DEVELOPMENT OF LIBRARIES INSPIRED BY SPARTEINE

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Submitted to the Department of Medicinal Chemistry and the Faculty of the Graduate School of the University of Kansas in partial fulfillment of the requirements for the degree of Master of Science.

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Date Defended: December 13, 2011

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ABSTRACT

This thesis describes the development of libraries inspired by the natural product sparteine. Multi-gram synthesis of important intermediate representing sparteine core has been carried out. A scalable process has been developed based on the previously reported total synthesis of (+)-sparteine from Aubé's group. Libraries were produced via parallel synthesis and submitted to NIH Molecular Libraries-Small Molecule Repository for biological screening.

ACKNOWLEDGEMENTS

The completion of this work would not have been possible without the support of the people whom I would like to thank here.

First, I would like to express my deepest gratitude to my advisor, Prof. Jeffrey Aubé, for his excellent guidance, patience, and for providing me excellent facilities for doing research. He is an amazing teacher and a really generous human being.

I would like to thank all the members of the Aubé group for providing a highly supportive and friendly atmosphere, which made it always easier to learn new things while working. In particular, I would like to thank Dr. Thomas Coombs for being a wonderful colleague and friend, and for always being available to answer all my questions.

I would like to sincerely thank Dr. Blake Peterson and Dr. Helena Malinakova for taking time out to serve on my committee. I am also thankful to Dr. Victor Day for X-ray crystallography.

To my mother, Rajinder Kaur, I would like to thank you for being my strength and always encouraging me to continue working towards my goals against all the odds in life.

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

Chapter 1

Introduction

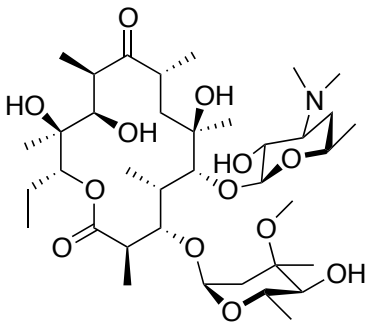
Natural products in drug discovery. Natural products have been used to counter human health problems since thousands of years. The medicinal effects of many natural products like cinchona and digitalis were recognized much before the isolation of their active constituents. Nothing was known about the chemistry of the plants and the applications were based on empirical observation. The traditional and folklore remedies in various cultures were based on using crude plant extracts and are recorded in ancient writings of different cultures (De Materia Medica, Chinese Materia Medica and Indian Ayurveda).[1]

Development of better purification techniques made it possible to isolate the pure biologically active components of natural products. Analytical techniques also made it possible to quantify the bioactivities of these compounds. Health care systems eventually matured to use the pure natural products as clinically validated drugs (e.g. erythromycin, chlortetracyclline, quinine, reserpine) (Figure 1). Discoveries of anti-cancer drug paclitaxel[2] and cholesterol lowering drug mevinolin (lovastatin)[3] are considered very significant achievements along these lines (Figure 1). Medicinally important substances from all kind of natural sources, animals (e.g. exetanide and ziconotide), plants (e.g. elliptinium, glantamine and huperzine) and microbes (e.g. daptomycin) have been derived since then.[4]

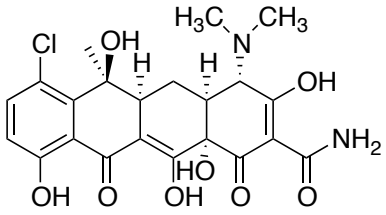
The advent of X-ray crystallography and later highly advanced techniques like NMR spectroscopy, have often led to the determination of the intricate structures of natural products. These structures provided an intriguing challenge to the organic chemist who was testing his scientific skills and hypothesis by constructing simple organic molecules. Since then, natural

product synthesis has come a long way. The field of organic synthesis, which started with the synthesis of urea, has achieved the milestones of synthesizing natural products like strychnine[5] in

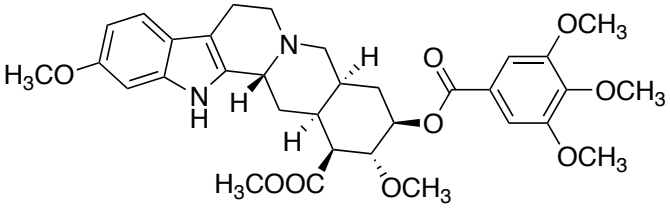
Figure 1. Natural product drugs



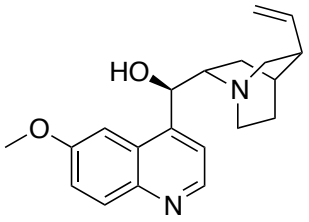
erythromycin



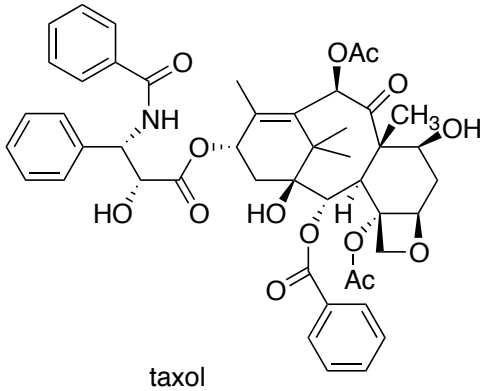
chlortetracyclline



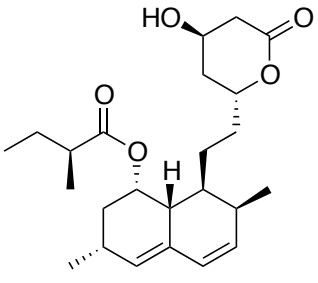
reserpine



quinine



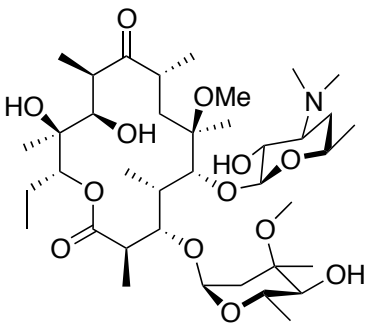
taxol



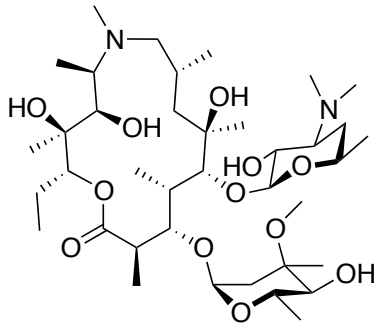
mevinolin

the mid-1950s and molecules like taxol[6] and calicheamicin[7] in recent years. The knowledge and skills gained along the way had significant impact on the area of drug discovery. Scalable synthetic routes were developed for the natural product drugs, which were not available in required quantities directly from natural resources or via fermentation processes. Two very noticeable achievements in this direction were the development of a scalable synthetic route to thienamycin[8] in 1981 and discodermolide[9] in recent years. Semi-synthesis of natural products provided drugs with improved pharmacokinetic and biological profile (e.g. clarithromycin, azithromycin, tigecycline, naloxone) (Figure 2).

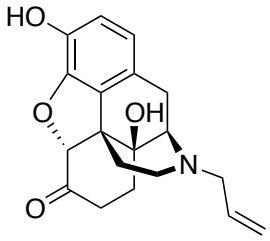
Figure 2. Semi-synthetic analogues of natural products



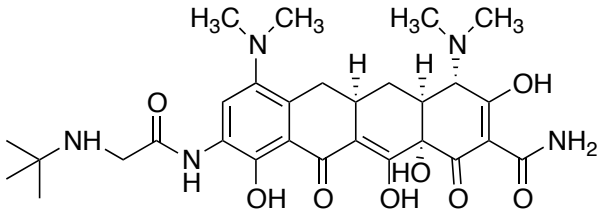
clarithromycin



azithromycin



naloxone



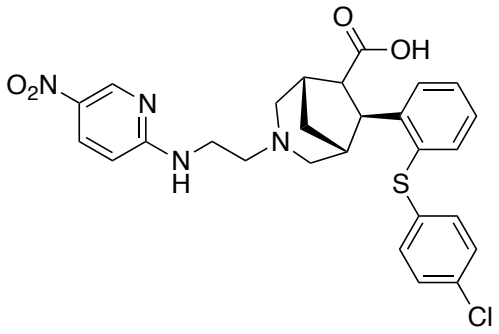
tigecyclline

An increasing understanding of molecular biology and the mapping of human genome revealed various new biological targets of both fundamental and therapeutic interest.[10] Researchers in both academics and industry began to explore therapeutic potential of newly revealed biological targets by developing libraries of small molecules for biological screening. With an aim of quickly building larger diverse libraries, the attention of the pharmaceutical industry moved away from natural products, which are often challenging to purify, structurally complex and available in only small quantities. The development of combinatorial chemistry offered the prospect of rapidly generating simpler, more drug-like screening libraries of wide chemical diversity. However the majority of the libraries examined was ineffective and provided disappointingly low hit rates.[11] This outcome suggested that random sampling of chemical space might not be an effective solution to target complex biological targets. Early libraries were generally designed on the basis of chemical accessibility and maximum achievable size. Theoretical calculations show that a complete set of possible small molecules is on the order of $10^{30} – 10^{200}$.[12] However, considering that at the molecular level biological systems work under strict solubility and structural constraints, only a small portion of this bewildering number may be relevant to biology. It has been a difficult but important question to answer that which regions of chemical space should be targeted to probe biology.

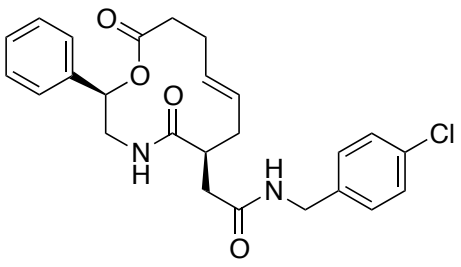
Natural product based libraries It is possible that many unsuccessful libraries underrepresented most of the natural product and metabolite scaffolds.[13] Hence, unmet expectations from completely synthetic libraries, and the historical role of natural products in human therapeutics, prompted a renewed interest in natural products as a source of chemical diversity and lead generation. Since small molecule natural products are biosynthesized under enzymatic control, these may have structurally evolved to interact with conserved protein

domains.[14] Hence compounds based on natural product scaffolds may be biologically relevant. However, the evolutionary reason behind the production of natural products is not therapeutic so these compounds may not have the optimal features needed for a drug candidate and must undergo additional structural modifications.[15] Recently, libraries based on underrepresented scaffolds and natural products have led to several successes in identifying novel chemical probes for various biological targets.[16] For example, Schreiber and coworkers discovered robotnikinin (Figure 3), a 12-membered macrocycle, an inhibitor of hedgehog signal transduction pathway, following screens of a 2070-membered macrocycle libraries based on natural product scaffolds.[17] Spring and coworkers identified gemmacin (Figure 3), a new antibacterial agent from a 242-membered library of 18 natural product-like scaffolds.[18]

Figure 3. Examples of leads based on natural product scaffolds



gemmacin

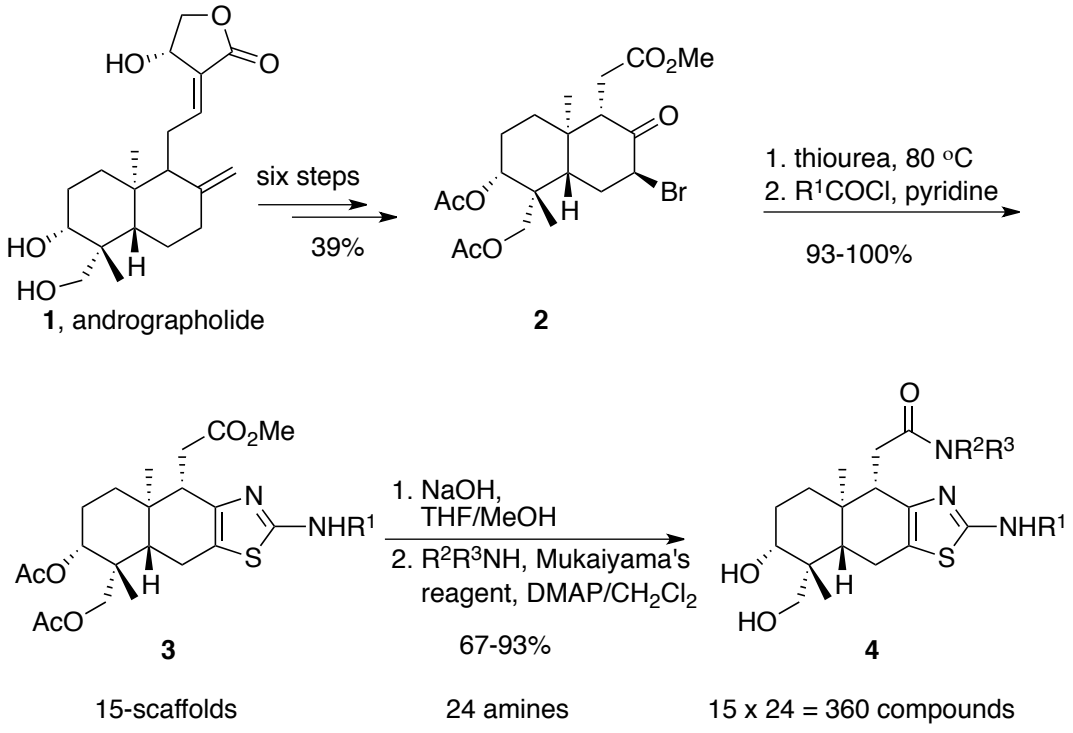


robotnikin

Development of libraries based on natural product scaffolds has been differentiated into two categories based on different synthetic requirements: Natural product derived libraries and natural product inspired libraries.[19] In the case of **natural product derived** libraries, the library scaffold is identical to the core of a leading natural product and is generally obtained by chemical modification of the isolated natural product rather than multistep synthesis. Diversification of the

scaffold depends upon the reactive functional groups of the natural product and stereochemical diversity (e.g., access to the opposite enantiomer) is generally not available. The library is developed by derivatization of the existing scaffold. The andrographolide-derived library shown in Scheme 1 is illustrative.[20] Andrographolide **1** was transformed into intermediate **2** via a six-step synthetic sequence in 39% overall yield. Compound **2** was treated with thiourea in pyridine resulting in a fused aminothiazole ring system, which was subjected to *N*-acylation with fifteen different acid chlorides to produce the scaffolds **3**. Alkaline hydrolysis of **3** led to dihydroxy carboxylic acids, which on activation with Mukaiyama reagent, followed by treatment with a set of twenty-four amines generated the 360-compound library **4**.

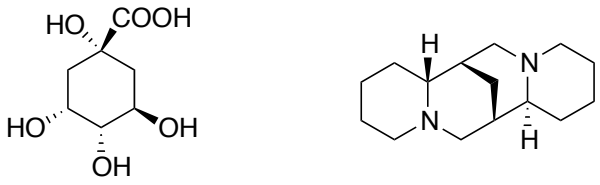
Scheme 1. Synthesis of andrographolide-derived library



Though the above-mentioned approach gives an advantage of quickly launching a multidimensional diversity campaign, it is limited by the following factors,

1. Availability of significant amounts of pure natural product, which is often problematic especially for newly-discovered natural products.
2. Multifunctional natural products present a challenge of chemoselectivity, so introducing desired modifications may not be practical (e.g., polyhydroxy natural products like quinic acid) (Figure 4).
3. Absence of reactive functional groups may also limit the scope of library synthesis (e.g., sparteine) (Figure 4).
4. The scope of introducing new stereocenters is limited by the inherent geometry and steric environment of the natural product core.
5. Unstable natural products under certain reaction conditions lead to complicated mixtures of products.

