Glycomimetics *via* a new glycoexoenitols–malonyl radical C–C bond formation

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C-Glycosyl methylenemalonates 2 and 4, useful precursors for the synthesis of glycopeptides and glycoproteins mimics, are obtained by reaction of a malonyl radical on the glycoexoenitols 1 and 3; reaction of the same radical with 6-deoxy-1,2:3,4-di-*O*-isopropylidene-β-L-*arabino*-hex-5-enopyranose 5 results in a mixture of the malonylderivatives 6, 7 and 8 and, in diluted THF solutions, also in the tetrahydrofuranyl derivative 9.

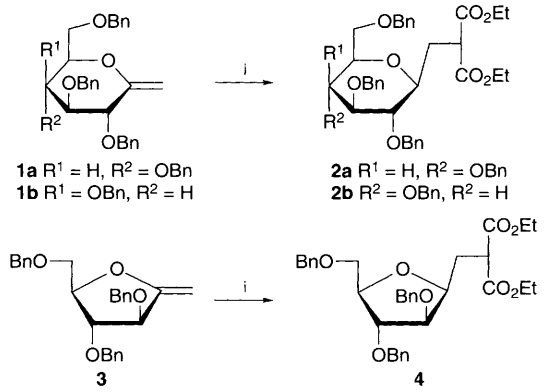
Glycomimetics, such as aza-sugars,[1] carba-sugars,[2] *C*-glycosides[3] and higher carbon sugars,[4] have gained interest as potential inhibitors or regulators of the metabolic processes in which the parent natural sugar is involved. In particular, efforts have been devoted to develop new methods of formation of a C–C bond at the two ends of the sugar skeleton. The possibility of linking appendages which can be easily and differently functionalized, in order to obtain stable analogues of glycolipids and glycoproteins, is of particular interest. The malonyl group fulfils these requirements: it can be reduced and esterified with fatty acids, to mimic glycolipids, or converted into an amino acidic function to produce glycoprotein analogues.

The synthesis of a *C*-glycosyl malonate was first described by Hanessian,[5a] by reaction of a malonyl anion on a glycosyl halide. Further examples involve a Knoevenagel-type condensation[5b,c] and a carbenoid displacement reaction with phenylthioglycosides.[5d] These procedures however afford *C*-glycosylmalonates that cannot be converted to isosteric analogues of glycolipids, as the products lack the methylene group displacing the glycosidic oxygen of the natural product. More recently Giese[6] described the attack of a mannopyranosyl radical on a methylene malonic ester. When applied to glucopyranosyl or mannopyranosyl bromides, this reaction affords stereoselectively the corresponding α-*C*-glycosyl methylenemalonates. Natural glycolipids and glycoproteins, however, usually have a β-glycopyranosidic configuration.

In this paper we describe a new approach that allows the introduction of a β-oriented methylenemalonyl group at the anomeric centre of glycopyranosides, as required for the synthesis of glycoconjugate analogues. The procedure has been also extended to the anomeric centre of a glycofuranoside and to the non-reducing end of a sugar. Our synthetic procedure involves the reaction of a malonyl radical with suitable glycoexoenitols such as **1** and **3**, and alternatively with the 5-enopyranose **5**. The synthetic strategy is based on two well-known facts. First, the synthetic application shown by carbon–carbon bond forming free radical processes is strongly dependent on polar effects.[7] Secondly, the photolysis of organotin hydrides and organic halides in THF provides an useful source for a radical chain reaction of synthetic utility.[7b,8] The use of enol ethers as scavengers of the malonyl radical takes advantage of both these points,[9] the generation of the malonyl radical from chloromalonate by tributyltin hydride and the favourable interaction between an electrophilic radical and an electron-rich substrate.[7] In the light of these observations, we investigated if the exoenitols, which possess electron-rich exocyclic and terminal[10] double bonds, could act as scavengers of malonyl radical.

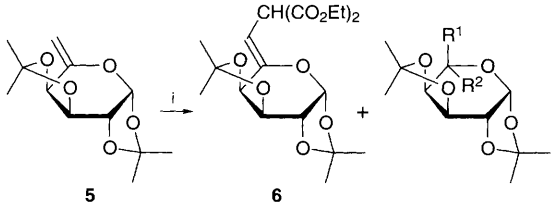
In a typical experiment, a solution of ethyl chloromalonate, tributyltin hydride and the sugar enol ether, in anhydrous THF, is irradiated for two hours with UV light with a mercury lamp under nitrogen atmosphere at room temperature.

