Notes

Synthesis of 3″-Desmethoxyazithromycin: Regioselectivity and Stereoselectivity of SmI_2-Mediated α-Deoxygenation Reaction

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Erythromycin and related macrolide antibiotics are well-established therapeutic agents. Numerous macrolide derivatives have been synthesized in an attempt to improve biological activity.[1] However, modification of the rather inaccessible C-3″ position of the cladinose moiety has captured little attention. A prior approach by Hauske and co-workers[2] utilized diazo phosphonate-mediated intramolecular cyclization, which resulted in formation of 4″-deoxy-3″,4″-dihydrofuranylcladinose, a potential precursor of C-3″-modified erythromycin. Recently, preparation of 3″-*epi*-erythromycin[3] and replacement of the 3″-methoxy with a fluorine atom[4] in the formation of 3″-fluoroerythromycin were reported. Azithromycin is a 15-membered macrolide with an additional nitrogen in the lactone ring. In this paper, we describe our work on C-3″-modified azithromycin: the synthesis of 3″-desmethoxyazithromycin **8** via a SmI_2-mediated α-deoxygenation reaction with high regioselectivity and stereoselectivity.

We chose 4″-ketoazithromycin **2**[5] as the key intermediate. Our retrosynthetic analysis of compound **8** was based upon the hypothesis that it might be possible to effect demethoxylation at C-3″ of **2** in which a 3″-methoxy group is located in the α-position to the carbonyl group at the 4″-position. The deoxy compound **4** may provide an expedient access to C-3″-modified azithromycin via carbonyl α-functionalization. We selected SmI_2 for this deoxygenation, based on its effectiveness under mild conditions and in the presence of other functional groups.[6] It is of note that the application of SmI_2-mediated deoxygenation in the carbohydrate field has been rarely reported. Hanessian utilized SmI_2 for removal of the anomeric acetoxyl group from ulosonic acid.[7] SmI_2-promoted deoxygenation at C-2 in lactone sugars were described by Inanaga[8] and Hannesian.[9] Enholm disclosed the synthesis of branched-chain carbohydrate lactones via a SmI_2-promoted deoxygenation−coupling reaction.[10] To our knowledge, there is no report on SmI_2-mediated deoxygenation occurring at positions other than the anomeric center in non-lactone sugars.

There are two potential paths of C-3″ deoxygenation, since the 4″-carbonyl group in cladinose is α,α′-dioxygenated by the 3″-methoxy group and the endocyclic pyranone oxygen. However, we envisioned that the 3″-methoxy might be more vulnerable to elimination due to its axial disposition. The methoxy−carbon bond is parallel to the p orbital of the carbonyl group, and hence, bond cleavage would be stereoelectronically more favorable than for the endocyclic C5″−O bond.

Indeed, when 4″-ketoazithromycin **2** was treated with SmI_2 in THF at −78 °C in the presence of methanol, deoxygenation occurred within minutes, providing deoxy products **4** and **5** in almost quantitative yield. Methanolysis afforded 3″-desmethoxy-4″-ketoazithromycin **6** (and its epimer **7**) (Scheme 1). The deoxygenation was regioselective with no detectable amount of the ring opening product. To our surprise, the deoxygenation was also controlled stereoselectively with a ratio[11] of 89/11 for the two isomeric products. NOE studies on the major product reveal that the 4″-ketocladinose adopts a boat conformation with the 5″-methyl and 3″-methyl groups *trans* to each other. Further, the C-3″ configuration of the major isomer **6** was unequivocally confirmed as 3″-(*R*) by single-crystal X-ray structure determination (Figure 1).

The synthetic sequence of deoxygenation and methanolysis can be altered. For example, the SmI_2 reaction of **3** is equally effective to generate **6**. Reduction of **6** with lithium tri-*tert*-butoxyaluminum hydride in THF affords (3″*R*)-3″-desmethoxyazithromycin (**8**) and its 4″-epimer (3″*R*,4″*S*)-3″-desmethoxyazithromycin (**9**) in 94% yield with a ratio of 4/1. The two epimers were readily separable by column chromatography. When sodium borohydride was used, **9** was obtained exclusively.

