Studies in biomimetic alkaloid syntheses. 13. Total syntheses of racemic aspidofractine, pleiocarpine, pleiocarpinine, kopsinine, N-methylkopsanone, and kopsanone

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mL) which was then dried over sodium sulfate and evaporated to give an oil. The oil was dissolved in acetic acid (2.7 mL) and diethylamine (0.56 mL) was added dropwise with stirring. Aqueous formalin (0.95 mL) and sodium acetate (0.84 g) were added after a further 15 and 45 min, respectively, and the solution was then heated on an oil bath at 80 °C for 10 min. Upon cooling, standard workup afforded a residue, purification of which [PTLC (I)] gave canadensolide as an oil (82 mg, 41% from **12**) which could not be induced to crystalline $[\alpha]^{23}_D$ −162° (*c*, 3.20 in $CHCl_3$) (lit.[16] $[\alpha]_D$ −168.9° (*c*, 1.02 in pyridine); IR (neat) ν_{max} 1780, 1670, 1470, 1350, 1295, 1262, 1180, 1102, 1060, 1010, 950, 912, 902, 790 cm^{-1}; MS *m/e* 124, 123, 110, 109, 96; 220-MHz NMR δ 0.93 (t, 3, CH_2CH_3), 1.44 (m, 4, $CH_2CH_2CH_2CH_3$), 1.86 (m, 2, $CH_2CH_2CH_2CH_3$), 4.05 (dt, 1, $J_{2,3}$ = 7.0 Hz, $J_{2,A}$ = 2.0 Hz, $J_{2,B}$ = 2.0 Hz, H-2), 4.67 (dt, 1, $J_{3,4}$ = 4.2 Hz, $J_{4,5}$ = 7.0 Hz, $J_{4,5'}$ = 7.0 Hz, H-4), 5.18 (dd, 1, H-3), 6.16 (d, q, *J* = 2.0 Hz, H-A), 6.46 (d, q, *J* = 2.0 Hz, H-b). The NMR and IR data are in excellent agreement with those in the literature[4,5] and the mass spectrum is identical with that displayed by (±)-canadensolide.[19]

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada for a predoctoral studentship (R.C.A.) and for financial support. We also thank Dr. N. J. McCorkindale for his interest and help.

Registry No. **1a**, 20421-31-2; **2a**, 23558-05-6; **2b**, 98760-37-3; **2c**, 79448-72-9; α-**3**, 98760-38-4; β-**3**, 79431-88-2; α-**4a**, 98760-39-5; β-**4a**, 79431-89-3; α-**4b**, 98760-40-8; β-**4b**, 98760-41-9; **5a**, 100-52-7; **5b**, 103-36-6; **6** (isomer 1), 98760-42-0; **6** (isomer 2), 98819-38-6; **6** (isomer 3), 98819-39-7; **6** (isomer 4), 98819-40-0; α-**7a**, 69681-87-4; β-**7a**, 69744-49-6; α-**8**, 98819-41-1; β-**8**, 98819-42-2; **9** (isomer 1), 69681-88-5; **9** (isomer 2), 69744-50-9; **10a** (isomer 1), 69681-89-6; **10a** (isomer 2), 69744-40-7; **10b**, 69744-41-8; **12** (isomer 1), 98819-44-4; **12** (isomer 2), 69681-93-2; **13a**, 98819-43-3; **14**, 70048-75-8; **15a**, 69681-91-0; **15b**, 69681-92-1; propenyltriphenylphosphorane, 16666-78-7; (carbethoxymethylene)triphenylphosphorane, 1099-45-2; ethyl dihydrocinnamate, 2021-28-5; ethyl chloroformate, 541-41-3; ethyl vinyl ether, 109-92-2.

Studies in Biomimetic Alkaloid Syntheses. 13. Total Syntheses of Racemic Aspidofractine, Pleiocarpine, Pleiocarpinine, Kopsinine, *N*-Methylkopsanone, and Kopsanone

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Syntheses of the title alkaloid structures **1** (R = CHO, CO_2CH_3, CH_3, H; X = H_2) and **2** (R = CH_3, H; X = H_2) were based on generation of pentacyclic diene intermediates **17**, **18**, and **23** and their Diels–Alder reactions with phenyl vinyl sulfone.

Reports of synthetic studies leading to the hexacyclic aspidosperma alkaloids of the kopsinine (**1**, R = H; X = H_2)–pleiocarpinine (**1**, R = CH_3; X = H_2) class and to those of the heptacyclic kopsanone (**2**, R = H; X = H_2) group are relative sparse. To this end, an obvious biogenetic relationship of such alkaloids to the simpler pentacyclic vincadifformine (**3**, X = H_2) type alkaloids is provocative of a biomimetic cyclization of minovincine (**3**, X = O) as a synthetic approach. We had established three synthetic paths to minovincine,[1,2] but, while its decarbomethoxylation and cyclization provides 19-oxoaspidofractinine and then aspidofractinine (decarbomethoxy **1**, R = H),[3-5] its direct cyclization leads, alas, to an anticipated hexacyclic product, which is C-16 epimeric with 19-oxokopsinine (**1**, R = H; X = O).[6]

For an alternative synthetic strategy, the central bicyclo[2.2.2]octane moiety of these alkaloids suggests, of course, a Diels–Alder addition as a route to the C-2 to C-20 ethylene-bridged compounds **1** or **2**. In accord with broad experience in terpene chemistry, where, for bicyclooctanes this synthetic approach is generally preferred to biomimetic cyclizations of substituted cyclohexanes, synthetic planning for the target structures is then reduced to a choice of desirable diene and dienophile components.

