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Asymmetric Total Syntheses of (−)-Fennebricin A, (−)-Renieramycin J, (−)-Renieramycin G, (−)-Renieramycin M, and (−)- Jorunnamycin A via C−H Activation

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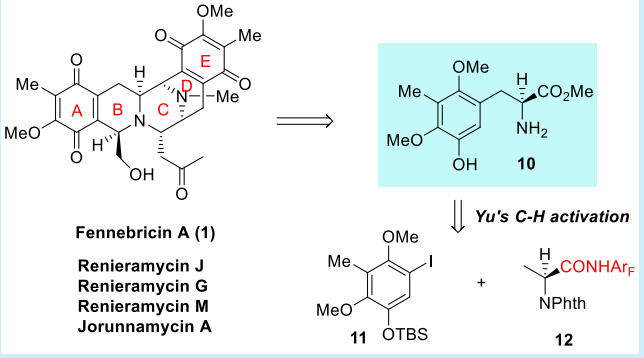
ABSTRACT: Collective total synthesis of five tetrahydroisoquinoline alkaloids including the first total synthesis of (−)-fennebricin A and (−)-renieramycin J has been accomplished. The synthesis features employing a single common amino acid to symmetrically construct the pentacycle of title alkaloids. The palladium-catalyzed arylation of alanine-derived amide developed by Yu was tactically utilized to afford unnatural amino acid building block rapidly and practically. The structure of synthetic (−)-renieramycin M has been confirmed by single crystal X-ray analysis for the first time.



The tetrahydroisoquinoline antibiotics that cover more than 50 natural products such as renieramycins, Et-743, jorumycin, saframycins, quinocarcin, and bioxalomycins have commanded considerable attention from the synthetic community over the past 40 years because of their intriguing chemical structures, potent antitumor and antimicrobial activities, and unique mechanisms of action.[1] Among them, Et-743 is a representative that is used clinically as a drug for the treatment of advanced soft tissue sarcoma.[2]

Fennebricin A (**1**), a new renieramycin-type tetrahydroisoquinoline, was first isolated by Guo and co-workers from the skin of the South China Sea nudibranch *Jorunna Funebris* and its sponge-prey *Xestospongia sp.* in 2014 (Figure 1).[3] Although the absolute configuration and bioactivities could not be determined then due to the scarcity and instability of **1**, fortuitously, Guo reisolated **1** (3.1 mg) from a different sample collected in Ximao Island, Hainan Province, China. Based on the second isolation, the absolute configuration of **1** was established by ECD computation. Primary bioassay results revealed that fennebricin A (**1**) exhibits significant cytotoxicity against A549 and HL-60 tumor cell lines with IC_{50} values of 6.2 and 2.5 μm, respectively. Given the less potent biological activity of renieramycin J (**2**), the C-1 hydroxyl group may be the key function for the bioactivities of **1**.[3] Intrigued by the chemical structure of **1**, in particular the presence of an acetone side chain at C-21 instead of a carbinolamine or cyano function,[4] we started its total synthesis, hoping to develop a unified and collective approach that would be applicable to other pentacyclic tetrahydroisoquinolines. Herein we wish to report the first total syntheses of **1** and **2** along with the syntheses of three tetrahydroisoquinoline alkaloids.

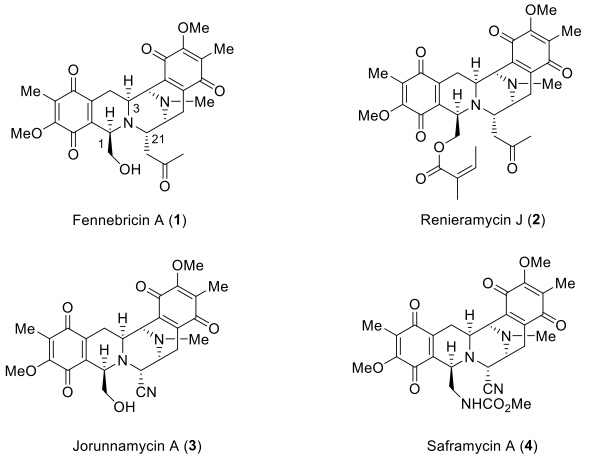


Figure 1. Tetrahydroisoquinoline alkaloids.

