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An Expeditious Enantioselective Synthesis of Antimycin A_{3b}

Yikang Wu* and Yong-Qing Yang

State Key Laboratory of Bio-organic & Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China

yikangwu@mail.sioc.ac.cn

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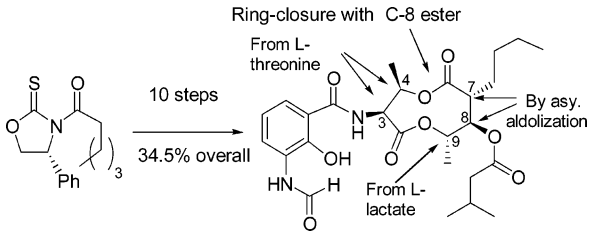

A straightforward enantioselective route to (+)-antimycin A_{3b} is presented, which used a $TiCl_4$-mediated asymmetric aldolization to construct C-7/C-8 and BnOH/DMAP to remove the chiral auxiliary with concurrent protection of the carboxylic group, respectively. Closing the dilactone ring was achieved in 62% yield (previously 0.8%, 13.4%, or 20%) in the presence of the C-8 ester functionality. The overall yield (34.5%) was significantly higher than that (0.019−3.6%) of the earlier routes.

Introduction

The antimycin family of antibiotics currently includes 26 members, which were discovered over many decades.[1−12] These compounds all share a common structural feature, i.e., a nine-membered dilactone ring (Figure 1). It has been shown that the

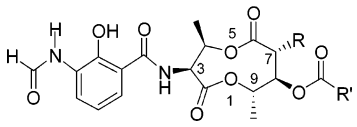

FIGURE 1. The general structure of the antimycins. For details of the R and R′, see refs 10−12.

antimycins possess an array of bioactivities, including killing insects,[13a] mites,[14a] and fungi,[13b−e] inhibition of electron transport[14a] as well as enzymes,[14b−d] and inducing[15] the death of cancer cells. The significant bioactivities, along with the interesting structure, inspired many chemists to carry out synthetic studies on this class of compounds.

Up to now synthetic studies on antimycins were performed only on the A_3 (mostly A_{3b}). To date, there have been one

(1) Leben, C.; Keitt, G. W. *Phytopathology* **1948**, *38*, 899−906.
(2) Dunshee, B. R.; Leben, C.; Keitt, G. W.; Strong, F. M. *J. Am. Chem. Soc.* **1949**, *71*, 2436−2437.
(3) (a) Schneider, H. G.; Tener, G. M.; Strong, F. M. *Arch. Biochem. Biophys.* **1952**, *37*, 147−157. (b) Lockwood, J. L.; Leben, C.; Keitt, G. W. *Phytopathology* **1954**, *44*, 438−446.
(4) (a) Sakagami, Y.; Takeuchi, S.; Yonehara, H.; Sakai, H.; Takashima, M. *J. Antibiot.* **1956**, *9*, 1−5. (b) Watanabe, K.; Tanaka, T.; Fukuhara, K.; Miyairi, N.; Yonehara, H.; Umezawa, H. *J. Antibiot. Ser. A* **1957**, *10*, 39−45. (c) Yonehara, H.; Takeuchi, S. *J. Antibiot. Ser. A* **1958**, *11*, 254−263.
(5) Liu, W.-C.; Strong, F. M. *J. Am. Chem. Soc.* **1959**, *81*, 4387−4390.
(6) (a) Van Tamelene, E. E.; Dickie, J. P.; Loomans, M. E.; Dewey, R. S.; Strong, F. M. *J. Am. Chem. Soc.* **1961**, *83*, 1639−1646. (b) Birch, A. J.; Cameron, D. W.; Harada, Y.; Rickards, R. W. *J. Chem. Soc.* **1961**, 889−895.
(7) Kinoshita, M.; Asuraki, S.; Umezawa, S. *J. Antibiot.* **1972**, *25*, 373−376.
(8) Schilling, G.; Berti, D.; Kluepfel, D. *J. Antibiot.* **1970**, *23*, 81−90.
(9) Barrow, C.; Oleynek, J.; Marinelli, V.; Sun, H. H.; Kaplita, P.; Sedlock, D. M.; Gillum, A. M.; Chadwick, C. C.; Cooper, R. *J. Antibiot.* **1997**, *50*, 729−733.
(10) Shiomi, K.; Hatae, K.; Hatanho, H.; Matsumoto, A.; Takahashi, Y.; Jiang, C.-L.; Tomoda, H.; Kobayashi, S.; Tanaka, H.; Omura, S. *J. Antibiot.* **2005**, *58*, 74−78.
(11) Hosotani, N.; Kumagai, K.; Nakagawa, H.; Shimatani, T.; Saji, I. *J. Antibiot.* **2005**, *58*, 460−467.
(12) Chen, G.; Lin, B.; Lin, Y.; Xie, F.; Lu, W.; Fong, W.-F. *J. Antibiot.* **2005**, *58*, 519−522.
(13) (a) Kido, G. S.; Spyhalski, E. *Science* **1950**, *112*, 172−173. (b) Sakagami, Y.; Takeuchi, S.; Yonehara, H.; Sakai, H.; Takashima, M. *J. Antibiot.* **1956**, *9*, 1−5. (c) Leben, C.; Keitt, G. W. *Phytopathology* **1949**, *39*, 529−540. (d) Chen, G.; Lin, B.; Lin, Y.; Xie, F.; Lu, W.; Fong, W.-F. *J. Antibiot.* **2005**, *58*, 519−522. (e) Nakayama, K.; Okamoto, F.; Harada, Y. *J. Antibiot.* **1956**, *9*, 63−66.
(14) (a) Potter, V. R.; Reif, A. E. *J. Biol. Chem.* **1952**, *194*, 287−297. (b) Barrow, C.; Oleynek, J.; Marinelli, V.; Sun, H. H.; Kaplita, P.; Sedlock, D. M.; Gillum, A. M.; Chadwick, C. C.; Cooper, R. *J. Antibiot.* **1997**, *50*, 729−733. (c) Thorn, M. B. *Biochem. J.* **1956**, *63*, 420−436. (d) Reif, A. E.; Potter, V. R. *Cancer Res.* **1953**, *13*, 49−57.
(15) (a) King, M. A. *Cytometry, Part A* **2005**, *63A*, 69−76. (b) Tzung, S.-P.; Kim, K. M.; Basañez, G.; Giedt, C. D.; Simon, J.; Zimmerberg, J.; Zhang, K. Y. J.; Hockenbery, D. M. *Nat. Cell Biol.* **2001**, *3*, 183−191.

