Cyclopentane-annelated Pyranosides: A New Approach to Chiral Iridoid Synthesis

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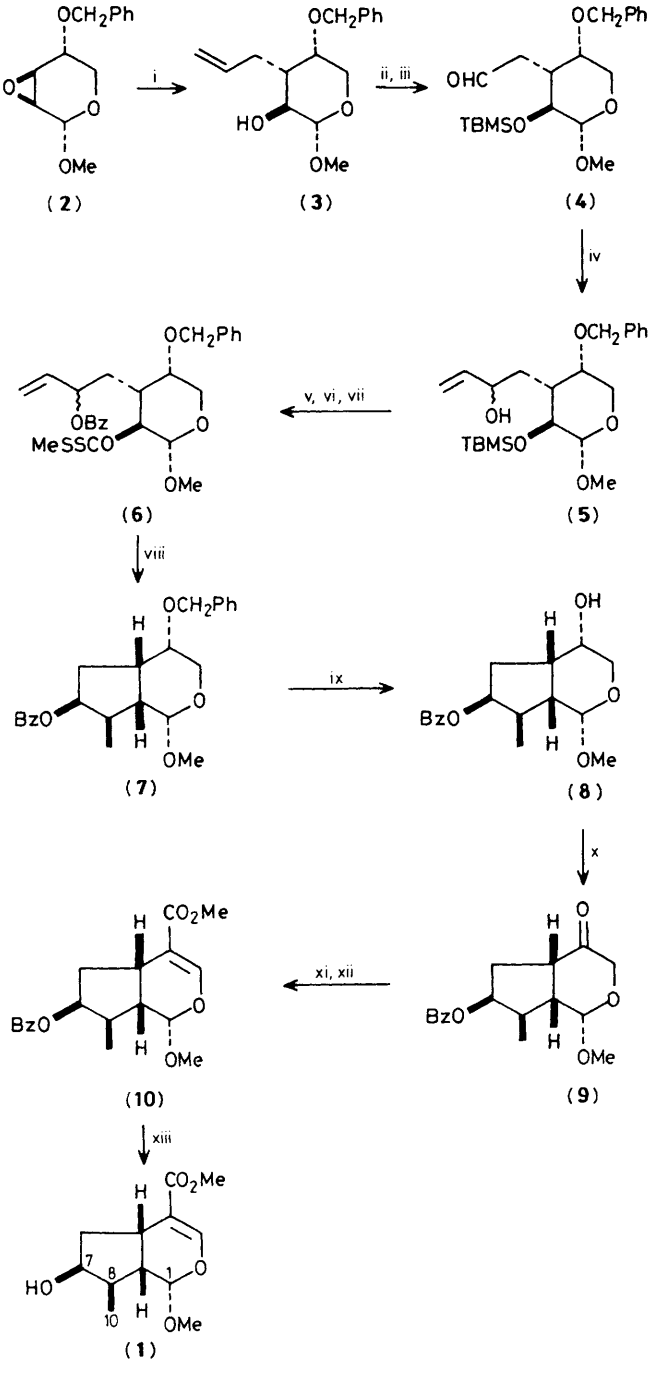
1-α-*O*-Methyl-loganin (**1**) was synthesised from methyl 2,3-*anhydro*-α-D-lyxopyranoside by cyclopentane annulation using the pyranose ring as the tetrahydrocoumalate skeleton.

Recently, many classes of natural products have been synthesised from carbohydrates as the chiral source.[1] A structural feature of the iridoid glycosides[2] is the tetrahydrocoumalate moiety, which resembles the pyranoside ring. Although many syntheses of iridoid glycoside aglycones have been published,[3] one of the most straightforward methods, formation of a cyclopentane ring on a pyranoside nucleus, appears not to have been reported. The cyclopentane annulation has been effected regio- and stereo-selectively by the intramolecular radical cyclisation[4] of a but-3-enyl side chain introduced on the



