Asymmetric Synthesis of Simplactones A and B

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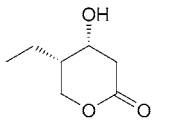
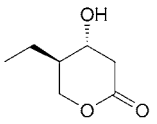
A new, simple, and short route for the synthesis of simplactones A (**1**) and B (**2**) was achieved from a synthetically prepared chiral auxiliary, *i.e.*, the *Oppolzer* camphor-derived sultam **4**, and (4-methoxybenzyl)-protected 3-hydroxypropanal, in 52 and 48% overall yield, respectively, and with high diastereoselectivity (*Schemes 2* and *3*).

Introduction. – Simplactones are pharmacologically active marine secondary metabolites isolated from the Caribbean sponge *Plakortis simplex* [1]. Simplactones show *in vitro* cytotoxic activity against WEHI 164, murine fibrosarcoma cells. Simplactone A (**1**) and simplactone B (**2**) were first isolated by *Fattorusso* and co-workers in 1999 [1]. The configuration of the structures was revised by *Ogasawara* and co-workers by the synthesis from enantiomerically pure 4-(cumyloxy)cyclopent-2-en-1-one [2], and the structures were asymmetrically synthesized by *Osorio–Lozada* and *Olivo* through a double-diastereoselective acetate aldol reaction [3]. Recently, *Kamal* and co-workers [4] and *Rama Rao* and co-workers [5] reported a synthesis of simplactone A [4] and simplactone B [5], respectively. Structurally, this type of lactones show very good cytotoxic activity against WEHI 164, and many biologically active compounds like mevinolin, massiolactone [6], compactin, pironetin, phomalactone, and asperlin [7] contained this type of lactone moiety.



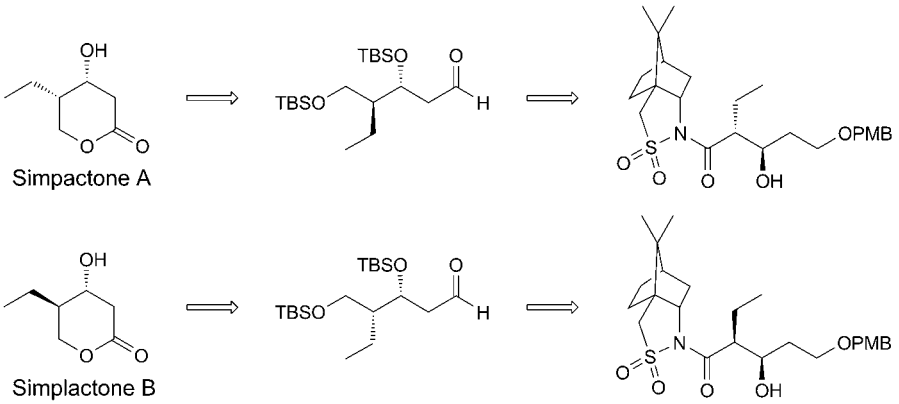
Simplactone A (**1**)



Simplactone B (**2**)

The biological potential of these compounds has stimulated us to synthesize **1** and **2** with *Oppolzer*'s camphor-derived sultam, which can be simply prepared compared with other chiral auxiliaries. The retrosynthetic analysis for the synthesis of **1** and **2** is shown in *Scheme 1* starting from (4-methoxybenzyl)-protected 3-hydroxypropanal and *N*-butanoylbornane-10,2-sultam (**3**). In this *Oppolzer* aldol addition, the '*syn*' aldol reaction is giving a higher diastereomer excess (94% *de*) when compared to the '*anti*'

Scheme 1. *Retrosynthetic Analysis*



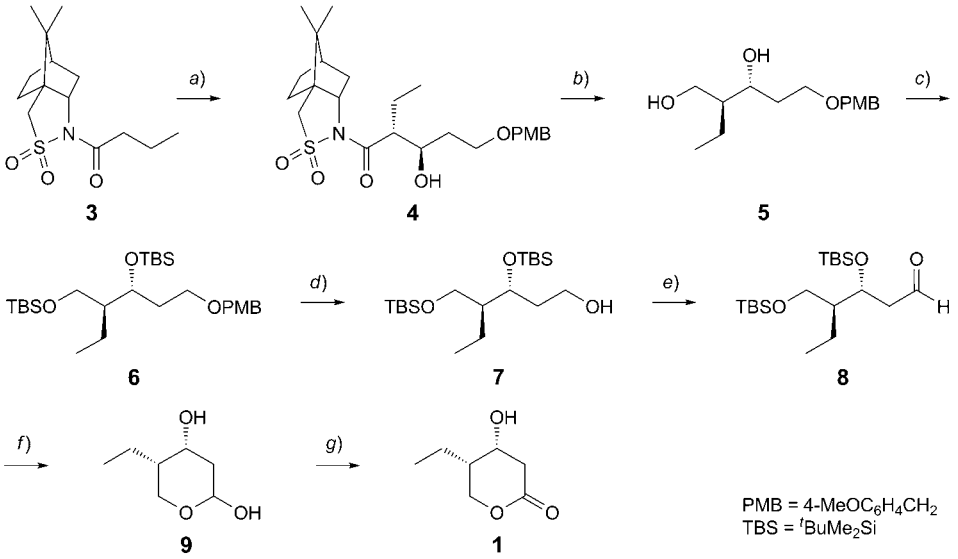
PMB = 4-$MeOC_6H_4CH_2$, TBS = ^{t}BuMe$_2$Si

aldol reaction with a *de* of 86%. Hence, we followed this approach for the synthesis of simplactones A and B.