The stereoselectivity observed for 3″-deoxygenation is probably attributed to the difference in the steric demand of axial vs equatorial enol protonation. Scheme 2 depicts a rationale for this hypothesis. The carbanion intermediate **I**, generated from reaction of SmI_2 with the carbonyl group, induces scission of the $C_{3''}$−methoxy bond, forming enol **II**. Tautomerization of **II** is expected to yield both 3″(*R*) and 3″(*S*) isomers, **4** and **5**. Since the macrolide aglycone moiety is axially situated at C-1″, it makes axial enol protonation less favorable. Enol protonation from the less hindered face results in **4**, with the C-3″ proton ($H_{3''}$) *trans* to the macrolide aglycone moiety.

To verify our hypothesis and to explore the scope of the SmI_2-mediated deoxygenation in the carbohydrate field, we prepared 1-*O*-benzyl-L-cladinoses **10** and **11** (Scheme 3). Selective cleavage of cladinose from azithromycin **1** with hydrogen chloride in ether−THF in the

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(11) The ratio of product mixture was determined from the integral of the proton NMR spectra for macrolides and by GC−MS for cladinose derivatives.

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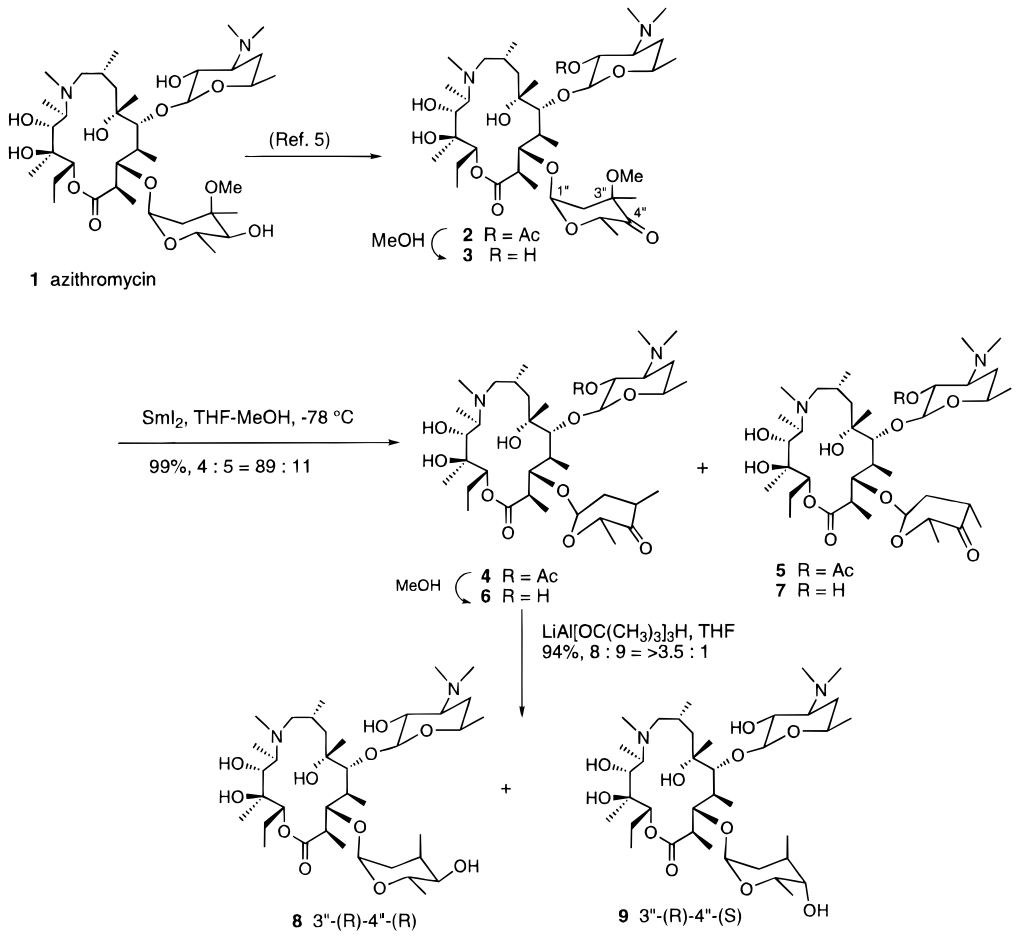
Scheme 1