Such an approach was first investigated in the C-16 decarbomethoxy series **4** leading, with nitroethylene and subsequent reduction and deamination steps, to another synthesis of aspidofractinine (decarbomethoxy **1**, R = H).[7] This concept was then used in an intramolecular sense for formation of the heptacyclic kopsane skeleton from a pentacyclic intermediate **5** (Scheme I). Introduction of the C-22 oxygen function of kopsanone (**2**, X = H_2) through a remarkable rearrangement reaction, cleavage of the C-6 to C-22 bond and esterification of the resultant acid then provided kopsinine (**1**, R = H; X = H_2), after reduction of the lactam function.[8b]

Extension of the intermolecular Diels–Alder reaction of the $\Delta^{2,16:17,20}$ diene **4**, to a synthesis of pleiocarpinine (**1**, R = CH_3; X = H_2) by a reaction of the diene with methyl acrylate, can be expected to lead to addition of the acrylic ester to the wrong face of the diene component **4**. Thus, an alternative, ethylene equivalent, reactive dienophile and the incorporation of the carbomethoxy function into the diene **4** were required for this synthesis.

In the present report we describe such a reaction scheme. By reversal of the last stages of the Magnus strategy this provides first syntheses of kopsinine and pleiocarpinine (**1**, R = H, CH_3; X = H_2) and then, in a possibly biomimetic formation of the C-6 to C-22 bond,[9] the generation of kopsanone and *N*-methylkopsanone (**2**, R = H, CH_3; X = H_2).

The key ring E diene intermediates **6** were obtained from an adaptation of our biomimetic secodine cyclization

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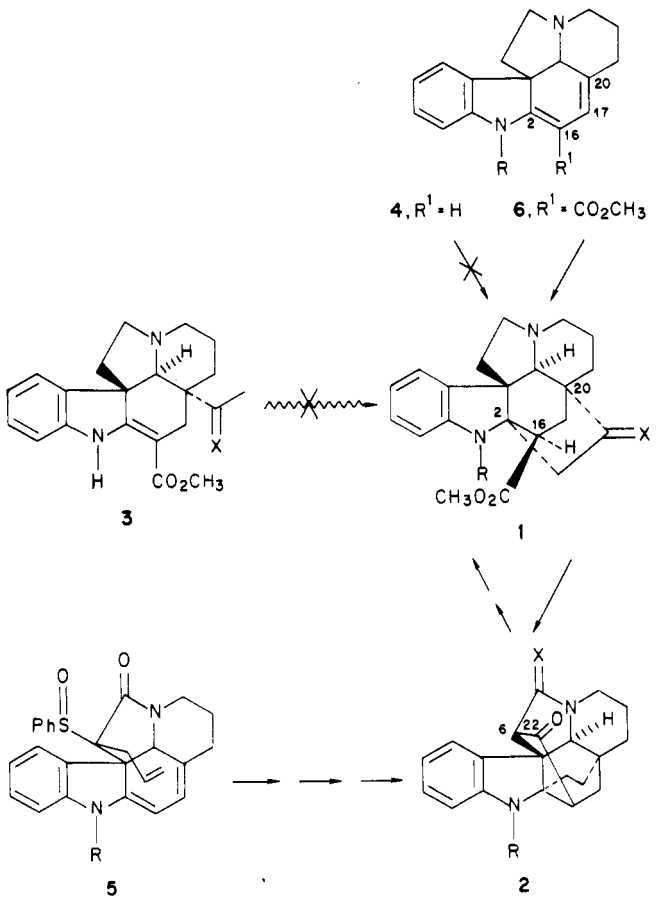

chemistry.[10] To this end a 2-phenylselenyl substituent was introduced onto 5-chloropentanal **7** by reaction of the latter with *N,N*-diethylbenzeneselenenamide (**8**).[11] The resulting α-phenylselenyl aldehyde **9**, on condensation with the indoloazepine **10**,[12] furnished a diastereomeric mixture of bridged azepines **11** (Scheme II). When this unpurified product mixture was heated in dichloromethane, it underwent intramolecular N-alkylation and rearrangement, with formation of the expected single diastereomer of the pentacyclic amine **12**. This compound showed the typical UV absorption maxima at 305 and 335 nm of a vincadifformine-type vinylogous urethane and a C-21 methinyl NMR singlet at δ 3.05.

Since the later generation of a C-2 to C-20 ethylene bridge is facilitated by N^a-alkylation (see below), such substitution was conveniently introduced at this stage. Methylation or benzylation of the vinylogous urethane **12** in dimethylformamide, with sodium hydride, gave the corresponding *N*-alkyl derivatives **13** and **14** in good yields, without significant interference by the C-alkylation, which is encountered with such vinylogous urethanes in less polar solvents.[10c]

On oxidation of the seleno ethers **13** and **14** with 2 equiv of *m*-chloroperbenzoic acid, the $\Delta^{2,16:17,20}$ diene *N*-oxides **15** and **16** were formed through the expected spontaneous selenoxide elimination. An NMR spectrum of the *N*-benzyl product **16** was complicated by the signals due to restricted rotational orientation of the *N*-benzyl vs. the carbomethoxy substituent as well as by the presence of a minor $\Delta^{15,20}$ component (see **22**, below).