Results and Discussion. – The stereoselective synthesis of simplactones A (**1**) and B (**2**) was carried out as shown in *Schemes 2* and *3*. Thus, the (2*S*)-*N*-butanoylbornane-10,2-sultam (**3**) [8] was subjected to asymmetric aldol reactions under two different conditions. When the reaction was carried out with 3.0 equiv. of (4-methoxybenzyl)-protected 3-hydroxypropanal, 3.0 equiv. of $TiCl_4$, and 2.2 equiv of ^{i}Pr$_2$NEt, the resulting major product was the '*anti*' product **4** [9] (*de* 86% by chiral HPLC; 84% yield) (*Scheme 2*). However, when the reaction was carried out with 1.0 equiv. of (4-methoxybenzyl)-protected 3-hydroxypropanal, 1.0 equiv. of $TiCl_4$, and 1.2 equiv. of ^{i}Pr$_2$NEt, the resulting major product was the '*syn*' product **10** [8–10] (*de* 94% by chiral HPLC; 92% yield) (*Scheme 3*). Hence we are reporting the same route for the synthesis of both simplactone isomers.

The '*anti*' aldol compound **4** was further treated with $LiAlH_4$ [10] in dry Et_2O at 0° for 4 h, to give '*anti*' diol **5** in 95% yield (*Scheme 2*), and in the same way, the '*syn*' diol **11** was obtained in 95% yield (*Scheme 3*). The two OH groups in both isomers **5** and **11** were protected with ^{t}BuMe$_2$SiOTf in the presence of 2,6-lutidine [11] in dry CH_2Cl_2 to give **6** and **12**, respectively, in 95% yield. The (4-methoxybenzyl)-protecting group in **6** and **12** was removed with DDQ [12] to give **7** in 89% yield and **13** in 90% yield, respectively, which were oxidized with iodobenzene diacetate [13] and TEMPO (cat.) in dry CH_2Cl_2 to give **8** in 90% yield and **14** in 88% yield. The removal of the ^{t}BuMe$_2$Si groups in **8** and **14** was achieved by treatment with Bu_4NF [14] in dry THF furnishing lactols **9** and **15** in 90% yield. Finally, compounds **9** and **15** were oxidized with iodobenzene diacetate and TEMPO (cat.) in dry CH_2Cl_2 at 0° to give the required compounds **1** and **2** in good yield. The structures of **1** and **2** were established by their IR, ^{1}H- and ^{13}C-NMR, and mass spectra, and their optical rotations were identical with those of the natural products reported by *Osorio–Lozada* and *Olivo* [3].

Scheme 2



a) (4-Methoxybenzyl)-protected 3-hydroxypropanal, $TiCl_4$, $^iPr_2NEt$, dry CH_2Cl_2, 3 h; 84%. *b*) $LiAlH_4$, dry Et_2O, 4 h; 95%. *c*) (*tert*-Butyl)dimethylsilyl trifluoromethanesulfonate (^{t}BuMe$_2$SiOTf = TBSOTf), 2,6-lutidine (=2,6-dimethylpyridine), dry CH_2Cl_2, 1 h; 95%. *d*) DDQ (4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile), CH_2Cl_2, H_2O, 2 h; 89%. *e*) Iodobenzene diacetate, (= bis(acetato-κO)phenyliodine), cat. 2,2,6,6-tetramethylpiperidin-1-yloxy (TEMPO), dry CH_2Cl_2, 3 h; 90%. *f*) Bu_4NF, THF, 2 h; 90%. *g*) Iodobenzene diacetate, cat. TEMPO, dry CH_2Cl_2, 3 h; 89%.

In conclusion, we have achieved a simple, short, and efficient total synthesis of simplactones A (**1**) and B (**2**) from (4-methoxybenzyl)-protected 3-hydroxypropanal and (2*S*)-*N*-butanoylbornane-10,2-sultam (**3**) in an overall yield of 52 and 48%, respectively. The advantage of this synthesis compared with the previous report [3] is the use of only one chiral auxiliary for the '*anti*' and '*syn*' isomers, the difference in the reaction conditions being the amount of $TiCl_4$ and aldehyde with respect to the chiral auxiliary **3**. In the synthesis of simplactones A and B reported by *Osorio–Lozada* and *Olivo* [3], two different chiral auxiliaries were used in a first step, and a further chiral auxiliary was present in a subsequent step.

