JOC*Article*

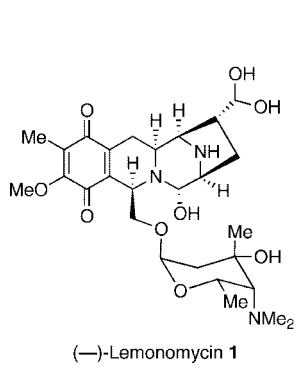
Synthetic Studies on (−)-Lemonomycin: An Efficient Asymmetric Synthesis of Lemonomycinone Amide

Yan-Chao Wu,[†] Guillaume Bernadat,[†] Géraldine Masson,[†] Cédric Couturier,[†] Thierry Schlama,[§,‡] and Jieping Zhu*[,†]

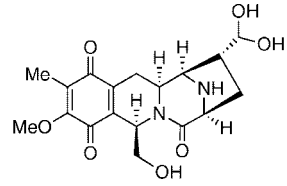
Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette Cedex, France, and RHODIA, Centre de Recherches et de Technologie de Lyon (CRTL), avenue des Frères Perret, BP 62, F-69192 Saint-Fons Cedex, France

zhu@icsn.cnrs-gif.fr

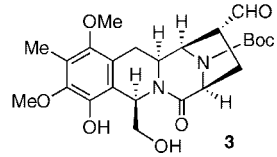
Received December 23, 2008



(—)-Lemonomycin **1**



Lemonomycinone amide **2**



3

Asymmetric synthesis of lemonomycinone amide (**2**) was accomplished from readily accessible starting materials. Enantioselective alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester (**11**) by 5-*tert*-butyldimethylsilyloxy-2,4-dimethoxy-3-methylbenzyl bromide (**10**) in the presence of Corey-Lygo's phase transfer catalyst [*O*-(9)-ally-*N*-(9′-anthracenylmethyl) cinchonidium bromide, 0.1 equiv] afforded, after chemoselective hydrolysis of the imine function (THF/H_2O/AcOH), the substituted L-*tert*-butyl phenylalanate **13** in 85% yield. A Pictet−Spengler reaction of **14** with benzyloxyacetaldehyde (**15**) provided the 1,3-*cis*-disubstituted tetrahydroisoquinoline **16** in 85% yield as a single diastereomer. Coupling of hindered secondary amine **16** with amino acid **9** was accomplished under carefully controlled conditions to furnish the amide **22**, which was in turn converted to hemiaminal **24**. A hafnium triflate catalyzed conversion of hemiaminal to α-amino thioether followed by a silver tetrafluoroborate promoted intramolecular Mannich reaction of **26** afforded the tetracycle **27** in excellent overall yields. Debenzylation of **27** [$Pd(OH)_2$, H_2, MeOH, 0 °C], removal of *N*-Boc function (aqueous 3 N HCl, MeOH/H_2O), and oxidation of hydroquinone to quinone [$(NH_4)_2Ce(NO_3)_6$, H_2O, rt] afforded the lemonomycinone amide **2** in 76% yield over three steps.

Introduction

(−)-Lemonomycin (**1**, Figure 1) is a tetrahydroisoquinoline alkaloid[1] that was isolated in 1964 from the fermentation broth of *Streptomyces candidus* (LL-AP191).[2] However, its structure was not elucidated until 2000 by He and co-workers at Wyeth-Ayerst.[3] Lemonomycin exhibited potent antibiotic activities against methicillin-resistant *Staphylococcus aureus* (MRSA), *Bacillus subtilis*, and vancomycin-resistant *Enterococcus faecium* (VREF).[4] It is also cytotoxic against a human colon tumor cell line (HCT-116). The broad spectra of antibiotic activities in conjunction with its fascinating molecular architecture have

[†] Institut de Chimie des Substances Naturelles.
[‡] RHODIA.
[§] Present address: Novartis Pharma AG, Chemical & Analytical Development (CHAD), CH-4002 Basel, Switzerland.

(1) For a comprehensive review of the chemistry and biology related to the antitumor antibiotic tetrahydroisoquinoline alkaloids, see: Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669–1730. For a recent review on the syntheses of naphthyridinomycin and lemonomycin, see: Siengalewicz, P.; Rinner, U.; Mulzer, J. *Chem. Soc. Rev.* **2008**, *37*, 2676–2690.

(2) Whaley, H. A.; Patterson, E. L.; Dann, M.; Shay, A. J.; Porter, J. N. *Antimicrob. Agents Chemother.* **1964**, *8*, 83–86.
(3) He, H.; Shen, B.; Carter, G. T. *Tetrahedron Lett.* **2000**, *41*, 2067–2071.
(4) Zhu, J. *Expert. Opin. Ther. Pat.* **1999**, *9*, 1005–1019.

10.1021/jo8027449 CCC: $40.75
Published on Web 02/05/2009

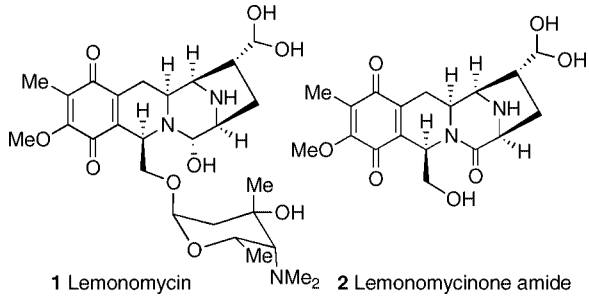
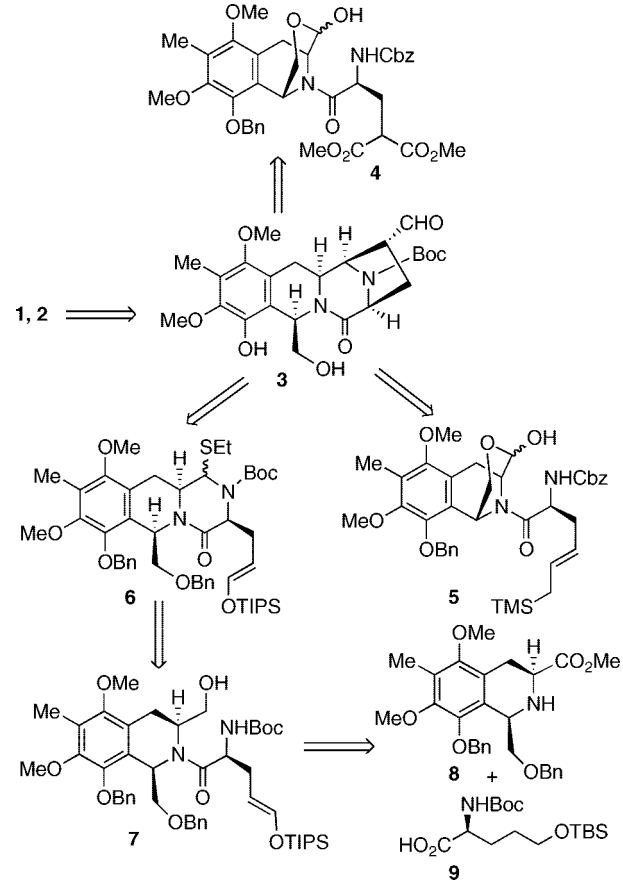


FIGURE 1. Structures of lemonomycin and lemonomycinone amide.

