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Synthetic Studies on CP-225,917 and CP-263,114: Access to Advanced Tetracyclic Systems by Intramolecular Conjugate Displacement and [2,3]-Wittig Rearrangement

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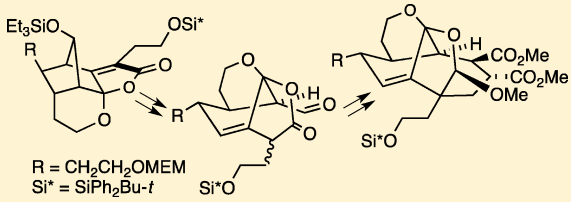
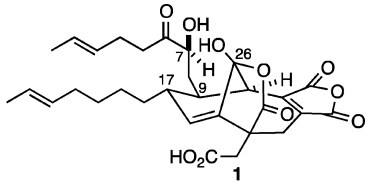
Supporting Information

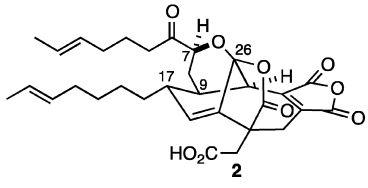
ABSTRACT: An advanced intermediate related to the structures of CP-225,917 and CP-263,114 was constructed by a sequence based on the use of Grob-like fragmentation, intramolecular conjugate displacement, and [2,3]-Wittig rearrangement. A variant of the [2,3]-Wittig rearrangement was developed.



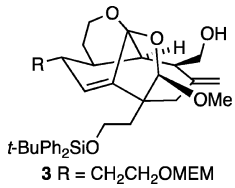
INTRODUCTION

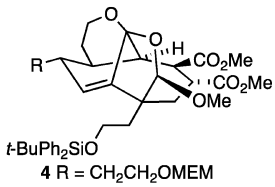
CP-225,917 (**1**)[1] and CP-263,114 (**2**)[1] are exceptionally complex fungal metabolites that are modest in vitro inhibitors of ras farnesyl transferase and squalene synthase, properties that imply the possibility of cholesterol-lowering and anticancer activity. As synthetic targets, they pose extremely difficult challenges; nonetheless, they have been synthesized by four groups led by (in alphabetical order) Danishefsky [*rac*-(**1**) and *rac*-(**2**)],[2] Fukuyama [(**2**)],[3] Nicolaou [*rac*-(**1**), *rac*-(**2**), *ent*-(**1**), *ent*-(**2**)],[4] and Shair [*ent*-(**2**)].[5] There are also very many model studies leading to compounds that incorporate some of the structural features of the natural products. The pioneering total syntheses also served to confirm the structures, establish the absolute configuration,[4] and provide information about corresponding 7*S*[6] isomers, which co-occur[6,7] with **1** and **2**. The massive body of chemical and biosynthetic[8] work on the compounds, including their interconversion,[7] has been reviewed comprehensively,[9] although a number of additional publications have since appeared.[3b,8,10]





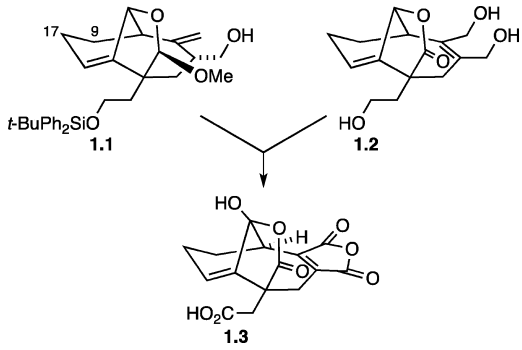
We describe here our own model studies that have led to the preparation of **3** and **4**. The methods we have used illustrate the power of intramolecular conjugate displacement[11] for making complex structures and the value of the [2,3]-Wittig rearrangement to install a hydroxymethyl group where other methods failed. We have also found a new variant of the [2,3]-Wittig rearrangement.





Publications from this laboratory on model studies[12] have resulted in procedures for the conversion of **1.1**[13] and **1.2**[14] into **1.3** (Scheme 1). Compound **1.3** was crystalline, and X-ray analysis confirmed the structure.[13] In the present work we sought to introduce additional substituents for potential elaboration to those present at C(9) and C(17) of **1** and **2**.

Scheme 1. Previous Work from This Laboratory



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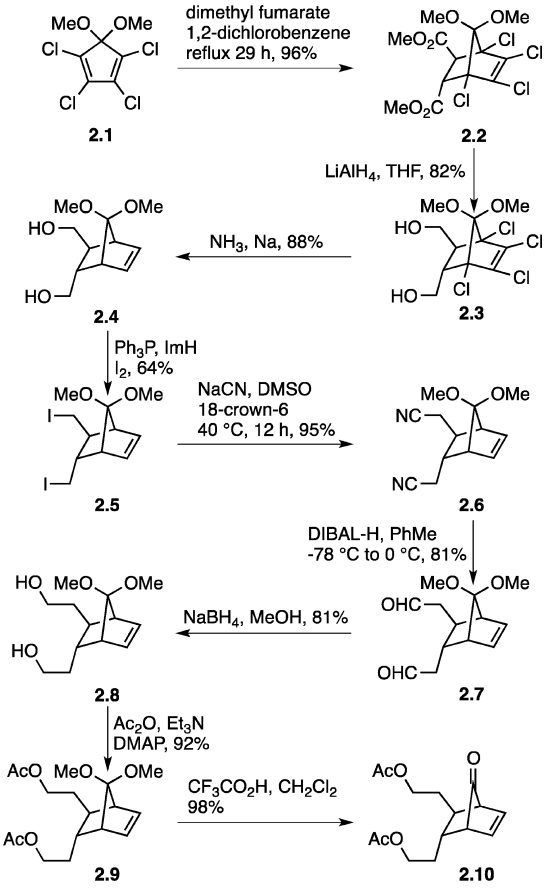
RESULTS AND DISCUSSION

The preparation of the first key intermediate (**2.10**) in our route to **3** and **4** began with the Diels–Alder cycloaddition of 1,1-dimethoxy-2,3,4,5-tetrachlorocyclopentadiene (**2.1**) with diethyl fumarate (Scheme 2). The starting diene was prepared[15]

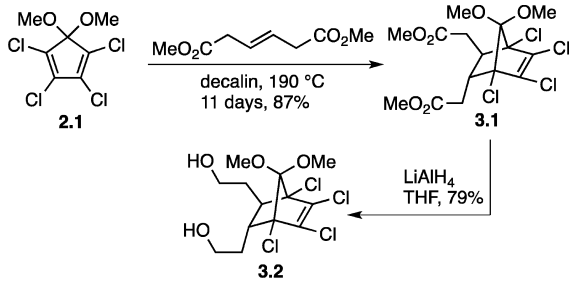
Scheme 2. Formation of Bicyclic Ketone 1.10



from commercially available hexachlorocyclopentadiene, and both this experiment as well as the subsequent Diels–Alder reaction (**2.1**→**2.2**) can easily be done on a 70 g scale, the yield in the Diels–Alder reaction being 96%. Both ester groups were then reduced with $LiAlH_4$ to the alcohol level, again in high yield and on a large scale (90 g). At this point, dechlorination using Na in liquid NH_3 afforded alcohol **2.4**, and the next task was to homologate both hydroxymethyl substituents so as to eventually gain access to diol **2.8**. To this end, both hydroxyls were replaced by iodine, and then displacement with cyanide gave the bis-nitrile **2.6**. That compound was easily reduced with DIBAL-H to the corresponding bis-aldehyde **2.7**, and reduction with $NaBH_4$ afforded diol **2.8**. The steps **2.4**→**2.5**→**2.6**→**2.7**→**2.8** were done on a large scale (20–60 g, depending on the step), and only replacement of the hydroxyls by iodine gave a modest yield (64%), the other steps being more efficient. Use of a bis-tosylate instead of the bis-iodide gave a poorer result for the synthesis of **2.6**.

The above route to diol **2.8** represents our optimized procedure, but we also examined two other approaches. In the first (Scheme 3), we carried out a Diels–Alder reaction between dimethyl (*E*)-3-hexenedioate and diene **2.1**, as reported by Bio and Leighton,[10b] but the reaction is very slow (11 days at 190 °C, 87%), and (*E*)-3-hexenedioic acid is

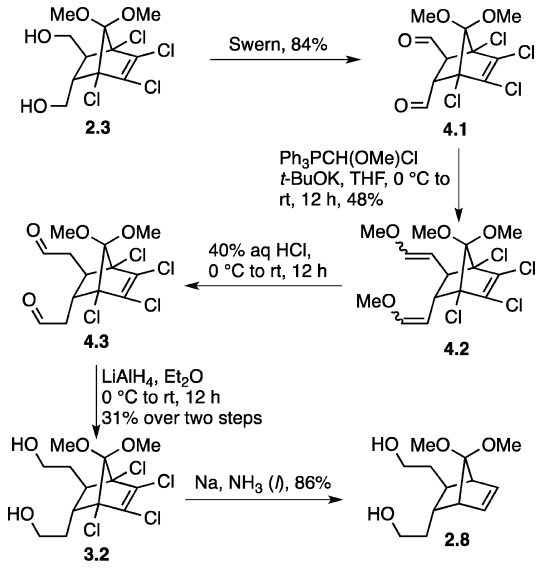
Scheme 3. First Alternative Diels–Alder Route



expensive. Reduction of the product **3.1** afforded the chlorinated diol **3.2**.[10b] The expense and duration of this procedure prompted us to examine another way of homologating our diol **2.3**.

For that purpose, diol **2.3** was oxidized under Swern conditions and then subjected to Wittig reaction with $Ph_3P{=}CH(OMe)$. Acidic hydrolysis of the resulting enol ethers **4.2** released the bis-aldehyde **4.3**, from which point reduction ($LiAlH_4$) and dechlorination (Na, liquid NH_3) gave diol **2.8** (Scheme 4). Although this route is shorter than that shown in Scheme 2, the overall yield is lower and so we decided to accept the sequence of Scheme 2.

Scheme 4. Alternative Homologation Route



Diol **2.8** was acetylated, and acid hydrolysis then released the parent ketone **2.10**. This ketone was elaborated to the tricyclic keto hemiacetal **5.6** as shown in Scheme 5.

Stereoselective reduction of the ketone carbonyl was cleanly effected with the hindered reducing agent $(t\text{-BuO})_3AlHLi$, and the resulting alcohol was then protected by silylation (**2.10**→**5.1**→**5.2**). Next, the double bond was dihydroxylated using catalytic OsO_4 with NMO as the stoichiometric oxidant.

Oxidation of diol **5.3** to the α-diketone **5.4** was initially troublesome, as the diketone is unstable to silica gel, but we eventually found that if the crude material is treated with aqueous methanolic K_2CO_3, one of the carbonyl groups is trapped as a hemiacetal (**5.3**→**5.4**→**5.5**). The yield of the hemiacetal was erratic until we found that, if the primary hydroxyl of the crude material (without concentrating its solutions to dryness) is protected (as a MEM ether), then the

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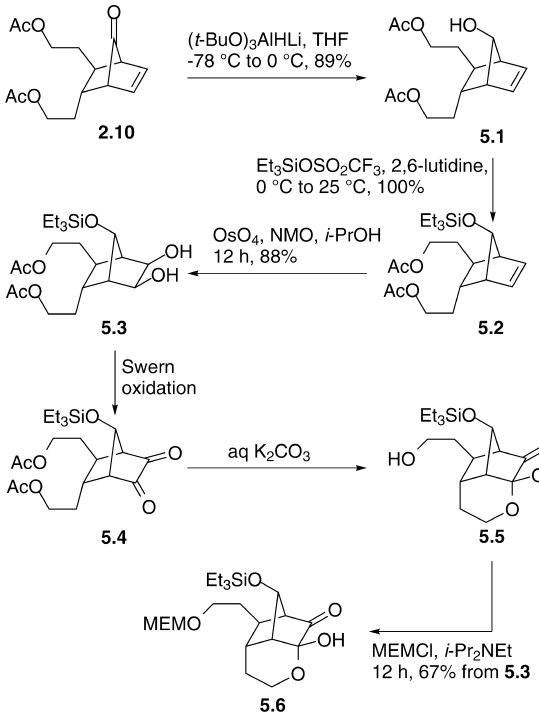
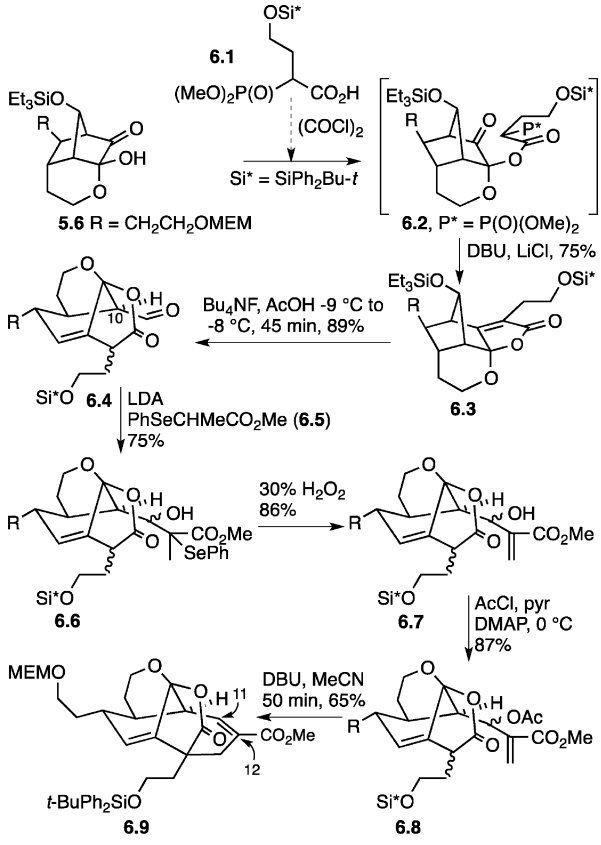
Scheme 5. Formation of Tricyclic Keto Hemiacetal 5.6



product (**5.6**) can be obtained reproducibly in 67% overall yield from diol **5.3**.

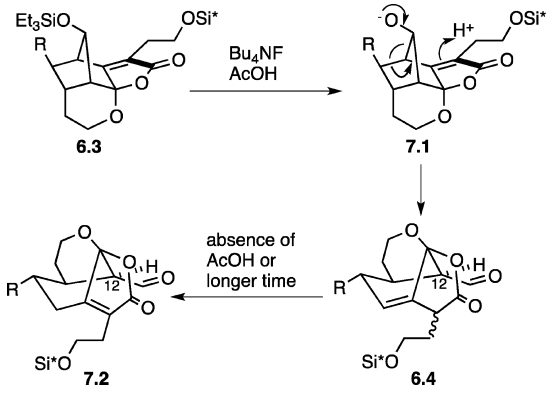
The next task was to incorporate the hemiacetal hydroxyl of **5.6** into a strained lactone subunit (Scheme 6). This was achieved by acylating the hemiacetal with the acid chloride derived from **6.1** in the presence of an excess of DBU. The acylation product **6.2** was not isolated but was subjected in situ to conditions of the Masamune–Roush procedure[16] by adding LiCl in order to increase the acidity of the hydrogen that must be removed for the required intramolecular Horner–Wadsworth–Emmons olefination. In this way, the hemiacetal **5.6** could be converted into the lactone **6.3** in 75% overall yield.

Scheme 6. Formation of ICD Product 6.9



The next step was a crucial one as it set the stage for using the method of intramolecular conjugate displacement[11] to generate the 9-membered ring that is characteristic of both CP-225,917 and CP-263,114. A critical requirement is that the stereochemistry at C(10)[17] of **6.4** should be as shown. In the event, when **6.3** was treated with buffered Bu_4NF, desilylation and fragmentation occurred as required, but a great number of optimization experiments were needed to identify conditions that give a satisfactory yield. It turned out that the bridgehead double bond in **6.4** is prone to move into conjugation with the lactone carbonyl under the influence of (basic) fluoride ion. Consequently, buffering with AcOH was required to suppress this pathway, but even so, isomerization occurs unless the reaction temperature is kept between −9 °C and −5 °C. At lower temperatures the reaction does not proceed, but under the correct conditions a very high yield (89%) can be obtained, provided the reaction is monitored by TLC and quenched as soon as it is over. The mechanistic pathway for the desired fragmentation and the unwanted double bond shift are summarized in Scheme 7.

Scheme 7. Fragmentation and Double Bond Shift



With aldehyde **6.4** in hand, we next applied a selenium-based version of the Baylis–Hillman reaction[11a] by adding the aldehyde to deprotonated $PhSeCH(Me)CO_2Me$ (**6.5**[18]) in THF at −78 °C (Scheme 6). This operation provided a mixture of hydroxy selenides **6.6**, and oxidation with an excess of 30% H_2O_2 generated the Baylis–Hillman alcohols **6.7**. Finally, acetylation gave **6.8**, the substrate for the intended intramolecular conjugate displacement (ICD). This second crucial step (**6.8**→**6.9**) worked satisfactorily under conditions established in this laboratory with model compounds.[11b,c] The ICD product **6.9** was crystalline, and single crystal X-ray analysis confirmed its structure (see Figure 1 in Supporting Information).

At this point, we examined a number of potential methods for completing the carbon skeleton of the anhydride unit.

First Approach. Our first approach actually started with alcohols **6.7**. They were treated with DBU in the hope that a simple Michael addition would occur, but only migration of the

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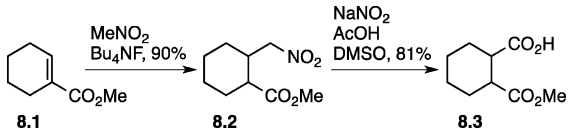
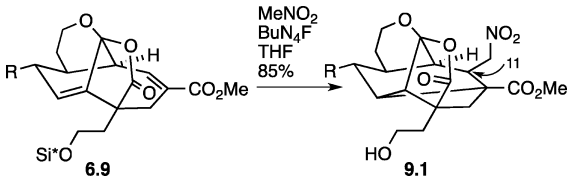
bridgehead double bond took place. Oxidation of the hydroxyl of **6.7** to further activate the Michael acceptor subunit and treatment with DBU caused decomposition. Had either of these routes been successful, the resulting hydroxyl or carbonyl at C(11)[17] would have provided several opportunities to introduce another carbon needed for the anhydride unit.

Second Approach. Our second approach was based on a model study (Scheme 8) in which Michael addition of $MeNO_2$ to methyl 1-cyclohexenecarboxylate (**8.1**[19]) gave the known nitro compound **8.2**[20] (as an isomer mixture) which was transformed into the ester acid **8.3**[21] (a single isomer of unestablished stereochemistry) by reaction with $NaNO_2$ and AcOH in DMSO.[22] We were unable to test this method on **6.9** because addition of $MeNO_2$ produced **9.1**, of unassigned stereochemistry at C(11) (Scheme 9), the formal product of a transannular reaction. The structure of **9.1** was established by extensive NMR measurements, and its formation was a most unwelcome fact, as it implied that Michael additions to the double bond of **6.9** would be an unpromising approach.

Scheme 8. Model Study for Second Approach

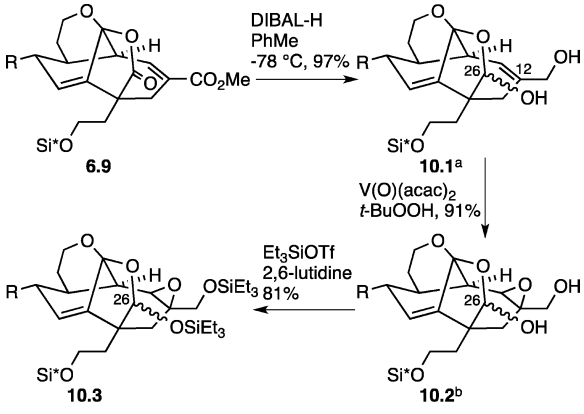


Scheme 9. Formal Transannular Reaction



Third Approach. We next reduced the ester and lactone groups of **6.9** using DIBAL-H (**6.9**→**10.1**) and used the Sharpless epoxidation to form **10.2** (Scheme 10); this method of epoxidation does not involve generation of a carbanion at C(12).[17] We assume that oxygen is delivered from the top face, as the X-ray structure of **6.9** suggests that approach to that face is less hindered. Both hydroxyls of **10.1** were silylated, and several attempts were then made to open the epoxide with lithiated dithiane and with $(2\text{-ethoxyvinyl})_2CuLi$, but **10.3** was recovered unchanged.

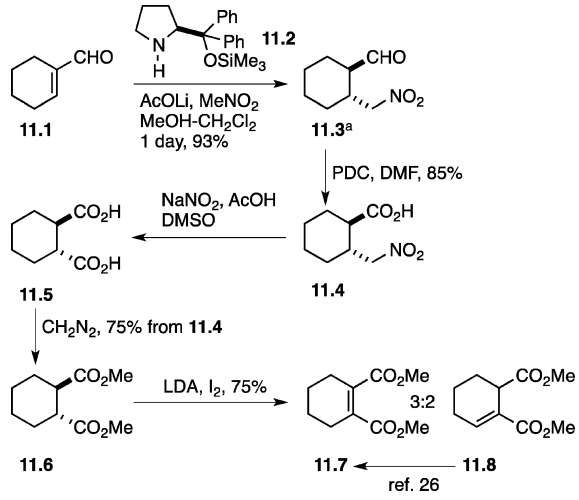
Scheme 10. Third Approach



[a]Compound **10.1** was a 3:1 mixture of C(26) epimers; compounds **10.2** and **10.3** were also C(26) epimers. [b]We did not establish the epoxide stereochemistry.