As shown in Scheme 1, the acetone side chain at C-21 was envisioned to be generated by utilizing a Mannich reaction

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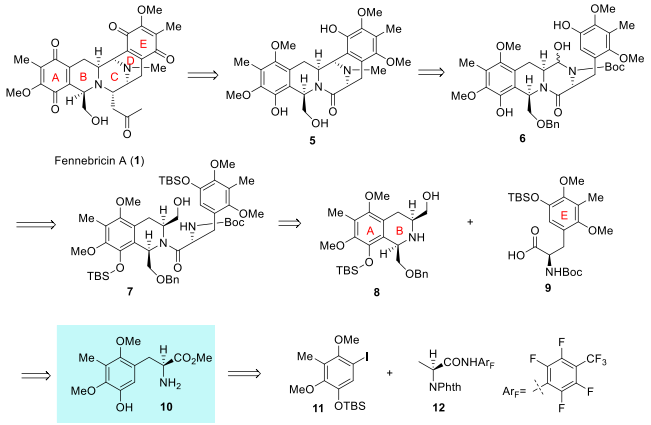
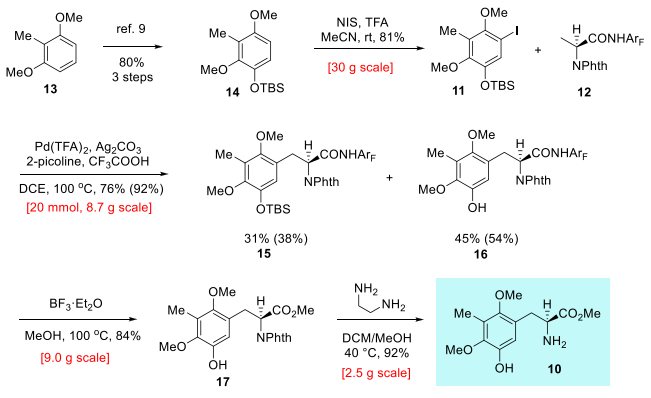
Scheme 1. Retrosynthetic Analysis of (−)-Fennebricin A



with an iminium intermediate derivative of **5**. The CDE ring system could be forged through a Pictet−Spengler cyclization of hemiaminal **6**, which was in turn derived from primary alcohol **7**. Peptide **7** was obviously coupled between a functionalized amine **8** bearing an AB ring system and carboxylic acid partner **9** containing an E ring. The above two partners would be eventually prepared from a single common amino acid derivative **10**. Because **10** is an unnatural amino acid derivative, whose preparation usually would require a lengthy process, and inspired by Yu's[5] recent methodology of palladium-catalyzed C−H activation and others,[6] we proposed that **10** could be prepared from arylation of alanine-derived amide **12** with aryl iodide **11**. To our knowledge, this methodology has not been applied in total synthesis yet. It is noteworthy that two reports utilizing C−H activation to synthesize tetrahydroisoquinoline alkaloids appeared in the literature after we had started the synthesis. In 2019, Stoltz and co-workers reported concise syntheses of (−)-jorunnamycin A and (−)-jorumycin enabled by asymmetric catalysis.[7] Shi and co-workers published a scalable formal synthesis of (−)-quinocarcin employing an 8-aminoquinoline directing group shortly thereafter.[8]

Our synthesis commenced with the preparation of aryl iodide **11** (Scheme 2), whose precursor **14** was readily prepared in 80% yield according to a three-step, well-known procedure[9] from commercially available 2, 6-dimethoxytoluene (**13**). Regiospecific iodination of aryl **14** with NIS/TFA gave rise to aryl iodide **11** in 81% yield at 30 g scale. With