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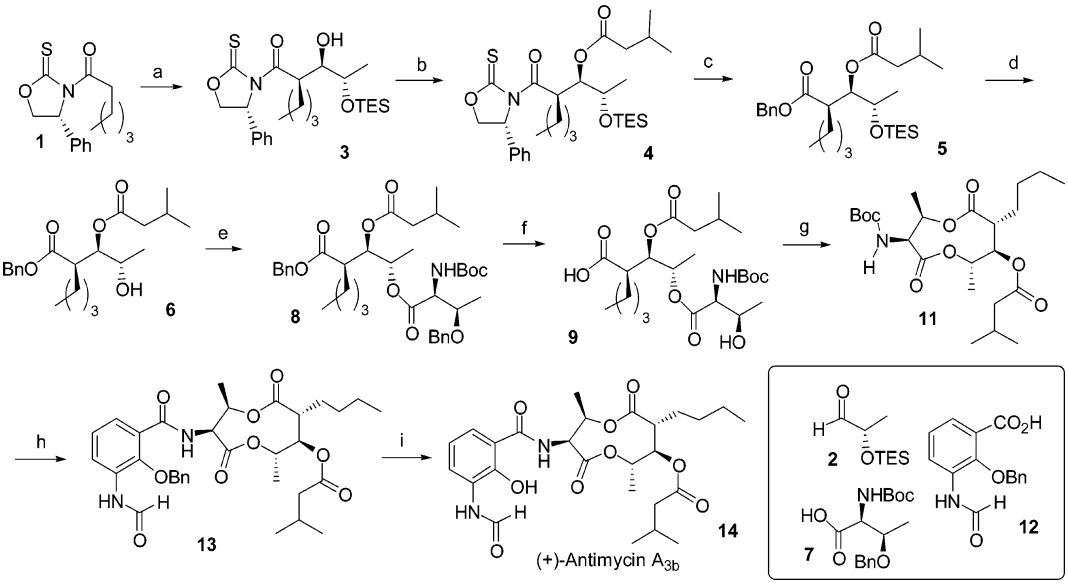
SCHEME 1[a]



[a] Reagents and conditions: (a) **2**/$TiCl_4$/TMEDA/CH_2Cl_2, 90%. (b) Me_2CHCH_2COCl/py/CH_2Cl_2, 89%. (c) BnOH/DMAP/CH_2Cl_2, 74%. (d) $NaIO_4$/THF−H_2O, 100%. (e) **7**/DCC/DMAP/CH_2Cl_2, 100%. (f) H_2 (30 atm)/$Pd(OH)_2$−C/MeOH, 100%. (g) **10**/DMAP/PhMe/4 Å MS, 62%. (h) (1) TFA/CH_2Cl_2, (2) **12**/EDC/HOBt/NMM/DMF, 94% from **11**. (i) H_2/Pd−C/EtOAc, 100%.

racemic[16] and two enantioselective[17] total syntheses in the literature, along with at least four formal[18] syntheses. However, these routes all suffered low overall yields despite the elegant methodologies illustrated therein. Now we wish to disclose an efficient synthesis of (+)-A_{3b}, which may also be adapted for synthesizing other members of this class of compounds.

The high efficiency of our synthesis stemmed mainly from (1) use of aldolization to construct the C-7/C-8, (2) elimination of the C-8 protecting group manipulation, and (3) successful ring-closure in the presence of the C-8 ester. It is obvious that an early installation of the C-8 acyl group may lead to a straightforward synthesis. However, the presence of this ester seriously lowered the ring-closure yield (0.8%,[17b] 13%,[18a] 20%[18c]). Therefore, later syntheses switched to using Bn[17a] or TIPS[17c,d] to mask the C-8 OH. We noticed that many new methods appeared since the 1970s and hence decided to address this long-pending lactonization problem in this work.

Results and Discussion

Our route is outlined in Scheme 1. Compound **1**[19] reacted with **2**[20] under the Crimmins[21] conditions to give **3**. The best results were obtained with 1.4 equiv of $TiCl_4$, 2.5 equiv of TMEDA, and 2.5 equiv of **2** at −5 °C (90% isolated yield, along with traces of other isomers). Acylation of **3** was achieved at 0 °C in 89% yield in pyridine containing 0.1 equiv of DMAP. The chiral auxiliary was then removed with BnOH/DMAP[22] (74%).

The next step was to remove the TES protecting group. Due to the great tendency to form[23] blastmycinone, this otherwise expected facile step was also tricky. Several mild reagents for removing silyl groups (e.g., TBAF buffered with *p*-TsOH, DDQ,[24a] Pd−C,[24b,c] IBX,[24d] $FeCl_3$,[24e] and HF·Py[24f]) all failed to deliver **6** in good yields. Finally, we were pleased to find that finely powdered $NaIO_4$[25] in aqueous THF with timely workup could satisfactorily generate the desired alcohol **6** in quantitative yield.

