TOTAL SYNTHESIS OF POLYHYDROXYLATED PIPERIDINE AND PYRROLIDINE : EXPECT AS GLUCOSIDASE INHIBITOR

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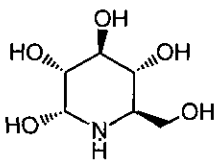
Abstract -A new method for preparation of optically active (-)-deoxymannojirimycin (**3**) and 2*R*,5*S*-dihydroxymethyl-3*R*,4*R*-dihydroxypyrrolidine (**13**) based on regioselective epoxide ring opening of 2-*tert*-butoxycarbonylamino-2-deoxy-3,4-*O*-isopropylidene-5,6-epoxy-D-glucitol (**12**) by intramolecular nucleophilic amination has been described.

Polyhydroxylated piperidine, pyrrolidine and their derivatives (aza sugars) such as nojirimycin (**1**), 1-deoxynojirimycin (**2**), deoxymannojirimycin (**3**) and 2*R*,5*R*-dihydroxymethyl-3*R*,4*R*-dihydroxypyrrolidine (**4**) gained an interest recently because of their stereochemical challenge and biological activity as potential glycosidase inhinitors.[1-4] Among these aza sugar derivatives, deoxymannojirimycin (**3**) has been shown to be potent as a specific inhibitor of both a glucoprotein-processing mannosidase I [5,6] and a bovine α-L-fucosidase.[7] 2*R*,5*R*-Dihydroxymethyl-3*R*,4*R*-dihydroxypyrrolidine (**4**) known as DMAP, has been shown to be a potent inhibitor of mouse intestinal α-glucosidase, β-glucosidase, and β-galactosidase.[8]
During the course of our investigation for the synthesis of compounds having biological activity, we reported a facile method for the synthesis of naturally occuring some piperidine and pyrrolidine compounds.[9,10]



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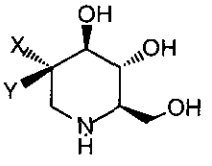
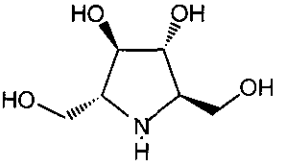


2; X=OH, Y=H
3; X=H, Y=OH



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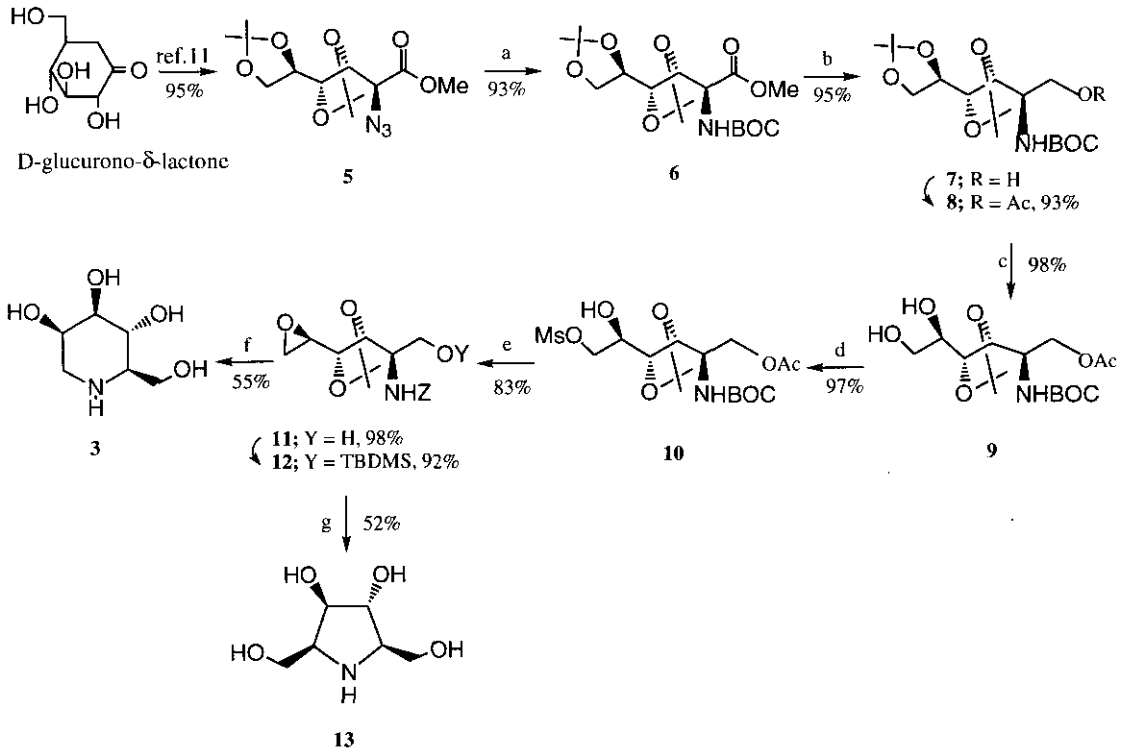
In our continuing work on the synthesis of aza sugars, we were interested to develope a convenient synthesis of unnaturally or naturally occurring piperidines and pyrrolidines. Since many of these naturally occurring and designed piperidines and pyrrolidines have attracted considerable attention as specific and potent glucosidase inhibitors, still many researchers have been under proceeding for development of new synthetic methodology. As shown in Scheme 1, we describe herein the synthesis of (-)-

