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Use of 1,3-dibenzyl-dihydrouracil in the chain extension of 2,3-*O*-isopropylidene-D-glyceraldehyde

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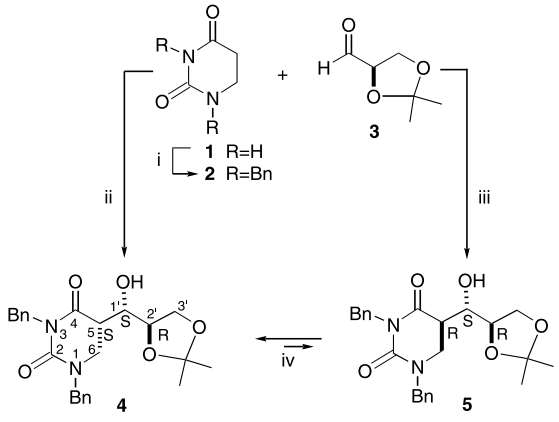
Abstract—The aldol-type addition of 1,3-dibenzyl-dihydrouracil **2** to 2,3-*O*-isopropylidene-D-glyceraldehyde **3** was examined in different solvents and under Lewis acid catalysis in order to establish the stereochemical preferences. A stereodivergent synthesis of 5-trihydroxypropyl-dihydrouracil derivatives **4** and its C-5 epimer **5** was realized. The synthesis of ureido polyols **8** and **10** was obtained via the reductive ring opening of the templates **4** and **5**. © 2003 Elsevier Science Ltd. All rights reserved.

In the synthesis of enantiomerically pure bioactive molecules, the synthetic strategy involving as a key operation the diastereoselective carbon–carbon bond formation between heterocyclic compounds and homochiral aldehydo or imino sugars has been widely used. Numerous five- or six-membered heterocycles such as 2-substituted-furans, -pyrroles, -thiophenes,[1] and -thiazoles,[2] 3-substituted-isoxazolines[3] and -2,5-diketopiperazines[4] have shown their utility for the synthesis of multichiral molecules with biological interest.

For this purpose, we decided to explore the potentialities of dihydrouracil **1** as a new homologating reagent both because of the biological importance of dihydropyrimidinone derivatives[5] or because of the interest that *C*-glycosylated dihydropyrimidinones have shown as *C*-linked glycoside analogues of *N*-linked natural products.[6] Furthermore reductive or hydrolytic DHU ring opening has been used for the synthesis of biologically important compounds as β-ureido-alcohols and -acids[7] or α-substituted-β-aminoacids.[8]

Herein we report a simple and stereodivergent homologating approach to 5-trihydroxypropyl-dihydrouracil derivatives based on the aldol-type addition of DBDHU (1,3-dibenzyl-dihydrouracil) **2** to 2,3-*O*-isopropylidene-D-glyceraldehyde **3** (Scheme 1).[9] In order to evaluate the synthetic potentialities of this procedure in the stereoselective synthesis of β-ureido polyols, the reductive ring opening of dihydrouracil adducts **4** and **5** was also investigated.[10] At first, the starting material DBDHU **2** was prepared by simple *N*-protection of commercially available DHU (dihydrouracil) **1** in a 92% yield (Scheme 1).[11]

To achieve the goal of a good stereochemical control at the newly formed C-5 and C-1′ stereocenters we have investigated a number of protocols in different anhydrous solvents. The effect of a binary reagent system composed of a lithium enolate and a Lewis-acid ($SnCl_4$ or $BF_3{\cdot}Et_2O$) was also examined as reported in Table 1.[12] At first, the influence of the solvent without any Lewis acid added was examined using aldehyde **3**



Scheme 1. *Reagents and conditions*: (i) NaH, BnBr, DMF; (ii) LDA, THF, 4 h, −78°C; (iii) LDA, $SnCl_4$, Et_2O, 4 h, −78°C; (iv) LDA 2 equiv., THF, −20°C, 2 h.

Keywords: dihydrouracil; dihydropyrimidin-2,4-dione; glyceraldehyde.

