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Synthetic Approaches and Total Synthesis of Natural Zoapatanol

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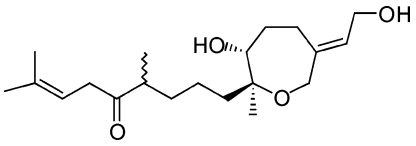
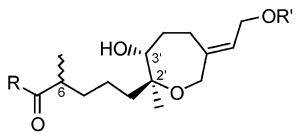


Zoapatanol

The total synthesis of (+)-zoapatanol utilizing an intramolecular Horner−Wadsworth−Emmons olefination and an enantioselective Sharpless dihydroxylation as the key steps has been achieved. An advanced oxepene intermediate has been obtained by applying a ring-closing metathesis to an unsaturated enol ether.

Introduction

(+)-Zoapatanol **1**, montanol **2**, tomentanol **3**, and tomentol **4** are diterpenoid oxepanes isolated from the leaves of the Mexican zoapatle plant *Montanoa tomentosa*, which Mexican women have been using for centuries to prepare "tea" to induce menses and labor and to terminate early pregnancy.[1] Recent studies support the belief that zoapatanol and its metabolites might be responsible for the observed antifertility activity.[2] In 1979, the isolation and the structure of zoapatanol were described.[3] Due to its biological profile and its challenging structure, several groups have reported six total syntheses of zoapatanol,[4] but only one of these was enantioselective.[5] A number of groups have also described synthetic approaches.[6] Key issues for a successful synthesis of zoapatanol **1** are the stereocontrolled construction of the oxepane ring, the introduction of the (*E*)-exocyclic double bond, and the installation of the nonenyl side chain. Since (+)-zoapatanol is isolated as a 1/1 mixture of epimers at C6, control of this stereocenter is not required.[7]



1 R = $(CH_3)_2C{=}CHCH_2$- R' = H Zoapatanol
2 R = $(CH_3)_2CHC(CH_3){=}CH$- R' = H Montanol
3 R = $H_2C{=}C(CH_3)CH(CH_3)CH_2$- R' = H Tomentanol
4 R = $(CH_3)_2C(OH)CH{=}CH$- R' = Ac Tomentol

FIGURE 1. Oxepane derivatives isolated from *Montanoa tomentosa*.

We now report two synthetic approaches that have been realized to construct the oxepane ring of zoapatanol, utilizing a ring-closing metathesis (RCM) and an intramolecular Horner−Wadsworth−Emmons reaction (HWE), and we report also the total synthesis of (+)-zoapatanol.

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(6) (a) Davies, M. J.; Heslin, J. C.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2473. (b) Pain, G.; Desmaële, D.; d'Angelo, J. *Tetrahedron Lett.* **1994**, *35*, 3085. (c) Shing, T. K. M.; Wong, C.-H.; Yip, T. *Tetrahedron: Asymmetry* **1996**, *7*, 1323. (d) Ovaa, H.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **2001**, *42*, 5749.

(7) Either the epimerization occurred during isolation or purification of the natural product, or the natural zoapatanol itself is a mixture of epimers at C6. Kanijoa, R. M.; Wachter, M. P.; Levine, S. D.; Adams, R. E.; Chen, R.; Chin, E.; Cotter, M. L.; Hirsch, A. F.; Huetteman, R.; Kane, V. V.; Ostrowski, P.; Shaw, C. J. *J. Org. Chem.* **1982**, *47*, 1310.

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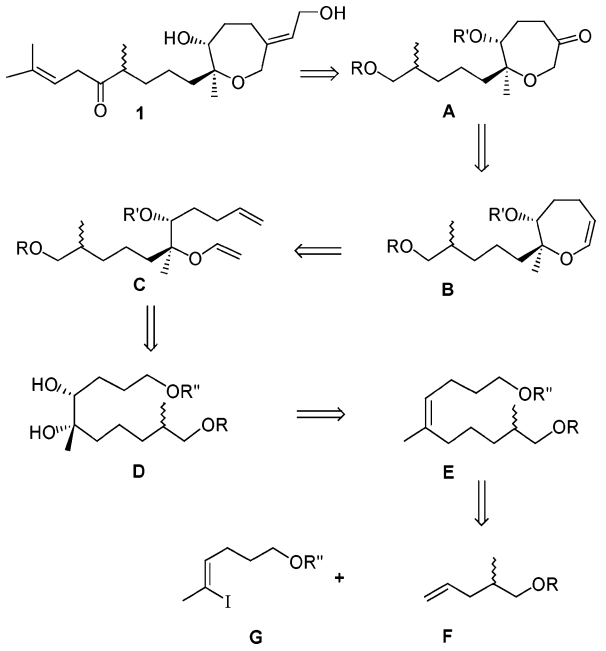
SCHEME 1. Retrosynthetic Analysis of Zoapatanol

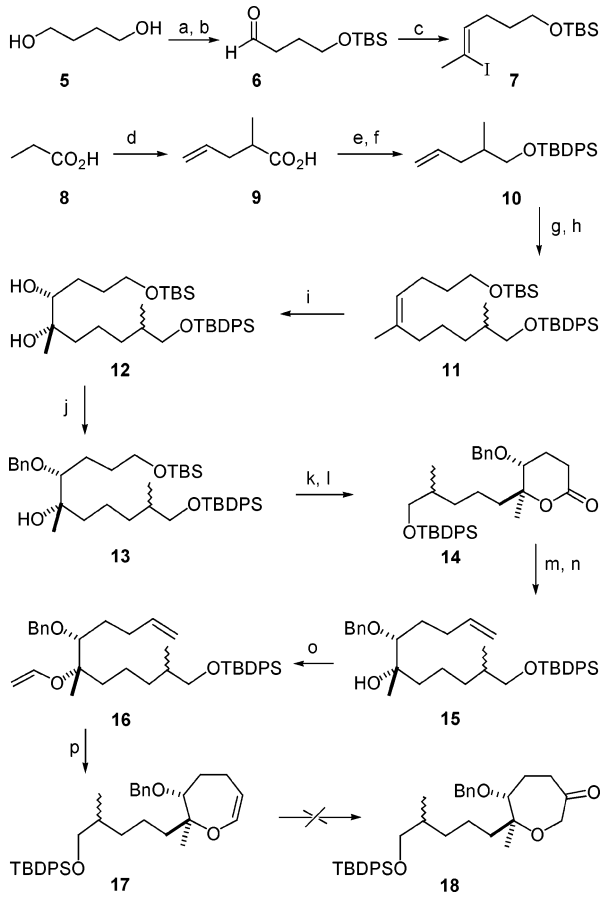


RCM Approach

The first strategy that we envisaged to synthesize zoapatanol relies on a RCM reaction. The retrosynthetic analysis revealed that an oxidation of oxepene **B** should lead to ketone **A**, which is a precursor of zoapatanol **1** according to Kane's synthesis.[4c] Oxepene **B** could potentially be obtained by using a RCM applied to the unsaturated enol ether **C** in which the two stereogenic centers could be controlled through application of a Sharpless asymmetric dihydroxylation of the trisubstituted (*Z*)-olefin **E**. This latter olefin could be synthesized by using a Suzuki−Miyaura cross-coupling between an organoborane derived from olefin **F** and (*Z*)-vinyl iodide **G** (Scheme 1). It was desirable to adopt an orthogonal protecting group strategy to permit a selective deprotection of the hydroxy groups. The use of two silylated ethers of different reactivity, a *tert*-butyldiphenylsilyl group (TBDPS) for R, a *tert*-butyldimethylsilyl group (TBS) for R″, and a benzyl group (Bn) for R′ was then envisaged. To test our strategy, a racemic synthetic approach toward zoapatanol was first achieved.

Results and Discussion. The synthesis of zoapatanol started with the preparation of the (*Z*)-olefin **11** from vinyl iodide **7** and olefin **10** (Scheme 2). Vinyl iodide **7** was prepared in 3 steps from 1,4-butanediol **5**. After monoprotection of **5** (TBSCl, Et_3N, CH_2Cl_2) the resulting monosilylated ether was oxidized to aldehyde **6** by using a Swern oxidation [$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2] with an overall yield of 94%. Aldehyde **6** was then transformed to the (*Z*)-vinyl iodide **7** in 47% yield by treatment with the α-iodophosphonium ylide prepared from ethyltriphenylphosphonium iodide (*n*-BuLi, then addition of I_2 and treatment with NaHMDS).[8] Furthermore, olefin **10** could be prepared in 3 steps from propionic acid **8**. Thus,

SCHEME 2. Synthetic Approach of (±)-Zoapatanol by Using RCM[a]



[a] Reagents and conditions: (a) TBSCl, Et_3N, CH_2Cl_2, 98%. (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 96%. (c) (i) $EtP(C_6H_5)_3I$, *n*-BuLi; I_2; NaHMDS; (ii) **6**, −20 °C to room temperature, 47%. (d) NaH (1 equiv), LDA (1 equiv), allylBr, 96%. (e) $LiAlH_4$, THF, rt, 94%. (f) TBDPSCl, imidazole, DMF, rt, 91%. (g) 9-BBN-H, THF, rt. (h) **7**, $Pd(PPh_3)_4$, K_3PO_4, dioxane, 85 °C, 82%. (i) OsO_4 cat., NMO, acetone/H_2O (1/6), rt, 61%. (j) NaH, *n*-Bu_4NI, HMPA/THF, BnBr, rt, 87%. (k) TBAF, THF, rt, 1 h. (l) PDC, DMF, rt. (m) DIBAL-H, THF, −78 °C. (n) $MeP(C_6H_5)_3Br$, *n*-BuLi, THF, −78 °C to room temperature, 68% (four steps). (o) Ethyl vinyl ether, $Hg(OCOCF_3)_2$, Et_3N, 50 °C, 47%. (p) $Cl_2(PCy_3)_2Ru$=CHPh (30 mol %), PhH, 50 °C, 70%.

the dianion of **8** was alkylated with allyl bromide (NaH, then LDA, allyl bromide) leading to 2-methylpent-4-enoic acid **9** in 96% yield.[9] The reduction of **9** by $LiAlH_4$ (THF, rt) followed by protection of the resulting alcohol (TBDPSCl, ImH, DMF, rt) led to the desired olefin **10** (86% yield, two steps). To achieve the Suzuki−Miyaura coupling, olefin **10** was transformed into the corresponding organoborane (9-BBN-H, THF) and this latter compound was treated with the (*Z*)-vinyl iodide **7** in the presence of a catalytic amount of $Pd(PPh_3)_4$ and K_3PO_4 in dioxane at 85 °C to afford (*Z*)-olefin **11** in 82% yield.[10] It is worth noting that the (*Z*)-configuration of **11** was determined by differential ^1H NMR-nOe experiments. To

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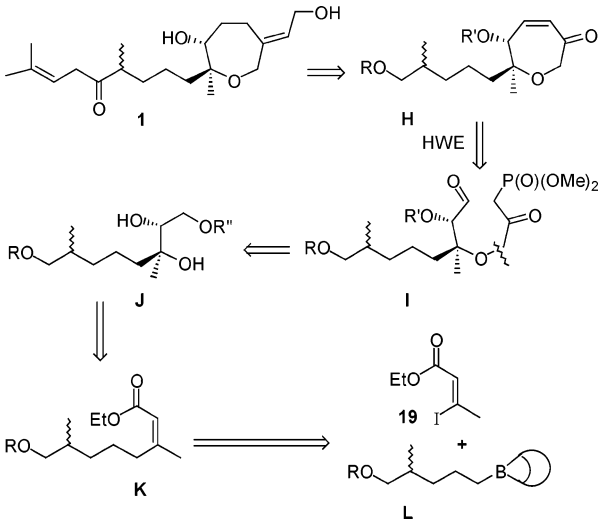
introduce the two contiguous hydroxy groups at C2′ and C3′, olefin **11** was dihydroxylated (OsO_4, NMO, acetone/H_2O (1/6), rt) to produce diol **12** in 61% yield, followed by transformation to benzyl ether **13**. The selective protection of the secondary alcohol in **12** as a benzyl ether turned out to be troublesome. Various bases (NaH, Cs_2CO_3, KHMDS, *t*-BuOK) and solvents (THF, DMF or mixtures of both) were screened. The desired benzylated product **13** was occasionally observed, but in most cases the results were not reproducible and decomposition occurred to a large extent. The best conditions for obtaining **13** in good yield were the treatment of **12** with NaH (2.2 equiv) in the presence of *n*-tetrabutylammonium iodide (40 mol %) and HMPA (3 equiv) followed by the addition of benzyl bromide (1.1 equiv). After 12 h at room temperature, compound **13** was isolated in 87% yield. To achieve the construction of the oxepene ring, compound **13** had to be transformed to diene **16**. After selective cleavage of the *tert*-butyl dimethylsilyl ether (TBAF, THF, rt, 1 h) and oxidation of the resulting primary alcohol by PDC (DMF, rt), lactone **14** was obtained in 84% yield (two steps). The reduction of **14** by DIBAL-H (THF, −78 °C) produced the corresponding lactol, which was treated directly with methyltriphenylphosphonium ylide ($MeP(C_6H_5)_3Br$, *n*-BuLi, THF) and transformed to olefin **15** (44% yield, two steps).[11] The tertiary alcohol of **15** was then etherified by treatment with $Hg(OCOCF_3)_2$ and ethyl vinyl ether (Et_3N, 50 °C)[12] to afford the desired diene **16** in 47% yield. Compound **16** was next converted to oxepene **17** in 70% yield by treatment with the "first generation" Grubbs' catalyst [$Cl_2(PCy_3)_2Ru$=CHPh (30 mol %), PhH, 50 °C].[13] The resulting oxepene **17**, in analogy to Kane's intermediate that had been transformed to an oxepanone by oxidative hydroboration (BH_3·THF; H_2O_2, NaOH) followed by oxidation (CrO_3, C_5H_5N, CH_2Cl_2), was expected to lead to **18**.[4c] Unfortunately, when **17** was subjected to BH_3·THF and then H_2O_2, NaOH, no reaction occurred. Moreover, when **17** was treated with various oxidizing agents (dimethyldioxirane or *m*-CPBA in MeOH) to produce a precursor of ketone **18**, only degradation or nonconversion of **17** was observed.

Due to this failure, a second route using a Horner−Wadsworth−Emmons (HWE) reaction was envisioned to construct the oxepane ring of zoapatanol.

