The Chiral Total Synthesis of (−)-Oncinotine

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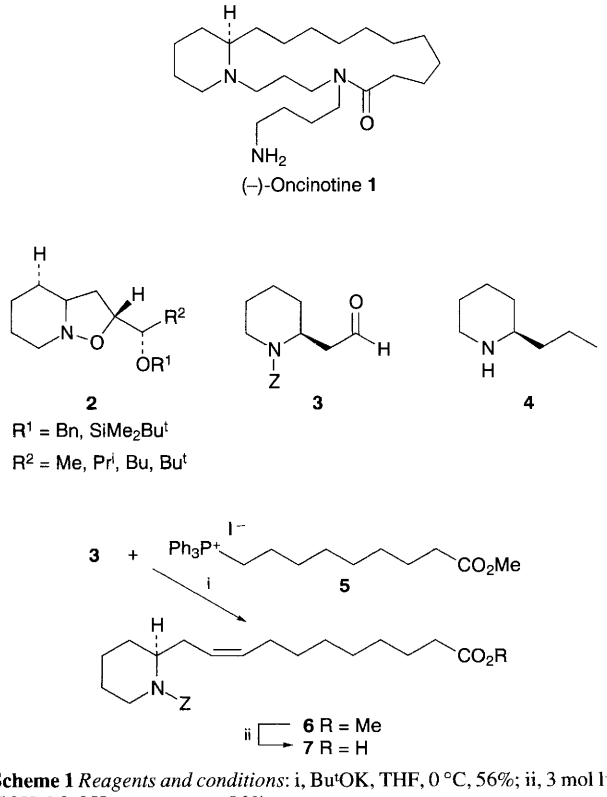
The first chiral synthesis of (−)-oncinotine **1** in natural form has been achieved starting from the protected (*S*)-*N*-benzyloxycarbonyl-2-piperidylacetaldehyde **3** based on a new route involving 17-membered ring formation *via* iminium cyclization, which establishes the 17*R* absolute configuration of natural **1**.

(−)-Oncinotine **1** is one of three macrocyclic spermidine alkaloids, isolated from *Oncinotis nitida*.[1] The structure of **1** was proposed by Schmid *et al.*[1,2] based on chemical and spectral evidence and the *R* configuration was deduced by means of CD measurement of the degradation product of **1** in comparison with that of (*R*)-(−)-*N*-methylconiine.[2] While the synthesis of racemic **1** has been performed by three routes,[3–5] there has been no report on the chiral synthesis of **1**.

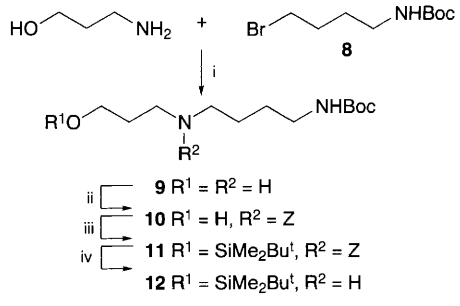
Recent investigations from this laboratory have demonstrated[6] that 1,3-dipolar cycloaddition of chiral allyl ethers to a cyclic nitrone proceeds in a diastereoselective manner owing to the 'inside alkoxy effect' to afford *erythro* adducts **2**, which can be converted to (*R*)-(−)-coniine **4** *via* enantiomerically pure (*S*)-*N*-benzyloxycarbonyl-2-piperidineacetaldehyde **3**. Here, we describe the first chiral synthesis of (−)-oncinotine **1** utilizing **3** as a chiral starting material, based on a new route involving 17-membered lactam formation *via* intramolecular iminium cyclization. Our synthesis established the absolute configuration of the naturally occurring (−)-enantiomer of **1** as 17*R*.

First, the piperidine segment with the long aliphatic chain was prepared as outlined in Scheme 1. Wittig condensation of **3** with the phosphonium salt **5**[7] (Bu^{t}OK, THF, 0 °C) gave the unsaturated ester **6** in 56% yield, and alkaline hydrolysis of **6** (aq. KOH, MeOH) was subsequently carried out to afford **7** in 96% yield. To construct the spermidine moiety, the *N*-propylbutane-1,4-diamine segment was prepared next *via* a straightforward sequence as shown in Scheme 2. Thus, alkylation of 3-aminopropan-1-ol with *N*-Boc-protected 4-bromobutylamine **8**, available by bromination (CBr_4, Ph_3P, CH_2Cl_2) of *N*-Boc-4-aminobutan-1-ol, in the presence of K_2CO_3 in DMF provided **9**, which immediately underwent *N*-protection with benzyl chloroformate to yield the carbamate **10** (46% overall yield). Subsequent silylation of the alcohol function (Bu^{t}Me$_2$SiCl, imidazole, DMF) followed by hydrogenolytic removal of the Z group over palladium hydroxide in methanol converted **10** to **12** in 78% overall yield.

