26 μL (0.36 mmol) of acetyl chloride. After 6 h at room temperature, the mixture was partitioned between water and dichloromethane. Concentration of the organic extracts and chromatography of the residue on 10 g of silica gel, eluting with 1:1 ethyl acetate/hexanes gave 38 mg (35%) of material which crystallized from ether with mp 203–205 °C (reported[8] 203–205 °C).[37] TLC (silica gel, ethyl acetate) R_f 0.24; UV (methanol) λ_{max} 220, 253, 303 nm; IR (film) ν_{max} 3680, 3035, 2960, 2880, 2835, 2805, 2715, 1740, 1610, 1595, 1500, 1430, 1370, 1240, 1220, 1170, 1140, 1120, 1085, 1030, 970, 940, 735 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 0.49 (t, 3 H^{18}), 1.13 (m, 1 H^{19}), 1.62 (m, 1 H^{19}), 2.08 (s, 3 H^{COCH_3}), 2.33 (m, 2 H^6), 2.51 (m, 1 H^5), 2.67 (s, 3 H^{NCH_3}), 2.82 (d, 1 H^3), 3.46 (m, 2 $H^{3,5}$), 3.75 (s, 1 H^2), 3.79 (2s, 6 $H^{2\,OCH_3}$), 5.23 (d, 1 H^{15}), 5.46 (s, 1 H^{17}), 5.84 (m, 1 H^{14}), 6.08 (d, 1 H^{12}), 6.30 (dd, 1 H^{10}), 6.89 (d, 1 H^9), 9.58 (br s, 1 H^{OH16}); direct insertion probe 70-eV mass spectrum, m/z (relative intensity) 456 (M^+, 10), 296 (13), 282 (21), 189 (34), 188 (50), 174 (36), 173 (10), 162 (16), 161 (22), 136 (13), 135 (100), 122 (37), 121 (60), 108 (14), 107 (31). Anal. Calcd for $C_{25}H_{32}N_2O_6$: C, 65.77; H, 7.07; N, 6.14. Found: C, 66.01; H, 7.36; N, 6.02.

By the same procedure 30 mg of synthetic (-)-deacetylvindoline **35b**, prepared above, was acylated to give 17 mg (52%) of (-)-vindoline (**1b**). Alternatively, acetylation of 20 mg of **35b** with acetic anhydride in pyridine[14] gave 12 mg (55%) of (**1b**), mp 171–172 °C, crystallized from ether (reported[38,39] 174–175 °C, 164–165 °C); $[\alpha]^{25}_D$ –62° (*c* 0.26, methanol); reported[38] $[\alpha]_{600}$ –48°, $[\alpha]_{500}$ –69° (methanol), $[\alpha]^{20}_D$ –18° (chloroform). A sample of natural vindoline gave $[\alpha]^{23}_D$ –60° (*c* 0.10, methanol) and $[\alpha]^{23}_D$ –28° (*c* 0.10, chloroform). Acylation of 75 mg of (+)-deacetyl vindoline (**35c**) from above, gave 55 mg (67%) of (+)-vindoline (**1c**), $[\alpha]^{23}_D$ +57° (*c* 0.088, methanol); mp 170–172 °C, crystallized from ether.

