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Alternative total synthesis of (+)-aspicilin

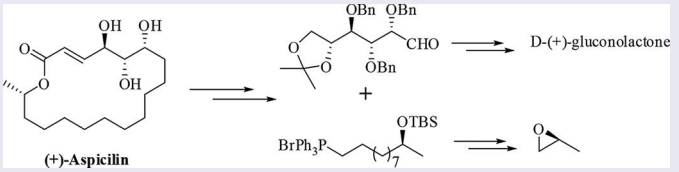
Sridhar Musulla[a,b], Bharathi Kumari Y[b], Mahesh Madala[a,b], Srinivasa Rao A[a], and Vema Venkata Naresh[a,b]

[a]Medicinal Chemistry Laboratories, GVK Biosciences Private Limited, Hyderabad, Telangana, India; [b]Department of Chemistry, JNT University, Hyderabad, Telangana, India

ABSTRACT

The total synthesis of an 18-membered polyhydroxylated macrolide (+)-Aspicilin was accomplished starting from commercially available enantiopure propylene oxide and D-(+)-gluconolactone by asymmetric synthetic approach. The key reactions involved are Witttig reaction, Sharpless asymmetric dihydroxylation, and Yamaguchi macrolactonization.

GRAPHICAL ABSTRACT



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Aspicilin; *S*-propylene oxide; sharpless asymmetric dihydroxylation and Yamaguchi macrolactonization; witttig olefination

Introduction

Polyhydroxylated macrolides[1] are interesting synthetic targets to many synthetic chemists due to their interesting structure and potential biological activities, including inhibition of cholesterol biosynthesis[2–5] and microfilament formation,[1b] antimalarial and antibacterial activity,[6,7] and phytotoxicity.[1c]

Aspicilin (**1**), an 18-membered polyhydroxylated macrolide, was isolated from lichen of the *Lecanoraceae* family in 1900 by Hesse.[8] The absolute configuration of Aspicilin (**1**) was determined as 4 R,5S,6 R,17S by a combination of various spectroscopic methods, single-crystal X-ray analysis, and synthetic studies.[9] The impressive structural features of Aspicilin (**1**), (four stereocenters in which three contiguous stereocenters (4 R,5S,6 R) and an 18-membered macrolactone ring) appeared to be an attractive target molecule for total synthesis. To date, several synthetic approaches have been reported for the total synthesis of Aspicilin **1** (Fig. 1).[10]

In continuation of our interest on the total synthesis of biologically active natural products,[11] we herein disclose our successful synthetic approach toward the total synthesis of **1** utilizing the Witttig reaction, Sharpless asymmetric dihydroxylation, and Yamaguchi macrolactonization as the key steps.

CONTACT Sridhar Musulla sm1org@rediffmail.com GVK Biosciences Private Limited, Nacharam, IDA Mallapur, Hyderabad, Telangana 500076, India; Department of Chemistry, JNT University, Hyderabad, Telangana 500082, India.
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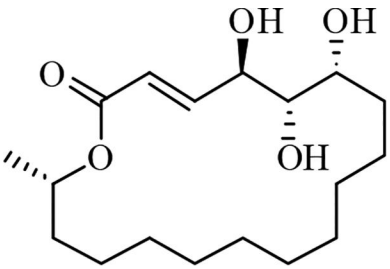
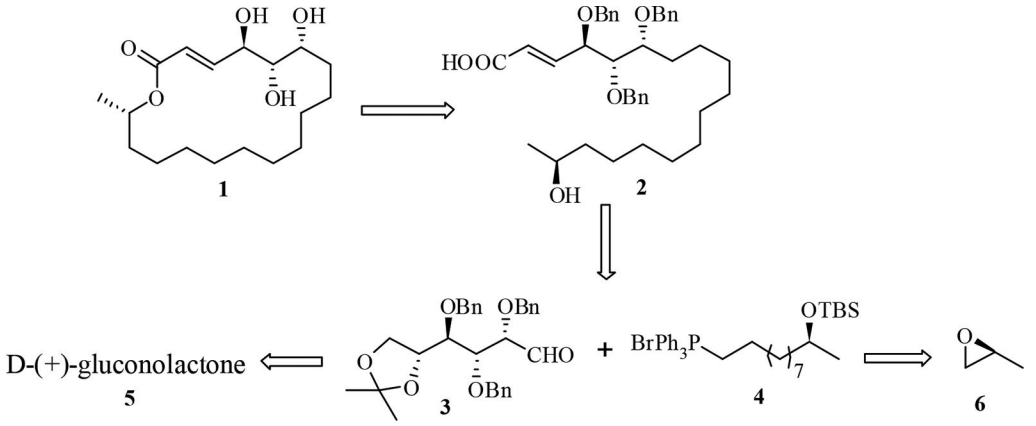


