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Synthesis of the oxa-bridged octalin system of two anti-anaerobe antibiotics, luminamicin and lustromycin

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Abstract—An efficient, stereocontrolled entry to the 11-oxatricyclo[5.3.1.^{1,7}0^{3,8}]undecane nucleus of luminamicin and lustromycin was afforded via intramolecular hetero-Michael addition of enone **7** followed by intramolecular aldol condensation of aldehyde **5** by way of the epimerization at the stereocenter attached by the aldehyde group.

The emergence of resistance against commonly-used antibiotics will be a long-lasting and serious clinical problem. We therefore need to continue the development of new medicines that have unique mechanisms of action. During the course of screening for biologically active compounds, we have found several novel anti-anaerobe antibiotics from actinomycetes origin, namely thiotetromycin,[1] clostomicin,[2] luminamicin (**1**),[3] and lustromycin (**2**).[4,5] The structure of luminamicin is identical to that of coloradocin, later isolated by McAlpin,[6] and is very similar to that of **2**. As shown in Figure 1, these structures consist of a *cis*-decalin ring system associated with a 10-membered macrolactone and a 14-membered macrolactone moiety having an enol ether conjugated with a maleic anhydride functionality. Luminamicin and lustromycin showed selective activity against anaerobic and micro-aerophilic bacteria, including pathogenic species of *Clostridium*, *Neisseria*, and *Haemophilus*, but were not active against most aerobic bacteria.[3,6] **1** and **2** might thus be new leads for medicines to compare with vancomycin, which is clinically used in pseudomembranous colitis therapy.

Kallmerten and Evans[7] have reported the construction of the C_{13}–O linkage of the 11-oxatricyclo[5.3.1.^{1,7}0^{3,8}]-undecane skeleton by intramolecular addition of a C_9 alcohol to an olefin using phenylselenenyl chloride in

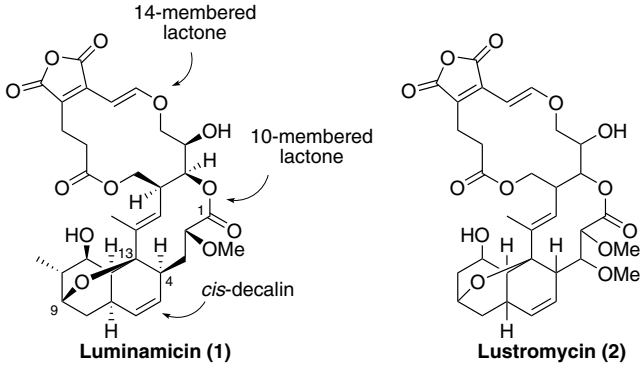

Figure 1. Structures of luminamicin (**1**) and lustromycin (**2**).

only modest yield. Gössinger et al.[8] have also reported the synthesis of the decalin subunit of coloradocin. Recently, our group has determined the absolute and relative stereochemistry of **1** using conformational analysis via high temperature molecular dynamics, NMR spectroscopy, and the modified Mosher method.[9] In conjunction with our continuing program directed toward the structure elucidation and syntheses of important antimicrobial natural products, we describe here studies of the synthesis of the oxa-bridged octalin system **4** of luminamicin and lustromycin.

We would set up compound **3** as a target compound for the southern moiety of **1**. Our retrosynthetic strategy of the southern moiety **3** was shown in Scheme 1. The

