Synthesis of the Major Oxepane Segment of Zoapatanol

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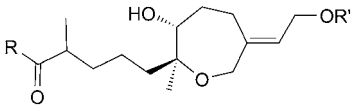
A linear synthesis of the major oxepane fragment of zoapatanol, showing the induction of uterine contractions, and cervical dilation and uterine bleeding (by the concentrated zoapatle tea) in early human pregnancy, isolated from the leaves of Mexican zoapatle plant *Montanoa tomentosa*, is described from known intermediate involving *Sharpless* asymmetric epoxidation, bis-epoxide opening reaction with *Corey–Chaykovsky* reagent, ring-closing metathesis reaction, and *Horner–Wadsworth–Emmons* olefination reaction as key steps.

Introduction. – Zoapatanol (**1**), montanol (**2**), tomentol (**3**), and tomentanol (**4**) are novel diterpenoid oxepanes (*Fig. 1*) isolated from the leaves of Mexican zoapatle plant *Montanoa tomentosa* [1]. For centuries, the Mexican women have been using the aqueous crude extract or 'tea' of zoapatle as a popular local folk medicine for various gynecological applications such as facilitation of labor, stimulation of menstruation, and termination of early pregnancy [2]. In 1979, the isolation and structure elucidation of zoapatanol (**1**) and montanol (**2**) were reported by *Levine et al.* [1a]. Zoapatanol (**1**) was assumed to be the biologically most active component isolated from zoapatle plant. Reports on the induction of uterine contractions, cervical dilation and uterine bleeding by the concentrated zoapatle tea in early human pregnancy were in good agreement with folk medicine of Mexico [3]. Due to its excellent biological profile and challenging structural feature, several groups have reported its synthesis [4][5]. A number of groups have also reported their studies towards its synthesis [6].



1 R = $Me_2C{=}CHCH_2$, R' = H
2 R = $^iPrC(Me){=}CH$, R' = H
3 R = $Me_2C(OH)CH{=}CH$, R' = Ac
4 R = $H_2C{=}C(Me)CH(Me)CH_2$, R' = H

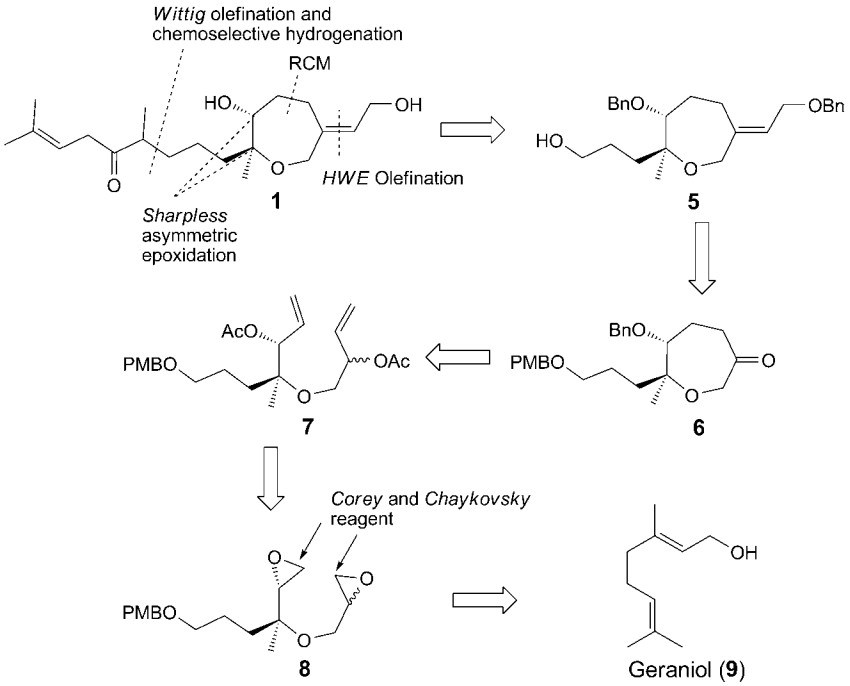
Fig. 1. *Structures of toapatanol* (**1**), *montanol* (**2**), *tomentol* (**3**), *and tomentanol* (**4**)

The successful synthesis of natural zoapatanol (**1**) includes the stereocontrolled oxepane ring formation, installation of the (*E*)-configured exocyclic C=C bond, and elongation of the side chain. Accordingly, we designed our synthetic strategy based on *Sharpless* asymmetric epoxidation, regioselective bis-epoxide opening reaction with

Corey–Chaykovsky reagent, ring-closing metathesis reaction, and stereoselective *Horner–Wadsworth–Emmons* (*HWE*) olefination reaction.

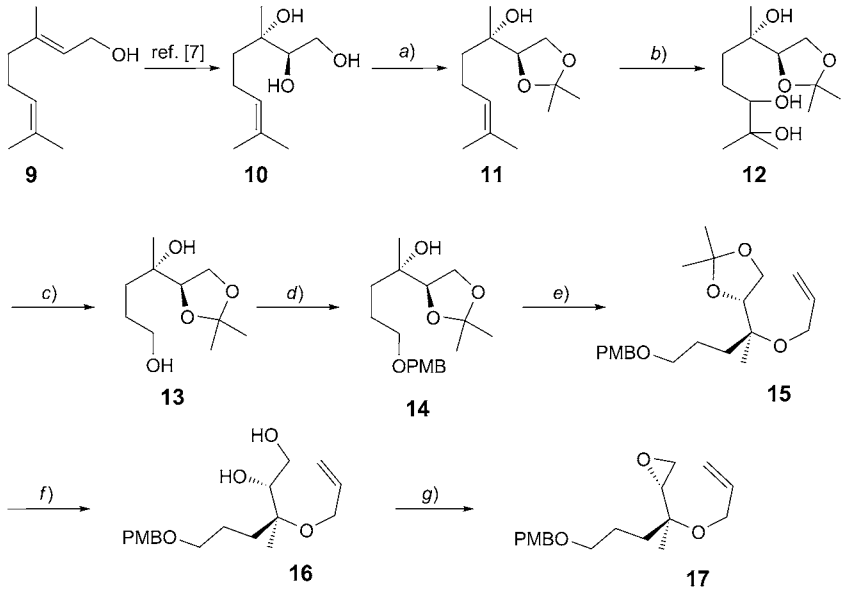
Retrosynthetic analysis revealed that the chain elongation could be achieved through *Wittig* olefination reaction of the aldehyde derived from alcohol **5**. The exocyclic C=C bond could be stereoselectively created by the *HWE* olefination of the oxepane ketone **6**, which, with the required configuration, could be constructed *via* a ring-closing metathesis reaction of the diene **7**. The latter could be formed by epoxide opening of **8** with *Corey–Chaykovsky* reagent (*Scheme 1*). Control of the two adjacent stereogenic centers would be achieved through the application of *Sharpless* asymmetric epoxidation to the commercially available geraniol (**9**).

Scheme 1. *Retrosynthetic Analysis*



Results and Discussion. – Our synthesis started from the known intermediate triol **10** [7], which was prepared from commercially available geraniol (**9**) according to a literature protocol (*Scheme 2*). Selective protection of **10** as its acetonide **11** was achieved using 2,2-dimethoxypropane (2,2-DMP) in the presence of a catalytic amount of camphor-10-sulfonic acid (CSA) in DMF [8]. Compound **11** was then treated with OsO_4 in the presence of *N*-methylmorpholine *N*-oxide (NMO) as co-oxidant to afford triol **12** in 95% yield [9]. Oxidative cleavage of triol **12** with silica-supported $NaIO_4$ [10] and subsequent reduction of the generated aldehyde with $NaBH_4$ [11] furnished diol **13**. The primary OH group in **13** was selectively protected as its 4-methoxybenzyl (PMB) ether **14**, using PMBBr and NaH in THF, in 96% yield. The tertiary OH group was then

