Total Synthesis

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Biomimetic Total Synthesis of (−)-Penibruguieramine A Using Memory of Chirality and Dynamic Kinetic Resolution

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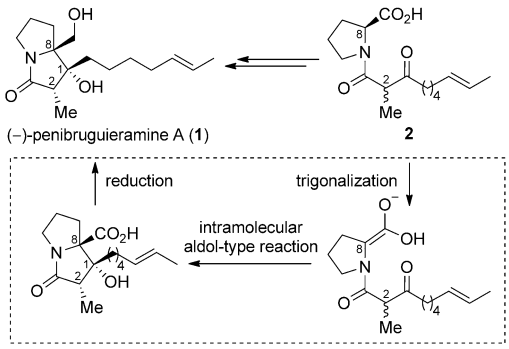
Abstract: *The fully stereocontrolled total synthesis of (−)-penibruguieramine A, a naturally occurring marine pyrrolizidine alkaloid, is described in this study for the first time. The key synthetic sequence is the biomimetic aldol reaction of the proline pentaketide amide. The principles of "memory of chirality" (MOC) and "dynamic kinetic resolution" (DKR) are applied to this reaction for the asymmetric synthesis using proline as the only chiral source. A mechanistic rationale is discussed for the excellent stereochemical outcome in a protic solvent environment.*

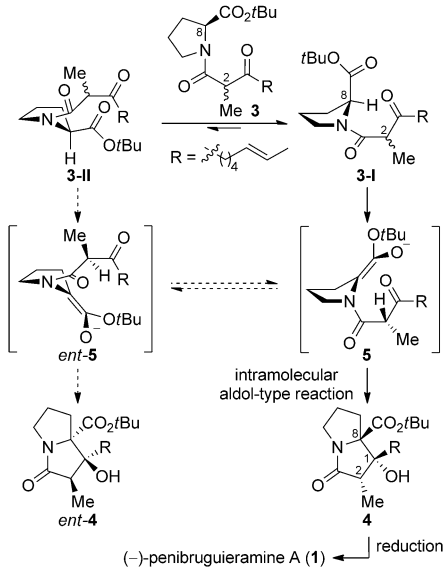
The marine pyrrolizidine alkaloid (−)-penibruguieramine A (**1**, Scheme 1) was recently identified by Guo and co-workers from the endophytic fungus *Penicillium* sp. GD6 associated with Chinese mangroves.[1] The relative configuration of **1** was established by rotating-frame Overhauser effect spectroscopy (ROESY) and its absolute configuration was determined by comparison of the experimentally obtained electronic circular dichroism (ECD) spectra with the calculated ECD data. This natural product has an unprecedented 1-hydroxy-2-methyl pyrrolizidin-3-one skeleton bearing an alkenyl chain at the C1 position and a hydroxymethyl group at the C8 position. A biosynthetic pathway has been proposed,[1] as shown in Scheme 1, in which the bicyclic ring system is generated by an intramolecular aldol-type reaction of proline pentaketide amide **2**.[2] In this process, the chiral center of the proline moiety in **2** might be destroyed by trigonalization and regenerated along with the adjacent stereocenters. Enzymes are most likely involved in this biosynthesis because most chiral natural products are synthesized in nature by enzyme-mediated catalysis.



Scheme 1. Structure of (−)-penibruguieramine A (**1**) and its proposed biosynthetic pathway.

We envisioned that the asymmetric synthesis of penibruguieramine A (**1**) could be achieved from the ester derivatives of **2** without the aid of external chiral influences if the principles of "memory of chirality" (MOC) and "dynamic kinetic resolution" (DKR) were applied to the aldol reaction step.[3–5] MOC and DKR are attractive strategies for asymmetric synthesis. Although there have been reports on the use of DKR, only few studies on the application of MOC to the total synthesis of natural products have been reported.[6,7] Additionally, the combination of these two concepts has not been previously reported for asymmetric synthesis.[8] In this Communication, we report the use of MOC and DKR for the first total synthesis of (−)-penibruguieramine A (**1**) from L-proline. Our synthesis follows the biosynthetic pathway proposed for **1** and features the asymmetric construction of stereocenters with essentially complete diastereo- and enantioselectivity in the absence of external chiral sources.[9]

As outlined in Scheme 2, we envisioned that the intramolecular aldol reaction of proline ester **3** would afford bicyclic compound **4** with the correct absolute and relative configuration required to proceed to penibruguieramine A



Scheme 2. Synthetic strategies for the total synthesis of(−)-penibruguieramine A (**1**).

