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A novel synthetic approach to isoindolobenzazepine alkaloid, chilenine, employing SmI_2-mediated pinacolic coupling reaction

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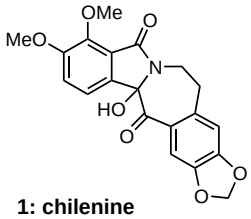
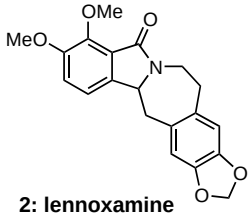
Abstract—Samarium(II) diiodide-mediated intramolecular reductive coupling reaction of phthalimides with *N*-formylated alkyl side chains is shown to afford dihydroxylated tricyclic lactams with 5–7-membered rings. This process was further applied for the preparation of an isoindolobenzazepine alkaloid, chilenine, by featuring the elaboration of the functionalized phthalimide derivative.

Chilenine (**1**) and lennoxamine (**2**) first found in the plants of the Chilean *Berberis* species, *Berberis empetrifolia* Lam and *Berberis darwinii* Hook, respectively, are a new class of alkaloids belonging to the aporhoedane series.[1] Although biogenetically related to protoberberines and usually classified as isoquinoline alkaloids, they are distinguished by the presence of an isoindolo[1,2-*b*][3]benzazepine unit embedded in their skeleton from the simple isoquinoline group. Due to the fact that their structures incorporating the 3*H*-3-benzazepine moiety and equally an isoindolinone ring system are architecturally sophisticated and possess the real and potential biological properties,[2] they have captured the interest as attractive and synthetically challenging targets.[3] Synthetic strategies described up to date, however, in general require multistep reactions or crucial techniques and were not necessarily satisfactory. On the other hand, as part of our work designed to explore the use of cyclic imides, we have demonstrated some significant stereoselective reactions[4] and their applications to the total syntheses of biologically active natural products.[5] In addition, recently, novel and stereoselective methods for the preparation of hydroxylactams via reductive coupling reactions mediated by SmI_2 have also been developed in this laboratory.[6] The purpose of the present communication is to describe the result that *N*-functionalized phthalimide derivatives underwent fast SmI_2-induced intramolecular pinacol-type coupling reaction, which in turn made it possible to provide a new expeditious and practical opportunity for the synthesis of an isoindolobenzazepine alkaloid, chilenine.



1: chilenine



2: lennoxamine

In formulating the synthetic plan for chilenine (**1**), we envisioned that the benzazepine ring of significant precursor **3** would originate from the intramolecular coupling reaction of **4**, which could be divided into two known fragments, acid ester **5**[7] and bromopiperonal (**6**),[8] respectively (Scheme 1).

In advance, initial experiments have been performed on the intramolecular coupling reaction in the presence of SmI_2 (2 equiv.) in THF at rt employing simple phthalimide derivatives **7**[9] with *N*-formylated alkyl substituents. As shown in Scheme 2, it became apparent that these conditions without additives brought about the desired dihydroxylated tricyclic lactams **8** with 5–7-membered rings in satisfactory yields, respectively.[10]

With these results in hand, we next focussed our attention on the synthesis of **1**, an isoindolobenzazepine natural product. The results from our survey are summarized in Scheme 3. To begin with, the ethylene acetal compound derived from bromopiperonal (**6**) was converted into **9** via aromatic allylation,[11] which underwent dihydroxylation and oxidative cleavage of the olefinic

Keywords: SmI_2; imide; coupling reaction; alkaloid; chilenine.

