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Amygdalin as Building Block in Oligosaccharide Synthesis

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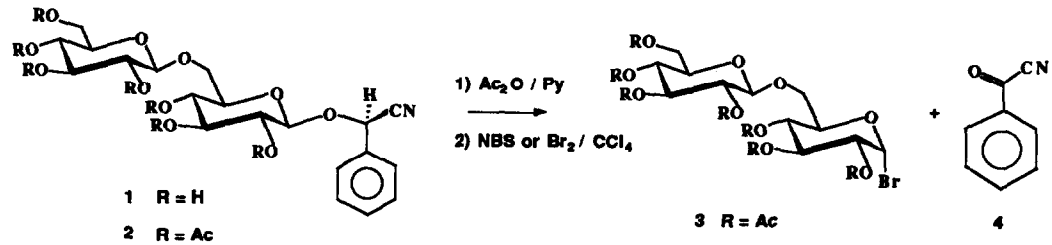
Abstract: Acetobromogentiobiose is prepared in two steps from amygdalin. Like other bromosugars it reacts on triphenylmethyl amygdalin derivatives with silver cyanide to afford tri-and tetrasaccharides in high yields.

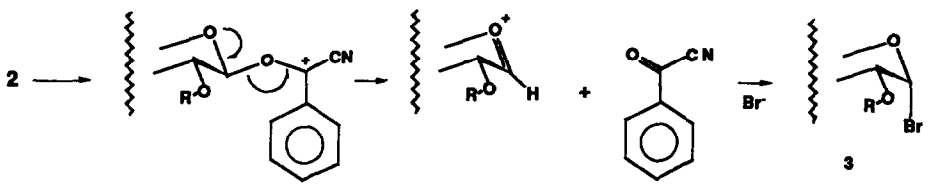
Amygdalin [(6-O-β-D-Glucopyranosyl-β-D-glucopyranosyl)oxy]phenylacetonitrile **1** belongs to the family of the so called cyanogenic glycosides[1]. Present in large quantities in the seeds of the Rosaceae plants, amygdalin can be considered a by-product of the fruit industry[2]. Despite its low cost, amygdalin has been rarely used as a source of gentiobiose in glycoside synthesis[3]. It is shown here that it is both a glycosyl donor and a glycosyl acceptor.

The hepta-acetate of amygdalin **2** is obtained under standard conditions (Ac_2O, Py). When a solution of **2** and dry $CaCO_3$ in carbon tetrachloride is treated with N-bromosuccinimide or bromine, **2** decomposes rapidly and exclusively into peracetobromogentiobiose **3** and benzoyl cyanide **4** [4].



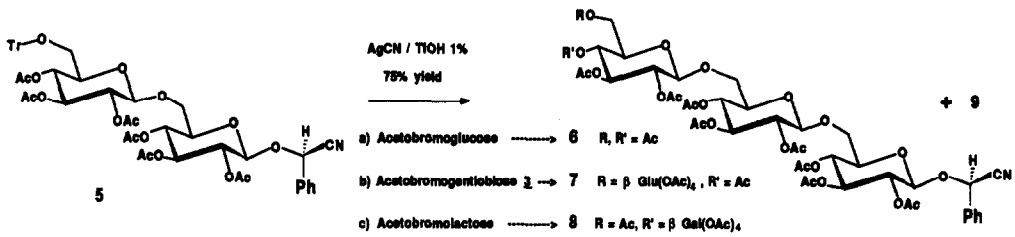
1 R = H
2 R = Ac
3 R = Ac
4

The formation of the two products is tentatively explained by hydride abstraction from the 1 position followed by decomposition into benzoyl cyanide and an oxonium ion, the latter of which is trapped by a bromide ion to give α-bromogentiobiose as a consequence of the anomeric effect [5].



3

In addition we found that amygdalin can be derivatized and used as a glycosyl acceptor. The 6"-triphenylmethyl derivative **5** was obtained in high yield in a one-pot procedure[6] from amygdalin. It reacts with acetobromosaccharides in the presence of a silver catalyst to give tri- and tetrasaccharides in good yields[7].



