5 M solution in THF, 9.8 mmol) was added at -78 °C. The reaction mixture was allowed to warm to rt over 12 h. Upon completion the reaction mixture was diluted with Et_2O (100 mL), and treated with 1M HCl (100 mL). The aqueous layer was extracted with Et_2O (2 x 100 mL), and the organic layers were combined and washed with brine. Concentration under vacuum afforded a oily residue which was dissolved in DMF (10 mL). Pulverized $KHCO_3$ (1.08 g, 1.07 mmol) was added at rt, followed by MeI (530 μL, 8.24 mmol). The reaction mixture was left stirring for 2h at rt, and then diluted with water (100 mL). The cloudy mixture was extracted (benzene-EtOAc, 1 : 9, v/v) (3 x 75 mL), the organic layers were combined, washed with brine (2 x 50 mL) and concentrated in vacuo. Purification by flash chromatography (gradient elution: hexanes-EtOAc, 32 : 1 to 19 : 1, v/v), afforded **70** (740 mg, 44%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.10-5.03 (m, 2H), 4.75 (d, J = 8.3 Hz, 1H), 3.72 (s, 3H), 1.63 (d, J = 7.1 Hz, 1H), 1.45 (s, 9H), 0.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.2, 172.1, 155.0, 95.4, 84.5, 80.0, 53.4, 52.1, 28.4, 13.2, -1.1; IR (thin film): ν 3373, 2955, 1943, 1749, 1720 cm^{-1}; MS *m/z* (%) 314 (6), 257 (43), 242 (45), 198 (100); EI-HRMS calcd for $C_{11}H_{19}NO_4Si$ *m/z* [M-56]$^+$ 257.1083; found 257.1080.

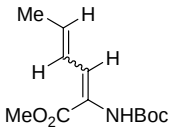
[ii] LDA was prepared as outlined in general procedure E.



71

2-*tert*-Butoxycarbonylaminohexa-3,4-dienoic acid methyl ester (71). To a solution of **70** (120 mg, 0.383 mmol), in THF (5 mL) was added TBAF (0.5 mL of a 1.0 M solution in THF, 0.5 mmol) premixed with phosphate buffer solution (pH = 7.3) (0.3 mL) at rt. The reaction was stirred for 30 min when TBAF (0.3 mL of a 1M solution in THF, 0.3 mmol) was added. The reaction was allowed to continue until TLC indicated absence of starting material (~ 3 h). Water was added, and the aqueous layer was extracted with Et_2O (3 x 20 mL). The organic layers were combined, washed with sat'd aq. NH_4Cl, dried over $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography (hexanes-EtOAc, 9 : 1, v/v) afforded **71** (72 mg, 79%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.39-5.36 (m, 1H), 5.29 (bs, 1H), 5.13 (m, 1H), 4.78 (br s, 1H), 3.76 (s, 3H), 1.69 (dd, *J* = 7.0, 3.1 Hz, 3H), 1.45 (s, 9H).



72

2-*tert*-Butoxycarbonylaminohexa-2,4-dienoic acid methyl ester (72). To a solution of **70** (41 mg, 0.13 mmol) in THF (2 mL) was added TBAF (157 μL of a 2.0 M solution in THF, 0.314 mmol) at rt. After 10 min. water was added, and the aqueous layer was extracted with Et_2O. The organic layers were combined, washed with sat'd aq NH_4Cl, dried over $MgSO_4$ and concentrated under vacuum to afford **72** (35 mg, >95%). Diene **72** was obtained as a mixture of isomers that were separated by semipreparative HPLC (hexanes-EtOAc 9 : 1, v/v).

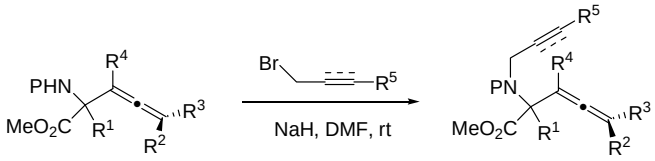
Spectral data of mixture: IR (thin film): ν 3358, 2980, 1727, 1159 cm^{-1}; MS *m/z* (%) 241 (26),

185 (10), 141 (21), 57 (100); EI-HRMS calcd for $C_{12}H_{19}NO_4$ *m/z* $[M]^+$ 241.1314; found 241.1308.

72a (isomer 1): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (d, *J* = 11.7 Hz, 1H), 6.28-6.21 (m, 1H), 6.11 (bs, 1H), 5.96 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.82 (s, 3H), 1.90 (d, *J* = 7.1 Hz, 3H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.0, 153.4, 134.9, 125.9, 124.4, 124.0, 80.9, 52.5, 28.3, 14.2.

72b (isomer 2): ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96 (d, *J* = 10.9 Hz, 1H), 6.35-6.26 (m, 1H), 6.19-6.07 (m, 1H), 6.02 (bs), 3.79 (s, 3H), 1.89 (d, *J* = 6.4 Hz, 1H), 1.48 (s, 9H).

General procedure F for N-alkylation allenic amino-esters.



73a-l
74a-i
75a-e

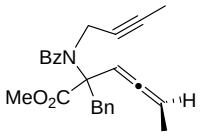
The following is a general procedure based on using 1.0 mmol of allenic amino ester.

To a solution of N-protected amino-ester (1.0 mmol) in DMF (4 mL), was added NaH (2.0 mmol of 95% dry or 60% dispersion in mineral oil) in one portion at rt under nitrogen atmosphere.[jj] The reaction flask was sealed with a rubber septum and after 2 min the propargyl or allyl bromide (1.5 – 2.0 mmol) was added dropwise via a syringe. The mixture was stirred at rt for 15 - 45 min and upon completion as determined by TLC analysis, the reaction was quenched by cautiously pouring into water (50 mL). The aqueous mixture was extracted three times with EtOAc, the organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated under vacuum. Purification of the crude residue by flash chromatography (hexanes-

[jj] See individual compound for details. In certain cases NaH was added at 0 °C.

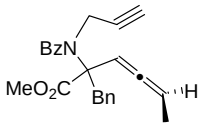
EtOAc, 9 : 1, v/v) afforded the corresponding alkyl-amide.

Note: Benzamide protected allenynes **73a-73e** and ene-allenes **75a**, **75b** and **75e** were obtained as mixtures of diastereomers in ~2 : 1 ratio originating from the starting allenic amino-ester. These diastereomers were not separated.



73a

2-(Benzoylbut-2-ynylamino)-2-benzylhexa-3,4-dienoic acid methyl ester (73a). Prepared by following general procedure F, using: **58a** (330 mg, 0.982 mmol), NaH (60 mg of 95%, 2.5 mmol), 1-bromo-2-butyne (86 μL, 0.98 mmol). Purification by flash chromatography (hexanes-EtOAc, 9 : 1, v/v) afforded **73a** (315 mg, 83%) as a mixture of diastereomers in a ~1.7 : 1 ratio. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67-7.64 (m, 2H), 7.48-7.38 (m, 3H), 7.31-7.21 (m, 5H), 5.89-85 (m, 1H), 5.52-5.38 (m, 1H), 3.98 (d, *J* = 13.6 Hz, 0.63H), 3.97 (d, *J* = 13.5 Hz, 0.37H), 3.75 (s, 3H), 3.75-3.68 (m, 1H), 3.58-3.51 (m, 1H), 3.40 (d, *J* = 13.6 Hz, 0.63H), 3.39 (d, *J* = 13.5 Hz, 0.37H), 1.80 (dd, *J* = 7.1, 3.2 Hz, 1.9H), 1.74 (dd, *J* = 7.1, 3.1 Hz, 1.1H), 1.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.4, 172.5, 171.7, 136.5, 136.1, 131.3, 130.5, 128.4, 128.0, 127.5, 126.9, 91.0, 90.5, 90.3, 80.5, 76.2, 69.2, 68.0, 52.4, 39.6, 39.2, 25.7, 14.0, 13.8, 3.7; IR (thin film): ν 2948, 1967, 1744, 1642, 1393 cm^{-1}; MS *m/z* (%) 386 (10), 328 (41), 296 (15), 105 (100); EI-HRMS calcd for $C_{25}H_{24}NO_3$ *m/z* $[M-1]^+$ 386.1756; found 386.1745.

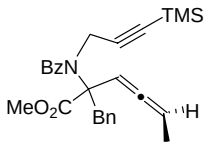


73b

2-(Benzoylprop-2-ynylamino)-2-benzylhexa-3,4-dienoic acid methyl ester (73b). Prepared by following general procedure F, using: **58a** (175 mg, 0.521 mmol), NaH (42 mg of 60%

dispersion in mineral oil, 1.0 mmol), propargyl bromide (80% wt. in toluene, 92 μL, 0.83 mmol). Purification by flash chromatography (hexanes-EtOAc, 6 : 1, v/v) afforded **73b** (143 mg, 73%) as a mixture of diastereomers in a ~1.7 : 1 ratio determined by integration of the methyl group resonances in the ^{1}H NMR spectrum.

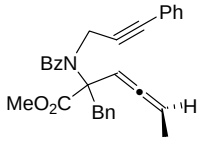
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67-7.62 (m, 2H), 7.49-7.39 (m, 3H), 7.28-7.23 (m, 5H), 5.85 (sex, *J* = 3.1 Hz, 1H), 5.56-5.41 (m, 1H), 3.97 (d, *J* = 13.5 Hz, 0.63H), 3.96 (d, *J* = 13.6 Hz, 0.37H), 3.76 (s, 1.1H), 3.76 (s, 1.9H), 3.72 (dt, *J* = 18.9, 3.0 Hz, 1H), 3.51 (dt, *J* = 18.8, 3.0 Hz, 1H), 3.42 (d, *J* =13.6 Hz, 0.63H), 3.41 (d, *J* = 13.6 Hz, 0.37H), 2.14 (t, *J* = 2.4 Hz, 0.63H), 2.12 (t, *J* = 2.4 Hz, 0.37H), 1.81 (dd, *J* = 7.2, 3.2 Hz, 1.9H),1.75 (dd, *J* = 7.1, 3.2 Hz, 1.1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.0, 172.7, 171.7, 136.7, 136.6, 136.2, 131.4, 130.7, 128.7, 128.4, 127.5, 127.1, 91.1, 91.0, 90.7, 81.2, 72.9, 72.9, 69.2, 52.7, 52.7, 39.3, 39.2, 14.1, 13.8; IR (thin film): ν 2948, 2118, 1968, 1743, 1643 cm^{-1}; MS *m/z* (%) 372 (50), 282 (40), 105 (100); EI-HRMS calcd for $C_{24}H_{22}NO_3$ *m/z* $[M]^+$ 372.1600; found 372.1613.



73c

2-[Benzoyl(3-trimethylsilylprop-2-ynyl)amino]-2-benzylhexa-3,4-dienoic acid methyl ester (73c). To a solution of **58a** (243 mg, 0.723 mmol), in THF (7 mL) was added KH (90 mg of 35% wt. dispersion in mineral oil, 0.80 mmol) at rt, followed by addition of (3-bromoprop-1-ynyl)-trimethylsilane (203 μL, 1.44 mmol). The reaction mixture was stirred at rt for 12 h and then carefully poured into a beaker containing EtOAc and water. The aqueous layer was extracted with EtOAc and organic layers were combined, washed with brine (20 mL), dried over $MgSO_4$, and concentrated under vacuum. Purification by flash chromatography (hexanes-EtOAc, 9 : 1, v/v) afforded **73c** (240 mg, 75%) as a mixture of diastereomers.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68-7.64 (m, 2H), 7.46-7.38 (m, 3H), 7.33-7.21 (m, 5H), 5.83-5.80 (m, 1H), 5.57-5.41 (m, 1H), 3.98-3.91 (m, 1H), 3.76 (s, 1.9H), 3.75 (s, 1.1H), 3.67-3.65 (m, 1H), 3.52-3.41 (m, 2H), 1.81 (dd, *J* = 7.2, 3.1 Hz, 1.9H), 1.77 (dd, *J* = 7.1, 3.1 Hz, 1.1H), 0.16 (s, 5.7H), 0.15 (s, 3.3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.6, 172.6, 171.5, 136.4, 136.3, 135.8, 130.9, 130.3, 128.2, 128.0, 127.3, 126.8, 103.2, 90.9, 90.4, 89.4, 68.8, 52.4, 39.8, 38.8, 38.5, 13.9, 13.7, -0.3; IR (thin film): ν 2952, 2177, 1967, 1745, 1649 cm^{-1}; MS *m/z* (%) 445 (21), 444 (36), 354 (50), 244 (74), 105 (100); EI-HRMS calcd for $C_{27}H_{30}NO_3Si$ *m/z* $[M-1]^+$ 444.1995; found 444.1984.

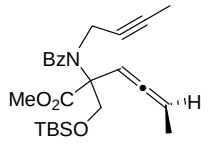


73d

2-[Benzoyl(3-phenylprop-2-ynyl)amino]-2-benzylhexa-3,4-dienoic acid methyl ester (73d). Prepared by following general procedure F, using: **58a** (72 mg, 0.21 mmol), NaH (17 mg of 60% dispersion in mineral oil, 0.43 mmol), (3-bromoprop-1-ynyl)-benzene (66 mg, 0.34 mmol). Purification by flash chromatography (hexanes-EtOAc, 9 : 1, v/v) afforded **73d** (86 mg, 89%) as a mixture of diastereomers in a ~1.6 : 1 ratio determined by integration of the methyl group resonances in the ^{1}H NMR.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79-7.77 (m, 2H), 7.57-7.51 (m, 4H), 7.41-7.23 (m, 9H), 5.98 (sept, *J* = 3.1 Hz, 1H), 5.65-5.50 (m, 1H), 4.11 (d, *J* = 13.6 Hz, 0.61H), 4.11-4.01 (m, 2H), 3.87 (s, 1.2H), 3.85 (s, 1.8H), 3.83-3.77 (m, 1H), 3.54 (d, *J* = 13.5 Hz, 1H), 1.89 (dd, *J* = 7.2, 3.2 Hz, 1.8H), 1.83 (dd, *J* = 7.1, 3.2 Hz, 1.2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.6, 172.7, 172.6, 171.7, 171.6, 136.4, 136.3, 131.6, 131.5, 131.0, 130.4, 128.4, 128.3, 128.2, 128.0, 127.3, 126.9, 122.6, 90.9, 90.8, 90.4, 86.4, 86.3, 84.2, 69.0, 68.9, 52.4, 39.8, 39.0, 38.7, 13.9, 13.7; IR (thin film): ν 2948, 1967, 1743, 1645, 1392 cm^{-1}; MS *m/z* (%) 448 (7), 390 (78), 358 (25), 105 (100);

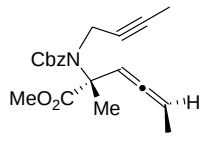
EI-HRMS calcd for $C_{30}H_{26}NO_3$ *m/z* $[M-1]^+$ 448.1913; found 448.1929.



73e

2-(Benzoylbut-2-ynylamino)-2-(*tert*-butyldimethylsilyloxymethyl)-hexa-3,4-dienoic acid methyl ester (73e). Prepared by following general procedure F, using: **58i** (245 mg, 0.629 mmol), NaH (50 mg of a 60% dispersion in mineral oil, 1.3 mmol), 1-bromo-2-butyne (88 μL, 1.1 mmol). Purification by flash chromatography (gradient elution; hexanes-EtOAc, 19 : 1 to 9 : 1, v/v) afforded **73e** (237 mg, 85%) as a mixture of diastereomers.

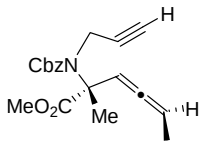
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71-7.65 (m, 2H), 7.46-7.37 (m, 3H), 5.90-5.86 (m, 1H), 5.41-5.31 (m, 1H), 4.45 (d, *J* = 10.1 Hz, 0.66H), 4.44 (d, *J* = 10.1 Hz, 0.33H), 4.31-4.16 (m, 2H), 3.99 (dq, *J* = 18.5, 2.3 Hz, 1H), 3.74 (s, 1H), 3.73 (s, 2H), 1.90-1.87 (m, 3H), 1.71 (dd, *J* = 7.1, 3.2 Hz, 1H), 1.71 (dd, *J* = 7.1, 3.2 Hz, 2H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.1, 205.0, 172.3, 172.2, 170.6, 136.1, 130.1, 128.1, 127.3, 127.3, 89.9, 89.8, 89.7, 79.8, 79.7, 77.2, 68.3, 68.2, 64.0, 63.9, 52.2, 52.1, 39.4, 39.3, 25.8, 25.7, 18.1, 14.0, 13.7, 3.6, -5.5, -5.6, -5.6, -5.7; IR (thin film): ν 2952, 1968, 1744, 1644 cm^{-1}; MS *m/z* (%) 384 (35), 296 (31), 84 (100); EI-HRMS calcd for $C_{21}H_{26}NO_4Si$ *m/z* $[M-57]^+$ 384.1631; found 384.1630.



73f

2-(Benzyloxycarbonylbut-2-ynylamino)-2-methylhexa-3,4-dienoic acid, methyl ester (73f). Prepared by following general procedure F, using: **65d** (400 mg, 1.38 mmol), NaH (110 mg of 60% dispersion in mineral oil, 2.76 mmol), 1-bromo-2-butyne (157 μL, 1.79 mmol). Flash chromatography (hexanes-EtOAc, 9 : 1, v/v) afforded **73f** (390 mg, 84%).

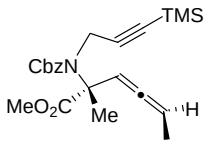
^{1}H NMR (300 MHz, DMSO-d_6, 323 K): δ 7.40-7.31 (m, 5H), 5.49-5.43 (m, 1H), 5.10 s, 2H), 4.22 (dq, J = 18.3, 2.3 Hz, 1H), 4.11 (dq, J = 18.2, 2.2 Hz, 1H), 3.50 (bs, 3H), 1.78 (d, J = 2.0 Hz, 3H), 1.66 (dd, J = 6.6, 3.4 Hz, 3H), 1.54 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, 323 K): δ 204.0, 171.5, 154.3, 136.1, 127.9, 127.5, 127.2, 92.5, 89.9, 78.5, 75.9, 66.5, 63.4, 51.6, 33.6, 20.5, 13.0, 2.6; IR (thin film): ν 2917, 1965, 1745, 1702, 1250 cm^{-1}; MS *m/z* (%) 341 (5), 326 (7), 282 (15), 91 (100); EI-HRMS calcd for $C_{20}H_{23}NO_4$ *m/z* $[M]^+$ 341.1627; found 341.1630.



73g

2-(Benzyloxycarbonylprop-2-ynylamino)-2-methylhexa-3,4-dienoic acid methyl ester (73g). Prepared by following general procedure F, using: **65d** (240 mg, 0.83 mmol), NaH (70 mg, 60% dispersion in mineral oil, 1.8 mmol), propargyl bromide (80% wt. in toluene, 137 μL, 1.25 mmol). Purification by flash chromatography (hexanes-EtOAc, 9 : 1, v/v) afforded **73g** (210 mg, 77%).

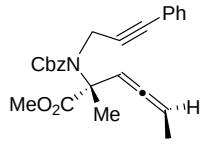
^{1}H NMR (300 MHz, C_6D_6, 323K): δ 7.22-7.01 (m, 5H), 5.63 (sex, J = 3.1 Hz, 1H), 5.13-5.04 (m, 1H), 5.04 (s, 2H), 4.21 (d, J = 18.1 Hz, 1H), 4.04 (dd, J = 18.1, 2.0 Hz, 1H), 3.38 (bs, 3H), 1.88 (t, J = 2.4 Hz, 1H), 1.77 (s, 3H), 1.43 (dd, J = 7.1, 3.2 Hz, 1H); ^{13}C NMR (75 MHz, C_6D_6, 323K): δ 205.5, 172.2, 155.3, 137.0, 93.8, 90.6, 81.3, 71.5, 67.8, 64.9, 52.1, 34.2, 21.3, 13.6; IR (thin film): ν 3288, 2950, 2115, 1966, 1745, 1704, 1254 cm^{-1}; MS *m/z* (%) 312 (13), 268 (34), 91 (100); EI-HRMS calcd for $C_{18}H_{18}NO_4$ *m/z* $[M-15]^+$ 312.1236; found 312.1243.



73h

2-[Benzyloxycarbonyl(3-trimethylsilylprop-2-ynyl)amino]-2-methylhexa-3,4-dienoic acid, methyl ester (73h). To a solution of **65d** (134 mg, 0.464 mmol), in THF (4 mL) was added KH (68 mg of 35% wt. dispersion in mineral oil, 0.51 mmol) at rt, followed by addition of (3-bromoprop-1-ynyl)-trimethylsilane (131 μL, 0.93 mmol). The reaction mixture was stirred at rt for 10 h. The reaction mixture was then poured into a beaker containing EtOAc (50 mL) and water (50 mL). The aqueous layer was extracted with EtOAc and the organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated under vacuum. Purification by flash chromatography (hexanes-EtOAc, 9 : 1, v/v) afforded **73h** (128 mg, 86%).

^{1}H NMR (300 MHz, $CDCl_3$, 310 K): δ 7.37-7.27 (m, 5H), 5.48 – 5.34 (m, 2H), 5.20 (d, *J* = 12.5 Hz, 1H), 5.15 (d, *J* = 12.7 Hz, 1H), 4.38 (d, *J* = 18.3 Hz, 1H), 4.18 (d, *J* = 18.4 Hz, 1H), 3.59 (bs, 3H), 1.73 (dd, *J* = 6.7, 2.9 Hz, 3H), 1.66 (s, 3H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, 310 K): δ 205.3, 172.5, 155.1, 136.3, 128.3, 127.9, 102.7, 92.9, 90.5, 88.0, 67.5, 64.5, 52.3, 34.8, 13.8, -0.3; IR (thin film): ν 2954, 2177, 1967, 1748, 1707, 1251 cm^{-1}; MS *m/z* (%) 399 (5), 384 (9), 340 (25), 91 (100); EI-HRMS calcd for $C_{22}H_{29}NO_4Si$ *m/z* $[M]^+$ 399.1866; found 339.1875.

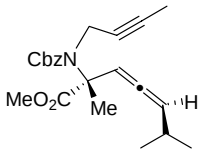


73i

2-[Benzyloxycarbonyl(3-phenylprop-2-ynyl)amino]-2-methylhexa-3,4-dienoic acid methyl ester (73i). Prepared by following general procedure F, using: **65d** (210 mg, 0.72 mmol), NaH (58 mg of 60% dispersion in mineral oil, 1.4 mmol), (3-bromoprop-1-ynyl)-benzene (281 mg, 1.44 mmol). Purification by flash chromatography (hexanes-EtOAc, 9 : 1, v/v) afforded **73i** (199

mg, 68%).

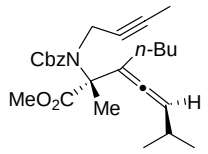
^{1}H NMR (300 MHz, DMSO-d_6, 323 K): δ 7.39-7.31 (m, 10 H), 5.55-5.45 (m, 2H), 5.14 (s, 2H), 4.52 (d, J = 18.6 Hz, 1H), 4.42 (d, J = 18.6 Hz, 1H), 3.50 (bs, 3H), 1.61 (dd, J = 7.0, 3.3 Hz, 3H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, 323 K): δ 204.2, 171.6, 154.4, 136.2, 130.9, 128.4, 128.3, 128.1, 127.6, 127.3, 122.0, 92.6, 90.2, 86.6, 82.5, 66.7, 63.5, 51.9, 34.1, 13.2; IR (thin film): ν 2949, 1966, 1746, 1704, 1251 cm^{-1}; MS *m/z* (%) 344 (39), 240 (40), 205 (49), 169 (61), 133 (84), 87 (100); EI-HRMS calcd for $C_{25}H_{25}NO_4$ *m/z* $[M]^+$ 403.1784, found 403.1788.



73j

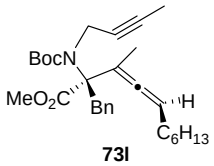
2-(Benzyloxycarbonylbut-2-ynylamino)-2,6-dimethylhepta-3,4-dienoic acid, methyl ester (73j). Prepared by following general procedure F, using: **65e** (125 mg, 0.394 mmol), NaH (31 mg of a 60% dispersion in mineral oil, 0.79 mmol), 1-bromo-2-butyne (69 μL, 0.79 mmol). Purification by flash chromatography (hexanes-EtOAc, 9 : 1, v/v) afforded **73j** (125 mg, 86%).

^{1}H NMR (300 MHz, DMSO-d_6, 323 K): δ 7.40-7.30 (m, 5H), 5.59-5.51 (m, 2H), 5.10 (s, 2H), 4.21 (dq, J = 18.2, 2.3 Hz, 1H), 4.11 (dq, J = 18.3, 2.4 Hz, 1H), 3.48 (s, 3H), 2.40-2.25 (m, 1H), 1.75 (t, J = 2.2 Hz, 3H), 1.52 (s, 3H), 1.01 (d, J = 6.8 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6, 323 K): δ 201.6, 171.3, 154.3, 136.0, 127.9, 127.4, 127.1, 102.4, 94.4, 78.5, 75.9, 66.5, 63.5, 51.6, 33.7, 27.0, 21.7, 21.5, 2.5; IR (thin film): ν 2959, 1964, 1746, 1704, 1253 cm^{-1}; MS *m/z* (%) 369 (24), 326 (18), 167 (20), 91 (50), 83 (100); EI-HRMS calcd for $C_{22}H_{27}NO_4$ *m/z* $[M]^+$ 369.1940; found 369.1957.



73k

2-(Benzyloxycarbonylbut-2-ynylamino)-3-butyl-2,6-dimethylhepta-3,4-dienoic acid methyl ester (73k). Prepared by following general procedure F, using: **65b** (135 mg, 0.361 mmol), NaH (29 mg of 60% dispersion in mineral oil, 0.72 mmol), 1-bromo-2-butyne (51 μL, 0.72 mmol). Purification by flash chromatography (hexanes-EtOAc, 19 : 1, v/v) afforded **73k** (120 mg, 78%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.27 (m, 5H), 5.38 (dt, *J* = 6.1, 3.3 Hz, 1H), 5.23 (d, *J* = 12.5 Hz, 1H), 5.13 (d, *J* = 12.5 Hz, 1H), 4.25 (d, *J* = 17.7 Hz, 1H), 3.78 (dd, *J* = 17.7, 2.2 Hz, 1H), 3.58 (bs, 3H), 2.36 (sex, *J* = 6.5 Hz, 1H), 1.99 (m, 2H), 1.75 (t, *J* = 2.1 Hz, 3H), 1.67 (s, 3H), 1.44-1.26 (m, 4H), 1.06 (d, *J* = 6.7 Hz, 6H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.8, 172.1, 156.5, 136.8, 128.6, 128.2, 107.1, 103.8, 78.9, 76.6, 67.7, 67.5, 52.3, 35.1, 31.9, 28.8, 27.8, 22.9, 22.8, 22.7, 22.0, 14.3, 3.7; IR (thin film): ν 2957, 1957, 1744, 1707, 1250 cm^{-1}; MS *m/z* (%) 425 (30), 383 (36), 366 (32), 223 (68), 183 (100); EI-HRMS calcd for $C_{26}H_{35}NO_4$ *m/z* $[M]^+$ 425.2566; found 425.2565.

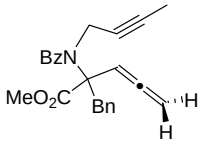


73l

2-Benzyl-2-(*tert*-butoxycarbonylbut-2-ynylamino)-3-methylundeca-3,4-dienoic acid methyl ester (73l). Prepared by following general procedure F, using: **65a** (59 mg, 0.14 mmol), NaH (7 mg of 95% dry, 0.3 mmol), 1-bromo-2-butyne (25 μL, 0.29 mmol). Purification by flash chromatography (hexanes-EtOAc, 4 : 1, v/v) afforded **73l** (48 mg, 73%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.17 (m, 5H), 5.38-5.31 (m, 1H), 3.78-3.76 (m, 1H), 3.70 (s, 3H), 3.62 (d, *J* = 13.9 Hz, 1H), 3.5-3.35 (m, 1H), 3.26 (d, *J* = 13.9 Hz, 1H), 2.11 (q, *J* = 7.1 Hz,

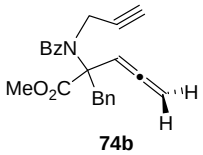
2H), 1.86 (d, *J* = 2.5 Hz, 3H), 1.80 (s, 3H), 1.44-1.31 (m, 8H), 1.31 (m, 9H), 0.89 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.3, 170.9, 155.3, 137.8, 131.3, 127.9, 126.4, 100.8, 94.4, 80.8, 78.2, 70.6, 51.8, 40.1, 36.3, 29.2, 29.0, 28.1, 22.7, 17.3, 14.2, 3.7; IR (thin film): ν 2926, 1957, 1742, 1698, 1165 cm^{-1}; MS *m/z* (%) 468 (28), 320 (50), 276 (63), 91 (56), 57 (100); EI-HRMS calcd for $C_{29}H_{42}NO_4$ *m/z* $[M+1]^+$ 468.3114; found 468.3082.



74a

2-(Benzoylbut-2-ynylamino)-2-benzylpenta-3,4-dienoic acid methyl ester (74a). Prepared by following general procedure F, using: **58b** (450 mg, 1.40 mmol), NaH (123 mg of a 60% dispersion in mineral oil, 3.08 mmol), 1-bromo-2-butyne (183 μL, 2.10 mmol). Purification by flash chromatography (hexanes-EtOAc, 9 : 1, v/v) afforded **74a** (438 mg, 84%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68-7.65 (m, 2H), 7.46-7.41 (m, 3H), 7.32-7.22 (m, 5H), 5.97 (t, *J* = 6.6 Hz, 1H), 5.10 (dd, *J* = 9.3, 6.6 Hz, 1H), 5.05 (dd, *J* = 9.3, 6.6 Hz, 1H), 3.98 (d, *J* = 13.6 Hz, 1H), 3.76 (s, 3H), 3.73 (dq, *J* = 18.6, 2.3 Hz, 1H), 3.55 (dq, *J* = 18.6, 2.3 Hz, 1H), 3.43 (d, *J* = 13.6 Hz, 1H), 1.69 (t, *J* = 2.3 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$): δ 207.6, 172.4, 171.3, 136.2, 135.9, 131.1, 130.3, 128.2, 128.2, 127.9, 127.3, 126.8, 90.8, 80.4, 79.2, 75.9, 68.7, 52.2, 39.4, 39.0, 3.5; IR (thin film): ν 2949, 2228, 1958, 1744, 1641 cm^{-1}; MS *m/z* (%) 372 (45), 342 (10), 282 (31), 105 (100); EI-HRMS calcd for $C_{24}H_{22}NO_3$ *m/z* $[M-1]^+$ 372.1600, found 372.1618.

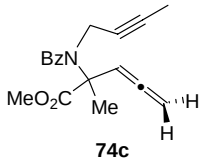


74b

2-(Benzoylprop-2-ynylamino)-2-benzylhexa-3,4-dienoic acid methyl ester (74b). Prepared by following general procedure F, using: **58b** (495 mg, 1.54 mmol), NaH (154 mg of a 60%

dispersion in mineral oil, 3.85 mmol), propargyl bromide (80% wt. in toluene) (257 μL, 2.31 mmol). Purification by flash chromatography (gradient elution; hexanes-EtOAc, 9 : 1 to 4 : 1, v/v) afforded **74b** (364 mg, 66%).

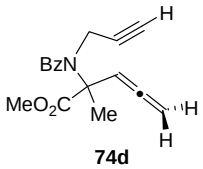
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66-7.64 (m, 2H), 7.46-7.40 (m, 3H), 7.27-7.24 (m, 5H), 5.94 (t, *J* = 6.6 Hz, 1H), 5.10 (app dd, *J* = 6.6, 2.9 Hz, 2H), 3.96 (d, *J* = 13.6 Hz, 1H), 3.76 (s, 3H), 3.73 (dd, *J* = 18.8, 1.8 Hz, 1H), 3.51 (dd, *J* = 18.8, 1.9 Hz, 1H), 3.45 (d, *J* = 13.7 Hz, 1H), 2.18 (s, 1H); ^{13}C NMR (75MHz, $CDCl_3$): δ 207.7, 172.4, 171.1, 135.9, 135.5, 130.9, 130.4, 128.3, 128.1, 127.1, 126.9, 90.5, 80.5, 79.6, 72.8, 68.5, 52.3, 38.8, 38.6; IR (thin film): ν 3302, 2950, 2115, 1957, 1742, 1640, 1433, 1398, 1266, 1246 cm^{-1}; MS *m/z* (%) 358 (35), 268 (42), 105 (100); EI HRMS calcd for $C_{23}H_{20}NO_3$ *m/z* $[M]^+$ 358.1443, found 358.1451.



74c

2-(Benzoylbut-2-ynylamino)-2-methylpenta-3,4-dienoic acid methyl ester (74c). Prepared by following general procedure F, using: **58c** (200 mg, 0.816 mmol), NaH (65 mg of a 60% dispersion in mineral oil, 1.6 mmol), 1-bromo-2-butyne (142 μL,1.6 mmol). Purification by flash chromatography (gradient elution; hexanes-EtOAc, 9 : 1 to 4 : 1, v/v) afforded **74c** (226 mg, 93%).

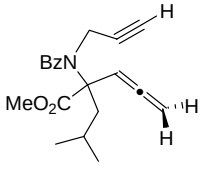
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60-7.57 (m, 2H), 7.40-7.34 (m, 3H), 5.79 (t, *J* = 6.6 Hz, 1H), 4.95 (d, *J* = 6.6 Hz, 1H), 3.96 (q, *J* = 2.2 Hz, 2H), 3.71 (s, 3H), 1.82 (t, *J* = 2.2 Hz, 3H), 1.72 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$): δ 208.2, 172.2, 171.8, 135.5, 130.2, 128.1, 128.1, 127.0, 92.5, 80.3, 78.9, 75.8, 63.4, 52.4, 43.0, 37.3, 20.5, 3.4; IR (thin film): ν 2949, 1957, 1742, 1637, 1398, 1264 cm^{-1}; MS *m/z* (%) 297 (19), 258 (20), 238 (52), 105 (100); EI HRMS calcd for $C_{18}H_{19}NO_3$ *m/z* $[M]^+$ 297.1365, found 297.1359.



74d

2-(Benzoylprop-2-ynylamino)-2-methylpenta-3,4-dienoic acid methyl ester (74d). Prepared by following general procedure F, using: **58c** (200 mg, 0.816 mmol), NaH (65 mg of a 60% dispersion in mineral oil, 1.6 mmol), propargyl bromide (80% wt. in toluene, 180 μL, 1.6 mmol). Purification by flash chromatography (gradient elution; hexanes-EtOAc, 9 : 1 to 4 : 1, v/v) afforded **74d** (217 mg, 94%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64-7.61 (m, 2H), 7.46-7.40 (m, 3H), 5.82 (t, *J* = 6.6 Hz, 1H), 5.01 (d, *J* = 6.5 Hz, 2H), 4.05 (d, *J* = 2.4 Hz, 2H), 3.76 (s, 3H), 2.39 (t, *J* = 2.4 Hz, 1H), 1.77 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$): δ 208.5, 172.2, 172.1, 135.5, 130.4, 128.4, 127.1, 92.6, 80.8, 79.2, 72.8, 63.8, 52.6, 37.1, 20.7; IR (thin film): ν 3256, 2950, 2115, 1956, 1740, 1640, 1397, 1264 cm^{-1}; MS *m/z* (%) 283 (20), 252 (24), 244 (26), 224 (51), 105 (100); EI HRMS calcd for $C_{17}H_{17}NO_3$ *m/z* $[M]^+$ 283.1208, found 283.1198.



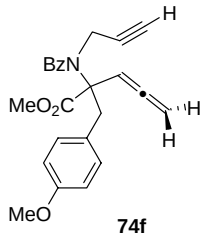
74e

2-(Benzoylprop-2-ynylamino)-2-isobutylpenta-3,4-dienoic acid methyl ester (74e).

An oven-dried three-neck flask equipped with an addition funnel was charged with NaH (2.7 g of a 60% dispersion in mineral oil, 0.066 mol) and DMF (60 mL) was added. The mixture was cooled to 0 °C and a solution of amide **58d** (9.5 g, 0.033 mol) in DMF (200 mL) was added via the addition funnel in a dropwise manner over 15-20 min. During this time, flow of nitrogen was maintained through the reaction setup to flush the H_2 generated during deprotonation. Upon

completion of the addition, the reaction mixture was stirred for additional 5 min, and then propargyl bromide (5.8 mL, 0.066 mol) was added via a syringe. Stirring was continued at 0 °C for additional 3 h. The reaction mixture was then slowly poured into cold water and this mixture was extracted with EtOAc three times. The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The resulting residue was purified by silica gel flash chromatography (hexanes/EtOAc, 6 : 1, v/v) to afford the desired allenyne **74e** (8.3 g, 77%) as a pale yellow solid (mp range 108.5-110.0 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66-7.63 (m, 2H), 7.48-7.38 (m, 3H), 6.06 (t, *J* = 6.6 Hz, 1H), 4.96 (d, *J* = 6.6 Hz, 2H), 4.06 (d, *J* = 2.3 Hz, 2H), 3.75 (s, 3H), 2.43 (t, *J* = 2.4 Hz, 1H), 2.31 (dd, *J* = 13.8, 5.8 Hz, 1H), 2.16 (dd, *J* = 13.8, 5.1 Hz, 1H), 1.91-1.76 (m, 1H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.7, 172.6, 171.6, 135.6, 130.5, 128.4, 127.3, 91.4, 81.1, 79.1, 73.0, 67.2, 52.3, 42.5, 37.8, 24.4, 24.1; IR (thin film): ν 3257, 2956, 2115, 1957, 1742, 1646 cm^{-1}; MS *m/z* (%) 324 (76), 310 (55), 294 (45), 266 (35), 105 (100); EI-HRMS calcd for $C_{20}H_{22}NO_3$ *m/z* $[M]^+$ 324.1600; found 324.1603.

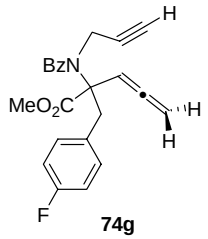


74f

2-(Benzoylprop-2-ynylamino)-2-(4-methoxybenzyl)-penta-3,4-dienoic acid methyl ester (74f). Prepared by following the procedure for preparation of **74e** (*vide ultra*), using: **58e** (17.5 g, 498 mmol), propargyl bromide (13.7 mL, 124 mmol), NaH (5.0 g of a 60% dispersion in mineral oil, 124 mmol). Stirred at 0 °C for 2 h. Purification by flash chromatography (gradient elution, hexanes/EtOAc, 9 : 1 to 1 : 1, v/v) afforded **74f** (16.4 g, 84%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67-7.64 (m, 2H), 7.46-7.42 (m, 3H), 7.17 (d, *J* = 8.6 Hz, 2H),

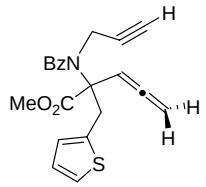
6.82 (d, *J* = 8.6 Hz, 2H), 5.92 (t, *J* = 6.6 Hz, 1H), 5.14-5.04 (m, 2H), 3.87 (d, *J* = 13.7 Hz, 1H), 3.78 (s, 3H), 3.74 (s, 3H), 3.74 (dd, *J* = 18.8, 2.2 Hz, 1H), 3.51 (dd, *J* = 19.0, 2.5 Hz, 1H), 3.40 (d, *J* = 13.7 Hz, 1H), 2.22 (t, *J* = 2.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.8, 172.4, 171.2, 158.6, 135.5, 131.8, 130.4, 128.3, 127.8, 127.1, 113.5, 90.6, 80.7, 79.6, 72.8, 68.5, 55.1, 52.4, 38.8, 37.8; IR (thin film): ν 3258, 2949, 2115, 1957, 1742, 1642, 1513 cm^{-1}; MS *m/z* (%) 388 (26), 330 (50), 268 (34), 230 (42), 105 (100); EI-HRMS calcd for $C_{24}H_{23}NO_4$ *m/z* $[M]^+$ 389.1627; found 389.1614.



74g

2-(Benzoylprop-2-ynylamino)-2-(4-fluorobenzyl)penta-3,4-dienoic acid methyl ester (74g). Prepared by following the general procedure F, using: **58f** (165 mg, 0.486 mmol), propargyl bromide (160 μL, 1.46 mmol), NaH (60% in mineral oil) (58 mg, 1.5 mmol). Stirred at rt for 1.5 h. Yield **74g** (156 mg, 85%).

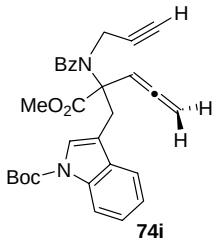
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66-7.58 (m, 2H), 7.48-7.38 (m, 3H), 7.27-7.19 (m, 2H), 7.01-6.95 (m, 2H), 5.93 (t, *J* = 5.8 Hz, 1H), 5.13-5.03 (m, 2H), 3.94 (d, *J* = 13.8 Hz, 1H), 3.60 (dd, *J* = 18.9, 2.2 Hz, 1H), 3.74 (s, 3H), 3.60 (dd, *J* = 18.8, 2.3 Hz, 1H), 3.39 (d, *J* = 13.8 Hz, 1H), 2.18 (t, *J* = 2.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.7, 172.4, 171.0, 163.6, 160.4, 135.4, 132.4, 132.3, 131.8, 130.5, 128.4, 127.1, 115.0, 114.7, 90.5, 80.5, 79.5, 72.8, 68.6, 52.3, 38.9, 38.1; IR (thin film): ν 3298, 2950, 2119, 1957, 1743, 1642, 1510 cm^{-1}; MS *m/z* (%) 376 (69), 346 (20), 268 (57), 105 (100); EI-HRMS calcd for $C_{23}H_{19}NO_3F$ *m/z* [M-1]$^+$ 376.1349; found 376.1358.



74h

2-(Benzoylprop-2-ynylamino)-2-thiophen-2-ylmethylpenta-3,4-dienoic acid methyl ester (74h). Prepared by following the general procedure F, using: **58g** (220 mg, 0.673 mmol), propargyl bromide (185 μL, 1.68 mmol), NaH (60% in mineral oil) (65 mg, 1.7 mmol). Stirred at rt for 30 min. Yield **74h** (220 mg, 89%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69-7.66 (m, 2H), 7.46-7.40 (m, 4H), 7.17 (dd, *J* = 4.9, 1.3 Hz, 1H), 6.94-6.90 (m, 2H), 6.02 (t, *J* = 6.6 Hz, 1H), 5.24-5.13 (m, 2H), 4.22 (d, *J* = 14.9 Hz, 1H), 3.78 (s, 3H), 3.72 (dd, *J* = 18.8, 2.4 Hz, 1H), 3.64 (d, *J* = 14.9 Hz, 1H), 3.46 (dd, *J* = 18.8, 2.5 Hz, 1H), 2.30 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.4, 172.4, 171.0, 137.5, 135.5, 130.3, 128.3, 128.1, 127.1, 126.6, 125.1, 90.3, 80.8, 80.6, 72.9, 68.0, 52.7, 38.8, 32.2; IR (thin film): ν 3264, 2949, 2118, 1956, 1742, 1641 cm^{-1}; MS *m/z* (%) 334 (6), 306 (21), 268 (15), 206 (18), 105 (100); EI-HRMS calcd for $C_{20}H_{16}NO_2S$ *m/z* $[M-31]^+$ 334.0902; found 334.0910.

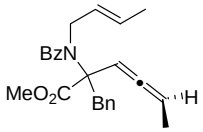


74i

3-[2-(Benzoylprop-2-ynylamino)-2-methoxycarbonylpenta-3,4-dienyl]-indole-1-carboxylic acid *tert*-butyl ester (74i). Prepared by following the general procedure F, using: **58h** (225 mg, 0.489 mmol), propargyl bromide (134 μL, 1.22 mmol), NaH (60% in mineral oil) (49 mg, 1.2 mmol). Stirred at rt for 1h. Yield **74i** (190 mg, 78%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.21 (d, *J* = 7.9 Hz, 1H), 7.78-7.20 (m, 9H), 6.04 (t, *J* = 6.6 Hz,

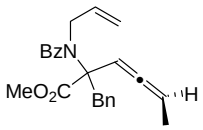
1H), 5.22-5.14 (m, 2H), 4.21 (d, *J* = 14.6 Hz, 1H), 3.85 (s, 3H), 3.63 (d, *J* = 14.6 Hz, 1H), 2.14 (s, 1H), 1.75 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.8, 171.4, 171.2, 149.6, 135.5, 135.1, 131.6, 130.4, 128.3, 127.2, 125.6, 124.3, 122.6, 119.6, 115.0, 114.8, 91.1, 83.6, 80.5, 79.5, 72.7, 68.8, 52.4, 39.1, 28.9, 28.2; IR (thin film): ν 3291, 2980, 2116, 1957, 1735, 1642, 1369 cm^{-1}; MS (EI) *m/z* (%) 498 (6), 398 (20), 339 (32), 293 (63), 105 (100); ESI-HRMS calcd for $C_{30}H_{30}N_2O_5Na$ *m/z* $[M+23]^+$ 521.2052; found 521.2076.



75a

2-(Benzoylbut-2-enylamino)-2-benzylhexa-3,4-dienoic acid methyl ester (75a). Prepared by following the general procedure F, using: **58a** (92 mg, 0.27 mmol), NaH (60% dispersion in mineral oil, 22 mg, 0.55 mmol), crotyl bromide (57 μL, 0.55 mmol). Purification by flash chromatography (hexanes-EtOAc, 9 : 1, v/v) afforded **75a** (60 mg, 56%).

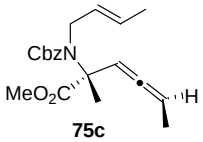
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.27 (m, 10H), 5.62-5.56 (m, 1H), 5.55-5.21 (m, 2H), 4.96-4.88 (m, 1H), 4.00 (d, *J* = 13.5 Hz, 0.63H), 3.97 (d, *J* = 13.5 Hz, 0.37H), 3.77 (s, 3H), 3.61-3.53 (m, 1H), 3.44-3.36 (m, 1H), 3.35 (d, *J* = 13.5 Hz, 1H), 1.80 (dd, *J* = 7.1, 3.3 Hz, 1.9H), 1.74 (dd, *J* = 7.1, 3.2 Hz, 1.1H), 1.53 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 204.7, 173.0, 172.1, 137.3, 137.0, 131.5, 131.5, 129.7, 129.0, 128.6, 128.5, 128.3, 127.7, 127.2, 127.1, 127.0, 126.8, 91.6, 91.5, 90.7, 90.4, 69.2, 52.6, 52.5, 50.4, 50.3, 39.5, 39.4, 18.0, 14.2, 13.9; IR (thin film): ν 2947, 1968, 1744, 1637, 1444 cm^{-1}; MS *m/z* (%) 388 (6), 358 (5), 330 (33), 298 (84), 244 (60), 105 (100); EI-HRMS calcd for $[M-1]^+$, *m/z* $C_{25}H_{26}NO_3$ 388.1913, found 388.1912.



75b

2-(Allylbenzoylamino)-2-benzylhexa-3,4-dienoic acid methyl ester (75b). Prepared by following the general procedure F, using: **58a** (100mg, 0.297 mmol), NaH (60% dispersion in mineral oil, 24 mg, 0.59 mmol), allyl bromide (40 μL, 0.45 mmol). Purification by flash chromatography (hexanes-EtOAc, 9 : 1, v/v) afforded **75b** (80 mg, 71%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.26 (m, 10H), 5.58 (dq, *J* = 9.7, 3.2 Hz, 1H), 5.52-5.41 (m, 2H), 5.25-5.14 (m, 1H), 5.06-5.03 (m, 1H), 3.99 (d, *J* = 13.5 Hz, 0.73H), 3.95 (d, *J* = 13.5 Hz, 0.37H), 3.78 (s, 1.1H), 3.77 (s, 1.9H), 3.65-3.57 (m, 1H), 3.39 (d, *J* = 13.5 Hz, 1H), 3.41-3.28 (m, 1H), 1.80 (dd, *J* = 7.1, 3.3 Hz, 1.9H), 1.74 (dd, J = 7.0, 3.2 Hz, 1.1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 204.6, 204.5, 172.8, 171.8, 171.7, 136.6, 136.6, 136.5, 136.2, 136.1, 131.1, 131.0, 129.5, 128.0, 126.9, 126.4, 116.6, 116.5, 91.1, 91.0, 90.6, 90.3, 68.7, 52.3, 50.6, 50.5, 38.9, 38.7, 13.8, 13.5; IR (thin film): ν 3028, 2947, 1968, 1743, 1639, 1444, 1393, 1266, 1225 cm^{-1}; MS *m/z* (%) 374 (26), 344 (9), 316 (10), 284 (52), 105 (100); EI-HRMS calcd for $C_{24}H_{24}NO_3$ $[M-1]^+$, *m/z* 374.1756, found 374.1761.

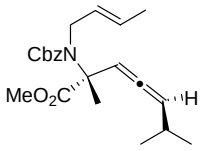


75c

2-(Benzyloxycarbonylbut-2-enylamino)-2-methyl-hexa-3,4-dienoic acid methyl ester (75c). Prepared by following the general procedure F, using: **65d** (66 mg, 0.23 mmol), NaH (60% dispersion in mineral oil) (14 mg, 0.34 mmol), crotyl bromide (50 μL, 0.45 mmol). Purification by flash chromatography (hexanes-EtOAc, 9 : 1, v/v) afforded **75c** (52mg, 66%).

