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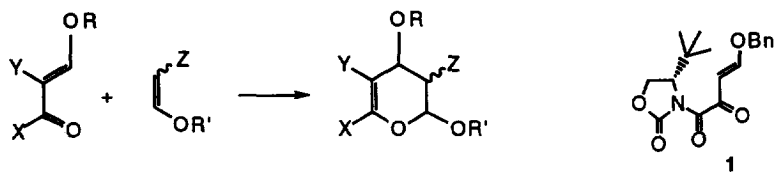
Chiral Enol Ethers in Carbohydrate Chemistry : *De Novo* Synthesis of Protected L-2-Deoxy Hexoses

Gilles Dujardin, Sandrine Rossignol and Eric Brown

Laboratoire de Synthèse Organique, associé au CNRS, Université du Maine,
Avenue Olivier Messiaen, B.P. 535 F-72017 Le Mans (France)

***Abstract** : (3,4,6)Tri- and (3,4,)-di-O-benzyl-2-deoxy-L-glucose **8** and **12** have been* de novo *synthesized in a convergent seven-step sequence involving asymmetric endo heterocycloaddition of the new heterodiene, methyl (E)-benzyloxylmethylene pyruvate **2b** with the O-vinyl mandelic ester (R)-(-)-**3**.* Copyright © 1996 Published by Elsevier Science Ltd

"Unnatural" hexose derivatives constitute a very interesting topic in the field of carbohydrate chemistry. For instance, they provide important subunits (and related useful intermediates) for several classes of biologically active products, as for example polyether antibiotics.[1] Their unavaibility from chiral pool (in the L series namely) entailed intensive efforts towards *de novo* asymmetric approaches during the last decade. One of the main strategies used involves as the key step inverse-electron demand hetero Diels-Alder cycloaddition between a 4-oxysubstituted-1-oxabudiene and an enol ether (Scheme 1).



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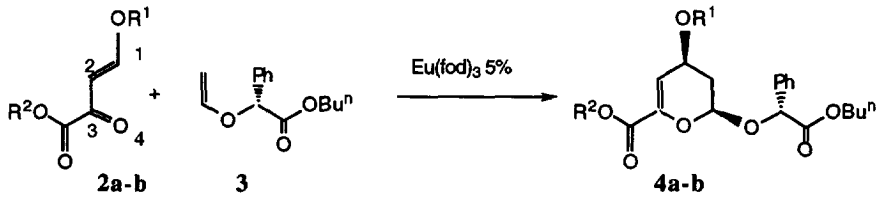
Scheme 1

Avaibility of such adducts to undergo numerous transformations in good overall yields into a wide range of racemic carbohydrate derivatives has been fully demonstrated. In contrast, asymmetric versions, requiring simultaneous *endo/exo* and site-(or enantio-)controls are few[2] and results reported in this restricted area suggest further improved solutions. Thus, Schmidt[3] and Tietze[4] groups have reported different heterodiene-induced processes. High endo selectivities (e.s.) together with variable facial selectivities (f.s.) have been so obtained with 1-oxabutadienes bearing a chiral substituent at position 2 or 4. The most significant results were obtained by the latter group with Me_2AlCl-catalyzed cycloaddition of chiral 2-oxazolidinone **1** (Scheme 1) and (Z)-1-acetoxy-2-ethoxyethene (e.s. >50/1 ; f.s., 54/1), allowing in few steps efficient access to β-D-ethyl-mannopyrannoside.[4b] Interestingly, with the same chiral 2-oxazolidinone **1**, reversal of the facial differentiation occurred (e.s., 32/1 ; f.s., 1/5) when TMSOTf was used as the catalyst and β-L-ethyl-mannopyrannoside was ultimately obtained. However, from a general standpoint, no satisfactory asymmetric induction together with complete *endo/exo* selection has been achieved so far in view of obtaining enantiopure L-glucopyranosides and their deoxy derivatives.

We recently described[5] an alternative (4+2) asymmetric access to dihydropyrans of unambiguous configurations,[6] using chiral vinyl ethers deriving from available enantiopure α-hydroxy esters (alkyl mandelates typically) and achiral electron deficient 1-oxabutadienes in Danishefski-type catalytic conditions (5% Eu(fod)3). The effective mercury-free preparation of such chiral vinyl ethers, which we related latter,[7] enhance its synthetic potential. We now report our results concerning extension of this dienophile-induced methodology to 2-deoxyhexose asymmetric synthesis.



