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Stereoselective total synthesis of C_2-symmetric natural products pyrenophorol and its derivatives

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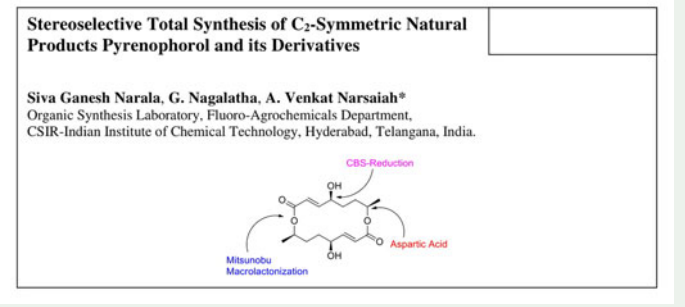
ABSTRACT

A stereoselective total synthesis of 16-membered C_2-symmetric macrodiolide Pyrenophorol, Tetrahydropyrenophorol and 4,4-diacetylpyrenophorol have been accomplished. The synthesis started from commercially available *L*-Aspartic acid and the key reactions involved are regioselective epoxide opening, CBS reduction, Pinnick oxidation and Mitsunobu dilactonization.



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Macrodiolide; antimicrobiol agent; CBS reduction; Pinnick oxidation; dilactonization

1. Introduction

Naturally occurring macrodiolides are showing interesting biological activities. Structurally, these are broadly classified as homodimeric (Pyrenophorols,Vermiculine) and heterodimeric (Elaiophylin) macrolides (Kis et al. 1969; Kastanias and Tokousbalides 2005). Pyrenophorol and its derivatives are 16-membered macrocyclic dilactones and arranged naturally head-to-tail connection of the two C_8 hydroxy acid subunits (Krohn et al. 2007; Zhang et al. 2008). Pyrenophorols are isolated from *Byssochlamys nivea*, *Pyrenophora avenae* and *Stemphylium radicinum* cultures (Kastanias and Tokousbalides 2000).

The broad spectrum of bioactivity and the unique structure has attracted the synthetic chemists and led to its synthesis in different routes (Dommerholl et al. 1991;

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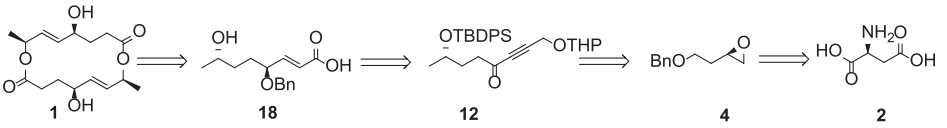


Scheme 1. Retrosynthetic analysis

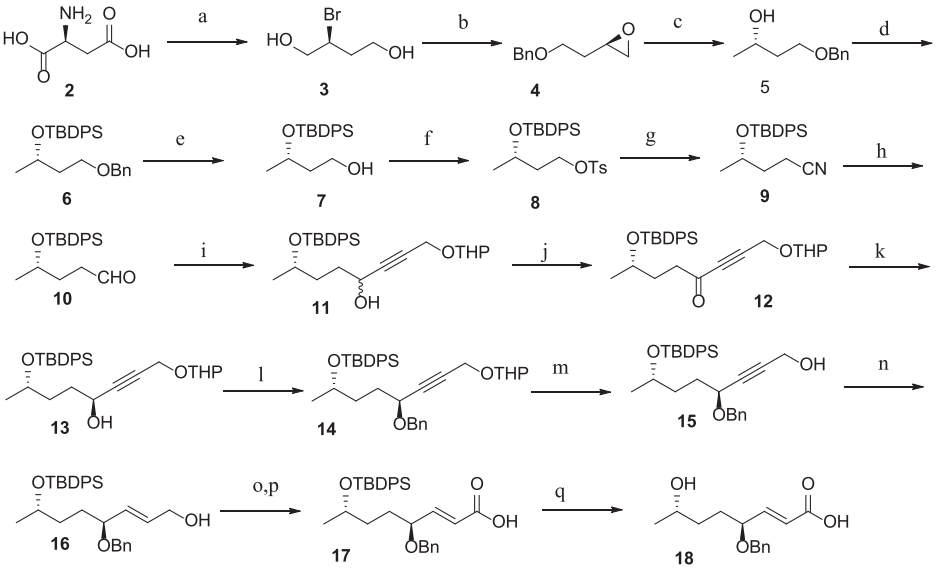
Machinaga and Kibayashi 1993; Amigoni and Le Floc'h 1997; Yadav et al. 2009; Oh and Kang 2011; Chatterjee et al. 2014; Edukondalu et al. 2015; Risi et al. 2015; Alluraiah et al. 2018; Ashok et al. 2018). As part of our regular research program in synthesis of biologically active molecules (Narsaiah et al. 2015a, 2015b, 2016, 2018), we have carry out the stereoselective total synthesis of Pyrenophorol and its derivatives. The reported methods followed expensive protocols like Grubbs and AD-mix and the resolution protocol involved the loss of one isomer. Our strategy was started from commercially available starting materials and completed with good yield.