Horner−Wadsworth−Emmons Approach

The retrosynthetic analysis of oxepinone **H** revealed that the oxepene ring with the required stereochemistry could potentially be constructed through application of

SCHEME 3. Second Retrosynthetic Analysis of Zoapatanol



an intramolecular HWE reaction applied to phosphonoaldehyde **I** derived from *anti*-diol **J** (Scheme 3). Control of the two contiguous stereocenters of **J** could be achieved by applying a Sharpless asymmetric dihydroxylation to the (*Z*)-trisubstituted olefin **K**, which could be derived from a Suzuki−Miyaura coupling between vinyl iodide **19** and organoborane **L**. In this approach, an orthogonal protecting group strategy for R, R′ was also required. Therefore we planned to protect the secondary alcohol in **I** by a benzyl group and the primary alcohol by a *tert*-butyldiphenylsilyl group.

Results and Discussion. The preparation of (+)-zoapatanol started with the synthesis of the phosphonoaldehyde **30** from silylated 2-methylpent-4-en-1-ol **10** and (*Z*)-vinyl iodide **19**, which was obtained by treatment of ethyl but-2-ynoic ester with NaI in acetic acid (70 °C, 95% yield).[14] Alkene **10** was treated with 9-BBN−H (9-BBN dimer, THF, rt) and the resulting organoborane product was then subjected to a Suzuki−Miyaura cross-coupling with (*Z*)-vinyl iodide **19** in the presence of Pd-(PPh_3)$_4$ and K_3PO_4 (dioxane, 85 °C) to afford the (*Z*)-α,*β*-unsaturated ester **20** in 74% yield.[10,15] To transform **20** to **22**, the unsaturated ester **20** was reduced with DIBAL-H and the resulting alcohol was treated with TBSCl (Et_3N, CH_2Cl_2) to afford **21** with an overall yield of 46%. After dihydroxylation with OsO_4/NMO, compound **21** was transformed to diol **22** (62%), in which the secondary alcohol was protected as a benzyl ether by treatment of **22** with NaH and benzyl bromide in the presence of *n*-Bu_4NI in a mixture of THF/HMPA. The product obtained in 98% yield appeared not to be the expected compound **23** but compound **24**, which resulted from the migration of the TBS group to the secondary alcohol and benzylation of the released primary alcohol. As the benzyl ether of **24** could not be selectively deprotected under hydrogenation conditions or by using BBr_3 or Li/NH_3(l), the sequence was slightly modified and the *syn*-dihydroxylation reaction was carried out on the α,*β*-unsaturated ester **20**. Thus, the enantioselective

(11) Compound **15** was isolated in an increased overall yield of 68% by performing the four consecutive steps from **13** without purification of intermediates.

(12) (a) Germanas, J.; Aubert, C.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1991**, *113*, 4006. (b) Nonoshita, K.; Banno, H.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 316. (c) Tulshian, D. P.; Tsang, R.; Fraser-Reid, B. *J. Org. Chem.* **1984**, *49*, 2347.

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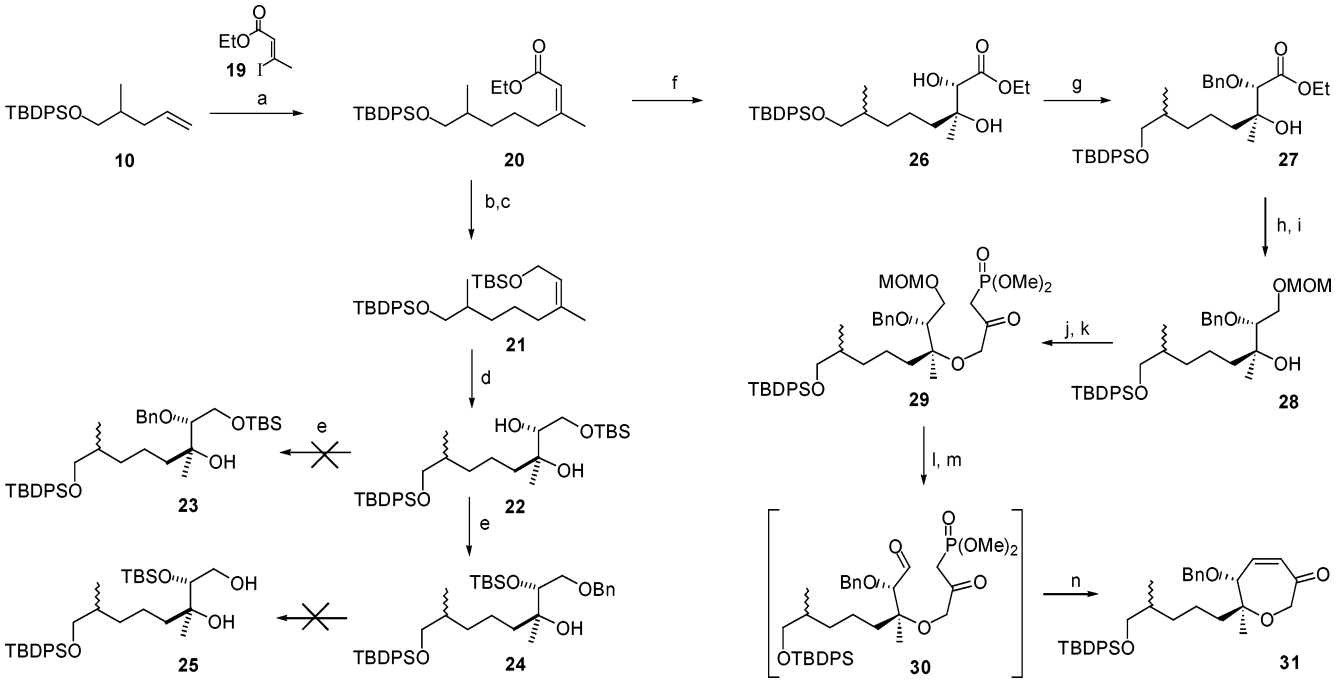
(15) (*Z*)-Configuration of the enoate **20** was confirmed by ^{1}H NMR-nOe analysis.

SCHEME 4. Synthesis of the Oxepinone 31[a]



[a] Reagents and conditions: (a) (i) 9-BBN dimer, THF, rt; (ii) **19**, $Pd(PPh_3)_4$, K_3PO_4, dioxane, 85 °C, 74%. (b) DIBAL-H, THF, −78 °C, 75%. (c) TBSCl, Et_3N, CH_2Cl_2, 61%. (d) OsO_4 cat., NMO, acetone/H_2O (1/6), rt, 62%. (e) BnBr, NaH, *n*-Bu_4NI, HMPA/THF, rt, 98%. (f) AD-mix-β, H_2NSO_2Me, *t*-BuOH/H_2O (1/1), 0 °C, 65%, ee 92%. (g) BnBr, Ag_2O, *n*-Bu_4NI, CH_2Cl_2, rt, 74%. (h) $LiAlH_4$, Et_2O, 0 °C to room temperature. (i) MOMCl, NaH, THF, 0 °C to room temperature, 89% (two steps). (j) N_2CHCO_2Et (10 equiv), $[Rh(OAc)_2]_2$ (10 mol %), toluene, 110 °C. (k) $MeP(O)(OMe)_2$ (10 equiv), *n*-BuLi (10 equiv), THF, −78 °C, 60% (two steps). (l) TMSBr, CH_2Cl_2, −40 °C, 84%. (m) PDC, 4 Å MS, CH_2Cl_2, 20 °C. (n) NaH, THF, 0 °C to room temperature, 53% (two steps).

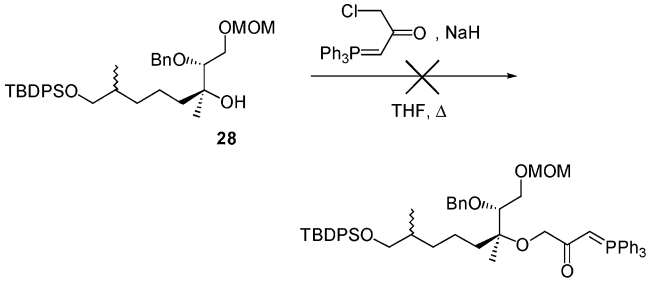
Sharpless dihydroxylation (AD-mix-β, H_2NSO_2Me, *t*-BuOH/H_2O (1/1), 0 °C) afforded the diol **26** in 65% yield and 92% ee as determined by ^1H NMR spectroscopy of the corresponding (*R*)- and (*S*)-methoxyphenylacetic esters.[16] Construction of the phosphono-aldehyde **30** was now investigated from **26**. The selective protection of the secondary alcohol in **26** as a benzyl ether turned out to be a difficult task. Among the reagents tested, benzyl bromide in the presence of silver oxide and *n*-tetrabutylammonium iodide was the most effective and afforded the desired product **27** in 74% yield.[17] After reduction of the carboxylic ester with $LiAlH_4$ in diethyl ether, the resulting primary hydroxyl group was protected as a methoxymethyl ether (MOMCl, NaH, THF, 0 °C to rt) to provide **28** (89%, two steps).[18] Rhodium-catalyzed insertion of ethyl diazoacetate (excess N_2CHCO_2Et, 10 mol % $[Rh(OAc)_2]_2$, toluene, 110 °C)[20] followed by the condensation of an excess of the lithium salt of methyldimethylphosphonate (10 equiv) with the resulting ester led to the β-keto-phosphonate **29** in 60% overall yield (two steps).[21] As an intramolecular Horner−Wadsworth−Emmons reaction was envisioned to construct the oxepane ring of zoapatanol, the methoxymethyl ether group had to be transformed into an aldehyde. Thus, after removal of the methoxymethyl ether protecting group with TMSBr, the corresponding hydroxy-phosphonate was obtained (84%)[22] and the oxidation of the primary alcohol was conveniently accomplished with PDC. The resulting crude aldehyde **30**, which turned out to be unstable, was subjected directly to treatment with NaH in THF to afford oxepinone **31** in 53% overall yield via an intramolecular Horner−Wadsworth−Emmons cyclization (Scheme 4).[23]

The conversion of oxepinone **31** to (+)-zoapatanol was envisioned to proceed via the oxepane **33** (Scheme 5) and involve several functional group transformations, namely the reduction of the α,β-unsaturated ketone to the corresponding ketone, a Wittig reaction to introduce the

(16) The (2*S*,3*S*) absolute configuration of **21** was confirmed by the ^1H NMR spectra of the two corresponding mandelates, following the procedure described by: Seco, J. M.; Quiñoa, E.; Riguera, R. *Tetrahedron*: *Asymmetry* **2001**, *12*, 2915.

(17) Bouzide, A.; Sauvé, G. *Tetrahedron Lett.* **1997**, *38*, 5945.

(18) It is worth noting that direct alkylation of the tertiary alcohol of compound **28** with triphenylchloroacetonylphosphorane, following a method previously described,[19] failed to produce the expected β-keto phosphorane:



(19) Cossy, J.; Taillier, C.; Bellosta, V. *Tetrahedron Lett.* **2002**, *43*, 7263−7266.

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(22) Hu, X. E.; Demuth, T. P., Jr. *J. Org. Chem.* **1998**, *63*, 1719.

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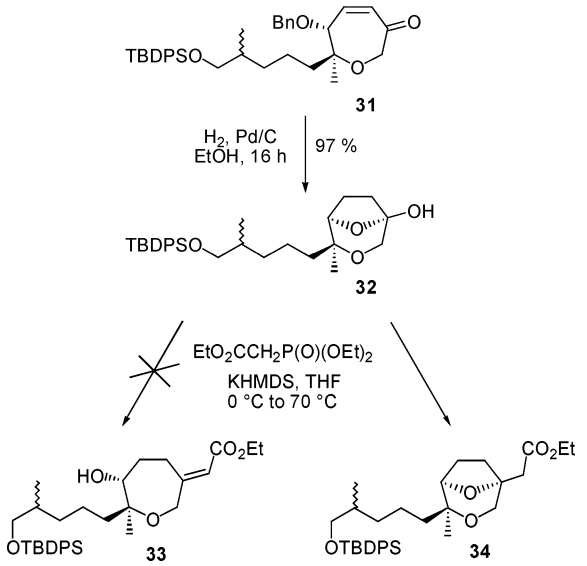
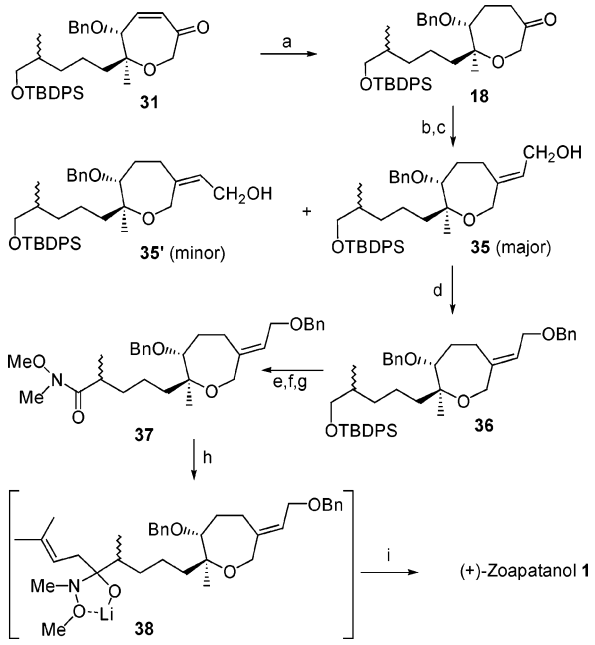
SCHEME 5. Debenzylation of 31 and Reactivity of the Resulting Lactol 32



unsaturated side chain, and finally the deprotection of the benzyl protected hydroxy group. When the hydrogenation of oxepinone **31** was performed in the presence of Pd/C (10%) in ethanol for 16 h, the bicyclic lactol **32** was obtained in good yield (97%). Unfortunately, all the conditions tested to accomplish a Wittig reaction, a HWE reaction, or a Peterson reaction on lactol **32** failed to produce compound **33**. Under the best conditions [$EtO_2CCH_2P(O)(OEt)_2$, KHMDS, THF, 0 °C to 70 °C], compound **34**, resulting from a HWE reaction followed by an intramolecular 1,4-addition of the alkoxide onto the unsaturated ester, was formed in 60% yield.

