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An enantioselective synthesis of the C(33)–C(37) fragment of Amphotericin B †

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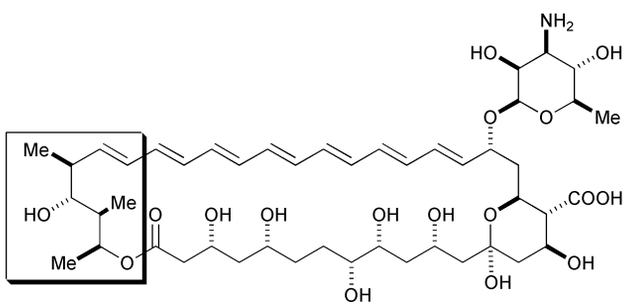
An enantioselective synthesis of the C(33)–C(37) tripropionate fragment of Amphotericin B has been developed in only 6 steps.

Introduction

Amphotericin B (AmB, **1**) produced by *Streptomyces nodosus*[1] is one of the most prominent members of the clinically important polyene macrolides.[2] It is a widely used antifungal agent, and serves as the drug of choice in the clinic for antifungal chemotherapy to treat life-threatening infections.[3]



1: Amphotericin B

The polypropionate fragment with varying stereochemistry is a common structural feature in natural products.[4] Their structural complexity and associated biological activities make them attractive and challenging target structures for organic chemists. As potentially every carbon in the backbone is a chiral center, the key to the synthesis of polypropionates is the control of both absolute and relative stereochemistry.

Amphotericin B (AmB) has succumbed to total synthesis.[5,6] However, improved syntheses of fragments are still required to allow the construction of analogues for biological testing. Recently, Tholander and Carreira have reported an elegant synthesis of the C33–C37 fragment in 14 steps and in 16% overall yield.[7] We have recently reported model studies on a diastereoselective synthesis of the tripropionate segment of Amphotericin B.[8] In this paper we report an enantioselective version of the synthetic path for the C(33)–C(37) fragment of AmB.

Results and discussion

The C(33)–C(37) fragment of Amphotericin B (boxed in **1**) is a tripropionate segment containing four stereocenters with *syn*, *anti*, *anti* stereochemistry. Our retrosynthetic analysis of the C(33)–C(37) stereotetrad of Amphotericin B, shown in Scheme 1, is based on the thiopyran ring strategy, which has occasionally been used in the synthesis of polypropionates.[9,10]

The key step in our enantioselective synthesis of the tripropionate of AmB is the creation of the first chiral center: addition of the formyl unit onto the thiopyranone ring. A poor electrophile, 2-methoxy-1,3-dioxolane **4** was reacted with the silyl enol ether of tetrahydrothiopyran-4-one 2 with the assistance of Lewis acid Zn(II) or Ti(IV) giving the racemate **3** in a good yield (Scheme 2).[8]

Our initial plan was to introduce the chirality *via* chiral Ti(IV) or Zn(II) catalyst. Several different chiral ligands were tested (Fig. 1) but practically no enantiomeric enhancement was observed.

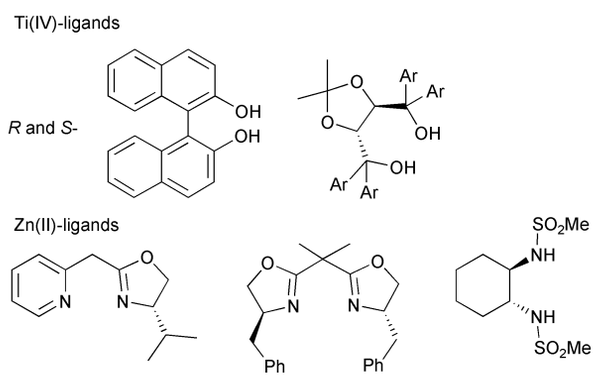


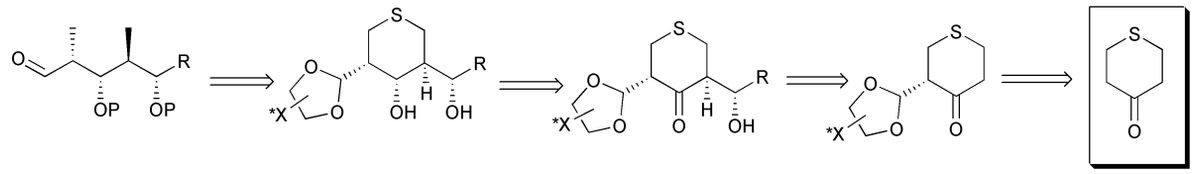
Fig. 1 Chiral ligands examined in the alkylation reaction shown in Scheme 2.

