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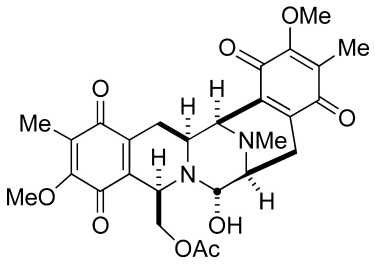
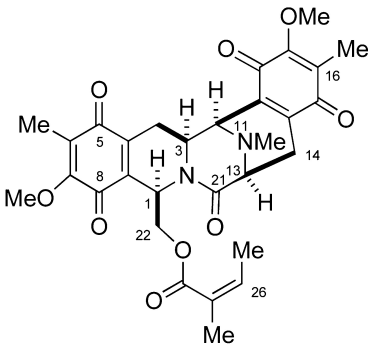
Jonathan W. Lane, Yuyin Chen, and Robert M. Williams

J. Am. Chem. Soc., **2005**, 127 (36), 12684-12690• DOI: 10.1021/ja0535918 • Publication Date (Web): 19 August 2005



1, Jorumycin



2, Renieramycin G

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Asymmetric Total Syntheses of (−)-Jorumycin, (−)-Renieramycin G, 3-*epi*-Jorumycin, and 3-*epi*-Renieramycin G

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Abstract: The total synthesis of (−)-jorumycin (**1**) and (−)-renieramycin G (**2**) has been accomplished in 25 and 23 steps, respectively, from 5-benzyloxy-2,4-dimethoxy-3-methyl-benzyl alcohol. The synthesis features a substrate-tunable stereoselective intramolecular Pictet−Spengler-type reaction for the construction of the key pentacyclic core of both targets, bearing either the natural configuration or the epimeric configuration at C-3. With access to a C-3 *epi*-pentacyclic framework, 3-*epi*-jorumycin (**32**) and 3-*epi*-renieramycin G (**34**) were also successfully synthesized. Furthermore, preliminary biological evaluation of 3-*epi*-jorumycin (**32**), in addition to relevant synthetic intermediates, revealed that significant cytotoxicity had been retained in these compounds. Therefore, these early studies constitute the basis for a new structure activity relationship (SAR) investigation for this class of antitumor antibiotics.

Introduction

The antitumor antibiotics belonging to the tetrahydroisoquinoline family have been studied thoroughly, and numerous natural products within the class have been isolated.[1] (−)-Jorumycin (**1**), a member of this family, was isolated from the mantle and mucus of the pacific nudibranch *Jorunna funebris* (Figure 1).[2] (−)-Jorumycin (**1**) is closely related to the safracins (**6**−**8**), members of the renieramycin family (**2**−**4**), and, most notably, Ecteinascidin 743 (Et)-743 (**5**), which was demonstrated to be a highly promising, exceedingly potent antitumor agent currently in phase II/III clinical trials.[3] In general, the tetrahydroisoquinoline family of alkaloids include potent cytotoxic agents that display a range of biological properties such as antitumor and antimicrobial activities.[1] Consistent with other members in the group, (−)-jorumycin (**1**) also harbors potent biological activities. Specifically, **1** has shown activity against NIH 3T3 tumor cells (100% of inhibition at 50 ng/mL) and has displayed cytotoxicity (IC_{50} 12.5 ng/mL) against other tumor cell lines at very low concentrations. Additionally, **1** was shown to inhibit the growth of various Gram-positive bacteria (e.g., *Bacillus subtilis*, *Staphylococcus aureus*) at a concentration lower than 50 ng/mL.[2] An efficient semisynthesis of **1** from a closely related natural product, renieramycin M (**4**), was recently reported by Saito and coworkers.[4]

(−)-Renieramycin G (**2**) was isolated from the marine sponge *Xestospongia caycedoi* by Davidson in 1992 (Figure 1).[5] Despite having an amide carbonyl residue at C-21, **2** was reported to retain cytotoxicity against human cancer cells with MIC values of 0.5 and 1.0 μg/mL against KB and LoVo cell lines, respectively.[5] This is surprising in light of the fact that virtually all biologically active members of this family of tetrahydroisoquinoline alkaloids possess a carbinolamine or cyano function at C-21 that permits the formation of a potent, electrophilic

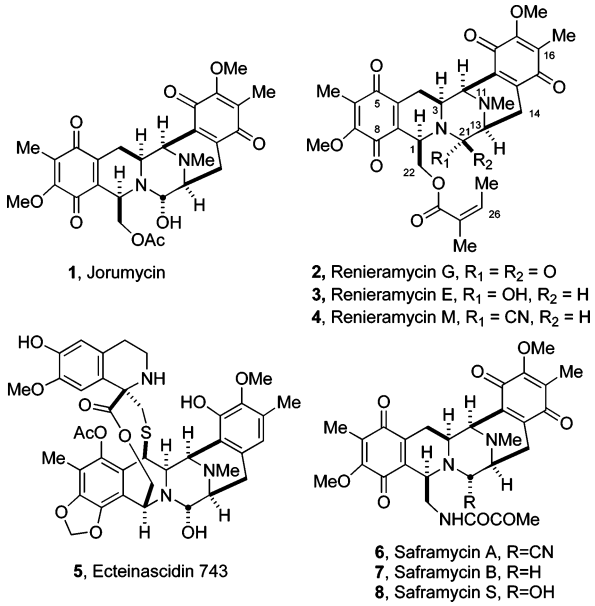


Figure 1. Tetrahydroisoquinoline alkaloids.

(1) For a review, see: Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669−1730.
(2) Fontana, A.; Cavaliere, P.; Wahidulla, S.; Naik, C. G.; Cimino, G. *Tetrahedron* **2000**, *56*, 7305−7308.
(3) Aune, G. J.; Furuta, T.; Pommier, Y. *Anti-Cancer Drugs* **2002**, *13*, 545−555.
(4) Saito, N.; Tanaka, C.; Koizumi, Y.-i.; Suwanborirux, K.; Amnuoypol, S.; Pummangura, S.; Kubo, A. *Tetrahedron* **2004**, *60*, 3873−3881.
(5) Davidson, B. S. *Tetrahedron Lett.* **1992**, *33*, 3721−3725.