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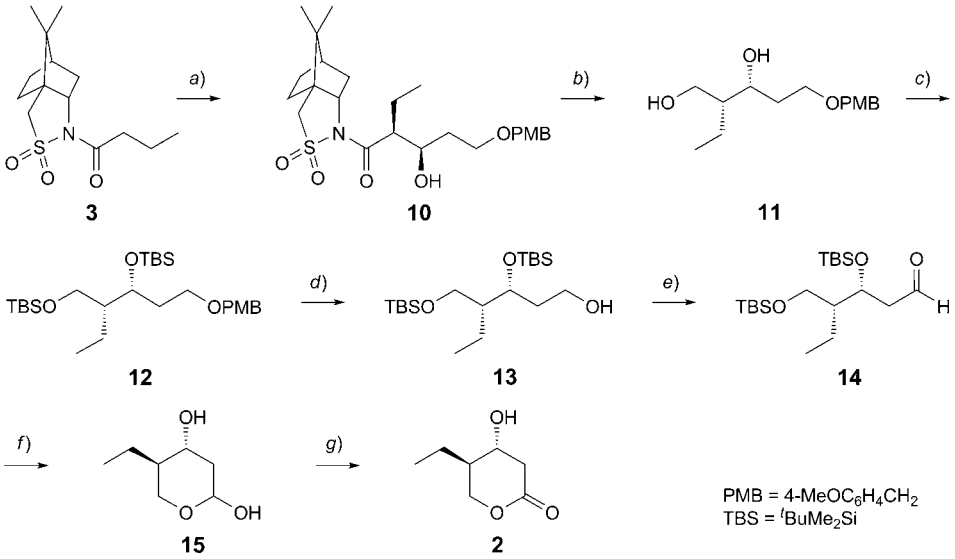
Experimental Part

General. Solvents were dried over standard drying agents and freshly distilled prior to use. The reagents were purchased from *Aldrich* and *Acros* and were used without further purification unless otherwise stated. All moisture-sensitive reactions were carried out under N_2. Org. solns. were concentrated *in vacuo* below 40°. Column chromatography (CC): silica gel (*Acme's* 60–120 mesh). Optical rotations: *Horiba* high sensitive polarimeter *SEPA-300* at 25°. IR Spectra: *Perkin–Elmer-IR-683*

Scheme 3



a) (4-Methoxybenzyl)-protected 3-hydroxypropanal, $TiCl_4$, $^iPr_2NEt$, dry CH_2Cl_2, 3 h; 92%. *b*) $LiAlH_4$, dry Et_2O, 4 h; 95%. *c*) ^{t}BuMe$_2$SiOTf, 2,6-lutidine, dry CH_2Cl_2, 1 h; 95%. *d*) DDQ, CH_2Cl_2, H_2O, 2 h; 90%. *e*) Iodobenzene diacetate, cat. TEMPO, dry CH_2Cl_2, 3 h; 88%. *f*) Bu_4NF, THF, 2 h; 90%. *g*) Iodobenzene diacetate, cat. TEMPO, dry CH_2Cl_2, 3 h; 88%.

spectrophotometer with NaCl optics; $\tilde{\nu}$ in cm^{-1}. ^{1}H- (300 MHz) and ^{13}C-NMR (75 MHz) Spectra: *Bruker-Avance-300* instrument; in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, J in Hz. MS: *Agilent-Technologies-1100* instrument (*Agilent* Chemistation software); in *m*/*z*.

*(2*S*)*-N-*Butanoylbornane-10,2-sultam* (=*1-[(3a*R*,6*R*,7a*S*)-Tetrahydro-8,8-dimethyl-2,2-dioxido-3*H*-3a,b-methano-2,1-benzisothiazol-1(4*H*)-yl]butan-1-one*; **3**). To a stirred soln. of (+)-camphor-derived sultam (5 g, 23.25 mmol) and butanoyl chloride (4.88 ml, 46.51 mmol) in dry benzene (50 ml) under N_2 was added anh. $CuCl_2$ (0.62 g, 4.65 mmol), and the mixture was refluxed for 12 h. The hot mixture was filtered, the filter, washed with CH_2Cl_2 (20 ml), the combined filtrate concentrated and, the residue purified by CC: **3** (6.0 g, 92%). Colorless crystals. $[\alpha]_D^{25} = +91.9$ ($c = 1.0$, $CHCl_3$). ^{1}H-NMR: 3.82 (*t*, *J* = 6.2, 1 H); 3.39 (*q*, *J* = 13.5, 2 H); 2.63 (*q*, *J* = 8.3, 2 H); 2.01–2.11 (*m*, 2 H); 1.81–1.91 (*m*, 3 H); 1.68 (*q*, *J* = 7.2, 2 H); 1.32–1.45 (*m*, 2 H); 1.14 (*s*, 3 H); 0.96 (*s*, 3 H); 0.96 (*t*, *J* = 7.2, 3 H). ESI-MS: 286 ([*M* + 1]$^+$).

