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ASYMMETRIC SYNTHESIS OF TRANS-(2R,5R)-BIS(BENZYLOXYMETHYL)PYRROLIDINE

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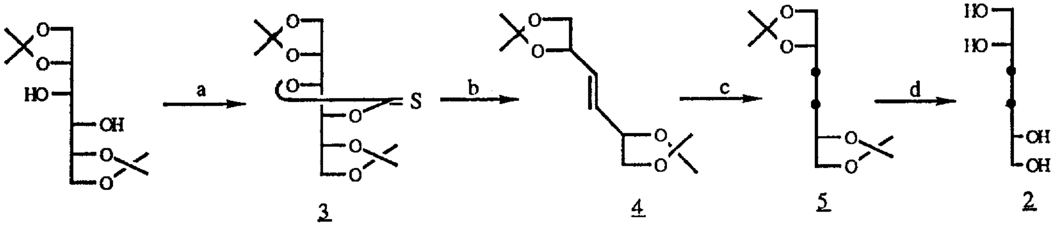
Summary: Trans-(2R,5R)-bis(benzyloxymethyl)-pyrrolidine (1) was prepared from 1,2:5,6-diisopropylidene mannitol. Key transformations included the selective protection of primary hydroxy groups and stereocontrolled cyclization.

Quite recently the remarkable advantages of using trans-2,5-bis(alkyloxymethyl)-pyrrolidines as chiral auxiliaries have been described.[1-3] Optically pure pyrrolidines were usually obtained via resolution of the corresponding racemates whereas only few examples of asymmetric synthetic routes have been reported.[4]

We now report an efficient, asymmetric synthesis of trans-(2R,5R)-bis(benzyloxymethyl) pyrrolidine 1 from 1,2:5,6-di-O-isopropylidene mannitol.

Our synthetic pathway includes first a synthesis of 3,4-dideoxy-D-threo-hexitol 2 with higher yields in comparison with those obtained by an alternative way[5] and then the transformation of 2 into the pyrrolidine 1.

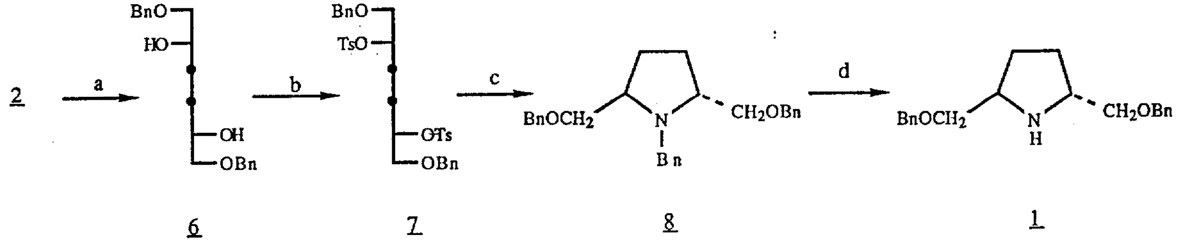
3,4-Thionocarbonate 3 was prepared by stirring 1,2:5,6-di-O-isopropylidene mannitol with 1,1-thionocarbonyldiimidazole (TCDI)[6] in anhydrous THF for 72 h at room temperature (98% yield; mp 162-163°C, $[\alpha]_D = -14°$, CH_2Cl_2).[7] The product was purified by chromatography on silica gel, and refluxed with redistilled triethyl phosphite[8] for 12 h to give trans-3,4-di-dehydro-3,4-dideoxy-1,2:5,6-di-O-isopropylidene-D-threo-hexitol 4 (93% yield; mp 80-82°C, $[\alpha]_D = +57°$, $CHCl_3$).[7] Reduction of 4 to 3,4-dideoxy-1,2:5,6-di-O-isopropylidene-D-threo-hexitol 5 was obtained by hydrogenation in ethanol using rhodium on activated alumina as catalyst[9] at room temperature for 20 h (95% yield; oil, $[\alpha]_D = +18.5°$, CH_2Cl_2). Finally, 5 was quantitatively hydrolyzed to 3,4-dideoxy-D-threo-hexitol 2 (mp 84°C, $[\alpha]_D = -24°$, CH_3OH).



