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DESIGN AND SYNTHESIS OF ORGANIC MOLECULES WITH NEW PHYSICAL AND BIOLOGICAL PROPERTIES

by

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Design and Synthesis of Organic Molecules with New Physical and Biological Properties

Gil Ma, PhD

University of Pittsburgh, 2005

ABSTRACT: Poly(cyclic urea) compounds were synthesized and tested as substitutes of hexamethylphosphoramide (HMPA). HMPA is a potent carcinogen but demonstrates excellent properties as an additive in organometal chemistry. The poly(cyclic urea), which showed similar properties to HMPA in solution, was attached to a variety of resins in an effort to create a new polymer-supported reagent. Polymer-supported HMPA was also prepared by suspension polymerization. In diverse reactions, these reagents showed very similar properties to HMPA, were easily removed by filtration and could be recycled without loss of chemical activity.

Highly functionalized spiroketals were designed and synthesized as mimics of calyculin A, a known protein phosphatase inhibitor. Regio- and stereoselective reductions, hetero-Diels-Alder reactions and spiroketalizations gave eight diastereomeric spiroketal compounds. Additionally, through asymmetric crotylations, phosphorylations and cross-metathesis, a series of new phosphoric acid compounds were also synthesized.

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Finally, I would like to thank my parents, brother, and sisters for their continual support and understanding during my whole life.

ABBREVIATIONS

Bn	Benzyl
BOMCl	Benzyloxymethyl chloride
CIP	Contact ion pair
DHP	Dihydropyran
DIB	(Diacetoxyiodo)benzene
DIBAL	Diisobutylaluminum hydride
DIPEA	Diisopropylethyl amine
DMAP	4-Dimethylaminopyridine
DMEU	*N*,*N*´-Dimethyl-*N*,*N*´-ethylenurea
DMF	Dimethylformamide
DMP	Dess-Martin periodinane
DMPU	*N*,*N*´-Dimethyl-*N*,*N*´-propylenurea
DVB	Divinylbenzene
EI	Electron ionization
ESI	Electro-spray ionization
HPLC	High performance liquid chromatography
HMBC	Heteronuclear multiple bond correlation
HMPA	Hexamethylphosphoramide
HMTTA	*N*,*N*,*N*',*N*'',*N*''',*N*'''-Hexamethyltriethylenetetraamine
IC_{50}	Median inhibition concentration
Imid.	Imidazole
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
LFRP	Living free radical polymerization
L-Selectride	Lithium tri-*sec*-butylborohydride
MS	Molecular sieves
NOESY	Nuclear Overhauser enhancement and exchange spectroscopy

PEG	Poly(ethylene glycol)
PK	Protein kinase
PMDTA	*N*,*N*,*N'*,*N''*,*N''*-Pentamethyldiethylenetriamine
PP	Protein phosphatase
PPM	Metal-dependent protein phosphatase
PPP	Phosphoprotein phosphatase
PPTS	Pyridinium p-toluenesulfonate
PS	Polystyrene
PSTPaes	Protein serine threonine phosphatase
PTB	Protein tyrosin phosphatase
PTHF	Polytetrahydrofuran
Py	Pyridine
ROMP	Ring opening metathesis polymerization
SAR	Structure activity relationship
SIP	Separated ion pair
TBAB	Tetrabutylammonium bromide
TBDPS	*t*-Butyldiphenylsilyl
TBS	*t*-Butyldimethylsilyl
TEA	Triethylamine
TES	Triethylsilyl
TFA	Trifluoroacetic acid
Tf	Trifluorosulfonyl
THF	Tetrahydrofuran
THP	2-Tetrahydropyran
TMS	Trimethylsilane
Ts	*p*-Toluenesulfonyl

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1. Synthesis and Application of New Urea Additives for Solid and Solution Phase Organic Syntheses

1.1. Introduction

Solid phase reagents and scavengers have become powerful tools for organic synthesis.[1] By using solid phase reagents and scavengers, one is able to employ reaction conditions developed in solution phase, without the re-optimization necessary for solid phase reactions. This technology takes advantage of the unique nature of these solid phase reagents, e.g. the ability to use excess reagents for the complete conversion and avoid chromatographic purifications (Figure 1). Reusable solid-supported reagents reduce the amount of waste and exposure to toxic reagents due to their simple removal by filtration.

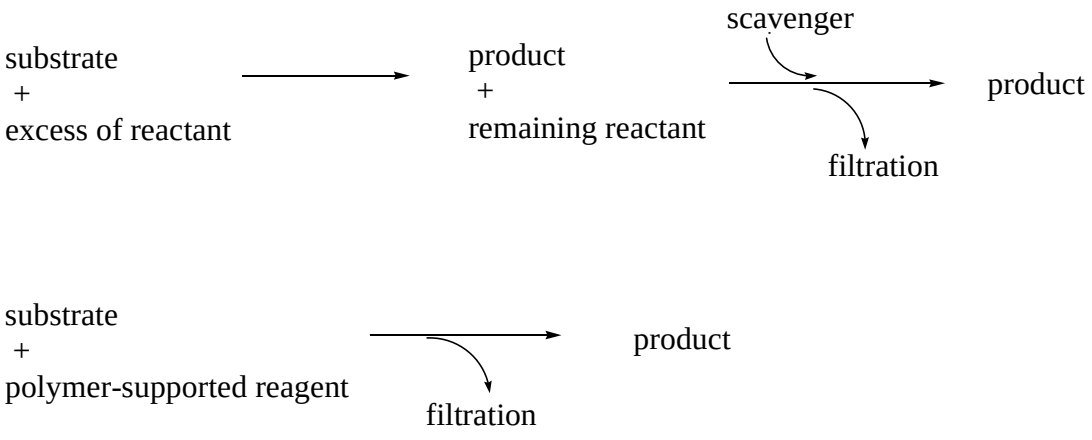


Figure 1. General concept for the use of solid phase reagents or scavengers.

One can design solid-supported reagents based on solution phase reagents that suffer from high toxicity and difficult removal from the reaction medium. Hexamethylphosphoramide

(HMPA) has been used catalytically, stoichiometrically or in excess to control the stereochemistry in the product or to bias the reaction selectivity. It has been extensively used in a variety of reactions due to its unique properties as a polar aprotic solvent and its superior ability to form cation-ligand complexes.[2] HMPA coordinates very well to metal ions, increasing the nucleophilicity of their counter ions and influencing the reaction kinetics. For example, HMPA coordinates well to lithium, approximately 300 times better than tetrahydrofuran (THF).[3] In the case of the nucleophilic addition to α,β-unsaturated carbonyl compounds, HMPA has been shown to alter the regioselectivity. In Figure 2, the proposed mechanisms for observed addition products are shown. Where contact ion pairs (CIP) exist with tightly associated C-Li species, the 1,2-addition product (**3**) is formed via a four-centered transition state, whereas solvent-separated ion pairs (SIP) give the 1,4-addition product (**2**) predominantly. For well-stabilized anions, in the absence of HMPA, where lithium is a possible catalyst and SIPs are energetically accessible reactive intermediates, mixtures of 1,2- and 1,4-addition products are observed.[4]

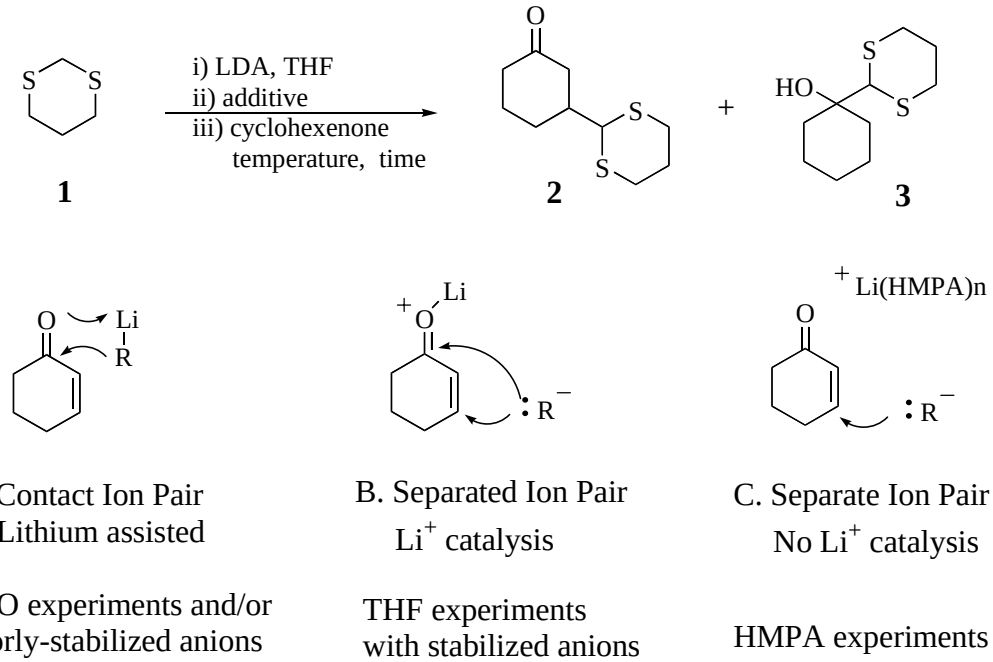
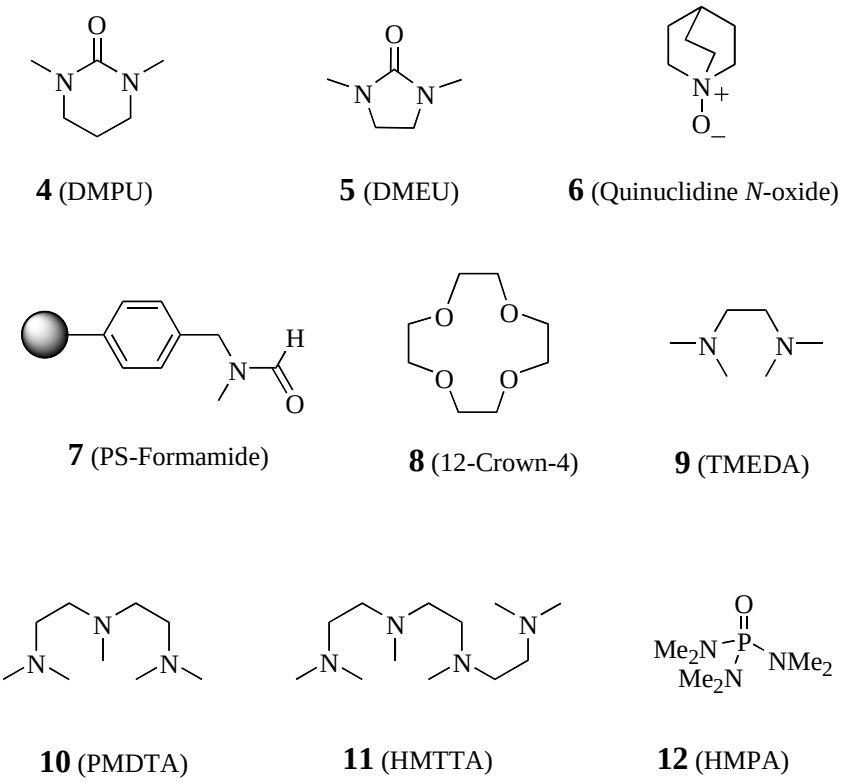


Figure 2. Mechanistic proposal for additions to α,β-unsaturated carbonyl compounds.

Reports surfaced in the literature in the early 1970's attesting to the toxicity of HMPA. In animal studies, low to moderate toxicity was observed either by ingestion, inhalation, or skin absorption. Chronic toxicity by HMPA was believed to have led to rare forms of cancer produced in rats by inhalation of HMPA (concentration of about 400 ppb) over 8 months.[5] Due to the toxicity and potential carcinogenicity of HMPA, its use has been restricted to small laboratory scale reactions. It therefore becomes necessary to find suitable alternatives to HMPA.



4 (DMPU) **5** (DMEU) **6** (Quinuclidine *N*-oxide)

7 (PS-Formamide) **8** (12-Crown-4) **9** (TMEDA)

10 (PMDTA) **11** (HMTTA) **12** (HMPA)

Figure 3. Examples of alternative additives to HMPA.

Since Seebach reported the use of DMPU as a safe alternative to the carcinogenic HMPA in a variety of reactions,[6] several research groups have shown that other types of compounds such as cyclic ureas **4** and **5**,[7] the N-oxide **6**,[8] amines **9**–**11**[9] and formamide **7**[10] have physical properties similar to those of HMPA (Figure 3). However, some of these have only limited uses.

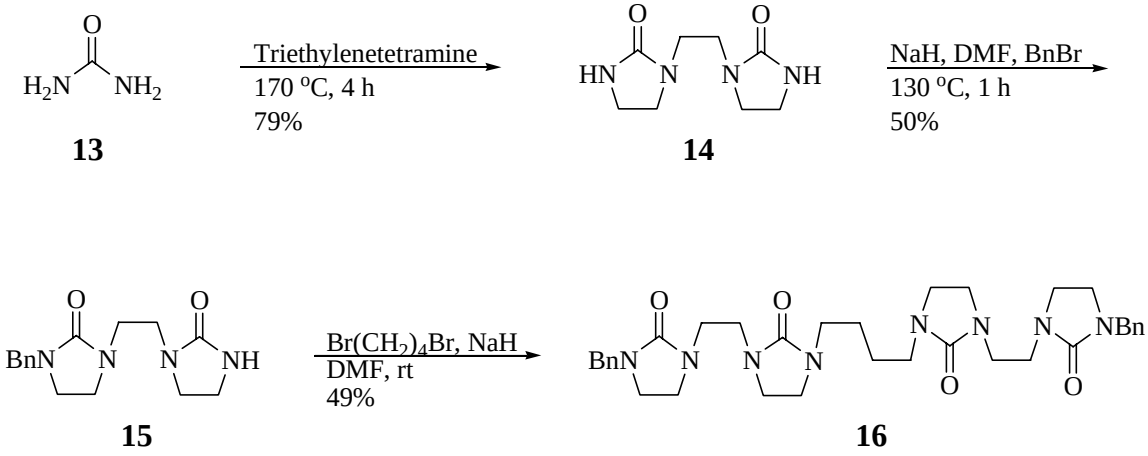
Among these compounds, cyclic ureas have been the most popular substitute. DMPU (**4**) and DMEU (**5**) possess physical properties quite similar to those of HMPA.[6a] In numerous reports, excess DMPU was necessary to elicit a similar effect like HMPA. Also, DMPU is hygroscopic and miscible with water at any ratio, thus it is easily removed from solutions of hydrocarbons or ether by washing with water. Additionally, although carrying a carbonyl group, DMPU is remarkably unreactive even in the presence of strong bases or nucleophiles at low temperatures (below –35 °C). The synthesis of this urea is quite simple and allows for modifications including the introduction of a chiral group on nitrogen or functional groups on the cyclic carbon chain.[7]

Based on these considerations, our approach aims at the development of new cyclic urea derivatives as substitutes of HMPA, eventually leading to the preparation and application of new solid phase reagents. Our ideal urea derivatives in both solution phase and later on solid-support must allow for an effective chelation of metal ion as demonstrated by DMPU in solution. We assumed that poly(cyclic urea) structures could serve this purpose. Poly(cyclic urea) can increase the loading of urea units on the resin, where each unit on the resin functions as an additive.

1.2. Results and Discussion

1.2.1. Synthesis of new poly(cyclic urea)

Poly(cyclic urea) compounds were synthesized to explore their properties as additives in solution and solid phase reactions. While DMPU (**4**) is the most popular alternative to HMPA and shows better solubility in common solvents at low temperatures, dimers containing DMEU (**5**) units were prepared more readily from commercially available reagents. The first generation of poly(cyclic urea) **16**, a linear tetramer of DMEU units, was constructed from two dimers **15**, joined by a flexible *n*-butyl linker as shown in Scheme 1.



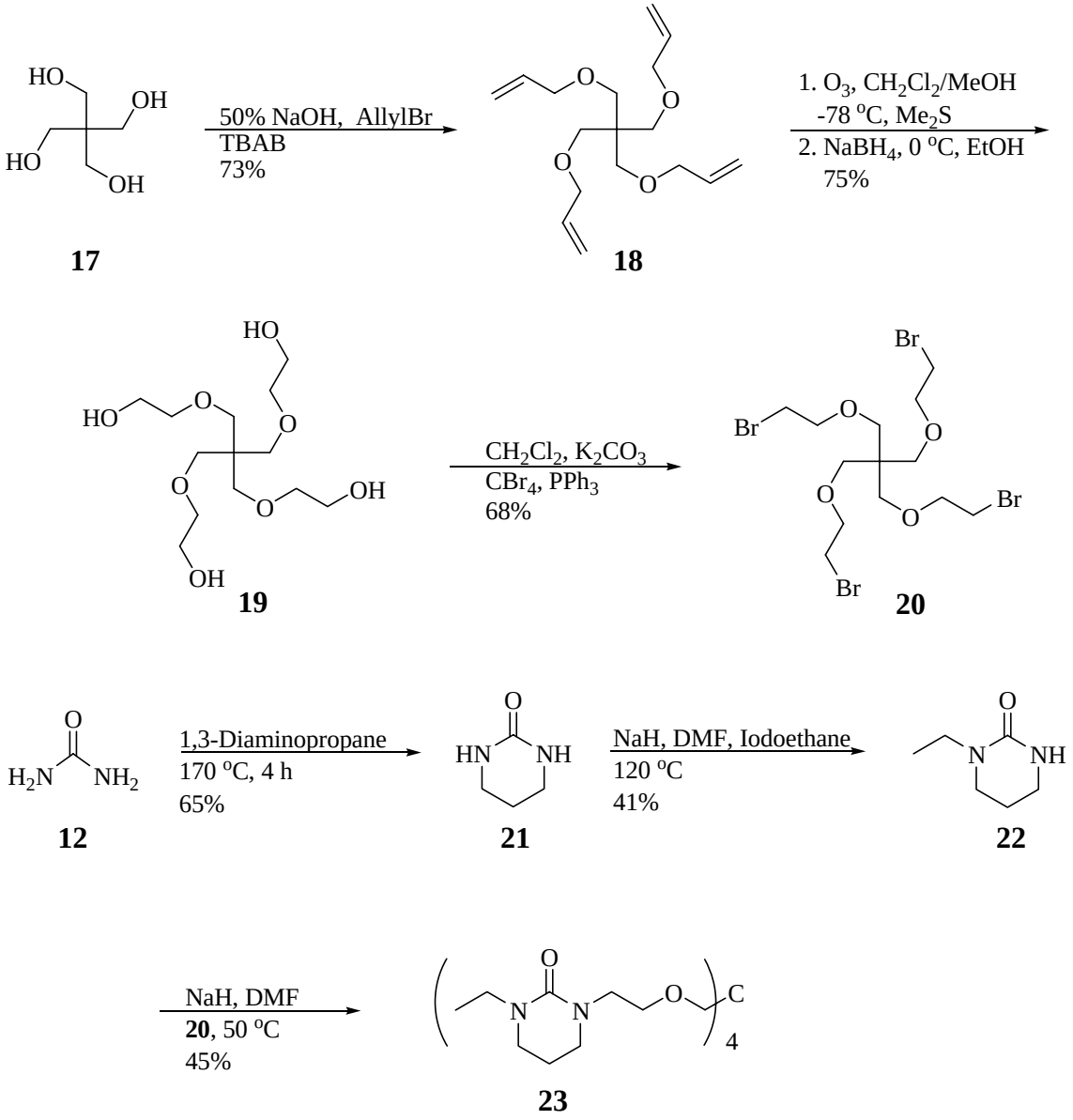
Scheme 1. Synthesis of tetracyclic urea **16.**

Heating urea **13** and triethylenetetramine at 170 °C for 4 h and precipitation of the product with MeOH gave the DMEU dimer **14** in 79% yield.[11] Monobenzylation of **14** was achieved only at high temperature (130 °C) in DMF due to the low solubility of **14**. Trituration of the crude monobenzylated urea **15** with ethyl ether resulted in a 50% yield of pure material. Dialkylation of **15** with 1,4–dibromobutane and recrystallization from THF led to a 49% yield of

the tetracyclic urea **16**. Thus, the synthesis of tetramer **16** was achieved in 3 steps without any chromatography. However, both intermediate **15** and additive **16** demonstrated low solubility at low temperatures (–78 °C) in THF, which is often the solvent used for reactions with Li-reagents such as LDA, *n*-BuLi, and *t*-BuLi. Therefore, the benzyl group, which might be responsible for intermolecular stacking, was replaced by ethyl and propyl groups. These poly(cyclic urea)s also precipitated readily from THF at low temperature. The lack of solubility prevented proper investigations of poly(cyclic urea)s such as **16** as additives, despite their easy preparation on multigram scale. We envisioned that, alternatively, the use of the more popular DMPU unit, which has a lower freezing point and better solubility than DMEU, would improve the solubility of the prospective additive at low temperatures in organic solvents. Additionally, a branched structure was believed to better situate the urea units for chelation of metal ions than the previously shown linear structure. Conceivably, this structure could be expanded into a dendrimer to provide higher loadings. Thus, the readily functionalized pentaerythritol **17**[12] was used as the core upon which the star-like polyurea structures were built (Scheme 2). Allylation of pentaerythritol with allyl bromide in the presence of 50% aqueous NaOH under phase transfer catalysis furnished the tetraallyl ether **18** in 73% yield.[12a] Allyl ether **18** was converted by ozonolysis and subsequent $NaBH_4$ treatment to the tetraalcohol **19** in 75% yield. Compound **19** was then brominated to give the tetrabromide **20** in 68% yield.

For the synthesis of the polyamine core of the DMPU dimer, numerous steps were necessary and the price of commercially available polyamines was prohibitive. Therefore, a monofunctionalized DMPU unit was prepared from readily available materials, as shown in Scheme 2. The DMPU unit **21**[13] was prepared in 65% yield by heating urea with 1,3-diaminopropane at 170 °C, followed by recrystallization from EtOH. Monoalkylation of urea **21**

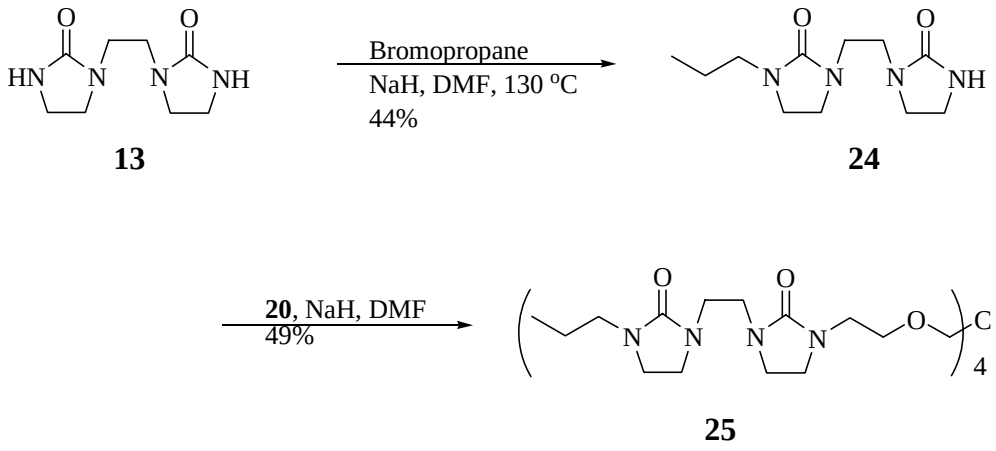
with iodoethane gave **22**[14] in 41% yield. Assembly of additive **23** was achieved by alkylation of **22** with tetrabromide **20** in 45% yield.



Scheme 2. Synthesis of poly(cyclic urea) **23.**

Similarly, additive **25** containing dimeric DMEU units in the star-like structure was also synthesized (Scheme 3). Compound **24** was prepared by mono-alkylation of bridged urea **13** with

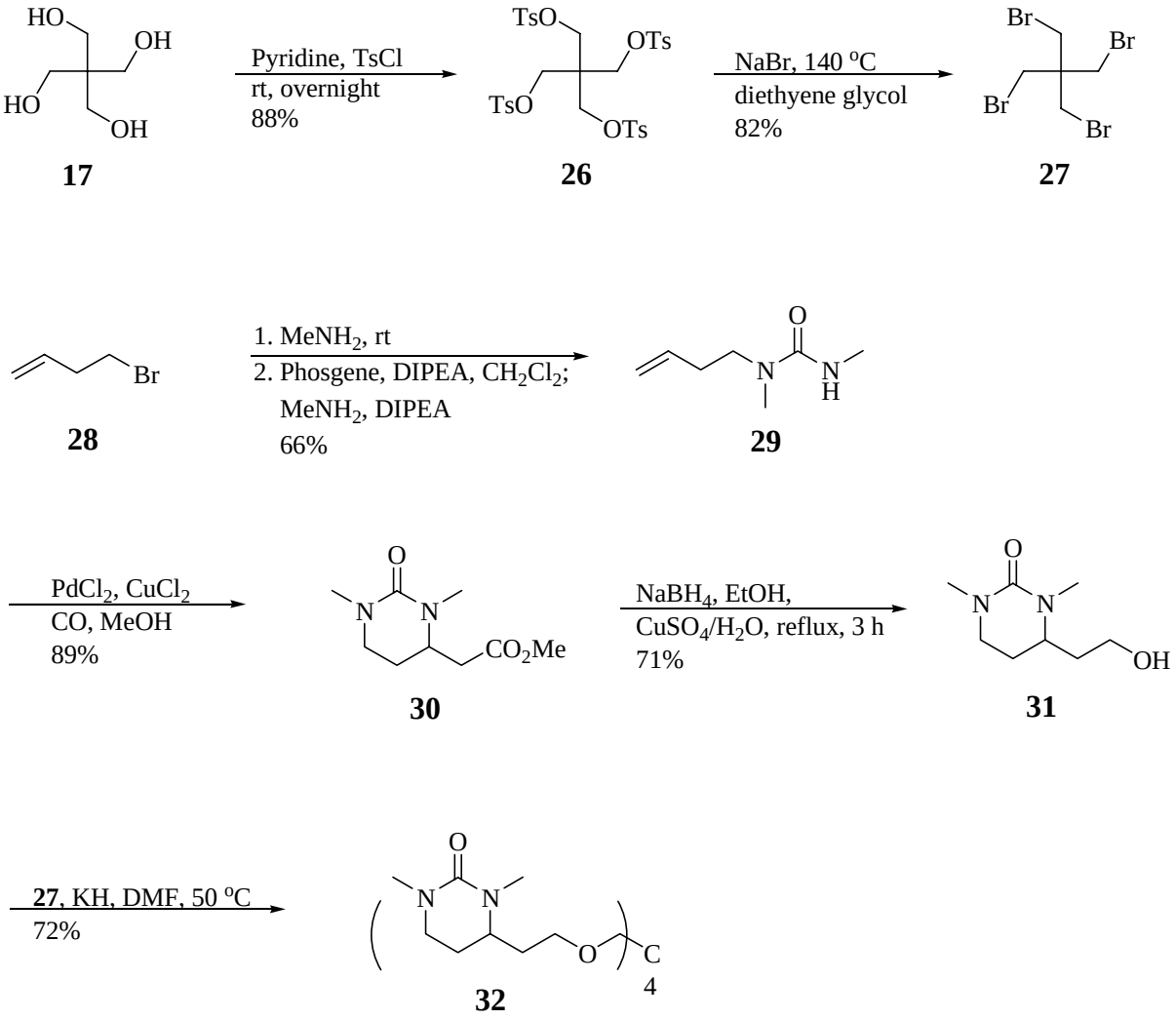
bromopropane in 44% yield. Alkylation of **24** with tetrabromide **20** gave poly(cyclic urea) **25** in 49% yield as outlined in Scheme 3**.**



13 **24** **25**

Scheme 3. Synthesis of poly(cyclic urea) **25.**

To reduce the steric hindrance around the carbonyl moiety by the linker chains in the poly(cyclic urea)s and to better mimic DMPU, poly(cyclic urea) **32** was synthesized as shown in Scheme 4. Tosylation, followed by bromination of pentaerythritol, provided the known compound **27** as the template for the new additive **32** in 72% yield over 2 steps.[15] *N*-3-Butenylurea **29** was prepared from 3-butenyl bromide (**28**) by successive treatment with methylamine (neat), phosgene and a solution of methylamine in THF in 66% yield over 2 steps. The synthesis of cyclic urea **30** was achieved by a Pd(II)-catalyzed intramolecular amidocarbonylation of **29** in 89% yield.[16]



Scheme 4. Synthesis of poly(cyclic urea) **32.**

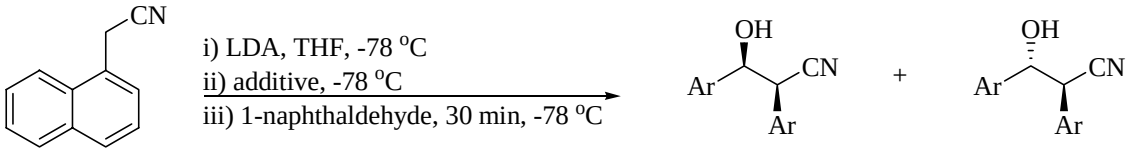
Reduction of the methylester **30** with $NaBH_4$ proceeded slowly and after 24 h gave only low yields of the expected alcohol. However, addition of an aqueous $CuSO_4$ solution (10 mol%)[17] accelerated the reaction rate and within 3 h alcohol **31** was obtained in 71% yield. Alkylation of **31** with compound **27** using KH, a more effective base in this case than NaH, gave a 72% yield of poly(cyclic urea) **32**. While no improvement in the solubility of additive **24** in THF at lower temperature was observed, poly(cyclic urea)s **23** and **32** readily dissolved in THF

at –78 °C at concentrations of up to 0.02 M. These polyureas were examined for their properties as alternatives to HMPA.

1.2.2. Application of additives in solution phase reactions

Three reactions, in which HMPA was previously used as an additive, were selected and studied in the presence of the new poly(cyclic urea)s.

Table 1. Aldol reaction in the presence of poly(cyclic urea)s.



33 ***Syn*-34** ***Anti*-34**

Entry	Additive	Ratio (*Syn*:*Anti*)[a]	Yield (%)[b]
1	-	32:68	91
2	6 eq HMPA	91:9	97
3	6 eq DMEU	67:33	58
4	20 eq DMEU	81:19	83
5	2 eq **16**	47:53	73
6	1 eq **25**	52:48	80

a) Determined by ^{1}H NMR; b) isolated yield.

The influence of additives on the aldol reaction of 1-naphthylacetonitrile and 1-naphthaldehyde was examined first. Carlier and co-workers reported that lithiated 1-naphthylacetonitrile underwent highly *syn*-selective addition to aromatic aldehydes in an HMPA-

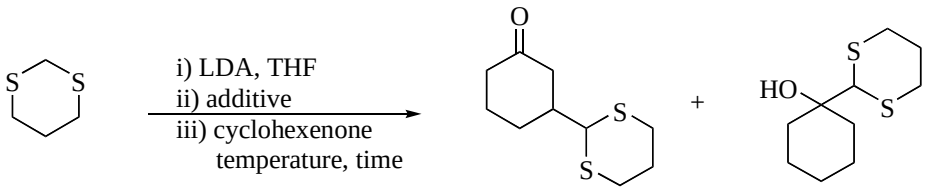
THF solution.[18] They suggested that the selectivity attained was traced to an HMPA-facilitated retro-aldol reaction under thermodynamic control. DMEU-based poly(cyclic urea)s **16** and **25** were tested as additives in this aldol reaction. The results are shown in Table 1. We observed an increase in the *syn*-selectivity of the addition to 1-naphthaldehyde in the presence of HMPA and DMEU (entries 2 to 4). However, in the presence of poly(cyclic urea) additives **16** and **25**, only low selectivity was observed after 30 min (entries 5 and 6). Larger equivalents of the additives would be necessary to show high *syn*-selectivity but the usage of these poly(cyclic urea)s was limited by their low solubilities.

The regiochemistry of addition to α,β-unsaturated carbonyl compounds can be altered in the presence of HMPA. The suppression of the 1,2-addition in favor of the 1,4-addition of lithiodithiane to 2-cyclohexen-1-one has been effectively demonstrated. A number of groups have also shown that DMPU was almost as efficient as HMPA in this reaction.[6] Also, they have directed extensive efforts at elucidating the effects that changes in solvent, temperature, and steric bulk on the carbonyl site have on the regioselectivity of these additions.[19] The effects of our poly(cyclic urea)s on the regiochemical outcome of the condensation of 1,3-dithiane anion and 2-cyclohexen-1-one are summarized in Table 2.

In the absence of any additives, the 1,2-addition product was obtained exclusively (entry 1). The addition of 2 equivalents of HMPA demonstrated a strong regiochemical bias towards the 1,4-addition of 1,3-dithiane (entry 2). While varying the reaction time had little effect on the regiochemical outcome and the yield of the addition, the presence of additives and lowering the reaction temperatures kinetically favored the 1,4-addition product. At high temperatures (entries 3 to 7), all cyclic urea additives (0.5 eq to 8 eq) performed poorly compared to HMPA. However, at –78 °C, along with DMPU (8 eq, entry 9), our additives **23** and **32** (1 eq, entries 10 and 11,

respectively) drove the reactions to give the 1,4-addition product predominantly. Generally, the use of excess 1,3-dithiane anion improved the yield of both regioisomers.

Table 2. Regioselective addition of 1,3-lithiodithiane to cyclohexenone in the presence of poly(cyclic urea)s.



1 **2** **3**

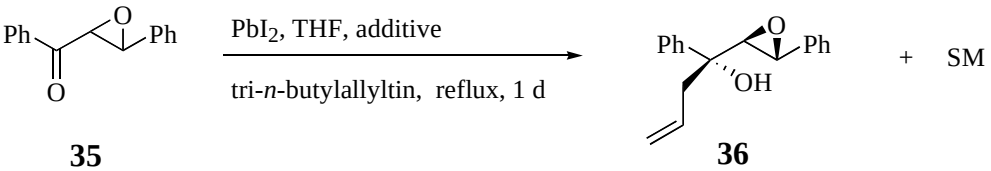
Entry	DS:CY:additive[a]	Additive	**2** : **3**[b]	Yield (%)[c]	mmol/mL[d]
1	2:1:0	-	0:100	83	0.02
2	2:1:2	HMPA	94 : 6	92	0.2
3	2:1:1	**16**	79 : 21	31	0.02
4	2:1:8	DMEU	35: 65	82	0.04
5	2:1:8	DMPU	42:58	88	0.04
6	2:1:0.5	**25**	28:72	71	0.04
7	2:1:2	**23**	67:33	72	0.02
8	2:1:8	DMEU	60:40	87	0.04
9	2:1:8	DMPU	92:8	72	0.02
10	2:1:1	**23**	87:13	94	0.02
11	2:1:1	**32**	90:10	90	0.02

a) DS = 1,3-dithiane, CY = 2-cyclohexen-1-one; b) ratio determined by ^{1}H NMR; c) isolated; d) concentration of 2-cyclohexen-1-one; e) reaction conditions; entries 1 and 2, –78 °C, 2 h; entries 3 to 7, –22 °C to 0 °C, 2 h; entries 8 to 10, –78 °C, 15 min; entry 11, –78 °C, 25 min.

The number of urea units in 1 equivalent of **23** or **32** is matched by 4 equivalents of DMPU. Interestingly, using only 1 equivalent of the synthetic additives **23** or **32** produced a

similar bias to the 1,4-addition product, as compared with 8 equivalents of either DMEU or DMPU (entries 8 to 11). Poly(cyclic urea) **32**, with its markedly improved solubility and reduced steric hindrance about the carbonyl site, provided the best regioselective outcome and yield comparable to HMPA.

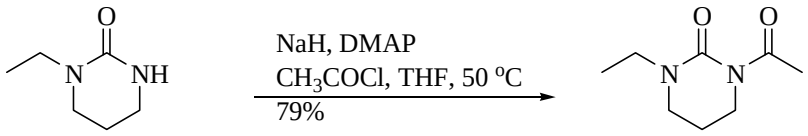
Table 3. Carbonyl-selective allylation of an α,β-epoxy ketone with poly(cyclic urea)s.



35 **36**

Entry	Additive	**36** (%)[a]	SM (%)[a]
1	1 eq DMPU	41	57
2	0.2 eq HMPA	78	25
3	0.2 eq **16**	38	51
4	0.2 eq **25**	6	87
5	0.2 eq **23**	5	95
6	0.2 eq **37**	16	80
7	1 eq **37**	57	37

a) Determined by ^{1}H NMR



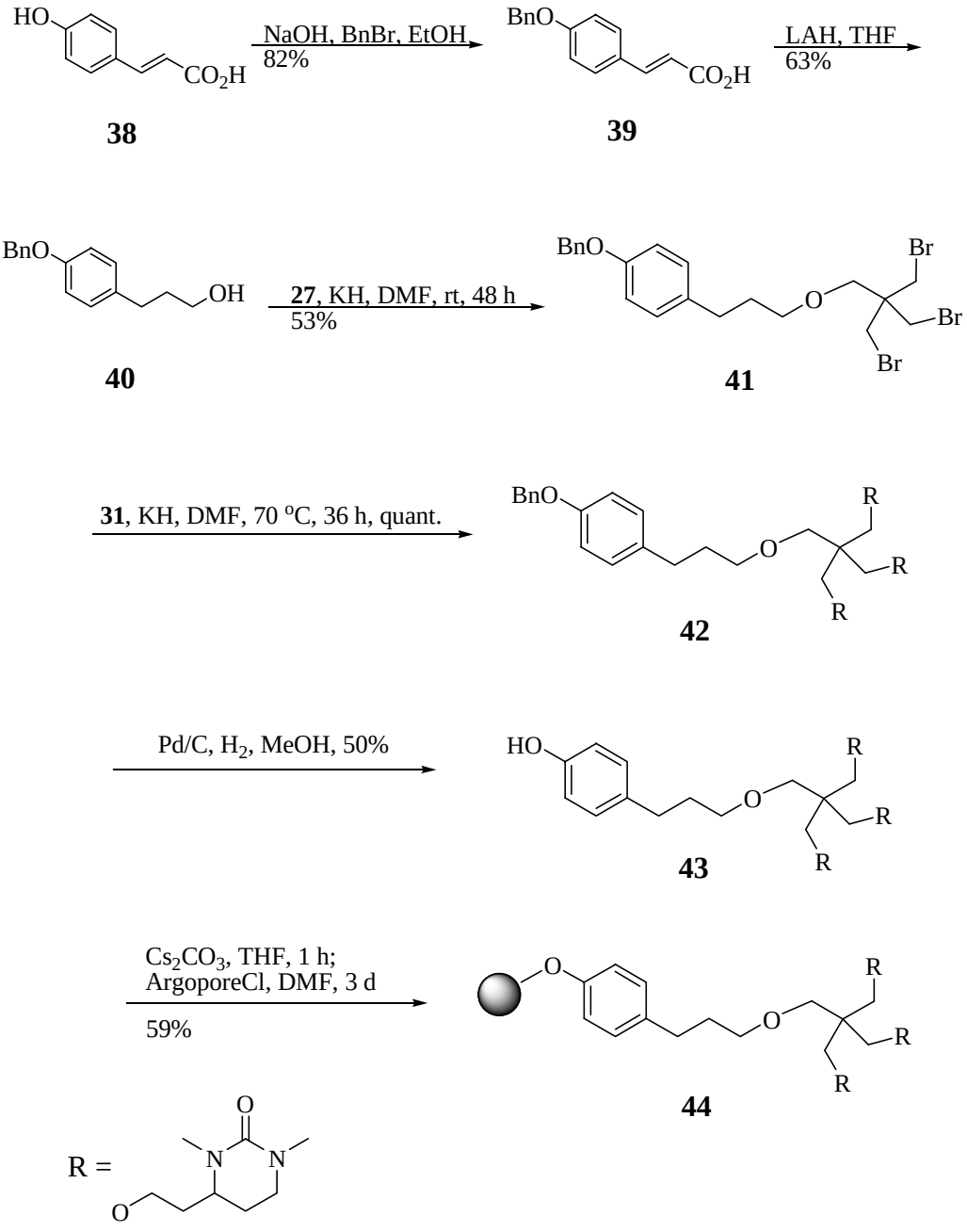
21 **37**

Since there are a number of examples to use HMPA as a catalyst in organometallic reactions,[2] we investigated whether the poly(cyclic urea)s could be used as catalytic additives. Baba and co-workers used PbI_2-HMPA as a catalyst for chemo- and diastereoselective carbonyl

allylation of α,β-epoxy ketones with allylic stannanes.[2b] When 0.2 equivalent of HMPA (entry 2) were added to the reaction mixture, high yields of the allylated product were obtained, almost as a single diastereoisomer, with an *anti*-relationship between the hydroxyl and epoxy groups. Table 3 shows our results with several poly(cyclic urea) additives (entries 3 to 6). Unfortunately, these poly(cyclic urea) compounds did not catalyze this reaction efficiently. According to Baba et al,[2b] HMPA increased the solubility of PbI_2 in THF. Even when up to 1 equivalent of DMPU was used, complete dissolution of PbI_2 was not observed (entry 1). This may account for the lower yields obtained with our poly(cyclic urea)s. Compound **37**, which has an additional carbonyl site on the urea, was prepared by acylation of **21** to examine whether this modification of the urea unit could improve its properties. Even though this compound gave a lower yield of product compared to HMPA, **37** proved more effective than DMPU (entry 7) in this reaction. We assume that the additional carbonyl group in **37** strengthened the chelating property of the urea.

1.2.3. Synthesis and application of new additives in solid phase synthesis

Based on the results obtained with poly(cyclic urea) **32**, a polymer-supported additive was designed that incorporated units of polycyclic urea **31** as shown in Scheme 5. This polymer-supported reagent consisted of the solid support, a linker and the poly(cyclic urea). The linker **41** was prepared by alkylation of the tetrabromide compound **27** with the alcohol **40**, which was obtained from 4-hydroxy cinnamic acid **38** by a known procedure in 52% yield over 2 steps.[11] The linker **41** and the urea **31** were coupled using KH in DMF to give polyurea **42** in high yield.

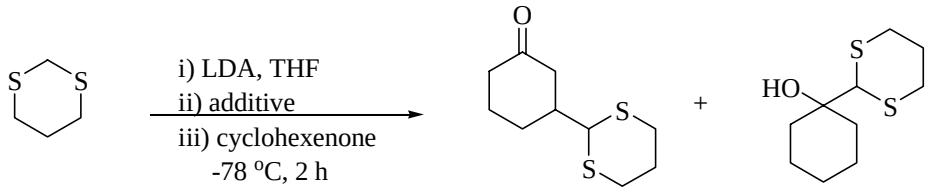


Scheme 5. Synthesis of polymer-supported poly(cyclic urea) **44**.

Pd-catalyzed deprotection of the benzyl group led to compound **43** in 53% yield. ArgoPore® resins are macroporous beads characterized by high internal surface and cross-linking levels. This macroporous resin thus offers advantages such as compatibility with a wide range of

solvents, low and predictable swelling in all solvents and accessibility to the polymer-supported intermediates under low-temperature reaction conditions. We anticipated that these properties of the ArgoPore® resin would be beneficial for our purposes. Compound **43** was attached to commercially available ArgoPore®-Cl resin (1.2 mmol/g) using Cs_2CO_3 to give polymer-supported polyurea **44**. We then performed the addition of 1,3-dithiane to 2-cyclohexen-1-one using the polymer-supported additive **44** (Table 4). The use of LDA as base with **44** showed only moderate regioselectivity and low yields (entry 1). However, while higher yields were obtained with *t*-BuLi, the regioselectivity was the same (entry 2). Using an excess of **44** led to an improvement in the regioselectivity (entry 3). Though **44** showed only moderate chemical utility as an additive, this polymer-supported urea could be easily recovered and recycled without decrease in efficacy.

Table 4. Regioselective addition of 1,3-lithiodithiane to cyclohexenone in the presence of **44**.



1 **2** **3**

Entry	DS:CY:additive[a]	Additive	**2** : **3**[b]	Yield (%)[c]	Base
1	2:1:1.2	**44**	54:46	<52	LDA
2	2:1:1.2	**44**	53:47	96	*t*-BuLi
3	2:1:2.4	**44**	63:37	85	*t*-BuLi

a) DS = 1,3-dithiane, CY = 2-cyclohexen-1-one; b) determined by ^{1}H NMR; c) isolated.

1.2.4. Ring opening metathesis polymerization (ROMP)

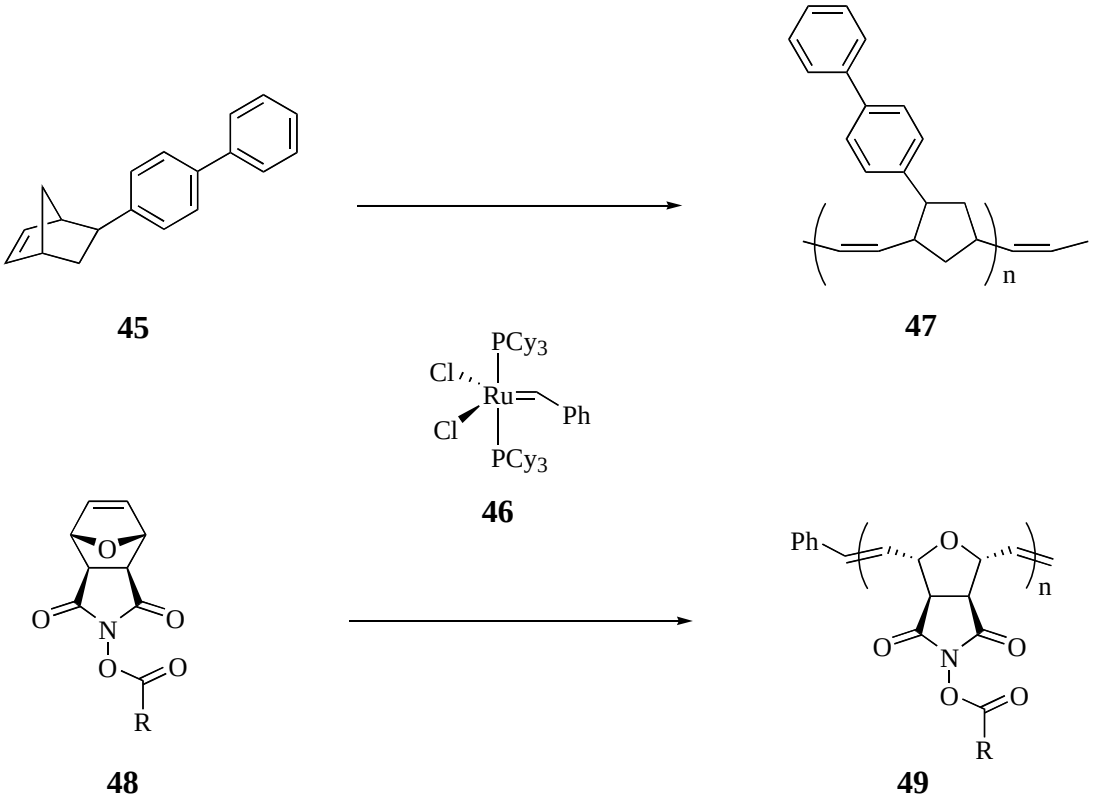
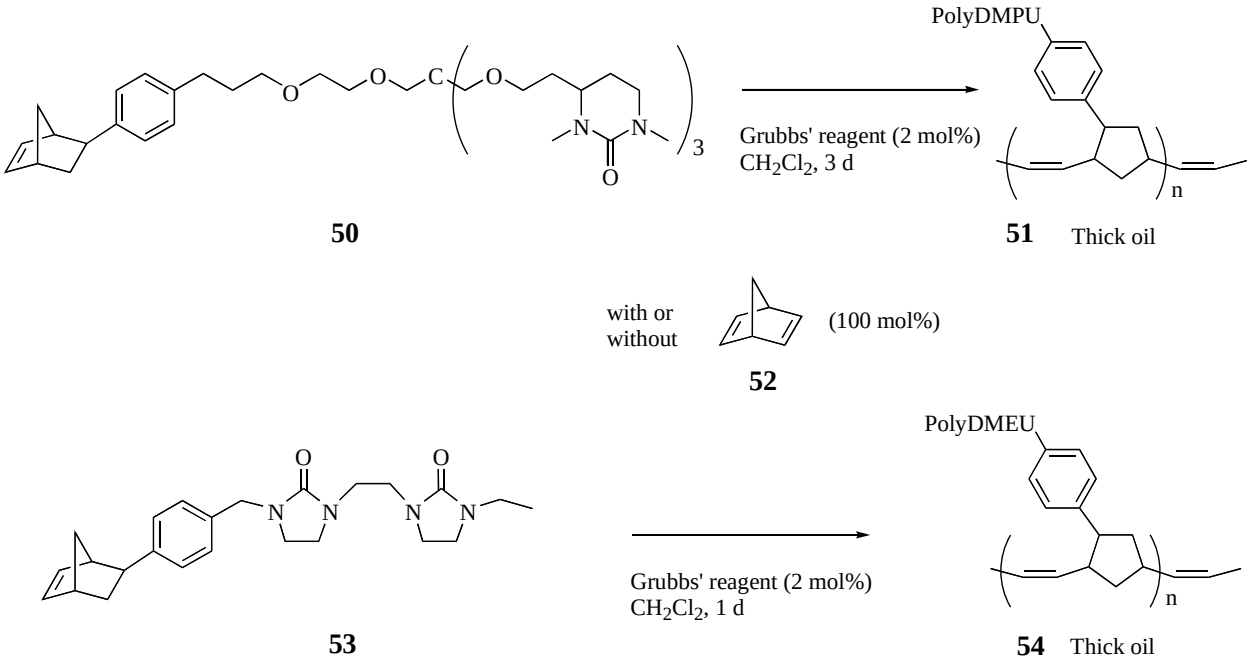


Figure 4. Ring opening metathesis polymerization (ROMP).

Most polymer-supported reagents to date have used cross-linked polystyrene as the insoluble support due to its commercial availability. With polystyrene, all synthetic modifications are invariably carried out post-polymerization. The quality of the resin is therefore an important consideration, since monitoring reactions on-resin is not straightforward and purification is generally not possible. Several groups have found an alternate method in the use of the ring opening metathesis polymerization (ROMP).[25] Monomer units containing all the desired functionality for the reagent and a strained alkene are synthesized in solution and are then polymerized using the Grubbs' catalyst **46**. The resulting polymers are soluble in the reaction solvent and thus reaction conditions optimized for solution phase can be applied without

reoptimization of the polymer-supported versions.[24] After the reaction is complete, the ROMP polymer is simply precipitated by the addition of the appropriate solvents and removed by filtration. In examples of ROMP in Figure 4,[25] the ROMP polymers are of excellent quality and provide quantitative loading; the polymer loading being equal to the molarity of the monomer. Increasing the amount of Grubbs' catalyst had a detrimental effect on the quality of the polymer with regards to its coloration and solubility. In some cases, a larger quantity of cross-linker had to be added to obtain a polymer of satisfactory insolubility.



50 **51** Thick oil **52** **53** **54** Thick oil

Scheme 6. Synthesis of poly(cyclic urea) polymer by ROMP.

To apply ROMP in our chemistry, monomer **50** was prepared via a Heck coupling[26] of the 4-bromophenyl analog to norbornadiene (**52**). Subsequently, polymerization of **50** in the presence of Grubbs' catalyst (2 mol%) and termination with ethyl vinyl ether afforded the brown oil **51** in 53% yield. This polymer was dissolved in CH_2Cl_2 and precipitated as an oil with the addition of ethyl ether or EtOAc. When a solution of polymer **51** in THF was mixed with Li-base

(*n*-BuLi), the polymer immediately aggregated and the reaction was unproductive. This flexible linear structure might be not suitable as a cation-chelating reagent. However, when polymer **51** was used in the carbonyl-selective allylation of an α,β-epoxy ketone, the reaction was slow, but still gave a 65% conversion after 4 d in the presence of 20 mol% of additive. No conversion was observed in the absence of the additive. To induce better precipitation by the addition of ethyl ether, 1 equivalent of norbornadiene **52** was added as the cross-linker to transform the linear structure to a cross-linked one. Unfortunately the cross-linked polymer showed very similar physical properties to linear-polymer **51**. The less flexible monomer **53** was also prepared and polymerized to give polymer **54** in 37% yield. This polymer was also soluble in CH_2Cl_2 and precipitated by the addition of ethyl ether. We expected that the polymer **54** could be precipitated better in ethyl ether for the easier isolation of the polymer. There was, however, no observed difference in the physical properties of polymer **54** as compared to **51**.

2. Synthesis and Application of New HMPA Additives for Solid Phase Organic Synthesis

2.1. Introduction

Hexamethylphosphoramide (HMPA) is a highly polar aprotic solvent and has been used extensively as a co-solvent or catalytic additive in organic chemistry. HMPA coordinates very well to metal ions, thus increasing the nucleophilicity of the counter ion and influencing reaction kinetics. However, HMPA is also a highly toxic mutagen and the use of HMPA has been limited in both industry and academia. Several groups have used a range of other substances, such as DMPU,[6] *N*-oxides,[8] and formamides[10] to replace HMPA. We have previously studied the use of polyureas and their solid-supported analogs as replacements for HMPA. Overall, they showed lower activities as additives compared to HMPA.

The driving force for the development of new additive reagents is to avoid contact with the carcinogenic HMPA. Benzyltrichloroacetimidate should be distilled before usage and kept under an inert atmosphere. However, polymer-supported benzyltrichloroacetimidate could be stored on the bench for 3 month without loss of activity.[27] We envisioned that the incorporation of HMPA into a polymer could be a way not only to maintain the activity of HMPA but also to reduce toxicity. As shown in Figure 5, the dimethyl moiety of HMPA has been replaced by other less volatile and less toxic diamines. Also many chiral HMPA derivatives[28] have been prepared and used in enantioselective synthesis. It is possible to use these chiral HMPA derivatives to generate polymer-supported chiral HMPA.

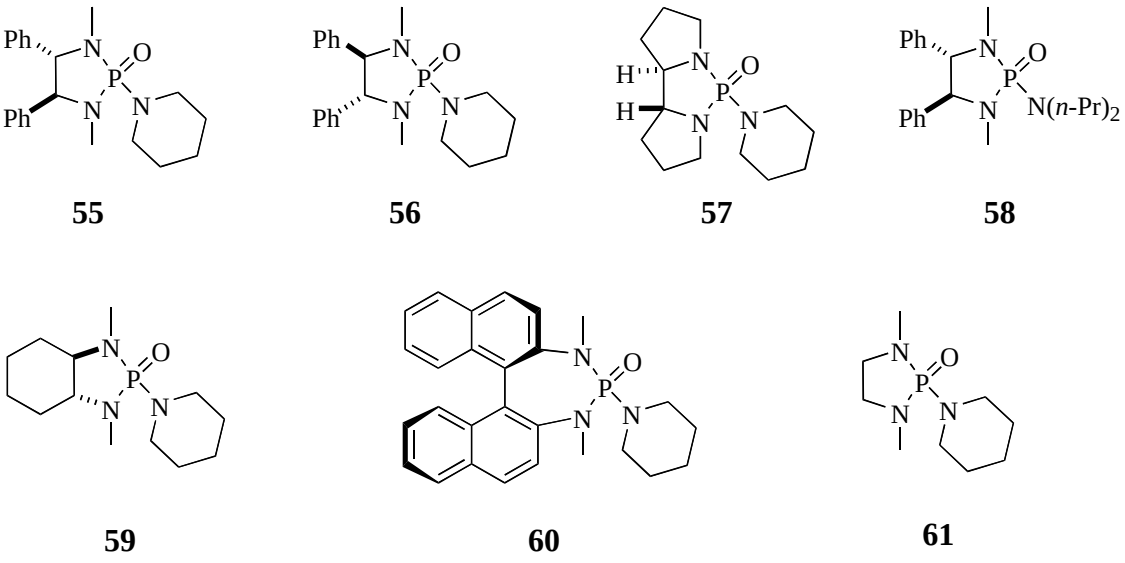
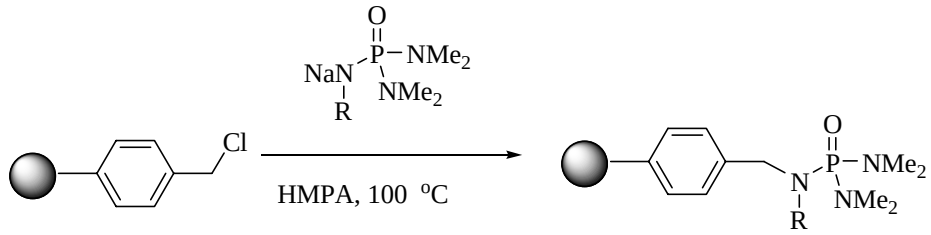


Figure 5. HMPA derivatives.

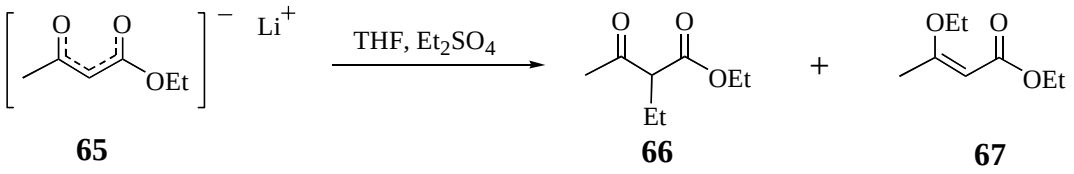
In the late 1970's, Tomoi and co-workers demonstrated the utility of polymer-supported phosphoric triamide **63** as a phase transfer catalyst.[29] They showed that immobilized phosphoric triamides such as **63** are better catalysts than the corresponding non-immobilized phosphoric triamides in biphasic reactions. However, HMPA was used as the solvent and heated at 100 °C to prepare these polymer-supported phosphoric triamides **63**, without consideration of the toxicity of HMPA (Figure 6). In 1981, Nee also reported the cooperative effect of **63** in the reaction of the Li-enolate of ethylacetoacetate with diethylsulfate (Scheme 7).[30]



62

63 R = CH_3, 1.6 mmol/g
64 R = H, 0.48 mmol/g

Figure 6. Early example of polymer-supported phosphoric triamide.

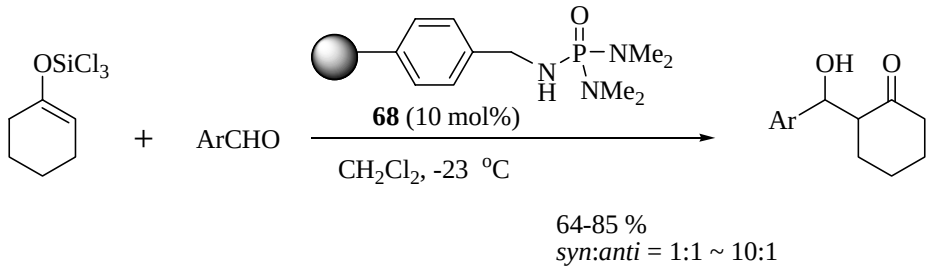


65 **66** **67**

Entry	cosolvent	Temp. (ºC)	**66** (%)	**67** (%)
1	-	50	-	-
2	1 eq polymer-supported HMPA	24	34	66
3	1 eq HMPA	24	41	59

Scheme 7. Early application of polymer-supported HMPA.

In a recent example of polymer-supported HMPA, Flowers used a polymer-supported phosphoramide as a Lewis-base catalyst in an aldol reaction (Scheme 8). Though this aldol reaction could occur in the absence of the catalyst, the process was accelerated in the presence of the PS-phosphoramide catalyst **68**, which was prepared from aminomethyl resin SS, and the yield was also increased.[31]



Scheme 8. Recent application of polymer-supported HMPA as a catalyst.

To avoid the use of HMPA as a solvent[29] and to manage the property of the polymer, we decided to prepare a polymer-supported HMPA by polymerization. We anticipated this polymer-

supported reagent would demonstrate the beneficial additive characteristics of HMPA along with the common advantages of a polymer-supported reagent, such as reusability and increased stability.

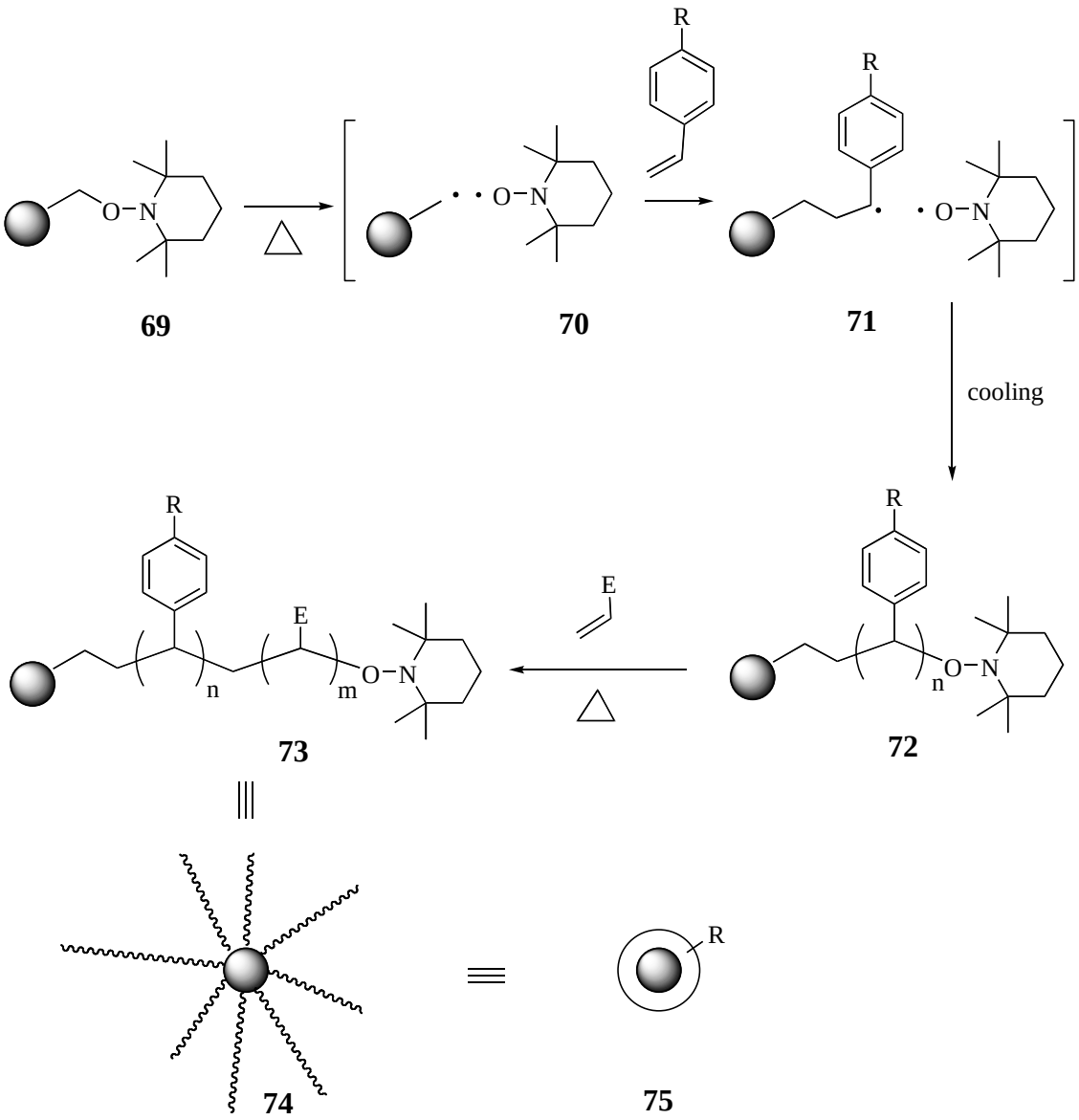


Figure 7. Solid-supported living free radical polymerization (LFRP); Rasta resins.

