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Total Synthesis of (−)-Lemonomycin

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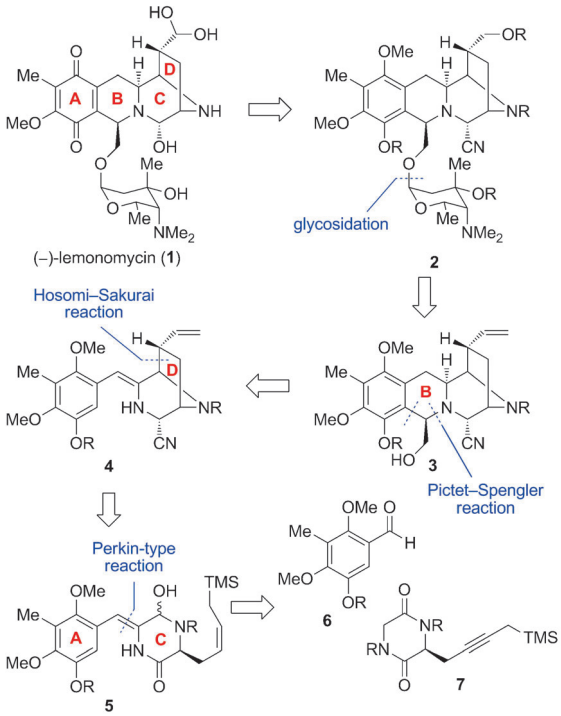
(−)-Lemonomycin (**1**) belongs to a large family of tetrahydroisoquinoline (THIQ) alkaloids,[1] and was isolated from the fermentation broth of *Streptomyces candidus* (LL-AP191) in 1964.[2] In 2000, researchers at Wyeth–Ayerst discovered that **1** shows antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VREF),[3] as well as cytotoxicity to a human colon-tumor cell line (HCT-116). They also determined the structure of **1** by means of NMR spectroscopy.[4] The compound features a tetracyclic ring system including a 3,8-diazabicyclo[3.2.1]octane core, which is typical of quinocarcin-type alkaloids. Moreover, **1** contains a 2,6-dideoxy-4-amino sugar (lemonose) that is only rarely found in nature.[5] To our knowledge, there is no other example of a hybrid natural product consisting of a THIQ alkaloid and a sugar subunit. Aminoglycosides constitute a large class of antibiotics, thus it seems likely that the sugar unit plays an important role in the unique bioactivity of **1** against multi-drug-resistant bacteria.

The structural novelty and remarkable biological activity of **1** make this molecule an attractive synthetic target.[6–8] To date, Stoltz and co-workers have reported the only total synthesis of **1**, in which the lemonose unit was incorporated as a part of an aldehyde by a Pictet–Spengler reaction.[7] In contrast, and bearing in mind the putative role of the sugar unit in the biological activity, we planned to couple the lemonose unit with the aglycon alkaloid subunit by using a glycosidation reaction. Such a route was expected to be readily applicable to the synthesis of a series of analogues that would be useful for structure–activity studies and the generation of drug candidates.

During the course of our studies into THIQ alkaloids,[9] we found that the intramolecular Hosomi–Sakurai reaction was effective for the construction of the diazabicyclo-[3.2.1]octane ring system.[9e,10] Although this reaction could be employed for the stereoselective construction of a tetracyclic key intermediate for **1**, we encountered poor reproducibility during large-scale reactions. Therefore, we set out to establish an alternative route to **1** that would be suitable for larger-scale applications.

The heart of our synthetic plan is illustrated in Scheme 1. The hemiaminal and quinone moieties of **1** would be highly labile under many reaction conditions; therefore, they must be formed in the final stages of the total synthesis. Initially,



Scheme 1. Retrosynthetic analysis of (−)-lemonomycin (**1**).

we designed the primary alcohol **3** as a key intermediate and a precursor for the glycosidation reaction. The construction of the B ring of the tetracyclic carbon framework of **3** would be accomplished by a Pictet–Spengler reaction following the stereoselective reduction of the enamine moiety of **4**. According to our previous study on related compounds, the bicyclo[3.2.1]octane framework of **4** could be constructed by an intramolecular Hosomi–Sakurai-type reaction. We

