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Synthesis of Umbilicin (2-*O*-β-D-Galactofuranosyl-D-arabinitol)

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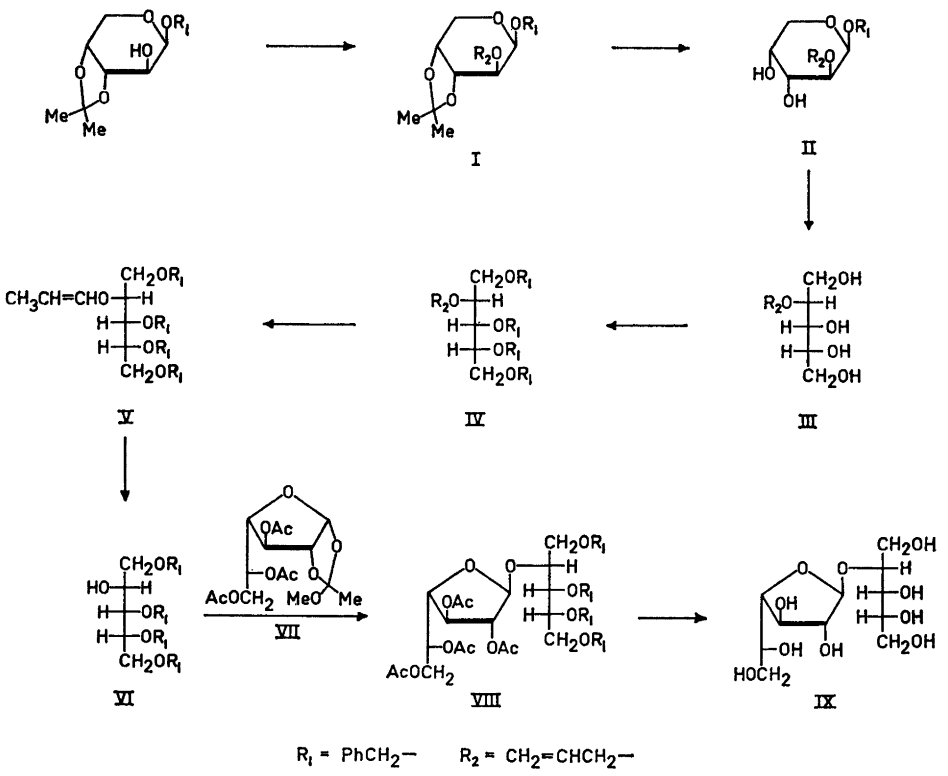
The structure of umbilicin (2-*O*-β-D-galactofuranosyl-D-arabinitol) has been confirmed by an unambiguous synthesis.

The arabinitol galactoside umbilicin, first isolated from the lichen *Umbilicaria pustulata* by Lindberg and coworkers [1] has been the subject of several reports.[1–4] Its structure was shown to be that of 2-*O*-β-D-galactofuranosyl-D-arabinitol by Lindberg and Wickberg.[4] So far, this structural assignment has not been confirmed by synthesis. This, the final stage in the elucidation of the structure of umbilicin, is described in the present report.

Kochetkov and coworkers [5] have described a stereospecific synthesis of glycosides starting from the appropriate sugar orthoesters, and have applied this in the synthesis of the galactofuranoside peltigeroside (3-*O*-β-D-galactofuranosyl-D-mannitol),[5] first isolated by Pueyo from the lichen *Peltigera horizontalis*.[6] In a previous report from this laboratory, this glycoside synthesis was used in the synthesis of 1-*O*-β-D-galactofuranosyl-D-glyceritol,[7] previously isolated from the lipid of *Bacteroides symbiosus* by Reeves and coworkers.[8] Analogously with the latter synthesis,[7] the appropriate benzylated alditol (1,3,4,5-tetra-*O*-benzyl-D-arabinitol) was chosen as a suitable alcohol for the glycoside synthesis.

Benzyl 3,4-*O*-isopropylidene-β-D-arabinopyranoside [9] was treated with allyl bromide and powdered sodium hydroxide in dioxane to yield the syrupy allyl ether, I. This, on treatment with acid under mild conditions gave crystalline benzyl 2-*O*-allyl-β-D-arabinopyranoside, II. Further hydrolysis of II with acid, and reduction with sodium borohydride of the resulting arabinose derivative to 2-*O*-allyl-D-arabinitol, III, yielded a chromatographically pure syrup. Benzylation of the remaining hydroxyls in III and isomerization with potassium t-butoxide of the allyl group in IV to yield the vinylic ether V and finally mild acid hydrolysis, following the general procedure described by Cunningham and coworkers,[10] yielded syrupy 1,3,4,5-tetra-*O*-benzyl-D-arabinitol, VI. A small amount of VI was methylated with dimethyl sulphate and potassium hydroxide in dioxane. The product was hydrogenated with 5 % palladium on charcoal and finally acetylated with acetic anhydride in pyridine. The methyl group in the presumed 1,3,4,5-tetra-*O*-acetyl-2-*O*-methyl-D-arabin-



