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Aspidosperma Alkaloids via Cyclization of Secodine Intermediate: Synthesis of (±)-3-Oxovincadifformine Ethyl Ester.[1]

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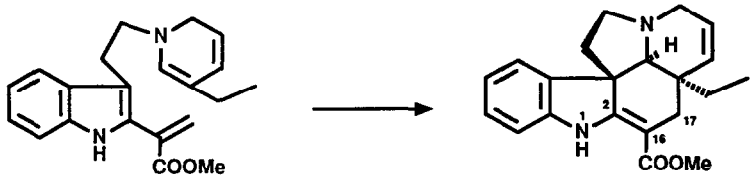
Abstract: (±)-3-oxovincadifformine ethyl ester **14** has been synthesized through an intramolecular [4π+2π] cycloaddition of the 3-oxosecodine **13** first prepared in turn from the enamide **10** by dehydrogenation with benzeneseleninic anhydride. An insight into the conversion of **10** into **13** was gained, resulting in the suggestion of a plausible mechanistic pathway.

The hypothesis of a dehydrosecodine[2] **1** as a key biogenetic intermediate in the *in vivo* formation of Aspidosperma type alkaloids, such as tabersonine **2**, has led to the development of efficient biomimetic syntheses that exploit the potential of a formal intramolecular [4π+2π] cycloaddition of secodine-type intermediates.[3]

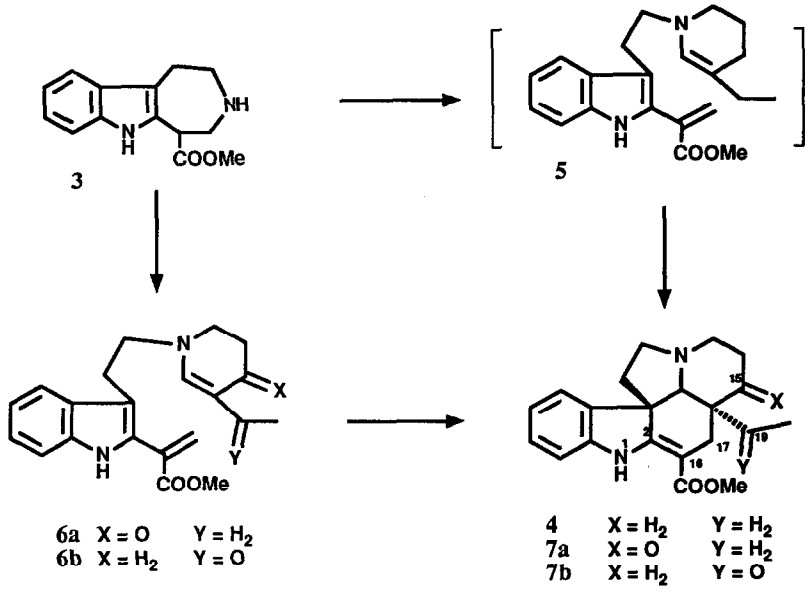


1 **2**

The most relevant contribution to this area has been given by Kuehne who realized a generalized synthetic strategy for members of Aspidosperma family through the reaction of the N^b-H-indoloazepine **3** with properly functionalized aldehydes, as reported in an impressive series of papers from 1978 to 1993.[4] Thus, by condensing **3** with 5-chloro-2-ethylpentanal, (±)-vincadifformine **4** has been directly obtained *via* the intermediacy of the inherently unstable secodine **5** which spontaneously cyclized to the pentacyclic

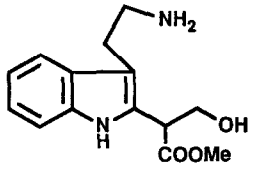
end product[5] **4**. (Scheme 1).

Only in the cases of 15-oxosecodine **6a**[6] and 19-oxosecodine **6b**[7], generated by reaction of **3** with 1-chloro-4-ethylpenta-1,4-dien-3-one and phenyl 2-acetyl-5-chloro-1-pentenyl sulfoxide respectively, did the vinylogous amide function provide a stabilized enamine, allowing the isolation of the seco intermediates **6a** and **6b**. (Scheme 1). Subsequent thermal cyclization converted **6a** and **6b** into racemic 15-oxo- and 19-oxovincadifformine **7a** and **7b**.



Scheme 1

Recently, Szantay has proposed a more conventional approach to the Aspidosperma skeleton, based on the reaction of the masked acrylate ester **8** with methyl 4-formylhexanoate or 5-(benzoyloxy)-2-ethylpentanal.[8]



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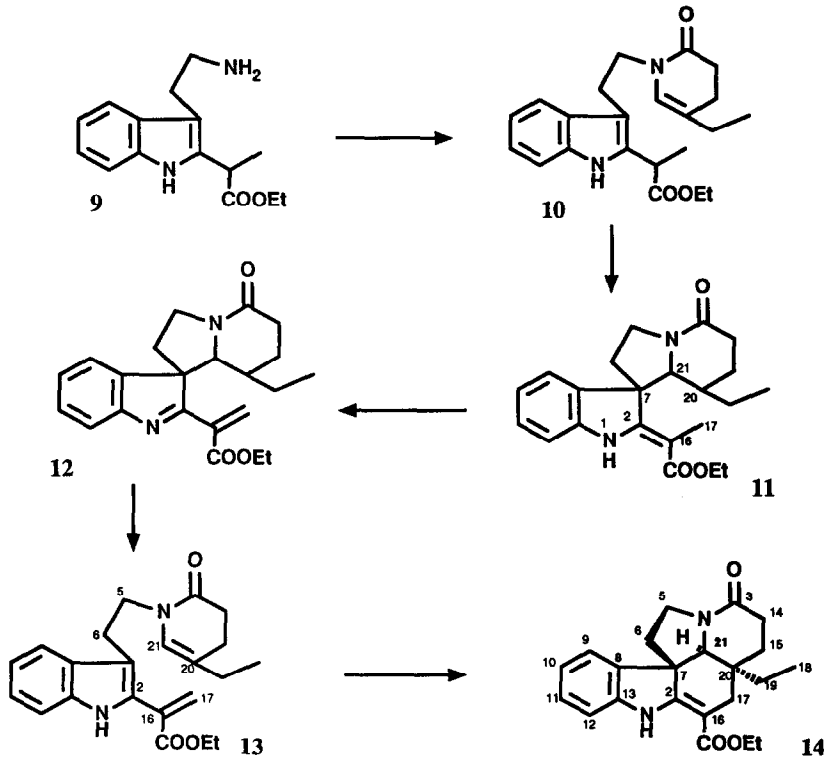
We have long been interested in the chemistry of Aspidosperma alkaloids,[9] and in continuing our work in this field, we wish to report here a synthesis of (±)-3-oxovincadifformine ethyl ester **14** *via* the intermediacy of the 3-oxosecodine **13**, along the route outlined in Scheme 2.

