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# Studies on the Synthesis of Strychnos Indole Alkaloids

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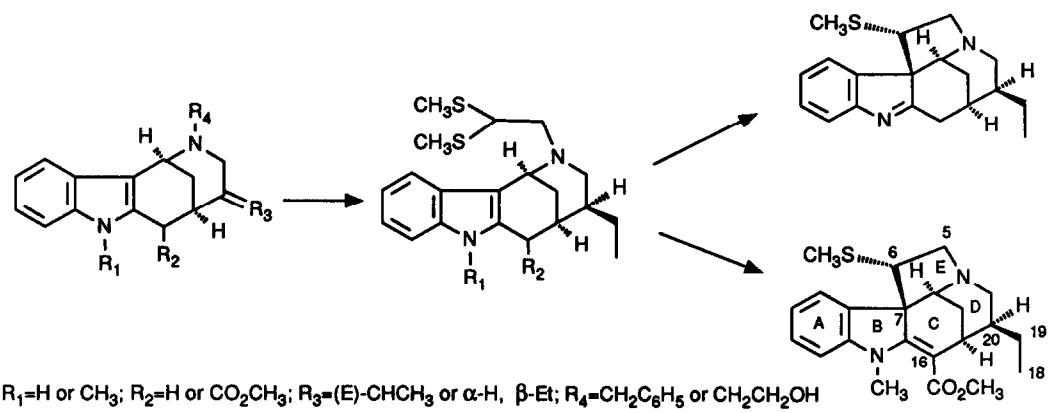
***Abstract***: Tetracycles **3b-d**, having the ABCD ring substructure of *Strychnos* alkaloids and a $N_b$-(formylmethyl) substituent protected as an oxime or hydrazone derivative, have been prepared by nucleophilic addition of the enolate of indoleacetic ester **1** to pyridinium salts **2b-d** followed by acid cyclization. The same one-pot, two-step sequence allowed the preparation of tetracycle **3f**, which incorporates an α-methoxyacrylate chain at the piperidine β-position.

We have recently developed a new strategy for the synthesis of pentacyclic *Strychnos* alkaloids.[1,2] It consists in the closure of the five-membered E ring by electrophilic cyclization upon the indole 3-position from appropriate tetracyclic derivatives (the ABCD substructure of *Strychnos* alkaloids) having a functionalized two-carbon chain at the piperidine nitrogen (bond formed $C_6$-$C_7$).[3]

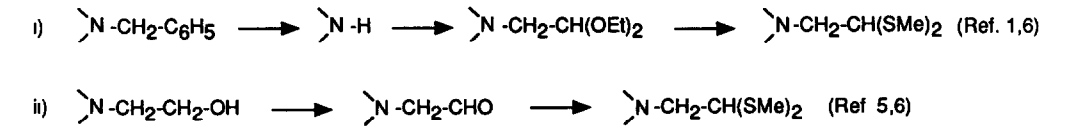



$R_1$=H or $CH_3$; $R_2$=H or $CO_2CH_3$; $R_3$=(E)-$CHCH_3$ or α-H, β-Et; $R_4$=$CH_2C_6H_5$ or $CH_2CH_2OH$

SCHEME 1

In this context, the nucleophilic addition of indole-2-acetic ester enolates to *N*-alkylpyridinium salts, followed by the cyclization of the resulting 1,4-dihydropyridine, has proved to be an efficient method of constructing the required tetracyclic ABCD ring derivative.[4] This methodology allows the solution of two problems associated with the synthesis of *Strychnos* alkaloids: the incorporation of the oxidized one-carbon substituent present at C-16 in the greater part of these alkaloids and the stereoselective elaboration of the C-20 β-ethyl or *E*-ethylidene substituents.[5]

With regard to the nature of the *N*-substituent required for the closure of the fifth ring, after a large amount of experimentation, we found that the electrophilic cyclization could only be successfully effected by way of a thionium ion generated by treatment of a *N*-[2,2-bis(methylthio)ethyl] derivative with dimethyl(methylthio)sulfonium fluoroborate.[1,6] This *N*-substituent was incorporated to the tetracyclic structures by one of the following multistep reaction sequences, with moderate overall yields:




We present here the results obtained by applying the nucleophilic addition-cyclization methodology to study: i) the appropriateness of other *N*-substituents in the elaboration of the bis(methylthio)ethyl chain needed for constructing the E ring, and ii) a possible way to functionalize the 18-position, as required for the synthesis of more complex *Strychnos* alkaloids, the Wieland-Gumlich aldehyde for instance, which have a 2-hydroxyethylidene chain at C-20.

## RESULTS AND DISCUSSION

*The N-substituent of the pyridinium salt.*

Pyridinium salts **2a** and **2b**, easily accessible by direct alkylation of methyl 3-pyridineacrylate **5a** with previously reported halides, were first tried as starting materials for the nucleophilic addition-cyclization sequence. The $sp^2$-hybridized β-carbon of the nitrogen chain in these salts could provide an efficient way to introduce the bis(methylthio) moiety required for the closure of the E ring. Previous attempts to prepare pyridinium salt **2** [R=$CH_2CH(OEt)_2$] either by direct alkylation with bromoacetaldehyde diethyl acetal or by reaction of **2a** or **2b** with hydrogen chloride in refluxing ethanol had been unsuccessful, whereas the direct preparation of **2** [R=$CH_2CH(SCH_3)_2$] could not be attempted because the required halide [$XCH_2CH(SCH_3)_2$] is not available.[1]

