Total Synthesis of Dihydroclerodin from (*R*)-(−)-Carvone

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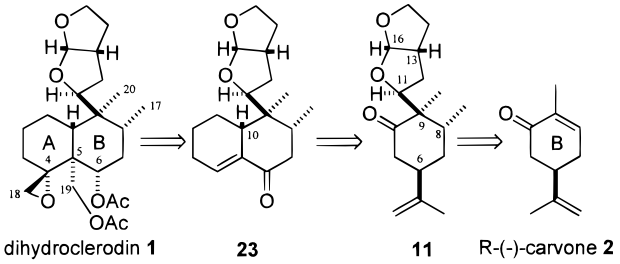
The first total synthesis of the natural enantiomer of the insect-antifeedant dihydroclerodin (**1**) and lupulin C (**40**) has been achieved starting from (*R*)-(−)-carvone (**2**). In the applied strategy, the hexahydrofuro[2,3-*b*]furan moiety was introduced in an early stage of the synthesis. The correct configuration at C-9, C-11, C-13, and C-16 was established by application of a remarkably diastereoselective Mukaiyama reaction. The desired configuration at C-10 was obtained by catalytic reduction of the intermediate enone **21**. After annulation of the second ring, the structural features at C-4, C-5, and C-6 were introduced. The successful finishing of the synthesis included a Chugaev elimination to give the exocyclic double bond at C-4 that is present in lupulin C. Oxidation of this double bond with *m*-CPBA afforded dihydroclerodin.

Introduction

Diterpenoids possessing the clerodane skeleton (Scheme 1) are widely distributed in nature, and new members of this subclass of diterpenes continue to appear in the literature.[1−3] Of the relatively few clerodanes that were tested for biological activity, many were found to possess interesting properties, which vary from antifeedant to antiviral, antitumor, antibiotic, antipeptic ulcer, and piscicidal activity.[2]

Despite the fact that so many clerodanes have been isolated, only a few were synthesized.[4] So far only one total synthesis is known of a clerodane that is oxidized in the A and in the B ring as well as on C-18.[1] To our knowledge, nobody yet has succeeded in the total synthesis of a clerodane with a chiral center at the difficult C-11 position. Much effort was put into tackling this problem of the stereochemistry at C-11 by Lallemand et al.[5] and in our group,[6] but it proved to be difficult to develop strategies in which either a hexahydrofuro[2,3-*b*]furan fragment could be attached to a completed decalin part or in which the decalin part could be finished with an already attached hexahydrofuro[2,3-*b*]furan moiety.

Scheme 1[7]



We now wish to report on the total synthesis of the natural enantiomer of dihydroclerodin and lupulin C, starting from (*R*)-(−)-carvone as is depicted in Scheme 1. A new strategy was developed in which the methyl group at C-8 was introduced first, followed by a remarkably diastereoselective Mukaiyama addition of the hexahydrofuro[2,3-*b*]furan moiety, which gave the correct configuration at C-9, C-11, C-13, and C-16.[7] Next, the isopropenyl group was removed and ring A was annulated with the correct stereochemistry at C-10. In the last stage of the synthesis the characteristic functionalities at C-5, C-6, and C-4 were introduced.

Results and Discussion

The first step of the total synthesis of dihydroclerodin required a conjugate addition of a methyl group to the

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(5) (a) Renard, P. Y.; Lallemand, J. Y. *Bull. Soc. Chim. Fr.* **1996**, *133*, 143−149. (b) Ducrot, P.-H.; Hervier, A.-C.; Lallemand, J. Y. *Synth. Commun.* **1996**, *26*, 4447−4457 and references cited herein.

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(7) Throughout the discussion the numbering of the clerodane skeleton is followed as given by Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman & Hall: New York, 1991; Vol. 1, pp XXXII.

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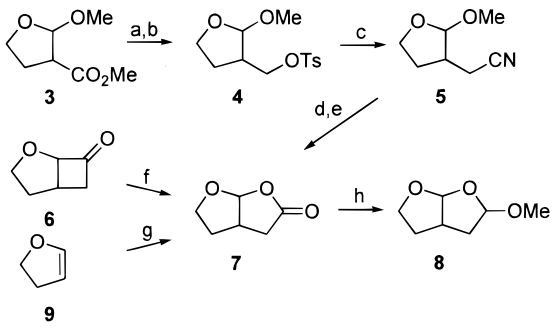
Scheme 2[a]



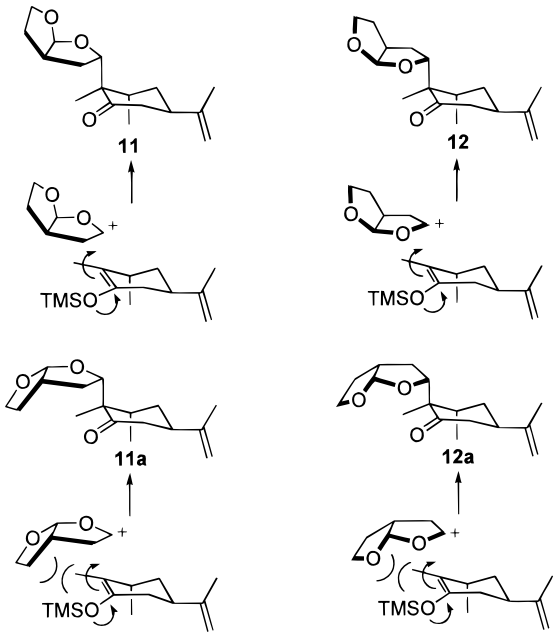
[a] Reagents: (a) $LiAlH_4$; (b) TsCl, pyridine; (c) NaCN; (d) NaOH, H_2O; (e) HCl, H_2O; (f) seven steps; (g) $ICH_2CO_2SnBu_3$, AIBN; (h) DiBALH, BF_3−etherate, MeOH.

enone in (*R*)-(−)-carvone and capturing of the enolate as its silylenol ether. The isopropenyl group in (*R*)-(−)-carvone ensures the correct configuration at C-8, and investigations with a variety of electrophiles have shown that the introduction of the second substituent in the ring takes place from the desired *β*-side, to give the correct configuration at C-9.[8] For the introduction of the hexahydrofuro[2,3-*b*]furan fragment in ring B, an enantioselective synthesis of 2-methoxyhexahydrofuro[2,3-*b*]furan had to be developed to make sure that the configuration at C-13 and C-16 would be correct. Finally, this leaves the stereochemistry at C-11 as an uncertain factor in this approach, and we intended to investigate several varieties of nonchelated or sterically influenced Mukaiyama reactions to solve this problem.

For the enantioselective synthesis of 2-methoxyhexahydrofuro[2,3-*b*]furan **8**, a resolution of methyl ester **3** was developed in our laboratory (Scheme 2). Enzymatic transesterification of **3** with butanol resulted in a mixture of (*R*)-methyl- and (*S*)-butylesters that could be separated by preparative gas chromatography.[9] Starting from racemic **3**, we have shown that this ester can be converted into **8**. This synthesis involved reduction of the ester followed by tosylation of the resulting alcohol and subsequent substitution of the tosylate in **4** by cyanide to afford the nitrile **5**. Saponification of this nitrile followed by addition of acid gave the lactone **7** in 91% yield, which then could be transformed into **8** by reduction and transacetalization in 62% yield. A seven-step synthesis of enantiomerically pure **8** has been developed by Furtoss, starting from cyclobutanone **6**.[10]

However, both syntheses are rather long and give low overall yields, and it proved unnecessary to use these methods for the following two reasons. First, we have found a short route to obtain racemic **8**,[11] which could be carried out on a multigram scale starting from enol ether **9** in 56% overall yield. Second, the use of racemic **8** in the Mukaiyama reaction with silylenol ether **10** proved to be remarkably diastereoselective. Only two of the possible eight diastereoisomers were formed, and these could easily be separated by crystallization of **12** from diisopropyl ether. The desired diastereoisomer **11** remained in solution, and in this way large quantities of **11** could be obtained in a short procedure, which in practice proved to be much easier than the more laborious routes using enantiomerically pure **8**.

Scheme 3

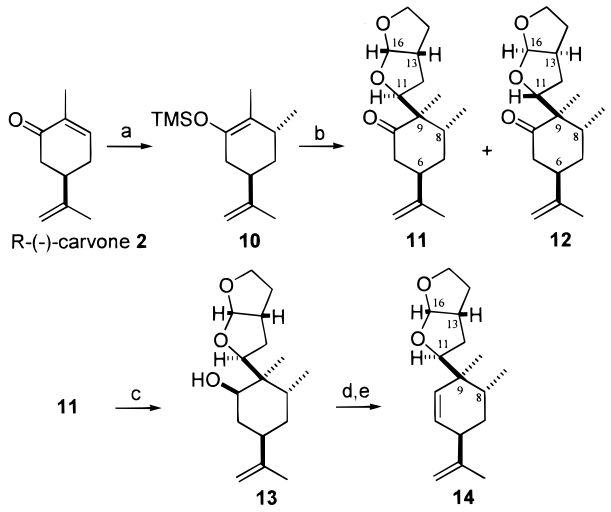


The diastereoselectivity of the Mukaiyama reaction can be explained by an approach of the silylenol ether to the less hindered convex side of both enantiomers of the hexahydrofuro[2,3-*b*]furan cation, which leads to the formation of diastereoisomers **11** and **12** (Scheme 3). In an approach from the concave side of this cation, serious steric hindrance would be developed between the substituents on the silylenol ether and C-14 and C-15 of the hexahydrofuro[2,3-*b*]furan moiety, and for this reason the diastereoisomers **11a** and **12a** are not formed.

The stereochemistry of the crystalline **12** was proven by X-ray analysis. The oily **11** was reduced to the alcohol **13**, which after mesylation and elimination gave the crystalline diene **14**. Structure elucidation by X-ray crystallography showed that **14** had the desired natural stereochemistry at C-8, C-9, C-11, C-13, and C-16.[12] For the annulation of ketone **11**, a Robinson annulation was investigated first. This reaction failed in our hands, but several modifications are under investigation and will be reported soon. Additions of alkyllithium or alkylmagnesium reagents to ketone **11** also failed, most likely due to steric hindrance of the large hexahydrofuro[2,3-*b*]furan moiety in combination with the other substituents. To reduce the steric congestion, it was decided to remove the isopropenyl group in this stage of the synthesis. The isopropenyl has transferred the chirality from C-6 to C-8 and C-9 in the desired sense, and as such, it is not necessary anymore. Reaction with ozone followed by treatment of the ozonide with $Cu(OAc)_2$ and $FeSO_4$[13] yielded the enone **15** (70%), which only could be obtained after workup using acidic and basic conditions to break the strong complexation between the metal ions and compound **15**.

(8) Meulemans, T. M.; Stork, G. A.; Jansen, B. J. M.; de Groot, A. *Tetrahedron Lett.* **1998**, *39*, 6565−6568.
(9) Franssen, M. C. R.; Jongejan, H.; Kooijman, H.; Spek, A. L.; Camacho Mondril, N. L. F. L.; Boavida dos Santos, P. M. A. C.; de Groot, A. *Tetrahedron: Asymmetry* **1996**, *7*, 497−510.
(10) Petit, F.; Furstoss, R. *Synthesis* **1995**, 1517−1520.
(11) Kraus, G. A.; Landgrebe, K. *Tetrahedron Lett.* **1984**, *25*, 3939−3942.
(12) X-ray crystallography was done by Veldman, N.; Menzer, S.; Spek, A. L. Bijvoet Center for Biomolecular Research, Department of Crystal and Structural Chemistry, Utrecht University.
(13) Schreiber, S. L. *J. Am. Chem. Soc.* **1980**, *102*, 6165−6166.

Scheme 4[a]

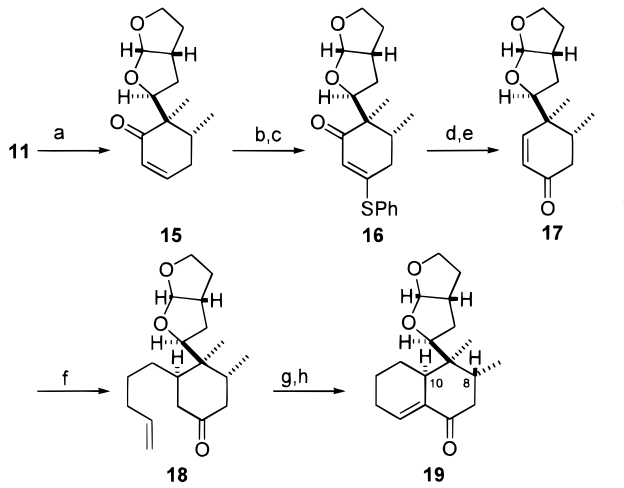


[a] Reagents: (a) MeMgI, CuBr.Me_2S, HMPA, TMSiCl; (b) Tr-ClO_4, 72%; (c) Li-Selectride; (d) MsCl, pyridine; (e) LiBr, Li_2CO_3.