*(2*R*,3*R*)-2-Ethyl-3-hydroxy-5-[(4-methoxyphenyl)methoxy]-1-[(3a*R*,6*R*,7a*S*)-tetrahydro-8,8-dimethyl-2,2-dioxido-3*H*-3a,6-methano-2,1-benzisothiazol-1(4*H*)-yl]-pentan-1-one* (**4**). To a cooled (−78°) soln. of **3** (1.0 g, 3.5 mmol) in dry CH_2Cl_2 (20 ml) and $TiCl_4$ (1.15 ml, 3.0 equiv.) was added slowly $^iPr_2NEt$ (1.85 ml, 2.2 equiv.), and the mixture was stirred for 90 min, followed by addition of (4-methoxybenzyl)-protected 3-hydroxypropanal (2.0 g, 10.3 mmol) at −78°, and further stirring for 90 min. After completion of the reaction (TLC), the reaction was quenched with sat. NH_4Cl soln. (10 ml), the mixture extracted with CH_2Cl_2 (3 × 20 ml), the extract dried (Na_2SO_4) and concentrated, and the residue purified by CC (hexane/AcOEt 4:1): **4** (1.42 g, 84%). Colorless liquid. $[\alpha]_D^{25} = +40$ ($c = 0.8$, $CHCl_3$). IR (neat): 3479, 2959, 2929, 1688, 1513, 1244. ^{1}H-NMR: 7.20 (*d*, *J* = 8.3, 2 H); 6.80 (*d*, *J* = 8.3, 2 H); 4.41 (*s*, 2 H); 3.98–4.09 (*m*, 1 H); 3.87 (*t*, *J* = 6.0, 1 H); 3.78 (*s*, 3 H); 3.52–3.67 (*m*, 2 H); 3.42 (*q*, *J* = 13.5, 2 H); 3.18 (br. *s*, 1 H); 3.07 (*q*, *J* = 5.2, 1 H); 2.07 (*d*, *J* = 6.0, 2 H); 1.77–1.94 (*m*, 6 H); 1.33–1.46 (*m*, 2 H); 1.26 (*s*, 1 H); 1.16 (*s*, 3 H); 0.98 (*s*, 3 H); 0.92 (*t*, *J* = 7.5, 3 H). ^{13}C-NMR: 171.1; 159.58; 129.35; 128.65 (2 C);

113.54 (2 C); 72.86; 72.10; 67.47; 65.40; 55.26; 53.28; 52.51; 44.58 (2 C); 40.93; 34.86; 32.90; 26.40; 21.68; 20.69; 19.94 (2 C); 11.62. ESI-MS: 480 ($[M+1]^+$).

*(2*S*,3*R*)-2-Ethyl-5-[(4-methoxyphenyl)methoxy)pentane-1,3-diol* (**5**). To a cooled (0°) stirred suspension of $LiAlH_4$ (168 mg, 4.42 mmol) in dry Et_2O (20 ml) was added **4** (1.0 g, 2.96 mmol), and the mixture was stirred for 3 h at 0°. After completion of the reaction (TLC), the reaction was quenched with sat. NH_4Cl soln., the mixture extracted with AcOEt (5 × 10 ml), the extract dried (Na_2SO_4) and concentrated, and the residue purified by CC (hexane/AcOEt 7:3): pure **5** (760 mg, 95%). Colorless liquid. $[\alpha]_D^{25} = -4.54$ ($c = 0.6$, $CHCl_3$). IR (neat): 3419, 2926, 2863, 1612, 1512, 1247, 1086, 1033. ^{1}H-NMR: 7.19 (*d*, *J* = 8.3, 2 H); 6.83 (*d*, *J* = 9.0, 2 H); 4.44 (*s*, 2 H); 3.81 (*dt*, *J* = 2.2, 5.2, 2 H); 3.79 (*s*, 3 H); 3.67–3.75 (*m*, 1 H); 3.54–3.67 (*m*, 2 H); 1.67–1.77(*m*, 1 H); 1.51–1.55 (*m*, 1 H); 1.23–1.46 (*m*, 3 H); 0.94 (*t*, *J* = 7.55, 3 H). ^{13}C-NMR: 159.5; 129.45; 129.36 (2 C); 113.87 (2 C); 76.46; 73.15; 69.64; 63.89; 55.26; 46.63; 34.64; 21.37; 11.77. ESI-MS: 291 ($[M+Na]^+$).