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Table 1. Diastereoselective synthesis of 5-trihydroxypropyl-DHU derivatives, effect of solvent and Lewis acid addition[a]

Entry	Solvent	Lewis acid	Isomer ratio[b]	Yield (%)[c]
1	THF[d]	–	**81**/16/3/0	88
2	Et_2O[d]	–	40/34/20/6	66
3	DME[e]	–	42/42/8/8	28
4	THF/TMEDA[d]	–	43/30/15/12	79
5	*n*-Hexane[d]	–	–	
6	THF[d]	$SnCl_4$	**77**/23/0/0	38
7	Et_2O[d]	$SnCl_4$	26/**69**/2/3	78
8	DME[e]	$SnCl_4$	34/34/16/16	28
9	*n*-Hexane[d]	$SnCl_4$	–	
10	THF[d]	$BF_3{\cdot}Et_2O$	51/34/13/2	22
11	Et_2O[d]	$BF_3{\cdot}Et_2O$	45/35/12/8	32
12	DME[e]	$BF_3{\cdot}Et_2O$	–	
13	*n*-Hexane[d]	$BF_3{\cdot}Et_2O$	–	

[a] All reactions were carried out on a 1 mmol scale under argon.
[b] Determined by NMR analysis, (5*S*,1′*S*,2′*R*) (**4**)/(5*R*,1′*S*,2′*R*) (**5**)/(5*S*,1′*R*,2′*R*)/(5*R*,1′*R*,2′*R*).
[c] Isolated yield of mixtures of diastereomers. When the reactions were incomplete the starting material DBDHU was recovered.
[d] Reaction temperature −78°C.
[e] Reaction temperature −50°C.

(entries 1–5). Low diastereoselectivity, modest yields and even no reactivity were observed when anhydrous DME, Et_2O, THF/TMEDA (1/1) and *n*-hexane were used (entries 2–5). Whereas using anhydrous THF in the same reaction conditions compound **4** (5*S*,1′*S*,2′*R*) was obtained in high yield and good diastereoselectivity with a small amount of its C-5 epimer **5** (5*R*,1′*S*,2′*R*) (entry 1).[13]

Formation of isomers **4** (5,1′-*syn*-1′,2′-*anti*) and **5** (5,1′-*anti*-1′,2′-*anti*) results by an unlike (*Re* enolate, *Si* aldehyde) and like (*Si* enolate, *Si* aldehyde) approach

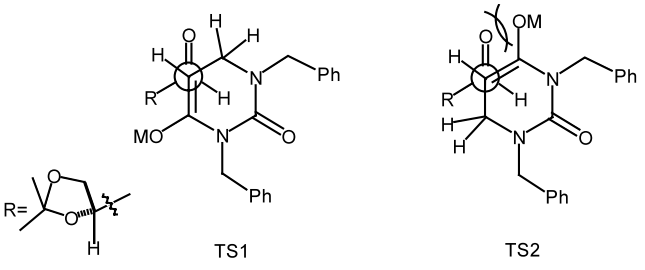


Figure 1.

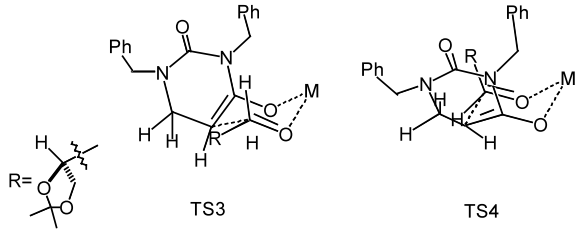


Figure 2.

of the reaction partners in the addition step. It should be noted that in both cases the *Si*-face of aldehyde **3** reacts selectively according to the Felkin–Anh model.[12,14] The preferential addition of the *Re*-face of the enolate to the *Si*-face of the aldehyde to give the aldol **4** can be explained considering an 'open' transition state TS1 preferred rather than TS2 (Fig. 1).

Moreover, the effect of $BF_3{\cdot}Et_2O$ or $SnCl_4$ addition to the aldehyde before adding the enolate was examined in different solvents. When anhydrous Et_2O along with $SnCl_4$ was used, reversal of the stereochemistry with respect to the uncatalyzed reaction occurred, resulting in the preferential formation of compound **5** over **4** and only a marginal amount of the other two diastereomers (entry 7).