For the construction of ring A, a four-carbon fragment had to be introduced at C-10, and for that reason a 1,3-enone transposition of **15** into **17** was undertaken to set the stage for a 1,4-addition. It has been shown by Ley et al.[1] that a copper-catalyzed conjugate addition gives the desired stereochemistry at C-10, when a 1,3-ditihiolan-2-yl substituent instead of a hexahydrofuro[2,3-*b*]furan substituent is present in the molecule at C-9. The 1,3-ditihiolan-2-yl moiety probably gives a large complex with the cuprate to block the β-side (axial) of the molecule allowing a second equivalent of the cuprate to attack from the desired α-side (equatorial). We had already observed the complexing capability of the hexahydrofuro[2,3-*b*]-furan moiety in the treatment of the ozonide with Cu-$(OAc)_2$ and $FeSO_4$ and therefore reasoned that this complexation might also be expected in the 1,4-addition, causing a similar effect as had been observed for the 1,3-ditihiolan-2-yl moiety.

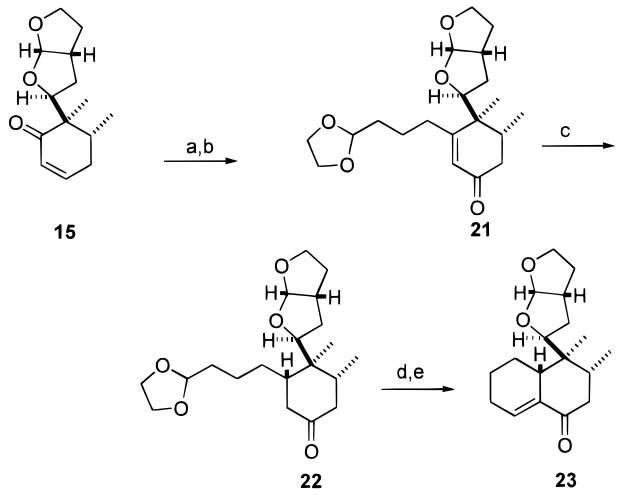
To achieve the 1,3-enone transposition, thiophenol was added to enone **15**, followed by chlorination using trichloroisocyanuric acid[14] and concomitant dehydrochlorination,[15] to give compound **16** in high yield. Reduction of the ketone in **16** and hydrolysis of the intermediate then gave the transposed enone **17** in 74% yield. The 1,4-addition of 4-pentenylmagnesiumbromide to enone **17** using CuBr·Me_2S as a catalyst gave only one adduct in 88% yield. The configuration at C-10 was determined in the cyclized decalin **19**, which was obtained after ozonolysis of the double bond followed by aldol condensation (Scheme 5). The stereochemistry of **19** was elucidated by NMR, where no NOE between H-10 and H-8 could be detected, whereas a clear NOE was observed between H-10 and both the methyl groups at C-8 and C-9, which is indicative for an α-position of this proton. This meant that the 1,4-addition to enone **17** had occurred from the β-side, to yield the wrong configuration at C-10. Apparently, the hexahydrofuro[2,3-*b*]furan moiety does not show the same effect as the 1,3-ditihiolan-2-yl moiety did in the synthesis of ajugarin I.[1]

Scheme 5[a]



[a] Reagents: (a) O_3, $Cu(OAc)_2$, $FeSO_4$; (b) PhSH, Et_3N; (c) trichloroisocyanuric acid; (d) $LiAlH_4$; (e) PTSA; (f) pent-4-enylMgBr, CuBr·Me_2S; (g) O_3, Ph_3P; (h) PPTS, Δ.

Scheme 6[a]



[a] Reagents: (a) 3-(1,3-dioxolan-2-yl)propyllithium **20**; (b) PCC; (c) Pd/C, H_2; (d) PPTS, H_2O; (e) PPTS, Δ.

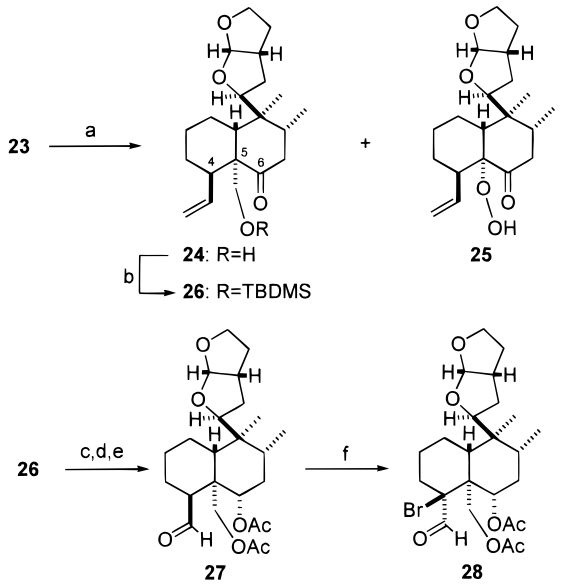
On the basis of this experience, it was expected that also other reagents would approach enones such as **17** from the β-side, because the methyl at C-9 blocks the approach from the α-side. Therefore, a reaction sequence was planned in which a four-carbon fragment was introduced at C-10 followed by addition of hydrogen at the C-5, C-10 double bond (Scheme 6).

First, the 1,2-addition of a four-carbon fragment to **16** was studied, but this did not yield an enone like **21**. The addition went poorly, and the planned hydrolysis of the intermediate gave the highly stable diene sulfide as a product of dehydration in low yield. Hydrolysis of this diene sulfide could not be achieved. In contrast to the failure of the 1,2-addition to ketone **11**, and the poor yield of the 1,2-addition to **16**, the 1,2-addition of 3-(1,3-dioxolan-2-yl)propyllithium **20** to the less hindered enone **15** could be accomplished in an acceptable yield of 42% to give a mixture of alcohols. Due to the basic character of **20**, the deconjugated derivative of enone **15** was obtained in 25% yield as the major side product.[16] This deconjugated enone could be used again for the 1,2-addition after reconversion to **15** by treatment with

(14) Mura, A. J.; Bennet, D. A.; Cohen, T. *Tetrahedron Lett.* **1975**, *50*, 4433−4436.

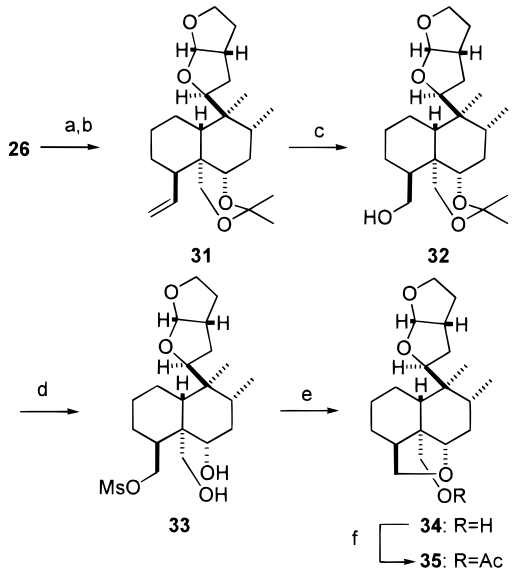
(15) (a) de Groot, A.; Peperzak, R. M.; Vader, J. *Synth. Commun.* **1987**, *17*, 1607−1616. (b) Bukuzis, P.; Bakuzis, M. L. F. *J. Org. Chem.* **1981**, *46*, 235−239.

Scheme 7[a]



[a] Reagents: (a) vinylMgBr, CuBr·Me_2S, CH_2O; (b) TBDMSiCl, imidazole; (c) $LiAlH_4$; (d) Ac_2O, DMAP; (e) O_3, Ph_3P; (d) Pyrolidone·$HBr·Br_2$.

Scheme 8[a]



[a] Reagents: (a) $LiAlH_4$; (b) MeO_2CMe_2, PPTS; (c) O_3, $NaBH_4$; (d) pyridine, MsCl; (e) LiBr, Li_2CO_3, 100 °C; (f) Ac_2O, pyridine, DMAP.

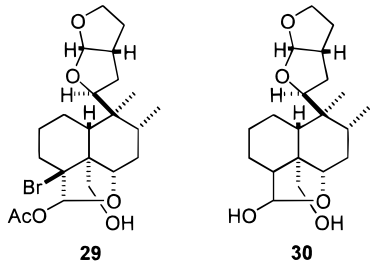


Figure 1.

MeONa. The mixture of alcohols was submitted to an oxidative rearrangement[17] to yield the transposed enone **21**. Catalytic hydrogenation of enone **21** with H_2 and Pd/C afforded one product **22** in 81% yield, and again the elucidation of the stereochemistry at C-10 was done in the cyclized decalin **23**, which was obtained after deprotection of **22** to the aldehyde and subsequent aldol condensation.[18] The correct configuration at C-10 in **23** could be concluded from NMR studies where now a clear NOE between H-10 and H-8 was observed.

With the top side of the decalin finished, we turned our attention to the introduction of the two additional carbons of the clerodane skeleton following the procedure of Ley.[1] The conjugate addition of vinylmagnesium bromide to **23** and trapping of the enolate with a solution of monomeric formaldehyde in THF[19] introduced the necessary fragments and established the desired stereochemistry at C-5 in 51% yield. When oxygen was not fully excluded in this reaction, the hydroperoxy **25** was obtained as the major product.[20] The hydroxymethyl group was protected as its *tert*-butyldimethylsilyl ether **26** to prevent hydroxyl-directed reduction of the carbonyl group. Now reduction of the carbonyl group with $LiAlH_4$ yielded the deprotected diol with the correct configuration at C-6. The final transformation of the vinyl substituent at C-4 into an epoxide with the correct stereochemistry proved to be the last problem, which only could be solved after major efforts. From the literature[1] and from our own experience,[21] it was concluded that the direct oxidation of an exocyclic double bond at C-4 would probably give the wrong configuration of the epoxide. The hydroxyl-directed epoxidation with $VO(acac)_2$ seemed more promising in this respect, but its chemoselectivity was questionable, and therefore, the route to construct the epoxide via a bromohydrine as intermediate was investigated first.

The two hydroxyl groups that were obtained after the reduction of **26** were transformed into their acetates to avoid extra protection−deprotection steps. The double bond was ozonolyzed and gave aldehyde **27** in 95% yield, and bromination of this aldehyde gave an 1:4 epimeric mixture with the axial bromine **28** as the major product in 63% yield (Scheme 7). The idea was to reduce the α-bromoaldehyde to an α-bromohydrine, which upon treatment with base should cyclize to the desired epoxide. However, the alcohol, obtained after reduction of **28** with $NaBH_4$, immediately reacted with the acetates to give a mixture of transposed acetates. An attempt to remove the acetates by treatment with MeONa before the reduction gave the ring closed product **29** in 75% yield. An acetonide as protecting group proved to be no solution, owing to the instability of the acetonide under the bromination conditions, and the hemiacetal **30** was isolated as the main product. Since this approach did not open an easy route to the desired epoxide, the synthesis of an exocyclic methylene at C-4 was investigated, to

(16) To prevent this base-catalyzed isomerization the less basic organocerium reagent was studied in the addition reaction, but this did not yield the addition product due to the low reactivity of the organocerium reagent.

(17) Ziegler, F. E.; Wallace, O. B. *J. Org. Chem.* **1995**, *60*, 3626−3636.

(18) PPTS was used as a catalyst for the aldol condensation, because the more acidic PTSA yielded many side products (see also note 26).

(19) Schlosser, M.; Jenny, T.; Guggisberg, Y. *Synlett* **1990**, 704.

(20) For similar fast trapping of enolates by oxygen, see: (a) Koreeda, M.; You, Z. *J. Org. Chem.* **1989**, *54*, 5195−5198. (b) Gallagher, T. F.; Adams, J. L. *J. Org. Chem.* **1992**, *57*, 3347−3353.

(21) Luteijn, J. M.; de Groot, A. *Tetrahedron Lett.* **1982**, *23*, 3421−3424.

epoxidize this double bond either by $VO(acac)_2$ or by *m*-CPBA. A third possibility to obtain the desired epoxide might be created by ozonolysis of this methylene to a ketone, which then could be submitted to a Corey epoxidation.