Figure 1. Structure of (+)-Aspicilin (**1**).

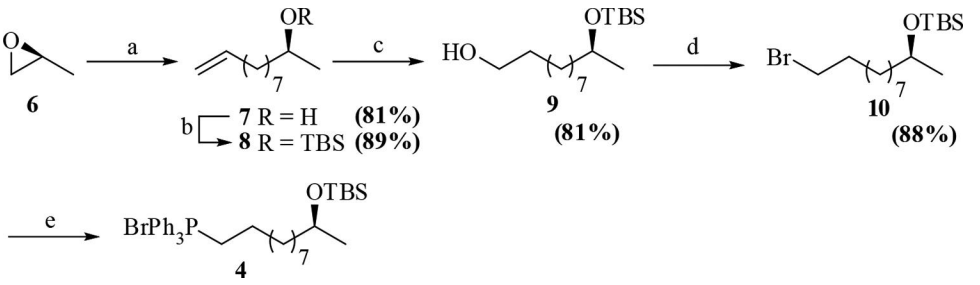
Results and discussion

Our retrosynthetic approach for the synthesis of Aspicilin is outlined in Scheme 1. The target molecule **1** could be made from hydroxy acid **2** by intramolecular Yamaguchi macrolactonization, whereas 2 could be synthesized from the coupling reaction of two key fragments aldehyde **3** and phosphonium salt **4**. Aldehyde **3** could be obtained from cheap and commercially available D-(+)-gluconolactone **5** and **4** was achieved from known chiral epoxide **6**.

Thus, the synthesis of (+)-Aspicilin **1** mainly involved the synthesis of two key fragments aldehyde **3** and phosphonium salt **4** followed by their coupling into the target molecule. First, our synthesis begins with the preparation of key fragment phosphonium salt **4**, which was shown in Scheme 1. Accordingly, opening of known chiral epoxide **6** with oct-7-enylmagnesium bromide (prepared from 1-bromooctene and Mg in THF) in the presence of CuCN in THF at −15 °C to rt furnished allyl alcohol **7** in 81% of yield. Subsequent Silyl ether formation of resulting alcohol **7** using TBSCl in the presence of Imidazole in CH_2Cl_2 at 0 °C to rt for 6 h provided **silyl** ether **8** in 89% of yield. Next, Silyl ether **8** was subjected to hydroboration with 9-BBN-H followed by treatment with sodium hydroxide and H_2O_2 to give alcohol **9** in 81% yield. Treatment of alcohol **9** with CBr_4 and PPh_3 in CH_2Cl_2 at 0 °C to rt for 4 h gave



Scheme 1. Retroanalysis of (+)-Aspicilin (**1**).



Scheme 2. Synthesis of fragment **4.** *Reagents and conditions*: (a) 1-bromooctene, Mg, CuCN, THF, reflux to −15 °C, 7 h; (b) TBSCl, imidazole, CH_2Cl_2, 0 °C to rt, 6 h; (c) i) 9-BBN, THF, **reflux**, 3 h ii) NaOH, H_2O_2, rt, 12 h; (d) CBr_4, PPh_3, CH_2Cl_2, 0 °C to rt, 12 h; (e) PPh_3, CH_3CN, 90 °C, 24 h, quantitative.

bromide **10** in 88% yield, which was later converted into corresponding phosphonium salt **4** using PPh_3 in CH_3CN at 90 °C for 24 h in quantitative yield (Scheme 2).

