A new method for the construction of the hydroxylated tropane skeleton: enantioselective synthesis of (−)-Bao Gong Teng A†

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An efficient and highly diastereoselective method for the construction of the hydroxylated tropane skeleton is described. The method features a new intramolecular reductive coupling reaction of *N*-acyl *N*,*O*-acetal with aldehyde, cooperatively mediated by $BF_3{\cdot}OEt_2$ and SmI_2. On the basis of this method, a new enantioselective total synthesis of (−)-Bao Gong Teng A has been accomplished.

Tropane alkaloids are a class of alkaloids possessing an 8-azabicyclo[3.2.1]octane skeleton, which have been known for more than 170 years.[1] Because of their remarkable medicinal significance, tropane alkaloids have received a great deal of attention of medicinal, natural product, and synthetic organic chemists.[2] The members of tropane alkaloids have been significantly expanded with the discovery of a number of hydroxylated tropane alkaloids, such as Bao Gong Teng A (**1**),[3] (+)-2α,7β-dihydroxynortropane (**2**),[4] (−)-vaccinine B (**3**),[5] and more generally calystegines (Fig. 1).[6]

Bao Gong Teng A (**1**) is a tropane alkaloid isolated from the stem of Chinese medicinal plant Baogongteng (*Erycibe obtusifolia* Benth).[3] It exhibits hypertensive and miotic activities. Being more effective and having fewer side effects than pilocarpine and physostigmine in curing glaucoma, this alkaloid is used as a miotic agent to treat glaucoma in clinics.[7] In addition, Bao Gong Teng A (**1**) is also the first naturally occurring tropane alkaloid acting as muscarinic acetylcholine receptor (mAChR) agonist.[8] However, due to scarcity of the herbs, the clinical use of this eyedrop has been severely limited. Consequently, Bao Gong Teng A has become an attractive synthetic target.[8–12] Because of the challenges in the construction of the unique hydroxylated 8-azabicyclo[3.2.1]octane skeleton, only one racemic[10] and two enantioselective[11,12] total syntheses of Bao Gong Teng A have been reported so far. As a continuation of our interest in the development of efficient synthetic methodologies[13] for the asymmetric synthesis of natural products,[14] we recently reported a method for the one-pot cross-coupling of *N*-acyl *N*,*O*-acetals with α,β-unsaturated compounds.[15] We now report an extension of this methodology and its application to the asymmetric total synthesis of (−)-Bao Gong Teng A.

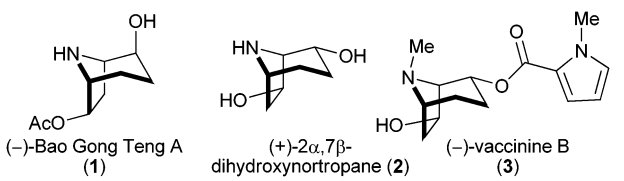
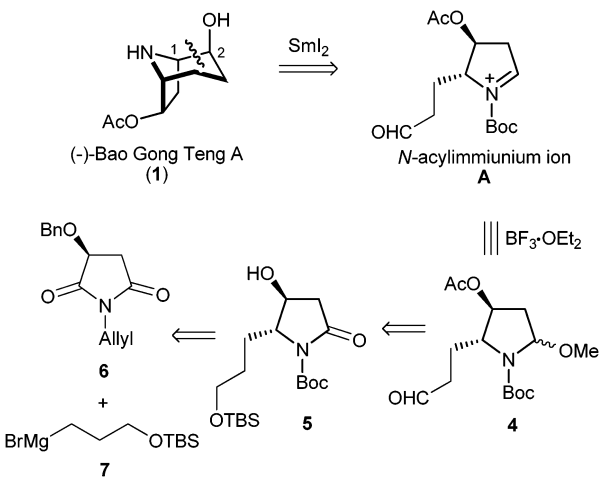


Fig. 1 Some hydroxylated tropane alkaloids.

The basic synthetic strategy was to extend our intermolecular cross-coupling method (*N*-acyl *N*,*O*-acetals with α,β-unsaturated compounds)[15] to intramolecular *N*-acyl *N*,*O*-acetal–aldehyde coupling, and merge it to our cyclic imide chiron-based synthetic methodology.[13] On the basis of this concept, our retrosynthetic analysis of (−)-Bao Gong Teng A is displayed in Scheme 1, in which the intramolecular reductive coupling of *N*,*O*-acetal with aldehyde (**4**) is the key step.