Furthermore, prior deprotection of the 6" position of compound **5** is not necessary for the glycosylation reactions. Like in Kochetkov's[8] orthoester oligomerisation, the triphenylmethyl cation liberated during the reaction is trapped by a cyanide ion to afford triphenylmethylcyanide $(Ph)_3C\text{-}CN$ **9**. The easily-handled and non-hygroscopic silver cyanide is used with a catalytic quantity of either silver triflate or triflic acid as a starter. Under our conditions, the coupling reactions proceed smoothly from **5** and are complete in less than one hour at the reflux temperature of dichloromethane. The change from the typical yellow colour of the triphenylmethylium cation to greenish-grey indicates the end of the reaction. At this point the mixture is diluted with dichloromethane followed by filtration on Celite. Unlike many other reaction conditions, neither decomposition nor 1-2 orthoester formation is observed. Finally, the resulting oligosaccharides are transformed into bromo- derivatives[9] in the same manner[4].

In our procedure, the mandelonitrile group is used first as the protecting element, then as the activator of the anomeric function at the reducing end of the oligosaccharide which is then ready for further glycosylation. These reactions point to the use of natural mandelonitrile glycosides[1, 10] as versatile building blocks in oligosaccharide synthesis.

References and notes

1. Seigler, S.D.; Phytochemistry, **14**, 9-29 (1975). Schwarzmaier, U., id., **11**, 2358 (1972). Courtois, J. E.; Percheron, F.; in *The Carbohydrates* ; Vol. IIA, Pigman, W., Ed. (Academic Press: New York, 1970), 217-218.
2. French Patent, Fr 2274568, 9 jan. 1976. Schwarzmaier, U.; J. Chromatogr., **114**, 235-236 (1975).
3. Rupe, H.; Engel, K.; Helv. Chim. Acta, **18**, 1190-1203 (1935).
4. Typical procedure : **2** (6g), $CaCO_3$ (6g), molec. sieves 4Å (1g), CCl_4 400ml with NBS or Br_2 (1.2 eq) are maintained under reflux for 3h under Ar, then filtered, evaporated (with NBS, succinimide is crystallised out in chloroform). The resulting mixture (8g) is used directly or can be purified by chromatography on neutral silica to afford 75% of pure **3**. (For tlc detection of the mandelonitrile derivatives see Schwarzmaier in ref. 2).
5. Lemieux, R. U.; in *Molecular Rearrangements*; P. de Mayo, Ed., (Interscience: New York, 1964), p 709. Lemieux, R. U.; Can. J. Chem., **30**, 295 (1952). Deslongchamps, P.; in *Stereoelectronic effects in Organic Chemistry* ; Baldwin, J.E., Ed. (Pergamon Press : Oxford, 1983) p 5-20.
6. **1** with TrCl (1.1 eq) in Py., then Ac_2O; 95% yield: $[\alpha]_D$ -15°(c 1.0, $CHCl_3$), nmr (300 MHz) $CDCl_3$ δH : 7.4-7.3 (m, 20H, 4 Ph), 5.6 (s, 1H,H1), 5.2 (t, 1H, $J_{2\text{-}3,3\text{-}4}$ = 10Hz, H3'), 5.2-5.0 (m, 5H, H2', H4', H2", H3", H4"), 4.65 (d, 1H, $J_{1'\text{-}2'}$ = 8Hz, H1"), 4.4 (d, 1H, $J_{1\text{-}2}$ ≈ 8Hz, H1'), 4.0 (m, 1H, H6'a), 3.7 (m, 3H, H5', H5", H6'b), 3.2 (m, 2H, H6"), 2.1-1.75 (m,18H, Ac).
7. **5** (1 eq), bromosugar (1.1 eq), AgCN (1.1 eq), AgTf or TfOH (10^{-2}eq), CH_2Cl_2 10ml/mmol. 75% yield.
8. Kochetkov, N.K.; Tetrahedron, **43**, 2389-2436 (1987).
9. Tri- and tetrasaccharides **6** to **8** are transformed into the corresponding acetobromoderivatives through the same procedure (ref. 4). On the ^1H nmr spectra the typical singlet of the H1 proton at 5.6 ppm disappears and the sharp doublet of the equatorial anomeric proton, typical of the bromosugar, shows at 6.55 ppm.
10. Vicianin, Prunasin, Sambunigrin, Taxiphyllin, Dhurrin, Holocalin, Zierin, Lucumin, Laetride®in ref. 1, 2.

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