An Efficient Ruthenium-Catalyzed Formal Synthesis of (−)-Isoavenaciolide

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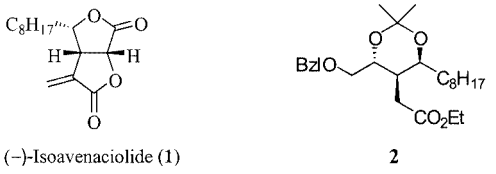
A formal synthesis of (–)-isoavenaciolide (**1**) by two different routes is reported. The first approach, leading to a key precursor **2** of (–)-isoavenaciolide (**1**), features the stereoselective construction of the three contiguous stereogenic centers by Evans diastereoselective reduction (*d.e.* = 80%) of β-hydroxy ketone **8**. In the more efficient second approach, the nine-step sequence leading to the key precursor **2** involves sequential ruthenium-catalyzed hydrogenation reactions of β-keto ester **4** and β-hydroxy ketone **14** to form the two hydroxyl groups with an excellent control of the *anti* stereochemistry (*d.e.* = 99%).

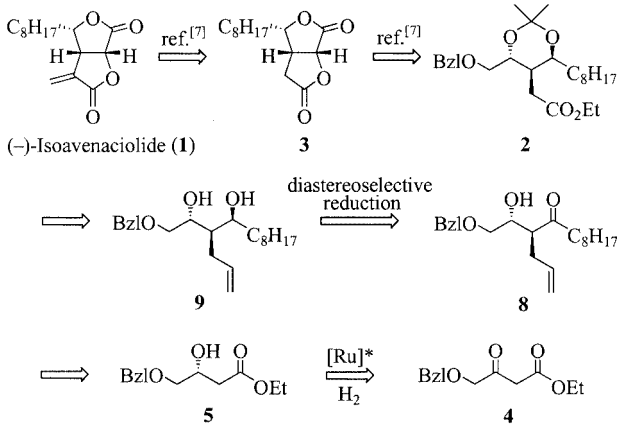
Introduction

(−)-Isoavenaciolide (**1**; Scheme 1), a naturally occurring secondary metabolite isolated from the fermentation broth of *Aspergillus* and *Penicillium* species,[1] has been found to exhibit antifungal activity and, more recently, to irreversibly inhibit vaccinia H1 related (VHR) phosphatase activity.[2] Due to its interesting α-methylene-bis(butyrolactone) skeleton and biological properties, numerous total syntheses of (−)-isoavenaciolide have been reported. Many of these approaches involve optically active natural products as the chiral sources,[3−6] while the other syntheses rely on stereoselective reactions.[7−10] Several formal syntheses of (−)-isoavenaciolide have also been described.[11−15] In connection with our ongoing program towards the preparation of biologically relevant natural products or pharmaceutical compounds,[16−22] we were interested in a synthesis of (−)-isoavenaciolide using ruthenium-mediated asymmetric hydrogenation[23,24] for the construction of two of the three contiguous stereogenic centers. We report herein an efficient synthesis of the known acetonide **2** (Scheme 1), which is an advanced precursor[7] of (−)-isoavenaciolide.



Scheme 1. Structures of (−)-isoavenaciolide (**1**) and advanced precursor **2**

Retrosynthetically, the target compound **2** was envisioned to be available from **9** by protection of the diol moiety and subsequent oxidation of the double bond (Scheme 2). The *anti*-diol **9** would result from enantiopure β-hydroxy ester **5** by diastereoselective alkylation and conversion of the ester function into the corresponding ketone, followed by stereoselective reduction of the keto group either with Evans' reagent[25] or by catalytic asymmetric hydrogenation. Asymmetric hydrogenation of β-keto ester **4** would set the first hydroxyl group with high enantioselectivity.



Scheme 2. Retrosynthetic analysis for (−)-isoavenaciolide (**1**)

Results and Discussion

The synthesis of the desired acetonide **2** began with ruthenium-mediated asymmetric hydrogenation of β-keto es-

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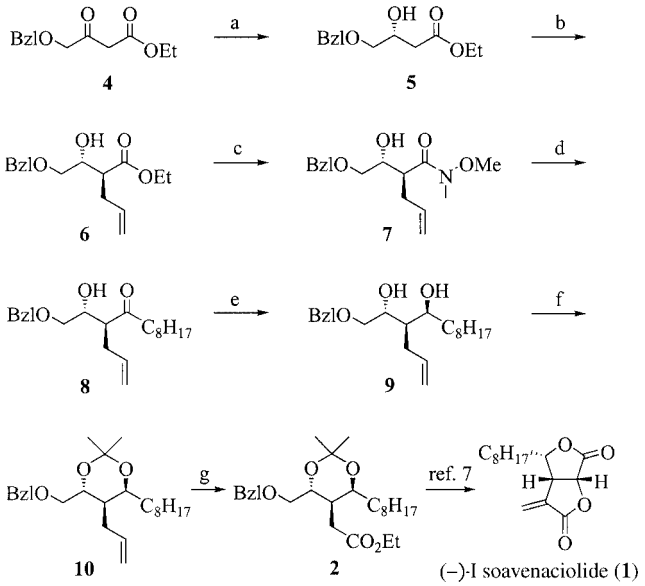
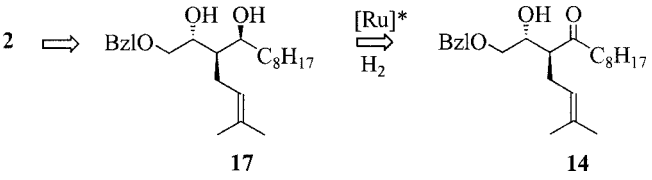


Scheme 3. Reagents and conditions: (a) 0.03 mol % [(*S*)-(MeO-BIPHEP)RuBr$_2$], H_2 (10 bar), EtOH, 80 °C, 48 h, 94%, *e.e.* = 98%; (b) LDA (2 equiv.), THF, −78 °C, 1 h; allyl bromide (2.5 equiv.), HMPA (1.2 equiv.), −78 °C for 1 h then −20 °C for 1 h, 81%, *d.e.* = 97%; (c) MeNHOMe·HCl (4.7 equiv.), *i*PrMgCl (9 equiv.), THF, −20 °C, 80%; (d) *n*C_8H_{17}Li (2.3 equiv.), Et_2O/THF, −10 °C, 5 h, 85%; (e) $Me_4NHB(OAc)_3$ (6 equiv.), CH_3CN/AcOH (1:1), −20 °C, 21 h, 94%, *d.e.* = 80%; (f) 2,2-dimethoxypropane, acetone, PTSA cat., room temp., 1 h, 94%; (g) O_3, 2.5 M ethanolic NaOH, CH_2Cl_2, −78 °C, 3 h, 80%