made lemonomycin an attractive synthetic target. Stoltz and coworkers reported the first and only total synthesis of (−)-lemonomycin in 2003,[5] whereas Magnus's group reported the synthesis of racemic lemonomycinone amide (**2**) in 2005.[6] Fukuyama,[7] Williams,[8] and Mulzer[9] have also developed efficient strategies for the access of the advanced tetracyclic core of lemonomycin. In connection with our ongoing program dealing with the synthesis of tetrahydroisoquinoline-containing alkaloids,[10] we have been interested in the synthesis of lemonomycin.[11] Since the quinone and the hemiaminal moiety of this alkaloid were labile to many reaction conditions, they were thought to be installed at latter stages of the synthesis. Consequently, tetracyclic core **3** was considered as a key intermediate in our synthesis (Scheme 1). For the construction of the 3,8-diazabicycle [3.2.1]-octane ring system of **3**, an intramolecular nucleophilic addition to the incipient *N*-acyliminium intermediate was sought.[12] However, cyclization of **4**[11] and **5**[13] using tethered malonate and allylsilane as nucleophiles was unsuccessful in our initial studies. The seminal contribution of Hiemstra[14] and Magnus[6] on the use of enolsilane as nucleophile for trapping the *N*-acyliminium intermediate,[15] as well as our own work on the application of such strategy for the synthesis of (−)-quinocarcin,[16] prompted us to examine the cyclization of **6**.[17] Compound **6** should be accessible from aminoalcohol **7**, which in turn could be prepared by coupling of tetrahydroisoquinoline **8** and amino acid **9**. We report herein the realization of this strategy for the synthesis of (−)-lemonomycin precursor **3** and lemonomycinone amide (**2**).

SCHEME 1. Retrosynthetic Analysis of 1 and 2



Results and Discussion

Synthesis of substituted tetrahydroisoquinoline **8** is shown in Scheme 2. 5-*tert*-Butyldimethylsilyloxy-2,4-dimethoxy-3-methylbenzyl bromide (**10**) was prepared from 2,6-dimethoxytoluene in seven steps with 61% overall yield (see Supporting Information).[18] Enantioselective alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester (**11**) by **10** in the presence of Corey-Lygo's phase transfer catalyst[19,20] (**12**, *O*-(9)-allyl-*N*-(9′-anthracenylmethyl) cinchonidium bromide, 0.1 equiv) afforded, after chemoselective hydrolysis of the imine function (THF/H_2O/AcOH), the amino ester **13** in 85% yield. The absolute configuration of **13** was deduced on the basis of the Corey-Lygo empiric model and was confirmed by Trost's method (Supporting Information).[21] The ee of **13** was determined to be higher than 98%. Removal of the silyl ether from **13** gave free amino phenol **14** in 92% yield. A slow addition of

(5) Ashley, E. R.; Cruz, E. G.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 15000–15001.

(6) Magnus, P.; Matthews, K. S. *J. Am. Chem. Soc.* **2005**, *127*, 12476–12477.

(7) Fukuyama, T.; Rikimaru, K.; Mori, K.; Kan, T. *Chem. Commun.* **2005**, 394–396.

(8) Vincent, G.; Chen, Y.; Lane, J. W.; Williams, R. M. *Heterocycles* **2007**, *72*, 385–398.

(9) Siengalewicz, P.; Brecker, L.; Mulzer, J. *Synlett* **2008**, 2443–2446.

(10) (a) Chen, X. C.; Chen, J. C.; De Paolis, M.; Zhu, J. *J. Org. Chem.* **2005**, *70*, 4397–4408. (b) Chen, J.; Chen, X.; Bois-Choussy, M.; Zhu, J. *J. Am. Chem. Soc.* **2006**, *128*, 87–89. (c) Chen, J. C.; Chen, X. C.; Willot, M.; Zhu, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 8028–8032. (d) Chen, X. C.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 3962–3965.

(11) Couturier, C.; Schlama, T.; Zhu, J. *Synlett* **2006**, 1691–1694.

(12) For recent reviews, see: (a) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organis Synthesis*; Trost, B., Fleming, I., Heathcock, C. H., Eds.; Pergmon: Oxford, 1991; Vol. 2, pp 1047−1082. (b) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431–1628. (c) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311–2352.

(13) Cedric Couturier, PhD thesis, Ecole Polytechnique, 17 October 2005. Cyclization using allylsilane as internal nucleophile wherein an amide group in **5** was replaced by aminonitrile function has been successfully applied to the synthesis of advanced lemonomycin intermediate and quinocarcin; see ref 9 and Kwon, S.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 16796–16797.

(14) Hiemstra, H.; Vijn, R. J.; Speckamp, W. N. *J. Org. Chem.* **1988**, *53*, 3884–3886.

(15) For intermolecular reaction of enolsilane and *N*-acyliminium, see: Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172–1176.

(16) Wu, Y.-C.; Liron, M.; Zhu, J. *J. Am. Chem. Soc.* **2008**, *130*, 7148–7152.

(17) For an example using amino thioether as a precursor of *N*-acyliminium, see: Padwa, A.; Waterson, A. G. *Tetrahedron* **2000**, *56*, 10159–10173.

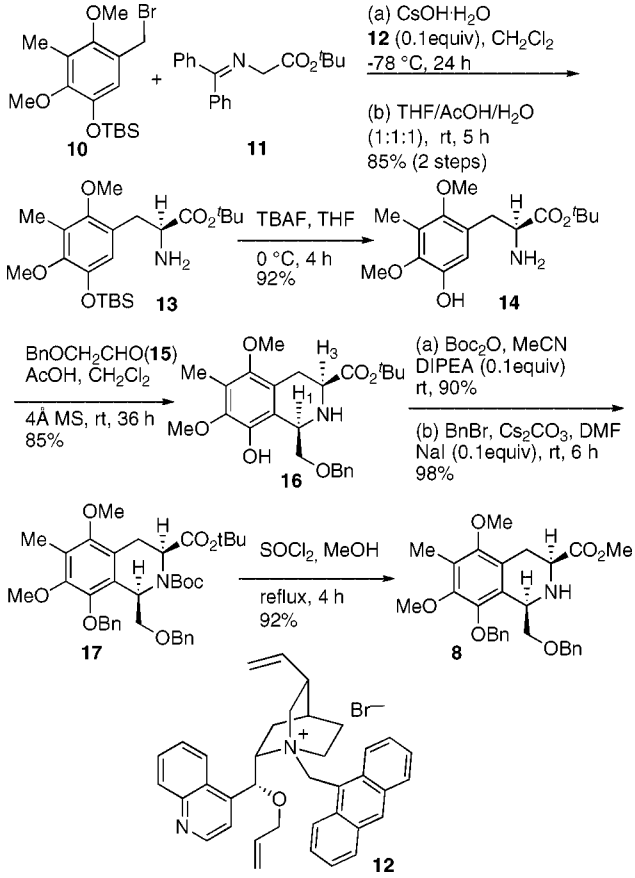
(18) (a) Godfrey, I. M.; Sargent, M. V.; Elix, J. A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1353–1354. (b) Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 2745–2752. (c) Fukuyama, T.; Sachleben, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 4957–4958. (d) Fukuyama, T.; Yang, L.; Ajeck, K. L.; Sachleben, R. A. *J. Am. Chem. Soc.* **1990**, *112*, 3712–3713.

(19) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414–12415.

(20) (a) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595–8598. (b) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518–525.

(21) (a) Ott, R.; Sauber, K. *Tetrahedron Lett.* **1972**, 3873–3878. (b) Trost, B. M.; Bunt, R. C.; Pulley, S. R. *J. Org. Chem.* **1994**, *59*, 4202–4205.

