Communication

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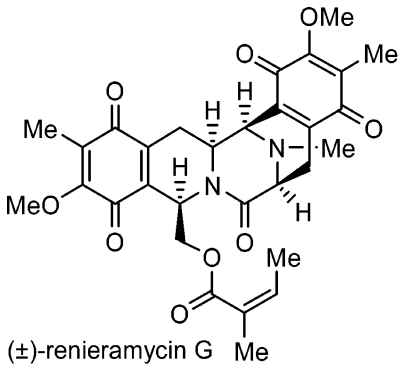
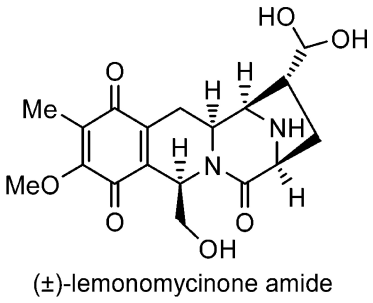


(±)-renieramycin G



(±)-lemonomycinone amide

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Synthesis of the Tetrahydroisoquinoline Alkaloid (±)-Renieramycin G and a (±)-Lemonomycinone Analogue from a Common Intermediate

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Recently, we reported a new strategy to construct the tetrahydroisoquinoline core structure common to a number of antitumor antibiotics, and it is exemplified by the conversion of **1** into **3** via **2** with complete control of the relative stereochemistry at C1 and C3 (Scheme 1).[1] Here, we report the application of this strategy to the synthesis of (±)-renieramycin G (**4**)[2] and the (±)-lemonomycinone congener **7** (Figure 1) from the same intermediate **17** (Scheme 2).

The tetrahydroisoquinoline alkaloids represented by saframycins, ecteinascidins, renieramycins, naphthyridinomycin, safracins, quinocarcins, tetrazomine, and lemonomycin have generated wide chemical and biological interest because of their potent antitumor and antimicrobial activity.[3] The renieramycins (A−S)[4] are isolated from various marine sponges and have the same core bisisoquinoline structure as the saframycins, except the C22 nitrogen atom of the saframycins is an oxygen atom in the renieramycins and frequently acylated as its (*Z*)-2-methylbut-2-enoic acid ester (angelic acid ester). Fukuyama and Danishefsky have reported total syntheses of renieramycins.[5] Lemonomycin (**5**) is a broad-spectrum antibiotic isolated from the fermentation broth of *Streptomyces candidus* (LL-AP191) in 1964.[6] The structure was elucidated in 2000,[7] and the only total synthesis was reported by Stoltz in 2003;[8] apart from the unusual presence of the aldehyde hydrate, it is the first member of this large class of compounds to have a carbohydrate appendage.

Our synthesis starts from the formation of the electron-rich isoquinoline **10** (Scheme 2), from a modification of the Larock isoquinoline synthesis,[9] by coupling *o*-iodoimine **8**[1] and acetylene **9** using room temperature Castro conditions,[10] followed by a copper-catalyzed ring closure. Treatment of isoquinoline **10** with benzyloxymethyllithium[11] followed by quenching with methyl chloroformate gave the 1,2-dihydroisoquinoline **11**. Attempted reduction of enecarbamate **11** directly to amino alcohol **13** was complicated by elimination products derived from the electron-rich isoquinoline.[12] Instead, amino alcohol **13** was obtained by first converting silyl ether **11** to oxazolidinone **12** by treatment with TBAF, then stereoselective reduction of the 3,4-olefin by ionic hydrogenation cleanly gave the 1,3-*cis*-substituted tetrahydroisoquinoline; hydrazinolysis then yielded amino alcohol **13** (X-ray). Silyl-activated amide coupling conditions were used to simultaneously protect the alcohol and activate the amine toward coupling with the mixed anhydride **14**, giving solely the amide-coupled product **15** upon acidic workup.[13] Swern oxidation gave hemiaminal **16** as a mixture of diastereomers (3:2),[14] which was converted to thioaminal **17** as a single diastereomer (X-ray).