(-)-Vindorosine (2). Acylation of 50 mg of the diol **36** according to the above generation of vindoline (**1a–c**) provided 59 mg (99%) of unchromatographed vindorosine **2**, mp 165–167 °C from ether (reported[33] 165 °C). TLC (silica gel, ethyl acetate) R_f 0.39 (CAS red); UV (ethanol) λ_{max} 218, 255, 305 nm; IR (film) ν_{max} 3020, 2960, 2860, 2800, 2720, 1732, 1600, 1465, 1230, 1040, 730 cm^{-1}; 270 MHz NMR ($CDCl_3$) δ 9.55 (s, 1 H^{OH16}), 7.19 (t, 1 H^{10}), 7.05 (d, 1 H^9), 6.83 (t, 1 H^{11}), 6.56 (d, 1 H^{12}), 5.90 (dd, 1 H^{14}), 5.50 (s, 1 H^{17}), 5.28 (d, 1 H^{15}), 3.82 (s, 3 H^{OCH_3}), 3.72 (s, 1 H^2), 3.48 (m, 2 $H^{3,5}$), 2.90 (d, 1 H^3), 2.70 (s, 3 H^{NCH_3}), 2.55 (m, 1 H^5), 2.45 (m, 2 H^6), 2.15 (s, 3 H^{COCH_3}), 1.70 (m, 1 H^{19}), 1.10 (m, 1 H^{19}), 0.44 (t, 3 H^{18}); direct insertion probe 70-eV mass spectrum, m/z (relative intensity) 426 (M^+, 16), 282 (12), 267 (13), 266 (42), 159 (10), 158 (45), 144 (12), 135 (100), 132 (8), 131 (8), 122 (17), 121 (22), 107 (15); $[\alpha]^{24}_D$ –31° (*c* 0.096 $CHCl_3$); reported[38] $[\alpha]^{16}_D$ –31° ($CHCl_3$). Anal. Calcd for $C_{24}H_{30}N_2O_5$: C, 66.97; H, 6.84; N, 6.79. Found: C, 66.65; H, 7.05; N, 6.39.

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A Short Stereoselective Synthesis of the Alkaloid Vincamine

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The indole alkaloid vincamine (1) has been prepared from 3,4-dihydro-β-carboline (3) in a six-step sequence. An imino Diels–Alder between 3 and methyl pentadienoate led to a mixture of indoloquinolizidines **4a** and **4b** which were directly deprotonated and alkylated affording indoloquinolizidine **5** as a single diastereoisomer. After a reduction–oxidation sequence compound **5** led to aldehyde **9**. This compound was directly transformed into vincamine (1) by treatment with methyl isocyanoacetate anion followed by an acidic and basic workup.

Vincamine (**1**),[1] a major alkaloid of Vinca minor used in the treatment of vascular diseases, has been the subject of a number of synthetic studies.[2] This Eburna alkaloid is biogenetically related to the Aspidosperma alkaloids,[3,4] and these two families show the same configurations at C_{20} and C_{21}.[5] Our strategy was first directed toward the synthesis of indolo[2,3-*a*]quinolizidines, bearing the appropriate configurations at these two centers. We anticipated that these compounds could be versatile synthons in the syntheses of both the above families of alkaloids.

Our recent work has demonstrated the synthetic usefulness of the imino Diels–Alder reaction in the preparation of octahydroindolo[2,3-*a*]quinolizidine derivatives,[6] which have been transformed into the Aspidosperma alkaloids vindorosine (**2a**) and vindoline (**2b**).[7] In this report we have applied the same reaction to a highly stereoselective synthesis of the Eburna alkaloid vincamine (1).

Thus, 3,4-dihydro-β-carboline (**3**)[8] was treated with methyl pentadienoate at 120 °C in chlorobenzene to afford two isomeric indoloquinolizidines **4a** and **4b** (total yield 69%) (Scheme I). The two compounds as a mixture were deprotonated at –70 °C with LDA–HMPA complex[9] (2.2 equiv) and alkylated at the same temperature with ethyl iodide (1 equiv). This led to the anticipated indolo-

