Efficient Chiral Pool Synthesis of the C1–C6 Fragment of Epothilones

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Received 7 September 2004; revised 6 October 2004

Abstract: An efficient chiral pool synthesis of the C1–C6 fragment of epothilones starting from readily available (–)-pantolactone is described.

Key words: epothilone, pantolactone, chiral pool synthesis

The discovery that the natural product class of epothilones parallels the biological activity of paclitaxel (PT) with respect to its action on the tubulin system stimulated intensive research activities in chemistry, pharmacology, and medicine. Epothilones, which have been isolated from the myxobacterial strain *sorangium cellulosum* were characterized by the groups of Reichenbach and Höfle.[1] They stabilize microtubules similar to PT by inhibiting their depolymerization.[2] As a consequence, the cell cycle is blocked in G2/M phase and the cells are driven into apoptosis. In contrast to PT, epothilones possess the potential to overcome multi-drug resistance in vitro and, most important, in vivo.[3–6]

Epothilone B (Figure 1), which is more potent than PT, displays significant toxicity at therapeutically relevant doses.[6]

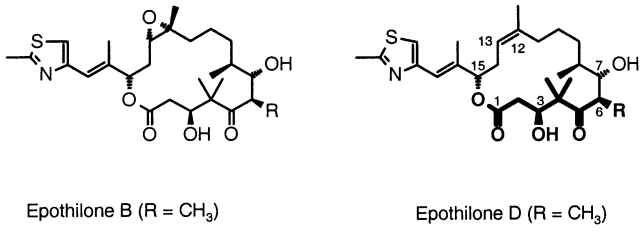


Figure 1 Natural products epothilone B and epothilone D

Therefore, an epothilone analog possessing an improved therapeutic window would be highly favorable for clinical applications. Due to the less complex structure, epothilones can be obtained and modified efficiently by total syntheses. This offers the opportunity for extensive structural modifications most of which cannot be achieved via a partial synthetic approach.

Like other groups we made use of a highly convergent strategy combining three modular building blocks A, B and C which represent the ring carbons C1–C6, C7–C12, and C13–C15, respectively.[7] As a prerequisite, each chiral module should offer the potential for flexible synthetic modifications as well as a large scale production with high optical purity. Based on this methodology we synthesized more than 350 epothilone analogs from which our clinical development candidate ZK-EPO was selected.

Herein we describe one of our syntheses of building block A.[8] Even though the synthesis is relatively long we selected it due to its standard and mature chemistry which allowed suitable large scale production of this building block.[9] As a readily available chiral starting material (–)-pantolactone (**1**) was chosen which already contains carbon atoms C2–C5 including the geminal dimethyl moiety at C4 (Scheme 1).

In a straightforward manner the hydroxyl group was protected as tetrahydropyrane ether (**2**) and the lactone was reduced to the lactol. The lacking carbon atom C1 was introduced by a Wittig reaction and the primary hydroxyl group was protected as benzyl ether to yield compound **4**. Interestingly, the THP isomers in **2**, which can be separated very easily, show remarkable differences with respect to their reactivity in the Wittig reaction. While the reaction is complete within three hours with one isomer, the use of the other isomer as well as the epimeric mixture elongates the reaction time to about 20 hours. Analysis at chiral HPLC columns with racemic reference material revealed that no racemization had occurred.

Then, olefin **4** was subjected to a hydroboration-oxidation sequence giving **5a** along with a mixture of stereoisomers **5c** (8%) resulting from a Markovnikov hydration and 1,3-diol **5b** (7%).[10] After separation by chromatography compounds **5a** and **5b** were transferred directly into acetonide **6** which served as stable key intermediate and was prepared in large scale in the lab by this methodology. Removal of the benzyl ether followed by Swern-oxidation led to aldehyde **7**. The introduction of different substituents at carbon 5 is achieved by subsequent Grignard reaction or the addition of the corresponding alkyl-lithium compounds followed by an oxidation of the resulting epimeric alcohols to yield ketones **8a** to **8k**. Alternatively, deprotonation of methyl ketone **8a** by LDA followed by an alkylation with the corresponding alkyl halides is also suitable. Methyl ketone **8a** proved to be a nicely crystalline compound from which a X-ray structure was obtained (Figure 2).

Starting from a relatively cheap optically active chiral pool material we have opened an efficient route to frag-

SYNTHESIS 2005, No. 2, pp 0301–0305
Advanced online publication: 01.12.2004
DOI: 10.1055/s-2004-834936; Art ID: Z16904SS

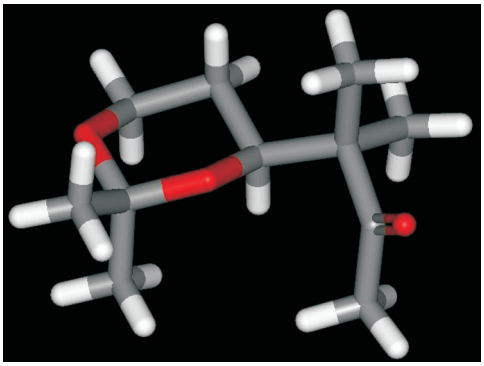


Figure 2 X-ray structure of compound **8a**

ment A for the synthesis of C6-modified epothilone analogs. There are several advantages to this approach:

1) Both enantiomers are commercially available.

2) No racemisation occurs during the synthesis.

3) All intermediates are stable.