Reduction of the *N*-oxide function with triethylphosphine required heating and thus provided the amino dienes **17** and **18**. Remarkably, however, this separate reduction step was not required for the further progress of our synthetic scheme. It was found that on heating of the two *N*-oxides **15** and **16** with excess phenyl vinyl sulfone, one achieved not only the key introduction of a C-2 to C-20 ethylene bridge but also a simultaneous reduction of the *N*-oxide function. A study of this reaction in the *N*-methyl series showed that after one hour at 100 °C the amino diene **17** and the *N*-oxide Diels–Alder product **19**, as well as the reduced adduct **20**, were present in the reaction mixture but that after 12 h at 100 °C the latter had become the major reaction product and was obtained crystalline in 69% yield.

Oxidation of the isolated tertiary amine **20** with *m*-chloroperbenzoic acid resulted in formation of its *N*-oxide **19**. The stereochemistry of the sulfone function in the hexacyclic products **19** and **20**, and in their *N*-benzyl analogue **21** is tentatively suggested to be that derived from an endo Diels–Alder addition of phenyl vinyl sulfone.

Starting from the N^aH compound **12** an analogous oxidation gave primarily the $\Delta^{15,20}$ diene N^b-oxide **22** and some of its $\Delta^{17,20}$ isomer (7:3). Reduction of this mixture with triphenylphosphine and purification provided the $\Delta^{15,20}$ diene amine **23**. When the diene mixture was heated with phenyl vinyl sulfone, the hexacyclic product **24** was formed, albeit in lower yield than that found with the N^a-alkylated diene N^b-oxides **15** or **16** or with amine **17**.

The alkaloid syntheses could now be continued by reduction of the sulfones **20**, **21**, and **24**. On heating with Raney Ni the N^a-methyl compound **20** furnished primarily (±)-pleiocarpinine **1** (R = CH_3; X = H_2) and its C-16–C-17 didehydro derivative **25** as a minor product. Similarly, the N^aH compound **24** provided (±)-kopsinine (**1**, R = H; X = H_2).

An analogous reaction of the *N*-benzyl compound **21** resulted in simultaneous debenzylation and formation of (±)-kopsinine (**1**, R = H; X = H_2). This latter alkaloid could also be obtained through oxidation of (±)-pleiocarpinine (**1**, R = CH_3; X = H_2) with phenyltriethylammonium permanganate,[13] which resulted in the formation of aspidofractine (**1**, R = CHO; X = H_2) and was followed by acid hydrolysis of its *N*-formyl substituent. A reaction of our synthetic (±)-kopsinine (**1**, R = H; X = H_2) with methyl chlorocarbonate provided (±)-pleiocarpine (**1**, R = CO_2CH_3; X = H_2).

NMR spectra of the latter product showed two pairs of methoxy group signals (4:5) at −50 °C, one very broad and one sharp methoxy singlet at +25 °C and two normal methoxy singlets at +50 °C. A corresponding variation of the aromatic C-12 proton signal was seen with this thermally increased mobility of the urethane function.

The natural C-16 stereochemistry of the interrelated saturated synthetic esters (±)-pleiocarpinine and (±)-kopsinine was initially assigned from a relative intensity of the mass fragmentation peaks *m/z* 109:124 (1:1.7), since it had been shown previously that this relative peak intensity depends dramatically on the relative stereochemistry of the ester function.[14] Epimerization of (±)-kop-