2. Results and discussion

As shown in the retrosynthetic analysis (Scheme 1), the target molecule has been achieved from the monomer of compound **18**, which obtained from stereoselective reduction of keto compound **12,** and which accomplished from compound **4**.

The synthesis started from commercially available of (*L*)-Aspartic acid (**2**). Brominative diazotisation of (*L*)-Aspartic acid using $NaNO_2$ and KBr followed by reduction of dicarboxylic acid to diol (**3**) by using BH_3DMS gave quantitative yield (Shibata et al. 1986; Rabinson and Brimble 2007). Elimination of bromine, one pot intramolecular, base induced epoxide formation insitu, remaining primary alcohol protected as benzyl ether using benzyl bromide NaH to furnish, (*R*)-epoxide (**4**) (Frick et al. 1992; Naysmith and Brimble 2013). Regioselective epoxide opening with $LiAlH_4$ gave secondary alcohol (**5**) exclusively (Kumar and Reddy 2012), which was protected as TBDPS ether using TBDPS-Cl and TBAI afforded compound (**6**) 90% in yield. Reductive cleavage of benzyl ether selectively by lithium naphthalene at −40 °C led to its primary alcohol (**7**) in quantitative yield. Free alcohol group converted to tosyl group followed by SN^2 substitution with NaCN in presence of catalytic amount NaI in DMSO at 80 °C to furnish cyano compound (**9**) in 88% yield (Motozaki et al. 2005; Kadam and Sudhakar 2015). Partial reduction of (**9**) with DIBAL-H at −78 °C gave aldehyde (Ishigami et al. 2006), which was subjected to nucleophilic addition with THP protected propargyl alcohol using *n*-BuLi at −78 °C to afford compound (**11**) in 78% yield (Dagmer and Philip 2010). The obtained secondary hydroxyl group was oxidized with IBX in DMSO and DCM mixture (1:3) gave alkynone in (**12**) very good yields (Sabitha et al. 2013) (Scheme 2).

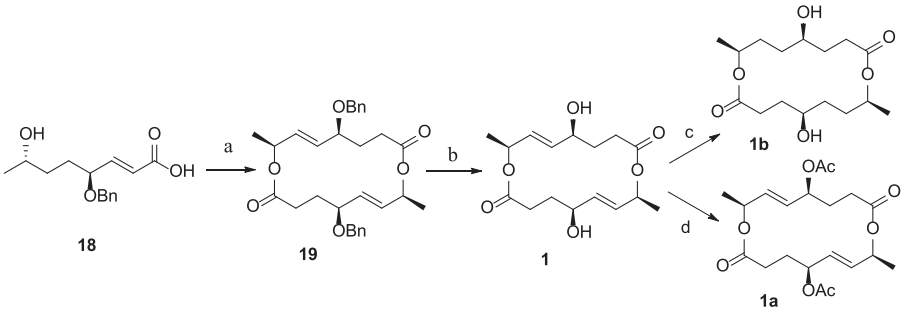
Compound **12** was subjected to enantioselective reduction of keto group with borane dimethyl sulfide and a chiral ligand, Corey-Bakshi-Shibata ligand [(*R*)-methyl-oxazaborolidine], at −40 °C in dry THF for 2 hr to afford compound (**13**) in very good yields (Corey et al. 1987; Parker and Ledeboer 1996) with diastereoselecivity ratio of 92:8, confirmed by ^{1}H NMR and with optical rotation $[\alpha]_D^{25}$ -16.79 (c = 1, $CHCl_3$). Thus obtained chiral secondary alcohol was protected as benzyl ether in presence of NaH and BnBr at 0 °C to rt in dry THF to furnished compound (**14**) in 78% yield (Bulow



