SYNTHESES OF ELLIPTICINE AND RELATED PYRIDOCARBAZOLE ALKALOIDS - A REVIEW

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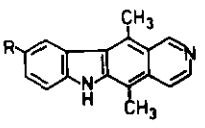
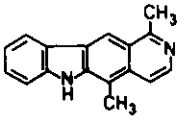
Abstract - Synthetic approaches to the anticancer alkaloid ellipticine and related pyridocarbazoles covering the period 1977 through November 1984 are reviewed.

1. Introduction

The Ochrosia, Aspidosperma, Tabernaemontana, and Strychnos plant alkaloids[1] ellipticine (1a) (5,11-dimethyl-6H-pyrido[4,3-b]carbazole), 9-methoxyellipticine (1b), and olivacine (2) exhibit pronounced anticancer activity in several animal and human tumor systems.[2] Recently, a derivative of 9-hydroxyellipticine (1c), 2-methyl-9-hydroxyellipticinium acetate (3) ("elliptinium"), was commercialized[3] for clinical use and is effective in the treatment of myleoblastic leukemia, advanced breast cancer, and other solid tumors.[2a,4]



1a, R = H
1b, R = OCH_3
1c, R = OH



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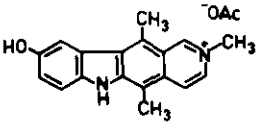

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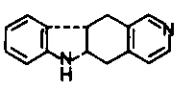
Since the original isolation[5] of these alkaloids and the initial discovery[6] of their anticancer activity, many synthetic approaches to the pyrido[4,3-b]carbazole ring system have been described. In 1977, Sainsbury[7] published an extensive review on the syntheses of this ring system, detailing about 15 different synthetic routes to pyrido[4,3-b]carbazoles. A more recent review[8], although considerably less detailed, updates the synthetic approaches to ellipticine to the middle of 1980 and

focuses on computer-generated strategies for the construction of this ring system. Following the completion of a draft of the present paper, an article appeared reviewing this field "from 1977 to December 1982."[9] Since this latter review is incomplete within the stated time-frame and because several important papers have appeared subsequently, we have completed the present review.

The primary purpose of this review is to update those significant synthetic improvements on existing strategies and to summarize the several new strategies for the synthesis of ellipticine and related pyridocarbazoles that have appeared in the literature since 1977. We believe that coverage is complete through November 1984.

2. Classification of Strategies

All known synthetic routes to the pyrido[4,3-b]carbazole ring system may be assembled into eight main strategies, I-VIII, for which the key bond formations are indicated.[8b] We feel that this classification is more useful than the original one,[7] which focused on which rings were generated rather than which bonds were formed.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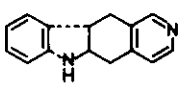
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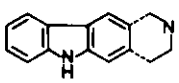
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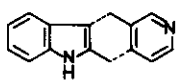
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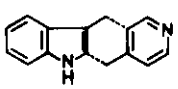
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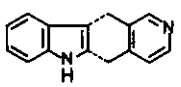
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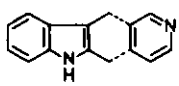
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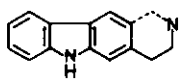
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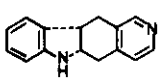
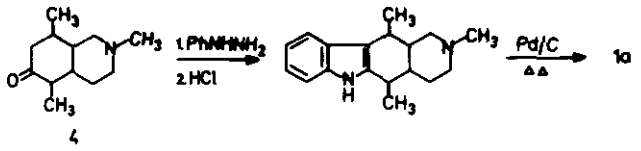
3. Strategy I



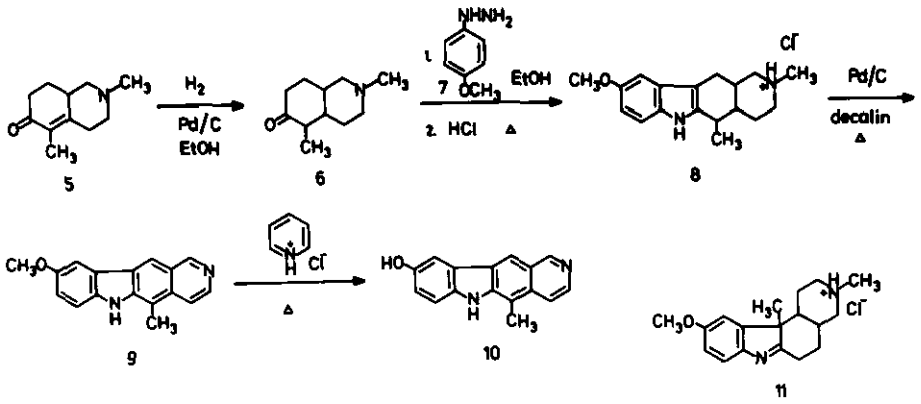
The bond forming strategy represented as I was originally employed by Stillwell[10] in 1964 (Scheme 1), as reviewed by Sainsbury.[7] This synthesis of ellipticine (1a) involved a Fischer-indole cyclization (82%) of decahydro-isoquinol-6-one 4, but, since the final dehydrogenation step proceeded in only 0.3% yield, this approach was thought to be of no practical value.

Scheme 1



However, a French team[11] has recently used the Stillwell approach to synthesize 9-methoxy-11-demethylellipticine (9) and 9-hydroxy-11-demethylellipticine (10) (Scheme 2), compounds of biological interest. Thus, enone 5, prepared by *Robinson annulation of ethyl vinyl ketone and the pyrrolidine enamine* of 1-methyl-4-piperidone (76%), was hydrogenated to isoquinolone 6 (93%). Fisher indolization of 6 with 4-methoxyphenylhydrazine (7) afforded indole 8 (54%) with only very little of the undesired isomeric indolenine 11 being produced. Dehydrogenation of 8 gave 9-methoxy-11-demethylellipticine (9) (26%), which could be demethylated with hot pyridine hydrochloride to afford the hydroxy derivative 10 (71%). A similar sequence starting with 1-benzyl-4-piperidone led to 9 in the same overall yield (10%).

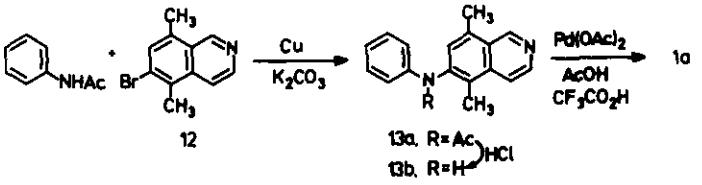
Scheme 2



Another recent ellipticine synthesis which encompasses Strategy I was reported by Miller.[12] In his original work (Scheme 3), Miller[12a] utilized a Goldberg-modified Ullmann coupling reaction between acetanilide and bromoisoquinoline 12 (prepared in six steps (69%) from 2-bromo-1,4-dimethylbenzene) to give diarylamide 13a (70%). Acid hydrolysis of 13a gave diarylamine 13b (90%). Unfortunately, the *anticipated photochemical cyclization* of 13b failed to yield any ellipticine (1a), and, furthermore, a control experiment revealed that 1a decomposed under the photolysis conditions. However, the cyclization was eventually accomplished with

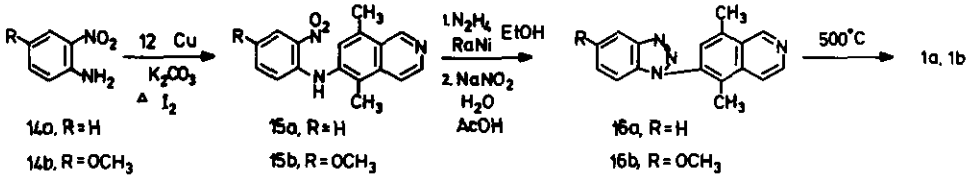
palladium acetate under acidic conditions to give 1a in 15-25% yield (46% based on unrecovered 13b).

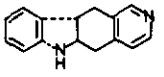
Scheme 3



More recently, Miller[12b] has described an improvement on his original procedure[12a] (Scheme 4). Thus, Goldberg coupling of 2-nitroanilines 14a and 14b with 12 gave the corresponding diarylamines 15a (54%) and 15b (53%). Reduction of the nitro group and diazotization of each amine afforded the desired benzotriazoles 16a (97%) and 16b (94%). Pyrolytic decomposition of 16a and 16b in a flow system gave 1a (69%) and 9-methoxyellipticine (1b) (62%), respectively. Lower yields of 1a were realized when 16a was heated (220°C) in polyphosphoric acid (16%) or photolyzed in methanol (33%).

Scheme 4



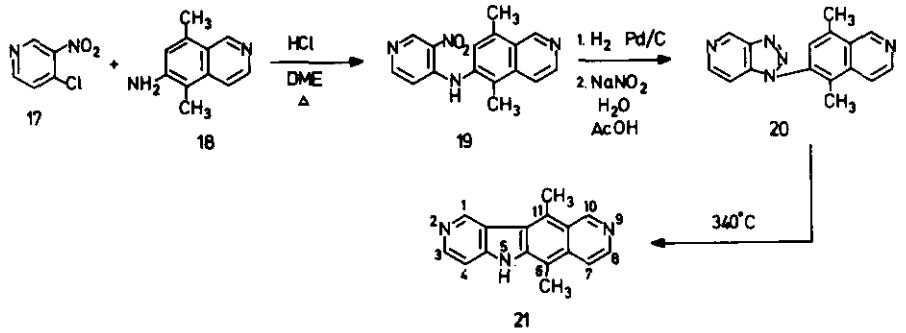
4. Strategy II 

This approach is obviously similar to Strategy I in that both involve prior construction of an isoquinoline unit and ring closure as indicated.

Bisagni and co-workers[13-17] have used Strategy II extensively in their syntheses of the potent anticancer azaellipticine derivatives such as 6,11-dimethyl-5H-pyrido[3',4':4,5]pyrrolo[2,3-g]isoquinoline (21) (Scheme 5). Treatment[13a] of 4-chloro-3-nitropyridine (17) with 6-amino-5,8-dimethylisoquinoline (18) and HCl gave the expected product 19 (29%). Catalytic hydrogenation of 19 (94%) followed by diazotization of the resulting amine furnished triazole 20 (84%). When 20 was heated in paraffin at 320 - 340°C the desired azaellipticine 21

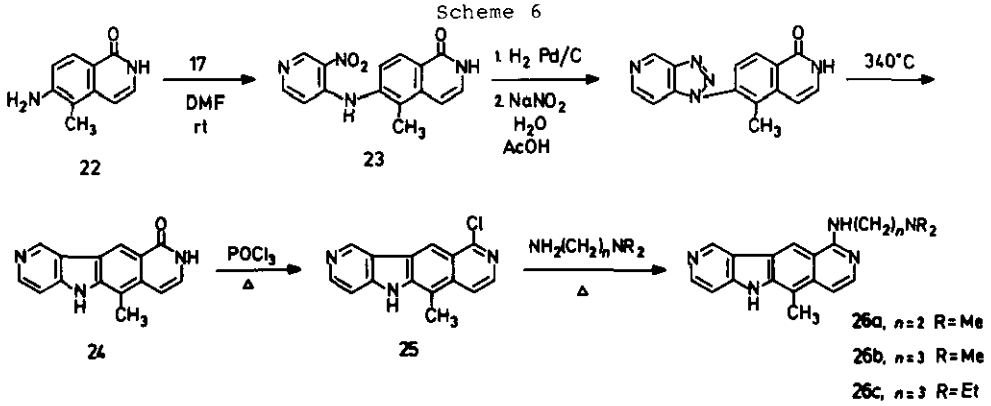
was obtained in 41% yield. Several other approaches to 21 were unsuccessful.[13a]

Scheme 5



The same group[13b] synthesized the 10-substituted azaellipticine derivatives 26 in analogous fashion (Scheme 6). Thus, 17 was joined to 6-amino-5-methylisoquinolin-1(2H)-one (22) (prepared in six steps (13%) from 3-amino-2-methylbenzonitrile) to afford 23 (72%). The usual sequence of catalytic *hydrogenation* (84%), *diazotization* (84%), and thermolysis (58%) gave lactam 24. Treatment of 24 with phosphorus oxychloride led to the key chloro intermediate 25 (54%), which, when heated with various [(dialkylamino)alkyl]amines, gave the target compounds 26 (38-75%).

Scheme 6

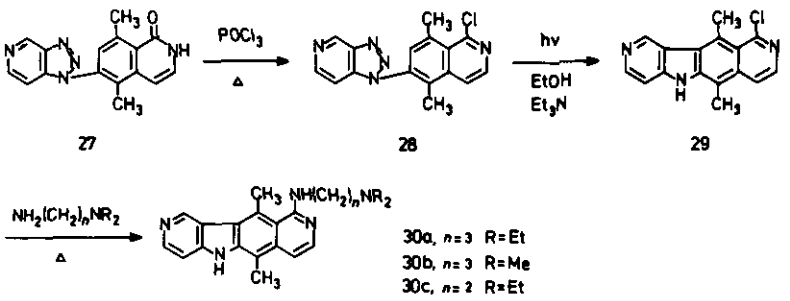


Screening results indicate that the presence of a [(dialkylamino)alkyl]amino side chain at the 1-position of ellipticine (10-position of 21) greatly increases the anticancer activity. For example, 26c is much more active than 21 in the L-1210 mouse leukemia system.[14,15]

Using a slightly modified synthetic protocol (Scheme 7), the Bisagni group[16] prepared the 6,11-dimethyl analogues of 26. Thus, triazolopyridine 27 was converted into the chloro derivative 28 upon treatment with phosphorus oxychloride (85%). Although thermal cyclization of 28 to 29 failed, this ring closure was

achieved upon photolysis (35%). The key chloroazaellipticine 29 was converted into the aminoalkyl derivatives 30 in the usual manner.