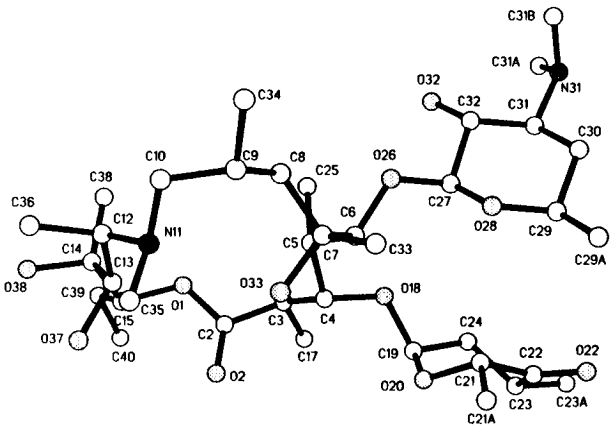
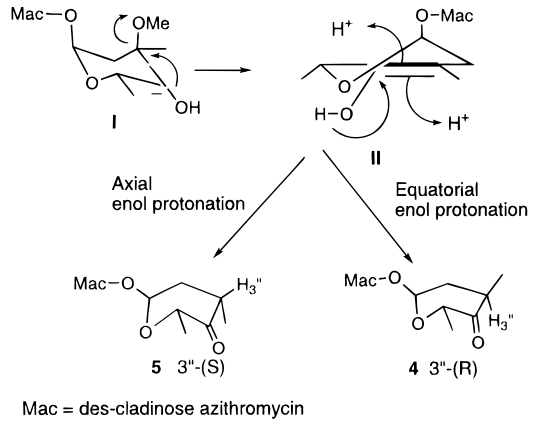


Figure 1. X-ray crystal structure of **6**.

Scheme 2



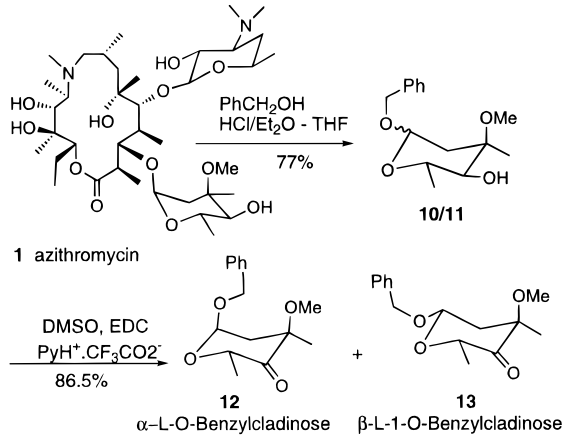
presence of benzyl alcohol provided 1-*O*-benzyl-L-cladinose as a mixture of **10** (α-isomer) and **11** (*β*-isomer) in a ratio of 1/4. Oxidation of this mixture following the procedure used for preparation of **2**[5] gave the 4-ketocladinoses **12** (α-isomer) and **13** (*β*-isomer), which were separated chromatographically.

