Communication

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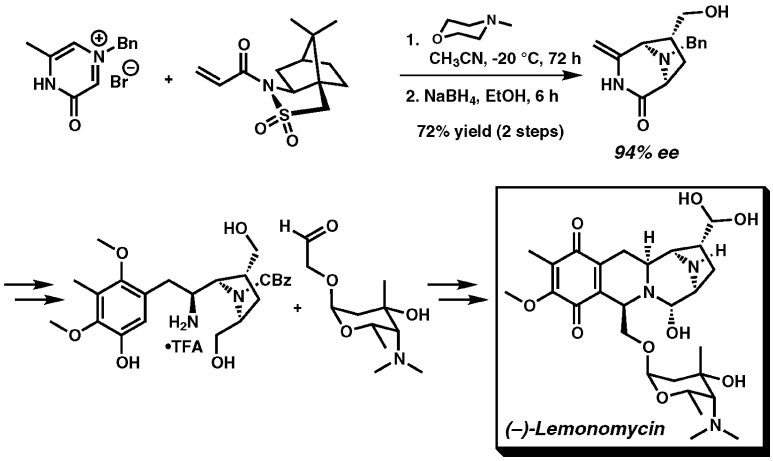

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The Total Synthesis of (−)-Lemonomycin

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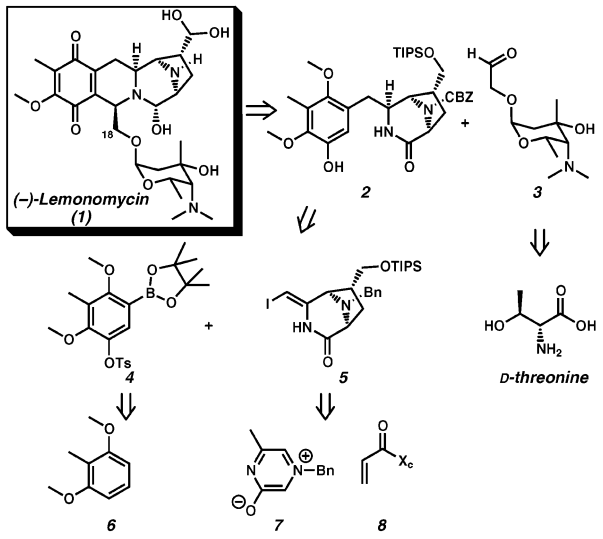
Lemonomycin (**1**), a member of the tetrahydroisoquinoline family of antitumor antibiotics that includes the saframycins, ecteinascidins, and quinocarcins was originally isolated in 1964 from a fermentation broth of *Streptomyces candidus* and was found to have potent antibiotic activity against *Staphylococcus aureus* and *Bacillus subtilis*.[1] The structure of lemonomycin, however, was not elucidated until 2000,[2] when researchers at Wyeth-Ayerst discovered its activity against a variety of antibiotic-resistant bacterial strains. In addition to the connectivity and relative stereochemistry of lemonomycin, the authors reported antibiotic activity against methicillin-resistant *S. aureus* and vancomycin-resistant *Enterococcus faecium*, as well as cytotoxicity against a human colon tumor cell line (i.e., HCT 116). Lemonomycin is unique among the nearly 60 natural products and hundreds of synthetic analogues in this family in that it bears a glycoside at C(18).[3] This is especially striking considering the vast numbers of analogues that have been prepared by derivatization at that position, particularly in the saframycin, quinocarcin, and ecteinascidin families. Moreover, the 2,6-dideoxy-4-amino sugar present in lemonomycin has never been prepared and is rare in nature.[4] The combination of potent biological activity and the challenging novel structure makes lemonomycin an attractive molecule for target-directed synthesis. Herein, we describe the first total synthesis of (−)-lemonomycin by use of a stereoselective dipolar cycloaddition and a novel, diastereoselective Pictet−Spengler cyclization.

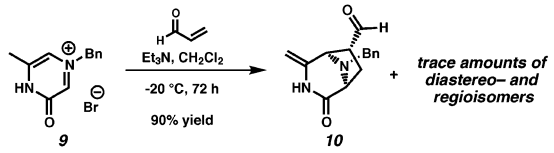
Our retrosynthetic plan for the preparation of lemonomycin is outlined in Scheme 1 and involves the rapid dissection of the alkaloid into three subunits: aryl boronic ester **4**, diaza-bicyclo-[3.2.1]octane **5**, and aminoglycosyloxy aldehyde **3**. To maximize convergency in our synthetic design, we pursued a strategy that would directly incorporate the aminopyranose as part of a Pictet−Spengler reaction to establish the tetrahydroisoquinoline core of the molecule (e.g., **2** + **3**), rather than append the aglycone via the glycosidic linkage. The diazabicycle was expected to arise via a Joule dipolar cycloaddition (e.g., **7** + **8**) with the absolute stereochemistry deriving from an auxiliary controller (i.e., X_c in **8**).[5]

