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Diastereoselective synthesis of 5-(alditol-1-*C*-yl)-hydantoins and their use as precursors of polyhydroxylated-α-amino acids

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Abstract—The synthesis of 5-(alditol-1-*C*-yl)-hydantoin derivatives was performed via diastereoselective aldol-type addition of 1,3-dibenzyl-hydantoin to enantiopure aldehydo sugars. Starting from the D-*ribo*-configured 5-(alditol-1-*C*-yl)-hydantoin template, the synthesis of (2*R*,3*S*,4*R*)-3,4,5-trihydroxynorvaline was carried out.

The search for new synthetic methodologies for the synthesis of enantiomerically pure bioactive molecules is an area of great interest in modern synthetic organic chemistry. A complex structure or the presence of multiple stereocentres makes the synthetic approach to these molecules a stimulating task.

Among the different strategies used, the stereoselective and versatile approach based, as a key operation, on carbon–carbon bond formation between heterocycles and enantiopure sugar-derived templates has been widely used. Five-membered heterocycles such as furan, pyrrole, thiophene,[1] thiazole[2] and isoxazoline[3] derivatives or six-membered heterocycles such as substituted 2,5-diketopiperazines[4] have shown their utility for the synthesis of a wide set of molecules of biological interest.

In this field we have recently reported the use of dihydrouracil for the diastereoselective chain extension of isopropylidene-protected glyceraldehyde.[5]

Proceeding with our programme aimed to develop new stereoselective procedures for the synthesis of enantiopure bioactive molecules, we have directed our attention towards hydantoin, a five-membered analogue of dihydrouracil, as a new homologating reagent for aldehydo sugars (Fig. 1).[6]

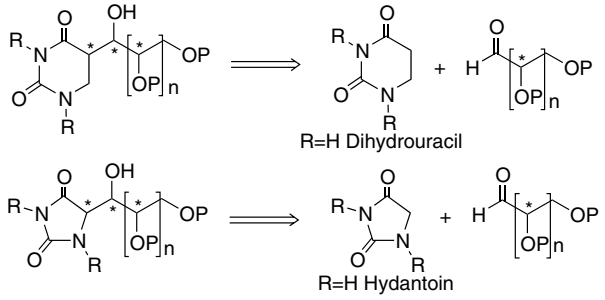

Figure 1.

For this purpose hydantoin is an important molecule because hydantoin derivatives such as 5-*C*-glycosylated hydantoins show pharmacological or phytopharmacological activity. Specifically, the spirohydantoin of glucopyranose **1** is a potent inhibitor of glycogen phosphorylase and has been examined for the treatment of late-onset diabetes,[7] while hydantocidin **2**, a ribofuranosyl spirohydantoin, displays potent herbicidal activity.[6,8,9]

Furthermore, since this heterocycle has been used as a synthetic equivalent of glycine by chemical or enzymatic ring opening,[10] 5-(alditol-1-*C*-yl)-hydantoin derivatives are precursors for the synthesis of sugar amino- and ureido-acid hybrids.

Herein is disclosed the simple and diastereoselective synthesis of 5-(alditol-1-*C*-yl)-hydantoin derivatives via

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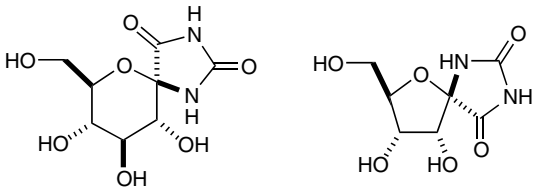
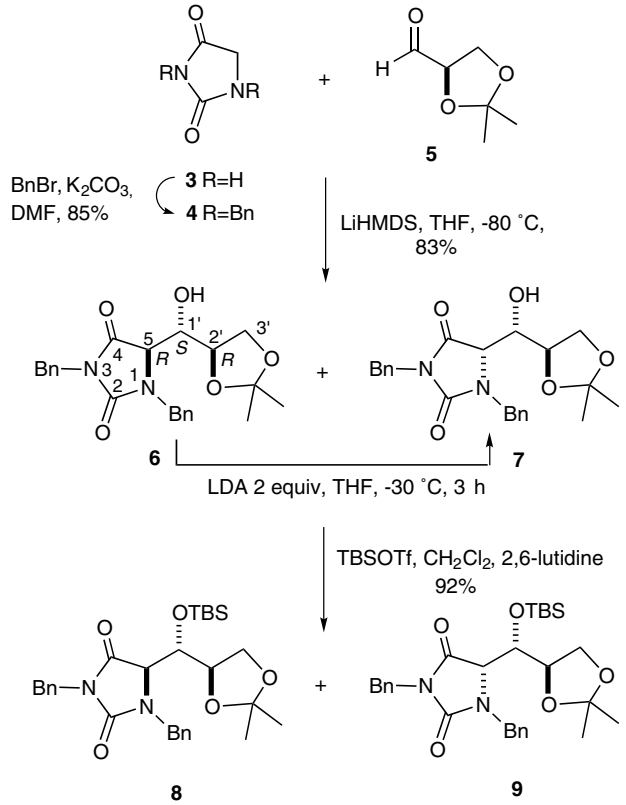
the aldol-type addition of 1,3-dibenzyl-hydantoin (DBH) **4** to enantiopure aldehydo sugars **5** and **10**. Extending the scope of this methodology, the synthesis of the polyhydroxylated-α-amino acid **12** is also reported. Trihydroxylated norvaline congeners are biologically important molecules. For example, (2*S*,3*S*,4*S*)-3,4,5-trihydroxynorvaline [(+)polyoxamic acid] is a component of the polyoxins, an important family of complex peptidyl nucleosides with potent antibiotic activity.[11]



