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Stereocontrolled construction of the *trans*-tetrahydrofuran units in Annonaceous acetogenins

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Abstract

An efficient synthetic method for the construction of *trans*-tetrahydrofuran (THF) unit from *trans*-1,5,9-decatriene was successfully developed by means of Sharpless AD reactions and oxidative cyclizations catalyzed by $Co(modp)_2$ under an oxygen atmosphere. Based on this new synthetic strategy, the *trans*-mono-THF unit, *trans*-bis-THF unit and *trans*-tris-THF unit in Annonaceous acetogenins were smoothly obtained.

1. Introduction

The Annonaceous acetogenins, polyketide-derived fatty acids isolated from the Annonaceae family of tropical and subtropical trees, are a growing class of fascinating natural compounds which show interesting cytotoxic, antitumor, antimicrobial, antimalarial, antifeedant, pesticidal and immunosuppressive effects.[1] They are characterized by the presence of one to three THF rings in the center of a long hydrocarbon chain with a butenolide moiety at the end. Both due to their potent biological activities and their unique and diverse structures, Annonaceous acetogenins are attractive targets for synthetic chemists. For example, gigantetrocin A was isolated by McLaughlin's group from *Goniothalamus giganteus* Hook. f. and Thomas (Annonaceae)[2] and significantly and selectively was demonstrated to be cytotoxic to human tumor cells in culture.[2,3] Its absolute configuration has been determined by spectroscopic analysis. The striking characteristics are the existence of four hydroxyl groups, an α,β-unsaturated γ-lactone and a mono *trans*-tetrahydrofuran (THF) ring unit (Fig. 1). Asimilobin, a relatively rare bulladecin type acetogenin,[1] was isolated by McLaughlin's group both from the seeds of *Asimina triloba*[4] and the bark of *Goniothalamus giganteus* (Annonaceae),[5] and showed cytotoxicity values comparable with adriamycin

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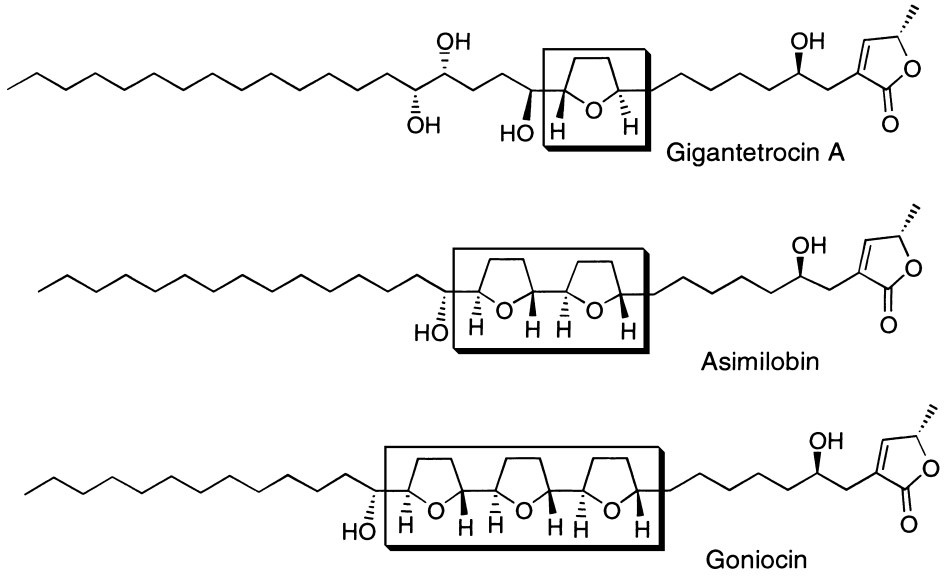


Figure 1.

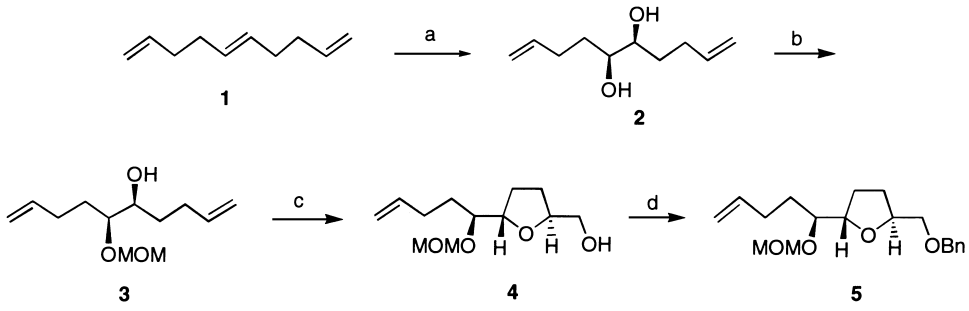
against six human solid tumor cell lines. Its absolute configuration had been first determined by spectroscopic analysis and was then corrected by the first total synthesis of this natural product (Fig. 1).[6] The remarkable features are the adjacent *threo/trans/threo/trans* bis-THF ring and one flanking hydroxyl group at the α-position of the THF core. Goniocin, a novel cytotoxic acetogenin, was isolated from *Goniothalamus giganteus*.[7] The structure of goniocin has been determined by spectroscopic analysis which was recently further verified by Sinha et al. in the first total synthesis of this compound.[8] It possesses a tris-THF moiety and represents the first, and so far the only, example of a new subgroup of this family (Fig. 1).

Since the γ-lactone unit could be very easily synthesized according to the literature,[9] obviously stereocontrolled construction of THF units played a central role in the total syntheses of Annonaceous acetogenins[10] and several recent reports majoring in dealing with this task exhibited more convenient approaches to mono- and bis-THF units.[11–15] Likewise, it is the most challenging research field in the total synthesis of Annonaceous acetogenins. Herein we wish to report the full details of our synthetic route to those *trans*- and *threo*-THF units utilizing the Sharpless AD reaction and Mukaiyama's oxidative cyclization catalyzed by $Co(modp)_2$ [bis(1-morpholinocarbamoyl-4,4-dimethyl-1,3-pentanedionato) cobalt(II)] from achiral triene **1**.