We considered performing a living free radical polymerization (LFRP)[32] and a suspension polymerization[33,34] to obtain polymer-supported HMPA. First, solid-supported living

free radical polymerization (LFRP) is initiated thermally by exposure of TEMPO-methyl resin to styrene monomers. The benzylic nitroxides reversibly thermolyze above 123 °C, generating benzyl radicals and nitroxyl radicals. The benzyl radicals are free to react with the styrene monomer, and the polymerization ensues. Chain termination reactions such as the condensation of two benzyl radicals are inhibited by the presence of nitroxyl radicals. Upon cooling, the nitroxyl radicals recombine with the benzyl radical at the polymer terminus to generate a polymer that can serve as an initiator in subsequent rounds of polymerization (Figure 7).[32a] This process can be described as a solvent-free suspension polymerization. These "Rasta resin" were believed to have a unique macromolecular architecture typified by long straight chain polymers bearing the desired functional groups that emanate from the phenyl groups of a cross-linked polystyrene core. With appropriate choice of the co-monomers and the polymerization strategy, the solvent affinity, loading capacity, and distance of functionality from the cross-linked core may be controlled giving beads with properties that are tailored to specific uses as polymer-supported reagents.

We expected that these unique structures, in which each monomer is connected linearly but each elongated oligomer is isolated from other oligomers, might help to solve the aggregation problems seen with the ROMP polymer. Examples of living free radical polymerization using styrene showed that an overall loading of 6~7 mmol/g was easily achieved from 1 mmol/g loading of the initial resin. If this range of high loading is achieved with actual monomers, then the amount of polymer-supported reagent can be reduced in the reactions (0.72 g of previous polymer-supported urea and 0.13 g of DMPU are matched with 1 mmol of urea unit).

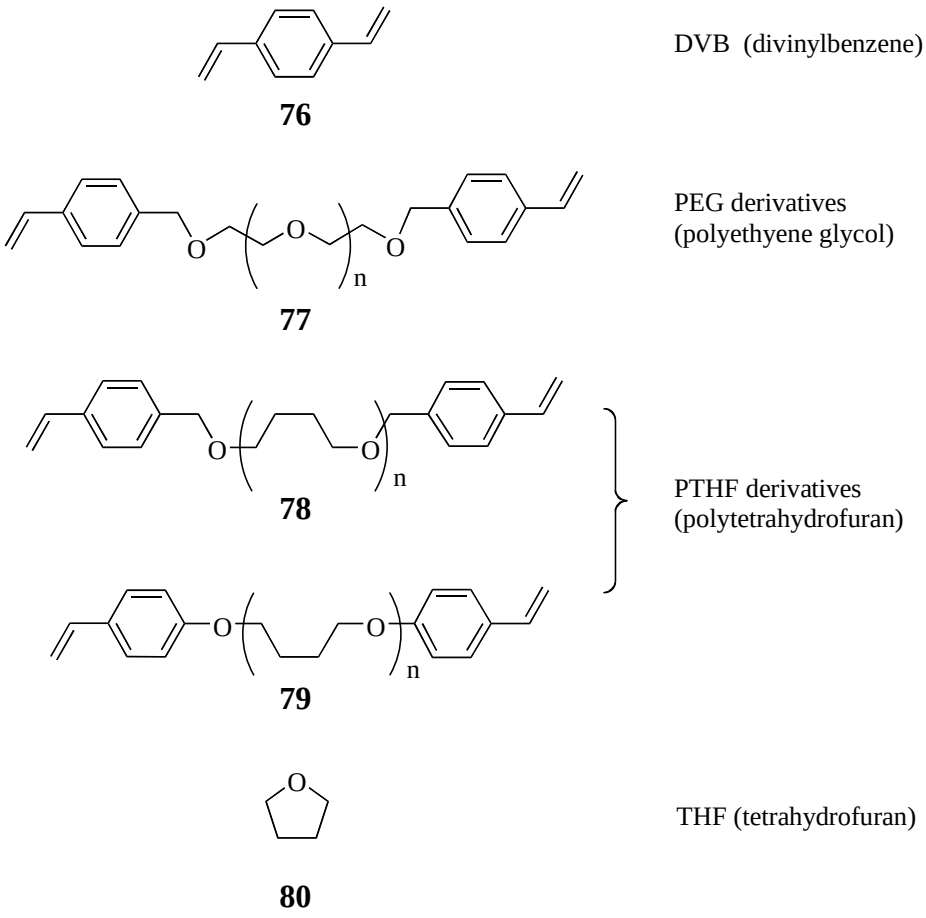


Figure 8. Cross-linkers in suspension polymerization.

Many commercially important polymers and co-polymers are manufactured by the suspension polymerization process. This process allows for easy control of the properties of the polymer by changing factors, such as the additives, ratio of reagents, concentrations, temperature, reaction time, and stirring speed. Janda and co-workers have studied the role of cross-linkers to devise new polymer-supports. The resins predominantly used are divinylbenzene (**76**) cross-linked polystyrenes (DVB-PS). Polyester, polyamide, poly(ethylene glycol) (PEG, **77**), or polysaccharide matrices have been used to make the polymers more compatible with highly polar solvents and reagents. For example, a new gel-type polymer resin was introduced by Itsuno in which polystyrenes were lightly cross-linked by PEG derivatives.[35] Resins

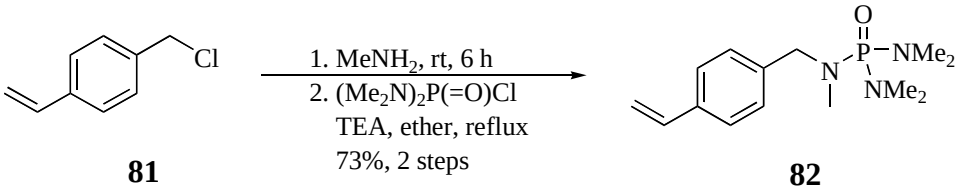
incorporating PEG derivatives were found to be superior to DVB-PS in terms of their ability to swell in common organic solvents and their mechanical stability. But PEG is a very hydrophilic material, and has a strong tendency to form helical structures that can bind metal cations. It is only sparingly soluble in cold THF. These properties can limit the utility of PEG in organometallic and anionic reactions performed at low temperatures.

Janda and co-workers have examined the use of polytetrahydrofuran (PTHF) based cross-linkers in gel-type polystyrene resins (*JandaJel*). These cross-linkers were designed to render the resins more 'organic solvent-like'. The amount of swelling decreased as the level of cross-linking increased, although even the 10 mol% cross-linked resin swelled significantly. These resins also showed good chemical stability. Resins cross-linked with 1 mol% or 2 mol% of **78** were degraded upon treatment with *n*-BuLi. Resins cross-linked with 5 mol% or 10 mol% of **78** were unaffected by this treatment. Furthermore, resins cross-linked with 1 mol% or 2 mol% of **79** also exhibited stability to *n*-BuLi. Finally, all resins were mechanically stable to magnetic stirring over a 48 h period.[34d]

After careful examination, we choose the PTHF (**79**) cross-linked polystyrene resin.[34a] We planned to utilize the solid-supported living free radical polymerization and JandaJel cross-linked with PTHF **79** as the new structure for our polymer-supported HMPA

2.2. Results and Discussion

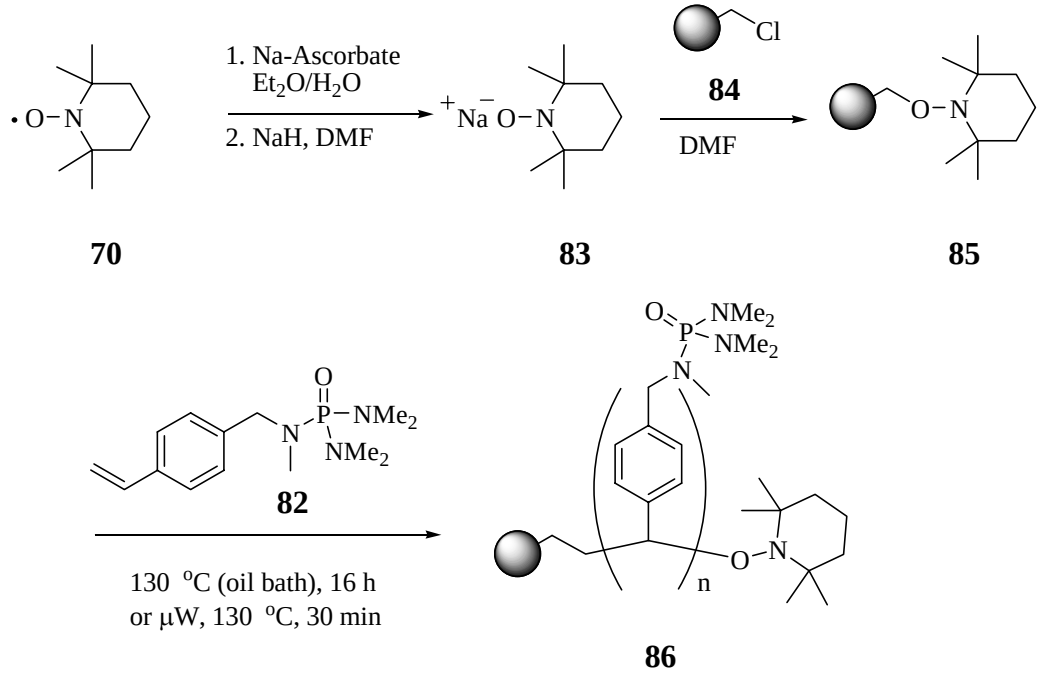
2.2.1. Living polymerization



81 **82**

Scheme 9. Synthesis of monomer **82**.

To perform the polymerization, monomers were prepared from the reaction of 4-vinylbenzyl chloride **81** with methylamine followed by bis(dimethylamino)phosphorochloride to give the desired styrene derivative **82**[36] in 73% yield (Scheme 9). This monomer was purified by chromatography and kept at 0 °C for 1 month without self-polymerization.

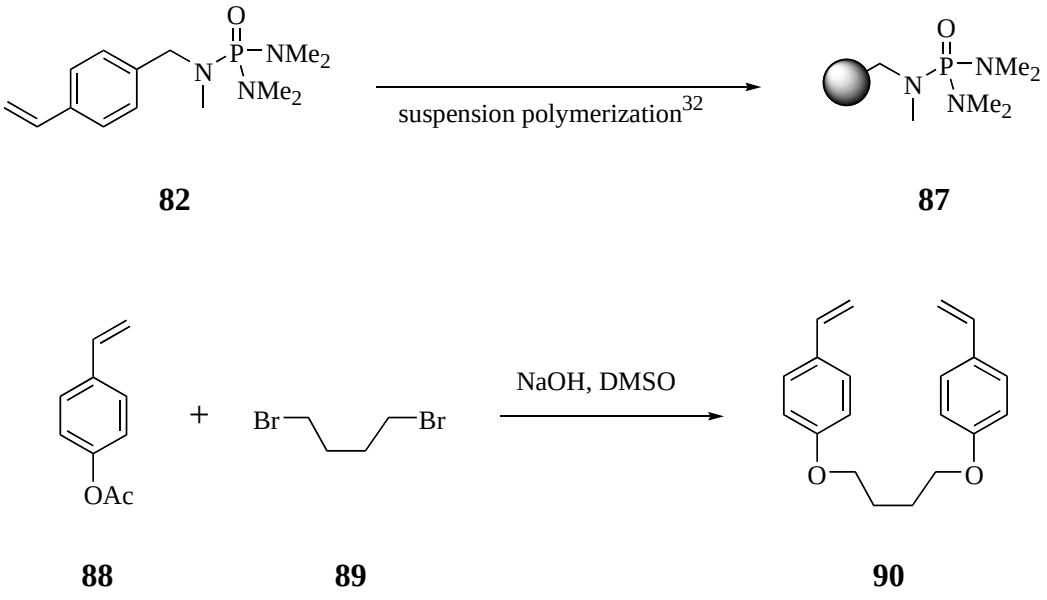


Scheme 10. Synthesis of HMPA Rasta resin **86**.

As shown in Scheme 10, reduction of commercially available TEMPO radical (**70**) by treatment with sodium ascorbate followed by deprotonation with NaH in DMF gave the sodium salt of TEMPO **83**. Addition of this sodium salt solution in DMF to ArgoPoreCl resin **84** (1.18 mmol/g) afforded the TEMPO-methyl resin **85**.[32a] Heating the TEMPO-methyl resin with an excess of monomer **82** under an inert atmosphere at 130 °C for 16 h led to the nearly complete solidification of the reaction mixture. After cooling the resulting polymeric mass, CH_2Cl_2 was added to dissolve any remaining monomer and soluble polymer. Filtration and washing with several cycles of alternating portions of diethyl ether and CH_2Cl_2 and drying under reduced pressure gave resin beads **86**. These beads **86**, which were visibly larger than the TEMPO-methyl resins and remained round in shape with a brown color, showed consistently about a 4-fold increase in mass (2.3 mmol/g to 2.7 mmol/g). We then investigated the addition of lithio-1,3-dithiane to 2-cyclohexen-1-one in the presence of Rasta resin **86**. Unfortunately, these polymers didn't show consistent activity, even when the loadings and appearance of polymers were similar; each batch gave different results. We are not sure if these derivatives can participate as additives, but we suspect the cause of the varied results was due to decomposition under the hash reaction conditions (at 130 °C for 16 h). To reduce the reaction time, microwave technology (130 °C, 30 min) was applied to prepare the Rasta HMPA **86**. The microwave-produced Rasta resin also gave inconsistent results. While living polymerization could be applied to synthesize the new polymer-supported HMPA, the new solid reagent did not show the desired properties as additives.

2.2.2. Synthesis of polymer-supported HMPA by suspension polymerization

To avoid the thermal decomposition of the HMPA moiety in Rasta resins, the polymerization temperature has to be low. The common temperature used for suspension polymerization is about 80 °C. As shown earlier, the JandaJel is a novel insoluble support that contains a flexible tetrahydrofuran-derived cross-linker offering several advantages over other commercially available polystyrene resins. The interior of the bead is more “organic solvent-like” than that of divinyl benzene cross-linked resins, demonstrates increased swelling/solvation in common solvents, improved chemical stability, increased site accessibility and increased homogeneity.



Scheme 11. Synthesis of polymer-supported HMPA **87** by suspension polymerization.

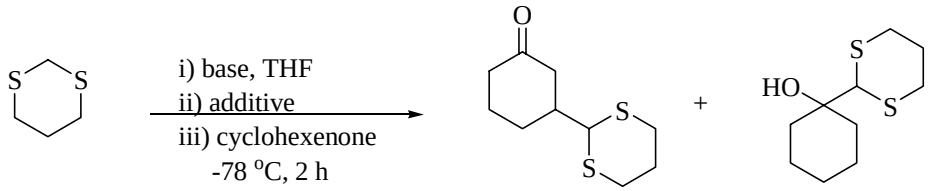
We applied the same monomer **82** to the suspension polymerization process. In the synthesis of the cross-linker **90**,[34d] 1,4-dibromobutane was alkylated with sodium 4-vinylphenoxide.[34d] Following the protocol described by Janda and co-workers,[34a] all reagents were added in a Morton flask equipped with a mechanical stirrer. Subsequent suspension copolymerization of styrene **82** and cross-linker **90** provided polymer-supported HMPA **87a** and **87b** with two different cross-linking ratio of 4 mmol% and 10 mmol% of **90**, respectively. Based on a nitrogen content of 6.40% and 7.22% determined by elemental analysis and assuming 17:7:1 and 12:5:2 ratio of styrene:**82**:**90**, the loadings **87a** and **87b** were calculated as 1.7 mmol/g and 1.5 mmol/g, respectively. These new resins demonstrated excellent swelling in THF and CH_2Cl_2, which are common reaction solvents in the model system. As expected, this gel structure was mechanically stable during magnetic stirring. Additionally, these polymer-supported reagents **87** were found to maintain their activity after storing on the bench for 2 months, and their properties remained the same after being reused 8 times in different reactions. They were also successfully applied over a wide range of temperatures from 75 °C to –78 °C.

2.2.3. Application of polymer-supported HMPA

First, we investigated the addition of lithio-1,3-dithiane to 2-cyclohexen-1-one in the presence of polymer-supported HMPA **87a** and **87b** (Table 5). Addition of HMPA demonstrated a strong regiochemical bias towards 1,4-addition of dithiane (entry 3). The addition of 1.3 and 1.5 equivalents of our synthetic derivatives **87a** and **87b**, with LDA as base, showed only a moderate regioselectivity bias (entries 4 and 5). The use of an excess of polymers gave lower yields, but certainly improved the regioselectivity of addition (entries 6, 7 and 8). The use of *t*-

BuLi as base and 2~4 equivalents of the polymer reagent provided a higher yield of the 1,4-addition product as compared to LDA. These results certainly suggest that the polymer-supported HMPA reagents are promising alternatives to HMPA. To ascertain the reliability of the data, each polymer was prepared 3 times and each batch was tested 3 times under the same conditions. In these experiments, polymer **87** showed consistent data. Additionally, the cross-linking ratio didn't alter the activity of the resin.

Table 5. Regioselective addition of 1,3-lithiodithiane to cyclohexenone in the presence of **87**.



1 **2** **3**

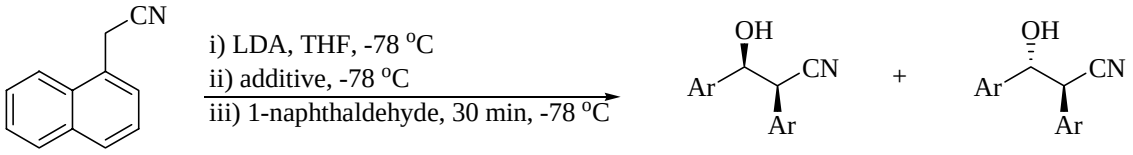
Entry	DS:CY:additive[a]	Additive	**2** : **3**[b]	Yield (%)[c]	Base[e]
1	2:1:0	-	0:100	83	LDA
2	2:1:1	HMPA	52 : 48	–[d]	LDA
3	2:1:2	HMPA	94 : 6	92	LDA
4	2:1:1.4	**87a**	64:36	92	LDA
5	2:1:1.2	**87b**	60:40	82	LDA
6	2:1:1.8	**87b**[f]	73:27	92	*t*-BuLi
7	2:1:2.7	**87b**[f]	84:16	68	*t*-BuLi
8	2:1:3.6	**87b**[f]	87:13	78	*t*-BuLi

a) DS = 1,3-dithiane, CY = 2-cyclohexen-1-one; b) ratio determined by ^{1}H NMR; c) isolated; d) no isolation; e) reaction run at 0.02 M concentration based on 2-cyclohexen-1-one; f) recycled resin was used.

Polymers **87a** and **87b** were also tested in the aldol reaction between 1-naphthylacetonitrile and 1-naphthaldehyde (Table 6). We observed excellent *syn*-selective

addition to 1-naphthaldehyde in the presence of HMPA versus in the absence of the additive (entries 1 and 2). In the presence of equal equivalents of polymers **87a** and **87b**, respectively, good *syn*-selectivity was also observed (entries 3 and 4) but with a decrease of the yield. Again no difference in activity was noticed between **87a** and **87b**.

Table 6. Aldol reaction in the presence of **87**.



33 ***Syn*-34** ***Anti*-34**

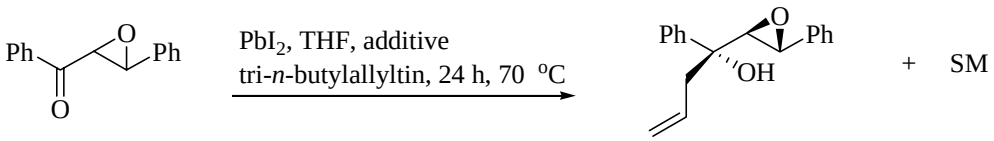
Entry	Additive	Ratio (*Syn:Anti*)[a]	Yield (%)[b]
1	-	36:64	90
2	6 eq HMPA	92:8	97
3	6.3 eq **87a**	85:15	57
4	5.3 eq **87b**	82:18	61

a) ratio determined by ^{1}H NMR; b) isolated.

To examine the use of polymer-supported HMPA as a catalyst, we tested two model reactions. First, we examined the effect of polymer-supported HMPA on the chemo- and diastereoselective carbonyl allylation of α,β-epoxy ketone with allylic stannane. As shown in Table 8, no addition proceeded without any additives, where both substrates were recovered quantitatively (entry 1).[2b] When HMPA (entry 2) was added to the reaction mixture, high yields of the allylated product were obtained, and the single diastereoisomer with the *anti*-relationship

between the hydroxyl and epoxy groups was predominated. Polymer **87a** also catalyzes this reaction in as high a yield and with the same diastereoselectivity as HMPA (entry 3).

Table 7. Carbonyl-selective allylation of α,β-epoxy ketone in the presence of **87**.



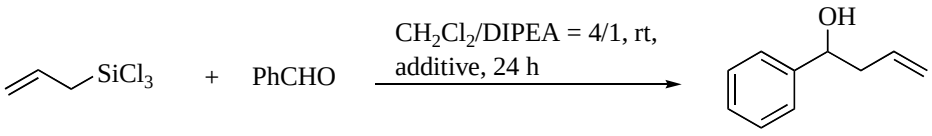
35 **36**

Entry	Additive	**36** (%)[a]	SM (%)[a]
1	-	0	100
2	0.2 eq HMPA	75	25
3	0.18 eq **87a**	78	22

a) ratio determined by ^{1}H NMR and isolated yield.

Finally, the allylation of aldehydes with allyltrichlorosilane in the presence of Lewis base was explored (Table 8). Denmark and co-workers[37] used chiral phosphoramides to promote the asymmetric allylation of aldehydes with allyltrichlorosilane while Kobayashi and co-workers used DMF and polymer-supported formamides in a similar context.[10] In the absence of additives, no adduct was obtained (entry 1).[10b] However, 1 equivalent of HMPA could promoted efficient conversion (entry 2).[37a] In the presence of catalytic amounts of polymer-supported HMPA **87a**, allylation of benzaldehyde occurred in high yields (entry 3). Increasing the number of equivalents saw a consistent increase in the conversion of **87a** (entry 4).

Table 8. Allylation of benzaldehyde and allyltrichlorosilane in the presence of **87**.



91 **92** **93**

Entry	Additive	Yield (%)[a]
1[b]	-	0
2[c]	1 eq of HMPA	85
3	0.27 eq **87a**	74
4	0.54 eq **87a**	82

a) isolated. b) in CH_2Cl_2/Et_3N as solvent. c) in $CDCl_3$ as solvent.

3. Synthesis of derivatives of calyculin A

3.1. Introduction

The reversible phosphorylation of proteins serine, threonine, and tyrosine amino acids is an essential regulatory mechanism in many cellular processes such as glycogen synthesis, cell division, gene expression, neurotransmission, muscle contraction, and a lot of other secondary messenger and signal transduction pathways (Figure 1). The phosphorylation level of a given protein is governed by the balance between protein kinases and protein phosphatase. These hydroxyl-bearing amino acid side chains are phosphorylated by protein kinases (PKs) using ATP as a phosphoryl donor, whereas dephosphorylations are catalyzed by protein phosphatases (PPs).[38]

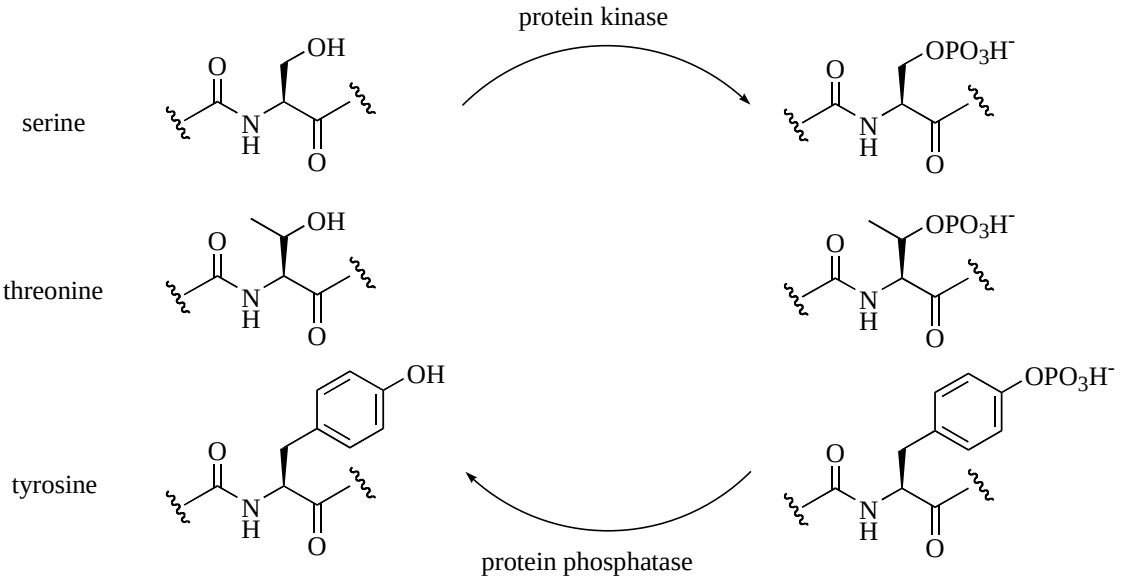


Figure 9. Phosphatase/kinase cycle.

This simple molecular 'on-off' switch modulates selectively the action of over 30 % of all cellular proteins and is ubiquitous in eukaryotic cells.[39b,40] Protein (de)phosphorylation induces changes in protein conformation, protein-protein interactions, protein-ligand interactions,

membrane permeability, and solute gradients, among others. Because the kinases and phosphatases affect other proteins and literally have hundreds of substrates, it has been a formidable challenge to decipher these complex pathways.

Protein PPs have been classified in two major families: the PTPases specific for tyrosine residues, the PSTPases specific for serine/threonine residues. The major representatives of the phosphoproteinphosphatase (PPP) family comprise PP1, PP2A, and PP2B, while the principal member of the metal-dependent protein phosphatase (PPM) family is PP2C. The latter family is characterized by an absolute requirement for a metal ion, particularly magnesium, for activity. While these protein phosphatases constitute the majority of serine/threonine dephosphorylation in all eukaryotic cells, a number of additional novel members of the PSTPase family have been discovered. These PPs differ in structure, substrate specificity, response to divalent cations, and sensitivity to inhibitors. [39]

In contrast to many enzymes, including the kinases, the Ser-Thr-specific PP family exhibits broad and overlapping substrate specificity (especially PP1 and PP2A) with no apparent substrate consensus sequence. Thus, discerning which phosphatase is responsible for controlling a particular cellular pathway has not been a trivial task, and naturally occurring small molecule toxins are often used on to achieve this goal.

PP1 and PP2A are stringently regulated by six endogenous protein inhibitors. Inhibitor-1 (I-1), Inhibitor-2 (I-2), dopamine and camp-regulated phosphoprotein (DARPP-32), and nuclear inhibitor of protein phosphatase 1 (NIPP-1) specifically inhibit PP1. Two proteins, $I\text{-}1^{PP2A}$ and $I\text{-}2^{PP2A}$ inhibit only PP2A without affecting the other phosphatases. Although the protein inhibitors give mechanistic information about how the protein phosphatases might be inhibited, they have

the inherent shortcomings of peptides, such as proteolytic degradation, poor membrane (blood-brain barrier) permeability, high molecular weight, and potential instability.

However, without the problems faced by protein inhibitors, several natural products have been identified as potent inhibitors of PSTPases (Figure 10). Microcystins,[41] nodularins,[42] and motuporin[43] are potent cyclic peptide toxins (IC_{50} of about 1 nM against both PP1 and PP2A, respectively), which were isolated from marine sponges. The microcystins are cyclic heptapeptides that possess several *D*-amino acids. The nodularins and motuporin are analogous cyclic pentapeptides. These cyclic peptides are 'suicide' inhibitors since they covalently modify the phosphatase via Michael addition of a nucleophilic cysteine in the protein to the dehydroalanine in the inhibitors. Thyrsiferyl-23-acetate[44] and cantharidin[45] were shown to be selective PP2A inhibitors, though less potent than the other inhibitors. Fostriecin[46] is the most selective small molecule inhibitor of the serine/threonine phosphatases and displays 40000-fold selectivity for PP2A over PP1.

The most interesting and complex inhibitors are the polyketides including okadaic acid,[47] dinophysistoxin-4, calyculin A-H, tautomycin,[47] and tautomycetin. These inhibitors have been the focus of considerable synthetic efforts and many groups have reported total syntheses of these polyketides.[49,50] Okadaic acid was the first of these inhibitors discovered and shown to be a potent and selective inhibitor of PP1 and PP2A, while PP2B is weakly inhibited and PP2C is not effected. This selectivity has made okadaic acid a powerful tool for the study of biological processes mediated by protein phosphorylation. Tautomycin inhibits PP1 with an IC_{50} of 0.2 nM and PP2A with an IC_{50} of 1 nM: it is the only small molecule inhibitor that is selective for PP1, albeit only 4 fold.

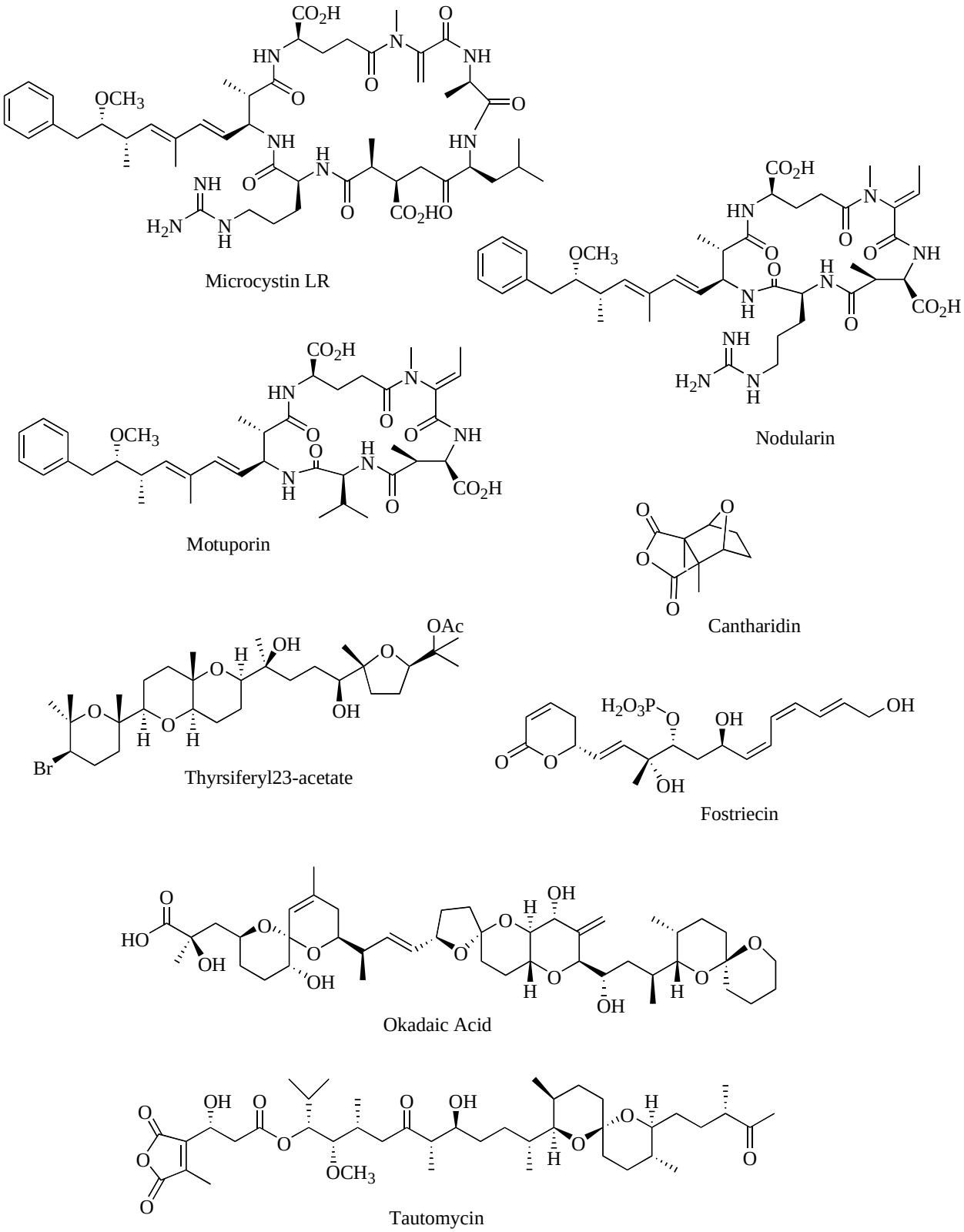
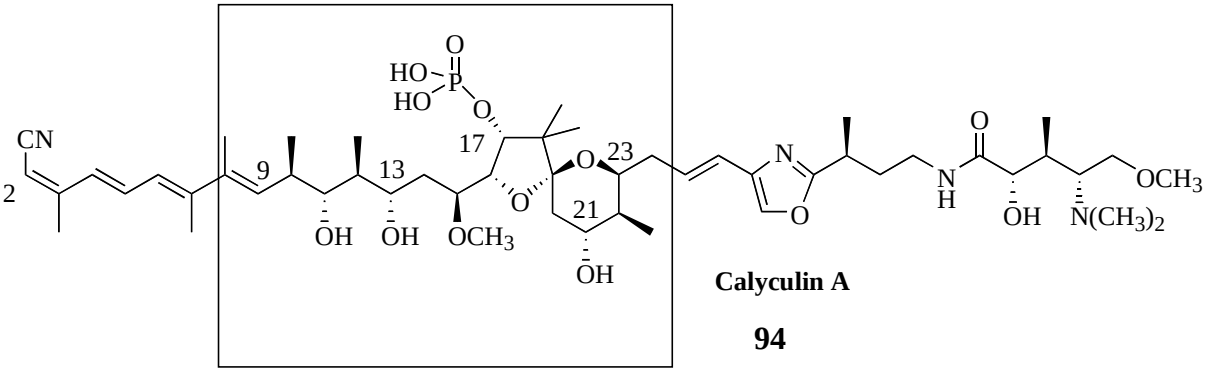


Figure 10. Natural products as inhibitors of PSTPases.

As one of the most potent inhibitors of PSTPases, calyculin A was isolated from the marine sponge *Discodermia calyx*. This natural product demonstrated antitumor activity and inhibition of PP1 and PP2A with IC_{50} values of 0.5-2 and 0.1-1 nM, respectively.[38] Interest in the biological activity of calyculin A has led to three total syntheses and extensive SAR studies.[50] The crystal structure of the complex between calyculin A and the catalytic subunit of PP1[51] and SAR data[52] have suggested the binding mode of calyculin A to PP1. The SAR data has shown that the C(17)-phosphoric acid, C(13)-OH and the hydrophobic tetraene moieties of calyculin A were essential for binding to the protein target. Though an earlier report suggested that dephosphorylated calyculin A remained biological activity,[53] the recent SAR data from Fusetani's group strongly supported the significance of the phosphoric acid moiety for the biological activity.[52] Also, many other natural phosphatase inhibitors such as okadaic acid, microcystin LR, nodularin and motuporin possess either a carboxylic acid or a phosphoric acid. Among the hydroxy groups of calyculin A, the protection of the C(13)-OH resulted in significant loss of the biological activity. The hydrophobic tetraene side chain was shown to fit into a hydrophobic pocket of the enzyme. Subtle changes of the structure of this side chain resulted in modest decreases of IC_{50}. However, the elimination of the side chain resulted in loss of activity. After consideration of all available data, we planned to synthesize a truncated core fragment of calyculin A in order to develop small molecules, selective serine/threonine inhibitors.

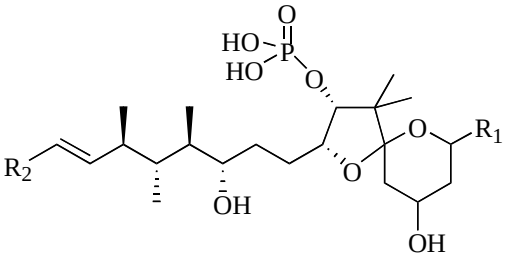
Our target structure **95** was an analog of the C(8)-C(24) fragment of calyculin A lacking the C(15)-methoxy group and the C(22)-methyl group because these structural features were shown not to be essential for enzyme inhibition (Figure 11). However, the C(13)-OH, phosphoric acid and the rigid skeleton of the spiroketal system were conserved to retain and ensure the biological activity. Diversity was introduced into compound **95** through the modification of the

hydrophobic tail (C1 to C7). Aromatic and aliphatic alkenes were appended to the core structure by cross metathesis.[60] The diastereomer of the 6-membered ring in the spiroketal backbone was initially synthesized to determine the effect of this change on the rigid backbone eventually on the biological activity.



Calyculin A

94



Target molecule

95

Figure 11. Calyculin A and target structure for inhibitor optimization.

The natural product phosphatase inhibitors except fostriecin normally show a similar activity between PP1 and PP2A.[46] From the SAR data of calyculin A, we can observe that 10-fold selectivity between PP1 and PP2A can be observed by the modification of calyculin A or other natural products in same family.[52] We aimed to identify potent small molecules and also examine whether these newly synthesized small molecules could increase the selectivity between PP1 and PP2A.

3.2. Retrosynthetic Analysis

Retrosynthetically, the side chain including the 1,3-diol of **95** could be installed by an asymmetric crotylation via Brown's or Roush's methodology[54] on the spiroketal **96**. The spiroketal segment of **96** would be prepared from bicyclic **97** by an intramolecular hydrogen abstraction reaction promoted by an alkoxy radical.[55] Bicyclic **97** could be derived from the aldehyde **98** by a hetero-Diels-Alder reaction with Danishefsky's diene.[56] An indium–mediated asymmetric prenylation of the hydroxy aldehyde **99** was anticipated to yield the dihydroxy aldehyde **98**.[57] Finally, the α-hydroxy aldehyde **99** would be formed by methanolysis and regioselective DIBAL reduction[58] of the commercially available (*R*)-(–)-5-oxotetrahydrofuran-2-carboxylic acid (**100**) as shown in Figure 12.

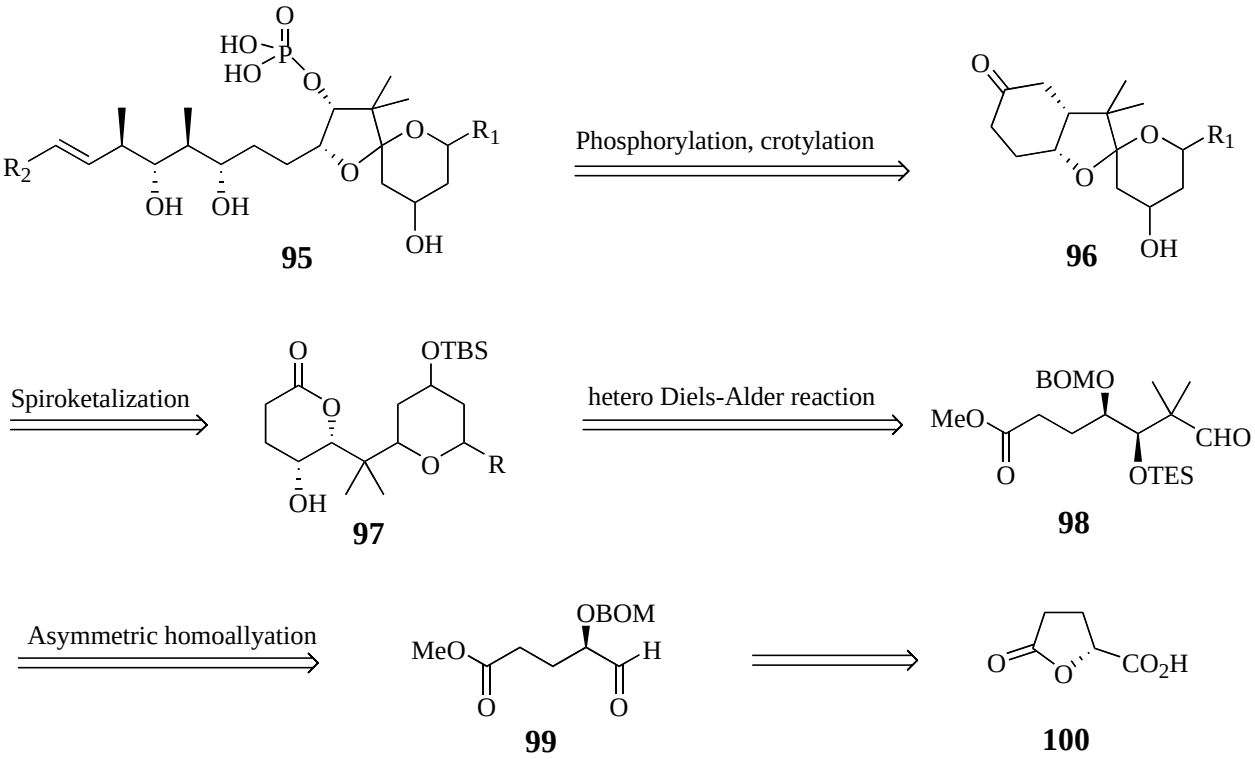
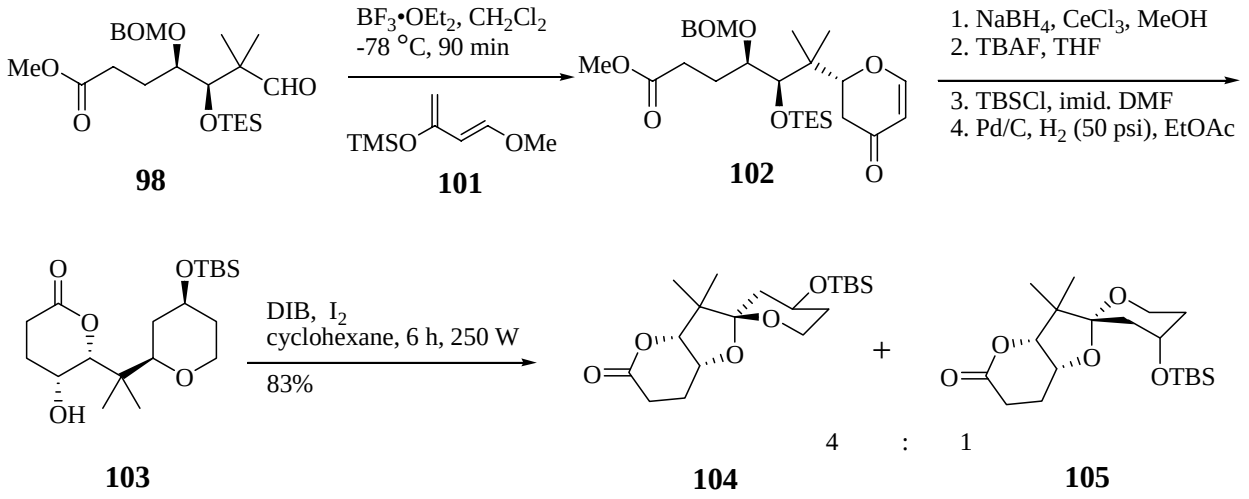


Figure 12. Retrosynthetic approach to **95**.

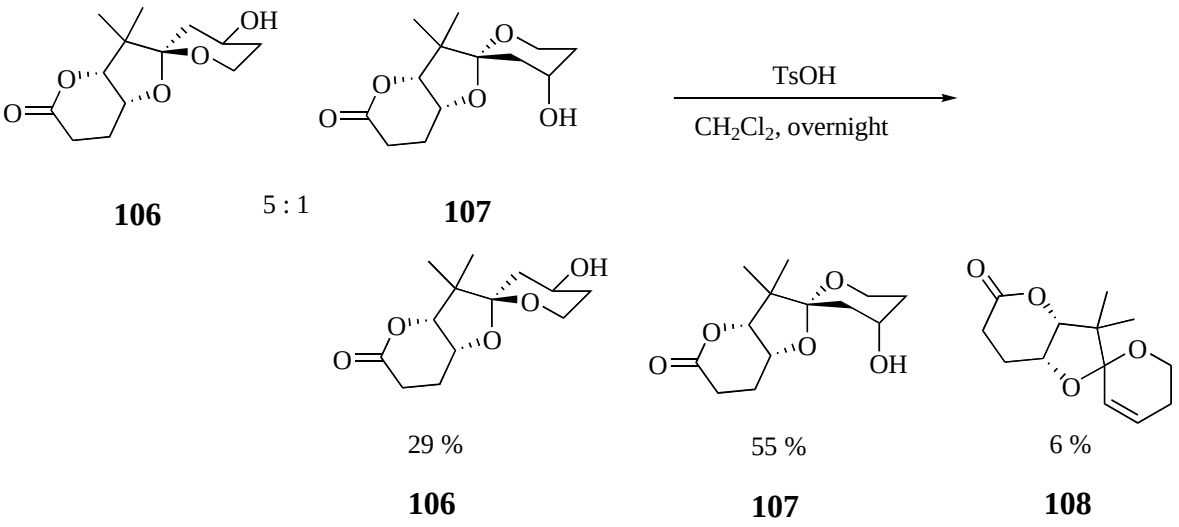
3.3. Previous Work in the Wipf group

To synthesize the truncated calyculin A derivatives, Dr. Wakimoto had launched the initial study as shown below.[59] The aldehyde **98** was prepared in 6 steps and a hetero-Diels-Alder reaction with Danishefsky's diene **101** provided **102** in 20-30% yield. The pyrone **102** was converted to the bicycle **103** in 33% yield over 4 steps. Spiroketalization of **103** yielded two isomers in 83% yield (Scheme 12). The analysis of the NMR data disclosed that the major product **104** exhibited different stereochemistry from that of calyculin A.



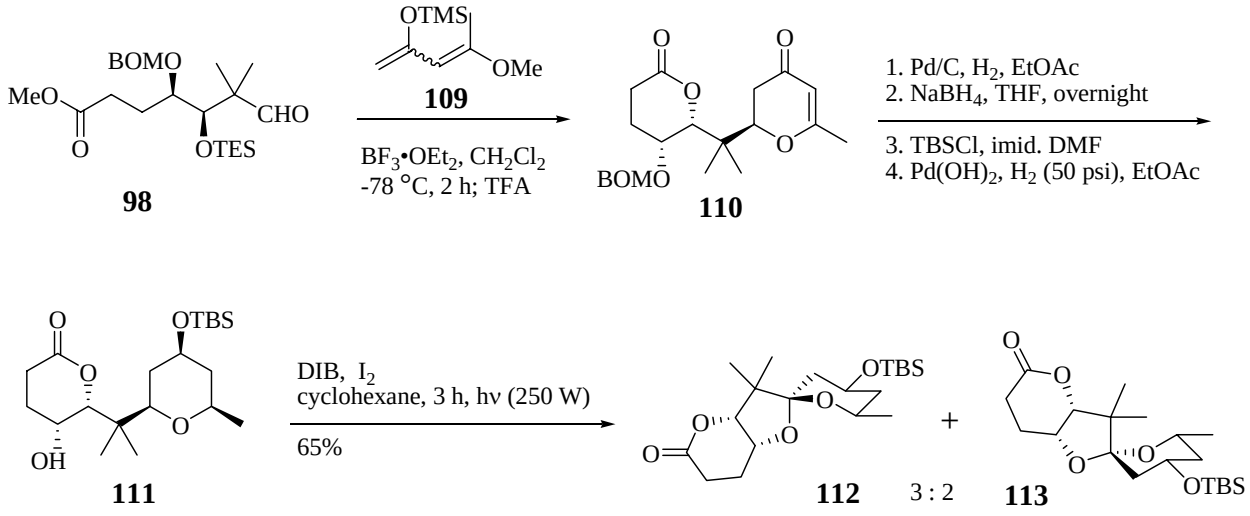
Scheme 12. Synthesis of two spiroketal isomers.

After the TBS-deprotection of **104** and **105**, the treatment of a mixture of **106** and **107** with TsOH in CH_2Cl_2 afforded the desired isomers **107** in 55% yield as the major product (Scheme 13). Unfortunately, the desired spiroketal compound was re-isomerized to the undesired epimer during the next transformations and the overall yield of this approach was too low to warrant further study.



Scheme 13. Isomerization of spiroketals.

In the initial route, the most critical step was the hetero-Diels-Alder reaction. After an extensive study of hetero-Diels-Alder conditions, the diene **109**[61] was found to provide the desired lactone **110** in 60% yield. The spiroketalization of **111**, which was obtained in 43% yield over 4 steps, gave two isomers **112** and **113** in 65% yield (Scheme 14). A more detailed discussion of the second route is given in the next chapter.

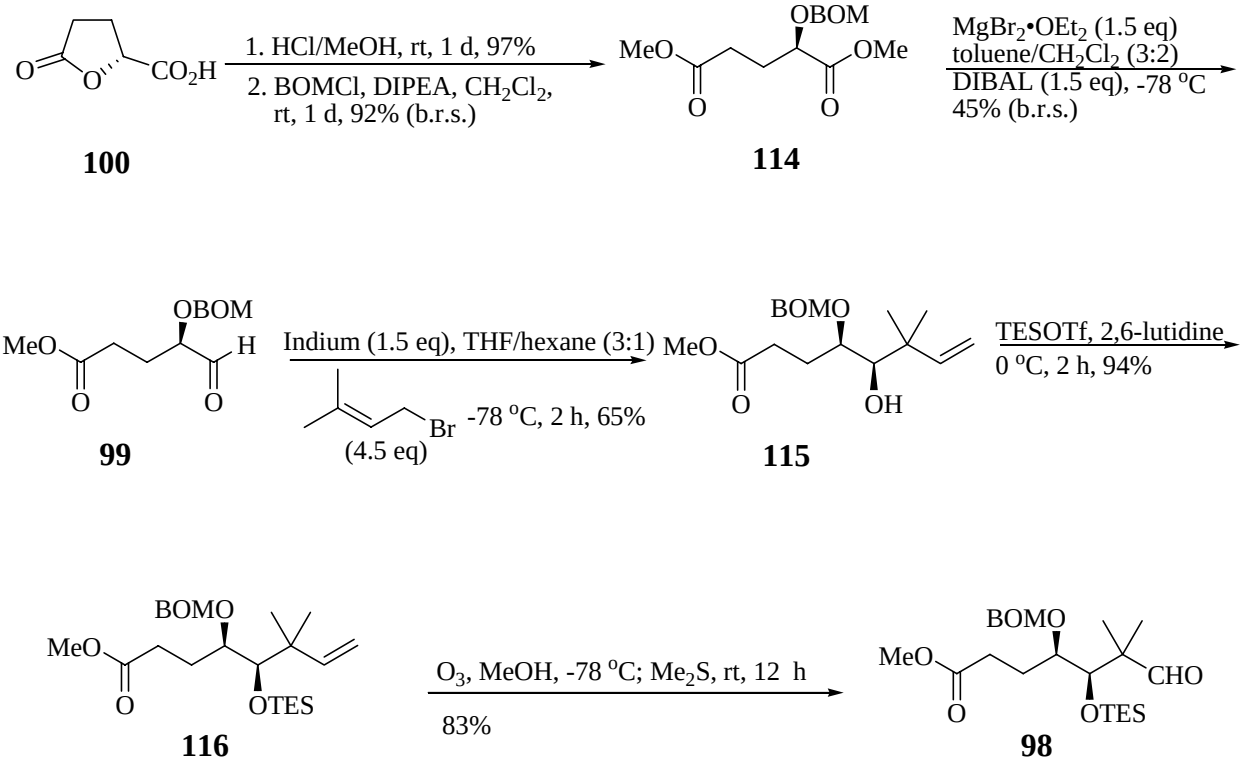


Scheme 14. Synthesis of **112** and **113**.

3.4. Results and Discussion

3.4.1. Synthesis of the first derivative of calyculin A

Based on Dr. Wakimoto's approach,[59] the synthesis of spiroketal compounds **115** and **116** was revisited with minor modifications. Methanolysis of (*R*)-(–)-5-oxotetrahydrofuran-2-carboxylic acid (**100**), followed by protection of the secondary alcohol with BOMCl, afforded the desired diester **114** in 85% yield over two steps. Chelation controlled regioselective reduction of **114** with DIBAL in the presence of $MgBr_2 \bullet Et_2O$ was then explored. According to the original report,[57] this reaction was initially conducted in CH_2Cl_2. However, the regioselectivity was low in our hands. Therefore, CH_2Cl_2 was replaced by toluene. Unfortunately, compound **114** was insoluble in toluene and required a mixture of both solvents.[59]



Scheme 15. Synthesis of aldehyde **98**.

Compound **114** and $MgBr_2 \bullet Et_2O$ were found to dissolve well in a mixture of CH_2Cl_2:toluene (3:2). Using only 1 equivalent of DIBAL resulted in the recovery of unreacted starting material. Optimally, 1.5 equivalents of DIBAL ensured the reduction of **114** to the desired aldehyde **99** in 38% yield along with unreacted starting material (15%) and over-reduced alcohol product (37%). The alcohol was converted to desired aldehyde **99** by a variety of oxidation conditions in moderate yield. Prenylation of compound **99** with indium and prenylbromide gave the desired product **115** in 76% yield. The hydroxylmethylester **115** was readily converted to the corresponding lactone **118** during work-up. However, the lactone **118** was easily converted to the desired hydroxylmethylester **115** by careful methanolysis. This indium-mediated prenylation was first reported to give a stereoselective addition in the presence of chiral additives such as (–)-cinchonidine or (+)-cinchonine.[57] However, we were able to obtain a single diastereomer without any chiral ligand. We assume that the high diastereoselectivity was achieved through the chelation control of the BOM-protected alcohol group of **117** (Figure 13).

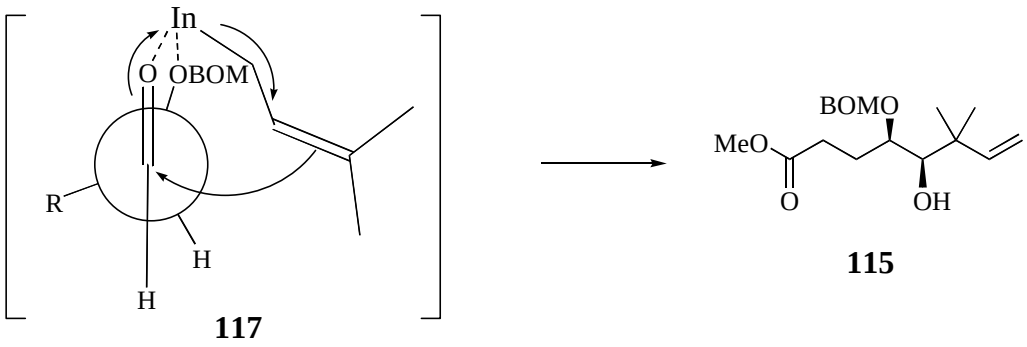
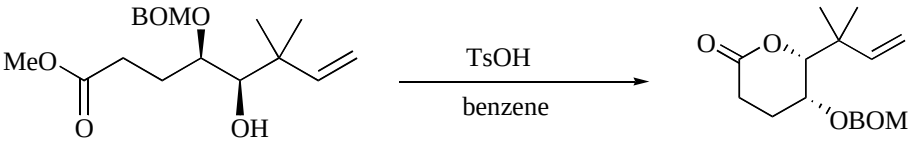


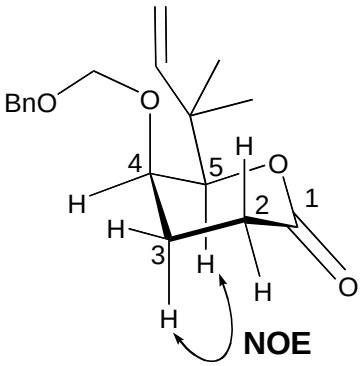
Figure 13. Postulated transition state for **117**.

As shown in Figure 14, the stereochemistry of the secondary alcohol **115** was confirmed by coupling constants and NOE correlations of the δ-lactone **118** derived from **115**.[59] Thus, as a

result of the chelation-controlled homoallylation, the desired isomer of the alcohol was obtained. The secondary alcohol **115** was subsequently protected with the TES group and then ozonolysis gave us the aldehyde **98** in a yield of 83% (Scheme 15).



115 **118**

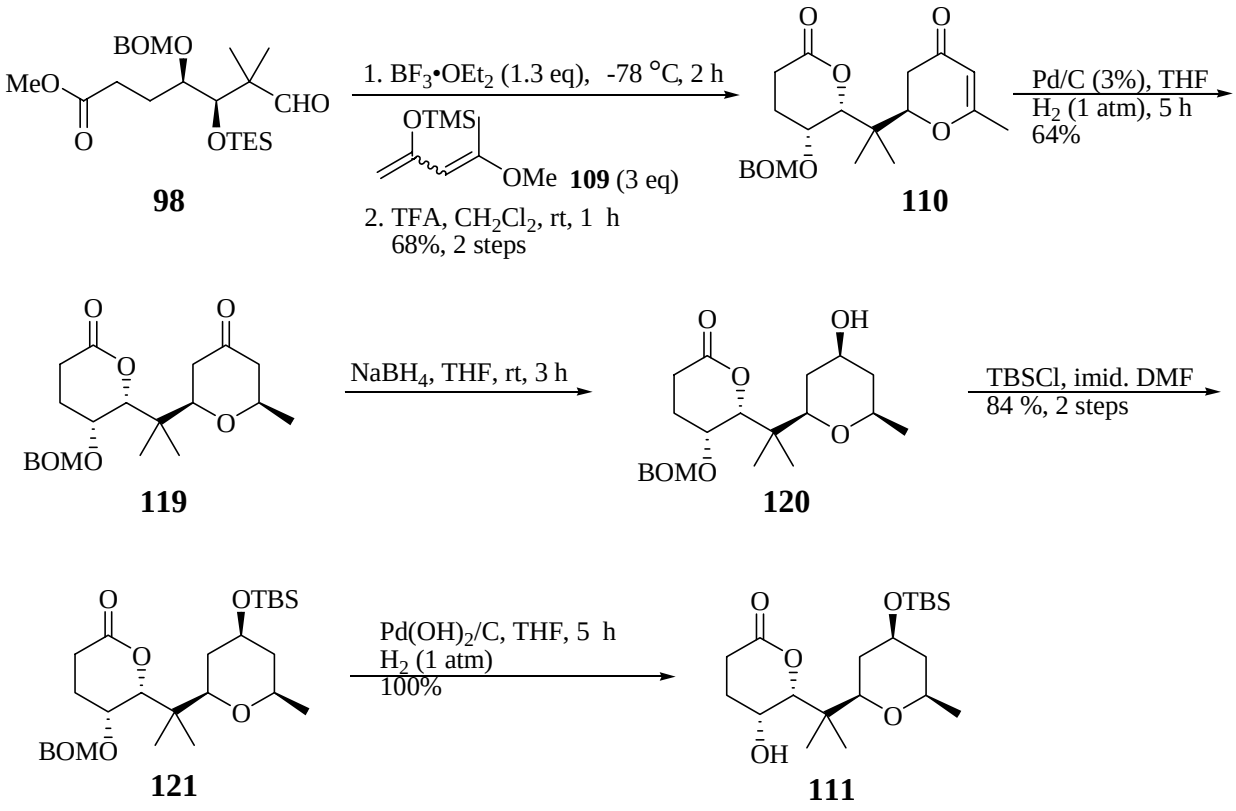


$^{3}J_{H4,H5}$ = 2.0 Hz
$^{3}J_{H4,H3\alpha}$ = 2.7 Hz
$^{3}J_{H4,H3\beta}$ = 3.2 Hz
$^{3}J_{H3\alpha,H2\alpha}$ = 7.7 Hz
$^{3}J_{H3\alpha,H2\beta}$ = 11.0 Hz
$^{3}J_{H3\beta,H2\alpha}$ = 2.8 Hz
$^{3}J_{H3\beta,H2\beta}$ = 7.6 Hz

Figure 14. NOE analysis of compound **118**.