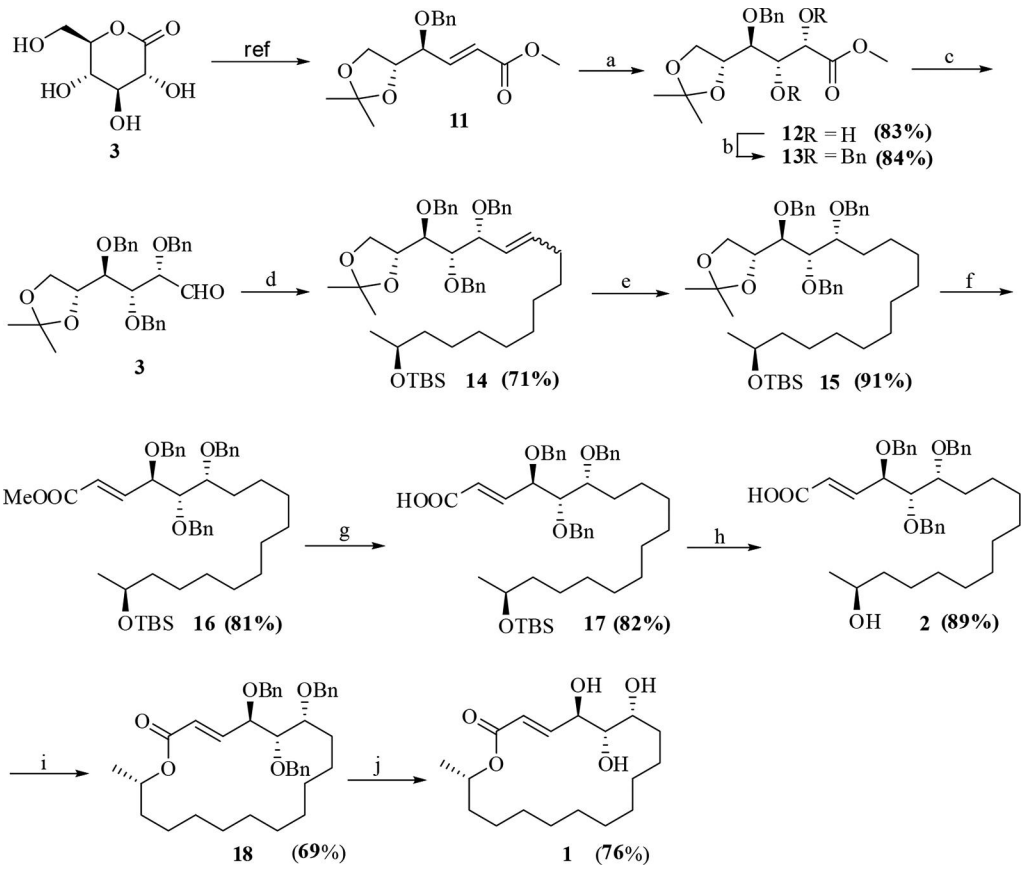
After successful synthesis of phosphonium salt **4**, we next focused on another key fragment aldehyde **3** followed by its coupling with phosphonium salt **4 lead to** the target molecule. Accordingly, commercially available D-(+)-gluconolactone **5** was converted into *trans*-ester **11** according to a known procedure.[12] Consequently, ester **11** was subjected to Sharpless asymmetric dihydroxylation[13] with AD-mix-β in *t*-BuOH-H_2O (1:1) at 0 °C for 22 h to give corresponding diol **12** in 83% yield as a single diastereomer. In the next step, the newly formed hydroxy groups in the resulting diol **12** were protected as its benzyl ethers using BnBr in the presence of NaH in THF at 0 °C to rt for 8 h to give tri-benzyl ether **13** in 84% yield. Treatment of the methyl ester in **13** using DIBAL-H gave an aldehyde **3** in 82% yield, which upon Wittig reaction with phosphonium salt **4** using NaHMDS in THF at 0 to −78 °C furnished isomeric mixture of **olefin 14** in 81% of yield. Next, the olefin mixture **14** was subjected to partial **hydrogenation** with 5% Pd-C in ethyl acetate to afford saturated compound **15** in 91% yield, which on treatment with H_5IO_6 in Et_2O at rt followed by a Wittig olefination of resulting aldehyde afforded the exclusively *trans* ester **16** in 81% yield (Scheme 3).