Figure 4. Examples of multi-functional and non-functional natural products

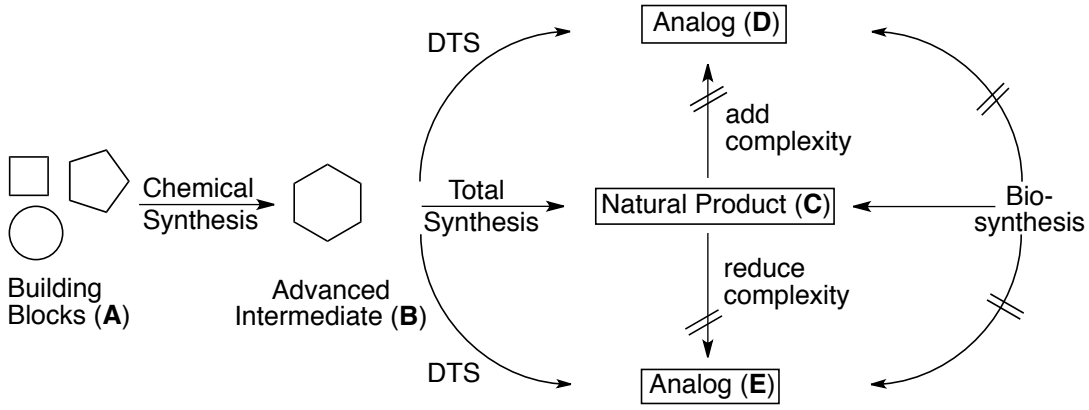


quinic acid (–)-sparteine

The diverted total synthesis **(DTS)**[21] approach of Danishefsky addresses these shortcomings. In this approach, which leads to a natural-product-inspired library, the scaffold is closely related, but not identical to the guiding natural product. The proposed scaffold is synthesized *de novo* by multistep synthesis. As depicted in Figure 5, one can anticipate the

desired future modifications earlier in the synthesis from an advanced intermediate **B** and can omit potentially troublesome moieties that might interfere with proposed biological applications or which could be problematic for the final molecular modifications. It provides a major advantage by allowing access of analogues with higher structural complexity (analogue **D)** or lower level of molecular complexity (analog **E**) than the natural product scaffold (**C**) under consideration. This, in turn, allows chemists to explore a wider chemical space not available by starting with the natural product itself.

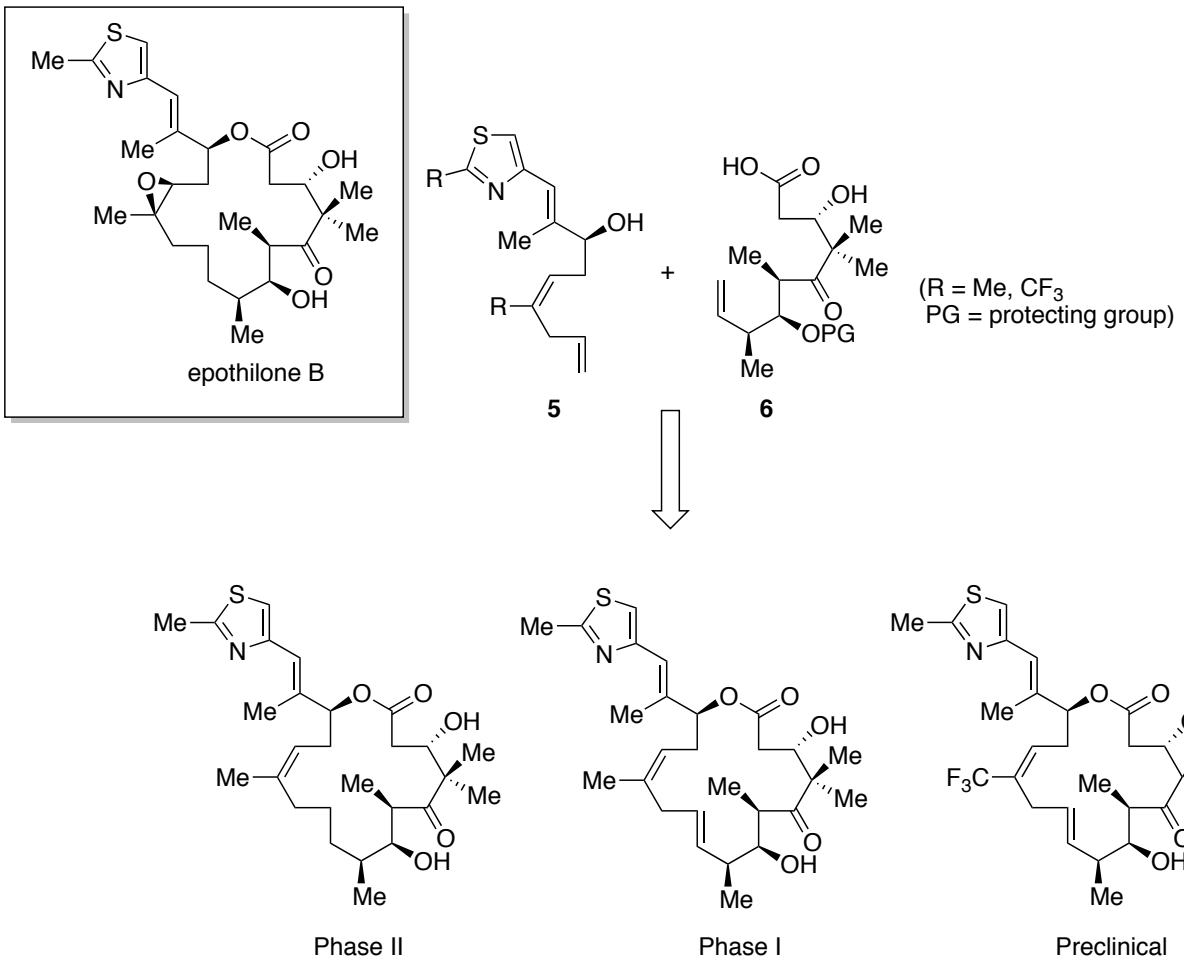
Figure 5. Danishefsky's diverted total synthesis (DTS)



Several natural-product inspired libraries have been reported in recent years. An illustrative example is the DTS of the epothilones from Danishefsky's group as shown in Figure 6.[22] Epothilone B is a natural product isolated from the *Sorangium cellulosum* myxobacterium and exhibits cytotoxicity through stabilization of microtubule polymerization. Synthetic analogues based on the epothilone framework were synthesized using esterification followed by ring closing metathesis of pre-organized fragments **5** and **6** as assembling steps. Many of these

analogues were highly potent against different cancer cell lines and are currently under preclinical or clinical evaluation.

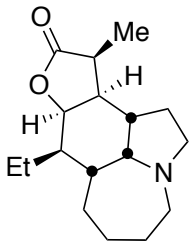
Figure 6. Diverted total synthesis of epothilones



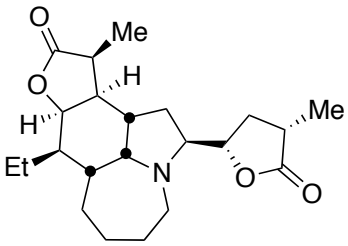
The Aubé group has focused on the chemistry of organic azides for many years and has demonstrated their utility by devising useful methodologies for natural product synthesis. Along these lines they have reported two total syntheses of stenine along with a route to the isomeric alkaloid neostenine (Figure 7).[23,24] Inspired by the rich biological profile of stemona alkaloids, a collection of stemona alkaloid analogues was generated.[25,26] A Diels-Alder/Schmidt reaction

sequence provided straightforward access to the tricyclic core of the stemona alkaloids (Scheme 2). Systematic chemical manipulation combined with parallel synthesis produced 104 analogs for 41-panel GPCR screening. This library campaign ultimately resulted in the identification of a highly potent class of sigma ligands.

Figure 7. Stenine alkaloids

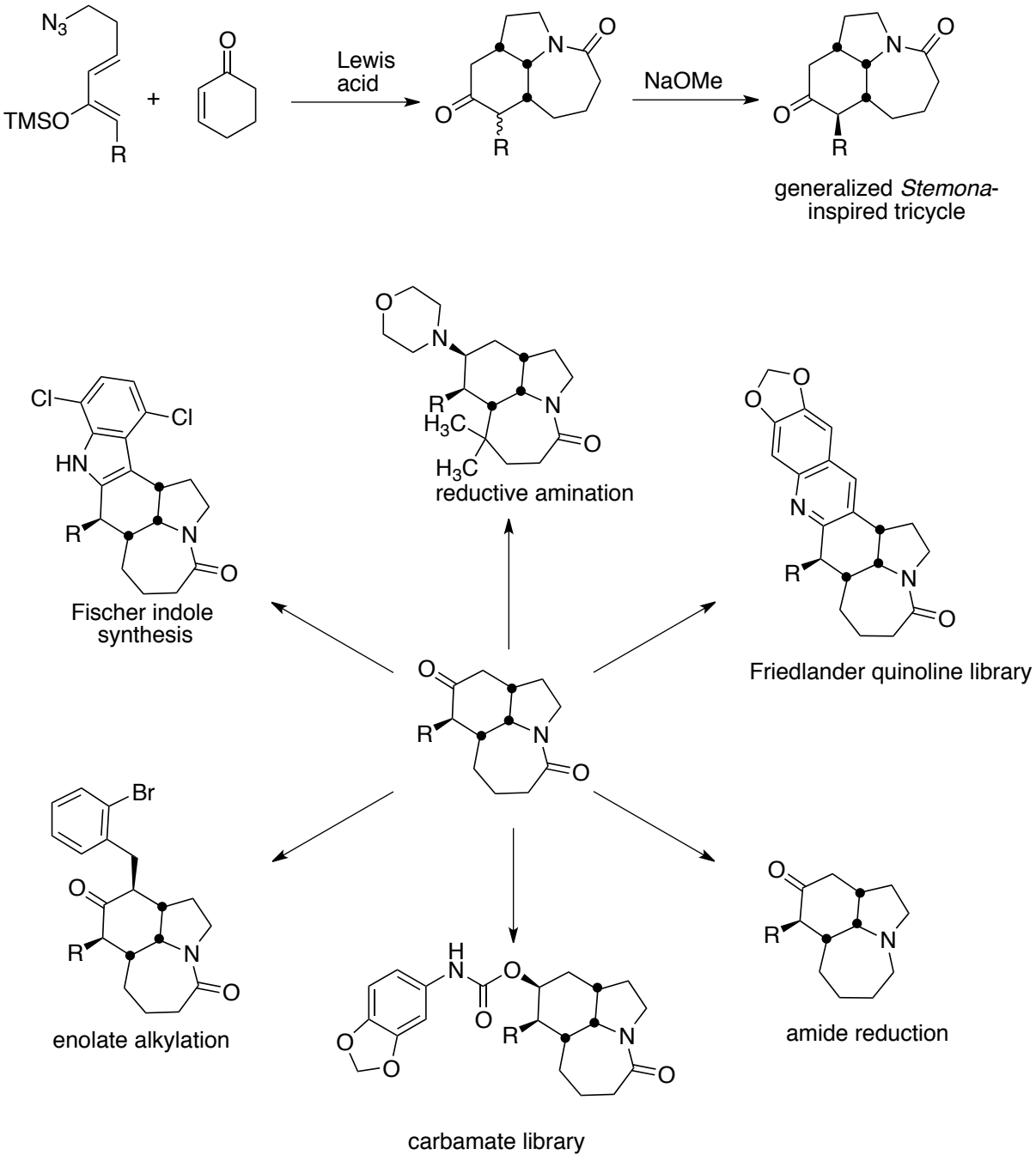


neostenine



neotuberostenine

Scheme 2. Synthesis of stemona alkaloid inspired analogues

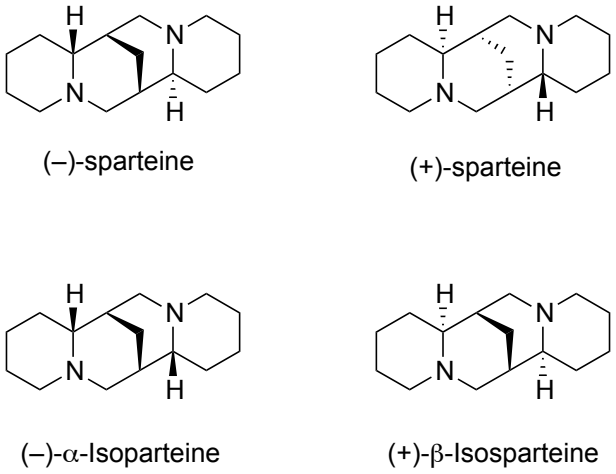


The outcome of the stenine library provides recent evidence that libraries based on natural products having rich biological profiles may provide potent ligands or probes for biological systems. Inspired by the results of the stenine library, we envisioned that the natural product sparteine would be an interesting starting point for library development for the following reasons: (1) Sparteine has a rich biological profile and (2) an effective route to the sparteine scaffold based on a previously reported total synthesis from this group.

Sparteine

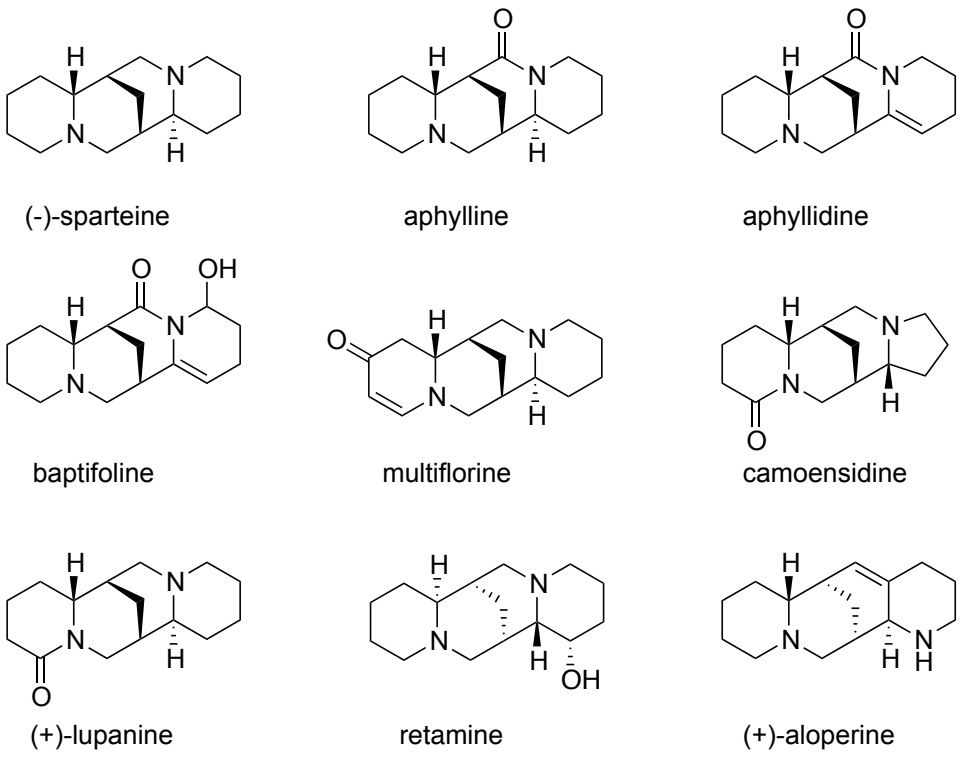
Introduction: Sparteine is a lupidine alkaloid, isolated from *Cytisus scoparius* (scotch broom) in 1851 by Stenhouse.[27] It exists as four isomers as depicted in Figure 8. It has also been identified in many papilionaceous plants. However, (+)-sparteine is much less abundant.