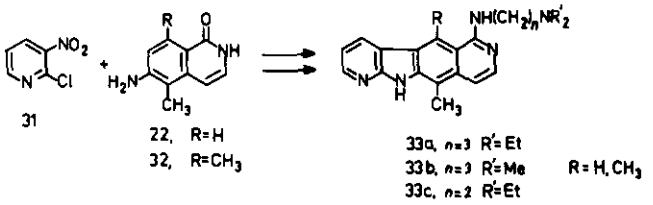
Scheme 7



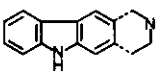
It was also found that this route could be applied to the synthesis of the monomethyl chloro intermediate 25, thereby circumventing the thermal cyclization (cf., Scheme 6).

Finally, the Bisagni group[17] has utilized this same Type II strategy to prepare the isomeric 7-azaellipticines (33; 1H-pyrido[3',2';4,5]pyrrolo[2,3-g]isoquinolines) (Scheme 8). Coupling of 2-chloro-3-nitropyridine (31) with the isoquinolinones 22 or 32, and following the reaction sequence outlined in Scheme 6 produced azaellipticines 33. These compounds proved to be much less active than their 9-azaellipticine analogues (26, 30).

Scheme 8



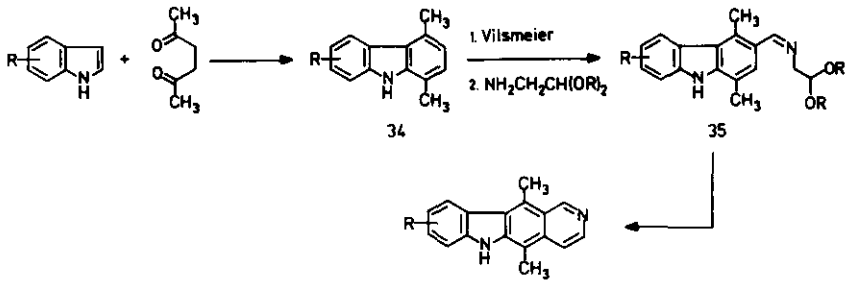
5. Strategy III



This strategy has been the most prevalent in the design of ellipticine syntheses and was first employed by Cranwell and Saxton[18] in one of the most efficient constructions of 6H-pyrido[4,3-b]carbazoles. This approach often involves the condensation of an indole and 2,5-hexanedione to give a 1,4-dimethylcarbazole (34) (Scheme 9). Vilsmeier formylation generally gives the 3-carboxaldehyde as the major product. Condensation with aminoacetaldehyde acetal gives an imine acetal (35), which, using various methods, can be cyclized to the

ellipticine ring system.

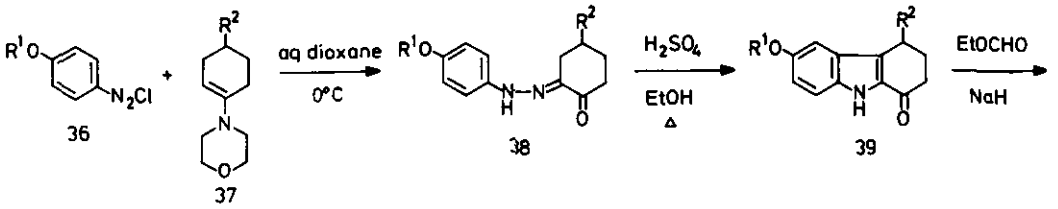
Scheme 9

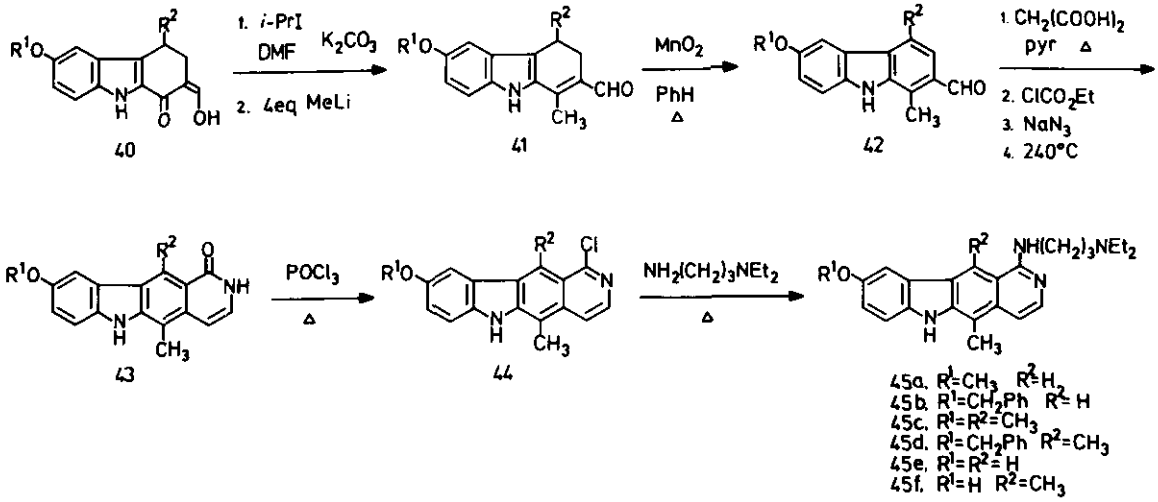


It is this approach that is employed in the commercial manufacture of 3 (Institut Pasteur brochure).

Recent synthetic advances that use a Type III strategy are numerous. Bisagni and his colleagues[19] have patterned the preparation of various 1-substituted ellipticines (Scheme 10) after the pioneering olivacine (2) synthesis of Wenkert and Dave.[20] Thus, treatment of aryldiazonium salts 36 with morpholine enamines 37 gave the corresponding phenylhydrazones 38 (76-85%). Fischer indolization of 38 afforded indole ketones 39 (30-60%) which were acylated with ethyl formate and sodium hydride to give the hydroxymethylene derivatives 40 (78-95%). Etherification of 40 with isopropyl iodide followed by treatment of the isopropyl ether with excess methyllithium gave, after hydrolysis, the dihydrocarbazole aldehydes 41 (46-81% from 40). Aromatization of 41 was accomplished with manganese dioxide, but proceeded poorly with palladium, to give the 1-methyl-2-formylcarbazoles 42 (50-88%). A three-step sequence was then used to fashion the pyridine ring. Knoevenagel condensation of 42 with malonic acid gave the E-acrylic acids (66-90%) which were converted to the respective acyl azides via a mixed anhydride. Thermal cyclization of the acyl azides furnished the pyrido[4,3-b]carbazol-1(2H)-ones 43 (30-72%). The usual formation of the chloro derivatives 44 (25-88%) and aminolysis with 3-diethylaminopropylamine gave the target ellipticines 45a-d (23-78%). Catalytic hydrogenation of the two benzyloxy derivatives gave the hydroxy analogues 45e (85%) and 45f (62%).

Scheme 10



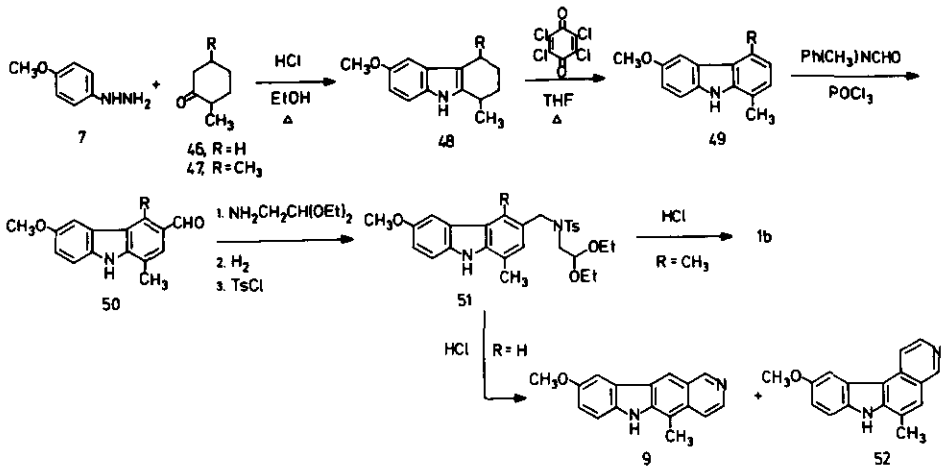


The Bisagni team has reported[19,21] that C-1 substitution in ellipticine by the 3-(diethylamino)propylamino side chain significantly increases the anticancer activity in the L-1210 leukemia system. Furthermore, these recent[21] testing results indicate that 45c and 26c exhibit both high in vitro cytotoxicity and in vivo anticancer properties. Further side chain modifications show no significant increase in biological activity over those expressed by 45c and 26c. The role of the [(dialkylamino)alkyl]amino side chains on the enhanced anticancer properties of these ellipticines is unknown but could involve a favorable interaction between the amino side chain and the phosphate backbone of the DNA, thus enhancing intercalation.

Synthetic investigations by Viel[22] also employ a Type III approach to ellipticine derivatives. In their earlier work[22a] (Scheme 11), a Borsche[23] indolization reaction between 4-methoxyphenylhydrazine (7) and cyclohexanone 46 or 47 gave the expected tetrahydrocarbazoles 48 (57, 67%). A Campbell[24] aromatization of 48 gave carbazoles 49 (73, 78%) which were formylated to give aldehydes 50 (62, 68%). Condensation with aminoacetaldehyde diethyl acetal gave the azomethine in essentially quantitative yield. Reduction of the imine double bond followed by tosylation and then treatment of 51 with acid, using conditions discovered by Jackson[25] for the synthesis of isoquinolines, to induce cyclization and aromatization gave the desired pyridocarbazoles. Thus, from 51 (R=CH_3) there was obtained 9-methoxyellipticine (1b) (29% overall yield), and from 51 (R=H) there was obtained a mixture of 9-methoxy-11-demethylellipticine (9) and the isomeric pyrido[3,4-c]carbazole 52 (20% overall yield). This synthesis is modeled after

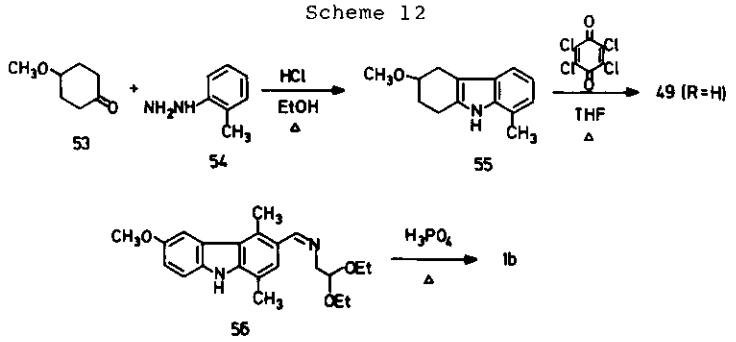
that originated by Cranwell and Saxton[18] and as later modified by Dalton[6a,26] and Guthrie.[27]

Scheme 11



In a subsequent paper, Viel[22b] condensed 4-methoxycyclohexanone (53) with 2-methylphenylhydrazine (54) to give tetrahydrocarbazole 55, which was oxidized with chloranil to 49 (R=H) (37%) (Scheme 12). The completion of this synthesis followed their earlier work[22a] except that the imine 56, in the dimethyl series, was converted directly to 9-methoxyellipticine (1b) by heating in orthophosphoric acid (55%)--an improvement noted by Dalton.[6a]

Scheme 12



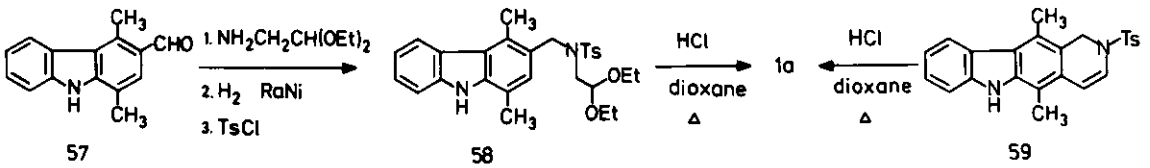
This approach (Scheme 12) of course precludes the formation of the isomeric indolenine Fischer cyclization products (not shown) that do form using the earlier[22a] approach (Scheme 11).

These general methods were used by the same scientists to synthesize 8-[28a] and 9-nitroellipticine[28b] and 9-aminoellipticine.