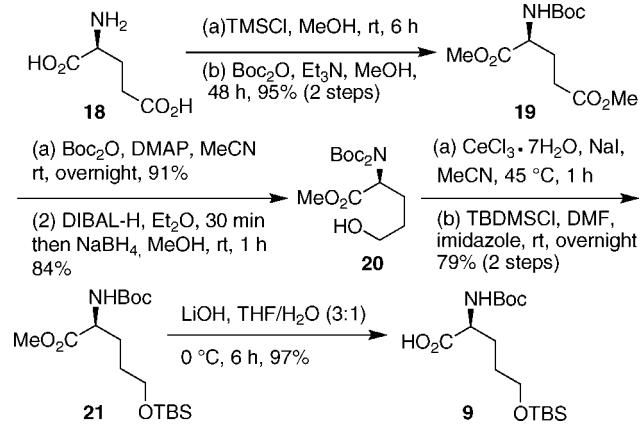
SCHEME 2. Synthesis of Tetrahydroisoquinoline 8



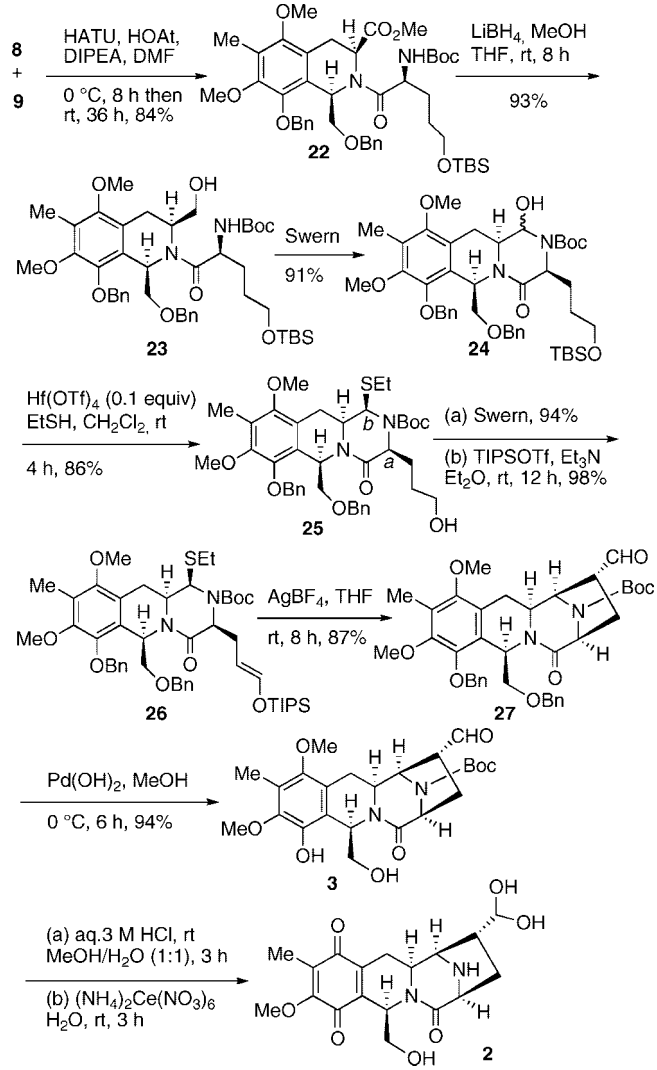
a dichloromethane solution of benzyloxyacetaldehyde (**15**) to the reaction mixture containing **14**, acetic acid (1.1 equiv), and 4 Å molecular sieves in dichloromethane provided the Pictet−Spengler adduct **16** in 85% yield as a single diastereomer. The 1,3-*cis* relative stereochemistry of **16** was deduced from the observed NOE correlation between H_1 and H_3 (Supporting Information) and is in accordance with literature precedents.[10,22] A *tert*-butoxycarbonylation of the secondary amine followed by benzylation of phenol (BnBr, Cs_2CO_3, DMF) in the presence of a catalytic amount of sodium iodide converted **16** to **17** in excellent overall yield. Transesterification of a *tert*-butyl ester to a methyl ester with concurrent removal of the *N*-Boc function from **17** was realized in one operation (MeOH/$SOCl_2$) to afford the desired tetrahydroisoquinoline **8** in 92% yield.

Synthesis of amino acid **9** is depicted in Scheme 3. The (*S*)-methyl 2-(*N*,*N*-di-Boc-amino)-5-hydroxypentanoate (**20**) was prepared from L-glutamic acid (**18**) in four steps with 73% overall yield.[23] *N*-Monodeprotection of **20** ($CeCl_3 \cdot 7H_2O$, NaI, MeCN) followed by silylation of the primary hydroxy group provided compound **21** in 79% yield. It has to be noted that lactonization of **20** was not observed under these mild conditions. Finally, hydrolysis of **21** with lithium hydroxide afforded amino acid **9** in 97% yield.

SCHEME 3. Synthesis of Amino Acid 9



SCHEME 4. Synthesis of the Core Structure of Lemonomycin and Lemonomycinone Amide

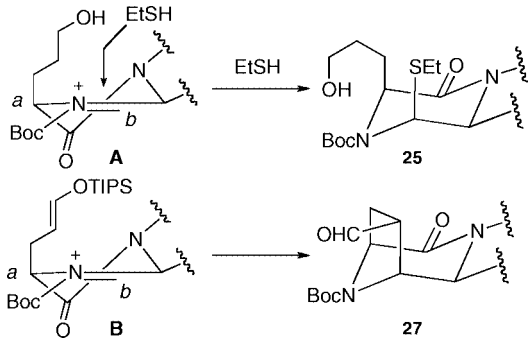


With the tetrahydroisoquinoline **8** and amino acid **9** in hands, synthesis of lemonomycinone amide was realized as shown in Scheme 4. Coupling of hindered secondary amine **8** with amino acid **9** was accomplished by a one-pot temperature-controlled peptide coupling strategy. Thus, esterification of **9** with 1-hy-

(22) For 1,3-*cis* selective Pictet−Spengler reactions, see: (a) Massiot, G.; Mulamba, T. *J. Chem. Soc., Chem. Commun.* **1983**, 1147–1149. (b) Bailey, P. D.; Hollinshead, S. P.; McLay, N. R.; Morgan, K.; Palmer, S. J.; Prince, S. N.; Reynolds, C. D.; Wood, S. D. *J. Chem. Soc., Perkin Trans. 1* **1993**, 431–439. (c) Myers, A. G.; Kung, D. W.; Zhong, B.; Movassaghi, M.; Kwon, S. *J. Am. Chem. Soc.* **1999**, *121*, 8401–8402. (d) Myers, A. G.; Kung, D. W. *J. Am. Chem. Soc.* **1999**, *121*, 10828–10829.

(23) (a) Kokotos, G.; Padron, J. M.; Martin, T.; Gibbons, W. A.; Martin, V. S. *J. Org. Chem.* **1998**, *63*, 3741–3744. (b) Jia, Y.; Zhu, J. *J. Org. Chem.* **2006**, *71*, 7826–7834.

SCHEME 5. Conformational Consideration on the Formation of 25 and 27



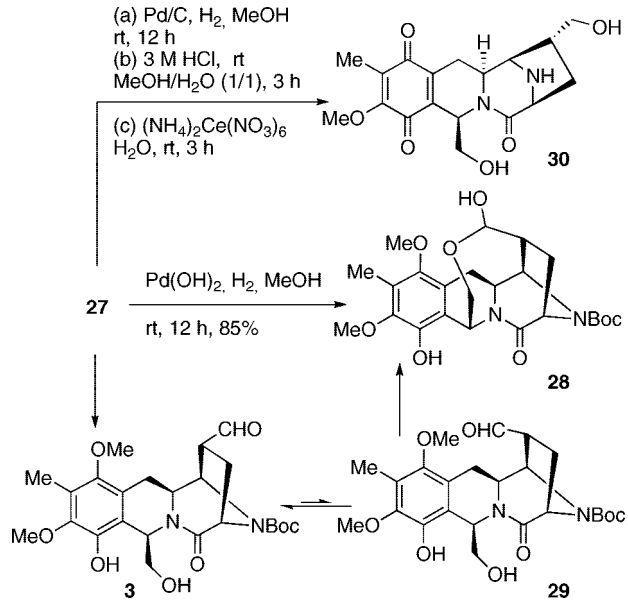
droxy-7-azabenzotriazol (HOAt) (HATU, DIPEA, DMF, 0 °C) afforded the transient activated ester, which underwent aminolysis with amine **8** at room temperature to produce the amide **22** in 84% yield (92% based on conversion) without detectable epimerization. Reduction of methyl ester **22** with lithium borohydride gave primary alcohol **23**, which upon Swern oxidation afforded directly the hemiaminal **24** as a mixture of two diastereomers (ratio 3/2).