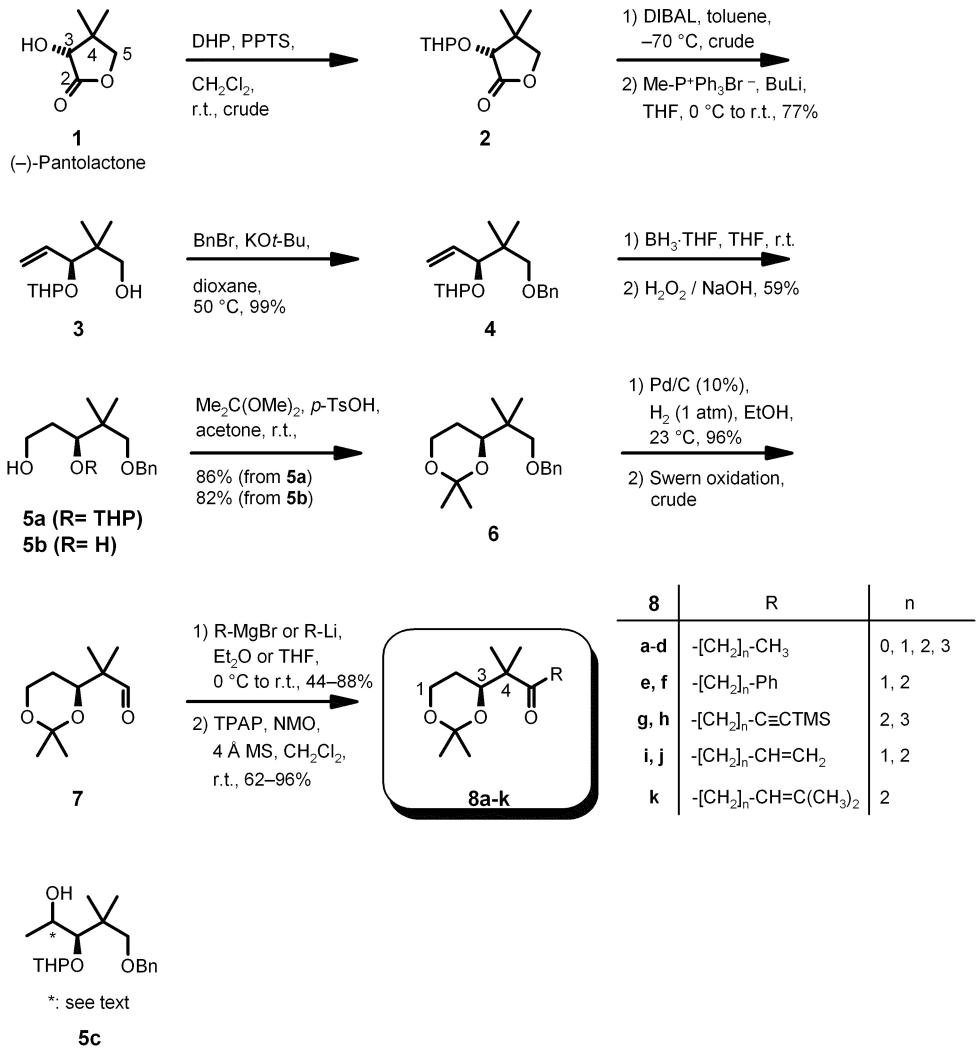
4) Large amounts can be synthesized.

5) There is high flexibility for synthetic modifications at C6.

All new compounds gave satisfactory analytical and spectral data. All experiments were conducted under Ar atmosphere. Chromatographic separations were carried out on 63–200 mesh silica gel until otherwise stated. ^{1}H NMR spectra (300 MHz) were recorded in $CDCl_3$ on a Bruker Avance 300 spectrometer. IR spectra were recorded on a Nicolet 710 spectrometer. CD spectra were recorded in dioxane on a JASCO J 715 spectrometer. Optical rotations were recorded in $CHCl_3$ on a Perkin-Elmer PE 343 spectrometer.

(3*R*)-4,4-Dimethyl-3-(tetrahydropyran-2-yloxy)dihydrofuran-2-one (2)

To a solution of D-(–)-pantolactone (1500 g, 11.52 mol) in CH_2Cl_2 (8 L) were added 3,4-dihydro-2*H*-pyran (1.87 L, 20.45 mol) and pyridinium *p*-toluenesulfonate (29 g, 115 mmol). After about 1.5 h the reaction was exothermic, the solution heated up to 32 °C and was recooled to 23 °C while stirring was continued for additional 2.5 h. The solution was added to a sat. aq solution of $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude tetrahydropyranyl isomers **2** were used without purification (2660 g, max. 11.25 mol, max. 100%). Samples of each THP-isomer were purified by chromatography for analytical purposes.



8	R	n
a-d	-$[CH_2]_n$-CH_3	0, 1, 2, 3
e, f	-$[CH_2]_n$-Ph	1, 2
g, h	-$[CH_2]_n$-C≡CTMS	2, 3
i, j	-$[CH_2]_n$-CH=CH_2	1, 2
k	-$[CH_2]_n$-CH=$C(CH_3)_2$	2

Scheme 1 Preparation of C1–C6 fragment of epothilones

^{1}H NMR (less polar tetrahydropyranyl isomer): δ = 5.17 (t, *J* = 3 Hz, 1 H, O-CH-O), 4.16 (s, 1 H, 3-H), 4.01 (d, *J* = 9 Hz, 1 H, 4-H), 3.92 (d, *J* = 9 Hz, 1 H, 4-H), 3.86 (m, 1 H, CH_2-O, THP-ether), 3.56 (m, 1 H, CH_2-O, THP-ether), 1.91–1.49 [m, 6 H, $(CH_2)_3$, THP-ether], 1.22 (s, 3 H, 4-CH_3), 1.14 (s, 3 H, 4-CH_3).