Another possible source for chirality is a chiral auxiliary strategy: the electrophile, 2-methoxy-1,3-dioxolane, can be replaced by a chiral analogue. Longobardo *et al*. published a paper in the beginning of the 1990s, where different orthoesters derived from tartaric acid were allowed to react with different silyl enol ethers with good diastereoselectivity.[11] This strategy also worked in our case: the electrophilic orthoester **5** derived from diethyl L-tartrate reacted with the silyl enol ether **2** and $ZnCl_2$ giving a mixture of two diastereomers in a ratio of 2.3 : 1 in 23% yield (Scheme 3, upper reaction scheme). The diastereomeric ratio was easy to determine from the ^{1}H NMR spectrum: the diastereomers have differing δ-values for the OCHOs of the dioxolane-ring. The diastereomers could not be separated on TLC or by HPLC.

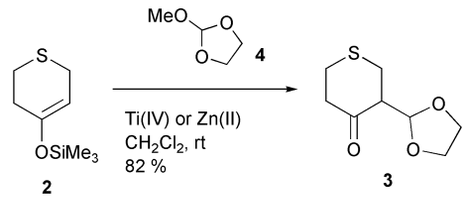
The use of di-isopropyl L-tartrate orthoester **6** as the electrophile (Scheme 3, lower reaction scheme) improved both the yield and diastereoselectivity. The reaction resulted in a mixture of two diastereomers in a ratio of 3 : 1 in 56% yield.

† Electronic supplementary information (ESI) available: Tables S1–S5: crystal data and structure refinement, atomic coordinates and equivalent isotropic displacement parameters, bond lengths and angles, anisotropic displacement parameters and torsion angles for compound **7b**. See http://www.rsc.org/suppdata/ob/b3/b305845j/

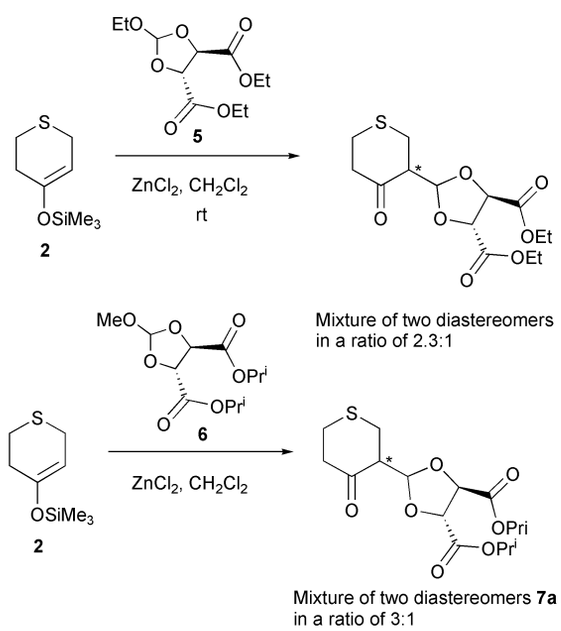
DOI: 10.1039/B305845J



Scheme 1



Scheme 2



Scheme 3

We succeeded in crystallizing the minor diastereomer **7b** from the 3 : 1 mixture under carefully controlled conditions in a crystal form suitable for X-ray crystallographic analysis (Fig. 2),[12] confirming the assignment of the relative stereochemistry. For preparative purposes, the major diastereomer **7a** can also be purified from the mixture by crystallization, but unfortunately the crystals were not suitable for X-ray analysis.