In our initial approach to (±)-lemonomycinone amide (**7**), alkylation of amide **17** with allyl bromide gave product **18** as a single diastereomer (Scheme 3). The relative stereochemistry was assigned by X-ray analysis, revealing that the alkylation occurred from the least hindered face, giving the undesired stereochemistry at the C13 stereocenter. Elaboration of product **18** to alcohol **21** proved unsuccessful. However, alkylation of amide **17** with iodide

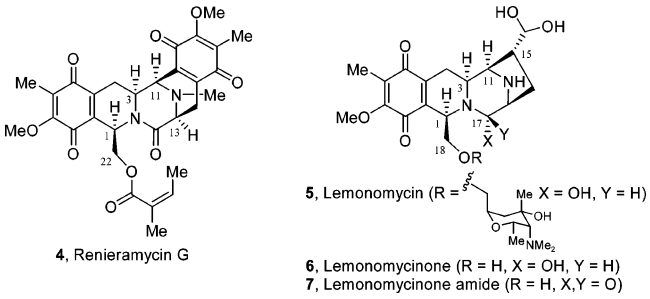
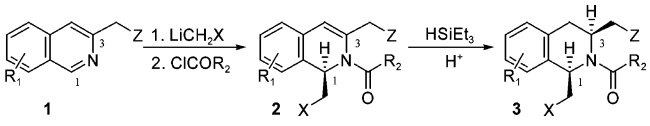
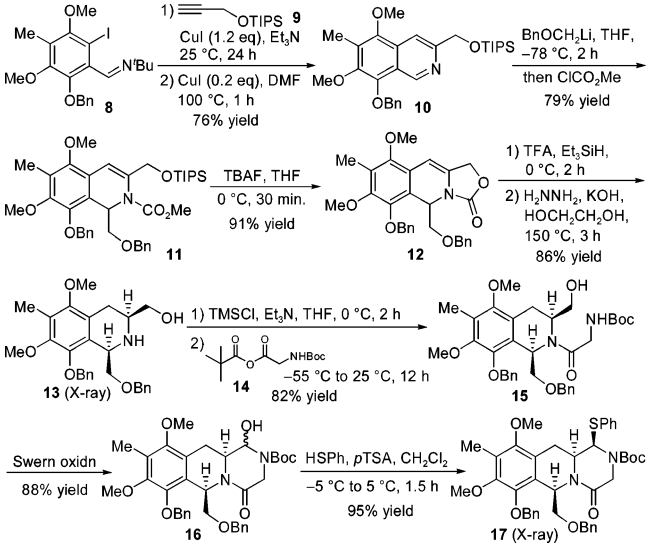


Figure 1. Tetrahydroisoquinoline alkaloids.

Scheme 1. General Approach to Isoquinoline Alkaloids



Scheme 2. Common Intermediate



19 gave a single diastereomer, **20**, which upon diastereoselective reprotonation by treatment with *tert*-butyllithium and quenching with BHT gave complete inversion at the C13 stereocenter with minimal degradation.[15] Alcohol **21** was isolated after TIPS removal. Subsequent Swern oxidation and silyl enol ether formation gave cyclization precursor **22**. The *N*-acyliminium cyclization was promoted with thiophile $AgBF_4$, providing aldehyde **23** as a single diastereomer at C15. The relative stereochemistry was assigned by X-ray analysis of the oxime derivative **24**.[16] The selectivity is attributed to the steric bulk of the C1 substituent, which exists in an axial orientation, as seen by X-ray analysis of **17**, **18**, and **24**. Hydrogenolysis of dibenzyl ether **22** formed diol **25** as the unhydrated aldehyde. Removal of the Boc group led to amine **26**,