The coupling of the labile **6** with a properly protected L-threonine (**7**[26]) was then attempted under several sets of conditions. After testing *N*,*N*′-diisopropylcarbodiimde (DIC), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC), and *N*,*N*′-dicyclohexylcarbodiimide (DCC) under various conditions,

(16) Kinoshita, M.; Wada, M.; Umezawa, S. *J. Antibiot*. **1969**, *22*, 580−582 (racemic A_{3b}).

(17) (a) Kinoshita, M.; Wada, M.; Aburagi, S.; Umezawa, S. *J. Antibiot*. **1971**, *24*, 724−726 ((+)-A_{3b}, communication). (b) Kinoshita, M.; Aburaki, S.; Wada, M.; Umezawa, S. *Bull. Chem. Soc. Jpn*. **1973**, 46, 1279−1287 (full paper). (c) Tsunoda, T.; Nishii, T.; Yoshizuka, M.; Yamasaki, C.; Suzuki, T.; Ito, S. *Tetrahedron Lett*. **2000**, *41*, 7667−7671 ((−)-A_{3b}). (d) Nishii, T.; Suzuki, S.; Yoshida, K.; Araki, K.; Tsunoda, T. *Tetrahedron Lett.* **2003**, *44*, 7829−7832 ((+)-A_{3b} and (+)-A_{3a}, using a same route as for (−)-A_{3b}).

(18) (a) Aburaki, S.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 198−203. (b) Nakata, T.; Fukui, M.; Oishi, T. *Tetrahedron Lett*. **1983**, *24*, 2657−2660. (c) Wasserman, H. H.; Gambale, R. J. *J. Am. Chem. Soc*. **1985**, *107*, 1423−1424. (d) Wasserman, H. H.; Gambale, R. J. *Tetrahedron* **1992**, *48*, 7059−7070. (e) Inghart, T.; Frejd, T. *Tetrahedron* **1991**, *47*, 6483−6492.

(19) Readily prepared ((a) Ho, G. J.; Mather, D. J. *J. Org. Chem*. **1995**, *60*, 2271−2273) in 100% yield from the corresponding auxiliary ((b) Wu, Y.-K.; Yang, Y.-Q.; Hu, Q. *J. Org. Chem*. **2004**, *69*, 3990−3992) and acyl chloride.

(20) Gainellio, G.; Panunzio, M.; Bandini, E.; Martelli, G.; Spunta, G. *Tetrahedron* **1996**, *52*, 1685−1698.

(21) Crimmins, M. T.; King, B. W.; Tabet, E. *J. Am. Chem. Soc*. **1997**, *119*, 7883−7884.

(22) Wu, Y.-K.; Sun, Y.-P.; Yang, Y.-Q.; Hu, Q.; Zhang, Q. *J. Org. Chem*. **2004**, *69*, 6141−6144.

(23) For preparaing **5** through the aldolization and acylation with the corresponding thiazolidinethione, see: Yang, Y.-Q.; Wu, Y.-K. *Chin. J. Chem*. **2005**, *23*, 1519−1522.

(24) (a) Tanemum, K.; Suzuki, T.; Horaguchi, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2997−2998. (b) Rotulo-Sims, D.; Prunet, J. *Org. Lett*. **2002**, *4*, 4701−4704. (c) Ikawa, T.; Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron* **2004**, *60*, 6901−6911. (d) Wu, Y.-K.; Huang, J.-H.; Shen, X.; Hu, Q.; Tang, C.-J.; Li, L. *Org. Lett*. **2002**, *4*, 2141−2144. (e) Yang, Y.-Q.; Cui, J.-R.; Zhu, L.-G.; Sun, Y.-P.; Wu, Y.-K. *Synlett* **2006**, in press (published as eFirst online on March 10, 2006, DOI 10.1055/s-2006−926256; Art ID W30105ST). (f) Nicolaou, K. C.; Weber, S. E. *Synthesis* **1986**, 453−461.

(25) Wang, M.; Li, C.; Yin, D.; Liang, X.-T. *Tetrahedron Lett*. **2002**, *43*, 8727−8729.

(26) Nakamura, Y.; Hirai, M.; Tamotsu, K.; Yonezawa, Y.; Shin, C.-g. *Bull. Chem. Soc. Jpn*. **1995**, *68*, 1369−1377.

TABLE 1. Representative Results[a] of the Lactonization (forming 11) under Various Conditions

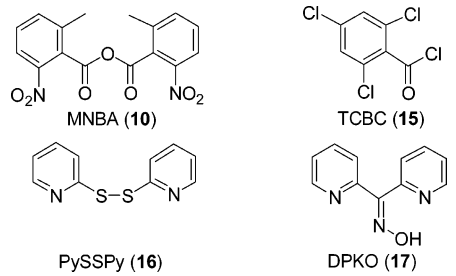
entry	reagents (equiv[b])	conditions	yield, %
1	TCBC (1.0)/NEt_3 (1.1)/DMAP (6.0)	PhMe/reflux/18 h	0
2	TCBC (1.6)/NEt_3 (2.0)/DMAP (10)	PhMe/reflux/20 h	7
3	TCBC (1.1)/NEt_3 (1.2)/DMAP (6.0)	PhMe/reflux/17 h	10
4	DCC (2.0)/DMAP (3.0)/DMAP·HCl (2.0)	$CHCl_3$/reflux/21 h	23[c]
5	PySSPy (1.1)/PPh_3 (1.1)/$Cu(OTf)_2$ (1.0)	PhH/reflux/5.5 h	15
6	PySSPy (2.0)/PPh_3 (2.0)/$(CuOTf)_2$·PhH (1.1)	PhH/reflux/2.5 h	13
7	PySSPy (4.0)/PPh_3 (4.0)/$(CuOTf)_2$·PhH (1.1)	PhH/reflux/4 h	18
8	DPKO (1.0)/EDC·HCl (1.0)/DMAP (0.01)/$(CuOTf)_2$·PhH (1.0)	MeCN/reflux/12 h	0
9	MNBA (1.3)/DMAP (3.5)	CH_2Cl_2/25 °C/22 h	35
10	MNBA (1.3)/DMAP (3.5)	CH_2Cl_2/40 °C/11 h	22
11	MNBA (1.3)/DMAP (6.0)	PhMe/20 °C/19 h	58
12	MNBA (1.5)/DMAP (6.0)/4 Å MS	PhMe/23 °C/23 h	62