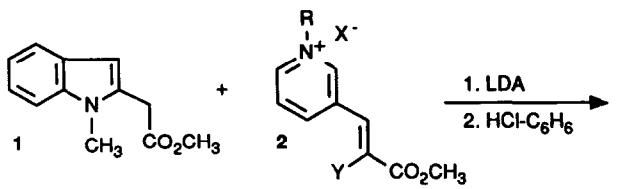
The reaction of the enolate derived of indoleacetic ester **1** with salt **2a** in the presence of an excess of LDA, followed by acidic cyclization, in the usual way,[4] gave the expected tetracyclic product **3a**, although in only 11% yield (mixture of epimers at C-6). A similar reaction from pyridinium salt **2b** did not lead to the expected tetracycle **3b**. In both cases, methyl 3-pyridineacrylate **5a** was obtained as the major product. Its formation can be rationalized by considering a Grob-type fragmentation promoted by the loss of the acidic OH or NH protons of the pyridine *N*-substituent under the basic reaction conditions.

For this reason, we turned our attention to the *N*- and *O*-methyl substituted hydrazone- and oxime-pyridinium salts **2c** and **2d**, respectively. As expected, interaction of the enolate of **1** with these salts, followed by acidic cyclization, afforded the corresponding tetracycles **3c** (60%) and **3d** (35%), respectively. In both cases, epimeric mixtures at C-6 were formed. Tetracycle **3c** was easily converted in 55% yield to **3a** by treatment with hydroxylamine in refluxing ethanol. However, attempts to convert either the oxime **3a** or the hydrazone **3c** to the corresponding aldehyde (**3**, R=$CH_2CHO$), acetal [**3**, R=$CH_2CH(OMe)_2$], or dithioacetal [**3**, R=$CH_2CH(SMe)_2$] under a variety of experimental conditions were unsuccessful. Worthy of mention was the isolation of the *N*-unsubstituted tetracycle **3e** in aproximately 50% yield when **3a** or **3c** were treated with hydrogen chloride in refluxing methanol.[7] In the latter case, *N*-methyl-2,4-dinitroaniline, formed

by cleavage of the nitrogen-nitrogen bond, was also isolated.

The undesired dealkylation of the piperidine nitrogen also took place under the acidic conditions required[8] for the elaboration of the ethylidene substituent. Thus, treatment of **3c** with refluxing hydrochloric acid, followed by reesterification of the C-6 carboxy group and sodium borohydride reduction gave the ethylidene bearing, *N*-unsubstituted tetracycle **4e**.

The *N*-substituents here studied do not constitute useful precursors of a 2,2-bis(methylthio)ethyl substituent. However, the above *N*-dealkylation deserves further exploration as it opens a short way of preparing *N*-unsubstituted tetracyclic ABCD systems having both the ethylidene and the methoxycarbonyl substituents characteristic of *Strychnos* alkaloids.




| | R | Y |
|---|---|---|
| a. | $CH_2CH$=N-OH | H |
| b. | $CH_2CH$=N-NH-$C_6H_3$-o,p$(NO_2)_2$ | H |
| c. | $CH_2CH$=N-$NCH_3$-$C_6H_3$-o,p$(NO_2)_2$ | H |
| d. | $CH_2CH$=N-$OCH_3$ | H |
| e. | H | H |
| f. | $CH_3$ | $OCH_3$ |

| | $R_1$ | $R_2$ |
|---|---|---|
| series α | $CO_2CH_3$ | H |
| series β | H | $CO_2CH_3$ |

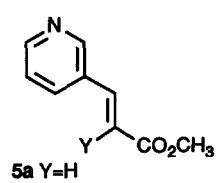
SCHEME 2

*Functionalization at C-18.*[3]

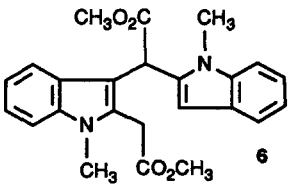
Taking into account that β-(1,4,5,6-tetrahydro-3-pyridyl)acrylates, such as **3** (Y=H), can be elaborated to 3-ethylidenepiperidines[8] by acid hydrolysis-decarboxylation and further sodium borohydride reduction of the resulting 3-ethylidene-3,4,5,6-tetrahydropyridinium cation, we decided to evaluate whether the presence of an alkoxy group at the α-position of the acrylate chain (C-18 in the biogenetic numbering[3]) would allow a similar transformation to take place to give a 2-alkoxyethylidene substituent. For this purpose, the *N*-methyl substituted pyridinium salt **2f** was selected as a simple model.

As expected, the reaction of the enolate of ester **1** with salt **2f**, followed by acid cyclization, gave tetracycle **3f** (epimeric mixture at C-6). The yield (~15%) of this one-pot, two step sequence was lower than in related nucleophilic addition-cyclization processes[4] as a consequence of the poor electron-withdrawing character of the substituent at the β-position of the pyridinium ring.[9] Interestingly, as could be indicative of the participation of radical species,[10] the dimeric diester **6** and esters **7a** and **7b**, in which an oxidation at the methylene α-carbon has occurred, were also isolated in low yields from the reaction mixture.

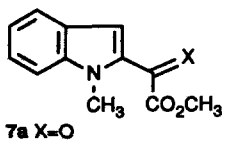
Treatment of tetracycle **3f** with refluxing hydrochloric acid, followed by reesterification of the C-6 carboxy group and sodium borohydride reduction, led to a complex mixture from which carbazole **8**[11] was the only isolable product.[12] Tetracycle **4f**, having a methoxyethylidene substituent, was not detected, thus



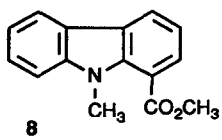

**5a** Y=H
**5b** Y=$OCH_3$




**6**




**7a** X=O
**7b** X=H, OH




**8**

indicating that the enol ether character of the doubly vinylogous urethane moiety of **3f** modifies the regioselectivity of the protonations which are required so that the desired transformation might take place.