1 **2**

Initially we prepared DBH **4** by N-protection of commercially available hydantoin **3** under weakly basic conditions in 85% yield (Scheme 1).[12]

Then we examined the addition reaction of the aldehyde **5** with the DBH lithium enolate, derived from the reaction of **4** with 1.2 equiv of LiHMDS in anhydrous THF at −80 °C. After quenching and aqueous workup, D-*ribo*-configured 5-(alditol-1-*C*-yl)-hydantoin **6** was obtained in high yield and good diastereoselectivity with a small amount of its C-5 epimer **7** (80/20 isomer ratio **6**/**7** determined by NMR analysis) (Scheme 1).[13] Purification of compound **6** was achieved at this stage by crystallization of the crude reaction mixture from CH_2Cl_2/hexane 1/3 or by flash chromatography (hexanes/EtOAc 6/4) of the protected mixture of **8** and **9** obtained by exposure of the crude material to TBSOTf in CH_2Cl_2 in the presence of 2,6-lutidine.[14] Epimerization at C-5 was observed when compound **6** was allowed to react from −80 to −30 °C with 2.0 equiv of LDA for 3 h. After aqueous workup, the two epimers **6** and **7** were obtained in a 73/27 isomeric ratio.



5 **6** **7** **8** **9**

Scheme 1.

The (5*R*,1′*S*) configuration of the two new stereocentres in 5-(alditol-1-*C*-yl)-hydantoin **6** was unambiguously established by single crystal X-ray analysis on the basis of the known (*R*) configuration at the 2′ carbon atom (Fig. 2).[15,16] On the basis of the configurations of the stereocentres of compound **6** the (5*S*,1′*S*) configuration of its C-5 epimer **7** can be inferred.

Formation of 5,1′-*anti*-1′,2′-*anti* aldol **6** and 5,1′-*syn*-1′,2′-*anti* aldol **7** results from an unlike (*Re* enolate, *Si* aldehyde) and like (*Si* enolate, *Si* aldehyde) approach, respectively, of the reaction partners in the addition step. In both cases the *Si*-face of aldehyde **5** reacts selectively.[17]

To demonstrate the synthetic versatility of this procedure for the diastereoselective preparation of 5-(alditol-1-*C*-yl)-hydantoin derivatives containing multiple stereogenic centres and different lengths of the polyol chains, the synthesis of hydantoin templates **11** was also undertaken (Scheme 2).

The addition of 2,3:4,5-di-*O*-isopropylidene-D-xylose **10** to DBH lithium enolate under the same reaction conditions reported for the glyceraldehyde derivative furnished preferentially D-*glycero*-L-*talo* configured 5-(alditol-1-*C*-yl)-hydantoin **11** in 70% yield (a 72/28 isomeric ratio was detected by NMR analysis of the crude material).[18]

