The Asymmetric Synthesis of D-Galactose via an Iterative *syn*-Glycolate Aldol Strategy

Stephen G. Davies,* Rebecca L. Nicholson, Andrew D. Smith

The Dyson Perrins Laboratory, University of Oxford, South Parks Road, Oxford, OX1 3QY, UK
E-mail: steve.davies@chem.ox.ac.uk

Received 2 August 2002

Abstract: The asymmetric synthesis of D-galactose has been completed in eight steps and in >14% yield from simple starting materials via an iterative *syn*-glycolate aldol strategy.

Key Words: asymmetric synthesis, monosaccharides, iterative glycolate aldol reaction, D-galactose

Monosaccharides represent a unique family of polyfunctional molecules that play an essential part in biochemical processes. The most common approach for their synthesis utilises the selective derivatisation and elaboration of the pre-existing functionality contained within a given monosaccharide for the synthesis of higher homologues.[1] Efficient, asymmetric methodology for the manipulation of simple, achiral materials into monosaccharides is therefore of considerable merit. Toward this aim a variety of asymmetric approaches have been developed, including the use of asymmetric Diels–Alder[2] and dihydroxylation reactions,[3] as well as chemoenzymatic approaches[4] amongst others.[5] Perhaps the most general asymmetric approach to date is that employed by Sharpless et al.,[6] delineating the synthesis of the L-hexoses via asymmetric epoxidation from a four carbon starting unit, furnishing L-galactose in 3% overall yield over nine steps. Any improved asymmetric synthesis of monosaccharides must utilise efficient and predictable methodology for the controlled production of the multiple stereogenic centres required in these important targets.

The asymmetric aldol reaction is one of the most reliable synthetic protocols, capable of the selective formation of a C–C bond and two stereogenic centres in a predictable *syn*- or *anti*-fashion. Iterative aldol strategies have enabled the synthesis of molecular fragments containing multiple stereogenic centres,[7] notably for the synthesis of polypropionates.[8] The related asymmetric glycolate aldol reactions of *N*-acyl oxazolidinones have shown applicability in the synthesis of complex molecular fragments,[9] although the generality of this protocol has yet to be fully realised.[10,11] Previous work from this laboratory utilising SuperQuat oxazolidinone[12] chiral auxiliaries have shown that reduction of *N*-acyl 5,5-dimethyl-oxazolidinones with DIBALH allows direct access to highly enantiomerically enriched aldehydes.[13] This approach offers significant advantages over the two step reduction and oxidation protocol typically used[14] to generate aldehydes from *N*-acyl oxazolidinones.[15] The extension and application of this methodology for the asymmetric synthesis of a hexose monosaccharide is described herein. It was predicted that the combination of an asymmetric glycolate aldol reaction combined with subsequent DIBALH reduction would allow direct access to homochiral O-protected tetrose **1**. Subsequent iterative glycolate aldol reaction would constitute a further two carbon chain extension, furnishing polyfunctionalised *N*-acyl oxazolidinone **2**, which after cleavage of the auxiliary and subsequent reduction would furnish the desired hexose **3** (Figure 1).