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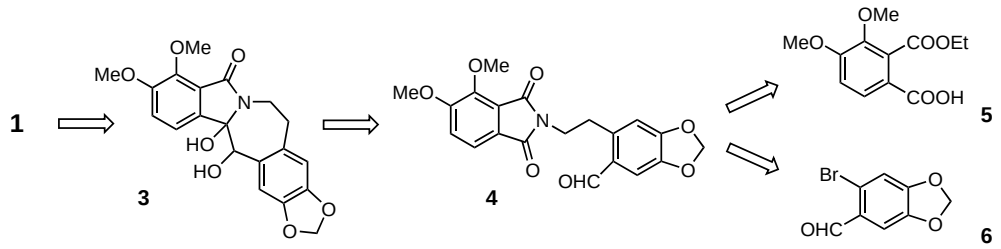
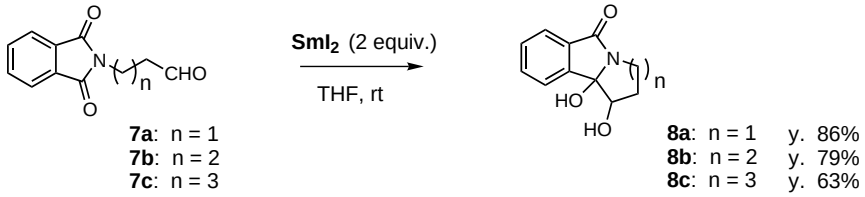
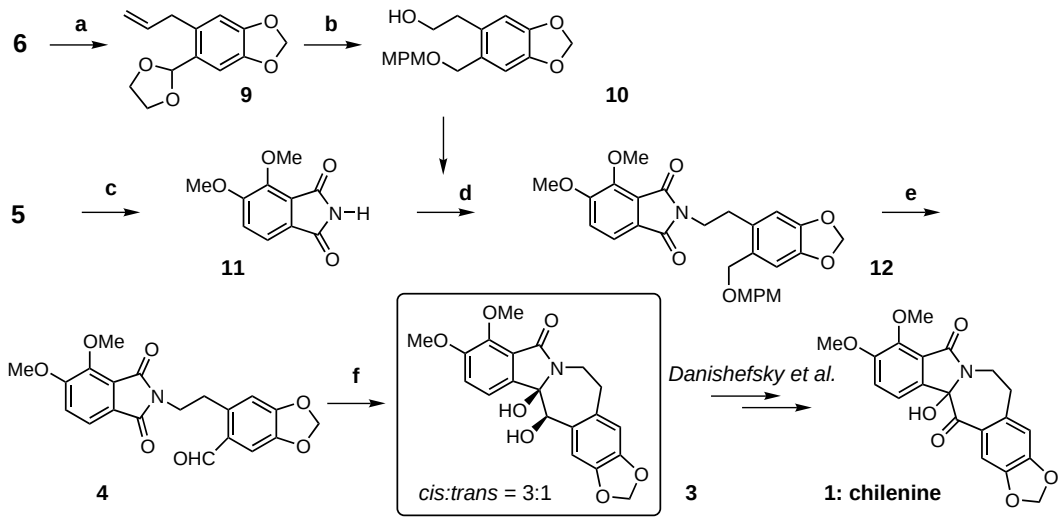


Scheme 1.



Scheme 2.



Scheme 3. *Reagents and conditions*: (**a**) **1**, $HO(CH_2)_2OH$, *p*-TsOH, toluene, reflux; quant.; **2**, BuLi, ether, −60°C, then allyl bromide; 63%; (**b**) **1**, conc. HCl, ether; **2**, $NaBH_4$, MeOH; 78% (two steps); **3**, MPMCl, Ag_2O, CH_3COOEt; 82%; **4**, OsO_4, NMO, acetone–H_2O (1:1), **5**, $NaIO_4$, ether–H_2O (1:1), −5°C; **6**, $NaBH_4$, MeOH; 80% (three steps); (**c**) **1**, $MPMNH_2$, DCC, CH_2Cl_2; 78%; **2**, CAN, CH_3CN–H_2O (9:1), −10°C; 65%; (**d**) (**10**), DEAD, PPh_3, THF; 46%; (**e**) DDQ, CH_2Cl_2–H_2O (10:1), −10°C; 54%; (**f**) SmI_2 (3 equiv.), THF; 65%.

part followed by reduction to give the alcohol **10** in high yield after successive reactions of deacetalization, reduction, and MPM(*p*-methoxybenzyl)-protection. On the other hand, acid ester **5** was submitted to coupling reaction with MPM-amine to afford the cyclic imide directly, which was then deprotected with cerium ammonium nitrate (CAN), leading to the *N*H-imide **11**. Thus, reaction of **11** with the alcohol **10** prepared above under Mitsunobu conditions proved to yield the condensation product **12** in moderate yield. When the subsequent deprotection of the MPM-group in **12** was effected by the use of DDQ, it was apparent that the desired aldehyde intermediate **4** could be obtained directly. Finally, SmI_2-mediated intramolecular pinacolic reaction of **4** was performed to give the crucial coupling product **3** in 65% yield with fortunately complete regioselectivity. The ratio of the two diastereomers (*cis:trans* = 3:1) was easily determined by ^1H NMR.[12] Since both of these isomers of **3** has already been converted into **1** via the same enol acetate[12] by Danishefsky et al.[13] in high yield, the whole sequence of reactions constitutes, in a formal sense, a total synthesis of natural chilenine.

In summary, we have found SmI_2-mediated intramolecular coupling reaction of cyclic imides with aldehyde-alkyl side chains to give some isoindolone derivatives directly and accomplished the formal synthesis of chilenine natural alkaloid employing this procedure. This process provides an easily accessible alternative to existing synthetic methods of isoindoloazepine alkaloids.

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