Figure 8. Naturally occurring sparteine isomers



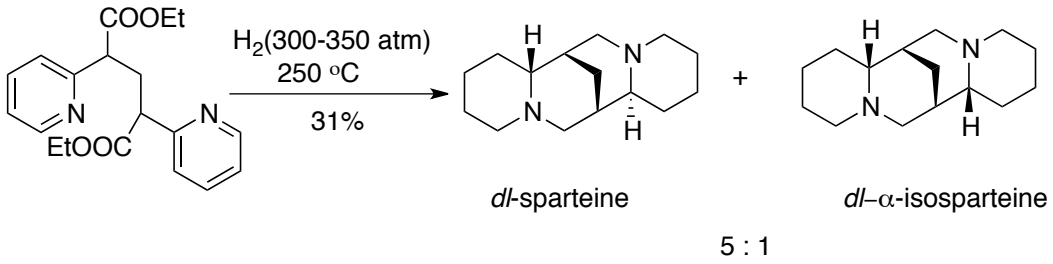
Biological activity of (−)-sparteine and other lupine alkaloids. The alkaloid (−)-sparteine has a rich biological profile that includes nicotinic ester antagonism,[28] application as a profiling agent in metabolic studies,[29] and clinical use as an antiarrythmic[30] agent. Other members of the lupanine class of alkaloids (Figure 9) also exhibit activity against muscarinic and nicotinic receptors. Cytisine (Tabex®) and vereniciline (Chantix®, a drug designed based on cytisine) have been used in Europe for smoking cessation due to their agonist activity against α4/32-nAChR.[31]

Figure 9. Other lupanine alkaloids structurally related to sparteine



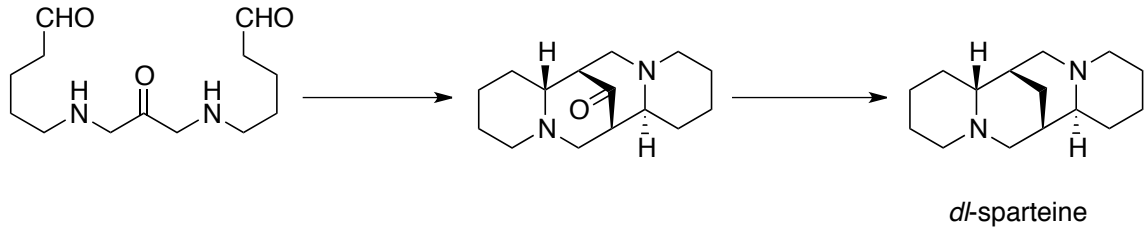
Sparteine syntheses. To the best of our knowledge, four racemic syntheses of sparteine have been reported to date. In 1950, Leonard and Byler accomplished the first racemic synthesis of sparteine using reductive alkylation of 2,4-di (α-pyridyl)-glutarate as the key step (Scheme 3).[32] The synthesis led to a 5:1 mixture of *dl*-sparteine and *dl*-α-isosparteine with a combined yield of 31%.

Scheme 3. Leonard and Beyler's synthesis of *dl*-sparteine



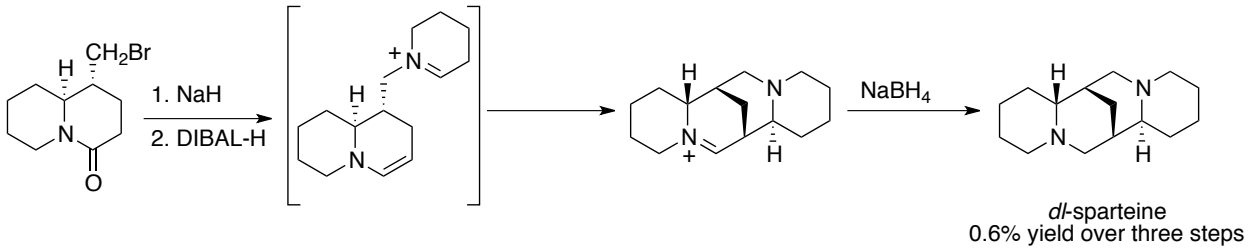
Van Tamelen and Foltz reported another racemic synthesis in 1960.[33] Their key step involved cyclization of the diaminoketoaldehyde, followed by *in situ* cyclization under mercuric acetate hydrogenation conditions (Scheme 4**)**. However, there was no explanation of the selectivity or the yield of the synthesis.

Scheme 4. Van Tamelen and Foltz's synthesis of *dl*-sparteine



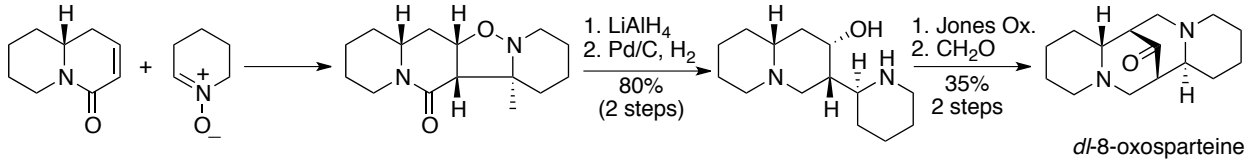
Bohlman and coworkers accomplished the synthesis of dl-sparteine in 0.6% overall yield via intramolecular cyclization of an enamine-imminium ion intermediate (Scheme 5).[34]

Scheme 5. Bohlmann's synthesis of *dl*-sparteine



A formal synthesis was reported from Otamasu's group in 1987.[35] They synthesized *dl*-8-oxosparteine by lactam/nitrone cyclization and a Mannich reaction with formalin as key steps in the synthesis (Scheme 6).

Scheme 6. Otamasu's synthesis of *dl*-8-oxosparteine

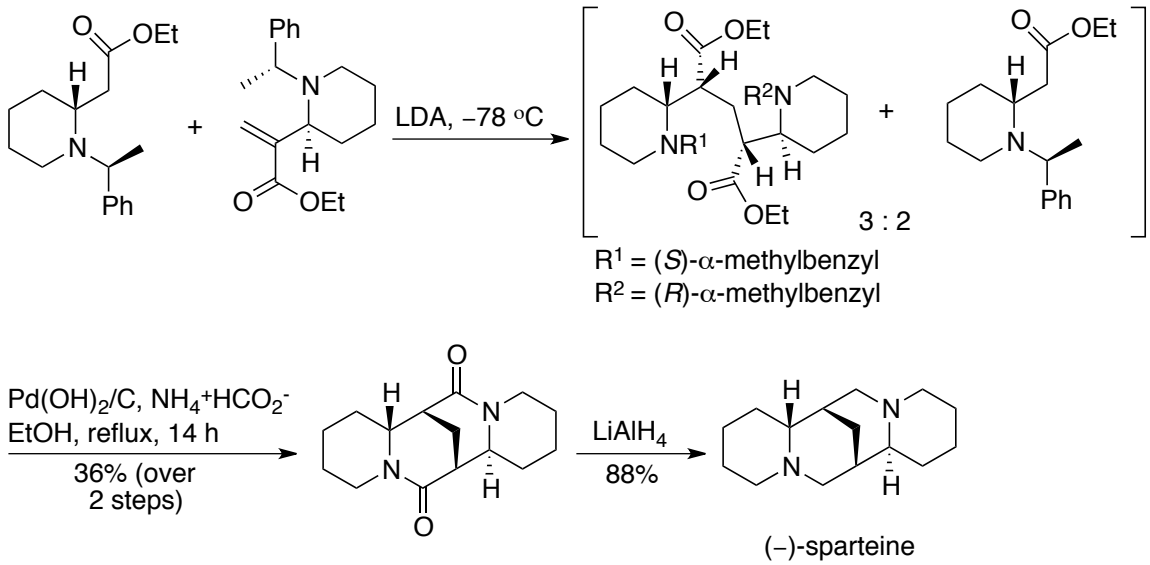


(−)-Sparteine has found extensive applications as a chiral ligand for asymmetric deprotonations, oxidations, conjugate addition, and other asymmetric reactions.[36] As discussed above (−)-sparteine is easily obtained from papilionaceous plants such as scotch broom and is commercially available. (+)-Sparteine, was highly desired as a chiral ligand in asymmetric synthesis. However, though (+)-sparteine is also naturally occurring, it is not present in large

quantities from natural products. There was no total synthesis of (+)-sparteine [or (–)-sparteine] reported before 2002.

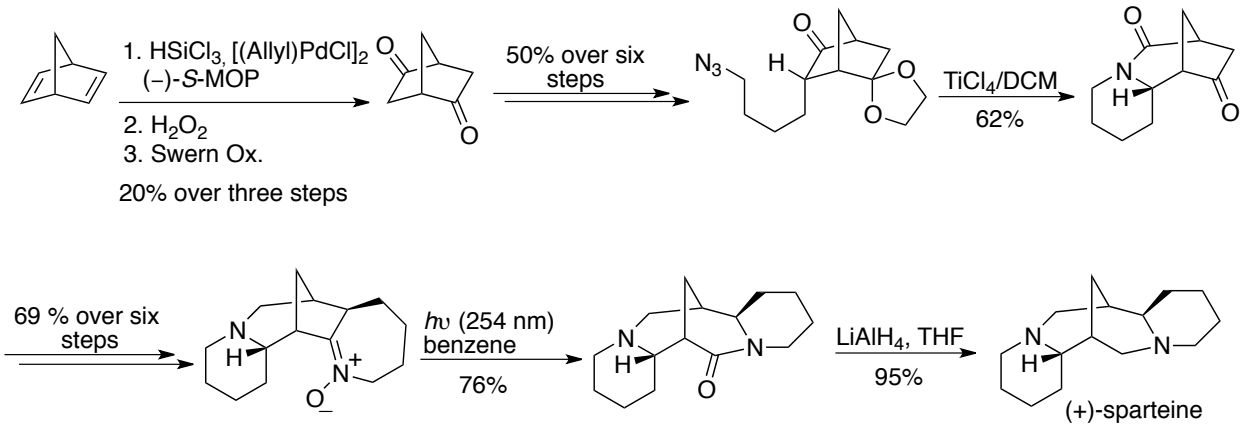
Two reports of the asymmetric synthesis of sparteine have appeared between 2002 and the present. In 2004, O'Brien reported an asymmetric synthesis of (–)-sparteine from ethyl-7-iodohept-2-enoate (Scheme 7).[37] The key feature of the route is a Michael reaction between an amino ester-derived enolate and a α,β-unsaturated amino ester.

Scheme 7. O'Brien's asymmetric synthesis of (–)-sparteine



In 2002 Aubé and co-workers reported the first asymmetric synthesis of (+)-sparteine in 15 steps and 15.7% overall yield from optically pure (1*S*, 4*S*)-2,5-norbornadione.[38] The total synthesis was accomplished from 2,5-norbornadione via two ring-expansion reactions, one involving an intramolecular Schmidt reaction and other one using a novel variant of the photo-Beckmann rearrangement as key steps (Scheme 8). The required chiral diketone was prepared via a three-step reaction sequence involving a chiral hydrosilation method developed by Hiyashi as a key step.[39] As either of the enantiomers of 2,5-norbornadione can be prepared by this method using the opposite ligand, both enantiomers of sparteine can be prepared in optically pure form by using the following synthetic route.

Scheme 8. Aubé's asymmetric synthesis of (+)-sparteine



In summary, for many years natural products have been a source of inspiration, both for discovering new drugs and for the fundamental advancement of chemistry and biology. Recent developments indicate that small molecule libraries based on natural product scaffolds have tremendous potential for finding new probes for biological systems.

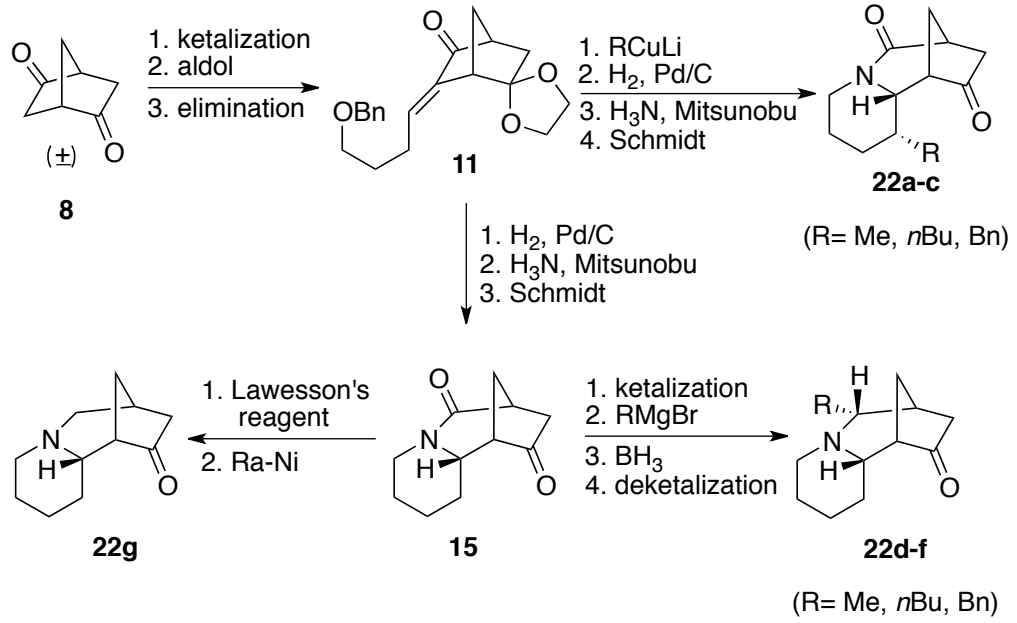
Inspired by the success of the stenine project and based on the rich biological profile of sparteine, we hypothesize that libraries inspired by the sparteine scaffold may be of considerable interest for biological exploration. The present work is focused on developing small libraries based on the sparteine scaffold and will be discussed in detail in the following chapter.

Chapter 2

Results and Discussion

The work reported in this thesis is focused on developing a collection of compounds based on the sparteine scaffold. Though scalable routes to racemic or asymmetric sparteine are available, it would be less desirable to launch a library directly from sparteine as starting point because of two reasons: (1) the absence of reactive functional groups and (2) even if one introduces the reactive groups, the scope of diversity will be very limited and so will be the probability of finding small molecules with novel biological properties. Based on analysis of the previously reported synthesis by Wendt and Smith from this group, we envisioned that by careful chemical manipulations of the advanced intermediates **11** and **15** as depicted in Scheme 9, it would be possible to gain access to the scaffolds **22a - g** related to the sparteine core.

Scheme 9. Synthetic plan for the synthesis of scaffolds



The aim of this work was to develop a 120-compound library for biological screening based on the above-proposed plan. From the strategic point, in this part of the work we have targeted racemic compound library. Depending upon the biological results of these compounds, focused enantio-pure libraries can also be generated using above methodology starting from the optically pure 2, 5-norbornadione. We have generated a library of 120 compounds following the racemic synthesis in following three phases,

1. Scale-up of the intermediate **15**
2. Gram scale synthesis of scaffolds **22d-g**
3. Development of library via parallel synthesis

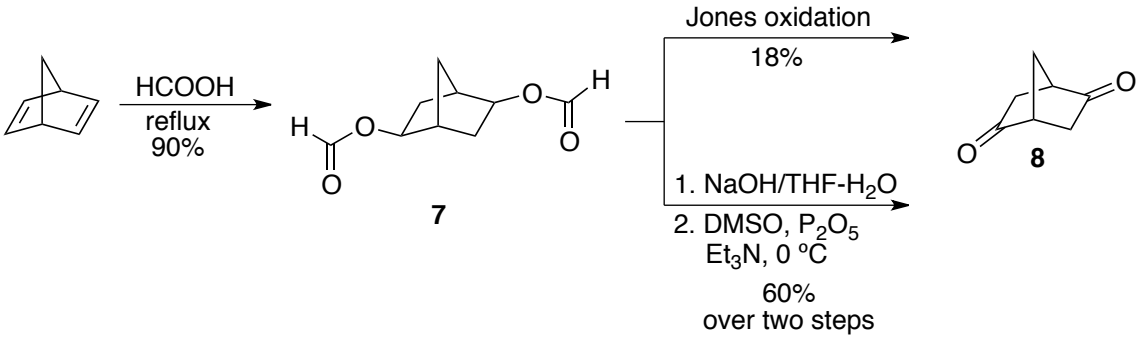
Racemic synthesis of the C2-symmetric diketone 8 (Scheme 10). The racemic synthesis of lactam **15** can be accomplished in 9 steps from norbornadiene as reported by Smith and Wendt. We have introduced a few modifications to the existing route for large-scale synthesis and will be discussed as we progress in this chapter. The racemic synthesis of diketone **8** was accomplished from commercially available 2, 5-norbornadiene via a method reported by Hawkins and coworkers.[40] Addition of 5 equivalents of formic acid to the diene under refluxing conditions gave the *trans*-diformate **7** in excellent yield after purification by vacuum distillation. Hydrolysis of the diformate and oxidation of the resulting diol happened under Jones oxidation conditions resulting in 18-22 % of the corresponding diketone. However, this method was undesirable for the large-scale synthesis because of the following reasons:

1. The large quantities of toxic chromium reagent are involved.
2. Handling and work-up – requires large solvent extractions to extract the product from the dark slush formed in the Jones oxidation.

