

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

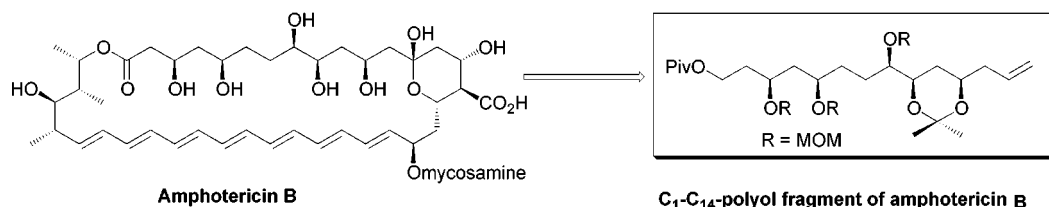
Samir BouzBouz\* and Janine Cossy\*

Laboratoire de Chimie Organique associé au CNRS, ESPCI, 10 rue Vauquelin,  
75231 Paris Cedex 05, France

janine.cossy@espci.fr

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## ABSTRACT



An efficient synthesis of the C<sub>1</sub>–C<sub>14</sub> fragment of amphotericin B is described. This synthesis is based on the formation of *syn*-1,3-diols from enantioselective allyltitanation of unprotected  $\beta$ -hydroxyaldehydes.

The polyene macrolide antibiotics have received considerable attention as a result of their selective cytotoxic properties.<sup>1</sup> Several of these compounds, most notably amphotericin B, have gained clinical prominence for treatment of systemic fungal infections.<sup>2,3</sup> 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).

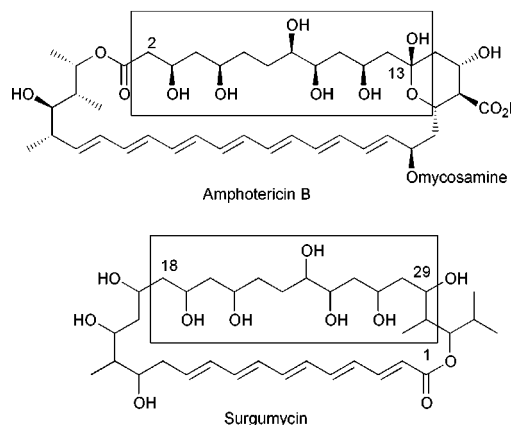


Figure 1.

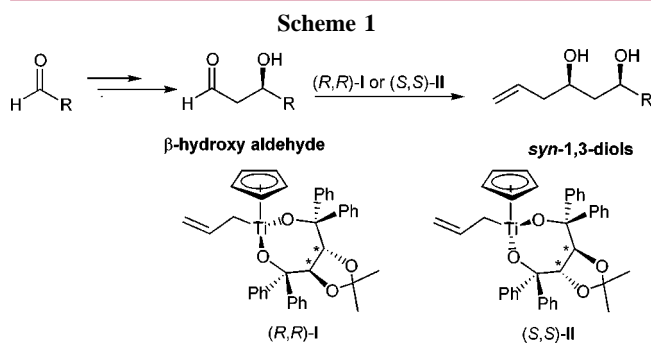
Amphotericin B and its aglycon, amphoteronolide B, represent important synthetic targets, providing unique opportunities for the development of both new and existing synthetic technologies.<sup>4,5</sup> Recently, we described a direct method for obtaining 1,3-diols with excellent diastereomeric

(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.

