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# Model studies on a diastereoselective synthesis of the C(33)–C(37) fragment of Amphotericin B

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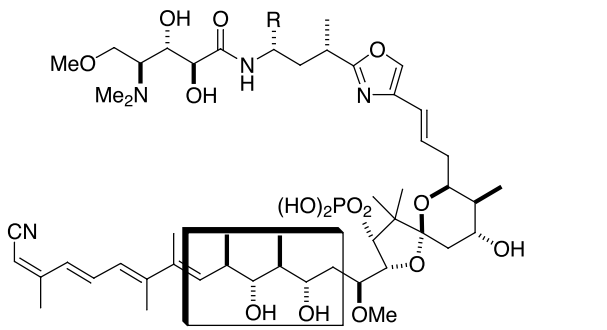
**Abstract**—A new, short and highly diastereoselective synthetic route aiming at the C(33)–C(37) fragment of Amphotericin B has been developed. Studies with a model aldehyde (benzaldehyde) have given very promising results: the desired stereochemistry of all four stereocenters of the target molecule has been achieved with high diastereoselection. The stereochemistry of three key intermediates and the target segment has been confirmed by X-ray crystallography. 

## 1. Introduction

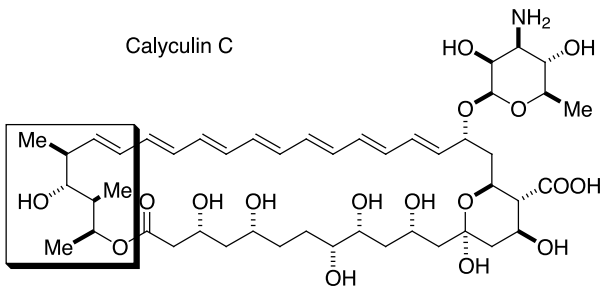
The polypropionate fragment with varying stereochemistry is a common structural feature in natural products.[1] Their structural complexity and associated biological activities make them attractive and challenging target structures for organic chemists. As potentially every carbon in the backbone is a chiral center, the key to the synthesis of polypropionates is the control of both absolute and relative stereochemistry.

The thiopyranone ring is a synthetic equivalent of 3-pentanone because the sulfur bridge is easily removed by Raney Nickel. The advantage of using the thiopyranone ring instead of linear 3-pentanone is the rigidity of the ring system. In the aldol reaction, the rigid structure enables only the *E*-enolate to be formed and makes the stereochemistry of the product easier to control.

A strategy, where the propionate segment is synthesized via a thiopyranone or thiopyran derivative, is an intriguing route to polypropionates. For example, Woodward et al. published a total synthesis of Erythromycin in the beginning of 1980s and the whole massive total synthesis was based on the thiopyran ring strategy.[2] During the 1990s extensive research about polypropionates with varying stereochemistry via thiopyranone derivatives has been conducted by Ward and his group.[3] Amphotericin B and Calyculin C are stereochemically complex natural products, which contain a tripropionate fragment (Fig. 1, boxed). Amphotericin B (produced by *Streptomyces nodosus*)[4] is one of the most prominent members of the clinically important polyene macrolides.[5] It is a widely used antifungal agent, which serves as a drug of choice in the clinic for antifungal chemotherapy in life-threatening infections.[6] Calyculin C (toxic metabolite of marine sponge *Discodermia calyx*) has proven to be a strong serine/threonine protein phosphatase inhibitor[7] and based on this property, it might be a potential anti-cancer agent.[8]




Calyculin C




Amphotericin B

**Figure 1.**

*Keywords*: diastereoselection; aldol reactions; desulfurisation.

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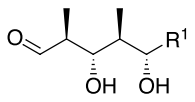
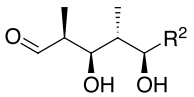



Tripropionate fragment of Calyculin C




Tripropionate fragment of Amphotericin B

**Figure 2.** $R^1$ is the spiroketal fragment of Calyculin C (see Figure 1) and $R^2$ is a methyl group.

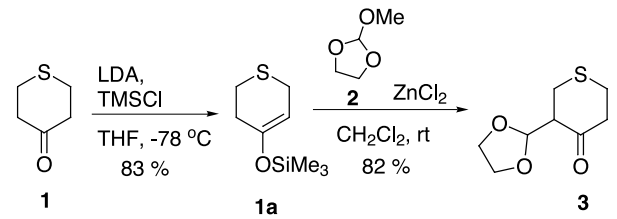
Amphotericin B (AmB) has succumbed to total synthesis.[9,10] However, improved syntheses of fragments thereof are still required to allow the construction of analogues for biological testing. Recently, Carreira has reported an elegant synthesis of the C33–C37 fragment in 14 steps.[11] While investigating the synthesis of tripropionates related to the calyculins' C9–C14 segment, we realized a short, efficient route to the C33–C37 fragment of AmB in only 6 steps. In this paper, we wish to report our preliminary results, in racemic form, for this particular fragment. Studies aimed at an enantioselective version of the initial aldol-like alkylation step are in progress, and the results will be reported in due course.

The tripropionate fragments of Amphotericin B and Calyculin C differ from each other only by the stereochemistry of one methyl group (Fig. 2). The synthetic route (Scheme 1), originally planned for the tripropionate fragment of Calyculin C, gives access to both tripropionates with suitable adjustments.