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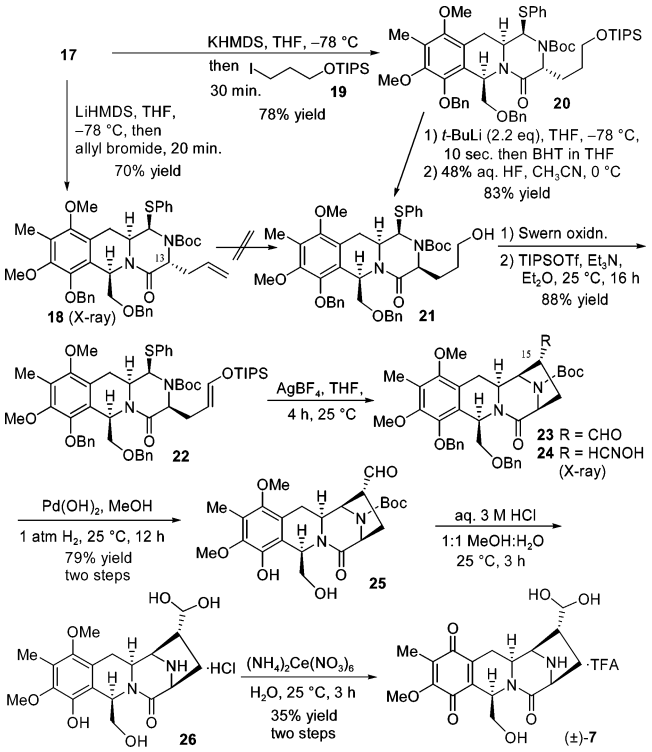
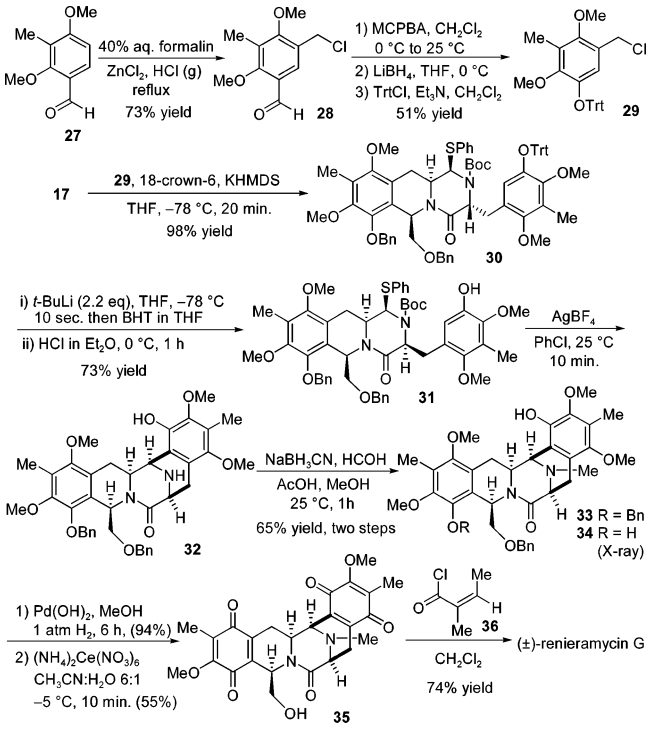
Scheme 3. (±)-Lemonomycinone Amide



Scheme 4. (±)-Renieramycin G



which exists entirely in the hydrated aldehyde form. Oxidation of phenol **26** with CAN[8a] gave (±)-lemonomycinone amide (**7**).

The synthesis of (±)-renieramycin G (**4**) (Scheme 4) started with the addition of KHMDS to a mixture of amide **17** and benzyl chloride **29** in the presence of 18-crown-6 to give very efficient conversion to product **30** as a single diastereomer. The previous conditions for diastereoselective reprotonation were employed; however, complete inversion was not observed, and instead, a 6:1 ratio of the desired isomer to starting material was obtained. These diastereomers were best separated after trityl deprotection to give phenol **31**. The cyclization was promoted by treatment with $AgBF_4$ as before; however, cyclization was complete within 10 min along with rapid loss of the Boc group, presumably due to the generation of HBF_4. Subsequent reductive methylation gave *N*-methylamine **33**. Hydrogenolysis was followed by oxidation with CAN to give bisisoquinolinequinone **35**. Incomplete hydrogenolysis gave the monobenzylated product **34** (X-ray).[17] Completion of the synthesis was achieved by treating alcohol **35** with excess angeloyl chloride **36**[18] to give (±)-renieramycin G (**4**).[19,20]

In conclusion, a general approach to both mono- and bistetrahydroisoquinoline alkaloids from a common advanced intermediate has been described. The common intermediate **17** was synthesized from imine **8** in 10 steps and 32% yield. From **17**, (±)-lemonomycinone amide (**7**) was synthesized in nine steps and 16% yield, while (±)-renieramycin G (**4**) was synthesized in eight steps and 18% yield.[21]

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Supporting Information Available: Detailed experimental procedures and spectroscopic data (^1H and ^{13}C NMR, FT-IR, and HRMS) for new compounds, and X-ray analysis data (cif). This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Oxime **24** from **23** ($HONH_3Cl$, KOAc, EtOH/H_2O, 85% yield, X-ray) gave a 1:1 mixture of cis:trans isomers, crystallizing as a 4:1 mixture.
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(20) An authentic sample of renieramycin G was not available for comparison, but spectral data were consistent with published data (ref 2).
(21) We are grateful to Prof. R. M. Williams for sending us a preprint of their manuscript describing the synthesis of (−)-renieramycin G.

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