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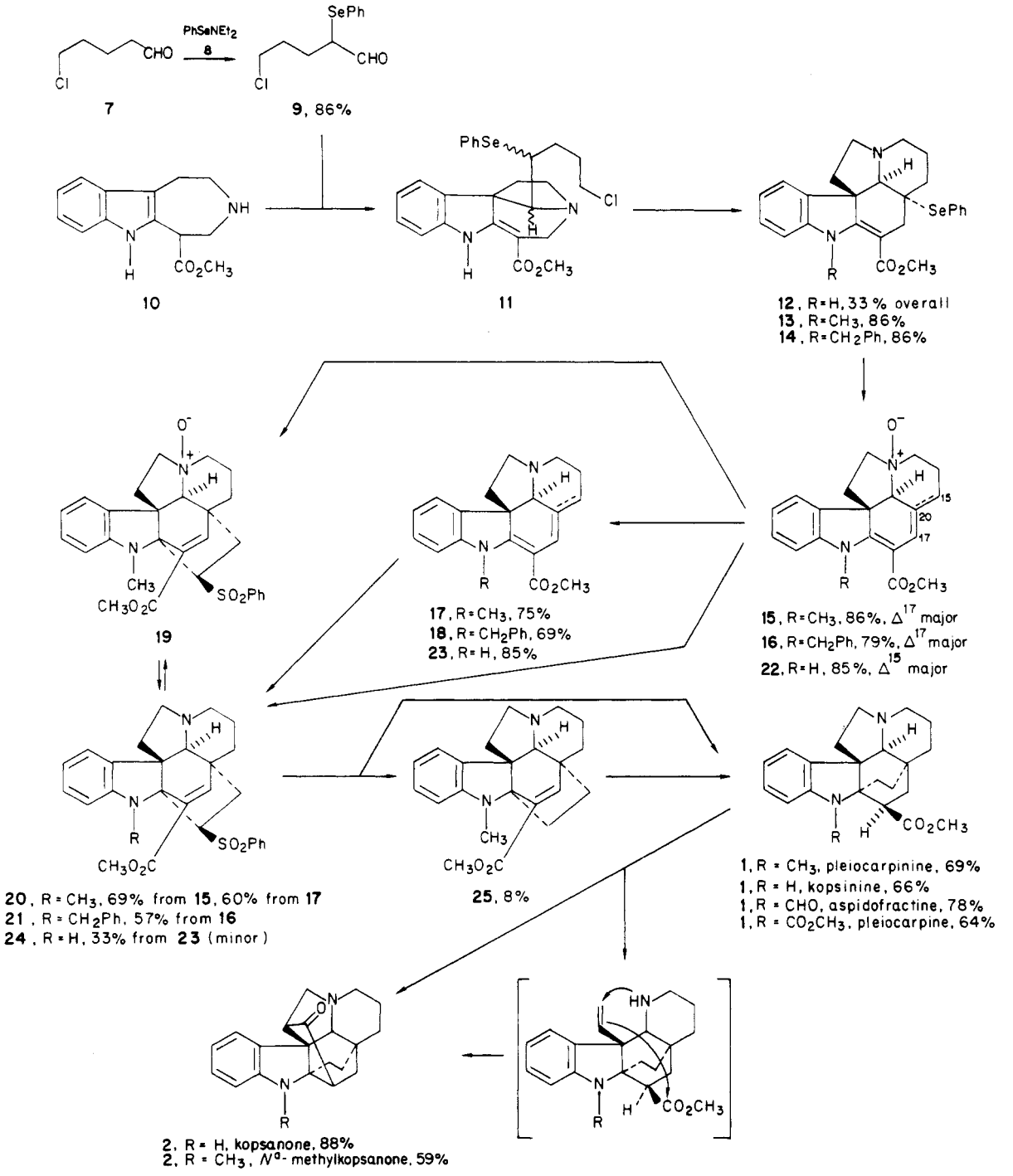
Scheme II



sinine in methanolic sodium methoxide then provided (±)-16-epikopsinine, where the relative peak intensity of m/z 109:124 (2:1) was reversed. N^a-formylation of this product gave (±)-16-epiaspidofractine. In contrast to (±)-pleiocarpinine and (±)-kopsinine, (±)-aspidofractine showed a m/z 109:124 (1.9:1) ratio, which increased to 2.2:1 in its C-16 epimer.

Additional evidence for the correct C-16 stereochemistry in our synthetic kopsinine (1, R = H; X = H_2) and in its derivative pleiocarpine (1, R = CO_2CH_3; X = H_2) was found in the failure to obtain, under identical conditions, an analogous epipleiocarpine derivative from 16-epikopsinine. N^a-Acylation is hindered here by the C-16 α-carbomethoxy substituent.

A chemical proof of the correct (±)-pleiocarpinine stereochemistry was then obtained from the conversion of our synthetic product (1, R = CH_3; X = H_2) to (±)-*N*-methylkopsanone (2, R = CH_3; X = H_2) by heating of the ester with methanol in a sealed tube at 200 °C. Analogously, (±)-kopsinine (1, R = H; X = H_2) could be cyclized to (±)-kopsanone (2, R = H; X = H_2). This interesting intramolecular acylation of a formally unactivated carbon position (which does not occur with the corresponding formally more activated 5-oxo derivative) had been previously reported for the natural product.[9] It was ascribed to an N-elimination–recyclization process, i.e., an enamine through space acylation reaction.

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Alternatively, a mechanism analogous to known σ–σ bond reactions, i.e., the predominant formation of nortricyclene from exo and endo norbornyl acetate or arenesulfonates under thermal and solvolytic elimination conditions,[15] may be considered.

The generation of ring E diene intermediates, by a variation of our biomimetic secodine chemistry has thus provided a facile synthetic access to the most complex fused variants of the aspidospermane alkaloids.

Experimental Section

General Methods. All reactions were carried out under nitrogen or argon. Melting points were obtained in a heated oil bath with or on a Kofler micro hot stage with thermometers calibrated against a National Bureau of Standards certified set. NMR spectra were recorded on a Bruker 250-MHz or a JEOL 100-MHz instrument. Mass spectra were obtained with a Finnegan 4610 quadrupole instrument at 70 eV, calibrated with perfluorotributylamine and bis(pentafluorophenyl)phenylphosphine for compounds below M_r 600 and with tris(perfluorononyl)-*s*-triazine for higher molecular weight compounds. IR spectra were obtained with a Nicolet 6000 FT or a Perkin-Elmer 267 grating instrument. UV spectra were recorded on a Perkin-Elmer 202 or 402 instrument. TLC data were obtained with E. Merck 60F-254 precoated silica on aluminum sheets. For visualization (10%) cerric ammonium sulfate (CAS) in phosphoric acid was employed as spray reagent. For centrifugal chromatography a Harrison chromatotron was used with E. Merck 60 PF 254 silica with gypsum. For column chromatography 60–200 mesh Baker R3405 silica was used. Microanalyses were provided by George Robertson, Robertson Laboratories, Florham Park, NJ.