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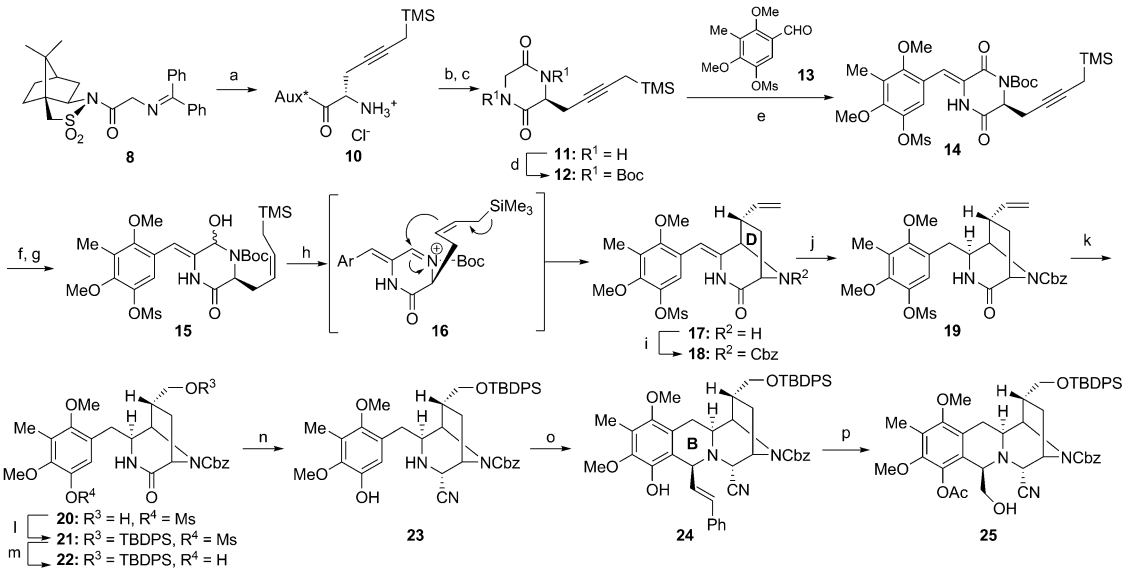


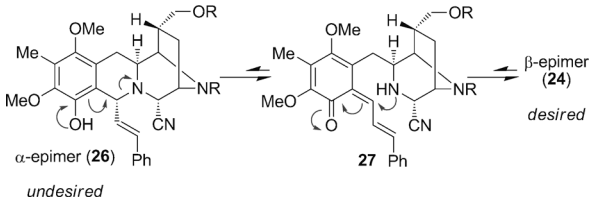
Scheme 2. Synthesis of the aglycon alkaloid unit **25**. Reagents and conditions: a) $TMSCH_2C{\equiv}CCH_2I$ (**9**), Cs_2CO_3, DMF, −10 °C; then HCl (2 M), Et_2O, single diastereomer; b) *N*-Boc glycine, EDCI, HOBt, Et_3N, CH_2Cl_2; c) ormic acid, 40 °C; then toluene, reflux, 84 % (3 steps); d) Boc_2O, DMAP, MeCN, 84 %; e) **13**, *t*BuOK, 4 Å MS, MeCN, −10 °C, 96 %, *Z*/*E* = 10:1; f) H_2, Pd/C, quinoline, EtOH, 96 %; g) $NaBH_4$, MeOH, 0 °C; h) TFA, CH_2Cl_2, 0 °C to RT; i) CbzCl, $NaHCO_3$, CH_2Cl_2, 53 % (3 steps); j) $NaBH_3CN$, TFA/AcOH, 60 °C; k) O_3, CH_2Cl_2/MeOH, −78 °C; then $NaBH_4$, 0 °C, 71 % (2 steps); l) TBDPSCl, imidazole, DMF, 85 %; m) LiHMDS, THF, 0 °C, 99 %; n) DIBAL, CH_2Cl_2, −78 °C; then NaCN, MeOH, 52 %; o) cinnamaldehyde, CSA, TMSCN, MeCN, 100 °C, 92 %; p) Ac_2O, pyridine; then O_3, CH_2Cl_2/MeOH, −78 °C; then $NaBH_4$, −78 °C, 84 %. Ac = acetyl, Aux* = Oppolzer chiral auxiliary, Boc = *tert*-butyloxycarbonyl, Cbz = benzyloxycarbonyl, CSA = 10-camphorsulfonic acid, DIBAL = diisobutylaluminium hydride, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, HOBt = 1-hydroxybenzotriazole, LiHMDS = lithium hexamethyldisilazide, Ms = mesyl, TBDPS = *tert*-butyldiphenylsilyl, TFA = trifluoroacetic acid, THF = tetrahydrofuran, TMS = trimethylsilyl.

