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A Novel Approach to Bicyclic Alkaloids Using a Tandem Diastereoselective Acyliminocyclization and Retro Diels-Alder Reaction Sequence. Synthesis of (+)-Indolizidine and (+)-Laburnine

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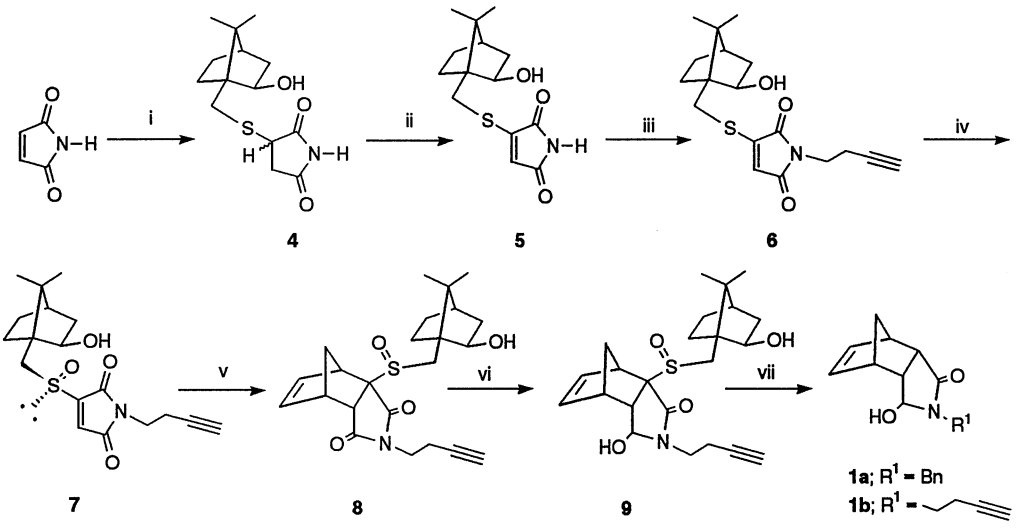
A new approach to a diastereoselective cationic cyclization by stereocontrol due to the bicyclo[2.2.1]heptene moiety in a chiral γ-hydroxy lactam is described. The diastereoselective reaction followed by Diels-Alder cycloreversion has been successfully applied to a chiral synthesis of (+)-indolizidine and (+)-laburnine (= trachelanthamidine).

Intra-[1] and intermolecular[2] nucleophilic additions to acyliminium ions have proven to be a useful method for the synthesis of nitrogen-containing natural products. In particular, a number of syntheses of bicyclic alkaloids such as pyrrolizidine and indolizidine families has been reported;[3] however, enantioselective synthesis by the methodology has received much less attention. Very recently there have been a few reports[4] of asymmetric syntheses based upon the strategy through the nucleophilic addition reaction. However, enantiomeric control in these syntheses has been achieved by the use of the chiral acyliminium ion with a stereogenic center (=chiral auxiliary) appended to the nitrogen atom in the γ-hydroxy lactam. The modest control in these reactions indicates a need for the achievement of high level of diastereoselection. Recently we have shown a short step entry to a chiral γ-hydroxy lactam **1a**.[5] The lactam **1** obtained has notable structural features: i) nucleophilic addition to the acyliminium generated *in situ* from **1** would take place from the convex face by the steric hindrance due to the fused bicyclo[2.2.1]heptene moiety, and ii) thermal cycloreversion of the bicyclic system could result in the formation of a Δ^3-pyrrolidinone ring. These structural features enabled us to exploit a new method that effects the addition reaction with a high degree of diastereoselectivity. We describe here a highly diastereoselective acyliminocyclization using a tricyclic lactam **1b** and its application to a chiral synthesis of (+)-indolizidine (**2**)[6] and (+)-laburnine (**3**).[7]