[a] In all runs (except entry 4) the starting **9** was fully consumed. Apart from **11**, there were also many so far unidentified trace components in the product mixture. [b] Molar equivalents with respect to **9**. [c] Along with 7% of recovered starting **9**.

a quantitative conversion into **8** was achieved with 3.0 equiv of DCC and 0.3 equiv of DMAP.

Removal of the benzyl groups was first attempted at −30 °C with Li-naphthlene[27] in THF. However, the reaction was very complicated, signaling the inapplicability of this method. Then, we tried hydrogenolysis[28] over $Pd(OH)_2$−C (with the catalyst loading ranging from 19% to 30% with respect to the substrate weight) at different H_2 pressures in different solvents with or without heating. The reaction was relatively slow and incomplete in MeCN or EtOH. Even with a rather high catalyst loading, the debenzylation occurred only at the carboxylic position. Under less forcing conditions but with MeOH as the solvent, the expected product **9** was obtained in 100% yield. The yield of **9**, however, dropped substantially (70%) if the hydrogen pressure was reduced to 1 atm.

The subsequent step was the lactonization. As already mentioned in the Introduction, closing the nine-membered dilactone ring in the presence of an ester functionality on the C-8 was part of the earliest endeavors because of the apparent conciseness associated with the synthesis. Kinoshita first tried this using $(F_3CCO)_2O$ to activate the carboxylic group. The yield was only 0.8%.[17b] A few years later, they used another reagent (**16**) to repeat the same reaction and managed to raise the yield



to 13%.[18a] Under otherwise identical conditions, a substrate with a benzyl group instead of an isovaleryl group on the C-8 oxygen resulted in a ring-closure yield of 33%,[18a] clearly showing the adverse effect of the ester group. Similarly, in Wasserman's synthesis, where the carboxylic group activated as an *N*,*N*-dibenzoyl amide, the ring-closure yield was only 20%. Probably discouraged by these earlier "hopeless" results, more recent synthetic studies[17c,d] abandoned the most straightforward strategy and turned to a round-about "C-8 protection−deprotection−acylation" one, which did succeed in an elegant lactonization. However, at the same time the new results also strengthened the notion that closing the dilactone ring in high yields in the presence of the C-8 ester group is impossible. After a careful literature study, we noticed that there were many other well-known lactonzation protocols that had never been examined in the context of antimycin synthesis. Therefore, we wished to explore the issue again in the present work.

Once the precursor **9** was in hand, we set out to probe the key issue of lactonization. Indeed, the acid **9** was extremely labile to side reactions leading to many unidentified fragments in trace amounts. We examined a number of existing mild lactonization protocols under a range of reaction conditions. Some of the results are listed in Table 1. First, we tried the 2,4,6-trichlorobenzoyl chloride[29] (TCBC), one of the best-known lactonization reagents. To our disappointment, the yield of the desired **11** was very low (entries 1−3). Changing the reactant ratios and/or the temperature/time did not help. In some cases, even no **11** could be detected. Next, we examined the DCC/DMAP/DMAP·HCl protocol[30] of Boden and Keck. The yield was somewhat improved (entry 4), but still too low. Then, we switched to the conditions[17c,d] of Tsunoda, which were reported to give the highest yield in closing the dilactone ring. Although in their case the C-8 hydroxyl group was masked with a TIPS rather than a labile ester group as in our substrate, under the given circumstances it still deserved a try.

However, to our disappointment again, repeated tries with either $Cu(OTf)_2$·PhH as reported in the literature[17d] or $(CuOTf)_2$·PhH under a variety of combinations of reagent ratios and/or temperatures/time led to **11** in yields up to only 15% (cf. entries 5−7), reconfirming that ring-closure in the presence of the C-8 ester functionality (which made the substrate much more labile than the TIPS protected one) was indeed a difficulty.

At this stage, a novel lactonization protocol developed by Palomo[31] et al. appeared in the literature and caught our attention immediately. However, experiments soon showed that this method was not applicable in our case either (entry 8). By then our bold plan to construct the nine-membered dilactone ring in the presence of the C-8 ester functionality looked almost

(27) Liu, H.-J.; Yip, J.; Shia, K.-S. *Tetrahedron Lett.* **1997**, *38*, 2253−2256.

(28) Shimano et al. have reported such a debenzylation of a similar intermediate under less forcing conditions in their synthesis of UK-2A: Shimano, M.; Kamei, N.; Shibata, T.; Inoguehi, K.; Ito, N.; Ikari, T.; Senda, H. *Tetrahedron* **1998**, *54*, 12745−12774.

(29) Yamaguchi, M.; Innaga, J.; Hirata, K.; Saeki, H.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.

(30) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394−2395.

