Asymmetric total synthesis of martinelline and martinellic acid†

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Herein, we describe the first asymmetric total synthesis of (−)-martinelline ((−)-2) and the second total synthesis of (−)-martinellic acid ((−)-1) by employing a tandem Mukaiyama–Mannich reaction/aminal cyclization as the key step.

The Martinella alkaloids **1** and **2** were isolated by scientists at the Merck Research Laboratories in 1995 from the root bark of the tropical plant *Martinella iquitosensis*, which has long been used by Amazon Indian tribes for medicinal purposes.[1,2] These alkaloids have attracted considerable attention because they are the first naturally occurring non-peptide bradykinin B_1 and B_2 receptor antagonists, and the first naturally occurring hexahydropyrrolo-[3,2-*c*]quinoline tricycles (Fig. 1).

Their interesting biological activities, coupled with their unique ring system, harbouring three consecutive stereocenters, have spurred intense efforts[3] to synthesize them, culminating in several total syntheses of **1** and **2**.[4] However, there has only been one reported asymmetric total synthesis of (−)-martinallic acid ((−)-**1**) by Ma's group,[4a,b] in which they pointed out that synthetic (−)-**1** exhibits a considerably larger value of specific rotation compared to natural (−)-**1**, indicating that **1** may be partially racemic or that a highly diluted solution was used when Merck's chemists measured its specific rotation. Thus, the issue of elucidating the absolute configurations of **1** and **2** is still the subject of serious argument. Herein, we describe the first asymmetric total synthesis of (−)-martinelline ((−)-**2**) and the second total synthesis of (−)-**1**, which supports the suggestion of Ma's group that natural Martinella alkaloids are partially racemic.

Our initial plan revolved around an intramolecular hetero-Diels–Alder (h-DA) reaction of *ortho*-azaxylylene **4**, which could potentially be generated *in situ* from (*E*)-imine **3**, with the aim of setting all three stereocenters of **1** and **2** in one step (Scheme 1). However, as pointed out by Aubé's group, the realization of a h-DA reaction *via* an *ortho*-azaxylylene using **3** (R^2 = alkyl or H, R^3 = H) has been suspended.[3g,5] We designed imine **7**, which has an electron-rich enol ether as the dienophile, by considering that this type of h-DA reaction favours the inverse-electron-demanding mode.[6] After considerable experimentation, it was found that $LiBF_4$[7] exclusively produced the *cis*-fused cycloadduct **9**, although in moderate yields. Interestingly, **9** was produced as a single diastereomer, irrespective of the geometry of the substrate (Scheme 2). These results suggest that the cycloaddition reaction proceeds in a stepwise manner *via* the Mukaiyama–Mannich reaction with subsequent aminal formation.[8] Note that the TBS group survives under conditions typical for desilylation.

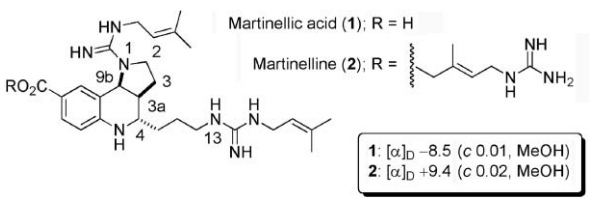
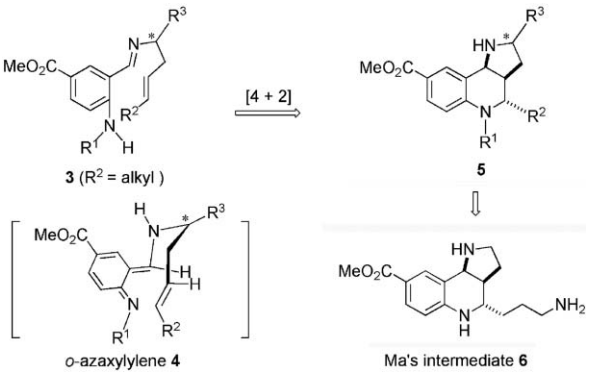
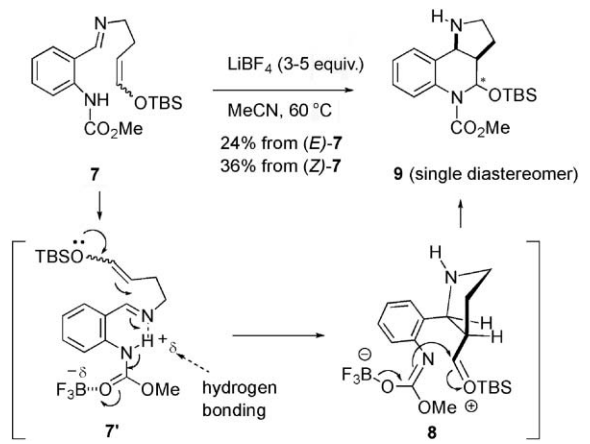