deoxymannojirimycin (**3**) and 2*R*,5*S*-dihydroxymethyl-3*R*,4*R*-dihydroxypyrrolidine (**13**).[11] Compound (**13**) is the C-5 epimer of the natural product (**4**). We used the synthetic strategy for synthesis of compound (**3**) and (**13**) based on regioselective epoxide ring opening of 2-*tert*-butoxycarbonylamino-2-deoxy-3,4-*O*-isopropylidene-5,6-epoxy-D-glucitol (**12**) and subsequent ring formation through intramolecular nucleophilic amination.



Scheme 1 : (a) (i) 10% Pd/C, H_2, EtOAc, rt, (ii) $(BOC)_2$, MeOH, Et_3N, rt, (b) (i) LAH, THF, 0° C, (ii) Ac_2O, py, rt (c) Dowex 50W-X8, 90% MeOH, (d) MsCl, Et_3N, CH_2Cl_2, -10° C, (e) (i) NaOH, MeOH, rt, (ii) TBDMSCl, imidazole, DMF, rt, (f) (i) Me_3SiCl, PhOH, CH_2Cl_2, rt → reflux, (ii)Dowex 50-W, 90% MeOH, reflux, (g) (i) $AlCl_3$, $LiAlH_4$, ether, rt → reflux, (ii) Dowex 50W-X8, 90% MeOH, reflux

The manno azide (**5**) was prepared (Scheme 1), starting from D-glucurono-δ–lactone according to known method.[12] Hydrogenation of the azide (**5**) was achieved through 10% palladium on charcol with H_2 under atmospheric pressure followed by protection with di-*tert* -butyl dicarbonate to give amino mannitol derivative (**6**) in 93% yield. Reduction of **6** with $LiAlH_4$ afforded corresponding alcohol (**7**), which was then reacted with acetic anhydride to give acetate (**8**). Selective removal of terminal isopropylidene group of acetate (**8**) was achieved through Dowex 50W-X8 resin (H^+-form) in 90% methanol to give diol (**8**) in 97% yield.[10] The primary hydroxy group of compound (**9**) was selectively mesylated by reaction with mesyl chloride at 0° C to give mesylate (**10**) in 83% yield. Quantitative conversion of **10** to epoxide (**11**) was achieved by treatment with sodium hydroxide. By the way, the C_1-acetate group was hydrolyzed in this reaction conditions, therefore, protected as TBDMS ether to give **12** in 92% yield. The ring formation of compound (**3**) and (**13**) were resulted from different ring open method of epoxide (**12**) followed by