We thought we could have access to **14** starting from the 3-oxo-16,17-dihydrosecodine **10** that by

acid catalyzed cyclization[10] should give the β-anilinoacrylate **11**. This in turn should be subjected to a regioselective dehydrogenation with benzeneseleninic anhydride (BSA) that we have already proved to be the reagent of choice for a similar dehydrogenation of tabersonine **2** and vincadifformine **4** to the corresponding 1,16-azadienes.[11] The dehydrogenation should result in the spiroazadiene **12**, tetracyclic synthetic equivalent of the required **13** that ultimately undergoes intramolecular [4π+2π] cycloaddition to **14**.



Scheme 2

Scheme 3 shows the preparation of the ethyl 2-(3-aminoethyl)-indolylpropanoate **9**, the precursor of the enamide **10**, that was obtained through a straightforward condensation of **9** with ethyl 4-formylhexanoate.

The ethyl 2-(2-indolyl)propanoate **17** was prepared by adapting the efficient procedure described by Capuano[12] for the synthesis of methyl 2-indolylacetate.[13, 14]

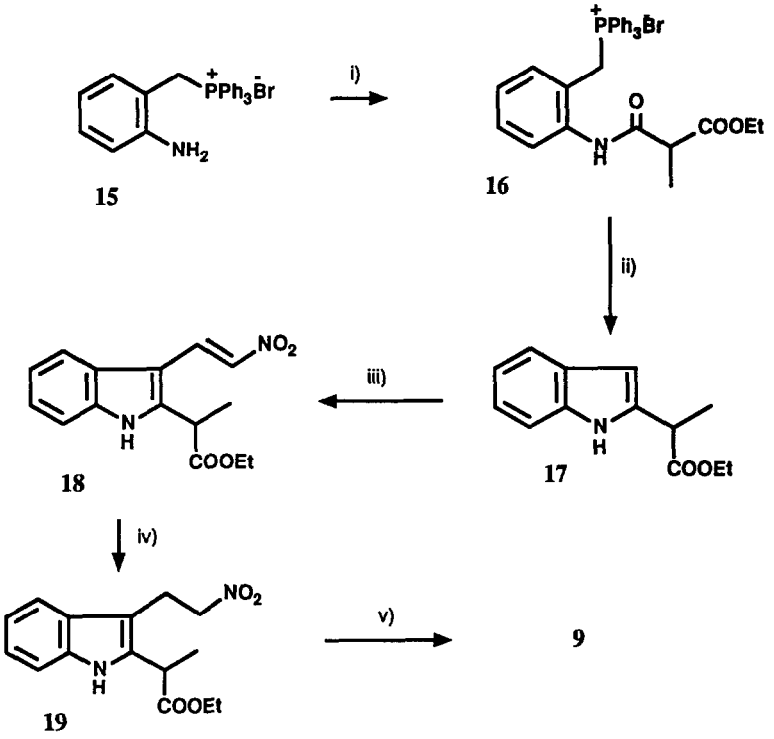
The essential feature of this procedure is an intramolecular Wittig-type reaction of N-(2-methyl)malonylamide **16**, prepared by condensation of the (2-aminobenzyl)triphenylphosphonium bromide **15** with ethyl (2-methyl)malonyl chloride. Cyclization of **16** induced by KOtBu proceeded smoothly and afforded **17** in 64% isolated yield.

Exposure of **17** to N,N-dimethyl-2-nitroethenamine[15] in the presence of trifluoracetic acid allowed

the introduction of the nitroethylene side-chain at C-3 to give **18**.

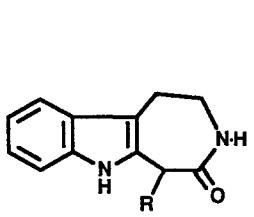
Reduction of the nitroethenamine appendage was performed in a two-steps sequence. First the double bond of **18** was selectively saturated with $NaBH_4$ in a THF-MeOH 9:1 solution[16] to form the nitroethane **19**. In order to minimize the Michael side-reaction products generally occurring in the reduction of nitrostyrene with sodium borohydride,[17] $NaBH_4$ was slowly added to the solution, providing **19** in 93% yield.

The hydrogenation of the nitro group of **19** proceeded smootly in EtOH over PtO_2 to give the desired derivative **9** in 80% yield (30% yield from **15**).

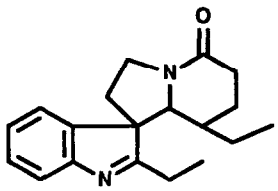


Scheme 3. *Reagents:* i) ClCOCH(CH_3)COOEt; ii) tBuOK, $PhCH_3$,120° C; iii) N,N-dimethyl-nitroethenamine CF_3COOH; iv) $NaBH_4$, THF-MeOH 9:1; v) H_2, PtO_2

The aminoester **9** is an oily compound, fairly stable at room temperature, however with heating in a benzene solution, particularly in the presence of traces of acid, it suffers a slow intramolecular cyclization to the indoloazepinone **20a**. Furthermore attempting to synthesize methyl 3-(2-amino ethyl)-1H-indole-2-acetate, Bernauer observed an easy spontaneous lactamization to **20b**.[18] His report together with the impossibility of reconverting the lactam to the aminoester by alcoholysis, led us to select the less reactive ethoxycarbonyl function for this synthesis since the reaction conditions for the conversion of **9** to **10** made it difficult to envision *a priori* the survival of the methoxycarbonyl group.



20a R = CH_3
20b R = H



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Having accomplished our initial goal of preparing the tryptamine propanoate **9**, we then condensed it with ethyl 4-formylhexanoate[19] in boiling toluene to obtain **10**. The reaction proceeds cleanly by distilling and draining off the toluene-water and toluene-ethanol azeotropes.

Various conditions were investigated in order to convert **10** into the spirotautomer **11** (Pictet-Spengler reaction). In principle this reaction should be possible by using acidic conditions[20] but Brønsted acid, such as H_3PO_4 (85%), in EtOH at 50°C gave cyclization with concomitant decarboxylation to form the indolenine **21**, ($M^{+\cdot}$ peak at m/z 296, lack of signals due to the ethoxycarbonyl function and olefinic protons in the ^{1}H-NMR spectrum and typical indolenine UV absorption at 220 and 262 nm). The use of $BF_3.Et_2O$ at -60° and 0° C gave no products, the starting material being recovered unchanged. With $SnCl_4$ in CH_2Cl_2 at -40°C a 10% yield of **11** was formed. A more satisfactory result was obtained with $TiCl_4$ in CH_2Cl_2 at 0° C giving **11** in 66% isolated yield as a single diastereoisomer of unknown relative stereochemistry. Spectroscopic data were in agreement with the proposed structure, UV absorptions at 228, 300, 330 nm for the β-anilinoacrylate moiety and ^{1}H-NMR signals at δ 2.05 for C-17H_3 and 4.15 for C-21H. The last mentioned signal is partially obscured by the multiplet due to one C5-H and CH_2 of the ethoxycarbonyl function but confirmed by COSY and HETCOR experiments.