*(5*R*,6*S*)-6-Ethyl-5-{2-[(4-methoxyphenyl)methoxy}ethyl}-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane* (**6**). To a cooled (0°) soln. of **5** (400 mg, 1.49 mmol) and 2,6-lutidine (0.672 ml, 6.28 mmol, 2 equiv.) in dry CH_2Cl_2 (10 ml) was added ^{t}BuMe$_2$SiOTf (0.696 ml, 2.86 mmol), and the mixture was stirred at r.t. for 45 min. After completion of the reaction (TLC), the reaction was quenched with sat. NH_4Cl soln. (5 ml), the mixture extracted with CH_2Cl_2 (3 × 10 ml), the extract dried (Na_2SO_4) and concentrated, and the residue purified by CC (hexane/AcOEt 9:1): pure **6** (700 mg, 95%). Pale yellow liquid. $[\alpha]_D^{25} = -4.11$ ($c = 0.8$, $CHCl_3$). IR (neat): 2929, 2856, 1639, 1250, 1092. ^{1}H-NMR: 7.25 (*d*, *J* = 9.06, 2 H); 6.87 (*d*, *J* = 9.06, 2 H); 4.41 (*d*, *J* = 2.26, 2 H); 3.92–4.04 (*s*, 1 H); 3.80 (*s*, 3 H); 3.42–3.60 (*m*, 4 H); 1.60–1.85 (*m*, 1 H); 1.23–1.60 (*m*, 3 H); 1.04–1.21 (*m*, 1 H); 0.90 (*t*, *J* = 7.55, 3 H); 0.88 (*s*, 9 H); 0.87 (*s*, 9 H); 0.04 (*s*, 6 H); 0.02 (*s*, 6 H). ^{13}C-NMR: 159.5; 129.34; 129.25 (2 C); 113.86 (2 C); 73.13; 72.81; 69.67; 63.90; 55.20; 48.43; 43.3; 34.58; 25.85 (3 C); 25.59 (3 C); 19.1 (2 C); 10.38; −3.6 (2 C); −5.7 (2 C). ESI-MS: 519 ($[M+Na]^+$).

*(3*R*,4*S*)-3-{[(*tert*-Butyl)dimethylsilyl]oxy}-4-{{[(*tert*-butyl)dimethylsilyl]oxy}methyl}hexan-1-ol* (**7**). To a soln. of **6** (600 mg, 1.2 mmol) in CH_2Cl_2/H_2O 9:1 (20 ml) was added DDQ (329 mg, 1.44 mmol), and the mixture was stirred at r.t. for 2 h. After completion of the reaction (TLC), the mixture was neutralized with sat. $NaHCO_3$ soln. (5 ml) and extracted with CH_2Cl_2 (3 × 10 ml), the combined org. phase washed with brine (10 ml), dried (Na_2SO_4), and concentrated, and the residue purified by CC (hexane/AcOEt 7:3): pure **7** (400 mg, 89%). Pale yellow liquid. $[\alpha]_D^{25} = +2.72$ ($c = 0.6$, $CHCl_3$). IR (neat): 3462, 2955, 1635,1219. ^{1}H-NMR: 4.03–4.11 (*m*, 1 H); 3.67 (*q*, *J* = 6.0, 2 H); 3.43–3.64 (*m*, 2 H); 1.56–1.75 (*m*, 2 H); 1.23–1.37 (*m*, 2 H); 1.02–1.17 (*m*, 1 H); 0.92 (*t*, *J* = 7.55, 3 H); 0.89 (*s*, 18 H); 0.08 (*s*, 3 H); 0.07 (*s*, 3 H); 0.04 (*s*, 3 H); 0.03 (*s*, 3 H). ^{13}C-NMR: 71.52; 61.68; 60.88; 47.90; 35.37; 29.70; 25.87 (6 C); 25.63; 20.34; 12.35; −4.46 (2 C); −5.49 (2 C). ESI-MS: 377 ($[M+1]^+$).

*(3*R*,4*S*)-3-{[(*tert*-Butyl)dimethylsilyl]oxy}-4-{{[(*tert*-butyl)dimethylsilyl]oxy}methyl}hexanal* (**8**). To a cooled (0°) soln. of **7** (300 mg, 0.79 mmol) in dry CH_2Cl_2 (15 ml) were added iodobenzene diacetate (384 mg, 1.19 mmol) and TEMPO (24.9 mg, 0.15 mmol), and the mixture was stirred at r.t. for 4 h. After completion of the reaction (TLC), the reaction was quenched with sat. NH_4Cl soln. (5 ml), the mixture extracted with CH_2Cl_2 (3 × 10 ml), the combined org. layer washed with brine (10 ml), dried (Na_2SO_4), and concentrated, and the residue purified by CC (hexane/AcOEt 9:1): pure **8** (270 mg, 90%). Pale yellow liquid. $[\alpha]_D^{25} = +6.0$ ($c = 1.0$, $CHCl_3$). IR (neat): 2956, 2857, 1728, 1253, 1089. ^{1}H-NMR: 9.80–9.76 (*m*, 1 H); 4.43–4.50 (*m*, 1 H); 3.57–3.68 (*m*, 1 H); 3.48 (*dd*, *J* = 7.5, 10.5, 1 H); 2.44–2.64 (*m*, 1 H); 1.51–1.69 (*m*, 1 H); 1.05–1.20 (*m*, 2 H); 0.92 (*t*, *J* = 7.5, 3 H); 0.89 (*s*, 9 H); 0.87 (*s*, 9 H); 0.07 (*s*, 3 H); 0.04 (*s*, 9 H). ^{13}C-NMR: 202.85; 68.36; 62.34; 48.64; 47.30; 25.86 (6 C); 18.5 (2 C); 18.1; 12.4; −4.48 (2 C); −5.46 (2 C). ESI-MS: 397 ($[M+Na]^+$).