Scheme 2. Reagents and conditions: (a) (i) $NaNO_2$, KBr, H_2SO_4, −10 °C, 5 hr, 82%; (ii) BH_3.DMS, dry THF, −10 °C to rt, 93%; (b) NaH, BnBr, TBAI, 0 °C, 5 hr, 70%; (c) LAH, dry THF, rt, 1 hr, 90%; (d) TBDPS-Cl, imidazole, DMAP, dry CH_2Cl_2, rt, 2 hr, 90%; (e) Li, Naphthalene, dry THF, −40 °C, 1 hr, 83%; (f) Ts-Cl, Et_3N, DMAP, dry CH_2Cl_2, 6 hr, 69%; (g) NaCN, NaI, dry DMSO, 80 °C, 1.5 hr, 88%; (h) DIBAL-H, −78 °C, dry CH_2Cl_2, 1 hr; (i) $C_8H_{12}O_2$, *n*-BuLi, −78 °C, dry THF, 3 hr (73%, over two steps); (j) IBX, DMSO, CH_2Cl_2 (1:3), rt, 1.5 hr, 86%; (k) (*R*)-CBS-catalyst, BH_3.DMS, dry THF, −40 °C, 1 hr, 81%; (l) NaH, BnBr, dry THF, rt, 4 hr, 78%; (m) PPTS, MeOH, rt, 2 hr, 89%; (n) Red-Al, dry THF, 0 °C to rt, 1 hr, 91%; (o) MnO_2, hexane, rt, 20 hr; (p) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH-H_2O (5:1) 30 min (over two steps 92%); (q) HF.Pyridine, dry THF, 20 hr, 85%.

et al. 2011). The tetrahedropyranyl ring was selectively deprotected with pyridinium *p*-toluene sulphanate (PPTS) in methanol to give compound **15**, in 89% yield (Suffert 1990; Shekar et al. 2011). The propargyl alcohol to desired trans olefinic allylic alchol was achieved by using Red-Al in dry THF at 0 °C for 1 hr in quantitative yields, exclusively trans allylic alcohol (**16**) (Oskari and Koskinen 2011). The allylic alcohol was oxidized by using MnO_2 in hexane for 20 hr to afford aldehyde. Thus obtained aldehyde, further oxidized under Pinnick conditions in presence of sodium chlorate, sodium dihydrogen phosphate, *t*-BuOH, 2-methyl-2-butene to obtained, α,β-unsaturated acid (**17**) (Dubost et al. 2006) (over two steps 92% yield). Deprotection of TBDPS group was achieved by using HF.Pyridine in dry THF for 20 hr to afford *sec*-acid (**18**) in 85% yield (Scheme 3).

The monomer was subjected to Mitsunobu cyclization under Gerlach's procedure, using TPP, DEAD in THF:H_2O solvent (10:1) mixture at −30 °C for 18 hr, complete inversion at C-4 configuration centre takes place to afford macrodilactone (**20**) in 55% yield (Gerlach et al. 1977). Finally debenzylation of macrodilactone achieved by using $TiCl_4$ in dry CH_2Cl_2 to afford, the Pyrenophorol (**1**) (Sharma et al. 2009) as white solid in 80% yield. Mp 130–132 °C, [Ref.](Krohn et al. 2007) (130–134 °C), with optical rotation $[\alpha]_D^{25}$ -10.5 (c = 1, $CHCl_3$), [Ref.](Krohn et al. 2007) $[\alpha]_D^{20}$ -10.2, (c = 1.04, $CHCl_3$). The spectral data and analytical data good agreement with the literature. Compound **1** subjected to hydrogenation in presence of Pd/C (10%) under hydrogen atmosphere for



Scheme 3. Reagents and conditions: (a) TPP, DEAD, THF:H_2O (10:1), −30 °C, 18 h, 55%; (b) $TiCl_4$, dry CH_2Cl_2, 2h, rt, 80%; (c) Pd/C, H_2, EtOAc, 8h, 78%; (d) Ac_2O, pyridine, rt, 18h 64%.

8 hr to afford Tetrahydropyrenophorol **(1b)** in 78% yield. Pyrenophorol (**1**) was treated with acetic anhydride in presence of pyridine for 18 hr to achieve, 4,4-diacetyl pyrenophorol (**1a**) in 64% yield. All the compounds were compared with literature reports.

3. Experimental section

See the supplementary material

4. Conclusion

In conclusion, we have demonstrated a stereoselective total synthesis of Pyrenophorol, Tetrahydropyrenophorol and diacetylpyrenophorols. The starting material used for synthesis is commercially available (*L*)-Aspartic acid. The important reactions involved are regioselective epoxide opening, CBS reduction, Pinnick oxidation and Mitsunobu macrolactanization. All the reactions were very clean and good yields and the final products were good agreement with naturally isolated products.

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Disclosure statement

No conflict of interest.

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