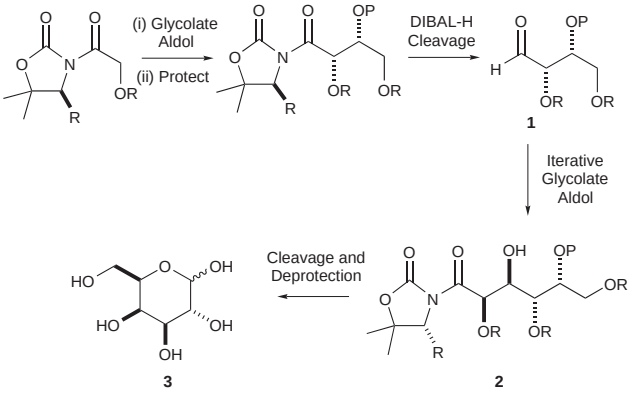


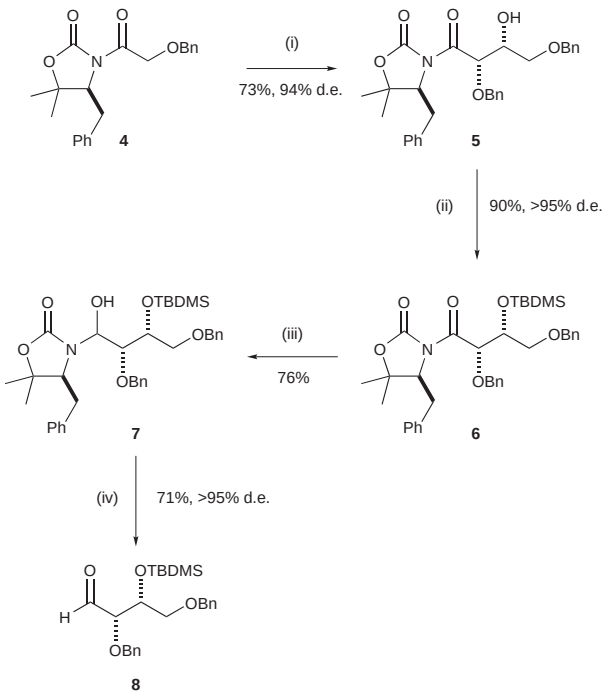
Figure 1

The use of two auxiliary directed *syn*-aldol reactions in this sequence from *N*-glycolate oxazolidinone **4** was predicted to give rise to a hexose with the absolute configuration of D-galactose. Treatment of (*S*)-*N*-gylcolate oxazolidinone **4** with Et_2BOTf and *i*-$PrNEt_2$ and subsequent reaction with benzyloxyacetaldehyde gave the expected *syn*-aldol product (4*S*,2′*S*,3′*R*)-**5**. ^1H NMR spectroscopic analysis of the crude reaction mixture showed that the d.e. of the reaction was 94%, with purification furnishing *syn*-aldol (4*S*,2′*S*,3′*R*)-**5** as a single diastereoisomer in 73% yield.[16] Attempted DIBALH reduction of unprotected (4*S*,2′*S*,3′*R*)-**5** resulted in a complex mixture of products, so the hydroxyl functionality was protected as its silyl ether via treatment with TBDMSCl and imidazole, giving O-silyl protected (4*S*,2′*S*,3′*R*)-**6** in high yield. As our previous studies concerning the reduction of α-alkyl substituted *N*-acyl-oxazolidinones with DIBALH had allowed direct access to the enantiomerically enriched aldehyde,[13] reduction of

Synlett 2002, No. 10, Print: 01 10 2002.
Art Id.1437-2096,E;2002,0,10,1637,1640,ftx,en;D15302ST.pdf.

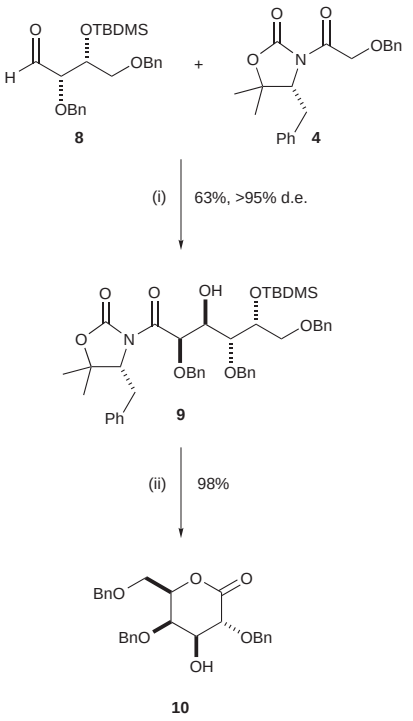
ISSN 0936-5214

protected aldol **6** was similarly expected to yield the required tetrose **8** directly. However, treatment of **6** with DIBALH gave the stable *N*-1′-hydroxy species **7** as a single diastereoisomer of unknown absolute configuration at the C(1′) stereogenic centre in 76% isolated yield.[17] Although both the high degree of stereoselectivity observed in this reduction and the intriguing kinetic stability of **7** are of interest, further studies were directed toward the development of a convenient experimental procedure for the fragmentation of **7** to the required tetrose. Treatment of **7** with K_2CO_3 (1.4 equiv) in MeOH–H_2O (4:1) for fifteen minutes promoted the required fragmentation, giving the O-protected D-threose derivative (2*S*,3*R*)-**8**[18] in good yield and in >95% de (Scheme 1).



