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A Novel C_2-Symmetric 2,6-Diallylpiperidine Carboxylic Acid Methyl Ester as a Promising Chiral Building Block for Piperidine-Related Alkaloids†

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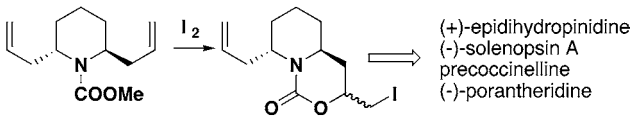
ABSTRACT



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C_2-Symmetric 2,6-diallylpiperidine 1-carboxylic acid methyl ester (5) was examined via the double asymmetric allylboration of glutaraldehyde followed by aminocyclization and carbamation as a promising chiral building block for piperidine-related alkaloids, which were synthesized by the desymmetrization of 5 using intramolecular iodocarbamation as a key step.

Substituted piperidines are among the most ubiquitous heterocyclic building blocks in both natural products and synthetic compounds with important biological activities. Therefore, considerable effort has been directed toward synthesizing these systems.[1] With respect to biologically active target molecules, there is an increasing interest in the diastereo- and enantioselective synthesis of piperidines.[2] Our interest in this field has been focused on the synthesis of C_2-symmetric 2,6-disubstituted piperidines using a double asymmetric reaction of achiral symmetrically bifunctionalized substrates.[3] Recently, Brown reported a double asymmetric allylboration of glutaraldehyde (**1**) to provide C_2-symmetric 1,5-diol **2** in 90% de and >98% ee.[4] However, its utility to date has been hampered by the difficulty of separating C_2 and meso diastereomers. To circumvent this drawback, we developed the following protocol for the transformation of acyclic compounds such as 1,5-diols to cyclic derivatives such as 2,6-disubstituted piperidines, which involves both rigid conformation and close proximity (1,3-relationship) between two chiral centers to give a better separation of diastereomers (Scheme 1).[5] In this Letter, we describe an asymmetric synthesis of C_2-symmetric 2,6-diallylpiperidine **5** as an attractive chiral building block and the subsequent synthesis of piperidine-related alkaloids via desymmetrization of **5** using iodocarbamation as a key step.

According to Brown's procedure,[4] treatment of **1** with *B*-allyldiisopinocamphenylborane, prepared using *B*-chloro-

† Dedicated to the memory of the late Professor Henry Rapoport, University of California, Berkeley.

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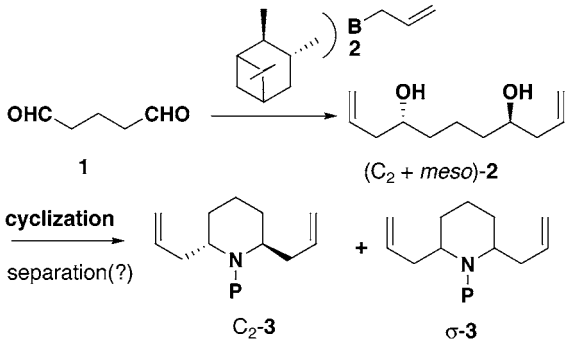
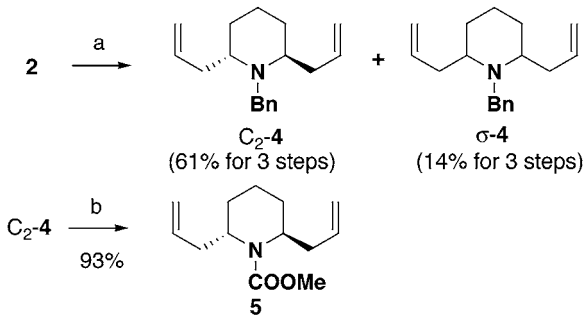
Scheme 1



diisocamphenylborane (DIP−chloride) and allylmagnesium bromide, followed by alkaline H_2O_2 oxidation gave a diastereomeric mixture of diols **2** in 74% yield. The diols **2** were successively subjected to ditosylation of secondary hydroxyls and cyclic amination with benzylamine to give diastereomeric isomers of piperidines **3**, which were separated as expected by chromatography to yield C_2-symmetric 2,6-diallylpiperidine **4** and σ-**4** in respective yields of 61 and 14%. Changing the *N*-protecting group from benzyl to a carbamate group using methyl chloroformate gave the title carbamate **5** in 93% yield.[6] With the C_2 chiral building block **5** in hand, we turned our attention to its transformation into biologically active 2,6-*trans*-disubstituted piperidine-related alkaloids (Figure 1).