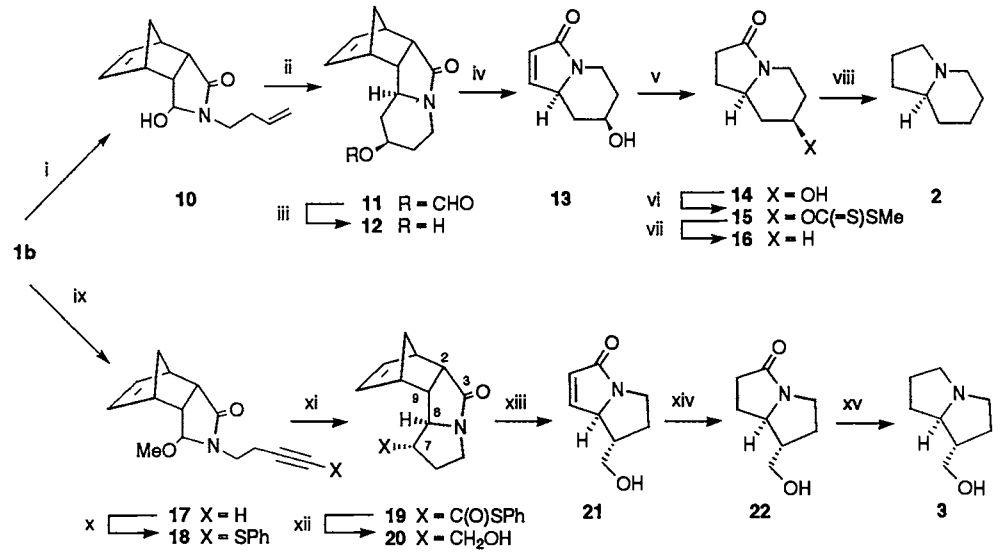
Chiral lactam **1b** was prepared as follows.[8] Treatment of maleimide with 10-mercaptoisoborneol[9] gave the succinimide **4** (Scheme 1). Heating of **4** with *N*-chlorosuccinimide (NCS) in carbon tetrachloride resulted in chlorination and spontaneous dehydrochlorination to form the maleimide **5** {mp 182-184 °C, $[\alpha]_D^{25}$ -27.1° (*c* 1, EtOH)}. Imide **5** was coupled with 3-butyn-1-ol under Mitsunobu conditions[10] to afford the *N*-3-butynyl maleimide **6**, which upon exposure to 3-chloroperoxybenzoic acid (MCPBA) gave the sulfoxide **7** { mp 130-131 °C, $[\alpha]_D^{25}$ -59° (*c* 1.05)}.[11] Dienophile **7** was allowed to react with cyclopentadiene ($ZnCl_2$, -75 °C, 0.5 h) giving the adduct **8** {mp 64-66 °C, $[\alpha]_D^{25}$ +3.9° (*c* 2)}, with 96% diastereoisomeric excess. Regioselective reduction of **8** with $NaBH_4$ (to give **9**) followed by desulphinylation by samarium-induced reduction [12] afforded the lactam **1b** as a diastereoisomeric mixture.[13]



Scheme 1. i, 10-Mercaptoisoborneol, Et_3N (cat.), CH_2Cl_2, room temp, 6 h (98%); ii, NCS, CCl_4, reflux, 6 h (95%); iii, 3-butyn-1-ol, Ph_3P, tetrahydrofuran (THF), 0 °C, 0.1 h; diethyl azodicarboxylate, THF, 0 °C → room temp, overnight (99%); iv, MCPBA (1.05 mol equiv.), CH_2Cl_2, 0 °C → room temp, 0.5 h (94%); v, cyclopentadiene (5 mol equiv.), $ZnCl_2$ (1.5 mol equiv.), CH_2Cl_2, -75±5 °C, 0.5 h (93%); vi, $NaBH_4$ (5 mol equiv.), HCl (cat.), MeOH, 0 °C, 2 h (80%); vii, SmI_2 (5 mol equiv., 0.1 mol dm^{-3} in THF), Bu^tOH (10 mol equiv.), hexamethylphosphoric triamide (10 mol equiv.), room temp, 0.5 h (92%)

The synthesis of **2** is illustrated in Scheme 2. Selective hydrogenation of **1b** over Pd-$BaSO_4$ afforded the *N*-3-butenyl lactam **10**. The chiral lactam **10** was subjected to an acyliminium cyclization according to the procedure explored by Speckamp,[1a] giving the formate **11** as a single product. The spectroscopic data of **10** and **11** were in good agreement with those for racemates.[1a] Hydrolysis of **11** produced the alcohol **12**, which upon flash vacuum pyrolysis (FVP, 450 °C / 0.5 Pa) was smoothly transformed into the bicyclic alcohol **13**. The unsaturated amide **13** was hydrogenated to provide **14**, which was then converted into the xanthate **15**. Reduction of **15** with tri-butyltin hydride gave the amide **16**,[14] which was transformed by reduction to (+)-indolizidine (**2**) { $[\alpha]_D^{24}$ +9.0° (*c* 0.7, EtOH), lit.[6a] $[\alpha]_D^{23}$ +9.3 ± 0.6° (*c* 1.77, EtOH)}.