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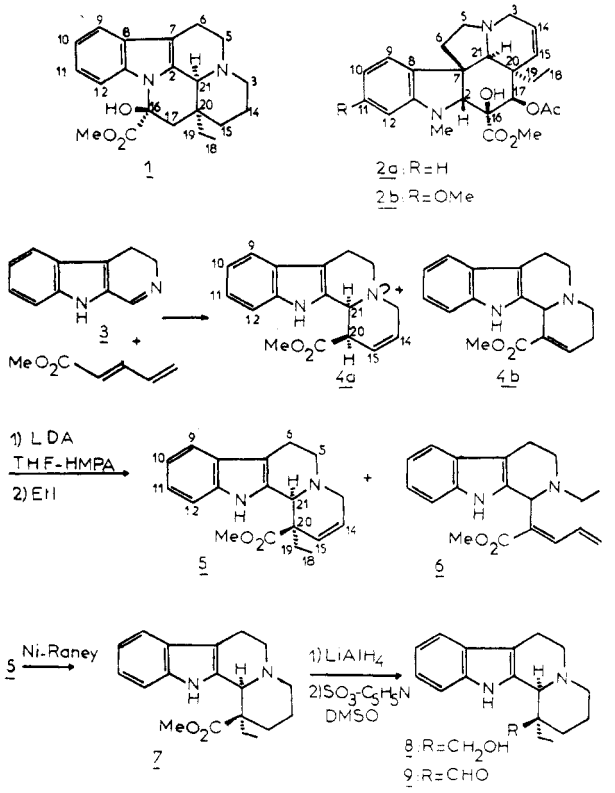
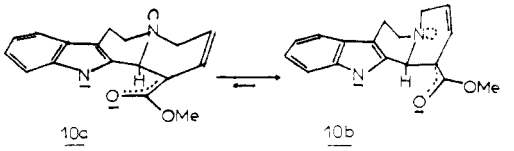
(9) Herrmann, J. L.; Kieczykowski, G. R.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 2433.

0022-3263/87/1952-0353$01.50/0

Scheme I



Scheme II

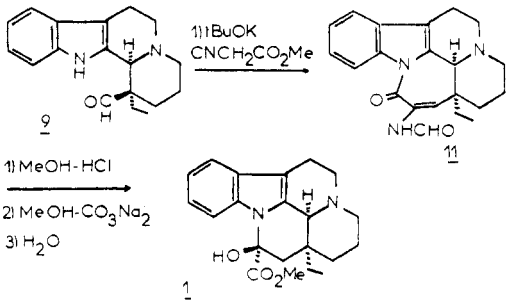


quinolizidine **5** (70%) together with a minor (9%) side product **6**, which was the result of N_b-alkylation followed by Hofmann elimination. The relative configurations at C_{20} and C_{21} in compound **5** were established by the following chemical correlation. Hydrogenation of indoloquinolizidine **5** gave rise to the saturated compound **7**[6] (96%), whose reduction with $LiAlH_4$ afforded the known alcohol **8**[10] (96%). The latter was oxidized with SO_3–C_5H_5N–Me_2SO to the target aldehyde **9**[10] (91%) (Scheme I).

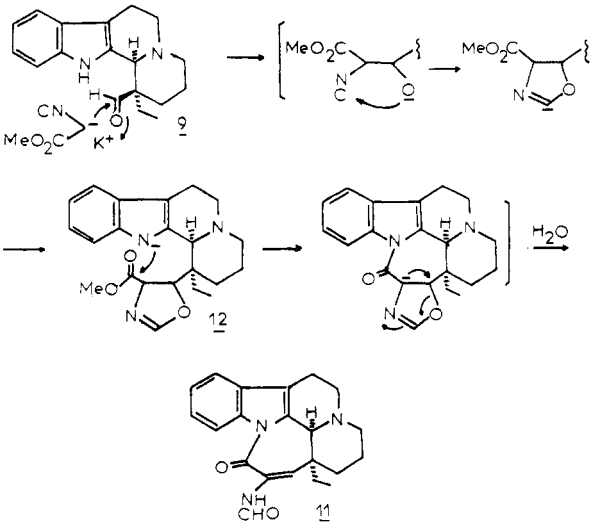
The stereoselective alkylation of the mixture of indoloquinolizidines **4a** and **4b** could be rationalized in terms of electronic interactions. As a matter of fact, the equilibrium which could exist between *trans*- and *cis*-quinolizidines **10a** and **10b** as the dianionic intermediate could be reversed in favor of the *cis*-quinolizidine **10b** because of charge repulsion between the ester enolate and the indole anion in *trans*-quinolizidine **10a**. Electrophilic attack of ethyl iodide from the convex face of conformer **10b** gave rise to the isolated diastereoisomer **5** (Scheme II).

