

Highly diastereoselective synthesis of densely functionalized cyclopentanoids by intramolecular azomethine imine cycloadditions in sugar templates

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Conversion of a sugar to a δ,ϵ -unsaturated aldehyde, and subsequent condensation of the aldehyde moiety with BnNHNHCO₂Et, yields the respective azomethine imine intermediate dipole which adds intramolecularly to the existing double bond, thus generating a bicyclic adduct with high diastereoselectivity.

The development of new synthetic methods for the construction of chiral polyoxygenated cyclopentane derivatives is of considerable importance in organic synthesis, since many natural products and synthetic materials of biological interest have skeletons of this type (modified nucleosides, prostaglandins, prostacyclins, cyclitols, aminocyclitols, *etc.*).¹ The use of carbohydrates as synthetic precursors, and the transfer of their chirality to the products, is today the most common strategy for the preparation of polyoxygenated carbocyclic synthons; a range of such methods have been developed in the last twenty years.² Among intramolecular dipolar cycloadditions, only those utilizing the nitron³ or nitrile oxide⁴ dipoles have been applied in carbohydrate derivatives.

As a part of our ongoing program for the synthesis of carbocycles from sugar templates,⁵ we report herein an efficient, highly stereoselective method for the synthesis of densely functionalized cyclopentanoids. Conversion of a monosaccharide to a δ,ϵ -unsaturated aldehyde and subsequent condensation of the aldehyde moiety with a properly substituted hydrazine derivative would afford an intermediate azomethine imine dipole,⁶ which could further add intramolecularly to the existing double bond, thus generating a bicyclic adduct. Furthermore, the heterocyclic ring of the adduct could be readily opened by reductive N–N bond cleavage⁷ to yield a densely functionalized cyclopentane derivative. We selected BnNHNHCO₂Et as the suitable hydrazine derivative, since the substituents (Bn and CO₂Et) stabilize the intermediate dipoles and could furthermore be easily removed from the adducts by conventional deprotection methods.⁸

As a model the alcohol **1**, prepared from 3,4-dihydro-2H-pyran by hydration and Wittig olefination with Ph₃P=CHCO₂Et, was oxidized with pyridinium chlorochromate (PCC) and the resulting aldehyde **2** was refluxed with BnNHNHCO₂Et and Et₃N in a Dean–Stark apparatus for 2 h to give compound **3** as the only cycloadduct, in 35% overall yield (Scheme 1). NOE experiments confirmed the expected *cis* relative configuration of the two bridgehead (1-H and 5-H) protons (15% enhancement) and the *trans* stereochemistry between the 4-H and 5-H protons (no enhancement).

With these encouraging results in hand, we then prepared the aldehydes **5**, **8** and **11**, which were selected with varying substituents on the double bond. In all cases the aldehyde was prepared *in situ* and was used further without purification. The known template **4**, prepared according to the literature from D-glucose in six steps,⁹ was treated with activated Zn in refluxing EtOH to give **5**. A toluene solution of the aldehyde **5**, along with BnNHNHCO₂Et and Et₃N, was refluxed in a Dean–Stark

apparatus for 2 h to give compound **6** as the only cycloadduct, in 33% overall yield from **4**.

Both aldehyde precursors **7** and **10** were prepared from D-ribose according to Scheme 2.¹⁰ Swern oxidation¹¹ of **7** and **10** afforded the aldehydes **8** and **11**, which upon condensation with BnNHNHCO₂Et in the presence of Et₃N gave the cycloadducts **9** and **12**, obtained from **7** and **10** in 41 and 53% yields, respectively.¹² The overall yield for the synthesis of cycloadduct **6** from D-glucose (eight steps) was 18%, of cycloadduct **9** from D-ribose (eight steps) was 19%, and of cycloadduct **12** also from D-ribose (11 steps) was 13%.