anticipated that the cyclization precursor **5** could be prepared by a Perkin-type condensation reaction of aldehyde **6** with diketopiperazine **7**. Because allylsilane is labile under various reaction conditions, the more stable propargylsilane was selected as the precursor compound.

As shown in Scheme 2, the preparation of aglycon **25** started from the glycine derivative **8**, which has an Oppolzer chiral auxiliary.[11] The alkylation reaction of **8** with iodopropargylsilane **9**[12] proceeded smoothly, and subsequent hydrolysis of the resulting imine provided **10** as a single diastereomer. Condensation with *N*-Boc glycine followed by cleavage of the Boc group gave the corresponding primary amine. This was then cyclized under reflux conditions to give **11**,[13] with the concomitant release of the sultam group (3 steps: 84 % yield). After the protection of **11** with a Boc group, diketopiperazine **12** was subjected to a Perkin condensation reaction.[14] The reaction of **12** with **13**[15] was promoted by *t*BuOK at −10 °C to give the *Z*-enamide **14** almost quantitatively with high stereoselectivity.[16] In this reaction, a significant decrease in the optical purity was observed at elevated temperatures. With the desired optically active compound **14** in hand, we then focused on the construction of the bicyclo[3.2.1]octane ring system. Partial reduction of the alkyne group and chemoselective reduction of one carbonyl group with $NaBH_4$ gave the cyclization precursor **15**. Upon treatment of **15** with TFA,[17] generation of the conjugated acyliminium cation **16** and the subsequent intramolecular attack of the allylsilane substituent proceeded immediately to provide **17** with perfect stereoselectivity in almost quantitative yield.

After protection of the newly formed secondary amine of **17** with a Cbz group, we examined the stereoselective construction of the B ring. In accordance with our total synthesis of the saframycins,[10a,b,c] an acyliminium-ion-mediated reduction under acidic conditions occurred from the less hindered α face of **18** to give the bicyclo[3.2.1]octane ring system with the required stereochemistry as a single isomer. Conversion of the vinyl group of **19** to a hydroxymethyl group was achieved by ozonolysis and subsequent reduction to an alcohol. After protection of the newly formed primary alcohol of **20** with a TBDPS group, the Ms group was removed by reaction with LiHMDS.[18] Since the electronic nature of the nitrogen atom was crucial for construction of the B ring, the amide carbonyl group of **22** was converted to an amino nitrile by partial reduction and subsequent treatment with NaCN. After examining the Pictet–Spengler reactions of either **22** or **23** with various aldehydes, we found that the reaction of **23** with cinnamaldehyde gave the best result in terms of both yield and diastereoselectivity.[19] When the reaction of **23** with cinnamaldehyde was performed in the presence of CSA and TMSCN[20] at 100 °C, the desired ring closure proceeded smoothly to give **24**.

A decreased diastereoselectivity (α/β = 1:1) was observed at a lower temperature (50 °C), thus we expect that the reaction is controlled by the thermodynamic equilibrium between the α isomer **26** and β isomer **24**. As shown in

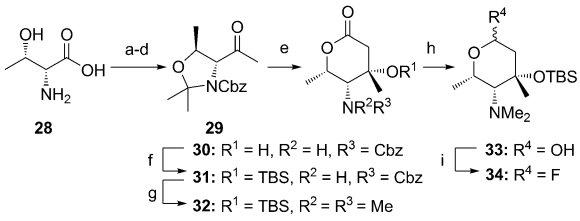


Scheme 3. Equilibrium between compounds **24** and **26**.

Scheme 3, the equilibrium presumably occurs during an acid-induced, ring-opening reaction to form the *para*-quinonemethide intermediate **27** that is stabilized by conjugation of the π-system with the styryl group. Thus, the thermodynamically more stable β isomer **24** was obtained exclusively at a high reaction temperature.