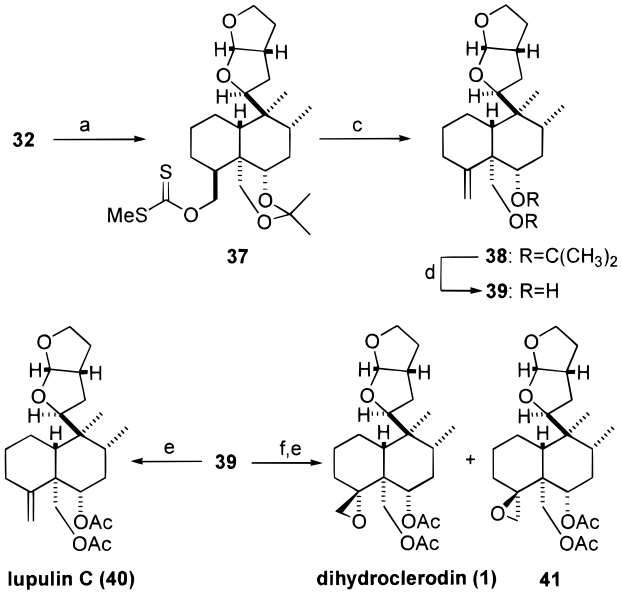
To obtain the exocyclic methylene group the vinyl group was ozonolyzed and the ozonide was reduced with $NaBH_4$ to yield alcohol **32**.[22] Elimination of the hydroxyl group in **32** through conversion into a phenylselenide or via its mesylate was investigated, but formation of the selenide failed and formation of the mesylate yielded the deprotected diol mesylate **33**, which under elimination conditions gave **34** in 61% yield.

Finally, **32** was transformed into the xanthate ester **37**. Now a Chugaev elimination[23] could be tried, and this elimination indeed gave the exomethylene **38** in 74% yield. It was difficult to follow this Chugaev reaction by TLC, because of similar R_f values of **37**, **38**, and several side products. Heating at reflux in *n*-dodecane for 48 h proved to be necessary to finish the reaction. Careful deprotection of the acetonide **38** with aqueous trifluoroacetic acid gave the diol **39**.

The hydroxyl directed epoxidation using $VO(acac)_2$ gave no epoxidation of the exocyclic double bond at room temperature. Only after heating for 48 h in CH_2Cl_2 did the starting material decompose, and no epoxide could be detected by NMR. However, using *m*-CPBA in a buffered solution yielded a 1:1 mixture of two epoxides, and acetylation of this mixture gave dihydroclerodin (**1**) (26%) and 4-*epi*-dihydroclerodin (**41**) (25%), which could be separated easily. NMR spectroscopy and the recording of an optical rotation of $[\alpha]_D$ −10[24] confirmed that the natural enantiomer of dihydroclerodin had been synthesized. Acetylation of diol **39** yielded the natural clerodane lupulin C (**40**).[25]

The Corey epoxidation was investigated to see whether the selectivity of the epoxide formation could be improved. For this purpose, lupulin C (**40**) was treated with ozone, followed by PPh_3 to yield the carbonyl group at C-4. This ketone was submitted to a reaction with trimethylsulfonium ylide, but during this reaction the acetates were removed and no epoxide was obtained. The first total synthesis of dihydroclerodin has been achieved in an overall yield of 0.35% in 18 steps. Characteristic for our approach is the early introduction of the hexahydrofuro[2,3-*b*]furan in a remarkably diastereoselective Mukaiyama reaction. In the course of this total synthesis, the hexahydrofuro[2,3-*b*]furan moiety has proven to be a stable fragment that, being an acetal, survived nearly all the applied reaction conditions.[26] A good solution was found for the annulation of ring A with the correct stereochemistry at C-10 via the selective catalytic reduction of enone **21**. The introduction of the

Scheme 9[a]



[a] Reagents: (a) O_3, $NaBH_4$; (b) NaH, CS_2, MeI; (c) 216 °C; (d) CF_3CO_2H; (e) Ac_2O, pyridine, DMAP; (f) *m*-CPBA.

functional groups at C-5, C-6, and especially at C-4 is still susceptible of improvement. It was observed that in many transformations the yields were clearly lower compared to similar reactions with a 1,3-dioxolan-2-yl substituent at C-9. This may explain why the promising results of some reactions which were described in the literature with other substituents at C-9 did not give good results in our compounds. The only case in which the hexahydrofuro[2,3-*b*]furan moiety seems to have a beneficial influence is in the final epoxidation, where a better yield of the natural epoxide was obtained in comparison with similar reactions in the literature.[1,21]

Experimental Section

General Methods. All reagents were purchased from Aldrich or Acros, except for carvone, which was a generous gift of Quest International, and were used without further purification unless otherwise stated. Melting points are uncorrected. Solvents were freshly distilled by common practice. Product solutions were dried over $MgSO_4$ prior to evaporation of the solvent under reduced pressure by using a rotary evaporator. For flash chromatography, Merck Kieselgel silica 60 (230−400 Mesh ASTM) was used with mixtures of ethyl acetate and petroleum ether bp 40−60 °C as eluent (10% EA/PE means 10 vol % of ethyl acetate in petroleum ether). Reactions were monitored by GC with a DB-17 column (30 m × 0.25 mm i.d.) or by TLC on silica gel plates, and visualization of compounds was accomplished by UV detection and by spraying with basic $KMnO_4$ or by acidic anisaldehyde solution. Ozone was generated by a Fisher ozone generator 502.

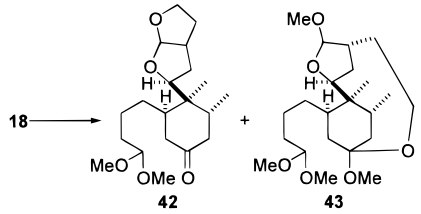
(22) The acetonide in **32** was not very stable and decomposed in $CDCl_3$ during NMR recording to give a triol.

(23) Tschugaeff, L. (Chugaev) *Chem. Ber.* **1899**, *32*, 3332−3335.

(24) Literature $[\alpha]_D$ −10.9 ($CDCl_3$) [see: Beauchamp, P. S.; Bottini, A. T.; Caselles, M. C.; Dev, V.; Hope, H.; Larter, M.; Lee, G.; Mathela, C. S.; Melkani, A. B.; Millar, P. D.; Miyatake, M.; Pant, A. K.; Raffel, R. J.; Sharma, V. K.; Wyatt, D. *Phytochemistry* **1996**, *43*, 827−834], $[\alpha]_D$ −20 ($CHCl_3$) [see: Barton, D. H. R.; Cheung, H. T.; Cross, A. D.; Jackman, L. M.; Martin-Smith, M. *J. Chem. Soc.* **1961**, 5061−5073], and $[\alpha]_D$ −12.8 (C_2H_5OH) [see: Akiko, O.; Haruhisa, K.; Tsuyoshi, T. *Chem. Pharm. Bull.* **1996**, *44*, 1540−1545].

(25) This compound is isolated from *Ajuga lupulina*. Chen, H.; Tan, R. X.; Liu, Z. L.; Zhang, Y. *J. Nat. Prod.* **1996**, *59*, 668−670. However, their reported fragment peaks are not in accordance with the ones we found.

(26) It should be noted that acidic reaction conditions have to be treated with care as was demonstrated by the isolation of compound **43** in reaction of the ozonide of **18** with PPh_3 and MeOH. See also ref 18.



(±)-*cis,trans*-Toluene-4-sulfonic acid (2-methoxytetrahydrofuran-3-ylmethyl) Ester (4). To a stirred solution of (±)-*cis,trans*-(2-methoxytetrahydro-furan-3-yl)methanol[6a] (37.5 g, 284 mmol) in pyridine (75 mL) and $CHCl_3$ (75 mL) was added *p*-toluenesulfonyl chloride (81 g, 425 mmol) in small portions. After addition, the reaction mixture was stirred for an additional 2 h. Then water was added, and the aqueous phase was extracted three times with $CHCl_3$. The combined organic layers were washed with brine and dried. After evaporation of the solvents, the last traces of pyridine were removed by azeotropic distillation with toluene. The remaining oil **4** (71 g, 249 mmol, 88%) was not purified any further: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.49 (m, 1H), 2.05 (m, 1H), 2.34 (s, 3H), 2.47 (m, 1H), 3.17 and 3.26 (s, 3H), 4.75−4.18 (m, 4H), 4.75 (d, J = 1.1 Hz, 0.7H, trans, 4.80 (d, J = 4.6 Hz, 0.3H, cis, 7.34 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) (trans) δ 21.6 (q), 26.3 (t), 44.9 (d), 54.7 (q), 65.9 (t), 70.1 (t), 105.9 (d), 127.9 (d, 2C), 129.9 (d, 2C), 132.7 (s), 145.0 (s); (cis) δ 21.6 (q), 26.3 (t), 43.2 (d), 54.4 (q), 66.4 (t), 69.4 (t), 103.1 (d), 127.9 (d, 2C), 129.9 (d, 2C), 132.7 (s), 145.0 (s).

(±)-*cis,trans*-(2-Methoxytetrahydrofuran-3-yl)acetonitrile (5). To a stirred solution of **4** (70 g, 245 mmol) in DMF (800 mL) was added NaCN (24 g, 490 mmol). The reaction mixture was heated at 70 °C for 18 h. After this period, the reaction mixture was poured into water (500 mL). The aqueous phase was extracted five times with ether. The combined organic layers were washed with brine and dried. After careful evaporation of the solvents, the residue was distilled under reduced pressure. First, DMF was collected at 10 mbar, followed by **5** (28.1 g, 200 mmol, 81%) as a mixture of cis and trans at 0.1 mbar 79−82 °C (distillation was done from a water bath to prevent the temperature from rising above 100 °C because above this temperature the product decomposed): ^{1}H NMR ($CDCl_3$, 200 MHz) (cis) δ 1.30 (m, 1H), 2.10 (m, 1H), 2.42 (m, 3H), 3.29 (m, 3H), 3.90 (m, 2H), 4.82 (d, J = 3.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) (cis) δ 16.8 (t), 28.9 (t), 40.4 (d), 54.8 (q), 66.6 (t), 103.4 (d), 119.1 (s); ^{1}H NMR ($CDCl_3$, 200 MHz) (trans) δ 1.63 (m, 1H), 2.15−2.51 (m, 4H), 3.28 (s. 3H), 3.92 (m, 2H), 4.71 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) (trans) δ 20.2 (t), 29.1 (t), 41.9 (d), 54.7 (q), 66.0 (t), 107.5 (d), 118.1 (s).

(±)-Tetrahydrofuro[2,3-*b*]furan-2-one (7). A well-stirred emulsion of **5** (9.6 g, 68.0 mmol) in an aqueous solution of NaOH (5 M, 20 mL) was refluxed for 2.5 h until a clear solution was formed. The reaction mixture was cooled to room temperature, followed by washing of the aqueous phase with 25 mL of ether. Then the aqueous phase was acidified with concentrated HCl until pH 1 and stirred for an additional 1.5 h. Then the aqueous phase was extracted five times with ethyl acetate. The combined organic layers were washed with brine and dried. After careful evaporation of the solvents, the residue was distilled under reduced pressure (Kugelrohr 0.2 mmHg, oven temperature 80 °C) to give **8** (7.89 g, 61.6 mmol, 91%). ^{1}H NMR spectra were in accordance with the literature.[10]

(±)-2-Methoxyhexahydrofuro[2,3-*b*]furan (8). To a stirred solution of **7**[11] (10.0 g, 78 mmol) in dry toluene (40 mL) was slowly added DIBALH (1.5 M in toluene, 55 mL, 82 mmol) at −78 °C. After addition, the reaction mixture was stirred for an additional 1.5 h at −78 °C and then quenched by adding dry MeOH (2.9 g, 90 mmol) together with BF_3·etherate (21 mL, 167 mmol) as quickly as possible without raising the temperature above −60 °C (>10 min). The reaction mixture was stirred for an additional 5 min and then poured into a large beaker with water (100 mL) and $NaHCO_3$ (50 g, 0.6 mol). The resulting slurry was stirred for 2 h, allowing the $NaHCO_3$ to react with the excess of BF_3·etherate. After this period, the aqueous phase was extracted three times with ether. The combined organic layers were washed with brine and dried. After careful evaporation of the solvents, a colorless oil was distilled (Kugelrohr 3 mmHg, oven temperature 80 °C) and afforded **8** (7.0 g, 49 mmol, 62%) as a 1:2 mixture of diastereoisomers, along with 1.1 g of the overreduced hexahydrofuro-[2,3-*b*]furan. Further purification was not necessary. NMR spectra were in accordance with the literature.[10]

(5*R*,3*R*)-(5-Isopropenyl-2,3-dimethylcyclohex-1-enyloxy)trimethylsilane[27] (10): $[\alpha]^{20}_D$ 72.7 (*c* 2.69, $CHCl_3$).

