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Synthetic Efforts toward the Spiroketal Core of Spirangien A

Amandine Guérinot,[†] Guillaume Lepesqueux,[†] Serge Sablé,[‡] Sébastien Reymond,*[,†] and Janine Cossy*[,†]

[†]*Laboratoire de Chimie Organique, ESPCI ParisTech, UMR CNRS 7084, 10 rue Vauquelin, 75231 Paris Cedex 05, France, and* [‡]*Sanofi-Aventis, Centre de recherche de Vitry-Alfortville, 9 Quai Jules Guesde, 94400 Vitry sur Seine, France*

janine.cossy@espci.fr; sebastien.reymond@espci.fr

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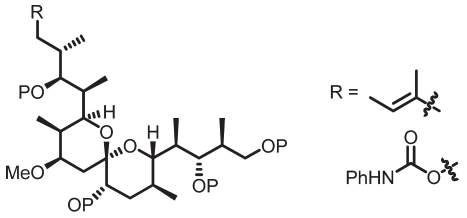

Spirangien A spiroketal core

Synthetic studies toward the spiroketal core of spirangien A are described. Two synthetic approaches were developed. Both of them use a diastereoselective aldol addition of a lithium enolate derived from a methyl ketone on an aldehyde. In the first approach, the introduction of the (*E*)-trisubstituted terminal olefin was achieved by using an iron-catalyzed cross-coupling between an alkyl iodide and a vinyl Grignard reagent and a randomly protected spiroketal was obtained. In the second approach, a highly functionalized spiroketal carbamate, which includes 13 stereogenic centers, was successfully isolated.

Introduction

Spirangiens A and B are polyketide metabolites isolated from the epothilone-producing myxobacterium *Sorangium cellulosum* (strain So ce90) (Scheme 1). These unique natural products display a significant *in vitro* cytotoxicity (IC_{50} = 1 pM against L929 mouse fibroblast cell line), as well as potent antibiotic and antifungal activities.[1] Spirangiens A and B possess 14 stereogenic centers and include a highly functionalized spiroketal core bearing two lateral side chains. One of them is constituted by a conjugated pentaenic moiety and a terminal carboxylic acid. The second one is ended by a trisubstituted double bond. Spirangiens A and B only differ by the substituent of the double bond at C31 (methyl or ethyl group). The structure of these natural products was determined by NMR studies and mass spectrometry. In order to establish the relative configuration of the 14 stereocenters, spirangien A was treated with ethylene in the presence of the second-generation Grubbs catalyst affording spiroketal **1** as the major product, and an X-ray crystal structure analysis of the latter furnished a secure determination of the relative stereochemistry (Scheme 1). The absolute configuration was hypothesized by analysis of the gene cluster[2] and finally confirmed by Paterson et al. by total synthesis.[3] Compared to spirangien A, the cytotoxicity of this simplified and more stable spiroketal **1** remains high (IC_{50} = 13 pM). Thus, the biological activity of the latter as well as the synthetic challenge related to its original structure has solicited interest among organic chemists, and in 2008, the first total synthesis of spirangien A was published by Paterson et al.[3,4] On the basis of its unique architectural features, we embarked on the elaboration of spiroketal **1**, and herein we would like to report a full account of our synthetic efforts.

Results and Discussion

First Strategy. In our retrosynthetic study of spiroketal **1**, the introduction of the (*Z*)-diene unit was planned to be performed at a late stage (Scheme 2). In order to form the spiroketal moiety, a one-pot deprotection/spiroketalization sequence applied to the linear precursor **A** was envisioned, and the C21

(1) (a) Niggeman, J. N.; Bedorf, N.; Flörke, U.; Steinmetz, H.; Gerth, K.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **2005**, 5013. (b) Höfle, G.; Bedorf, N.; Gerth, K.; Reichenbach, H. DE-4211056, 1993; *Chem. Abstr.* **1993**, *119*, 180598.

(2) Frank, B.; Knauber, J.; Steinmetz, H.; Scharfe, M.; Blöcker, H.; Beyer, S.; Müller, R. *Chem. Biol.* **2007**, *14*, 221.

(3) Paterson, I.; Findlay, A. D.; Anderson, E. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 6699.

(4) (a) Lorenz, M.; Kalesse, M. *Tetrahedron Lett.* **2007**, *48*, 2905. (b) Lorenz, M.; Kalesse, M. *Org. Lett.* **2008**, *10*, 4371. (c) Paterson, I.; Findlay, A.; Noti, C. *Chem. Commun.* **2008**, 6408. (d) Paterson, I.; Findlay, A.; Noti, C. *Chem.—Asian J.* **2009**, *4*, 594.

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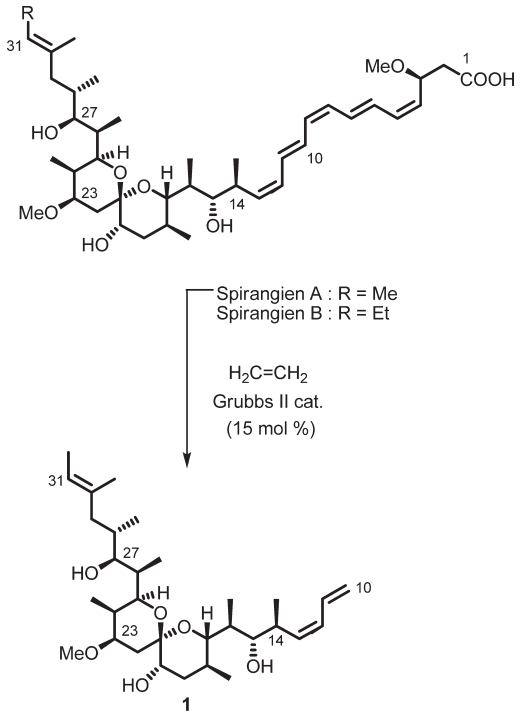
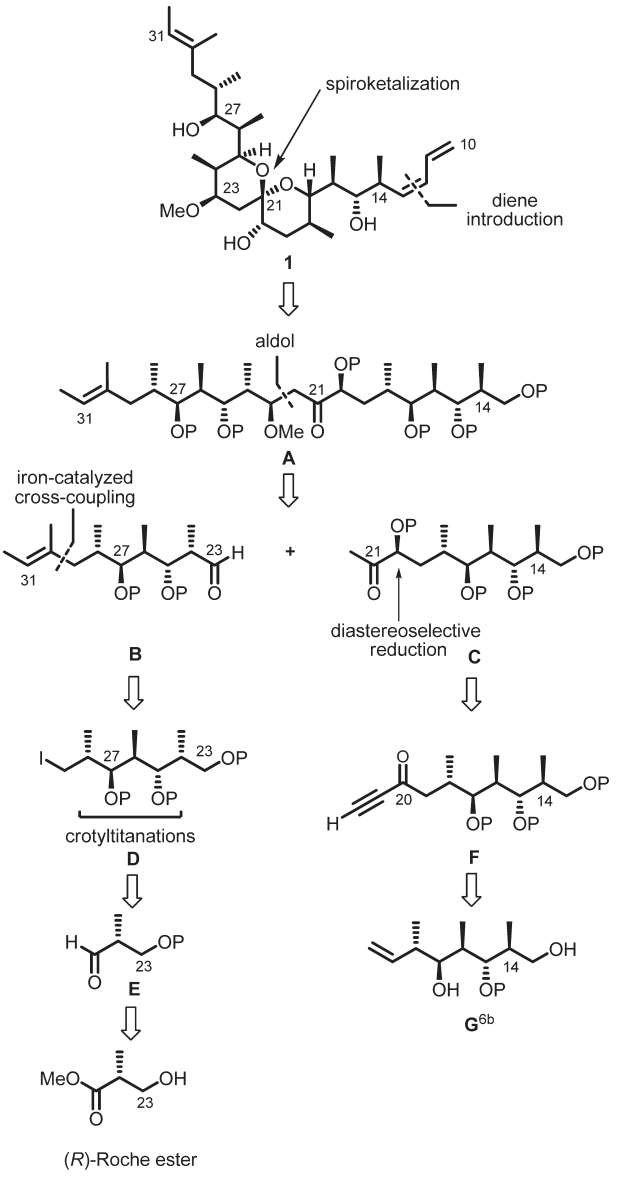
SCHEME 1



SCHEME 2



stereocenter would be controlled by taking advantage of a double anomeric effect. Fragment **A** would be assembled by an aldolisation between aldehyde **B** and methyl ketone **C**. The terminal trisubstituted double bond in aldehyde **B** could be introduced according to our recently reported iron-catalyzed cross-coupling between alkyl halides and alkenyl Grignard reagents that would be applied to alkyl iodide **D**.[5] The C24−C28 stereopentad would be built by using two consecutive stereoselective crotyltitanations applied to aldehyde **E**, which would be easily prepared from the (*R*)-Roche ester. The C20 stereogenic center in ketone **C** would be controlled by a stereoselective reduction of propargylic ketone **F**, which would be prepared from diol **G** synthesized according to reported procedures.[6,7]

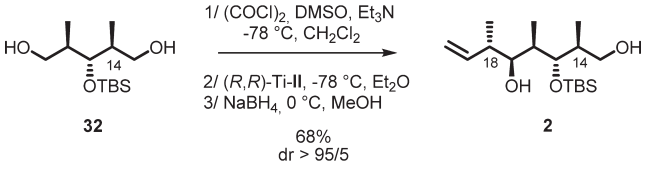
As depicted in Scheme 3, the synthesis of the C13−C22 fragment of spiroketal **1** started with the *tert*-butyldimethylsilyl (TBS) protection of diol **2**[8] to yield olefin **3** (TBSOTf, 2,6-lutidine, −78 °C, CH_2Cl_2, 89%). A regioselective hydroboration of the C19−C20 double bond was applied to **3**, and alcohol **4** was produced ($BH_3 \cdot THF$, rt, THF then H_2O_2, NaOH, 62%). This latter was oxidized to an aldehyde (Dess−Martin periodinane, rt, CH_2Cl_2) and after addition of ethynylmagnesium bromide, the resulting secondary alcohol was oxidized to the corresponding propargylic ketone **5** (3 steps, 61% yield). In order to control the C20 stereocenter, a diastereoselective reduction of propargylic ketone **5** was achieved with (*S*)-Me-CBS oxazaborolidine in the presence of $BH_3 \cdot Me_2S$ complex to afford the desired alcohol as a mixture of two diastereomers (dr = 97/3).[9,10] After separation by flash chromatography

(5) (a) Guérinot, A.; Reymond, S.; Cossy, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 6521. (b) Reymond, S.; Ferrié, L.; Guérinot, A.; Capdevielle, P.; Cossy, J. *Pure Appl. Chem.* **2008**, *80*, 1665. (c) See also: Cahiez, G.; Duplais, C.; Moyeux, A. *Org. Lett.* **2007**, *9*, 3253.

(6) (a) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321. (b) BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, *3*, 3995.

(7) (a) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487. (b) Harada, T.; Matsuda, Y.; Wada, I.; Uchimura, J.; Oku, A. *J. Chem. Soc., Chem. Commun.* **1990**, 21.

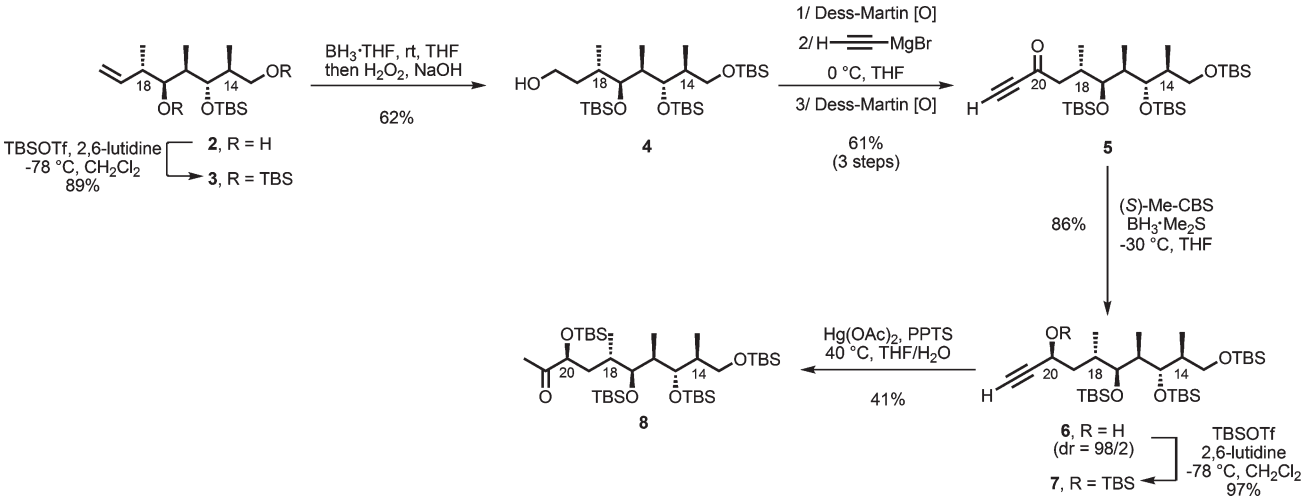
(8) Obtained from *meso*-diol (2*R**,3*S**,4*S**)-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethyl-1,5-pentanediol **32** according to reported procedures; see refs 6 and 7.