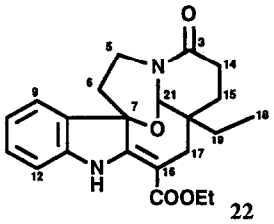
Surprisingly, the reaction of **11** with BSA in benzene at 30-50° C resulted in an intractable mixture of products in spite of much experimentation. Among the reaction products, a trace amount of **13** (*vide infra*) could be identified by TLC comparison. We have no convincing explanation for this disappointing behaviour, and in an attempt to circumvent the impossibility of converting the spiro-β-anilino acrylate **11** to **12** or **13**, we examined the direct formal dehydrogenation of **10**.

The reaction of **10** with 1 equivalent of BSA in benzene at 25° C for 1h and then at 50° for 12h proceeded cleanly and exhibited remarkable regioselectivity, affording after chromatographic separation and purification the 3-oxosecodine **13** in 35% yield as a stable compound. The 3-oxosecodine **13** was fully characterized by spectroscopic methods. The MS spectrum contained structurally diagnostic fragments at m/z 228 ($C_{14}H_{14}NO_2$) and 138 deriving from the cleavage of the C5-C6 bond. The ^{1}H-NMR spectrum displayed two doublets at δ 6.56 and 6.32 (J=1Hz) for the acrylic protons and a singlet at δ 5.60 for the enamide proton at C-21. The UV spectrum with λ_{max} 219, 227, 236 nm was consistent with the indoleacrylate and dehydrolactam functionalities.

In the oxidation reaction mixture of **10** we isolated, in 9.7% yield, a further oxidation product, spectroscopic investigation led to the assignment of structure **22**.

In addition to the $M^{+\cdot}$ at m/z 382 (16 amu more than **13**) and UV absorption at 230, 285, 330 nm,

relevant structural information was deduced from the NMR spectra. The ^{1}H-NMR spectrum contained a singlet at δ 4.55 due to C-21H, an AB system at δ 2.45 and 2.07 (J=16Hz) for C-17H$_2$ and a multiplet at δ 4.25 (overlapped on the signal of the methylene of the ethyl ester group) for one proton at C-5, deshielded by the amide carbonyl group. The last mentioned signal has a small long-range coupling to C-21H (COSY spectrum) due to a W-arrangement. The ^{13}C spectrum showed down-field shift for the C-21 doublet at δ 79.4 and for the singlet of C-7 at 62.0 (with respect to 68.1 and 56.7 for 3-oxo-vincadifformine ethyl ester) in agreement with the presence of an oxygen atom on these carbons. Although these data unequivocally support the presence of an oxygen bridge between C-7 and C-21, the relative stereochemistry of the molecule could not be ascertained.



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Refluxing the 3-oxosecodine **13** in toluene for 8h converted it to the target (±)-3-oxovincadifformine ethyl ester **14** in almost quantitative yield. The expected *cis*-relationship between C-21H and the ethyl appendage at C-20 was deduced from the fact that the NMR spectra of **13** and (±)-3-oxovincadifformine[21] were identical, except for ester functions.

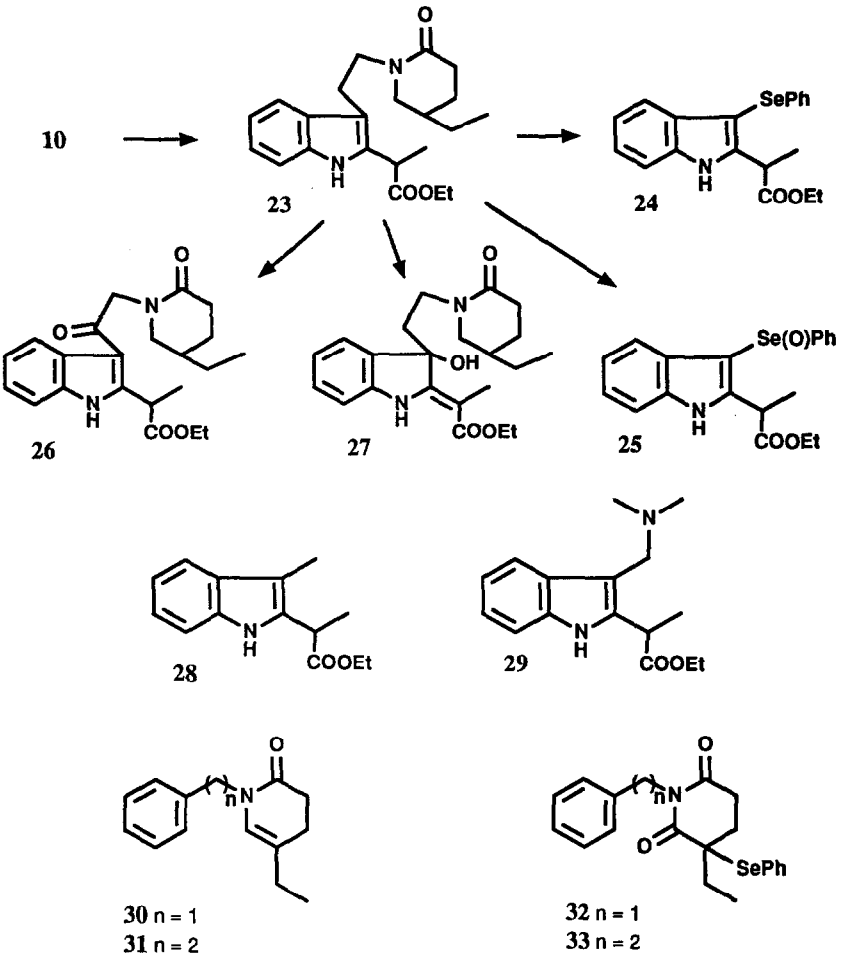
Thus, although the initial synthetic plan reported in Scheme 2 could not be followed, access was obtained to the pentacyclic *Aspidosperma* skeleton. After Kuehne's reports,[6,7] this is the third example of the isolation of a secodine intermediate during the synthesis of an *Aspidosperma* alkaloid, and gives further support to the biogenetic proposal that this class of naturally occurring compounds derives from the fragmentation of *Strychnos* precursors.

With regard to the formation of **13** from **10**, an over-simplified explanation is the direct dehydrogenation of the α-substituted propionate moiety to the corresponding acrylate.[22] However, we have performed several experiments that ruled out this possibility completely, and led to the suggestion of a more plausible mechanistic pathway.

Catalytic hydrogenation of **10** furnished in quantitative yield the lactam **23** as a mixture of two main diastereoisomers (NMR). When **23** was subjected to the action of BSA in benzene at 25°C, four products were formed: the selenide **24** (15 %) and the selenoxide **25** (9.5 %) deriving from the cleavage of the side chain at C-7, the ketolactam **26** (14 %) and hydroxyindolenine **27** (13 %), the product of allylic hydroxylation. No compounds containing the acrylate moiety could be detected, at least in isolable amount.

The formation of the selenide **24** seems to be a common behaviour of 2-indolylpropionates substituted by an alkyl group at position 3 of the indole nucleus. In fact, on reaction with BSA the indolylpropionates **28** and **29** furnishes **24** as the unique product in 58 % and 64 % yield respectively.

