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Stereocontrolled Total Synthesis of (−)-Ephedradine A (Orantine)

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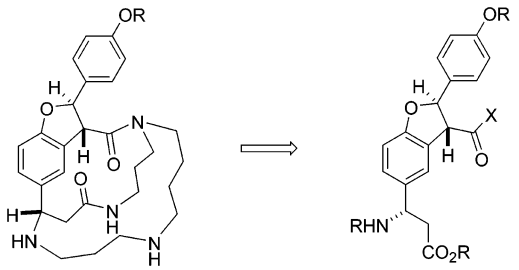
(−)-Ephedradine A (orantine, **1**) is a complex macrocyclic spermine alkaloid isolated by Hikino and co-workers in 1979 as one of the hypotensive components of the Chinese traditional drug "mao-kon."[1,2] While synthesis of racemic O-methylated orantine (**2**) was achieved by Wasserman and co-workers in 1985,[3] total synthesis of **1** has not been reported to date. Clearly, construction of the two macrocyclic rings in the presence of a labile dihydrobenzofuran moiety constitutes the major challenge in the total synthesis of **1**. Recently, we have developed a highly efficient methodology for construction of medium- and large-sized cyclic amines via 2-nitrobenzenesulfonamides (Ns-strategy).[4,5] We envisioned this strategy being applied to the construction of the macrocyclic ring of **1**. Herein, we report an efficient total synthesis of (−)-ephedradine A (**1**) by the stereocontrolled synthesis of optically active intermediate **3** and subsequent construction of the macrocyclic polyamine ring by the Ns-strategy.



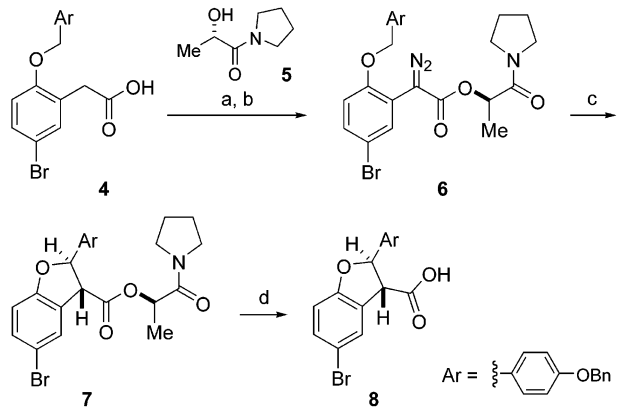
(–)-Ephedradine A (Orantine): R = H (**1**)
O-Methylorantine: R = Me (**2**)

3

Recently, we have developed a novel methodology for the construction of optically active dihydrobenzofuran rings by an intramolecular C−H insertion reaction.[6] According to the protocol, the cyclization precursor **6** was prepared by condensation of carboxylic acid **4** with the lactamide-type chiral auxiliary **5** under Mitsunobu conditions[7] and a subsequent diazo transfer reaction (Scheme 1). Upon treatment of **6** with 0.3 mol % of the Davies catalyst,[8] the C−H insertion reaction proceeded smoothly to afford exclusively the *trans*-dihydrobenzofuran **7** in 63% yield (two steps) and high diastereoselective manner (13:1). Removal of the chiral auxiliary by hydrolysis and subsequent recrystallization gave the optically pure carboxylic acid **8**.

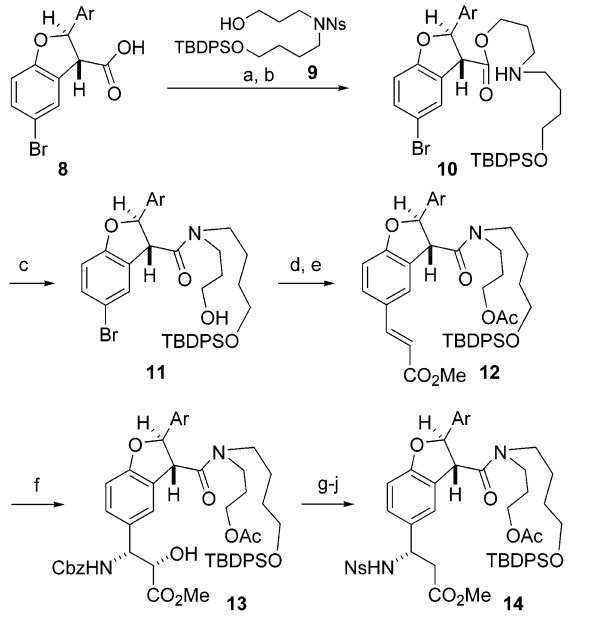
Direct condensation of **8** with secondary amine derivatives of **9** was unsuccessful due to decomposition of the dihydrobenzofuran ring brought about by activation of the carboxylic acid **8**. After numerous efforts to construct the amide bond, an intramolecular ester−amide exchange reaction of **10** was found to be suitable for the synthesis of **11**. Upon treatment of **8** and the alcohol **9** with DEAD and PPh_3, the condensation reaction proceeded smoothly to provide **10** (Scheme 2). Removal of the Ns group and subsequent treatment of the secondary amine **10** with dimethylaluminum chloride[9,10] in refluxing CH_2Cl_2 gave the amide **11** in 67% yield.