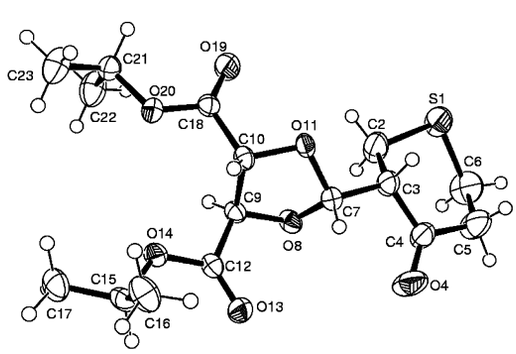
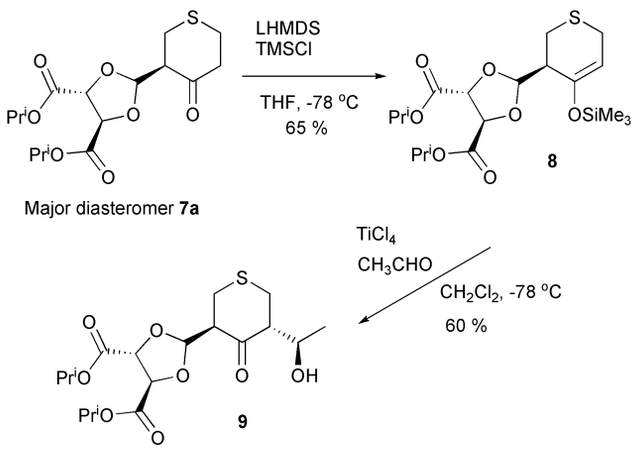


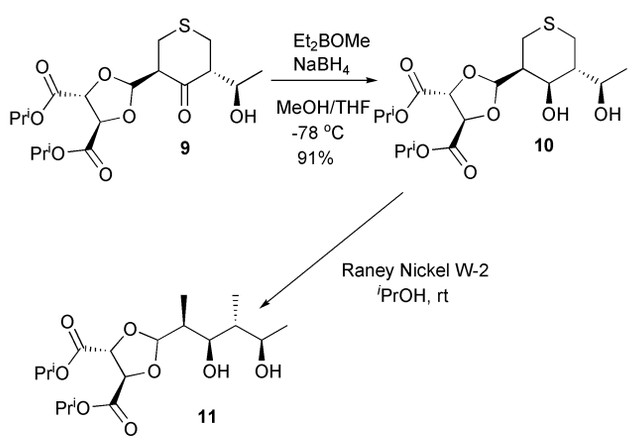
Fig. 2 Molecular structure of **7b**. The thermal displacement parameters are shown at 50% probability level.

On the basis of the results of the model studies,[8] the next step in the synthetic route was the Mukaiyama aldol reaction. The pure major diastereomer **7a** was first converted into the corresponding kinetic silyl enol ether **8**, which after purification was allowed to react with acetaldehyde in the presence of Lewis acid $TiCl_4$ (Scheme 4). The Mukaiyama aldol reaction was, as well as in the model studies, highly diastereoselective. After purification by column chromatography, the single diastereomer **9**[13] was obtained in fair yield (60%).



Scheme 4

After the crucial aldol addition, the next task was a diastereoselective reduction of the ketone. Following a common literature procedure,[14] the aldol adduct **9** was reduced to the corresponding 1,3-*syn* diol **10** with high diastereoselectivity (10 : 1 according to NMR) and in excellent yield (91%, Scheme 5, step 1).



Scheme 5

The final reaction step in the enantioselective synthesis of the enantiomer of the tripropionate of AmB was reductive desulfurisation with Raney Nickel[15] (Scheme 5, step 2), which was achieved in quantitative yield.

In summary, we have realized a highly stereoselective synthesis of the enantiomer of the C(33)–C(37) tripropionate of Amphotericin B starting from the natural L-tartaric acid derivative and tetrahydrothiopyran-4-one. The synthesis involves only six steps and yields **11** in 14% overall yield. The other enantiomer of the tripropionate of AmB can be easily synthesized using the same route starting from the unnatural D-tartaric acid derivative and tetrahydrothiopyran-4-one.