(2*R*,3*R*,5*R*,2′*S*,3a′*R*,6a′*S*)-2-(Hexahydrofuro[2,3-*b*]furan-2′-yl)-5-isopropenyl-2,3-dimethylcyclohexanone (11) and (2*R*,3*R*,5*R*,2′*R*,3a′*S*,6a′*R*)-2-(Hexahydrofuro[2,3-*b*]furan-2′-yl)-5-isopropenyl-2,3-dimethylcyclohexanone (12). To a stirred solution of racemic **8** (16.0 g, 110 mmol) and **10** (22.0 g, 92.3 mmol) in CH_2Cl_2 (150 mL) at −78 °C was added dropwise triphenylmethyl perchlorate[28] (3.4 g, 10 mmol) dissolved in CH_2Cl_2 (150 mL). The reaction mixture was stirred for 78 h at −78 °C until **10** was not detectable anymore on TLC (samples for monitoring the reaction were diluted using ether with Et_3N). After this period, the reaction was quenched by addition of a saturated aqueous $NaHCO_3$ solution (100 mL). The aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried, and evaporated. The residue was distilled (Kugelrohr 0.01 mmHg, oven temperature 110 °C). The mixture of two diastereoisomers were separated via crystallization from diisopropyl ether. After two recrystallizations, the diastereoisomers were completely separated, yielding crystalline **12** (9.1 g, 32.7 mmol, 35%) as white crystals: mp 120 °C; $[\alpha]^{20}_D$ 65.7 (*c* 2.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.89 (s, 3H), 0.89 (d, J = 7.0 Hz, 3H), 1.52 (m, 1H), 1.69 (bs, 3H), 1.69 (m, 2H), 1.92−2.16 (m, 4H), 2.33 (m, 1H), 2.55 (m, 1H), 2.71 (d, J = 12.6 Hz, 1H), 2.82 (m, 1H), 3.87 (m, 2H), 4.63 (dd, J = 9.6, 6.2 Hz, 1H), 4.75 (m, 2H), 5.66 (d, J = 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.4 (q), 16.7 (q), 20.4 (q), 32.6 (t), 33.0 (t), 33.1 (t), 36.8 (d), 40.4 (d), 41.9 (d), 43.3 (t), 54.3 (s), 68.0 (t), 82.6 (t), 109.0 (d), 109.4 (t), 147.4 (s), 213.4 (s).

Compound **11** (11.0 g, 39 mmol, 40%) was obtained as a colorless oil (90% purity). A small sample was further purified for analysis by flash chromatography (20% EA/PE): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.82 (s, 3H), 0.84 (d, J = 5.0 Hz, 3H), 1.45 (ddd, J = 13.4, 6.8, 5.2 Hz, 1H), 1.50−2.31 (m, 7H), 1.67 (bs, 3H), 2.48 (m, 2H), 2.80 (m, 1H), 3.87 (dd, J = 8.6, 4.6 Hz, 2H), 4.70 (m, 3H), 5.69 (d, J = 10.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.8 (q), 16.7 (q), 20.5 (q), 32.6 (t), 32.9 (t), 33.0 (t), 36.2 (d), 40.5 (d), 42.6 (d), 44.8 (t), 56.0 (s), 67.8 (t), 80.3 (d), 109.5 (d), 109.7 (t), 147.4 (s), 213.2 (s).

(1*R*,2*S*,3*R*,5*R*,2′*S*,3a′*R*,6a′*S*)-2-(Hexahydrofuro[2,3-*b*]furan-2′-yl)-5-isopropenyl-2,3-dimethyl-1-cyclohexanol (13). To a stirred solution of **11** (0.94 g, 3.4 mmol) in THF (30 mL) was added dropwise lithium tri-*sec*-butylborohydride (1 M in THF, 5 mL) at −78 °C. The reaction mixture was allowed to come to room temperature and stirred for an additional 8 h. After this period, the reaction mixture was cooled to −10 °C, and an aqueous solution of NaOH (1 M, 10 mL) and an aqueous solution of H_2O_2 (30%, 8 mL) were added slowly, followed by 2 h vigorous stirring. Water (20 mL) was added, and then the aqueous phase was extracted three times with ether. The combined organic layers were carefully washed with an aqueous solution of Na_2SO_3 and brine, dried, and evaporated. The residue was purified by flash chromatography (30% EA/PE) to give **13** (0.91 g, 3.25 mmol, 96%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (s, 3H), 0.99 (d, J = 7.4 Hz, 3H), 1.38 (m, 1H), 1.60−2.40 (m, 10H), 1.76 (bs, 3H), 2.78 (m, 1H), 3.71 (dd, J = 10.2, 5.1 Hz, 1H), 3.88 (m, 2H), 4.41 (dd, J = 10.7, 5.5 Hz, 1H), 4.76 (m, 2H), 5.65 (d, J = 5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.4 (q), 16.5 (q), 21.0 (q), 32.8 (t), 33.1 (d), 33.4 (t), 34.6 (t), 35.2 (t), 38.2 (d), 42.1 (s), 42.4 (d), 68.3 (t), 74.1 (d), 80.1 (d), 107.9 (d), 108.9 (t), 149.7 (s).

(3*S*,4*R*,6*R*,2′*S*,3a′*R*,6a′*S*)-3-(Hexahydrofuro[2,3-*b*]furan-2′-yl)-6-isopropenyl-3,4-dimethylcyclohexene (14). To a stirred solution of **13** (0.91 g, 3.25 mmol) in pyridine (5 mL) and CH_2Cl_2 (5 mL) was added MsCl (0.6 mL, 5 mmol) at 0 °C. The reaction mixture was stirred overnight, followed by addition of water (50 mL). The aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried, and evaporated. The residue was

(27) Verstegen-Haaksma, A. A.; Swarts, H. J.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **1994**, *50*, 10073−10082.
(28) Dauben, H. J.; Honnen, L. R.; Harmon, K. M. *J. Org. Chem.* **1960**, *25*, 1442−1445.

purified by flash chromatography (30% EA/PE) to give the mesylate (0.49 g, 1.37 mmol, 42%) as a colorless oil.

To a solution of the mesylate (400 mg, 1.12 mmol) in dry DMF (20 mL) were added LiBr (0.5 g) and Li_2CO_3 (0.5 g). The reaction mixture was heated at 100 °C for 36 h, cooled to room temperature, and poured into water (20 mL). The aqueous phase was extracted thee times with petroleum ether. The combined organic layers were washed two times with brine, dried, and evaporated. The residue was purified by flash chromatography (5% EA/PE) to give **14** (290 mg, 1.24 mmol, 90%) as white crystals. For X-ray analysis, the crystals were recrystallized from hexanes to afford almost colorless needles: mp 68−70 °C; $[\alpha]^{20}_D$ 114 (*c* 3.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.81 (d, J = 6.3 Hz, 3H), 0.96 (s, 3H), 1.35−2.18 (m, 7H), 1.72 (s, 3H), 2.61 (m, 1H), 2.77 (m, 1H), 3.86 (m, 2H), 4.12 (dd, J = 10.2, 5.9 Hz, 1H), 4.63 (bs, 1H), 4.77 (bs, 1H), 5.60 (s, 2H), 5.68 (d, J = 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.9 (q), 18.3 (q), 22.1 (q), 29.4 (d), 30.7 (t), 32.9 (t), 34.0 (t), 41.2 (d), 41.2 (s), 42.4 (d), 68.1 (t), 84.9 (d), 109.0 (d), 111.2 (t), 129.3 (d), 132.5 (d), 148.2 (s); MS *m*/*z* (relative intensity) 113 (100); HRMS calcd for $C_{17}H_{26}O_2$ (M^+) 262.1932, found 262.1932 (σ = 0.057 mmu).

(5*R*,6*R*,2′*S*,3a′*R*,6a′*S*)-6-(Hexahydrofuro[2,3-*b*]furan-2′-yl)-5,6-dimethylcyclohex-2-enone (15). A stirred solution of **11** (12.5 g, 45 mmol) in CH_2Cl_2 (300 mL) and MeOH (250 mL) at −78 °C was purged through with ozone until a pale blue color appeared. Then nitrogen was purged through to remove the excess of ozone, followed by addition of $FeSO_4 \cdot 7H_2O$ (12.5 g, 45 mmol) and $Cu(OAc)_2 \cdot H_2O$ (17.7 g, 90 mmol). The reaction mixture was allowed to come to room temperature and stirred overnight. After this period, the reaction mixture was concentrated to 100 mL, followed by addition of aqueous HCl (4 M, 150 mL). The aqueous phase was extracted three times with ether. The combined organic layers were washed with an aqueous solution of NaOH (4 M) and brine, dried, and evaporated. The residue was purified by flash chromatography (30% EA/PE) to give **15** (7.3 g, 31 mmol, 70%) as a colorless oil: $[\alpha]^{20}_D$ −36.5 (*c* 2.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.91 (s, 3H), 0.95 (d, J = 4.7 Hz, 3H), 1.38 (ddd, J = 13.4, 6.8, 3.1 Hz, 1H), 1.65 (m, 1H), 1.89−2.17 (m, 3H), 2.48 (m, 1H), 2.88 (m, 2H), 3.82 (m, 2H), 4,45 (dd, J = 8.8, 6.6 Hz, 1H), 5.67 (d, J = 5.0 Hz, 1H), 5.88 (ddd, J = 10.0, 2.8, 1.2 Hz, 1H), 6.77 (dddd, J = 10.0, 5.3, 2.8, 1.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.6 (q), 16.3 (q), 31.7 (t), 32.8 (t), 33.0 (t), 34.8 (t), 42.6 (d), 53.0 (s), 67.7 (t), 80.0 (d), 109.6 (d), 128.8 (d), 147.7 (d), 202.2 (s); MS *m*/*z* (relative intensity) 124 (100), 113 (90); HRMS calcd for $C_{14}H_{20}O_3$ (M^+) 236.1412, found 236.1413 (σ = 0.083 mmu).

(5*R*,6*R*,2′*S*,3a′*R*,6a′*S*)-6-(Hexahydrofuro[2,3-*b*]furan-2′-yl)-5,6-dimethyl-3-phenylsulfanylcyclohex-2-enone (16). To a stirred solution of **15** (10.4 g, 43.8 mmol) in pentane (300 mL) and THF (100 mL) were added thiophenol (5.5 g, 50 mmol) and Et_3N (1 mL). The reaction mixture was stirred for 27 h, followed by evaporation of the solvents. The residue was purified by flash chromatography (first 10% EA/PE, then 30% EA/PE) to give a mixture of the α- and β-phenyl sulfide (11.02 g, 31.8 mmol, 73%) as a colorless and slightly smelly oil. This mixture (9.0 g, 26 mmol) was dissolved in ether (100 mL) and benzene (100 mL), and trichloroisocyanuric acid (2.0 g, 8.67 mmol) was added in three portions within 5 min, at 0 °C (ice−salt bath). The reaction mixture was stirred for no more than 5 min. Then K_2CO_3 (5 g) was added, followed by filtration over silica. The solvents were evaporated under reduced pressure at 0 °C. The residue was purified by flash chromatography (20% EA/PE) to give **16** (8.3 g, 24.1 mmol, 93%) as a colorless oil: ^{1}H NMR ($CDCl_3$), 200 MHz) δ 0.91 (s, 3H), 0.96 (d, J = 4.6 Hz, 3H), 1.40 (ddd, J = 13.4, 6.8, 3.4 Hz, 1H), 1.65 (m, 1H), 2.02−1.93 (m, 2H), 2.21 (dd, J = 18.3, 2.8 Hz, 1H), 2.54 (m, 1H), 2.81 (m, 1H), 3.09 (ddd, J = 18.3, 5.1, 2.1 Hz, 1H), 3.87 (m, 2H), 4.44 (dd, J = 8.3, 6.9 Hz, 1H), 5.40 (d, J = 2.1 Hz, 1H), 5.69 (d, J = 5.0 Hz, 1H), 7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.9 (q), 16.2 (q), 32.7 (t), 32.8 (t), 35.0 (d), 35.1 (t), 42.5 (d), 52.0 (s), 67.6 (t), 80.1 (d), 109.5 (d), 119.8 (d), 128.0 (s), 129.7 (d, 2C), 130.0 (d, 2C), 135.4 (d), 163.6 (s), 198.1 (s); MS *m*/*z* (relative intensity) 113 (100); HRMS calcd for $C_{20}H_{24}O_3S$ (M^+) 344.1446, found 344.1445 (σ = 0.12 mmu).

