An Entry to Enantiomerically Pure *cis* Decalinic Structures from Carbohydrates

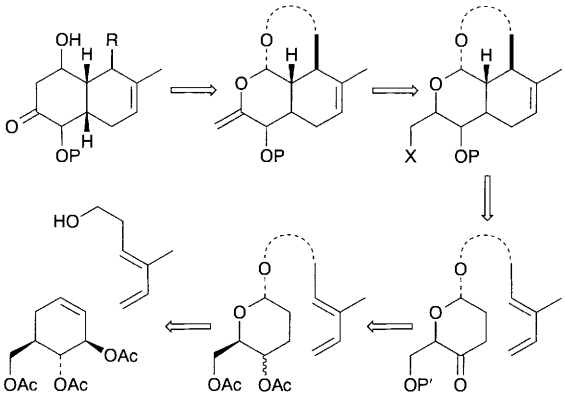
Claude Taillefumier,[a] Yves Chapleur,*[a] Daniel Bayeul[b] and André Aubry[b]

[a] *Laboratoire de Méthodologie et Synthèse Enantiospécifique de Biomolécules, associé au CNRS, Institut Nancéien de Chimie Moléculaire, Université Henri Poincaré-Nancy I, B.P. 239, F 54506 Vandoeuvre, France*
[b] *Laboratoire de Cristallographie et Modélisation des Matériaux Minéraux et Biologiques, associé au CNRS, Université Henri Poincaré-Nancy I, B.P. 239, F 54506 Vandoeuvre, France*

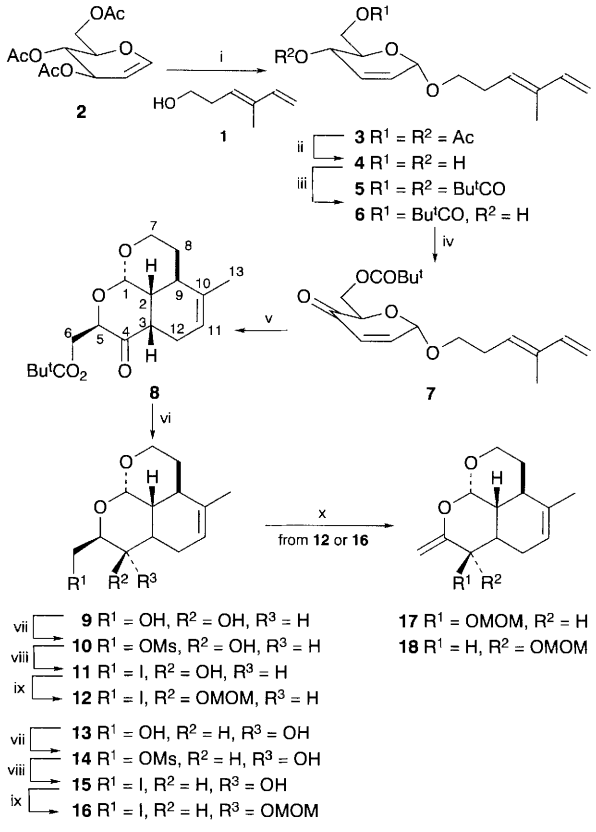
Tri-*O*-acetylglucal is the starting material of a new route to chiral highly oxygenated *cis* decalinic structures by tandem IMDA–Ferrier carbocyclization reactions, single-crystal X-ray analysis of one of these aldol structures is performed.

Functionalized decalinic structures are often involved in natural products or as intermediates in the synthesis of complex structures. Compounds such as mevinic acids, derivatives including pravastatin and mevinolin,[1] or diterpenes[2] such as forskolin[3] and other representatives of the labdane series embody such decalinic structures. In this context the synthesis of enantiomerically pure advanced intermediates is of interest. Accordingly, we have explored a new approach in which a pyranosidic carbohydrate derivative would serve as a template in a stereocontrolled formation of a six-membered carbocycle and then would afford the basic skeleton of a second fused cylohexane ring. On this basis intramolecular Diels–Alder (IMDA) a well precedented reaction on carbohydrate templates,[4,5] was envisioned to form the first carbocycle. According to the retrosynthetic analysis depicted in Scheme 1, Ferrier carbocyclization[5] should enable the formation of the second ring to occur. This reaction on a 5,6-unsaturated sugar fused to another carbocyclic ring has not been extensively studied.[6] In this communication, we report the preliminary results of our investigations along these lines.