ring close respectively. Removal of the BOC group of epoxide (**12**) with Me_3SiCl and phenol in CH_2Cl_2 at room temperature for 30 min[13] followed by intramolecular nucleophilic amination under heating at reflux afforded the piperidine ring. Subsequent deprotection of isopropylidene and TBDMS groups with Dowex 50W-X8 resin gave desired polyhydroxylated aza sugar, (-)-deoxymannojirimycin (**3**) in 55% yield. In the case of piperidine ring formaion, the amine moiety of the epoxide (**12**) can attack intramolecularly both of the C-5 and C-6 carbon atoms, but the attack on C-5 did not occur before removal of isopropylidine group. We supose this may be due to the steric difficulty arising from the *trans* acetal system in epoxide (**11**).[14] The pyrrolidine ring formation resulted from removal of the BOC and isopropylidene groups of the epoxide (**12**) with $AlCl_3$ and $LiAlH_4$ in ether at 0° C followed by refluxing for 2 h. Subsequent deprotection of TBDMS group of corresponding pyrrolidine gave desired polyhydroxylated aza sugar, 2*R*,5*S*-dihydroxymethyl-3*R*,4*R*-dihydroxypyrrolidine (**13**) in 52% yield as a major and **3** as a trace amount. On the other hand, the epoxide (**12**) has no *trans* acetal group, and the amine moiety of the epoxide (**12**) attacked the C-5 than C-6 carbon atom and resulted in formation of pyrrolidine ring. In summary, our approach to construction of diffrent ring size nitrogen heterocycles utilized regioselective epoxide ring opening. Using this methodology we synthesized important natural aza sugar (-)-deoxymannojirimycin (**3**) and unnatural aza sugar 2*R*,5*S*-dihydroxymethyl-3*R*,4*R*-dihydroxypyrrolidine (**13**) with synchronously.

EXPERIMENTAL

General procedures. Dowex 50W-X8 was purchased from Sigma Chemical Co. All non-aqueous reactions were carried out under nitrogen. THF and ether were distilled from Na/benzophenon; methanol was distilled from Mg; DMF and methylene chloride were distilled from CaH_2. Melting points were determined by using a Thomas-Hoover melting point apparatus and are uncorrected. Optical rotation were measured with a JASCO DIP-1000 digital polarimeter in a 1-dm cell. IR spectra were determined on a Hitachi 270-50 spectrophotometer. ^1H NMR, ^{13}C NMR and 2D COSY spectra were recorded on either Varian 200 MHz, 400 MHz, or Bruker ARX-300 (500 MHz) spectrometer in $CDCl_3$ used as an internal standard unless otherwise noted (value in ppm); coupling constants are reported in Hz. The elemental analysis were performed with a LECO Micro Carbon Hydrogen Determinator (CHN - 800). TLC was run on Merck precoated silicagel plates. Merck silica gel 60 (230-400 mesh) was used for column chromatography.

Methyl 2-Azido-2-deoxy-3,4;5,6-di-*O*-isopropylidene-D-mannoate (**5**). This compound was prepared as described.[12]

Methyl 2-*tert*-Butoxycarbonylamino-2-deoxy-3,4;5,6-di-*O*-isopropylidene-D-mannoate (6)

A solution of azido mannoate (**5**) (3.5g, 11.1 mmol) in dry EtOAc (30 mL) was treated at rt with 10% palladium on charcoal (350 mg) under hydrogen at atmospheric pressure and was stirred for 1 h. The mixture was filtered, and the filterate was evaporated at reduced pressure to afford gel-like product. The crude product was used for next reaction without purification.The product was dried for 1 h with vacuum pump and dissolved in MeOH (30 mL). To this solution was added triethyl amine (1.45g, 14.4 mmol) and

di-*tert*-butyl dicarbonate (3.12 g, 14.4 mmol) and the mixture was srirred at rt for 20 min. After addition of water (15 mL), the mixture was extracted three times with CH_2Cl_2 (50 mL), the combined organic phases were washed with brine, and dried over $MgSO_4$ and the solvent was evaporated at reduced pressure. The crude product was purified by flash chromatography (silica gel, hexane/EtOAc, 1:1) to afford **6** (4.02 g, 93%) as colorless oil. $[\alpha]^{20}_D$ +17.8° (c 1.03, CH_2Cl_2) ; IR (film) 3400, 2950, 1735, 1715, 1640, 1620 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.62 (d, 1H, J = 7.2 Hz), 4.42 (t, 1H, J = 6.5 Hz), 4.17 (m, 2H), 3.76 (m, 3H), 1.47 (m, 2H), 3.76 (m, 3H), 1.42 (s, OH), 1.34 (s, 9H) ; Anal. Calcd for $C_{18}H_{31}NO_8$: C; 55.50, H; 8.03, N; 3.60. Found: C; 55.37, H; 8.04, N; 3.55