When we tested the reaction of ethyl chloromalonate, the enol ethers **1**[11] and **3**, and Bu_3SnH, in 1:1:1:3 ratio, useful and interesting results were obtained. From a synthetic point of view, although the yields of the desired product are not very high [35% of **2a**,† 32% of **2b**† and 30% of **4**† in (10:4 β:α ratio)], the unreacted glycoexoenitol can be quantitatively and easily recovered after the reaction and recycled. The yields calculated for the converted starting material are quantitative; this indicates that no side reactions, such as abstraction of benzylic hydrogen, occur. Slightly better results can be obtained by slow (3 h) addition of Bu_3SnH to the reaction in THF; following this procedure **2a** was obtained in 50% yield, the remaining starting material being recovered. Changing the solvent led to lower yields; in benzene **2a** was recovered in 5% yield and in MeCN the yield of **2a** was 15%. The radical source was also changed. Using $Bu_3SnSnBu_3$, which is unable to produce a radical chain,[12] **2a** was obtained in 25% yield together with the substitution product **9** (25% yield). In this case



1a R^1 = H, R^2 = OBn
1b R^1 = OBn, R^2 = H
2a R^1 = H, R^2 = OBn
2b R^2 = OBn, R^2 = H

Scheme 1 *Reagents and conditions*: i, Bu_3SnH, $ClCH(CO_2Et)_2$ THF, room temp., *hν*



7 $R^1 = CH_2CH(CO_2Et)_2$, R^2 = H
8 R^1 = H, $R^2 = CH_2CH(CO_2Et)_2$

Scheme 2 *Reagents and conditions*: i, Bu_3SnH, $ClCH(CO_2Et)_2$ THF, room temp., *hν*

the intermediate radical disproportionates to the addition and substitution products. Using $(Me_3Si)_3SiH$[13] **2a** was obtained in 30% yield; in this case however the starting material was not recovered.

The enol ether **5**[14] gave significantly different results. In fact, when the reagents are employed in equimolecular amounts in a 0.06 mol dm^{-3} THF solution, the sugar does not react. Increasing the molar ratio of **5**, with respect to the chloromalonate and Bu_3SnH, to 7 : 1 : 1.3, and its concentration to 0.28 mol dm^{-3} gave three different malonyl glycosides **6**, **7** and **8** in 16% overall yield (based on chloromalonate). In a 1 : 1.8 : 1.3 molar ratio, the α-tetrahydrofuranyl derivatives **10** (9%) were also found, due to the formation and trapping of the nucleophilic α-tetrahydrofuranyl radical.[15] The formation of **10** can be minimized by working with more concentrated solutions. At a 4.2 mol dm^{-3} concentration of **5** the yield of **10** is reduced to 2%, and the malonyl derivatives **6**, **7** and **8** were obtained in 27% overall yield, their ratio changing to 1 : 2.1 : 0.2. The low yields observed in this reaction, and the formation of **10**, can be attributed to the ambiguous 'electron-rich' character of the double bond of **5**. This hypothesis is supported by the observed reaction of this double bond with the α-tetrahydrofuranyl radical, the nucleophilicity of which has been demonstrated.[16] The stereochemistry of the new stereocentres of **2a** and **2b** was attributed on the basis of the ^1H NMR coupling constants. In both the molecules, the coupling constant between H-4 and H-5 (9.0 Hz in the case of **2a** and 9.5 Hz in the case of **2b**) clearly indicates their axial–axial orientation and consequently the β-orientation of the malonyl substituent. The high stereoselection of these reactions (≥95% de, based on the isolated materials) can be explained on the basis of the preferred α-orientation of the glycopyranosyl radical[17] as a consequence of the anomeric effect.

In the case of **4**, the absence of an efficient anomeric effect in the furanosidic ring results in a low level of stereoselection, 10 to 4 in favour of the β-isomer, as calculated from the ^{13}C NMR spectra of the mixture. In fact the carbon atom linked at the anomeric centre of the more abundant isomer resonates at higher field (δ 29.21) with respect to the same carbon of the less abundant isomer (δ 33.06), so indicating its *cis* relationship with the oxygen at C-5 (γ-effect) and consequently its β-orientation.[18] The lack of stereoselection in the reaction of **5** could be attributed to the conformational rigidity of the molecule, due to the isopropylidene protecting groups.