However, when the hydrogenation of **31** was performed in the presence of Pd/C (10%) in ethanol for 5 min, the benzyl protecting group was not affected and oxepanone **18** was isolated in 98% yield (Scheme 6).[24] The resulting oxepanone **18** was then treated with the lithium salt of triethylphosphonoacetate [$EtO_2CCH_2P(O)(OEt)_2$, LiHMDS, THF, rt] to generate the corresponding α,β-unsaturated esters (97%) as an inseparable mixture of *E*/*Z* isomers (*E*/*Z* = 70/30 ratio by ^{1}H NMR spectroscopy).[23a,25] After reduction with $LiAlH_4$, the corresponding stereoisomeric allylic alcohols **35** and **35′** were separated by SiO_2 flash chromatography, and the desired (*E*)-allylic alcohol **35**[26] was obtained in 63% overall yield (from **18**). This latter compound was then protected as a benzyl ether (BnBr, Ag_2O, *n*-Bu_4NI, CH_2Cl_2) in 98% yield. Elaboration of the nonenyl side chain present in (+)-zoapatanol required the conversion of **36** to the corresponding Weinreb amide **37**. This transformation seemed feasible, as we have recently demonstrated that a stable tetrahedral intermediate resulting from the addition of an organolithium to a Weinreb amide can serve as a carbonyl protecting group during the debenzylation of hydroxy groups under Birch reduction conditions.[27] After removal of the silyl protecting group of **36**, the resulting primary hydroxy group was oxidized to the corresponding carboxylic acid (Jones reagent, acetone, 0 °C) and the latter was directly converted to the Weinreb amide **37** [HN(OMe)Me·HCl, EDCI, *i*-Pr_2NEt, DMAP cat., CH_2Cl_2, rt] with an overall yield of 60% (three steps).[28] Treatment of amide **37** with prenyllithium[29]

SCHEME 6. Total Synthesis of (+)-Zoapatanol[a]



[a] Reagents and conditions: (a) H_2, Pd/C (10%), EtOH, 5 min, 98%. (b) $EtO_2CCH_2P(O)(OEt)_2$ (10 equiv), LiHMDS, THF, rt, 97%, *E*/*Z* = 70/30. (c) $LiAlH_4$, Et_2O, 0 °C to room temperature; flash chromatography, (*E*)-isomer: 63%, (*Z*)-isomer: 27% from **18** (two steps). (d) BnBr, Ag_2O, *n*-Bu_4NI, CH_2Cl_2, rt, 98%. (e) *n*-Bu_4NF, THF, rt. (f) CrO_3/H_2SO_4, acetone, 0 °C. (g) HN(OMe)Me·HCl, EDCI, *i*-Pr_2NEt, DMAP cat., CH_2Cl_2, 0 °C to room temperature, 60% (three steps). (h) Prenyllithium, Et_2O/THF (1:1), −78 °C. (i) Li/NH_3(l), *t*-BuOH (20 equiv), THF, −78 °C, 66%.

(THF/Et_2O, −78 °C) led to the stable intermediate **38**, which was directly subjected to Birch reduction conditions[30] (Li/NH_3(l), *t*-BuOH/THF, −78 °C) to afford the desired (+)-zoapatanol in 66% yield. The analytical and spectral data were in agreement with those previously reported in the literature for (+)-zoapatanol (Scheme 6).[3,4]

In summary, two approaches to zoapatanol have been carried out: one involving a ring-closing metathesis reaction of an unsaturated vinyl ether, which produced an advanced oxepene intermediate for the synthesis of zoapatanol, and a second approach which led to (+)-zoapatanol and involved a Sharpless asymmetric dihydroxylation to control the contiguous stereocenters. Furthermore, an intramolecular Horner−Wadsworth−Emmons cyclization was used to construct the oxepane core, and an organolithium addition/Birch reduction sequence was applied on a Weinreb amide to introduce the ketone at C5 of zoapatanol. By using this methodology, the synthesis of structurally related analogues of zoapatanol might be easily realized.

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Experimental Section

4-(*tert*-Butyldimethylsilanyloxy)butanal (6). To a solution of oxalyl chloride (2.1 mL, 24 mmol, 1.2 equiv) in CH_2Cl_2 (30 mL) cooled at −78 °C was added dropwise a solution of DMSO (3.3 mL, 21 mmol, 1.1 equiv) in CH_2Cl_2 (32 mL). After 5 min, a solution of 4-(*tert*-butyldimethylsilanyloxy)butan-1-ol[31] (4.0 g, 20 mmol, 1.0 equiv) in CH_2Cl_2 (26 mL) was added. The reaction mixture was then stirred for 15 min at −78 °C and triethylamine (14.0 mL, 100 mmol, 5.00 equiv) was added in one portion. After 10 min at −78 °C, the mixture was allowed to warm to room temperature and diluted with CH_2Cl_2 (140 mL). The organic layer was successively washed with a saturated aqueous solution of NH_4Cl (30 mL) and brine (2 × 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/EtOAc: 90/10) afforded 3.88 g (96%) of aldehyde **6**[32] as a colorless oil. IR (film) 2720, 1730, 1260, 1100, 840, 780 cm^{-1}; ^1H NMR δ 9.78 (t, J = 1.8 Hz, 1H), 3.65 (t, J = 5.9 Hz, 2H), 2.50 (td, J = 7.2 and 1.8 Hz, 2H), 1.85 (m, 2H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR δ 202.4 (d), 61.9 (t), 40.6 (t), 25.8 (q, 3C), 25.3 (t), 18.1 (s), −5.6 (q, 2C); MS-EI *m/z* (rel intensity) 201 (M − H^+, 1), 187 (M − CH_3^+, 1), 145 (67), 127 (10), 115 (12), 75 (100), 73 (12), 59 (11); HRMS (CI^+, CH_4) calcd for $C_{10}H_{21}O_2Si$ (M − H) 201.1311, found 201.1325.

6-(*tert*-Butyldimethylsilanyloxy)-2-iodohex-2-ene (7). To a suspension of ethyltriphenylphosphonium iodide (0.80 g, 2.0 mmol, 1.2 equiv) in THF (10 mL) was added a solution of *n*-BuLi (0.80 mL, 2.5 mol·L^{-1} in hexanes, 2.0 mmol, 1.2 equiv) at room temperature. After complete dissolution, the orange solution was added via cannula to a solution of iodine (0.46 g, 1.8 mmol, 1.1 equiv) in THF (15 mL) cooled to −78 °C. After 5 min of stirring at −78 °C, the suspension was warmed to −20 °C and a solution of NaHMDS (0.90 mL, 2 mol·L^{-1} in THF, 1.8 mmol, 1.1 equiv) was added dropwise. The resulting red solution was then stirred for 5 min at −20 °C and aldehyde **6** (0.34 g, 1.70 mmol, 1.00 equiv) was added neat. The reaction mixture was then warmed to room temperature and diluted with diethyl ether (50 mL) and washed successively with a saturated aqueous solution of NH_4Cl (20 mL) and brine (2 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/EtOAc: 98/02) next afforded 272 mg (47%) of vinyl iodide **7** as a pale yellow oil. IR (film) 1255, 1100, 835, 775 cm^{-1}; ^1H NMR δ 5.42 (tq, J = 6.6 and 1.5 Hz, 1H), 3.61 (t, J = 6.4 Hz, 2H), 2.47 (br s, 3H), 2.17−2.07 (m, 2H), 1.65−1.53 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR δ 134.9 (d), 100.9 (s), 62.4 (t), 33.4 (q), 33.1 (t), 31.4 (t), 25.8 (q, 3C), 18.1 (s), −5.4 (q, 2C); MS-EI *m/z* (rel intensity) 339 (M − H^+, 1), 325 (M − CH_3^+, 1), 283 (M − *t*-Bu^+, 100), 255 (52), 215 (39), 185 (40), 155 (21), 81 (28), 75 (25); HRMS (CI^+, CH_4) calcd for $C_8H_{16}IOSi$ (M − *t*-Bu) 283.00152, found 283.00155.

2-Methylpent-4-enoic Acid (9).[33] Propionic acid (0.70 g, 10 mmol, 1.0 equiv) was added to a mixture of NaH (0.40 g, 60% in oil, 11 mmol, 1.1 equiv) and diisopropylamine (1.5 mL, 11 mmol, 1.1 equiv) in THF (12 mL) at room temperature. After 10 min of heating at reflux, the solution was cooled to a temperature between 0 and 10 °C and a solution of *n*-BuLi (4.4 mL, 2.5 mol·L^{-1} in hexanes, 11 mmol, 1.1 equiv) was added slowly. The mixture was briefly heated to reflux to complete the metalation and was then cooled to 0 °C. Allyl bromide (0.90 mL, 10 mmol, 1.0 equiv) was added and the mixture was warmed to 30 °C. After 2 h, an aqueous solution of HCl (1 mol·L^{-1}) was added to the reaction mixture at 0 °C (until pH <4). The aqueous layer was extracted with diethyl ether (2 × 20 mL) and the combined organic extracts were washed with brine (2 × 10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/EtOAc gradient 95/05 to 80/20) afforded 1.09 g (96%) of acid **9** as a colorless oil. IR (film) 3440, 1720, 1640 cm^{-1}; ^1H NMR δ 11.3 (br s, 1H), 5.75 (m, 1H), 5.10−4.85 (m, 2H), 2.61−2.32 (m, 2H), 2.25−2.12 (m, 1H), 1.17 (d, J = 7.0 Hz, 3H); ^{13}C NMR δ 182.5 (s), 134.9 (d), 116.9 (t), 39.0 (d), 37.3 (t), 16.1 (q); MS-EI *m/z* (rel intensity) 114 ($M^{+\bullet}$, 15), 99 (M − CH_3^+, 27), 73 (12), 71 (13), 69 (M − $COOH^+$, 100), 68 (23), 67 (27), 56 (18).

***tert*-Butyl(2-methylpent-4-enyloxy)diphenylsilane (10).** To a stirred suspension of $LiAlH_4$ (1.9 g, 50 mmol, 1.0 equiv) in anhydrous THF (100 mL) was slowly added a solution of 2-methylpent-4-enoic acid **9** (5.7 g, 50 mmol, 1.0 equiv) in THF (10 mL). After 16 h at room temperature, the reaction mixture was cooled to 0 °C and cautiously treated with water (1.9 mL), then with a 15% aqueous solution of NaOH (1.9 mL), and then with water (5.7 mL). After 1 h of stirring at room temperature, the resulting suspension was filtered through Celite. The insoluble salts were washed with diethyl ether (2 × 20 mL) and the filtrate was dried over $MgSO_4$. Filtration and concentration under reduced pressure gave 4.7 g (94%) of 2-methylpent-4-en-1-ol, which was directly engaged in the next step without further purification.

To a solution of 2-methylpent-4-en-1-ol (1.0 g, 10 mmol, 1.0 equiv) in DMF (10 mL) were added imidazole (1.7 g, 25 mmol, 2.5 equiv) and *tert*-butyldiphenylsilyl chloride (2.6 mL, 10 mmol, 1.0 equiv). After 12 h at room temperature, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl (5 mL). The aqueous layer was extracted with diethyl ether (2 × 20 mL) and the combined organic extracts were washed with water (2 × 10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was then purified by flash chromatography on silica gel (petroleum ether/EtOAc: 95/05) to give 3.06 g (91%) of alkene **10** as a colorless oil. IR (film) 1640, 1590, 1430, 1110, 710, 700 cm^{-1}; ^1H NMR δ 7.77−7.68 (m, 4H), 7.48−7.38 (m, 6H), 5.81 (m, 1H), 5.10−4.97 (m, 2H), 3.56 (br d, J = 6.3 Hz, 2H), 2.31 (m, 1H), 1.96 (m, 1H), 1.80 (m, 1H), 1.12 (s, 9H), 0.97 (d, J = 6.6 Hz, 3H); ^{13}C NMR δ 137.2 (d), 135.5 (d, 4C), 133.9 (s, 2C), 129.4 (d, 2C), 127.5 (d, 4C), 115.6 (t), 68.3 (t), 37.5 (t), 35.6 (d), 26.8 (q, 3C), 19.2 (s), 16.3 (q); MS-EI *m/z* (rel intensity) 281 (M − *t*-Bu^+, 58), 225 (11), 203 (19), 200 (19), 199 (100), 183 (23), 181 (18), 135 (14), 123 (15), 105 (14), 77 (17); HRMS (CI^+, CH_4) calcd for $C_{22}H_{31}OSi$ (M + H^+) 339.2144, found 339.2146.

(*Z*)-1-(*tert*-Butyldimethylsilanyloxy)-10-(*tert*-butyldiphenylsilanyloxy)-5,9-dimethyldec-4-ene (11). To *tert*-butyl(2-methylpent-4-enyloxy)diphenylsilane **10** (1.6 g, 4.6 mmol, 1.1 equiv) at 0 °C was added dropwise a solution of 9-BBN-H (10 mL, 0.5 M in THF, 5.0 mmol, 1.2 equiv). The solution was stirred at 0 °C until complete conversion of the starting alkene (approximatively 2 h, followed by TLC). Besides, a suspension of K_3PO_4 (1.4 g, 6.3 mmol, 1.5 equiv) and iodide **7** (1.4 g, 4.2 mmol, 1.0 equiv) in freshly distilled dioxane (12.5 mL) was degassed 30 min by argon bubbling. The solution of borane and $Pd(PPh_3)_4$ (0.12 g, 0.10 mmol, 0.025 equiv) were then added to the iodide solution and the reaction mixture was heated for 5 h at 85 °C. After cooling to room temperature, the unreacted borane was oxidized by addition of an aqueous solution of sodium acetate (0.8 mL, 3 mol·L^{-1}) and hydrogen peroxide (30%, 0.8 mL). After 1 h of stirring at room temperature, the red solution was diluted with diethyl ether (40 mL) and washed with a saturated aqueous solution of NH_4Cl (20 mL) and brine (2 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (Hexane/Et_2O gradient 100/0 to 98/02) to give 1.90 g (82%) of (*Z*)-alkene **11** as a colorless oil. IR (film) 1640, 1470, 1460, 1430, 1260, 1100, 870, 710, 700 cm^{-1}; ^1H NMR δ 7.75−

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7.67 (m, 4H), 7.48−7.37 (m, 6H), 5.16 (br t, J = 6.6 Hz, 1H), 3.64 (t, J = 6.6 Hz, 2H), 3.56 (dd, $J_{syst\ AB}$ = 9.9 Hz, J = 5.7 Hz, 1H), 3.49 (dd, $J_{syst\ AB}$ = 9.9 Hz, J = 6.2 Hz, 1H), 2.11−1.98 (m, 4H), 1.70 (br s, 3H), 1.65−1.18 (m, 7H), 1.10 (s, 9H), 0.96 (d, J = 6.6 Hz, 3H), 0.93 (s, 9H), 0.08 (s, 6H); ^{13}C NMR δ 135.6 (s), 135.5 (d, 4C), 134.0 (s, 2C), 129.3 (d, 2C), 127.4 (d, 4C), 124.5 (d), 68.8 (t), 62.7 (t), 35.6 (d), 33.2 (t), 33.0 (t), 31.9 (t), 26.8 (q, 3C), 25.9 (q, 3C), 25.3 (t), 24.0 (t), 23.3 (q), 19.2 (s), 18.2 (s), 16.8 (q), −5.4 (q, 2C); MS-EI *m/z* (rel intensity) 552 ($M^{+\bullet}$, 1), 495 (M − *t*-Bu^+, 2), 363 (19), 313 (20), 271 (18), 253 (43), 199 (100), 197 (35), 165 (30), 137 (30), 135 (33), 109 (92), 95 (86), 81 (84); HRMS (CI^+, CH_4) calcd for $C_{34}H_{57}O_2Si_2$ (M + H^+) 553.3897, found 553.3914.