(4*S*,5*R*,2′*S*,3a′*R*,6a′*S*)-4-(Hexahydrofuro[2,3-*b*]furan-2′-yl)-4,5-dimethylcyclohex-2-enone (17). To a stirred suspension of $LiAlH_4$ (1.0 g, 26.3 mmol) in dry ether (150 mL) was added **16** (8.3 g, 24.1 mmol) dissolved in dry ether (50 mL). The reaction mixture was stirred for 30 min at room temperature. After this period, water (50 mL) was added. The aqueous phase was extracted three times with ether. The combined organic layers were washed with brine, dried, and evaporated. The residue was dissolved in $CHCl_3$ (100 mL), followed by addition of PTSA (0.5 g). The reaction mixture was stirred overnight. After this period, $CHCl_3$ (100 mL) was added, and the mixture was washed twice with an aqueous solution of NaOH (4 M, 10 mL) and brine (10 mL), dried, and evaporated. The residue was purified by flash chromatography (30% EA/PE) to give **17** (4.2 g, 17.8 mmol, 74%) as white crystals: mp 90 °C; $[\alpha]^{20}_D$ −12.6 (*c* 3.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.94 (d, J = 6.6 Hz, 3H), 1.13 (s, 3H), 1.61−1.75 (m, 3H), 1.98−2.30 (m, 4H), 2.84 (m, 1H), 3.88 (m, 2H), 4.17 (dd, J = 9.9, 6.5 Hz, 1H), 5.73 (d, J = 5.0 Hz, 1H) 5.97 (d, J = 10.3 Hz, 1H), 6.89 (d, J = 10.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.5 (q), 16.4 (q), 32.8 (t), 34.3 (d), 34.7 (t), 42.0 (t), 42.4 (d), 42.5 (s), 68.4 (t), 83.1 (d), 109.0 (d), 129.1 (d), 155.1 (d), 199.5 (s). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.09; H, 8.57.

(3*R*,4*S*,5*R*,2′*S*,3a′*R*,6a′*S*)-4-(Hexahydrofuro[2,3-*b*]furan-2′-yl)-4,5-dimethyl-3-pent-4-enylcyclohexanone (18). To a stirred solution of $CuBr \cdot Me_2S$ (1.5 g, 7.3 mmol) in THF (80 mL) and HMPA (5 mL) was added dropwise a freshly prepared solution of pent-4-enylmagnesium bromide in ether (50 mL, 30 mmol) at −78 °C. The reaction mixture was stirred for 1.5 h at −78 °C, followed by addition of **17** (1.82 g, 7.71 mmol) dissolved in THF (20 mL) and TMSCl (2 mL). The reaction mixture was stirred for 5 h. After this period, water (10 mL) was added slowly, followed by an aqueous solution of HCl (4 M, 20 mL). The aqueous phase was extracted three times with ether. The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (30% EA/PE) to give **18** (2.07 g, 6.76 mmol, 88%) as white crystals: mp 109 °C; $[\alpha]^{20}_D$ −24.0 (*c* 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (s, 3H), 0.95 (d, J = 6.8 Hz, 3H), 1.11−1.20 (m, 2H), 1.38−1.78 (m, 5H), 1.90−2.25 (m, 6H), 2.41 (d, J = 6.6 Hz, 2H), 2.62 (dd, J = 14.4, 4.8 Hz, 1H), 2.78 (m, 1H), 3.85 (m, 2H), 4.17 (dd, J = 11.1, 5.2 Hz, 1H), 4.94 (m, 2H), 5.65 (d, J = 5.3 Hz, 1H), 5.76 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.2 (q), 17.8 (q), 26.9 (t), 28.3 (t), 32.6 (t), 33.6 (t), 34.0 (t), 35.9 (d), 40.1 (s), 41.4 (d), 42.5 (t), 43.6 (d), 46.6 (t), 68.3 (t), 83.9 (d), 108.6 (d), 114.7 (t), 138.4 (d), 212.9 (s). Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 73.52; H, 9.92.

(3*R*,4*S*,4a*S*,2′*S*,3a′*R*,6a′*S*)-3,4,4a,5,6,7-Hexahydro-4-(hexahydrofuro[2,3-*b*]furan-2′-yl)-3,4-dimethyl-2*H*-naphthalen-1-one (19). A solution of **18** (2.1 g, 6.76 mmol) in CH_2Cl_2 (80 mL) at −78 °C was purged through with ozone until a pale blue color appeared. Then nitrogen was purged through, followed by addition of Ph_3P (2.1 g, 8.0 mmol). The reaction mixture was allowed to come to room temperature and stirred overnight. Then the solvent was evaporated. The residue was purified by flash chromatography (60% EA/PE) to give **(1*R*,2*S*,3*R*,2′*S*,3a′*R*,6a′*S*)-4-(4-(hexahydrofuro[2,3-*b*]furan-2′-yl)-2,3-dimethyl-5-oxocyclohexyl)butyraldehyde** (1.87 g, 6.1 mmol, 90%) as white crystals: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.86 (s, 3H), 0.92 (d, J = 6.7 Hz, 3H), 1.06−2.22 (m, 11H), 2.39 (m, 4H), 2.59 (dd, J = 14.2, 4.6 Hz, 1H), 2.76 (m, 1H), 3.82 (m, 2H), 4.11 (dd, J = 11.1, 5.2 Hz, 1H), 5.62 (d, J = 5.1, 1H), 9.67 (bs, 1H).

A solution of the aldehyde (0.9 g, 2.9 mmol) in benzene (40 mL) and PPTS (50 mg) was refluxed using a Dean−Stark apparatus for 4 h. The reaction mixture was cooled, followed by addition of a saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous phase was extracted three times with ether. The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (20% EA/PE) to give **19** (0.53 g, 1.8 mmol, 63%) as a colorless

oil: $[\alpha]^{20}_D$ −35.1 (*c* 1.50, $CHCl_3$); ^1H NMR (C_6D_6, 400 MHz) δ 0.75 (s, 3H), 0.93 (d, J = 6.8 Hz, 3H), 1.20−1.30 (m, 2H), 1.37 (m, 1H) 1.50−1.76 (m, 5H), 1.98−2.05 (m, 2H), 2.13 (ddq, J = 7.1, 2.6, 7.1 Hz, 1H), 2.33 (m, 1H), 2.33 (dd, J = 17.5, 2.7 Hz, 1H), 2.43 (ddd, J = 14.8, 7.5, 3.8 Hz, 1H), 3.10 (dd, J = 17.5, 6.1 Hz, 1H), 3.64 (m, 2H), 4.12 (dd, J = 10.8, 5.4 Hz, 1H), 5.60 (d, J = 5.1 Hz, 1H), 7.15 (m, 1H); ^{13}C NMR (C_6H_6, 100 MHz) δ 17.7 (q), 20.9 (q), 23.1 (t), 24.2 (t), 26.3 (t), 33.1 (t), 33.6 (d), 34.5 (t), 39.3 (s), 41.8 (d), 42.3 (d), 44.2 (t), 68.2t, 82.9 (d), 108.4 (d), 135.5 (d), 138.0 (s), 198.0 (s); MS *m*/*z* (relative intensity) 113 (100); HRMS calcd for $C_{18}H_{26}O_3$ (M^+) 290.1882, found 290.1881 (σ = 0.09 mmu).

(4*S*,5*R*,2′*S*,3a′*R*,6a′*S*)-3-(3-[1,3]Dioxolan-2-ylpropyl)-4-(hexahydrofuro[2,3-*b*]furan-2′-yl)-4,5-dimethylcyclohex-2-enone (21). A solution of 3-(1,3-dioxolan-2-yl)propyllithium was prepared by adding *t*-BuLi (1.5M in pentane, 33 mL, 49.5 mmol) to a degassed solution of 2-(3-iodopropyl)[1,3]dioxolane[29] (6.0 g, 24.8 mmol) in dry ether (80 mL) at −78 °C under argon. The temperature was allowed to rise to room temperature, and the reaction mixture was stirred for an additional 45 min. The fresh prepared lithium reagent was added to a stirred solution of **15** (4.0 g, 17 mmol) in dry ether (80 mL) at −78 °C. After addition, the reaction mixture was stirred for an additional 3 h at −78 °C and then quenched with water (30 mL). The aqueous phase was extracted three times with ethyl acetate, and the combined organic layers were washed with brine, dried, and evaporated. The residue was dissolved in CH_2Cl_2 (100 mL) and DMF (4 mL), followed by addition of PCC (8.0 g, 37 mmol) in three portions at 0 °C. The reaction mixture was stirred overnight at room temperature. After this period, ether (200 mL) was added and the reaction mixture was filtered over a short path of silica. The filter was washed extensively, followed by evaporation of the solvents. The residue was purified by flash chromatography (first 20% EA/PE, then 60% EA/PE) to give **(5*R*,6*R*,2′*S*,3a′*R*,6a′*S*)-6-(Hexahydrofuro[2,3-*b*]furan-2′-yl)-5,6-dimethylcyclohex-3-enone** (1.0 g, 4.2 mmol, 25%) as a colorless oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 086 (d, J = 4.8 Hz, 3H), 0.91 (s, 3H), 1.47 (ddd, J = 13.2, 6.9, 3.3 Hz, 1H), 1.58−2.12 (m, 4H), 2.74 (m, 2H), 2.84 (m, 1H), 3.85 (m, 2H), 4.75 (dd, J = 8.6, 6.9 Hz, 1H), 5.58 (m, 1H), 5.65 (d, J = 4.9 Hz, 1H), 5.77 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.6 (q), 17.2 (q), 32.9 (t), 33.3 (t), 39.4 (t), 40.5 (d), 42.7 (d), 56.2 (s), 67.7 (t), 80 4 (d), 109.4 (d), 121.7 (d), 133.1 (d), 211.2 (s); MS *m*/*z* (relative intensity) 166 (15), 151 (11), 124 (16), 113 (100); HRMS calcd for $C_{14}H_{20}O_3$ (M^+) 236.1412, found 236.1410 (σ = 0.059 mmu).

Followed by **21** (2.5 g, 7.1 mmol, 42%) as a colorless oil: $[\alpha]^{20}_D$ 43.2 (*c* 2.57, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 089 (d, J = 6.9 Hz, 3H), 1.02 (s, 3H), 1.3−2.3 (m H), 2.68−2.89 (m, 3H), 3.77−3.92 (m, 6H), 4.12 (dd, J = 10.6, 5.6 Hz, 1H), 4.79 (t, J = 4.0 Hz, 1H) 5.60 (d, J = 5.0 Hz, 1H), 5.86 (bs, 1H); IR 1666 cm^{-1}.

(3*S*,4*S*,5*R*,2′*S*,3a′*R*,6a′*S*)-3-(3-[1,3]Dioxolan-2-ylpropyl)-4-(hexahydrofuro[2,3-*b*]furan-2′-yl)-4,5-dimethylcyclohexanone (22). To a stirred suspension of Pd/C (10%) (690 mg) in THF (100 mL) saturated with hydrogen was added a solution of **21** (2.7 g, 7.7 mmol) in THF. The reaction mixture was stirred under hydrogen for 20 h. Then the Pd/C was filtered and washed with ethyl acetate. The solvents were evaporated, and the residue was purified by flash chromatography (60% EA/PE) to give **22** (2.2 g, 6.2 mmol, 81%) as a colorless oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 088 (d, J = 6.8 Hz, 3H), 0.99 (s, 3H), 1.38−2.26 (m, 15H), 2.39 (dd, J = 14.8, 3.9 Hz, 1H), 2.85 (m, 1H), 3.82 (m, 6H), 4.22 (dd, J = 11.1, 5.7 Hz, 1H), 4.79 (t, J = 4.4 Hz, 1H), 5.63 (d, J = 5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 11.7 (q), 17.2 (q), 22.1 (t), 30.6 (t), 32.3 (t), 32.8 (t), 33.9 (t), 36.5 (d), 40.3 (s), 41.4 (d), 42.1 (d), 42.7 (t), 46.0 (t), 64.8 (t, 2C), 68.3 (t), 84.7 (d), 104.3 (d), 108.2 (d), 211.5 (s); MS *m*/*z* (relative intensity) 113 (100); HRMS calcd for $C_{20}H_{32}O_5$ (M^+) 352.2250, found 352.2246 (σ = 0.026 mmu); IR 1717 cm^{-1}.

(3*R*,4*S*,4a*R*,2′*S*,3a′*R*,6a′*S*)-3,4,4a,5,6,7-Hexahydro-4-(hexahydrofuro[2,3-*b*]furan-2′-yl)-3,4-dimethyl-2*H*-naphthalen-1-one (23). A solution of THF (25 mL), water (20 mL), PPTS (0.5 g), and **22** (1.5 g, 4.3 mmol) was refluxed for 12 h and then cooled to room temperature, followed by addition of a saturated aqueous $NaHCO_3$ solution (3 mL). After the THF was evaporated, the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried, and evaporated. The residue was treated with PPTS as described for compound **19** yielding **23** (0.78 g, 2.68 mmol, 63%) as a colorless oil: $[\alpha]^{20}_D$ −52.7 (*c* 1.0, $CHCl_3$); ^1H NMR (C_6D_6, 400 MHz) δ 0.70 (d, J = 6.8 Hz, 3H), 0.85 (s, 3H), 1.22 (ddd, J = 12.8, 5.6, 1.5 Hz, 1H), 1.27−1.41 (m, 2H), 1.57−1.82 (m, 5H), 1.95 (m, 2H), 2.07 (m, 1H), 2.14 (dd, J = 17.5, 10.8 Hz, 1H), 2.42, (m, 1H), 2.48 (dd, J = 17.5, 5.9 Hz, 1H) 2.59 (m, 1H), 3.72 (m, 2H), 4.12 (dd, J = 11.2, 5.6 Hz, 1H), 5.69 (d, 5.0 Hz, 1H), 7.22 (m, 1H); ^{13}C NMR (C_6D_6, 100 MHz) δ 12.3 (q), 17.4 (q), 22.4 (t), 24.1 (t), 24.9 (t), 33.0 (d), 40.5 (s), 42.5 (d), 42.6 (d), 44.8 (t), 68.3 (t), 84.1 (t), 108.6 (d), 138.0 (s), 138.3 (d), 198.0 (s).