When **12** and **13** were submitted to the SmI_2 reaction conditions, instantaneous deoxygenation was observed. The deoxy compounds were isolated in 84% and 86% yields, respectively (Scheme 4). In the case of **13**, the ratio of products generated from axial vs equatorial enol protonation is 69/31 (**17** vs **16**), whereas for **12** the ratio is 54/46 (**15** vs **14**). It should be noted that when the C-1 benzyloxyl group is changed from the equatorial position (in **13**) to the axial position (in **12**), the ratio decreased, with the C-3 equatorial-methyl product being less predominant as a result of increased steric hindrance for the axial enol protonation. This is reflected in the case of deoxygenation of **2**.

The epimerization of the deoxy compounds was also examined. The thermodynamically unfavorable axial-methyl derivatives **14** and **16** were treated with potassium *tert*-butoxide followed by quenching with aqueous ammonium chloride.[12] In both cases, a mixture of axial-methyl and equatorial-methyl derivatives was obtained, with a ratio of 3e-methyl/3a-methyl at 52/48 (**15** vs **14**) for **14** and 71/29 (**17** vs **16**) for **16**. Apparently, product

(12) Under the same conditions (potassium *tert*-butoxide, then NH_4Cl), **15** and **17** isomerized to their corresponding epimers, but in addition, generated a third, uncharacterized, compound.

Scheme 3



Scheme 4

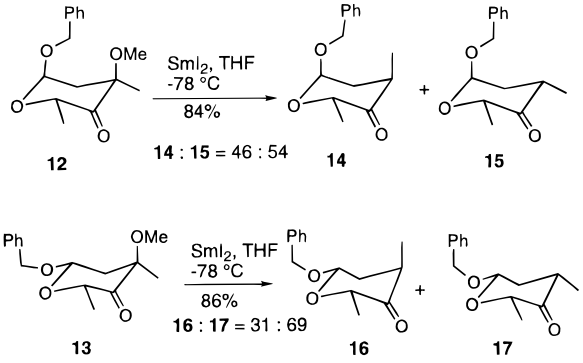


Table 1. *In Vitro* Antibacterial Activity of 3″-Desmethoxyazithromycin Derivatives, MIC (μg/mL)

		compound			
strains		**8**	**6**	**9**	azithromycin (**1**)
Staphylococcus aureus	1A052[a]	1.56	1.56	6.25	0.39
	1A005	0.78	0.78	3.12	0.2
Staphylococcus epidermisis	1B111	1.56	0.78	3.12	<0.1
	1B258	12.5	3.12	6.25	25
Streptococcus pyogenes	2C203	0.2	<0.1	<0.1	<0.1
	2C054	50	25	50	25
Enterococcus faecalies	2A006	3.12	1.56	3.12	3.12
Escherichia coli	51A470	3.12	0.39	0.78	3.12
	51A125	>50	12.5	>50	12.5
Klebsiella pneumoniae	53A031	>50	12.5	50	>50

[a] Pfizer culture designations.

composition determined by thermodynamic control is similar to product composition determined by kinetic control. Similarly, when the crude product mixture **6**/**7** was subjected to the same reaction conditions (potassium *tert*-butoxide), the ratio of 3″(*R*)/3″(*S*) remained unchanged.

The *in vitro* antibacterial activity of compounds **6**, **8**, and **9** was also examined. The MIC (minimum inhibition concentration) data are summarized in Table 1. **8** and **9** showed only modest antibacterial activity. However, compound **6** possesses good Gram-positive activity, with increased Gram-negative activity compared to azithromycin. With **6** as a versatile intermediate, a group of desmethoxyazithromycin derivatives were synthesized. Their preparation and antibacterial activity will be reported elsewhere.