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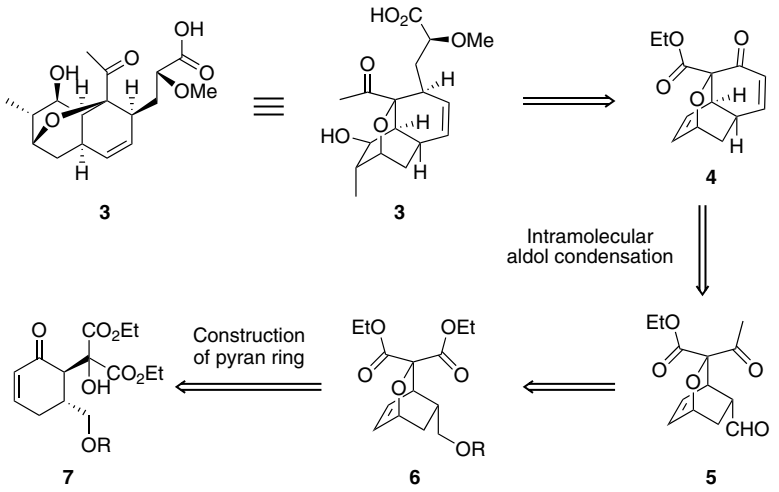
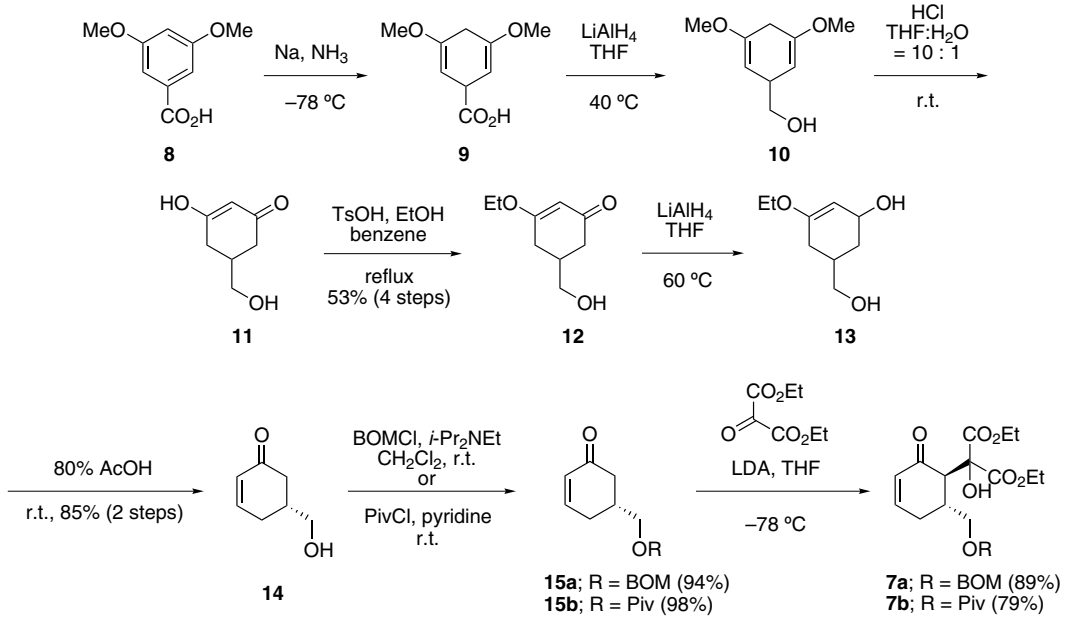


Scheme 1. Synthetic strategy of the 11-oxatricyclo[5.3.1.$^{1,7}0^{3,8}$]undecane nucleus **4**.

oxa-bridged octalin system **4** removed from **3** could be obtained via intramolecular hetero-Michael addition of enone **7** to form the 2-oxabicyclo[2.2.2]octene nucleus **6** first, followed by intramolecular aldol condensation of aldehyde **5** with the epimerization event at the stereocenter attached by the aldehyde group. The selective conversion of diester **6** into **5** would not be a matter due to the necessity to form the methyl ketone moiety at the further stage and the intramolecular discrimination in the intramolecular aldol condensation step.

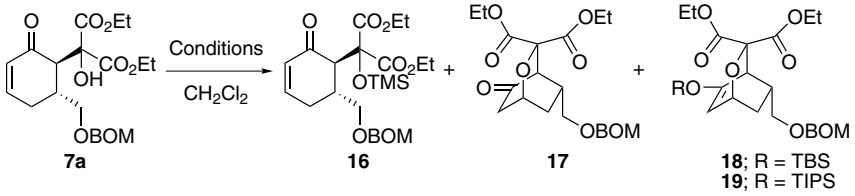
Enone **7** is conveniently available from 3,5-dimethoxybenzoic acid **8** as a starting material, as a minor modification of the van Tamelen[10] and Smith[11] protocol (Scheme 2). Here, Birch reduction of **8,** followed by $LiAlH_4$ reduction (**9**), acid hydrolysis (**10**), and esterification of vinylogous acid group (**11**), then afforded enol ether **12** in 53% yield for 4 steps. 1,2-Reduction of **12** followed by acid hydrolysis of **13** produced 5-(hydroxymethyl)-2-cyclohexenone **14** in 85% yield for 2 steps. Protection of **14** with benzyloxymethyl chloride or pivaloyl chloride gave **15a** or **15b** in 94% and 98% yields, respectively. Finally, diastereoselective aldol reaction[12] of **15a/b** with diethyl ketomalonate at −78 °C rendered the tertiary alcohol (±)-**7a/b** in 89% and 79% yields, respectively.

