ORGANIC LETTERS

2001
Vol. 3, No. 18
2811−2814

Studies on the Total Synthesis of Tallysomycin. Synthesis of the Threonylbithiazole Moiety Containing a Structurally Unique Glycosylcarbinolamide

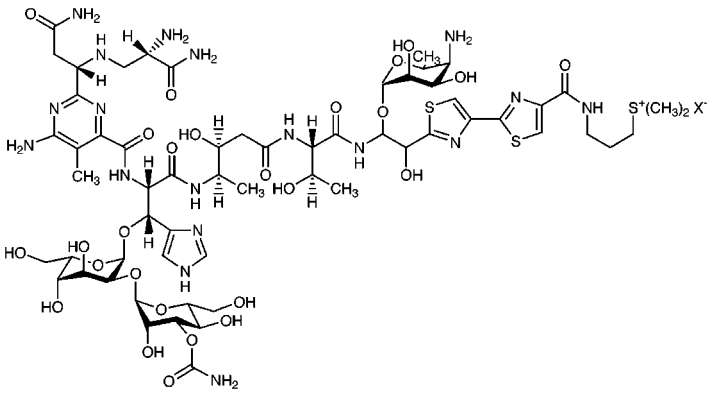
Marcos L. Sznaidman and Sidney M. Hecht*

Departments of Chemistry and Biology, University of Virginia, Charlottesville, Virginia 22901

sidhecht@virginia.edu

Received June 1, 2001

ABSTRACT



Tallysomycins are glycopeptide antibiotics that were first isolated from fermentation broths of *Streptoalloteichus hindustanus*. They are structurally related to the bleomycins but contain an additional talose sugar attached via a unique glycosylcarbinolamide linkage. Herein we report the synthesis of a key tallysomycin intermediate that incorporates the glycosylcarbinolamide moiety unique to the tallysomycins.

Tallysomycins A (**1**) and B (**2**) (Figure 1) are glycopeptide-derived antitumor antibiotics[1] structurally related to the bleomycins.[1,2] New biosynthetic derivatives of tallysomycin differing at the C-terminus were obtained by adding a variety of amines to the fermentation medium on which the producing organism (*Streptoalloteichus hindustanus*, strain No E465-94; ATCC 31158) was grown.[3] One of these derivatives, tallysomycin S_2B (**3**), was among the most effective tallysomycins in animal tumor models; this derivative has the same C-terminal substituent as bleomycin A_2 (**4**).[1,2] To facilitate an understanding of the molecular basis for the differences noted between the tallysomycins and

(1) (a) Kawaguchi, H.; Tsukiura, H.; Tomita, K.; Konishi, M.; Saito, K.-I.; Kobaru, S.; Numata, K.-I.; Fujisawa, K.-I.; Miyaki, T.; Hatori, M.; Koshiyama, H. *J. Antibiot.* **1977**, *30*, 779. (b) Konishi, M.; Saito, K.-I.; Numata, K.-I.; Tsuono, T.; Asama, K.; Tsukiura, H.; Naito, T.; Kawaguchi, H. *J. Antibiot.* **1977**, *30*, 789. (c) Tomita, K.; Uenoyama, Y.; Numata, K.-I.; Sasahira, T.; Hoshino, Y.; Fujisawa, K.-I.; Tsukiura, H.; Kawaguchi, H. *J. Antibiot.* **1978**, *31*, 497. (d) Takita, T.; Muraoka, Y.; Nakatani, T.; Fujii, A.; Umezawa, Y.; Naganawa, H.; Umezawa, H. *J. Antibiot.* **1978**, *31*, 801. (e) Bradner, W. T. In *Bleomycin, Current Status and New Developments*; Carter, S. K., Crooke, S. T., Umezawa, H., Eds.; Academic Press Inc.: New York, 1978; pp 333−342.

(2) (a) Hecht, S. M. In *Cancer Chemotherapeutic Agents*; Foye, W. O., Ed.; American Chemical Society: Washington, DC, 1995; pp 369−388. (b) Hecht, S. M. *J. Nat. Prod.* **2000**, *63*, 158.

(3) Miyaki, T.; Tenmyo, O.; Numata, K.-I.; Matsumoto, K.; Yamamoto, M.; Nishiyama, Y.; Ohbayashi, M.; Imanishi, M.; Konishi, M.; Kawaguchi, H. *J. Antibiot.* **1981**, *34*, 658.