(4*R,5*S**)-1-(*tert*-Butyldimethylsilanyloxy)-10-(*tert*-butyldiphenylsilanyloxy)-5,9-dimethyldecane-4,5-diol (12).** To a mixture of water (1 mL), acetone (6 mL), and NMO (0.107 g, 0.90 mmol, 1 equiv), at 0 °C, was added OsO_4 (0.563 mL, 2.5% in *t*-BuOH, 0.045 mmol, 0.05 equiv). A solution of alkene **11** (0.50 g, 0.90 mmol, 1.0 equiv) in acetone (2.5 mL) was then added dropwise at 0 °C. After 30 min, the reaction mixture was stirred for 12 h at room temperature. The reaction was stopped by addition of a mixture of water (2.5 mL), florisil (605 mg), and $Na_2S_2O_3{\cdot}5H_2O$ (160 mg). After 30 min of stirring, the mixture was filtered and the solvent was evaporated under reduced pressure. The aqueous residue was then diluted with brine (7.5 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (petroleum ether/EtOAc: 85/15) afforded 322 mg (61%) of diol **12** as a colorless oil. IR (film) 3410, 1640, 1470, 1430, 1260, 1110, 870 cm^{-1}; ^{1}H NMR δ 7.71−7.64 (m, 4H), 7.44−7.34 (m, 6H), 3.79−3.62 (m, 2H), 3.56−3.36 (m, 3H), 1.80−1.65 (m, 4H), 1.65−1.20 (m, 8H), 1.15 (m, 1H), 1.15 (s, 3H), 1.06 (s, 9H), 0.94 (d, J = 7.3 Hz, 3H), 0.92 (s, 9H), 0.09 (s, 6H); ^{13}C NMR δ 135.5 (d, 4C), 134.0 (s, 2C), 129.3 (d, 2C), 127.4 (d, 4C), 78.0 (d), 74.3 (s), 68.8 (t), 63.4 (t), 36.4 (t), 35.6 (d), 33.8 (t), 29.8 (t), 26.6 (t), 26.8 (q, 3C), 25.8 (q, 3C), 23.3 (q), 20.6 (t), 19.2 (s), 18.2 (s), 16.8 (q), −5.5 (q, 2C); MS-EI *m/z* (rel intensity) 511 (M − H_2O − *t*-Bu^+, 12), 397 (11), 379 (12), 305 (12), 199 (100), 181 (20), 163 (36), 135 (22), 105 (21). Anal. Calcd for $C_{34}H_{58}O_4Si_2$: C, 69.57; H, 9.96. Found: C, 69.39; H, 9.95.

(4*R,5*S**)-4-Benzyloxy-1-(*tert*-butyldimethylsilanyloxy)-10-(*tert*-butyldiphenylsilanyloxy)-5,9-dimethyldecan-5-ol (13).** To a suspension of NaH (45 mg, 60% in oil, 1.1 mmol, 2.2 equiv) in THF (2 mL) at 0 °C was added a solution of diol **12** (0.30 g, 0.5 mmol, 1.0 equiv) and HMPA (0.27 mL, 1.5 mmol, 3.0 equiv) in THF (1 mL). After 30 min at 0 °C, the solution was stirred for 1 h at room temperature. The reaction mixture was cooled at 0 °C and benzyl bromide (73 μL, 0.61 mmol, 1.2 equiv) and *n*-Bu_4NI (75 mg, 0.20 mmol, 0.4 equiv) were added. After 20 h at room temperature, the reaction mixture was diluted with diethyl ether (10 mL) and then poured into a saturated aqueous solution of NH_4Cl (5 mL). The aqueous layer was extracted with diethyl ether (3 × 10 mL) and the combined organic extracts were washed with water (2 × 5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/Et_2O: 95/05) to give 294 mg (87%) of benzyl ether **13** as a colorless oil. IR (film) 3450, 1580, 1470, 1425, 1255, 1100, 830, 710, 700 cm^{-1}; ^{1}H NMR δ 7.72−7.65 (m, 4H), 7.46−7.28 (m, 11H), 4.73 (d syst AB, J = 11.2 Hz, 1H), 4.60 (d syst AB, J = 11.2 Hz, 1H), 3.73−3.58 (m, 2H), 3.57−3.42 (m, 2H), 3.29 (br dd, J = 7.7 and 2.9 Hz, 1H), 2.20−1.10 (m, 12H), 1.18 (s, 3H), 1.07 (s, 9H), 0.94 (d, J = 7.5 Hz, 3H), 0.91 (s, 9H), 0.07 (s, 6H); ^{13}C NMR δ 138.5 (s), 135.5 (d, 4C), 134.0 (s, 2C), 129.3 (d, 2C), 128.3 (d, 2C), 127.5 (d, 2C), 127.5 (d), 127.4 (d, 4C), 86.7 (d), 75.0 (s), 74.5 (t), 68.8 (t), 63.1(t), 37.3 (t), 35.6 (d), 33.8 (t), 30.2 (t), 26.9 (t), 26.8 (q, 3C), 25.8 (q, 3C), 23.7 (q, C), 20.6 (t), 19.2 (s), 18.2 (s), 16.7 (q), −5.4 (q, 2C).

(5*R,6*S**)-5-Benzyloxy-6-[5-(*tert*-butyldiphenylsilanyloxy)-4-methylpentyl]-6-methyltetrahydro-2*H*-pyran-2-one (14).** A TBAF solution (1.2 mL, 1 mol·L^{-1} in THF, 1.2 mmol, 1 equiv) was added to a solution of **13** (0.78 g, 1.20 mmol, 1.0 equiv) in THF (30 mL). After 1 h at room temperature, the reaction mixture was diluted with diethyl ether (60 mL) and washed with brine (2 × 30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 672 mg (100%) of crude (4*R**,5*S**)-4-benzyloxy-10-(*tert*-butyldiphenylsilanyloxy)-5,9-dimethyldecane-1,5-diol as a colorless oil, which was engaged in the next step without further purification.

The crude intermediate diol (0.6 g, 1 mmol, 1 equiv) was dissolved in DMF (2 mL) and the resulting solution was added to a stirred solution of PDC (1.3 g, 3.5 mmol, 3.5 equiv) in DMF (6 mL), at 0 °C. After 30 min, diethyl ether (30 mL) was added and the mixture was filtered through florisil. The filtrate was then washed with water (3 × 5 mL) and brine (10 mL). The combined extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 0.56 g (100%) of lactone **14** as a colorless oil, which was engaged in the next step without further purification. An analytical sample was obtained after purification by flash chromatography (petroleum ether/EtOAc: 90/10). IR (film) 1730, 1590, 1425, 1105, 710, 700 cm^{-1}; ^{1}H NMR δ 7.72−7.65 (m, 4H), 7.45−7.28 (m, 11H), 4.68 (d syst AB, J = 11.8 Hz, 1H), 4.49 (d syst AB, J = 11.8 Hz, 1H), 3.58−3.40 (m, 3H), 2.71 (dt, $J_{syst\ AB}$ = 18.4, J = 7.5 Hz, 1H), 2.49 (dt, $J_{syst\ AB}$= 18.4 Hz, J = 6.6 Hz, 1H), 2.10−1.98 (m, 2H), 1.76−1.50 (m, 3H), 1.45−1.00 (m, 4H), 1.40 (s, 3H), 1.08 (s, 9H), 0.92 (d, J = 6.3 Hz, 3H); ^{13}C NMR δ 170.4 (s), 137.6 (s), 135.5 (d, 4C), 133.9 (s, 2C), 129.4 (d, 2C), 128.3 (d, 2C), 127.8 (d), 127.5 (d, 6C), 85.7 (s), 74.1 (d), 71.1 (t), 68.7 (t), 40.3 (t), 35.5 (d), 33.3 (t), 26.8 (q, 3C), 26.0 (t), 21.4 (q), 20.6 (t), 20.3 (t), 19.2 (s), 16.7 (q); MS-EI *m/z* (rel intensity) 393 (7), 315 (28), 199 (54), 181 (10), 139 (14) 135 (18), 91 (100), 85 (16). Anal. Calcd for $C_{35}H_{46}O_4Si$: C, 75.23; H, 8.30. Found: C, 75.49; H, 8.24.

(4*R,5*S**)-5-Benzyloxy-10-(*tert*-butyldiphenylsilanyloxy)-6-methylundec-1-en-6-ol (15).** To a solution of lactone **14** (0.52 g, 0.92 mmol, 1 equiv) in anhydrous ether (4 mL), at −78 °C, was slowly added a solution of diisobutylaluminum hydride (0.92 mL, 1 M in hexanes, 0.92 mmol, 1 equiv). After 1 h at −78 °C, the reaction mixture was diluted with diethyl ether (20 mL) and poured into a saturated aqueous solution of Rochelle's salt (20 mL). After the mixture was stirred for 1 h at room temperature, the organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 40 mL). The combined organic extracts were washed with a saturated aqueous solution of Rochelle's salt (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 516 mg of crude lactol as a colorless oil. The crude material was directly engaged in the next step without further purification.

To a suspension of methyltriphenylphosphonium bromide (0.56 g, 1.60 mmol, 2 equiv) in anhydrous THF (8 mL) at room temperature was added dropwise a solution of *n*-BuLi (0.64 mL, 2.5 M in hexanes, 1.60 mmol, 2 equiv). The ylide solution was next added via cannula to a solution of crude lactol (0.44 g, 0.80 mmol) in anhydrous THF (4 mL), at −78 °C. After 20 min at −78 °C, the mixture was warmed to room temperature over 1 h and the stirring was continued for 1 h at room temperature. The reaction mixture was then poured into a saturated aqueous solution of NH_4Cl (20 mL) and the aqueous layer was extracted with diethyl ether (3 × 40 mL). The combined extracts were successively washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/E.E.: 80/20) to give 304 mg (68%, four steps) of alkene **15** as a colorless oil. IR (film) 3400, 1640, 1460, 1425, 1105, 910 cm^{-1}; ^{1}H NMR δ 7.75−7.69 (m, 4H), 7.50−7.30 (m, 11H), 5.89 (ddt, J = 17.3, 10.3, and 7.0 Hz, 1H), 5.15−5.02 (m, 2H), 4.76 (d syst AB, J = 11.4 Hz, 1H), 4.65 (d syst AB, J = 11.4 Hz, 1H), 3.61−3.45 (m, 2H), 3.33 (dd, J = 7.4 and 4.8 Hz, 1H),

2.39 (m, 1H), 2.29−2.10 (m, 2H), 1.82−1.25 (m, 9H), 1.22 (s, 3H), 1.11 (s, 9H), 0.99 (d, J = 6.3 Hz, 3H); ^{13}C NMR δ 138.5 (s), 138.5 (d), 135.5 (d, 4C), 134.0 (s, 2C), 129.4 (d, 3C), 128.4 (d, 3C), 127.6 (d), 127.5 (d, 4C), 114.8 (t), 86.1 (d), 75.1 (s), 74.8 (t), 68.8 and 68.7 (t), 37.3 (t), 35.7 and 35.6 (d), 33.8 (t), 31.0 (t), 30.0 (t), 26.8 (q, 3C), 23.7 (q), 20.7 (t), 20.6 (s), 16.8 (q); MS-EI *m/z* (rel intensity) 501 (M − *t*-Bu$^+$,1), 483 (M − *t*-Bu − H_2O^+,1), 393 (9), 305 (31), 200 (15), 199 (79), 197 (12), 183 (11), 181 (11), 177 (19), 139 (23), 135 (22), 127 (10), 121 (13), 109 (29), 95 (18), 91 (100), 81 (12); HRMS (CI$^+$, NH_3) calcd for $C_{36}H_{54}O_3NSi$ (M + NH_4^+) 576.3873, found 576.3860; HRMS (CI$^+$, CH_4) calcd for $C_{36}H_{51}O_3Si$ (M + H^+) 559.3607, found 559.3596.