The synthesis started from the known building block **6**.[14f] Stepwise reductive alkylation of **6** was accomplished by treatment of **6** with Grignard reagent **7** (THF/CH_2Cl_2, 0 °C, 8 h) followed by $BF_3{\cdot}OEt_2$-mediated dehydroxylative reduction of the resulting diastereomeric mixture of *N*,*O*-acetals with Et_3SiH (−50 °C, overnight; rt, 2 days), giving regioselectively the concomitant desilylated 4,5-*trans*-lactam **8** in 82% overall yield (Scheme 2). The stereoselectivity was >98 : 2 as determined by ^1H NMR spectroscopy at 400 MHz and the *trans*-stereochemistry of the product was deduced from the observed coupling constant between the protons H-4 and H-5 ($J_{4,5}$ = 2.0 Hz).[16] *N*-Deallylation of **8** was achieved by $RhCl_3{\cdot}xH_2O$-catalyzed double bond migration[17] (EtOH, refl., 6 h) followed by acid-catalyzed hydrolysis ($AcOH/H_2O$, refl., 2 days; then HCl/EtOH, rt, 1 day), affording lactam **9** in 75% yield. *O*-Protection (TBSCl, DMAP, imid., CH_2Cl_2, rt, overnight) of **9** afforded compound **10** in 85% yield. Treatment of lactam **10** with



Scheme 1 Retrosynthetic analysis of (−)-Bao Gong Teng A.

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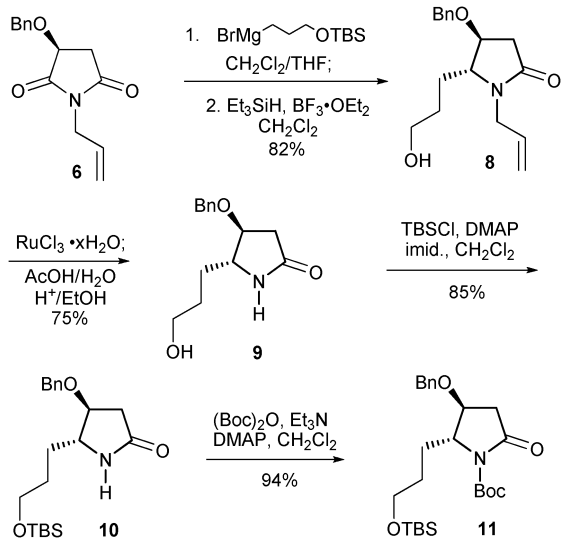
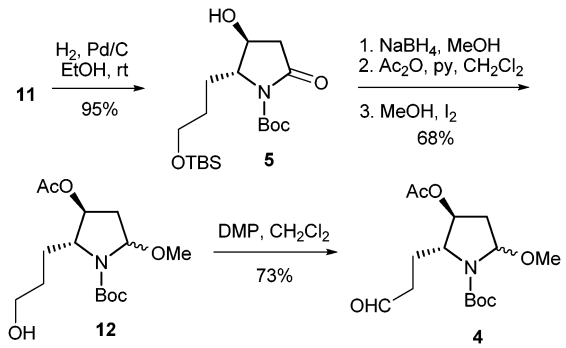


Scheme 2 Reductive alkylation of chiron **6**.

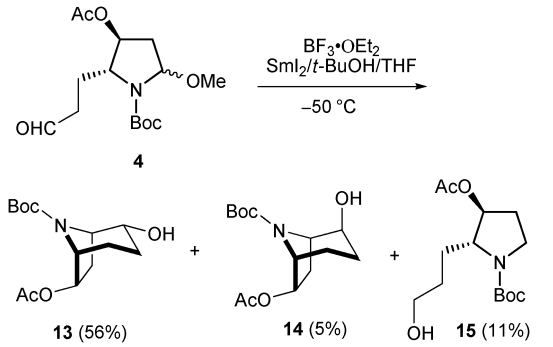
di-*tert*-butyl dicarbonate (TEA, DMAP (cat.), CH_2Cl_2) afforded the activated amide **11** in 94% yield.

O-Debenzylation (H_2, 1 atm, 10% Pd/C, EtOH, rt) of compound **11** gave amido alcohol **5** in 95% yield (Scheme 3). Controlled partial reduction of the activated amide **5** with $NaBH_4$ in MeOH produced the hemiaminal as a diastereomeric mixture, which without separation, was treated with Ac_2O/py in CH_2Cl_2 to yield the bis-acetate. Treatment of the crude labile bis-acetate with iodine in MeOH[18] gave chemoselectively desilylated and transacetylated product *N*,*O*-acetal **12** in 68% yield over three steps. Dess–Martin oxidation[19] of the diastereomeric mixture **12** provided the key precursor **4** as a 1 : 1 diastereomeric mixture (determined by ^{1}H NMR) in 73% yield.

