Synthetic studies on (−)-lemonomycin: stereocontrolled construction of the 3,8-diazabicyclo[3.2.1] skeleton

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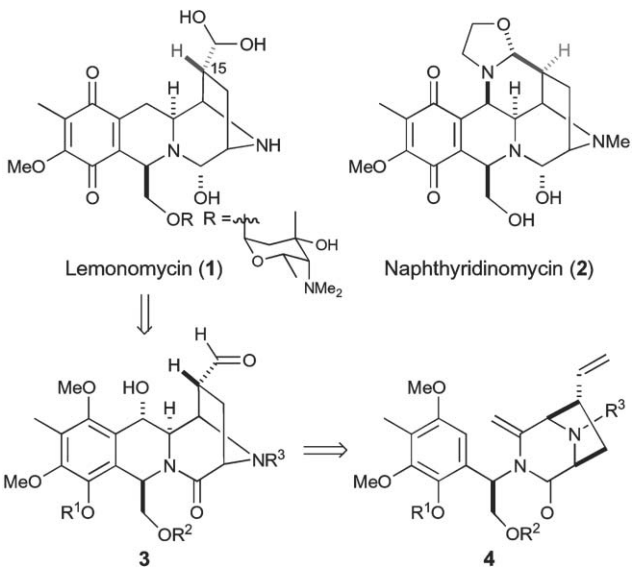
Stereoselective synthesis of the pentacyclic key intermediate 22 for (−)-lemonomycin (1) has been accomplished using the Ugi 4-CC reaction with our novel isocyanide 8, a cross-metathesis of 13 and allylsilane and a subsequent intramolecular Hosomi–Sakurai type reaction.

(−)-Lemonomycin (**1**) is a tetrahydroisoquinoline alkaloid[1] isolated from *Streptomyces candidus* (LL-AP191).[2] Although the isolation of **1** was achieved in 1964, the structure determination was not reported until 2000 by researchers at Wyeth-Ayerst.[3] It was also discovered that the compound possessed interesting antibiotic activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VREF), as well as cytotoxicity against a human colon tumor cell line (HCT-116).[3] Because of its potent biological activity and challenging structure, lemonomycin has become an attractive target for synthesis, and indeed the first total synthesis of **1** was achieved by Stoltz and co-workers in 2003.[4]

During the course of our total synthesis of ecteinascidin 743,[5] we established an efficient synthetic strategy for the tetrahydroisoquinoline alkaloids *via* the Ugi four-component condensation (4-CC)[6] and the intramolecular Mizoroki–Heck reaction. Furthermore, an application of this protocol was demonstrated by the stereoselective construction of the highly strained 3,8-diazabicyclo[3.2.1]octane framework of (+)-naphthyridinomycin (**2**).[7] In a subsequent synthetic investigation, we developed an efficient synthetic methodology for (−)-lemonomycin (**1**) and report herein the stereocontrolled synthesis of the tetracyclic key intermediate **22** for **1**.

The heart of our synthetic plan is illustrated in Scheme 1. Incorporation of a unique amino sugar moiety and transformation to a labile quinone and hemiaminal moiety would be carried out at later stages of the total synthesis. Thus, the tetracyclic compound **3** was designed as a key intermediate in our total synthesis of **1**. According to our synthetic study on **2**,[7] the preparation of **3** from **4** would be readily achieved by hydration of the enamide of **4** and subsequent electrophilic cyclization between an electron-rich aromatic ring and an aldehyde. Since there is a significant difference between **1** and **2** in the stereochemistry at the C-15 position, the stereoselective construction of the bicyclo[3.2.1] system bearing an *exo*-oriented side chain in **4** would be a crucial step for the total synthesis of **1**.[8]