**Table 1. Significant $^{13}$C-NMR Chemical Shifts[a] of Tetracyclic Compounds**

| Compound | C-1 | C-3 | C-4 | C-5 | C-6 | C-12 | C=O | $OCH_3$ | $NCH_3$ | =CY | =CHβ | Other | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **3c**(6α) | 48.1 | 145.9 | 108.6 | 30.4 | 43.8 | 26.3 | 169.1<br>171.7 | 51.0<br>52.6 | 29.8<br>34.7 | 103.7 | 143 3 | 56.1 | 137.0[b] |
| **3c**(6β) | 48.0 | 147.7 | 106.5 | 28.7 | 47.4 | 29.5 | 169.2<br>172.4 | 51.0<br>52.5 | 30 6<br>34.9 | 103.7 | 144.3 | 56.2 | 137 1[b] |
| **3e**(6α) | 43.7 | 146.5 | 108.3 | 31.1 | 42.3 | 25.7 | 169.1<br>171.9 | 51.0<br>52.6 | 29.8 | 103.8 | 141.4 | | |
| **3f** (6α) | 48.9 | 144.2 | 105.9 | 31.3 | 46.0 | 26.9 | 166.2<br>172.0 | 51.4<br>52.1<br>60.7 | 30.1<br>42.1 | 135.4 | 128.9 | | |
| **3f** (6β) | 48.3 | 143.7 | 100.2 | 33.1 | 49.1 | 29.5 | 166.0<br>172.0 | 51.3<br>52.2<br>58.3 | 30.8<br>42.2 | 136.0 | 128.5 | | |
| **4e**(6α) | 44.7 | 45.9 | 136.4 | 33.1 | 44.3 | 30.0 | 172.3 | 52.3 | 29.4 | | | 12 0 | 119.8[c] |

[a] The δ values are in ppm downfield from $Me_4Si$. Measured in $CDCl_3$ solution at 50.3 MHz . [b] Signals due to $CH_2CH$=N. [c] Signals due to =CH-$CH_3$

## EXPERIMENTAL PART

Melting points were determined in open capillary tubes on a Büchi apparatus and are uncorrected. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Varian XL-200 instrument or, when indicated, on a Perkin-Elmer R-24B (60 MHz) or a Bruker AC-300 spectrometer. Chemical shifts are expressed in parts per million downfield from TMS as internal standard. IR spectra were taken with a Perkin-Elmer 1430 spectrophotometer, and only noteworthy absorptions are listed. Mass spectra were determined on a Hewlett-Packard 5930A mass spectrometer. Column chromatography was carried out on $SiO_2$ (silica gel 60, 0.063-0.200 mm). Flash chromatography was carried out on $SiO_2$ (silica gel 60, 0.040-0.063 mm). Thin layer chromatography was carried out on $SiO_2$ (silica gel 60 $F_{254}$, 0.063-0.200 mm), and the spots were located with iodoplatinate reagent or UV light. Purification of reagents and solvents was effected according to standard methods. All reactions were carried out under nitrogen or argon atmosphere. Prior to concentration, under reduced pressure, all organic extracts were dried over anhydrous $MgSO_4$ or $Na_2SO_4$ powder. Microanalyses were performed on a Carlo-Erba 1106 analyzer by Centro de Investigación y Desarrollo (CSIC), Barcelona.

**1-[2-(Hydroxyimino)ethyl]-3-[(*E*)-2-(methoxycarbonyl)vinyl]pyridinium Bromide (2a).** A mixture of **5a** (2.3 g, 14.2 mmol) and 2-bromoacetaldehyde oxime[13] (2.2 g, impurified with the corresponding chloride) was stirred at 100 °C for 15 min under nitrogen. The resulting residue was washed with ether and digested with ethyl acetate to give **2a** as a solid (3.8 g, 88%): mp 195-200 °C (acetone-methanol); IR (KBr) 3110, 3050, 1710 cm$^{-1}$; $^1$H-NMR (60 MHz, DMSO-$d_6$) 9.8 (br s, 1H, H-2 pyr), 9.2 (m, 2H, H-4 and H-6 pyr), 8.3 (m, 1H, H-5 pyr), 7.8 (d, *J*=16 Hz, 1H, Hβ acrylate), 7.8 (t, *J*=3 Hz, 1H, CH=N), 7.1 (d, *J*=16 Hz, 1H, Hα acrylate), 5.6 (d, *J*=3 Hz, 2H, $NCH_2$), 3.8 (s, 3H, $OCH_3$). Anal. Calcd for $C_{11}H_{13}Cl_{0.4}Br_{0.6}N_2O_3$: C, 46.63; H, 4.62; N, 9.89. Found: C, 46.68; H, 4.55; N, 9.41.