With the requisite indoloquinolizidine **9** in hand, we next examined the last steps of the synthesis of vincamine (**1**). This aldehyde **9** was known to be easily isomerized under basic conditions by a retro-Mannich reaction.[10,11] Furthermore, its aldehyde is in an environment (neopentyl-like) which precludes nucleophilic attack of bulky reagents.

Scheme III



Scheme IV



In addition, the indole nitrogen bearing a relatively acidic hydrogen can be deprotonated easily with strong base. However, aldehyde **9** has been used in two syntheses of vincamine (**1**). In the first one,[10] this compound gave rise to the target alkaloid in a six-step sequence (overall yield $\simeq$ 8%). In a recent European patent[12] aldehyde **9** led in two steps to a mixture of vincamine (**1**) and three other compounds without stated yield.

Our goal at this stage of the synthesis was a direct, high-yield route to vincamine (**1**) from aldehyde **9**, which could be scaled up easily for an industrial process. It appeared that a nucleophilic bifunctional group would be necessary to transform aldehyde **9** into the homologous α-keto ester **15**, a direct precursor of vincamine (**1**). Alkyl isocyanoacetates which have been introduced by Schöllkopf[13] to perform a formamido-alkylidation seemed to be the reagents of choice.

Thus, exposure of the aldehyde **9** to the potassium salt of methyl isocyanoacetate in THF at −30 °C afforded the lactam **11** (85%) after warming to 0 °C and hydrolysis (Scheme III).

Treatment of the lactam **11** with hydrochloric acid in anhydrous methanol followed by treatment with an excess of sodium carbonate and hydrolysis completed the synthesis of vincamine (**1**) in 73% yield. It should be noted that vincamine (**1**) could be obtained in 45% overall yield from the aldehyde **9** in a one-pot experiment without isolation of lactam **11**.

The possible mechanism of the formation of lactam **11** is shown in Scheme IV. The nucleophilic attack of methyl

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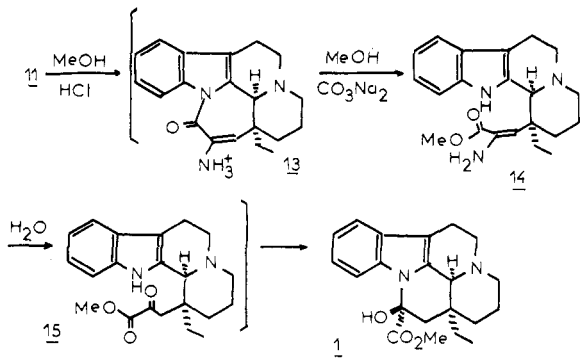
Scheme V



isocyanoacetate anion was followed by cyclization leading to the oxazoline intermediate **12**,[14] whose fragmentation gave rise to lactam **11**. Acidic hydrolysis of lactam **11** could lead to the enamino lactam hydrochloride intermediate **13**,[15] (Scheme V). In basic medium the lactam group of this intermediate is converted into a methyl ester and the enamine hydrolyzed to give a ketone. The α-keto ester **15** was known to cyclize spontaneously into vincamine (**1**). It is noteworthy that all these reactions were performed in a two- or even one-pot process. In summary, vincamine (**1**) was synthesized in a highly stereoselective manner in 24.5% overall yield from 3,4-dihydro-β-carboline (**3**). An enantioselective synthesis of this alkaloid and derivatives is in progress in our laboratory.

Experimental Section

IR spectra (ν, cm^{-1}, $CHCl_3$) were recorded on a Perkin-Elmer 297 spectrometer and UV spectra [CH_3OH, λ_{max}, nm (ϵ)] on a Jobin-Yvon Duospac 203 spectrometer. ^1H NMR spectra were obtained if not specified on a Brucker WM 400 spectrometer (δ = 0 (Me_4Si), $CDCl_3$). Coupling constants, J, are given in hertz; s, d, t, dd, and m indicate singlet, doublet, triplet, doublet of doublets, and multiplet, respectively. Biogenetical numbering[5] has been used for NMR spectra. Mass spectra were measured on an MS 50. Preparative-layer chromatography (preparative TLC) was performed with Kieselgel HF 254 (Merck) and column chromatography on Kieselgel 60 (70–230 mesh) (Merck).