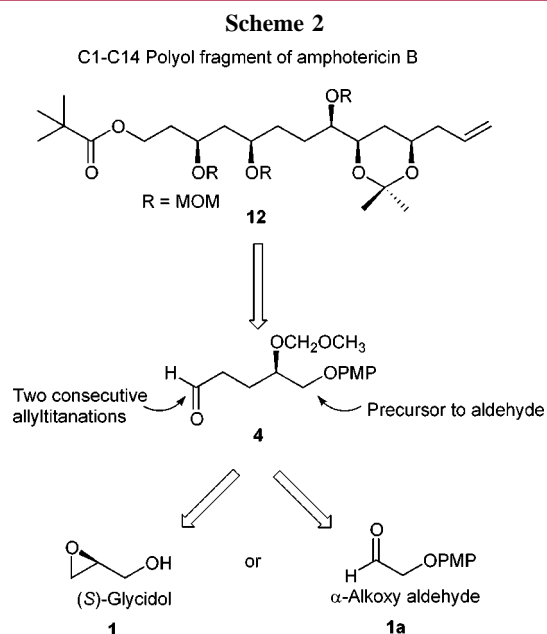
(3) Sabra, R.; Branch, R. A. *Drug Safety* **1990**, 5, 94.

excess by the allyltitanation<sup>6</sup> of unprotected  $\beta$ -hydroxy-aldehydes<sup>7</sup> (Scheme 1). This strategy was exploited to good



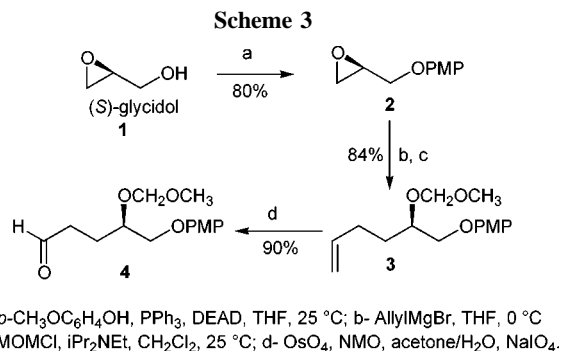
advantage in our recently reported synthesis of lactone units of mevinolin and compactin.<sup>8</sup> Herein, we report an application of this approach for the construction of the C1–C14 fragment of amphotericin B.

As shown in the retrosynthetic analysis of the C1–C14 fragment (acetone) 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  $\alpha$ -alkoxyaldehyde **1a** (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**<sup>9</sup> in 90% yield (Scheme 3).



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 transformation of this alcohol to the corresponding  $\beta$ -hydroxyaldehyde was achieved by the use of sodium periodate in the presence of 1.8 mol % of osmium tetroxide. This  $\beta$ -hydroxyaldehyde was immediately treated with allyltitanium complex (*R,R*)-I to deliver homoallylic 1,3-diol **6**<sup>10</sup>

(4) (a) Nicolaou, K. C.; Daines, R. A.; Uenishi, J.; Li, W. S.; Papahatjis, D. P.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1988**, *110*, 4672. (b) Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K.; Ogawa, Y. *J. Am. Chem. Soc.* **1988**, *110*, 4685. (c) Nicolaou, K. C.; Daines, R. A.; Ogawa, Y.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1988**, *110*, 4696. (d) Masamune, S.; Ma, P.; Okumoto, H.; Ellingboe, J. W.; Ito, Y. *J. Org. Chem.* **1984**, *49*, 2837.

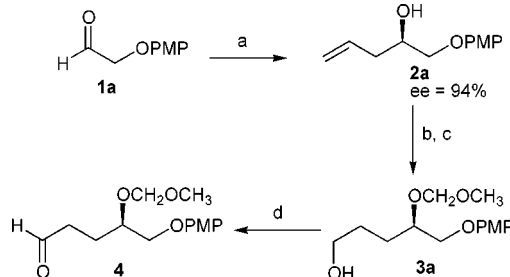
(5) (a) McGarvey, G. J.; Mathys, J. A.; Wilson, K. J.; Overly, K. R.; Buonora, P. T.; Spoors, P. G. *J. Org. Chem.* **1995**, *60*, 7778. (b) McGarvey, G. J.; Mathys, J. A.; Wilson, K. J. *J. Org. Chem.* **1996**, *61*, 5704. (c) Krüger, J.; Carreira, E. M. *Tetrahedron Lett.* **1998**, *39*, 7013.

