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Carbohydrate-based first stereoselective total synthesis of bioactive cytospolide P†

Pathi Suman and Bhimapaka China Raju*

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A facile carbohydrate-based highly stereoselective synthetic route has been developed for the cytospolide P (1) from D-ribose for the first time. Key steps of the synthesis include, Wittig homologation, regioselective epoxide ring opening, Sharpless asymmetric epoxidation, Evans aldol reaction, and Yamaguchi macrolactonization.

The pharmaceutical industry has been continuously searching for new biologically active compounds. The main goal of research is to synthesize the compounds with potential biological applications particularly for cancer. Macrolides, particularly lactones with medium-sized rings (8-10 membered) are scarce, and continued to attract the attention of chemists due to interesting biological properties.[1] Zhang *et al*. isolated cytospolides A-E,[2] cytospolides F-Q and decytospolides A-B[3] from the endophytic fungus *Cytospora* sp.. Cytospolides (A-E) has unprecedented 15-carbon skeleton with unique C-2 methyl group. These structures were elucidated by spectroscopic analysis, chemical inter conversion, and X-ray single crystal diffraction studies. Cytospolide P (Fig. 1) with (2*S*) configuration was cytotoxic against A549, QGY, and U973 cell lines. It is interesting to note that the cytospolide P has different functional groups (keto at C-3, acetate at C-5 and hydroxy at C-8) when compared to other cytospolides. The design and synthesis of any molecule is sensible by implementing important protocols and suitable protecting groups to accomplish the target molecule in an efficient manner. Though, cytospolide P is an interesting molecule, there has been no report of its successful total

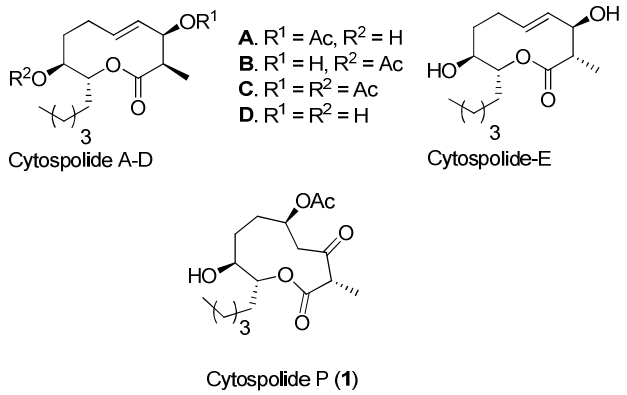
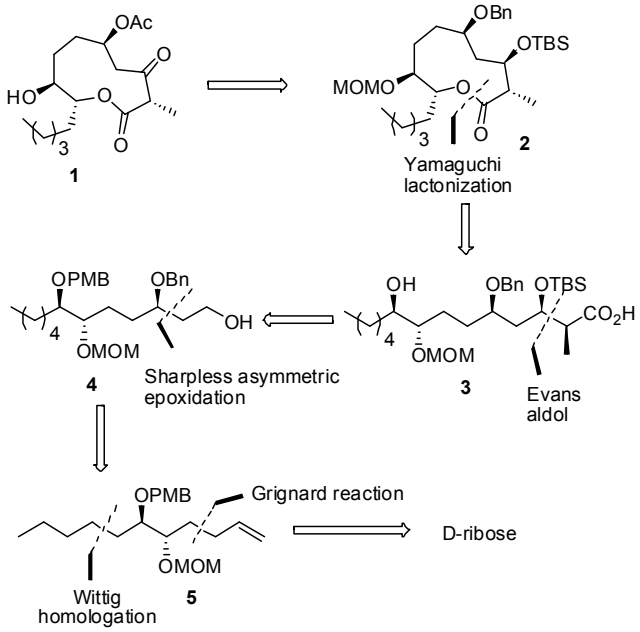


Fig. 1 Structures of cytopsolide A-D, E, and P (**1**).

synthesis. We have long term interest in total synthesis of natural products[4] and biologically active heterocyclic compounds,[5] herein, we report the first stereoselective total synthesis of cytospolide P starting from D-ribose.