## 2. Results and discussion

The first step of the synthesis was to introduce a masked formyl unit onto the thiopyranone ring. Direct addition of a poor electrophile, 2-methoxy-1,3-dioxolane **2** to the lithium enolate of **1** did not lead to the desired product; only the self-condensation adduct of the ketone was observed as the main product. Literature precedent suggested that the addition of electrophiles similar to **2** to the enolate succeeds when the ketone is first converted into the corresponding silyl enol ether **1a**.[12] Also in our case it worked and 3-(1,3-dioxolan)-tetrahydrothiopyran-4-one **3** was obtained in high yield (Scheme 2).

Aldol addition, the key step, which creates two of the four requisite stereocenters, was the next reaction to be investigated. Benzaldehyde was chosen as the test aldehyde

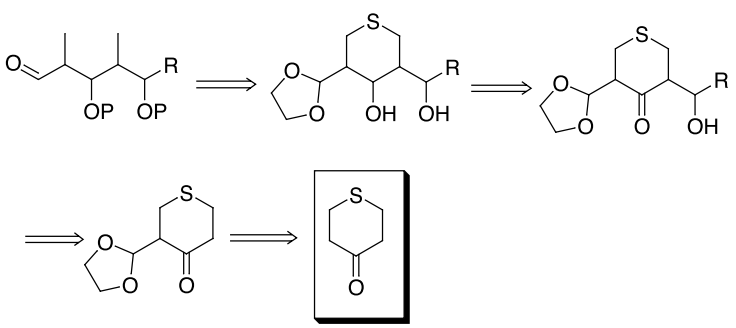



**Scheme 2.**

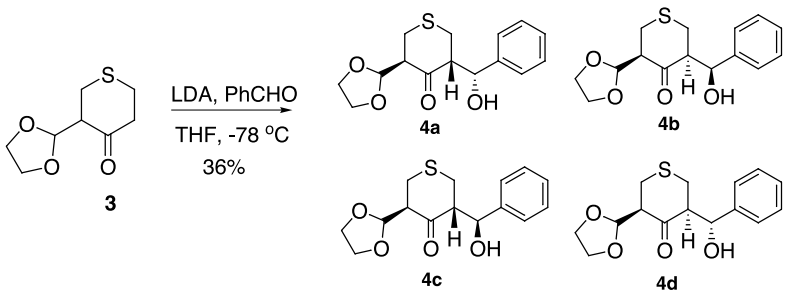
because of its UV activity and high reactivity. The enolate of **3** was generated with LDA (1 h, −78°C) and after the addition of benzaldehyde, the reaction took 2 h to complete (Scheme 3). HPLC[13] and $^1$H NMR spectroscopy analysis of the crude reaction mixture revealed all four diastereoisomers to be present. The crude mixture was purified by preparative HPLC and all four diastereomers were obtained in pure form. The diastereoisomers were fully analysed (NMR, HRMS) and two of them were crystalline. The crystals were analysed by X-ray crystallography[14] and the results confirmed the stereochemistry of **4c** and **4d**, the X-ray structures of which are shown in Figure 3 with crystallographic numbering.

After the diastereoisomers were isolated and identified, the diastereomeric ratio was determined; **4a**+**4b**–**4c**–**4d** was 2.7:2.9:2.1. The reaction was repeated with TMEDA, which was added before benzaldehyde and the reaction yielded the diastereomers **4a**–**4d** in a ratio of 2.5:1.6:1.4 in a 60% combined yield. One can thus conclude that the reaction itself does not show intrinsic diastereoselectivity but the Lewis acid (in the first case lithium) strongly influences the reaction outcome. Results shown in Table 1 corroborate this conclusion.

The Mukayiama type aldol reaction via the silyl enol ether **5** and $TiCl_4$ as the Lewis acid was very diastereoselective: the desired aldol product (*anti*, *anti*) was obtained as the major product with the diastereomeric ratio **4a**+**4b**–**4c**–**4d**/1:10:1 (Scheme 4). The major product **4c** is the *anti* aldol product, with aldehyde electrophile approaching from the face opposite to the dioxolane substituent in the silyl enol ether educt. Co-ordination of Ti (IV) presumably enhances the allylic strain effect of this substituent. Despite poor conversion of **5** to **4c** (26%), the relative yield remained quite high because 45% of **3** was recovered after purification. The reaction proved capricious because of retro-aldolisation; quenching and work-up required careful attention.