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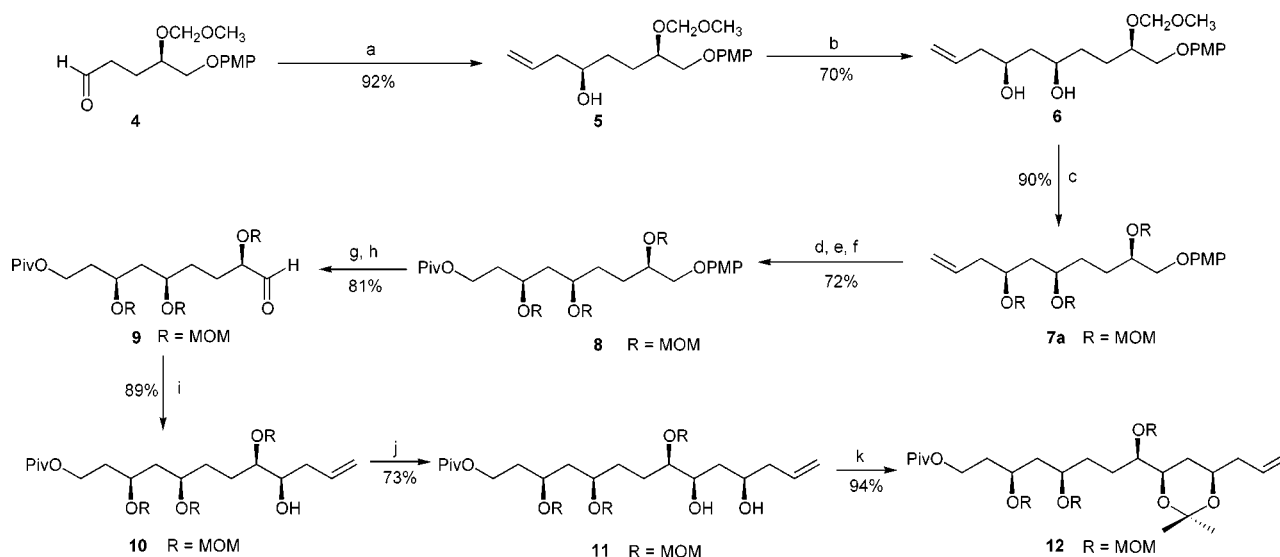
(7) BouzBouz, S.; Cossy, J. *Org. Lett.* **2000**, *2*, 501.

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

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



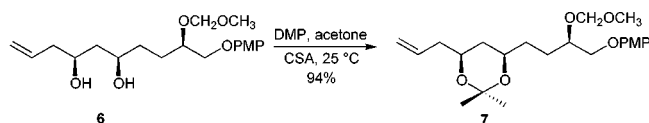
(10) **Synthesis of 6.** A solution of **5** (0.124 g, 0.4 mmol, 1 equiv), *N*-methylmorpholine *N*-oxide hydrate (0.132 g, 0.68 mmol, 1.7 equiv), and OsO<sub>4</sub> (2.5% in *t*-BuOH, 0.07 mL, 7.23  $\times 10^{-3}$  mmol) in acetone (3 mL) and H<sub>2</sub>O (1 mL) was vigorously stirred at 25 °C. After 20 min (TLC analysis showed complete consumption of the starting alkene), a solution of NaIO<sub>4</sub> (0.352 g, 2 mmol, 2 equiv) in H<sub>2</sub>O (10 mL) was added, and stirring was continued for 30 min. The mixture was diluted with water and extracted with EtOAc (3  $\times$  10 mL), and the combined organic phases were washed

