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CONCISE SYNTHESIS OF C_2-SYMMETRIC *TRANS*-2,5-DIOXYMETHYLPYRROLIDINE DERIVATIVES BY NOVEL CYCLIZATION

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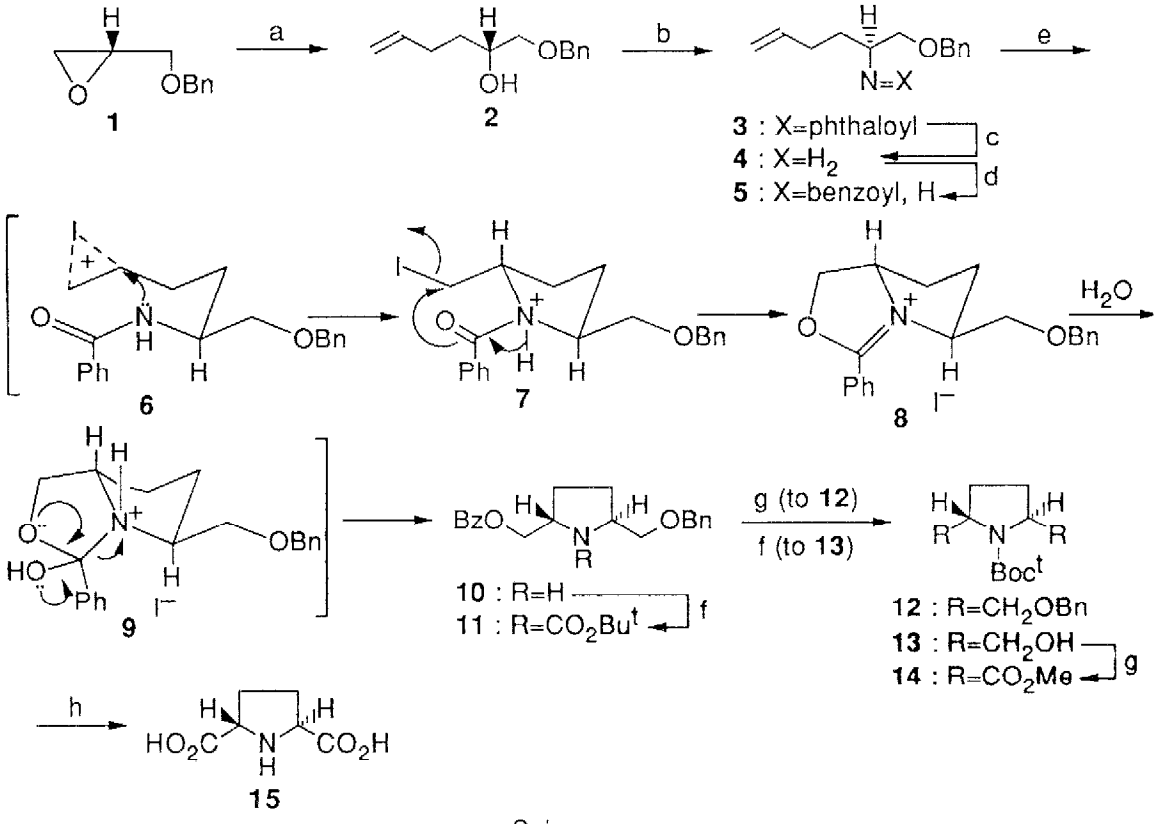
Summary: Treatment of (*S*)-1-benzyloxy-2-benzoylaminohex-5-ene with iodine in aqueous acetonitrile furnished (2*S*,5*S*)-5-benzoyloxymethyl-2-benzyloxymethylpyrrolidine stereoselectively in a single step. The product was converted into C_2-symmetric (2*S*,5*S*)-2,5-dioxymethylpyrrolidines potentially utilizable as chiral auxiliaries and (2*S*,5*S*)-(−)-pyrrolidine-2,5-dicarboxylic acid isolated from marine alga *Schizymenia dubyi*.