Preparation of Indoloquinolizidines 4a and 4b. 1,4,6,7,12,12b-Hexahydroindolo[2,3-*a*]quinolizine-1-carboxylic Acid Methyl Ester (4a) and 3,4,6,7,12,12b-Hexahydroindolo[2,3-*a*]quinolizine-1-carboxylic Acid Methyl Ester 4b. 3,4-Dihydro-β-carboline (**3**) (3 g, 17.6 mmol) and pentadienoic acid methyl ester (2.35 g, 21 mmol) in chlorobenzene (10 mL) were heated at 120 °C for 90 min. After evaporation of chlorobenzene the residue was purified by chromatography (SiO_2, hexane–ethyl acetate 50:50) and afforded indoloquinolizidines **4a** (1.32 g, 4.67 mmol), mp 124 °C (ether–pentane), and **4b** (2.09 g, 7.4 mmol), mp 160 °C (ethyl acetate–pentane); total yield 69%.

4a: IR 3450, 2850, 2800, 2750 (Wenkert–Bohlmann bands),[16] 1725; ^1H NMR δ 8.51 (bs, 1 H, N_a–H), 7.48 (d, J = 7.5, 1 H) and 7.29 (d, J = 7.5, 1 H) (C_9–H and C_{12}–H), 7.13 (dd, J = 7.5, 1 H) and 7.06 (dd, J = 7.5, 1 H), (C_{10}–H and C_{11}–H), 5.96 (m, 1 H) and 5.81 (m, 1 H) (C_{14}–H and C_{15}–H), 4.03 (bd, $J_{20\text{-}21}$ = 9, 1 H, C_{21}–H), 3.85 (s, 3 H, CO_2CH_3); MS, m/e 282 $M^{\bullet+}$, 170 (100%), 169; UV 285, 292 (H_3O^+), 275, 282, 291. Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.51; H, 6.31; N, 9.94.

4b: IR 3450, 1690; ^1H NMR δ 8.68 (bs, 1 H) N_a–H, 7.47 (d, J = 7.5, 1 H) and 7.29 (d, J = 7.5, 1 H) (C_9–H and C_{12}–H), 7.26 (s, 1 H, C_{15}–H), 7.12 (dd, J = 7.5, 1 H) and 7.06 (dd, J = 7.5, 1 H) (C_{10}–H and C_{11}–H), 5.07 (bs, 1 H, C_{21}–H), 3.88 (s, 3 H, CO_2CH_3); MS, m/e 282 $M^{\bullet+}$ (100%), 281. UV 285, 292 (H_3O^+), 275, 283, 292. Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 71.82; H, 6.36; N, 10.01.