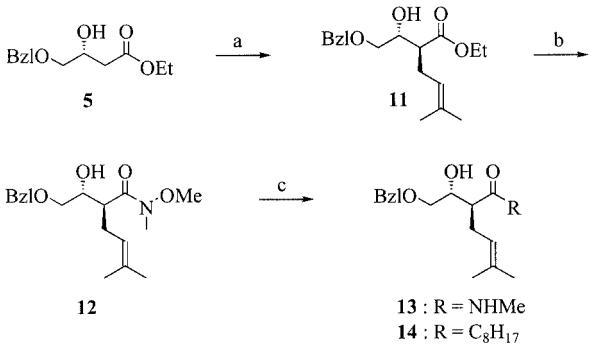
ter **4**[26] (Scheme 3). The reaction was carried out in ethanol at 80 °C under 10 bar of hydrogen, using 0.03 mol % of the complex [(*S*)-(MeO-BIPHEP)RuBr$_2$] prepared in situ according to our convenient procedure[27] from commercially available [(COD)Ru(2-methylallyl)$_2$]. Under these conditions, β-hydroxy ester **5** was obtained in 94% yield and with excellent enantiomeric excess (*e.e.* = 98%, determined by chiral HPLC, Chiralcel OD-H column; flow rate: 0.8 mL/min; eluent: hexane/propan-2-ol (9:1); detection at 215 nm). Under optimized conditions, alkylation of enantiomerically enriched **5** with allyl bromide following the Fráter−Seebach procedure[28,29] afforded hydroxy ester **6** in 81% yield with high diastereoselectivity (*d.e.* = 97%, determined by chiral HPLC, Chiralcel OD-H column; flow rate: 0.5 mL/min; eluent: hexane/propan-2-ol (95:5); detection at 215 nm). The resulting ester **6** was then converted into the corresponding Weinreb amide **7**[30] upon reaction with *N*,*O*-dimethylhydroxylamine hydrochloride in the presence of isopropylmagnesium chloride.[31] Subsequent treatment of **7** with *n*-octylmagnesium bromide or chloride afforded β-hydroxy ketone **8** in only 20−25% yield. However, the use of the more reactive *n*-octyllithium allowed the formation of **8** in a good 85% yield. Reduction of the ketone moiety with tetramethylammonium triacetoxyborohydride in acetic acid[25] then afforded the expected *anti*-diol **9** with 80% diastereomeric excess (determined by chiral HPLC, Chiralcel OD-H column; flow rate: 1 mL/min; eluent: hexane/propan-2-ol (95:5); detection at 215 nm). The 90:10 mixture of *anti*/*syn* diols **9** was converted into the corresponding acetonides **10** and direct conversion of olefin **10** into ester **2** was achieved by ozonolysis in dichloromethane in the presence of a 2.5 M ethanolic sodium hydroxide solution.[32] The spectroscopic data of **2** were found to be in agreement with reported literature data.[7,8] Since this advanced intermediate is used for the total synthesis of (−)-isoavenaciolide (**1**), our seven-step sequence leading to **2** in 37% overall yield represents a formal total synthesis of this natural product and compares favorably with Suzuki's twelve-step approach (30% overall yield) to **2**.[7,8]

However, a major drawback in the above synthesis of **2** is the use of tetramethylammonium triacetoxyborohydride for the stereoselective reduction of **8**, especially when working on large scale, since at least six equivalents of this expensive reagent are needed for complete conversion. Moreover, the diastereomeric excess obtained for the reduction step (*d.e.* = 80%) is quite unsatisfactory and could be improved. Thus, we were interested in a catalytic preparation of **2** by ruthenium-mediated asymmetric hydrogenation of **8**, which would avoid the use of a large excess of expensive tetramethylammonium triacetoxyborohydride and should allow a higher diastereomeric excess. Unfortunately, the presence of an allyl moiety on β-hydroxy ketone **8** is inconsistent with the hydrogenation reaction because of the expected competitive reduction of the monosubstituted alkene function. However, the asymmetric hydrogenation of β-keto esters bearing a remote di- or trisubstituted alkene moiety has been reported[33,34] and under controlled reaction conditions, chemoselective reduction of the keto group over the alkene function can be achieved in high yield and with excellent enantiomeric excess. Thus, we designed a new pathway to **2** via the *anti*-diol **17** which would result from asymmetric hydrogenation of β-hydroxy ketone **14** bearing a trisubstituted alkene moiety (Scheme 4).



Scheme 4. New pathway to compound **2** by asymmetric hydrogenation of β-hydroxy ketone **14**

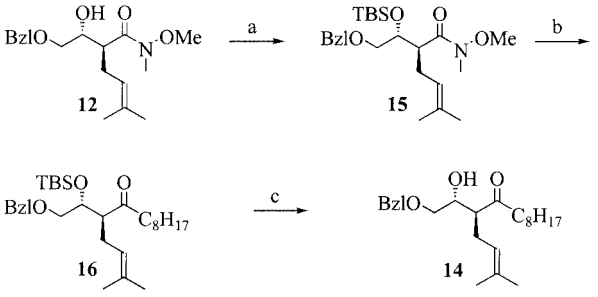
The preparation of compound **17** followed a similar synthetic route as for **8**, and started with alkylation of the enantiomerically enriched β-hydroxy ester **5** with 4-bromo-2-methylbut-2-ene (Scheme 5), which afforded **11** in 78% yield as a single diastereomer after separation by flash chromatography (*d.e.* = 99%, determined by chiral HPLC, Chiralcel OD-H column; flow rate: 0.5 mL/min; eluent: hexane/propan-2-ol (95:5); detection at 215 nm). After conversion of **11** into the corresponding Weinreb amide **12** by reaction with *N*,*O*-dimethylhydroxylamine hydrochloride and *n*-butyllithium,[35] subsequent treatment with *n*-octyllithium under various conditions furnished ketone **14** in only 5−24% yield. Indeed, in contrast with compound **7**, direct addition of *n*-octyllithium to **12** led to competitive decomposition



Scheme 5. Reagents and conditions: (a) LDA (2.5 equiv.), THF, −78 °C, 1 h; 4-bromo-2-methylbut-2-ene (2.5 equiv.), HMPA (1.2 equiv.), −78 °C for 3 h then −20 °C for 1 h, 78%, *d.e.* = 99%; (b) MeNHOMe·HCl (3 equiv.), *n*BuLi (6 equiv.), THF, −78 °C, 2 h, 92%; (c) $nC_8H_{17}Li$ (2.7 to 4 equiv.), THF or Et_2O, −40 °C, 3 h, 36−63% of **13** and 5−24% of **14**

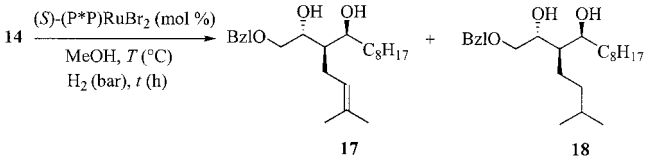
of the amide function[36] to yield hydroxy amide **13** with liberation of formaldehyde, probably due to the more demanding steric hindrance of the *gem*-dimethylallyl moiety compared to the allyl function.