Scheme 2[a]



[a] Reaction conditions: (a) (i) TsCl, NEt_3; (ii) $BnNH_2$. (b) ClCOOMe.

Our synthesis began with the selective monofunctionalization of diallyl appendages in **5**. All attempts such as hydroboration, dihydroxylation, and the Wacker oxidation nonselectively resulted in a mixture of mono- and difunctionalized products together with the recovery of starting **5**. We considered that this trouble could be overcome by intramolecular iodocarbamation with one of two allyls, since a second iodocarbamation could not occur with the other allyl. Thus, the intramolecular iodocarbamation of **5** with

(6) Attempts with other alkyl chloroformates such as ethyl, benzyl, and trichloromethyl chlorofornates were unsuccessful.

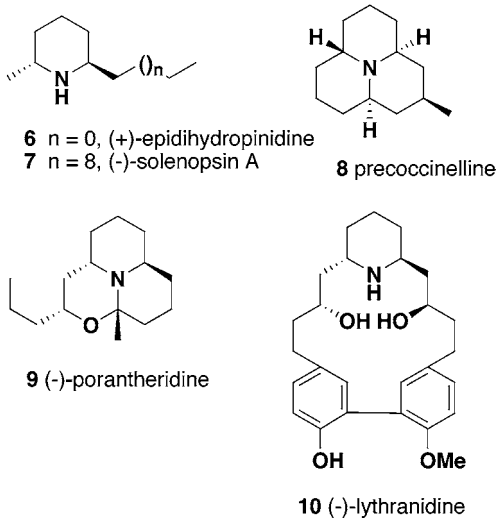
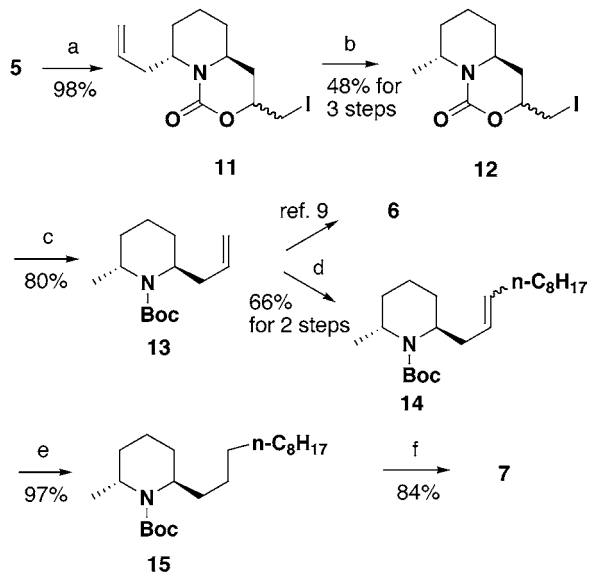


Figure 1. 2,6-*trans*-Disubstituted piperidine-related alkaloids.

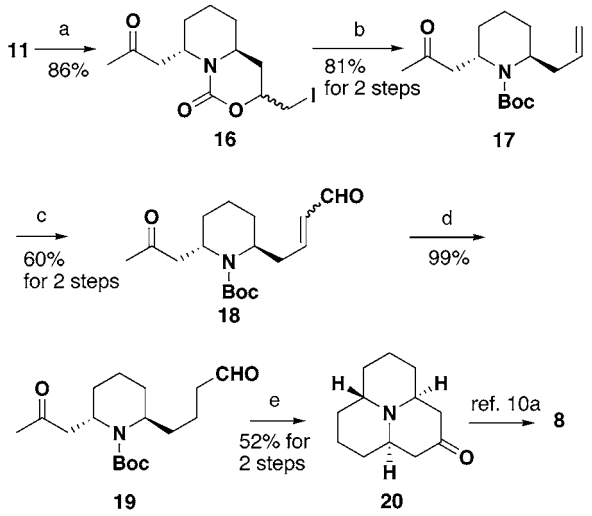
iodine was carried out to provide a diastereomeric and inseparable mixture of oxazolidinones **11** in 98% yield. This desymmetrization means that one of two allyl groups is protected. With the promising piperidine **11**, we then focused on the synthesis of 2,6-*trans*-dialkylpiperidines such as (−)-epi-dihydropinidine (**6**),[7] a constituent of pine and spruce species, and (2*R*,6*R*)-*trans*-solenopsin A (**7**),[8] a constituent of fire ant venom. Cat. OsO_4-mediated dihydroxylation of **11** followed by an oxidative cleavage of the resulting diol with $NaIO_4$ provided the aldehyde, which was decarbonylated with $(Ph_3P)_3RhCl$ to afford the methyl-substituted piperidine