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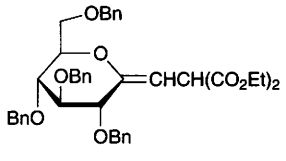

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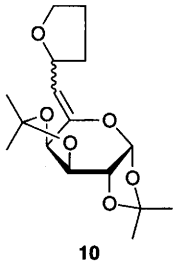

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Footnote

† *Selected data for* **2a**: ^1H NMR (500 MHz, C_6D_6): δ 0.90 (2t, 6 H, 2 × OCH_2CH_3), 2.24 (ddd, 1 H, H-3, J_{2-3} = 5.6, $J_{3-3'}$ = 9.0, J_{3-4} = 7.9 Hz), 2.87 (ddd, 1 H, H-3′, $J_{2-3'}$ = 2.8, $J_{3'-4}$ = 1.6 Hz), 3.23 (t, 1 H, H-5, J_{4-5} = J_{5-6} = 9.0 Hz), 3.30 (ddd, 1 H, H-8, J_{7-8} = 10.0, J_{8-9} = 2.0, $J_{8-9'}$ = 4.0 Hz), 3.47 (dt, 1 H, H-4), 3.63 (dd, 1 H, H-9, $J_{9-9'}$ = 10.8 Hz), 3.64 (t, 1 H, H-6, J_{6-7} = 9.0 Hz), 3.67 (dd, 1 H, H-9′), 3.77 (t, 1 H, H-7), 3.95 (dd, 1 H, H-2), 3.90–4.05 (4 H, 2 × OCH_2CH_3), 4.35–4.90 (8 H, 4 × $OCH_2C_6H_5$), 7.00–7.40 (20 H, 4 × $OCH_2C_6H_5$); mp 95 °C; $[\alpha]_D^{20}$ +4.6 (*c* 0.5 in $CHCl_3$); *m/z* (FAB): 698 (M + 1). For **2b**: ^1H NMR (500 MHz, C_6D_6): δ 1.15 (2t, 6 H, 2 × OCH_2CH_3), 2.59 (ddd, 1 H, H-3, J_{2-3} = 4.9, $J_{3-3'}$ = 14.5, J_{3-4} = 9.7 Hz), 3.16 (ddd, 1 H, H-3′, $J_{2-3'}$ = 9.8, $J_{3'-4}$ = 2.5 Hz), 3.65 (dd, 1 H, H-6, J_{5-6} = 9.4, J_{6-7} = 2.8 Hz), 3.72 (dd, 1 H, H-8, J_{7-8} ≅ 0, J_{8-9} = 5.5, $J_{8-9'}$ = 8.4 Hz), 3.78 (dt, 1 H, H-4, J_{4-5} = 9.5 Hz), 3.85 (dd, 1 H, H-9, $J_{9-9'}$ = 8.8 Hz), 3.99 (dt, 1 H, H-9′), 4.08 (t, 1 H, H-5), 4.15–4.25 (4 H, 2 × OCH_2CH_3), 4.21 (d, 1 H, H-7), 4.27 (dd, 1 H, H-2), 4.47–5.30 (8 H, 4 × $OCH_2C_6H_5$), 7.30–7.65 (20 H, 4 × $OCH_2C_6H_5$); Oil; $[\alpha]_D^{20}$ −5.0 (*c* 0.7 in $CHCl_3$); *m/z* (FAB): 698 (M + 1). For **4** (major isomer): ^1H NMR (500 MHz, C_6D_6): δ 0.85–0.95 (2t, 6 H, 2 × OCH_2CH_3), 2.68 (ddd, 1 H, H-3, J_{2-3} = 9.2, $J_{3-3'}$ = 12.9, J_{3-4} = 4.0 Hz) 2.79 (ddd, 1 H, H-3′, $J_{2-3'}$ = 5.4, $J_{3'-4}$ = 9.2 Hz), 3.56 (dd, 1 H, H-8, J_{7-8} = 7.2, $J_{8-8'}$ = 9.7 Hz), 3.64 (dd, 1 H, H-8′, $J_{7-8'}$ = 5.2 Hz), 3.84 (dd, 1 H, H-5, J_{4-5} = 3.8, J_{5-6} = 1.2 Hz), 3.85–3.95 (4 H, 2 × OCH_2CH_3), 3.98 (dd, 1 H, H-2), 4.08 (d, 1 H, H-6, J_{6-7} = 2 Hz), 4.27 (ddd, 1 H, H-7), 4.20–4.40 (8 H, 4 × $OCH_2C_6H_5$), 4.39 (ddd, 1 H, H-4), 7.00–7.30 (20 H, 4 × $OCH_2C_6H_5$).

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