(31) Palomo, C.; Oiarbide, M.; Garcia, J. M.; Gonzalez, A.; Pazos, R.; Odriozola, J. M.; Banuelos, P.; Tello, M.; Linden, A. *J. Org. Chem.* **2004**, *69*, 4126−4134.

hopeless and all the potential merits of the carefully designed synthetic sequence would be simply spoiled by the discouragingly low yielding ring-closure. As a last try before giving up, we next tried Shiina's[32] MNBA (**10**) protocol, which was actually reported two years before Palomo's procedure. In the beginning we did not consider it as one of the potentially promising methods for our transformation because all the examples shown in those papers were relatively simple and did not carry sensitive functionalities. Interestingly, in the end this method previously ignored by us turned out to be the right one for the key step of our synthesis, which was apparently much superior to all other methods so far examined. After a few optimization efforts, the yield of **11** reached an unprecedented summit (58%, entry 11), which was further raised later to 62% by addition[33] of finely powdered activated 4 Å molecular sieves to the reaction system (entry 12).

The subsequent two steps were done in a manner similar to that in Shimano's[29] synthesis of UK-2A. Thus, the Boc group in **11** was cleaved with trifluoroacetic acid in CH_2Cl_2 and the intermediate amine was immediately coupled with the properly protected aromatic acid **12**[29] by treatment with EDC/HOBt to give **13**, which on removal of the benzyl protecting group by hydrogenolysis over 10% Pd on charcoal under 1 atm of H_2 led to the target molecule antimycin A_{3b} (**14**) in quantitative yield.

In brief, a straightforward synthesis of A_{3b} has been completed. By employing a low-cost yet effective $TiCl_4$-mediated aldolization, early installation of the C-8 ester, minimizing protecting group manipulation, and closing the dilactone ring in the presence of the C-8 ester (a long-pending problem in the synthesis of antimycins), the efficiency of the whole sequence was greatly improved, providing a seemingly most efficient approach to the enantioselective synthesis of this class of compounds to date. Apart from the advantages of this route in the number of steps of the reactions involved, the cost of the reagents/starting materials, and the operational convenience, the 34.5% overall yield was striking, which was much higher than those in the literature (<3.6%, the highest formal overall yield, without taking into account the yield over the 12 steps leading to the advanced chiral starting material[18a]).

Experimental Section

Acylation of the Chiral Auxiliary (1). With cooling (ice−water bath) and stirring, NEt_3 (1.28 mL, 9.1 mmmol) was added dropwise to a mixture of (*R*)-4-phenyloxazolidine-2-thione (1.162 g, 6.5 mmol) and LiCl (327 mg, 7.7 mmol) in dry THF (35 mL), followed by hexanoyl chloride (1.20 mL, 8.4 mmol). The cooling bath was removed. The mixture was stirred at ambient temperature until TLC showed completion of the reaction (16.5 h). The solvent was removed on a rotary evaporator. To the yellow residue was added aqueous saturated $NaHCO_3$. The mixture was then extracted with EtOAc three times. The combined organic phases were washed with water and dried over Na_2SO_4. Removal of the solvent left an oily residue, which was chromatographed on silica gel (5:1 *n*-hexane/EtOAc) to produce **1** as a yellow gum (1.80 g, 100%): $[\alpha]^{27}_D$ −26.56 (*c* 0.45, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.42−7.23 (m, 5H), 6.64 (dd, J = 8.9, 3.5 Hz, 1H), 4.89 (t, J = 8.7 Hz, 1H), 4.42 (dd, J = 9.2, 3.2 Hz, 1H), 3.40−3.19 (m, 2H), 1.70−1.53 (m, 2H), 1.38−1.21 (m, 4H), 0.85 (t, J = 7.0 Hz, 3H). FT-IR (NaCl) 1702, 1374, 1274, 1242, 1189, 1091, 1069 cm^{-1}. EI-MS *m*/*z* (%) 277 (M^+, 12.4), 100 (100), 43 (85), 120 (72.5), 180 (69.9), 55 (49.3), 41 (39.8), 91 (37.9), 103 (28.7). Anal. Calcd for $C_{15}H_{19}NO_2S$: C, 64.95; H, 6.90; N, 5.05. Found C, 65.19; H, 6.92; N, 4.83.

Aldol Condensation between 1 and 2 (3). $TiCl_4$ (0.56 mL, 5.6 mmol) was added dropwise to a solution of **1** (1.108 g, 4.0 mmol) in dry CH_2Cl_2 (16 mL) stirred at −50 °C under an argon atmosphere. The mixture was stirred at the same temperature for 20 min then at −20 °C for another 2 h before TMEDA (1.51 mL, 10 mmol) was introduced (yielding a dark red mixture). Stirring was continued at −20 °C for 1 h. The aldehyde **2** (1.692 g, 9.0 mmol) was then added dropwise. The mixture was stirred at −20 °C for 3 h then at −5 °C until TLC showed complete disappearance of the starting **1** (ca. 6 h). The reaction was quenched with water (4 mL). The mixture was filtered through Celite and the filtrate was extracted with diethyl ether (3 × 100 mL). The combined organic phases were washed with water and brine, then dried over Na_2SO_4. Removal of the solvent left a yellow residue, which was chromatographed on silica gel (8:1 *n*-hexane/EtOAc) to afford **3** as a yellow oil (1.680 g, 90%): $[\alpha]^{24}_D$ −60.49 (*c* 0.98, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.42−7.24 (m, 5H), 5.75 (dd, J = 8.8, 3.5 Hz,1H), 5.15 (dt, J = 4.9, 6.9 Hz, 1H), 4.79 (t, J = 9.0 Hz, 1H), 4.46 (dd, J = 9.3, 3.6 Hz, 1H), 3.91−3.77 (m, 2H), 2.65 (br s, 1H), 1.81−1.68 (m, 2H), 1.17 (d, J = 5.9 Hz, 3H), 1.14−0.76 (m, 4H), 0.97 (t, J = 8.0 Hz, 9H), 0.70 (t, J = 7.3 Hz, 3H), 0.61 (q, J = 8.0 Hz, 6H). FT-IR (film) 3535, 1699, 1457, 1367, 1339, 1183, 1084 cm^{-1}. ESI-MS *m*/*z* 488.3 ($[M + Na]^+$). Anal. Calcd for $C_{24}H_{39}NO_4SSi$: C, 61.89; H, 8.44; N, 3.01. Found C, 62.12; H, 8.69; N, 2.79.