Anchorage of a dienic system to a sugar residue by a glycosidic bond was first investigated (Scheme 2). Thus, homoallylic alcohol **1**, easily prepared from commercially available ocimen by an ozonolysis–reduction sequence according to patent literature,[7] was reacted with tri-*O*-acetyl-D-glucal **2** in the presence of $BF_3{\cdot}OEt_2$ as a catalyst under carefully controlled conditions. An α/β mixture (81 : 19) of the expected glycoside was obtained in 84% yield from which pure α derivative **3** was isolated. Subsequent saponification of the acetates gave quantitatively alcohol **4** which was treated with pivaloyl chloride to give a mixture of the expected 6-*O* pivaloyl derivative **6** together with the diester **5**† as a 7 : 3 mixture. Compound **6** was oxidized with pyridinium dichromate or manganese dioxide to create the key activated double bond



Scheme 1 Retrosynthetic analysis. P = protecting group.



Scheme 2 *Reagents and conditions*: i, **1**, $BF_3{\cdot}OEt_2$, CH_2Cl_2; ii, MeONa, MeOH; iii, ButCOCl, CH_2Cl_2–pyridine, −5 °C; iv, activated MnO_2, CCl_4; v, toluene, hydroquinone, 155 °C, sealed tube, 14 h; vi, LAH, THF; vii, MsCl, pyridine; viii, NaI, butanone, reflux; ix, MOMCl, $NEtPr^i_2$, CH_2Cl_2; x, AgF, pyridine

Table 1 Formation of decalinic structures

Entry	Starting compound	Conditions	Yield (%)	Products	Ratio
1	**17**	H_2SO_4 (5 mmol dm^{-3}), (3 dm^{-3} $mmol^{-1}$),[a] $HgSO_4$ (0.06 equiv.), 1,4-dioxane, 50 °C	84	**19**, **20**, **23**	1 : 1 : 2
2	**18**	H_2SO_4 (5 mmol dm^{-3}), (3 dm^{-3} $mmol^{-1}$),[a] $HgSO_4$ (0.06 equiv.), 1,4-dioxane, 50 °C	95	**21**, **22**, **24**	1 : 1 : 6
3	**17**	$Hg(OAc)_2$, AcOH, acetone–water, reflux, overnight	61	**19**, **20**, **23**	2.5 : 1 : 1.7
4	**23**	Na_2CO_3, DBU, THF–MeOH, 48 h, room temp.	50	**19**	—

[a] Refers to the amount of starting material.

needed for the IMDA reaction. The resulting ketone **7** was then heated in toluene (155 °C sealed tube, hydroquinone) to give the cycloadduct **8** in 75% overall yield. A single isomer was formed as seen from the NMR spectrum of the crude mixture. At this stage the observed coupling constants $J_{1,2}$ = 2.0 Hz and $J_{2,3}$ = 3.5 Hz indicated an all *cis* arrangement of these protons. This was in agreement with an attack of the activated double bond from the α face as expected. However, due to signals overlapping, the coupling constant between H-2 and H-9 was difficult to estimate and the configuration at C-9 could not be ascertained with certainty.

The next problem to address was the chemical manipulation of the pyranoside residue to secure the formation of the 5,6-unsaturation required for the Ferrier carbocyclization. Reduction to the keto group of **8** was first examined. After some experiments we found that reduction of keto ester **8** with LAH gave a 1 : 1.7 mixture of **9** and **13**. Selective mesylation at the primary position gave mesylates **10** and **14** which were easily separated by column chromatography. The iodo derivatives **11** and **15** were formed in 82 and 60% yield respectively upon treatment of **10** and **14** with sodium iodide in butanone. Protection of the secondary hydroxyl group of the iodo derivative **11** was achieved by treatment with methoxymethyl chloride (MOMCl) and $NEtPr^i_2$ in dichloromethane giving the expected MOM derivative **12** in 62% yield which on treatment with silver fluoride in pyridine cleanly gave the key intermediate **17** in 87% yield. Methoxymethylation of **15** proceeded in 61% yield to give **16** which was transformed into the other key intermediate **18** in 72% yield.