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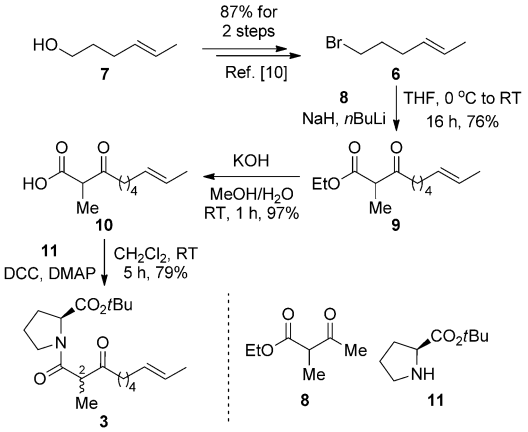
(**1**). The chiral center of the proline moiety could direct the stereochemical course of the aldol reaction and could be preserved in the reaction product. For the success of this MOC reaction, axially chiral enolate **5** (with an arbitrary enolate geometry) should be formed selectively over *ent*-**5** via the favored conformer **3**-**I**. Additionally, chiral enolate **5** must have a sufficiently large energy barrier against racemization.[3] We anticipated the successful outcome of this reaction after considering the study reported by Stoodley et al. demonstrating the use of MOC in an aldol reaction of simpler proline derivatives.[10] In that report, although the diastereoselectivity and yield were low, a certain degree of configuration retention was obtained at the chiral center of the proline moiety.

The stereochemistry at the C2 position of aldol product **4** can be introduced prior to the aldol reaction step. However, the C2 stereocenter of **3** would not be retained over the course of the reaction due to facile enolization. We envisioned that if the DKR process occurred at the C2 position during the aldol reaction and the reaction proceeded via conformationally favored intermediate **5**, then the C2 stereocenter would not require installation. Based on this assumption, the aldol substrate employed in this total synthesis was prepared as a diastereomeric mixture at the C2 position.

Our total synthesis started from known bromide **6**,[11] which was readily prepared from commercial alcohol **7** (Scheme 3). The alkylation of the dianion of ethyl-2-methyl-

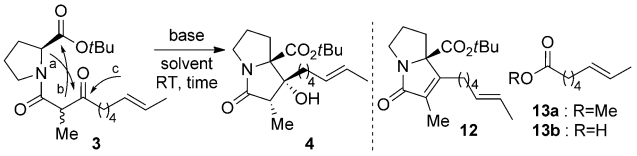


Scheme 3. Synthesis of proline pentaketide amide **3**. DCC = *N*,*N*′-dicyclohexylcarbodiimide, DMAP = 4-(*N*,*N*-dimethylamino)pyridine, THF = tetrahydrofuran.

acetoacetate (**8**) with bromide **6** afforded the racemate of ketoester **9**.[12] Subsequent hydrolysis with KOH in aqueous MeOH afforded β-ketoacid **10**, which was coupled with L-proline *tert*-butyl ester (**11**) to yield aldol substrate **3** as a diastereomeric mixture at the C2 position in an overall good yield. The diastereomeric ratio of **3** was 1.4:1, implying that epimerization at the C2 position occurred during the coupling reaction process (see below).

With substrate **3** in hand, we investigated the envisioned intramolecular aldol reaction. In addition to the desired aldol reaction (denoted path a; results of the reaction given in Table 1), **3** can undergo other competitive side reactions,

Table 1: Reaction conditions for the intramolecular aldol reaction of **3**.[a]

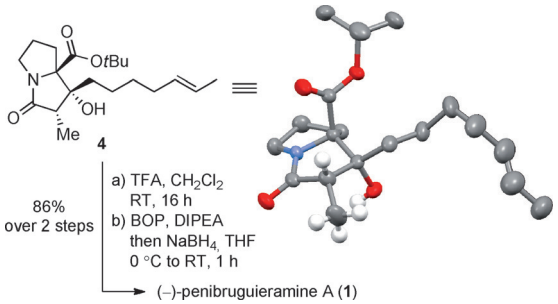


Entry	Base (equiv)	Solvent	*t* [h]	Yield of **4**[b] [%]
1	NaOEt (5)	EtOH	9	77[c]
2	LiOEt (5)	EtOH	9	72
3	KOEt (5)	EtOH	6	66
4	NaOMe (5)	MeOH	24	30
5	NaO*i*Pr (5)	*i*PrOH	3	49
6	NaO*t*Bu (5)	*t*BuOH	16	0[d]
7	TBAOH·30 H_2O (5)	THF	12	61

[a] Reactions were run with **3** (105 mg, 0.3 mmol) at a substrate concentration of 0.1 M. [b] Yield of isolated product. [c] **12** was also obtained in 10% yield. [d] Complex mixture. TBAOH = tetra-*n*-butylammonium hydroxide.