**1-{2-[(2,4-Dinitrophenyl)hydrazono]ethyl}-3-[(*E*)-2-(methoxycarbonyl)vinyl]pyridinium Bromide**

(**2b**). A solution **5a** (200 mg, 1.2 mmol) in acetonitrile (3 ml) was added to a solution of 2-bromoacetaldehyde 2,4-dinitrophenylhydrazone[14] (370 mg, impurified with the corresponding chloride) in acetonitrile (15 ml), and the resulting mixture was stirred at room temperature for 12 h. The solid was filtered and washed with acetonitrile to give **2b** (539 mg, 97%): mp 216-217 °C (acetone-methanol); IR (KBr) 1725, 1710, 1615, 1588, $cm^{-1}$; $^1$H-NMR (60 MHz, DMSO-$d_6$) 11.3 (s, 1H, NH), 9.4 (br s, 1H, H-2 pyr), 8.9 (m, 2H, H-4 and H-6 pyr), 8.5 (d, *J*=3 Hz, 1H, ArH-3), 8.2-7.9 (m, 3H, ArH-5, H-5 pyr, and CH=N), 7.6 (d, *J*=16 Hz, 1H, Hβ acrylate), 7.2 (d, *J*=9 Hz, 1H, ArH-6), 6.8 ( d, *J*=16 Hz, 1H, Hα acrylate), 5.6 (d, *J*=3 Hz, 2H, $NCH_2$), 3.6 (s, 3H, $OCH_3$). Anal. Calcd for $C_{17}H_{16}Br_{0.7}Cl_{0.3}N_5O_6$: C, 45.08; H, 3.56; Br, 12.35; N, 15.46. Found: C, 44.61; H, 3.50; Br, 12.35; N, 15.29.

**1-{2-[(2,4-Dinitrophenyl)methylhydrazono]ethyl}-3-[(*E*)-2-(methoxycarbonyl)vinyl]pyridinium Chloride (2c).** 2-Bromoacetaldehyde diethyl acetal (6.3 g, 31.9 mmol) was added to a cooled solution of 1-(2,4-dinitrophenyl)-1-methylhydrazine (4.8 g, 22.4 mmol) in 6 N hydrochloric acid (480 ml). The mixture was stirred at room temperature for 3 h. The resulting yellow solid was filtered, washed with water, and dried to give **2-chloroacetaldehyde 2-(2,4-dinitrophenyl)-2-methylhydrazone** (5.6 g, 91%): mp 113-114°C (diethyl ether); IR (KBr) 1595, 1530, 1310 $cm^{-1}$; $^1$H-NMR (60 MHz, $CDCl_3$) 8.2 (d, *J*=3 Hz, 1H, ArH-3), 8.0 (dd, *J*=9 and 3 Hz, 1H, ArH-5), 7.1 (d, *J*=9 Hz, 1H, ArH-6), 6.7 (t, *J*=6 Hz, 1H, CH=N), 4.1 (d, *J*=6 Hz, 2H, $CH_2Br$), 3.3 (s, 3H, $NCH_3$). Anal. Calcd for $C_9H_9ClN_4O_4$: C, 39.65; H, 3.33; Cl, 13.00; N, 20.55. Found: C, 39.79; H, 3.18; Cl, 12.52; N, 20.47. When the reaction was done using 12 N hydrochloric acid for 12 h, ***N*-methyl-2,4-dinitroaniline** was obtained in 95% yield as an orange solid: mp 174-176°C (toluene); IR (KBr) 3350, 3250, 3100, 1510, 1335 $cm^{-1}$; $^1$H-NMR (200 MHz, $CDCl_3$) 9.15 (d, *J*=2.5 Hz, 1H, ArH-3), 8.57 (br s, 1H, NH), 8.31 (ddd, *J*=10.2, 2.5, and 0.7 Hz, 1H, ArH-5), 6.93 (d, *J*=10.2 Hz, 1H, ArH-6), 3.16 (d, *J*=5.0 Hz, 3H, $CH_3$); $^{13}$C-NMR ($d_6$-DMSO) 148.7 (C-1), 134.5 (C-4), 129.8 (C-5), 129.5 (C-2), 123.3 (C-3), 115.0 (C-6), 30.2 ($CH_3$). Anal. Calcd for $C_7H_7N_3O_4$: C, 42.65; H, 3.58; N, 21.31. Found: C, 42.55; H, 3.63; N, 21.32.

A solid mixture of the above hydrazone (15.7 g, 49.5 mmol) and **5a** (8.1 g, 49.5 mmol) was mechanically stirred at 100 °C for 20 min under nitrogen. The hygroscopic solid residue was digested several times with ethyl acetate to give **2c** as a yellow solid (21.2 g, 89 %): mp 185-187 °C (acetone-methanol--ether); IR (KBr) 1720, 1600, 1505, 1330 $cm^{-1}$; $^1$H-NMR (60 MHz, DMSO-$d_6$) 9.4 (br s, 1H, H-2 pyr), 8.9 (m, 2H, H-4 and H-6 pyr), 8.2-7.8 (m, 3H, ArH-3, ArH-5, and H-5 pyr), 7.7-7.2 (m, 3H, Hβ acrylate, ArH-6, and CH=N), 6.8 (d, *J*=16 Hz, 1H, Hα acrylate), 5.5 (br s, 2H, $NCH_2$), 3.6 (s, 3H, $OCH_3$), 3.4 (s, 3H, $NCH_3$). Anal. Calcd for $C_{18}H_{18}ClN_5O_6.1/2\ H_2O$: C, 48.60; H, 4.31; Cl, 7.79; N, 15.74. Found: C, 48.88; H, 4.31; Cl, 7.62; N, 15.13 .