*(4*R*,5*S*)-5-Ethyltetrahydro-2*H*-pyran-2,4-diol* (**9**). To a cooled (0°) soln. of **8** (200 mg, 0.53 mmol) in dry THF (10 ml) was added 1.0M Bu_4NF in THF (0.53 ml, 0.53 mmol), and the mixture was stirred for 2 h at 0°. After completion of the reaction (TLC), the reaction was quenched with sat. NH_4Cl soln. (5 ml), the mixture extracted with AcOEt (3 × 10 ml), the combined org. phase washed with brine (10 ml), dried (Na_2SO_4), and concentrated, and the residual liquid purified by CC (hexane/AcOEt 7:3): pure **9** (70 mg, 90%). Pale yellow liquid. $[\alpha]_D^{25} = +16.5$ ($c = 3.0$, $CHCl_3$). IR (neat): 3453, 2924, 1639, 1381, 1048. ^{1}H-NMR: 5.31 (*t*, *J* = 3.0, 1 H); 4.72 (br. *s*, 1 H); 4.63 (*dd*, *J* = 3.0, 6.0, 1 H); 4.17–4.10 (*m*, 1 H); 3.69 (*dd*, *J* = 3.7, 10.3, 1 H); 3.53 (*dd*, *J* = 6.7, 11.3, 1 H); 1.98 (br. *s*, 1 H); 1.77–1.86 (*m*, 1 H); 1.50–1.69 (*m*, 2 H);

1.30–1.47 (*m*, 1 H); 0.96 (*t*, *J* = 6.7, 3 H). ^{13}C-NMR: 92.83; 67.73; 61.52; 43.76; 37.03; 21.08; 11.28. ESI-MS: 147 ($[M+1]^+$).

*(4*R*,5*S*)-5-Ethyltetrahydro-4-hydroxy-2*H*-pyran-2-one* (**1**). To a cooled (0°) soln. of **9** (40 mg, 0.27 mmol) in dry CH_2Cl_2 (10 ml) were added iodobenzene diacetate (88 mg, 0.27 mmol) and TEMPO (cat.), and the mixture was stirred at r.t. for 4 h. After completion of the reaction (TLC), the reaction was quenched with sat. NH_4Cl soln. (5 ml), the mixture extracted with CH_2Cl_2 (3 × 10 ml), the combined org. layer washed with brine (10 ml), dried (Na_2SO_4), and concentrated, and the residual liquid purified by CC (hexane/AcOEt 4:1): pure **1** (35 mg, 89%). Colourless liquid. $[\alpha]_D^{25} = +23.0$ (*c* = 1.0, $CHCl_3$) [3]. IR (neat): 3420, 2945, 1721, 1415, 1205. ^{1}H-NMR: 4.38 (*dd*, *J* = 10.4, 11.2, 1 H); 4.21 (*dd*, *J* = 5.1, 11.2, 1 H); 4.10 (br. *s*, 1 H); 2.90 (br. *s*, 1 H); 2.72 (*dd*, *J* = 3.6, 17.8, 1 H); 2.61 (*dd*, *J* = 3.6, 17.8, 1 H); 1.80–1.98 (*m*, 1 H); 1.40–1.50 (*m*, 1 H); 1.25–1.38 (*m*, 1 H); 0.98 (*t*, *J* = 7.5, 3 H). ^{13}C-NMR: 170.6; 69.2; 64.4; 39.2; 39.1; 19.2; 11.1. ESI-MS: 145 ($[M+1]^+$).