Scheme 2. *Synthesis of the Fragment* **17**

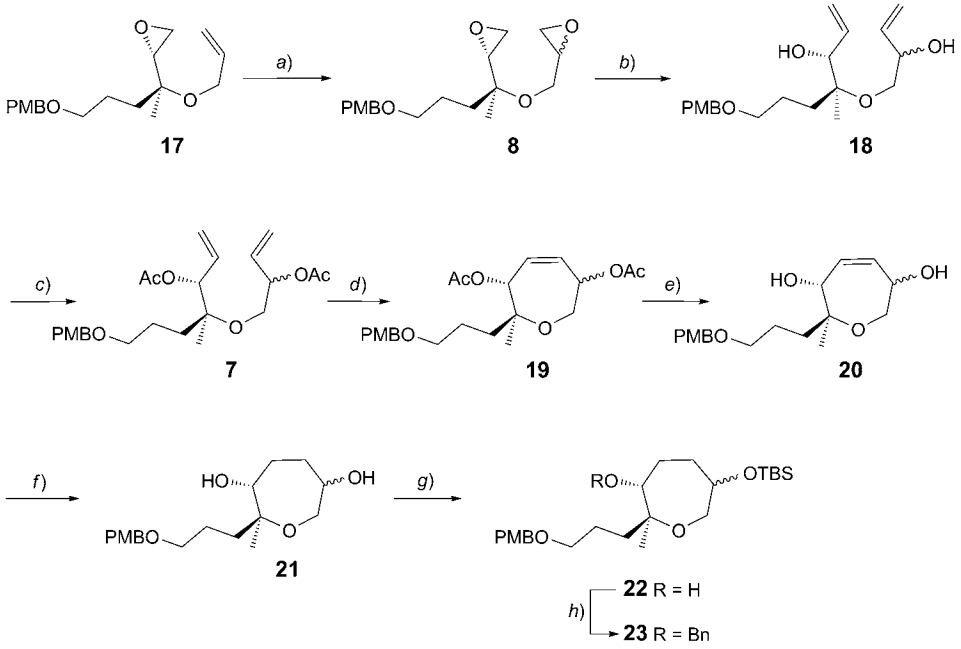


a) 2,2-Dimethoxypropane (2,2-DMP), DMF, 0° – room temperature, 1 h; 96%. *b*) OsO_4, *N*-methylmorpholine N-oxide (NMO) acetone/H_2O, room temperature, 48 h; 95%. *c*) SiO_2-$NaIO_4$, CH_2Cl_2, 10 min, then $NaBH_4$, MeOH, room temperature, 30 min; 92%. *d*) 4-Methoxybenzyl bromide (PMB-Br), NaH, THF, 0° – room temperature, 5 h; 96%. *e*) NaH, allyl bromide, DMF, 0° – room temperature, 3 h; 87%. *f*) Camphor-10-sulfonic acid (CSA), MeOH, room temperature, 24 h; 85%. *g*) NaH, 1-trisyl-1*H*-imidazole (=1-[(2,4,6-triisopropylphenyl)sulfonyl]-1*H*-imidazole), THF, 0° – room temperature, 15 min; 82%.

converted to its allyl ether **15** using allyl bromide and NaH in DMF, and subsequent deprotection of acetonide by using CSA yielded diol **16**. The latter was then treated with trisyl-1*H*-imidazole (=1-[(2,4,6-triisopropylphenyl)sulfonyl]-1*H*-imidiazole) [12] and NaH in THF to furnish the epoxide **17** in a single step (*Scheme 2*). Olefin **17** was then treated with 3-chloroperbenzoic acid (*m*-CPBA; *Scheme 3*) to afford the inseparable diastereoisomer mixture of diepoxide **8**. As the newly formed stereogenic center has to be oxidized after a few steps, we proceeded with the mixture of diastereoisomers. Treatment of **8** with *Corey–Chaykovsky* reagent [13], *i.e.*, Me_3SI in presence of BuLi, at $-10°$ yielded diene **18** in 94% yield. Having **18** in hand, our next task was to perform the crucial ring-closing metathesis reaction (RCM) [14]. The RCM reaction of **18** in the presence of *Grubbs* 1st-generation catalyst in refluxing degassed CH_2Cl_2 under inert atmosphere failed to provide the desired oxepane ring. The RCM reaction even failed in refluxing toluene under the same reaction conditions.

To overcome this problem, **18** was converted to diester **7** using Ac_2O [15] and Et_3N in CH_2Cl_2 in 95% yield. RCM Reaction of **7** with *Grubbs* 1st-generation catalyst in CH_2Cl_2 under reflux yielded the oxepane **19** in 70% yield with 20% recovery of starting material. Both ester groups of **19** were hydrolyzed using K_2CO_3 in MeOH to furnish the unsaturated diol **20** [16], which was then subjected to catalytic hydrogenation in the

Scheme 3. *Synthesis of the Fragment* **23**

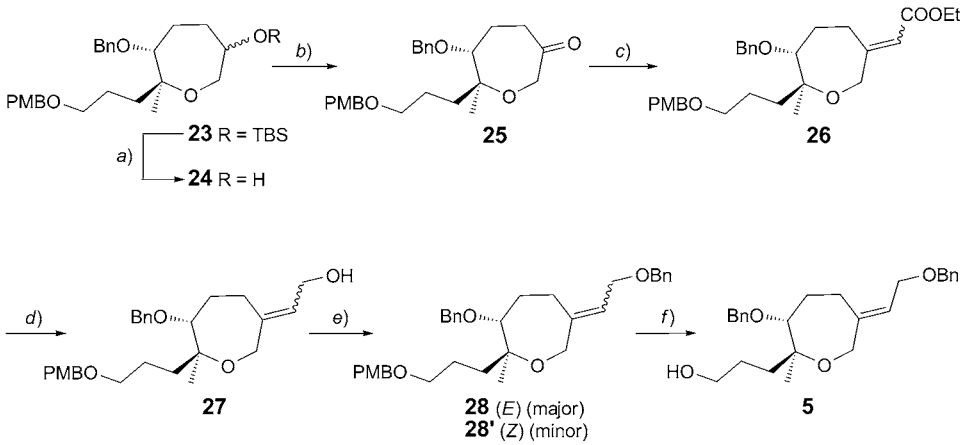


a) *m*-CPBA, CH_2Cl_2, 0° – room temperature, 8 h; 83%. *b*) Me_3SI, BuLi, THF, – 10°, 45 min; 94%. *c*) Ac_2O, Et_3N, 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, 0° – room temperature, 4 h; 95%. *d*) *Grubbs* 1st-generation cat., CH_2Cl_2, reflux, 28 h; 70%. *e*) K_2CO_3, MeOH, 0° – room temperature, 10 h; 90%. *f*) Pd/C, AcOEt, room temperature, 10 min; 78%. *g*) ^{t}BuMe$_2$SiCl (TBSCl), 1*H*-imidazole, CH_2Cl_2, 0° – room temperature, 2 h; 88%. *h*) NaH, BnBr, DMF, 0° – room temperature, 12 h; 87%.

presence of Pd/C [17] under H_2 to furnish its saturated derivative **21**. Regioselective (*tert*-butyl)dimethylsilyl (TBS) protection [18] of the less crowded OH group in **21**, and subsequent protection of the crowded OH group using BnBr in presence of NaH and a catalytic amount of Bu_4NI (TBAI) [19] in DMF afforded **23** in 77% yield over two steps. The TBS group was then selectively removed with a catalytic amount of CSA in MeOH to obtain **24**, and subsequent oxidation of resulting secondary alcohol using *Dess–Martin* periodinane (DMP) [20] yielded **25** in 92% yield over two steps. The latter was then subjected to *Horner–Wadsworth–Emmons* olefination using ethyl 2-(diethylphosphono)acetate [4d][21] and NaH (*Scheme 4*) in THF to generate the corresponding α,β-unsaturated ester **26** as an inseparable (*E*)/(*Z*)-mixture of isomers ((*E*)/(*Z*) 60:40; ^{1}H-NMR). This mixture was then reduced with $LiAlH_4$ in THF to provide an inseparable mixture of allyl alcohols **27** in 90% yield. Benzylation [5b] of **27** using Ag_2O, BnBr, and TBAI afforded the mixture **28**/**28′** ((*E*)/(*Z*) 63:37; HPLC) in 94% yield.

The two isomers were separated by simple silica-gel flash chromatography, and the configuration of the two isomers was established by spectroscopy (*Fig. 2*). Finally, the PMB group of **28** was selectively removed using CAN [22] in MeCN/H_2O to afford the

Scheme 4. *Synthesis of the Fragment* **5**



a) CSA, MeOH, room temperature, 15 h. *b*) *Dess–Martin* periodinane, CH_2Cl_2, 0°, 1 h; 92% over two steps. *c*) $Et_2COCH_2P(O)(OEt)_2$, NaH, THF, room temperature; 97%. *d*) $LiAlH_4$ (LAH), THF, 0° – room temperature, 2 h; 90%. *e*) Ag_2O, BnBr, Bu_4NI (TBAI), CH_2Cl_2, room temperature, 16 h; 94%. *f*) Cerium(IV) ammonium nitrate (CAN), $MeCN/H_2O$, 0° – room temperature, 11 h; 90%.

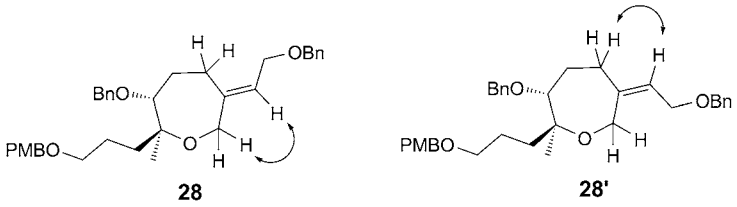


Fig. 2. *NOE Interactions of compounds* **28** *and* **28′**

key intermediate **5** towards the synthesis of natural (+)-(2′*S*,3′*R*)-zoapatanol and its analogs.

Conclusions. – In summary, we have accomplished a stereoselective synthesis of a key intermediate for the synthesis of natural zoapatanol (**1**) by using *Sharpless* asymmetric epoxidation, bis-epoxide opening reaction with *Corey–Chaykovsky* reagent, ring-closing metathesis reaction, and *Horner–Wadsworth–Emmons* olefination reaction as key steps. Elongation of the side chain to complete the synthesis of natural zoapatanol is in progress in our laboratory.