3. The poor overall yield is poor.

To overcome above problems we tried a two-step protocol. Diformate **7** was hydrolyzed using aq. NaOH/THF. Our attempts to oxidize the resulting diol using bleach resulted in complex mixture of products. Swern oxidation did not provide optimum results because of the poor solubility of diol in dichloromethane. Further, below zero temperature conditions and greater dilutions required for the Swern oxidation makes it less attractive for the large-scale reactions. At this point we performed the diol oxidation using Taber's modified conditions of the Albright-Onodera oxidation.[41] The reaction was carried out at 1M concentration at 0 °C. Though phosphorous pentoxide used in this reaction is highly hygroscopic however it does not require slow addition and can be quickly charged to the reaction. We have scaled-up >50 g of diketone **8** using these conditions in 60% yield over two steps from **7**.

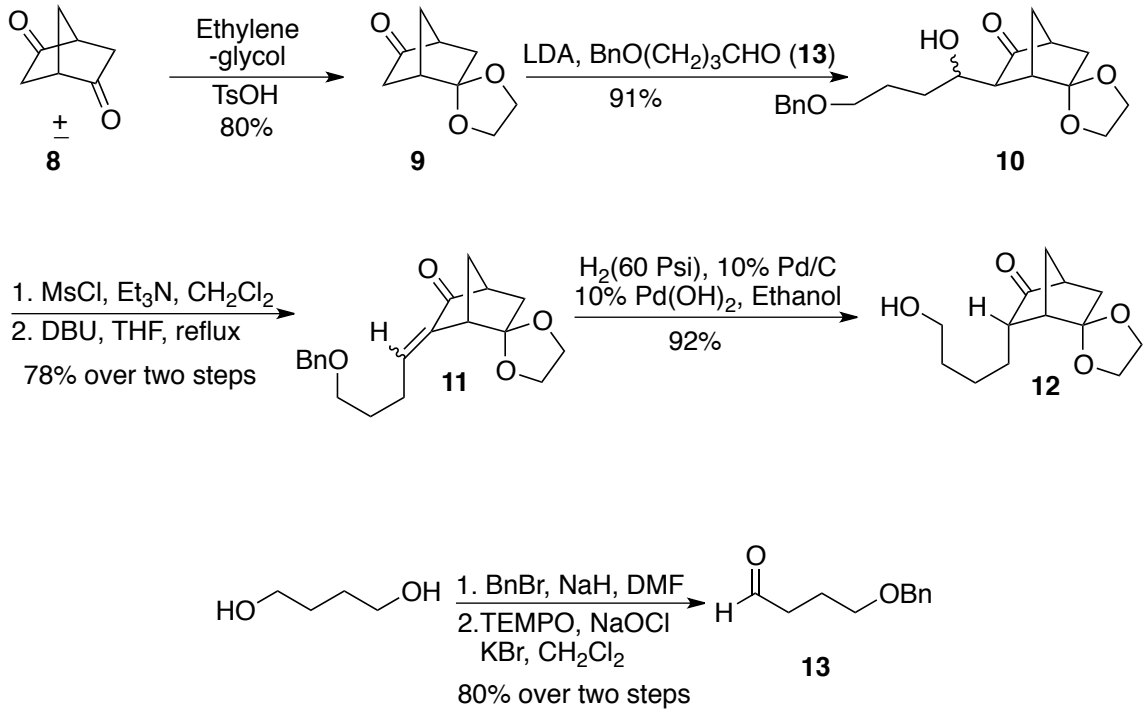
Scheme 10. Synthesis of racemic diketone



Alkylation of diketone 8 (Scheme 11)**.** Diketone **8** was transformed to monoketal product **9** by refluxing with ethylene glycol in THF for 24 hours. The product was isolated in 80% yield. With the synthesis of the monoketal product complete, the aldehyde **13** required for the next aldol step was prepared in two steps from commercially available 1,4-butanediol via a

previously reported procedure in 80% yield.[42] The aldol reaction of **9** with aldehyde **13** using LDA gave **10** in 91% yield as predominately one diastereomer with side chain presumably in the exo position resulting from the alkylation of the enolate from the less hindered exo face. Mesylation of alcohol **10** followed by refluxing in DBU/THF gave **11** as a mixture of E/Z olefins. The mixture **11** was submitted to hydrogenation conditions (10% $Pd(OH)_2$, 10% Pd-C, Ethanol, 60 psi H_2) for 24 h. Hydrogenation of the olefin from the *exo* face and *O*-debenzylation gave **12** in 92% yield with the side chain in the *endo* position. It was interesting to note that the previously published yields in this synthesis proved highly reproducible in the current scale-up.

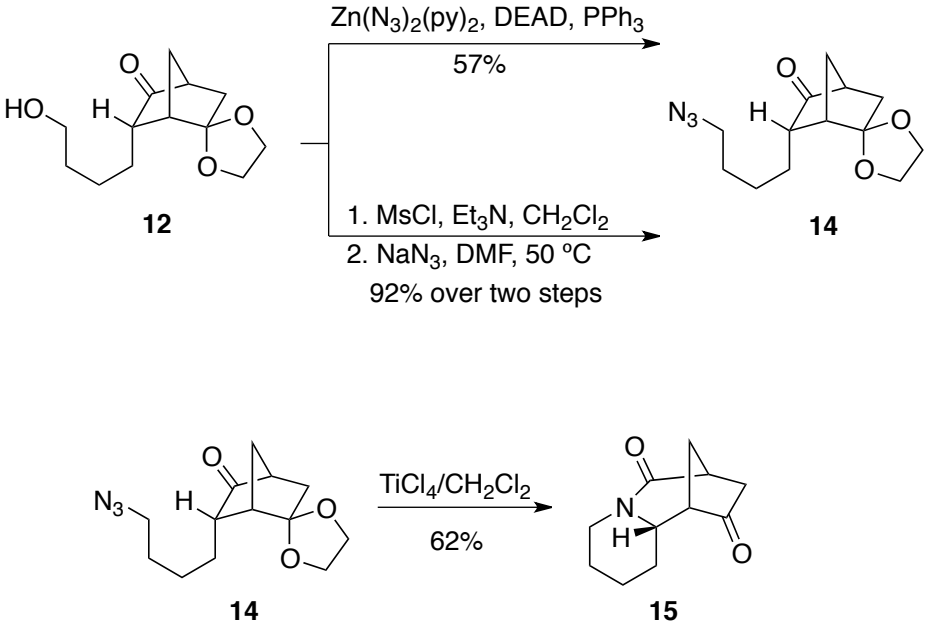
Scheme 11. Alkylation of diketone



Synthesis of tricyclic lactam 15 (Scheme 12)**.** During the total synthesis of (+)-sparteine, conversion of **12** to azide has been originally carried out in > 90% yield using

modified aza-Mitsunobu reaction conditions developed by Rollin.[43] These conditions were employed to prevent the epimerization of the α–carbon to the carbonyl. However, using this method we could obtain **14** in only 57% yield during the current scale-up. Though the yield was still respectable, the loss of material was significant considering the scale and the number of steps involved in the synthesis of **12**. To improve the yield, a two-step protocol was tested which involved conversion of alcohol **12** to the mesylate at 0 °C followed by S_N2 displacement of the mesylate with an azide nucleophile. Conversion of alcohol to azide was achieved in 92% yield over two steps with no epimerization at the α-alkylated center. The intramolecular Schmidt reaction of azide **14** proceeded upon treatment with $TiCl_4$ to obtain the required tricyclic lactam **15** in 62% yield.

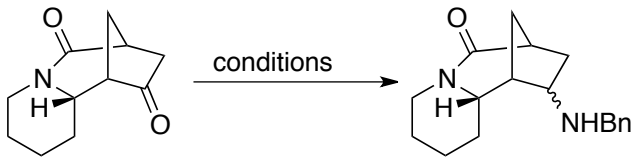
Scheme 12. Synthesis of tricyclic lactam



Following the above route, we prepared 12 g of tricyclic ketolactam **15**.

Reductive amination of tricyclic ketolactam 15. The reductive amination of ketolactam **15** did not work under various conditions attempted (Table 1). The product was obtained only when a mixture of starting ketone and benzyl amine was stirred in neat $TiCl_4$ followed by reduction with $NaCNBH_3$/MeOH.[44,45] The product was isolated in 70% yield (entry 4). However these conditions were not amenable for the development of library by parallel synthesis on Mini-Block.

Table 1. Reductive amination of ketone

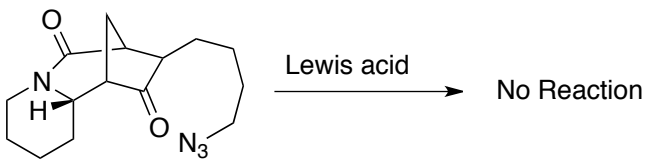


entry	conditions	result
1	$BnNH_2$/$NaCNBH_3$/solvent[a]	S.M.
2	$BnNH_2$/$Na(OAc)_3BH$/solvent[a]	S.M.
3	1. $BnNH_2$/benzene/4Å MS/reflux 2. $NaCNBH_3$	S.M.
4	1.$TiCl_4$ (neat) 2. $NaCNBH_3$/MeOH	70%

a. THF, 1,2-dichloroethane or Acetonitrile.

These results are in coherence with the observations made by Wendt. He noticed the non-reactivity of the alkylated form of this ketone under intramolecular Schmidt reaction conditions (Figure 10).[46] It has also been noticed that even simple ketal protection of ketone **15** does not occur under standarad conditions.

Figure 10. Reactivity of alkylated ketone **15** under Schmidt conditions



Development of lactam 18a-x (Scheme 13). We envisioned that conversion of the ketone **15** to alcohol can be easily carried out in the presence of lactam and the resulting alcohol would provide opportunities for further modifications. To make our first library of lactams, ketone **15** was reduced to alcohol **16** using $NaBH_4$/MeOH in 88% yield with complete diastereoselectivity (*endo:exo* > 19:1). Stereochemistry of *endo*-fused ring as well as the *endo*-C-4-hydroxy was confirmed by transforming alcohol **16** to *p*-bromobenzoate **16a** and developing a single crystal X-ray (Figure 11). Alcohol **16** was converted to *p*-nitrophenylcarbonate **17** in 95% yield on reacting with *p*-nitrophenylchloroformate in THF/Pyridine. We have chosen a set of diverse, alkyl (e.g., entries 4 and 5 in table 1), benzyl (entry 6), substituted benzyl (e.g., entries 1and 2), heterocyclic (e.g., entries 3, 18 and 19) and heteroalkyl (e.g., entries 15 and 16) amines. Treatment of **17** with 5 eq. of these amines gave the carbamates **18a-x**. A 24-compound library was produced with yield ranging from 38-100% and purities 84-100% (Table 2).

Scheme 13. Development of lactam-carbamate library

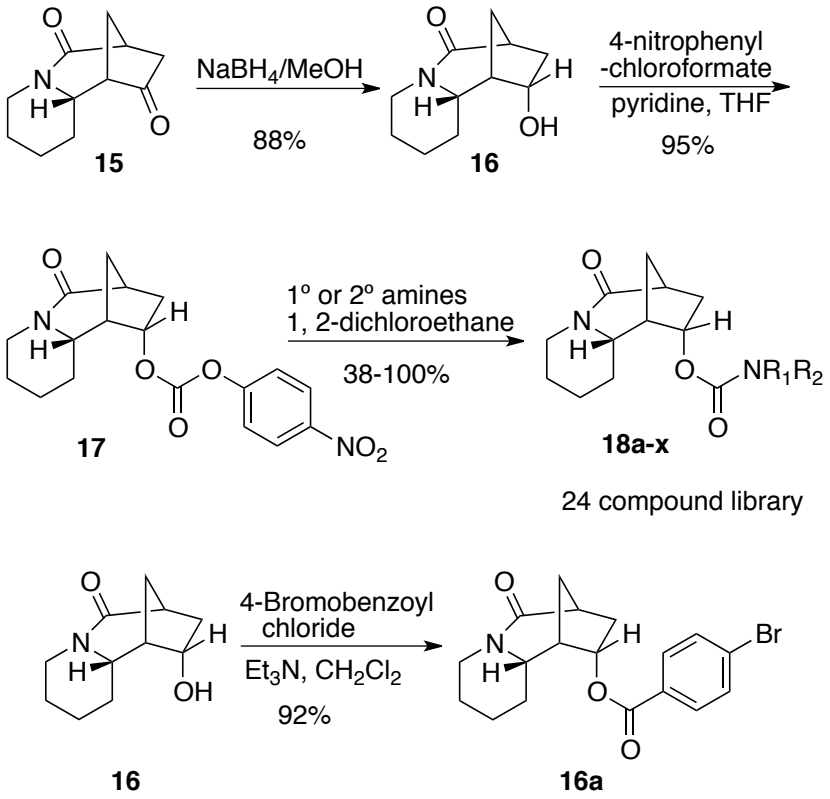


Figure 11. X-ray crystal structure of **16a**

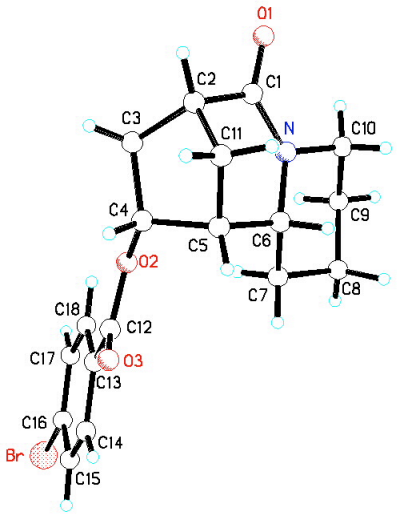


Table 2. Lactam library[a]

entry	alcohol	Amine	carbamate	yield (%)	purity (%)
1	**16**	4-fluorobenzyl amine	**18a**	100	100
2	**16**	4-methoxybenzylamine	**18b**	100	100
3	**16**	morpholine	**18c**	100	100
4	**16**	*n*-butylamine	**18d**	100	100
5	**16**	cyclohexylamine	**18e**	100	100
6	**16**	benzylamine	**18f**	50	100
7	**16**	4-bromobenzylamine	**18g**	65	99
8	**16**	4-methylbenzyl amine	**18h**	90	98
9	**16**	3, 5-dimethoxybenzyl amine	**18i**	80	96
10	**16**	methyl amine	**18j**	100	100
11	**16**	*n*-propyl amine	**18k**	100	99
12	**16**	isopropyl amine	**18l**	75	93
13	**16**	ethanolamine	**18m**	100	99
14	**16**	*N, N*-dimethylamino-1, 3-propanediamine	**18n**	100	99
15	**16**	pyridine-3-yl-methanamine	**18o**	38	100
16	**16**	2-(1*H*-indol-3-yl)ethanamine	**18p**	83	98
17	**16**	piperidine	**18q**	85	99
18	**16**	4-phenylpiperidine	**18r**	86	98
19	**16**	4-methylpiperazine	**18s**	68	100
20	**16**	4-phenylpiperazine	**18t**	100	95
21	**16**	4-benzenesulphonylpiperazine	**18u**	100	96
22	**16**	4-benzoylpiperazine	**18v**	73	91
23	**16**	4-acetylpiperazine	**18w**	63	98
24	**16**	4-(3'-thiophencarbonyl)-piperazine	**18x**	75	84

a. HPLC methods of purification and analysis used for these compounds are provided in detail in the experimental section.

Development of amine library 20 (Scheme 14)**.** Lactam **15** was refluxed with 10eq. of $LiAlH_4$ in THF leading to **19** in 80% yield. A set of 24 differently substituted phenyl isocyanates (e.g., entries 1, 3 and 13), benzyl isocyanate (entry 15), alkyl isocyanates (entry 18), cycloalkyl isocyanate (entry 17), arylalkyl isocyanates (e.g., entries 16 and 22) and heterocyclic isocyanates (entries 4 and 21) was selected. Amino alcohol **19** was reacted with isocyanates in acetonitrile under microwave conditions at 110 °C to produce 24 carbamates **20a-x** in 40-100% yield and purities 33-100% (Table 2). Relative stereochemistry of the product was confirmed through X-ray crystallography of compound **20i** (Figure 12).