(6*S,7*R**)-(7-Benzyloxy-2,6-dimethyl-6-vinyloxy)undec-10-enyloxy-*tert*-butyldiphenylsilane (16).** In a tube fitted with a screw-cap was placed a solution of alcohol **15** (600 mg, 1.07 mmol, 1 equiv) in ethyl vinyl ether (5 mL). Triethylamine (150 μL, 1.07 mmol, 1 equiv) and mercuric trifluoroacetate (573 mg, 1.34 mmol, 1.25 equiv) were successively added and the reaction mixture was heated to 50 °C. After 2.5 h, the reaction mixture was hydrolyzed at room temperature with a saturated aqueous solution of $NaHCO_3$ (5 mL). The biphasic mixture was stirred 20 min at room temperature and the aqueous layer was extracted with diethyl ether (3 × 15 mL). The combined organic extracts were washed with water and with a saturated aqueous solution of $NaHCO_3$ (3 × 10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/Et_2O, gradient 98/02 to 90/10) afforded 298 mg (47%) of diene **16**, as a colorless oil, and 209 mg (35%) of unreacted alcohol **15**. IR (film) 1630, 1460, 1425, 1390, 1165, 1110 cm^{-1}; ^{1}H NMR δ 7.71−7.64 (m, 4H), 7.46−7.28 (m, 11H), 6.52 (dd, J = 13.6 and 6.2 Hz, 1H), 5.84 (ddt, J = 17.3, 10.3, and 6.6 Hz, 1H), 5.09−4.97 (m, 2H), 4.67 (d syst AB, J = 11.4 Hz, 1H), 4.58 (d syst AB, J = 11.4 Hz, 1H), 4.41 (d, J = 13.6 Hz, 1H), 4.03 (d, J = 6.2 Hz, 1H), 3.55−3.38 (m, 3H), 2.33 (m, 1H), 2.13 (m, 1H), 1.90−1.26 (m, 9H), 1.23 (s, 3H), 1.07 (s, 9H), 0.93 (d, J = 7.7 Hz, 3H); ^{13}C NMR δ 146.5 (d), 138.7 (s), 138.6 (d), 135.5 (d, 4C), 134.0 (s, 2C), 129.3 (d, 3C), 128.2 (d, 3C), 127.5 (d, 4C), 127.4 (d), 114.7 (t), 90.4 (t), 83.3 (d), 82.3 (s), 74.3 (t), 68.7 (t), 36.1 (t), 35.5 (d), 33.5 (t), 30.9 (t), 30.0 (t), 26.8 (q, 3C), 20.1 (t), 19.9 (q), 19.2 (s), 16.8 (q); HRMS (CI$^+$, NH_3) calcd for $C_{38}H_{56}O_3NSi$ (M + NH_4^+) 602.4029, found 602.4033.

{5-[(2*S,3*R**)-3-Benzyloxy-2-methyl-2,3,4,5-tetrahydrooxepin-2-yl]-2-methylbutoxy}*tert*-butyldiphenylsilane (17).** A solution of diene **16** (76 mg, 0.13 mmol) in freshly distilled benzene (30 mL, 4.3 × 10^{-3}M) was degassed for 20 min by argon bubbling. The solution was then heated to 50 °C and Grubbs' catalyst $Cl_2(PCy_3)_2Ru{=}CHPh$ (32 mg, 39 μmol, 30%) was added in three portions over a period of 3 h. Heating was continued 4 h after the end of addition. The reaction mixture was then allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/Et_2O: 95/05) to give 50 mg (70%) of oxepene **17** as a colorless oil. IR (film) 1650, 1425, 1265, 1110, 745 cm^{-1}; ^{1}H NMR δ 7.71−7.66 (m, 4H), 7.45−7.28 (m, 11H), 6.04 (dt, J = 6.3 and 1.5 Hz, 1H), 4.99 (apparent q, J = 6.3 Hz, 1H), 4.68 (dd, $J_{\text{syst AB}}$ = 11.8 Hz, J = 1.1 Hz, 1H), 4.45 (dd, $J_{\text{syst AB}}$ = 11.8 Hz, J = 1.1 Hz, 1H), 3.56−3.36 (m, 3H), 2.28 (m, 1H), 2.06−1.55 (m, 6H), 1.47−1.25 (m, 4H), 1.23 (s, 3H), 1.07 (s, 9H), 0.93 (2d, J = 6.6 Hz, 2 × 1.5H); ^{13}C NMR δ 143.5 (d), 138.5 (s), 135.5 (d, 4C), 134.0 (s, 2C), 129.3 (d, 2C), 128.2 (d, 2C), 128.1 (d, 2C), 127.6 (d), 127.4 (d, 4C), 113.6 (d), 83.6 and 83.5 (d), 82.2 (s), 71.4 (t), 68.8 (t), 38.6 (t), 35.6 (d), 33.6 (t), 26.8 (q, 3C), 24.5 (t), 21.1 (t), 20.5 and 20.4 (t), 19.3 (s), 19.2 (q), 16.8 (q); MS-EI *m/z* (rel intensity) 499 (M − *t*-Bu$^+$,1), 391 (12), 200 (11), 199 (63), 197 (10), 183 (13), 181 (10), 175 (15), 139 (16), 135 (15), 91 (100). Anal. Calcd for $C_{36}H_{48}O_3Si$: C, 77.65; H, 8.69. Found: C, 77.70; H, 8.87.

(*Z*)-Ethyl 8-(*tert*-Butyldiphenylsilanyloxy)-3,7-dimethyloct-2-enoate (20). To *tert*-butyl(2-methylpent-4-enyloxy)-diphenylsilane **10** (1.55 g, 4.58 mmol, 1.1 equiv) at 0 °C was added dropwise a solution of 9-BBN dimer (0.615 g, 2.52 mmol, 0.6 equiv) in anhydrous THF (10 mL, 0.5 M). The solution was stirred at 0 °C until complete conversion of the starting alkene (ca. 2 h, followed by TLC). Besides, a suspension of K_3PO_4 (1.33 g, 6.26 mmol, 1.50 equiv) and iodide **19**[34] (1.0 g, 4.2 mmol, 1 equiv) in freshly distilled dioxane (12 mL) was degassed 30 min by argon bubbling. The solution of borane and $Pd(PPh_3)_4$ (0.12 g, 0.10 mmol, 2.5 mol %) were then added to the iodide and the reaction mixture was heated 5 h at 85 °C. After cooling to room temperature, the unreacted borane was oxidized by addition of an aqueous solution of sodium acetate (1.2 mL, 3 mol·L^{-1}) and hydrogen peroxide (30%, 1.2 mL). After 1 h of stirring at room temperature, the red solution was diluted with diethyl ether (50 mL) and washed with a saturated aqueous solution of NH_4Cl (25 mL) and with a saturated aqueous solution of NaCl (2 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (petroleum ether/diethyl ether: 95/05 to 80/20) afforded 1.40 g (74%) of alkene **20** as a colorless oil. IR (film) 1710, 1645, 1425, 1255, 1150, 1110 cm^{-1}; ^{1}H NMR δ 7.74−7.64 (m, 4H), 7.48−7.34 (m, 6H), 5.67 (br s, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.54 (dd, J = 9.6 and 5.7 Hz, 1H), 3.47 (dd, J = 9.6 and 6.3 Hz, 1H), 2.62 (br t, J = 7.4 Hz, 2H), 1.88 (d, J = 1.5 Hz, 3H), 1.77−1.15 (m, 5H), 1.28 (t, J = 7.2 Hz, 3H), 1.09 (s, 9H), 0.96 (d, J = 6.6 Hz, 3H); ^{13}C NMR δ 66.2 (s), 160.3 (s), 135.5 (d, 4C), 134.0 (s, 2C), 129.3 (d, 2C), 127.4 (d, 4C), 116.0 (d), 68.8 (t), 59.2 (t), 35.5 (d), 33.4 (t), 33.0 (t), 26.8 (q, 3C), 25.5 (t), 25.0 (q), 19.2 (s), 16.7 (q), 14.2 (q); MS-EI *m/z* (rel intensity) 437 (M − CH_3^+, 1), 407 (M OEt$^+$, 3), 396 (32), 395 (M − *t*-Bu$^+$, 100), 227 (17), 199 (34), 183 (14), 181 (11), 123 (12), 95 (11); HRMS (CI$^+$, CH_4) calcd for $C_{28}H_{41}O_3Si$ (M + H^+) 453.2825, found 453.2815.

(*Z*)-1-(*tert*-Butyldimethylsilanyloxy)-8-(*tert*-butyldiphenylsilanyloxy)-3,7-dimethyloct-2-ene (21) To a solution of ester **20** (1.0 g, 2.2 mmol, 1 equiv) in anhydrous diethyl ether (20 mL) at −78 °C was added dropwise a solution of diisobutylaluminum hydride (4.64 mL, 1 mol·L^{-1} in hexanes, 4.64 mmol, 2.1 equiv). After 30 min at −78 °C, the cold reaction mixture was poured into a saturated aqueous solution of Rochelle's salt (20 mL). The mixture was diluted with diethyl ether (20 mL) and, after 2 h of stirring at room temperature, the two phases were separated. The aqueous layer was extracted with diethyl ether (2 × 20 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/Et_2O 70/30 then 60/40) afforded 0.68 g (75%) of allylic alcohol as a colorless oil. The alcohol (0.600 g, 1.46 mmol, 1 equiv) was then diluted in DMF (4 mL) and imidazole (0.250 g, 3.65 mmol, 2.5 equiv) and *tert*-butyldimethylsilyl chloride (0.220 g, 1.46 mmol, 1.0 equiv) were added. After 12 h at room temperature, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl (5 mL). The aqueous layer was extracted with diethyl ether (3 × 20 mL) and the combined organic extracts were washed with water (2 × 10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was then purified by flash chromatography on silica gel (petroleum ether/Et_2O: 80/20) to give 465 mg (61%) of silylated ether **21** as a colorless oil. IR (film) 1470, 1460, 1425, 1250, 1105, 835 cm^{-1}; ^{1}H NMR δ 7.72−7.66 (m, 4H), 7.48−7.36 (m, 6H), 5.33 (apparent t, J = 6.6 Hz, 1H), 4.18 (dd, J = 6.6 and 1.1 Hz, 2H), 3.57−3.43 (m, 2H), 2.06−1.98 (m, 2H), 1.71 (d, J = 1.1 Hz, 3H), 1.67 (m, 1H), 1.50−1.27 (m, 4H), 1.08 (s, 9H), 0.94 (d, J = 6.6 Hz, 3H), 0.92 (s, 9H), 0.09 (s, 6H); ^{13}C NMR δ 137.7 (s), 135.5 (d, 4C), 134.0 (s, 2C), 129.4 (d, 2C), 127.4 (d, 4C), 124.9 (d), 68.7 (t), 59.8 (t), 35.6 (d), 32.9 (t), 32.3 (t), 26.8 (q, 3C), 25.9 (q, 3C), 25.4 (t), 23.3 (q), 19.2 (s), 18.3 (s), 16.7 (q), −5.2 (q, 2C); MS-EI *m/z* (rel intensity) 524 ($M^{+\bullet}$,1), 335 (21), 313 (24), 271 (25), 253 (40), 211 (21), 209 (34), 200 (19), 199 (100), 197 (26), 195 (21), 183 (17), 181 (17), 137 (62), 135 (27), 95 (44), 91 (20), 81 (99), 75 (59), 73 (19).

Anal. Calcd for $C_{32}H_{52}O_2Si_2$: C, 73.22; H, 9.98. Found: C, 73.25; H, 10.06.

(2*R,3*S**)-1-(*tert*-Butyldimethylsilanyloxy)-8-(*tert*-butyldiphenylsilanyloxy)-3,7-dimethyloctane-2,3-diol (22).** To a solution of alkene **21** (0.25 g, 0.48 mmol, 1 equiv) in a mixture of water and *tert*-butyl alcohol (1:1, 5 mL) at room temperature were successively added $K_3Fe(CN)_6$ (0.47 g, 1.43 mmol, 3 equiv), K_2CO_3 (0.200 g, 1.43 mmol, 3 equiv), DABCO (27 mg, 0.24 mmol, 0.5 equiv), and OsO_4 (30 mL, 4% in water, 4.8 mmol, 0.01 equiv).[35] After 16 h at room temperature, the reaction mixture was diluted with water (5 mL) and Na_2SO_3 (ca. 250 mg) was added. After the mixture was stirred for 2 h at room temperature, the aqueous layer was extracted with EtOAc (5 × 10 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/EtOAc: 95/05) to give 195 mg (73%) of diol **22** as a colorless oil. IR (film) 3400 (br), 1245, 1060 (br), 825 cm^{-1}; ^1H NMR δ 7.72−7.65 (m, 4H), 7.48−7.36 (m, 6H), 3.80 (d, J = 4.4 Hz, 2H), 3.56−3.40 (m, 3H), 2.86 (d, 1H), 2.78 (s, 1H), 1.78−1.26 (m, 6H), 1.21 (s, 3H), 1.15 (m, 1H), 1.08 (s, 9H), 0.95 (d, J = 6.6 Hz, 3H), 0.93 (s, 9H), 0.12 (s, 6H); ^{13}C NMR δ 135.5 (d, 4C), 133.9 (s, 2C), 129.4 (d, 2C), 127.4 (d, 4C), 75.1 (d), 74.0 (s), 68.7 (t), 64.1 (t), 38.7 (t), 35.6 and 35.5 (d), 33.7 (t), 26.8 (q, 3C), 25.7 (q, 3C), 23.1 (q), 20.8 and 20.7 (t), 19.2 (s), 18.0 (s), 16.7 (q), −5.6 (q), −5.7 (q); MS-EI *m/z* (rel intensity) 483 (M − H_2O − *t*-Bu^+, 8), 325 (11), 311 (11), 305 (22), 267 (10), 239 (10), 227 (14), 213 (17), 200 (19), 199 (100), 197 (21), 195 (14), 183 (14), 181 (16), 139 (18), 135 (79), 115 (13), 109 (24), 107 (13), 93 (15), 89 (34), 75 (30), 73 (34). Anal. Calcd for $C_{32}H_{54}O_4Si_2$: C, 68.76; H, 9.74. Found: C, 68.67; H, 9.87.