The methyl-substituted diene **109** was selected for the hetero-Diels-Alder reaction since this diene is more stable than the original Danishefsky's diene[56] and resulted in much higher yield of the cycloadduct. Additionally, we anticipated that the methyl group in the spiroketal would have no deleterious effects on enzyme inhibition based on the SAR data.[52] This hetero-Diels-Alder reaction proceeded in a stepwise rather than a concerted fashion. Initially, the aldol product **123** was obtained which could be cyclized to the dihydropyrone in the presence of TFA. Under these conditions, the TES group was removed, and the spontaneous ring closure led to the

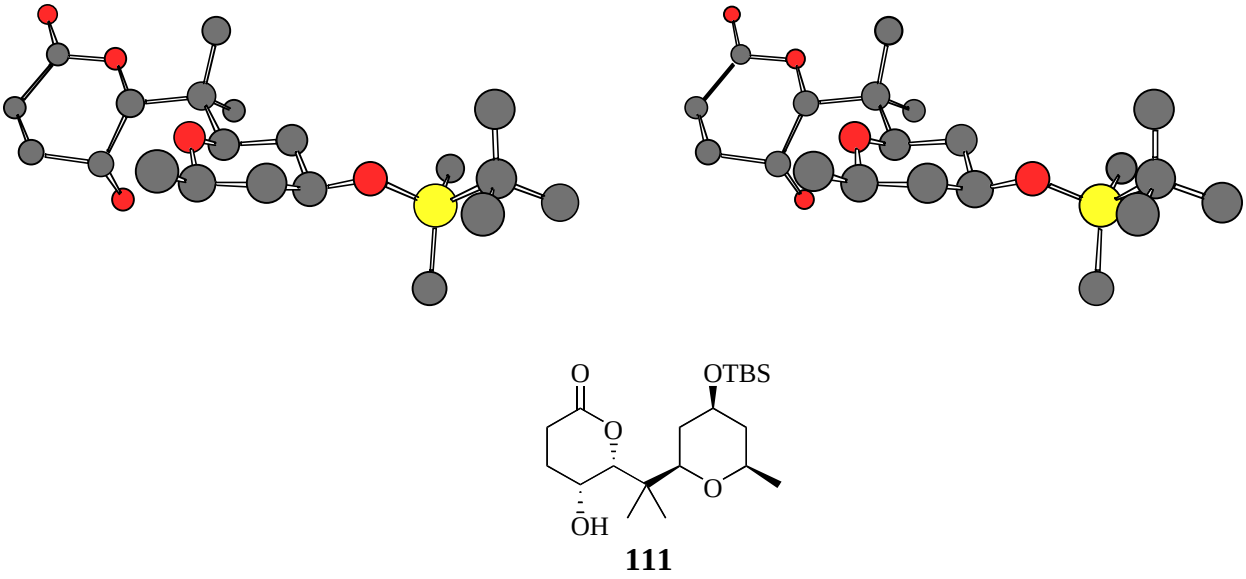
lactone **110** as a single diastereomer in 60% yield over 2 steps. The high diastereoselectivity of the aldol reaction will be postulated in Figure 17.



Scheme 16. Synthesis of compound **111**.

With compound **110** in hand, we then examined the synthesis of the spiroketal intermediate. The conjugated olefin of γ-pyrone **110** was first reduced by hydrogenation. During the hydrogenation under various conditions, we observed partial deprotection of the BOM group. However, the loss of the BOM group was minimized by using 3% Pd on charcoal as the catalyst in THF under 1 atmosphere of hydrogen. The resulting ketone of **119** was then reduced with $NaBH_4$ to give a single diastereomer **120**, whose stereochemistry could be predicted by the axial attack of a small reducing reagent and was confirmed later by the X-ray structure of **111**, in good yield. The secondary alcohol of **120** was protected with TBSCl and then the BOM group of **121**

was removed in quantitative yield by hydrogenation (Scheme 16). In Figure 15, the X-ray structure of compound **111** confirms the relative stereochemistry of **111** and the absolute stereochemistry of **111** was determined via the (*R*)-OH group originated from the chiral starting material **100**. Clearly, during the hetero-Diels-Alder reaction, the newly formed stereocenter assumed the (*R*)-configuration. Also, as we expected, the three substituents on the tetrahydropyran ring are in the equatorial position.

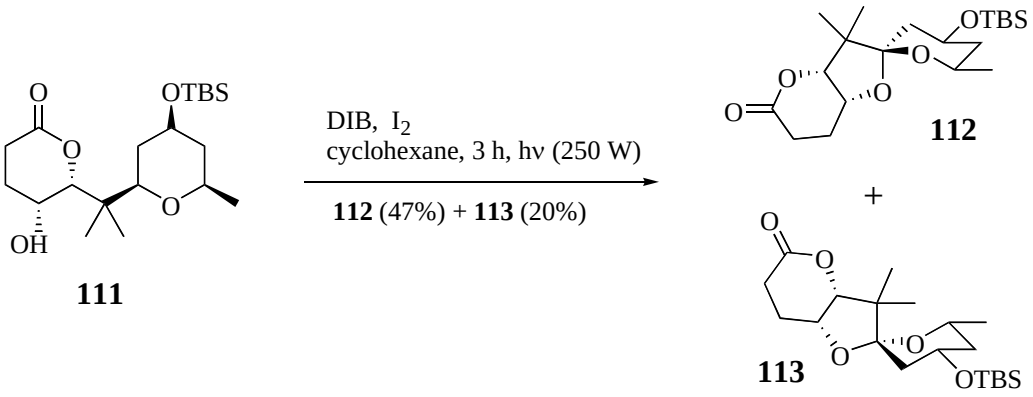


111

Figure 15. X-ray structure of **111**.

The spiroketalization was effected by irradiating the substituted tetrahydropyran **111** in the presence of (diacetoxyiodo)benzene (DIB)/iodine.[55] This process afforded two spiroketal isomers (**112**:**113** = 2.4:1) in 67% yield (Scheme 17). Due to the inability to determine the conformation of the major isomer by NOE, we determined the stereochemistry of the major product **112** indirectly based on the structure of the minor product **113**.[59] The key NOE data used for the elucidation of the stereochemistry of **113** are shown in Figure 16. In the desired

conformation **122** (Figure 16), the spiroketal segment is stabilized by two anomeric effects but also destabilized by the $A^{1,3}$-interaction among axial substituents on the tetrahydropyran ring. NOE analysis[59] of **113** indicated that the conformation of O-silylated spiroketal positioned both the methyl and the silyloxy group into an equatorial orientation most likely to avoid a serious $A^{1,3}$-interaction and anomeric stabilization was only partially obtained. Based on the analysis of **113**, the stereochemistry of **112** was inferred as shown in Scheme 17. This conformation of **112** is highly stabilized by two anomeric effects and three equatorial substituents on the tetrahydropyran ring.



Scheme 17. Synthesis of spiroketals **112** and **113**.

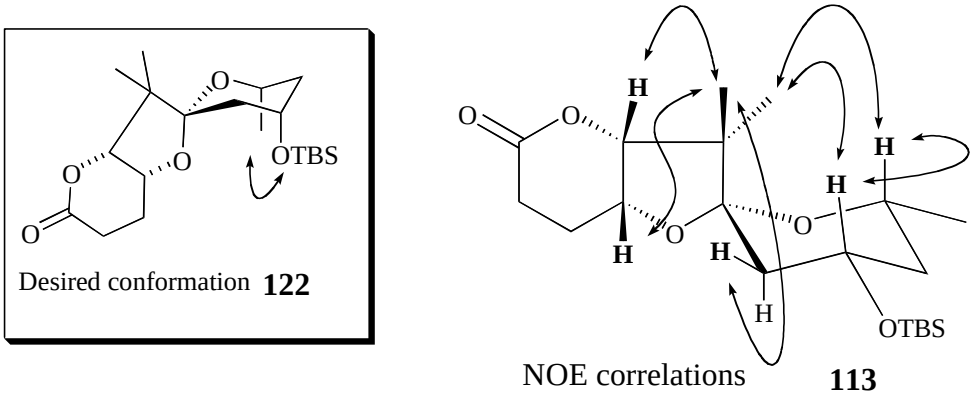
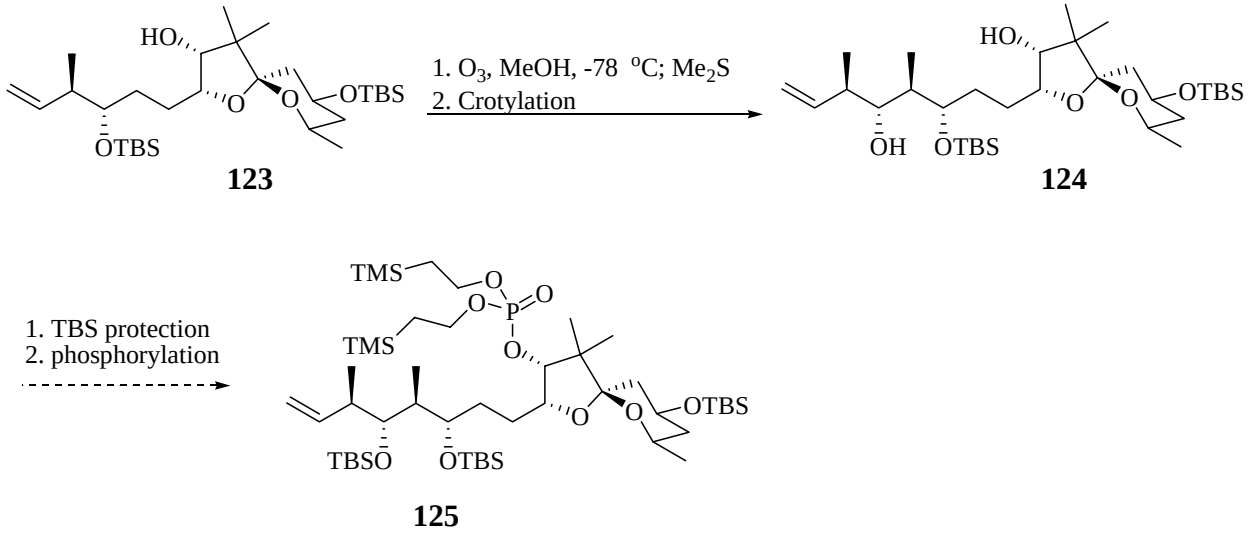


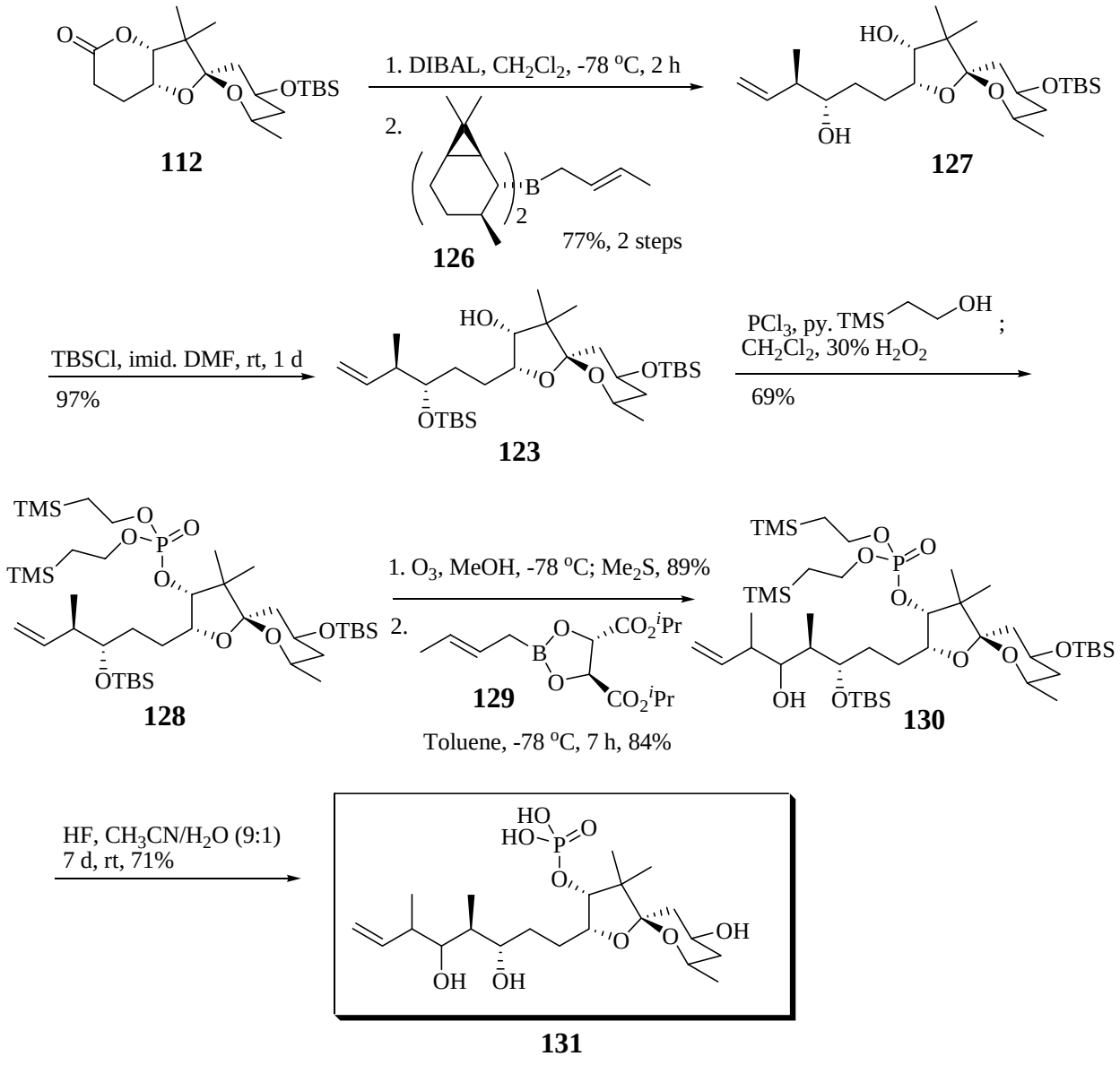
Figure 16. NOE analysis of compound **113**.



Scheme 18. The first attempt to introduce the phosphoric acid ester.

With the major spiroketal **112** in hand, we proceeded to the next steps necessary for the construction and the installation of the side chain 1,3-diol, which is one of the essential structural features for the enzyme inhibition by calyculin A. DIBAL reduction of **112** yielded a mixture of lactol and aldehyde. The crude lactol was first subjected to a Roush asymmetric crotylboration,[54c] which resulted in a mixture of two crotylated compounds in about a 1:1 ratio. The precise ratio was not determined due to the difficult separation. However, Brown asymmetric crotylboration[54a,b] afforded the desired product **127** in 77% yield along with a trace amount of another diastereomer (Scheme 19). The crotylated product **127** matched one of two products from a Roush asymmetric crotylation. Regioselective alcohol protection of **127** was successfully achieved with TBSCl without silylation of the sterically hindered hydroxy group on the spiroketal ring. The first approach to synthesize the phosphoric acid ester **125** from **123** involved an ozonolysis, a second crotylation, an anticipated regioselective mono TBS-protection of the resulting alcohol, and the final phosphorylation (Scheme 18). The alcohols in **124** were

unreactive toward TBSCl due to high steric hindrance. No selectivity between the two hydroxy groups of this intermediate **124** was observed with the more reactive TBSOTf.



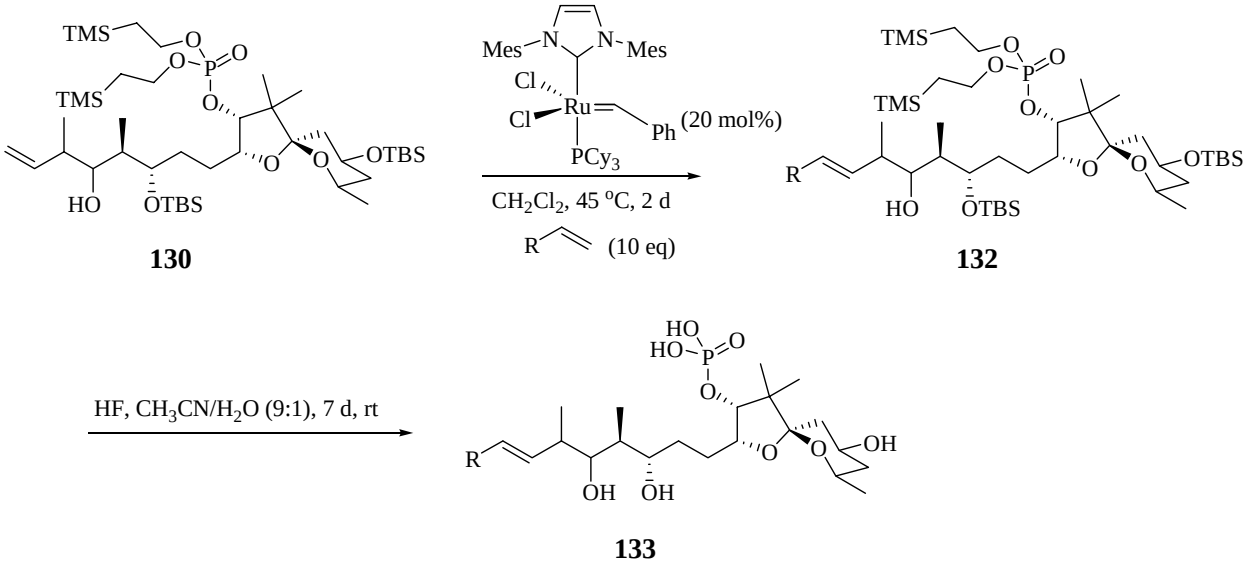
112 **126** **127** **123** **128** **129** **130** **131**

Scheme 19. Synthesis of the first analog **131**.

In our second approach shown in Scheme 19, the phosphoric acid ester was introduced earlier to give **128** in 69% yield. Phosphoric acid ester **128** was then subjected to ozonolysis and Roush asymmetric crotylation to give the final intermediate **130** as a single diastereomer in 75% yield over the 2 steps. The newly formed stereocenters of **130** were assumed as the (*R*)-OH and (*R*)-methyl groups based on the known induction of the chiral reagent.[54c] However, from the information of the X-ray structure of **152** (Figure 19), the possibility of (*S*)-(OH) and (*S*)-methyl groups in **130** could not be excluded. Further study is necessary to reveal the correct stereochemistry of the second crotylation. Global deprotection of **130** was achieved with HF in CH_3CN/H_2O over 7 d to yield the phosphoric acid **131**.[50] The first phosphoric acid analog **131** was thus obtained in 20 steps in a 1.4% overall yield.

3.4.2. Introduction of hydrophobic tail by cross-metathesis

SAR data[52] indicated that the hydrophobic tetraene moiety (C1 to C9) of calyculin A was very important for the inhibitor to bind to a hydrophobic pocket of the enzyme. We used the cross-metathesis protocol[60] to modify and extend the terminal alkene of **130**. Six alkene derivatives, in which R was phenyl, 4-methoxy phenyl, 4-chloro phenyl, cyclohexyl, *n*-butyl, and *n*-octyl, were successfully introduced in moderate yields as shown in Scheme 20. Global deprotections of **132** analogs were achieved with HF in CH_3CN/H_2O over 7 d to yield the phosphoric acids **133** analogs.



130 **132** **133**

R	Yield (%)	Yield (%)
Phenyl	**132a** (68%)	**133a**[a]
4-Chlorophenyl	**132b** (74%)	**133b** (66%)
4-Methoxyphenyl	**132c** (38%)	**133c** (quant)
Cyclohexyl	**132d** (68%)	**133d**[a]
C_4H_9	**132e**[a]	**133e**[a]
C_8H_{17}	**132f** (67%)	**133f** (70%)

a. Yield is not determined.

Scheme 20. Introduction of the hydrophobic tail by cross-metathesis.

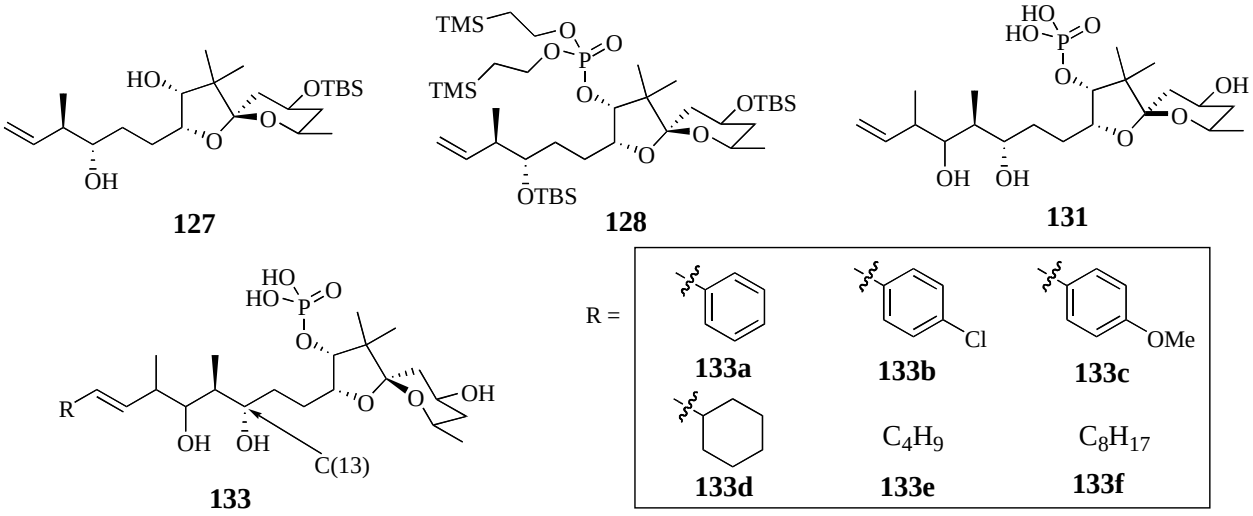
3.4.3. Biological activity of synthetic derivatives

The enzyme inhibitory activities of analogs **127**, **128**, **131**, and **133** analogs (Table 9) were tested against the PP2A catalytic domain.[62] The ProFluor™ assay kit from Promega[63] was used for this assay. The ProFluor™ PKA assay measures cAMP-dependent protein kinase (PKA, serine/threonine protein kinase) activity using purified kinase to find compounds that inhibit kinase activity. Using the ProFluor™ PKA Assay, compounds that inhibit the kinase result in

increased fluorescence and are easily distinguishable from compounds that only inhibit protease activity, which decreases fluorescence.[63]

Table 9. IC_{50} values of synthesized analogs against the PP2A catalytic domain.

Analog	IC_{50} (μM)
127	28.1 ± 0.8
128	24.4 ± 0.1
131	23.3 ± 7.1
133a	23.4 ± 3.2
133b	32.9 ± 6.6
133c	30.7 ± 6.7
133d	27.4 ± 1.5
133e	29.4 ± 0.9
133f	57.6 ± 16



IC_{50} values showed that the compounds in Table 9 were essentially inactive. The alcohol **127** and the protected phosphoric acid ester **128** were expected to be inactive due to the absence

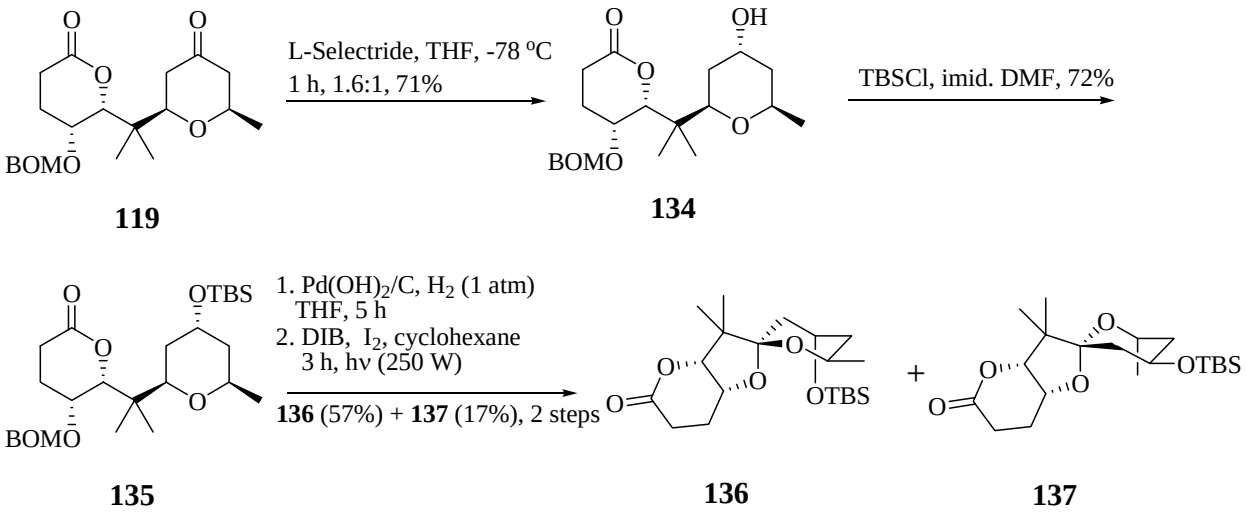
of the phosphoric acid group. However, from the inactivity of **131** and **133** analogs, we could conclude that the configuration of the spiroketal ring and the specific hydrophobic tail is important for retaining biological activity. Even though **131** and **133** had the correct phosphoric acid and C(13)-OH, the improper orientation of other functional groups, compared with the calyculin A core, could prohibit their binding on the enzyme. The presence of different aliphatic or aromatic tails did not induce a higher inhibition. In order to choose the proper hydrophobic tails, not only the hydrophobicity but also the specificity should be considered. Significantly, geometrical isomers of the tetraene terminus of calyculin A were less potent.[52] These results motivated us to synthesize close structural analogs of calyculin A.

3.4.4. Synthesis of diastereomeric spiroketal compounds

As mentioned previously, the hydroxyl group of the tetrahydropyran ring should be placed in an axial orientation to maintain the natural conformation of the spiroketal compounds. To introduce an axial OH and obtain other diastereomers of the spiroketal quickly, compound **119** was modified systematically (Scheme 21). In compounds **112** and **113**, methyl and hydroxyl groups were placed in a *syn*-orientation. To obtain an *anti*-relationship between methyl and hydroxyl groups in the tetrahydropyran ring, compound **119** was reduced with L-Selectride, a bulkier reducing reagent, to afford a 1.6:1 mixture of diastereomers in 71% yield. The minor product of the reduction matched compound **120** and the stereochemistry of major product was easily postulated as **134**. Though the diastereoselectivity was moderate, the major product possessed the desired configuration. The secondary alcohol of **134** was protected with TBSCl, followed by BOM deprotection using hydrogenation in the presence of $Pd(OH)_2$.

Spiroketalization of **135** was performed as previously described with DIB and iodine, which produced 3.4:1 mixture of two separable spiroketals **136** and **137** in 74% yield over 2 steps.

The conformations of the two spiroketals were presumed to be as shown in Scheme 21. A methyl or OTBS group in either diastereomer is placed in an axial position. Both conformations are stabilized by anomeric effects. However, the amount of the new spiroketals was not sufficient to allow for further conversion to the phosphoric acid derivatives.



119 **134** **135** **136** **137**

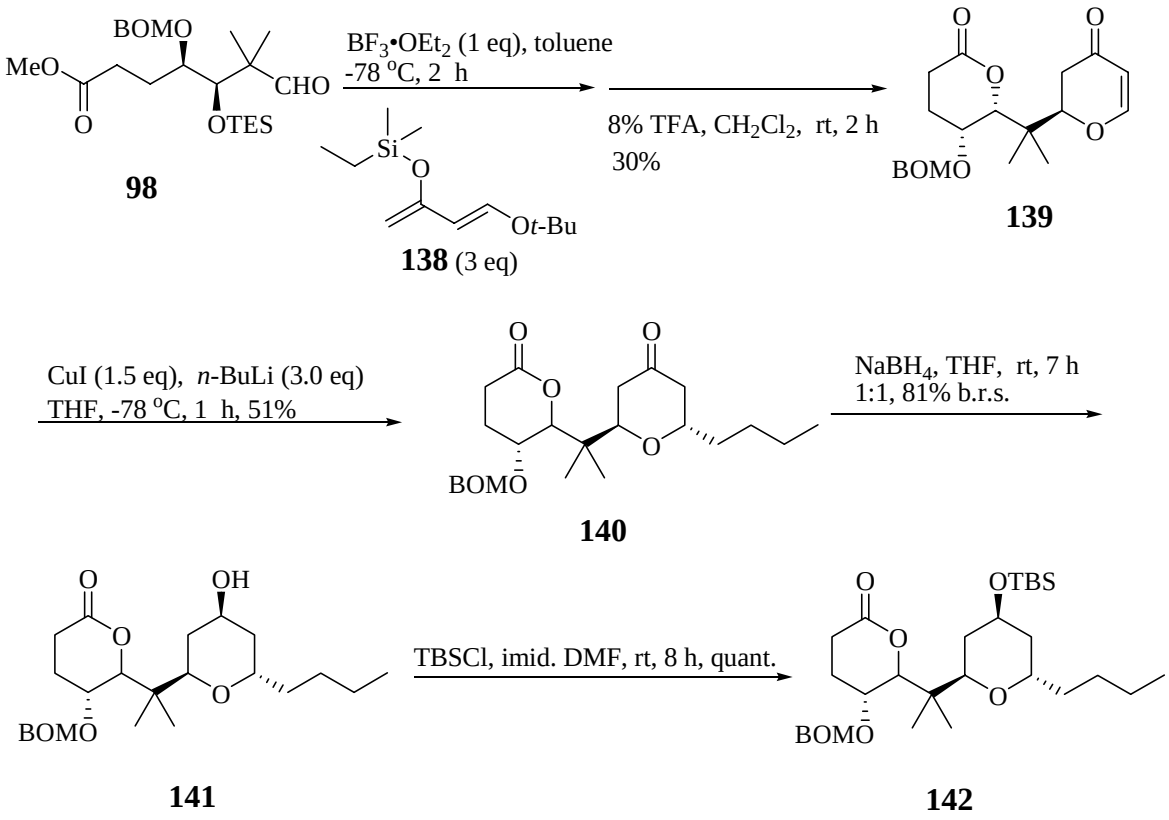
Scheme 21. Synthesis of spiroketals **136** and **137**.

Although spiroketals **136** and **137** possess the *anti*-relationship of methyl and OTBS groups on the tetrahydropyran ring, the stereochemistry of these groups does not match the spiroketal core of calyculin A. In the correct structure, the methyl and hydroxyl groups on the tetrahydropyran ring should have (*S*)-configurations. To obtain the (*S*)-configuration of the methyl group on the tetrahydropyran ring, we explored a copper-mediated 1,4-addition, in which the alkyl group was added from the sterically less hindered α-face of **139** (Scheme 22). As

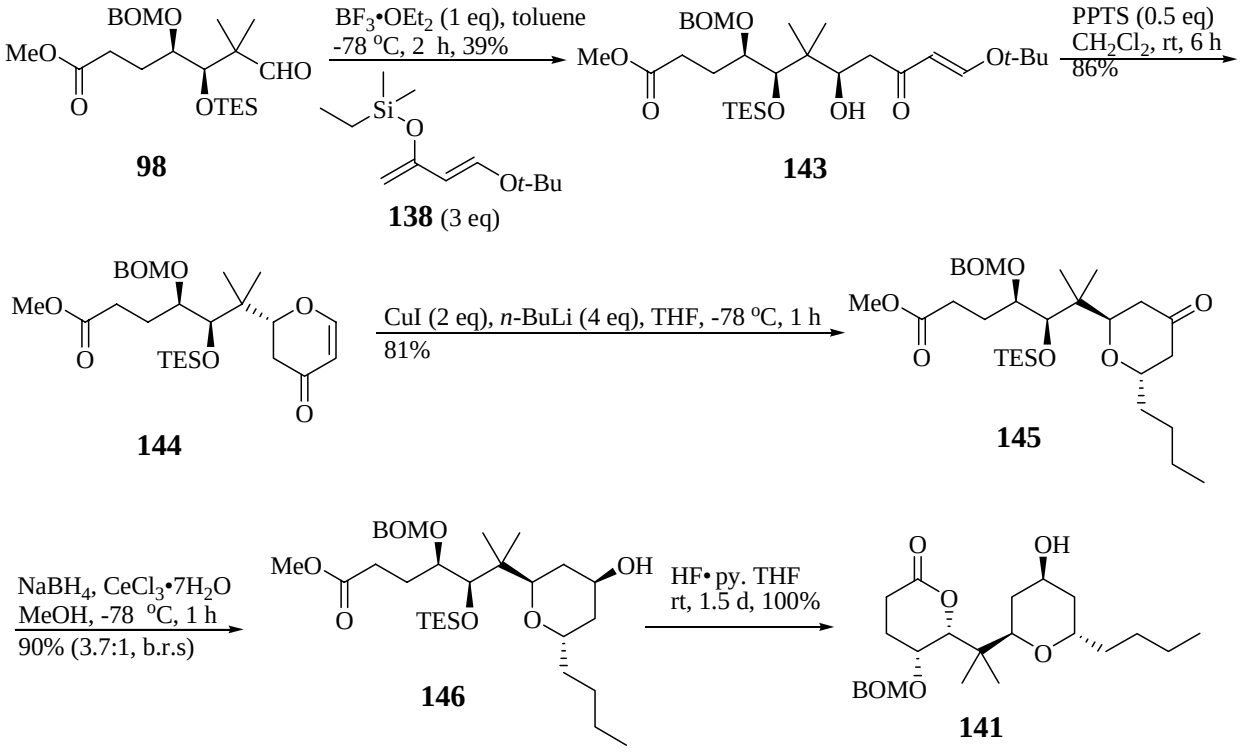
mentioned earlier, the original Danishefsky's diene[56] gave poor yields in our hetero-Diels-Alder reactions, which prevented further study of the intermediate **102** (Scheme 12). Additionally, the sterically hindered aldehyde **98** was less reactive and the extended reaction time led to the rapid decomposition of Danishefsky's diene. Even with other Lewis acids including $AlCl_3$, Et_2AlCl, TMSOTf or $Sc(OTf)_3$, there were no improvements in the yield of the cycloadduct.[59] Rawal's diene,[64] 1-amino-3-siloxy-1,3-diene, was also examined in this reaction. However, Rawal's diene decomposed in the presence of Lewis acid. Under thermal conditions with hydrogen-bonding solvents such as 2-butanol,[64] the desired product was obtained in about 30% yield. However, no facial selectivity was observed, and a mixture of the two diastereomers prevailed. A more stable diene was sought to prevent the rapid decomposition during the extended reaction time. To conserve the excellent stereoselectivity in the hetero-Diels-Alder reaction, the thermal conditions were avoided. The diene **138**[65] showed the best outcome. Employing the bulky silyloxy diene **138** with BF_3•OEt_2 and aldehyde **98** at –78 °C in toluene, followed by treatment with TFA, gave the desired product **139** reproducibly in <30% yield (Scheme 22).

To introduce alkyl substituents on the dihydropyrone ring of **139**, Cu-mediated 1,4-addition was tested. Methyl or vinyl cuprate reagents gave poor yields of the addition products. However, the butyl cuprate reagent, which was prepared from a 1:2 mixture of CuI and *n*-BuLi, gave the desired product **140** as a single diastereomer in 51% yield. Incoming nucleophile should approach from less hindered α-face of **139** to give an *anti*-relationship of two alkyl groups on the tetrahydrofuran ring. $NaBH_4$ reduction of **140** yielded a mixture of two diastereomers (**141**:**159** = 1:1) in 81% yield based on recovered starting material. To improve the diastereoselectivity of the reduction and reduce the reaction time for the formation of the alcohol **141**, several reducing conditions, including $LiBH_4$ at diverse temperatures and $NaBH_4$ with $CeCl_3$•$7H_2O$, were

exploded. However, the lactone moiety of **140** was sensitive to these conditions, and the stereoselectivity and the yield were not improved. Each stereochemistry of two diastereomers from the $NaBH_4$ reduction was postulated by comparison with **141** (Scheme 23) and **159** (Scheme 29), which were prepared through alternative routes, and confirmed later by the X-ray structure of **147** (Figure 18). The desired secondary alcohol **141** was protected with a TBS group to give **142** in quantitative yield. Though we were able to access the desired intermediate **142**, the overall route was inefficient and produced **141** in 6% yield over 3 steps from **98**. Alternative routes to **141** were therefore examined.



Scheme 22. Synthesis of compound **142**.



Scheme 23. Alternative route for synthesis of compound **141**.

During the hetero-Diels-Alder reaction, the use of PPTS instead of TFA gave the dihydropyrone but did not lead to concomitant lactonization. Since the lactone was proven to be sensitive to subsequent transformations of the dihydropyrone ring, we postponed the introduction of the lactone to a later step. Cu-mediated 1,4-addition to the dihydropyrone **144** proceeded in high yields to give the 3,5-dialkylated tetrahydropyrone **145** as a single diastereomer. The incoming butyl cuprate reagent should approach from the less hindered face of **144** to give an *anti*-relationship of the two alkyl groups on the tetrahydrofuran ring of **145**. The reduction of the tetrahydropyrone **145** with $NaBH_4$ in the presence of $CeCl_3•7H_2O$ resulted in an improved diastereoselectivity from 1:1 to 3.7:1 with a shorter reaction time and higher yield. Deprotection

of the TES group in **146** with the HF•pyridine complex, followed by spontaneous lactonization, gave the bicyclic compound **141** in quantitative yield as depicted in Scheme 23. This alternative strategy provided the bicyclic alcohol **141** in better selectivity and higher yield of up to 19% over 4 steps.

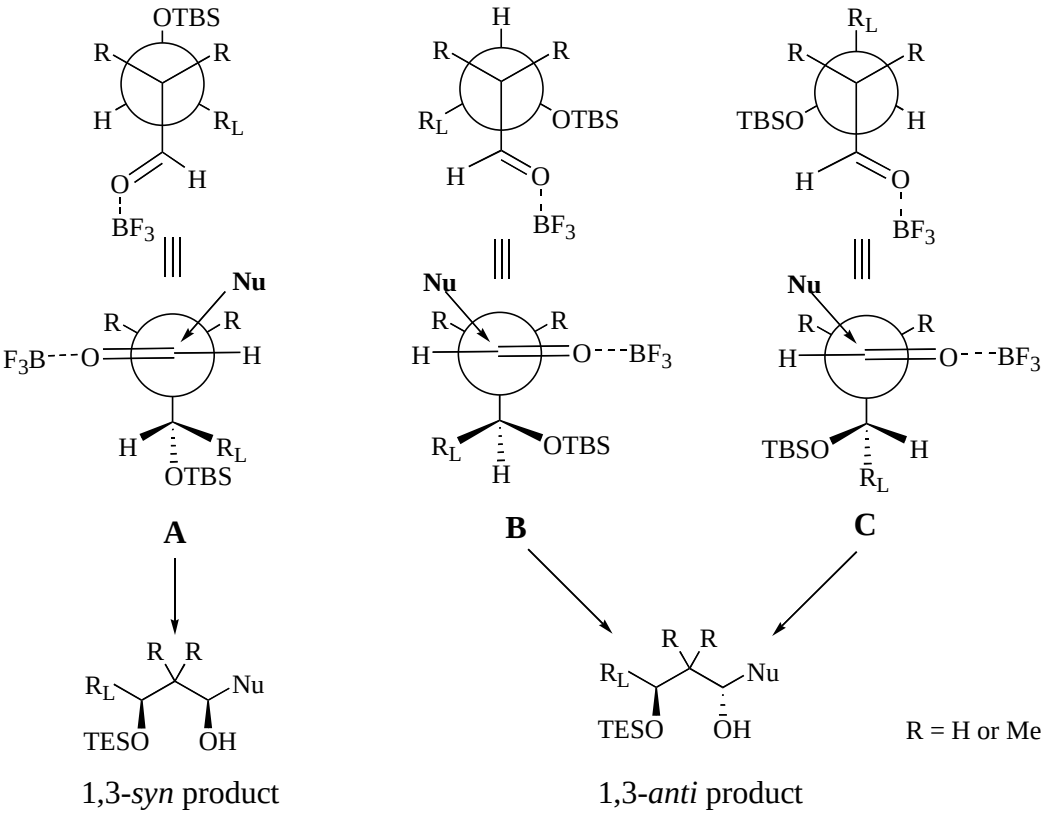
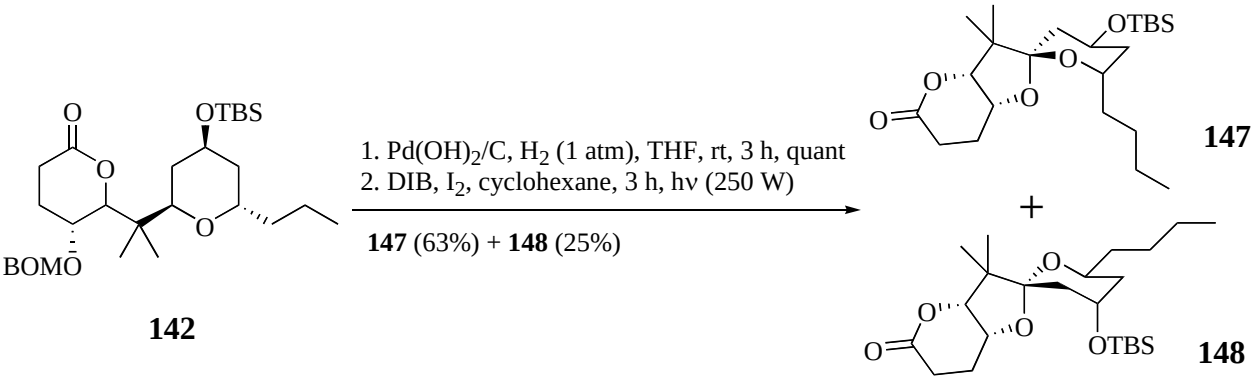


Figure 17. Postulated transition state for **143**.

We propose a model for 1,3-asymmetric induction of the Mukaiyama aldol reaction during hetero-Diels-Alder reactions (Scheme 16, Scheme 22, and Scheme 23). With a β-substitute aldehyde containing two α-hydrogens, the formation of the 1,3-*anti* product diastereomer is generally preferred and this aldehyde face selectivity is governed by steric and

electrostatic effects in the aldehyde that originate from interactions between the β-substituents and the carbonyl reaction center. In that case, the transition state can be postulated like **C** in Figure 17.[66] However, with the aldehyde **98**, the geometry in transition state **A** reduces nonbonded interactions between α- and β-substituents and provides 1,3-*syn* product **143**. In transition state **B**, a destabilizing dipolar interaction between the C-X and the C=O bonds is present. In the case of R=Me, *gauche* interactions between R_L and two other groups are assumed to be larger in transition state **C** than transition state **B**.



Scheme 24. Synthesis of spiroketals **147** and **148**.

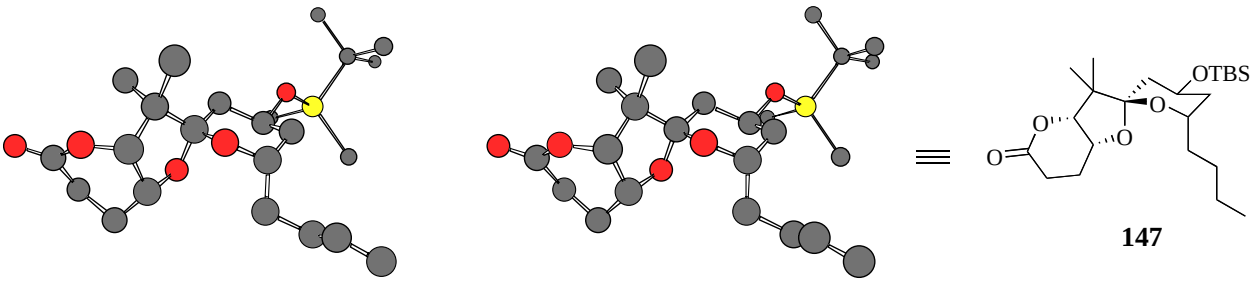
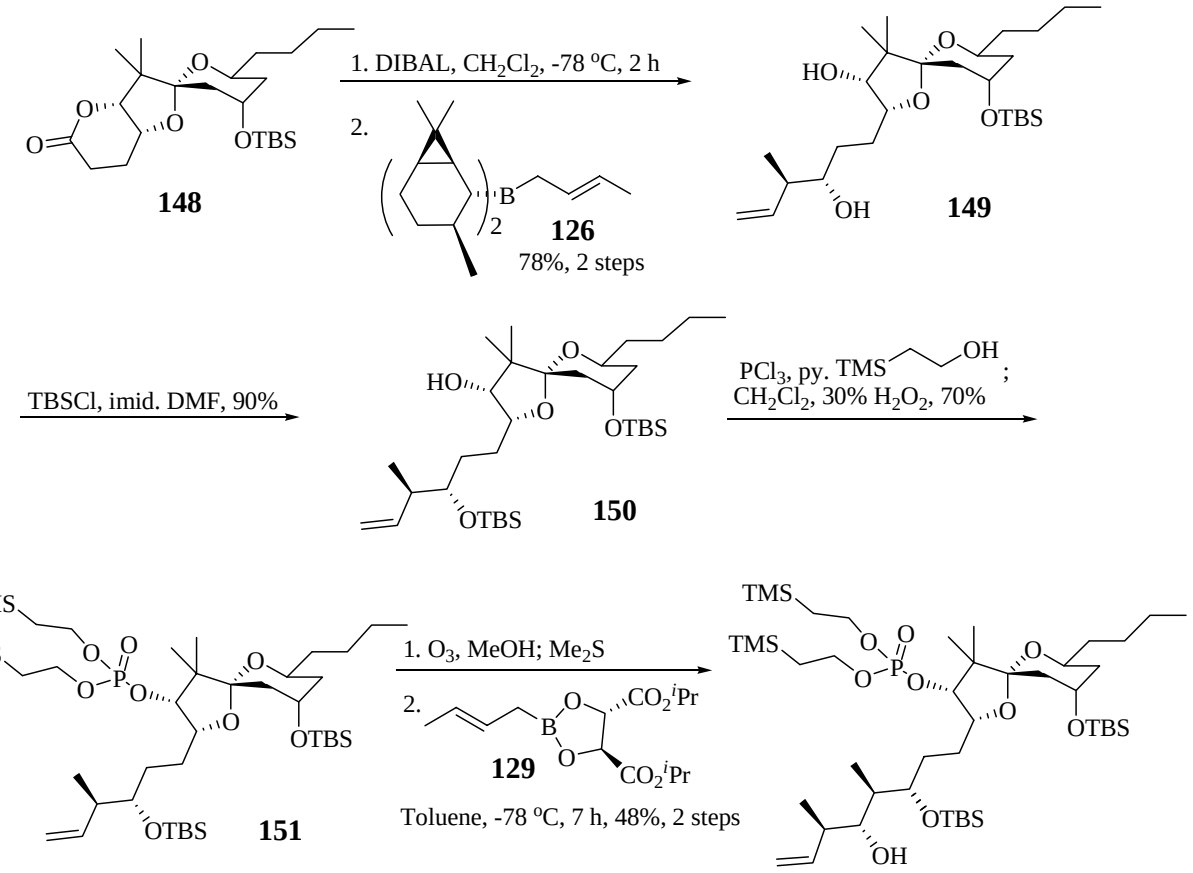


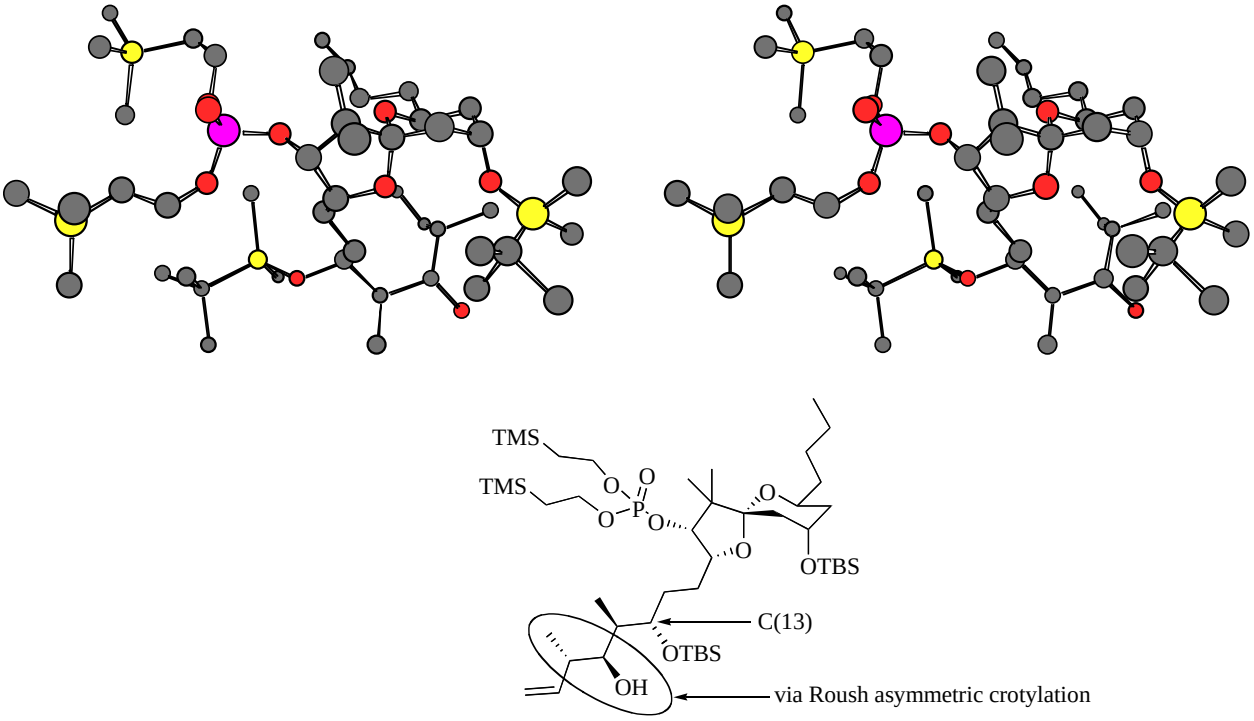
Figure 18. X-ray structure of 147.

As shown in Scheme 24, the deprotection of the BOM group of **142**, followed by spiroketalization, gave a 2.5:1 ratio of two diastereomers **147** and **148** in 88% yield. The relative configuration of the major spiroketal compound **147** was determined by the X-ray structure. The configuration and conformation of **147** matched those predicted (Figure 18). The conformation of the spiroketal segment was stabilized by an anomeric effect, and butyl and silyloxy groups were placed in axial and equatorial orientations, respectively. Based on the X-ray crystallographic information of **147**, the stereochemistry of the minor product **148** was assigned as shown in Scheme 24, and was later confirmed by the X-ray structure of **152**. The minor diastereomer **148** shows the same configuration as the spiroketal core of calyculin A.



Scheme 25. Synthesis of compound **152**.

Spiroketal product **148** was further functionalized by DIBAL reduction and subsequent Brown asymmetric crotylation to give the bicyclic **149** as a single diastereomer in 78% yield (Scheme 25). The expected stereochemistry from crotylation of **149** was confirmed by the X-ray structure of **152**. The diol **149** was protected regioselectively with TBSCl to give **150** in 90% yield. The alcohol **150** was converted to the phosphoric acid ester **151** in 70% yield following the established procedure. The ozonolysis of **151** and the subsequent crotylation with Roush crotylation reagent afforded the 1,3-diol **152** as a single diastereomer in 48% yield over 2 steps.

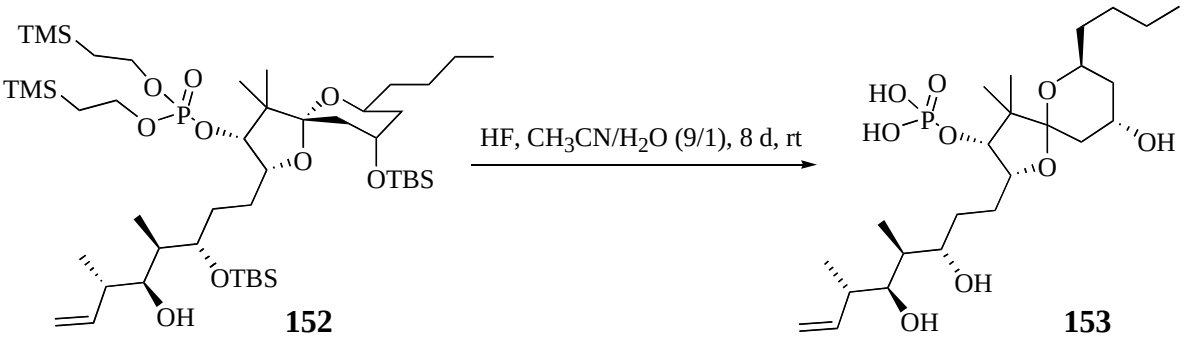


152 (correct structure)

Figure 19. X-ray structure of **152**.

In Figure 19, the relative stereochemistry of **152** is shown as determined by the X-ray structure. The conformation of the spiroketal segment and the stereochemistry of initial

crotylation were thus confirmed as originally assigned. This structure matched the most important functional groups of the calyculin A core; C(13)-OH, phosphoric acid ester and the rigid spiroketal segment. However, the second crotylation produced an undesired diastereomer. This result can be explained through a Felkin transition state.[67] In order to give the desired stereochemistry of **152**, the combination of aldehyde **151** and chiral reagent **129** is referred to as a "mismatched pair".[68] High levels of diastereofacial selectivity in the mismatched direction are observed with α-methyl-β-alkoxy aldehydes without β stereocenter.[69] It is unclear why the chiral reagent **129** failed to show the expected chiral induction.

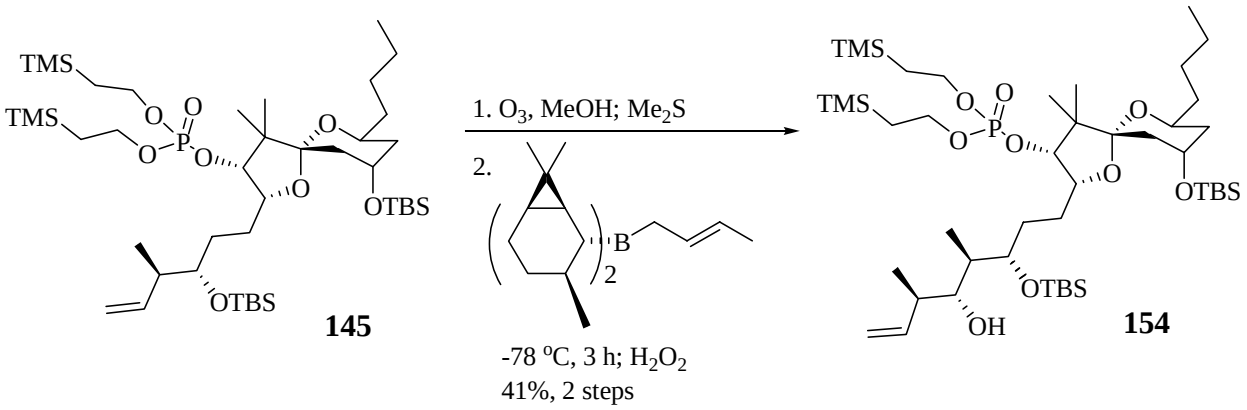


152 **153**

Scheme 26. Deprotection of **152**.

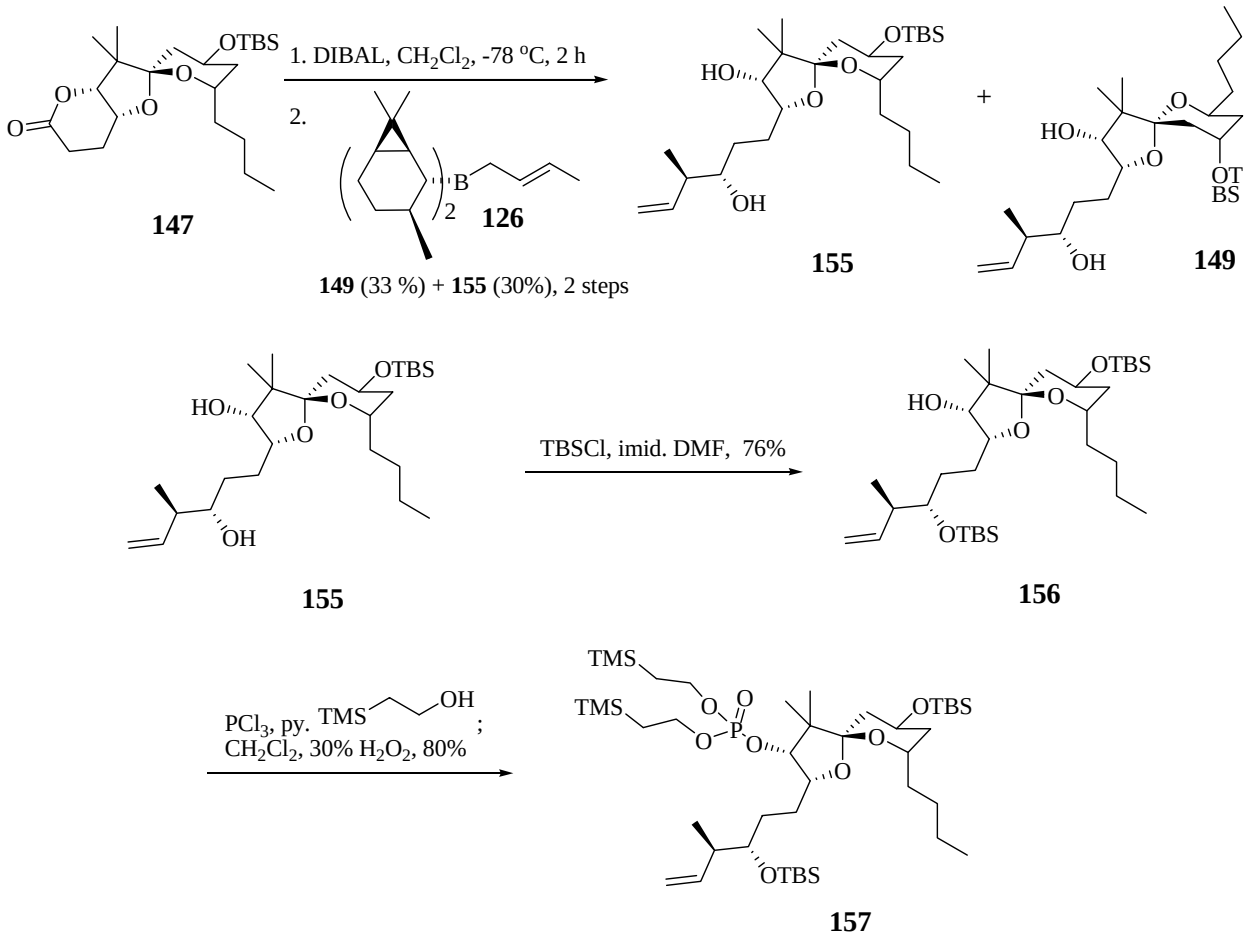
Global deprotection of **152** was achieved with HF in CH_3CN/H_2O over 8 d to yield the phosphoric acid **153** (Scheme 26). Unlike the deprotection of **130** (Scheme 19), the deprotection of **152** was not completed in 8 d and led to an inseparable mixture of **153**, which was identified by HRMS, and side products. We suspected an isomerization of spiroketals occurred under the strong acidic reaction conditions. The mixture of phosphoric acids could be purified by chromatography on SiO_2 (CH_3CN:MeOH = 3:1) but was not separable.

Using the Brown crotylation reagent instead of Roush's reagent, the resulting product **154** decomposed under basic hydrogen peroxide conditions during work-up. When only an excess of H_2O_2 was used to oxidize the borate, the conversion to the desired compound **154** occurred very slowly under reflux condition (Scheme 27)



Scheme 27. Synthesis of compound **154**.

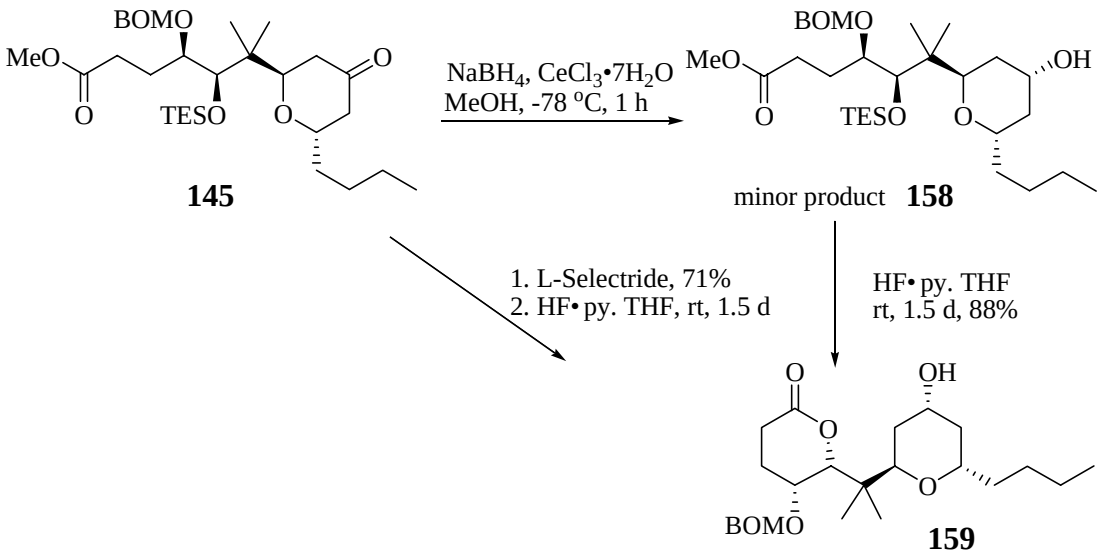
In contrast to **148**, DIBAL reduction and crotylation of the major spiroketal product **147** gave a separable mixture of diastereomers. One of the diastereomers from the crotylation of **147** matched the spectral data of the compound **149**. This could be due to isomerization of the spiroketal segment of **147** during the crotylation; the boron species might act as a Lewis acid and catalyze the isomerization. The compound **155** was converted to the phosphoric acid ester **157** via TBS protection and phosphorylation as shown in Scheme 28.