2. Results and discussion

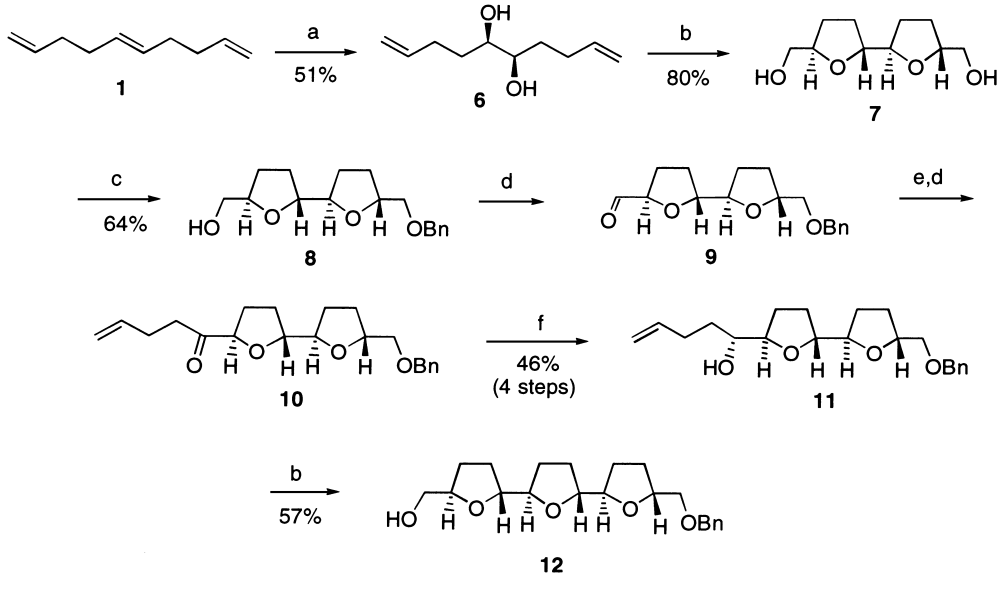
Regioselective oxidation of *trans*-1,5,9-decatriene **1** by Sharpless AD reaction[16] installed the two prime stereogenic centers, with greater than 94% ee,[17] in the mono-THF ring backbone. The obtained diol **2** was subsequently mono-protected by MOMCl and then oxidatively cyclized to form a mono *trans*-THF ring compound **4** with greater than 95% de[18] in 74% yield using $Co(modp)_2$[19] as a catalyst under an oxygen atmosphere (Scheme 1). This compound was then monoprotected by a benzyl group to give the benzyl ether **5** which has been successfully used in the first total synthesis of gigantetrocin A.[20]

Using this new synthetic strategy we can also synthesize the adjacent *trans*-bis-THF and tris-THF unit (Scheme 2). The resulting diendiol **6**, which is the enantiomer of **2**, was oxidized and cyclized under



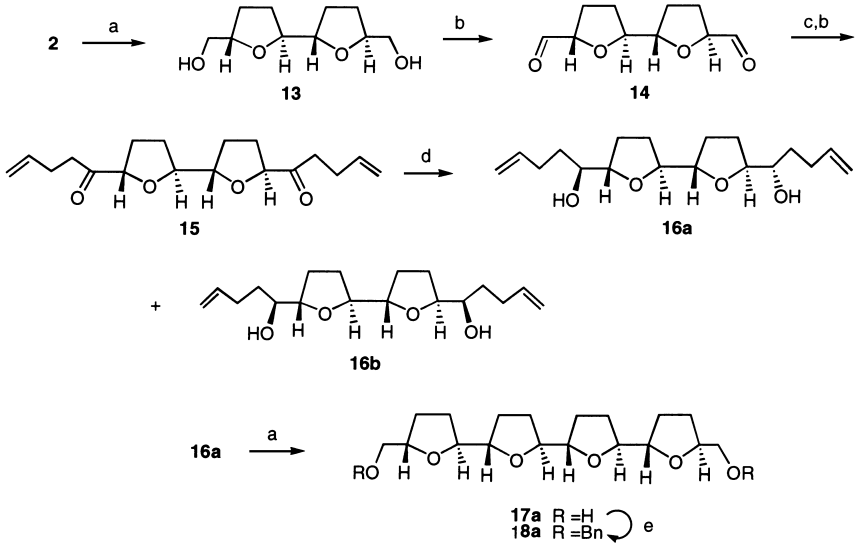
Scheme 1. Conditions: (a) $K_3Fe(CN)_6$, K_2CO_3, $NaHCO_3$, $MeSO_2NH_2$, $(DHQ)_2PHAL$, $K_2OsO_2(OH)_4$, *t*-BuOH: H_2O (1:1), 0°C; 57%. (b) NaH, MOMCl, THF; 67%. (c) $Co(modp)_2$, TBHP, O_2, *i*-PrOH; 74%. (d) NaH, BnBr, THF; 98%

the catalysis of $Co(modp)_2$ to form a *trans/threo/trans* bis-THF ring building block **7** with greater than 95% de. Compound **7** was mono-protected with a benzyl group to afford the benzyl ether **8**[21] which has been successfully used in the first total synthesis of asimilobin.[6] The compound **8** was subjected to Swern oxidation to give the aldehyde **9** which was subsequently coupled with (3-buten-1-yl)magnesium bromide[22] and followed by another Swern oxidation to afford the ketone **10**. The compounds **9** and **10** were directly used for the next reaction without purification or characterization. Compound **10** was then reduced by L-Selectride[23] to give the enol **11** with 90% de.[24] By forming a new THF ring via another step of oxidative cyclization catalyzed by $Co(modp)_2$, compound **11** was smoothly transformed to the tris-THF unit **12**, with high diastereoselectivity (greater than 95% de), which constitutes the central core of THF unit in goniocin. To the best of our knowledge, this is the most convenient and efficient synthetic method to construct the adjacent *trans*-bis-THF ring and tris-THF ring building block in high yield and high stereoselectivity. In particular, the adjacent *trans*-bis-THF ring can be readily synthesized in only two steps (Scheme 2). Moreover, the enantiomers **7**–**12** could be readily obtained simply by changing the chiral ligand in the Sharpless AD reaction.[16] Thus, based on catalytic asymmetric reaction, this new synthetic method has a great advantage in the synthesis of THF units in Annonaceous acetogenins.