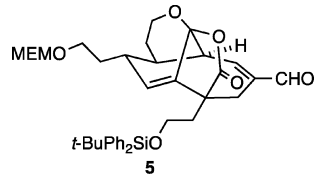
Fourth Approach. Treatment of the simple model aldehyde **11.1** with $MeNO_2$ under conditions of organocatalysis[23−25] (Scheme 11) gave the expected adduct **11.3**[24] in such a high yield that we were prompted to complete its further transformation into the diester **11.7**, as shown in Scheme 11. The critical step here is the conversion of **11.6** to the unsaturated bis-ester **11.7** by treatment with LDA and then I_2, a known[26] process that gave a 3:2 mixture of **11.7** and **11.8**. Isomer **11.8** is easily converted[26] into **11.7**. However, we were not successful in our attempt to apply the same organocatalytic process to the aldehyde lactone **5** that was obtained in poor yield (and not fully characterized) by Parikh−Doering oxidation of both hydroxyls of **10.1**.

Scheme 11. Model Study for Introducing the Double Bond

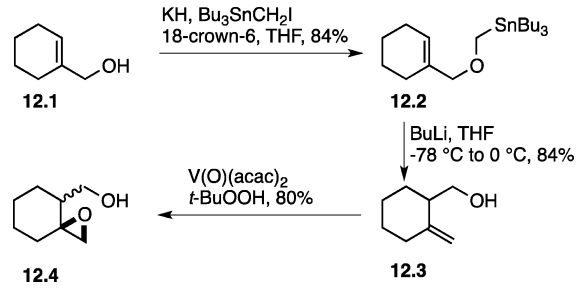


[a]Trans/cis = 6:1.

Fifth Approach: A Promising Advance. At this stage, we began a study of *intramolecular* processes to introduce the additional carbon required for the anhydride subunit, and once more, we began with a model study (Scheme 12). The



Scheme 12. Model Study of [2,3]-Wittig Rearrangement



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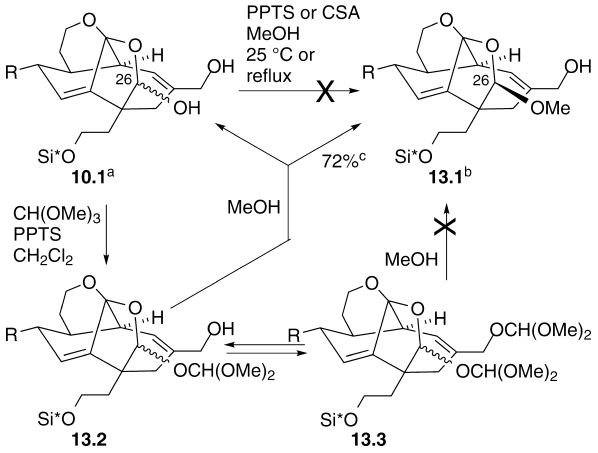
cyclohexenylmethanol **12.1**[27] was alkylated with Bu_3SnCH_2I.[28] Surprisingly, our initial attempt at the alkylation, using NaH[29] in THF, was unsuccessful (starting material recovered), but addition of HMPA resulted in substantial, though incomplete, reaction. However, deprotonation with the more commonly used KH[30] and alkylation in the presence of 18-crown-6 was satisfactory, and treatment of the resulting stannane **12.2** with BuLi in THF at −78 °C, followed by warming to 0 °C, served to generate the expected Wittig product **12.3** in 84% yield. This was then epoxidized (**12.3**→**12.4**) so as to serve as a model for an anticipated subsequent reaction.

For application to our own system, the initial plan was to mask both hydroxyls of **10.1** with Bu_3SnCH_2 groups so that treatment with BuLi would bring about [2,3]-Wittig rearrangement of the homoallylic system with simultaneous generation of a lactol methyl ether. This idea could not be tested, however, as our attempt to alkylate the hydroxyls of **10.1** resulted in decomposition of the compound. Consequently, we were obliged to selectively mask the lactol hydroxyl as a lactol methyl ether.

To that end, we first tried the simple process of treating **10.1** with MeOH in the presence of PPTS or CSA, but these experiments were not successful and so we treated the compound with $HC(OMe)_3$ in the presence of PPTS in CH_2Cl_2 (Scheme 13). The reaction was monitored closely by

Scheme 13. Formation of Lactol Methyl Ether 13.1

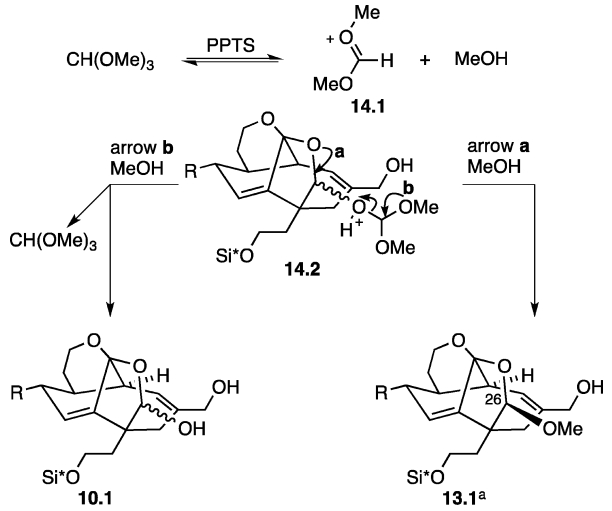


[a]A 3:1 mixture of C(26) epimers. [b]A 10:1 mixture of C(26) epimers; we believe (see later discussion) that the major component has the indicated C(26) stereochemistry. [c]Corrected for recovered **10.1** (51%).

measuring the low-resolution mass spectra of samples removed at short intervals, and after numerous experiments, we were able to unravel the sequence of events taking place and could control them, so as to afford the desired lactol methyl ethers **13.1** [largely with the depicted C(26)[17] stereochemistry, as discussed later].

On the basis of the mass spectral changes that we observed, it became clear that the fastest process is conversion of **10.1** to **13.2** and that compound, in turn, is converted into **13.3** on prolonged reaction. Treatment of **13.3** with dry MeOH (in the presence of PPTS) did not afford **13.1**. However, the rate difference between the formation of **13.2** and **13.3** is sufficiently large that it was possible to identify the stage at which the amount of **13.3** was far less than the amount of **13.2** and, when we added an excess of dry MeOH at that point, extensive conversion of **13.2** to a mixture of **13.1** and **10.1** took place. The latter (51%) was easily recycled. The addition of MeOH effectively stops further reaction of the substrate by competing for the reactive species **14.1** generated from the $HC(OMe)_3$ (Scheme 14). We interpret the effect of the

Scheme 14. Mechanism of Lactol Methyl Ether Formation



[a]A 10:1 mixture of C(26) epimers; we believe (see later discussion) that the major component has the indicated C(26) stereochemistry.

addition of MeOH, as shown in Scheme 14. It is reasonable to propose that the intermediate **14.2** can collapse in one of two ways: expulsion of $(MeO)_2CHOH$ (arrow **a**), gives an oxocarbenium ion that would be quenched by MeOH to give **13.1**, while disengagement of the $(MeO)_2CH$ unit (arrow **b**) affords the starting lactols. Under optimized conditions, we were able to obtain **13.1**[31] in 35% yield [72% yield, corrected for recovered **10.1** (51%)]. Having reached **13.1**, we were now able to apply the Wittig rearrangement method of Scheme 12.

We used the KH/18-crown-6 procedure, established with the model compound **12.1** to alkylate **13.1** with Bu_3SnCH_2I, and obtained the Wittig rearrangement precursor **15.1** in 85% yield. We noticed that the reagent combination KH/18-crown-6 removed the *t*-$BuPh_2Si$ group on prolonged reaction and so the alkylation should be quenched as soon as it is complete.

When we treated **15.1** with BuLi under exactly the standard[32] conditions that had worked with the model **12.2** we were surprised to recover **13.1** exclusively (Scheme 15). We assume that steric factors suppress the desired [2,3]-Wittig rearrangement at the low temperature used (−78 to −40 °C) and that a carbenoid mechanism[33] is followed that converts the intermediate carbanion into an alkoxide ($-CH_2OCH_2^- \rightarrow -CH_2O^- + CH_2$), giving **13.1** on protonation. We also isolated the expected stannane Bu_4Sn.

We then examined the effect of using a higher temperature[30b] and, after a number of experiments, found that changing the solvent to hexane and using a temperature of −9 to 0 °C was very effective in producing the desired alcohol **3** as the major product, together with small amounts of **13.1** and a compound to which we tentatively assign the structure **15.2**, based on its elemental composition (exact mass measurement) and the similarity of its ^{13}C NMR spectrum to that of **13.1**. We suspect that the C(26) stereochemistry is as shown for the reasons given below. Unfortunately, chromatographic separation of alcohol **3** from **13.1** was not practicable on a preparative scale,

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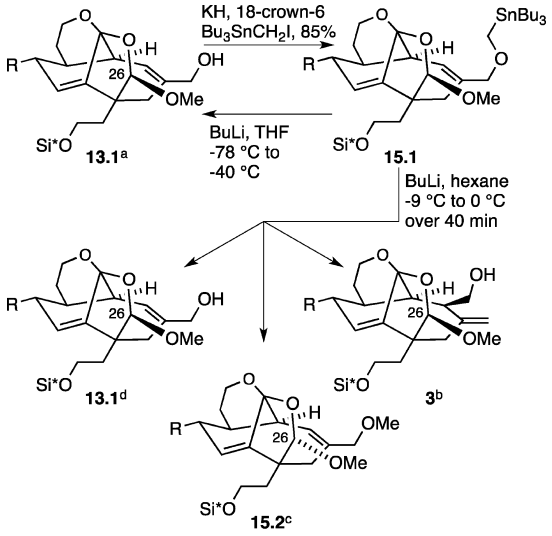
Scheme 15. [2,3]-Wittig Rearrangement

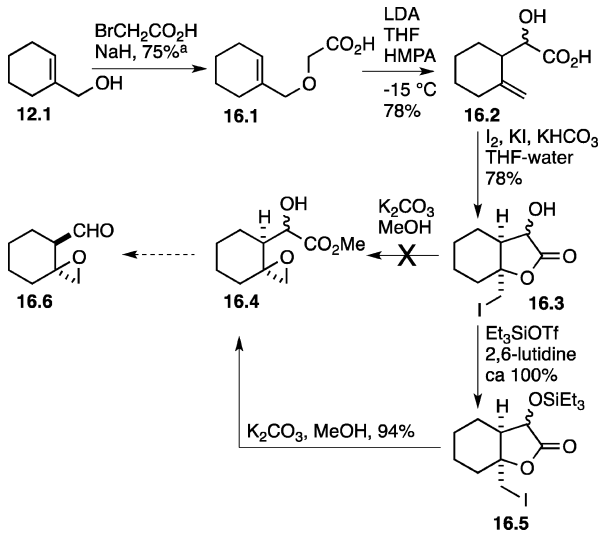


[a]Mixture (10:1) of C(26) isomers; major isomer shown. [b]A single C(26) epimer. The compound was mixed with some **13.1**; the content of the mixture corresponds to a yield >70% for **3**. [c]A single C(26) epimer. As discussed later, we believe **3** and **15.2** have the indicated C(26) stereochemistry. [d]We did not establish the C(26) isomer ratio of this sample.

and so we diverted our attention (in the event, briefly) to explore other ways of effecting similar rearrangements.

The model alcohol **12.1**[27] was alkylated with $BrCH_2CO_2H$, and treatment with LDA caused smooth rearrangement[32] to **16.2**. The advantage of generating structures of type **16.2** is that they should be convertible to epoxy aldehydes along the lines[34] shown in Scheme 16. The sequence (**16.2**→**16.3**→

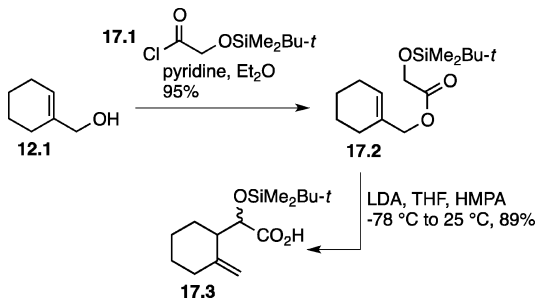
Scheme 16. [2,3]-Wittig Rearrangement of Acid 16



[a]Corrected for recovered **12.1**.

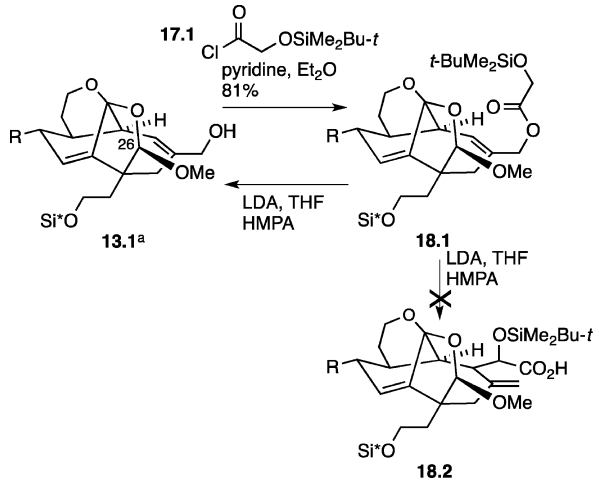
16.5→**16.4**) was carried out with the results shown, but the last step (**16.4**→**16.6**) was not examined because, when we tried to alkylate **13.1** with $BrCH_2CO_2H$ or ICH_2COOH we found the compound to be totally resistant to alkylation. Therefore, we modified the approach slightly by examining the variant shown in Scheme 17.

Scheme 17. Ester Enolate Rearrangement Related to the [2,3]-Wittig Rearrangement



The model alcohol **12.1** was acylated with acid chloride **17.1**[35,36] On treatment with LDA, the resulting ester **17.2** underwent smooth ester enolate rearrangement[38] to **17.3**. Desilylation should give the same product (i.e., **16.2**) as the Wittig rearrangement shown in Scheme 16, but before validating that prediction we tried to apply the rearrangement to **13.1** (Scheme 18). Acylation of **13.1** was easily

Scheme 18. Attempted Ester Enolate Rearrangement of 18.1



[a]A 10:1 mixture of C(26) isomers.

accomplished, but deprotonation of the product **18.1** resulted in recovery of the parent alcohol **13.1**; evidently, steric factors hindered rearrangement and the enolate merely ejected an alkoxide which gave **13.1** on protonation. When we added Me_3SiCl to the enolate in an attempt to suppress this pathway no rearrangement or fragmentation occurred and we recovered **18.1**. We assume that the activation barrier for rearrangement of the carbanion derived from the stannane **15.1** is smaller than that for the stabilized carbanions from **18.1** and **17.2**. The sequence **17.2**→**17.3**, if followed by desilylation, represents a new version of the [2,3]-Wittig rearrangement[32] (cf. **16.1**→**16.2**).

The disappointing observations that several rearrangements worked well on simple models but failed when applied to our advanced intermediates compelled us to return to the Wittig rearrangement summarized in Scheme 15, and we made the arbitrary decision to silylate the total reaction product of that rearrangement in the hope that chromatographic purification would then be possible. Gratifyingly, this modification worked nicely and each of the products was easily separated (Scheme 19). Although the bis-methyl ether **15.2** can be separated from

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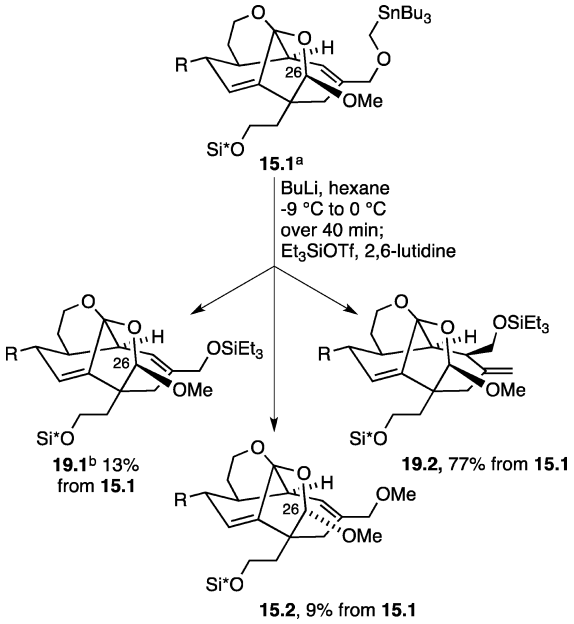
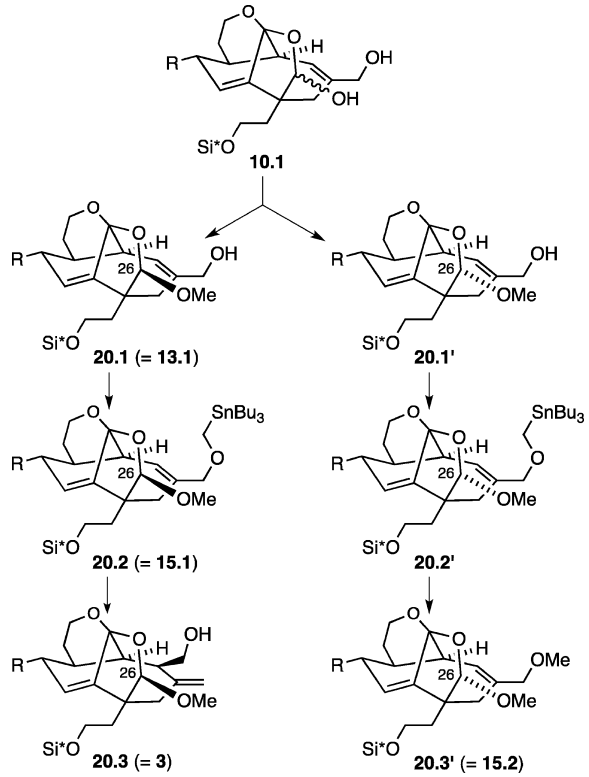
Scheme 19. Improved Procedure for [2,3]-Wittig Rearrangement of 15.1



[a]A 10:1 mixture of C(26) isomers. [b]Possibly a C(26) epimeric mixture (see the following discussion).

Scheme 20. Rationalization of C(26) Stereochemical Assignment



the mixture resulting directly from the [2,3]-Wittig rearrangement of **15.1**, it was convenient not to do so, but to silylate the total product from the rearrangement and then to separate the three components. With this procedure the overall yield of the desired compound (**19.2**) was 77%. The bis-methyl ether **15.2** (9% from **15.1**) was discarded, while **19.1** (13% from **15.1**) was desilylated (85%) and recycled. The key compound (**19.2**) was carried forward.

We noticed that **19.2** was a single C(26) epimer as was **15.2**, but we did not establish if **19.1** was also a single epimer. The yield in the subsequent [2,3]-Wittig rearrangement with recycled material derived from **19.1** by desilylation and alkylation with Bu_3SnCH_2I, was 67% versus 77% when (nonrecycled) **13.1** was used. This drop suggests the possibility that **19.1** contains a small amount of the C(26) epimer with respect to **19.2**. The stereochemistry shown for **15.2** and **19.2** at C(26) is tentative but is reasonable on the basis of the following considerations. The C(26) center is destined to be converted to sp^2 hybridization as a lactone carbonyl and so is ultimately inconsequential (Scheme 20).

When the lactols **10.1** are converted into the acetal **20.1** (= **13.1**), the material always contains a small proportion (ca. 10%) of what we take to be the isomer **20.1′**. It is reasonable to assume that the major product has the stereochemistry shown in **20.1** (= **13.1**) because the precursor oxonium ion would be expected to suffer attack by methanol from the less hindered face. The mixture of **20.1** and **20.1′** is then converted into the tributylstannyl ethers **20.2** (= **15.1**) and **20.2′**, respectively. When these (still as a 10:1 mixture) are subjected to the action of BuLi at a moderately low temperature (−8 °C), both are converted into the corresponding carbanions. The intended [2,3]-sigmatropic rearrangement can most easily occur from the top face; in the case of the carbanion from **20.2**, this leads to the observed product **20.3** (= **3**).

However, we suspect that similar top-face rearrangement of the carbanion derived from **20.2′** is sterically hindered by the methoxy group, and that rearrangement to the bottom face is also hindered. Consequently the carbanion derived from **20.2′** does not rearrange, or does so very slowly. On quenching the reaction mixture with aqueous NH_4Cl, the carbanion from **20.2′** affords the methyl ether **20.3′** (= **15.2**), which was isolated in 9% yield.