Experimental Part

General. All reactions were performed under Ar. All glassware used for reactions are oven/flame-dried. Anh. solvents were distilled prior to use: THF from Na and benzophenone; CH_2Cl_2 and DMSO from CaH_2; and MeOH from Mg cake. Commercial reagents were used without purification. Column chromatography (CC): silica gel (60–120 mesh), unless otherwise mentioned. Anal. TLC: silica gel *60 F254* pre-coated plates (250 μm thickness). Optical rotations: *Perkin–Elmer 343* polarimeter; in 10^{-1} deg

$cm^2\ g^{-1}$. IR Spectra: *Perkin–Elmer Infrared-683* spectrometer; in $CHCl_3$ or KBr; $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Varian Gemini 200*, *Varian Unity 400*, *Varian Inova 500* or *Bruker Avance 300* spectrometers; at 300, 400, and 500 MHz (^1H), and 75 MHz (^{13}C); in $CDCl_3$ soln., unless otherwise mentioned, chemical shifts (δ) in ppm downfield from TMS; coupling constants (J) in Hz. ESI- or HR-ESI-MS: *Finnigan MAT 1020B* or *Micro Mass 70–70 H* spectrometers; at 70 eV; *m/z* (rel. %).

*(2*R*,3*S*)-3,7-Dimethyloct-6-ene-1,2,3-triol* (**10**). To a stirred soln. of epoxygeraniol [7] (20.0 g, 117.64 mmol) in THF (250 ml)/H_2O (50 ml), $HClO_4$ (60%, 2 ml) was added dropwise during 30 min at 0°. The mixture was gradually warmed and stirred at 15–20° for 3 h. The reaction was quenched by addition of sat. aq. $NaHCO_3$ (50 ml) soln. The mixture was extracted with AcOEt (4 × 100 ml), and the combined org. layers were washed with brine (2 × 50 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The crude mass was purified by CC (AcOEt/hexane 1:1) to furnish **10** (17.25 g, 78%). $[\alpha]_D^{27} = +5.8$ ($c = 0.97$, $CHCl_3$). IR (KBr): 3374, 2967, 2924, 1448, 1377, 1081, 1027, 872, 773. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.10 (*t*, *J* = 6.7, 1 H); 3.73 (*d*, *J* = 4.5, 2 H); 3.45 (*t*, *J* = 4.5, 1 H); 2.21–1.93 (*m*, 2 H); 1.70 (*s*, 3 H); 1.64 (*s*, 3 H); 1.58–1.53 (*m*, 1 H); 1.45–1.34 (*m*, 1 H); 1.23 (s, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 131.7; 124.0; 77.0; 74.3; 62.9; 37.5; 25.5; 23.0; 22.0; 17.5. ESI-MS: 211 ($[M + Na]^+$).

*(2*S*)-2-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-6-methylhept-5-en-2-ol* (**11**). To a stirred soln. of **10** (5.23 g, 27.81 mmol) in dry DMF (25 ml) under inert atm. was added 2,2-DMP (8.52 ml, 69.54 mmol) and CSA (0.64 g, 2.78 mmol) at 0°. The mixture was stirred at r.t. for 1 h, and then the reaction was quenched by addition of sat. aq. $NaHCO_3$ soln. (60 ml). The mixture was diluted with AcOEt (75 ml). The org. layer was separated, and the aq. layer was extracted with AcOEt (3 × 50 ml). The combined org. layers were washed with brine (2 × 70 ml) and dried (Na_2SO_4). Removal of solvent *in vacuo* and purification on CC (AcOEt/hexane 1:9) afforded **11** (6.08 g, 96%). Colorless liquid. $[\alpha]_D^{27} = +12.3$ ($c = 3.96$, $CHCl_3$). IR (KBr): 3438, 2977, 2925, 2358, 2342, 1643, 1455, 1375, 1215, 1069. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.06 (*t*, *J* = 5.8, 1 H); 3.91–3.87 (*m*, 2 H); 3.86–3.79 (*m*, 1 H); 2.12–2.05 (*m*, 1 H); 2.03–1.95 (*m*, 1 H); 1.67 (*s*, 3 H); 1.61 (*s*, 3 H); 1.42–1.28 (*m*, 2 H); 1.39 (*s*, 3 H); 1.33 (*s*, 3 H); 1.20 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 131.4; 124.0; 108.7; 81.3; 71.5; 64.6; 37.5; 26.1; 25.4; 25.0; 23.2; 21.7; 17.3. ESI-MS: 251 ($[M + Na]^+$). HR-ESI-MS: 251.1634 ($[M + Na]^+$, $C_{13}H_{24}NaO_3^+$; calc. 251.1617).

*(6*S*)-6-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2-methylheptane-2,3,6-triol* (**12**). To a stirred soln. of **11** (7.9 g, 34.64 mmol) in acetone (50 ml) were added OsO_4 (44 mg, 0.17 mmol) and NMO (50 wt-% in H_2O, 37.4 ml, 138.56 mmol) at 25°. The resulting soln. was stirred for 48 h at the same temp. After completion of the reaction, solid Na_2SO_3 was added, and the mixture was stirred for another 30 min. Acetone was removed under reduced pressure. The residue was diluted with AcOEt (50 ml) and H_2O (20 ml). The org. layer was separated, and the aq. layer extracted with AcOEt (4 × 50 ml). The combined org. layer was washed with brine (50 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by CC (AcOEt/hexane 3:2) to furnish **12** (8.62 g, 95%). Colorless liquid. $[\alpha]_D^{27} = +8.8$ ($c = 1.33$, $CHCl_3$). IR (KBr): 3319, 2977, 2932, 2371, 2304, 1375, 1216, 1156, 1070. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.98–3.83 (*m*, 3 H); 3.35 (*d*, *J* = 10.0, 0.6 H); 3.24 (*d*, *J* = 10.0, 0.4 H); 1.67–1.45 (*m*, 4 H); 1.40 (*s*, 3 H); 1.34 (*s*, 3 H); 1.20 (*s*, 3 H); 1.18 (*s*, 3 H); 1.14 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 109.1; 109.0; 81.9; 80.8; 78.8; 78.4; 73.1; 73.0; 71.9; 71.8; 64.8; 64.7; 34.8; 34.7; 26.3; 26.2; 24.9; 24.8; 23.3; 23.1; 22.3. ESI-MS: 285 ($[M + Na]^+$). HR-ESI-MS: 285.1677 ($[M + Na]^+$, $C_{13}H_{26}NaO_5^+$; calc. 285.1677).

*(4*S*)-4-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)pentane-1,4-diol* (**13**). To a vigorously stirred soln. of **12** (9.1 g, 34.73 mmol) in CH_2Cl_2 (200 ml) at r.t. was added silica-supported $NaIO_4$ (75 g). After 10 min, the mixture was filtered over *Celite* and concentrated to afford crude aldehyde as unstable yellow oil, which was used immediately for the next step without further purification. To a stirred soln. of crude aldehyde in MeOH (75 ml) at 0° was added $NaBH_4$ (1.51 g, 41.0 mmol). After warming to 25° and stirring for 30 min, the reaction was quenched by adding sat. aq. NH_4Cl sol. (50 ml). MeOH was removed under reduced pressure, and the residue was extracted with AcOEt (3 × 100 ml). The combined org. layer was washed with brine (2 × 75 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by CC (AcOEt/hexane 7:3) to afford **13** (5.6 g, 91% over two steps). Yellow oil. $[\alpha]_D^{27} = +8.0$ ($c = 0.77$, $CHCl_3$). IR (KBr): 3364, 2981, 2928, 1456, 1371, 1264, 1212, 1063, 1014. ^{1}H-NMR (300 MHz, $CDCl_3$): 3.95–3.83 (*m*, 3 H); 3.68–3.54 (*m*, 2 H); 1.79–1.58 (*m*, 2 H); 1.48 (*t*, *J* = 7.5, 2 H); 1.40 (*s*, 3 H); 1.33 (*s*, 3 H); 1.19 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 108.9; 81.2; 71.5; 64.7; 62.5; 34.6;

26.1; 26.0; 24.9; 22.5. ESI-MS: 227 ([M + Na]$^+$). HR-ESI-MS: 227.1269 ([M + Na]$^+$, $C_{10}H_{20}NaO_4^+$; calc. 227.1259).

*(2*S*)-2-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-5-[(4-methoxybenzyl)oxy]pentan-2-ol* (**14**). To a suspension of NaH (3.05 g, 76.27 mmol, 60% in mineral oil) in dry THF (100 ml), **13** (7.78 g, 38.13 mmol, dissolved in 30 ml of dry THF) was added slowly at 0° under N_2. The suspension was stirred for 30 min at the same temp. PMB-Br (8.43 ml, 57.22 mmol) was added slowly at 0°. After stirring at r.t. for 5 h, the reaction was quenched by adding H_2O (50 ml) at 0°. The mixture was extracted with AcOEt (3 × 50 ml). The combined org. layer was washed with brine (50 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The crude mass was purified by CC (AcOEt/hexane 1:6) to afford **14** (11.86 g, 96%). Light-yellow liquid. $[\alpha]_D^{27} = +3.5$ ($c = 2.20$, $CHCl_3$). IR (KBr): 3462, 2930, 2861, 1612, 1513, 1247, 1214, 1068, 1036. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.17 (*d*, *J* = 7.8, 2 H); 6.80 (*d*, *J* = 7.8, 2 H); 4.40 (*s*, 2 H); 3.92–3.81 (*m*, 3 H); 3.78 (*s*, 3 H); 3.46–3.37 (*m*, 2 H); 2.39 (*s*, 1 H); 1.78–1.60 (*m*, 2 H); 1.46 (*t*, *J* = 7.8, 2 H); 1.38 (*s*, 3 H); 1.32 (*s*, 3 H); 1.15 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.0; 130.1; 129.1; 113.6; 108.9; 81.3; 72.4; 71.4; 70.2; 64.8, 55.1, 34.8, 26.2, 25.1, 23.5, 23.1. ESI-MS: 347 ([M + Na]$^+$). HR-ESI-MS: 347.1845 ([M + Na]$^+$, $C_{18}H_{28}NaO_5^+$; calc. 347.1834).