2a-b **3** **4a-b**

Reaction conditions : a) hexane /toluene 60°C / 72h or b) toluene 110°C / 72h

	R1	R2	Conditions		Selectivities endo/exo (e.s.)	facial (f.s.) crude	facial (f.s.) after chromatography	Yield (%)
2a	Et	Et	a)	**4a**	> 98/2	95/ 5	95/5 c)	87
2b	Bn	Me	a)	**4b**	> 98/2	93/ 7	100/0 d)	61
2b	Bn	Me	b)	**4b**	> 98/2	90/10	90/10 c)	80

Purification conditions : c) eluent : cyclohexane/ethyl acetate or d) eluent : toluene/ethyl acetate (97/3).

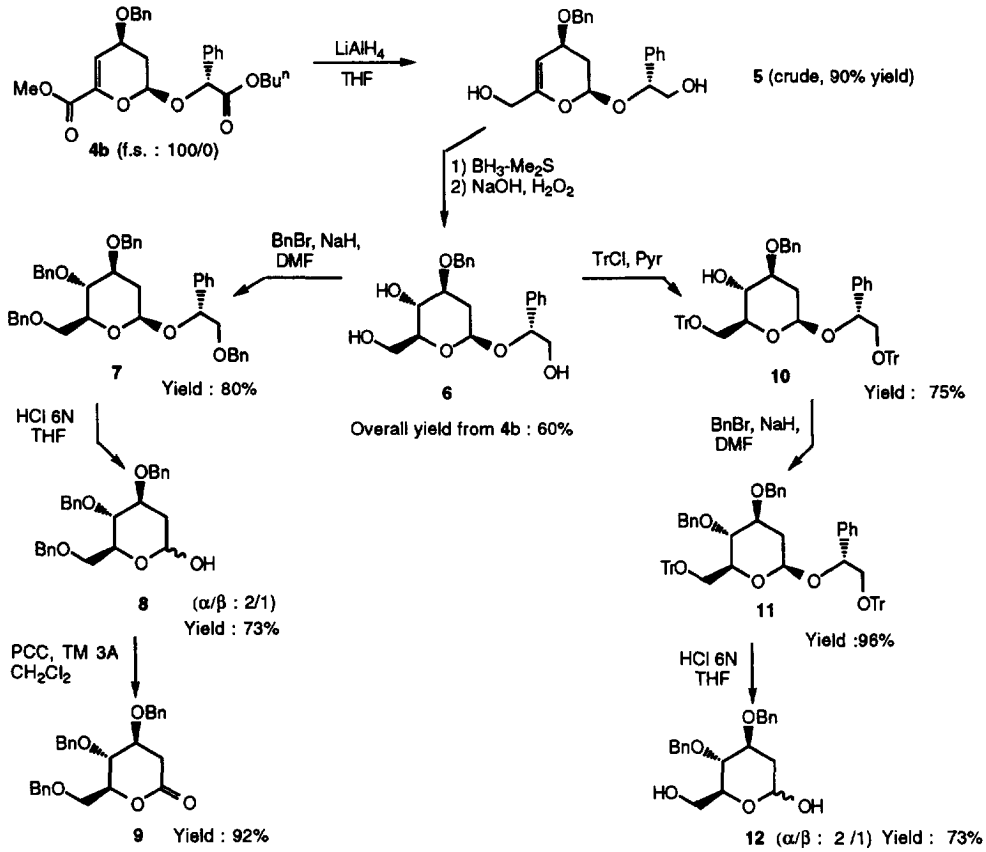
Scheme 2

As a model, we first studied the cycloaddition of the known (E)-ethoxymethylene pyruvic ester **2a** with n-butyl-(R)-(-)-O-vinylmandelate **3**.[7] Very promising stereochemical results : (e.s. >50/1 ; f.s., 19/1) together with good yields of pure adduct **4a** were thus observed in standard reaction conditions (5% Eu(fod)3, hexane/ toluene, reflux, 60h) (Scheme 2). As in previous results,[5] spectral data of the two sole isomers are in accordance with a *cis* geometry of the dihydropyranyl substituents in a di-pseudoequatorial conformation.[8]