Acylation of C-8 OH (4). To a solution of **3** (3.695 g, 8.0 mmol) in dry CH_2Cl_2 (40 mL) stirred in an ice−water bath were added in turn dry pyridine (1.285 mL, 15.9 mmol), DMAP (97 mg, 0.8 mmol), and isovaleryl chloride (1.950 mL, 1.92 mmol). The mixture was stirred at the same temperature for 8 h before being quenched with aqueous saturated $CuSO_4$ (5 mL). The mixture was extracted with diethyl ether (3 × 50 mL). The combined organic phases were washed with water and brine, then dried over Na_2SO_4. Removal of the solvent left a yellow residue, which was chromatographed on silica gel (20:1 *n*-hexane/EtOAc) to afford **4** as a pale yellow oil (3.909 g, 89%): $[\alpha]^{27}_D$ −80.29 (*c* 1.00, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.40 (m, 5H), 5.52 (dd, J = 8.4, 2.4 Hz, 1H), 5.42 (dt, J = 10.2, 3.7 Hz, 1H), 5.10 (dd, J = 6.7, 4.6 Hz, 1H), 4.80 (t, J = 8.6 Hz, 1H), 4.40 (dd, J = 8.9, 2.7 Hz, 1H), 3.92 (quint, J = 6.0 Hz, 1H), 2.19 (d, J = 6.1 Hz, 2H), 2.18−2.00 (m, 1H), 1.80−1.62 (m, 1H), 1.16 (d, J = 6.1 Hz, 6H), 1.00−0.82 (m, 17H), 0.78 (t, J = 7.1 Hz, 3H), 0.60 (q, J = 7.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.2, 174.5, 172.7, 139.1, 129.1, 128.6, 125.8, 76.4, 73.8, 67.7, 62.9, 43.4, 43.3, 28.7, 25.5, 25.2, 22.9, 22.44, 22.40, 20.7, 13.8, 6.9, 5.1. FT-IR (film) 3034, 1738, 1704, 1457, 1367, 1185, 1012 cm^{-1}. ESI-MS *m*/*z* 572.7 ($[M + Na]^+$). Anal. Calcd for $C_{29}H_{47}NO_5SSi$: C, 63.35; H, 8.62; N, 2.55. Found: C, 63.61; H, 8.64; N, 2.46.

Removal of the Chiral Auxiliary (5). A solution of **4** (628 mg, 1.14 mmol), BnOH (0.35 mL, 3.42 mmol), and DMAP (140 mg, 1.14 mmol) in CH_2Cl_2 (5.7 mL) was stirred at ambient temperature for 32 h. Another portion of BnOH (0.23 mL, 2.28 mmol) was added. After being stirred for another 14.5 h, the reaction mixture was diluted with diethyl ether (100 mL), washed with water (3 × 30 mL), and dried over anhydrous Na_2SO_4. The crude residue after removal of the solvents was chromatographed on silica gel (30:1 *n*-hexane/EtOAc) to afford the pure **5**[22] as a colorless oil (403 mg, 74%).

Removal of the TES Group in 5 (6). Powdered $NaIO_4$ (321 mg, 1.5 mmol) was added to a solution of **5** (288 mg, 0.6 mmol) in a mixture of THF (3.0 mL) and water (1.0 mL) stirred in an ice−water bath until TLC showed disappearance of the starting **5**

(32) (a) Shiina, I.; Kubota, M.; Ibuka, R. *Tetrahedron Lett.* **2002**, *43*, 7535−7539. (b) Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822−1830.

(33) For an earlier example of using molecular sieves in the TCBC protocol, see: Fleming, I.; Ghosh, S. K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2733−2747. When using the TCBC protocol in our case, addition of 4 Å MS raised the yield of **11** to 21%.

(ca. 3 h). The reaction mixture was diluted with diethyl ether, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent on a rotary evaporator left **6** as a colorless oil (215 mg, 98%): $[\alpha]^{19}_D$ +14.10 (*c* 0.80, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.32−7.42 (m, 5H), 5.13 (s, 2H), 5.11 (dd, J = 8.0, 5.2 Hz, 1H), 3.87−3.78 (m. 1H), 2.70 (dq, J = 10.4, 3.9 Hz, 1H), 2.22 (d, J = 8.1 Hz, 2H), 2.20−2.02 (m, 1H), 1.95 (br s, 1H), 1.60−1.40 (m, 1H), 1.38−1.20 (m, 5H), 1.18 (d, J = 8.6 Hz, 3H), 0.95 (d, J = 6.5 Hz, 6H), 0.82 (t, J = 6.0 Hz, 3H). FT-IR (film) 3495, 1739, 1456, 1293, 1167, 1119 cm^{-1}. ESI-MS *m*/*z* 387.2 ([M + Na]$^+$). ESI-HRMS calcd for $C_{21}H_{32}O_5Na$ ([M + Na]$^+$) 387.2142, found 387.2152. (Note: Compound **6** is not very stable and therefore should be utilized in the next step as soon as possible.)