including the Dieckmann condensation (path b) and the retro-Claisen reaction (path c). The bulky *tert*-butyl ester group of **3** was expected to be appropriate to avoid the side reaction which might occur through path b.[13] Various bases and conditions were screened to obtain the desired product. The typical results are listed in Table 1. When substrate **3** was treated with NaOEt in EtOH, the reaction proceeded with satisfactory results to afford the desired aldol product **4** as a single diastereomer in 77% yield after 9 h (entry 1). The only notable side product present in the reaction mixture was the aldol dehydration product **12**. Other alkali metal ethoxides, such as LiOE and KOEt, also yielded the desired **4** without significant loss of yield (entries 2 and 3). However, when **3** was treated with NaOMe (entry 4), the reaction suffered from low yield due to retro-Claisen cleavage to provide **13a** (21%) via path c and transesterification (8%). Other sodium alkoxides having bulky organic substituents, such as NaO*i*Pr and NaO*t*Bu, were also inappropriate for the aldol reaction and suffered from low yield and decomposition (entries 5 and 6). Sterically hindered organic bases, including 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), failed to yield the desired product in an aprotic solvent (see the Supporting Information). Alkali metal hydroxides produced only a negligible amount of product, with most of the starting material remaining along with a small amount of **13b** formed through hydrolytic retro-Claisen cleavage (path c). On the other hand, the quaternary ammonium hydroxide base in THF gave the product **4** in moderate yield (entry 7). These results indicated that the nature of the base, considering its bulkiness in particular, was important in determining the outcome of the reaction.

Regardless of the nature of the base, the intramolecular aldol reaction of **3** resulted in a single diastereomer of **4**. The other possible isomers were not detected in the crude mixture. The relative stereochemistry of **4**, which was determined by 2D NMR analysis, was identical to that of penibruguieramine A. The absolute and relative stereochemistry of **4** was later confirmed by X-ray crystallography (Scheme 4).[14] With this excellent stereochemical outcome in hand, the total

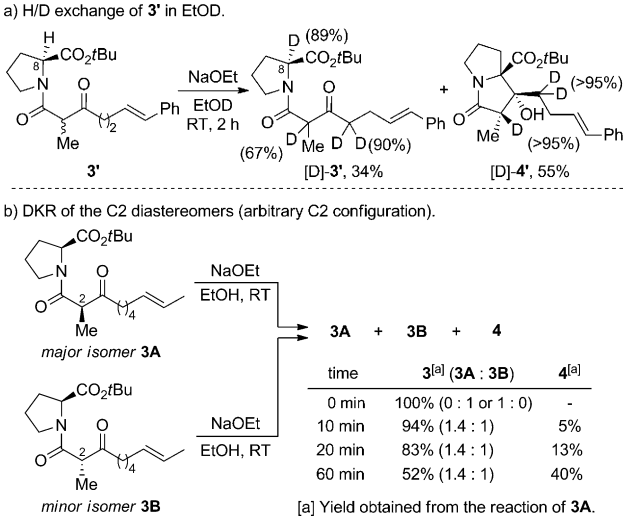


Scheme 4. Crystal structure of **4**[14] and synthetic route for the completion of the synthesis of (−)-penibruguieramine A (**1**). Atom colors: N = blue; O = red; C = gray; H = white. BOP = benzotriazolyloxy-tris(dimethylamino) phosphonium hexafluorophosphate, DIPEA = *N*,*N*-diisopropylethylamine, TFA = trifluoroacetic acid.

synthesis of **1** was completed by reducing the sterically hindered *tert*-butyl ester group in **4** to the corresponding alcohol by a two-step method.[15] The NMR and mass spectral data of the resulting product **1** were identical to those of the natural product. The synthetic sample exhibited a negative optical rotation ($[\alpha]_D^{22} = -21.3°$, $c = 0.05$, $CHCl_3$), which is consistent with that of the natural compound ($[\alpha]_D^{22} = -22°$, $c = 0.05$, $CHCl_3$).[1] This result indicates that the absolute configuration proposed for the natural compound was correct.

The enantiomeric purity of **1** was greater than 99% (see the Supporting Information). These results confirmed that MOC was exerted during the intramolecular aldol reaction of **3**. The virtually complete retention of chirality obtained in the polar protic solvent is remarkable considering the prior observations in which the competitive protonation of the enolate decreased the enantioselectivities of the MOC reactions in protic solvents.[16]

To understand the excellent stereochemical outcome, we performed additional experiments with model substrate **3′** (Scheme 5a), which consists of a UV-absorbing chromophore that allows for facile reaction analysis. When we analyzed the