**Scheme 1.**




**Scheme 3.**

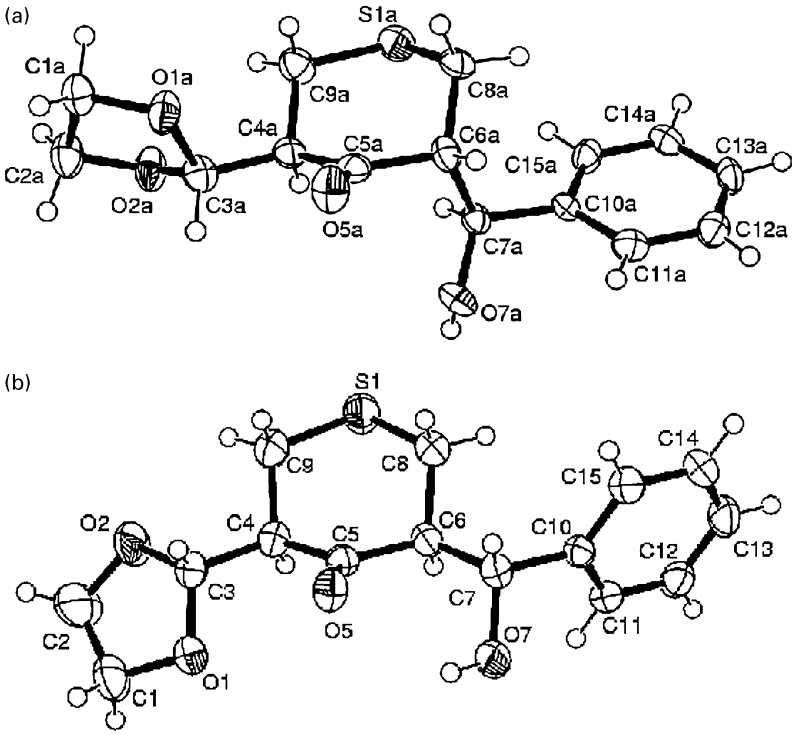



**Figure 3.** X-Ray crystal structures of **4c** (below) and **4d** (above).

Diastereoselective reduction of the ketone was the next reaction to be performed and the procedure of Prasad and co-workers[15] (Scheme 5) afforded a 6:1 mixture of *syn*/*anti* diastereomers from which the *syn* diol **6** was crystallized in 63% yield (combined yield 85%). In this reaction, the diastereoselectivity comes from the precomplexation of $MeOBEt_2$ with OH and C=O groups of the starting material; hydride nucleophile is then forced to attack from the axial position. X-Ray crystallographic analysis confirmed the stereochemistry, shown in Figure 4.

**Table 1.**

| Base/reagent/catalyst | **4a+4b** | **4c** | **4d** |
|---|---|---|---|
| LDA[a] | 2.7 | 2.9 | 2.1 |
| LDA/TMEDA[b] | 2.5 | 1.6 | 1.4 |
| DIPEA/$TiCl_4$[c] | 13 | 5.6 | 1 |
| LDA/TMSCl[d]/$TiCl_4$[e] | 1 | 10 | 1 |
| DIPEA/$BF_3{\cdot}Et_2O$[f] | 4.8 | – | – |
| DIPEA/$SnCl_4$[f] | 6.1 | 4.5 | 3.6 |

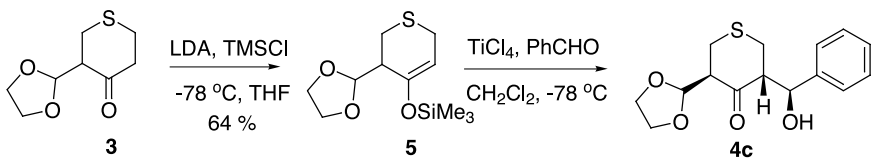
All reactions were performed under argon atmosphere, at −78°C. The diastereomeric ratios were determined by HPLC and $^1H$ NMR spectroscopy of the crude products.
[a] Yield 36%.
[b] Yield 60%.
[c] Yield 53%.
[d] Yield 69%.
[e] Yield 26 and 45% of **3**.
[f] The crude products were not purified.

Finally, expulsion of the sulfur atom with Raney Nickel[16] resulted in the model version of the tripropionate fragment of Amphotericin B in acceptable yield (Scheme 6).

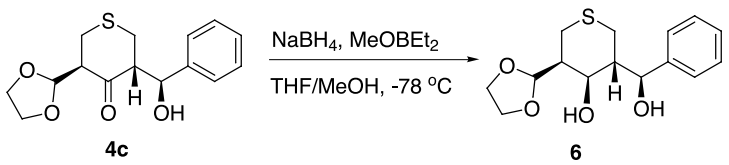
The product **7** crystallized in the refrigerator and X-ray quality crystals were obtained from 50% EtOAc–hexane. The crystal structure is shown in Figure 5.

## 3. Conclusions

In this paper we have demonstrated that the C(33)–C(37) fragment of Amphotericin B can be synthesized diastereoselectively in 6 steps from the commercially available tetrahydrothiopyran-4-one **1**. The key step is the aldol




**Scheme 4.**




**Scheme 5.**

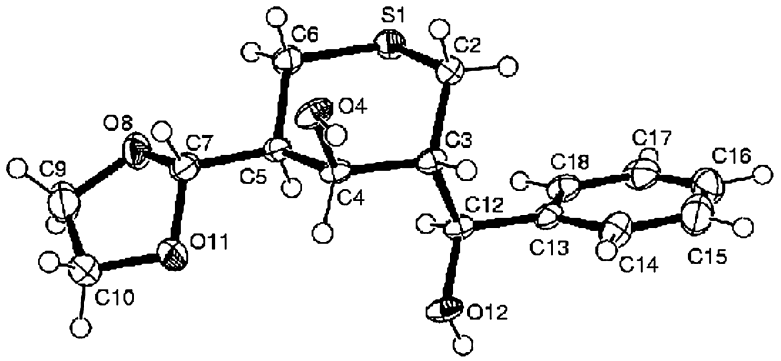
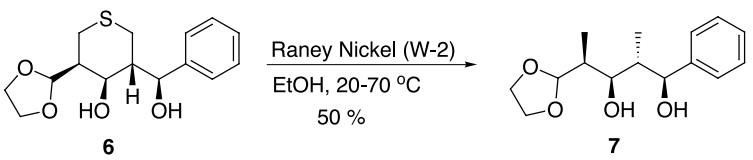