Further Elaboration of the Silylated [2,3]-Wittig Rearrangement Product 19.2. With **19.2** in hand, we treated the compound with 9-BBN, hoping to selectively hydroborate the exocyclic double bond without attacking the bridgehead double bond which we suspected might be very reactive. However, no reaction occurred with 9-BBN and so we used $BH_3{\cdot}SMe_2$. With this reagent, the desired selective hydroboration took place with the advantage that the Et_3Si group was removed during the oxidative workup. We tentatively assign the stereochemistry shown for the product **21.1** (isolated as a single isomer) on the assumption that hydroboration takes place from the top face, and we justify this assumption based on the shape of **6.9**, as revealed by X-ray analysis. Oxidation to the corresponding diacid **21.3** was achieved by sequential Swern and Pinnick oxidation. Direct conversion of diol **21.1** to the diacid was not possible with PDC in DMF.[37] For ease of handling the diacid was esterified with CH_2N_2. Treatment of the bis-ester **4** with LDA and iodine, however, did not generate the double bond, and the ester was recovered, despite the fact that simple cycloalkyl-1,2-bis esters give unsaturated esters smoothly under these conditions (see Scheme 11).[26] Several additional experiments indicate that some modifications to Scheme 21 will be required in order to introduce the double bond of the natural anhydride unit, and a number of opportunities for this exploration are obviously provided by the functionality already present in its precursors.

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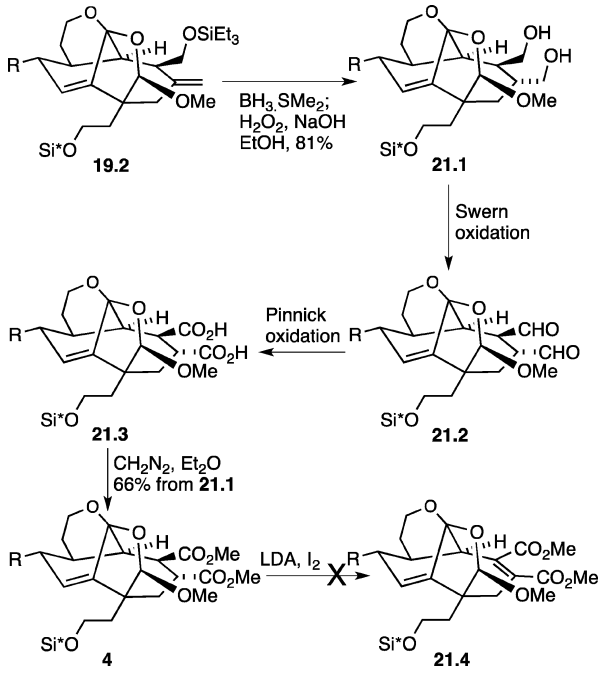
Scheme 21. Elaboration of 19.2



CONCLUSIONS

Our experiments show that intramolecular conjugate displacement can be used to make complex polycyclic structures and that the [2,3]-Wittig rearrangement works in sterically demanding situations. We observed a minor pathway in the Wittig rearrangement which we attribute to the presence of steric impediments to the normal mechanism. Several model studies suggested promising approaches for introducing the anhydride present in CP-225,917 and CP-263,144, but our experiments show that these approaches will have to be modified if they are to be successful with our advanced intermediates. We have, however, been able to introduce all the carbons of the anhydride subunit. During our studies we found that a variant of the Ireland-ester enolate rearrangement (see Scheme 17) represents a new approach to the particular [2,3]-Wittig rearrangement we needed to introduce the final carbon of the anhydride subunit.

EXPERIMENTAL SECTION

General Procedures. The symbols s, d, t, and q used for ^{13}C NMR spectra indicate zero, one, two, or three attached hydrogens, respectively, the assignments being made from APT spectra. Solutions were evaporated under water pump vacuum, and the residue was then kept under oil pump vacuum.

Unless specified, reactions were carried out under a slight static pressure of Ar or N_2 that had been purified by passage through a column (3.5 × 42 cm) of R-311 catalyst and then through a similar column of Drierite. Glassware was dried in an oven (140 °C) overnight before use and either cooled in a desiccator over Drierite or assembled quickly, sealed with rubber septa, and allowed to cool under a light static pressure of Ar or N_2.

Solvents used for chromatography were distilled before use. Commercial thin-layer chromatography plates (silica gel, Merck 60F-254) were used. Silica gel for flash chromatography was Merck type 60 (230–400 mesh). Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. Dry THF and Et_2O were distilled from sodium and benzophenone ketyl. Dry MeCN, Et_3N and pyridine were distilled from CaH_2. Dry MeOH was distilled from $Mg(OMe)_2$, generated in situ.

Electrospray ionization was used for mass spectra. For high resolution spectra an orthogonal time-of-flight analyzer was used and a quadrupole analyzer for low resolution spectra.

1,2,3,4-Tetrachloro-5,5-dimethoxycyclopenta-1,3-diene (2.1).[15] A solution of KOH (33 g, 0.59 mol) in MeOH (165 mL) was added dropwise from an addition funnel over 2 h to a stirred solution of hexachlorocyclopentadiene (70 g, 0.26 mol) in MeOH (220 mL) at room temperature. Stirring was continued for an additional 2.5 h, and the mixture was then poured onto chopped ice (850 mL). After the ice had melted, the mixture was extracted with CH_2Cl_2 (3 × 150 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was distilled through a vacuum-jacketed Vigreux column at 65 °C under vacuum (0.5 mmHg) to yield **2.1** (59.3 g, 87%) as a yellow oil: FTIR ($CHCl_3$ cast) 3003, 2951, 2839, 1644, 1614, 1457, 1314, 1244, 1213, 1175, 1127, 1099, 1067 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.35 (s, 6 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.9 (q), 104.7 (s), 128.5 (s), 129.4 (s); exact mass (electrospray) m/z calcd for $C_7H_6{}^{35}Cl_4NaO_2$ (M + Na) 284.9014, found 284.9015.

(1*R*,2*S*,3*S*,4*S*)-*rel*-2,3-Dimethyl 1,4,5,6-tetrachloro-7,7-dimethoxybicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (2.2). A mixture of 1,1-dimethoxy-2,3,4,5-tetrachlorocyclopentadiene (**2.1**) (59.3 g, 0.22 mol), dimethyl fumarate (32.37 g, 0.22 mol), and hydroquinone (211 mg, 1.92 mmol) in *o*-dichlorobenzene (21 mL) was refluxed (oil bath at 200 °C) for 20 h. The mixture was cooled to room temperature and applied directly to a column of flash chromatography silica gel (10 × 23 cm) made up with 1:7 EtOAc–hexane. The column was developed with 1:7 EtOAc–hexane to give the adduct **2.2** (87.47 g, 96%) as a viscous liquid: FTIR (CH_2Cl_2 cast) 2997, 2954, 2846, 1740, 1608, 1437, 1243, 991 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.22 (d, J = 5.2 Hz, 1 H), 3.55 (s, 3 H), 3.57 (s, 3 H), 3.75 (s, 3 H), 3.79 (s, 3 H), 4.06 (d, J = 5.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 51.7 (d), 52.4 (q), 52.5 (d), 52.6 (q), 52.7 (q), 53.4 (q), 75.7 (s), 111.7 (s), 129.9 (s), 131.4 (s), 167.6 (s), 169.6 (s); exact mass (electrospray) m/z calcd for $C_{13}H_{14}{}^{35}Cl_4NaO_6$ (M + Na) 428.9437, found 428.9441.

(1*R*,2*S*,3*S*,4*S*)-*rel*-[1,4,5,6-Tetrachloro-3-(hydroxymethyl)-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl]methanol (2.3). $LiAlH_4$ (25 g, 0.66 mol) was added in portions to a stirred solution of **2.2** (91 g, 0.22 mol) in THF (1.7 L), and the mixture was then refluxed for 12 h, cooled to room temperature, and quenched by dropwise addition of water (25 mL), followed by continued stirring for 5 min. Aqueous NaOH (1 N, 25 mL) was added and stirring was continued for 5 min; water (75 mL) was added and stirring was continued for 15 min; finally, aqueous NaOH (1 N, 75 mL) was added, and stirring was continued for 15 min. The mixture was filtered and evaporated. Flash chromatography of the residue over silica gel (10 × 20 cm), using 1:1 EtOAc-hexane, gave **2.3** (63 g, 82%) as a white solid: FTIR (CH_2Cl_2 cast) 3328, 2952, 2847, 1605, 1450, 1266, 1199, 1177, 1118, 1039 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.96–2.00 (m, 1 H), 2.67–2.72 (m, 1 H), 2.95 (br s, 2 H), 3.24 (t, J = 10.3 Hz, 1 H), 3.54 (s, 3 H), 3.58 (s, 3 H), 3.92 (t, J = 10.0 Hz, 1 H), 4.00 (dt, J = 10.5, 3.7 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.5 (d), 52.7 (d), 53.7 (q), 53.8 (q), 61.9 (t), 62.0 (t), 76.3 (s), 76.5 (s), 111.8 (s), 128.6 (s), 131.7 (s); exact mass (electrospray) m/z calcd for $C_{11}H_{14}{}^{35}Cl_4NaO_4$ (M + Na) 372.9538, found 372.9536.

(1*R*,2*R*,3*R*,4*S*)-*rel*-[3-(Hydroxymethyl)-7,7-dimethoxybicyclo-[2.2.1]hept-5-en-2-yl]methanol (2.4). Liquid NH_3 (1.4 L), followed by small pieces of Na (39 g, 1.70 mol), were added to a stirred and cooled (−78 °C) solution of **2.3** (63 g, 0.18 mol) in THF (1.4 L). The resulting blue solution was stirred for 4 h at −78 °C, and then the cold bath was removed. Within 3 h, the solution became colorless and most of the NH_3 had evaporated. The mixture was carefully quenched by adding solid NH_4Cl (50 g) in portions, and the reaction flask was left open for 2 h to allow the remaining NH_3 to evaporate. Finally, water (500 mL) was added to the residue, which was then extracted with EtOAc (3 × 300 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (10 × 20 cm), using 5% MeOH–EtOAc, gave **2.4** (33.9 g, 88%) as a pale yellow oil: FTIR (neat) 3355, 2938, 2832, 1457, 1286, 1119, 1081, 1061, 1028 cm^{-1};

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^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.34−1.39 (m, 1 H), 2.21−2.26 (m, 1 H), 2.67 (s, 1 H), 2.80 (br s, 1 H), 2.88 (s, 1 H), 2.95 (br s, 1 H), 3.10−3.18 [m, including a singlet at δ 3.14 (3 H), 4 H in all], 3.19 (s, 3 H), 3.61−3.65 (m, 1 H), 3.73−3.78 (m, 1 H), 3.85 (t, J = 9.3 Hz, 1 H), 6.00 (dd, J = 6.2, 3.3 Hz, 1 H), 6.27 (ddd, J = 6.2, 3.5, 0.7 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 43.9 (d), 47.4 (d), 47.5 (d), 47.9 (d), 49.5 (q), 51.9 (q), 64.0 (t), 65.2 (t), 119.0 (s), 130.4 (d), 135.3 (d); exact mass (electrospray) m/z calcd for $C_{11}H_{18}NaO_4$ (M + Na) 237.1097, found 237.1099.

(1*R*,4*S*,5*S*,6*S*)-*rel*-5,6-Bis(iodomethyl)-7,7-dimethoxybicyclo-[2.2.1]hept-2-ene (2.5). Ph_3P (98.93 g, 0.37 mol) was added to a stirred (mechanical stirrer) solution of **2.4** (33.6 g, 0.16 mol) in a mixture of PhMe (820 mL) and CH_2Cl_2 (328 mL). After the Ph_3P had dissolved, imidazole (51.38 g, 0.76 mol) and I_2 (96 g, 0.37 mol) were added sequentially, and stirring was continued for 15 h. The mixture was diluted with Et_2O (200 mL), washed with aqueous $Na_2S_2O_3$ (2 × 250 mL) and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (10 × 20 cm), using EtOAc−hexane mixtures from pure hexane to 1:5 EtOAc−hexane, gave **2.5** (44.05 g, 64%) as a light yellow oil: FTIR (neat) 3062, 2982, 2954, 2934, 2828, 1452, 1424, 1301, 1282, 1248, 1147, 1119, 1076 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48−1.56 (m, 1 H), 2.30−2.37 (m, 1 H), 2.85 (t, J = 10.4 Hz, 1 H), 2.10 (br s, 1 H), 3.18 (s, 3 H), 3.19 (br s, 1 H), 3.22 (s, 3 H), 3.31 (dd, J = 9.5, 6.1 Hz, 1 H), 3.46 (t, J = 9.0 Hz, 1 H), 3.67 (dd, J = 9.4, 7.4 Hz, 1 H), 6.12 (dd, J = 6.1, 3.2 Hz, 1 H), 6.34 (ddd, J = 6.2, 3.6, 0.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.2 (t), 47.8 (d), 49.8 (d), 51.3 (d), 51.5 (d), 51.8 (q), 52.4 (q), 118.6 (s), 130.5 (d), 136.2 (d); exact mass m/z calcd for $C_{11}H_{16}I_2O_2$ 433.9240, found 433.9244.

(1*R*,2*R*,3*R*,4*S*)-*rel*-2-[3-(Cyanomethyl)-7,7-dimethoxybicyclo-[2.2.1]hept-5-en-2-yl]acetonitrile (2.6). NaCN (104 g, 2.11 mol) followed by a catalytic amount (2−4 crystals) of 18-crown-6 were added to a solution of **2.5** (46.1 g, 0.11 mol) in dry DMSO (600 mL), and the mixture was heated at 40 °C for 12 h, cooled to room temperature, diluted with EtOAc (300 mL), and quenched with water (1.8 L). The aqueous layer was extracted with EtOAc (5 × 300 mL), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (10 × 20 cm), using 1:1 EtOAc−hexane, gave **2.6** (24.2 g, 95%) as a light yellow oil: FTIR (neat) 2978, 2939, 2246, 1427, 1283, 1240, 1121, 1084, 1049 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.36−1.44 (m, 1 H), 2.15−2.25 (m, 2 H), 2.30−2.40 (m, 1 H), 2.72−2.85 (m, 3 H), 3.06 (br s, 1 H), 3.15 (s, 3 H), 3.22 (s, 3 H), 6.11−6.15 (m, 1 H), 6.34−6.38 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.1 (t), 20.8 (t), 39.3 (d), 42.9 (d), 48.5 (q), 49.2 (q), 49.6 (d), 52.1 (d), 118.3 (s), 118.9 (s), 119.3 (s), 130.9 (d), 136.1 (d); exact mass (electrospray) m/z calcd for $C_{13}H_{16}NaN_2O_2$ (M + Na) 255.1104, found 255.1106.

(1*R*,2*R*,3*R*,4*S*)-*rel*-2-[7,7-Dimethoxy-3-(2-oxoethyl)bicyclo-[2.2.1]hept-5-en-2-yl]acetaldehyde (2.7). DIBAL-H (1 M in PhMe, 316 mL, 316 mmol) was added dropwise over 20 min to a stirred and cooled (−78 °C) solution of **2.6** (24 g, 0.10 mol) in PhMe (860 mL). Stirring at −78 °C was continued for 1 h, and the cold bath was then replaced by an ice bath. Stirring was continued for 30 min, the ice bath was removed, and stirring was continued for 10 min. Hydrochloric acid (0.5 N, 1.6 L) was added, and the mixture was stirred for 12 h. The aqueous layer was extracted with EtOAc (3 × 200 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was passed through a pad of silica gel [6 (diameter) × 5 cm] to remove polar material, using 1:2 EtOAc−hexane, to afford **2.7** (19.94 g, 81%) as a yellow oil: FTIR (CH_2Cl_2, cast) 2938, 2831, 2724, 1721, 1121, 1081 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.52 (dd, J = 7.0, 5.5 Hz, 1 H), 2.25−2.40 (m, 2 H), 2.53−2.59 (m, 2 H), 2.87−3.06 (m, 3 H), 3.12 (s, 3 H), 3.22 (s, 3 H), 6.02 (dd, J = 6.2, 3.3 Hz, 1 H), 6.29−6.32 (m, 1 H), 9.73 (d, J = 1.1 Hz, 1 H), 9.78 (d, J = 0.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 36.0 (d), 39.5 (d), 47.8 (t), 48.0 (t), 48.7 (q), 48.8 (q), 49.5 (d), 51.8 (d), 119.0 (s), 130.7 (d), 135.9 (d), 201.6 (d), 202.3 (d); exact mass (electrospray) m/z calcd for $C_{13}H_{18}NaO_4$ (M + Na) 261.1097, found 261.1101.

(1*R*,2*R*,3*R*,4*S*)-*rel*-2-[3-(2-Hydroxyethyl)-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl]ethan-1-ol (2.8). $NaBH_4$ (9.5 g, 0.261 mol) was added in portions to a stirred solution of **2.7** (20 g, 84 mmol) in MeOH (740 mL), and stirring was continued for 8 h. The mixture was evaporated and the residue was partitioned between EtOAc (150 mL) and water (80 mL). The aqueous phase was extracted with EtOAc (3 × 50 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4.5 × 15 cm), using 10:1 EtOAc−MeOH, gave **2.8** (16.47 g, 81%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3388, 2935, 2832, 1452, 1288, 1226, 1195, 1121, 1061 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.11−1.14 (m, 1 H), 1.36−1.52 (m, 2 H), 1.86−1.92 (m, 2 H), 1.94−2.01 (m, 1 H), 2.08 (br s, 2 H), 2.56 (t, J = 1.7 Hz, 1 H), 2.80−2.82 (m, 1 H), 3.13 (s, 3 H), 3.19 (s, 3 H), 3.58−3.72 (m, 4 H), 6.00 (apparent q, J = 3.2 Hz, 1 H), 6.24 (dq, J = 3.6, 0.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 35.9 (t), 36.8 (t), 39.4 (d), 43.4 (d), 48.3 (q), 48.7 (q), 49.6 (d), 51.6 (d), 61.7 (t), 62.3 (t), 119.1 (s), 130.4 (d), 135.7 (d); exact mass (electrospray) m/z calcd for $C_{13}H_{22}NaO_4$ (M + Na) 265.1410, found 265.1411.

(1*R*,2*R*,3*R*,4*S*)-*rel*-2-[3-[2-(Acetyloxy)ethyl]-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl]ethyl Acetate (2.9). DMAP (734 mg, 6 mmol), Ac_2O (18.9 mL, 0.20 mol) and Et_3N (31.6 mL, 0.23 mol) were added sequentially to a stirred solution of **2.8** (12 g, 49.59 mmol) in CH_2Cl_2 (310 mL). Stirring was continued for 6 h, and the organic phase was then washed with water (2 × 150 mL) and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (6 × 15 cm), using 1:1 EtOAc−hexane, gave **2.9** (14.94 g, 92%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3019, 2917, 2849, 1732, 1366, 1247, 1217, 1121, 1036 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.00−1.04 (m, 1 H), 1.40−1.46 (m, 1 H), 1.51−1.58 (m, 1 H), 1.87−2.00 (m, 3 H), 2.04 (s, 3 H), 2.05 (s, 3 H), 2.57 (t, J = 1.9 Hz, 1 H), 2.84 (br s, 1 H), 3.14 (s, 3 H), 3.18 (s, 3 H), 4.00−4.11 (m, 4 H), 6.01 (dd, J = 5.8, 2.6 Hz, 1 H), 6.22−6.25 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.0 (q), 21.0 (q), 31.4 (t), 32.5 (t), 39.6 (d), 43.7 (d), 47.8 (q), 48.4 (q), 49.5 (d), 51.7 (d), 63.5 (t), 64.1 (t), 119.1 (s), 130.4 (d), 135.7 (d), 171.1 (s), 171.1 (s); exact mass (electrospray) m/z calcd for $C_{17}H_{26}NaO_6$ (M + Na) 349.1622, found 349.1620.

(1*R*,2*R*,3*R*,4*S*)-*rel*-2-[3-[2-(Acetyloxy)ethyl]-7-oxobicyclo-[2.2.1]hept-5-en-2-yl]ethyl Acetate (2.10). CF_3CO_2H (43 mL, 579 mmol) was added to a stirred solution of **2.9** (14.94 g, 45.83 mmol) in CH_2Cl_2 (201 mL). Stirring was continued for 5 h, and the solution was then evaporated. CH_2Cl_2 (200 mL) was added to the residue, and the organic phase was washed twice with saturated aqueous K_2CO_3 (50 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4.5 × 15 cm), using 40% EtOAc−hexane, gave **2.10** (12.58 g, 98%), as a yellow oil: FTIR (CH_2Cl_2 cast) 2957, 2849, 1779, 1739, 1435, 1368, 1242, 1038 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.20−1.25 (m, 1 H), 1.48−1.64 (m, 2 H), 1.68−1.82 (m, 2 H), 1.86−1.94 (m, 1 H), 2.06 (s, 6 H), 2.70 (d, J = 3.8 Hz, 1 H), 2.94 (t, J = 3.6 Hz, 1 H), 4.00−4.20 (m, 4 H), 6.44 (apparent q, J = 3.5 Hz, 1 H), 6.60 (dq, J = 3.8, 1.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.9 (q), 32.3 (t), 32.6 (t), 38.9 (d), 40.3 (d), 50.4 (d), 51.6 (d), 62.4 (t), 62.6 (t), 130.7 (d), 133.4 (d), 170.9 (s), 204.0 (s); exact mass (electrospray) m/z calcd for $C_{15}H_{20}NaO_5$ (M + Na) 303.1203, found 303.1207.

