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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 is one of the most prominent members of the clinically important polyene macrolides. 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. Amphotericin B (AmB) has succumbed to total synthesis. 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 C(33)–C(37) fragment in 14 steps and in 16% overall yield. We have recently reported model studies on a diastereoselective synthesis of the tripropionate segment of Amphotericin B. 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 varying stereochemistry 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.

An enantioselective synthesis of the tripropionate fragment of Amphotericin B, shown in Scheme 1, is based on the thiopyran ring strategy, which has occasionally been used in the synthesis of polypropionates. 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 was reacted with the silyl enol ether of tetrahydrothiopyran-4-one 2 with the assistance of Lewis acid ZnCl2 giving the racemate in a good yield (Scheme 1). 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.

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. This strategy also worked in our case: the electrophilic orthoester derived from diethyl tartrate reacted with the silyl enol ether 2 and ZnCl2 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 1H NMR spectrum: the diastereomers have different 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 tartrate orthoester improved both the yield and diastereoselectivity. The reaction resulted in a mixture of two diastereomers in a ratio of 3 : 1 in 56% yield.
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), 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.

After the crucial aldol addition, the next task was a diastereoselective reduction of the ketone. Following a common literature procedure, 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).

The final reaction step in the enantioselective synthesis of the enantiomer of the tripropionate of AmB was reductive desulfurisation with Raney Nickel, 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 CaCl₂ and distilled from CaH₂. MeOH was distilled from Mg(OEt)₂. TMSCl was distilled from CaH₂ and stored under argon at room temperature. Diisopropylamine 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.

Preparation of the orthoesters

The orthoesters were synthesized following the procedure of Longobardo et al.¹⁰ 100 mol% of diol, 400–500 mol% of orthoformate and a catalytic amount of conc. HCl were distilled from Na/benzophenone and used without further purification.

Data for (4R,5R)-Di-isopropyl-2-methoxy-1,3-dioxolane-4,5-dicarboxylate 6. Transparent liquid; yield 81% [α]₂₀ [c = 1.0, CHCl₃] –29.5°; Rf 0.48 (30% MTBE–hexane); IR (film) 1739 cm⁻¹: δH (400 MHz, CDCl₃) 1.28–1.32 (12H, m, 2 × (CH₃)₂CH), 3.39 (3H, s, CH₃O), 4.64 (1H, d, OCHR, J 4.5), 4.95 (1H, d, OCHR, J 4.5). 5.05–5.17 (2H, m, 2 × (CH₃)₂CHO), 6.01 (1H, s, OCHR); δC (100 MHz, CDCl₃) 21.6, 21.7, 51.9, 69.9, 70.0, 76.0, 76.4, 117.7, 168.4, 168.5; HRMS m/z (ES+) calecd for C₇H₁₄O₃S 245.1025, found 245.1024. The crude product was purified by flash chromatography using 20% EtOAc–hexane as eluent.

Major diastereomer 3(S)–[4(R,5R)-Di-isopropylcarbonyl-1’,3’-dioxolane-2’-yl]-tetrahydro-thiopyran-4-one 7a. White solid; Mp 84 °C; [α]₀ [c = 1.0, CHCl₃] –21.5°; Rf 0.18 (30% MTBE–hexane); IR (film) 1750 cm⁻¹; δH (400 MHz, CDCl₃) 1.25–1.31 (12H, m, 2 × (CH₃)₂CH), 2.67–3.16 (7H, m, SCH₂CH₂, SCH₂CH), 4.64 (1H, d, OCHR, J 3.9), 4.68 (1H, d, OCHR, J 3.9), 5.05–5.17 (2H, m, 2 × (CH₃)₂CHO), 5.77 (1H, d, OCHR, J 3.9); δC (100 MHz, CDCl₃) 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+) calecd for C₅H₇O₂S 360.1243, found 360.1239.

Minor diastereomer 3(R)–[4(R,5R)-Di-isopropylcarbonyl-1’,3’-dioxolane-2’-yl]-tetrahydro-thiopyran-4-one 7b. Glassy crystals; Mp 89 °C; [α]₀ [c = 0.45, CHCl₃] –27.3°; Rf 0.18 (30% MTBE–hexane); IR (film) 1751 cm⁻¹; δH (400 MHz, CDCl₃) 1.28–1.32 (12H, m, 2 × (CH₃)₂CH), 2.69–3.23 (7H, m, SCH₂CH₂, SCH₂CH), 4.66 (2H, s, 2 × OCHR), 5.05–5.15 (2H, m, 2 × (CH₃)₂CHO), 5.69 (1H, d, OCHR, J 3.0); δC (100 MHz, CDCl₃) 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+) calecd for C₅H₇O₂S 360.1243, found 360.1245.