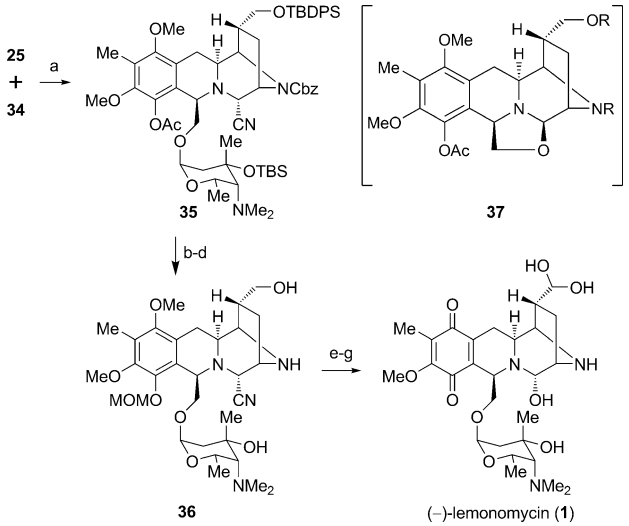
One-pot conversion from **24** to the aglycon alkaloid **25** was accomplished by acetylation of the phenol group, ozonolysis, and a subsequent reduction reaction. Notably, the nature of the amino nitrile group on the C ring allowed us to construct the B ring directly, without any change to the C ring. This is in contrast to related reports[7,8] in which the reductive conversion of the C-ring lactam to the corresponding amino alcohol has generally been required to achieve a successful Pictet–Spengler reaction, and therefore subsequent oxidative re-cyclization of the C ring was required.

Having successfully obtained the key intermediate **25**, we then turned our attention to the preparation of the glycosyl donor **34** (Scheme 4). By using a slight modification of the reported protocol for the conversion of related sugar derivatives, conversion of D-threonine (**28**) to the lemonose derivative **34** was accomplished. The methyl ketone **29** was synthesized by a four-step sequence involving Cbz-protection of the amino group, formation of the Weinreb amide, acetonide protection, and treatment with excess MeMgBr. Upon treatment of **29** with the lithium enolate of ethyl acetate, the chelation-controlled aldol reaction[7,21] proceeded in a highly diastereoselective manner to afford compound **30** in 85% yield. After protection of the tertiary alcohol of **30** with a TBS group, removal of the Cbz group of the resulting compound **31** and the subsequent in situ formation of the dimethyl amino group of **32** were achieved by a hydrogenolysis reaction performed in the presence of formaldehyde. As described later, the glycosyl fluoride **34**[22] was found to be suitable for the glycosidation reaction with **25**. Thus, lactone **32** was subjected to reduction with DIBAL, followed by fluorination with DAST.[23]



Scheme 4. Preparation of the glycosyl subunit **34**. Reagents and conditions: a) CbzCl, THF/$NaHCO_3$ aqueous; b) MeNHOMe·HCl, EDCI, NMM, THF, −10 °C; c) $Me_2C(OMe)_2$, BF_3·OEt_2, CH_2Cl_2, 92% (3 steps); d) MeMgBr, THF, −78 °C to RT, 85%; e) LDA, AcOEt, THF, −78 °C; then HCl (3 M), 85%; f) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 93%; g) H_2, HCHO, $Pd(OH)_2$, EtOH, 92%; h) DIBAL, CH_2Cl_2 −78 °C, 100%; i) DAST, THF, −45 °C, 84%. DAST = *N*,*N*-diethylaminosulfur trifluoride, LDA = lithium diisopropylamide, NMM = *N*-methylmorpholine, TBS = *tert*-butyldimethylsilyl, TfO = trifluoromethanesulfonate.