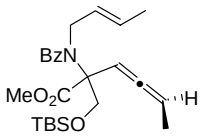
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.30 (m, 5H), 5.64 (dq, *J* = 14.5, 6.3 Hz, 1H), 5.51-5.46 (m,

2H), 5.39-5.30 (m, 1H), 5.13 (s, 2H), 3.96 (br d, 2H), 3.67 (bs, 3H), 1.68 (dd, J = 7.0, 3.1 Hz, 3H), 1.69-1.67 (m, 3H), 1.52 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 205.0, 173.3, 156.0, 136.8, 128.7, 128.5, 128.2, 127.4, 125.2, 93.9, 90.9, 67.6, 64.5, 52.6, 17.9, 14.0; IR (thin film): ν 2949, 1965, 1746, 1698, 1450 cm^{-1}; MS (GC/MS) *m/z* 284 $[M-59]^+$.



75d

2-(Benzyloxycarbonylbut-2-enylamino)-2,6-dimethylhepta-3,4-dienoic acid methyl ester (75d). Prepared by following the general procedure F, using: **65e** (60 mg, 0.19 mmol), NaH (60% dispersion in mineral oil, 15 mg, 0.38 mmol), crotyl bromide (39 μL, 0.38 mmol). Purification by flash chromatography (hexanes-EtOAc, 9 : 1, v/v) afforded **75d** (43 mg, 61%). ^{1}H NMR (300 MHz, $CDCl_3$, 323K): δ 7.34-7.27 (m, 5H), 5.69-5.50 (m, 3H), 5.40 (t, J = 6.1 Hz, 1H), 5.13 (s, 2H), 3.98 (d, J = 4.1 Hz, 2H), 3.59 (s, 3H), 2.41-2.29 (m, 1H), 1.1.68 (d, J = 6.2 Hz, 3H), 1.54 (s, 3H), 1.04 (d, J = 6.7 Hz, 6H); Two additional signals were observed in the ^{1}H NMR spectrum at 4.10 (d, J = 2.8 Hz), 1.61 (d, J = 4.3 Hz) and are attributed to carbamate rotational isomerism. ^{13}C NMR ($CDCl_3$, 75 MHz, 323 K): δ 202.4, 172.8, 155.8, 136.6, 128.3, 128.0, 127.9, 127.0, 103.0, 95.3, 67.3, 64.5, 52.2, 28.1, 22.5, 22.4, 17.5, 12.8; IR (thin film): ν 2959, 1962, 1747, 1701, 1252 cm^{-1}; MS *m/z* (%) 371 (24), 312 (25), 258 (31), 91 (100); EI-HRMS calcd for $C_{22}H_{29}NO_4$ $[M]^+$, *m/z* 371.2097, found 371.2104.

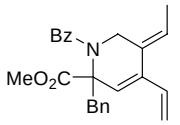


75e

2-(Benzoylbut-2-enylamino)-2-(*tert*-butyldimethylsilyloxymethyl)-hexa-3,4-dienoic acid methyl ester (75e). Prepared by following the general procedure F, using: **58i** (90 mg, 0.23 mmol), NaH (60% dispersion in mineral oil) (19 mg, 0.46 mmol), crotyl bromide (47 μL, 0.46 mmol). Purification by flash chromatography (hexanes-EtOAc, 9 : 1, v/v) afforded **75e** (43 mg, 42%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-7.27 (m, 5H), 5.65-5.43 (m, 3H), 5.35-5.29 (m, 1H), 4.51-4.45 (m, 1H), 4.10 (d, *J* = 10.2 Hz, 1H), 4.09-4.00 (m, 1H), 3.92 (bd, *J* = 16.4 Hz, 1H), 3.74 (s, 3H), 1.70-1.67 (m, 6H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 205.1, 204.9, 172.5, 170.8, 136.9, 129.8, 129.5, 129.3, 128.1, 127.9, 127.1, 127.0, 126.7, 126.5, 126.5, 89.9, 89.8, 89.5, 68.3, 64.0, 63.8, 52.1, 50.2, 50.1, 25.8, 25.8, 18.1, 17.7, 13.9, 13.6, 12.7, -5.5, 5.6; IR (thin film): ν 2951, 1968, 1743, 1639, 1401, 1250 cm^{-1}; MS *m/z* (%) 443 (25), 386 (43), 298 (35), 244 (32), 105 (100); EI-HRMS calcd for $C_{25}H_{37}NO_4Si$ $[M]^+$, *m/z* 443.2492, found 443.2503.

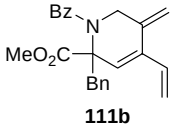
General procedure G for the Rh(I)-catalyzed allenic Alder-ene reaction.



111a

1-Benzoyl-2-benzyl-5-ethylidene-4-vinyl-1,2,5,6-tetrahydropyridine-2-carboxylic acid methyl ester (111a). Allenyne **73a** (20 mg, 52 μmol) was placed in a new 15 mL test tube equipped with a stirring bar and toluene (1 mL) was added followed by $[Rh(CO)_2Cl]_2$ (1 mg, 3 μmol) at rt. Upon completion of the reaction based on TLC analysis (10 min) the solution was directly applied to a short column of silica gel. Elution with (hexanes-EtOAc, 9 : 1, v/v) afforded **111a** (16 mg, 80%) after concentration under vacuum.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47-7.39 (m, 5H), 7.31-7.28 (m, 5H), 6.36 (dd, *J* = 17.2, 10.7 Hz, 1H), 5.75 (s, 1H), 5.63 (q, *J* = 7.0 Hz, 1H), 5.50 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.27 (dd, *J* = 10.7, 1.5 Hz, 1H), 4.13 (d, *J* = 13.6 Hz, 1H), 4.13 (d, *J* = 14.6 Hz, 1H), 3.80 (s, 3H), 3.41 (d, *J* = 13.6 Hz, 1H), 2.46 (d, *J* = 14.3 Hz, 1H), 1.42 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 171.3, 139.5, 137.0, 136.7, 134.6, 131.0, 130.1, 129.5, 128.8, 128.3, 127.2, 127.0, 123.5, 123.0, 117.9, 67.0, 53.1, 44.7, 40.3, 13.4; IR (thin film) ν 2949, 1738, 1640, 1415 cm^{-1}; MS *m/z* (%) 387 (8), 356 (7), 296 (25), 105 (100); EI-HRMS calcd for $C_{18}H_{18}NO_3$ *m/z* $[M-91]^+$ 296.1287; found 296.1283.

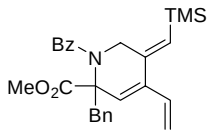


111b

1-Benzoyl-2-benzyl-5-methylene-4-vinyl-1,2,5,6-tetrahydropyridine-2-carboxylic acid methyl ester (111b). Prepared by following general procedure G, using: **73b** (29 mg, 78 μmol), $[Rh(CO)_2Cl]_2$ (1.5 mg, 4 μmol). Yield **111b** (21 mg, 74%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.38 (m, 5 H), 7.25-7.20 (m, 5H), 6.37 (dd, *J* = 17.3, 10.8

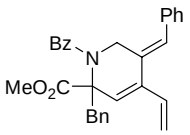
Hz, 1H), 5.85 (s, 1H), 5.52 (dd, *J* = 17.3, 1.2 Hz, 1H), 5.28 (dd, *J* = 10.8, 1.1 Hz, 1H), 5.09 (s, 1H), 4.76 (s, 1H), 4.10 (d, *J* = 13.7 Hz, 1H), 3.84 (d, *J* = 13.9 Hz, 1H), 3.77 (s, 3H), 3.39 (d, *J* = 13.7 Hz, 1H), 2.67 (d, *J* = 14.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 170.6, 137.9, 136.4, 136.0, 135.8, 133.3, 130.6, 129.9, 128.4, 128.0, 126.9, 126.8, 125.7, 117.8, 112.5, 66.5, 52.9, 50.6, 39.8; IR (thin film): ν 2949, 1739, 1638, 1410, 1242 cm^{-1}; MS *m/z* (%) 373 (20), 342 (8), 314 (8), 282 (25), 105 (100); EI-HRMS calcd for $C_{24}H_{23}NO_3$ *m/z* $[M]^+$ 373.1678, found 373.1664.



111c

1-Benzoyl-2-benzyl-5-trimethylsilylmethylene-4-vinyl-1,2,5,6-tetrahydropyridine-2-carboxylic acid methyl ester (111c). Prepared by following general procedure G, using: **73c** (46 mg, 103 μmol), $[Rh(CO)_2Cl]_2$ (2 mg, 5 μmol). Yield **111c** (42 mg, 92%).

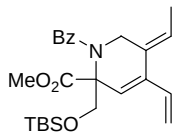
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.18 (m, 10H), 6.32 (dd, *J* = 17.3, 10.8 Hz, 1H), 5.82 (s, 1H), 5.52 (s, 1H), 5.43 (dd, *J* = 17.3, 1.5 Hz, 1H), 5.21 (dd, *J* = 10.8, 1.5 Hz, 1H), 4.06 (d, *J* = 13.7 Hz, 1H), 4.00 (d, *J* = 14.1 Hz, 1H), 3.75 (s, 3H), 3.34 (d, *J* = 13.7 Hz, 1H), 2.70 (d, *J* = 14.1, 1.2 Hz, 1H), -0.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8, 170.3, 142.5, 139.5, 136.5, 136.3, 134.0, 130.6, 129.7, 128.5, 128.0, 126.9, 126.7, 124.9, 117.7, 65.7, 52.8, 49.3, 39.7, -0.7; IR (thin film): ν 3029, 2951, 1740, 1642, 1408, 1252, 1218 cm^{-1}; MS *m/z* (%) 445 (5), 430 (5), 354 (40), 105 (100); EI-HRMS calcd for $C_{27}H_{31}NO_3Si$ $[M]^+$ *m/z* 445.2073, found 445.2076.



111d

1-Benzoyl-2-benzyl-5-benzylidene-4-vinyl-1,2,5,6-tetrahydropyridine-2-carboxylic acid methyl ester (111d). Prepared by following general procedure G, using: **73d** (26 mg, 58 μmol), $[Rh(CO)_2Cl]_2$ (1 mg, 3 μmol). Yield **111d** (21 mg, 81%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29-7.00 (m, 13 H), 6.82-6.79 (m, 2H), 6.61 (s, 1H), 6.43 (ddd, *J* = 17.3, 10.7, 0.8 Hz, 1H), 5.89 (s, 1H), 5.56 (dd, *J* = 17.3, 1.5 Hz, 1H), 5.33 (dd, *J* = 10.7, 1.5 Hz, 1H), 4.41 (d, *J* = 14.2 Hz, 1H), 4.10 (d, *J* = 13.6 Hz, 1H), 3.77 (s, 3H), 3.41 (d, *J* = 13.6 Hz, 1H), 2.68 (d, *J* = 14.2, 1.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.1, 171.2, 139.8, 136.9, 136.1, 135.8, 134.5, 131.0, 130.5, 129.7, 128.8, 128.5, 128.4, 128.0, 127.5, 127.1, 127.0, 125.6, 118.5, 66.9, 53.2, 45.4, 40.3; IR (thin film): ν 2918, 1738, 1639, 1413, 1223 cm^{-1}; MS *m/z* (%) 449 (10), 390 (15), 358 (50), 105 (100); EI-HRMS calcd for $C_{30}H_{27}NO_3$ *m/z* $[M]^+$ 449.1991; found 449.2011.

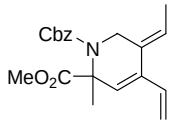


111e

1-Benzoyl-2-(*tert*-butyldimethylsilyloxymethyl)-5-ethylidene-4-vinyl-1,2,5,6-tetrahydropyridine-2-carboxylic acid methyl ester (111e). Prepared by following general procedure G, using: **73e** (36 mg, 83 μmol), $[Rh(CO)_2Cl]_2$ (1.5 mg, 5 μmol). Yield **111e** (32 mg, 89%).

^{1}H NMR (300 MHz, $CDCl_3$): δ (7.47-7.40 (m, 5H), 6.38 (dd, *J* = 17.2, 10.7 Hz, 1H), 5.75 (q, *J* = 7.0 Hz, 1H), 5.57 (s, 1H), 5.44 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.21 (dd, *J* = 10.7, 1.5 Hz, 1H), 4.70 (d, *J* = 10.2 Hz, 1H), 4.51 (d, *J* = 14.1 Hz, 1H), 4.19 (d, *J* = 10.2 Hz, 1H), 3.99 (d, *J* = 14.0 Hz,

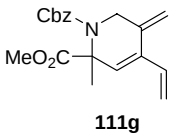
1H), 3.69 (s, 3H), 1.58 (d, J = 7.1 Hz, 1H), 0.85 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 170.8, 139.6, 136.2, 134.4, 129.9, 129.7, 128.5, 127.0, 122.6, 122.4, 117.5, 66.3, 65.4, 52.5, 45.4, 25.8, 18.1, 13.4, -5.4, -5.5; IR (thin film): ν 2954, 2929, 2037, 1740, 1644 cm^{-1}; MS *m/z* (%) 441 (23), 411 (63), 384 (66), 296 (100); EI-HRMS calcd for $C_{25}H_{35}NO_4Si$ *m/z* $[M]^+$ 441.2335; found 441.2333.



111f

5-Ethylidene-2-methyl-4-vinyl-5,6-dihydro-2H-pyridine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (111f). Prepared by following general procedure G, using: **73f** (0.515 g, 1.51 mmol), $[Rh(CO)_2Cl]_2$ (24 mg, 62 μmol). Yield **111f** (420 mg, 81%).

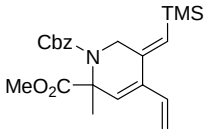
^{1}H NMR (300 MHz, DMSO-d_6, 323 K): δ 7.37-7.33 (m, 5H), 6.40 (dd, J = 17.2, 10.8 Hz 1H), 5.76 (q, J = 7.0 Hz, 1H), 5.50 (bs, 1H), 5.40 (dd, J = 17.2, 1.3 Hz 1H), 5.19 (dd, J = 10.8, 1.3 Hz, 1H), 5.15 (d, J = 12.4 Hz, 1H), 5.10 (d, J = 12.4 Hz, 1H), 4.58 (d, J = 14.6 Hz, 1H), 3.79 (d, J = 14.6 Hz, 1H), 3.49 (s, 3H), 1.76 (d, J = 7.0 Hz, 3H), 1.55 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, 323K): δ 171.5, 154.1, 136.1, 135.3, 133.6, 128.9, 128.0, 127.5, 127.2, 123.9, 122.2, 117.0, 66.4, 61.6, 51.8, 12.7; IR (thin film): ν 2949, 1743, 1704, 1404, 1243, 1110 cm^{-1}; MS *m/z* (%) 341 (26), 282 (26), 238 (15), 91 (100); EI-HRMS calcd for $C_{20}H_{23}NO_4$ $[M]^+$ *m/z* 341.1621, found 341.1627.



111g

2-Methyl-5-methylene-4-vinyl-5,6-dihydro-2H-pyridine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (111g). Prepared by following general procedure G, using: **73g** (37 mg, 110 μmol), $[Rh(CO)_2Cl]_2$ (2 mg, 5 μmol). Yield **111g** (31 mg, 84%).

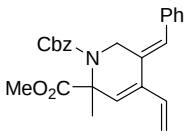
^{1}H NMR (300 MHz, DMSO-d_6, 323 K): δ 7.35 (m, 5H), 6.43 (dd, J = 17.3, 11.0 Hz, 1H), 5.68 (s, 1H), 5.48 (d, J = 17.3 Hz, 1H), 5.26-5.24 (m, 2H), 5.11 (s, 2H), 4.39 (d, J = 14.2 Hz, 1H), 3.88 (d, J = 14.2 Hz, 1H), 3.49 (bs, 3H), 1.55 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, 323 K): δ 171.3, 154.0, 136.1, 135.8, 134.2, 132.9, 128.1, 127.6, 127.4, 126.5, 117.3, 112.6, 66.5, 62.0, 52.0, 45.6, 21.5; IR (thin film): ν 2950, 1743, 1704, 1247 cm^{-1}; MS *m/z* (%) 327 (12), 268 (85), 224 (59), 91 (100); EI-HRMS calcd for $C_{19}H_{21}NO_4$ *m/z* $[M]^+$ 327.1471; found 327.1473.



111h

2-Methyl-5-trimethylsilylmethylene-4-vinyl-5,6-dihydro-2H-pyridine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (111h). Prepared by following general procedure G, using: **73h** (30 mg, 75 μmol), $[Rh(CO)_2Cl]_2$ (1.5 mg, 4 μmol). Yield **111h** (26 mg, 87%).

^{1}H NMR (300 MHz, DMSO-d_6, 323 K): δ 7.39-7.30 (m, 5H), 6.43 (dd, J = 17.2, 10.8 Hz, 1H), 5.76 (s, 1H), 5.66 (s, 1H), 5.41 (d, J = 17.2 Hz, 1H), 5.21 (dd, J = 10.8, 0.7 Hz, 1H), 5.13 (1d, J = 13.4 Hz, 1H), 5.07 (d, J = 13.4 Hz, 1H), 4.54 (d, J = 14.4 Hz, 1H), 3.94 (d, J = 14.4 Hz, 1H), 3.52 (s, 3H), 1.57 (s, 3H), 0.13 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6, 323K): δ 171.2, 153.9, 143.4, 136.1, 135.9, 123.3, 128.0, 127.6, 127.5, 126.9, 126.8, 126.1 117.3, 66.6, 61.7, 51.9, 44.1, 21.2, -0.5; IR (thin film): ν 2953, 1745, 1706, 1405, 1248, 1113 cm^{-1}; MS *m/z* (%) 399 (25), 340 (34), 296 (15), 91 (100); EI-HRMS calcd for $C_{22}H_{29}NO_4Si$ $[M]^+$ *m/z* 399.1866, found 399.1843.

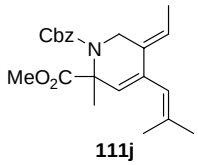


111i

5-Benzylidene-2-methyl-4-vinyl-5,6-dihydro-2H-pyridine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (111i). Prepared by following general procedure G, using: **73i** (25 mg, 62

μmol), $[Rh(CO)_2Cl]_2$ (1 mg, 3 μmol). Yield **111i** (25 mg, 95%).

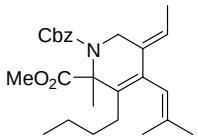
^{1}H NMR (300 MHz, DMSO-d_6, 323 K): δ 7.46-7.21 (m, 10H), 6.76 (s, 1H), 6.57 (dd, *J* = 17.1, 10.7 Hz, 1H), 5.72 (s, 1H), 5.52 (d, *J* = 17.2 Hz, 1H), 5.29 (d, *J* = 10.8 Hz, 1H), 5.07 (d, *J* = 12.6 Hz, 1H), 5.01 (d, *J* = 12.7 Hz, 1H), 4.87 (d, *J* = 14.7 Hz, 1H), 4.09 (d, *J* = 14.7 Hz, 1H), 3.52 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, 323 K): δ 171.4, 153.9, 135.9, 135.9, 135.7, 133.7, 130.0, 128.8, 128.1, 127.6, 127.2, 127.1, 126.9, 126.0, 117.8, 66.4, 61.8, 52.1, 21.3; IR (thin film): ν 2949, 1742, 1704, 1408, 1248 cm^{-1}; MS *m/z* (%) 403 (37), 344 (45), 300 (17), 91 (35), 84 (100); EI-HRMS calcd for $C_{25}H_{25}NO_4$ *m/z* $[M]^+$ 403.1784, found 403.1789.



111j

5-Ethylidene-2-methyl-4-(2-methylpropenyl)-5,6-dihydro-2H-pyridine-1,2-dicarboxylic acid 1-benzylester 2-methyl ester (111j). Prepared by following general procedure G, using: **73j** (40 mg, 110 μmol), $[Rh(CO)_2Cl]_2$ (2 mg, 5 μmol). Yield **111j** (40 mg, 95%).

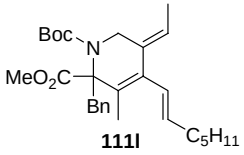
^{1}H NMR (300 MHz, DMSO-d_6, 323 K): δ 7.35 (s, 5H), 5.64 (s, 1H), 5.58 (q, *J* = 6.9 Hz, 1H), 5.12 (s, 3H), 4.65 (d, *J* = 14.9 Hz, 1H), 3.71 (d, *J* = 14.7 Hz, 1H), 3.47 (bs, 3H), 1.77 (s, 3H), 1.72 (d, *J* = 6.8 Hz, 3H), 1.58 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, 323 K): δ 171.9, 154.2, 137.2, 136.2, 134.2, 130.2, 128.1, 128.1, 127.7, 127.4, 125.5, 122.0, 121.1, 66.5, 61.5, 51.8, 25.3, 18.5, 12.8; IR (thin film): ν 2930, 1742, 1687, 1424, 1253 cm^{-1}; MS *m/z* (%) 369 (10), 310 (50), 266 (36), 91 (100); EI-HRMS calcd for $C_{22}H_{27}NO_4$ *m/z* $[M]^+$ 369.1940; found 369.1952.



111k

5-Ethylidene-2-methyl-4-(2-methylpropenyl)-3-pentyl-5,6-dihydro-2H-pyridine-1,2-dicarboxylic acid-1-benzyl ester 2-methyl ester (111k). Prepared by following general procedure G, using: **73k** (33 mg, 77 μmol), $[Rh(CO)_2Cl]_2$ (2 mg, 5 μmol). Yield **111k** (29 mg, 78%).

^{1}H NMR (300 MHz, DMSO-d_6, 323 K): δ 7.45-7.38 (m, 5H), 5.61 (s, 1H), 5.52 (q, J = 7.0 Hz, 1H), 5.20-5.11 (m, 2H), 4.73 (d, J = 14.7 Hz, 1H), 3.66 (d, J = 14.7 Hz, 1H), 2.00-1.93 (m, 1H), 1.83 (s, 3H), 1.74 (d, J = 7.0 Hz, 1H), 1.57 (s, 3H), 1.48 (s, 3H), 1.34-1.23 (m, 4H), 0.86 (t, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, 323 K): δ 172.2, 154.6, 137.0, 136.1, 134.0, 133.2, 131.4, 128.9, 128.4, 128.1, 121.2, 120.7, 67.2, 65.4, 52.2, 31.4, 29.0, 25.0, 23.1, 19.1, 13.9, 13.5; IR (thin film): ν 1745, 1703, 1408, 1245 cm^{-1}; MS *m/z* (%) 425 (20), 366 (6), 135 (95), 133 (100); EI-HRMS calcd for $C_{26}H_{35}NO_4$ *m/z* $[M]^+$ 425.2566; found 425.2549.



111l

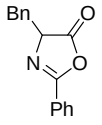
2-Benzyl-5-ethylidene-4-hept-1-enyl-3-methyl-5,6-dihydro-2H-pyridine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester (111l). Prepared by following general procedure G, using: **73l** (45 mg, 96 μmol), $[Rh(CO)_2Cl]_2$ (3 mg, 8 μmol). Yield **111l** (36 mg, 80%).

^{1}H NMR (300 MHz, DMSO-d_6, 325 K): δ 7.21-7.15 (m, 3H), 7.02-6.93 (m, 2H), 5.82 (d, J = 16.0 Hz, 1H), 5.44 (dt, J = 16.0, 6.8 Hz, 1H), 5.20 (q, J = 7.1 Hz, 1H), 3.96 (d, J = 14.5 Hz, 1H), 3.70-3.56 (m, 4H), 3.63 (s, 3H), 3.59 (d, J = 13.7 Hz, 1H), 3.24 (d, J = 13.8 Hz, 1H), 2.90 (d, J = 14.6 Hz, 1H), 2.11 (q, J = 6.8 Hz, 1H), 1.80 (s, 3H), 1.46 (s, 9H), 1.41 (d, J = 7.0 Hz, 3H), 1.36-

1.25 (m, 6H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, 325 K): δ 171.7, 153.2, 136.0, 135.9, 134.2, 130.2, 129.8, 127.2, 126.1, 125.3, 123.9, 120.0, 79.9, 67.7, 51.6, 31.9, 30.4, 27.9, 27.7, 21.5, 15.6, 13.4, 12.4; IR (thin film): ν 2926, 1744, 1696, 1240 cm^{-1}; MS *m/z* (%) 458 (6), 394 (42), 376 (30), 276 (78), 91 (50), 57 (100); EI-HRMS calcd for $C_{22}H_{34}NO_4$ *m/z* [M-91]$^+$ 376.2488; found 376.2479.

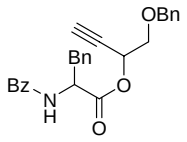
Compounds **120-125** were prepared as part of a preliminary study which was later discontinued; These compounds were characterized only by their ^{1}H NMR spectrum:

The TBS protected diol **118** was prepared according to a previously reported procedure (Lafontaine, J. A.; Provencal, D. P.; Gardelli, C.; Leahy, J. W. *J. Org. Chem.* **2003**, *68*, 4215). Alcohols **116a** and **116b** were prepared according to a previously reported procedure (Aurrecoechea, J. M.; Perez, E.; Solay, M. *J. Org. Chem.* **2001**, *66*, 564).



55a

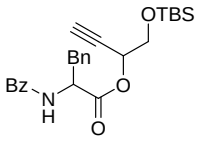
4-Benzyl-2-phenyloxazol-5(4H)-one (55a). *N*-Bz-phenylalanine **119** (489 mg, 1.82 mmol) was dissolved in CH_2Cl_2 (10 mL) at rt and DCC (374 mg, 1.82 mmol) was added followed by DMAP (11 mg, 0.09 mmol). Dicyclohexylurea byproduct formed immediately as a white precipitate. After 10 min, the reaction mixture was filtered over a short pad of silica gel using a fritted funnel and eluted with hexanes-EtOAc (3 : 1). The filtrate was concentrated under vacuum to afford **55a** (365 mg, 80%) as a white solid. This compound was used in the next step without additional purification.



120a

1-(Benzyloxy)but-3-yn-2-yl 2-(benzamido)-3-phenylpropanoate (120a). Oxazolone **55a** (365 mg, 1.45 mmol) was dissolved in CH_2Cl_2 and alcohol **116a** (329 mg, 1.89 mmol) was added, followed by Et_3N (100 μL, 0.72 mmol). The solution was concentrated under vacuum, resulting in a viscous oil. After 1h the reaction mixture was re-dissolved in benzene (1 mL) and purified by flash chromatography (gradient elution, hexanes-EtOAc, 1 : 0 to 4 : 1, v/v) to afford **120a** (335 mg, 54%) as a mixture of diastereomers in 1 : 1 ratio.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, *J* = 7.3 Hz, 2H), 7.54-7.17 (m, 13H), 6.54 (t, *J* = 6.0 Hz, 1H), 5.68-5.61 (m, 1H), 5.22-5.14 (m, 1H), 4.67-4.59 (m, 2H), 3.84-3.70 (m, 2H), 3.39-3.23 (m, 2H), 2.60 (d, *J* = 2.2 Hz, 0.5H), 2.52 (d, *J* = 2.1 Hz, 0.5H); IR (thin film): ν 3288, 3030, 2931, 2124, 1749, 1648 cm^{-1}.

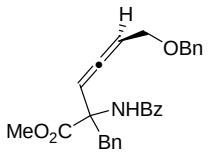


120b

1-(*tert*-Butyldimethylsilyloxy)but-3-yn-2-yl 2-(benzamido)-3-phenylpropanoate (120b). Oxazolone **55a** (1.50 g, 5.97 mmol) was dissolved in CH_2Cl_2 (3 mL) and alcohol **116b** (1.10 g, 6.57 mmol) was added, followed by Et_3N (83 μL, 0.60 mmol). The solution was concentrated under vacuum, resulting in a viscous oil. After 30 min the reaction mixture was re-dissolved in benzene (~1 mL) and purified by flash chromatography (gradient elution, hexanes-EtOAc, 20 : 1 to 10 : 1, v/v) to afford **120b** (790 mg, 32%) as a mixture of diastereomers in 1 : 1 ratio.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (d, *J* = 7.0 Hz, 2H), 7.65-7.54 (m, 3H), 7.42-7.32 (m, 5H),

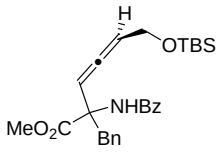
6.72 (d, *J* = 7.6 Hz, 0.5H), 6.68 (d, *J* = 7.6 Hz, 0.5H), 5.63 (td, *J* = 5.9, 2.0 Hz, 0.5H), 5.56-5.53 (m, 0.5H), 5.36-5.25 (m, 1H), 4.04-4.00 (m, 2H), 3.53-3.36 (m, 2H), 2.70 (d, *J* = 2.0 Hz, 0.5H), 2.63 (d, *J* = 2.1 Hz, 0.5H), 1.06 (s, 4.5H), 1.03 (s, 4.5H), 0.27 (s, 1.5H), 0.26 (s, 1.5H), 0.23 (s, 3H).



121a

Methyl 2-(benzamido)-2-benzyl-6-(benzyloxy)hexa-3,4-dienoate (121a). Propargylic ester **120a** (100 mg, 0.234 mmol) was dissolved in MeCN (5 mL) at rt. Then, Et_3N (137 μL, 0.983 mmol), CCl_4 (81 μL, 0.84 mmol) and PPh_3 (190 mg, 0.725 mmol) were added in consecutive order. The reaction mixture was stirred at 40 °C for 1.5 h when MeOH (1 mL) was added and the solution was concentrated under vacuum. The crude brown residue was dissolved in MeOH (5 mL) and Et_3N (100 μL) was added and the reaction was stirred for 12 h at rt. The reaction mixture was again concentrated under vacuum, and the crude residue was purified by flash chromatography (hexanes-EtOAc, 4 : 1, v/v) to afford **121a** (102 mg, >95%) as a mixture of diastereomers in ~2 : 1 ratio (determined by integration of the allene proton resonances in the ^1H NMR spectrum).

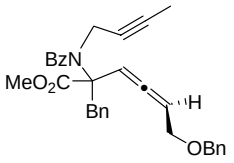
^1H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.07 Hz, 2H), 7.60-7.19 (m, 13H), 6.96 (bs, 0.67H), 6.92 (bs, 0.33H), 5.88-5.84 (m, 0.67H), 5.79-5.75 (m, 0.33H), 5.73-5.66 (m, 0.33H), 5.62-5.56 (m, 0.67H), 4.56 (s, 1.34H), 4.46 (1/2 ABq, *J* = 11.2 Hz, 0.33H), 4.41 (1/2 ABq, *J* = 11.2 Hz, 0.33H), 4.20-4.14 (m, 1.34H), 4.06-4.02 (m, 0.66H), 3.91 (s, 1H), 3.90 (s, 2H), 3.84-3.62 (m, 2H).



121b

Methyl 2-(benzamido)-2-benzyl-6-(*tert*-butyldimethylsilyloxy)hexa-3,4-dienoate (121b). Propargylic ester **120b** (180 mg, 0.429 mmol) was dissolved in MeCN (5 mL) at rt. Then, Et_3N (251 μL, 1.80 mmol), CCl_4 (149 μL, 1.54 mmol) and PPh_3 (348 mg, 1.33 mmol) were added in consecutive order. The reaction mixture was stirred at 60 °C for 1.5 h when MeOH (1 mL) was added and the solution was concentrated under vacuum. The crude brown residue was dissolved in MeOH (5 mL) and Et_3N (100 μL) was added and the reaction was stirred for 12 h at rt. The reaction mixture was again concentrated under vacuum, and the crude residue was purified by flash chromatography (gradient elution, hexanes-EtOAc, 1 : 0 to 4 : 1, v/v) to afford **121b** (140 mg, 76%) as a mixture of diastereomers in ~2 : 1 ratio (determined by integration of the allene proton resonances in the ^{1}H NMR spectrum).

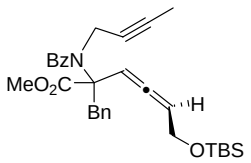
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85-7.81 (m, 2H), 7.66-7.52 (m, 3H), 7.41-7.34 (m, 3H), 7.26-7.24 (m, 2H), 6.92 (bs, 0.67H), 6.91 (bs, 0.33H), 5.85 (dt, J = 6.2, 2.6 Hz, 0.67H), 5.77 (dt, J = 6.2, 2.6 Hz, 0.33H), 5.62 (dt, $J_1 = J_2$ = 6.2 Hz, 0.33H), 5.56 (dt, $J_1 = J_2$ = 6.2 Hz, 0.67H), 4.31 (dd, J = 6.0, 2.7 Hz, 1.34H), 4.29-4.17 (m, 0.33H), 4.11-4.07 (m, 0.33H), 3.96 (s, 3H), 3.87 (1/2 ABq, J = 13.5 Hz, 0.67H), 3.84 (1/2 ABq, J = 13.5 Hz, 0.33H), 3.76 (1/2 ABq, J = 13.5 Hz, 0.33H), 3.72 (1/2 ABq, J = 13.5 Hz, 0.67H), 1.00 (s, 9H), 0.17 (s, 2H), 0.16 (s, 2H), 0.15 (s, 1H), 0.13 (s, 1H).



122a

Methyl-2-(*N*-(but-2-ynyl)benzamido)-2-benzyl-6-(benzyloxy)hexa-3,4-dienoate (122a). Prepared by following general procedure F with: **121a** (60 mg, 0.14 mmol), 1-bromo-2-butyne (30 μL, 0.34 mmol) and NaH (14 mg from a 60% dispersion in mineral oil, 0.34 mmol). Yield of **122a** (54 mg, 81%) obtained as a mixture of diastereomers in ~2 : 1 ratio determined by integration of the benzyloxy methylene resonances (4.73 and 4.70 ppm) in the ^{1}H NMR spectrum.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81-7.78 (m, 2H), 7.62-7.39 (m, 13H), 6.21-6.17 (m, 1H), 5.79 (dt, $J_1 = J_2$ = 6.6 Hz, 0.33H), 5.74 (dt, $J_1 = J_2$ = 6.6 Hz, 0.67H), 4.73 (s, 1.34H), 4.70 (s, 0.66H), 4.30 (dd, J = 6.5, 2.2 Hz, 1.34H), 4.25 (dd, J = 6.4, 2.1 Hz, 0.66H), 4.12 (1/2 ABq, J = 13.5 Hz, 0.67H), 4.11 (1/2 ABq, J = 13.5 Hz, 0.33H), 3.87 (s, 3H), 3.80-3.92 (m, 1.34H), 3.76-71 (m, 0.66H), 3.56 (1/2 ABq, J = 13.5 Hz, 0.33H), 3.54 (1/2 ABq, J = 13.5 Hz, 0.67H), 1.82-1.80 (m, 3H); IR (thin film): ν 3029, 2854, 1969, 2228, 1743, 1641 cm^{-1}.

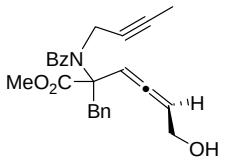


122b

Methyl-2-(*N*-(but-2-ynyl)benzamido)-2-benzyl-6-(*tert*-butyldimethylsilyloxy)hexa-3,4-dienoate (122b). Prepared by following general procedure F with: **121b** (380 mg, 0.88 mmol), 1-bromo-2-butyne (231 μL, 2.65 mmol) and NaH (123 mg from a 60% dispersion in mineral oil, 3.08 mmol). Yield of **122b** (300 mg, 66%) obtained as a mixture of diastereomers in ~2 : 1 ratio determined by integration of the allylic methylene resonances (4.29 and 4.25-4.22 ppm) in the

^{1}H NMR spectrum.

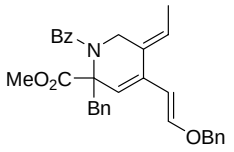
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67-7.65 (m, 2H), 7.45-7.41 (m, 3H), 7.33-7.25 (m, 5H), 6.04-6.00 (m, 1H), 5.63-5.52 (m, 1H), 4.29 (dd, *J* = 6.1, 2.6 Hz, 1.34H), 4.25-4.22 (m, 0.66H), 4.00 (1/2 ABq, *J* = 13.6 Hz, 0.67H), 3.94 (1/2 ABq, 13.5 Hz, 0.33H), 3.74 (s, 3H), 3.83-3.73 (m, 1H), 3.64-3.58 (m, 1H), 3.43 (1/2 ABq, *J* = 13.3 Hz, 0.33H), 3.39 (1/2 ABq, *J* = 13.6 Hz, 0.67H), 1.67 (s, 3H), 0.93 (s, 6H), 0.90 (s, 3H), 0.12 (s, 4H), 0.09 (s, 2H).



122c

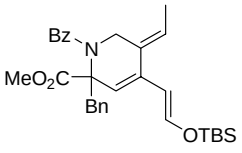
Methyl-2-(*N*-(but-2-ynyl)benzamido)-2-benzyl-6-hydroxyhexa-3,4-dienoate (122c). To a solution of **122b** (80 mg, 0.15 mmol, crude residue prior to purification by chromatogprahy) in THF (2 mL) was added TBAF (240 μL of a 1.0 M solution in THF, 0.24 mmol). After 1 h, the solution was diluted with EtOAc (50 mL) and washed with brine (2 x 20 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified by flash chromatography (gradient elution, hexanes-EtOAc, 4 : 1 to 1 : 1, v/v) to afford alcohol **122c** (41 mg, 62% for the two steps from **121b**) as a ~2 : 1 mixture of diastereomers determined by integration of the allenic resonances in the ^{1}H NMR spectrum.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81-7.80 (m, 2H), 7.61-7.56 (m, 3H), 7.47-7.40 (m, 5H), 6.26 (dt, *J* = 6.2, 3.1 Hz, 0.33H), 6.12 (dt, *J* = 6.2, 3.1 Hz, 0.67H), 5.85 (dt, $J_1 = J_2$ = 5.7 Hz, 0.33H), 5.74 (dt, $J_1 = J_2$ = 5.7 Hz, 0.67H), 4.34-4.29 (m, 2H), 4.13 (1/2 ABq, *J* = 13.8 Hz, 0.33H), 4.07-3.97 (m, 2.67H), 3.90 (s, 1H), 3.83 (s, 2H), 3.63 (1/2 ABq, *J* = 13.1 Hz, 0.67H), 3.51 (1/2 ABq, *J* = 13.6 Hz, 0.33H), 1.85 (s, 2H), 1.80 (s, 1H).



123a

1-Benzoyl-2-benzyl-4-(2-benzyloxyvinyl)-5-ethylidene-1,2,5,6-tetrahydro-pyridine-2-carboxylic acid methyl ester (123a). To a solution of allenyne **122a** (22 mg, 0.045 mmol) in toluene-d^8 (1 mL) was added $[Rh(CO)_2Cl]_2$ (1 mg, 2 μmol) at rt. After 1 h, the reaction solution was directly applied to a short silica gel column and eluted (hexanes-EtOAc, 4 : 1, v/v) to afford **123a** (14 mg, 64%). Triene **123a** was obtained as a mixture of *E* and *Z* isomers of the enol-ether olefin in 8 : 1 ratio (determined by integration of the olefin resonances in the ^{1}H NMR spectrum). **123a-(*E*)**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-7.38 (m, 10H), 7.26-7.20 (m, 5H), 6.70 (d, *J* = 12.5 Hz, 1H), 5.55 (q, *J* = 6.9 Hz, 1H), 5.53 (s, 1H), 5.45 (d, *J* = 12.5 Hz, 1H), 4.86 (s, 2H), 4.09-4.05 (m, 2H), 3.75 (s, 3H), 3.35 (d, *J* = 13.6 Hz, 1H), 2.40 (d, *J* = 14.4 Hz, 1H), 1.36 (d, *J* = 6.9 Hz, 3H).

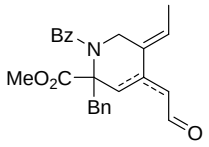


123b

1-Benzoyl-2-benzyl-4-[2-(*tert*-butyldimethylsilanyloxy)vinyl]-5-ethylidene-1,2,5,6-tetrahydropyridine-2-carboxylic acid methyl ester (123b). To a solution of allenyne **122b** (45 mg, 0.087 mmol) in toluene (1 mL) was added $[Rh(CO)_2Cl]_2$ (2 mg, 4 μmol) at rt. After 40 min, the reaction solution was directly applied to a short silica gel column and eluted (hexanes-EtOAc) to afford **123b** (27 mg, 60%). Triene **123b** was obtained as a mixture of *E* and *Z* isomers of the enol-ether olefin in >10 : 1 ratio (determined by integration of the olefin resonances in the ^{1}H NMR spectrum).

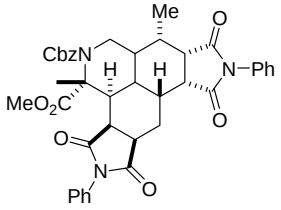
123b-(*E*): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-7.35 (m, 5H), 7.30-7.20 (m, 5H), 6.60 (d, *J* =

11.9 Hz, 1H), 5.58 (q, *J* = 6.8 Hz, 1H), 5.54 (d, J = 12.7 Hz, 1H), 5.51 (s, 1H), 4.07 (d, *J* = 13.8 Hz, 2H), 3.75 (s, 3H), 3.35 (d, *J* = 13.5 Hz, 1H), 2.41 (d, J = 14.3 Hz, 1H), 1.36 (d, *J* = 7.0 Hz, 3H), 0.96 (s, 9H), 0.21 (s, 3H), 0.20 (s, 3H).



124 and **125**

Aldehydes **124** and **125** : To a solution of allenyne **122c** (20 mg, 0.050 mmol) in DCE (1 mL) was added $[Rh(CO)_2Cl]_2$ (1 mg, 2 μmol) at rt. After 90 min, the reaction solution was directly applied to a short silica gel column and eluted (hexanes-EtOAc, 3 : 1, v/v) to afford a mixture of aldehydes **124** and **125** (10 mg, 50% by mass recovery).

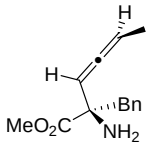


144

Diels-Alder cycloadduct 144. To a solution of triene **111f** (0.018 g, 0.053 mmol), in toluene (1 mL), was added *N*-phenylmaleimide (31 mg, 0.23 mmol). The reaction was heated to reflux for 2 h. The solution was then cooled to rt, and directly applied to a silica gel column and purified by flash chromatography (hexanes-EtOAc, 1 : 4, v/v then EtOAc) to afford **144** as a mixture of diastereomers (30 mg, 83%). Further purification of the major diastereomer was performed using HPLC (hexanes-EtOAc, 3 : 2, v/v, flow rate 3 mL/min, RI detector).

144 (major diastereomer, R_t = 26.1 min): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.13 (m, 5 H), 7.31-7.22 (m, 5H), 7.20-7.16 (m, 3H), 7.04 (d, *J* = 7.2 Hz, 2H), 5.11 (d, *J* = 12.7 Hz, 1H), 5.01 (d, *J* = 12.7 Hz, 1H), 4.46 (d, *J* = 18.9 Hz, 1H), 3.54-2.51 (m, 2H), 3.42-3.39 (m, 1H), 3.36 (s, 3H), 3.29 (bs, 1H), 3.15 (dd, *J* = 8.8, 6.7 Hz, 1H), 3.03 (dd, *J* = 8.8, 5.6 Hz, 1H), 2.65 (dd, *J* =

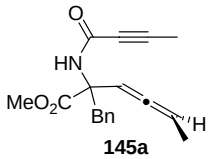
13.9, 5.3 Hz, 1H), 2.51-2.47 (m, 1H), 2.45 (bs, 1H), 2.25 (bs, 1H), 2.06 (s, 3H), 1.42 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.2, 176.2, 175.4, 175.2, 174.3, 156.2, 136.8, 133.4, 131.8, 131.6, 129.1, 128.7, 128.6, 128.3, 127.6, 127.4, 126.7, 126.2, 67.0, 63.7, 53.0, 45.7, 44.3, 43.3, 40.8, 40.4, 39.9, 33.5, 32.7, 24.5, 23.2, 12.7; IR (thin film): ν 2945, 1708, 1499, 1383 cm^{-1}; EI-HRMS calcd for $C_{40}H_{38}N_3O_8$ *m/z* $[M+1]^+$ 688.2659; found 688.2637.



152

Methyl-2-amino-2-benzylhexa-3,4-dienoate (152). To a solution of Boc-protected amine **65f** (0.80 g, 2.4 mmol) in CH_2Cl_2 (3 mL), was added TFA (3 mL) and the light brown solution was stirred at rt for 10 min. The volatiles were removed under vacuum (rotary evaporator was used with a dry ice-cooled trap to collect the TFA) to afford a brown oil which was dissolved in CH_2Cl_2 (100 mL) and washed with sat'd aq. $NaHCO_3$ (3 x 50 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum to afford **152** (0.53 g, 95%) as a colorless oil.

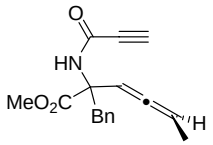
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.16 (m, 5H), 5.47 (dq, J = 6.3, 3.1 Hz, 1H), 5.35 (dq, J = 6.5, 6.5 Hz, 1H), 3.75 (s, 3H), 3.27 (d, J = 13.2 Hz, 1H), 2.91 (d, J = 13.2 Hz, 1H), 1.70 (dd, J = 7.1, 3.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.5, 175.1, 135.8, 129.9, 128.0, 126.8, 96.3, 90.6, 61.0, 52.1, 45.6, 14.0; IR (thin film): ν 3380, 3304, 2950, 1962, 1737, 1197 cm^{-1}; MS *m/z* (%) 231 (7), 216 (25), 199 (19), 178 (27), 172 (35), 140 (100), 91 (76), 80 (57); EI-HRMS calcd for *m/z* $C_{14}H_{17}NO_2$ $[M]^+$ 231.1259 found 231.1251.



145a

Methyl 2-benzyl-2-(but-2-ynamido)hexa-3,4-dienoate (145a). To a solution of 2-butynoic acid (0.34 g, 4.08 mmol) in THF (25 mL), was added *N*-methylmorpholine (1.12 mL, 10.2 mmol) at rt. The solution was then cooled to -10 °C with a NaCl/ice bath and isobutyl chloroformate (0.53 mL, 4.08 mmol) was added. After 30 min at -10 °C, amine **152** (0.78 g, 3.40 mmol) in THF (15 mL) was added and the reaction was allowed to warm to rt and stirred for 3 h. The reaction was quenched with sat'd aqueous $NaHCO_3$ and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. Purification of the residue by column chromatography (hexanes-EtOAc, 9 : 1, v/v) afforded **145a** (0.86 g, 85%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.30 (m, 3H), 7.19-7.16 (m, 2H), 6.42 (s, 1H), 5.51 (sex, *J* = 3.1 Hz, 1H), 5.41 (quin, *J* = 7.0 Hz, 1H), 3.86 (s, 3H), 3.68 (d, *J* = 13.6 Hz, 1H), 3.48 (d, *J* = 13.6 Hz, 1H), 1.99 (s, 3H), 1.77 (dd, *J* = 7.1, 3.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.1, 171.7, 152.2, 135.6, 130.1, 128.1, 126.9, 92.4, 91.6, 82.9, 74.9, 63.6, 52.8, 39.7, 13.8, 3.6; IR (thin film): ν 3400, 3292, 2244, 1968, 1740, 1656, 1495 cm^{-1}; EI-HRMS calcd for $C_{16}H_{16}NO$ *m/z* $[M-59]^+$ 238.1232; found 238.1230.

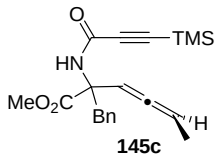


145b

Methyl 2-benzyl-2-(propiolamido)hexa-3,4-dienoate (145b). To a solution of amine **152** (0.168 g, 0.727 mmol) in CH_2Cl_2 (4 mL) was added propiolic acid (0.049 mL, 0.800 mmol) followed by DCC (0.165 g, 0.800 mmol). Formation of a white precipitate was observed. After

15 min the solvent was removed under vacuum and the remaining residue was dissolved in EtOAc and filtered through a plug of silica gel on a fritted funnel eluting with EtOAc/hexanes (1 : 1). Concentration of the solution under vacuum afforded an orange oil that was purified by flash chromatography (hexanes-EtOAc, 6 : 1, v/v) to afford **145b** (0.170 g, 82%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.28 (m, 3H), 7.21-7.13 (m, 2H), 6.61 (s, 1H), 5.51 (dq, *J* = 6.3, 3.2 Hz, 1H), 5.45 (quin, *J* = 6.5 Hz, 1H), 3.87 (s, 3H), 3.69 (d, *J* = 13.7 Hz, 1H), 3.47 (d, *J* = 13.7 Hz, 1H), 2.84 (s, 1H), 1.77 (dd, *J* = 7.0, 3.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.2, 171.4, 150.8, 135.3, 129.9, 128.2, 127.0, 92.1, 91.8, 77.2, 72.8, 63.9, 52.9, 39.6, 13.7; IR (thin film): ν 3392, 3271, 2950, 2110, 1968, 1740, 1662 cm^{-1}; EI-HRMS calcd for $C_{17}H_{17}NO_3$ *m/z* $[M]^+$ 283.1208; found 283.1198.

