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Synthesis of the Amino Sugar from C-1027

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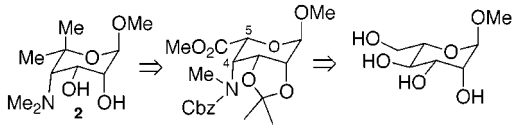
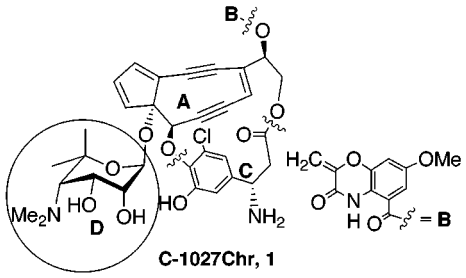
ABSTRACT



The amino sugar side chain (2) from C-1027Chr was synthesized in 12 steps from mannose. The key reactions are an internal displacement by nitrogen to introduce the cis amino group at C-4 and the methylation of an enolate at C-5.

C-1027[1] is one of the more intriguing of the enediyne toxins because it is exceedingly toxic against certain cell lines[2] and shows no simple chemical trigger to initiate its biological activity.[3] It belongs to the neocarzinostatin subfamily, where the "chromophore" (C-1027Chr, **1**) is bound to a small protein[4] before being transferred to the minor groove of DNA during the activation process.[5]

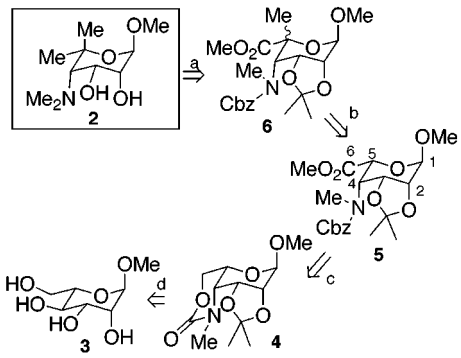


C-1027Chr, 1

C-1027Chr is easily dissected into four subunits, a core structure (**A**), a heteroaromatic side chain (**B**), a lactone "strap" bearing a phenol unit and a primary amine (**C**), and a reduced amino sugar unit (**D**). The amino sugar is expected to be important in the binding to DNA through interaction of the protonated amino group with the backbone phosphate of the DNA. Modeling suggests that the sugar protrudes from the protein in C-1027 and may be important in the transfer from the protein to the DNA.[6]

The sugar **2** (Scheme 1) is structurally interesting, with the *gem*-dimethyl group at C-5 and the *N*,*N*-dimethyl amino group at C-4 in cis arrangement with the OH substituents at C-2 and C-3. There is a variety of pyranose analogues with two carbon substituents at C-5, including more than 10 with the same *gem*-dimethyl arrangement.[7,8] In general, the syntheses of such structures proceed by creating the *gem*-

Scheme 1. Retrosynthesis of the C-1027 Sugar



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(1) For the absolute configuration and leading references, see: Iida, K.-i., Fukuda, S., Tanaka, T., Hirama, M. *Tetrahedron Lett.* **1996**, *37*, 4997.

(2) Zhen, Y.-S.; Ming, X.-Y.; Yu, B.; Otani, T.; Saito, H.; Yamada, Y. *J. Antibiot.* **1989**, *XLII*, 1294.

(3) Hirama, M. *Pure Appl. Chem.* **1997**, *69*, 525.

(4) (a) Okuno, Y.; Otsuka, M.; Sugiura, Y. *J Med. Chem.* **1994**, *37*, 2266. (b) Motojima, F.; Inaka, K.; Minami, Y.; Otani, T.; Miki, K. *Acta Crystallogr. Sect. D* **1994**, *51*, 1084.

(5) (a) Xu Y. J.; Zhen Y. S.; Goldberg, I. H. *Biochemistry* **1994**, *33*, 5947. (b) Kirk, C. A.; Goodisman, J.; Beerman, T. A. *Biophys. Chem.* **1997**, *63*, 201.