Treatment of **24** with EtSH under our recently developed conditions [0.1 equiv of $Hf(OTf)_4$, CH_2Cl_2, rt][24] afforded amino thioether **25** in 86% yield, with concurrent removal of *O*-TBS function as a single diastereomer. The stereoselective formation of **25** with a C_a,C_b-*cis* relative stereochemistry indicated that conformer **A** (Scheme 5), wherein the C_a substituent adopted a pseudoaxial position, was the low-energy conformation of the *N*-acyliminium intermediate resulting from **24**. Such spatial arrangement minimized indeed the unfavorable allylic $A^{1,2}$ strain[25] encountered in the alternative conformation wherein the C_a substitutent was in a pseudoequatorial position. Although the selectivity observed in the formation of **25** is of no consequence, it did provide an important hint that the subsequent intramolecular Mannich reaction of **26** could be a conformationally favored process.[26] Indeed, if the *N*-acyliminium intermediate resulting from **26** has the same conformational preference, then the desired cyclization would be expected to be facile via conformer **B** (Scheme 5).

Chemoselective Swern oxidation of **25** followed by silyl enol ether formation (TIPSOTf, Et_3N, Et_2O, room temperature) afforded compound **26** as a single diastereomer in 92% overall yield. The intramolecular Mannich reaction of **26** in the presence of silver tetrafluoroborate furnished tetracyclic aldehyde **27** as a single diastereomer in 87% yield. Removal of two *O*-Bn functions in compound **27** under carefully controlled hydrogenolysis conditions [$Pd(OH)_2$/C, MeOH, 0 °C] afforded tetracyclic alcohol **3** in 94% yield. Compound **3** was properly protected for the further elaboration to (−)-lemonomycin. In the present study, we converted **3** to lemonomycinone amide (**2**) following literature precedents.[6] Thus, treatment of **3** under mild acidic conditions followed by oxidation with ammonium cerium(VI) nitrate afforded **2** in 81% yield.

It is interesting to note that hydrogenolysis of **27** in the presence of Pearlman's catalyst has to be carried out at 0 °C. Indeed, performing this transformation at room temperature under otherwise identical conditions led to the formation of hemiacetal **28** in 85% yield (Scheme 6). We hypothesized that

SCHEME 6. Hydrogenolysis of 27: Unexpected Observation



under the basic hydrogenolysis conditions, compound **3** with an *exo*-aldehyde function is partially epimerized to *endo*-aldehyde **29**. Although **29** might be thermodynamically less stable than **3** for steric reasons, the formation of hemiacetal might drive the equilibrium toward the final formation of **28**. This epimerization was, however, effectively suppressed when the reaction was carried out at 0 °C. We have also performed *O*-debenzylation in the presence of Pd/C (H_2, MeOH, rt). However, under these conditions, aldehyde was reduced to primary alcohol, as was confirmed by its further conversion to quinone **30** following a *N*-deprotection/oxidation sequence (78% yield over three steps).

Conclusions

In summary, we describe concise syntheses of advanced intermediate **3** for lemonomycin and lemonomycinone amide **2** with an overall yield of 15% and 12%, respectively, starting from readily accessible 2,6-dimethoxytoluene. Key steps included (a) enantioselective alkylation of glycine template for the synthesis of non-proteinogenic amino acid, (b) epimerization-free coupling of hindered secondary amine with amino acid, (c) hafnium triflate catalyzed conversion of highly functionalized aminal to amino thioether, and (d) intramolecular Mannich reaction for the construction of bridged bicyclic ring system. We assumed that formation of hemiacetal **28** from **27** could have an important implication in designing a synthetic strategy for bioxalomycin,[27] and we are currently exploiting opportunities offered by this serendipity.

Experimental Section

(1*R*,3*S*)-*tert*-Butyl 1-((Benzyloxy)methyl)-1,2,3,4-tetrahydro-8-hydroxy-5,7-dimethoxy-6-methylisoquinoline-3-carboxylate (16). To a solution of amino phenol **14** (250.0 mg, 800.0 μmol) in 8 mL of dichloromethane were added acetic acid (AcOH, 51 μL, 880.0 μmol) and 4 Å molecular sieves sequentially at room temperature.

(24) Wu, Y.-C.; Zhu, J. *J. Org. Chem.* **2008**, *73*, 9522–9524.
(25) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289–296.
(26) Blankenstein, J.; Zhu, J. *Eur. J. Org. Chem.* **2005**, 1949–1964.

(27) For total synthesis of bioxalomycin, see: (a) Evans, D. A.; Illig, C. R.; Saddler, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 2478–2479. (b) Fukuyama, T.; Li, L.; Laird, A. A.; Frank, R. K. *J. Am. Chem. Soc.* **1987**, *109*, 1587–1589. (c) Kaniskan, H. Ü.; Garner, P. *J. Am. Chem. Soc.* **2007**, *129*, 15460–15461.

The mixture was degassed with argon and added slowly to a solution of benzyloxyacetaldehyde (**15**, 136.7 mg, 880.0 μmol) in 4 mL of dichloromethane over 12 h. The mixture was stirred at room temperature for 24 h, filtered though celite, and saturated aqueous sodium bicarbonate solution ($NaHCO_3$, 20 mL) was added. The two layers were separated, and the aqueous layer was extracted with dichloromethane (20 mL × 3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography (gradient elution 0.5% → 5% methanol in dichloromethanes) to provide tetrahydroisoquinoline **16** (302.7 mg) in 85% yield. Pale yellow foam; $[\alpha]^{27}_D$ −114.6° (*c* 2.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.25 (m, 5 H), 6.49 (br, 1 H), 4.58 (d, 1 H, *J* = 12.0 Hz), 4.53 (d, 1 H, *J* = 12.0 Hz), 4.49 (br, 1 H), 4.10 (dd, 1 H, *J* = 9.0, 4.5 Hz), 3.75−3.72 (m, 4 H), 3.66 (s, 3 H), 3.38 (dd, 1 H, *J* = 11.0, 2.5 Hz), 3.18 (dd, 1 H, *J* = 15.5, 2.5 Hz), 2.56 (dd, 1 H, *J* = 15.5, 11.0 Hz), 2.22 (s, 3 H), 1.51 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 149.1, 144.1, 142.8, 138.0, 128.2, 127.53, 127.50, 127.46, 125.1, 122.0, 120.5, 81.3, 73.5, 73.1, 60.5, 60.3, 55.4, 53.4, 28.0, 27.9, 9.4 ppm; FTIR (film) 2977, 2934, 1730, 1455, 1412, 1367, 1280, 1248, 1192, 1156, 1110, 1059, 1004, 847, 739, 698 cm^{-1}; HRMS (TOF MS ES$^+$) *m*/*z* calcd for $C_{25}H_{34}NO_6$ [M + H]$^+$ 444.2386, found 444.2394.