(3*R*,4*S*,4a*S*,8*R*,8a*S*,2′*S*,3a′*R*,6a′*S*)-8a-(*tert*-Butyldimethylsilanyloxymethyl)-4-(hexahydrofuro[2,3-*b*]furan-2′-yl)-3,4-dimethyloctahydro-8-vinylnaphthalen-1-one (26). To a degassed solution of $CuBr{\cdot}Me_2S$ (100 mg, 0.5 mmol), HMPA (0.3 mL), and dry THF (20 mL) under argon was added vinylMgBr (1 M in THF, 2.5 mL, 2.5 mmol) at −78 °C. The reaction mixture was stirred for 1.5 h at −78 °C, followed by addition of **23** (237 mg, 0.82 mmol) dissolved in THF (3 mL). After addition, the reaction mixture was stirred for an additional 1 h. Then a freshly prepared oxygen free solution of formaldehyde in THF (15 mL) was added quickly.[30] Stirring was continued for no more than 10 min. Then the reaction was quenched in an aqueous NH_4Cl solution (60 mL), followed by vigorous extraction with ethyl acetate (three times). The combined organic layers were washed with brine, dried, and evaporated. The residue was dissolved in DMF (5 mL), *tert*-butyldimethylsilyl chloride (0.3 g, 2.0 mmol) and a trace of imidazole. The reaction mixture was stirred for 12 h at room temperature. After this period, water (10 mL) was added, and the aqueous phase was extracted three times with ether. The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (20% EA/PE) to give **26** (190 mg, 0.41 mmol, 51%): $[\alpha]^{20}_D$ 89.5 (*c* 2.95, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ −0.01 (s, 3H), 0.01 (s, 3H), 0.84 (s, 9H), 0.88 (d, J = 7.1 Hz, 3H), 0.96 (s, 3H), 1.40−2.42 (m, 14H), 2.82 (m, 1H), 2.97 (m, 1H), 3.86 (m, 2H), 3.95 (s, 2H), 4.20 (dd, J = 11.6, 5.8 Hz, 1H), 5.03 (m, 2H), 5.63 (d, J = 5.1 Hz, 1H), 5.90 (ddd, J = 17.1, 9.8, 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −5.7 (q, 2C), 15.4 (q), 17.9 (q), 18.3 (s), 21.4 (t), 22.5 (t), 22.6 (t), 22.8 (q, 3C), 32.8 (t, 2C), 33.8 (d), 40.0 (s), 41.2 (d), 42.2 (d), 42.3 (d), 46.2 (t), 56.2 (s), 63.9 (t), 68.2 (t), 85.9 (d), 108.5 (d), 116.2 (t), 138.8 (d), 213.1 (s); MS *m*/*z* (relative intensity) 405 (11), 113 (100); HRMS calcd for $C_{23}H_{37}O_4Si$ (M^+-57) 405.2461, found 405.2460 (σ = 0.113 mmu).

(1*S*,3*R*,4*S*,4a*S*,8*S*,8a*R*,2′*S*,3a′*R*,6a′*S*)-Acetic Acid 1-Acetoxy-8-formyldecahydro-4-(hexahydrofuro[2,3-*b*]furan-2′-yl)-3,4-dimethylnaphthalen-8a-ylmethyl Ester (27). To a stirred solution of **26** (94 mg, 21 mmol) in ether (25 mL) was added $LiAlH_4$ (50 mg) at 0 °C. The reaction mixture was stirred for 3 h at room temperature. After this period, ice−water (5 mL) was added, followed by an aqueous solution of HCl (2 M, 10 mL). The aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried, and evaporated to yield the crude diol. A solution of the crude diol in pyridine (5 mL), acetic anhydride (1 mL), and a trace of DMAP was stirred overnight. Then water was added, and the aqueous phase was extracted three times with ether. The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (30% EA/PE) to give

(29) Pleshakov, M. G.; Vasil'ev, A. E.; Sarycheva, I. K.; Preobrazhenskii, N. A. *J. Gen. Chem. U.S.S.R.* **1961**, *31*, 1433−1435.

(30) Schlosser, M.; Jenny, T.; Guggisberg, Y. *Synlett* **1990**, 704. For oxygen free, a cooled solution of THF, paraformaldehyde, and acid was degassed prior to slowly distillation under argon.

(1*S*,3*R*,4*S*,4a*S*,8*R*,8a*S*,2′*S*,3a′*R*,6a′*S*)-Acetic acid 1-Acetoxydecahydro-4-(hexahydrofuro[2,3-*b*]furan-2′-yl)-3,4-dimethyl-8-vinylnaphthalen-8a-ylmethyl ester (67 mg, 0.15 mmol, 71%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.81 (d, J = 6.2 Hz, 3H), 0.91 (s, 3H), 1.30−2.15 (m, 14H), 1.90 (s, 3H), 2.03 (s, 3H), 2.80 (m, 2H), 3.73 (m, 2H), 4.04 (dd, J = 11.3, 5.4 Hz, 1H), 4.16 (d, J = 12.3 Hz, 1H), 4.48 (dd, J = 9.8, 4.9 Hz, 1H), 4.87 (d, J = 12.3 Hz, 1H), 4.91 (dd, J = 16.7, 2.2 Hz, 1H), 5.04 (dd, J = 10.1, 2.2 Hz, 1H), 5.57 (d, J = 5.1 Hz, 1H), 6.14 (ddd, J = 16.7, 10.1, 10.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.0 (q), 16.5 (q), 20.9 (t), 21.1 (q), 21.2 (q), 22.4 (t), 27.2 (t), 31.9 (t), 32.5 (t, 2C), 35.9 (d), 40.3 (s), 41.4 (d), 41.5 (d), 42.1 (d), 43.9 (s), 61.3 (t), 68.3 (t), 77.0 (d), 85.9 (d), 107.7 (d), 117.3 (t), 137.7 (d), 170.1 (s), 170.7 (s); MS *m*/*z* (relative intensity) 113 (100); HRMS calcd for $C_{25}H_{38}O_6$ (M^+) 434.2668, found 434.2659 (6 scans), calcd for $C_{17}H_{24}O_2$ (M^+-174) 260.1776, found 260.1774 (σ = 0.096 mmu).

A solution of this vinyldiacetate (67 mg, 0.15 mmol) was ozonized as described for compound **19** to give **27** (64 mg, 0.15 mmol, 95%): $[\alpha]^{20}_D$ −26.2 (*c* 3.0, $CHCl_3$); ^{1}H NMR (C_6D_6, 200 MHz) δ 0.59 (d, J = 6.7 Hz, 3H), 0.92 (s, 3H), 1.05−1.78 (m, 11H), 1.70 (s, 3H), 1.74 (s, 3H), 2.11−2.46 (m, 3H), 2.98 (m, 1H), 3.59 (m, 2H), 3.94 (dd, J = 10.3, 5.3 Hz, 1H), 4.00 (d, J = 12.3 Hz, 1H), 5.02 (d, J = 12.3 Hz, 1H), 5.48 (dd, J = 10.4, 5.4 Hz, 1H), 5.56 (d, J = 5.1 Hz, 1H), 9.81 (d, J = 1.5 Hz, 1H); ^{13}C NMR (C_6D_6, 50 MHz) δ 14.8 (q), 16.1 (q), 20.4 (q), 20.5 (q), 21.0 (t), 22.1 (t), 32.3 (t, 2C), 32.5 (t, 2C), 35.9 (d), 40.3 (s), 41.9 (d), 42.1 (d), 43.9 (s), 47.9 (d), 60.5 (t), 67.9 (t), 74.7 (d), 85.7 (d), 107.7 (d), 169.2 (s), 169.5 (s), 202.3 (d); MS *m*/*z* (relative intensity) 113 (100); HRMS calcd for $C_{24}H_{35}O_7$ (M^+ − 1) 435.2383, found 435.2383 (σ = 0.510 mmu); HRMS calcd for $C_{22}H_{32}O_5$ (M^+ − 60) 376.2250, found 376.2245 (σ = 0.134 mmu).

(1*S*,3*R*,4*S*,4a*S*,8*S*,8a*S*,2′*S*,3a′*R*,6a′*S*)-Acetic Acid 1-Acetoxy-8-bromo-8-formyldecahydro-4-(hexahydrofuro[2,3-*b*]furan-2′-yl)-3,4-dimethylnaphthalen-8a-ylmethyl Ester (28). To a stirred solution of CH_2Cl_2 (5 mL) and **27** (35 mg, 8.3×10^{-5} mol) was added pyrrolidone·HBr·Br_2 (82 mg, 16.5×10^{-5} mol). The reaction mixture was stirred for 5 d at room temperature. After this period, CH_2Cl_2 (30 mL) was added, followed by a saturated aqueous $NaHCO_3$ solution (4 mL). The aqueous phase was extracted with CH_2Cl_2 (10 mL). The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (35% EA/PE) to give **28** (26.8 mg, 5.2×10^{-5} mol) (63%): $[\alpha]^{20}_D$ 33.1 (*c* 1.6, $CHCl_3$); ^{1}H NMR (C_6D_6, 200 MHz) δ 0.54 (d, J = 6.5 Hz, 3H), 0.84 (s, 3H), 1.05−1.89 (m, 11H), 1.59 (s, 3H), 1.79 (s, 3H), 2.00−2.52 (m, 4H), 3.58 (m, 2H), 3.88 (dd, J = 11.1, 5.2 Hz, 1H), 4.09 (d, J = 12.3 Hz, 1H), 4.96 (d, J = 12.3 Hz, 1H), 5.46 (dd, J = 10.2, 3.5 Hz, 1H), 5.52 (d, J = 5.1 Hz, 1H), 9.81 (s, 1H); ^{13}C NMR (C_6D_6, 50 MHz) δ 14.2 (q), 16.0 (q), 20.0 (q), 20.8 (q), 21.8 (t), 22.0 (t), 30.5 (t), 32.2 (t), 32.4 (t), 32.6 (t), 35.93 (d), 40.3 (s), 41.9 (d), 43.5 (d), 50.2 (s), 60.6 (t), 67.9 (t), 77.5 (d), 85.3 (d), 87.5 (s), 107.6 (d), 168.4 (s), 168.9 (s), 188 (d); MS *m*/*z* (relative intensity) 113 (100); HRMS calcd for $C_{24}H_{35}O_7$ (M^+ − Br) 435.2383, found 435.2382 (σ = 0.325 mmu).

(2*,2a*S*,5a*R*,6*S*,7*R*,8a*S*,8b*R*,2′*S*,3a′*R*,6a′*S*)-Acetic Acid 2a-Bromo-8b-formyldecahydro-6-(hexahydrofuro[2,3-*b*]-furan-2′-yl)-6,7-dimethylnaphtho[1,8-*bc*]furan-2-ylmethyl Ester (29). To a stirred solution of **28** (16 mg, 3.1×10^{-5} mol) in MeOH (4 mL) was added MeONa (1.0 M in MeOH, 0.1 mL) at 0 °C. After 20 min, an aqueous solution of HCl (0.5 M, 10 mL) was added. The aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (60% EA/PE) to give **29** (11 mg, 2.3×10^{-5} mol) (75%): ^{1}H NMR (C_6D_6, CD_3OD, 200 MHz) δ 0.58 (d, J = 6.0 Hz, 3H), 0.66 (s, 3H), 0.82−2.52 (m, 16H), 1.90 (s), 3H), 3.54 (m, 2H), 3.90 (dd, J = 11.4, 5.7 Hz, 1H), 4.03 (d, J = 9.0 Hz, 1H), 4.14 (d, J = 9.0 Hz, 1H), 5.20 (m, 1H), 5.48 (d, 5.1 Hz, 1H), 6.00 (s, 1H); ^{13}C NMR (C_6D_6, 50 MHz) δ 13.7 (q), 16.1 (q), 21.3 (q), 22.1 (t), 23.0 (t), 32.2 (t), 32.8 (t), 33.4 (t), 33.5 (t), 35.9 (d), 41.0 (s), 42.2 (d), 43.0 (d), 53.0 (s), 65.9 (t), 68.2 (t), 74.9 (s), 78.9 (d), 84.9 (d), 103.6 (d), 107.9 (d), 168.7 (s); MS *m*/*z* (relative intensity) 113 (100); HRMS calcd for $C_{16}H_{23}O_3{}^{79}Br$ (M^+ − 130) 342.0831, found 342.0823 (σ = 0.149 mmu).