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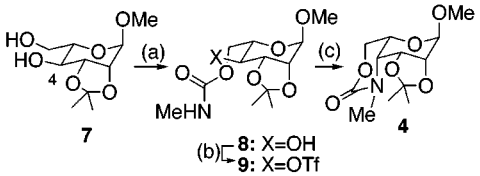
dialkyl quaternary center at an early stage followed by ring closure. The previous synthesis of **2** began with the *gem*-dimethyl group in place using the epoxide (80% ee) from asymmetric epoxidation of 3,3-dimethylallyl alcohol.[9] That synthesis involved about 17 steps and 1−2% overall yield, with good stereoselectivity except in the step that introduced the vicinal *cis*-diol grouping (C-2/C-3).

We viewed the target molecule as an interesting problem in alkylation of a pyranose ring at C-5, an approach made difficult by the presence of a potential leaving group at C-4 and the deactivating effect of the ring oxygen toward generation of an enolate anion at C-5.[10] Success in this alkylation step would allow for direct variation of the substitution pattern at C-5 in this and related sugars. Our approach also takes advantage of the availability of common sugars as single enantiomers. The retrosynthesis is summarized in Scheme 1.

A key transform is the displacement of the C-4 hydroxyl group of mannose (**3**) by an amine function, using an intramolecular delivery and resulting in **4**. Oxidation of C-6 sets up the molecule (**5**) for enolate generation and methylation to give **6**.

The synthesis began with α-methyl-D-mannopyranoside (**3**) of >99% enantiopurity.[11] According to well-established procedures,[12] double acetonide formation followed by selective hydrolysis of one acetonide produced **7**, Scheme 2.

Scheme 2. Internal Substitution[a]



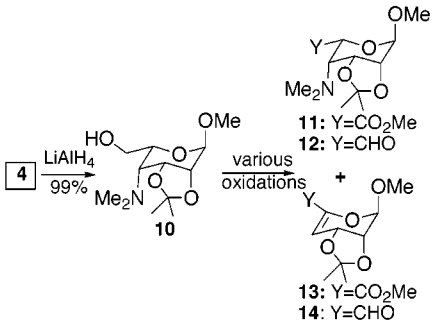
[a] (a) MeNCO, Et_3N, 23 °C, 7 days, 98%; (b) Tf_2O, CH_2Cl_2, 0 °C, 0.5 h, 90%; (c) KH, THF, 18-crown-6, −30 °C, 3 h, 78%.

Selective reaction with methyl isocyanate gave the carbamate **8**, poised for internal displacement. The best yields (98%) were obtained with long reaction times (7 days) at 23 °C; attempts to accelerate the process with, for example, CuCl[13] gave lower yields. The hydroxyl group at C-4 was activated as the triflate (**9**; pale yellow needles with mp 67−71 °C), which was quite sensitive toward handling at room temperature. The internal S_N2 reaction was initiated with KH in THF at −30 °C and gave the bicyclic compound **4** as colorless crystals of mp 153−154 °C, in 78% yield.[14]

In a direct approach, $LiAlH_4$ reduction of **4** produced the dimethyl amino alcohol **10** in quantitative yield. The oxidation of **10** to **11** or **12** was difficult, and over 16 different oxidation conditions were evaluated. Conventional conditions for producing the carboxylic acid oxidation level (e.g., **11**) such as $KMnO_4$ or $K_2Cr_2O_7$ gave complex mixtures of the products from oxidation and elimination. PDC,[15] PCC,[16] the Dess−Martin reagent,[17] Pd(II) under various conditions,[18] Pt/C with O_2,[19] and photo-oxidation,[20] also gave oxidation products *with* elimination (**13**/**14**). Swern,[21] Moffatt,[21] TEMPO,[22] and NCS/Me_2S[23] produced the aldehyde, but always with elimination (**14**) and significant byproducts. For example, Swern oxidation of **10** (oxalyl chloride, DMSO, TEA, THF, −60 °C) gave **14** in 67% yield. Finally, the use of catalytic Ru(II) with NMO as the stoichiometric oxidant[24] under mildly basic conditions gave acceptable results, producing the aldehyde **12** in 81% yield. Unfortunately, the amino aldehyde **12** was quite unstable on handling and could not be oxidized efficiently to the carboxylic acid or ester under either basic [Ag(I)][25] or acidic oxidizing conditions.