However, this side-reaction could be circumvented by protecting the hydroxyl group as its *tert*-butyldimethylsilyl ether **15**. Treatment with *n*-octyllithium furnished the corresponding ketone **16** in a satisfactory 73% yield (Scheme 6). Finally, deprotection of the hydroxyl function with tetrabutylammonium fluoride afforded β-hydroxy ketone **14**, required for the asymmetric hydrogenation.



Scheme 6. Reagents and conditions: (a) 2,6-lutidine, TBSOTf, CH_2Cl_2, 0 °C, 1 h, 99%; (b) $nC_8H_{17}Li$ (2 equiv.), THF, −50 °C, 2 h, 73%; (c) nBu_4NF, THF, 0 °C, 2 h, 96%

The asymmetric hydrogenation reaction was first attempted under a low pressure of hydrogen to avoid the reduction of the alkene function (Scheme 7, Table 1). Thus, in the presence of 2 mol % of [(*S*)-(MeO-BIPHEP)$RuBr_2$] at 50 °C in methanol under either 1 or 15 bar of hydrogen, low conversions were observed (20 or 50%, entries 1 and 2). Increasing the temperature to 80 °C afforded complete conversion, but only the saturated diol **18** was isolated (entry 3). When the reaction was carried out at 50 °C under 50 bar of hydrogen, complete conversion was observed after 72 h and the desired diol **17** was obtained in 86% yield with excellent diastereoselectivity (*d.e.* = 99%), accompanied by 14% of the saturated product **18** (entry 4).



Scheme 7

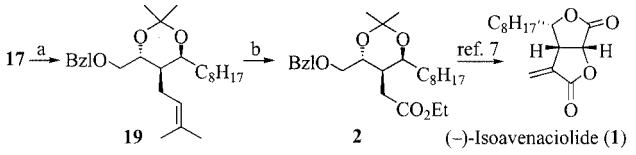
Upon reducing the reaction time to 6 h a high conversion (95%) was still observed and the **17/18** ratio increased in favour of the desired *anti*-diol **17** (from 86:14 to 97:3, entries 4 and 5), again with high diastereoselectivity (*d.e.* = 99%). The asymmetric hydrogenation reaction was also performed using (*S*)-SYNPHOS®, a new atropisomeric ligand bearing a benzodioxane core synthesized in our group.[37−39] Thus, in the presence of 2 mol % of [(*S*)-(SYNPHOS)$RuBr_2$] at 50 °C under 50 bar of hydrogen, *anti*-diol **17** was obtained with high diastereomeric excess (*d.e.* = 99%, entry 6) and the **17/18** ratio was improved slightly to 98:2. Under the same reaction conditions but with 4 mol % of [(*S*)-(MeO-BIPHEP)$RuBr_2$] instead of 2 mol %, similar results were observed but this time complete conversion was obtained (entry 7). As observed previously with the parent compound **8**, reduction of β-hydroxy ketone **14** with tetramethylammonium triacetoxyborohydride afforded a lower diastereomeric excess (*d.e.* = 83%) than for the ruthenium-mediated hydrogenation (*d.e.* = 99%), thus validating our

Table 1. Catalytic asymmetric hydrogenation of β-hydroxy ketone **14** in the presence of [(*S*)-(MeO−BiPHEP)$RuBr_2$] or [(*S*)-(SYNPHOS)-$RuBr_2$]

Entry	ligand	% cat.	*T* (°C)	*P* (bar)	*t* (h)	Conv. (%)[a]	**17/18**[b]	*d.e.* (%)[c]
1	(*S*)-MeO-BIPHEP	2	50	1	24	20	100:0	99
2	(*S*)-MeO-BIPHEP	2	50	15	72	50	97:3	99
3	(*S*)-MeO-BIPHEP	2	80	15	72	100	0:100	–
4	(*S*)-MeO-BIPHEP	2	50	50	72	100	86:14	99
5	(*S*)-MeO-BIPHEP	2	50	50	6	95	97:3	99
6	(*S*)-SYNPHOS®	2	50	50	6	95	98:2	99
7	(*S*)-MeO-BIPHEP	4	50	50	6	100	97:3	99

[a] Conversions were determined by ^1H NMR analysis of the crude reaction mixture. [b] The **17/18** ratio was measured by HPLC: column, Chiralcel OD-H; flow rate: 1.0 mL/min; eluent: hexane/propan-2-ol (95:5); detection at 215 nm; t_R 13.8 min, *anti*-**18** isomer; t_R 11.5 min, *syn*-**18** isomer; t_R 15.7 min, *anti*-**17** (2*R*,3*R*,4*S*) isomer; t_R 12.7 min, *syn*-**17** (2*R*,3*R*,4*R*) isomer. [c] Diastereomeric excess of **17** was determined by chiral HPLC: column, Chiralcel OD-H; flow rate: 1.0 mL/min; eluent: hexane/propan-2-ol (95:5); detection at 215 nm; t_R 15.7 min, *anti*-**17** (2*R*,3*R*,4*S*) isomer; t_R 12.7 min, *syn*-**17** (2*R*,3*R*,4*R*) isomer.

new approach to the *anti*-diol **17**. Synthesis of compound **2** was then achieved by converting *anti*-diol **17** into the corresponding acetonide **19** by ozonolysis in dichloromethane with a 2.5 M ethanolic sodium hydroxide solution (Scheme 8). Thus, the advanced precursor **2** of (−)-isoavenaciolide (**1**) was obtained in 86% overall yield from **17** and its spectroscopic data were found to be in agreement with those reported previously for this compound.[7,8]



Scheme 8. Reagents and conditions: (a) 2,2-dimethoxypropane, acetone, PPTS cat., room temp., 20 min, 98%; (b) O_3, 2.5 M ethanolic NaOH, CH_2Cl_2, −78 °C, 1 h, 88%

Conclusion

In summary, a formal synthesis of (−)-isoavenaciolide (**1**) has been achieved following two routes. In a first approach, a seven-step sequence leading to the key intermediate **2** in 37% overall yield allowed the stereoselective construction of the three contiguous stereogenic centers with reasonable diastereoselectivity for the 1,3 *anti*-diol moiety (*d.e.* = 80%). In the more efficient second route, the key precursor **2** was synthesized in a highly stereoselective manner in nine steps and 38% overall yield, which compares favorably with other reported approaches. The two hydroxyl groups of the natural product were successfully formed by sequential catalytic asymmetric hydrogenation reactions of β-keto ester **4** and β-hydroxy ketone **14** with an excellent control of the *anti* stereochemistry (*d.e.* = 99%) and high chemoselectivity. This efficient preparation of enantiomerically pure 1,3-*anti* diols by asymmetric hydrogenation of β-hydroxy ketones has been extended to various other substrates and will be reported in a forthcoming paper.