In summary, we have been able to prepare 3″-desmethoxyazithromycin (**8**) via deoxygenation by using SmI_2. The deoxygenation of 4″-ketoazithromycin (**2**) proceeded with high regioselectivity and stereoselectivity (>8:1); the stereochemistry was determined by X-ray crystallography. The stereochemical preference reuslted from steric hindrance of the axially situated macrolide at C-1″, which makes the axial enol protonation of the enol intermediate unfavorable, giving rise to 3″(*R*)-isomer predominantly. The scope of application of SmI_2-mediated deoxygenation in the carbohydrate field was also explored. 1-*O*-Benzyl-L-cladinose sugars were converted to their 4-keto form. Subsequent deoxygenation with SmI_2 generated C-3 deoxy sugars. Studies on product composition of deoxygenation reveal that the product ratio from thermodynamic control is similar to that from kinetic control. This work constitutes the first application of SmI_2 to the deoxygenation of macrolide antibiotics. The present investigation also indicates that SmI_2-mediated deoxygenation has considerable potential utility in the carbohydrate field.

Experimental Section

Preparation of (3″*R*)-3″-Desmethoxy-4″-oxoazithromycin (6). To a solution of SmI_2 in THF (0.1 M, 170 mL) at −78 °C was added a solution of 2′-acetyl-4″-deoxy-4″-oxoazithromycin **2**[5] (4.55 g, 5.77 mmol) in methanol (15 mL), which was degassed with nitrogen. After 5 min, the saturated aqueous solution of potassium carbonate (10 mL) and water (30 mL) were added, and the slurry was gradually warmed to room temperature. THF was removed *in vacuo* on a rotary evaporator followed by addition of ethyl acetate (30 mL). The mixture was filtered through Celite, and the filtrate was separated. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated to afford the crude product **4**/**5** as a white solid. This solid was dissolved in methanol. The solution was refluxed for 3 h and allowed to stir at room temperature overnight. The solvent was removed *in vacuo*, giving the title compounds as a white solid, 4.11 g (5.73 mmol, 99% yield), which contained the 3″(*R*)-isomer **6** and its epimer **7** in a ratio of 89/11. A pure sample of **6** was obtained after chromatographic purification (silica gel with $MeOH/CHCl_3/NH_4OH$ 4:95.9:0.1 as eluents), mp 113−117 °C.

^{1}H-NMR ($CDCl_3$): 5.31 (dd, J = 8.2, 6.4 Hz, 1H), 4.60 (d, J = 9.2 Hz, 1H), 4.39 (q, J = 6.8 Hz, 1H), 4.27 (d, J = 7.3 Hz, 1H), 4.22 (dd, J = 8.4, 2.2 Hz, 1H), 3.66 (d, J = 5.4 Hz, 1H), 3.59 (d, J = 4.54 Hz, 1H), 3.52 (br d, 1H), 3.33 (ddq, 1H), 3.21 (dd, J = 10.2, 7.3 Hz, 1H), 2.87 (qd, J = 7.3, 2.7 Hz, 1H), 2.68 (qd, J = 6.9, 1.8 Hz, 1H), 2.56 (dqd, J = 11.8, 6.8, 4.9 Hz, 1H), 2.41 (d, J = 11.8 Hz, 1H), 2.35 (m, 1H), 2.31 (s, 3H), 2.23 (s, 6H), 2.04 (d, J = 11.8 Hz, 1H), 2.00 (m, 1H), 1.90 (dqd, J = 14.4, 7.3, 2.0 Hz, 1H), 1.76 (d, J = 14.6 Hz, 1H), 1.68 (dd, J = 14.4, 8.28 Hz, 1H), 1.64 (br d, J = 12.5 Hz, 1H), 1.5 (dqd, J = 14.4, 10.1, 7.3 Hz, 1H), 1.34 (d, J = 6.8 Hz, 3H), 1.27 (s, 3H), 1.21 (d, J = 7.1 Hz, 3H), 1.18 (d, J = 6.1 Hz, 3H), 1.05 (d, J = 6.7 Hz, 3H), 1.03 (d, J = 6.7 Hz, 3H), 1.0 (s, 3H), 0.99 (d, J = 8.0 Hz, 3H), 0.86 (d, J = 7.3 Hz, 3H), 0.85 (t, J = 7.8 Hz, 3H). ^{13}C-NMR ($CDCl_3$): 215.0 (s), 178.3 (s), 103.8 (d), 97.4 (d), 85.2 (d), 79.0 (d), 78.1 (d), 75.6 (d), 74.5 (s), 73.6 (s), 72.0 (d), 71.2 (d), 70.4 (t), 69.4 (d), 65.4 (d), 62.1 (d), 44.6 (d), 42.3 (t), 40.5 (q), 39.4 (d), 37.4 (d), 36.9 (q), 35.3 (t), 29.2 (t), 26.9 (q), 26.7 (d), 21.9 (q), 21.5 (q), 21.1 (t), 16.4 (q), 16.3 (q), 15.8 (q), 13.4 (q), 11.3 (q), 9.5 (q), 7.7 (q). FAB-HRMS: *m/e* 717.4920 ($M^+ + H$, $C_{37}H_{69}N_2O_{11}$ requires 717.4901).