After securing the access to the key *N*,*O*-acetal/aldehyde **4**, we turned to investigate its intramolecular reductive coupling reaction. In this regard, we have recently established the conditions for the one-pot cross-coupling of *N*-acyl *N*,*O*-acetals with α,β-unsaturated compounds.[15] Prior to this, the homo-coupling of acetals[20] and intramolecular coupling of benzylic acetals with benzylic aldehydes[21] had been reported. It was envisioned that the conditions we developed for the coupling of *N*-acyl *N*,*O*-acetals with α,β-unsaturated compounds would also be applicable to intramolecular coupling of *N*,*O*-acetal/aldehyde **4**. Indeed, successive treatment of a THF solution of *N*,*O*-acetal **4** with boron



Scheme 3 Synthesis of the *N*-acyl *N*,*O*-acetal/aldehyde **4**.



Scheme 4 BF_3·OEt_2 and SmI_2-mediated intramolecular reductive coupling of compound **4** (*N*,*O*-acetal–aldehyde).

trifluoride etherate, and a solution of SmI_2/*t*-BuOH/THF[15] at −50 °C produced the desired intramolecular coupling product **13** and its diastereomer **14** in 56% and 5% yield, respectively, along with 11% of the reduced product **15** (Scheme 4).

Although we were unable to determine the stereochemistry of the diastereomers **13** and **14** at this stage due to rotamerism (rotameric ratio of **13** was 63 : 37 as determined by ^{1}H NMR), they were deduced as shown in Scheme 4 on the basis of the mechanistic considerations, and confirmed by the subsequent transformations (*cf. vide infra*). Considering two plausible biradical intermediates **B** and **C**, intermediate **B** is favored over **C** due to electronic effects (Fig. 2).

Oxidation of the major diastereomer **13** with Dess–Martin periodinane (Scheme 5) followed by reduction of the resulting ketone **16** with L-selectride[12] afforded compound **14** (**14** : **13** > 98 : 2 as determined by ^{1}H NMR at 400 MHz on the crude product) in 84% yield. It is worthy mentioning that reduction with superhydride ($LiBEt_3H$) gave **13** and **14** in a ratio of 1 : 2, while the reduction with $LiAl(Ot\text{-}Bu)_3H$ gave **13** as the major diastereomer (**13** : **14** = 1.5 : 1).

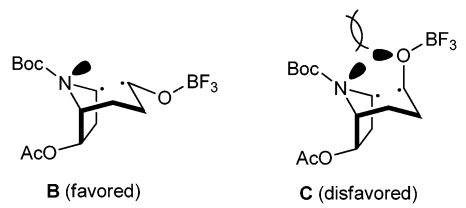
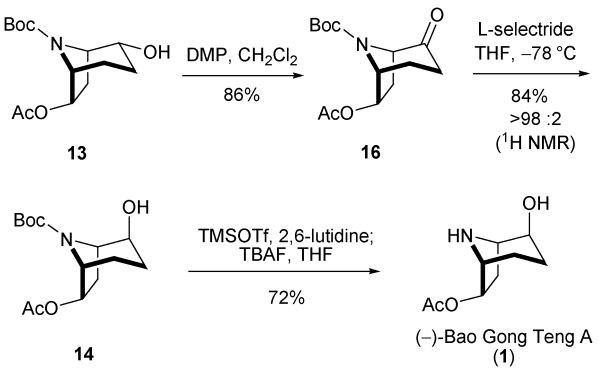


Fig. 2 Plausible electronic effects in the highly diastereoselective SmI_2-mediated intramolecular coupling of compound **4**.



Scheme 5 Synthesis of (−)-Bao Gong Teng A.

Finally, chemoselective cleavage of the Boc group in compound **14** was achieved by treatment of compound **14** with TMSOTf/2,6-lutidine,[22] and the concomitantly formed TMS ether was desilylated with TBAF in THF, which afforded (−)-Bao Gong Teng A (**1**) in 72% yield from **14**. Our synthetic product exhibited the same physical and spectral properties as those reported {colorless crystalline solid, mp 75–76 °C (CH_2Cl_2/PE); lit.[12] colorless crystalline solid: mp 76–78 °C; $[\alpha]_D^{24}$ –31.6 (*c* 0.59 in EtOH); lit.[12] $[\alpha]_D^{25}$ –29.6 (*c* 0.97 in EtOH)}.

In summary, we have demonstrated that by cooperative action of $BF_3{\cdot}OEt_2$ and SmI_2, the intramolecular reductive coupling reaction of *N*-acyl *N*,*O*-acetal with aldehyde could be achieved efficiently and highly diastereoselectively.[23] This established a novel approach to hydroxylated tropane skeleton. On the basis of this method, a new enantioselective total synthesis of (−)-Bao Gong Teng A (**1**) was accomplished in 14 steps with 7.58% overall yield from the malimide chiron **6**. Application of this strategy to the synthesis of other *N*-containing hydroxylated heterocycles, in particular hydroxylated tropanoids such as (+)-2α,7β-dihydroxynortropane (**2**) and (−)-vaccinine B (**3**), is in progress.

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