Scheme 2. Conditions: (a) $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, $(DHQD)_2PHAL$, $K_2OsO_2(OH)_4$, *t*-BuOH:H_2O (1:1), 0°C. (b) $Co(modp)_2$, TBHP, O_2, *i*-PrOH. (c) NaH, BnBr, THF. (d) Swern oxidation. (e) $CH_2{=}CHCH_2CH_2MgBr$, THF, −20°C. (f) L-Selectride, THF, −78°C

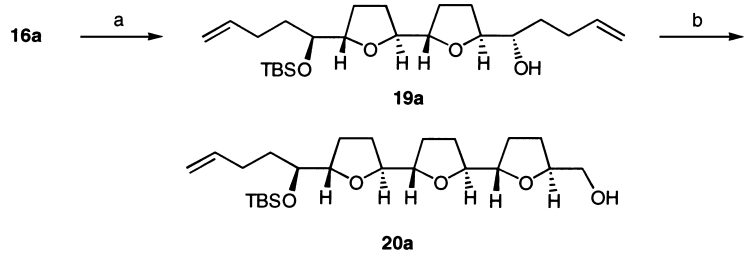
On the other hand, since the number and stereochemistry of the substituted THF rings strikingly affect the activity of acetogenins and only one to three THF rings were found in these polyketide-derived fatty acids, it will be very interesting to observe the bioactivity of the nonnatural acetogenins containing more than three THF rings. Moreover, non-natural oligo-THFs are suitable for ion binding and 2,5-*trans*-linked oligo-THFs represent potential building blocks for a membrane-bound artificial ion channel.[25] Thus, we started to synthesize the tetrakis-*trans*-THF unit using our synthetic method. Regioselective oxidation of *trans*-1,5,9-decatriene **1** by Sharpless AD reaction and cyclization catalyzed by $Co(modp)_2$ under oxygen atmosphere to form a *trans/threo/trans* bis-THF ring building block **13**, which is the enantiomer of **7**, with more than 95% de (Scheme 3). This C_2-symmetric compound was subjected to Swern oxidation and the resulting dial **14** was coupled with two molar (3-buten-1-yl)magnesium bromide and followed by another Swern oxidation to afford dione **15**. The compounds **14** and **15** were directly used for the next reaction without purification and characterization. Reduction of compound **15** with L-Selectride gave the diendiol **16a** with diastereoselectivity of **16a**:**16b**=2.6:1.[26] By forming two new THF rings via another oxidative cyclization reaction catalyzed by $Co(modp)_2$, compound **16a** was smoothly transformed to a C_2-symmetric tetrakis-THF unit **17a**[27] which was protected as the benzyl ether to give **18a**. Repeating these procedures on compound **17a** will certainly produce some other interesting C_2-symmetric building blocks with more *trans*-2,5-linked THF rings.



Scheme 3. Conditions: (a) $Co(modp)_2$, TBHP, O_2, *i*-PrOH; 78%. (b) Swern oxidation. (c) (3-Buten-1-yl)magnesium bromide, THF, de 45%. (d) L-Selectride, THF, −78°C; 40% (four steps). (e) NaH, BnBr, THF; 40% (two steps)

Due to its intrinsic property of C_2 symmetry, compound **16a** was mono-protected as a TBS ether **19a** (Scheme 4) then catalytically oxidized under an oxygen atmosphere to give a tris-THF compound **20a**, which could be used to construct the THF unit of cyclogoniodenin T (Fig. 2).[5]

In conclusion, the key building blocks for the total synthesis of gigantetrocin A, asimilobin, goniocin and cyclogoniodenin T have been successfully synthesized by using Sharpless AD and $Co(modp)_2$ catalyzed cyclization reaction. Especially by expanding a new *trans*-THF ring from a *trans*-2,5-linked bis-THF unit, the construction of the THF unit in goniocin was successfully achieved in eight steps. In the meantime, expansion of two *trans*-THF rings from a *trans*-2,5-linked THF unit both bidirectionally and simultaneously was achieved by taking advantage of its intrinsic property of C_2 symmetry, although the de was not so high. This new synthetic strategy has great applicable potency in the synthesis of *trans*-



Scheme 4. Conditions: (a) TBSCl, imidazole, THF; 75%. (b) $Co(modp)_2$, TBHP, O_2, *i*-PrOH; 76%

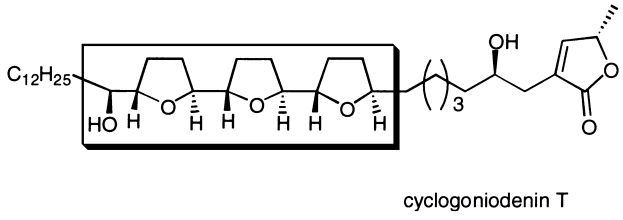


Figure 2.

2,5-linked THF units with more than four THF rings toward a polyether helix with ion channel activity,[28] and this work is in progress.

3. Experimental

Optical rotations were determined in a solution of $CHCl_3$ and methanol at room temperature by using a Perkin–Elmer 241 MC digital polarimeter; $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. ^1H NMR spectra were determined for solutions in $CDCl_3$ with tetramethylsilane (TMS) as internal standard on a Bruker AMX-300 spectrometer; *J* values are in hertz. IR spectra were determined by a Perkin–Elmer 983 spectrometer. Mass spectra were recorded with an HP-5989 instrument. High resolution mass spectra were recorded on a Finnigan MA+ instrument. Microanalyses were carried out using an Italian Carlo-Erba 1106 analyzer.