(1*R*,3*S*)-Di-*tert*-butyl 8-(Benzyloxy)-1-((benzyloxy)methyl)-3,4-dihydro-5,7-dimethoxy-6-methylisoquinoline-2,3(1*H*)-dicarboxylate (17). To a solution of amine **16** (769.8 mg, 1.7 mmol) in acetonitrile (ACN, 43 mL) were added *N*,*N*-diisopropylethylamine (DIPEA, 30.0 μL, 0.2 mmol) and di-*tert*-butyldicarbonate (Boc_2O, 401.7 mg, 1.8 mmol) sequentially at 0 °C. The mixture was stirred at room temperature for overnight, and 100 mL of ethyl acetate and 50 mL of water were added. The two layers were separated, and the aqueous layer was extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography (gradient elution 10% → 25% ethyl acetate in heptanes) to afford (1*R*,3*S*)-di-*tert*-butyl 1-((benzyloxy)methyl)-3,4-dihydro-8-hydroxy-5,7-dimethoxy-6-methylisoquinoline-2,3(1*H*)-dicarboxylate (849.2 mg) in 90% yield. White solids; mp = 35−36 °C; $[\alpha]^{27}_D$ −4.0° (*c* 9.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 1.6:1 mixture of rotamers, the major rotamer was listed) δ 7.40−7.15 (m, 5 H), 6.39 (s, 1 H), 5.75 (dd, 1 H, *J* = 9.0, 4.5 Hz), 4.63 (d, 1 H, *J* = 11.7 Hz), 4.52 (d, 1 H, *J* = 11.7 Hz), 4.14 (dd, 1 H, *J* = 12.0, 6.9 Hz), 3.96 (dd, 1 H, *J* = 8.4, 4.5 Hz), 3.77 (s, 3 H), 3.66 (dd, 1 H, *J* = 9.0, 8.4 Hz), 3.65 (s, 3 H), 3.43 (dd, 1 H, *J* = 15.3, 6.9 Hz), 2.61 (dd, 1 H, *J* = 15.3, 12.0 Hz), 2.22 (s, 3 H), 1.48 (s, 9 H), 1.45 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, the major rotamer was listed) δ 172.3, 154.7, 148.5, 145.4, 142.6, 137.7, 128.1, 127.5, 127.4, 123.6, 122.4, 120.6, 81.1, 80.8, 73.1, 72.7, 61.0, 60.4, 55.9, 48.7, 28.2, 27.9, 23.8, 9.5 ppm; FTIR (film) 2976, 2864, 1732, 1684, 1455, 1414, 1392, 1365, 1348, 1317, 1253, 1150, 1111, 1057, 1004, 848, 750, 697 cm^{-1}; HRMS (TOF MS ES$^+$) *m*/*z* calcd for $C_{30}H_{41}NO_8Na$ [M + Na]$^+$ 566.2730, found 566.2723.

To a mixture of (1*R*,3*S*)-di-*tert*-butyl 1-((benzyloxy)methyl)-3,4-dihydro-8-hydroxy-5,7-dimethoxy-6-methylisoquinoline-2,3(1*H*)-dicarboxylate (840.7 mg, 1.5 mmol), cesium carbonate (Cs_2CO_3, 658.2 mg, 2.0 mmol), and sodium iodine (NaI, 22.7 mg, 0.15 mmol) in 6 mL of *N*,*N*-dimethyl formamide (DMF) was added benzyl bromide (BnBr, 225 μL, 1.8 mmol) at room temperature. The mixture was stirred at room temperature for 6 h, and 50 mL of ethyl acetate and 30 mL of water were added. The two layers were separated, and the aqueous layer was extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography (gradient elution 1% → 20% ethyl acetate in heptanes) to afford protected tetrahydroisoquinoline **17** (926.6 mg) in 98% yield. Colorless oil; $[\alpha]^{27}_D$ −17.3° (*c* 7.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52−7.15 (m, 10 H), 6.04 and 5.83 (t, 1 H, *J* = 5.0 Hz), 5.12−5.01 (m, 2 H), 4.50−4.47 (m, 2 H), 4.18−4.08 (m, 1 H), 3.84−3.65 (m, 8 H), 3.53−3.47 (m, 1 H), 2.83−2.77 (m, 1 H), 2.26 (s, 3 H), 1.52 (s, 9 H), 1.50 and 1.48 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6 (171.4), 154.2 (154.1), 151.2 (151.1), 150.0, 144.4 (144.3), 138.1 (137.9), 137.6 (137.2), 127.9 (d), 127.5 (127.4), 127.3, 127.2, 127.0 (126.9), 126.7 (126.6), 124.1 (123.9), 121.4, 80.3 (80.1), 79.8 (79.6), 77.2, 74.3, 73.8, 72.1 (71.8), 60.2 (59.6), 56.1 (55.6), 49.1 (48.3), 27.8, 27.5 (27.3), 23.7, 8.9 ppm; FTIR (film) 2974, 2934, 1737, 1693, 1454, 1412, 1390, 1365, 1315, 1253, 1152, 1136, 1114, 1067, 1028, 1006, 966, 851, 736, 697 cm^{-1}; HRMS (TOF MS ES$^+$) *m*/*z* calcd for $C_{37}H_{47}NO_8Na$ [M + Na]$^+$ 656.3199, found 656.3157.

(1*R*,3*S*)-Methyl 8-(Benzyloxy)-1-((benzyloxy)methyl)-1,2,3,4-tetrahydro-5,7-dimethoxy-6-methylisoquinoline-3-carboxylate (8). To a solution of protected tetrahydroisoquinoline **17** (127.7 mg, 2.0 mmol) in 5 mL of methanol was added sulfonyl chloride ($SOCl_2$, 0.1 mL) at 0 °C. The mixture was stirred at reflux for 4 h and concentrated, and 50 mL of ethyl acetate and 20 mL of saturated aqueous sodium bicarbonate solution were added. The two layers were separated, and the aqueous layer was extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography (gradient elution 10% → 30% ethyl acetate in heptanes) to afford tetrahydroisoquinoline **8** (90.6 mg) in 92% yield. Pale yellow foam; $[\alpha]^{26}_D$ −49.5° (*c* 1.7, $CHCl_3$); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 1.6:1 mixture of rotamers, the major rotamer was listed) δ 7.41−7.25 (m, 10 H), 5.08 (d, 1 H, *J* = 11.1 Hz), 4.89 (d, 1 H, *J* = 11.1 Hz), 4.48 (s, 2 H), 4.43 (dd, 1 H, *J* = 7.8, 2.1 Hz), 4.18 (dd, 1 H, *J* = 8.4, 2.1 Hz), 3.84 (s, 3 H), 3.79 (s, 3 H), 3.72 (s, 3 H), 3.66 (dd, 1 H, *J* = 8.4, 7.8 Hz), 3.50 (dd, 1 H, *J* = 10.8, 3.0 Hz), 3.26 (dd, 1 H, *J* = 15.9, 3.0 Hz), 2.69 (dd, 1 H, *J* = 15.9, 10.8 Hz), 2.27 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, the major rotamer was listed) δ 173.3, 152.1, 150.0, 148.5, 145.3, 138.3, 137.4, 128.2, 128.0, 127.9, 127.7, 127.2, 127.1, 126.9, 124.6, 123.4, 74.3, 73.6, 72.7, 60.0, 59.9, 54.5, 53.6, 51.8, 27.6, 9.1 ppm; FTIR (film) 3365, 2934, 2858, 1738, 1454, 1409, 1335, 1280, 1255, 1196, 1110, 1061, 1028, 1002, 735, 697 cm^{-1}; HRMS (TOF MS ES$^+$) *m*/*z* calcd for $C_{29}H_{33}NO_6Na$ [M + Na]$^+$ 514.2206, found 514.2219.