(4a*S*,6*R*,7*S*,7a*R*,11*R*,2′*S*,3a′*R*,6a′*S*)-7-(Hexahydrofuro-[2,3-*b*]furan-2′-yl)-3,3,6,7-tetramethyloctahydro-11-vinylnaphtho[1,8a-*d*][1,3]dioxine (31). Reduction of compound **26** was done as described for compound **27**. To a stirred solution of the crude diol (234 mg, 0.68 mmol) in dry DMF (5 mL) and 2,2-dimethoxypropane (5 mL) was added a crystal of PPTS. The reaction mixture was stirred for 0.5 h, followed by addition of a saturated aqueous $NaHCO_3$ solution (5 mL) and water (5 mL). The aqueous phase was extracted three times with ether. The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (20% EA/PE) to give **31** (175 mg, 0.45 mmol, 66%): $[\alpha]^{20}_D$ 8.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (C_6D_6, 200 MHz) δ 0.85 (d, J = 5.8 Hz, 3H), 0.96 (s, 3H), 1.05−1.18 (m, 3H), 1.41 (s, 6H), 1.30−2.05 (m, 11H), 2.22 (m, 1H), 3.13 (m, 1H), 3.56 (m, 2H), 3.76 (d, J = 12.1 Hz, 1H), 3.84 (dd, J = 8.9, 4.2 Hz, 1H), 3.96 (dd, J = 11.2, 5.3 Hz, 1H), 4.04 (d, J = 12.1 Hz, 1H), 5.06 (dd, J = 10.0, 2.5 Hz, 1H), 5.21 (dd, J = 16.8, 2.5 Hz, 1H), 5.57 (d, J = 5.0 Hz, 1H), 6.12 (ddd, J = 16.8, 10.0, 10.0 Hz, 1H); ^{13}C NMR (C_6D_6, 50 MHz) δ 15.5 (q), 18.7 (q), 21.8 (t), 22.6 (t), 26.7 (q), 26.9 (q), 27.4 (t), 32.6 (t, 2C), 32.7 (d), 34.8 (t), 40.1 (d), 40.5 (d), 41.8 (s), 42.0 (d), 44.7 (d), 61.1 (t), 67.9 (t), 73.5 (d), 85 3 (d), 98.6 (s), 108.2 (d), 116.8 (t), 138.9 (d).

(2*,2a*,5a*R*,6*S*,7*R*,8a*S*,8b*R*,2′*S*,3a′*R*,6a′*S*)-8b-Hydroxymethyl-decahydro-6-(hexahydro-furo[2,3-*b*]furan-2′-yl)-6,7-dimethyl-naphtho[1,8-*bc*]furan-2-ol (30). Compound **31** (20 mg, 5.1×10^{-5} mol) was ozonized as described for compound **19** yielding **(4a*S*,6*R*,7*S*,7a*R*,11*S*,2′*S*,3a′*R*,6a′*S*)-7-(Hexahydrofuro[2,3-*b*]furan-2′-yl)-3,3,6,7-tetramethyl-octahydronaphtho[1,8a-*d*][1,3]dioxine-11-carbaldehyde** (18.7 mg, 4.8×10^{-5} mol, 93%) as a white gum, which was used directly in the next reaction: $[\alpha]^{20}_D$ −13.6 (*c* 1.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (d, J = 6.3 Hz, 3H), 0.99 (s, 3H), 1.12−2.21 (m, 14H), 1.33 (s, 3H), 1.45 (s, 3H), 2.78 (m, 1H), 3.37 (brd, J = 5.1 Hz, 1H), 3.83 (m, 3H), 4.08 (dd, J = 11.1, 5.7 Hz, 1H), 4.15 (d, J = 12.4 Hz, 1H), 4.21 (dd, J = 12.5, 4.4 Hz, 1H), 5.57 (d, J = 5.1 Hz, 1H), 9.92 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.4 (q), 17.2 (q), 21.2 (t), 21.6 (t), 23.4 (t), 26.4 (q), 29.3 (q), 32.3 (t), 32.7 (t), 34.9 (t), 35.2 (d), 40.3 (s), 41.3 (s), 42.0 (d), 42.2 (d), 50.2 (d), 60.2 (t), 68.3 (t), 73.9 (d), 86.5 (d), 98.5 (s), 108.0 (d), 205.7 (s); MS *m*/*z* (relative intensity) 113 (100); HRMS calcd for $C_{23}H_{36}O_5$ (M^+) 392.2563, found 392.2552 (σ = 0.262 mmu).

To a stirred solution of the aldehyde (18 mg, 4.7×10^{-5} mol) in CH_2Cl_2 (4 mL) was added pyrrolidone·HBr·Br_2 (36 mg, 7.0×10^{-5} mol). After 5 min, the reaction mixture was filtered through a silica filter**,** the filter was washed thoroughly with ethyl acetate. The solvents were evaporated to give **30** (12 mg, 3.4×10^{-5} mol, 73%) as a white powder: ^{1}H NMR (C_6D_6, CD_3OD, 200 MHz) δ 0.69 (d, J = 6.9 Hz, 3H), 0.71 (s, 3H), 0.71−2.05 (m, 17H), 2.27 (m, 1H), 3.37 (dd, J = 11.3, 4.6 Hz, 1H), 3.60 (m, 2H), 3.88 (d, J = 9.0 Hz, 1H), 3.99 (dd, J = 11.4, 5.6 Hz, 1H), 4.19 (dd, J = 11.4, 9.0 Hz, 1H), 5.08 (s, 1H), 5.54 (d, 5.1 Hz, 1H); ^{13}C NMR (C_6D_6, CD_3OD, 50 MHz) δ 13.4 (q), 16.7 (q), 22.5 (t), 23.3 (t), 28.4 (t), 32.4 (t), 32.8 (t), 36.2 (d), 37.3 (t), 41.2 (s), 42.1 (d), 43.8 (d), 50.7 (s), 54.5 (d), 68.1 (t), 68.5 (t), 77.6 (d), 85.2 (d), 104.6 (d), 108.0 (d); MS *m*/*z* (relative intensity) 113 (100); HRMS calcd for $C_{20}H_{30}O_4$ (M^+ − 18) 334.2144, found 334.2148 (σ = 0.126 mmu).

(2a*S*,5a*R*,6*S*,7*R*,8a*S*,8b*R*,2′*S*,3a′*R*,6a′*S*)-Acetic Acid 2a-Decahydro-6-(hexahydrofuro[2,3-*b*]furan-2′-yl)-6,7-dimethylnaphtho[1,8-*bc*]furan-8b-ylmethyl Ester (35). A solution of **31** (30 mg, 7.7×10^{-5} mol) dissolved in MeOH (30 mL) was purged through with ozone at −78 °C until a pale bleu color appeared. Then nitrogen was purged through, followed by addition of $NaBH_4$ (20 mg). The reaction mixture was allowed to come to room temperature and stirred for an additional 3 h. After this period water (10 mL) was added. The aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried, and evaporated. The remaining alcohol **32** was dissolved in pyridine (5 mL), followed by addition of MsCl (0.2 mL) at 0

°C. The reaction mixture was stirred for 3 h. Then ether (30 mL) was added, followed by water (15 mL). The aqueous phase was extracted three times with ether. The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (60% EA/PE) to give mesylate **33** (30 mg, 6.9×10^{-5} mol, 90%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.85 (s, 3H), 0.87 (d, J = 6.6 Hz, 3H), 1.16−2.16 (m, 14H), 2.69−2.95 (m, 4H), 3.02 (s, 3H), 3.65 (m, 1H), 3.84 (m, 3H), 4.03 (dd, J = 11.1, 5.4 Hz, 1H), 4.23 (d, J = 11.7 Hz, 1H), 4.39 (dd, J = 9.9, 7.0 Hz, 1H), 4.57 (dd, J = 9.9, 5.6 Hz, 1H), 5.56 (d, J = 5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.5 (q), 17.0 (q), 21.5 (t), 22.3 (t), 23.3 (t), 32.5 (t), 32.8 (t), 33.4 (d), 35.8 (d), 36.4 (t), 37.5 (q), 40.5 (s), 41.8 (d), 42.1 (d), 45.0 (s), 61.1 (t), 68.3 (t), 70.8 (d), 74.8 (d), 85.9 (d), 107.7 (d).

To a solution of **33** (30 mg, 6.9×10^{-5} mol) in DMF (5 mL) and HMPA (1.0 mL) were added LiBr (30 mg) and Li_2CO_3 (26 mg). The reaction mixture was heated at 100 °C for 12 h. Then the reaction mixture was cooled, followed by addition of water (20 mL). The aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (60% EA/PE) to give **34** (15.8 mg, 4.7×10^{-5} mol, 61%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.83 (s, 3H), 1.03 (d, J = 6.7 Hz, 3H), 1.16−2.20 (m, 15H), 2.35 (m, 1H), 2.81 (m, 1H), 3.14−3.29 (m, 3H), 3.85 (m, 2H), 3.92 (dd, J = 10.7, 5.4 Hz, 1H), 4.08 (d, J = 10.8 Hz, 1H), 4.22 (dd, J = 8.6, 8.6 Hz, 1H), 5.61 (d, J = 5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.7 (q), 17.8 (t), 19.3 (q), 20.9 (t), 22.5 (t), 32.3 (t), 33.4 (t), 34.4 (t), 35.0 (d), 40.6 (d), 40.9 (d), 41.5 (s), 42.3 (d), 46.6 (s), 64.6 (t), 68.2 (t), 75.7 (t), 86.6 (d), 86.8 (d), 108.1 (d); MS m/z (relative intensity) 113 (100).

For proper structure elucidation alcohol **34** was converted into its acetate **35**.

To a stirred solution of **34** (15 mg, 4.7×10^{-5} mol) in pyridine (2 mL) and Ac_2O (0.3 mL) was added one crystal of DMAP. The reaction mixture was stirred for 1 h. Then ether (20 mL) was added, followed by water (10 mL). The aqueous phase was extracted three times with ether. The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (40% EA/PE) to give **35** (13 mg, 3.4×10^{-5} mol, 73%): $[\alpha]^{20}_D$ −16.5 (c 1.3, $CHCl_3$); ^{1}H NMR (C_6D_6, 400 MHz) δ 0.90 (d, J = 6.8 Hz, 3H), 1.03 (s, 3H), 1.24 (m, 4H), 1.42 (m, 1H), 1.62−1.90 (m, 7H), 1.85 (s, 3H), 2.07 (s, 3H), 2.38 (m, 1H), 3.27(dd, J = 12.8, 4.3 Hz, 1H), 3.31 (dd, J = 8.9, 6.7 Hz, 1H), 3.69 (ddd, J = 8.5, 8.5, 4.2 Hz, 1H), 3.77 (ddd, J = 8.5, 8.5, 6.7 Hz, 1H), 3.98 (dd, J = 11.1, 5.1 Hz, 1H), 4.31 (dd, J = 8.5, 8.5 Hz, 1H), 4.40 (d, J = 11.5 Hz, 1H), 4.45 (d, J = 11.5 Hz, 1H), 5.71 (d, J = 5.1 Hz, 1H); ^{13}C NMR (C_6D_6, 100 MHz) δ 16.2 (q), 18.6 (t), 18.7 (q), 20.5 (q), 21.3 (t), 23.1 (t), 32.2 (t), 33.1 (t), 34.3 (t), 34.5 (d), 41.3 (d), 41.6 (s), 41.7 (d), 42.2 (d), 45.3 (s), 67.3 (t), 67.8 (t), 74.7 (t), 85.5 (d), 85.8 (d), 108.0 (d), 170.1 (s); MS m/z (relative intensity) 113 (100); HRMS calcd for $C_{22}H_{33}O_5$ ($M^+ - 1$) 377.23287, found 377.2324 (σ = 0.139 mmu).