Experimental

General notes

All reagents and solvents were purchased from commercial suppliers and used without further purification with following exceptions: Tetrahydrofuran was distilled from Na/benzophenone. Dichloromethane was pre-dried with $CaCl_2$ and distilled from CaH_2. MeOH was distilled from $Mg(OMe)_2$. TMSCl was distilled from CaH_2 and stored under argon at room temperature. Di-isopropylamine was distilled from NaOH and stored under argon at room temperature. Methyl *tert*-butyl ether (MTBE) for chromatography was used as obtained from suppliers. Unless otherwise noted, all experiments were performed under an Ar-atmosphere using flame-dried glassware. Silica gel (230–400 mesh) for column chromatography as well as the corresponding TLC plates were purchased from Merck. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded in deuterochloroform on a Bruker Avance-400 spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. Chemical shifts are reported in ppm on the δ scale from an internal standard of residual chloroform (7.26 ppm in ^{1}H NMR spectra and 77.0 in ^{13}C NMR spectra). HRMS spectra were recorded on JEOL JMS-DX 303 and Micromass LCT. Melting points were measured with Fisher-Johns melting point apparatus. HPLC analyses were performed using a Waters 501 pump and Waters 486 detector. Separations were performed using the following columns: Shandon's Hypersil (5 μm, 250 × 4.6 mm) for analytical runs, Shandon's Hyperprep (12 μm, 250 × 10 mm) for preparative runs. Optical rotations are given in 10^{-1} deg cm^2 g^{-1}.

Preparation of the orthoesters

The orthoesters were synthesized following the procedure of Longobardo *et al.*[16] 100 mol% of diol, 400–500 mol% of orthoformate and a catalytic amount of conc. H_2SO_4 were boiled in toluene until the spot of the diol had disappeared (TLC). The reaction was quenched with saturated $NaHCO_3$, the layers were separated, the aqueous layer was extracted three times with EtOAc. The combined organic layer was dried over Na_2SO_4, the drying agent was filtered and the solvent evaporated. Crude products were purified by flash chromatography using 20% EtOAc:–hexane as eluent.

Data for (4*R*,5*R*)-Di-isopropyl-2-methoxy-1,3-dioxolane-4,5-dicarboxylate 6. Transparent liquid; yield 81%; $[\alpha]_D$ (c = 1.0, $CHCl_3$) −29.5; R_f 0.48 (30% MTBE–hexane); IR (film) 1739 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.28–1.32 (12H, m, 2 × (C*H*$_3$)$_2$CH), 3.39 (3H, s, C*H*$_3$OCH), 4.64 (1H, d, OC*H*RCOO, *J* 4.5), 4.95 (1H, d, OC*H*RCOO, *J* 4.5), 5.09–5.17 (2H, m, 2 × (CH$_3$)$_2$-C*H*O), 6.01 (1H, s, OC*H*RO); δ_C (100 MHz, $CDCl_3$) 21.6, 21.7, 51.9, 69.9, 70.0, 76.0, 76.4, 117.7, 168.4, 168.5; HRMS *m*/*z* (ES+) calcd for $C_{12}H_{20}O_7$ 276.1209, found 245.1043 $C_{11}H_{17}O_6$ (calcd for M–OCH_3 245.1025).

Diastereoselective alkylation with L-tartrate derived orthoester 6

$ZnCl_2$ (0.99 g, 7.2 mmol, 200 mol%) was dissolved in 36 mL of CH_2Cl_2 in a 100 mL flask under argon and then silyl enol ether **2** (1.35 g, 7.2 mmol, 200 mol%) was added to the solution at room temperature. The suspension was stirred at room temperature for 15 minutes before addition of the orthoester **6** (1.0 g, 3.6 mmol, 100 mol%). The reaction mixture was stirred for 21 hours at room temperature and then sat. $NaHCO_3$ (35 mL) was added and the phases were separated. The aqueous phase was extracted three times with EtOAc. The combined organic phase was dried over Na_2SO_4, filtered and the solvent was evaporated giving 1.82 g crude product. The crude product was purified by flash chromatography (silica, 30% MTBE–hexane) and 725 mg (56%) of the desired product was obtained in a 3 : 1 diastereomeric ratio. A fraction of both diastereomers was successfully crystallized (toluene–hexane) out from the mixture.