10.1021/ol0101178 CCC: $20.00
Published on Web 08/10/2001

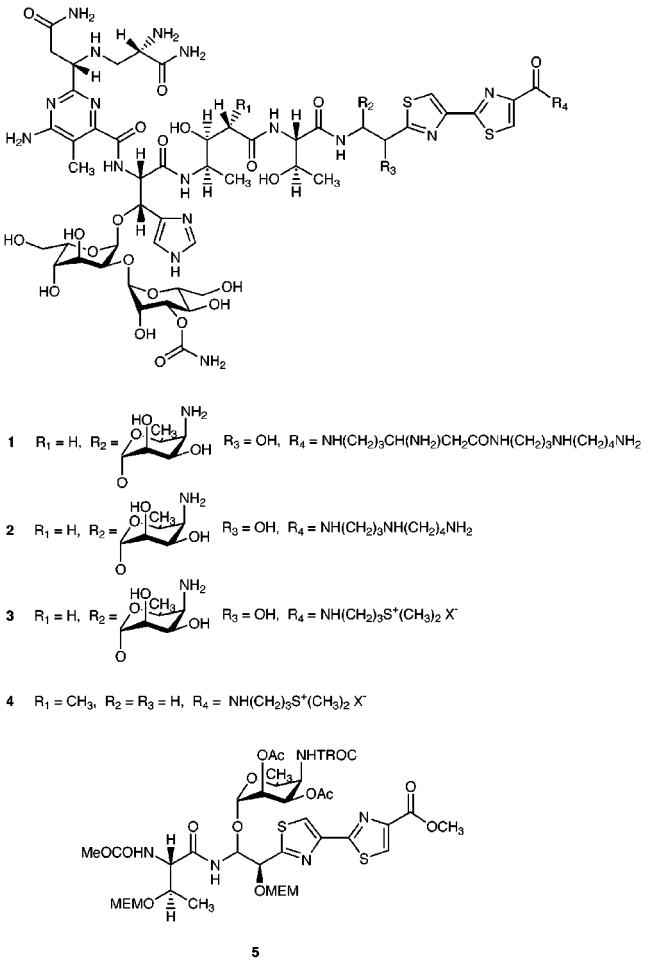


Figure 1. Structures of tallysomycins (**1**−**3**), bleomycin A_2 (**4**), and key synthetic tallysomycin intermediate **5**.

bleomycins in DNA interaction,[4] toxicities,[5,6] and antitumor activities,[5] we have embarked on a program to effect the total synthesis of tallysomycin S_2B (**3**), as well as structural congeners useful for mechanistic analysis.

Structurally, the tallysomycins are quite similar to the bleomycins. They differ primarily in that tallysomycin contains a talose sugar as part of a glycosylcarbinolamide.[7] While there are published examples of the synthesis of alkyl carbinolamides,[8] including the natural products pederin, onnamide A, and mycalamides A and B,[9] no glycosylcarbinolamide has been reported as a synthetic product to date. Presently, we describe the synthesis of one isomer of the threonylbithiazole moiety of tallysomycin (**5**), which includes the structurally unique glycosylcarbinolamide moiety.

Threonine derivative **6**[10] and benzyl imidate **7**[11] (Scheme 1) were coupled following the procedure described by Matsuda et al.[9a] for the total synthesis of pederin. Crude **8** was then reduced with $NaBH_4$ in EtOH, affording benzyl carbinolamide **9** in 36% overall yield from **6** + **7**.[12] Hydrogenation over palladium hydroxide in EtOH afforded carbinolamide **10** as a syrup in quantitative yield. It was not possible to carry out both reductive processes in a single step under any condition tested.

The bromosugar (**15**) required for glycosylation of carbinolamide **10** was prepared starting from L-rhamnose, which was converted to oxime **12** in four steps.[13] Treatment of **12** with $LiA1H_4$ in dry ether effected reduction to the amine with excellent control of stereochemistry; this intermediate was converted directly to trichloroethylcarbamate **13** (colorless crystals, mp 87−89 °C, 84% overall yield from **12**). Removal of the acetonide was realized by treatment with Dowex 50W-X8 resin; following acetylation, methyl taloside **14** was isolated in 99% overall yield (colorless crystals from hexane, mp 85−87 °C). Methyl taloside **14** was converted to the respective acetoxy sugar by treatment with AcOH and Ac_2O in the presence of catalytic amounts of H_2SO_4;[16] bromination was then effected in 51% yield by treatment

(4) (a) Strong, J. E.; Crooke, S. T. In *Bleomycin: Chemical, Biochemical and Biological Aspects*; Hecht, S. M., Ed.; Springer-Verlag: New York, 1979; pp 244−254. (b) Mirabelli, C. K.; Huang, C.-H.; Crooke, S. T. *Biochemistry* **1983**, *22*, 300.