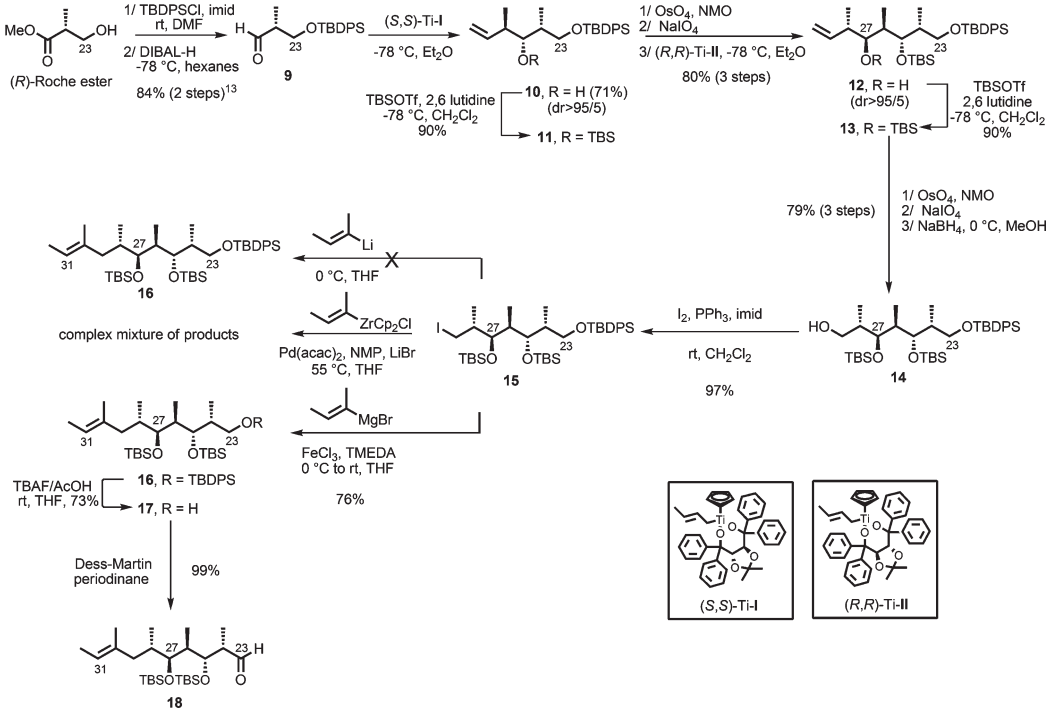
(9) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925. (c) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861. (d) For a review, see: Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986. (e) For application to propargylic ketones, see: Parker, K. A.; Ledeboer, M. W. *J. Org. Chem.* **1996**, *61*, 3214.

(10) The diastereomeric ratio was determined by ^1H NMR analysis and/or GC/MS analysis of the crude reaction mixture.

SCHEME 3



SCHEME 4



on silica gel, alcohol **6** was isolated (dr >98/2, 86% yield) and subsequently protected, giving rise to **7** (TBSOTf, 2,6-lutidine, −78 °C, CH_2Cl_2, 97%). In order to complete the synthesis of methyl ketone **8**, an hydration of the triple bond has to be performed. At this stage, difficulties were encountered due to the required acidic conditions for the hydration of the triple bond and the lability of the silyl ethers. Several set of conditions were evaluated, and the best results were obtained with $Hg(OAc)_2$ (0.3 equiv) in the presence of PPTS (0.5 equiv) in a THF/H_2O mixture (41%).[11,12]

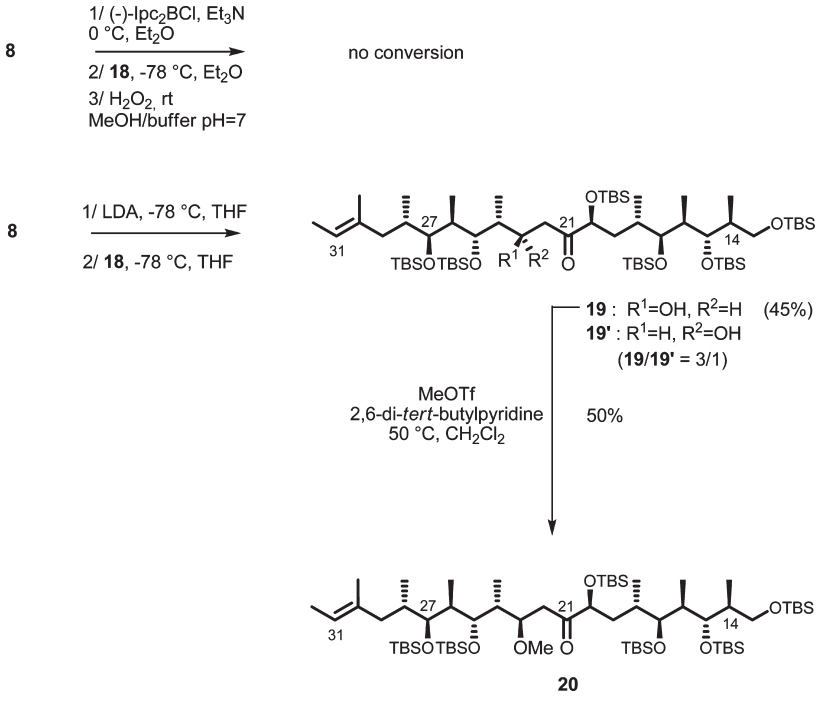
Our efforts were then directed to the preparation of the second aldol coupling partner **B** which started with the transformation of the (*R*)-Roche ester to aldehyde **9**[13] (TBDPSCl, imidazole then DIBAL-H, −78 °C, hexanes, 84% for the 2 steps) (Scheme 4). In order to control the C25 and C26 stereogenic centers, a first stereoselective crotyltitanation using (*S*,*S*)-Ti-**I** was performed (−78 °C, Et_2O), and the corresponding homoallylic alcohol **10** was obtained in 71% yield with a good

(11) For recent examples in synthesis, see: (a) Witulski, B.; Bergsträber, U.; Gössmann, M. *Tetrahedron* **2000**, *56*, 4747. (b) Paterson, I.; Tudge, M. *Tetrahedron* **2003**, *59*, 6833. (c) Paterson, I.; Mühltau, F. A.; Cordier, C. J.; Housden, M. P.; Burton, P. M.; Loiseleur, O. *Org. Lett.* **2009**, *11* (2), 353.

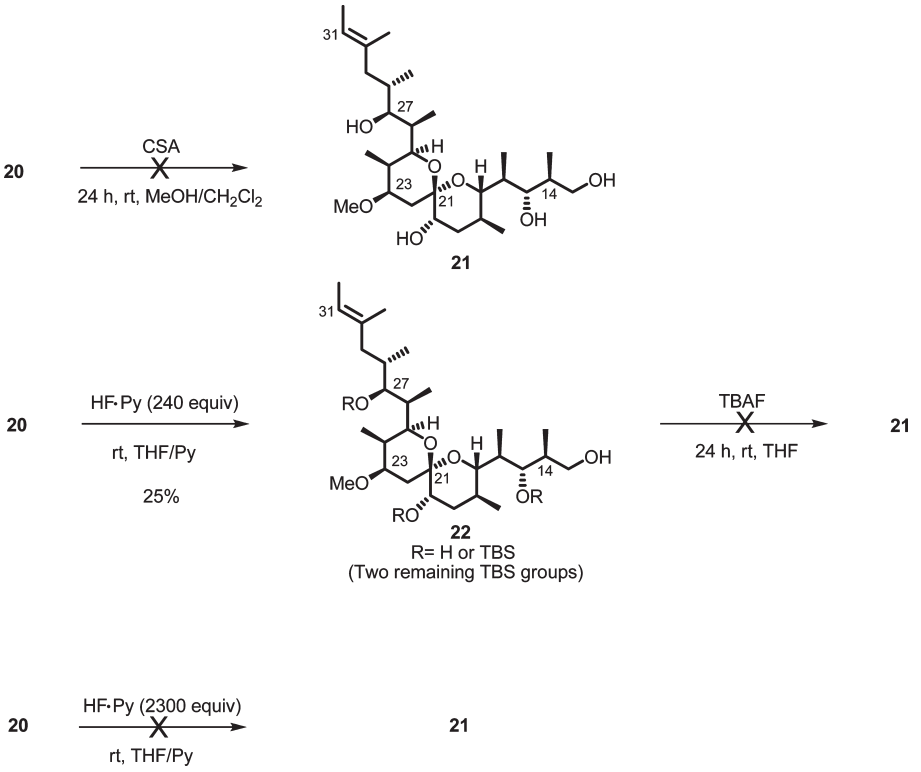
(12) Other conditions did not give any satisfactory results; when the reaction was performed with $Hg(SO_4)_2$/AcOH at rt, the cleavage of silyl ethers was observed. When $Hg(SO_4)_2$ was used without any acid at 40 °C, no conversion of the alkyne was noticed, whereas at 70 °C, the silyl ethers were cleaved.

(13) Prepared according to a reported procedure by Johns, B. A.; Grant, C. M.; Marshall, J. M. *Organic Synthesis*; Wiley: New York, 2004; Collect. Vol. X, p 170.

SCHEME 5

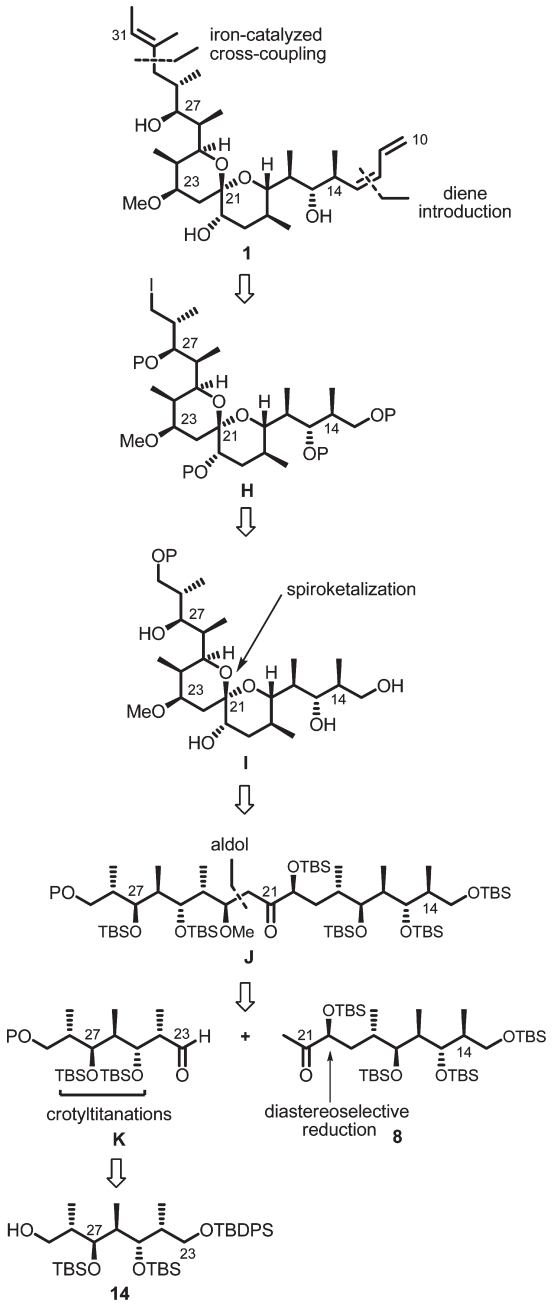


SCHEME 6



diastereomeric ratio (dr >95/5).[10] After protection of alcohol **10** as a TBS ether, the double bond was oxidatively cleaved (OsO_4, NMO then $NaIO_4$), and the resulting aldehyde was treated with the crotyltitanium reagent (*R*,*R*)-Ti-**II** to afford alcohol **12** (72% for the four steps, dr >95/5).[10] After TBS protection (TBSOTf, 2,6-lutidine, −78 °C, CH_2Cl_2, 90%) and oxidative cleavage of the double bond (OsO_4, NMO then $NaIO_4$) followed by a sodium borohydride reduction of the obtained aldehyde, primary alcohol **14** was isolated in 79% yield (3 steps). This alcohol was subsequently transformed to the corresponding alkyl iodide **15** under standard conditions (PPh_3, I_2, imidazole, rt, CH_2Cl_2, 97%). At this point, the completion of the synthesis of aldehyde **18** required only the introduction of the trisubstituted C30−C31 double bond.

SCHEME 7



However, the addition of (*E*)-1-methyl-1-propenyllithium to iodide **15** led to the migration of the TBS group from the C27 hydroxyl group to C29, and a mixture of products was obtained. A Pd-catalyzed Negishi cross-coupling[14] was applied to alkyl iodide **15**, but unfortunately, a complex mixture of products was observed without any traces of the desired alkene. In order to circumvent this difficulty, an iron-catalyzed cross-coupling between alkenyl Grignard reagents and alkyl halides developed in our laboratory was successfully applied to iodide **15** [$FeCl_3$ (10 mol %), (*E*)-1-methyl-1-propenylmagnesium bromide (5 equiv), TMEDA (1.9 equiv), 0 °C to rt, THF] leading to alkene **16** in a good yield of 76%.[5] The primary TBDPS ether was then selectively cleaved (TBAF/AcOH, rt, THF, 73%),[15,16] and the corresponding primary alcohol was oxidized to give the required aldehyde **18**.

With ketone **8** and aldehyde **18** in hand, the challenging aldol coupling was then examined. In order to favor the anti Felkin−Anh adduct, the use of a chiral boron enolate was first evaluated.[17] Unfortunately, treatment of ketone **8** with (−)-Ipc_2BCl/Et_3N followed by addition of aldehyde **18** did not afford the aldol product as no conversion of the starting materials was observed. Gratifyingly, the addition of the lithium enolate derived from **8** (LDA, −78 °C, THF) on aldehyde **18** provided the aldol adducts with a diastereomeric ratio of 3/1 in favor of the desired diastereomer **19**.[18] This diastereomeric ratio is similar to the one obtained by Paterson et al. (using a chiral boron enolate, dr = 2.5/1)[3] or Kalesse et al. (using LiHMDS to generate the methylketone lithium enolate, dr = 3/1).[4b] However, in our case, we were able to separate the two isomers by flash chromatography. In Paterson et al. synthesis, when LDA was used to generate a methylketone lithium enolate, the undesired Felkin adduct was obtained in a 3.5/1 ratio, thus underlining the high substrate dependence on the diastereoselectivity of this aldol condensation.[19] Alcohol **19** was isolated in 45% yield and then transformed to its corresponding methyl ether **20** (MeOTf, 2,6-di-*tert*-butylpyridine, 50 °C, CH_2Cl_2) with a yield of 50% (Scheme 5).[20,21]

At this point, the one-pot deprotection/spiroketalization sequence was investigated. Unfortunately, treatment of the linear compound **20** with CSA in a CH_2Cl_2/MeOH mixture led to the formation of a side product that did not possess any double bond. Under acidic conditions, the electron-rich double bond could be activated, and then an intramolecular nucleophilic attack of the C27 hydroxyl group could proceed to form a furan ring.[22] In order to prevent this side reaction,

(14) (a) Wiskur, S. L.; Korte, A.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 82. (b) For the hydrozirconation step, see: Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679.

(15) (a) Zhu, B.; Panek, J. S. *Eur. J. Org. Chem.* **2001**, 1701. (b) Zhu, B.; Panek, J. S. *Org. Lett.* **2000**, *2*, 2575. (c) Mitchell, I. S.; Pattenden, G.; Stonehouse, J. P. *Tetrahedron Lett.* **2002**, *43*, 493.

(16) No reaction occurred under other conditions such as NH_4F in MeOH.