Major diastereomer 3(*S*)-[(4′*R*,5′*R*)-Di-isopropylcarbonyl-1′,3′-dioxolan-2′-yl]-tetrahydro-thiopyran-4-one 7a. White solid; Mp 84 °C; $[\alpha]_D$ (c = 1.0, $CHCl_3$) −21.5; R_f 0.18 (30% MTBE–hexane); IR(film) 1750 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.25–1.31 (12H, m, 2 × (C*H*$_3$)$_2$CH), 2.67–3.16 (7H, m, SC*H*$_2$C*H*$_2$, SC*H*$_2$C*H*), 4.64 (1H, d, OC*H*RCOO, *J* 3.9), 4.68 (1H, d, OC*H*RCOO, *J* 3.9), 5.05–5.17 (2H, m, 2 × (CH$_3$)$_2$-C*H*O), 5.77 (1H, d, OC*H*RO, *J* 3.9); δ_C (100 MHz, $CDCl_3$) 21.6, 29.8, 30.2, 44.2, 55.8, 69.9, 70.0, 76.7, 76.9, 104.3, 168.5, 168.8; 206.4; HRMS *m*/*z* (ES+) calcd for $C_{16}H_{24}O_7S$ 360.1243, found 360.1239.

Minor diastereomer 3(*R*)-[(4′*R*,5′*R*)-Di-isopropylcarbonyl-1′,3′-dioxolan-2′-yl]-tetrahydro-thiopyran-4-one 7b. Glassy crystals; Mp 89 °C; $[\alpha]_D$ (c = 0.45, $CHCl_3$) −27.3; R_f 0.18 (30% MTBE–hexane); IR(film) 1751 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.28–1.32 (12H, m, 2 × (C*H*$_3$)$_2$CH), 2.69–3.23 (7H, m, SC*H*$_2$-C*H*$_2$, SC*H*$_2$C*H*), 4.66 (2H, s, 2 × OC*H*RCOO), 5.05–5.15 (2H, m, 2 × (CH$_3$)$_2$C*H*O), 5.69 (1H, d, OC*H*RO, *J* 5.0); δ_C (100 MHz, $CDCl_3$) 21.7, 30.3, 30.6, 44.5, 56.3, 70.0, 70.1, 76.7, 77.7, 104.6, 168.7, 206.6; HRMS *m*/*z* (ES+) calcd for $C_{16}H_{24}O_7S$ 360.1243, found 360.1245.

5(*S*)-[(4′*R*,5′*R*)-Di-isopropylcarbonyl-1′,3′-dioxolan-2′-yl]-4-trimethylsilyloxy-thiopyr-3-ene 8

HMDS (190 mg, 0.25 mL, 155 mol%) was dissolved in 4 mL of dry THF in a flame-dried flask under an argon atmosphere and the mixture was cooled in an ice-bath. *n*-BuLi (0.81 mL, c = 1.41, 150 mol%) was added dropwise and the yellowish mixture was allowed to stir at 0 °C for 30 minutes. Then it was cooled in an acetone–dry-ice-bath (−78 °C) and the ketone **7a** (274 mg, 100 mol%, in 1 mL of THF) was added. The pale yellow mixture was stirred at −78 °C for one hour and then TMSCl (288 mg, 0.33 mL, 300 mol%) was added and the cooling bath was replaced with an ice-bath. After 1 hour the reaction was quenched by cannulating the reaction mixture into ice-cold $NaHCO_3$–EtOAc (8 mL + 8 mL) solution. The phases were separated and the aqueous phase was extracted once with EtOAc. The combined organic phase was dried over Na_2SO_4, filtered and the solvent was evaporated giving 311 mg of crude product as a yellow oil. The crude product was purified by filtering it through a short silica pad (20% MTBE–hexane) and after evaporation of the solvent 214 mg (65%) of the desired kinetic silyl enol ether **8** was obtained in pure form.

Yellowish oil; $[\alpha]_D$ (c = 1, $CHCl_3$) −16.0; R_f 0.49 (30% MTBE–hexane); IR(film) 1736, 1664 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.20 (9H, s, OSi(CH$_3$)$_3$), 1.27 (6H, d, (C*H*$_3$)$_2$CH, *J* 6.3), 1.29 (6H, d, (C*H*$_3$)$_2$CH, *J* 6.3), 2.72–2.77 (1H, br s, SCH$_2$-C*H*R$_2$), 2.80 (1H, ddd, SC*H*$_a$H$_b$CH=, *J* 13.4, 4.6, 1.4), 3.01–3.08 (2H, m, H$_a$*H*$_b$CSCH$_a$*H*$_b$), 3.23 (1H, dt, R$_2$CHC*H*$_a$H$_b$S, *J* 16.5, 2.4), 4.57 (1H, d, OC*H*RCOO, *J* 4.4), 4.67 (1H, d, OC*H*RCOO, *J* 4.4), 5.04–5.15 (2H, m, 2 × (CH$_3$)$_2$C*H*O), 5.18 (1H, td, C=C*H*–R, *J* 4.6, 1.4), 5.65 (1H, d, OC*H*RO, *J* 4.0); δ_C (100 MHz, $CDCl_3$) 0.5, 22.0, 25.2, 25.4, 43.4, 69.99, 70.03, 77.6, 78.0, 105.1, 107.1, 150.1, 168.9, 169.4; HRMS *m*/*z* (ES+) calcd for $C_{19}H_{32}O_7SSi$ 432.1638, found 432.1642.