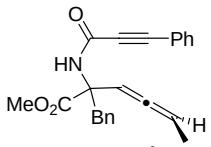


145c

Methyl 2-(3-(trimethylsilyl)propiolamido)-2-benzylhexa-3,4-dienoate (145c). To a solution of 3-(trimethylsilyl)propiolic acid (74 mg, 520 μmol) in THF (6 mL), was added *N*-methylmorpholine (0.21 mL, 1.9 mmol) at rt. The solution was then cooled to -10 °C and isobutyl chloroformate (68 μL, 520 μmol) was added. After 30 min at -10 °C amine **152** (110 mg, 480 μmol) in THF (4 mL) was added and the reaction was allowed to warm to rt, then stirred for additional 3 h. The reaction was quenched with sat'd aq. $NaHCO_3$ (50 mL) and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. Purification of the residue by column chromatography (hexanes-EtOAc, 19 : 1, v/v) afforded **145c** (121 mg, 72%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.35 (m, 3H), 7.26-7.19 (m, 2H), 6.61 (s, 1H), 5.59 (dq, *J* = 6.3, 3.2 Hz, 1H), 5.55–5.45 (m, 1H), 3.93 (s, 3H), 3.79 (d, *J* = 13.7 Hz, 1H), 3.52 (d, *J* = 13.6 Hz,

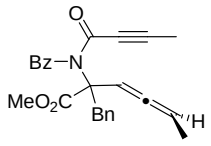
1H), 1.84 (dd, *J* = 7.1, 3.2 Hz, 3H), 0.36 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.3, 171.6, 151.6, 135.5, 130.0, 128.1, 126.9, 97.6, 92.3, 91.6, 90.9, 64.1, 52.9, 39.7, 13.7, -0.8; IR (thin film): ν 3397, 2955, 2165, 1968, 1741, 1662 cm^{-1}; EI-HRMS calcd for $C_{20}H_{25}NO_3Si$ *m/z* $[M]^+$ 355.1604; found 355.1589.



145d

Methyl 2-(3-phenylpropiolamido)-2-benzylhexa-3,4-dienoate (145d). To a solution of amine **152** (131 mg, 567 μmol) in CH_2Cl_2 (4 mL) was added 3-phenylpropiolic acid (83 mg, 568 μmol) and DCC (117 mg, 570 μmol). The reaction mixture was stirred for 30 min, and then filtered to remove the white solid. The solution was concentrated under vacuum and the resulting oil purified by flash chromatography to afford **145d** (112 mg, 55%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63-7.61 (m, 2H), 7.53-7.30 (m, 6H), 7.25-7.23 (m, 2H), 6.66 (s, 1H), 5.60–5.55 (m, 1H), 5.52-5.44 (m, 1H), 3.90 (s, 3H), 3.78 (d, *J* = 13.7 Hz, 1H), 3.53 (d, *J* = 13.7 Hz, 1H), 1.81 (dd, *J* = 7.1, 3.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.3, 171.7, 152.3, 135.6, 132.6, 130.1, 130.0, 128.4, 128.2, 127.0, 120.1, 92.4, 91.7, 84.2, 83.1, 64.1, 53.0, 39.8, 13.8; IR (thin film): ν 3393, 3292, 2950, 2214, 1968, 1741, 1654 cm^{-1}; EI-HRMS calcd for $C_{23}H_{21}NO_3$ *m/z* $[M]^+$ 359.1521; found 359.1526.

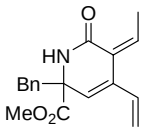


145e

2-[Benzoyl-(1-oxobut-2-ynyl)-amino]-2-benzylhexa-3,4-dienoic acid methyl ester (145e). To a solution of **145a** (0.15 g, 0.49 mmol), in 1,2-dichloroethane (5 mL) were added Et_3N (0.399 mL, 2.44 mmol), DMAP (catalytic amount ~ 10 mg), and 4Å molecular sieves (0.5 g) at rt.

Benzoyl chloride (0.169 mL, 1.46 mmol) was added and the reaction mixture was heated to 70 °C for 1 h. Upon completion of the reaction, as observed by TLC, the reaction solution was transferred to a separate flask via a pipette, and concentrated under vacuum. The crude residue was purified by flash chromatography (EtOAc /hexanes, 1 : 9, v/v) to afford **145e** (0.19 g, 69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09-8.06 (m, 2H), 7.61-7.56 (m, 1H), 7.50-7.45 (m, 2H), 7.27-7.23 (m, 5H), 5.54 (dq, *J* = 6.3, 3.1 Hz, 1H), 5.43–5.33 (m, 1H), 3.72 (d, *J* = 13.0 Hz, 1H), 3.70 (s, 3H), 3.21 (d, *J* = 13.0 Hz, 1H), 1.68 (dd, *J* = 7.1, 3.2 Hz, 3H), 1.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.1, 172.8, 170.9, 152.5, 137.1, 135.1, 133.5, 130.8, 130.4, 128.6, 128.0, 127.0, 93.7, 90.9, 90.9, 74.8, 69.0, 52.5, 41.4, 13.6, 3.6; IR (thin film): ν 2945, 2238, 1972, 1744, 1706, 1653, 1234 cm^{-1}; MS *m/z* (%) 401 (43), 310 (28), 244 (15), 105 (100), 67 (43); EI-HRMS calcd for $C_{25}H_{23}NO_4$ *m/z* $[M]^+$ 401.1627; found 401.1621.

General procedure H for the Rh(I)-catalyzed Alder-ene reaction of 145a-d.

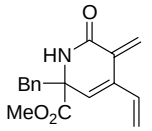


146a

2-Benzyl-5-ethylidene-6-oxo-4-vinyl-1,2,5,6-tetrahydropyridine-2-carboxylic acid methyl ester (146a). Allenyne **145a** (0.996 g, 3.35 mmol) was placed in a reaction vessel equipped with a magnetic stirring bar, a septum and an Ar balloon inlet, and toluene (130 mL, ~0.03 M) was added. The solution was degassed by bubbling argon via a needle for 5 min and then $[Rh(CO)_2Cl]_2$ (0.13 g, 0.33 mmol) was added. The reaction vessel was then immersed in an oil bath pre-heated to 90 °C. The progress of the reaction was followed by TLC and upon completion (30 min) it was cooled to rt. The solution was then directly applied to a silica gel column and eluted (hexanes-EtOAc, 3 : 1, v/v) to give cross-conjugated triene **146a** (0.916 g,

92%).

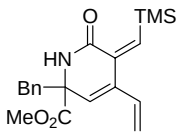
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30-7.22 (m, 3H), 7.11-7.08 (m, 2H), 6.30 (dd, *J* = 17.2, 10.7 Hz, 1H), 6.15 (bs, 1H), 6.13 (q, *J* = 7.5 Hz, 1H), 6.00 (s, 1H), 5.49 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.25 (dd, *J* = 10.8, 1.4 Hz, 1H), 3.77 (s, 3H), 3.21 (d, *J* = 13.1 Hz, 1H), 2.97 (d, *J* = 13.1 Hz, 1H), 2.16 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.7, 164.9, 139.2, 138.7, 134.1, 133.9, 130.8, 128.7, 127.8, 126.1, 119.7, 118.5, 64.8, 53.3, 47.9, 16.3; IR (thin film): ν 3206, 2952, 2029, 1739, 1674, 1241 cm^{-1}; MS *m/z* (%) 297 (25), 238 (40), 206 (100), 174 (77), 146 (71), 91 (83); EI-HRMS calcd for $C_{18}H_{19}NO_3$ *m/z* $[M]^+$ 297.1365; found 297.1375.



146b

Methyl 2-benzyl-1,2,5,6-tetrahydro-5-methylene-6-oxo-4-vinylpyridine-2-carboxylate (146b). Prepared by following general procedure H, using: **145b** (20 mg, 78 μmol), $[Rh(CO)_2Cl]_2$ (3.0 mg, 7.8 μmol). Reaction time 2 h. Yield **145b** (10 mg, 45%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.36 (m, 3H), 7.21-7.15 (m, 2H), 6.49 (ddd, *J* = 17.2, 10.9, 1.0 Hz, 1H), 6.39 (s, 1H), 6.24 (s, 1H), 5.65 (d, *J* = 0.8 Hz, 1H), 5.64 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.39 (dd, *J* = 10.8, 1.4 Hz, 1H), 3.84 (s, 3H), 3.38 (d, *J* = 13.2 Hz, 1H), 3.07 (d, *J* = 13.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 163.0, 135.6, 133.3, 132.6, 132.1, 130.3, 128.6, 127.6, 121.8, 121.3, 118.4, 64.6, 53.1, 47.6; IR (thin film): ν 3215, 2952, 1738, 1679, 1234 cm^{-1}.

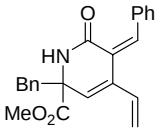


146c

(5Z)-Methyl-2-benzyl-1,2,5,6-tetrahydro-5-((trimethylsilyl)methylene)-6-oxo-4-vinyl-pyridine-2-carboxylate (146c). Prepared by following general procedure H, using: **145c** (40

mg, 0.11 mmol), $[Rh(CO)_2Cl]_2$ (4 mg, 11 μmol). Reaction time 15 min. Isolated yield **146c** (30 mg, 75%).

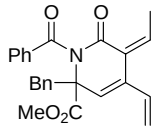
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.39 (m, 3H), 7.25-7.22 (m, 2H), 6.57 (dd, *J* = 17.1, 10.8 Hz, 1H), 6.56 (bs, 1H), 6.32 (s, 1H), 6.26 (s, 1H), 5.65 (dd, *J* = 17.1, 1.1 Hz, 1H), 5.41 (dd, *J* = 10.8, 1.2 Hz, 1H), 3.90 (s, 3H), 3.42 (d, *J* = 13.1 Hz, 1H), 3.16 (d, *J* = 13.1 Hz, 1H), 0.29 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 163.5, 143.0, 138.1, 137.4, 133.6, 133.4, 130.4, 128.5, 127.5, 121.3, 118.1, 64.6, 53.0, 47.3, 0.2; IR (thin film): ν 3205, 2951, 1736, 1673, 1243 cm^{-1}; MS *m/z* (%) 355 (3), 340 (30), 296 (36), 264 (95), 249 (57), 73 (100); EI-HRMS calcd for $C_{20}H_{25}NO_3Si$ *m/z* $[M]^+$ 355.1604; found 355.1593.



146d

(5Z)-Methyl-2-benzyl-5-benzylidene-1,2,5,6-tetrahydro-6-oxo-4-vinylpyridine-2-carboxylate (146d). Prepared by following general procedure H, using: **145d** (30 mg, 84 μmol), $[Rh(CO)_2Cl]_2$ (3.0 mg, 8.4 μmol). Reaction time 30 min. Isolated yield **146d** (20 mg, 66%). Note: the reaction also resulted in minor amount (<10%) of the exocyclic olefin isomer which was separable by silica gel chromatography.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47-7.44 (m, 2H), 7.34-7.13 (m, 8H), 6.80 (s, 1H), 6.45 (ddd, *J* = 17.1, 10.9, 0.7 Hz, 1H), 6.34 (bs, 1H), 6.19 (s, 1H), 5.62 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.36 (dd, *J* = 10.9, 1.5 Hz, 1H), 3.81 (s, 3H), 3.27 (d, *J* = 13.2 Hz, 1H), 3.06 (d, *J* = 13.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 163.6, 139.2, 138.0, 135.3, 133.7, 133.6, 130.5, 130.3, 128.4, 127.6, 127.5, 125.4, 121.8, 118.8, 64.7, 53.1, 47.3; IR (thin film): ν 3197, 3061, 2952, 1738, 1673, 1242 cm^{-1}. MS *m/z* (%) 359 (10), 300 (23), 268 (100), 208 (67), 91 (74); EI-HRMS calcd for $C_{23}H_{21}NO_3$ *m/z* $[M]^+$ 359.1521; found 359.1517.

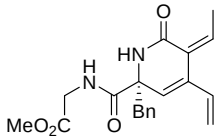


146e

1-Benzoyl-2-benzyl-5-ethylidene-6-oxo-4-vinyl-1,2,5,6-tetrahydropyridine-2-carboxylic acid methyl ester (146e). To a solution of **145e** (28 mg, 70 μmol), in toluene (2 mL), was added $[Rh(CO)_2Cl]_2$ (2.7 mg, 6.9 μmol) at rt under Ar atmosphere. The reaction was stirred for 1 h at rt and the yellow solution was then applied to a small silica gel column and eluted (EtOAc/hexanes, 1 : 9, v/v) to give **146e** (21 mg, 75%) after removal of the solvents.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58-7.55 (m, 2H), 7.49-7.44 (m, 1H), 7.39–7.34 (m, 2H), 6.27 (dd, *J* = 17.3, 10.8 Hz, 1H), 6.01 (q, *J* = 7.5 Hz, 1H), 5.80 (s, 1H), 5.56 (dd, *J* = 17.3, 1.4 Hz, 1H), 5.31 (dd, *J* = 10.8, 1.4 Hz, 1H), 4.03 (d, *J* = 13.8 Hz, 1H), 3.75 (s, 3H), 3.41 (d, *J* = 13.8 Hz, 1H), 1.78 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.1, 171.3, 165.6, 141.1, 138.6, 136.4, 134.5, 133.1, 131.5, 131.5, 128.3, 128.1, 127.8, 127.1, 125.9, 120.0, 118.6, 69.9, 53.3, 42.0, 16.3; IR (thin film): ν 3027, 2945, 1746, 1686, 1271, 1219 cm^{-1}; EI-HRMS calcd for $C_{25}H_{23}NO_4$ *m/z* $[M]^+$ 401.1627; found 401.1639.

General procedure I for preparation of diamides 154a and 154b.



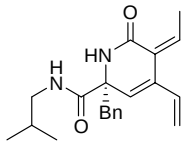
154a

[(2-Benzyl-5-ethylidene-6-oxo-4-vinyl-1,2,5,6-tetrahydropyridine-2-carbonyl)amino]acetic acid methyl ester (154a). To a solution of ester **146a** (0.916 g, 3.08 mmol) in THF (60 mL) was added water (60 mL) at rt, followed by $LiOH{\cdot}H_2O$ (0.264 g, 6.15 mmol). The homogeneous solution was stirred for 5 min, and then acidified with sat'd aq. NH_4Cl (200 mL) and 1M HCl (20

mL).[kk] The aqueous layer was extracted with EtOAc (3 x 100 mL) and the extracts were combined, dried over $MgSO_4$ and concentrated under vacuum to afford the desired carboxylic acid, which was then dissolved in CH_2Cl_2 (70 mL). To this solution were then added, HOBt (0.407 g 3.10 mmol), EDCI (0.579 g, 3.10 mmol), DMAP (0.738 g, 6.20 mmol) and gycine methylester·HCl (0.379 g, 3.10 mmol) at rt. The reaction was stirred at rt for 90 min, and then diluted with CH_2Cl_2 (150 mL). The solution was washed with water (50 mL), sat'd aq. NH_4Cl (2 x 50 mL), then dried over $MgSO_4$, filtered and concentrated under vacuum. Purification of the crude residue by flash chromatography (hexanes-EtOAc, 4 : 1 to 1 : 1, v/v) afforded **154a** (0.710 g, 65%) which was used in the next step without additional purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.35 (m, 1H), 7.28-7.15 (m, 5H), 6.96 (bs, 1H), 6.27 (dd, *J* = 17.1, 10.7 Hz, 1H), 6.14 (q, *J* = 7.5 Hz, 1H), 5.88 (s, 1H), 5.45 (dd, *J* = 17.1, 1.6 Hz, 1H), 5.21 (dd, *J* = 10.8, 1.63 Hz, 1H), 4.16 (dd, *J* = 18.0, 5.9 Hz, 1H), 3.93 (dd, *J* = 18.0, 5.2 Hz, 1H), 3.72 (s, 3H), 3.41 (d, *J* = 13.4 Hz, 1H), 3.16 (d, *J* = 13.4 Hz, 1H), 2.12 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8, 170.2, 165.8, 138.9, 137.4, 134.5, 133.6, 130.8, 128.1, 127.1, 125.1, 120.9, 118.2, 65.8, 52.3, 44.9, 41.4, 16.0; IR (thin film): ν 3304, 2951, 1745, 1669, 1635, 1209 cm^{-1}; MS *m/z* (%) 354 (9), 263 (40), 238 (100), 174 (31), 91 (90); EI-HRMS calc'd for $C_{20}H_{22}N_2O_4$ *m/z* $[M]^+$ 354.1580; found 354.1582.

[kk] In certain cases the homogeneous solution separated into two layers upon addition of LiOH and saponification did not proceed to completion. In these cases it is advantageous to add additional amount of water under vigorous stirring until the reaction mixture becomes homogeneous again.

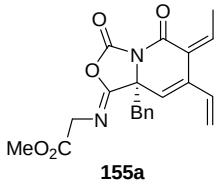


154b

2-Benzyl-5-ethylidene-6-oxo-4-vinyl-1,2,5,6-tetrahydropyridine-2-carboxylic acid isobutyl-amide (154b). Prepared by following general procedure I, using **146a** (0.240 g, 0.808 mmol), HOBt (0.109 g, 0.808 mmol), EDCI (0.155 g, 0.808 mmol), DMAP (0.098 g, 0.81 mmol) and *i*-butylamine (0.081 mL, 0.81 mmol). Isolated yield **154b** (0.178 g, 60%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28-7.15 (m, 5H), 6.55 (bs, 1H), 6.43-6.35 (m, 1H), 6.31 (ddd, *J* = 17.2, 10.8, 0.9 Hz, 1H), 6.24 (q, *J* = 7.5 Hz, 1H), 5.98 (s, 1H), 5.47 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.23 (dd, *J* = 10.8, 1.6 Hz, 1H), 3.53 (d, *J* = 13.2 Hz, 1H), 3.04-2.96 (m, 3H), 2.18 (d, *J* = 7.5 Hz, 3H), 1.70 (sep, *J* = 6.7 Hz, 1H), 0.79 (d, *J* = 6.7 Hz, 3H), 0.78 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.8, 165.7, 139.0, 136.6, 134.3, 133.6, 130.5, 128.4, 127.2, 125.2, 122.1, 118.2, 65.8, 47.2, 45.3, 28.2, 19.9, 16.1; IR (thin film): ν 3337, 2959, 1671, 1636 cm^{-1}; MS *m/z* (%) 338 (9), 247 (11), 238 (100), 91 (65).

General procedure J for preparation of imino-oxazolidinones 155a and 15b.

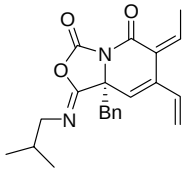


155a

8a-Benzyl-6-ethylidene-1-ethylimino-7-vinyl-6,8a-dihydro-1H-oxazolo[3,4-a]pyridine-3,5-dione (155a). A solution of diamide **154a** (0.710 g, 2.01 mmol) in CH_2Cl_2 (150 mL) was cooled to -10 ºC, and Et_3N (0.839 mL, 6.03 mmol) was added. Then, phosgene (1.42 mL, 3.02 mmol of a 20 % solution in toluene) was added dropwise, and the reaction was stirred for 10 min at -10

ºC. After quenching the reaction by adding water (10 mL), the organic layer was washed with diluted NH_4Cl solution (2 x 100 mL) to remove the excess Et_3N, dried over $MgSO_4$, and concentrated under vacuum. The crude residue was purifed by flash chromatography (hexanes-EtOAc, 4 : 1 to 1 : 1, v/v) to afford the imino-oxazolidinone **155a** (0.645 g, 85%). Note: extended exposure of **155a** to silica gel causes hydrolysis to **154a**. All operations during the aqueous workup procedure and chromatography were performed fast in order to minimize the decomposition of **155a**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25-7.21 (m, 3H), 7.09-7.06 (m, 2H), 6.23 (s, 1H), 6.23 (q, *J* = 7.5 Hz, 1H), 6.19 (dd, *J* = 17.2, 10.8 Hz, 1H), 5.56 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.32 (dd, *J* = 10.8, 1.2 Hz, 1H), 4.25 (s, 2H), 3.81 (s, 3H), 3.22 (d, *J* = 13.6 Hz, 1H), 3.11 (d, *J* = 13.6 Hz, 1H), 2.04 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 160.4, 153.3, 146.0, 144.7, 138.8, 132.7, 132.1, 131.0, 128.5, 128.0, 126.8, 119.6, 118.9, 66.6, 52.3, 49.2, 47.5, 16.3; IR (thin film): ν 2953, 1840, 1744, 1272 cm^{-1}; MS *m/z* (%) 380 (32), 336 (14), 245 (61), 217 (35), 91 (100); EI-HRMS calcd for $C_{21}H_{20}N_2O_5$ *m/z* $[M]^+$ 380.1372; found 380.1370.



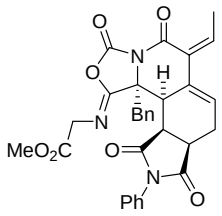
155b

8a-Benzyl-6-ethylidene-1-isobutylimino-7-vinyl-6,8a-dihydro-1H-oxazolo[3,4-a]pyridine-3,5-dione (155b). Prepared by following general procedure J, using **154b** (0.170 g, 0.503 mmol), Et_3N (0.182 mL, 0.159 mmol) and phosgene (0.310 mL, 0.657 mmol of a 20 % solution in toluene). Isolated yield **155b** (0.125 g, 68%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22-7.20 (m, 3H), 7.05-7.03 (m, 2H), 6.22-6.12 (m, 3H), 5.54 (dd, *J* = 17.4, 1.2 Hz, 1H), 5.29 (dd, *J* = 10.8, 1.2 Hz, 1H), 3.23 (d, *J* = 6.8 Hz, 2H), 3.12 (d, *J* =

13.5 Hz, 1H), 3.03 (d, *J* = 13.5 Hz, 1H), 1.99 (d, *J* = 7.5 Hz, 3H), 1.90 (sep, *J* = 6.7 Hz, 1H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.5, 149.1, 146.9, 144.0, 138.5, 132.7, 132.2, 130.8, 128.2, 127.8, 126.8, 119.3, 119.2, 66.0, 55.3, 47.4, 29.2, 20.4, 16.2; IR (thin film): ν 2956, 1836, 1743, 1269 cm^{-1}; MS *m/z* (%) 364 (6), 320 (19), 229 (33), 173 (100), 91 (63); EI-HRMS calcd for $C_{22}H_{24}N_2O_3$ *m/z* $[M]^+$ 364.1787; found 364.1786.

General procedure K for preparation of cycloadducts 156a and 156b.

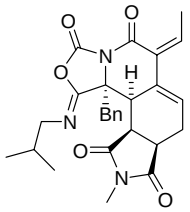


156a

(10c-Benzyl-5-ethylidene-3,4,8,10-tetraoxo-9-phenyl-4,5,7,7a,8,9,10,10a,10b,10c-decahydro-2-oxa-3a,9-diazadicyclopenta[a,h]naphthalen-1-ylideneamino)-acetic acid methyl ester (156a). A solution of triene **155a** (0.063 g, 0.17 mmol) and *N*-phenylmaleimide (0.037 g, 0.22 mmol) in toluene (4 mL) was heated to 90 ºC until the starting material was completely consumed as evidenced by TLC analysis. During this time, **156a** began precipitating as a white solid. The mixture was cooled to 0 ºC in a test tube and centrifuged for 15 min. The toluene was decanted away and the solid was rinsed with hexanes and dried under vacuum to afford **156a** (0.067 g, 73%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.29 (m, 6H), 7.09-7.00 (m, 4H), 6.65 (q, *J* = 7.3 Hz, 1H), 6.25-6.19 (m, 1H), 4.36 (d, *J* = 18.0 Hz, 1H), 4.34 (dd, *J* = 9.0, 5.2 Hz, 1H), 4.22 (d, *J* = 18.1 Hz, 1H), 3.78 (s, 3H), 3.46 (t, *J* = 7.9 Hz, 1H), 3.37 (d, *J* = 13.5 Hz, 1H), 3.27 (d, *J* = 13.5 Hz, 1H), 3.10 (bs, 1H), 3.09-3.02 (m, 1H), 2.31 (d, *J* = 7.4 Hz, 3H), 2.35-2.25 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.8, 176.1, 170.1, 159.5, 153.6, 146.2, 141.3, 135.6, 132.2, 131.1, 130.0,

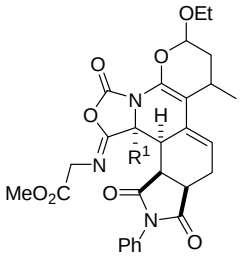
129.8, 129.0, 128.7, 128.4, 126.2, 126.0, 123.7, 66.2, 52.2, 48.9, 48.4, 41.6, 40.6, 39.6, 25.7, 16.0; IR (thin film): ν 1842, 1741, 1711, 1290 cm^{-1}; MS *m/z* (%) 553 (5), 509 (18), 462 (76), 418 (85), 319 (83), 91 (100); EI-HRMS calcd for $C_{31}H_{27}N_3O_7$ *m/z* $[M]^+$ 553.1849; found 553.1830.



156b

10c-Benzyl-5-ethylidene-1-isobutylimino-9-methyl-5,7,7a,10a,10b,10c-hexahydro-1H-2-oxa-3a,9-diaza-dicyclopenta[a,h]naphthalene-3,4,8,10-tetraone (156b). Prepared by following general procedure K, using **155b** (0.115 g, 0.276 mmol), *N*-methylmaleimide (0.040 g, 0.359 mmol). Precipitation of the product from the toluene solution was accomplished by addition of hexanes (2 mL) and refrigeration at -10 °C for 2 days under nitrogen atmosphere. Isolated yield **156b** (0.133 g, >95%).

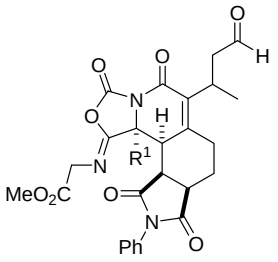
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.27 (m, 3H), 6.98-6.95 (m, 2H), 6.58 (q, *J* = 7.4, 1H), 6.12-6.08 (m, 1H), 3.88 (dd, *J* = 8.9, 5.2 Hz, 1H), 3.36-3.20 (m, 5H), 3.16 (d, *J* = 13.4 Hz, 1H), 3.02-2.92 (m, 2H), 2.86 (d, *J* = 3.8 Hz, 1H), 2.83 (s, 3H), 2.28 (d, *J* = 7.4 Hz, 3H), 1.91 (sep, *J* = 6.7 Hz, 1H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.6, 176.5, 159.8, 149.7, 147.1, 140.7, 135.6, 132.5, 130.2, 129.8, 128.9, 128.2, 123.4, 65.8, 55.5, 48.6, 41.4, 40.7, 39.5, 29.3, 25.3, 25.1, 20.8, 20.7, 15.8; IR (thin film): ν 2955, 1835, 1740, 1699 cm^{-1}; MS *m/z* (%) 475 (15), 384 (77), 340 (100), 284 (80), 257 (63), 91 (58); EI-HRMS calcd for $C_{27}H_{29}N_3O_5$ *m/z* $[M]^+$ 475.2107; found 475.2107.



157a

(5-Ethoxy-7,12c-dimethyl-3,10,12-trioxo-11-phenyl-6,7,9,9a,10,11,12,12a,12b,12c-decahydro-5H-2,4-dioxa-3a,11-diazadicyclopenta[a,l]phenanthren-1-ylideneamino)-acetic acid methyl ester (157a). To a solution of unsaturated amide **156a** (10 mg, 18 μmol) in 1,2-dichloroethane (100 μL), were added ethyl vinyl ether (50 μL) and $Eu(fod)_3$ (2 mg, 2 μmol). The reaction vessel was then sealed and placed in a sonicator (Branson 2510), and sonication was continued at rt for 6h. The reaction mixture was purified by flash chromatography (hexanes-EtOAc, 1 : 1, v/v) to afford **157a** (11 mg, >95%).

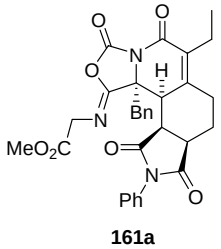
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.28 (m, 6H), 7.14-7.07 (m, 4H), 5.72-5.65 (m, 1H), 5.30 (t, *J* = 2.6 Hz, 1H), 4.35 (d, *J* = 18.1 Hz, 1H), 4.20 (d, *J* = 18.1 Hz, 1H), 4.21 (dd, *J* = 8.8, 4.4 Hz, 1H), 3.87-3.76 (m, 1H), 3.79 (s, 3H), 3.58 (dq, *J* = 9.9, 7.1 Hz, 1H), 3.45-3.43 (m, 1H), 3.42 (d, *J* = 13.4 Hz, 1H), 3.09 (d, *J* = 13.4 Hz, 1H),3.07 (bs, 1H), 2.99 (dd, *J* = 15.2, 7.7 Hz, 1H), 2.81 (dt, *J* = 10.3, 6.9 Hz, 1H), 2.41-2.31 (m, 1H), 2.28 (ddd, *J* = 13.9, 6.7, 2.5 Hz, 1H), 1.86-1.77 (m, 1H), 1.23 (d, *J* = 6.7 Hz, 3H), 0.93 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, toluene-d^8): δ 177.7, 176.1, 170.1, 156.0, 146.4, 137.9, 134.5, 132.9, 132.7, 130.7, 128.7, 128.1, 126.8, 116.0, 99.6, 97.4, 66.1, 64.5, 51.4, 40.0, 45.0, 44.7, 42.1, 41.8, 37.0, 26.0, 21.4, 21.2, 20.4, 19.7, 14.7; IR (thin film): ν 2594, 1822, 1735, 1712 cm^{-1}; MS *m/z* (%) 649 (50), 648 (100), 576 (15); HRMS calcd. for $C_{35}H_{35}N_3O_8Na$ $[M+23]^+$ *m/z* 648.2322, found 648.2310.



158a

[10c-Methyl-5-(1-methyl-3-oxo-propyl)-3,4,8,10-tetraoxo-9-phenyl-4,6,7,7a,8,9,10,10a,10b,10c-decahydro-2-oxa-3a,9-diaza-dicyclopenta[a,h]naphthalen-1-ylideneamino]-acetic acid methyl ester (158a). A solution of pyran **157a** (11 mg, 18 μmol) in $CDCl_3$ was allowed to stand at rt for 24 h (slow hydrolysis to **158a** was catalyzed by traces of acid in $CDCl_3$). The solvent was removed under vacuum to afford **158a** (11mg, >95%). Alternatively, addition of 1M HCl (50 μL) accelerates the hydrolysis to 3 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.58 (s, 1H), 7.48-7.31 (m, 6H), 7.18-7.16 (m, 2H), 7.08-7.06 (m, 2H), 4.36 (d, *J* = 18.0 Hz, 1H), 4.37-4.34 (m, 1H), 4.21 (d, *J* = 18.1 Hz, 1H), 3.79 (s, 3H), 3.44-3.31 (m, 7H), 2.87 (dd, *J* = 19.1, 6.2 Hz, 1H), 2.72 (dd, *J* = 19.2, 5.7 Hz, 1H), 2.60-2.46 (m, 1H), 2.28-2.13 (m, 1H), 1.25 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.8, 176.8, 175.8, 170.1, 158.3, 153.6, 147.7, 146.0, 134.2, 132.0, 131.1, 130.0, 128.9, 128.5, 128.4, 125.8, 64.5, 52.2, 49.0, 48.9, 47.4, 41.2, 40.6, 39.8, 27.0, 26.6, 20.2, 18.5; IR (thin film): ν 2954, 2256, 1838, 1743, 1710 cm^{-1}.

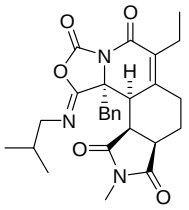


161a

(10c-Benzyl-5-ethyl-3,4,8,10-tetraoxo-9-phenyl-4,6,7,7a,8,9,10,10a,10b,10c-decahydro-2-oxa-3a,9-diazadicyclopenta[a,h]naphthalen-1-ylideneamino)acetic acid methyl ester (161a).

To a solution of diene **156a** (20 mg, 36 μmol) in THF (2.5 mL) was added Pd/C (5 mg, 10% by wt.), and the reaction vessel was sealed with a rubber septum and H_2 atmosphere was introduced from a balloon via a needle. The heterogeneous reaction mixture was stirred for 4 h at rt. The mixture was then filtered over a plug of celite eluting with CH_2Cl_2 and the collected solution was concentrated under vacuum. The crude residue was purified by flash chromatography (EtOAc : hexanes, 1 : 1 to 1 : 0, v/v) to afford **161a** (16 mg, 80%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-7.30 (m, 6H), 7.08-7.03 (m, 4H), 4.37 (d, *J* = 18.2 Hz, 1H), 4.38-4.34 (m, 1H), 4.21 (d, *J* = 18.2 Hz, 1H), 3.78 (s, 3H), 3.43-3.33 (m, 3H), 3.22 (d, *J* = 13.2 Hz, 1H), 2.68-2.65 (m, 2H), 2.50 (dq, *J* = 12.9, 2.6 Hz, 1H), 2.34 (sept, *J* = 7.2 Hz, 2H), 2.27-2.15 (m, 1H), 0.98 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.1, 175.9, 170.2, 158.4, 153.8, 146.0, 133.6, 132.3, 131.0, 130.0, 129.2, 128.9, 128.8, 128.4, 125.9, 64.7, 52.2, 48.9, 47.9, 40.8, 40.6, 40.1, 26.1, 20.0, 19.3, 12.7; IR (thin film): ν 2953, 1837, 1743, 1709 cm^{-1}; MS *m/z* (%) 555 (10), 464 (80), 420 (65), 321 (100); HRMS calcd. for $C_{31}H_{29}N_3O_7$ $[M]^+$ *m/z* 555.2005, found 555.1992.

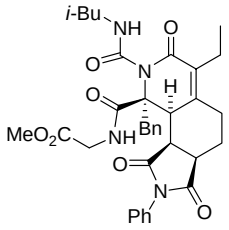


161b

10c-Benzyl-5-ethyl-1-isobutylimino-9-methyl-6,7,7a,10a,10b,10c-hexahydro-1H-2-oxa-3a,9-diazadicyclopenta[a,h]naphthalene-3,4,8,10-tetraone (161b). To a solution of diene **156b** (56 mg, 0.12 mmol) in THF (7 mL) was added Pd/C (10 mg, 10% by wt.), and the reaction vessel was sealed with a rubber septum and H_2 atmosphere was introduced from a balloon via a needle. The heterogeneous reaction mixture was stirred for 4 h at rt. The mixture was then filtered over a plug of celite eluting with CH_2Cl_2 and the collected solution was concentrated under vacuum.

The crude residue was purified by flash chromatography (EtOAc : hexanes, 1 : 1 to 1 : 0, v/v) to give **161b** (56 mg, 95%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.40 (m, 3H), 7.16-7.12 (m, 2H), 4.05 (dd, *J* = 9.4, 5.6 Hz, 1H), 3.42 (dd, *J* = 13.3, 7.0 Hz, 1H), 3.39 (d, *J* = 13.2 Hz, 1H), 3.37-3.29 (m, 3H), 3.22 (d, *J* = 13.3 Hz, 1H), 2.95 (s, 3H), 2.75-2.64 (m, 2H), 2.58-2.40 (m, 2H), 2.35-2.22 (m, 2H), 2.04 (sept, *J* = 6.7 Hz, 1H), 1.13 (d, *J* = 6.7 Hz, 3H), 1.10 (d, *J* = 6.7 Hz, 3H), 1.04 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.0, 176.5, 158.4, 149.8, 147.1, 145.9, 133.2, 132.5, 129.9, 128.7, 128.2, 64.3, 55.5, 48.0, 41.0, 40.1, 40.0, 29.3, 25.8, 24.7, 20.8, 20.7, 19.5, 19.1, 12.5; IR (thin film): ν 2959, 1832, 1741, 1700 cm^{-1}; MS $[M+H_2O]^+$ *m/z* (%) 495 (50), 386 (77), 342 (100), 286 (90).



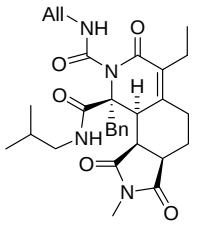
163a

[(9-Benzyl-6-ethyl-8-isobutylcarbamoyl-1,3,7-trioxo-2-phenyl-2,3,3a,4,5,7,8,9,9a,9b-decahydro-1H-pyrrolo[3,4-h]isoquinoline-9-carbonyl)amino]acetic acid methyl ester (163a). *i*-Butylamine (~10 μmol) was added to a solution of imino-oxazolidinone **161a** (8 mg, 14 μmol) in $CDCl_3$ (1 mL) and the reaction was stirred at rt for 15 min. The reaction mixture was diluted with $CHCl_3$ and washed with sat'd aq. NH_4Cl. The organic layer was separated, dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified by flash chromatography (EtOAc : hexanes, 1 : 1 to 1 : 0, v/v) to give **163a** (7 mg, 75%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.20 (t, *J* = 5.8 Hz, 1H), 8.46 (dd, *J* = 7.1, 4.6 Hz, 1H), 7.45-7.37 (m, 3H), 7.22-7.17 (m, 3H), 7.12-7.04 (m, 4H), 4.64 (dd, *J* = 9.6, 3.9 Hz, 1H), 4.48 (dd, *J* = 17.7,

7.4 Hz, 1H), 4.00 (d, *J* = 14.4 Hz, 1H), 3.72 (s, 3H), 3.60 (dd, *J* = 17.7, 4.6 Hz, 1H), 3.57 (d, *J* = 14.4 Hz, 1H), 3.40-3.35 (m, 1H), 3.28-3.10 (m, 3H), 2.34-2.22 (m, 2H), 2.17-2.09 (m, 1H), 1.94-1.81 (m, 2H), 1.75-1.60 (m, 2H), 0.98 (d, *J* = 6.7 Hz, 6H), 0.53 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.0, 177.7, 171.5, 171.4, 166.5, 154.9, 143.5, 138.1, 132.7, 131.3, 130.0, 129.2, 128.9, 128.4, 126.9, 126.2, 66.9, 52.1, 48.0, 45.3, 44.2, 42.5, 41.6, 41.1, 28.5, 25.2, 20.9, 20.2, 20.2, 19.4, 12.6; IR (thin film): ν 3305, 2958, 1748, 1704, 1637 cm^{-1}; HRMS calcd. for $C_{23}H_{24}N_3O_6$ [M-190]$^+$ *m/z* 438.1665, found 438.1675.

Note: Fragment with *m/z* = 438 likely results from loss of a benzyl group and the CONH-*i*-Bu fragment.



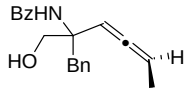
163b

9-Benzyl-6-ethyl-2-methyl-1,3,7-trioxo-2,3,3a,4,5,9,9a,9b-octahydro-1H,7H-pyrrolo[3,4-h]isoquinoline-8,9-dicarboxylic acid 8-allylamide 9-(isobutylamide) (163b). Allylamine (18 μL, 250 μmol) was added to a solution of **161b** (12 mg, 25 μmol) in $CHCl_3$ (1 mL) and the reaction was stirred at rt for 1.5 h. The reaction mixture was diluted with $CHCl_3$ and washed with sat'd aq. NH_4Cl. The organic layer was separated, dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified by flash chromatography (EtOAc : hexanes, 1 : 1 to 1 : 0, v/v) to give **163b** (12 mg, 92%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.19 (t, *J* = 5.6 Hz, 1H), 7.90 (dd, *J* = 6.6, 3.9 Hz, 1H), 7.21-7.11 (m, 3H), 7.04-7.01 (m, 2H), 6.04-5.90 (m, 1H), 5.33 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.20 (dq, *J* = 10.2, 1.4 Hz, 1H), 4.17-4.08 (m, 1H), 4.02 (d, *J* = 14.4 Hz, 1H), 3.99-3.90 (m, 1H), 3.54 (d, *J* =

14.4 Hz, 1H), 3.49-3.39 (m, 2H), 3.13-3.08 (bm, 2H), 2.85 (s, 3H), 2.79-2.71 (m, 1H), 2.23-2.21 (m, 1H), 2.15-1.94 (m, 3H), 1.80 (sept, J = 6.6 Hz, 1H), 1.69-1.63 (m, 2H), 1.45 (sex, J = 6.2 Hz, 1H), 0.95 (d, J = 6.7 Hz, 6H), 0.57 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.6, 178.3, 170.5, 166.5, 154.5, 143.0, 138.4, 134.1, 132.7, 129.8, 128.3, 126.8, 116.3, 67.2, 47.3, 45.0, 44.7, 43.0, 42.3, 41.0, 28.2, 25.0, 24.7, 20.5, 20.4, 20.3, 19.4, 12.5; IR (thin film): ν 3325, 2959, 1770, 1697, 1642 cm^{-1}; MS *m/z* (%) 534 (7), 469 (70), 360 (90), 287 (55); HRMS calcd. for $C_{30}H_{38}N_4O_5$ $[M]^+$ *m/z* 534.2842, found 534.2851.

Compounds **172-174** were synthesized as part of a preliminary study and only partial spectral data was collected:

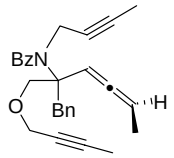


172

***N*-(1-Benzyl-1-hydroxymethylpenta-2,3-dienyl)benzamide (172)**. To a solution of methyl ester **58a** (100 mg, 0.297 mmol) in CH_2Cl_2 (1.2 mL) was added DIBAL-H (750 μL of 1.0 M solution in hexanes, 0.75 mmol) at -78 °C via a syringe in a dropwise manner. The reaction mixture was allowed to warm up to -10 °C and maintained at that temperature until TLC indicated absence of starting material (~10 min). The reaction was quenched by adding MeOH (200 μL) followed by sat'd aq. NH_4Cl (600 μL). Vigorous stirring for 10 min led to formation of white solid that was filtered on a fritted funnel and washed with excess CH_2Cl_2. The filtrate was concentrated under vacuum, and the crude residue was purified by flash chromatography (gradient elution, hexanes-EtOAc, 4 : 1 to 3 : 2, v/v) to afford **172** (61 mg, 67%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67-7.20 (m, 10H), 6.33 (s, 1H), 5.43-5.19 (m, 2H), 3.94-3.83 (m, 2H), 3.59 (d, J = 13.6 Hz, 0.5H), 3.45 (d, J = 13.5 Hz, 0.5H), 3.08 (d, J = 13.5 Hz, 0.5H),

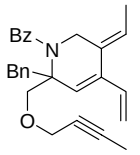
3.00 (d, *J* = 13.6 Hz, 0.5H), 1.64-1.60 (m, 3H), 1.45 (dd, *J* = 7.1, 3.2 Hz, 3H).



173

***N*-(1-Benzyl-1-but-2-ynyloxymethylpenta-2,3-dienyl)-*N*-but-2-ynylbenzamide (173)**. To a solution of amide-alcohol **172** (170 mg, 0.554 mmol) in DMF (1.5 mL) was added NaH (110 mg of a 60% dispersion in mineral oil, 2.75 mmol), followed by 1-bromo-2-butyne (145 μL, 1.65 mmol) at rt. The reaction mixture was stirred at rt for 30 min when it was quenched by pouring into water. The aqueous mixture was extracted with EtOAc, the organic layers were combined, dried over $MgSO_4$, and concentrated under vacuum. The crude oily residue was purified by flash chromatography to afford **173** (150 mg, 66%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54-7.23 (m, 10H), 5.83-5.79 (m, 1H), 5.35-5.21 (m, 1H), 4.28-4.14 (m, 3H), 3.93-3.73 (m, 4H), 3.25 (d, *J* = 13.0 Hz, 0.5H), 3.16 (d, *J* = 13.1 Hz, 0.5H), 1.86 (t, *J* = 2.2 Hz, 3H), 1.71 (dd, *J* = 7.0, 3.2 Hz, 0.5H), 1.67-1.64 (m, 6H).



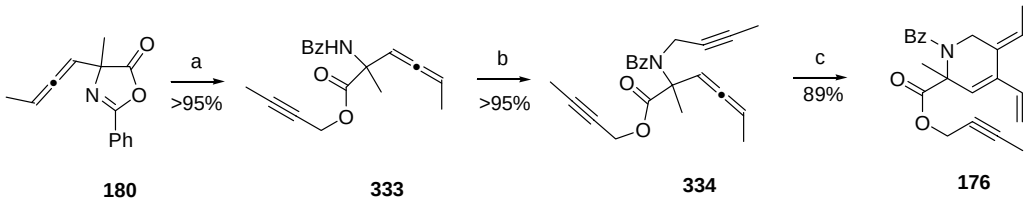
174

(6-But-2-ynyloxymethyl-3-ethylidene-6-methyl-4-vinyl-3,6-dihydro-2H-pyridin-1-yl)-phenylmethanone (174). To a solution of allene-diyne **173** (140 mg, 0.340 mmol) in toluene (1.5 mL) was added $[Rh(CO)_2Cl]_2$ (7 mg, 18 μmol) at rt. The reaction mixture was stirred at rt for 1 h and then directly applied to a silica gel column. Elution (hexanes-EtOAc, 9 : 1, v/v) afforded **174** (112 mg, 80%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.19 (m, 10H), 6.32 (dd, *J* = 17.2, 10.7 Hz, 1H), 5.80 (s,

1H), 5.49 (dd, *J* = 17.3, 1.8 Hz, 1H), 5.43 (q, *J* = 7.1 Hz, 1H), 5.18 (dd, *J* = 10.7, 1.8 Hz, 1H), 4.46 (d, *J* = 9.0 Hz, 1H), 4.23-4.11 (m, 2H), 4.06 (d, *J* = 9.0 Hz, 1H), 4.02 (d, *J* = 13.3 Hz, 1H), 3.78 (d, *J* = 14.2 Hz, 1H), 3.35 (d, *J* = 14.1 Hz, 1H), 2.95 (d, *J* = 13.2 Hz, 1H), 1.86 (t, *J* = 2.3 Hz, 3H), 1.30 (d, *J* = 7.1 Hz, 1H).

176: Synthesized according to the following scheme:



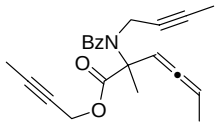
180 **333** **334** **176**

a) 2-butyne-1-ol (2 equiv.), Et_3N (cat.); b) NaH (2 equiv.), 1-bromo-2-butyne (2 equiv.), DMF; c) 5 mol% $[Rh(CO)_2Cl]_2$, toluene, rt.

2-Benzoylamino-2-methylhexa-3,4-dienoic acid but-2-ynyl ester (333). 2-Butyn-1-ol (0.170 mL, 2.23 mmol) was added to neat oxazolone **180**[ll] (0.253 g, 1.11 mmol) followed by addition of Et_3N (10 μL) and the reaction was stirred for 30 min. All volatiles were removed under vacuum, and the remaining yellow residue was purified by flash chromatography (hexanes/EtOAc, 4 : 1, v/v) to afford **333** (0.320 g, 96% as a mixture of inseparable diastereomers in 1.5 : 1 ratio).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78-7.75 (m, 2H), 7.50-7.38 (m, 3H), 6.93 (bs, 0.4H), 6.90 (bs, 0.6H), 5.56-5.38 (m, 2H), 4.80-4.64 (m, 2H), 1.83-1.81 (m, 3H), 1.79 (s, 1.2H), 1.77 (s, 1.8H), 1.73-1.69 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.0, 202.9, 171.9, 171.8, 166.3, 166.3, 134.3, 131.4, 128.4, 128.2, 126.9, 94.0, 91.6, 83.3, 83.2, 72.8, 72.8, 58.4, 54.0, 54.0, 23.0, 22.9, 13.9, 13.9, 3.5; IR (thin film): ν 3308, 2322, 2923, 2243, 2117, 1968, 1744, 1640 cm^{-1}; MS *m/z* (%) 297 (38), 282 (21), 244 (73), 200 (55), 105 (100); EI-HRMS calcd for $C_{18}H_{19}NO_3$ *m/z* $[M]^+$ 297.1365; found 297.1364.

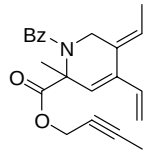
[ll] See page 224 for preparation of intermediate **180**.



334

2-(Benzoylbut-2-ynyl-amino)-2-methylhexa-3,4-dienoic acid but-2-ynyl ester (334). A solution of amide **333** (0.320 g, 1.08 mmol) in DMF (8 mL) was cooled to 0 °C, and NaH (95% wt) (0.056 g, 2.23 mmol) was added in one portion. After 2 min, 1-bromo-2-butyne (0.19 mL, 2.23 mmol) was added via a syringe and the reaction mixture was stirred for 30 min at rt. The reaction mixture was then carefully poured over cold water (100 mL), and the aqueous layer was extracted with EtOAc (2 x 50 mL). The organic layers were combined and washed with brine, dried over $MgSO_4$, and concentrated under vacuum to afford **334** (0.415 g, >95% as a mixture of inseparable diastereomers in 1.5 : 1 ratio).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61-7.59 (m, 2H), 7.42-7.38 (m, 3H), 5.73-5.66 (m, 1H), 5.42-5.34 (m, 1H), 4.77-4.65 (m, 2H), 4.05-4.01 (m, 2H), 1.85-1.83 (m, 6H), 1.76-1.71 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.2, 205.2, 171.8, 171.7, 171.3, 136.0, 129.9, 128.3, 128.2, 127.1, 127.0, 92.5, 92.4, 90.2, 90.1, 82.8, 82.7, 80.3, 76.0, 73.4, 64.2, 64.0, 53.6, 53.6, 37.5, 37.4, 20.6, 20.6, 13.8, 13.7, 3.6, 3.5; IR (thin film): ν 2921, 2242, 1967, 1746, 1643 cm^{-1}; MS *m/z* (%) 349 (21), 296 (50), 268 (48), 252 (35), 105 (100); EI-HRMS calcd for $C_{22}H_{23}NO_3$ *m/z* $[M]^+$ 349.1678; found 349.1685.

