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A stereocontrolled cycloaddition route to β-D-glucopyranosyl (1→4)-linked glycals

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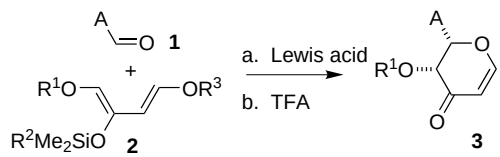
Abstract—The facial reactivity of the diene **4** towards electron-deficient aldehydes can be controlled by $Ln(fod)_3$ catalyst selection, providing the basis of a route to glycals of type **9** [using $Yb(fod)_3$] or **10** [using $La(fod)_3$].

Because of their key roles in biological recognition and regulation processes, oligosaccharides have become the focus of an intense synthetic effort.[1] At the heart of both the chemical and enzymatic routes is the construction of the glycosidic bond between the glycosyl acceptor (usually a glycosyl alcohol) and the glycosyl donor (a glycosyl unit that features a leaving group at the anomeric site). In general, the stereochemistry of the glycosidic linkage can be controlled in the chemical syntheses by the design of the glycosyl donor, permitting the use of the majority of monosaccharides. However, complicated protecting-group regimes are often required to assemble the acceptor/donor partners, resulting in inefficiency. These problems can become acute when there is a need to explore structural novelty/diversity at specific glycose sites (e.g. to define structure–activity relationships). Under such circumstances, intermediates that can be manipulated to provide multiple variants are of much greater utility.

We now report a conceptually new method for the synthesis of (1→4)-linked disaccharides that addresses some of the shortcomings of the current procedures. It utilises the versatile technology of Danishefsky involving the Lewis acid-promoted cyclocondensation of an aldehyde of type **1** and a (*Z*,*E*)-1,4-dioxy-2-siloxybuta-1,3-diene of type **2** to give a *cis*-enulopyranose of type **3** (Scheme 1).[2] The new concept is to install a protected glycopyranosyl unit at the 1-oxy site of the diene and to exploit it to induce stereoselectivity in the cyclocondensation reaction.[3,4]

Initially, we decided to prepare the 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl diene **4** because, on the basis of our previous experience with related dienes,[4] we anticipated that it could be induced to react with electron-deficient aromatic aldehydes to give cycloadducts of type **5** in preference to ones of type **6**; after a desilylative elimination, *cis*-enuloses of type **7** would be favoured over ones of type **8** (Scheme 2). Clearly, such enuloses would permit the installation of an array of functionality at the C(4), C(5) and C(6) sites. In particular, Luche-type reductions would deliver novel glycals of types **9** and **10**,[5] intermediates expected to be of considerable versatility.[1b,d]

To our knowledge, no diene of type **2** (R^1 = chiral auxiliary) has been described. After extensive studies, we found that Scheeren's methodology[6] could be adapted for the synthesis of the diene **4**. Thus, without purification of intermediates, the acid **11**[7] was converted via the acid chloride **12** into the cyclobutanone **13** (as a complex mixture of diastereomers) which pro-



Scheme 1.

Keywords: asymmetric synthesis; carbohydrates; Diels–Alder reactions; diastereoselection; glycals; lanthanides.

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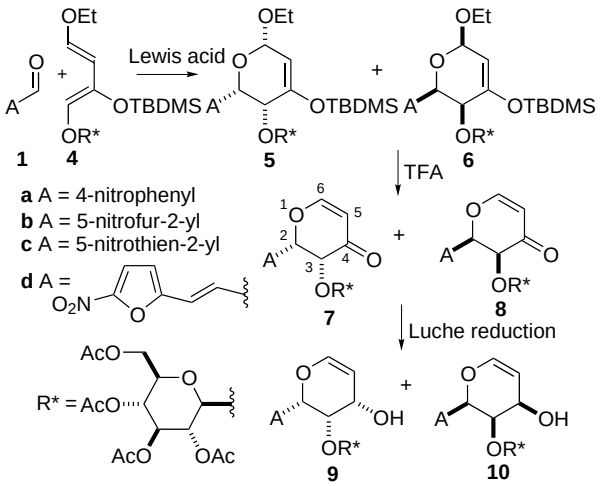
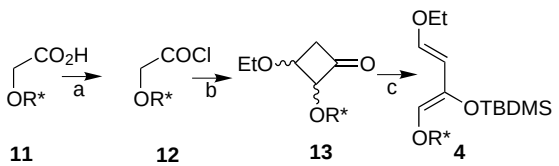


Scheme 2.

vided the diene **4** {mp 109–110°C; $[\alpha]_D^{21}$ −52 (*c* 0.5, CH_2Cl_2)} in 20% overall yield after chromatography and crystallisation (Scheme 3).

