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Convergent Synthesis of the Amphotericin Polyol Subunit Employing Asymmetric Dienolate Addition Reactions

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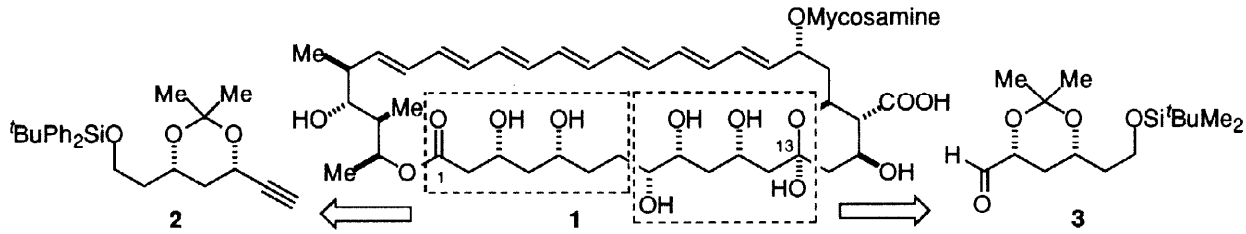
Abstract. We have described a convergent asymmetric synthesis of the polyol fragment of amphotericin B that utilizes a versatile dienolate aldol addition reaction of furfural to rapidly assemble the constituent polyol subunit. This strategy allows for the efficient synthesis of large quantities of the desired fragment while being inherently flexible to allow the construction of analogs. The synthesis of the C_1-C_{13} fragment of amphotericin requires only eleven steps and proceeds in 28% overall yield.

Keywords: aldol reactions, polyols, amphotericin, asymmetric reactions

Amphotericin B (**1**) is the drug of choice for antifungal chemotherapy in life-threatening infections. However, this prominent member of the polyene-macrolide antibiotics is poorly tolerated and elicits adverse symptoms.[1] With a rising number of fungal infections resistant to existing remedies, the necessity for developing analogs with fewer undesirable side-effects is increasing. Additionally, synthetic strategies that provide access to biologically active models to elucidate the mode of action of these natural products are needed.[2] Several total and partial syntheses of **1** have been completed to date.[3] Stereochemical control in the syntheses of the polyol subunit have primarily relied on either the use of starting materials from the chiral pool or optically active epoxyalcohols prepared with the Sharpless asymmetric epoxidation process.

Structural analysis of **1** reveals that segment C_1-C_{13} possesses a repeating stereoregular 1,3-diol motif that is interrupted only at C_7–C_8. This distinctive feature of the polyol subunit suggests a convergent synthesis strategy utilizing fragments **2** and **3** as coupling partners. Importantly, the latent symmetry in these allows for the preparation of both from enantiomeric precursors. In this communication we report the implementation of such a strategy leading to a convergent and efficient synthesis of the amphotericin C_1–C_{13} polyol fragment.



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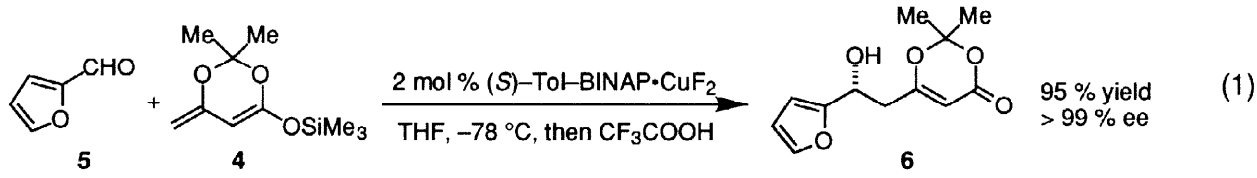
We have recently developed a catalytic, enantioselective process utilizing a Tol-BINAP•CuF_2 complex generated *in situ* that effects the aldol addition of dienolate **4** to a broad range of aldehydes in up to 98% yield and 95% ee (Eq 1).[4] In particular, the dienolate aldol adduct **6** is an attractive chiral building block for synthesis as a consequence of the ready availability of furfural ($ 0.02/gram) and the well-known chemistry of the aromatic heterocycle.[5] For example, oxidation of the electron-rich furan ring provides the corresponding carboxylic acid. As a test of the utility of adducts such as **6** and a demonstration of the versatility and experimental practicality of the aldol process, we embarked on a synthetic study leading to the convergent construction of the amphotericin polyol.

