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SYNTHESIS OF METHYL α-TRIOXACARCINOSIDE B

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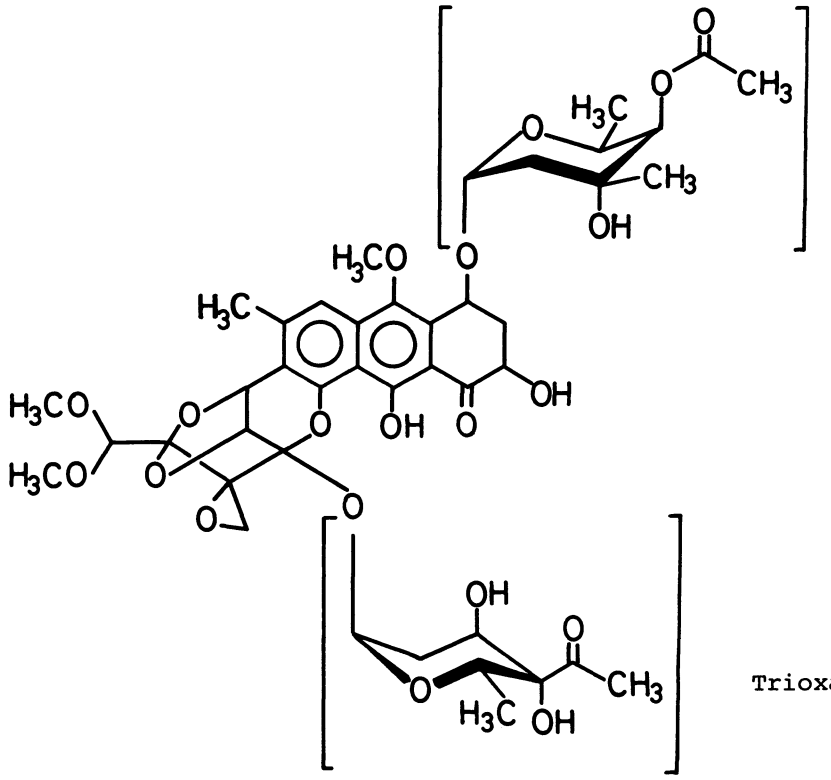
The synthesis of methyl glycoside of trioxacarcinose B, one of the carbohydrate components of antitumor antibiotic trioxacarcin A, is described.

Trioxacarcinose A and B are unique carbohydrate components of antitumor antibiotic trioxacarcin A produced by a fermentation of Streptomyces ochraceus.[1,2] The structure of trioxacarcin A has been established as shown below.[3] Methanolysis of trioxacarcin A afforded a mixture of methyl trioxacarcinosides A and B, together with partially degraded products.



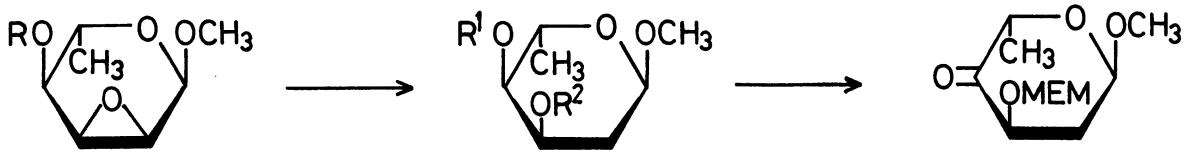
Trioxacarcin A

Deacetyl-trioxacarcinose A is a known sugar named axenose which has been synthesized in 1975 by Swedish Chemists, Garegg and Norberg[4] in a form of methyl glycoside.

The second sugar component, trioxacarcinose B is also known in nature as a component of isoquinocycline B,[5] but its synthesis has never been described. A closely related carbohydrate, methyl 2,6-dideoxy-4-C-(L-glycero-4[1]-hydroxyethyl)-α-L-xylo-hexopyranoside which is methyl glycoside of a constituent of isoquinocycline A[5] has been synthesized by Paulsen and Sinnwell.[6]

We have attempted to synthesize methyl α-trioxacarcinoside B from a readily accesible methyl 2,3-anhydro-6-deoxy-α-L-allo-hexopyranoside (1).[6]