(5) Miyaki, T.; Numata, K.-I.; Nishiyama, Y.; Tempo, O.; Hatori, M.; Imanishi, H.; Konishi, M.; Kawaguchi, H. *J. Antibiot.* **1981**, *34*, 665.

(6) Ginsburg, E.; Gram, T. E.; Trush, M. A. *Cancer Chemother. Pharmacol.* **1984**, *12*, 111.

(7) Although the structures of tallysomycins A (**1**) and B (**2**) have been established,[1b,d] only limited data is available concerning the absolute stereochemistry at the 25 asymmetric centers common to all tallysomycins. Given the published work on the talose moiety[1d] and the probability that the 18 asymmetric centers that bleomycin A_2 (**4**) and tallysomycin S_2B (**3**) share in common have the same absolute configurations, only the two (non-carbohydrate) asymmetric centers unique to tallysomycin lack tentative assignments. Aside from possible stereochemical differences, tallysomycin S_2B differs from bleomycin A_2 in two ways, namely, the absence of a methyl group in the valerate moiety and the presence of two hydroxyl groups of undefined stereochemistry within the aminoethylbithiazole moiety, one of which is conjugated to a talose sugar as part of a glycosylcarbinolamide.

(8) Katritzky, A. R.; Fan, W. Q.; Black, M.; Pernak, J. *J. Org. Chem.* **1992**, *57*, 547.

(9) (a) Matsuda, F.; Tomiyoshi, N.; Yanagiya, M.; Matsumoto, T. *Tetrahedron* **1988**, *44*, 7063. (b) Hong, C. Y.; Kishi, Y. *J. Org. Chem.* **1990**, *55*, 4242. (c) Hong, C. Y.; Kishi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 9693. (d) Roush, W. R.; Marron, T. G.; Pfeifer, L. A. *J. Org. Chem.* **1997**, *62*, 474 and references therein.

(10) (*S*)-Threonine was N-protected by treatment with a basic, aqueous solution of methyl chloroformate (Seebach, D.; Charczuk, R.; Gerber, C.; Renaud, P.; Berner, H.; Schneider, H. *Helv. Chim. Acta* **1989**, *72*, 401), followed by silylation in an overall yield of 41%.

(11) (*R*)-2,2-Dimethyl-1,3-dioxolane-4-carboxamide (Iwadare, K. *Bull. Chem. Soc. Jpn.* **1939**, *14*, 131) was converted to benzyl imidate **7** essentially quantitatively by treatment with benzyl iodide−silver oxide (Pougny, J.-R.; Sinaÿ, P. *Tetrahedron Lett.* **1976**, 4073). The product contained ~15% of the *N*-benzylamide and was used in the next step without further purification.

(12) Carbinolamide **9** was isolated as colorless crystals after SiO_2 column chromatography and crystallization from hexane. ^1H NMR indicated that a single isomer, presently of unknown absolute configuration at the newly formed stereocenter, had been separated from the mixture of isomers formed during the reduction.