Later, Ester **16** was subjected to base (LiOH) hydrolysis in THF:MeOH:H_2O (3:1:1) to afford the corresponding acid **17**, which on desilylation with TBAF in THF at 0 °C to room temperature for 3 h afforded hydroxy acid **2** in 89% yield. After successful synthesis of hydroxyl acid fragment **2**, it was then focused at macrolactonization and further transformations to complete the synthesis of Aspicilin **1**. Accordingly, **hydroxy**-acid **2** was subjected to macrolactonization under Yamaguchi high dilution conditions[14] ((i) 2,4,6-trichlorobenzoyl chloride, Et_3N, dry THF, rt, 2 h; ii) DMAP, toluene, 90 °C) to provide the lactone **18** in 69% yield. In the final step, deprotection of three benzyl ethers in lactone **18 was** removed successfully in a single step using $TiCl_4$ at 0 °C to r.t to afford Aspicilin **1** [m.p. 151–153 °C. $[\alpha]_D^{25} = +36.8$ (*c* 0.6, $CHCl_3$) in 76% yield. The characterization (^1H and ^{13}C NMR spectroscopy and optical rotation) of our synthetic sample was identical to the literature data.

Experimental section

(5R,6S,7R,18S,E)-5,6,7-tris(benzyloxy)-18-methyloxacyclooctadec-3-en-2-one (18)

To a stirred solution of **2** (0.38 g, 0.61 mmol) and Et_3N (0.26 mL, 1.83 mmol) in dry THF (3 mL), a solution of 2, 4, 6-trichlorobenzoyl chloride (0.22 mL, 0.91 mmol) in



Scheme 3. Synthesis of (+)-Aspicilin (**1**). *Reagents and conditions*: (a) AD-mix-β, $MeSO_2NH_2$, *t*-BuOH-H_2O, 0 °C, 22 h; (b) BnBr, NaH, THF, 0 °C to rt, 8 h; (c) DiBAL-H, -78 °C, CH_2Cl_2, 2 h; (d) **4**, NaHMDS, THF, 0 °C, then −78 °C, 6 h; (e) H_2, Pd/C, EtOAc, rt, 3 h; (f) i) H_5IO_6, Et_2O, 0 °C to rt, 5 h. Ii) Ph_3P=CHCOOMe, Benzene, reflux, 2 h; (g) LiOH, THF:MeOH:H_2O (3:1:1), rt, 4 h; (h) TBAF, THF, 0 °C to rt, 3 h; (i) i) 2,4,6-trichlorobenzoyl chloride, Et_3N, dry THF, rt, 2 h, ii) DMAP, toluene, 90 °C, 10 h; (j) $TiCl_4$, 0 °C to rt, 2 h.