A very similar route to ellipticine was published by Jackson[29a] (Scheme 13) at about the same time that the Viel[22] studies were reported. Thus, 3-formyl-1,4-

dimethylcarbazole (57)--originally prepared by Cranwell and Saxton[18] by formylating 1,4-dimethylcarbazole (42%)--was condensed with aminoacetaldehyde diethyl acetal, and the resulting imine was hydrogenated to the amine acetal, apparently using the original[18] procedure (61% overall). Whereas Cranwell and Saxton[18] obtained ellipticine (1a) from the amine acetal in low yield, Jackson and coworkers[29a] described a greatly improved cyclization protocol. Thus, tosylation of the amine acetal (93%) followed by treatment of the derived sulfonamide 58 with HCl in dioxane gave ellipticine (1a) in 87% yield. The presumed intermediate 59 could be isolated from the reaction mixture (13%) and converted to 1a under the same conditions.

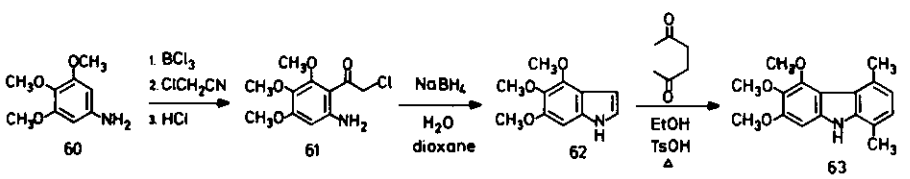
Scheme 13

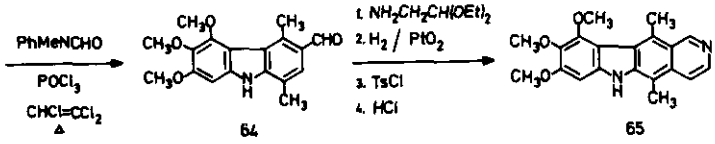


More recently, another synthesis of 58 was reported[29d] which used the N-benzyl derivative of 57 and employed a Birch reduction to reduce the imine double bond and effect debenzylation. The overall yield of 58 in this sequence was 66%. This same group[29d] synthesized olivacine (2) in a similar manner from the appropriate monomethyl formylcarbazole but the overall yield was very low (3.5%).

The Jackson group[29b,c] synthesized the novel but somewhat labile 8,9,10-trimethoxyellipticine (65) using the same general approach (Scheme 14). The synthesis required 4,5,6-trimethoxyindole (62) and this compound was prepared in 62% yield from 3,4,5-trimethoxyaniline (60) using the Sugasawa indole synthesis.[30] Condensation of 62 with 2,5-hexanedione afforded the desired carbazole 63 (35%). Vilsmeier formylation gave a separable mixture of the 3-formyl (46%), 8-formyl (37%), and 3,8-diformyl (12%) derivatives. The requisite 3-formylcarbazole 64 was then transformed into the target ellipticine derivative 65 using the standard four-step methodology (78% yield from 64).

Scheme 14

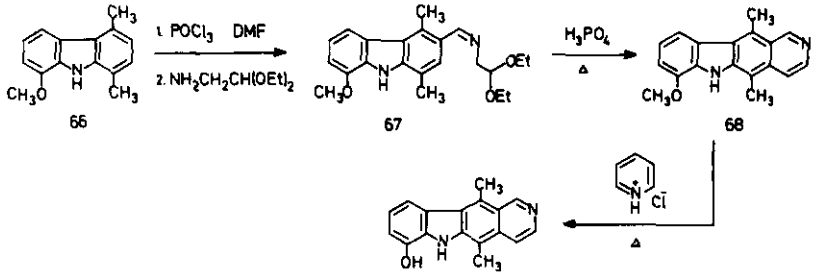




64 65

Lallemand and coworkers[31] have synthesized 7-hydroxyellipticine (69) by a very similar Type III strategy (Scheme 15). This material is a minor rat metabolite[31] of ellipticine, the major metabolite being 9-hydroxyellipticine.[32] Condensation of 7-methoxyindole with 2,5-hexanedione gave carbazole 66 (48%). Formylation (47%) and imine formation produced imine acetal 67 (81%). Cyclization and aromatization was accomplished by heating 67 in orthophosphoric acid, but this procedure gave 7-methoxyellipticine (68) in only 18% yield. Demethylation to 69 was effected with pyridinium hydrochloride (45%).

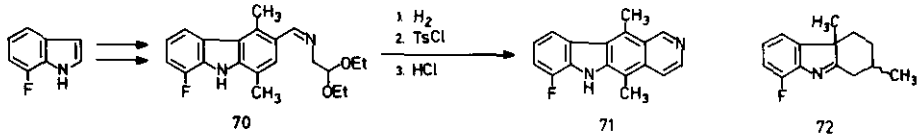
Scheme 15



66 67 68 69

Taylor[33] has reported the synthesis of 7-fluoroellipticine (71) using an analogous route starting with 7-fluoroindole (Scheme 16). The usual condensation with 2,5-hexanedione, Vilsmeier formylation, and imine formation gave imine 70 (yields unreported). Transformation of 70 into 7-fluoroellipticine (71) was achieved using Guthrie's conditions[27] although the yield of the final cyclization-aromatization step was disappointing (14%), even under forcing conditions. This was ascribed to an unusually stubborn detosylation step.

Scheme 16



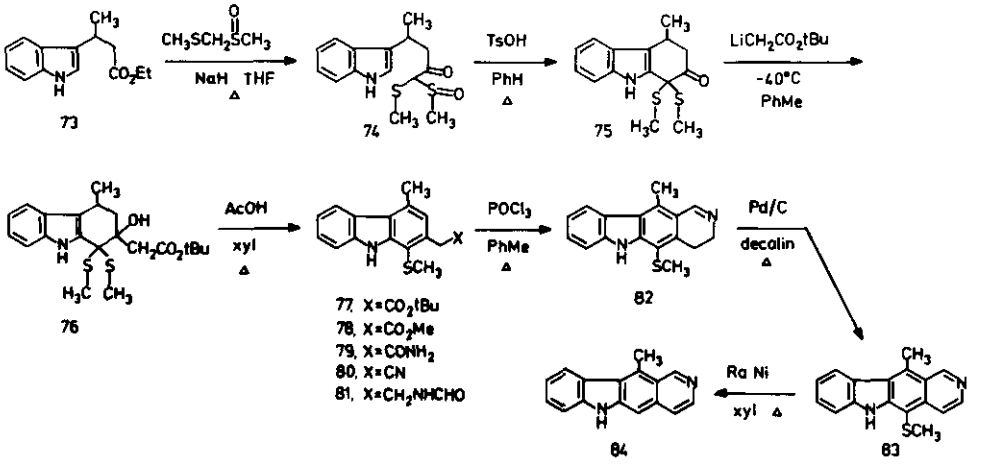
70 71 72

It is interesting to note that an attempt[33] to use the Viel[22] tetrahydrocarbazole approach to 71 failed. Thus, a Borsche reaction between 2-fluorophenylhydrazine and 2,5-dimethylcyclohexanone gave only the unwanted

indolenine 72 as a mixture of diastereomers.

Using a somewhat different Type III strategy, Yonemitsu[34] has described the synthesis of several 5-substituted 5-demethylated ellipticines using his earlier published methodology[35] (Scheme 17). Sodium hydride induced condensation of formaldehyde dimethyldithioacetal S-oxide (FAMSO) with indole ester 73 (prepared[36] in two steps (78%) from indole) gave β-keto sulfoxide 74 (88%). Acid-catalyzed cyclization of 74 produced tetrahydrocarbazole 75 (81%), which on treatment with tert-butyl α-lithioacetate gave adduct 76 (97%) as a mixture of diastereomers. This material represented a key intermediate in the synthesis of the 5-methylthio (83) and 5-methoxy (91) derivatives. Aromatization of 76 was readily accomplished with acetic acid in hot xylene to give carbazole ester 77 (82%). This was converted in excellent overall yield to formamide 81 by the following reaction sequence: transesterification (methanol, p-toluenesulfonic acid; 98%) to 78, ammonolysis (ammonia, methanol, methoxide; 97%) to 79, dehydration (p-toluenesulfonyl chloride, pyridine; 94%) to nitrile 80, reduction (lithium aluminum hydride, aluminum chloride) to the primary amine and formylation (neat ethyl formate; 92%) to give 81. Cyclization of 81 with phosphorus oxychloride gave dihydroellipticine derivative 82 (92%). Dehydrogenation with palladium/carbon in refluxing decalin afforded 83 (63%), which could be desulfurized with Raney nickel to the known[37] 5-demethylellipticine (84) (61%). The overall yield of 83 from ester 73 is 27% for ten steps.

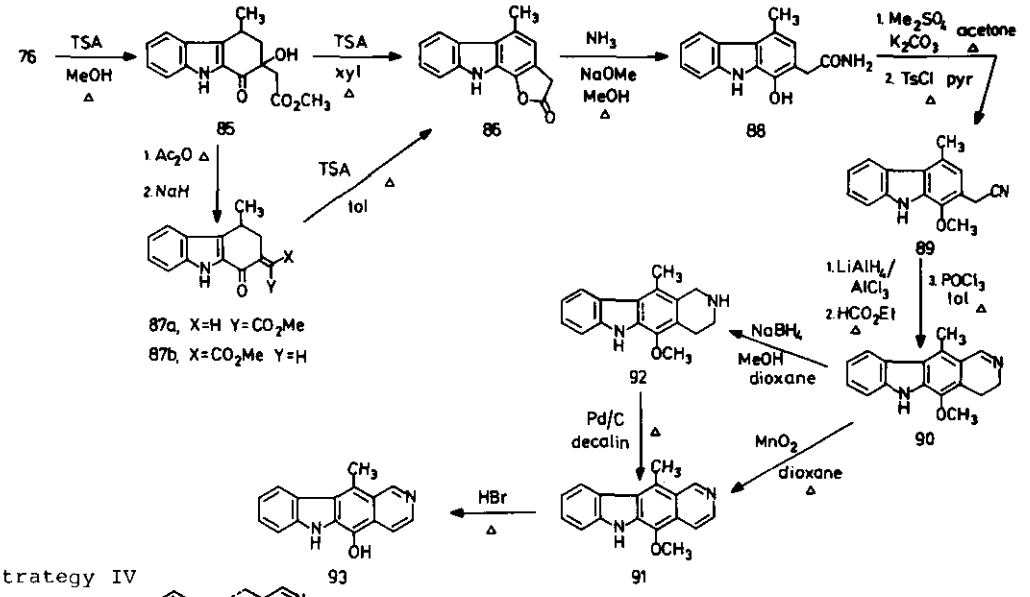
Scheme 17



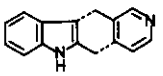
Yonemitsu's synthesis of 5-methoxy-5-demethylellipticine (91) followed a different route[34] (Scheme 18). The hydroxy ester 76, prepared earlier (Scheme 17),

was converted to ketone ester 85 by heating with p-toluenesulfonic acid in methanol (87%). The highest yield obtained for the direct conversion of 85 to lactone 86 was 50% (p-toluenesulfonic acid, refluxing xylene), although a three-step sequence gave 86 in 58% yield. Thus, 85 was acetylated (91%) and the resulting tertiary acetate was exposed to sodium hydride to effect elimination affording keto esters 87a/87b (14:1 ratio) (75%). Heating the 87 mixture with p-toluenesulfonic acid in toluene gave lactone carbazole 86 (81%). With 86 in hand, Yonemitsu prepared hydroxyamide 88 by treating 86 with ammonia and methoxide in methanol (95%). Methylation and dehydration afforded methoxy nitrile 89 (88%). The synthesis of 91 was completed in a manner similar to that for 83 (Scheme 17). Thus, reduction of 89 to the primary amine, formylation, and cyclization gave the dihydroellipticine derivative 90 (74% from 89). Oxidation to the target 5-methoxy-5-demethyl-ellipticine (91) was achieved with activated MnO_2 (52%), or better by reducing 90 to 92 and then oxidizing the latter to 91 (66% from 90). Finally, 91 was demethylated with hydrogen bromide to give 5-hydroxy-5-demethylellipticine (93) (85%).

