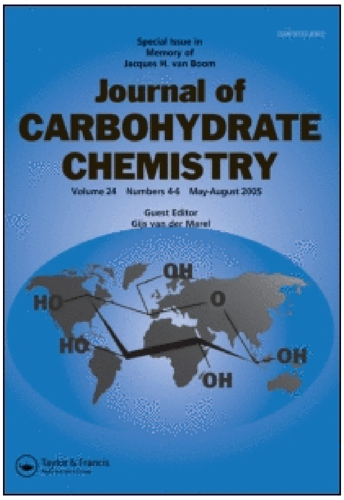

Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Synthesis and X-Ray Crystal Structure of Methyl D,L-Desmeihyl-Holantosaminide

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To cite this Article Welch, John T. and Svahn, Britt-Marie(1985) 'Synthesis and X-Ray Crystal Structure of Methyl D,L-Desmeihyl-Holantosaminide', Journal of Carbohydrate Chemistry, 4: 3, 421 — 427

To link to this Article: DOI: 10.1080/07328308508070191

URL: http://dx.doi.org/10.1080/07328308508070191

J. CARBOHYDRATE CHEMISTRY, 4(3), 421-427 (1985)

Communication

SYNTHESIS AND X-RAY CRYSTAL STRUCTURE OF METHYL D,L-DESMETHYL-HOLANTOSAMINIDE.

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Received March 22, 1985, - Final Form June 5, 1985

ABSTRACT

4-Acetamido-2,4,6-trideoxy-D,L-arabino-hexopyranose, a desmethyl analog of N-acetyl-L-holantosamine, the glycosidic residue of the cardenolide Holarosine A and holantosines C and D, has been prepared via a novel intramolecular rearrangement of an amino alcohol and has been characterized by single-crystal X-ray diffraction.

Holarrhena antidysenterica has proven to be a fertile source of glycosteroids with therapeutic activity.[1] Holarosine A and holantosine C and D, α-glycosides of L-holantosamine[2] (1, 4-amino-4-deoxyoleandrose), are closely related to the premier example of an amino sugar cardenolide with cardiotonic activity, mitiphylline.[3] Although the synthesis of holantosamine from D-glucose and L-rhamnose has been reported,[4] we found that simple modification of an acosamine (2) synthesis,[5] makes possible the ready preparation of otherwise relatively inaccessible holantosamine derivatives.

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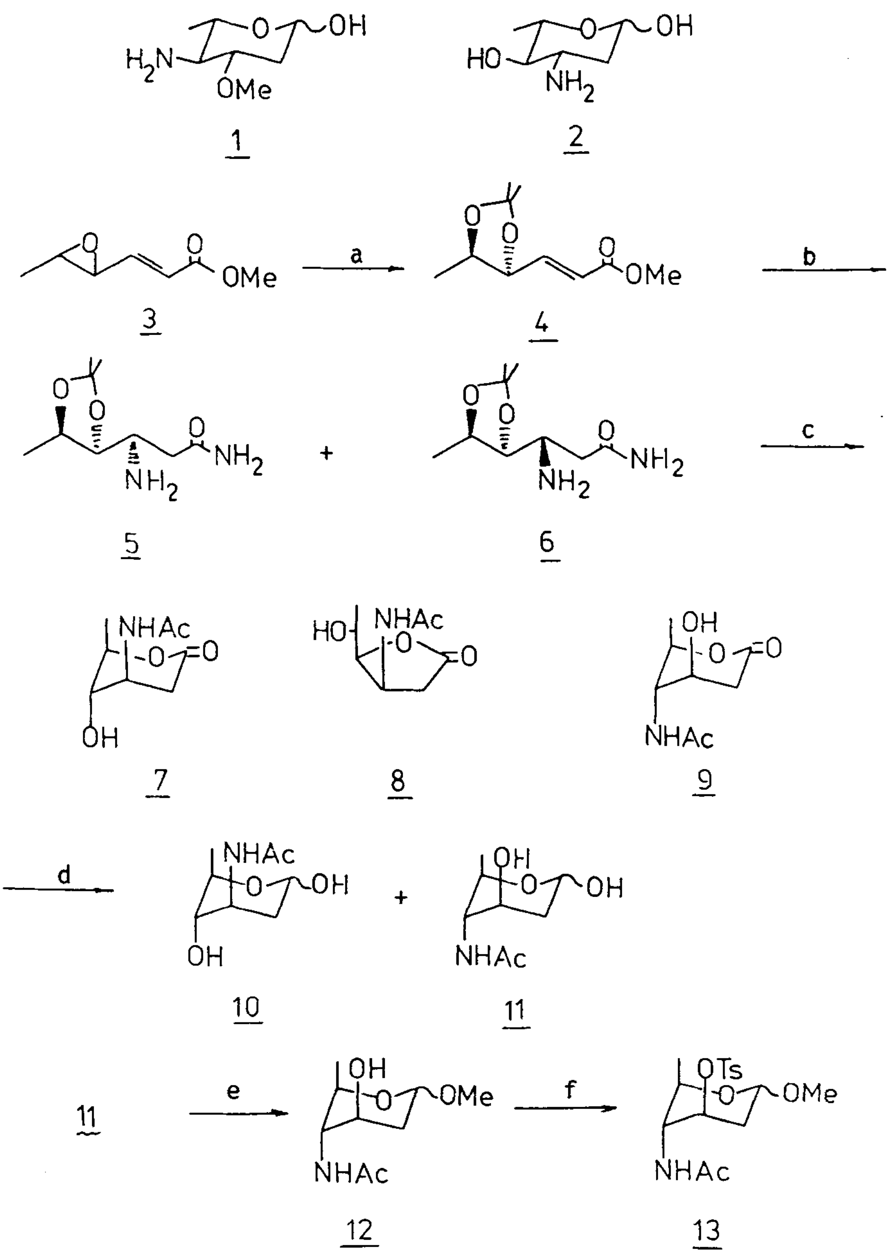