Scheme 3[a]



[a] Reaction conditions: (a) I_2. (b) (i) cat. OsO_4; (ii) $NaIO_4$; (iii) $(Ph_3P)_3RhCl$. (c) (i) Zn, CH_3CO_2H; (ii) Boc_2O, NaOH. (d) (i) cat. OsO_4, $NaIO_4$; (ii) $Ph_3P^+CH_2(CH_2)_8Br^-$, *n*-BuLi. (e) H_2, cat. $Pd(OH)_2$. (f) TFA.

Scheme 4[a]

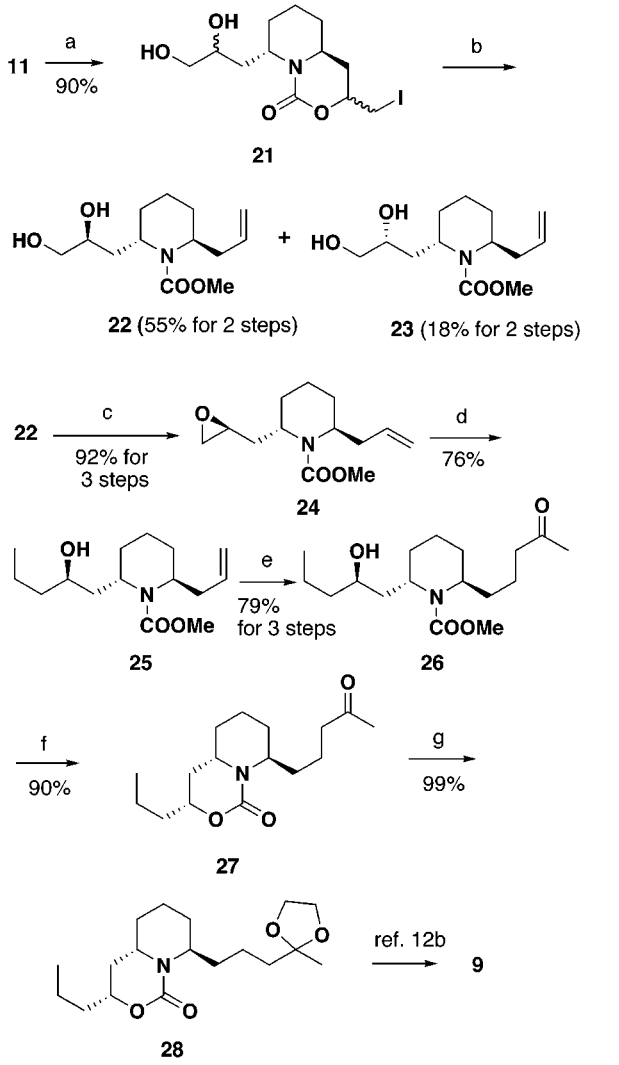


[a] Reaction conditions: (a) cat. $PdCl_2$, O_2, DMF, H_2O. (b) (i) Zn, CH_3CO_2H; (ii) Boc_2O, K_2CO_3. (c) (i) cat. OsO_4, $NaIO_4$; (ii) $Ph_3P{=}CHCHO$. (d) H_2, cat. $Pd(OH)_2$. (e) (i) TFA; (ii) CSA.