Preparation of Compounds 5 and 6. 14,15-Dihydro-17,18-didehydro-21-nor-1,14-secoeburnamenin-20-oic Acid Methyl Ester (5). BuLi (2.46 mL, 3.94 mmol, 1.6 M in hexane) was added to a solution of diisopropylamine (0.4 g, 3.96 mmol) in THF (1 mL) at −50 °C. The solution was warmed to −30 °C for 15 min and cooled to −70 °C before addition of HMPA (0.7 g, 3.9 mmol). After standing for 30 min at −70 °C, a solution of indoloquinolizidines **4a** and **4b** (0.5 g, 1.77 mmol) in THF (5.2 mL) was added to the solution of LDA–HMPA. The reaction medium was kept at −70 °C for 20 min and warmed at −40 °C for an additional 20 min before addition of ethyl iodide (0.283 g, 1.8 mmol). After 20 min at the same temperature, the mixture was hydrolyzed and extracted with ether. After the usual treatment the residue was purified by chromatography (SiO_2, hexane–ethyl acetate 50:50) and afforded **5** (0.385 g, 1.24 mmol) yield, 70% and **6** (0.049 g, 0.16 mmol) yield, 9%. **5**: IR 3400, 2850, 2800, 2750, 1710; ^1H NMR δ 7.89 (bs, 1 H, N_a–H), 7.48 (d, J = 7.5, 1 H) and 7.31 (d, J = 7.5, 1 H) (C_9–H and C_{12}–H), 7.15 (dd, J = 7.5, 1 H) and 7.08 (dd, J = 7.5, 1 H) (C_{10}–H and C_{11}–H), 5.96 (ddd, $J_{14,15}$ = 10.5, $J_{14\text{-}3}$ = 4.5, 1 H, C_{14}–H), 5.78 (ddd, $J_{14\text{-}15}$ = 10.5, 1 H, C_{15}–H), 3.82 (s, 1 H, C_{21}–H), 3.46 (s, 3 H, CO_2CH_3), 1.07 (t, $J_{18\text{-}19}$ = 7.5, 3 H, C_{18}–H_3); MS, m/e 310 $M^{\bullet+}$, 170 (100%), 169; UV 285, 292 (H_3O^+), 275, 283, 292. Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.62; H, 7.14; N, 9.02. Found: C, 73.43; H, 7.07; N, 9.14.

6: IR 3400, 1700; ^1H NMR δ 7.86 (s, 1 H), 7.5 (d, 1 H), 7.26 (d, 1 H), 7.32 (d, J = 12, 1 H), 7.2 (m, 2 H), 5.39 (dd, J = 17, J = 2, 1 H), 5.28 (dd, J = 10, J = 2, 1 H), 4.85 (s, 1 H), 3.85 (s, 3 H, CO_2CH_3), 1.07 (t, J = 7, 3 H); MS, m/e 310 $M^{\bullet+}$, 295, 281 (100%), 199; UV 227, 260, 285, 292 (H_3O^+), 260, 295.

Preparation of Indoloquinolizidine 7. 14,15-Dihydro-21-nor-1,14-secoeburnamenin-20-oic Acid Methyl Ester (7). To a suspension of Raney Ni (4 mL, 50% in H_2O) was added ester **5** (0.69 g, 2.22 mmol) in acetone (9 mL). The mixture was refluxed for 3 h, filtered on Celite, and evaporated. The residue was dissolved in dichloromethane and washed with brine. After evaporation of the organic layer, **7** was isolated (0.67 g, 2.14 mmol) (96%): mp 124–126 °C (ether–pentane); IR 3400, 2850, 2800, 2750, 1720; ^1H NMR δ 7.85 (s, 1 H, N_a–H), 7.49 (d, J = 8, 1 H) and 7.34 (d, J = 8, 1 H) (C_9–H and C_{12}–H), 7.17 (dd, J = 8, 1 H) and 7.12 (dd, J = 8, 1 H) (C_{10}–H and C_{11}–H), 3.72 (s, 3 H, CO_2CH_3), 0.90 (t, J = 7, 3 H, C_{18}–H_3); MS, m/e 312 $M^{\bullet+}$, 297, 253, 170, 169; UV 228, 277, 286, 293. Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 73.10; H, 7.69; N, 9.01.

Preparation of Indoloquinolizidine 8. 14,15-Dihydro-21-nor-1,14-secoeburnamenin-20-ol (8).[10] To a suspension of $LiAlH_4$ (0.2 g, 5.27 mmol) in THF (5 mL) at −70 °C was added dropwise a solution of ester **7** (1.48 g, 4.75 mmol) in THF (20 mL). The reaction mediun was warmed to 20 °C in 90 min. Excess $LiAlH_4$ was carefully hydrolyzed with a saturated aqueous solution of Na_2SO_4 (20 mL). After filtration the resulting solution was extracted with dichloromethane. Alcohol **8** was isolated after the usual workup (1.29 g, 4.54 mmol): yield 96%; mp 228–229 °C (CH_2Cl_2–pentane); IR 3500, 3300, 2850, 2750); ^1H NMR (80 MHz, Me_2SO-d_6) δ 9.75 (s, 1 H, N_a–H), 6.88–7.6 (m, 4 H) aromatics, 4.95 (s, 1 H, OH), 3.7 (d, $J_{HA\text{-}HB}$ = 10.5, 1 H, C_{17}–H_A), 3.38 (s, 1 H, C_{21}–H), 3.1 (d, $J_{HA\text{-}HB}$ = 10.5, 1 H, C_{17}–H_B); 1.0 (t, J = 7, 3 H, C_{18}–H_3); MS, m/e 284 $M^{\bullet+}$, 267, 170, 169; UV 278, 286, 295.