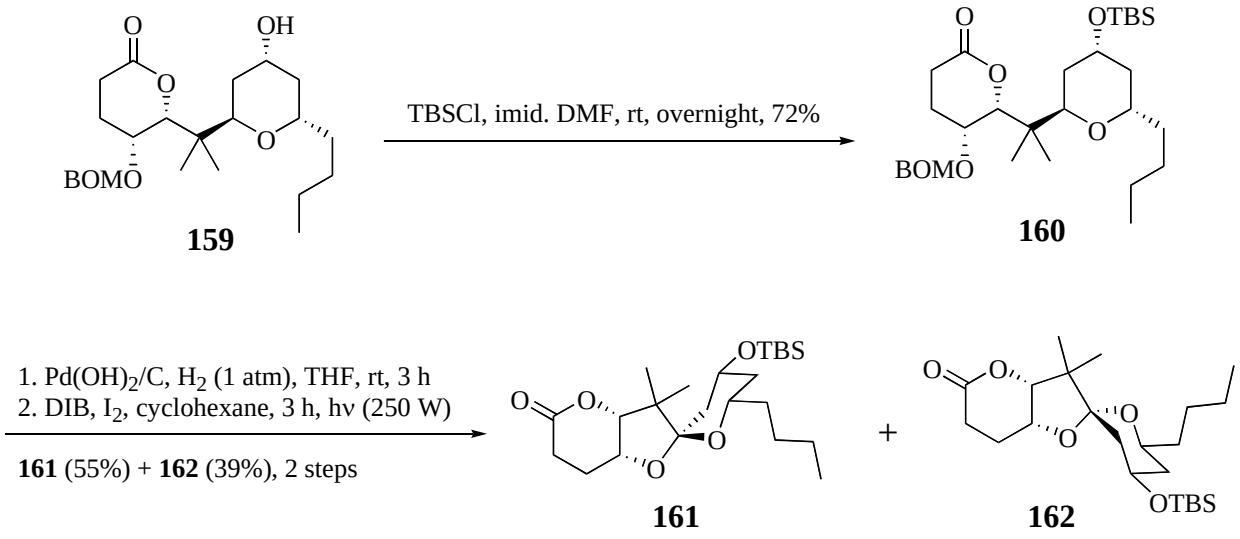
Scheme 28. Synthesis of compound **157**.

To synthesize spiroketals with (*R*)-OH and (*S*)-butyl groups on the tetrahydropyran ring, the TES group of the minor reduction product **158** was deprotected to give the bicyclic compound **159** in 88% yield. To obtain **159** more efficiently, compound **145** was reduced with L-Selectride and the subsequent TES deprotection gave the desired product **159** as a single diastereomer in good yield (Scheme 29). Unlike the reduction of **119** with L-Selectride (Scheme 21), the bulky reducing reagent was able to approach from the opposite side of the axial butyl group to avoid the amplified steric hindrance, which resulted in excellent diastereoselectivity.

The stereochemistry of **159** was postulated by the comparison of **141** and **159** prepared under different conditions, and later confirmed by the X-ray structure of **166** (Figure 20).

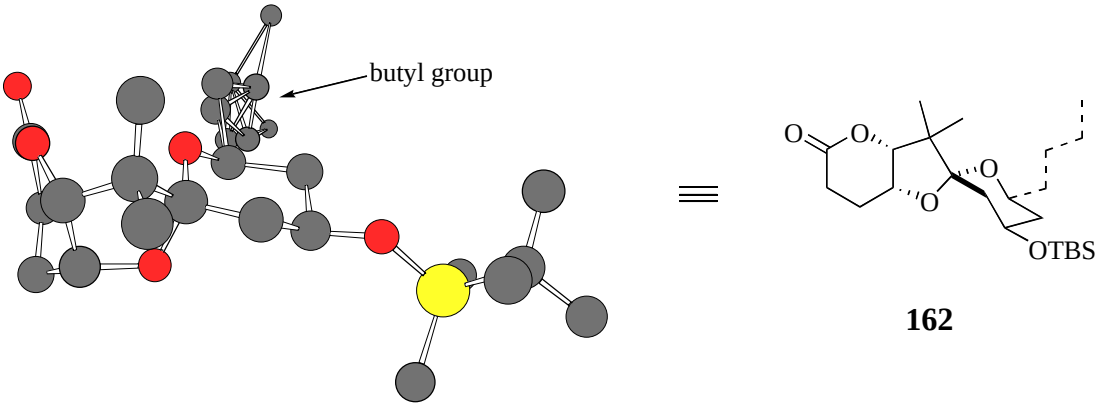


Scheme 29. Alternative routes for the synthesis of **159**.



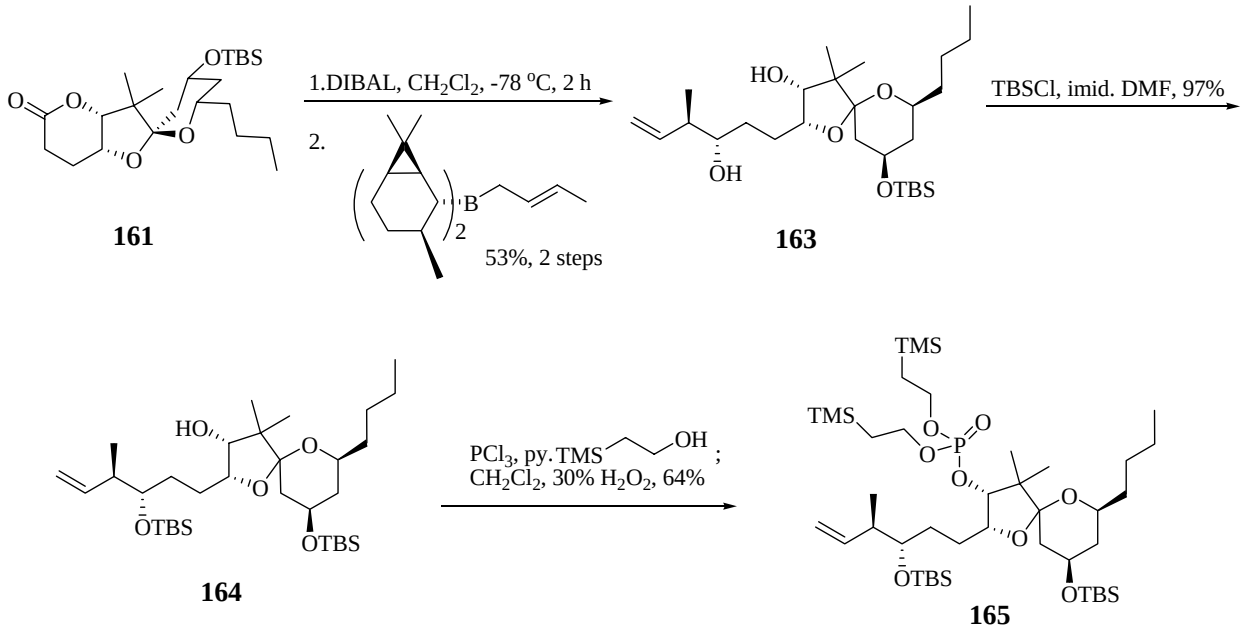
Scheme 30. Synthesis of spiroketals **161** and **162**.

Scheme 30 shows the conversion of compound **159** to the two new spiroketal lactones **161** and **162** in 94% yield over 3 steps. The relative stereochemistry of **162** was elucidated via X-ray crystallography (Figure 20). In the X-ray structure, the butyl group in the tetrahydropyran ring was disordered. However, the relative stereochemistry of tricyclic rings was able to be determined as shown below. The major spiroketal lactone **161** was then converted to the phosphoric acid ester **165** through a standard reaction sequence (Scheme 31).



162

Figure 20. X-ray structure of **162**.



161 **163** **164** **165**

Scheme 31. Synthesis of compound **165**.

In future work, other crotylation methods should be tested to more efficiently synthesize **154**, and efficient deprotection conditions of **154** should be studied to obtain the desired calyculin A analog. After the biological data of the correct **153** is obtained, further modification of spiroketals can be studied.

4. Conclusion

In summary, we synthesized a number of poly(cyclic urea) compounds and investigated them as possible alternatives to the dipolar solvent HMPA. In a series of test reactions, these additives showed similar or better effects than the monocyclic urea compounds DMPU and DMEU. The additive **32** was particularly good and gave results similar to HMPA in the addition of lithiated 1,3-dithiane to cyclohexenone. The corresponding solid-supported reagent **44** was also prepared and showed moderate additive properties. Poly(cyclic urea) polymers with linear structure were prepared by ROMP. Although these polymers precipitated from the reaction solution upon addition of excess ethyl ether and could be recovered, their physical properties were inadequate. These materials were not easily crystallized and formed aggregates with the metal cation of the reaction mixture, preventing their use in Li-base reaction. However, we have shown that by careful assembly of functionalized urea-monomers into linear, and eventual star-shaped structures, additives with improved properties could be prepared. Also polymer-supported urea **44** showed a moderate success as an additive.

Polymer-supported HMPA reagents were synthesized as safe and reusable alternatives to liquid HMPA using solid-supported living free radical polymerization or suspension polymerization with tetrahydrofuran-derived cross-linkers. Polymer **86** was easily obtained in high loading and its physical appearance was very promising. Unfortunately, this polymer did not show consistent results during both its synthesis and application. We observed a decomposition of this polymer evidenced by changes in color and smell under harsh reaction conditions. Microwave irradiation did not improve the synthesis. Alternatively, JandaJel-type HMPA polymers were synthesized and applied as additives. These reagents showed very

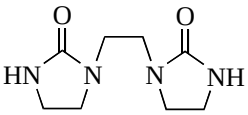
promising properties as compared to HMPA. We have demonstrated the general usage of our polymer-supported HMPA in a variety of reactions. While an excess of the polymer was required in most cases, we have found that the resin could be recovered and reused at least 8 times without any loss of activity. Also, the resin showed consistent activity after it was used in different reactions. In the future, the synthesis of polymer-supported HMPA can certainly be optimized to improve the yield and loading. The replacement of the dimethyl amine moiety with bulkier amines such as piperidine could lead to even less toxic materials. Also, the introduction of chiral HMPA moieties may give rise to chirality-inducing polymer-supported HMPA analogs.

The synthesis of substituted spiroketal derivatives as mimics of the calyculin A core was achieved in 20-22 steps for the longest linear sequence. The design of these simplified analogs of calyculin A was based on SAR data, which pointed toward the structural features necessary for inhibitor activity. The highlights of our approach were regio- and stereoselective reductions, hetero-Diels-Alder reactions, intramolecular hydrogen abstractions and asymmetric crotylations. This synthetic strategy provided a ready access to structural analogs of interest for 2nd generation structure-activity relationships in phosphatase inhibition.

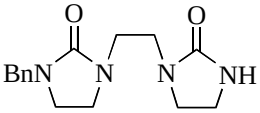
5. Experimental Section

General. All moisture-sensitive reactions were performed under an atmosphere of N_2 or Ar and all glassware was dried in an oven at 130 °C prior to use. THF was dried by distillation over Na/benzophenone. Et_2O, Toluene, DMF and CH_2Cl_2 were obtained by distillation from CaH_2. Other solvents or reagents were used without further purification unless otherwise stated. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel 60 F-254 plates (particle size 0.040-0.055 mm, 230-400 mesh) and visualization was accomplished with a 254 nm UV light or by staining with a basic $KMnO_4$ solution (1.5 g of $KMnO_4$, 10 g of K_2CO_3 and 2.5 mL of 5% aqueous NaOH in 150 mL of water) or PMA solution (5 g of PMA and 100 mL of EtOH). Flash chromatography was performed using silica gel 60 (230-400 mesh) available from EM.

NMR spectra were recorded in $CDCl_3$ at either 300 MHz (^{1}H NMR) or 75 MHz (^{13}C NMR) using a Bruker Avance 300 with XWINNMR software (unless otherwise noted). Chemical shifts (δ) were reported in parts per million and the residual solvent peak was used as an internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sx = sextet, m = multiplet, br = broad), integration, and coupling constants. IR spectra were obtained on a Nicolet Avatar 360 FT-IR spectrometer. Mass spectra were obtained on a Waters Autospec double focusing mass spectrometer (EI) or a Waters Q-Tof mass spectrometer (ESI).

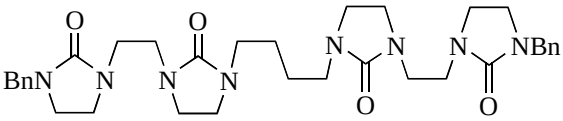


1,2-Bis-1-(2-imidazolidonyl)ethane (14).[11] A mixture of triethylenetetramine (72.0 g, 492 mmol) and urea (40.0 g, 666 mmol) was heated to 180 °C and stirred until the generation of ammonia gas ceased. After the suspension was cooled to room temperature, the residue was suspended in MeOH, filtered, and washed with MeOH. The resulting colorless solid was recrystallized from MeOH to give **14 (**52.3 g, 26.4 mmol, 79%) as a white solid: Mp 246-249 °C; IR (KBr film) 3226, 3085, 2867, 1681, 1504, 1445, 1276, 1104, 965, 764 cm^{-1}; ^{1}H NMR (D_2O) δ 4.66 (s, 2 H), 3.39 (dd, 4 H, *J* = 7.6, 8.6 Hz), 3.22(dd, 4 H, *J* = 7.6, 8.6 Hz), 3.15 (s, 4 H).

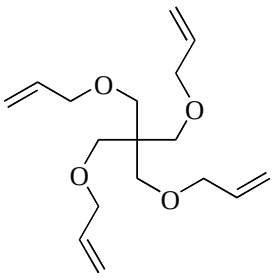


1-(1-(Benzyl)-2-imidazolidonyl)-2-(1'-(2'-imidazolidonyl))ethane (15). A suspension of **14** (8.00 g, 40.4 mmol) and NaH (60% dispersion in mineral oil, 1.94 g, 48.5 mmol) in DMF (70 mL) was heated to 130 °C, stirred for 30 min, and treated slowly with a solution of benzyl bromide (5.53 g, 32.3 mmol) in DMF (5 mL). The reaction mixture was stirred at 130 °C for 1 h, cooled to room temperature, stirred overnight, and quenched with MeOH (10 mL). DMF was distilled off under vacuum and water (100 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was triturated with ethyl ether (50 mL) and filtration gave **15** (4.64 g, 16.1 mmol, 50%) as a white solid: Mp 65-68 °C; IR (KBr film) 3441, 3234, 3085, 2931, 2870, 1674, 1498, 1440, 1363, 1283, 1255, 1241, 1106, 758 cm^{-1}; ^{1}H NMR δ 7.30-7.15 (m, 5 H), 5.20 (br. s, 1 H), 4.31 (s, 2 H), 3.49 (dd, 2 H, *J* = 6.8, 8.4 Hz), 3.36-3.20 (m, 8 H), 3.14 (dd, 2 H, *J* = 7.3, 8.4 Hz); ^{13}C NMR δ 163.1, 161.1, 137.3, 128.6, 128.0, 127.3, 48.2, 44.5, 42.2, 42.0, 41.3, 40.6, 38.2; MS (EI)

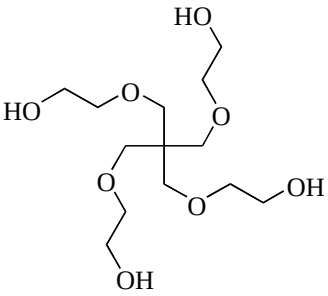
m/z (relative intensity) 288 (M^+, 4), 202 (70), 189 (37), 177 (6), 112 (12), 99 (22), 91 (100); HRMS (EI) *m/z* calculated for $C_{15}H_{20}N_4O_2$ 288.1586, found 288.1573.



1,4-Bis-(1-(3-(2-(1-benzyl-2-imidazolidonyl))ethyl-2-imidazolidonyl))butane (16). To a suspension of NaH (60% dispersion in mineral oil, 0.832 g, 20.8 mmol) in DMF (8 mL) at 0 °C was added a solution of **15** (2.00 g, 6.94 mmol) in DMF (8 mL). The reaction mixture was stirred at room temperature for 30 min and a solution of 1,4-dibromobutane (0.800 g, 3.71 mmol) in DMF (2 mL) was added slowly. The reaction mixture was stirred at room temperature overnight and quenched with MeOH (5 mL). The solvents were distilled off under vacuum and water (50 mL) was added. The aqueous layer was extracted with $CHCl_3$ (3×30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 ($CHCl_3$/MeOH, 100:1) and the resulting solid was recrystallized from THF to give **16** (1.06 g, 1.68 mmol, 49%) as a white solid: Mp 108-113 °C; IR (KBr film) 3459, 3358, 3026, 2935, 2866, 1685, 1501, 1441, 1377, 1363, 1259, 1107, 983, 778, 754 cm^{-1}; ^1H NMR δ 7.35-7.23 (m, 10 H), 4.35 (s, 4 H), 3.42-3.34 (m, 16 H), 3.31-3.26 (m, 4 H), 3.20-3.15 (m, 8 H), 1.50 (br, 4 H); ^{13}C NMR δ 161.4, 161.2, 137.4, 128.6, 128.1, 127.4, 48.4, 44.1, 42.8, 42.34, 42.26, 42.0, 41.4, 25.1; MS (EI) *m/z* (relative intensity) 630 (M^+, 8), 539 (10), 455 (15), 441 (83), 278 (24), 252 (43), 227 (31), 202 (33), 189 (39), 91 (100); HRMS (EI) *m/z* calculated for $C_{34}H_{46}N_8O_4$ 630.3642, found 630.3684.

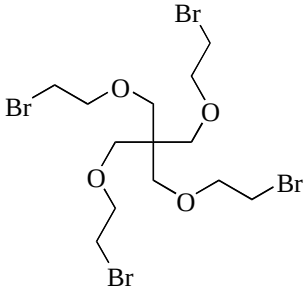


3-(3-Allyloxy-2,2-bisallyloxymethylpropoxy)propene (18).[12a] A suspension of a 50% aqueous NaOH solution (58.0 g, 725 mmol) and pentaerythritol (5.00 g, 36.7 mmol) was stirred at 50~70 °C until a homogeneous solution formed, and cooled to room temperature. To this mixture were added *tert*-butyl ammonium bromide (5.92 g, 18.4 mmol) and allyl bromide (26.6 g, 220 mmol). The reaction mixture was stirred at room temperature for 5 h and at 55 °C for 1 d, and cooled to room temperature. The aqueous layer was extracted with ethyl ether (3×60 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), and concentrated. The residue was purified by chromatography on SiO_2 (hexane/EtOAc, 25:1) to give **18** (8.00 g, 27.0 mmol, 73%) as a colorless oil: IR (neat) 3477, 3080, 2909, 2868, 1731, 1646, 1478, 1421, 1350, 1266, 1137, 1093, 991, 923 cm^{-1}; ^1H NMR δ 5.89 (ddt, 4 H, *J* = 5.4, 10.4, 17.3 Hz), 5.26 (dq, 4 H, *J* = 1.6, 17.2 Hz), 5.14 (dq, 4 H, *J* = 1.5, 10.4 Hz), 3.96 (dt, 8 H, *J* = 1.4, 5.4 Hz), 3.47 (s, 8 H); ^{13}C NMR δ 135.5, 116.2, 72.4, 69.6, 45.6.



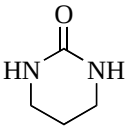
2-[3-(2-Hydroxyethoxy)-2,2-bis-(2-hydroxyethoxymethyl)propoxy]ethanol (19). O_3 was bubbled through a solution of **18** (6.00 g, 20.2 mmol) in CH_2Cl_2/MeOH (100/100 mL) at –78 °C until the solution was saturated. N_2 was bubbled through the solution for 15 min to remove the

residual ozone and methyl sulfide (11.9 mL, 162 mmol) was added. The mixture was allowed to warm to room temperature and concentrated to a syrup, that then was dissolved in EtOH (100 mL). $NaBH_4$ (6.13 g, 162 mmol) was added slowly to the cooled solution at 0 °C. After stirring for 18 h at room temperature, the reaction mixture was acidified with 20% HCl to pH 6. All solvents were removed and the residue was purified by chromatography on SiO_2 ($CHCl_3$/MeOH, 10:1) to give **19** (4.73 g, 15.1 mmol, 75%) as a colorless oil: IR (neat) 3374, 2925, 2875, 1653, 1456, 1362, 1309, 1228, 1172, 1117, 1067, 886 cm^{-1}; ^1H NMR δ 3.71-3.68 (m, 8 H), 3.57-3.54 (m, 8 H), 3.49 (s, 8 H), 3.30 (br, 4 H); ^{13}C NMR δ 72.9, 70.5, 61.6, 45.6; MS (EI) *m/z* (relative intensity) 313 ($[M+H]^+$, 0.4), 282 (0.4), 188 (3), 145 (3), 135 (5), 113 (28), 83 (29), 73 (100); HRMS (EI) *m/z* calculated for $C_{13}H_{29}O_8$ (M+H) 313.1862, found 313.1850.

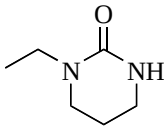


1,3-Bis-(2-bromoethoxy)-2,2-bis-(2-bromoethoxymethyl)propane (20). A solution of **19** (5.90 g, 18.9 mmol) was cooled to 0 °C, and treated with K_2CO_3 (102 g, 756 mmol), CBr_4 (50.0 g, 151 mmol), and PPh_3 (59.5 g, 227 mmol). After stirring for 24 h, the cold mixture was filtered through a pad of SiO_2. The filtrate was concentrated and purified by chromatography on SiO_2 (hexane/EtOAc, 10:1) to give **20** (7.27 g, 12.9 mmol, 68%) as a yellow oil: IR (neat) 2962, 2915, 2875, 1480, 1454, 1441, 1423, 1367, 1275, 1185, 1100, 1044, 1007, 961, 823 cm^{-1}; ^1H NMR δ 3.76 (t, 8 H, *J* = 5.9 Hz), 3.51 (s, 8 H), 3.48 (t, 8 H, *J* = 6.0 Hz); ^{13}C NMR δ 71.2, 69.1, 45.9, 31.0; MS (EI) *m/z* (relative intensity) 565 ($[M+H]^+$, 0.1), 441 (0.4), 403 (0.1), 314 (50), 301 (18),

285 (10), 261 (94), 207 (38), 163 (44), 137 (42), 107 (58), 73 (100); HRMS (EI) *m/z* calculated for $C_{11}H_{20}Br_3O_3$ (M-BrC_2H_4O) 436.8963, found 436.8953.

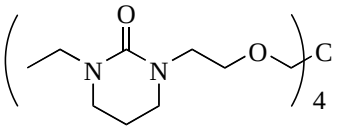


Tetrahydropyrimidin-2-one (21).[13] A mixture of 1,3-diaminopropane (21.0 g, 283 mmol) and urea (10.0 g, 167 mmol) was heated to 180 °C and stirred until the generation of ammonia gas ceased. After the suspension was cooled to room temperature, the residue was suspended in EtOH (150 mL), filtered, and washed with EtOH. The resulting colorless solid was recrystallized from EtOH to give **21 (**10.9 g, 109 mmol, 65%) as a white solid: Mp 260-263 °C; IR (KBr film) 3333, 3238, 3085, 2944, 2850, 1685, 1540, 1437, 1312, 1181, 1006, 968, 786 cm^{-1}; ^1H NMR (D_2O) δ 4.65 (s, 2 H), 3.07 (t, 4 H, *J* = 5.5 Hz), 1.66 (qn, 2 H, *J* = 5.5 Hz).

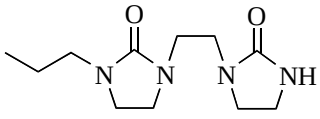


1-Ethyltetrahydropyrimidin-2-one (22).[14] A suspension of **21** (10.0 g, 999 mmol) and NaH (60% dispersion in mineral oil, 4.79 g, 120 mmol) in DMF (125 mL) was heated to 110~120 °C, stirred for 30 min, and treated slowly with a solution of iodoethane (6.40 mL, 800 mmol) in DMF (25 mL). The reaction mixture was stirred at 110 °C for 3 h, cooled to room temperature, and stirred overnight. DMF was distilled off under vacuum and quenched with ice water (50 mL). The aqueous layer was extracted with $CHCl_3$ (4×50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 ($CHCl_3$/MeOH, 25:1) to give **22** (4.20 g, 32.8 mmol, 41%) as a white solid: Mp 87-90 °C; IR (KBr film) 3290, 3210, 3059, 2966, 2864, 1653, 1525, 1380, 1347, 1306, 1236, 1196, 1112, 1079, 758 cm^{-1}; ^1H NMR δ 4.80 (br, 1 H), 3.38 (q, 2 H, *J* = 7.1 Hz), 3.31-3.23 (m, 4 H), 1.98-

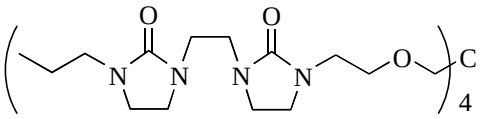
1.89 (m, 2 H), 1.12 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 156.6, 44.8, 42.1, 40.4, 22.3, 13.0; MS (EI) *m/z* (relative intensity) 128 (M^+, 100), 113 (90), 99 (31), 85 (49), 71 (22), 58 (42); HRMS (EI) *m/z* calculated for $C_6H_{12}N_2O$ 128.0950, found 128.0944.



1,3-Bis-(2-(1-ethyltetrahydropyrimidin-2-onyl)ethoxy)-2,2-bis-(2-(1-ethyltetrahydropyrimidin-2-onyl)ethoxymethyl)propane (23). To a suspension of NaH (60% dispersion in mineral oil, 920 mg, 23.0 mmol) in DMF (3 mL) was added a solution of **22** (1.48 g, 11.5 mmol) in DMF (7 mL) slowly at 0 °C. The mixture was stirred at 0 °C for 1 h and a solution of **20** (1.08 g, 1.92 mmol) in DMF (5 mL) was added. After stirring at 50 °C overnight, the reaction mixture was cooled to room temperature and quenched with ice. The aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on SiO_2 (CH_2Cl_2/MeOH, 10:1) to give **23** (650 mg, 0.864 mmol, 45%) as a white solid: Mp 85-90 °C; IR (neat) 3435, 3227, 3030, 2933, 2874, 1788, 1676, 1481, 1448, 1408, 1357, 1280, 1205, 1106, 991 cm^{-1}; ^{1}H NMR δ 3.54-3.46 (m, 16 H), 3.41-3.34 (m, 24 H), 3.24 (t, 8 H, *J* = 5.8 Hz), 1.93 (qn, 8 H, *J* = 5.9 Hz), 1.10 (t, 12 H, *J* = 7.1 Hz); ^{13}C NMR δ 155.8, 71.5, 70.4, 48.4, 47.8, 45.35, 45.3, 42.8, 22.8, 13.1; MS (EI) *m/z* (relative intensity) 753 (M^+, 13), 624 (1), 597 (8), 469 (1), 443 (5), 155 (100), 70 (10); HRMS (EI) *m/z* calculated for $C_{37}H_{68}N_8O_8$ 752.5160, found 752.5184.

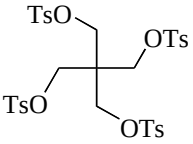


1-(1-(Propyl)-2-imidazolidonyl)-2-(1'-(2'-imidazolidonyl))ethane (24). A suspension of **14** (9.33 g, 471 mmol) and NaH (60% dispersion in mineral oil, 2.12 g, 529 mmol) in DMF (90 mL) was heated to 130 °C, stirred for 30 min, and treated slowly with a solution of propyl iodide (2.9 mL, 29 mmol) in DMF (5 mL). The reaction mixture was stirred at 130 °C for 1 h and at room temperature overnight. DMF was distilled off under vacuum and the mixture was quenched with ice. The aqueous layer was extracted with CH_2Cl_2 (5×50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 ($CHCl_3$/MeOH, 25:1) to give **24** (3.14 g, 13.1 mmol, 44%) as a white solid: Mp 225-229 °C; IR (KBr film) 3229, 3086, 2968, 2928, 2871, 1674, 1504, 1445, 1278, 1104, 763 cm^{-1}; ^1H NMR δ 3.57-3.53 (m, 2 H), 3.44-3.27 (m, 10 H), 3.14 (t, 2 H, *J* = 7.1 Hz), 1.56-1.48 (m, 2 H), 0.90 (t, 3 H, *J* = 7.3 Hz); ^{13}C NMR δ 163.1, 161.5, 45.9, 44.6, 42.7, 42.3, 41.4, 40.8, 38.4, 21.0, 11.3; MS (EI) *m/z* (relative intensity) 240 (M^+, 2), 211 (2), 182 (3), 154 (52), 141 (100), 125 (26), 112 (26), 99 (75); HRMS (EI) *m/z* calculated for $C_{11}H_{20}N_4O_2$ 240.1586, found 240.1583.

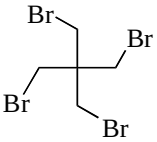


1,3-Bis-(2-(1-(1-(propyl)-2-imidazolidonyl)-2-(1'-(2'-imidazolidonyl))ethyl)ethoxy)-2,2-bis-(2-(1-(1-(propyl)-2-imidazolidonyl)-2-(1'-(2'-imidazolidonyl))ethyl)ethoxymethyl)propane (25). To a suspension of NaH (60% dispersion in mineral oil, 1.36 g, 340 mmol) in DMF (5 mL) was added a solution of **24 (**4.09 g, 170 mmol) in DMF (21 mL) slowly at 0 °C. The mixture was stirred at 0 °C for 1 h and a solution of **20** (1.92 g, 340 mmol) in DMF (4 mL) was added. After stirring at 50 °C overnight, the reaction mixture was cooled to room temperature and quenched with ice. The aqueous layer was extracted with CH_2Cl_2 (3×40 mL). The combined organic layers were washed with brine (40 mL), dried ($MgSO_4$), and concentrated. The residue was purified by

chromatography on SiO_2 (CH_2Cl_2/MeOH, 10:1) to give **25** (1.99 g, 1.65 mmol, 49%) as a colorless gel: IR (neat) 3365, 2956, 2934, 2873, 1682, 1495, 1445, 1359, 1260, 1111, 901, 758 cm^{-1}; ^1H NMR δ 3.55-3.20 (m, 72 H), 3.09 (t, 8 H, *J* = 7.1 Hz), 1.93 (sx, 8 H, *J* = 7.3 Hz), 0.85 (t, 12 H, *J* = 7.3 Hz); ^{13}C NMR δ 161.5, 161.3, 70.8, 70.2, 45.9, 44.3, 42.7, 42.5, 42.3, 41.5, 21.0, 11.4; MS (FAB+) *m/z* (relative intensity) 1201.5 (M^+, 100), 1059.9 (10), 979.8 (18), 792.4 (15), 643.4 (34), 523.2 (44).

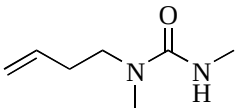


Tetrakis(toluenesulfonylacidmethylester)methane (26).[15] To a solution of pentaerythritol (5.00 g, 367 mmol) in pyridine (12 mL) was added a solution of TsCl (30.8 g, 161 mmol) in pyridine (40 mL) dropwise at 0 °C. After stirred at 0 °C overnight, the reaction mixture was added slowly to a vigorously stirred solution of HCl (50 mL), water (70 mL), and MeOH (100 mL). The resulting suspension was cooled and filtered. The filtrate was washed with water (50 mL) and MeOH (100 mL) and triturated in MeOH. The filtration gave **26** (24.2 g, 32.2 mmol, 88%) as a white solid: ^1H NMR δ 7.69 (d, 8 H, *J* = 8.3 Hz), 7.37 (d, 8 H, *J* = 8.1 Hz), 3.82 (s, 8 H), 2.48 (s, 12 H); MS (EI) *m/z* (relative intensity) 752 (M^+, 1), 580 (3), 427 (3), 225 (7), 155 (42) 107 (5), 91 (100), 65 (14); HRMS (EI) *m/z* calculated for $C_{33}H_{36}O_{12}S_4$ 752.1090, found 752.1086.

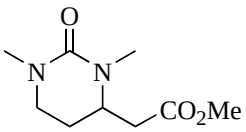


1,3-Dibromo-2,2-bisbromomethylpropane (27).[15] To a solution of **26** (24.2 g, 321 mmol) in diethylene glycol (110 mL) was added NaBr (26.5 g, 257 mmol) and the reaction mixture was heated to 140 °C with slow stirring overnight. The resulting orange mixture was allowed to cool

to 90 °C, diluted with ice water (170 mL), and cooled by the direct addition of ice. The precipitate was filtered and washed with water (250 mL) to give **27** (10.3 g, 26.4 mmol, 82%) as a white solid: ^{1}H NMR δ 3.60 (s, 8 H).

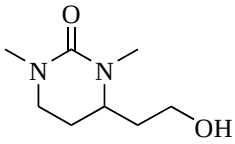


1-But-3-enyl-1,3-dimethylurea (29).[16] 3-butenylbromide (6.38 g, 47.3 mmol) was added to methylamine (20 mL, 0.44 mol) at 0 °C. After the addition was completed, the ice bath was removed and the mixture was stirred at room temperature for 1 d. The excess of methylamine was evaporated. To a solution of phosgene (5.85 g, 59.1 mmol) in CH_2Cl_2 (120 mL) was added a solution of crude but-3-enylmethylamine and DIPEA (20.6 mL, 118 mmol) in CH_2Cl_2 (120 mL) at 0 °C. After stirring at 0 °C for 30 min, a solution of methylamine (2 M in THF, 47.3 mL, 94.6 mmol)) and DIPEA (8.2 mL, 47 mmol) were added to this mixture. The reaction mixture was stirred at room temperature overnight and quenched with ice. All solvents and excess DIPEA were evaporated and the residue was purified by chromatography on SiO_2 ($CHCl_3$/EtOAc, 1:2) to give **29** (4.41 g, 32.0 mmol, 66%) as a yellow oil: IR (neat) 3348, 3077, 2974, 2934, 1633, 1538, 1412, 1378, 1289, 1224, 1159, 914, 770 cm^{-1}; ^{1}H NMR δ 5.84-5.70 (m, 1 H), 5.09-4.99 (m, 2 H), 4.45 (br, 1 H), 3.31 (t, 2 H, *J* = 7.1 Hz), 2.85 (s, 3 H), 2.78 (s, 3 H), 2.26 (q, 2 H, *J* = 7.1 Hz); ^{13}C NMR δ 158.8, 135.5, 116.7, 48.5, 34.4, 32.7, 27.7; MS (EI) *m/z* (relative intensity) 142 (M^+, 7), 101 (100) 58 (28); HRMS (EI) *m/z* calculated for $C_7H_{14}N_2O$ 142.1106, found 142.1102.



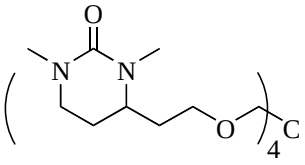
(1,3-Dimethyl-4-[(methoxycarbonyl)methyl]-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone (30).[16] A flask containing $CuCl_2$ (9.76 g, 72.6 mmol) and $PdCl_2$ (429 mg, 2.42 mmol) was filled with

carbon monoxide gas. At 0 °C, a solution of **29** (3.44 g, 24.2 mmol) in MeOH (80 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 18 h and at room temperature for 4 h. After the evaporation of MeOH, the mixture was diluted with EtOAc and filtered through a celite pad. The filter cake was washed several times with EtOAc and the filtrate was washed with saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on SiO_2 ($CHCl_3$/MeOH, 25:1) to give **30** (4.32 g, 21.6 mmol, 89%) as a yellow oil: IR (neat) 3453, 2949, 2865, 1736, 1631, 1514, 1440, 1413, 1316, 1235, 1166, 1055, 752 cm^{-1}; ^1H NMR δ 3.80-3.73 (m, 1 H), 3.70 (s, 3 H), 3.40 (dt, 1 H, *J* = 4.4, 12.2 Hz), 3.15 (ddd, 1 H, *J* = 2.5, 5.6, 11.9 Hz), 2.94 (s, 6 H), 2.72 (dd, 1 H, *J* = 4.7, 15.4 Hz), 2.44 (dd, 1 H, *J* = 9.4, 15.4 Hz), 2.15 (tt, 1 H, *J* = 5.4, 13.1 Hz), 1.87-1.79 (m, 1 H); ^{13}C NMR δ 171.7, 156.0, 54.0, 52.1, 44.2, 37.0, 35.8, 34.7, 25.6; MS (EI) *m/z* (relative intensity) 200 (M^+, 24), 127 (100), 84 (20), 70 (28), 58 (10); HRMS (EI) *m/z* calculated for $C_9H_{16}N_2O_3$ 200.1161, found 200.1163.



4-(2-Hydroxyethyl)-1,3-dimethyltetrahydropyrimidin-2-one (31). To a solution of **30** (4.32 g, 21.6 mmol) in EtOH (100 mL) was added 2 M aqueous $CuSO_4$ solution (1.08 mL, 2.16 mmol). After the mixture was cooled to 0 ºC, $NaBH_4$ (4.08 g, 108 mmol) was added portionwise. The reaction mixture was heated at reflux for 3 h and cooled to room temperature. The mixture was diluted with EtOAc (400 mL) and the organic layer was washed with water (100 mL). The aqueous layer was extracted with EtOAc (3×50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 ($CHCl_3$/MeOH, 20:1) to give **31** (2.72 g, 15.8 mmol, 71%) as a colorless oil: IR (neat) 3374, 2936, 2871, 1614, 1526, 1415, 1317, 1237, 1063, 1018, 925, 880, 754 cm^{-1}; ^1H NMR δ 3.73 (dt,

2 H, *J* = 1.2, 6.2 Hz), 3.54-3.48 (m, 1 H), 3.40 (dt, 1 H, *J* = 4.6, 12.0 Hz), 3.16 (ddd, 1 H, *J* = 2.0, 5.0, 12.1 Hz), 3.01 (s, 3 H), 2.98 (s, 3 H), 2.46 (br, 1 H), 2.10 (tt, 1 H, *J* = 5.5, 13.3 Hz), 2.01-1.90 (m, 1 H), 1.89-1.82 (m, 1 H), 1.73-1.65 (m, 1 H); ^{13}C NMR δ 156.5, 59.7, 54.2, 44.6, 35.8, 35.3, 29.9, 25.3; MS (EI) *m/z* (relative intensity) 172 (M^+, 13), 127 (100), 84 (20), 70 (25), 55 (5); HRMS (EI) *m/z* calculated for $C_8H_{16}N_2O_2$ 172.1212, found 172.1211.



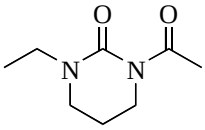
1,3-Bis-(4-(1,3-dimethyltetrahydropyrimidin-2-onyl)-2-ethoxy)-2,2-bis-(4-(1,3-dimethyltetrahydropyrimidin-2-onyl)-2-ethoxymethyl)propane (32). To a suspension of KH (362 mg, 9.02 mmol) in DMF (5 mL) was added a solution of **31** (400 mg, 2.26 mmol) in DMF (5 mL) dropwise at 0 °C. After stirring at 0 °C for 30 min, **27** (158 mg, 0.407 mmol) was added. The reaction mixture was stirred at 60 °C for 36 h and quenched with ice. All solvents were evaporated and the residue was extracted with $CHCl_3$ (3×30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 ($CHCl_3$/MeOH, 10:1) to give **32** (220 mg, 0.292 mmol, 72%) as a yellow oil: IR (neat) 3462, 1965, 2930, 2865, 1630, 1509, 1452, 1357, 1292, 1212, 1110, 1079, 1050, 753 cm^{-1}; ^{1}H NMR (CD_2Cl_2) δ 3.40-3.26 (m, 24 H), 3.05 (ddd, 4 H, *J* = 2.3, 5.2, 11.6 Hz), 2.83 (s, 12 H), 2.81 (s, 12 H), 2.03-1.91 (m, 4 H), 1.90-1.80 (m, 4 H), 1.80-1.72 (m, 4 H), 1.65-1.53 (m, 4 H); ^{13}C NMR (CD_2Cl_2) δ 156.0, 71.0, 70.0, 54.8, 45.4, 44.6, 35.5, 34.9, 32.6, 25.5; MS (EI) *m/z* (relative intensity) 752 (M^+, 4), 625 (25), 597 (19), 471 (8), 455 (15), 397 (10), 285 (6), 243 (5), 171 (13), 155 (45), 127 (100), 96 (15), 70 (30); HRMS (EI) *m/z* calculated for $C_{37}H_{68}N_8O_8$ 752.5160, found 752.5160.

General procedure for aldol reaction of 1-naphthylacetonitrile with 1-naphthaldehyde in the presence of additives (Table 1).[18] To a solution of LDA (2.0 M in THF/*n*-heptanes, 0.12 mL, 0.24 mmol)) in THF (2 mL) was added a solution of 1-naphthylacetonitrile (40 mg, 0.24 mmol) in THF (1.5 mL) at –78 °C. After 30 min, a solution of **24** (288 mg, 0.240 mmol) in THF (6 mL) was added and after an additional 30 min, a solution of 1-naphthaldehyde (38 mg, 0.24 mmol) in THF (1.5 mL) was added. The reaction mixture was stirred for 30 min at –78 °C and quenched with saturated aqueous NH_4Cl solution. 1 M HCl solution was added and the aqueous layer was extracted with ethyl ether (2x20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on SiO_2 (hexane/EtOAc/CH_2Cl_2, 10:2:1) to give a mixture of *syn*-**34** and *anti*-**34** (63 mg, 0.19 mmol, 80%, 52:48) as a white solid. *syn*-**34**[10]: ^{1}H NMR δ 7.95-7.60 (m, 6 H), 7.55-7.10 (m, 8 H), 6.07 (d, 1 H, J = 3.4 Hz), 5.29 (d, 1 H, J = 5.4 Hz), 2.92 (d, 1 H, J = 2.0 Hz).

General procedure for the reaction between 1,3-lithiodithiane and 2-cyclohexen-1-one in the presence of additives (Table 2).[6a,19] To a solution of 1,3-dithiane (48 mg, 0.40 mmol) in THF (2 mL) was added LDA (2 M in THF/*n*-heptane, 0.21 mL, 0.42 mmol) at –78 °C. The reaction mixture was warmed to –22 °C over 1 h, and treated with a solution of **32** (150 mg, 0.199 mmol) in THF (6 mL) and a solution of 2-cyclohexen-1-one (20 mg, 0.20 mmol) in THF (2 mL). The reaction mixture was stirred for 25 min at –78 °C and quenched with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with ethyl ether (2x20 mL). The combined organic layers were washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on SiO_2 (hexane/EtOAc, 10:1) to give of a mixture of **2**[3a, 11] and **3**[3a,11] (40.3 mg, 0.186 mmol, 90%, 9:1) as a colorless oil. **2**: ^{1}H NMR δ 4.10 (d, 1 H, J = 4.9 Hz), 2.95-2.85 (m, 4 H), 2.61-2.32 (m, 4 H), 2.30-2.05 (m, 4 H), 1.95-1.80 (m, 1 H),

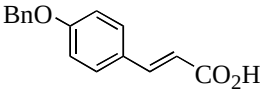
1.75-1.60 (m, 2 H); **3**: ^{1}H NMR δ 6.00-5.92 (m, 1 H), 5.80-5.70 (m, 1 H), 4.24 (s, 1 H), 3.00-2.80 (m, 4 H), 2.33 (s, 1 H), 2.15-1.90 (m, 4 H), 1.90-1.70 (m, 4 H).

General procedure for the reaction between allyltributyltin and α,β-epoxy ketone in the presence of PbI_2-additive (Table 3).[2b] A solution of PbI_2 (23 mg, 0.050 mmol) in THF (2 mL) was treated with DMPU (64 mg, 0.50 mmol). After 30 min, a solution of chalcone oxide (112 mg, 0.500 mmol) and allyltri-*n*-butyltin (166 mg, 0.500 mmol) in THF (1.5 mL) was added. The reaction mixture was heated at reflux for 24 h. After quenching with MeOH, volatiles were removed under reduced pressure. The residue was purified by chromatography on SiO_2 (hexane/EtOAc, 10:1) to give **36**[2b] (54 mg, 0.20 mmol, 41%) and chalcone oxide (64 mg, 0.29 mmol, 57%); ^{1}H NMR δ 7.55-7.20 (m, 10 H), 5.95-5.75 (m, 1 H), 5.30-5.15 (m, 2 H), 3.99 (d, 1 H, *J* = 1.8 Hz), 3.44 (d, 1 H, *J* = 2.0 Hz), 2.86 (d, 2 H, *J* = 7.2 Hz), 2.53 (s, 1 H).

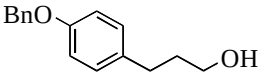


1-Acetyl-3-ethyltetrahydropyrimidin-2-one (37). To a suspension of KH (156 mg, 1.56 mmol) in THF (5 mL) was added a solution of **22** (200 mg, 1.56 mmol) in THF (5 mL) at 0 °C. After stirring at 0 °C for 30 min, acetyl chloride (0.55 mL, 7.8 mmol) was added. The reaction mixture was stirred at 55 °C overnight, cooled, and quenched with ice. The aqueous layer was extracted with $CHCl_3$ (3×30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 ($CHCl_3$/EtOAc, 20:1) to give **37** (210 mg, 1.23 mmol, 79%) as a colorless oil: IR (neat) 2971, 2938, 2875, 1734, 1683, 1490, 1451, 1431, 1369, 1317, 1292, 1241, 1200, 1114, 1027, 932 cm^{-1}; ^{1}H NMR δ 3.78 (t, 2 H, *J* = 6.0 Hz), 3.44 (q, 2 H, *J* = 7.1 Hz), 3.33 (t, 2 H, *J* = 6.1 Hz), 2.55 (s, 3 H), 2.00-1.92 (m, 2 H), 1.19 (t, 3 H, *J* = 7.1 Hz); ^{13}C NMR δ 173.4, 153.5, 45.9, 43.6, 41.8, 27.1, 26.7, 22.5, 12.6; MS (EI) *m/z* (relative intensity)

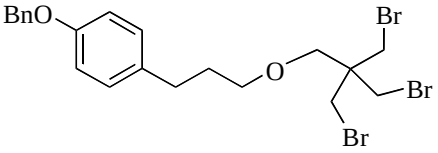
170 (M^+, 48), 127 (44), 113 (100), 100 (77), 70 (7), 59 (13); HRMS (EI) *m/z* calculated for $C_8H_{14}N_2O_2$ 170.1055, found 170.1053.



3-(4-Benzyloxyphenyl)acrylic acid (39). Prepared according to literature procedures:[11] ^{1}H NMR (acetone-d_6) δ 7.66-7.33 (m, 7 H), 7.09 (d, 2 H, *J* = 8.7 Hz), 6.41 (d, 2 H, *J* = 8.8 Hz), 5.20 (s, 2 H).

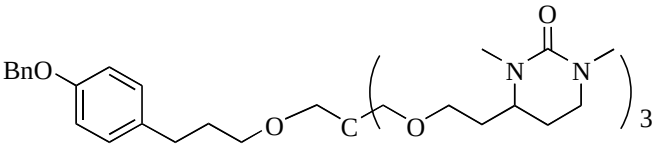


3-(4-Benzyloxyphenyl)propan-1-ol (40). Prepared according to literature procedures:[11] ^{1}H NMR δ 7.45-7.26 (m, 5 H), 7.13 (d, 2 H, *J* = 8.5 Hz), 6.92 (d, 2 H, *J* = 8.5 Hz), 5.06 (s, 2 H), 3.68 (t, 2 H, *J* = 6.4 Hz), 2.67 (t, 2 H, *J* = 7.6 Hz), 1.88 (qn, 2 H, *J* = 7.0 Hz).

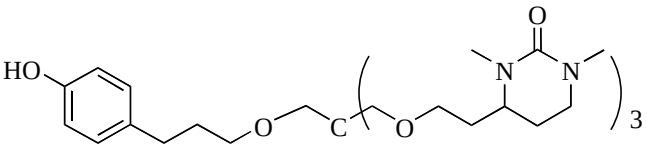


1-{3-[2-(3-Bromo-2,2-bisbromomethylpropoxy)propyl}-4-benzyloxy benzene (41). To a suspension of NaH (60% dispersion in mineral oil, 1.17 g, 29.2 mmol) in DMF (30 mL) was added a solution of **40** (3.54 g, 14.6 mmol) in DMF (20 mL) dropwise at 0 °C. After stirring at 0 °C for 1 h, **27** (6.80 g, 17.5 mmol) was added. The reaction mixture was stirred at 65 ºC for 20 h, cooled to room temperature, and quenched with ice. The aqueous layer was extracted with EtOAc (3x30 ml). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on SiO_2 (hexane/EtOAc, 25:1) to give **41** (4.07 g, 7.46 mmol, 51%) as a white solid: Mp 93°C; IR (KBr film) 3028, 2953, 2931, 2861, 2793, 1610, 1581, 1513, 1453, 1429, 1382, 1297, 1275, 1239, 1173, 1121, 1012, 910, 832 cm $^{-1}$; ^{1}H NMR δ 7.48-7.33 (m, 5 H), 7.15 (d, 2 H, *J* = 8.6 Hz), 6.95 (d, 2 H, *J* = 8.7 Hz), 5.08 (s,

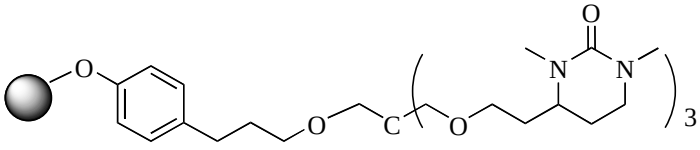
2 H), 3.57 (s, 6 H), 3.50 (t, 2 H, *J* = 6.2 Hz), 3.49 (s, 2 H), 2.68 (t, 2 H, *J* = 7.3 Hz), 1.94-1.85 (m, 2 H); ^{13}C NMR δ 157.2, 137.3, 134.2, 129.6, 128.7, 128.1, 127.6, 114.9, 70.7, 70.2, 69.4, 43.9, 35.1, 31.6, 31.4; MS (EI) *m/z* (relative intensity) 548 (M^+, 1), 224 (6), 134 (8), 91 (100); HRMS (EI) *m/z* calculated for $C_{21}H_{25}Br_3O_2$ 545.9405, found 545.9419.



1-{3-[2-(3-(4-(1,3-Dimethyltetrahydropyrimidin-2-onyl)-2-ethoxy)-2,2-bis-(4-(1,3-dimethyltetrahydropyrimidin-2-onyl)-2-ethoxy)methylpropoxy)propyl}-4-benzyloxybenzene (42). To a suspension of KH (1.02 g, 25.5 mmol) in DMF (15 mL) was added a solution of **31** (1.63 g, 9.18 mmol) in DMF (20 mL) dropwise at 0 °C. The mixture was stirred at 0 °C for 1 h and treated with a solution of **41 (**1.40 g, 2.55 mmol) in DMF (35 mL). The reaction mixture was stirred at 70 °C for 36 h, cooled to room temperature, and quenched with ice. The solvents were distilled off and the residue was purified by chromatography on SiO_2 ($CHCl_3$/MeOH, 20:1) to give **42** (1.20 g, 1.46 mmol, 57%) as a colorless oil: IR (neat) 3445, 3027, 2932, 2865, 2225, 1633, 1513, 1469, 1403, 1368, 1315, 1235, 1175, 1103, 1035, 925, 834 cm^{-1}; ^{1}H NMR δ 7.43-7.30 (m, 5 H), 7.07 (d, 2 H, *J* = 8.6 Hz), 6.88 (d, 2 H, *J* = 8.7 Hz), 5.03 (s, 2 H), 3.42-3.30 (m, 22 H), 3.09 (ddd, 3 H, *J* = 2.2, 5.3, 11.3 Hz), 2.93 (s, 9 H), 2.91 (s, 9 H), 2.59 (dd, 2 H, *J* = 7.2, 8.0 Hz), 2.04 (tt, 3 H, *J* = 5.4, 12.9 Hz), 1.92-1.74 (m, 8 H), 1.68-1.58 (m, 3 H); ^{13}C NMR δ 157.2, 156.2, 137.3, 134.4, 129.4, 128.7, 128.1, 127.6, 114.9, 70.7, 70.2, 70.1, 69.6, 68.3, 54.6, 45.4, 44.5, 35.7, 35.2, 32.6, 31.6, 25.4; MS (ESI) *m/z* (relative intensity) 846 ([M-H+Na]$^+$, 100), 824 (25); HRMS (ESI) *m/z* calculated for $C_{45}H_{69}N_6O_8Na$ (M-H+Na) 845.5092, found 845.5081.



1-{3-[2-(3-(4-(1,3-Dimethyltetrahydropyrimidin-2-onyl)-2-ethoxy)-2,2-bis-(4-(1,3-dimethyltetrahydropyrimidin-2-onyl)-2-ethoxy)methylpropoxy)propyl}-4-hydroxybenzene (43). A suspension of **42** (1.20 g, 1.46 mmol) and Pd/C (10 wt%, 120 mg) in MeOH (10 mL) was stirred at room temperature overnight under H_2 gas. The reaction mixture was filtered through celite pad and washed with MeOH. The filtrate was concentrated and the residue was purified by chromatography on SiO_2 (CH_2Cl_2/MeOH, 10:1) to give **43** (1.00 g, 1.37 mmol, 93%) as a brown oil: IR (neat) 3411, 3195, 2933, 2866, 1615, 1516, 1470, 1414, 1368, 1316, 1236, 1170, 1103, 925, 834, 753, 729 cm^{-1}; ^1H NMR δ 8.78 (s, 1 H), 6.96 (d, 2 H, *J* = 8.4 Hz), 6.79 (d, 2 H, *J* = 8.4 Hz), 3.41-3.29 (m, 22 H), 3.09 (ddd, 3 H, *J* = 2.3, 3.2, 11.8 Hz), 2.92 (s, 9 H), 2.91 (s, 9 H), 2.54 (t, 2 H, *J* = 7.1 Hz), 2.05-1.93 (m, 3 H), 1.91-1.73 (m, 8 H), 1.67-1.58 (m, 3 H); ^{13}C NMR δ 156.3, 155.6, 132.4, 129.3, 115.5, 70.5, 70.0, 69.5, 68.2, 54.6, 45.3, 44.5, 35.8, 35.3, 32.6, 31.4, 25.3; MS (ESI) *m/z* (relative intensity) 755 ($[M-H+Na]^+$, 100), 733 (40); HRMS (ESI) *m/z* calculated for $C_{38}H_{63}N_6O_8Na$ (M-H+Na) 755.4608, found 755.4612.



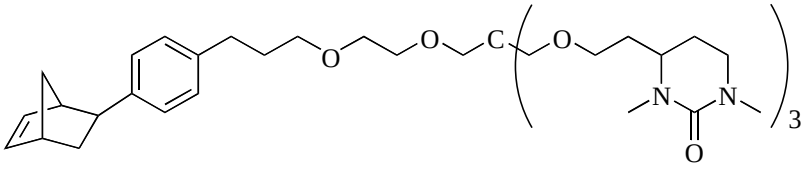
Polymer-supported DMPU (44). The mixture of **43** (1.53 g, 2.07 mmol) and Cs_2CO_3 (0.884 g, 2.71 mmol) in THF (8 mL), which was placed in a flask equipped with a mechanical stirrer, was stirred at room temperature for 1 h and THF was evaporated. The residue was dissolved in DMF (7 mL) and ArgoPoreCl (0.494 g, 0.593 mmol, 1.20 mmol/g loading) was added. The resulting mixture was stirred at 70°C for 3 d and quenched with ice. The resin was filtered and washed

with 20 mL portions of water, DMF, MeOH, toluene, CH_2Cl_2, and ethyl ether. The resin was dried *in vacuo* to give **44** (0.75 g, 59%, 0.46 mmol/g loading) as a yellow bead: IR (KBr film) 3427, 3027, 2925, 2863, 1638, 1511, 1452, 1413, 1368, 1315, 1235, 1173, 1105, 1035, 892, 828 cm^{-1}.

General procedure for the reaction between 1,3-lithiodithiane and 2-cyclohexen-1-one in the presence of polymer-supported additive 44 (Table 4). Using LDA as base: To a solution of 1,3-dithiane (60 mg, 0.50 mmol) in THF (1.5 mL) at –78 °C was added LDA (0.93 M in THF, 0.60 mL, 0.55 mmol). After warming to –20 °C for 1 h, this solution was added via cannula to a suspension of polymer-supported additive **44** (685 mg, 0.32 mmol, 0.46 mmol/g loading) in THF (3.5 mL), which was placed in a flask equipped with a mechanical stirrer, and cooled to –78 °C. After an additional 30 min at –78 °C, a solution of 2-cyclohexen-1-one (24 mg, 0.25 mmol) in THF (0.2 mL) was added. The reaction mixture was stirred for 2 h at –78 °C and quenched with saturated aqueous NH_4Cl solution. The polymer was filtered and washed with water and ethyl ether (3x20 mL). The aqueous layer was extracted with ethyl ether (3x20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexane/EtOAc, 4:1) to give a mixture of **2** and **3** (28 mg, 0.13 mmol, 52%, 54:46) as a colorless oil, which was analyzed by ^1H NMR.

with *t*-BuLi as base: To a solution of 1,3-dithiane (6o mg, 0.50 mmol) in THF (1.5 mL) at –78 °C was added *t*-BuLi (1.7 M in pentane, 0.32 mL, 0.55 mmol). After 15 min at –78 °C, this solution was added via cannula to a suspension of polymer-supported additive **44** (650 mg, 0.30 mmol, 0.46 mmol/g loading) in THF (3.5 mL), which was placed in a flask equipped with a mechanical stirrer, and cooled to –78 °C. After an additional 10 min at –78 °C, the solution of 2-cyclohexen-1-one (24 mg, 0.25 mmol) in THF (0.2 mL) was added. The reaction mixture was

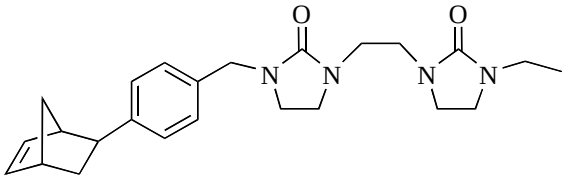
stirred for 2 h at –78 °C and quenched with saturated aqueous NH_4Cl solution. The polymer was filtered and washed with water and ethyl ether (3x20 mL). The aqueous layer was extracted with ethyl ether. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexane/ EtOAc, 4:1) to give a mixture of **2** and **3** (51 mg, 0.24 mmol, 96%, 53:47) as a colorless oil, which was analyzed by ^1H NMR.



1-{3-[2-(3-(4-(1,3-Dimethyltetrahydropyrimidin-2-onyl)-2-ethoxy)-2,2-bis-(4-(1,3-dimethyltetrahydropyrimidin-2-onyl)-2-ethoxy)methylpropoxy)ehoxypropyl}-4-bicyclo[2.2.1]hept-5-en-2-ylbenzene (50): IR (neat) 3441, 2935, 2866, 1621, 1516, 1471, 1366, 1316, 1235, 1104, 1059 cm^{-1}; ^1H NMR δ 7.20 (d, 2 H, *J* = 8.1 Hz), 7.11 (d, 2 H, *J* = 8.0 Hz), 6.25 (dd, 1 H, *J* = 3.2, 5.7 Hz), 6.16 (dd, 1 H, *J* = 2.8, 5.8 Hz), 3.55 (s, 4 H), 3.49-3.31 (m, 22 H), 3.10 (ddd, 3 H, *J* = 2.3, 5.4, 11.6 Hz), 2.98-2.95 (m, 1 H), 2.94 (s, 9 H), 2.93 (s, 9 H), 2.88 (br, 1 H), 2.72-2.58 (m, 1 H), 2.66 (t, 2 H, *J* = 7.4 Hz), 2.04 (tt, 3 H, *J* = 5.2, 12.8 Hz), 1.93-1.85 (m, 5 H), 1.83-1.75 (m, 3 H), 1.72-1.56 (m, 6 H), 1.44-1.40 (m, 1 H); MS (EI) *m/z* (relative intensity) 852 (M^+, 1), 787 (1), 725 (1), 699 (1.2), 155 (63), 127 (100); HRMS (EI) *m/z* calculated for $C_{47}H_{76}N_6O_8$ 852.5725, found 852.5718.

General procedure for ROMP of 50. To a solution of **50** (215 mg, 0.252 mmol) in CH_2Cl_2 (0.5 ml) was added a solution of Grubbs' catalyst (3.1 mg, 1.5 mol%) in CH_2Cl_2 (0.5 mL) dropwise. After stirring for 2 d at room temperature, additional CH_2Cl_2 (1 mL) was added and the reaction mixture was stirred for additional 1 d at room temperature. After the addition of ethyl vinyl ether (1 mL) and CH_2Cl_2 (1.5 mL), the reaction mixture was diluted with EtOAc and decanted repeatedly to obtain the polymer **51** (113 mg, 53%) as a brown gel: IR (neat) 3412, 2935, 2867,

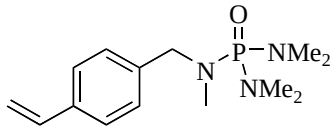
1618, 1522, 1469, 1414, 1366, 1316, 1237, 1104, 1058 cm^{-1}; ^1H NMR δ 7.20-7.05 (m, 2 H), 5.62 (br, 1 H), 5.35 (br, 1 H), 3.55 (s, 4 H), 3.49-3.31 (m, 22 H), 3.16-3.00 (m, 4 H), 2.94 (s, 9 H), 2.93 (s, 9 H), 2.72-2.63 (m, 2 H), 2.10-1.96 (m, 3 H), 1.93-1.84 (m, 7 H), 1.83-1.74 (m, 4 H), 1.70-1.59 (m, 6 H).



