

First Asymmetric Synthesis of Piperidine Alkaloid (–)-Morusimic Acid D

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Abstract: The first asymmetric synthesis of (–)-morusimic acid D, a 2,3-*trans*-2,6-*cis*-2-methyl-6-substituted piperidin-3-ol containing alkaloid is reported. The key steps are the reductive alkylation of N,O-diprotected 3-hydroxyglutarimide, a stepwise reductive alkylation, and an asymmetric aldol-type reaction using a modified Evans chiral auxiliary.

Key words: asymmetric synthesis, *N*-acyliminium ions, imides, aldol reaction, piperidines, alkaloids, morusimic acid D

Substituted, hydroxylated piperidines constitute a class of natural products exhibiting important bioactivities.¹ As a key structural feature shared by many piperidine alkaloids, 2-methyl-6-substituted piperidin-3-ols with different stereochemical patterns have been the targets of numerous synthetic efforts, which have culminated in a number of methods for the synthesis of these molecules.^{2–8} Because most of this class of piperidine alkaloids possess a 2,3-*cis* stereochemistry with either a 2,6-*cis*-stereochemical pattern (**A**, Figure 1), or a 2,6-*trans* stereochemistry pattern (**B**), much attention has been devoted to the construction of *cis*-2-methylpiperidin-3-ol skeleton.³ Only a few methods are available for the synthesis of *trans*-2-methylpiperidin-3-ols,⁴ although several methods have been developed for the syntheses of structurally related piperidine alkaloids prosopphylline⁵ and micropine,⁶ quinolizidine alkaloids clavopictines⁷ and pictamine,^{7a} as well as decahydroquinoline alkaloid lepadin D.⁸ In 2002, two 2,3-*trans*-2,6-*cis*-2-methyl-6-substituted piperidin-3-ol containing alkaloids, morusimic acids C (**1**) and D (**2**) were isolated from white ripened fruit of *M. alba* grown in Turkey.⁹

In continuation of our studies on the development of protected 3-hydroxyglutarimide-based synthetic methodology,^{10–12} we now report an application of this methodology to the first asymmetric synthesis of morusimic acid D (**2**), an alkaloid having a 2,3,6-*trans,trans* stereochemistry.

As displayed retrosynthetically in Scheme 1, both the C2 methyl group and the 2,3-*trans* stereochemistry were envisioned to be introduced by the reductive alkylation method^{10,11} starting from the protected 3-hydroxyglutarimide **6**.¹² The C6 side chain with 2,6-*cis* stereochemistry

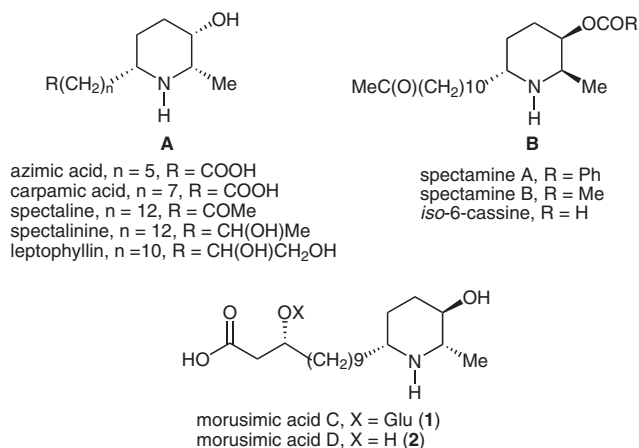
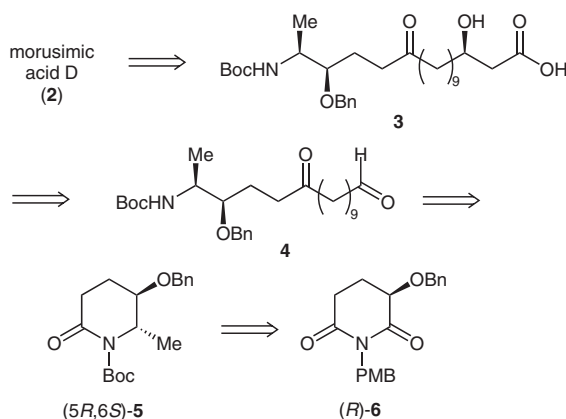