(1*R*,2*S*,3*S*,4*S*)-*rel*-1,4,5,6-Tetrachloro-7,7-dimethoxybicyclo-[2.2.1]hept-5-ene-2,3-dicarbaldehyde (4.1). DMSO (1.33 mL, 18.7 mmol) was added dropwise to $(COCl)_2$ (0.90 mL, 9.4 mmol) in CH_2Cl_2 (12 mL) at −78 °C. After 15 min, a solution of **2.3** (1.09 g, 3.11 mmol) in CH_2Cl_2 (6 mL) was added dropwise over 15 min. Stirring was continued for 1 h, and then Et_3N (3.3 mL, 23.7 mmol) was added dropwise over 5 min. After 1 h, the ice bath was removed, and stirring was continued for 20 min. The mixture was quenched with water, and the organic layer was separated and passed through a pad of silica gel (4 × 4 cm), using CH_2Cl_2. Evaporation of the filtrate gave the unstable but pure dialdehyde **4.1** (0.91 g, 84%) as a yellow oil: FTIR ($CHCl_3$, cast) 2954, 2848, 1730, 1606, 1461, 1244, 1207, 1179, 1127, 1033 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.01 (d, J = 4.5 Hz, 1 H), 3.79 (dd, J = 4.5, 0.3 Hz, 1 H), 3.55 (s, 3 H), 3.79 (s, 3 H), 9.84 (s, 1

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H), 9.91 (d, J = 0.3 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 52.1 (d), 53.5 (d), 54.4 (q), 59.3 (q), 75.6 (s), 76.0 (s), 112.7 (s), 130.4 (s), 131.4 (s), 196.6 (d), 197.1 (d); exact mass (electrospray) m/z calcd for $C_{11}H_{10}{}^{35}Cl_4NaO_4$ (M + Na) 368.9225, found 368.9225.

(1*R*,2*S*,3*S*,4*S*)-*rel*-[1,4,5,6-Tetrachloro-7,7-dimethoxy-3-(2-oxoethyl)bicyclo[2.2.1]hept-5-en-2-yl]acetaldehyde (4.3). A solution of *t*-BuOK (1.09 g, 9.23 mmol) in THF (7 mL) was added to a stirred and cooled (0 °C) suspension of $MeOCHPh_3PCl$ (3.25 g, 9.48 mmol) in THF (15 mL). Stirring was continued for 15 min, and then a solution of **4.1** (0.91 g, 2.6 mmol) in THF (6 mL) was added dropwise over 20 min. After the addition, the mixture was stirred at 0 °C for 3 h, the ice bath was removed, and stirring was continued for 14 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 × 25 cm), using 1% Et_3N in 1:10 EtOAc–hexane, gave **4.2** (0.48 g, 48%) as a yellowish oil that was a mixture of several isomers: FTIR (CH_2Cl_2, cast) 2950, 2842, 1655, 1605, 1394, 1318, 1265, 1212, 1155, 1115, 1039 cm^{-1}. The material was hydrolyzed directly.

Hydrochloric acid (40% v/v, 3 mL) was added dropwise over 20 min to a stirred and cooled (0 °C) solution of **4.2** (0.44 g, 1.3 mmol) in THF (9 mL). Stirring was continued at 0 °C for 2 h, the ice bath was removed, and stirring was continued for 16 h. The mixture was diluted with water (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated to give crude **4.3** (0.36 g, 89%) as an unstable, yellow oil: FTIR (CH_2Cl_2, cast) 2952, 2845, 2730, 1725, 1607, 1458, 1388, 1265, 1200, 1177, 1121, 1025 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.27 (dd, J = 10.8, 5.6 Hz, 1 H), 2.24–2.51 (m, 1 H), 2.83–2.89 (m, 2 H), 3.10–3.26 (m, 2 H), 3.54 (s, 3 H), 3.61 (s, 3 H), 9.76 (s, 1 H), 9.78 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 44.9 (t), 45.4 (t), 46.6 (q), 47.1 (q), 51.5 (d), 52.7 (d), 111.5 (s), 128.7 (s), 131.8 (s), 199.5 (d), 200.1 (d); exact mass (electrospray) m/z calcd for $C_{13}H_{14}{}^{35}Cl_4NaO_4$ (M + Na) 396.9538, found 396.9536.

(1*R*,2*S*,3*S*,4*S*)-*rel*-2-[1,4,5,6-Tetrachloro-3-(2-hydroxyethyl)-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl]ethanol (3.2).[10b] A solution of crude **4.3** (0.37 g, 0.98 mmol) in Et_2O (15 mL) was added dropwise over 10 min to a stirred and cooled (0 °C) solution of $LiAlH_4$ (55.0 mg, 1.39 mmol) in Et_2O (30 mL). After 2 h, the cold bath was removed and stirring was continued for 12 h. The reaction was quenched with aqueous NaOH (2 N, 6 mL) and the solution was passed through a pad of silica gel (2 × 3 cm) covered by Na_2SO_4, using Et_2O as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 × 15 cm), using 1:1 EtOAc-hexane, gave **3.2**[10b] (0.13 g, 31% over 2 steps) as a yellow oil: FTIR (CH_2Cl_2, cast) 3349, 2950, 2882, 2845, 1604, 1456, 1265, 1199, 1142, 1110, 1059, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35–1.46 (m, 1 H), 1.78 (dd, J = 11.2, 5.6 Hz, 1 H), 1.87–1.98 (m, 2 H), 2.21–2.32 (m, 1 H), 2.49–2.56 (m, 1 H), 2.72 (br s, 2 H), 3.54 (s, 3 H), 3.57 (s, 3 H), 3.68–3.76 (m, 1 H), 3.75–3.85 (m, 3 H); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 33.6 (t), 33.8 (t), 49.0 (q), 51.0 (q), 51.4 (d), 52.6 (d), 60.8 (t), 61.9 (t), 78.6 (s), 78.7 (s), 111.7 (s), 128.8 (s), 131.7 (s); exact mass (electrospray) m/z calcd for $C_{13}H_{18}{}^{35}Cl_4NaO_4$ (M + Na) 400.9851, found 400.9855.

(1*R*,2*S*,3*S*,4*S*)-*rel*-2-[3-(2-Hydroxyethyl)-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-yl]ethanol (2.8). Liquid NH_3 (350 mL), followed by small pieces of Na (1.13 g, 49.4 mmol) were added to a cooled (−78 °C) and stirred solution of **3.2** (1.14 g, 3.0 mmol) in THF (50 mL). The blue solution was stirred for 3 h at −78 °C, and then the cold bath was removed. Within 30 min the blue color disappeared, and the mixture was carefully quenched with NH_4Cl (5 g) and saturated aqueous NH_4Cl (10 mL). The mixture was stirred for 4 h to allow the NH_3 to evaporate. Finally, water (20 mL) was added to the residue which was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (4.5 × 23 cm), using 10% MeOH–EtOAc, gave **2.8** (0.62 g, 86%) as an oil, spectroscopically identical to material made from **2.7**.

(1*R*,2*R*,3*R*,4*S*,7*R*)-*rel*-2-[3-[2-(Acetyloxy)ethyl]-7-hydroxybicyclo[2.2.1]hept-5-en-2-yl]ethyl Acetate (5.1). (*t*-BuO)$_3$AlHLi (1 M in THF, 7.6 mL, 7.6 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of keto acetate **2.10** (1.77 g, 6.3 mmol) in THF (45 mL). Stirring was continued for 2 h at −78 °C, and then the cold bath was replaced by an ice bath and stirring was continued for 1 h at 0 °C. The mixture was quenched by dropwise addition of saturated aqueous Rochelle salt (7.6 mL). Et_2O (40 mL) and water (40 mL) were then added, and the mixture was stirred for 3 h and then filtered through a pad of Celite (5 × 2 cm high), using Et_2O as a rinse. The aqueous phase was extracted with Et_2O [three times; the extent of extraction from the aqueous layer was monitored by TLC (silica, 1:1 hexane–EtOAc)], and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (40 g silica, 2.8 × 15 cm), using 45% EtOAc–hexane, gave **5.1** (1.6 g, 89%) as a yellow oil: FTIR (neat) 3461, 2960, 2917, 1731, 1367, 1247, 1036 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.04–1.09 (m, 1 H), 1.46–1.56 (m, 1 H), 1.61–1.70 (m, 1 H), 2.00–2.10 (m, 9 H), 2.10–2.18 (m, 1 H), 2.42 (br s, 1 H), 2.65 (br s, 1 H), 3.77 (s, 1 H), 4.04–4.14 (m, 4 H), 5.88 (dd, J = 6.1, 3.2 Hz, 1 H), 6.10 (dd, J = 6.1, 3.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.0 (q), 31.5 (t), 32.2 (t), 39.8 (d), 42.9 (d), 49.6 (d), 50.3 (d), 63.9 (t), 64.3 (t), 84.7 (d), 131.6 (d), 136.4 (d), 170.0 (s); exact mass (electrospray) m/z calcd for $C_{15}H_{22}NaO_5$ (M + Na) 305.1359, found 305.1359.

(1*R*,2*R*,3*R*,4*S*,7*R*)-*rel*-2-[3-[2-(Acetyloxy)ethyl]-7-[(triethylsilyl)oxy]bicyclo[2.2.1]hept-5-en-2-yl]ethyl Acetate (5.2). 2,6-Lutidine (16.7 mL, 143.6 mmol), followed by $Et_3SiOSO_2CF_3$ (13.4 mL, 62.8 mmol), were added to a stirred and cooled (0 °C) solution of **5.1** (12.66 g, 44.8 mmol) in CH_2Cl_2 (500 mL). The ice bath was removed after 40 min, and stirring was continued for 13 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (300 mL), and the organic phase was washed with water (50 mL) and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 × 15 cm), using 1:5 EtOAc–hexane, gave **5.2** (17.78 g, 100%) as a pale yellow oil: FTIR (neat) 2958, 1740, 1458, 1366, 1243, 1112, 1036 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.56 (q, J = 7.8 Hz, 6 H), 0.94 (t, J = 7.9 Hz, 9 H), 1.01–1.10 (m, 1 H), 1.42–1.53 (m, 1 H), 1.60–1.70 (m, 1 H), 1.98–2.16 [m, including singlets at δ 2.04 (3 H) and 2.05 (3 H), 9 H in all], 2.33 (br s, 1 H), 2.55 (br s, 1 H), 3.62 (s, 1 H), 4.02–4.16 (m, 4 H), 5.86 (dd, J = 6.1, 3.3 Hz, 1 H), 6.08–6.12 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.6 (t), 4.6 (t), 6.7 (q), 20.9 (q), 20.9 (q), 31.3 (t), 32.1 (t), 39.7 (d), 43.1 (d), 49.9 (d), 50.8 (d), 63.8 (t), 64.3 (t), 84.7 (d), 131.3 (d), 136.1 (d), 171.0 (s), 171.1 (s); exact mass (electrospray) m/z calcd for $C_{21}H_{36}NaO_5Si$ (M + Na) 419.2224, found 419.2225.

(1*R*,2*R*,3*R*,4*S*,5*S*,6*R*,7*S*)-*rel*-2-[3-[2-(Acetyloxy)ethyl]-5,6-dihydroxy-7-[(triethylsilyl)oxy]bicyclo[2.2.1]heptan-2-yl]ethyl Acetate (5.3). NMO (8.1 g, 690 mmol) was added to a stirred solution of **5.2** (18.1 g, 44.9 mmol) in a mixture of acetone (362 mL) and water (90 mL). A freshly made solution of OsO_4 (23 mg, 0.09 mmol) in *i*-PrOH (2.26 mL) was added dropwise, and stirring was continued in the dark for 9 h (reaction was left overnight, but we did not establish if it is complete sooner). Solid $Na_2S_2O_3$ (5.88 g, 37 mmol) was tipped in, and stirring was continued for 30 min. The mixture was diluted with water (100 mL) and saturated with NaCl and extracted with EtOAc (4 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm), using EtOAc, gave **5.3** (17.3 g, 88%) as a colorless oil: FTIR ($CHCl_3$ cast) 3420, 2956, 2914, 2877, 1740, 1242, 1117, 1036 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.60 (q, J = 8.0 Hz, 6 H), 0.96 (t, J = 8.2 Hz, 9 H), 1.56–1.67 (m, 1 H), 1.71–1.88 (m, 3 H), 1.92–2.01 (m, 2 H), 2.03–2.12 [m, including singlets at δ 2.05 (3 H) and δ 2.06 (3 H), 8 H in all], 3.60 (d, J = 7.0 Hz, 1 H), 3.98 (d, J = 6.7 Hz, 1 H), 4.04–4.16 (m, 4 H), 4.43 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 4.5 (t), 6.7 (q), 20.8 (q), 20.9 (q), 28.9 (t), 34.0 (t), 38.4 (d), 42.3 (d), 51.4 (d), 51.5 (d), 63.5 (t), 63.6 (t), 67.2 (d), 72.3 (d), 76.6 (d), 171.2 (s), 171.2 (s); exact mass (electrospray) m/z calcd for $C_{21}H_{38}NaO_7Si$ (M + Na) 453.2279, found 453.2276.

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(1*S*,3*R*,7*R*,8*R*,9*R*,10*R*)-*rel*-3-Hydroxy-10-[2-[(2-methoxyethoxy)methoxy]ethyl]-9-[(triethylsilyl)oxy]-4-oxatricylco[5.2.1.0^{3,8}]decan-2-one (5.6). Dry DMSO (0.64 mL, 9.01 mmol) was added to a stirred and cooled (−78 °C) solution of $(COCl)_2$ (0.52 mL, 6.05 mmol) in dry CH_2Cl_2 (8.5 mL). After 30 min, a solution of **5.3** (500 mg, 1.16 mmol) in CH_2Cl_2 (8.5 mL) was added dropwise over 15 min, and stirring was continued at −78 °C for 1.5 h. Dry Et_3N (1.6 mL, 11.82 mmol) was then added dropwise over 15 min, and stirring was continued at −78 °C for 1.5 h. The cold bath was removed, stirring was continued for 30 min, and the mixture was then poured into water (150 mL) and extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give crude **5.4** as a yellow oil, which was kept under oil pump vacuum for 35 min. The compound should be used promptly.

A solution of aqueous K_2CO_3 (1.2 M, 1.5 mL, 1.8 mmol) was added dropwise over ca. 15 min to a stirred and cooled (0 °C) solution of the above crude oil in MeOH (15 mL). The ice bath was removed, stirring was continued for 4 h, and the mixture was partitioned between water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts (containing **5.5**) were dried ($MgSO_4$) and concentrated to a volume of 13 mL (using a premarked flask). The solution should not be evaporated to dryness. The solution was stirred and *i*-Pr_2NEt (0.8 mL, 4.59 mmol) was injected dropwise, followed by MEMCl (0.334 mL, 2.92 mmol). The large excess of the base is to ensure that the mixture does not become acidic. Stirring was continued overnight, and the mixture was diluted with water and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (12 g, 1.5 × 15 cm), using 40% EtOAc−hexane, gave pure **5.6** (335 mg, 67% over three steps) as a yellow oil: FTIR (neat film) 3335, 2955, 2877, 1762, 1458, 1414, 1293, 1240, 1152, 1115, 1091 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.63 (q, J = 7.8 Hz, 6 H), 0.97 (t, J = 7.8 Hz, 9 H), 1.56 (d, J = 11.7 Hz, 1 H), 1.82−1.96 (m, 2 H), 2.04−2.14 (m, 2 H), 2.19−2.22 (m, 1 H), 2.48−2.53 (m, 1 H), 2.58 (s, 1 H), 3.10 (s, 1 H), 3.4 (s, 3 H), 3.52−3.62 (m, 5 H), 3.65−3.72 (m, 2 H), 3.91 (dd, J = 12.5, 5.1 Hz, 1 H), 4.48 (s, 1 H), 4.69 (s, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.6 (t), 6.7 (q), 25.3 (t), 35.5 (t), 36.3 (d), 37.7 (d), 50.7 (d), 59.0 (d), 59.2 (q), 61.2 (t), 65.9 (t), 66.8 (t), 71.8 (t), 74.4 (d), 95.4 (t), 97.2 (s), 212.1 (s); exact mass (electrospray) m/z calcd for $C_{21}H_{38}NaO_7Si$ (M + Na) 453.2279, found 453.2277.

4-[(*tert*-Butyldiphenylsilyl)oxy]-2-(dimethoxyphosphoryl)-butanoic Acid (6.1). *a. Methyl 4-[(tert-butyldiphenylsilyl)oxy]-2-(dimethoxyphosphoryl)butanoate.* Trimethyl phosphonoacetate (0.8 mL, 4.96 mmol) was added dropwise over 30 min to a stirred suspension of NaH (60%w/w suspension in mineral oil, 0.24 g, 5.94 mmol) in DMSO (9.35 mL) at room temperature. After 70 min, (2-bromoethoxy)(*tert*-butyl)diphenylsilane[39] (600 mg, 1.65 mmol) in DMSO (2.6 mL) was added. Stirring was continued for 8 h, and then water (60 mL) was added. The aqueous phase was extracted with Et_2O (3 × 30 mL), and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash column chromatography of the residue over silica gel (3 × 15 cm), using EtOAc, gave methyl 4-[(*tert*-butyldiphenylsilyl)oxy]-2-(dimethoxyphosphoryl)butanoate (3.20 g, 71%) as a clear oil: FTIR ($CHCl_3$, cast) 3072, 3049, 2955, 2857, 1739, 1463, 1429, 1261, 1190, 1160, 1112, 1054, 1031 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.04 (s, 9 H), 2.09−2.14 (m, 1 H), 2.21−2.25 (m, 1 H), 3.39 (ddd, $^2J_{PH}$ = 23.5, J = 11.0, 3.5 Hz, 1 H), 3.59−3.64 (m, 1 H), 3.70−3.75 [m, including a singlet at δ 3.72 (3 H), 4 H in all], 3.79 (d, J = 11.0 Hz, 3 H), 3.80 (d, J = 11.0 Hz, 3 H), 7.36−7.45 (m, 6 H), 7.61−7.65 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (the symbol d before the J value refers to multiplicity due to coupling with ^{31}P; the symbols s, d, t, q after the J value refer to zero, one, two, or three attached hydrogens, respectively) δ 19.2 (s), 26.8 (q), 29.7 (d, J = 4.5 Hz, t), 41.4 (d, J = 131.3 Hz, d), 52.5 (q), 53.3 (d, J = 6.6 Hz, q), 53.4 (d, J = 6.5 Hz, q), 61.6 (d, J = 15.6 Hz, t), 127.7 (d), 129.7 (d), 133.3 (s), 133.4 (s), 135.50 (d), 135.51 (d), 169.4 (d, J = 4.9 Hz, s); exact mass (electrospray) m/z calcd for $C_{23}H_{33}NaO_6PSi$ (M + Na) 487.1676, found 487.1680.

b. 4-[(tert-Butyldiphenylsilyl)oxy]-2-(dimethoxyphosphoryl)-butanoic Acid (6.1). A solution of LiOH·H_2O (18 mg, 0.43 mmol) in water (0.35 mL) was added to a stirred solution of 4-[(*tert*-butyldiphenylsilyl)oxy]-2-(dimethoxyphosphoryl)butanoate (100 mg, 0.22 mmol) in THF (0.77 mL). Stirring was continued for 5 h, and the reaction mixture was quenched with dilute hydrochloric acid (10%, 0.5 mL) to pH = 3. The mixture was diluted with brine (5 mL), and solid NaCl was added to saturate the aqueous phase. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was recrystallized from CH_2Cl_2−hexane to give **6.1** (88 mg, 89%) as a white solid: mp 93−94 °C; FTIR ($CHCl_3$, cast) 3072, 3049, 3012, 2999, 2957, 2933, 2890, 2858, 1727, 1609, 1463, 1428, 1389, 1220, 1188, 1112, 1059, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (s, 9 H), 2.0−2.11 (m, 1 H), 2.19−2.29 (m, 1 H), 3.43 (ddd, $^2J_{PH}$ = 23.6, J = 10.4, 3.2 Hz, 1 H), 3.65−3.77 (m, 2 H), 3.80 (d, J = 10.8 Hz, 3 H), 3.84 (d, J = 11.2 Hz, 3 H), 7.36−7.43 (m, 6 H), 7.64−7.67 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (the symbol d before the J value refers to multiplicity due to coupling with ^{31}P; the symbols s, d, t, q after the J value refer to zero, one, two, or three attached hydrogens, respectively) δ 19.2 (s), 26.8 (q), 29.7 (d, J = 4.9 Hz, t), 41.6 (d, J = 130.8 Hz, d), 53.4 (d, J = 6.8 Hz, q), 54.0 (d, J = 6.8 Hz, q), 61.4 (d, J = 15.0 Hz, t), 127.7 (d), 129.7 (d), 133.3 (s), 133.4 (s), 135.50 (d), 135.52 (d), 170.4 (s); exact mass (electrospray) m/z calcd for $C_{22}H_{31}NaO_6PSi$ (M + Na) 473.1520, found 473.1520.