1-(1-(Benzyl)-2-imidazolidonyl)-2-(1'(4-bicyclo[2.2.1]hept-5-en-2-ylbenzyl)-(2'-imidazolidonyl))ethane (53): IR (neat) 3474, 3054, 2967, 2935, 1686, 1492, 1448, 1357, 1260, 1110 cm^{-1}; ^1H NMR δ 7.22 (d, 2 H, *J* = 8.2 Hz), 7.16 (d, 2 H, *J* = 8.1 Hz), 6.25 (dd, 1 H, *J* = 3.1, 5.6 Hz), 6.16 (dd, 1 H, *J* = 2.8, 5.6 Hz), 4.31 (s, 2 H), 3.46-3.33 (m, 8 H), 3.32-3.14 (m, 6 H), 2.96 (br. s, 1 H), 2.88 (br. s, 1 H), 2.69 (dd, 1 H, *J* = 4.8, 8.5 Hz), 1.72 (ddd, 1 H, *J* = 3.6, 4.6, 11.9 Hz), 1.64 (dd, 1 H, *J* = 2.2, 8.7 Hz), 1.59-1.53 (m, 1 H), 1.44-1.40 (m, 1 H), 1.09 (t, 3 H, *J* = 7.2 Hz); ^{13}C NMR (acetone-d_6) δ 162.0 (2C), 146.2, 138.6, 138.5, 136.6, 129.3, 129.0, 49.7, 48.8, 46.8, 44.7, 43.5, 43.4, 43.3, 43.2, 43.0, 42.5, 42.4, 39.9, 34.6, 13.6; MS (ESI) *m/z* (relative intensity) 840 ($[2M+Na]^+$, 100), 431(94), 409 (100); HRMS (ESI) *m/z* calculated for $C_{24}H_{33}N_4O_2$ (M+H) 409.2604, found 409.2618.

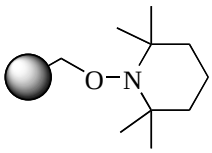
General procedure for ROMP of 53. To a solution of **53** (190 mg, 0.465 mmol) in CH_2Cl_2 (1 mL) was added a solution of Grubbs' catalyst (5.9 mg, 1.5 mol%) in CH_2Cl_2 (1 mL) dropwise. After stirring for 1 d at room temperature, the reaction mixture was quenched by the addition of ethyl vinyl ether (1 mL) and CH_2Cl_2 (3 mL). After an additional 2 h, all volatiles were removed. The residue was washed with EtOAc and diluted with CH_2Cl_2. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated to give the polymer

54 (70 mg, 37%) as a brown gel: IR (neat) 2931, 2861, 1694, 1493, 1448, 1358, 1261, 1108, 968 cm^{-1}; ^1H NMR δ 7.12 (br, 4 H), 5.31 (br, 2 H), 4.30 (s, 2 H), 3.45-3.10 (m, 14 H), 2.70 (br, 2 H), 2.43 (br, 1 H), 1.90 (br, 4 H), 1.09 (t, 3 H, *J* = 6.9 Hz).

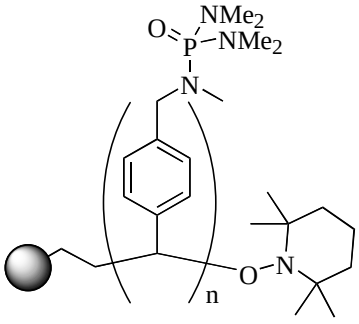


Bis(dimethylamino)-(methyl-4-vinylbenzylamino)phosphoroamide (82). 4-Vinylbenzyl chloride (4.62 g, 30.3 mmol) was added to condensed methylamine (10 mL) at –78 °C. After the addition, a cooling bath was removed and the mixture was stirred at room temperature for 6 h. An excess of methylamine was evaporated and the reaction was quenched with 50% aqueous NaOH (4 mL). The aqueous layer was extracted with ethyl ether (3x20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was diluted in ethyl ether (20 mL) and the activated 4 Å MS (2 g), triethylamine (6.27 mL, 45.0 mmol), and bis(dimethylamino)phosphorochloride (4.34 mL, 30.0 mmol) were added. The reaction mixture was refluxed for 12 h and a white precipitate was removed by filtration. The filtrate was diluted in ethyl ether (100 mL), washed with brine (3x30 mL), dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on SiO_2 ($CHCl_3$/acetone, 4:1) to give the desired monomer **82** (6.12 g, 21.8 mmol, 73%) as a colorless oil: IR (neat) 3438, 2999, 2885, 2845, 2804, 1629, 1511, 1460, 1296, 1205, 989, 936, 855, 827 cm^{-1}; ^1H NMR δ 7.39 (d, 2 H, *J* = 8.2 Hz), 7.32 (d, 2 H, *J* = 8.2 Hz), 6.72 (dd, 1 H, *J* = 10.9, 17.6 Hz), 5.75 (dd, 1 H, *J* = 0.9, 17.6 Hz), 5.24 (dd, 1 H, *J* = 0.9, 10.9 Hz), 4.14 (d, 2 H, *J* = 8.3 Hz), 2.68 (d, 12 H, *J* = 9.4 Hz), 2.54 (d, 3 H, *J* = 9.1 Hz); ^{13}C NMR δ 138.5, 138.4, 136.7, 136.6, 128.4, 126.3 113.6, 53.03, 52.97, 37.04, 36.99, 34.04, 33.99; MS (EI) *m/z* (relative intensity) 281 (M^+, 33), 236 (9), 221 (8), 192

(10), 146 (100), 135 (30), 117 (50), 91 (13); HRMS (EI) *m/z* calculated for $C_{14}H_{24}N_3OP$ 281.1657, found 281.1662.



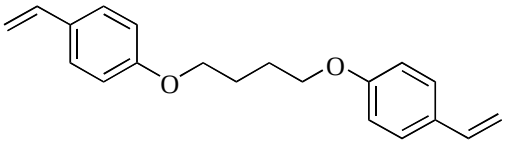
TEMPO-methyl resin 85.[32a] A solution of Na ascorbate (4.8 g, 24.2 mmol) in water (60 mL) was stirred vigorously with a solution of TEMPO (3.12 g, 20 mmol) in ethyl ether (50 mL) until the deep burgundy color faded to pure orange. The organic layer was dried ($MgSO_4$) and concentrated under 20 ºC to give an orange oil. After drying under vacuum, this oil was dissolved in DMF (10 mL) and added to a suspension of NaH (60% dispersion in mineral oil, 1.2 g, 30 mmol) in DMF (10 mL) at 0 ºC dropwise. After the mixture was stirred for an additional 30 min at room temperature, ArgoPoreCl resin (1.29 g, 1.53 mmol, 1.18 mmol/g loading) was quickly added. Stirring was continued for 20 h at room temperature with mechanical stirrer and the reaction mixture was quenched with ice at 0 ºC. The resin was filtered and washed successively with 20 mL portions of H_2O, DMF (x3), MeOH (x3), toluene, CH_2Cl_2, and ethyl ether (x3). The resulting resin was dried under vacuum to give TEMPO-methyl resin **85** (1.08 g).



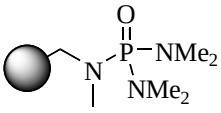
General procedure for the synthesis of Rasta resin 86. Using oil bath; A suspension of TEMPO-methyl resin **85** (310 mg) and the monomer **82** (1.6 g, 5.69 mmol) was stirred at 125 ºC for 16 h and cooled to room temperature. The reaction mixture was diluted with CH_2Cl_2. The

solid was filtered and washed with 10 mL portions of CH_2Cl_2, ethyl ether, and THF repeatedly to give HMPA rasta resin **86** (1.3 g, 2.71 mmol/g loading) as a dark brown bead: IR (neat) 3422, 2996, 2921, 2803, 1655, 1605, 1510, 1453, 1297, 1202, 1067, 989, 933, 813 cm^{-1}.

Using microwave reactor; the suspension of TEMPO-Methyl resin **85** (134 mg) and the monomer **82** (600 mg, 2.13 mmol) was treated on microwave at 135 ºC for 30 min (x2) and cooled to room temperature. The reaction mixture was diluted with CH_2Cl_2. The solid was filtered and washed with 10 mL portions of MeOH, CH_2Cl_2, and acetone repeatedly to give HMPA rasta resin **86** (376 mg, 2.29 mmol/g loading) as a dark brown bead: IR (neat) 3424, 2923, 2842, 2807, 1604, 1510, 1454, 1297, 1202, 1067, 990, 933, 823 cm^{-1}.



Cross-Linker (90). Prepared according to literature procedures:[34a] ^{1}H NMR δ 7.35 (d, 4 H, *J* = 8.7 Hz), 6.86 (d, 4 H, *J* = 8.7 Hz), 6.67 (dd, 2 H, *J* = 10.9, 17.6 Hz), 5.62 (dd, 2 H, *J* = 0.7, 17.6 Hz), 5.13 (dd, 2 H, *J* = 0.6, 10.9 Hz), 4.05 (t, 4 H, *J* = 5.7 Hz), 1.99 (qn, 4 H, *J* = 3.0 Hz).



General procedure for the preparation of polymer (87a and 87b). A solution of acacia gum (1.80 g) and NaCl (1.13 g) in water (45 mL) was placed in a Morton flask equipped with a mechanical stirrer and deoxygenated by purging with N_2. A solution of **82** (0.96 g, 3.4 mmol), styrene (0.71 g, 6.8 mmol), **90** (0.12 g, 0.41 mmol), and benzoyl peroxide (0.09 g) in chlorobenzene (5 mL) was added into the vigorously stirred aqueous solution. The mixture was heated at 85°C for 20 h. The polymer was filtered and washed with 20 mL portions of water, THF, and hexanes. The polymer was dried *in vacuo* to give **87a** (1.31 g, 73%, loading of 1.7

mmol/g) as a white solid: IR (KBr film) 3431, 3024, 2921, 2801, 1719, 1602, 1509, 1493, 1452, 1334, 1297, 1210, 1067, 988, 932, 826 cm^{-1}; Anal. Calcd for 1.7 mmol/g loading and a 17:7:1 ratio of styrene:**82**:**90**: C, 75.32; H, 8.38; N, 7.32. Found: C, 72.55; H, 8.01; N, 7.22.

10 mmol% of **90** was used to prepare **87b** (loading of 1.5 mmol/g): IR (KBr film) 3422, 3025, 2920, 2802, 1719, 1606, 1510, 1493, 1452, 1297, 1210, 1067, 988, 932, 827 cm^{-1}; Anal. Calcd for 1.5 mmol/g loading and a 12:5:2 ratio of styrene:**82**:**90**: C, 76.24; H, 8.08; N, 6.47. Found: C, 70.78; H, 7.90; N, 6.40.

General procedure for the reaction between 1,3-lithiodithiane and 2-cyclohexen-1-one in the presence of additives (Table 5). Using LDA as base: To a solution of 1,3-dithiane (60 mg, 0.50 mmol) in THF (1.5 mL) at –78 °C was added LDA (0.94 M in THF, 0.60 mL, 0.55mmol), which was freshly prepared. After warming to –20 °C for 1 h, this solution was added via cannula to a suspension of polymer-supported HMPA **87a** (200 mg, 0.34 mmol) in THF (10 mL), which was placed in a flask equipped with a mechanical stirrer and cooled to –78 °C. After an additional 30 min at –78 °C, a solution of 2-cyclohexen-1-one (25 mg, 0.25 mmol) in THF (0.2 mL) was added. The reaction mixture was stirred for 2 h at –78 °C and quenched with saturated aqueous NH_4Cl solution. The polymer was filtered and washed with water and ethyl ether. The aqueous layer was extracted with ethyl ether (3x20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexane/EtOAc, 4:1) to give a mixture of **2** and **3** (49 mg, 0.23 mmol, 92%, 64:36) as a colorless oil, which was analyzed by ^1H NMR.

With *t*-BuLi as base: To a cold solution of 1,3-dithiane (60 mg, 0.50 mmol) in THF (2 mL) at –78 °C was added *t*-BuLi (1.7 M in pentane, 0.32 mL, 0.55 mmol). After 15 min at –78 °C, this solution was added via cannula to a suspension of polymer-supported HMPA **87b** (300 mg, 0.46

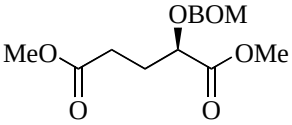
mmol) in THF (10 mL), which was placed in a flask equipped with a mechanical stirrer and cooled to –78° C. After an additional 10 min at –78 °C, the solution of 2-cyclohexen-1-one (24 mg, 0.25 mmol) in THF (0.2 mL) was added. The reaction mixture was stirred for 2 h at –78 °C and quenched with saturated aqueous NH_4Cl solution. The polymer was filtered and washed with water and ethyl ether. The aqueous layer was extracted with ethyl ether (3x20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexane/EtOAc, 4:1) to give a mixture of **2** and **3** (50 mg, 0.23 mmol, 92%, 73:27) as a colorless oil, which was analyzed by ^{1}H NMR.

General procedure for aldol reaction of 1-naphthylacetonitrile and 1-naphthaldehyde in the presence of additives (Table 6). To a solution of LDA (2 M in THF/*n*-heptane, 0.12 mL, 0.24 mmol) was added a solution of naphthylacetonitrile (36 mg, 0.22 mmol) in THF (2 mL) at –78 °C. After 30 min at –78 °C, this solution was added via cannula to a suspension of polymer-supported HMPA **87b** (700 mg, 1.06 mmol) in THF (11 mL), which was placed in a flask equipped with a mechanical stirrer and cooled to –78 °C. After an additional 10 min, a solution of naphthaldehyde (28 mg, 0.18 mmol) in THF (1 mL) was added. The reaction mixture was stirred for 30 min at –78 °C and quenched with saturated aqueous NH_4Cl. The polymer was filtered and washed with water and ethyl ether. The aqueous layer was extracted with ethyl ether (3x20 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on SiO_2 (hexane/EtOAc, 10:1-4:1) to give a mixture of *syn*-**34** and *anti*-**34** (35 mg, 0.11 mmol, 61%, 82:18) as a white solid, which was analyzed by ^{1}H NMR.

General procedure for the reaction between allyltributyltin and α,β-epoxy ketonein the presence of PbI_2-additive (Table 7). A suspension of PbI_2 (30 mg, 0.065 mmol) and polymer-

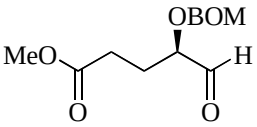
supported HMPA **87a** (60 mg, 0.10 mmol) in THF (4 mL) was stirred at 70 °C for 30 min. a solution of α,β-epoxy ketone (146 mg, 0.65 mmol) in THF (2 mL) and allyltri-*n*-butyltin (0.20 mL, 0.65 mmol) were added to this suspension. The mixture was stirred under reflux condition for 3 d. The polymer was filtered and washed with THF. All volatiles were removed under reduced pressure. The residue gave a mixture of the starting epoxy ketone and the desired product **36** (78% conversion after 1 d, 81% conversion after 2 d, and 86% conversion after 3 d), which was analyzed by ^{1}H NMR.

General procedure for allylation of benzaldehyde with allytrichlorosilane in the presence of additives (Table 8). To a suspension of polymer-supported HMPA **87a** (78 mg, 0.13 mmol) in CH_2Cl_2 (2 mL) and *N*,*N*-diisopropylethylamine (0.5 mL) at –78 °C was added allyltrichlorosilane (0.26 g, 1.5 mmol). The reaction mixture was shaken at –78 °C for 5 min before benzaldehyde (53 mg, 0.50 mmol) was added. The resulting suspension was shaken at room temperature for 1 d and poured into an ice water. The polymer was filtered and washed with water and ethyl ether. The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexane/ethyl ether, 4:1) to give the desired product **93** (55 mg, 0.37 mmol, 74%) as a colorless oil: ^{1}H NMR δ 7.38-7.26 (m, 5 H), 5.90-5.76 (m, 1 H), 5.33-5.14 (m, 2 H), 4.76 (dd, 1 H, *J* = 5.4, 7.4 Hz), 2.60-2.45 (m, 2 H), 2.00 (br, 1 H).



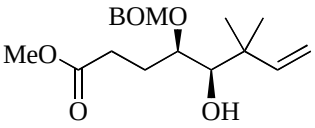
(*R*)-Dimethyl-2-((benzyloxy)methoxy)pentanedioate (114). A solution of (*R*)-(–)-5-oxo-2-tetrahydrofuran carboxylic acid **100** (15.0 g, 115 mmol) and concentrated HCl (15 drops) in MeOH (300 mL) was stirred at room temperature for 1 d. To the reaction mixture was added solid $NaHCO_3$ at 0 ºC. The mixture was filtered, concentrated, then dissolved in H_2O, and

extracted with CH_2Cl_2 (3x40 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give the desired product (19.6 g, 111 mmol, 97 %) as a yellow oil. The resulting residue (19.0 g, 108 mmol) was dissolved in CH_2Cl_2 (100 mL) and *N*,*N*-diisopropylethylamine (47.0 mL, 270 mmol) was added. To the mixture was added BOMCl (30.0 mL, 216 mmol) dropwise. After stirring for 1 d, the reaction mixture was washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine at 0 ºC, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on SiO_2 (hexane/ethyl ether, 4:1) to give **114** (18.9 g, 63.8 mmol, 92% based on recovered starting material) and unreacted alcohol (6.86 g, 38.9 mmol, 35%): $[\alpha]_D$ +46 (*c* 1.4, $CHCl_3$); IR (neat) 2953, 2889, 1739, 1438, 1260, 1203, 1173, 1027 cm^{-1}; ^1H NMR δ 7.36-7.25 (m, 5 H), 4.81, 4.79 (AB, 2 H, *J* = 7.2 Hz), 4.62 (s, 2 H), 4.25 (dd, 1 H, *J* = 4.9, 7.6 Hz), 3.69 (s, 3 H), 3.65 (s, 3 H), 2.55-2.38 (m, 2 H), 2.20-1.99 (m, 2 H); ^{13}C NMR δ 173.2, 172.5, 137.6, 128.5, 127.9 (2C), 94.4, 74.5, 70.2, 52.1, 51.7, 29.6, 27.9; MS (ESI) *m/z* (relative intensity) 319 ($[M+Na]^+$, 100); HRMS (ESI) *m/z* calculated for $C_{15}H_{20}O_6Na$ (M+Na) 319.1182, found 319.1162.



(*R*)-Methyl-4-((benzyloxy)methoxy)-4-formylbutanoate (99). A solution of the protected diester **114** (18.6 g, 62.8 mmol) in CH_2Cl_2 (140 mL) and toluene (90 mL) was treated with a solution of $MgBr_2 \bullet OEt_2$ (24.3 g, 94.2 mmol) in ethyl ether (90 mL), stirred at room temperature for 1 h, and cooled to –78 ºC. DIBAL (1 M solution in hexane, 94.0 mL, 94.0 mmol) was added over 2 h dropwise via dropping funnel. After an additional 30 min, MeOH (80 mL) was added in the same manner and the reaction mixture was then allowed to warm to room temperature. Saturated aqueous Rochelle salt (100 mL) was added. The mixture was stirred overnight and the

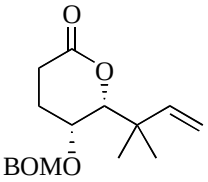
aqueous layer was extracted with CH_2Cl_2 (3x40 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexane/ethyl ether, 3:2) gave the desired aldehyde **99** (6.33 g, 23.8 mmol, 45% based on recovered starting material) along with over-reduced alcohol (6.28 g, 23.4 mmol, 37%) and starting material **114** (2.84 g, 9.58 mmol, 15%): $[\alpha]_D$ +25 (*c* 1.0, $CHCl_3$); IR (neat) 2951, 2893, 1736, 1438, 1380, 1256, 1198, 1162, 1027 cm^{-1}; ^1H NMR δ 9.63 (d, 1 H, *J* = 1.5 Hz), 7.35-7.27 (m, 5 H), 4.86, 4.81 (AB, 2 H, *J* = 7.1 Hz), 4.68, 4.63 (AB, 2 H, *J* = 11.8 Hz), 4.06 (ddd, 1 H, *J* = 1.5, 5.1, 7.8 Hz), 3.65 (s, 3 H), 2.46 (t, 2 H, *J* = 7.3 Hz), 2.12-1.91 (m, 2 H); ^{13}C NMR δ 201.9, 173.2, 137.3, 128.6, 128.0, 127.9, 94.9, 81.2, 70.3, 51.8, 29.2, 25.1; MS (EI) *m/z* (relative intensity) 207 ([M-$CO_2Me]^+$, 4), 159 (3), 130 (6), 120 (5), 91 (100); HRMS (EI) *m/z* calculated for $C_{12}H_{15}O_3$ (M-CO_2Me) 207.1021, found 207.1030.



(4*R*,5*R*)-Methyl-4-((benzyloxy)methoxy)-5-hydroxy-6,6-dimethyloct-7-enoate (115). Indium powder (4.10 g, 35.7 mmol) was azeotropically dried with dry THF (1 mL) twice and then treated with THF (180 mL) and 4-bromo-2-methyl-2-butene (12.3 mL, 107 mmol). The mixture was stirred vigorously till it turned into a clear solution, then to which was added dropwise hexane (60 mL). The resulting clear solution was cooled to –78 ºC, followed by addition of the aldehyde **99** (6.34 g, 23.8 mmol) dropwise. The reaction mixture was stirred at –78 ºC for 2 h, allowed to warm up to room temperature over 4 h, and quenched with saturated aqueous $NaHCO_3$. White emulsion was filtered and the aqueous layer was extracted with ethyl ether (3x50 mL). The combined organic layers were dried ($MgSO_4$), concentrated, and purified by

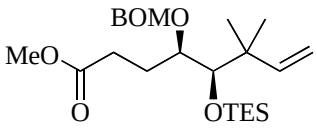
chromatography on SiO_2 (hexane/ethyl ether, 85:15) to afford the desired product **115** (2.41 g, 7.16 mmol, 30%) and the lactone **118** (3.34 g, 11.1 mmol, 46%) as a colorless oil.

Or a solution of lactone **118** (6.42 g, 21.1 mmol) and concentrated HCl (3 drops) in MeOH (100 mL) was stirred at room temperature for 3 h. To a reaction mixture was added solid $NaHCO_3$ at 0 ºC. The mixture was filtered, concentrated, then dissolved in H_2O, and extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were dried ($MgSO_4$), concentrated, and purified by chromatography on SiO_2 (hexane/ethyl ether, 85:15) to afford **115** (5.42 g, 16.1 mmol, 76%) as a colorless oil. $[\alpha]_D$ +16 (*c* 0.45, CH_2Cl_2); IR (neat) 3535, 2953, 1737, 1454, 1381, 1260, 1198, 1163, 1097, 1027, 914 cm^{-1}; ^1H NMR (C_6D_6) δ 7.36-7.12 (m, 5 H), 5.90 (dd, 1 H, *J* = 10.5, 17.9 Hz), 5.01 (dd, 1 H, *J* = 1.5, 5.1 Hz), 4.97 (dd, 1 H, *J* = 1.7, 2.1 Hz), 4.57 (s, 2 H), 4.54, 4.44 (AB, 2 H, *J* = 12.1 Hz), 3.70 (dt, 1 H, *J* = 2.6, 5.6 Hz), 3.39 (s, 3 H), 3.19 (dd, 1 H, *J* = 2.6, 8.0 Hz), 2.70 (d, 1 H, *J* = 8.0 Hz), 2.46-2.30 (m, 2 H), 2.19-2.07 (m, 1 H), 1.97-1.86 (m, 1 H), 1.15 (s, 3 H), 1.09 (s, 3 H); ^{13}C NMR (C_6D_6) δ 173.3, 145.4, 138.3, 128.6, 127.9, 127.8, 112.2, 94.9, 78.8, 76.5, 70.3, 51.0, 41.6, 29.7, 29.5, 25.0, 22.5; MS (ESI) *m/z* (relative intensity) 359 ($[M+Na]^+$, 100), 289 (11); HRMS (ESI) *m/z* calculated for $C_{19}H_{28}O_5Na$ (M+Na) 359.1834, found 359.1830.

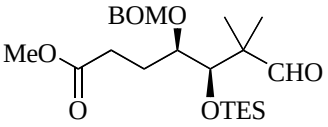


(4*R*,5*R*)-5-Benzyloxymethoxy-6-(1,1-dimethylallyl)tetrahydropyran-2-one (118): Mp 62 °C; $[\alpha]_D$ –9.1 (*c* 0.11, CH_2Cl_2); IR (neat) 2960, 2924, 1734, 1455, 1362, 1204, 1096, 1022 cm^{-1}; ^1H NMR δ 7.39-7.30 (m, 5 H), 6.05 (dd, 1 H, *J* = 10.8, 17.5 Hz), 5.12-5.03 (m, 2 H), 4.82, 4.76 (AB, 2 H, *J* = 7.2 Hz), 4.64 (s, 2 H), 4.17 (br. s, 1 H), 3.95 (br. s, 1 H), 2.70 (ddd, 1 H, *J* = 7.6, 10.9, 18.3 Hz), 2.56 (ddd, 1 H, *J* = 2.2, 7.5, 18.0 Hz), 2.25 (tt, 1 H, *J* = 3.4, 10.6 Hz), 1.92-1.80

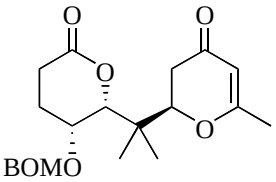
(m, 1 H), 1.22 (s, 3 H), 1.20 (s, 3 H); ^{13}C NMR δ 170.9, 144.2, 137.6, 128.7, 128.1, 127.9, 112.4, 93.9, 88.2, 70.8, 69.4, 40.6, 25.7, 25.3, 24.9,23.4; MS (ESI) *m/z* (relative intensity) 327 ([M+Na]$^+$, 100), 289 (5); HRMS (ESI) *m/z* calculated for $C_{18}H_{24}O_4Na$ (M+Na) 327.1572, found 327.1572.



(4*R*,5*R*)-Methyl-4-((benzyloxy)methoxy)-6,6-dimethyl-5-(triethylsilanyloxy)oct-7-enoate (116). To a solution of **115** (8.14 g, 24.2 mmol) and 2,6-lutidine (8.45 mL, 72.6 mmol) in CH_2Cl_2 (120 mL) was added TESOTf (8.21 mL, 36.3 mmol) at 0 ºC, and the solution was stirred for 2 h at 0 °C. The reaction mixture was quenched with brine and the aqueous layer was extracted with EtOAc (3x50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexane/ethyl ether, 95:5) to yield the desired TES ether **116** (10.3 g, 22.9 mmol, 94%) as a colorless oil: $[\alpha]_D$ +52 (*c* 1.0, $CHCl_3$); IR (neat) 2954, 2911, 2877, 1741, 1458, 1437, 1379, 1358, 1239, 1160, 1119, 1039, 912, 831 cm^{-1}; ^{1}H NMR δ 7.37-7.29 (m, 5 H), 6.02 (dd, 1 H, *J* = 11.0, 17.4 Hz), 5.02 (dd, 1 H, *J* = 1.4, 8.0 Hz), 4.98 (s, 1 H), 4.78, 4.73 (AB, 2 H, *J* = 7.0 Hz), 4.71, 4.57 (AB, 2 H, *J* = 11.9 Hz), 3.65 (s, 3 H), 3.59 (qn, 1 H, *J* = 4.5 Hz), 3.45 (d, 1 H, *J* = 5.0 Hz), 2.56-2.34 (m, 2 H), 1.95-1.80 (m, 2 H), 1.09 (s, 3 H), 1.06 (s, 3 H), 0.99 (t, 9 H, *J* = 8.1 Hz), 0.65 (q, 6 H, *J* = 7.5 Hz); ^{13}C NMR δ 174.2, 145.8, 138.3, 128.6, 127.9, 127.8, 111.6, 95.2, 80.8, 78.3, 70.1, 51.6, 42.0, 31.4, 29.4, 24.8, 24.7, 7.3, 5.6; MS (EI) *m/z* (relative intensity) 391 ([M-CO_2Me]$^+$, 1), 351 (4), 213 (55), 115 (18), 91 (100); HRMS (EI) *m/z* calculated for $C_{23}H_{39}O_3Si$ (M-CO_2Me) 391.2668, found 391.2653.

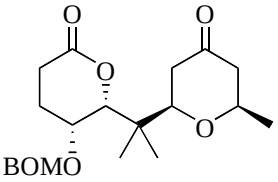


(4*R*,5*R*)-Methyl-4-((benzyloxy)methoxy)-6-formyl-6-methyl-5-(triethylsilanyloxy) heptanoate (98). A stream of O_3 was bubbled through a solution of **116** (5.4 g, 12 mmol) in MeOH (100 mL) at –78 ºC until the color of solution turned blue. After N_2 was bubbled through the solution for 15 min, Me_2S (5.0 L, 68 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The solution was concentrated. The residue was purified by chromatography on SiO_2 (hexane/ethyl ether, 10:1) to afford the desired aldehyde **98** (4.5 g, 9.9 mmol, 83%) as a colorless oil: $[\alpha]_D$ +22 (*c* 1.0, $CHCl_3$); IR (neat) 2955, 2877, 1739, 1457, 1159, 1101, 1040, 821 cm^{-1}; ^1H NMR (C_6D_6) δ 9.83 (m, 1 H), 7.35-7.14 (m, 5 H), 4.65, 4.60 (AB, 2 H, *J* = 7.0 Hz), 4.54, 4.46 (AB, 2 H, *J* = 12.1 Hz), 3.89 (d, 1 H, *J* = 3.8 Hz), 3.73 (dt, 1 H, *J* = 3.9, 9.2 Hz), 3.38 (s, 3 H), 2.40 (dd, 2 H, *J* = 7.0, 7.6 Hz), 2.18-2.07 (m, 1 H), 2.04-1.91 (m, 1 H), 1.14 (s, 3 H), 1.11 (s, 3 H), 1.02 (t, 9 H, *J* = 8.0 Hz), 0.65 (q, 6 H, *J* = 7.7 Hz); ^{13}C NMR (C_6D_6) δ 203.4, 173.0, 138.3, 128.5, 127.9, 127.7, 95.3, 80.1, 78.7, 70.2, 51.0, 50.2, 31.2, 27.4, 20.34, 20.29, 7.1, 5.5; MS (EI) *m/z* (relative intensity) 393 ($[M\text{-}CO_2Me]^+$, 3), 336 (6), 315 (7), 231 (37), 187 (45), 115 (40), 91 (100); HRMS (EI) *m/z* calculated for $C_{19}H_{32}O_3Si$ (M-$C_5H_8O_3$) 336.2121, found 336.2123.



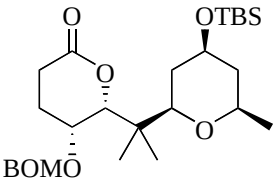
2-(2-((2*R*,3*R*)-3-((Benzyloxy)methoxy)tetrahydro-6-oxo-2*H*-pyran-2-yl)propan-2-yl)-2,3-dihydro-6-methylpyran-4-one (110). To a solution of **98** (1.32 g, 2.92 mmol) and diene **109** (3.0 mL) in CH_2Cl_2 (30 mL) was added BF_3•OEt_2 (0.50 mL, 3.9 mmol) dropwise. The mixture

was stirred for 3 h at –78 ºC, quenched with saturated aqueous $NaHCO_3$, warmed up to room temperature, and extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. To a solution of crude **123** (1.8 g) in CH_2Cl_2 (80 mL) was added TFA (3.0 mL) dropwise at 0 ºC. The reaction mixture was stirred for 1 h at room temperature, quenched with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (CH_2Cl_2/EtOAc, 10:1-4:1) to give the desired lactone **110** (773 mg, 1.99 mmol, 68%) as a yellow oil: $[\alpha]_D$ –74 (*c* 1.5, $CHCl_3$); IR (neat) 1735, 1663, 1612, 1399, 1335, 1243, 1200, 1167, 1061 cm^{-1}; ^1H NMR δ 7.38-7.28 (m, 5 H), 5.31 (s, 1 H), 4.87, 4.79 (AB, 2 H, *J* = 7.2 Hz), 4.63 (s, 2 H), 4.41 (dd, 1 H, *J* = 3.2, 14.8 Hz), 4.30 (d, 1 H, *J* = 1.3 Hz), 4.25-4.21 (m, 1 H), 2.75-2.52 (m, 3 H), 2.48-2.41 (m, 1 H), 2.36-2.26 (m, 1 H), 1.98 (s, 3 H), 1.96-1.84 (m, 1 H), 1.23 (s, 3 H), 1.14 (s, 3 H); ^{13}C NMR δ 193.1, 173.9, 170.3, 137.2, 128.7, 128.2, 127.7, 105.3, 93.3, 84.5, 84.0, 71.1, 68.7, 40.9, 36.7, 25.5, 24.7, 21.0, 20.5, 19.5; MS (EI) *m/z* (relative intensity) 388 (M^+, 1), 297 (2), 282 (1.4), 183 (8), 153 (10), 111 (75), 91 (100); HRMS (EI) *m/z* calculated for $C_{22}H_{28}O_6$ 388.1886, found 388.1881.



(5*R*,6*R*)-5-((Benzyloxy)methoxy)tetrahydro-6-(2-((2*R*,6*R*)-tetrahydro-6-methyl-4-oxo-2*H*-pyran-2-yl)propan-2-yl)pyran-2-one (119). A suspension of **110** (385 mg, 0.991 mmol) and Pd/C (3 wt%, 70 mg) in THF (15 mL) was stirred for 10 h at room temperature under H_2 gas, then filtered, and concentrated. The residue was purified by chromatography on SiO_2 (hexane/EtOAc, 10:1) to give **119** (249 mg 0.638 mmol, 64%) as a colorless oil: $[\alpha]_D$ –14 (*c*

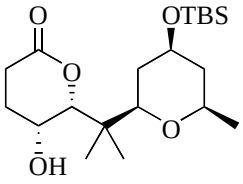
0.50, $CHCl_3$); IR (neat) 2927, 2868, 1774, 1722, 1455, 1365, 1244, 1167, 1102, 1024, 927 cm^{-1}; ^1H NMR (acetone-d_6) δ 7.37-7.26 (m, 5 H), 4.93, 4.87 (AB, 2 H, *J* = 7.0 Hz), 4.68, 4.63 (AB, 2 H, *J* = 12.1 Hz), 4.39 (d, 1 H, *J* = 1.3 Hz), 4.29 (dt, 1 H, *J* = 1.4, 3.3 Hz), 3.71 (dd, 1 H, *J* = 2.6, 11.6 Hz), 3.66-3.59 (m, 1 H), 2.61-2.49 (m, 2 H), 2.43 (dd, 1 H, *J* = 11.6, 14.0 Hz), 2.33-2.20 (m, 4 H), 2.11-1.95 (m, 1 H), 1.23 (d, 2 H, *J* = 6.1 Hz), 1.13 (s, 3 H), 1.05 (s, 3 H); ^{13}C NMR δ 207.5, 170.8, 137.3, 128.7, 128.1, 127.7, 93.2, 84.9, 81.2, 73.2, 70.9, 68.8, 49.4, 42.5, 41.3, 25.6, 24.6, 22.2, 20.1, 19.6; MS (EI) *m/z* (relative intensity) 299 ($[M-C_2H_7]^+$, 1), 269 (3), 198 (4), 185 (4), 91 (100); HRMS (EI) *m/z* calculated for $C_{15}H_{23}O_6$ (M-C_7H_7) 299.1495, found 299.1482.



(5*R*,6*R*)-5-((Benzyloxy)methoxy)tetrahydro-6-(2-((2*R*,4*S*,6*R*)-tetrahydro-6-methyl-4-(*tert*-butyldimethylsilanyloxy)-2*H*-pyran-2-yl)propan-2-yl)pyran-2-one (121). To a solution of **119** (249 mg, 0.638 mmol) in THF (10 mL) was added $NaBH_4$ (35 mg, 0.96 mmol) at 0 ºC and the mixture was stirred for 3 h at room temperature. The mixture was quenched with saturated aqueous NH_4Cl and the aqueous layer was extracted with EtOAc (3x25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give a crude product **120** (300 mg) as a yellow oil: $[\alpha]_D$ –17 (*c* 0.31, $CHCl_3$); IR (neat) 3427, 2960, 2932, 2873, 1726, 1453, 1366, 1249, 1024, 740 cm^{-1}; ^1H NMR δ 7.41-7.28 (m, 5 H), 4.88, 4.80 (AB, 2 H, *J* = 7.2 Hz), 4.69, 4.65 (AB, 2 H, *J* = 12.9 Hz), 4.30 (br. s, 1 H), 4.20 (br. s, 1 H), 3.55 (tt, 1 H, *J* = 4.4, 10.9 Hz), 3.35-2.29 (m, 1 H), 3.26 (dd, 1 H, *J* = 1.6, 11.3 Hz), 2.69 (ddd, 1 H, *J* = 7.6, 10.8, 18.2 Hz), 2.57 (ddd, 1 H, *J* = 3.1, 8.0, 18.2 Hz), 2.31-2.21 (m, 1 H), 1.95-1.81 (m, 3 H), 1.25 (q, 2 H, *J* = 11.6 Hz), 1.14 (d, 3 H, *J* = 6.2 Hz), 1.10 (s, 3 H), 1.07 (s, 3 H); ^{13}C NMR δ 171.3, 137.6, 128.8, 128.2, 127.7,

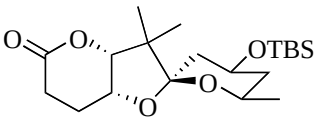
93.5, 85.5, 80.1, 71.9, 70.9, 69.3, 68.9, 43.3, 41.0, 35.2, 25.8, 25.1, 21.9, 20.8, 19.7; MS (ESI) *m/z* (relative intensity) 415 ($[M+Na]^+$, 100), 337 (25), 257 (14); HRMS (ESI) *m/z* calculated for $C_{22}H_{32}O_6Na$ (M+Na) 415.2097, found 415.2111.

To a solution of crude **120** (300 mg) and imidazole (500 mg, 7.34 mmol) in DMF (5 L) was added TBSCl (300 mg, 1.99 mmol). The mixture was stirred overnight and water was added. The aqueous layer was extracted with EtOAc (3x30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexane/EtOAc, 10:1) to give **121** (272 mg, 0.537 mmol, 84% over 2 steps) as a colorless oil: $[\alpha]_D$ –10 (*c* 0.71, $CHCl_3$); IR (neat) 2956, 2932, 2856, 1736, 1454, 1363, 1250, 1153, 1025, 837 cm^{-1}; ^1H NMR δ 7.40-7.29 (m, 5 H), 4.88, 4.81 (AB, 2 H, *J* = 7.2 Hz), 4.69, 4.64 (AB, 2 H, *J* = 12.1 Hz), 4.28 (br. s, 1 H), 4.21 (br, 1 H), 3.69-3.60 (m, 1 H), 3.34-3.24 (m, 1 H), 3.26 (dd, 1 H, *J* = 1.3, 11.3 Hz), 2.68 (ddd, 1 H, *J* = 7.5, 10.5, 18.1 Hz), 2.56 (ddd, 1 H, *J* = 3.2, 8.0, 18.2 Hz), 2.30-2.21 (m, 1 H), 1.94-1.85 (m, 1 H), 1.83-1.73 (m, 2 H), 1.34-1.18 (m, 2 H), 1.13 (d, 3 H, *J* = 6.1 Hz), 1.10 (s, 3 H), 1.06 (s, 3 H), 0.88 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR δ 171.4, 137.6, 128.8, 128.1, 127.7, 93.6, 85.7, 80.0, 71.9, 70.9, 69.6, 69.3, 43.8, 41.0, 35.4, 26.1, 25.9, 25.1, 22.0, 20.9, 19.4, 18.3, –4.3; MS (ESI) *m/z* (relative intensity) 529 ($[M+Na]^+$, 100), 507 (5), 447 (8); HRMS (ESI) *m/z* calculated for $C_{28}H_{46}O_6NaSi$ (M+Na) 529.2961, found 529.2974.



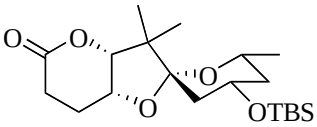
(5*R*,6*R*)-Tetrahydro-6-(2-((2*R*,4*S*,6*R*)-tetrahydro-6-methyl-4-(*tert*-butyldimethylsilanyloxy)-2*H*-pyran-2-yl)propan-2-yl)-5-hydroxypyran-2-one (111). To a solution of **121** (246 mg,

0.485 mmol) in THF (15 mL) was added $Pd(OH)_2/C$ (20 wt%, 60 mg). The mixture was stirred under H_2 gas for 5 h and filtered through celite pad. The residue was concentrated and purified by chromatography on SiO_2 (hexane/EtOAc, 4:1) to give **111** (188 mg, 0.486 mmol, 100%) as a white solid: Mp 51 °C; $[\alpha]_D$ –12 (*c* 0.33, $CHCl_3$); IR (neat) 3435, 2956, 2931, 2884, 1775, 1472, 1385, 1253, 1152, 1070, 837 cm^{-1}; ^1H NMR δ 5.80 (d, 1 H, *J* = 1.4 Hz), 4.15 (t, 1 H, *J* = 2.8 Hz), 3.92 (s, 1 H), 3.79 (tt, 1 H, *J* = 4.8, 10.7 Hz), 3.70 (dd, 1 H, *J* = 1.8, 11.9 Hz), 3.62-3.51 (m, 1 H), 2.83 (ddd, 1 H, *J* = 8.3, 10.4, 18.6 Hz), 2.52 (ddd, 1 H, *J* = 2.4, 8.2, 18.3 Hz), 2.13-2.04 (m, 1 H), 1.94-1.72 (m, 3 H), 1.31-1.23 (m, 2 H), 1.20 (d, 3 H, *J* = 6.2 Hz), 1.08 (s, 3 H), 1.03 (s, 3 H), 0.89 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR δ 171.8, 90.7, 75.4, 72.4, 68.9, 61.4, 43.2, 41.5, 35.6, 27.5, 26.6, 26.1, 25.5, 21.2, 18.34, 18.30, –4.36, –4.38; MS (EI) *m/z* (relative intensity) 329 ($[M-C_4H_9]^+$, 35), 285 (15), 227 (13), 169 (36), 145 (88), 97 (54), 85 (100); HRMS (EI) *m/z* calculated for $C_{16}H_{29}O_5Si$ (M-C_4H_9) 329.1784, found 329.1780.

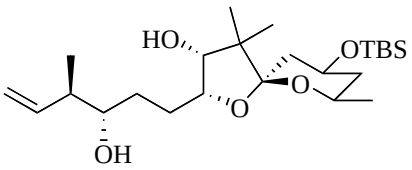


(2*R*,3*R*,5*S*,7*R*,9*S*)-9-(*tert*-Butyldimethylsilanyloxy)-(hexahydrofuro[3,2-*b*]pyran-5-onyl)-4,4,7-trimethyl-1,6-dioxaspiro[4.5]decane (112). To a solution of **111** (337 mg, 0.872 mmol) in cyclohexane (60 mL) were added iodobenzene diacetate (560 mg, 1.74 mmol) and I_2 (442 mg, 1.74 mmol). The reaction mixture was stirred for 5 h at room temperature under irradiation by light (250 W), quenched with saturated aqueous $Na_2S_2O_3$, and stirred for 30 min. The aqueous layer was extracted with EtOAc (2×25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexane/ethyl ether, 10:1) to give the major product **112** (159 mg, 0.413 mmol, 47%) as a white solid and the minor product **113** (66 mg, 0.17 mmol, 20%) as a colorless oil: $[\alpha]_D$ +43 (*c* 1.0, $CHCl_3$); IR (neat)

2955, 2931, 2886, 2857, 1750, 1472, 1385, 1250, 1155, 1115, 1040, 837 cm^{-1}; ^1H NMR δ 4.71 (d, 1 H, *J* = 7.6 Hz), 4.21 (dt, 1 H, *J* = 5.9, 7.3 Hz), 4.04 (tt, 1 H, *J* = 4.8, 11.0 Hz), 3.81-3.70 (m, 1 H), 2.58 (ddd, 1 H, *J* = 4.2, 8.4, 16.9 Hz), 2.33 (ddd, 1 H, *J* = 4.1, 9.2, 16.9 Hz), 2.14-2.04 (m, 1 H), 1.98-1.89 (m, 1 H), 1.88-1.79 (m, 2 H), 1.35-1.20 (m, 2 H), 1.14 (d, 3 H, *J* = 6.2 Hz), 1.137 (s, 3 H), 0.93 (s, 3 H), 0.89 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR δ 172.1, 108.8, 88.0, 69.5, 66.0, 64.9, 49.8, 42.9, 36.9, 27.1, 26.0, 24.0, 21.5, 21.1, 18.9, 18.2, –4.4; MS (EI) *m/z* (relative intensity) 327 ($[M-C_4H_9]^+$, 4), 185 (22), 169 (60), 140 (100), 97 (100); HRMS (EI) *m/z* calculated for $C_{16}H_{27}O_5Si$ (M-C_4H_9) 327.1628, found 327.1629.

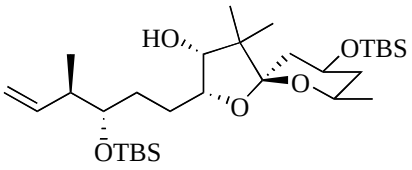


(2*R*,3*R*,5*R*,7*R*,9*S*)-9-(*tert*-Butyldimethylsilanyloxy)-(hexahydrofuro[3,2-*b*]pyran-5-onyl)-4,4,7-trimethyl-1,6-dioxaspiro[4.5]decane (113): $[\alpha]_D$ –37 (*c* 1.0, $CHCl_3$); IR (neat) 2971, 2931, 1723, 1384, 1247, 1185, 1102, 1066, 1042, 996, 883 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$+C_6D_6): δ 4.09 (br. s, 1 H), 3.97 (d, 1 H, *J* = 5.3 Hz), 3.88 (dq, 1 H, *J* = 5.1, 14.9 Hz), 3.72 (ddt, 1 H, *J* = 2.2, 6.1, 12.1 Hz), 2.89 (ddd, 1 H, *J* = 5.8, 13.7, 17.5 Hz), 2.24 (d, 1 H, *J* = 16.3 Hz), 2.09 (dd, 1 H, *J* = 5.0, 13.8 Hz), 1.90-1.84 (m, 1 H), 1.72 (dt, 1 H, *J* = 2.4, 12.6 Hz), 1.64 (dd, 1 H, *J* = 9.6, 13.9 Hz), 1.47 (ddt, 1 H, *J* = 2.5, 4.8, 14.1 Hz), 1.36 (q, 1 H, *J* = 11.8 Hz), 1.19 (s, 3 H), 1.13 (d, 3 H, *J* = 6.1 Hz), 0.95 (s, 9 H), 0.84 (s, 3 H), 0.09 (s, 6 H); ^{13}C NMR δ 171.3, 109.5, 90.2, 71.0, 69.3, 65.7, 51.2, 42.1, 39.2, 26.0, 25.4, 25.0, 23.7, 22.1, 19.5, 18.3, –4.4; MS (EI) *m/z* (relative intensity) 369 ($[M-CH_3]^+$, 1), 327 (55), 283 (15), 213 (25), 171 (70), 140 (58), 101 (50), 75 (100); HRMS (EI) *m/z* calculated for $C_{19}H_{33}O_5Si$ (M-CH_3) 369.2097, found 369.2099.



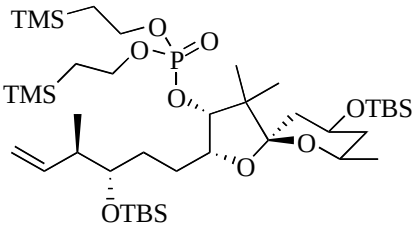
(2*R*,3*R*,5*S*,7*R*,9*S*)-9-(*tert*-Butyldimethylsilanyloxy)-2-((3*S*,4*R*)-3-hydroxy-4-methylhex-5-enyl)-4,4,7-trimethyl-1,6-dioxaspiro[4.5]decan-3-ol (127). To a solution of **112** (225 mg, 0.585 mmol) in CH_2Cl_2 (25 mL) was added DIBAL (1.0 M in hexane, 0.70 mL, 0.70 mmol) at –78 ºC and the mixture was stirred for 2 h at –78 ºC. The mixture was quenched with MeOH (1 mL), allowed to warm to room temperature, and treated with saturated aqueous Rochelle salt (2 mL). After stirred overnight at room temperature, the aqueous layer was extracted with CH_2Cl_2 (3x25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give a crude aldehyde. Without further purification, this crude aldehyde was used for the next step. To a well-stirred mixture of trans-2-butene (0.54 mL) and KO*t*-Bu (145 mg, 2.01 mmol) in THF (2 mL), *n*-BuLi (1.6 M in hexane, 1.30 mL, 2.08 mmol) was added at –78 ºC. Following the completion of addition, the mixture was stirred at –45 ºC for 15 min and again cooled to –78 ºC. To the reaction mixture, a solution of *B*-methoxylbis(2-isocaranyl)borane (788 mg, 2.68 mmol) in ethyl ether (2 mL) was added dropwise and the resulting mixture was stirred for 30 min at –78 ºC. The addition of BF_3•etherate (0.34 mL, 2.7 mmol) and stirring the mixture at –78 ºC for 15 min afforded *B*-[*E*]-crotyl(2-isocaranyl)borane **126**. A solution of the crude aldehyde (40 mg, 0.10 mmol) in ethyl ether (0.7 mL) was added at –78 ºC and the resulting mixture was stirred for 3 h at –78 ºC. The reaction mixture was quenched with MeOH (0.4 mL), brought to room temperature, and oxidized with alkalin hydrogen peroxide (30% H_2O_2 (1.4 mL) and 3 N NaOH (0.74 mL) by refluxing for 3 h. The aqueous layer was extracted with EtOAc (3x30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexane/ethyl ether, 10:1-4:1) to give **127** (35 mg, 0.079 mmol, 77%

over 2 steps) as a colorless oil: $[\alpha]_D$ +46 (*c* 1.0, $CHCl_3$); IR (neat) 3478, 2956, 2930, 2885, 2857, 1472, 1386, 1255, 1040, 836 cm^{-1}; ^1H NMR δ 5.87-5.74 (m, 1 H), 5.12 (br. s, 1 H), 5.08 (d, 1 H, *J* = 4.1 Hz), 4.23 (d, 1 H, *J* = 7.5 Hz), 4.09-3.98 (m, 1 H), 3.90 (dt, 1 H, *J* = 4.9, 7.8 Hz), 3.78-3.68 (m, 1 H), 3.50-3.44 (m, 1 H), 2.28-2.17 (m, 1 H), 1.85-1.65 (m, 4 H), 1.62-1.40 (m, 1 H), 1.33-1.15 (m, 3 H), 1.11 (d, 3 H, *J* = 6.1 Hz), 1.05 (d, 3 H, *J* = 7.0 Hz), 1.02 (s, 3 H), 0.89 (br. s, 12 H), 0.07 (s, 6 H); ^{13}C NMR δ 140.8, 116.0, 107.6, 79.6, 77.9, 75.0, 66.4, 64.8, 48.2, 44.3, 43.4, 38.0, 31.7, 26.6, 26.1, 21.7, 20.9, 18.3, 18.2, 16.5, –4.3; MS (EI) *m/z* (relative intensity) 385 ($[M-C_4H_9]^+$, 0.1), 297 (33), 203 (40), 171 (47), 125 (33), 75 (100); HRMS (EI) *m/z* calculated for $C_{20}H_{37}O_5Si$ (M-C_4H_9) 385.2410, found 385.2418.



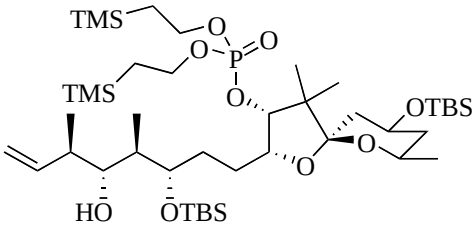
(2*R*,3*R*,5*S*,7*R*,9*S*)-9-(*tert*-Butyldimethylsilanyloxy)-2-[(3*S*,4*R*)-3-(*tert*-butyldimethylsilanyloxy)-4-methylhex-5-enyl]-4,4,7-trimethyl-1,6-dioxaspiro[4.5]decan-3-ol (123). To a solution of **127** (35 mg, 0.079 mmol) and imidazole (54 mg, 0.79 mmol) in DMF (1 mL) was added TBSCl (60 mg, 0.40 mmol). The mixture was stirred overnight and quenched with water. The aqueous layer was extracted with EtOAc (3x20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexane/ethyl ether, 10:1) to give **123** (43 mg, 0.077 mmol, 97%) as a colorless oil: $[\alpha]_D$ +39 (*c* 1.0, $CHCl_3$); IR (neat) 3462, 2956, 2930, 2885, 2857, 1472, 1386, 1255, 1112, 1069, 1006, 836 cm^{-1}; ^1H NMR δ 5.87-5.75 (m, 1 H), 5.04-5.01 (m, 1 H), 4.99-4.97 (m, 1 H), 4.20 (d, 1 H, *J* = 7.6 Hz), 4.05 (tt, 1 H, *J* = 4.9, 10.9 Hz), 3.87-3.80 (m, 1 H), 3.78-3.67 (m, 1 H), 3.59 (q, 1 H, *J* = 4.7 Hz), 2.37-2.28 (m, 1 H), 1.83-1.75 (m, 2 H), 1.65-1.55 (m, 2 H), 1.49-1.35 (m, 2 H), 1.31-1.15 (m, 2 H), 1.10 (d, 3 H, *J* = 6.3 Hz), 1.02 (s, 3 H), 1.00 (d, 3 H, *J* = 6.9 Hz), 0.90 (s, 9

H), 0.89 (s, 9 H), 0.88 (s, 3 H), 0.07 (s, 9 H), 0.05 (s, 3 H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 141.7, 114.4, 107.6, 79.7, 77.5, 76.1, 66.7, 64.8, 48.3, 43.7, 43.2, 38.2, 30.9, 26.4, 26.14, 26.07, 21.6, 20.9, 18.5, 18.4, 18.2, 15.9, –4.0, –4.4; MS (EI) *m/z* (relative intensity) 556 (M^+, 0.2), 541 (0.3), 499 (11), 367 (28), 271 (29), 237 (100), 203 (50), 145 (55), 73 (79); HRMS (EI) *m/z* calculated for $C_{30}H_{60}O_5Si_2$ (M) 556.3979, found 556.4000.



(2*R*,3*R*,5*S*,7*R*,9*S*)-Phosphoric acid 9-(*tert*-butyldimethylsilanyloxy)-2-[(3*S*,4*R*)-3-(*tert*-butyldimethylsilanyloxy)-4-methylhex-5-enyl]-4,4,7-trimethyl-1,6-dioxaspiro[4.5]dec-3-yl ester bis-[2-(trimethylsilanyl)-ethyl] ester (128). PCl_3 (2 M in CH_2Cl_2, 0.50 mL, 1.0 mmol) was added to a solution of the alcohol **123** (140 mg, 0.252 mmol) in pyridine (4 mL) at 0 ºC by one portion. After 10 min, 2-trimethylsilylethanol (0.86 mL, 6.0 mmol) and DMAP (5.0 mg) were added and the mixture was warmed to room temperature over 1 h. CH_2Cl_2 (24 mL) and 30% aqueous H_2O_2 (2.8 mL) were added and the stirring was continued for 1 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (3x25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexane/ethyl ether, 10:1) to give **128** (145 mg, 0.173 mmol, 69%) as a colorless oil: $[\alpha]_D$ +36 (*c* 1.0, $CHCl_3$); IR (neat) 2956, 2930, 2895, 2857, 1383, 1362, 1252, 997, 836 cm^{-1}; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 5.82 (ddd, 1 H, *J* = 7.8, 10.6, 18.2 Hz), 5.01 (d, 1 H, *J* = 7.5 Hz), 4.98 (s, 1 H), 4.78 (dd, 1 H, *J* = 7.8, 9.2 Hz), 4.18-4.10 (m, 4 H), 4.09-4.02 (m, 1 H), 3.92-3.89 (m, 1 H), 3.75-3.69 (m, 1 H), 3.62 (q, 1 H, *J* = 4.7 Hz), 2.31 (dt, 1 H, *J* = 6.7, 18.4 Hz), 1.80 (dd, 2 H, *J* = 4.5, 12.5 Hz), 1.71-1.59 (m, 2 H),

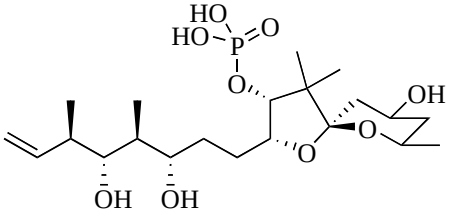
1.50-1.42 (m, 2 H), 1.31-1.19 (m, 2 H), 1.12-1.08 (m, 7 H), 1.07 (s, 3 H), 1.00 (d, 3 H, *J* = 6.9 Hz), 0.90 (br. s, 12 H), 0.88 (s, 9 H), 0.08-0.05 (m, 30 H); ^{13}C NMR δ 141.3, 114.4, 107.4, 84.8, 84.7, 76.3, 76.2, 75.6, 66.4, 66.3, 64.7, 48.3, 48.2, 43.3, 42.7, 37.4, 30.8, 26.23, 26.19, 26.1, 21.6, 20.4, 19.93, 19.88, 18.7, 18.4, 18.3, 16.2, –1.3, –3.9, –4.3, –4.35, –4.39; MS (EI) *m/z* (relative intensity) 779 ([M-C_4H_9]$^+$, 0.2), 723 (5), 649 (1.5), 573 (2.5), 461 (55), 407 (100), 349 (75), 243 (82); HRMS (EI) *m/z* calculated for $C_{36}H_{76}O_8Si_4P$ (M-C_4H_9) 779.4355, found 779.4320.



Desired structure

(2*R*,3*R*,5*S*,7*R*,9*S*)-Phosphoric acid 9-(*tert*-butyldimethylsilanyloxy)-2-[(3*S*,4*R*,5*R*,6*R*)-3-(*tert*-butyldimethylsilanyloxy)-5-hydroxy-4,6-dimethyloct-7-enyl]-4,4,7-trimethyl-1,6-dioxaspiro[4.5]dec-3-yl ester bis-[2-(trimethylsilanyl)ethyl]ester (130). A stream of O_3 was bubbled through a solution of **128** (36 mg, 0.043 mmol) in MeOH (5 mL) at –78 ºC until the color of solution turned blue. After N_2 was bubbled through the solution for 15 min, Me_2S (0.50 L, 6.8 mmol) was added. Then the mixture was allowed to warm to room temperature and stirred for 12 h. The solution was concentrated. The residue was purified by chromatography on SiO_2 (hexane/ethyl ether, 4:1) to give the crude aldehyde (32 mg, 0.038 mmol, 89 %) as colorless oil. To a suspension of Roush's reagent **129**[54c] (1 M in toluene, 1.0 mL, 1.0 mmol) and 4 Å MS (50 mg) was added a solution of the crude aldehyde (32 mg, 0.038 mmol) in toluene (1 mL) at –78 ºC. After stirring at –78 ºC for 5 h, the reaction mixture was filtered through a SiO_2 pad and washed with EtOAc and CH_2Cl_2. The filtrate was concentrated and the residue was purified by chromatography on SiO_2 (hexane/ethyl ether, 10:1) to give **130** (29 mg, 0.032 mmol, 84%) as a colorless oil: $[\alpha]_D$ +46 (*c* 1.0, $CHCl_3$); IR (neat) 3434, 2956, 2930, 2896, 2857, 1471, 1384,

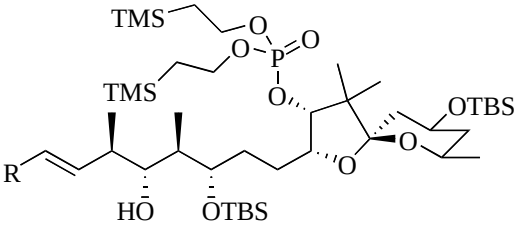
1252, 1113, 1074, 998, 836, 774 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.09 (ddd, 1 H, *J* = 7.7, 10.3, 17.6 Hz), 5.29 (dd, 1 H, *J* = 8.0, 8.9 Hz), 5.13 (d, 1 H, *J* = 17.3 Hz), 5.08 (d, 1 H, *J* = 10.3 Hz), 4.36-4.23 (m, 6 H), 4.04-4.01 (m, 1 H), 3.88 (d, 1 H, *J* = 8.6 Hz), 3.86-3.80 (m, 1 H), 2.79 (d, 1 H, *J* = 1.6 Hz), 2.38 (sx, 1 H, *J* = 7.4 Hz), 2.22-2.15 (m, 1 H), 2.12-2.06 (m, 2 H), 1.97-1.84 (m, 3 H), 1.83-1.78 (m, 1 H), 1.51 (t, 1 H, *J* = 11.3 Hz), 1.38 (s, 3 H), 1.29 (q, 1 H, *J* = 11.6 Hz), 1.15 (s, 3 H), 1.13-1.06 (m, 10 H), 1.03 (s, 3 H), 1.02 (s, 9 H), 1.01 (s, 9 H), 0.24 (s, 3 H), 0.17 (s, 3 H), 0.16 (s, 3 H), 0.13 (s, 3 H), –0.04 (s, 9 H), –0.09 (s, 9 H); ^{13}C NMR (CD_2Cl_2) δ 142.7, 113.4, 107.1, 84.04, 83.97, 76.8, 75.2, 75.1, 73.3, 65.9, 65.8, 65.7, 64.4, 47.71, 47.65, 42.9, 41.1, 36.8, 35.6, 30.6, 25.7, 25.4, 25.3, 20.9, 19.7, 19.4, 19.3, 18.0, 17.64, 17.59, 16.1, 10.2, –2.1, –4.7, –5.0, –5.1, –5.4; MS (ESI) *m/z* (relative intensity) 918 ($[M+Na]^+$, 75), 896 (100); HRMS (ESI) *m/z* calculated for $C_{43}H_{92}O_9PSi_4$ (M+H) 895.5556, found 895.5508.



