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Enantioselective Allyltitanation. Efficient Synthesis of the C1–C14 Polyol Subunit of Amphotericin B

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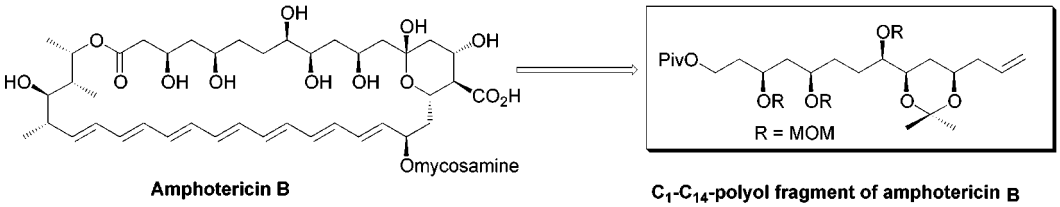
ABSTRACT



An efficient synthesis of the C_1–C_{14} fragment of amphotericin B is described. This synthesis is based on the formation of *syn*-1,3-diols from enantioselective allyltitanation of unprotected *β*-hydroxyaldehydes.

The polyene macrolide antibiotics have received considerable attention as a result of their selective cytotoxic properties.[1] Several of these compounds, most notably amphotericin B, have gained clinical prominence for treatment of systemic fungal infections.[2,3] As a consequence of the interest in the structural and biological features of the polyene macrolide antibiotics, they have become appealing targets for synthetic studies. Accordingly, a conspicuous synthetic challenge is found in the 1,3-polyol regions that are ubiquitous to this family of compounds. A feature of the polyol segment of amphotericin B compared to other macrolides is that it possesses a varied disposition of hydroxyl substituents (1,3-diols, 1,4-diols, and 1,2-diols). The only member of this family of macrolides that contains a similar pattern of hydroxyl substitution is surgumycin. The C2−C13 segment of amphotericin compares to the C18−C29 segment of surgumycin, and this could be a common fragment for their synthesis if the relative stereochemistry of the hydroxy groups is identical (Figure 1).

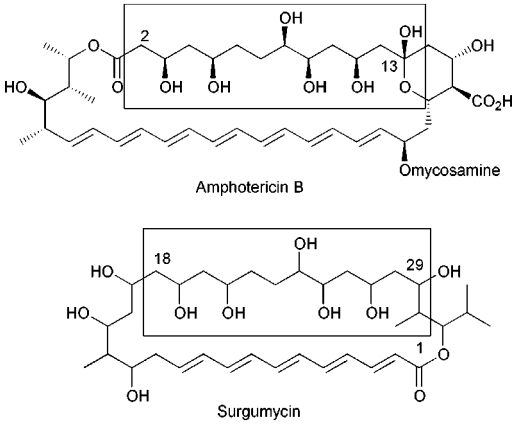


Figure 1.

Amphotericin B and its aglycon, amphoteronolide B, represent important synthetic targets, providing unique opportunities for the development of both new and existing synthetic technologies.[4,5] Recently, we described a direct method for obtaining 1,3-diols with excellent diastereomeric

(1) (a) Omura, S. *Macrolide Antibiotics*: *Chemistry, Biology, Practice*; Academic Press: New York, 1984. (b) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021. (c) Hunter, P. A. *Drug Discov. Today* **1996**, *1*, 227.
(2) Sarosi, G. A. *Postgrad. Med.* **1990**, *88*, 151.
(3) Sabra, R.; Branch, R. A. *Drug Safety* **1990**, *5*, 94.

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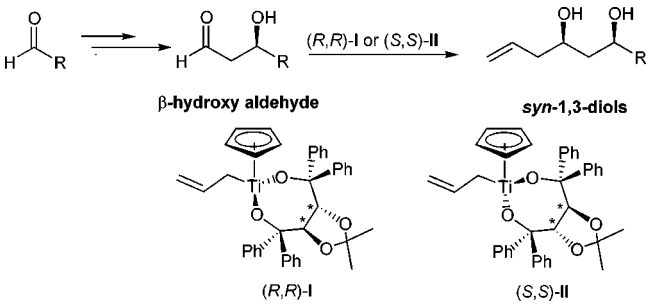
excess by the allyltitanation[6] of unprotected β-hydroxyaldehydes[7] (Scheme 1). This strategy was exploited to good