Our synthesis started from the two chiral amino acid derivatives **5**[7,9] and **6**[10] (see Scheme 2). In our synthetic investigation of the related alkaloids,[5,7] condensation of the amino acid derivatives was accomplished by the Ugi 4-CC reaction with *p*-methoxyphenyl isocyanide and acetaldehyde to access easily the corresponding diketopiperazine. However, we found that the Ugi 4-CC reaction of the isocyanide **8** and glyoxyaldehyde dimethylacetal **7** in trifluoroethanol[11] was more suitable for an efficient preparation of **13**. Thus, after conversion to the dipeptide **9**, the transformation to the cyclic enamide **10** was performed by treatment with CSA (10-camphorsulfonic acid) and quinoline. Although cleavage of the amide bond derived from the isocyanide of the Ugi adducts often requires harsh conditions, we discovered recently that the amide bond derived from the phenyl carbonate-type isocyanide was readily converted *via* the corresponding *N*-acyloxazolidinone derivatives.[12] Thus, upon treatment of the amidocarbonate **10** with *t*-BuOK, the oxazolidinone formation proceeded smoothly to provide **11** with release of phenol. The imide **11** was readily converted to the hydroxymethyl derivative **12** by simple reduction with $NaBH_4$. Changing the protecting group from TIPS to Ac proceeded smoothly in one step to provide **13** in high yield. For the crucial construction of the bicyclo[3.2.1] system, we found that an acyliminium ion-mediated cyclization was more suitable to obtain the desired stereochemistry.[13] The elaboration of the cyclization precursor **15** was achieved by a cross-metathesis of **13** and allyltrimethylsilane in the presence of 2 mol% of the Grubbs 2nd generation catalyst (**14**).[14,15] Upon treatment of **15** with $BF_3{\cdot}Et_2O$, generation of the conjugate acyliminium cation **16** and subsequent cyclization of the allylsilane moiety proceeded immediately to



Scheme 1 Structure and synthetic strategy of lemonomycin (**1**).

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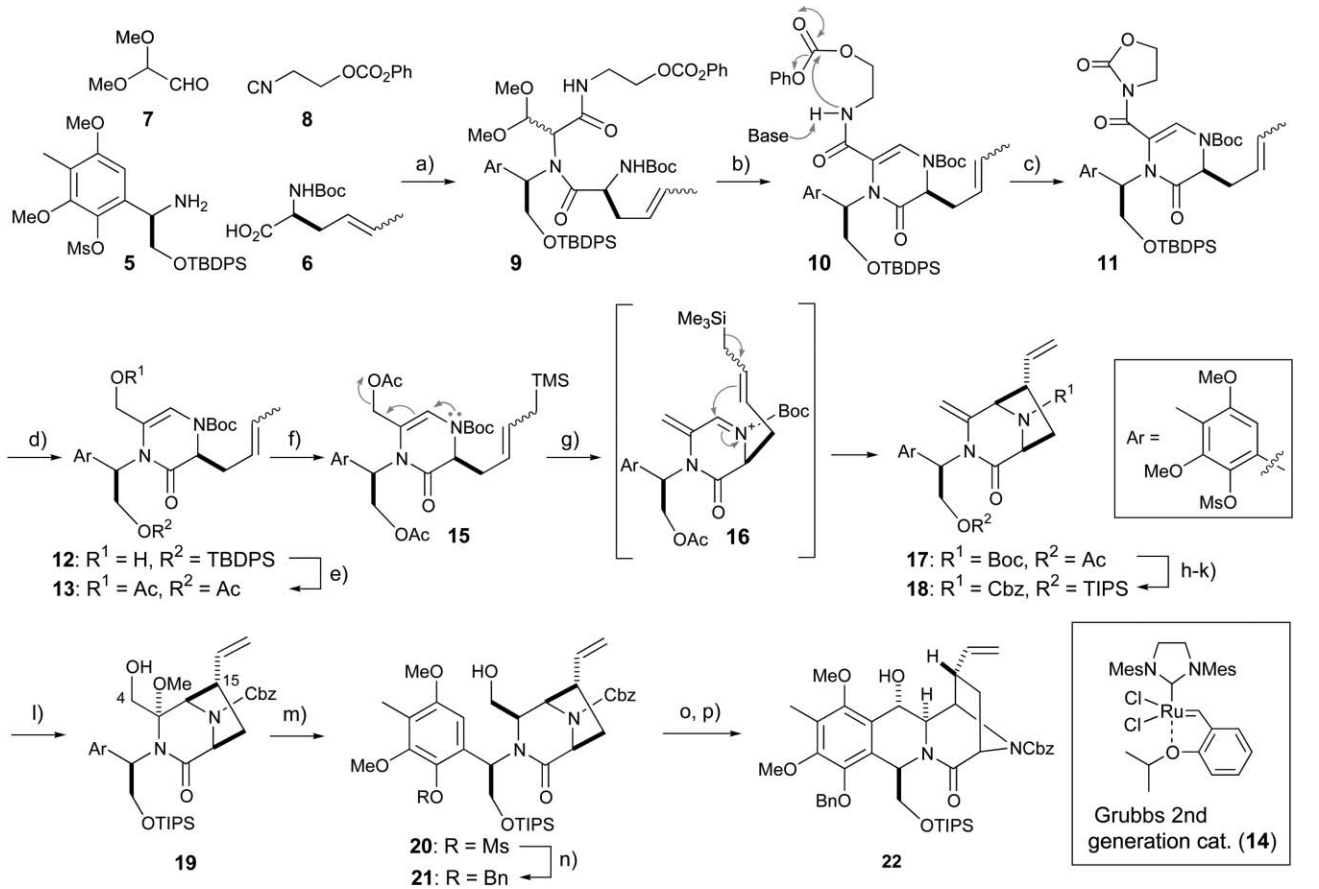