3(*S*),5(*R*)-[(4′*R*,5′*R*)-Di-isopropylcarbonyl-1′,3′-dioxolan-2′-yl]-5-[1(*R*)-hydroxyethyl]-tetrahydrothio-pyran-4-one 9

Acetaldehyde (21 μL, 100 mol%) was dissolved in 3.5 mL of dry CH_2Cl_2 argon and the mixture was cooled with an acetone–dry-ice bath (−78 °C). $TiCl_4$ (48 μL, 120 mol%) was added (bright yellow suspension) and after three minutes of stirring, the silyl enol ether **8** (190 mg, 120 mol%) in 1 mL of CH_2Cl_2 was added (the reaction mixture turned orange). After 5 minutes the reaction mixture was cannulated into ice-cold $NaHCO_3$–EtOAc (5 mL + 5 mL) solution. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phase was dried over Na_2SO_4, filtered and

the solvent evaporated giving 191 mg of crude product, which was purified by flash chromatography (silica, 50% MTBE–hexane as eluent). After purification 90 mg (60%) of the desired diastereomer **9** was obtained in pure form.

Transparent oil; $[\alpha]_D$ (c = 1.0, $CHCl_3$) +24.9; R_f 0.11 (50% MTBE–hexane); IR 3502, 1738 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.26 (3H, d, C*H*$_3$CHOH, *J* 6.3), 1.28–1.31 (12H, m, 2 × (C*H*$_3$)$_2$-CH), 2.68 (1H, d, OH, *J* 5.6), 2.73–3.21 (6H, m, C*H*CH$_2$-SCH$_2$C*H*), 4.13–4.21 (1H, m, CH$_3$C*H*OH), 4.63 (1H, d, OC*H*RCOO, *J* 3.8), 4.69 (1H, d, OC*H*RCOO, *J* 3.8), 5.07–5.17 (2H, m, 2 × (CH$_3$)$_2$C*H*O), 5.88 (1H, d, OC*H*RO, *J* 5.1); δ_C (100 MHz, $CDCl_3$) 20.8, 21.7, 29.9, 32.3, 55.7, 57.6, 68.0, 69.99, 70.02, 77.2, 77.6, 104.8, 168.4, 168.7, 209.2; HRMS *m*/*z* (ES+) calcd for $C_{18}H_{28}O_8S$ 404.1505, found 404.1499.

3(*S*),5(*R*),4(*R*)-[(4′*R*,5′*R*)-Di-isopropylcarbonyl-1′,3′-dioxolan-2′-yl]-5-[1(*R*)-hydroxyethyl]-tetrahydro-thiopyran-4-ol 10

The aldol adduct **9** (68 mg, 0.17 mmol) was dissolved in THF–MeOH (1.5 mL + 0.3 mL) and the mixture was cooled in acetone–dry-ice bath (−78 °C). Et_2BOMe (0.19 mL of 1 M solution in THF, 110 mol%) was added and the yellowish mixture was stirred at −78 °C for 15 minutes before addition of $NaBH_4$ (7 mg, 110 mol%). After 1 hour the reaction was quenched with 0.17 mL of acetic acid. The mixture was diluted with EtOAc and washed with Na_2CO_3. The aqueous phase was extracted 3 times with EtOAc, and the combined organic phase was dried over Na_2SO_4, filtered and the solvent was evaporated giving 63 mg (91%) of 10 : 1 mixture of *syn* : *anti* diols. After flash chromatography 49 mg of the pure *syn*-diol **10** was obtained.

