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A convergent preparation of the C1–C13 fragment of amphotericin B from a single chiral precursor

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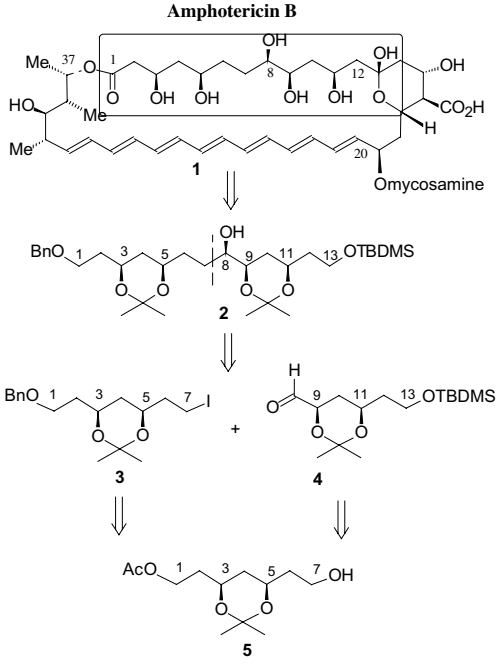
Abstract—A short, highly efficient, stereoconvergent synthesis of the polyolic chain, C1–C13, of the macrolide antibiotic amphotericin B is described. The key features of the synthesis are the use of a single chiral precursor for the establishment of the stereogenic centres in a short synthetic sequence, and the final alkyl lithium addition to the appropriate aldehyde, which showed high diastereoselectivity for the correct stereochemistry at the fifth stereogenic centre.

Extensive work on the polyene macrolide amphotericin B, a potent fungicide in clinical use[1] produced by *Streptomyces nodosus*, has led to three landmark total syntheses of this antibiotic.[2–4] In particular, the polyolic segment of its aglycon, amphoteronolide B, has been the target of synthetic organic chemists and several approaches to different long polyolic chains have been described.[2–5] The C1–C13 fragment is particularly useful since it has been already utilized for two total syntheses[2,4] and therefore its improved preparation remains an intriguing objective.

Our retrosynthetic analysis (see Scheme 1) was focused on the Nicolaou fully protected C1–C13 polyol **2**[2] with a hidden *plane of symmetry:* this compound **2** could be derived by the coupling of the two fragments **3** and **4** already possessing four of the five stereogenic centres. Both **3** and **4** can be eventually derived from a single chiral precursor such as **5**, possessing the 1,3-*syn* diol moiety required for both fragments **3** and **4**.

Compound **5** is a polyfunctional seven-carbon tetrol, which can be easily prepared[6] in both optically pure forms by an optimized eight-step procedure,[7] with the final biocatalytic desymmetrization of the corresponding *meso* compound as a key reaction. This desymmetrization with PSL (*Pseudomonas* sp. lipase) as catalyst has been carried out several times on a multigram scale, always with quantitative overall yield and with ee[6] values of more than 98%. This chiral synthon **5** has been already utilized for the preparation of the polyolic chain of other macrolide antibiotics such as the C1–C10[8] and C1–C13[9] fragments of nystatin A_1, as well as for mevinic acid analogues.[6]



Scheme 1. Retrosynthetic analysis.

Keywords: Amphotericin B; Polyols; Asymmetric synthesis; Diastereoselective addition.

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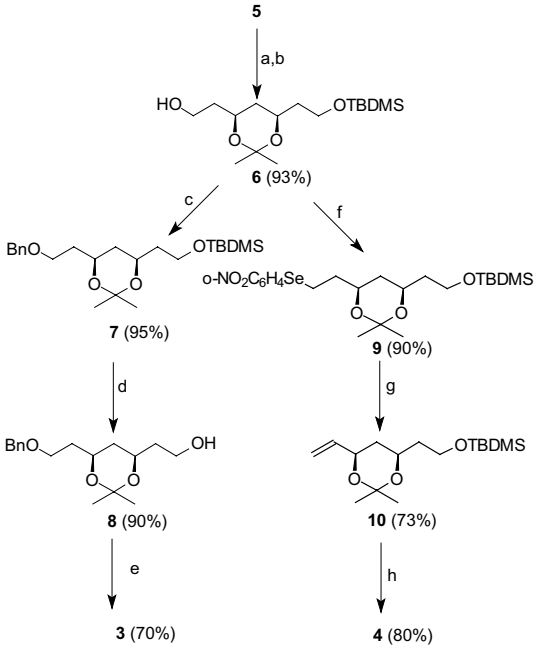


Scheme 2. Preparation of the synthons **3** and **4**. Reagents and conditions: (a) imid., TBSCI, DMAP, CH_2Cl_2, 0 °C, 20 h; (b) Na, CH_3OH, rt, 4 h; (c) BnBr, NaH, THF, rt, 48 h; (d) TBAF, THF, rt, 3 h; (e) I_2, Ph_3P, imid., toluene, 70 °C, 2 h; (f) *o*-$(NO_2)C_6H_4SeNC$, *n*-Bu_3P, THF, rt, 3 h; (g) H_2O_2, THF, rt, 4 h; (h) OsO_4, NMO/$NaIO_4$, THF/H_2O, rt, 12 h.

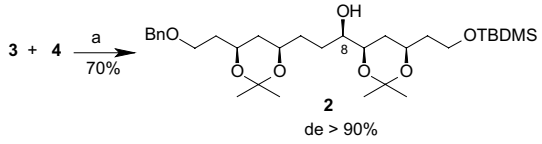
With a large quantity of the starting synthon **5** available, the synthetic sequences (see Scheme 2) were accomplished.