^{1}H NMR (more polar tetrahydropyranyl isomer): δ = 4.87 (t, *J* = 3 Hz, 1 H, O-CH-O), 4.22 (s, 1 H, 3-H), 4.20 (m, 1 H, CH_2-O, THP-ether), 3.98 (d, *J* = 10 Hz, 1 H, 4-H), 3.89 (d, *J* = 10 Hz, 1 H, 4-H), 3.54 (m, 1 H, CH_2-O, THP-ether), 1.98–1.50 [m, 6 H, $(CH_2)_3$, THP-ether], 1.20 (s, 3 H, 4-CH_3), 1.01 (s, 3 H, 4-CH_3).

(3*S*)-2,2-Dimethyl-3-(tetrahydropyran-2-yloxy)pent-4-en-1-ol (3)

To a solution of **2** (448 g, 2091 mmol) in toluene (2 L) at –70 °C was added a solution of DIBAL (2.4 L, 1.2 M in toluene) over 5 h. The reaction temperature should not exceed –65 °C, otherwise 1,4-diol is produced as side product. After 1 h at –70 °C the solution was added slowly to a mixture of water (1 L) and *i*-PrOH (500 mL). Due to a strong exothermic reaction the temperature rose to 60 °C. The mixture was stirred at 23 °C until a fine crystalline precipitate had formed which was removed by filtration. The filtrate was concentrated in vacuo to yield (2*R*S,3*R*)-1-oxa-2-hydroxy-3-[tetrahydropyran-2(*RS*)-yloxy]-4,4-dimethylcyclopentane (457 g, max. 2091 mmol, max. 100%) as colorless oil which was used without further purification.

IR ($CHCl_3$): 3480, 3013, 2950, 2874, 1262, 1133, 1074, 1026, 808 cm^{-1}.

To a mixture of methyltriphenylphosphonium bromide (3000 g, 8.4 mol; dried in circulating air at 120 °C before use) in THF (11 L) at –60 °C was added the solution of *n*-BuLi (3.2 L, 8.0 mol, 2.4 M in hexane). After warming to 20 °C (4 h) the solution of (2*RS*,3*R*)-1-oxa-2-hydroxy-3-[tetrahydropyran-2(*RS*)-yloxy]-4,4-dimethyl-cyclopentane (669 g, 3.1 mmol) in THF (2 L) was added and the mixture stirred for 25 h at 23 °C. To the mixture was added sat. $NaHCO_3$. After extraction with EtOAc and CH_2Cl_2 the organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (EtAOc–hexane, 0:100 → 50:50) to give **3** (512 g, 2.389 mol, 77.1%) as colorless oil of tetrahydropyranyl ether isomers. Samples of each THP-isomer were separated by chromatography for analytical purposes.

Less Polar Tetrahydropyran Isomer

$[\alpha]^{22}_D$ +83.5 (*c* = 0.51).

^{1}H NMR: δ = 5.74 (ddd, $^3J_1$ = 17.3 Hz, $^3J_2$ = 10.7 Hz, $^3J_3$ = 7.7 Hz, 1 H, 4-H), 5.26 [m, 1 H, 5-H(*Z*)], 5.20 [m, 1 H, 5-H(*E*)], 4.44 (m, 1 H, O-CH-O), 4.40 (d, *J* = 7.7 Hz, 1 H, 3-H), 3.95 (m, 1 H, CH_2-O, THP-ether), 3.68 (dd, ^2J = 11.0 Hz, ^3J = 5.1 Hz, 1 H, 1-H), 3.49 (m, 1 H, CH_2-O, THP-ether), 3.45 (dd, $^3J_1$ = 8.5 Hz, $^3J_2$ = 5.1 Hz, 1 H, OH), 3.18 (dd, ^2J = 11.0 Hz, ^3J = 8.5 Hz, 1 H, 1-H), 1.83–1.45 [m, 6 H, $(CH_2)_3$, THP-ether], 0.93 (s, 3 H, 2-CH_3), 0.78 (s, 3 H, 2-CH_3).

More Polar Tetrahydropyran Isomer

$[\alpha]^{22}_D$ –89.0 (*c* = 0.50).

^{1}H NMR: δ = 5.92 (m, 1 H, 4-H), 5.21 (m, 2 H, 5-H), 4.67 (m, 1 H, O-CH-O), 3.93 (m, 1 H, CH_2-O, THP-ether), 3.84 (d, *J* = 8.1 Hz, 1 H, 3-H), 3.59 (dd, ^2J = 10.7 Hz, ^3J = 5.1 Hz, 1 H, 1-H), 3.50 (m, 1 H, CH_2-O, THP-ether), 3.31 (dd, ^2J = 11.0 Hz, ^3J = 6.6 Hz, 1 H, 1-H), 3.18 (dd, $^3J_1$ = 6.6 Hz, $^3J_2$ = 5.1 Hz, 1 H, OH), 1.83–1.45 [m, 6 H, $(CH_2)_3$, THP-ether], 0.94 (s, 3 H, 2-CH_3), 0.84 (s, 3 H, 2-CH_3).