Figure 1 Some alkaloids containing a 2-methyl-6-substituted piperidin-3-ol moiety

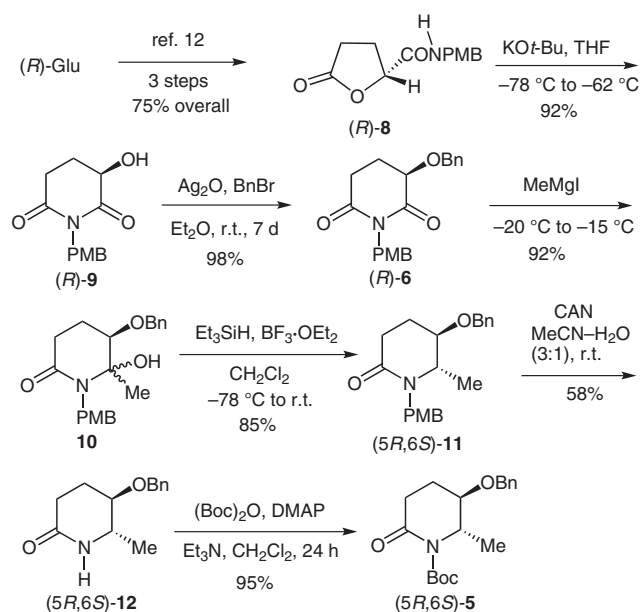


Scheme 1 Retrosynthetic analysis of (–)-morusimic acid D

was considered to be accessible by another diastereoselective reductive alkylation method.¹³

The synthesis commenced with (*R*)-3-benzyloxy-1-(4-methoxybenzyl)glutarimide [(*R*)-**6**],¹² which was prepared from D-glutamic acid following essentially the procedure described for its enantiomer (Scheme 2).¹²

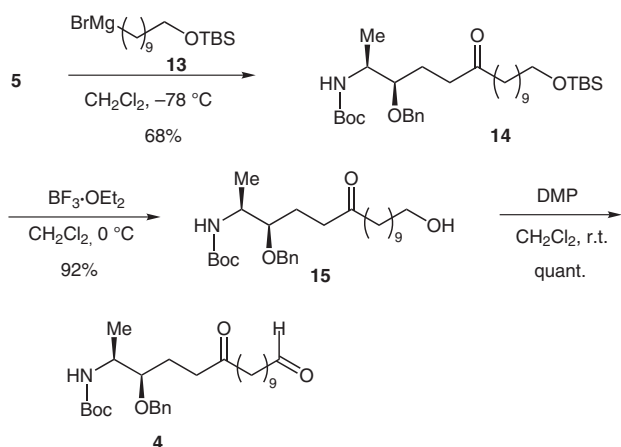
For the reductive methylation, although our previous study showed that the addition of methyl magnesium iodide (3 molar equiv) to (*S*)-3-hydroxyglutarimide derivative (*S*)-**6** in THF at –78 °C yielded a diastereomeric mixture of *N,O*-acetal **10** and its C6 adduct in 86:14 C2/C6 regioselectivity, it was found that almost only the C2 addition product was obtained when undertaking the reac-



Scheme 2

tion in CH_2Cl_2 and at -20°C . The subsequent reductive dehydroxylation under ionic hydrogenolytic conditions¹⁴ ($\text{Et}_3\text{SiH}/\text{BF}_3\cdot\text{OEt}_2$, CH_2Cl_2 , -78°C to r.t.) furnished predominantly *trans*-**11** (*trans/cis* = 92:8). Cleavage of the *N*-(4-methoxybenzyl) group by treating (5*R*,6*S*)-**11** with ceric ammonium nitrate (CAN) in $\text{MeCN}-\text{H}_2\text{O}$ (3:1)¹⁵ at room temperature gave lactam (5*R*,6*S*)-**12** in 58% yield (Scheme 2).