**Figure 4.** X-Ray crystal structure of **6**.




**Scheme 6.**

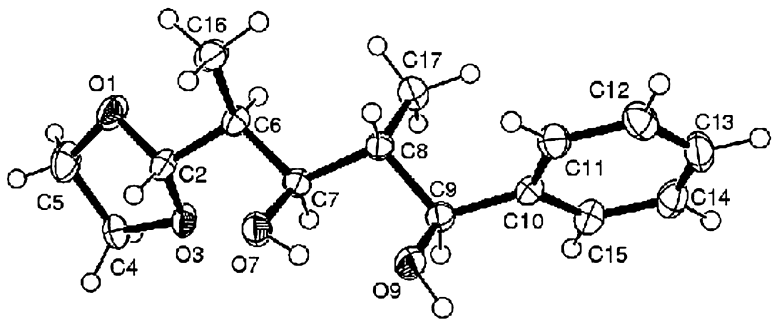



**Figure 5.** X-Ray crystal structure of **7**.

reaction, which creates two of the four stereocenters. Diastereoselectivity of this reaction can be directed with different Lewis acids ($TiCl_4$, $BF_3{\cdot}Et_2O$, $SnCl_4$). The best diastereoselectivity was observed with Mukaiyama type aldol reaction ($TiCl_4$, aldehyde and silyl enol ether of the ketone). The reduction with $NaBH_4$ and $Et_2BOMe$ gave the desired *syn* diol in good stereoselectivity over the *anti* diol (*syn*–*anti*/6:1).

Studies aimed at an enantioselective version of the initial aldol-like alkylation step are in progress as well as optimisation of the conditions for alkyl aldehydes, and the results will be reported in due course.

## 4. Experimental

### 4.1. General

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 $CaH_2$. TMSCl was distilled from $CaH_2$ and stored under argon in the refrigerator. Di-isopropylamine was distilled from NaOH and stored under argon at room temperature. Benzaldehyde was freshly distilled before use. Unless otherwise noted, all experiments were performed under Ar-atmosphere using oven-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 $\delta$ 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 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.

**4.1.1. 3,6-Dihydrothiopyran 4-(trimethylsilyloxy)-2*H*-thiopyran (1a).**[3c] Di-isopropylamine (1.51 g, 15.0 mmol, 120 mol%) was dissolved in dry THF (100 mL) under Ar-atmosphere and the reaction flask was cooled to −0°C. *n*-BuLi (10.45 mL, 1.34 M in hexane, 112 mol%) was added dropwise and when the addition was completed the mixture was cooled to −78°C. Then tetrahydrothiopyran-4-one **1** (1.45 g, 12.5 mmol, 100 mol%) (in 5 mL of THF) was added slowly and the mixture was stirred for 45 min. Finally chlorotrimethylsilane (2.37 g, 18.8 mmol, 150 mol%) was added and the reaction was allowed to stir at −78°C for 45 min. The reaction was quenched with brine (50 mL) and the mixture was extracted with diethyl ether (3×50 mL). The combined organic phases were dried over $Na_2SO_4$ and the drying agent was filtered. Finally, the solvent was evaporated giving crude product as a yellow oil. The crude product was purified by flash chromatography (silica, 50% EtOAc–hexane) giving the product as a light yellow liquid (1.96 g, 83%). $R_f$=0.66 (50% EtOAc–hexane); $\delta_H$ (400 MHz, $CDCl_3$) 0.15 (9H, s, $OSi(CH_3)_3$), 2.25–2.29 (2H, m, $CH_2CH_2S$), 2.75–2.78 (2H, m, $SCH_2CH_2$), 3.15–3.18 (2H, m, $SCH_2CH{=}C$), 5.06–5.08 (1H, m, $CH{=}C$); $\delta_C$ (100 MHz, $CDCl_3$) 0.8, 25.5, 26.1, 31.6, 102.6, 151.7; HRMS (EI) *m*/*z* calcd for $C_8H_{16}OSSi$ 188.0691, found 188.0697.

**4.1.2. (±)-3-(1,3-Dioxolan)-tetrahydrothiopyran-4-one (3).** $ZnCl_2$ (89 mg, 0.65 mmol, 65 mol%) was suspended in 16 mL of dry $CH_2Cl_2$ at room temperature under argon and 2-methoxy-1,3-dioxolane (156 mg, 1.5 mmol, 150 mol%) followed by the above silylenolether **1a** (188 mg, 1.0 mmol, 100 mol%) (in 1 mL of $CH_2Cl_2$) were added dropwise. The reaction mixture was stirred for 2 h at room temperature. Then the reaction was quenched with 20 mL of saturated $Na_2CO_3$ and the mixture was extracted with EtOAc (3×20 mL). The combined organic phases were dried over $Na_2SO_4$, the drying agent was filtered and the solvent evaporated giving crude product as a yellow oil. The crude product was purified by flash chromatography (silica, 50% hexane–EtOAc) giving the desired product (154 mg, 82%) as a transparent oil. $R_f$=0.28 (50% hexane–EtOAc); $\nu_{max}$ (film) 1712 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 2.70–2.77 (2H, m, $CH_2CH_2S$), 2.93–2.98 (4H, m, $CH_2SCH_2$), 3.06–3.09 (1H, m, $SCH_2CHR_2$), 3.89–3.99 (4H, m, $OCH_2CH_2O$), 5.39 (1H, d, $J$=4.2 Hz, $OCHO$); $\delta_C$ (100 MHz, $CDCl_3$) 30.3, 30.6, 44.5, 56.7, 65.5, 101.8, 207.5; HRMS (EI) *m*/*z* calcd for $C_8H_{12}O_3S$ 188.0507, found 188.0510.