Scheme 14. Development of microwave-assisted amine library

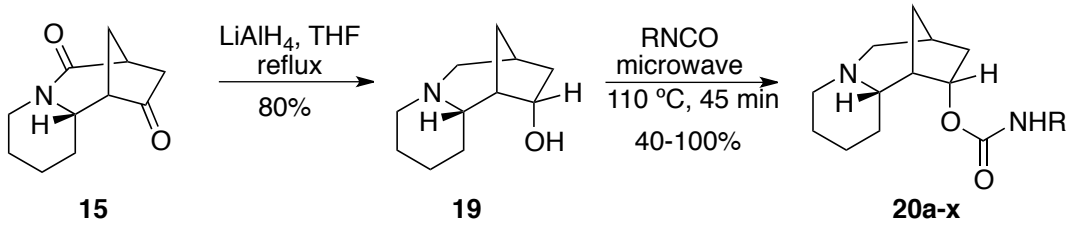


Figure 12. X-ray crystal structure of **20i**

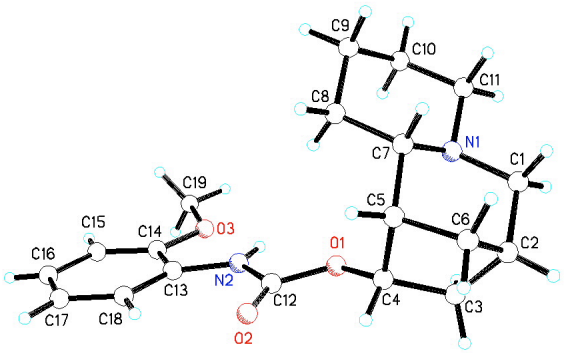


Table 3. Amine library[a]

entry	alcohol	R	carbamate	yield (%)	purity (%)
1	**19**	3, 5-dimethylphenyl	**20a**	100	87
2	**19**	3, 4-dimethylphenyl	**20b**	100	99
3	**19**	4-methoxybenzyl	**20c**	80	91
4	**19**	2-thiophene	**20d**	92	97
5	**19**	4-fluorophenyl	**20e**	82	100
6	**19**	4-methylphenyl	**20f**	84	95
7	**19**	2-trifluoromethylphenyl	**20g**	85	90
8	**19**	3-trifluoromethylphenyl	**20h**	90	90
9	**19**	2-methoxyphenyl	**20i**	65	99
10	**19**	3-methylphenyl	**20j**	70	98
11	**19**	4-bromomethylphenyl	**20k**	88	99
12	**19**	3-bromomethylphenyl	**20l**	84	99
13	**19**	4-cyanophenyl	**20m**	90	98
14	**19**	4-(N,N-dimethylamino)phenyl	**20n**	40	33
15	**19**	benzyl	**20o**	90	97
16	**19**	4-ethylphenethyl	**20p**	92	92
17	**19**	cyclohexyl	**20q**	84	92
18	**19**	*n*-butyl	**20r**	80	100
19	**19**	4-*n*-pentylphenyl	**20s**	88	82
20	**19**	*tert*-butyl	**20t**	90	96
21	**19**	3-indolyl	**20u**	73	41
22	**19**	phenylpropyl	**20v**	93	98
23	**19**	3-cyanophenyl	**20w**	92	100
24	**19**	ethylbutanoate	**20x**	76	95

a. HPLC methods of purification and analysis used for these compounds are provided in detail in the experimental section.

Synthesis of scaffolds 23d-f (Scheme 15). Ketal protection of the ketone **15** did not occur under *p*-toluenesulfonicacid/ethyleneglycol/benzene conditions. The ketone **15** was protected using TMSCl/ethylene glycol to obtain ketal **21** in 70% yield.[47] Compound **21** was treated with Grignard reagent under reflux and the resulting iminium salt was in situ reduced with sodium cyanoborohydride.[48] The crude product obtained from this reaction was refluxed in HCl/acetone to give the unprotected ketone **22**, which was found as a single diastereomer in 85-90 % yield over two steps. The ketone **22** was converted to *endo* alcohol **23** in 85-88% yield using $NaBH_4$/MeOH conditions. A set of 24 differently substituted phenyl, benzyl, alkyl, cycloalkyl, arylalkyl and heterocyclic isocyantes was selected. Alcohol **23** was transformed to carbamate **24** by reacting with isocyanate in THF in the presence of triethylamine at 50 °C. Using 24 different isocyanates for each of the scaffold (**23d-f**) a 72-compound carbamate library was produced by parallel synthesis on Mini-Block in 37-100% yield and purity 16-100% (Table 3). The relative stereochemistry was confirmed through X-ray crystallography of compound **39e** (Figure 13).

Scheme 15. Synthesis of scaffolds

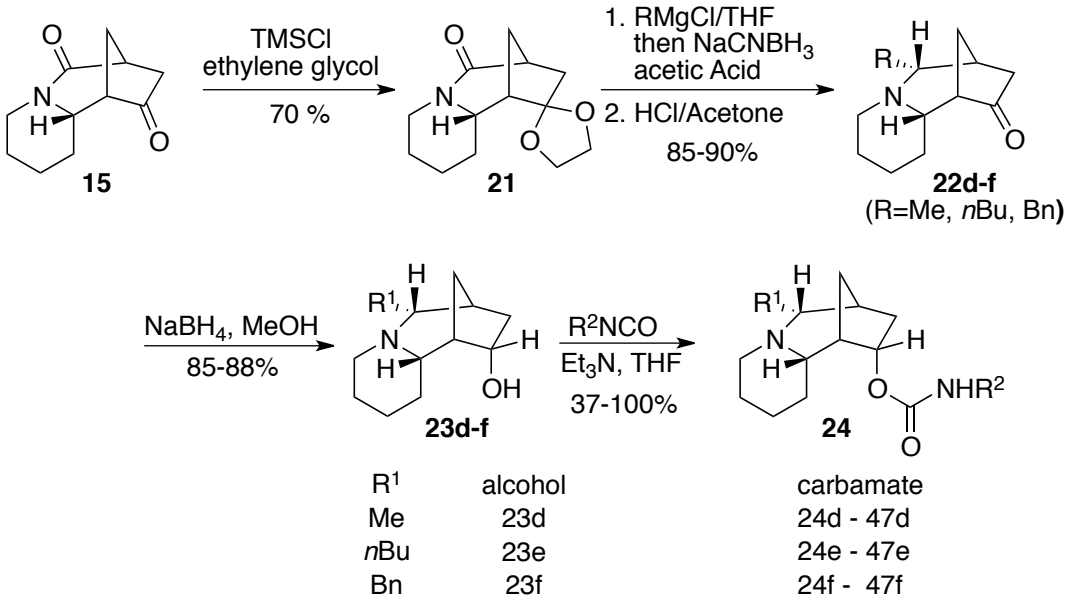
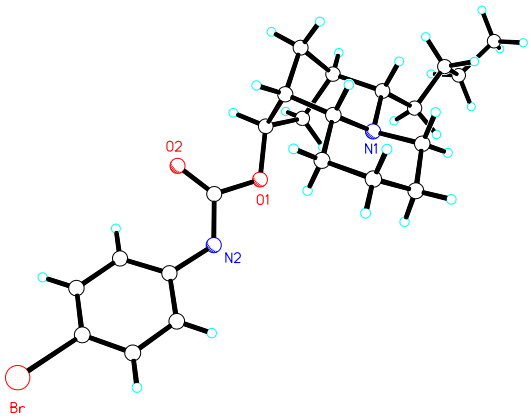


Figure 13. X-ray crystal structure of **39e**



In summary, we have produced a 120 compound library based on the sparteine scaffold. 105 compounds passed the purity standards (> 90% by HPLC). Molecular properties of these compounds, HBA (number of hydrogen bond acceptors), HBD (number of hydrogen bond donors), number of rotatable bonds, PSA (polar surface area), and ClogP values have been calculated using SYBYL from TRIPOS (Table 5). For majority of the compounds, these values are within the range as defined by the Lipinski and Veber's rules. The compounds have been submitted for biological screening to the NIH Molecular Libraries-Small Molecule Repository. During the course of this work, we have also developed an improved and Chromium-free route for the synthesis racemic diketone and demonstrated multigram synthesis of intermediate **15**, which will facilitate to develop more libraries based on sparteine scaffold in future.

Table 4. Alkylated-amine library[a]

entry	alcohol	R^1	R^2	carbamate	yield (%)	purity (%)
1	**23d**	Me	*n*-butyl	**24d**	37	23
2	**23d**	Me	*t*-butyl	**25d**	58	18
3	**23d**	Me	ethylbutanoate	**26d**	68	96
4	**23d**	Me	4-chlorobenzyl	**27d**	78	99
5	**23d**	Me	4-methylphenyl	**28d**	85	98
6	**23d**	Me	4-cyanophenyl	**29d**	88	99
7	**23d**	Me	3-cyanophenyl	**30d**	85	99
8	**23d**	Me	2-trifluoromethylphenyl	**31d**	88	91
9	**23d**	Me	benzyl	**32d**	93	98
10	**23d**	Me	3-phenylpropyl	**33d**	90	97
11	**23d**	Me	2-(4-ethylphenyl)ethyl	**34d**	95	95
12	**23d**	Me	2-methoxyphenyl	**35d**	78	98
13	**23d**	Me	3-fluoroohenyl	**36d**	83	99
14	**23d**	Me	4-fluorophenyl	**37d**	86	99
15	**23d**	Me	3-bromophenyl	**38d**	63	40
16	**23d**	Me	4-bromophenyl	**39d**	92	90
17	**23d**	Me	2-chlorophenyl	**40d**	90	57
18	**23d**	Me	3-chlorophenyl	**41d**	90	99
19	**23d**	Me	4-chlorophenyl	**42d**	83	87
20	**23d**	Me	5-benzo[*d*][1,3]dioxole	**43d**	100	97
21	**23d**	Me	3-trifluorometylphenyl	**44d**	98	98
22	**23d**	Me	4-trifluoromethylphenyl	**45d**	96	98

23	**23d**	Me	3, 5-dimethylphenyl	**46d**	100	85
24	**23d**	Me	4-(*N, N*-dimethylamino)phenyl	**47d**	92	52
25	**23e**	*n*-butyl	*n*-butyl	**24e**	60	67
26	**23e**	*n*-butyl	4-ethylbutanoate	**25e**	59	67
27	**23e**	*n*-butyl	2-methylphenyl	**26e**	85	95
28	**23e**	*n*-butyl	4-methylphenyl	**27e**	88	92
29	**23e**	*n*-butyl	4-cyanophenyl	**28e**	90	98
30	**23e**	*n*-butyl	3-cyanophenyl	**29e**	87	98
31	**23e**	*n*-butyl	phenyl	**30e**	90	95
32	**23e**	*n*-butyl	benzyl	**31e**	100	100
33	**23e**	*n*-butyl	4-chlortobenzyl	**32e**	100	93
34	**23e**	*n*-butyl	3-phenylpropyl	**33e**	100	93
35	**23e**	*n*-butyl	2-(4-ethylphenyl)ethyl	**34e**	100	91
36	**23e**	*n*-butyl	2-methoxyphenyl	**35e**	98	96
37	**23e**	*n*-butyl	3-fluoroohenyl	**36e**	85	94
38	**23e**	*n*-butyl	4-fluorophenyl	**37e**	78	94
39	**23e**	*n*-butyl	3-bromophenyl	**38e**	90	67
40	**23e**	*n*-butyl	4-bromophenyl	**39e**	92	93
41	**23e**	*n*-butyl	2-chlorophenyl	**40e**	78	85
42	**23e**	*n*-butyl	3-chlorophenyl	**41e**	88	92
43	**23e**	*n*-butyl	4-chlorophenyl	**42e**	87	95
44	**23e**	*n*-butyl	5-benzo[*d*][1,3]dioxole	**43e**	98	99
45	**23e**	*n*-butyl	3-trifluorometylphenyl	**44e**	88	92
46	**23e**	*n*-butyl	4-trifluoromethylphenyl	**45e**	86	91
47	**23e**	*n*-butyl	3, 5-dimethylphenyl	**46e**	92	97
48	**23e**	*n*-butyl	3-trifluoromethylphenyl	**47e**	88	87
49	**23f**	benzyl	*n*-butyl	**24f**	70	16
50	**23f**	benzyl	t-butyl	**25f**	54	48

51	**23f**	benzyl	4-ethylbutanoate	**26f**	72	98
52	**23f**	benzyl	2-methylphenyl	**27f**	87	99
53	**23f**	benzyl	4-methylphenyl	**28f**	88	97
54	**23f**	benzyl	4-cyanophenyl	**29f**	97	99
55	**23f**	benzyl	3-cyanophenyl	**30f**	92	100
56	**23f**	benzyl	phenyl	**31f**	88	99
57	**23f**	benzyl	benzyl	**32f**	100	76
58	**23f**	benzyl	3-phenylpropyl	**33f**	75	97
59	**23f**	benzyl	2-(4-ethylphenyl)ethyl	**34f**	94	97
60	**23f**	benzyl	2-methoxyphenyl	**35f**	80	98
61	**23f**	benzyl	3-fluoroohenyl	**36f**	75	99
62	**23f**	benzyl	4-fluorophenyl	**37f**	82	99
63	**23f**	benzyl	3-bromophenyl	**38f**	90	84
64	**23f**	benzyl	4-bromophenyl	**39f**	92	94
65	**23f**	benzyl	2-chlorophenyl	**40f**	90	98
66	**23f**	benzyl	3-chlorophenyl	**41f**	82	98
67	**23f**	benzyl	4-chlorophenyl	**42f**	92	86
68	**23f**	benzyl	5-benzo[*d*][1,3]dioxole	**43f**	97	100
69	**23f**	benzyl	3-trifluorometylphenyl	**44f**	100	100
70	**23f**	benzyl	4-trifluoromethylphenyl	**45f**	100	100
71	**23f**	benzyl	3, 5-dimethylphenyl	**46f**	100	100
72	**23f**	benzyl	4-(*N, N*-dimethylamino)phenyl	**47f**	69	47

a. HPLC methods of purification and analysis used for these compounds are provided in detail in the experimental section.