Desired structure

(2*R*,3*R*,5*S*,7*R*,9*S*)-Phosphoric acid mono-[2-((3*S*,4*R*,5*R*,6*R*)-3,5-dihydroxy-4,6-dimethyloct-7-enyl)-9-hydroxy-4,4,7-trimethyl-1,6-dioxaspiro[4.5]dec-3-yl] ester (131). A solution of **130** (15 mg, 0.017 mmol) in HF solution (1.0 mL, from the stock solution with 48% HF (0.5 mL), CH_3CN (4.5 mL), and water (0.5 mL)) was stirred at room temperature for 6 d. Argon gas was bubbled into the reaction mixture to remove the solvent and the mixture was dried under reduced pressure. The residue was washed with $CHCl_3$ and water, and extracted with MeOH to give **131** (5.5 mg, 0.012 mmol, 71%) as a white solid: Mp 136-140 °C (dec.); IR (neat) 3272, 2925, 2863, 1668, 1447, 1372, 1241, 1149, 1049, 1025, 995, 940 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 5.85 (ddd, 1 H, *J* = 8.3, 10.1, 17.8 Hz), 5.05 (d, 1 H, *J* = 17.4 Hz), 5.01 (d, 1 H, *J* = 10.3 Hz), 4.76

(dd, 1 H, *J* = 8.3, 9.0 Hz), 4.00-3.95 (m, 2 H), 3.79-3.74 (m, 1 H), 3.65 (dd, 1 H, *J* = 2.5, 8.1 Hz), 3.63-3.60 (m, 1 H), 2.30-2.23 (m, 1 H), 1.94-1.87 (m, 3 H), 1.80-1.74 (m, 1 H), 1.72-1.66 (m, 1 H), 1.54-1.43 (m, 2 H), 1.23 (t, 1 H, *J* = 12.0 Hz), 1.13 (d, 3 H, *J* = 6.1 Hz), 1.09 (s, 3 H), 1.05 (q, 1 H, *J* = 11.8 Hz), 0.951 (s, 3 H), 0.946 (d, 3 H, *J* = 6.1 Hz), 0.92 (d, 3 H, *J* = 6.9 Hz); ^{13}C NMR (150 MHz, CD_3OD) δ 143.3, 115.0, 108.7, 85.21, 85.17, 78.24, 78.21, 75.6, 75.3, 66.0, 65.9, 43.4, 42.9, 40.9, 37.7, 32.5, 30.8, 28.3, 21.8, 20.7, 19.2, 17.4, 10.2 (HMBC shows that one peak is inside the solvent peaks); MS (ESI) *m/z* (relative intensity) 489 ($[M+Na]^+$, 80), 471 (100), 453 (40), 413 (20), 382 (28); HRMS (ESI) *m/z* calculated for $C_{21}H_{39}O_9NaP$ (M+Na) 489.2229, found 489.2244.



Desired structure

General Procedure for the cross-metathesis reaction. To a solution of **130** (6.6 mg, 0.0074 mmol) and 1-decene (14 μL, 0.074 mmol) in a sealed tube was added a solution of second generation Grubbs' reagent (1.5 mg, 0.0018 mmol) in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred at 40 °C for 1 d. After removing all volatiles, the residue was purified by chromatography on SiO_2 (hexane/EtOAc, 10:1) to give the desired product **132a** (5.0 mg, 0.0050 mmol, 68%) as a colorless oil.

R = phenyl; (2*R*,3*R*,5*S*,7*R*,9*S*)-Phosphoric acid 9-(*tert*-butyldimethylsilanyloxy)-2-[(3*S*,4*R*,5*R*,6*R*)-3-(*tert*-butyldimethylsilanyloxy)-5-hydroxy-4,6-dimethyl-8-phenyloct-7-enyl]-4,4,7-trimethyl-1,6-dioxaspiro[4.5]dec-3-yl ester bis-[2-(trimethylsilanyl)-ethyl]ester (132a): ^{1}H NMR (600 MHz, CD_2Cl_2) δ 7.36 (dd, 2 H, *J* = 1.2, 8.4 Hz), 7.28 (t, 2 H, *J* = 7.5 Hz), 7.20-7.16 (m, 1 H), 6.42 (d, 1 H, *J* = 15.9 Hz), 6.27 (dd, 1 H, *J* = 8.1, 15.9 Hz), 4.79 (dd, 1 H, *J* =

7.8, 9.2 Hz), 4.16-4.11 (m, 4 H), 4.10-4.05 (m, 1 H), 3.95 (ddd, 1 H, *J* = 3.0, 7.7, 10.7 Hz), 3.88-3.85 (m, 1 H), 3.79 (dd, 1 H, *J* = 1.1, 9.0 Hz), 3.76-3.71 (m, 1 H), 3.25 (s, 1 H), 2.44-2.36 (m, 1 H), 1.98-1.92 (m, 1 H), 1.84-1.78 (m, 3 H), 1.68-1.57 (m, 3 H), 1.52-1.47 (m, 1 H), 1.27 (t, 1 H, *J* = 11.7 Hz), 1.12 (d, 3 H, *J* = 6.3 Hz), 1.11-1.08 (m, 4 H), 1.07 (s, 3 H), 1.00 (d, 3 H, *J* = 4.5 Hz), 0.99 (d, 3 H, *J* = 4.2 Hz), 0.91 (s, 3 H), 0.90 (s, 9 H), 0.88 (s, 9 H), 0.12 (s, 3 H), 0.10 (s, 3 H), 0.06 (s, 6 H), 0.05 (s, 9 H), 0.048 (s, 9 H); ^{13}C NMR (125 MHz, CD_2Cl_2) δ 137.5, 134.5, 129.0, 128.1, 126.5, 125.6, 107.0, 83.9, 77.0, 75.0, 73.6, 65.82, 65.78, 65.7, 64.3, 47.62, 47.59, 42.8, 40.5, 36.7, 35.4, 30.5, 25.7, 25.34, 25.27, 20.8, 19.6, 19.29, 19.25 19.2, 18.0, 17.6, 17.5, 16.5, 10.3, –2.1, –2.2, –4.7, –5.11, –5.14, –5.5; MS (ESI) *m/z* (relative intensity) 993 ($[M+Na]^+$, 78), 537 (100); HRMS (ESI) *m/z* calculated for $C_{49}H_{95}O_9NaPSi_4$ **(**M+Na**)** 993.5689, found 993.5652.

R = 4-chlorophenyl; (2*R*,3*R*,5*S*,7*R*,9*S*)-Phosphoric acid 9-(*tert*-butyldimethylsilanyloxy)-2-[(3*S*,4*R*,5*R*,6*R*)-3-(*tert*-butyldimethylsilanyloxy)-8-(4-chlorophenyl)-5-hydroxy-4,6-dimethyloct-7-enyl]-4,4,7-trimethyl-1,6-dioxaspiro[4.5]dec-3-yl ester bis-[2-(trimethylsilanyl)-ethyl]ester (132b): ^{1}H NMR δ 7.30 (d, 2 H, *J* = 8.7 Hz), 7.23 (d, 2 H, *J* = 8.6 Hz), 6.42 (d, 1 H, *J* = 16.0 Hz), 6.30 (dd, 1 H, *J* = 7.5, 15.9 Hz), 4.84 (dd, 1 H, *J* = 7.8, 9.3 Hz), 4.21-4.11 (m, 4 H), 4.09-4.00 (m, 1 H), 3.98-3.91 (m, 1 H), 3.89-3.80 (m, 2 H), 3.75-3.69 (m, 1 H), 3.50 (br. s, 1 H), 2.48-2.40 (m, 1 H), 1.97-1.91 (m, 1 H), 1.84-1.78 (m, 3 H), 1.70-1.60 (m, 2 H), 1.32-1.21 (m, 3 H), 1.17-1.07 (m, 10 H), 1.03 (d, 3 H, *J* = 7.1 Hz), 1.00 (d, 3 H, *J* = 6.8 Hz), 0.92 (s, 3 H), 0.91 (s, 9 H), 0.89 (s, 9 H), 0.12-0.03 (m, 30 H); MS (ESI) *m/z* (relative intensity) 1028 ($[M+Na]^+$, 100), 431 (10), 353 (12); HRMS (ESI) *m/z* calculated for $C_{49}H_{94}O_9NaClPSi_4$ (M+Na) 1027.5299, found 1027.5232.

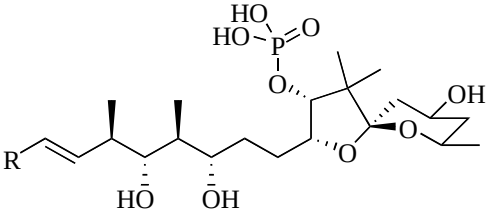
R = 4-methoxyphenyl; (2*R*,3*R*,5*S*,7*R*,9*S*)-Phosphoric acid 9-(*tert*-butyldimethylsilanyloxy)-2-[(3*S*,4*R*,5*R*,6*R*)-3-(*tert*-butyldimethylsilanyloxy)-5-hydroxy-8-(4-methoxyphenyl)-4,6-dimethyloct-7-enyl]-4,4,7-trimethyl-1,6-dioxaspiro[4.5]dec-3-yl ester bis-[2-(trimethylsilanyl)-ethyl]ester (132c): ^{1}H NMR δ 7.32 (d, 2 H, *J* = 8.8 Hz), 6.82 (d, 2 H, *J* = 8.8 Hz), 6.42 (d, 1 H, *J* = 16.0 Hz), 6.15 (dd, 1 H, *J* = 7.9, 16.0 Hz), 4.84 (dd, 1 H, *J* = 7.7, 9.0 Hz), 4.20-4.12 (m, 4 H), 4.09-4.02 (m, 1 H), 3.95-3.90 (m, 1 H), 3.88-3.82 (m, 2 H), 3.78 (s, 3 H), 3.75-3.67 (m, 1 H), 3.40 (s, 1 H), 2.44-2.36 (m, 1 H), 1.98-1.90 (m, 2 H), 1.84-1.77 (m, 3 H), 1.70-1.60 (m, 2 H), 1.41-1.20 (m, 3 H), 1.14-1.07 (m, 10 H), 1.03-0.99 (m, 6 H), 0.92-0.88 (m, 21 H), 0.11-0.05 (m, 30 H); MS (ESI) *m/z* (relative intensity) 1024 ([M+Na]$^+$, 100), 1002 (12), 850 (11), 682 (10); HRMS (ESI) *m/z* calculated for $C_{50}H_{97}O_{10}NaPSi_4$ (M+Na) 1023.5794, found 1023.5745.

R = cyclohexyl; (2*R*,3*R*,5*S*,7*R*,9*S*)-Phosphoric acid 9-(*tert*-butyldimethylsilanyloxy)-2-[(3*S*,4*R*,5*R*,6*R*)-3-(*tert*-butyldimethylsilanyloxy)-8-cyclohexyl-5-hydroxy-4,6-dimethyloct-7-enyl]-4,4,7-trimethyl-1,6-dioxaspiro[4.5]dec-3-yl ester bis-[2-(trimethylsilanyl)-ethyl] ester (132d): ^{1}H NMR δ 5.48 (dd, 1 H, *J* = 5.7, 15.6 Hz), 5.39 (dd, 1 H, *J* = 7.0, 15.5 Hz), 4.83 (dd, 1 H, *J* = 7.8, 9.2 Hz), 4.20-4.10 (m, 4 H), 4.09-4.00 (m, 1 H), 3.96-3.88 (m, 1 H), 3.85-3.79 (m, 1 H), 3.75-3.68 (m, 1 H), 3.65 (d, 1 H, *J* = 9.3 Hz), 3.05 (s, 1 H), 2.22-2.14 (m, 1 H), 2.01-1.85 (m, 2 H), 1.85-1.60 (m, 10 H), 1.31-1.15 (m, 7 H), 1.14-1.04 (m, 14 H), 0.95 (d, 3 H, *J* = 7.0 Hz), 0.90 (s, 9 H), 0.897 (br. s, 12 H), 0.11-0.04 (m, 30 H); MS (ESI) *m/z* (relative intensity) 1000 ([M+Na]$^+$, 100), 918 (85), 861 (25); HRMS (ESI) *m/z* calculated for $C_{49}H_{101}O_9NaPSi_4$ (M+Na) 999.6158, found 999.6201.

R = butyl; (2*R*,3*R*,5*S*,7*R*,9*S*)-Phosphoric acid 9-(*tert*-butyldimethylsilanyloxy)-2-[(3*S*,4*R*,5*R*,6*R*)-3-(*tert*-butyldimethylsilanyloxy)-5-hydroxy-4,6-dimethyldodec-7-enyl]-4,4,7-

trimethyl-1,6-dioxaspiro[4.5]dec-3-yl ester bis-[2-(trimethylsilanyl)-ethyl] ester (132e): ^{1}H NMR δ 5.56-5.39 (m, 2 H), 4.83 (dd, 1 H, *J* = 8.0, 9.2 Hz), 4.20-4.10 (m, 4 H), 4.09-4.00 (m, 1 H), 3.96-3.88 (m, 1 H), 3.86-3.79 (m, 1 H), 3.75-3.62 (m, 2 H), 3.21 (s, 1 H), 2.25-2.17 (m, 1 H), 2.10-1.89 (m, 3 H), 1.84-1.70 (m, 3 H), 1.69-1.45 (m, 4 H), 1.40-1.23 (m, 7 H), 1.16-1.03 (m, 11 H), 0.96 (d, 3 H, *J* = 6.9 Hz), 0.93-0.85 (m, 24 H), 0.12-0.04 (m, 30 H); MS (ESI) *m/z* (relative intensity) 974 ([M+Na]$^+$, 100), 952 (30), 890 (10); HRMS (ESI) *m/z* calculated for $C_{47}H_{99}O_9NaPSi_4$ (M+Na) 973.6002, found 973.5988.

R = octyl; (2*R*,3*R*,5*S*,7*R*,9*S*)-Phosphoric acid 9-(*tert*-butyldimethylsilanyloxy)-2-[(3*S*,4*R*,5*R*,6*R*)-3-(*tert*-butyldimethylsilanyloxy)-5-hydroxy-4,6-dimethylhexadec-7-enyl]-4,4,7-trimethyl-1,6-dioxaspiro[4.5]dec-3-yl ester bis-[2-(trimethylsilanyl)-ethyl] ester (132f): ^{1}H NMR δ 5.55-5.38 (m, 2 H), 4.83 (dd, 1 H, *J* = 7.9, 9.1 Hz), 4.19-4.10 (m, 4 H), 4.09-4.01 (m, 1 H), 3.96-3.87 (m, 1 H), 3.85-3.80 (m, 1 H), 3.74-3.61 (m, 2 H), 3.20 (s, 1 H), 2.25-2.18 (m, 1 H), 2.08-1.89 (m, 3 H), 1.85-1.71 (m, 3 H), 1.70-1.45 (m, 4 H), 1.40-1.20 (m, 13 H), 1.18-1.05 (m, 12 H), 1.00-0.95 (m, 4 H), 0.92-0.87 (m, 24 H), 0.12-0.05 (m, 30 H); MS (ESI) *m/z* (relative intensity) 1030 ([M+Na]$^+$, 100), 974 (35); HRMS (ESI) *m/z* calculated for $C_{51}H_{107}O_9NaPSi_4$ (M+Na) 1029.6628, found 1029.6565.



Desired structure

General Procedure for the cross-metathesis reaction. A solution of **132f** (5.0 mg, 0.0050 mmol) in HF solution (0.4 mL, from the stock solution with 48% HF (0.5 mL), CH_3CN (4.5 mL), and water (0.5 mL)) was stirred at room temperature for 7 d. An additional HF solution (0.2 mL) was added after 3 d. N_2 gas was bubbled into the reaction mixture to remove the solvent and

the mixture was dried under reduced pressure. The residue was washed with $CHCl_3$ and water, and extracted with MeOH to give **133f** (2.0 mg, 0.0035 mmol, 70%).

R = phenyl; (2*R*,3*R*,5*S*,7*R*,9*S*)-Phosphoric acid mono-[2-((3*S*,4*R*,5*R*,6*R*)-3,5-dihydroxy-4,6-dimethyl-8-phenyloct-7-enyl)-9-hydroxy-4,4,7-trimethyl-1,6-dioxaspiro[4.5]dec-3-yl] ester (133a): ^{1}H NMR (600 MHz, CD_3OD) δ 7.37 (d, 2 H, *J* = 7.6 Hz), 7.25 (t, 2 H, *J* = 7.6 Hz), 7.15 (t, 1 H, *J* = 7.2 Hz), 6.43 (d, 1 H, *J* = 15.8 Hz), 6.28 (dd, 1 H, *J* = 8.3, 15.8 Hz), 4.75 (br, 1 H), 4.02-3.95 (m, 2 H), 3.80-3.75 (m, 2 H), 3.65 (br, 1 H), 2.45 (q, 1 H, *J* = 7.1 Hz), 1.98-1.88 (m, 3 H), 1.80-1.73 (m, 2 H), 1.54-1.45 (m, 2 H), 1.23 (t, 1 H, *J* = 11.6 Hz), 1.13 (d, 3 H, *J* = 6.2 Hz), 1.10 (s, 3 H), 1.07-1.03 (m, 1 H), 1.05 (d, 3 H, *J* = 6.8 Hz), 0.95 (d, 3 H, *J* = 6.5 Hz), 0.95 (s, 3 H).

R = 4-chlorophenyl; (2*R*,3*R*,5*S*,7*R*,9*S*)-Phosphoric acid mono-[2-((3*S*,4*R*,5*R*,6*R*)-8-(4-chlorophenyl)-3,5-dihydroxy-4,6-dimethyloct-7-enyl)-9-hydroxy-4,4,7-trimethyl-1,6-dioxaspiro[4.5]dec-3-yl] ester (133b): ^{1}H NMR (600 MHz, CD_3OD) δ 7.36 (d, 2 H, *J* = 8.5 Hz), 7.26 (d, 2 H, *J* = 8.5 Hz), 6.41 (d, 1 H, *J* = 15.9 Hz), 6.29 (dd, 1 H, *J* = 8.3, 15.9 Hz), 4.76 (br, 1 H), 4.05-3.95 (m, 2 H), 3.78-3.74 (m, 2 H), 3.68-3.63 (m, 1 H), 2.45 (q, 1 H, *J* = 7.3 Hz), 2.00-1.88 (m, 3 H), 1.79-1.73 (m, 2 H), 1.55-1.45 (m, 2 H), 1.23 (t, 1 H, *J* = 11.5 Hz), 1.13 (d, 3 H, *J* = 6.2 Hz), 1.09 (s, 3 H), 1.08-1.02 (m, 1 H), 1.04 (d, 3 H, *J* = 6.8 Hz), 0.96-0.94 (m, 6 H).

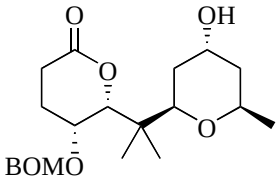
R = 4-methoxyphenyl; (2*R*,3*R*,5*S*,7*R*,9*S*)-Phosphoric acid mono-[2-((3*S*,4*R*,5*R*,6*R*)-3,5-dihydroxy-4,6-dimethyloct-7-enyl)-9-hydroxy-8-(4-methoxyphenyl)-4,4,7-trimethyl-1,6-dioxaspiro[4.5]dec-3-yl] ester (133c): ^{1}H NMR (600 MHz, CD_3OD) δ 7.30 (d, 2 H, *J* = 8.7 Hz), 6.83 (d, 2 H, *J* = 8.6 Hz), 6.37 (d, 1 H, *J* = 15.6 Hz), 6.11 (dd, 1 H, *J* = 8.1, 15.6 Hz), 4.75 (br, 1 H), 4.02-3.94 (m, 2 H), 3.80-3.72 (m, 3 H), 3.76 (s, 3 H), 2.41 (q, 1 H, *J* = 7.2 Hz), 1.97-1.87 (m,

3 H), 1.80-1.74 (m, 2 H), 1.56-1.46 (m, 2 H), 1.23 (t, 1 H, *J* = 11.5 Hz), 1.13 (d, 3 H, *J* = 6.2 Hz), 1.10 (s, 3 H), 1.06-1.03 (m, 4 H), 0.97-0.94 (m, 6 H).

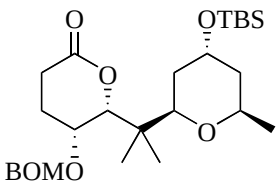
R = cyclohexyl; (2*R*,3*R*,5*S*,7*R*,9*S*)-Phosphoric acid mono-[2-((3*S*,4*R*,5*R*,6*R*)-8-cyclohexyl-3,5-dihydroxy-4,6-dimethyloct-7-enyl)-9-hydroxy-4,4,7-trimethyl-1,6-dioxaspiro[4.5]dec-3-yl] ester (133d): ^{1}H NMR (600 MHz, CD_3OD) δ 5.49-5.37 (m, 2 H), 4.76 (dd, 1 H, *J* = 7.7, 9.8 Hz), 4.00-3.95 (m, 2 H), 3.78-3.75 (m, 1 H), 3.65-3.58 (m, 2 H), 2.18 (q, 1 H, *J* = 6.2 Hz), 1.95-1.87 (m, 4 H), 1.77-1.63 (m, 6 H), 1.55-1.44 (m, 2 H), 1.32-1.15 (m, 5 H), 1.13 (d, 3 H, *J* = 6.2 Hz), 1.09 (s, 3 H), 1.07-1.01 (m, 3 H), 0.95-0.90 (m, 9 H).

R = butyl; (2*R*,3*R*,5*S*,7*R*,9*S*)-Phosphoric acid mono-[2-((3*S*,4*R*,5*R*,6*R*)-3,5-dihydroxy-4,6-dimethyldodec-7-enyl)-9-hydroxy-4,4,7-trimethyl-1,6-dioxaspiro[4.5]dec-3-yl] ester (133e): ^{1}H NMR (600 MHz, CD_3OD) δ 5.49-5.40 (m, 2 H), 4.76 (dd, 1 H, *J* = 7.3, 9.3 Hz), 4.00-3.95 (m, 2 H), 3.80-3.74 (m, 1 H), 3.64-3.58 (m, 2 H), 2.21 (q, 1 H, *J* = 7.5 Hz), 2.04-1.98 (m, 2 H), 1.93-1.88 (m, 3 H), 1.80-1.73 (m, 1 H), 1.71-1.66 (m, 1 H), 1.51-1.44 (m, 1 H), 1.41-1.28 (m, 5 H), 1.23 (t, 1 H, *J* = 12.0 Hz), 1.13 (d, 3 H, *J* = 6.3 Hz), 1.09 (s, 3 H), 1.05 (q, 1 H, *J* = 12.0 Hz), 0.95 (s, 3 H), 0.93-0.88 (m, 9 H).

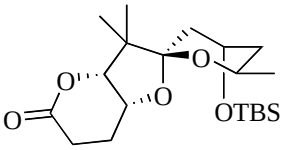
R = octyl; (2*R*,3*R*,5*S*,7*R*,9*S*)-Phosphoric acid mono-[2-((3*S*,4*R*,5*R*,6*R*)-3,5-dihydroxy-4,6-dimethylhexadec-7-enyl)-9-hydroxy-4,4,7-trimethyl-1,6-dioxaspiro[4.5]dec-3-yl] ester (133f): ^{1}H NMR (600 MHz, CD_3OD) δ 5.49-5.40 (m, 2 H), 4.75 (br, 1 H), 4.00-3.95 (m, 2 H), 3.79-3.75 (m, 1 H), 3.67-3.59 (m, 2 H), 2.21 (q, 1 H, *J* = 7.2 Hz), 2.09-1.96 (m, 2 H), 1.95-1.87 (m, 3 H), 1.82-1.71 (m, 1 H), 1.70-1.65 (m, 1 H), 1.54-1.45 (m, 1 H), 1.39-1.28 (m, 13 H), 1.23 (t, 1 H, *J* = 11.8 Hz), 1.13 (d, 3 H, *J* = 6.2 Hz), 1.09 (s, 3 H), 1.04 (q, 1 H, *J* = 11.8 Hz), 0.96-0.87 (m, 12 H).



(5*R*,6*R*)-5-((Benzyloxy)methoxy)tetrahydro-6-(2-((2*R*,4*R*,6*R*)-tetrahydro-4-hydroxy-6-methyl-2*H*-pyran-2-yl)propan-2-yl)pyran-2-one (134). To a solution of **119** (65 mg, 0. 17 mmol) in THF (6.5 mL) was added L-Selectride (1 M in THF, 0.17 mL, 0.17 mmol) at –78 ºC, and the mixture was stirred for 1 h at –78 ºC. The reaction mixture was quenched with saturated aqueous NH_4Cl and warmed up to room temperature. The aqueous layer was extracted with EtOAc (3x25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (CH_2Cl_2/EtOAc, 20:1-10:1) to give the major product **134** (29 mg, 0.074 mmol, 44%) and the minor product **120** (16 mg, 0.046mmol, 27%) as colorless oils. **134**: $[\alpha]_D$ –8.9 (*c* 0.45, $CHCl_3$); IR (neat) 3451, 2965, 2931, 2879, 1720, 1454, 1365, 1250, 1025 cm^{-1}; ^1H NMR δ 7.38-7.29 (m, 5 H), 4.89, 4.83 (AB, 2 H, *J* = 7.2 Hz), 4.73, 4.66 (AB, 2 H, *J* = 12.0 Hz), 4.35 (d, 1 H, *J* = 1.2 Hz), 4.30-4.24 (m, 2 H), 3.89-3.83 (m, 1 H), 3.80 (dd, 1 H, *J* = 4.0, 9.7 Hz), 2.68 (ddd, 1 H, *J* = 7.5, 10.8, 18.2 Hz), 2.57 (ddd, 1 H, *J* = 3.1, 7.9, 18.1 Hz), 2.32-2.23 (m, 1 H), 1.95-1.84 (m, 1 H), 1.68-1.58 (m, 3 H), 1.56-1.47 (m, 1 H), 1.42 (ddd, 1 H, *J* = 2.8, 11.4, 14.0), 1.09 (d, 3 H, *J* = 6.5 Hz), 1.08 (s, 3 H), 1.05 (s, 3 H); ^{13}C NMR δ 171.7, 137.7, 128.7, 128.1, 127.9, 93.5, 85.7, 76.2, 70.9, 69.2, 68.2, 65.1, 40.8, 40.4, 32.5, 25.8, 25.0, 22.1, 20.5, 19.9; MS (ESI) *m/z* (relative intensity) 415 ($[M+Na]^+$, 100), 381 (20), 353 (11), 279 (6); HRMS (ESI) *m/z* calculated for $C_{22}H_{32}O_6Na$ (M+Na) 415.2097, found 415.2117.

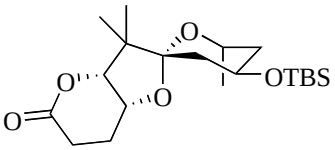


(5*R*,6*R*)-5-((Benzyloxy)methoxy)tetrahydro-6-(2-((2*R*,4*R*,6*R*)-tetrahydro-6-methyl-4-(*tert*-butyldimethylsilanyloxy)-2*H*-pyran-2-yl)propan-2-yl)pyran-2-one (135). To a solution of **134** (29 mg, 0.074 mmol) and imidazole (40 mg, 0.59 mmol) in DMF (1 mL) was added TBSCl (40 mg, 0.27 mmol). The mixture was stirred overnight and water was added. The aqueous layer was extracted with EtOAc (3x25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexane/EtOAc, 10:1) to give **135** (27 mg, 0.53 mmol, 72%) as a colorless oil: $[\alpha]_D$ +26 (*c* 0.76, $CHCl_3$); IR (neat) 2950, 2929, 2856, 1740, 1471, 1361, 1249, 1099, 1036, 836 cm^{-1}; ^1H NMR δ 7.39-7.28 (m, 5 H), 4.86 (s, 2 H), 4.72, 4.59 (AB, 2 H, *J* = 11.9 Hz), 4.33 (br. s, 1 H), 4.23-4.20 (m, 1 H), 4.18-4.16 (m, 1 H), 3.89-3.78 (m, 1 H), 3.73 (dd, 1 H, *J* = 3.5, 9.5 Hz), 2.72 (ddd, 1 H, *J* = 7.7, 10.8, 18.3 Hz), 2.57 (ddd, 1 H, *J* = 2.9, 7.8, 18.1 Hz), 2.34-2.24 (m, 1 H), 1.97-1.85 (m, 1 H), 1.59-1.49 (m, 3 H), 1.34 (ddd, 1 H, *J* = 2.4, 11.3, 13.5 Hz), 1.08 (d, 3 H, *J* = 6.3 Hz), 1.05 (s, 3 H), 1.00 (s, 3 H), 0.88 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR δ 171.8, 137.6, 128.8, 128.1, 128.0, 95.0, 85.8, 71.2, 70.7, 68.5, 65.5, 41.3, 40.7, 33.2, 26.1 (2C), 26.0, 22.2, 20.5, 19.9, 18.2, –4.7 (DEPT shows that one peak is overlapped with solvent); MS (ESI) *m/z* (relative intensity) 1036 ($[2M+Na]^+$, 8), 529 (100); HRMS (ESI) *m/z* calculated for $C_{28}H_{46}O_6NaSi$ (M+Na) 529.2961, found 529.2972.



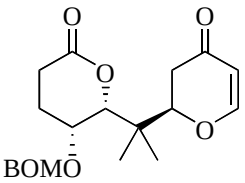
(2*R*,3*R*,5*S*,7*R*,9*R*)-9-(*tert*-Butyldimethylsilanyloxy)-(hexahydrofuro[3,2-*b*]pyran-5-onyl)-4,4,7-trimethyl-1,6-dioxaspiro[4.5]decane (136). To a solution of **135** (39 mg, 0.077 mmol) in THF (5 mL) was added $Pd(OH)_2/C$ (20 wt%, 10 mg). The mixture was stirred under H_2 gas for 5 h and filtered through celite pad. The filtrate was concentrated and dried *in vacuo*. The alcohol was used without further purification. To a solution of the crude alcohol (35 mg) in cyclohexane

(8 mL) were added iodobenzene diacetate (74 mg, 0.23 mmol) and I_2 (59 mg, 0.23 mmol). The reaction mixture was stirred for 3 h at room temperature under irradiation by light (250 W), quenched with saturated aqueous $Na_2S_2O_3$, and stirred for 30 min. The aqueous layer was extracted with EtOAc (3×25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexane/ethyl ether, 10:1-4:1) to give the major product **136** (17 mg, 0.044 mmol, 57% over 2 steps) as a waxy solid and the minor product **137** (5.0 mg, 0.013mmol, 17% over 2 steps) as a colorless oil. **136**: $[\alpha]_D$ +38 (*c* 1.0, $CHCl_3$); IR (neat) 2954, 2928, 2855, 1751, 1472, 1379, 1250, 1151, 1111, 1054, 996, 837 cm^{-1}; ^1H NMR (acetone-d_6) δ 4.67 (d, 1 H, *J* = 7.6 Hz), 4.32 (dd, 1 H, *J* = 5.8, 7.4 Hz), 4.29-4.21 (m, 2 H), 2.44 (ddd, 1 H, *J* = 4.6, 7.8, 16.8 Hz), 2.34 (ddd, 1 H, *J* = 4.3, 9.1, 16.8 Hz), 2.14-2.07 (m, 1 H), 1.87-1.75 (m, 1 H), 1.67-1.65 (m, 2 H), 1.62-1.54 (m, 1 H), 1.37 (ddd, 1 H, *J* = 2.8, 11.2, 13.8 Hz), 1.08 (d, 3 H, *J* = 6.2 Hz), 1.07 (s, 3 H), 0.90 (s, 9 H), 0.85 (s, 3 H), 0.07 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (150 MHz) δ 172.5, 107.3, 88.4, 69.3, 64.6, 61.1, 50.7, 40.4, 33.8, 27.2, 25.9, 24.0, 21.6, 21.4, 18.9, 18.2, –4.5, –4.6; MS (ESI) *m/z* (relative intensity) 792 ($[2M+Na]^+$, 25), 407 (95); HRMS (ESI) *m/z* calculated for $C_{20}H_{36}O_5NaSi$ (M+Na) 407.2230, found 407.2251.



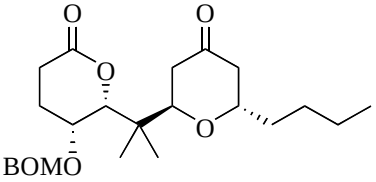
(2*R*,3*R*,5*R*,7*R*,9*R*)-9-(*tert*-Butyldimethylsilanyloxy)-(hexahydrofuro[3,2-*b*]pyran-5-onyl)-4,4,7-trimethyl-1,6-dioxaspiro[4.5]decane (137): $[\alpha]_D$ –13 (*c* 0.50, $CHCl_3$); IR (neat) 2950, 2928, 2853, 1738, 1384, 1257, 1173, 1105, 1061, 1038, 958 cm^{-1}; ^1H NMR δ 4.49-4.45 (m, 1 H), 4.34 (d, 1 H, *J* = 5.2 Hz), 4.29-4.18 (m, 1 H), 4.06-3.96 (m, 1 H), 2.82 (ddd, 1 H, *J* = 5.7, 13.1, 17.8 Hz), 2.38 (dt, 1 H, *J* = 3.8, 17.3 Hz), 2.15-2.06 (m, 1 H), 1.98-1.80 (m, 3 H), 1.69 (dd, 1 H,

J = 8.8, 13.5 Hz), 1.52-1.47 (m, 1 H), 1.19 (s, 3 H), 1.15 (d, 3 H, *J* = 6.3 Hz), 1.01 (s, 3 H), 0.90 (s, 9 H), 0.08 (s, 6 H); ^{13}C NMR (125 MHz) δ 171.2, 110.0, 89.2, 71.6, 67.3, 63.5, 50.8, 41.0, 35.7, 26.1, 25.8, 23.9, 23.6, 21.7, 18.3, 17.5, -4.4; MS (ESI) *m/z* (relative intensity) 792 ([2M+Na]$^+$, 5), 407 (48); HRMS (ESI) *m/z* calculated for $C_{20}H_{36}O_5NaSi$ (M+Na) 407.2230, found 407.2236.

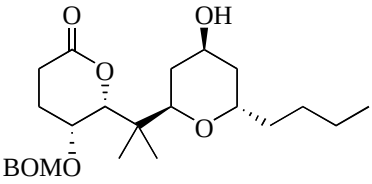


(*R*)-2-(2-((2*R*,3*R*)-3-((Benzyloxy)methoxy)tetrahydro-6-oxo-2*H*-pyran-2-yl)propan-2-yl)-2,3-dihydropyran-4-one (139). To a solution of **98** (1.80 g, 3.98 mmol) and the diene **138** (2.27 g, 9.94 mmol) in toluene (30 mL) was added BF_3•OEt_2 (0.76 mL, 6.0 mmol) at –78 ºC dropwise. The reaction mixture was stirred for 3 h at –78 ºC, quenched with saturated aqueous $NaHCO_3$, warmed up to room temperature, and extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. To a solution of crude **143** in CH_2Cl_2 (80 mL) was added TFA (4 mL) at 0 ºC dropwise. The reaction mixture was stirred for 2 h at room temperature, quenched with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (3x50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (CH_2Cl_2/EtOAc, 10:1-4:1) to give **139** (450 mg, 1.20 mmol, 30%) as a yellow oil: $[\alpha]_D$ –55 (*c* 0.50, $CHCl_3$); IR (neat) 2925, 1736, 1676, 1596, 1454, 1406, 1368, 1234, 1108, 1025 cm^{-1}; ^{1}H NMR δ 7.39-7.27 (m, 6 H), 5.42 (d, 1 H, *J* = 5.9 Hz), 4.87, 4.80 (AB, 2 H, *J* = 7.1 Hz), 4.64 (s, 2 H), 4.47 (dd, 1 H, *J* = 2.8, 15.0 Hz), 4.29 (br. s, 1 H), 4.25 (br. s, 1 H), 2.78-2.49 (m, 4 H), 2.35-2.27 (m, 1 H), 1.96-1.84 (m, 1 H), 1.23 (s, 3 H), 1.15 (s, 3 H); ^{13}C NMR δ 192.9, 170.3, 162.9, 137.2, 128.8, 128.3, 127.8, 107.6, 93.3, 84.6, 84.3, 71.2, 68.8, 41.1, 37.8,

25.6, 24.7, 20.5, 19.6; MS (ESI) *m/z* (relative intensity) 772 ($[2M+Na]^+$, 38), 397 (100); HRMS (ESI) *m/z* calculated for $C_{21}H_{26}O_6Na$ (M+Na) 397.1627, found 397.1646.



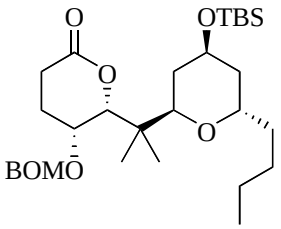
(5*R*,6*R*)-5-((Benzyloxy)methoxy)-6-(2-((2*R*,6*S*)-6-butyltetrahydro-4-oxo-2*H*-pyran-2-yl)propan-2-yl)tetrahydropyran-2-one (140). To a suspension of CuI (84 mg, 0.44 mmol) in THF (4 mL) was added *n*-BuLi (1.6 M in hexane, 0.55 mL, 0.88 mmol) at 0 ºC dropwise. After stirring for 5 min, the mixture was cooled to –78 ºC. A solution of **139** (110 mg, 0.294 mmol) in THF (1 mL) was added to this solution at –78 ºC dropwise. After an additional 30 min at –78 ºC, the mixture was quenched with saturated aqueous NH_4Cl and warmed up to room temperature. The mixture was filtered through celite pad and washed with EtOAc. The organic filtrate was washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on SiO_2 (CH_2Cl_2/EtOAc, 20:1) to give **140** (66 mg, 0.15 mmol, 51%) as a colorless oil: $[\alpha]_D$ –7.4 (*c* 0.53, $CHCl_3$); IR (neat) 2960, 2929, 2872, 2853, 1732, 1454, 1365, 1260, 1024, 801 cm^{-1}; ^1H NMR (acetone-d_6) δ 7.40-7.25 (m, 5 H), 4.87, 4.79 (AB, 2 H, *J* = 7.2 Hz), 4.65 (s, 2 H), 4.40 (d, 1 H, *J* = 1.0 Hz), 4.29-4.24 (m, 1 H), 4.23-4.19 (m, 1 H), 3.85 (dd, 1 H, *J* = 2.9, 11.8 Hz), 2.75-2.53 (m, 3 H), 2.46-2.39 (m, 1 H), 2.34-2.27 (m, 1 H), 2.22 (ddd, 1 H, *J* = 1.3, 3.8, 14.7 Hz), 1.97-1.85 (m, 1 H), 1.62-1.53 (m, 1 H), 1.43-1.23 (m, 6 H), 1.16 (s, 3 H), 1.09 (s, 3 H), 0.89 (t, 3 H, *J* = 6.6 Hz); ^{13}C NMR δ 208.4, 170.9, 137.3, 128.8, 128.2, 127.8, 93.3, 84.3, 75.3, 73.9, 71.0, 69.1, 45.8, 43.0, 41.5, 32.8, 28.1, 25.6, 24.7, 22.5, 20.6, 20.0, 14.2; MS (ESI) *m/z* (relative intensity) 455 ($[M+Na]^+$, 100), 403 (4), 399 (7); HRMS (ESI) *m/z* calculated for $C_{25}H_{36}O_6Na$ (M+Na) 455.2410, found 455.2425.



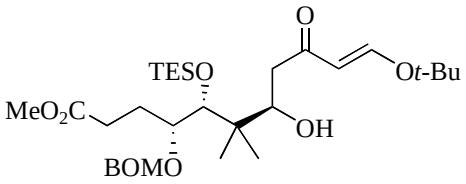
(5*R*,6*R*)-5-((Benzyloxy)methoxy)-6-(2-((2*R*,4*S*,6*S*)-6-butyltetrahydro-4-hydroxy-2*H*-pyran-2-yl)propan-2-yl)tetrahydropyran-2-one (141). To a solution of **140** (65 mg, 0.15 mmol) in THF (6 mL) was added $NaBH_4$ (11 mg, 0.30 mmol) at 0 ºC. The mixture was stirred for 7 h at room temperature, treated with saturated aqueous NH_4Cl, and extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (CH_2Cl_2/EtOAc, 10:1-4:1) to give a 1:1 mixture of two separable diastereomers **141** and **158** (40 mg, 0.092 mmol, 81% based on recovered starting material) along with recovered **140** (16 mg, 0.037 mmol, 25 %) as a colorless oil.

The alcohol **141** was also prepared by following procedure: to a solution of **146** (110 mg, 0.189 mmol) in THF (5 mL) was added HF•pyridine (0.5 mL) at 0 ºC. The mixture was stirred at room temperature for 36 h and diluted with ethyl ether. The organic layer was washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (3x30 mL). The combined organic layers were washed with saturated aqueous NH_4Cl, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on SiO_2 (CH_2Cl_2/EtOAc, 4:1) to give the desired lactone **141** (82 mg, 0.19 mmol, 100%) as a colorless oil: $[\alpha]_D$ –32 (*c* 1.0, $CHCl_3$); IR (neat) 3391, 2930, 2868, 1736, 1454, 1366, 1249, 1024 cm^{-1}; ^1H NMR δ 7.40-7.29 (m, 5 H), 4.87, 4.79 (AB, 2 H, *J* = 7.2 Hz), 4.65 (s, 2 H), 4.31 (br. s, 1 H), 4.27 (br. s, 1 H), 4.01-3.93 (m, 1 H), 3.72 (dt, 1 H, *J* = 4.5, 11.0 Hz), 3.48 (dd, 1 H, *J* = 1.6, 11.7 Hz), 2.68 (ddd, 1 H, *J* = 7.7, 10.5, 18.1 Hz), 2.57 (ddd, 1 H, *J* = 3.3, 8.3, 18.4 Hz), 2.29-2.20 (m, 1 H), 1.98-1.86 (m, 2 H), 1.85-1.79 (m ,1 H), 1.68-1.47 (m, 2 H), 1.41-1.21 (m, 6 H), 1.12 (s, 3 H), 1.07 (s, 3 H), 0.90 (t, 3 H, *J* = 6.5

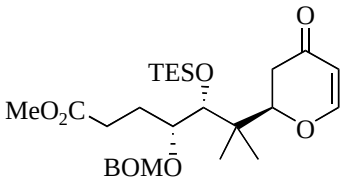
Hz); ^{13}C NMR (acetone-d_6) δ 171.2, 139.5, 129.6, 128.8, 128.7, 94.4, 85.3, 74.8, 74.0, 71.6, 70.0, 65.1, 42.0, 39.9, 37.2, 32.1, 26.6, 25.6, 23.6, 21.3, 20.5, 14.8 (DEPT shows that one peak is inside solvent); MS (ESI) *m/z* (relative intensity) 457 ([M+Na]$^+$, 100), 413 (10); HRMS (ESI) *m/z* calculated for $C_{25}H_{38}O_6Na$ (M+Na) 457.2566, found 457.2587.



(5*R*,6*R*)-5-((Benzyloxy)methoxy)-6-(2-((2*R*,4*S*,6*S*)-6-butyltetrahydro-4-(*tert*-butyldimethylsilanyloxy)-2*H*-pyran-2-yl)propan-2-yl)tetrahydropyran-2-one (142). To a solution of **141** (20 mg, 0.046 mmol) and imidazole (50 mg, 0.73 mmol) in DMF (0.5 mL) was added TBSCl (50 mg, 0.33 mmol). The mixture was stirred overnight and water was added. The aqueous layer was extracted with EtOAc (3x20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexane/EtOAc, 10:1) to give **142** (26 mg, 0.47 mmol, 100%) as a colorless oil: $[\alpha]_D$ –21 (*c* 0.99, $CHCl_3$); IR (neat) 2954, 2931, 2857, 1736, 1471, 1362, 1249, 1095, 1026, 836 cm^{-1}; ^{1}H NMR δ 7.37-7.31 (m, 5 H), 4.87, 4.80 (AB, 2 H, *J* = 7.2 Hz), 4.66 (s, 2 H), 4.30 (br. s, 1 H), 4.28 (s, 1 H), 3.96-3.88 (m, 1 H), 3.86-3.79 (m, 1 H), 3.51 (d, 1 H, *J* = 10.9 Hz), 2.68 (ddd, 1 H, *J* = 7.8, 10.2, 18.5 Hz), 2.57 (ddd, 1 H, *J* = 3.1, 8.2, 18.1 Hz), 1.95-1.80 (m, 2 H), 1.76-1.53 (m, 3 H), 1.40-1.20 (m, 6 H), 1.12 (s, 3 H), 1.06 (s, 3 H), 0.89 (br. s, 12 H), 0.06 (s, 3 H), 0.05 (s, 3 H); ^{13}C NMR δ 171.2, 137.6, 128.7, 128.0, 127.6, 93.5, 84.9, 73.6, 73.4, 70.8, 69.2, 66.0, 41.1, 39.0, 36.3, 31.1, 29.2, 26.0, 25.8, 25.0, 22.6, 20.7, 19.8, 18.3, 14.2, –4.3, –4.4; MS (ESI) *m/z* (relative intensity) 571 ([M+Na]$^+$, 100), 555 (3), 467 (15); HRMS (ESI) *m/z* calculated for $C_{31}H_{52}O_6NaSi$ (M+Na) 571.3431, found 571.3444.

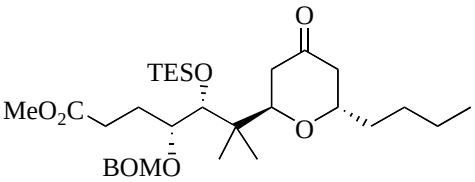


(*E*,4*R*,5*R*,7*R*)-Methyl-4-((benzyloxy)methoxy)-11-*tert*-butoxy-7-hydroxy-6,6-dimethyl-9-oxo-5-(triethylsilanyloxy)undec-10-enoate (143). To a solution of **98** (0.40 g, 0.88 mmol) and the diene **138** (0.60 g, 2.7 mmol) in CH_2Cl_2 (10 mL) was added BF_3•OEt_2 (0.15 mL, 1.2 mmol) at –78 ºC dropwise. The reaction mixture was stirred for 2 h at –78 ºC, quenched with saturated aqueous $NaHCO_3$, warmed up to room temperature, and extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexane/EtOAc, 10:1) to give **143** (0.20 g, 0.34 mmol, 39%) as a yellow oil: $[\alpha]_D$ +41 (*c* 1.0, $CHCl_3$); IR (neat) 3469, 2953, 2909, 2873, 1738, 1673, 1631, 1595, 1373, 1163, 1027 cm^{-1}; ^1H NMR (acetone-d_6) δ 7.79 (d, 1 H, *J* = 12.0 Hz), 7.34-7.25 (m, 5 H), 5.66 (d, 1 H, *J* = 12.1 Hz), 4.84, 4.80 (AB, 2 H, *J* = 6.7 Hz), 4.68, 4.58 (AB, 2 H, *J* = 12.0 Hz), 4.13 (ddd, 1 H, *J* = 2.1, 3.6, 9.8 Hz), 3.84-3.78 (m, 2 H), 3.58 (s, 3 H), 2.72 (dd, 1 H, *J* = 2.0, 16.1 Hz), 2.56-2.33 (m, 3 H), 2.05-1.85 (m, 2 H), 1.35 (s, 9 H), 0.98 (t, 9 H, *J* = 8.0 Hz), 0.96 (s, 3 H), 0.89 (s, 3 H), 0.66 (q, 6 H, *J* = 7.9 Hz); ^{13}C NMR δ 193.6, 173.8, 163.4, 137.9, 128.6, 127.9, 127.8, 107.4, 94.2, 83.2, 77.4, 76.9, 76.6, 70.2, 51.8, 42.1, 37.7, 31.6, 28.7, 28.4, 21.0, 19.3, 7.2, 5.5; MS (ESI) *m/z* (relative intensity) 618 ($[M+Na]^+$, 100), 561 (4), 544 (4); HRMS (ESI) *m/z* calculated for $C_{32}H_{54}O_8NaSi$ (M+Na) 617.3486, found 617.3502.



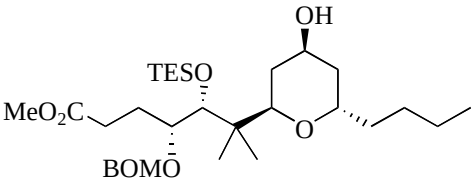
(4*R*,5*R*)-Methyl-4-((benzyloxy)methoxy)-6-((*R*)-3,4-dihydro-4-oxo-2*H*-pyran-2-yl)-6-methyl-5-(triethylsilanyloxy)heptanoate (144). To a solution of **143** (122 mg, 0.205 mmol) in

CH_2Cl_2 (5 mL) was added PPTS (26 mg, 0.11 mmol) at 0 ºC. The reaction mixture was stirred for 6 h at room temperature. The organic layer was washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on SiO_2 (CH_2Cl_2/EtOAc, 10:1) to give the desired pyrone **144** (92 mg, 0.18 mmol, 86%) as a yellow oil: $[\alpha]_D$ +48 (c 0.95, $CHCl_3$); IR (neat) 2953, 2911, 2877, 1739, 1679, 1597, 1456, 1404, 1276, 1040 cm^{-1}; ^1H NMR δ 7.38-7.26 (m, 6 H), 5.39 (d, 1 H, *J* = 5.9 Hz), 4.79, 4.71 (AB, 2 H, *J* = 6.9 Hz), 4.69, 4.54 (AB, 2 H, *J* = 12.1 Hz), 4.60 (dd, 1 H, *J* = 3.1, 15.0 Hz), 3.80-3.75 (m, 2 H), 3.63 (s, 3 H), 2.65-2.34 (m, 4 H), 2.00-1.81 (m, 2 H), 1.07 (s, 3 H), 0.98 (t, 9 H, *J* = 8.0 Hz), 0.96 (s, 3 H), 0.63 (q, 6 H, J = 7.8 Hz); ^{13}C NMR δ 193.4, 173.8, 163.3, 138.0, 128.6, 127.85, 127.78, 107.4, 94.3, 83.3, 77.1, 76.7, 70.2, 51.7, 42.2, 37.8, 31.6, 28.7, 21.0, 19.4, 7.2, 5.6; MS (ESI) *m/z* (relative intensity) 543 ($[M+Na]^+$, 100), 479 (4), 339 (9); HRMS (ESI) *m/z* calculated for $C_{28}H_{44}O_7NaSi$ (M+Na) 543.2754, found 543.2778.



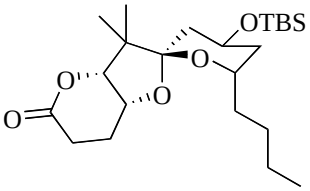
(4*R*,5*R*)-Methyl-4-((benzyloxy)methoxy)-6-((2*R*,6*S*)-6-butyl-tetrahydro-4-oxo-2*H*-pyran-2-yl)-6-methyl-5-(triethylsilanyloxy)heptanoate (145). To a suspension of CuI (146 mg, 0.767 mmol) in THF (8 mL) was added *n*-BuLi (1.42 M in hexane, 1.08 mL, 1.53 mmol) at 0 ºC dropwise. After stirring for 5 min, the mixture was cooled to –78 ºC. A solution of **144** (200 mg, 0.384 mmol) in THF (2 mL) was added to this solution at –78 ºC dropwise. After an additional 30 min at –78 ºC, the mixture was quenched with saturated aqueous NH_4Cl and warmed up to room temperature. The mixture was filtered through celite pad and washed with EtOAc. The organic filtrate was washed with brine, dried ($MgSO_4$), and concentrated. The residue was

purified by chromatography on SiO_2 (hexane/EtOAc, 20:1) to give **145** (180 mg, 0.311 mmol, 81%) as a yellow oil: $[\alpha]_D$ +62 (*c* 1.0, $CHCl_3$); IR (neat) 2955, 2930, 2876, 1736, 1716, 1457, 1363, 1239, 1162, 1037, 825 cm^{-1}; ^1H NMR δ 7.35-7.26 (m, 5 H), 4.78, 4.75 (AB, 2 H, *J* = 7.0 Hz), 4.70, 4.56 (AB, 2 H, *J* = 12.0 Hz), 4.20 (dt, 1 H, *J* = 4.9, 13.4 Hz), 3.96 (dd, 1 H, *J* = 4.3, 10.2 Hz), 3. 75 (qn, 1 H, *J* = 4.3 Hz), 3.63 (s, 3 H), 3.626 (d, 1 H, *J* = 3.8 Hz), 2.57 (dd, 1 H, *J* = 5.9, 15.0 Hz), 2.52-2.35 (m, 3 H), 2.26 (dd, 1 H, *J* = 4.6, 15.0 Hz), 1.97-1.83 (m, 2 H), 1.62-1.51 (m, 1 H), 1.40-1.24 (m, 6 H), 1.03 (s, 3 H), 0.98 (t, 9 H, *J* = 8.0 Hz), 0.92 (s, 3 H), 0.89 (t, 3 H, *J* = 6.7 Hz), 0.64 (q, 6 H, *J* = 8.0 Hz); ^{13}C NMR δ 209.1, 173.9, 138.1, 128.5, 127.8, 94.7, 77.5, 76.5, 73.9, 73.3, 70.2, 51.6, 46.0, 42.8, 42.5, 33.4, 31.4, 29.5, 28.0, 22.6, 20.5, 18.8, 14.1, 7.2, 5.7; MS (ESI) *m/z* (relative intensity) 601 ($[M+Na]^+$, 100), 598 (10); HRMS (ESI) *m/z* calculated for $C_{32}H_{54}O_7NaSi$ (M+Na) 601.3537, found 601.3558.



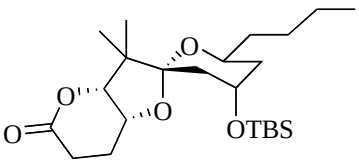
(4*R*,5*R*)-Methyl-4-((benzyloxy)methoxy)-6-((2*R*,4*S*,6*S*)-6-butyl-tetrahydro-4-hydroxy-2*H*-pyran-2-yl)-6-methyl-5-(triethylsilanyloxy)heptanoate (146). To a solution of **145** (175 mg, 0.302 mmol) and $CeCl_3 \cdot 7H_2O$ (113 mg, 0.302 mmol) in MeOH (10 mL) was added $NaBH_4$ (12.3 mg, 0.332 mmol) at –78 ºC and the mixture was stirred for 30 min at –78 ºC. The reaction mixture was quenched with saturated aqueous NH_4Cl and warmed up to room temperature. The organic layer was extracted with CH_2Cl_2 (3x25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (CH_2Cl_2/EtOAc, 10:1-4:1) to give a 3.7:1 mixture of two separable diastereomers **146** and **158** (125 mg, 0.215 mmol, 90% based on recovered starting material) with the recovered **145** (34 mg,

0.059 mmol, 19%) as a colorless oil: $[\alpha]_D$ +30 (*c* 1.5, $CHCl_3$); IR (neat) 3453, 2953, 2873, 1741, 1455, 1364, 1240, 1148, 1120, 1037, 828 cm^{-1}; ^1H NMR δ 7.36-7.29 (m, 5 H), 4.79 (s, 2 H), 4.70, 4.59 (AB, 2 H, *J* = 12.0 Hz), 4.01-3.94 (m, 1 H), 3.87 (tt, 1 H, *J* = 4.4, 10.9 Hz), 3. 74 (dt, 1 H, *J* = 4.6, 6.3 Hz), 3.65 (s, 3 H), 3.60 (d, 1 H, *J* = 4.4 Hz), 3.50 (dd, 1 H, *J* = 1.3, 11.4 Hz), 2.53 (dt, 1 H, *J* = 7.5, 16.3 Hz), 2.40 (dt, 1 H, *J* = 7.7, 16.3 Hz), 1.94-1.80 (m, 4 H), 1.69-1.61 (m, 1 H), 1.51 (dt, 1 H, *J* = 6.0, 12.0 Hz), 1.43-1.22 (m, 6 H), 1.18 (q, 1 H, *J* = 11.3 Hz), 0.99 (t, 9 H, *J* = 8.1 Hz), 0.99 (s, 3 H), 0.90 (s, 3 H), 0.89 (t, 3 H, *J* = 6.6 Hz), 0.65 (q, 6 H, *J* = 7.7 Hz); ^{13}C NMR δ 174.0, 138.3, 128.5, 127.8, 127.7, 94.9, 77.7, 76.7, 73.2, 72.2, 70.2, 65.5, 51.6, 42.2, 38.5, 36.3, 31.5, 31.3, 29.7, 28.7, 22.7, 20.7, 19.0, 14.2, 7.3, 5.8; MS (ESI) *m/z* (relative intensity) 604 ($[M+Na]^+$, 100), 541 (10), 463 (5); HRMS (ESI) *m/z* calculated for $C_{32}H_{56}O_7NaSi$ (M+Na) 603.3693, found 603.3710

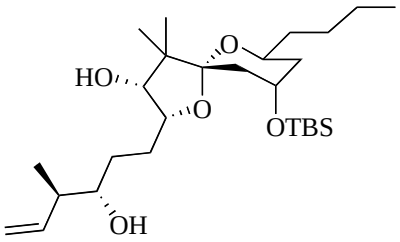


(2*R*,3*R*,5*S*,7*S*,9*S*)-7-Butyl-9-(*tert*-butyldimethylsilanyloxy)-(hexahydrofuro[3,2-*b*]pyran-5-onyl)-4,4-dimethyl-1,6-dioxaspiro[4.5]decane (147). To a solution of **142** (105 mg, 0.191 mmol) in THF (10 mL) was added $Pd(OH)_2/C$ (20 wt %, 20 mg). The mixture was stirred under H_2 gas for 3 h and then filtered through celite pad. The filtrate was concentrated and dried *in vacuo*. The alcohol was used without further purification. To a solution of crude alcohol (86 mg) in cyclohexane (15 mL) were added iodobenzene diacetate (203 mg, 0.630 mmol) and I_2 (163 mg, 0.630 mmol). The reaction mixture was stirred for 3 h at room temperature under irradiation by light (250 W), quenched with saturated aqueous $Na_2S_2O_3$, and stirred for 30 min. The aqueous layer was extracted with EtOAc (2×30 mL). The combined organic layers were dried ($MgSO_4$)

and concentrated. The residue was purified by chromatography on SiO_2 (hexane/ethyl ether, 10:1-4:1) to give the major product **147** (51 mg, 0.12 mmol, 63%) as a white solid and the minor product **148** (20 mg, 0.047mmol, 25%) as a colorless oil. **147**: Mp 57-59 °C; $[\alpha]_D$ +25 (*c* 1.0, $CHCl_3$); IR (neat) 2955, 2930, 2857, 1754, 1469, 1383, 1251, 1158, 1050, 836, 776 cm^{-1}; ^1H NMR δ 4.71 (d, 1 H, *J* = 7.5 Hz), 4.36 (dt, 1 H, *J* = 5.9, 7.6 Hz), 4.19 (tt, 1 H, *J* = 5.0, 9.5 Hz), 3.99-3.91 (m, 1 H), 2.57 (ddd, 1 H, *J* = 4.1, 7.6, 16.9 Hz), 2.31 (ddd, 1 H, *J* = 4.2, 10.0, 16.9 Hz), 2.15-2.05 (m, 1 H), 1.97-1.81 (m, 3 H), 1.70-1.52 (m, 3 H), 1.47 (dd, 1 H, *J* = 10.1, 13.0 Hz), 1.38-1.24 (m, 4 H), 1.12 (s, 3 H), 0.94 (s, 3 H), 0.92-0.89 (m, 12 H), 0.09 (s, 6 H); ^{13}C NMR δ 172.0, 109.8, 87.9, 73.8, 70.0, 62.6, 50.7, 38.0, 37.7, 34.9, 29.3, 27.2, 26.1, 24.3, 22.9, 21.6, 19.0, 18.3, 14.3, –4.4; MS (EI) *m/z* (relative intensity) 369 ($[M-C_4H_9]^+$, 15), 276 (10), 208 (23), 140 (27), 75 (100); HRMS (EI) *m/z* calculated for $C_{19}H_{33}O_5Si$ (M-C_4H_9) 369.2097, found 369.2101.

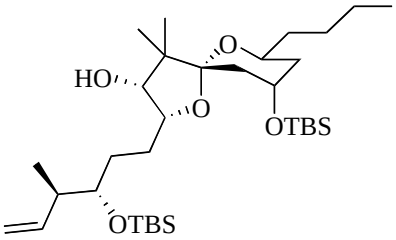


(2*R*,3*R*,5*R*,7*S*,9*S*)-7-Butyl-9-(*tert*-butyldimethylsilanyloxy)-(hexahydrofuro[3,2-*b*]pyran-5-onyl)-4,4-dimethyl-1,6-dioxaspiro[4.5]decane (148): $[\alpha]_D$ –75 (*c* 1.4, $CHCl_3$); IR (neat) 2955, 2927, 2858, 1743, 1470, 1383, 1248, 1173, 1112, 1070, 836 cm^{-1}; ^1H NMR δ 4.51 (dd, 1 H, *J* = 3.6, 8.2 Hz), 4.30 (d, 1 H, *J* = 5.2 Hz), 4.24-4.12 (m, 2 H), 2.54-2.35 (m, 2 H), 2.14-2.03 (m, 1 H), 1.97-1.85 (m, 1 H), 1.67-1.51 (m, 2 H), 1.48-1.17 (m, 8 H), 1.11 (s, 3 H), 0.96 (s, 3 H), 0.90 (s, 9 H), 0.89 (t, 3 H, *J* = 7.4 Hz), 0.04 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR δ 171.1, 108.0, 88.6, 71.8, 65.0, 64.3, 51.4, 37.4, 35.2, 34.8, 27.0, 25.9, 25.5, 24.2, 23.2, 23.0, 18.2, 17.3, 14.3, –4.5, –4.6; MS (ESI) *m/z* (relative intensity) 449 ($[M+Na]^+$, 100), 403 (5), 365 (28), 317 (14); HRMS (ESI) *m/z* calculated for $C_{23}H_{42}O_5NaSi$ (M+Na) 449.2699, found 449.2721.