Fig. 1 Structures of **1** and **2**.



Scheme 1 Initial plan for construction of the core system.

Encouraged by the discovery of conditions that promote a formal [4 + 2] cycloaddition, we designed and synthesized chiral imine **10**, possessing a TBDPS-oxymethyl group. Compound **10** could be accessed from aldehyde **11** and chiral amine **12**.[9] The key [4 + 2] reaction of **10** was best promoted by $BF_3{\cdot}OEt_2$, in this



Scheme 2 Model study of the [4 + 2] cycloaddition reaction and a plausible Mukaiyama–Mannich reaction/aminal cyclization mechanism.

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† Electronic supplementary information (ESI) available: Detailed experimental procedures, copies of spectral data and full characterization of all new compounds. See DOI: 10.1039/b611121a

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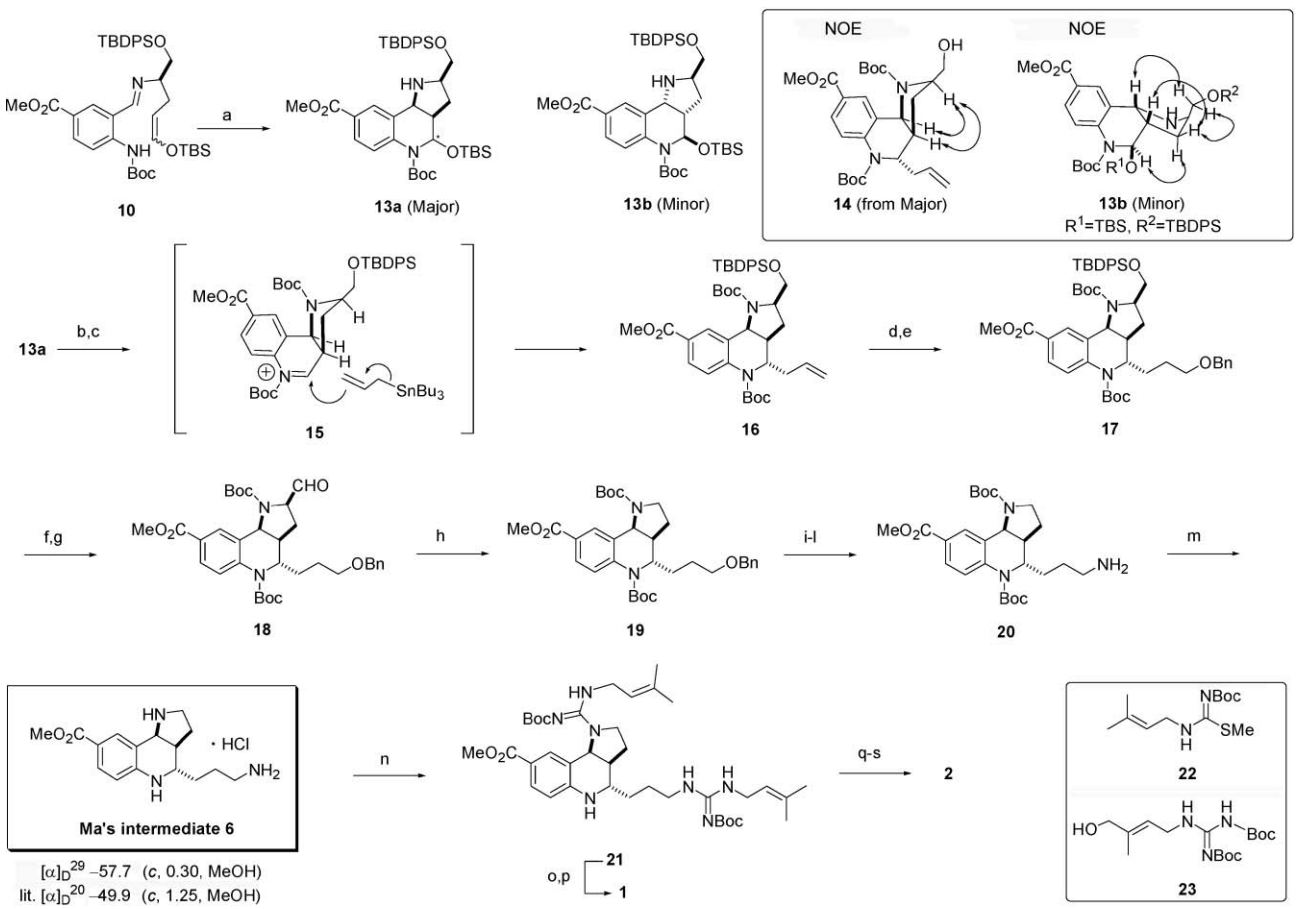
particular case to obtain the adducts **13a** and **13b** (47%, dr = 4.2 : 1) as a chromatographically separable mixture; $LiBF_4$ conditions [$LiBF_4$ (5 equiv.), MeCN, rt] also yielded such adducts (29%, dr = 3.8 : 1). The stereochemistry of cycloadducts were determined by NOE experiments. The major isomer, **13a**, was subjected to Hosomi–Sakurai type allylation using allyltributyltin.[10] As expected, an allyl group was successfully introduced in a highly diastereoselective manner from its convex face to furnish **16**. Unfortunately, our attempted one-pot synthesis of an allylated compound from **10** was unsuccessful,[11] only yielding **13a** and **13b**, indicating the need for suitable capping of N1 to generate an acyliminium ion at C4. After hydroboration–oxidation and protection of the resulting hydroxyl group as a benzyl