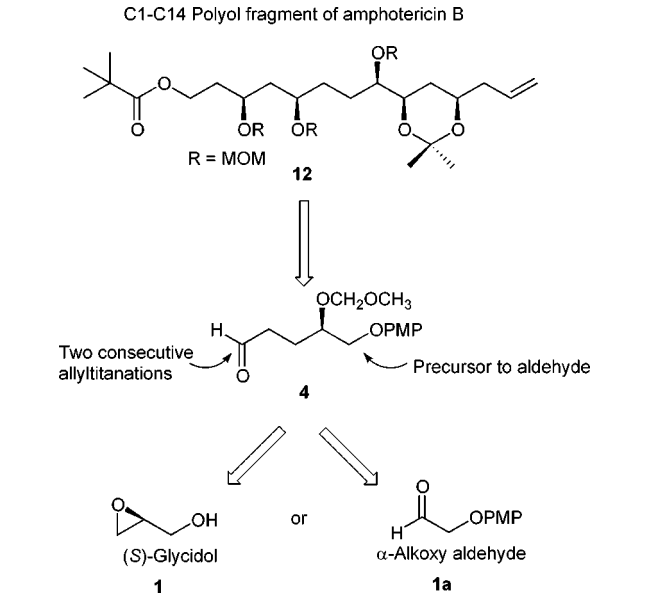
Scheme 1



advantage in our recently reported synthesis of lactone units of mevinolin and compactin.[8] Herein, we report an application of this approach for the construction of the C1−C14 fragment of amphotericin B.

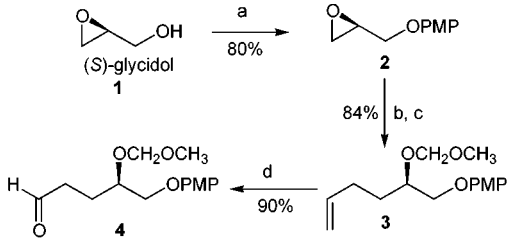
As shown in the retrosynthetic analysis of the C1−C14 fragment (acetonide) of amphotericin B, we envisioned the introduction of the desired C3, C5, C9, and C11 stereogenic centers through asymmetric allyltitanation starting from aldehyde **4**. The requisite aldehyde would be potentially available from (*S*)-glycidol or α-alkoxyaldehyde **1a** (Scheme 2).

Scheme 2



(*S*)-Glycidol **1** was transformed to the corresponding *p*-methoxybenzyl (PMP) derivative **2** (80%) by the Mitsunobu procedure. The epoxide ring of **2** was opened with allylmagnesium chloride in THF, and the resulting secondary alcohol was protected with methoxymethyl chloride to afford diether **3** (84% for two steps). The double bond was oxidized with aqueous osmium tetroxide/sodium periodate to afford the stable aldehyde **4**[9] in 90% yield (Scheme 3).

Scheme 3



a- p-$CH_3OC_6H_4OH$, PPh_3, DEAD, THF, 25 °C; b- AllylMgBr, THF, 0 °C
c- MOMCl, iPr_2NEt, CH_2Cl_2, 25 °C; d- OsO_4, NMO, acetone/H_2O, $NaIO_4$.

With the intermediate **4** available in enantiopure form and in high overall yield (60%), we turned our attention to the elaboration of the C1−C14 fragment of amphotericin B (Scheme 4). Enantioselective allyltitanation of aldehyde **4** with cyclopentadienyldialkoxyallyltitanium complex (*R*,*R*)-**I** gave homoallylic alcohol **5** in high yield (92%). The transfomation of this alcohol to the corresponding β-hydroxyaldehyde was achieved by the use of sodium periodate in the presence of 1.8 mol % of osmium tetroxide. This β-hydroxyaldehyde was immediately treated with allyltitanium complex (*R*,*R*)-**I** to deliver homoallylic 1,3-diol **6**[10]

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(5) (a) McGarvey, G. J.; Mathys, J. A.; Wilson, K. J.; Overly, K. R.; Buonora, P. T.; Spoors, P. G. *J. Org. Chem.* **1995**, *60*, 7778. (b) McGarvey, G. J.; Mathys, J. A.; Wilson, K. J. *J. Org. Chem.* **1996**, *61*, 5704. (c) Krüger, J.; Carreira, E. M. *Tetrahedron Lett.* **1998**, *39*, 7013.

(6) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, J.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321.

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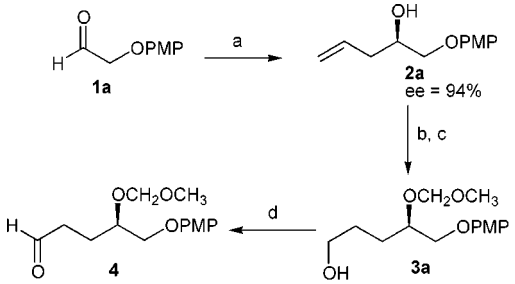
(8) BouzBouz, S.; Cossy, J. *Tetrahedron Lett.* **2000**, *41*, 3363.