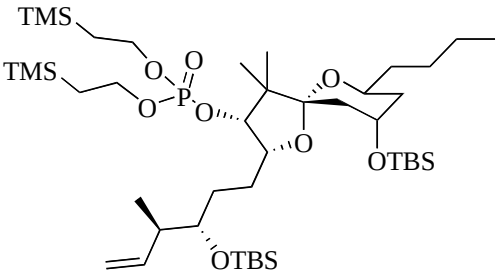
(2*R*,3*R*,5*R*,7*S*,9*S*)-7-Butyl-9-(*tert*-butyldimethylsilanyloxy)-2-((*3S*,*4R*)-3-hydroxy-4-methylhex-5-enyl)-4,4-dimethyl-1,6-dioxaspiro[4.5]decan-3-ol (149). To a solution of **148** (54 mg, 0.13 mmol) in CH_2Cl_2 (10 mL) was added DIBAL (1.0 M in hexane, 0.17 mL, 0.17 mmol) at –78 ºC and the mixture was stirred for 2 h at –78 ºC. The reaction mixture was quenched with MeOH/EtOAc (1 mL/1 mL), allowed to warm to room temperature, and treated with 5 mL of saturated aqueous Rochelle salt. After stirred for 5 h at room temperature, the aqueous layer was extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give a crude aldehyde. Without further purification, this aldehyde was used for the next step. To a well-stirred mixture of *trans*-2-butene (0.2 mL) and KO*t*-Bu (112 mg, 1.00 mmol) in THF (1 mL), *n*-BuLi (1.6 M in hexane, 0.63 mL, 1.0 mmol) was added at –78 ºC. Following completion of addition, the mixture was stirred at –45 ºC for 15 min and again cooled to –78 ºC. To the mixture, a solution of *B*-methoxylbis(2-isocaranyl)borane (380 mg, 1.20 mmol) in ethyl ether (0.5 mL) was added dropwise and the resulting mixture was stirred for 30 min at –78 ºC. The addition of BF_3•etherate (0.16 mL, 1.3 mmol) and stirring the mixture at –78 ºC for 15 min afforded *B*-[*E*]-crotyl(2-isocaranyl)borane. A solution of crude aldehyde (52 mg) in ethyl ether (1 mL) was added at –78 ºC and the mixture was stirred for 3 h at –78 ºC. MeOH (0.16 mL) was added, the mixture was brought to room temperature and oxidized with alkaline hydrogen peroxide (30% H_2O_2 (0.8 mL) and 3N NaOH (0.4 mL)) at reflux for 3 h. The aqueous layer was extracted with EtOAc (3x25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexane/ethyl ether,

10:1-4:1) to give **149** (48 mg, 0.099 mmol, 78%) as a colorless oil: $[\alpha]_D$ –27 (*c* 1.0, $CHCl_3$); IR (neat) 3507, 2955, 2928, 2853, 1463, 1253, 1108, 1083, 998, 836, 773 cm^{-1}; ^1H NMR δ 5.83 (ddd, 1 H, *J* = 8.0, 9.7, 17.8 Hz), 5.13-5.05 (m, 2 H), 4.28-4.19 (m, 1 H), 4.17-4.09 (m, 2 H), 3.56-3.46 (m, 2 H), 3.35 (d, 1 H, *J* = 11.8 Hz), 2.26 (sx, 1 H, *J* = 6.8 Hz), 1.85-1.63 (m, 4 H), 1.59 (d, 1 H, *J* = 3.1 Hz), 1.54-1.24 (m, 10 H), 1.09 (s, 3 H), 1.06 (d, 3 H, *J* = 6.9 Hz), 0.91 (br. s, 15 H), 0.05 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR δ 140.9, 115.7, 108.5, 82.3, 80.7, 75.1, 65.0, 64.7, 50.1, 44.2, 38.8, 35.8, 34.4, 31.6, 28.1, 28.0, 26.1, 23.0, 22.7, 18.4, 17.3, 16.4, 14.1, –4.5, –4.6; MS (ESI) *m/z* (relative intensity) 507 ($[M+Na]^+$, 100), 451 (10); HRMS (ESI) *m/z* calculated for $C_{27}H_{52}O_5NaSi$ (M+Na) 507.3482, found 507.3497.



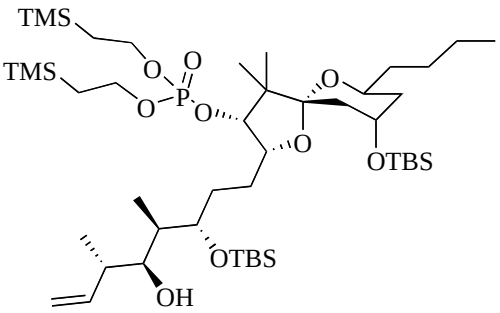
(2*R*,3*R*,5*R*,7*S*,9*S*)-7-Butyl-9-(*tert*-butyldimethylsilanyloxy)-2-[(*3S*,*4R*)-3-(*tert*-butyldimethylsilanyloxy)-4-methylhex-5-enyl]-4,4-dimethyl-1,6-dioxaspiro[4.5]decan-3-ol (150). To a solution of **149** (44 mg, 0.091 mmol) and imidazole (100 mg, 1.47 mmol) in DMF (1.4 L) was added TBSCl (100 mg, 0.663 mmol). The mixture was stirred overnight and water was added. The aqueous layer was extracted with EtOAc (3x20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexane/EtOAc, 10:1) to give **150** (49 mg, 0.082 mmol, 90%) as a colorless oil: $[\alpha]_D$ –24 (*c* 0.70, $CHCl_3$); IR (neat) 3512, 2956, 2929, 2857, 1471, 1361, 1255, 1106, 1060, 835 cm^{-1}; ^1H NMR δ 5.83 (ddd, 1 H, *J* = 7.8, 10.4, 17.6 Hz), 5.03-4.97 (m, 2 H), 4.27-4.18 (m, 1 H), 4.16-4.12 (m, 1 H), 4.06-4.01 (m, 1 H), 3.59-3.54 (m, 1 H), 3.50 (dd, 1 H, *J* = 4.5, 12.2 Hz), 3.31 (d, 1 H, *J* = 12.1 Hz), 2.33 (dt, 1 H, *J* = 6.9, 17.9 Hz), 1.65-1.45 (m, 7 H), 1.41-1.23 (m, 7 H), 1.08 (s, 3 H),

1.01 (d, 3 H, *J* = 6.8 Hz), 0.91 (br. s, 24 H), 0.06 (s, 3 H), 0.05 (s, 3 H), 0.04 (s, 3 H), 0.02 (s, 3 H); ^{13}C NMR (CD_2Cl_2) δ 141.4, 114.4, 108.3, 82.6, 80.5, 76.6, 64.9, 64.5, 50.0, 43.4, 38.8, 35.9, 34.4, 30.9, 28.2, 28.1, 26.2, 26.0, 23.1, 22.7, 18.4, 18.2, 17.3, 15.9, 14.2, –4.0, –4.3, –4.5, –4.7; MS (EI) *m/z* (relative intensity) 556 (M, 0.2), 541 (0.3), 499 (11), 367 (28), 271 (29), 237 (100), 203 (50), 145 (55), 73 (79); MS (ESI) *m/z* (relative intensity) 621 ([M+Na]$^+$, 100), 541 (22), 413 (17); HRMS (ESI) *m/z* calculated for $C_{33}H_{66}O_5NaSi_2$ (M+Na) 621.4347, found 621.4333.



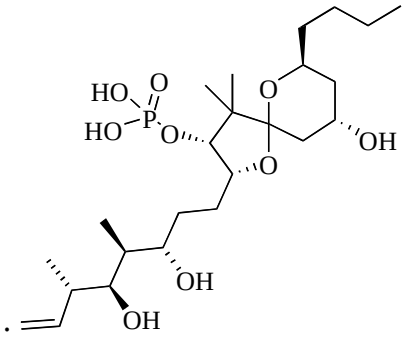
(2*R*,3*R*,5*R*,7*S*,9*S*)-Phosphoric acid 7-butyl-9-(*tert*-butyldimethylsilanyloxy)-2-[(*3S*,*4R*)-3-(*tert*-butyldimethylsilanyloxy)-4-methylhex-5-enyl]-4,4-dimethyl-1,6-dioxaspiro[4.5]dec-3-yl ester bis-[2-(trimethylsilanyl)-ethyl]ester (151). PCl_3 (2 M in CH_2Cl_2, 70 µL, 0.14 mmol) was added to a solution of **150** (32 mg, 0.054 mmol) in pyridine (0.6 mL) at 0 ºC in one portion. After 10 min, 2-trimethylsilylethanol (0.13 mL, 0.90 mmol) and DMAP (1.0 mg, 0.0082 mmol) were added and the mixture was warmed to room temperature over 1 h. CH_2Cl_2 (5.4 mL) and 30% aqueous H_2O_2 (0.54 mL) were added and the stirring was continued for 1 h at room temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (3x20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified directly by chromatography on SiO_2 (hexane/ethyl ether, 10:1) to give **151** (33 mg, 0.038 mmol, 70%) as a colorless oil: $[\alpha]_D$ –22 (*c* 1.0, $CHCl_3$); IR (neat) 2955, 2925, 2889, 2857, 1472, 1373, 1252, 998, 861 cm^{-1}; ^{1}H NMR (CD_3CN) δ 5.83 (ddd, 1 H, *J* = 7.6, 10.3, 17.5 Hz), 5.04-4.94 (m, 2 H), 4.32 (dd, 1 H, *J* = 5.8, 10.1 Hz), 4.18-4.04 (m, 7

H), 3.58 (ddd, 1 H, *J* = 3.1, 4.5, 7.7 Hz), 2.32 (dt, 1 H, *J* = 3.3, 7.0 Hz), 1.89-1.79 (m, 1 H), 1.64-1.46 (m, 5 H), 1.45-1.20 (m, 8 H), 1.09-1.04 (m, 4 H), 1.03 (s, 3 H), 0.99 (d, 3 H, *J* = 6.9 Hz), 0.89 (s, 21 H), 0.88 (t, 3 H, *J* = 6.9 Hz), 0.07 (s, 3 H), 0.06 (s, 3 H), 0.02 (s, 24 H); ^{13}C NMR (CD_3CN) δ 142.0, 115.1, 107.7, 85.9, 85.8, 82.0, 81.9, 77.9, 66.70, 66.66, 66.62, 66.57, 65.9, 64.9, 51.4, 51.3, 44.4, 39.3, 36.9, 35.6, 32.5, 29.8, 28.6, 26.5, 26.4, 24.0, 23.8, 20.5, 20.4, 20.3, 20.2, 18.81, 18.77, 17.8, 16.0, 14.6, –1.3, –3.6, –4.1, –4.4, –4.6; MS (ESI) *m/z* (relative intensity) 902 ([M+Na]$^+$, 100), 786 (5), 748 (3); HRMS (ESI) *m/z* calculated for $C_{43}H_{91}O_8NaSi_4P$ (M+Na) 901.5426, found 901.5450.



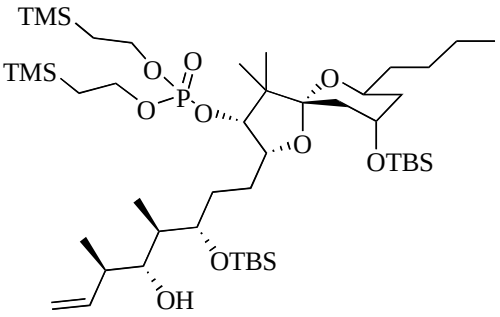
(2*R*,3*R*,5*R*,7*S*,9*S*)-Phosphoric acid 7-butyl-9-(*tert*-butyldimethylsilanyloxy)-2-[(*3S*,*4R*,5*S*,6*S*)-3-(*tert*-butyldimethylsilanyloxy)-5-hydroxy-4,6-dimethyloct-7-enyl]-4,4-dimethyl-1,6-dioxaspiro[4.5]dec-3-yl ester bis-[2-(trimethylsilanyl)-ethyl] ester (152). A stream of O_3 was bubbled through a solution of **151** (20 mg, 0.023 mmol) in MeOH (8 mL) at –78 ºC until the color of the solution turned blue. After N_2 was bubbled through the solution for 15 min, Me_2S (0.50 L, 6.8 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 6 h. The solution was concentrated. The crude aldehyde was used without further purification. To a suspension of Roush's crotylation reagent (1 M in toluene, 1.0 mL, 1.0 mmol) and 4 Å MS (60 mg) was added a solution of crude aldehyde (21 mg) in toluene (0.5 mL) at –78 ºC. After stirring at –78 ºC for 5 h, the reaction mixture was filtered through SiO_2 and washed with EtOAc and CH_2Cl_2. The filtrate was concentrated and the residue was

purified by chromatography on SiO_2 (hexane/ethyl ether, 10:1) to give **152** (10 mg, 0.011 mmol, 48%) as a colorless oil: Mp 78-80 °C; $[\alpha]_D$ –15 (*c* 1.5, CH_2Cl_2); IR (neat) 3428, 2955, 2928, 2857, 1472, 1385, 1251, 1110, 1003, 835 cm^{-1}; ^1H NMR (600 MHz, acetone-d_6) δ 5.98 (ddd, 1 H, *J* = 8.2, 10.4, 17.4 Hz), 5.04 (dd, 1 H, *J* = 1.3, 17.5 Hz), 5.00 (dd, 1 H, *J* = 2.0, 10.4 Hz), 4.39 (dd, 1 H, *J* = 5.7, 10.2 Hz), 4.24 (qn, 1 H, *J* = 3.0 Hz), 4.21-4.10 (m, 6 H), 3.85 (dt, 1 H, *J* = 4.2, 7.3 Hz), 3.57 (dd, 1 H, *J* = 5.5, 9.6 Hz), 3.38 (d, 1 H, *J* = 4.0 Hz), 2.29 (sx, 1 H, *J* = 6.6 Hz), 1.95-1.90 (m, 1 H), 1.77-1.70 (m, 2 H), 1.66-1.47 (m, 6 H), 1.60 (d, 1 H, *J* = 3.2 Hz), 1.40-1.28 (m, 6 H), 1.13-1.08 (m, 4 H), 1.10 (s, 3 H), 1.02 (d, 3 H, *J* = 6.9 Hz), 1.00 (d, 3 H, *J* = 6.9 Hz), 0.94-0.91 (m, 24 H), 0.14 (s, 3 H), 0.10 (s, 3 H), 0.07 (s, 3 H), 0.059 (s, 9 H), 0.057 (s, 9 H), 0.05 (s, 3 H); ^{13}C NMR (150 MHz) δ 142.8, 114.3, 106.9, 85.61, 85.57, 81.29, 81.27, 80.0, 74.1, 66.1, 66.0, 64.9, 64.3, 50.70, 50.68, 41.7, 38.6, 36.8, 36.3, 35.1, 33.6, 28.7, 27.7, 26.2, 26.1, 23.5, 23.4, 20.0, 19.94, 19.86, 19.8, 18.3, 18.2, 17.6, 17.3, 14.3, 11.7, –1.3, –3.9, –4.4, –4.5, –4.6; MS (ESI) *m/z* (relative intensity) 960 ($[M+Na]^+$, 100), 844 (20), 758 (4), 563 (27); HRMS (ESI) *m/z* calculated for $C_{46}H_{97}O_9NaPSi_4$ (M+Na) 959.5845, found 959.5804.



(2*R*,3*R*,5*R*,7*S*,9*S*)-Phosphoric acid 7-butyl-mono-[2-((3*S*,4*R*,5*S*,6*S*)-3,5-dihydroxy-4,6-dimethyloct-7-enyl)-9-hydroxy-4,4-dimethyl-1,6-dioxaspiro[4.5]dec-3-yl] ester (153). A solution of **152** (5.0 mg, 0.0053 mmol) in HF (0.5 mL, from stock solution with 48% HF (0.5 mL), CH_3CN (4.5 mL) and water (0.5 mL)) was stirred at room temperature for 8 d. N_2 gas was

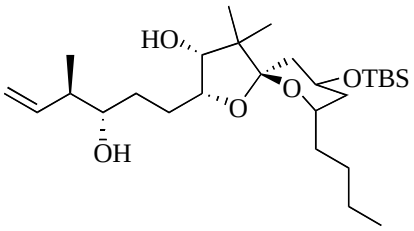
bubbled into the reaction mixture to remove the solvent and the mixture was dried under vacuum, washed with hexane, and extracted with CH_2Cl_2. The residue was purified by chromatography on SiO_2 (CH_3CN/MeOH, 10:1-3:1) to give an inseparable mixture of the product **153** and side products (2.0 mg) as a colorless solid: IR (neat) 3350, 2958, 2929, 2876, 1462, 1377, 1217, 1144, 1107, 1058, 1015, 984, 858 cm^{-1}; ^1H NMR δ 5.93-5.82 (m, 1 H), 5.08-4.90 (m, 2 H), 4.40-4.24 (m, 1 H), 4.23-4.08 (m, 1 H), 4.06-3.89 (m, 1 H), 3.70-3.58 (m, 3 H), 2.31-2.23 (m, 1 H), 2.03-1.81 (m, 2 H), 1.79-1.60 (m, 3 H), 1.55-1.41 (m, 3 H), 1.40-1.19 (m, 7 H), 1.12 (s, 3 H), 1.20-0.85 (m, 12 H); MS (ESI) *m/z* (relative intensity) 1039 ($[2M+Na]^+$, 30), 531 (52), 513 (100), 495 (60), 427 (35); HRMS (ESI) *m/z* calculated for $C_{24}H_{45}O_9NaP$ (M+Na) 531.2699, found 531.2722.



(2*R*,3*R*,5*R*,7*S*,9*S*)-Phosphoric acid 7-butyl-9-(*tert*-butyldimethylsilanyloxy)-2-[(*3S*,*4R*,5*R*,6*R*)-3-(*tert*-butyldimethylsilanyloxy)-5-hydroxy-4,6-dimethyloct-7-enyl]-4,4-dimethyl-1,6-dioxaspiro[4.5]dec-3-yl ester bis-[2-(trimethylsilanyl)-ethyl] ester (154). A stream of O_3 was bubbled through a solution of **145** (65 mg, 0.074 mmol) in MeOH (10 mL) at –78 ºC until the color of the solution turned blue. After N_2 was bubbled through the solution for 15 min, Me_2S (0.50 mL, 6.8 mmol) was added, and the mixture was allowed to warm to room temperature, and stirred for 7 h. The solution was concentrated *in vacuo*. The crude aldehyde (65 mg) was used without further purification. To a well-stirred mixture of *trans*-2-butene (0.2 mL), THF (1.5 mL) and KO*t*-Bu (74 mg, 0.66 mmol), *n*-BuLi (1.6 M in hexane, 0.41 mL, 0.66 mmol)

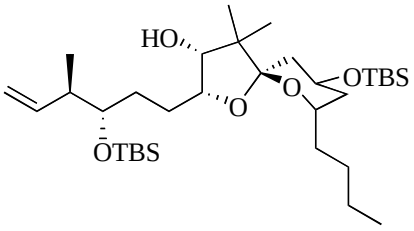
was added at –78 ºC. Following completion of addition, the mixture was stirred at –45 ºC for 15 min and again cooled to –78 ºC. To the mixture, a solution of *B*-methoxylbis(2-isocaranyl)borane (0.25 g, 0.79 mmol) in ethyl ether (0.5 mL) was added dropwise and the resulting mixture was stirred for 0.5 h at –78 ºC. The addition of BF_3•etherate (0.11 mL, 0.86 mmol) and stirring the mixture at –78 ºC for 15 min afforded *B*-[*E*]-crotyl(2-isocaranyl)borane. A solution of crude aldehyde (30 mg, 0.034 mmol) in ethyl ether (0.5 mL) was added at –78 ºC and the mixture was stirred for 3 h at –78 ºC. The reaction mixture was quenched with MeOH (0.16 mL), brought to room temperature, and oxidized with 30% H_2O_2 (0.4 mL) at reflux for 3 h. The aqueous layer was extracted with EtOAc (3x25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexane/ethyl ether, 10:1-4:1) to give the borate compound (21 mg, 0.017 mmol). The solution of the borate compound (3.5 mg, 0.0029 mmol) in THF/ethyl ether (1 mL/1 mL) was oxidized with 30% H_2O_2 (0.8 mL) at reflux for 2 d. The aqueous layer was extracted with EtOAc (2x10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexane/ethyl ether, 20:1-10:1) to give **154** (1.2 mg, 0.0024 mmol) in 41% yield over 2 steps as a colorless oil: $[\alpha]_D$ –4.6 (*c* 0.21, CH_2Cl_2); IR (neat) 3428, 2955, 2929, 2856, 1472, 1381, 1252, 1107, 1070, 1003, 858, 836 cm^{-1}; ^1H NMR δ 5.96-5.85 (m, 1 H), 5.11-5.01 (m, 2 H), 4.40 (dd, 1 H, *J* = 5.5, 9.6 Hz), 4.22-4.06 (m, 7 H), 3.96-3.89 (m, 1 H), 3.33 (d, 1 H, *J* = 9.9 Hz), 2.44-2.33 (m, 1 H), 1.85-1.57 (m, 6 H), 1.56-1.40 (m, 5 H), 1.39-1.22 (m, 8 H), 1.14-1.05 (m, 9 H), 0.94-0.86 (m, 21 H), 0.82 (d, 3 H, *J* = 6.7 Hz), 0.10-0.03 (m, 30 H); ^{13}C NMR (100 MHz) δ 139.3, 115.5, 106.6, 85.4, 80.5, 74.9, 66.14, 66.08, 66.0, 65.0, 64.2, 50.8, 42.9, 40.4, 38.9, 36.2, 34.9, 30.6, 28.5, 27.9, 26.2, 26.1, 23.6, 23.2, 20.0, 19.9, 19.82, 19.77, 18.3, 18.2, 17.6, 14.4, 11.8, –1.26, –1.30, –4.0, –4.2, –4.5, –4.7; MS (ESI) *m/z* (relative intensity) 960 ($[M+Na]^+$, 100), 806

(35), 727 (15); HRMS (ESI) *m/z* calculated for $C_{46}H_{97}O_9NaPSi_4$ (M+Na) 959.5845, found 959.5811.



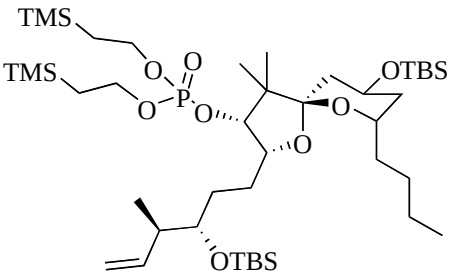
(2*R*,3*R*,5*S*,7*S*,9*S*)-7-Butyl-9-(*tert*-butyldimethylsilanyloxy)-2-((*3S,4R*)-*3*-hydroxy-4-methylhex-5-enyl)-4,4-dimethyl-1,6-dioxaspiro[4.5]decan-3-ol (155). To a solution of **147** (243 mg, 0.570 mmol) in CH_2Cl_2 (25 mL) was added DIBAL (1.0 M in hexane, 0.68 mL, 0.68 mmol) at –78 ºC and the mixture was stirred for 2 h at –78 ºC. The reaction mixture was quenched with MeOH/EtOAc (8 mL/8 mL), allowed to warm to room temperature, and treated with saturated aqueous Rochelle salt (15 mL). After stirring for 6 h at room temperature, the aqueous layer was extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give crude aldehyde. Without further purification, this aldehyde was used for the next step. To a well-stirred mixture of *trans*-2-butene (0.5 mL) and KO*t*-Bu (224 mg, 2.00 mmol) in THF (3 mL), *n*-BuLi (1.6 M in hexane, 1.26 mL, 2.02 mmol) was added at –78 ºC. Following completion of addition, the mixture was stirred at –45 ºC for 15 min and again cooled to –78 ºC. To the mixture, a solution of *B*-methoxylbis(2-isocaranyl)borane (760 mg, 2.40 mmol) in ethyl ether (1.0 mL) was added dropwise and the resulting mixture was stirred for 30 min at –78 ºC. The addition of BF_3•etherate (0.25 mL, 2.0 mmol) and stirring the mixture at –78 ºC for 15 min afforded *B*-[*E*]-crotyl(2-isocaranyl)borane. A solution of crude aldehyde (250 mg) in ethyl ether (4 mL) was added at –78 ºC and the mixture was stirred for 3 h at –78 ºC. MeOH (0.32 mL) was added, then the mixture was brought to room temperature and oxidized with alkaline hydrogen peroxide (30% H_2O_2 (1.6 mL) and 3 N NaOH (0.8 mL)) at

reflux for 2 h. The aqueous layer was extracted with EtOAc (3x25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexane/ethyl ether, 10:1-4:1) to give **149** (90 mg, 0.19 mmol, 33% over 2 steps) and **155** (80 mg, 0.17 mmol, 30% over 2 steps) as a colorless oil. **155** was contaminated with an inseparable impurity and used without further purification.



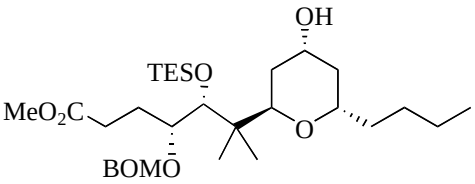
(2*R*,3*R*,5*S*,7*S*,9*S*)-7-Butyl-9-(*tert*-butyldimethylsilanyloxy)-2-[(*3S*,*4R*)-3-(*tert*-butyldimethylsilanyloxy)-4-methylhex-5-enyl]-4,4-dimethyl-1,6-dioxaspiro[4.5]decan-3-ol (156). To a solution of crude **155** (80 mg, 0.17 mmol) and imidazole (50 mg, 0.73 mmol) in DMF (3 mL) was added TBSCl (50 mg, 0.33 mmol). The mixture was stirred overnight and water was added. The aqueous layer was extracted with EtOAc (3x20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexane/EtOAc, 10:1) to give **156** (80 mg, 0.13 mmol, 76%) as a colorless oil: $[\alpha]_D$ +21 (*c* 1.0, $CHCl_3$); IR (neat) 3462, 2956, 2925, 2858, 1472, 1383, 1255, 1107, 1053, 1004, 836 cm^{-1}; ^1H NMR δ 5.87-5.74 (m, 1 H), 5.03-4.97 (m, 2 H), 4.27-4.19 (m, 1 H), 4.19 (d, 1 H, *J* = 7.5 Hz), 4.00-3.86 (m, 2 H), 3.59 (q, 1 H, *J* = 4.7 Hz), 2.34-2.28 (m, 1 H), 1.93-1.82 (m, 2 H), 1.80-1.69 (m, 1 H), 1.61-1.50 (m, 5 H), 1.46-1.20 (m, 7 H), 1.01 (s, 3 H), 1.00 (d, 3 H, *J* = 7.1 Hz), 0.90 (br. s, 21 H), 0.88 (s, 3 H), 0.08 (s, 6 H), 0.07 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR δ 141.3, 114. 4, 108.6, 79.7, 77.9, 76.0, 73.7, 63.1, 49.2, 43.1, 39.2, 38.7, 35.4, 30.8, 29.5, 26.4, 26.2, 22.9, 21.5, 18.41, 18.39, 18.2, 15.8, 14.3, –3.9, –4.3, –4.4; MS (ESI) *m/z*

(relative intensity) 621 ([M+Na]$^+$, 95), 571 (35), 467 (100), 413 (48), 287 (92); HRMS (ESI) *m/z* calculated for $C_{33}H_{66}O_5NaSi_2$ (M+Na) 621.4347, found 621.4389.



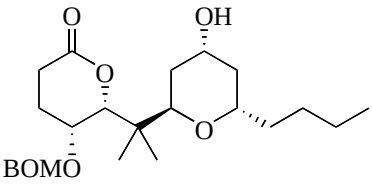
(2*R*,3*R*,5*S*,7*S*,9*S*)-Phosphoric acid 7-butyl-9-(*tert*-butyldimethylsilanyloxy)-2-[(*3S*,*4R*)-3-(*tert*-butyldimethylsilanyloxy)-4-methylhex-5-enyl]-4,4-dimethyl-1,6-dioxaspiro[4.5]dec-3-yl ester bis-[2-(trimethylsilanyl)ethyl] ester (157). PCl_3 (2 M in CH_2Cl_2, 70 μL, 0.14 mmol) was added to a solution of **156** (32 mg, 0.054 mmol) in pyridine (0.6 mL) at 0 ºC in one portion. After 10 min, 2-trimethylsilylethanol (0.13 mL, 0.90 mmol) and DMAP (1 mg, 0.0082 mmol) were added and the mixture was warmed to room temperature over 1 h. CH_2Cl_2 (5.4 mL) and 30% aqueous H_2O_2 (0.54 mL) were added and the stirring was continued for 1 h at room temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (3x20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexane/ethyl ether, 10:1) to give **157** (38 mg, 0.043 mmol, 80%) as a colorless oil: $[\alpha]_D$ +31 (*c* 1.0, $CHCl_3$); IR (neat) 2955, 2929, 2894, 2857, 1471, 1386, 1252, 1109, 1002, 856 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 6.00 (ddd, 1 H, *J* = 7.9, 10.3, 17.6 Hz), 5.33 (dd, 1 H, *J* = 7.7, 9.1 Hz), 5.16 (d, 1 H, *J* = 17.4 Hz), 5.12 (dd, 1 H, *J* = 1.9, 10.4 Hz), 4.48 (tt, 1 H, *J* = 4.7, 10.1 Hz), 4.38 (ddd, 1 H, *J* = 2.9, 7.7, 10.6 Hz), 4.34-4.26 (m, 4 H), 3.95 (dq, 1 H, *J* = 2.8, 7.2 Hz), 3.75 (dt, 1 H, *J* = 4.2, 5.8 Hz), 2.52-2.46 (m, 1 H), 2.21-2.18 (m, 1 H), 2.15-2.08 (m, 1 H), 2.00-1.93 (m, 2 H), 1.89-1.79 (m, 2 H), 1.76-1.67 (m, 3 H), 1.63 (dd, 1 H, *J* = 10.6, 12.4 Hz), 1.38 (s, 3 H), 1.35-1.28 (m, 4 H),

1.15 (s, 3 H), 1.13 (d, 3 H, *J* = 6.9 Hz), 1.12-1.06 (m, 4 H), 1.05 (s, 9 H), 1.02 (s, 9 H), 0.91 (t, 3 H, *J* = 6.9 Hz), 0.24 (s, 3 H), 0.16 (s, 3 H), 0.15 (s, 3 H), 0.14 (s, 3 H), –0.06 (s, 9 H), –0.09 (s, 9 H); ^{13}C NMR (CD_3CN) δ 142.0, 114.9, 109.4, 85.2, 85.1, 77.63, 77.57, 76.3, 74.9, 67.1, 67.03, 66.99, 66.9, 63.6, 49.8, 49.7, 43.4, 39.5, 39.2, 35.9, 31.7, 30.2, 27.1, 26.4, 26.3, 23.5, 21.2, 20.4, 20.29, 20.26, 20.2, 18.9, 18.84, 18.80, 16.5, 14.5, –1.4, –3.7, –4.2, –4.26, –4.32; MS (ESI) *m/z* (relative intensity) 902 ([M+Na]$^+$, 100), 783 (20), 538 (23); HRMS (ESI) *m/z* calculated for $C_{43}H_{91}O_8NaSi_4P$ (M+Na) 901.5426, found 901.5450.



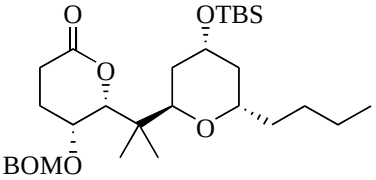
(4*R*,5*R*)-Methyl-4-((benzyloxy)methoxy)-6-((2*R*,4*R*,6*S*)-6-butyltetrahydro-4-hydroxy-2*H*-pyran-2-yl)-6-methyl-5-(triethylsilanyloxy)heptanoate (158). To a solution of **145** (18 mg, 0. 031 mmol) in THF (1 mL) was added L-Selectride (1 M in THF, 80 µL, 0.080 mmol) at –78 ºC and the mixture was stirred for 1 h at –78 ºC, quenched with saturated aqueous NH_4Cl and warmed up to room temperature. The organic layer was extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (CH_2Cl_2/EtOAc, 4:1) to give **158** (13 mg, 0.022 mmol, 71%) as a colorless oil: $[\alpha]_D$ +35 (*c* 1.0, $CHCl_3$); IR (neat) 3493, 2953, 2876, 1740, 1455, 1379, 1240, 1161, 1118, 1040, 827 cm^{-1}; ^{1}H NMR δ 7.36-7.27 (m, 5 H), 4.81, 4.78 (AB, 2 H, *J* = 6.9 Hz), 4.72, 4.58 (AB, 2 H, *J* = 12.0 Hz), 4.19 (ddd, 1 H, *J* = 4.1, 4.6, 8.7 Hz), 3.93 (dd, 1 H, *J* = 3.2, 11.1 Hz), 3.79-3.68 (m, 2 H), 3.65 (d, 1 H, *J* = 5.5 Hz), 3.64 (s, 3 H), 2.58-2.38 (m, 2 H), 2.07-1.83 (m, 3 H), 1.82-1.72 (m, 1 H), 1.69-1.63 (m, 2 H), 1.54-1.20 (m, 7 H), 0.99 (t, 9 H, *J* = 8.0 Hz), 0.96 (s, 3 H), 0.89 (t, 3 H, *J* = 6.8 Hz), 0.88 (s, 3 H), 0.66 (q, 6 H, *J* = 8.0 Hz); ^{13}C NMR δ

174.2, 138.4, 128.5, 127.9, 127.7, 94.8, 78.1, 76.4, 71.6, 70.2, 69.2, 65.3, 51.6, 42.6, 36.8, 34.7, 32.9, 31.5, 29.6, 28.9, 22.9, 21.3, 19.1, 14.3, 7.3, 5.8; MS (ESI) *m/z* (relative intensity) 604 ($[M+Na]^+$, 100), 541 (10), 463 (5); HRMS (ESI) *m/z* calculated for $C_{32}H_{56}O_7NaSi$ (M+Na) 603.3693, found 603.3715.

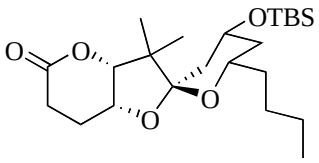


(5*R*,6*R*)-5-((Benzyloxy)methoxy)-6-(2-((2*R*,4*R*,6*S*)-6-butyltetrahydro-4-hydroxy-2*H*-pyran-2-yl)propan-2-yl)tetrahydropyran-2-one (159). To a solution of **158** (90 mg, 0.17 mmol) in THF (5 mL) was added HF•pyridine (0.5 mL) at 0 ºC. The mixture was stirred at room temperature for 36 h and diluted with ethyl ether (50 mL). The organic layer was washed with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (3x20 mL). The combined organic layers were washed with saturated aqueous NH_4Cl, dried ($MgSO_4$), and concentrated. The residue was purified by chromatography on SiO_2 (CH_2Cl_2/EtOAc, 4:1) to give the desired lactone **159** (64 mg, 0.15 mmol, 88%) as a colorless oil: $[\alpha]_D$ –19 (*c* 1.1, $CHCl_3$); IR (neat) 3448, 2950, 2929, 2873, 1718, 1456, 1364, 1248, 1205, 1025 cm^{-1}; ^1H NMR δ 7.38-7.29 (m, 5 H), 4.86, 4.80 (AB, 2 H, *J* = 7.1 Hz), 4.69, 4.64 (AB, 2 H, *J* = 12.0 Hz), 4.34-4.30 (m, 2 H), 4.22 (qn, 1 H, *J* = 4.0 Hz), 3.92 (dd, 1 H, *J* = 2.6, 11.2 Hz), 3.83-3.75 (m, 1 H), 2.66 (ddd, 1 H, *J* = 7.7, 10.4, 18.1 Hz), 2.53 (ddd, 1 H, *J* = 3.1, 8.0, 18.1 Hz), 2.24 (tt, 1 H, *J* = 3.2, 11.1 Hz), 1.94-1.85 (m, 3 H), 1.83-1.77 (m, 1 H), 1.74-1.61 (m, 2 H), 1.60-1.50 (m, 2 H), 1.35-1.20 (m, 4 H), 1.10 (s, 3 H), 1.06 (s, 3 H), 0.89 (t, 3 H, *J* = 6.8 Hz); ^{13}C NMR δ 171.4, 137.7, 128.7, 128.0, 127.8, 93.6, 85.0, 72.5, 70.9, 69.8, 69.3, 65.0, 41.2, 35.8, 34.0, 33.2, 29.3, 25.8, 25.0, 22.8, 20.53,

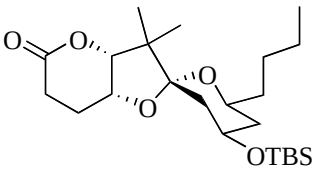
20.45, 14.3; MS (ESI) *m/z* (relative intensity) 457 ([M+Na]$^+$, 100), 377 (10); HRMS (ESI) *m/z* calculated for $C_{25}H_{38}O_6Na$ (M+Na) 457.2566, found 457.2579.



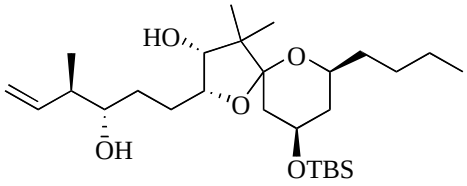
(5*R*,6*R*)-5-((Benzyloxy)methoxy)-6-(2-((2*R*,4*R*,6*S*)-6-butyltetrahydro-4-(*tert*-butyldimethylsilanyloxy)-2*H*-pyran-2-yl)propan-2-yl)tetrahydropyran-2-one (160). To a solution of **159** (80 mg, 0.18 mmol) and imidazole (50 mg, 0.73 mmol) in DMF (1 mL) was added TBSCl (55 mg, 0.37 mmol). The mixture was stirred overnight and water was added. The aqueous layer was extracted with EtOAc (3x20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexane/EtOAc, 10:1) to give **160** (74 mg, 0.13 mmol, 72%) as a colorless oil: $[\alpha]_D$ +2.9 (*c* 1.6, $CHCl_3$); IR (neat) 2954, 2928, 2856, 1741, 1469, 1360, 1251, 1090, 1036, 835 cm^{-1}; ^{1}H NMR δ 7.37-7.31 (m, 5 H), 4.86, 4.82 (AB, 2 H, *J* = 7.1 Hz), 4.70, 4.62 (AB, 2 H, *J* = 11.9 Hz), 4.38 (s, 1 H), 4.27 (br. s, 1 H), 4.19 (qn, 1 H, *J* = 3.3 Hz), 3.83 (dd, 1 H, *J* = 3.3, 9.8 Hz), 3.81-3.78 (m, 1 H), 2.69 (ddd, 1 H, *J* = 7.8, 10.5, 18.2 Hz), 2.56 (ddd, 1 H, *J* = 3.0, 8.0, 18.1 Hz), 2.32-2.23 (m, 1 H), 1.98-1.89 (m, 2 H), 1.81 (ddd, 1 H, *J* = 3.4, 6.5, 14.0 Hz), 1.73-1.62 (m, 2 H), 1.37-1.22 (m, 6 H), 1.08 (s, 3 H), 1.05 (s, 3 H), 0.90 (t, 3 H, *J* = 6.7 Hz), 0.89 (s, 9 H), 0.04 (s, 6 H); ^{13}C NMR δ 171.5, 137.6, 128.7, 128.0, 127.9, 94.2, 84.6, 73.2, 70.4, 69.8, 65.5, 40.8, 35.4, 33.8, 33.5, 29.5, 25.9, 25.8, 25.6, 22.9, 21.0, 20.3, 18.1, 14.3, –4.8; MS (ESI) *m/z* (relative intensity) 571 ([M+Na]$^+$, 100), 549 (15), 519 (28), 441 (10), 387 (17); HRMS (ESI) *m/z* calculated for $C_{31}H_{52}O_6NaSi$ (M+Na) 571.3431, found 571.3439.



(2*R*,3*R*,5*S*,7*S*,9*R*)-7-Butyl-9-(*tert*-butyldimethylsilanyloxy)-(hexahydrofuro[3,2-*b*]pyran-5-onyl)-4,4-dimethyl-1,6-dioxaspiro[4.5]decane (161). To a solution of **160** (90.0 mg, 0.178 mmol) in THF (10 mL) was added $Pd(OH)_2/C$ (20 wt%, 20 mg). The mixture was stirred under H_2 gas for 3 h and then filtered through celite pad. The filtrate was concentrated and dried *in vacuo*. The alcohol was used without further purification. To a solution of the crude alcohol (71 mg) in cyclohexane (15 mL) were added iodobenzene diacetate (160 mg, 0.497 mmol) and I_2 (126 mg, 0.497 mmol). The reaction mixture was stirred for 3 h at room temperature under irradiation by light (250 W), quenched with saturated aqueous $Na_2S_2O_3$, and stirred for 30 min. The aqueous layer was extracted with ethyl ether (2×20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexane/EtOAc, 10:1) to give the major product **161** (42 mg, 0.098 mmol, 55% over 2 steps) as a colorless oil and the minor product **162** (16 mg, 0.070 mmol, 39% over 2 steps) as a white solid. **161**: $[\alpha]_D$ +17 (*c* 0.95, $CHCl_3$); IR (neat) 2955, 2930, 2857, 1749, 1470, 1383, 1250, 1155, 1113, 1039, 836 cm^{-1}; ^1H NMR δ 4.53-4.45 (m, 2 H), 4.00-3.90 (m, 1 H), 3.62-3.56 (m, 1 H), 2.61 (ddd, 1 H, *J* = 5.6, 8.7, 17.1 Hz), 2.34 (ddd, 1 H, *J* = 5.2, 7.0, 17.0 Hz), 2.15 (dd, 1 H, *J* = 5.7, 13.7 Hz), 2.10-1.97 (m, 2 H), 1.83-1.77 (m, 1 H), 1.64-1.44 (m, 5 H), 1.36-1.25 (m, 4 H), 1.15 (s, 3 H), 1.12 (s, 3 H), 0.88 (br. s, 12 H), 0.06 (s, 6 H); ^{13}C NMR δ 171.2, 109.5, 89.9, 72.9, 69.6, 65.7, 50.6, 40.8, 39.1, 37.0, 28.2, 26.3, 26.0, 23.8, 22.9, 22.3, 20.1, 18.3, 14.3, –4.3, –4.4; MS (ESI) *m/z* (relative intensity) 876 ($[2M+Na]^+$, 2), 509 (100), 449 (70), 365 (10); HRMS (ESI) *m/z* calculated for $C_{23}H_{42}O_5NaSi$ (M+Na) 449.2699, found 449.2718.



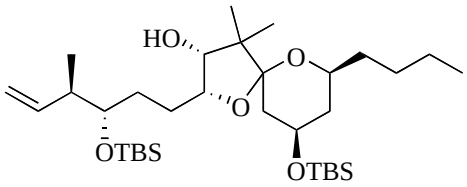
(2*R*,3*R*,5*R*,7*S*,9*R*)-7-Butyl-9-(*tert*-butyldimethylsilanyloxy)-(hexahydrofuro[3,2-*b*]pyran-5-onyl)-4,4-dimethyl-1,6-dioxaspiro[4.5]decane (162): Mp 101 °C; $[\alpha]_D$ –47 (*c* 1.5, $CHCl_3$); IR (neat) 2953, 2928, 2857, 1722, 1471, 1386, 1249, 1186, 1110, 1071, 837, 774 cm^{-1}; ^1H NMR (600 MHz, acetone-d_6) δ 4.62 (q, 1 H, *J* = 4.9 Hz), 4.40 (d, 1 H, *J* = 5.3 Hz), 4.05 (ddd, 1 H, *J* = 4.6, 10.9, 15.6 Hz), 3.73 (dqn, 1 H, *J* = 2.0, 5.7 Hz), 2.33-2.24 (m, 2 H), 2.09-2.05 (m, 1 H), 1.95 (dq, 1 H, *J* = 5.1, 14.0 Hz), 1.89-1.83 (m ,2 H), 1.45-1.34 (m, 2 H), 1.32-1.24 (m, 5 H), 1.12-1.06 (m, 1 H), 1.10 (s, 3 H), 1.02 (s, 3 H), 0.88 (s, 9 H), 0.87 (t, 3 H, *J* = 7.2 Hz), 0.08 (s, 3 H), 0.07 (s, 3 H); ^{13}C NMR δ 170.7, 109.6, 88.5, 72.4, 69.5, 66.4, 50.7, 40.3, 38.8, 35.0, 27.0, 26.1, 25.4, 24.1, 23.5, 23.0, 18.3, 17.1, 14.2, –4.25, –4.33; MS (ESI) *m/z* (relative intensity) 449 ($[M+Na]^+$, 100), 427 (15), 335 (18), 295 (20); HRMS (ESI) *m/z* calculated for $C_{23}H_{42}O_5NaSi$ (M+Na) 449.2699, found 449.2712.



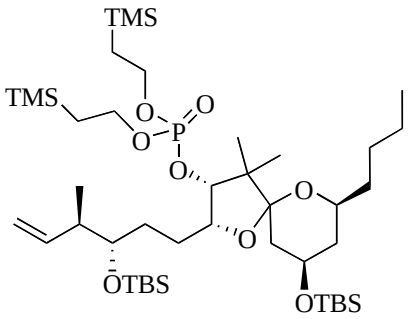
(2*R*,3*R*,7*S*,9*R*)-7-Butyl-9-(*tert*-butyldimethylsilanyloxy)-2-((*3S*,*4R*)-3-hydroxy-4-methylhex-5-enyl)-4,4-dimethyl-1,6-dioxaspiro[4.5]decan-3-ol (163). To a solution of **161** (30 mg, 0.70 mmol) in CH_2Cl_2 (7 mL) was added DIBAL (1.0 M in hexane, 90 μL, 0.090 mmol) at –78 ºC and the mixture was stirred for 2 h at –78 ºC. The reaction mixture was quenched with MeOH/EtOAc (2 mL/2 mL), allowed to warm to room temperature, and treated with saturated aqueous Rochelle salt (3 mL). After stirred for 5 h at room temperature, the aqueous layer was extracted with CH_2Cl_2 (3x20 mL). The combined organic layers were dried ($MgSO_4$) and

concentrated to give crude aldehyde. Without further purification, this aldehyde was used for the next step. To a well-stirred mixture of *trans*-2-butene (0.2 mL) and KO*t*-Bu (112 mg, 1.00 mmol) in THF (1 mL), *n*-BuLi (1.4 M in hexane, 0.70 mL, 1.0 mmol) was added at –78 ºC. Following the completion of addition, the mixture was stirred at –45 ºC for 15 min and again cooled to –78 ºC. To the mixture, a solution of *B*-methoxylbis(2-isocaranyl)borane (380 mg, 1.20 mmol) in ethyl ether (0.5 mL) was added dropwise and the resulting mixture was stirred for 30 min at –78 ºC. The addition of BF_3•etherate (0.16 mL, 1.3 mmol) and stirring the mixture at –78 ºC for 15 min afforded *B*-[*E*]-crotyl(2-isocaranyl)borane. A solution of crude aldehyde (30 mg) in ethyl ether (0.5 mL) was added at –78 ºC and the mixture was stirred for 3 h at –78 ºC. MeOH (0.16 mL) was added, then the mixture was brought to room temperature and oxidized with alkaline hydrogen peroxide (30% H_2O_2 (0.8 mL) and 3N NaOH (0.4 mL)) at reflux for 3 h. The aqueous layer was extracted with EtOAc (3x25 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexane/ethyl ether, 10:1-4:1) to give **163** (18 mg, 0.037 mmol, 53% over 2 steps) as a colorless oil: $[\alpha]_D$ –30 (*c* 1.0, $CHCl_3$); IR (neat) 3510, 2955, 2929, 2858, 1467, 1388, 1252, 1143, 1111, 1076, 1050, 1001, 963, 933, 866 cm^{-1}; ^1H NMR δ 5.86-5.74 (m, 1 H), 5.13 (s, 1 H), 5.10-5.07 (m, 1 H), 4.15 (dt, 1 H, *J* = 4.5, 6.8 Hz), 4.02 (tt, 1 H, *J* = 4.7, 11.0 Hz), 3.82-3.75 (m, 1 H), 3.59 (br. s, 1 H), 3.47 (ddd, 1 H, *J* = 3.3, 6.0, 8.6 Hz), 3.30 (br, 1 H), 2.26 (sx, 1 H, *J* = 6.8 Hz), 1.84-1.63 (m, 6 H), 1.57-1.40 (m, 3 H), 1.37-1.22 (m, 5 H), 1.23-1.15 (m, 1 H), 1.12 (s, 3 H), 1.06 (d, 3 H, *J* = 6.8 Hz), 0.96 (s, 3 H), 0.90 (t, 3 H, *J* = 6.9 Hz), 0.89 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR δ (125 MHz) 140.8, 116.1, 109.9, 82.5, 80.5, 74.9, 69.0, 66.2, 49.5, 44.1, 41.5, 37.8, 35.8, 30.9, 28.1, 27.2, 26.1, 23.0, 22.9, 18.3, 17.0, 16.5, 14.2, –4.2; MS (ESI) *m/z* (relative intensity) 507

([M+Na]$^+$, 100), 480 (10), 353 (12); HRMS (ESI) *m/z* calculated for $C_{27}H_{52}O_5NaSi$ (M+Na) 507.3482, found 507.3490.



(2*R*,3*R*,7*S*,9*R*)-7-Butyl-9-(*tert*-butyldimethylsilanyloxy)-2-[(*3S*,*4R*)-3-(*tert*-butyldimethylsilanyloxy)-4-methylhex-5-enyl]-4,4-dimethyl-1,6-dioxaspiro[4.5]decan-3-ol (164). To a solution of **163** (14 mg, 0.029 mmol) and imidazole (27 mg, 0.43 mmol) in DMF (0.5 L) was added TBSCl (44 mg, 0.29 mmol). The mixture was stirred overnight and water was added. The aqueous layer was extracted with EtOAc (3x20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexane/EtOAc, 10:1) to give **164** (17 mg, 0.028 mmol, 97%) as a colorless oil: $[\alpha]_D$ –21 (*c* 1.2, $CHCl_3$); IR (neat) 3515, 2956, 2929, 2857, 1463, 1389, 1254, 1110, 1081, 1052, 1004, 865, 836 cm^{-1}; ^{1}H NMR δ 5.88-5.77 (m, 1 H), 5.04-4.98 (m, 2 H), 4.10-3.98 (m, 2 H), 3.82-3.73 (m, 1 H), 3.60-3.55 (m, 1 H), 3.54 (dd, 1 H, *J* = 4.3, 12.1 Hz), 3.19 (d, 1 H, *J* = 12.2 Hz), 2.37-2.28 (m, 1 H), 1.82-1.73 (m, 2 H), 1.66-1.40 (m, 7 H), 1.37-1.26 (m, 4 H), 1.22-1.14 (m, 1 H), 1.11 (s, 3 H), 1.02 (d, 3 H, *J* = 6.9 Hz), 0.95 (s, 3 H), 0.94-0.89 (m, 21 H), 0.075 (m, 6 H), 0.069 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR δ 141.4, 114.5, 109.7, 82.6, 80.5, 76.3, 68.9, 66.3, 49.6, 43.1, 41.5, 37.8, 35.9, 30.5, 28.2, 27.6, 26.2, 26.1, 23.1, 22.9, 18.4, 18.3, 17.0, 16.1, 14.2, –4.0, –4.2, –4.26, –4.32; MS (ESI) *m/z* (relative intensity) 622 ([M+Na]$^+$, 100), 566 (8), 413 (13); HRMS (ESI) *m/z* calculated for $C_{33}H_{66}O_5NaSi_2$ (M+Na) 621.4347, found 621.4370.



(2*R*,3*R*,7*S*,9*R*)-Phosphoric acid 7-butyl-9-(*tert*-butyldimethylsilanyloxy)-2-[(*3S*,*4R*)-3-(*tert*-butyldimethylsilanyloxy)-4-methylhex-5-enyl]-4,4-dimethyl-1,6-dioxaspiro[4.5]dec-3-yl ester bis-[2-(trimethylsilanyl)ethyl] ester (165). PCl_3 (2 M in CH_2Cl_2, 50 μL, 0.10 mmol) was added to a solution of **164** (17 mg, 0.028 mmol) in pyridine (0.6 mL) at 0 ºC in one portion. After 10 min, 2-trimethylsilylethanol (86 μL, 0.60 mmol) and DMAP (1 mg) were added and the mixture was warmed to room temperature over 1 h. CH_2Cl_2 (3.6 mL) and 30% aqueous H_2O_2 (0.36 mL) were added and the stirring was continued for 1 h at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (3x15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on SiO_2 (hexane/ethyl ether, 10:1) to give **165** (16 mg, 0.018 mmol, 64%) as a white solid: Mp 49 °C; $[\alpha]_D$ –11 (*c* 1.0, $CHCl_3$); IR (neat) 2956, 2929, 2894, 2857, 1472, 1385, 1252, 1005, 860, 836 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 6.04 (ddd, 1 H, *J* = 7.7, 10.3, 17.8 Hz), 5.16 (d, 1 H, *J* = 17.3 Hz), 5.12 (dd, 1 H, *J* = 1.3, 10.4 Hz), 4.66 (dd, 1 H, *J* = 5.6, 10.2 Hz), 4.40-4.30 (m, 5 H), 4.21-4.17 (m, 1 H), 3.97-3.92 (m, 1 H), 3.81 (dt, 1 H, *J* = 3.2, 5.2 Hz), 2.55-2.50 (m, 1 H), 2.07-2.01 (m, 2 H), 1.99-1.93 (m, 2 H), 1.87 (q, 1 H, *J* = 10.2 Hz), 1.79-1.70 (m, 2 H), 1.64-1.58 (m, 1 H), 1.50-1.34 (m, 6 H), 1.38 (s, 3 H), 1.20 (t, 2 H, *J* = 8.6 Hz), 1.17 (d, 3 H, *J* = 6.9 Hz), 1.14 (t, 2 H, *J* = 8.6 Hz), 1.06 (s, 9 H), 1.03 (t, 3 H, *J* = 7.2 Hz), 1.01 (s, 9 H), 0.84 (s, 3 H), 0.28 (s, 3 H), 0.16 (s, 3 H), 0.12 (s, 3 H), 0.11 (s, 3 H), –0.03 (s, 9 H), –0.05 (s, 9 H); ^{13}C NMR δ 141.1, 114.5, 108.2, 85.64, 85.56, 80.6, 80.5, 76.3, 68.4, 66.9, 66.2, 66.1,

50.3, 50.2, 43.1, 41.6, 38.5, 36.1, 31.4, 28.2, 27.9, 26.2, 26.1, 23.8, 23.2, 20.1, 20.0, 19.94, 19.86, 18.4, 18.3, 17.4, 16.1, 14.3, –1.3, –3.8, –4.2, –4.3, –4.4; MS (ESI) *m/z* (relative intensity) 902 ($[M+Na]^+$, 100), 880 (6), 817 (5), 747 (6); HRMS (ESI) *m/z* calculated for $C_{43}H_{91}O_8NaSi_4P$ (M+Na) 901.5426, found 901.5460.

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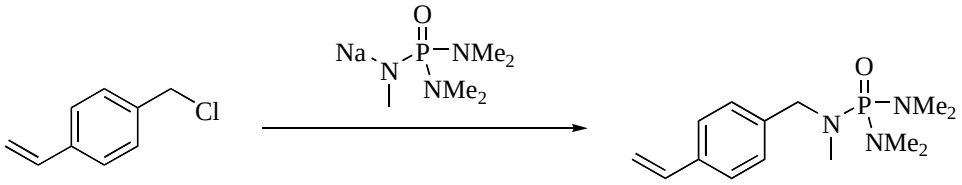

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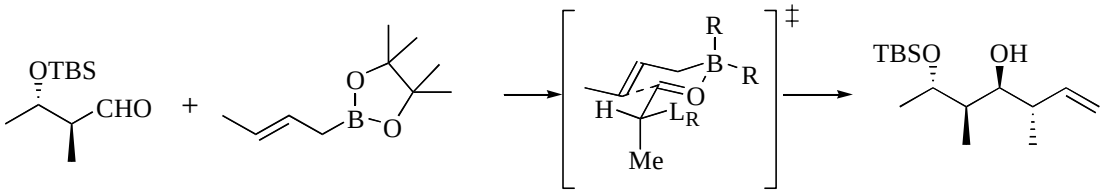

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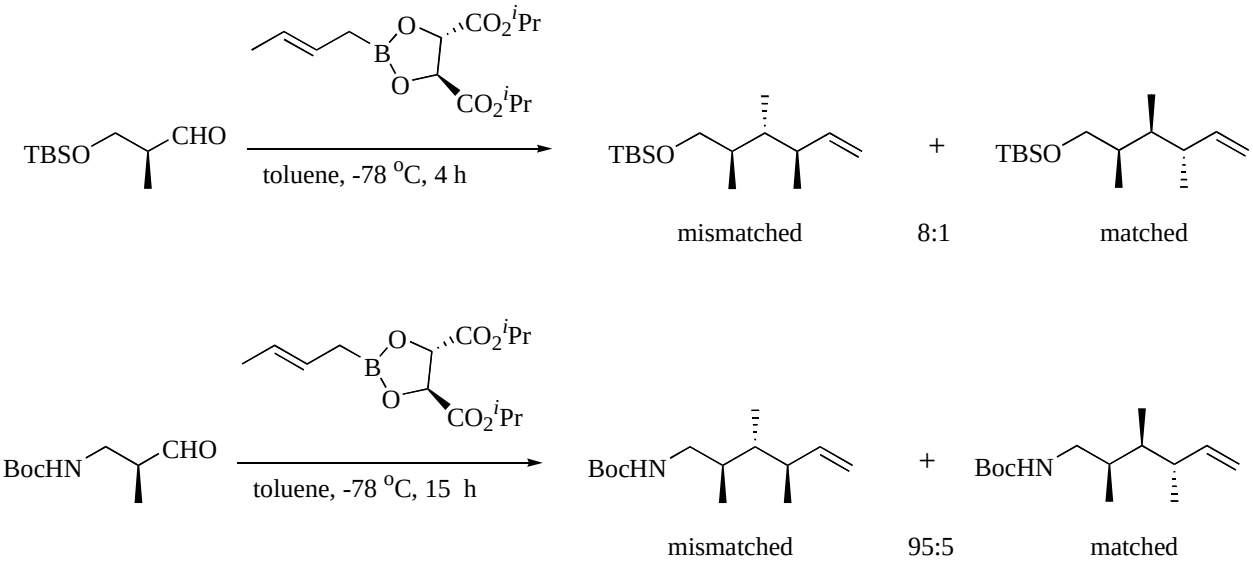
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APPENDIX A

X-ray crystal data for 111

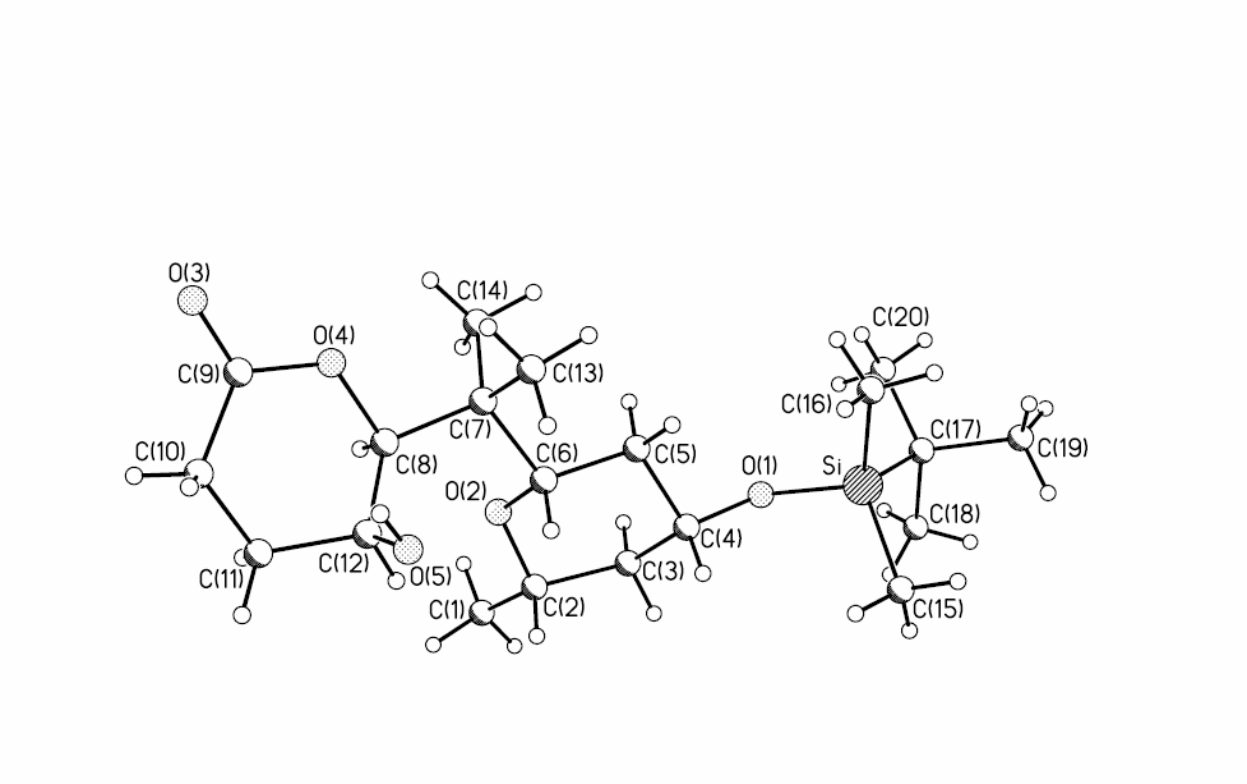

Table 1. Crystal data and structure refinement for gm0524m.