**3-[(*E*)-2-(Methoxycarbonyl)vinyl]-1-[2-(methoxyimino)ethyl]pyridinium Bromide (2d).** A mixture of **5a** (690 mg, 4.2 mmol) and 2-bromoacetaldehyde *O*-methyloxime[15] (650 mg, 4.3 mmol) was stirred under nitrogen at 100 °C for 15 min. The solid residue was digested with ether and then with ethyl acetate to give **2d** (0.5 g, 38 %): mp 160-161 °C (methanol-acetone); IR (KBr) 1705 $cm^{-1}$; $^1$H-NMR (60 MHz, $CD_3OD$) 9.0 (br s, 1H, H-2 pyr), 8.7-8.6 (m, 2H, H-4 and H-6 pyr), 8.0-7.4 (m, 2H, H-5 pyr and CH=N), 7.5 (d, *J*=16 Hz, 1H, Hβ acrylate), 6.7 (d, *J*=16 Hz, 1H, Hα acrylate), 5.3 (apparent t, 2H, $NCH_2$), 3.6 (s, 6H, $OCH_3$). Anal. Calcd for $C_{12}H_{15}BrN_2O_3$: C, 45.73; H, 4.80; N, 8.89. Found: C, 45.97; H, 4.84; N, 8.77.

**1-Methyl-3-[(*Z*)-2-methoxy-2-(methoxycarbonyl)vinyl]pyridinium Iodide (2f).** A solution of methyl methoxyacetate (12 ml, 121 mmol) in toluene (75 ml) and a solution of pyridine-3-carbaldehyde (8.7 ml, 93 mmol) in toluene (75 ml) were added successively under nitrogen to a solution of sodium methoxide (6.5 g, 121 mmol) in anhydrous toluene (250 ml) . The mixture was refluxed for 2 h, cooled, and poured into 1.2 N aqueous hydrocloric acid. The aqueous layer was made alkaline with sodium carbonate and extracted with benzene. The combined organic extracts were dried and evaporated to give an oil, which was distilled affording methyl nicotinate (1.3 g, 10%) and **methyl α-methoxy-(*Z*)-β-(3-pyridyl)acrylate (5b)** (5.5 g, 31%): IR (neat) 1720 $cm^{-1}$; $^1$H-NMR (60 MHz, $CDCl_3$) 8.5 (d, *J*=2 Hz, 1H, H-2), 8.2 (dm, *J*=5 Hz, 1H, H-6), 7.9 (dm, *J*=8 Hz, 1H, H-4), 7.0 (dd, *J*=8 and 5 Hz, 1H, H-5), 6.6 (s, 1H, Hβ acrylate), 3.6 (s, 6H, $2CH_3O$). The aqueous layer was concentrated, and the resulting solid residue was dried and digested with ethyl acetate. Evaporation of the organic solution afforded 3-hydroxymethylpyridine.

A solution of methyl iodide (14.1 ml, 227 mmol) in benzene (30 ml) was added to a solution of **5b** (14.6 g, 75.6 mmol) in acetone (25 ml) at 0°C. The mixture was stirred at 0°C for 3.5 h and then was left on standing overnight. The solid was filtered and washed with anhydrous ether to give **2f** (18.1 g, 72%): mp 135-137°C (acetone-methanol); IR (KBr) 1710 $cm^{-1}$; $^1$H-NMR (60 MHz, $CDCl_3$) 9.1 (br s, 1H, H-2), 8.9 (d, *J*=6 Hz, 1H, H-6), 8.5 (d, *J*=8 Hz, 1H, H-4), 7.9 (dd, *J*=8 and 6 Hz, H-5), 6.6 (1H, Hβ acrylate), 4.5 (s, 3H, $NCH_3$), 3.7 and 3.8 (2s, 6H, $OCH_3$). Anal. Calcd for $C_{11}H_{14}O_3IN$: C, 39.19; H, 4.18; N, 3.92. Found: C, 39.41; H, 4.42; N, 3.92.

**Methyl 2-[2-(Hydroxyimino)ethyl]-6-(methoxycarbonyl)-7-methyl-1,2,5,6-tetrahydro-1,5-methanoazocino[4,3-*b*]indole-4-(*E*)-acrylate (3a).** A solution of ester **1**[4] (607 mg, 3 mmol) in THF (45 ml) was slowly added to a solution of LDA (3 mmol) in THF (30 ml) cooled at -70 °C, and the resulting mixture was stirred at this temperature for 1h. Then, pyridinium salt **2a** (300 mg, 1.1 mmol) was added portionwise, and the mixture was allowed to rise to 0°C and stirred at this temperature for 12 h. Enough of a saturated benzene solution of dry hydrogen chloride was added dropwise to adjust the pH to 3-4, and the reaction mixture was stirred at -15°C for 1.5 h, poured into a saturated aqueous potassium carbonate solution, and extracted with ether. The organic layer was washed with brine, dried, and evaporated to give a residue which was chromatographed. Elution with toluene afforded ester **1** (386 mg). Further elution with 4:1 toluene-ethyl acetate gave a mixture of pyridine **5a** and tetracycle **3a** (C-6 epimeric *Z,E*-oximes), from which the latter (**3a**, 46 mg, 11%) was obtained after extraction with 2 N aqueous hydrochloric acid: $^1$H-NMR (300 MHz, $CDCl_3$) 6.16 (s, 1H, H-3), 5.48 (2d, J=15.0 Hz, 1H, Hα acrylate), 4.53 (2t, 1H, H-1), 4.19-4.03 (m, 2H, $NCH_2$), 3.67 (s, 3H, $OCH_3$), 3.59 (s, 3H, $OCH_3$), 3.43 (s, 3H, $NCH_3$), 3.20 (br s, 1H, H-5), 2.20 (dm, *J*=12.8 Hz, 1H, H-12), 1.93 (2dt, *J*=12.8 Hz, 1H, H-12).