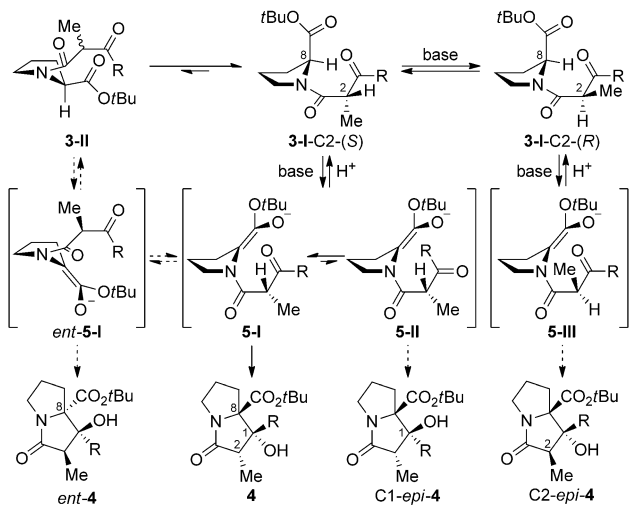
Scheme 5. Exploratory studies to determine the mechanism of the aldol reaction.

remaining aldol substrate in the incomplete reaction mixture, it was found that the proline stereocenter was not racemized (see the Supporting Information). Additionally, the hydrogen at the proline stereocenter was gradually replaced with deuterium when the aldol reaction was conducted in EtOD (Scheme 5a; for details, see the Supporting Information). These observations suggested that the unreacted ester enolate intermediate was protonated with complete retention of configuration to regenerate the aldol substrate, which may result in excellent MOC in a protic solvent environment. A major factor for this MOC during deprotonation/protonation may be the torsional strain that develops when the axially chiral enolate, such as **5**, is protonated from the *si* face, leading to formation of the C8 epimer of **3**.

When the two separated C2 diastereomers of **3** (**3A** and **3B**) were independently subjected to the optimized aldol reaction conditions, each reaction yielded the same results and afforded product **4** in good yield. Monitoring each reaction by NMR spectroscopy indicated that rapid epimerization occurred at the C2 position and aldol product **4** was gradually formed as the only diastereomer (Scheme 5b; for details, see the Supporting Information). The diastereomeric ratio of the two isomers from the two reactions was 1.4:1 after 10 min, and the ratio remained constant. The ratio was the same prior to the separation, and may reflect the thermodynamic stability of the isomers. Based on these observations, we are confident that DKR occurred during the reaction.

Considering that **4** was the only aldol product that appeared from the beginning of the reaction and because other diastereomers were not detected during the reaction, **4** can be regarded as the kinetic product. Our computational study indicated that the obtained aldol product **4** is the most stable among all of the possible diastereomers (see the Supporting Information). Therefore, the aldol product **4** is not only the kinetic product but also the thermodynamically favored product.

Based on these results and earlier reports, an aldol reaction mechanism of **3** was proposed, as shown in Scheme 6. The presence of an acidic proton at the C2 stereocenter of substrate **3** allows for easy epimerization under basic conditions. The conformer **3-I** is energetically more favored than **3-II** due to minimized 1,3-allylic strain,[10,17] and the deprotonation reaction at the proline α position on conformer **3-I** generates an axially chiral enolate **5**. This transient enolate can be converted back into **3** by protonation with complete configuration retention at the C8 position. Upon formation of **5**, the C2-(*S*) isomer (denoted **3-I**-C2-(*S*)) undergoes an intramolecular aldol reaction via conformer **5-I** to yield aldol product **4**. The reaction via conformer **5-II** would be less favorable because of steric repulsion between the alkyl chain and the proline moiety. The aldol reaction of the C2-(*R*) isomer via conformer **5-III** would not be favored because the methyl group hinders enolate addition to the carbonyl group. However, based on the DKR principle, this unfavorable C2 epimer could participate in the reaction through epimerization.[18] The excellent stereochemical outcome of the reaction may result from these kinetic factors as well as the thermodynamic preference for aldol product **4**.



Scheme 6. Proposed mechanism for the aldol reaction.

In summary, using a biomimetic approach, the first total synthesis of (−)-penibruguieramine A (**1**) was achieved. The principles of memory of chirality and dynamic kinetic resolution were employed for the asymmetric synthesis using proline as the only chiral source. All three stereocenters were established in an intramolecular aldol reaction of proline pentaketide amide **3** with complete diastereo- and enantioselectivity without the aid of an external chiral influence. The excellent MOC in the protic solvent environment may be associated with the return of the unreacted chiral enolate intermediate to the starting material by protonation, with complete retention of configuration. The excellent diastereoselectivity is most likely related to the kinetic and thermodynamic preferences for the desired aldol product. Our synthesis is the first reported example of the combined use of MOC and DKR for the asymmetric construction of stereocenters.

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Keywords: aldol reaction · biomimetic synthesis · dynamic kinetic resolution · memory of chirality · total synthesis

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