Non-oxidative Methodology for the Synthesis of Vinblastine and Vincristine Models

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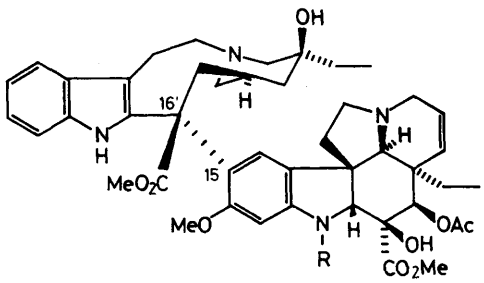
Fragmentation of the tetracyclic amine (**5**), initiated by a chloroformate to give the putative iminium ion (**6**) in the presence of an aromatic nucleophile, provides convenient access to model bis-alkaloids such as (**7**)—(**15**).

The clinically active antitumour agents vinblastine (**1**) and vincristine (**2**) have been the objects of considerable synthetic interest for the past twenty years.[1] Two methods have been used to establish the crucial C(15)–C(16′) bond connecting vindoline (**3**) to methoxycarbonylvelbanamine (upper-half): the chloroindolenine route[2] and the Polonovski rearrangement.[3] Both of these methods depend upon oxidative activation of precursors to the upper-half, that produce putative iminium ions of the general type (**4**). The original chloroindolenine method leads to the unnatural stereochemistry at C(15)–C(16′), while the Potier–Polonovski route produced the correct absolute stereochemistry at this crucial bond.

Iminium ions such as (**4**) can be generated by fragmentation reactions, although in the cases described in the literature the C(16′) methoxycarbonyl group is not present.[4] The conceptual basis of the new procedure described here for making the C(15)–C(16′) bond in the presence of the C(16′)-methoxycarbonyl group relies on the chloroformate induced fragmentation of the tetracyclic amine (**5**) to generate the iminium ion (**6**) in the presence of aromatic nucleophiles to give adducts (**7**). (See Scheme 1).

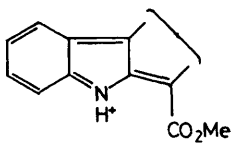
The racemic tetracyclic amine (**5**)[5] was treated with $PhOCOCl/CH_2Cl_2/PhNMe_2$ at 25 °C for 20 h to give the adduct (**7**) in 86% yield. Similarly, treatment of (**5**) with $PhOCOCl/CH_2Cl_2/3\text{-}MeOC_6H_4NMe_2$ and 3,5-$(MeO)_2C_6H_3NMe_2$ gave the adducts (**8**) (92%) and (**9**) (87%) respectively. The ^1H n.m.r. spectra of these adducts are complicated by the slow dynamic processes of carbamate resonance and nine-membered ring conformational mobility.[6] Treatment of (**5**) with $PhOCOCl/CH_2Cl_2$/vindoline at 25 °C gave the adducts (**10**) and (**11**) in 24% and 29% yield respectively.[7] As expected, the N–CO_2Ph functionality was resistant to hydrolysis. Cleavage of the amine (**5**) with $ClCO_2CH_2C_6H_4NO_2\text{-}p/CH_2Cl_2$/25 °C for 48 h in the presence of vindoline gave the bis-alkaloids (**12**) and (**13**) (33% and 42% respectively), which on exposure to transfer hydrogenation conditions (10% Pd/C; 88% HCO_2H, MeOH) gave the corresponding secondary amines (**14**) and (**15**) (73% and 85% respectively).[8]

The above coupling reaction cannot be carried out with $3\text{-}MeOC_6H_4NHMe$, because it reacts with the chloroformate

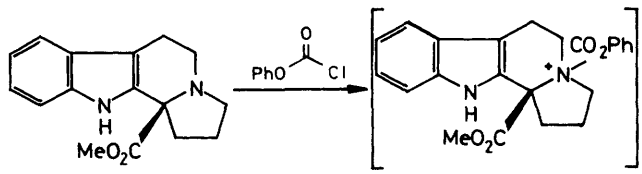


(1);R = Me, Vinblastine
(2);R = CHO, Vincristine

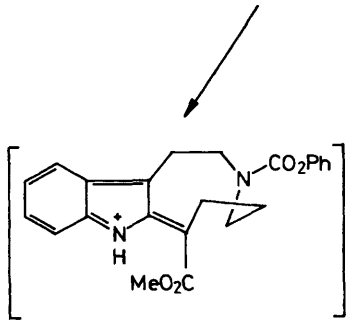
(3);Vindoline (lower half)