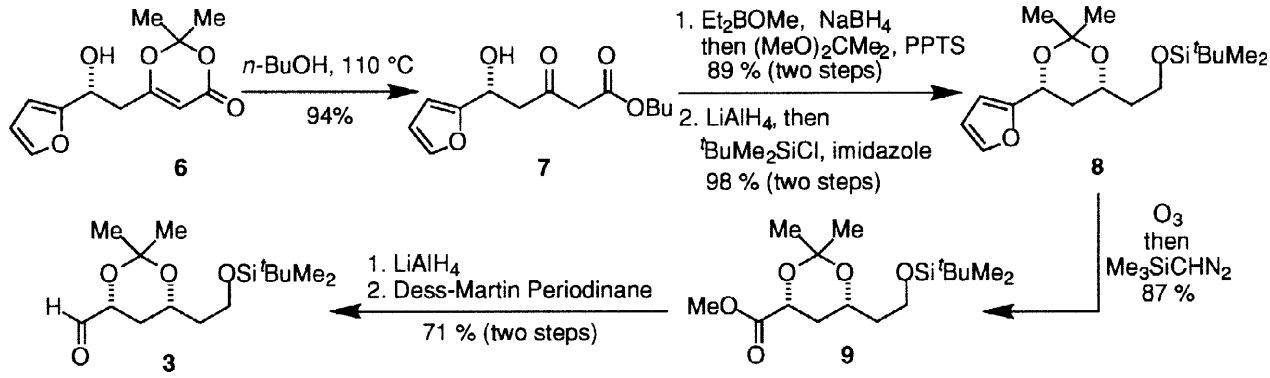
The aldol addition of TMS-dienolate **4** to furfural (**5**) can be readily conducted on a multi-gram scale utilizing as little as 2 mol% catalyst to furnish aldol adduct **6** in 94% ee (Eq 1). We have observed that the dienolate adducts bearing the dioxenone moiety have a tendency to be crystalline and allow for ease of enantiomeric enrichment. Therefore, a single crystallization from hexanes/ether (1:3) furnished optically pure material **6** (>99 % ee by HPLC) in 95% yield.[6]



5 **4** **6**

The synthesis of the C_8–C_{13} fragment of amphotericin commenced with the conversion of **6** to the corresponding *n*–butyl ester **7** in 94% yield by heating in *n*–BuOH (Scheme 1).[7] The desired 1,3-syn-diol was installed through a diastereoselective reduction of **7** employing the method of Prasad ($NaBH_4$, Et_2BOMe, THF, –78 °C)[8] and protected as an acetonide by treatment with dimethoxypropane and PPTS (89 %, two steps). Analysis of the unpurified acetonide by ^1H NMR spectroscopy revealed that the *syn* diastereomer had been formed exclusively in the reduction of hydroxy keto ester **7**. Treatment of the protected diol with $LiAlH_4$ afforded a primary alcohol which was subsequently silylated with $^tBuMe_2SiCl$ and imidazole to afford **8** in 98 % yield (two steps). Oxidative cleavage of the furan was readily effected upon exposure of **8** to ozone (–78 °C, CH_2Cl_2/MeOH 1:1) to give a carboxylic acid which, without isolation, was esterified upon treatment with Me_3SiCHN_2 to furnish ester **9**.[9] Conversion of ester **9** to the corresponding aldehyde was carried out by reduction with $LiAlH_4$ followed by oxidation with the Dess-Martin periodinane reagent (71%, two steps).[10]

