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A novel diastereoselective route to α-hydroxyalkyl dihydropyrans using a hetero Diels–Alder/allylboration sequence

Michael Deligny,[a] François Carreaux,*[a] Bertrand Carboni,[a] Loïc Toupet[b] and Gilles Dujardin[c]

[a] *Synthèse et Electrosynthèse organiques, Institut de Chimie, UMR 6510 CNRS, Campus de Beaulieu, 35042 Rennes Cedex, France. E-mail: francois.carreaux@univ-rennes1.fr*

[b] *GMCM, CNRS, Université de Rennes 1, 35042 Rennes Cedex, France*

[c] *Laboratoire de Synthèse Organique, UMR 6011 CNRS, Université du Maine, 72085 Le Mans Cedex, France*

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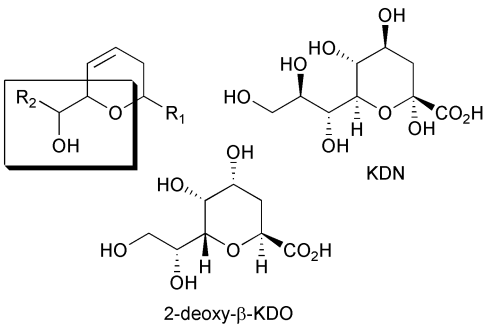
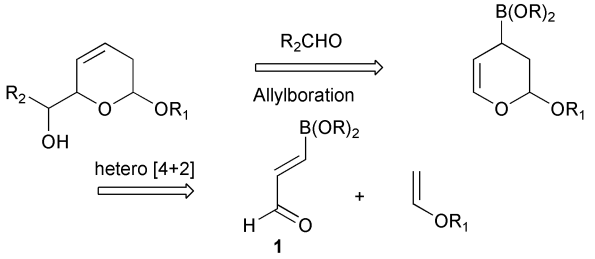
The development of a new strategy for the synthesis of α-hydroxyalkyl dihydropyrans is reported. This approach is based on a tandem hetero[4+2]/allylboration reaction.

2,6-Disubstituted dihydropyrans occur frequently in nature as a structural core in a wide range of natural products.[1] In addition, these compounds could serve as useful building blocks for the synthesis of biologically active saturated oxygen heterocycles *via* functionalization of the double bond. More specifically, dihydropyrans flanked with a stereodefined hydroxyalkyl group at the α-position have recently been used as intermediates in the synthesis of higher-order sugars[2] such as (+)-3-deoxy-D-*glycero*-D-*galacto*-2-nonulosonic acid (KDN) possessing oncofoetal antigen properties[3] and 2-deoxy-β-KDO, the most potent inhibitor of the enzyme CMP-KDO synthetase.[4] The synthesis of such β-alkoxy alcohol units presents a challenging problem of stereochemical control. Although, many approaches were reported, most of them require several linear steps to establish the correct stereochemistry prior to or after a ring closure event. The Ireland–Claisen rearrangement of acetylated glycal ester is one of the most elegant and straightforward methods used, but lacks stereochemical control.[5]

Herein, we present our preliminary investigations on a simple stereoconvergent strategy shown in Scheme 1. We envisioned that a tandem reaction initiated by the [4+2] heterocycloaddition of (2*E*)-3-borylacrolein **1** with appropriate vinyl ethers could be followed by reaction of the allylboronate intermediate with added aldehydes, thus providing α-hydroxyalkyl dihydropyran derivatives in one operation.





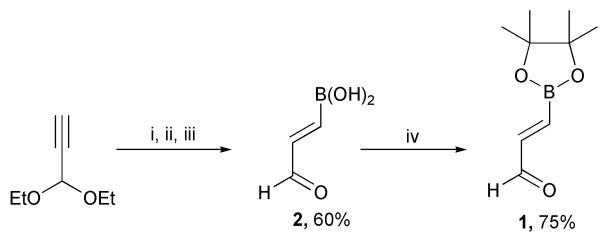
Scheme 1 Retrosynthetic approach to substituted dihydropyrans using a tandem hetero [4+2]/allylboration reaction.

Whereas the inverse electron demand hetero Diels–Alder reaction of electron-rich alkenes with α,β-unsaturated carbonyl compounds is known,[6,7] cycloaddition of the heterodiene (*e.g.*, **1**) with as substituent a boron atom is unprecedented. It should be noted that normal electron demand Diels–Alder reactions involving 1,3-dienylboronates[8] and 1-aza-4-borono-1,3-butadienes[9] have been already reported in the literature. From the intermediate cycloadducts, addition of aldehydes leads to homoallylic alcohols *via* a highly diastereoselective allylboration.