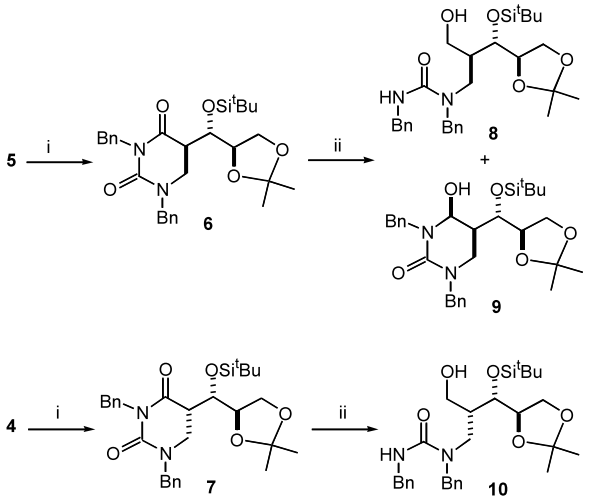
The preferential 5,1′-*anti*-1′,2′-*anti* selectivity comes from a 'like' approach and may be attributed to a cyclic transition state because of the tin(IV) coordination.[15] In this case a Zimmerman–Traxler model can be considered so the transition state TS3 leading to the aldol **5** results preferred rather than TS4 (Fig. 2).[16]

As described in entry 6, the addition of $SnCl_4$ to the THF solution reduces yield and diastereoselectivity with respect to entry 1 but no prevalence of compound **5** was observed. Unsatisfactory yields and diastereoselectivity were obtained when $BF_3{\cdot}Et_2O$ was added in different solvents (entries 10–13). Starting from the readily available isopropylidene-protected L-glyceraldehyde, we have synthesized *ent*-**4** and *ent*-**5** by using the same reaction protocols described for their enantiomers.

A clean C-5 epimerization was also obtained when compound **5** was treated with 2 equiv. of LDA at −20°C for 2 h resulting in the formation of compound **4** (54/46 isomer ratio **4**/**5**)[17] or when compound **5** was allowed to react in a thermostated (50°C) Tris–HCl buffer/THF 1/1 solution pH 8.3 for 7 days (9/91 isomer ratio **4**/**5**) (Scheme 1). On the other hand no epimerization at the C-5 stereocenter was observed when a THF solution of the adduct **5** or **4** was allowed to react with 2 equiv. of LDA at −78°C for 3 h.

Extending the scope of this procedure we have investigated the reductive ring cleavage of DHU templates **4** and **5**. At first the free hydroxyl group within **5** was protected as TBS–ether by exposure to TBSTf in CH_2Cl_2 in the presence of 2,6-lutidine. Then the addition of a large excess of $NaBH_4$ to an EtOH/H_2O (3/1) solution of compound **6** effected the cleavage of DHU ring. Ureido polyol **8** was synthesized in a 68% yield for the two steps with a small amount (~3%) of partially reduced compound **9**.[18] The same procedure was applied to compound **4** to give the ureido polyol **10** in a 61% yield for the two steps (Scheme 2).[19]

The (5*R*,1′*S*) configuration of the two new stereocenters in the pyrimidindione **5** was unambiguously determined by a single-crystal X-ray analysis of compound **9** (Fig. 3).[20] The absolute configuration of compound **5** confirms the (5*S*,1′*S*) configuration for its C-5 epimer **4**.



Scheme 2. *Reagents and conditions*: (i) TBSCl, DMF, imidazole or TBSTf, CH_2Cl_2, 2,6-lutidine; (ii) $NaBH_4$, $EtOH/H_2O$ (3/1), rt.