Experimental Section

General Remarks: All solvents were reagent grade and were distilled under argon prior to use. Amines were distilled from potassium hydroxide and CH_2Cl_2 from calcium hydride. THF and Et_2O were distilled from sodium-benzophenone. Unless stated otherwise, all reactions were carried out under an argon atmosphere. All commercially available reagents were used without further purification unless otherwise indicated. Nuclear magnetic resonance: ^1H and ^{13}C NMR spectra were recorded either at 200 MHz and 50 MHz, respectively, on an AC200 Bruker spectrometer, at 300 MHz and 75 MHz, respectively, on an AC300 Bruker spectrometer, or at 400 MHz and 100 MHz, respectively, on an ARX400 Bruker spectrometer. Chemical shifts are given in ppm referenced to the residual proton resonance of the solvent (δ = 7.26 ppm for $CDCl_3$) for ^1H NMR spectroscopy. For ^{13}C NMR, chemical shifts are referenced to the central peak of the solvent (δ = 77.1 ppm for $CDCl_3$). Coupling constants (J) are given in Hertz (Hz). Infrared spectra (IR) were recorded on either a Perkin−Elmer 783G spectrometer or an IRFT Nicolet 205 spectrometer. Mass spectra (MS) were measured on a Hewlett−Packard 5989A (70 eV) mass spectrometer. Flash column chromatography was performed on Merck silica gel (0.040−0.063 mesh). Thin layer chromatography (TLC) analysis was performed on Merck silica gel 60 PF 254 and revealed with either a ultra-violet lamp (λ = 254 nm) or a potassium permanganate solution. Specific rotation values were recorded on a Perkin−Elmer 241 polarimeter.

β-Hydroxy Ester 5: Asymmetric hydrogenation of β-keto ester **4** was performed as follows: (*S*)-MeO-BIPHEP (16.4 mg, 0.028 mmol) and [(COD)Ru(2-methylallyl)$_2$] (7.5 mg, 0.023 mmol, commercially available from Acros) were placed in a round-bottomed flask and dissolved in 2 mL of acetone (degassed by three cycles of vacuum/argon at room temperature). A 0.15 N methanolic HBr solution (343 μL, 0.05 mmol) was added to this suspension and the solution was stirred at room temperature for 30 min. After evaporation of the solvent under vacuum, a solution of β-keto ester **4** (18.4 g, 78 mmol) in ethanol (1.4 mL) was added to the ruthenium catalyst. The resulting mixture was heated at 80 °C under 10 bar of hydrogen for 48 h. After removal of the solvent, purification of the residual oil by flash chromatography (silica gel, 10% EtOAc in cyclohexane) afforded β-hydroxy ester **5** (17.5 g, 94%) as a colorless oil. $[\alpha]_D^{25}$ = +10.9 (c = 1.1, EtOH). IR (film): $\tilde{\nu}$ = 3453 (broad), 3031, 2981, 2925, 2860, 1734, 739, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.32 (m, 5 H), 4.56 (s, 2 H), 4.24 (m, 1 H), 4.16 (q, J = 7.2 Hz, 2 H), 3.52 (dd, J = 9.6, 4.7 Hz, 1 H), 3.47 (dd, J = 9.6, 5.9 Hz, 1 H), 3.00 (d, J = 4.3 Hz, 1 H, *OH*), 2.54 (d, J = 6.2 Hz, 2 H), 1.26 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.2, 137.9, 128.5, 127.8 (2 C), 73.4, 73.2, 67.2, 60.7, 38.3, 14.2 ppm. MS (EI): m/z = 239 [M + H]$^+$. $C_{13}H_{18}O_4$ (238.3): calcd. C 65.53, H 7.61; found C 65.49, H 7.65. HPLC analysis: Chiralcel OD-H column; flow rate: 0.8 mL/min; eluent: hexane/propan-2-ol (9:1); detection at 215 nm; t_R = 12.5 min, (*R*)-**5** isomer; t_R = 14.1 min, (*S*)-**5** isomer; *e.e.* = 98%.

β-Hydroxy Ester 6: A solution of β-hydroxy ester **5** (5.0 g, 21.0 mmol) in THF (50 mL) was added to a solution of LDA (51.0 mmol) in THF at −78 °C. After stirring at −78 °C for 1 h, HMPA (4.5 mL, 25.1 mmol) and allyl bromide (4.6 mL, 52.7 mmol) were added. The reaction mixture was stirred at −78 °C for 1 h, then at −20 °C for 1 h before more allyl bromide (1.5 mL, 17.1 mmol) was added. After stirring at −20 °C and at 0 °C for 1 h each, the mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (silica gel, 1 to 10% EtOAc in cyclohexane) afforded **6** (4.7 g, 81%) as a colorless oil. $[\alpha]_D^{25}$ = +9.4 (c = 1.2, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3480 (broad), 3040, 2990, 2940, 2870, 1730, 1455, 740, 700 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.36 (m, 5 H), 5.78 (ddt, J = 17.0, 10.1, 7.0 Hz, 1 H), 5.03−5.15 (m, 2 H), 4.60 (d, J = 12.0 Hz, 1 H), 4.53 (d, J = 12.0 Hz, 1 H), 4.07−4.22 (m, 2 H), 3.94 (m, 1 H), 3.59 (dd, J = 9.8, 4.4 Hz, 1 H), 3.54 (dd, J = 9.8, 5.3 Hz, 1 H), 3.16 (d, J = 7.4 Hz, 1 H, *OH*), 2.74 (m, 1 H), 2.39 (m, 2 H), 1.25 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.4, 137.9, 134.8, 128.5, 127.9, 127.8, 117.4, 73.5, 72.3, 71.0, 60.7, 47.7, 33.6, 14.3 ppm. MS (EI): m/z = 278 [M]$^+$. $C_{16}H_{22}O_4$ (278.3): calcd. C 69.04, H 7.96; found C 69.01, H 8.12. HPLC analysis: Chiralcel OD-H column; flow rate: 0.5 mL/min; eluent: hexane/propan-2-ol (95:5); detection at 215 nm; t_R = 19.6 min, (2*S*,3*R*)-**6** isomer; t_R = 22.1 min, (2*R*,3*R*)-**6** isomer; *d.e.* = 97%.