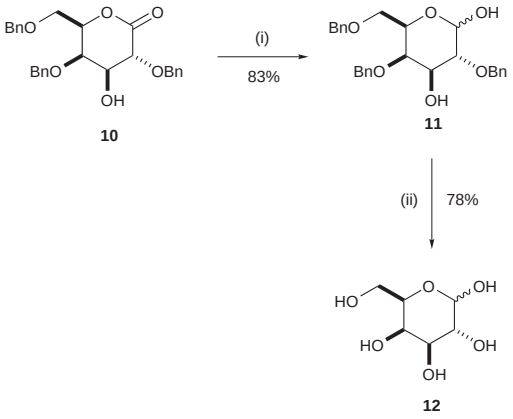
Scheme 1 *Reagents and Conditions*: (i) Et_2BOTf, *i*-Pr_2NEt, benzyloxyacetaldehyde, THF, –78 °C; (ii) TBDMSCl, imidazole, DMAP, DMF, r.t.; (iii) DIBALH, DCM; (iv) K_2CO_3 (1.4 equiv), MeOH–H_2O (4:1), r.t.

With homochiral aldehyde (2*S*,3*R*)-**8** in hand, iteration of the aldol procedure using (*R*)-*N*-glycolate oxazolidinone **4** was pursued, furnishing the *syn*-aldol product (4*R*,2′*R*,3′*S*,4′*R*,5′*R*)-**9** in >95% de by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Purification on silica furnished (4*R*,2′*R*,3′*S*,4′*R*,5′*R*)-**9** as a single diastereoisomer in 63% yield. Cleavage of the oxazolidinone auxiliary was readily achieved by treatment of (4*R*,2′*R*,3′*S*,4′*R*,5′*R*)-**9** with TBAF in HOAc–THF,[19] which promoted both desilylation of the C(4′) TBDMS protected hydroxyl group and in situ cyclisation to furnish lactone **10** in 98% yield.[20] ^{1}H NOE difference experiments served to confirm the relative configuration within lactone **10**, with the absolute configuration following from the known stereodirecting preference of oxazolidinone auxiliaries in simple glycolate aldol reactions (Scheme 2).



Scheme 2 *Reagents and Conditions*: (i) Et_2BOTf, *i*-Pr_2NEt, THF, –78 °C; (ii) TBAF, HOAc, THF, r.t.

Reduction of lactone **10** with DIBALH gave **11** as a 2:1 mixture of anomers in 83% yield. Subsequent hydrogenation and recrystallisation gave D-galactose **12** {$[\alpha]_D^{25}$ +79.8 (c 0.5, H_2O, 15 min, $[\alpha]_D^{25}$ +76.8 (c 0.5, H_2O, 24 h); specific rotation of an authentic sample,[21] $[\alpha]_D^{25}$ +76.7 (c 0.55, H_2O, 15 min), $[\alpha]_D^{25}$ +73.3 (c 0.55, H_2O, 24 h)} with spectroscopic properties identical to those (including mixed ^{1}H NMR) of an authentic sample (Scheme 3).



Scheme 3 *Reagents and Conditions*: (i) DIBALH, DCM; (ii) Pd/C, H_2 (1 atm), EtOAc–EtOH (5:1).