The reaction of the diene **4** with 4-nitrobenzaldehyde **1a** was examined initially. In carbon tetrachloride containing $Eu(fod)_3$ (5 mol%) for 20 h, it provided (after addition of CF_3CO_2H and work-up) a 30:70 mixture of the *cis*-enuloses **7a** and **8a** on the basis of evidence that will be presented. Disappointed by the poor selectivity (and the failure of our model to predict the stereostructure of the major product), the evaluation of a range of $Ln(fod)_3$ catalysts was undertaken. As Table 1 shows, the outcome was gratifying. Not only was it possible to



Scheme 3. *Reagents and conditions*: (a) $(COCl)_2$ (500 mol%), DMF (cat.), CH_2Cl_2, reflux, 1 h; (b) CH_2:CHOEt (200 mol%), Et_3N (110 mol%), MeCN, reflux, 1.5 h; (c) TBDMSOTf (120 mol%), Et_3N (200 mol%), CH_2Cl_2, 0.5 h.

Table 1. Effect of $Ln(fod)_3$ (5 mol%) on the reaction of the diene **4** with 4-nitrobenzaldehyde **1a** in CCl_4[a]

$Ln(fod)_3$	**7a**:**8a**[b]	Ln^{3+} radius (Å)[c]
$La(fod)_3$	8:92	1.061
$Pr(fod)_3$	13:87	1.013
$Nd(fod)_3$	18:82	0.995
$Eu(fod)_3$	30:70	0.950
$Gd(fod)_3$	41:59	0.938
$Dy(fod)_3$	68:32	0.908
$Ho(fod)_3$	75:25	0.894
$Yb(fod)_3$	85:15	0.858

[a] Reactions were carried out for 20 h.
[b] Ratios were determined by 300 MHz ^{1}H NMR spectroscopy.
[c] Quoted from Ref. 8.

improve the stereoselectivity to 8:92 using $La(fod)_3$ but to reverse it to 85:15 using $Yb(fod)_3$. Moreover, there was a clear correlation between the stereoselectivity and the cationic radius of the lanthanide metal.[8,9] In the reaction involving $La(fod)_3$, no change in selectivity was observed when the catalyst concentration was decreased to 1 mol% or increased to 20 mol%.

A study of solvent effects on the reaction of the diene **4** with 4-nitrobenzaldehyde **1a** in the presence of 5 mol% $La(fod)_3$ indicated that non-chlorinated solvents led to poorer selectivities and/or slower reaction times. Marginally, 1,2-dichloroethane and carbon tetrachloride were the preferred chlorinated solvents.

In 1,2-dichloroethane containing 5 mol% $La(fod)_3$, the diene **4** reacted with 4-nitrobenzaldehyde **1a** to give mainly a 10:90 mixture of the cycloadducts **5a** and **6a** by ^{1}H NMR spectroscopy;[10] following treatment with trifluoroacetic acid and fractional crystallisation of the product, the *cis*-enulose **8a** {mp 151–152°C; $[\alpha]_D^{21}$ −73 (*c* 0.2, CH_2Cl_2)} was isolated in 68% yield. Similarly, the reaction in the presence of $Yb(fod)_3$ (5 mol%) provided mainly an 82:18 mixture of the cycloadducts **5a** and **6a**;[10] acidic treatment and crystallisation provided the *cis*-enulose **7a** {mp 75–76°C; $[\alpha]_D^{21}$ +35 (*c* 0.5, CH_2Cl_2)} in 52% yield.

