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Stereoselective total synthesis of cytotoxic sporiolide A

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Dedicated to Dr. J. Madhusudhana Rao on his 60th birthday and for his excellent contributions in natural products

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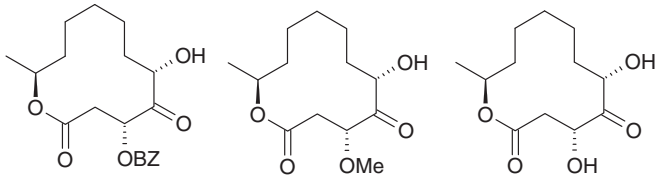
ABSTRACT

A simple and highly efficient stereoselective total synthesis of cytotoxic agent sporiolide A has been achieved starting from D-mannitol; the strategy of synthesis utilizes stereoselective zinc-mediated allylation, aldol coupling and ring-closing metathesis as key steps.

1. Introduction

Marine fungi are attractive sources for anticancer, antifungal and antibacterial secondary metabolites with various exotic structural features.[1] Sporiolide A (**1**), sporiolide B (**2**) and pandangolide 1 (**3**) are 12-membered lactones isolated from the cultured fungal broth of *Cladosporium* sp. of an Okinawan brown alga *Actinotrichia fragilis* and the Red sea sponge *Niphates rowi*, respectively.[2] Sporiolides A and B were found to exhibit cytotoxicity against L1210 cells with IC_{50} values of 0.13 and 0.81 μg/mL, respectively. Further assays revealed that sporiolide A exhibits antifungal activity against *Candida albicans* (MIC 16.7 μg/mL), *Cryptococcus neoformans* (8.4 μg/mL), *Aspergillus niger* (16.7 μg/mL) and *Neurospora crassa* (8.4 μg/mL) and showed antibacterial activity against *Micrococcus luteus* (16.7 μg/mL), while sporiolide B (**2**) had antibacterial activity against *M. luteus* (16.7 μg/mL). Its structure was determined on the basis of spectroscopic methods.[3] To our knowledge, only one synthesis was reported on sporiolide A (**1**) starting from D-glucal by Yuguo Du et al.[4a] Yuguo Du et al. also reported synthesis of sporiolide B.[4b] Our continued interest towards the total synthesis of biologically active natural products[5] prompted us to undertake the synthesis of this demanding target from commercially available D-mannitol.



1 **2** **3**

Our planned approach to sporiolide A (**1**) involved the stereo selective zinc-mediated allylation, aldol coupling and ring-closing metathesis as key steps from D-mannitol as a chiral starting material. The retro synthesis is depicted in Scheme 1.

2. Results and discussion

The synthesis of sporiolide A (**1**) was achieved starting from the readily available D-mannitol diacetonide, which was oxidized following a known procedure,[6] to give (*R*)-2,3-*O*-isopropylidene aldehyde **4** (Scheme 2). Compound **4** was subjected to the Zn-mediated allylation in aqueous medium following operationally simple Luche's[7] procedure to afford highly diastereoselective *anti* homoallylic alcohol[8] (*syn*/*anti* = 5%:95%) which was protected as the benzyl ether **5**. The acetonide protection group in **5** was removed on treatment with aqueous TFA to afford diol **6** which was selectively protected with TBSCl to afford monosilyl ether **7**. The secondary hydroxyl in **7** was protected with *p*-methoxy benzyl bromide to afford *p*-methoxybenzyl ether **8**. The *tert*-butyldimethylsilyl ether in