Identification code	gm0524m	
Empirical formula	C20 H38 O5 Si	
Formula weight	386.59	
Temperature	295(2) K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 6.820(3) Å	a= 90°.
	b = 6.419(3) Å	b= 92.122(10)°.
	c = 26.668(12) Å	g = 90°.
Volume	1166.6(9) $Å^3$	
Z	2	
Density (calculated)	1.101 Mg/m^3	
Absorption coefficient	0.125 mm^{-1}	

F(000)	424
Crystal size	0.07 x 0.07 x 0.24 mm^3
Theta range for data collection	1.53 to 23.00°.
Index ranges	-7<=h<=7, -6<=k<=7, -29<=l<=29
Reflections collected	7260
Independent reflections	3050 [R(int) = 0.3388]
Completeness to theta = 23.00°	99.9 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3050 / 1 / 210
Goodness-of-fit on F^2	0.940
Final R indices [I>2sigma(I)]	R1 = 0.1218, wR2 = 0.2322
R indices (all data)	R1 = 0.3016, wR2 = 0.3322
Absolute structure parameter	1.4(8)
Extinction coefficient	0.009(5)
Largest diff. peak and hole	0.341 and -0.269 $e.Å^{-3}$

Table 2. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2x10^3$) for gm0524m. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Si	8711(8)	10036(9)	1325(2)	64(2)
O(1)	9487(17)	8069(15)	1694(3)	61(4)
C(1)	13860(20)	3930(20)	2798(7)	69(6)
O(2)	11559(13)	6411(15)	3104(3)	41(3)
C(2)	12940(20)	6020(20)	2727(6)	46(4)
O(3)	9344(14)	8753(16)	5263(3)	47(3)
C(3)	11810(20)	6230(30)	2204(6)	66(5)
O(4)	9672(12)	8638(15)	4458(3)	37(3)
C(4)	10700(20)	8210(30)	2131(6)	59(5)
C(5)	9400(20)	8520(30)	2596(6)	63(5)
O(5)	12904(16)	11324(17)	4023(4)	57(3)
C(6)	10658(19)	8360(20)	3081(5)	32(3)
C(7)	9460(20)	8620(20)	3573(6)	39(4)
C(8)	10893(18)	8150(20)	4018(4)	29(3)
C(9)	10430(20)	8610(20)	4928(5)	30(3)
C(10)	12620(20)	8780(30)	5005(6)	61(5)
C(11)	13840(20)	8360(30)	4560(5)	54(5)
C(12)	12839(19)	9190(20)	4073(5)	30(4)
C(13)	8690(20)	10890(20)	3570(6)	59(5)
C(14)	7760(19)	7050(20)	3577(5)	48(5)
C(15)	10760(30)	11650(30)	1156(7)	94(7)
C(16)	6860(30)	11680(40)	1662(9)	134(9)
C(17)	7400(40)	8710(30)	797(7)	87(7)
C(18)	9040(40)	7400(40)	505(7)	155(14)
C(19)	6570(30)	10380(30)	413(7)	104(8)
C(20)	5740(40)	7350(40)	994(9)	149(12)

Table 3. Bond lengths [Å] and angles [°] for gm0524m.

Si-O(1) 1.675(10)	C(6)-O(2)-C(2)115.4(11)
Si-C(15) 1.808(19)	O(2)-C(2)-C(1)110.9(13)
Si-C(17) 1.849(19)	O(2)-C(2)-C(3)107.2(11)
Si-C(16) 1.90(2)	C(1)-C(2)-C(3)112.3(13)
O(1)-C(4) 1.408(17)	C(4)-C(3)-C(2)114.7(14)
C(1)-C(2) 1.490(19)	C(9)-O(4)-C(8)121.6(10)
O(2)-C(6) 1.394(16)	O(1)-C(4)-C(3)109.5(13)
O(2)-C(2) 1.424(16)	O(1)-C(4)-C(5)109.1(13)
C(2)-C(3) 1.57(2)	C(3)-C(4)-C(5)107.8(13)
O(3)-C(9) 1.187(14)	C(6)-C(5)-C(4)110.1(12)
C(3)-C(4) 1.49(2)	O(2)-C(6)-C(5)109.2(11)
O(4)-C(9) 1.340(15)	O(2)-C(6)-C(7)107.6(11)
O(4)-C(8) 1.496(15)	C(5)-C(6)-C(7)113.7(11)
C(4)-C(5) 1.57(2)	C(8)-C(7)-C(14)108.8(12)
C(5)-C(6) 1.532(18)	C(8)-C(7)-C(13)113.1(12)
O(5)-C(12) 1.379(15)	C(14)-C(7)-C(13)111.4(11)
C(6)-C(7) 1.580(19)	C(8)-C(7)-C(6)106.5(10)
C(7)-C(8) 1.542(18)	C(14)-C(7)-C(6)110.5(12)
C(7)-C(14) 1.536(19)	C(13)-C(7)-C(6)106.4(12)
C(7)-C(13) 1.55(2)	C(12)-C(8)-O(4)110.5(10)
C(8)-C(12) 1.487(17)	C(12)-C(8)-C(7)121.8(12)
C(9)-C(10) 1.50(2)	O(4)-C(8)-C(7)101.9(9)
C(10)-C(11) 1.50(2)	O(3)-C(9)-O(4)118.2(12)
C(11)-C(12) 1.541(19)	O(3)-C(9)-C(10)122.5(12)
C(17)-C(20) 1.54(3)	O(4)-C(9)-C(10)118.4(13)
C(17)-C(19) 1.58(2)	C(9)-C(10)-C(11)117.2(13)
C(17)-C(18) 1.62(3)	C(10)-C(11)-C(12)111.2(12)
O(1)-Si-C(15)110.3(8)	O(5)-C(12)-C(8)117.9(12)
O(1)-Si-C(17)103.5(7)	O(5)-C(12)-C(11)114.3(13)
C(15)-Si-C(17)115.5(10)	C(8)-C(12)-C(11)107.1(12)
O(1)-Si-C(16)110.0(9)	C(20)-C(17)-C(19)110.8(19)
C(15)-Si-C(16)109.6(11)	C(20)-C(17)-C(18)113.6(19)
C(17)-Si-C(16)107.8(10)	C(19)-C(17)-C(18)106.5(16)
C(4)-O(1)-Si127.0(10)	C(20)-C(17)-Si110.0(14)
	C(19)-C(17)-Si109.4(13)
	C(18)-C(17)-Si106.4(15)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2x10^3$) for gm0524m. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si	83(4)	66(3)	43(3)	4(3)	-5(3)	8(3)
O(1)	122(10)	39(7)	21(5)	9(5)	-33(6)	18(7)
C(1)	80(13)	38(11)	92(14)	-27(10)	17(11)	27(10)
O(2)	48(6)	37(6)	37(6)	-17(5)	12(5)	8(5)
O(3)	51(7)	51(7)	40(6)	1(5)	18(6)	-13(6)
C(3)	77(12)	75(14)	46(11)	-22(10)	5(9)	-5(12)
O(4)	21(5)	52(7)	40(6)	-13(5)	11(4)	-10(5)
C(4)	88(13)	19(10)	69(12)	-2(9)	-6(11)	20(10)
C(5)	76(12)	48(12)	64(11)	-12(10)	-14(10)	47(10)
O(5)	54(7)	41(7)	78(9)	7(6)	40(6)	-18(6)
C(7)	36(9)	19(9)	64(10)	-6(8)	20(8)	14(7)
C(10)	85(12)	64(13)	34(9)	-18(9)	11(9)	6(11)
C(11)	62(11)	51(12)	48(10)	-24(9)	-19(9)	22(10)
C(14)	33(9)	59(12)	52(10)	-15(8)	8(8)	29(9)
C(15)	93(15)	95(17)	93(16)	25(13)	-8(13)	3(14)
C(17)	180(20)	21(11)	57(11)	7(10)	-33(13)	15(14)
C(18)	300(30)	120(20)	43(12)	-18(13)	-17(17)	140(20)
C(19)	190(20)	53(14)	62(11)	16(11)	-59(13)	29(15)
C(20)	240(30)	80(20)	120(20)	14(17)	-70(20)	-80(20)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x10^3) for gm0524m.

	x	y	z	U(eq)
H(1A)	14879	4015	3057	104
H(1B)	14422	3498	2490	104
H(1C)	12889	2947	2893	104
H(2)	13968	7089	2751	55
H(3A)	12757	6113	1942	79
H(3B)	10905	5074	2165	79
H(4)	11615	9382	2103	71
H(5A)	8769	9874	2577	76
H(5B)	8379	7463	2594	76
H(5)	12387	11870	4262	85
H(6)	11676	9435	3078	38
H(8)	11127	6643	4021	34
H(10A)	13026	7814	5270	73
H(10B)	12926	10171	5125	73
H(11A)	14051	6866	4529	65
H(11B)	15115	9015	4610	65
H(12)	13610	8636	3800	36
H(13A)	7658	11040	3318	88
H(13B)	9743	11826	3499	88
H(13C)	8192	11221	3893	88
H(14A)	8244	5684	3500	71
H(14B)	6768	7441	3330	71
H(14C)	7210	7030	3903	71
H(15A)	11552	11962	1451	141
H(15B)	10278	12916	1007	141
H(15C)	11536	10913	920	141
H(16A)	7527	12527	1910	201
H(16B)	5943	10781	1822	201
H(16C)	6162	12553	1423	201
H(18A)	8997	7778	157	233
H(18B)	8781	5932	536	233

H(18C)	10320	7701	650	233
H(19A)	7622	10964	230	156
H(19B)	5929	11474	593	156
H(19C)	5636	9739	183	156
H(20A)	5222	7988	1287	224
H(20B)	6243	5993	1080	224
H(20C)	4715	7217	739	224

APPENDIX B

X-ray crystal data for 147

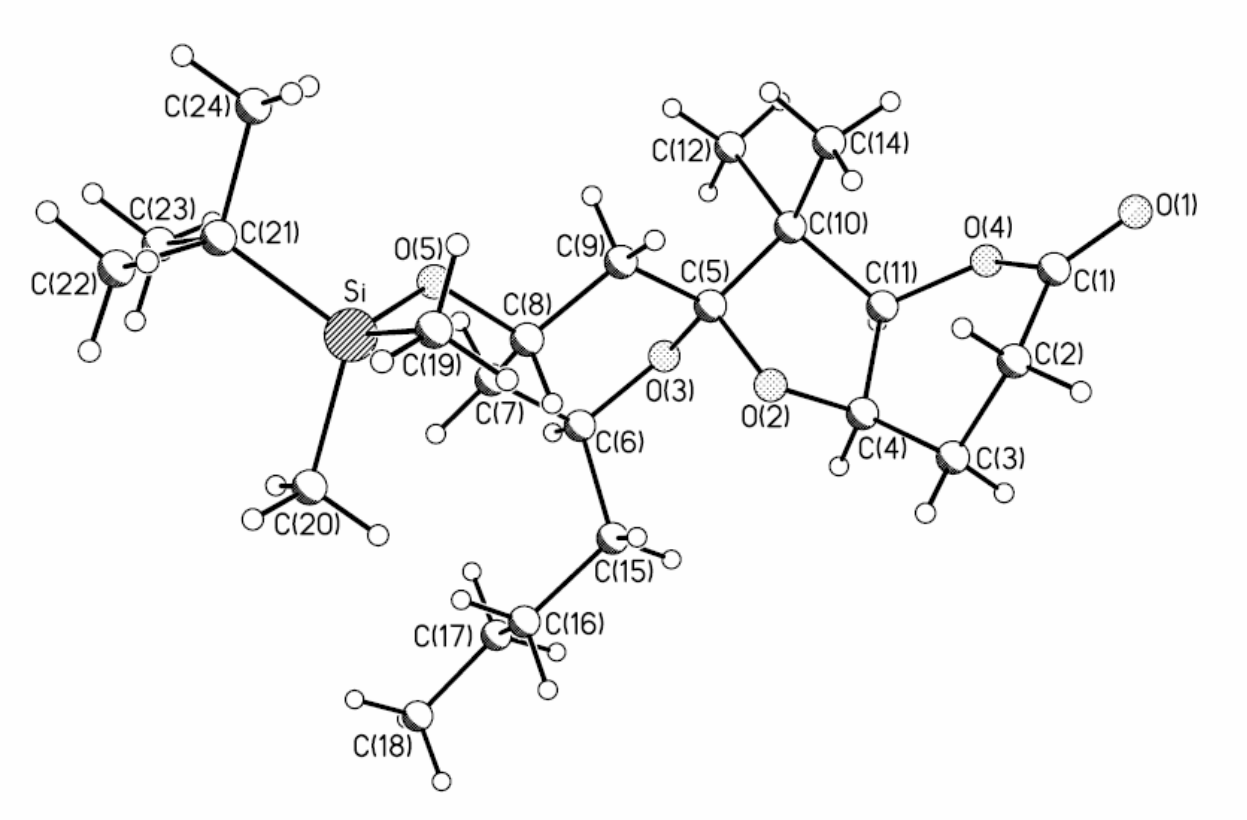

Table 1. Crystal data and structure refinement for gm0514s.

Identification code	gm0514s	
Empirical formula	C23 H42 O5 Si	
Formula weight	426.66	
Temperature	295(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 6.659(2) Å	α= 90°.
	b = 10.646(4) Å	β= 99.486(7)°.
	c = 17.916(6) Å	γ = 90°.
Volume	1252.6(7) Å^3	
Z	2	
Density (calculated)	1.131 Mg/m^3	

Absorption coefficient	0.122 mm^{-1}
F(000)	468
Crystal size	0.12 x 0.12 x 0.24 mm^3
Theta range for data collection	2.23 to 24.00°.
Index ranges	-7<=h<=7, -12<=k<=12, -20<=l<=20
Reflections collected	8906
Independent reflections	3929 [R(int) = 0.1087]
Completeness to theta = 24.00°	100.0 %
Absorption correction	Sadabs
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3929 / 1 / 247
Goodness-of-fit on F^2	1.404
Final R indices [I>2sigma(I)]	R1 = 0.1280, wR2 = 0.2392
R indices (all data)	R1 = 0.2061, wR2 = 0.2564
Absolute structure parameter	0.1(5)
Largest diff. peak and hole	1.219 and -0.258 e.$Å^{-3}$

Table 2. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2x10^3$) for gm0514s. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Si	1701(4)	4058(3)	4166(2)	51(1)
O(1)	-4223(14)	-1758(10)	393(5)	105(4)
C(1)	-2910(20)	-976(17)	532(6)	68(3)
O(2)	323(10)	1477(6)	1503(4)	44(2)
C(2)	-3316(18)	428(14)	520(6)	78(4)
O(3)	3731(11)	980(6)	1908(4)	48(2)
C(3)	-1648(18)	1220(12)	263(6)	64(4)
O(4)	-942(13)	-1318(7)	657(4)	71(3)
C(4)	381(17)	926(11)	792(5)	55(3)
O(5)	2336(12)	2716(7)	3821(4)	67(2)
C(5)	1738(15)	754(9)	2043(5)	36(3)
C(6)	4720(16)	2147(10)	2121(6)	47(3)
C(7)	4563(16)	2511(11)	2904(6)	59(3)
C(8)	2428(16)	2464(10)	3054(5)	45(3)
C(9)	1532(17)	1218(10)	2840(5)	50(3)
C(10)	1303(15)	-595(10)	1842(5)	47(3)
C(11)	698(17)	-467(9)	962(6)	52(3)
C(12)	3139(19)	-1559(13)	2134(7)	91(4)
C(14)	-653(17)	-1048(12)	2179(6)	68(3)
C(15)	3967(15)	3186(11)	1520(6)	51(3)
C(16)	5230(20)	4403(11)	1645(6)	77(4)
C(17)	7366(19)	4265(13)	1482(10)	114(6)
C(18)	8580(20)	5513(15)	1607(9)	127(7)
C(19)	-1053(15)	4158(16)	3938(7)	102(5)
C(20)	2894(19)	5412(10)	3755(6)	72(4)
C(21)	2681(17)	3919(12)	5202(5)	53(3)
C(22)	2180(20)	5053(13)	5673(9)	117(6)
C(23)	4935(18)	3820(15)	5380(7)	97(5)
C(24)	1730(20)	2835(15)	5514(7)	108(5)

Table 3. Bond lengths [Å] and angles [°] for gm0514s.

Si-O(5) 1.640(8)	O(5)-Si-C(19)106.2(6)	C(8)-C(9)-C(5)115.7(9)
Si-C(19) 1.815(10)	O(5)-Si-C(20)111.9(4)	C(5)-C(10)-C(11)99.5(8)
Si-C(20) 1.856(12)	C(19)-Si-C(20)110.4(7)	C(5)-C(10)-C(14)109.7(9)
Si-C(21) 1.869(10)	O(5)-Si-C(21)103.7(5)	C(11)-C(10)-C(14)108.4(8)
O(1)-C(1) 1.205(14)	C(19)-Si-C(21)113.7(5)	C(5)-C(10)-C(12)115.2(9)
C(1)-O(4) 1.341(13)	C(20)-Si-C(21)110.7(5)	C(11)-C(10)-C(12)115.8(9)
C(1)-C(2) 1.518(18)	O(1)-C(1)-O(4)120.2(15)	C(14)-C(10)-C(12)107.9(9)
O(2)-C(4) 1.409(11)	O(1)-C(1)-C(2)123.7(13)	O(4)-C(11)-C(4)117.4(9)
O(2)-C(5) 1.454(11)	O(4)-C(1)-C(2)116.0(13)	O(4)-C(11)-C(10)112.1(8)
C(2)-C(3) 1.525(15)	C(4)-O(2)-C(5)105.6(7)	C(4)-C(11)-C(10)106.9(8)
O(3)-C(5) 1.408(10)	C(1)-C(2)-C(3)114.2(12)	C(16)-C(15)-C(6)112.8(8)
O(3)-C(6) 1.429(10)	C(5)-O(3)-C(6)120.6(8)	C(17)-C(16)-C(15)113.6(10)
C(3)-C(4) 1.549(15)	C(2)-C(3)-C(4)108.0(10)	C(16)-C(17)-C(18)112.0(12)
O(4)-C(11) 1.455(11)	C(1)-O(4)-C(11)123.1(10)	C(24)-C(21)-C(23)110.2(13)
C(4)-C(11) 1.521(14)	O(2)-C(4)-C(11)104.4(8)	C(24)-C(21)-C(22)105.2(10)
O(5)-C(8) 1.412(12)	O(2)-C(4)-C(3)108.5(8)	C(23)-C(21)-C(22)104.0(10)
C(5)-C(10) 1.497(13)	C(11)-C(4)-C(3)113.5(10)	C(24)-C(21)-Si109.8(8)
C(5)-C(9) 1.540(12)	C(8)-O(5)-Si126.0(7)	C(23)-C(21)-Si113.1(8)
C(6)-C(7) 1.475(13)	O(3)-C(5)-O(2)108.8(8)	C(22)-C(21)-Si114.2(10)
C(6)-C(15) 1.567(15)	O(3)-C(5)-C(10)105.9(8)	
C(7)-C(8) 1.490(14)	O(2)-C(5)-C(10)105.7(8)	
C(8)-C(9) 1.479(13)	O(3)-C(5)-C(9)109.6(8)	
C(10)-C(11) 1.568(13)	O(2)-C(5)-C(9)107.4(7)	
C(10)-C(14) 1.598(13)	C(10)-C(5)-C(9)119.2(8)	
C(10)-C(12) 1.615(15)	O(3)-C(6)-C(7)112.4(9)	
C(15)-C(16) 1.542(14)	O(3)-C(6)-C(15)110.4(8)	
C(16)-C(17) 1.505(17)	C(7)-C(6)-C(15)113.8(9)	
C(17)-C(18) 1.553(17)	C(6)-C(7)-C(8)112.4(9)	
C(21)-C(24) 1.469(16)	O(5)-C(8)-C(9)110.0(9)	
C(21)-C(23) 1.486(14)	O(5)-C(8)-C(7)111.4(8)	
C(21)-C(22) 1.539(16)	C(9)-C(8)-C(7)109.9(9)	

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for gm0514s. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si	50(2)	52(2)	50(2)	-28(2)	5(1)	-1(2)
O(1)	91(7)	135(10)	87(7)	-19(6)	9(6)	-59(8)
C(1)	64(9)	89(11)	48(7)	-21(9)	-1(6)	-5(10)
O(2)	42(4)	41(5)	52(5)	-18(4)	11(4)	-10(4)
C(2)	59(9)	126(14)	41(8)	-15(8)	-17(7)	-4(9)
O(3)	55(5)	35(4)	57(5)	-3(4)	20(4)	2(4)
C(3)	74(9)	85(10)	37(7)	-23(7)	20(6)	-18(8)
O(4)	65(6)	75(7)	73(6)	-23(5)	8(4)	-3(5)
C(4)	61(8)	82(9)	26(6)	4(6)	19(5)	28(7)
O(5)	86(6)	72(6)	41(5)	-1(4)	6(4)	-1(5)
C(6)	48(7)	54(8)	41(7)	-14(6)	15(6)	-35(6)
C(7)	46(7)	86(10)	42(7)	7(7)	-6(6)	-29(7)
C(8)	58(8)	45(7)	23(6)	-4(5)	-16(5)	-5(6)
C(9)	64(8)	55(8)	30(6)	-4(5)	5(5)	2(6)
C(11)	54(7)	37(7)	68(8)	-19(6)	14(6)	-14(6)
C(14)	100(9)	54(7)	56(7)	-18(7)	29(6)	-38(8)
C(15)	47(7)	68(9)	44(7)	-14(6)	21(5)	-18(6)
C(16)	124(13)	56(10)	48(7)	14(6)	3(7)	0(9)
C(17)	51(8)	56(10)	225(17)	10(11)	-7(10)	-22(8)
C(18)	89(12)	104(14)	182(17)	63(12)	7(11)	-2(11)
C(19)	38(7)	146(15)	115(10)	-24(13)	-12(7)	6(10)
C(20)	113(11)	53(8)	48(7)	-18(6)	6(7)	4(8)
C(21)	71(8)	45(7)	42(6)	-19(6)	4(5)	-33(7)
C(22)	133(14)	89(12)	145(15)	-64(11)	69(12)	-33(11)
C(23)	69(9)	144(15)	72(9)	-29(10)	-4(7)	13(10)
C(24)	150(14)	127(14)	47(9)	-7(9)	16(9)	6(13)

Table 5. Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($Å^2 x10^3$) for gm0514s.

	x	y	z	U(eq)
H(2A)	-3482	692	1024	94
H(2B)	-4589	591	185	94
H(3A)	-1971	2106	291	77
H(3B)	-1534	1020	-256	77
H(4A)	1530	1262	576	66
H(6A)	6171	2019	2107	56
H(7A)	5087	3357	2997	71
H(7B)	5400	1952	3253	71
H(8A)	1630	3104	2742	53
H(9A)	96	1247	2878	60
H(9B)	2168	607	3206	60
H(11A)	1892	-723	744	63
H(12A)	4335	-1307	1938	137
H(12B)	2753	-2391	1960	137
H(12C)	3421	-1552	2677	137
H(14A)	-1742	-459	2041	103
H(14B)	-324	-1096	2721	103
H(14C)	-1068	-1861	1979	103
H(15A)	4035	2861	1019	62
H(15B)	2553	3379	1541	62
H(16A)	4543	5056	1322	93
H(16B)	5293	4672	2166	93
H(17A)	7314	3993	963	137
H(17B)	8069	3622	1810	137
H(18A)	9947	5379	1516	190
H(18B)	8618	5793	2119	190
H(18C)	7933	6140	1264	190
H(19A)	-1649	3452	4154	154
H(19B)	-1460	4152	3399	154
H(19C)	-1506	4922	4142	154
H(20A)	2395	5456	3221	108

H(20B)	4346	5306	3837	108
H(20C)	2559	6174	3993	108
H(22A)	2714	4911	6197	176
H(22B)	729	5157	5612	176
H(22C)	2781	5797	5502	176
H(23A)	5350	3759	5918	145
H(23B)	5538	4551	5195	145
H(23C)	5373	3084	5142	145
H(24A)	2217	2779	6048	162
H(24B)	2080	2081	5271	162
H(24C)	280	2938	5427	162

APPENDIX C

X-ray crystal data for 152

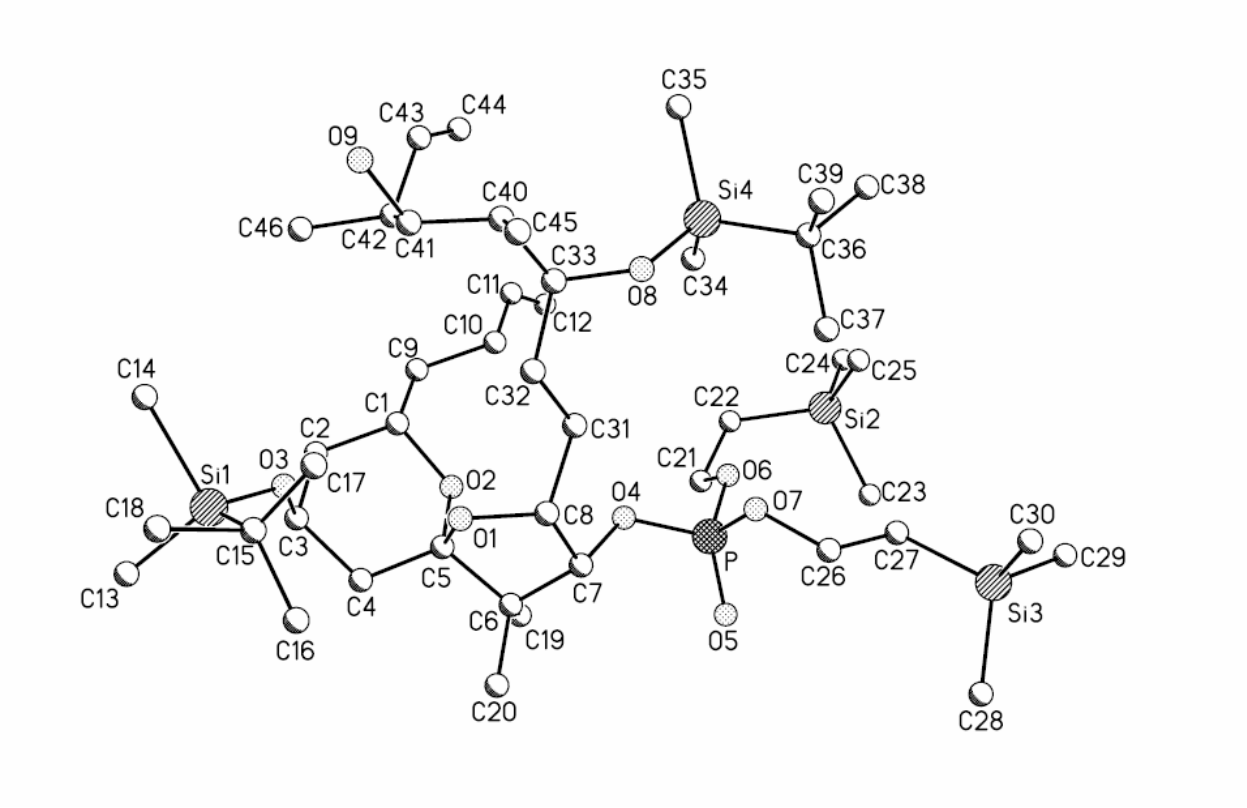

Table 1. Crystal data and structure refinement for gilma2s.

Identification code	gilma2s	
Empirical formula	C46 H97 O9 P Si4	
Formula weight	937.57	
Temperature	295(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 12.3756(6) Å	α= 90°.
	b = 14.1440(7) Å	β= 90°.
	c = 35.1624(17) Å	γ = 90°.
Volume	6154.8(5) Å^3	
Z	4	
Density (calculated)	1.012 Mg/m^3	

Absorption coefficient	0.165 mm^{-1}
F(000)	2064
Crystal size	0.13 x 0.15 x 0.22 mm^3
Theta range for data collection	1.55 to 24.00°.
Index ranges	-14<=h<=14, -16<=k<=16, -40<=l<=40
Reflections collected	45522
Independent reflections	9665 [R(int) = 0.0720]
Completeness to theta = 24.00°	99.9 %
Absorption correction	Sadabs
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9665 / 4 / 541
Goodness-of-fit on F^2	1.172
Final R indices [I>2sigma(I)]	R1 = 0.0717, wR2 = 0.1632
R indices (all data)	R1 = 0.1295, wR2 = 0.1798
Absolute structure parameter	0.00(15)
Largest diff. peak and hole	0.409 and -0.431 $e.Å^{-3}$

Table 2. Atomic coordinates ($x10^4$) and equivalent isotropic displacement parameters ($Å^2x10^3$) for gilma2s. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
P	6372(1)	10490(1)	8579(1)	78(1)
Si(1)	10683(3)	5766(2)	9320(1)	176(1)
Si(2)	6029(2)	13608(1)	8874(1)	136(1)
Si(3)	5070(2)	11587(2)	7276(1)	103(1)
Si(4)	10797(1)	11657(1)	8165(1)	88(1)
O(1)	8770(2)	7944(2)	8890(1)	60(1)
O(2)	8415(2)	8820(2)	9438(1)	62(1)
O(3)	10154(3)	6780(2)	9388(1)	88(1)
O(4)	7174(2)	9860(2)	8807(1)	62(1)
O(5)	5254(3)	10174(3)	8570(1)	119(2)
O(6)	6586(4)	11474(3)	8755(1)	108(1)
O(7)	6903(3)	10574(3)	8179(1)	96(1)
O(8)	10862(2)	10501(2)	8140(1)	69(1)
O(9)	13794(3)	8717(3)	8708(1)	113(2)
C(1)	9507(4)	8785(4)	9591(1)	70(1)
C(2)	9646(5)	7940(5)	9844(2)	98(2)
C(3)	9335(4)	7035(5)	9647(2)	88(2)
C(4)	8232(4)	7127(4)	9456(2)	78(2)
C(5)	8127(3)	8014(3)	9223(1)	61(1)
C(6)	6971(4)	8240(3)	9063(1)	66(1)
C(7)	7245(3)	8859(3)	8719(1)	55(1)
C(8)	8392(3)	8586(3)	8602(1)	55(1)
C(9)	9678(5)	9712(5)	9801(2)	104(2)
C(10)	9499(6)	10582(5)	9581(2)	115(2)
C(11)	9632(10)	11484(8)	9804(4)	230(6)
C(12)	9000(20)	12004(12)	9893(8)	500(20)
C(13)	10228(16)	4843(6)	9653(4)	328(11)
C(14)	12177(7)	5835(11)	9469(5)	344(12)
C(15)	10665(8)	5531(7)	8834(3)	242(8)
C(16)	9459(10)	5331(12)	8749(5)	349(11)
C(17)	11139(10)	6301(7)	8620(2)	185(4)

C(18)	11447(13)	4621(10)	8819(5)	312(8)
C(19)	6245(4)	8703(4)	9355(2)	89(2)
C(20)	6456(5)	7326(4)	8904(2)	108(2)
C(21)	6187(10)	11700(6)	9117(3)	170(4)
C(22)	6444(11)	12714(6)	9207(3)	209(5)
C(23)	4706(8)	13297(8)	8670(5)	274(8)
C(24)	5987(13)	14723(6)	9120(4)	270(8)
C(25)	6929(9)	13633(6)	8472(3)	179(4)
C(26)	6288(6)	10605(5)	7814(2)	124(2)
C(27)	5828(6)	11510(5)	7742(2)	117(2)
C(28)	4000(6)	10669(6)	7253(2)	150(3)
C(29)	4512(7)	12779(5)	7266(2)	145(3)
C(30)	6022(7)	11428(6)	6871(2)	155(3)
C(31)	9183(3)	9412(3)	8550(1)	58(1)
C(32)	10319(3)	9089(3)	8464(1)	60(1)
C(33)	11122(3)	9892(3)	8454(1)	55(1)
C(34)	9873(6)	12031(4)	8556(2)	117(2)
C(35)	12172(6)	12171(5)	8244(2)	135(3)
C(36)	10256(5)	12056(5)	7707(2)	117(2)
C(37)	9131(6)	11578(8)	7637(2)	192(5)
C(38)	10193(10)	13170(6)	7706(3)	213(5)
C(39)	11016(7)	11720(7)	7377(2)	169(4)
C(40)	12315(4)	9562(4)	8418(2)	74(2)
C(41)	12684(4)	8975(4)	8751(2)	83(2)
C(42)	12495(4)	9415(5)	9137(2)	99(2)
C(43)	13072(6)	10321(7)	9193(2)	126(3)
C(44)	12675(9)	11103(10)	9328(3)	218(6)
C(45)	12493(5)	9048(5)	8039(2)	102(2)
C(46)	12788(6)	8731(7)	9464(2)	178(4)

Table 3. Bond lengths [Å] and angles [°] for gilma2s.

P-O(5) 1.454(4)	C(4)-H(4B) 0.9700	C(19)-H(19C) 0.9600
P-O(6) 1.546(4)	C(5)-C(6) 1.570(6)	C(20)-H(20A) 0.9600
P-O(4) 1.556(3)	C(6)-C(19) 1.512(7)	C(20)-H(20B) 0.9600
P-O(7) 1.557(4)	C(6)-C(7) 1.532(6)	C(20)-H(20C) 0.9600
Si(1)-O(3) 1.596(4)	C(6)-C(20) 1.547(7)	C(21)-C(22) 1.503(11)
Si(1)-C(15) 1.743(9)	C(7)-C(8) 1.528(6)	C(21)-H(21A) 0.9700
Si(1)-C(13) 1.841(8)	C(7)-H(7A) 0.9800	C(21)-H(21B) 0.9700
Si(1)-C(14) 1.924(8)	C(8)-C(31) 1.534(6)	C(22)-H(22A) 0.9700
Si(2)-C(22) 1.799(11)	C(8)-H(8A) 0.9800	C(22)-H(22B) 0.9700
Si(2)-C(24) 1.800(9)	C(9)-C(10) 1.471(9)	C(23)-H(23A) 0.9600
Si(2)-C(25) 1.799(10)	C(9)-H(9A) 0.9700	C(23)-H(23B) 0.9600
Si(2)-C(23) 1.840(11)	C(9)-H(9B) 0.9700	C(23)-H(23C) 0.9600
Si(3)-C(29) 1.823(7)	C(10)-C(11) 1.506(11)	C(24)-H(24A) 0.9600
Si(3)-C(28) 1.856(8)	C(10)-H(10A) 0.9700	C(24)-H(24B) 0.9600
Si(3)-C(30) 1.862(7)	C(10)-H(10B) 0.9700	C(24)-H(24C) 0.9600
Si(3)-C(27) 1.892(7)	C(11)-C(12) 1.118(18)	C(25)-H(25A) 0.9600
Si(4)-O(8) 1.640(4)	C(11)-H(11A) 0.9700	C(25)-H(25B) 0.9600
Si(4)-C(36) 1.832(7)	C(11)-H(11B) 0.9700	C(25)-H(25C) 0.9600
Si(4)-C(34) 1.867(6)	C(12)-H(12A) 0.9600	C(26)-C(27) 1.424(8)
Si(4)-C(35) 1.872(7)	C(12)-H(12B) 0.9600	C(26)-H(26A) 0.9700
O(1)-C(5) 1.417(5)	C(12)-H(12C) 0.9600	C(26)-H(26B) 0.9700
O(1)-C(8) 1.440(5)	C(13)-H(13A) 0.9600	C(27)-H(27A) 0.9700
O(2)-C(5) 1.415(6)	C(13)-H(13B) 0.9600	C(27)-H(27B) 0.9700
O(2)-C(1) 1.455(5)	C(13)-H(13C) 0.9600	C(28)-H(28A) 0.9600
O(3)-C(3) 1.407(6)	C(14)-H(14A) 0.9600	C(28)-H(28B) 0.9600
O(4)-C(7) 1.452(5)	C(14)-H(14B) 0.9600	C(28)-H(28C) 0.9600
O(6)-C(21) 1.404(9)	C(14)-H(14C) 0.9600	C(29)-H(29A) 0.9600
O(7)-C(26) 1.490(7)	C(15)-C(17) 1.449(12)	C(29)-H(29B) 0.9600
O(8)-C(33) 1.437(5)	C(15)-C(16) 1.548(14)	C(29)-H(29C) 0.9600
O(9)-C(41) 1.429(6)	C(15)-C(18) 1.611(9)	C(30)-H(30A) 0.9600
O(9)-H(9C) 0.91(7)	C(16)-H(16A) 0.9600	C(30)-H(30B) 0.9600
C(1)-C(2) 1.501(7)	C(16)-H(16B) 0.9600	C(30)-H(30C) 0.9600
C(1)-C(9) 1.519(8)	C(16)-H(16C) 0.9600	C(31)-C(32) 1.509(6)
C(1)-H(1A) 0.9800	C(17)-H(17A) 0.9600	C(31)-H(31A) 0.9700
C(2)-C(3) 1.506(8)	C(17)-H(17B) 0.9600	C(31)-H(31B) 0.9700
C(2)-H(2A) 0.9700	C(17)-H(17C) 0.9600	C(32)-C(33) 1.510(6)
C(2)-H(2B) 0.9700	C(18)-H(18A) 0.9600	C(32)-H(32A) 0.9700
C(3)-C(4) 1.526(7)	C(18)-H(18B) 0.9600	C(32)-H(32B) 0.9700
C(3)-H(3A) 0.9800	C(18)-H(18C) 0.9600	C(33)-C(40) 1.554(7)
C(4)-C(5) 1.505(6)	C(19)-H(19A) 0.9600	C(33)-H(33A) 0.9800
C(4)-H(4A) 0.9700	C(19)-H(19B) 0.9600	C(34)-H(34A) 0.9600

C(34)-H(34B) 0.9600
C(34)-H(34C) 0.9600
C(35)-H(35A) 0.9600
C(35)-H(35B) 0.9600
C(35)-H(35C) 0.9600
C(36)-C(37) 1.567(10)
C(36)-C(39) 1.568(10)
C(36)-C(38) 1.578(11)
C(37)-H(37A) 0.9600
C(37)-H(37B) 0.9600
C(37)-H(37C) 0.9600
C(38)-H(38A) 0.9600
C(38)-H(38B) 0.9600
C(38)-H(38C) 0.9600
C(39)-H(39A) 0.9600
C(39)-H(39B) 0.9600
C(39)-H(39C) 0.9600
C(40)-C(41) 1.506(7)
C(40)-C(45) 1.532(7)
C(40)-H(40A) 0.9800
C(41)-C(42) 1.513(8)
C(41)-H(41A) 0.9800
C(42)-C(43) 1.480(10)
C(42)-C(46) 1.545(8)
C(42)-H(42A) 0.9800
C(43)-C(44) 1.300(13)
C(43)-H(43A) 0.9300
C(44)-H(44A) 0.9300
C(44)-H(44B) 0.9300
C(45)-H(45A) 0.9600
C(45)-H(45B) 0.9600
C(45)-H(45C) 0.9600
C(46)-H(46A) 0.9600
C(46)-H(46B) 0.9600
C(46)-H(46C) 0.9600
O(5)-P-O(6)116.6(3)
O(5)-P-O(4)116.3(2)
O(6)-P-O(4)101.6(2)
O(5)-P-O(7)113.9(3)
O(6)-P-O(7)102.7(3)
O(4)-P-O(7)103.91(19)
O(3)-Si(1)-C(15)108.3(4)
O(3)-Si(1)-C(13)114.6(5)
C(15)-Si(1)-C(13)119.0(6)
O(3)-Si(1)-C(14)108.0(5)
C(15)-Si(1)-C(14)106.7(6)
C(13)-Si(1)-C(14)99.0(8)
C(22)-Si(2)-C(24)108.1(6)
C(22)-Si(2)-C(25)110.5(5)
C(24)-Si(2)-C(25)112.2(5)
C(22)-Si(2)-C(23)109.8(7)
C(24)-Si(2)-C(23)111.8(7)
C(25)-Si(2)-C(23)104.5(6)
C(29)-Si(3)-C(28)112.1(4)
C(29)-Si(3)-C(30)109.6(4)
C(28)-Si(3)-C(30)109.4(4)
C(29)-Si(3)-C(27)105.0(4)
C(28)-Si(3)-C(27)110.7(3)
C(30)-Si(3)-C(27)110.0(4)
O(8)-Si(4)-C(36)106.2(3)
O(8)-Si(4)-C(34)110.6(2)
C(36)-Si(4)-C(34)109.7(3)
O(8)-Si(4)-C(35)110.5(3)
C(36)-Si(4)-C(35)110.1(3)
C(34)-Si(4)-C(35)109.7(4)
C(5)-O(1)-C(8)110.8(3)
C(5)-O(2)-C(1)113.8(3)
C(3)-O(3)-Si(1)128.5(4)
C(7)-O(4)-P119.2(3)
C(21)-O(6)-P120.5(5)
C(26)-O(7)-P124.3(4)
C(33)-O(8)-Si(4)124.6(3)
C(41)-O(9)-H(9C)114(4)
O(2)-C(1)-C(2)110.6(4)
O(2)-C(1)-C(9)106.2(4)
C(2)-C(1)-C(9)112.5(5)
O(2)-C(1)-H(1A)109.1
C(2)-C(1)-H(1A)109.1
C(9)-C(1)-H(1A)109.1
C(1)-C(2)-C(3)112.0(4)
C(1)-C(2)-H(2A)109.2
C(3)-C(2)-H(2A)109.2
C(1)-C(2)-H(2B)109.2
C(3)-C(2)-H(2B)109.2
H(2A)-C(2)-H(2B)107.9
O(3)-C(3)-C(2)109.4(5)
O(3)-C(3)-C(4)112.5(5)
C(2)-C(3)-C(4)110.9(5)
O(3)-C(3)-H(3A)108.0
C(2)-C(3)-H(3A)108.0
C(4)-C(3)-H(3A)108.0
C(5)-C(4)-C(3)112.8(4)
C(5)-C(4)-H(4A)109.0
C(3)-C(4)-H(4A)109.0
C(5)-C(4)-H(4B)109.0
C(3)-C(4)-H(4B)109.0
H(4A)-C(4)-H(4B)107.8
O(1)-C(5)-O(2)110.9(3)
O(1)-C(5)-C(4)110.1(4)
O(2)-C(5)-C(4)110.9(4)
O(1)-C(5)-C(6)103.4(4)
O(2)-C(5)-C(6)104.8(4)
C(4)-C(5)-C(6)116.3(4)
C(19)-C(6)-C(7)114.9(4)
C(19)-C(6)-C(20)111.3(5)
C(7)-C(6)-C(20)106.4(4)
C(19)-C(6)-C(5)112.8(4)
C(7)-C(6)-C(5)101.3(3)
C(20)-C(6)-C(5)109.5(4)
O(4)-C(7)-C(8)111.1(3)
O(4)-C(7)-C(6)112.0(4)
C(8)-C(7)-C(6)106.0(3)
O(4)-C(7)-H(7A)109.2
C(8)-C(7)-H(7A)109.2
C(6)-C(7)-H(7A)109.2
O(1)-C(8)-C(31)110.9(3)
O(1)-C(8)-C(7)105.7(3)
C(31)-C(8)-C(7)115.6(4)
O(1)-C(8)-H(8A)108.2
C(31)-C(8)-H(8A)108.2
C(7)-C(8)-H(8A)108.2
C(10)-C(9)-C(1)116.4(5)
C(10)-C(9)-H(9A)108.2

C(1)-C(9)-H(9A)108.2
C(10)-C(9)-H(9B)108.2
C(1)-C(9)-H(9B)108.2
H(9A)-C(9)-H(9B)107.3
C(9)-C(10)-C(11)114.8(8)
C(9)-C(10)-H(10A)108.6
C(11)-C(10)-H(10A)108.6
C(9)-C(10)-H(10B)108.6
C(11)-C(10)-H(10B)108.6
H(10A)-C(10)-H(10B)107.6
C(12)-C(11)-C(10)128.8(15)
C(12)-C(11)-H(11A)105.1
C(10)-C(11)-H(11A)105.1
C(12)-C(11)-H(11B)105.1
C(10)-C(11)-H(11B)105.1
H(11A)-C(11)-H(11B)105.9
C(11)-C(12)-H(12A)109.5
C(11)-C(12)-H(12B)109.5
H(12A)-C(12)-H(12B)109.5
C(11)-C(12)-H(12C)109.5
H(12A)-C(12)-H(12C)109.5
H(12B)-C(12)-H(12C)109.5
Si(1)-C(13)-H(13A)109.5
Si(1)-C(13)-H(13B)109.4
H(13A)-C(13)-H(13B)109.5
Si(1)-C(13)-H(13C)109.4
H(13A)-C(13)-H(13C)109.5
H(13B)-C(13)-H(13C)109.5
Si(1)-C(14)-H(14A)109.3
Si(1)-C(14)-H(14B)109.6
H(14A)-C(14)-H(14B)109.5
Si(1)-C(14)-H(14C)109.5
H(14A)-C(14)-H(14C)109.5
H(14B)-C(14)-H(14C)109.5
C(17)-C(15)-C(16)115.3(10)
C(17)-C(15)-C(18)110.0(10)
C(16)-C(15)-C(18)115.3(11)
C(17)-C(15)-Si(1)111.2(7)
C(16)-C(15)-Si(1)103.6(9)
C(18)-C(15)-Si(1)100.2(7)
C(15)-C(16)-H(16A)109.4
C(15)-C(16)-H(16B)109.5
H(16A)-C(16)-H(16B)109.5
C(15)-C(16)-H(16C)109.5
H(16A)-C(16)-H(16C)109.5
H(16B)-C(16)-H(16C)109.5
C(15)-C(17)-H(17A)109.5
C(15)-C(17)-H(17B)109.5
H(17A)-C(17)-H(17B)109.5
C(15)-C(17)-H(17C)109.5
H(17A)-C(17)-H(17C)109.5
H(17B)-C(17)-H(17C)109.5
C(15)-C(18)-H(18A)109.5
C(15)-C(18)-H(18B)109.4
H(18A)-C(18)-H(18B)109.5
C(15)-C(18)-H(18C)109.5
H(18A)-C(18)-H(18C)109.5
H(18B)-C(18)-H(18C)109.5
C(6)-C(19)-H(19A)109.5
C(6)-C(19)-H(19B)109.5
H(19A)-C(19)-H(19B)109.5
C(6)-C(19)-H(19C)109.5
H(19A)-C(19)-H(19C)109.5
H(19B)-C(19)-H(19C)109.5
C(6)-C(20)-H(20A)109.5
C(6)-C(20)-H(20B)109.5
H(20A)-C(20)-H(20B)109.5
C(6)-C(20)-H(20C)109.5
H(20A)-C(20)-H(20C)109.5
H(20B)-C(20)-H(20C)109.5
O(6)-C(21)-C(22)109.5(7)
O(6)-C(21)-H(21A)109.8
C(22)-C(21)-H(21A)109.8
O(6)-C(21)-H(21B)109.8
C(22)-C(21)-H(21B)109.8
H(21A)-C(21)-H(21B)108.2
C(21)-C(22)-Si(2)118.2(8)
C(21)-C(22)-H(22A)107.8
Si(2)-C(22)-H(22A)107.8
C(21)-C(22)-H(22B)107.8
Si(2)-C(22)-H(22B)107.8
H(22A)-C(22)-H(22B)107.1
Si(2)-C(23)-H(23A)109.5
Si(2)-C(23)-H(23B)109.5
H(23A)-C(23)-H(23B)109.5
Si(2)-C(23)-H(23C)109.5
H(23A)-C(23)-H(23C)109.5
H(23B)-C(23)-H(23C)109.5
Si(2)-C(24)-H(24A)109.5
Si(2)-C(24)-H(24B)109.5
H(24A)-C(24)-H(24B)109.5
Si(2)-C(24)-H(24C)109.5
H(24A)-C(24)-H(24C)109.5
H(24B)-C(24)-H(24C)109.5
Si(2)-C(25)-H(25A)109.5
Si(2)-C(25)-H(25B)109.5
H(25A)-C(25)-H(25B)109.5
Si(2)-C(25)-H(25C)109.5
H(25A)-C(25)-H(25C)109.5
H(25B)-C(25)-H(25C)109.5
C(27)-C(26)-O(7)112.5(6)
C(27)-C(26)-H(26A)109.1
O(7)-C(26)-H(26A)109.1
C(27)-C(26)-H(26B)109.1
O(7)-C(26)-H(26B)109.1
H(26A)-C(26)-H(26B)107.8
C(26)-C(27)-Si(3)113.8(5)
C(26)-C(27)-H(27A)108.8
Si(3)-C(27)-H(27A)108.8
C(26)-C(27)-H(27B)108.8
Si(3)-C(27)-H(27B)108.8
H(27A)-C(27)-H(27B)107.7
Si(3)-C(28)-H(28A)109.5
Si(3)-C(28)-H(28B)109.5
H(28A)-C(28)-H(28B)109.5
Si(3)-C(28)-H(28C)109.5
H(28A)-C(28)-H(28C)109.5
H(28B)-C(28)-H(28C)109.5
Si(3)-C(29)-H(29A)109.5
Si(3)-C(29)-H(29B)109.5
H(29A)-C(29)-H(29B)109.5
Si(3)-C(29)-H(29C)109.5
H(29A)-C(29)-H(29C)109.5

H(29B)-C(29)-H(29C)109.5
Si(3)-C(30)-H(30A)109.5
Si(3)-C(30)-H(30B)109.5
H(30A)-C(30)-H(30B)109.5
Si(3)-C(30)-H(30C)109.5
H(30A)-C(30)-H(30C)109.5
H(30B)-C(30)-H(30C)109.5
C(32)-C(31)-C(8)112.8(4)
C(32)-C(31)-H(31A)109.0
C(8)-C(31)-H(31A)109.0
C(32)-C(31)-H(31B)109.0
C(8)-C(31)-H(31B)109.0
H(31A)-C(31)-H(31B)107.8
C(33)-C(32)-C(31)113.0(4)
C(33)-C(32)-H(32A)109.0
C(31)-C(32)-H(32A)109.0
C(33)-C(32)-H(32B)109.0
C(31)-C(32)-H(32B)109.0
H(32A)-C(32)-H(32B)107.8
O(8)-C(33)-C(32)108.7(3)
O(8)-C(33)-C(40)109.2(3)
C(32)-C(33)-C(40)113.6(4)
O(8)-C(33)-H(33A)108.4
C(32)-C(33)-H(33A)108.4
C(40)-C(33)-H(33A)108.4
Si(4)-C(34)-H(34A)109.5
Si(4)-C(34)-H(34B)109.5
H(34A)-C(34)-H(34B)109.5
Si(4)-C(34)-H(34C)109.5
H(34A)-C(34)-H(34C)109.5
H(34B)-C(34)-H(34C)109.5
Si(4)-C(35)-H(35A)109.5
Si(4)-C(35)-H(35B)109.5
H(35A)-C(35)-H(35B)109.5
Si(4)-C(35)-H(35C)109.5
H(35A)-C(35)-H(35C)109.5
H(35B)-C(35)-H(35C)109.5
C(37)-C(36)-C(39)106.6(7)
C(37)-C(36)-C(38)112.7(8)
C(39)-C(36)-C(38)109.3(6)
C(37)-C(36)-Si(4)109.3(4)
C(39)-C(36)-Si(4)109.8(5)
C(38)-C(36)-Si(4)109.1(6)
C(36)-C(37)-H(37A)109.5
C(36)-C(37)-H(37B)109.5
H(37A)-C(37)-H(37B)109.5
C(36)-C(37)-H(37C)109.5
H(37A)-C(37)-H(37C)109.5
H(37B)-C(37)-H(37C)109.5
C(36)-C(38)-H(38A)109.5
C(36)-C(38)-H(38B)109.5
H(38A)-C(38)-H(38B)109.5
C(36)-C(38)-H(38C)109.5
H(38A)-C(38)-H(38C)109.5
H(38B)-C(38)-H(38C)109.5
C(36)-C(39)-H(39A)109.5
C(36)-C(39)-H(39B)109.5
H(39A)-C(39)-H(39B)109.5
C(36)-C(39)-H(39C)109.5
H(39A)-C(39)-H(39C)109.5
H(39B)-C(39)-H(39C)109.5
C(41)-C(40)-C(45)111.7(5)
C(41)-C(40)-C(33)112.9(4)
C(45)-C(40)-C(33)110.6(4)
C(41)-C(40)-H(40A)107.1
C(45)-C(40)-H(40A)107.1
C(33)-C(40)-H(40A)107.1
O(9)-C(41)-C(40)110.5(5)
O(9)-C(41)-C(42)110.4(5)
C(40)-C(41)-C(42)115.1(5)
O(9)-C(41)-H(41A)106.8
C(40)-C(41)-H(41A)106.8
C(42)-C(41)-H(41A)106.8
C(43)-C(42)-C(41)113.7(5)
C(43)-C(42)-C(46)109.2(6)
C(41)-C(42)-C(46)111.9(7)
C(43)-C(42)-H(42A)107.2
C(41)-C(42)-H(42A)107.2
C(46)-C(42)-H(42A)107.2
C(44)-C(43)-C(42)127.1(8)
C(44)-C(43)-H(43A)116.5
C(42)-C(43)-H(43A)116.5
C(43)-C(44)-H(44A)120.0
C(43)-C(44)-H(44B)120.0
H(44A)-C(44)-H(44B)120.0
C(40)-C(45)-H(45A)109.5
C(40)-C(45)-H(45B)109.5
H(45A)-C(45)-H(45B)109.5
C(40)-C(45)-H(45C)109.5
H(45A)-C(45)-H(45C)109.5
H(45B)-C(45)-H(45C)109.5
C(42)-C(46)-H(46A)109.5
C(42)-C(46)-H(46B)109.5
H(46A)-C(46)-H(46B)109.5
C(42)-C(46)-H(46C)109.4
H(46A)-C(46)-H(46C)109.5
H(46B)-C(46)-H(46C)109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2x10^3$) for gilma2s. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
P	54(1)	72(1)	108(1)	22(1)	4(1)	6(1)
Si(1)	184(3)	122(2)	221(3)	22(2)	39(3)	54(2)
Si(2)	127(2)	76(1)	203(2)	-2(1)	14(2)	1(1)
Si(3)	91(1)	124(2)	93(1)	30(1)	-12(1)	-8(1)
Si(4)	83(1)	88(1)	92(1)	27(1)	5(1)	5(1)
O(1)	54(2)	54(2)	71(2)	5(2)	5(2)	2(2)
O(2)	49(2)	74(2)	62(2)	5(2)	1(2)	1(2)
O(3)	75(2)	78(2)	111(3)	21(2)	17(2)	19(2)
O(4)	52(2)	61(2)	72(2)	7(2)	1(2)	-2(2)
O(5)	46(2)	126(3)	184(4)	57(3)	-5(2)	7(2)
O(6)	124(3)	74(3)	127(4)	5(2)	29(3)	17(2)
O(7)	72(2)	127(3)	88(3)	31(3)	-9(2)	10(2)
O(8)	62(2)	78(2)	68(2)	20(2)	-2(2)	0(2)
O(9)	57(2)	96(3)	187(5)	26(3)	-12(3)	3(2)
C(1)	53(3)	102(4)	54(3)	1(3)	1(2)	-2(3)
C(2)	82(4)	147(6)	66(4)	22(4)	-8(3)	18(4)
C(3)	72(4)	99(5)	92(4)	46(4)	4(3)	17(3)
C(4)	68(3)	73(4)	92(4)	27(3)	6(3)	-1(3)
C(5)	45(3)	59(3)	79(3)	9(3)	4(3)	-4(2)
C(6)	52(3)	64(3)	82(3)	20(3)	-9(3)	-11(3)
C(7)	44(3)	53(3)	68(3)	-2(2)	-9(2)	-4(2)
C(8)	55(3)	56(3)	54(3)	0(2)	0(2)	-3(2)
C(9)	89(4)	147(7)	75(4)	-25(4)	-13(3)	-11(4)
C(10)	116(5)	101(5)	129(6)	-45(5)	-6(4)	-26(4)
C(11)	215(12)	179(11)	297(14)	-148(11)	17(10)	12(9)
C(12)	550(40)	300(20)	650(40)	-350(30)	-320(30)	240(30)
C(13)	620(30)	97(7)	269(14)	64(8)	136(19)	31(12)
C(14)	179(11)	390(20)	470(20)	-185(19)	-160(14)	187(13)
C(15)	163(9)	166(9)	400(20)	152(12)	-148(12)	-43(8)
C(16)	190(12)	420(20)	440(20)	-217(19)	-184(14)	1(13)
C(17)	263(12)	155(8)	138(7)	-13(6)	58(8)	19(8)

C(19)	50(3)	123(5)	93(4)	34(3)	11(3)	6(3)
C(20)	92(4)	85(4)	147(6)	25(4)	-20(4)	-41(4)
C(21)	249(11)	96(6)	166(8)	24(6)	46(8)	20(7)
C(22)	307(15)	108(7)	212(10)	-36(7)	45(10)	34(8)
C(23)	135(8)	197(11)	490(20)	-97(14)	-6(11)	-6(8)
C(24)	351(19)	110(7)	349(17)	-57(9)	117(15)	-48(9)
C(25)	216(10)	125(7)	196(9)	15(6)	4(8)	-11(7)
C(26)	133(6)	116(6)	124(6)	20(5)	-14(5)	7(5)
C(27)	114(5)	99(5)	139(6)	21(4)	-18(4)	2(4)
C(28)	126(6)	157(7)	169(7)	-3(6)	-30(6)	-22(6)
C(29)	151(7)	133(6)	151(7)	49(5)	-17(5)	7(5)
C(30)	171(8)	174(8)	120(6)	26(5)	36(6)	25(6)
C(31)	50(3)	61(3)	62(3)	11(2)	-5(2)	-2(2)
C(32)	52(3)	70(3)	58(3)	2(2)	3(2)	0(2)
C(33)	48(3)	64(3)	54(3)	6(2)	0(2)	-7(2)
C(34)	141(6)	97(5)	114(5)	8(4)	21(4)	30(4)
C(35)	115(6)	121(6)	168(7)	26(5)	-23(5)	-30(5)
C(36)	98(5)	139(6)	114(5)	59(5)	15(4)	0(4)
C(37)	90(5)	346(14)	141(6)	83(8)	-55(5)	-42(7)
C(38)	307(14)	137(8)	196(9)	81(7)	-30(9)	76(9)
C(39)	185(9)	244(10)	78(5)	40(6)	5(5)	2(8)
C(40)	52(3)	82(4)	88(4)	24(3)	7(3)	-9(3)
C(41)	44(3)	94(4)	112(5)	33(4)	-9(3)	-6(3)
C(42)	47(3)	140(6)	109(5)	40(5)	-13(3)	-10(4)
C(43)	80(5)	185(9)	114(6)	-20(6)	4(4)	-21(6)
C(44)	151(9)	287(16)	217(12)	-112(11)	42(8)	-99(10)
C(45)	73(4)	121(5)	111(5)	-4(4)	33(3)	15(3)
C(46)	91(5)	262(11)	181(8)	139(8)	-27(5)	22(6)

Table 5. Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($Å^2x10^3$) for gilma2s.

	x	y	z	U(eq)
H(9C)	14250(60)	9210(50)	8689(18)	130(30)
H(1A)	10023	8745	9380	84
H(2A)	9202	8018	10069	118
H(2B)	10394	7900	9925	118
H(3A)	9285	6536	9839	105
H(4A)	8114	6583	9293	93
H(4B)	7676	7125	9651	93
H(7A)	6747	8711	8511	66
H(8A)	8352	8240	8361	66
H(9A)	9199	9722	10019	124
H(9B)	10413	9722	9897	124
H(10A)	8774	10566	9476	138
H(10B)	10001	10591	9369	138
H(11A)	9990	11298	10037	277
H(11B)	10157	11852	9662	277
H(12A)	9340	12534	10015	754
H(12B)	8510	11707	10068	754
H(12C)	8609	12218	9674	754
H(13A)	9472	4724	9615	492
H(13B)	10347	5051	9910	492
H(13C)	10628	4273	9608	492
H(14A)	12547	6280	9309	516
H(14B)	12505	5223	9442	516
H(14C)	12226	6035	9729	516
H(16A)	9045	5896	8791	524
H(16B)	9203	4840	8915	524
H(16C)	9380	5135	8489	524
H(17A)	10680	6847	8636	278
H(17B)	11216	6117	8358	278
H(17C)	11837	6451	8723	278

H(18A)	11172	4140	8986	468
H(18B)	12160	4799	8899	468
H(18C)	11474	4381	8564	468
H(19A)	5547	8818	9245	133
H(19B)	6557	9291	9435	133
H(19C)	6168	8292	9571	133
H(20A)	5744	7462	8811	162
H(20B)	6413	6860	9102	162
H(20C)	6893	7087	8699	162
H(21A)	6514	11290	9306	204
H(21B)	5411	11604	9124	204
H(22A)	7220	12765	9239	250
H(22B)	6117	12863	9451	250
H(23A)	4174	13280	8869	410
H(23B)	4750	12688	8551	410
H(23C)	4504	13762	8485	410
H(24A)	6690	14864	9221	405
H(24B)	5474	14688	9324	405
H(24C)	5776	15213	8946	405
H(25A)	7644	13791	8556	268
H(25B)	6684	14099	8293	268
H(25C)	6938	13023	8352	268
H(26A)	6769	10440	7607	149
H(26B)	5716	10137	7823	149
H(27A)	6401	11978	7742	141
H(27B)	5338	11666	7948	141
H(28A)	3636	10709	7012	226
H(28B)	3489	10769	7454	226
H(28C)	4320	10055	7280	226
H(29A)	4107	12866	7035	217
H(29B)	5090	13231	7275	217
H(29C)	4045	12868	7481	217
H(30A)	5628	11447	6636	233
H(30B)	6380	10828	6895	233
H(30C)	6549	11926	6874	233
H(31A)	8931	9811	8344	69

H(31B)	9189	9790	8781	69
H(32A)	10542	8637	8656	72
H(32B)	10325	8769	8220	72
H(33A)	11050	10257	8690	66
H(34A)	9168	11767	8515	176
H(34B)	9824	12708	8561	176
H(34C)	10152	11810	8795	176
H(35A)	12646	11973	8043	202
H(35B)	12451	11955	8483	202
H(35C)	12125	12849	8246	202
H(37A)	8841	11793	7399	289
H(37B)	8646	11746	7839	289
H(37C)	9217	10904	7630	289
H(38A)	9905	13383	7468	320
H(38B)	10904	13428	7741	320
H(38C)	9732	13378	7909	320
H(39A)	10732	11934	7138	254
H(39B)	11056	11042	7377	254
H(39C)	11726	11979	7414	254
H(40A)	12765	10132	8413	89
H(41A)	12265	8387	8744	100
H(42A)	11720	9549	9157	118
H(43A)	13798	10332	9125	152
H(44A)	11953	11131	9402	262
H(44B)	13112	11635	9352	262
H(45A)	13236	8861	8019	153
H(45B)	12315	9464	7833	153
H(45C)	12039	8498	8029	153
H(46A)	12436	8135	9423	267
H(46B)	12553	8995	9701	267
H(46C)	13556	8640	9470	267