Luche reduction[11] [$CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH–THF (1:1)] of the *cis*-enulose **8a** gave the glycal **10a** {mp 199–200°C; $[\alpha]_D^{20}$ −82 (*c* 0.2, CH_2Cl_2)} in 75% yield. Similarly, the *cis*-enulose **7a** afforded the glycal **9a** {mp 184–185°C; $[\alpha]_D^{20}$ +21 (*c* 0.2, CH_2Cl_2)} in 55% yield. The stereostructure of the glycal **10a** was secured by a single-crystal X-ray crystallographic analysis (Fig. 1).[12]

As Table 2 reveals, the diene **4** also reacted with the heteroaryl aldehydes **1b** and **1c** and, significantly, with (*E*)-3-(5-nitrofur-2-yl)propenal **1d**. In each case, a switch in selectivity was observed when the Lewis acid was changed from $La(fod)_3$ to $Yb(fod)_3$. It was usually possible to isolate the major cyclocondensation product in a diastereopure state simply by fractional crystallisation.

At the outset of this work, we had envisaged that the reaction of the diene **4** with aldehydes of type **1** in the presence of $Ln(fod)_3$ catalysts would lead to cycloadducts of type **5** preferentially. This expectation was based on the assumption that a pericyclic-like pathway would operate in which the aldehyde [activated by complexation to $Ln(fod)_3$] would add to the less-hindered *Re*-face of the diene conformer **14** in an *endo*-selective manner.[4] Whilst the $Yb(fod)_3$-catalysed reactions could be accommodated by such a pathway, the $La(fod)_3$-catalysed reactions would require a formal *endo*-selective cycloaddition of the aldehyde to the more-hindered *Si*-face of the diene conformer **14**. In the latter situation, it is difficult to envisage how the catalyst (which would be remote from the sugar residue) could switch the facial reactivity of the diene. Accordingly, it is concluded that pericyclic-like pathways are not involved.

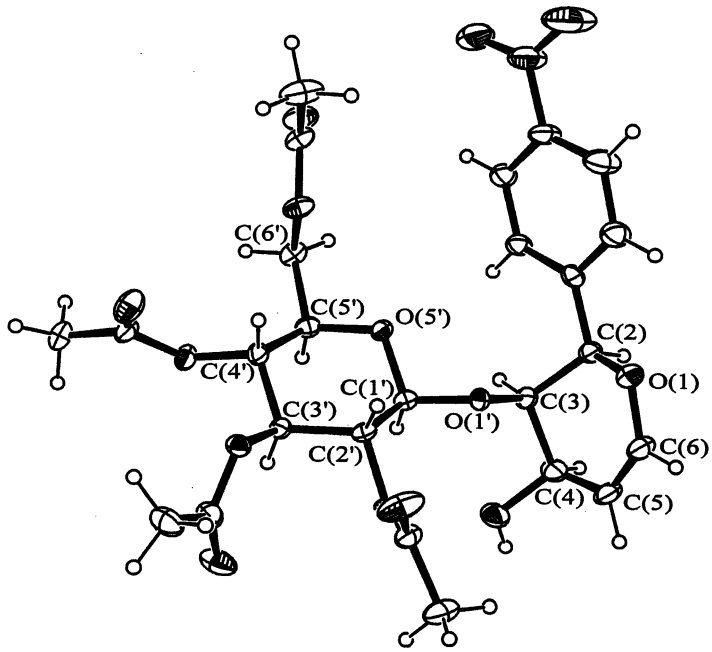
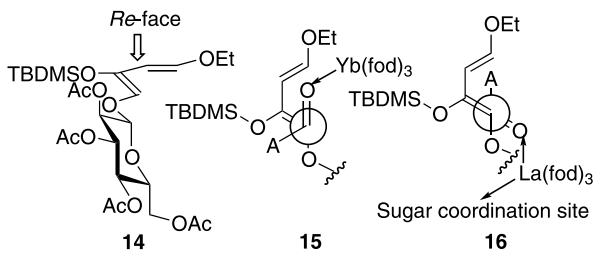


Figure 1. X-Ray crystal structure of compound **10a**.