1-*O*-Acetyl-2-*tert*-butoxycarbonylamino-2-deoxy-3,4;5,6-di-*O*-isopropylidene-D-mannitol (8)

A solution of the mannoate derivatives (**6**) (1.02 g, 2.6 mmol) in dry THF (20 mL) was treated at 0° C with $LiAlH_4$ (0.2 g, 5.2 mmol) for 20 min, then the mixture was allowed to warm to rt and stirring was continued for 13 h. The reaction mixture was cooled down to 0° C and hydrolyzed by addition of an aqueous solution of NaOH (15 %, 0.5 mL) and water (1 mL) and stirring was continued for 30 min at rt, then the mixture was filtered, and filtrate was evaporated at reduced pressure. The crude product was purified by flash chromatography (silica gel, hexane/EtOAc, 3:1) to afford **7** (0.89 g, 95.0%) as colorless oil. This was used next step directly. To a solution of the methyl mannoate (**7**) (1.54 g, 4.3 mmol) in dry pyridine (25 mL) at rt was added acetic anhydride (0.06 mL, 6.3 mmol) for 3 min and stirring was continued for 15 h. The solution was then hydrolyzed by addition of water (30 mL), extracted three times with EtOAc (30 mL), the combined organic phases were washed with saturated $CuSO_4$, brine and dried over $MgSO_4$ and the solvent was evaporated at reduced pressure. The crude product was purified by flash chromatography (silica gel, hexane/EtOAc, 2:1) to afford **8** (1.60 g, 93.0%) as white solid. $[\alpha]^{20}_D$ +4.6° (c 1.2, CH_2Cl_2) ; IR (film), 3425, 2900, 1770, 1710 1510 cm^{-1}; ^1HNMR (400 MHz, $CDCl_3$) δ 5.07 (1H, J = 7.47 Hz), 4.37 (dd, 1H, J = 3.13, 3.30 Hz), 4.09 - 4.15 (m, 2H), 4.04 - 4.00 (m, 3H), 3.96 - 3.94 (m, 1H), 3.91 - 3.87 (m, 2H), 2.08 (s, 3H), 1.45 (s, 3H), 1.44 (s, 9H), 1.39 (s, 3H), 1.37 (d, 6H, J = 2.56 Hz) ; Anal. Calcd for $C_{19}H_{33}NO_8$: C; 56.54, H; 8.25, N; 3.47. Found: C; 55.51, H; 8.18, N; 3.43

1-*O*-Acetyl-2-*tert*-butoxycarbonylamino-2-deoxy-3,4-*O*-isopropylidene-D-mannitol (9)

A solution of the acetate (**8**) (3.87 g, 9.6 mmol) in 90% MeOH (30 mL) was treated with Dowex 50W-X8 (0.5 g) and stirring was continued for 18 h at rt. The reaction mixture was filtered through a pad of Celite to remove the Dowex 50W-X8 resin and the solvent was removed at reduced pressure. The crude product was purified by the flash chromatography (silica gel, hexane/EtOAc, 1:1) to afford **9** (3.57 g, 97.0%) as white solid. $[\alpha]^{20}_D$ +7.2° (c 1.0, CH_2Cl_2); mp 94°C ; IR (film), 3500, 3400, 3000, 1750 1720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.41 (δ, 1H, J = 7.66 Hz), 4.33 (d, 1H, J = 9.79 Hz), 4.20 (t, 1H, J = 10.5 Hz), 4.12 (t, 2H, J = 6.12 Hz), 3.97 - 3.94 (m, 2H), 3.82 (d, 2H, J = 9.04 Hz), 3.68 (s, 2H), 3.55 (s, 1H), 2.08 (s, 3H), 1.45 (s, 9H), 1.39 (d, 6H, J = 8.47 Hz) ; Anal. Calcd for $C_{16}H_{29}NO_8$: C; 52.86, H; 8.05, N; 3.86. Found: C; 52.81, H; 8.01, N; 3.83