The first key reaction, intramolecular hetero-Michael addition was investigated to obtain the oxa-bicyclic compound **17** by using **7a** protected with BOM ether. Firstly, treatment of **7a** with any base did not produce desired **17**. Retro-Michael addition should occur due to one of the α-methylene protons being placed antiperiplanar against the bridged oxygen bond. Therefore, we attempted to use the Lewis acid conditions, not only because of the activation of the carbonyl group but also to capture the enolate formed after hetero-Michael addition (Table 1). Using TMSOTf in the presence of



Scheme 2. Synthesis of the tertiary alcohol **7a/b**.

Table 1. Intramolecular hetro-Michael addition of the tertiary alcohol **7a** using Lewis acid

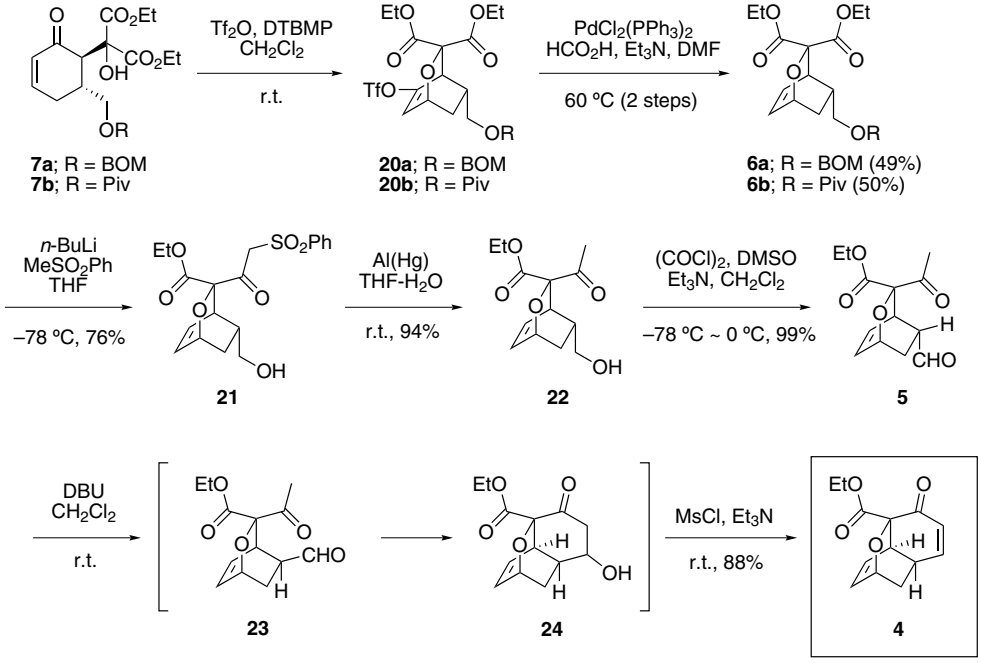


Entry	Reagent	Temperature[a]	Products[b] (%)			
			7a	**16**	**17**	**18/19**
1	TMSOTf (4 equiv) 2,6-Lutidine (6 equiv)	−78 °C	40	23	28	—
2	TMSOTf (2 equiv) 2,6-Lutidine (3 equiv)	rt	8	40	39	—
3	TMSOTf (2 equiv) 2,6-Lutidine (3 equiv)	40 °C	—	56	—	—
4	TBSOTf (6 equiv) 2,6-Lutidine (9 equiv)	rt	—	—	—	**18**: 87
5	TIPSOTf (4 equiv) 2,6-Lutidine (6 equiv)	40 °C	—	—	—	**19**: 87

[a] Reagents were added at the indicated temperature and the reaction was performed at the temperature.
[b] Isolation yields after column chromatography.

2,6-lutidine at −78 °C afforded desired **17** (28%) with TMS ether **16** (23%), and recovered enone **7a** (40%) (entry 1). Ketone **17** was generated from the corresponding enol silyl ether during the column chromatography. Warming to room temperature to consume the starting material **7a** obtained **17** in 39% yield (entry 2). Heating to 40 °C did not obtain **17** but produced **16** in 56% yield (entry 3). Furthermore, treatment of **7a** with TBSOTf or TIPSOTf gave the oxa-bicyclic TBS enol ether **18** or TIPS enol ether **19**, both in 87% yields (entries 4 and 5). Efforts to convert from **18** and **19** into ketone **17** followed by methylation or olefination were unfruitful because of the retro-Micheal reaction. We therefore needed to construct the synthetic pathway without formation of ketone **17**.