Scheme 1 [a]



[a] Reagents and conditions: (a) **5**, PPh_3, DEAD, toluene (80%); (b) $AcNHC_6H_4SO_2N_3$, DBU, CH_3CN; (c) Rh_2(*S*-DOSP)$_4$ (0.3 mol %), CH_2Cl_2 (63% in two steps); (d) $Ba(OH)_2 \cdot 8H_2O$, THF/MeOH/H_2O (90%).

Scheme 2 [a]



[a] Reagents and conditions: (a) **9**, PPh_3, DEAD, toluene (96%); (b) PhSH, K_2CO_3, DMF/CH_3CN, 50 °C (88%); (c) Me_2AlCl, CH_2Cl_2, reflux (67%); (d) Ac_2O, pyr (88%); (e) methyl acrylate, $Pd(OAc)_2$ (6 mol %), P(*o*-tol)$_3$ (18 mol %), Et_3N, DMF, 100 °C (84%); (f) CbzNClNa, $K_2OsO_2(OH)_4$ (6 mol %), $(DHQD)_2PHAL$ (8 mol %), *n*-PrOH/H_2O (66%); (g) PPh_3, CCl_4, toluene, 100 °C (87%); (h) Pd/C (20 mol %), HCO_2NH_4, MeOH, 60 °C; (i) BnOH, PPh_3, DEAD, toluene, 60 °C (61% in two steps); (j) NsCl, Na_2CO_3, CH_2Cl_2/H_2O (72%).

Acetylation of the alcohol **11** followed by a conventional Heck reaction[11] with methyl acrylate furnished the cinnamate derivative **12**.

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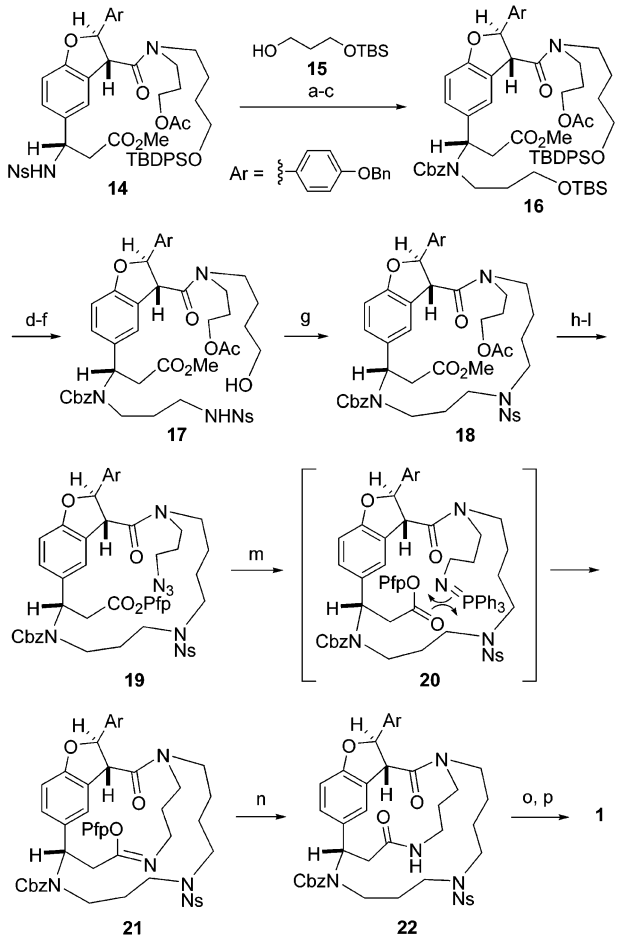
Scheme 3 [a]