Scheme 1. a. Acetone, $AlCl_3$; b. NH_3, methanol; c. HCl, acetic anhydride; d. Diisobutylaluminum hydride; e. Methanol, Amberlite IR-120[H+]; f. *p*-Toluenesulfonyl chloride, pyridine.

The *erythro* acetonide **4**, readily prepared from *threo* epoxide **3**, may be treated with anhydrous ammonia in methanol to form the *arabino* amino amide **5** after known procedures.[5] As described,[5] the product with the *ribo* configuration, **6**, was not isolated. In contrast to the published method, the mixture was treated with 4N hydrochloric acid, followed by acylation with acetic anhydride. The mixture of γ- and δ- lactones **7**, **8** and **9** was purified by chromatography on silica gel (ethyl acetate-ethanol, 20:1). Reduction of the latter with diisobutylaluminum hydride afforded a mixture of carbohydrates which was separated by further chromatography (ethyl acetate-ethanol, 10:1). The purified sugars **10** and **11** were separately converted to the methyl glycosides after the method of Bollenback[6] to yield methyl *N*-acetyl-D,L-acosamine,[7] mp 126-130 °C, and a second sugar **12**, mp 175-178 °C, indistinguishable by spectroscopic means[8] (See Scheme 1).

Although the methyl glycoside **12** was a solid, the sugar failed to crystallize. The more readily crystalline tosylate **13**,[9] mp 172-175 °C, prepared in pyridine in the usual manner, was recrystallized from dichloromethane-acetone to yield crystals suitable for single-crystal X-ray diffraction studies (See Figure 1).

The crystal structure clearly establishes the presence of the acetamide at C-4 and the tosylate at C-3.[10] (See Table 1). The formation of **13** is not easily rationalized. Formation requires the retention of configuration at both C-3 and C-4. The *erythro* configuration of acetonide **4** is firmly established, arising from the Lewis acid promoted opening of the trans γ-epoxide of methyl sorbate. The conjugate addition of ammonia from either face to **4** to form *arabino* **6** or the unobserved *ribo* **5** amino amides has no effect on the configuration at C-4. Further studies on the origin of this rearrangement and optimization of the reaction conditions to afford holantosamine are in progress.

The assistance of Prof. J. Zubieta and Dr. J. Hutchinson in performing the X-ray crystallographic studies and the financial support of the Research Corporation is gratefully acknowledged.