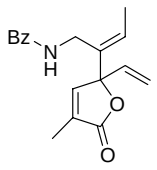


176

1-Benzoyl-5-ethylidene-2-methyl-4-vinyl-1,2,5,6-tetrahydropyridine-2-carboxylic acid but-2-ynyl ester (176). To a solution of allene-diyne **334** (0.173 g, 0.495 mmol) in toluene (5 mL) was added $[Rh(CO)_2Cl]_2$ (7 mg, 18 μmol) under nitrogen atmosphere. The light yellow solution

was stirred at rt for 1 h when it was directly applied to a silica gel column and eluted (gradient elution, hexanes-EtOAc, 1 : 0 to 4 : 1, v/v) to afford **176** (0.154 g, 89%) after removal of the solvents.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51-7.39 (m, 5H), 6.36 (dd, *J* = 17.2, 10.6 Hz, 1H), 5.78 (q, *J* = 7.1 Hz, 1H), 5.61 (s, 1H), 5.46 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.22 (dd, *J* = 10.7, 1.7 Hz, 1H), 4.75 (dq, *J* = 15.2, 2.3 Hz, 1H), 4.61 (dq, *J* = 15.2, 2.3 Hz, 1H), 4.45 (d, *J* = 14.6 Hz, 1H), 3.70 (d, *J* = 14.6 Hz, 1H), 1.81 (t, *J* = 2.3 Hz, 3H), 1.78 (s, 3H), 1.62 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 171.0, 137.5, 136.0, 134.3, 130.2, 130.0, 128.5, 127.5, 124.7, 122.8, 117.8, 82.8, 73.4, 62.8, 53.8, 43.5, 20.7, 13.3, 3.6; IR (thin film): ν 2921, 2242, 1743, 1642, 1412, 1106 cm^{-1}. MS *m/z* (%) 349 (17), 284 (5), 252 (40), 105 (100); EI-HRMS calcd for $C_{22}H_{23}NO_3$ *m/z* $[M]^+$ 349.1678; found 349.1674.

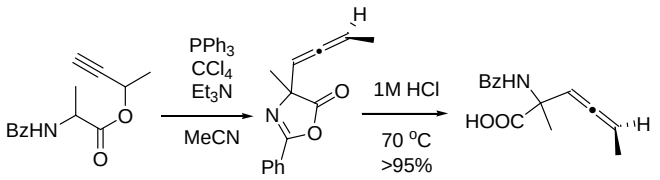


178

***N*-[2-(4-Methyl-5-oxo-2-vinyl-2,5-dihydrofuran-2-yl)-but-2-enyl]benzamide (178)**. To a solution of trienyne **176** (15 mg, 43 μmol) in 1,2-dichloroethane (0.5 mL), was added $[Rh(dppe)Cl]_2$ (4 mg, 4 μmol), and $AgSbF_6$ (172 μL of a 0.05 M solution in 1,2-dichloroethane, 8 μmol). The reaction was heated to 95 °C for 12 h. After cooling to rt the reaction mixture was directly applied to a silica gel column and eluted (hexanes-EtOAc, 1 : 1, v/v), to afford **178** (10 mg, 78%).

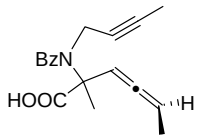
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.80-7.74 (m, 2H), 7.52-7.40 (m, 3H), 7.14 (q, *J* = 1.6 Hz, 1H), 6.39 (bs, 1H), 5.90 (dd, *J* = 17.3, 10.7 Hz, 1H), 5.84 (q, *J* = 6.9 Hz, 1H), 5.38 (d, *J* = 17.3 Hz, 1H), 5.26 (d, *J* = 10.7 Hz, 1H), 4.20 (dd, *J* = 14.5, 5.8 Hz, 1H), 4.11 (dd, *J* = 14.5, 5.8 Hz, 1H),

1.93 (d, *J* = 1.6 Hz, 3H), 1.85 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7, 166.8, 149.6, 135.4, 134.2, 131.4, 130.3, 129.0, 128.6, 128.3, 126.8, 116.9, 90.5, 35.9, 13.9, 10.7; IR (thin film): ν 3344, 2924, 1758, 1639 cm^{-1}; MS *m/z* (%) 297 (81), 252 (38), 192 (49), 174 (84), 105 (100); EI-HRMS calcd for $C_{18}H_{19}NO_3$ *m/z* $[M]^+$ 297.1365; found 297.1379.



2-(Benzamido)-2-methylhexa-3,4-dienoic acid (181). Propargylic ester **179** (1.05g, 4.29 mmol) was dissolved in acetonitrile (10 mL) at rt. Then Et_3N (1.67 mL, 12.0 mmol), CCl_4 (0.99 mL, 10.3 mmol) and PPh_3 (2.36 g, 9.0 mmol) were added in consecutive order. The reaction mixture was stirred for 2 h at rt while gradually turning brown color. The volatiles were removed under vacuum (using a rotary evaporator heated to ~40 °C) and the crude brown residue was dissolved in acetone (5 mL) and poured in an Erlenmeyer flask. Under vigorous stirring, Et_2O (50 mL) was added followed by hexanes (20 mL) which led to formation of a viscous precipitate (Ph_3PO). The mixture was filtered on a fritted funnel over a plug of silica gel (~ 2 cm height) eluting with hexanes-EtOAc (1 : 1). The collected filtrate was concentrated under vacuum to afford allenyl oxazolone **180** (718 mg, 74%).

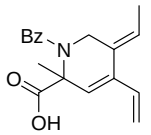
Oxazolone **180** (105 mg, 0.415 mmol) was dissolved in 1,4-dioxane (3 mL) in a 25 mL round-bottom flask and 1M HCl (3 mL) was added. The flask was sealed with a rubber septum and heated to 70 °C for 10 min. The reaction solution was then diluted with water and extracted with Et_2O. The organics were combined, washed with brine, dried over $MgSO_4$ and concentrated under vacuum to afford acid **181** (100 mg, >95%) which was used in the next step without additional purification.



182

2-(*N*-(but-2-ynyl)benzamido)-2-methylhexa-3,4-dienoic acid (182). To a solution of amido-acid **181** (100 mg, 0.408 mmol) in DMF (3 mL) was added NaH (23 mg, 0.90 mmol) at rt. The reaction mixture turned bright yellow and after 2 min, 1-bromo-2-butyne (39 μL, 0.45 mmol) was added. The reaction mixture was stirred at rt for 1 h and then poured into a diluted aq. $NaHCO_3$ solution. The aqueous layer was extracted once with EtOAc and the organic layer was discarded. The aqueous layer was acidified to approximately pH = 2.0 by dropwise addition of 6M HCl (pH was followed using pHydrion strips) and then extracted with EtOAc (3 x 25 mL). The organics were combined, washed with water, dried over $MgSO_4$ and concentrated under vacuum to afford **182** (103 mg, 85%) as a mixture of diastereomers in ~ 2 : 1 ratio.

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.61 (bs, 1H), 7.79-7.76 (m, 0.67H), 7.65-7.63 (m, 1.33H), 7.53-36 (m, 3H), 5.74-5.68 (m, 1H), 5.54-5.34 (m, 1H), 4.03-4.00 (m, 2H), 1.85 (s, 3H), 1.75 (s, 3H), 1.75-1.68 (m, 3H); IR (thin film): ν 3062, 2990, 2629, 1967, 1714, 1641 cm^{-1}; MS *m/z* (%) 297 (42), 282 (15), 252 (70), 200 (55), 105 (100); EI-HRMS calcd for $C_{18}H_{19}NO_3$ *m/z* $[M]^+$ 297.1365, found 297.1363.



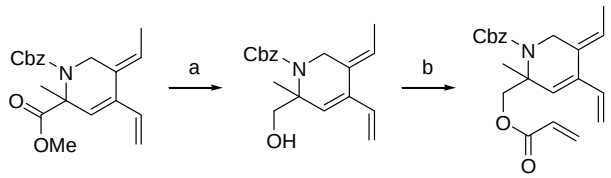
177

1-Benzoyl-5-ethylidene-2-methyl-4-vinyl-1,2,5,6-tetrahydropyridine-2-carboxylic acid (177). Allenyne **182** (103 mg, 0.347 mmol) was placed in a 15 mL test tube and toluene (3 mL) was added. The resulting solution was deoxygenated by bubbling Ar via a needle for 3 min.

Then, $[Rh(CO)_2Cl]_2$ (7 mg, 18 μmol) was added at rt, and the test-tube was sealed with a rubber septum and heated to 35 °C in an oil bath. After 1 h, another portion of $[Rh(CO)_2Cl]_2$ (7 mg, 18 μmol) was added by briefly opening the reaction vessel, and heating was continued for 1 h. During this time, the product of the reaction (**177**) partially percipitated from the solution as a light orange solid. The precipitate was collected by filtering the reaction mixture through a small pipette over a cotton plug. The filtrate was concentrated under vacuum and the crude residue was purified by flash chromatography (hexanes-EtOAc, 9 : 1 to 0 : 1, v/v) to give **177** (60 mg, 58% after combining with the portion obtained by filtration).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91-7.71 (bs, 1H), 7.55-7.39 (m, 5H), 6.33 (dd, *J* = 17.2, 10.7 Hz, 1H), 5.78 (q, *J* = 7.1 Hz, 1H), 5.62 (s, 1H), 5.47 (dd, *J* = 17.2, 1.3 Hz, 1H), 5.21 (dd, *J* = 10.7, 1.3 Hz, 1H), 4.41 (d, *J* = 14.5 Hz, 1H), 3.71 (d, *J* = 14.5 Hz, 1H), 1.75 (s, 3H), 1.60 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.6, 171.6, 137.4, 135.5, 134.0, 130.4, 129.6, 128.5, 127.5, 124.6, 123.1, 118.0, 62.8, 43.7, 20.6, 13.3; IR (thin film): ν 2983, 2025, 1742, 1593 cm^{-1}; MS *m/z* (%) 297 (7), 253 (67), 252 (80), 105 (100); EI-HRMS calcd for $C_{18}H_{19}NO_3$ *m/z* $[M]^+$ 297.1365; found 297.1372.

184: Synthesized according to the following scheme:



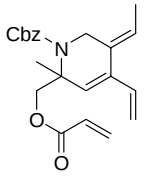
111f **183** **184**

a) DIBALH (3 equiv.), CH_2Cl_2, -78 °C-rt; b) acryloyl chloride (1.2 equiv.), Et_3N (1.2 equiv.), CH_2Cl_2.

3-Ethylidene-6-hydroxymethyl-6-methyl-4-vinyl-3,6-dihydro-2H-pyridine-1-carboxylic acid benzyl ester (183). A solution of **111f** (50 mg, 0.15 mmol), in toluene (1 mL), was cooled to -50

°C and DIBAL-H (0.440 mL of a 1.0M solution in hexanes, 0.440 mmol), was added dropwise. The reaction was allowed to warm up to rt over a period of 1 h, when it was quenched by addition of MeOH (0.1 mL) and sat'd aq. NH_4Cl (0.5 mL). Vigorous stirring for 10 min led to formation of white solid that was filtered on a fritted funnel and washed with excess CH_2Cl_2. The filtrate was concentrated under vacuum, and the crude residue was purified by flash chromatography (hexanes-EtOAc, 4 : 1, v/v) to afford **183** (30 mg, 65%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.33 (m, 5H), 6.34 (dd, *J* = 17.2, 10.7 Hz, 1H), 5.69 (q, *J* = 7.0 Hz, 1H), 5.46-5.40 (m, 2H), 5.22-5.13 (m, 2H), 4.71 (d, *J* = 14.3 Hz, 1H), 3.97-3.90 (m, 1H), 3.78 (d, *J* = 14.3 Hz, 1H), 3.66 (d, *J* = 9.0 Hz, 1H), 1.76 (d, *J* = 7.0 Hz, 3H), 1.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.8, 136.7, 136.4, 134.5, 130.2, 129.4, 128.5, 128.0, 127.7, 122.1, 116.8, 69.0, 67.3, 61.5, 41.3, 20.2, 13.4; IR (thin film): ν 3427, 2927, 1685, 1406 cm^{-1}; MS *m/z* (%) 313 (32), 282 (45), 238 (29), 192 (30), 91 (100); EI-HRMS calcd for $C_{18}H_{20}NO_2$ *m/z* [M-31]$^+$ 282.1494; found 282.1485.

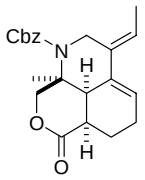


184

6-Acryloyloxymethyl-3-ethylidene-6-methyl-4-vinyl-3,6-dihydro-2H-pyridine-1-carboxylic acid benzyl ester (184). To a solution of alcohol **183** (30 mg, 0.096 mmol), in CH_2Cl_2 (0.5 mL) was added Et_3N (0.016 mL, 0.11 mmol), followed by acryloyl chloride (0.010 mL, 0.11 mmol) at rt. After 10 min at rt, the reaction was diluted with benzene (0.5 mL) and purified by flash chromatography (hexanes-EtOAc, 9 : 1, v/v) to afford ester **184** (18 mg, 51%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.34 (m, 5H), 6.37-6.28 (m, 1H), 6.31 (dd, *J* = 17.3, 1.6 Hz, 1H), 6.04 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.77 (dd, *J* = 10.4, 1.6 Hz, 1H), 5.66 (q, *J* = 7.1 Hz, 1H),

5.44 (s, 1H), 5.39 (dd, *J* = 17.2, 1.8 Hz, 1H), 5.22 (d, *J* = 12.4 Hz, 1H), 5.16 (d, *J* = 12.4 Hz, 1H), 5.14 (dd, *J* = 10.7, 1.8 Hz, 1H), 4.79 (d, *J* = 10.9 Hz, 1H), 4.40-4.34 (m, 2H), 4.18 (d, *J* = 14.3 Hz, 1H), 1.78 (d, *J* = 6.9 Hz, 3H), 1.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.7, 155.2, 136.6, 136.3, 134.5, 130.7, 130.1, 128.6, 128.5, 128.2, 127.9, 127.7, 121.9, 116.8, 67.5, 67.0, 58.6, 42.0, 22.8, 13.4; IR (thin film): ν 2924, 1727, 1699, 1403 cm^{-1}; MS *m/z* (%) 367 (40), 282 (66), 238 (45), 91 (100); EI-HRMS calcd for $C_{22}H_{25}NO_4$ *m/z* $[M]^+$ 367.1784; found 367.1775.



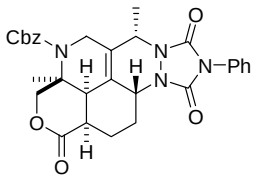
185

3-Ethylidene-9a-methyl-7-oxo-2,3,5,6a,7,9,9a,9b-octahydro-6H-8-oxa-1-azaphenalene-1-carboxylic acid benzyl ester (185). A solution of tetraene **184** (0.120 g, 0.327 mmol) in DMSO (60 mL), was heated to 80 °C for 8 h. The solution was then allowed to cool to rt and diluted with 120 mL of water. The cloudy mixture was extracted with Et_2O (3 x 70 mL), the extracts were combined and washed with water (100 mL), dried over $MgSO_4$ and concentrated under vacuum. Purification of the crude residue by flash chromatography (hexanes-EtOAc, 1 : 1, v/v) afforded **185** (0.052 g, 43%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.41-7.32 (m, 5H), 6.34 (bs, 1H), 5.93 (q, *J* = 7.1 Hz, 1H), 5.18 (d, *J* = 12.2 Hz, 1H), 5.11 (d, *J* = 12.2 Hz, 1H), 5.00 (d, *J* = 14.9 Hz, 1H), 4.89 (d, *J* = 10.8 Hz, 1H), 3.96 (d, *J* = 10.8 Hz, 1H), 3.56 (d, *J* = 14.9 Hz, 1H), 3.10 (dt, *J* = 6.6, 3.8 Hz, 1H), 3.00-2.97 (m, 1H), 2.49 (dq, *J* = 12.9, 3.4 Hz, 1H), 2.14-2.11 (m, 2H), 1.72 (s, 3H), 1.71 (d, *J* = 7.1 Hz, 3H), 1.55 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.0, 154.6, 136.2, 131.8, 128.6, 128.2, 128.0, 121.8, 116.9, 70.5, 67.4, 55.5, 42.0, 40.1, 37.0, 24.4, 21.0, 19.6, 13.4; IR (thin film): ν 2920, 1732, 1693, 1403, 1354, 1221, 1167, 1053 cm^{-1}; MS *m/z* (%) 367 (10), 316 (15), 276 (23),

129 (62), 91 (100); EI-HRMS calculated for $C_{22}H_{25}NO_4$ *m/z* $[M]^+$ 367.1784; found 367.1785.

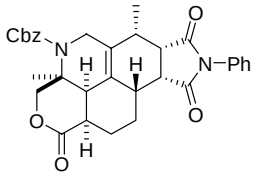
General procedure L for preparation of cycloadducts 186a-c.



186a

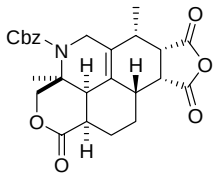
3a,6-Dimethyl-1,7,9-trioxo-8-phenyl-3,3a,6,8,9,9b,10,11,11a,11b-decahydro-1H,5H,7H-2-oxa-4,6a,8,9a-tetraazacyclopenta[a]pyrene-4-carboxylic acid benzyl ester (186a). To a solution of diene **185** (10 mg, 27 μmol) in toluene (0.5 mL) was added 4-phenyl-1,2,4-triazoline-3,5-dione (5 mg, 27 μmol) and the reaction was stirred at rt for 10 min until the red color of the dienophile disappeared. The reaction mixture was then directly purified by flash chromatography (hexanes/EtOAc, 4 : 1 to 1 : 1, v/v) to afford **186a** (15 mg, >95%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48-7.28 (m, 10H), 5.19 (d, *J* = 12.1 Hz, 1H), 5.14 (d, *J* = 12.2 Hz, 1H), 4.62-4.57 (m, 1H), 4.51-4.41 (m, 2H), 4.20-4.14 (m, 1H), 3.64 (d, *J* = 15.4 Hz, 1H), 3.26-3.17 (m, 1H), 3.00-2.96 (m, 1H), 2.86-2.81 (m, 1H), 2.07-1.95 (m, 1H), 1.75 (s, 3H), 1.71-1.59 (m, 1H), 1.31 (d, *J* = 6.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8, 154.7, 154.6, 150.5, 135.8, 131.0, 130.8, 129.1, 128.8, 128.5, 128.4, 128.3, 128.3, 125.6, 72.8, 67.9, 56.1, 54.1, 51.1, 42.8, 42.3, 33.6, 23.4, 21.7, 19.4, 16.4; IR (thin film): ν 2928, 1772, 1713, 1415 cm^{-1}; MS *m/z* (%) 542 (18), 451 (32), 91 (100); EI-HRMS calcd for $C_{30}H_{30}N_4O_6$ *m/z* $[M]^+$ 542.2165; found 542.2181.



186b

3a,6-Dimethyl-1,7,9-trioxo-8-phenyl-3,3a,5,6,6a,7,8,9,9a,9b,10,11,11a,11b-tetradecahydro-1H-2-oxa-4,8-diazacyclopenta[a]pyrene-4-carboxylic acid benzyl ester (186b). Prepared by following general procedure L, using **185** (10 mg, 27 μmol), *N*-phenylmaleimide (7 mg, 40 μmol). Reaction time (6 h at rt). Isolated yield **186b** (15 mg, >95%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.33 (m, 8H), 7.14-7.09 (m, 2H), 5.31 (d, *J* = 11.8 Hz, 1H), 5.13 (s, 2H), 4.44 (d, *J* = 18.1 Hz, 1H), 4.13 (d, *J* = 11.8 Hz, 1H), 3.67 (dq, *J* = 18.1, 2.2 Hz, 1H), 3.30 (dd, *J* = 8.5, 6.3 Hz, 1H), 3.19 (dd, *J* = 8.5, 5.2 Hz, 1H), 3.13-3.04 (m, 1H), 2.69-2.61 (m, 2H), 2.45 (bs, 1H), 2.30-2.17 (m, 1H), 2.13-1.90 (m, 2H), 1.54 (d, *J* = 7.3 Hz, 3H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.4, 176.2, 173.8, 155.9, 136.2, 132.1, 131.5, 129.1, 128.6, 128.6, 128.1, 127.7, 127.4, 126.1, 71.1, 67.3, 56.1, 46.4, 44.4, 42.1, 41.6, 36.9, 33.0, 23.3, 21.8, 20.7, 12.9, 1.0; IR (thin film): ν 2940, 1747, 1706, 1381 cm^{-1}; MS *m/z* (%) 540 (8), 495 (37), 449 (29), 405 (65), 91 (100); EI-HRMS calcd for $C_{32}H_{32}N_2O_6$ *m/z* $[M]^+$ 540.2260; found 540.2281.



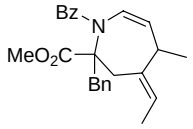
186c

3a,6-Dimethyl-1,7,9-trioxo-3,3a,6,6a,7,9,9a,9b,10,11,11a,11b-dodecahydro-1H,5H-2,8-dioxa-4-azacyclopenta[a]pyrene-4-carboxylic acid benzyl ester (186c). Prepared by following general procedure L, using **185** (18 mg, 49 μmol), maleic anhydride (7 mg, 71 μmol). Reaction time (3 h at rt). Isolated yield **186c** (18 mg, 78%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.33 (m, 5H), 5.22 (d, *J* = 11.9 Hz, 1H), 5.13 (s, 2H), 4.37

(d, *J* = 18.0 Hz, 1H), 4.14 (d, *J* = 11.9 Hz, 1H), 3.69 (d, *J* = 16.5 Hz, 1H), 3.40 (dd, *J* = 9.2, 6.2 Hz, 1H), 3.30 (dd, *J* = 9.1, 4.8 Hz, 1H), 3.08 (q, *J* = 8.1 Hz, 1H), 2.64-2.62 (m, 1H), 2.41 (bs, 1H), 2.10-1.89 (m, 2H), 1.47 (d, *J* = 7.0 Hz, 3H), 1.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 171.2, 171.1, 155.8, 136.9, 132.8, 128.6, 128.1, 128.1, 127.8, 71.5, 67.5, 56.1, 47.2, 45.1, 42.1, 41.7, 36.5, 35.6, 32.3, 22.7, 22.1, 20.4, 12.5; IR (thin film): ν 2947, 1775, 1746, 1705 cm^{-1}. MS *m/z* (%) 465 (10), 437 (28), 330 (38), 91 (100); EI-HRMS calcd for $C_{26}H_{27}NO_7$ *m/z* $[M]^+$ 465.1788; found 465.1782.

General procedure M for the Rh(I)-catalyzed cycloisomerization of ene-allenes.

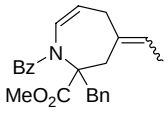


189

1-Benzoyl-2-benzyl-4-ethylidene-5-methyl-2,3,4,5-tetrahydro-1*H*-azepine-2-carboxylic acid methyl ester (189). To a solution of ene-allene **75a** (30 mg, 77 μmol) in 1,2-dichloroethane (1 mL) in a test tube, was added $[Rh(CO)_2Cl]_2$ (1.5 mg, 3.8 μmol) at rt under Ar atmosphere. The test tube was then immersed in an oil-bath preheated to 90 °C and heating was continued for 2 h. After this time, another portion of the catalyst was added $[Rh(CO)_2Cl]_2$ (1.5 mg, 3.8 μmol) and the reaction was heated to 90 °C for additional 15 min when it was complete according to TLC. The reaction mixture was then cooled to rt, and filtered through a plug of silica gel eluting with (hexanes-EtOAc, 1 : 1, v/v) to give azepine **189** (30 mg, > 95%).

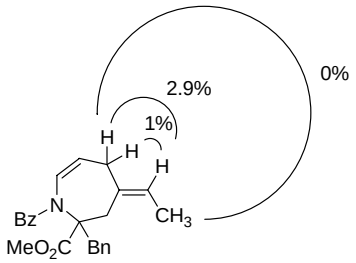
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57-7.54 (m, 2H), 7.42-7.35 (m, 3H), 7.23-7.19 (m, 5H), 5.52 (q, *J* = 6.8 Hz, 1H), 5.03 (dd, *J* = 8.1, 2.5 Hz, 1H), 4.53 (dd, *J* = 8.1, 4.1 Hz, 1H), 4.20 (d, *J* = 13.6 Hz, 1H), 3.75 (s, 3H), 3.40 (bs, 1H), 3.14 (d, *J* = 13.6 Hz, 1H), 2.83 (d, *J* = 14.6 Hz, 1H), 2.66 (d, 14.6 Hz, 1H), 1.63 (d, *J* = 6.8 Hz, 3H), 1.08 (d, *J* = 7.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75

MHz): δ 172.7, 171.4, 137.0, 136.4, 135.1, 130.9, 130.4, 128.4, 128.1, 128.0, 127.8, 126.8, 125.7, 121.9, 69.0, 52.5, 40.4, 36.9, 34.7, 21.4, 13.6; IR (thin film): ν 2950, 1736, 1637, 1446, 1350, 1223 cm^{-1}; MS *m/z* (%) 389 (38), 358 (15), 330 (42), 298 (42), 105 (100); EI-HRMS calcd for $C_{25}H_{27}NO_3$ $[M]^+$, *m/z* 389.1991 found 389.1984.

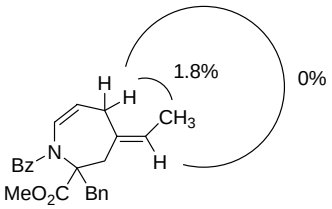


211

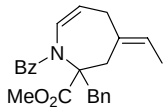
1-Benzoyl-2-benzyl-4-ethylidene-2,3,4,5-tetrahydro-1*H*-azepine-2-carboxylic acid methyl ester (211). Prepared by following general procedure M using: **75b** (0.12 g, 0.32 mmol). First portion of $[Rh(CO)_2Cl]_2$ (6 mg, 15 μmol) was added at 70 °C. After 2 h at 90 °C another portion of $[Rh(CO)_2Cl]$ (6 mg, 15 μmol) was added and the reaction was heated to 90 °C for additional 2 h. Upon completion, the reaction mixture was filtered through a plug of silica gel to afford **211** (80 mg, 66%) as a mixture of *E* and *Z* olefin isomers in ratio of ~2.5 : 1. The isomers were separated by semi-preparative HPLC (hexanes-EtOAc, 24 : 1, v/v, flow rate 3 mL/min, UV detector at 254 nm) and assigned by nOe spectroscopy.



major 211a



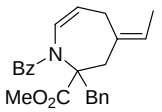
minor 211b



211a

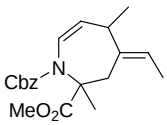
(*Z*)-211a: (major isomer – R_t = 35 min): ^1H NMR ($CDCl_3$, 300MHz): δ 7.55-7.51 (m, 2H), 7.42-7.34 (m, 3H), 7.26-7.16 (m, 5H), 5.44 (q, *J* = 7.0 Hz, 1H), 5.13 (dd, *J* = 7.7, 2.5 Hz, 1H),

4.98 (dt, *J* = 7.7, 5.1 Hz, 1H), 4.19 (d, *J* = 13.7 Hz, 1H), 3.75 (s, 3H), 3.36 (d, *J* = 16.6 Hz, 1H), 3.14 (d, *J* = 13.7 Hz, 1H), 2.84 (d, *J* = 14.9 Hz, 1H), 2.71-2.58 (m, 2H), 1.62 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.7, 171.2, 136.9, 136.4, 130.9, 130.4, 129.9, 129.6, 128.2, 128.1, 128.0, 126.8, 122.2, 120.0, 68.3, 52.4, 40.3, 35.6, 33.1, 13.4; IR (thin film): ν 2949, 1736, 1663, 1635, 1446, 1352 cm^{-1}; MS *m/z* (%) 375 (38), 344 (8), 316 (15), 284 (22), 105 (100); EI-HRMS calcd for $C_{24}H_{25}NO_3$ $[M]^+$, *m/z* 375.1834; found 375.1831.



211b

(*E*)-211b: (minor isomer – R_t = 37 min): ^{1}H NMR ($CDCl_3$, 300MHz): δ 7.54-7.51 (m, 2H), 7.45-7.34 (m, 3H), 7.25-7.17 (m, 5H), 5.38 (bq, 1H), 5.16 (dd, *J* = 7.6, 2.6 Hz, 1H), 5.04 (dt, *J* = 7.8, 4.8 Hz, 1H), 4.18 (d, *J* = 13.7 Hz. 1H), 3.71 (s, 3H), 3.16-3.11 (m, 1H), 3.08 (d, *J* = 13.7 Hz, 1H), 2.90 (d, *J* = 14.3 Hz, 1H), 2.75 (dd, *J* = 17.6, 8.2 Hz, 1H), 2.36 (d, *J* = 14.3 Hz, 1H), 1.58 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 172.8, 171.1, 137.0, 136.5, 130.9, 130.6, 130.4, 128.1, 126.7, 121.8, 120.0, 69.2, 52.0, 44.2, 40.0, 26.3, 13.1; IR (thin film): ν 2948, 1736, 1664, 1635, 1446, 1353 cm^{-1}; MS *m/z* (%) 375 (45), 344 (26), 316 (47), 284 (22), 105 (100); EI-HRMS calcd for $C_{24}H_{25}NO_3$ $[M]^+$, *m/z* 375.1834; found 375.1850.

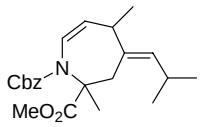


212

4-Ethylidene-2,5-dimethyl-2,3,4,5-tetrahydroazepine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (212). Prepared by following general procedure M using: **75c** (0.105 g, 0.306 mmol). First portion of $[Rh(CO)_2Cl]_2$ (6 mg, 15 μmol) was added at 70 °C. After 2 h at 90 °C another portion of $[Rh(CO)_2Cl]$ (6 mg, 15 μmol) was added and the reaction was heated to 90 °C

for additional 2 h.. Upon completion, the reaction mixture was purified by flash chromatography (hexanes-EtOAc, 30 : 1 to 20 : 1, v/v) to afford **212** (70 mg, 63%).

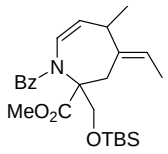
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.29 (m, 5H), 6.24 (d, *J* = 8.8 Hz, 1H), 5.48 (q, *J* = 6.9 Hz, 1H), 5.19 (d, *J* = 12.3 Hz, 1H), 5.10 (d, *J* = 12.3 Hz, 1H), 4.91 (dd, *J* = 8.8, 4.1 Hz, 1H), 3.66 (bs, 3H), 3.23 (m, 1H), 2.73 (d, *J* = 14.6 Hz, 1H), 2.51 (d, *J* = 14.6 Hz, 1H), 1.61 (s, 3H), 1.56 (d, *J* = 6.9 Hz, 3H), 1.14 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.6, 154.8, 135.5, 128.6, 128.2, 123.9, 123.0, 122.1, 67.8, 65.9, 52.5, 38.2, 37.3, 23.7, 21.6, 14.0; IR (thin film): ν 3400, 2951, 1742, 1710, 1456, 1387, 1304 cm^{-1}; MS (by GC/MS) *m/z* 284 $[M-59]^+$.



213

4-Isobutylidene-2,5-dimethyl-2,3,4,5-tetrahydroazepine-1,2-dicarboxylic acid 1-benzyl ester 2-methyl ester (213). Prepared by following general procedure M using: **75d** (35 mg, 94 μmol), $[Rh(CO)_2Cl]_2$ (3.6 mg, 9.4 μmol) added in one portion at rt. Heated at 90 °C for 5 h. Yield of **213** (18 mg, 51 %).

^{1}H NMR ($CDCl_3$, 300MHz): δ 7.35 (s, 5H), 6.23 (d, *J* = 7.2 Hz, 1H), 5.22-5.09 (m, 3H), 4.99 (s, 1H), 3.67 (bs, 3H), 3.29 (s, 1H), 2.72 (d, *J* = 14.9 Hz, 1H), 2.53 (d, *J* = 15.0 Hz, 1H), 2.48-2.30 (m, 1H), 1.61 (s, 3H), 1.15 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75MHz): δ 173.5, 154.7, 135.0, 131.9, 128.6, 128.2, 124.2, 67.7, 65.2, 52.3, 38.2, 36.3, 29.8, 27.4, 23.4, 20.4; IR (thin film): ν 2956, 1743, 1710, 1306 cm^{-1}.

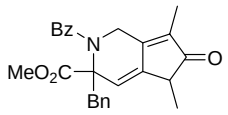


214

1-Benzoyl-2-(*tert*-butyl-dimethylsilyloxymethyl)-4-ethylidene-5-methyl-2,3,4,5-tetrahydro-1*H*-azepine-2-carboxylic acid methyl ester (214). Prepared by following general procedure M using: **75e** (32 mg, 72 μmol). First portion of $[Rh(CO)_2Cl]_2$ (1.5 mg, 3.8 μmol) was added at rt °C. After 15 min at 90 °C another portion of $[Rh(CO)_2Cl]$ (3 mg, 7.6 μmol) was added and the reaction was heated to 90 °C for additional 2 h. Upon completion, the reaction mixture was purified by flash chromatography (pentanes-Et_2O, 3 : 1, v/v) to afford **214** (23 mg, 72 %) as a 4 : 1 mixture of diastereomers determined by ^1H NMR.

214: (major diastereomer): ^1H NMR ($CDCl_3$, 300MHz): δ 7.57-7.52 (m, 2H), 7.42-7.33 (m, 3H), 5.89 (dd, *J* = 8.3, 2.6 Hz, 1H), 5.55 (q, *J* = 6.8 Hz, 1H), 4.83 (dd, *J* = 8.3, 3.9 Hz, 1H), 4.66 (d, *J* = 9.9 Hz, 1H), 3.89 (d, *J* = 9.9 Hz, 1H), 3.69 (s, 3H), 3.46 (bs, 1H), 3.04 (d, *J* = 14.9 Hz, 1H), 2.64 (d, *J* = 14.8 Hz, 1H), 1.58 (d, *J* = 6.8 Hz, 3H), 1.19 (d, *J* = 7.2 Hz, 3H), 0.86 (s, 9H), 0.07 (s, 3H), 0.03 (s, 3H): ^{13}C NMR ($CDCl_3$, 75MHz): δ 171.5, 171.4, 136.2, 135.3, 130.4, 129.2, 128.6, 128.0, 124.1, 121.9, 69.2, 64.6, 52.2, 37.8, 32.4, 25.8, 21.9, 18.0, 13.6, -5.3, -5.6; IR (thin film): ν 2953, 1734, 1641, 1342 cm^{-1}; MS *m/z* (%) 443 (67), 428 (49), 413 (37), 386 (40), 105 (100); EI-HRMS calcd for $C_{25}H_{37}NO_4Si$ $[M]^+$, *m/z* 443.2492; found 443.2500.

General procedure N for the Rh(I)-catalyzed cyclocarbonylation reaction affording 4-alkylidene cyclopentenones.



270a

2-Benzoyl-3-benzyl-5,7-dimethyl-6-oxo-2,3,5,6-tetrahydro-1H-[2]pyrindine-3-carboxylic acid methyl ester (270a). To a test tube equipped with a magnetic stirring bar was added $[Rh(CO)_2Cl]_2$ (18 mg, 46 μmol) and DCE (1 mL). To this solution, PPh_3 (36 mg, 137 μmol) in DCE (1 mL) was added dropwise via a syringe at rt. The test tube was evacuated under vacuum by inserting a needle and charged three times with CO from a balloon. After 5 min, $AgBF_4$ (2 mL of a 0.05 M solution in DCE, 0.102 mmol) was added dropwise via a syringe. The mixture was stirred for additional 5 min at rt and then the allenyne **73a** (0.180 g, 0.465 mmol) in DCE (1 mL) was added via a syringe. After 1 h the reaction mixture was directly applied to a silica gel column eluted (gradient elution, hexanes-EtOAc, 4 : 1 to 1 : 1, v/v) to afford the 4-alkylidene cyclopentenone **270a** (0.142 g, 73%) in 1.7 : 1 diastereomeric ratio determined by integration of the olefin resonances in the ^1H NMR spectrum.

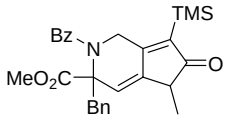
Notes: $[Rh(CO)_2Cl]_2$ and PPh_3 were both weighed out in an open atmosphere. $AgBF_4$ was weighed out in a vial, in the glove box under nitrogen atmosphere and caution was taken to limit exposure to light by wrapping the vial in aluminum foil. DCE solution of $AgBF_4$ was prepared by sonication for 5 min.

IR (thin film): ν 3027, 2918, 1740, 1704, 1644, 1384, 1250 cm^{-1}; MS *m/z* (%) 415 (15), 384 (15), 324 (31), 105 (100); EI-HRMS calcd for $C_{26}H_{25}NO_4$ $[M]^+$ *m/z* 415.1784, found 415.1802.

The diastereomers were separated by HPLC (hexanes:EtOAc 4 : 1, flow rate 3 mL/min, UV detector at 254 nm).

270a (major diastereomer-eluting first, R_f = 0.21, TLC, hexanes : EtOAc, 2 : 1): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-6.98 (m, 10H), 5.71 (s, 1H), 4.34 (d, *J* = 17.7 Hz, 1H), 4.15 (d, *J* = 13.7 Hz ,1H), 3.79 (s, 3H), 3.38 (d, *J* = 13.7 Hz, 1H), 2.86 (d, *J* = 17.7 Hz, 1H), 2.84 (q, *J* = 7.4 Hz, 1H), 1.46 (s, 3H), 1.25 (d, *J* = 7.4Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.5, 171.8, 171.6, 153.6, 140.8, 136.4, 135.9, 134.4, 130.6, 130.2, 128.9, 128.4, 127.4, 126.7, 119.9, 66.3, 53.2, 44.4, 42.0, 40.0, 13.6, 8.1.

270a (minor diastereomer-eluting second, R_f = 0.16, TLC, hexanes : EtOAc, 2 : 1): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47-6.89 (m, 10H), 5.72 (s, 1 H), 4.34 (d, *J* = 18.2 Hz, 1H), 4.16 (d, *J* = 13.8 Hz 1H), 3.81 (s, 3H), 3.39 (d, *J* = 13.8 Hz, 1H), 2.99 (d, *J* = 18.2 Hz, 1H), 2.86 (q, *J* = 7.6 Hz, 1H), 1.44 (s, 3H), 1.31 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.6, 172.1, 171.9, 154.0, 140.5, 136.5, 134.5, 130.9, 130.3, 129.1, 128.4, 127.5, 126.8, 120.2, 66.3, 53.3, 44.9, 41.9, 40.2, 14.5, 8.1.



270c

2-Benzoyl-3-benzyl-5-methyl-6-oxo-7-trimethylsilyl-2,3,5,6-tetrahydro-1H-[2]pyrindine-3-carboxylic acid methyl ester (270c). Prepared by following general procedure N, using:

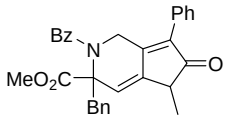
73c (50 mg, 112 μmol), $[Rh(CO)_2Cl]_2$ (4 mg, 11 μmol), PPh_3 (9 mg, 34 μmol), $AgBF_4$ (250 μL of 0.1 M solution in DCE, 25 μmol). The reaction was heated at 35 °C for 1 h.

Yield **270c** (52 mg, 98%) as a mixture of diastereomers in 1.6 : 1 ratio. The diastereomers were separated by semi-preparative HPLC (hexanes-EtOAc, 4 : 1 v/v, flow rate 3 mL/min, UV detector at 254 nm).

270c (major diastereomer – eluting first): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.19 (m, 10H), 5.78 (s, 1H), 4.41 (d, *J* = 18.1 Hz, 1H), 4.15 (d, *J* = 13.7 Hz, 1H), 3.82 (s, 3H), 3.38 (d, *J* = 13.7

Hz, 1H), 2.86-2.79 (m, 1H), 2.82 (d, *J* = 16.8 Hz, 1H), 1.23 (d, *J* = 7.4 Hz, 1H), -0.14 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.2, 171.7, 171.6, 165.5, 142.8, 138.2, 136.3, 136.0, 130.6, 130.0, 128.9, 128.4, 127.3, 126.3, 121.5, 65.7, 53.2, 46.4, 42.9, 40.0, 13.8, -1.3; IR (thin film): ν 2952, 1742, 1694, 1647, 1250 cm^{-1}; MS *m/z* (%) 473 (5), 458 (22), 382 (45), 105 (100); EI-HRMS calcd for $C_{28}H_{31}NO_4Si$ *m/z* $[M]^+$ 473.2022; found 473.2033.

270c (minor diastereomer – eluting second): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.42 (m, 3H), 7.34-7.31 (m, 2H), 7.27-7.24 (m, 3H), 7.19-7.16 (m, 2H), 5.77 (d, *J* = 1.0 Hz, 1H), 4.39 (d, *J* = 18.5, 1.2 Hz, 1H), 4.15 (d, *J* = 13.7 Hz, 1H), 3.83 (s, 3H), 3.38 (d, *J* = 13.7 Hz, 1H), 2.94 (d, *J* = 18.5 Hz, 1H), 2.80 (q, *J* = 7.6 Hz, 1H), 1.29 (d, *J* = 7.5 Hz, 3H), -0.15 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.0, 171.7, 171.5, 165.8, 142.2, 138.0, 136.0, 130.7, 129.9, 128.8, 128.1, 127.2, 126.2, 121.5, 65.5, 53.0, 46.7, 42.5, 39.9, 14.2, -1.5; IR (thin film): ν 2953, 1742, 1695, 1649, 1250 cm^{-1}; MS *m/z* (%) 473 (5), 458 (22), 382 (45), 105 (100); EI-HRMS calcd for $C_{28}H_{31}NO_4Si$ *m/z* $[M]^+$ 473.2022; found 473.2042.



270d

2-Benzoyl-3-benzyl-5-methyl-6-oxo-7-phenyl-2,3,5,6-tetrahydro-1H-[2]pyrindine-3-carboxylic acid methyl ester (270d). Prepared by following general procedure N, using:

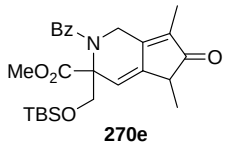
73d (37 mg, 82 μmol), $[Rh(CO)_2Cl]_2$ (3 mg, 8 μmol), PPh_3 (6 mg, 25 μmol), $AgBF_4$ (180 μL of 0.1 M solution in DCE, 18 μmol). The reaction was heated at 35 °C for 1 h.

Yield **270d** (29 mg, 74%) as a mixture of diastereomers in ratio 1.6 : 1. The diastereomers were separated by semi-preparative HPLC (hexanes/EtOAc, 5 : 1, v/v, flow rate 3 mL/min, UV detector at 254 nm).

270d (major diastereomer, R_t = 15 min, HPLC, hexanes/EtOAc, 5 : 1, v/v): ^{1}H NMR (300 MHz,

$CDCl_3$): δ 7.42-7.17 (m, 13H), 7.04-7.00 (m, 2H), 5.88 (d, *J* = 1.1 Hz, 1H), 4.60 (d, *J* = 17.7 Hz, 1H), 4.18 (d, *J* = 13.7 Hz, 1H), 3.81 (s, 3H), 3.44 (d, *J* = 13.8 Hz, 1H), 3.10-2.98 (m, 2H), 1.36 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.7, 171.8, 171.7, 153.6, 141.2, 136.6, 135.9, 135.5, 130.8, 130.3, 130.1, 128.9, 128.8, 128.7, 128.7, 128.6, 127.6, 126.8, 122.2, 66.6, 59.9, 53.3, 45.2, 42.9, 40.3, 13.9; IR (thin film): ν 2949, 1741, 1706, 1643 1259 cm^{-1}; MS *m/z* (%) 477 (6), 418 (63), 386 (55), 105 (100); EI-HRMS calcd for $C_{31}H_{27}NO_4$ *m/z* $[M]^+$ 477.1940; found 477.1954.

270d (minor diastereomer, R_t = 18 min HPLC, hexanes/EtOAc 5 : 1, v/v): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.20 (m, 13H), 7.03-6.99 (m, 2H), 5.90 (d, *J* = 0.9 Hz, 1H), 4.59 (d, *J* = 18.2, 1.2 Hz, 1H), 4.19 (d, *J* = 13.8 Hz, 1H), 3.83 (s, 3H), 3.45 (d, *J* = 13.8 Hz, 1H), 3.17 (d, *J* = 18.3 Hz, 1H), 3.03 (q, *J* = 7.5 Hz, 1H), 1.41 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.9, 172.1, 171.7, 153.8, 140.7, 136.4, 136.0, 135.5, 130.9, 130.3, 130.1, 129.1, 128.8, 128.7, 128.6, 128.5, 127.6, 126.8, 122.5, 66.4, 53.3, 45.6, 42.6, 40.3, 14.9; IR (thin film): ν 2950, 1741, 1706, 1645, 1235 cm^{-1}; MS *m/z* (%) 477 (10), 418 (15), 386 (25), 105 (100); EI-HRMS calcd for $C_{31}H_{27}NO_4$ *m/z* $[M]^+$ 477.1940; found 477.1941.



270e

2-Benzoyl-3-(*tert*-butyldimethylsilyloxymethyl)-5,7-dimethyl-6-oxo-2,3,5,6-tetrahydro-1H-[2]pyrindine-3-carboxylic acid methyl ester (270e). Prepared by following general procedure N, using: **73e** (50 mg, 113 μmol), $[Rh(CO)_2Cl]_2$ (4 mg, 11 μmol), PPh_3 (9 mg, 34 μmol), $AgBF_4$ (250 μL of 0.1 M solution in DCE, 25 μmol). The reaction was heated at 35 °C for 1 h.

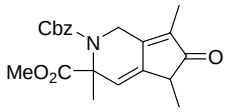
Yield **270e** (43 mg, 81%) as a mixture of diastereomers in 1.7 : 1 ratio. The diastereomers were separated by semi-preparative HPLC (hexanes-EtOAc, 6 : 1 v/v, flow rate 3 mL/min, UV

detector at 254 nm).

IR (thin film): ν 2953, 1741, 1708, 1648, 1258 cm^{-1}.

270e (major diastereomer, R_t = 17 min, HPLC, hexanes-EtOAc, 6 : 1 v/v): ^1H NMR (300 MHz, $CDCl_3$): δ 7.49-7.43 (m, 5H), 5.56 (s, 1H), 4.75 (d, *J* = 17.1 Hz, 1H), 4.74 (d, *J* = 10.4 Hz, 1H), 4.45 (d, *J* = 17.4 Hz, 1H), 4.15 (d, *J* = 10.3 Hz, 1H), 3.74 (s, 3H), 2.89 (q, *J* = 7.5 Hz, 1H), 1.65 (s, 3H), 1.28 (d, *J* = 7.5 Hz, 3H), 0.81 (s, 9H), 0.07 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.5, 171.7, 170.5, 154.3, 144.3, 141.3, 135.9, 134.3, 130.0, 128.8, 126.5, 118.8, 66.1, 65.3, 52.6, 45.6, 41.9, 25.7, 18.0, 13.6, 7.9, -5.4, -5.6; MS *m/z* (%) 469 (37), 439 (30), 412 (30), 324 (20), 105 (100); EI-HRMS calcd for $C_{26}H_{35}NO_5Si$ *m/z* $[M]^+$ 469.2285; found 469.2280.

270e (minor diastereomer, R_t = 26 min, HPLC, hexanes-EtOAc, 6 : 1 v/v): ^1H NMR (300 MHz, $CDCl_3$): δ 7.50-7.42 (m, 5H), 5.59 (s, 1H), 4.74 (d, *J* = 18.0 Hz, 1H), 4.72 (d, *J* = 10.2 Hz, 1H), 4.47 (1d, *J* = 17.8 Hz, 1H), 4.15 (d, *J* = 10.3 Hz, 1H), 3.75 (s, 3H), 2.91 (q, *J* = 7.6 Hz, 1H), 1.64 (s, 3H), 1.27 (d, *J* = 7.6 Hz, 9H), 0.80 (s, 3H), 0.07 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 206.6, 171.9, 170.4, 154.6, 141.2, 135.9, 134.2, 130.0, 128.9, 126.5, 118.8, 65.9, 65.1, 52.6, 45.9, 41.6, 25.6, 17.9, 14.2, 7.9, -5.5, -5.7; MS *m/z* (%) 469 (7), 439 (30), 412 (35), 324 (22), 105 (100); EI-HRMS calcd for $C_{26}H_{35}NO_5Si$ *m/z* $[M]^+$ 469.2285; found 469.2299.

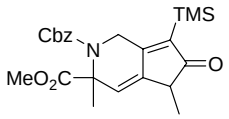


270f

3,5,7-Trimethyl-6-oxo-1,3,5,6-tetrahydro-[2]pyrindine-2,3-dicarboxylic acid 2-benzyl ester 3-methyl ester (270f). Prepared by following general procedure N, using: **73f** (25 mg, 73 μmol), $[Rh(CO)_2Cl]_2$ (3 mg, 8 μmol), PPh_3 (5 mg, 20 μmol), $AgBF_4$ (150 μL of 0.1 M solution in DCE, 15 μmol). The reaction was stirred at rt for 1 h. Yield **270f** (19 mg, 75%).