Amide 7: A 2 M solution of isopropylmagnesium chloride in THF (5.4 mL, 10.8 mmol) was added to a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (943 mg, 5.6 mmol) and β-hydroxy ester **6** (1.0 g, 3.6 mmol) in THF (7 mL) at −20 °C. After stirring for 2 h at −20 °C, more *N*,*O*-dimethylhydroxylamine hydrochloride (943 mg, 5.6 mmol) and isopropylmagnesium chloride (5.4 mL, 10.8 mmol) were added and the reaction mixture was stirred for 2 h at −10 °C. A third addition of *N*,*O*-dimethylhydroxylamine hydrochloride (943 mg, 5.6 mmol) and isopropylmagnesium chloride (5.4 mL, 10.8 mmol) allowed complete conversion after stirring at −10 °C for 2 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl, followed by 1 N HCl, and then extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (silica gel, 10 to 40% EtOAc in cyclohexane) afforded **7** (844 mg, 80%) as a colorless oil. $[\alpha]_D^{25} = -12.0$ (c = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3400 (broad), 3030, 2930, 2860, 1640, 1450, 740, 700 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.35 (m, 5 H), 5.81 (ddt, J = 17.1, 9.9, 7.1 Hz, 1 H), 5.11 (m, 2 H), 4.56 (s, 2 H), 3.95 (m, 1 H), 3.68 (s, 3 H), 3.55 (m, 2 H), 3.27 (m, 1 H), 3.17 (s, 3 H), 2.47 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.0, 137.9, 135.1, 128.3, 127.6 (2 C), 117.1, 73.4, 72.8, 71.0, 61.3, 41.3, 33.8, 31.7 ppm. MS (EI): m/z = 294 $[M + H]^+$. $C_{16}H_{23}NO_4$ (293.35): calcd. C 65.51, H 7.90, N 4.77; found C 65.68, H 7.93, N 4.85.

β-Hydroxy Ketone 8: Octyllithium (0.58 M in Et_2O, 13.5 mL, 7.8 mmol) was added dropwise to a solution of **7** (1.0 g, 3.4 mmol) in THF/Et_2O (6.8 mL, 1:1) at −10 °C. After stirring at −10 °C for 5 h, the reaction mixture was quenched at 0 °C with saturated aqueous NH_4Cl, followed by 1 N HCl, and then extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. Purification of the residual oil by flash chromatography (silica gel, 5 to 20% EtOAc in cyclohexane) afforded **8** (1.0 g, 85%) as a colorless oil. $[\alpha]_D^{25} = -4.7$ (c = 0.19, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3400 (broad), 3040, 2940, 2870, 1715, 1650, 1455, 740, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33 (m, 5 H), 5.70 (ddt, J = 17.1, 10.0, 7.1 Hz, 1 H), 5.06 (m, 2 H), 4.53 (d, J = 11.9 Hz, 1 H), 4.49 (d, J = 11.9 Hz, 1 H), 3.90 (m, 1 H), 3.50 (d, J = 5.0 Hz, 2 H), 3.24 (d, J = 7.3 Hz, 1 H, *OH*), 2.84 (ddd, J = 7.9, 6.4, 5.4 Hz, 1 H), 2.44 (m, 2 H), 2.34 (m, 2 H), 1.49 (m, 2 H), 1.25 (m, 10 H), 0.88 (t, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.4, 137.8, 134.9, 128.5, 127.9, 127.8, 117.6, 73.6, 72.6, 71.6, 52.6, 44.9, 33.6, 31.9, 29.5, 29.2, 29.1, 22.9, 22.7, 14.2 ppm. MS (EI): m/z = 347 $[M + H]^+$. $C_{22}H_{34}O_3$ (346.51): calcd. C 76.26, H 9.89; found C 75.78, H 10.05.

Diol 9: A solution of hydroxy ketone **8** (370 mg, 1.07 mmol) in acetonitrile (1.1 mL) was added to a solution of tetramethylammonium triacetoxyborohydride (1.7 g, 6.4 mmol) in acetonitrile/acetic acid (8 mL, 1:1) at −40 °C. The reaction mixture was stirred at −20 °C for 21 h then quenched with a 0.5 N solution of sodium potassium tartrate. After addition of CH_2Cl_2, the mixture was washed with saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (silica gel, 5 to 30% EtOAc in cyclohexane) afforded **9** (350 mg, 94%) as a colorless oil. $[\alpha]_D^{25} = -13.5$ (c = 1.1, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3400 (broad), 3040, 2980, 2910, 1455, 735, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34 (m, 5 H), 5.77 (ddt, J = 17.1, 10.0, 7.1 Hz, 1 H), 5.05 (m, 2 H), 4.58 (d, J = 11.9 Hz, 1 H), 4.54 (d, J = 11.9 Hz, 1 H), 4.03 (m, 1 H), 3.90 (m, 1 H), 3.54 (m, 2 H), 3.23 (d, J = 3.5 Hz, 1 H, *OH*), 3.07 (d, J = 3.0 Hz, 1 H, *OH*), 2.21 (m, 3 H), 1.58 (m, 2 H), 1.00−1.50 (m, 12 H), 0.89 (t, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.9, 137.4, 128.6, 128.0, 127.9, 116.6, 73.5, 73.2, 72.1, 72.0, 43.5, 34.0, 32.0, 30.0, 29.8, 29.7, 29.4, 26.5, 22.8, 14.2 ppm. MS (EI): m/z = 349 $[M + H]^+$. $C_{22}H_{36}O_3$ (348.52): calcd. C 75.82, H 10.41; found C 75.69, H 10.52. HPLC analysis: Chiralcel OD-H column; flow rate: 1.0 mL/min; eluent: hexane/propan-2-ol (95:5); detection at 215 nm; t_R = 14.1 min, *syn*-**9** isomer; t_R = 16.5 min, *anti*-**9** isomer; *d.e.* = 80%.