itol was shown to be in the 2- or 4-position by mass spectrometry as described by Björndal and coworkers.[11] Reaction of VI with 3,5,6-tri-*O*-acetyl-1,2,-*O*-methylorthoacetyl-α-D-galactofuranose, VII, under the conditions described by Kochetkov and coworkers [5] yielded the galactofuranoside VIII, which upon deacetylation followed by catalytic hydrogenation gave 2-*O*-β-D-galactofuranosyl-D-arabinitol, IX. The synthetic material, IX, crystallised, yielding crystals indistinguishable from those of the natural product (m.p., mixed m.p., IR). The acetate of IX was similarly indistinguishable from umbilicin octaacetate.

The overall yield of IX from I was 5 %.

EXPERIMENTAL

All melting points are corrected. Optical rotations were measured at room temperature (20—22°). Evaporations were carried out under reduced pressure at a bath temperature below 50°.

Benzyl 2-O-allyl-3,4-O-isopropylidene-β-D-arabinopyranoside, (I). Benzyl 3,4-*O*-isopropylidene-β-D-arabinopyranoside [9] (63 g) was allowed to react with allyl bromide (120 ml) in dry dioxane (600 ml) in the presence of powdered sodium hydroxide (56 g). The mixture was stirred mechanically for 5 h after which thin layer chromatography

(silica gel-ethyl ether) indicated complete reaction. The mixture was diluted with benzene, and the benzene layer was shaken with water until all the alkali had been removed. The benzene solution was dried over sodium sulphate, filtered and concentrated. The resulting syrup, which was not further characterized, was used directly in the subsequent step.

Benzyl 2-O-allyl-β-D-arabinopyranoside, (II). The above syrup, I, (77 g) was dissolved in acetone (1000 ml). Aqueous formic acid (0.1 M, 2000 ml) was added slowly at reflux temperature under mechanical stirring. After all the acid was added (25 h reaction time) thin layer chromatography (silica gel-butanone) indicated complete reaction. The solution was concentrated to dryness and the resulting crystals recrystallised from benzene-ligroin to yield 52.5 g, m.p. 83–86°. Further recrystallisations gave material with m.p. 84.5–85.5°, $[\alpha]_D$ −248° (*c*, 2, chloroform). (Found: C 64.1; H 7.02; O 28.7. Calc. for $C_{15}H_{20}O_5$: C 64.3; H 7.19; O 28.5).

2-O-Allyl-D-arabinitol, (III). The arabinoside, II, (30 g) was treated with aqueous sulphuric acid (0.25 M, 1500 ml) at 100° for 4 h, neutralised with barium carbonate, filtered and concentrated to yield a syrup (20 g). The syrup (18 g) was dissolved in water (65 ml). Sodium borohydride (3.75 g) in water (90 ml) was added dropwise during 10 min under mechanical stirring at room temperature. After a further 10 min, Dowex 50 W-X8 was added until the evolution of gas ceased. The mixture was filtered and the filtrate concentrated to dryness. Boric acid was removed by several distillations with methanol. The resulting syrup (18 g) which contained one major component and small amounts of impurities was used directly in the subsequent step.

2-O-Allyl-1,3,4,5-tetra-O-benzyl-D-arabinitol, (IV). The syrup, III, (17 g) was benzylated with benzyl chloride (280 ml) and powdered potassium hydroxide (157 g) at 130–140° for 2.5 h, diluted with water (600 ml) and the arabinitol derivative, IV, extracted with chloroform. The chloroform solution was extracted with water and dried over magnesium sulphate. Filtration and concentration yielded a syrup which was purified by chromatography on a silica gel column using first benzene and subsequently benzene:ethyl ether 10:1 as eluent. Concentration of the major fraction yielded a syrup (31 g) which was pure on thin layer chromatography (silica gel-benzene:ethyl ether 10:1).

1,3,4,5-Tetra-O-benzyl-D-arabinitol, (VI). The arabinitol derivative, IV, (25 g) was treated with potassium t-butoxide (20 g) in dimethyl sulphoxide (150 ml) at 100° under mechanical stirring for 4 h, when thin layer chromatography (silica gel-benzene:ethyl ether 10:1) indicated complete reaction. The mixture was diluted with water (500 ml) and extracted with chloroform. The chloroform extract was extracted with water and dried over magnesium sulphate. Filtration and concentration yielded a syrup. This was hydrolysed with aqueous sulphuric acid (0.5 M, 30 ml) in acetone (300 ml) at reflux temperature for 4.5 h. The solution was neutralised with barium carbonate, filtered and concentrated to give a syrup (20 g) which was chromatographically pure (silica gel-benzene:ethyl ether 10:1).