Based on these results, we attempted the conversion into olefin via the enol triflate in the hetero-Michael reaction (Scheme 3). Treatment of **7a/b** with Tf_2O in the presence of 2,6-di-*t*-butyl-4-methylpyridine (DTBMP)[13] at room temperature, followed by reduction of the formed enol triflate **20a/b** with HCO_2H and a catalytic amount of



Scheme 3. Synthesis of the 11-oxatricyclo[5.3.1.^{1,7}0^{3,8}]undecane nucleus **4**.

$PdCl_2(PPh_3)_2$[14] to afford the desired oxa-bicyclic olefin **6a/b** in 49% and 50% yields for 2 steps, respectively. Substrate **6b,** having a pivaloyl ester, was then used due to its efficient convertibility. Diastereoselective alkylation and deprotection of the pivaloyl ester of **6b** with an excess amount of (phenylsulfonyl)methyllithium[15] at −78 °C followed by reductive elimination of phenylsulfone group of **21** with Al(Hg)[16] afforded methylketone **22** in 70% yield for 2 steps. In the alkylation step,[17] we observed the useful diastereoselectivity (10:1) due to the decreased reactivity of the left-hand ester by the interaction with the adjacent olefin. Swern oxidation of **22** then gave ketoaldehyde **5** quantitatively. The second key reaction, the intramolecular aldol condensation of **5** through epimerization toward the more hindered isomer **23** of the aldehyde group, was investigated to afford the tricyclic compound **4**. First, treatment of **5** with DBU[18] in CH_2Cl_2 at room temperature gave the aldol product **24** (16%) and the desired enone **4** (73%). Aldol compound **24** was converted to **4** quantitatively via in the treatment with MsCl and Et_3N at room temperature. Then, the one-pot reaction was carried out. Treatment with DBU followed by addition of MsCl and Et_3N after the consumption of **5**, afforded desired **4** in 88% yield.[19]

In summary, we have developed a concise, stereocontrolled entry to the novel 11-oxatricyclo[5.3.1.^{1,7}0^{3,8}]-undecane nucleus of luminamicin and lustromycin. Further studies toward the total syntheses of these compounds are now in progress.