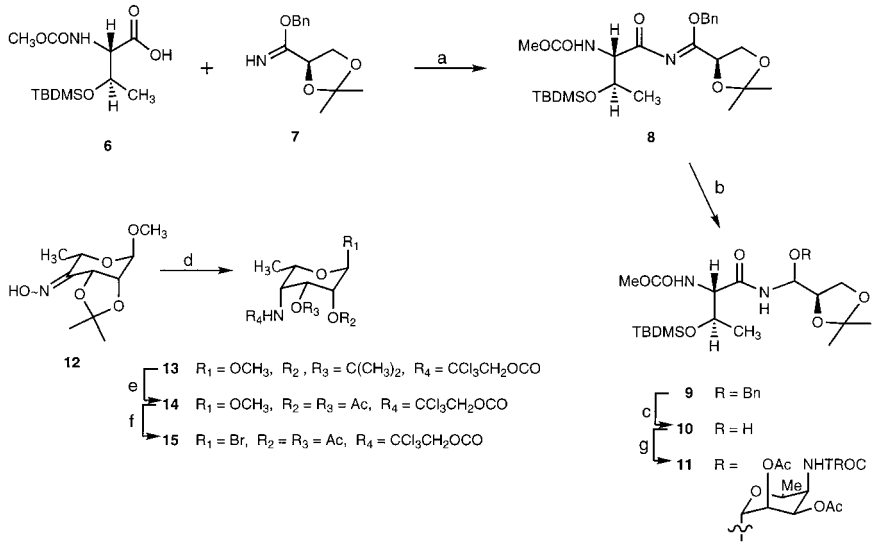
(13) Following conversion to methyl rhamnoside (Binkley, R. W.; Goewey, G. S.; Johnston, J. C. *J. Org. Chem.* **1984**, *49*, 992) and introduction of the isopropylidene group (Bebault, G. M.; Dutton, G. S. *Can. J. Chem.* **1972**, *50*, 3373), the 4-OH group was oxidized with RuO_2 and KIO_4.[14,15] Treatment with hydroxylamine hydrochloride then afforded **12** as colorless crystals in 50% overall yield from rhamnose.

(14) (a) Lawton, B. T.; Szarek, W. A.; Jones, J. K. N. *Carbohydr. Res.* **1969**, *10*, 456. (b) Aspinall, G. O.; Takeo, K. *Carbohydr. Res.* **1983**, *121*, 61.

(15) Gunner, S. W.; Overend, W. G.; Williams, N. R. *Carbohydr. Res.* **1967**, *4*, 498.

(16) Baker, B. R.; Joseph, J. P.; Schaub, R. E. *J. Am. Chem. Soc.* **1955**, *77*, 5905.

Scheme 1[a]

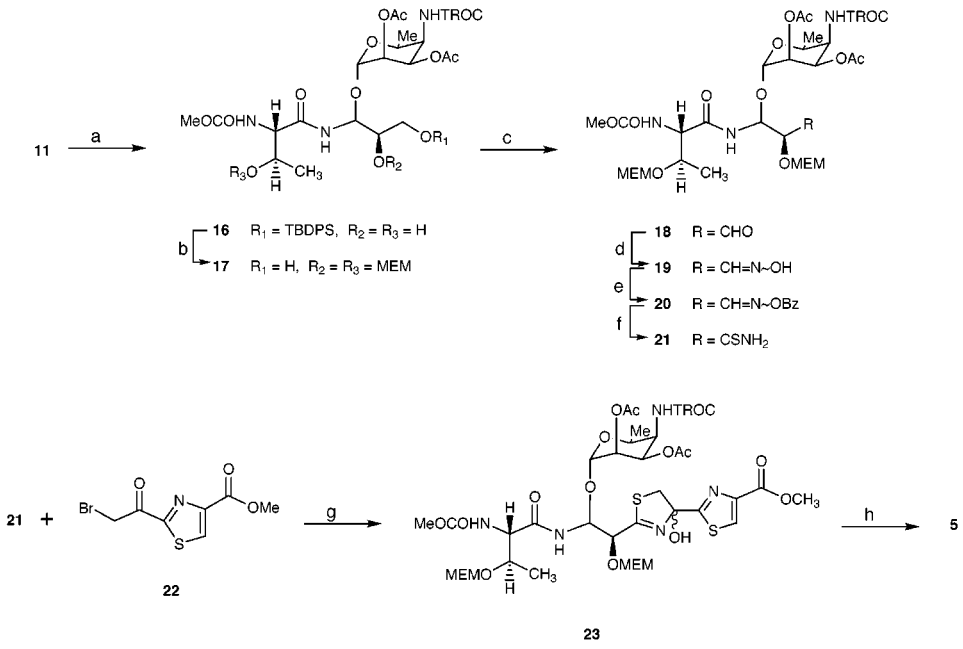


[a] (a) **6** + $SOCl_2$, pyridine, CH_2Cl_2, 25 °C; then **7** + Et_3N, 25 °C; (b) $NaBH_4$, EtOH, 0 °C; (c) H_2, palladium hydroxide, EtOH, 25 °C; (d) $LiAlH_4$, ether, 25 °C; then $ClC(O)OCH_2CCl_3$, pyridine, 25 °C; (e) Dowex 50W-X8, MeOH, 25 °C, 36 h; then Ac_2O, pyridine, 25 °C; (f) AcOH, Ac_2O, cat. H_2SO_4, 0 → 25 °C; 24 h; then 33% HBr in AcOH, 25 °C; (g) **15**, AgOTf, CH_2Cl_2, Ar, −78 → 0 °C, 12 h.

with a 33% solution of HBr in HOAc. Bromosugar **15** crystallized from ether−hexane, mp 136−138 °C.