*(4*R*)-4-{(2*S*)-5-[(4-Methoxybenzyl)oxy]-2-(prop-2-en-1-yloxy)pentan-2-yl}-2,2-dimethyl-1,3-dioxolane* (**15**). To a suspension of NaH (1.40 g, 35.18 mmol, 60% in mineral oil) in dry DMF (50 ml), **14** (5.7 g, 17.59 mmol, dissolved in 10 ml of dry DMF), was added dropwise at 0° under N_2. The suspension was stirred for 30 min at the same temp. Allyl bromide (2.3 ml, 26.38 mmol) was added slowly at 0°. After stirring at r.t. for 3 h, the reaction was quenched by adding H_2O (30 ml) at 0°. The mixture was extracted with AcOEt (3 × 50 ml). The combined org. layers were washed with brine (2 × 50 ml), dried over (Na_2SO_4) and concentrated under reduced pressure. The crude mass was purified by CC (AcOEt/hexane 1:19) to afford **15** (5.57 g, 87%). Light-yellow liquid. $[\alpha]_D^{27} = +5.4$ ($c = 1.16$, $CHCl_3$). IR (KBr): 2924, 2855, 1513, 1372, 1247, 1213, 1078, 1037. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.18 (*d*, *J* = 8.5, 2 H); 6.80 (*d*, *J* = 8.5, 2 H); 5.85–5.78 (*m*, 1 H); 5.17 (*d*, *J* = 16.2, 1 H); 5.04 (*dd*, *J* = 10.4, 1.9, 1 H); 4.39 (*s*, 2 H); 4.04 (*t*, *J* = 6.6, 1 H); 3.97–3.87 (*m*, 4 H); 3.78 (*s*, 3 H); 3.44–3.36 (*m*, 2 H); 1.68–1.54 (*m*, 4 H); 1.39 (*s*, 3 H); 1.29 (*s*, 3 H); 1.13 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 158.9; 135.6; 130.5; 129.0; 115.2; 113.5; 108.8; 79.0; 76.7; 72.3; 70.2; 65.1; 63.0; 55.0; 31.8; 26.1; 24.6; 23.0; 18.3. ESI-MS: 387 ([M + Na]$^+$). HR-ESI-MS: 387.2143 ([M + Na]$^+$, $C_{21}H_{32}NaO_5^+$; calc. 387.2147).

*(2*R*,3*S*)-6-[(4-Methoxybenzyl)oxy]-3-methyl-3-(prop-2-en-1-yloxy)hexane-1,2-diol* (**16**). To a stirred soln. of **15** (5.0 g, 13.73 mmol) in MeOH (70 ml) was added CSA (317 mg, 1.37 mmol) at 0°, and the resulting soln. was stirred for 24 h at r.t. The reaction was quenched with sat. aq. $NaHCO_3$ soln. (30 ml). MeOH was removed under reduced pressure, and the residue was extracted with AcOEt (3 × 70 ml). The combined org. layer was washed with brine (100 ml), dried (Na_2SO_4), and evaporated under reduced pressure. The crude product was purified by CC (AcOEt/hexane 1:1) to furnish **16** (3.78 g, 85%). Viscous colorless liquid. $[\alpha]_D^{27} = +2.0$ ($c = 1.68$, $CHCl_3$). IR (KBr): 3365, 2926, 2857, 1609, 1513, 1460, 1368, 1249, 1173, 1094, 1034. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.20 (*d*, *J* = 7.8, 2 H); 6.82 (*d*, *J* = 7.8, 2 H); 5.87–5.80 (*m*, 1 H); 5.20 (*d*, *J* = 17.5, 1 H); 5.08 (*d*, *J* = 8.7, 1 H); 4.40 (*s*, 2 H); 3.93–3.89 (*m*, 2 H); 3.79 (*s*, 3 H); 3.69 (*t*, *J* = 6.8, 1 H); 3.63–3.51 (*m*, 2 H); 3.41–3.40 (*m*, 2 H); 1.74–1.65 (*m*, 2 H); 1.61–1.45 (*m*, 2 H); 1.17 (*d*, *J* = 7.8, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 158.8; 135.2; 130.1; 128.9; 115.3; 113.4; 78.3; 74.2; 72.2; 70.0; 62.7; 62.1; 54.9; 31.1; 22.9; 18.6. ESI-MS: 325 ([M + 1]), 347 ([M + Na]$^+$). HR-ESI-MS: 347.1838 ([M + Na]$^+$, $C_{18}H_{28}NaO_5^+$; calc. 347.1834).

*(2*R*)-2-{(2*S*)-5-[(4-Methoxybenzyl)oxy]-2-(prop-2-en-1-yloxy)pentan-2-yl}oxirane* (**17**). To a suspension of NaH (1.33 g, 33.3 mmol, 60% in mineral oil) in THF (30 ml) was added a soln. of **16** (2.7 g, 8.33 mmol) in THF (10 ml) at 0°. After stirring for 30 min at 0°, the reaction mass became semisolid. 1-Trisyl-1*H*-imidazole (2.53 g, 10.82 mmol) was then added portionwise, and the mixture was stirred for another 15 min. The reaction mass turned to a clear soln., and TLC showed complete consumption of starting material. The reaction was quenched by adding H_2O (30 ml), and the mixture was extracted with AcOEt (3 × 60 ml). The combined org. layers were dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by CC (AcOEt/hexane 1:9) to furnish **17** (2.09 g, 82%). Light-yellow liquid. $[\alpha]_D^{27} = +2.0$ ($c = 1.82$, $CHCl_3$). IR (KBr): 2926, 2856, 2361, 2335, 1612, 1513, 1247, 1094, 1034. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.18 (*d*, *J* = 8.3, 2 H); 6.80 (*d*, *J* = 8.3, 2 H); 5.83 (*dquint.*, *J* = 17.3, 5.2, 1 H); 5.21 (*dq*, *J* = 17.3, 1.5, 1 H); 5.04 (*dq*, *J* = 10.5, 1.5, 1 H); 4.38 (*s*, 2 H); 3.94–3.91 (*m*, 2 H); 3.77 (*s*,

3 H); 3.42–3.36 (*m*, 2 H); 2.88 (*t*, *J* = 3.0, 1 H); 2.67–2.61 (*m*, 2 H); 1.72–1.58 (*m*, 3 H); 1.48–1.41 (*m*, 1 H); 1.15 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 158.8; 135.4; 130.4; 128.9; 115.3; 113.5; 74.5; 72.2; 70.0; 63.5; 57.0; 54.9; 43.3; 31.7; 23.0; 20.0. ESI-MS: 329 ($[M+Na]^+$). HR-ESI-MS: 329.1739 ($[M+Na]^+$, $C_{18}H_{26}NaO_4^+$; calc. 329.1728).

*(2*R*)-2-[(2*S*)-5-[(4-Methoxybenzyl)oxy]-2-(oxiran-2-ylmethoxy)pentan-2-yl]oxirane* (**8**). To a stirred soln. of **17** (6.1 g, 19.93 mmol) in CH_2Cl_2 (100 ml) was added *m*-CPBA (77%, 6.67 g, 29.90 mmol) at 0°, and the resulting soln. was stirred at r.t. for 7 h. Solid Na_2SO_3 (3 g) was added, and the soln. was stirred for another h at r.t. The mixture was diluted by adding H_2O (50 ml). The org. layer was separated, and the aq. layer was extracted with CH_2Cl_2 (3 × 100 ml). The combined org. layers were washed with sat. aq. soln. of $NaHCO_3$ (2 × 50 ml) and brine (50 ml). The org. layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude mass was purified by CC (AcOEt/hexane 1:4) to afford diastereoisomer mixture of **8** (4.6 g, 73%). Colorless liquid. $[\alpha]_D^{27} = -0.6$ ($c = 1.86$, $CHCl_3$). IR (KBr): 2928, 2860, 2361, 2336, 1513, 1248, 1088, 1032. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.18 (*d*, *J* = 8.8, 2 H); 6.80 (*d*, *J* = 8.8, 2 H); 4.38 (*s*, 2 H); 3.78 (*s*, 3 H); 3.62 (*dt*, *J* = 10.7, 2.9, 1 H); 3.43–3.35 (*m*, 3 H); 3.05–2.98 (*m*, 1 H); 2.91–2.84 (*m*, 1 H); 2.73–2.61 (*m*, 3 H); 2.57–2.50 (*m*, 1 H); 1.69–1.56 (*m*, 3 H); 1.46–1.39 (*m*, 1 H); 1.16 (*s*, 1.5 H); 1.15 (*s*, 1.5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 158.9; 131.4; 130.5; 129.0; 113.6; 74.7; 74.6; 72.4; 70.1; 63.8; 63.6; 57.2; 55.1; 51.0; 44.5; 44.4; 43.4; 31.7; 31.6; 23.0; 22.9; 20.2; 20.1. ESI-MS: 345 ($[M+Na]^+$). HR-ESI-MS: 345.1682 ($[M+Na]^+$, $C_{18}H_{26}NaO_5^+$; calc. 345.1677).