Amide Ester 22. To a solution of tetrahydroisoquinoline **8** (800.0 mg, 1.6 mmol) and (*S*)-5-*tert*-butyl-dimethylsilyloxy-2-(*N*-Boc-amino)pentanoic acid (**9**, 678.7 mg, 2.0 mmol) in 8 mL of DMF, DIPEA (1.3 mL, 8.1 mmol) were added 3*H*-1,2,3-triazolo-[4,5-*b*]pyridin-3-ol (HOAt, 265.8 mg, 2.0 mmol) and *O*-(7-azabenzoptriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluroniumhexafluorophosphat (HATU, 742.6 mg, 2.0 mmol) sequentially at 0 °C. The mixture was stirred at 0 °C for overnight, stirred at room temperature for 36 h, and ethyl acetate (50 mL) and water (20 mL) were added sequentially. The two layers were separated, and the aqueous layer was extracted with ethyl acetate (50 mL × 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography (gradient elution 10% → 30% ethyl acetate in heptanes) to afford amide ester **22** (1.1 g) in 84% yield. Yellow oil; $[\alpha]^{25}_D$ +2.1° (*c* 1.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 6.2:1 mixture of rotamers, the major rotamer was listed) δ 7.63−7.17 (m, 10 H), 5.91 (t, 1 H, *J* = 6.0 Hz), 5.21 (d, 1 H, *J* = 10.8 Hz), 5.09−4.83 (m, 3 H), 4.55−4.40 (m, 3 H), 3.78 (s, 3 H), 3.77 (s, 3 H), 3.68 (s, 3 H), 3.60−3.43 (m, 5 H), 2.77 (dd, 1 H, *J* = 15.3, 12.0 Hz), 2.23 (s, 3 H), 1.90−1.70 (m, 2 H), 1.68−1.47 (m, 2 H), 1.33 (s, 9 H), 0.89 (s, 9 H), 0.03 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 172.6, 155.1, 151.5, 150.7, 144.8, 138.0, 137.9, 128.3, 128.2, 127.7, 127.6, 127.5, 127.2, 126.9, 125.3, 121.5, 79.1, 74.8, 73.1, 72.4, 62.9, 60.9, 60.3, 55.2, 52.2, 51.6, 50.6, 29.8, 28.8, 28.3, 26.0, 23.6, 18.3, 9.4, −5.3 ppm; FTIR (film) 2930, 2856, 1750, 1705, 1645, 1497, 1455, 1418, 1365, 1254, 1172, 1094, 1066, 1008, 835, 299, 735, 698 cm^{-1}; HRMS (TOF MS ES$^+$) *m*/*z* calcd for $C_{45}H_{64}N_2O_{10}NaSi$ [M + Na]$^+$ 843.4228, found 843.4232.

Amide Alcohol 23. To a solution of amide ester **22** (50.0 mg, 60.9 μmol) in 6 mL of tetrahydrofuran (THF) were added lithium borohydride ($LiBH_4$, 5.6 mg, 243.6 μmol) and methanol (10 μL, 243.6 μmol) sequentially at 0 °C. The mixture was stirred at room temperature for 8 h, and ethyl acetate (20 mL) and water (10 mL) were added sequentially. The two layers were separated, and the aqueous layer was extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography (gradient elution 10% → 50% ethyl acetate in heptanes) to afford amide alcohol **23** (45.0 mg) in 93% yield. Pale foam; $[\alpha]^{25}_D$ +1.7° (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 1:1 mixture of rotamers) δ 7.60−7.10 (m, 10 H), 6.30 (dd, 1 H, *J* = 9.0, 5.1 Hz), 5.42 (d, 1 H, *J* = 8.4 Hz), 5.21 (d, 1 H, *J* = 11.1 Hz), 4.99 (d, 1 H, *J* = 11.1 Hz), 4.93−4.82 (m, 1 H), 4.68−4.33 (m, 3 H), 3.80 (d, 1 H, *J* = 3.9 Hz), 3.67 (s, 6 H), 3.65−2.71 (m, 6 H), 2.22 (s, 3 H), 1.90−1.52 (m, 4 H), 1.44 (s, 9 H), 0.90 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 173.5, 150.0, 144.7, 136.9, 128.5, 128.4, 128.34, 128.30, 128.2, 128.1, 128.0, 127.8, 127.7, 127.4, 122.9, 79.5, 75.0, 73.3, 71.1, 66.2, 62.7, 60.7, 60.3, 52.8, 51.4, 47.3, 30.0, 28.9, 28.4, 25.9, 22.5, 18.3, 9.4, −5.4 ppm; FTIR (film) 2928, 2856, 1709, 1633, 1497, 1454, 1414, 1365, 1251, 1169, 1097, 1007, 835, 776, 734, 698 cm^{-1}; HRMS (TOF MS ES$^+$) *m*/*z* calcd for $C_{44}H_{64}N_2O_9NaSi$ $[M + Na]^+$: 815.4279, found 815.4279.

Hemiaminal 24. To a solution of oxalyl chloride (85 μL, 974.7 μmol) in 3 mL of dichloromethane, dimethyl sulfoxide (DMSO, 175 μL, 2.4 mmol) was added at −78 °C. The mixture was stirred at −78 °C for 30 min, and then amide alcohol **23** (386.5 mg, 487.3 μmol) in a solution of dichloromethane (1 mL) was added. The obtained mixture was stirred at −78 °C for 30 min, and added dropwise with triethylamine (Et_3N, 409 μL, 2.9 mmol). The mixture was stirred at −78 °C for 30 min, stirred at 0 °C for 30 min, and 10 mL of water was added. The two layers were separated, and the aqueous layer was extracted with dichloromethane (50 mL × 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography (gradient elution 5% → 25% ethyl acetate in heptanes) to afford hemiaminal **24** (350.0 mg, 91% yield) as foam in a 3:2 mixture of diastereomers.

trans-Isomer **24a**: foam; $[\alpha]^{25}_D$ +8.5° (*c* 4.0, $CHCl_3$); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5 H), 7.20−7.19 (m, 3 H), 7.05−7.03 (m, 2 H), 6.66 (d, 1 H, *J* = 1.0 Hz), 5.57 (t, 1 H, *J* = 3.0 Hz), 5.01 (d, 1 H, *J* = 11.5 Hz), 4.98 (d, 1 H, *J* = 11.5 Hz), 4.78 (t, 1 H, *J* = 8.5 Hz), 4.45 (dd, 1 H, *J* = 11.5, 4.0 Hz), 4.32 (s, 2 H), 3.84 (d, 1 H, *J* = 5.0 Hz), 3.82 (s, 3 H), 3.68 (s, 3 H), 3.66 (d, 1 H, *J* = 5.0 Hz), 3.46 (dd, 1 H, *J* = 9.5, 3.0 Hz), 3.40 (dd, 1 H, *J* = 14.5, 4.0 Hz), 3.28 (dt, 1 H, *J* = 9.5, 3.0 Hz), 2.62 (dd, 1 H, *J* = 14.5, 11.5 Hz), 2.26 (s, 3 H), 2.13−1.76 (m, 2 H), 1.73−1.60 (m, 2 H), 1.48 (s, 9 H), 0.91 (s, 9 H), 0.07 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$, the major rotamer was listed) δ 167.9, 156.3, 151.4, 150.4, 144.4, 138.4, 137.2, 128.5, 128.4, 128.3, 128.14, 128.09, 127.6, 127.3, 124.6, 124.5, 82.5, 81.4, 74.7, 73.0, 72.3, 63.3, 62.6, 60.9, 60.3, 58.5, 57.0, 50.6, 49.0, 28.3, 26.0, 25.4, 18.4, 9.4, −5.3 ppm; FTIR (film) 2928, 2855, 1697, 1651, 1454, 1392, 1366, 1336, 1255, 1164, 1100, 1061, 1006, 835, 775, 735, 698 cm^{-1}; HRMS (TOF MS ES$^+$) *m*/*z* calcd for $C_{44}H_{62}N_2O_9NaSi$ $[M + Na]^+$ 813.4122, found 813.4141.