1-*O*-Acetyl-2-*tert*-butoxycarbonylamino-2-deoxy-3,4-*O*-isopropylidene-6-*O*-methanesulfonyloxy-D-mannitol (10)

To a solution of the diol (**9**) (3.87 g, 9.6 mmol) in dry CH_2Cl_2 (30 mL) at -10° C was added Et_3N (0.44 mL, 3.2 mmol) for 5min, then added methanesulfonyl chloride (0.41 mL, 5.28 mmol) and stirring was continued for 5 min. The solution was then hydrolized by addition of water (20 mL) and extracted three times with CH_2Cl_2 (90 mL), and the extract was dried over $MgSO_4$ and the solvent was removed at reduced pressure. The crude product was purified by flash chromatography (silica gel, hexane/EtOAc, 3:2) to afford **10** (1.03 g,83.0 %) as colorless oil. $[\alpha]^{20}_D$ +13.2° (c 1.0, CH_2Cl_2) ; IR (film), 3500, 3400, 1750, 1720 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.13 (d, 1H, J = 14.55 Hz), 4.47 (d, 1H, J = 22 Hz), 4.30 - 4.24 (m, 3H), 4.14 - 4.06 (m, 2H), 3.92 - 3.82 (m, 3H), 3.08 (s, 3H), 2.08 (s, 3H), 1.42 (s, 9H), 1.36 (d, 6H, J = 4.4 Hz) ; Anal. Calcd for $C_{17}H_{31}NO_{10}S$: C; 46.24, H; 7.08, N; 3.17. Found: C; 46.19, H; 7.11, N; 3.12

1-*O*-(*tert*-Butyldimethylsilyl)oxy-2-*tert*-butoxycarbonylamino-2-deoxy-3,4-*O*-isopropylidene-5,6-epoxy-D-mannitol (12)

A solution of mesylate (**10**) (920 mg, 2 mmol) in dry MeOH (20 mL) was treated with NaOH (100 mg, 3.0 mmol) and stirring was continued for 5 min at rt.The solution was then hydrolized by addition of water (10 mL) and extracted three times with EtOAc (90 mL), and the extract was dried over $MgSO_4$ and the solvent was removed at reduced pressure to give a corresponding epoxide (**11**). The crude product was used for next step without purification. A solution of epoxide (0.46 g, 1.7 mmol) in dry DMF (15 mL) was treated with imidazole (0.23 g, 3.39 mmol) and *tert* -butyldimethylchlorosilane (0.38 g, 2.54 mmol) and stirring was continued for 15 h at rt. The solution was then hydrolized by addition of water (30 mL) and extracted three times with EtOAc (90 mL) and the combined organic layers were washed with 100 mL of brine and dried over $MgSO_4$. The solvent was removed at reduced pressure and the residue was flash chromatographed (silica gel, hexane/EtOAc, 5:1) to give **12** (0.60 g, 92.0%) as colorless oil. $[\alpha]^{20}_D$ -5.0° (c 4.6, CH_2Cl_2) ; IR (film), 3450, 2960, 1730, 1520 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.02 (d, 1H, J = 8.90 Hz), 4.05 - 4.00 (m, 2H), 3.92 (d, 1H, J = 9.84 Hz), 3.72 (dd, 2H, J = 12.0, 3.1 Hz), 3.05 (s, 1H), 2.84 (t, 1H, J = 4.86 Hz), 2.80 - 2.75 (m, 1H), 1.47 (s, 9H), 1.43 (s, 6H), 0.93 (s, 9H), 0.10 (s, 6H) ; Anal. Calcd for $C_{20}H_{39}NO_6Si$: C; 57.52, H; 9.42, N; 3.36. Found: C; 57.49, H; 9.41, N; 3.32

(-)-Deoxymannojirimycin (3)