5-Chloro-2-(phenylselenenyl)pentanal (9). *N,N*-Diethylbenzeneselenenamide was prepared by stirring benzeneselenenyl chloride (3.1 g, 16 mmol) with *N,N*-diethylamine (5.0 g, 68 mmol) in dry pentane (50 mL) at 35 °C under nitrogen. After 30 min, the orange benzeneselenenyl chloride had completely dissolved and reacted, leaving a yellow solution of the amide over the hydrochloride salt of diethylamine. After cooling, the solution was filtered and concentrated under reduced pressure to give 3.2 g (86% crude yield) of the amide as a yellow oil.[11]

The crude *N,N*-diethylbenzeneselenenamide (8, 3.2 g, 14 mmol) was added dropwise to a solution of 5-chloropentanal (1.40 g, 12 mmol) in dry dichloromethane (50 mL). After being stirred at 20 °C under N_2 for 30 min, the reaction mixture was concentrated under reduced pressure. Chromatography of the resulting oil (SiO_2, 3 × 30 cm column, 1.9 ether–pentane) gave 1.94 g (61% yield) of **9** as a pale yellow oil: IR (neat) ν_{max} 3057, 2956, 2821, 2721, 1706, 1477, 1439, 1022, 741 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 9.45 (d, J = 2.9 Hz, 1 H), 7.48–7.52 (2 H, m), 7.25–7.35 (3 H, m), 3.52–3.60 (3 H, m), 1.78–2.03 (4 H, m); mass spectrum, m/z (relative intensity) 278 (29), 276 (65), 274 (34), 249 (19), 247 (44), 245 (22), 157 (33), 155 (53), 77 (86), 55 (100).

(±)-20-(Phenylselenenyl)desethylvincadifformine (12). A mixture of the indoloazepine **10** (200 mg, 0.82 mmol), the aldehyde **9** (240 mg, 0.87 mmol), and boric acid (50 mg) in dry dichloromethane (50 mL) was heated at reflux under N_2. After 2 h, TLC (1:1 ether–pentane) showed the presence of two products: the major product **11** with R_f 0.18 (CAS, yellow) and the minor product **12** with R_f 0.60 (CAS, green-yellow). After an additional 12 h at reflux, TLC showed the disappearance of the more polar-bridged azepine **11** while the pentacyclic product **12** (R_f 0.60) had become the major component in the reaction mixture. After cooling, the reaction mixture was washed with saturated $NaHCO_3$ (20 mL). The organic phase was dried (anhydrous $MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on a 2-mm SiO_2 chromatotron plate. Elution with ether–pentane (1:1), concentration of the appropriate fractions, and crystallization from ether–pentane afforded 126 mg (33%) of **12** as white needles: mp 74–76 °C; UV (ethanol) λ_{max} 229, 302, 335 nm; IR (KBr) ν_{max} 3377, 2945, 2932, 1672, 1605, 1464, 1251, 1237, 1154, 739 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 9.09 (br s, 1 H) 7.14–7.31 (m, 7 H) 6.94 (t, J = 7.2 Hz, 1 H), 6.87 (d, J = 7.8 Hz, 1 H), 3.74 (3 H, s) 3.17 (d, J = 15.6 Hz, 1 H), 3.03 (s, 1 H), 3.03–3.08 (m, 1 H), 2.94 (t, J = 7.0 Hz, 1 H), 2.62–2.70 (m, 1 H), 2.55 (dd, J = 15.6 Hz, J = 1.5 Hz, 1 H), 2.34 (td, J = 11.6 Hz, 1 H), 2.01–2.09 (m, 2 H), 1.71–1.90 (m, 3 H), 1.47 (dt, J = 11.6 Hz, 1 H); mass spectrum, m/z (relative intensity) 466 (1), 309 (100), 310 (20), 277 (30), 252 (7), 249 (7), 206 (7), 180 (5), 167 (4), 157 (14), 154 (8), 77 (7), 58 (22). Anal. Calcd for $C_{25}H_{26}N_2O_2Se$: C, 64.51; H, 5.63; N, 6.02. Found: C, 64.47; H, 5.82; N, 6.23.