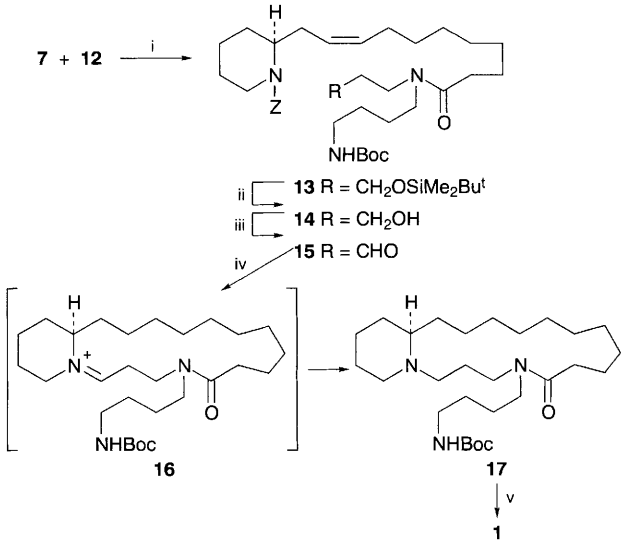
The piperidine segment **7** was coupled with the *N*-propylbutane-1,4-diamine segment **12** by using diethylphosphoryl cyanide[8] in the presence of Et_3N in DMF to furnish the amide **13** in 95% yield (Scheme 3). Removal of the silyl group of **13** (Bu$^n_4$NF, THF) followed by Swern oxidation[9] [$(COCl)_2$, Me_2SO, Et_3N] gave the aldehyde **15** (72% overall yield). The construction of the macrocyclic lactam ring has been a pivotal object in the total synthesis of macrocyclic lactam alkaloids, and in many cases has been performed by intramolecular amidation.[10] For an alternative elaboration of macrocyclic lactam, we



Scheme 1 *Reagents and conditions*: i, Bu^{t}OK, THF, 0 °C, 56%; ii, 3 mol l^{-1} KOH, MeOH, room temp., 96%



Scheme 2 *Reagents and conditions*: i, K_2CO_3, DMF, 90 °C, 52%; ii, ZCl, aq. Na_2CO_3, CH_2Cl_2, 0 °C, 88%; iii, Bu^{t}Me$_2$SiCl, imidazole, DMF, room temp., 82%; iv, H_2, $Pd(OH)_2$, MeOH, room temp., 95%



Scheme 3 *Reagents and conditions*: i, $(EtO)_2P(O)CN$, Et_3N, DMF, room temp., 14 h, 95%; ii, Bu$^n_4$NF, THF, room temp., 100%; iii, $(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2, −78 °C → room temp., 72%; iv, H_2, $Pd(OH)_2$, MeOH, room temp., 4 d, 66%; v, 3 mol l^{-1} HCl, MeOH, then aq. K_2CO_3, room temp., 71%

envisaged the use of a more efficient route based on iminium cyclization, previously developed in this laboratory.[11] Accordingly, treatment of **15** with hydrogen over a $Pd(OH)_2$ catalyst under high dilution (4×10^{-3} mol dm^{-3} in MeOH) led to the *in situ* generation of the transient iminium ion **16** by way of hydrogenation of the alkene and deprotection of the amine, which was further hydrogenated to form the 17-membered lactam **17** in a single step in 66% yield.

Finally, removal of the Boc protecting group of **17** with methanolic HCl followed by neutralization with K_2CO_3 resulted in (*R*)-(−)-oncinotine **1** in 71% yield. Synthetic **1** had optical rotation {$[\alpha]_D^{26}$ −28.7 (*c* 2.6, $CHCl_3$), $[\alpha]_D^{26}$ −32.7 (*c* 2.1, MeOH)} and spectra (IR and MS) virtually identical with those reported[1,2] for the natural sample of **1** {$[\alpha]_D$ −29 ($CHCl_3$), $[\alpha]_D$ −33° (MeOH)}. Furthermore, the spectra (^1H and ^{13}C NMR) of the HCl salt of synthetic **1** agreed with those of the HCl salt of racemic **1**.[5] The chiral synthesis of **1** utilizing **3** has now been accomplished. These results established the absolute configuration of the natural oncinotine as 17*R* (**1**).

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