(17) This method was successfully used by Paterson et al. in their synthesis of spirangien A. See ref 3 and (a) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P.; Sereinig, N. *J. Am. Chem. Soc.* **2001**, *123*, 9535. (b) Paterson, I.; Florence, G. J.; Gerlach, K.; Scott, J. P. *Angew. Chem., Int. Ed.* **2000**, *39*, 377. (c) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron Lett.* **1990**, *46*, 4663.

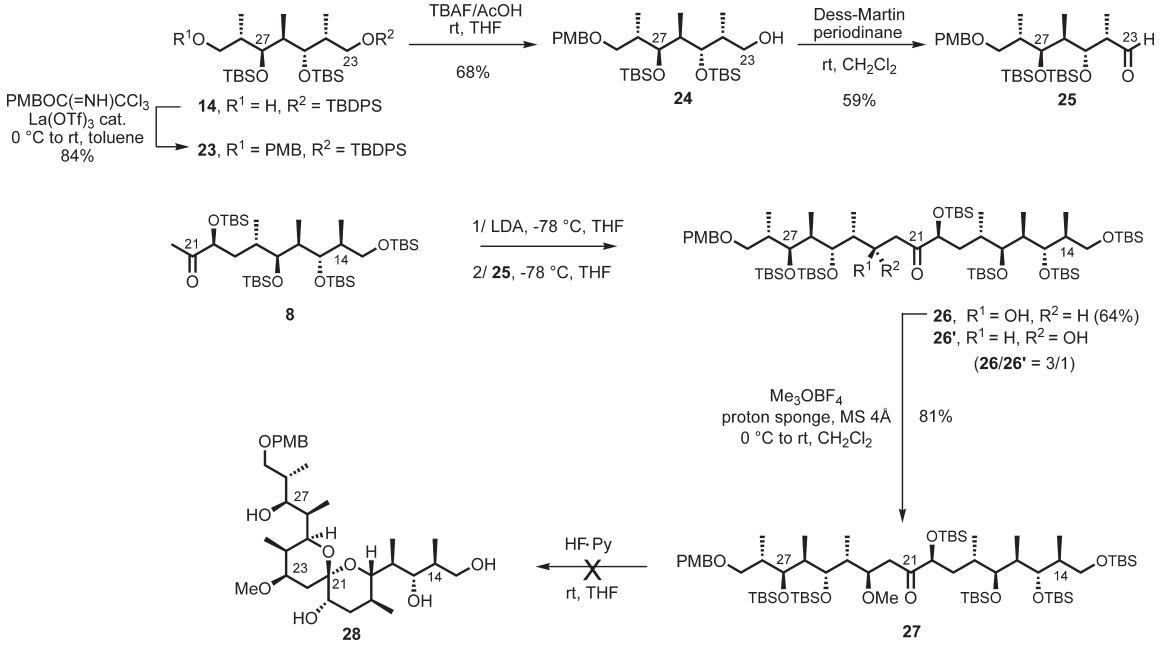
(18) The diastereomeric ratio was determined by analysis of the ^1H NMR spectrum of the crude product. Assignment of each diastereomer was hypothesized by analysis of the ABX pattern of the C22 methylene unit; see: Roush, W. R.; Bannister, T. D.; Wendt, M. D.; VanNieuwenhze, M. S.; Gustin, D. J.; Dilley, G. J.; Lane, G. C.; Scheidt, K. A.; Smith, W. J. *J. Org. Chem.* **2002**, *67*, 4284. See Supporting Information for details. The stereochemistry was also confirmed by NOESY studies on spiroketal **22**, see Supporting Information for details.

(19) For a detailed study, see: Lorenz, M.; Bluhm, N.; Kalesse, M. *Synthesis* **2009**, 3061.

(20) (a) Arnarp, J.; Kenne, L.; Lindberg, B.; Lönngren, J. *Carbohydr. Res.* **1975**, *44*, C5–C7. For examples, see: (b) Walba, D. M.; Thurmes, W. N.; Haltiwanger, R. C. *J. Org. Chem.* **1988**, *53*, 1046. (c) Paterson, I.; Ward, R. A.; Smith, J. D.; Cumming, J. G.; Yeung, K.-S. *Tetrahedron* **1995**, *51*, 9437. (d) O'Neill, J. A.; Gallagher, O. P.; Devine, K. J.; Jones, P. W.; Maguire, A. R. *J. Nat. Prod.* **2005**, *68*, 125.

(21) Difficulties were encountered for the transformation of **19** to its corresponding methyl ether **20**. Treatment of **19** with the Meerwein's salt successfully used in both Paterson et al. and Kalesse et al. syntheses led to poor conversion of the substrate with 14 equiv of the reagent, whereas degradation of **19** was observed in the presence of a larger excess (30 equiv). Under our conditions [MeOTf (15 equiv), di-*tert*-butylpyridine (31 equiv), 50 °C, CH_2Cl_2] an excess of the reagents at 50 °C was required in order to reach full conversion of **19**, but a partial degradation was also observed thus explaining the moderate 50% yield.

SCHEME 8

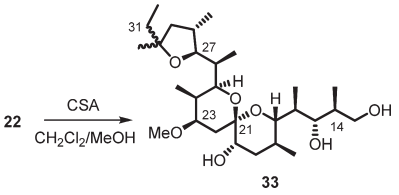


HF·Py was added by portions to ketone **20** in a THF/Py mixture. Spiroketal **22** possessing two silyl ethers was isolated and a NOESY experiment provided the assignment of the relative stereochemistry of the substituents at C21 and C23. However, we were unable to determine the position of the two remaining silyl ethers in the spiroketal **22**. Furthermore, treatment of **22** with an excess of TBAF did not cleave the two remaining silyl ethers. In order to perform the global deprotection, **20** was treated with a large excess of HF·Py, but once again, the undesired reaction of the C30−C31 double bond was observed (Scheme 6).[22,23] In order to avoid this side reaction which took place under the required acidic conditions for the cleavage of the silyl ethers, a second strategy was designed.[24]

Second Strategy. In order to circumvent the difficulty related to the presence of the electron-rich C30−C31 double bond during the spiroketalization step, the iron-catalyzed introduction of the olefinic moiety was planned after the spiroketalization step. Spiroketal **1** would come from iodide **H**, which would be obtained from spiroketal **I**. The latter would result from a deprotection/spiroketalization sequence applied to ketone **J**, which should be formed through an aldol coupling between methyl ketone **8** and aldehyde **K** prepared from alcohol **14**. This strategy is taking advantage of the already prepared ketone **8** and alcohol **14** (Scheme 7).

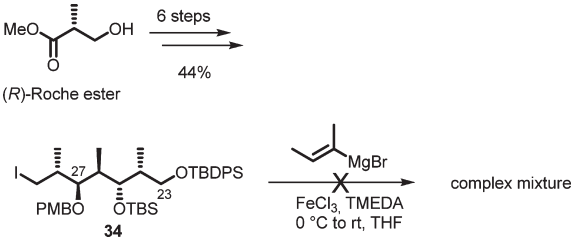
As previously described in our first strategy, primary alcohol **14** was prepared from the (*R*)-Roche ester in nine steps with an overall yield of 31% (Scheme 4). After protection of the primary hydroxyl group as a PMB ether (PMBOC(=NH)-CCl_3, $La(OTf)_3$, 0 °C to rt, toluene, 84%), the primary TBDPS ether was selectively cleaved under treatment with TBAF/AcOH (1/1) (68%). The oxidation of the resulting primary alcohol **24** furnished aldehyde **25** (Dess−Martin periodinane, rt, CH_2Cl_2) in 59% yield. At this stage, the aldol coupling between aldehyde **25** and methyl ketone **8** was considered, and the conditions described previously for the condensation of **8** with **18** (LDA, −78 °C, THF) were selected. The aldol adducts **26** and **26′** were produced with a diastereomeric ratio of 3/1 in favor of the desired diastereomer **26**.[18] Alcohols **26** and **26′** were separated by flash chromatography and **26** was isolated in 64% yield. It is worth noting that the use of aldehyde **25** as the new coupling partner considerably increased the yield of the aldolisation (64% versus 45% in the first strategy) without affecting the diastereoselectivity. Compound **26** was converted to its corresponding methyl ether **27** using the Meerwein reagent

(22) Hypothetical structure for **33**:

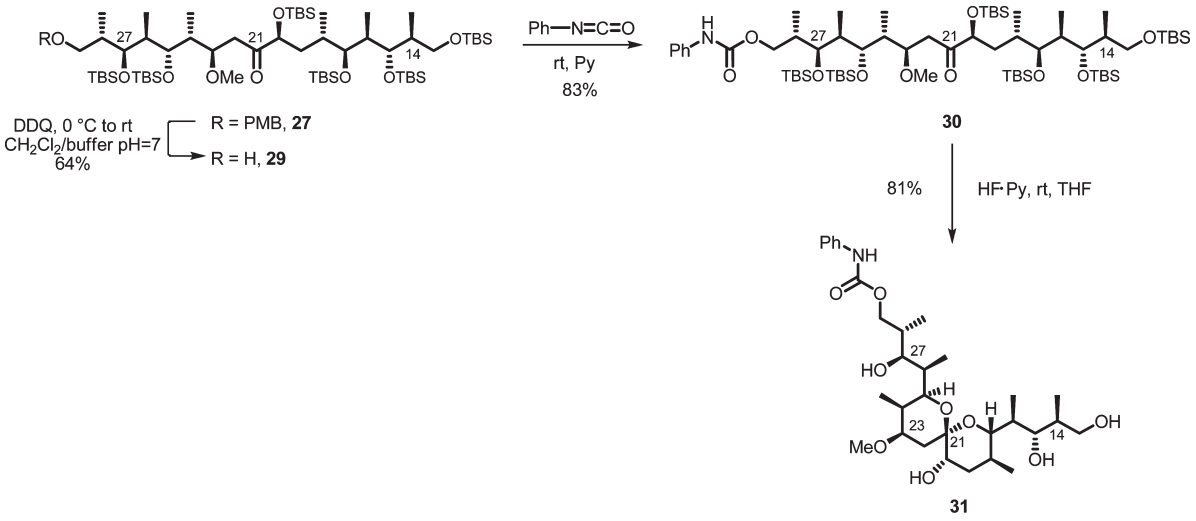


(23) This side reaction was not observed by Paterson et al.[3,4] probably because acetonide protecting groups are more labile than TBS ethers, thus allowing the use of soft acidic conditions for their deprotection. Kalesse et al.[4] clearly mentioned that when TBS ethers were used instead of TES ethers the deprotection/spiroketalisation step failed.

(24) The protection of the C27 hydroxyl group as a PMB ether was first envisioned in order to avoid the side reaction observed during the HF·Py mediated spiroketalization step. Unfortunately, the iron-catalyzed cross-coupling of **34** with (*E*)-1-methyl-1-propenylmagnesium bromide failed in the presence of the PMB ether group, and consequently, the synthesis of the aldehyde partner for the aldol coupling could not be completed.



SCHEME 9



(Me_3OBF_4, proton sponge, MS 4 Å, 0 °C to rt, CH_2Cl_2, 81%).[25] Ketone **27** was then subjected to the deprotection/spiroketalization step. Unfortunately, the acidic conditions required for the deprotection of the hydroxyl groups (HF·Py) also caused the cleavage of the PMB ether and a mixture of products was obtained (Scheme 8).

Consequently, an acid-resistant protective group had to be found for the C29 hydroxyl group, and we turned our choice to a carbamate group. The primary PMB ether in **27** was cleaved by using DDQ, and the resulting alcohol was treated with phenylisocyanate to furnish carbamate **30** (53% for the last two steps). The linear ketone **30** was then submitted to HF·Py, and pleasingly the desired spiroketal **31** was isolated in a good yield of 81% (Scheme 9). An unequivocal determination of the C21/C23 stereochemistry was achieved by NOESY analysis. This second strategy is promising and constitutes an efficient way to access an highly functionalized analogue of spiroketal **1** (Scheme 9).[26]

Conclusion

Two convergent synthetic approaches of the spiroketal core of spirangien A are described. Synthetic highlights include a CBS reduction, an aldol coupling, and a deprotection/spiroketalization step that proceed with good diastereoselectivities and excellent yields. In the first strategy, the (*E*)-trisubstituted double bond was introduced *via* an iron-catalyzed cross-coupling. In the second approach, we were able to isolate a carbamate derivative featuring the C13−C23 fragment of spirangien A incorporating 13 stereogenic centers.

Experimental Section

(3*S*,4*S*,5*R*,6*S*,7*S*)-3,5,7-Trimethyl-4,6,8-[*tert*-butyldimethylsilyloxy]-oct-1-ene (3). To a solution of **2**[8] (587 mg, 1.86 mmol, 1 equiv) in CH_2Cl_2 (20 mL) at −78 °C were successively added 2,6-lutidine (1.5 mL, 13.02 mmol, 7 equiv) and TBSOTf (1.5 mL, 6.50 mmol, 3.5 equiv). The reaction mixture was allowed to warm to rt slowly without removing the bath and stirred overnight. Then, a saturated aqueous solution of $NaHCO_3$ was added, and the two phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (PE) to give **3** (889 mg, 89%): $[\alpha]^{20}_D = -9.1$ (*c* 1.45, $CHCl_3$); IR (neat) 2929, 2857, 1474, 1360, 1251, 1037, 1004 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.90 (m, 1H), 5.05−4.97 (m, 2H), 3.76 (dd, J = 9.6, 4.6 Hz, 1H), 3.65−3.60 (m, 2H), 3.37 (dd, J = 10.0, 8.6 Hz, 1H), 2.30 (m, 1H), 1.86−1.72 (m, 2H), 1.01 (d, J = 7.0 Hz, 3H), 0.96 (d, J = 7.0 Hz, 3H), 0.95−0.85 (m, 30H), 0.08−0.01 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8 (d), 114.8 (t), 76.8 (d), 76.5 (d), 65.2 (t), 43.8 (d), 42.7 (d), 39.1 (d), 26.3 (3q), 26.3 (3q), 26.1 (3q), 18.6 (s), 18.4 (s), 18.3 (s), 17.7 (q), 16.1 (q), 12.3 (q), −3.2 (q), −3.4 (q), −3.5 (q), −4.3 (q), −5.5 (2q); MS (EI) 488 (1), 357 (12), 317 (32), 273 (16), 225 (48), 199 (100), 185 (15), 145 (20), 133 (13), 89 (63), 75 (25), 73 (97); HRMS (ESI) calcd for $C_{29}H_{64}O_3Si_3 + Li^+$ 551.4318, found 551.4306.

