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Stereoselective Synthesis of *N*-Acetyl-L-Tolyposamine from (S) Ethyl β-Hydroxybutyrate

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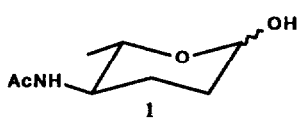
Abstract: The title aminosugar **1** was stereoselectively prepared in 13 steps and 16% overall yield from L-*allo*-threonine synthetic equivalent **2**, which is in turn obtained in one step from (*S*) ethyl β-hydroxybutyrate.

2,3,4,6-Tetradeoxy-4-aminohexoses are important aminosugars present in nature as subunits of some antibiotics.[1] Moreover it has been recently shown that the L-isomers can be used as substitutes of L-daunosamine as sugar components in antitumor antibiotics of the adriamycin family.[2] While all the non-racemic syntheses known to date utilize other sugars as starting materials, we thought that a non-carbohydrate-based approach would provide higher flexibility especially in view of the projected preparation of analogues. We now report the successful preparation in high overall yield of *N*-acetylated L-tolyposamine **1** (2,3,4,6-tetradeoxy-4-acetylamino-L-*erythro*-hexose),[3] from the protected α-hydrazino-β-hydroxyester **2** as chiral building block. **2**, which is a synthetic equivalent of L-*allo*-threonine, is in turn efficiently and stereoselectively synthesized in one step[4a] from easily available (*S*) ethyl β-hydroxybutyrate through "electrophilic amination" of its dianion with di-t-butylazodicarboxylate.



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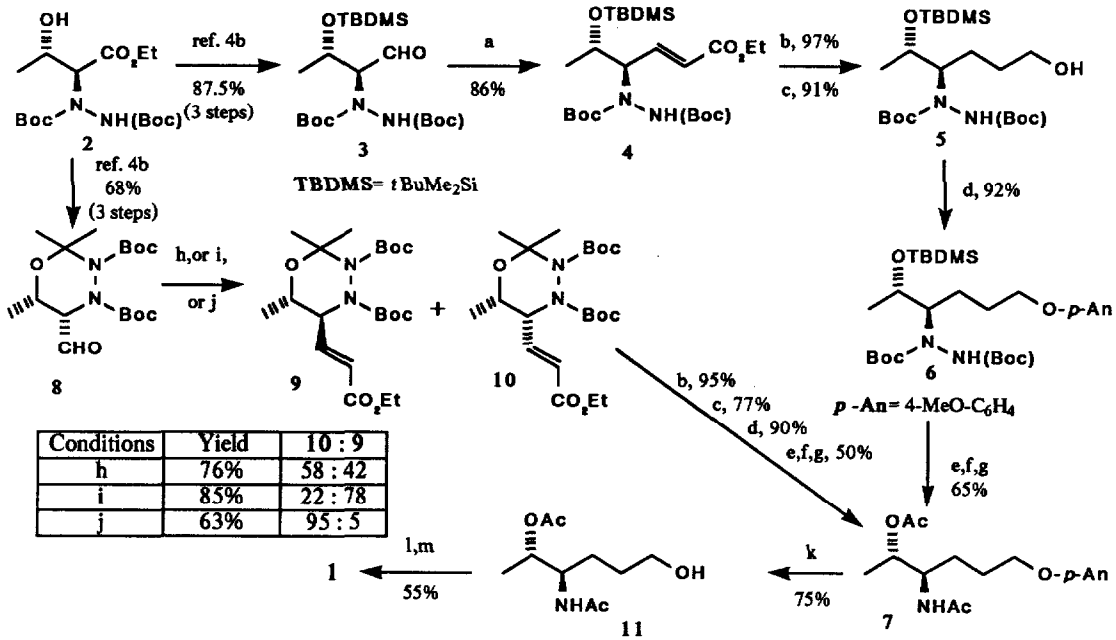
Compound **2** was converted, as already reported by us,[4b] into aldehyde **3**, where the 3-hydroxyl group is protected as t-butyldimethylsilyl ether. This aldehyde was then extended *via* a Wittig condensation with a stabilized phosphorane.[5] Hydrogenation of the double bond and reduction of the ester moiety[6] furnished alcohol **5**, which was in turn protected as the *p*-anisyl ether.[7] Deblocking under acidic conditions of silyl ether and Boc groups, followed by N-N bond hydrogenolysis and acetylation afforded the advanced intermediate **7**, in 40% overall yield from **2**. **7** was also prepared through an alternative route, involving the cyclic aldehyde **8**. In this case 2-carbon homologation *via* the Wittig condensation turned out to be very sluggish and a substantial epimerization to the *trans* isomer **9** took place (see Scheme). We succeeded in avoiding this problem by using the Roush-Masamune modification of the Wadsworth-Horner-Emmons condensation.[8] Interestingly, the choice of base had a dramatic influence on the degree of epimerization. Transformation of **10** into **7** was then carried out uneventfully through a sequence of reactions similar to that employed for **4**. The overall yield of **7** from **2** (14%) was however lower in this case.