(1*R*,6*S*,10*R*,11*R*,12*R*,13*R*)-*rel*-3-[2-[(*tert*-Butyldiphenylsilyl)-oxy]ethyl]-13-[2-[(2-methoxyethoxy)methoxy]ethyl]-12-[(triethylsilyl)oxy]-5,7-dioxatetracyclo[8.2.1.0^{2,6}.0^{6,11}]tridec-2-en-4-one (6.3). In the first part of this experiment, **6.1** was converted into the acid chloride as follows: $(COCl)_2$ (0.21 mL, 2.44 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **6.1** (363 mg, 0.81 mmol) in CH_2Cl_2 (3.2 mL). Dry DMF (2 drops from a 19-gauge syringe needle) was added. After 15 min, the ice bath was removed and stirring was continued for 4 h. The solvent was evaporated under water pump vacuum with protection from moisture, Ar being admitted to the flask, and residual $(COCl)_2$ was then removed under oil pump vacuum (45 min).

All of the above acid chloride in THF (4.3 mL, including the rinse) was added at a fast dropwise rate to a stirred and cooled (−78 °C) solution of **5.6** (216 mg, 0.502 mmol) in THF (2.1 mL), followed by neat DBU (0.38 mL, 2.54 mmol), which was added at a slow dropwise rate (over ca. 2 min). The dry ice bath was removed after the DBU addition, and stirring was continued for 6 h. LiCl (kept overnight in an oven at 160 °C and then cooled, 55 mg, 1.29 mmol) (material from a new bottle, without drying is also satisfactory) was tipped in, and stirring was continued overnight. The reaction mixture was passed through a pad of flash chromatography silica gel (2 × 1.5 cm high) covered by $MgSO_4$ (0.5 cm thick), using 1:1 EtOAc−hexane (100 mL) as a rinse. Evaporation of the eluate and flash chromatography of the residue over silica gel (5 g, 1 × 15 cm high), using 20% EtOAc−hexane, gave **6.3** (277 mg, 75%) as a yellow oil: FTIR ($CDCl_3$ cast) 2954, 2932, 2876, 1769, 1686, 1472, 1428, 1389, 1362, 1243, 1211, 1180, 1112, 1089, 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.58 (q, J = 8.1 Hz, 6 H), 0.90 (t, J = 8.1 Hz, 9 H), 1.05 (s, 9 H), 1.78−2.0 (m, 4 H), 2.1 (q, 1 H), 2.4−2.56 (m, 2 H), 2.58 (d, J = 4.0 Hz, 1 H), 2.61−2.70 (m, 1 H), 2.84 (s, 1 H), 3.39 (s, 3 H), 3.50−3.60 (m, 4 H), 3.65−3.69 (m, 2 H), 3.70−3.85 (m, 4 H), 3.95−4.01 (m, 1 H), 4.68 (s, 2 H), 7.35−7.45 (m, 6 H), 7.65−7.69 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 4.5 (t), 6.7 (q), 19.14 (s) 25.1 (t), 26.8 (q), 27.8 (d), 34.8 (t), 36.5 (t), 41.7 (d), 46.7 (d), 53.1 (d), 59.0 (q), 61.7 (t), 62.0 (t), 66.2 (t), 66.8 (t), 71.8 (t), 81.9 (d), 95.4 (t), 107.0 (s), 121.1 (s), 127.7 (d), 129.66 (d), 129.67 (d), 133.47 (s), 133.54 (s), 135.5 (s), 166.1 (s), 172.9 (s); exact mass (electrospray) m/z calcd for $C_{41}H_{60}NaO_8Si_2$ (M + Na) 759.3710, found 759.3712.

(1*S*,7*R*,8*R*,12*R*)-*rel*-4-[2-[(*tert*-Butyldiphenylsilyl)oxy]ethyl]-7-[2-[(2-methoxyethoxy)methoxy]ethyl]-3-oxo-2,11-dioxatricyclo[6.3.1.0^{1,5}]dodec-5-ene-12-carbaldehyde (6.4). AcOH (18 μL, 0.31 mmol) and then Bu_4NF (1 M in THF, 0.2 mL, 0.2 mmol) were added dropwise to a stirred and cooled (−9 °C; obtained by using an immersion cooler probe in a cooling bath) solution of **6.3** (133 mg, 0.181 mmol) in THF (11 mL). Stirring at −9 to −8 °C was continued for 45 min, and samples were examined by

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TLC (silica, 1:1 EtOAc−hexane) at 5 min intervals. In some runs the reaction was over in 30 min. As soon as the TLC spot for **6.3** was faint (a better yield is obtained if the reaction is stopped just before absolute completion), the mixture was quenched with saturated aqueous NH_4Cl (6 mL). Stirring at −10 °C was continued for 10 min and the cold bath was then removed and stirring was continued for 10 min. The mixture was diluted with water and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 g, 1 × 15 cm), using 45% EtOAc−hexane, gave **6.4** (50 mg of each isomer, 100 mg in total, 89%) as colorless oils. The less polar isomer had: FTIR (microscope) 3071, 3049, 3014, 2931, 2879, 2859, 1793, 1734, 1472, 1448, 1428, 1389, 1362, 1251, 1199, 1167, 1111, 1064, 1044 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.08 (s, 9 H), 1.45−1.62 (m, 3 H), 1.72−1.85 (m, 1 H), 1.87−2.11 (m, 1 H), 2.16−2.36 (m, 2 H), 2.84 (s, 2 H), 3.39 (s, 3 H), 3.42−3.78 (m, 9 H), 3.80−3.94 (m, 2 H), 4.70 (s, 2 H), 5.94 (d, J = 3.0 Hz, 1 H), 7.35−7.49 (m, 6 H), 7.62−7.72 (m, 4 H), 9.63 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.2 (s), 26.9 (q), 33.6 (t), 34.4 (t), 34.98 (t), 35.05 (d), 37.5 (d), 39.5 (d), 53.5 (d), 59.1 (q), 60.3.(t), 62.3 (t), 65.5 (t), 67.0 (t), 71.8 (t), 95.5 (t), 101.6 (s), 127.8 (d), 129.8 (d), 131.4 (s), 132.9 (d), 133.25 (s), 133.59 (s), 135.6 (d), 175.8 (s), 199.5 (s); exact mass (electrospray) m/z calcd for $C_{35}H_{46}NaO_8Si$ (M + Na) 645.2854, found 645.2857.

The more polar isomer isomer had: FTIR (microscope) 3071, 3049, 2931, 2883, 2859, 1787, 1737, 1472, 1446, 1428, 1389, 1362, 1256, 1188, 1170, 1110, 1043 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.06 (s, 9 H), 1.45−1.62 (m, 4 H), 1.89−2.16 (m, 3 H), 2.20−2.32 (m, 1 H), 2.80−2.91 (m, 2 H), 3.39 (s, 3 H), 3.42−3.70 (m, 7 H), 3.70−4.04 (m, 4 H), 4.69 (s, 2 H), 5.92 (d, J = 2.8 Hz, 1 H), 7.35−7.49 (m, 6 H), 7.64−7.72 (m, 4 H), 9.53 (d, J = 1.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.2 (s), 26.9 (q), 31.3 (t), 33.6 (t), 34.5 (t), 35.1 (d), 37.2 (d), 39.5 (d), 53.5 (d), 59.1 (q), 60.7 (t), 62.7 (t), 65.4 (t), 67.0 (t), 71.8 (t), 95.5 (t), 101.7 (s), 127.8 (d), 129.7 (d), 130.3 (d), 132.1 (d), 133.33 (s), 133.53 (s), 135.5 (d), 135.7 (d), 175.2 (s), 199.5 (d); exact mass (electrospray) m/z calcd for $C_{35}H_{46}NaO_8Si$ (M + Na) 645.2854, found 645.2853.

Methyl 2-(Phenylselanyl)propanoate (6.5).[18] $NaBH_4$ (2.4 g, 63.4 mmol) was added in several portions to a stirred and cooled (0 °C) solution of PhSeSePh (4.0 g, 12.8 mmol) in MeOH (75 mL). After the addition, a solution of methyl 2-bromopropionate (4.01 g, 24.0 mmol) in MeOH (30 mL) was added dropwise. Stirring was continued for 2 h, the ice bath was removed and stirring was continued for 2.5 h. The solution was quenched with water (30 mL) and diluted with Et_2O (30 mL). The aqueous phase was extracted with Et_2O (3 × 15 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4.5 × 21 cm), using 1:10 EtOAc−hexane, gave **6.5**[18] (4.74 g, 81%) as a yellow oil: FTIR ($CHCl_3$, cast) 3072, 3058, 2991, 2950, 2928, 1730, 1579, 1477, 1450, 1438, 1376, 1333, 1258, 1213, 1148, 1062, 1022 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.55 (d, J = 7.1 Hz, 3 H), 3.65 (s, 3 H), 3.78 (q, J = 7.2 Hz, 1 H), 7.26−7.38 (m, 3 H), 7.58−7.62 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.6 (q), 37.1 (q), 52.0 (d), 127.6 (s), 128.5 (d), 128.9 (d), 135.7 (d), 173.7 (s); exact mass (electrospray) m/z calcd for $C_{10}H_{12}NaO_2{}^{80}Se$ (M + Na) 266.9895, found 266.9896.

Methyl 3-[(1*S*,7*R*,8*R*,12*R*)-*rel*-(4-[2-[(*tert*-Butyldiphenylsilyl)-oxy]ethyl]-7-[2-[(2-methoxyethoxy)methoxy]ethyl]-3-oxo-2,11-dioxatricyclo[6.3.1.0^{1,5}]dodec-5-en-12-yl)]-3-hydroxy-2-methyl-2-(phenylselanyl)propanoate (6.6). BuLi (2.5 M in hexane, 0.17 mL, 0.42 mmol) was injected dropwise into a stirred and cooled (−78 °C) solution of *i*-Pr_2NH (0.15 mL, 1.05 mmol) in THF (3.1 mL). Stirring was continued for 50 min, and a solution of methyl 2-(phenylseleno)propionate (**6.5**) (124 mg, 0.47 mmol) in THF (3.1 mL) was injected dropwise over 5 min. Note that it is important to weigh the phenylseleno compound and keep it under oil pump vacuum (with protection from light) for 4 h before checking the weight and dissolving the substance in dry THF; the yield in this reaction is exceptionally sensitive to traces of moisture. Stirring was continued at −78 °C for 1 h (with protection from light). A solution of **6.4** (87 mg, 0.14 mmol) in THF (6.2 mL) was added dropwise over ca. 3 min. Stirring was continued at −78 °C for 5 h (with protection from light), and the mixture was quenched with saturated aqueous NH_4Cl. Vigorous stirring was continued for 10 min, and the cold bath was then removed and the mixture diluted with water. Stirring was continued for 10 min, and the mixture was extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 g, 1 × 15 cm), using 2:1 hexane−EtOAc, gave **6.6** (90 mg, 75%) as a light yellow oil, which was an inseparable mixture of isomers: exact mass (electrospray) m/z calcd for $C_{45}H_{58}NaO_{10}{}^{80}SeSi$ (M + Na) 889.2857, found 889.2862.

Methyl 2-[(1*S*,7*R*,8*R*,12*R*)-*rel*-[(4-[2-[(*tert*-Butyldiphenylsilyl)-oxy]ethyl]-7-[2-[(2-methoxyethoxy)methoxy]ethyl]-3-oxo-2,11-dioxa-3-oxotricyclo[6.3.1.0^{1,5}]dodec-5-en-12-yl)]-(hydroxy)methyl]prop-2-enoate (6.7). H_2O_2 (30%, 0.32 mL, 3.7 mmol) was added to a stirred and cooled (0 °C) solution of **6.6** (57 mg, 0.066 mmol) in a mixture of THF (3.8 mL) and water (0.38 mL). Stirring at 0 °C was continued for 1 h, and the mixture was quenched by dropwise addition of saturated aqueous $Na_2S_2O_3$ (12 mL), diluted with water, and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.6 g, 0.5 × 15 cm), using 1:1 hexane−EtOAc, gave **6.7** (40 mg, 86%) as a colorless oil which was an inseparable mixture of isomers: FTIR (microscope) 3464, 3071, 3048, 2930, 2878, 2858, 1791, 1717, 1629, 1472, 1441, 1428, 1362, 1261, 1197, 1160, 1112, 1041 cm^{-1}; exact mass (electrospray) m/z calcd for $C_{39}H_{52}NaO_{10}Si$ (M + Na) 731.3222, found 731.3223.

Methyl 2-[(1*S*,7*R*,8*R*,12*R*)-*rel*-[(Acetyloxy)(4-[2-[(*tert*-butyldiphenylsilyl)oxy]ethyl]-7-[2-[(2-methoxyethoxy)-methoxy]ethyl]-3-oxo-2,11-dioxatricyclo[6.3.1.0^{1,5}]dodec-5-en-12-yl)]methyl]prop-2-enoate (6.8). DMAP (3.6 mg, 0.017 mmol), pyridine (100 μL, 1.27 mmol), and AcCl (36 μL, 0.59 mmol) were added sequentially to a stirred and cooled (0 °C) solution of **6.7** (60 mg, 0.085 mmol) in CH_2Cl_2 (3.6 mL). Stirring at 0 °C was continued for 2 h, and then the mixture was diluted with water. Dilute hydrochloric acid (10%, 0.5 mL) was added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 g, 1 × 15 cm), using 1:1 EtOAc−hexane, gave **6.8** (55 mg, 87%) as a colorless oil which was an inseparable mixture of isomers: FTIR (cast film) 3071, 3048, 2932, 2877, 2859, 1791, 1794, 1742, 1722, 1632, 1472, 1441, 1429, 1366, 1298, 1277, 1236, 1196, 1154, 1112, 1064, 1023 cm^{-1}; exact mass (electrospray) m/z calcd for $C_{41}H_{54}NaO_{11}Si$ (M + Na) 773.3328, found 773.3321.

Methyl (1*S*,5*R*,6*R*,9*S*,13*R*)-*rel*-9-[2-[(*tert*-Butyldiphenylsilyl)-oxy]ethyl]-6-[2-[(2-methoxyethoxy)methoxy]ethyl]-15-oxo-2,14-dioxatetracyclo[7.4.2.0^{1,8}.0^{5,13}]pentadeca-7,11-diene-11-carboxylate (6.9). DBU (73 μL, 0.47 mmol) was added to a stirred solution of **6.8** (55 mg, 0.073 mmol) in MeCN (7.3 mL) at room temperature. Stirring was continued for 50 min (TLC control, silica, 1:1 EtOAc−hexane), and the solution was then passed through a pad of flash chromatography silica gel (2.5 × 2.5 cm) to remove DBU (which causes decomposition of the product on concentrating the solution), using 50% EtOAc−hexane as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 g silica, 6 mm × 15 cm), using 1:1 EtOAc−hexane, gave **6.9** (33 mg, 65%) as an oil which slowly partially crystallized on storage at −78 °C for several days: FTIR (cast film) 3071, 3048, 2930, 2881, 2858, 1788, 1713, 1615, 1472, 1428, 1388, 1363, 1332, 1303, 1250, 1158, 1113, 1064, 1048 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.04 (s, 9 H), 1.41−1.54 (m, 2 H), 1.60−1.66 (m, 1 H), 1.85−1.94 (m, 1 H), 1.96−2.04 (m, 1 H), 2.31−2.39 (m, 2 H), 2.41−2.54 (m, 2 H), 2.85−2.94 (m, 1 H), 2.96 (s, 1 H), 3.38 (s, 3 H), 3.52−3.56 (m, 2 H), 3.56−3.62 (m, 2 H), 3.64−3.72 (m, 6 H), 3.78−3.88 (m, 2 H), 3.96 (dd, J = 10.4, 5.2 Hz, 1 H), 4.70 (s, 2 H), 5.52 (s, 1 H), 6.75−6.8 (m, 1 H), 7.35−7.45 (m, 6 H), 7.62−7.72 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.0 (s), 26.6 (q), 33.3 (t), 34.4 (t), 36.2 (t), 36.4 (d), 37.8 (d), 47.1 (d), 49.1 (s), 49.9 (t), 52.3 (q), 59.1 (q), 60.4.(t), 61.3 (t), 65.5 (t), 67.0 (t), 71.8 (t), 95.5 (t), 103.8 (s), 127.59 (d), 127.62 (d), 128.8 (s), 129.54 (d) 129.57 (d), 130.7 (d), 133.4 (s), 133.6 (s), 135.66 (d), 135.69 (d), 136.5 (s), 138.5 (d), 168.0 (s), 176.1 (s); exact mass

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(electrospray) m/z calcd for $C_{39}H_{50}NaO_9Si$ (M + Na) 713.3116, found 713.3111.

A sample for X-ray analysis was crystallized from EtOAc−hexane.

2-(Methoxycarbonyl)cyclohexane-1-carboxylic Acid (8.3).[21] AcOH (212 μL, 3.71 mmol) was added to a stirred solution of **8.2**[20] (isomer mixture) (74.5 mg, 0.371 mmol) and $NaNO_2$ (0.077 g, 1.11 mmol) in dry DMSO (1.5 mL). The reaction mixture was stirred at 40 °C for 8 h and then diluted with water (30 mL) and acidified with hydrochloric acid (3 N) to below pH 2. The resulting mixture was extracted with Et_2O (5 × 30 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:1 hexane−EtOAc, gave **8.3** (56 mg, 81%) as a pale yellow oil, which was a single isomer of unestablished stereochemistry: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.36−1.64 (m, 4 H), 1.72−1.88 (m, 2 H), 1.96−2.10 (m, 2 H), 2.80−2.92 (m, 2 H), 3.79 (s, 3 H), 10.2−10.8 (br s, 1 H).

Methyl (1*R*,5*S*,6*S*,7*R*,8R,9*R*,11*S*,13*S*)-*rel*-9-(2-Hydroxyethyl)-6-[2-[(2-methoxyethoxy)methoxy]ethyl]-12-(nitromethyl)-15-oxo-2,14-dioxapentacyclo[7.4.2.0^{1,8}.0^{5,13}.0^{7,11}]pentadecane-11-carboxylate (9.1). $MeNO_2$ (24 μL, 0.43 mmol) and Bu_4NF (1 M in THF, 33 μL, 0.033 mmol) were added to a stirred solution of **6.9** (10 mg, 0.0145 mmol) in THF (0.15 mL), and stirring was continued for 6 h, by which time all the starting material had been consumed (TLC control, silica, 1:1 hexane−EtOAc). The reaction mixture was evaporated and flash chromatography of the residue over silica gel (Pasteur pipet, 4 cm), using 2:98 MeOH−EtOAc, gave **9.1** (6 mg, 85%) as a colorless oil: FTIR (cast film) 3467, 2925, 2886, 1779, 1727, 1556, 1458, 1435, 1384, 1307, 1239, 1189, 1158, 1114, 1100, 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.02 (s, 1 H), 1.32−1.54 (m, 2 H), 1.60−1.72 (m, 1 H), 1.85−2.02 (m, 5 H), 2.08−2.18 (m, 2 H), 2.32 (d, J = 14.8, 1 H), 2.84−2.91 (m, 2 H), 3.17 (dd, J = 9.7, 4.8, 1 H), 3.40 (s, 3 H), 3.46−3.72 (m, 6 H), 3.74 (s, 3 H), 3.80−3.90 (m, 3 H), 3.98 (dd, J = 12.9, 5.4 Hz, 1 H), 4.37 (dd, J = 12.8, 9.9 Hz, 1 H), 4.49 (dd, J = 12.8, 4.8 Hz, 1 H), 4.69 (s, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.8 (t), 31.8 (d), 35.5 (t), 37.1 (t), 38.5 (d), 38.6 (d), 39.8 (d), 45.9 (t), 47.8 (d), 49.9 (s), 51.4 (s), 52.3 (d), 53.0 (q), 59.1 (q), 59.2.(t), 60.7 (t), 65.0 (t), 67.1 (t), 71.8 (t), 76.3 (t), 95.6 (t), 106.9 (s), 174.9 (s), 177.8 (s); exact mass (electrospray) m/z calcd for $C_{24}H_{35}NNaO_{11}$ (M + Na) 536.2102, found 536.2100.