Scheme 18



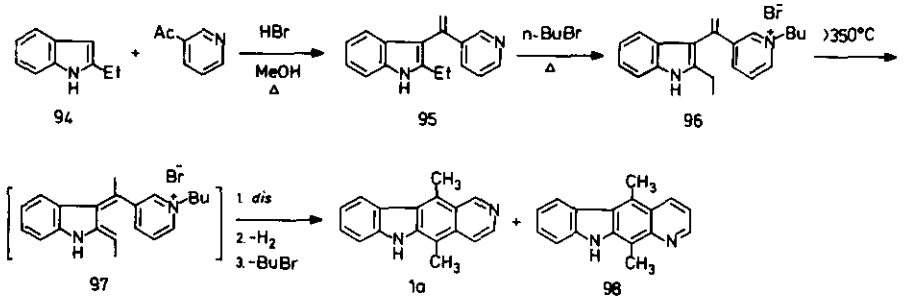
6. Strategy IV



In 1977, Bergman and Carlsson[38] announced the most efficient synthesis of ellipticine (1a) reported up to that time (Scheme 19). It is noteworthy that this synthesis is conceptually similar to Woodward's[39] original synthesis of

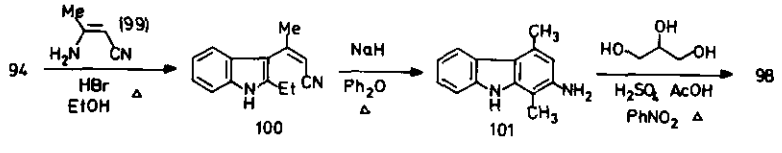
ellipticine, which, although proceeding in very low yield, paved the way for Bergman's accomplishment. Acid-promoted condensation of 2-ethylindole (94), which was prepared via a Madelung-indole synthesis,[40] with 3-acetylpyridine gave alkene 95 (90%). Alkylation of the pyridine nitrogen with n-butyl bromide (100%) and rapid pyrolysis (>350°C, 5 min) of the resulting salt 96 gave ellipticine (1a) in 72% yield, along with about 10% of the pyrido[2,3-b]carbazole regioisomer 98. Slower heating of 96 gave 98 as the major product (220°C, 30 min). The reaction is presumed to involve a 1,5-hydrogen shift leading to indole-2,3-quinodimethane 97. Subsequent disrotatory electrocyclization, dehydrogenation, and loss of n-butyl bromide would afford 1a.

Scheme 19



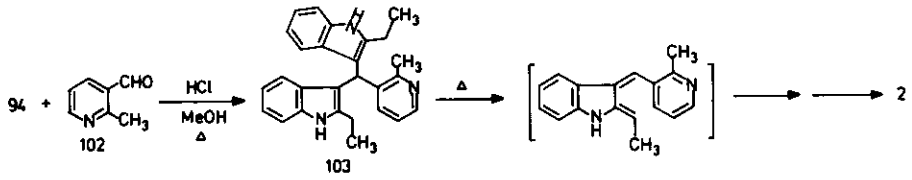
The structure of the novel "isoellipticine" 98 was confirmed by independent synthesis[41,42] (Scheme 20). Thus, 2-ethylindole (94) condensed with amine nitrile 99 to give 100 (70%), which smoothly cyclized to carbazole 101 (44%) under the influence of sodium hydride. A Skraup reaction (70%) completed the preparation of 98.

Scheme 20



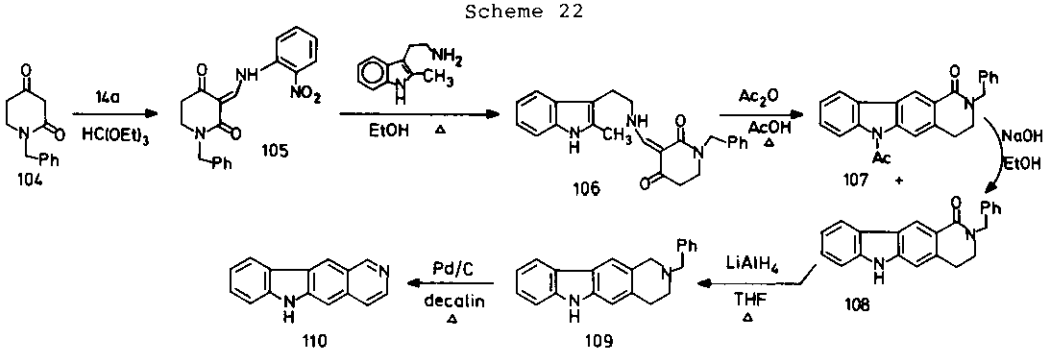
These same workers[42,43] have synthesized olivacine (2) using similar methodology (Scheme 21). In this instance, like that observed by Woodward[39] earlier, the condensation of 94 with pyridine aldehyde 102 stopped at the 2:1 adduct 103 (65%). Thermolysis of 103 over an open flame under vacuum (<0.1 torr) for a few minutes gave olivacine (2) directly (40%).

Scheme 21



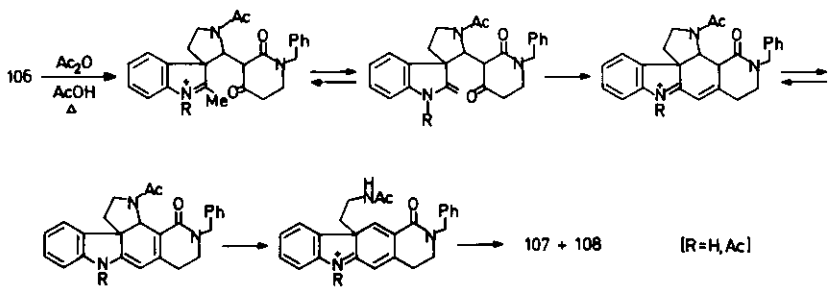
In 1979, Takano[44] reported the synthesis of the parent 6H-pyrido[4,3-b]carbazole (5,11-didemethylellipticine) (110) via a novel Type IV strategy (Scheme 22). Condensation of 1-benzylpiperidine-2,4-dione (104) with triethyl orthoformate and 2-nitroaniline (14a) gave vinylogous urea 105 (83%). An amine exchange reaction with 2-methyltryptamine transformed 105 into 106 (90%), which, upon heating with acetic anhydride-acetic acid (5:3), underwent a remarkable series of transformations to give, after basic hydrolysis of the mixture of 107 and 108 (6:11), carbazole 108 (46% from 106). Reduction of 108 with lithium aluminum hydride gave amine 109 (100%), which was dehydrogenated and debenzylated with palladium in boiling decalin to give didemethylellipticine 110 (69%).

Scheme 22



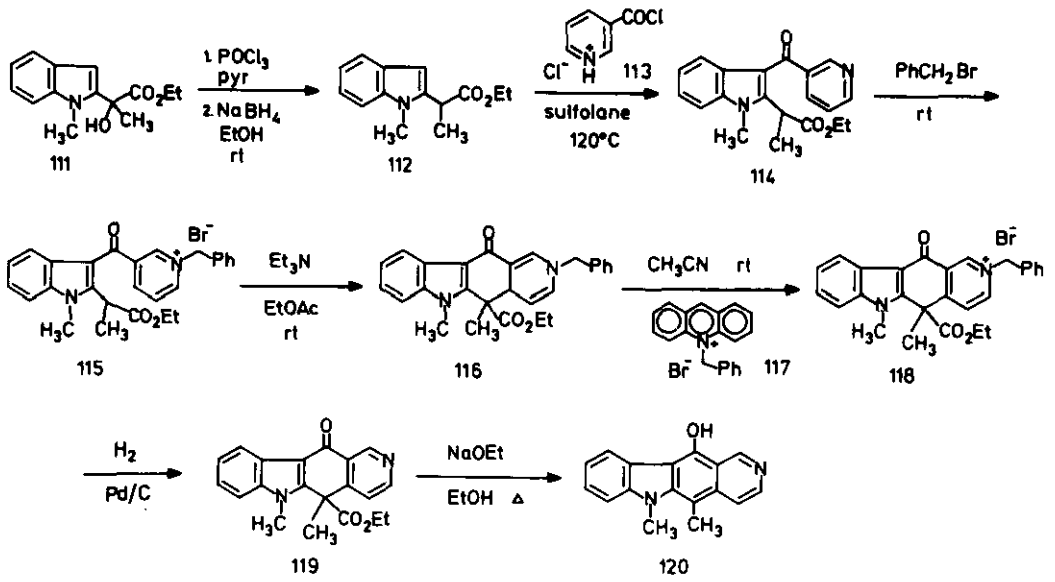
The authors[44] propose the following pathway for the conversion of 106 to 107 (Scheme 23).

Scheme 23



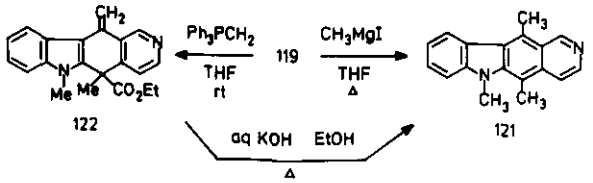
Pandit[45] has recently reported the syntheses of 11-hydroxy-5,6-dimethyl-6H-pyrido[4,3-b]carbazole (120), 6-methylellipticine (121), and 6-methylolivacine (126), utilizing a mild base-catalyzed version of the Woodward-Bergman approach (Scheme 24). Indole ester 111 was readily assembled from 2-lithio-1-methylindole and ethyl pyruvate (63%). Deoxygenation to 112 was accomplished via the unsaturated ester followed by conjugate reduction with sodium borohydride (58%). Acylation of 112 with nicotinoyl chloride hydrochloride (113) in hot sulfolane gave keto ester 114 (55%), which was alkylated with benzyl bromide to yield the pyridinium salt 115. This smoothly cyclized under remarkably mild conditions to dihydropyridine 116 (81% from 114), and the 1:1 mixture of diastereomers was oxidized very efficiently with N-benzylacridinium bromide (117) to afford salt 118 (90%). Reductive debenzylation to 119 and base-induced decarboethyoxylation gave the desired hydroxyellipticine derivative 120 (45%).[45a]

Scheme 24



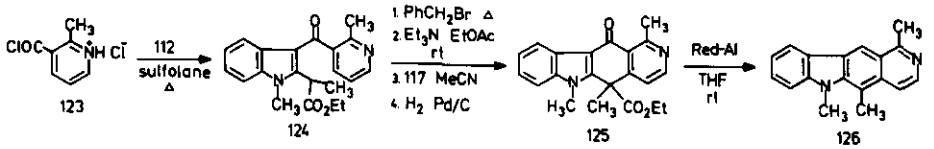
In a subsequent paper, Pandit[45b] used the same strategy to construct the 6-methyl derivatives of ellipticine and olivacine (121 and 126). Thus, keto ester 119 was converted to 121 in a single step with excess methylmagnesium iodide (40%) (Scheme 25). A second route to 121 involved a Wittig reaction on 119 with methylenetriphenylphosphorane to give 122 (65%), followed by base hydrolysis and decarboxylation to yield 121 (60%).

Scheme 25



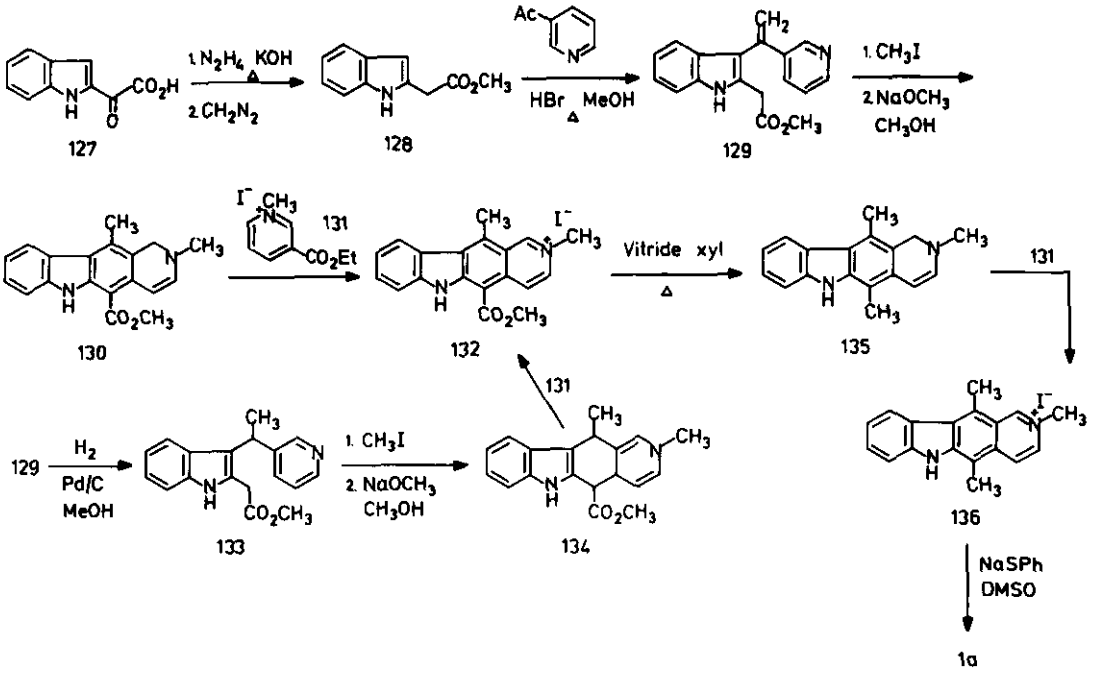
In similar fashion, Pandit[45b] acylated indole ester 112 with 2-methylnicotinoyl chloride hydrochloride (123) to give 124 (30%) (Scheme 26). An identical sequence to that presented in Scheme 24 transformed 124 into 125 (49% from 124), which, upon treatment with Red-Al, led directly to 6-methylolivacine (126) (57%).