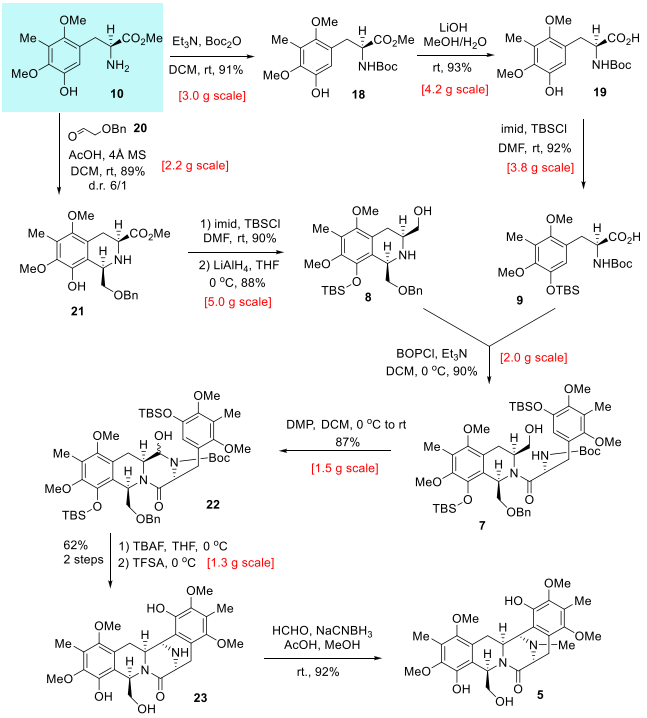
Scheme 2. Preparation of Amino Ester 10 through the Yu's C−H Activation



decagram quantities of **11** in hand, we turned our attention to Yu's C−H arylation. Despite the wide substrate scope recorded, it is uncertain whether Yu's method can be workable in our substrate because there were few cases in which aryl ring were substituted with more than two groups. To this end, alanine derivative **12**, which contains a $CONHAr_F$ amide auxiliary as a directing group, was used as an amino acid building block. The proposed reaction between **11** and **12** proceeded smoothly under Yu's optimal conditions, where 10 mol % $Pd(TFA)_2$ and 20 mol % 2-picoline ligand were used to give coupled products **15** and **16** in 76% combined yield, with 92% yield based on the recovered starting material. Elongating the reaction is not recommended due to the decomposition. Although cleavage of the phenolic *O*-TBS group was observed, this was inconsequential because both **15** and **16** could be converted into the same methyl ester **17** after removal of the $CONHAr_F$ amide directing group under $BF_3{\cdot}Et_2O$ conditions. Further removal of the phthalimide protecting group with ethylenediamine generated amino ester **10**. It is noteworthy that key amino ester **10** could be prepared in approximately 60% yield over three steps from readily available aryl iodide **11** and alanine **12** at gram scale, highlighting the potentialities of C−H activation in total synthesis.[10]

As shown in Scheme 3, with versatile amino ester **10** in hand, the stage was set to access the key peptide coupling

Scheme 3. Synthesis of the Common Pentacyclic Ring System of Tetrahydroisoquinoline



components, amino alcohol **8** and carboxylic acid **9**. To this end, in one pathway, protection of amino ester **10** with a Boc group at the nitrogen atom followed by hydrolysis of ester **18** with LiOH yielded carboxylic acid **19**, which was converted to phenolic *O*-TBS protected compound **9**; in another pathway, intermolecular Pictet−Spengler reaction of **10** with benzoxyacetaldehyde (**20**) under Zhu's conditions[11] provided tetrahydroisoquinoline **21** with 6:1 dr. Silylation of phenol **21** followed by LAH reduction of the ester provided amino