Scheme 2 *Reagents and conditions*: a) CF_3CH_2OH, rt to 50 °C; b) CSA, quinoline, PhMe, reflux, 73% (2 steps); c) *t*-BuOK, MS4A, THF, 0 °C; d) $NaBH_4$, THF–H_2O (3 : 1); e) TBAF, THF, 50 °C; Ac_2O, Py, 68% (3 steps); f) Grubbs 2nd generation cat. (**14**) (2 mol%), allyltrimethylsilane, CH_2Cl_2, reflux, 51%; g) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C, 95%; h) TMSOTf, CH_2Cl_2, 0 °C; i) CbzCl, DMAP, MeCN; j) K_2CO_3, MeOH; k) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 55% (4 steps); l) DMDO (dimethyldioxirane), Na_2SO_4, MeOH, −78 °C to rt; CSA; m) $NaBH_3CN$, TFA–THF (9 : 1), 0 °C; n) $KOSiMe_3$, MeCN, 0 °C; BnBr, 50 °C, 53% (4 steps); o) DMP (Dess–Martin periodinane), CH_2Cl_2; p) TFA–CH_2Cl_2 (1 : 9), 76% (2 steps).

provide **17** with complete stereoselectivity[16] in almost quantitative yield.

With the desired enamide **17** in hand, we next focused on the stereoselective construction of the tetracyclic system of **22**. According to our synthetic study on **2**,[7] the cyclic enamide was oxidized by DMDO[17] in methanol followed by addition of CSA to give the hemiaminal. However, acidic reduction of the aminal moiety, which was demonstrated in the synthetic studies on naphthyridinomycin, led to decomposition. Thus, after exchange of the protecting groups from Boc to Cbz and from Ac to TIPS ether, DMDO oxidation of **18** provided **19**. The acyliminium ion-mediated reduction of **19** occurred from the less hindered *exo*-face of the molecule to afford **20** as a single isomer with the correct stereochemistry. Since the reactivity of the aromatic ring was dependent on its electron-donating nature, the protecting group of the phenol **20** was changed from the mesyl to the corresponding benzyl group. After oxidation of the alcohol **21** with Dess–Martin periodinane, treatment of the resulting aldehyde with TFA allowed the desired cyclization to proceed smoothly providing **22**, which implies all the carbon atoms with the requisite stereochemistry needed for the lemonomycin (**1**) aglycon.

In summary, we have accomplished the efficient synthesis of the tetracyclic backbone **22** of (−)-lemonomycin (**1**), including the highly strained bicyclo[3.2.1]octane framework. The present synthesis features the Ugi 4-CC reaction with our novel isocyanide **8**, which allows the easy preparation of the cyclic enamide **13**. The combination of cross-metathesis for a facile preparation of the allylsilane **15** and the intramolecular Hosomi–Sakurai type reaction provided the bicyclo[3.2.1]octane framework **17** with complete stereoselectivity. Further conversion of **22** to (−)-lemonomycin (**1**) is currently under investigation in our laboratory.

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