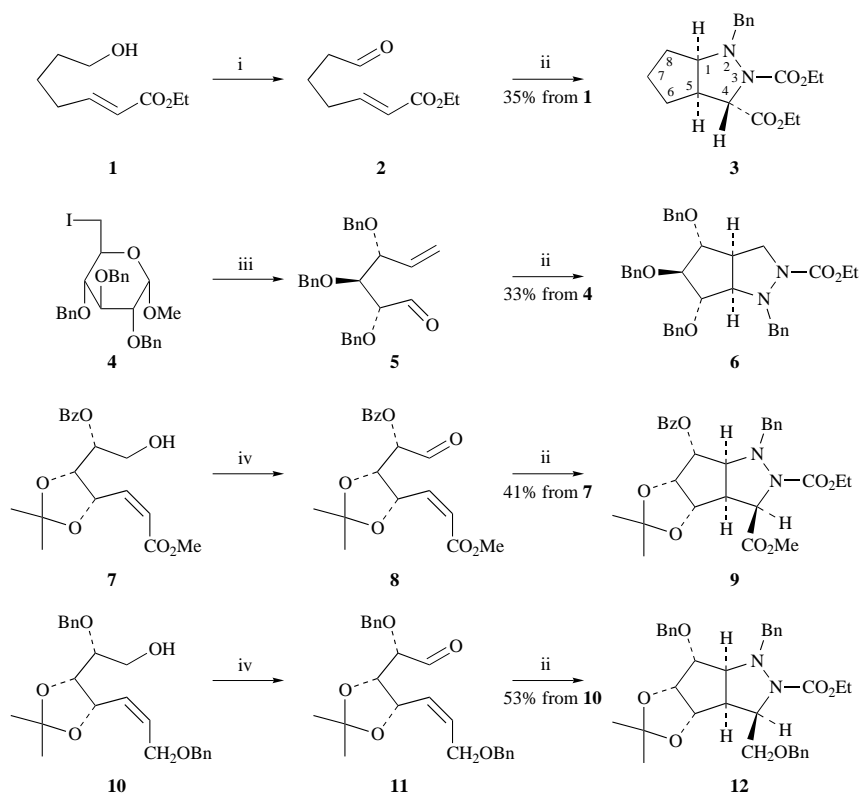
It is noteworthy that only one diastereomer was isolated in all azomethane imine cycloadditions performed. The absolute configuration of the cycloadducts **6**, **9** and **12** was deduced by NOE experiments. The procedure applied can be exemplified by reference to adduct **9**, given in Fig. 1. The proton spectral assignment was made by successive proton decouplings starting from the unequivocally assigned 5-H signal (δ 3.03). The two bridgehead protons are in a *cis* disposition, as shown by the significant NOE enhancements observed. The 4-H and 5-H protons also retain the relative *cis* configuration of the starting double bond (significant enhancement). Finally, the relative stereochemistry of the pairs 1-H/8-H and 5-H/6-H was found to be *trans* since they show no NOE enhancement.

In conclusion, densely functionalized cyclopentanoid synthons can be easily obtained with high diastereoselectivity by intramolecular azomethine cycloadditions in sugar derivatives, which could be further used for the synthesis of enantiomerically pure aminocyclitols and related nitrogen-containing compounds. The scope of the present method is under investigation and further examples, as well as more details of intramolecular cycloadditions analogous to those reported here, will be given elsewhere.

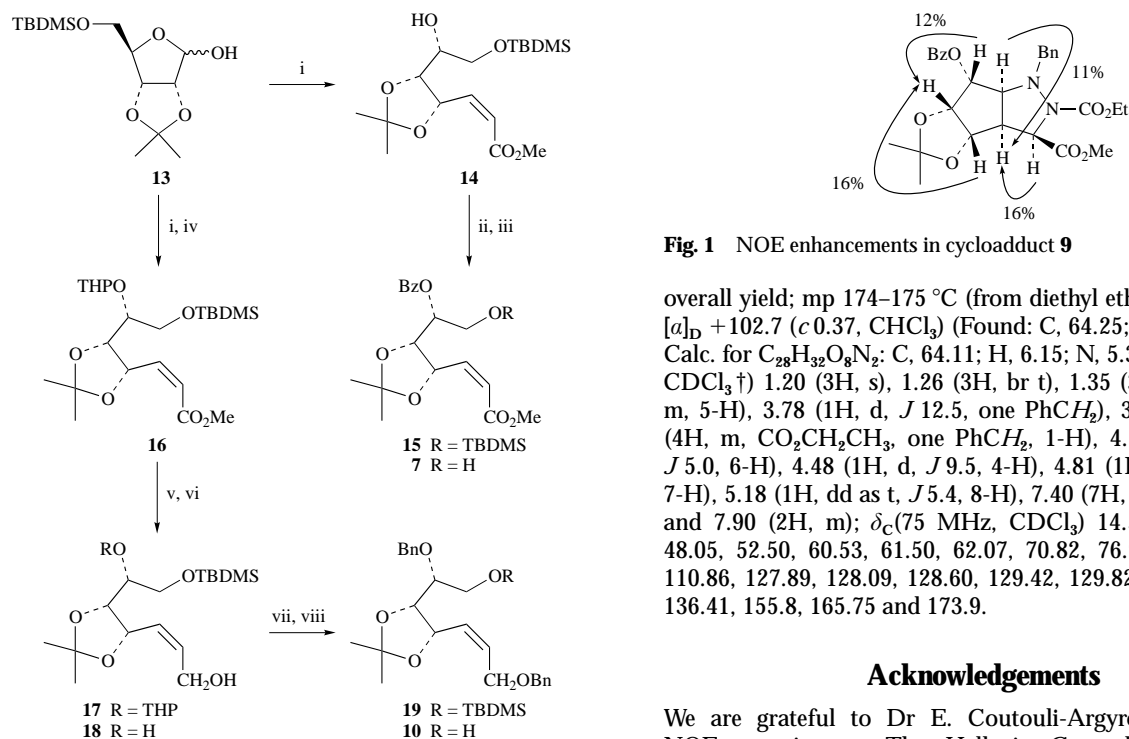
Experimental

(1S,4R,5S,6S,7S,8R)-8-O-Benzoyl-4-methoxycarbonyl-2-benzyl-6,7-O-isopropylidene-3-ethoxycarbonyl-2,3-diazabicyclo[3.3.0]octane-6,7,8-triol **9**

