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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. © 1998 Elsevier Science Ltd. All rights reserved.

Spiropyrrolidinyl-oxindole alkaloid skeletons are found in spirotryprostatine A and spirotryprostatine B¹ which were found to be new inhibitors of mammalian cell cycle at G2/M phase, from the secondary metabolites of *Aspergillus fugimatus*. Elacomine² was isolated from *Eleagnus commutata* and horsfiline³ 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 Heck⁴ reaction.



Recently, we have reported⁵ 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 1⁶. 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 (AlEt₃) 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, ClCO₂Me), 6 was isolated in 62 % yield. Treatment of a solution of 6 in benzene by tri-*n*-butyltin hydride (Bu₃SnH) 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

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 11⁸ 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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- 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) v 3450, 1695 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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⁺, 28), 187 (87), 159 (21), 146 (100), 130 (27); HRMS calculated for C₁₁H₁₁N₂O 187.1226, found 187.1226.