(3*S*,4*S*,5*R*,6*S*,7*S*)-3,5,7-Trimethyl-4,6,8-[*tert*-butyldimethylsilyloxy]-octan-1-ol (4). To a solution of alkene **3** (1.413 g, 2.60 mmol, 1 equiv) in THF (2 mL) at 0 °C was added dropwise BH_3·THF (1 M in THF, 2.86 mmol, 2.86 mL, 1.1 equiv). The reaction mixture was stirred for 5 min at 0 °C and then allowed to warm to rt. After 24 h, the reaction mixture was cooled to 0 °C, and an aqueous sodium hydroxide solution (2.5 M, 5.71 mmol, 2.3 mL, 2.2 equiv) was added dropwise followed by the addition of a hydrogen peroxide solution (35%, 23.58 mmol, 2.6 mL, 9.1 equiv). The resulting mixture was stirred at rt for 2 h and then heated at reflux for 1 h. The two phases were separated, the aqueous layer was extracted with Et_2O (3 × 20 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. A purification by flash chromatography on silica gel (PE/Et_2O 100/5 to 9/1) yielded the alcohol **4** (898 mg, 62%) as a colorless oil: $[\alpha]^{20}_D = -10.7$ (*c* 1.06, $CHCl_3$); IR (neat) 3337, 2928, 2856, 1472, 1463, 1388, 1361, 1252, 1040, 1005 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.78−3.69 (m, 2H), 3.65−3.55 (m, 3H), 3.38 (dd, J = 9.9, 8.2 Hz, 1H), 1.91−1.81 (m, 2H), 1.80−1.63 (m, 3H), 1.49 (m, 1H), 0.99−0.85 (m, 36H), 0.09−0.01 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 77.5 (d) 76.7 (d), 65.3 (t),

(25) (a) Hans Meerwein, H.; Hinz, G.; Hofmann, P.; Kroning, E.; Pfeil, E. *J. Prakt. Chem.* **1937**, *147*, 257. (b) Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *Tetrahedron Lett.* **1994**, *35*, 7171. Also see refs 3 and 4.

(26) At this stage, we had to transform the carbamate group into an iodide in order to install the C30-C31 double bond by mean of an iron-catalyzed cross-coupling. In that goal, we first envisioned a protection of the four alcohols as TES ethers, but unfortunately, a degradation of the substrate was observed in presence of TESOTf, thus unabling us to complete the synthesis of spiroketal **1**.

60.9 (t), 42.1 (d), 39.4 (d), 35.4 (d), 34.2 (t), 26.3 (3q), 26.1 (3q), 26.1 (3q), 18.7 (s), 18.4 (s), 18.4 (s), 17.1 (q), 15.7 (q), 12.4 (q), −3.2 (q), −3.3 (q), −3.5 (q), −4.2 (q), −5.3 (2q); MS (EI) 357 (1), 75 (100), 73 (16), 56 (11); HRMS (ESI) calcd for $C_{29}H_{66}O_4Si_3$ + Li^+ 569.4424, found 569.4410.

(5*S*,6*S*,7*R*,8*S*,9*S*)-6,8,10-Tris(*tert*-butyldimethylsilyloxy)-5,7,9-trimethyl-dec-1-yn-3-one (5). To a solution of alcohol **4** (1.36 g, 2.42 mmol, 1 equiv) in CH_2Cl_2 (50 mL) at 0 °C was added Dess−Martin periodinane (1.54 g, 3.63 mmol, 1.5 equiv). The reaction mixture was stirred for 15 min at 0 °C and then allowed to warm to rt. After 2 h, a 10% aqueous solution of $Na_2S_2O_3$ (25 mL) and a saturated aqueous solution of $NaHCO_3$ (25 mL) were added. After 30 min, the two phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was filtered through a pad of silica gel to give the desired aldehyde which was used in the following reaction without any further purification.

The aldehyde (1.17 g, 2.09 mmol, 1 equiv) was dissolved in THF (15 mL), and the resulting solution was cooled to 0 °C. Ethynyl magnesium bromide (0.5 M in THF, 8.4 mL, 4.17 mmol, 2 equiv) was added dropwise. After 2 h at 0 °C, the reaction mixture was quenched by addition of a saturated solution of NH_4Cl (10 mL). The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, and the solvents were removed *in vacuo*. The residue was purified by flash chromatography on silica gel (PE/EtOAc 100/3) and the alcohol was obtained as a 1:1 mixture of diastereomers as a colorless oil (281 mg, 69% from **4**). To a solution of the obtained alcohol (843 mg, 1.44 mmol, 1 equiv) in CH_2Cl_2 (30 mL) at 0 °C was added Dess−Martin periodinane (913 mg, 2.15 mmol, 1.5 equiv). After 15 min at 0 °C and 2 h at rt, a 10% aqueous solution of $Na_2S_2O_3$ (15 mL) and saturated aqueous $NaHCO_3$ (15 mL) were added. The mixture was stirred for 30 min, and the two phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. A flash chromatography on silica gel (PE/EtOAc 100/2) afforded the propargylic ketone **5** as a colorless oil (787 mg, 61% for the three steps): $[\alpha]^{20}_D$ = +2.5 (*c* 1.80, $CHCl_3$); IR (neat) 2956, 2930, 2886, 2858, 1686, 1472, 1463, 1388, 1361, 1255, 1071 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.73 (dd, *J* = 10.1, 5.7 Hz, 1H), 3.65 (dd, *J* = 6.8, 3.0 Hz, 1H), 3.62 (dd, *J* = 5.0, 2.91 Hz, 1H), 3.38 (dd, *J* = 10.0, 8.0 Hz, 1H), 3.19 (s, 1H), 2.73 (dd, *J* = 15.7, 2.7 Hz, 1H), 2.38 (dd, *J* = 15.6, 10.4 Hz, 1H), 2.30 (m, 1H), 1.86 (m, 1H), 1.75 (qd, *J* = 6.2, 1.5 Hz, 1H), 0.97−0.88 (m, 36H), 0.09 (s, 3H), 0.08 (s, 6H), 0.07 (s, 3H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.6 (s), 81.8 (d), 78.2 (s), 76.7 (d), 76.5 (d), 65.3 (t), 47.9 (t), 42.2 (d), 39.9 (d), 34.9 (d), 26.4 (3q), 26.2 (3q), 26.1 (3q), 18.7 (s), 18.5 (s), 18.4 (s), 17.6 (q), 15.3 (q), 12.5 (q), −3.0 (q), −3.4 (2q), −4.1 (q), −5.1 (2q); MS (EI) 395 (1), 239 (10), 147 (16), 115 (15), 89 (32), 75 (31), 73 (100), 57 (11); HRMS (ESI) calcd for $C_{31}H_{64}O_4Si_3$ + Na^+ 607.4005, found 607.3991.

(3*S*,5*S*,6*S*,7*R*,8*S*,9*S*)-6,8,10-Tris(*tert*-butyldimethylsilyloxy)-5,7,9-trimethyl-dec-1-yn-3-ol (6). To a solution of **5** (606 mg, 1.04 mmol, 1 equiv) in THF (12 mL) was added (*S*)-CBS (1 M in toluene, 2.1 mL, 2.07 mmol, 2 equiv). The reaction mixture was stirred for 15 min at rt, and then cooled to −30 °C. $BH_3 \cdot Me_2S$ (2 M in THF, 2.6 mL, 5.18 mmol, 5 equiv) was added over 1.5 h *via* a syringe pump. Once the addition was completed, the reaction mixture was stirred for 1 h and ethanol (3.7 mL) was added carefully. The mixture was warmed to rt and water and EtOAc were added. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. A flash chromatography on silica gel (PE/EtOAc 100/1 to 100/3) furnished the propargylic alcohol **6** (520 mg, 86%) as a colorless oil. According to GC/MS analysis of the crude product, the diastereoselectivity of the reaction was 97/3. **6**: $[\alpha]^{20}_D$ = −20.3 (*c* 0.95, $CHCl_3$); IR (neat) 3314, 2955, 2929, 2886, 2857, 1472, 1463, 1388, 1361, 1254, 1054 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.41 (m, 1H), 3.76 (dd, *J* = 10.0, 5.3 Hz, 1H), 3.65 (dd, *J* = 6.4, 2.7 Hz, 1H), 3.62 (dd, *J* = 4.9, 3.0 Hz, 1H), 3.38 (dd, *J* = 10.0, 8.4 Hz, 1H), 2.46 (d, *J* = 2.0 Hz, 1H), 1.98−1.72 (m, 5H), 1.61−1.47 (m, 1H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.95−0.84 (m, 3H), 0.91 (s, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.10 (s, 6H), 0.08 (s, 6H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 85.8 (s), 77.0 (d), 76.7 (d), 72.7 (d), 65.5 (t), 60.5 (d), 42.0 (d), 39.9 (t), 39.6 (d), 35.0 (d), 26.4 (3q), 26.2 (3q), 26.2 (3q), 18.7 (s), 18.5 (s), 18.5 (s), 16.8 (q), 15.7 (q), 12.3 (q), −3.2 (q), −3.3 (q), −3.4 (q), −4.1 (q) −5.2 (2q); MS (EI) 317 (1), 147 (19), 133 (11), 115 (15), 109 (20), 89 (46), 75 (49), 74 (11), 73 (100), 57 (12), 55 (12); HRMS (ESI) calcd for $C_{31}H_{66}O_4Si_3$ + Na^+ 609.4161, found 609.4154.

(3*S*,5*S*,6*S*,7*R*,8*S*,9*S*)-3,6,8,10-Tetrakis(*tert*-butyldimethylsilyloxy)-5,7,9-trimethyl-dec-1-yne (7). To a solution of alcohol **6** (508 mg, 0.87 mmol, 1 equiv) in CH_2Cl_2 (50 mL) at −78 °C were added successively 2,6-lutidine (400 μL, 3.46 mmol, 4 equiv) and TBSOTf (400 μL, 1.73 mmol, 2 equiv). After 2 h at −78 °C, the reaction mixture was warmed to rt. After 20 h, a saturated aqueous solution of $NaHCO_3$ (50 mL) was added, and the two phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (PE/EtOAc 100/0 to 100/3) to give the alkyne **7** as a colorless oil (590 mg, 97%): $[\alpha]^{20}_D$ = −32.1 (*c* 1.30, $CHCl_3$); IR (neat) 3313, 2956, 2929, 2886, 2858, 2367, 1472, 1463, 1389, 1361, 1254, 1086, 1039, 1005 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.39 (ddd, *J* = 9.8, 3.4, 2.0 Hz, 1H), 3.78 (dd, *J* = 10.0, 5.2 Hz, 1H), 3.69−3.58 (m, 2H), 3.34 (dd, *J* = 10.0, 8.6 Hz, 1H), 2.37 (d, *J* = 2.1 Hz, 1H), 1.95−1.75 (m, 4H), 1.45 (m, 1H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.94−0.86 (m, 42H), 0.16 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.07 (s, 3H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 86.5 (s), 77.4 (d), 77.2 (d), 72.0 (d), 65.5 (t), 60.6 (d), 41.9 (d), 40.2 (t), 39.3 (d), 34.7 (d), 26.4 (3q), 26.2 (3q), 26.2 (3q), 26.0 (3q), 18.7 (s), 18.5 (s), 18.5 (s), 18.3 (s), 15.9 (q), 15.8 (q), 12.4 (q), −3.3 (q), −3.3 (q), −3.4 (q), −4.1 (q), −4.3 (q), −4.9 (q), −5.2 (q), −5.2 (q); HRMS (ESI) calcd for $C_{37}H_{80}O_4Si_4$ + Na^+ 723.5026, found 723.5027.

(3*S*,5*S*,6*S*,7*R*,8*S*,9*S*)-3,6,8,10-Tetrakis(*tert*-butyldimethylsilyloxy)-5,7,9-trimethyl-decan-2-one (8). To a solution of **13** (60 mg, 0.086 mmol, 1 equiv) in THF (2 mL) were added successively $Hg(OAc)_2$ (5 mg, 0.019 mmol, 0.22 equiv), PPTS (11 mg, 0.120 mmol, 1.4 equiv), and water (20 μL). The reaction mixture was heated at 45 °C and stirred at this temperature overnight. A saturated aqueous solution of $NaHCO_3$ (2 mL) and Et_2O (2 mL) were added. The two phases were separated, and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (PE/EtOAc 100/2), and the methyl ketone **8** (25 mg, 41%) was obtained: $[\alpha]^{20}_D$ = −30.3 (*c* 0.65, $CHCl_3$); IR (neat) 2929, 2857, 1718, 1462,1388, 1361, 1252, 1072, 1037, 1005 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.01 (dd, *J* = 10.8, 2.3 Hz, 1H), 3.75 (dd, *J* = 10.1, 5.7 Hz, 1H), 3.65 (dd, *J* = 3.9, 3.9 Hz, 1H), 3.61 (dd, *J* = 7.2, 2.6 Hz, 1H), 3.35 (dd, *J* = 10.0, 7.8 Hz, 1H), 2.14 (s, 3H), 1.95−1.80 (m, 2H), 1.78−1.73 (m, 1H), 1.67 (ddd, *J* = 13.3, 10.8, 2.1 Hz, 1H), 1.25 (m, 1H), 0.97−0.87 (m, 45H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.5 (s), 77.4 (d), 77.2 (d), 77.0 (d), 65.3 (t), 41.5 (d), 39.7 (d), 36.4 (t), 34.5 (d), 26.3 (3q), 26.2 (3q), 26.2 (3q), 26.0 (3q), 24.7 (q), 18.7 (s), 18.5 (2s), 18.2 (s), 15.9 (q), 15.3 (q), 12.4 (q), −3.0 (q), −3.3 (q), −3.4 (q),

−3.9 (q), −4.6 (q), −4.9 (q), −5.2 (q), −5.2 (q); HRMS (ESI) calcd for $C_{37}H_{82}O_5Si_4 + Na^+$ 741.5132, found 741.5131.