(1*S*,5*R*,6*R*,9*S*,13*R*)-*rel*-9-[2-[(*tert*-Butyldiphenylsilyl)oxy]-ethyl]-11-(hydroxymethyl)-6-[2-[(2-methoxyethoxy)methoxy]-ethyl]-2,14-dioxatetracyclo[7.4.2.0^{1,8}.0^{5,13}]pentadeca-7,11-dien-15-ol (10.1). DIBAL-H (1 M in PhMe, 0.9 mL, 0.9 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of **6.9** (32 mg, 0.05 mmol) in THF (2 mL). Stirring at −78 °C was continued for 3.5 h, and the cold bath was replaced by an ice bath. After 5 min, the mixture was quenched with $Na_2SO_4{\cdot}10H_2O$. The ice bath was removed, Et_2O (2 mL) was added, and stirring was continued for 40 min. The mixture was filtered through a fritted funnel. Evaporation of the filtrate and flash chromatography of the residue over silica gel (Pasteur pipet, 7 cm), using EtOAc, gave **10.1** (30 mg, 97%) as a colorless oil which was a 3:1 mixture of two stereoisomers: FTIR (cast film) 3421, 3071, 3048, 2930, 2877, 2858, 1472, 1428, 1389, 1363, 1281, 1246, 1199, 1039, 1008 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) (major isomer signals) δ 1.04 (s, 9 H), 1.49−1.64 (m, 4 H), 1.80−2.03 (m, 3 H), 2.10−2.42 (m, 4 H), 2.54 (s, 1 H), 3.33 (d, J = 4.0 Hz, 1 H), 3.39 (s, 3 H), 3.52−3.60 (m, 4 H), 3.64−3.71 (m, 2 H), 3.74−3.90 (m, 6 H), 4.70 (s, 2 H), 5.19 (s, 1 H), 5.27 (d, J = 4.0 Hz, 1 H), 5.54 (s, 1 H), 6.75−6.8 (m, 1 H), 7.35−7.45 (m, 6 H), 7.62−7.72 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) (major isomer signals) δ 19.0 (s), 26.8 (q), 33.8 (t), 34.2 (t), 36.3 (t), 37.1 (d), 37.6 (d), 45.8 (s), 46.1 (d), 53.8 (t), 59.0 (q), 60.7 (t), 61.1 (t), 66.1 (t), 66.9 (t), 70.8 (t), 71.8 (t), 95.5 (t), 103.4 (d), 104.3 (s), 124.0 (d), 127.7 (d), 127.9 (d), 129.72 (d), 129.75 (d), 133.26 (s), 133.35 (s), 135.59 (d), 135.61 (d), 137.9 (s), 140.4 (s); exact mass (electrospray) m/z calcd for $C_{38}H_{52}NaO_8Si$ (M + Na) 687.3324, found 687.3321.

(1*S*,5*R*,6*R*,9*R*,14*R*)-*rel*-9-[2-[(*tert*-Butyldimethylsilyl)oxy]-ethyl]-11-(hydroxymethyl)-6-[2-[(2-methoxyethoxy)methoxy]-ethyl]-2,12,15-trioxapentacyclo[7.5.2.0^{1,8}.0^{5,14}.0^{11,13}]hexadec-7-en-16-ol (10.2). A stock solution of $VO(acac)_2$ (25 mg) in PhH (1 mL) was prepared, and an aliquot of this solution (0.1 mL, 0.009 mmol) was added to a stirred solution of **10.1** (31 mg, 0.047 mmol) in PhH (2.5 mL). The mixture turned green after the addition. *t*-BuOOH (5.5 M in decane, 20 μL, 0.11 mmol) was added dropwise to the stirred mixture; the color changed immediately to burgundy. TLC (silica, EtOAc) showed that the starting material had been consumed after 30 min. The mixture was then diluted with EtOAc (2.5 mL) and quenched with saturated aqueous Na_2SO_3 (2.5 mL). The mixture was stirred for 1 h until the organic phase was clear. The organic phase was then washed with water (2.5 mL) and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (Pasteur pipet, 7 cm), using 5:95 MeOH−EtOAc, gave **10.2** (28 mg, 91%) as a colorless oil which was mixture of two inseparable isomers (1.6:1 based on NMR): FTIR (cast film) 3444, 3071, 3048, 2931, 2883, 2858, 2247, 1472, 1428, 1389, 1363, 1281, 1247, 1197, 1169, 1112, 1089, 1041, 1008 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) (major isomer signals) δ 1.06 (s, 9 H), 1.44−1.64 (m, 4 H), 1.78−2.03 (m, 3 H), 2.14−2.36 (m, 3 H), 2.59 (s, 1 H), 2.86 (d, J = 1.2 Hz, 1 H), 3.12 (d, J = 5.4 Hz, 1 H), 3.34 (d, J = 5.4 Hz, 1 H), 3.39 (s, 3 H), 3.52−3.59 (m, 2 H), 3.59−3.76 (m, 5 H), 3.76−3.90 (m, 3 H), 4.72 (s, 2 H), 5.11 (d, J = 4.8 Hz, 1 H), 5.53 (s, 1 H), 7.35−7.52 (m, 6 H), 7.62−7.72 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) (major isomer signals) δ 19.0 (s), 26.8 (q), 33.9 (t), 34.8 (t), 36.6 (t), 37.3 (d), 37.4 (d), 42.1 (s), 42.3 (d), 54.1 (t), 59.0 (q), 60.55.(t), 60.60 (t), 61.48 (d), 65.0 (t), 65.7 (t), 65.9 (t), 67.0 (t), 71.8 (t), 95.6 (t), 102.9 (d), 104.0 (s), 127.70 (d), 127.74 (d), 127.8 (d), 129.8 (d), 133.17 (s), 133.24 (s), 135.58 (d), 135.60 (d), 141.5 (s); exact mass (electrospray) m/z calcd for $C_{38}H_{52}NaO_9Si$ (M + Na) 703.3273, found 703.3268.

[(1*S*,5*R*,6*R*,9*R*,14*R*)-*rel*-(9-[2-[(*tert*-Butyldiphenylsilyl)oxy]-ethyl]-6-[2-[(2-methoxyethoxy)methoxy]ethyl]-16-[(triethylsilyl)oxy]-2,12,15-trioxapentacyclo-[7.5.2.0^{1,8}.0^{5,14}.0^{1,13}]hexadec-7-en-11-yl)methoxy]triethylsilane (10.3). 2,6-Lutidine (20 μL, 0.165 mmol) followed by $Et_3SiOSO_2CF_3$ (35 μL, 0.165 mmol) were added to a stirred and cooled (0 °C) solution of **10.2** (28 mg, 0.041 mmol) in CH_2Cl_2 (1.5 mL). After 40 min, the ice bath was removed, and stirring was continued for 2.5 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (0.1 mL), diluted with water, and extracted with CH_2Cl_2 (3 × 4 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (Pasteur pipet, 7 cm), using 3:7 EtOAc−hexane, gave **10.3** (30 mg, 81%) as a colorless oil which was a mixture of two inseparable isomers (6:1 based on ^{1}H NMR): FTIR (cast film) 3071, 3049, 2934, 2954, 2876, 1461, 1428, 1414, 1241, 1199, 1111, 1092, 1019 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) (major isomer signals) δ 0.46−0.68 (m, 12 H), 0.82−098 (m, 18 H), 1.06 (s, 9 H), 1.44−1.54 (m, 1 H), 1.54−1.81 (m, 3 H), 1.82−2.04 (m, 3 H), 2.1 (d, J = 15.4 Hz, 1 H), 2.14−2.26 (m, 2 H), 2.51 (s, 1 H), 2.57 (d, J = 1.3 Hz, 1 H), 3.08 (d, J = 10.4 Hz, 1 H), 3.41 (s, 3 H), 3.49 (d, J = 10.4 Hz, 1 H), 3.52−3.59 (m, 2 H), 3.59−3.70 (m, 5 H), 3.70−3.88 (m, 3 H), 4.73 (s, 2 H), 4.96 (s, 1 H), 5.44 (s, 1 H), 7.35−7.52 (m, 6 H), 7.62−7.72 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) (major isomer signals) δ 4.3 (t), 4.8 (t), 6.7 (q), 6.8 (q), 19.1 (s), 26.9 (q), 34.2 (t), 36.1 (t), 36.3 (t), 37.37 (d), 37.40 (d), 42.2 (s), 43.0 (d), 54.5 (t), 59.1 (q), 60.0.(t), 60.9 (t), 64.0 (d), 65.1 (t), 65.9 (t), 66.9 (t), 69.7 (t), 71.8 (t), 95.6 (t), 102.9 (d), 104.0 (s), 127.0 (d), 127.61 (d), 127.62 (d), 129.5 (d), 133.8 (s), 133.9 (s), 135.5 (d), 135.6 (d), 142.1 (s); exact mass (electrospray) m/z calcd for $C_{50}H_{80}NaO_9Si_3$ (M + Na) 931.5002, found 931.5006.

(1*R*,2*R*)-2-(Nitromethyl)cyclohexane-1-carbaldehyde (11.3).[24] $MeNO_2$ (50 μL, 0.9 mmol) followed by (2*S*)-2-[diphenyl-[(trimethylsilyl)oxy]methyl]pyrrolidine[25] (**11.2**) (30 mg, 30% mmol) and AcOLi (11 mg, 0.03 mmol) were added to a solution of **11.1** (33 mg, 0.3 mmol) in 9:1 CH_2Cl_2−MeOH (0.8 mL) at room temperature. Stirring was continued for 24 h, and the mixture was diluted with water and extracted with CH_2Cl_2 (4 × 3 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (Pasteur pipet, 7 cm), using hexane−EtOAc, gave **11.3** (48 mg, 94%) as an oil, which was a 6:1 mixture of diastereoisomers in favor of the *trans* compound: FTIR (cast film on the mixture) 2935, 2859, 1722, 1647, 1551, 1526, 1449, 1382, 1352, 1238 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) (major isomer signals) δ

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1.15−1.42 (m, 4 H), 1.72−1.80 (m, 1 H), 1.81−1.92 (m, 2 H), 2.06−2.12 (m, 1 H), 2.24−2.34 (m, 1 H), 2.38−2.48 (m, 1 H), 4.35 (dd, J = 11.9, 7.7 Hz, 1 H), 4.53 (dd, J = 11.9, 4.4 Hz, 1 H), 9.61 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (major isomer signals) δ 24.5 (t), 24.8 (t), 25.9 (t), 28.5 (t), 35.1 (d), 51.4 (d), 78.9 (t), 202.3 (d).

(1*R*,2*R*)-2-(Nitromethyl)cyclohexane-1-carboxylic Acid (11.4).[24] PDC (34 mg, 0.09 mmol) was added to a stirred solution of **11.3** (10 mg, 0.06 mmol) in DMF (0.3 mL) at room temperature. Stirring was continued overnight, and the mixture was diluted with water (2 mL) and extracted with EtOAc (4 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Preparative TLC (silica gel, 5 × 5 cm x 0.25 mm thick) of the residue, using EtOAc, gave **11.4** (9 mg, ca. 85%) as an oil containing EtOAc: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15−1.42 (m, 3 H), 1.46−1.62 (m, 1 H), 1.72−1.92 (m, 3 H), 2.06−2.15 (m, 1 H), 2.78 (dt, J = 12.0, 3.8 Hz, 1 H), 2.34−2.48 (m, 1 H), 4.35 (dd, J = 11.5, 7.5 Hz, 1 H), 4.53 (dd, J = 11.3, 3.8 Hz, 1 H), 9.61 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.7 (t), 24.9 (t), 28.8 (t), 29.8 (t), 37.3 (d), 45.5 (d), 79.5 (t), 179.7 (s); exact mass (electrospray) m/z calcd for $C_8H_{12}NO_4$ (M − H) 186.0772, found 186.0776.

(1*R*,2*R*)-Cyclohexane-1,2-dicarboxylic Acid (11.5). $NaNO_2$ (113 mg, 1.65 mmol) and AcOH (0.32 mL, 5.5 mmol) were added to a stirred solution of **11.4** (103 mg, 0.55 mmol) in dry DMSO (2.3 mL), and the mixture was heated at 40 °C for 8 h, cooled, quenched with water (15 mL), and extracted with Et_2O (5 × 8 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue (**11.5**) had low resolution (electrospray) m/z 171.1 for $C_8H_{11}O_4$ (M − H), and the crude material was esterified without further purification.

1,2-Dimethyl (1*R*,2*R*)-Cyclohexane-1,2-dicarboxylate (11.6).[40,41] CH_2N_2 was bubbled into a cooled (0 °C) solution of crude **11.5** in Et_2O (5 mL) until the solution turned yellow (fume hood). The ice bath was then removed, and the reaction mixture was left open to allow the excess of CH_2N_2 to evaporate. Water was added, and the aqueous phase was extracted with EtOAc (3 × 4 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15), using 1:1 hexane−EtOAc, gave **11.6**[40,41] (151 mg, 75%) as a yellow oil containing EtOAc: FTIR 2940, 2861, 1737, 1553, 1436, 1323, 1254, 1195, 1171, 1115, 1043, 1009 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.24−1.42 (m, 6 H), 1.72−1.86 (m, 2 H), 2.55−2.65 (m, 2 H), 2.66 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.1 (t), 28.9 (t), 44.8 (q), 51.7 (d), 175.5 (s); exact mass (electrospray) m/z calcd for $C_{10}H_{16}NaO_4$ (M + Na) 223.0941, found 223.0943.

1,2-Dimethyl Cyclohex-1-ene-1,2-dicarboxylate (11.7) and 1,2-Dimethyl cyclohex-2-ene-1,2-dicarboxylate (11.8).[26] BuLi (2.5 M in THF, 0.26 mL, 0.62 mmol) was added to a stirred and cooled (−78 °C) solution of i-Pr_2NH (92 μL, 0.66 mmol) in THF (1.6 mL). After 40 min, a solution of **11.6** (50 mg, 0.25 mmol) in THF (4 mL) was added over 4 min and the mixture was stirred for 10 min at −78 °C. A solution of I_2 (507.8 mg, 0.5 mmol) in THF (1.5 mL) was then added dropwise at −78 °C, and after the addition the mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (Pasteur pipet, 7 cm), using 4:1 hexane−EtOAc, gave a 3:2 mixture (75% yield) of **11.7** and **11.8** as an oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ (major isomer signals) 1.42−1.64 (m, 4 H), 2.21−2.37 (m, 4 H), 3.75 (s, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz) (major isomer signals) δ 21.2 (t), 26.2 (t), 52.1 (q), 135.3 (s), 169.0 (s).

Tributyl[(cyclohex-1-en-1-ylmethoxy)methyl]stannane (12.2). KH (160 mg (35%), 1.4 mmol) followed by Bu_3SnCH_2I[28] (203 mg, 0.47 mmol) were added to a stirred and cooled (0 °C) solution of **12.1**[27] (53 mg, 0.47 mmol) and a catalytic amount of 18-crown-6 (1 crystal) in THF (7 mL). The ice bath was removed after the addition, and stirring was continued for 40 min, at which time TLC (silica, 10:1 hexane−EtOAc) showed the disappearance of **12.1**. The mixture was quenched with water and extracted with Et_2O (3 × 7 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 10:1 hexane−EtOAc, gave **12.2** (164 mg, 84%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.84−0.99 (m, 15 H), 1.24−1.37 (m, 6 H), 1.45−1.54 (m, 6 H), 1.55−1.66 (m, 4 H), 1.92−1.98 (m, 2 H), 1.99−2.08 (m, 2 H), 3.65 (s, 2 H), 3.71 (s, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.0 (t), 13.7 (q), 22.5 (t), 22.6 (t), 25.0 (t), 25 8 (t), 27.3 (t), 29.1 (t), 60.7 (t), 79.9 (t), 124.4 (d), 135.2 (s); exact mass (electrospray) m/z calcd for $C_{20}H_{40}NaO^{120}Sn$ (M + Na) 439.1993, found 439.1995.

(2-Methylidenecyclohexyl)methanol (12.3).[42] BuLi (2.5 M solution in hexane, 1.5 mL, 0.39 mmol) was added to a stirred and cooled (−78 °C) solution of **12.2** (160 mg, 0.385 mmol) in hexane (50 mL). The cold bath was not recharged and was allowed to rise to 0 °C over a few h (the precise time has no effect on the outcome, but quenching must be done at or below 0 °C). The mixture was quenched with water and extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (Pasteur pipet, 7 cm), using 1:1 hexane−EtOAc, gave **12.3**[42] (40 mg, ca. 84%) as a colorless oil, containing some EtOAc: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.84−0.99 (m, 15 H), 1.32−1.41 (m, 1 H), 1.42−1.54 (m, 2 H), 1.55−1.66 (m, 2 H), 1.75 (ddd, J = 12.7, 8.4, 4.2 Hz, 1 H), 2.03−2.10 (m, 1 H), 2.15−2.21 (m, 1 H), 2.23−2.31 (m, 1 H), 3.57 (dd, J = 10.5, 6.0 Hz, 1 H), 3.77 (dd, J = 10.5, 7.9 Hz, 1 H), 4.64 (s, 1 H), 4.76 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.0 (t), 28.3 (t), 30.2 (t), 34.4 (t), 456 (d), 64.0 (t), 107.3 (t), 149.7 (s).

(3*R*,4*R*)-*rel*-1-Oxaspiro[2.5]octan-4-ylmethanol (12.4). $VO(acac)_2$ (6 mg, 0.02 mmol) was added to a stirred solution of **12.3** (15 mg, 0.12 mmol) in PhH (6 mL). t-BuOOH (5.5 M in decane, 47 μL, 0.29 mmol) was added to the mixture, and the color changed immediately to burgundy. Stirring was continued for 1 h, and the mixture was quenched with saturated aqueous Na_2SO_3 (2 mL). Stirring was continued until the color was discharged (ca. 1 h), and the resulting mixture was diluted with water and extracted with EtOAc (3 × 6 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Purification of the residue by preparative TLC (silica plate, 10 × 5 cm, 0.25 mm thick), using 1:1 hexane−EtOAc, gave **12.4** (23 mg, 80%) as a colorless oil, which was a mixture of isomers. The major isomer had: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.32−1.48 (m, 3 H), 1.62−1.91 (m, 5 H), 2.03−2.10 (m, 1 H), 2.59 (d, J = 4.0 Hz, 1 H m, 1 H), 2.6−2.7 (br s, 1 H), 3.05 (dd, J = 4.0, 2.0 Hz, 1 H), 3.34−3.42 (m, 1 H), 3.42−3.51 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.5 (t), 25.4 (t), 28.2 (t), 34.8 (t), 424 (d), 63.2 (t), 64.3 (t); exact mass (electrospray) m/z calcd for $C_8H_{15}O_2$ (M) 143.1067, found 143.1065.

(1*S*,5*R*,6*R*,9*S*,13*R*)-*rel*-9-[2-[(*tert*-Butyldiphenylsilyl)oxy]-ethyl]-15-methoxy-6-[2-[(2-methoxyethoxy)methoxy]ethyl]-2,14-dioxatetracyclo[7.4.2.0^{1,8}.0^{5,13}]pentadeca-7,11-dien-11-yl)methanol (13.1). Pyridinium p-toluenesulfonate (4.6 mg, 0.3 equiv, 0.019 mmol) followed by $HC(OMe)_3$ (60 μL, 0.62 mmol, 9 equiv) were added sequentially to a stirred solution of **10.1** (41 mg, 0.062 mmol) in CH_2Cl_2 (5 mL). Stirring at room temperature was continued for 40 min, a sample for mass spectral analysis being removed after 30 min. The mass spectrum showed peaks at m/z 761 (M + 23) [C(15) OH attached to $CH(OMe)_2$] and disappearance of the **10.1** signal at m/z 687. Dry MeOH (3 mL) was added, and stirring was continued for 5 h. At this time, the mass spectrum showed the presence of **10.1** and **13.1**. The reaction was quenched by addition of solid K_2CO_3, and the mixture was stirred for 5 min, filtered through Celite (packed in a Pasteur pipet, 2 cm), and evaporated. The crude product was purified by TLC (20 × 20 cm, 0.25 mm thick analytical plate, EtOAc) to afford a 10:1 mixture of two isomers of **13.1** [17 mg, 72% corrected for recovered **10.1** (21 mg)] as an oil: FTIR (cast film of the isomer mixture) 3450, 3071, 3048, 2930, 2875, 1725, 1670, 1589, 1472, 1428, 1388, 1364, 1281, 1243, 1199, 1112, 1041 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) (major isomer signals only) δ 1.08 (s, 9 H), 1.42−1.64 (m, 4 H), 1.80−2.03 (m, 4 H), 2.14−2.27 (m, 2 H), 2.3−2.42 (m, 1 H), 2.52 (s, 1 H), 2.71 (d, J = 17.4 Hz, 1 H), 3.41 (s, 3 H), 3.43 (s, 3 H), 3.52−3.62 (m, 4 H), 3.66−3.91 (m, 8 H), 4.73 (s, 2 H), 5.14 (s, 1 H), 5.31 (br s, 1 H), 5.42 (s, 1 H), 7.35−7.45 (m, 6 H), 7.62−7.72 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (major isomer signals only) δ 19.1 (s), 26.9 (q), 33.9 (t), 35.2 (t), 36.3 (t), 36.9 (d),

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37.5 (d), 41.7 (s), 46.0 (d), 51.1 (t), 58.1 (q), 59.1 (q), 60.5.(t), 61.0 (t), 66.1 (t), 66.9 (t), 70.7 (t), 71.8 (t), 95.6 (t), 101.5 (s), 108.1 (d), 123.6 (d), 127.3 (d), 127.7 (d), 129.65 (d), 129.67 (d), 133.72 (s), 133.73 (s), 135.60 (d), 135.64 (d), 138.5 (s), 140.3 (s); exact mass (electrospray) *m*/*z* calcd for $C_{39}H_{54}NaO_8Si$ (M + Na) 701.3480, found 701.3483.