(2*R,3*S**)-1-Benzyloxy-2-(*tert*-butyldimethylsilanyloxy)-8-(*tert*-butyldiphenylsilanyloxy)-3,7-dimethyloctan-3-ol (24).** To a stirred suspension of NaH (16 mg, 60% in oil, 0.39 mmol, 2.2 equiv) in THF (1 mL) at 0 °C was added dropwise a mixture of diol **22** (0.10 g, 0.18 mmol, 1.0 equiv), HMPA (93 μL, 0.54 mmol, 3.0 equiv), benzyl bromide (32 μL, 0.27 mmol, 1.5 equiv), and *n*-Bu_4NI (26 mg, 0.07 mmol, 0.4 equiv) in THF (1 mL). After 15 min at 0 °C and 1 h at room temperature, the reaction mixture was diluted with diethyl ether (5 mL) and poured into a mixture of ice/water. The aqueous layer was first neutralized by addition of a saturated aqueous solution of NH_4Cl (ca. 5 mL) and, then, extracted with diethyl ether (3 × 10 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/Et_2O gradient 98/02 to 90/10) next afforded 114 mg (98%) of benzylated ether **24** as a colorless oil. IR (film) 3480 (br), 1470, 1460, 1425, 1390, 1360, 1255, 1110, 835 cm^{-1}; ^1H NMR δ 7.75−7.68 (m, 4H), 7.49−7.28 (m, 11H), 4.57 (d syst AB, J = 11.8 Hz, 1H), 4.51 (d syst AB, J = 11.8 Hz, 1H), 3.78−3.63 (m, 2H), 3.60−3.45 (m, 3H), 2.82 (d, J = 4.4 Hz, 1H), 1.72 (m, 1H), 1.62−1.22 (m, 6H), 1.17 (s, 3H), 1.10 (s, 9H), 0.97 (d, J = 7.0 Hz, 3H), 0.93 (s, 9H), 0.14−0.11 (m, 6H); ^{13}C NMR δ 137.6 (s), 135.5 (d, 4C), 134.0 (s, 2C), 129.4 (d, 2C), 128.3 (d, 2C), 127.6 (d, 3C), 127.4 (d, 4C), 76.4 (d), 74.1 (s), 73.4 (t), 72.2 (t), 68.9 (t), 38.5 (t), 35.8 and 35.7 (d), 33.8 (t), 26.8 (q, 3C), 25.8 (q, 3C), 22.8 and 22.7 (q), 20.4 (t), 19.2 (s), 18.0 (s), 16.8 and 16.7 (q), −4.1 (q), −5.1 (q); MS-EI *m/z* (rel intensity) 483 (M − *t*-Bu − $PhCH_2OH^+$, 3), 325 (24), 199 (50), 194 (19), 139 (12), 137 (13), 135 (48), 109 (12), 91 (100), 75 (11), 73 (13); Anal. Calcd for $C_{39}H_{60}O_4Si_2$: C, 72.17; H, 9.32. Found: C, 71.99; H. 9.49.

Ethyl (2*S*,3*S*)-8-(*tert*-Butyldiphenylsilanyloxy)-2,3-dihydroxy-3,7-dimethyloctanoate (26). To a stirred mixture of water and *tert*-butyl alcohol (1/1, 7 mL) at room temperature was added AD-mix-β (0.976 g). Once the two phases were clear, the mixture was cooled at 0 °C and solid methanesulfonamide (67 mg, 0.67 mmol, 1 equiv) was added in one portion. After 20 min at 0 °C, a solution of alkene **20** (0.32 g, 0.71 mmol, 1 equiv) in toluene (1 mL) was added via cannula and the reaction mixture was vigorously stirred for 30 h at 0 °C. After dilution with EtOAc (3 mL) at 0 °C and addition of Na_2SO_3 portionwise (ca. 1 g), the mixture was stirred for 1 h at room temperature. The aqueous layer was then extracted with EtOAc (3 × 15 mL) and the combined organic extracts were washed with water, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (petroleum ether/EtOAc: 80/20) afforded 0.222 g (65%) of diol **26** as a colorless oil. $[\alpha]^{20}_D$ +6.9 (*c* 1.10, $CHCl_3$); IR (film) 3460 (br), 1730, 1470, 1460, 1425, 1385, 1110, 710, 700 cm^{-1}; ^1H NMR rotamers δ 7.71−7.65 (m, 4H), 7.47−7.35 (m, 6H), 4.31 (m, 2H), 4.02 (2d, J = 6.6 Hz, 1H), 3.53 (dd, J = 9.7 and 5.7 Hz, 1H), 3.47 (dd, J = 9.7 and 5.7 Hz, 1H), 3.16 (d, J = 6.6 Hz, 1H), 2.53 (s, 1H), 1.75−1.26 (m, 7H), 1.34 and 1.33 (2t, J = 7.2 Hz, 3H), 1.23 (s, 3H), 1.07 (s, 9H), 0.95 (d, J = 7.0 Hz, 3H); ^{13}C NMR rotamers δ 173.3 (s), 135.5 (d, 4C), 134.0 (s, 2C), 129.4 (d, 2C), 127.4 (d, 4C), 76.2 and 76.1 (d), 73.8 (s), 68.8 (t), 61.9 (t), 38.1 and 38.0 (t), 35.6 and 35.5 (d), 33.5 (t), 26.8 (q, 3C), 22.8 and 22.7 (q), 20.5 (t), 19.2 (s), 16.7 and 16.6 (q), 14.1 (q); MS-EI *m/z* (rel intensity) 367 (1), 326 (12), 325 (42), 200 (19), 199 (100), 181 (12), 139 (24), 109 (12). Anal. Calcd for $C_{28}H_{42}O_5Si$: C, 69.10; H, 8.70. Found: C, 68.79; H, 9.01.

Ethyl (2*S*,3*S*)-2-Benzyloxy-8-(*tert*-butyldiphenylsilanyloxy)-3-hydroxy-3,7-dimethyloctanoate (27). To a solution of diol **26** (0.954 g, 1.96 mmol) in anhydrous CH_2Cl_2 (20 mL) at room temperature were successively added benzyl bromide (235 mL, 1.96 mmol, 1 equiv), *n*-Bu_4NI (0.362 g, 0.981 mmol, 0.5 equiv), and freshly prepared silver oxide (0.455 g, 1.96 mmol, 1 equiv)[36] in three portions over a period of 30 min. After 5 h at room temperature with exclusion of light, the reaction mixture was filtered through Celite and concentrated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/Et_2O: 80/20) to give 836 mg (74%) of monobenzylated diol **27** as a colorless oil. $[\alpha]^{20}_D$ −26.7 (*c* 1.0, $CHCl_3$); IR (film) 3425 (br), 1735, 1460, 1425, 1385, 1265, 1190, 1110, 1025 cm^{-1}; ^1H NMR rotamers δ 7.71−7.64 (m, 4H), 7.47−7.28 (m, 11H), 4.75 (d syst AB, J = 11.4 Hz, 1H), 4.41 (d syst AB, J = 11.4 Hz, 1H), 4.27 (m, 2H), 3.84 (s, 1H), 3.56−3.40 (m, 2H), 2.68 (br s, 1H), 1.70−1.09 (m, 10H), 1.24 (s, 3H), 1.06 (s, 9H), 0.89 (d, J = 6.6 Hz, 3H); ^{13}C NMR δ 171.2 (s), 137.0 (s), 135.5 (d, 4C), 134.0 (s, 2C), 129.3 (d, 2C), 128.3 (d, 2C), 128.1 (d, 2C), 127.9 (d), 127.4 (d, 4C), 83.9 and 83.8 (d), 73.6 (s), 72.9 (t), 68.8 (t), 60.9 (t), 38.4 and 38.3 (t), 35.7 and 35.6 (d), 33.5 (t), 26.8 (q, 3C), 23.3 and 23.2 (q), 20.5 and 20.4 (t), 19.2 (s), 16.7 (q), 14.2 (q); MS-EI *m/z* (rel intensity) 367 (1), 326 (14), 325 (51), 200 (20), 199 (100), 181 (13), 139 (24), 109 (11). Anal. Calcd for $C_{35}H_{48}O_5Si$: C, 72.88; H, 8.39. Found: C, 72.83; H, 8.42.

(2*R*,3*S*)-2-Benzyloxy-8-(*tert*-butyldiphenylsilanyloxy)-1-methoxymethoxy-3,7-dimethyloctan-3-ol (28). To a suspension of lithium aluminum hydride (65 mg, 1.71 mmol, 2 equiv) in anhydrous diethyl ether (2 mL) at 0 °C was added a solution of ester **27** (0.500 g, 0.868 mmol) in diethyl ether (2 mL). After 5 min at 0 °C and 1 h at room temperature, the reaction mixture was cooled to 0 °C and treated successively with water (65 μL), then with a 15% aqueous solution of NaOH (65 μL), and finally with water (195 μL). After 1 h of stirring at room temperature, the resulting suspension was filtered through Celite. The insoluble salts were washed with diethyl ether (2 × 25 mL) and the filtrate was dried over $MgSO_4$. Filtration and concentration under reduced pressure give 463 mg of (2*R*,3*S*)-2-benzyloxy-8-(*tert*-butyldiphenylsilanyloxy)-3,7-dimethyloctan-1,3-diol, which was directly engaged in the next step without further purification.

To a stirred suspension of NaH (76 mg, 60% in oil, 1.9 mmol, 2.2 equiv) in anhydrous THF (2 mL) at 0 °C were added

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successively a solution of the crude intermediate diol (0.463 g, 0.868 mmol, 1 equiv) in THF (3 mL) and methoxymethyl chloride (73 mL, 0.95 mmol, 1.1 equiv). After 5 min at 0 °C and 3 h at room temperature, the reaction mixture was hydrolyzed with water (2 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The crude material was purified by flash chromatography (petroleum ether/Et_2O gradient 80/20 to 60/40) to give 0.445 g (89% from **27**, 2 steps) of compound **28** as a colorless oil. $[\alpha]^{20}_D$ −10.1 (*c* 1.0, $CHCl_3$); IR (film) 3460 (br), 1470, 1460, 1425, 1385, 1150, 1110, 1040 cm^{-1}; ^1H NMR δ 7.71−7.64 (m, 4H), 7.47−7.27 (m, 11H), 4.87 (d syst AB, J = 11.4 Hz, 1H), 4.66 (s, 2H), 4.59 (d syst AB, J = 11.4 Hz, 1H), 3.83 (dd, $J_{syst\ AB}$ = 10.7 Hz, J = 3.7 Hz, 1H), 3.72 (dd, $J_{syst\ AB}$ = 10.7 Hz, J = 6.3 Hz, 1H), 3.55−3.40 (m, 3H), 3.39 (s, 3H), 2.48 (s, 1H), 1.79−1.11 (m, 7H), 1.19 (s, 3H), 1.06 (s, 9H), 0.93 (d, J = 6.6 Hz, 3H); ^{13}C NMR δ 138.4 (s), 135.5 (d, 4C), 134.0 (s, 2C), 129.3 (d, 2C), 128.2 (d, 2C), 127.7 (d, 2C), 127.6 (d), 127.4 (d, 4C), 96.6 (t), 85.7 (s), 84.0 and 83.9 (d), 73.8 and 73.7 (t), 68.8 and 68.7 (t), 68.1 (t), 55.3 (q), 38.3 and 38.2 (t), 35.7 and 35.6 (d), 33.7 (t), 26.8 (q, 3C), 23.2 and 23.1 (q), 20.5 and 20.4 (t), 19.2 (s), 16.7 and 16.6 (q); MS-EI *m/z* (rel intensity) 481 (1), 351 (22), 326 (17), 325 (60), 305 (10), 291 (16), 200 (16), 199 (85), 139 (23), 135 (51), 91 (100); HRMS (CI^+, NH_3) calcd for $C_{35}H_{54}0_5NSi$ (M + NH_4^+) 596.3771, found 596.3765. Anal. Calcd for $C_{35}H_{50}O_5Si$: C, 72.62; H, 8.71. Found: C, 72.58; H, 8.84.

Dimethyl 3-{(1*S*)-1-[(1*R*)-1-Benzyloxy-2-methoxymethoxyethyl]-6-(*tert*-butyldiphenylsilanyloxy)-1,5-dimethylhexyloxy}-2-oxopropylphosphonate (29). To a solution of alcohol **28** (500 mg, 0.865 mmol) and rhodium acetate (38 mg, 86 μmol, 10 mol %) in refluxing toluene (5 mL) was added dropwise, over a period of 2 h, a solution of ethyl diazoacetate (1.82 mL, 17.3 mmol, 20 equiv) in toluene (40 mL). After cooling to room temperature, the reaction mixture was filtered through a short pad of Celite and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/Et_2O gradient: 90/10 to 60/40) afforded a mixture of inseparable products (1.10 g), as a colorless oil, in which the major component is ethyl {(1*S*)-1-[(1*R*)-1-benzyloxy-2-methoxymethoxyethyl]-6-(*tert*-butyldiphenylsilanyloxy)-1,5-dimethylhexyloxy}acetate. This ester was directly engaged in the next step without further purification.

To a solution of methyldimethylphosphonate (290 μL, 2.66 mmol, 10.1 equiv) in anhydrous THF (4 mL) at −78 °C was added a solution of *n*-BuLi (1.06 μL, 2.5 M in hexanes, 2.64 mmol, 10 equiv). After 30 min at −78 °C, a solution of the crude ester (176 mg, 0.26 mmol, 1 equiv) in dry THF (2 mL) was added via cannula to the solution of phosphonate anion and the mixture was stirred for 1 h at −78 °C. The reaction mixture was then poured into an aqueous solution of citric acid (5%, 10 mL) and the aqueous layer was extracted with diethyl ether (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (EtOAc) afforded 118 mg (60%) of phosphonate **29** as a colorless oil. $[\alpha]^{20}_D$ − 2.8 (*c* 1.0, $CHCl_3$); IR (film) 1720, 1460, 1425, 1260, 1110, 1030, 740, 710, 700 cm^{-1}; ^1H NMR δ 7.69−7.61 (m, 4H), 7.45−7.22 (m, 11H), 4.87 (d syst AB, J = 11.4 Hz, 1H), 4.65 (s, 2H), 4.54 (d syst AB, J = 11.4 Hz, 1H), 4.17−3.96 (m, 3H), 3.73 (m, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.59 (dd, J = 6.6 and 1.8 Hz, 1H), 3.53−3.39 (m, 2H), 3.37 (s, 3H), 3.18 (br d, J_{H-P} = 22.4 Hz, 2H), 1.77−1.18 (m, 7H), 1.16 (s, 3H), 1.05 (s, 9H), 0.89 (2d, J = 6.6 Hz, 3H); ^{13}C NMR δ 200.8 and 200.7 (s), 138.6 (s), 135.5 (d, 4C), 133.9 (s, 2C), 129.4 (d, 2C), 128.1 (d, 2C), 127.5 (d, 2C), 127.4 (d, 4C), 127.3 (d), 96.7 (t), 81.8 and 81.7 (d), 79.6 (s), 73.5 and 73.4 (t), 69.1 (t), 68.9 and 68.8 (t), 68.3 (t), 55.2 (q), 52.9 (q), 52.8 (q), 36.8 (t, J_{C-P} = 121.6 Hz), 35.9 (t), 35.6 and 35.5 (d), 33.5 (t), 26.8 (q, 3C), 20.4 and 20.3 (t), 19.2 (q), 18.8 (s), 16.6 and 16.5 (q); MS-CI^+ (NH_3) *m/z* (rel intensity) 760 (M + NH_4^+, 100), 184 (13); HRMS (CI^+, NH_3) calcd for (M + NH_4^+) 760.4010, found 760.4017. Anal. Calcd for $C_{40}H_{59}O_9SiP$: C, 64.66; H, 8.00. Found: C, 64.30; H, 8.22.