(1*S*)-2-[1-(2-Benzyloxy-1,1-dimethylethyl)allyloxy]tetrahydropyran (4)

To a suspension of *t*-BuOK (1600 g, 14.258 mol) in dioxane (11 L) was added the solution of **3** (1475 g, 6.883 mol) in dioxane (2 L) over a period of 2 h (slightly exothermic; 30 °C). After 2 h benzyl bromide (910 mL, 7.651 mol) was added over a period of 75 min (slightly exothermic; 50 °C). The mixture was stirred at 23 °C overnight, sat. NH_4Cl solution and water were added (5 L) and extracted with EtOAc (30 L). The organic layers were concentrated in vacuo and the residue filtrated over silica gel (9 L, 0.2–0.5 mesh) with a mixture of *n*-hexane–EtOAc (95:5) to give **4** (2076 g, 6.819 mol, 99.1%).

^{1}H NMR: δ = 7.38–7.23 (m, 5 H, Ph), 5.88, 5.67 (ddd, $^3J_1$ = 17.2 Hz, $^3J_2$ = 10.5 Hz, $^3J_3$ = 8.0 Hz, 0.4 H, 0.6 H, =CH), 5.28–5.13 (m, 2 H, =CH_2), 4.66, 4.59 (m, 0.6 H, 0.4 H, O-CH-O), 4.53–4.44 (m, 2 H, O-CH_2-Ph), 4.03, 3.93 (d, ^3J = 8.0 Hz, 0.6 H, 0.4 H, CH-O), 3.86 (m, 1 H, CH_2-O, THP-ether), 3.46 (m, 1 H, CH_2-O, THP-ether), 3.38, 3.34 (d, ^2J = 8.4 Hz, 0.6 H, 0.4 H, 2-H), 3.25, 3.12 (d, ^2J = 8.4 Hz, 0.6 H, 0.4 H, 2-H), 1.87–1.46 [m, 6 H, $(CH_2)_3$], 0.99, 0.91 (s, 1.8 H, 1.2 H, 1-CH_3), 0.92, 0.89 (s, 1.8 H, 1.2 H, 1-CH_3).

(3*S*)-5-Benzyloxy-4,4-dimethyl-3-(tetrahydropyran-2-yloxy)pentan-1-ol (5a) and (3*S*)-1-Benzyloxy-2,2-dimethylpentane-3,5-diol (5b)

To a solution of **4** (1038 g, 3.41 mol) in THF (13 L) was added borane–tetrahydrofuran complex (2.1 L, 1 M in THF) at 23 °C over a period of 20 min. After 2 h (slightly exothermic, temperature → 27 °C) the mixture was cooled to 3 °C and a solution of NaOH (1.7 L, 5% in water) was added over a period of 1 h (→ 7 °C) while a constant N_2 flow was used to remove the released H_2 gas. After recooling to 0 °C a solution of H_2O_2 (845 mL, 30% in water) was added (→ 10 °C) and stirring was continued for 1 h at 4 °C. The mixture was added portion wise (5 L) to a mixture of a sat. sodium thiosulfate solution (2500 g in 8.5 L water; this is absolutely necessary to decompose all H_2O_2 before concentration in vacuo is started) and EtOAc (15 L). After extraction with additional EtOAc (7 L) the organic layers were concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc–hexane, 90:10 → 50:50) to give **5a** (572.5 g, 1.775 mol, 52.1%) as a colorless oil along with **5b** (59 g, 247.5 mmol, 7.2%) and (3*S*,4*RS*)-1-benzyloxy-2,2-dimethylpentane-3-[tetrahydropyran-2(*RS*)-yloxy]-4-ol (**5c**; 86 g, 266.5 mmol, 7.8%).

5a

^{1}H NMR: δ = 7.37–7.24 (m, 5 H, Ph), 4.67 (m, 1 H, O-CH-O), 4.53 (d, ^2J = 12.0 Hz, 1 H, O-CH_2-Ph), 4.44 (d, ^2J = 12.0 Hz, 1 H, O-CH_2-Ph), 4.02–3.65 (m, 4 H, CH_2-O, THP-ether, 1-H), 3.44 (m, 1 H, 3-H), 3.44, 3.28 (d, ^2J = 8.9 Hz, 0.7 H, 0.3 H, 5-H), 3.22, 3.08 (d, ^2J = 8.9 Hz, 0.7 H, 0.3 H, 5-H), 2.04 (m, 1 H, OH), 1.91–1.39 [m, 8 H, $(CH_2)_3$, 2-H], 0.97, 0.91 (s, 2.1 H, 0.9 H, 4-CH_3), 0.93, 0.88 (s, 2.1 H, 0.9 H, 4-CH_3).

5b

^{1}H NMR: δ = 7.39–7.26 (m, 5 H, Ph), 4.51 (s, 2 H, CH_2Ph), 3.87–3.80 (m, 3 H, 5-H, 3-OH), 3.72 (m, 1 H, 3-H), 3.40 (d, ^2J = 8.9 Hz, 1 H, 1-H), 3.31 (d, ^2J = 8.9 Hz, 1 H, 1-H), 3.20 (t, ^3J = 5.1 Hz, 1 H, 1-OH), 1.68–1.61 (m, 2 H, 4-H), 0.93 (s, 3 H, 2-CH_3), 0.90 (s, 3 H, 2-CH_3).

(4*S*)-4-(2-Benzyloxy-1,1-dimethylethyl)-2,2-dimethyl[1,3]dioxane (6)

Method 1

To a solution of **5a** (471 g, 1.46 mol) in acetone (2.3 L) were added 2,2-dimethoxypropane (900 mL, 7.345 mol), *p*-toluenesulfonic acid (27.8 g, 146 mmol) and the mixture was stirred at 23 °C for 22 h. The mixture was then poured into sat. $NaHCO_3$ diluted with water (1 L) and extracted with CH_2Cl_2 (5 L). The organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc–hexane, 0:100 → 40:60) to give **6** (349 g, 1.254 mol, 85.8%) as colorless oil along with 2(*RS*),4(*S*)-[2-methyl-1-benzyloxyprop-2-yl]-2-(1-hydroxybut-4-yl)[1,3]dioxane (56 g, 201 mmol, 13.8%).