12 in 48% yield. Deprotection of oxazolidine occurred upon exposure of **12** to zinc in acetic acid to give the allylpiperidine, *N*-protection of which with Boc_2O gave *N*-Boc-2-allyl-6-methylpiperidine **13**. Transformation of **13** into **6** has been reported previously.[9] The oxidative cleavage of **13** with catalytic OsO_4 in combination with $NaIO_4$ provided the aldehyde, which was coupled by the Wittig olefination with *n*-nonyltriphenylphosphonium bromide in the presence of *n*-BuLi to give the 2,6-disubstituted piperidine **14** in 66% yield. Hydrogenation of **14** with catalytic $Pd(OH)_2$ gave **15** in 97% yield. *N*-Deprotection of **15** by treatment with trifluoroacetic acid (TFA) in CH_2Cl_2 provided **7** in 84% yield.

Next, the transformation of **11** into precoccinelline (**8**),[10] a ladybug defense alkaloid, was pursued. Wacker oxidation of **11** provided the ketone **16** in 86% yield. By a procedure similar to that described for **13**, a two-step treatnent (deprotection of the oxazolidine and *N*-protection) of **16** gave the allylpiperidine **17** in 81% yield. Treatment of **17** with catalytic OsO_4 in combination with $NaIO_4$ followed by the Wittig reaction of the resulting aldehyde with (triphenylphosphoranylidene)acetaldehyde afforded the α,β-unsaturated aldehyde **18** in 60% yield. Exposure of **18** to hydrogen in the presence of catalytic $Pd(OH)_2$ in ethyl acetate gave the keto aldehyde **19** in 99% yield. *N*-Deprotection of **19** with TFA followed by an intramolecular Mannich-type cyclization

Scheme 5[a]



[a] Reaction conditions: (a) AD-mix-α. (b) (i) Zn/CH_3CO_2H; (ii) $ClCOOCH_3$, K_2CO_3. (c) (i) *n*-Bu_2SnO; (ii) TsCl, Et_3N; (iii) K_2CO_3. (d) EtMgBr, $CuBr{-}Me_2S$. (e) (i) cat. OsO_4, $NaIO_4$; (ii) $Ph_3PCH{=}COCH_3$; (iii) H_2, cat. $Pd(OH)_2$. (f) *n*-PrSLi; (g) ethylene glycol, TsOH.

with 10-camphorsulfonic acid (CSA) gave the known synthetic intermediate **20**[10a] for **8** in 52% yield, which constitutes a formal synthesis of precoccinelline.

In addition, we sought an efficient synthesis of (−)-porantheridine (**9**),[11,12] a novel tricyclic alkaloid of *Porantheria corymbosa*, from **11**. The Sharpless asymmetric dihydroxylation (AD-mix-α) of **11** provided diastereomeric mixtures of diols **21** in 90% yield. A two-step treatment (deprotection and *N*-carbamation) of **21** gave **22** and **23** in respective yields of 43 and 12%. Treatment of the diol **22** with a three-step process (cyclic stannoxanation, primary

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tosylation, and epoxidation) gave the epoxide **24** in 92% yield, which was cleaved with ethylmagnesium bromide in the presence of CuBr−Me_2S to give the hydroxyl **25** in 76% yield. Oxidative cleavage of **25** with catalytic OsO_4 in combination with $NaIO_4$ followed by Wittig reaction of the resulting aldehyde with 1-triphenylphosphoranylidene-2-propanone afforded the α,β-unsaturated ketone, which was hydrogenated with catalytic $Pd(OH)_2$ to give the keto alcohol **26** in 79% yield. Decarbamation of **26** with *n*-PrSLi[13] unpredictably provided the oxazolidinone **27** in 90% yield. It is possible that an intramolecular attack by a secondary alkoxide anion, generated by *n*-PrSLi, of the carbamate carbonyl would occur. Fortunately, **27** was converted by acetalization to Comin's synthetic intermediate **28**[12b] for **9** in quantitative yield.

In summary, we explored a novel C_2-symmetric 2,6-diallylpiperidine **5** as a chiral building block via the double asymmetric allylboration of **1** followed by aminocyclization and carbamation. Its synthetic utility has been demonstrated in the expedient synthesis of piperidine-related alkaloids such as **6**−**9** based on distinctive desymmetrization using iodocarbamation as a key step, along with the protection of one allyl group. Further application of this procedure to other alkaloids such as **10** is currently under investigation.

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Supporting Information Available: Experimental procedures, characterization data, and copies of ^1H NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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