Table 5. Molecular properties

Entry	Compound	M. W.	HBA	HBD	Rot. Bonds	PSA	CLogP
1	**18a**	346	3	1	4	60.78	2.20
2	**18b**	358	4	1	5	67.51	1.98
3	**18c**	308	4	0	3	62.54	0.84
4	**18d**	294	3	1	5	61.5	1.91
5	**18e**	320	3	1	3	49.77	2.35
6	**18f**	328	3	1	4	55.61	2.06
7	**18g**	407	3	1	4	55.61	2.92
8	**18h**	342	3	1	4	48.71	2.56
9	**18i**	388	5	1	6	69.06	2.07
10	**18j**	252	3	1	2	56.84	0.32
11	**18k**	280	3	1	4	56.49	1.38
12	**18l**	280	3	1	3	44.29	1.16
13	**18m**	282	4	2	4	99.40	0.24
14	**18n**	323	3	2	6	58.58	1.01
15	**18o**	329	4	2	4	72.96	0.56
16	**18p**	381	3	2	5	79.79	2.41
17	**18q**	306	3	0	3	53.02	2.13
18	**18r**	382	3	0	4	53.02	3.54
19	**18s**	321	3	1	3	55.00	1.41
20	**18t**	383	4	1	4	55.00	2.84
21	**18u**	447	5	0	5	78.97	2.52
22	**18v**	411	4	0	5	74.67	2.01
23	**18w**	349	4	0	4	83.03	0.43
24	**18x**	417	4	0	5	102.55	1.79
25	**20a**	328	2	2	3	21.41	4.23
26	**20b**	328	2	2	3	23.99	4.18

27	**20c**	344	3	2	5	41.98	3.23
28	**20d**	306	2	2	3	35.61	3.03
29	**20e**	318	2	2	3	23.99	3.59
30	**20f**	314	2	2	3	16.31	3.73
31	**20g**	368	2	2	3	16.32	4.49
32	**20h**	368	2	2	3	14.71	3.61
33	**20i**	330	3	2	4	17.45	3.28
34	**20j**	314	2	2	3	15.18	3.73
35	**20k**	379	2	2	3	16.31	4.31
36	**20l**	379	2	2	3	16.31	4.31
37	**20m**	325	3	2	3	72.18	3.16
38	**20n**	343	3	3	4	18.48	3.40
39	**20o**	314	2	2	4	27.48	3.31
40	**20p**	356	2	2	6	24.42	4.70
41	**20q**	306	2	2	3	16.65	3.61
42	**20r**	280	2	2	5	28.42	3.16
43	**20s**	370	2	2	7	16.39	5.85
44	**20t**	280	2	2	2	16.44	2.81
45	**20u**	339	2	3	3	42.73	3.23
46	**20v**	342	2	2	6	28.43	4.05
47	**20w**	325	3	2	3	70.24	3.16
48	**20x**	338	4	2	8	59.12	2.77
49	**24e**	336	2	2	8	28.37	5.27
50	**25e**	394	4	2	11	59.04	4.88
51	**26e**	370	2	2	6	14.93	5.28
52	**27e**	370	2	2	6	16.02	5.84
53	**28e**	381	3	2	6	71.94	5.26
54	**29e**	381	3	2	6	70.08	5.26

55	**30e**	356	2	2	6	16.04	5.34
56	**31e**	370	2	2	7	27.14	5.42
57	**32e**	404	2	2	7	27.11	6.13
58	**33e**	398	2	2	9	15.59	6.16
59	**34e**	412	2	2	9	24.17	6.81
60	**35e**	386	3	2	7	19.14	5.39
61	**36e**	374	2	2	6	15.97	5.69
62	**37e**	374	2	2	6	16.05	5.69
63	**38e**	435	2	2	6	16.02	6.41
64	**39e**	435	2	2	6	16.05	6.41
65	**40e**	390	2	2	6	15.75	5.70
66	**41e**	390	2	2	6	16.13	6.26
67	**42e**	390	2	2	6	16.09	6.26
68	**43e**	400	4	2	6	37.08	5.36
69	**44e**	424	2	2	6	14.28	6.59
70	**45e**	424	2	2	6	16.09	6.59
71	**46e**	384	2	2	6	14.88	6.34
72	**47e**	424	2	2	6	14.43	5.71
73	**24f**	370	2	2	7	27.85	5.25
74	**25f**	370	2	2	4	16.03	4.90
75	**26f**	414	2	4	9	59.12	4.33
76	**27f**	404	2	2	5	14.65	5.26
77	**28f**	404	2	2	5	15.78	5.82
78	**29f**	415	2	3	5	71.63	5.24
79	**30f**	415	2	3	5	69.72	5.24
80	**31f**	390	2	2	5	15.79	5.32
81	**32f**	404	2	2	6	26.60	5.40
82	**33f**	432	2	2	8	15.27	6.14

83	**34f**	446	2	2	8	23.87	6.79
84	**35f**	420	2	3	6	18.51	5.37
85	**36f**	408	2	2	5	15.41	5.68
86	**37f**	408	2	2	5	15.49	5.68
87	**38f**	469	2	2	5	15.72	6.40
88	**39f**	469	2	2	5	15.49	6.40
89	**40f**	425	2	2	5	15.43	5.69
90	**41f**	425	2	2	5	15.78	6.25
91	**42f**	425	2	2	5	15.78	6.25
92	**43f**	434	2	4	5	36.76	5.34
93	**44f**	458	2	2	5	13.90	6.57
94	**44f**	458	2	2	5	15.77	6.57
95	**46f**	418	2	2	5	14.33	6.32
96	**24d**	294	2	2	5	28.43	3.68
97	**25d**	294	2	2	2	16.39	3.33
98	**26d**	352	2	4	8	59.15	3.29
99	**28d**	328	2	2	3	16.22	4.25
100	**29d**	339	2	3	3	72.07	3.68
101	**30d**	339	2	3	3	70.16	3.68
102	**31d**	382	2	2	3	14.34	5.01
103	**32d**	328	2	2	4	27.34	3.83
104	**33d**	356	2	2	6	15.71	4.57
105	**34d**	370	2	2	6	24.29	5.22
106	**35d**	344	2	3	4	19.24	3.80
107	**36d**	332	2	2	3	16.15	4.11
108	**37d**	332	2	2	3	16.23	4.11
109	**38d**	393	2	2	3	16.15	4.83
110	**39d**	393	2	2	3	16.23	4.83

111	**40d**	348	2	2	3	15.86	4.12
112	**41d**	348	2	2	3	16.22	4.68
113	**42d**	348	2	2	3	16.22	4.68
114	**43d**	358	2	4	3	37.14	3.77
115	**44d**	382	2	2	3	14.34	5.01
116	**45d**	382	2	2	3	16.23	5.01
117	**46d**	342	2	2	3	15.07	4.75

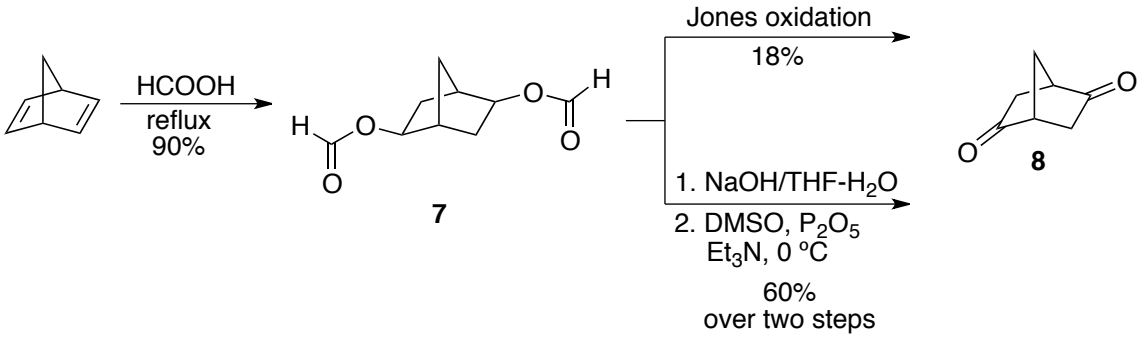
CHAPTER 3

EXPERIMENTAL SECTION

General Procedures. All non-aqueous reactions were carried out in oven- or flame-dried flasks under argon atmosphere. CH_2Cl_2, THF, and MeCN were dried by using Innovative Technology Pure-Solv 400 commercial solvent purification system. Microwave reactions were carried out using a Biotage Initiator equipped with robot automation. Parallel syntheses were conducted with 24-position Mettler-Toledo Bohdan MiniBlocks, and parallel evaporations were carried using a Techne sample concentrator and a GeneVac EZ-2 personal evaporator. HPLC analysis was carried out using a Waters Acquity system with UV detection and mass detection (Waters LCT Premier). The analytical method utilized a linear gradient of 5% CH_3CN in pH 9.8 buffered aqueous NH_4HCO_2 to 100% CH_3CN at a flow rate of 0.6 mL/min. Purity was determined using UV peak area at 214 nm. Preparative reverse-phase HPLC purification was performed using a Waters 2767 preparative system with UV detection (Waters 2996 PAD) and mass detection (Waters Micromass ZQ). The preparative method utilized a Waters X-Bridge C18 column (19 x 150 mm, w/ 19 x 10 mm guard column), elution with a water and CH_3CN gradient which increases 20% in CH_3CN content over 4 minutes at a flow rate of 20 mL/min (modified to pH 9.8 through addition of NH_4OH by auxiliary pump), and sample dilution in DMSO. Thin-layer chromatography (TLC) was performed using commercial Analtech glass-backed silica plates (250 microns) with an organic binder. Visualization was accomplished using UV light or aqueous $KMnO_4$. Flash chromatography was carried out using Sorbent Technologies standard grade silica gel (40-63 μm particle size, 230 Å~ 400 mesh) with compressed nitrogen as a source

of positive pressure. Melting points were performed in open capillary tubes using either a Mel-Temp or Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were acquired as thin films on a PerkinElmer Spectrum 100 FT-IR spectrometer, and the absorptions are reported in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 400 spectrometer (operating at 400 and 100 MHz respectively) in CDCl3 with 0.03% TMS as an internal standard. Chemical shifts are reported in parts per million (ppm), and referenced to $CDCl_3$ with $CHCl_3$ as internal reference (7.26 ppm for ^{1}H and 77.23 ppm for ^{13}C. Coupling constants are reported in Hertz (Hz). High resolution mass spectra were obtained using a Waters LCT Premier instrument with a time of flight (TOF) mass analyzer and an electrospray ion source (ESI).

Materials. All starting materials were purchased from Aldrich, Fluka or Fischer Chemical companies and used as received. The following compounds **7** through **15** were prepared by following reported procedures. We have prepared compounds **8** and **14** on significantly larger scales than the previously reported synthesis.[38] Large-scale synthesis of these compounds was also carried out via improved alternative procedures. Experimental procedures for both old and new routes are provided below.

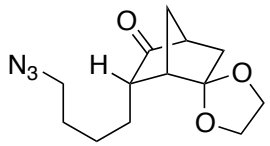


Bicyclo[2.2.1]heptane-2,5-dione (8). In a 1L round bottom flask, 100 g of 2, 5-norbornadiene was added. The 600 mL of formic acid (97%) was added to it under argon atmosphere. The reaction was refluxed at 120 ºC for 24h. Finally the formic acid was distilled off and the diformate was obtained by vacuum distillation (120-130 ºC at 10 mmHg) as clear liquid. Diformate was transformed to 23 via two different methods (method A and B) as described below.

Method A: 100 g of diformate (0.53 mol) was transferred into a 2L round bottom flask kept in a large ice bath and fitted with a mechanical stirrer. 300 mL of acetone was added to it. The solution was cooled to 0 ºC. At this temperature 700 mL (8N) of Jones reagent was added dropwise over a period of 2 h. The reaction mixture was allowed to come to room temperature for over night. Following this the reaction was repeatedly extracted with diethyl ether (700 mL x 4). The combined organic layer was transferred to another 4L round bottom flask and cooled to 0 ºC by keeping in ice-water bath. Solid sodium carbonate was added in portions to this solution till no more effervescence was seen. The solvent was decanted and concentrated under reduced pressure to obtain 12 g (19%) of diketone **8** as a low melting solid.

Method B: In a 3L round bottom flask containg 1.5 L of THF, was added 200 g (1.06 mol) of diformate. The solution was cooled to 0 ºC and NaOH (424 g in 600 mL water) solution was added to it via a dropping funnel in 30 min. The reaction mixture was stirred at room temperature for 10h was transeferred to a 4 L separating funnel and extracted with ethylacetate. Organic layer was separated and the aqueous layer was again extracted with ethyl acetate on saturating with sodium chloride. The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to obtain 100 g of crude diol as a white solid. The diol was vacuum dried for 4h and transferred to a three-neck 4L round bottom flask fitted with a mechanical stirred. 225 mL

of anhydrous dimethylsulfoxide was added to it and the mixture was stirred till the solution became completely clear. Then the solution was diluted with dichloromethane (800 mL) and phosphorous pentoxide (450 g, 1.58 mol) was charged into it. The reaction mixture was stirred vigorously for 1h at rt. Then it was cooled to 0 ºC on keeping in ice-water bath. Triethyl amine (661 mL, 4.75 mol) was added to it dropwise over a period of 1 h. The reaction was stirred at 0 ºC for further 1 h before it was quenched with 10% HCl (800 mL). Finally it was transferred to a separating funnel and was extracted with dichloromethane. The combined organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by flash coulumn chromatography to obtain 80 g of the diketone **8** in 60% yield.

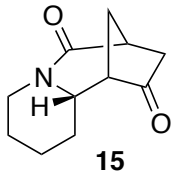


14

(1*S*,4*S*,6*S*)-6-(4-azidobutyl)spiro[bicyclo[2.2.1]heptane-2,2'-[1,3]dioxolan]-5-one (14).

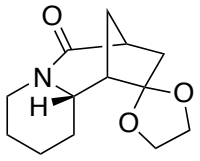
Compound **12** (10 g, 41.6 mmol) was dissolved in 200 mL of CH_2Cl_2 and the solution was cooled to 0 °C under argon. Methanesulfonyl chloride (4.83 mL, 62.4 mmol) and triethylamine (8.68 mL, 62.4 mmol) were added dropwise and the mixture was stirred for 1 h at 0 °C. The reaction was quenched with saturated NH_4Cl, extracted with EtOAc, and the combined organic layers dried over Na_2SO_4. The solvent was evaporated to obtain the mesylate product. The product was dried over high vacuum for 30 min and the residue was dissolved in 100 mL of DMF. Sodium azide (9.42 g, 14.5 mmol) was added to the solution and the mixture was stirred at 50 ºC for 7 h. The reaction was diluted with water, extracted with EtOAc; the combined organic layers were dried over Na_2SO_4. Concentration followed by chromatography (10%

EtOAc/hexane) afforded 10.14 g (92%) of **14** isolated as a colorless liquid.



15

(7*S*,10*S*,10a*S*)-octahydro-7,10-methanopyrido[1,2-*a*]azepine-6,9-dione (15). Azide **14** (10 g, 37.7 mmol) was dissolved in 350 mL of CH_2Cl_2 under argon and cooled to 0 °C. $TiCl_4$ (20.7 mL, 188.5 mmol) was added dropwise by syringe. A yellow precipitate was formed. The reaction was allowed to warm to room temperature and stirred for 24 h. The reaction was quenched with water and the aqueous layer was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated to give a oil. Flash chromatography (100% EtOAc) afforded 4.5 g (62%) of **15** isolated as white solid.

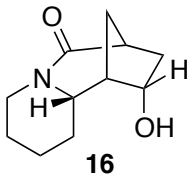


21

(7*S*,10*S*,10a*S*)-hexahydro-1*H*-spiro[7,10-methanopyrido[1,2-*a*]azepine-9,2'-[1,3]dioxolan]-6(2*H*)-one (21). Chlorotrimethylsilane (13.1 mL, 103.2 mmol) was added to a solution of **15** (5 g, 25.89 mmol) in dry ethylene glycol (80 mL) under an argon atmosphere and the reaction mixture stirred for 6 h at room temperature. Water (50 mL) was added and the mixture was extracted with diethylether. The organic layer was dried over anhydrous sodium sulfate. Concentration followed by flash column chromatography gave 4.29 g (70 %) of **21** as a white solid (m.p. 90-91 ºC): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.52 (ddt, *J* = 13.3, 4.2, 2.0 Hz, 1H), 4.04

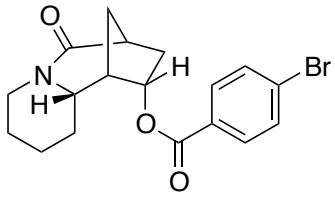
– 3.69 (m, 4H), 3.19 (dt, *J* = 12.3, 2.9 Hz, 1H), 2.69 (ddd, *J* = 7.3, 4.5, 1.6 Hz, 1H), 2.36 (td, *J* = 13.0, 3.2 Hz, 1H), 2.27 – 1.98 (m, 5H), 1.87 – 1.73 (m, 2H), 1.70 – 1.58 (m, 1H), 1.58 – 1.46 (m, 1H), 1.42 – 1.16 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.26, 117.13, 65.17, 63.29, 61.16, 45.98, 42.16, 41.98, 41.21, 32.52, 29.78, 25.25, 25.02; IR (neat) 1638, 2940, cm^{-1}; HRMS calcd for (M^+ +1): 237.138, found 237.1365.

