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A Convenient Route to Spiropyrrolidinyl-Oxindole Alkaloids via C-3 Substituted Ene-Pyrrolidine Carbamate Radical Cyclization

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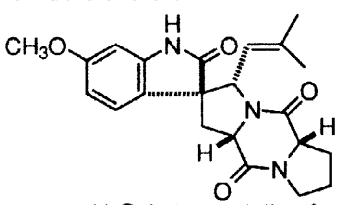
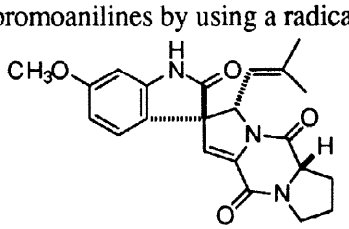
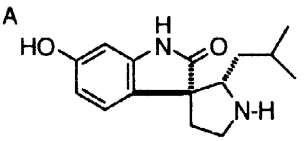
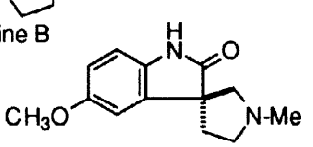
Abstract: A short access to spiropyrrolidinyl-oxindole alkaloids via a substituted ene-pyrrolidine carbamate, synthesized from the commercially available *tert*-butyl 1-pyrrolidine carboxylate, is described.

Spiropyrrolidinyl-oxindole alkaloid skeletons are found in spirotryprostatine A and spirotryprostatine B[1] which were found to be new inhibitors of mammalian cell cycle at G2/M phase, from the secondary metabolites of *Aspergillus fugimatus*. Elacomine[2] was isolated from *Eleagnus commutata* and horsfiline[3] was isolated from *Horsfieldia superba*, a small Malaysian tree, extracts of which have found use in indigenous medecine. 3,3-Spiroindole skeleton can be obtained from orthobromoanilines by using a radical[3c] or a Heck[4] reaction.


(-)-Spirotryprostatine A


(-)-Spirotryprostatine B


(+)-Elacomine


(-)-Horsfiline

Recently, we have reported[5] a very simple method for obtaining enecarbamates from *N*-Boc protected 2-hydroxypyrrolidine derivatives, and the use of enecarbamates in the preparation of the pyrrolidinyl-oxindole alkaloid skeleton has been envisaged. The synthesis of compound **4** was achieved in three steps from *tert*-butyl 1-pyrrolidinecarboxylate **1**[6]. Treatment of **1** with a solution of LiHMDS (1 equiv.) in THF, followed by the addition *n*-BuLi (1 equiv.) and then quenching of the resulting enolate with benzyl chloroformate produced the amido ester **2** (85 %). The reduction of the *N*-Boc protected pyrrolidine **2** was achieved with Dibal-H to give the *N*-Boc protected 2-hydroxypyrrolidine **3** which was treated directly with a catalytic amount of quinolinium camphorsulfonate (QCS, 0.15 equiv.) for a few minutes in toluene at 80 °C, to form the corresponding enecarbamate **4** with an overall yield of 89 % for the two steps.

Attempts to couple the carboxylic acid (in the presence of DCI) or acid chloride derived from ester **4** with *o*-iodoaniline were unsuccessful. Alternatively, when the nucleophilicity of the aniline was increased by using triethylaluminium ($AlEt_3$) in toluene, the coupling reaction with ester **4** afforded the desired amide **5** (82 %). After protection of the amide nitrogen in **5**, with a methoxy-carbonyl group, under standard conditions (NaH, $ClCO_2Me$), **6** was isolated in 62 % yield. Treatment of a solution of **6** in benzene by tri-*n*-butyltin hydride (Bu_3SnH) and a catalytic amount of azobisisobutyronitrile (AIBN) at 80 °C for 1 h, followed by a simple aqueous work-up, led to a mixture of two products which could not be separated by flash chromatography. The

