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AN APPROACH TO VINDOLINE SKELETON UTILIZING SUBSTITUTED METHYLENETETRAHYDROFOLATE (5,10-CHR-THF) MODELS

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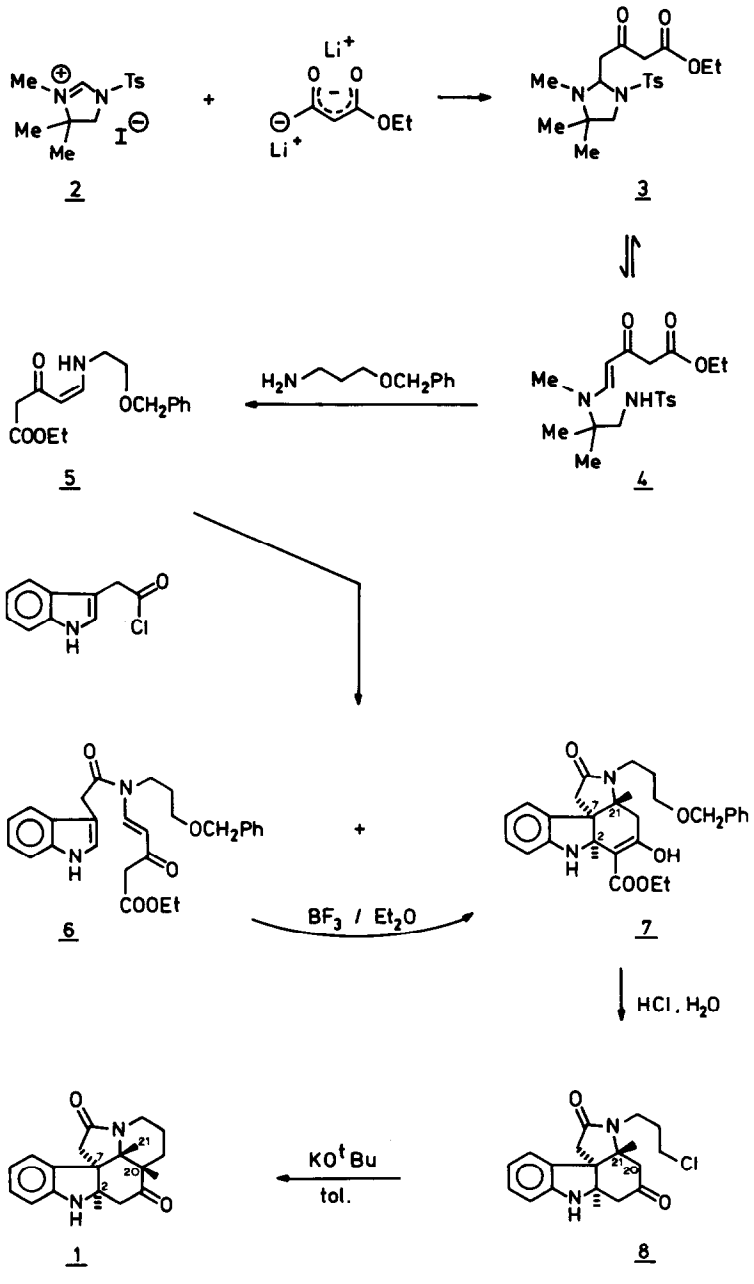
Abstract: Starting from a substituted methylenetetrahydrofolate model [4-(2-N(1)--tosyl-N(3)-methyl-4,4-dimethylimidazolidyl)-3-ketobutanoate], an efficient synthesis of the pentacyclic system corresponding to vindoline is described.

5,10-Methylenetetrahydrofolate (5,10-CH_2-THF) models constitute a class of methylene (CH_2) transfer reagents which operate via a mechanism analogous to that observed for the coenzyme[3]. Substituted models of the type 5,10-CHR-THF, allow, in a similar manner, the transfer of whole (functionalized) carbon fragments in synthetically useful reactions[4]. The strategy involving such transfers has been employed in the synthesis of several heterocycles related to alkaloids[5a,b]. This communication describes the application of a 5,10-CHR-THF model in a facile synthesis of the known pentacyclic skeleton (1) of vindoline.