3.1. (5S,6S)-1,9-Decadiene-5,6-diol ***2***

To a well-stirred solution of $(DHQ)_2PHAL$ (1.09 g, 1.40 mmol), $K_2OsO_2(OH)_4$ (309 mg, 0.840 mmol), $K_3Fe(CN)_6$ (139 g, 421 mmol), K_2CO_3 (58.1 g, 421 mmol) and $MeSO_2NH_2$ (13.3 g, 140 mmol) in *t*-BuOH:H_2O (1:1) (1400 mL) at 0°C was added triene **1** (19.1 g, 140 mmol). After being stirred vigorously for 12 h, the reaction mixture was quenched with Na_2SO_3 (140 g) and extracted with EtOAc. The organic layers were dried over $MgSO_4$ and then concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc:petroleum ether, 1:10) to give **2** (13.6 g, 57%) as a colorless oil. $[\alpha]_D^{20}$ −21.3 (*c* 3.30, $CHCl_3$); IR (neat) ν 3402, 1639 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.48–1.68 (4H, m), 2.10–2.39 (4H, m), 2.37 (2H, br, s), 3.42–3.53 (2H, m), 4.98 (2H, dm, *J*=10.0), 5.04 (2H, dm, *J*=17.3), 5.83 (2H, ddt, *J*=17.3, 10.0, 6.6); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.87, 32.56, 73.82, 114.91, 138.23; MS (EI) *m/z* (%) 171 (MH^+, 14.5), 153 (100), 135 (50.0), 85 (14.3); [HRMS found: 170.1309 (M^+); $C_{10}H_{18}O_2$ requires: 170.1307].

3.2. (5S,6S)-6-Methoxymethoxy-1,9-decadiene-5-ol **3**

To a solution of **2** (3.85 g, 22.6 mmol) in 50 mL anhydrous THF was added 75% NaH (724 mg, 22.6 mmol) and the reaction mixture was stirred for 1 h at room temperature. Then, a 5 mL THF solution of methoxymethyl chloride (1.82 g, 1.72 mL, 22.6 mmol) was added into the mixture and further stirred for 24 h at room temperature. The reaction was quenched by adding water and extracted with ether and washed with brine. The organic layer was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (eluent: EtOAc:petroleum ether, 1:5) to give **3** (3.23 g, 67%) as a colorless oil. $[\alpha]_D^{20}$ +21.4 (*c* 3.08, $CHCl_3$); IR (neat) ν 3446, 3075, 1640, 1103, 916 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.46–1.75 (4H, m), 2.09–2.33 (4H, m), 2.78 (1H, d, *J*=4.8), 3.36–3.45 (1H, m), 3.41 (3H, s), 3.49–3.57 (1H, m), 4.69 (1H, d, *J*=6.7), 4.72 (1H, d, *J*=6.7), 4.98 (2H, dm, *J*=10.2), 5.04 (2H, dm, *J*=17.1), 5.82 (2H, ddt, *J*=17.1, 10.2, 6.7); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.48, 29.93, 30.31, 32.57, 55.91, 72.22, 82.74, 97.28, 114.83, 114.97, 138.24, 138.53; MS (EI) *m/z* (%) 215 (MH^+, 2.0), 183 (2.0), 169 (2.6), 153 (1.5), 135 (2.0), 129 (1.0); [found: C, 67.33; H, 10.18%; $C_{12}H_{22}O_3$ requires: C, 67.26; H, 10.35%].

3.3. (2S,5S,6S)-2,5-Epoxy-6-methoxymethoxy-9-decanene-1-ol **4**

To a solution of **3** (3.0 g, 14.0 mmol) in 200 mL 2-propanol was added $Co(modp)_2$ (755 mg, 1.40 mmol, 10 mol%) and *tert*-butyl hydroperoxide (1.26 g, 14.0 mmol) and the reaction mixture was stirred at 60°C under an oxygen atmosphere for 4 h. After cooling to room temperature, the reaction was quenched by adding saturated aqueous sodium thiosulfate ($Na_2S_2O_3$) solution and stirred for 30 min. 2-Propanol was removed under reduced pressure and extracted with ethyl acetate. The organic layer was washed with brine and dried over Mg_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (eluent: EtOAc:petroleum ether, 1:4) to give **4** (2.38 g, 74%) as a colorless oil. $[\alpha]_D^{20}$ −24.1 (*c* 1.58, $CHCl_3$); IR (neat) ν 3426, 1639 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.50–1.76 (4H, m), 1.89–2.03 (2H, m), 2.08–2.27 (2H, m), 3.41 (3H, s), 3.46–3.55 (2H, m), 3.62–3.68 (1H, m), 3.99–4.13 (2H, m), 4.70 (1H, d, *J*=6.8), 4.81 (1H, d, *J*=6.8), 4.98 (1H, dm, *J*=10.2), 5.04 (1H, dm, *J*=17.1), 5.82 (1H, ddt, *J*=17.1, 10.2, 6.6); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.56, 28.49, 29.62, 30.54, 55.83, 64.79, 79.42, 79.61, 81.37, 96.92, 114.84, 138.45; [HRMS (EI) found: 230.1521 (M^+); $C_{12}H_{22}O_4$ requires: 230.1518].

3.4. (5S,6S,9S)-5-Methoxymethoxy-6,9-epoxy-10-benzyloxy-1-decanene **5**

To a solution of **4** (2.24 g, 9.74 mmol) in THF (30 mL) was added 75% NaH (375 mg, 11.7 mmol) and the reaction mixture was stirred at room temperature for 1 h. Then benzyl bromide (2.0 g, 1.39 mL, 11.7 mmol) was added into the mixture and further stirred for 12 h. The solvent was removed under reduced pressure and the residue was extracted with ether (3×50 mL). The organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (eluent: EtOAc:petroleum ether, 1:20) to give **5** (3.05 g, 98%) as a colorless oil. $[\alpha]_D^{20}$ −35.6 (*c* 1.92, $CHCl_3$); IR (neat) ν 3063, 3026, 1639, 1496, 1453, 1099, 920 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.50–1.76 (4H, m), 1.89–2.03 (2H, m), 2.10–2.26 (2H, m), 3.39 (3H, s), 3.45–3.50 (2H, m), 3.50–3.55 (1H, m), 4.04–4.10 (1H, m), 4.15–4.24 (1H, m), 4.55 (1H, d, *J*=12.1), 4.60 (1H, d, *J*=12.1), 4.69 (1H, d, *J*=6.7), 4.81 (1H, d, *J*=6.7), 4.98 (1H, dm, *J*=10.2), 5.04 (1H, dm, *J*=17.1), 5.82 (1H, ddt, *J*=17.1, 10.2, 6.6), 7.27–7.39 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.99, 28.85, 29.84,

30.45, 55.85, 72.91, 73.37, 78.29, 79.35, 81.31, 96.97, 114.77, 127.58, 127.68, 128.39, 138.56, 138.61; [HRMS (EI) found: 320.2000 (M^+); $C_{19}H_{28}O_4$ requires: 320.1988].