(±)-N^a-Methyl- and -Benzyl-20-(phenylselenenyl)-desethylvincadifformine (13 and 14). Sodium hydride (3.0 equiv) was added to a solution of **12** (450 mg, 0.97 mmol) in dry DMF (20 mL) at 25 °C under N_2. After 30 min methyl iodide (200 μL, 3.1 mmol) was added dropwise, and the mixture was stirred under N_2 for an additional 30 min. TLC (SiO_2, 1:1 ether–pentane) of the reaction mixture then showed a single product with R_f = 0.55 (CAS, red → yellow). Water (100 mL) was added to the reaction mixture and the resulting suspension was extracted with ether (3 × 50 mL). The combined organic phases were washed with brine, dried (anhydrous $MgSO_4$) and concentrated under reduced pressure. Column chromatography of the residue (SiO_2, 2 × 10 cm column, 1:2 ether–pentane) gave 400 mg (86%) of **13** as a pale yellow oil: UV (ethanol) λ_{max} 234, 307, 350 nm; IR (KBr, foam) ν_{max} 2936, 2778, 1677, 1601, 1573, 1488, 1434, 1221, 1209, 1118, 741 cm^{-1}; 250-MHz NMR ($CDCl_3$) δ 7.12–7.32 (m, 7 H), 7.03 (t, J = 7.0 Hz, 1 H), 6.93 (d, J = 8.0 Hz, 1 H), 3.77 (s, 3 H), 3.41 (d, J = 16 Hz, 1 H), 3.38 (s, 3 H), 3.05 (s, 1 H), 2.96–3.05 (m, 2 H), 2.83 (d, J = 16 Hz, 1 H), 2.70–2.77 (m, 1 H), 2.33 (dt, 1 H), 1.88–2.05 (m, 3 H), 1.62–1.76 (m, 3 H), 1.40–1.46 (m, 1 H); mass spectrum, m/z (relative intensity) 480 (1), 469 (1), 324 (23), 323 (100), 291 (2), 252 (12), 248 (10), 194 (7), 157 (17), 96 (7), 77 (13), 58 (58).

(±)-N^a-Benzyl-20-(phenylselenenyl)desethylvincadifformine (**14**) was prepared by the same procedure with substitution of benzyl bromide for methyl iodide. The product, formed in 86% yield, had TLC (SiO_2, 1:1 ether–pentane) R_f 0.55: UV (ethanol) λ_{max} 233, 300, 345 nm; IR (KBr, film) ν_{max} 2941, 2784, 1678, 1619, 1580, 1463, 1436, 1246, 1199, 1166, 742 cm^{-1}; 250-MHz NMR ($CDCl_3$) [complex due to presence of rotational isomers of benzyl vs. CO_2CH_3 substituents] δ 6.98–7.39 (m, 16 H), 5.12, 5.13 (2 d, 1.5 H), 3.96, 3.29 (2 s, 1:3, 3 H), 3.89, 3.35 (2 d, 0.5 H), 2.97–3.21 (m, 3 H), 2.65–2.81 (m, 3 H), 2.31–2.41 (m, 1 H), 2.05–2.17 (m, 1 H), 1.68–2.01 (m, 4 H), 1.40–1.46 (m, 1 H); mass spectrum, m/z (relative intensity) 556 (1), 399 (54), 252 (8), 157 (2), 134 (10), 91 (100), 58 (60).

(±)-N^a-Methyl- and -Benzyl-17,20-dehydrodesethylvincadifformine N^b-Oxide (15 and 16). A solution of *m*-chloroperbenzoic acid (110 mg, 2.2 equiv) in dichloromethane (2 mL) was added dropwise to the selenide **14** (120 mg, 0.25 mmol) in dichloromethane (50 mL) at −78 °C. TLC (SiO_2, 1:9 methanol–CH_2Cl_2) of the reaction mixture showed a single product with R_f = 0.20 (CAS, yellow). The mixture was allowed to warm to 0 °C, saturated $NaHCO_3$ (200 mL) and triphenylphosphine (100 mg) (to reduce any excess peracid) were added, and the mixture was stirred for 1 h at 25 °C. The organic phase was separated, dried (anhydrous $MgSO_4$) and concentrated under reduced pressure. Column chromatography of the residue (SiO_2, 2 × 20 cm column, 1:9 MeOH–CH_2Cl_2) and crystallization from ether gave 73 mg (86%) of **15** as yellow crystals: mp 168–170 °C; UV (ethanol) λ_{max} (ϵ) 235 (7600), 267 (11 300), 302 (3600), 398 (7500) nm; IR (KBr) ν_{max} 2935, 1685, 1650, 1562, 1246, 1213, 1188 cm^{-1}; NMR ($CDCl_3$) δ 8.89 (dd, J = 8.7 Hz, J = 0.6 Hz, 1 H), 7.31 (td, J = 7.7 Hz, J = 0.9 Hz, 1 H), 7.10 (td, J = 7.8 Hz, J = 0.6 Hz, 1 H), 6.93 (d, J = 7.9 Hz, 1 H), 6.56 (s, 1 H), 4.57 (s, 1 H), 3.87–3.95 (m, 1 H), 3.79 (s, 3 H), 3.70–3.83 (m, 1 H), 3.39 (s, 3 H), 2.71–2.83 (m, 1 H), 2.53–2.59 (m, 1 H), 2.24–2.32 (m, 3 H), 2.00–2.05 (m, 2 H), 1.72–1.78 (m, 1 H); mass spectrum, m/z (relative intensity) 338 (8), 323 (20), 322 (100), 320 (24), 291 (10), 278 (14), 263 (52), 261 (29), 252 (23), 235 (18), 220 (15), 181 (19), 57 (50).