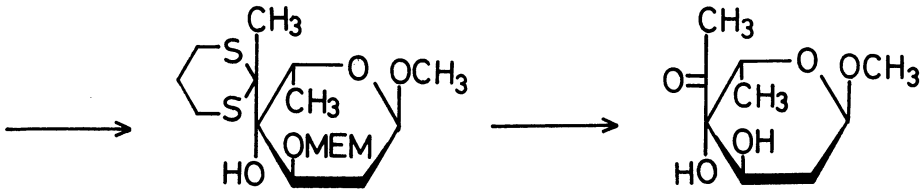
Scheme 1



(1) R=H
(2) R=THP

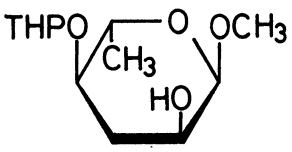
(3) R^1=THP, R^2=H
(5) R^1=THP, R^2=MEM
(6) R^1=H, R^2=MEM

(8)

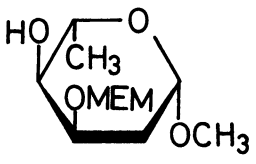


(9)

(10)



(4)



(7)

Tetrahydropyranylation of 1 with 2,3-dihydro-4H-pyran in the presence of pyridinium p-toluenesulfonate[7] gave the compound (2). (Diasteromeric mixture, syrup, 95.7%, Rf 0.29 using 3:1 (v/v) = toluene : ethylacetate): ^{1}H NMR δ 1.13, 1.21, 1.28 (3H, H-6), 4.77 (3/2 H, d, J=3.0Hz, H-1 and THP's H-1), 5.00 (1/2 H, bs, THP's H-1).

Reduction of 2 with $LiAlH_4$ in THF afforded the 2-deoxy derivative (3) and the 3-deoxy derivative (4) in 80 and 19% yield, respectively. [Compound 3, diasteromeric mixture, syrup, Rf 0.40 using 3:1 (v/v) = hexane : acetone, this mixture was separated on silica gel column using 5:1 (v/v) = toluene : ethylacetate, Rf for 3a, 0.35, Rf for 3b, 0.28 using 1:1 (v/v) = toluene : ethylacetate.]: ^{1}H NMR for 3a, δ 1.34 (3H, d, $J_{5,6}$=6.5Hz, H-6), 2.17 (1H, ddd, $J_{1,2eq.}$=1.5Hz, $J_{2ax.,2eq.}$=15.0Hz, $J_{2eq.,3}$=4.0Hz, H-2eq.), 3.07 (3H, S, OCH_3), 4.76 (1H, bd, J=3.0Hz, H-1), 4.93 (1H, bs, THP's H-1), and for 3b, δ 1.23 (3H, d, $J_{5,6}$=6.5Hz, H-6), 2.12 (1H, ddd, $J_{1,2eq.}$=1.5Hz, $J_{2ax.,2eq.}$=15.0Hz, $J_{2eq.,3}$=3.0Hz, H-2eq.), 3.06 (3H, S, OCH_3), 4.67-4.71 (2H, m, H-1 and THP's H-1). [Compound 4, diastereomeric mixture, syrup, Rf 0.30 using 3:1 (v/v) = hexane : acetone]: ^{1}H NMR δ 1.14, 1.22, 1.23, 1.31 (3H, H-6), 3.43 (3H, S, OCH_3), 4.55-4.85 (2H, m, H-1 and THP's H-1).

Protection of the OH group of 3 with 2-methoxyethoxymethyl chloride[8,9] gave the compound (5) in 74% yield. [Diastereomeric mixture, syrup, Rf 0.22 using 1:1 (v/v) = toluene : ethylacetate]: ^{1}H NMR δ 1.15, 1.22, 1.24, 1.31 (3H, H-6), 3.30 (3H, S, OCH_3), 3.36 (3H, S, OCH_3), 4.57-4.95 (4H, m, H-1, THP's H-1 and $-OCH_2O-$ of MEM).