*(2*S*,3*R*)-2-Ethyl-3-hydroxy-5-[(4-methoxyphenyl)methoxy]-1-[(3a*R*,6*R*,7a*S*)-tetrahydro-8,8-dimethyl-2,2-dioxido-3*H*-3a,6-methano-2,1-benzisothiazol-1(4*H*)-yl]pentan-1-one* (**10**). As described for **4**, with **3** (1.0 g, 3.5 mmol), $TiCl_4$ (0.38 ml, 1.0 equiv.), CH_2Cl_2 (20 ml), $^iPr_2NEt$ (0.73 ml, 1.2 equiv.), and (4-methoxybenzyl)-protected 3-hydroxyproanal (0.68 g, 3.5 mmol): pure **10** (1.55 g, 92%). White solid. $[\alpha]_D^{25} = +33.07$ (*c* = 0.7, $CHCl_3$). IR (KBr): 3509, 2956, 2878, 1691, 1613, 1515, 1022. ^{1}H-NMR: 7.20 (*d*, *J* = 8.3, 2 H); 6.81 (*d*, *J* = 8.3, 2 H); 4.41 (*s*, 2 H); 3.99–4.11 (*m*, 1 H); 3.87 (*t*, *J* = 6.0, 1 H); 3.78 (*s*, 3 H); 3.53–3.67 (*m*, 2 H); 3.43 (*q*, *J* = 13.5, 2 H); 3.19 (*d*, *J* = 1.51, 1 H); 3.08 (*q*, *J* = 5.2, 1 H); 2.07 (*d*, *J* = 6.79, 2 H); 1.65–1.96 (*m*, 7 H); 1.33–1.51 (*m*, 2 H); 1.16 (*s*, 3 H); 0.97 (*s*, 3 H); 0.92 (*t*, *J* = 7.5, 3 H). ^{13}C-NMR: 175.1; 159.0; 130.1; 129.22 (2C); 113.68 (2 C); 72.66; 70.05; 68.33; 65.25; 55.18; 53.20; 52.49; 48.3; 47.6; 44.56; 38.57; 33.89; 32.89; 26.32; 21.67; 20.71; 19.83; 11.02. ESI-MS: 502 ($[M+Na]^+$).

*(2*R*,3*R*)-2-Ethyl-5-[4-methoxyphenyl)methoxy]pentane-1,3-diol* (**11**). As described for **5**, with $LiAlH_4$ (166 mg, 4.36 mmol), Et_2O (20 ml), and **10** (1.4 g, 2.92 mmol) (quenching with sat. Na_2SO_4 soln.): pure **11** (740 mg, 95%). Colorless liquid. $[\alpha]_D^{25} = -16.0$ (*c* = 0.7, $CHCl_3$). IR (neat): 3419, 2926, 2863, 1612, 1086, 1033. ^{1}H-NMR: 7.19 (*d*, *J* = 8.3, 2 H); 6.83 (*d*, *J* = 9.0, 2 H); 4.44 (*s*, 2 H); 4.03 (*td*, *J* = 3.0, 9.8, 1 H); 3.79 (*s*, 3 H); 3.55–3.75 (*m*, 4 H); 1.84–1.99 (*m*, 1 H); 1.51–1.65 (*m*, 2 H); 1.22–1.39 (*m*, 2 H); 0.95(*t*, *J* = 7.5, 3 H). ^{13}C-NMR: 159.67; 129.43; 129.35 (2 C); 113.86 (2 C); 75.97; 73.12; 69.89; 64.20; 55.25; 46.09; 31.79; 19.03; 12.28. ESI-MS: 291 ($[M+Na]^+$).

*(5*R*,6*R*)-6-Ethyl-5-{2-[(4-methoxyphenyl)methoxy]ethyl}-2,2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecane* (**12**). As described for **6**, with **11** (400 mg, 1.49 mmol), CH_2Cl_2 (20 ml), 2,6-lutidine (0.672 ml, 6.28 mmol), and ^{t}BuMe$_2$SiOTf (0.696 ml, 2.86 mmol) (quenching with sat. NH_4Cl soln. (10 ml)): **12** (700 mg, 95%). Pale yellow liquid. $[\alpha]_D^{25} = +3.75$ (*c* = 0.8, $CHCl_3$). IR (neat): 2931, 2858, 1513, 1464, 1250, 1094. ^{1}H-NMR: 7.25 (*d*, *J* = 8.3, 2 H); 6.87 (*d*, *J* = 8.3, 2 H); 4.41 (*s*, 2 H); 3.91–4.00 (*m*, 1 H); 3.80 (*s*, 3 H); 3.6–3.68 (*dd*, *J* = 5.2, 9.8, 1 H); 3.41–3.58 (*m*, 3 H); 1.54–1.86 (*m*, 2 H); 1.23–1.48 (*m*, 3 H); 0.91 (*t*, *J* = 7.5, 3 H); 0.88 (*s*, 9 H); 0.87 (*s*, 9 H); 0.04 (*s*, 6 H); 0.02 (*s*, 6 H). ^{13}C-NMR: 159.72; 129.34; 129.22 (2 C); 113.83 (2 C); 75.90; 73.10; 69.85; 67.40; 64.14; 55.21; 48.17; 46.40; 25.86 (4 C); 25.60 (2 C); 18.99 (2 C); 12.23; −3.63 (2 C); −4.62 (2 C). ESI-MS: 519 ($[M+Na]^+$).