We initiated our efforts toward the synthesis of lemonomycin by investigating the dipolar cycloadditions of an oxidopyrazinium salt (e.g., **7**) with various dipolarophiles. Although these cycloadditions could be viewed as a powerful method to access the desired diazabicylic framework of lemonomycin, such reactions (first reported by Joule) have suffered from modest yields and regioselectivity. Moreover, dipole **7** is typically generated and purified using ion exchange chromatography. We sought improvements to produce the quantities of material necessary for advancement through the synthesis and for the eventual development of asymmetric variants.[6,7] To our delight, in situ generation of **7** by deprotonation of bromide salt **9** with Et_3N followed by treatment with acrolein, a dipolarophile not studied by Joule, resulted in a facile cycloaddition to provide bicycle **10** along with significant quantities of inseparable diastereo- and regioisomeric byproducts.

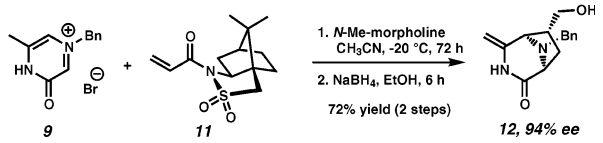
Scheme 1



Scheme 2



Scheme 3



These undesired adducts could be minimized to trace amounts by performing the reaction at −20 °C (Scheme 2).[8]

With a suitable variant of the Joule reaction in hand, we turned our attention to the development of an asymmetric route to the diazabicycle. Implementation of the Oppolzer sultam-derived acrylamide **11**[7] under slightly modified cycloaddition conditions, employing *N*-methyl morpholine as base and CH_3CN as solvent, produced a cycloadduct, which upon treatment with $NaBH_4$ in EtOH provided alcohol **12** in 72% yield and 94% ee (Scheme 3).[9]

Elaboration of enamide **12** by protection of the free hydroxyl functionality as a silyl ether and iodination produced *Z*-iodoenamide **5** as a single isomer (Scheme 4). Suzuki fragment coupling of iodide **5** with boronic ester **4**[9b] afforded aryl enamide **13**. Catalytic hydrogenation of the hindered trisubstituted olefin was sluggish but proceeded at 1000 psi with concomitant cleavage of the benzylamine unit to produce **14** as a single diastereomer.[10] To convert **14** into a suitable substrate for the key Pictet−Spengler cyclization, the 2° amine was converted to a urethane (CBZCl,

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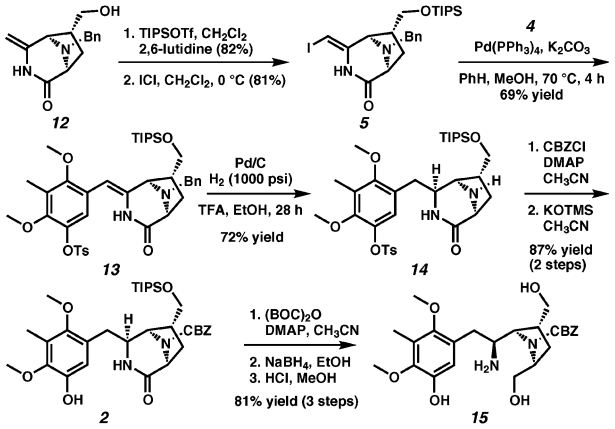
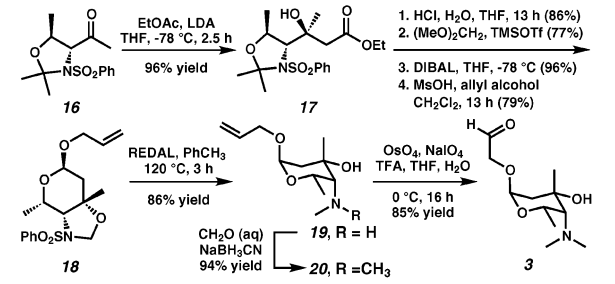
Scheme 4



Scheme 5

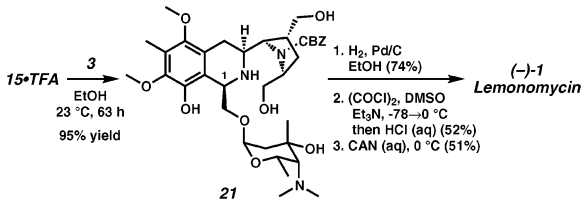


DMAP), and the phenol was liberated from its sulfonate ester (KOTMS) to provide **2**. Unfortunately, this amide was highly unreactive, and all attempts to couple **2** to aldehydes via Pictet−Spengler cyclization failed. Thus, we turned to the more reactive aminotriol **15**, which was accessed by activation of the amide with BOC_2O (with concomitant protection of the phenol), reduction with $NaBH_4$,[11] and cleavage of the two BOC moieties and TIPS ether by methanolic HCl. This compound (employed as a TFA salt) proved much more active in Pictet−Spengler cyclizations, and in model studies with a variety of α-hydroxy acetaldehyde derivatives it typically produced diastereomerically pure tetrahydroisoquinoline products.

