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

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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.1-3 Zhang et al. isolated cytospolides A-E, cytospolides F-Q and decytospolides A-B 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 (2S) 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 synthesis. We have long term interest in total synthesis of natural products4 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).](image-url)

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 NaBH₄ and oxidation using NaIO₄ to furnish 2,3-O-isopropylidene-L-erythrose 6 in 79% yield.6 Four carbon Wittig

Fig. 1 Structures of cytospolide A-D, E, and P (1).
homologation of 6 and subsequent hydrogenation with Pd/C led to primary alcohol 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 K₂CO₃/MeOH² to give epoxy alcohol and protection of the secondary alcohol with PMB-Br led to 9. Initially, we opened the terminal epoxide with allyl magnesium bromide in the presence of Cul resulted in lower yields of product 10. However, on further optimization, we observed the formation of product 10 with CuBr in good yield (87%). The resulting secondary alcohol was then protected with MOMCl to obtain 5.

Scheme 2: Reagents and conditions: (a) (1) Acetone, conc. H₂SO₄, r.t., 2.5 h; (2) NaBH₄, MeOH, 0 °C, 1 h then NaOAc, t-BuOH, H₂O, 25 °C, 79% over two steps; (b) (1) n-BuPh₂PBr, n-BuLi, THF, −78 °C to r.t., 3 h; (2) Pd/C, H₂, EtOH, r.t., 4 h, 83% over two steps; (c) (1) TsCl, Et₃N, cat. DMAP, CH₂Cl₂, 0 °C to r.t., 4 h; (2) p-TsOH, MeOH, 0 °C to r.t., 2 h, 82% over two steps; (d) (1) K₂CO₃, MeOH, 0 °C, 2 h; (2) PMB-Br, NaN₃, TBAI, THF, 0 °C to r.t., 4 h, 80% over two steps; (e) Allyl magnesium bromide, CuBr, THF, 0 °C, 3 h, 87%; (f) MOMCl, DIPEA, CH₂Cl₂, 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, ozonolysis⁹ of terminal olefin 5 afforded the corresponding aldehyde and subsequent two carbon Wittig homologation lead to α,β-unsaturated ester (83% yield), which was subjected to DIBAL-H reduction resulting allylic alcohol 12. Sharpless asymmetric epoxidation of 12 in presence of (−)-diisopropyl tartrate, Ti(O₂Pr)₄ and TBHP at −20 °C gave epoxy alcohol 13 in 87% yield.¹⁰ Regioselective ring opening of epoxide 13 in presence of Red-Al obtained corresponding 1,3-diol¹¹ and on subsequent protection with benzyl dimethoxymethylene 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

Initially, the Evans aldol reactions with boron enolate afforded aldot adduct 16 in moderate yield (25%, Scheme 4). However, over the past few years it has been reported,¹⁴ that TiCl₄ has replaced Bu₂BOTf. After switching from boron to titanium (TiCl₄) mediated aldol reaction under crimmings conditions 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 a single product. Next, series of experiments were carried out selectively to obtain 16 from 15. We found that the molar ratio of TiCl₄ 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, Bu₂BOTf, DIPEA, CH₂Cl₂, −78 °C, 25% yield; (b) propionyloxazolidinone (1.0 mmol), TiCl₄ (1.2 mmol), 5 min., 0 °C, DIPEA, 30 min., NMP, CH₂Cl₂, −78 °C to 0 °C, 1 h; (c) propionyloxazolidinone (1.0 mmol), TiCl₄ (1.0 mmol), 25 min., 0 °C, DIPEA, 45 min., NMP, CH₂Cl₂, −78 °C to 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 (LiOH, H₂O₂, THF-H₂O (4:1)) to get the seco acid 3 (87% yield over two steps).
Having established all the required four stereogenic centres, Yamaguchi macrolactonization of seco acid resulted in 2 in 76% yield (Scheme 6). With three protecting groups on 2 (benzyl, silyl and methoxymethyl ether) groups, 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 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 BF₃·Et₂O was adopted to get the target molecule cytopsylide P (1). Physical and spectral data of compound 1 are identical to those reported in the literature.

In summary, the first stereoselective total synthesis of cytopsylide 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 cytopsylide A-E family with appropriate chirality and functional groups for further studies towards the synthesis of cytopsylides are under investigation.

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Electronic Supplementary Information (ESI) available: [Experimental details and scanned copies of 1H and 13C 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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Notes and references