Transformation of intermediate **7** into *N*-acetyl-L-tolyposamine was then accomplished *via* oxidative removal of *p*-anisyl group to give the primary alcohol **11**, which was then oxidized under mild conditions using the method recently developed by Ley *et al*.[9] Finally, selective deacetylation furnished the desired *N*-acetyl L-tolyposamine **1**. The overall yield from **2** following the best route was an excellent 16.4% (13 steps). We are currently exploring the synthesis of the L-*threo* isomer of **1** (L-*epi*-tolyposamine) by a similar strategy.

We wish to thank miss Giuseppina Ageno for her collaboration to this work, and C.N.R. (Progetto Finalizzato Chimica Fine) and M.U.R.S.T. for financial assistance.

SCHEME

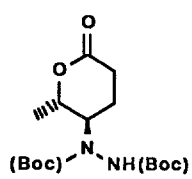


Conditions	Yield	10 : 9
h	76%	58 : 42
i	85%	22 : 78
j	63%	95 : 5

a) Ph_3P=CH-COOEt, toluene, powdered 4 Å mol. sieves, 70°C, 2h; b) H_2, PtO_2, EtOH, r.t., 5d (from 4) or 3d (from 10); c) $Ca(BH_4)_2$, EtOH, THF, -20°C → r.t.; d) *p*$MeOC_6H_4OH$, Ph_3P, DEAD, CH_2Cl_2, r.t.; e) AcOH / 1N HCl 2:1, 70°C (from 6) or 80°C (from 10), 45 min; f) H_2, PtO_2, EtOH-H_2O, 50h; g) Ac_2O, pyridine, DMAP, 20h, r.t.; h) Ph_3P=CH-COOEt, 4 Å mol. sieves, toluene, 9h at 70°C + 2 h at reflux; i) $(EtO)_2PO$-CH_2COOEt, DBU, LiCl, 4 Å mol. sieves, CH_3CN, r.t., 3h; j) $(EtO)_2PO$-CH_2COOEt, $EtN(i\ Pr)_2$, LiCl, r.t., CH_3CN, 4 Å mol. sieves, 30h; k) $(NH_4)_2Ce(NO_3)_6$, H_2O, CH_3CN, pyridine, 0°C, 3h; l) $(n\text{-}Pr)_4NRuO_4$, N-methylmorpholine N-oxide, CH_2Cl_2, 4 Å mol. sieves, r.t.; m) DBU, MeOH, 70°C, 2.5h.

REFERENCES AND NOTES

1) *The Carbohydrates: Chemistry and Biochemistry*, Pigman & Horton Eds., Academic Press, New York, 1970; vol. IB, p. 643; vol. IIA, p. 139.
2) Cipollone A., Peirone E., Animati F., Lombardi P., III Convegno sulla Chimica dei Carboidrati, June 3-5, 1990, Ferrara (Italy), p. 63.
3) L-Tolyposamine is a component of antibiotic tolypomycin: Kishi T., Harada S., Asai M., Muroi M., Mizuno K., *Tetrahedron Lett.*, **1969**, 97. Previous syntheses: Bastian G., *et al.*, *J. Med. Chem.*, **1981**, *24*, 1383; see also ref. 2.
4) a) Guanti G., Banfi L., Narisano E., *Tetrahedron*, **1988**, 5553. b) Guanti G., Banfi L., Narisano E., *Tetrahedron Lett.*, **1989**, *30*, 5511; c) Guanti, G.; Banfi, L.; Narisano, E.; Thea, S., *Synlett*, in the press.
5) Enoates **4**, **9**, and **10** were obtained with (*E*) configuration; only minor amounts (<5%) of (*Z*) isomers were detected.
6) An alternative way, involving δ-lactone **12** as intermediate, failed, since **12**, upon attempted hydrolysis of Boc groups (CF_3COOH, CH_2Cl_2) followed by N-N bond hydrogenolysis (H_2, PtO_2, EtOH-H_2O) and acetylation, furnished 5-(1-acetoxyethyl)-1-acetylamino-2-pyrrolidinone, instead of the desired 5-acetylamino-6-methyl-tetrahydropyran-2-one. This result is in line with a similar behaviour shown by other 4-[N,N-*bis*(*t*-butoxycarbonyl)hydrazino]hexonic acids.[4c]



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7) Fukuyama T., Laird A.A., Hotchkiss L.M., *Tetrahedron Lett.*, **1985**, *26*, 6291.
8) Blanchette M.A., Choy W., Davis J.T., Essenfeld A.P., Masamune S., Roush W.R., Sakai T., *Tetrahedron Lett.*, **1984**, *25*, 2183.
9) Griffith W.P., Ley S.V., *Aldrichimica Acta*, **1990**, *23*, 13.

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