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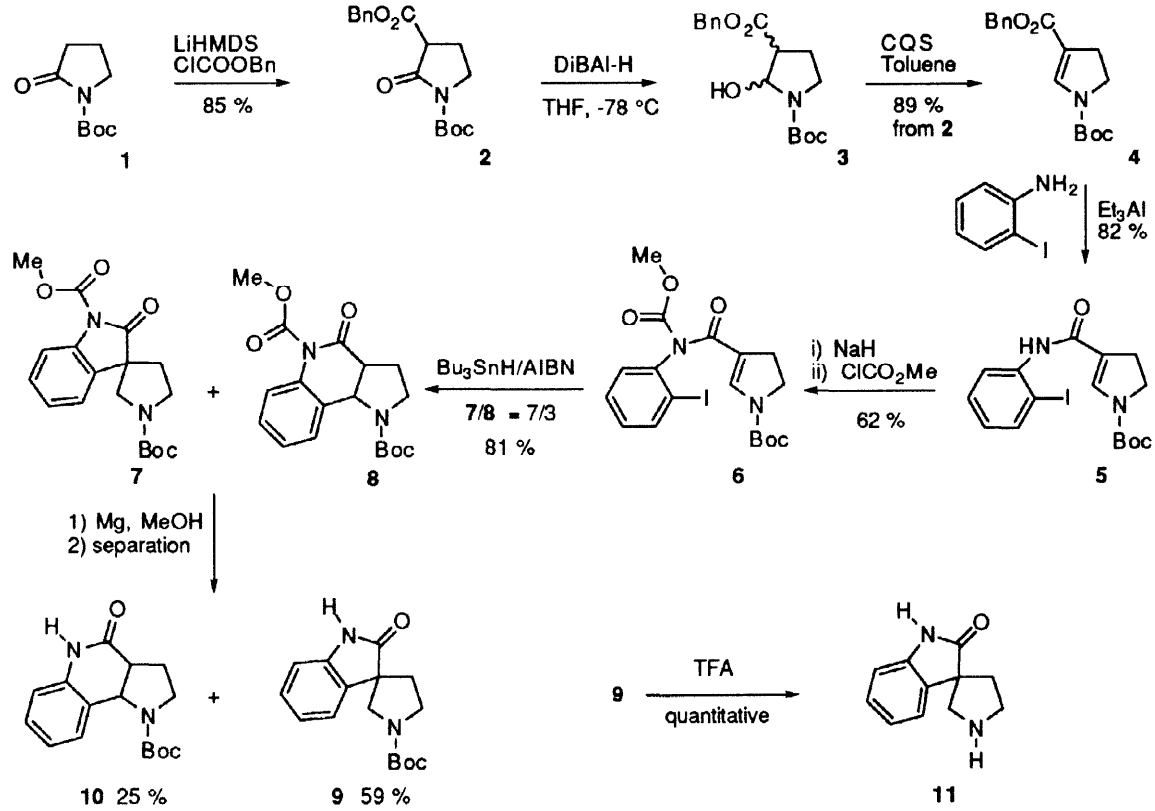
desired spiropyrrolidine **7** and the pyrrolidino quinolone **8** were formed in a ratio of 7/3 with a yield of 81%. The removal of the carbamate group using magnesium in methanol (rt, 24 h) afforded compounds **9** and **10** in a ratio 7/3[7] which were separated by flash chromatography (yield 84 %). The spiro compound **9** was then treated with trifluoroacetic acid (TFA) to produce the spiropyrrolidinyl-oxindole **11**[8] in quantitative yield. During the transformation of **7**, **8** to **9**, **10** interconversion of the spiropyrrolidine compounds to the pyrrolidino quinoline compound was not observed. The use of enecarbamates in radical cyclization provides an easy access to spiropyrrolidinyl-oxindole skeletons.



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References and Notes

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4. For example: Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130-4133.
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7. If a 5-*exo*-trig process[a] is favoured, the presence of the carbonyl group of a conjugated amide also allows a 6-*endo*-trig cyclization process[b]. a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734-736. b) Hanessian, S.; Danhoa, D. S.; Beaulieu, P. L. *Can. J. Chem.* **1987**, *65*, 1859-1866.
8. Data for **11**: colorless oil; IR (neat) ν 3450, 1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.60-8.23 (ls, 1H), 7.11-6.99 (m, 2H), 6.97-6.85 (m, 1H), 6.81-6.69 (m,1H), 3.35-3.18 (m, 2H), 3.16-3.01 (m, 1H), 3.86 (d, J = 14 Hz, 1H), 2.76-2.50 (ls, 1H), 2.27-2.11 (m, 1H), 2.04-1.89 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.4 (s), 140.4 (s), 133.7 (s), 127.5 (d), 122.6 (d), 122.3 (d), 109.5 (d), 59.6 (t), 54.7 (s), 48.6 (t), 38.8 (t); MS (EI, 70eV) m/z 188 ($M^{+\cdot}$, 28), 187 (87), 159 (21), 146 (100), 130 (27); HRMS calculated for $C_{11}H_{11}N_2O$ 187.1226, found 187.1226.