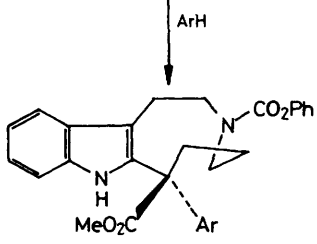
(4)



(5) (5a)

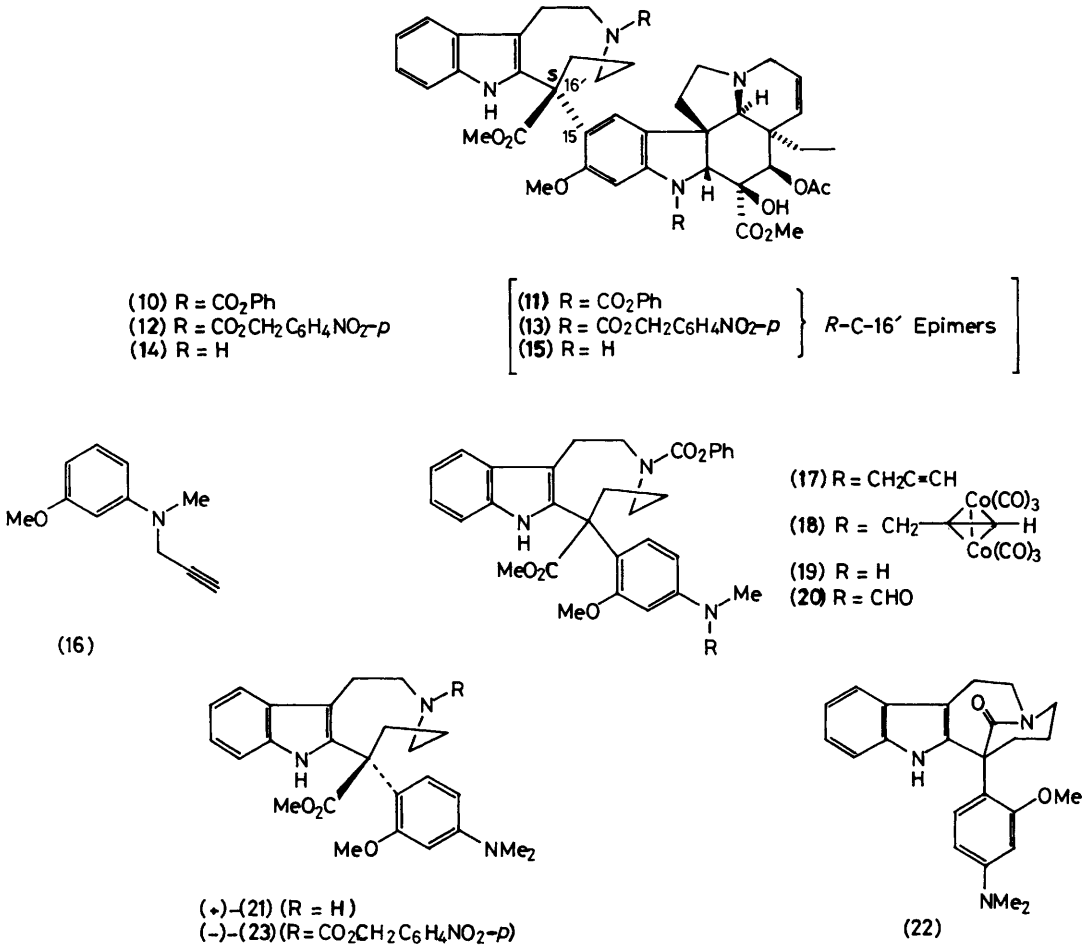


(6)