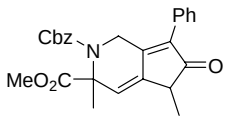
^1H NMR (300 MHz, DMSO-d_6): δ 7.41-7.30 (m, 5H), 5.72 (s, 1H), 5.15 (s, 2H), 4.86 (d, *J* =

18.6 Hz, 1H), 4.34 (d, *J* = 18.0 Hz, 1H), 3.48 (bs, 3H), 2.87 (q, *J* = 7.4 Hz, 1H), 1.73 (s, 3H), 1.57 (s, 3H), 1.07 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 206.4, 192.6, 172.7, 155.5, 154.9, 138.6, 137.0, 134.6, 129.2, 128.8, 128.5, 121.7, 67.7, 62.5, 53.1, 41.6, 40.7, 22.9, 14.1, 8.5; IR (thin film): ν 2916, 1744, 1700, 1234 cm^{-1}; MS *m/z* (%) 369 (15), 310 (40), 266 (27), 91 (100); EI-HRMS calcd for $C_{21}H_{23}NO_5$ *m/z* $[M]^+$ 369.1576; found 369.1581.



270h

3,5-Dimethyl-6-oxo-7-trimethylsilyl-1,3,5,6-tetrahydro-[2]pyrindine-2,3-dicarboxylic acid 2-benzyl ester 3-methyl ester (270h). Prepared by following general procedure N, using: **73h** (30 mg, 75 μmol), $[Rh(CO)_2Cl]_2$ (3 mg, 8 μmol), PPh_3 (6 mg, 23 μmol), $AgBF_4$ (335 μL of 0.05 M solution in DCE, 17 μmol). The reaction was stirred at rt for 2 h. Yield **270h** (25 mg, 78%). ^{1}H NMR (300 MHz, DMSO-d_6, 323 K): δ 7.37 (s, 5H), 5.80 (s, 1H), 5.18-5.09 (m, 2H), 5.01 (d, *J* = 18.6 Hz, 1H), 4.46 (d, *J* = 18.6 Hz, 1H), 3.53 (s, 3H), 2.84 (q, *J* = 7.4 Hz, 1H), 1.61 (s, 3H), 1.07 (d, *J* = 7.4 Hz, 3H), 0.12 (s, 9H); ^{13}C NMR (75 MHz, DMSO-d_6, 323 K): δ 209.5, 171.4, 166.2, 154.4, 139.7, 136.7, 135.9, 128.1, 127.8, 127.4, 122.9, 66.8, 61.3, 52.1, 41.7, 41.6, 21.3, 13.3, -1.3; IR (thin film): ν 2953, 1746, 1694, 1248 cm^{-1}; MS *m/z* (%) 427 (11), 384 (30), 368 (32), 324 (27), 91 (100); EI-HRMS calcd for $C_{23}H_{29}NO_5Si$ *m/z* $[M]^+$ 427.1815; found 427.1821.

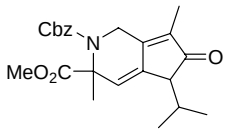


270i

3,5-Dimethyl-6-oxo-7-phenyl-1,3,5,6-tetrahydro-[2]pyrindine-2,3-dicarboxylic acid 2-benzyl ester 3-methyl ester (270i). Prepared by following general procedure N, using: **73i** (31 mg, 77 μmol), $[Rh(CO)_2Cl]_2$ (3 mg, 8 μmol), PPh_3 (6 mg, 23 μmol), $AgBF_4$ (340 μL of 0.05 M

solution in DCE, 17 μmol). The reaction was stirred at rt for 2 h. Yield **270i** (25 mg, 75%).

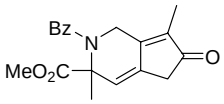
^{1}H NMR (300 MHz, DMSO-d_6, 323 K): δ 7.47-7.32 (m, 10H), 5.90 (s, 1H), 5.16-5.08 (m, 2H), 4.99 (d, J = 18.6 Hz, 1H), 4.66 (d, J = 18.6 Hz, 1H), 3.51 (s, 3H), 3.09 (q, J = 7.4 Hz, 1H), 1.65 (s, 3H), 1.20 (d, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, 323 K): δ 203.7, 171.4, 154.4, 154.1, 137.7, 135.9, 134.3, 130.0, 128.4, 128.2, 128.1, 127.7, 127.3, 123.2, 66.7, 61.7, 52.1, 40.2, 21.4, 13.1; IR (thin film): ν 2931, 1745, 1703, 1241 cm^{-1}; MS *m/z* (%) 431 (10), 372 (86), 328 (45), 91 (100); EI-HRMS calcd for $C_{26}H_{25}NO_5$ *m/z* $[M]^+$ 431.1733; found 431.1735.



270j

5-Isopropyl-3,7-dimethyl-6-oxo-1,3,5,6-tetrahydro-[2]pyrindine-2,3-dicarboxylic acid 2-benzyl ester 3-methyl ester (270j). Prepared by following general procedure N, using: **111j** (98 mg, 265 μmol), $[Rh(CO)_2Cl]_2$ (5 mg, 13 μmol), PPh_3 (10 mg, 39 μmol), $AgBF_4$ (583 μL of 0.05 M solution in DCE, 29 μmol). The reaction was heated to 35 °C for 2 h. Yield **270j** (78 mg, 74%).

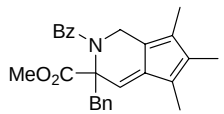
^{1}H NMR (300 MHz, $CDCl_3$, 320 K): δ 7.39-7.33 (m, 5H), 5.54 (s, 1H), 5.25 (d, J = 12.2 Hz, 1H), 5.17 (d, J = 12.2 Hz, 1H), 4.95 (d, J = 18.6 Hz, 1H), 4.21 (d, J = 18.6 Hz, 1H), 3.56 (bs, 3H), 2.77-2.76 (m, 1H), 2.30-2.17 (m, 1H), 1.81 (s, 3H), 1.69 (s, 3H), 0.93 (d, J = 7.0 Hz, 3H), 0.86 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 320 K): δ 205.9, 172.5, 155.4, 155.3, 136.0, 135.9, 135.8, 128.5, 128.3, 121.6, 67.8, 62.3, 52.5, 52.1, 40.5, 29.8, 22.5, 19.7, 17.9, 7.9; IR (thin film): ν 2958, 1745, 1701, 1238 cm^{-1}; MS *m/z* (%) 397 (33), 338 (30), 294 (21), 91 (100); EI-HRMS calcd for $C_{23}H_{27}NO_5$ *m/z* $[M]^+$ 397.1889; found 397.1888.



277

2-Benzoyl-3,7-dimethyl-6-oxo-2,3,5,6-tetrahydro-1H-[2]pyrindine-3-carboxylic acid methyl ester (277). $[Rh(CO)_2Cl]_2$ (1.5 mg, 3.8 μmol) was placed in a test tube and DCE (0.3 mL) was added. The test tube was sealed with a rubber septum, the atmosphere evacuated by inserting a needle and replaced with CO (balloon) three times. Allenyne **74c** (23 mg, 77 μmol) in DCE (0.7 mL) was added via syringe and the reaction was stirred for 2.5 h at rt. The light yellow solution was directly applied to a silica gel column and eluted (hexanes-EtOAc, 4 : 1 to 2 : 1, v/v) to afford **277** (18 mg, 72%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51-7.43 (m, 5H), 5.69 (s, 1H), 4.78 (d, *J* = 17.6 Hz, 1H), 4.19 (dd, *J* = 17.6, 0.9 Hz, 1H), 3.74 (s, 3H), 3.02 (s, 1H), 1.79 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.5, 172.1, 171.8, 155.3, 136.2, 135.2, 133.0, 130.6, 128.8, 127.1, 123.0, 62.4, 52.9, 43.2, 37.4, 20.6, 8.0; IR (thin film): ν 2950, 1740, 1704, 1645, 1394 cm^{-1}. MS *m/z* (%) 325 (25), 294 (9), 266 (47), 105 (100); EI-HRMS calcd for $C_{19}H_{19}NO_4$ *m/z* $[M]^+$ 325.1314; found 325.1324.



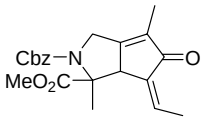
280a

2-Benzoyl-3-benzyl-5,6,7-trimethyl-2,3-dihydro-1H-[2]pyrindine-3-carboxylic acid methyl ester (280a). $CeCl_3 \cdot 7H_2O$ (2.7 g) was dried under vacuum for 24 h at 140 °C and then THF (10 mL) was added to prepare a 0.72 M suspension. The suspension was stirred overnight at rt.

To a 10 mL round-bottom flask was added $CeCl_3$ (180 μL of a 0.72 M suspension in THF, 130 μmol). THF (2 mL) was added and the suspension was cooled to -78 °C. CH_3Li (1.2 M in Et_2O,

81 μL, 98 μmol) was added and the suspension was stirred at -78 °C for 1.5 h. The resulting suspension was cannulated to a solution of **270a** (27 mg, 65 μmol) in THF (1 mL) at -78 °C. After 1h the reaction was quenched with 0.2 M HCl (10 mL) at -78 °C and warmed to rt. After 30 min sat'd aq. $NaHCO_3$ was added and the aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under vacuum. The dark yellow residue was purified by flash chromatography (hexanes-EtOAc, 9 : 1, v/v) to afford **280a** (20 mg, 74%). The product was stored as a solution in benzene under nitrogen atmosphere.

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.48-7.47 (m, 2H), 7.27-7.13 (m, 8H), 6.29 (s, 1H), 4.04 (d, J = 15.8 Hz, 1H), 3.92 (d, J = 13.4 Hz, 1H), 3.63 (s, 3H), 3.40 (d, J = 13.4 Hz, 1H), 2.79 (d, J = 15.8 Hz, 1H), 1.87 (s, 3H), 1.71 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 171.0, 170.7, 143.3, 140.4, 136.2, 136.0, 134.4, 130.2, 129.7, 128.7, 128.1, 126.9, 126.0, 124.8, 121.9, 117.5, 66.4, 52.5, 44.1, 10.7, 10.5, 8.9; IR (thin film): ν 3348, 2949, 1740, 1636 cm^{-1}; MS *m/z* (%) 413 (10), 322 (18), 105 (100); EI-HRMS calcd for $C_{27}H_{27}NO_3$ $[M]^+$ *m/z* 413.1991, found 413.2007.



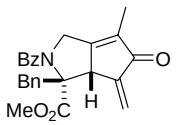
274f

6-Ethylidene-1,4-dimethyl-5-oxo-3,5,6,6a-tetrahydro-1H-cyclopenta[c]pyrrole-1,2-dicarboxylic acid 2-benzyl ester 1-methyl ester (274f). To a solution of allenyne **73f** (56 mg, 0.16 mmol) in toluene (1 mL) was added DMSO (116 μL, 1.64 mmol) followed by $Mo(CO)_6$ (54 mg, 0.20 mmol) at rt. The reaction vessel was immersed in a preheated oil bath at 70 °C and then slowly heated to 90 °C where it was stirred for 45 min. The reaction mixture was then cooled to rt, and applied directly to a silica gel column. Gradient elution (hexanes-EtOAc, 9 : 1 to 4 : 1

v/v) afforded a mixture of compounds (60 mg, >95%). The major component of the mixture (***Z***)-**274f** (R_t = 20.5 min) was purified for characterization by semipreparative HPLC (hexanes-EtOAc, 4 : 1 v/v, flow rate 3 mL/min, UV detector 254 nm).

(***Z***)-**274f** : ^{1}H NMR (300 MHz, DMSO-d_6 353K): δ 7.38-7.33 (m, 5H), 5.98 (q, *J* = 7.3 Hz, 1H), 5.11 (s, 2H), 4.43 (d, *J* = 16.2 Hz, 1H), 4.36 (d, *J* = 16.3 Hz, 1H), 3.89 (s, 1H), 3.67 (s, 3H), 2.20 (d, *J* = 7.3 Hz, 3H), 1.75 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6 353K): δ 195.9, 172.0, 160.4, 152.7, 135.9, 135.8, 135.5, 132.0, 127.7, 127.3, 127.0, 66.0, 65.4, 53.7, 51.7, 44.8, 12.9, 12.7, 7.7; IR (thin film): ν 2951, 1743, 1698, 1646, 1408 cm^{-1}; MS *m/z* (%) 369 (13), 310 (7), 266 (10), 91 (100); EI-HRMS calcd for $C_{21}H_{23}NO_5$ *m/z* $[M]^+$ 369.1576 found 369.1580.

General procedure O, for the Mo(CO)$_6$-mediated cyclocarbonylation reaction.



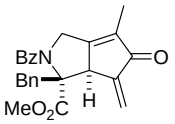
287a

2-Benzoyl-1-benzyl-4-methyl-6-methylene-5-oxo-1,2,3,5,6,6a-hexahydrocyclopenta[c]-pyrrole-1-carboxylic acid methyl ester (287a). To a solution of allenyne **74a** (338 mg, 0.906 mmol) in toluene (5 mL), were added DMSO (323 μL, 4.55 mmol) and Mo(CO)$_6$ (300 mg, 1.13 mmol) at rt under nitrogen atmosphere. The reaction mixture was heated to 90 °C for 45 min. After cooling to rt, the reaction mixture was directly purified by flash chromatography (gradient elution, hexanes-EtOAc, 19 : 1 to 3 : 2, v/v) to afford **287a** (210 mg, 57%) and a mixture of **288a** and **289a** (82 mg, 22%). The correct product ratios listed in Scheme 4.30 were determined by integration of the olefinic resonances in the ^{1}H NMR spectrum taken after complete removal of all volatiles from a small reaction sample.

287a (R_f = 0.3, TLC, hexanes-EtOAc, 3 : 1 v/v): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60-7.28 (m,

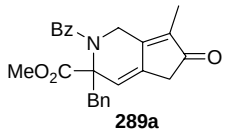
10 H), 6.21 (s, 1H), 5.62 (s, 1H), 4.24 (d, *J* = 14.6 Hz, 1H), 4.19 (d, *J* = 14.3 Hz, 1H), 3.99 (d, *J* = 14.6, 1.2 Hz, 1H), 3.90 (s, 1H), 3.61 (s, 3H), 3.38 (d, *J* = 14.3 Hz, 1H), 1.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.5, 171.0, 170.2, 162.6, 140.6, 136.1, 135.9, 134.7, 131.3, 131.1, 128.7, 128.5, 127.5, 127.3, 117.6, 71.0, 52.2, 50.5, 49.5, 37.9, 8.9; IR (thin film): ν 2950, 1741, 1707, 1644, 1378, 1340 cm^{-1}; MS *m/z* (%) 401 (40), 342 (22), 296 (35), 105 (100); EI-HRMS calcd for $C_{25}H_{23}NO_4$ *m/z* $[M]^+$ 401.1627 found 401.1641.

Mixture of **288a** and **289a** (R_f = 0.2, TLC, hexanes-EtOAc, 3 : 1 v/v).



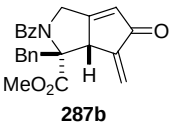
288a

288a: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59-7.44 (m, 5H), 7.17-7.10 (m, 3H), 7.01-6.98 (m, 2H), 6.43 (d, *J* = 1.9 Hz, 1H), 5.66 (d, *J* = 1.3 Hz, 1H), 4.32 (d, *J* = 15.7, 1H), 4.01 (bs, 1H), 3.94 (s, 3H), 3.84 (d, *J* = 14.3 Hz, 1H), 3.59 (d, *J* = 15.6 Hz, 1H), 3.29 (d, *J* = 14.3 Hz, 1H), 1.22 (s, 3H).



289a

289a: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-7.22 (m, 10H), 5.77 (s, 1H), 4.34 (d, *J* = 17.8 Hz, 1H), 4.15 (d, *J* = 13.8 Hz, 1H), 3.80 (s, 3H), 3.37 (d, *J* = 13.7 Hz, 1H), 3.03 (s, 2H), 2.91 (d, *J* = 17.9 Hz, 1H), 1.45 (s, 3H).

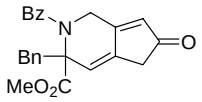


287b

2-Benzoyl-1-benzyl-6-methylene-5-oxo-1,2,3,5,6,6a-hexahydrocyclopenta[c]pyrrole-1-carboxylic acid methyl ester (287b). Prepared by following general procedure O, using: **74b**

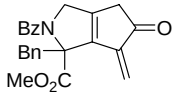
(435 mg, 1.21 mmol), DMSO (429 μL, 6.06 mmol), $Mo(CO)_6$ (400 mg, 1.51 mmol). Heated to 90 °C for 20 min. The crude mixture was purified by flash chromatography (gradient elution, hexanes-EtOAc, 19 : 1 to 2 : 1, v/v) to afford **287b** (260 mg, 55%). The correct product ratios listed in Scheme 4.30 were determined in a separate experiment by integration of the olefinic resonances in the ^{1}H NMR spectrum taken after complete removal of all volatiles from a small reaction sample.

287b: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52-7.27 (m, 10H), 6.19 (s, 1H), 6.07 (s, 1H), 5.63 (s, 1H), 4.24 (d, *J* = 14.9 Hz, 1H), 4.23 (d, *J* = 14.2 Hz, 1H), 4.03 (d, *J* = 15.0 Hz, 1H), 3.98 (s, 1H), 3.62 (s, 3H), 3.39 (d, *J* = 14.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.2, 170.9, 170.2, 170.1, 140.6, 135.7, 135.5, 131.1, 128.6, 128.5, 127.3, 126.2, 118.0, 70.8, 52.3, 51.5, 50.9, 37.7; IR (thin film): ν 3027, 1741, 1710, 1641, 1383 cm^{-1}; MS *m/z* (%) 387 (15), 328 (10), 282 (22), 105 (100); EI-HRMS calcd for $C_{24}H_{21}NO_4$ *m/z* $[M]^+$ 387.1471 found 387.1470.



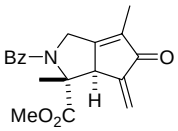
289b

2-Benzoyl-3-benzyl-6-oxo-2,3,5,6-tetrahydro-1H-[2]pyrindine-3-carboxylic acid methyl ester (289b). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49-7.41 (m, 3H), 7.34-7.27 (m, 5H), 7.21-7.17 (m, 2H), 5.90 (s, 1H), 5.70 (s, 1H), 4.39 (d, *J* = 18.1 Hz, 1H), 4.15 (d, *J* = 13.8 Hz, 1H), 3.81 (s, 3H), 3.38 (d, *J* = 13.8 Hz, 1H), 3.05 (s, 2H), 3.01 (d, *J* = 18.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.9, 171.3, 171.1, 161.1, 135.8, 135.4, 135.2, 130.3, 129.9, 128.7, 128.3, 127.4, 127.2, 126.3, 123.5, 65.9, 53.0, 45.1, 39.6, 37.7; IR (thin film): ν 2950, 1740, 1710, 1643, 1391 cm^{-1}; MS *m/z* (%) 387 (47), 356 (15), 328 (12), 296 (30), 105 (100); EI-HRMS calcd for $C_{24}H_{21}NO_4$ *m/z* $[M]^+$ 387.1471 found 387.1489.



290b

2-Benzoyl-1-benzyl-6-methylene-5-oxo-1,2,3,4,5,6-hexahydrocyclopenta[c]pyrrole-1-carboxylic acid methyl ester (290b). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-7.35 (m, 5H), 7.27-7.25 (m, 3H), 7.11-7.08 (m, 2H), 5.94 (s, 1H), 5.58 (s, 1H), 4.08 (d, *J* = 15.7 Hz, 1H), 4.04 (d, *J* = 13.8 Hz, 1H), 3.84 (s, 3H), 3.56-3.52 (m, 2H), 2.85 (d, *J* = 22.5 Hz, 1H), 2.70 (d, *J* = 22.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.5, 170.1, 169.2, 145.2, 142.5, 138.5, 136.2, 136.1, 130.1, 128.5, 127.9, 127.0, 126.4, 112.6, 74.3, 55.1, 52.9, 38.4, 36.2; IR (thin film): ν 2950, 1743, 1631, 1405, 1253 cm^{-1}; ESI-HRMS calcd for $C_{24}H_{21}NO_4Na$ *m/z* $[M+23]^+$ 410.1368; found 410.1375.



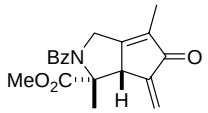
287c

2-Benzoyl-1,4-dimethyl-6-methylene-5-oxo-1,2,3,5,6,6a-hexahydrocyclopenta[c]pyrrole-1-carboxylic acid methyl ester (287c). Prepared by following general procedure O, using:

74c (50 mg, 0.17 mmol), DMSO (120 μL, 1.68 mmol), $Mo(CO)_6$ (55 mg, 0.21 mmol). Heated to 80 °C for 2 hours. The crude mixture (53 mg, >95%) was purified by flash chromatography (gradient elution, hexanes-EtOAc, 9 : 1 to 2 : 1, v/v) to afford **287c** (41 mg, 74 %). The correct product ratios listed in Scheme 4.32 were determined in a separate experiment by integration of the olefinic resonances in the ^{1}H NMR spectrum taken after complete removal of all volatiles from a small reaction sample.

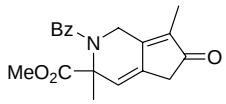
287c: **(**R_f = 0.23, TLC, hexanes-EtOAc, 2 : 1, v/v) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54-7.44 (m, 5H), 6.26 (d, *J* = 1.9 Hz, 1H), 5.44 (s, 1H), 4.58 (d, *J* = 15.7 Hz, 1H), 4.22 (d, *J* = 15.7 Hz, 1H),

4.02 (s, 1H), 3.88 (s, 3H), 1.82 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.7, 172.6, 169.3, 162.4, 139.6, 136.0, 136.0, 130.2, 128.6, 126.5, 119.2, 66.5, 53.3, 52.9, 47.8, 14.6, 9.0; IR (thin film): ν 2950, 1740, 1707, 1689, 1642, 1404 cm^{-1}; MS *m/z* (%) 325 (30), 266 (28), 220 (15), 105 (100); EI-HRMS calcd for $C_{19}H_{19}NO_4$ *m/z* $[M]^+$ 325.1314; found 325.1305.



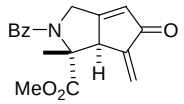
288c

288c: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61-7.59 (m, 2H), 7.54-7.44 (m, 3H), 6.17 (d, *J* = 1.9 Hz, 1H), 5.54 (s, 1H), 4.58 (d, *J* = 14.9 Hz, 1H), 4.30 (d, *J* = 14.9 Hz, 1H), 3.76 (s, 1H), 3.55 (s, 3H), 2.04 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.4, 171.2, 170.5, 162.7, 140.2, 135.9, 135.1, 131.0, 128.6, 127.5, 118.0, 68.3, 55.0, 52.1, 50.3, 23.6, 9.1; IR (thin film): ν 2950, 1734, 1707, 1689, 1643, 1378 cm^{-1}; MS *m/z* (%) 325 (10), 266 (18), 105 (100); EI-HRMS calcd for $C_{19}H_{19}N_1O_4$ *m/z* $[M]^+$ 325.1314; found 325.1308.



289c

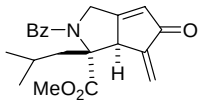
289c: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51-7.43 (m, 5H), 5.69 (s, 1H), 4.78 (d, *J* = 17.6 Hz, 1H), 4.19 (d, *J* = 17.6, 0.9 Hz, 1H), 3.74 (s, 3H), 3.02 (s, 1H), 1.79 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.5, 172.1, 171.8, 155.3, 136.2, 135.2, 133.0, 130.6, 128.8, 127.1, 123.0, 62.4, 52.9, 43.2, 37.4, 20.6, 8.0; IR (thin film): ν 2950, 1740, 1704, 1645, 1394 cm^{-1}; MS *m/z* (%) 325 (25), 294 (9), 266 (47), 105 (100); EI-HRMS calcd for $C_{19}H_{19}NO_4$ *m/z* $[M]^+$ 325.1314; found 325.1324.



287d

2-Benzoyl-1-methyl-6-methylene-5-oxo-1,2,3,5,6,6a-hexahydrocyclopenta[c]pyrrole-1-carboxylic acid methyl ester (287d). Prepared by following general procedure O, using: **74d** (72 mg, 0.25 mmol), DMSO (180 μL, 2.54 mmol), $Mo(CO)_6$ (84 mg, 0.32 mmol). Heated to 80 °C for 2 hours. The crude mixture (80 mg, >95%) was purified by flash chromatography (gradient elution, hexanes-EtOAc, 9 : 1 to 2 : 1, v/v) to afford **287d** (49 mg, 62 %). The correct product ratios listed in Scheme 4.32 were determined in a separate experiment by integration of the olefinic resonances in the ^{1}H NMR taken after complete removal of all volatiles from a small reaction sample.

287d: R_f = 0.15 (TLC, hexanes-EtOAc, 2 : 1, v/v) ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51-7.41 (m, 5H), 6.26-6.25 (m, 2H), 5.46 (s, 1H), 4.66 (d, *J* = 16.0 Hz, 1H), 4.29 (d, *J* = 16.0 Hz, 1H), 4.13 (s, 1H), 3.88 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.6, 172.8, 170.4, 169.6, 140.2, 136.2, 130.6, 129.0, 127.9, 126.8, 120.0, 66.8, 55.4, 53.3, 49.2, 17.3, 15.0; IR (thin film): ν 2950, 1739, 1709, 1638, 1402 cm^{-1}; MS *m/z* (%) 311 (18), 252 (22), 206 (9), 105 (100); EI-HRMS calcd for $C_{18}H_{17}NO_4$ *m/z* $[M]^+$ 311.1158; found 311.1151.



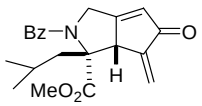
287e

2-Benzoyl-1-isobutyl-6-methylene-5-oxo-1,2,3,5,6,6a-hexahydrocyclopenta[c]pyrrole-1-carboxylic acid methyl ester (287e). Prepared by following general procedure O, using: **74e** (199 mg, 0.612 mmol), DMSO (218 μL, 3.06 mmol), $Mo(CO)_6$ (202 mg, 0.765 mmol). Heated to 80 °C for 1.5 hours. Flash chromatography (gradient elution, hexanes-EtOAc 20 : 1 to 1 : 1 v/v (1% AcOH)) did not afford complete separation of all compounds. Yield of mixture

(207 mg, 96%) consisting of **287e** (74%), **288e** (14%) and **289e** (7%) determined by integration of the olefinic resonances in the ^{1}H NMR spectrum.

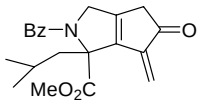
Isomerization of **287e** to **290e**: addition of Et_3N to a solution of **287e** in $CDCl_3$ or adsorbing **287e** onto silica gel gave rapid isomerization to **290e** (~1h).

287e: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 (s, 5H), 6.27 (d, *J* = 1.9 Hz, 1H), 6.23 (s, 1H), 5.50 (s, 1H), 4.62 (d, *J* = 16.4 Hz, 1H), 4.39 (d, *J* = 16.4 Hz, 1H), 4.13 (s, 1H), 3.89 (s, 3H), 2.31 (dd, *J* = 15.0, 7.5 Hz, 1H), 1.63 (dd, *J* = 15.3, 3.6 Hz, 1H), 1.60-1.51 (m, 1H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.81 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.5, 172.7, 171.6, 169.6, 140.3, 136.3, 130.0, 128.8, 126.5, 126.0, 119.4, 69.1, 55.7, 53.0, 50.0, 37.8, 25.2, 23.7, 23.4; IR (thin film): ν 2956, 1739, 1709, 1640, 1400 cm^{-1}; MS *m/z* (%) 354 (26), 353 (40), 297 (67), 265 (70), 105 (100); EI-HRMS calcd for $C_{21}H_{23}NO_4$ *m/z* $[M]^+$ 353.1627; found 353.1625.



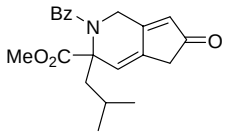
288e

2-Benzoyl-1-isobutyl-6-methylene-5-oxo-1,2,3,5,6,6a-hexahydrocyclopenta[c]pyrrole-1-carboxylic acid methyl ester (288e). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54-7.39 (m, 5H), 6.14 (s, 1H), 6.11 (d, *J* = 1.8 Hz, 1H), 5.49 (s, 1H), 4.62 (d, *J* = 15.2 Hz, 1H), 4.38 (d, *J* = 15.2 Hz, 1H), 4.10 (s, 1H), 3.51 (s, 3H), 2.77 (dd, *J* = 15.2, 7.0 Hz, 1H), 2.13 (dd, *J* = 15.2, 4.6 Hz, 1H), 2.01-1.86 (m, 1H), 1.11 (d, *J* = 6.7 Hz, 3H), 1.06 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.2, 170.9, 170.5, 170.5, 140.7, 135.5, 131.0, 128.5, 127.2, 126.4, 118.0, 70.9, 52.0, 51.9, 51.8, 39.9, 25.3, 24.3, 23.7; IR (thin film): ν 2955, 1740, 1709, 1640, 1383 cm^{-1}; MS *m/z* (%) 353 (51), 310 (15), 294 (32) 105 (100); EI-HRMS calcd for $C_{21}H_{23}NO_4$ *m/z* $[M]^+$ 353.1627; found 353.1632.



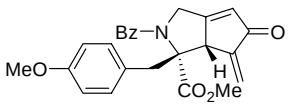
290e

2-Benzoyl-1-isobutyl-6-methylene-5-oxo-1,2,3,4,5,6-hexahydrocyclopenta[c]pyrrole-1-carboxylic acid methyl ester (290e). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51-7.40 (m, 5H), 5.81 (s, 1H), 5.40 (s, 1H), 4.54 (d, *J* = 16.6 Hz, 1H), 4.40 (d, *J* = 16.6 Hz, 1H), 3.76 (s, 3H), 2.98 (s, 2H), 2.69 (dd, *J* = 15.0, 7.1 Hz, 1H), 2.35 (dd, *J* = 15.0, 5.2 Hz, 1H), 1.64-1.49 (m, 1H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.6, 170.7, 169.7, 143.6, 143.5, 138.3, 136.4, 130.1, 128.5, 126.3, 112.4, 74.3, 55.6, 52.6, 38.6, 38.2, 24.7, 24.2, 23.7; IR (thin film): ν 2954, 1742, 1632, 1399 cm^{-1}; MS *m/z* (%) 329 (5), 294 (43), 84 (100).



289e

2-Benzoyl-3-isobutyl-6-oxo-2,3,5,6-tetrahydro-1H-[2]pyrindine-3-carboxylic acid methyl ester (289e). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50-7.41 (m, 5H), 5.97 (q, *J* = 1.6 Hz, 1H), 5.80 (d, *J* = 1.2 Hz, 1H), 4.72 (d, *J* = 18.2 Hz, 1H), 4.57 (d, *J* = 18.6 Hz, 1H), 3.76 (s, 3H), 3.05 (s, 2H), 2.75 (dd, *J* = 14.7, 5.8 Hz, 1H), 2.09 (dd, *J* = 14.7, 6.4 Hz, 1H), 1.80-1.67 (m, 1H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.0, 172.2, 171.5, 161.5, 135.8, 134.1, 130.3, 128.9, 127.6, 126.6, 125.3, 65.6, 52.8, 45.8, 42.7, 37.9, 24.5, 24.3; IR (thin film): ν 2954, 1740, 1709, 1644 cm^{-1}; MS *m/z* (%) 353 (5), 294 (25), 105 (100).



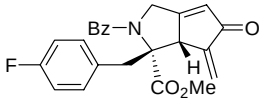
287f

2-Benzoyl-1-(4-methoxybenzyl)-6-methylene-5-oxo-1,2,3,5,6,6a-hexahydro-cyclopenta[c]pyrrole-1-carboxylic acid methyl ester (287f). Prepared by following general

procedure O, using: **74f** (110 mg, 0.286 mmol), $Mo(CO)_6$ (95 mg, 0.36 mmol), DMSO (102 μL, 1.43 mmol). The reaction was heated to 80 °C for 4 h. Flash chromatography (gradient elution, hexanes-EtOAc v/v (1% AcOH)) afforded the major diastereomer **287f** (50 mg, 42%) and an unseparable mixture of minor diastereomer and [6,5] product (62 mg, 53%).

When the reaction was performed with 5.25 g of **73f**, the yield of **287f** was 2.0 g (36%).

287f: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52-7.41 (m, 5H), 7.23-7.18 (m, 2H), 6.94-6.89 (m, 2H), 6.18 (d, *J* = 2.1 Hz, 1H), 6.07 (s, 1H), 5.61 (s, 1H), 4.24 (d, *J* = 15.0 Hz, 1H), 4.15 (d, *J* = 14.5 Hz, 1H), 4.06 (dt, *J* = 14.9, 1.5 Hz, 1H), 3.97 (s, 1H), 3.82 (s, 3H), 3.60 (s, 3H), 3.32 (d, *J* = 14.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.3, 170.8, 170.4, 170.1, 158.9, 140.7, 135.5, 132.1, 131.1, 128.7, 127.5, 127.3, 126.1, 118.0, 113.9, 71.0, 55.2, 52.3, 51.5, 50.9, 36.8; IR (thin film): ν 2951, 1740, 1709, 1640, 1513, 1383 cm^{-1}; ESI-HRMS calcd for $C_{25}H_{23}NO_5Na$ *m/z* $[M+23]^+$ 440.1474; found 440.1479.

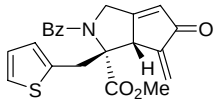


287g

2-Benzoyl-1-(4-fluorobenzyl)-6-methylene-5-oxo-1,2,3,5,6,6a-hexahydrocyclopenta[c]pyrrole-1-carboxylic acid methyl ester (287g). Prepared by following general procedure O, using: **74g** (70 mg, 0.19 mmol), $Mo(CO)_6$ (61 mg, 0.23 mmol), DMSO (132 μL, 1.87 mmol). The reaction was heated to 85 °C for 2 h. After filtration of the reaction mixture on a small silica gel pad eluting with (hexanes-EtOAc 3 : 1 to 1 : 1 v/v (1% AcOH)), the major component was isolated by flash chromatography (hexanes-EtOAc 20 : 1 to 1 : 1 v/v (1% AcOH)) to give **287g** (25 mg, 33%). Yield of mixture (57mg, 76%).

287g: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55-7.43 (m, 5H), 7.29-7.24 (m, 2H), 7.11-7.06 (m, 2H), 6.20 (d, *J* = 1.7 Hz, 1H), 6.10 (s, 1H), 5.62 (s, 1H), 4.27 (d, *J* = 15.1 Hz, 1H), 4.21 (d, *J* = 14.5

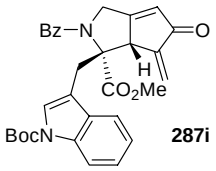
Hz, 1H), 4.07 (d, *J* = 15.0 Hz, 1H), 3.93 (s, 1H), 3.62 (s, 3H), 3.37 (d, J = 14.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.1, 171.1, 170.0, 169.9, 163.9, 160.7, 140.7, 135.5, 132.7, 132.6, 131.5, 131.5, 131.3, 128.7, 127.3, 126.4, 118.0, 115.6, 115.4, 71.0, 52.3, 51.6, 51.0, 37.1; IR (thin film): ν 2951, 1742, 1709, 1640, 1509 cm^{-1}; MS *m/z* (%) 405 (15), 346 (5), 300 (20), 296 (13), 105 (100); EI-HRMS calcd for $C_{24}H_{20}NO_4F$ *m/z* $[M]^+$ 405.1376; found 405.1371.



287h

2-Benzoyl-6-methylene-5-oxo-1-thiophen-2-ylmethyl-1,2,3,5,6,6a-hexahydrocyclopenta[c]pyrrole-1-carboxylic acid methyl ester (287h). Prepared by following general procedure O, using: **74h** (115 mg, 0.315 mmol), $Mo(CO)_6$ (104 mg, 0.393 mmol), DMSO (224 μL, 3.15 mmol). Heated to 85 °C for 2 h. Flash chromatography (gradient elution, hexanes-EtOAc v/v (1% AcOH)) afforded the major diastereomer **287h** (48 mg, 39%) and an unseparable mixture of minor diastereomer and [6,5] product (67 mg, 54%).

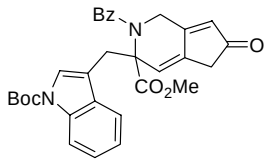
287h: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65-7.62 (m, 2H), 7.55-7.44 (m, 3H), 7.33-7.32 (m, 1H), 7.05-7.01 (m, 2H), 6.16 (d, *J* = 2.0 Hz, 1H), 6.11 (s, 1H), 5.53 (s, 1H), 4.41-4.30 (m, 3H), 3.99 (s, 1H), 3.78 (d, *J* = 15.6 Hz, 1H), 3.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.4, 171.1, 170.5, 170.0, 141.0, 137.8, 135.8, 131.5, 129.1, 128.9, 127.8, 127.2, 126.8, 126.3, 118.4, 71.4, 52.6, 52.0, 51.7, 33.5; IR (thin film): ν 2951, 1741, 1708, 1640, 1378 cm^{-1}; ESI-HRMS calcd for $C_{22}H_{19}NO_4NaS$ *m/z* $[M+23]^+$ 416.0932; found 416.0950.



287i

3-(2-Benzoyl-1-methoxycarbonyl-6-methylene-5-oxo-1,2,3,5,6,6a-hexahydrocyclopenta[c]pyrrol-1-ylmethyl)-indole-1-carboxylic acid *tert*-butyl ester (287i). Prepared by following general procedure O, using: **74i** (65 mg, 0.13 mmol), $Mo(CO)_6$ (43 mg, 0.16 mmol), DMSO (93 μL, 1.3 mmol). The reaction was heated to 85 °C for 1 h. Flash chromatography (gradient elution, hexanes-EtOAc v/v (1% AcOH)) did not afford complete separation of all compounds. **287i** (12 mg) and the [6,5] product (3 mg) were collected pure for characterization purposes. Yield of mixture (53 mg, 77%).

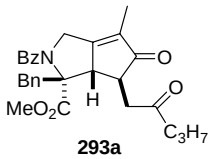
287i: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22 (d, *J* = 8.3 Hz, 1H), 7.58-7.1 (m, 10H), 6.23 (d, *J* = 2.0 Hz, 1H), 6.07 (s, 1H), 5.74 (s, 1H), 4.28 (d, *J* = 15.5 Hz, 1H), 4.28 (d, *J* = 15.0 Hz, 1H), 4.15 (d, *J* = 14.9 Hz, 1H), 4.05 (s, 1H), 3.65 (s, 3H), 3.64 (d, *J* = 15.2 Hz, 1H), 1.66 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.2, 171.1, 170.3, 170.1, 149.5, 140.9, 135.6, 135.3, 131.5, 131.1, 128.6, 127.4, 126.2, 125.7, 124.8, 123.1, 118.9, 117.9, 115.4, 114.7, 84.0, 71.2, 52.3, 51.8, 28.2, 27.6; IR (thin film): ν 2979, 2244, 1736, 1712, 1640, 1371 cm^{-1}; ESI-HRMS calcd for $C_{31}H_{30}N_2O_6Na$ *m/z* $[M+23]^+$ 549.2002; found 549.2015.



3-(2-Benzoyl-3-methoxycarbonyl-6-oxo-2,3,4,4a,5,6-hexahydro-1H-[2]pyrindin-3-ylmethyl)indole-1-carboxylic acid *tert*-butyl ester. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.1 Hz, 1H), 7.63-7.11 (m, 9H), 5.95 (d, *J* = 1.3 Hz, 1H), 5.68 (d, *J* = 1.4 Hz, 1H), 4.40 (d, *J* = 18.3 Hz, 1H), 4.36 (d, *J* = 14.7 Hz, 1H), 3.84 (s, 3H), 3.45 (d, *J* = 14.8 Hz, 1H), 3.34 (d, *J* = 18.5

Hz, 1H), 3.05 (d, J = 20.2 Hz, 1H), 2.93 (d, J = 20.8 Hz, 1H), 1.63 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.5, 177.8, 171.9, 171.2, 161.0, 149.3, 135.6, 135.4, 135.2, 130.8, 130.0, 128.7, 127.5, 126.5, 124.9, 124.7, 123.9, 122.7, 119.6, 115.3, 114.9, 83.9, 65.9, 53.1, 45.5, 37.8, 29.4, 28.2; IR (thin film): ν 2979, 1736, 1717, 1644, 1371 cm^{-1}; ESI-HRMS calcd for $C_{31}H_{30}N_2O_6Na$ *m/z* $[M+23]^+$ 549.2002; found 549.2018.

General procedure P for the Stetter reaction with butyraldehyde.



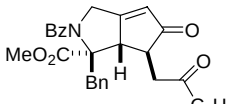
293a

2-Benzoyl-1-benzyl-4-methyl-5-oxo-6-(2-oxopentyl)-1,2,3,5,6,6a-hexahydrocyclopenta[c]pyrrole-1-carboxylic acid methyl ester (293a). To a solution of cyclopentenone **287a** (163 mg, 0.403 mmol) in 1,4-dioxane (2 mL), were added Et_3N (42 μL, 0.30 mmol), butyraldehyde (184 μL, 2.03 mmol) and 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride **292** (22 mg, 0.080 mmol). The reaction vessel was sealed with a rubber septum and heated to 70 °C for 6 h. The reaction mixture was then poured into water, and the aqueous layer extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. Hexanes (5 mL) was added and a white precipitate formed. The precipitate was collected by decantation, and purified by flash chromatography (gradient elution; hexanes-EtOAc, 4 : 1 to 2 : 1, v/v) to afford **293a** (121 mg, 63%). The decanted liquid was concentrated under vacuum and the crude residue was purified by flash chromatorgraphy (gradient elution; hexanes-EtOAc, 4 : 1 to 2 : 1, v/v) to afford **293b** (19 mg, 10%).

293a: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55-7.44 (m, 5H), 7.33-7.27 (m, 3H), 7.17-7.14 (m, 2H),

4.17 (d, *J* = 15.0 Hz, 1H), 4.10 (d, *J* = 14.2 Hz, 1H), 3.99 (d, *J* = 15.1 Hz, 1H), 3.75 (s, 3H), 3.44-3.39 (m, 1H), 3.28 (d, *J* = 14.2 Hz, 1H), 3.03 (dd, *J* = 18.4, 5.1 Hz, 1H), 2.86 (dd, *J* = 18.4, 3.9 Hz, 1H), 2.50 (t, *J* = 7.2 Hz, 2H), 2.13 (dd, *J* = 8.5, 4.1 Hz, 1H), 1.66 (sex, *J* = 7.4 Hz, 2H), 1.62 (s, 3H), 0.99 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.4, 207.8, 171.6, 171.3, 166.0, 136.1, 136.0, 131.8, 131.2, 131.0, 128.6, 128.4, 128.3, 127.4, 127.2, 71.7, 52.4, 51.7, 50.8, 45.4, 44.5, 40.9, 37.7, 17.1, 13.7, 8.8; IR (thin film): ν 2953, 1740, 1719, 1687, 1638, 1390 cm^{-1}; MS *m/z* (%) 473 (7), 441 (8), 414 (17), 382 (20), 350 (18), 105 (100); EI HRMS calcd for $C_{29}H_{31}NO_5$ *m/z* $[M]^+$ 473.2202, found 473.2181.

293b: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55-7.29 (m, 10H), 4.21 (d, *J* = 14.8 Hz, 1H), 4.03-3.94 (m, 2H), 3.71 (s, 3H), 3.68 (bs, 1H), 3.34-3.27 (m, 1H), 3.11 (d, *J* = 14.1 Hz, 1H), 2.91 (dd, *J* = 19.2, 3.5 Hz, 1H), 2.52 (t, *J* = 7.4 Hz, 2H), 2.43 (dd, *J* = 19.2, 11.3 Hz, 1H), 1.73 (sex, *J* = 7.4 Hz, 2H), 1.62 (s, 3H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 209.0, 208.9, 172.6, 171.6, 168.2, 136.5, 135.8, 131.6, 131.4, 131.2, 128.7, 128.2, 127.6, 127.0, 69.7, 52.4, 50.7, 49.0, 44.1, 42.0, 39.4, 36.3, 17.2, 13.8, 8.5.



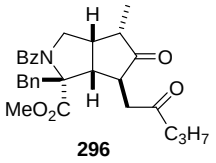
294a

2-Benzoyl-1-benzyl-5-oxo-6-(2-oxo-pentyl)-1,2,3,5,6,6a-hexahydrocyclopenta[c]pyrrole-1-carboxylic acid methyl ester (294a). Prepared by using general procedure P, using: **287b** (100 mg, 0.258 mmol), Et_3N (107 μL, 0.774 mmol), butyraldehyde (117 μL, 1.29 mmol) and 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride **292** (14 mg, 0.052 mmol). Flash chromatography (gradient elution; hexanes-EtOAc, 9 : 1 to 2 : 1, v/v) afforded **294a** (major diastereomer) (78 mg, 66%). The minor diastereomer remains in the decanted liquid.

294a (major diastereomer, eluting second, TLC, hexanes-EtOAc) ^{1}H NMR (300 MHz, $CDCl_3$): δ

7.50-7.45 (m, 5H), 7.31-7.27 (m, 3H), 7.16-7.14 (m, 2H), 5.91 (s, 1H), 4.24 (d, *J* = 15.5 Hz, 1H), 4.08 (d, *J* = 14.1 Hz, 1H), 4.06 (d, *J* = 15.5 Hz, 1H), 3.76 (s, 3H), 3.55 (s, 1H), 3.28 (d, *J* = 14.2 Hz, 1H), 3.04 (dd, *J* = 18.5, 5.0 Hz, 1H), 2.84 (dd, *J* = 18.5, 3.6 Hz, 1H), 2.49 (t, *J* = 7.2 Hz, 2H), 2.15 (q, *J* = 4.2 Hz, 1H), 1.66 (sex, *J* = 7.3 Hz, 2H), 0.98 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.4, 207.6, 173.7, 171.5, 171.3, 135.9, 135.7, 131.0, 130.5, 128.6, 128.4, 127.2, 124.1, 123.7, 123.3, 71.6, 53.2, 52.5, 51.7, 45.9, 44.4, 40.6, 37.6, 17.0, 13.7; IR (thin film): ν 2960, 1713, 1645, 1383 cm^{-1}; MS *m/z* (%) 459 (7), 388 (58), 358 (54), 298 (78), 105 (100); EI-HRMS calcd for $C_{28}H_{29}NO_5$ *m/z* $[M]^+$ 459.2046, found 459.2061.

General procedure Q for reduction of enones.

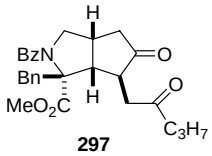


296

2-Benzoyl-1-benzyl-4-methyl-5-oxo-6-(2-oxopentyl)octahydrocyclopenta[c]pyrrole-1-carboxylic acid methyl ester (296). To a solution of the enone **293a** (121 mg, 0.256 mmol) in MeOH (15 mL) was added Pd/C (100 mg of 10 % by wt.) at rt. The reaction vessel was connected to a hydrogenation apparatus and purged with H_2 three times. The reaction mixture was stirred at rt under H_2 pressure (2.5 atm) for 4 h. The mixture was then filtered using a fritted funnel through a plug of celite and washed with CH_2Cl_2. The filtrate was concentrated under vacuum to afford **296** (115 mg, 95%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47-7.42 (m, 5H), 7.34-7.24 (m, 5H), 4.22 (d, *J* = 13.8 Hz, 1H), 3.84 (s, 3H), 3.27 (d, *J* = 13.8 Hz, 1H), 3.20-3.00 (m, 3H), 2.85 (dd, *J* = 10.2, 6.9 Hz, 1H), 2.63-2.46 (m, 3H), 2.39 (t, *J* = 7.3 Hz, 2H), 1.79-1.68 (m, 1H), 1.61 (sex, *J* = 7.4 Hz, 2H), 0.94 (t, *J* = 7.3 Hz, 3H), 0.75 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 218.2, 208.6, 171.9, 169.9,

137.1, 136.9, 130.4, 129.8, 128.5, 127.1, 126.1, 72.8, 52.6, 51.5, 50.3, 44.4, 44.2, 44.0, 41.6, 41.4, 39.8, 17.2, 13.6, 10.2; IR (thin film): ν 2962, 1737, 1712, 1639, 1404, 1250 cm^{-1}; MS *m/z* (%) 416 (16), 384 (43), 352 (21), 324 (23), 105 (100); EI-HRMS calcd for $C_{27}H_{30}NO_3$ *m/z* $[M-59]^+$ 416.2226, found 416.2239.