To minimize loss of the amino group at C-4 during oxidation, the cyclic carbamate **4** was cleaved with NaOH to give the *N*-methyl amino alcohol **15** (99% yield) and the amino group was modified with a Cbz group (**16**; Scheme 3). This protected version behaved well during Swern

Scheme 3. Oxidation of Amino Alcohol **10**



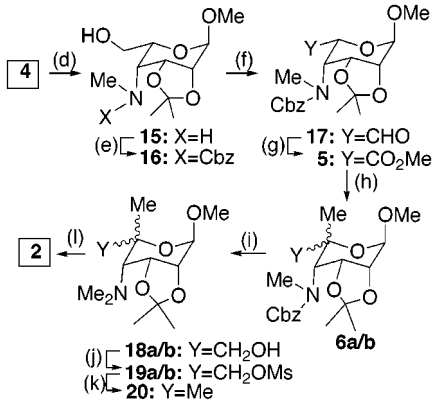
oxidation to the aldehyde (**17**, 97%). Further oxidation to the ester was best achieved with iodine under basic conditions,[26] giving ester **5** in about 70% yield overall for the two-

(6) Okuno, Y. Otsuka, M.; Sugiura, Y. *J. Med. Chem*. **1994**, *37*, 2266.
(7) For a 5,5-dimethyl sugar in a gyrase B inhibitor (novobiocin), see: Laurin, P.; Ferroud, D.; Klich, M.; Dupuis-Hamelin, C.; Mauvais, P.; Lassaigne, P.; Bonnefoy, A.; Musicki, B. *Bioorg. Med. Chem. Lett*. **1999**, 2079. For a 5,5-dimethyl sugar in an antibiotic (lipiarmycin), see: Arnome, A.; Nasini, G. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1353.
(8) One specific solution is the introduction of a hydroxymethyl group (HCHO, NaOH, H_2O) α to a CHO group at C-5: Mazur, A. W.; Hiler, G. D. *J. Org. Chem*. **1997**, *62*, 4471.
(9) Lida, K.-I.; Ishii, T.; Hirama, M. *Tetrahedron Lett*. **1993**, *34*, 4079
(10) This difficulty has been discussed explicitly, e.g.: Werschkun, B.; Theim, J. *Synthesis* **1999**, 121. Also described in this paper is a Claisen rearrangement approach to introduction of a quaternary center at C-4 of a furanose derivative.
(11) Purchased as 99% ee from the Aldrich Chemical Co.
(12) Evans, M.; Parrish, F. W. *Carbohydr. Res*. **1977**, *54*, 105.
(13) Duggan, M. E.; Imagire, J. S. *Synthesis* **1989**, 131.
(14) This reaction was performed 15 times on a scale of 0.2−5 g. The yields ranged from 95% to 65%, with an average of 78%.
(15) Corey, E. J.; Schmidt, G. *Tetrahedron Lett*. **1979**, *32*, 399.
(16) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc*. **1975**, *97*, 6908.
(17) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc*. **1991**, *113*, 7277.
(18) Tamaru, Y.; Yamamoto, Y.; Yamada, Y.; Yoshida, Z−i. *Tetrahedron Lett*. **1979**, *32*, 1401.
(19) Pravdic, N.; Keglevic, C. *Tetrahedron* **1965**, *21*, 1897.
(20) Ottenheim, H. C. J.; DeMan, J. H. M. *Synthesis* **1975**, 163.
(21) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
(22) TEMPO was used in stoichiometric amounts according to an early procedure: Semmelhack, M. F.; Chou, C. S.; Cortes, D. A. *J. Am. Chem. Soc*. **1983**, *105*, 4492.
(23) Corey, E. J.; Kim, C. V. *J. Am. Chem. Soc*. **1972**, *94*, 7586.

stage oxidation; during large scale procedures, small amounts of the epimer of **5** at C-5 were observed.