ether, the TBDPS-oxymethyl group, which played a key enantiocontrolling role, was removed *via* aldehyde **18** using the Tsuji–Wilkinson reaction[12] to furnish the desired chiral core **19**. **19** was successfully converted to Ma's intermediate **6** by the five-step sequence shown in Scheme 3. Because all the analytical data for our synthetic triamine **6** were identical to Ma's[4a,b], the absolute configuration of the tricyclic core was confirmed to be (3a-*S*,4-*S*,9b-*S*) (Scheme 3).

6 was converted to **1** and **2** by following Ma's[4a,b] and Batey's[4d] procedures, respectively. The analytical data (^{1}H NMR, ^{13}C NMR and HR-FAB-MS) obtained were identical to the original data. Significantly, the optical rotation of our synthetic martinellic acid ((−)-**1**) exhibited a levorotatory sense with a considerable increase in its value {$[\alpha]_D^{29}$ −164.3 (*c* 0.14, MeOH)} compared to that of natural **1** {lit.[1] $[\alpha]_D$ −8.5 (*c* 0.01, MeOH)}. However, our data were almost consistent with that of Ma {lit.[4a,b] $[\alpha]_D^{20}$ −122.7 (*c* 0.31, MeOH)}. On the other hand, our synthetic martinelline ((−)-**2**) also exhibited an increased value of specific rotation {$[\alpha]_D^{28}$ −108.0 (*c* 0.09, MeOH)}, but in a sense opposite to that of the reported value {lit.[1] $[\alpha]_D$ 9.4 (*c* 0.02, MeOH)}. However, because our further synthesis of (+)-**1** and (+)-**2** from the minor [4 + 2] cycloadduct **13b** was achieved, and they also exhibited similar values of specific rotation with opposite senses {(+)-**1**: $[\alpha]_D^{28}$ 165.5 (*c* 0.11, MeOH); (+)-**2**: $[\alpha]_D^{29}$ 98.6 (*c* 0.02, MeOH)},[13] we suppose that the natural products isolated by Merck's scientists[1] were nearly racemic.[14,15]

