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Synthesis of Branched-Chain Azafuranose Derivatives from Secondary Nitroalkanes. Facile Synthesis of (±) 4-Amino-4,4-bis(hydroxymethyl)-4-deoxythreonic-1,4-lactam

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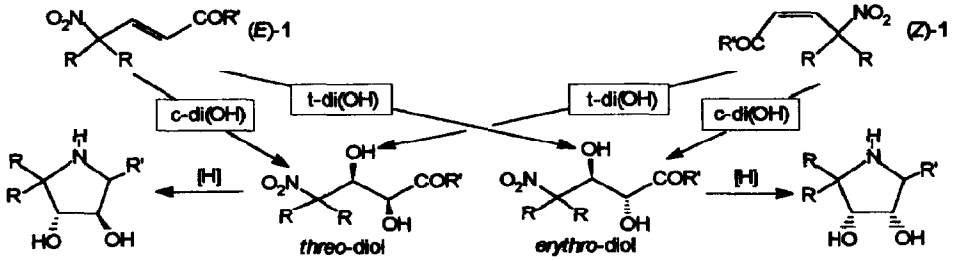
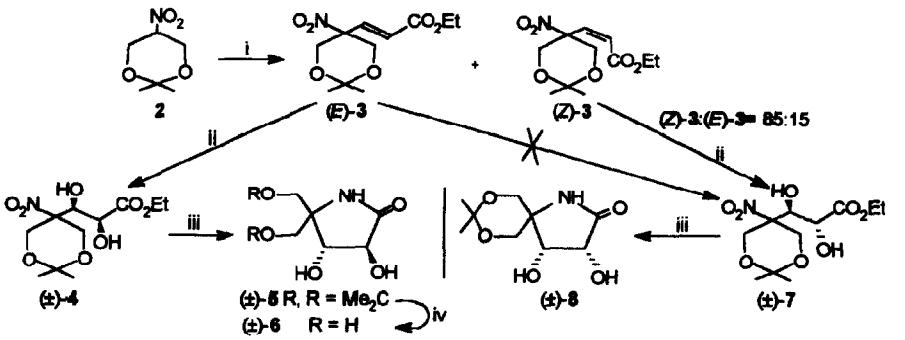
Abstract: The title branched-chain threonic-1,4-lactam **6** was smoothly prepared in four steps from readily available 2,2-dimethyl-5-nitro-1,3-dioxane **2**.

Azasugars, i.e. sugars in which ring oxygen was replaced by nitrogen, have attracted a considerable attention as glycosidase inhibitors[2,3] and potential chemotherapeutic agents.[3,4] Consequently, numerous syntheses of divers azasugars have been described recently.[3,5] However, amongst their variety we found only one procedure, described by Vogel and co-workers,[6] which yields branched-chain derivatives of azahexopyranose. It seemed to us that unknown branched-chain azafuranoses might show interesting biological activity. We conceived that these azafuranose derivatives might be conveniently prepared from secondary nitroalkanes (Scheme 1). The key step in our method involves the synthesis of an (*E*) or (*Z*) isomer of a compound having the structure **1**. Each isomer of **1** can be subsequently converted stereospecifically into *threo*-diol or *erythro*-diol by *cis*-dihydoxylation [c-di(OH); e.g. catalytic osmylation] or by *trans*-dihydroxylation [t-di(OH); e.g. epoxydation followed hydrolysis] as it is outlined in the Scheme 1. Reduction of nitro group affords corresponding azafuranose branched at C-4. The function at C-1 depends on type of R'; e.g. compound **1** with R' = O-alkyl gives azasugar g-lactam.



Scheme 1

There is a little information on the synthesis of the derivatives of type **1**. Michael addition of nitroalkanes to alkyl propynoates, which affords mainly isomer (*E*) of esters of the type **1** (R' = OMe or OEt),[7] was suitable for our purpose. Thus, to examine the idea we set as the first synthetic target the azasugar g-lactam, namely 4-amino-4,4-bis(hydroxymethyl)-4-deoxythreonic-1,4-lactam (**6**) (Scheme 2). Michael addition of 2,2-dimethyl-5-nitro-1,3-dioxane (**2**)[8] to ethyl propynoate in the presence of N,N,N',N'-tetramethylguanidine (TMG) catalyst gave the mixture of (*E*)-**3** and (*Z*)-**3** in ratio the 4:1. Crystallisation of the mixture from hexane afforded the isomer (*E*)-**3** (m. p. 71-72 °C)[9] in 64% yield calculated on the dioxane **2**.



Reagents and conditions: i) ethyl propynoate, MeCN, 0 °C, TMG (10 mol%); ii) 70% *t*-BuOOH, acetone, OsO_4 cat., AcONa, $(n\text{-}Bu)_4N^+HSO_4^-$, 24 h; iii) H_2, 9 Atm, 10% Pd-C, MeOH, sonication, 50 °C, *ca.* 16 h; iv) 90% CF_3CO_2H aq. r. t., 1 h.

Scheme 2

The liquid residue obtained after isolation of (*E*)-**3** was an inseparable mixture of both stereoisomers (*Z*) and (*E*) in the ratio 85:15. Catalytic osmylation of (*E*)-**3** in the presence of *tert*-butylhydroperoxide[10] furnished (±) *threo*-diol **4** (m.p. 124-125 °C from ethyl acetate-hexane mixture) in 79.5% yield. Hydrogenation of **4** over palladium catalyst afforded instantly the lactam **5** (m.p. 190-191 °C from isopropanol) in yield varied from 20% to 80% depended on the conditions. The highest yield of **5** (80%) was obtained when the hydrogenation was carried out under sonication. The isopropylidene group was removed by aqueous trifluoroacetic acid giving the lactam **6** (m. p. 163-164 °C from isopropanol) in 67.2% yield (total yield of **6** from **2** was 25%).

Next we tried to transform (*E*)-**3** into *erythro*-diol **7**, the key intermediate in the synthesis of lactam **8**, by an epoxidation-hydrolysis sequence but this could not be achieved since attempted epoxidation of (*E*)-**3** under variety conditions failed. Therefore, the *erythro*-lactam **8** was prepared from the crude mixture of the isomers obtained after the separation of (*E*)-**3**. *Cis*-dihydroxylation followed catalytic hydrogenation converted the (*Z*)-**3** and (*E*)-**3** mixture into the mixture of the lactams **5** and **8** in the proportion similar to the ratio (*Z*)-**3** : (*E*)-**3**. Column chromatography separation followed crystallisation from isopropanol yielded a small sample of **8** (m. p. 184 -185 °C) with NMR purity >95%. This was not deprotected.

The efficient stereocontrolled synthesis of the title lactam **6** proved usefulness of nitroalkanes at the preparation of the azasugars. Further studies on improvement and extension of this methodology as well as on its asymmetric version are under way.

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