At this stage, we needed an analogue of **2a**, with labile O-protection on C4. Methyl (E)-benzyloxy-methylene pyruvate **2b** was prepared in reasonable yields (50-67% on 5-100 mmol scale) *via* a modified-Effenberger procedure,[9] from benzyl vinyl ether and oxalyl chloride at -20°C and subsequent quenching at 0°C of the intermediate mono acylchloride with excess methanol and in the presence of triethylamine.[8] This new heterodiene is less stable than **2a** in our cycloaddition conditions, possibly due to the avaibility of the benzyl vinyl ether moiety to partially undergo Claisen rearrangement. However, with suitable excess (1.5-1.7) of heterodiene **2b**, the desired adduct **4b** is obtained in satisfactory yields with efficient selectivities (e.s. >50/1 ; f.s., up to 13/1) when the reaction was carried out at 60°C.[8] In this optimal case, careful silica gel column chromatography afforded the stereomerically pure adduct **4b** in 61% yield.

In order to transform the adduct **4b** into enantiopure carbohydrate derivatives, we needed to find a compatibility between stereocontrolled establishment of the hydroxyl functionnalities and the presence of the bulky chiral aglycone. According to Mash's sequence,[10] we envisaged removal of the chiral auxiliary in a

reduced form at a latter stage of our synthetic plan. After reduction with excess $LiAlH_4$ in THF of a 90/10 diastereomeric *endo* mixture of adduct **4b**, isolation of the diastereomerically pure allylic diol **5** was effective after flash chromatography (eluent : toluene / ethanol), but in moderated yield due to some instability of **5** in these purification conditions. However, starting from the stereomerically pure adduct **4b**, the crude reduction product **5** successfully underwent 1,2-stereocontrolled hydroboration / oxidation, thus leading to the β-L-2-desoxypyranoside **6** in 60% overall yield of purified product for the two steps (scheme 3).[8]



Scheme 3

Perbenzylation of triol **6** occurred readily and gave **7**. Subsequent acidic hydrolysis of the latter afforded an anomeric mixture of 3,4,6-tri-O-benzyl-2-deoxy-L-glucose **8**.[8] The L character and enantiopurity of **8** were confirmed after oxidization into the gluconolactone derivative **9** : α_D - 47.6 (c 0.75, EtOH). Lit.:[11] +48 (c 1, EtOH) for 3,4,6-tri-O-benzyl-2-deoxy-D-gluconolactone. From a synthetic point of view, the possibility of differentiating O-protections at C-3, C-4 and C-6 positions is crucial for use in subsequent synthetic schemes.[12] Indeed, triol **6** could be regioselectively O-tritylated [13] at both primary positions, thus leading to **10** in satisfactory yields. Benzylation of the latter gave **11** whose acidic hydrolysis (carried out as above) yielded the expected primary OH-unprotected analogue **12** of **8**.[8] Concurrently with our own project in this field,[14] the methyl glycoside of **12** has been very recently reported as a potentially valuable intermediate for Ambruticine.[15]

Current investigations are in progress in our laboratory to optimize the asymmetric sequence described here, especially in the definition of the ideal **2**-type heterodiene and **3**-type dienophile partners. However, the present report validates for the first time the asymmetric (4+2) heterocycloaddition pathway to enantiopure deoxy derivatives of L-glucopyranosides such as **12**, and constitute an alternative to the *de novo* synthesis proposed by Roush's group[12] (*via* the allylboration of 2,3-epoxy aldehydes) or to the excellent homologating hemisynthesis from L-arabinose described a few months ago.[15]

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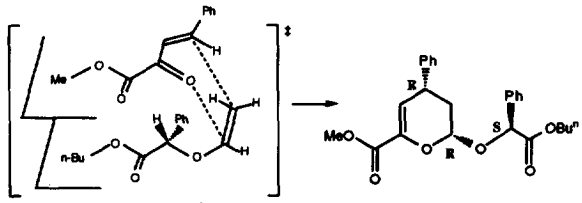
6. Correlative identification of absolute configurations of major adducts[5b] agreed with a favoured Eu-chelated-endo-transition state, leading to a (u,u) relationship between the initial stereogenic center and the two newly created ones.