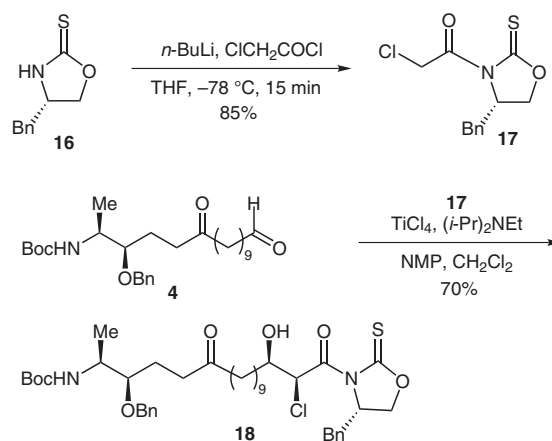
Next, we turned our attention to the introduction of the chiral C6 side chain. To this end, another diastereoselective reductive alkylation method¹³ was adopted. Thus, lactam **12** was first converted [$(\text{Boc})_2\text{O}$, Et_3N , DMAP, CH_2Cl_2 , 24 h] to imide (5*R*,6*S*)-**5**, an activated form^{13b} of the former (Scheme 2). Reaction of Grignard reagent **13**¹⁶ with imide (5*R*,6*S*)-**5** in CH_2Cl_2 at -78°C proceeded smoothly to give the ring-opening product **14** in 68% yield. To introduce the ethoxycarbonylmethyl group, the TBS group in compound **14** was cleaved under acidic conditions ($\text{BF}_3\cdot\text{OEt}_2$, CH_2Cl_2 , 0°C) to give **15** in 92% yield. Oxidation of **15** with Dess–Martin periodinane (DMP) in CH_2Cl_2 at r.t. gave aldehyde **4** in quantitative yield (Scheme 3).



Scheme 3

yield.¹⁷ The resulting alcohol **15** was oxidized with Dess–Martin periodinane (DMP)¹⁸ to give aldehyde **4** in quantitative yield (Scheme 3).

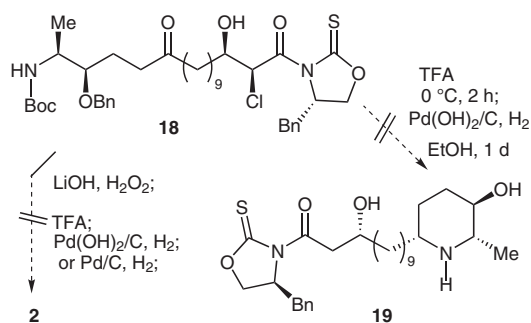
For the asymmetric carboxymethylation, an enzymatic method,¹⁹ Evans asymmetric aldol-type reaction,²⁰ and Brown's asymmetric allylation reaction²¹ were all plausible. We sought to use Evans' aldol chemistry in view of its excellent enantio- and diastereoselectivities, as well as its compatibility with different substituents that may be useful for the synthesis of analogues of (–)-morusic acid D. To take advantages of the progress in Evans aldol chemistry,^{22,23} oxazolidine-2-thione derivative **17** was selected for the asymmetric aldol reaction, where the chloro atom will serve as a stereodirecting group for the asymmetric aldol-type reaction.²⁰ The starting oxazolidine-2-thione **16** was prepared in 91% yield by the method reported by Wu.²⁴ Successive treatment of oxazolidine-2-thione **16** with *n*-butyllithium and chloroacetyl chloride gave **17** in 85% yield. Asymmetric aldol reaction of **4** with **17** under Crimmins' conditions [TiCl_4 , (*i*-Pr)₂EtN, *N*-methylpyrrolidin-2-one (NMP), CH_2Cl_2 , 0°C]²³ provided **18** as the only isolable diastereomer in 70% yield (Scheme 4).