The MS spectrum of the ketolactam **26** displayed intense complementary fragments at m/z 244



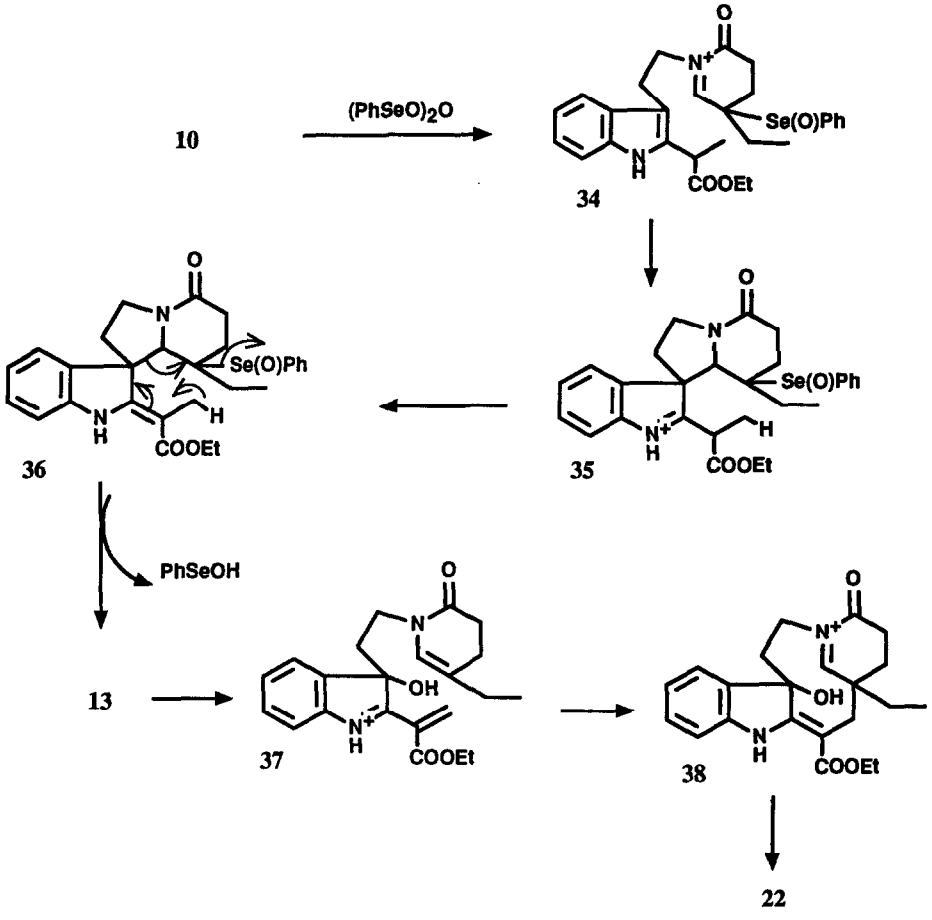
($C_{14}H_{14}NO_3$) and 140 due to the cleavage of the C5-C6 bond. The main feature of the ^{1}H-NMR spectrum was the presence of two AB systems at δ 4.71, 4.91 and δ 4.73, 4.93 due to the isolated C-5H_2 of the two diastereoisomers.

The formation of these products can be explained by an electrophilic attack of a $[PhSeO]^+$ species (or equivalent) at the β-position of the indole nucleus[22] and indicates that the 2-substituted propionate moiety is not affected by the oxidant, at least in these conditions.

On the other hand, the enamide double bond is highly reactive, as suggested by literature data and by the formation of the selenylimides **32** and **33** upon exposure of the N-benzyl and N-phenethylsubstituted unsaturated lactams **30**[19] and **31**[23] to BSA.

The accumulated evidences led to the mechanism depicted in Scheme 4, the initial step of which is the electrophilic attack by $[PhSeO]^+$ on the enamide double bond to produce the acyliminium salt **34.** Intramolecular capture of this reactive species by nucleophilic β-carbon of indole generates the tetracyclic

indoleninium ion **35** which on deprotonation gives the thermodynamic anilinoacrylate isomer **36**. Benzeneselenenic acid elimination affords the final product **13**.



Scheme 4

The formation of the oxocyclic compound **22** deserves a closing comment. Once **13** has been formed, further attack by BSA produces the highly reactive hydroxy-1-azadienium ion **37** by allylic hydroxylation. This suffers an annulation process by nucleophilic attack of C-20 to C-17 with concomitant intramolecular capture by hydroxy group.

In conclusion, we have developed an approach to the *Aspidosperma* alkaloid (±)-3-oxovincadifformine ethyl ester **14** by thermal cyclization of a stable secodine intermediate. The production of the last mentioned compound was achieved by the dehydrogenation of the corresponding propionate with benzeneseleninic anhydride and a pertinent mechanism has been proposed. This finding highlights the versatility of this reagent and broadens its applications in organic synthesis.

EXPERIMENTAL

IR spectra were recorded on Perkin-Elmer 681 spectrometer for chloroform solutions. UV spectra on a Perkin-Elmer 554 for methanol solutions. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker WP-80 (^{1}H, 80 MHz; ^{13}C, 20.1 MHz), Varian XL-200 (^{1}H, 200 MHz; ^{13}C, 50.2 MHz) and Bruker AC-300 (^{1}H, 300 MHz; ^{13}C, 75.4 MHz) spectrometers using $CDCl_3$ as solvent unless otherwise stated. EI and FAB mass spectra in the positive mode were determined on VG 70-70 EQ-HF instrument equipped with its standard sources. TLC data were obtained with Merck 60F-254 precoated silica gel on alumina sheets. Flash chromatography (FC) was carried out using Merck Kieselgel 60, 230-400 mesh. Preparative tlc (PLC) was performed on 0.25 thick layers of Merck silica gel HF_{254} coated on 20 X 20 cm glass plates.

Ethyl 2-methyl-3-chloro-3-oxopropanoate. 22 gr (0.126 mol) of diethyl methylmalonate were dissolved in EtOH (100 ml) with 8.11 gr (0.151 mol) of KOH, and stirred at r.t.. After 24 h the solvent was evaporated and water (100 ml) was added to the residue. The solution was acidified (pH 3) with HCl 1N and extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4 and after removal of the solvent at low temperature, gave 9.8 gr (53%) of mono-acid. ^{1}H-NMR (300 MHz) δ 1.26 (3H, t, J=7.2 Hz), 1.42 (3H, d, J=7.5 Hz), 3.45 (2H, q, J=7.5 Hz), 4.20 (1H, q, J=7.2 Hz), 10.3 (1H, bs). The mono-acid was directly added to 16.5 gr (0.13 mol) of thionyl chloride and the reaction mixture was stirred at 40° C for 4 h. Excess of thionyl chloride was removed by vacuum distillation (40-60° C, 4 mm). The remaining brown liquid (18.8 gr. 91%) was essentially pure acid chloride which was utilized directly in the next step.