Acknowledgments

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References and notes

1. Ōmura, S.; Iwai, Y.; Nakagawa, A.; Iwata, R.; Takahashi, Y.; Shimizu, H.; Tanaka, H. *J. Antibiot.* **1983**, *36*, 109.
2. Ōmura, S.; Imamura, N.; Oiwa, R.; Kuga, H.; Iwata, R.; Masuma, R.; Iwai, Y. *J. Antibiot.* **1986**, *39*, 1407.
3. Ōmura, S.; Iwata, R.; Iwai, Y.; Taga, S.; Tanaka, Y.; Tomoda, H. *J. Antibiot.* **1985**, *38*, 1322.
4. Tomoda, T.; Iwata, R.; Takahashi, Y.; Iwai, Y.; Oiwa, R.; Ōmura, S. *J. Antibiot.* **1986**, *39*, 1205.
5. Handa, M.; Ui, H.; Yamamoto, D.; Monma, S.; Iwai, Y.; Sunazuka, T.; Ōmura, S. *Heterocycles* **2003**, *59*, 497.
6. Rasmussen, R. R.; Scherr, M. H.; Whittern, D. N.; Buko, A. M.; McAlpine, J. B. *J. Antibiot.* **1987**, *40*, 1383.
7. Evans, J. M.; Kallmerten, J. *Synlett* **1992**, 269.
8. Gössinger, E.; Schwartz, A.; Sereinig, N. *Tetrahedron* **2000**, *56*, 2007.
9. Gouda, H.; Sunazuka, T.; Ui, H.; Handa, M.; Sakoh, Y.; Iwai, Y.; Hirono, S.; Ōmura, S. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 18286.
10. van Tamelen, E.; Hildahl, G. T. *J. Am. Chem. Soc.* **1956**, *78*, 4405.
11. Smith, A. B., III; Richmond, R. E. *J. Am. Chem. Soc.* **1983**, *105*, 575.
12. Armstrong, A.; Critchley, T. J.; Gourdel-Martin, M.-E.; Kelsey, R. D.; Mortlock, A. A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1344.
13. (a) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85; (b) Stang, P. J.; Treptow, W. *Synthesis* **1980**, 283.
14. (a) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1984**, *25*, 4821; (b) Yang, M.-S.; Chang, S.-Y.; Lu, S.-S.; Rao, P. D.; Liao, C.-C. *Synlett* **1999**, 225.
15. Chun, J.; Li, G.; Byun, H.-S.; Bittman, R. *J. Org. Chem.* **2002**, *67*, 2600.
16. Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1345.
17. To a solution of methyl phenyl sulfone (5.77 g, 36.9 mmol) in THF (246 mL) was added 1.54 M *n*-BuLi (24.0 mL, 36.9 mmol) in hexane at −15 °C. The mixture was stirred for 30 min at the temperature, and then cooled to −78 °C. To the mixture was added **6b** (1.36 g, 3.69 mmol) in THF (38.0 mL) over 15 min. After the addition, the resultant mixture was stirred for 10 min at −78 °C, and saturated aqueous NH_4Cl was added. The organic layer was extracted with EtOAc. The combined organic layers were dried and concentrated. The crude product was purified by flash chromatography ($CHCl_3$/MeOH = 200:1) to give a sulfone **21** (1.11 g, 2.82 mmol, 76%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (1H, ddd, J = 13.5, 4.5, 1.5 Hz), 1.16 (3H, t, J = 7.0 Hz), 1.82 (1H, m), 2.13 (1H, ddd, J = 13.5, 9.0, 4.0 Hz), 3.17 (1H, dd, J = 11.0, 9.0 Hz), 3.31 (1H, dd, J = 11.0, 6.0 Hz), 3.75 (1H, dt, J = 6.5, 2.0 Hz), 4.02 (1H, dq, J = 11.0, 7.0 Hz), 4.10 (1H, dq, J = 11.0, 7.0 Hz), 4.45 (1H, d, J = 16.0 Hz), 4.68 (1H, d, J = 16.0 Hz), 4.73 (1H, m), 6.32 (1H, m), 6.49 (1H, ddd, J = 8.0, 5.0, 1.5 Hz), 7.57 (2H, m), 7.67 (1H, m), 7.96 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 29.4, 31.6, 36.8, 61.5, 62.4, 65.9, 68.5, 87.9, 128.6 (2C), 129.1 (2C), 130.8, 134.1, 134.2, 139.4, 168.0, 195.8; IR (KBr) 3388, 1738, 1319, 1228, 1159, 1026 cm^{-1}; HRMS (FAB, NBA, PEG200 + 400 + NaI matrix) m/z for $C_{19}H_{22}O_7NaS$ [M+Na]$^+$ calcd 417.0984, found 417.0980.
18. (a) Hecker, S. J.; Heathcock, C. H. *J. Am. Chem. Soc.* **1986**, *108*, 4586; (b) Farr, R. A.; Peet, N. P.; Kang, M. S. *Tetrahedron Lett.* **1990**, *31*, 7109.
19. To a solution of aldehyde **5** (75.8 mg, 300 μmol) in CH_2Cl_2 (15.0 mL) was added DBU (21 μL, 150 μmol) at room temperature. The resultant mixture was stirred for 18 h at the same temperature until the starting material was consumed. Then Et_3N (377 μL, 2.70 mmol) and MsCl (70 μL, 902 μmol) were added at room temperature, the mixture was stirred for 15 min, and H_2O was added. The organic layer was extracted with $CHCl_3$. The combined organic layers were washed with 0.2 N HCl, dried over, and concentrated. The crude product was purified by flash chromatography (hexane/EtOAc = 3:1) to give a tricyclic compound **4** (61.8 mg, 264 μmol, 88%) as a colorless solid: mp 58–60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (3H, t, J = 7.0 Hz), 1.56 (1H, m), 1.99 (1H, ddd, J = 13.0, 4.5, 3.0 Hz), 2.35 (1H, m), 3.72 (1H, ddd, J = 6.5, 3.5, 1.5 Hz), 4.16–4.27 (2H, m), 4.88 (1H, m), 5.89 (1H, d, J = 10.0 Hz), 6.47 (1H, m), 6.68 (1H, ddd, J = 8.0, 5.5, 1.5 Hz), 7.36 (1H, dd, J = 10.0, 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 26.1, 31.1, 39.4, 61.4, 69.5, 79.4, 122.7, 131.6, 136.4, 156.2, 170.2, 193.0; IR (KBr) 1750, 1685, 1263, 1074 cm^{-1}; HRMS (FAB, NBA, PEG200 + 400 + NaI matrix) m/z for $C_{13}H_{14}O_4Na$ [M+Na]$^+$ calcd 257.0790, found 257.0784.