^{1}H NMR: δ = 7.39–7.29 (m, 5 H, Ph), 4.48 (s, 2 H, CH_2Ph), 3.94 (dt, $^2J = {}^3J_1$ = 11.8 Hz, $^3J_2$ = 2.9 Hz, 1 H, 6-H), 3.88–3.81 (m, 2 H, 6-H, 4-H), 3.32 (d, ^2J = 8.6 Hz, 1 H, CH_2-OBn), 3.14 (d, ^2J = 8.6 Hz, 1 H, CH_2-OBn), 1.67 (dddd, ^2J = 12.6 Hz, $^3J_1 = {}^3J_2$ = 12.0 Hz, $^3J_3$ = 5.5 Hz, 1 H, 5-H_{ax}), 1.41 (s, 3 H, 2-CH_3), 1.34 (s, 3 H, 2-CH_3), 1.30 (dq, ^2J = 12.6 Hz, $^3J_1 = {}^3J_2 = {}^3J_3$ = 2.6 Hz, 1 H, 5-H_{eq}), 0.89 (s, 3 H, 1-CH_3), 0.88 (s, 3 H, 1-CH_3).

HRMS (EI+): *m/z* [M$^+$] calcd for $C_{17}H_{26}O_3$: 278.1882; found: 278.1904.

Method 2

To a solution of **5b** (118 g, 495 mmol) in CH_2Cl_2 (2.5 L) were added 2,2-dimethoxypropane (340 mL, 2.775 mol), (±)-camphor-10-sulfonic acid (4.3 g, 18.5 mmol) and the mixture was stirred at 23 °C for 16 h. The mixture was poured into sat. $NaHCO_3$ and extracted with CH_2Cl_2. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc–hexane, 20:80) to give **6** (113 g, 406 mmol, 82.0%) as a colorless oil.

(4*S*)-2-(2,2-Dimethyl[1,3]dioxan-4-yl)-2-methylpropionaldehyde (7)

To a solution of **6** (113,5 g, 407.7 mmol) in EtOH (1.9 L) was added Pd/C (16 g, 10%) and the mixture was shaken under 1 atm of H_2 gas at 23 °C until an uptake of 9.2 L hydrogen was reached (about 2 h). CH_2Cl_2 was added, the mixture filtered through celite to remove the catalyst and the filtrate concentrated in vacuo to give (4*S*)-4-(2-methyl-1-hydroxyprop-2-yl)-2,2-dimethyl[1,3]dioxane (73.4 g, 389.9 mmol, 95.6%) as a colorless oil; $[\alpha]^{22}_D$ +14.7 (*c* = 0.645).

^{1}H NMR: δ = 3.96 (ddd, $^2J = {}^3J_1$ = 11.8 Hz, $^3J_2$ = 2.9 Hz, 1 H, 6-H_{ax}), 3.87 (dd, ^2J = 11.8 Hz, ^3J = 5.5 Hz, 1 H, 6-H_{eq}), 3.80 (dd, $^3J_1$ = 11.8 Hz, $^3J_2$ = 2.6 Hz, 1 H, 4-H_{ax}), 3.55 (dd, ^2J = 11.0 Hz, ^3J = 5.9 Hz, 1 H, CH*H*OH), 3.37 (dd, ^2J = 11.0 Hz, ^3J = 5.5 Hz, 1 H, C*H*HOH), 2.99 (t, ^3J = 5.7 Hz, 1 H, OH), 1.77 (dq, $^2J = {}^3J_1 = {}^3J_2$ = 12.2 Hz, $^3J_3$ = 5.7 Hz, 1 H, 5-H_{ax}), 1.45 (s, 3 H, 2-CH_3), 1.38 (s, 3 H, 2-CH_3), 1.36 (ddd, ^2J = 12.2 Hz, $^3J_1$ = 5.1 Hz, $^3J_2$ = 2.5 Hz, 1 H, 5-H_{eq}), 0.90 (s, 3 H, 2′-CH_3), 0.88 (s, 3 H, 2′-CH_3).

To a solution of oxalyl chloride (13.0 mL, 151.6 mmol) in CH_2Cl_2 (0.5 L) at –70 °C was added DMSO (21.1 mL, 297 mmol) and after 10 min the solution of (4*S*)-4-(2-methyl-1-hydroxyprop-2-yl)-2,2-dimethyl[1,3]dioxane (20.0 g, 106.2 mmol) in CH_2Cl_2 (0.5 L) was added. After 30 min Et_3N (64.8 mL, 467 mmol) was added and the solution stirred at –35 °C for 1 h. Water was added and the mixture was extracted with CH_2Cl_2. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product **7** (20.9 g) was used without further purification.

(4*S*)-4-(2-Methyl-3-oxobut-2-yl)-2,2-dimethyl[1,3]dioxane (8a); General Procedure

To Et_2O (350 mL) was added a solution of methylmagnesium bromide (2287 mL, 860 mmol, 3 M in Et_2O) at 0 °C, followed by the solution of crude **7** (103.5 g, 543 mmol) in Et_2O (1.7 L) and the mixture was stirred at 0 °C for 0.5 h. The mixture was poured into sat. NH_4Cl solution and extracted with EtOAc. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column chromatography (EtOAc–hexane, 15:85) to give epimeric alcohols (4*S*)-4-(2-methyl-3(*RS*)-hydroxybut-2-yl)-2,2-dimethyl[1,3]dioxane (95.1 g, 470 mmol, 86.6%) as a colorless oil.