(3*R*,4*R*,5*R*)-3,5-Dimethyl-6-[*tert*-butyldiphenylsilyloxy]-hex-1-en-4-ol (10). To a solution of (*S*,*S*)-Ti-**I** (11.5 mmol, 1.15 equiv) at −78 °C in Et_2O (100 mL) was added a solution of (*R*)-3-(*tert*-butyldiphethylsilyloxy)-2-methyl-propionaldehyde **9**[13] (3.26 g, 10 mmol, 1 equiv) in Et_2O (15 mL). After 20 h at −78 °C, deionized water (50 mL) was added. After 24 h at rt, the reaction media was filtered on a pad of Celite, the two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The organic layer was washed with a saturated aqueous solution of NaCl, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. Pentane (150 mL) was added and after 3 h of vigorous stirring at rt, (*S*,*S*)-Taddol was filtered off. The filtrate was concentrated and the crude was purified by flash chromatography on silica gel (PE/Et_2O 100/5, 95/5 then 9/1) to give the homoallylic alcohol **10** (2.707 g, 71%) as a colorless oil. The diastereomeric ratio was estimated to be 95/5 by ^1H NMR analysis. **10**: $[\alpha]^{20}_D = -4.4$ (*c* 1.09, $CHCl_3$); IR (neat) 3504, 2930, 2857, 1638, 1471, 1427, 1389, 1107 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71−7.65 (m, 4H), 7.46−7.35 (m, 6H), 5.88−5.77 (ddd, J = 16.6, 10.5, 8.5 Hz, 1H), 5.15−5.05 (m, 2H), 3.72 (d, J = 5.0 Hz, 2H), 3.59 (dt_{app}, J = 8.5, 2.9 Hz, 1H), 2.42 (d, J = 2.5 Hz, 1H), 2.28 (m, 1H), 1.82 (m, 1H), 1.06 (s, 9H), 0.94 (d, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0 (d), 135.8 (2d), 135.7 (2d), 133.5 (s), 133.4 (s), 129.8 (2d), 127.8 (4d), 115.5 (t), 76.2 (d), 68.5 (t), 41.8 (d), 36.7 (d), 27.0 (3q), 19.3 (s), 16.8 (q), 9.7 (q); MS (EI) 325 ([M − *t*-Bu]$^+$, 2), 269 (13), 200 (19), 199 (100), 197 (11), 183 (16), 181 (12), 135 (17), 109 (71), 67 (11); HRMS (ESI) calcd for $C_{24}H_{34}O_2Si + Na^+$ 405.2226, found 405.2225.

(3*R*,4*R*,5*R*)-3,5-Dimethyl-4-[*tert*-butyldimethylsilyloxy]-6-[*tert*-butyldiphenylsilyloxy]-hex-1-ene (11). To a solution of alcohol **10** (4.63 g, 12.08 mmol, 1 equiv) in CH_2Cl_2 (120 mL) at −78 °C were added successively 2,6-lutidine (4.1 mL, 36.23 mmol, 3 equiv) and TBSOTf (4.1 mL, 18.11 mmol, 1.5 equiv). The reaction mixture was allowed to slowly warm to rt and stirred overnight. A saturated aqueous solution of $NaHCO_3$ (100 mL) was added, the two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (PE/Et_2O: 100/5) to afford alkene **11** (5.35 g, 90%) as a colorless oil: $[\alpha]^{20}_D = -1.7$ (*c* 0.95, $CHCl_3$); IR (neat) 2929, 2856, 1639, 1589, 1461, 1360, 1251, 1110, 1048, 1004 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68−7.62 (m, 4H), 7.44−7.33 (m, 6H), 5.80 (m, 1H), 4.96−4.88 (m, 2H), 3.75 (dd, J = 3.5, 4.8 Hz, 1H), 3.54 (dd, J = 10.1 Hz, 7.2 Hz, 1H), 3.42 (dd, J = 9.1, 6.4 Hz, 1H), 2.31 (m, 1H), 1.81 (m, 1H), 1.05 (s, 9H), 0.97 (d, J = 7.2 Hz, 3H), 0.87 (s, 9H), 0.84 (d, J = 6.9 Hz, 3H), 0.03 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0 (d), 135.7 (2d), 135.7 (2d), 134.1 (s), 134.1 (s), 129.6 (2d), 127.6 (4d), 114.1 (t), 75.3 (d), 66.9 (t), 43.2 (d), 39.1 (d), 27.0 (3q), 26.2 (3q), 19.4 (s), 18.5 (s), 17.1 (q), 12.0 (q), −3.6 (q), −4.0 (q); MS (EI) 443 (2), 439 ([M − *t*-Bu]$^+$,15), 383 (11), 382 (28), 381 (79), 313 (21), 307 (25), 293 (13), 272 (12), 271 (44), 269 (12), 257 (12), 253 (13), 251 (17), 235 (20), 227 (14), 211 (19), 210 (16), 209 (74), 200 (13), 199 (74), 198 (13), 197 (64), 195 (42), 193 (29), 191 (16), 189 (18), 181 (26), 179 (11), 175 (15), 165 (17), 163 (16), 145 (31), 136 (14), 135 (100), 121 (10), 115 (12), 109 (56), 105 (19), 91 (39), 75 (35), 73 (53), 67 (10), 59 (12); HRMS (ESI) calcd for $C_{30}H_{48}O_2Si_2 + Na^+$ 519.3085, found 519.3084.

(3*S*,4*S*,5*R*,6*S*,7*R*)-3,5,7-Trimethyl-6-[*tert*-butyldimethylsilyloxy]-8-[*tert*-butyldiphenylsilyloxy]-oct-1-en-4-ol (12). To a solution of alkene **11** (3.753 g, 7.49 mmol, 1 equiv) in a mixture of water and *tert*-butanol (1/1, 40 mL) were added osmium tetroxide (0.079 M in *tert*-butanol, 1.9 mL, 0.15 mmol, 0.02 equiv) and NMO (964 mg, 8.24 mmol, 1.1 equiv). The reaction mixture was stirred for 8 h, and additional portions of osmium tetroxide (0.079 M in *tert*-butanol, 1.9 mL, 0.15 mmol, 0.02 equiv) and NMO (964 mg, 8.24 mmol, 1.1 equiv) were added. After 20 h at rt, solid $Na_2S_2O_3$ (8 g), Celite (16 g), and EtOAc (30 mL) were added. The mixture was filtered through a pad of Celite which was thoroughly washed with EtOAc. The filtrate was evaporated under reduced pressure, and the residue was dissolved in a 1/1 mixture of water and THF (80 mL). Sodium periodate (4.00 g, 18.69 mmol, 2.5 equiv) was added to this solution and after 3 h, the mixture was filtered through a pad of Celite. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the aldehyde which was used without further purification in the following step. To a solution of (*R*,*R*)-Ti-**II** (10.49 mmol, 1.4 equiv) at −78 °C in Et_2O (70 mL) was added a solution of the previous aldehyde (7.49 mmol, 1 equiv) in Et_2O (15 mL). After 20 h at −78 °C, deionized water (100 mL) was added, and the mixture was allowed to warm to rt. After 72 h at rt, the reaction mixture was filtered through a pad of Celite, the two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The organic layer was washed with a saturated aqueous solution of NaCl, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. Pentane (100 mL) was added, and after 20 h of vigorous stirring at rt, the precipitated (*R*,*R*)-Taddol was filtered off. The filtrate was concentrated, and the crude was purified by flash chromatography on silica gel (PE/Et_2O 100/3 to 100/5) to give homoallylic alcohol **12** (3.317 g, 80%, 3 steps) as a colorless oil. The diastereomeric ratio was estimated to 98/2 by ^1H NMR analysis. **12**: $[\alpha]^{20}_D = -20.9$ (*c* 1.12, $CHCl_3$); IR (neat) 3497, 2957, 2929, 2856, 1638, 1589, 1471, 1461, 1387, 1360, 1252, 1105, 1044, 1001 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67−7.61 (m, 4H), 7.45−7.34 (m, 6H), 5.79 (m, 1H), 5.12−5.03 (m, 2H), 3.92 (t, J = 3.5 Hz, 1H), 3.61−3.55 (m, 2H), 3.48 (dd, J = 9.9, 6.5 Hz, 1H), 2.90 (d, J = 1.7 Hz, 1H), 2.22 ($sext_{app}$, J = 7.8 Hz, 1H), 1.95 (m, 1H), 1.71 (m, 1H), 1.05 (s, 9H), 0.95 (d, J = 7.1 Hz, 3H), 0.93 (d, J = 7.4 Hz, 3H), 0.88 (s, 9H), 0.79 (d, J = 7.1 Hz, 3H), 0.09 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5 (d), 135.7 (4d), 133.8 (2s), 129.7 (2d), 127.7 (4d), 114.9 (t), 77.6 (d), 74.3 (d), 66.9 (t), 41.7 (d), 39.4 (d), 37.4 (d), 27.0 (3q), 26.3 (3q), 19.3 (s), 18.5 (s), 16.5 (q), 12.9 (q), 11.1 (q), −3.6 (q), −3.9 (q); MS (EI) 365 (3), 281 (10), 239 (15), 199 (44), 197 (17), 195 (10), 183 (16), 149 (12), 91 (12), 78 (25), 75 (100), 73 (18), 56 (13), 55 (13); HRMS (ESI) calcd for $C_{33}H_{54}O_3Si_2 + Na^+$: 577.3504, found 577.3504.

(3*S*,4*S*,5*R*,6*S*,7*R*)-3,5,7-Trimethyl-4,6-[*tert*-butyldimethylsilyloxy]-8-[*tert*-butyldiphenylsilyloxy]-oct-1-ene (13). To a solution of alcohol **12** (3.317 g, 5.98 mmol, 1 equiv) in CH_2Cl_2 (60 mL) at −78 °C were added successively 2,6-lutidine (2.1 mL, 17.94 mmol, 3 equiv) and TBSOTf (2.1 mL, 8.97 mmol, 1.5 equiv). The reaction mixture was allowed to slowly warm to rt. After 20 h, the mixture was cooled to −78 °C and treated with additional portions of 2,6-lutidine (0.7 mL, 5.98 mmol, 1 equiv) and TBSOTf (0.7 mL, 2.99 mmol, 0.5 equiv). A saturated aqueous solution of $NaHCO_3$ (50 mL) was added, the two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (PE/Et_2O 100/5) to afford alkene **13** (5.35 g, 90%) as a colorless oil: $[\alpha]^{20}_D = -7.0$ (*c* 1.01, $CHCl_3$); IR (neat) 2928, 1471, 1360, 1251, 1110, 1040, 1004 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69−7.61 (m, 4H), 7.45−7.33 (m, 6H), 5.85 (m, 1H), 5.07−4.99 (m, 2H), 3.90 (d, J = 6.0 Hz, 1H), 3.55 (dd, J = 6.0, 2.5 Hz, 1H), 3.46 (dd, J = 9.6, 9.6 Hz, 1H), 3.33 (dd, J = 9.5 Hz, 6.1 Hz, 1H), 2.39 (m, 1H), 1.88−1.76 (m, 2H), 1.06 (s, 9H), 0.98 (d, J = 7.1 Hz, 3H), 0.92 (s, 9H), 0.89 (d, J = 7.0 Hz, 3H), 0.84 (s, 9H), 0.78 (d, J = 6.5 Hz, 3H), 0.08 (s, 6H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5 (d), 135.7 (2d), 135.7 (2d), 134.0 (s), 134.0 (s), 129.6 (2d), 127.7

(4d), 114.9 (t), 76.7 (d), 71.7 (d), 67.6 (t), 43.4 (d), 42.4 (d), 37.6 (d), 27.0 (3q), 26.3 (3q), 26.1 (3q), 19.3 (s), 18.6 (s), 18.4 (s), 17.1 (q), 12.3 (q), 11.3 (q), −3.3 (q), −3.3 (q), −3.4 (q), −4.6 (q); MS (EI) 482 (3), 349 (10), 293 (10), 253 (13), 251 (16), 239 (26), 227 (20), 209 (17), 207 (10), 200 (17), 199 (100), 195 (19), 193 (10), 191 (12), 185 (10), 183 (22), 149 (15), 147 (11), 145 (22), 135 (65), 133 (12), 115 (21), 91 (39), 75 (55), 73 (83); HRMS (ESI) calcd for $C_{39}H_{68}O_3Si_3 + Na^+$ 691.4369, found 691.4375.

(2*S*,3*S*,4*R*,5*S*,6*R*)-2,4,6-Trimethyl-3,5-[*tert*-butyldimethylsilyloxy]-7-[*tert*-butyldiphenylsilyloxy]-heptan-1-ol (14). To a solution of alkene **13** (2.589 g, 3.88 mmol, 1 equiv) in a 1/1 mixture of water and *tert*-butanol (20 mL) were added osmium tetroxide (0.079 M in *tert*-butanol, 1.5 mL, 0.12 mmol, 0.03 equiv) and NMO (500 mg, 4.26 mmol, 1.1 equiv). The reaction mixture was stirred for 8 h, and additional portions of osmium tetroxide (0.079 M in *tert*-butanol, 1.5 mL, 0.12 mmol, 0.03 equiv) and NMO (500 mg, 4.26 mmol, 1.1 equiv) were added. After 20 h at rt, solid $Na_2S_2O_3$ (8 g), Celite (16 g) and EtOAc (30 mL) were added. The mixture was filtered through a pad of Celite which was thoroughly washed with EtOAc. The filtrate was evaporated under reduced pressure, and the residue was dissolved in a 1/1 mixture of water/THF (80 mL). Sodium periodate (4.00 g, 18.69 mmol, 4.9 equiv) was added to this solution. After 5 h, the mixture was filtered through a pad of Celite. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the aldehyde which was used without any further purification in the following step. To a solution of the previous synthesized aldehyde (3.88 mmol, 1 equiv) in methanol (40 mL) at 0 °C was added portionwise $NaBH_4$ (442 mg, 11.63 mmol, 3 equiv). The reaction mixture was warmed to rt and after 1 h, a saturated aqueous solution of NH_4Cl (40 mL), a saturated aqueous solution of potassium/sodium tartrate (40 mL) and EtOAc (120 mL) were added. After 1 h, the two phases were separated. The aqueous layer was extracted with EtOAc (3 × 100 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (PE/Et_2O 9/1) to afford the primary alcohol **14** (2.07 g, 79%, 3 steps) as a colorless oil: $[\alpha]^{20}_D$ = −9.8 (*c* 1.05, $CHCl_3$); IR (neat) 3440, 2928, 2856, 1471, 1360, 1251, 1108, 1043, 1004 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67−7.58 (m, 4H), 7.45−7.33 (m, 6H), 3.96 (d_{app}, J = 6.0 Hz, 1H), 3.92 (dd, J = 10.9, 4.1 Hz, 1H), 3.69 (dd, J = 6.7, 2.3 Hz, 1H), 3.53 (dd, J = 10.9, 4.1 Hz, 1H), 3.47 (t_{app}, J = 9.4 Hz, 1H), 3.35 (dd, J = 9.0, 6.0 Hz, 1H), 2.59 (m, 1H, OH), 1.98 ($sext_{app}$, J = 7.0 Hz, 1H), 1.84 (m, 1H), 1.75 (m, 1H), 1.05 (s, 9H), 1.02 (d, J = 7.1 Hz, 3H), 0.96 (d, J = 7.1 Hz, 3H), 0.92 (s, 9H), 0.85 (s, 9H), 0.78 (d, J= 7.1 Hz, 3H), 0.14 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6 (2d), 135.5 (2d), 133.9 (s), 133.8 (s), 129.7 (2d), 127.7 (4d), 79.1 (d), 71.6 (d), 67.1 (t), 65.1 (t), 43.1 (d), 38.2 (d), 37.7 (d), 27.0 (3q), 26.3 (3q), 26.1 (3q), 19.2 (s), 18.5 (s), 18.5 (s), 15.8 (q), 13.0 (q), 11.0 (q), −3.1 (q), −3.3 (2q), −4.4 (q); MS (EI) 483 (3), 227 (12), 207 (13), 199 (19), 197 (20), 185 (25), 145 (17), 115 (10), 91 (12), 78 (45), 77 (18), 75 (100), 73 (31), 56 (18); HRMS (ESI) calcd for $C_{38}H_{68}O_4Si_3 + Na^+$ 695.4318, found 695.4314.