Part of the syrup (1 g) was methylated with dimethyl sulphate (4.5 ml) and powdered potassium hydroxide (10 g) in dioxane (60 ml) at 50° overnight. Excess dimethyl sulphate was removed by adding water (20 ml) and refluxing for 30 min. The mixture was poured into water and the arabinitol derivative extracted with chloroform. The chloroform extracts were dried over magnesium sulphate, filtered and concentrated. The resulting syrup (1.2 g) was hydrogenated in methanol with 5 % palladium on charcoal to yield 285 mg of the presumed 2-*O*-methyl-D-arabinitol. The methyl arabinitol (95 mg) was acetylated with acetic anhydride (2 ml) in pyridine (2 ml) at 100° for 10 min. The product was poured into water and the acetylated methyl arabinitol extracted with chloroform. The chloroform extract was shaken with ice-cold 0.5 M sulphuric acid, ice-cold aqueous sodium bicarbonate and finally water. After drying over magnesium sulphate and filtering, a chromatographically pure syrup (200 mg) (silica gel-ethyl ether) was obtained. The mass spectrum of the presumed 1,3,4,5-tetra-*O*-acetyl-2-*O*-methyl-D-arabinitol was determined as described by Björndal and coworkers.[11]

2-O-(2,3,5,6-Tetra-O-acetyl-β-D-galactofuranosyl)-1,3,4,5-tetra-O-benzyl-D-arabinitol, (VIII). 3,5,6-Tri-*O*-acetyl-1,2-*O*-methylorthoacetyl-α-D-galactofuranose, VII, (6.5 g) and the tetrabenzylarabinitol, VI, (7.4 g) were dissolved in nitromethane (72 ml). Methanol, together with nitromethane, was removed by distillation, the volume being kept constant by continuous addition of nitromethane. The distillation was followed by

gas chromatography. After 3.5 h, mercury(II) bromide (260 mg) was added and the mixture was refluxed for a further 1.5 h. Concentration yielded a yellow oil (13.8 g) which was used directly in the deacetylation step.

2-O-β-D-Galactofuranosyl-D-arabinitol, (IX). The mixture obtained in the previous reaction was deacetylated in methanol (180 ml) by the addition of 10 % ammoniacal methanol (35 ml). The solution was allowed to stand at room temperature overnight. Concentration gave a mixture which was chromatographed on an aluminium oxide column using water-saturated butanone as solvent. The fractionation was followed by thin layer chromatography in the same system. The first UV absorbing component to be eluted was unreacted tetrabenzylarabinitol, VI, the second was the presumed arabinitol galactoside derivative. Concentration of the fractions containing the presumed 1,3,4,5-tetra-*O*-benzyl-2-*O*-(β-D-galactofuranosyl)-D-arabinitol gave a syrup (2.6 g). This was hydrogenated with 5 % palladium on charcoal in methanol to give 0.575 g crystalline umbilicin m.p. 139—140°, $[\alpha]_D$ −78° (*c*, 2, water). The values given by Lindberg *et al.*[1] are m.p. 139—140°, $[\alpha]_D$ −81° (*c*, 2, water). (Found: C 42.1; H 7.13; O 50.6. Calc. for $C_{11}H_{22}O_{10}$: C 42.0; H 7.06; O 50.9).

2-O-β-D-Galactofuranosyl-D-arabinitol octaacetate, (X). Acetylation of IX yielded crystals m.p. 84.5—85.5°, $[\alpha]_D$ −22° (*c*, 2, chloroform). The values given by Lindberg *et al.*[1] are m.p. 84—85° $[\alpha]_D$ −21.9° (*c*, 2, chloroform). (Found: C 49.7; H 6.03; O 44.2. Calc. for $C_{27}H_{38}O_{18}$: C 49.8; H 5.89; O 44.3).

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REFERENCES

1. Lindberg, B., Wachtmeister, C. A. and Wickberg, B. *Acta Chem. Scand.* **6** (1952) 1052.
2. Lindberg, B., Misiorny, A. and Wachtmeister, C. A. *Acta Chem. Scand.* **7** (1953) 591.
3. Lindberg, B. and Wickberg, B. *Acta Chem. Scand.* **8** (1954) 821.
4. Lindberg, B. and Wickberg, B. *Acta Chem. Scand.* **16** (1962) 2240.
5. Kochetkov, N. K., Khorlin, A. J. and Bochkov, A. F. *Dokl. Akad. Nauk. SSSR* **161** (1965) 1342; *Tetrahedron* **23** (1967) 693.
6. Pueyo, G. *Compt. Rend.* **248** (1959) 2788.
7. Beving, H. F. G., Borén, H. B. and Garegg, P. J. *Acta Chem. Scand.* **21** (1967) 2083.
8. Reeves, R. E., Latour, N. G. and Lousteau, R. J. *Biochemistry* **3** (1964) 1248.
9. Ballou, C. E. *J. Am. Chem. Soc.* **79** (1957) 165.
10. Cunningham, J., Gigg, R. and Warren, C. D. *Tetrahedron Letters* **1964** 1191.
11. Björndal, H., Lindberg, B. and Svensson, S. *Carbohyd. Res.* **5** (1967) 433.

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