{2-[2-(Methyl)-2-(Methoxycarbonyl)-acetamido]benzyl}triphenyl phosphonium Bromide (16). Ethyl 2-methyl-3-chloro-3-oxopropanoate (3.18 gr, 21 mmol) dissolved in CH_2Cl_2 (30 ml) was slowly dropped into a stirred mixture of (2-aminobenzyl)triphenylphosphonium bromide **15**[11] (8.78 gr, 19.5 mmol), obtained from reaction between 2-aminobenzyl alcohol and triphenylphosphine hydrobromide,[12c] and CH_2Cl_2 (150 ml). Pyridine (28.5 mmol) was then added dropwise, and the resultant mixture heated under reflux for 30 min.. After cooling to r.t. the reaction mixture was washed with 5% H_3PO_4 (20 ml) and 15% aq. Na_2CO_3 (20 ml). The combined organic phases were washed with H_2O (2 X 60 ml) and dried with Na_2SO_4. After removal of the solvent, the crude product was obtained and treated with dry ether. The solid was separated to give 11.2 gr (97%) of white product: $C_{26}H_{25}BrNP$ (576.47) calc. C(64.59), H(5.42), N(2.42) found. C(64.01), H(5.11), N(2.51). M.p. > 230° C dec.

Ethyl 2-(indol-1H-2-yl) propanoate (17). 13.03 gr (22 mmol) of amide **16** was suspended in dry toluene (200 ml) and heated under reflux for 30 min.. A portion of toluene (50 ml) was removed by distillation. The concentrated mixture was allowed to cool, then 2.53 gr (22.3 mmol) of tBuOK were added in six portions, and the mixture heated under reflux for 3 h. The cooled mixture was then filtered, the filtrate was concentrated to a volume of 50 ml, and addition of Et_2O (80 ml) caused precipitation of most of the phosphine oxide formed. The filtrated was concentrated. The resulting mixture was chromatographed on silica gel with Hexane/CH_2Cl_2/EtOAc 4:2:1 to obtain 2.1 gr (64%) of oily **17**: R_f = 0.74 ($CHCl_3$/MeOH/NH_4OH 90:10:1); IR ($CHCl_3$) 3460,1740 cm^{-1}; ^{1}H-NMR (200 MHz) δ 1.26 (3H, t, J=7.2 Hz), 1.61 (3H, d, J=7.6 Hz), 3.93 (1H, q, J=7.6 Hz), 4.18 (2H, q, J=7.2 Hz), 6.35 (1 H, bs), 7.02-7.2 (2H, m), 7.32 (1H, d, J=7.5 Hz), 7.55 (1H, d, J=7.5 Hz), 8.5 (1H, bs); ^{13}C-NMR (20.1 MHz) δ 14.2, 17.6, 39.5, 61.4, 100.3, 110.9, 119.9, 120.3, 121.8, 128.3, 132.0, 136.4, 173.8; EIMS m/z 217(76), 144(100);

HRMS calc. for $C_{13}H_{15}NO_2$: 217.1102. found 217.1132.

Ethyl 2-[3-(E)-(2-Nitroethenyl)-indol-1H-2-yl]propanoate (18). To a stirred solution of N,N-dimethyl-2-nitroethenamine (1.68 gr, 14.5 mmol) in CH_2Cl_2 (20 ml), CF_3COOH (2.6 ml) was added dropwise at 0° C, followed by a solution of **17** (2.09 gr, 9.6 mmol) in CH_2Cl_2 (30 ml). Stirring was continued at 0° C for 1h and then at 20° C for 6h. After removal of the solvent, the residue was chromatographed with $CHCl_3$ over silica gel to obtain 1.8 gr (65%) of amorphous **18**: R_f = 0.25 (Hexane/$CHCl_3$/EtOAc 4:2:1); IR ($CHCl_3$) 3410, 1720, 1615, 1490 cm^{-1}; ^{1}H-NMR (200 MHz) δ 1.30 (3H t, J=7.2 Hz), 1.65 (3H, d, J=7.5 Hz), 4.24 (2H, q, J=7.2 Hz), 4.26 (1, q, J=7.5 Hz), 7.2-7.8 (4H, m), 7.83 (1H, d, J=10 Hz), 8.31 (1H, d, J=10 Hz), 9.6 (1H, bs); ^{13}C-NMR (50.2 MHz) δ 13.9, 19.9, 36.7, 61.8, 105.7, 112.1, 120.3, 123.9, 123.9, 124.9, 132.2, 132.4, 136.2, 144.8, 173.2; EIMS m/z 288(52), 215(18), 169(100); HRMS calc. for $C_{15}H_{16}N_2O_4$: 288.1110. found 288.1143.

Ethyl 2-[3-(2-Nitroethyl)-indol-1H-2-yl]propanoate (19). To a solution of 1.5 gr (5.2 mmol) of **18** in 30 ml of THF-MeOH 10:1, 246 mg (6.5 mmol) of sodium borohydride were added in four portions. The reaction mixture was stirred for 40 min. at r.t. then quenched with water, and extracted with ether (3 X 40 ml). The combined organic layers were washed successively with water and brine, dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. Nearly pure product was obtained which could be purified by passing it through a short column of silica gel ($CHCl_3$/EtOAc 9:1) to yield 1.4 gr (93%) of **19** as a foam: R_f = 0.61 ($CHCl_3$/EtOAc 9:1); IR ($CHCl_3$) 3440, 1720, 1545 cm^{-1}; ^{1}H-NMR (300 MHz) δ 1.27 (3H, t, J=7.2 Hz), 1.55 (3H, d, J=7.5 Hz), 3.35-3.60 (2H, m), 4.05 (1H, q, J=7.5 Hz), 4.10-4.27 (2H, m), 4.61 (2H, t, J=7.7 Hz), 7.13 (1H, t, J=8 Hz), 7.19 (1H, t, J=8 Hz), 7.34 (1H, d, J=8 Hz), 7.50 (1H, d, J=8 Hz), 8.6 (1H, bs); ^{13}C-NMR (75.4 MHz) δ 14.7, 19.6, 23.2, 37.4, 62.1, 75.8, 106.5, 111.9, 118.3, 120.6, 123.0, 127.7, 134.8, 136.8, 174.0; EIMS m/z 290(75), 244(44), 230(29), 217(34), 170(100), 156(56); HRMS calc. for $C_{15}H_{18}N_2O_4$: 290.1266. found 290.1224.

Ethyl 2-[3-(2-aminoethyl)-indol-1H-2-yl]-propanoate (9). 715 mg (2.46 mmol) of **19** in EtOH (40 ml) were hydrogenated over PtO_2 (0.4 gr). After 20h the catalyst was removed by filtration under N_2, the filtrate evaporated at 20° C. The residue was chromatographed on silica gel with $CHCl_3$/MeOH/NH_4OH 90:10:1 to obtain 517 mg (80%) of **9** as an amorphous solid: R_f = 0.44 ($CHCl_3$/MeOH/NH_4OH 90:10:1); IR ($CHCl_3$) 3440, 1720, 1510 cm^{-1}; ^{1}H-NMR (300 MHz) δ 1.23 (3H, t, J=7.1 Hz), 1.54 (3H, d, J=7.5 Hz), 2.8-3.0 (4H, m), 3.5 (2H, bs, NH_2), 4.1 (1H, q, J=7.5 Hz), 4.15 (2H, q, J=7.1 Hz), 7.07 (1H, t, J=7.7 Hz), 7.15 (1H, t, J=7.7 Hz), 7.32 (1H, d, J=7.7 Hz), 7.55 (1H, d, J=7.5 Hz), 8.6 (1H, bs, NH); ^{13}C-NMR (20.1 MHz) δ 14.2, 19.0, 28.4, 37.2, 42.8, 61.3, 109.9, 111.0, 118.7, 119.4, 121.9, 128.2, 133.6, 135.9, 174.4; EIMS m/z 260(30), 230(74), 156(100); HRMS calc. for $C_{15}H_{20}N_2O_2$: 260.1525. found 260.1547.