Glycosylation of carbinolamide **10** with bromosugar **15** was achieved in CH_2Cl_2 using silver triflate as a catalyst. The desired glycosylcarbinolamide **11** was obtained in 40% yield as a colorless foam after SiO_2 column chromatography. Removal of the acetonide and TBDMS protecting groups was accomplished in a single step (60% yield) by treatment with 1:1 1 N HCl−THF,[17] and the primary alcohol was selectively protected with a TBDPS group to afford **16** in

Scheme 2[a]



[a] (a) 1:1 1 N HCl−THF, 25 °C; 9 h, then TBDPSiCl, imidazole, DMF, 25 °C, 15 h; (b) MEMCl, $^iPr_2EtN$, CH_2Cl_2; then 1.0 M Bu_4NF, THF, −78 → 0 °C, 1 h; (c) oxalyl chloride, DMSO, CH_2Cl_2, −60 °C, then Et_3N; (d) NH_2OH·HCl, 1:1 pyridine−EtOH, 25 °C; (e) benzoyl chloride, CH_2Cl_2, pyridine, 25 °C, 1 h; (f) H_2S, triethanolamine, Et_3N, EtOH, −78 → 0 °C, pressure bottle; (g) **22**, DMF, 4 Å molecular sieves, 25 °C, 2 h; (h) $(CF_3CO)_2O$, pyridine, CH_2Cl_2, 25 °C.

83% yield (Scheme 2). Following protection of the secondary alcohols with the MEM group, the silyl group was removed selectively by treatment with 1.0 M Bu_4NF in THF, affording key intermediate **17** as a syrup in 80% overall yield from **16**. Oxidation of the primary alcohol was accomplished by treating **17** under Swern[18] conditions; the aldehyde **18** was isolated in 90% yield. Treatment of this material with hydroxylamine hydrochloride afforded oxime **19** in 72% yield as a colorless foam. Benzoylation afforded benzoyl oxime **20** in 83% yield, from which thioamide **21** was obtained in 60% yield by treatment with H_2S in a pressure bottle in the presence of triethanolamine and triethylamine.[19] Formation of the hydroxythiazolinylthiazole ring system was accomplished by treating thioamide **21** with thiazole **22**[20] in the presence of 4 Å molecular sieves. Crude product **23** was treated with pyridine and trifluoroacetic anhydride to afford final product **5** in 76% overall yield from **21**. Threonylbithiazole **5** was isolated as a low melting solid and was characterized by ^1H NMR and by low- and high-resolution mass spectrometry.

The synthesis of threonylbithiazole **5** constitutes the first reported synthesis of any glycosylcarbinolamide. Although the absolute and relative stereochemistry within the carbinolamide moiety of tallysomycin is presently unknown, the availability of a route for preparing **5** should provide ready access to tallysomycin S_2B itself. In fact, it seems likely that the four possible isomers within the glycosylcarbinolamide moiety can be prepared by modification of the route described here, thus facilitating the assignment of stereochemistry to the natural product.

Acknowledgment. We thank Dr. Ralph Scannell for assistance with the preparation of the talose moiety of tallysomycin. This work was supported by NIH research grants CA53913 and CA77284, awarded by the National Cancer Institute.

Supporting Information Available: Synthesis and characterization of compounds **5** and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0101178

(17) Corey, E. J.; Kim, S.; Yoo, S.-E.; Nicolaou, K. C.; Melvin, L. S., Jr.; Brunelle, D. J.; Falck, J. R.; Trybluski, E. J.; Lett, R.; Sheldrake, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 4620.

(18) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

(19) It seems likely that this reaction proceeds in two steps, by elimination of elements of benzoic acid to form the nitrile, followed by addition of H_2S to afford the thioamide.

(20) Thiazole **22** was obtained in six steps in 42% overall yield from benzoyl chloride, acetaldehyde, sodium cyanide and ethyl bromopyruvate by minor modification of a published procedure (Sakai, T. T.; Riordan, J. M.; Booth, T. E.; Glickson, J. D. *J. Med. Chem.* **1981**, *24*, 279).