Coupling of 6 with 7 (8). A solution of **6** (215 mg, 0.59 mmol) in dry CH_2Cl_2 (3 mL) was added to a mixture of **7** (556 mg, 1.80 mmol) and DCC (371 mg, 1.80 mmol) in dry CH_2Cl_2 (4.2 mL) stirred in an ice−water bath. The mixture was stirred at the same temperature for 50 min before DMAP (22 mg, 0.18 mmol) was introduced. The stirring was then continued at ambient temperature until TLC showed disappearance of the starting **6** (ca. 26 h). The reaction mixture was then diluted with diethyl ether (50 mL), washed with water and brine, and dried over anhydrous Na_2SO_4. The residue after removal of the solvent on a rotary evaporator was chromatographed on silica gel (5:1 *n*-hexane/EtOAc) to afford **8** as a colorless sticky oil (391 mg, 100%): $[\alpha]^{28}_D$ +7.25 (*c* 1.3, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.20 (m, 10H), 5.36−5.24 (m, 2H), 5.17−5.01 (m, 3H), 4.50 (d, J = 11.0 Hz, 1H), 4.41 (d, J = 11.3 Hz, 1H), 4.25 (d, J = 9.7 Hz, 1H), 4.21−4.10 (m, 1H), 2.65−2.56 (m, 1H), 2.16 (d, J = 5.4 Hz, 2H), 2.14−2.03 (m, 1H), 1.40 (s, 9H), 1.40−1.00 (m, 6H), 1.20 (d, J = 6.3 Hz, 6H), 0.92 (d, J = 6.2 Hz, 6H), 0.78 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 171.9, 170.1, 156.0, 138.1, 135.5, 128.5, 128.5, 128.33, 128.26, 127.6, 127.5, 79.8, 75.1, 73.5, 71.1, 70.9, 66.8, 58.3, 46.5, 43.3, 29.1, 28.2, 27.6, 25.6, 22.5, 22.3, 16.4, 14.9, 13.7. FT-IR (film) 3452, 1740, 1721, 1498, 1455, 1367, 1252, 1164, 1096 cm^{-1}. ESI-MS *m*/*z* 678.3 ([M + Na]$^+$). ESI-HRMS calcd for $C_{37}H_{53}O_9NNa$ ([M + Na]$^+$) 678.3635, found 678.3612.

Removal of the Benzyl Groups (9). A solution of **8** (202 mg, 0.31 mmol) in MeOH (18 mL) containing 20% $Pd(OH)_2$−C (30 mg) was stirred in a stainless bomb under H_2 (30 atm) at 40 °C for 8 h. The solid was filtered off. The combined filtrate and washings were concentrated to dryness to give **9** (150 mg, 100%): $[\alpha]^{17}_D$ +2.25 (*c* 1.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 5.58−6.04 (br s, 2H), 5.51 (d, J = 9.7 Hz, 1H), 5.36 (dd, J = 9.7, 3.2 Hz, 1H), 5.13 (dd, J = 6.4, 3.7 Hz, 1H), 4.30−4.15 (m, 2H), 2.57 (dt, J = 3.4, 9.5 Hz, 1H), 2.28 (d, J = 7.1 Hz, 2H), 2.20−2.05 (m, 1H), 1.70−1.48 (m, 1H), 1.44 (s, 9H), 1.38−1.18 (m, 5H), 1.28 (d, J = 6.3 Hz, 3H), 1.21 (d, J = 6.3 Hz, 3H), 0.98 (d, J = 6.7 Hz, 6H), 0.87 (t, J = 6.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 173.2, 170.3, 156.4, 79.9, 73.5, 71.5, 67.1, 58.9, 47.1, 43.3, 29.6, 28.9, 28.2, 25.6, 22.4, 22.3, 22.3, 19.4, 14.2, 13.7. FT-IR (film) 3448 (br), 1743, 1721, 1509, 1368, 1166, 1068 cm^{-1}. ESI-MS *m*/*z* 474.3 ([M−H]$^-$). ESI-HRMS calcd for $C_{23}H_{41}O_9NNa$ ([M + Na]$^+$) 498.2674, found 498.2687.

Closure of the Nine-Membered Dilactone Ring (11). A solution of **9** (24 mg, 0.05 mol) in dry toleune (8 mL) was added over 7 h through a syringe pump to a solution of **10** (26 mg, 0.075 mmol), DMAP (27 mg, 0.30 mmol), and crushed activated 4 Å molecular sieves (595 mg) in dry toluene (17 mL) stirred at the ambient temperature under an atmosphere of argon. After the completion of the addition, the stirring was continued for another 16 h. The reaction mixture was then filtered. The filtrate was diluted with EtOAc (50 mL), washed with aqueous saturated $NaHCO_3$, water, and brine, and dried over anhydrous Na_2SO_4. The residue after removal of the solvent on a rotary evaporator was chromatographed on silica gel (10:1 *n*-hexane/EtOAc) to afford **11** as a colorless oil (14 mg, 62%): $[\alpha]^{26}_D$ +48.1 (*c* 0.60, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 5.53 (t, J = 5.3 Hz, 1H), 5.25 (br s, 1H), 5.04 (t, J = 10 Hz, 1H), 4.96−4.75 (m, 2H), 2.46 (td, J = 10.8, 2.4 Hz, 1H), 2.23 (d, J = 6.7 Hz, 2H), 2.13 (septet, J = 6.8 Hz, 1H), 1.74−1.61 (m, 1H), 1.45 (s, 9H), 1.35−1.19 (m, 4H), 1.29 (d, J = 6.7 Hz, 3H), 1.26 (d, J = 6.2 Hz, 3H), 1.18−1.07 (m, 1H), 0.98 (d, J = 6.6 Hz, 6H), 0.85 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 171.7, 170.6, 154.8, 80.3, 75.6, 74.2, 71.3, 54.5, 50.1, 43.2, 29.7, 29.2, 28.2, 25.5, 22.4, 17.9, 14.7, 13.8. FT-IR (film) 3381, 1750, 1720, 1502, 1453, 1367, 1250, 1162, 1113, 1028 cm^{-1}. ESI-MS *m*/*z* 457 ([M + NH_4]$^+$). ESI-HRMS calcd for $C_{23}H_{39}O_8NNa$ ([M + Na]$^+$) 480.2568, found 480.2578.