The synthesis of the model 3 from salt 2 and the dianion of acetoacetic ester, has been reported previously from this laboratory[5b]. The imidazolidine 3 opens to enamino ketone 4 under acidic or basic conditions[6] and the latter transfers its functionalized carbon-residue to 3-benzyloxy-propylamine, in an efficient reaction (MeCN, AcOH, Δ, 60%). It should be pointed out that while the double bond in 4 has an E configuration (J = 14 Hz), it assumes a Z configuration (J = 7 Hz) in the transfer-product (5), presumably due to the stabilization via hydrogen bonding, accessible to the Z-structure.


Me
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HN
OCH2Ph
COOEt
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NHTs
6
7
Cl
OH
BF3 / Et2O
HCl . H2O
KOtBu
tol.
1
8

Reaction of 5 with indolyl-3-acetyl chloride in the presence of pyridine (MeCN, room temp., 48h) led to a mixture of two products 6[7] (32%) and 7[8] (31%). The enamino ketone 6 could be cyclized to 7 by treatment with BF_3/Et_2O at 0°. The stereochemistry at positions C(2), C(7) and C(21) (vindoline numbering) in 7, was established by Nuclear Overhauser Differential spectroscopy of the subsequently obtained keto lactam 1. Treatment of 7 with $HCl-H_2O$, caused hydrolysis and decarboxylation of the β-keto ester, together with cleavage of the benzyl group. The resulting chloride 8[9], was made to undergo a base-catalyzed cyclization (KOtBu/toluene) to the crystalline pentacyclic product 1 m.p. 197-200°, MS: Calcd, 282.1368, Found, 282.1379. The structure of 1 followed from its spectral data, which was identical to that reported for the same compound by other workers[10]. Furthermore, the 2D NMR spectroscopy supported the assigned structure[11]. The conversion of model 3 ⇌ 4 to tetracyclic product 7, in two simple steps, is of significance to an approach to the practical synthesis of vindoline and related compounds, especially since an ester moiety can be introduced at the correct position (C-16) in the skeleton. Although in the transformation of 7 → 1 by the procedure employed presently, this ester function is lost, it may be possible to retain it by a judicious choice of the leaving group and cyclization conditions. Attempts in this direction and for the development of models which would allow the introduction of the C-20 ethyl group, are currently in progress.

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1. To whom all correspondence should be adressed.

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5. (a) H. Bieräugel, R. Plemp and U.K. Pandit, Tetrahedron, 39, 3987 (1983).
(b) H.C. Hiemstra, H. Bieräugel and U.K. Pandit, Tetrahedron Letters, 23, 3301 (1982).

6. The ring-opening is reversible. In most cases the acidic conditions (MeCN, AcOH) allow transfer from the model to the substrate in one practical step.

7. 6 oily product; salient spectral data, IR ($CHCl_3$): 3470, 1725, 1685, 1610, and 1575 cm^{-1}; PMR ($CDCl_3$): 5.78 (1H,d,J = 14 Hz, = CH), 8,3[8] (1H,d,J = 14 Hz, HC =). MS (FD) : 462 (M^+).

8. 7 oily product; salient spectral data, IR ($CHCl_3$) : 3400, 1740 and 1680 cm^{-1}; PMR ($CDCl_3$) : 1.60 - 1.90 (2H,m,$-CH_2-\underline{CH_2}-CH_2-$), 2.40 - 2.90 (4H,m,C - $6H_2$ + C - $20H_2$), 2.90 - 3.15 (1H,m,C-21H), 3.45 - 3.60 (2H,m,$CH_2-\underline{CH_2}-O$), 4.40 - 4.50, (3H,m, $O-\underline{CH_2}Ph$ + C - 2H), 6.55 - 7.15 (4H, m, Ar-H) and 7.20 - 7.35 (5H, m, Ar-H). MS (FD) : 462 (M^+).

9. 8[10b], m.p. 152-154°C (lit.[10b], 161-163°C); salient spectral data, IR ($CHCl_3$) : 3390, 1720 and 1685 cm^{-1}; PMR ($COCl_3$) : δ,2.68 (ZH, m, C-$20H_2$), 3.87 (1H, t, J = 3Hz, C-21H) and 4.11(1H, m, C - 2H). MS(FD) : 318, 320 (m^+).

10. (a) E. Wenkert, J.S. Bindra and B. Chauncy, Synth. Commun., 2, 285 (1972); (b) S.J. Veenstra, Thesis, University of Amsterdam, 1982, p. 172.

11. Details of 2D NMR and Nuclear Overhauser Differential spectroscopy will be presented elsewhere.

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