**Methyl 2-{2-[(2,4-Dinitrophenyl)methylhydrazono]ethyl}-6-(methoxycarbonyl)-7-methyl-1,2,5,6-tetrahydro-1,5-methanoazocino[4,3-*b*]indole-4-(*E*)-acrylate (3c)** was prepared as a C-6 epimeric mixture operating as above from ester **1**[4] (0.5 g, 2.4 mmol), LDA (4.1 mmol), and pyridinium chloride **2c** (0.4 g, 0.8 mmol). The crude residue was chromatographed. Elution with 9:1 toluene-ethyl acetate gave the ester **1** (0.2 g). Elution with 4:1 toluene-ethyl acetate afforded **3c** (epimer 6α, 284 mg, 50%): mp 156-158 °C (acetone-ether); IR (KBr) 1720, 1680, 1510, 1330 cm$^{-1}$; $^1$H-NMR (200 MHz, $CDCl_3$) 8.56 (d, *J*=3.0 Hz, 1H, ArH-3), 8.29 (dd, *J*=9.0 and 3.0 Hz, 1H, ArH-5), 7.59 (dd, *J*=8.0 and 1.3 Hz, 1H, H-8), 7.31-7.03 (m, 5H, ArH-6, H-9, H-10, H-11, Hβ acrylate), 6.71 (dd, *J*=6.7 and 4.4 Hz, 1H, CH=N), 6.40 (s, 1H, H-3), 5.69 (d, *J*=15.0 Hz, 1H, Hα acrylate), 4.65 (t, 1H, H-1), 4.28 (dd, *J*=16.0 and 6.7 Hz, 1H, NCH), 4.00 (dd, *J*=16.0 and 4.4 Hz, 1H, NCH), 3.95 (d, *J*=1.5 Hz, 1H, H-6), 3.79 (s, 3H, $OCH_3$), 3.73 (s, 3H, $OCH_3$), 3.55 (s, 3H, $N_aCH_3$), 3.31 (br s, 1H, H-5), 3.08 (s, 3H, $NCH_3$), 2.33 (dt, *J*=12.8 and 2.0 Hz, 1H, H-12ax), 1.95 (ddd, *J*=12.8, 4.2, and 3.5 Hz, 1H, H-12eq). Anal. Calcd for $C_{30}H_{30}N_6O_8$: C, 59.80; H, 5.02; N, 13.95. Found: C, 59.59; H, 4.86; N, 13.63. Further elution with 7:3 toluene-ethyl acetate afforded **3c** (epimer 6β, 52 mg, 10%): $^1$H-NMR (200 MHz, $CDCl_3$) 8.59 (d, *J*=3.0 Hz, 1H, ArH-3), 8.32 (dd, *J*=9.0 and 3.0 Hz, 1H, ArH-5), 7.58 (dd, *J*=8.0 and 1.3 Hz, 1H, H-8), 7.32-7.01 (m, 5H, ArH-6, H-9, H-10, H-11, Hβ acrylate), 6.77 (dd, *J*=6.7 and 4.4 Hz, 1H, CH=N), 6.58 (s, 1H, H-3), 5.44 (d, *J*=15.0 Hz, 1H, Hα acrylate), 4.64 (m, 1H, H-1), 4.29 (dd, *J*=16.0 and 6.7 Hz, 1H, N-CH), 4.28 (d, *J*=5.4 Hz, 1H, H-6), 4.07 (dd, *J*=16.0 and 4.4 Hz, 1H, N-CH), 3.70 (s, 3H, $OCH_3$), 3.68 (s, 3H, $OCH_3$), 3.50 (s, 3H, $N_iCH_3$), 3.07 (s, 3H, $NCH_3$), 2.06 (m, 2H, H-12).

**Oxime 3a from hydrazone 3c.** A solution of **3c** (0.5 g, 0.8 mmol) in methylene chloride (10 ml) was added to a solution of hydroxylamine hydrochloride (0.4 g , 5.7 mmol) in ethanol (30 ml), and the mixture was stirred at 80 °C for 24 h. The solvent was evaporated, and the residue was dissolved in water and extracted with methylene chloride. Evaporation of the organic solution gave a yellow solid which was chromatographed. On elution with toluene-ethyl acetate (9:1 to 5:5), oximes **3a** (0.18 g, 51%) were obtained.

**Methyl 6-(Methoxycarbonyl)-2-[2-(methoxyimino)ethyl]-7-methyl-1,2,5,6-tetrahydro-1,5-methanoazocino[4,3-*b*]indole-4-(*E*)-acrylate (3d)** was prepared in 35% yield as a C-6 epimeric mixture of *Z, E* oximes operating as above from ester **1**[4] (387 mg, 1.9 mmol), LDA (1.9 mmol), and pyridinium bromide **2d** (200 mg, 0.6 mmol), after column chromatography (4:1 toluene-ethyl acetate). The major isomer [*E*-(6α)] was obtained in a pure form: $^1$H NMR (200 MHz, $CDCl_3$) 7.71 (dd, *J*=7.6 and 1.7 Hz, 1H, H-8), 7.34 (dd, *J*=7.6 and 7.3 Hz, 1H, CH=N), 7.30-7.10 (m, 5H, ArH-6, H-9, H-10, H-11, Hβ acrylate), 6.34 (s, 1H, H-3), 5.68 (d, *J*=15.0 Hz, 1H, Hα acrylate), 4.66 (t, 1H, H-1), 4.21 (dd, *J*=16.0 and 7.6 Hz, 1H, N-CH), 3.94 (d, *J*=1.5 Hz, 1H, H-6), 3.93 (s, 3H, $=NOCH_3$), 3.79 (s, 3H, $OCH_3$), 3.74 (s, 3H, $OCH_3$), 3.65 (dd, *J*=16.0 and 7.3 Hz, 1H, N-CH), 3.55 (s, 3H, $N_aCH_3$), 3.30 (br, 1H, H-5), 2.26 and 1.94 (2dt, *J*=12.8 Hz, 2H, H-12). Significant $^1$H-NMR signals for other isomers were: 6.71 (dd, *J*=5.6 and 5.3 Hz, 1H, CH=N), 6.31 (s, 1H, H-3), 4.61 (t, 1H, H-1), 4.52 (dd, *J*=17.8 and 5.3 Hz, 1H, NCH), 3.96 (s, 3H, $=NOCH_3$)for the *Z*-(6α) isomer; 7.38 (dd, *J*=7.5 and 7.3 Hz, 1H, CH=N), 6.51 (s, 1H, H-3), 5.42 (d, *J*=15.3 Hz, 1H, Hα acrylate), 4.64 (t, 1H, H-1), 4.27 (d, *J*=5.6 Hz, 1H, H-6), 2.05 (m, 2H, H-12) for the *E*-(6β) isomer; and 6.74 (dd, *J*= 7.5 and 7.3 Hz, 1H, CH=N), 6.49 (s, 1H, H-3), 5.43 (d, *J*=15.3 Hz, 1H, Hα acrylate), 4.58 (t, 1H, H-1), 4.27 (d, *J*=5.6 Hz, 1H, H-6), 2.05 (m, 2H, H-12) for the *Z*-(6β) isomer.