The *N*-benzyl compound **14** was oxidized by the same procedure to provide the corresponding diene *N*-oxides **16**: mp 137–140 °C dec; 79%; TLC (SiO_2, 1:9 MeOH–CH_2Cl_2) R_f = 0.16; UV (ethanol) λ_{max} 234, 263, 385 nm; IR (KBr) ν_{max} 2945, 1735, 1685, 1653, 1568, 1560, 1457, 1215, 1157 cm^{-1}; 250-MHz NMR ($CDCl_3$) [complex due to *N*-benzyl vs. carbomethoxy rotational isomers and Δ^{17} vs. Δ^{15}] δ 8.96, 8.78, 8.59 (3 d, j = 7 Hz, ratio 15:5:3, 1 H), 7.59–6.72

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(m, 8 H), 6.48, 5.80, 5.72 (3 s, 15:3:5, 1 H), 5.14, 4.64 (2 s, 2:1, 2 H), 3.90, 3.75, 3.35 (3 s, 5:3:15, 3 H), 4.14–3.41 (m, 5 H), 3.21–1.73 (m, 6 H); mass spectrum, m/z (relative intensity) 414 (1), 398 (14), 307 (16), 219 (6), 156 (8), 139 (9), 91 (100), 56 (36).

(±)-15,20-Dehydrodesethylvincadifformine N^b-Oxide (22). This compound was prepared from the selenide **12**, following the procedure given above. After chromatography, the diene N-oxide (SiO_2, TLC, R_f 0.03, 1:9 MeOH–CH_2Cl_2; CAS, green → yellow) was crystallized from CH_2Cl_2–pentane as yellow crystals (85%): mp 149–152 °C dec; UV (ethanol) λ_{max} 247, 296, 335 nm; IR (KBr) ν_{max} 2947, 1686, 1604, 1586, 1465, 1279, 1212, 1196, 1086 cm^{-1}; NMR ($CDCl_3$) δ 9.24 (br s, 1 H), 9.12 (d, J = 7.7 Hz, 1 H), 7.17 (t, J = 7.6 Hz, 1 H), 6.90 (t, J = 7.5 Hz, 1 H), 6.78 (d, J = 7.7 Hz, 1 H), 5.96 (s, 1 H), 4.40 (s, 1 H), 3.81–3.94 (m, 4 H), 3.78 (s, 3 H), 3.26 (br s, 2 H) 1.70–2.85 (m, 4 H) [30% signals at δ 8.74 (d, J = 7.7 Hz, C-9), 6.46 (s, C-17), 4.56 (s, C-21), and 3.81 (s, OCH_3) indicated the presence of a minor $\Delta^{17,20}$ component]; mass spectrum, m/z (relative intensity) 324 (3), 308 (16), 220 (11), 193 (7), 84 (9), 57 (100).

(±)-N^a-Methyl- and -Benzyl-17,20-Dehydrodesethylvincadifformine (17 and 18). The diene N-oxide **16** (70 mg, 0.21 mmol) was heated with triphenylphosphine (200 mg, 0.76 mmol) in benzene (0.5 mL) at 100 °C under N_2 for 5 h. TLC (SiO_2, 1:9 methanol–CH_2Cl_2) showed the starting material to be almost completely converted to the diene **17** (R_f 0.80; CAS, yellow → orange). Chromatography (SiO_2, 2 × 20 cm column, 1:1 ether–pentane) and crystallization from CH_2Cl_2–pentane gave 50 mg (75%) of **17** as bright yellow crystals: mp 146–147 °C; UV (ethanol) λ_{max} (ϵ) 233 (6600), 262 (8600), 305 (3400), 400 (6300) nm; IR (KBr) ν_{max} 2924, 2854, 1687, 1642, 1564, 1224, 1190, 1079, 747 cm^{-1}; NMR ($CDCl_3$) δ 7.65 (d, J = 7.1 Hz, 1 H), 7.26 (t, J = 7.7 Hz, 1 H), 7.02 (t, J = 7.6 Hz, 1 H), 6.91 (d, J = 7.9 Hz, 1 H), 6.18 (s, 1 H), 3.78 (s, 3 H), 3.75 (s, 1 H), 3.41 (s, 3 H), 3.09–3.22 (m, 3 H), 2.89–2.97 (m, 1 H), 2.47–2.53 (m, 1 H), 2.22–2.34 (m, 1 H), 2.01–2.15 (m, 1 H), 1.78–1.96 (m, 2 H), 1.49–1.59 (m, 1 H); mass spectrum, m/z (relative intensity) 322 (100), 307 (6), 291 (7), 266 (16), 263 (43), 252 (10), 235 (16), 220 (12), 125 (23), 96 (16), 77 (24), 57 (53). Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.21; H, 7.05; N, 8.42.

An analogous reduction of N^a-benzyl compound **16**, for 1 h provided the amorphous amine **18** (69%): TLC (SiO_2, 1:9 methanol–CH_2Cl_2) R_f 0.64; UV (ethanol) λ_{max} 235, 255, 375 nm; IR (film) ν_{max} 2947, 1704, 1693, 1565, 1432, 1380, 1355, 1248, 1222, 1198, 752 cm^{-1}; NMR ($CDCl_3$) δ 6.65–7.99 (m, 9 H), 5.95, 6.39 (2 s, 1 H), 5.24 (s, 1 H), 4.84, 5.02 (2 s, 3:1, 1 H), 3.98–4.10 (m, 1 H), 3.49–3.78 (m, 3 H), 3.39, 3.45 (2 s, 1:3, 3 H), 3.14–3.22 (m, 1 H), 2.52–2.67 (m, 2 H), 2.09–2.31 (m, 2 H), 1.80–1.91 (m, 2 H); mass spectrum, m/z (relative intensity) 398 (24), 339 (9), 307 (12), 158 (30), 156 (97), 141 (32), 139 (100), 111 (60), 91 (47), 75 (47), 50 (43).