Removal of Boc and Acylation with 12 (13). F_3CCO_2H (0.25 mL) was added dropwise to a solution of **11** (15 mg, 0.033 mmol) in CH_2Cl_2 (0.25 mL) stirred at ambient temperature (ca. 20 °C). The mixture was then stirred for 9.5 h before being diluted with ethyl acetate (20 mL), then washed successively with saturated $NaHCO_3$ (1 × 10 mL), water (3 × 10 mL), and brine. The combined organic phases were dried over Na_2SO_4. Removal of the solvent left the crude de-Boc product as a pale yellow oil (12 mg, 100%), which was used directly in the subsequent step without further purification.

To a stirred solution of the above obtained crude de-Boc product (12 mg, 0.033 mmol) and **12** (12 mg, 0.033 mmol) in dry DMF (0.5 mL) was added HOBt (8 mg, 0.060 mmol), EDC·HCl (12 mg, 0.060 mmol), and *N*-methylmorphorine (24 mg, 0.231 mmol) successively. After being stirringed at 30 °C for 23 h, the mixture was diluted with EtOAc (30 mL), washed with water (3 × 10 mL) and brine, and dried over Na_2SO_4. The residue after removal of the solvent was chromatographed on silica gel (3:1 *n*-hexane/EtOAc) to give **13** as a white solid (19 mg, 94%): Mp 159−160 °C. $[\alpha]^{25}_D$ +6.8 (*c* 0.39, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, J = 11.2 Hz, 0.3H), 8.44 (dd, J = 8.1, 1.5 Hz, 1H), 8.22−8.08 (m, 2H), 7.75 (dd, J = 7.9, 1.4 Hz, 1H), 7.45−7.30 (m, 5.7H), 7.26 (t, J = 8.2 Hz, 1H), 5.70 (br quint, J = 7.0 Hz, 1H), 5.35 (t, J = 7.8 Hz, 1H), 5.19 (d, J = 11.4 Hz, 1H), 5.09 (t, J = 10.2 Hz, 1H), 4.97 (dq, J = 10.1, 6.2 Hz, 1H), 4.85 (d, J = 11.2 Hz, 1H), 2.50 (td, J = 10.5, 2.2 Hz, 1H), 2.26 (d, J = 6.5 Hz, 2H), 2.21−2.10 (m, 1H), 1.30 (d, J = 5.8 Hz, 3H), 1.29 (d, J = 7.0 Hz, 3H), 1.34−1.20 (m, 6H), 0.99 (d, J = 6.5 Hz, 6H), 0.86 (t, J = 6.9 Hz, 3H). FT-IR (film) 3366, 1749, 1701, 1665, 1519, 1161, 1029 cm^{-1}. MALDI-MS *m*/*z* 633.6 ([M + Na]$^+$). MALDI-HRMS calcd for $C_{33}H_{42}N_2O_9Na$ ([M + Na]$^+$) 633.2783, found 633.2786.

Freeing the Phenolic OH Leading to Antimycin A_{3b} (14). A mixture of **13** (10 mg, 0.016 mmol) and 10% Pd−C (5 mg) in EtOAc (1 mL) was stirred at 30 °C under H_2 (1 atm) until TLC showed disappearance of **13** (ca. 6.5 h). The catalyst was removed by filtration and the filtrate was concentrated to dryness to give a white needle (10 mg, 100%): Mp 173−174 °C. $[\alpha]^{23}_D$ +79.3 (*c* 0.33, $CHCl_3$) (lit.[17b] mp 174−174.5 °C, $[\alpha]^{24}_D$ +80 (*c* 0.2, $CHCl_3$); lit.[32] mp 174.5−175 °C, $[\alpha]^{23}_D$ +79.4 (*c* 1.0, $CHCl_3$); lit.[5] mp 170.5−171.5 °C, $[\alpha]^{23}_D$ +64.3 (*c* 1.0, $CHCl_3$)). ^1H NMR (300 MHz, $CDCl_3$) δ 12.63 (s, 1H), 8.56 (d, J = 7.8 Hz, 1H), 8.51 (d, J = 1.3 Hz, 1H), 7.93 (s, 1H), 7.23 (d, J = 1.1 Hz, 1H), 7.07 (d, J = 7.4 Hz, 1H), 6.93 (t, J = 8.1 Hz, 1H), 5.73 (dq, J = 7.4, 6.7 Hz, 1H), 5.29 (t, J = 7.7 Hz, 1H), 5.10 (t, J = 9.9 Hz, 1H), 4.99 (dq, J = 9.8, 6.0 Hz, 1H), 2.51 (td, J = 10.8, 2.7 Hz, 1H), 2.26 (d, J = 6.6 Hz, 2H), 2.21−2.07 (m, 1H), 1.78−1.63 (m, 1H), 1.40−1.10 (m, 5H), 1.32 (d, J = 6.1 Hz, 3H), 1.30 (d, J = 6.4 Hz, 3H), 0.99 (d, J = 6.8 Hz, 6H), 0.87 (t, J = 6.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 171.7, 170.0, 169.3, 159.1, 150.6, 127.4, 124.7, 120.1, 118.9, 112.4, 75.3, 74.8, 70.9, 53.6, 50.1, 43.2, 29.2, 28.2, 25.5, 22.4, 22.4, 17.8, 15.0, 13.8. FT-IR (film) 3368, 1749, 1686, 1642, 1610, 1534, 1431, 1364, 1254, 1179, 1161, 1114, 1027 cm^{-1}. ESI-MS *m*/*z* 543.2 ([M + Na]$^+$). (Consistent with data reported in the literature.)

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Supporting Information Available: The NMR spectra of **6**, **8**, **9**, **11**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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