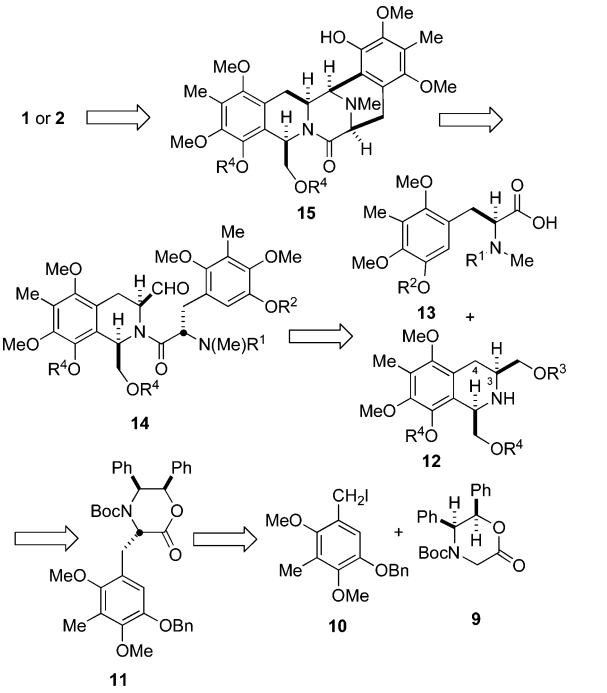
10.1021/ja0535918 CCC: $30.25

iminium ion species that has been implicated in the formation of covalent bonds to DNA and possibly other biomacromolecules.[1]

Previously, our laboratory reported an efficient method for the construction of a highly functionalized pentacyclic tetrahydroisoquinoline relevant to the ecteinascidin, saframycin, safracin, and renieramycin families of antitumor alkaloids.[6a] The approach, which was based on the use of sequential asymmetric Staudinger and Pictet−Spengler cyclization reactions, ultimately afforded a pentacyclic core containing an alkene group at the C3−C4 position (renieramycin numbering). Further employment of this intermediate in the synthesis of relevant natural product targets mandates retention of the alkene (for cribrostatin 4), saturation, or, in the case of the ecteinascidins and bioxalomycins, heteroatom functionalization at C3−C4 position. As part of a program directed toward efficient, asymmetric total syntheses of relevant members of the tetrahydroisoquinoline family,[6] improvements were sought with respect to the construction of a necessarily versatile pentacyclic ring system that would be of potential use in accessing a variety of these targets. We report here a general method to construct a saturated pentacyclic ring system that should prove useful for the asymmetric total synthesis of several members of this family of natural products and congeners. The utility of this approach is demonstrated here through the first asymmetric total syntheses of (−)-jorumycin (**1**) and (−)-renieramycin G (**2**). Furthermore, en route to **1** and **2**, a serendipitous discovery afforded a method to efficiently and selectively access a related pentacyclic intermediate, epimeric at the C-3 position. The C-3-*epi*-pentacycle was subsequently employed in the synthesis of 3-*epi*-jorumycin (**32**) and 3-*epi*-renieramycin G (**34**). The biological activity of this hitherto unreported stereochemical series is also reported herein.

Our strategy for the total synthesis of (−)-jorumycin (**1**) and (−)-renieramycin G (**2**) is illustrated in Scheme 1. Nucleophilic coupling between the appropriately functionalized aryl iodide **10** and chiral glycine template **9**[7,10] would afford intermediate **11**. Based on the intrinsic symmetry of **1** and **2**, coupling partners **12** and **13**, representing the western and eastern halves of our targets, respectively, can both be derived from **11**. Importantly, compound **12** will bear full saturation at the C3−C4 position (renieramycin numbering), obviating the difficult reduction required through our previous approach.[6a] Cyclization substrate **14** would be available through a convergent coupling between intermediates **12** and **13** followed by oxidation at the appropriate primary alcohol position. An intramolecular Pictet−Spengler condensation through the aldehyde group of intermediate **14** would provide the versatile pentacyclic intermediate **15**. Our intermediate **15** would provide **1** or **2** through straightforward functional group manipulations and should prove useful in the synthesis of related targets and their congeners.

Scheme 1. Retrosynthetic Analysis



Results and Discussion

Historically, numerous synthetic efforts toward members of the saframycin and renieramycin families of antitumor antibiotics have exploited a symmetry-based approach.[8] Such a strategy is logical because, unlike Et-743 which contains a pseudo-symmetrical pentacyclic core,[6a,b,9] the saframycins and renieramycins possess a symmetrical substitution pattern on both the eastern and the western arene units. Indeed, the notion of employing a single common intermediate in a stereoselective and highly symmetrical approach toward any member of the saframycin or renieramycin families was pioneered by Myers