(6*R*,7*S*)-6-Benzyloxy-7-[5-(*tert*-butyldiphenylsilanyloxy)-4-methylpentyl]-7-methyl-6,7-dihydrooxepin-3-one (31). To a solution of phosphonate **29** (91 mg, 12.3 μmol) in anhydrous CH_2Cl_2 (1.5 mL) at −40 °C was added bromotrimethylsilane (65 μL, 0.50 mmol, 4 equiv). After 30 min at −40 °C, the reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$ (7.5 mL). The aqueous layer was then extracted with dichloromethane (3 × 20 mL) and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (EtOAc) afforded 72 mg (84%) of the deprotected alcohol as a colorless oil.

To a stirred solution of this intermediate alcohol (65 mg, 94 μmol, 1 equiv) in dry dichloromethane (2 mL) were added pyridinium dichromate (107 mg, 29 μmol, 3 equiv) and molecular sieves 4 Å (213 mg). After stirring for 2 h at room temperature, the reaction mixture was diluted with ether (25 mL) and stirring was continued for 20 min. The resulting suspension was filtered through a pad of Celite (washed with 2 × 25 mL of diethyl ether) and the filtrate was concentrated in vacuo to afford the crude aldehyde **30**, which was used in the next step without further purification. A solution of the crude aldehyde in anhydrous THF (25 mL) was then added dropwise via cannula to a suspension of sodium hydride (60% dispersion in oil, 38 mg, 0.94 mmol, 10 equiv) in dry THF (20 mL) at 0 °C. After 15 min at 0 °C, the cooling bath was removed and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was then poured into a saturated aqueous solution of NH_4Cl (10 mL) and the aqueous layer was extracted with diethyl ether (3 × 25 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 90/10) afforded 29 mg (53%) of cyclic enone **31** as a colorless oil. $[\alpha]^{20}_D$ − 64.0 (*c* 1.0, $CHCl_3$); IR (film) 1685, 1465, 1455, 1425, 1385, 1375, 1265, 1105, 740, 710, 700 cm^{-1}; ^1H NMR δ 7.69−7.63 (m, 4H), 7.45−7.24 (m, 11H), 6.71 (dd, J = 12.0 and 4.0 Hz, 1H), 6.12 (d, J = 12.0 Hz, 1H), 4.67 (d syst AB, J = 11.8 Hz, 1H), 4.41 (d syst AB, J = 11.8 Hz, 1H), 4.20 (br d, $J_{syst\ AB}$ = 18.0 Hz, 1H), 4.04 (d, J = 4.0 Hz, 1H), 4.02 (dd, $J_{syst\ AB}$ = 18.0 Hz, J = 4.0 Hz, 1H), 3.50 (dd, $J_{syst\ AB}$ = 10.1 and 6.1 Hz, 1H), 3.45 (dd, $J_{syst\ AB}$ = 10.1 and 6.8 Hz, 1H), 1.73−1.22 (m, 7H), 1.20 (s, 3H), 1.05 (s, 9H), 0.92 (2d, J = 6.6 Hz, 2 × 1.5H); ^{13}C NMR ($CDCl_3$) δ 205.5 (s), 146.3 (d), 137.2 (s), 135.5 (d, 4C), 133.9 (s, 2C), 131.0 (d), 129.4 (d, 2C), 128.3 (d, 2C), 127.8 (d, C), 127.7 (d, 2C), 127.4 (d, 4C), 82.0 (d), 79.3 (s), 72.5 (t), 69.9 (t), 68.7 (t), 37.7 (t), 35.6 and 35.5 (d), 33.5 (t), 26.8 (q, 3C), 20.6 (t), 19.2 (q), 19.1 (s), 16.8 (q); MS-EI *m/z* (rel intensity) 513 (M − *t*-Bu^+, 6), 357 (9), 281 (10), 253 (16), 207 (49), 200 (18), 199 (100), 181 (16), 139 (18), 117 (19), 91 (72). Anal. Calcd for $C_{36}H_{46}O_4Si$: C, 75.75; H, 8.12. Found: C, 75.71; H, 8.22.

(4*S*,5*R*)-4-[5-(*tert*-Butyldiphenylsilanyloxy)-4-methylpentyl]-4-methyl-3,8-dioxabicyclo[3.2.1]octan-1-ol (32). To a solution of enone **31** (27 mg, 47 μmol) in absolute ethanol (2 mL) was added Pd/C (5 mg, 10%, 4.7 μmol, 10% mol). The mixture was stirred under 1 atm of hydrogen at room temperature. After 16 h of stirring, the reaction mixture was filtered through Celite (rinsing with Et_2O) and the volatiles were evaporated under reduced pressure. The crude material was purified by flash chromatography (petroleum ether/Et_2O: 60/40) to give 22 mg (97%) of hemiketal **32** as a colorless oil. IR (film) 3350 (br), 1465, 1455, 1425, 1365, 1260, 1200, 1110, 820, 740, 710, 700 cm^{-1}; ^1H NMR δ 7.69−7.62 (m, 4H), 7.46−7.33 (m, 6H), 3.93 (d, J = 6.6 Hz, 1H), 3.69 (d syst AB, J = 10.7 Hz, 1H), 3.53−3.38 (m, 3H), 3.02 (s, 1H), 2.20 (m, 1H), 2.09−1.89 (m, 2H), 1.71−1.59 (m, 2H), 1.47−1.08 (m, 6H), 1.32 (2s, 2 × 1.5H), 1.05 (s, 9H), 0.92 and 0.90 (2d, J = 6.6 Hz, 2 × 1.5H); ^{13}C NMR δ 135.5 (d, 4C), 133.9 (s, 2C), 129.4 (d, 2C), 127.4 (d, 4C), 102.1 (s), 81.0 (d), 74.8 (s), 69.0 (t), 68.7 and 68.6 (t), 38.1 (t), 35.5 and 35.4 (d), 33.7 (t), 33.0 (t), 26.7 (q,

3C), 23.5 (t), 20.8 and 20.7 (t), 19.2 (s), 18.2 (q), 16.8 and 16.7 (q); MS-EI *m/z* (rel intensity) 425 (M − *t*-Bu$^+$, 1), 407 (M − *t*-Bu − H_2O^+, 5), 329 (12), 317 (27), 253 (12), 207 (14), 200 (18), 199 (100), 193 (16), 181 (19), 139 (23), 135 (25), 109 (15), 107 (11), 93 (14), 81 (15), 69 (16), 55 (11).

Ethyl {(4*S*,5*R*)-4-[5-(*tert*-Butyldiphenylsilanyloxy)-4-methylpentyl]-4-methyl-3,8-dioxabicyclo[3.2.1]octan-1-yl}acetate (34). To a solution of ethyl triethylphosphonoacetate (17 μL, 86 μmol, 2.8 equiv) in anhydrous THF (0.5 mL) at 0 °C was added dropwise a solution of KHMDS (0.34 mL, 0.5 M in toluene, 0.17 mmol, 5.5 equiv). After 5 min at 0 °C, a solution of compound **32** (15 mg, 31 μmol, 1 equiv) in THF (1 mL) was added and after 2 h of stirring at room temperature, the reaction mixture was heated overnight at 70 °C, cooled to room temperature, hydrolyzed with water (1 mL), and extracted with diethyl ether (3 × 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/Et_2O gradient 95/05 to 70/30) afforded 10 mg (60%) of **34** as a colorless oil. IR (film) 1730, 1460, 1425, 1370, 1265, 1110, 745, 710, 700 cm^{-1} ; ^{1}H NMR δ 7.69−7.62 (m, 4H), 7.46−7.32 (m, 6H), 4.15 (q, J = 7.3 Hz, 2H), 3.83 (d, ^3J = 6.6 Hz, 1H), 3.79 (d, J = 11.0 Hz, 1H), 3.53−3.39 (m, 3H), 2.64 (d, J = 14.5 Hz, 1H), 2.55 (d, J = 14.5 Hz, 1H), 2.18−1.10 (m, 14H), 1.26 (s, 3H), 1.04 (s, 9H), 0.91 (m, 3H); ^{13}C NMR δ 169.8 (s), 135.5 (d, 4C), 133.9 (s, 2C), 129.3 (d, 2C), 127.4 (d, 4C), 81.1 (d), 79.1 (s), 75.0 (s), 69.5 (t), 68.7 and 68.6 (t), 60.4 (t), 40.7 (t), 38.9 (t), 35.5 and 35.4 (d), 33.7 (t), 31.5 (t), 26.7 (q, 3C), 24.8 (t), 22.5 (t), 19.2 (s), 18.1 (q), 16.8 and 16.7 (q), 14.2 (q); MS-EI *m/z* (rel intensity) 446 (M − EtOAc − *t*-Bu$^+$, 1), 222 (2), 177 (27), 176 (10), 150 (12), 149 (100).

(6*R*,7*S*)-6-Benzyloxy-7-[5-(*tert*-butyldiphenylsilanyloxy)-4-methylpentyl]-7-methyloxepan-3-one (18). To a solution of enone **31** (250 mg, 440 μmol) in absolute ethanol (15 mL) was added Pd/C (47 mg, 10%, 44 μmol, 10% mol). The mixture was stirred under 1 atm of hydrogen at room temperature and, after 5 min (**caution**: the time is important), was filtered through Celite (rinsing with Et_2O). The filtrate was concentrated under reduced pressure and the crude material was purified by flash chromatography (petroleum ether/Et_2O 80/20) to give 245 mg (98%) of ketone **18** as a colorless oil. $[\alpha]^{20}_D$ +5.6 (*c* 1.0, $CHCl_3$); IR (film) 1715, 1460, 1425, 1265, 1105, 740, 710, 700 cm^{-1}; ^{1}H NMR δ 7.69−7.63 (m, 4H), 7.46−7.24 (m, 11H), 4.62 (d syst AB, J = 11.4 Hz, 1H), 4.38 (d syst AB, J = 11.4 Hz, 1H), 4.13 (d syst AB, J = 18.7 Hz, 1H), 3.94 (d syst AB, J = 18.7 Hz, 1H), 3.54−3.41 (m, 2H), 3.39 (dd, J = 8.8 and J = 3.1 Hz, 1H), 2.69 (m, 1H), 2.54 (m, 1H), 2.09 (m, 1H), 1.85 (m, 1H), 1.72−1.18 (m, 7H), 1.15 (s, 3H), 1.05 (s, 9H), 0.92 (2d, J = 6.6 Hz, 2 × 1.5H); ^{13}C NMR δ 214.6 (s), 137.9 (s), 135.5 (d, 4C), 134.0 (s, 2C), 129.4 (d, 2C), 128.2 (d, 2C), 127.6 (d), 127.5 (d, 2C), 127.4 (d, 4C), 83.0 and 82.9 (d), 80.6 (s), 71.8 (t), 70.5 (t), 68.8 (t), 39.5 (t), 36.9 (t), 35.6 and 35.5 (d), 33.6 (t), 26.8 (q, 3C), 22.3 (t), 20.5 and 20.4 (t), 19.2 (s), 16.9 (q), 16.8 (q); MS-EI *m/z* (rel intensity) 515 (M − *t*-Bu$^+$, 6), 347 (8), 255 (7), 207 (12), 200 (8), 199 (45), 139 (10), 135 (11), 109 (11), 91 (100). Anal. Calcd for $C_{36}H_{48}O_4Si$: C, 75.48; H, 8.45. Found: C, 75.32; H, 8.56.

2-{(*E*)-(6*R*,7*S*)-6-Benzyloxy-7-[5-(*tert*-butyldiphenylsilanyloxy)-4-methylpentyl]-7-methyloxepan-3-ylidene}-ethanol (35) and 2-{(*Z*)-(6*R*,7*S*)-6-Benzyloxy-7-[5-(*tert*-butyldiphenylsilanyloxy)-4-methylpentyl]-7-methyloxepan-3-ylidene}ethanol (35′). To a solution of ethyl triethylphosphonoacetate (0.77 mL, 3.85 mmol, 10.1 equiv) in anhydrous THF (2 mL) at 0 °C was added dropwise a solution of LiHMDS (3.85 mL, 1 M in THF, 3.85 mmol, 10 equiv). After 5 min at 0 °C, a solution of ketone **18** (0.22 g, 0.385 mmol, 1 equiv) in THF (7 mL) was added. After 1 h at 0 °C and 30 min at room temperature, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl (20 mL) and extracted with diethyl ether (3 × 30 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Analysis of the ^{1}H NMR spectrum of the crude material indicated the formation of two geometric isomers *E*/*Z* (70/30 ratio). After purification by flash chromatography on silica gel (petroleum ether/Et_2O 90/10), 0.24 g (97%) of a diastereomeric mixture *E*/*Z* (70/30) of unsaturated esters was obtained as a colorless oil. This mixture was dissolved in diethyl ether (4 mL) and the resulting solution was added to a suspension of lithium aluminum hydride (28 mg, 0.74 mmol, 2 equiv) in anhydrous diethyl ether (3 mL), at 0 °C. After 5 min at 0 °C and 1 h at room temperature, the reaction mixture was cooled to 0 °C and treated successively with water (28 μL), then with a 15% aqueous solution of NaOH (28 μL), and finally with water (84 μL). After 1 h of stirring at room temperature, the resulting suspension was filtered through Celite. The insoluble salts were washed with diethyl ether (2 × 15 mL) and the filtrate was dried over $MgSO_4$. After filtration and concentration under reduced pressure, the crude material was purified by flash chromatography (petroleum ether/Et_2O gradient: 80/20 to 50/50) to afford 140 mg (63%) of alcohol **35** and 59 mg (27%) of its geometric isomer **35′**, as colorless oils.