3.5. (5R,6R)-1,9-Decadiene-5,6-diol **6**

The reaction procedure was the same as that of **2** except adding chiral ligand $(DHQD)_2PHAL$ instead of $(DHQ)_2PHAL$. $[\alpha]_D^{20}$ +22.0 (*c* 4.00, $CHCl_3$).

3.6. (2R,5R,6R,9R)-2,5;6,9-Diepoxydeca-1,10-diol **7**

To a solution of **6** (1.70 g, 10.0 mmol) in *i*-PrOH (250 mL) were added $Co(modp)_2$ (2.16 g, 4.00 mmol) and *t*-BuOOH (1.80 g, 20.0 mmol). After being heated at 60°C under oxygen for 3 h, the reaction mixture was cooled to room temperature, then saturated aqueous $Na_2S_2O_3$ (10 mL) was added and the mixture was stirred for a further 10 min. *i*-PrOH was evaporated under reduced pressure. The resulting mixture was extracted with EtOAc. The organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc:petroleum ether, 1:1) to give **7** (1.57 g, 78%) as a colorless oil. $[\alpha]_D^{18}$ −18.5 (*c* 0.80, $CHCl_3$); {lit.[28] 80% de. $[\alpha]_D^{20}$ +12.5 (*c* 0.80, $CHCl_3$)}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.52–1.68 (2H, m), 1.70–1.85 (2H, m), 1.91–2.05 (4H, m), 2.49 (2H, br, s), 3.50 (2H, dd, *J*=11.8, 5.3), 3.71 (2H, dd, *J*=11.8, 2.6), 3.85–3.95 (2H, m), 4.10–4.21 (2H, m); MS (EI) *m/z* 171 (M^+-2H_2O), 153, 101.

3.7. (2R,5R,6R,9R)-10-Benzyloxy-2,5;6,9-diepoxy-1-decanol **8**

To a solution of diol **7** (1.01 g, 5.0 mmol) in dry THF (50 mL) at 0°C was added NaH (120 mg, 5.0 mmol). After being stirred for 1 h, a solution of benzyl bromide (855 mg, 0.60 mL, 5.0 mmol) in THF (2 mL) was added dropwise over 10 min. After being stirred for 8 h, the solvent was removed under reduced pressure. To the mixture was added water and EtOAc. After separation, the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc:petroleum ether, 2:3) to give **8** (1.03 g, 71%) as a colorless oil. $[\alpha]_D^{20}$ +6.3 (*c* 1.00, $CHCl_3$); IR (neat) ν 3426, 1601, 1495 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.55–1.81 (4H, m), 1.91–2.10 (4H, m), 3.46–3.57 (3H, m), 3.70 (1H, dd, *J*=11.7, 3.2), 3.86–3.96 (2H, m), 4.09–4.17 (1H, m), 4.18–4.26 (1H, m), 4.56 (2H, s), 7.25–7.39 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.47, 28.44, 28.79, 64.64, 72.79, 73.39, 78.48, 79.95, 82.21, 127.68, 128.36, 138.45; MS (EI) *m/z* (%) 293 (MH^+, 11.0), 261 (3.21), 201 (26.6); [HRMS (EI) found: 292.1678 (M^+); $C_{17}H_{24}O_4$ requires: 292.1675].

3.8. (2R,5R,6R,9R)-10-Benzyloxy-2,5;6,9-diepoxy-1-decanal **9**, ketone **10** and alcohol **11**

To a solution of oxalyl chloride (522 mg, 0.36 mL, 4.1 mmol) in dry CH_2Cl_2 (10 mL) at −78°C under nitrogen was added DMSO (641 mg, 0.58 mL, 8.22 mmol) as a solution in CH_2Cl_2 (10 mL). After being stirred for 10 min, a solution of **8** (425 mg, 1.46 mmol) in CH_2Cl_2 (2 mL) was added and the reaction mixture was allowed to stir for 2 h at −78°C. Then triethylamine (1.5 mL) was added and the mixture was warmed naturally to room temperature. After 1 h the reaction was quenched with water and extracted with CH_2Cl_2. The organic extracts were washed with saturated brine and dried over $MgSO_4$. After concentration, the crude aldehyde **9** was obtained.

To freshly prepared $CH_2{=}CHCH_2CH_2MgCl$ (0.50 M, 6 mL, 3.0 mmol) in THF was added a solution of **9** (ca. 1.2 mmol) in THF (10 mL) under nitrogen at −20°C. After being stirred for 30 min, the mixture was warmed to room temperature naturally. The reaction mixture was stirred for 1 h. Saturated aqueous ammonium chloride was added into the reaction solution and the mixture was extracted with ether. The organic layer was washed with saturated brine and dried over $MgSO_4$. After concentration, the residue was purified by flash chromatography (EtOAc:petroleum ether, 1:1) to give the crude product (ca. 1.0 mmol) which was subjected to the Swern oxidation mentioned above again to afford the crude ketone **10**.