(4a*S*,6*R*,7*S*,11*S*,11a*R*,2′*S*,3a′*R*,6a′*S*)-Dithiocarbonic Acid *S*-Methyl Ester *O*-[7-(Hexahydrofuro[2,3-*b*]furan-2′-yl)-3,3,6,7-tetramethyloctahydronaphtho[1,8a-*d*][1,3]dioxin-11-ylmethyl] Ester (37). To a stirred solution of the crude alcohol **32** (100 mg, 0.25 mmol) in THF (20 mL) was added sodium hydride (100 mg, 60% in mineral oil) at 0 °C. The reaction mixture was stirred for 2 h, followed by addition of CS_2 (1 mL), and the reaction mixture was stirred for an additional 1.5 h. After this period, MeI (0.5 mL) was added and the reaction mixture was allowed to come to room temperature and stirred overnight. Then ether (20 mL) was added, followed by ice−water (10 mL). The aqueous phase was extracted three times with ether. The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (10% EA/PE) to give **37** (61 mg, 0.13 mmol, 51%) as a colorless oil: $[\alpha]^{20}_D$ 9.7 (c 1.25 CH_2Cl_2); ^{1}H NMR (C_6D_6, 200 MHz) δ 0.91 (d, J = 7.0 Hz, 3H), 1.00 (s, 3H), 1.00−1.82 (m, 12H), 1.48 (s, 3H), 1.49 (s, 3H), 1.95−2.40 (m, 3H), 2.23 (s, 3H), 3.14 (m, 1H), 3.68 (m, 2H), 3.80 (d, J = 12.1 Hz, 1H), 3.98 (m, 2H), 4.09 (d, J = 12.1 Hz, 1H), 4.91 (dd, J = 11.0, 7.8 Hz, 1H), 5.10 (dd, J = 11.0, 4.8 Hz, 1H), 5.64 (d, J = 5.0 Hz, 1H); ^{13}C NMR (C_6D_6, 50 MHz) δ 15.8 (q), 18.38 (q), 18.45 (q), 21.5 (t), 22.6 (t), 23.9 (t), 26.3 (q), 27.4 (q), 27.4 (t), 32.6 (t), 32.6 (d), 32.8 (t), 34.8 (d), 37.7 (d), 40.0 (s), 40.7 (d), 41.9 (d), 41.9 (s), 60.7 (t), 67.9 (t), 73.3 (d), 74.3 (t), 85 3 (d), 98.8 (s), 108.1 (d); MS m/z (relative intensity) 113 (100); HRMS calcd for $C_{25}H_{40}O_5S_2$ (M^+) 484.2317, found 484.2314 (σ = 6.453 mmu, 4 scans); HRMS calcd for $C_{23}H_{36}O_4$ ($M^+ - 108$) 376.2614, found 376.2610 (σ = 0.174 mmu).

(4a*S*,6*R*,7*S*,7a*R*,11a*R*,2′*S*,3a′*R*,6a′*S*)-7-(Hexahydrofuro[2,3-*b*]furan-2′-yl)-3,3,6,7-tetramethyl-11-methyleneoctahydronaphtho[1,8a-*d*][1,3]dioxine (38). A solution of degassed and freshly distilled dodecane (5 mL) and **37** (61 mg, 0.13 mmol) was heated for 48 h at reflux temperature (216 °C). Then the solvent was evaporated until 1 mL of the volume remained, followed by flash chromatography (10% EA/PE) to give **38** (35 mg, 9.3×10^{-5} mol, 74%) as a colorless oil: $[\alpha]^{20}_D$ 13.2 (c 0.43 CH_2Cl_2); ^{1}H NMR (C_6D_6, 200 MHz) δ 0.80 (d, J = 6.8 Hz, 3H), 1.15 (s, 3H), 1.05−1.80 (m, 10H), 1.56 (s, 6H), 2.15−2.39 (m, 5H), 3.66 (m, 2H), 3.96 (d, J = 12.1 Hz, 1H), 4.06 (dd, J = 11.2, 5.4 Hz, 1H), 4.21 (dd, J = 12.3, 5.0 Hz, 1H), 4.22 (d, J = 12.1 Hz, 1H), 5.10 (bs, 1H), 5.44 (bs, 1H), 5.62 (d, J = 5.0 Hz, 1H); ^{13}C NMR (C_6D_6, 50 MHz) δ 15.0 (q), 17.2 (q), 22.6 (t), 27.9 (q), 28.8 (q), 28.8 (t), 32.6 (t), 33.0 (t), 34.0 (t), 36.2 (d), 36.6 (t), 41.3 (s), 42.3 (d), 45.6 (s), 49.4 (d), 61.1 (t), 68.2 (t), 74.3 (d), 86.0 (d), 99.0 (s), 108.2 (d), 108.4 (t), 153.7 (s); MS m/z (relative intensity) 361 (16), 113 (100); HRMS calcd for $C_{23}H_{36}O_4$ (M^+) 376.2614, found 376.2609 (σ = 0.308 mmu).

(1*S*,3*R*,4*S*,4a*R*,8a*R*,2′*S*,3a′*R*,6a′*S*)-Decahydro-4-(hexahydrofuro[2,3-*b*]furan-2′-yl)-8a-hydroxymethyl-3,4-dimethyl-8-methylenenaphthalen-1-ol (39). To a stirred solution of **38** (35 mg, 9.3×10^{-5} mol) in THF (20 mL) and water (10 mL) was added one drop of (10%) trifluoroacetic acid. The reaction mixture was stirred for 4 h. After this period, a saturated aqueous $NaHCO_3$ solution (5 mL) was added, followed by evaporation of THF. The aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (60% EA/PE) to give **39** (23 mg, 7.0×10^{-5} mmol, 75%) as a colorless oil: $[\alpha]^{20}_D$ 17.0 (c 0.50 CH_2Cl_2); ^{1}H NMR (C_6D_6, 200 MHz) δ 0.73 (d, J = 6.7 Hz, 3H), 0.89 (s, 3H), 1.03−1.88 (m, 11H), 2.09−2.42 (m, 6H), 3.62 (m, 2H), 3.95 (m, 3H), 4.08 (d, J = 10.8 Hz, 1H), 5.13 (bs, 1H), 5.40 (bs, 1H), 5.59 (d, J = 5.1 Hz, 1H); ^{13}C NMR (C_6D_6, 100 MHz) δ 15.0 (q), 17.0 (q), 23.2 (t), 29.2 (t), 32.8 (t), 33.0 (t), 34.6 (t), 36.2 (d), 37.5 (t), 41.3 (s), 42.4 (d), 49.5 (d), 52.0 (s), 61.1 (t), 68.2 (t), 75.3 (d), 85.6 (d), 108.1 (d), 109.7 (t), 152.8 (s); MS m/z (relative intensity) 113 (100); HRMS calcd for $C_{20}H_{32}O_4$ (M^+) 336.2301, found 336.2290 (σ = 0.259 mmu), calcd for $C_{20}H_{30}O_3$ ($M^+ - 18$) 318.2195, found 318.2188 (σ = 0.337 mmu).

Dihydroclerodin (1) and 4-*epi*-Dihydroclerodin (41). To a stirred solution of CH_2Cl_2 (0.5 mL) and **39** (7.4 mg, 2.2×10^{-5} mol) was added a mixture of Na_2HPO_4 (15 mg) and *m*-CPBA (10 mg) in CH_2Cl_2 (0.5 mL). The reaction mixture was stirred for 4 h. After this period, ethyl acetate (10 mL) and water (5 mL) were added. The aqueous phase was extracted two times with ethyl acetate. The combined organic layers were washed with brine, dried, and evaporated. The residue was dissolved in pyridine (0.3 mL) and acidic anhydride (0.2 mL), followed by addition of one crystal of DMAP. The reaction mixture was stirred for 4 h, followed by addition of water (5 mL). The aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (60% EA/PE) to elute first **41** (2.5 mg, 5.7×10^{-6} mol, 26%) as a colorless oil: $[\alpha]^{20}_D$ 14.9 (c 0.21, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (d, J = 6.4 Hz, 3H), 0.98 (s, 3H), 1.15 (m, 1H), 1.38−2.25 (m, 13H), 1.96 (s, 3H), 2.05 (s, 3H), 2.55 (d, J = 4.4 Hz, 1H), 2.71 (d, J = 4.4 Hz, 1H), 2.90 (m, 1H), 3.89 (m, 2H), 4.12 (dd, J = 11.3, 5.5 Hz, 1H), 4.31 (d, J = 12.0 Hz, 1H), 4.60 (dd, J = 10.4, 6.2 Hz, 1H), 4.89 (d, J = 12.0 Hz, 1H), 5.65 (d, J = 5.1 Hz, 1H); ^{13}C NMR (C_6D_6,

100 MHz) δ 14.4 (q), 16.7 (q), 21.6 (q), 22.0 (q), 22.2 (t), 23.5 (t), 26.1 (t), 32.0 (t), 32.5 (t), 32.7 (t), 33.1 (t), 35.8 (d), 40.6 (s), 42.5 (d), 46.0 (d), 55.6 (s), 61.4 (t), 62.2 (t), 69.0 (t), 72.3 (d), 86.0 (d), 108.1 (d), 170.4 (s), 171.1 (s); MS *m*/*z* (relative intensity) 113 (100); HRMS calcd for $C_{22}H_{33}O_6$ ($M^+ - 43$) 393.2277, found 393.2267 ($\sigma = 0.164$ mmu).

Compound **1** (2.4 mg, 5.5×10^{-6} mol, 25%) was eluted next as a colorless oil: $[\alpha]^{20}_D$ −9.6 (*c* 0.22, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (d, $J = 6.5$ Hz, 3H), 0.98 (s, 3H), 1.04 (m, 1H), 1.37−1.95 (m, 11H), 1.97 (s, 3H), 2.13 (s, 3H), 2.10−2.23 (m, 3H), 2.24 (d, $J = 4.0$ Hz, 1H), 2.91 (m, 1H), 3.00 (dd, $J = 3.9$, 2.3 Hz, 1H), 3.89 (m, 1H), 4.12 (dd, $J = 11.3$, 5.5 Hz, 1H), 4.37 (d, $J = 12.2$ Hz, 1H), 4.70 (dd, $J = 11.4$, 4.8 Hz, 1H), 4.93 (d, $J = 12.2$ Hz, 1H), 5.66 (d, $J = 5.1$ Hz, 1H); ^{13}C NMR (C_6D_6, 100 MHz) δ 14.6 (q), 17.0 (q), 21.7 (q), 21.8 (q), 22.6 (t), 25.4 (t), 32.8 (t), 33.0 (t), 33.1 (t), 33.7 (t), 36.4 (d), 40.8 (s), 42.5 (d), 45.9 (s), 48.5 (d), 48.9 (t), 62.1 (t), 65.5 (s), 69.0 (t), 72.3 (d), 85.7 (d), 108.1 (d), 170.7 (s), 171.5 (s); MS *m*/*z* (relative intensity) 113 (100); HRMS calcd for $C_{22}H_{33}O_6$ ($M^+ - 43$) 393.2277, found 393.2273 ($\sigma = 0.278$ mmu).

Lupucin-C (40). A solution of pyridine (0.3 mL), Ac_2O (0.2 mL), **39** (9.0 mg, 2.7×10^{-5} mol), and a trace of DMAP was stirred for 4 h. Then water (5 mL) was added. The aqueous phase was extracted three times with ether. The combined organic layers were washed with brine, dried, and evaporated. The residue was purified by flash chromatography (40% EA/PE) to give **40** (10 mg, 2.4×10^{-5} mol, 90%); ^{1}H NMR (C_6D_6, 400 MHz) δ 0.67 (d, $J = 6.8$ Hz, 3H), 1.01 (s, 3H), 1.05 (m, 1H), 1.15−1.89 (m, 11H), 1.83 (s, 3H), 1.88 (s, 3H), 2.18−2.35 (m, 4H), 3.68 (m, 2H), 4.00 (dd, $J = 11.2$, 5.2 Hz, 1H), 4.23 (d, $J = 12.0$ Hz, 1H), 4.95 (d, $J = 10.0$ Hz, 1H), 5.21 (d, $J = 12.0$ Hz, 1H), 5.40 (dd, $J = 10.8$, 4.4, 1H), 5.63 (d, $J = 5.2$ Hz, 1H); ^{13}C NMR (C_6D_6, 100 MHz) δ 14.7 (q), 16.5 (q), 21.1 (q), 21.1 (q), 23.1 (t), 29.2 (t), 32.5 (t), 32.9 (t), 33.2 (t), 34.7 (t), 36.1 (d), 41.3 (s), 42.3 (d), 49.4 (s), 50.4 (d), 61.2 (t), 68.3 (t), 75.8 (d), 85.4 (d), 106.7 (t), 108.0 (d), 152.6 (s), 169.9 (s), 170.0 (s); MS *m*/*z* (relative intensity) 113 (100); HRMS calcd for $C_{24}H_{36}O_6$ (M^+) 420.2512, found 420.2510 ($\sigma = 0.167$ mmu).

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Supporting Information Available: ^{1}H NMR spectra of **1**, **11**−**13**, **21**, **23**, **29**−**31**, **33**, **40**, **41**, and **43**. This material is available free of charge via the Internet at http://pubs.acs.org.

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