Acetonide 10: 2,2-Dimethoxypropane (1.0 mL, 8.2 mmol) and *p*-toluenesulfonic acid (7.1 mg, 4.1 10^{-2} mmol) were added to a solution of diol **9** (287 mg, 0.82 mmol) in acetone (2 mL) at room temperature. The reaction mixture was stirred for 1 h then concentrated and the residual oil was washed with saturated aqueous $NaHCO_3$. After extraction with Et_2O, the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (silica gel, 5 to 20% EtOAc in cyclohexane) afforded **10** (299 mg, 94%) as a colorless oil. $[\alpha]_D^{25} = +15.1$ (c = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3040, 3000, 2940, 2860, 1455, 735, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (m, 5 H), 5.66 (ddt, J = 17.0, 10.0, 7.2 Hz, 1 H), 4.94 (d, J = 17.0 Hz, 1 H), 4.85 (d, J = 10.0 Hz, 1 H), 4.54 (d, J = 12.5 Hz, 1 H), 4.49 (d, J = 12.5 Hz, 1 H), 3.76 (m, 1 H), 3.63 (m, 1 H), 3.41 (m, 2 H), 2.11 (m, 1 H), 2.02 (m, 1 H), 1.57 (m, 1 H), 1.31 (s, 3 H), 1.28 (s, 3 H), 1.30 (m, 14 H), 0.80 (t, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.9, 137.4, 128.7, 128.0, 127.9, 116.9, 100.9, 73.5, 73.0, 72.6, 69.6, 40.6, 32.5, 32.3, 31.4, 30.1, 30.0, 29.7, 26.6, 25.8, 24.4, 23.1, 14.5 ppm. MS (EI): m/z = 389 $[M + H]^+$. $C_{25}H_{40}O_3$ (388.59): calcd. C 77.27, H 10.37; found C 77.31, H 10.40.

β-Hydroxy Ester 11: A solution of β-hydroxy ester **5** (1.0 g, 4.2 mmol) in THF (10 mL) was added to a solution of LDA (10.3 mmol) in THF at −78 °C. After stirring at −78 °C for 1 h, HMPA (0.88 mL, 5.1 mmol) and 4-bromo-2-methylbut-2-ene (1.23 mL, 10.5 mmol) were added. The reaction mixture was stirred at −78 °C for 2 h, then at −20 °C for 1 h before more 4-bromo-2-methylbut-2-ene (0.1 mL, 0.8 mmol) was added. After stirring at −20 °C and at 0 °C for 1 h each the mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (silica gel, 20% EtOAc in cyclohexane) afforded **11** (999 mg, 78%) as a colorless oil. $[\alpha]_D^{25} = -1.4$ (c = 1.0, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3479 (broad), 3064, 3032, 2979, 2916, 2863, 1725, 1454, 739, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.31 (m, 5 H), 5.07 (m, 1 H), 4.56 (d, J = 12.0 Hz, 1 H), 4.52 (d, J = 12.0 Hz, 1 H), 4.12 (dq, J = 10.9, 7.0 Hz, 1 H), 4.06 (dq, J = 10.9, 7.2 Hz, 1 H), 3.90 (m, 1 H), 3.55 (dd, J = 9.7, 4.3 Hz, 1 H), 3.51 (dd, J = 9.7 Hz, 1 H and 5.3 Hz), 3.10 (d, J = 7.5 Hz, 1 H, *OH*), 2.61 (ddd, J = 7.9, 6.8, 5.5 Hz, 1 H), 2.34 (m, 2 H), 1.68 (s, 3 H), 1.59 (s, 3 H), 1.22 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.9, 138.0, 134.3, 128.5, 127.8 (2 C), 120.5, 73.6, 72.6, 71.0, 60.6, 48.2, 28.0, 25.8, 17.8, 14.3 ppm. MS (DCI/NH_3): m/z = 307 $[M + H]^+$, 324 $[M + NH_4]^+$. $C_{18}H_{26}O_4$ (306.40): calcd. C 70.56, H 8.55; found C 70.28, H 8.71. HPLC analysis: Chiralcel OD-H column; flow rate: 0.5 mL/min; eluent: hexane/propan-2-ol (95:5); detection at 215 nm; t_R = 20.5 min, (2*S*,3*R*)-**11** isomer; t_R = 18.4 min, (2*R*,3*R*)-**11** isomer; *d.e.* = 99%.

Amide 12: *n*BuLi (2.40 M in hexanes, 26.8 mL, 64.3 mmol) was added to a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (3.1 g, 32.2 mmol) in THF (60 mL) at −78 °C. After stirring at room temperature for 10 min, the mixture was cooled to −78 °C and a solution of β-hydroxy ester **11** (3.3 g, 10.7 mmol) in THF (40 mL) was added. The reaction mixture was stirred at −78 °C

for 2 h, then quenched with a saturated aqueous solution of NH_4Cl and allowed to warm to room temperature. After extraction with Et_2O, the combined organic layers were dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (silica gel, 15% EtOAc in cyclohexane) afforded **12** (3.2 g, 92%) as a pale-yellow oil. $[\alpha]_D^{25} = +5.2$ ($c = 1.0$, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3417 (broad), 3065, 3031, 2969, 2917, 2861, 1650, 1454, 738, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.31 (m, 5 H), 5.12 (m, 1 H), 4.55 (d, J = 12.1 Hz, 1 H), 4.51 (d, J = 12.1 Hz, 1 H), 4.12 (d, J = 8.6 Hz, 1 H, *OH*), 3.90 (m, 1 H), 3.63 (s, 3 H), 3.56 (dd, J = 9.7, 5.1 Hz, 1 H), 3.48 (dd, J = 9.7, 6.2 Hz, 1 H), 3.13 (br. s, 4 H), 2.40 (t, J = 7.3 Hz, 2 H), 1.68 (s, 3 H), 1.62 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$,): δ = 176.8, 138.2, 134.4, 128.4, 127.8, 127.7, 120.9, 73.6, 73.2, 71.1, 61.4, 41.7, 31.9, 28.2, 25.9, 17.8 ppm. MS (DCI/NH_3): m/z = 322 $[M + H]^+$. $C_{18}H_{27}NO_4$ (321.41): calcd. C 67.26, H 8.47, N 4.36; found C 66.98, H 8.61, N 4.12.