Synthesis of the scaffolds

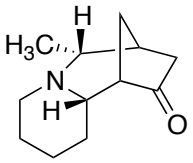


16

(7*S*,9*S*,10*S*,10a*S*)-9-hydroxyoctahydro-7,10-methanopyrido[1,2-*a*]azepin-6(2*H*)-one (16). Lactam **15** (500 mg, 2.58 mmol) was dissolved in methanol. The solution was cooled to 0 °C and sodiumborohydride (196 mg, 5.178 mmol) was added to it. The reaction mixture was stirred at room temperature for 4h. The reaction mixture was quenched with 10% aq. NaOH solution and was extracted with ethyl acetate. The organic layer was dried over anhyd.Na_2SO_4 and concentrated to give the crude product. The crude product was purified by flash column chromatography to obtain 444 mg (88%) of **16** as a the only diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.60 – 4.38 (m, 2H), 3.32 (d, *J* = 12.4 Hz, 1H), 3.12 (s, 1H), 2.67 – 2.51 (m, 1H), 2.48 – 2.19 (m, 4H), 1.80 (dd, *J* = 12.8, 1.6 Hz, 1H), 1.75 – 1.53 (m, 5H), 1.43 – 1.10 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.12, 75.30, 62.72, 43.12, 42.23, 42.09, 38.28, 31.80, 30.57, 25.51, 25.19; IR (neat) 1623, 2931, 3355 cm^{-1}; HRMS calcd for (M^+ +1): 195.1271, found 195.1259.



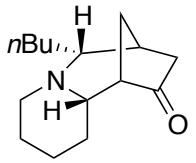
(7*S*,9*S*,10*S*,10a*S*)-6-oxodecahydro-7,10-methanopyrido[1,2-*a*]azepin-9-yl 4-bromobenzoate (16a). To a solution of **16** (50 mg, 0.25 mmol) in dichloromethane (3 mL) was added triethylamine (0.071 mL, 0.51 mmol) and N, N-dimethylaminopyridine (2 mg). Then p-bromobenzoyl chloride was added to it and the reaction mixture was stirred at room temperature for 8h. Finally the solvent was evaporated and the crude reaction mixture was purified by flash column chromatography to obtain 89 mg (92%) of **16a** as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.74 (m, 1H), 7.71 – 7.44 (m, 1H), 5.56 – 5.27 (m, 1H), 4.64 – 4.40 (m, 1H), 3.45 – 3.22 (m, 1H), 2.82 – 2.70 (m, 1H), 2.56 (ddd, *J* = 14.4, 10.5, 8.1 Hz, 1H), 2.41 (td, *J* = 13.0, 3.1 Hz, 1H), 1.97 – 1.82 (m, 2H), 1.81 – 1.64 (m, 1H), 1.64 – 1.54 (m, 1H), 1.44 – 1.15 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.13, 165.81, 131.94, 131.11, 128.79, 128.40, 77.39, 77.07, 77.04, 76.76, 62.13, 42.09, 41.52, 41.39, 35.12, 31.74, 30.42, 25.46, 25.26; IR (neat) 1647, 1716, 2938 cm^{-}1;HRMS calcd for (M^{+} +1): 377.0645, found 377.0627.



22d

(6*R*,7*S*,10*S*,10a*S*)-6-methyloctahydro-7,10-methanopyrido[1,2-*a*]azepin-9(6*H*)-one (22d). To a stirring solution of lactam **21** (500 mg, 2.1 mmoL) in dry THF (20 mL) was added a solution of MeMgCl in THF (2.8 mL, 3M in THF) was added dropwise. After the mixture was allowed to

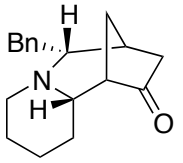
heat at 60 °C for 3 h, it was then cooled to 0 °C. Then $NaBH_3CN$ (792 mg, 12.6 mmoL) was added followed by addition of glacial acetic acid (1.0 mL). The resultant mixture was stirred for 1 h and was quenched with 10% NaOH solution. It was extracted with ethylacetate. The combined organic layer was dried over anhydrous sodium sulfate and concentrated. The residue obtained on concentration was dissolved in a mixture of conc. HCl (2 mL) and acetone (20 mL) and was refluxed for 2h. The reaction mixture was cooled to 0 °C and neutralized by adding 10 % aq.NaOH. Finally it was extracted with ethylacetate and the combined organic layer was dried over anhyd. sodium sulfate. Concentration followed by flash column chromatography gave 354 mg (87%) of **22d** as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.05 (dd, *J* = 7.3, 3.9 Hz, 1H), 2.42 (dd, *J* = 6.3, 1.4 Hz, 1H), 2.28 (dt, *J* = 10.7, 5.3 Hz, 2H), 2.15 (dd, *J* = 10.5, 3.2 Hz, 1H), 2.07 – 1.89 (m, 3H), 1.88 – 1.76 (m, 1H), 1.75 – 1.61 (m, 3H), 1.59 – 1.10 (m, 7H), 1.06 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 218.42, 67.31, 60.99, 52.04, 51.03, 40.34, 39.63, 37.16, 30.12, 25.72, 24.44, 18.85; IR (neat) 1733, 2932 cm^{-1}; HRMS calcd for (M^+ +1): 194.1546, found 194.1554.



22e

(6*R*,7*S*,10*S*,10a*S*)-6-butyloctahydro-7,10-methanopyrido[1,2-*a*]azepin-9(6*H*)-one (22e). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.08 (d, *J* = 11.2 Hz, 1H), 2.42 (s, 1H), 2.27 – 2.03 (m, 3H), 2.01 – 1.84 (m, 3H), 1.71 (dd, *J* = 11.0, 3.6 Hz, 1H), 1.67 – 1.55 (m, 3H), 1.55 – 1.02 (m, 10H), 0.83 (dd, *J* = 10.0, 4.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 67.46, 66.35, 52.05, 51.04, 39.72,

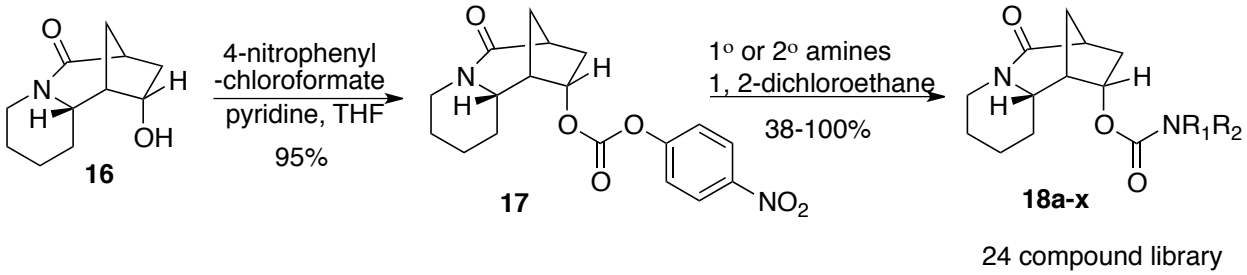
36.76, 36.57, 31.24, 30.31, 29.53, 25.78, 24.42, 23.00, 14.02; IR (neat); 2933, 1741 cm^{-1}; HRMS calcd for (M^+ +1): 235.1954, found 235.1936.



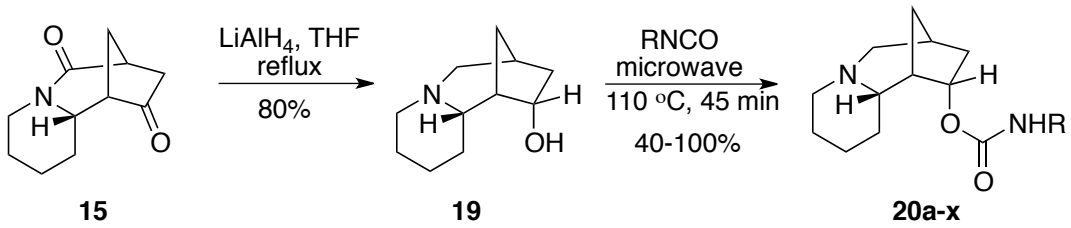
22f

(6*R*,7*S*,10*S*,10a*S*)-6-benzyloctahydro-7,10-methanopyrido[1,2-*a*]azepin-9(6*H*)-one (22f). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 10.1, 4.5 Hz, 2H), 7.21 (dd, *J* = 8.4, 6.3 Hz, 1H), 7.17 – 7.08 (m, 2H), 3.34 (d, *J* = 11.2 Hz, 1H), 3.20 (dd, *J* = 13.6, 4.1 Hz, 1H), 2.58 (ddd, *J* = 9.9, 4.1, 1.4 Hz, 1H), 2.41-2.36 (m, 2H), 2.27 – 2.14 (m, 2H), 2.07 – 1.78 (m, 4H), 1.78 – 1.38 (m, 6H), 1.35 – 1.14 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 217.74, 139.79, 129.35, 128.47, 126.10, 67.71, 67.50, 52.14, 51.30, 39.45, 37.55, 36.64, 35.24, 30.40, 25.89, 24.46; IR (neat) 1740, 2935 cm^{-1}; HRMS calcd for (M^+ +1): 269.1802, found 269.178.

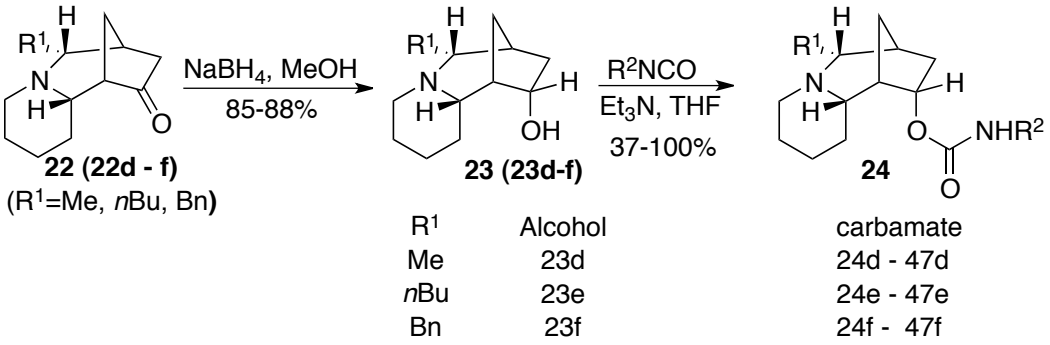
Library Synthesis



Procedure for the synthesis of lactams 18a-x. To a solution alcohol **16** (1.5 g, 7.68 mmol) in anhydrous THF (40 mL), pyridine (0.92 mL, 11.5 mmol) and 4-nitorphenyl chloroformate (1.86 g, 9.2 mmol) were added sequentially. The reaction mixture was stirred at room temperature for 2h. The solvent was evaporated and the crude residue was purified by flash column chromatography to yield 2.62 g (95%) of **17** as white solid. To each reaction tube of a 24-position Bohdan MiniBlock XT was added a solution of **17** in 1, 2-dichloroethane (2.1mL, 0.12 M), the appropriate amine (1.26 mmol) was added via syringe. The reactions were shaken for 4 hours at 450 rpm, and then 20 % HCl (3 mL) was added to each tube. The reactions were shaken for 15 additional minutes, and then passed into hydrophobic phase separator tubes, which allowed the halogenated organic layer to pass through into the collection tubes. The phase separators were closed, CH_2Cl_2 (3 mL) was added to each, and then shaking was continued for 10 minutes. The organic layers were again passed into the collection tubes containing the solutions from the first separation. Solvents were removed using a sample concentrator, and the reaction products were subjected to mass-directed preparative HPLC purification to give the product.

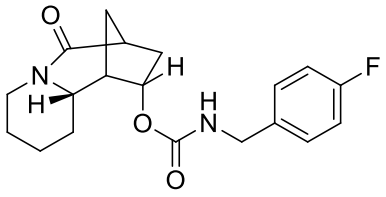


Procedure for the synthesis of amines 20a-x. Lactam **15** (2 g, 10.32 mmol) was dissolved in methanol. The solution was cooled to 0 °C and sodiumborohydride (784 mg, 20.71 mmol) was added to it. The reaction mixture was stirred at room temperature for 4h. The reaction mixture was quenched with 10% aq. NaOH solution and was extracted with ethyl acetate. The organic layer was dried over anhyd. Na_2SO_4 and concentrated to give the product **19** which was taken for the library development without further chromatpgraphic purification. To each pyrex glass vial placed on a 24-position block was added a solution of **19** in acetonitrile (1 mL, 0.5 M), the appropriate isocyanate (1 mmol) was added to each vial. The vials were irradiated in microwave at 110 ºC for 1 h and then the contents of each vial were transferred to a phase separators fitted on a 24 position Mini Block. Dichloromethane (3 mL) and saturated sodiumbicarbonate solution (3 mL) were added to each tube. The reactions were shaken for 15 minutes, and then allowed the halogenated organic layer to pass through into the collection tubes. The phase separators were closed, CH_2Cl_2 (3 mL) was added to each, and then shaking was continued for 10 minutes. The organic layers were again passed into the collection tubes containing the solutions from the first separation. Solvents were removed using a sample concentrator, and the reaction products were subjected to mass-directed preparative HPLC purification to give the product.

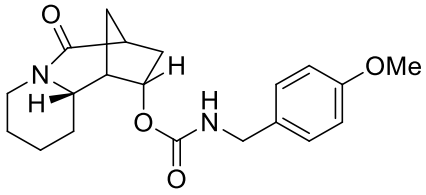


Procedure for the synthesis of amines 24. 7.77 mmol of **22** was dissolved in methanol (40 mL). The solution was cooled to 0 °C and sodiumborohydride (23.31 mmol) was added to it. The reaction mixture was stirred at room temperature for 4h. The reaction mixture was quenched with 10% aq. NaOH solution and was extracted with ethyl acetate. The organic layer was dried over anhyd. Na_2SO_4 and concentrated to obtain amino-alcohol **23** as a liquid. To be noted that the product was highly polar and not considered suitable for purification by column chromatography so was taken as such ahead for next step. To each reaction tube of a 24-position Bohdan MiniBlock XT was added a solution of **23** in THF (1 mL, 0.25 M), the appropriate isocyanate (0.5 mmol) was added. The reactions were shaken for 7 hours at 450 rpm. Then saturated $NaHCO_3$ (2 mL) and dichloromethane (4 mL) were added to each tube. The reactions were shaken for 15 additional minutes, and then passed into hydrophobic phase separator tubes, which allowed the halogenated organic layer to pass through into the collection tubes. The phase separators were closed, CH_2Cl_2 (3 mL) was added to each, and then shaking was continued for 10 minutes. The organic layers were again passed into the collection tubes containing the solutions from the first separation. Solvents were removed using a sample concentrator, and the reaction products were subjected to mass-directed preparative HPLC purification to give the product.

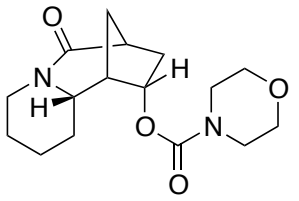
Spectral data of the representative members of the library compounds is listed below.



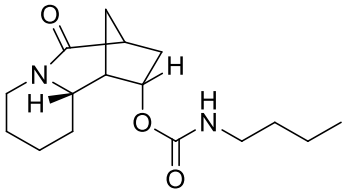
(7*S*,9*S*,10*S*,10a*S*)-6-oxodecahydro-7,10-methanopyrido[1,2-*a*]azepin-9-yl 4-fluorobenzylcarbamate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.11 (m, 2H), 7.10 – 6.88 (m, 2H), 5.35 – 5.00 (m, 2H), 4.62 – 4.44 (m, 1H), 4.36 – 4.27 (m, 2H), 3.40 – 3.25 (m, 1H), 2.75 – 2.60 (m, 2H), 2.52 – 2.25 (m, 2H), 2.00 – 1.50 (m, 7H), 1.45 – 1.03 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ174.3, 163.4, 160.9, 156.1, 134.3, 129.3, 129.2, 115.6, 115.4, 62.2, 44.3, 42.0, 41.4, 35.0, 30.2, 25.5, 25.2; IR (neat) ; IR (neat) 1634, 1709, 2943 cm^{-1}; HRMS calcd for (M^+ +1): 347.1771, found 347.1798.



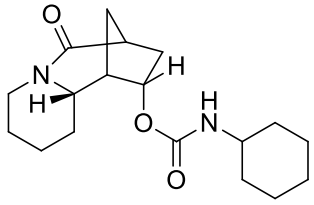
(7*S*,9*S*,10*S*,10a*S*)-6-oxodecahydro-7,10-methanopyrido[1,2-*a*]azepin-9-yl 4-methoxybenzylcarbamate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.04 (m, 2H), 6.95 – 6.65 (m, 2H), 5.33 – 4.93 (m, 2H), 4.62 – 4.44 (m, 1H), 4.39 – 4.18 (m, 2H), 3.76 (s, 3H), 3.40 – 3.25 (m, 1H), 2.77 – 2.52 (m, 2H), 2.52 – 2.22 (m, 2H), 2.02 – 1.47 (m, 7H), 1.44 – 1.04 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 159.0, 156.0, 130.6, 128.9, 114.0, 76.7, 62.1, 55.3, 44.5, 42.0, 41.4, 41.3, 35.0, 31.4, 30.1, 25.5, 25.1; IR (neat) 1634, 1710, 2941 cm^{-1}; HRMS calcd for (M^+ +1): 359.1971, found 359.2099.