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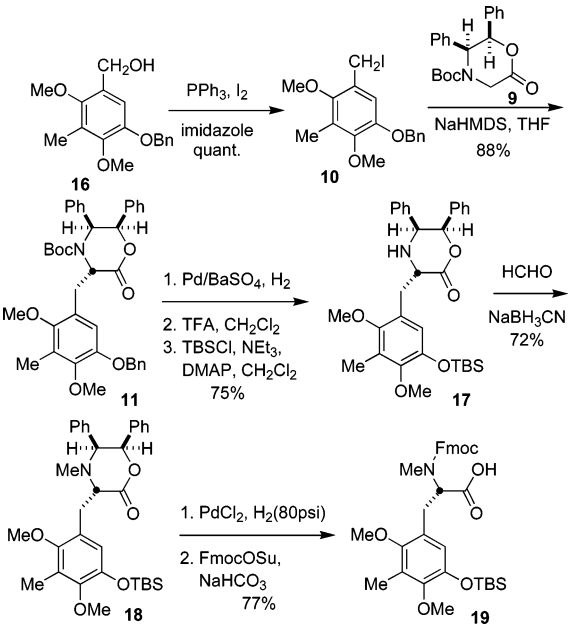
(9) For synthetic approaches to Et-743 and congeners, see: (a) Corey, E. J.; Gin, D. Y.; Kania, R. *J. Am. Chem. Soc.* **1996**, *118*, 9202−9203. (b) Martinez, E. J.; Corey, E. J. *Org. Lett.* **2000**, *2*, 993−996. (c) Martinez, E. J.; Owa, T.; Schreiber, S. L.; Corey, E. J. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 3496−3501. (d) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552−6554. (e) Cuevas, C.; Pérez, M.; Martín, M. J.; Chicharro, J. L.; Fernández-Rivas, C.; Flores, M.; Francesch, A.; Gallego, P.; Zarzuelo, M.; de la Calle, F.; García, J.; Polanco, C.; Rodríguez, I.; Manzanares, I. *Org. Lett.* **2000**, *16*, 2545−2548. (f) Menchaca, R.; Martínez, V.; Rodríguez, A.; Rodríguez, N.; Flores, M.; Gallego, P.; Manzanares, I.; Cuevas, C. *J. Org. Chem.* **2003**, *68*, 8859−8866. (g) Saito, N.; Toshiro, K.; Maru, Y.; Yamaguchi, K.; Kubo, A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 53−69. (h) Saito, N.; Kamayachi, H.; Tachi, M.; Kubo, A. *Heterocycles* **1999**, *51*, 9−12. (i) Saito, N.; Tachi, M.; Seki, R.-I.; Kamayachi, H.; Kubo, A. *Chem. Pharm. Bull.* **2000**, *48*, 1549−1557. (j) Saito, N.; Seki, R.-I.; Kameyama, N.; Sugimoto, R.; Kubo, A. *Chem. Pharm. Bull.* **2003**, *51*, 821−831. (k) Zhou, B.; Guo, J.; Danishefsky, S. J. *Tetrahedron Lett.* **2000**, *41*, 2043−2046. (l) Zhou, B.; Edmondson, S.; Padron, J.; Danishefsky, S. J. *Tetrahedron Lett.* **2000**, *41*, 2039−2042. (m) Zhou, B.; Guo, J.; Danishefsky, S. J. *Org. Lett.* **2002**, *4*, 43−46. (n) Tang, Y.; Liu, Z.; Chen, S. *Chin. Chem. Lett.* **2003**, *14*, 1−2. (o) Tang, Y.; Liu, Z.; Chen, S. *Tetrahedron Lett.* **2003**, *44*, 7091−7094. (p) De Paolis, M.; Chiaroni, A.; Zhu, J. *Chem. Commun.* **2003**, *23*, 2896−2897. (q) Chen, X.; Chen, J.; De Paolis, M.; Zhu, J. *J. Org. Chem.* **2005**, *70*, 4397−4408.

(10) Both antipodes of **9** are commercially available from Aldrich Chemical Co.: **9**, catalog #33, 184-8; antipode of **9**, catalog #33, 181-3.

Scheme 2. Synthesis of Tyrosine Derivative **19**



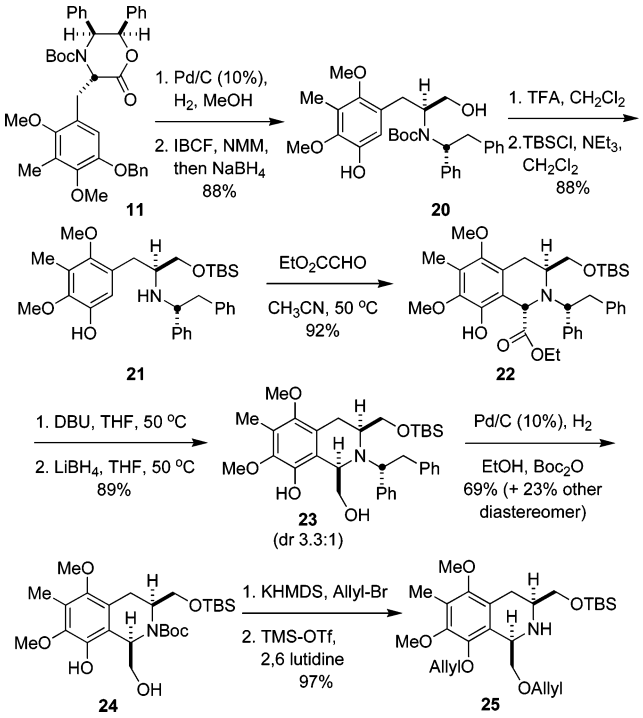
and co-workers in their elegant total synthesis of (−)-saframycin A.[8a] The efficiency of this strategy ultimately culminated in a viable solid-phase route to saframycin A and analogues.[8b]

Our universal building block, compound **11**, was readily available through straightforward methods (Scheme 2).[6b] Initially, alcohol **16**[8e] was converted to the corresponding benzyl iodide derivative **10** in quantitative yield. However, compound **10** was found to be unstable and was therefore utilized crude through immediate condensation with the sodium enolate of oxazinone **9** to afford the alkylation product **11** in 88% yield.[7,10]

Conversion of compound **11** to the requisite amino acid component **13** (Scheme 1), representing the eastern half of **1** and **2**, proceeded as follows. The *O*-benzyl group of **11** was initially removed by catalytic hydrogenation to give the corresponding phenol, followed by removal of the *N*-*t*-Boc protecting group by treatment with TFA to afford an amine intermediate. Subsequent reprotection of the phenol group of this intermediate as the corresponding *O*-TBS ether under standard conditions afforded compound **17** in 75% for three steps. The requisite *N*-Me group was then installed through reductive amination of the secondary amine group in **17** producing *N*-methyl lactone **18** in 72% yield. Removal of the chiral auxiliary in compound **18** by catalytic hydrogenation, followed by protection of the secondary amine as the corresponding Fmoc derivative, furnished amino acid **19** in 77% yield for two steps.