Scheme 26

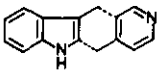


Independently, Weller[46] has recently extended this same approach to a synthesis of ellipticine (1a) (Scheme 27). Thus, keto acid 127 was prepared from indole (58%) using unspecified indole C-2 lithiation methodology, and converted to ester 128 by a Wolff-Kishner reduction and esterification (81%). Condensation of 128 with 3-acetylpyridine using Bergman's conditions (cf., Scheme 19) gave 1:1 adduct 129 (82%). Methylation and immediate exposure of the resulting pyridinium salt to methoxide gave the labile dihydropyridine 130 (62%). When the crude reaction mixture containing 130 was treated directly with the oxidizing agent, ethyl nicotinate methiodide (131), the desired pyridinium salt 132 was isolated in 78% yield from 129. Alternatively, 129 was hydrogenated to 133 which could be converted in the same fashion, via dihydropyridine 134 (84%), to pyridinium salt 132 (57% from 133). It is important to note that in these enolate additions to pyridinium salts (Schemes 24, 26, 27) 1,4-addition greatly predominates over 1,2-addition. Completion of the synthesis of 1a was achieved by reducing 132 to the presumed dihydroellipticine 135 with Vitride (=Red-Al). Without being isolated, 135 was oxidized with 131 to the 2-methylellipticine salt 136 (85% from 132). Nucleophilic demethylation of 136 with thiophenoxide gave ellipticine (1a) (91%).

Scheme 27

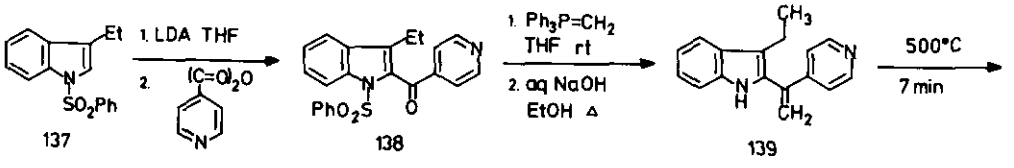


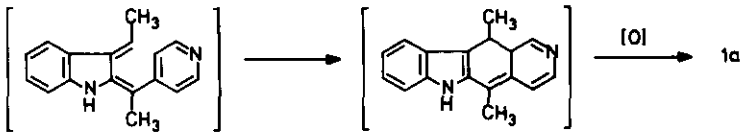
7. Strategy V



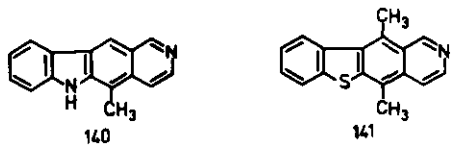
Kano's approach[47] to the pyrido[4,3-b]carbazole ring system parallels the Bergman method[38] in that both involve the thermal generation and cyclization of an indole-2,3-quinodimethane intermediate, but Kano's synthesis involves the bond-forming strategy classified as Type V (Scheme 28). Thus, treatment of 1-(benzenesulfonyl)-3-ethylindole (137) with lithium diisopropylamide (LDA) followed by quenching the resulting 2-lithio species with isonicotinic anhydride gave ketone 138 (75%). A Wittig reaction and base-cleavage of the protecting group gave alkene 139 (67%). Rapid thermolysis of 139 at 500°C for 7 min led directly to ellipticine (1a) (50%).

Scheme 28



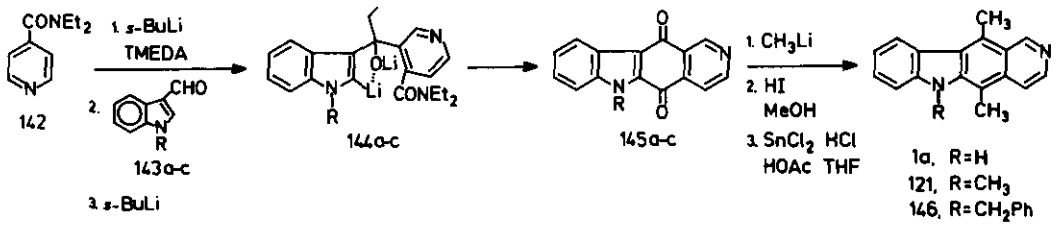


The same group has applied this methodology to syntheses of 11-demethylellipticine (140),[47] 6-thioellipticine (141),[48] and several related heterocycles[48] that are outside the scope of this review.



An exceptionally short synthesis of the ellipticine ring system, which utilizes "tandem metalation," has been described by Snieckus[49] (Scheme 29). Thus, lithiation of N,N-diethylisonicotinamide (142) with sec-butyllithium/N,N,N',N'-tetramethylethylenediamine (TMEDA) followed by sequential addition of an N-protected indole-3-carboxaldehyde 143 and sec-butyllithium presumably generates 144. Upon warming to room temperature 144 undergoes cyclization and spontaneous oxidation to give the quinones 145a-c in fair to good yield (145a, 26%; 145b, 76%; 145c, 40%). These quinones were converted to the corresponding ellipticines (1a, 40%; 121, 62%; 146, 40%) by sequential treatment with methyllithium, 47% hydrogen iodide, and stannous chloride/hydrochloric acid. These conditions removed the MOM group in 145a giving ellipticine (1a) directly.

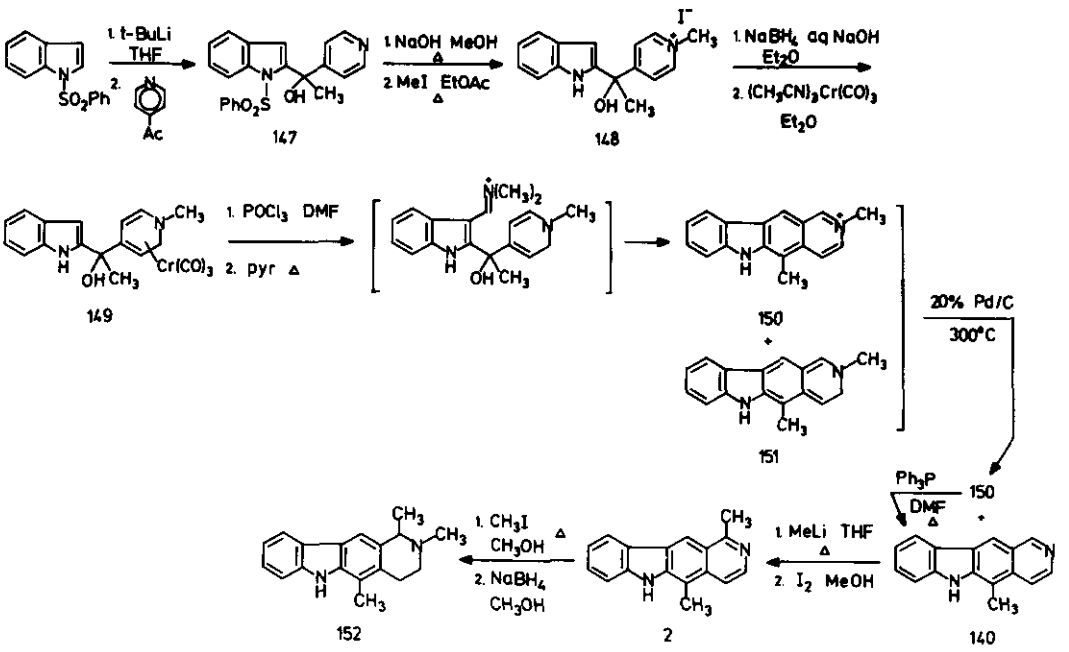
Scheme 29



Kutney[50] has employed tricarbonylchromium complexes in a Type V strategy to synthesize olivacine (2) and (±)-guatambuine (152) (Scheme 30). Thus, 1-

(benzenesulfonyl)indole was metalated at C-2 and then allowed to react with 4-acetylpyridine to give alcohol 147 (65%). Hydrolysis of the protecting group (72%) and iodomethylation gave pyridinium salt 148 (89%). Reduction of this material with sodium borohydride in a two-phase system (ether-aqueous sodium hydroxide) followed by the addition of the dried ether solution to a solution of trisacetonitriletricarbonyl chromium gave the red dihydropyridine complex 149 (56%), as two diastereomers (2:1 ratio). A Vilsmeier reaction on 149 gave two products: 150 (major) and 151 (minor) (7:3 ratio) (91%) after treatment of the reaction mixture with pyridine. This mixture of 150 and 151, which could only be separated with difficulty, was dehydrogenated to a mixture of 150 and 11-demethylellipticine (140) (9.5% from 149). Demethylation of 150 with triphenylphosphine gave 140 (54%). Treatment of 140 with methyllithium and then oxidation of the dihydropyridine intermediate with iodine afforded olivacine (2) (54%). Finally, iodomethylation of 2 followed by sodium borohydride reduction gave (±)-guatambuine (152) (40%).

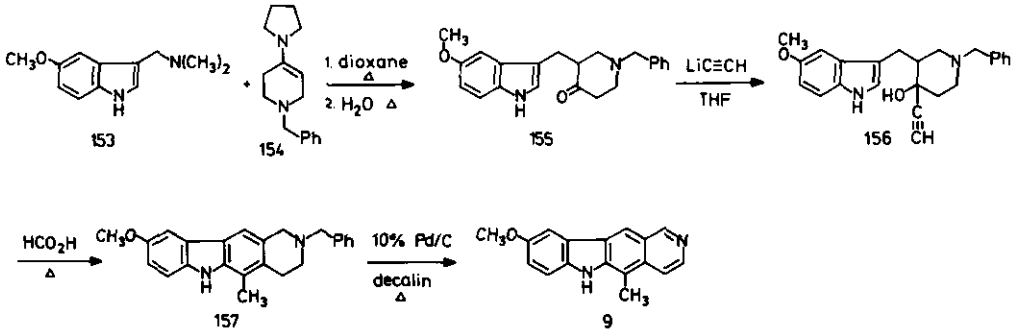
Scheme 30



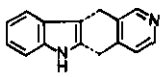
The French group whose work was discussed earlier[11,22] has also synthesized 9-methoxy-11-demethylellipticine (9)[11] using the same Type V strategy (Scheme 31) that they used to prepare ellipticine (1a) earlier.[51] Thus, 5-methoxygramine

(153), obtained via a Mannich reaction of 5-methoxyindole (78%), and the pyrrolidine enamine of N-benzyl-4-piperidone (154) condensed to form ketone 155 (92%). Reaction of 155 with lithium acetylenide gave the diastereomeric alcohols 156 (83%). A Rupe rearrangement was effected by heating 156 in formic acid to afford the cyclized carbazole 157 (32%). Catalytic debenzylation proved to be difficult but 157 was eventually converted to 9-methoxy-11-demethylellipticine (9) by boiling it with palladium/carbon in decalin (40%; 8% overall). As described earlier (Scheme 2) 9 could be converted to the 9-hydroxy derivative 10.

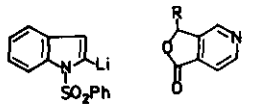
Scheme 31



153 154 155 156 157 9

8. Strategy VI 

Joule has developed[52-53] three quite versatile synthetic schemes for the preparation of pyridocarbazoles using the Type VI strategy. The reaction between 2-lithio-1-(benzenesulfonyl)indole (158) and a 3-(hydroxymethyl)isonicotinic acid lactone 159 is common to all three approaches.

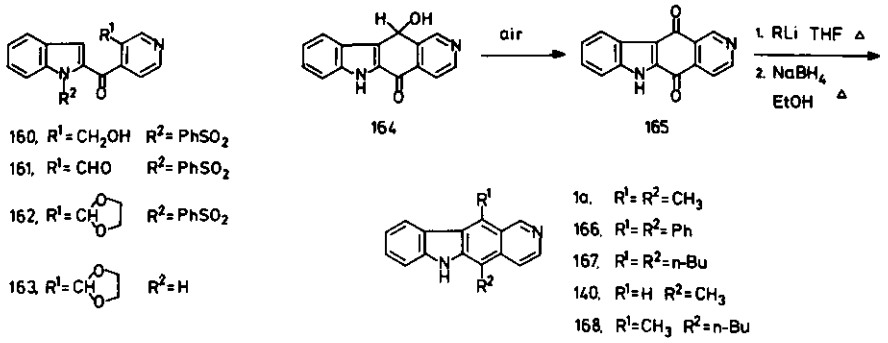


158 159a, R=H 159b, R=CH3

In the original strategy,[52a] Joule coupled 158 with lactone 159a, prepared[54] in three steps (16%) from dimethyl pyridine-3,4-dicarboxylate, to give keto alcohol 160 (58%) (Scheme 32). Oxidation of 160 with manganese dioxide in refluxing chloroform gave keto aldehyde 161 (44%), which was selectively protected as acetal 162 (100%) (ethylene glycol, p-TSA, refluxing chloroform). Base cleavage of the N-protecting group (50% aqueous sodium hydroxide in methanol, reflux) gave 163

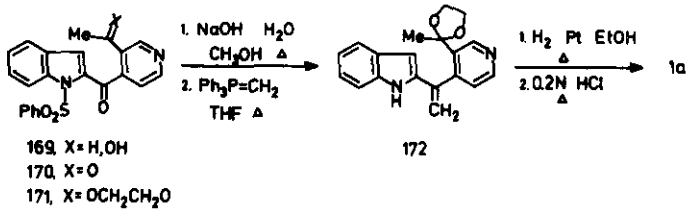
(96%). Simply treating 163 with 1N hydrochloric acid at 95°C in the presence of air formed the desired ellipticine-quinone 165 in 90% yield, presumably via intermediate semiquinone 164. Reaction of 165 with an alkyl- or aryllithium followed by reduction of the derived diols with sodium borohydride gave the corresponding ellipticines (1a, 166, 167) in high yield. Moreover, treatment of 165 with only two equivalents of methyllithium followed by reduction gave 11-demethylelliptine (140). Indeed, reaction of 165 with two equivalents of n-butyllithium and then with one equivalent of methyllithium followed by reduction gave, with high regioselectivity, 5-n-butyl-11-methyl-6H-pyrido[4,3-b]carbazole (168) in excellent yield.