Direct methylation of **5** to give **6** could be achieved in up to 80% yield by enolate generation under carefully controlled conditions; elimination of the N at C-4 was the competing process. For example, by using lithium (tetramethylpiperidide) (LiTMP), in THF at −78 °C, the elimination product **13** was obtained in 96% yield. With $KN(SiMe_3)_2$ added to a mixture of **5** and excess MeI in THF/HMPA at −78 °C, the desired methylation produced a mixture **6a** and **6b** (3:2) in 76% yield (averaged over 13 runs on various scales) accompanied by minor amounts of the elimination product. The mixture could not be separated. The final stage involved reduction to the epimeric alcohols **18a** and **18b**, activation as the mesylate (**19a** and **19b**), and a second reduction to produce **20**. Removal of the acetonide unit completed the synthesis of C-1027 sugar **2** (Scheme 4).[27]

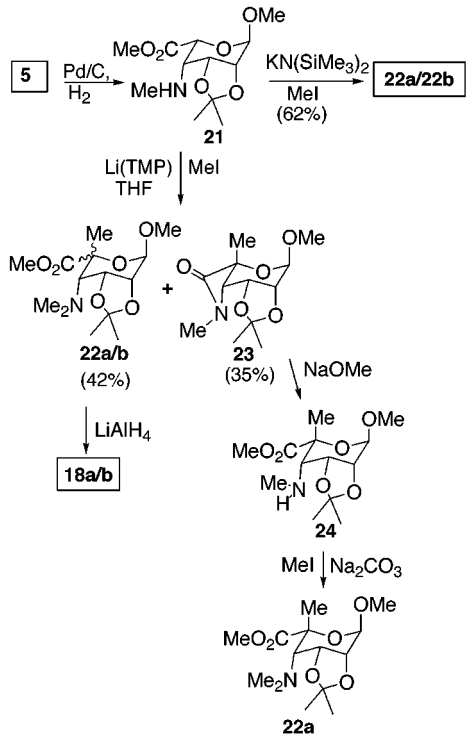
Scheme 4. Completon of the Synthesis[a]



[a] (d) $NaOH/H_2O$, Δ, 4 h, 99%; (e) Cbz-Cl, K_2CO_3, dioxane−water, 23 °C, 8 h, 95%; (f) DMSO, oxalyl chloride, TEA, THF, −60 °C, 97%; (g) KOH, I_2, MeOH, 45 min, 0 °C, 71%; (h) $KN(SiMe_3)_2$, MeI, THF/HMPA, −78 °C, 45 min, 76% as mixture of diastereomers; (i) $LiAlH_4$, ether, 23 °C, 4 h, 96%; (j) MsCl, NaH, ether, 0 °C, 2 h, 85%; (k) $LiAlH_4$, ether, 23 °C, 4 h, 59%; (l) HF, MeCN, 23 °C, 40 min, 79%.

A double methylation approach was also explored, by using the unprotected amino group in place to inhibit elimination during enolate generation. The Cbz group was removed from **5** to give the amino-ester **21**. Simultaneous deprotonation of the amino group and generation of the

Scheme 5. Appearance of a β-Lactam During Dimethylation



enolate with excess $KN(SiMe_3)_2$ followed by addition of excess MeI led to double methylation and a mixture of epimers, **22a** and **22b**, in 62% yield. The dimethylation is a delicate reaction. For example, reaction of **5** with excess of LiTMP at −78 °C followed by addition of MeI produced three major products, the expected methylated products **22a** and **22b** (ratio ca. 3:2, 42% yield) along with the β-lactam **23** (35% yield). The structure of the unexpected product **23** was confirmed by X-ray crystallography.[28] We assume that deprotonation of the amino group occurs first and that the potassium base gives more rapid enolate formation, removing the possibility of β-lactam formation. With slower proton abstraction (LiTMP), deprotonation at nitrogen occurs first, but ring closure to the lactam competes with the second deprotonation at C-5; a final methylation gives **22a/b** and **23**.