(1*S*,5*R*,6*R*,9*S*,13*R*)-*rel*-*tert*-Butyl[2-(15-methoxy-6-[2-[(2-methoxyethoxy)methoxy]ethyl]-11-[[(tributylstannyl)-methoxy]methyl]-2,14-dioxatetracyclo[7.4.2.0^{1,8}.0^{5,13}]-pentadeca-7,11-dien-9-yl)ethoxy]diphenylsilane (15.1). KH (35% w/w in oil, 48 mg, 0.42 mmol) was added to a stirred and cooled (0 °C) solution of **13.1** (70 mg, 0.103 mmol) in dry THF (1.4 mL). 18-Crown-6 (one crystal) was added, followed Bu_3SnCH_2I[28] (56 mg, 0.12 mmol), using THF as a rinse (0.5 mL). The ice bath was removed after the addition, and after 35 min, all **13.1** and stannane had been consumed (TLC, EtOAc). The mixture was quenched with water and extracted with Et_2O, and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (Pasteur pipet, 7 cm), using 1:1 EtOAc–hexane, gave **15.1** (86 mg, 85%) as a yellow oil which was a 10:1 mixture of two isomers: FTIR (cast film on the isomer mixture) 3071, 3048, 2955, 2928, 2871, 2856, 1735, 1589, 1464, 1428, 1388, 1363, 1339, 1242, 1213, 1180, 1113, 1091, 1052 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) (major isomer signals only) δ 0.8–0.94 (m, 12 H), 1.05 (s, 9 H), 1.2–1.34 (m, 9 H) 1.42–1.58 (m, 9 H), 1.80–1.98 (m, 2 H), 2.0–2.12 (m, 1 H), 2.16–2.28 (m, 2 H), 2.47 (s, 1 H), 2.62 (d, *J* = 17.6 Hz, 1 H), 3.38 (s, 6 H), 3.46–3.62 (m, 7 H), 3.62–3.68 (m, 4 H), 3.69–3.88 (m, 4 H), 4.70 (s, 2 H), 5.10 (s, 1 H), 5.21 (d, *J* = 4.6 Hz, 1 H), 5.37 (s, 1 H), 7.35–7.45 (m, 6 H), 7.62–7.72 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (major isomer signals only) δ 8.9 (t), 13.7 (q), 19.1 (s), 26.9 (q), 27.3 (t), 29.2 (t), 33.9 (t), 35.3 (t), 36.3 (t), 36.8 (d), 37.2 (d), 41.9 (s), 46.1 (d), 51.0 (t), 57.9 (q), 59.1 (q), 60.6 (t), 60.7 (t), 61.0 (t), 65.9 (t), 66.9 (t), 71.8 (t), 83.6 (t), 95.5 (t), 101.6 (d), 107.9 (s), 124.8 (d), 127.2 (d), 127.7 (d), 129.6 (d), 133.8 (s), 135.6 (d), 136.4 (s), 140.2 (s); exact mass (electrospray) *m*/*z* calcd for $C_{52}H_{82}NaO_8Si^{120}Sn$ (M + Na) 1005.4693, found 1005.4699.

(1*S*,5*R*,6*R*,9*S*,12*R*,13*R*)-*rel*-(9-[2-[(*tert*-Butyldiphenylsilyl)oxy]-ethyl]-15-methoxy-6-[2-[(2-methoxyethoxy)methoxy]ethyl]-11-methylidene-2,14-dioxatetracyclo[7.4.2.0^{1,8}.0^{5,13}]pentadec-7-en-12-yl)methanol (3). A solution of **15.1** (74 mg, 0.075 mmol) in dry, but not degassed, hexane (9.9 mL) (25 mL round-bottomed flask) was cooled to −9 °C (dry ice added to acetone to maintain −9 °C; double-walled, silvered Dewar), and BuLi (2.5 M in hexane, 0.30 mL, 10 equiv) was then added dropwise over a few seconds (ca. 10 s). The reaction mixture was allowed to warm to −3 °C over 40 min (the cold bath was left to warm spontaneously without further addition of dry ice). TLC (silica, EtOAc) showed that the reaction was complete within a few minutes, even at −9 °C. The mixture was quenched with saturated aqueous NH_4Cl (ca. 4.5 mL), diluted with EtOAc, and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was subjected to preparative TLC (silica plate, 10 × 10 cm, 0.25 mm thick), using EtOAc. Both bands were extracted together with 10% MeOH in EtOAc, and the solution was evaporated. The products (i.e., **3** and **13.1**) (40 mg) were taken forward, as described later (see preparation of **19.2**).

In previous runs, the two compounds were separated using a TLC analytical plate with EtOAc as eluent to obtain samples for characterization. In later preparative experiments, the crude material was used directly in the next step. Compound **3** was an oil and had: FTIR (cast film) 3465, 3071, 2929, 2857, 1732, 1632, 1471, 1428, 1390, 1362, 1112, 1039 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.08 (s, 9 H), 1.72–1.90 (m, 5 H), 1.98–2.14 (m, 2 H), 2.2–2.32 (m, 2 H), 2.87 (d, *J* = 12.5 Hz, 1 H), 3.40 (s, 3 H), 3.42 (s, 3 H), 3.55–3.62 (m, 2 H), 3.62–3.74 (m, 5 H), 3.74–3.92 (m, 5 H), 4.75 (s, 2 H), 4.85 (s, 1 H), 4.93 (s, 1 H), 5.14 (s, 1 H), 5.43 (s, 1 H), 7.35–7.45 (m, 6 H), 7.62–7.72 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.1 (s), 26.9 (q), 33.8 (t), 34.0 (t), 37.5 (t), 37.76 (d), 37.84 (d), 45.0 (d), 49.4 (d), 49.7 (s), 51.8 (t), 57.6 (q), 59.1 (q), 60.3.(t), 60.4 (t), 62.4 (t), 66.1 (t), 67.0 (t), 71.8 (t), 95.6 (s), 102.1 (t), 108.8 (d), 113.3 (t), 126.8 (d), 127.7 (d), 129.64 (d), 129.66 (d), 133.8 (s), 135.62 (d), 135.64 (d), 142.4 (s), 146.3 (s); exact mass (electrospray) *m*/*z* calcd for $C_{40}H_{56}NaO_8Si$ (M + Na) 715.3637, found 715.3628.

2-(Cyclohex-1-en-1-ylmethoxy)acetic Acid (16.1).[43] A solution of **12.1**[27] (169 mg, 1.5 mmol) in THF (1.7 mL) was added dropwise to a stirred and cooled (0 °C) suspension of NaH (60%w/w in oil, 169 mg, 4.2 mmol) in THF (1.7 mL). The ice bath was removed after the addition, and stirring was continued for 1 h. The mixture was then recooled to 0 °C, and a solution of $BrCH_2CO_2H$ (209 mg, 1.5 mmol) in THF (1.7 mL) was added dropwise. The ice bath was removed after the addition, and stirring was continued overnight. The mixture was quenched with water, acidified with dilute hydrochloric acid (10%) to pH 1 (pH paper), and extracted with EtOAc (4 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using EtOAc, gave **16.1**[43] [114 mg, 75%, corrected for recovered starting material (22 mg)] as a colorless oil: FTIR (cast film) 2500–3500, 3051, 2999, 2927, 2856, 2658, 1730, 1448, 1436, 1339, 1310, 1240, 1179, 1161, 1137, 1127, 1107 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.51–1.62 (m, 2 H), 1.62–1.68 (m, 2 H), 1.95–2.10 (m, 4 H), 3.95 (s, 2 H), 4.06 (s, 2 H), 5.69–5.75 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.2 (t), 22.4 (t), 25.0 (t), 25.8 (t), 66.0 (t), 127.2 (d), 133.5 (s), 174.9 (s); exact mass (electrospray) *m*/*z* calcd for $C_9H_{13}O_3$ (M − H) 169.0872, found 169.0872.

2-Hydroxy-2-(2-methylidenecyclohexyl)acetic Acid (16.2). BuLi (2.4 M solution in THF, 4.57 mL, 10.98 mmol) was added to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (1.70 mL, 11.9 mmol) and HMPA (1.91 mL, 11 mmol) in THF (60 mL). After 7 min, the mixture was cooled to −20 °C, and a solution of **16.1** (933 mg, 5.49 mmol) in THF (10 mL) was added dropwise. Stirring at −15 °C was continued for 24 h, and the mixture was quenched with water and acidified with dilute hydrochloric acid (10%) to pH 1. The mixture was extracted with EtOAc (4 × 10 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using 1:1 hexane–EtOAc, gave **16.2** (727 mg, 78%) as a colorless oil (which was a 4:1 mixture of isomers): FTIR (cast film) 2500–3500, 3073, 2932, 2858, 1722, 1648, 1447, 1340, 1207, 1159, 1132, 1088, 1066 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) (major isomer signals) δ 1.51–1.62 (m, 2 H), 1.62–1.75 (m, 3 H), 1.81–1.88 (m, 1 H), 2.14–2.24 (m, 2 H), 2.48–2.55 (m, 1 H), 4.34 (d, *J* = 7.6 Hz, 1 H), 4.81 (s, 1 H), 4.91 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (major isomer signals) δ 23.1 (t), 27.7 (t), 29.7 (t), 33.8 (t), 47.1 (d), 71.2 (d), 110.8 (t), 147.3 (s), 176.5 (s); exact mass (electrospray) *m*/*z* calcd for $C_9H_{13}O_3$ (M − H) 169.0859, found 169.0872.

3-Hydroxy-7a-(iodomethyl)octahydro-1-benzofuran-2-one (16.3). $KHCO_3$ (448 mg, 4.50 mmol), KI (744 mg, 4.50 mmol), and I_2 (1.143 g, 4.50 mmol) were added sequentially to a stirred solution of **16.2** (381 mg, 2.25 mmol) in a mixture of THF (8.5 mL) and water (2.9 mL) at room temperature. The mixture was stirred at room temperature for 40 min and then quenched with saturated aqueous $Na_2S_2O_3$ (4 mL). Stirring was continued until the iodine color was discharged. EtOAc (10 mL) was then added, the mixture was washed with brine, and the organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 × 15 cm), using 1:1 hexane–EtOAc, gave **16.3** (519 mg, 78%) as a yellow oil: FTIR (cast film) 3423, 2938, 2861, 1775, 1447, 1369, 1332, 1268, 1214, 1176, 1139, 1118, 1093, 1047 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.12–1.26 (m, 2 H), 1.32–1.45 (m, 1 H), 1.57–1.66 (m, 1 H), 1.66–1.79 (m, 1 H), 1.80–1.93 (m, 2 H), 2.13 (dtd, *J* = 14.9, 3.9, 1.9 Hz, 1 H), 2.75- 2.90 (m, 2 H), 3.33 (d, *J* = 10.0 Hz, 1 H) 3.37 (d, *J* = 14.9 Hz, 1 H), 4.76 (dd, *J* = 7.1, 3.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 12.5 (t), 20.6 (t), 22.1 (t), 22.4 (t), 33.0 (t), 41.8 (d), 71.4 (d), 82.5 (s), 177.0 (s); exact mass (electrospray) *m*/*z* calcd for $C_9H_{13}INaO_3$ (M + Na) 318.9802, found 318.9800.

7a-(Iodomethyl)-3-[(triethylsilyl)oxy]octahydro-1-benzofuran-2-one (16.5). 2,6-Lutidine (0.65 mL, 5.56 mmol) followed by $Et_3SiOSO_2CF_3$ (0.49 mL, 2.42 mmol) were added to a solution of **16.3** (358 mg, 1.21 mmol) in CH_2Cl_2 (18 mL) at room temperature. The mixture was stirred for 1.5 h, quenched with water, and extracted

with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using 4:1 hexane−EtOAc, gave **16.5** (495 mg, 100%) as an oil: FTIR (cast film): 2952, 2876, 1790, 1458, 1413, 1240, 1225, 1164, 1142, 1122, 1003 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.68 (q, J = 10.0 Hz, 6 H), 0.98 (t, J = 10.0 Hz, 9.0 H), 1.17−1.26 (m, 1 H), 1.32−1.42 (m, 1 H), 1.42−1.66 (m, 2 H), 1.66−1.79 (m, 2 H), 1.91 (ddd, J = 14.7, 10.9, 4.9 Hz, 1 H), 2.55 (dt, J = 14.7, 10.1 Hz, 1 H), 2.64 (dt, J = 9.3, 6.6 Hz, 1 H), 3.36 (s, 2 H), 4.63 (d, J = 6.8, Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.7 (t), 6.7 (q), 13.1 (t), 20.9 (t), 22.2 (t), 22.7 (t), 33.2 (t), 42.8 (d), 72.0 (d), 81.4 (s), 175.0 (s); exact mass (electrospray) m/z calcd for $C_{15}H_{27}INaO_3Si$ (M + Na) 433.0666, found 433.0662.

Methyl 2-Hydroxy-2-[1-oxaspiro[2.5]octan-4-yl]acetate (16.4). MeONa (58 mg, 1.08 mmol) was added to a solution of **16.5** (75 mg, 0.18 mmol) in MeOH (3 mL) at room temperature, and the mixture was stirred for 5 h, diluted with water, and extracted with EtOAc (4 × 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (Pasteur pipet, 7 cm), using 4:1 hexane−EtOAc, gave **16.4** (54 mg, 94%) as a colorless oil which was a 1:2.86 inseparable mixture of two isomers: FTIR (cast film) 3457, 2938, 2861, 1742, 1486, 1444, 1259, 1214, 1129, 1107, 1070, 1014 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) (major isomer signals) δ 1.38−1.92 (m, 8 H), 2.01- 2.08 (m, 1 H), 2.58 (d, J = 4.0 Hz, 1 H), 2.95 (d, J = 4.0 Hz, 1 H), 3.51 (br s, 1 H), 3.77 (s, 3 H), 4.18 (d, J = 6.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (major isomer signals) δ 23.6 (t), 24.2 (t), 28.6 (t), 33.3 (t), 43.2 (d), 52.2 (q), 53.5 (t), 60.8 (s) 73.1 (d), 174.5 (s); exact mass (electrospray) m/z calcd for $C_{10}H_{16}NaO_4$ (M + Na) 223.0941, found 223.0937.

Cyclohex-1-en-1-ylmethyl 2-[(*tert*-Butyldimethylsilyl)oxy]-acetate (17.2). Pyridine (1.37 mL, 17.8 mmol) followed by a solution of **12.1**[27] (955 mg from 1:1 mixture of *t*-$BuMe_2SiCl$ and **17.1**, 2.67 mmol of **17.1**) in Et_2O (11 mL) were added to a stirred and cooled (0 °C) solution of **12.1** (200 mg, 1.78 mmol) in Et_2O (11 mL). Stirring at 0 °C was continued for 2 h, by which time all starting material had reacted (TLC, silica, 1:1 hexane−EtOAc), and the mixture was quenched with water and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using 4:1 hexane−EtOAc, gave **17.2** (480 mg, 95%) as a colorless impure oil, which was used directly in the next step: ^1H NMR ($CDCl_3$, 500 MHz) δ 0.13 (s, 6 H), 0.95 (s, 9 H), 1.56−1.64 (m, 2 H), 1.64−1.72 (m, 2 H), 1.98−2.11 (m, 4 H), 4.28 (s, 2 H), 4.53 (s, 2 H), 5.74−5.78 (m, 1 H).

2-[(*tert*-Butyldimethylsilyl)oxy]-2-(2-methylidenecyclohexyl)acetic Acid (17.3). BuLi (2.5 M in THF, 0.27 mL, 0.67 mmol) was added to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (0.1 mL, 0.72 mmol) and HMPA (1 mL, 0.72 mmol) in THF (3 mL). After 7 min, the mixture was cooled to −78 °C, and a solution of **17.2** (120 mg, 0.42 mmol) in THF (0.7 mL) was added dropwise, followed by a mixture of *t*-$BuMe_2SiCl$ (73 μL, 0.59 mmol) and Et_3N (40 μL) that had been stirred for 5 min in THF (1 mL). After 5 min, the ice bath was removed, and stirring was continued for 24 h. The mixture was quenched with water and acidified with dilute hydrochloric acid (10%) to pH 1. The mixture then was extracted with EtOAc (4 × 10 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using 1:1 hexane−EtOAc, gave **17.3** (107 mg, 89%) as a colorless oil (which was a 4.4:1 mixture of isomers): FTIR (cast film) 2500−3500, 3073, 2931, 2858, 1722, 1648, 1472, 1463, 1449, 1362, 1257, 1214, 1186, 1120, 1037, 1006 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) (major isomer signals) δ 0.1 (s, 6 H), 0.92 (s, 9 H), 1.51−1.62 (m, 3 H), 1.62−1.75 (m, 2 H), 1.81−1.95 (m, 1 H), 2.07−2.24 (m, 2 H), 2.48−2.55 (m, 1 H), 4.37 (d, J = 8.5 Hz, 1 H), 4.68 (s, 1 H), 4.72 (s, 1 H), 8.2−9.8 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) (major isomer signals) δ −5.59 (q), 17.76 (s), 21.7 (t), 25.3 (q), 27.2 (t), 27.5 (t), 33.1 (t), 47.5 (d), 72.7 (d), 109.3 (t), 147.3 (s), 177.3 (s); exact mass (electrospray) m/z calcd for $C_{15}H_{27}O_3Si$ (M - H) 283.1735, found 283.1735.

(1*S*,5*R*,6*R*,9*S*,13*R*)-*rel*-9-[2-[(*tert*-Butyldimethylsilyl)oxy]-ethyl]-15-methoxy-6-[2-[(2-methoxyethoxy)methoxy]ethyl]-2,14-dioxatetracyclo[7.4.2.0^{1,8}.0^{5,13}]pentadeca-7,11-dien-11-yl]methyl 2-[(*tert*-Butyldimethylsilyl)oxy]acetate (18.1). Pyridine (0.11 mL, 0.147 mmol) followed by a solution of **17.1** (79 mg from the 1:1 mixture of *t*-$BuMe_2SiCl$ and **17.1**, 0.22 mmol) in Et_2O (1 mL) were added to a stirred and cooled (0 °C) solution of **13.1** (a 10:1 isomer mixture, 100 mg, 0.147 mmol) in Et_2O (1 mL). Stirring at 0 °C was continued for 2 h, by which time all starting material had reacted (TLC, silica, EtOAc). The mixture was quenched with water and extracted with EtOAc (3 × 5 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 1:1 hexane−EtOAc, gave **18.1** (101 mg, 81%) as a colorless oil: FTIR (cast film) 2930, 2882, 2857, 1759, 1731, 1472, 1589, 1472, 1428, 1389, 1362, 1252, 1141, 1112, 1042 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) (major isomer signals only) δ 0.1 (s, 6 H), 0.91 (s, 9 H), 1.08 (s, 9 H), 1.42−1.64 (m, 3 H), 1.80−2.03 (m, 3 H), 2.14−2.42 (m, 2 H), 2.52 (s, 1 H), 2.71 (d, J = 17.4 Hz, 1 H), 3.32 (s, 1 H), 3.41 (s, 3 H), 3.43 (s, 3 H), 3.52−3.62 (m, 4 H), 3.66−3.91 (m, 6 H), 4.15−4.22 (m, 2 H), 4.30−4.40 (m, 2 H), 4.74 (s, 2 H), 5.13 (s, 1 H), 5.35 (br s, 1 H), 5.42 (s, 1 H), 7.35−7.45 (m, 6 H), 7.62−7.72 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ −5.4 (q), 18.4 (s), 19.1 (s), 25.8 (q), 26.9 (q), 33.8 (t), 35.1 (t), 36.1 (t), 36.7 (d), 37.2 (d), 42.0 (t), 46.0 (d), 51.1 (t), 58.1 (q), 59.1 (q), 60.5 (t), 61.0 (t), 61.7 (t), 65.8 (t), 66.9 (t), 71.8 (t), 72.5 (t), 95.5 (t), 101.2 (d), 107.7 (s), 127.6 (d), 127.66 (d), 127.68 (d), 127.9 (d), 129.64 (d), 129.65 (d), 133.5 (s), 133.6 (s), 135.5 (d), 135.59 (d), 135.6, 139.8 (s), 171.4 (s); exact mass (electrospray) m/z calcd for $C_{47}H_{70}NaO_{10}Si_2$ (M + Na) 873.4400, found 873.4386.