*(3*R*,4*S*)-4-[(2-Hydroxybut-3-en-1-yl)oxy]-7-[(4-methoxybenzyl)oxy]-4-methylhept-1-en-3-ol* (**18**). To a suspension of Me_3SI (32.37 g, 158.69 mmol) in THF (200 ml) was added BuLi (58.9, 2.5M in hexane, 147.35 mmol) at −15°. After stirring 20 min at the same temp., **8** (7.3 g, 22.67 mmol) in THF (15 ml) was added. The mixture was slowly allowed to warm to r.t. and stirred for another 45 min. The reaction was quenched with H_2O (60 ml), and the mixture was extracted with AcOEt (3 × 100 ml). The combined extracts were washed with brine (150 ml), dried (anh. Na_2SO_4), and concentrated under reduced pressure. The residue was purified CC (AcOEt/hexane 1:4) to give diastereoisomer mixture of **18** (7.45 g, 94%). Light-yellow liquid. $[\alpha]_D^{27} = +5.9$ ($c = 1.25$, $CHCl_3$). IR (KBr): 3341, 2926, 2861, 1611, 1513, 1367, 1247, 1089, 1036. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.17 (*d*, *J* = 8.3, 2 H); 6.80 (*d*, *J* = 8.3, 2 H); 5.91–5.70 (*m*, 2 H); 5.34–5.27 (*m*, 2 H); 5.19–5.12 (*m*, 2 H); 4.38 (*s*, 2 H); 4.24–4.16 (*m*, 1 H); 4.11–4.05 (*m*, 1 H); 3.78 (*s*, 3 H); 3.47–3.32 (*m*, 3 H); 3.25 (*t*, *J* = 8.3, 1 H); 1.77–1.34 (*m*, 4 H); 1.10 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 158.9; 137.1; 136.8; 136.4; 130.3; 129.1; 116.6; 116.2; 116.1; 113.6; 78.5; 76.1; 75.5; 72.3; 71.8; 70.4; 70.3; 65.3; 65.2; 55.1; 30.8; 30.7; 23.3; 19.2; 19.0. ESI-MS: 373 ($[M+Na]^+$). HR-ESI-MS: 3373.2000 ($[M+Na]^+$, $C_{20}H_{30}NaO_5^+$; calc. 373.1990).

*(3*R*,4*S*)-4-{[2-(Acetyloxy)but-3-en-1-yl]oxy}-7-[(4-methoxybenzyl)oxy]-4-methylhept-1-en-3-yl Acetate* (**7**). To a stirred soln. of **18** (2.72 g, 7.77 mmol) and Et_3N (8.6 ml, 62.26 mmol) in CH_2Cl_2 (30 ml) was added Ac_2O (5.1 ml, 53.9 mmol), followed by DMAP (47.4 mg, 0.38 mmol) at 0°. The resulting soln. was stirred at r.t. for 4 h. The reaction was quenched with H_2O (50 ml), and the org. layer was separated. The aq. layer was extracted with CH_2Cl_2 (2 × 50 ml). The combined org. layer was washed with brine (2 × 30 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by CC (AcOEt/hexane 1:6) to afford diastereoisomer mixture of **7** (3.20 g, 95%). Colorless liquid. $[\alpha]_D^{27} = +10.0$ ($c = 1.10$, $CHCl_3$). IR (KBr): 2934, 2856, 1741, 1644, 1614, 1513, 1372, 1242, 1096, 1031. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.17 (*d*, *J* = 8.3, 2 H); 6.80 (*d*, *J* = 8.3, 2 H); 5.90–5.70 (*m*, 2 H); 5.34–5.13 (*m*, 6 H); 4.37 (*s*, 2 H); 3.78 (*s*, 3 H); 3.49–3.29 (*m*, 4 H); 2.06 (2*s*, 2 × 1.5 H); 2.04 (*s*, 3 H); 1.66–1.42 (*m*, 4 H); 1.10 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 169.8; 169.5; 159.3; 134.0; 133.9; 133.4; 130.9; 129.3; 117.9; 113.9; 96.4; 77.8; 76.7; 73.8; 72.6; 70.3; 63.8; 63.6; 55.3; 32.2; 23.4; 21.3; 19.3. ESI-MS: 457 ($[M+Na]^+$). HR-ESI-MS: 457.2208 ($[M+Na]^+$, $C_{24}H_{34}NaO_7^+$; calc. 457.2202).

*(2*S*,3*R*)-2,3,6,7-Tetrahydro-2-{3-[(4-methoxybenzyl)oxy]propyl}-2-methyloxepine-3,6-diyl Diacetate* (**19**). To a stirred soln. of **7** (4.6 g, 10.6 mmol) in CH_2Cl_2 (700 ml), Ar gas was bubbled for 15 min. *Grubbs* 1st-generation catalyst (872 mg, 1.06 mmol) was added, and the mixture was degassed with Ar for another 15 min and refluxed for 28 h. TLC showed 80% conversion of starting material. The mixture was then allowed to cool to r.t., and the solvent was evaporated under reduced pressure. The crude material was purified by CC (AcOEt/hexane 1:6) to furnish the diastereoisomer mixture of **19** (3.0 g, 70%) as a light green colored liquid with the recovery of starting material (0.92 g, 20%). $[\alpha]_D^{27} = -23.9$ ($c = 0.5$, $CHCl_3$). IR (KBr): 2925, 2854, 1739, 1638, 1513, 1371, 1234, 1097, 1034. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.16

(*d*, *J* = 8.3, 2 H); 6.80 (*d*, *J* = 8.3, 2 H); 5.77–5.28 (*m*, 4 H); 4.37 (*s*, 2 H); 3.97–3.68 (*m*, 2 H); 3.78 (*s*, 3 H); 3.44–3.31 (*m*, 2 H); 2.07 (*s*, 1 H); 2.06 (*s*, 2 H); 2.05 (*s*, 3 H); 1.68–1.41 (*m*, 4 H); 1.19 (*s*, 1.8 H); 1.12 (*s*, 1.2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 170.0; 169.7; 158.9; 130.9; 130.4; 129.3; 128.9; 113.5; 79.4; 78.6; 77.0; 75.2; 74.9; 73.0; 72.2; 71.5; 69.9; 63.1; 62.7; 55.0; 34.6; 34.5; 23.4; 23.1; 20.8; 19.6; 18.8. ESI-MS: 429 ($[M+Na]^+$). HR-ESI-MS: 429.1895 ($[M+Na]^+$, $C_{22}H_{30}NaO_7^+$; calc. 429.1889).

*(2*S*,3*R*)-2,3,6,7-Tetrahydro-2-{3-[(4-methoxybenzyl)oxy]propyl}-2-methyloxepine-3,6-diol* (**20**). To a soln. of **19** (2.6 g, 6.4 mmol) in MeOH (30 ml), powdered K_2CO_3 (4.41 g, 32.01 mmol) was added at 0°, and the mixture was stirred at r.t. for 10 h. TLC showed the complete conversion of starting material. H_2O (25 ml) was added, and MeOH was removed under reduced pressure. The crude mass was extracted with AcOEt (4 × 40 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was purified by CC (AcOEt/hexane 2:1) to afford diastereoisomer mixture of **20** (1.85 g, 90%). Viscous liquid. $[\alpha]_D^{27} = +13.9$ ($c = 0.77$, $CHCl_3$). IR (KBr): 3412, 2937, 2863, 1612, 1513, 1457, 1302, 1248, 1175, 1069, 1036. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.17 (*d*, *J* = 8.5, 2 H); 6.80 (*d*, *J* = 8.5, 2 H); 5.81–5.65 (*m*, 2 H); 4.40 (*s*, 2 H); 4.15–4.06 (*m*, 2 H); 3.78 (*s*, 3 H); 3.75–3.58 (*m*, 2 H); 3.48–3.4 (*m*, 2 H); 1.79–1.48 (*m*, 4 H); 1.15 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.1; 134.0; 132.6; 130.2; 129.2; 113.7; 79.5; 73.7; 72.5; 70.3; 69.8; 65.7; 55.2; 32.9; 23.1; 20.2. ESI-MS: 345 ($[M+Na]^+$). HR-ESI-MS: 345.1681 ($[M+Na]^+$, $C_{18}H_{26}NaO_5^+$; calc. 345.1677).

*(2*S*,3*R*)-2-{3-[(4-Methoxybenzyl)oxy]propyl}-2-methyloxepane-3,6-diol* (**21**). To a stirred soln. of **20** (2.0 g, 6.21 mmol) in AcOEt (30 ml), Pd/C (catalytic) was added, and the mixture was stirred for 10 min under H_2. After complete conversion of starting material (TLC), the black reaction mass was filtered through small pad of *Celite*, and the filtrate was concentrated under reduced pressure. The crude mass was purified by CC (AcOEt/hexane 2:1) to yield diastereoisomer mixture of **21** (1.55 g, 78%). Colorless liquid. $[\alpha]_D^{27} = +0.3$ ($c = 0.62$, $CHCl_3$). IR (KBr): 3422, 2934, 2859, 1612, 1513, 1463, 1302, 1248, 1057, 1033. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.18 (*d*, *J* = 8.6, 2 H); 6.80 (*d*, *J* = 8.6, 2 H); 4.39 (*s*, 2 H); 3.78 (*s*, 3 H); 3.70–3.67 (*m*, 2 H); 3.50–3.46 (*m*, 2 H); 3.45–3.36 (*m*, 2 H); 2.14–1.45 (*m*, 8 H); 1.12 (*s*, 1.5 H); 1.09 (*s*, 1.5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 159.0; 130.4; 129.1; 113.6; 79.7; 79.2; 78.2; 77.2; 72.3; 70.4; 70.3; 70.0; 68.5; 66.5; 65.1; 55.1; 35.2; 33.5; 32.6; 31.6; 27.0; 26.5; 23.8; 23.5; 19.0; 18.2. ESI-MS: 325 ($[M+1]^+$). HR-ESI-MS: 347.1826 ($[M+Na]^+$, $C_{18}H_{28}NaO_5^+$; calc. 347.1834).