Firstly compound **5** was transformed in two steps (TBDMS introduction and then deacetylation) into the more conveniently functionalized compound **6**[10] in an overall 93% yield. This compound was then subjected to two different synthetic sequences to obtain the fragments **3** and **4**.

In the first sequence, **6** (see Scheme 2) was benzylated to compound **7**. Desilylation to compound **8** was followed by the introduction of the required iodine functionalization to give compound **3**, with an overall 66% yield (from **6**) and in 13 steps starting from commercially available compounds.[6,7] Compound **3** is the same synthon already prepared in the McGarvey total synthesis[4] by a longer sequence of steps compared to ours.

In the other sequence, the one-carbon shortening of compound **6** was achieved via a selenium oxide preparation (compound **9**) and then *syn* elimination to the olefin **10** (two steps with an overall 65% yield). The final six-carbon fragment **4** was then obtained via double bond oxidation to the required aldehyde: the aldehyde **4** is the same as the fragment prepared by Carreira and Krüger.[5e]

With the two fragments **3** and **4** in hand, we faced the coupling to give the desired target **2**, possibly with the direct introduction of the correct configuration at C-8.[11]



Scheme 3. Coupling reaction between **3** and **4**. Reagents and conditions: (a) *t*-BuLi, Et_2O, −78 °C, 30 min, $MgBr_2$, CuI, −78 °C, 2 h.

After several attempts to prepare different organometallic reagents in different solvents, the Li-derived fragment **3** (see Scheme 3) was successfully added, in the presence of $MgBr_2$ and CuI, to the aldehyde **4** to give[12] the single diastereoisomer **2**. Compound **2** showed an identical ^1H NMR spectrum and $[\alpha]_D^{25}$ +6.3° (*c* 0.30, $CHCl_3$) to the reported C1–C13 fragment (by Nicolaou et al.).[2a]

The success of the diastereoselective addition of **3**–**4**, could have been anticipated by considering the reaction conditions. In fact, it has already been reported in cases with a similar polyfunctional structure, for example, glyceraldehyde acetonide,[13] that the chelation of the Mg^{2+} between the carbonyl and an α-alkoxyl group allows an easier approach for the incoming nucleophile on one side of the C=O. As shown in Figure 1, the probable role of the Mg^{2+} is in chelating the aldehyde function and the protected hydroxy group in compound **3**, allowing the preferred approach of the alkylcopper complex to afford the required *syn*-diastereoisomer.

This synthesis of the C1–C13 fragment of amphotericin B, represents the shortest route to this key polyol, with a total of 17 steps starting from commercially available starting materials and with the use of simple reactions and easily available and cheap reagents. Furthermore four of the five stereogenic centres can be introduced via a well researched biocatalytic reaction to **5**. Finally the fifth stereogenic centre has been successfully introduced via a metal-chelated addition of the two fragments with a high diastereoselection in favor of the correct fragment **2**.

The further application of this chemistry to other related polyol fragments of complex molecules is under investigation.

Experimental procedure for the coupling reaction between **3** *and* **4**. To a stirred solution of **3** (0.100 g, 0.24 mmol) in ether (5 mL) at −78 °C under argon was added dropwise a solution 1.5 M in ether of *t*-BuLi (0.24 mL, 0.36 mmol). The resulting mixture was stirred for 30 min. After this period the mixture was cannulated into a solution of CuI (0.055 g, 0.29 mmol) in ether

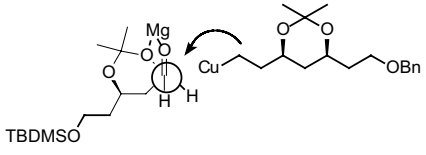


Figure 1.

(3 mL) and stirred for 10 min. A solution of **4** (0.048 g, 0.16 mmol) and $MgBr_2$ etherate (0.082 g, 0.32 mmol) in ether (2 mL) was cannulated therein and the reaction mixture was heated to room temperature for 2 h and quenched with aqueous NH_4Cl. The layers were separated and the aqueous layer was extract with ether. The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by chromatography (petroleum ether/EtOAc 7:3) on silica gel to provide the alcohol **2** (0.065 g, 70%) as an oil: $[\alpha]_D^{25}$ +6.3° (*c* 0.30, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) $\delta = 7.40$–7.30 (m, 5H), 4.51 (s, 2H), 4.10–3.36 (m, 9H), 2.70 (br s, 1H), 1.80–1.15 (m, 12H), 1.45 (s, 3H), 1.43 (s, 3H), 1.40 (s, 3H), 1.39 (s, 3H), 0.90 (s, 9H), 0.05 (s, 6H). Anal. calcd for $C_{32}H_{56}O_7Si$ (580.87): C, 66.17; H, 9.72. Found: C, 66.34; H, 9.66.

Acknowledgements

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7. Compound **5** was prepared in eight steps (47% overall yield) according to our previous report[6] with an increase in the yield of the corresponding γ-hydroxy-β-keto ester (above 70%), that was directly reduced to the 1,3-*syn* diol without any purification.
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10. The choice of the protecting groups was determined in order to obtain the known polyol fragment **2** for comparison with the reported data. The use of another protecting group sequence, leading to a differently protected C1–C13 fragment, would allow a shortcut of the synthetic sequence.
11. In all the described syntheses of the C1–C13 fragment of amphotericin B,[2a,4] the direct introduction of the OH group on the C-8, always gave an unsatisfactory diastereomeric ratio. Therefore all syntheses follow the Nicolaou original approach with the diastereoselective reduction of the corresponding ketone.
12. The diastereoisomeric ratio was determined, as reported in Ref. 2a, via ^1H NMR analysis on the acetyl derivative of compound **2**, which showed only a single detectable acetyl signal.
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