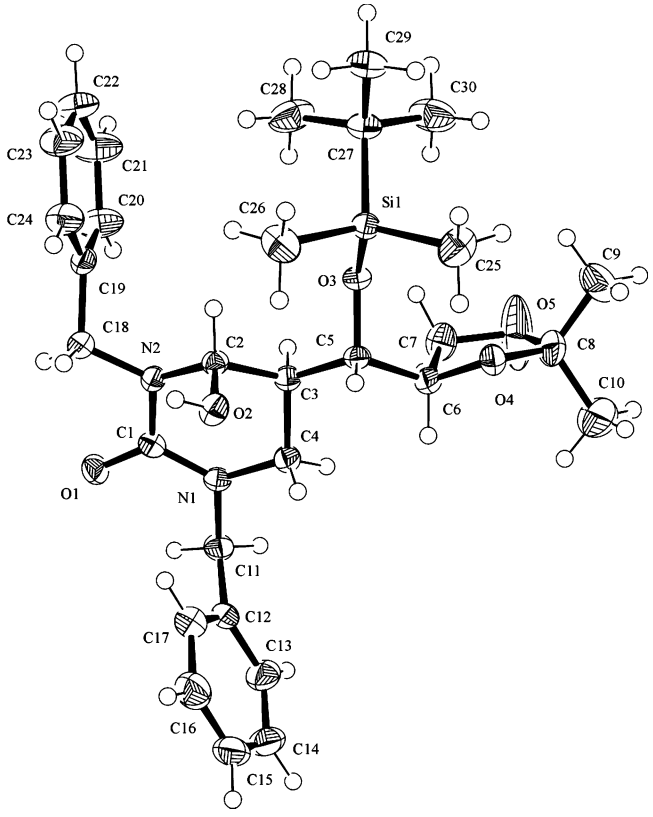


Figure 3. X-Ray structure of compound **9**.

In summary we have shown the first use of dihydrouracil as a new homologating reagent for the chain extension of isopropylidene protected glyceraldehyde. Enantiomerically pure 5-trihydroxypropyl-DHU derivatives have been synthesized in high yields and good diastereoselectivity in a stereodivergent way. Starting from compounds **4** and **5** the synthesis of ureido polyols **8** and **10** was realized via the reductive heterocycle ring cleavage. Studies are currently in progress for the synthesis of enantiopure, *C*-glycosyl-β-amino acids and iminosugars.

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11. Compound **2**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.08 (t, $J=6.6$, 2H), 4.67 (t, $J=6.6$, 2H), 6.04 (s, 2H), 6.43 (s, 2H), 7.22–7.44 (m, 10H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 168.9, 153.8, 137.8, 136.3, 128.8, 128.6, 128.3, 127.9, 127.8, 127.3, 51.6, 43.9, 41.8, 31.7. White solid, mp 81–83°C.
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13. Typical procedure: DBDHU lithium enolate obtained by adding LDA (1.2 equiv.) to a solution of DBDHU **2** (1.0 equiv.) in anhydrous solvent at −78°C under argon, was allowed to react at a same temperature for 4 h with 2,3-*O*-isopropylidene-D- or -L-glyceraldehyde (1.1 equiv.). When Lewis acid assisted couplings were examined the Li enolate was transferred via cannula to the solution containing glyceraldehyde (1.1 equiv.) and Lewis acid (1.2 equiv.). After quenching the reaction mixture with aqueous citric acid solution, the crude material was purified by flash chromatography. The ratio of the four diastereomers was determined on the crude product by NMR.