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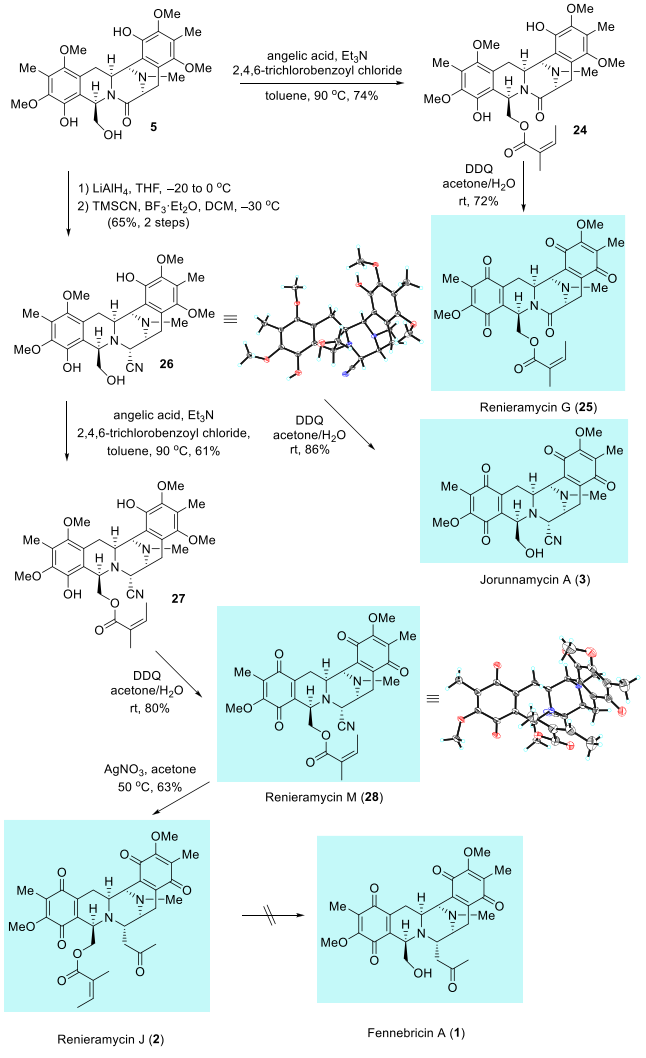
alcohol **8**. Notably, all of the above-mentioned reactions resulted in excellent yields and could be carried out at gram scale. Although acylation of 1,3-*cis*-disubstituted tetrahydroisoquinoline proved difficult,[12] after extensive efforts, peptide **7** was finally synthesized in 90% yield from coupling of **8** and **9** in the presence of BOPCl and Et_3N.[13] The undesired coupling reaction of primary alcohol of **8** with carboxylic acid **9** was not observed under the conditions. Oxidation of the primary alcohol **7** with DMP provided hemiaminal **22**, whose NMR signals are too complicated to be assigned. In spite of this, after removal of the phenolic TBS protecting group and treatment of phenol intermediate with trifluoromethanesulfonic aicd (TFSA), clean product **23** was obtained, in which the Boc group was concomitantly removed during the intramolecular Pictet–Spengler reaction.[14] Subsequent reductive amination of **23** gave *N*-methylamine **5** in 92% yield.