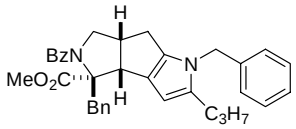


297

2-Benzoyl-1-benzyl-5-oxo-6-(2-oxopentyl)octahydrocyclopenta[c]pyrrole-1-carboxylic acid methyl ester (297). Prepared by following the general procedure Q, using: **294a** (140 mg, 0.305 mmol), MeOH (10 mL), Pd/C (50 mg of 10% by wt.), H_2 (1 atm). The reaction mixture was stirred for 4 h at rt. Yield of **297** (140 mg, >95%). Note: The reaction was performed under 1 atm of H_2 using a balloon.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49-7.24 (m, 10H), 4.18 (d, *J* = 13.7 Hz, 1H), 3.83 (s, 3H), 3.37-3.12 (m, 3H), 2.96-2.88 (m, 2H), 2.66-2.57 (m, 2H), 2.43 (t, *J* = 7.3 Hz, 2H), 2.33 (dd, *J* = 19.0, 8.3 Hz, 1H), 1.99 (d, *J* = 19.0 Hz, 1H), 1.89-1.77 (m, 1H), 1.64 (sex, *J* = 7.3 Hz, 2H), 0.96 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR : δ 216.6, 208.4, 171.8, 169.6, 137.0, 136.7, 130.5, 129.9, 128.5, 127.1, 126.2, 72.9, 56.5, 52.6, 52.2, 45.1, 44.5, 41.6, 39.6, 36.1, 17.2, 13.6; IR (thin film): ν 2959, 1740, 1712, 1636, 1405, 1250 cm^{-1}; EI-HRMS calcd for $C_{26}H_{28}NO_3$ *m/z* $[M-59]^+$ 402.2069, found 402.2069.

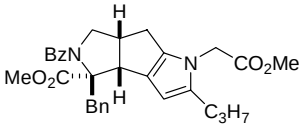
General procedure R for preparation of alkyl pyrroles.



298a

5-Benzoyl-1,4-dibenzyl-2-propyl-3b,4,5,6,6a,7-hexahydro-1H-1,5-diazacyclopenta[a]-pentalene-4-carboxylic acid methyl ester (298a). To a solution of **297** (10 mg, 0.021 mmol) in MeOH (0.5 mL), was added benzylamine (23 μL, 0.21 mmol), AcOH (12 μL, 0.21 mmol) and molecular sieves (4 Å) (30 mg). The reaction mixture was stirred at 70 °C for 4 h. Upon completion, the reaction mixture was diluted with EtOAc and washed with 1M HCl. The organic layer was then dried over $MgSO_4$, and the solvents removed under vacuum. The crude residue was purified by flash chromatography (gradient elution; hexanes-EtOAc, 19 : 1 to 3 : 1, v/v), to afford **298a** (10 mg, 90%).

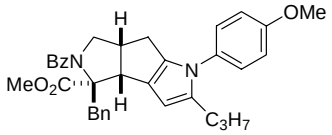
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-7.22 (m, 13H), 6.87 (d, *J* = 7.0 Hz, 2H), 5.70 (s, 1H), 4.85 (s, 2H), 4.24 (d, *J* = 13.6 Hz, 1H), 3.91 (d, *J* = 7.2 Hz, 1H), 3.71 (s, 3H), 3.37 (d, *J* = 13.6 Hz, 1H), 3.36-3.30 (m, 1H), 3.20-3.14 (m, 1H), 2.39 (t, *J* = 7.6 Hz, 2H), 2.39-2.31 (m, 1H), 2.22 (quin, *J* = 7.6 Hz, 1H), 2.01 (d, *J* = 14.5 Hz, 1H), 1.55 (sex, *J* = 7.6 Hz, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4, 169.9, 138.5, 138.0, 137.6, 137.5, 134.9, 131.2, 129.6, 128.7, 128.4, 128.2, 127.3, 126.7, 126.4, 126.1, 122.4, 73.1, 56.8, 52.9, 52.1, 48.3, 45.5, 39.4, 29.1, 28.8, 22.4, 14.1; IR (thin film): ν 2950, 1734, 1642, 1402 cm^{-1}; MS *m/z* (%) 532 (24), 441 (16), 250 (20), 105 (100); EI-HRMS calcd for $C_{35}H_{36}N_2O_3$ *m/z* $[M]^+$ 532.2726; found 532.2724.



298b

5-Benzoyl-4-benzyl-1-methoxycarbonylmethyl-2-propyl-3b,4,5,6,6a,7-hexahydro-1H-1,5-diazacyclopenta[a]pentalene-4-carboxylic acid methyl ester (298b). Prepared by following the general procedure R, using: **297** (17 mg, 0.037 mmol), MeOH (1 mL), glycine methyl ester hydrochloride (23 mg, 0.18 mmol), AcOH (10 μL, 0.18 mmol), molecular sieves (4 Å) (50 mg). The reaction mixture was stirred at 70 °C for 4 h. Upon completion, the reaction mixture was concentrated under vacuum. The crude residue was purified by flash chromatography (hexanes-EtOAc, 4 : 1, v/v) to afford **298b** (14 mg, 70%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46-7.27 (m, 10H), 5.66 (s, 1H), 4.40 (d, *J* = 17.7 Hz, 1H), 3.82 (d, *J* = 17.8 Hz, 1H), 4.23 (d, *J* = 13.5 Hz, 1H), 3.90 (d, *J* = 7.3 Hz, 1H), 3.72 (s, 3H), 3.69 (s, 3H), 3.41 (d, *J* = 13.6 Hz, 1H), 3.37 (dd, *J* = 10.3, 8.5 Hz, 1H), 3.24-3.18 (m, 1H), 2.46 (dd, *J* = 14.3, 7.0 Hz, 1H), 2.39 (t, *J* = 7.7 Hz, 2H), 2.27-2.17 (m, 1H), 2.09 (d, *J* = 14.6 Hz, 1H), 1.59 (sex, *J* = 7.6 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 1H); IR (thin film): ν 2952, 1736, 1638, 1403, 1205 cm^{-1}; MS *m/z* (%) 514 (21), 455 (7), 423 (33), 105 (100); EI-HRMS calcd for $C_{31}H_{34}N_2O_5$, *m/z* $[M]^+$ 514.2468; found 514.2471.

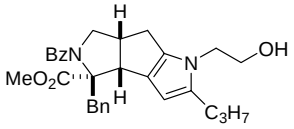


298c

5-Benzoyl-4-benzyl-1-(4-methoxyphenyl)-2-propyl-3b,4,5,6,6a,7-hexahydro-1H-1,5-diazacyclopenta[a]pentalene-4-carboxylic acid methyl ester (298c). Prepared by following the general procedure R, using: **297** (20 mg, 0.043 mmol) in methanol (0.5 mL), *p*-anisidine (27 mg, 0.22 mmol), AcOH (12 μL, 0.22 mmol), molecular sieves (4 Å) (50 mg). The reaction

mixture was stirred at 60 °C for 2 h. The crude residue was purified by flash chromatography (gradient elution; hexanes-EtOAc, 9 : 1 to 3 : 1, v/v) to afford **298c** (20 mg, 85%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47-7.27 (m, 10H), 7.08 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 4.26 (d, *J* = 13.5 Hz, 1H), 3.92 (d, *J* = 7.2 Hz, 1H), 3.82 (s, 3H), 3.75 (s, 3H), 3.44 (d, *J* = 13.5 Hz, 1H), 3.37-3.21 (m, 2H), 2.43-2.39 (m, 1H), 2.39 (t, *J* = 7.5 Hz, 2H), 2.22 (quin, *J* = 7.5 Hz, 1H), 2.06 (d, *J* = 14.9 Hz, 1H), 1.48 (sex, *J* = 7.5 Hz, 2H), 0.87 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 169.7, 158.5, 138.3, 138.0, 137.4, 135.2, 131.9, 131.1, 129.4, 128.3, 128.1, 127.4, 126.7, 126.3, 122.7, 114.2, 73.0, 56.7, 55.4, 52.9, 52.0, 45.2, 39.4, 29.4, 29.1, 22.5, 13.9; IR (thin film): ν 2954, 1734, 1641, 1515, 1403, 1249 cm^{-1}; MS *m/z* (%) 548 (52), 457 (36), 425 (24), 266 (52), 105 (100); EI-HRMS calcd for $C_{35}H_{36}N_2O_4$ *m/z* $[M]^+$ 548.2675, found 548.2677.



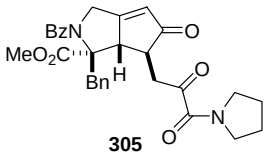
298d

5-Benzoyl-4-benzyl-1-(2-hydroxyethyl)-2-propyl-3b,4,5,6,6a,7-hexahydro-1H-1,5-diazacyclopenta[a]pentalene-4-carboxylic acid methyl ester (298d). Prepared by following the general procedure R, using: **297** (20 mg, 0.043 mmol), ethanolamine (26 μL, 0.43 mmol), AcOH (20 μL, 0.36 mmol), molecular sieves (4 Å) (50 mg). The reaction mixture was stirred at 70 °C for 1 h. The crude residue was purified by flash chromatography (gradient elution; hexanes-EtOAc, 3 : 1 to 2 : 1, v/v) to afford **298d** (16 mg, 76%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.27 (m, 10 H), 5.65 (s, 1H), 4.20 (d, *J* = 13.6 Hz, 1H), 3.89 (d, *J* = 7.2 Hz, 1H), 3.79-3.73 (m, 4H), 3.67 (s, 3H), 3.37 (d, *J* = 13.5 Hz, 1H), 3.26-3.23 (m, 2H), 2.55 (dd, *J* = 14.4, 7.1 Hz, 1H), 2.47 (t, *J* = 7.8 Hz, 2H), 2.37 (quind, *J* = 7.2, 2.0 Hz, 1H), 2.29 (d, *J* = 14.3 Hz, 1H), 2.06-1.94 (bs, 1H), 1.70-1.58 (m, 2H), 1.01 (t, *J* = 7.4 Hz, 3H); ^{13}C

NMR (75 MHz, $CDCl_3$): δ 172.3, 169.7, 137.7, 137.3, 137.2, 135.4, 131.1, 129.5, 128.3, 128.1, 126.7, 126.4, 122.0, 101.2, 73.1, 62.3, 56.4, 52.6, 52.0, 47.1, 45.7, 39.1, 29.4, 29.0, 22.3, 14.1; IR (thin film): ν 3418, 2928, 1732, 1622, 1405, 1259 cm^{-1}; MS *m/z* (%) 486 (26), 395 (30), 105 (76), 57 (100). EI-HRMS calcd for $C_{30}H_{34}N_2O_4$ *m/z* $[M]^+$ 486.2519; found 486.2510.

General procedure S for the Stetter reaction with glyoxylamides.



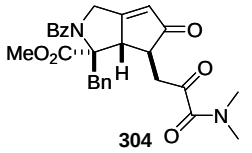
305

2-Benzoyl-1-benzyl-6-(2,3-dioxo-3-pyrrolidin-1-ylpropyl)-5-oxo-1,2,3,5,6,6a-hexahydrocyclopenta[c]pyrrole-1-carboxylic acid methyl ester (305). To a solution of **287b** (840 mg, 2.17 mmol) in 1,4-dioxane (20 mL) was added oxo-pyrrolidin-1-yl-acetaldehyde **303**[mm] (1.38 g, 11.8 mmol), **292** (175 mg, 0.651 mmol) and Et_3N (905 μL, 6.51 mmol). The reaction mixture was heated to 70 °C for 10 min and then poured in water (200 mL). The aqueous layer was extracted with Et_2O (3 x 100 mL) and the extracts were combined, washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified by flash chromatography (gradient elution; hexanes-EtOAc, 3 : 1 to 0 : 1, v/v) to give **305** (1.17 g, >95%).

^1H NMR (300 MHz, $CDCl_3$): δ 7.54-7.42 (m, 5H), 7.36-7.29 (m, 3H), 7.23-7.20 (m, 2H), 5.91 (s, 1H), 4.27 (d, *J* = 15.7 Hz, 1H), 4.17 (d, *J* = 14.3 Hz, 1H), 4.07 (d, *J* = 15.7 Hz, 1H), 3.82 (s, 3H), 3.66 (t, *J* = 6.4 Hz, 2H), 3.58 (t, *J* = 6.4 Hz, 2H), 3.52-3.44 (m, 2H), 3.33 (dd, *J* = 18.7, 5.3 Hz, 1H), 3.23 (d, *J* = 14.3 Hz, 1H), 2.47 (q, *J* = 4.7 Hz, 1H), 1.99-1.90 (m, 4H); ^{13}C NMR (75 MHz,

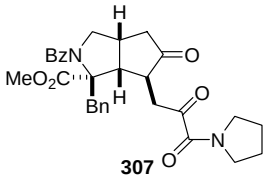
[mm] Aldehydes **302** and **303** was prepared according to previously reported procedures.[208, 209]

$CDCl_3$): δ 207.4, 198.2, 174.1, 171.2, 161.9, 135.6, 131.2, 131.0, 128.6, 128.4, 127.2, 123.4, 71.5, 53.2, 52.6, 51.7, 47.3, 46.4, 46.0, 37.6, 37.1, 26.3, 23.6; IR (thin film): ν 2952, 1716, 1638, 11447, 1384 cm^{-1}; MS *m/z* (%) 514 (13), 455 (6), 416 (17), 105 (100); EI-HRMS calcd for $C_{30}H_{30}N_2O_6$ *m/z* $[M]^+$ 514.2104; found 514.2115.



304

2-Benzoyl-1-benzyl-6-(2-dimethylcarbamoyl-2-oxoethyl)-5-oxo-1,2,3,5,6,6a-hexahydro-cyclopenta[c]pyrrole-1-carboxylic acid methyl ester (304). Prepared by following the general procedure S, with: **287b** (94 mg, 0.24 mmol), *N*,*N*-dimethyl-2-oxo-acetamide (125 mg, 1.21 mol), Et_3N (100 μL, 0.729 mmol), **292** (19 mg, 0.073 mmol). Yield of **304** (76 mg, 70%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.52-7.40 (m, 5H), 7.35-7.22 (m, 5H), 5.90 (s, 1H), 4.25 (d, *J* = 15.7 Hz, 1H), 4.16 (d, *J* = 14.2 Hz, 1H), 4.04 (d, *J* = 15.7 Hz, 1H), 3.80 (s, 3H), 3.51-3.49 (m, 1H), 3.40 (dd, *J* = 18.9, 5.1 Hz, 1H), 3.27 (dd, *J* = 18.9, 5.1 Hz, 1H), 3.23 (d, *J* = 14.4 Hz, 1H), 3.05 (s, 3H), 3.02 (s, 3H), 2.43 (q, *J* = 4.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.3, 198.3, 174.2, 171.3, 165.8, 135.8, 135.6, 131.3, 131.0, 128.6, 128.4, 127.2, 123.3, 71.6, 53.1, 52.5, 51.7, 45.9, 38.0, 37.2, 37.0, 34.7; IR (thin film): ν 2951, 1716, 1647, 1386 cm^{-1}; MS *m/z* (%) 488 (45), 416 (73), 365 (43), 281 (51), 105 (100); EI-HRMS calcd for $C_{28}H_{28}N_2O_6$ *m/z* $[M]^+$ 488.1947; found 488.1943.

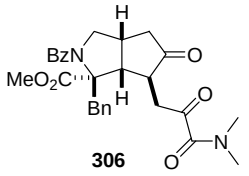


307

2-Benzoyl-1-benzyl-6-(2,3-dioxo-3-pyrrolidin-1-ylpropyl)-5-oxooctahydrocyclopenta[c]pyrrole-1-carboxylic acid methyl ester (307). Prepared by

following the general procedure Q, using: **305** (1.17g, 2.27 mmol), Pd/C (200 mg of 10 % by wt.), H_2 (1 atm). Note: the reaction was performed under 1 atm of H_2 using a balloon.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50-7.24 (m, 10H), 4.18 (d, *J* = 13.8 Hz, 1H), 3.86 (s, 3H), 3.65 (t, *J* = 6.7, 2H), 3.53 (t, *J* = 6.7 Hz, 2H), 3.30-3.17 (m, 3H), 3.11-3.08 (m, 2H), 2.89-2.87 (m, 2H), 2.22 (dd, *J* = 19.3, 8.5 Hz, 1H), 2.08-1.80 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.6, 198.1, 171.5, 169.6, 161.9, 136.9, 136.7, 130.6, 129.9, 128.5, 127.1, 126.3, 72.8, 55.4, 52.7, 52.1, 47.3, 46.5, 45.6, 39.3, 38.7, 36.1, 26.3, 23.6; IR (thin film): ν 2950, 1737, 1636, 1404 cm^{-1}; MS *m/z* (%) 516 (8), 485 (7), 457 (36), 425 (51), 105 (100); EI-HRMS calcd for $C_{30}H_{32}N_2O_6$ *m/z* $[M]^+$ 516.2260; found 516.2255.

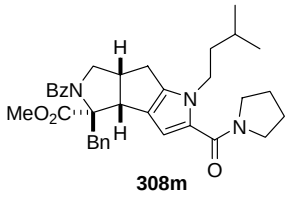


306

2-Benzoyl-1-benzyl-6-(2-dimethylcarbamoyl-2-oxoethyl)-5-oxooctahydrocyclopenta[c]pyrrole-1-carboxylic acid methyl ester (306). Prepared by following general procedure Q using: **304** (85 mg, 0.17 mmol), Pd/C (15 mg of 10% by weight), H_2 (1 atm). Yield of **306** (69 mg, 81%). Note: the reaction was performed under 1 atm of H_2 using a balloon.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50-7.42 (m, 5H), 7.36-7.25 (m, 5H), 4.18 (d, *J* = 13.8 Hz, 1H), 3.86 (s, 3H), 3.34-2.77 (m, 7H), 3.05 (s, 3H), 3.01 (s, 3H), 2.23 (dd, *J* = 19.3, 8.4 Hz, 1H), 2.05 (dd, *J* = 19.3, 2.9 Hz, 1H), 1.92-1.79 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 216.5, 198.4, 171.5, 169.5, 165.6, 136.9, 136.7, 130.6, 129.9, 128.5, 127.0, 126.2, 72.7, 55.4, 52.6, 51.9, 45.3, 39.2, 39.0, 37.0, 36.1, 34.8; IR (thin film): ν 2950, 1740, 1644, 1405, 1250 cm^{-1}; MS *m/z* (%) 490 (10), 459 (18), 431 (68), 399 (43), 105 (100); EI-HRMS calcd for $C_{28}H_{30}N_2O_6$ *m/z* $[M]^+$ 490.2104; found 490.2099.

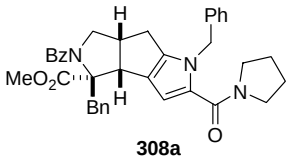
General procedure T for preparation of pyrroles 308a-p.



308m

5-Benzoyl-4-benzyl-1-(3-methylbutyl)-2-(pyrrolidine-1-carbonyl)-3b,4,5,6,6a,7-hexahydro1H-1,5-diazacyclopenta[a]pentalene-4-carboxylic acid methyl ester (308m). To a solution of **307** (35 mg, 0.068 mmol) in EtOH (0.9 mL) was added 3-methyl butylamine (21 μL, 0.020 mmol) followed by glacial acetic acid (90 μL) at rt. The test tube was then heated to 50 °C in an oil bath for 2 h when the reaction was complete based upon TLC. The light yellow solution was then diluted with EtOAc and poured into 1M HCl. The aqueous layer was extracted with EtOAc and the extracts combined and washed again with 1M HCl. The organic layer was then separated, dried over $MgSO_4$ and concentrated under vacuum. The crude residue was purified by flash chromatography (gradient elution, hexanes-EtOAc, v/v) to afford **308m** (36 mg, 95%).

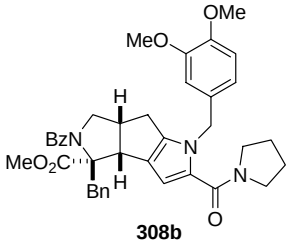
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48-7.27 (m, 10H), 4.23 (d, *J* = 13.5 Hz, 1H), 4.17-4.10 (m, 1H), 3.98-3.85 (m, 2H), 3.74-3.55 (m, 7H), 3.40 (d, *J* = 13.7 Hz, 1H), 3.37-3.30 (m, 1H), 3.21-3.15 (m, 1H), 2.53 (dd, *J* = 15.1, 6.9 Hz, 1H), 2.36-2.25 (m, 1H), 2.21 (d, *J* = 16.1 Hz, 1H), 2.01-1.85 (m, 4H), 1.50-1.45 (m, 3H), 0.85 (d, *J* = 5.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 169.7, 162.0, 140.3, 137.6, 137.1, 130.9, 130.6, 129.5, 129.2, 128.5, 128.3, 128.1, 126.7, 126.2, 122.1, 72.9, 56.3, 52.0, 45.4, 45.2, 40.3, 39.2, 28.5, 25.7, 22.5, 22.4; IR (thin film): ν 2951, 1735, 1639, 1611, 1446, 1399 cm^{-1}; MS *m/z* (%) 567 (32), 476 (41), 405 (24), 301 (61), 91 (100); EI-HRMS calcd for $C_{35}H_{41}N_3O_4$ *m/z* $[M]^+$ 567.3097; found 567.3114.



308a

5-Benzoyl-1,4-dibenzyl-2-(pyrrolidine-1-carbonyl)-3b,4,5,6,6a,7-hexahydro-1H-1,5-diaza-cyclopenta[a]pentalene-4-carboxylic acid methyl ester (308a). Prepared by following general procedure T with: **307** (20 mg, 0.039 mmol), benzylamine (13 μL, 0.12 mmol), AcOH (50 μL). Yield **308a** (18 mg, 80%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.19 (m, 13H), 6.98 (d, *J* = 6.8 Hz, 1H), 6.23 (s, 1H), 5.44 (d, *J* = 15.4 Hz, 1H), 5.14 (d, *J* = 15.4 Hz, 1H), 4.23 (d, *J* = 13.6 Hz, 1H), 3.88 (d, *J* = 7.2 Hz, 1H), 3.62 (s, 3H), 3.59-3.49 (m, 4H), 3.42-3.29 (m, 2H), 3.19-3.13 (m, 1H), 2.40 (dd, *J* = 15.0, 6.9 Hz, 1H), 2.34-2.25 (m, 1H), 2.12 (d, *J* = 15.2 Hz, 1H), 1.92-1.78 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 169.8, 162.1, 140.8, 138.7, 137.7, 137.2, 131.0, 130.1, 129.6, 128.5, 128.4, 128.2, 127.2, 126.9, 126.8, 126.3, 122.8, 108.6, 73.9, 56.4, 52.2, 52.0, 50.0, 45.6, 39.4, 28.8; IR (thin film): ν 2949, 1735, 1639, 1447, 1400 cm^{-1}; MS *m/z* (%) 587 (66), 496 (83), 425 (75), 321 (86), 105 (100); EI-HRMS calcd for $C_{37}H_{37}N_3O_4$ *m/z* $[M]^+$ 587.2784; found 587.2777.

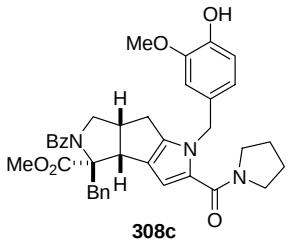


308b

5-Benzoyl-4-benzyl-1-(3,4-dimethoxybenzyl)-2-(pyrrolidine-1-carbonyl)-3b,4,5,6,6a,7-hexahydro-1H-1,5-diaza-cyclopenta[a]pentalene-4-carboxylic acid methyl ester (308b). Prepared by following general procedure T with: **307** (26 mg, 0.05 mmol), 3,4-dimethoxybenzylamine (22 μL, 0.15 mmol), AcOH (65 μL). Yield **308b** (29 mg, 88%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.27 (m, 10H), 6.72 (d, *J* = 8.2 Hz, 1H), 6.62 (d, *J* = 1.9 Hz,

1H), 6.52 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.22 (s, 1H), 5.34 (d, *J* = 15.1 Hz, 1H), 5.11 (d, *J* = 15.1 Hz, 1H), 4.23 (d, *J* = 13.6 Hz, 1H), 3.87 (d, *J* = 7.3 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 3.62 (s, 3H), 3.59-3.55 (m, 4H), 3.39 (d, *J* = 13.7 Hz, 1H), 3.36-3.30 (m, 1H), 3.18-3.12 (m, 1H), 2.42 (dd, *J* = 15.1, 6.9 Hz, 1H), 2.33-2.23 (m, 1H), 2.13 (d, *J* = 15.6 Hz, 1H), 1.82-1.92 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 169.9, 162.2, 149.0, 148.2, 141.0, 137.7, 137.2, 131.3, 131.1, 129.8, 129.7, 128.5, 128.3, 126.9, 126.4, 122.9, 119.3, 110.9, 110.5, 108.8, 73.1, 56.5, 56.0, 55.9, 52.2, 49.8, 48.0, 45.7, 39.4, 28.8, 25.5; IR (thin film): ν 2949, 1734, 1638, 1605, 1445, 1400 cm^{-1}; MS *m/z* (%) 647 (51), 556 (42), 381 (27), 151 (100), 105 (65); EI-HRMS calcd for $C_{39}H_{41}N_3O_6$ *m/z* $[M]^+$ 647.2995; found 647.2991.

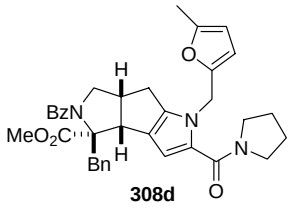


308c

5-Benzoyl-4-benzyl-1-(4-hydroxy-3-methoxybenzyl)-2-(pyrrolidine-1-carbonyl)-3b,4,5,6,6a,7-hexahydro-1H-1,5-diazacyclopenta[a]pentalene-4-carboxylic acid methyl ester (308c). Prepared by following general procedure T with: **307** (35 mg, 0.068 mmol), 4-aminomethyl-2-methoxyphenol hydrochloride (39 mg, 0.20 mmol), AcOH (80 μL). Yield **308c** (31 mg, 72%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.27 (m, 10H), 6.75 (d, *J* = 8.1 Hz, 1H), 6.64 (s, 1H), 6.44 (d, *J* = 8.1 Hz, 1H), 6.21 (s, 1H), 5.72 (bs, 1H), 5.31 (d, *J* = 15.0 Hz, 1H), 5.07 (d, *J* = 15.0 Hz, 1H), 4.22 (d, *J* = 13.6 Hz, 1H), 3.86 (d, *J* = 7.2 Hz, 1H), 3.79 (s, 3H), 3.61 (s, 3H), 3.61-3.50 (m, 4H), 3.44-3.29 (m, 2H), 3.18-3.11 (m, 1H), 2.42 (dd, *J* = 15.2, 7.0 Hz, 1H), 2.33-2.22 (m, 1H), 2.13 (d, *J* = 15.4 Hz, 1H), 1.93-1.80 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 169.8, 162.1, 146.5, 144.8, 140.8, 137.5, 137.0, 130.9, 130.5, 129.7, 129.6, 128.4, 128.2, 126.8, 126.2, 122.7,

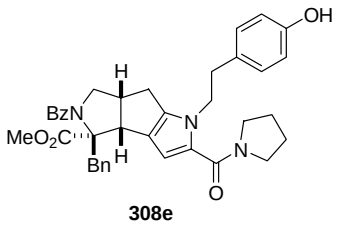
119.9, 114.1, 109.9, 108.6, 73.0, 56.4, 55.8, 52.0, 49.7, 45.5, 39.2, 28.7; IR (thin film): ν 3253, 2949, 1734, 1602, 1447, 1401 cm^{-1}; ESI-HRMS calcd for $C_{38}H_{40}N_3O_6$ *m/z* $[M+1]^+$ 634.2917; found 634.2938.



308d

5-Benzoyl-4-benzyl-1-(5-methylfuran-2-ylmethyl)-2-(pyrrolidine-1-carbonyl)-3b,4,5,6,6a,7-hexahydro-1H-1,5-diazacyclopenta[a]pentalene-4-carboxylic acid methyl ester (308d). Prepared by following general procedure T with: **307** (35 mg, 0.068 mmol), C-(5-Methylfuran-2-yl)-methylamine (23 μL, 0.20 mmol), AcOH (90 μL). Yield **308d** (34 mg, 85%).

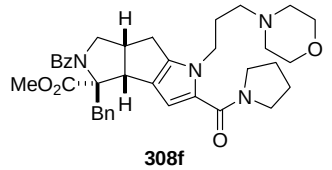
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.27 (m, 10H), 6.18 (s, 1H), 6.01 (d, *J* = 3.0 Hz, 1H), 5.81 (d, *J* = 2.2 Hz, 1H), 5.35 (d, *J* = 15.5 Hz, 1H), 5.06 (d, *J* = 15.5 Hz, 1H), 4.22 (d, *J* = 13.6 Hz, 1H), 3.85 (d, *J* = 7.3 Hz, 1H), 3.65-3.55 (m, 4H), 3.57 (s, 3H), 3.39 (d, *J* = 13.6 Hz, 1H), 3.35-3.29 (m, 1H), 3.21-3.16 (m 1H), 2.53 (dd, *J* = 15.1, 7.3 Hz, 1H), 2.33-2.20 (m, 2H), 2.17 (s, 3H), 1.97-1.86 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 169.7, 162.1, 151.6, 149.5, 140.7, 137.6, 137.0, 130.9, 129.5, 129.4, 128.3, 128.1, 126.7, 126.2, 122.5, 108.6, 106.2, 72.9, 56.3, 52.1, 52.0, 48.7, 45.4, 42.9, 39.2, 28.6, 13.5; IR (thin film): ν 2949, 1734, 1638, 1605, 1445, 1400 cm^{-1}; MS *m/z* (%) 591 (30), 500 (16), 406 (10), 105 (88), 95 (100); EI-HRMS calcd for $C_{36}H_{37}N_3O_5$ *m/z* $[M]^+$ 591.2733; found 591.2735.



308e

5-Benzoyl-4-benzyl-1-[2-(4-hydroxyphenyl)ethyl]-2-(pyrrolidine-1-carbonyl)-3b,4,5,6,6a,7-hexahydro-1H-1,5-diaza-cyclopenta[a]pentalene-4-carboxylic acid methyl ester (308e). Prepared by following general procedure T with: **307** (29 mg, 0.056 mmol), 4-(2-aminoethyl)-phenol (23 μL, 0.17 mmol), AcOH (70 μL). Yield **308e** (22 mg, 63%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.41 (m, 5H), 7.34-7.27 (m, 5H), 6.75 (d, *J* = 8.3 Hz, 1H), 6.62 (d, *J* = 8.3 Hz, 1H), 6.19 (s, 1H), 4.35-4.15 (m 2H), 4.22 (d, *J* = 13.6 Hz, 1H), 3.82 (d, *J* = 7.2 Hz, 1H), 3.66 (s, 3H), 3.63-3.53 (m, 4H), 3.39 (d, *J* = 13.6 Hz, 1H), 3.28 (dd, *J* = 10.2, 8.2 Hz, 1H), 3.03-2.97 (m, 1H), 2.89-2.76 (m, 2H), 2.29-2.16 (m, 2H), 1.98-1.86 (m, 4H), 1.82 (d, *J* = 14.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 169.8, 162.0, 154.8, 141.1, 137.6, 137.0, 130.9, 130.1, 130.0, 129.7, 128.8, 128.5, 128.2, 126.8, 126.3, 122.1, 115.2, 109.1, 73.1, 56.3, 52.1, 48.7, 45.2, 39.3, 37.1, 28.2, 25.4; IR (thin film): ν 3237, 2950, 1733, 1601, 1447 cm^{-1}; MS *m/z* (%) 617 (18), 526 (22), 351 (11), 335 (9), 105 (100); EI-HRMS calcd for $C_{38}H_{39}N_3O_5$ *m/z* $[M]^+$ 617.2890; found 617.2875.

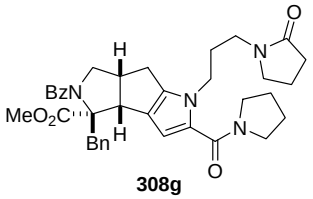


308f

5-Benzoyl-4-benzyl-1-(3-morpholin-4-ylpropyl)-2-(pyrrolidine-1-carbonyl)-3b,4,5,6,6a,7-hexahydro-1H-1,5-diaza-cyclopenta[a]pentalene-4-carboxylic acid methyl ester (308f). Prepared by following general procedure T with: **307** (34 mg, 0.066 mmol), 3-Morpholin-4-yl propylamine (29 μL, 0.20 mmol), AcOH (80 μL). Yield **308f** (16 mg, 39%).

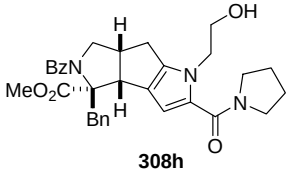
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.28 (m, 10H), 6.21 (s, 1H), 4.23 (d, *J* = 13.7 Hz, 1H), 4.18-

4.11 (m, 1H), 4.07-3.98 (m, 1H), 3.87 (d, *J* = 7.3 Hz, 1H), 3.70-3.56 (m, 8H), 3.62 (s, 3H), 3.39 (d, *J* = 13.6 Hz, 1H), 3.33 (dd, *J* = 10.4, 8.3 Hz, 1H), 3.17 (dd, *J* = 10.2, 8.3 Hz, 1H), 3.09 (q, *J* = 7.3 Hz, 2H), 2.55 (dd, *J* = 15.0, 6.9 Hz, 1H), 2.41-.2.20 (m, 9H); IR (thin film): ν 2950, 1734, 1637, 1603, 1445, 1400 cm^{-1}; MS *m/z* (%) 624 (25), 211 (32), 105 (100); EI-HRMS calcd for $C_{37}H_{44}N_4O_5$ *m/z* $[M]^+$ 624.3312; found 624.3291.



308g

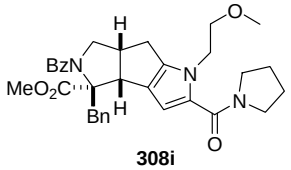
5-Benzoyl-4-benzyl-1-[3-(2-oxo-pyrrolidin-1-yl)-propyl]-2-(pyrrolidine-1-carbonyl)-3b,4,5,6,6a,7-hexahydro-1H-1,5-diazacyclopenta[a]pentalene-4-carboxylic acid methyl ester (308g). Prepared by following general procedure T with: **307** (39 mg, 0.076 mmol), 1-(3-aminopropyl)-pyrrolidin-2-one (32 μL, 0.23 mmol), AcOH (90 μL). Yield **308g** (38 mg, 81%). ^1H NMR (300 MHz, $CDCl_3$): δ 7.43-7.38 (m, 5H), 7.34-7.27 (m, 5H), 6.20 (s, 1H), 4.21 (d, *J* = 13.6 Hz, 1H), 4.14-4.04 (m, 1H), 3.94-3.84 (m, 2H), 3.67-3.57 (m, 4H), 3.61 (s, 3H), 3.39-3.30 (m, 4H), 3.25-3.14 (m, 3H), 2.53 (dd, *J* = 15.1, 7.0 Hz, 1H), 2.35-2.30 (m, 3H), 2.21 (d, *J* = 15.3 Hz, 1H), 2.00-1.87 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.9, 172.2, 169.7, 140.6, 137.5, 136.9, 130.9, 129.6, 129.1, 128.3, 128.1, 126.8, 126.2, 122.4, 108.8, 72.9, 56.2, 52.0, 46.9, 45.4, 44.8, 39.9, 39.2, 31.0, 28.9, 28.5, 17.8, 14.1; IR (thin film): ν 2948, 1733, 1683, 1639, 1606, 1445, 1399 cm^{-1}; MS *m/z* (%) 622 (21), 531 (24), 460 (6), 105 (100); EI-HRMS calcd for $C_{37}H_{42}N_4O_5$ *m/z* $[M]^+$ 622.3155; found 622.3147.



308h

5-Benzoyl-4-benzyl-1-(2-hydroxyethyl)-2-(pyrrolidine-1-carbonyl)-3b,4,5,6,6a,7-hexahydro-1H-1,5-diazacyclopenta[a]pentalene-4-carboxylic acid methyl ester (308h). Prepared by following general procedure T with: **307** (50 mg, 0.097 mmol), ethanolamine (18 μL, 0.29 mmol), AcOH (100 μL). Yield **308h** (42 mg, 80%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48-7.40 (m, 5H), 7.36-7.30 (m, 5H), 6.26 (s, 1H), 4.23 (d, *J* = 13.6 Hz, 1H), 4.18-4.09 (m, 2H), 3.88 (d, *J* = 7.4 Hz, 1H), 3.80 (t, *J* = 5.1 Hz, 1H), 3.75-3.57 (m, 4H), 3.64 (s, 3H), 3.39 (d, *J* = 13.7 Hz, 1H), 3.37-3.20 (m, 2H), 2.57 (dd, *J* = 15.3, 8.1 Hz, 1H), 2.41-2.31 (m, 1H), 2.25 (d, *J* = 15.4 Hz, 1H), 2.03-1.90 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 169.7, 162.0, 141.3, 137.5, 137.0, 131.0, 129.7, 129.6, 128.4, 128.2, 126.8, 126.3, 123.2, 109.3, 72.9, 62.6, 56.2, 52.1, 52.0, 49.9, 48.8, 46.7, 45.6, 39.2, 28.6, 26.5, 24.1; IR (thin film): ν 3394, 2949, 1734, 1600, 1448, 1402 cm^{-1}; MS *m/z* (%) 541 (45), 482 (13), 450 (54), 379 (28), 328 (20), 105 (100); EI-HRMS calcd for $C_{32}H_{35}N_3O_5$ *m/z* $[M]^+$ 541.2577; found 541.2574.

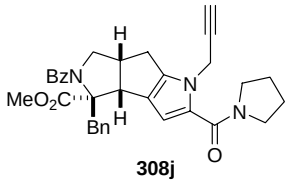


308i

5-Benzoyl-4-benzyl-1-(2-methoxyethyl)-2-(pyrrolidine-1-carbonyl)-3b,4,5,6,6a,7-hexahydro-1H-1,5-diazacyclopenta[a]pentalene-4-carboxylic acid methyl ester (308i). Prepared by following general procedure T with: **307** (35 mg, 0.068 mmol), 2-methoxyethylamine (18 μL, 0.20 mmol), AcOH (80 μL). Yield **308i** (35 mg, 93%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44-7.27 (m, 10H), 6.23 (s, 1H), 4.32 (dt, *J* = 14.1, 4.9 Hz, 1H), 4.23 (d, *J* = 13.6 Hz, 1H), 4.07 (dt, *J* = 14.1, 5.0 Hz, 1H), 3.88 (d, *J* = 7.4 Hz, 1H), 3.70-3.51 (m, 9H), 3.40 (d, *J* = 13.7 Hz, 1H), 3.37-3.31 (m, 1H), 3.21 (s, 3H), 3.21-3.15 (m, 1H), 2.58 (dd, *J* = 15.6, 7.0 Hz, 1H), 2.33-2.26 (m, 1H), 2.25 (d, J = 16.0 Hz, 1H), 2.00-1.90 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 169.7, 161.9, 141.8, 137.6, 137.0, 131.0, 129.5, 129.0, 128.3, 128.1,

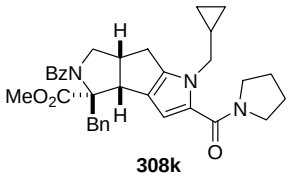
126.8, 126.2, 109.0, 72.9, 58.7, 56.4, 52.2, 52.0, 47.0, 45.2, 39.3, 28.8, 25.7; IR (thin film): ν 2948, 1733, 1640, 1605, 1445, 1399 cm^{-1}; MS *m/z* (%) 555 (46), 496 (10), 465 (43), 289 (42), 105 (100); EI-HRMS calcd for $C_{33}H_{37}N_3O_5$ *m/z* $[M]^+$ 555.2733; found 555.2742.



308j

5-Benzoyl-4-benzyl-1-prop-2-ynyl-2-(pyrrolidine-1-carbonyl)-3b,4,5,6,6a,7-hexahydro-1H-1,5-diazacyclopenta[a]pentalene-4-carboxylic acid methyl ester (308j). Prepared by following general procedure T with: **307** (37 mg, 0.072 mmol), propargylamine (15 μL, 0.22 mmol), AcOH (90 μL). Yield **308j** (34 mg, 89%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.39 (m, 5H), 7.35-7.27 (m, 5H), 6.25 (s, 1H), 5.09 (dd, *J* = 17.6, 1.7 Hz, 1H), 4.87 (dd, *J* = 17.6, 1.4 Hz, 1H), 4.23 (d, *J* = 13.6 Hz, 1H), 3.87 (d, *J* = 7.2 Hz, 1H), 3.74-3.58 (m, 4H), 3.62 (s, 3H), 3.39 (d, *J* = 13.3 Hz, 1H), 3.37-3.31 (m, 1H), 3.23-3.17 (m, 1H), 3.65 (dd, *J* = 15.8, 7.4 Hz, 1H), 2.35-2.23 (m, 3H), 1.98-1.90 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 169.7, 161.5, 141.0, 137.5, 137.0, 130.9, 129.6, 129.0, 128.4, 128.2, 126.8, 126.2, 123.1, 109.3, 79.0, 72.8, 72.1, 56.2, 52.1, 52.0, 45.5, 39.2, 35.9, 28.7; IR (thin film): ν 3254, 2949, 2115, 1733, 1637, 1603, 1446, 1401 cm^{-1}; MS *m/z* (%) 535 (5), 444 (11), 269 (10), 105 (100); EI-HRMS calcd for $C_{33}H_{33}N_3O_4$ *m/z* $[M]^+$ 535.2471; found 535.2485.

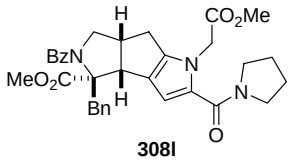


308k

5-Benzoyl-4-benzyl-1-cyclopropylmethyl-2-(pyrrolidine-1-carbonyl)-3b,4,5,6,6a,7-hexahydro-1H-1,5-diazacyclopenta[a]pentalene-4-carboxylic acid methyl ester (308k).

Prepared by following general procedure T with: **307** (30 mg, 0.058 mmol), C-cyclopropylmethylamine (15 μL, 0.17 mmol), AcOH (70 μL). Yield **308k** (22 mg, 69%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.27 (m, 10H), 6.20 (s, 1H), 4.24 (d, *J* = 13.6 Hz, 1H), 4.06 (dd, *J* = 14.1, 7.0 Hz, 1H), 3.89 (d, *J* = 7.4 Hz, 1H), 3.81 (dd, *J* = 14.1, 6.8 Hz, 1H), 3.70-3.60 (m, 4H), 3.63 (s, 3H), 3.41 (d, *J* = 13.7 Hz, 1H), 3.34 (dd, *J* = 10.1, 8.3 Hz, 1H), 3.23-3.17 (m, 1H), 2.58 (dd, *J* = 14.9, 6.8 Hz, 1H), 2.37-2.27 (m, 1H), 2.25 (d, *J* = 14.6 Hz, 1H), 2.00-1.88 (m, 4H), 1.16-1.02 (m, 1H), 0.49-0.38 (m, 2H), 0.23-0.18 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 169.7, 162.3, 140.3, 137.6, 137.1, 131.0, 129.6, 129.4, 128.4, 128.2, 126.8, 126.3, 122.3, 108.5, 73.0, 56.3, 52.1, 51.0, 45.5, 39.3, 29.0, 12.6, 3.8, 3.5; IR (thin film): ν 2948, 1734, 1638, 1609, 1445, 1400 cm^{-1}; MS *m/z* (%) 551 (36), 460 (37), 389 (19), 105 (100); EI-HRMS calcd for $C_{34}H_{37}N_3O_4$ *m/z* $[M]^+$ 551.2784; found 551.2768.

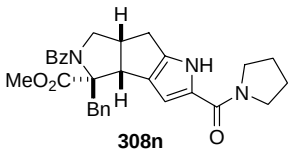


308l

5-Benzoyl-4-benzyl-1-methoxycarbonylmethyl-2-(pyrrolidine-1-carbonyl)-3b,4,5,6,6a,7-hexahydro-1H-1,5-diazacyclopenta[a]pentalene-4-carboxylic acid methyl ester (308l). Prepared by following general procedure T with: **307** (24 mg, 0.047 mmol), glycine methyl ester hydrochloride (18 mg, 0.14 mmol), AcOH (70 μL) and Et_3N (19 μL, 0.14 mmol). Yield **308l** (21 mg, 79%). Note: Et_3N was added to help dissolve the insoluble hydrochloride salt of the primary amine.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.27 (m, 10H), 6.32 (m, 1H), 4.98 (d, *J* = 17.3 Hz, 1H), 4.67 (d, *J* = 17.3 Hz, 1H), 4.23 (d, *J* = 13.6 Hz, 1H), 3.92 (d, *J* = 7.4 Hz, 1H), 3.72 (s, 3H), 3.65 (s, 3H), 3.71-3.58 (m, 4H), 3.40 (d, *J* = 13.5 Hz, 1H), 3.38-3.32 (m, 1H), 3.24-3.18 (m, 1H), 2.52 (dd, *J* = 15.1, 7.1 Hz, 1H), 2.39-2.29 (m, 1H), 2.18 (d, *J* = 15.5 Hz, 1H), 2.03-1.86 (m, 4H); ^{13}C

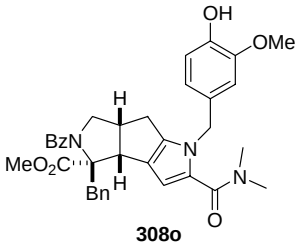
NMR (75 MHz, $CDCl_3$): δ 172.2, 169.8, 169.5, 161.5, 141.5, 137.5, 137.0, 131.0, 129.6, 129.4, 128.4, 128.2, 126.8, 126.3, 124.8, 122.8, 109.5, 72.8, 56.2, 52.3, 52.1, 48.4, 45.3, 39.2, 28.2; IR (thin film): ν 2950, 1736, 1638, 1601, 1447, 1401 cm^{-1}; MS *m/z* (%) 569 (18), 478 (50), 303 (49), 105 (100); EI-HRMS calcd for $C_{33}H_{35}N_3O_6$ *m/z* $[M]^+$ 569.2526; found 569.2538.



308n

5-Benzoyl-4-benzyl-2-(pyrrolidine-1-carbonyl)-3b,4,5,6,6a,7-hexahydro-1H-1,5-diazacyclopenta[a]pentalene-4-carboxylic acid methyl ester (308n). Prepared by following general procedure T with: **307** (42 mg, 0.081 mmol), ammonium acetate (19 mg, 0.24 mmol), AcOH (100 μL). Yield **308n** (27 mg, 64%).

^1H NMR (300 MHz, $CDCl_3$): δ 9.81 (s, 1H), 7.44-7.27 (m, 10H), 6.27 (s, 1H), 4.24 (d, *J* = 13.6 Hz, 1H), 3.89 (d, *J* = 7.4 Hz, 1H), 3.76-3.55 (m, 4H), 3.62 (s, 3H), 3.43-3.32 (m, 2H), 3.23-3.17 (m, 1H), 2.59 (dd, *J* = 15.3, 6.9 Hz, 1H), 2.39-2.29 (m, 1H), 2.27 (d, *J* = 15.2 Hz, 1H), 2.12-1.81 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 169.8, 160.4, 137.9, 137.5, 137.0, 130.9, 129.8, 129.5, 128.4, 128.2, 126.8, 126.2, 126.0, 72.9, 56.3, 52.0, 47.9, 47.0, 46.0, 39.2, 28.8, 26.6, 23.8; IR (thin film): ν 3219, 2949, 1733, 1635, 1579, 1456, 1401 cm^{-1}; MS *m/z* (%) 497 (20), 438 (16), 406 (33), 105 (100); EI-HRMS calcd for $C_{30}H_{31}N_3O_4$ *m/z* $[M]^+$ 497.2315; found 497.2292.

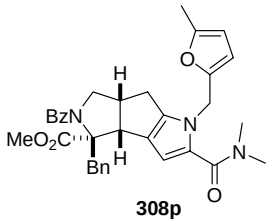


308o

5-Benzoyl-4-benzyl-2-dimethylcarbamoyl-1-(4-hydroxy-3-methoxy-benzyl)-3b,4,5,6,6a,7-hexahydro-1H-1,5-diazacyclopenta[a]pentalene-4-carboxylic acid methyl ester (308o).

Prepared by following general procedure T with: **306** (29 mg, 0.059 mmol), 4-aminomethyl-2-methoxyphenol hydrochloride (34 mg, 0.18 mmol), AcOH (80 μL) and Et_3N (25 μL, 0.18 mmol). Yield **308o** (13 mg, 36%). Note: Et_3N was added to help dissolve the insoluble hydrochloride salt of the primary amine.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.38 (m, 5H), 7.34-7.29 (m, 5H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.61 (s, 1H), 6.44 (d, *J* = 8.0 Hz, 1H), 6.10 (s, 1H), 5.54 (bs, 1H), 5.19 (d, *J* = 15.2 Hz, 1H), 5.00 (d, *J* = 15.2 Hz, 1H), 4.23 (d, *J* = 13.6 Hz, 1H), 3.87 (d, *J* = 7.2 Hz, 1H), 3.81 (s, 3H), 3.62 (s, 3H), 3.39 (d, *J* = 13.6 Hz, 1H), 3.36-3.29 (m, 1H), 3.18-3.12 (m, 1H), 3.07 (s, 6H), 2.41 (dd, *J* = 15.0, 6.8 Hz, 1H), 2.34-2.24 (m, 1H), 2.12 (d, *J* = 15.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 169.8, 164.2, 146.6, 144.9, 140.5, 137.7, 137.1, 131.0, 130.4, 129.6, 128.8, 128.4, 128.2, 126.8, 126.3, 122.8, 120.0, 114.2, 110.0, 108.5, 73.1, 56.4, 55.9, 53.4, 52.1, 51.9, 49.5, 45.7, 39.4, 28.9; IR (thin film): ν 3273, 2950, 1733, 1616, 1514, 1403 cm^{-1}; MS *m/z* (%) 607 (25), 516 (20), 471 (5), 105 (100); EI-HRMS calcd for $C_{36}H_{37}N_3O_6$ *m/z* $[M]^+$ 607.2682; found 607.2687.