cis-Isomer **24b**: foam; $[\alpha]^{25}_D$ +10.5 ° (*c* 5.0, $CHCl_3$); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.09 (m, 10 H), 5.98−5.55 (m, 2 H), 5.01 (d, 1 H, *J* = 10.8 Hz), 4.95 (d, 1 H, *J* = 10.8 Hz), 4.51−4.32 (m, 3 H), 3.93−3.75 (m, 4 H), 3.68 (s, 3 H), 3.62 (t, 2 H, *J* = 6.0 Hz), 3.49 (dd, 1 H, *J* = 9.3, 3.0 Hz), 3.38 (dd, 1 H, *J* = 12.3, 3.6 Hz), 3.08 (dd, 1 H, *J* = 15.0, 3.6 Hz), 3.28 (dd, 1 H, *J* = 15.0, 12.3 Hz), 2.25 (s, 3 H), 2.16−1.55 (m, 4 H), 1.49 (s, 9 H), 0.90 (s, 9 H), 0.06 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 151.3, 150.4, 144.7, 138.0, 137.2, 128.5, 128.4, 128.1, 127.9, 127.6, 127.4, 127.3, 126.9, 124.6, 124.0, 81.2, 74.7, 73.0, 72.3, 63.3, 62.6, 60.9, 60.3, 57.0, 55.9, 49.0, 29.7, 28.3, 26.0, 25.9, 25.4, 18.4, 9.4, −5.3 ppm; FTIR (film) 2927, 2855, 1693, 1651, 1454, 1392, 1365, 1335, 1291, 1255, 1163, 1097, 1057, 1006, 939, 910, 834, 774, 752, 734, 697 cm^{-1}; HRMS (TOF MS ES$^+$) *m*/*z* calcd for $C_{44}H_{62}N_2O_9NaSi$ $[M + Na]^+$ 813.4122, found 813.4102.

Thioaminal 25. To a solution of hemiaminal **24** (66.7 mg, 84.3 μmol) and ethanethiol (EtSH, 630 μL, 8.4 mmol) in 1 mL of dichloromethane was added hafnium trifluoromethanesulfonate [$Hf(OTf)_4$, 6.5 mg, 8.4 μmol] at 0 °C. The mixture was stirred at room temperature for 4 h, and dichloromethane (20 mL) and water (10 mL) were added sequentially. The two layers were separated, and the aqueous layer was extracted with dichloromethane (20 mL × 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography (gradient elution 10% → 80% ethyl acetate in heptanes) to afford thioaminal **25** (53.3 mg) in 86% yield. Foam; $[\alpha]^{25}_D$ +44.2° (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28−7.03 (m, 10 H), 5.67−5.41 (m, 2 H), 4.91 (s, br, 2 H), 4.41−4.24 (m, 3 H), 3.74 (s, 3 H), 3.70−3.56 (m, 7 H), 3.43−3.35 (m, 1 H), 2.92−2.87 (m, 2 H), 2.69−2.38 (m, 4 H), 2.17 (s, 3 H), 1.42 (s, 9 H), 1.28−1.19 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$, the major rotamer was listed) δ 169.1, 150.5, 144.8, 138.6, 137.2, 128.6, 128.4, 128.3, 127.9, 127.8, 127.7, 127.4, 127.1, 126.7, 123.7, 81.7, 74.6, 72.7, 61.1, 60.3, 57.6, 57.3, 56.2, 54.2, 49.5, 33.7, 31.9, 29.7, 28.3, 26.8, 22.7, 14.9, 9.4 ppm; FTIR (film) 2929, 1693, 1651, 1455, 1413, 1385, 1311, 1257, 1161, 1117, 1058, 1008, 735, 697, 668 cm^{-1}; HRMS (TOF MS ES$^+$) *m*/*z* calcd for $C_{40}H_{52}N_2O_8NaS$ $[M + Na]^+$ 743.3342, found 743.3335.

Silyl Enol Ether 26. To a solution of oxalyl chloride (93 μL, 1.1 mmol) in 2 mL of dichloromethane was added dimethyl sulfoxide (183 μL, 2.5 mmol) at −78 °C. The mixture was stirred at −78 °C for 30 min, and amide thioaminal **25** (153.0 mg, 212.0 μmol) in a solution of dichloromethane (1 mL) was added. The obtained mixture was stirred at −78 °C for 30 min, and triethylamine (445.1 μL, 3.2 mmol) was added dropwise. The mixture was stirred at −78 °C for 30 min and stirred at 0 °C for 30 min, and 10 mL of water was added. The two layers were separated, and the aqueous layer was extracted with dichloromethane (30 mL × 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography (gradient elution 10% → 80% ethyl acetate in heptanes) to afford the aldehyde (143.4 mg) in 94% yield. Colorless oil; $[\alpha]^{27}_D$ +49.2° (*c* 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (s, 1 H), 7.25−7.05 (m, 10 H), 5.70−5.41 (m, 2 H), 4.91 (s, br, 2 H), 4.37−4.20 (m, 3 H), 3.73 (s, 3 H), 3.59−3.40 (m, 6 H), 2.94−2.89 (m, 4 H), 2.60−2.50 (m, 4 H), 2.16 (s, 3 H), 1.41 (s, 9 H), 1.26 (t, 3 H, *J* = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, the major rotamer was listed) δ 201.7, 167.8, 150.4, 144.8, 138.5, 137.3, 137.0, 128.6, 128.4, 128.2, 127.9, 127.7, 127.3, 127.0, 126.5, 124.6, 123.6, 81.6, 74.6, 72.7, 72.2, 61.0, 60.3, 49.3, 42.8, 31.8, 29.6, 29.3, 28.2, 26.7, 22.6, 14.8, 14.0, 9.4 ppm; FTIR (film) 2922, 1725, 1694, 1651, 1454, 1415, 1385, 1310, 1259, 1162, 1118, 699, 668 cm^{-1}; HRMS (TOF MS ES$^+$) *m*/*z* calcd for $C_{41}H_{53}N_2O_9NaS$ $[M + MeOH + Na]^+$ 773.3448, found 773.3442.

To a solution of this aldehyde (83.8 mg, 116.6 μmol) in 2 mL of diethyl ether (Et_2O) were added triethylamine (Et_3N, 82 μL, 582.8 μmol) and triisopropylsilyl trifluoromethanesulfonate (TIPSOTf, 63 μL, 233.1 μmol) sequentially at 0 °C. The mixture was stirred at room temperature for 12 h and quenched with saturated aqueous sodium bicarbonate solution (10 mL). The two layers were separated, and the aqueous layer was extracted with ethyl acetate (30 mL × 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography (gradient elution 1% → 20% ethyl acetate in heptanes) to afford silyl enol ether **26** (100.0 mg) in 98% yield. Colorless oil; $[\alpha]^{27}_D$ +62.0° (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29−7.02 (m, 10 H), 6.28 (d, 1 H, *J* = 11.7 Hz), 5.74 (t, 1 H, *J* = 4.8 Hz), 5.68 (d, 1 H, *J* =

2.7 Hz), 5.46−5.05 (m, 1 H), 4.95−4.85 (m, 2 H), 4.49−4.30 (m, 3 H), 3.73 (s, 3 H), 3.58−3.40 (m, 6 H), 3.16−2.43 (m, 6 H), 2.16 (s, 3 H), 1.41 (s, 9 H), 1.29−0.97 (m, 30 H); ^{13}C NMR (75 MHz, $CDCl_3$, the major rotamer was listed) δ 175.4, 167.8, 154.1, 151.2, 150.4, 144.8, 141.3, 138.6, 137.2, 128.5, 128.2, 127.9, 127.7, 127.3, 127.0, 124.5, 123.9, 108.5, 81.3, 72.7, 72.4, 61.0, 60.3, 59.5, 57.4, 49.3, 33.8, 28.1, 26.9, 24.4, 22.6, 17.7, 14.7, 11.9, 9.4 ppm; FTIR (film) 2927, 2865, 1693, 1656, 1454, 1413, 1384, 1307, 1248, 1165, 1117, 1009, 883, 696, 668 cm^{-1}; HRMS (TOF MS ES$^+$) *m/z* calcd for $C_{47}H_{72}N_2O_8NaSiS$ $[M + Na]^+$ 875.4676, found 875.4693.