To a solution of **10** (ca. 1.0 mmol) in anhydrous THF (3 mL) was added slowly L-Selectride (1.0 M in THF) (2.0 mL, 2.0 mmol) at −78°C under argon and the reaction mixture was stirred for 1 h. The reaction was quenched by adding methanol (1.0 mL). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (EtOAc:petroleum ether, 1:2) to give **11** (231 mg, 4 steps 46%) as a colorless oil. $[\alpha]_D^{22}$ +11.9 (*c* 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.41–1.58 (2H, m), 1.58–1.80 (4H, m), 1.90–2.11 (4H, m), 2.11–2.21 (1H, m), 2.21–2.35 (1H, m), 2.29 (1H, br, s), 3.38–3.43 (1H, m), 3.47 (1H, dd, *J*=10.0, 5.0), 3.53 (1H, dd, *J*=10.0, 5.3), 3.80–3.99 (3H, m), 4.15–4.24 (1H, m), 4.57 (2H, s), 4.97 (1H, dm, *J*=10.2), 5.04 (1H, dm, *J*=17.1), 5.84 (1H, ddt, *J*=17.1, 10.2, 6.6), 7.22–7.39 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.37, 28.48, 28.77, 28.89, 29.87, 32.68, 72.36, 72.78, 78.55, 81.94, 82.01, 82.98, 114.73, 127.57, 127.69, 128.36, 138.59; MS (EI) *m/z* (%) 346 (M^+, 1.3), 329 (9.9), 310 (1.2), 287 (2.0), 261 (8.7); [HRMS (EI) found: 346.2157 (M^+); $C_{21}H_{30}O_4$ requires: 346.2144].

*3.9. (2*R*,5*R*,6*R*,9*R*,10*R*,13*R*)-10-Benzyloxy-2,5;6,9;10,13-triepoxy-1-decanol **12***

Treatment of **11** (231 mg, 0.67 mmol), in the same manner as that described in the preparation of **4** from **3**, afforded **12** (236 mg, 98%) as a colorless oil. $[\alpha]_D^{20}$ +3.9 (*c* 1.35, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.57–1.80 (6H, m), 1.89–2.10 (6H, m), 3.42–3.54 (3H, m), 3.67 (1H, dd, *J*=11.6, 3.2), 3.87–4.01 (4H, m), 4.08–4.15 (1H, m), 4.15–4.24 (1H, m), 4.54 (1H, d, *J*=12.2), 4.59 (1H, d, *J*=12.2), 7.22–7.39 (10H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.47, 28.09, 28.22, 28.45, 28.64, 28.85, 64.77, 72.93, 73.32, 78.39, 79.85, 81.67, 81.89, 81.98, 82.09, 127.50, 127.65, 128.32, 138.50; MS (EI) *m/z* (%) 362 (M^+, 0.41), 345 (2.4), 331 (0.8), 271 (3.9), 261 (5.8); [HRMS (FAB) found: 363.2182 (MH^+); $C_{21}H_{31}O_5$ requires: 363.2172].

*3.10. (2*S*,5*S*,6*S*,9*S*)-2,5;6,9-Diepoxydeca-1,10-diol **13***

To a solution of **2** (1.70 g, 10.0 mmol) in *i*-PrOH (250 mL) was added $Co(modp)_2$ (2.16 g, 4.0 mmol) and *t*-BuOOH (1.80 g, 20.0 mmol). After being heated at 60°C under oxygen for 3 h, the reaction mixture was cooled to room temperature and stirred for a further 10 min after adding saturated aqueous $Na_2S_2O_3$ (10 mL). *i*-PrOH was evaporated under reduced pressure. The resulting mixture was extracted with EtOAc. The organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc:petroleum ether, 1:1) to give **13** (1.57 g, 78%) as a colorless oil. $[\alpha]_D^{18}$ +18.5 (*c* 0.80, $CHCl_3$); {lit.[28] 80% de. $[\alpha]_D^{20}$ +12.5 (*c* 0.80, $CHCl_3$)}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.52–1.68 (2H, m), 1.70–1.85 (2H, m), 1.91–2.05 (4H, m), 2.49 (2H, br, s), 3.50 (2H, dd, *J*=11.8, 5.3), 3.71 (2H, dd, *J*=11.8, 2.6), 3.85–3.95 (2H, m), 4.10–4.21 (2H, m); MS (EI) *m/z* 171 (M^+-2H_2O), 153, 101.

3.11. (2S,5S,6S,9S)-2,5;6,9-Diepoxydecadial **14**, diketone **15** and diol **16**

To a solution of oxalyl chloride (3.18 g, 2.18 mL, 25.0 mmol) in dry CH_2Cl_2 (150 mL) at −78°C under a nitrogen atmosphere was added DMSO (4.29 g, 3.90 mL, 55.0 mmol) as a solution in CH_2Cl_2 (10 mL). After being stirred for 10 min, a solution of **13** (1.68 g, 8.32 mmol) in CH_2Cl_2 (20 mL) was added and the reaction mixture was allowed to stir for a further 2 h. Then triethylamine (10 mL) was added and the mixture was warmed naturally to room temperature. After 1 h the reaction was quenched with water and extracted with CH_2Cl_2. The organic extracts were washed with saturated brine and dried over $MgSO_4$. After concentration, the crude aldehyde **14** was obtained which was used for the next reaction without further purification.

To freshly prepared $CH_2{=}CHCH_2CH_2MgCl$ (0.40 M, 40 mL, 16.6 mmol) in THF was added a solution of **14** (ca. 8.3 mmol) in THF (10 mL) under a nitrogen atmosphere at −78°C. After being stirred for 15 min, the mixture was warmed to room temperature naturally. The reaction mixture was stirred for 1 h. Saturated aqueous ammonium chloride was added and the mixture was extracted with ether. The organic layer was washed with saturated brine and dried over $MgSO_4$. After concentration, the residue was purified by flash chromatography (EtOAc:petroleum ether, 1:1) to give the product (2.5 g, 80%) which was subjected to the Swern oxidation mentioned above again to afford the crude diketone **15**.