Scheme 4<sup>a</sup>

<sup>a</sup> (a) (*R,R*)-**I**, ether,  $-78^{\circ}\text{C}$ , 4 h; (b) (1)  $\text{OsO}_4$ , NMO, acetone/ $\text{H}_2\text{O}$ ,  $\text{NaIO}_4$ ,  $25^{\circ}\text{C}$ , (2) (*R,R*)-**I**, ether,  $-78^{\circ}\text{C}$ , 4 h; (c) MOMCl,  $\text{Pr}_2\text{NEt}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $25^{\circ}\text{C}$ ; (d)  $\text{OsO}_4$ , NMO, acetone/ $\text{H}_2\text{O}$ ,  $\text{NaIO}_4$ ,  $25^{\circ}\text{C}$ ; (e)  $\text{NaBH}_4$ , MeOH,  $0^{\circ}\text{C}$ ; (f) PivCl, pyridine,  $25^{\circ}\text{C}$ ; (g) CAN,  $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ , 30 min,  $0^{\circ}\text{C}$ ; (h)  $(\text{COCl})_2$ , DMSO,  $\text{CH}_2\text{Cl}_2$ ,  $-78^{\circ}\text{C}$ ,  $\text{Et}_3\text{N}$ ,  $25^{\circ}\text{C}$ ; (i) (*S,S*)-**II**, ether,  $-78^{\circ}\text{C}$ , 4 h; (j) (1)  $\text{OsO}_4$ , NMO, acetone/ $\text{H}_2\text{O}$ ,  $\text{NaIO}_4$ ,  $25^{\circ}\text{C}$ , (2) (*S,S*)-**II**, ether,  $-78^{\circ}\text{C}$ , 4 h; (k) DMP/acetone, CSA,  $25^{\circ}\text{C}$ .

(70%) with high diastereoselectivity ( $\text{dr} = 97/3$ ). The relative stereochemistry of the *syn*-1,3-diol **6** was determined by converting it to the corresponding acetonide **7** and by analyzing the  $^{13}\text{C}$  NMR chemical shifts<sup>11</sup> (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 ( $\text{OsO}_4$ , NMO;

with brine, dried with  $\text{MgSO}_4$ , 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  $0^{\circ}\text{C}$  to a solution of (*R,R*)-**I** (0.285 g, 0.46 mmol) in ether (8 mL). After stirring for 90 min at  $0^{\circ}\text{C}$ , the slightly orange suspension was cooled at  $-78^{\circ}\text{C}$ , and the crude aldehyde dissolved in ether (3 mL) was added dropwise over a period of 5 min. Stirring at  $-78^{\circ}\text{C}$  was continued for 4 h. The reaction mixture was then treated with water (10 mL), stirred for 14 h at  $25^{\circ}\text{C}$ , filtered through Celite, and extracted twice with  $\text{Et}_2\text{O}$  ( $2 \times 20$  mL) and then with  $\text{EtOAc}$  (10 mL). The combined organic phases were washed with brine, dried over  $\text{MgSO}_4$ , and concentrated. Purification of the residue by silica gel chromatography ( $\text{EtOAc}/\text{hexane}$  2/8) furnished 0.089 g of diol **6** (70% yield, calculated from the aldehyde). The Taddoll ligand was recovered (75%).

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$\text{NaIO}_4$ ), reduction of the aldehyde with sodium borohydride in the presence of methanol at  $0^{\circ}\text{C}$ , 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 ( $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ ), 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  $\beta$ -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  $^{13}\text{C}$  NMR analysis of the acetonide **12**.<sup>11,12</sup>

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  $\beta$ -hydroxy aldehydes, without any protective or deprotective steps.

**Acknowledgment.** The authors are indebted to Dr. R. O. Duthaler for a generous gift of chiral cyclopentadienyl-dialkoxytitanium chloride complexes and C. Ferroud and A. Falguières for HPLC analysis.

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(12) **Data for acetonide 12:**  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 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);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) 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 ( $\text{M}^+$ ), 533 (3), 427 (2), 353 (10), 323 (4), 287 (46), 257 (11), 155 (100), 97 (86), 79 (20), 57 (23).