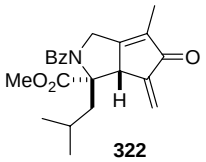


308p

5-Benzoyl-4-benzyl-2-dimethylcarbamoyl-1-(5-methylfuran-2-ylmethyl)-3b,4,5,6,6a,7-hexahydro-1H-1,5-diazacyclopenta[a]pentalene-4-carboxylic acid methyl ester (308p). Prepared by following general procedure T with: **306** (38 mg, 0.078 mmol), C-(5-methylfuran-2-yl)methylamine (26 μL, 0.23 mmol), AcOH (90 μL). Yield **308p** (31 mg, 70%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43-7.39 (m, 5H), 7.34-7.28 (m, 5H), 6.07 (s, 1H), 5.98 (d, *J* =

3.0 Hz, 1H), 5.82-5.80 (m, 1H), 5.22 (d, *J* = 15.6 Hz, 1H), 4.98 (d, *J* = 15.6 Hz, 1H), 4.22 (d, *J* = 13.6 Hz, 1H), 3.85 (d, *J* = 7.4 Hz, 1H), 3.57 (s, 3H), 3.39 (d, *J* = 13.6 Hz, 1H), 3.32 (dd, *J* = 10.5, 8.3 Hz, 1H), 3.19 (dd, *J* = 10.3, 8.3 Hz, 1H), 3.11 (s, 6H), 2.51 (dd, *J* = 15.0, 6.6 Hz, 1H), 2.34-2.24 (m, 2H), 2.17 (d, *J* = 0.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 169.8, 164.3, 151.8, 149.3, 140.4, 137.7, 137.1, 131.0, 129.5, 128.4, 128.2, 126.8, 126.2, 122.5, 108.6, 106.2, 73.0, 56.4, 52.1, 51.9, 45.6, 42.7, 39.3, 37.6, 28.6, 13.4; IR (thin film): ν 2948, 1734, 1622, 1402 cm^{-1}; ESI-HRMS calcd for $C_{38}H_{40}N_3O_6$ *m/z* $[M+1]^+$ 566.2655; found 566.2653.



322

2-Benzoyl-1-isobutyl-4-methyl-6-methylene-5-oxo-1,2,3,5,6,6a-hexahydrocyclopenta[c]pyrrole-1-carboxylic acid methyl ester (322). $[Rh(CO)_2Cl]_2$ (3 mg, 7 μmol) was placed in an oven-dried test tube, the atmosphere was replaced with Ar and DCE (0.5 mL) was added. Then dppb (6.3 mg, 15 μmol) in DCE (0.5 mL) was added at rt via a syringe followed by $AgBF_4$ (163 μL of a 0.1 M solution in toluene, 16 μmol). After 1 min, allenyne **321** (25 mg, 74 μmol) in DCE (0.5 mL) was added. After 30 min, half of the reaction mixture (0.6 mL) was taken out via a syringe and filtered on a small plug of silica gel to give **322** (5 mg, 37%).

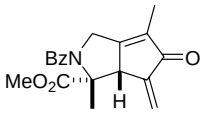
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60-7.57 (m, 2H), 7.52-7.43 (m, 3H), 6.15 (d, *J* = 2.0 Hz, 1H), 5.50 (d, *J* = 1.4 Hz, 1H), 4.56 (dt, *J* = 14.9, 1.6 Hz, 1H), 4.33 (d, *J* = 14.9 Hz, 1H), 3.52 (s, 3H), 2.80 (dd, *J* = 15.1, 7.0 Hz, 1H), 2.14 (dd, *J* = 15.1, 4.7 Hz, 1H), 2.05-1.90 (m, 1H), 1.77 (t, *J* = 1.8 Hz, 3H), 1.13 (d, *J* = 6.7 Hz, 3H), 1.08 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.6, 171.0, 170.7, 162.9, 140.5, 135.7, 135.0, 131.1, 128.6, 127.4, 117.8, 71.0, 52.1, 50.8, 50.4, 40.0, 25.4, 24.4, 23.8, 9.1; IR (thin film): ν 2951, 1735, 1703, 1689, 1643, 1378 cm^{-1}; MS *m/z*

(%) 367 (60), 308 (72), 262 (8), 105 (100); EI-HRMS calcd for $C_{22}H_{25}N_1O_4$ *m/z* $[M]^+$ 367.1784; found 367.1771.

$[Rh(dppb)(CO)_2]BF_4$ (**325**). $[Rh(cod)_2]BF_4$ (30 mg, 0.074 mmol) was placed in an oven-dried 25 mL Schlenk flask under Ar, and DCE (3 mL) was added to form a dark red solution. Then a solution of dppb (34 mg, 0.081 mmol) in DCE (2 mL) was added via a syringe over 1 min and the reaction mixture turned bright yellow. The atmosphere was replaced with CO via a balloon and the reaction vessel was immersed in an oil-bath preheated to 70 °C and stirred for 5 min. After cooling to rt, the solution was transferred to an oven-dried test tube under Ar via a canula and Et_2O (10 mL) and hexanes (2 mL) were added to form a yellow precipitate. The test tube was centrifuged for 15 min, and the pale yellow liquid was removed via a syringe. After removal of the residual solvent under vacuum, **325** (45 mg, 91%) was obtained as a yellow powder.

Note: this complex was stored under Ar at -10 °C and used for up to two weeks without noticeable effect on the performance in the cyclocarbonylation reaction.

^{31}P NMR (121.4 MHz, $CDCl_3$, external standard H_3PO_4): δ 21.40 (d, J = 119.7 Hz); IR (thin film): ν 2024 (CO), 1481, 1435, 1049 cm^{-1}



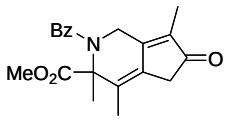
288c

2-Benzoyl-1,4-dimethyl-6-methylene-5-oxo-1,2,3,5,6,6a-hexahydrocyclopenta[c]pyrrole-1-carboxylic acid methyl ester (288c). To a solution of allenyne **74c** (21 mg, 0.071 mmol) in DCE (1.4 mmol) in a new 15 mL test tube was added $[Rh(CO)_2(dppb)]BF_4$ (2 mg, 3 μmol) under Ar atmosphere. The test tube was sealed with a rubber septum and CO (3 mL) was injected via a syringe. The reaction vessel was heated to 80 °C for 1.5 h, and then cooled to rt and filtered on a plug of silica gel eluting with EtOAc : hexanes 1 : 1 to afford a mixture of products (26 mg,

87%). The diastereomeric ratio (**288c** : **287c** = 2.1 : 1) was determined by integration of the two olefinic resonances in the ^{1}H NMR spectrum.

287c has been characterized previously from the Mo-mediated cyclocarbonylation reaction of **74c**. Separation of **288c** from **287c** was achieved by HPLC (35 % EtOAc/hexanes, flow rate 3 mL/min, UV detection at 254 nm) with the following retention times: **288c** (15.15 min); **287c** (15.62 min).

288c: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61-7.59 (m, 2H), 7.54-7.44 (m, 3H), 6.17 (d, *J* = 1.9 Hz, 1H), 5.54 (s, 1H), 4.58 (d, *J* = 14.9 Hz, 1H), 4.30 (d, *J* = 14.9 Hz, 1H), 3.76 (s, 1H), 3.55 (s, 3H), 2.04 (s, 3H), 1.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.4, 171.2, 170.5, 162.7, 140.2, 135.9, 135.1, 131.0, 128.6, 127.5, 118.0, 68.3, 55.0, 52.1, 50.3, 23.6, 9.1; IR (thin film): ν 2950, 1734, 1707, 1689, 1643, 1378 cm^{-1}; MS *m/z* (%) 325 (10), 266 (18), 105 (100); EI-HRMS calcd for $C_{19}H_{19}N_1O_4$ *m/z* $[M]^+$ 325.1314; found 325.1308.



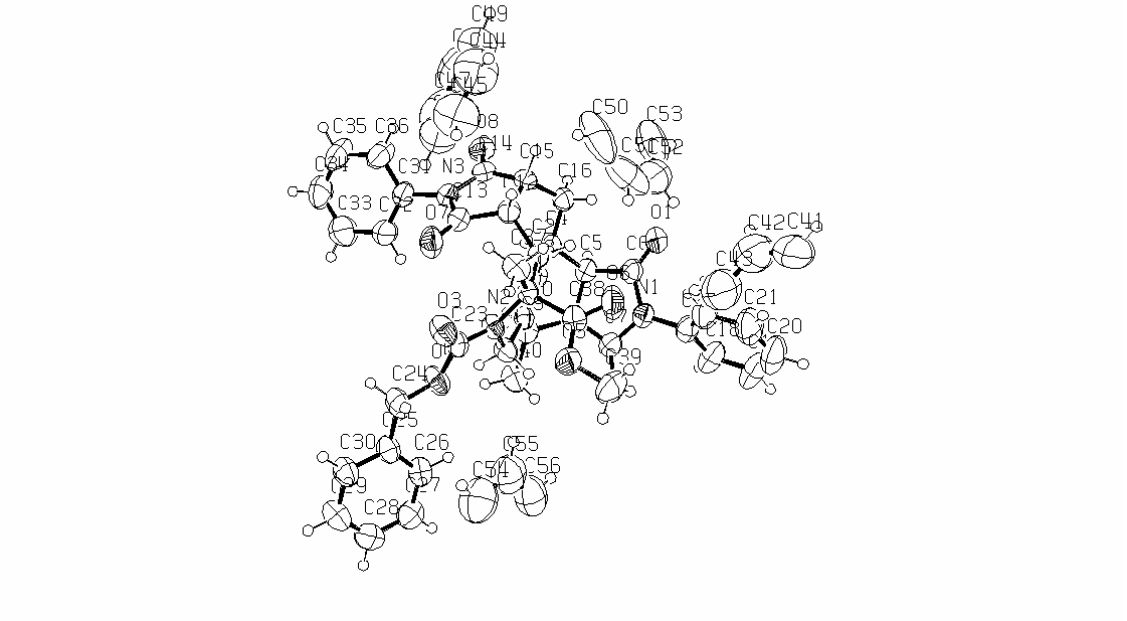
329

2-Benzoyl-3,4,7-trimethyl-6-oxo-2,3,5,6-tetrahydro-1H-[2]pyrindine-3-carboxylic acid methyl ester (329). To a solution of allenyne **328** (31 mg, 0.10 mmol) in DCE/toluene (3 mL, 9 : 1) in a 15 mL test tube was added $[Rh(CO)_2(dppb)]BF_4$ (3 mg, 5 μmol) under Ar atmosphere. The test tube was sealed with a rubber septum and CO (3 mL) was injected via syringe. The reaction vessel was heated to 80 °C for 6 h, and then cooled to rt. Purification by flash chromatography (hexanes-EtOAc, v/v) afforded **329** (16.5 mg, 48%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50-7.40 (m, 5H), 4.84 (d, *J* = 17.6 Hz, 1H), 4.01 (d, *J* = 17.7 Hz, 1H), 3.73 (s, 3H), 3.01 (d, *J* = 20.1 Hz, 1H), 2.94 (d, *J* = 20.1 Hz, 1H), 1.79 (s, 3H), 1.76 (s,

3H), 1.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.3, 171.7, 171.1, 155.8, 135.2, 134.2, 130.6, 130.3, 129.8, 128.8, 127.2, 65.2, 52.7, 42.6, 37.1, 18.1, 15.4, 7.8; MS *m/z* (%) 339 (25), 280 (94), 77 (100); EI-HRMS calcd for $C_{20}H_{21}N_1O_4$ *m/z* $[M]^+$ 339.1471; found 339.1481.

APPENDIX A: X-ray crystal structure of **144**



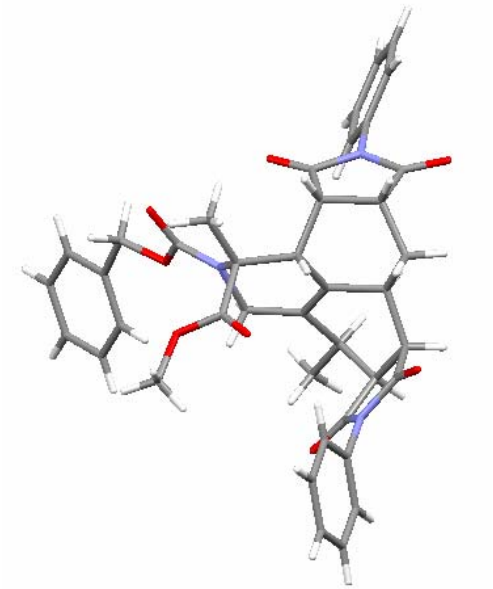
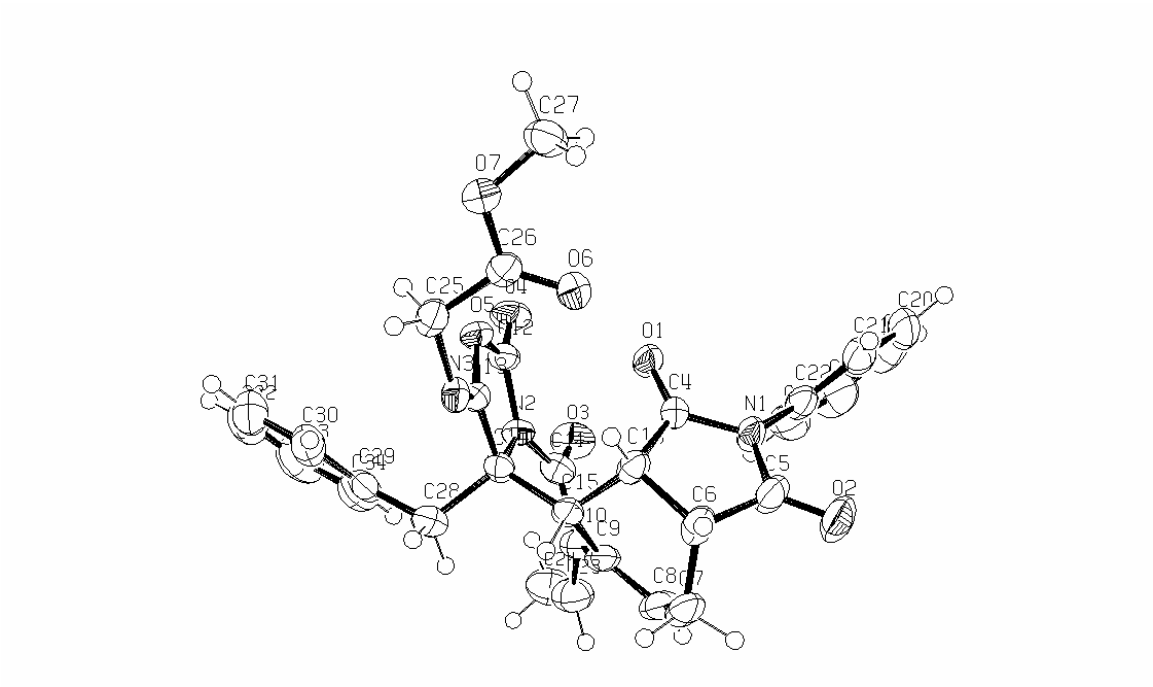


Table 1. Crystal data and structure refinement for **144**.

Identification code	**BM144**	
Empirical formula	C55 H52 N3 O8	
Formula weight	883.00	
Temperature	294(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2/n	
Unit cell dimensions	a = 21.898(2) Å	α= 90°.
	b = 10.0835(10) Å	β= 111.998(2)°.
	c = 23.066(2) Å	γ = 90°.
Volume	4722.3(8) $Å^3$	
Z	4	
Density (calculated)	1.242 Mg/m^3	
Absorption coefficient	0.083 mm^{-1}	
F(000)	1868	
Crystal size	0.27 x 0.23 x 0.23 mm^3	
Theta range for data collection	1.62 to 27.50°.	
Index ranges	-28<=h<=28, -13<=k<=13, -29<=l<=29	
Reflections collected	45046	
Independent reflections	10857 [R(int) = 0.0391]	
Completeness to theta = 27.50°	100.0 %	
Absorption correction	None	
Max. and min. transmission	0.9811 and 0.9779	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	10857 / 0 / 596	
Goodness-of-fit on F^2	1.007	
Final R indices [I>2sigma(I)]	R1 = 0.0530, wR2 = 0.1396	
R indices (all data)	R1 = 0.0928, wR2 = 0.1547	
Largest diff. peak and hole	0.240 and -0.191 $e.Å^{-3}$	

APPENDIX B: X-ray crystal structure of **156a**



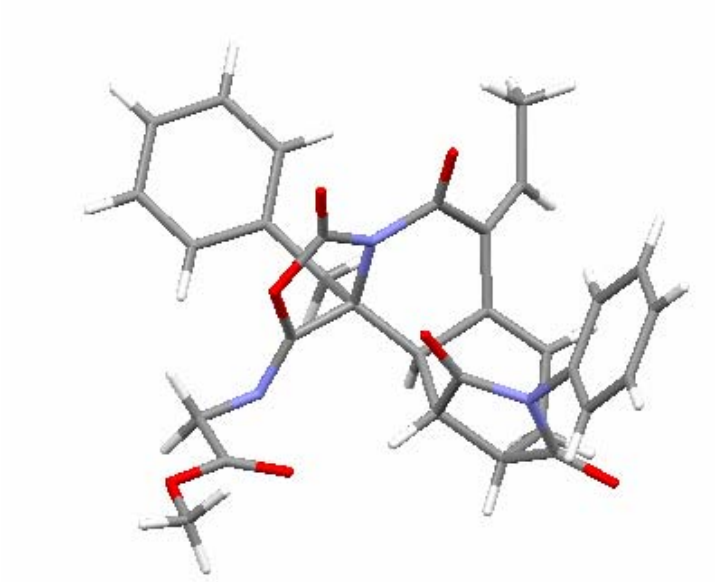
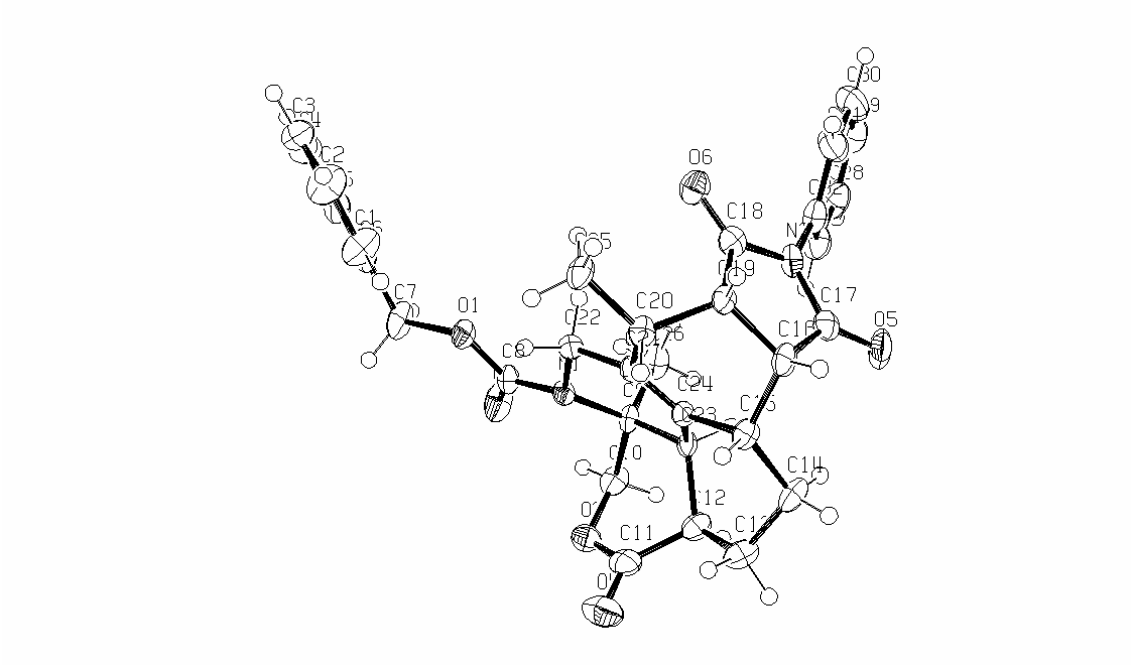


Table 1. Crystal data and structure refinement for **156a**.

Identification code	**BM156a**	
Empirical formula	C31 H27 N3 O7	
Formula weight	553.56	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.6228(6) Å	α= 90.994(2)°.
	b = 10.7043(8) Å	β= 94.584(2)°.
	c = 16.4329(13) Å	γ = 96.331(2)°.
Volume	1327.97(18) $Å^3$	
Z	2	
Density (calculated)	1.384 Mg/m^3	
Absorption coefficient	0.099 mm^{-1}	
F(000)	580	
Theta range for data collection	1.91 to 25.00°.	
Index ranges	-9<=h<=9, -12<=k<=12, -19<=l<=19	
Reflections collected	10796	
Independent reflections	4671 [R(int) = 0.0462]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4671 / 0 / 372	
Goodness-of-fit on F^2	1.120	
Final R indices [I>2sigma(I)]	R1 = 0.0771, wR2 = 0.1696	
R indices (all data)	R1 = 0.1168, wR2 = 0.1847	
Largest diff. peak and hole	0.366 and -0.220 $e.Å^{-3}$	

APPENDIX C: X-ray crystal structure of **186b**



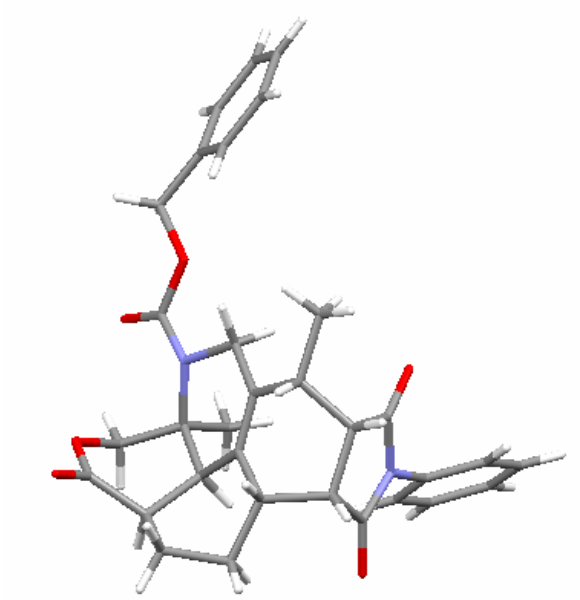
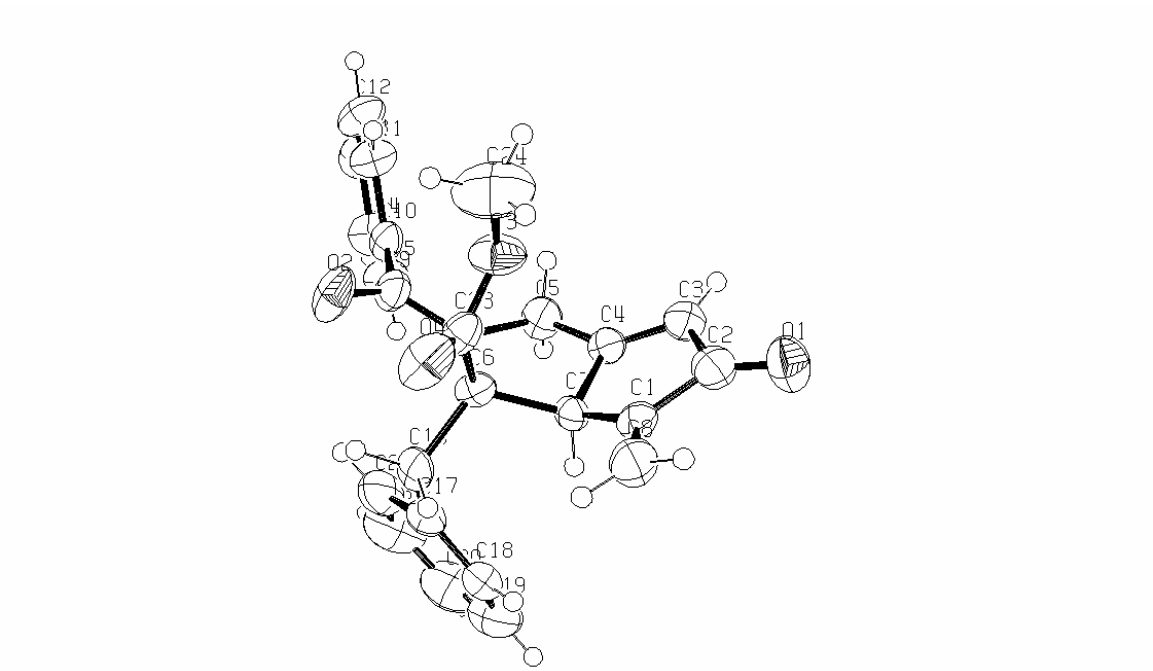


Table 1. Crystal data and structure refinement for **186b**.

Identification code	**BM186b**	
Empirical formula	C32 H32 N2 O6	
Formula weight	540.60	
Temperature	273(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 9.7369(19) Å	α= 90°.
	b = 9.4212(19) Å	β= 90.290(4)°.
	c = 14.780(3) Å	γ = 90°.
Volume	1355.8(5) $Å^3$	
Z	2	
Density (calculated)	1.324 Mg/m^3	
Absorption coefficient	0.092 mm^{-1}	
F(000)	572	
Theta range for data collection	2.09 to 32.66°.	
Index ranges	-14<=h<=14, -14<=k<=13, -21<=l<=22	
Reflections collected	17593	
Independent reflections	9201 [R(int) = 0.1028]	
Completeness to theta = 32.66°	95.6 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9201 / 1 / 363	
Goodness-of-fit on F^2	0.940	
Final R indices [I>2sigma(I)]	R1 = 0.0954, wR2 = 0.1984	
R indices (all data)	R1 = 0.1901, wR2 = 0.2444	
Absolute structure parameter	6.3(18)	
Largest diff. peak and hole	0.383 and -0.307 $e.Å^{-3}$	

APPENDIX D: X-ray crystal structure of **287b**



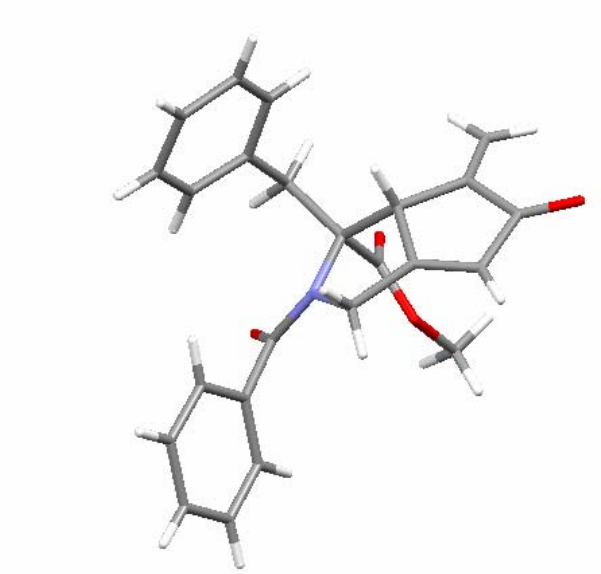
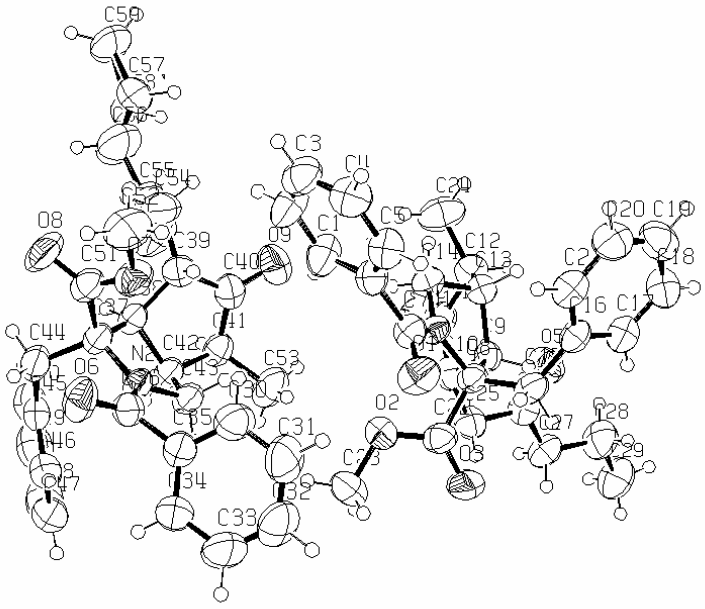


Table 1. Crystal data and structure refinement for **287b**.

Identification code	**BM287b**	
Empirical formula	C24 H21 N O4	
Formula weight	387.42	
Temperature	295(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pna2(1)	
Unit cell dimensions	a = 15.4047(9) Å	α= 90°.
	b = 8.2720(5) Å	β= 90°.
	c = 15.9411(9) Å	γ = 90°.
Volume	2031.3(2) $Å^3$	
Z	4	
Density (calculated)	1.267 Mg/m^3	
Absorption coefficient	0.086 mm^{-1}	
F(000)	816	
Crystal size	0.16 x 0.11 x 0.04 mm^3	
Theta range for data collection	2.56 to 24.98°.	
Index ranges	-18<=h<=18, -9<=k<=9, -18<=l<=18	
Reflections collected	15471	
Independent reflections	3576 [R(int) = 0.1112]	
Completeness to theta = 24.98°	100.0 %	
Absorption correction	Sadabs	
Max. and min. transmission	0.9966 and 0.9863	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3576 / 1 / 262	
Goodness-of-fit on F^2	1.089	
Final R indices [I>2sigma(I)]	R1 = 0.0704, wR2 = 0.1252	
R indices (all data)	R1 = 0.1158, wR2 = 0.1393	
Largest diff. peak and hole	0.151 and -0.175 $e.Å^{-3}$	

APPENDIX E: X-ray crystal structure of **296**



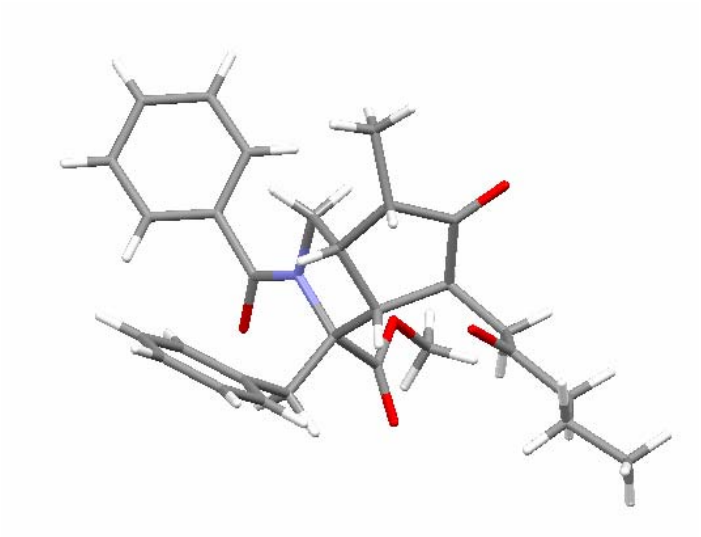


Table 1. Crystal data and structure refinement for **296**.

Identification code	**BM296**	
Empirical formula	C29 H33 N O5	
Formula weight	475.56	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 26.4650(13) Å	α= 90°.
	b = 9.6298(5) Å	β= 105.3700(10)°.
	c = 21.3983(11) Å	γ = 90°.
Volume	5258.4(5) $Å^3$	
Z	8	
Density (calculated)	1.201 Mg/m^3	
Absorption coefficient	0.082 mm^{-1}	
F(000)	2032	
Crystal size	0.14 x 0.14 x 0.18 mm^3	
Theta range for data collection	1.92 to 25.00°.	
Index ranges	-31<=h<=31, -11<=k<=11, -25<=l<=25	
Reflections collected	40981	
Independent reflections	9272 [R(int) = 0.0604]	
Completeness to theta = 25.00°	100.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	9272 / 0 / 641	
Goodness-of-fit on F^2	1.088	
Final R indices [I>2sigma(I)]	R1 = 0.0718, wR2 = 0.1676	
R indices (all data)	R1 = 0.1235, wR2 = 0.1877	
Largest diff. peak and hole	0.387 and -0.159 $e.Å^{-3}$	

APPENDIX F: QikProp property predictions for **308h**

QikProp v2.1 (rel 8) - Property predictions for tricyclic pyrrole **308h**.

Principal Descriptors: (Range 95% of Drugs)

Solute Molecular Weight = 541.6 (130.0 / 725.0)

Solute Molecular Volume (A^3) = 1602 (500.0 /2000.0)

Solute No. of Rotatable Bonds= 8.000 (0.0 / 15.0)

Solute as Donor - Hydrogen Bonds = 1.000 (0.0 / 6.0)

Solute as Acceptor - Hydrogen Bonds = 9.7 (2.0 / 20.0)

Predictions for Properties:

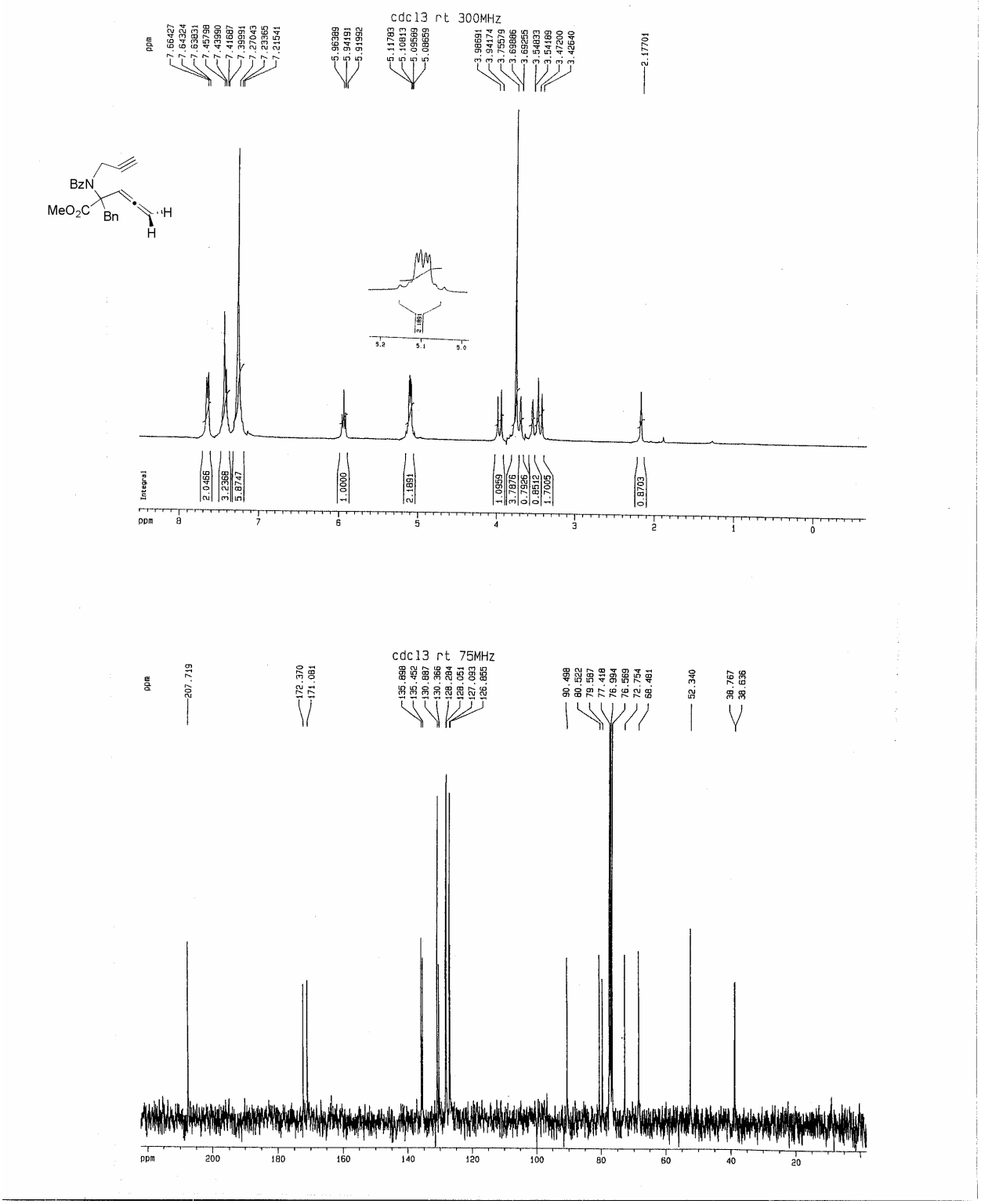
QP log P for octanol/water = 5.11 (-2.0 / 6.0)

QP log S for aqueous solubility = -6.12 (-6.0 / 0.5)

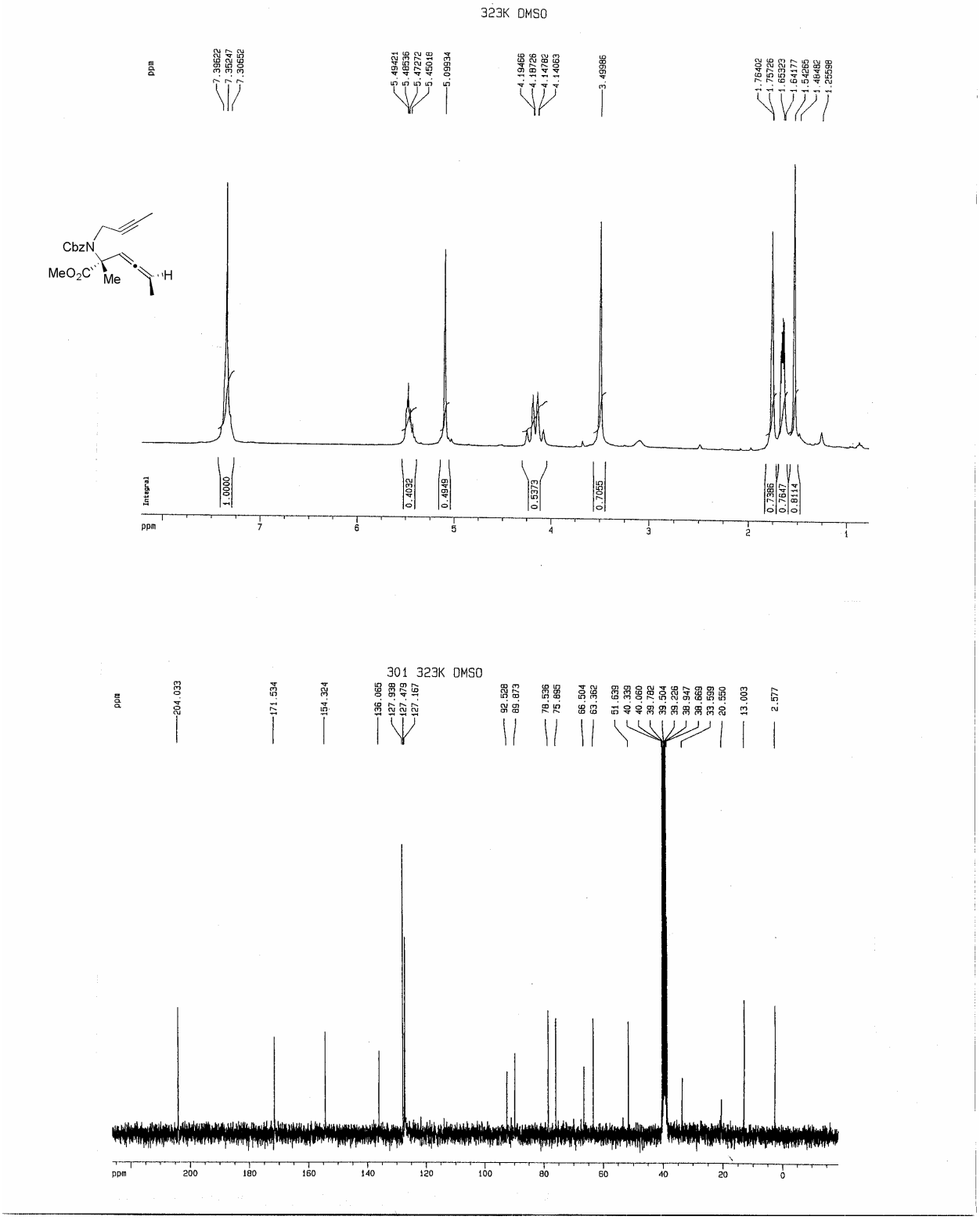
QP log K hsa Serum Protein Binding = 0.86 (-1.5 / 1.2)

No. of Primary Metabolites = 4 (1.0 / 8.0)

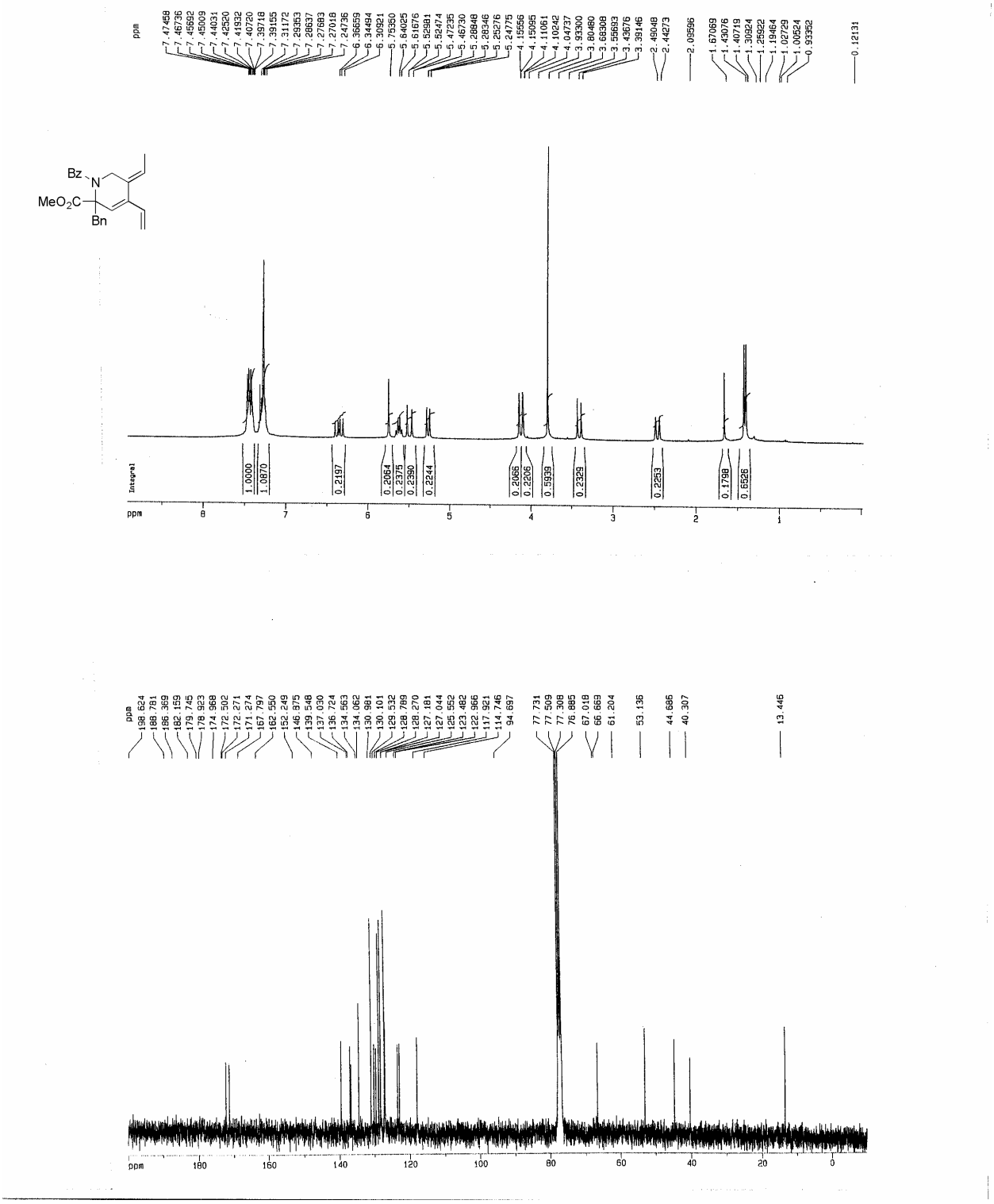
APPENDIX G: ^{1}H NMR and ^{13}C NMR spectra of selected compounds:



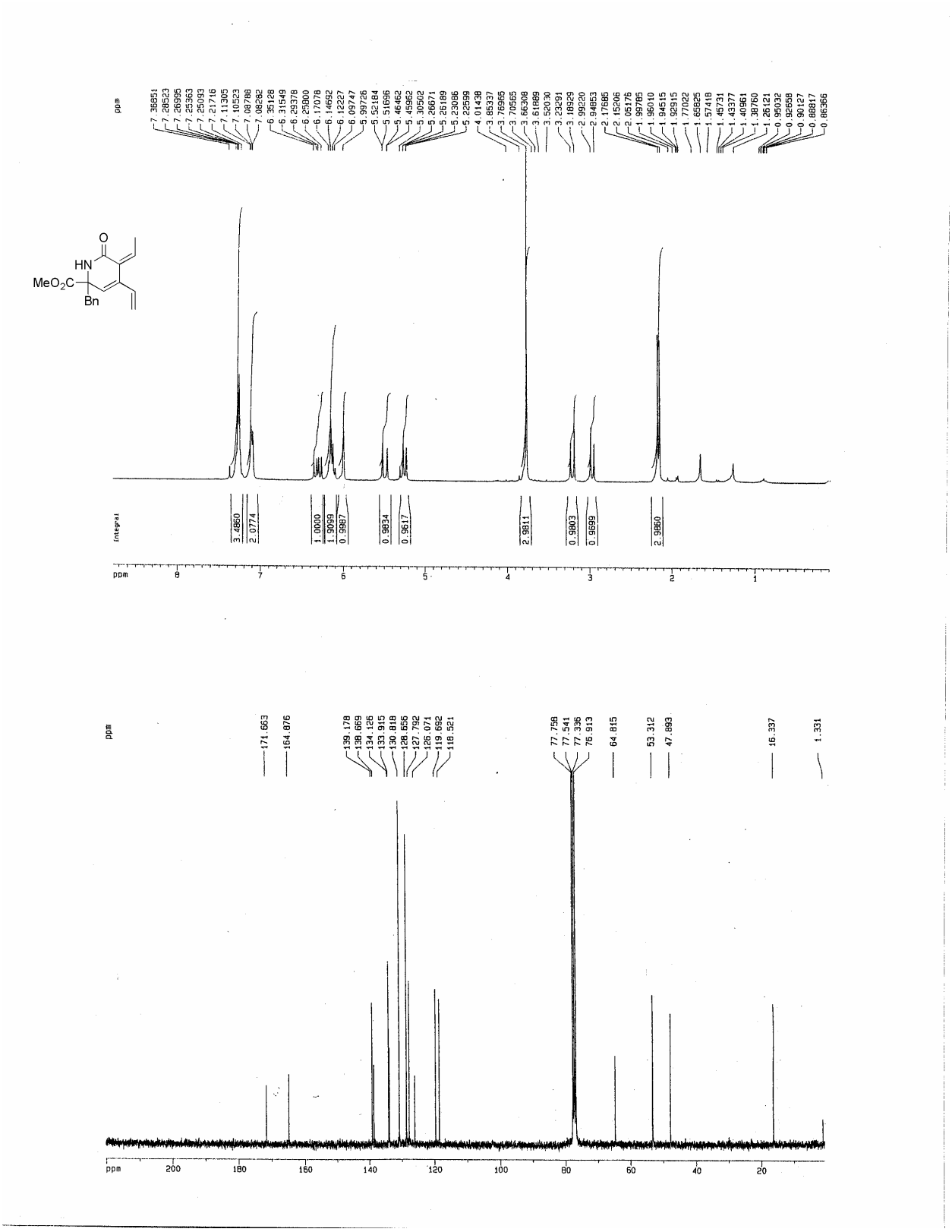
^{1}H and ^{13}C NMRs of **74b**



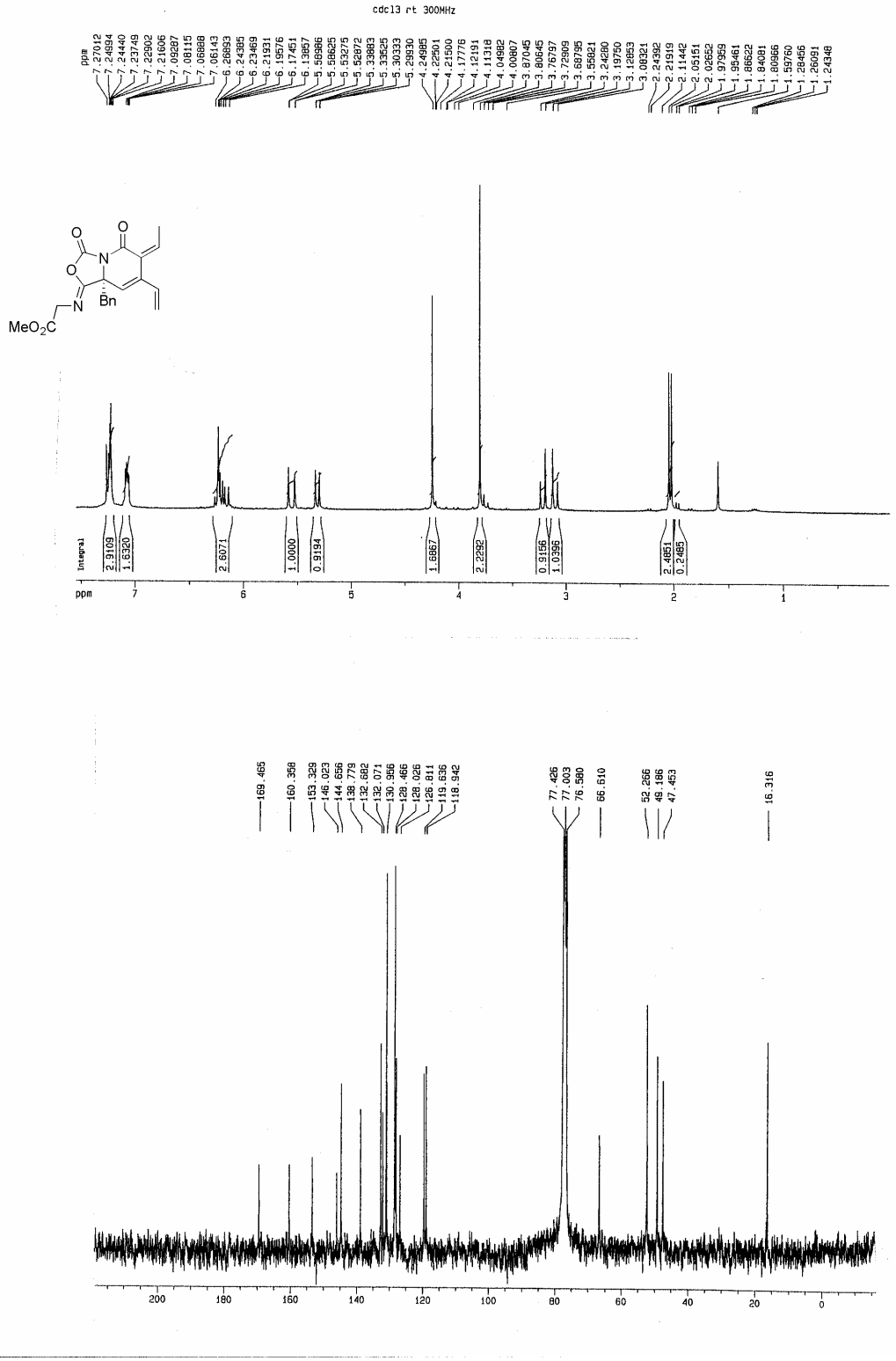
^{1}H and ^{13}C NMRs of **73f**



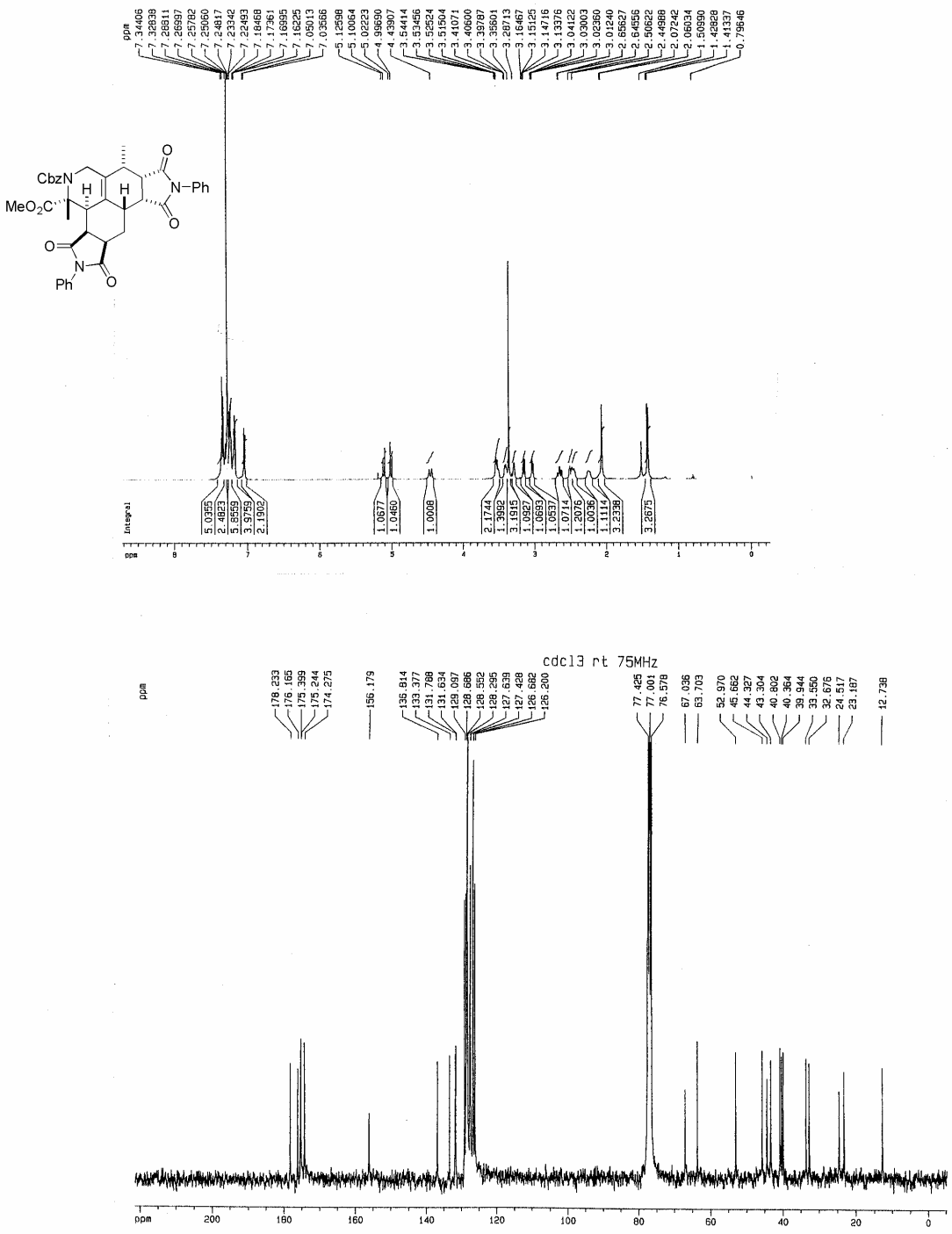
^{1}H and ^{13}C NMRs of **111a**



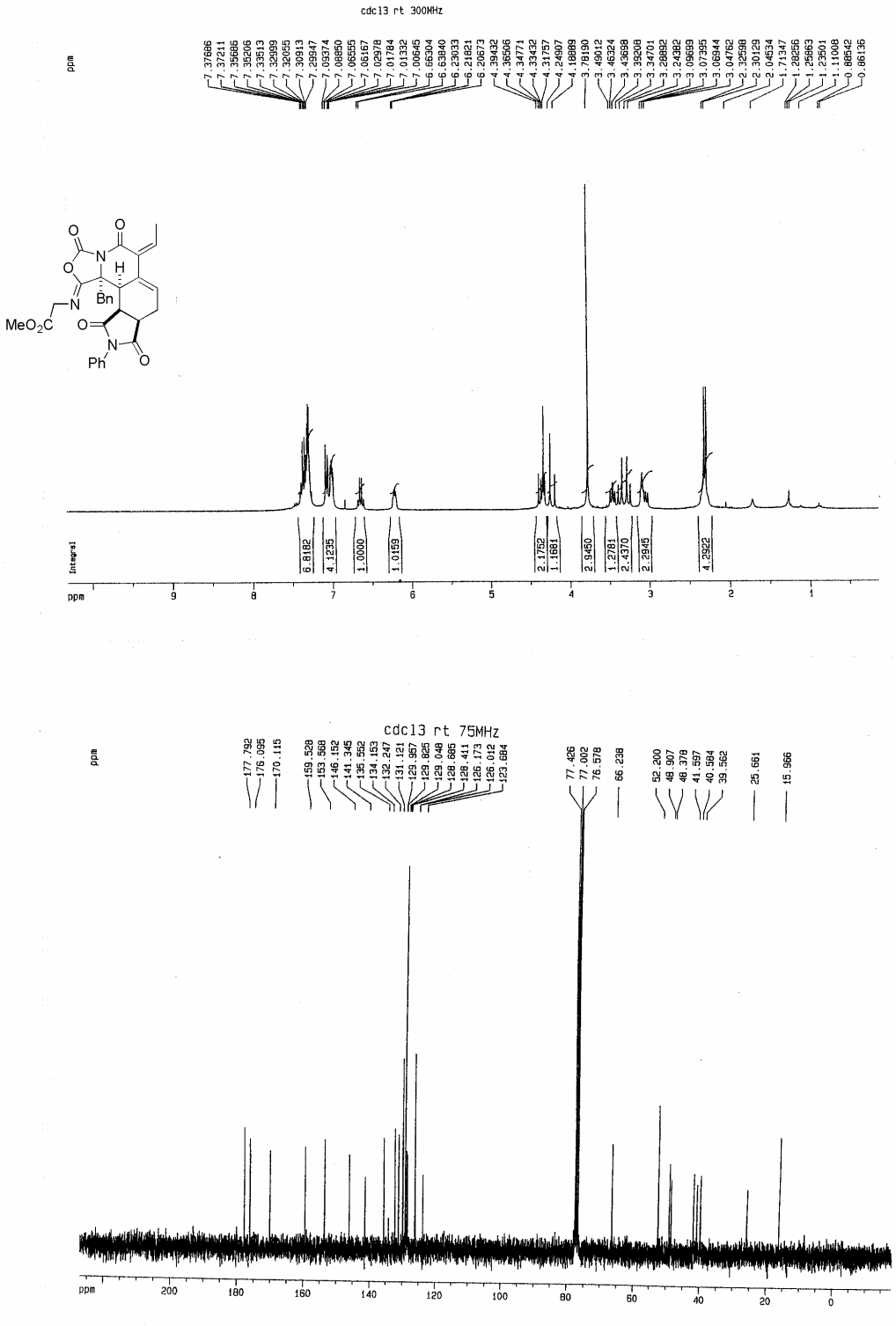
^{1}H and ^{13}C NMRs of **146a**



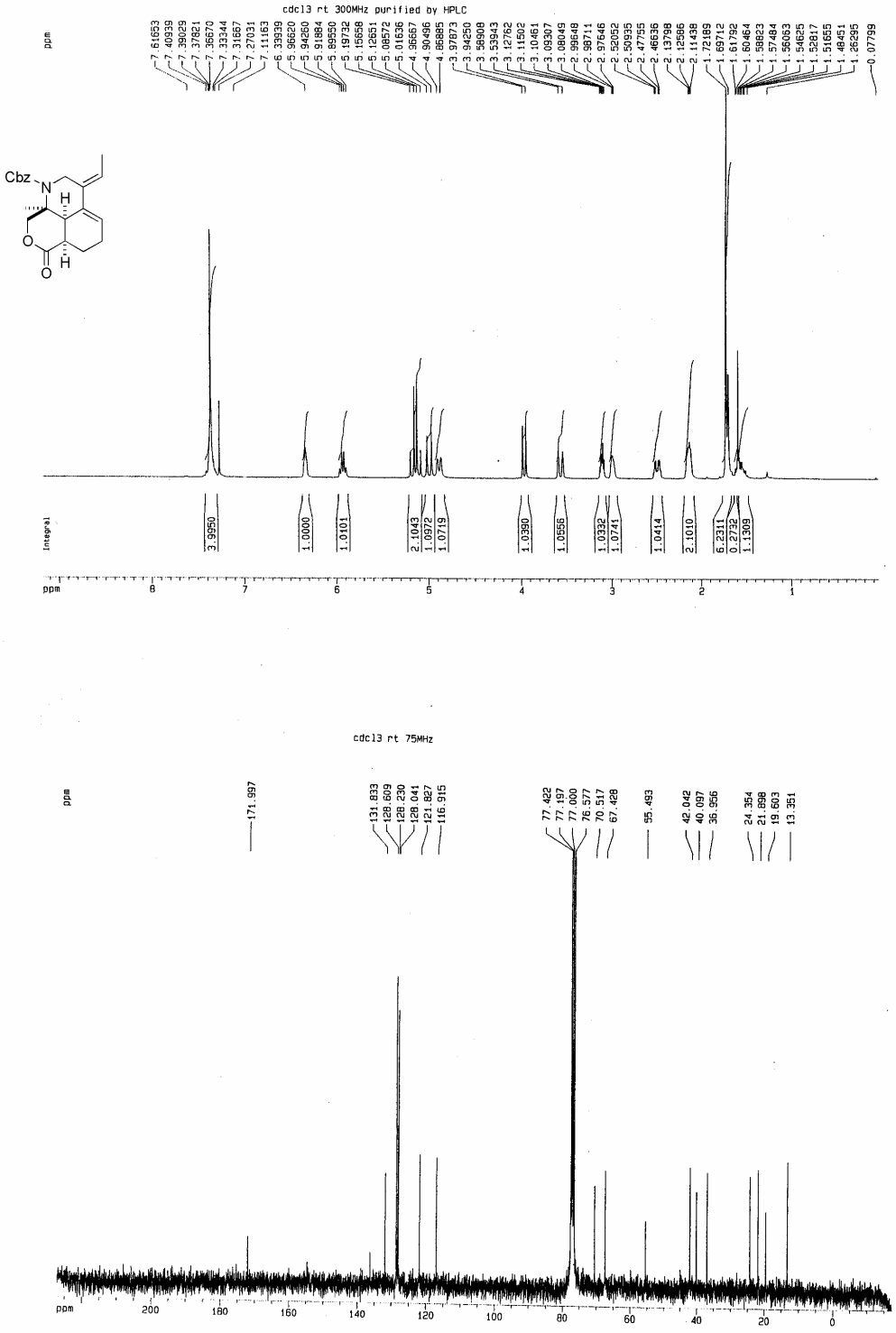
^{1}H and ^{13}C NMRs of **155a**



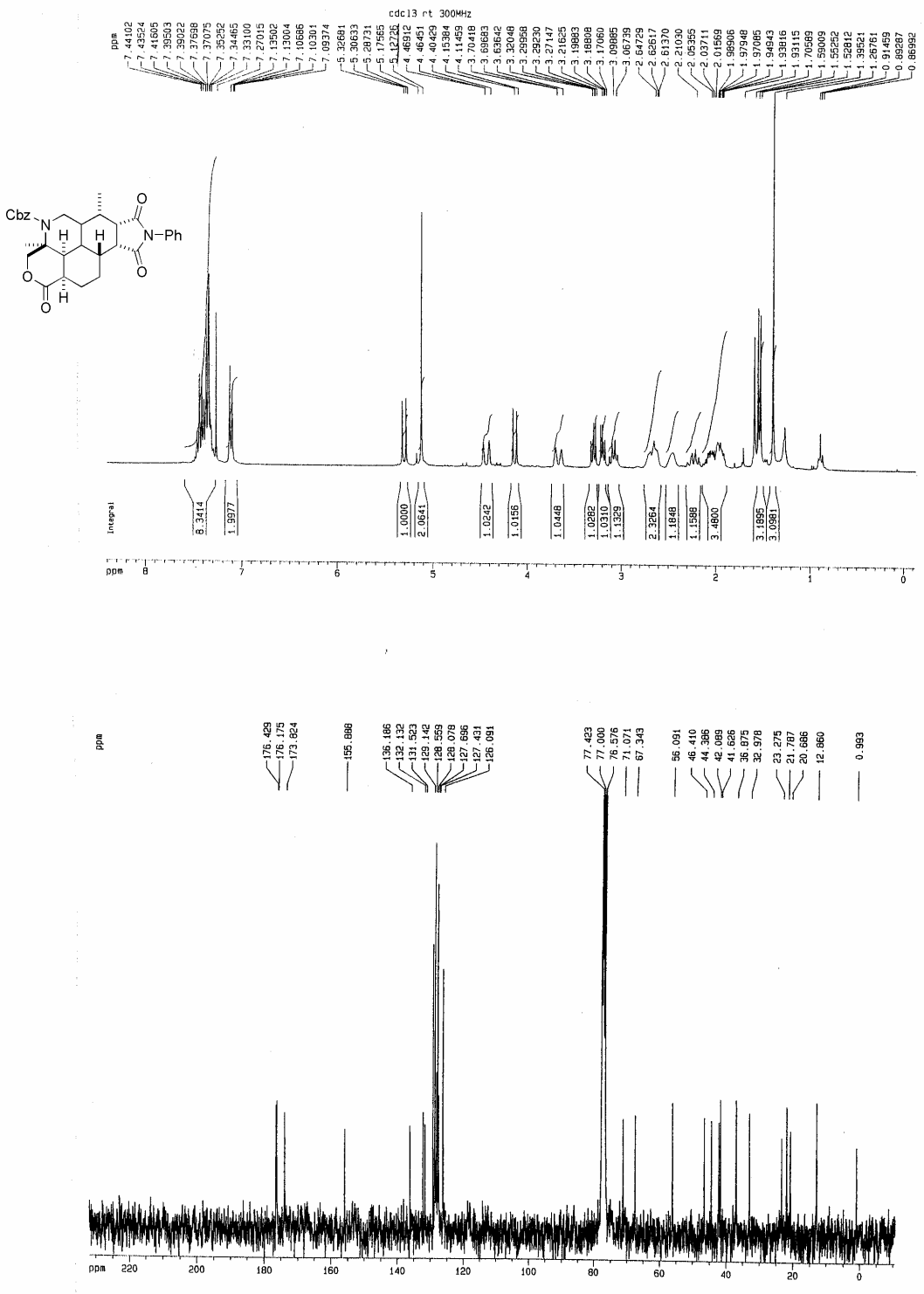
^{1}H and ^{13}C NMRs of **144**



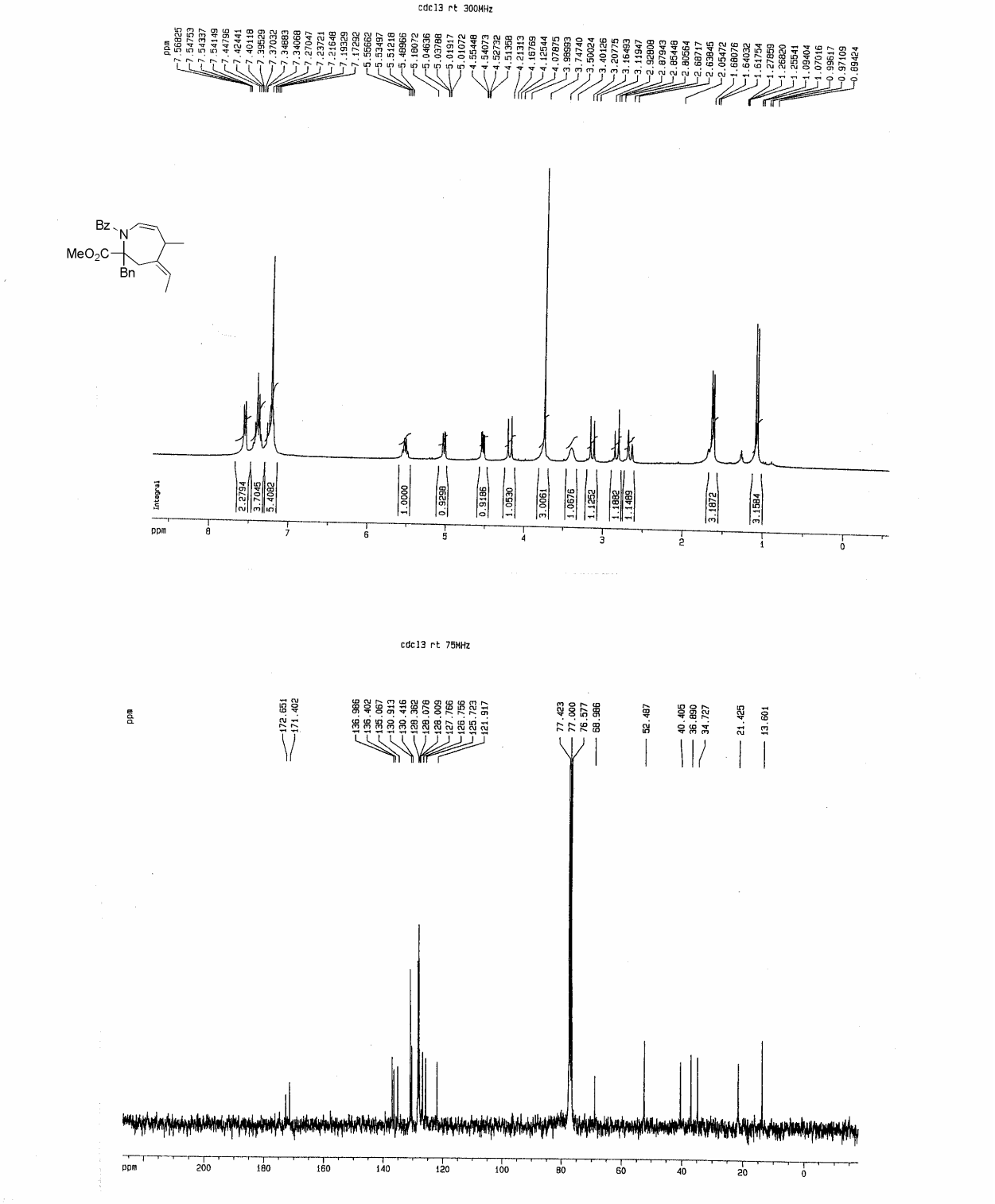
^{1}H and ^{13}C NMRs of **156a**



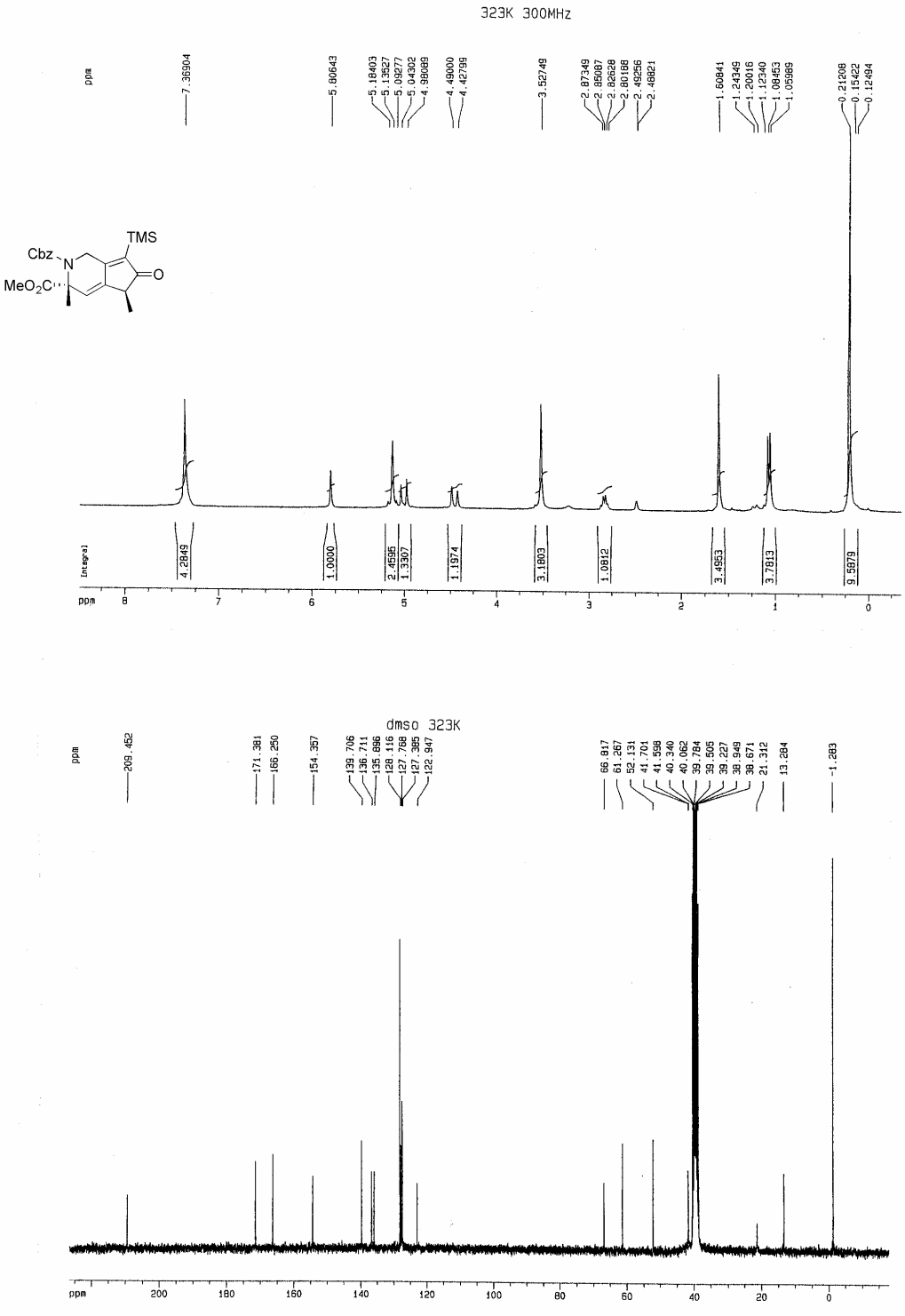
^{1}H and ^{13}C NMRs of **185**



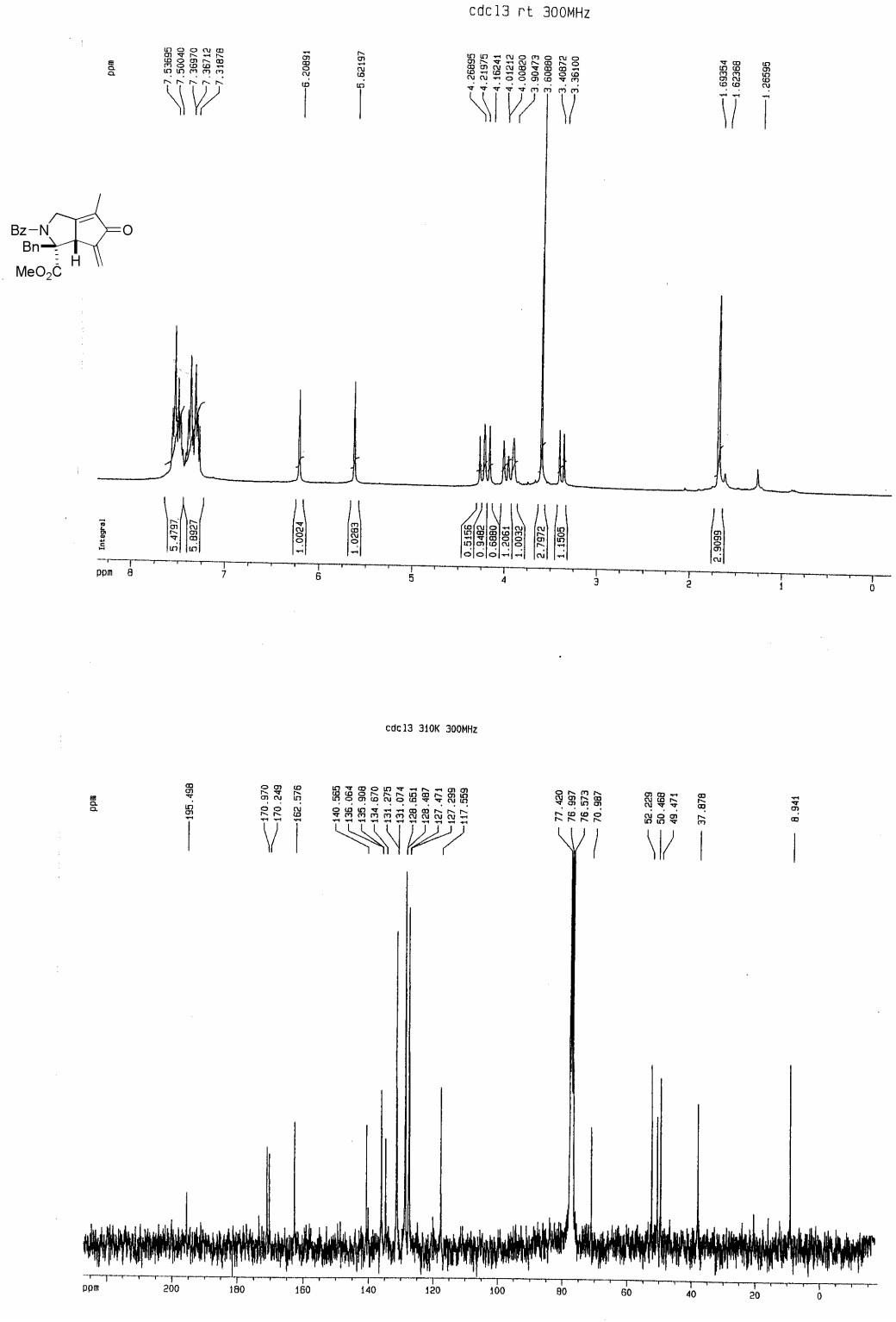
^{1}H and ^{13}C NMRs of **186b**



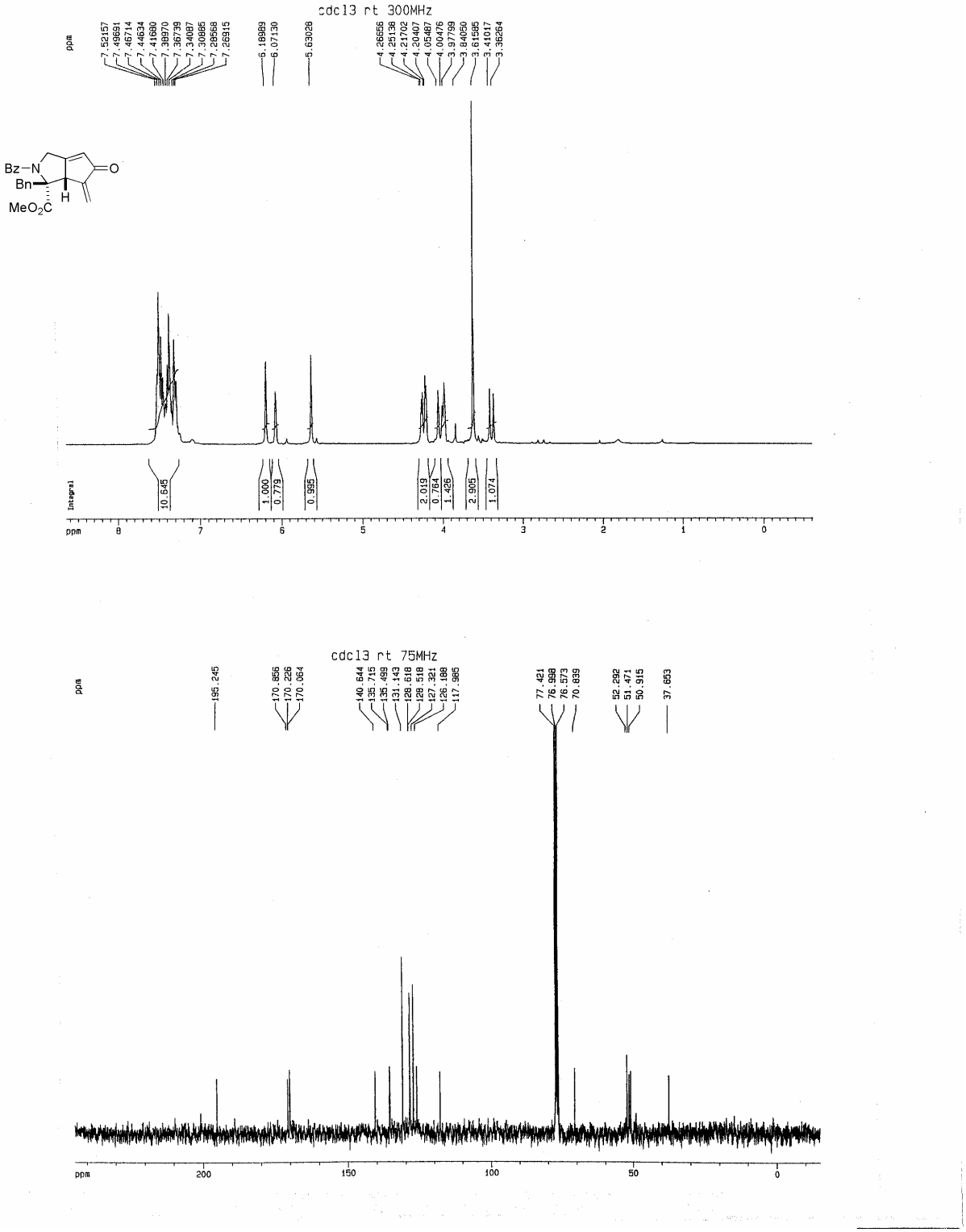
^{1}H and ^{13}C NMRs of **189**



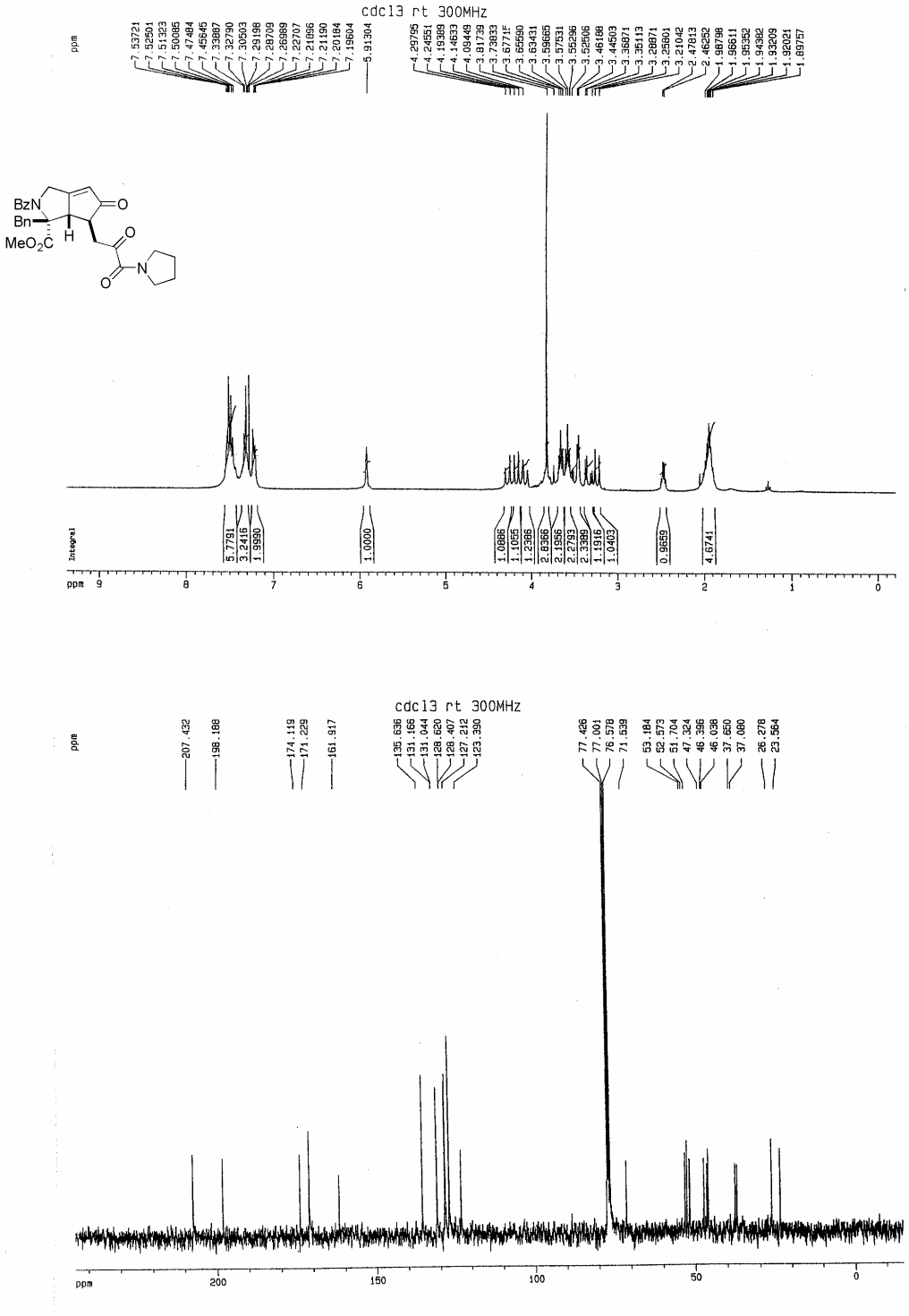
^{1}H and ^{13}C NMRs of **270h**



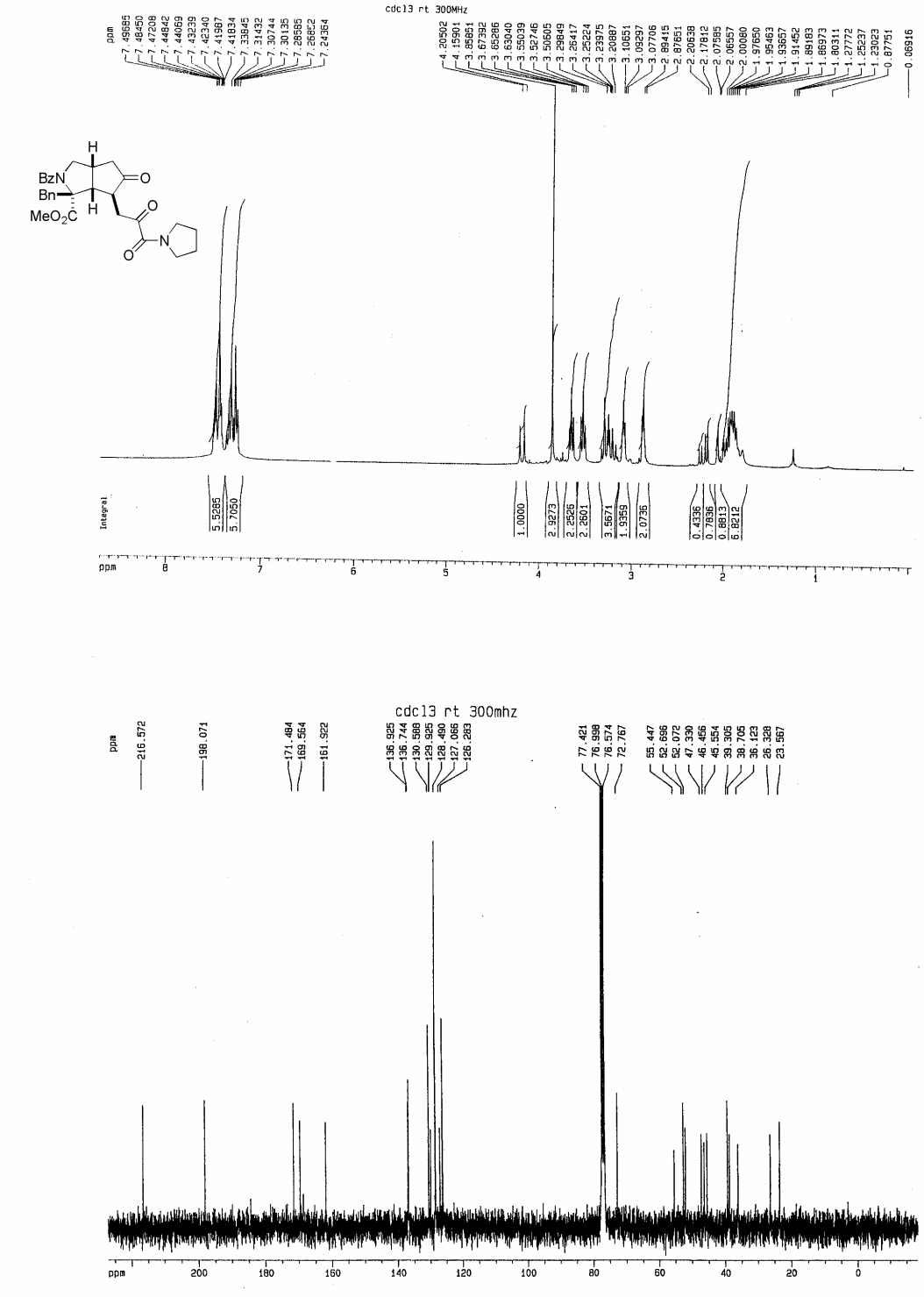
^{1}H and ^{13}C NMRs of **287a**



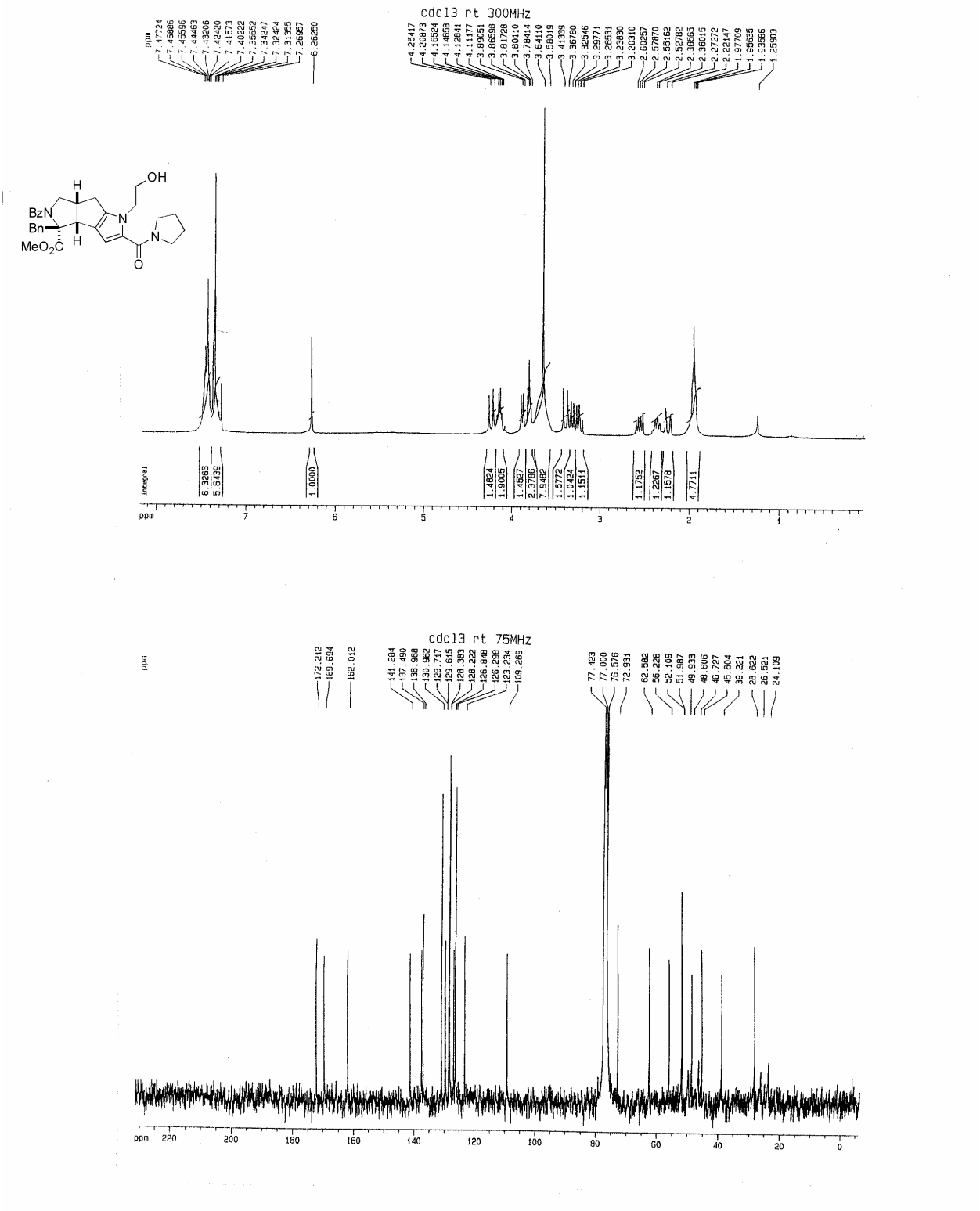
^{1}H and ^{13}C NMRs of **287b**



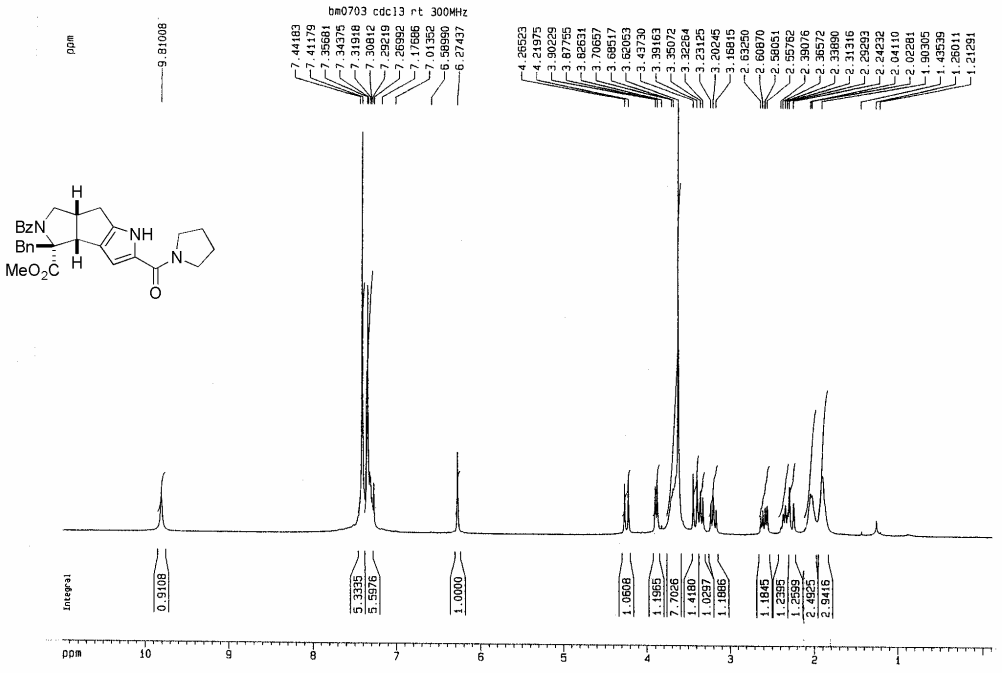
^{1}H and ^{13}C NMRs of **305**

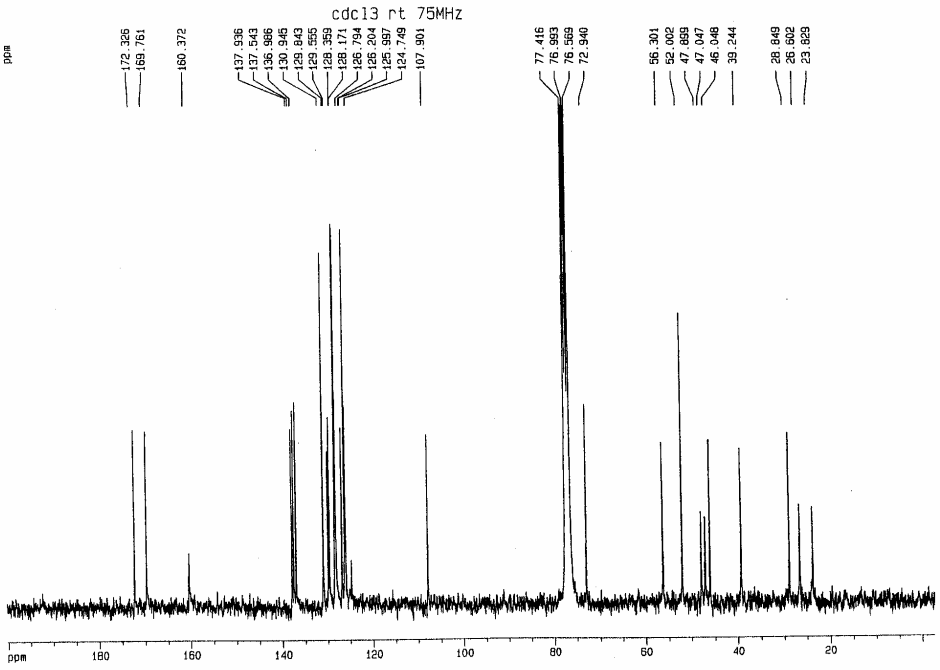


^{1}H and ^{13}C NMRs of **307**



^{1}H and ^{13}C NMRs of **308h**





^{1}H and ^{13}C NMRs of **308n**

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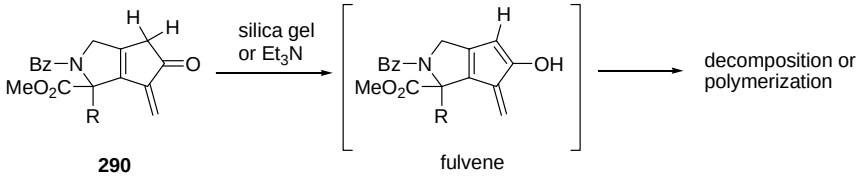

290 fulvene

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