A solution of dry DMSO (0.22 g, 2.8 mmol) in dry CH₂Cl₂ (0.8 ml) was added to a solution of (COCl)₂ (0.14 ml, 1.5 mmol) in dry CH₂Cl₂ (3 ml) which had been cooled to –60 to –55 °C under an argon atmosphere. The resulting mixture was further stirred at the same temperature for another 2 min before a solution of **7** (0.350 g, 1 mmol) in dry CH₂Cl₂ (1.2 ml) was added carefully during a period of 5 min, while the temperature was kept at –60 to –55 °C. The stirring was continued for 15 min and then Et₃N (0.85 ml, 6 mmol) was added at the same temperature. After another 10 min stirring at low temperature the mixture was allowed to warm to room temperature. CH₂Cl₂ (50 ml) was subsequently added and the solution was washed with saturated aqueous NaCl (2 × 30 ml). The organic layer was dried over Na₂SO₄, the solvent was removed on a rotary evaporator and a solution of the resulting residue along with Et₃N (4.5



Scheme 1 Reagents and conditions: i, PCC, CH_2Cl_2 , room temp., 2 h; ii, $\text{BnNHNHCO}_2\text{Et}$, Et_3N , toluene, reflux, 2 h; iii, Zn, EtOH (95%), reflux 2 h; iv, $(\text{COCl})_2$, DMSO, Et_3N , CH_2Cl_2 , -55 to 20°C



Scheme 2 Reagents and conditions: i, $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Me}$, PhCO_2H (cat.), CH_2Cl_2 , reflux, 36 h, 95%, *Z*:*E* = 11:1; ii, PhCOCl , pyridine, DMAP (cat.), 0°C to room temp., 92%; iii, $\text{CH}_3\text{CO}_2\text{H}-\text{H}_2\text{O}-\text{THF}$, room temp., 30 h, 87%; iv, DHP, PPTS (cat.), CH_2Cl_2 , room temp., 24 h, 97%; v, DIBAL-H, Et_2O , 0°C ; vi, MgBr_2 , Et_2O , room temp., 12 h; vii, NaH, DMF, 0°C , then BnCl , 0°C to room temp., 52% from **16**; viii, TBAF, THF, room temp., 85%

mmol) and $\text{BnNHNHCO}_2\text{Et}$ (0.291 g, 1.5 mmol) in toluene (10 ml) was refluxed for 2 h. The solvent was then evaporated and the mixture chromatographed on silica gel with hexane-ethyl acetate as the eluent to give cycloadduct **9** (0.215 g) in 41%

Fig. 1 NOE enhancements in cycloadduct **9**

overall yield; mp $174\text{--}175^\circ\text{C}$ (from diethyl ether-hexane, 1:1); $[\alpha]_{\text{D}}^{25} +102.7$ (c 0.37, CHCl_3) (Found: C, 64.25; H, 6.30; N, 5.40. Calc. for $\text{C}_{28}\text{H}_{32}\text{O}_8\text{N}_2$: C, 64.11; H, 6.15; N, 5.34); δ_{H} (300 MHz, CDCl_3) 1.20 (3H, s), 1.26 (3H, br t), 1.35 (3H, s), 3.03 (1H, m, 5-H), 3.78 (1H, d, J 12.5, one PhCH_2), 3.80 (3H, s), 4.10 (4H, m, $\text{CO}_2\text{CH}_2\text{CH}_3$, one PhCH_2 , 1-H), 4.26 (1H, dd as t, J 5.0, 6-H), 4.48 (1H, d, J 9.5, 4-H), 4.81 (1H, dd as t, J 5.0, 7-H), 5.18 (1H, dd as t, J 5.4, 8-H), 7.40 (7H, m), 7.55 (1H, m) and 7.90 (2H, m); δ_{C} (75 MHz, CDCl_3) 14.53, 24.09, 26.38, 48.05, 52.50, 60.53, 61.50, 62.07, 70.82, 76.95, 77.19, 79.47, 110.86, 127.89, 128.09, 128.60, 129.42, 129.82, 129.91, 132.84, 136.41, 155.8, 165.75 and 173.9.

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† J values are given in Hz.

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