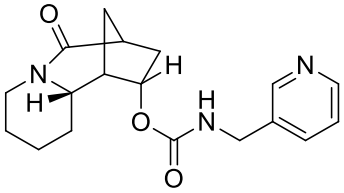
(7*S*,9*S*,10*S*,10a*S*)-6-oxodecahydro-7,10-methanopyrido[1,2-*a*]azepin-9-yl morpholine-4-carboxylate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17 (dt, *J* = 11.1, 5.8 Hz, 1H), 4.74 – 4.35 (m, 1H), 4.00 – 3.10 (m, 9H), 2.74 – 2.59 (m, 2H), 2.50 – 2.28 (m, 2H), 1.89 – 1.53 (m, 7H), 1.39 – 1.15 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 154.8, 76.7, 66.5, 62.0, 44.3, 43.9, 41.9, 41.4, 41.2, 35.0, 30.2, 25.4, 25.3; IR (neat) 1636, 1697, 2943 cm^{-1}; HRMS calcd for (M^+ +1): 309.1814, found 309.2050.



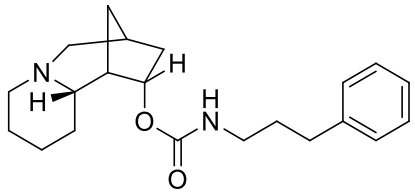
(7*S*,9*S*,10*S*,10a*S*)-6-oxodecahydro-7,10-methanopyrido[1,2-*a*]azepin-9-yl butylcarbamate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 – 4.76 (m, 2H), 4.54 – 4.44 (m, 1H), 3.35 – 3.20 (m, 1H), 3.11 – 2.98 (m, 2H), 2.46 – 2.20 (m, 4H), 1.95 – 1.50 (m, 7H), 1.47 – 1.06 (m, 6H), 0.83 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 156.0, 76.3, 62.1, 41.9, 41.3, 41.2, 40.6, 34.9, 31.9, 31.4, 29.9, 25.4, 25.1, 19.7, 13.6; IR (neat) 1635, 1711, 2938 cm^{-1}; HRMS calcd for (M^+ +1): 295.2021, found 295.2288.



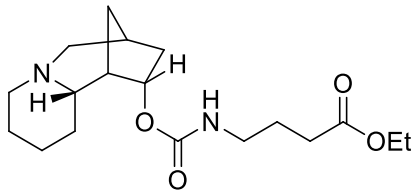
(7*S*,9*S*,10*S*,10a*S*)-6-oxodecahydro-7,10-methanopyrido[1,2-*a*]azepin-9-yl 2-cyclohexylacetate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 – 4.95 (m, 1H), 4.80 – 4.36 (m, 2H), 3.60 – 3.20 (m, 2H), 2.75 – 2.25 (m, 4H), 2.20 – 1.45 (m, 12H), 1.45 – 1.00 (m, 7H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 155.2, 76.3, 62.1, 49.8, 42.0, 41.4, 41.3, 34.9, 33.5, 33.2, 31.4, 30.0, 25.5, 25.4, 25.2, 24.8, 24.7; IR (neat) 1635, 1710, 2936 cm^{-1}; HRMS calcd for (M^+ +1): 321.2178, found 321.2421.



(7*S*,9*S*,10*S*,10a*S*)-6-oxodecahydro-7,10-methanopyrido[1,2-*a*]azepin-9-yl (pyridin-3-ylmethyl)carbamate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 – 8.25 (m, 2H), 7.61 (d, J = 7.8 Hz, 1H), 7.38 – 7.07 (m, 1H), 6.11 (t, J = 5.8 Hz, 1H), 5.14 (dt, J = 10.8, 5.5 Hz, 1H), 4.57 – 4.25 (m, 3H), 3.35 – 3.15 (m, 1H), 2.36 – 2.29 (m, 4H), 1.93 – 1.36 (m, 7H), 1.30 – 0.90 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 156.2, 148.9, 148.6, 135.4, 134.4, 123.5, 76.7, 62.1, 42.4, 42.0, 41.4, 41.2, 35.1, 31.4, 30.0, 25.4, 25.1; IR (neat) 1635, 1712, 2940, 3261 cm^{-1}; HRMS calcd for (M^+ +1): 330.1820, found 330.1818.

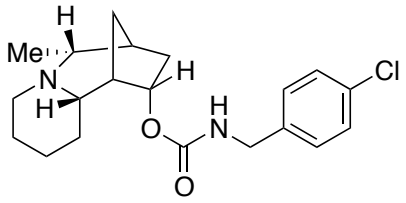


(7*S*,9*S*,10*S*,10a*S*)-decahydro-7,10-methanopyrido[1,2-*a*]azepin-9-yl(3-phenylpropyl)carbamate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.03 (m, 5H), 5.25 – 4.75 (m, 2H), 3.43 – 2.90 (m, 3H), 2.90 – 2.70 (m, 2H), 2.70 – 2.30 (m, 4H), 2.25 – 1.25 (m, 13H), 1.30 – 1.10 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.8, 141.5, 128.4, 128.3, 125.9, 67.9, 63.2, 56.6, 42.4, 40.8, 40.4, 37.5, 34.1, 33.9, 33.0, 31.6, 30.6, 25.5, 25.3; IR (neat) 1695, 2934 cm^{-1} ; HRMS calcd for (M^+ +1): 343.2387, found 343.2325.

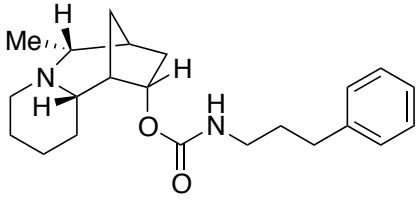


Ethyl 4-(7*S*,9*S*,10*S*,10a*S*)-decahydro-7,10-methanopyrido[1,2-*a*]azepin-9-yl)oxy)carbonyl)amino)butanoate:^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21 – 4.90 (m, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.50 – 2.80 (m, 4H), 2.80 – 2.60 (m, 2H), 2.31 (t, *J* = 7.4 Hz, 2H), 2.22 – 1.44 (m, 13H), 1.44 – 1.29 (m, 2H), 1.21 (t, *J* = 8 Hz, 3H), 1.21 – 0.99 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 156.8, 76.7, 67.8, 63.1, 60.4, 56.6, 42.3, 40.9, 40.2, 37.4, 34.0, 33.9, 31.4, 30.6,

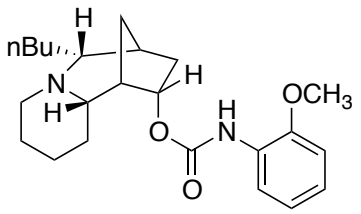
25.5, 25.2, 14.1; IR (neat) 1715, 2934 cm^{-1}; HRMS calcd for (M^+ +1): 339.2285, found 339.2277.



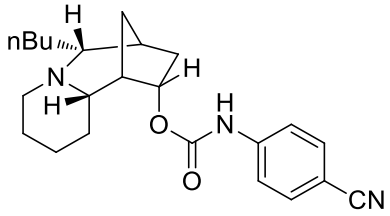
(6*R*,7*S*,9*S*,10*S*,10a*S*)-6-methyldecahydro-7,10-methanopyrido[1,2-*a*]azepin-9-yl]4-chlorobenzylcarbamate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 4.7, 3.6 Hz, 2H), 7.23 (d, *J* = 8.3 Hz, 2H), 5.35 (bs, 1H), 5.10 (dt, *J* = 10.8, 5.4 Hz, 1H), 4.38 (dd, *J* = 15.2, 6.4 Hz, 1H), 4.28 (dd, *J* = 15.2, 5.9 Hz, 1H), 3.30 – 3.10 (m, 1H), 2.15 – 1.92 (m, 4H), 1.89 – 1.42 (m, 9H), 1.37 (d, *J* = 12.4 Hz, 1H), 1.27 – 1.08 (m, 1H), 1.03 (d, *J* = 8.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.8, 137.3, 133.0, 128.8, 128.6, 68.3, 63.7, 52.7, 44.3, 43.1, 41.0, 40.9, 37.7, 31.2, 29.9, 25.9, 25.7, 18.3; IR (neat) 1704, 2935 cm^{-1}; HRMS calcd for (M^+ +1): , found.



(6*R*,7*S*,9*S*,10*S*,10a*S*)-6-methyldecahydro-7,10-methanopyrido[1,2-*a*]azepin-9-yl(3-phenylpropyl)carbamate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.24 (m, 2H), 7.19 (dd, *J* = 10.2, 4.5 Hz, 3H), 5.10 (dt, *J* = 10.8, 5.4 Hz, 1H), 4.96 (bs, 1H), 3.34 – 3.08 (m, 3H), 2.79 – 2.49 (m, 4H), 2.14 – 1.98 (m, 4H), 1.93 – 1.33 (m, 10H), 1.25 – 1.05 (m, 1H); 1.05 (d, *J* = 8.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.8, 141.5, 128.4, 128.3, 125.9, 68.4, 63.7, 52.8, 43.1, 41.0, 40.9, 40.4, 37.7, 33.0, 31.6, 31.2, 29.9, 26.0, 25.8, 18.3; IR (neat) 1697, 2931 cm^{-1}; HRMS calcd for (M^+ +1): , found.



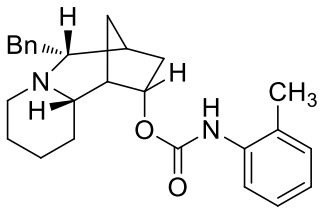
(6*R*,7*S*,9*S*,10*S*,10a*S*)-6-butyldecahydro-7,10-methanopyrido[1,2-*a*]azepin-9-yl(2-methoxyphenyl)carbamate. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (dd, *J* = 7.6, 2.1 Hz, 1H), 7.39 (bs, 1H), 7.05 – 6.89 (m, 2H), 6.87 – 6.76 (m, 1H), 5.18 (dt, *J* = 10.9, 5.6 Hz, 1H), 3.83 (s, 3H), 3.40 – 3.25 (m, 1H), 2.21 (m, 1H), 2.13 – 1.95 (m, 3H), 1.96 – 1.00 (m, 17H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7, 147.6, 127.9, 122.4, 121.0, 118.1, 109.9, 77.5, 69.4, 68.9, 55.5, 52.9, 43.1, 37.3, 37.1, 31.4, 30.7, 29.8, 29.6, 26.1, 25.8, 23.0, 14.0; IR (neat) 1602, 1723, 2935 cm^{-1}; HRMS calcd for (M^+ +1): 386.264, found 387.2618.



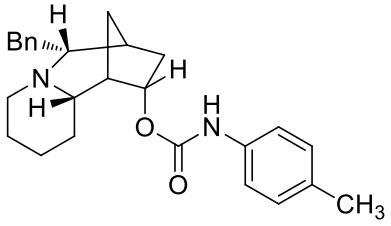
(6*R*,7*S*,9*S*,10*S*,10a*S*)-6-butyldecahydro-7,10-methanopyrido[1,2-*a*]azepin-9-yl (4-cyanophenyl)carbamate

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.37 (m, 5H), 5.15 (dt, *J* = 11.0, 5.5 Hz, 1H), 3.28 (d, *J* = 11.2 Hz, 1H), 2.20 – 2.15 (m, 1H), 2.11 – 1.95 (m, 3H), 1.89 (d, *J* = 6.7 Hz, 1H), 1.85 – 1.34 (m, 11H), 1.34 – 1.05 (m, 6H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.26, 142.6, 133.2, 119.0, 118.2, 105.7, 78.1, 69.2, 68.6, 52.7, 43.0, 40.9, 37.1, 31.5, 30.7, 30.1, 29.5,

26.0, 25.7, 23.0, 14.0. IR (neat) 1596, 1727, 2222, 2931 cm^{-1}; HRMS calcd for (M^+ +1): 382.2496, found 382.2486.

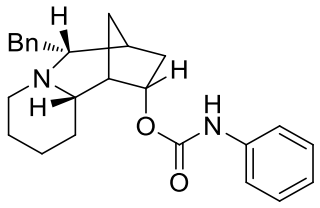


(6*R*,7*S*,9*S*,10*S*,10a*S*)-6-benzyldecahydro-7,10-methanopyrido[1,2-*a*]azepin-9-yl]*o*-tolylcarbamate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.29 (dd, *J* = 8.1, 6.6 Hz, 2H), 7.25 – 7.10 (m, 5H), 7.04 (t, *J* = 7.3 Hz, 1H), 6.63 (s, 1H), 5.17 (dt, *J* = 10.9, 5.6 Hz, 1H), 3.60 – 3.40 (d, *J* = 10.3 Hz, 1H), 3.20 (dd, *J* = 13.3, 2.7 Hz, 1H), 2.50 – 1.20 (m, 19H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8, 140.2, 136.0, 130.4, 129.5, 128.3, 126.7, 125.9, 124.2, 70.6, 68.7, 52.9, 43.1, 41.0, 37.2, 37.1, 35.8, 31.4, 29.7, 26.1, 25.7, 17.9; IR (neat) 1720, 2935 cm^{-1}; HRMS calcd for (M^+ +1): 405.2543, found 405.2528.



(6*R*,7*S*,9*S*,10*S*,10a*S*)-6-benzyldecahydro-7,10-methanopyrido[1,2-*a*]azepin-9-yl *p*-tolylcarbamate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.25 (m, 4H), 7.25-7.21 (m, 1H), 7.18 – 7.06 (m, 4H), 6.85 (s, 1H), 5.19 (dt, *J* = 10.9, 5.5 Hz, 1H), 3.57 (d, *J* = 11.1 Hz, 1H), 3.21 (dd, *J* = 13.3, 2.9 Hz, 1H), 2.63 (s, 3H), 2.40 – 2.35 (m, 1H), 2.25 – 1.60 (m, 12H), 1.60 – 1.40 (m,

1H), 1.37 (dd, *J* = 11.6, 2.3 Hz, 1H), 1.31 – 1.12 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8, 140.21, 135.59, 132.79, 129.5, 128.3, 125.9, 120.0, 118.6, 70.6, 68.9, 53.0, 43.2, 41.0, 37.3, 37.2, 35.8, 31.5, 29.9, 26.1, 25.8, 20.7; IR (neat) 1718, 2935 cm^{-1}; HRMS calcd for (M^+ +1): 405.2543, found 405.2544.



(6*R*,7*S*,9*S*,10*S*,10a*S*)-6-benzyldecahydro-7,10-methanopyrido[1,2-*a*]azepin-9-yl phenylcarbamate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 8.6, 1.0 Hz, 2H), 7.39 – 7.26 (m, 4H), 7.22 (dd, *J* = 8.4, 6.3 Hz, 1H), 7.18 – 7.12 (m, 2H), 7.12 – 7.04 (m, 1H), 6.88 (s, 1H), 5.32 – 5.08 (m, 1H), 3.59 – 3.56 (m, 1H), 3.22 (dd, *J* = 13.3, 3.0 Hz, 1H), 2.41 (dd, *J* = 13.2, 10.1 Hz, 1H), 2.36 – 2.24 (m, 1H), 2.25 – 2.06 (m, 3H), 2.06 – 1.56 (m, 8H), 1.52 – 1.45 (m, 1H), 1.37 (dd, *J* = 11.6, 2.4 Hz, 1H), 1.24 (m, 1H): ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6, 140.1, 138.1, 129.5, 129.0, 128.3, 125.9, 123.2, 118.5, 70.6, 68.9, 53.0, 43.2, 41.0, 37.3, 37.2, 35.8, 31.6, 29.9, 26.1, 25.7; IR (neat) 1600, 1702, 2933 cm^{-1}; HRMS calcd for (M^+ +1): 391.2387, found 391.2295.

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