(7) Ar = $C_6H_4NMe_2\text{-}p$
(8) Ar = 3-$(MeO)C_6H_3NMe_2\text{-}p$
(9) Ar = 3,5-$(MeO)_2C_6H_2NMe_2\text{-}p$

Scheme 1



to give 3-$MeOC_6H_4NMeCO_2R$, which is now deactivated towards electrophilic aromatic substitution with the iminium ion (**6**). Consequently, we required a nitrogen protecting group for 3-$MeOC_6H_4NHMe$, which would not decrease the availablity of the nitrogen lone-pair to allow effective trapping of (**6**) and be removed under sufficiently mild conditions that do not destroy the intact bis-adducts. The usual range of nitrogen protecting groups such as amides and carbamates are obviously unsuitable, and unfortunately, *p*-methoxybenzyl did not allow the coupling process to take place efficiently. Given these rigorous constraints and lack of adequate literature precedent, a less than conventional solution was well worthy of exploration.

Treatment of 3-$MeOC_6H_4NHMe$ with $BrCH_2C{\equiv}CH/K_2CO_3$/MeCN gave the *N*-propargyl derivative (**16**) (82%), which was coupled with (**5**) using $PhOCOCl/CH_2Cl_2$ to give (**17**) (78%). The adduct (**17**) was treated with $Co_2(CO)_8$/EtOAc to give the adduct (**18**) (93%).[9] When (**18**) was exposed to trifluoroacetic acid at 25 °C the $Co_2(CO)_6$–propargyl cation was released to give the secondary amine (**19**) (85%).[10] *N*-Formylation of (**19**) with Ac_2O/HCO_2H gave the vincristine model (**20**) (55%).

Finally, in experiments designed to investigate whether or not the iminium ions such as (**6**) could retain chirality, because of potentially slow conformational processes associated with the nine-membered ring,[11] we treated (+)-(**5**)[12] with α-chloroethyl chloroformate[13]/CH_2Cl_2/3-$MeOC_6H_4NMe_2$ at 25 °C for 16 h, followed by methanol to give (+)-(**21**) (43%) $[\alpha]_D^{20}$ + 19.8° (*c*, 0.52 in MeOH). Similarly, (−)-(**5**) gave (−)-(**21**) (44%) $[\alpha]_D^{20}$ − 19.8° (*c*, 0.56 in MeOH). The enantiomeric purity of (**21**) was determined by conversion of (**21**) (either enantiomer) into the bridged amide (**22**) {1,8-diazabicyclo[5.4.0]undec-7-ene (DBU/PhMe/ heated at reflux for 3 h}, and examination of the ^1H n.m.r. spectrum, which was run in the presence of the chiral shift reagent (+)-Pr(hfc)$_3$. It was found to be 80% (±5%) [60% enantiometric excess (e.e.)]. Corresponding cleavage of (+)-(**5**) with $ClCO_2CH_2C_6H_4NO_2$-*p*/CH_2Cl_2/25 °C for 48 h in the presence of 3-$MeOC_6H_4NMe_2$ gave (**23**) (R = 4-NO_2PhCH_2) (72%), $[\alpha]_D^{23}$ −30° (*c*, 0.52 in CH_2Cl_2), which was shown to be 58% e.e. after transfer hydrogenation and conversion into the bridged amide (**22**). From optical rotatory dispersion (ORD)/circular dichroism (CD) studies on the enantiomerically enriched adducts (**21**) and (**22**) it can be concluded that the conversion of (+)-(**5**) into (+)-(**21**) occurs with predominant retention of absolute configuration at C(16′). This demonstrates that the energetically restricted conformations of the nine-membered ring in (**6**) are a very important controlling factor in determining the absolute stereochemistry of the C(15)–C(16′) bond forming process in these simple model systems.†

† This appears to be a unique example of the translation of the overall dissymmetry (atropoisomerism) of the iminium ion (**6**) into a single stereogenic centre at C(16′).

In summary, this new coupling methodology allows access to both vinblastine and vincristine bis-alkaloid models, where the absolute stereochemistry of the crucial C(15), C(16′) bond is controlled by the absolute stereochemistry of the starting tetracyclic amine (**5**).[14]

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