dry THF (1 mL) was added. The resulting mixture was stirred for 2 h at room temperature under nitrogen atmosphere and evaporated to afford the mixed anhydride. It was diluted with toluene (10 mL) and filtered quickly through celite. The filtrate was added dropwise to a stirred solution of DMAP (0.07 g, 0.61 mmol) in toluene (490 mL) (total volume used for this operation was 500 mL) at 90 °C over a period of 8 h. After the complete addition, the reaction mixture was stirred at same temperature for 2 h. It was cooled; washed with 7% aq $NaHCO_3$ (40 mL), 2 M aqueous HCl (40 mL), brine (40 mL); and dried (Na_2SO_4). The organic layer was evaporated and the obtained residue was purified by column chromatography (silica gel, 60–120 mesh, 15% EtOAc in pet. ether) to give **18** (0.24 g, 69%) as a syrup. $[\alpha]_D^{25}$ -10.6 (*c* 0.56, CH_2Cl_2); IR (neat): 2931, 2851, 1719, 1649, 1455, 1366, 1166, 1067 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 7.34–7.21 (m, 15H, ArH), 7.12 (dd, 1H, $J = 8.3$, 16.1 Hz, olefinic), 6.01 (d, 1H, $J = 16.1$ Hz, olefinic), 4.99 (m, 1H, benzylic), 4.88 (d, 1H, $J = 14.49$ Hz, benzylic), 4.66 (d, 1H, $J = 14.49$ Hz, benzylic), 4.64 (d, 1H, $J = 11.25$ Hz, benzylic), 4.57 (d, 1H, $J = 11.91$ Hz, benzylic), 4.39 (d, 1H, $J = 11.25$ Hz, benzylic), 4.32

(d, 1H, 11.91 Hz, –OCH), 4.12 (d, 1H, $J = 8.61$ Hz, –OCH), 3.84 (dd, 1H, $J = 1.05$, 8.61 Hz, –OCH), 3.31 (m, 1H, –OCH), 1.62–0.99 (m, 23H, 10 x $-CH_2$, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.5, 144.0, 138.8, 138.7, 138.1, 128.5, 128.4, 128.1, 128.0, 127.9, 127.7, 127.53, 127.1, 125.4, 84.3, 79.6, 78.8, 74.3, 74.2, 71.1, 70.6, 35.4, 31.0, 29.2, 28.2, 28.0, 27.4, 26.7, 26.5, 25.8, 23.2, 20.1; HRMS (ESI): *m/z* calculated for $C_{39}H_{50}O_5Na$ $[M+Na]^+$ 621.3556, found 621.3559.

(+)-Aspicilin (1)

To a stirred solution of **18** (0.2 g, 0.33 mmol) in CH_2Cl_2 (1 mL), $TiCl_4$ (0.15 mL, 1.33 mmol) in CH_2Cl_2 (1 mL) was added at 0 °C and stirred at room temperature for 2 h. The reaction mixture was treated with saturated $NaHCO_3$ solution (5 mL) and extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were washed with water (10 mL), brine (10 mL) and dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (silica gel, 60–120 mesh, 30% EtOAc in pet. ether) to afford **1** (82 mg, 76%) as a colorless syrup, $[\alpha]_D^{25} + 35.8$ (*c* 0.9, CH_2Cl_2); m.p.: 151–153 °C; IR (neat): 3444, 3277, 2928, 2854, 1709, 1649, 1455, 1366, 1245, 1163, 1075 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.91 (dd, 1H, $J = 5.3$, 16.0 Hz, olefinic), 6.13 (d, 1H, $J = 16.0$ Hz, olefinic), 5.08–5.02 (m, 1H, –OCH), 4.63–4.57 (m, 1H, –OCH), 3.79–3.73 (m, 1H, –OCH), 3.62–3.54 (m, 1H, –OCH), 3.31 (brs, 1H, –OH), 3.14 (brs, 1H, –OH), 2.88 (brs, 1H, –OH), 1.59–1.54 (m, 4H, 2 x $-CH_2$), 1.49–1.26 (m, 19H, 8 x $-CH_2$, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.5, 144.6, 123.1, 74.8, 73.3, 71.2, 69.9, 35.8, 32.0, 28.1, 27.7, 27.5, 27.2, 27.1, 26.4, 24.2, 23.7, 20.5; HRMS (ESI): *m/z* calculated for $C_{18}H_{32}O_5Na$ $[M+Na]^+$ 351.2147, found 351.2154.

Conclusion

Thus, in summary, an efficient stereoselective total synthesis of Aspicilin (**1**) has been achieved from commercially available D-(+)-gluconolactone. The key steps involved in this synthesis are Wittig olefination, Sharpless asymmetric dihydroxylation, and Yamaguchi macrolatonization.

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