a) TCDI, an. THF b) $P(OEt)_3$, Δ c) H_2, Rh/Al_2O_3, EtOH d) TsOH, acq. MeOH

Selective protection of the two primary hydroxy groups of 2 was achieved through the preparation of the organotin derivative[10]: hexitol 2 was refluxed for 5 h in toluene with dibutyltinoxide, with azeotropic removal of water; then benzyl bromide and tetrabutylammonium bromide were added and the solution stirred at 70°C for 5 h[11-12]. The so obtained

1,6-dibenzyl-3,4-dideoxy-D-threo-hexitol 6 was purified by chromatography on silica gel column (60% yield; oil, $[\alpha]_D = -5.9°$, MeOH) and then treated with TsCl[13] to give 1,6-dibenzyl-2,5-ditosyl-3,4-dideoxy-D-threo-hexitol 7, isolated by chromatography on silica gel column (70% yield; mp 67-68°C, $[\alpha]_D = +3.25°$, CH_2Cl_2). The above ditosylate as then transformed in the pyrrolidine 8 by stirring a solution of 7 in benzylamine for 20 min at 80°C.[13] Ring closure proceeded with complete inversion at C-2 and C-5 of the hexitol, and the N-benzyl-trans-(2R,5R)-bis(benzyloxymethyl)pyrrolidine 8 was the only reaction product (90% yield; oil, $[\alpha]_D = +68.3°$, CH_2Cl_2). N-Debenzylation was selectively accomplished by $Pd(OH)_2/C$ hydrogenation[14-15] to produce trans-(2R,5R)-bis(benzyloxymethyl)- pyrrolidine 1 (90% yield; oil, $[\alpha]_D = -3.2°$, MeOH).



a) Bu_2SnO, Toluene, reflux; BnBr, $Bu_4N^+Br^-$ b) TsCl, Py, 0°C c) $BnNH_2$, Δ d) H_2, $Pd(OH)_2/C$, EtOH

The above reported results can be easily generalized and they represent a facile and practical way to obtain optically pure 2,5-disubstituted pyrrolidines.

References

1) Kawanami, Y.; Fujitu, I.; Taniguchi, Y.; Katsuki, T.; Yamaguchi, M. Chem. Lett. (1987) 2021
2) Kawanami, Y.; Ito, Y.; Kitagawa, T.; Taniguchi, Y.; Katsuki, T.; Yamaguchi, M. Tetrahedron Lett. (1984) 25, 857
3) Kawanami, Y.; Katsuki, T.; Yamaguchi, M. Bull. Chem. Soc. Japan (1987) 60, 4190
4) Shing T.K.M. J. Chem. Soc. Chem. Commun. (1987) 262 and references therein
5) Kuszmann, J.; Sohar, P. Carbohydrate Res. (1980) 83, 6372
6) Vedejs, E.; Wu, E.S. Tetrahedron Lett. (1973) 24, 3793
7) Haines, A.H. Carbohydrate Res. (1965) 1, 214
8) Corey, E.J.; Winter, R.A. J. Am. Chem. Soc. (1963) 85, 2677 and references therein
9) Fieser, L.F.; Fieser, M. in "Reagents for Organic Synthesis", vol.1, p. 979, J. Wiley and Sons, New York (1967) and references therein
10) David, S.; Hanessian, S. Tetrahedron (1985) 41, 643
11) Dasgupta, F.; Garegg, P.J. Synthesis (1988) 8, 626
12) Garegg, P.J.; Lindberg, B. Carbohydrate Res. (1988), 173, 205
13) Lamm, B.; Ankner, K.; Frantsi, M. Acta Chem. Scand. (1987) 41, 202
14) Yoshida, K.; Nakajima, S.; Wakamatsu, T.; Bau, Y.; Shibasaki, M. Heterocycles (1988) 27, (1167)
15) Zilcha, A.; Rachiman, E.S.; Rivlin, J. J. Org. Chem. (1961) 26, 376

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