Preparation of (3″*R*,4″*R*)-3″-Desmethoxyazithromycin (8) and (3″*R*,4″*S*)-3″-Desmethoxyazithromycin (9). To a solution of **6** (470 mg, 0.655 mmol) in THF (30 mL) at −78 °C was added a THF solution of lithium tri-*tert*-butoxyaluminum hydride (0.1 M, 1.0 mL). The reaction mixture was stirred at 0 °C for 3.5 h and then at room temperature for 30 min. The reaction was diluted with 30 mL of H_2O and then concentrated *in vacuo* to remove THF. The resulting basic aqueous solution was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concen-

trated to afford the crude product as a white solid. The crude product was chromatographed on silica gel with MeOH−$CHCl_3$−NH_4OH (4:95.9:0.1) as eluents. Three fractions were collected. The fast moving fraction upon evaporation afforded **8** (4″*R*-isomer) as a white solid, mp 120−123 °C, 215.5 mg (0.30 mmol, 46% yield). The slow moving fraction afforded **9** (4*S*″-isomer), 95 mg (0.132 mmol, 20% yield). In addition, a mixture of the two isomers were obtained from the middle fraction (132 mg, 0.183 mmol, 28% yield).

Spectral Data of **8**. ^{1}H-NMR ($CDCl_3$): 4.77 (dd, J = 9.68, 2.3 Hz, 1H), 4.61 (d, J = 10.7 Hz, 1H), 4.32 (d, J = 7.2 Hz, 1H), 4.14 (q, J = 6.8 Hz, 1H), 4.08 (br s, 1H), 3.81 (d, J = 10.3 Hz, 1H), 3.60 (br s, 1H), 3.56 (m, 1H), 3.48 (dqd, J = 10.6, 5.9, 2.0 Hz, 1H), 3.36 (m, 1H), 3.35 (br s, 1H), 3.19 (br s, 1H), 2.87 (br t, J = 7.9 Hz, 1H), 2.86 (m, 2H), 2.85 (m, 1H), 2.62 (br s, 1H), 2.5 (d, J = 12.1 Hz, 1H), 2.36 (s, 6H), 2.34 (s, 3H), 2.24 (br d, J = 7.2 Hz, 1H), 2.02 (t, J = 11.6 Hz, 1H), 1.92−1.84 (m, 3H), 1.77 (d, J = 14.4 Hz, 1H), 1.66 (br d, J = 11.2 Hz, 1H), 1.60 (br d, J = 13.6 Hz, 1H), 1.52 (m, 1H), 1.48 (m, 1H), 1.34 (s, 3H), 1.23 (d, J = 7.1 Hz, 3H), 1.20 (d, J = 6.4 Hz, 3H), 1.19 (d, J = 6.1 Hz, 3H), 1.07 (d, J = 6.8 Hz, 3H), 1.03 (s, 3H), 0.99 (d, J = 6.7 Hz, 3H), 0.96 (d, J = 7.4 Hz, 3H), 0.88 (t, J = 7.0 Hz, 3H), 0.86 (d, J = 7.8 Hz, 3H). ^{13}C-NMR ($CDCl_3$): 177.3 (s), 105.4 (d), 96.4 (d), 90.2 (d), 84.4 (d), 77.7 (d), 75.4 (d), 75.3 (d), 74.0 (s), 72.9 (s), 71.9 (d), 71.4 (d), 70.8 (t), 68.8 (d), 63.9 (d), 62.2 (d), 44.0 (d), 41.9 (t), 40.8 (q), 36.6 (d), 36.5 (q), 32.6 (t), 31.5 (t), 28.1 (d), 26.2 (d), 26.0 (q), 21.3 (q), 20.9 (q), 20.6 (t), 17.3 (q), 15.9 (q), 15.7 (q), 10.8 (q), 9.1 (q), 7.2 (q). HREIMS: *m/e* 718.5049 (M^+ for $C_{37}H_{70}N_2O_{11}$ requires 718.4961).