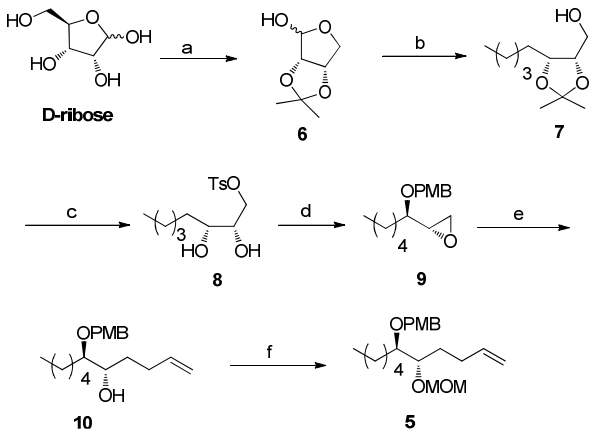
The hypothesized retrosynthetic analysis indicated that cytospolide P (**1**) can arise via the Yamaguchi lactonization of *seco* acid **3** followed by selective deprotection and oxidation. *Seco* acid **3** in turn could be accessed from chiral primary alcohol **4** by means of Evans aldol reaction. The chiral primary alcohol **4** could be synthesized by six step sequence from olefin **5** using Sharpless epoxidation protocol, which in turn could easily be accessed from commercially available D-ribose. Accordingly, a retrosynthetic analysis is delineated in Scheme 1.



Scheme 1 Retrosynthetic analysis of cytospolide P (**1**).

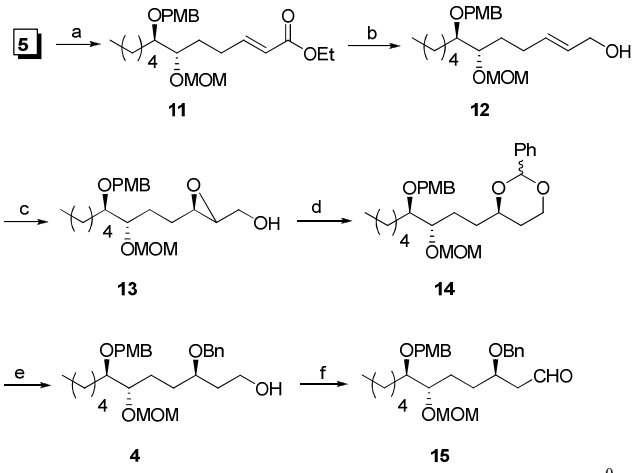
Synthesis of olefin **5** (Scheme 2) having two stereo centres was accomplished from D-ribose in an efficient manner. Acetonide protection of D-ribose followed by reduction with $NaBH_4$ and oxidation using $NaIO_4$ to furnish 2,3-O-isopropylidene-L-erythrose **6** in 79% yield.[6] Four carbon Wittig

homologation of **6** and subsequent hydrogenation with Pd/C led to primary alcohol **7**.[7] The alcohol was treated with TsCl in presence of DMAP to yield tosylated compound and subsequent acetonide deprotection with *p*-TsOH in methanol to obtain diol **8** in 82% yield. Compound **8** was treated with K_2CO_3/MeOH[8] to give epoxy alcohol and protection of the secondary alcohol with PMB-Br led to **9**. Initially, we opened the terminal epoxide with ally magnesium bromide in the presence of CuI resulted in lower yields of product **10.** However, on further optimization, we observed the formation of product **10** with CuBr in good yield (87%).[8a] The resulting secondary alcohol was then protected with MOMCl to obtain **5**.



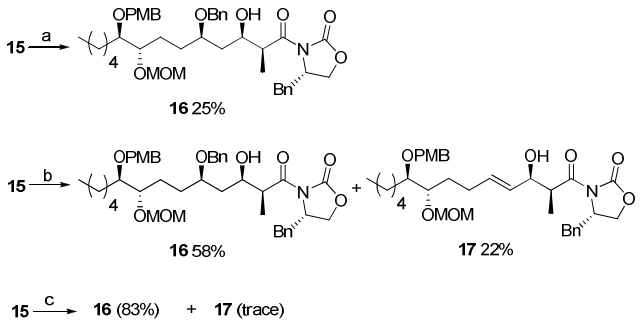
Scheme 2 *Reagents and conditions*: (a) (1) Acetone, conc. H_2SO_4, r.t., 2.5 h; (2) $NaBH_4$, MeOH, 0 ^{0}C, 1 h then $NaIO_4$, *t*-BuOH, H_2O, 25 ^{0}C, 79% over two steps; (b) (1) *n*-$BuPh_3PBr$, *n*-BuLi, THF, –78 ^{0}C to r.t., 3 h; (2) Pd/C, H_2, EtOH, r.t., 4 h, 83% over two steps; (c) (1) TsCl, Et_3N, cat. DMAP, CH_2Cl_2, 0 ^{0}C to r.t., 4 h; (2) *p*-TsOH, MeOH, 0 ^{0}C to r.t., 2 h, 82% over two steps; (d) (1) K_2CO_3, MeOH, 0 ^{0}C, 2 h; (2) PMB-Br, NaH, TBAI, THF, 0 ^{0}C to r.t., 4 h, 80% over two steps; (e) Allyl magnesium bromide, CuBr, THF, 0 ^{0}C, 3 h, 87%; (f) MOMCl, DIPEA, CH_2Cl_2, 0 ^{0}C to r.t., 8 h, 85%.