With the eastern tyrosine derivative in hand, synthesis of tetrahydroisoquinoline component **12**, representing the western half of **1** and **2**, commenced as above, from compound **11** (Scheme 3). Initially, subjection of compound **11** to catalytic hydrogenation conditions affected removal of the *O*-benzyl group as well as partial cleavage of the chiral auxiliary, affording a carboxylic acid intermediate. The carboxylic acid group in this intermediate was subsequently converted to the corresponding primary alcohol through a mixed-anhydride reduction producing compound **20** in 88% yield for two steps. Removal of the *N*-*t*-Boc protecting group in compound **20** by treatment with TFA followed by selective protection of the free primary alcohol as the corresponding *O*-TBS ether under standard

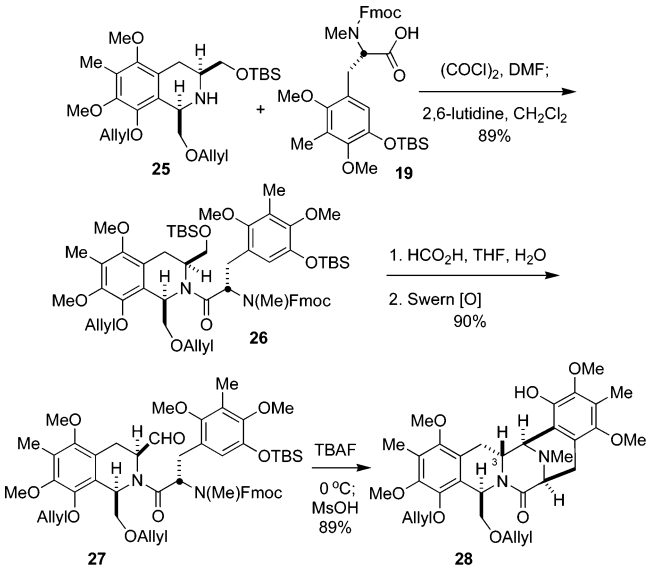
Scheme 3. Construction of Tetrahydroisoquinoline **25**



conditions afforded compound **21** in 88% yield for two steps. Treatment of this substance with ethyl glyoxylate afforded the corresponding *anti*-tetrahydroisoquinoline **22** as a single stereoisomer in 92% yield.

Consistent with prior observations regarding peptide couplings of similarly functionalized amine substrates with sterically demanding carboxylic acid partners,[6a] a syn relationship with respect to the C-1 and C-3 positions was determined to be required for a successful marriage of the eastern and western core units. Therefore, equilibration of the *anti*-carboethoxy group in **22** with DBU[9p,q] afforded an inseparable (3.3:1) mixture of diastereomers in favor of the ester intermediate bearing the desired syn configuration at C-1. Conversion of the ester group in this intermediate to the corresponding primary alcohol was accomplished by subjecting the product mixture to reductive conditions ($LiBH_4$), successfully producing compound **23** (dr 3.3:1) in 89% yield. Exchange of the chiral auxiliary in compound **23** for the corresponding *N*-*t*-Boc protecting group was accomplished in one step by hydrogenolysis of the isomeric mixture in the presence of Boc_2O. This operation afforded the desired substance **24** in 69% yield in addition to 23% of the corresponding *anti*-isomer, which, at this juncture, were easily separated by conventional flash chromatography. In addition to providing a pair of chromatographically separable isomers, the functional group exchange installed appropriate, temporary protection at the nitrogen position on compound **24**. Nitrogen protection was found to be essential for subsequent protecting group installation at the two remaining free alcohol positions, and, furthermore, the *N*-*t*-Boc group could be easily removed under conditions compatible with the overall protection strategy. Therefore, bis-allyl protection of the free alcohol positions in compound **24** afforded a fully protected carbamate intermediate. Finally, the *N*-*t*-Boc group was selectively removed under Lewis-acid conditions, producing compound **25** in excellent yield for two steps. Importantly, the allyl ether groups were chosen for their orthogonal characteristics with respect to the

Scheme 4. Construction of 3-*epi*-Pentacycle **28**



other protecting groups present. Additionally, it was reasoned that the compact size of these groups would minimize steric shielding of the secondary amine and improve the reactivity of compound **25** for coupling with compound **19**.

With straightforward access to compounds **19** and **25** bearing the appropriate features necessary for the convergent peptide coupling, the stage was set for joining the eastern and western halves of **1** and **2**. Amino acid **19** was initially converted into the corresponding acid chloride by treatment with oxalyl chloride and was then coupled to compound **25** in the presence of 2,6-lutidine to afford the desired peptide **26** in 89% yield (Scheme 4).

The next step entailed installation of the requisite aldehyde group in compound **26** to produce the desired cyclization substrate **14** (Scheme 1). Therefore, initial selective removal of the *O*-TBS group at the relevant primary hydroxyl position afforded a free alcohol intermediate, which was subsequently converted to the corresponding aldehyde **27** through a Swern protocol[11] (oxalyl chloride, DMSO, NEt_3) in excellent yield for two steps. Cyclization of compound **27** was accomplished in a one-pot procedure. Initial treatment of compound **27** with TBAF simultaneously removed the phenolic *O*-TBS and *N*-Fmoc groups, producing an iminium intermediate through collapse of the resulting free secondary amine group onto the aldehyde group. Subsequent treatment of this reactive intermediate in situ with excess MsOH promoted nucleophilic attack of the electron-rich eastern arene unit onto the electrophilic iminium species. This reaction generated compound **28**, exclusively, in 89% yield bearing the opposite configuration at C-3 with respect to the natural products. The structure of compound **28** was subsequently confirmed through single-crystal X-ray analysis (Figure 2).