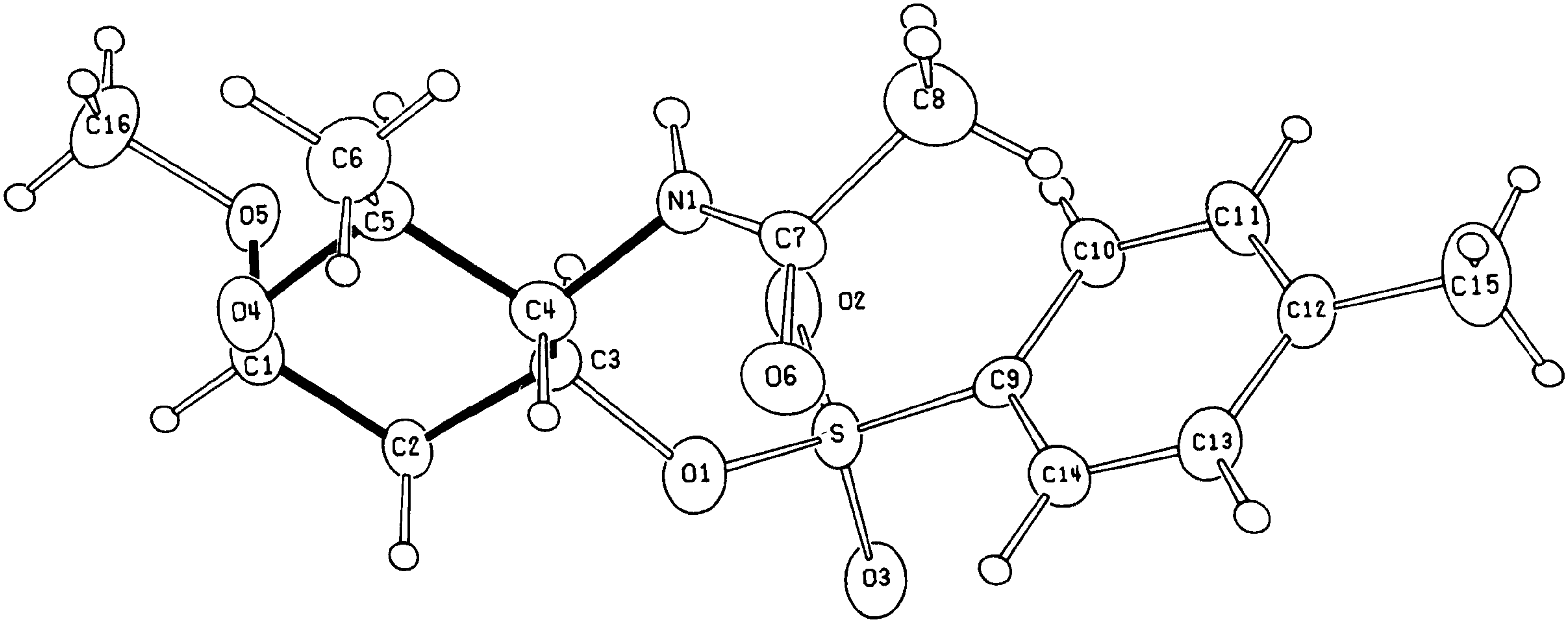

Figure 1. Perspective view of 13 showing atom numbering and 50%-thermal ellipsoids for the anisotropic atoms.

Table 1. Atom Coordinates ($\times 10^4$) and temperature factors ($A^2 \times 10^3$)