Tetracyclic Aldehyde 27. To a solution of silyl enol ether **26** (57.8 mg, 66.0 μmol) in 3 mL of THF was added silver tetrafluoroborate ($AgBF_4$, 23.1 mg, 118.9 μmol) at room temperature. The mixture was stirred at room temperature for 8 h, and saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (20 mL) were added sequentially. The two layers were separated, and the aqueous layer was extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography (gradient elution 10% → 40% ethyl acetate in heptanes) to afford tetracyclic aldehyde **27** (37.8 mg) in 87% yield. White foam; $[\alpha]^{27}_D$ −41.5 ° (*c* 0.5, $CHCl_3$); colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.56 (s, 1H) 7.38−7.02 (m, 10 H), 5.43 (s, br, 1 H), 4.99 (d, 1 H, J = 11.0 Hz), 4.96 (d, 1 H, J = 11.0 Hz), 4.63 (s, br, 1 H), 4.57 (s, br, 1 H), 4.29 (d, 1 H, J = 11.5 Hz), 4.24 (d, 1 H, J = 11.5 Hz), 4.12 (dd, 1 H, J = 9.5, 3.5 Hz), 3.81 (s, 3 H), 3.69 (s, 3 H), 3.66−3.57 (m, 1 H), 3.34 (dd, 1 H, J = 9.5, 2.0 Hz), 3.08 (t, 1 H, J = 8.0 Hz), 2.92 (dd, 1 H, J = 13.5, 2.0 Hz), 2.71 (t, 1 H, J = 13.5 Hz), 2.42−2.32 (m, 1 H), 2.27 (s, 3 H), 2.04 (t, 1 H, J = 11.0 Hz), 1.43 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$, the major rotamer was listed) δ 198.9, 167.9, 150.9, 150.3, 144.2, 138.1, 136.9, 128.4, 128.2, 128.1, 127.8, 127.4, 126.4, 124.6, 124.3, 81.0, 74.4, 72.9, 71.4, 60.7, 60.1, 57.5, 56.8, 49.9, 48.5, 32.2, 28.0, 25.2, 9.3 ppm; FTIR (film) 2936, 2922, 2868, 2852, 1726, 1700, 1663, 1660, 1456, 1454, 1411, 1367, 1316, 1288, 1259, 1160, 1110, 1057, 1010, 801, 754, 698 cm^{-1}; HRMS (TOF MS ES$^+$) *m/z* calcd for $C_{38}H_{44}N_2O_8Na$ $[M + Na]^+$ 679.2995, found 679.3026.

Tetracyclic Alcohol 3. To a solution of tetracyclic aldehyde **27** (32.8 mg, 50.0 μmol) in 3 mL of methanol was added palladium hydroxide ($Pd(OH)_2$, moist, Pd content 20%, 10 mg] at 0 °C. The mixture was stirred at 0 °C under an atmosphere of hydrogen for 6 h, filtered through a plug of Celite, washed with methanol, and concentrated. The residue was purified by column chromatography (gradient elution 50% → 100% ethyl acetate in heptanes) to afford tetracyclic alcohol **3** (22.4 mg) in 94% yield. Foam; $[\alpha]^{25}_D$ −101.7° (*c* 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.74 (s, 1 H), 5.93 (s, 1 H), 5.63 (s, br, 1 H), 4.74 (s, 1 H), 4.67 (s, br, 1 H), 3.97 (dd, 1 H, J = 13.0, 3.5 Hz), 3.78 (s, 3 H), 3.68 (s, 3 H), 3.66−3.60 (m, 1 H), 3.33 (t, 1 H, J = 8.0 Hz), 3.07 (dd, 1 H, J = 13.0, 2.5 Hz), 2.61 (dd, 1 H, J = 14.5, 7.0 Hz), 2.57−2.47 (m, 1 H), 2.41−2.37 (m, 1 H), 2.24 (s, 3 H), 2.21 (m, 1 H), 1.43 (s, 9 H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.0, 170.1, 148.3, 144.6, 142.2, 124.0 (d), 123.5, 117.9, 81.6, 66.2, 61.2, 60.8, 60.4, 51.9, 50.8, 32.5, 28.2, 25.3, 21.0, 14.2, 9.7 ppm; FTIR (film) 3382, 2974, 2937, 1678, 1658, 1643, 1454, 1393, 1414, 1368, 1319, 1286, 1249, 1161, 1006, 913, 731 cm^{-1}; HRMS (TOF MS ES$^+$) *m/z* calcd for $C_{24}H_{32}N_2O_8Na$ $[M + Na]^+$ 499.2056. Found 499.2052.

Lemonomycinone Amide (2). To a solution of tetracyclic alcohol **3** (28.1 mg, 58.9 μmol) in 1.5 mL of methanol was added hydrochloric acid (HCl, 12 M, 0.5 mL) at 0 °C. The mixture was stirred at room temperature for 3 h, and concentrated. The residue was diluted with water (1.0 mL), and ammonium cerium(IV) nitrate (129.2 mg, 235.6 μmol) was added at room temperature. The mixture was stirred at room temperature for 3 h, purified on reverse phase HPLC, and lyophilized to afford lemonomycinone amide (**2**, 18.1 mg) in 81% yield. Orange foam; UV = 267.8; $[\alpha]^{25}_D$ −72.9° (*c* 0.8, D_2O); ^{1}H NMR (500 MHz, D_2O) δ 5.13 (d, 1 H, J = 4.5 Hz), 5.04 (s, br, 1 H), 4.38 (s, 1 H), 4.31 (d, 1 H, J = 6.5 Hz), 4.09 (dd, 1 H, J = 12.0, 3.5 Hz), 3.84 (dt, 1 H, J = 11.5, 3.0 Hz), 3.85 (s, 3 H); 3.51 (dd, 1 H, J = 12.0, 2.0 Hz), 2.93 (dd, J = 16.5, 3.0 Hz, 1 H), 2.81−2.77 (m, 1 H), 2.48−2.43 (m, 2 H), 2.26 (dt, 1 H, J = 14.5, 6.5 Hz), 1.96 (s, 3 H) ppm; ^{13}C NMR (75 MHz, D_2O) δ 187.0, 181.5, 167.2, 155.8, 142.7, 136.5, 131.2, 89.9, 61.5, 61.0, 59.6, 58.7, 55.0, 52.3, 41.5, 31.5, 23.5, 8.7 ppm; FTIR (D_2O): 3372, 1670, 1649, 1452, 1208 cm^{-1}; HRMS (TOF MS ES$^+$) *m/z* calcd for $C_{18}H_{23}N_2O_7$ $[M + H]^+$ 379.1505. Found 379.1511.

Acknowledgment. Financial support from CNRS is gratefully acknowledged. Y.C.W thanks a postdoctoral fellowship from ICSN and C.C. thanks Rhodia for a doctoral fellowship.

Supporting Information Available: Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8027449