The observed epimerization at C-3 was quite unexpected. On one hand, Danishefsky and co-workers obtained a 3-*epi*-pentacyclic intermediate en route to cribrostatin IV (renieramycin H) through an intramolecular C3−C11 bond-forming Mannich condensation.[12] On the other hand, Corey and co-

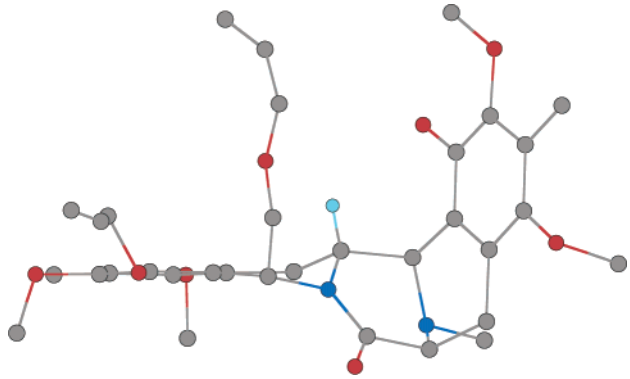


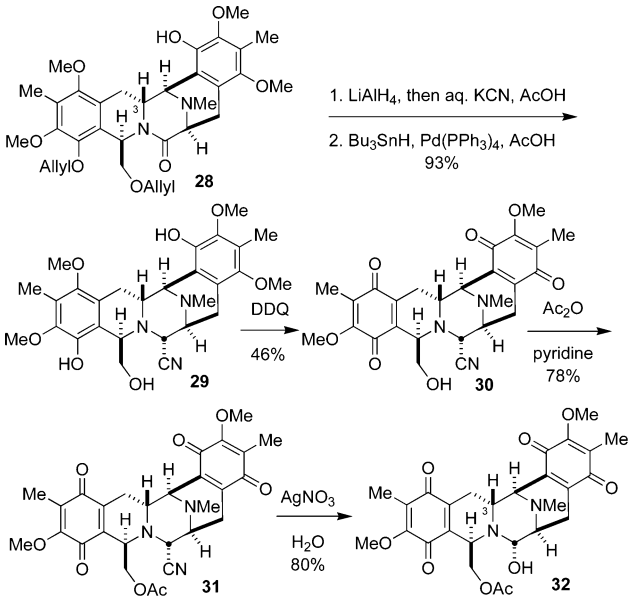
Figure 2. X-ray structure of 3-*epi*-pentacycle **28**.

workers, in their groundbreaking total synthesis of Et-743, deployed a hemi-aminoacetal derivative to effect a C19−C11 bond-forming process that selectively cyclized to a key pentacyclic intermediate bearing the natural configuration at C-3.[9a,b] Although the C3-*epi* cyclization conundrum posed an initial obstacle with respect to the synthesis of **1** and **2**, the efficient route to compound **28** fortuitously presented a unique opportunity. Indeed, selective access to a pentacyclic intermediate bearing the opposite configuration at C-3 would, in turn, provide a gateway to a hitherto unexplored series of C3-*epi*-tetrahydroisoquinoline natural product analogues. Structure−activity relationships (SARs) have been reported on potent analogues of saframycin A (**6**) by Myers and co-workers,[8b,d] and Corey, Schreiber, and co-workers have prepared synthetic analogues of Et-743 (**5**) (e.g., phthalascidin, Pt-650) that maintained virtually the same cytotoxicity as the parent natural product.[9c] Additionally, studies by Ong and co-workers toward the development of a pentacyclic scaffold mimic of saframycin A resulted in a compound of diminished potency with respect to the parent natural product.[8k] However, to date SAR investigations have not addressed the cytotoxicity profiles of epimeric members of the tetrahydroisoquinoline family bearing the pentacyclic skeleton characteristic of the saframycins. The specific global conformations of these compounds will most likely reflect the individual stereochemical configurations contained within the pentacyclic system. Therefore, one could hypothesize that a structural modification of this variety could manifest into a significantly altered backbone conformation for the epimeric analogues relative to their respective natural product counterparts. These structural differences could, in turn, enhance or diminish the ability of these epimeric compounds to participate in noncovalent and covalent binding in the minor groove of DNA.[13]

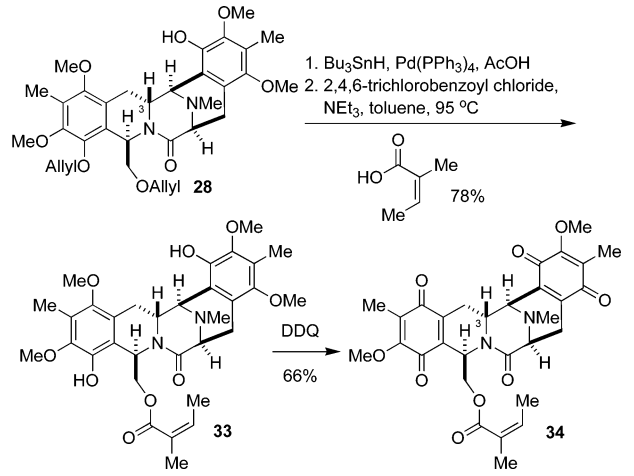
With these thoughts in mind, we turned our attention toward the conversion of compound **28** to the C-3-*epi* variants of compounds **1** and **2**, 3-*epi*-jorumycin (**32**) and 3-*epi*-renieramycin G (**34**), respectively. The synthesis of 3-*epi*-jorumycin (**32**) commenced with conversion of the amide group in compound **28** to the corresponding aminonitrile (Scheme 5). This conversion entailed initial reduction of the amide group ($LiAlH_4$, THF) followed by trapping of the resulting carbinolamine group with cyanide (aqueous KCN, AcOH) affording the desired aminonitrile intermediate. Subsequent reductive removal of the allyl groups from this species afforded compound **29** in 93% yield for two steps. Initial DDQ oxidation of the

(11) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651−1660.
(12) Chan, C.; Heid, R.; Zheng, S.; Guo, J.; Zhou, B.; Furuuchi, T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 4596−4598.
(13) Hill, G. C.; Remers, W. A. *J. Med. Chem.* **1991**, *34*, 1990−1998.