[a] Reagents and conditions: (a) **15**, PPh_3, DEAD, toluene, 60 °C (95%); (b) PhSH, KOH, CH_3CN, 60 °C (93%); (c) CbzCl, $NaHCO_3$, CH_2Cl_2/H_2O (91%); (d) CSA, MeOH (94%); (e) $NsNH_2$, DEAD, PPh_3, toluene/THF (quant.); (f) aqueous HF, CH_3CN (84%); (g) PPh_3, DEAD, toluene (77%); (h) K_2CO_3, MeOH/THF (96%); (i) MsCl, Et_3N, CH_2Cl_2, 0 °C; (j) NaN_3, DMF, 60 °C (82% in two steps); (k) LiOH, MeOH/THF/H_2O (97%); (l) pentafluorophenol, WSCD·HCl, CH_2Cl_2 (93%); (m) PPh_3, toluene, reflux; (n) CH_3CN/H_2O, reflux (73% in two steps); (o) PhSH, KOH, CH_3CN, 50 °C (75%); (p) BCl_3, CH_2Cl_2, −78 to 0 °C (73%).

Facile and diastereoselective incorporation of the nitrogen atom in **12** was achieved by the Sharpless asymmetric aminohydroxylation reaction[12] to afford **13** as the predominant product (12:1). After conversion of the hydroxyl group of **13** to the corresponding chloride by treatment with PPh_3 and CCl_4, removal of the chlorine under transfer hydrogenation conditions provided the β-amino ester with concomitant cleavage of the Cbz group and benzyl ether. Selective protection of the resultant phenol with the benzyl group under Mitsunobu conditions and subsequent introduction of the Ns group on the primary amine furnished the sulfonamide **14**.

The next challenge in the synthesis was the crucial construction of the 16-membered polyamine ring **(**Scheme 3). Coupling between the sulfonamide **14** and the alcohol **15**[13] under Mitsunobu conditions followed by switching the protecting group of the amine to the corresponding *N*-Cbz derivative yielded **16**. Acid-catalyzed selective deprotection of the TBS group, coupling with $NsNH_2$ under Mitsunobu conditions, and subsequent cleavage of the TBDPS ether furnished the cyclization precursor **17**. Upon treatment of **17** with DEAD and PPh_3 in a 0.05 M solution of toluene at room temperature, the desired cyclization reaction proceeded smoothly to afford **18** in 77% yield.

With the desired macrocyclic polyamine in hand, we next focused on the construction of the 13-membered macrolactam ring. The cyclization precursor **19** bearing an activated ester was prepared from **18** in a five-step sequence involving deprotection of the acetyl group, mesylation of the alcohol, displacement of the mesylate with NaN_3, basic hydrolysis of the methyl ester, and condensation of the resultant carboxylic acid with pentafluorophenol. While generation of the amine moiety from the azide **19** under hydrogenation conditions resulted in exclusive dimerization, treatment with PPh_3 in refluxing toluene under high-dilution conditions (7.0 mM) successfully afforded the 13-membered iminoether **21** via the Staudinger[14] and the intramolecular aza-Wittig reactions.[15,16] Subsequent hydrolysis of **21** by refluxing in CH_3CN-H_2O afforded the desired 13-membered macrolactam **22** in 73% yield (two steps). Removal of the Ns group and simultaneous cleavage of the Cbz group and benzyl ether with BCl_3 yielded (−)-ephedradine A (**1**), the spectral data of which (^{1}H NMR, ^{13}C NMR, IR, and HRMS) were in full agreement with those of the natural product.[1]

In conclusion, a stereocontrolled total synthesis of (−)-ephedradine A (**1**) has been accomplished by a Rh-catalyzed C−H insertion reaction and a Sharpless asymmetric aminohydroxylation reaction. Furthermore, our synthesis features construction of all the secondary amines using the Ns-strategy, including macrocyclization and formation of the two amide bonds by the intramolecular ester−amide exchange reaction and the aza-Wittig reaction.

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Supporting Information Available: Experimental details and spectroscopic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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