    Compound **4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 3H), 1.27 (s, 3H), 2.55 (d, $J=4.5$, 1H), 2.95 (ddd, $J=3.9$, 6.3 and 11.2, 1H), 3.10 (dd, $J=6.3$ and 12.0, 1H), 3.52 (t, $J=12.0$, 1H), 3.83–3.91 (m, 2H), 4.08 (td, $J=3.0$ and 7.8, 1H), 4.15-4.19 (m, 1H), 4.56 (d, $J=15.0$, 1H), 4.71 (d, $J=15.0$, 1H), 5.01 (s, 2H), 7.22–7.31 (m, 10H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.5, 153.0, 137.4, 136.0, 128.5, 128.1, 128.0, 127.8, 127.5, 127.0, 109.3, 74.6, 68.9, 67.1, 51.7, 44.1, 43.1, 40.4, 26.5, 24.8. Colorless oil, $[\alpha]_D^{20}=+9$ (*c* 1.7, $CHCl_3$). Compound **5**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 3H), 1.29 (s, 3H), 2.95 (ddd, $J=4.8$, 9.3 and 9.3, 1H), 3.35 (d, $J=9.3$, 2H), 3.51–3.59 (m, 1H), 3.91 (dd, $J=5.1$ and 8.4, 1H), 4.01–4.17 (m, 3H), 4.65 (s, 2H), 5.51 (s, 2H), 7.22–7.41 (m, 10H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 171.7, 152.9, 137.2, 135.9, 128.8, 128.4, 128.1, 127.4, 109.6, 76.9, 72.4, 67.6, 51.7, 44.3, 44.0, 43.3, 26.6, 25.2. Colorless oil $[\alpha]_D^{20}=-22$ (*c* 1.3, $CHCl_3$).
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17. Only 3% of epimerization was observed for the compound **4** in the same reaction condition.
18. By changing the reaction conditions ($EtOH/H_2O$ ratio and $NaBH_4$ equiv.) we obtained a larger amount of the compound **9** up to 35%. Whereas using $LiBH_4$ (6 equiv.) in THF we obtained only the product **9**.
19. Compound **8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.28 (s, 3H), 0.32 (s, 3H), 0.81 (s, 9H), 1.31 (s, 3H), 1.39 (s, 3H), 1.94–1.99 (m, 1H), 3.14 (dd, $J=3.3$ and 15.0, 1H), 3.66–3.82 (m, 6H), 3.96–4.06 (m, 2H), 4.21 (d, $J=16.2$, 1H) 4.33–4.15 (m, 2H), 4.80 (d, $J=16.2$, 1H), 6.19 (bs, 1H), 7.19–7.37 (m, 10H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 159.6, 140.0, 138.0, 128.6, 128.4, 127.5, 127.2, 126.8, 109.5, 76.1, 75.7, 67.6, 60.0, 50.0, 45.0, 44.0, 29.7, 26.4, 25.7, 25.3, 17.9, −3.9, −4.6. Colorless oil $[\alpha]_D^{20}=-12$ (*c* 0.8, $CHCl_3$). Compound **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.10 (s, 3H), 0.86 (s, 9H), 1.31 (s, 3H), 1.39

(s, 3H), 2.34 (m, 1H), 3.08 (dd, $J=5.4$ and 10.5, 1H), 3.56–3.66 (m, 1H), 3.72–3.76 (m, 1H), 3.81–3.84 (m, 1H), 3.94 (s, 1H), 3.95–4.03 (m, 2H), 4.43 (d, $J=10.6$, 1H), 4.75 (s, 2H), 5.11 (bs, 1H), 5.28 (d, $J=15.3$, 1H), 7.23–7.65 (m, 10H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 155.5, 138.8, 137.9, 128.5, 127.8, 127.7, 127.1, 127.0, 109.4, 77.8, 76.2, 72.5, 67.1, 51.6, 49.4, 42.2, 41.3, 26.3, 25.6, 25.1, 17.9, –4.4, –4.6. Colorless crystals, mp 152–154°C, $[\alpha]_D^{20}=+21$ (c 0.9, $CHCl_3$). Compound **10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.20 (s, 3H), 0.28 (s, 3H), 0.82 (s, 9H), 1.24 (s, 3H), 1.31 (s, 3H), 1.90–1.98 (s, 1H), 3.13 (dd, $J=3.6$ and 15.3, 1H), 3.56–3.64 (m, 1H), 3.67–3.76 (m, 3H), 3.79 (dd, $J=3.9$ and 6.0, 1H), 3.81–3.86 (m, 1H), 3.97 (dd, $J=6.3$ and 7.5 1H), 4.06–4.14 (m, 2H), 4.36–4.42 (m, 2H), 4.5 (s, 1H), 5.48 (bs, 1H), 7.14–7.38 (m, 10H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 159.0, 139.4, 137.1, 128.8, 128.4, 127.5, 127.1, 126.7, 108.8, 76.6, 72.8, 67.1, 59.4, 50.6, 45.5, 44.6, 29.1, 26.4, 25.7, 25.0, 17.9, –4.4. Colorless oil $[\alpha]_D^{20}=+15$ (c 1.5, $CHCl_3$).

20. Crystallographic data for this structure have been deposited with the Cambridge Crystallographic Data centre as supplementary publication no. CCDC 193684. Copies of the data can be obtained free of charge on application to CCDC 12 Union Road, Cambridge CB21EZ (Fax: (+44) 1223-336-036. E-mail: deposit@ccdc.cam.ac.uk).