Scheme 5. Synthesis of 3-*epi*-Jorumycin (**32**)



Scheme 6. Synthesis of 3-*epi*-Renieramycin G (**34**)



hydroquinone units in compound **29** afforded bis-quinone **30** in 46% yield. The primary hydroxyl group in compound **30** was then acylated to give compound **31** in 78% yield. Treatment of compound **31** with aqueous $AgNO_3$ cleanly afforded 3-*epi*-jorumycin (**32**) in 80% yield. The relative configurations at the aminonitrile and carbinolamine positions (C-21) of compounds **30** and **32**, respectively, were verified through ^{1}H NMR coupling constant analysis.[14]

With our first epimeric target in hand, efforts were then directed toward the conversion of compound **28** to 3-*epi*-renieramycin G (**34**). Thus, initial removal of the allyl groups in compound **28** afforded a triol intermediate (Scheme 6). Selective acylation of the primary alcohol group in this intermediate with angelic acid was accomplished under modified Yamaguchi conditions[15] to afford compound **33** in 78% yield for two steps. Subsequent DDQ oxidation of the hydroquinone units in compound **33** to the corresponding bis-quinone produced 3-*epi*-renieramycin G (**34**) in 66% yield.

Table 1. Antiproliferative Activity of 3-*epi*-Jorumycin (**32**) and Related Synthetic Intermediates[a]

	cell line	
compound	A549	HCT-116
29	>10	>10
30	6.2	4.4
31	5.1	2.0
32	>10	4.9

[a] Values reported are GI_{50} in μM.

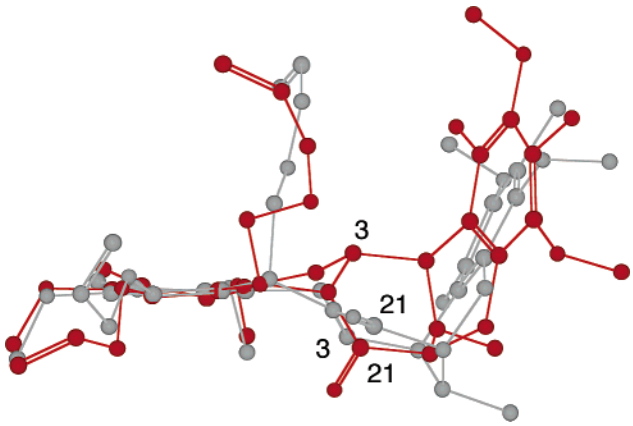


Figure 3. Overlay of compounds **28** (red) and **41** (gray).

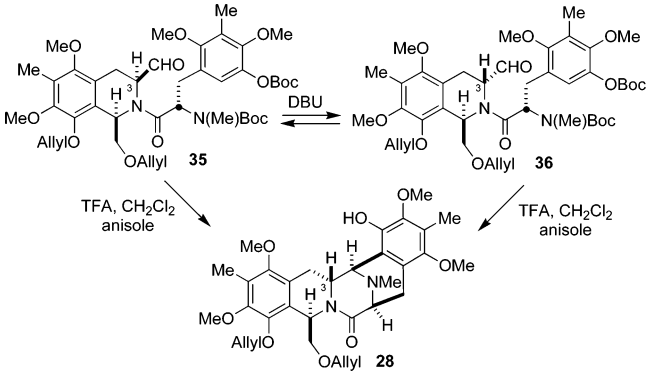
Preliminary cytotoxicity assays were conducted on compounds **29**−**32** to determine whether antiproliferative activity had been retained. Compounds **29**−**32** were screened against two human cancer cell lines (A549 and HCT-116) (Table 1), and results revealed low micromolar inhibition profiles for all compounds tested, verifying the retention of antitumor potential for this new class of agents despite the inversion of configuration at C-3. However, as (−)-jorumycin (**1**) and presumably related intermediates are known to be unstable,[2] accurate determinations of relative cytotoxicity for the 3-*epi* analogues in comparison to the parent natural products (**1** and **2**) would have to be conducted simultaneously. This requirement, therefore, provided additional motivation for the development of a viable synthetic route to our original targets, compounds **1** and **2**.

It is quite significant that the C-3-*epi* substances display substantial cytotoxicity, and this was quite unexpected based on an initial consideration of the anticipated substantial change in geometry that the C-3-*epi* stereochemistry would render on C-21, the well-accepted site of DNA alkylation within the saframycin-ecteinascidin family of antitumor agents.[1] To gain some preliminary insight into the C-3-*epi* series, we have compared the geometry of compound **28** as revealed through X-ray analysis with the energy minimized geometry of **41** (vide infra) as shown in the overlay presented in Figure 3. While these are both amide-containing substrates, the overall spatial arrangements of the C-21 carbon atom in both substrates are found in a surprisingly similar region of space when the left-hand A−B ring systems are overlapped. This preliminary modeling exercise provides the reasonable expectation that the C-3-*epi* compounds, such as **30** and **31**, should be functionally capable of alkylating the exocyclic amine group of guanine residues in the minor groove of DNA in a fashion similar to that established for the

(14) 2D NOe analyses of compounds **29**−**32** were inconclusive in regards to establishing the respective configurations at C-21. However, the coupling constants (*J*'s) between H-21 and H-13 were successfully measured for compounds **30** and **32** at 1.9 and 2.1 Hz, respectively. Based on dihedral angles derived from energy-minimized structures of **30** and **32** bearing both possible configurations at C-21, these *J*'s were consistent with the respective assigned stereochemistries at this position.

(15) Hartmann, B.; Kanazawa, A. M.; Depres, J.-P.; Green, A. E. *Tetrahedron Lett.* **1991**, *32*, 5077−5080.

