Applications of Radical Addition Reactions to the Synthesis of a *C*-Glucoside and a Functionalised Amino-acid

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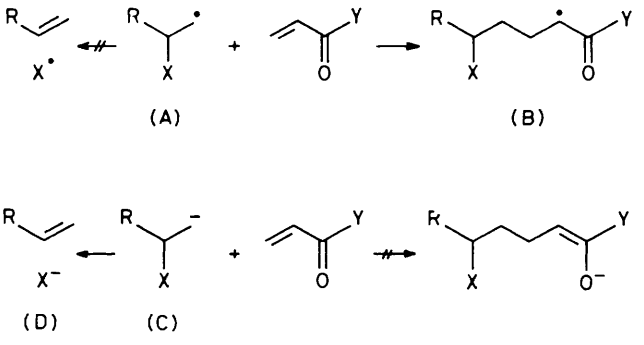
Addition of carbon radicals derived from tetra-acetylglucosyl and β-alanyl derivatives to acrylic acid or esters provides a short route to a *C*-glucoside and a functionalised α-amino-acid, respectively.

The use of radical additions in natural product synthesis may provide a method for carbon–carbon bond formation through radical intermediates which are essentially orthogonal in reactivity towards many of the common functional groups, *e.g.* carbonyl, hydroxy, and amido groups. Consequently such processes, (A) to (B), might not require extensive and elaborate protection of functional groups and also might avoid neighbouring group problems, especially competing carbanion type eliminations, (C) to (D), Scheme 1. To assess the scope of this approach we have examined the coupling of radicals[1] derived from two classes of natural products, notorious for their sometimes difficult functionality, *i.e.* sugars and amino-acids. In the first case we demonstrate the generation and trapping of the C-1 glucosyl radical (**1**) to provide a *C*-glucosyl derivative in one step, using simple ester protection of the remaining hydroxy groups. Thus a mixture of phenyl tetra-acetyl-β-D-selenoglucoside (**2**)[2] (1.2 mmol) and methyl acrylate (10 equiv.) in refluxing toluene (2.0 ml) was treated with triphenyltin hydride (Scheme 2) (3 equiv. over 13 h, slow addition by syringe) in toluene (2.5 ml).[1b] The product, purified by chromatography on silica gel, was the *C*-glucoside (**3**) as an oil (40% isolated).† That this was the α-isomer (>90%) was demonstrated by ^{1}H n.m.r. spectroscopy, using the additivity rules of Altona and Haasnoot,[3] since the observed coupling between the proton on C-1 [δ 4.12—4.20 (m)] and that on C-2 [δ 5.09 (dd)] was $J_{1,2}$ 5.9 Hz, in accord with an equatorial–axial relationship (predicted 5.4 Hz) rather than a diaxial relation ship (predicted 9.4 Hz). A second product (<10%)



Scheme 1. X ≡ electronegative group.

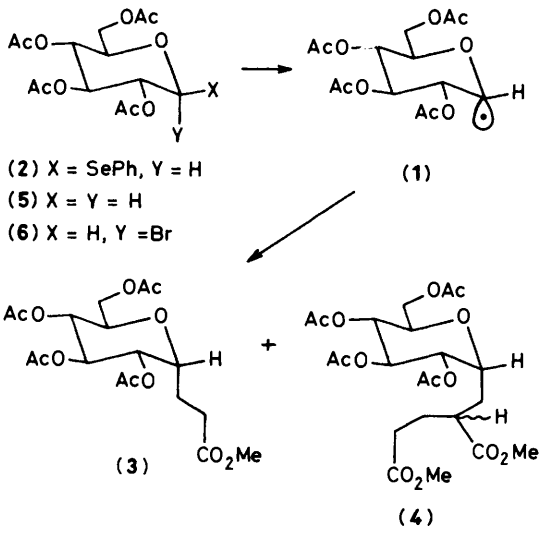
was the double adduct (**4**).‡ Attempts to reduce the level of (**4**) by lowering the acrylate level were unsuccessful since large amounts (15—20%) of the reduction product (**5**) began to appear. A similar coupling to give (**3**) was obtained (35% yield) with the tetra-acetobromoglucose (**6**).[4] Apparently, therefore, the glucosyl radical (**1**) appears preferentially to couple to give the axial product (**3**).

As another example of this principle, in the amino-acid series we generated and trapped the optically active alanyl radical (**7**) with acrylic aid to yield optically active aminoadipic acid. Thus the protected 3-iodo-L-alanine (**8**),§ m.p. 58 °C,

† New compounds were characterised by spectral [^{1}H n.m.r. (300 MHz), i.r., u.v., mass, and optical] and combustion data.

‡ The structural assignments for (**4**) and (**10**) are tentatively based upon spectral data.

§ Obtained from *N*-benzyloxycarbonyl-L-serine benzyl ester in 60% overall yield by sequential treatment with PCl_5 and NaI–acetone.



Scheme 2

(1.0 mmol) reacted with Bu^n_3SnH (2 equiv. added over 10 h) in refluxing benzene containing acrylic acid (2 equiv., half added initially and then half after 5 h)¶ to give three products, readily separated by chromatography on silica gel, as (**9**), 30% isolated, m.p. 87 °C, $[\alpha]_D^{20}$ −13.0° (*c* 1.5, acetone) {lit.[5] m.p. 87—89 °C, $[\alpha]_D^{20}$ −13.3 °C (*c* 2, acetone)}, (**10**), (6%),‡ and the reduction product *N*-benzyloxycarbonyl-L-alanine benzyl ester (17%). That the aminoadipic product (**9**) was optically pure was also proved by conversion[6] into the known L,L,D-tripeptide (**11**) (Scheme 3). We have shown that contaminating levels of 2—3% of the D-antipode can be assayed reliably by ^1H n.m.r. spectroscopy of (**11**). In contrast, attempts to effect nucleophilic displacement on (**8**) with carbon nucleophiles led always to elimination to dehydroalanine derivatives.

In conclusion it seems clear that the radical coupling of highly functionalised entities with unsaturated species may provide a useful and relatively simple methodology for carbon–carbon bond formation.

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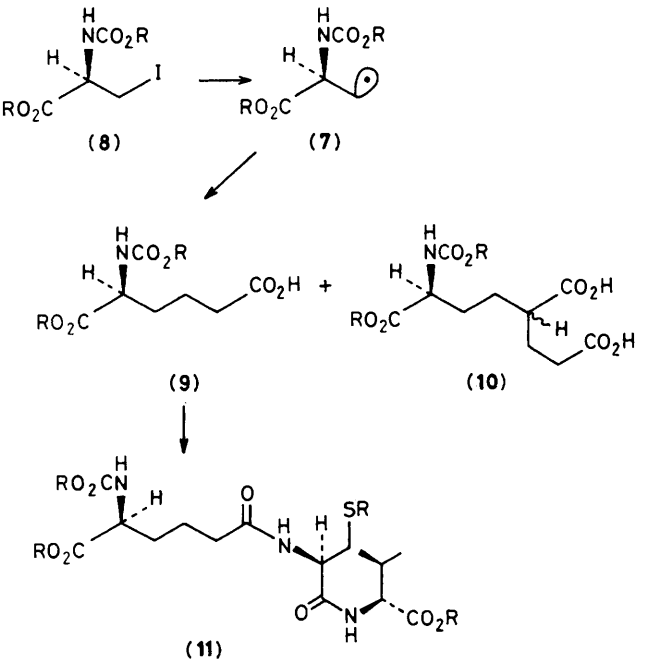
¶ Azoisobutyronitrile (1 mg) added every hour.



Scheme 3. R = CH_2Ph.

References

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