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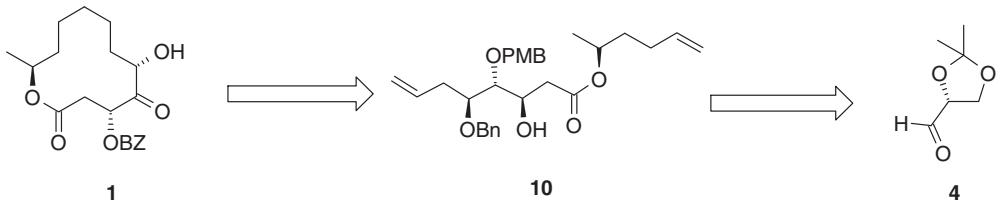
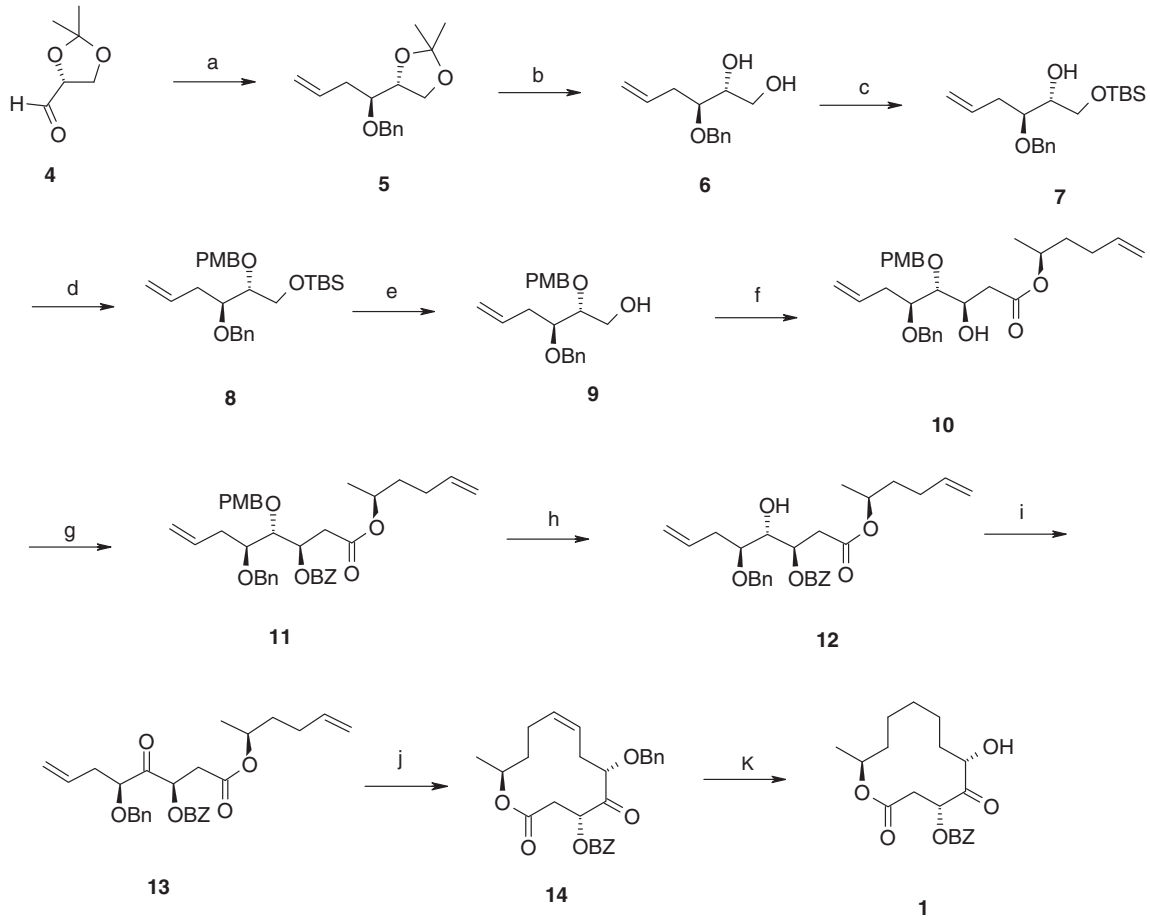
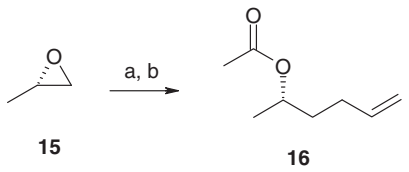


Scheme 1.



Scheme 2. Reagents and conditions: (a) (i) Zn, allyl bromide, THF, saturated solution of NH_4Cl (cat), 6 h, 90%; (ii) BnBr, NaH, TBAI, THF.0 °C to rt, 2 h, 85%; (b) TFA–water, rt, 5 h, 90%; (c) TBDMSCl, imidazole, dry CH_2Cl_2, 4 h, 93%; (d) PMBCl, NaH, DMF, 2 h, 82%; (e) TBAF, THF, 0 °C to rt, 85%; (f) (i) 2-iodoxybenzoic acid, DMSO, CH_2Cl_2, 3 h, 92%; (ii) **16**, LiHMDS, dry THF, −78 °C, 6 h, 54%; (g) BzCl, Pyr, DMAP, 4 h, 92%; (h) DDQ, CH_2Cl_2/H_2O, 2 h, 85%; (i) Dess–Martin periodinane, CH_2Cl_2, 3 h, 80%; (j) 30% Grubbs I catalyst CH_2Cl_2, reflux, 24 h, 70%; (k) H_2, Pd/C, MeOH, 24 h, 95%.

compound **8** was removed using TBAF to afford primary alcohol **9**.[9] The primary alcohol in **9** was oxidized using IBX (2-iodoxybenzoic acid) in DMSO to afford the corresponding aldehyde, which was subjected to the aldol coupling with ester **16** (Scheme 3)[10] using LiHMDS as base[11] to furnish secondary alcohol compound **10** with high diastereoselectivity (*syn*/*anti* = 20%:80%) favoring *anti*-isomer. The pure *anti*-isomer was separated by column chromatography. The absolute stereochemistry of the newly generated center in compound **10** bearing the hydroxyl group was determined by modified Mosher's method[12] and found to be in *R*-configuration (Fig. 1). The negative chemical shift difference to the left side of MTPA plane and positive chemical shift differences to the right side of MTPA plane determined that hydroxyl stereochemistry is in *R*-configuration (Fig. 1).