Scheme 7. Cyclization Studies on Alternate Substrates **35**, **36**



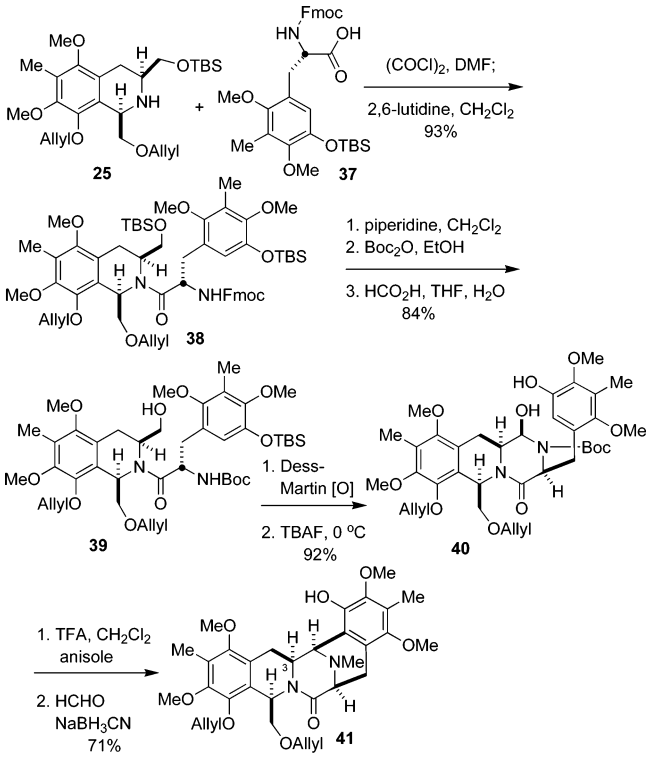
natural products.[1] Efforts to explore the biochemical reactivity of these compounds are presently under study and will be the subject of a separate disclosure.

Access to the natural substances **1** and **2** required a method for the synthesis of a versatile pentacyclic intermediate (**15**) bearing the natural configuration at C-3. To achieve this goal, a thorough investigation was conducted to determine a viable route to obviate the undesired epimerization at C-3. The cyclization of our original substrate, compound **27**, was initially conducted under basic conditions (TBAF) followed by treatment of the incipient iminium intermediate with excess acid (MsOH). Therefore, it was initially conjectured that perhaps the epimerization was mediated by base. This postulate seemed reasonable based on previous reports by Corey and co-workers of similar cyclizations whereby iminium formation and subsequent cyclization were both conducted under acidic conditions to successfully afford compounds bearing the natural configuration at C-3.[9a,b]

To test our theory, a cyclization substrate bearing acid-labile protecting groups at the relevant positions was desired. This new protection strategy would also permit access to a C-3-*epi* cyclization substrate through deliberate base-mediated equilibration at the C-3 aldehyde position (renieramycin numbering). The epimeric substrate would serve to determine the dependence, if any, of the initial configuration at C-3 on the stereochemical outcome of the cyclization. In accord with this strategy, compound **35**, bearing Boc protection at the nitrogen and phenol positions, was synthesized by straightforward methods from peptide **26**.[16] Subsequent treatment of compound **35** with DBU effectively equilibrated the configuration at C-3, affording a diastereomeric mixture of **35** and **36** (dr ∼1:1, Scheme 7). Subjection of compounds **35** and **36**, individually, to TFA afforded exclusively, the 3-*epi* pentacycle **28**, which is consistent with the behavior of compound **27** (Scheme 4).

These studies on compounds **35** and **36** confirmed that the stereochemical outcome of the cyclization at C-3 under these conditions was independent of the initial substrate configuration at C-3, and, importantly, this confirmed that the epimerization was pervasive even in the absence of base. Guided by these preliminary findings, extensive studies were then conducted to determine the appropriate cyclization substrate and reaction conditions necessary to maintain the desired configuration at the C-3 position. These efforts ultimately led to the discovery

Scheme 8. Synthesis of Pentacycle **41**



of compound **40**, a modified substrate lacking a methyl group at the nitrogen position and bearing a free phenol group on the eastern arene unit.

Preparation of compound **40** proved straightforward and commenced with the coupling of modified amino acid **37**,[17] through its corresponding acid chloride, to compound **25** in the presence of 2,6-lutidine to afford the desired peptide **38** in 93% yield (Scheme 8). The *N*-Fmoc group in compound **38** was then removed with piperidine, and the resulting free amine was reprotected as the corresponding Boc carbamate to afford the desired intermediate. Selective removal of the *O*-TBS protecting group at the primary hydroxyl position in this intermediate was accomplished under acidic conditions producing alcohol **39** in 84% yield for three steps. Subsequent oxidation of the primary hydroxyl group in **39** to the corresponding aldehyde through the agency of the Dess−Martin reagent[18] resulted in a hemiaminal intermediate. Removal of the phenolic *O*-TBS group in the intermediate produced compound **40** as a single diastereomer (hemi-aminal configuration established by 2D ROESY NMR) in 92% yield for two steps. Gratifyingly, subjection of substrate **40** to TFA afforded a pentacyclic compound in high yield bearing the desired natural configuration at C-3. Installation of the *N*-Me group in this intermediate through reductive amination with formaldehyde produced compound **41** in 71% yield for two steps, appropriately endowed for conversion to the natural alkaloids.