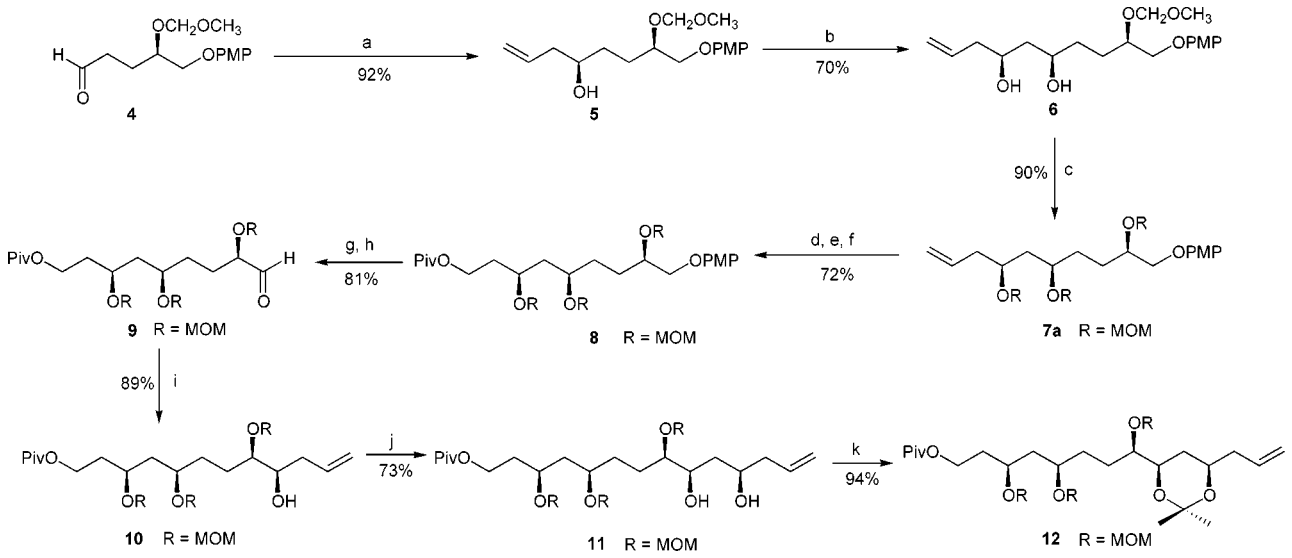
(9) Aldehyde **4** was prepared by an alternative method from the protected α-alkoxyaldehyde **1a** in high overall yield (69%):



a- (*S*,*S*)-**II**, ether, -78 °C, 91%; b- MOMCl, iPr_2NEt, CH_2Cl_2, 25 °C, 96%
c- 9-BBN, THF, NaOH, H_2O_2, 90% d- PCC, CH_2Cl_2, 25 °C, 88%.

(10) **Synthesis of 6.** A solution of **5** (0.124 g, 0.4 mmol, 1 equiv), *N*-methylmorpholine *N*-oxide hydrate (0.132 g, 0.68 mmol, 1.7 equiv), and OsO_4 (2.5% in *t*-BuOH, 0.07 mL, 7.23 10^{-3} mmol) in acetone (3 mL) and H_2O (1 mL) was vigourously stirred at 25 °C. After 20 min (TLC analysis showed complete consumption of the starting alkene), a solution of $NaIO_4$ (0.352 g, 2 mmol, 2 equiv) in H_2O (10 mL) was added, and stirring was continued for 30 min. The mixture was diluted with water and extracted with EtOAc (3 × 10 mL), and the combined organic phases were washed

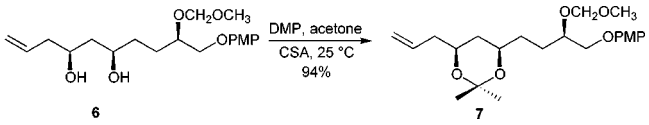
Scheme 4[a]



[a] (a) (*R*,*R*)-**I**, ether, −78 °C, 4 h; (b) (1) OsO_4, NMO, acetone/H_2O, $NaIO_4$, 25 °C, (2) (*R*,*R*)-**I**, ether, −78 °C, 4 h; (c) MOMCl, $^iPr_2NEt$, CH_2Cl_2, 25 °C; (d) OsO_4, NMO, acetone/H_2O, $NaIO_4$, 25 °C; (e) $NaBH_4$, MeOH, 0 °C; (f) PivCl, pyridine, 25 °C; (g) CAN, CH_3CN/H_2O, 30 min, 0 °C; (h) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, Et_3N, 25 °C; (i) (*S*,*S*)-**II**, ether, −78 °C, 4 h; (j) (1) OsO_4, NMO, acetone/H_2O, $NaIO_4$, 25 °C, (2) (*S*,*S*)-**II**, ether, −78 °C, 4 h; (k) DMP/acetone, CSA, 25 °C.