The synthesis of the aminopyranose began following conversion of D-threonine to ketone **16**.[12,13] Felkin-controlled addition of the lithium enolate of ethyl acetate to ketone **16** produced aldol adduct **17** as a single observable diastereomer (Scheme 5).[10,14] Hydroxy ester **17** was further processed by acid-mediated acetonide cleavage with subsequent lactonization, conversion to an oxazolidine, diastereoselective reduction to the corresponding lactol and incorporation of allyl alcohol to produce bicycle **18**. Reductive cleavage of the oxazolidine with concomitant removal of the benzenesulfonyl group provided the 2° amine **19**, which was methylated by reductive amination to afford allyl glycoside **20**. Oxidative cleavage of the allyl group by catalytic dihydroxylation of **20** in the presence of $NaIO_4$ furnished α-glycosyloxy acetaldehyde derivative **3**.

The completion of the total synthesis now relied on the success of the unprecedented Pictet−Spengler cyclization of the aminoglycosyloxy aldehyde **3** and the TFA salt of aminotriol **15** (Scheme 6). In the event, simply mixing the two compounds in EtOH at room temperature produced the desired adduct **21** as a single diastereomer at C(1) in 95% yield.[15] Elaboration of tetrahydroisoquinoline **21** to the natural product was straightforward and involved hydrogenolytic cleavage of the CBZ group, bis Swern oxidation, and treatment with CAN to provide (−)-lemonomycin (**1**). The fully synthetic material obtained by this sequence proved identical in all respects to a sample obtained from natural sources.

Scheme 6



In summary, we have developed the first total synthesis of the novel glycosylated tetrahydroisoquinoline antitumor antibiotic (−)-lemonomycin (15 steps from **9**). The highly convergent synthesis features an asymmetric dipolar cycloaddition that sets the stereochemistry of the aglycone core, a Suzuki coupling to connect the diazabicycle to the aryl subunit, and a stereoselective Pictet−Spengler reaction that incorporates the aminoglycoside directly without the need for late-stage glycosylation or protecting group manipulations. The novel aminopyranose was prepared using a highly diastereoselective Felkin-controlled acetate aldol reaction to a threonine-derived ketone. The utilization of this strategy for the synthesis of nonnatural glycosylated tetrahydroisoquinoline derivatives for biological evaluation is currently under investigation.

Acknowledgment. This work is dedicated to Professor E. J. Corey on the occasion of his 75th birthday. The authors are grateful to Caltech, the University of California TRDRP (predoctoral fellowship to E.R.A.), and the J. Irvine Foundation (predoctoral fellowship to E.G.C.) for financial support. We also thank T. Y. Lam for experimental assistance and Dr. H. He (Wyeth-Ayerst) for an authentic sample of (−)-**1**.

Supporting Information Available: Experimental details (PDF) and crystallographic details (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(3) For a comprehensive review of the chemistry and biology related to the tetrahydroisoquinoline alkaloids, see: Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669−1730.
(4) The aminopyranose of **1** has been found in only two unrelated natural product families. For a list of references, see the Supporting Information.
(5) (a) Kiss, M.; Russell-Maynard, J.; Joule, J. A. *Tetrahedron Lett.* **1987**, *28*, 2187−2190. (b) Allway, P. A.; Sutherland, J. K.; Joule, J. A. *Tetrahedron Lett.* **1990**, *31*, 4781−4782. (c) Yates, N. D.; Peters, D. A.; Allway, P. A.; Beddeoes, R. L.; Scopes, D. I. C.; Joule, J. A. *Heterocycles* **1995**, *40*, 331−347.
(6) Scott and Williams have developed an oxidative dipolar cycloaddition for the synthesis of related natural products. See: Scott, J. D.; Williams, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 2951−2956 and references therein.
(7) Garner et al. have utilized a related dipolar cycloaddition that resulted in the elegant enantioselective total synthesis of quinocarcin. See: Garner, P.; Ho, W. B.; Shin, H. *J. Am. Chem. Soc.* **1993**, *115*, 10742−10753.
(8) To facilitate isolation of the desired isomer, we have adopted an in situ procedure that involves reduction of the aldehyde to a 1° alcohol and protection as a TIPS ether. The overall yield for this three-step transformation is 72% and has been carried out on a 10 g scale.
(9) (a) Unless otherwise noted, all reactions were performed at ambient temperature (20 °C) for 1 h or less. (b) See Supporting Information for full experimental details.
(10) The relative configuration has been established by X-ray crystallographic analysis of a derivative; see the Supporting Information.
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(15) Although we have not fully characterized any other products of this PS cyclization, purification by HPLC must remove any trace diastereomers (<3%) resulting from the initial cycloaddition (94% ee).

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