[[(1*S*,5*R*,6*R*,9*S*,12*R*,13*R*,15*R*)-*rel*-9-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-15-methoxy-6-[2-[(2-methoxyethoxy)methoxy]ethyl]-11-methylidene-2,14-dioxatetracyclo[7.4.2.0^{1,8}.0^{5,13}]pentadec-7-en-12-yl]methoxy]-triethylsilane (19.2). 2,6-Lutidine (28 μL, 0.24 mmol, 4 equiv) followed by $Et_3SiOSO_2CF_3$ (26 μL, 0.12 mmol, 2 equiv) were added at room temperature to a stirred solution of a mixture (40 mg, 0.057 mmol) of the two alcohols (i.e., **3** and **13.1**) in CH_2Cl_2 (9 mL). Stirring was continued for 3 h, and the mixture was then quenched with water and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Preparative TLC over silica gel (5 × 10 x cm, 0.25 mm thick), using 4:1 hexane−EtOAc, gave **19.2** as a single isomer (36 mg, 77% over two steps) and **19.1** (11 mg, 21%). Both compounds were oils. Compound **19.2** had: ^1H NMR ($CDCl_3$, 500 MHz) δ 0.62 (q, J = 10.0 Hz, 6 H), 0.97 (t, J = 10.0 Hz, 9 H), 1.08 (s, 9 H), 1.42−1.74 (m, 3 H), 1.78−1.90 (m, 5 H), 2.0−2.12 (m, 1 H), 2.25 (t, J = 7.5 Hz, 1 H), 2.35−2.42 (m, 1 H), 2.53 (s, 1 H), 2.77 (d, J = 12.5 Hz, 1 H), 3.40 (s, 3 H), 3.43 (s, 3 H), 3.55−3.62 (m, 2 H), 3.62−3.68 (m, 3 H), 3.69−3.75 (m, 2 H), 3.75−3.88 (m, 4 H), 4.65 (s, 1 H), 4.74 (s, 1 H), 4.76 (s, 2 H), 5.13 (s, 1 H), 5.43 (s, 1 H), 7.35−7.45 (m, 6 H), 7.62−7.72 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 4.3 (t), 6.8 (q), 19.1 (s), 26.9 (q), 33.9 (t), 34.0 (t), 37.55 (d) (two carbons), 37.60 (t), 47.0 (d), 47.5 (d), 50.33 (s), 51.7 (t), 57.6 (q), 59.1 (q), 60.39.(t), 60.44 (t), 66.11 (t), 66.14 (t), 66.9 (t), 71.8 (t), 95.6 (s), 102.6 (t), 108.8 (d), 113.4 (t), 127.0 (d), 127.69 (d), 127.72 (d), 129.61 (d), 129.64 (d), 133.8 (s), 135.63 (d), 135.65 (d), 142.6 (s), 147.1 (s); exact mass (electrospray) m/z calcd for $C_{46}H_{70}NaO_8Si_2$ (M + Na) 829.4501, found 829.4486.

Compound **19.1** had: exact mass (electrospray) m/z calcd for $C_{45}H_{68}NaO_8Si_2$ (M + Na) 815.4345, found 815.4331 and was converted back into **13.1** by treatment with Bu_4NF in THF (see below).

When the experiment was preformed without prior removal of **15.2**, the yield of **19.1** was 13%: 2,6-Lutidine (45 μL, 0.27 mmol, 4 equiv) followed by $Et_3SiOSO_2CF_3$ (42 μL, 0.18 mmol, 2 equiv) were added at room temperature to a stirred solution of a mixture of crude product from the [2,3]-Wittig rearrangement (i.e., **3** and **13.1** and **15.2**) (64 mg) in CH_2Cl_2 (14 mL). Stirring was continued for 3 h, and the mixture was then quenched with water and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated. Preparative TLC over silica gel (15 × 10 cm, 0.25 mm thick), using 4:1

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hexane−EtOAc, gave **19.2** as a single isomer (41 mg, 77% over two steps), **19.1** (8 mg, 13%) and **15.2** (5 mg, 9%). All three compounds were oils. Compound **15.2** had: FTIR (cast film) 1735 cm^{-1}; ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.1 (s), 26.9 (q), 33.9 (t), 35.3 (t), 36.3(t), 36.8 (d), 37.3 (d), 41.8 (s), 46.2 (d), 51.1 (t), 57.3 (q), 57.9 (q), 59.1 (q), 60.6 (t), 61.0 (t), 66.0 (t), 66.9 (t), 71.8 (t), 80.9 (t), 95.5 (s), 101.5 (s), 108.0 (s), 125.2 (d), 127.2 (d), 127.7 (d), 129.63 (d), 129.67 (d), 133.8 (s), 133.8 (s), 135.60 (d), 135.64 (d), 136.0 (s), 140.4 (s); exact mass (electrospray) m/z calcd for $C_{40}H_{56}NaO_8Si$ (M + Na) 715.3637, found 715.3637.

(1*S*,5*R*,6*R*,9*S*,13*R*)-*rel*-9-[2-[(*tert*-Butyldiphenylsilyl)oxy]-ethyl]-15-methoxy-6-[2-[(2-methoxyethoxy)methoxy]ethyl]-2,14-dioxatetracyclo[7.4.2.0^{1,8}.0^{5,13}]pentadeca-7,11-dien-11-yl)methanol (13.1) from 19.1. A catalytic amount of pyridinium *p*-toluenesulfonate (ca. 1 mg) was added to a stirred solution of **19.1** (10 mg, 0.012 mmol) in 4:1 CH_2Cl_2−dry MeOH (1 mL). Stirring was continued for 35 min, at which point TLC (silica, EtOAc) and a low-resolution mass spectrum of a sample confirmed that all **19.1** had been consumed. The mixture was evaporated at room temperature and applied to a TLC plate (3 × 7 cm), which was developed with EtOAc. The main band was scraped off and extracted in a Pasteur pipet with 10% MeOH−EtOAc (10 mL). Evaporation of the solvent gave **13.1** (7 mg, 85%).

(1*S*,5*R*,6*R*,9*S*,12*R*,13*R*)-*rel*-(9-[2-[(*tert*-Butyldiphenylsilyl)oxy]-ethyl]-15-methoxy-6-[2-[(2-methoxyethoxy)methoxy]ethyl]-11-methylidene-2,14-dioxatetracyclo[7.4.2.0^{1,8}.0^{5,13}]pentadec-7-en-12-yl)methanol (3) from 19.2. A catalytic amount of pyridinium *p*-toluenesulfonate (ca. 1 mg) was added to a stirred solution of **19.2** (10 mg, 0.012 mmol) in 4:1 CH_2Cl_2−dry MeOH (1 mL). Stirring was continued for 35 min, at which point TLC (silica, EtOAc) and a low-resolution mass spectrum of a sample confirmed that all **19.2** had been consumed. The mixture was evaporated at room temperature and applied to a TLC plate (3 × 7 cm), which was developed with EtOAc. The main band was scraped off and extracted in a Pasteur pipet with 10% MeOH−EtOAc (10 mL). Evaporation of the solvent gave **3** (8 mg, 92%) as an oil.

[(1*S*,5*R*,6*R*,9*S*,11*R*,12*S*,13*R*,15*R*)-*rel*-9-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-11-(hydroxymethyl)-15-methoxy-6-[2-[(2-methoxyethoxy)methoxy]ethyl]-2,14-dioxatetracyclo[7.4.2.0^{1,8}.0^{5,13}]pentadec-7-en-12-yl]methanol (21.1). $BH_3{\cdot}SMe_2$ (10 M solution in THF, 1.5 μL, 0.015 mmol) was added to a stirred solution of **19.2** (10 mg, 0.012 mmol) in THF (1 mL) at room temperature. The mixture was stirred for 1 h and was then quenched by sequential addition of EtOH (10 μL), aqueous NaOH (2 N, 20 μL), and H_2O_2 (30%, 20 μL, 0.23 mmol). The mixture was stirred for an additional 20 min and then diluted with water and extracted with EtOAc (3 × 3 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Preparative TLC (silica plate, 5 × 7 cm, 0.25 mm thick), using 5% MeOH−EtOAc, gave **21.1** (7 mg, 78%) as a colorless oil: FTIR (cast film) 3348, 3071, 3049, 2928, 2857, 1735, 1653, 1589, 1544, 1471, 1451, 1428, 1390, 1363, 1243, 1218, 1157, 1112, 1045 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.08 (s, 9 H), 1.42−1.74 (m, 3 H), 1.78−1.90 (m, 5 H), 2.0−2.12 (m, 2 H), 2.19 (br s, 1 H), 2.25 (d, J = 10.8 Hz, 2 H), 3.42 (s, 3 H), 3.45 (s, 3 H), 3.52 (s, 1 H), 3.55−3.62 (m, 2 H), 3.62−3.69 (m, 4 H), 3.69−3.75 (m, 5 H), 3.75−3.88 (m, 2 H), 3.9 (br s, 2 H), 4.75 (s, 2 H), 5.10 (s, 1 H), 5.33 (s, 1 H), 7.35−7.45 (m, 6 H), 7.62−7.72 (m, 4 H); exact mass (electrospray) m/z calcd for $C_{40}H_{58}NaO_9Si$ (M + Na) 733.3742, found 733.3733.

In a subsequent experiment starting with 12 mg of **19.2**, the yield of **21.1** was 81%.

11,12-Dimethyl (1*S*,5*R*,6*R*,9*S*,11*R*,12*R*,13*R*,15*R*)-*rel*-9-[2-[(*tert*-Butyldimethylsilyl)oxy]ethyl]-15-methoxy-6-[2-[(2-methoxyethoxy)methoxy]ethyl]-2,14-dioxatetracyclo-[7.4.2.0^{1,8}.0^{5,13}]pentadec-7-ene-11,12-dicarboxylate (4). Dry DMSO (6 μL, 0.08 mmol) was added to a stirred and cooled (−78 °C) solution of $(COCl)_2$ (5 μL, 0.06 mmol) in dry CH_2Cl_2 (0.5 mL). After 30 min, a solution of **21.1** (7 mg, 0.01 mmol) in CH_2Cl_2 (0.6 mL) was added dropwise, and stirring was continued at −78 °C for 1 h. Dry Et_3N (18 μL, 0.12 mmol) was then added dropwise, the cold bath was removed, and stirring was continued for 30 min. The mixture was then poured into water (3 mL) in a separatory funnel and extracted with CH_2Cl_2 (2 × 2.5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give **21.2** as an oil which showed a nominal mass of 729.3 in its low-resolution mass spectrum (electrospray) and two aldehyde hydrogen signals at δ 9.48 and 9.76 ppm in its ^1H NMR spectrum. This crude material was taken forward as it was not stable to chromatography.

An aliquot (50 μL, 0.04 mmol $NaClO_2$) from a stock solution made up of $NaClO_2$ (1.0 g, 8.8 mmol) and $NaHPO_4$ (1 g) in water (10 mL) was added to a stirred solution of crude **21.2** (7 mg, 0.01 mmol) in *t*-BuOH (0.65 mL) and 2-methyl-2-butene (0.15 mL) (protection from light) at room temperature. The mixture was stirred overnight by which time TLC (silica, EtOAc) showed the consumption of **21.2**. The reaction mixture was diluted with water and acidified with dilute hydrochloric acid (10%) to pH = 2−3 (pH paper), and the aqueous phase was saturated with salt and extracted with EtOAc (5 × 4 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give **21.3** as an oil: exact mass (electrospray) m/z calcd for $C_{40}H_{53}O_{11}Si$ (M − H) 737.3363, found 737.3363. For ease of handling the diacid was esterified directly.

CH_2N_2 was bubbled into a solution of crude **21.3** in Et_2O (2 mL) at 0 °C until the solution turned yellow (fumehood). The ice bath was then removed, and the reaction mixture left open to allow the excess of CH_2N_2 to evaporate. Water was added and the aqueous phase was extracted with EtOAc (3 × 4 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated, and the residue was purified by preparative TLC on a silica plate (2.5 × 7 cm, 0.25 mm thick), using 2:1 EtOAc−hexane, to give **4** (5 mg, 66% over three steps) as an oil: ^1H NMR ($CDCl_3$, 500 MHz) δ 1.08 (s, 9 H), 1.48−1.54 (m, 1 H), 1.60−1.84 (m, 4 H), 1.95−2.06 (m, 2 H), 2.12 (dd, J = 7.9, 3.1 Hz, 1 H), 2.20−2.32 (m, 1 H), 2.34−2.42 (m, 1 H), 2.85−2.90 (m, 1 H), 3.37 (s, 3 H), 3.42 (s, 3 H), 3.45−3.52 (m, 1 H), 3.55−3.62 (m, 2 H), 3.62−3.68 (m including a singlet for MeO, 5 H in all), 3.69 (s, 3 H), 3.70−3.82 (m, 5 H), 3.82−3.92 (m, 2 H), 4.75 (s, 2 H), 5.03 (s, 1 H), 5.37 (s, 1 H), 7.39−7.49 (m, 6 H), 7.65−7.78 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.1 (s), 26.9 (q), 33.2 (t), 33.7 (t), 37.16 (d), 37.19 (d), 38.1 (t), 39.1 (d), 40.0 (t), 45.6 (d), 46.9 (d), 51.3 (t), 51.4 (q), 52.1 (q), 57.4 (q), 59.1 (q), 60.1.(t), 60.5 (t), 65.9 (t), 67.0 (t), 71.8 (t), 95.6 (s), 101.7 (t), 107.5 (d), 125.0 (d), 127.67 (d), 127.68 (d), 127.72 (d), 129.64 (d), 129.66 (d), 133.7 (s), 133.8 (s), 142.0 (s), 172.4 (s), 173.7 (s); exact mass (electrospray) m/z calcd for $C_{42}H_{58}NaO_{11}Si$ (M + Na) 789.3641, found 789.3625.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

X-ray data (CIF) for **6.9** and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Dabrah, T. T.; Kaneko, T.; Massefski, W., Jr.; Whipple, E. B. *J. Am. Chem. Soc.* **1997**, *119*, 1594−1598.

(2) Tan, Q.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 4509−4511 , and earlier papers in the series..

(3) (a) Waizumi, N.; Itoh, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2000**, *122*, 7825−7826. (b) Hayashi, Y.; Itoh, T.; Fukuyama, T. *Org. Lett.* **2003**, *5*, 2235−2238.
(4) (a) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S.; Jung, J.; Choi, H.-S.; Yoon, W. H. *J. Am. Chem. Soc.* **2002**, *124*, 2202−2211 and previous papers in the series. (b) Review: Nicolaou, K. C.; Baran, P. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2678−2720.
(5) Chen, C.; Layton, M. E.; Sheehan, S. M.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 7424−7425.
(6) Meng, D.; Tan, Q.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3197−3201.
(7) Spencer, P.; Agnelli, F.; Sulikowski, G. A. *Org. Lett.* **2001**, *3*, 1443−1445.
(8) Sulikowski, G. A.; Pongdee, R. *Synlett* **2006**, 354−363.
(9) Spiegel, D. A.; Njardarson, J. T.; McDonald, I. M.; Wood, J. L. *Chem. Rev.* **2003**, *103*, 2691−2727.
(10) (a) Banwell, M. G.; Coster, M. J.; Edwards, A. J.; Vögtle, M. *Aust. J. Chem.* **2003**, *56*, 577−583. (b) Bio, M. M.; Leighton, J. L. *J. Org. Chem.* **2003**, *68*, 1693−1700. (c) Armstrong, A.; Davies, N. G. M.; Martin, N. G.; Rutherford, A. P. *Tetrahedron Lett.* **2003**, *44*, 3915−3918. (d) Clive, D. L. J.; Cheng, H.; Gangopadhyay, P.; Hunag, X.; Prabhudas, B. *Tetrahedron* **2004**, *60*, 4205−4221. (e) Yoshimitsu, T.; Sasaki, S.; Arano, Y.; Nagaoka, H. *J. Org. Chem.* **2004**, *69*, 9262−9268. (f) Ashenhurst, J. A.; Gleason, J. L. *Tetrahedron Lett.* **2008**, *49*, 504−507. (g) Ashenhurst, J. A.; Isakovic, L.; Gleason, J. L. *Tetrahedron* **2010**, *66*, 368−378. (h) Murphy, G. K.; Hama, N.; Bedermann, A.; Dong, P.; Schneider, C. M.; McMahon, T. C.; Tao, R. N.; Twenter, B. M.; Spiegel, D. A.; Wood, J. L. *Org. Lett.* **2012**, *14*, 4544−4547.
(11) (a) Clive, D. L. J.; Li, Z.; Yu, M. *J. Org. Chem.* **2007**, *72*, 5608−5617. (b) Prabhudas, B.; Clive, D. L. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 9295−9297. (c) Wang, L.; Prabhudas, B.; Clive, D. L. J. *J. Am. Chem. Soc.* **2009**, *131*, 6003−6012. (d) Cheng, P.; Clive, D. L. J. *J. Org. Chem.* **2012**, *77*, 3348−3364.
(12) Clive, D. L. J.; Sgarbi, P. W. M.; He, X.; Sun, S.; Zhang, J.; Ou, L. *Can. J. Chem.* **2003**, *81*, 811−824.
(13) Clive, D. L. J.; Sun, S. *Tetrahedron Lett.* **2001**, *42*, 6267−6270.
(14) Clive, D. L. J.; Ou, L. *Tetrahedron Lett.* **2002**, *43*, 4559−4563.
(15) Gassman, P. G.; Marshall, J. L. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. *5*, pp 424−427.
(16) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183−2186.
(17) The numbering system for **1** and **2** is used here, but not in the systematic names in the Experimental Section.
(18) Ryu, I.; Muraoka, H.; Kambe, N.; Komatsu, M.; Sonoda, N. *J. Org. Chem.* **1996**, *61*, 6396−6403.
(19) Lange, G. L.; Otulakowski, J. A. *J. Org. Chem.* **1982**, *47*, 5093−5096.
(20) Receveur, J.-M.; Bryans, J. S.; Field, M. J.; Singh, L.; Horwell, D. C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2329−2334.
(21) (a) Norman, M. H.; Rigdon, G. C.; Navas, F., III; Cooper, B. R. *J. Med. Chem.* **1994**, *37*, 2552−2563. (b) Cavell, E. A. S.; Chapman, N. B.; Johnson, M. D. *J. Chem. Soc.* **1960**, 1413−1426.
(22) Matt, C.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **1997**, *62*, 234−235.
(23) Wang, Y.; Li, P.; Liang, X.; Zhang, T. Y.; Ye, J. *Chem. Commun.* **2008**, 1232−1234.
(24) (a) Gellman, S. H.; Guo, L.; Giuliano, M. WO2011/47190 A1, 2011. (b) Guo, L.; Zhang, W.; Guzei, I. A.; Spencer, L. C.; Gellman, S. H. *Org. Lett.* **2012**, *14*, 2582−2585.
(25) Preparation of the organocatalyst: Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212−4215.
(26) Wilkening, D.; Mundy, B. P. *Synth. Commun.* **1984**, *14*, 227−238.
(27) Warmerdam, E. G. J. C.; van den Nieuwendijk, A. M. C. H.; Kruse, C. G.; Brussee, J.; van der Gen, A. *Rec. Trav. Chim. Pays-Bas* **1996**, *115*, 20−24.
(28) Groesbeek, M.; de Vries, E. F. J.; Berden, J. A.; Lugtenburg, J. *Rec. Trav. Chim. Pays-Bas* **1993**, *112*, 303−308.
(29) Cf. Férézou, J.-P.; Julia, M.; Li, Y.; Liu, L. W.; Pancrazi, A.; Porteu, F. *Bull. Soc. Chim. France* **1994**, *131*, 865−894.
(30) E.g. (a) Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927−1928. (b) Watanabe, K.; Iwasaki, K.; Abe, T.; Inoue, M.; Ohkubo, K.; Suzuki, T.; Katoh, T. *Org. Lett.* **2005**, *7*, 3745−3748.
(31) A 10:1 mixture of C(26) epimers; we believe (see the Discussion) that the major component has the indicated C(26) stereochemistry.
(32) Review: Nakai, T.; Mikami, K. *Org. Reacts* **1994**, *46*, 105−209.
(33) Carbenes from (alkoxymethyl)lithiums: (a) Maercker. *Angew. Chem., Int. Ed.* **1987**, *26*, 972−989. (b) Naruse, Y.; Hayashi, A.; Sou, S.-i.; Ikeda, H.; Inagaki, S. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 245−254.
(34) For reduction of hydroxy esters (cf. **16.4**) with $NaBH_4$, see, for example: Wróblewski, A. E.; Karolczak, W. *Tetrahedron* **2003**, *59*, 6075−6082.
(35) Compound **17.1** contained some *t*-BuMe_2SiCl, but this did not interfere with the formation of **17.2**.
(36) (a) Kaura, A. C.; Pearson, M. J. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2183−2186. (b) Mukaiyama, T.; Shiina, I.; Uchiro, H.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1708−1716. (c) Roth, G. A.; McClymont, E. L. *Synth. Commun.* **1992**, *22*, 411−420.
(37) (a) Ireland, R. E.; Wipf, P.; Armstrong, J. D., III. *J. Org. Chem.* **1991**, *56*, 650−657. (b) Pereira, S.; Srebnik, M. *Aldrichimica Acta* **1993**, *26*, 17−29.
(38) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399−402.
(39) Paquette, L. A.; Doherty, A. M.; Rayner, C. M. *J. Am. Chem. Soc.* **1992**, *114*, 3910−3926.
(40) Berkessel, A.; Glaubitz, K.; Lex, J. *Eur. J. Org. Chem.* **2002**, 2948−2952.
(41) Williamson, K. L.; Hasan, M. U.; Clutter, D. R. *J. Magn. Reson.* **1978**, *30*, 367−383.
(42) Maruoka, K.; Concepcion, A. B.; Hirayama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 7422−7423.
(43) Clark, J. S.; Dossetter, A. G.; Wong, Y.-S.; Townsend, R. J.; Whittingham, W. G.; Russell, C. A. *J. Org. Chem.* **2004**, *69*, 3886−3898.