Preparation of Indoloquinolizidine 9. 14,15-Dihydro-21-nor-1,14-secoeburnamenin-20-al (9).[10] To a solution of alcohol **8** (1.29 g, 4.54 mmol) in Me_2SO (11 mL) and triethylamine (10 mL) was added at 20 °C a solution of SO_3–pyridine (2.38 g, 15 mmol) in Me_2SO (11 mL). The mixture was stirred for 60 min and extracted with dichloromethane. After the usual workup the residue was purified by chromatography (SiO_2, hexane–ethyl acetate 50:50) and afforded **9** (1.159 g, 4.10 mmol), yield 90%; mp 155–158 °C (Et_2O–pentane) lit.[12] mp 150 °C (Et_2O); IR 3490, 2810, 2755, 1710; ^1H NMR δ 9.4 (2 s, 1 H, CHO); 7.84 (s, 1 H, N_a–H), 7.50 (d, J = 7, 1 H) and 7.33 (d, J = 7, 1 H) (C_9–H and C_{12}–H); 7.17 (dd, J = 7, 1 H) and 7.11 (dd, J = 7, 1 H) (C_{10}–H and C_{11}–H); 3.59 (s, 1 H, C_{21}–H), 1.03 (t, J = 7, 3 H C_{18}–H_3); MS m/e 282 $M^{\bullet+}$, 281, 267, 253, 170, 169; UV 278, 286, 295.

Preparation of Compound 11. 15a-Dehydro-15-formamido-*D*-homoeburnamenin-14-one (11). To a solution of *t*-BuOK (295 mg, 2.63 mmol) in THF (5.7 mL) was added methyl

(14) When the reaction medium was quenched at −10 °C with water, the oxazoline intermediate corresponding to anion **12** was isolated.

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isocyanoacetate (174 mg, 1.75 mmol) at +10 °C. The mixture was stirred for 10 min at the same temperature and cooled at -70 °C before dropwise addition of aldehyde **9** (239 mg, 0.85 mmol) in THF. After warming to 0 °C over 150 min, the mixture was treated with water and extracted with Et_2O. After the usual treatment enamide **11** was isolated (251 mg, 0.72 mmol., 85%): IR 3380, 1690, 1640, 1600; ^1H NMR δ 8.5 (d, J = 7, 1 H, C_{12}-H); 8.38 (s, 1 H, C*H*O); 8.25 (bs, 1 H, N*H*CHO); 7.65 (s, 1 H, C_{17}-H); 7.39 (d, J = 7, 1 H, C_9-H), 7.32 (dd, J = 7, 1 H) and 7.27 (dd, J = 7, 1 H) (C_{10}-H and C_{11}-H); 4.27 (s, 1 H, C_{21}-H), 1.05 (t, J = 7, 3 H, C_{18}-H_3), MS, m/e 350, 349 $M^{\bullet+}$ (100%), 348, 334, 320; M_r 349.1734, calcd 349.1790 for $C_{21}H_{23}N_3O_2$; UV 203 (24 100), 259 (13 000), 317 (3680), MeOH + HCl 204, 254, 317.