Scheme 3. Reagents and conditions: (a) allyl chloride, Mg, CuCN, THF, 0 °C to rt, overnight; (b) Ac_2O, pyridine, 0 °C to rt, 3 h, 92%.

The hydroxyl group was subjected to benzoylation with BzCl in pyridine to afford benzoyl ester **11**. The deprotection of PMB group in **11** with DDQ afforded secondary alcohol **12** which was oxidized following the Dess–Martin periodinane oxidation to afford keto diene **13**. We also tried the same conversion with known procedures using IBX oxidation and Swern oxidation, without success. The diene was then subjected to ring-closing metathesis (RCM)

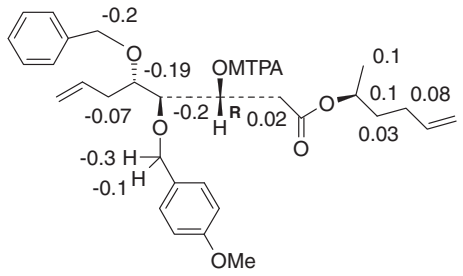


Figure 1. Determination of absolute configuration and $\Delta\delta$ values for the *S* and *R*-MTPA ester derivatives of **10** ($\Delta\delta = \delta_S - \delta_R$).

using Grubbs 1st generation catalyst[13] to afford macrolide **14**. Finally, the reduction of the double bond and debenzylation in **14** was achieved by hydrogenation over Pd/C to afford sporiolide A (**1**)[14] (Scheme 2). The physical and spectral data of compound **1** were found to be identical with that of reported natural product[3] {$[\alpha]_D^{25}$ −15.2 (*c* 0.1, MeOH), reported $[\alpha]_D^{25}$ −14 (*c* 0.1, MeOH)}.

In conclusion, an efficient stereoselective total synthesis of sporiolide A (**1**) has been achieved in 13 steps with a 7.00% overall yield from D-mannitol.

Acknowledgement

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10. Acetyl fragment **16** was synthesized (Scheme 3) from commercially available epoxide **15**, which was subjected to copper (I) cyanide-promoted regioselective nucleophilic ring-opening with allyl magnesium chloride to provide the corresponding alcohol in 85% yield; acetylation of alcohol by use of acetic anhydride and pyridine yielded **16**.
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14. Spectral data for selected compounds:
Compound **10**: $[\alpha]_D^{25}$ −13.6 (*c* 1, $CHCl_3$); IR (neat): 3480, 3072, 2932, 1723, 1612, 1513, 1454, 1248, 1175, 1085,1034, 914, 768, 699 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.35–7.16 (m, 7H), 6.87–6.79 (m, 2H), 5.97–5.67 (m, 2H), 5.17–5.00 (m, 3H), 4.99–4.87 (m, 2H), 4.64 (d, 1H, *J* = 10.9 Hz), 4.58 (d, 1H, *J* = 10. 7), 4.57–4.51 (m, 2H), 4.14 (t, 1H, *J* = 6.3 Hz), 3.77 (s, 3H), 3.74–3.67 (m, 1H), 3.59–3.52 (m, 1H), 3.08 (br s, OH), 2.61–2.56 (m, 1H), 2.51–2.40 (m, 3H), 2.12–2.97 (m, 2H), 1.75–1.59 (m, 1H), 1.48–1.61(m, 1H), 1.21 (d, 3H, *J* = 6.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7, 159.1, 138.2, 137.5, 135.1, 130.4, 129.5, 128.2, 127.7, 127.5, 117.1, 115.1, 113.6, 96.1, 81.4, 79.0, 73.3, 70.6, 68.5, 55.0, 37.5, 35.0, 34.5, 29.6, 19.9. MS-ESIMS: *m*/*z* = 483 $[M+H]^+$.
Compound **1**: $[\alpha]_D^{25}$ −15.2 (*c* 0.1, MeOH); IR (neat): 3447, 2934, 1722, 1452, 1263, 1173, 1110, 766, 713 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.07–8.01 (m, 2H), 7.62–7.55 (m, 1H), 7.49–7.41 (m, 2H), 5.99 (d, 1H, *J* = 10.3 Hz), 5.04–4.90 (m, 1H), 4.41 (t, 1H, *J* = 5.2 Hz), 3.47 (dd, 1H, *J* = 10.2, 16.8 Hz), 2.81 (d, 1H, *J* = 16.8 Hz), 2.06–1.95 (m, 1H), 1.71–1.54 (m, 1H), 1.51–1.36 (m, 3H), 1.35–1.28 (m, 3H), 1.27 (d, 3H, *J* = 5.6 Hz), 1.26–1.22 (m, 1H), 1.20–1.06 (m, 1H). ^{13}CNMR (75 MHz, $CDCl_3$): δ 207.4, 168.3, 165.2, 134.0, 129.9, 128.6, 128.3, 75.6, 73.5, 67.6, 39.9, 34.9, 31.5, 26.0, 20.7, 19.7. MS-ESIMS: *m*/*z* = 371 $[M+Na]^+$.