**4.1.3. (±)-1,6-Dihydro-4-(trimethylsilyloxy)-3-(1,3-dioxolan)-2*H*-thiopyran (5).** Di-isopropylamine (0.21 mL, 1.5 mmol, 150 mol%) was dissolved in 9 mL of THF under argon and the mixture was cooled in an ice-bath. *n*-BuLi (1.12 mL, 150 mol%, 1.34 M in hexane) was added dropwise and then the mixture was cooled to −78°C (acetone/dry-ice bath). 3-(1,3-Dioxolan)-tetrahydrothiopyran-4-one **3** (188 mg, 1.0 mmol, 100 mol%) in 1 mL of THF was added and the enolate was allowed to form for 1 h at −78°C. TMSCl (190 mg, 1.5 mmol, 150 mol%) was added and after 1 h the reaction was quenched with 10 mL of brine, and extracted with EtOAc (3×10 mL). The combined organic phases were washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL) and dried over $Na_2SO_4$. Filtration of the drying agent and evaporation gave the crude product, which was purified by flash chromatography (silica, 40% EtOAc–hexane) giving 165 mg (0.63 mmol, 64%) of the desired product as a yellow oil. $R_f$=0.64 (50% EtOAc–hexane); $\nu_{max}$ (film) 1665 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 0.20 (9H, s, $OSi(CH_3)_3$), 2.61–2.66 (1H, m, $R_2CHCH_2S$), 2.79 (1H, ddd, $R_2CHCH_aH_bS$, $J$=13.7, 5.2, 1.5 Hz, 1H), 2.87 (1H, dd, $R_2CHCH_aH_bS$, $J$=13.7, 7.7 Hz), 3.03 (1H, ddt, $SCH_aH_bCH{=}$, $J$=16.5, 5.2, 1.6 Hz) 3.25 (1H, dt, $SH_aH_bCH{=}$, $J$=16.5, 3.2 Hz), 3.87–3.99 (4H, m, $OCH_2CH_2O$), 5.18 (1H, td, $CH{=}COSiMe_3$, $J$=3.2, 1.6 Hz), 5.30 (1H, d, $OCHO$, $J$=3.6 Hz); $\delta_C$ (100 MHz, $CDCl_3$) 0.71, 25.4, 32.4, 43.8, 65.5, 65.6, 104.0, 104.9, 150.9; HRMS (EI) *m*/*z* calcd for $C_{11}H_{20}O_3SSi$ 260.0902, found 260.0892.

**4.1.4. (±)-3-(1,3-Dioxolan)-5-(benzyl-1-ol)-tetrahydrothiopyran-4-one (4c).** Benzaldehyde (22 mg, 0.21 mmol,

100 mol%) was dissolved in $CH_2Cl_2$ (3 mL) and freshly distilled $TiCl_4$ (41 mg, 0.22 mmol, 105 mol%) was added dropwise to solution under argon atmosphere at room temperature. The fine yellow suspension was then cooled to −78°C (acetone/dry-ice cooling bath) and then the silyl enol ether **5** (80 mg, 0.31 mmol, 150 mol%) in 1 mL of $CH_2Cl_2$ was added drop-wise (the mixture turned orange). After 30 min stirring at −78°C the reaction was quenched with distilled water (5 mL) and the cool mixture was extracted 3 times with EtOAc. The combined organic phases were dried over $Na_2SO_4$, the drying agent was filtered and the solvent evaporated giving 134 mg of a yellowish oily crude product. The crude product was purified by flash chromatography (silica, 50% EtOAc–hexane) giving 16 mg (0.054 mmol, 26%) of the desired diastereomer (fine crystals) and 27 mg (0.14 mmol, 45% of the starting material silyl enol ether) of the corresponding ketone of the silyl enol ether **4c**. Mp 139°C; $R_f$=0.23 (50% hexane–EtOAc); $\nu_{max}$ (film) 1711, 3461 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 2.50 (1H, $SCH_{a1}H_{b1}$, ddd, $J$=13.7, 8.2, 1.2 Hz), 2.66 (1H, ddd, $SCH_{a1}H_{b1}$, $J$=13.7, 4.6, 1.4 Hz), 3.01–3.18 (5H, m, $SCH_{a2}H_{b2}$, $SCH_{a2}H_{b2}$, $CHR_3$, $CHR_3$ and OH), 3.89–4.02 (4H, m, $OCH_2CH_2O$), 5.16 (1H, d, $RCHOHPh$, $J$=9.1 Hz), 5.51 (1H, d, $OCHO$, $J$=5.1 Hz), 7.27–7.39 (5H, m, ArH); $\delta_C$ (100 MHz, $CDCl_3$) 30.8, 32.3, 55.5, 58.4, 65.1, 65.4, 73.8, 101.8, 126.9, 128.5, 128.7, 140.5, 209.6. HRMS (EI) *m/z* calcd for $C_{15}H_{18}O_4S$ 294.0926, found 294.0926.