Scheme 32



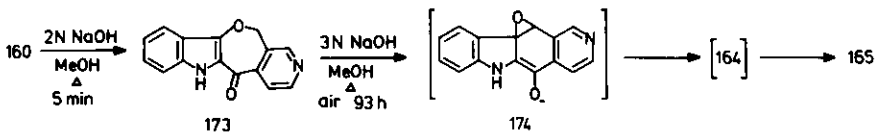
In a related methodology (Scheme 33), Joule[52b,56] coupled 2-lithioindole 158 with lactone 159b, prepared[55] in five steps (19%) from 3-ethyl-4-methylpyridine, to give alcohol 169 (58%). Oxidation with manganese dioxide (refluxing chloroform) furnished dione 170 (63%) in which the methyl ketone functionality could be selectively ketalized (ethylene glycol, p-TSA, refluxing chloroform) to produce 171 (80%). Alkaline hydrolysis of the sulfonamide and a Wittig reaction gave alkene 172. Hydrogenation and acid treatment converted 172 to ellipticine (1a) (32% from 171). Joule has also used this route to synthesize 11-demethylellipticine (140) from lactone 159a (22% overall yield from 160).

Scheme 33

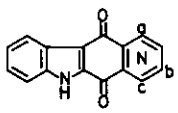


In a more recent publication, Joule[53] has reported an improved synthesis of ellipticine (1a) (ca. 20% overall yield from indole), although the preparation of the requisite lactone 159a proceeds in low yield[54] (vide supra). Thus, keto alcohol 160 was efficiently transformed into the pyrido-oxepino-indolone 173 (83%)[57] by a novel intramolecular nucleophilic addition reaction at the indole C-3 position (Scheme 34). Refluxing 173 in basic media in the presence of air gave ellipticinequinone 165 (46%) by the presumed pathway shown.

Scheme 34



173 174

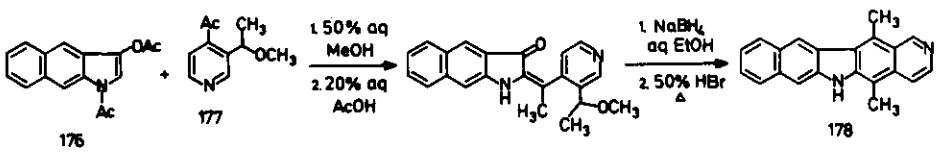


175

Similarly, Joule[53] has synthesized the other three isomeric quinones 175a-c from the respective pyrido-oxepino-indolones (71-89%), after much shorter reflux periods than for 173 → 165 (93 h).

Sainsbury[59] has described a synthesis of benzo[k]ellipticine (178) using a similar scheme to that previously developed[60] for the preparation of 9-phenyl-ellipticine[61] (Scheme 35). The yield of the key condensation reaction between diacetylindoxyl 176 and the 4-acetylpyridine ether 177 was less than anticipated and insufficient 178 was secured for biological evaluation.

Scheme 35

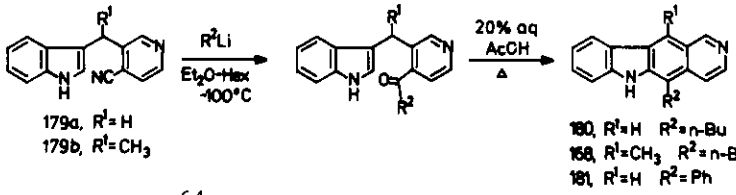


176 177 178

In another Type VI approach, Sainsbury[59] has demonstrated the versatility of his previously reported[7,62,63] route to ellipticines (Scheme 36). Thus, when nitrile 179a (prepared by the same general route[7] depicted in Scheme 37) was treated with n-butyllithium and the resulting ketone exposed to mild acidic conditions the ellipticine derivative 180 was obtained (87%). In similar fashion,

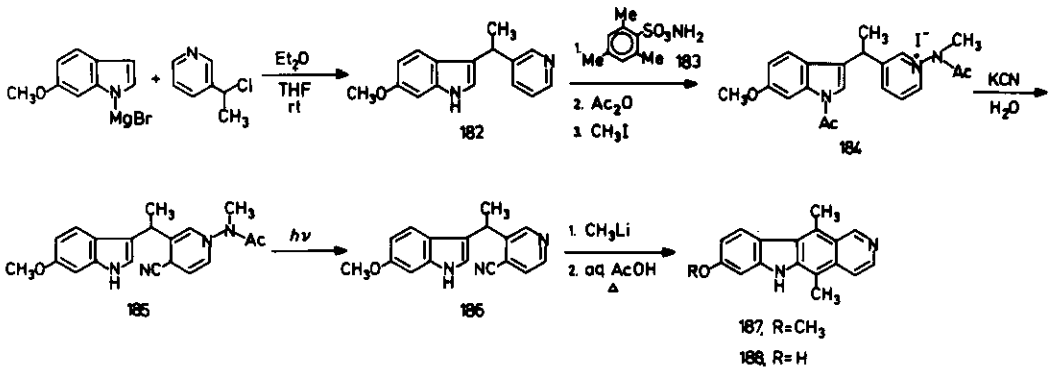
nitrile 179b with n-butyllithium gave 168 (78%) and 179a with phenyllithium gave 181 (20%).

Scheme 36



Furthermore, Sainsbury[64] has extended his "standard" ellipticine methodology[7,62,63] to a synthesis of 8-methoxyellipticine (187) and 8-hydroxyellipticine (188) (Scheme 37). This work comprises the first synthesis of 188, which is a metabolite of ellipticine (1a) in Aspergillus alliaceus.[65] Thus, a coupling reaction between 6-methoxy-1-indolylmagnesium bromide and 3-(1-chloroethyl)pyridine gave 182 (40%). Amination of 182 with 183, followed by acetylation, and iodomethylation afforded salt 184. Cyanide addition to 184 gave cyanodihydropyridine 185 which upon photolysis yielded cyanopyridine 186. The usual addition of methyllithium to 186 and acid-induced cyclization gave the target 8-methoxyellipticine (187) (42% from 182). Conversion to 188 was achieved under the usual conditions of hot pyridine hydrochloride (30%).

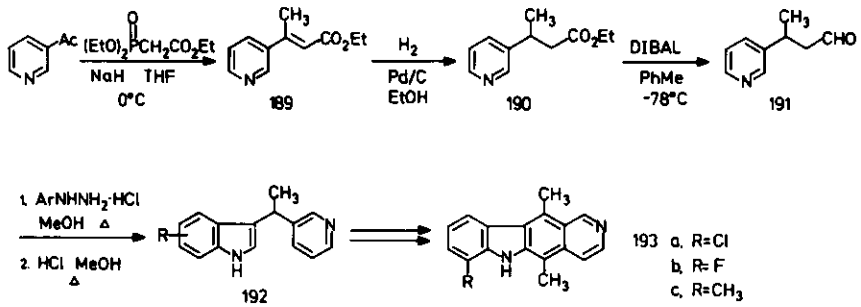
Scheme 37



The main disadvantage of the Sainsbury pyrido[4,3-b]carbazole synthesis is that the reaction between indolylmagnesium halides and pyridylethyl chloride typically proceeds in 10-30% yield. A solution to this difficulty has recently been developed in the Sainsbury laboratory.[66,67] Thus, an Emmons-Wadsworth condensation between 3-acetylpyridine and triethylphosphonoacetate gave unsaturated ester 189 (94%) (Scheme 38). Hydrogenation to 190 (98%) and DIBAL reduction to aldehyde 191 (93%) also proceeded very well. Fischer indolization of 191 with

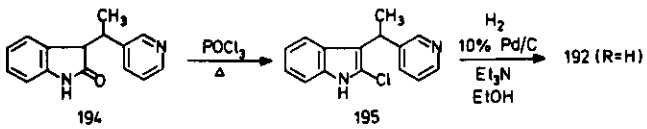
substituted phenylhydrazine hydrochlorides gave the expected pyridylethylindoles 192 (R=alkyl, alkoxy, halogen) in 65-80% yield. When 3-substituted phenylhydrazines were employed, both 4- and 6-substituted indoles were formed, with the latter predominating. The completion of the pyridocarbazole synthesis involved the same methodology described above (Scheme 37). In this fashion, the following new ellipticine derivatives were prepared: 7-chloro (193a), 7-fluoro (193b), and 7-methyl (193c). In addition, 9-methoxyellipticine (1b) was prepared in 40% overall yield from 4-methoxyphenylhydrazine and aldehyde 191.

Scheme 38



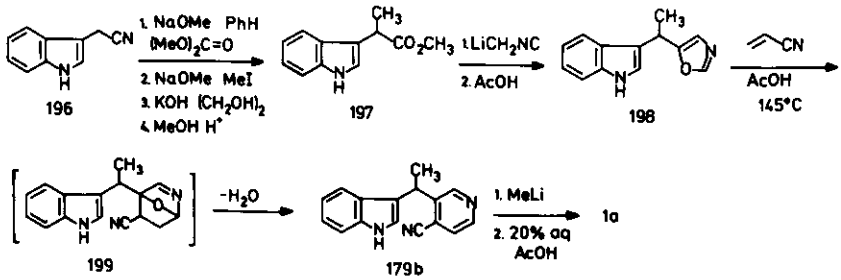
It is appropriate here to mention that Kubo[68] has reported an improved synthesis of the key Sainsbury pyridylindole 192, R=H (Scheme 39). Thus, oxindole 194, prepared by Sainsbury earlier,[61] was converted to the 2-chloroindole 195 (78%) with phosphorus oxychloride and then by hydrogenation to 192 (R=H) (71%). In fact, the yield of 192 is higher (73% from 194) if 195 is not isolated and purified, but simply hydrogenated directly.

Scheme 39



Kozikowski[69] has described a novel but less efficient synthesis of the Sainsbury nitrile 179b (vide supra) that utilizes oxazole Diels-Alder methodology (Scheme 40). Indole-3-acetonitrile (196), which is readily prepared from gramine methiodide and potassium cyanide, was converted to methyl 2-(3-indolyl)propionate (197) in four steps (74%). Reaction of 197 with excess α-lithio-methylisocyanide followed by acetic acid workup gave oxazole 198 (80%). This substance underwent a [4+2] cycloaddition reaction with acrylonitrile to afford nitrile 179b (16%). The usual[61,63] manipulation gave ellipticine (1a) in 80% yield.

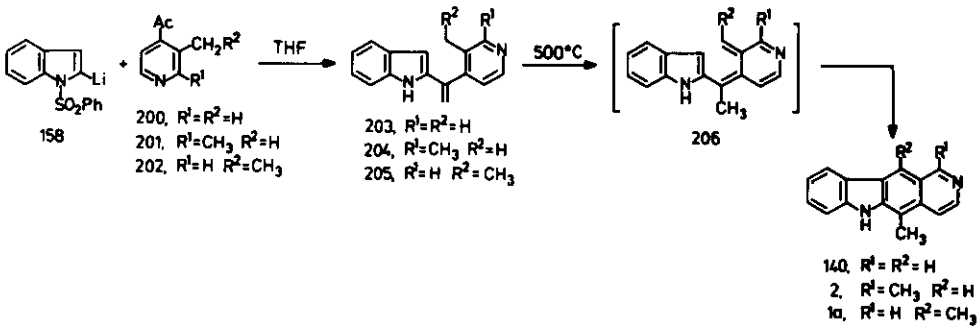
Scheme 40



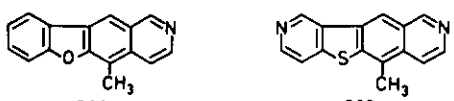
196 197 198 199 179b

Kano[70] has also utilized a Type VI thermolysis strategy to prepare ellipticines (Scheme 41). Condensation of 2-lithio-1-(phenylsulfonyl)indole (158) with 3-methyl-4-acetylpyridine (200), 2,3-dimethyl-4-acetylpyridine (201), and 3-ethyl-4-acetylpyridine (202), afforded the respective 2-vinylindoles 203 (35%), 204 (14%), and 205 (24%). Thermolysis of each of the latter compounds produced 11-demethylellipticine (140) (57%), olivacine (2) (57%), and ellipticine (1a) (30%), respectively. The last thermolysis reaction also gave 140 (43%), presumably as a result of methane elimination by a radical process during aromatization.

