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

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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 glycopeptidederived antitumor antibiotics<sup>1</sup> structurally related to the bleomycins.<sup>1,2</sup> 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.<sup>3</sup> One of these derivatives, tallysomycin S<sub>2</sub>B (**3**), was among the most effective tallysomycins in animal tumor models; this derivative has the same C-terminal substituent as bleomycin A<sub>2</sub> (**4**).<sup>1,2</sup> To facilitate an understanding of the molecular basis for the differences noted between the tallysomycins and

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ABSTRACT

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4  $R_1 = CH_3, R_2 = R_3 = H, R_4 = NH(CH_2)_3S^+(CH_3)_2X^-$ 



Figure 1. Structures of tallysomycins (1-3), bleomycin A<sub>2</sub> (4), and key synthetic tallysomycin intermediate 5.

bleomycins in DNA interaction,<sup>4</sup> toxicities,<sup>5,6</sup> and antitumor activities,<sup>5</sup> 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.<sup>7</sup> While there are published examples of the synthesis of alkyl carbinolamides,<sup>8</sup> including the natural products pederin, onnamide A, and mycalamides A and B,<sup>9</sup> 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.<sup>9a</sup> for the total synthesis of pederin. Crude **8** was then reduced with NaBH<sub>4</sub> in EtOH, affording benzyl carbinolamide **9** in 36% overall yield from **6** + **7**.<sup>12</sup> 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.<sup>13</sup> Treatment of 12 with LiA1H<sub>4</sub> 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<sub>2</sub>O in the presence of catalytic amounts of H<sub>2</sub>SO<sub>4</sub>;<sup>16</sup> bromination was then effected in 51% yield by treatment

(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.; Sinay, 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<sub>2</sub> column chromatography and crystallization from hexane. <sup>1</sup>H 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<sub>2</sub> and KIO<sub>4</sub>.<sup>14,15</sup> Treatment with hydroxylamine hydrochloride then afforded **12** as colorless crystals in 50% overall yield from rhamnose.

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<sup>(7)</sup> Although the structures of tallysomycins A (1) and B (2) have been established, <sup>1b,d</sup> 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<sup>1d</sup> and the probability that the 18 asymmetric centers that bleomycin A<sub>2</sub> (4) and tallysomycin S<sub>2</sub>B (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<sub>2</sub>B differs from bleomycin A<sub>2</sub> 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.

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<sup>*a*</sup> (a) **6** + SOCl<sub>2</sub>, pyridine, CH<sub>2</sub>Cl<sub>2</sub>, 25 °C; then **7** + Et<sub>3</sub>N, 25 °C; (b) NaBH<sub>4</sub>, EtOH, 0 °C; (c) H<sub>2</sub>, palladium hydroxide, EtOH, 25 °C; (d) LiAlH<sub>4</sub>, ether, 25 °C; then ClC(O)OCH<sub>2</sub>CCl<sub>3</sub>, pyridine, 25 °C; (e) Dowex 50W-X8, MeOH, 25 °C, 36 h; then Ac<sub>2</sub>O, pyridine, 25 °C; (f) AcOH, Ac<sub>2</sub>O, cat. H<sub>2</sub>SO<sub>4</sub>,  $0 \rightarrow 25$  °C; 24 h; then 33% HBr in AcOH, 25 °C; (g) **15**, AgOTf, CH<sub>2</sub>Cl<sub>2</sub>, Ar,  $-78 \rightarrow 0$  °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<sub>2</sub> 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,<sup>17</sup> and the primary alcohol was selectively protected with a TBDPS group to afford **16** in



<sup>*a*</sup> (a) 1:1 1 N HCl–THF, 25 °C; 9 h, then TBDPSiCl, imidazole, DMF, 25 °C, 15 h; (b) MEMCl,  $P_{2}EtN$ , CH<sub>2</sub>Cl<sub>2</sub>; then 1.0 M Bu<sub>4</sub>NF, THF,  $-78 \rightarrow 0$  °C, 1 h; (c) oxalyl chloride, DMSO, CH<sub>2</sub>Cl<sub>2</sub>, -60 °C, then Et<sub>3</sub>N; (d) NH<sub>2</sub>OH·HCl, 1:1 pyridine–EtOH, 25 °C; (e) benzoyl chloride, CH<sub>2</sub>Cl<sub>2</sub>, pyridine, 25 °C, 1 h; (f) H<sub>2</sub>S, triethanolamine, Et<sub>3</sub>N, EtOH,  $-78 \rightarrow 0$  °C, pressure bottle; (g) **22**, DMF, 4 Å molecular sieves, 25 °C, 2 h; (h) (CF<sub>3</sub>CO)<sub>2</sub>O, pyridine, CH<sub>2</sub>Cl<sub>2</sub>, 25 °C.

83% yield (Scheme 2). Following protection of the secondary alcohols with the MEM group, the silvl group was removed selectively by treatment with 1.0 M Bu<sub>4</sub>NF 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<sup>18</sup> 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<sub>2</sub>S in a pressure bottle in the presence of triethanolamine and triethylamine.<sup>19</sup> 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 <sup>1</sup>H 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<sub>2</sub>B 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.

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**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.

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<sup>(20)</sup> 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).