*(2*S*,3*R*)-6-{[(*tert*-Butyl)(dimethyl)silyl]oxy}-2-{3-[(4-methoxybenzyl)oxy]propyl}-2-methyloxepan-3-ol* (**22**). To a stirred soln. of **20** (1.55 g, 4.78 mmol) in CH_2Cl_2 (25 ml) was added TBSCl (860 mg, 5.73 mmol), followed by 1*H*-imidazole (975 mg, 14.34 mmol) at 0°. The mixture was slowly warmed to r.t. and stirred for 2 h. TLC indicated complete conversion of starting material. The reaction was quenched by adding sat. aq. soln. of NH_4Cl (20 ml). The org. layer was separated, and the aq. layer extracted with CH_2Cl_2 (3 × 30 ml). The combined org. layer was washed with brine (2 × 50 ml), dried (Na_2SO_4), and evaporated to dryness, which, on purification by CC (EtOAc/hexane 1:9), furnished diastereoisomeric mixture of **22** (1.84 g, 88%). Colorless liquid. $[\alpha]_D^{27} = +3.3$ ($c = 0.52$, $CHCl_3$). IR (KBr): 3449, 2926, 2855, 1637, 1513, 1463, 1361, 1249, 1084. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.21–7.17 (*m*, 2 H); 6.80 (*d*, *J* = 8.3, 2 H); 4.39 (*s*, 1.3 H); 4.38 (*s*, 0.7 H); 3.78 (*s*, 3 H); 3.66–3.34 (*m*, 5 H); 3.23 (*dd*, *J* = 12.0, 9.0, 1 H); 2.01–1.31 (*m*, 8 H); 1.16 (*s*, 1 H); 1.01 (*s*, 2 H); 0.88 (*s*, 3 H); 0.85 (*s*, 6 H); 0.04 (*s*, 2 H); 0.03 (*s*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.0; 130.6; 129.2; 113.7; 79.2; 79.0; 76.2; 72.4; 71.4; 71.3; 70.5; 67.9; 67.2; 55.2; 34.9; 34.8; 33.5; 30.3; 28.4; 26.1; 25.7; 23.9; 23.6; 19.3; 18.6; 18.0; −4.8. ESI-MS: 461 ($[M+Na]^+$). HR-ESI-MS: 461.2718 ($[M+Na]^+$, $C_{24}H_{42}NaO_5Si^+$; calc. 461.2699).

*{[(6*R*,7*S*)-6-(Benzyloxy)-7-{3-[(4-methoxybenzyl)oxy]propyl}-7-methyloxepan-3-yl]oxy}(*tert*-butyl)(dimethyl)silane* (**23**). To a suspension of NaH (300 mg, 7.51 mmol, 60% in mineral oil) in dry DMF (20 ml), **22** (1.65 g, 3.75 mmol) in DMF (5 ml) was added at 0° under Ar. A cat. amount of TBAI was added, and the mixture was stirred for 30 min at r.t. It was again cooled to 0° and BnBr (0.67 ml, 5.62 mmol) was added slowly at the same temp. The mixture was allowed to stir at r.t. for 12 h, and the reaction was quenched by addition of H_2O (20 ml) at 0°. The reaction mass was diluted with AcOEt (20 ml). The org. layer was separated, and the aq. layer was extracted with AcOEt (3 × 30 ml). The combined org. layers were washed with brine (2 × 50 ml) and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude mass was purified by CC (AcOEt/hexane 1:19) to afford diastereoisomeric mixture of **23** (1.72 g, 87%). Light-yellow liquid. $[\alpha]_D^{27} = -15.4$ ($c = 0.52$, $CHCl_3$). IR (KBr): 2932, 2856, 1634, 1513, 1463, 1248, 1085. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.30–7.16 (*m*, 7 H); 6.80

(*d*, *J* = 8.0, 2 H); 4.58 (*d*, *J* = 11.5, 0.6 H); 4.57 (*d*, *J* = 11.5, 0.4 H); 4.39 (*s*, 1.3 H); 4.37 (*s*, 0.7 H); 4.32 (*d*, *J* = 11.5, 0.6 H); 4.28 (*d*, *J* = 11.5, 0.4 H); 3.78 (*s*, 3 H); 3.71 (*t*, *J* = 6.2, 1 H); 3.67–3.53 (*m*, 1 H); 3.46–3.18 (*m*, 4 H); 2.06–1.48 (*m*, 8 H); 1.17 (*s*, 1.8 H); 1.04 (*s*, 1.2 H); 0.87 (*s*, 3.6 H); 0.86 (*s*, 5.4 H); 0.04 (*s*, 2.4 H); 0.03 (*s*, 3.6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.0; 157.2; 138.7; 138.5; 131.5; 130.7; 129.1; 128.3; 128.2; 127.5; 127.3; 113.7; 87.3; 83.1; 79.8; 78.8; 72.4; 72.3; 71.8; 71.3; 71.2; 70.5; 68.2; 67.1; 55.2; 37.4; 35.5; 33.4; 30.0; 29.6; 25.8; 24.4; 23.6; 23.1; 21.2; 19.2; 18.8; 18.1; 18.0; −4.7; −4.8. ESI-MS: 551 ([*M* + Na]$^+$). HR-ESI-MS: 551.3190 ([*M* + Na]$^+$, $C_{31}H_{48}NaO_5Si^+$; calc. 551.3168).

*(6*R*,7*S*)-6-(Benzyloxy)-7-{3-[(4-methoxybenzyl)oxy]propyl}-7-methyloxepan-3-one* (**25**). To a stirred soln. of **23** (1.6 g, 3.03 mmol) in MeOH (25 ml) was added CSA (69 mg, 0.30 mmol) at 0°, and the resulting soln. was stirred for 1.5 h at r.t. The reaction was quenched with sat. aq. $NaHCO_3$ soln. (20 ml). MeOH was removed under reduced pressure, and the residue was extracted with AcOEt (3 × 30 ml). The combined org. layer was washed with brine (50 ml), dried (anh. Na_2SO_4), and evaporated to dryness, which, on purification by CC (AcOEt/hexane 3:7), furnished the diastereoisomeric mixture of *(6*R*,7*S*)-6-(benzyloxy)-7-{3-[(4-methoxybenzyl)oxy]propyl}-7-methyloxepan-3-ol* (**24**; 1.12 g, 90%). Viscous colorless liquid. $[\alpha]_D^{27} = -14.0$ (*c* = 0.29, $CHCl_3$). IR (KBr): 3444, 2934, 2859, 1613, 1513, 1454, 1247, 1073. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.32–7.23 (*m*, 5 H); 7.18 (*d*, *J* = 7.9, 2 H); 6.81 (*d*, *J* = 7.9, 2 H); 4.59 (*d*, *J* = 10.8, 0.3 H); 4.54 (*d*, *J* = 10.8, 0.7 H); 4.39 (*s*, 2 H); 4.35 (*d*, *J* = 11.8, 0.3 H); 4.28 (*d*, *J* = 11.8, 0.7 H); 3.79 (*s*, 3 H); 3.76–3.64 (*m*, 2 H); 3.56–3.33 (*m*, 4 H); 1.94–1.38 (*m*, 8 H); 1.19 (*s*, 2.2 H); 1.13 (*s*, 0.8 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 159.0; 138.4; 138.3; 130.5; 129.2; 129.1; 128.3; 127.5; 127.3; 113.7; 86.3; 83.8; 80.7; 79.1; 72.5; 72.4; 71.7; 71.6; 70.3; 69.5; 68.6; 66.2; 65.2; 55.2; 40.8; 36.6; 36.3; 33.9; 33.0; 30.2; 29.6; 28.3; 25.9; 24.6; 24.3; 23.8; 23.6; 23.3; 21.8; 20.8; 19.4; 19.0; 17.4; 17.2. ESI-MS: 437 ([*M* + Na]$^+$). HR-ESI-MS: 437.2293 ([*M* + Na]$^+$, $C_{25}H_{34}NaO_5^+$; calc. 437.2298).