Scheme 41



Kano[48] has also used this pyridine-3,4-quinodimethane strategy to prepare several ellipticine analogues, such as 207 and 208, compounds which may be of biological interest but whose syntheses are outside the scope of the present review.

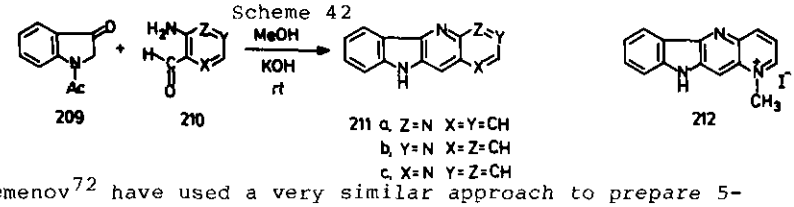


207 208

Quéguiner[71a] has used a Type VI approach to synthesize several novel azaellipticines of the 6H-indolo[3,2-b]naphthyridine type (Scheme 42). Thus, a Friedländer quinoline synthesis using 1-acetylindoxyl (209) and an appropriate

*aminoformyl*pyridine 210, prepared[71b] from the corresponding carboxylic acid, gave directly in unspecified yield the 6H-indolo[3,2-b]naphthyridines 211a-c. Moreover, iodomethylation of 211c gave naphthyridinium salt 212.

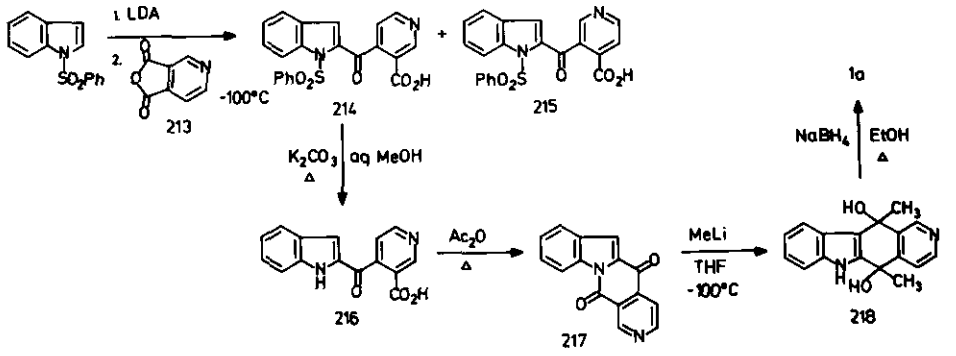
Scheme 42



Kononova and Semenov[72] have used a very similar approach to prepare 5-azaellipticine.

We[73a] have used a Type VI strategy to synthesize ellipticine (1a) in an approach that relies on the regioselective ring opening of cinchomeronic anhydride (Scheme 43). Thus, 1-(phenylsulfonyl)indole, prepared from indole with n-butyllithium and benzenesulfonyl chloride (91%), was lithiated at C-2 with LDA and the resulting anion (158) was treated at -100°C with cinchomeronic anhydride (213) to give a 92:8 mixture of keto acids 214 and 215 (78%). The major isomer 214 was hydrolyzed to 216 (~100%) which could be cyclized to keto lactam 217 upon treatment with hot acetic anhydride (~100%). Reaction of 217 with methyllithium (2 equiv) at -100°C gave diol 218 (mixture of diastereomers). This rather unstable material was directly treated with sodium borohydride to afford ellipticine (1a) (82% yield from 217). The overall yield of 1a from indole is 54%, representing one of the most efficient syntheses of ellipticine. The same sequence, when applied to 5-methoxyindole, gave 9-methoxyellipticine (1b) in 47% overall yield.[73b]

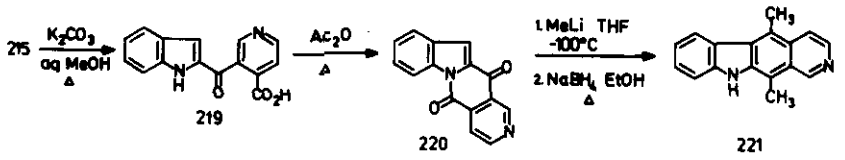
Scheme 43



In identical fashion we[74] have converted the minor keto acid 215 to "isoellipticine" 221 (5,11-dimethyl-10H-pyrido[3,4-b]carbazole) (Scheme 44). Thus, base hydrolysis of 215 (95%) followed by cyclization of keto acid 219 with acetic

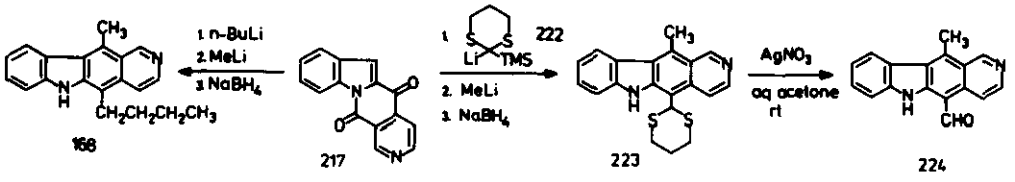
anhydride gave keto lactam 220 (98%). Treatment of 220 with methyllithium followed by sodium borohydride gave isoellipticine (221) (91%).

Scheme 44



It has been found[75] that keto lactam 217 can be used to construct unsymmetrically substituted ellipticine derivatives (Scheme 45). Thus, sequential treatment of 217 with n-butyllithium, methyllithium, and then sodium borohydride gave 5-n-butyl-11-methyl-6H-pyrido[4,3-b]carbazole (168) (70%) along with 18% of the 5,11-di-n-butyl derivative. Moreover, this methodology was also used[75] to synthesize the Strychnos dinklagei alkaloid 17-oxoellipticine (224) by using the formyl anion synthetic equivalent 222 as shown in Scheme 45. Thus, sequential treatment of 217 with 2-lithio-2-trimethylsilyl-1,3-dithiane, methyllithium, and then sodium borohydride gave 223 (25% yield from 217). Hydrolysis of 223 with aqueous silver nitrate gave 224 (~100%).

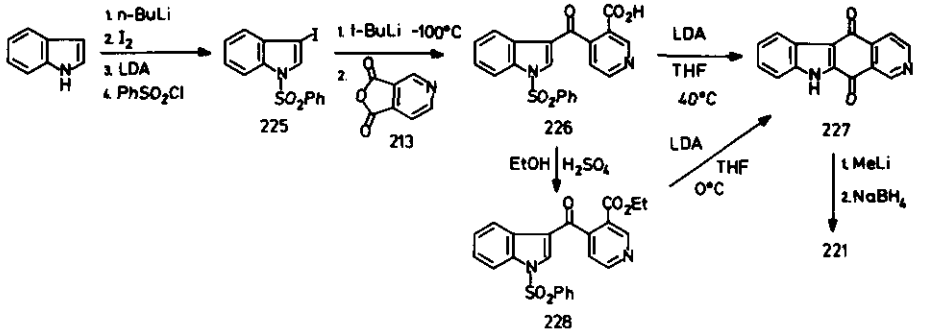
Scheme 45



We[74] have also used the regioselective acylation of pyridine anhydride 213 with the previously unknown 3-lithio-1-(phenylsulfonyl)indole to synthesize isoellipticine (Scheme 46). Indole was converted[76] to 3-iodo-1-(phenylsulfonyl)-indole 225 in one pot by successive treatment with n-butyllithium, iodine, LDA, and benzenesulfonyl chloride (88%). Halogen-metal exchange with t-butyllithium followed by quenching the 3-lithioindole species with cinchomeronic anhydride (213) gave with apparent complete regioselectively the keto acid 226 (57%). This substance was directly converted to the target isoellipticinequinone 227 upon treatment with excess LDA (41%), a transformation which presumably involves lithiation at the indole C-2 position, cyclization at the carboxylate carbonyl, and in situ desulfonylation. This process was improved by converting keto acid 226 to ester 228 (89%) and treating the latter with LDA to give quinone 227 (66%). In

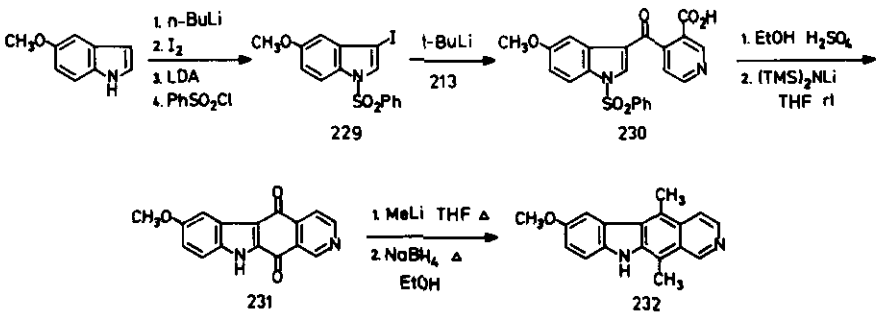
accord with the earlier work (cf., Schemes 29, 32), quinone 227 reacted with methyllithium and then sodium borohydride to furnish isoellipticine 221 (67%).

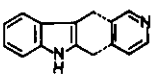
Scheme 46



The same sequence when applied to 5-methoxyindole gave 7-methoxyisoellipticine (232) (Scheme 47).[74] The requisite 3-iodo derivative 229 was prepared in one pot from 5-methoxyindole (75%) and then converted to keto acid 230 in the usual fashion with complete regioselectivity (77%). Esterification (98%) and cyclization with lithium bis(trimethylsilyl)amide gave methoxyquinone 231 (60%). Treatment of 231 with methyllithium and then with sodium borohydride gave 7-methoxyisoellipticine (232) (62%).

Scheme 47



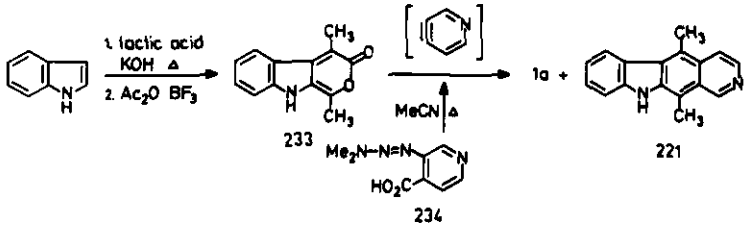
9. Strategy VII 

This bond-forming protocol has been the least studied of the eight strategies discussed herein.

Moody[77] has very recently described a short synthesis of ellipticine (1a) and isoellipticine (221) using a Diels-Alder Type VII strategy (Scheme 48). The

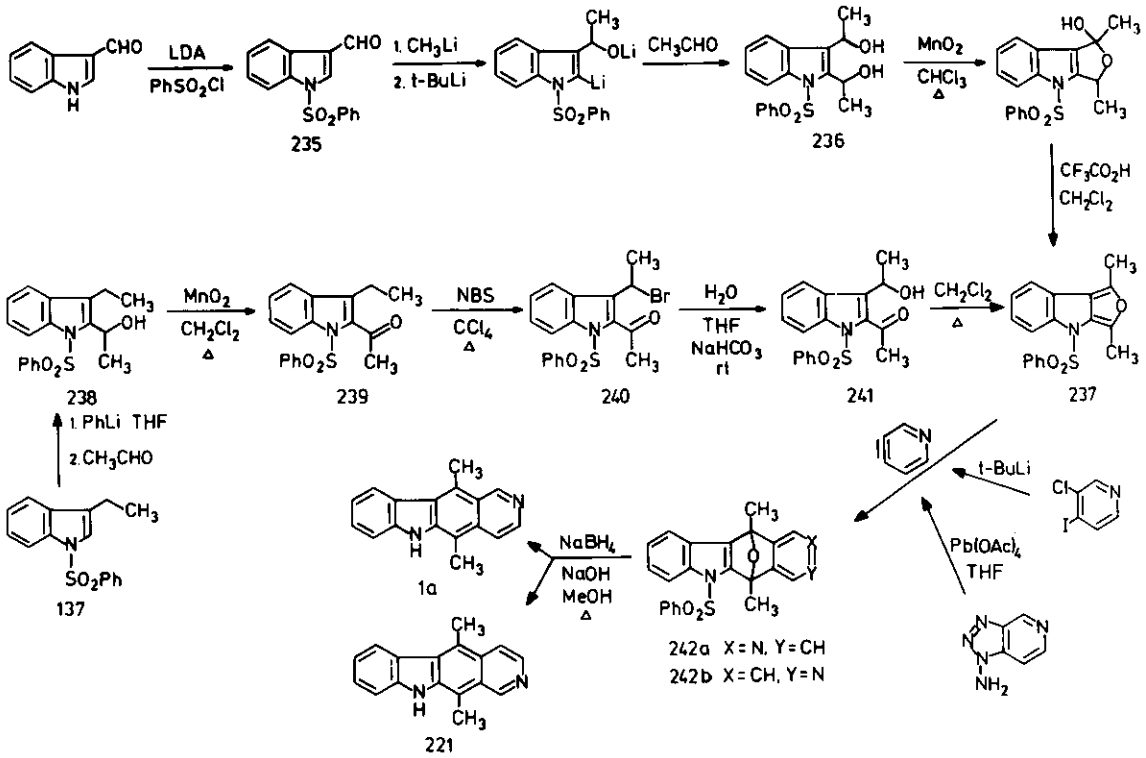
pyranoindolone 233, which is easily prepared from indole in two steps (44%), underwent a cycloaddition reaction with 3,4-pyridyne to give, after loss of carbon dioxide, an equal amount of ellipticine (1a) and isoellipticine (1b) (20% each). The pyridyne was generated in novel fashion by the thermolysis of triazene acid 234, prepared by diazotization of 3-aminopyridine-4-carboxylic acid and treatment with dimethylamine (72%).