To a solution of (4*S*)-4-(2-methyl-3(*RS*)-hydroxybut-2-yl)-2,2-dimethyl[1,3]dioxane (95.1 g, 470 mmol) in CH_2Cl_2 (2.5 L) were added molecular sieves (4 Å, 2.0 g), *N*-methylmorpholine-*N*-oxide (82.8 g, 706.8 mmol) and tetrapropylammonium perruthenate (6.9 g, 19.6 mmol). The mixture was stirred overnight and purified by flash column chromatography (EtOAc–hexane, 90:10) to give **8a** (89.2 g, 445 mmol, 94.8%) as colorless crystalline solid.

^{1}H NMR: δ = 4.03 (dd, $^3J_1$ = 11.8 Hz, $^3J_2$ = 2.6 Hz, 1 H, 4-H), 3.96 (dt, ^2J = 11.8 Hz, $^3J_1$ = 11.8 Hz, $^3J_2$ = 2.8 Hz, 1 H, 6-H_{ax}), 3.85 (ddd, ^2J = 11.8 Hz, $^3J_1$ = 5.5 Hz, $^3J_2$ = 1.8 Hz, 1 H, 6-H_{eq}), 2.16 (s, 3 H, 4′-H), 1.62 (m, 1 H, 5-H), 1.42 (s, 3 H, 2-CH_3), 1.34 (m, 1 H, 5-H), 1.33 (s, 3 H, 2-CH_3), 1.12 (s, 3 H, 2′-CH_3), 1.07 (s, 3 H, 1′-H).

CD: [Θ] (λ) = +0.144 (295 nm).

MS (CI+): *m/z* [M$^+$] calcd for $C_{11}H_{20}O_3$: 200.27; found: 201 [M + H$^+$].

Compounds **8b** to **8k** could be prepared in an analogous manner to **8a**.

(4*S*)-4-(2-Methyl-3-oxopent-2-yl)-2,2-dimethyl[1,3]dioxane (8b)

$[\alpha]^{22}_D$ +13.5 (*c* = 0.465) {Lit.[9k] $[\alpha]^{20}_D$ = +12.4 (*c* = 1.0, $CHCl_3$)}.

^{1}H NMR: δ = 4.03 (dd, $^3J_1$ = 11.8 Hz, $^3J_2$ = 2.6 Hz, 1 H, 4-H), 3.95 (dt, ^2J = 11.8 Hz, $^3J_1$ = 11.8 Hz, $^3J_2$ = 2.6 Hz, 1 H, 6-H_{ax}), 3.84 (ddd, ^2J = 11.8 Hz, $^3J_1$ = 5.5 Hz, $^3J_2$ = 1.8 Hz, 1 H, 6-H_{eq}), 2.50 (q, *J* = 7.3 Hz, 2 H, 4′-H), 1.61 (m, 1 H, 5-H), 1.40 (s, 3 H, 2-CH_3), 1.32 (m, 1 H, 5-H), 1.31 (s, 3 H, 2-CH_3), 1.12 (s, 3 H, 2′-CH_3), 1.05 (s, 3 H, 1′-H), 1.00 (t, *J* = 7.3 Hz, 3 H, 5′-H).

CD: [Θ] (λ) = +0.209 (291 nm).

MS (CI+): *m/z* calcd [M$^+$] for $C_{12}H_{22}O_3$: 214.30; found [M + H$^+$]: 215.

(4*S*)-4-(2-Methyl-3-oxohex-2-yl)-2,2-dimethyl[1,3]dioxane (8c)

^{1}H NMR: δ = 4.05 (dd, $^3J_1$ = 11.8 Hz, $^3J_2$ = 2.6 Hz, 1 H, 4-H), 3.96 (dt, ^2J = 11.8 Hz, $^3J_1$ = 11.8 Hz, $^3J_2$ = 2.9 Hz, 1 H, 6-H_{ax}), 3.85 (ddd, ^2J = 11.8 Hz, $^3J_1$ = 5.5 Hz, $^3J_2$ = 1.8 Hz, 1 H, 6-H_{eq}), 2.47 (t, *J* = 7.3 Hz, 2 H, 4′-H), 1.62 (m, 1 H, 5-H), 1.56 (m, 2 H, 5′-H), 1.41 (s, 3 H, 2-CH_3), 1.32 (s, 3 H, 2-CH_3), 1.31 (m, 1 H, 5-H), 1.13 (s, 3 H, 2′-CH_3), 1.05 (s, 3 H, 1′-H), 0.88 (t, *J* = 7.3 Hz, 3 H, 5′-H).

CD: [Θ] (λ) = +0.224 (292 nm).

MS (CI+): *m/z* calcd [M$^+$] for $C_{13}H_{24}O_3$: 228.33; found [M + H$^+$]; 229.

(4*S*)-4-(2-Methyl-3-oxohept-2-yl)-2,2-dimethyl[1,3]dioxane (8d)

^{1}H NMR: δ = 4.04 (dd, $^3J_1$ = 11.8 Hz, $^3J_2$ = 2.6 Hz, 1 H, 4-H), 3.95 (dt, ^2J = 11.8 Hz, $^3J_1$ = 11.8 Hz, $^3J_2$ = 2.6 Hz, 1 H, 6-H_{ax}), 3.85 (ddd, ^2J = 11.8 Hz, $^3J_1$ = 5.5 Hz, $^3J_2$ = 1.8 Hz, 1 H, 6-H_{eq}), 2.49 (t, *J* = 7.4 Hz, 2 H, 4′-H), 1.69–1.47 (m, 3 H), 1.41 (s, 3 H, 2-CH_3), 1.35–1.20 (m, 3 H), 1.32 (s, 3 H, 2-CH_3), 1.12 (s, 3 H, 2′-CH_3), 1.05 (s, 3 H, 1′-H), 0.90 (t, *J* = 7.4 Hz, 3 H, 7′-H).