*(3*R*,4*R*)-3-{[(*tert*-Butyl)dimethylsilyl]oxy}-4-{{[(*tert*-butyl)dimethylsilyl]oxy}methyl}hexan-1-ol* (**13**). As described for **7**, with **12**, CH_2Cl_2/H_2O 9:1, and DDQ. After completion of the reaction, the mixture was diluted with H_2O (10 ml) and extracted as described for **7**: pure **13** (410 mg, 90%). Pale yellow liquid. $[\alpha]_D^{25} = -2.7$ (*c* = 0.5, $CHCl_3$). IR (neat): 3453, 2929, 2858, 1638, 1253, 1090. ^{1}H-NMR: 3.94–4.04 (*m*, 1 H); 3.61–3.73 (*m*, 3 H); 3.51–3.59 (*m*, 1 H); 1.59–1.79 (*m*, 2 H); 1.32–1.46 (*m*, 1 H); 1.23–1.32 (*m*, 2 H); 0.93 (*t*, *J* = 7.5, 3 H); 0.89 (*s*, 9 H); 0.88 (*s*, 9 H); 0.09 (*s*, 3 H); 0.06 (*s*, 3 H); 0.03 (*s*, 6 H). ^{13}C-NMR: 71.52; 61.68; 60.89; 47.90; 35.37; 25.87 (6 C); 20.34; 18.72 (2 C); 12.35; −4.54 (2 C); −5.45 (2 C). ESI-MS: 377 ($[M+1]^+$).

*(3*R*,4*R*)-3-{[(*tert*-Butyl)dimethylsilyl]oxy}-4-{{[(*tert*-butyl)dimethylsilyl]oxy}methyl}hexanal* (**14**). As described for **8**, with **13**, CH_2Cl_2, iodobenzene diacetate, and TEMPO: pure **14** (260 mg, 88%). Pale yellow liquid. $[\alpha]_D^{25} = -4.0$ (*c* = 1.5, $CHCl_3$). IR (neat): 2927, 2856, 1635, 1219. ^{1}H-NMR: 9.78–9.74 (*m*, 1 H); 4.31–4.37 (*m*, 1 H); 3.57–3.68 (*m*, 2 H); 2.43–2.63 (*m*, 2 H); 1.69–1.92 (*m*, 1 H); 1.18–1.66 (*m*, 1 H); 1.02–1.17 (*m*, 1 H); 0.92 (*t*, *J* = 7.5, 3 H), 0.89 (*s*, 9 H); 0.86 (*s*, 9 H); 0.06 (*s*, 3 H); 0.04 (*s*, 3 H); 0.04 (*s*, 6 H). ^{13}C-NMR: 202.56; 68.25; 60.88; 48.52; 48.38; 25.86 (4 C); 25.77 (2 C); 20.36; 18.18; 18.03; 12.21; −4.56 (2 C); −4.97 (2 C). ESI-MS: 397 ($[M+Na]^+$).

*(4*R,*5*R*)-5-Ethyltetrahydro-2*H*-pyran-2,4-diol* (**15**). As described for **9**, with **14**, THF, and 1.0M Bu_4NF in THF: pure **15** (70 mg, 90%). Pale yellow liquid. $[\alpha]_D^{25} = -32.3$ ($c = 1.0$, $CHCl_3$). IR (neat): 3450, 2923, 2854, 1639, 1460, 1220. ^{1}H-NMR: 5.35 (*t*, *J* = 3.0, 1 H); 4.95 (br. *s*, 1 H); 3.63–3.90 (*m*, 2 H); 3.27 (*dd*, *J* = 6.0, 12.0, 1 H); 2.15 (br. *s*, 1 H); 1.70–1.86 (*m*, 1 H); 1.55–1.69 (*m*, 2 H); 1.15–1.52 (*m*, 2 H); 0.94 (*t*, *J* = 6.7, 3 H). ^{13}C-NMR: 93.67; 69.66; 62.41; 45.19; 38.97; 21.37; 11.70. ESI-MS: 147 ($[M+1]^+$).

*(4*R,*5*R*)-5-Ethyltetrahydro-4-hydroxy-2*H*-pyran-2-one* (**2**). As described for **1**, with **15**, CH_2Cl_2, iodobenzene diacetate, and TEMPO: pure **2** (34 mg, 88%). Colorless liquid. $[\alpha]_D^{25} = -24.0$ ($c = 1.0$, $CHCl_3$) [3]. IR (neat): 3475, 2989, 2930, 1721, 1265, 1014. ^{1}H-NMR: 4.44 (*dd*, *J* = 5.2, 10.4, 1 H); 3.90–4.05 (*m*, 1 H); 2.78 (*dd*, *J* = 5.8, 11.6, 1 H); 2.52 (*dd*, *J* = 5.8, 11.6, 1 H); 1.50–1.88 (*m*, 2 H); 1.20–1.45 (*m*, 1 H); 1.01 (*t*, *J* = 7.55, 3 H). ^{13}C-NMR: 171.0; 69.1; 67.8; 42.5; 38.4; 20.8; 11.1. ESI-MS: *m/z* 145 ($[M+1]^+$).

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