The next challenge in the synthesis was glycosidation of the aglycon **25** with the fluoride **34** (Scheme 5). Considering the strong acid-sensitivity of the tertiary amine, we initially selected a soft Lewis acid for the activation of the glycosyl fluoride. When Sn, Hf, and Ag salts, which have conventionally been used in similar cases,[24] were used, the formation of the undesired oxazolidine **37** occurred.[25] Next, we examined the reaction with the use of hard Lewis acids, such as BF_3·OEt_2 or trimethylsilyl trifluoromethanesulfonate (TMSOTf). Upon treatment of **25** and **34** with TMSOTf and Drierite at −40 °C,[15] the desired glycosidation reaction proceeded smoothly to give **35** in 86% yield with good stereoselectivity (α/β = 5:1). After a one-pot conversion of the acetate of **35** to the corresponding MOM ether,[26] stepwise cleavage of the Cbz and TBS groups gave the amino alcohol **36**. In accordance with the protocol reported by Stoltz et al., conversion to the *geminal* diol was performed by Swern oxidation. In this reaction, an acidic workup was particularly effective, enabling the simultaneous cleavage of the MOM ether and the methylthiomethyl (MTM) ether.[27] After generation of the labile hemiaminal from the amino nitrile by treatment with $AgNO_3$ in CH_3CN/H_2O, CAN-mediated oxi-



Scheme 5. Completion of the total synthesis of **1**. Reagents and conditions: a) TMSOTf, Drierite, CH_2Cl_2, −40 °C, 86%, α/β = 5:1; b) K_2CO_3, MeOH; then MOMCl, *i*Pr_2NEt, CH_2Cl_2, 99%; c) H_2, Pd/C, EtOH, 73%; d) TBAF, THF, 75 °C; e) Swern oxidation; then HCl (2 M), 69% (2 steps); f) $AgNO_3$, MeCN/H_2O, 70%; g) CAN, H_2O, 0 °C, 67%. CAN = ceric ammonium nitrate, MOM = methoxymethyl, TBAF = tetrabutylammonium fluoride.

dation furnished (−)-lemonomycin (**1**). The spectral data (^{1}H NMR, ^{13}C NMR, and IR spectroscopy, HRMS, and $[\alpha]_D$ values) for the final product were in full agreement with those of the natural product.[4,7]

In conclusion, we have achieved an efficient and enantioselective total synthesis of (−)-lemonomycin (**1**). Our synthesis features a Perkin-type condensation reaction, an intramolecular Hosomi–Sakurai reaction of the cyclic enamide **15** to give **17** with a bicyclo[3.2.1] ring system, a thermodynamically controlled Pictet–Spengler reaction to construct the tetracyclic key intermediate **25**, and TMSOTf-promoted glycosidation to provide **35** (despite the presence of the tertiary amine and the amino nitrile functional groups). Further work regarding this approach to **1** and its analogues is under way in our laboratory.

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Keywords: alkaloids · glycosidation · Hosomi–Sakurai reaction · Pictet–Spengler reaction · total synthesis

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[25] Oxazolidine compound **37** was formed as a result of elimination of the nitrile group and addition of the adjacent hydroxyl group.
[26] Neither acetyl nor benzyl groups were suitable as protecting groups for the phenol oxygen atom. The acetylated compound showed marked decomposition during desilylation, and in the case of the benzyl group, the reductive removal of the nitrile group occurred faster than that of the Cbz group.
[27] ESI-MS analysis of the crude product indicated that an MTM ether was formed at either the tertiary hydroxyl group or the secondary amino group during Swern oxidation.

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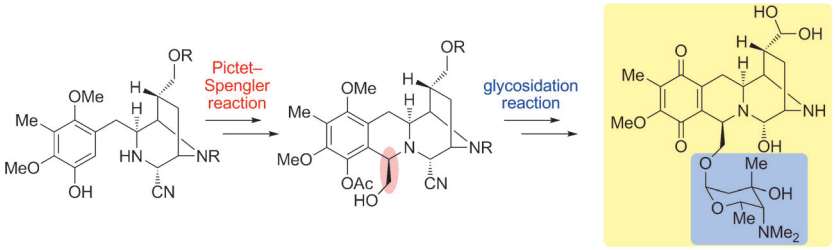

When life gives you lemons: An efficient and convergent enantioselective total synthesis of (−)-lemonomycin, which shows potent activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* (VREF), is presented. The key reaction steps are a Hosomi–Sakurai-type cyclization, a thermodynamically controlled Pictet–Spengler reaction, and a glycosidation reaction with lemonose (see scheme).

Natural Product Synthesis

A. Yoshida, M. Akaiwa, T. Asakawa, Y. Hamashima, S. Yokoshima, T. Fukuyama, T. Kan** ..... ▮▮▮▮–▮▮▮▮

Total Synthesis of (−)-Lemonomycin