A consequence of the 'lanthanide contraction' is that heptacoordination is favoured by the 'late' lanthanides, e.g. $Yb(fod)_3$, and octacoordination (or greater) by the 'early' lanthanides, e.g. $La(fod)_3$.[13] Therefore, it is proposed that $Yb(fod)_3$ forms a monodentate complex with the aldehyde (by coordinating to the carbonyl *O*-atom *syn* to the H-atom); the *Re*-face of the complexed aldehyde then reacts with the less-hindered *Re*-face of the diene conformer **14** via an aldol-like pathway, e.g. **15**. In the case of $La(fod)_3$, a bidentate complex is required involving the aldehyde (complexed as before) and a coordination site on the sugar (presumably, the *O*-atom of the ring or one associated with the 6′-position); as a result of this 'steering effect', the *Si*-face of the complexed aldehyde reacts with the *Si*-face of the diene conformer **14**, again via an aldol-like pathway, e.g. **16**. In both reactions, the aldol-like intermediates are postulated to collapse to the observed *endo*-cycloadducts. Recent calculations support an aldol-like pathway for related cycloadditions induced by aluminium-based Lewis acids.[14]



In summary, the work reported herein is significant in a number of respects. Overall, new and practical technology for the synthesis of (1→4)-linked disaccharide glycals is introduced. By delivering the dienyl glucoside **4**, Scheeren's methodology is shown to be applicable to complex substrates. The finding that the facial reactivity of the diene **4** towards electron-deficient aldehydes can be correlated with the atomic radius of the lanthanide catalyst used is striking; it raises interesting mechanistic issues. Finally, the work provides a further illustration of the stereodirecting capabilities of the 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl unit in reactions of dienyl glycosides.

Table 2. Reaction of the diene **4** with the aldehydes **1b–d** in CCl_4 in the presence of $Ln(fod)_3$

ACHO	$Ln(fod)_3$	Products	Ratio	Yield (%)[a]
1b	$La(fod)_3$	**7b**:**8b**	24:76	–
1b	$Yb(fod)_3$	**7b**:**8b**	95:5	52
1c	$La(fod)_3$	**7c**:**8c**	8:92	84
1c	$Yb(fod)_3$	**7c**:**8c**	80:20	36
1d	$La(fod)_3$	**7d**:**8d**	10:90	51
1d	$Yb(fod)_3$	**7d**:**8d**	90:10	43

[a] Refers to the yield of the major product isolated in a diastereopure state after fractional crystallisation.

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4. We have shown that the diene **2** (R^1 = Ac, R^2 = Bu^t, R^3 = 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl) and a relative lacking the OAc substituent undergo *endo*-selective cycloadditions with electron-deficient aryl/heteroaryl aldehydes in the presence of Eu(fod)$_3$, preferentially to their *Re*-faces. See: (a) Lowe, R. F.; Stoodley, R. J. *Tetrahedron Lett.* **1994**, *35*, 6351–6355; (b) Helliwell, M.; Phillips, I. M.; Pritchard, R. G.; Stoodley, R. J. *Tetrahedron Lett.* **1999**, *40*, 8651–8655. The cycloadducts may be regarded as (1→1)-linked disaccharide prototypes.
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10. We have shown that related cycloadducts (cf. Ref. 4) adopt a half-chair conformation with an equatorial disposition of the C(2) aryl group. Accordingly, the C(6) oxy group is pseudo-equatorial when a *syn*-relationship exists between the C(2) and C(6) substituents and pseudo-axial for *anti*-cycloadducts. Typically, the coupling constant between the C(5) and C(6) hydrogen atoms is $\leq$1.5 Hz for *syn*-cycloadducts and $\sim$3.5 Hz for *anti*-cycloadducts. In cycloadducts **5a** and **6a**, there was no discernible coupling between the C(5) and C(6) hydrogen atoms.
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12. Crystal data for compound **10a**: $C_{25}H_{29}NO_{14}$, M = 567.5, monoclinic, space group $P2_1$, a = 10.0292(10), b = 11.805(2), c = 12.172(2) Å, β = 110.49(2)°, D_{calcd} = 1.396 g cm^{-3}, V = 1349.9(3) Å^3, Z = 2, μ(Mo Kα) = 0.116 mm^{-1}, $F(000)$ = 596, T = 203(2) K. Nonius MACH3 diffractometer, crystal size 0.40×0.30×0.15 mm, θ_{max} = 25.0°, 2630 reflections measured, 2495 unique. Structure solution by direct methods, full-matrix least-squares refinement (SHELXL-97) on F^2 with all non-hydrogen atoms anisotropic and hydrogen atoms constrained in calculated positions. The final cycle converged to R = 0.0408 [for reflections $I>2\sigma(I)$] and wR_2 = 0.1008 (for all reflections). Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 167438.
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