In this communication, we have reported the total synthesis of (−)-martinellic acid ((−)-**1**), (−)-martinelline ((−)-**2**) and their enantiomers. A comparison of their specific rotations suggests that



Scheme 3 Completion of the asymmetric total synthesis of **1** and **2**. *Reagents and conditions*: (a) $BF_3{\cdot}OEt_2$, 4 Å MS, CH_2Cl_2, −40 to 0 °C, 47% (dr = 4.2 : 1); (b) Boc_2O, NaHMDS, THF, 0 °C to rt, 94%; (c) $BF_3{\cdot}OEt_2$, allyltributyltin, CH_2Cl_2, −40 to 0 °C; (d) 9-BBN, THF, 0 °C then aq. NaOH, 30% H_2O_2, 81% (2 steps); (e) BnBr, NaH, cat. TBAI, THF, 45 °C, 71%; (f) TBAF, THF, 0 °C to rt, 99%; (g) cat. TPAP, NMO, 4 Å MS, CH_2Cl_2; (h) $(Ph_3P)_3RhCl$, xylene, reflux, 82% (2 steps); (i) H_2, Pd–C, MeOH, quantitative; (j) MsCl, Et_3N, CH_2Cl_2, 0 °C; (k) NaN_3, DMF, 50 °C, 92% (2 steps); (l) H_2, Lindlar's catalyst, MeOH, 97%; (m) HCl–MeOH, 0 °C to rt, quantitative (from NMR); (n) **22**, $AgNO_3$, Et_3N, MeCN–MeOH (1 : 2 v/v), 56%; (o) aq. NaOH–MeOH, reflux; (p) TFA, anisole, CH_2Cl_2, 60% (2 steps); (q) aq. NaOH–MeOH, reflux; (r) **23**, BOP-Cl, *i*-Pr_2NEt, CH_2Cl_2, 75% (2 steps); (s) TFA, CH_2Cl_2, 70%.

the previously reported Martinella alkaloids are nearly racemic. To confirm this hypothesis, determining which of the two enantiomers confer biological activity is a topic of future research on the development of pharmaceuticals based on Martinella alkaloids. The biological evaluation of the two enantiomers is ongoing.

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5 Although Aubé's group attempted various treatments, including the use of heat, acids, electrophiles and bases to generate an *ortho*-azaxylylene, they obtained no Diels–Alder adducts.

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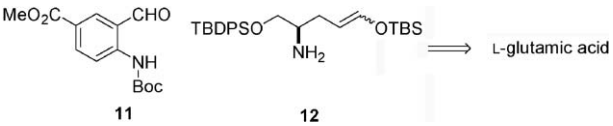
8 Aubé's group (see ref. 3*g*) pointed out that hydrogen bonding between the imino nitrogen and carbamate hydrogen could be responsible for the lack of direct imine activation. Indeed, the ^{1}H NMR signal of the carbamate hydrogen (**7** and **10**) shifts significantly downfield (*ca.* 12.4–12.5 ppm). Therefore, we believe that the mechanism of the Mukaiyama–Mannich reaction is *via* an indirect activation route rather than a direct one.

9 Detailed procedures for the preparation of **10**, **11** and **12** are available in the ESI†.



11 **12**

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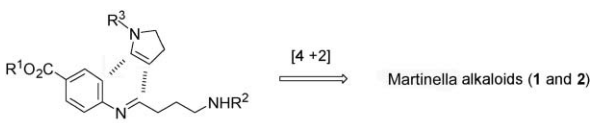
13 The detailed procedures for the conversion of **13b** to (+)-**1** and **2** are available in the ESI†.

14 We know that, in the absence of a direct comparison with a natural product, we cannot conclude with certainty that the natural Martinella alkaloids are racemic, because there might be several factors associated with the difference in optical rotation; for example, purity, the degree of protonation and the state of aggregation.

15 It is interesting to note Batey's insightful proposal[4d] that Martinella alkaloids are conceivably biosynthesized through an unprecedented enzyme-catalyzed Povarov-type intermolecular h-DA reaction between an aniline-derived imine and an endocyclic enamine.



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