*Compound* **4a**. Yellowish oil; $R_f$=0.35 (50% hexane–EtOAc); $\nu_{max}$ (film) 1708, 3468 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 2.68 (1H, dd, $SCH_{a1}H_{b1}$, $J$=8.4, 2.2 Hz), 2.93 (1H, dd, $SCH_{a2}H_{b2}$, $J$=10.6, 5.8 Hz), 2.99–3.15 (5H, m, $SCH_{a1}H_{b1}$, $SCH_{a2}H_{b2}$, $CHR_3$, $CHR_3$ and OH), 3.89–4.02 (4H, m, $OCH_2CH_2O$), 5.43 (1H, bs, $RCHOHPh$), 5.55 (1H, d, $OCHO$, $J$=6.1 Hz, 1H), 7.26–7.38 (5H, m, ArH); $\delta_C$ (100 MHz, $CDCl_3$) 28.6, 30.5, 56.5, 57.4, 64.8, 65.3, 70.9, 102.0, 125.6, 126.9, 128.0, 140.5, 209.9. HRMS (EI) *m/z* calcd for $C_{15}H_{18}O_4S$ 294.0926, found 294.0889.

*Compound* **4b**. Yellowish oil; $R_f$=0.28 (50% hexane–EtOAc); $\nu_{max}$ (film) 1706, 3502 $cm^{-1}$ $\delta_H$ (400 MHz, $CDCl_3$) 2.63 (1H, dt, $SCH_{a1}H_{b1}$, $J$=13.2, 3.3 Hz), 2.90–3.13 (6H, m, $SCH_{a2}H_{b2}$, $SCH_{a1}H_{b1}$, $SCH_{a2}H_{b2}$, $CHR_3$, $CHR_3$ and OH), 3.86–4.00 (4H, m, $OCH_2CH_2O$), 5.25 (1H, d, $OCHO$, $J$=4.3 Hz, 1H), 5.40 (1H, bs, $RCHOHPh$), 7.26–7.38 (5H, m, ArH); $\delta_C$ (100 MHz, $CDCl_3$) 31.0, 32.1, 58.4, 61.0, 66.0, 66.1, 71.4, 102.0, 126.4, 128.1, 129.2.0, 141.2, 212.2. HRMS (EI) *m/z* calcd for $C_{15}H_{18}O_4S$ 294.0926, found 294.0937.

*Compound* **4d**. Fine crystals, mp 128–130°C; $R_f$=0.20 (50% hexane–EtOAc); $\nu_{max}$ (film) 1709, 3468 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 2.39 (1H, ddd, $SCH_{a1}H_{b1}$, $J$=13.5, 4.8, 3.1 Hz), 2.63 (1H, dd, $SCH_{a1}H_{b1}$, $J$=13.5, 12.1 Hz), 2.92 (1H, dd, $CH_{a2}H_{b2}$, $J$=14.2, 12.8 Hz), 3.02–3.10 (3H, m, $SCH_{a2}H_{b2}$, $SCH_{a2}H_{b2}CHR_2$, $SCH_{a1}H_{b1}CHR_2$), 3.50 (1H, d, OH $J$=3.3 Hz), 3.90–3.99 (4H, m, $OCH_2CH_2O$), 4.88 (1H, dd, $R_2CHOHPh$, $J$=8.6, 3.3 Hz), 5.28 (1H, d, $OCHO$, $J$=4.3 Hz), 7.26–7.37 (5H, m, ArH); $^{13}C$ NMR ($CDCl_3$, 400 MHz) $\delta_C$ (100 MHz, $CDCl_3$) 31.6, 34.0, 58.0, 61.0, 65.5, 65.6, 73.8, 101.5, 127.3, 128.6, 129.0, 140.2, 211.7. HRMS (EI) *m/z* calcd for $C_{15}H_{18}O_4S$ 294.0926, found 294.0926.

**4.1.5. (±)-3-(1,3-Dioxolan)-5-(benzyl-1-ol)-tetrahydrothiopyran-4-ol (6).** 3-(1,3-Dioxolan)-5-(benzyl-1-ol)-tetrahydrothiopyran-4-one **4c** (40 mg, 0.14 mmol, 100 mol%) was dissolved in mixture of THF and MeOH (1.5 mL/0.25 mL) under argon and the mixture was cooled to −78°C (acetone/dry-ice bath). $MeOBEt_2$ (0.155 mmol, 155 μL of 1 M solution in THF, 110 mol%) was added, the mixture was stirred for 15 min and then $NaBH_4$ (8 mg, 0.21 mmol, 150 mol%) was added in one portion. The mixture was stirred for 1 h, quenched with 0.15 mL of acetic acid and then the mixture was poured into 5 mL of saturated $Na_2CO_3$, and extracted with EtOAc (3×6 mL). The combined organic phases were washed with brine and dried over $Na_2SO_4$. Drying agent was filtered, the solvent was evaporated and the residue dissolved in MeOH (5 mL) (this procedure was repeated 10 times). The product (two diastereomers, *syn* diol–*anti* diol/6:1) was obtained as a white solid (34 mg, 85%) and the desired *syn* diol was obtained in pure form (transparent, needle-like crystals, 25 mg, 63%) after crystallizing the mixture from EtOAc. Mp 183°C; $R_f$=0.22 (75% EtOAc–hexane); $\nu_{max}$ (film) 3401 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 1.95 (1H, dd, $SCH_{a1}H_{b1}$, $J$=13.8, 7.0 Hz), 2.23–2.29 (1H, m, $SCH_2CHCHOHPh$), 2.41–2.46 (1H, m, $SCH_2CHCHOO$), 2.59 (1H, dd, $SCH_{a2}H_{b2}CH_2$, $J$=13.5, 3.0 Hz), 2.69 (1H, dd, $SCH_{a1}H_{b1}$, $J$=13.8, 2.2 Hz), 2.97 (1H, ddd, $SCH_{a2}H_{b2}$, $J$=13.5, 8.4, 1.3 Hz), 3.48 (1H, OH, bs), 3.76 (1H, d, OH, $J$=4.7 Hz), 3.89–4.06 (4H, m, $OCH_2CH_2O$), 4.21–4.23 (1H, m, $RCHOHR$), 4.99 (1H, dd, $RCHOHPh$, $J$=9.0, 1.8 Hz), 5.26 (1H, d, $OCHO$, $J$=5.3 Hz), 7.19–7.40 (5H, m, ArH); $\delta_C$ (100 MHz, $CDCl_3$) 25.9, 27.5, 42.3, 47.2, 65.1, 65.6, 71.4, 100.7, 105.6, 127.4, 128.5, 129.0, 142.7; HRMS *m/z* (as sodium adduct) (ES+) calcd for $C_{15}H_{20}O_4NaS$ 319.0980, found 319.0980.