After successful synthesis of compound **5**, we focused on creating two other stereo centres (at C-5 and C-2) to obtain *seco* acid **3** (Scheme 3-5). Accordingly, ozonolysis[9] of terminal olefin **5** afforded the corresponding aldehyde and subsequent two carbon Wittig homologation lead to α,β-unsaturated ester **11** (*E*-isomer, 85% yield), which was subjected to DIBAL-H reduction resulting allylic alcohol **12**. Sharpless asymmetric epoxidation of **12** in presence of (–)-diisopropyl tartrate, Ti(O*i*Pr)$_4$ and TBHP at –20 ^{0}C gave epoxy alcohol **13** in 87% yield.[10] Regioselective ring opening of epoxide **13** in presence of Red-Al obtained corresponding 1,3-diol[11] and on subsequent protection with benzyl dimethoxyl acetal in presence of catalytic amount of PPTS furnished cyclic phenyl acetal **14**. The regioselective reductive ring opening of the cyclic phenyl acetal **14** with DIBAL-H afforded alcohol **4** in 86% yield.[12] In order to generate *seco* acid **3**, primary alcohol **4** was converted to aldehyde **15** by employing Dess-Martin conditions (Scheme 3).[13]



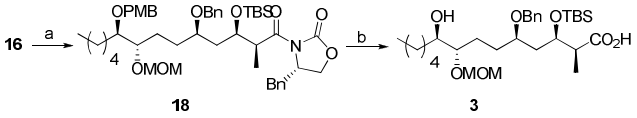
Scheme 3 *Reagents and conditions*: (a) (1) O_3, CH_2Cl_2, –78 ^{0}C; (2) $Ph_3P{=}CHCO_2C_2H_5$, benzene, r.t, 2 h, 85% over two steps; (b) DIBAL-H, CH_2Cl_2, 0 ^{0}C-rt, 3 h, 78%; (c) (–)-DIPT, Ti(O*i*Pr)$_4$, TBHP, CH_2Cl_2, –20 ^{0}C, 3 h, 87%; (d) (1) Red-Al, THF, 0 ^{0}C to r.t., 2 h; (2) $PhCH(OMe)_2$, PPTS, CH_2Cl_2, 0 ^{0}C, 3 h, 85% over two steps (e) DIBAL-H, CH_2Cl_2, –20 ^{0}C, 2 h, 86%; (f) Dess-Martin periodinane, CH_2Cl_2, 0 ^{0}C to r.t., 1 h.

Initially, the Evans aldol reactions with boron enolate afforded aldol adduct **16** in moderate yield (25%, Scheme 4). However, over the past few years it has been reported,[14] that $TiCl_4$ has replaced Bu_2BOTf. After switching from boron to titanium ($TiCl_4$) mediated aldol reaction under crimmins conditions[15] resulted in the formation of two products **16** (58% yield) and **17** (22% yield). The required aldol product **16** was confirmed by spectral analysis and the other product confirmed as **17** (benzyloxy eliminated product). Next, series of experiments were carried out selectively to obtain **16** from **15.** We found that the mole ratio of $TiCl_4$ and reaction time play major role to form titanium enolate complex to get the desired compound **16** (83% yield, >20:1 d.r, see supporting information).