Atom	x	y	z	$U_{equiv./iso}$
S	7540(2)	-1454(1)	2513(1)	45(1)*
O(1)	7188(6)	-362(4)	1482(4)	68(2)*
O(2)	7957(5)	-919(4)	3557(4)	59(2)*
O(3)	8744(5)	-2486(4)	1801(4)	70(2)*
C(9)	5599(7)	-1981(5)	3087(5)	37(2)*
C(14)	5016(8)	-2192(6)	4380(5)	58(3)*
C(13)	3590(8)	-2730(6)	4807(6)	65(3)*
C(12)	2692(8)	-3068(5)	3988(6)	53(2)*
C(11)	3266(8)	-2892(5)	2699(5)	52(3)*
C(10)	4691(8)	-2297(5)	2268(5)	49(2)*
C(15)	1160(9)	-3683(7)	4438(7)	83(3)*
O(4)	6201(5)	3481(3)	676(3)	48(2)*
O(5)	8162(5)	3347(3)	1980(4)	49(2)*
O(6)	2515(5)	577(4)	1256(4)	61(2)*
C(16)	8035(9)	4681(5)	2049(7)	71(3)*
C(1)	7892(7)	2974(5)	833(5)	42(2)*
C(2)	8280(7)	1548(5)	793(5)	40(2)*
C(3)	6889(7)	1009(5)	1724(5)	38(2)*
C(4)	5101(6)	1699(5)	1575(5)	41(2)*
C(5)	4852(7)	3101(5)	1625(5)	43(2)*
C(6)	3124(7)	3780(6)	1372(7)	66(3)*
N	3799(4)	1297(4)	2599(3)	21(1)*
C(7)	2576(7)	791(5)	2347(5)	42(2)*
C(8)	1285(7)	530(6)	3494(6)	62(3)*

* Equivalent isotropic U defined as one third the trace of the orthogonalized U tensor.

Complete details of the X-ray structural determination are available from the author.

References and Footnotes.

1. A. Chatterjee, *Prog. Chem. Nat. Prod.*, *10*, 391 (1953).
2. Q. Khuong-Huu, C. Monneret, I. Kabore, P, Choay, J-.M. Tekam, and R. Goutarel, *Bull. Soc. Chim. Fr.*, 874-869 (1971).
3. M-.M. Janot, M. Leboeuf, A. Cave, R. Wijesekera, R. Goutarel *C. R. Acad. Paris*, *267*, 1050-1052 (1968).
4. C. Monneret, C. Conreur, Q. Kuong-Huu, *Carbohydr. Res.*, *65*, 35-45 (1978).
5. I. Dyong and H. Bendlin, *Chem. Ber.*, *111*, 1677-1684 (1978).
6. G.N. Bollenback, *Methods Carbohydr. Chem.*, *2*, 326-328 (1963).

7. ^{13}C NMR (D_2O, external TMS) δ 174.7, 98.3, 75.0, 69.4, 55.2, 48.8, 35.7, 22.9, 17.7.
8. ^{13}C NMR (D_2O, external TMS) δ 176.17, 98.3, 75.0, 69.3, 55.2, 48.9, 35.6, 22.9, 17.7.
9. ^{1}H NMR (CCl_4 , internal TMS) δ 7.2 m, 5.65-5.48 m, 4.5-3.2 m, 3.16 s, 2.3 s, 1.82 s, 1.7 s, 1.2 m.
10. A single crystal of methyl 4-acetamido-3-(4'-toluenesulfonyl)-2,4,6-trideoxy-*arabino-D,L*-hexopyranose was obtained by recrystallization from dichloromethane-petroleum ether. X-ray data collection was carried out on a Nicolet R3m automated diffractometer equipped with a Mo target X-ray tube (λ = 0.710730 A) and a graphite crystal monochromator. The sugar crystallized in the P 1 space group and possessed unit cell constants of a= 8.050(1), b= 10.852(2) and c= 10.800(2) A with α = 87.40(1)°, β = 76.23(1)°, γ = 77.57(1)° and Z= 2. The absorption coefficient μ (Mo) = 1.98cm^{-1} . X-ray intensity data were measured for a total of 1516 independent observed reflections with $I_o \geq 3\sigma I_o$. The structure was solved by direct methods which revealed the locations of all nonhydrogen atoms on the initial *E* map. The structure was refined down to a final value of R_1 = 6.9 % and R_2 = 7.1 % by full matrix least squares techniques with anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms were placed in idealized positions with isotropic thermal parameters set to 1.2 x the attached carbon thermal parameter. All structural determinations and refinement

calculations were carried out with the SHELXTL package on the Nicolet R3m Nova 3 crystallographic system. On the basis of two molecules of $C_{16}H_{23}SO_6N$ in a unit cell of volume of 894.89 A^3 , the calculated density was 1.32 g/cm.^{3} The final difference map revealed no abnormal features (Final difference Fourier map peak equals 0.25 electrons per A^3).