CD: [Θ] (λ) = +0.130 (291 nm).

MS (CI+): *m/z* [M$^+$] calcd for $C_{14}H_{26}O_3$: 242.36; found: [M + H$^+$]: 243.

(4*S*)-4-(2-Methyl-3-oxo-4-phenylbut-2-yl)-2,2-dimethyl[1,3]dioxane (8e)

^{1}H NMR: δ = 7.30 (m, 3 H, *m*,*p*-Ph), 7.19 (m, 2 H, *o*-Ph), 4.07 (dd, $^3J_1$ = 11.8 Hz, $^3J_2$ = 2.6 Hz, 1 H, 4-H), 3.97 (dt, ^2J = 11.8 Hz, $^3J_1$ = 11.8 Hz, $^3J_2$ = 2.6 Hz, 1 H, 6-H_{ax}), 3.87 (ddd, ^2J = 11.8 Hz, $^3J_1$ = 5.1 Hz, $^3J_2$ = 1.5 Hz, 1 H, 6-H_{eq}), 3.85 (s, 2 H, 4′-H), 1.66 (m, 1 H, 5-H), 1.43 (s, 3 H, 2-CH_3), 1.38 (m, 1 H, 5-H), 1.38 (s, 3 H, 2-CH_3), 1.20 (s, 3 H, 2′-CH_3), 1.15 (s, 3 H, 1′-H).

CD: [Θ] (λ) = +0.310.

HRMS (EI+): *m/z* [M$^+$] calcd for $C_{17}H_{24}O_3$: 276.1725; found: 276.1729.

(4*S*)-4-(2-Methyl-3-oxo-5-phenylpent-2-yl)-2,2-dimethyl[1,3]dioxane (8f)

^{1}H NMR: δ = 7.27 (m, 3 H, *m*,*p*-Ph), 7.14 (m, 2 H, *o*-Ph), 4.01 (dd, $^3J_1$ = 11.8 Hz, $^3J_2$ = 2.6 Hz, 1 H, 4-H), 3.93 (dt, ^2J = 11.8 Hz, $^3J_1$ = 11.8 Hz, $^3J_2$ = 2.6 Hz, 1 H, 6-H_{ax}), 3.83 (ddd, ^2J = 11.8 Hz, $^3J_1$ = 5.5 Hz, $^3J_2$ = 1.8 Hz, 1 H, 6-H_{eq}), 2.84 (m, 4 H, 4′-H, 5′-H), 1.60 (m, 1

H, 5-H), 1.36 (s, 3 H, 2-CH_3), 1.31 (s, 3 H, 2-CH_3), 1.28 (m, 1 H, 5-H), 1.12 (s, 3 H, 2′-CH_3), 1.03 (s, 3 H, 1′-H).

CD: [Θ] (λ) = +0.174 (292 nm).

HRMS (EI+): *m/z* [M+] calcd for $C_{18}H_{26}O_3$: 290.1882; found: 290.1859.

(4*S*)-4-(2-Methyl-3-oxo-7-trimethylsilylhept-6-in-2-yl)-2,2-dimethyl[1,3]dioxane (8g)

^{1}H NMR: δ = 4.02 (dd, $^3J_1$ = 11.8 Hz, $^3J_2$ = 2.6 Hz, 1 H, 4-H), 3.94 (dt, ^2J = 11.8 Hz, $^3J_1$ = 11.8 Hz, $^3J_2$ = 2.6 Hz, 1 H, 6-H_{ax}), 3.84 (ddd, ^2J = 11.8 Hz, $^3J_1$ = 5.5 Hz, $^3J_2$ = 1.8 Hz, 1 H, 6-H_{eq}), 2.73 (dd, $^3J_1$ = 9.2 Hz, $^3J_1$ = 7.0 Hz, 2 H, 5′-H), 2.44 (dd, $^3J_1$ = 8.1 Hz, $^3J_1$ = 5.9 Hz, 2 H, 4′-H), 1.69 (m, 1 H, 5-H), 1.41 (s, 3 H, 2-CH_3), 1.33 (s, 3 H, 2-CH_3), 1.31 (m, 1 H, 5-H), 1.13 (s, 3 H, 2′-CH_3), 1.07 (s, 3 H, 1′-H), 0.12 (s, 9 H, $SiCH_3$).

CD: [Θ] (λ) = +0.170 (290 nm).

(4*S*)-4-(2-Methyl-3-oxo-8-trimethylsilyloct-7-in-2-yl)-2,2-dimethyl[1,3]dioxane (8h)

^{1}H NMR: δ = 4.05 (dd, $^3J_1$ = 11.8 Hz, $^3J_2$ = 2.6 Hz, 1 H, 4-H), 3.95 (dt, ^2J = 11.8 Hz, $^3J_1$ = 11.8 Hz, $^3J_2$ = 2.6 Hz, 1 H, 6-H_{ax}), 3.85 (ddd, ^2J = 11.8 Hz, $^3J_1$ = 5.5 Hz, $^3J_2$ = 1.8 Hz, 1 H, 6-H_{eq}), 2.62 (m, 2 H, 4′-H), 2.23 (m, 2 H, 6′-H), 1.74 (m, 2 H, 5′-H), 1.63 (m, 1 H, 5-H), 1.41 (s, 3 H, 2-CH_3), 1.33 (s, 3 H, 2-CH_3), 1.31 (m, 1 H, 5-H), 1.14 (s, 3 H, 2′-CH_3), 1.06 (s, 3 H, 1′-H), 0.14 (s, 9 H, $SiCH_3$).