Preparation of Indoloazepinone 20a. A solution of 10 mg (0.036 mmol) of **9** in 2 ml of benzene containing p-toluenesulfonic acid (1 mg) was refluxed for 20h. The lactone **20a** (8 mg, 87%) was isolated by PLC ($CHCl_3$/MeOH 90:10): R_f = 0.62 ($CHCl_3$/MeOH/NH_4OH 90:10:1); ^{1}H-NMR (300 MHz) δ 1.62 (3H, d, J=7.3 Hz), 3.81 (1H, q, J=7.3 Hz), 6.90-7.40 (4H, m, arom); EIMS 214 (M^+, 40), 170(15), 144; HRMS calc. for $C_{13}H_{14}N_2O$: 214.1106. found 214.1120.

3-Oxo-16,17-dihydrosecodine (10). Ethyl 4-formylhexanoate (130 mg, 0.76 mmol), ethyl-2-[3-Aminoethyl-indol-1H-2-yl]-propionate **9** (200 mg, 0.76 mmol), and dry toluene (20 ml) were placed in a round-bottomed flask equipped with a Dean-Stark trap. The reaction mixture was heated at

reflux for 2h, and 5 ml of the toluene-water azeotrope was drained off. An additional 10 ml of toluene was added and the solution was heated at 95° C for 10h. The reaction mixture was heated to reflux, and 8 ml of the toluene-ethanol azeotrope was drained off. The remaining solvent was removed. The residue was chromatographed over a column of silica gel eluted with Hexane/EtOAc 85:15 to give 138 mg (49%) of product **10**: R_f = 0.40 (EtOAc); ^{1}H-NMR (200 MHz) δ 0.88 (3H, t, J=7.9 Hz), 1.24 (3H, t, J=7.5 Hz), 1.55 (3H, d, J=6.9 Hz), 1.93 (2H, q, J=7.9 Hz), 2.15 (2H, t, J=7.5 Hz), 2.48 (2H, t, J=7.5 Hz), 2.93 (1H, dt, J=15, 7.5 Hz), 3.03 (1H, dt, J=15, 7.5 Hz), 3.64 (2H, t, J=7.9 Hz), 4.0-4.3 (3H, m), 5.56 (1H, bs), 7.08 (1H, dbd, J=6.2, 7.5 Hz), 7.15 (1H, dbd, J=6.2, 7.1 Hz), 7.31 (1H, bd, J=7.5 Hz), 7.59 (1H, bd, J=7.1 Hz), 8.5 (1H, bs, NH); ^{13}C-NMR (20.1 MHz) δ 12.5, 14.0, 19.1, 23.5, 24.0, 26.5, 31.5, 37.1, 47.5, 61.5, 109.1, 110.9, 118.5, 119.5, 121.0, 122.1, 123.9, 128.2, 133.5, 136.0, 169.1, 174.2; EIMS m/z 368(30), 243(100), 230(68), 170(42), 156(65); HRMS calc. for $C_{22}H_{28}N_2O_3$: 368.2100. found 368.2143.

Ethyl spiro-β-anilino acrylate (11). 3-Oxo-16,17-dihydrosecodine **10** (10 mg, 0.027 mmol) was dissolved in CH_2Cl_2 (3 ml) and titanium(IV)chloride (5 µl, 0.036 mmol, 1M CH_2Cl_2 solution) was added at 0° C. After 30 min. the mixture was warmed to r.t.. During the period of 72 h, 49 µl (0.35 mmol) of titanium(IV)chloride was added. The solution was quenched with saturated $NaHCO_3$ 5% solution and extracted with CH_2Cl_2, and the combined organic extracts were dried, filtered and concentrated. The residue was purified by PLC (Et_2O), affording **11** (6.6 mg, 66%): R_f = 0.15 (Et_2O); UV (MeOH) λ_{max} 228, 300, 330 nm; ^{1}H-NMR (300 MHz) δ 0.63 (3H, t, J=8 Hz), 0.94 (1H, dq, J=14, 7 Hz), 1.09-1.45 (3H, m), 1.32 (3H, t, J=8 Hz), 1.78-1.90 (1H, m), 2.01-2.15 (1H, m), 2.05 (3H, s), 2.28 (1H, ddd, J=18, 11, 6 Hz), 2.49 (1H, dd, J=18, 5 Hz), 2.72 (1H, dt, J=10, 12.5 Hz), 3.69 (1H, td, J=10, 4 Hz), 4.01-4.25 (3H, m), 4.15 (1H, d, J=7 Hz), 6.75-6.85 (3H, m) 7.14 (1H, td, J=8 2 Hz), 10.15 (1H, bs, NH); ^{13}C-NMR (75.4 MHz) δ 10.9, 13.0, 15.0, 23.8, 26.2, 32.0, 33.7, 38.9, 43.7, 60.5, 60.7, 67.1, 91.3, 108.3, 121.4, 123.9, 129.1, 132.5, 143.6, 160.5, 170.5, 171.6; EIMS m/z 368(35), 243(100), 230(45); HRMS calc. for $C_{22}H_{28}N_2O_3$: 368.2100. found 368.2146.

3-Oxo-secodine ethyl ester (13). To a solution of 100 mg (0.271 mmol) of 3-oxo-16,17-dihydrosecodine **10** in 20 ml of dry benzene, was added 49 mg (0.136 mmol) of benzeneseleninic anhydride. The mixture was stirred for 1h at r.t., then heated at 50° C for 12 h. A second portion of 49 mg (0.136 mmol) of BSA was added and the solution was stirred for 4 h. The solvent was evaporated, and the secodine was chromatographed on silica gel. Elution with $CHCl_3$/EtOAc 9:1 provided 35 mg (35%) of secodine **13** and 10 mg (9.7%) of product **22**.