(2*S*,3*S*,4*S*,5*R*,6*R*)-1-Iodo-2,4,6-trimethyl-3,5-[*tert*-butyldimethylsilyloxy]-7-[*tert*-butyldiphenylsilyloxy]-heptane (15). To a solution of **14** (1.06 g, 1.58 mmol, 1 equiv) in CH_2Cl_2 (20 mL) were added successively triphenylphosphine (870 mg, 3.31 mmol, 2.1 equiv) and imidazole (343 mg, 5.05 mmol, 2.1 equiv). After complete dissolution, the mixture was cooled to 0 °C, and iodine (841 mg, 3.31 mmol, 2.1 equiv) was added. After 30 min at 0 °C, the mixture was warmed to rt and stirred overnight. The solvent was removed *in vacuo*, and the crude was purified by flash chromatography on silica gel (PE/Et_2O 100/2 to 100/4) to afford primary alkyl iodide **15** (1.197 g, 97%) as a colorless oil: $[\alpha]^{20}_D$ = −4.2 (*c* 1.28, $CHCl_3$); IR (neat) 2928, 2856, 1471, 1427, 1388, 1360, 1522, 1106, 1042, 1005 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68−7.62 (m, 4H), 7.44−7.34 (m, 6H), 3.81 (dd, J = 6.4, 0.9 Hz, 1H), 3.66 (t_{app}, J = 4.0 Hz, 1H), 3.49 (dd, J = 9.5, 8.0 Hz, 1H), 3.38 (dd, J = 10.1, 6.5 Hz, 1H), 3.35 (dd, J = 9.6, 4.0 Hz, 1H), 2.95 (t_{app}, J = 9.6 Hz, 1H), 1.93 (m, 1H), 1.88−1.74 (m, 2H), 1.07 (s, 9H), 1.03 (d, J = 6.9 Hz, 3H), 0.90 (s, 9H), 0.88 (d, J = 7.6 Hz, 3H), 0.84 (s, 9H), 0.81 (d, J = 6.6 Hz, 3H), 0.09 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7 (4d), 133.9 (2s), 129.6 (2d), 127.7 (4d), 75.8 (d), 73.1 (d), 67.5 (t), 42.5 (d), 42.3 (d), 38.1 (d), 27.1 (3q), 26.2 (3q), 26.1 (3q), 19.3 (s), 18.6 (s), 18.5 (s), 18.0 (q), 12.1 (q), 11.1 (q), 11.1 (t), −3.0 (q), −3.0 (q), −3.1 (q), −3.4 (q); MS (EI) 511 (1), 313 (21), 309 (14), 199 (18), 197 (12), 185 (11), 157 (14), 135 (23), 115 (29), 91 (12), 78 (30), 77 (17), 75 (100), 67 (10), 57 (20), 56 (21), 55 (11); HRMS (ESI) calcd for $C_{38}H_{67}O_3ISi_3 + Na^+$ 805.3335, found 805.3339.

(*E*)-1-Methyl-1-propenylmagnesium Bromide. (*E*)-2-bromobut-2-ene (510 μL, 5 mmol, 1 equiv) was dissolved in Et_2O (3 mL), and the solution was cooled to −78 °C. *t*-BuLi (1.7 M pentane, 6 mL, 10 mmol, 2 equiv) was added dropwise, and the mixture was stirred for 2 h at −78 °C and then 45 min at 0 °C. After cooling to −78 °C, the mixture was added dropwise to a suspension of $MgBr_2 \cdot OEt_2$ (1.455 g, 5.680 mmol, 1.1 equiv) in THF (4 mL) at −78 °C. Once the addition was complete, the mixture was allowed to warm to rt and stirred for 2 h. Pentane and Et_2O were removed carefully under reduced pressure. THF (6 mL) was added to the mixture in order to obtain a ca. 0.5 M solution of the Grignard reagent.

(*E*)-(5*S*,6*S*,7*R*,8*S*,9*R*)-6,8-Bis(*tert*-butyldimethylsilyloxy)-10-(*tert*-butyldiphenylsilyloxy)-3,5,7,9-tetramethyl-dec-2-ene (16). To a solution of primary alkyl iodide **15** (312 mg, 0.40 mmol, 1 equiv) and anhydrous $FeCl_3$ (0.1 M in THF, 400 μL, 0.04 mmol, 0.1 equiv) at 0 °C in THF (1 mL) was added a premixed solution of TMEDA (380 μL, 0.76 mmol, 1.9 equiv) and (*E*)-1-methyl-1-propenylmagnesium bromide (0.5 M in THF, 4 mL, 2.00 mmol, 5 equiv) *via* a syringe pump at a 5 mL/h rate. Once the addition was completed, the reaction mixture was warmed to rt. After 30 min, the mixture was quenched by addition of a saturated aqueous solution of NH_4Cl (1 mL). The two phases were separated, and the aqueous layer was extracted with diethyl ether (3 × 5 mL). The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated. The same reaction was repeated on alkyl iodide **22** (344 mg, 0.440 mmol, 1 equiv). The two crude products were combined for purification, which was achieved by flash chromatography on silica gel (PE/EtOAc 100/1 to 100/5) to give the alkene **16** (451 mg, 76%) as a colorless oil: $[\alpha]^{20}_D$ = −1.33 (*c* 0.75, $CHCl_3$); IR (neat) 2956, 2929, 2857, 1472, 1428, 1388, 1361, 1252, 1112, 1044, 1006 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69−7.61 (m, 4H), 7.44−7.33 (m, 6H), 5.17 (q, J = 5.7 Hz, 1H), 3.77 (d_{app}, J = 5.8 Hz, 1H), 3.57−3.54 (m, 1H), 3.47 (m, 1H), 3.36 (dd, J = 12.5, 9.7 Hz, 1H), 2.09 (d, J = 9.7 Hz, 1H), 1.92 (m, 1H), 1.85 (m, 1H), 1.78−1.71 (m, 2H), 1.56−1.54 (2s, 6H), 1.06 (s, 9H), 0.94−0.89 (m, 12H), 0.86−0.82 (m, 12H), 0.78 (d, J = 6.4 Hz, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8 (2d), 135.8 (2d), 134.4 (s), 134.1 (s), 134.0 (s), 129.7 (2d), 127.7 (4d), 120.1 (d), 76.8 (d), 73.4 (d), 67.9 (t), 42.4 (t), 41.7 (d), 37.8 (d), 37.4 (d), 27.1 (3q), 26.4 (3q), 26.2 (3q), 19.4 (s), 18.7 (s), 18.5 (s), 15.8 (q), 15.5 (q), 13.6 (q), 11.9 (q), 11.4 (q), −3.2 (q), −3.3 (q), −3.5 (q), −4.4 (q); HRMS (ESI) calcd for $C_{42}H_{74}O_3Si_3 + Na^+$ 733.4838, found 733.4842.

(*E*)-(2*R*,3*S*,4*R*,5*S*,6*S*)-3,5-Bis(*tert*-butyldimethylsilyloxy)-2,4,6,8-tetramethyl-dec-8-en-1-ol (17). To a solution of alkene **16** (585 mg, 0.82 mmol, 1 equiv) in THF (10 mL) was added an equimolar mixture of AcOH/TBAF portionwise over 2 days (7 additions of 1.7 mL, ca. 11.9 mL added over two days, 11.54 mmol, 14 equiv). A saturated aqueous solution of $NaHCO_3$ was then added (20 mL), and the two phases were separated. The aqueous layer was extracted

with Et_2O (3 × 30 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (PE/EtOAc 100/2), and the primary alcohol **17** was obtained (284 mg, 73%) as a colorless oil: $[\alpha]^{20}_D = -19.9$ (*c* 1.15, $CHCl_3$); IR (neat) 2929, 2857, 1472, 1386, 1361, 1253, 1037, 1006 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.24−5.15 (m, 1H), 3.79 (dd, *J* = 6.3, 1.3 Hz, 1H), 3.53 (dd, *J* = 4.3, 3.1 Hz, 1H), 3.51−3.41 (m, 2H), 2.11 (d_{app}, *J* = 9.5 Hz, 1H), 1.92−1.71 (m, 4H), 1.57 (2 br s, 6H), 1.39 (br s, 1H, OH), 0.94−0.90 (m, 3H), 0.92 (s, 9H), 0.91 (s, 9H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.79 (d, *J* = 6.4 Hz, 3H), 0.10 (s, 3H), 0.08 (s, 3H), 0.07 (2s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.4 (s), 120.2 (d), 77.1 (d), 73.7 (d), 67.2 (t), 42.2 (t), 41.5 (d), 37.8 (d), 36.6 (d), 26.3 (3q), 26.2 (3q), 18.7 (s), 18.5 (s), 15.9 (q), 15.7 (q), 13.5 (q), 12.0 (q), 11.6 (q), −3.1 (q), −3.2 (q), −3.4 (q), −4.4 (q); HRMS (ESI) calcd for $C_{26}H_{56}O_3Si_2 + Na^+$ 495.3660, found 495.3653.

(*E*)-(2*S*,3*S*,4*R*,5*S*,6*S*,8*S*,11*R*,12*R*,13*S*,14*R*,15*S*,16*S*)-1,3,5,8,13,15-Hexakis(*tert*-butyldimethylsilyloxy)-11-hydroxy-2,4,6,12,14,16,18-heptamethyl-icos-18-en-9-one (19). To a solution of alcohol **17** (176 mg, 0.37 mmol, 1 equiv) in CH_2Cl_2 (30 mL) at 0 °C was added Dess−Martin periodinane (395 mg, 0.93 mmol, 2.5 equiv). The reaction mixture was stirred for 15 min at 0 °C and then warmed to rt. After 2 h at rt, a saturated aqueous solution of $Na_2S_2O_3$ (15 mL) and a saturated aqueous solution of $NaHCO_3$ (15 mL) were added, and the mixture was stirred for 45 min. The two phases were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was filtered on silica gel (PE/EtOAc 100/3) to afford aldehyde **18** (174 mg, 99%). To a solution of methyl ketone **8** (302 mg, 0.420 mmol, 1 equiv) at −78 °C in THF (2 mL) was added a freshly prepared solution of LDA (0.5 M in THF, 1.09 mL, 0.55 mmol, 1.3 equiv). The reaction mixture was stirred for 2 h at −78 °C and a solution of aldehyde **18** (99 mg, 0.21 mmol, 0.5 equiv) in THF (1 mL) was added. After 2 h at −78 °C a saturated aqueous solution of NH_4Cl (3 mL) was added, and the mixture was warmed to rt. The two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. A ^1H NMR analysis of the crude product allowed to estimate the diastereomeric ratio **19**/**19′** to be 3/1. The crude product was purified by flash chromatography (PE/toluene 85/15 to 5/5) to afford the ketone **19** (112 mg, 45%), its diastereomer **19′** as a mixture with aldehyde **18** (25 mg), and the recovered methyl ketone **8** (150 mg). Compound **19**: $[\alpha]^{20}_D = -10.0$ (*c* 1.65, $CHCl_3$); IR (neat) 2956, 2929, 2886, 2858, 2366, 1707, 1472, 1463, 1388, 1361, 1254, 1077, 1034, 1006 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.20 (m, 1H), 4.18 (d, *J* = 6.2 Hz, 1H), 4.02 (d, *J* = 11.0 Hz, 1H), 3.81−3.70 (m, 2H), 3.70−3.60 (m, 3H), 3.40−3.27 (m, 2H), 3.01 (d, *J* = 18.4 Hz, 1H), 2.34 (dd, *J* = 18.7, 10.0 Hz, 1H), 2.13 (d, *J* = 12.5 Hz, 1H), 1.95−1.62 (m, 9H), 1.57 (br s, 6H), 0.98−0.85 (m, 66H), 0.78 (d, *J* = 7.0 Hz, 6H), 0.13−0.01 (m, 36H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.7 (s), 134.6 (s), 120.0 (d), 77.4 (d), 77.3 (d), 77.3 (d), 77.0 (d), 76.8 (d), 72.0 (d), 69.0 (d), 65.3 (t), 42.1 (t), 41.6 (d), 41.5 (d), 41.2 (t), 39.9 (d), 39.6 (d), 36.6 (d), 36.3 (t), 26.4 (6q), 26.3 (3q), 26.2 (3q), 26.2 (3q), 26.0 (3q), 18.7 (s), 18.7 (s), 18.6 (s), 18.5 (2s), 18.2 (s), 16.1 (q), 15.8 (q), 15.6 (q), 15.3 (q), 13.5 (q), 12.5 (q), 12.0 (q), 11.0 (q), −3.0 (q), −3.1 (q), −3.2 (q), −3.3 (2q), −3.4 (q), −3.9 (q), −4.3 (q), −4.6 (q), −4.9 (q), −5.2 (q), −5.2 (q); HRMS (ESI) calcd for $C_{63}H_{136}O_8Si_6 + Na^+$ 1211.8743, found 1211.8740.