CD: [Θ] (λ) = +0.194 (291 nm).

HRMS (EI+): *m/z* [M+] calcd for $C_{14}H_{24}O_3$: 240.1725; found: 240.1799.

(4*S*)-4-(2-Methyl-3-oxohex-5-en-2-yl)-2,2-dimethyl[1,3]dioxane (8i)

^{1}H NMR: δ = 5.93 (m, 1 H, 5′-H), 5.14 [dq, ^3J_Z = 10.3 Hz, $^2J \approx {}^4J_1 \approx {}^4J_2 \approx$ 1.5 Hz, 1 H, 6′-H(*Z*)], 5.06 [dq, ^3J_E = 17.3 Hz, $^2J \approx {}^4J_1 \approx {}^4J_2 \approx$ 1.5 Hz, 1 H, 6′-H(*E*)], 4.02 (dd, $^3J_1$ = 11.8 Hz, $^3J_2$ = 2.6 Hz, 1 H, 4-H), 3.95 (dt, ^2J = 11.8 Hz, $^3J_1$ = 11.8 Hz, $^3J_2$ = 2.6 Hz, 1 H, 6-H_{ax}), 3.85 (ddd, ^2J = 11.8 Hz, $^3J_1$ = 5.5 Hz, $^3J_2$ = 1.8 Hz, 1 H, 6-H_{eq}), 3.30 (m, 2 H, 4′-H), 1.62 (m, 1 H, 5-H), 1.41 (s, 3 H, 2-CH_3), 1.34 (s, 3 H, 2-CH_3), 1.33 (m, 1 H, 5-H), 1.14 (s, 3 H, 2′-CH_3), 1.09 (s, 3 H, 1′-H).

CD: [Θ] (λ) = +0.115 (290 nm).

HRMS (EI+): *m/z* [M+] calcd for $C_{17}H_{30}O_3Si$: 310.1964; found: 310.1952.

(4*S*)-4-(2-Methyl-3-oxohept-6-en-2-yl)-2,2-dimethyl[1,3]dioxane (8j)

^{1}H NMR: δ = 5.81 (m, 1 H, 5′-H), 5.02 [dq, ^3J_E = 17.3 Hz, $^2J \approx {}^4J_1 \approx {}^4J_2 \approx$ 1.7 Hz, 1 H, 6′-H(*E*)], 4.95 [m, 1 H, 6′-H(*Z*)], 4.04 (dd, $^3J_1$ = 11.8 Hz, $^3J_2$ = 2.6 Hz, 1 H, 4-H), 3.95 (dt, ^2J = 11.8 Hz, $^3J_1$ = 11.8 Hz, $^3J_2$ = 2.6 Hz, 1 H, 6-H_{ax}), 3.85 (ddd, ^2J = 11.8 Hz, $^3J_1$ = 5.5 Hz, $^3J_2$ = 1.8 Hz, 1 H, 6-H_{eq}), 2.60 (t, ^3J = 7.1 Hz, 2 H, 4′-H), 2.29 (m, 2 H, 5′-H), 1.62 (m, 1 H, 5-H), 1.41 (s, 3 H, 2-CH_3), 1.32 (s, 3 H, 2-CH_3), 1.31 (m, 1 H, 5-H), 1.13 (s, 3 H, 2′-CH_3), 1.06 (s, 3 H, 1′-H).

CD: [Θ] (λ) = +0.200 (291 nm).

HRMS (EI+): *m/z* [M+] calcd for $C_{18}H_{32}O_3Si$: 324.2121; found: 324.2134.

(4*S*)-4-(2,7-Dimethyl-3-oxooct-6-en-2-yl)-2,2-dimethyl[1,3]dioxane (8k)

^{1}H NMR: δ = 5.06 (t, *J* = 7.2 Hz, 1 H, 6′-H), 4.03 (dd, $^3J_1$ = 11.8 Hz, $^3J_2$ = 2.6 Hz, 1 H, 4-H), 3.95 (dt, ^2J = 11.8 Hz, $^3J_1$ = 11.8 Hz, $^3J_2$ = 2.6 Hz, 1 H, 6-H_{ax}), 3.84 (ddd, ^2J = 11.8 Hz, $^3J_1$ = 5.5 Hz, $^3J_2$ = 1.8 Hz, 1 H, 6-H_{eq}), 2.51 (t, *J* = 7.3 Hz, 2 H, 4′-H), 2.21 (q, ^3J = 7.3 Hz, 2 H, 5′-H), 1.67 (s, 3 H, 7′-CH_3), 1.63 (m, 1 H, 5-H), 1.62 (s, 3 H, 8′-H), 1.41 (s, 3 H, 2-CH_3), 1.32 (s, 3 H, 2-CH_3), 1.31 (m, 1 H, 5-H), 1.12 (s, 3 H, 2′-CH_3), 1.05 (s, 3 H, 1′-H).

CD: [Θ] (λ) = +0.225 (291 nm).

HRMS (EI+): *m/z* [M+] calcd for $C_{16}H_{28}O_3$: 268.2038; found: 268.2030.

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