Spectral Data of **9**. ^{1}H-NMR ($CDCl_3$): 4.96 (dd, J = 7.9, 3.0 Hz, 1H), 4.66 (br d, J = 8.6 Hz, 1H), 4.56 (d, J = 7.4 Hz, 1H), 4.25 (m, 1H), 4.18 (dq, J = 4.4, 6.8 Hz, 1H), 3.98 (d, J = 8.4 Hz, 1H), 3.87 (d, J = 4.1 Hz, 1H), 3.6 (br s, 1H), 3.46 (ddq, 1H), 3.34 (dd, J = 8.3, 4.4 Hz, 1H), 3.24 (dd, J = 10.0, 7.4 Hz, 1H), 2.84 (qd, J = 7.4, 2.0 Hz, 1H), 2.78 (m, 1H), 2.68 (d, J = 8.9 Hz, 1H), 2.32 (s, 3H), 2.29 (s, 6H), 2.04 (d, J = 8.9 Hz, 1H), 2.02 (m, 1H), 1.95 (m, 1H), 1.84 (ddq, 1H), 1.73 (d, J = 14.6 Hz, 1H), 1.64 (br d, J = 10.7 Hz, 1H), 1.51 (ddq, 1H), 1.28 (d, J = 6.1 Hz, 3H), 1.27 (s, 3H), 1.21 (d, J = 6.1 Hz, 3H), 1.19 (d, J = 6.0 Hz, 3H), 1.07 (d, J = 6.6 Hz, 3H), 1.05 (d, J = 7.1 Hz, 3H), 1.04 (s, 3H), 0.99 (d, J = 7.4 Hz, 3H), 0.86 (d, J = 7.1 Hz, 3H), 0.84 (t, J = 7.7 Hz, 3H). ^{13}C-NMR ($CDCl_3$): 177.7 (s), 102.8 (d), 95.9 (d), 85.4 (d), 81.5 (d), 77.6 (d), 75.4 (d), 74.4 (d), 74.2 (s), 73.2 (s), 71.0 (d), 70.6 (t), 70.4 (d), 68.7 (d), 65.9 (d), 62.1 (d), 44.4 (d), 41.9 (t), 40.5 (q), 37.9 (d), 36.7 (t), 36.6 (q), 31.3 (d), 29.9 (t), 26.45 (q), 26.4 (d), 21.5 (q), 21.2 (q), 20.8 (t), 18.5 (q), 16.0 (q), 15.9 (q), 13.1 (q), 11.0 (q), 9.1 (q), 7.5 (q). FABHRMS: *m/e* 719.5055 (M^+ + H, $C_{37}H_{71}N_2O_{11}$ requires 719.5039).

Acknowledgment. We are grateful to Mr. Jon Bordner and Mrs. Debra DeCosta for the X-ray crystallographic analysis of compound **6**. We also thank Dr. Art Girard's laboratory for the *in vitro* antibacterial evaluation.

Supporting Information Available: NMR spectra for **6**, **8**, and **9** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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