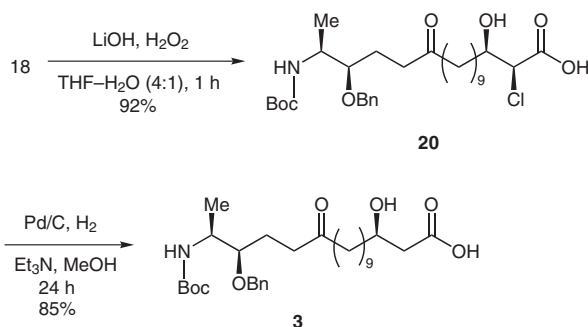
Scheme 4

The subsequent steps required for the synthesis of morusic acid D (**2**) included *N*-Boc deprotection, one-pot reductive cyclization–debenzylation, dechlorination, and cleavage of the chiral auxiliary. Attempts to cleave the protecting group Boc by TFA, followed by $\text{Pd}(\text{OH})_2$ or Pd/C -catalyzed hydrogenolysis to obtain **19** was unsuccessful, and other attempts under the conditions shown in Scheme 5 also failed.

After extensive trials, it was found that after the cleavage of the chiral auxiliary under Evans' conditions²⁵ (LiOH , H_2O_2 , $\text{THF}-\text{H}_2\text{O}$, 1 h) selective dechlorination could be achieved by subjecting **20** (colorless oil, yield 92%) to Abushanab's hydrogenation conditions²⁶ [H_2 (1 atm), 10% Pd/C , Et_3N , MeOH , 24 h, r.t.], which furnished the dechloro product **3** in 85% yield along with 10% of the recovered starting material (Scheme 6).



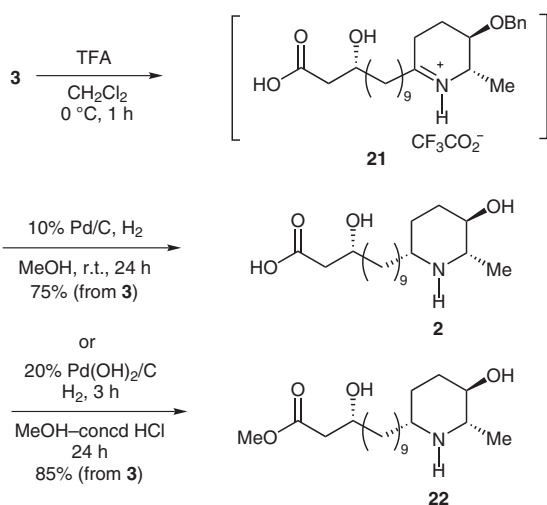
Scheme 5



Scheme 6

Finally, treatment of **3** with trifluoroacetic acid in dichloromethane at 0 °C for one hour, followed by subjecting the resulting crude product to catalytic hydrogenolysis (10% Pd/C, H₂, MeOH, r.t., 24 h) led, in one pot, to the formation of morusimic acid D (**2**) in 75% yield as a white powder [$[\alpha]_D^{20}$ –14.0 (*c* 0.25, MeOH), lit.⁹ [$[\alpha]_D^{20}$ –14.6 (*c* 0.25, MeOH)]. The ¹H NMR and ¹³C NMR spectral data of the synthetic material are identical with those reported for the natural morusimic acid D (**2**).⁹

Alternatively, morusimic acid D methyl ester (**22**)²⁷ could be obtained in one pot by treatment of **3** with trifluoroacetic acid, followed by catalytic hydrogenolysis in methanol using Pearlman's catalyst [Pd(OH)₂/C (20 mol%), H₂, 1



Scheme 7

atm] for three hours, and then stirring with concentrated hydrochloric acid for 24 hours (Scheme 7).

In summary, by modifying the reaction conditions, the C2/C6 regioselectivity of the addition of methyl magnesium iodide to N,O-diprotected 3-benzoyloxyglutarimide **6** was improved from 86:14 to at least 95:5. On the basis of this reaction, the first asymmetric synthesis of (–)-morusimic acid D is achieved in 11 steps with an overall yield of 13% from (*R*)-**6**, with all the three stereocenters established in excellent diastereoselectivities.

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