To a stirred soln. of **24** (0.8 g, 1.93 mmol) in CH_2Cl_2 (20 ml) at 0° was added *Dess–Martin* periodinane (1.22 g, 2.89 mmol). The mixture was stirred at 0° for 1 h. After completion of the reaction (TLC), it was diluted with Et_2O (25 ml), and the precipitate was filtered off on a small pad of *Celite*. The filtrate was washed with sat. aq. $NaHCO_3$ soln. (25 ml), H_2O (25 ml), and brine (25 ml), and dried (Na_2SO_4). Evaporation of the solvent and purification by CC (AcOEt/hexane 1:6) afforded **25** (550 mg, 69%). Colorless liquid. $[\alpha]_D^{27} = +7.2$ (*c* = 1.53, $CHCl_3$). IR (KBr): 2924, 2855, 1709, 1609, 1508, 1243, 1093, 1031. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.34–7.21 (*m*, 7 H); 6.83 (*d*, *J* = 8.6, 2 H); 4.63 (*d*, *J* = 11.5, 1 H); 4.41 (*s*, 2 H); 4.37 (*d*, *J* = 11.5, 1 H); 4.10 (*d*, *J* = 18.6, 1 H); 3.94 (*d*, *J* = 18.6, 1 H); 3.79 (*s*, 3 H); 3.42–3.37 (*m*, 3 H); 2.71–2.64 (*m*, 1 H); 2.53–2.48 (*m*, 1 H); 2.10–2.05 (*m*, 1 H); 1.85–1.79 (*m*, 1 H); 1.71–1.61 (*m*, 4 H); 1.16 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 214.4; 158.8; 137.8; 130.3; 128.9; 128.1; 127.3; 113.4; 82.8; 80.2; 72.2; 71.6; 70.3; 70.0; 54.9; 36.7; 35.5; 23.4; 22.1; 16.5. ESI-MS: 435 ([*M* + Na]$^+$). HR-ESI-MS: 435.2129 ([*M* + Na]$^+$, $C_{25}H_{32}NaO_5^+$; calc. 435.2141).

*Ethyl 2-[(2*E*/2*Z*,6*R*,7*S*)-6-(Benzyloxy)-7-{3-[(4-methoxybenzyl)oxy]propyl}-7-methyloxepan-3-ylidene]acetate* (**26**). To a soln. of ethyl 2-(diethylphosphono)acetate (4.07 g, 18.2 mmol) in dry THF (60 ml) taken in a two-necked round-bottom flask (250 ml), NaH (576 mg, 14.4 mmol, 60% in mineral oil) was added portionwise at 0°. After 30 min of stirring at r.t., **25** (750 mg, 1.82 mmol), dissolved in dry THF (10 ml), was added at r.t. After 30 min, TLC showed complete consumption of starting material. The reaction was quenched by adding H_2O (30 ml) at 0°. The mixture was extracted with AcOEt (3 × 50 ml). The combined org. layers were washed with brine (2 × 70 ml), dried (anh. Na_2SO_4), and evaporated under reduced pressure. The crude product was purified by CC (AcOEt/hexane 1:9) to furnish the inseparable mixture of α,β-unsaturated ester **26** (851 mg, 97%) as a colorless liquid. The ^{1}H-NMR spectrum of the mixture of diastereoisomers indicated the formation of two geometrical isomers ((*E*)/(*Z*) 3:2). $[\alpha]_D^{27} = +1.0$ (*c* = 0.68, $CHCl_3$). IR (KBr): 2926, 2853, 1710, 1455, 1247, 1144, 1095, 1036. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.29–7.17 (*m*, 7 H); 6.78 (*d*, *J* = 7.6, 2 H); 5.60 (*s*, 0.4 H); 5.58 (*s*, 0.6 H); 4.58 (*d*, *J* = 16.3, 0.4 H); 4.57 (*d*, *J* = 16.3, 0.6 H); 4.42–4.37 (*m*, 3 H); 4.22–4.06 (*m*, 4 H); 3.77 (*s*, 3 H); 3.43–3.33 (*m*, 2 H); 3.29–3.23 (*m*, 1 H); 2.52–2.37 (*m*, 1 H); 2.11–2.04 (*m*, 1 H); 1.77–1.49 (*m*, 6 H); 1.27 (*t*, *J* = 6.7, 1.8 H); 1.26 (*t*, *J* = 6.7, 1.2 H); 1.13 (*s*, 1.8 H); 1.11 (*s*, 1.2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 166.7; 166.3; 162.6; 159.0; 138.6; 138.5; 130.7; 129.1; 128.2; 127.6; 127.4; 113.9; 113.7; 113.1; 84.0; 83.7; 80.2; 79.9; 72.4; 72.3; 72.0; 71.7; 70.5; 70.4; 68.7; 65.0; 59.7; 55.2; 35.9; 35.6; 31.7; 27.7; 26.3; 24.7; 23.5; 23.3; 17.0; 16.3; 14.2. ESI-MS: 505 ([*M* + Na]$^+$). HR-ESI-MS: 505.2569 ([*M* + Na]$^+$, $C_{29}H_{38}NaO_6^+$; calc. 505.2566).

*2-[(2*E*/2*Z*,6*R*,7*S*)-6-(Benzyloxy)-7-{3-[(4-methoxybenzyl)oxy]propyl}-7-methyloxepan-3-ylidene]-ethanol* (**27**). The diastereoisomeric mixture **26** (623 mg, 1.29 mmol) was dissolved in THF (10 ml), and the resulting soln. was added to a suspension of $LiAlH_4$ (98 mg, 2.58 mmol) in anh. THF (10 ml) at 0°. After 5 min at 0° and 2 h at r.t., the mixture was cooled to 0° and treated with sat. aq. soln. of Na_2SO_4 (20 ml), followed by 15% aq. soln. of NaOH (5 ml). After 2 h of stirring at r.t., the resulting suspension was filtered through *Celite*. The insoluble salts were washed with AcOEt (4 × 25 ml), and the filtrate was dried (Na_2SO_4). The filtrate was concentrated under reduced pressure, and the crude material purified by CC (AcOEt/hexane 2:3) to afford an inseparable mixture of **27** (511 mg, 90%). Colorless viscous liquid. $[\alpha]_D^{27} = -4.1$ ($c = 1.29$, $CHCl_3$). IR (KBr): 3422, 2925, 2856, 1610, 1456, 1245, 1171, 1091, 1032. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.30–7.21 (*m*, 5 H); 7.19 (*d*, *J* = 8.4, 2 H); 6.70 (*d*, *J* = 8.4, 2 H); 5.38 (*t*, *J* = 6.4, 1 H); 4.58 (*d*, *J* = 11.5, 1 H); 4.38 (*s*, 2 H); 4.37 (*d*, *J* = 11.5, 1 H); 4.15–3.94 (*m*, 4 H); 3.77 (*s*, 3 H); 3.38–3.36 (*m*, 2 H); 3.25 (*dd*, *J* = 9.6, 2.4, 1 H); 2.52–2.47 (*m*, 0.7 H); 2.35–2.30 (*m*, 0.3 H); 2.24–1.80 (*m*, 3 H); 1.78–1.44 (*m*, 4 H); 1.14 (*s*, 1.8 H); 1.12 (*s*, 1.2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 158.9; 142.6; 142.4; 138.4; 130.5; 129.1; 128.1; 127.4; 127.3; 123.7; 122.7; 113.6; 84.6; 84.2; 80.0; 79.6; 72.3; 71.6; 70.4; 68.6; 62.2; 58.5; 57.9; 55.1; 35.6; 31.2; 28.1; 26.6; 24.1; 23.5; 17.5; 16.9. ESI-MS: 463 ($[M + Na]^+$). HR-ESI-MS: 463.2468 ($[M + Na]^+$, $C_{27}H_{36}NaO_5^+$; calc. 463.2454).

*(2*S*,3*R*,6*E*)-3-(Benzyloxy)-6-[2-(benzyloxy)ethylidene]-2-{3-[(4-methoxybenzyl)oxy]propyl}-2-methyloxepane* (**28**) *and Its (*Z*)-Isomer* **28′**. To a soln. of diastereoisomeric mixture **27** (540 mg, 1.22 mmol) in anh. CH_2Cl_2 (20 ml) were successively added BnBr (0.3 ml, 2.44 mmol), TBAI (225 mg, 0.61 mmol), and Ag_2O (338 mg, 1.46 mmol). After 16 h of stirring at r.t. in absence of light, the mixture was filtered through *Celite* and concentrated under reduced pressure. Purification of the crude material by FC (230–400 mesh silica gel; AcOEt/hexane 1:9) afforded the (*E*/*Z*)-mixture **28**/**28′** (611 mg, 94%; (*E*)-isomer **28**: 385 mg; (*Z*)-isomer **28′**: 226 mg) as a colorless liquid.

Major Isomer **28**. $[\alpha]_D^{27} = -1.0$ ($c = 1.55$, $CHCl_3$). IR (KBr): 2926, 2854, 1613, 1512, 1301, 1247, 1171, 1096. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.39–7.26 (*m*, 10 H); 7.25 (*d*, *J* = 8.3, 2 H); 6.80 (*d*, *J* = 8.3, 2 H); 5.44 (*t*, *J* = 6.4, 1 H); 4.57 (*d*, *J* = 12.0, 1 H); 4.50 (*s*, 2 H); 4.41 (*s*, 2 H); 4.38 (*d*, *J* = 12.0, 1 H); 4.18–4.02 (*m*, 4 H); 3.79 (*s*, 3 H); 3.44–3.37 (*m*, 2 H); 3.28 (*dd*, *J* = 9.8, 3.0, 1 H); 2.54–2.47 (*m*, 1 H); 2.11–2.04 (*m*, 1 H); 1.96–1.89 (*m*, 1 H); 1.77–1.49 (*m*, 5 H); 1.17 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 158.9; 143.7; 138.5; 130.6; 129.0; 128.2; 128.1; 127.6; 127.5; 127.4; 127.3; 120.9; 113.6; 84.7; 79.6; 72.3; 72.1; 71.7; 70.5; 68.6; 65.8; 55.1; 35.7; 26.7; 24.3; 23.5; 17.4. ESI-MS: 553 ($[M + Na]^+$). HR-ESI-MS: 553.2932 ($[M + Na]^+$, $C_{34}H_{42}NaO_5^+$; calc. 553.2929).