Product **13**: amorphous; R_f = 0.32 ($CHCl_3$/EtOAc 9:1 CAS blue/aqua green); UV (MeOH) λ_{max} 219, 227, 236 nm; ^{1}H-NMR (300 MHz) δ 0.91 (3H, t, J=7.9 Hz), 1.38 (3H, t, J=7.5 Hz), 2.18 (2H, t, J=8 Hz), 2.48 (2H, t, J=8 Hz), 3.10 (2H, t, J=7.2 Hz), 3.70 (2H, t, J=7.2 Hz), 4.15 (2H, q, J=7.9 Hz), 4.32 (2H, q, J=7.5 Hz), 5.60 (1H, s), 6.32 (1H, d, J=1 Hz), 6.56 (1H, d, J=1 Hz), 7.10 (1H, t, J=8 Hz), 7.20 (1H, t, J=8 Hz), 7.35 (1H, d, J=8 Hz), 7.65 (1H, d, J=8 Hz), 9.39 (1H, bs, NH); ^{13}C-NMR (75.4 MHz) δ 12.9, 14.7, 24.8, 25.4, 27.3, 31.8, 47.5, 62.1, 110.0, 111.8, 119.4, 120.2, 120.9, 123.5, 124.3, 127.1, 128.3, 130.0, 131.5, 135.8, 168.1, 169.4; EIMS m/z 366(33), 241(100), 228(64), 195(68), 168(24), 154(45), 138(13); HRMS calc. for $C_{22}H_{26}N_2O_3$: 366.1943. found 366.1986; calc. for $C_{14}H_{14}NO_2$ 228.1024 found 228.1009.

Product **22**: amorphous; R_f = 0.20 ($CHCl_3$/EtOAc 9:1 CAS pink/orange); UV (MeOH) λ_{max} 230, 285, 330 nm; IR ($CHCl_3$) 3440, 1670, 1630, 1600 cm^{-1}; ^{1}H-NMR (300 MHz) δ 1.15 (3H, t, J=7.8 Hz), 1.32

(3H, t, J=7.5 Hz), 1.42 (1H, bd, J=12 Hz), 1.61-1.80 (3H, m), 1.85-2.05 (2H, m), 2.05-2.20 (1H, m), 2.07 (1H,B part of AB system, J=16 Hz), 2.35-2.45 (2H, m), 2.45 (1H,A part of AB system, J=16 Hz), 4.15-4.35 (3H, m), 4.55 (1H, s), 6.91 (1H, d, J=7.5 Hz), 7.0 (1H, s), 7.12 (1H, t, J=7.5 Hz), 7.28 (1H, t, J=7.5 Hz), 7.35 (1H, d, J=7.5 Hz); ^{13}C-NMR (300 MHz) δ 8.5, 15.0, 28.5, 29.0, 33.5, 34.0, 40.5, 41.4, 44.3, 62.0, 62.1, 79.4, 86.1, 112.0, 119.0, 123.1, 124.9, 135.5, 147.1, 165.2, 167.8, 172; EIMS 382(100), 353(10), 244(23), 185(20); HRMS calc. for $C_{22}H_{26}N_2O_4$: 382.1892. found 382.1845.

3-Oxovincadifformine ethyl ester (14). A solution of 3-oxo-secodine **13** (13 mg, 0.035 mmol) in 5 ml of toluene was heated at 110° C for 8 h. From the cooled reaction mixture the solvent was evaporated at 50° C under vacuum, and the residue was purified by PLC eluting with EtOAc (NH_3-saturated atmosphere) to give amorphous **14** (12 mg, 92%): R_f = 0.3 (EtOAc/NH_4OH 99.5:0.5 CAS blue); ^{1}H-NMR (300 MHz) δ 0.7 (3H, t, J=7 Hz), 0.85 (3H, m), 0.98 (2H, m), 1.83 (1H, dd, J=5, 13 Hz), 1.91 (1H, d, J= 14 Hz), 1.93-2.15 (2H, m), 2.2-2.4 (3H, m), 2.65 (1H, dd, J=1.8, 14 Hz), 3.40 (1H, m), 3.46 (1H, bs), 4.10-4.45 (3H, m), 6.80-7.25 (4H, m), 9.0(1H, bs, NH); ^{13}C-NMR (75.4 MHz) δ 8.0, 15.0, 28.5, 29.2, 30.6, 31.8, 39.9, 41.1, 43.6, 57.1, 60.1, 68.8), 91.8, 110.2, 121.6, 122.2, 129.2, 134.9, 144.2, 164.3, 169.9, 172.1; EIMS m/z 382(100), 353(15), 244(31), 185(24); HRMS calc. for $C_{22}H_{26}N_2O_3$: 366.1943. found 366.1904.

3-Oxo-16,17,20,21-tetrahydrosecodine ethyl ester (23). 200 mg (0.543 mmol) of 3-oxo-16,17-dihydrosecodine **10** in EtOH (10 ml) were hydrogenated over Pd/C. After 3 hs the catalyst was removed by filtration under N_2, the filtrate evaporated at 20° C. The residue was chromatographed on silica gel with Et_2O to give 195 mg (97%) of product **23**: R_f = 0.1 (Et_2O); ^{1}H-NMR (300 MHz) δ 0.70-0.90 (3H, m), 1.10-1.45 (4H, m), 1.52 (3H, d, J=6.9 Hz), 1.60-1.81 (2H, m), 2.15-2.35 (2H, m), 2.70-2.81 (2H, m), 2.81-3.10 (6H, m), 3.91-4.31 (3H, m), 6.97 (1H, bt, J=7.1 Hz), 7.04 (1H, bt, J=7.1 Hz), 7.31 (1H, bd, J=7.1 Hz), 7.52 (1H, bd, J=7.1 Hz), 10.8 (1H, bs, NH); EIMS m/z 370(34), 243(57), 230(49), 170(100); HRMS calc. for $C_{22}H_{30}N_2O_3$: 370.2256. found 370.2208.

Oxidation of (23). 100 mg (0.270 mmol) of **23** were submitted to reaction with BSA in the same conditions described for preparation of **13**. The residue was chromatographed over a column of silica gel eluted with $CHCl_3$ to give **24** (15 mg, 15 %), **25** (10 mg, 9.5 %), **26** (14 mg, 14 %), **27** (13 mg, 13 %).

24: R_f = 0.24 (EtOAc/Hexane 4:1); ^{1}H-NMR (80 MHz) δ 1.28 (3H, t, J=7.1 Hz), 1.60 (3H, d, J=7.7 Hz), 4.14 (2H, q, J=7.1 Hz), 4.45 (1H, q, J=7.7 Hz), 6.90-7.70 (9H, m), 9.15 (1H, bs, NH); EIMS m/z 373(24), 300(36), 293(68), 220(57), 143(100); HRMS calc. for $C_{19}H_{19}NO_2Se$: 373.0581. found 373.0566.

25: R_f = 0.14 ($CHCl_3$/MeOH/NH_4OH 95:5:0.2); ^{1}H-NMR (300 MHz, 80° C) δ 1.28 (3H, t, J=7.1 Hz), 1.60 (3H, d, J=7.7 Hz), 3.99 (1H, q, J=7.7 Hz), 4.05-4.15 (2H, m), 7.01-7.61 (9H, m), 9.05 (1H, bs, NH); EIMS m/z 389(43), 316(67), 230(100); HRMS calc. for $C_{19}H_{19}NO_3Se$: 389.0530. found 389.0579.