Amide 15: 2,6-Lutidine (4.9 mL, 42.0 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (7.6 mL, 32.4 mmol) were added to a solution of **12** (6.7 g, 20.8 mmol) in CH_2Cl_2 (45 mL) at 0 °C. After stirring at 0 °C for 1 h, the mixture was diluted with water (20 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (silica gel, 10 to 20% EtOAc in cyclohexane) afforded **15** (8.9 g, 98%) as a colorless oil. $[\alpha]_D^{25} = +13.3$ ($c = 1.05$, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3031, 2955, 2929, 2855, 1661, 1471, 1253, 836, 735, 698 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$,): δ = 7.31 (m, 5 H), 5.05 (m, 1 H), 4.57 (d, J = 12.1 Hz, 1 H), 4.50 (d, J = 12.1 Hz, 1 H,), 4.06 (m, 1 H), 3.67 (s, 3 H), 3.57 (dd, J = 10.4, 2.6 Hz, 1 H), 3.50 (dd, J = 10.4, 4.9 Hz, 1 H), 3.22 (m, 1 H), 3.15 (s, 3 H), 2.25 (m, 2 H), 1.64 (s, 3 H), 1.57 (s, 3 H), 0.86 (s, 9 H), 0.05 (s, 3 H), 0.03 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$,): δ = 174.8, 138.6, 133.1, 128.3, 127.7, 127.5, 121.5, 73.4, 73.1, 73.0, 61.3, 45.4, 32.0, 26.8, 25.9, 25.8, 18.1, 17.8, −4.5, −4.9 ppm. MS (DCI/NH_3): m/z = 436 $[M + H]^+$. $C_{24}H_{41}NO_4Si$ (435.58): calcd. C 66.16, H 9.49, N 3.21; found C 65.88, H 9.68, N 3.12.

Ketone 16: *n*-Octyllithium (0.5 M in Et_2O, 9.0 mL, 4.5 mmol) was added dropwise to a solution of **15** (1.96 g, 4.5 mmol) in THF (40 mL) at −50 °C. After stirring at −50 °C for 1 h, *n*-octyllithium was added again (9.0 mL, 4.5 mmol) and the solution was stirred for 1 h. After quenching with methanol and saturated aqueous NH_4Cl, the mixture was allowed to warm to room temperature and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated. Purification of the residual oil by flash chromatography (silica gel, 3% EtOAc in cyclohexane) afforded **16** (1.6 g, 73%) as a pale-yellow oil. $[\alpha]_D^{25} = +16.2$ ($c = 1.02$, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3031, 2953, 2927, 2855, 1716, 1471, 1253, 836, 735, 697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$,): δ = 7.31 (m, 5 H), 4.99 (m, 1 H), 4.53 (d, J = 12.1 Hz, 1 H), 4.47 (d, J = 12.1 Hz, 1 H), 3.99 (dt, J = 7.6, 3.8 Hz, 1 H), 3.46 (dd, J = 10.3, 3.8 Hz, 1 H), 3.41 (dd, J = 10.3, 4.3 Hz, 1 H), 2.84 (ddd, J = 10.3, 7.3 Hz and 4.5 Hz, 1 H), 2.42 (t, J = 7.3 Hz, 2 H), 2.26 (m, 1 H), 2.07 (m, 1 H), 1.64 (s, 3 H), 1.55 (s, 3 H), 1.49 (m, 2 H), 1.24 (br. s, 10 H), 0.90 (t, J = 6.3 Hz, 3 H), 0.84 (s, 9 H), 0.02 (s, 3 H), 0.00 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 213.3, 138.2, 133.4, 128.4, 127.8, 127.7, 121.3, 73.5, 73.3, 72.8, 55.5, 45.5, 31.9, 29.5 (2 C), 29.3, 27.2, 25.9, 25.8, 23.0, 22.7, 18.1, 17.8, 14.2, −4.4, −5.0 ppm. MS (DCI/NH_3): m/z = 489 $[M + H]^+$, 506 $[M + NH_4]^+$. $C_{30}H_{52}O_3Si$ (488.74): calcd. C 73.71, H 10.72; found C 73.73, H 10.76.

Hydroxy Ketone 14: Tetrabutylammonium fluoride (1 M in THF, 14.3 mL, 14.3 mmol) was added dropwise to a solution of **16** (2.9 g, 6.0 mmol) in THF (50 mL) at 0 °C. After stirring at 0 °C for 4 h, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (15 mL), allowed to warm to room temperature and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (silica gel, 10 to 15% EtOAc in cyclohexane) afforded **14** (2.1 g, 96%) as a pale-yellow oil. $[\alpha]_D^{25} = -18.8$ ($c = 1.0$, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3469 (broad), 3030, 2980, 2923, 2853, 1713, 1454, 736, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35 (m, 5 H), 5.03 (m, 1 H), 4.55 (d, J = 12.2 Hz, 1 H), 4.49 (d, J = 12.2 Hz, 1 H), 3.88 (m, 1 H), 3.48 (d, J = 5.1 Hz, 2 H), 3.30 (d, J = 7.2 Hz, 2 H, *OH*), 2.75 (ddd, J = 8.0, 6.6, 5.6 Hz, 1 H), 2.42 (t, J = 7.3 Hz, 2 H), 2.26 (m, 2 H), 1.67 (s, 3 H), 1.58 (s, 3 H), 1.46 (m, 2 H), 1.24 (br. s, 10 H), 0.88 (t, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 216.0, 137.9, 134.4, 128.5, 127.8 (2 C), 120.7, 73.6, 72.9, 71.8, 53.0, 44.8, 31.9, 29.4 (2C), 29.2, 28.0, 25.8, 23.0, 22.7, 17.8, 14.2 ppm. MS (DCI/NH_3): m/z = 375 $[M + H]^+$, 392 $[M + NH_4]^+$. $C_{24}H_{38}O_3$ (374.56): calcd. C 76.96, H 10.22; found C 76.83, H 10.40.