To a solution of **15** (ca. 2.64 mmol) in anhydrous THF (10 mL) was added slowly L-Selectride (1.0 M in THF) (6.5 mL, 6.5 mmol) at −78°C under an argon atmosphere and the reaction mixture was stirred for 40 min. The reaction was quenched by adding methanol (1.0 mL). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (EtOAc:petroleum ether, 1:2) to give the mixture **16a** and **16b** (500 mg, 61%) as a colorless oil. **16a**: $[\alpha]_D^{20}$ −12.4 (*c* 2.50, $CHCl_3$); IR (neat) ν 3426, 3073, 1636, 1065 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.41–1.58 (4H, m), 1.58–1.74 (4H, m), 1.90–2.04 (4H, m), 2.08–2.23 (2H, m), 2.23–2.37 (2H, m), 2.29 (2H, br, s), 3.39–3.46 (2H, m), 3.81–3.97 (4H, m), 4.97 (2H, dm, *J*=10.2), 5.04 (2H, dm, *J*=17.1), 5.84 (2H, ddt, *J*=17.1, 10.2, 6.6); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.41, 29.07, 29.90, 32.70, 73.39, 81.95, 83.16, 114.81, 138.59; MS (EI) *m/z* (%) 310 (M^+, 0.11), 293 (1.1), 275 (0.6), 251 (5.9); [HRMS (EI) found: 310.2154 (M^+); $C_{18}H_{30}O_3$ requires: 310.2144]. **16b**: IR (neat) ν 3428, 3072, 1634, 1062 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.40–1.54 (4H, m), 1.58–1.74 (4H, m), 1.90–2.04 (4H, m), 2.08–2.23 (2H, m), 2.23–2.37 (2H, m), 2.29 (2H, br, s), 3.39–3.46 (2H, m), 3.81–3.97 (4H, m), 4.97 (2H, dm, *J*=10.2), 5.04 (2H, dm, *J*=17.1), 5.84 (2H, ddt, *J*=17.1, 10.2, 6.6); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.68, 30.32, 31.63, 32.55, 70.87, 73.46, 82.37, 82.61, 82.82, 83.24, 114.90, 138.42; MS (EI) *m/z* (%) 310 (M^+, 0.14), 293 (3.1), 275 (1.2), 251 (6.4); [HRMS (EI) found: 310.2150 (M^+); $C_{18}H_{30}O_3$ requires: 310.2144].

3.12. (2S,5S,6S,9S,10S,13S,14S,17S)-2,5;6,9;10,13;14,17-Tetraepoxyoctadeca-1,18-diol **17a**

This compound was prepared from **16a** (96 mg, 0.31 mmol) in the same manner as that described in the preparation of **3** and it was used for the next reaction without further purification.

3.13. (2S,5S,6S,9S,10S,13S,14S,17S)-1,18-Dibenzyloxy-2,5;6,9;10,13;14,17-tetraepoxyoctadecane **18**

To a solution of **17a** (106 mg, 0.31 mmol) in anhydrous THF (2 mL) was added NaH (75%, 30 mg, 0.94 mmol) and the reaction mixture was stirred for 1 h at room temperature. Benzyl bromide (137 mg, 0.095 mL, 0.80 mmol) was added into the reaction solution and the mixture was further stirred for 24 h. After usual workup, the residue was purified by flash chromatography (EtOAc:petroleum ether, 1:3) to give **18** (70 mg, 43%) as a colorless oil. $[\alpha]_D^{22}$ −9.2 (*c* 1.90, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ

1.61–1.84 (8H, m), 1.86–2.10 (8H, m), 3.45 (2H, dd, *J*=10.0, 5.0), 3.52 (2H, dd, *J*=10.0, 5.3), 3.88–4.01 (6H, m), 4.15–4.24 (2H, m), 4.54 (2H, d, *J*=12.2), 4.59 (2H, d, *J*=12.2), 7.22–7.39 (10H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.10, 28.17, 28.43, 28.85, 72.91, 73.32, 78.37, 81.57, 81.77, 81.89, 127.52, 127.69, 128.34, 138.52; MS (EI) *m/z* (%) 522 (M^+, 0.35), 431 (0.83); [HRMS (FAB) found: 523.3046 (MH^+); $C_{32}H_{43}O_6$ requires: 523.3060].

*3.14. (5S,6S,9S,10S,13S,14S)-5-*tert*-Butyldimethylsiloxy-14-hydroxy-6,9;10,13-diepoxy-1,18-octadecadiene **19a***

To a solution of **16a** (155 mg, 0.50 mmol) and imidazole (84 mg, 1.24 mmol) in THF (5 mL) was added TBDMSCl (75 mg, 0.50 mmol) and the reaction mixture was stirred for 24 h at room temperature. After usual workup, the residue was purified by flash chromatography (EtOAc:petroleum ether, 1:10) to give **19a** (159 mg, 75%) as a colorless oil. $[\alpha]_D^{22}$ −15.6 (*c* 2.50, $CHCl_3$); IR (neat) ν 3426, 3074, 1635, 1101 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.05 (3H, s, SiMe), 0.08 (3H, s, SiMe), 0.88 (9H, s, Me_3C), 1.39–1.77 (8H, m), 1.79–2.0 (4H, m), 2.0–2.37 (4H, m), 3.39–3.46 (1H, m), 3.60–3.68 (1H, m), 3.80–3.91 (3H, m), 3.91–3.99 (1H, m), 4.90–5.08 (4H, m), 5.73–5.90 (2H, m); MS (EI) *m/z* (%) 425 (MH^+), 366 (4.6), 348 (7.1), 321 (3.8); [HRMS (FAB) found: 425.3076 (MH^+); $C_{24}H_{45}O_4Si$ requires: 425.3087].

*3.15. (5S,6S,9S,10S,13S,14S,17S)-5-*tert*-Butyldimethylsiloxy-18-hydroxy-6,9;10,13;14,17-triepoxy-1-octadecene **20a***

This compound was prepared in the same manner as that described in the preparation of **7** or **12** as a colorless oil. $[\alpha]_D^{22}$ −11.9 (*c* 2.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.06 (3H, s), 0.07 (3H, s), 0.89 (9H, s), 1.35–1.50 (1H, m), 1.51–1.84 (7H, m), 1.85–2.10 (7H, m), 2.10–2.32 (1H, m), 3.48 (1H, dd, *J*=11.6, 5.6), 3.60–3.68 (1H, m), 3.68 (1H, dd, *J*=11.6, 3.2), 3.87–4.01 (5H, m), 4.10–4.16 (1H, m), 4.90–5.05 (2H, m), 5.78–5.88 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.28, 26.03, 27.43, 27.50, 28.27, 28.39, 28.49, 28.72, 30.07, 31.97, 74.37, 79.91, 81.65, 81.78, 81.98, 82.14, 82.19, 114.33, 139.08; MS (EI) *m/z* (%) 441 (MH^+), 382 (3.4), 365 (6.6), 347 (1.8), 321 (1.7); [HRMS (FAB) found: 441.3052 (MH^+); $C_{24}H_{45}O_4Si$ requires: 441.3036].