Preparation of Vincamine (1). (±)-Vincamine (1). A solution of enamide **11** (79 mg, 0.225 mmol) in dry methanol-hydrochloric acid (prepared by addition of acetyl chloride (0.048 mL, 0.67 mmol) in anhydrous methanol (3.5 mL)) was refluxed for 4 h. After cooling to 15 °C, excess anhydrous sodium carbonate (143 mg, 1.35 mmol) was added, and the heterogeneous mixture was stirred for 30 min. After hydrolysis, the reaction medium was extracted with dichloromethane. The crude material obtained after the usual treatment was purified by chromatography (SiO_2, hexane-ethyl acetate 50:50) and afforded (±)-vincamine (**1**) (59 mg, 0.163 mmol, 73%): mp 230-231 °C (CH_2Cl_2-Et_2O) IR 3500, 2935, 2850, 1730; ^1H NMR δ 7.47 (m, 1 H) and 7.06 (m, 3 H) (aromatics), 3.93 (bs, 1 H, C_{21}-H), 3.82 (s, 3 H, CO_2CH_3), 0.74 (t, J = 7.5, 3 H, C_{18}-H_3), MS, m/e 355, 354 $M^{\bullet+}$, 353, 339, 325, 307, 295, 284, 267, 252.

Transmission of Polar Substituent Effects in Saturated Systems: Synthesis and ^{19}F NMR Study of 3-Substituted Adamant-1-yl Fluorides

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An extensive series of 3-substituted adamant-1-yl fluorides (**3**) covering a diverse range of substituents has been synthesized and characterized and the ^{19}F chemical shifts measured. By use of multiple linear regression analysis, it is revealed that there is no discernible relationship between the ^{19}F substituent chemical shifts (SCS; electron density monitors) of **3** and polar substituent constants (electric field (σ_F) and electronegativity ($\Delta\iota$) parameters). Most importantly, this result stands in stark contrast to the situation previously defined for the ^{19}F SCS of 4-substituted bicyclo[2.2.2]oct-1-yl fluorides (**1**) and the corresponding bicyclo[2.2.1]hept-1-yl fluorides (**2**). For these systems, the ^{19}F SCS are satisfactorily modelled by a linear two-parameter equation (SCS = $\rho_F\sigma_F + \rho_\iota\Delta\iota + c$). Factorization of the ^{19}F SCS of **3** into polar field ($\rho_F\sigma_F$) and residual contributions (^{19}F SCS - $\rho_F\sigma_F$) reveals the importance of the former solvent-dependent component. With respect to the origin of the solvent-independent residual contributions, several possible electronic transmission modes in the adamantane ring have been canvassed and discussed. It is concluded that the residuals are probably composite quantities which, in the main, are dominated by hyperconjugative and/or homohyperconjugative effects. For those substituents (D, CH_3, and $Sn(CH_3)_3$) with negligible polar field influences ($\sigma_F \approx 0$), an interesting parallel is noted between the pattern of σ-inductive or electronegativity effects as reflected by their ^{19}F SCS in **3**, on the one hand, and, on the other, the corresponding relative rates of solvolysis of 3-substituted adamant-1-yl bromides (or tosylates). A common electronic origin (inductive perturbation of C-C hyperconjugation and/or homohyperconjugation) is implicated.

Introduction

Suitable model compounds to study the transmission modes of polar substituent effects in saturated systems should be structurally rigid in order to avoid problems of uncertain conformation. In this respect, bridgehead-bridgehead disubstituted polycyclic alkanes are excellent model substrates and, over the years, several systematic substituent effect studies in these systems have been reported. For those investigations in which chemical reactivity probes (energy monitors) have been employed to monitor the polar substituent perturbation,[1-8] the appropriate experimental parameters ($\log_{10} K/K_0$ or $\log_{10} k/k_0$) have been found to correlate well against the polar field constant (σ_F),[9] i.e., a satisfactory description of the energy changes for equilibria or rate processes in these systems is achieved in terms of the electrostatic field model.

The ability to be able to probe substituent electronic effects via changes in NMR chemical shifts (charge density monitors) has provided a different perspective to the problem of the nature of electronic transmission modes in saturated systems. Unlike rate or equilibria data, NMR chemical shifts are single-state property parameters (generally the neutral ground state) which respond sen-

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