The heterodiene **1** required in the current investigation was synthesized using a modified literature procedure (Scheme 2).[10] The hydroboration of propionaldehyde diethyl acetal with diisopinocamphenylborane and the dealkylation with excess acetaldehyde was followed by hydrolysis to produce the boronic acid **2** in 60% yield.[11] To the best of our knowledge, this compound was never described in the literature as its boronic acid form and is interesting from the point of view of combinatorial chemistry on solid support.[12] The esterification of **2** with pinacol afforded the desired (2*E*)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-2-enal **1** in 75% yield.

For this preliminary study, ethyl vinyl ether was used as the model dienophile. The heterodiene **1** exhibited a low thermal reactivity (40 °C, 2 days) with ethyl vinyl ether.[13] In order to enhanced reactivity of **1** and obtain the cycloadduct with a good stereoselectivity, the hetero Diels–Alder was carried out in the presence of a Lewis acid. We chose an organosoluble lanthanide catalyst such as $Yb(fod)_3$ which was successfully used in cycloadditions of enol ethers with α,β-unsaturated aldehydes.[14] With 5 mol% of $Yb(fod)_3$, the reaction was complete in less than 24 h at room temperature in CH_2Cl_2. Given the suspected instability of this cycloadduct, aldehyde was added directly to the reaction mixture. The allylboration time of 12 h at reflux in CH_2Cl_2 was the optimal condition found to achieve full consumption of the cycloadduct product. The compounds **3** were obtained following a basic aqueous workup required to hydrolyze the resulting pinacol borate and flash chromatographic purification.

Several aldehydes were examined to assess the generality of this process (Table 1). The isolation of compounds **3a–f** (entries 1–6) shows that a wide range of aromatic aldehydes can be employed including both electron-rich and electron-poor deriv-



Scheme 2 *Reagents and conditions*: i, $(Ipc)_2BH$ (1 equiv.), THF, 0 °C, 1 h and rt, 5 h; ii, CH_3CHO (15 equiv.), 0 °C, 1 h and rt, 12 h; iii, H_2O; iv, pinacol (1.2 equiv.), Et_2O, rt, 12 h.

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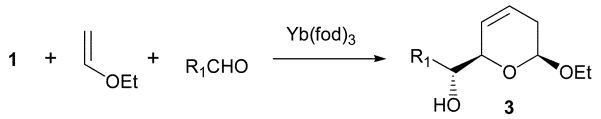
Table 1 Cyclic products **3** from tandem hetero [4+2]/allylboration[a]



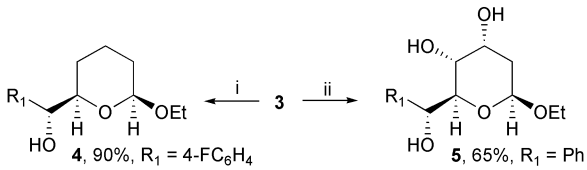
Entry	Aldehyde R_1	Product	Yield (%)[b]
1	Ph	**3a**	77
2	4-$MeOC_6H_4$	**3b**	70
3	4-ClC_6H_4	**3c**	66
4	4-FC_6H_4	**3d**	81
5	4-$NO_2C_6H_4$	**3e**	95
6	2-$NO_2C_6H_4$	**3f**	80
7	$PhCH_2$	**3g**	95
8	$PhCH_2CH_2$	**3h**	92
9	C_6H_{13}	**3i**	45

[a] All reactions were carried out using a 1:10:0.05 mixture of diene/dienophile/Lewis acid in dry methylene chloride [~0.1 M] at rt for 24 h. After addition of aldehyde (2 equiv. from **1**), the mixture is heated at reflux in methylene chloride for 12 h, diluted with EtOAc and stirred at rt for 30 min with a saturated solution of sodium hydrogen carbonate. [b] Unoptimized yields of products after flash chromatography purification.

atives. As seen with the formation of products **3g–i** (entries 7–9), aliphatic aldehydes are also valid substrates.[15] In all cases, a single or highly predominant stereoisomer is observed by ^{1}H NMR analysis of crude reaction products. We consider the moderate yield of purified compound **3i** quite acceptable considering the ready availability of starting materials and the simplicity of this tandem reaction as well as the high level of stereoselectivity afforded to the product.