5(S)–[4(R,5R)-Di-isopropylcarbonyl-1’,3’-dioxolane-2’-yl]-4 Trimethylsilyloxy-thiopyran-3-one 8. HMDMS (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-ButLi (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 NaHCO₃–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 Na₂SO₄, 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; [α]₀ [c = 1, CHCl₃] –16.0°; Rf 0.49 (30% MTBE–hexane); IR (film) 1736, 1664 cm⁻¹; δH (400 MHz, CDCl₃) 0.20 (9H, s, SCH₂CH₂, 2.67–3.16 (7H, m, SCH₂CH₂, SCH₂CH), 4.64 (1H, d, OCHR, J 4.5), 5.05–5.17 (2H, m, 2 × (CH₃)₂CHO), 6.01 (1H, s, OCHR); δC (100 MHz, CDCl₃) 21.6, 21.7, 51.9, 69.9, 70.0, 76.0, 76.4, 117.7, 168.4, 168.5; HRMS m/z (ES+) calecd for C₅H₇O₂S 245.1025, found 245.1024.

Diastereoselective alkylation with L-tartrate derived orthoester 6

ZnCl₂ (0.99 g, 7.2 mmol, 200 mol%) was dissolved in 36 mL of CH₂Cl₂ 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 the NaHCO₃ (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 Na₂SO₄, 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.

Acetaldehyde (21 µL, 100 mol%) was dissolved in 3.5 mL of dry CH₂Cl₂ argon and the mixture was cooled with an acetone–dry ice bath (–78 °C). TiCl₄ (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 CH₂Cl₂ was added (the reaction mixture turned orange). After 5 minutes the reaction mixture was cannulated into ice-cold NaHCO₃–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 Na₂SO₄, 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 diastereomeric 9 was obtained in pure form.

Transparent oil; [α]D = 1.22 (c = 1, CHCl3) −10.6; Rf 0.17 (60% EtOAc–hexane); IR (film) 3436, 1735 cm−1; δH (400 MHz, CDCl3) 1.22 (3H, d, CH3CHOH, J 6.3); 1.29 (6H, d, (CH3)2CH, J 6.3). The mixture was stirred at 70 °C for 15 minutes before addition of NaBH4 (68 mg, 0.17 mmol) was dissolved in THF, 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 30 minutes. After the reaction mixture was filtered through Celite, the Celite pad was washed with EtOAc and the combined organic phase was dried over Na2SO4, filtered and the solvent was evaporated giving 191 mg of 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.

[α]D = 1.0 (c = 1, CHCl3) −52; Rf 0.23 (60% EtOAc–hexane); IR (film) 3367, 1734 cm−1; δH (400 MHz, CDCl3) 0.75 (3H, d, CH3CHOH, J 6.9); 1.03 (3H, d, CH3CHOH, J 7.1); 1.19 (6H, d, (CH3)2CH, J 6.3); 1.31 (6H, d, (CH3)2CH, J 6.3). 3.81–3.87 (1H, m, RCHOHCH3), 3.96 (1H, dd, RCHOH J 9.7, 1.0), 4.62 (1H, d, OCHRCOO, J 4.0), 4.71 (1H, d, OCHRCOO, J 4.0), 5.09–5.16 (2H, m, 2 × (CH3)2CHO), 5.27 (1H, d, OCHRCOO, J 3.6); δC (100 MHz, CDCl3) 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 calculated for C20H18O3Na 399.95, found 399.12.

Acknowledgements

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Notes and references

12 C13H16O3S.Crystal size 0.1 × 0.15 × 0.35 mm, monoclinic, P21, a = 5.254(2) Å, b = 12.375(1) Å, c = 14.238(1) Å, β = 97.688(1)°, V = 913.59(7) Å3, Z = 2, D = 1.310 g cm−3, µ = 0.210 mm−1, 2θmax = 50.08, 222 parameters, S = 1.021, R1 (I > 2σ(I)) = 0.0435, wR2 (I > 2σ(I)) = 0.1030. RI (all data) = 0.0553, wR2 (all data) = 0.1099, Absolute structure parameter −0.02(11), Extinction coefficient 0.0224, Å (min peak) = −0.3480×0.533 Å−1. CCDC reference number 215705. See http://www.ccdc.cam.ac.uk/suppdata/hobf3/b035045f/ for crystallographic data in cif or other electronic format.
13 According to H NMR.