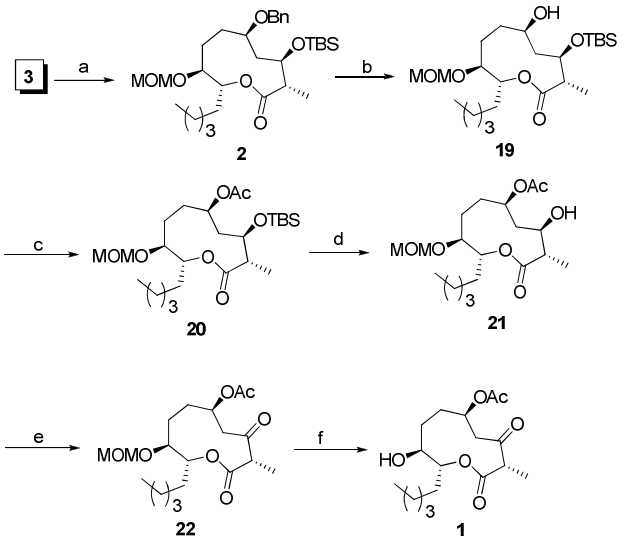
Scheme 4 *Reagents and conditions*: (a) propionyloxazolidinone, Bu_2BOTf, DIPEA, CH_2Cl_2, –78 ^{0}C, 25% yield; (b) propionyloxazolidinone (1.0 mmol), $TiCl_4$ (1.2 mmol), 5 min., 0 ^{0}C, DIPEA, 30 min., NMP, CH_2Cl_2, –78 ^{0}C to 0 ^{0}C, 1 h; (c) propionyloxazolidinone (1.0 mmol), $TiCl_4$ (1.0 mmol), 25 min., 0 ^{0}C, DIPEA, 45 min., NMP, CH_2Cl_2, –78 ^{0}C to 0 ^{0}C, 1 h.

TBS protection of secondary alcohol **16** with TBSOTf/2,6-lutidine afforded **18** (Scheme 5). The PMB protected hydroxyl derivative **18** was freed by DDQ,[16] and the Evans chiral auxiliary was removed under basic conditions[17] (LiOH, H_2O_2, THF-H_2O (4:1)) to get the *seco* acid **3** (87% yield over two steps).



Scheme 5 *Reagents and conditions*: (a) TBSOTf/2,6-lutidine, CH_2Cl_2, –78 ^{0}C, 2 h, 92%; (b) (1) DDQ, CH_2Cl_2, 0 ^{0}C, 30 min; (2) LiOH, H_2O_2, THF/H_2O (4:1), 0 ^{0}C, 5 h, 87% over two steps.

Having established all the required four stereogenic centres, Yamaguchi macrolactonization[18] of *seco* acid **3** resulted **2** in 76% yield (Scheme 6). With three protecting groups on **2** (benzyl, silyl and methoxymethyl ether), sequential and selective functional group interconversions play a major role to obtain the target molecule. To deprotect these groups delicately, we have planned for selective debenzylation and desilylation procedures. Using Pd/C hydrogenolysis method, compound **2** was converted to **19** followed by acylation[19] using acetic anhydride to obtain **20**. Silyl ether on **20** was removed by TBAF to obtain the corresponding alcohol **21**. Oxidation of secondary alcohol **21** under Dess Martin conditions obtained ketone **22**, which was purified by crystallization. Finally, MOM deprotection with $BF_3.Et_2O$[20] was adopted to get the target molecule cytospolide P (**1**). Physical and spectral data of compound **1** are identical to those reported in the literature.[3]



Scheme 6 *Reagents and conditions*: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 0 ^{0}C, 1 h, DMAP, Toluene, 80 ^{0}C, 8 h, 76%; (b) 10% Pd/C, H_2, EtOAc, 4 h, 97%; (c) Ac_2O, Et_3N, CH_2Cl_2, cat. DMAP, 0 ^{0}C, 2 h, 93%; (d) TBAF, THF, 0 ^{0}C to r.t., 5 h, 95%; (e) Dess-Martin periodinane, CH_2Cl_2, 0 ^{0}C to r.t., 2 h, 89%; (f) SMe_2, $BF_3{\cdot}Et_2O$, –10 ^{0}C, 30 min, 82%.

In summary, the first stereoselective total synthesis of cytospolide P (**1**) was accomplished from commercially available D-ribose. Four stereogenic centres were created by employing Wittig homologation, regioselective epoxide ring opening, Sharpless asymmetric epoxidation and Evans aldol reaction. Finally, Yamaguchi macrolactonization was adopted to accomplish the target molecule. The obtained product **17** having a unique C2-C5 carbon skeleton of cytospolide A-E family with appropriate chirality and functional groups for further studies towards the synthesis of cytospolides are under investigation.

Natural Products Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad 500 007, India. E-mail: chinaraju@iict.res.in; Fax: (+91)-40-27160512.

†Electronic Supplementary Information (ESI) available: [Experimental details and scanned copies of ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet or from the author]. See DOI: 10.1039/b000000x/

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