Synthesis of the Carbazole Alkaloids Carbazomycin A and B and Hyellazole

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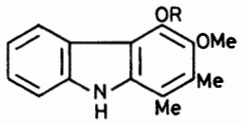
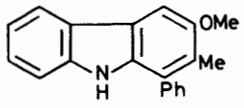
The first synthesis of carbazomycins A and B (**1**) is described; the route involves Diels-Alder reaction of 1-methylpyrano[3,4-*b*]indol-3-one with ethyl 3-trimethylsilylpropynoate followed by functional group interconversions; the marine alkaloid hyellazole (**2**) was synthesized by a similar route.

Although carbazole itself was first isolated from coal tar in 1872, interest in the chemistry of carbazoles and fused derivatives has been maintained,[1] since despite their structural simplicity, polysubstituted carbazoles remain difficult to synthesize.[2] We have recently described a versatile route to carbazoles based on the Diels-Alder reaction of pyrano[3,4-*b*]indol-3-ones with alkynes,[3,4] and we now report the application of this chemistry to the first synthesis of the 1,2,3,4-tetrasubstituted carbazoles carbazomycins A (**1a**) and B (**1b**), and to a short synthesis of the marine alkaloid hyellazole (**2**).

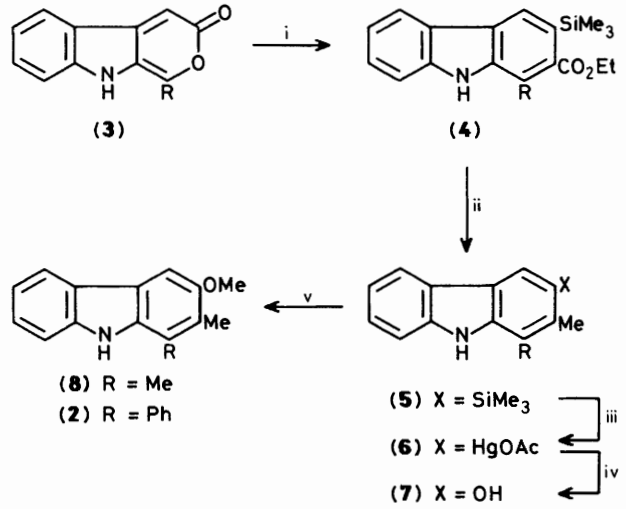


(**1**) **a**, R = Me; **b**, R = H



(**2**)

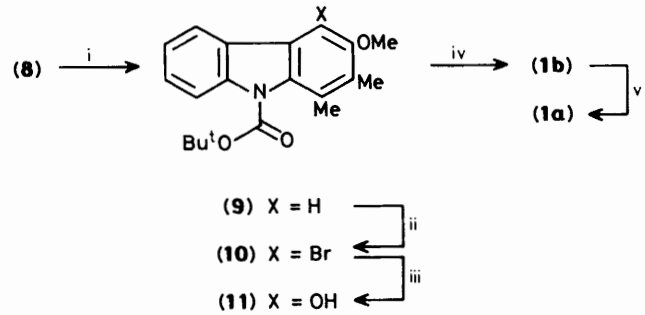
The carbazomycins (**1**), isolated from *Streptoverticillium*, are the first antibiotics containing the carbazole nucleus. The structures were determined by spectroscopic means, and in the case of carbazomycin B (**1b**) confirmed by *X*-ray crystallography.[5] The fact that these relatively simple compounds have not been synthesized, highlights the drawbacks of existing routes to carbazoles. Both 3- and 4-deoxycarbazomycins have been prepared, however, although the yield in the key Diels-Alder reaction of a 3-vinylindole was very low in both cases.[6,7] Our approach, based on the Diels-Alder reaction of the fused indole α-pyrone (**3a**), allows an appropriately 1,2,3-trisubstituted carbazole to be synthesized in good yield in just two steps from commercially available indol-3-ylacetic acid (Scheme 1).[8]



Scheme 1. [Compounds (**3**)—(**7**): *a*, R = Me; **b**, R = Ph] *Reagents:* i, $EtO_2CC{\equiv}CSiMe_3$, PhBr, reflux; ii, $LiAlH_4$, dioxane, reflux; iii, $Hg(OAc)_2$, AcOH; iv, BH_3·THF; alkaline H_2O_2 work-up; v, MeI, K_2CO_3, acetone, reflux.