Alternatively, treatment of **1b** with pyridinium *p*-toluenesulfonate[15] and methanol gave the lactam **17** {mp 46-47 °C, $[\alpha]_D^{25}$ +69.2° (*c* 1.06)} as a single diastereoisomer. The amide **17** was treated with diphenyl disulfide and lithium hexamethyldisilazide to give **18**, which upon exposure to formic acid produced the phenylthioester **19**, exclusively. In contrast to the results of the similar cyclization in monocyclic system,[16] the cyclization proceeded with high diastereoselectivity, which resulted in stereocontrol of the newly formed asymmetric centers, *i.e.* C(7) and C(8) positions in **19**. It seemed likely that the C(7) sp^2 carbon of the enol derivative via the intermediate vinyl cation could be captured by formic acid from the less-hindered convex face. Reduction of **19** with $NaBH_4$ afforded the alcohol **20**,[17] which was subjected to FVP (500 °C /1.3 x 10^{-3} Pa) giving the bicyclic amide **21** {mp 62-64 °C, $[\alpha]_D^{26}$ +38.6° (*c* 0.91)}. Catalytic hydrogenation over platinum oxide (to give **22**) followed by reduction gave (+)-laburnine (**3**) { $[\alpha]_D^{25}$ +11.1° (*c* 1.1, EtOH), lit.[7b] $[\alpha]_D$ +15.4° (*c* 1.44, EtOH), lit.[7c] $[\alpha]_D^{20}$ +13.63° (*c* 1.22, EtOH), lit.[7d] $[\alpha]_D^{22}$ +14.6° (*c* 3.25, EtOH)}, whose ^1H and ^{13}C NMR spectra were in good agreement with those of (-)-**3** reported by Ishibashi *et al.* [18]



Scheme 2. i, H_2, Pd-$BaSO_4$, pyridine (cat.), MeOH, room temp, 15 h (99%); ii, HCO_2H, room temp, 12 h (92%); iii, 2 mol dm^{-3} KOH aq., EtOH, room temp, 2 h (95%); iv, flash vacuum pyrolysis (FVP), 450 °C, 0.5 Pa (83%); v, H_2, PtO_2 (cat.), MeOH, room temp, 3 h (99%); vi, NaH, imidazole (cat.), THF, reflux, 1 h; CS_2 and then CH_3I, reflux, 0.6 h (80%); vii, Bu_3SnH (1.5 mol equiv.), 2,2'-azobisisobutyronitrile (cat.), benzene, reflux, 10 h (76%); viii, $LiAlH_4$, Et_2O, reflux, 1 h (74%); ix, pyridinium *p*-toluenesulfonate (cat.), MeOH, room temp, 15 h (90%); x, $(PhS)_2$, lithium hexamethyldisilazide, THF, -70 °C → room temp, 1 h (96%); xi, HCO_2H, room temp, 15 h (80%); xii, $NaBH_4$ (2 mol equiv.), MeOH, 0 °C, 0.5 h (94%); xiii, FVP, 500 °C, 1.3 x 10^{-3} Pa (86%); xiv, H_2, PtO_2 (cat.), EtOH, room temp, 4 h (99%); xv, $LiAlH_4$ (2 mol equiv.), THF, reflux, 4 h (60%)

In summary, the enantioselective synthesis of bicyclic alkaloids, (+)-**2** and (+)-**3** has been accomplished by a novel strategy involving acid-catalysed cyclization and Diels-Alder cycloreversion. By choosing an appropriate *N*-substituted maleimide as a chiral dienophile, this synthetic strategy is capable of application to chiral syntheses of a variety of the alkaloids.

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