A solution of epoxide (**12**) (300 mg, 0.72 mmol) in EtOAc (20 mL) was treated with Me_3SiCl (233 mg, 2.16 mmol) and phenol (203 mg, 2.16 mmol) in CH_2Cl_2 (0.5 mL) at room temperarure. After 30 min the mixture was allowed to heat at reflux and stirring was continued for 12h (TLC monitoring). The solution was then hydrolized by addition of water (10 mL) and extracted three times with EtOAc (60 mL) and the combined organic layers were washed with 60 mL of brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to give crude product. The crude product was used for next step without purification. To a solution of the crude product in 90% MeOH (20 mL) at rt was added Dowex 50W-X8 (300 mg) and the reaction mixture was refluxed for 3 h. The reaction mixture was filtered through a pad of Celite, and the remaining Dowex 50W-X8 was eluted with 2N NH_4OH (20 mL), then the filterate and

eluted aqueous solution of NH_4Cl were combined together. The combined solution was evaporated with benzene (60 mL) under reduced pressure to afford compound (**3**) (64.5 mg, 55%) as white solid. The physical and spectral data of **3** were consistent with literature.[3a,9]

2*R*,5*S*-Dihydroxymethyl-3*R*,4*R*-dihydroxypyrrolidine (13)

A solution of $AlCl_3$ (0.04 g, 0.32 mmol) in dry ether (10 mL) was treated at 0° C under nitrogen with $LiAlH_4$ (0.01 g, 0.32 mmol).The mixture was stirred for 15 min and a solution of epoxide (**12**) (0.06 g, 0.16 mmol) in ether (8 mL) was added. The reaction mixture was refluxed for 3 h (TLC monitoring) and allowed to cool to rt. The reaction mixture was then hydrolyzed by addition of an 5% aqueous solution of NaOH (0.5 mL) and stirring was continued for 2 h. The mixture was then filtered through a pad of Celite and the solvent was evaporated under reduced pressure to afford compound (**13**) (0.04 g, 86.3%) as white solid and trace amount of **3**. The physical and spectral data of **13** were consistent with literature.[11]

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REFERENCES

1. U. Fuhrmann, E. Bause, and H. Ploegh, *Biochim. Biophys. Acta* , 1985, 825, 95.
2. S. V. Evans, L. E. Fellows, T. K. M. Shing, and G. W. J. Fleet, *Phytochem.*, 1985, **24**, 1953.
3. G. W, J. Fleet, S. J. Nicholas, P. W. Smith, S. V. Evans, L. E. Fellow, and R. J. Nash, *Tetrahedron Lett.*, 1985, **26**, 31274; B. P. Bashyal, G. W. J. Fleet, M. J. Gough, and P. W. Smith, *Tetrahedron* , 1987, **43**, 3087.
5. U. Fuhrmann, E. Bause, G. Legler, and H. Ploegh, *Nature*, 1984, **307**, 755.
6. A. D.Elbein, G. Legler, A. Tlutsy, W. McDowel, and R. Schwarz, *Arch. Biochem. Biophys.*, 1984, 235, 579.
7. S. V. Evans, L. E. Fellows, T. K. M. Shing, and G. W. J. Fleet, *Phytochemistry*, 1985, **24**, 1953.
8. H. Eilingsfeld, G. Neubauer, M. Seefelder, and H. Weidinger, *Chem. Ber.*, 1964, **97**, 1232.
9. K. H. Park, Y. J. Yoon, and S. G. Lee, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2621.
10. K. H. Park, Y. J. Yoon, and S. G. Lee, *Tetrahedron Lett.*, 1994, **35**, 9737.
11. K. K. -C. Liu, T. Kajimoto, L. Chen, Z. Zhong, Y. Ichikawa, and C.-H. Wong, *J. Org. Chem.*, 1991, **56**, 6280; A. B. Rietz, and E. W. Baxter, *Tetrahedron Lett.*, 1990, **31**, 6777.
12. H. Regeling, E. de Rouville and G. J. F. Chittenden, Recl. *Trav. Chim. Pays-Bas*, 1987, **106**, 461; R. Csuk, M. Hugemer, and A. Vasella, *Helv. Chim. Acta*, 1988, **71**, 609.
13. Sr. K. Emil, J. P. Tam, T. M. Kubiak, and R. B. Merrifield, *Tetrahedron Lett.*, 1988, **29**, 303.
14 B. B. Lohray, Y. Jayamma, and M. Chatterjee, *J. Org. Chem.*, 1995, **60**, 5958.

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