In conclusion, the use of an auxiliary controlled, iterative glycolate aldol strategy has enabled the efficient synthesis of D-galactose **12** in eight steps and in >14% yield. As both *R*- and *S*-enantiomers of the SuperQuat oxazolidinone auxiliary are used in this strategy, this protocol is equally applicable to the synthesis of L-galactose. Further

work is currently being directed toward the extension of this strategy to allow the incorporation of both *syn*- and *anti*-aldol combinations in this iterative, three stage, two carbon homologation protocol for the synthesis of the set of D- and L-hexoses and its application to higher homologues. The automation of this process for the synthesis of libraries of monosaccharides is simultaneously underway.

Acknowledgement

The authors wish to thank Astra–Zeneca for a studentship (R. L. N.) and New College, Oxford for a Junior Research Fellowship (A. D. S.).

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(16) Experimental Procedure for Aldol Reactions: CF_3SO_3H (1.2 equiv) was added to BEt_3 (1 M in hexanes, 1.2 equiv) at r.t. then warmed to 40 °C for 10 minutes before cooling to 0 °C and subsequent addition via cannula to a solution of *N*-acyl-oxazolidin-2-one (1 equiv) in CH_2Cl_2. After 10 minutes, *i*-Pr_2NEt (1.4 equiv) was added and the reaction mixture stirred for a further 20 minutes before cooling to –78 °C and the addition of freshly distilled aldehyde (1.1 equiv). After 30 minutes the reaction mixture was warmed to 0 °C and stirred for a further hour before the addition of MeOH–H_2O_2 (v/v, 1:1). The reaction mixture was extracted with CH_2Cl_2, washed with brine, dried and concentrated in vacuo before purification by flash column chromatography.

(17) Experimental Procedure for DIBALH Reduction: DIBALH (1 M in hexanes, 2 equiv) was added to a stirred solution of *N*-acyl-oxazolidin-2-one (1 equiv) in anhydrous CH_2Cl_2 at –78 °C. After 30 minutes, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and stirred for a further 20 minutes. The resultant emulsion was filtered through Celite®, dried and concentrated in vacuo before purification by flash column chromatography.

(18) ^1H NMR data for tetrose **8**; δ_H (400 MHz, $CDCl_3$) 0.01, 0.04 [2 × 3 H, s, $Si(CH_3)_2t$-Bu], 0.86 [9 H, s, $SiC(CH_3)_3$], 3.53 [1 H, dd, J = 9.8 Hz, 4.9, C(4)H_A], 3.61 [1 H, dd, J = 9.8 Hz, 5.6, C(4)H_B], 3.88 [1 H, dd, J = 4.5 Hz, 1.3, C(2)*H*], 4.16–4.19 [1 H, m, C(3)*H*], 4.48 [2 H, ABq, J = 12.2 Hz,

OCH_2Ph], 4.57 [1 H, AB, J = 12.0 Hz, C(2)OCH_AH$_B$Ph], 4.77 [1 H, AB, J = 12.0 Hz, C(2)OCH$_A$$H_B$Ph], 7.27–7.37 (10 H, m, Ph*H*), 9.76 (1 H, d, J = 1.3 Hz, C*H*O).

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(20) ^{1}H NMR data for lactone **10**; δ_H (400 MHz, $CDCl_3$) 2.56 (1 H, d, J = 2.3 Hz, O*H*), 3.68–3.76 [2 H, m, C(6)H_2OBn], 4.08–4.11 [1 H, m, C(3)*H*], 4.17 [1 H, t, J = 2.3 Hz, C(4)*H*], 4.32 [1 H, d, J = 9.7 Hz, C(2)*H*], 4.43–4.47 [1 H, m, C(5)*H*], 4.52 [2 H, ABq, J = 11.7 Hz, C(6)H$_2$OCH_2Ph], 4.62 [1 H, d, J = 11.2 Hz, C(4)OCH_AH$_B$Ph], 4.72 [1 H, d, J = 11.2 Hz, C(2)OCH_AH$_B$Ph], 4.85 [1 H, d, J = 11.2 Hz, C(4)OCH$_A$$H_B$Ph], 5.19 [1 H, d, J = 11.2 Hz, C(2)OCH$_A$$H_B$Ph], 7.21–7.43 (15 H, m, Ph*H*).

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