26: R_f = 0.30 (Et_2O/NH_4OH 98.8:0.2); ^{1}H-NMR (300 MHz, d_6-DMSO, 90° C) δ 1.01 (3H, t, J=7.15 Hz, C-18H_3), 1.22 (3H, t, J=7.5 Hz, OCH_2CH_3), 1.43-2.05 (5H, m, C-15H_2, C-17H_3), 2.10-2.52 (3H, m, C-20H, C-14H_2), 3.05-3.45 (2H, m, C-21H_2), 4.15 (2H, q, J=7.5 Hz, OCH_2CH_3), 4.28 (1H, m, C-16H), 4.71 (1H, two A parts of two AB systems, J=17 Hz, C-5H), 4.92 (1H, two B portions of two AB systems, J=17 Hz, C-5H), 7.10-7.30 (2H, m, C-10H, C-11H), 7.52 (1H, d, J=8.5 Hz, C-12H), 7.88 (1H, d, J=8.5 Hz, C-9H), 11.8 (1H, bs, NH); EIMS m/z 384(57), 368(35), 339(67), 244(100), 140(89); HRMS calc. for $C_{22}H_{28}N_2O_4$: 384.2049. found 384.2087.

27: R_f = 0.2 (Et_2O/NH_4OH 98.8:0.2); ^{1}H-NMR (300 MHz) δ 0.77-0.81 (3H, m, C-18H_3), 1.15-1.28 (3H, m, OCH_2CH_3), 1.61 (1H, bs, OH), 1.95 (3H, s, C-17H_3), 4.01-4.44 (3H, m, C-16H, OCH_2CH_3), 7.11 (1H, t, J=7.1 Hz, C-10H), 7.19 (1H, t, J=7.1 Hz, C-11H), 7.31 (1H, d, J=7.1 Hz, C-12H), 7.62 (1H, d, J=7.1 Hz, C-9H), 8.4 (1H, bs, NH); EIMS m/z 369(36), 259(100), 242(46), 196(57); HRMS calc. for $C_{22}H_{30}N_2O_4$: 386.2206. found 386.2285.

Ethyl 2-[3-methyl-indol-1H-2-yl] propanoate (28). To a solution of 300 mg (1.3 mmol) of **17** in DMF (5 ml), 138 µl (1.52 mmol) of $POCl_3$ dissolved in DMF (1 ml) were added at room temperature. After 24h at 35° C the solution was poured into $NaHCO_3$ (5% aqueous solution) and extracted with EtOAc. The crude product (285 mg; 84%) was immediately dissolved in CH_2Cl_2 (20 ml). 543 mg (1.68 mmol) of ZnI_2 and 318 mg (5 mmol) of $NaCNBH_3$ were added at room temperature. After 2 h aqueous 2N NH_4Cl solution was added and the organic layer was separated. By purification (FC Et_2O/Hexane 1:1) compound **28** was obtained (120 mg; 25%): R_f = 0.42 (Hexane/Et_2O 1:1); ^{1}H-NMR (80 MHz) δ 1.25 (3H, t, J=7.5 Hz), 1.55 (3H, d, J=8 Hz), 2.25 (3H, s), 3.80-4.40 (3H, m), 6.90-7.60 (4H, m), 10.25 (1H, bs, NH); HRMS calc. for $C_{14}H_{17}NO_2$: 231.1259. found 231.1287.

Ethyl 2-[3-N,N-dimethylaminomethyl-indol-1H-2-yl] propanoate (29). To a solution of 500 mg (2.30 mmol) of **17**, 317 µl (2.53 mmol) of dimethylamine (40% aqueous solution) and 187 µl (2.30 mmol) of formaldehyde (37% aqueous solution), acetic acid (5 ml) was added at 0° C. After 50 min. the reaction mixture was treated with $NaHCO_3$ (5% aqueous solution) and ether. The ether extracts were washed with water, dried (Na_2SO_4) and evaporated. The residue was purified by FC ($CHCl_3$/MeOH/NH_4OH 90:10:1) to give 140 mg (22%) of **29**: R_f = 0.49 ($CHCl_3$/MeOH/NH_4OH 90:10:1); ^{1}H-NMR (300 MHz) δ 1.25 (3H, t, J=7.3 Hz), 1.61 (3H, d, J=7.8 Hz), 2.31 (6H, s), 3.3-3.85 (2H,AB system,-CH_2N), 4.10-4.30 (3H, m), 7.05-7.85 (4H, m), 9.10 (1H, bs, NH); EIMS m/z 274(20), 230(100), 185(22); HRMS calc. for $C_{16}H_{22}N_2O_2$: 264.1681. found 264.1664.

Preparation of 31. Ethyl 4-formylhexanoate (200 mg, 1.16 mmol), phenetylamine (140 mg, 1.16 mmol), and dry toluene (20 ml) in the same conditions described for the preparation of **10** gave after FC purification (EtOAc/Hexane 8:2) 250 mg (94%) of oily compound **31**: R_f = 0.45 ($CHCl_3$); IR ($CHCl_3$) 1650 cm^{-1}; ^{1}H NMR (80 MHz) δ 0.95 (3H, t, J=7.3 Hz), 1.98 (2H, q, J=7.3 Hz), 2.0-2.6 (4H, m), 2.85 and 3.65 (4H, AA'BB' system $PhCH_2CH_2N$), 5.55 (1H, quint, J=1.2 Hz), 7.0-7.3 (5H, m); HRMS calc. for $C_{15}H_{19}NO$: 229.1467. found 229.1452

Preparation of 32. Obtained from **30**[18] in 65% yield using the same conditions described for the preparation of **13**. Purification with FC using EtOAc/Hexane 8:2. R_f = 0.69 (Hexane/EtOAc 4:1); ^{1}H-NMR (300 MHz) δ 0.91 (3H, t, J=7 Hz), 1.82 (1H, dq, J=14, 7 Hz), 1.92 (1H, dq, J=14, 7 Hz), 2.01 (1H, ddd, J=14.1, 6.4, 2.5 Hz), 2.18 (1H, ddd, J=14.1, 13.7, 5.1 Hz), 2.80 (1H, ddd, J=18.5, 5.1, 2.5 Hz), 3.02 (1H, ddd, J=18.5, 13.7, 6.4 Hz), 4.78 (1H, d, J=13.0 Hz), 5.04 (1H, d, J=13.0 Hz), 7.11-7.41 (10H, m); EIMS m/z 387(15), 230(47), 152(100); HRMS calc. for $C_{20}H_{21}NO_2Se$: 387.0737. found 387.0745.

Preparation of 33. Obtained from **31** in 70 % yield using the same conditions described for the preparation of **13**. Purification by FC using EtOAc/Hexane 7:3 as eluent. R_f = 0.43 ($CHCl_2$/Hexane 4:1); IR ($CHCl_3$) 1670, 1720 cm^{-1}; ^{1}H NMR (300 MHz) δ 0.89 (3H, t, J=7 Hz), 1.87 (1H, dq, J=14, 7 Hz), 1.91 (1H, dq, J=14, 7 Hz), 1.97 (1H, ddd, J=14.1, 13.7, 5.1 Hz), 2.10 (1H, td, J=13.7, 5.1 Hz), 2.65-2.84 (3H, m), 3.02 (1H, ddd, J=18, 13.7, 6.8 Hz), 3.9 (2H, AA' part of AA'BB' system), 7.1-7.6 (10H, m); FABMS

m/z 402(MH^+,67), 244(100). 401.0894. found 401.0853.

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