Scheme 1

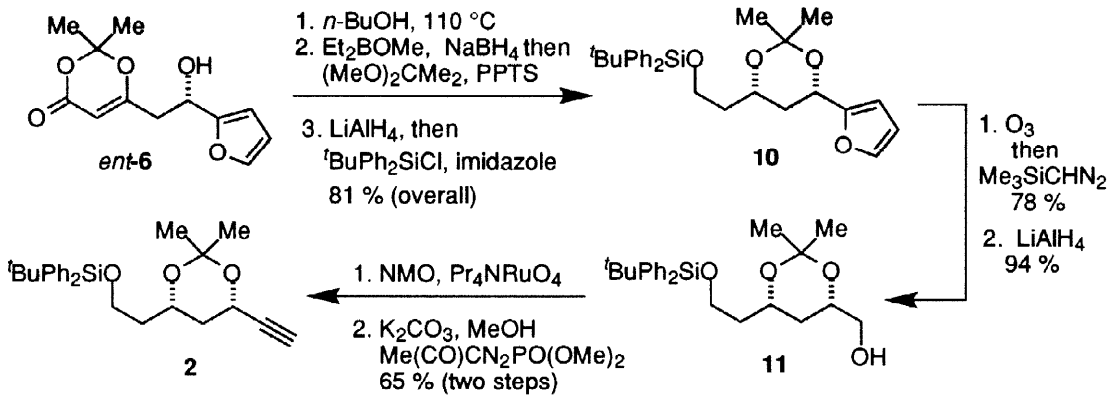


6 **7** **8** **9** **3**

The enantiomeric furan-dienolate adduct, *ent*-**6**, obtained by employing the (*R*)–Tol–BINAP•CuF_2 complex under otherwise identical conditions to those described above, was used for the construction of the C_1–C_7 polyol subunit of **1**. Following a sequence of transformations analogous to those discussed for **6**, acetonide

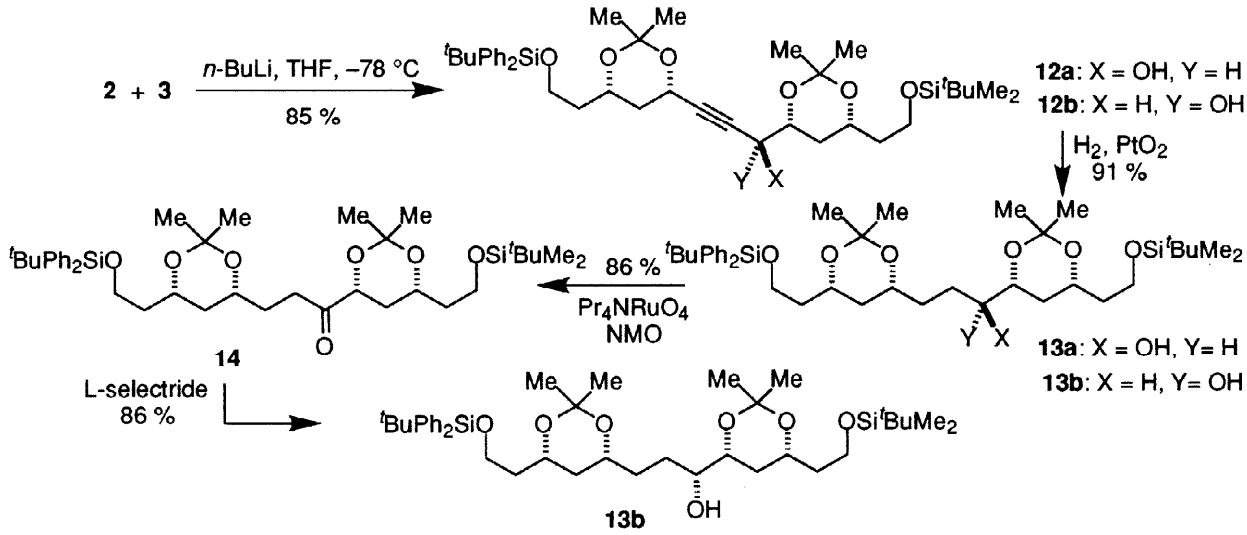
10 was isolated in 81% overall yield from *ent*–**6**. Treatment of this substituted furan with ozone followed by reduction of the isolated ester with $LiAlH_4$ provided **11** in 94% yield. This primary alcohol was oxidized to the corresponding aldehyde which was transformed without purification to alkyne **2** using the ketophosphonate reagent recently described by Bestmann (65%, two steps). [11,12]