Optically active *trans*-2,5-substituted pyrrolidine derivatives with C_2-symmetry are highly useful as chiral auxiliaries.[1] However, a significant drawback to using these amines is difficulty of preparation of these compounds which mostly require optical resolution[2] though some stereoselective syntheses utilizing optically active starting materials have been developed.[3] We report here a concise stereoselective synthesis of the 2,5-dioxymethylpyrrolidine derivatives by iodine-mediated cyclization[4] of (*S*)-1-benzyloxy-2-benzoylaminohex-5-ene (**5**) obtained from (*S*)-*O*-benzyl-glycidol (**1**).[5]

Treatment of **1** with allylmagnesium chloride afforded the unsaturated alcohol **2** (95%), $[\alpha]_D^{27}$ −7.38° (*c* 1.002, $CHCl_3$). On Mitsunobu reaction[6] followed by deacylation **2** gave the primary amine **4** which was transformed to the benzamide **5** (86% overall), mp 80 – 81 °C, $[\alpha]_D^{26}$ −35.7° (*c* 0.996, $CHCl_3$). Exposure of **5** to iodine (3 equiv) in aqueous acetonitrile (1:3 v/v) at room temperature brought about concomitant cyclization and rearrangement to furnish (2*S*,5*S*)-2-benzyloxymethyl-5-benzoyloxymethylpyrrolidine **10** in one step presumably *via* a reaction sequence shown in Scheme. Because of its instability crude **10** was immediately converted into the carbamate **11**, $[\alpha]_D^{26}$ −65.13° (*c* 1.004, $CHCl_3$) (63% overall yield from **5**). On sequential debenzoylation and benzylation **11** afforded the C_2-symmetric (2*S*,5*S*)-*trans*-2,5-dibenzyloxymethylpyrrolidine **12** (50% overall), $[\alpha]_D^{26}$ −64.24° (*c* 3.00, $CHCl_3$), while on sequential debenzoylation and debenzylation it afforded the C_2-symmetric (2*S*,5*S*)-*trans*-2,5-dihydroxymethylpyrrolidne **13** (85% overall), $[\alpha]_D$ −66.9° (*c* 3.00, MeOH).

The latter was transformed to the diester **14**, mp 73 – 75 °C, $[\alpha]_D^{21.5}$ −72.7° (*c* 0.994, $CHCl_3$) (54% overall) by sequential oxidation[7] and methylation. On sequential decarbamoylation and saponification **14** afforded naturally occurring amino acid (2*S*,5*S*)-pyrrolidine-2,5-dicarboxylic acid (**15**), mp >300 °C, $[\alpha]_D^{31}$ −102° (*c* 0.983, H_2O) (86% overall) [natural[8]: mp >300 °C, $[\alpha]_D^{20}$ −112° (*c* 1, H_2O)], isolated from marine red alga *Schizymenia dubyi*.[8,9]



Scheme

Reagents and conditions: a, CH_2=CH–CH_2MgCl, THF, 0 °C; b, phthalimide, PPh_3, diisopropyl azodicarboxylate, THF; c, H_2NNH_2·H_2O, EtOH, reflux; d, PhCOCl, Et_3N, CH_2Cl_2; e, I_2 (3 eq), CH_3CN-H_2O (3:1 v/v), r.t.; f, Boc_2O, Et_3N, CH_2Cl_2; g, MeOH, K_2CO_3; h, NaH, $PhCH_2Br$, DMF; i, H_2, $Pd(OH)_2$/C, MeOH; j, 2.8%mol $RuCl_3$·H_2O, $NaIO_4$, CCl_4:CH_3CN:H_2O (2:2:3 v/v) then CH_2N_2; k, CF_3COOH (10 eq), CH_2Cl_2; l, aq. 1N KOH.

References and Notes

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