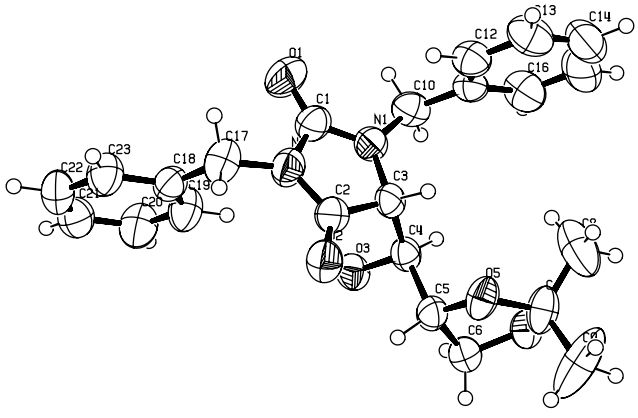
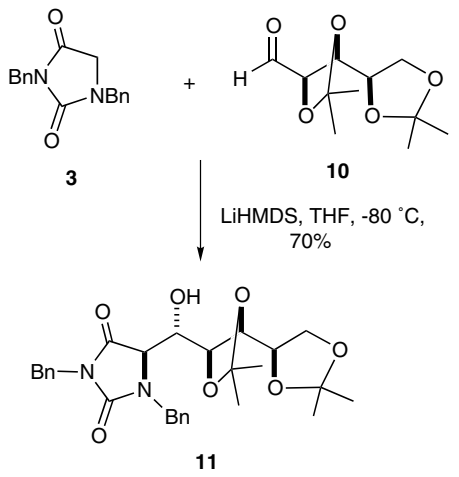
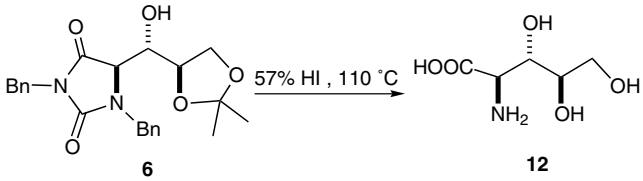


Figure 2. X-ray diffraction structure of compound **6**. Thermal ellipsoids are drawn at the 30% probability level. Stereocentres at positions 5, 1′ and 2′ are labelled as C3, C4 and C5, respectively.



Scheme 2.



Scheme 3.

Starting from the D-*ribo*-configured enantiopure precursor a simple procedure for the synthesis of the biologically important polyhydroxylated-α-amino acid **12** was carried out. When compound **6** was refluxed with 57% HI, the acetonide and benzyl protecting groups were removed with concomitant hydrolytic cleavage of the heterocyclic ring (Scheme 3). After ion-exchange chromatography with Amberlyst H 15 (H^+ form), 2-amino-2-deoxy-D-ribonic acid **12** was obtained in 48% yield. The optical rotation for **12** [−3.0 (*c* 0.37, H_2O)] and its NMR spectra matched well with the reported data of an authentic sample of **12**.[11b,c]

In conclusion, we have shown the use of 1,3-dibenzylhydantoin as homologating reagent for the diastereoselective chain extension of aldehydo sugars. Enantiomerically pure 5-(alditol-1-*C*-yl)-hydantoin derivatives with variable polyol chains have been synthesized in good diastereoselectivity and yield. Starting from the D-*ribo*-configured enantiopure precursor, a simple procedure for the synthesis of the biologically important trihydroxylated norvaline **12** was realized. Application of this procedure to the synthesis of sugar amino and ureido acid hybrids is in progress.

Acknowledgements

The authors thank the Regione Autonoma della Sardegna for generous financial support, and Ms. Manuela Azara and Mrs. Barbara Sechi for GC and HPLC Mass spectra.