**4.1.6. (±)-1-(1,3-dioxolan)-1,3-dimethyl-4-phenyl-butan-2,4-diol (7).** 3-(1,3-Dioxolan)-5-(benzyl-1-ol)-tetrahydrothiopyran-4-ol **6** (24 mg, 0.081 mg, 100 mol%) was dissolved in EtOH (5 mL) (few drops of MeOH were needed to dissolve the starting material properly). Raney Nickel suspension (24 mg, 0.41 mmol, 500 mol% in EtOH) was added with syringe through a septum and the mixture was allowed to stir at room temperature for 1 h. Then the temperature was gradually raised up to 70°C (during 4 h) and 100 mol% Raney Nickel was added 3 times (after 2, 4 and 5 h). After 6 h the reaction was complete and the reaction mixture was filtered through Celite. The Celite cake was washed 3 times with EtOAc and the solvent was evaporated giving the crude product (26 mg) as a pale yellow oil. Purification by flash chromatography (silica, 50% EtOAc–hexane) gave the desired product as a transparent oil (10 mg, 50%). The product was crystallized from hexane–EtOAc/2:1, transparent glassy crystals, mp 95°C; $R_f$=0.19 (50% EtOAc–hexane); $\nu_{max}$ (film) 3400 $cm^{-1}$; $\delta_H$ (400 MHz, $CDCl_3$) 0.49 (3H, d, $R_2C_aHCH_3$, $J$=6.9 Hz), 1.04 (3H, d, $R_2C_bHCH_3$, $J$=7.2 Hz), 1.92–2.02 (1H, m, $R_2C_aHCH_3$), 2.04–2.10 (1H, ddq, $R_2C_bHCH_3$, $J$=14.3, 7.2, 1.4 Hz), 3.83 (1H, bs, OH), 3.84–4.06 (5H, m, $OCH_2CH_2O$ and $RCHOHR$), 4.61 (1H, d, $RCHOHPh$, $J$=8.7 Hz), 4.85 (1H, bs, OH), 4.90 (1H, d, $OCHO$, $J$=2.9 Hz), 7.25–7.36 (5H, m, ArH); $\delta_C$ (100 MHz, $CDCl_3$) 6.7, 13.4, 37.7, 41.8, 64.8, 65.1, 80.7, 100.4, 107.5, 127.4, 127.5, 128.2, 143.4. HRMS *m/z* (as

sodium adduct) (ES+) calcd for $C_{15}H_{22}O_4Na$ 289.1416, found 289.1422.

### 4.2. X-Ray crystallography

Suitable single crystals for X-ray analysis were obtained from 50% hexane–EtOAc for **4c** and for **4d**, EtOAc for **6** and 80% EtOAc–hexane for **7**. The X-ray crystallographic data were recorded with a Nonius Kappa CCD diffractometer. Graphite monochromatised Mo Kα radiation [λ(Mo Kα)=0.71073 Å] and temperature of 173.0±0.1 K were used for all compounds. The CCD data were processed with Denzo-SMN v0.93.0[17] and the structures were solved by direct methods (SHELXS-97[18]) and refined on $F^2$ by full-matrix least-squares techniques (SHELXL-97[19]). The hydrogen atoms were located from the difference Fourier and refined isotropically for **4c** and **4d** and with fixed isotropic temperature factors (1.5 or 1.2 times the carbon temperature factor) for **6** and **7**. Crystallographic data (excluding structure factors) has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC196852, 196853, 195940 and 195941 for **4c**, **4d**, **6** and **7**, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].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## References