(*E*)-(2*S*,3*S*,4*R*,5*S*,6*S*,8*S*,11*R*,12*R*,13*S*,14*R*,15*S*,16*S*)-1,3,5,8,13,15-Hexakis(*tert*-butyldimethylsilyloxy)-11-methoxy-2,4,6,12,14,16,18-heptamethyl-icos-18-en-9-one (20). To a solution of **19** (42 mg, 0.035 mmol, 1 equiv) in CH_2Cl_2 (400 μL) were added di-*tert*-butylpyridine (142 μL, 1.08 mmol, 31 equiv) and methyl triflate (107 μL, 0.533 mmol, 15 equiv). After 24 h at 50 °C, the reaction mixture was poured into water (1 mL), the two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 1 mL). The combined organic layers were washed with a saturated aqueous solution of NH_4Cl (3 mL), dried over $MgSO_4$, and concentrated *in vacuo*. A flash chromatography on silica gel (PE/toluene 95/5 to 8/2) afforded **20** (21 mg, 50%): $[\alpha]^{20}_D = -12.4$ (*c* 0.25, $CHCl_3$); IR (neat): 2932, 2858, 2362, 1721, 1472, 1361, 1255, 1091, 1037, 1006 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.20 (m, 1H), 4.09 (d_{app}, *J* = 10.0 Hz, 1H), 3.85 (d, *J* = 5.0 Hz, 1H), 3.74 (dd, *J* = 10.3, 5.7 Hz, 1H), 3.67−3.56 (m, 3H), 3.51 (br d, *J* = 4.8 Hz, 1H), 3.35 (t_{app}, *J* = 9.3 Hz, 1H), 3.23 (s, 3H), 2.71 (dd, *J* = 17.4, 7.9 Hz, 1H), 2.48 (dd, *J* = 17.7, 2.6 Hz, 1H), 2.07 (m, 1H), 1.93−1.72 (m, 8H), 1.59 (s, 3H), 1.55 (s, 3H), 1.34 (m, 1H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.93−0.87 (m, 3H), 0.92 (s, 9H), 0.91 (s, 18H), 0.89 (s, 9H), 0.89 (s, 9H), 0.87 (s, 9H), 0.86 (d, *J* = 7.4 Hz, 3H), 0.79 (d, *J* = 6.4 Hz, 3H), 0.78 (d, *J* = 6.8 Hz, 3H), 0.09 (s, 3H), 0.09 (s, 3H), 0.08−0.05 (m, 18H), 0.04 (s, 3H), 0.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.3 (s), 134.4 (s), 120.1 (d), 79.8 (d), 77.5 (d), 77.3 (d), 76.9 (d), 76.8 (d), 73.1 (d), 65.3 (t), 57.8 (q), 42.4 (d), 41.7 (t), 41.7 (d), 40.6 (d), 39.8 (t), 38.1 (d), 36.3 (d), 35.6 (t), 34.7 (d), 26.4 (6q), 26.2 (6q), 26.1 (3q), 26.1 (3q), 18.7 (s), 18.7 (s), 18.5 (2s), 18.4 (s), 18.3 (s), 16.3 (q), 16.0 (q), 15.7 (q), 15.2 (q), 13.5 (q), 12.5 (q), 11.7 (q), 11.0 (q), −2.9 (q), −3.2 (q), −3.2 (q), −3.3 (q), −3.4 (q), −3.5 (q), −3.9 (q), −4.2 (q), −4.4 (q), −4.9 (q), −5.2 (q), −5.2 (q); HRMS (ESI) calcd for $C_{64}H_{138}O_8Si_6 + Na^+$ 1225.8900, found 1225.8904.

Spiroketal 22. To a solution of **20** (40 mg, 0.033 mmol, 1 equiv) in THF/Py (1.2 mL/10 μL) was added portionwise HF·Py (200 μL, 7.920 mmol, 240 equiv) over 16 h. $NaHCO_3$ solid was added until pH 6−7, the suspension was filtered, and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/MeOH 100/0 to 100/3) to give **22** (6 mg, 25%) contaminated with an unknown impurity: $[\alpha]^{20}_D = -5.8$ (*c* 0.6, $CHCl_3$); IR (neat): 3384, 2957, 2929, 2857, 1716, 1462, 1386, 1361, 1253, 1033, 1005 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 5.60−5.53 (m, 1H), 4.25 (m, 1H), 4.07−3.99 (m, 1H), 3.99−3.93 (m, 2H), 3.87−3.78 (m, 2H), 3.72−3.66 (m, 1H), 3.52−3.46 (m, 1H), 3.40 (s, 3H), 2.61−2.51 (m, 1H), 2.40−2.12 (m, 7H), 2.06−1.91 (m, 2H), 1.91−1.84 (m, 4H), 1.77−1.70 (m, 3H), 1.70−1.60 (m, 1H), 1.55−0.89 (m, 30H), 0.57−0.49 (m, 6H), 0.49−0.22 (m, 12H); ^{13}C NMR (100 MHz, C_6D_6) δ 135.0 (s), 121.0 (d), 97.8 (s), 80.8 (d), 80.5 (d), 78.3 (d), 77.3 (d), 73.7 (d), 70.0 (d), 64.0 (t), 55.4 (q), 44.6 (d), 42.7 (t), 41.9 (t), 38.0 (d), 37.2 (d), 36.7 (t), 35.7 (d), 35.1 (d), 27.9 (d), 26.3 (3q), 26.2 (3q), 21.9 (q), 18.7 (s), 18.5 (s), 17.7 (q), 16.4 (q), 16.4 (q), 14.1 (q), 13.8 (q), 12.4 (q), 10.2 (q), −3.1 (q), −3.3 (q), −3.4 (q), −4.5 (q); HRMS (ESI) calcd for $C_{40}H_{80}O_7Si_2 + Na^+$ 751.5335, found 751.5352.

1-Methoxy-4-[(2*S*,3*S*,4*R*,5*S*,6*R*)-3,5-bis(*tert*-butyldimethylsilyloxy)-7-(*tert*-butyldiphenylsilyloxy)-2,4,6-trimethylheptyloxymethyl]benzene (23). To a solution of **14** (1.21 g, 1.78 mmol, 1 equiv) in toluene (12 mL) were added at 0 °C PMBOC(=NH)-CCl_3 (1.00 g, 3.56 mmol, 2 equiv) and $La(OTf)_3$ (52 mg, 0.09 mmol, 0.05 equiv). After 2 h at rt, the reaction mixture was filtered through a pad of Celite (Et_2O), and the resulting filtrate was evaporated under vacuum. The residue was purified by flash chromatography on silica gel (PE/Et_2O 100/0 to 100/3) to give **23** (1.19 g, 84%): $[\alpha]^{20}_D = -0.30$ (*c* 3.0, $CHCl_3$); IR (neat) 3072, 2956, 2930, 2886, 2858, 1613, 1588, 1513, 1472, 1462, 1428, 1389, 1361, 1302, 1249, 1172, 1111, 1085, 1040, 1006 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70−7.65 (m, 4H), 7.45−7.34 (m, 6H), 7.26−7.22 (m, 2H), 6.87−6.84 (m, 2H), 4.44 (d, *J* = 11.6 Hz, 1H), 4.40 (d, *J* = 11.6 Hz, 1H), 3.85 (d, *J* = 7.0 Hz, 1H), 3.79 (s, 3H), 3.68 (t_{app}, *J* = 4.0 Hz, 1H), 3.58−3.49 (m, 2H), 3.38 (dd, *J* = 10.1, 7.0 Hz, 1H), 3.22 (dd, *J* = 9.0, 7.8 Hz, 1H), 2.05 (m, 1H), 1.94−1.85 (m, 2H), 1.08 (s, 9H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.91 (s, 9H), 0.90 (m, 3H), 0.85 (s, 9H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.03 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1 (s), 135.7 (2d), 135.7 (2d), 134.1 (s), 134.0 (s), 131.0 (s), 129.6 (d), 129.6 (d), 129.2 (2d), 127.7 (4d), 113.8

(2d), 75.3 (d), 73.0 (d), 72.8 (t), 72.2 (t), 67.7 (t), 55.3 (q), 42.2 (d), 39.5 (d), 37.9 (d), 27.1 (3q), 26.3 (3q), 26.1 (3q), 19.3 (s), 18.7 (s), 18.5 (s), 15.0 (q), 12.1 (q), 11.1 (q), −3.3 (2q), −3.4 (q), −4.5 (q); HRMS (ESI) calcd for $C_{46}H_{76}O_5Si_3 + Na^+$ 815.4893, found 815.4905.

(2*R*,3*S*,4*S*,5*S*,6*S*)-3,5-Bis(*tert*-butyldimethylsilyloxy)-7-(4-methoxybenzyloxy)-2,4,6-trimethylheptan-1-ol (24). To a solution of **23** (1.19 g, 1.49 mmol, 1 equiv) in THF (20 mL) was added an equimolar mixture of AcOH/TBAF portionwise over 2 days (6 additions of 1.0 mL, a total of ca. 6.0 mL added over 2 days, 17.88 mmol, 12 equiv). A saturated aqueous solution of $NaHCO_3$ was then added (20 mL), and the two phases were separated. The aqueous layer was extracted with Et_2O (3 × 30 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (PE/Et_2O 100/0 to 9/1), and the primary alcohol **24** was obtained (644 mg, 68%) as a colorless oil: $[\alpha]^{20}_D = -13.6$ (*c* 0.85, $CHCl_3$); IR (neat) 3435, 2956, 2930, 2885, 2857, 1613, 1587, 1514, 1463, 1387, 1361, 1302, 1250, 1173, 1085, 1037, 1006 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.0 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 4.42 (m, 2H), 3.80 (s, 3H), 3.78 (dd, J = 6.3, 1.3 Hz, 1H), 3.68 (t_{app}, J = 4.2 Hz, 1H), 3.56−3.40 (m, 3H), 3.24 (dd, J = 7.9, 0.6 Hz, 1H), 1.98 (m, 1H), 1.91−1.77 (m, 2H), 1.59 (m, 1H, OH), 0.95 (d, J = 6.8 Hz, 3H), 0.90−0.86 (m, 6H), 0.89 (s, 9H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (2s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1 (s), 130.8 (s), 129.2 (2d), 113.8 (2d), 74.8 (d), 73.7 (d), 72.8 (t), 72.3 (t), 66.9 (t), 55.4 (q), 41.7 (d), 39.3 (d), 38.0 (d), 26.2 (3q), 26.1 (3q), 18.6 (s), 18.5 (s), 14.7 (q), 11.8 (q), 11.3 (q), −3.3 (2q), −3.5 (q), −4.4 (q); HRMS (ESI) calcd for $C_{30}H_{58}O_5Si_2 + Na^+$ 577.3715, found 577.3706.

(2*S*,3*S*,4*R*,5*S*,6*R*,7*R*,10*S*,12*S*,13*S*,14*R*,15*S*,16*S*)-3,5,10,13,15,17-Hexakis(*tert*-butyldimethylsilyloxy)-7-hydroxy-1-(4-methoxybenzyloxy)-2,4,6,12,14,16-hexamethylheptadecan-9-one (26). To a solution of alcohol **24** (300 mg, 0.48 mmol, 1 equiv) in CH_2Cl_2 (40 mL) at 0 °C was added Dess−Martin periodinane (402 mg, 0.95 mmol, 2 equiv). After 15 min at 0 °C and 2 h at rt, saturated aqueous solutions of $Na_2S_2O_3$ (20 mL) and $NaHCO_3$ (20 mL) were added, and the mixture was stirred for 45 min. The two phases were separated, the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was filtered on silica gel (PE/Et_2O 100/5) to afford aldehyde **25** (178 mg, 59%). To a solution of methyl ketone **8** (320 mg, 0.45 mmol, 1 equiv) at −78 °C in THF (2 mL) was added LDA (0.5 M in THF, 1.2 mL, 0.58 mmol, 1.3 equiv). The reaction mixture was stirred for 2 h at −78 °C, and a solution of the previously prepared aldehyde **25** (140 mg, 0.22 mmol, 0.5 equiv) in THF (1 mL) was added. After 2 h at −78 °C, a saturated aqueous solution of NH_4Cl (3 mL) was added, the mixture was warmed to rt, the two phases were separated, and the aqueous layer was extracted with EtOAc (3 × 3 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The diastereomeric ratio **26**/**26′** was estimated to 3/1 by ^1H NMR analysis. The crude product was purified by flash chromatography (PE/toluene 8/2 to 5/5 and then PE/EtOAc 100/2 to 100/4) to afford ketone **26** (192 mg, 64%), a mixture of diastereomer **26′** and aldehyde **25** (74 mg) and the recovered methyl ketone **8** (118 mg). Compound **26**: $[\alpha]^{20}_D = -11.8$ (*c* 0.65, $CHCl_3$); IR (neat) 3552, 3527, 2954, 2928, 2885, 2856, 1705, 1613, 1513, 1471, 1462, 1387, 1360, 1302, 1250, 1216, 1171, 1076, 1032, 1005 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 2H), 6.66 (m, 2H), 4.44 (d, J = 11.6 Hz, 1H), 4.39 (d, J = 11.6 Hz, 1H), 4.17 (d, J = 7.4 Hz, 1H), 4.02 (dd, J = 10.7, 1.9 Hz, 1H), 3.80 (s, 3H), 3.78−3.71 (m, 3H), 3.66−3.55 (m, 3H), 3.35 (dd, J = 9.9, 8.0 Hz, 1H), 3.24 (t_{app}, J = 8.7 Hz, 1H), 3.01 (dd, J = 18.7, 1.9 Hz, 1H), 2.35 (dd, J = 18.2, 9.4 Hz, 1H), 2.02 (m, 1H), 1.95−1.53 (m, 6H), 1.25 (m, 1H), 0.97 (d, J = 6.9 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H), 0.94−0.91 (m, 6H), 0.92 (s, 9H), 0.90 (s, 9H), 0.89 (2s, 18H), 0.88 (s, 9H), 0.87 (s, 9H), 0.83 (d, J = 7.0 Hz, 3H), 0.76 (d, J = 7.0 Hz, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.08 (2s, 6H), 0.07 (2s, 6H), 0.06 (2s, 6H), 0.04 (3s, 9H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.5 (s), 159.1 (s), 131.0 (s), 129.2 (2d), 113.8 (2d), 77.4 (d), 77.2 (d), 76.9 (d), 74.7 (d), 72.8 (t), 72.5 (t), 72.3 (d), 68.7 (d), 65.3 (t), 55.3 (q), 41.8 (d), 41.6 (d), 41.2 (t), 40.1 (d), 39.6 (2d), 36.2 (t), 34.4 (d), 26.3 (3q), 26.3 (3q), 26.3 (3q), 26.3 (3q), 26.2 (3q), 25.9 (3q), 18.7 (s), 18.6 (s), 18.6 (s), 18.4 (2s), 18.1 (s), 16.1 (q), 15.2 (q), 15.0 (q), 12.4 (q), 11.7 (q), 10.5 (q), −3.0 (q), −3.1 (q), −3.1 (q), −3.3 (q), −3.4 (q), −3.5 (q), −3.9 (q), −4.1 (q), −4.6 (q), −5.0 (q), −5.2 (q), −5.3 (q); HRMS (ESI) calcd for $C_{67}H_{138}O_{10}Si_6 + Na^+$ 1293.8799, found 1293.8805.