Partly to confirm the structures and also to recycle material, **23** was treated with MeONa to give the methylamine **24**, and then *N*-methylation gave **22a** as a single isomer. The mixture **22a/22b** underwent $LiAlH_4$ reduction to **18a/b**, which are on the path to **2** in Scheme 5.

The most efficient pathway follows 12 steps (Schemes 2 and 3; steps a through l) in 10% overall yield with high

(24) Sharpless, K. B.; Akashi, K.; Oshima, K. *Tetrahedron Lett.* **1976**, *29*, 2503.

(25) Based on the procedure of Campaigne, E. and LeSuer, W. M. in *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 919.

(26) Yamada, S.; Morizone, D.; Yamamoto, K. *Tetrahedron Lett.* **1992**, *45*, 2503.

(27) Comparison with the natural material[9] was primarily via ^1H NMR spectral data comparison. Synthetic: ^1H NMR (400 MHz, $CDCl_3$) δ 4.61 (1H, d, J = 7.84, H_1), 4.45 (1H, dd, J = 2.95, 3.3 Hz, H_3), 3.49 (3H, s, OCH_3), 3.25 (1H, dd, J = 3.1, 7.5 Hz, H_2), 2.45 (6H, s, NMe_2), 2.30 (1H, d, J = 2.95 Hz, H_4), 1.55 (3H, s, Me at C_5), 1.30 (3H, s, Me at C_5). Natural: ^1H NMR (400 MHz, $CDCl_3$) δ 4.65 (1H, d, J = 7.8, H_1), 4.42 (1H, dd, J = 2.8, 3.1 Hz, H_3), 3.52 (3H, s, OCH_3), 3.35 (1H, dd, J = 3.1, 7.5 Hz, H_2), 2.45 (6H, s, NMe_2), 2.30 (1H, d, J = 2.95 Hz, H_4), 1.55 (3H, s, Me at C_5), 1.30 (3H, s, Me at C_5).

(28) A few other examples of a β-lactam fused to a pyranose have been examined by X-ray crystallography, but none with the orientation of substitutents (4-amino-5-acyl) of **23**. Preparation by a Mitsunobu reaction produced a 4-amino-3-acyl lactam: Zegrodka, O.; Abramski, W.; Urbanczyk-Lipowska, Z.; Chmielewski, M. *Carbohydr. Res.* **1998**, *307*, 33. Preparation by a cycloaddition to a glycal produced a 2-amino-3-acyl lactam: Chmielewski, M.; Kaluza, Z.; Suwinska, K.; Rosenbaum, D.; Duddek, H.; Magnus, P. D.; Huffman, J. C. *Carbohydr. Res.* **1990**, *203*, 183. Assembly of the pyranose ring onto a β-lactam gave a 3-amino-4-acyl derivative: Hart, D. J.; Leroy, V.; Merriman, G. H.; Young, D. G. J. *J. Org. Chem.* **1992**, *57*, 5670.

diastereoselectivity following from a convenient enantiomerically pure starting material. It demonstrates that, while delicate, the alkylation of a C-5 enolate in this series is a viable approach to creating the quaternary center.

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Supporting Information Available: Experimental procedures and characterizations for compounds **2**, **4**, **5**, **6a/b**, **8**, **10**, **15**, **16**, **17**, **18a**, **20**, **21**, **22a**, and **23** and the X-ray data for **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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