1. For leading references, see: (a) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Koseki, K. *J. Org. Chem.* **1988**, *53*, 3930–3932. (b) Mechlinski, W.; Schaffef, C.; Ganis, P.; Avitabile, G. *Tetrahedron Lett.* **1970**, *44*, 3873–3876. (c) Davies-Coleman, M.; Garson, M. *Nat. Prod. Rep.* **1998**, *15*, 477–493. (d) Höfle, G.; Bedorf, N.; Steinmetz, H.; Schomburg, D.; Gerth, K.; Reichenbach, H. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1567–1569. (e) Kobayashi, M.; Higuchi, K.; Murakami, N.; Tajima, H.; Aoki, S. *Tetrahedron Lett.* **1997**, *38*, 2859–2862. (f) Brooks, H.; Gardner, P.; Pyser, P.; King, T. *J. Antibiot.* **1984**, *37*, 1501–1504.
2. Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B.-W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chênevert, R. B.; Fliri, A.; Frobel, K.; Gais, H.-J.; Garrat, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R. S.; Ong, B. S.; Press, J. B.; Rajan Babu, T. V.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, H. N.-C. *J. Am. Chem. Soc.* **1981**, *103*, 3210.
3. (a) Ward, D. E.; Sales, M.; Man, C. C.; Shen, J.; Sasmal, P. K.; Guo, C. *J. Org. Chem.* **2002**, *67*, 1618. (b) Ward, D. E.; Guo, C.; Sasmal, P. K.; Man, C. C.; Marcelo, S. *Org. Lett.* **2000**, *2*, 1325. (c) Ward, D. E.; Man, C. C.; Guo, C. *Tetrahedron Lett.* **1997**, *38*, 2201.
4. Linke, H.; Mechlinski, W.; Schaffner, C. *J. Antibiot.* **1974**, *27*, 155.
5. Omura, S.; Tanaka, H. In *Macrolide Antibiotics: Chemistry, Biology and Practice*; Omura, S., Ed.; Academic: New York, 1984.
6. Hunter, P. A. *Drug Discov. Today* **1996**, *1*, 227.
7. Sheppeck, II., J. E.; Gauss, C.-M.; Chamberlin, A. R. *Bioorg. Med. Chem.* **1997**, *5*, 1739.
8. Bridges, A. J. *Chemtracts-Org. Chem.* **1995**, *8*, 73.
9. Nicolaou, K. C.; Daines, R. A.; Ogawa, Y.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1988**, *110*, 4696.
10. McGarvey, G. J.; Mathys, J. A.; Wilson, K. *J. Org. Chem.* **1996**, *61*, 5704.
11. Tholander, J.; Carreira, E. M. *Helv. Chim. Acta* **2001**, *84*, 613.
12. Markó, I. E.; Ates, A. *Synlett* **1999**, *7*, 1033.
13. HPLC analyses were run using Waters 501 pump and Waters 486 detector. Separations were done using the following columns: Shandon's Hypersil (5μ, 250×4.6 mm) for analytical runs and Shandon's Hyperprep (12μ, 250×10 mm) for preparative runs.
14. The X-ray crystal data for **4c**, **4d**, **6** and **7**. Compound **4c**: $C_{15}H_{18}O_4S$, $M$=294.35, monoclinic, space group $P2_1/a$ (No. 14), $a$=19.655(1), $b$=6.751(1), $c$=23.220(3) Å, $\beta$=114.89(1)°, $V$=2794.8(5) Å$^3$, $Z$=8, $D_c$=1.399 g cm$^{-3}$, $\mu$=0.242 mm$^{-1}$, 12489 reflections, 5059 independent, $R_{int}$=0.106, final $R1$=0.081, $wR2$=0.167 for $I>2\sigma I$. Compound **4d**: $C_{15}H_{18}O_4S$, $M$=294.35, monoclinic, space group $C2/c$ (No. 15), $a$=21.303(5), $b$=5.749(5), $c$=23.224(5) Å, $\beta$=96.938(5)°, $V$=2823(3) Å$^3$, $Z$=8, $D_c$=1.385 g cm$^{-3}$, $\mu$=0.240 mm$^{-1}$, 4159 reflections, 2479 independent, $R_{int}$=0.045, final $R1$=0.051, $wR2$=0.101 for $I>2\sigma I$. Compound **6**: $C_{15}H_{20}O_4S$, $M$=296.37, monoclinic, space group $P2_1/n$ (No. 14), $a$=12.0779(4), $b$=6.8349(3), $c$=18.0810(6) Å, $\beta$=100.280(3)°, $V$=1468.65(9) Å$^3$, $Z$=4, $D_c$=1.340 g cm$^{-3}$, $\mu$=0.231 mm$^{-1}$, 4729 reflections, 2559 independent, $R_{int}$=0.047, final $R1$=0.043, $wR2$=0.079 for $I>2\sigma I$. Compound **7**: $C_{15}H_{22}O_4$, $M$=266.33, monoclinic, space group $P2_1/c$ (No. 14), $a$=11.9269(4), $b$=7.2978(2), $c$=16.1536(5) Å, $\beta$=90.078(2)°, $V$=1406.01(7) Å$^3$, $Z$=4, $D_c$=1.258 g cm$^{-3}$, $\mu$=0.090 mm$^{-1}$, 7032 reflections, 2494 independent, $R_{int}$=0.036, final $R1$=0.039, $wR2$=0.084 for $I>2\sigma I$.
15. Chen, K.-M.; Hardtmann, G.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155.
16. Raney Nickel (W-2) was prepared according to the procedure in Vogel's textbook of Practical Organic Chemistry, 5th ed., p 451.
17. Otwinowski, Z.; Minor, W. Processing of X-ray Diffraction Data Collected in Oscillation Mode. In *Macromolecular Crystallography, Part A. Methoods in Enzymology*; Carter, C. W. Jr., Sweet, R. M., Eds.; Academic: New York, 1997; Vol. 276, p 307.
18. Sheldrick, G. M. *SHELXS-97, A program for Automatic Solution of Crystal Structures*; University of Göttingen: Germany, 1997.
19. Sheldrick, G. M. *SHELXS-97, A program for Crystal Structure Refinement*; University of Göttingen: Germany, 1997.