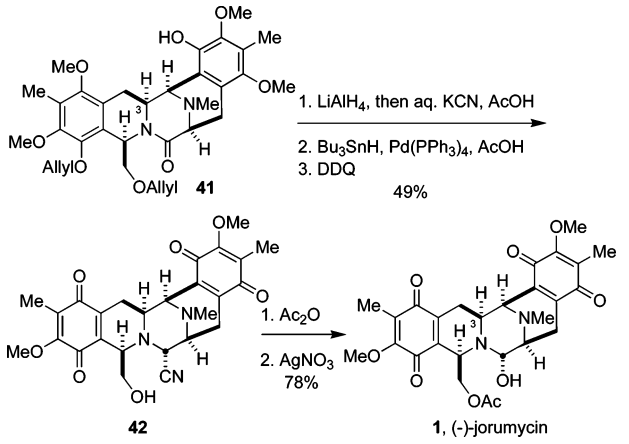
The modified cyclization strategy proceeding through compound **40** was somewhat less convergent than our previous route to 3-*epi*-pentacycle **28** due to necessary protecting group manipulations and a late-stage installation of the requisite *N*-Me group. Nonetheless, the specific structural features of compound

(16) Compound **35** was prepared from peptide **26** through the following sequence: (1) TBAF, THF, room temperature; then excess Boc_2O; (2) Boc_2O, EtOH, room temperature; (3) Dess−Martin [O].

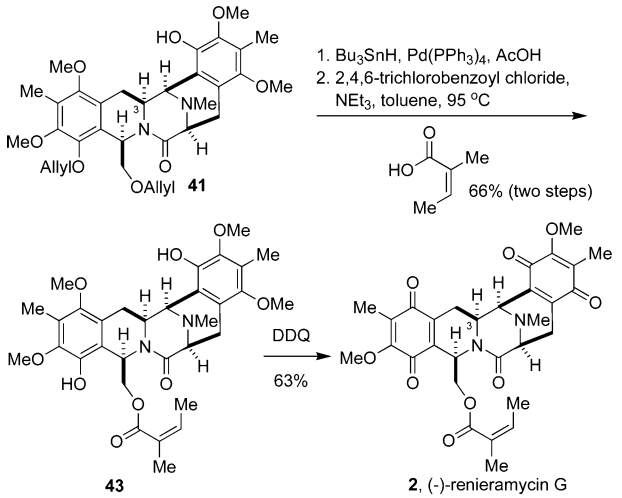
(17) Compound **37** was prepared from amine **17** in two steps: (1) $PdCl_2$, EtOH, H_2; (2) FmocOSu, aqueous $NaHCO_3$, CH_2Cl_2 (see Supporting Information).

(18) Dess, B. D.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.

Scheme 9. Synthesis of (−)-Jorumycin (**1**)



Scheme 10. Synthesis of (−)-Renieramycin G (**2**)



40 were found to be crucial to the success of the cyclization. Indeed, any attempts to cyclize substrates incorporating an acid labile group at the eastern phenolic position or an *N*-Me group resulted only in the production of 3-*epi*-pentacycle products in addition to undesired byproducts.

With compound **41** in hand, we initially endeavored to complete the synthesis of (−)-jorumycin (**1**). In accord with the route to 3-*epi*-jorumycin (**32**), conversion of the amide group in compound **41** to the corresponding aminonitrile proceeded as before ($LiAlH_4$, THF, then aqueous KCN, AcOH). Subsequent reductive removal of the allyl groups in this intermediate afforded the corresponding triol. Oxidation of the hydroquinone units in the triol intermediate afforded the bis-quinone **42** in 49% yield for three steps. Importantly, spectroscopic data from compound **42** matched data from the same intermediate reported previously by Saito and co-workers in their semisynthesis of (−)-jorumycin (**1**) from renieramycin M (**4**).[4] The primary hydroxyl group in compound **42** was then acylated to give an acetate intermediate, after which treatment of this intermediate with aqueous silver nitrate cleanly afforded (−)-jorumycin (**1**) in 78% yield for two steps (Scheme 9). The synthetic jorumycin had spectral data consistent with that previously reported for the natural substance[2] and for the material derived through semisynthetic methods.[4]

Consistent with our route to 3-*epi*-renieramycin G (**34**), conversion of compound **41** to (−)-renieramycin G (**2**) proved straightforward. Initial removal of the *O*-allyl groups from compound **41** afforded a triol intermediate, which was subjected to selective acylation of the primary alcohol group with angelic acid under modified Yamaguchi conditions[15] as above, to afford compound **43** in 66% yield for two steps. Subsequent DDQ oxidation of the hydroquinone units in compound **43** to the corresponding bis-quinone produced (−)-renieramycin G (**2**) in 63% yield (Scheme 10). The synthetic (−)-renieramycin G had spectral data fully consistent with those previously reported for the natural substance.[5,19]

(19) We were unable to acquire an authentic specimen of natural renieramycin G from Prof. B. S. Davidson (ref 5) with which to compare our synthetic sample. The isolation paper (ref 5) notes that the natural product was unstable. Furthermore, an optical rotation for this natural product has heretofore not been recorded.

Conclusion

The asymmetric total syntheses of (−)-jorumycin (**1**) and (−)-renieramycin G (**2**) have been accomplished in 25 and 23 steps, respectively. Additionally, 3-*epi*-jorumycin (**32**) and 3-*epi*-renieramycin G (**34**) were also successfully synthesized, the former of which, including related synthetic intermediates, displayed significant cytotoxicity in preliminary biological evaluation. Efforts to utilize this approach for the concise asymmetric synthesis of other members of the renieramycin family, the ecteinascidins, saframycins, as well as the safracins and some mechanistically inspired analogues, including epimers, are currently under study in our laboratories.

Acknowledgment. We thank the National Institutes of Health for financial support (Grant CA85419) and the NIH National Cancer Institute for postdoctoral fellowship support for J.W.L. (Grant CA105898). We are indebted to Dr. Jeff Spencer, Peter Sabbatini, and Jason Oeh of Celera-SSF for kindly providing the cytotoxicity data for compounds **29**−**32**. We thank Prof. Angelo Fontana (Istituto di Chimica Biomolecolare (ICB) del CNR, Italy) for providing spectral data for (−)-jorumycin. We are grateful to Professor Phil Magnus of the University of Texas, Austin, for sending us a preprint of their manuscript describing the synthesis of (±)-renieramycin G (see accompanying communication in this issue, http://dx.doi.org/10.1021/ja0535817).

Supporting Information Available: Complete experimental and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JA0535918