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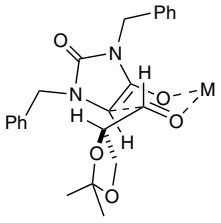
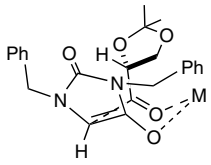
12. Compound **4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.20 (m, 10H), 4.66 (s, 2H), 4.52 (s, 2H), 3.68 (s, 2H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.3, 156.4, 135.9, 135.2, 128.8, 128.6, 128.5, 128.0, 127.8, 48.9, 46.6, 42.5. White solid, mp 46–48 °C.
13. Only a marginal amount (<7%) of the other two diastereomers were detected by NMR analysis. Compound **6**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.22 (m, 10H), 5.02 (d, $J = 15.3$, 1H), 4.69 and 4.64 (AB system, $J_{AB} = 14.7$, 2H), 4.36 (ddd, $J = 8.7$, 6.0, 4.0, 1H), 4.27 (d, $J = 15.3$, 1H), 4.11 (d, $J = 2.1$, 1H), 4.02 (dd, $J = 8.7$, 6.0, 1H), 3.93 (dd, $J = 9.0$, 4.2, 1H), 3.93–3.87 (m, 1H), 2.33 (d, $J = 5.4$, 1H, OH), 1.22 (s, 3H), 1.21 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.2, 157.3, 135.8, 129.2, 128.8, 128.5, 127.9, 109.2, 74.2, 71.1, 67.0, 61.4, 45.5, 42.8, 26.8, 25.0. White solid, mp 182–184 °C, $[\alpha]_D^{20}$ +44 (*c* 0.6, $CHCl_3$).
14. Compound **8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.20 (m, 10H), 5.21 (d, $J = 15.3$, 1H), 4.68 and 4.62 (AB system, $J_{AB} = 14.1$, 2H), 4.32–4.23 (m, 1H), 4.13 (d, $J = 15.3$, 1H), 4.06 (d, $J = 1.5$, 1H), 4.04 (dd, $J = 8.7$, 3.3, 1H), 4.04–4.00 (m, 1H), 3.83 (dd, $J = 8.7$, 4.5, 1H), 1.16 (s, 3H), 1.15 (s, 3H), 0.79 (s, 9H), 0.10 (s, 3H), −0.10 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.9, 155.8, 136.0, 135.5, 129.3, 128.9, 128.4, 128.1, 127.6, 109.7, 75.0, 73.0, 67.0, 61.9, 44.6, 42.6, 26.5, 25.9, 25.4, 17.9, −1.5, −2.5. Colourless oil $[\alpha]_D^{20}$ +34 (*c* 0.7, $CHCl_3$).
Compound **9**: ^{1} H NMR (300 MHz, $CDCl_3$) δ 7.50–7.30 (m, 10H), 4.96 (d, $J = 15.9$, 1H), 4.69 and 4.64 (AB system, $J_{AB} = 14.4$, 2H), 4.41 (d, $J = 15.3$, 1H), 4.22 (s, 1H), 4.08 (d, $J = 9.0$, 1H), 3.99 (dd, $J = 8.4$, 6.0, 1H), 3.85 (m, 1H), 3.71 (dd, $J = 8.1$, 5.4, 1H), 1.33 (s, 3H), 1.22 (s, 3H), 0.81 (s, 9H), 0.22 (s, 3H), 0.14 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 171.8, 157.8, 136.4, 135.9, 129.2, 128.9, 128.1, 127.9, 127.4, 127.1, 109.5, 75.7, 72.9, 68.5, 62.0, 46.7, 42.8, 26.3, 25.8, 25.3, 24.8, 17.8, −4.0, −5.3. Colourless oil $[\alpha]_D^{20}$ −35 (*c* 0.5, $CHCl_3$).
15. Crystallographic data for **6**: $C_{23}H_{26}N_2O_5$; crystal system: monoclinic; space group: $P2_1$. Unit cell parameters: $a = 14.157(3)$, $b = 5.469(2)$, $c = 14.598(3)$ Å, $\beta = 110.40(4)°$. $Z = 2$. $V = 1059.4(5)$ Å^3. $R_1 = 0.0501$ [on $F \geqslant 4\sigma(F)$]; $wR_2 = 0.1389$ (on F^2, all data). Data/restraints/parameters: 2119/13/247. Goodness-of-fit on $F^2 = 1.018$.
16. Crystallographic data for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 220239. Copies of the data can be obtained free of charge on application to CCDC 12 Union Road, Cambridge CB2 1EZ (Fax: +44-1223-336-036. E-mail: deposit@ccdc.cam.ac.uk).
17. The diastereoselectivity observed can be explained by the preferential formation of the cyclic transition state TS1 over TS2.



TS1



TS2

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18. The D-*glycero*-L-*talo* configuration of compound **11** was proposed based upon ^{1}H NMR spectral data and reasonable assumptions based upon mechanistic analogy. Compound **11**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.22 (m, 10H), 5.05 (d, $J = 15.3$, 1H), 4.65 (d, $J = 2.7$, 2H), 4.41–4.43 (m, 1H), 4.28 (d, $J = 15.3$, 1H), 4.18–4.08 (m, 2H), 4.40–3.75 (m, 2H), 3.83 (dd, $J = 8.7$, 6.6, 1H), 3.50 (d, $J = 2.7$, 1H), 1.39 (s, 3H), 1.35 (s, 3H), 1.20 (s, 3H), 1.13 (s, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.2, 157.3, 136.0, 135.8, 128.9, 128.4, 128.0, 127.6, 110.6, 110.2, 80.2, 75.1, 74.3, 72.3, 65.3, 61.4, 45.5, 42.5, 26.8, 26.3, 25.8, 24.5. Light yellow oil $[\alpha]_D^{20}$ −24 (*c* 0.5, $CHCl_3$).