Acknowledgements

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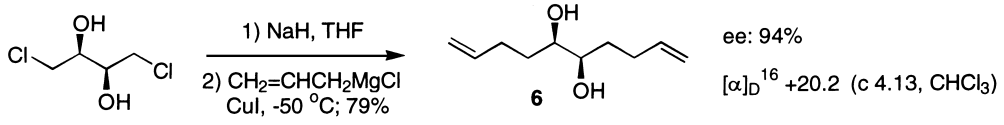

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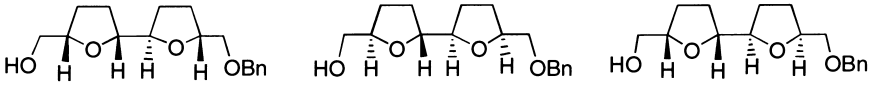
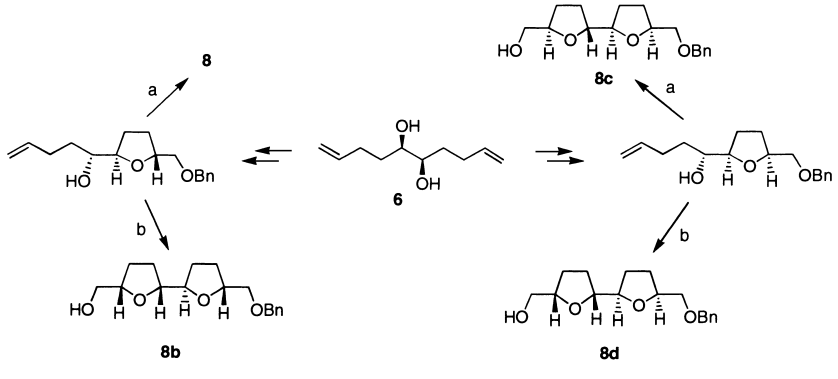


8b **8c** **8d**

8b: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.69–1.85 (3H, m), 1.85–1.97 (3H, m), 1.97–2.10 (2H, m), 3.46–3.57 (3H, m), 3.77 (1H, dd, *J*=11.7, 2.8), 3.86–3.94 (1H, m), 3.95–4.03 (1H, m), 4.08–4.16 (1H, m), 4.19–4.28 (1H, m), 4.56 (2H, s), 7.25–7.39 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.35, 28.79, 65.68, 72.57, 73.38, 78.76, 80.16, 81.67, 81.98, 82.23, 127.67, 128.39, 138.42. **8c**: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.55–1.77 (3H, m), 1.77–1.90 (2H, m), 1.90–2.04 (3H, m), 3.42–3.57 (3H, m), 3.68 (1H, dd, *J*=11.7, 3.1), 3.78–3.87 (1H, m), 3.88–3.98 (1H, m), 4.06–4.22 (2H, m), 4.56 (2H, s), 7.25–7.39 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.50, 27.69, 28.33, 28.89, 64.66, 72.81, 73.39, 78.60, 80.05, 82.13, 82.66, 127.71, 128.39, 138.47. **8d**: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.73–1.84 (3H, m), 1.84–2.02 (5H, m), 3.41–3.56 (3H, m), 3.74 (1H, dd, *J*=11.7, 2.8), 3.84–3.96 (2H, m), 4.05–4.18 (2H, m), 4.56 (2H, s), 7.25–7.39 (5H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.32, 27.97, 28.18, 28.70, 65.43, 72.50, 73.36, 78.48, 80.06, 81.59, 81.89, 127.60, 127.77, 128.38, 138.24.



Conditions: a) $Co(modp)_2$, TBHP, O_2, *i*-PrOH. b) 1) $K_3Fe(CN)_6$, K_2CO_3, $(DHQ)_2PYR$, $K_2OsO_2(OH)_4$, ^tBuOH:H_2O (1:1), 0 °C. 2) NaH, TosIm, THF. 3) $BF_3{\cdot}OEt_2$, CH_2Cl_2.

22. No satisfactory diastereoselectivity (de 32%) was obtained by direct coupling of these two reagents in the presence of $CuBr{\cdot}SMe_2$ (Mead, K.; Macdonald, T. L. *J. Org. Chem*. **1985**, *50*, 422).

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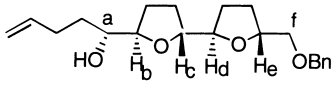
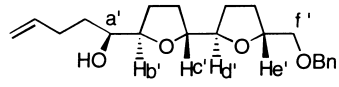
24. The de value is calculated according to the ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of **11** and its diastereomer **11′**. The integration of the signal located at δ 3.38–3.59 [**11**: 3H (Ha, Hf) and **11′**: 2H (Hf′)] is 0.609 and that located at δ 3.80–3.99 [**11**: 3H (Hb–Hd) and **11′**: 4H (Ha′–Hd′)] is 0.629. From the equation (3×**11**+2×**11′**):(3×**11**+4×**11′**)=0.609:0.629 we obtained **11**:**11′**=20:1.



11



11'

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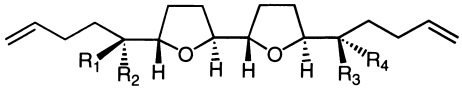
26. Ignoring **16c**, the diastereoselectivity value is calculated according to the ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of the mixtures. The integration of the signal located at δ 3.39–3.46 (*threo*, **16a**: 2H, **16b**: 1H) is 0.899 and that located at δ 3.81–3.97 (*erythro*,[1b] **16a**: 4H, **16b**: 5H) is 2.239. From the equation (**16a**×2+**16b**×1):(**16a**×4+**16b**×5)=0.899:2.239 we obtained **16a**:**16b**=2.6:1.



16a $R_1=R_4=OH$, $R_2=R_3=H$
16b $R_1=R_3=OH$, $R_2=R_4=H$
16c $R_1=R_4=H$, $R_2=R_3=OH$

27. No diastereoisomer with *cis*-THF ring was detected from the ^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of **18a**.
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