Minor Isomer **28′**. $[\alpha]_D^{27} = -5.8$ ($c = 0.97$, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): 7.36–7.23 (*m*, 12 H); 6.86 (*d*, *J* = 8.4, 2 H); 5.42 (*t*, *J* = 6.4, 1 H); 4.60 (*d*, *J* = 11.7, 1 H); 4.47 (*s*, 2 H); 4.41 (*s*, 2 H); 4.41 (*d*, *J* = 11.7, 1 H); 4.29–4.04 (*m*, 3 H); 3.98–3.89 (*m*, 1 H); 3.78 (*s*, 3 H); 3.48–3.41 (*m*, 2 H); 3.27 (*dd*, *J* = 10.1, 3.5, 1 H); 2.40–2.33 (*m*, 1 H); 2.25–2.19 (*m*, 1 H); 2.06–1.99 (*m*, 1 H); 1.81–1.43 (*m*, 5 H); 1.13 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 158.9; 145.2; 138.7; 138.2; 130.7; 129.1; 128.3; 128.2; 127.7; 127.5; 127.4; 127.3; 119.8; 113.6; 84.3; 79.9; 72.3; 72.1; 71.7; 70.5; 65.3; 62.6; 55.1; 35.8; 31.1; 28.4; 23.4; 16.5. ESI-MS: 553 ($[M + Na]^+$).

*3-{(2*S*,3*R*,6*E*)-3-(Benzyloxy)-6-[2-(benzyloxy)ethylidene]-2-methyloxepan-2-yl}propan-1-ol* (**5**). A 100-ml round-bottom flask was charged with **28** (150 mg, 0.28 mmol) in MeCN (10 ml) and H_2O (2 ml). The soln. was cooled to 0°, and CAN (153.4 mg, 1.12 mmol) was added in portions over 5 min. The resulting clear orange soln. was allowed to stir at 0° for 1 h at which time it was diluted with H_2O (5 ml) and Et_2O (10 ml). The org. layer was separated, and the aq. layer was extracted with Et_2O (3 × 10 ml). The combined org. layers were then dried (Na_2SO_4), filtered, concentrated, and purified by CC (AcOEt/hexanes 2:3) to give **5** (104 mg, 90%). Viscous liquid. $[\alpha]_D^{27} = +0.8$ ($c = 2.75$, $CHCl_3$). IR (KBr): 3430, 2926, 2857, 1452, 1371, 1251, 1064. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.34–7.19 (*m*, 10 H); 5.43 (*t*, *J* = 6.7, 1 H); 4.59 (*d*, *J* = 12.0, 1 H); 4.48 (*s*, 2 H); 4.36 (*d*, *J* = 12.0, 1 H); 4.17 (*d*, *J* = 14.3, 1 H); 4.02 (*d*, *J* = 14.3, 1 H); 4.00 (*d*, *J* = 6.7, 2 H); 3.60–3.54 (*m*, 2 H); 3.27 (*dd*, *J* = 10.5, 3.0, 1 H); 2.51–2.46 (*m*, 1 H); 2.12–1.91 (*m*, 2 H); 1.75–1.50 (*m*, 5 H); 1.19 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 143.3; 138.4; 138.1; 128.3; 128.2; 127.6; 127.5; 127.4; 121.1; 84.6; 79.8; 72.2; 71.6; 68.6; 65.8; 63.2; 36.2; 26.7; 26.5; 24.3; 17.0. ESI-MS: 433 ($[M + Na]^+$). HR-ESI-MS: 433.2362 ($[M + Na]^+$, $C_{26}H_{34}NaO_4^+$; calc. 433.2349).

REFERENCES

[1] a) S. D. Levine, R. E. Adams, R. Chen, M. L. Cotter, A. F. Hirsch, V. V. Kane, R. M. Kanijoa, C. J. Shaw, M. P. Wachter, E. Chin, R. Huetteman, P. Ostrowski, J. L. Mateos, L. Noriega, A. Guzmán, A. Mijarez, L. Tovar, *J. Am. Chem. Soc.* **1979**, *101*, 3404; b) Y. Oshima, G. A. Cordial, H. S. Fong, *Phytochemistry* **1986**, *25*, 2567, and refs. cit. therein.

[2] S. D. Levine, D. W. Hahn, M. L. Cotter, F. C. Greenslade, R. M. Kanijoa, S. A. Pasquale, M. P. Wachter, J. L. McGuire, *J. Reprod. Chem.* **1981**, 524; H. P. Monter, H. Giron, X. Lozoya, R. G. Enriquez, E. Bejar, A. V. Estrada, A. J. Gallegos, *Contraception* **1983**, *27*, 239.

[3] R. M. Kanojia, E. Chin, C. Smith, R. Chen, D. Rowand, S. D. Levine, M. P. Wachter, R. E. Adams, D. W. Hahn, *J. Med. Chem*. **1985**, *28*, 796, and refs. cit. therein.

[4] a) R. Chen, D. A. Rowand, *J. Am. Chem. Soc.* **1980**, *102*, 6609; b) K. C. Nicolaou, D. E. Claremon, W. E. Barnett, *J. Am. Chem. Soc.* **1980**, *102*, 6611; c) V. V. Kane, D. L. Doyle, *Tetrahedron Lett.* **1981**, *22*, 3027; d) V. V. Kane, D. L. Doyle, *Tetrahedron Lett.* **1981**, *22*, 3031; e) R. C. Cookson, N. J. Liverton, *J. Chem. Soc., Perkin Trans. 1* **1985**, 1589; f) P. J. Kocienski, C. J. Love, R. J. Whitby, *Tetrahedron* **1989**, *45*, 3839.

[5] a) B. M. Trost, P. D. Greenspan, H. Geissler, J. H. Kim, N. Greeves, *Angew. Chem.*, *Int. Ed*. **1994**, *33*, 2182; b) C. Taillier, V. Bellosta, J. Cossy, *Org. Lett.* **2004**, *6*, 2149; c) C. Taillier, B. Gille, V. Bellosta, J. Cossy, *J. Org. Chem.* **2005**, *70*, 2097; d) S. Raghavan, V. S. Babu, *Chem. – Eur. J.* **2011**, *17*, 8487.

[6] M. J. Davies, J. C. Heslin, C. J. Moody, *J. Chem. Soc., Perkin Trans. 1* **1989**, 2473; G. Pain, D. Desmaële, J. d'Angelo, *Tetrahedron Lett.* **1994**, *35*, 3085; T. K. M. Shing, C.-H. Wong, T. Yip, *Tetrahedron: Asymmetry* **1996**, *7*, 1323; H. Ovaa, G. A. van der Marel, J. H. van Boom, *Tetrahedron Lett.* **2001**, *42*, 5749; I. Garcia, M. Perez, P. Besada, G. Gomez, Y. Fall, *Tetrahedron Lett.* **2008**, *49*, 1344.

[7] I. C. Gonzalez, C. J. Forsyth, *J. Am. Chem. Soc.* **2000**, *122*, 9099; E. J. Corey, D.-C. Ha, *Tetrahedron Lett.* **1988**, *29*, 3171.

[8] B. H. Lipshutz, J. C. Barton, *J. Org. Chem.* **1988**, *53*, 4495; W. Yu, Y. Zhang, Z. Jin, *Org. Lett.* **2001**, *3*, 1447.

[9] F. He, Y. Bo, J. D. Altom, E. J. Corey, *J. Am. Chem. Soc.* **1999**, *121*, 6771.

[10] Y.-L. Zhong, T. K. M. Shing, *J. Org. Chem.* **1997**, *62*, 2622.

[11] H. C. Brown, S. Krishnamurthy, *Tetrahedron* **1979**, *35*, 567.

[12] A. B. Smith III, R. J. Fox, J. A. Vanecko, *Org. Lett.* **2005**, *7*, 3099.

[13] E. J. Corey, M. Chaykovsky, *J. Am. Chem. Soc.* **1965**, *87*, 1353; B. Baylon, M.-P. Heck, C. Mioskowski, *J. Org. Chem.* **1999**, *64*, 3354.

[14] R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413; R. H. Grubbs, *Tetrahedron* **2004**, *60*, 7117; A. Deiters, S. F. Martin, *Chem. Rev.* **2004**, *104*, 2199; A. Gradillas, J. Pérez-Castells, *Angew. Chem., Int. Ed.* **2006**, *45*, 6086, and refs. cit. therein.

[15] H. Weber, H. G. Khorana, *J. Mol. Biol.* **1972**, *72*, 219; R. I. Zhdanov, S. M. Zhenodarova, *Synthesis* **1975**, 222.

[16] J. J. Plattner, R. D. Gless, H. Rapoport, *J. Am. Chem. Soc.* **1972**, *94*, 8613.

[17] R. A. W. Johnstone, A. H. Willby, I. D. Entwistle, *Chem. Rev.* **1985**, *85*, 129.

[18] E. J. Corey, A. Venkateswarlu, *J. Am. Chem. Soc.* **1972**, *94*, 6190.

[19] K. Kanai, I. Sakamoto, S. Ogawa, T. Suami, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1529.

[20] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155.

[21] W. S. Wadsworth Jr., W. D. Emmons, *J. Am. Chem. Soc.* **1961**, *83*, 1733; B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, *89*, 863.

[22] R. Johansson, B. Samuelsson, *J. Chem. Soc., Perkin Trans. 1* **1984**, 2371.

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