(2*S*,3*S*,4*R*,5*S*,6*R*,7*R*,10*S*,12*S*,13*S*,14*R*,15*S*,16*S*)-3,5,10,13,15,17-Hexakis(*tert*-butyldimethylsilyloxy)-7-methoxy-1-(4-methoxybenzyloxy)-2,4,6,12,14,16-hexamethylheptadecan-9-one (27). To a solution of alcohol **26** (128 mg, 0.10 mmol, 1 equiv) in CH_2Cl_2 (1.8 mL) at 0 °C were added MS 4 Å (55 mg), proton sponge (134 mg, 0.61 mmol, 6 equiv), and Me_3OBF_4 (77 mg, 0.50 mmol, 5 equiv). The reaction mixture was warmed to rt and after 2 h, additional portions of proton sponge (134 mg, 0.605 mmol, 6 equiv) and Me_3OBF_4 (77 mg, 0.502 mmol, 5 equiv) were added. After 2 h, a saturated aqueous solution of $NaHCO_3$ (1 mL) was added. The two phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (PE/EtOAc 100/1 to 100/3) to give **27** (104 mg, 81%): $[\alpha]^{20}_D = -9.8$ (*c* 1.05, $CHCl_3$); IR (neat) 2956, 2930, 2857, 1727, 1614, 1514, 1463, 1388, 1361, 1252, 1087, 1038, 1005 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 4.45 (d, J = 11.5 Hz, 1H), 4.39 (d, J = 11.8 Hz, 1H), 4.09 (dd, J = 10.6, 2.0 Hz, 1H), 3.83 (d, J = 5.0 Hz, 1H), 3.80 (s, 3H), 3.74 (dd, J = 9.9, 5.4 Hz, 1H), 3.67−3.58 (m, 4H), 3.54 (dd, J = 9.1, 5.4 Hz, 1H), 3.34 (dd, J = 9.8, 8.4 Hz, 1H), 3.23 (m, 1H), 3.21 (s, 3H), 2.71 (dd, J = 17.3, 8.1 Hz, 1H), 2.46 (dd, J = 17.4, 3.0 Hz, 1H), 2.03 (m, 1H), 1.94−1.63 (m, 6H), 1.35 (m, 1H), 0.98−0.93 (m, 9H), 0.92 (s, 9H), 0.98 (3s, 27H), 0.90−0.86 (m, 6H), 0.88 (2s, 18H), 0.76 (d, J = 7.0 Hz, 3H), 0.07 (s, 6H), 0.07 (s, 3H), 0.06 (s, 6H), 0.06 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 3H), 0.03 (s, 6H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.1 (s), 159.1 (s), 130.9 (s), 129.2 (2d), 113.8 (2d), 79.5 (d), 77.5 (d), 77.3 (d), 76.9 (d), 75.1 (d), 73.2 (d), 72.9 (t), 72.2 (t), 65.3 (t), 57.6 (q), 55.3 (q), 42.9 (d), 41.7 (d), 40.3 (t), 39.7 (d), 39.1 (d), 38.2 (d), 35.5 (t), 34.6 (d), 26.3 (3q), 26.3 (3q), 26.2 (3q), 26.2 (3q), 26.1 (3q), 26.0 (3q), 18.6 (2s), 18.5 (s), 18.4 (s), 18.4 (s), 18.2 (s), 16.3 (q), 15.1 (q), 15.1 (q), 12.4 (q), 11.7 (q), 10.8 (q), −3.0 (q), −3.4 (3q), −3.5 (q), −3.5 (q), −4.0 (q), −4.2 (q), −4.5 (q), −5.0 (q), −5.2 (q), −5.3 (q); HRMS (ESI) calcd for $C_{68}H_{140}O_{10}Si_6 + Na^+$ 1307.8954, found 1307.8955.

(2*S*,3*S*,4*R*,5*S*,6*R*,7*R*,10*S*,12*S*,13*S*,14*R*,15*S*,16*S*)-3,5,10,13,15,17-Hexakis(*tert*-butyldimethylsilyloxy)-1-hydroxy-7-methoxy-2,4,6,12,14,16-hexamethyl-heptadecan-9-one (29). To a solution of **27** (80 mg, 0.062 mmol, 1 equiv) in a 5/1 mixture of CH_2Cl_2 / buffer pH = 7 (1 mL/0.2 mL) at 0 °C was added DDQ (17 mg, 0.075 mmol, 1.2 equiv). The reaction mixture was warmed to rt over 1 h. After 30 min, a saturated aqueous solution of $NaHCO_3$ (1 mL) and Et_2O (2 mL) were added. After 30 min, water (2 mL) was added, and the two phases were separated. The aqueous phase was extracted with Et_2O (3 × 4 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (PE/EtOAc 100/2 to 100/4) to give the primary alcohol **29** (47 mg, 64%): $[\alpha]^{20}_D = -12.6$ (*c* 2.35, $CHCl_3$); IR (neat) 2956, 2930, 2886, 2858, 1719, 1472, 1388, 1361, 1254, 1083, 1035, 1005 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.09 (dd, J = 10.7, 2.0 Hz, 1H), 3.87 (dd, J = 4.8, 1.5 Hz, 1H), 3.83 (m, 1H), 3.74 (dd, J = 10.0, 5.8 Hz, 1H),

3.70−3.55 (m, 5H), 3.35 (dd, J = 9.9, 8.4 Hz, 1H), 3.24 (s, 3H), 2.72 (dd, J = 17.6, 7.5 Hz, 1H), 2.54 (m, 1H, OH), 2.50 (dd, J = 17.8, 3.2 Hz, 1H), 2.63−1.62 (m, 7H), 1.38−1.23 (m, 1H), 1.05 (d, J = 7.2 Hz, 3H), 0.95 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H), 0.93−0.85 (m, 6H), 0.93 (s, 9H), 0.92 (s, 9H), 0.91 (s, 9H), 0.89 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.78 (d, J = 7.0 Hz, 3H), 0.13 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.10 (s, 3H), 0.08 (2s, 6H), 0.07 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.03 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.0 (s), 79.2 (d), 77.6 (d), 77.5 (d), 77.3 (d), 77.0 (d), 72.4 (d), 65.3 (t), 65.1 (t), 57.6 (q), 44.0 (d), 41.7 (d), 40.2 (t), 39.7 (d), 39.1 (d), 38.5 (d), 35.7 (t), 34.6 (d), 26.3 (6q), 26.2 (3q), 26.2 (3q), 26.1 (3q), 26.0 (3q), 18.6 (s), 18.5 (s), 18.5 (s), 18.4 (s), 18.4 (s), 18.2 (s), 16.2 (q), 15.3 (q), 15.1 (q), 12.4 (q), 12.1 (q), 11.0 (q), −3.0 (q), −3.4 (2q), −3.4 (2q), −3.5 (q), −3.9 (q), −4.1 (q), −4.5 (q), −4.9 (q), −5.2 (q), −5.3 (q); HRMS (ESI) calcd for $C_{60}H_{132}O_9Si_6 + Na^+$ 1187.8379, found 1187.8408.

Phenyl Carbamic Acid (2*S*,3*S*,4*R*,5*S*,6*R*,7*R*,10*S*,12*S*,13*S*,14*R*,15*S*,16*S*)-3,5,10,13,15,17-hexakis(*tert*-butyldimethylsilyloxy)-7-methoxy-2,4,6,12,14,16-hexamethyl-9-oxo-heptadecyl Ester (30). Alcohol **29** (47 mg, 0.040 mmol, 1 equiv) was dissolved in pyridine (400 μL) and phenylisocyanate (44 μL, 0.400 mmol, 10 equiv) was added. After 4 h at rt, a 10% solution of $CuSO_4$ in water was added (1 mL), the two phases were separated, and the aqueous layer was extracted with Et_2O (3 × 2 mL). The combined organic phases were washed with a solution of $CuSO_4$ (10 wt % in H_2O, 3 × 5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. A flash chromatography on silica gel (PE/EtOAc 100/1 to 100/2) afforded carbamate **30** (43 mg, 83%): $[\alpha]^{20}_D$ = −9.2 (*c* 2.15, $CHCl_3$); IR (neat) 2956, 2930, 2858, 1721, 1602, 1536, 1501, 1472, 1444, 1388, 1361, 1312, 1253, 1215, 1081, 1005 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.1 Hz, 2H), 7.30 (t, J = 7.8 Hz, 2H), 7.03 (m, 1H, NH), 7.05 (t, J = 7.3 Hz, 1H), 4.20−4.09 (m, 3H), 3.86 (dd, J = 4.6, 1.3 Hz, 1H), 3.75 (dd, J = 10.0, 5.8 Hz, 1H), 3.72−3.65 (m, 3H), 3.63 (dd, J = 7.6, 2.5 Hz, 1H), 3.36 (dd, J = 9.9, 8.4 Hz, 1H), 3.24 (s, 3H), 2.75 (dd, J = 17.5, 8.6 Hz, 1H), 2.45 (dd, J = 17.7, 2.8 Hz, 1H), 2.19−2.11 (m, 1H), 1.99−1.66 (m, 6H), 1.38−1.25 (m, 1H), 0.99 (d, J = 7.0 Hz, 3H), 0.96 (d, J = 6.8 Hz, 6H), 0.93 (s, 9H), 0.92 (s, 9H), 0.91 (s, 9H), 0.89 (2s, 18H), 0.88 (s, 9H), 0.93−0.88 (m, 6H), 0.80 (d, J = 6.9 Hz, 3H), 0.13 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.08 (3s, 9H), 0.06 (s, 3H), 0.04 (4s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.5 (s), 153.7 (s), 138.3 (s), 129.1 (2d), 123.3 (d), 118.8 (2d), 79.8 (d), 77.6 (d), 77.3 (d), 77.0 (d), 73.9 (d), 72.9 (d), 67.1 (t), 65.3 (t), 57.5 (q), 42.6 (d), 41.6 (d), 39.9 (t), 39.8 (d), 38.6 (d), 37.8 (d), 35.7 (t), 34.7 (d), 26.3 (3q), 26.2 (3q), 26.2 (6q), 26.1 (3q), 26.0 (3q), 18.6 (s), 18.6 (s), 18.5 (s), 18.4 (s), 18.4 (s), 18.2 (s), 16.2 (q), 15.0 (q), 13.9 (q), 12.4 (q), 11.4 (q), 10.6 (q), −3.0 (q), −3.2 (q), −3.4 (q), −3.4 (q), −3.6 (q), −3.7 (q), −3.9 (q), −4.1 (q), −4.5 (q), −4.9 (q), −5.2 (q), −5.3 (q); HRMS (ESI) calcd for $C_{67}H_{137}NO_{10}Si_6 + Na^+$ 1306.8789, found 1306.8750.

Phenyl Carbamic Acid (2*S*,3*R*,4*S*)-4-[(2*R*,3*S*,4*R*,6*R*,7*S*,9*S*)-10-((1*R*,2*R*,3*S*)-2,4-dihydroxy-1,3-dimethylbutyl)-7-hydroxy-4-methoxy-3,9-dimethylspiro[5.5]undec-2-yl]-3-hydroxy-2-methylpentyl Ester (31). To a solution of **30** (43 mg, 0.034 mmol, 1 equiv) in THF (2 mL) at 0 °C was added HF·Py (1.5 mL, 61.20 mmol, 1800 equiv). The reaction mixture was stirred for 5 min at 0 °C and then allowed to warm to rt. After 2 h, solid $NaHCO_3$ was added carefully until pH 5−6. The resulting suspension was filtered, and the filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH 100/1 to 100/5) to give spiroketal **31** (16 mg, 81%): $[\alpha]^{20}_D$ = +0.4 (*c* 0.8, $CHCl_3$); IR (neat) 3393, 2971, 2929, 1710, 1602, 1544, 1502, 1445, 1383, 1314, 1228, 1180, 1153, 1083, 1056, 1028 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (d, J = 7.3 Hz, 2H), 7.30 (t, J = 7.6 Hz, 2H), 7.07 (t, J = 7.3 Hz, 1H), 6.70 (br s, 1H), 4.47 (dd, J = 10.8, 4.8 Hz, 1H), 4.24 (dd, J = 10.8, 3.8 Hz, 1H), 3.89 (dd, J = 8.9, 8.9 Hz, 1H), 3.87 (d, J = 11.1 Hz, 1H), 3.77 (d, J = 10.2 Hz, 1H), 3.67 (dd, J = 11.1, 4.5 Hz, 1H), 3.58 (d, J = 10.2 Hz, 1H), 3.56−3.50 (m, 2H), 3.46 (br s, 1H), 3.35 (s, 3H), 2.15 (quint, J = 6.6 Hz, 1H), 2.04 (dd, J = 13.4, 4.8 Hz, 1H), 1.98 (td, J = 7.2, 3.5 Hz, 1H), 1.95−1.90 (m, 1H), 1.90−1.78 (m, 3H), 1.74 (t, J = 13.4 Hz, 1H), 1.65 (ddd, J = 13.0, 3.3, 3.0 Hz, 1H), 1.41 (t, J = 12.6 Hz, 1H), 1.09 (d, J = 7.0 Hz, 3H), 0.97 (d, J = 6.7 Hz, 3H), 0.91 (d, J = 7.0 Hz, 3H), 0.84 (d, J = 7.0 Hz, 3H), 0.79 (d, J = 6.7 Hz, 3H), 0.74 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7 (s), 138.3 (s), 129.5 (2d), 124.0 (d), 119.3 (2d), 98.8 (s), 79.4 (d), 77.4 (d), 74.3 (d), 72.2 (d), 71.1 (d), 70.8 (d), 69.2 (t), 66.8 (t), 55.8 (q), 37.6 (d), 37.2 (d), 36.4 (d), 35.8 (d), 35.7 (t), 33.1 (t), 32.3 (d), 24.9 (d), 17.9 (q), 16.0 (q), 14.6 (q), 10.5 (q), 8.0 (q), 4.4 (q). HRMS (ESI) calcd for $C_{31}H_{51}O_9N + Na^+$ 604.3456, found 604.3445.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **3**−**8**, **10**−**17**, **19**, **20**, **22**−**24**, **26**−**27**, and **29**-**31**, NMR assignment for diastereoisomers **19**/**19′** and **26**/**26′**, measurable coupling constants and NOE diagnostics for the spiroketal core of **31**. This material is available free of charge via the Internet at http://pubs.acs.org.