With the key pentacyclic tetrahydroisoquinoline **5** in hand, we continued the collective total synthesis. As shown in Scheme 4, acylation of primary alcohol **5** with angelic acid under modified Yamaguchi conditions[15] afforded **24**. DDQ oxidation of **24** gave renieramycin G (**25**) smoothly. Meanwhile, LAH reduction of peptide **5** provided a labile hemiaminal intermediate, which was immediately subjected to the conditions of TMSCN and $BF_3{\cdot}OEt_2$ and was then converted to more stable aminonitrile **26**.[16] Aminonitrile **26** is a crystalline compound whose chemical structure including absolute configuration was secured by a single crystal X-ray analysis (CCDC 1972948). Furthermore, DDQ oxidation of aminonitrile **26** provided jorunnamycin A (**3**) in high yield. Similarly, acylation of alcohol **26** gave rise to angelic acid ester **27** using the same procedure as that for **24**. Subsequent DDQ oxidation of **27** furnished renieramycin M (**28**). Our synthetic renieramycin M is also a crystalline compound, and its chemical structure was confirmed by X-ray crystallographic analysis (CCDC 1972949). To our best knowledge, it is the first time acquiring X-ray data for pentacyclic tetrahydroisoquinoline that contains two quinone rings. Moreover, we surprisingly found that there were a few of the previous syntheses in which similar X-ray crystallographic analysis of the synthetic tetrahydroisoquinoline had been performed. Undoubtedly, the crystallographic information would be instructive in the structural elucidation, understanding of the SAR, and drug design for these natural products. Eventually, reieramycin M (**28**), upon treatment with $AgNO_3$ in acetone, underwent an intermolecular Mannich reaction and yielded renieramycin J (**2**).[17,4] As renieramycin J (**2**) is the angelated analogue of (−)-fennebricin A (**1**), logically, direct hydrolysis of **2** would give (−)-fennebricin A (**1**). However, our attempts (Na_2CO_3, K_2CO_3, LiOH, and Bu_2SnO) to accomplish the requisite hydrolysis failed.

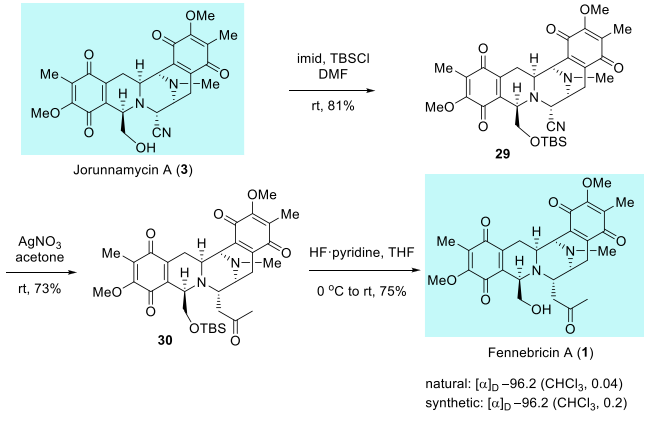
To accomplish the first total synthesis of (−)-fennebricin A (**1**) (Scheme 5), we were redirected to start with jorunnamycin A (**3**). Protection of jorunnamycin A (**3**) gave its TBS ether **29**. Intermolecular Mannich reaction of aminonitrile **29** installed the acetone side chain of compound **30**. Removal of the TBS protecting group with HF·pyridine furnished synthetic fennebricin A (**1**). The synthetic material exhibited physical, spectroscopic, and spectrometric characteristics (NMR, IR, HRMS, and $[\alpha]_D$) identical to those reported for the natural product. As discussed previously, Guo and coworkers assigned the absolute configuration of **1** with the ECD method. In this work, the absolute configuration of **1** could be confirmed unequivocally with the single crystal X-ray analysis of **26** and reieramycin M (**28**), and optical rotation comparison for **1**.

In summary, we successfully completed the first asymmetric total synthesis of (−)-fennebricin A (**1**) and (−)-renieramycin

Scheme 4. Total Syntheses of (−)-Renieramycin G, (−)-Jorunnamycin A, (−)-Renieramycin M, and (−)-Renieramycin J



Scheme 5. Total Synthesis of (−)-Fennebricin A



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J (**2**) in a longest linear sequence of 20 steps from 2,6-dimethoxy-toluene with an overall yield of 4% and 3%, respectively. (−)-Renieramycin G, (−)-jorunnamycin A, and (−)-renieramycin M have also been synthesized using the same strategies. Our synthesis features symmetrically constructing the pentacycle of title alkaloids from a single common amino acid that was readily prepared with the palladium-catalyzed arylation of alanine-derived amide developed by Yu. Further applications of Yu's C−H logic in other natural product syntheses are ongoing, and the results will be disclosed in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01493.

Experimental procedures and analytical data for all new compounds (PDF)

Accession Codes

CCDC 1972948−1972949 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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