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8. New compounds were characterized by IR, ^1H and ^{13}C NMR, elemental analysis or HRMS. **2b** : oil, IR (neat), 1748, 1691, 1654, 1610 cm^{-1}; ^1H NMR (400 MHz) $CDCl_3$, δ : 3.88 (s, 3H), 5.05 (s, 2H), 6.33 (d, J 12.5Hz, H^2), 7.35-7.43 (m, 5H), 7.98 (d, J 12.5Hz, H^3). **4a** (I / II : 95/5) : oil, $(\alpha)_D$ +21.9 (c 1.12, MeOH), IR (neat), 1654, 1747 cm^{-1}; ^1H NMR (400 MHz) $CDCl_3$, δ : 0.85 (t, 3H), 1.25 (m,2H), 1.25(2t, 6H), 2.25 (m,2H) , 3.60 (s,3H), 4,13 (t,2H), 4,20 (q,2H), 5.02 (dd, 1H, dia II, H^1), 5.33 (s, 1H, dia II, $H^{2'}$), 5.02 (dd, 1H, J 5 and 2 Hz, dia II, H^1), 5.40 (dd, J 5.1, 2.9 Hz, 1H, dia I, H^1), 5.45 (s, 1H, dia I, $H^{2'}$), 6.18 (d, 1H, J 4 Hz, dia II, H^4), 6.22 (d, 1H, J 3.7 Hz, dia I, H^4), 7.2-7.5 (m, 5H).**4b** : (I / II : 100/0) oil, $(\alpha)_D$ +31.7 (c 1.42, CH_2Cl_2), IR (neat), 1654, 1733 cm^{-1}; ^1H NMR (400 MHz) $CDCl_3$, δ : 0.84 (t, 3H), 1.23 (m,2H), 1.52 (m, 2H), 2.21 (ddd, J 14.3, 6.4, 2.9 Hz, H^2_{ax}), 2.43 (dt, J 14.3, 4.5 Hz, H^2_{eq}), 3.71 (s,3H), 4,08 (t,2H), 4,19 (m, 1H), 4,57 (m,2H), 5.43 (m, 2H, , H^2 and $H^{2'}$), 6.23 (d, 1H, J 4.0 Hz, dia I, H^4), 7.15-7.5 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ : 13.6, 18.9, 30.5, 32.3, 52.3, 65.2, 66.0, 70.1, 77.2, 96.3, 111.3, 125.3-129.0, 136.0, 138.2, 141.9, 162.8, 170.7. **12** :(α/β : 2/1) oil, $(\alpha)_D$ -18.6 (c 1.29, EtOH), IR (neat), 3400 cm^{-1}; ^1H NMR (400 MHz) $CDCl_3$, δ : 1.51 (dq, J 12.2, 2.1Hz, 1H anom β, H^2_{ax}), 1.58 (dt, J 12.0, 3.3Hz, 1H anom α, H^2_{ax}), 1.7-2.5 (m,1H anom αβ, OH), 2.23 (dd, J 12.5, 4.9Hz, 1H anom α, H^2_{eq}), 2.32 (ddd, J 12.5, 4.9, 1.7Hz, 1H anom β, H^2_{eq}), 3.32 (m, 1H anom β, H^5), 3.45 (m, H^4 anom αβ and OH anom α), 3.68 (m, 1H^6 anom αβ and H^3 anom β), 3.80 (dd, J 11.0, 1.5Hz, 1H anom α, H^6), 3.82 (dd,J 11.0, 1.5Hz, 1H anom β, H^6), 3.94 (m, 1H anom α, H^5), 4.05 (m, 1H anom α, H^3), 4.59-4.70 (m, 3H anom αβ, H benzyl.), 4.78 (m, 1H anom β, H^1),4.88 (d, J 11Hz, 1H anom αβ, H benzyl.), 5.34 (bs, 1H anom α, H^1), 7.25-7.40 (m, 10H anom αβ).
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