Scheme 2



With both fragments in hand, we next examined the coupling of **2** and **3**, establishing the fully funtionalized backbone of the polyol subunit (Scheme 3). Lithiation of alkyne **2** (*n*–BuLi, –78 °C, THF) and addition to aldehyde **3** at –78 °C in THF produced propargyl alcohol **12a/12b** in 85% yield as a 78:22 mixture of diastereomers. Hydrogenation of this mixture (PtO_2, H_2) afforded the saturated secondary alcohol **13a/13b** in 91% yield. Stereochemical assignment was possible by ^1H NMR analysis of **13a/13b** and comparison of the spectra to that of similarly functionalized polyol fragments that have been reported in other synthetic routes. This study revealed that the predominant adduct formed in the alkyne addition step was the unnatural diastereomer of the desired amphotericin polyol fragment **12a**. Nevertheless, the hydroxyl stereocenter could be installed with the requisite stereochemistry by oxidation of the mixture of **13a/13b** ($Pr_4N(RuO_4)$, NMO) and subsequent reduction with L–selectride following Nicolaou's procedure.[3a] This protocol afforded **13b** in 86% yield as a single stereoisomer as determined by ^1H NMR spectroscopy.

Scheme 3



In summary, we have described a convergent asymmetric synthesis for the polyol fragment of amphotericin B that utilizes a versatile dienolate aldol addition of TMS-dienolate **4** to furfural (**5**) to rapidly

assemble the target molecule **13**. This strategy allows for the efficient synthesis of large quantities of the desired fragment while being inherently flexible to allow the construction of analogs. Moreover, the synthesis of the polyol subunit **13** requires only eleven steps and proceeds in 28% overall yield.

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(6) The procedure for addition of **4** to furfural: a mixture of $Cu(OTf)_2$ (217 mg, 0.60 mmol, 2 mol%) and (*S*)-Tol-BINAP (475 mg, 0.70 mmol, 2.1 mol%) in 150 mL THF was stirred at 23 °C for 15 min giving a clear yellow solution. A solution of $(Bu_4N)Ph_3SiF_2$ (647 mg, 1.20 mmol, 4 mol%) in 5 mL THF was then added and stirring was continued for 10 min. After cooling the mixture to –78 °C a solution of the TMS-dienolate **4** (8.00 g, 37.0 mmol) in 10 mL THF was added dropwise followed by a solution of furfural (2.49 mL, 30.0 mmol) in 5 mL THF. The solution was stirred at –78 °C for 4 hr. Trifluoroacetic acid (5 mL) was added and the cooling bath was removed. After 5 min, 5 mL water was added and the mixture was allowed to reach 23 °C during which time the progress of the desilylation was monitored by thin layer chromatography. Upon completion, the mixture was diluted with 50 mL ether; the organic solution was repeatedly washed with a 0.5 M aq NaOH solution until the extracts reached pH 7. The combined aqueous solutions (ca. 100 mL) were extracted with 200 mL ether. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The unpurified material was filtered through a short plug of silica using a 3:1 mixture of ether/hexanes as eluent. The resulting yellow oil was redissolved in 30 mL of ether/hexanes (3:1) and, after adding several seed crystals, was stored at 0 °C for several hours. The resulting white needles were filtered off, washed with hexanes and dried *in vacuo* to yield 5.75 g (24.2 mmol) of adduct **6**. A second crop of crystals (1.04 g, 4.40 mmol) could be obtained. The combined 6.79 g (26.6 mmol, 95%) of **6** proved to be >99% ee as determined by HPLC: OD CHIRALCEL column, hexanes/isopropanol 80:20, flow rate 0.8 mL/min, major enantiomer 8.3 min, minor enantiomer 10.0 min. mp (not corrected) 52 °C; $[\alpha]_D^{25}$ +27.8° (*c* = 0.46, $CHCl_3$); IR (thin film) ν 3406, 3000, 1711, 1632, 1392, 1378, 1277, 1203, 1146, 1014, 906, 810, 744; ^1H NMR (300 MHz, $CDCl_3$) δ 1.61 (s, 3H), 1.65 (s, 3H), 2.56 (s, broad, 1H), 2.77 (m, 2H), 4.98 (t, *J* = 7.4, 1H), 5.30 (s, 1H), 6.27 (d, *J* = 3.2, 1H), 6.32 (dd, *J* = 1.8, 3.2, 1H), 7.37 (d, *J* = 1.7, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.7, 25.1, 39.8, 64.4, 95.4, 106.7, 142.4, 154.7, 161.2, 167.9; HRMS (CI) calcd for $C_{12}H_{15}O_5$ $(M+H)^+$ 239.0919, found 239.0916; anal. calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92; found: C, 60.30; H, 5.99.

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