Among the various conditions proposed for the Ferrier carbocyclization,[8,9] a catalytic method was investigated first.[10] Under these conditions, compound **17** gave a mixture of three products **19**, **20** and **23** in a 1 : 1 : 2 ratio in 84% overall yield (see Table 1, entry 1). Compounds **19** and **20** were the expected decalones, epimeric at C-3 as shown by ^{1}H NMR, but the major product **23** resulted from (mixture of epimers at C-5) direct hydration of the double bond. Assuming that this compound should result from an interruption of the catalytic cycle of mercury,[11] we used a stoichiometric amount of mercuric sulfate in dioxane 5 mmol dm^{-3} H_2SO_4, but compound **23** was again the major product. The reactivity of olefin **18** under the catalytic conditions was next examined. In this case a mixture of three compounds **21**, **22** and **24** was formed in 95% yield (Table 1, entry 2). The hydration product **24** predominated and was a 1 : 1 mixture of two C-5 epimers as shown by proton NMR. Such a hydration reaction (formation of **23** and **24**) has been previously reported by Ferrier and coworkers in the case of 5,6-unsaturated sugars having a benzoate group at the anomeric position and was believed to proceed by hydrolysis of an intermediate 6-mercuriated species.[12] In this case, the use of mercuric acetate in stoichiometric amount gave only the carbocyclized products. These conditions (Table 1, entry 3) were tested on compound **17** and a mixture of compounds **19**, **20** and **23** (2.5 : 1 : 1.7) was obtained (Table 1, entry 3). It is noteworthy that the main aldol compound **19** had a relative 3,5-*trans* stereochemistry in agreement with a general postulate for the stereochemical outcome of the Ferrier reaction.[13]

Finally we examined the possibility of transforming compound **23** into carbocycles **19** or **20** without use of mercury catalysis. After some experiments we found that basic conditions in a protic medium (Na_2CO_3, DBU in THF·MeOH), were well suited to transform compound **23** into aldol **19** as the sole product in 50% yield (50% recovered starting material) within 48 hours at room temperature (Table 1, entry 4).

The structure of compound **19** was confirmed by single-crystal X-ray diffraction,‡ firmly establishing the absolute configurations at C-3, C-4, C-5, C-9 and C-10 which were tentatively assigned by NMR spectroscopy, and consequently the configurations of all the series of compounds. In particular, this confirms the *cis* arrangement of the ring fusion and thus the complete stereocontrol of the IMDA reaction which occurs in the *exo* mode with attack of the diene from the bottom face (α) of the dienophile. Subsequent Ferrier carbocyclization gave a mixture of cyclized products as a 1 : 1 C-3 epimeric mixture together with the product resulting from direct hydration. This reaction could be due to the fact that, in this case, the 'aglycon' is included in a cycle.

In conclusion, we have used with success tandem IMDA–Ferrier carbocyclization for the formation of highly oxygenated *cis* decalinic systems. Conditions have been found to achieve highly stereocontrolled carbocyclization of the undesired hydrated compound **23** in the absence of mercury and giving essentially one isomer, thus offering a useful alternative to the Ferrier reaction.

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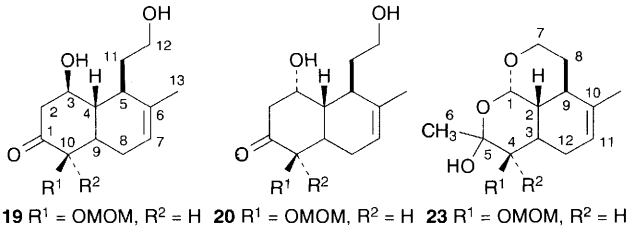

19 R^1 = OMOM, R^2 = H **20** R^1 = OMOM, R^2 = H **23** R^1 = OMOM, R^2 = H
21 R^1 = H, R^2 = OMOM **22** R^1 = H, R^2 = OMOM **24** R^1 = H, R^2 = OMOM

Footnotes

† This material can be recycled to diol **4** by LAH reduction.

‡ *Crystal data* for: **19** $C_{30}H_{48}O_{10}$, M = 568.68, triclinic. Space group $P\bar{1}$, a = 10.645(2), b = 5.503(2), c = 12.672(2) Å, α = 88.99(1), β = 101.84(1), γ = 90.18(1)°, Z = 2, V = 726.4(3) Å^3, D_c = 1.3 g cm^{-3}, Cu-Kα (λ = 1.540 56 Å): data were collected at room temperature on a CAD4 Enraf-Nonius diffractometer in the θ–2θ scanning mode (θ < 70°), 1935 reflections having $I > 2\sigma(I)$ were used in the structure solution. The structure was solved using the SHELXL 93 program.[14] The final R_1 and wR_2 factors were 0.041 and 0.10 respectively. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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