Removal of the THP group of 5 with pyridinium p-toluenesulfonate in methanol gave methyl 2,6-dideoxy-3-O-(2-methoxyethoxymethyl)-α-L-allo-hexopyranoside (6) and the corresponding β-glycoside (7) in 66 and 18% yields, respectively. [Compound 6, syrup, Rf 0.10 using 1:1 (v/v) = toluene : ethylacetate]: $[\alpha]_D^{24}$ -184.4° (C 1.28, $CHCl_3$), ^{1}H NMR δ 1.25 (3H, d, $J_{5,6}$=6.5Hz, H-6), 1.84 (1H, ddd, $J_{1,2ax.}$=4.5Hz, $J_{2ax.,2eq.}$=15.0Hz, $J_{2ax.,3}$=4.0Hz, H-2ax.), 2.21 (1H, ddd, $J_{1,2eq.}$=1.5Hz, $J_{2ax.,2eq.}$=15.0Hz, $J_{2eq.,3}$=3.5Hz, H-2eq.), 3.32 (3H, S, OCH_3), 3.37 (3H, S, OCH_3), 4.64 (1H, dd, $J_{1,2ax.}$=4.5H, $J_{1,2eq.}$=1.5Hz, H-1), 4.80 (2H, S, $-OCH_2O-$ of MEM). [Compound 7, syrup, Rf 0.16 using 1:1 (v/v) =toluene : ethylacetate]: $[\alpha]_D^{24}$ -36.5° (C 1.24, $CHCl_3$), ^{1}H NMR δ 1.28 (3H, d, $J_{5,6}$=6.5Hz, H-6), 1.61 (1H, ddd, $J_{1,2ax.}$=9.5Hz, $J_{2ax.,2eq.}$=14.0Hz, $J_{2ax.,3}$=3.0Hz, H-2ax.), 2.11 (1H, ddd, $J_{1,2eq.}$=2.5Hz, $J_{2ax.,2eq.}$=14.0Hz, $J_{2eq.,3}$=4.0Hz, H-2eq.), 3.35 (3H, S, OCH_3), 3.44 (3H, S, OCH_3), 4.60 (1H, dd, $J_{1,2ax.}$=9.5Hz, $J_{1,2eq.}$=2.5Hz, H-1), 4.77 (2H, S, $-OCH_2O-$ of MEM).

Oxidation of 6 with ruthenium tetroxide yielded methyl 2,6-dideoxy-3-O-(2-methoxyethoxymethyl)-4-oxo-α-L-allo-hexopyranoside (8) in 86% yield. [Syrup, Rf 0.36 using 1:1 (v/v) = toluene : ethylacetate]: $[\alpha]_D^{22}$ -127.7° (C 5.68, $CHCl_3$), ^{1}H NMR δ 1.29 (3H, d, $J_{5,6}$=6.5Hz, H-6), 1.86 (1H, ddd, $J_{1,2}$=6.0Hz, $J_{2,2'}$=13.5Hz, $J_{2,3}$=13.0Hz, H-2), 2.63 (1H, dt, $J_{1,2'}$=7.0Hz, $J_{2,2'}$=13.5Hz, $J_{2',3}$=7.0Hz, H-2'), 3.36 (3H, S, OCH_3), 3.37 (3H, S, OCH_3), 4.31 (1H, q, $J_{5,6}$=6.5Hz, H-5), 4.51 (1H, dd, $J_{2,3}$=13.0Hz, $J_{2',3}$=7.0Hz, H-3), 4.80 (2H, S, $-OCH_2O-$ of MEM), 4.97 (1H, dd, $J_{1,2}$=6.0Hz, $J_{1,2'}$=7.0Hz, H-1).

Treatment of 8 with 2-methyl-1,3-dithiane[10] in the presence of n-butyl lithium afforded the compound (9) in 54% yield. [Syrup, Rf 0.49 using 1:1 (v/v) = toluene : ethylacetate]: $[\alpha]_D^{24}$ -82.8° (C 1.69, $CHCl_3$), ^{1}H NMR δ 1.35 (3H, d, $J_{5,6}$=

6.5Hz, H-6), 1.75 (3H, S, CH_3), 2.92 (1H, S, OH), 3.31 (3H, S, OCH_3), 3.36 (3H, S, OCH_3), 4.30 (1H, t, J=3.0Hz, H-3), 4.36 (1H, q, $J_{5,6}$=6.5Hz, H-5), 4.64 (1H, t, J=2.5Hz, H-1), 4.84 (1H, d, J=13.5Hz, -OCH(H')O- of MEM), 4.92 (1H, d, J=13.5Hz, -OCH(H')O- of MEM).

Removal of the protective group of 9 with 10% methanolic hydrogen chloride, followed by chromatographic purification gave the crystalline product (10), mp 111-112°C; $[\alpha]_D^{24}$ -154.2° (C 0.34, $CHCl_3$), which was identical with an authentic sample of methyl α-trioxacarcinoside B[11] in all respects.

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11) An authentic sample was kindly supplied by Dr. Kunikatsu Shirahata of Kyowa Hakko Co. Ltd..

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