(70%) with high diastereoselectivity (dr = 97/3). The relative stereochemistry of the *syn*-1,3-diol **6** was determined by converting it to the corresponding acetonide **7** and by analyzing the ^{13}C NMR chemical shifts[11] (Scheme 5). As the acetonide of compound **7** is sensitive to ceric ammonium nitrate (CAN), compound **6** was transformed to **7a**, which was obtained by protection of diol **6** with MOMCl in the presence of Hunig's base in high yield (90%).

Scheme 5



The double bond of **7a** was then transformed to the protected ether **8** by oxidative cleavage (OsO_4, NMO; $NaIO_4$), reduction of the aldehyde with sodium borohydride in the presence of methanol at 0 °C, and protection of the alcohol with pivaloyl chloride in the presence of pyridine (72%, three steps).

Treatment of **8** with CAN in a biphasic mixture (CH_3CN/H_2O), followed by Swern oxidation, afforded the aldehyde **9** (81%). This compound was immediately treated with allyltitanium complex (*S*,*S*)-**II** to provide the secondary alcohol **10** (89%). Similarly, the transformation of homoallylic alcohol **10** to the corresponding β-hydroxyaldehyde and immediate treatment of the aldehyde with allyltitanium complex (*S*,*S*)-**II** gave the diol **11** (73%). The relative stereochemistry of the *syn*-1,3-diol was confirmed by ^{13}C NMR analysis of the acetonide **12**.[11,12]

In conclusion, we have described an efficient and stereoselective synthesis of the C1−C14 polyol fragment of amphotericin B that utilizes a versatile and rapid method for the formation of *syn*-1,3,-diol from β-hydroxy aldehydes, without any protective or deprotective steps.

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with brine, dried with $MgSO_4$, and concentrated under vacuum to furnished the crude hydroxyaldehyde (0.112 g). The crude hydroxyaldehyde was used immediately for the preparation of diol **6**. Allylmagnesium chloride in THF (0.195 mL of a 2 M solution, 0.388 mmol) was added dropwise over 5 min at 0 °C to a solution of (*R*,*R*)-**I** (0.285 g, 0.46 mmol) in ether (8 mL). After stirring for 90 min at 0 °C, the slightly orange suspension was cooled at −78 °C, and the crude aldehyde dissolved in ether (3 mL) was added dropwise over a period of 5 min. Stirring at −78 °C was continued for 4 h. The reaction mixture was then treated with water (10 mL), stirred for 14 h at 25 °C, filtered through Celite, and extracted twice with Et_2O (2 × 20 mL) and then with EtOAc (10 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated. Purification of the residue by silica gel chromatography (EtOAc/hexane 2/8) furnished 0.089 g of diol **6** (70% yield, calculated from the aldehyde). The Taddol ligand was recovered (75%).

(11) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945.

(12) **Data for acetonide 12:** ^1H NMR ($CDCl_3$, 300 MHz) 5.90−5.70 (m, 1H), 5.17−5.07 (m, 2H), 4.80−4.61 (m, 6H), 4.20−4.13 (m, 2H), 4.02−3.51 (m, 5H), 3.45 (3s, 9H), 2.41−2.10 (m, 2H), 2.02−1.40 (m, 10H), 1.47 (s, 3H), 1.37 (s, 3H), 1.20 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) 178.3 (s), 134.1 (d), 117.1(t), 98.5 (s), 96.9 (t), 95.6 (t), 95.5 (t), 79.8 (d), 74.5 (d), 71.9 (d), 70.9 (d), 68.5 (d), 61.0 (t), 55.7 (3q), 40.9 (t), 39.8 (t), 38.5 (s), 33.6 (t), 31.5 (t), 30.4 (t), 30.0 (q), 27.2 (q, *t*-Bu), 25.2 (t), 19.7 (q); MS (IE) *m*/*z* 534 (M^+), 533 (3), 427 (2), 353 (10), 323 (4), 287 (46), 257 (11), 155 (100), 97 (86), 79 (20), 57 (23).