Diol 17: (*S*)-MeO-BIPHEP (7.0 mg, 0.012 mmol) and [(COD)Ru(2-methylallyl)$_2$] (3.2 mg, 0.01 mmol, commercially available from Acros), were placed in a round-bottomed flask and dissolved in 1 mL of acetone (degassed by three cycles of vacuum/argon at room temperature). A 0.175 N methanolic HBr solution (126 μL, 0.022 mmol) was added to this suspension and the mixture was stirred at room temperature for 30 min. After evaporation of the solvent under vacuum, a solution of β-hydroxy ketone **14** (98.6 mg, 0.25 mmol) in MeOH (2 mL) was added to the ruthenium catalyst. The resulting mixture was placed under hydrogen pressure (50 bar) at 50 °C for 6 h. After removal of the solvent, the residue was purified by flash chromatography (silica gel, 15% EtOAc in cyclohexane) to afford a 97:3 mixture of **17**/**18** (90 mg, 94%) as a pale-yellow oil. $[\alpha]_D^{25} = -11.7$ ($c = 1.0$, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3406 (broad), 3031, 2980, 2922, 2852, 1496, 736, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.35 (m, 5 H), 5.11 (m, 1 H), 4.50 (d, J = 11.7 Hz, 1 H), 4.45 (d, J = 11.7 Hz, 1 H), 3.99 (m, 1 H), 3.86 (m, 1 H), 3.53 (m, 2 H), 3.16 (d, J = 3.8 Hz, 1 H, *OH*), 2.85 (d, J = 2.9 Hz, 1 H, *OH*), 2.24 (m, 1 H), 2.05 (m, 1 H), 1.69 (s, 3 H), 1.61 (s, 3 H), 1.28 (br. s, 10 H), 1.70−1.10 (m, 5 H), 0.89 (t, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.9, 133.2, 128.6, 128.0, 127.9, 123.0, 73.6, 73.5, 72.4, 72.3, 44.5, 34.0, 32.0, 29.8, 29.7, 29.4, 26.5, 25.9, 24.0, 22.7, 17.9, 14.2 ppm. MS (DCI/NH_3): m/z = 377 $[M + H]^+$, 394 $[M + NH_4]^+$. $C_{24}H_{40}O_3$ (376.58): calcd. C 76.55, H 10.71; found C 76.47, H 10.84. HPLC analysis: column, Chiralcel OD-H; flow rate: 1.0 mL/min; eluent: hexane/propan-2-ol (95:5); detection at 215 nm; t_R = 15.7 min, *anti*-**17** (2*R*,3*R*,4*S*) isomer; t_R = 12.7 min, *syn*-**17** (2*R*,3*R*,4*R*) isomer; t_R = 13.8 min, *anti*-**18** isomer; t_R = 11.5 min, *syn*-**18** isomer; *d.e.* = 99%.

Acetonide 19: 2,2-Dimethoxypropane (4.5 mL, 36.6 mmol) and pyridinium *p*-toluenesulfonate (7.7 mg, 0.031 mmol) were added to a solution of diol **17** (230 mg, 0.61 mmol) in acetone (3.5 mL) at room temperature. After stirring at room temperature for 0.5 h, the reaction mixture was concentrated and the residual oil was washed with saturated aqueous $NaHCO_3$. After extraction with Et_2O, the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (silica gel, 5% EtOAc in cyclohexane) afforded **19** (250 mg, 98%) as a pale-yellow oil. $[\alpha]_D^{25} = +16.9$ ($c = 1.00$, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3030, 2984, 2925, 2854, 1454, 736, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.31 (m, 5 H), 5.01 (m, 1 H), 4.60 (d, J = 12.5 Hz, 1 H), 4.55 (d, J = 12.5 Hz, 1 H), 3.83 (m, 1 H), 3.65 (m, 1 H), 3.47 (m, 2 H), 2.07 (t, J = 7.0 Hz, 2 H), 1.61 (s, 3 H), 1.58

(s, 3 H), 1.42 (s, 3 H), 1.39 (s, 3 H), 1.49−1.14 (m, 5 H), 1.27 (br. s, 10 H), 0.88 (t, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.7, 132.6, 128.4, 127.7, 127.6, 122.7, 100.5, 73.2, 73.0, 72.7, 69.4, 41.0, 31.9, 31.0, 29.7, 29.6, 29.4, 26.3, 25.9 (2 C), 25.6, 24.1, 22.7, 17.9, 14.2 ppm. MS (DCI/NH_3): m/z = 417 $[M + H]^+$, 434 $[M + NH_4]^+$. $C_{27}H_{44}O_3$ (416.64): calcd. C 77.83, H 10.64; found C 77.63, H 10.84.

Ester 2 from Acetonide 10: A 2.5 M ethanolic NaOH solution (1 mL) was added to a solution of acetonide **10** (100 mg, 0.26 mmol) in CH_2Cl_2 (4 mL). A stream of ozone was bubbled through the mixture at −78 °C until a persistent blue color was achieved (3 h). Water and Et_2O were added at −78 °C and the mixture was allowed to warm to room temperature. After extraction with Et_2O, the combined organic layers were dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (silica gel, 5% EtOAc in cyclohexane) afforded **2** (90 mg, 80%) as a colorless oil. $[\alpha]_D^{25}$ = +2.0 (c = 1.4, $CHCl_3$), {ref.[7,8] $[\alpha]_D^{20}$ = 0.0 (c = 1.0, $CHCl_3$)}.

Ester 2 from Acetonide 19: A 2.5 M ethanolic NaOH solution (2 mL) was added to a solution of acetonide **19** (50 mg, 0.12 mmol) in CH_2Cl_2 (8 mL). A stream of ozone was bubbled through the mixture at −78 °C for 1 h. Water and Et_2O were added at −78 °C and the mixture was allowed to warm to room temperature. After extraction with Et_2O, the combined organic layers were dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography (silica gel, 5% EtOAc in cyclohexane) afforded **2** (46 mg, 88%) as a colorless oil. $[\alpha]_D^{25}$ = +4.6 (c = 1.0, $CHCl_3$) {ref.[7,8] $[\alpha]_D^{20}$ = 0.0 (c = 1.0, $CHCl_3$)}. IR (film): $\tilde{\nu}$ = 3030, 2983, 2926, 2855, 1735, 1454, 736, 698 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (m, 5 H), 4.61 (d, J = 12.3 Hz, 1 H), 4.55 (d, J = 12.3 Hz, 1 H), 4.05 (m, 2 H), 3.87 (dt, J = 9.1, 3.6 Hz, 1 H), 3.67 (dt, J = 6.4, 3.9 Hz, 1 H), 3.56 (dd, J = 10.6, 6.2 Hz, 1 H), 3.50 (dd, J = 10.6, 3.8 Hz, 1 H), 2.51 (m, 1 H), 1.49−1.21 (m, 6 H), 1.37 (s, 3 H), 1.35 (s, 3 H), 1.26 (br. s, 10 H), 1.21 (t, J = 7.2 Hz, 3 H), 0.88 (t, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2, 138.5, 128.4, 127.7, 127.6, 100.7, 73.4, 72.9, 72.3, 68.8, 60.5, 38.6, 33.1, 31.9, 30.6, 29.6, 29.5, 29.3, 26.1, 25.4, 24.2, 22.7, 14.2, 14.1 ppm. MS (DCI/NH_3): m/z = 435 $[M + H]^+$, 452 $[M + NH_4]^+$. $C_{26}H_{42}O_5$ (434.61): calcd. C 71.85, H 9.74; found C 71.93, H 9.92.

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