1-Methylpyrano[3,4-*b*]indol-3-one, prepared by reaction of indol-3-ylacetic acid with acetic anhydride,[3,4] underwent Diels-Alder reaction with ethyl 3-trimethylsilylpropynoate with concomitant loss of carbon dioxide to give the carbazole (**4a**), m.p. 191—194 °C,† in 53% yield on a multi-gram scale, with no evidence for the formation of the isomeric carbazole. The regiochemistry of this selective Diels-Alder reaction was proved by protodesilylation of (**4a**) to give the known ethyl 1-methylcarbazole-2-carboxylate.[9] This regiospecificity was expected on the basis of our previous studies of the steric and electronic effects on the Diels-Alder reactivity of pyranoindolones.[4] Having directed the cycloaddition in the desired sense, the second role of the trimethylsilyl group was as a potential hydroxy group, with the ester to become the 2-methyl group. Initially we transformed the silyl substituent first, but this proved unsatisfactory owing to low yields in the subsequent reduction of the ester group,and therefore the reduction had to be carried out first. Thus the carbazole ester (**4a**) was reduced to the 2-methylcarbazole (**5a**) (98%) with lithium aluminium hydride in refluxing dioxane. Mercurio-desilylation[10] of the carbazole (**5a**) gave the arylmercury compound (**6a**), hydroboration and oxidation[11] of which gave the required hydroxycarbazole (**7a**) [56% yield from (**5a**)], readily converted into 4-deoxycarbazomycin (**8**) (95%), m.p. 120—121 °C (lit.,[3b] 129—130 °C; lit.,[7] 129—131 °C).‡

Several attempts to introduce the extra hydroxy group at C-4 using oxidants such as manganese(IV) oxide, Fremy's salt, dibenzoyl peroxide, or benzoyl t-butyl nitroxide resulted in either complete decomposition of the hydroxycarbazole (**7a**), or the formation of dimeric 4,4′-bicarbazoles. Therefore, the 4-hydroxy substituent had to be introduced *via* the corresponding bromide in a longer, but high yielding, sequence (Scheme 2).



Scheme 2. *Reagents:* i, $(Bu^tOCO)_2O$, 4-dimethylaminopyridine, MeCN; ii, NBS, MeCN; iii, Bu^tLi, THF, −78 °C, then $B(OMe)_3$, −78 °C to 0 °C; alkaline H_2O_2 work-up; iv, heat; v, MeI, K_2CO_3, acetone, reflux.

† Satisfactory spectroscopic and analytical data were obtained for all new compounds.

‡ Additional evidence for the structure of this compound was obtained by nuclear Overhauser effect spectroscopy.

Although bromination of the carbazole (**8**) with *N*-bromosuccinimide (NBS) in acetonitrile gave the corresponding 6-bromo compound (82%), bromination of the *N*-t-butoxycarbonylcarbazole (**9**) under the same conditions gave the required 4-bromo derivative (**10**) in excellent yield (95%). Treatment of the bromide (**10**) with t-butyl-lithium in tetrahydrofuran (THF) at −78 °C, followed by reaction of the resulting aryl-lithium with trimethyl borate, and alkaline hydrogen peroxide work-up gave the 4-hydroxycarbazole (**11**) (73%). The t-butoxycarbonyl group was removed in excellent yield simply by heating[12] the carbazole (**11**) to 180—190 °C to give carbazomycin B (**1b**) (98%), methylation of which gave carbazomycin A (**1a**) (94%). The ^{1}H and ^{13}C n.m.r. and mass spectral data for the synthetic carbazomycins closely matched those described in the literature.[5]§

The application of pyranoindolones in the preparation of polysubstituted carbazoles was further demonstrated by a short synthesis of the marine alkaloid hyellazole (**2**)[13] (Scheme 1). 1-Phenylpyrano[3,4-*b*]indol-3-one (**3b**)[14] reacted regiospecifically with ethyl trimethylsilylpropynoate to give the carbazole (**4b**) (62%), which was converted into the 2-methylcarbazole (**5b**) (92%),‡ and hence the 3-hydroxycarbazole (**7b**) [41% from (**5b**)]. Finally, methylation of the hydroxy group gave hyellazole (**2**) (92%), m.p. 133—134 °C (lit.,[13] 133—134 °C).

§ Although the n.m.r. data closely matched those described in the literature, the m.p. of carbazomycin A (**1a**) was different from the literature value; (**1a**) colourless plates (from dichloromethane–hexane), m.p. 143—146 °C [lit.,[5a] pale yellow needles (from ethyl acetate–hexane), m.p. 51—52.5 °C]; the structure of our synthetic (**1a**) was confirmed by an *X*-ray crystallographic study carried out by Dr. D. J. Williams in this department.

Acknowledgements

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