Bz = PhCO; TBMS = Bu^{t}Me$_2$Si

Scheme 1. *Reagents:* i, CH_2=$CHCH_2MgBr$, Et_2O, room temp., 0.5 h, 88%; ii, Bu^{t}Me$_2$SiCl, imidazole, dimethylformamide (DMF), 30 °C, overnight, 96%; iii, O_3, CH_2Cl_2, −78 °C, Et_3N, room temp., 4 h, 93%; iv, CH_2=CHMgBr, tetrahydrofuran (THF), −78 °C, 1.5 h, 82%; v, PhCOCl, Et_3N, 4-*N*,*N*-dimethylaminopyridine (DMAP), CH_2Cl_2, room temp., overnight, 91%; vi, Bu$^n_4$NF, NH_4Cl, THF, room temp., 24 h, 92%; vii, $(Me_3Si)_2NH$, Bu^{n}Li, THF, CS_2, MeI, room temp., 15 h, quant.; viii, Bu$^n_3$SnH, C_6H_6, reflux, AIBN, 1 h, 62—73%; ix, Raney Ni, H_2, AcOEt, reflux, 5 h, 85%; x, pyridinium chlorochromate (PCC), NaOAc, CH_2Cl_2, room temp., overnight, 80%; xi, lithium di-isopropylamide (LDA), 1,2-dimethoxyethane (DME), − 70 °C$(F_3CSO_2)_2NPh$, −70 to 0 °C, 1 h, room temp., overnight, 60%; xii, $Pd(Ph_3P)_4$, MeOH, Et_3N, LiCl, THF, CO bubbled, 5 min, reflux, 2 days, 68%; xiii, NaOMe, MeOH, room temp., overnight, 72%.

pyranoside ring. We illustrate this strategy by the synthesis of 1-α-*O*-methyl-loganin aglycone (**1**) (Scheme 1).

The starting material (**2**) was easily prepared by the benzylation of methyl 2,3-*anhydro*-α-D-lyxopyranoside[5] in 87% yield. After many unsuccessful attempts to open the epoxide ring with a but-3-enyl nucleophile, allylmagnesium bromide was found to cleave the ether linkage to give the *C*-allyl-pyranosie (**3**) in excellent yield. Homologation of the side chain was achieved by protection of the 2-hydroxy group, followed by ozonisation and reaction of the resulting aldehyde (**4**) with vinylmagnesium bromide. The vinylation gave a 1 : 1 mixture of the diastereoisomeric alcohols (**5**), which were separated by chromatography on silica gel. The isomeric alcohols were separately cyclised by benzoylation, cleavage of the silyl group, conversion into the xanthates (**6**), and boiling the xanthates in benzene with tributyltin hydride in the presence of azoisobutyronitrile (AIBN) to give (**7**) or its epimer in good yield with several isomers as minor products. The fact that (**7**) showed the methyl ^{13}C resonance at higher field (δ 15.4) than its epimer (δ 20.2) suggested that in the former the methyl group is *cis* to the benzoyloxy group, as in loganin. The epimer showing δ 20.2 was deprotected by methanolysis followed by the Mitsunobu reaction to produce (**7**).

The final step, the introduction of the ester function and unsaturation to the pyranoside ring, was accomplished by palladium-mediated carbonylation. The benzyl group of (**7**) was removed by hydrogenolysis in the presence of Raney nickel; the resulting alcohol (**8**) was oxidised to the ketone (**9**). Trapping the kinetic enolate of the ketone with triflate reagent[6] $(F_3CSO_2)_2NPh$ gave the Δ^3-enol trifluoromethanesulphonate as the major product. Carbonylation of the trifluoromethanesulphonate in the presence of methanol and palladium(0) catalyst under carbon monoxide[7] gave the desired 7-*O*-benzoyl-1-α-*O*-methyl-loganin aglucone (**10**) ($[\alpha]_D^{26}$ +115°) in moderate yield. The ^1H n.m.r. spectrum of the benzoate was identical to that of an authentic sample.[3b] Methanolysis of the benzoate gave 1-α-*O*-methyl-loganin aglucone (**1**) ($[\alpha]_D^{23}$ +202°; lit[8] +191°).

In the homologation step, use of ethynyl magnesium bromide instead of the vinyl reagent would give the versatile $\Delta^{8,10}$-iridoid aglucone, and this variation is being studied.

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