**Methyl 6-(Methoxycarbonyl)-7-methyl-1,2,5,6-tetrahydro-1,5-methanoazocino[4,3-*b*]indole-4(*E*)-acrylate (3e).** A solution of **3c** (0.4 g; 0.7 mmol) in a 2.8 N methanolic solution of dry hydrogen chloride (40 ml) was refluxed under nitrogen for 2 h. The solvent was evaporated, and a saturated aqueous potassium carbonate solution was poured into the resulting residue. The aqueous layer was extracted with methylene chloride. Drying and evaporation of the organic extracts gave a residue, which was chromatographed. On elution with 4:1 toluene-ethyl acetate, a C-6 epimeric mixture (ratio 4:1) of **3e** (124 mg, 51%) was obtained.

From this mixture, by column chromatography, the major epimer **3e**-(6α) was isolated: mp 156-158 °C (ether-acetone); IR (KBr) 3320, 1730, 1670 $cm^{-1}$; $^1$H-NMR (200 MHz, $CDCl_3$) 7.56 (d, *J*=8.0 Hz, 1H, H-8), 7.29-7.05 (m, 4H, H-9, H-10, H-11, and Hβ acrylate), 6.49 (d, *J*=5.5 Hz, 1H, H-3), 5.70 (d, *J*=16.0 Hz, 1H, Hα acrylate), 5.14 (br s, 1H, NH), 4.75 (br s, 1H, H-1), 3.91 (d, *J*=1.5 Hz, 1H, H-6), 3.80 (s, 3H, $OCH_3$), 3.73 (s, 3H, $OCH_3$), 3.55 (s, 3H, $NCH_3$), 3.36 (br s, 1H, H-5), 2.29 (dt, *J*=13.0 and 1.8 Hz, 1H, H-12), 1.99 (ddd, *J*=13.0, 4.0, and 3.0 Hz, 1H, H-12). Anal. Calcd for $C_{21}H_{22}N_2O_4.H_2O$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.80; H, 6.01; N, 7.63.