Transparent oil; $[\alpha]_D$ (c = 1, $CHCl_3$) −10.6; R_f 0.17 (60 % EtOAc–hexane) IR(film) 3436, 1735 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 1.22 (3H, d, C*H*$_3$CHOH, *J* 6.2), 1.27 (6H, d, (C*H*$_3$)$_2$CH, *J* 6.3), 1.29 (6H, d, (C*H*$_3$)$_2$CH, *J* 6.3), 1.83–1.89 (1H, m, R$_2$C*H*-CHOHCH$_3$), 2.23 (1H, dd, SC*H*$_{a1}$H$_{b1}$, *J* 13.9, 5.5), 2.42–2.47 (1H, m, OOCHC*H*R$_2$), 2.50 (1H, dd, SC*H*$_{a2}$H$_{b2}$, *J* 13.2, 2.7), 2.82 (1H, br s, OH), 3.01 (1H, dd, SCH$_{a2}$*H*$_{b2}$, *J* 13.2, 9.8), 3.12 (1H, dd, SCH$_{a1}$*H*$_{b1}$, *J* 13.9, 3.4), 3.19 (1H, br s, OH), 4.13–4.19 (1H, m, CH$_3$C*H*OH), 4.25 (1H, dd, RC*H*OHR, *J* 5.6, 2.1) 4.57 (1H, d, OC*H*RCOO, *J* 4.1), 4.69 (1H, d, OC*H*RCOO, *J* 4.1), 5.04–5.14 (2H, m, 2 × (CH$_3$)$_2$C*H*O), 5.44 (1H, d, OC*H*RO, *J* 5.7); δ_C (100 MHz, $CDCl_3$); 21.4, 21.61, 21.64, 24.2, 26.4, 42.0, 47.2, 68.4, 68.5, 70.0, 70.1, 76.9, 77.1, 108.0, 168.3, 168.8; HRMS *m*/*z* (ES+) calcd for $C_{18}H_{30}O_8S$ 406.1661, found 406.1613.

1(*S*),2(*R*),3(*R*),4(*R*)-1-[(4′*R*,5′*R*)-Di-isopropylcarbonyl-1′,3′-dioxolan-2′-yl]-1,3-dimethylpentane-2,4-diol 11

The diol **10** (20 mg, 0.049 mmol, 100 mol%) was dissolved in 3 mL of IPA and Raney Nickel suspension (0.05 mL, approximately 1000 mol%) was added. The black reaction mixture was stirred at 70 °C for 23.5 hours, then the reaction mixture was filtered through Celite, the Celite pad was washed with EtOAc and the solvent was evaporated giving 16 mg of the crude product, which contained both the starting material and the product (1 : 1). After purification by flash chromatography a sample of pure **11** was obtained.

$[\alpha]_D$ (c = 0.1, $CHCl_3$) −52; R_f 0.23 (60% EtOAc–hexane); IR(film) 3367, 1734 cm^{-1} δ_H (400 MHz, $CDCl_3$) 0.75 (3H, d, C*H*$_3$CHR$_2$, *J* 6.9), 1.03 (3H, d, C*H*$_3$CHR$_2$, *J* 7.1), 1.19 (3H, d, C*H*$_3$CHOH, *J* 6.2) 1.30 (6H, d, (C*H*$_3$)$_2$CH, *J* 6.3), 1.31 (6H, d, (C*H*$_3$)$_2$CH, *J* 6.3), 1.58–1.67 (1H, m, RC*H*CH$_3$R), 2.13–2.19 (1H, m, OCHOC*H*CH$_3$R), 3.81–3.87 (1H, m, R$_2$C*H*OHCH$_3$), 3.96 (1H, dd, RC*H*OHR *J* 9.7, 1.0), 4.62 (1H, d, OC*H*RCOO, *J* 4.0), 4.71 (1H, d, OC*H*RCOO, *J* 4.0), 5.09–5.16 (2H, m, 2 × (CH$_3$)$_2$C*H*O), 5.27 (1H, d, OC*H*RO, *J* 3.6); δ_C (100 MHz, $CDCl_3$); 6.3, 12.9, 21.1, 21.6, 37.7, 42.1, 69.97, 70.02, 72.3, 75.9, 77.1, 110.0, 168.4, 168.9; HRMS *m*/*z* (ES+) as sodium adduct calcd for $C_{18}H_{32}O_8Na$ 399.1995, found 399.2012.

Acknowledgements

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Notes and references

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