As shown with the formation of **4** from **3d** (Scheme 3), the double bond can be hydrogenated under palladium on charcoal. On the other hand, the homoallylic alcohol **3a** was subjected to the usual dihydroxylation conditions using a catalytic amount of OsO_4, with *N*-methylmorpholine *N*-oxide as a cooxidant to afford the desired triol **5** as a single diastereoisomer.

The relative stereochemistry of the C-2 and of the C-4, C-5 vicinal diol can be determined by ^{1}H NMR coupling constants ($H3\text{-}_{ax}$:H2 = 9.55 Hz; $H3\text{-}_{eq}$:H2 = 1.9 Hz; $H3\text{-}_{ax}$:H4 = 2.5 Hz; $H3\text{-}_{eq}$:H4 = 3.5 Hz). X-Ray crystal structure determination† on the compound **5** (Fig. 1) confirmed this assignment and established the relative configuration of the C-6 confirming that the relative stereochemistry from the tandem [4+2]/allylboration reaction of heterodiene **1** is identical to that obtained with a normal electron hetero Diels–Alder.[9]



Scheme 3 *Reagents and conditions*: i, H_2 (1 atm), 10% Pd(C), EtOH, rt, 2 h; ii, cat. OSO_4 (0.3 mol%), NMO (1.5 equiv.), acetone/H_2O, rt, 3 days.

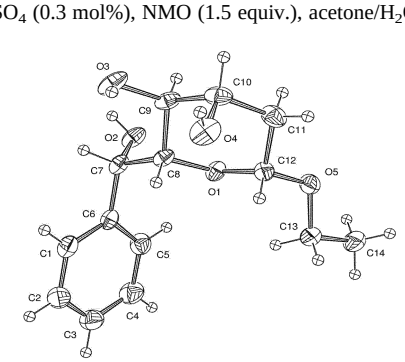


Fig. 1 ORTEP diagram of **5** with selected bond distances (Å): O(1)–C(8) 1.434(2), C(6)–C(7) 1.520(3), C(7)–C(8) 1.532(3), O(5)–C(12) 1.394(2), O(3)–C(9) 1.428(3), O(2)–C(7) 1.440(2).

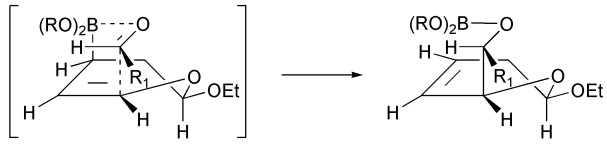


Fig. 2 Proposed transition state to rationalize the stereochemistry resulting from the allylboration step.

Mechanistically, the [4+2] cycloaddition of heterodiene **1** with ethyl vinyl ether is expected to proceed with complete *endo*-selectivity to give the allylboronate intermediate shown in Fig. 2. From the latter, the stereochemical outcome of the allylation step can be explained *via* a cyclic chair-like transition state involving *anti* coordination of the aldehyde to the boronyl group oriented axially on the *endo* face of the pyran ring.

To the best of our knowledge, the current examples are the first ones involving γ-alkoxy-substituted allylboryl reagents.[16] Moreover, the stereochemistry of the resulting 1,2-alkoxy alcohol unit is the same as that of several higher-order sugars including KDN, thus confirming the potential of this strategy for natural product synthesis.

In conclusion, we have developed a new tandem hetero [4+2]/allylboration with a high level of diastereoselectivity. Work toward extending the scope and applications of this methodology is in progress.

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Notes and references

† *Crystal data for* **5**: $C_{14}H_{20}O_5$, M = 268.30, monoclinic, space group *P* 21, *a* = 8.972 (4), *b* = 6.264 (2), *c* = 12.190 (4) Å, *β* = 101.00 (4)°, *V* = 672.5 (4) Å^3, *Z* = 2, D_x = 1.325 g cm^{-3}; *F*(000) = 288, *μ* = 1.00 cm^{-1}, Mo-Kα (*λ* = 0.71073 Å), *T* = 293 K. 1459 reflections with $I > 2\sigma(I)$. R1 = 0.033, *w*R2 = 0.089 and *w*S = 1.053. The crystal observed is enantiomerically pure: this constitutes a beautiful example of conglomerate. CCDC reference number 188816. See http://www.rsc.org/suppdata/cc/b2/b208572k/ for crystallographic data in CIF or other electronic format.

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