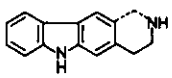
Scheme 48



In a related approach, we[78] have used the Diels-Alder reaction between 3,4-pyridyne and 1,3-dimethyl-4-(phenylsulfonyl)-4H-furo[3,4-b]indole (237) to synthesize ellipticine (1a) and isoellipticine (221) (Scheme 49). The key furoindole 237 was prepared by two routes. In the first,[79] indole-3-carboxaldehyde was converted to the 1-phenylsulfonyl derivative 235 using LDA and benzenesulfonyl chloride (86%). Sequential treatment of 235 with methyllithium, t-butyllithium, and then acetaldehyde gave diol 236 as a mixture of diastereomers (81%). Oxidation of 236 with activated manganese dioxide followed by dehydration of the resulting lactol with a catalytic amount of trifluoroacetic acid gave furoindole 237 (30%). Alternatively,[78] 3-ethylindole was converted to the 1-phenylsulfonyl derivative 137 using n-butyllithium and benzenesulfonyl chloride (74%). This substance was lithiated at C-2 with phenyllithium and the resulting anion was quenched with acetaldehyde to give alcohol 238 (73%). This was transformed into hydroxy ketone 241 by a sequence of oxidation, bromination, and solvolysis (86% yield from 238). Attempted recrystallization of 241 from dichloromethane gave furoindole 237 (~100%). Generation of 3,4-pyridyne in the presence of furoindole 237 was accomplished either from 3-chloro-4-iodopyridine and t-butyllithium or from 1-aminotriazolo[4,5-c]pyridine and lead tetraacetate to give a mixture of the Diels-Alder adducts 242a,b (34% and 38% from the two reactions, respectively). Treatment of this mixture with sodium borohydride gave an easily separable mixture of ellipticine (1a) (23%) and isoellipticine (221) (29%).

Scheme 49



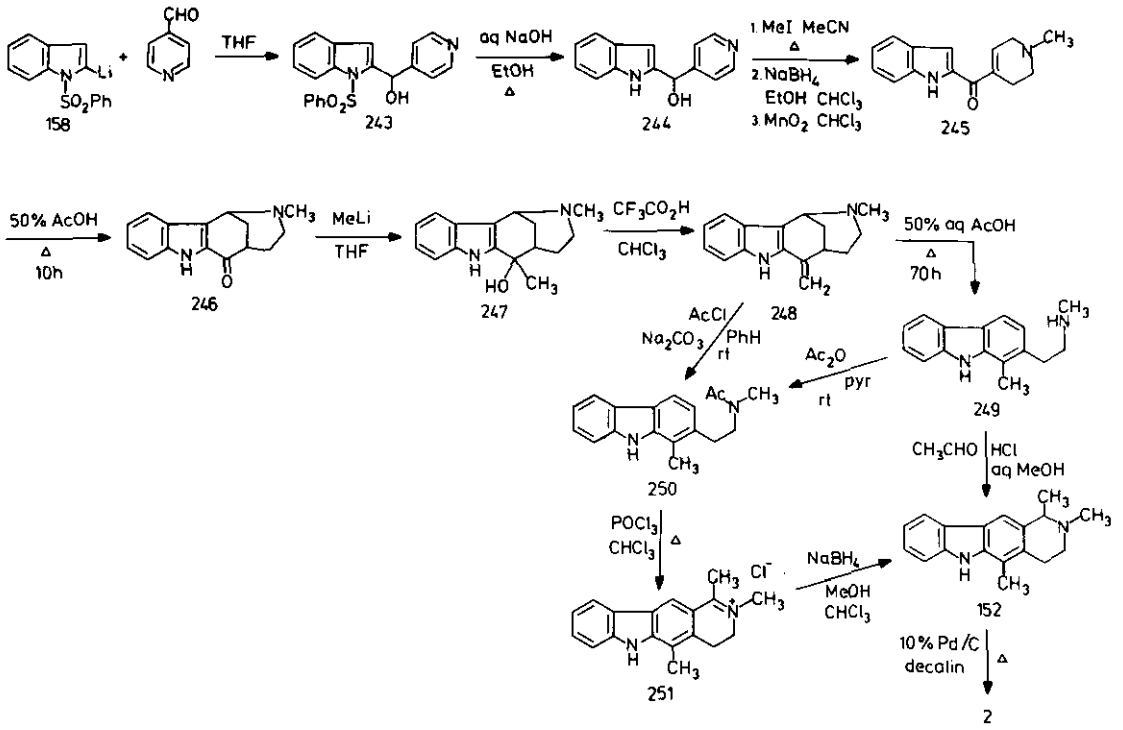
10. Strategy VIII 

The final bond-forming strategy to be reviewed mimics the proposed[80] biogenesis of olivacine (2), and two groups have described work along these lines.

Husson[81] has used the generation and fragmentation of desethyluleine 248 in a simple biomimetic synthesis of (±)-guatambuine (152) and olivacine (2) (Scheme 50). The approach was patterned after Joule's[82] synthesis of uleine and dasycarpidone alkaloids, but Husson used a different synthesis, at the outset, of desethyldasycarpidone 246. Thus, reaction of 158 with pyridine-4-carboxaldehyde gave alcohol 243 (62%). Base hydrolysis gave 244 (57%) which was transformed into 246 using Joule's original procedure,[82] although Joule used dimsyl sodium to isomerize 245 to the corresponding enamine isomer prior to the acetic acid-induced Mannich cyclization (to 246). Reaction of 246 with methyllithium gave alcohol 247 (~100%) and dehydration to desethyluleine 248 occurred readily with trifluoroacetic acid (~100%). Further treatment with hot aqueous acetic acid led to carbazole 249

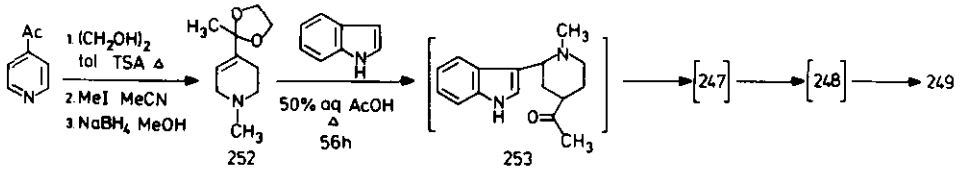
(90%), which was acetylated under standard conditions to give amide 250 (95%). This amide was also obtained directly from 248 (or even 247) by treatment with acetyl chloride (95%). A conventional Bischler-Napieralski reaction converted 250 into immonium salt 251 which upon treatment with sodium borohydride gave (±)-guatambuine (152) (72% from 250). Oxidation of 152 with palladium gave olivacine (2) (24%). Alternatively, a Mannich reaction between amine 249 and acetaldehyde gave guatambuine (152) in one step (33%).

Scheme 50



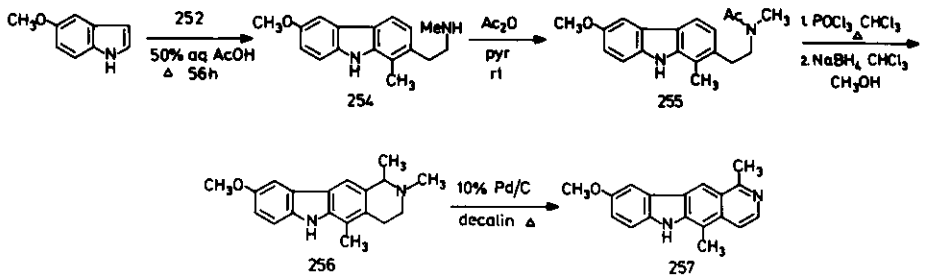
A much shorter route to carbazole amine 249 was also devised by Husson[81] (Scheme 51). Thus, 4-acetylpyridine was easily converted to ketal 252 by a sequence of ketalization, iodomethylation and reduction (72% overall). With elegant simplicity, piperideine ketal 252 reacted with indole in acid media to give 249 in a single operation (74%), presumably via 253 → 247 → 248 → 249.

Scheme 51



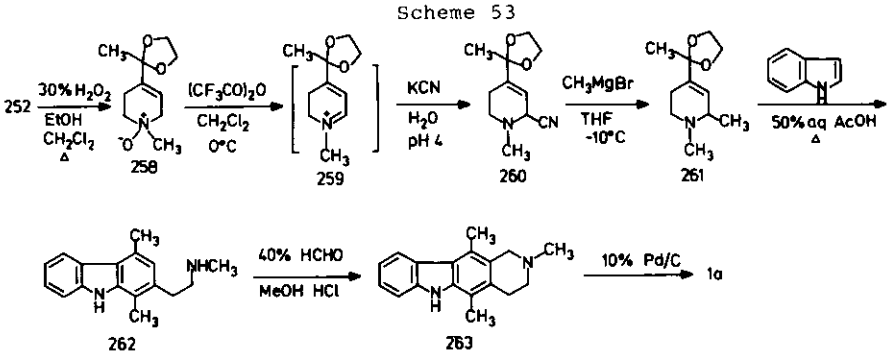
This latter sequence was also applied[81a] to the synthesis of the naturally occurring[83] 9-methoxyolivacine (257) (Scheme 52). Thus, 5-methoxyindole and piperidine ketal 252 condensed to give carbazole-amine 254 (90%). Acetylation (63%) and Bischler-Napieralski cyclization (76%) gave (±)-9-methoxy-guatambuine (256), which, upon dehydrogenation and demethylation with palladium, gave 9-methoxyolivacine (257) (52%).

Scheme 52



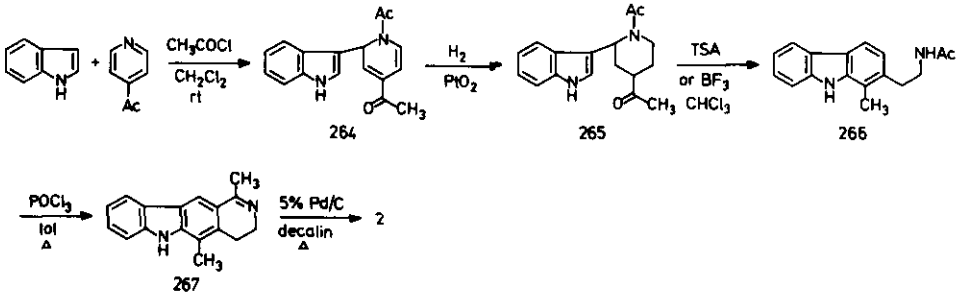
Husson[81a] has also extended this methodology to a synthesis of ellipticine (1a) (Scheme 53). The requisite piperidine ketal 261 was prepared using Husson's[84] piperidine-functionalization methodology. Thus, oxidation of piperidine ketal 252 gave N-oxide 258 (~100%). This substance underwent a Polonovski-Potier reaction to give the conjugated immonium salt 259 which was trapped as cyano-amine 260 (45% from 258). Reaction with methylmagnesium bromide gave piperidine ketal 261 (57%). Unfortunately, condensation between 261 and indole gave the target carbazole 262 in very low yield (5%), presumably due to steric effects in the Mannich reaction between indole and the tetrasubstituted immonium ion from 261. Nevertheless, carbazole amine 262 gave tetrahydroellipticine 263 when treated with formaldehyde in a Pictet-Spengler reaction (53%). Dehydrogenation-demethylation under the usual conditions gave ellipticine (1a) (36%).

Scheme 53



The second group to have used a biomimetic approach to the synthesis of olivacine (2) is Ninomiya and coworkers[85] (Scheme 54). Reaction of indole with 4-acetylpyridine in the presence of acetyl chloride (benzoyl chloride was also used) gave adduct 264 (35%). Hydrogenation of 264 gave 265 (55%) which, upon exposure to p-toluenesulfonic acid or boron trifluoride etherate, gave carbazole amide 266 (62%), originally prepared by Schmutz.[86] This reaction sequence leading to 266 presumably involves intermediates of the type 247 (cf., Scheme 50). Amide 266 was converted to olivacine (2) following the original procedure[86] via a Bischler-Napieralski cyclization to dihydroolivacine 267 (88%[86]) and dehydrogenation to 2 (88%[86]).

Scheme 54



In conclusion, it is obvious that interest in the ellipticine family of alkaloids amongst synthetic organic chemists remains exceptionally high. As this intense search for even more potent anticancer ellipticine-derived drugs continues, we can be certain that new and efficient syntheses of pyridocarbazoles will be discovered in the future.

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