**Methyl α-Methoxy-6-(methoxycarbonyl)-2,7-dimethyl-1,2,5,6-tetrahydro-1,5-methanoazocino-[4,3-*b*]indole-4-(*Z*)-acrylate (3f).** Operating as for compound **3a**, from ester **1**[4] (1 g, 5 mmol), LDA (5.1 mmol), and pyridinium iodide **2f** (1.7 g, 5 mmol), a crude mixture was obtained, from which the following compounds were separated by flash chromatography: elution with 1:2 ethyl acetate-hexane afforded ester **1** (731 mg) and **methyl 2-(methoxycarbonylmethyl)-1-methyl-α-(1-methyl-2-indolyl)-3-indoleacetate (6)** (28 mg, 2%): mp 167-168°C (acetone); IR (KBr) 1725 $cm^{-1}$; $^1$H-NMR (200 MHz, $CDCl_3$) 7.62 and 7.55 (2dm, *J*=8.0 Hz, 2H, H-8 and H-8'), 7.36-7-00 (m, 6H, indole), 6.50 (s, 1H, H-3 indole), 5.49 (s, 1H, CHCO), 3.70 and 4.05 (2d, *J*=7.5 Hz, 2H, $CH_2CO$), 3.65 and 3.76 (2s, 6H, 2 $OCH_3$), 3.17 and 3.37 (2s, 6H, 2 $NCH_3$); $^{13}$C-NMR ($CDCl_3$) 29.7 and 29.8 ($2CH_3N$), 30.2 (*C*HCO), 41.6 ($CH_2CO$), 51.7 and 52.5 ($2CH_3O$), 101.2 (C-3'), 107.7 (C-3), 108.8 and 109.3 (C-7 and C-7'), 118.3 and 119.3 (C-4 and C-4'), 119.8 and 120.4 (C-5 and C-5'), 121.3 and 121.8 (C-6 and C-6'), 126.6 (C-3a), 127.2 (C-3a'), 131.5 (C-2), 136.3 (C-2'), 136.5 and 137.7 (C-7 and C-7'), 169.6 and 171.1 (2C=O). Anal. Calcd for $C_{24}H_{24}N_2O_4.3/4H_2O$: C, 68.97; H, 5.78; N, 6.70. Found: C, 69.28; H, 6.03; N, 6.77. On elution with 1:1 ethyl acetate-hexane, the following compounds were isolated: **methyl 1-methyl-2-indoleglyoxylate**[16] **(7a)** (9 mg, 1%): IR (neat) 1725 and 1645 $cm^{-1}$; $^1$H-NMR (60 MHz, $CDCl_3$) 6.7-7.5 (m, 5H, ArH), 3.8 and 3.9 (2s, 6H, $CH_3N$ and $CH_3O$); **methyl α-hydroxy-1-methyl-2-indoleacetate (7b)** (14 mg, 2%): IR ($CHCl_3$) 3520 and 1735 $cm^{-1}$; $^1$H-NMR (200 MHz, $CDCl_3$) 7.56 (dt, *J*=8.0 and 1.0 Hz, 1H, H-7), 7.29 (dm, *J*=8.4 Hz, 1H, H-4), 7.23 (td, *J*=8.4 and 1.4 Hz, 1H, H-5), 7.09 (ddd, *J*=8.4, 8.0, and 1.6 Hz, 1H, H-6), 6.43 (s, 1H, H-3 ind), 5.40 (s, 1H, CHCO), 3.80 (s, 3H, $CH_3O$), 3.73 (s, 3H, $CH_3N$); MS *m/e*, (relative intensity) 219 ($M^+$, 38), 160 (100), 158 (22), 144 (20), 132 (86), 130 (31), 117 (83); **3f** (epimer 6α, 100 mg, 5%): mp 183-185°C (acetone); IR (KBr) 1695 and 1660 $cm^{-1}$; $^1$H-NMR (200 MHz, $CDCl_3$) 7.60 (dm, *J*=8.0 Hz, 1H, H-8), 7.05-7.30 (m, 3H, indole), 6.54 (s, 1H, Hβ acrylate), 6.31 (s, 1H, H-3), 4.53 (br s, 1H, H-1), 4.20 (d, *J*=1.8 Hz, 1H, H-6), 3.77 (s, 6H, $2CH_3O$), 3.74 (s, 3H, $CH_3O$), 3.70 (br s, 1H, H-5), 3.60 (s, 3H, $CH_3N_a$), 3.07 (s, 3H, $CH_3N$), 2.35 (ddd, *J*=12.6, 3.0, and 2.2 Hz, 1H, H-12), 2.02 (ddd, *J*=12.6, 4.2, and 3.2 Hz, 1H, H-12). Anal. Calcd for $C_{23}H_{26}N_2O_5.1/4H_2O$: C, 66.6; H, 6.31; N, 6.75. Found: C, 66.61; H, 6.53; N, 6.61; **3f** (epimer 6β, 80 mg, 4%): mp 177-178°C (ethyl acetate-hexane); IR (KBr) 1722 and 1680 $cm^{-1}$; $^1$H-NMR (200 MHz, $CDCl_3$) 7.62 (dm, *J*=8.0 Hz, 1H, H-8), 7.10-7.30 (m, 3H, indole), 7.20 (s, 1H, Hβ acrylate), 6.47 (s, 1H, H-3), 4.50 (br s, 1H, H-1), 4.23 (d, *J*=5.6 Hz, 1H, H-6), 3.73 (s, 3H, $CH_3O$), 3.72 (s, 3H, $CH_3O$), 3.55 (s, 3H, $CH_3O$), 3.53 (s, 3H, $CH_3N_{ind}$), 3.50 (br s, 1H, H-5), 3.14 (s, 3H, $CH_3N$), 2.14 (dt, *J*=12.0 and 3.5 Hz, 1H, H-12), 2.01 (dt, *J*=12.0 and 2.7 Hz, 1H, H-12). Anal. Calcd for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.38; N, 6.82. Found: C, 67.16; H, 6.25; N, 6.87.

**Methyl 4-(*E*)-Ethylidene-7-methyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-*b*]indole-6-carboxylate (4e).** A solution of tetracycle **3c** (7.2 g, 11.9 mmol) in a 2.8 N methanolic solution of dry hydrogen chloride (250 ml) was refluxed for 2 h under nitrogen. The solvent was evaporated, and the residue was dissolved in 4 N aqueous hydrochloric acid (55 ml). The resulting solution was refluxed for 2 h and then evaporated. The residue was dried and dissolved in a 2.8 N methanolic solution of dry hydrogen chloride (400 ml). The resulting solution was stirred at room temperature for 16 h. The solvent was evaporated, and the residue was dissolved in methanol (45 ml), treated with an excess of sodium borohydride at 0 °C, and stirred at this temperature for 1 h. The solvent was evaporated, and the residue was dissolved in 10% aqueous hydrochloric acid and extracted with ether. The aqueous solution was basified with 2N sodium hydroxide solution and extracted with methylene chloride. The organic layer was dried and evaporated to give an oil, which was chromatographed. Elution with 97:3 ether-diethylamine afforded **4e** as a C-6 epimeric mixture (479 mg, 13%). Major isomer (6α): $^1$H-NMR (200 MHz, $CDCl_3$) 7.55 (d, *J*=8.0 Hz, 1H, H-8), 7.28-7.02 (m, 3H, H-9, H-10, and H-11), 5.27 (m, 1H, CH=), 4.47 (apparent t, 1H, H-1), 3.68 (s, 3H, $OCH_3$), 3.59 (d, *J*=1.5 Hz, 1H, H-6), 3.52 (s, 3H, $NCH_3$), 3.09-2.95 (m, 3H, H-3 and H-5), 2.17 ( dt, *J*=12.8 Hz, 1H, H-12), 1.93 (dt, *J*=12.8 Hz, 1H, H-12), 1.73 (dd, *J*=6.9 and 1.8 Hz, 3H, $CH_3C$=).

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