Major diastereomer **35**: R_f 0.4 (petroleum ether/EtOAc 70/30); $[\alpha]^{20}_D$ −4.0 (*c* 1.0, $CHCl_3$); IR (film) 3380, 1470, 1460, 1425, 1390, 1110, 825, 740, 710, 700 cm^{-1}; ^{1}H NMR δ 7.69−7.63 (m, 4H), 7.44−7.22 (m, 11H), 5.44 (t, J = 6.6 Hz, 1H), 4.61 (d syst AB, J = 11.6 Hz, 1H), 4.39 (d syst AB, J = 11.6 Hz, 1H), 4.17 (d, J = 6.6 Hz, 2H), 4.12 (d syst AB, J = 14.3 Hz, 1H), 3.99 (d syst AB, J = 14.3 Hz, 1H), 3.54−3.39 (m, 2H), 3.29 (m, 1H), 2.55 (m, 1H), 2.13 (m, 1H), 1.93 (m, 1H), 1.83−1.10 (m, 9H), 1.16 (s, 3H), 1.05 (s, 9H), 0.92 (2d, J = 6.8 Hz, 2 × 1.5H); ^{13}C NMR δ 142.9 (s), 138.5 (s), 135.5 (d, 4C), 134.0 (s, 2C), 129.3 (d, 3C), 128.2 (d, 3C), 127.5 (d), 127.4 (d, 4C), 123.5 (d), 84.6 and 84.5 (d), 79.9 (s), 71.7 (t), 68.9 (t), 68.6 (t), 58.7 (t), 39.6 (t), 35.7 and 35.6 (d), 33.7 (t), 26.8 (q, 3C), 26.5 (t), 24.1 (t), 20.6 and 20.5 (t), 19.2 (s), 17.7 and 17.6 (q), 16.8 (q); MS-EI *m/z* (rel intensity) 435 (M − *t*-Bu − $PhCH_2OH^+$, 4), 267 (11), 201 (14), 200 (18), 199 (100), 139 (19), 135 (14), 109 (15), 93 (12), 81 (14), 55 (11). Anal. Calcd for $C_{38}H_{52}O_4Si$: C, 75.95; H, 8.72. Found: C, 75.85; H, 8.89.

Minor diastereomer **35′**: R_f 0.45 (petroleum ether/EtOAc 70/30); $[\alpha]^{20}_D$ −4.7 (*c* 1.0, $CHCl_3$); IR (film) 3390, 1425, 1110, 740, 710, 700 cm^{-1}; ^{1}H NMR δ 7.69−7.63 (m, 4H), 7.45−7.22 (m, 11H), 5.43 (t, J = 6.6 Hz, 1H), 4.61 (d syst AB, J = 11.7 Hz, 1H), 4.41 (d syst AB, J = 11.7 Hz, 1H), 4.30 (d syst AB, J = 16.1 Hz, 1H), 4.20−4.00 (m, 2H), 4.13 (d syst AB, J = 16.1 Hz, 1H), 3.54−3.39 (m, 2H), 3.27 (dd, J = 9.5 and 3.5 Hz, 1H), 2.37 (m, 1H), 2.22 (m, 1H), 2.00 (m, 1H), 1.75−1.10 (m, 9H), 1.13 (s, 3H), 1.05 (s, 9H), 0.92 (2d, ^3J = 6.6 Hz, 2 × 1.5H); ^{13}C NMR δ 144.3 (s), 138.6 (s), 135.5 (d, 4C), 134.0 (s, 2C), 129.3 (d, 3C), 128.1 (d, 3C), 127.4 (d, 4C), 127.3 (d), 122.3 (d), 84.3 and 84.2 (d), 80.2 (s), 71.7 (t), 68.9 (t), 62.2 (t), 58.2 (t), 39.7 (t), 35.7 and 35.6 (d), 33.7 (t), 31.3 (t), 28.1 (t), 26.8 (q, 3C), 20.4 (t), 19.2 (s), 16.9 (2q, 2C); MS-EI *m/z* (rel intensity) 435 (M − *t*-Bu − $PhCH_2OH^+$, 4), 417 (3), 267 (12), 201 (15), 200 (19), 199 (100), 139 (19), 135 (14), 121 (11), 109 (15), 93 (13), 81 (16), 55 (12).

***E*-{5-[(2*S*,3*R*)-3-Benzyloxy-6-(2-benzyloxyethylidene)-2-methyloxepan-2-yl]-2-methylpentyloxy}-*tert*-butyldiphenylsilane (36).** To a solution of alcohol **35** (186 mg, 0.310 mmol) in anhydrous CH_2Cl_2 (7 mL) were successively added at room temperature benzyl bromide (41 μL, 0.34 mmol, 1.1 equiv), *n*-Bu_4NI (57 mg, 0.15 mmol, 0.5 equiv), and freshly prepared silver oxide (79 mg, 0.34 mmol, 1.1 equiv).[36] After 18 h of stirring at room temperature, the reaction mixture was filtered through Celite and concentrated under reduced pressure. Purification of the crude material by flash chromatography on silica gel (pentane/Et_2O: 80/20) afforded 209 mg (98%) of dibenzylated compound **36** as a colorless oil. $[\alpha]^{20}_D$ −2.3 (*c* 1.02, $CHCl_3$); IR (film) 1450, 1425, 1105, 1070, 740, 710, 700 cm^{-1} ; ^{1}H NMR δ 7.71−7.65 (m, 4H), 7.47−7.24 (m, 16H), 5.48 (t, J = 6.3 Hz, 1H), 4.62 (d syst AB, J = 11.8 Hz, 1H), 4.53 (s, 2H), 4.41 (d syst AB, J = 11.8 Hz, 1H), 4.16 (d syst AB, J =

14.3 Hz, 1H), 4.07 (d, J = 6.3 Hz, 2H), 4.05 (d syst AB, J = 14.3 Hz, 1H), 3.56−3.40 (m, 2H), 3.30 (br d, J = 9.1 Hz, 1H), 2.53 (m, 1H), 2.18−1.10 (m, 10H), 1.17 (s, 3H), 1.07 (s, 9H), 0.94 and 0.93 (2d, J = 6.6 Hz, 2 × 1.5H); ^{13}C NMR δ 143.8 (s), 138.6 (s), 138.2 (s), 135.5 (d, 6C), 134.0 (s), 129.3 (d, 2C), 128,2 (d, 2C), 128.1 (d, 2C), 127.6 (d, 2C), 127.4 (d, 6C), 127.3 (s), 120.9 (d), 84.7 and 84.6 (d), 79.8 (s), 72.1 (t), 71.7 (t), 68.9 (t), 68.6 (t), 65.9 (t), 39.7 (t), 35.7 and 35.6 (d), 33.7 (t), 26.8 (q, 3C), 26.6 (t), 24.3 (t), 20.5 and 20.4 (t), 19.2 (s), 17.6 and 17.5 (q), 16.8 (q). Anal. Calcd for $C_{45}H_{58}O_4Si$: C, 78.21; H, 8.46. Found: C, 78.19; H, 8.59.

***E*-5-[3-(2*S*,3*R*)-Benzyloxy-6-(2-benzyloxyethylidene)-2-methyloxepan-2-yl]-*N*-methoxy-2,*N*-dimethylpentanamide (37).** To a solution of compound **36** (100 mg, 144 μmol) in anhydrous THF (10 mL) at 0 °C was added a solution of TBAF (0.58 mL, mol·L^{-1} in THF, 0.58 mmol, 2 equiv). After 30 min at 0 °C and 16 h at room temperature, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl (10 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. After concentration under reduced pressure, 276 mg of crude alcohol was obtained as a colorless oil, which was directly oxidized to the corresponding carboxylic acid.

To prepare a solution of Jones reagent, concentrated sulfuric acid (0.21 mL, 37%) was added to CrO_3 (274 mg, 2.74 mmol). The resulting mixture was stirred at room temperature and the volume of the solution was completed to 2 mL by addition of water (**Caution**: exothermic). The solution of Jones reagent (110 μL) was then added to a solution of crude alcohol (144 μmol) in acetone (5 mL) at 0 °C. After 30 min of stirring at 0 °C, 2-propanol (0.4 mL) and water (2 mL) were added and the mixture was stirred 1 h at room temperature. Acetone was evaporated under reduced pressure and the resulting aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried over $MgSO_4$ and filtered. After concentration under reduced pressure, 134 mg of crude acid was obtained as a colorless oil, which was directly transformed to the corresponding Weinreb amide.

To a solution of crude acid (144 μmol) in anhydrous CH_2Cl_2 (2 mL) were added *N*,*O*-dimethylhydroxylamine hydrochloride (22 mg, 0.022 mmol, 1.5 equiv) and DMAP (4.0 mg, 28 μmol, 20% mol). After complete dissolution, the solution was cooled to 0 °C and diisopropylamine (38 μL, 0.022 mmol, 1.5 equiv) and EDCI (42 mg, 0.022 mmol, 1.5 equiv) were added. After 30 min of stirring at 0 °C and 16 h at room temperature, the reaction mixture was washed with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 × 30 mL) and the combined organic extracts were washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography (CH_2Cl_2/EtOAc: 90/10) to give 44 mg (60%, 3 steps) of Weinreb amide **37** as an oil. IR (film) 1725, 1665, 1465, 1455, 1110, 1070, 740, 700 cm^{-1}; ^{1}H δ 7.38−7.25 (m, 10H), 5.46 (t, J = 6.6 Hz, 1H), 4.61 (dd, $J_{\text{syst AB}}$ = 11.8 Hz, J = 1.1 Hz, 1H), 4.51 (s, 2H), 4.40 (d syst AB, J = 11.8 Hz, 1H), 4.15 (d syst AB, J = 14.3 Hz, 1H), 4.06 (d, J = 6.3 Hz, 2H), 4.04 (d syst AB, J = 14.3 Hz, 1H), 3.67 and 3.65 (2s, 2 × 1.5H), 3.30 and 3.27 (2t, J = 2.9 Hz, 2 × 0.5H), 3.18 (2s, 2 × 1.5H), 2.87 (m, 1H), 2.52 (m, 1H), 2.18−1.19 (m, 9H), 1.17 and 1.16 (2s, 3H), 1.11 (d, J = 6.6 Hz, 3H); ^{13}C NMR δ (s, C=O, not detected), 143.7 and 143.6 (s), 138.5 and 138.4 (s), 138.1 (s), 128,2 (d, 2C), 128.1 (d, 2C), 127.6 (d, 2C), 127.5 (d, 2C), 127.4 (d), 127.3 (d), 121.0 (d), 84.7 (d), 79.7 (s), 72.1 (t), 71.7 and 71.6 (t), 68.6 (t), 65.8 (t), 61.3 (q), 39.3 and 39.2 (t), 35.1 and 34.9 (d), 34.2 and 34.1 (t), 32.1 (q), 26.5 (t), 24.3 (t), 21.1 and 20.9 (t), 17.5 and 17.4 (q), 17.3 and 17.2 (q); MS-CI$^+$ (NH_3) m/z (rel intensity) 527 (M + NH_4^+, 100), 437 (15), 202 (37), 182 (16), 141 (19), 124 (30), 106 (45); HRMS (CI$^+$, NH_3) calcd for $C_{31}H_{47}O_5N_2$ (M + NH_4^+) 527.3485, found 527.3488.

(+)-(2′*S*,3′*R*)-Zoapatanol (1).[4b,e,5,7] To a solution of phenyl prenyl ether (162 mg, 1.00 mmol, 20 equiv) in a mixture of anhydrous diethyl ether and tetrahydrofuran (1/1, 2 mL) was added lithium (235 mg, 34 mmol) portionwise. A few drops of anhydrous methanol were first added to clean the surface of lithium. The mixture was then vigorously stirred at room temperature until the solution turned yellow. The reaction mixture was then cooled to 15 °C and stirring was continued for 2 h at 15 °C. The supernatant solution of organolithium reagent was then added via cannula to a solution of the Weinreb amide **37** (25 mg, 49 μmol, 1 equiv) in dry THF (1 mL) at −78 °C. After 10 min at −78 °C (conversion of **37** was monitored by TLC), the reaction mixture was added dropwise to a solution of lithium (108 mg, 15.6 mmol) in ammoniac (ca. 20 mL) at −78 °C, in the presence of a mixture of *tert*-butyl alcohol and tetrahydrofuran (1/4, 0.5 mL). After 5 min at −78 °C, solid NH_4Cl was added portionwise until complete disparition of the dark blue color. The reaction mixture was then diluted with diethyl ether (10 mL) and ammonia was evaporated. Water (10 mL) was further added and the aqueous layer was extracted with diethyl ether (3 × 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography on silica gel (EtOAc) and zoapatanol **1** (11 mg, 33 μmol, 66%) was isolated as a colorless oil. Physical and spectral data match those previously reported in the literature. R_f 0.6 (EtOAc); $[\alpha]^{20}_D$ +4.16 (*c* 0.31, $CHCl_3$) {lit.[5] $[\alpha]^{20}_D$ +12.00 (*c* 0.31, $CHCl_3$)};[37] IR (film) 3390 (br), 1707, 1450, 1375, 1100, 1060, 1025, 740 cm^{-1}; ^{1}H NMR δ 5.47 (br t, J = 7.0 Hz, 1H), 5.30 (br t, J = 7.0 Hz, 1H), 4.20 (d, J = 7.0 Hz, 2H), 4.13 (br s, 2H), 3.55 (m, 1H), 3.16 (d, J = 7.0 Hz, 2H), 2.59 (q, J = 7.0 Hz, 1H), 2.48 (m, 1H), 2.23 (m, 1H), 1.73 (br s, 3H), 1.63 (apparent s, 3H), 1.85−1.20 (m, 10H), 1.16 and 1.15 (2s, 2 × 1.5H), 1.09 (d, J = 7.0 Hz, 3H); ^{13}C NMR δ 213.1 (s), 143.3 (s), 135.4 (s), 123.1 (d), 115.9 (d), 79.7 (s), 76.3 and 76.1 (d), 69.1 (t), 58.6 (t), 45.7 (d), 40.8 and 40.7 (t), 38.0 and 37.9 (t), 33.3 (t), 31.5 (t), 25.6 (q), 23.3 and 23.2 (t), 20.9 and 20.8 (t), 18.3 (q), 18.0 (q), 16.5 (q); MS-CI$^+$ (NH_3) m/z (%) 356 (M + NH_4^+, 100), 341 (8), 321 (9), 274 (7), 228 (10), 124 (7); HRMS (CI$^+$, NH_3) calcd for $C_{20}H_{38}O_4N$ (M + NH_4^+) 356.2801, found 356.2806.

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Supporting Information Available: Tables of comparison of the NMR data of synthetic zoapatanol **1** with those reported in the literature; copies of the NMR spectra of compounds **6**, **7**, **9**, **10**, **11**, **13**, **15**, **16**, **20**, **32**, **34**, **35′**, **37**, and zoapatanol **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(37) The comparison of the obtained $[\alpha]^{20}_D$ value with the optical rotation of the natural zoapatanol is not possible since the latter has never been published.