(±)-15,20-Dehydrodesethylvincadifformine (23). This compound was prepared from the corresponding N-oxide diene mixture **22** according to the procedure given above. After chromatography, crystallization from CH_2Cl_2–pentane gave the diene (TLC, SiO_2, 1:9 MeOH–CH_2Cl_2, R_f = 0.60, CAS, green → yellow) in 79–85% yield, as pale yellow crystals, mp 139.0–140.5 °C; UV (ethanol) λ_{max} 233, 300, 332 nm; IR (KBr) ν_{max} 3367, 2897, 1681, 1624, 1607, 1435, 1265, 1232, 1199, 1124, 1082, 749 cm^{-1}; NMR ($CDCl_3$) δ 9.12 (br s, 1 H), 7.61 (d, J = 7.4 Hz, 1 H), 7.14 (t, J = 7.6 Hz, 1 H), 6.88 (t, J = 7.5 Hz, 1 H), 6.79 (d, J = 7.7 Hz, 1 H), 5.80 (s, 1 H), 3.76 (s, 3 H), 3.65 (br s, 1 H), 2.95–3.32 (m, 6 H), 2.50–2.60 (m, 1 H), 2.11–2.24 (m, 1 H), 1.70–1.88 (m, 2 H); mass spectrum, m/z (relative intensity) 308 (34), 249 (8), 220 (14), 193 (8), 125 (5), 77 (7), 57 (100). Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.84; H, 6.74; N, 8.98.

(±)-16,17-Dehydro-18-(phenylsulfonyl)pleiocarpinine (20). **a.** Phenyl vinyl sulfone (150 mg, 0.89 mmol) was heated with the diene N-oxide **15** (100 mg, 0.30 mmol) in benzene (0.5 mL) at 100 °C under N_2. After 1 h, TLC (SiO_2, 1:9 MeOH–CH_2Cl_2) showed starting material and three other components: R_f = 0.15, CAS, pink (Diels–Alder N-oxide product **19**); R_f 0.56, CAS, pink (Diels–Alder amine product **20**); R_f 0.80, CAS, yellow → orange (diene amine **17**). After 12 h at 100 °C the Diels–Alder amine product **20** (R_f 0.56; CAS, pink), was the major component present by TLC. Chromatography of the reaction mixture (2 mm SiO_2 chromatotron plate, 1:9 MeOH–CH_2Cl_2) concentration of the appropriate fractions and crystallization from ethyl acetate gave 100 mg (69%) of **20** as colorless crystals: mp 186–188 °C; UV (ethanol) λ_{max} (ϵ) 220 (9200), 260 (7500), 305 (3200) nm; IR (KBr) ν_{max} 2935, 1722, 1606, 1307, 1274, 1250, 1151, 736 cm^{-1}; NMR ($CDCl_3$) δ 7.65 (d, J = 7.01 Hz, 2 H), 7.54 (d, J = 7.43 Hz, 1 H), 7.44 (t, J = 6.6 Hz, 2 H), 7.13–7.20 (m, 2 H), 6.96 (s, 1 H), 6.72 (t, J = 7.2 Hz, 1 H), 6.49 (d, J = 7.7 Hz, 1 H) 3.89 (s, 3 H) 3.83 (t, J = 8.9 Hz, 1 H) 3.22 (s, 1 H) 3.18 (s, 3 H), 2.96–3.01 (m, 2 H) 2.53–2.69 (m, 3 H), 1.63–2.04 (m, 3 H), 1.23–1.33 (m, 2 H), 1.12 (d, J = 8.9 Hz, 12 H); mass spectrum, m/z (relative intensity) 490 (9), 395 (12), 349 (5), 322 (100), 277 (60), 262 (44), 183 (29), 77 (71), 57 (29), 51 (39). This compound was found to undergo slow, partial retro Diels–Alder fragmentation on drying, and consequently it did not allow good elemental analyses.

b. A reaction of the amino diene **17** (23 mg, 0.07 mmol) with 30 mg (0.18 mmol) of phenyl vinyl sulfone in benzene heated at reflux for 16 h gave 21 mg (60%) of **20**.

(±)-16,17-Didehydro-18-(phenylsulfonyl)pleiocarpinine N^b-Oxide (19). The sulfone **20** (2 mg, 0.004 mmol) was stirred with m-chloroperbenzoic acid (1 mg, 0.006 mmol) in dichloromethane (10 mL) at 0 °C. After 10 min, TLC (SiO_2, 1:9 MeOH–CH_2Cl_2) showed a single product at R_f 0.15 (CAS, pink), which cospotted with the Diels–Alder N-oxide product **19**, generated from the reaction of the diene N-oxide **15** with phenyl vinyl sulfone. The reaction mixture was then washed with saturated $NaHCO_3$ (5 mL), dried (anhydrous Na_2CO_3), and concentrated under reduced pressure to give the N-oxide sulfone **19**: mass spectrum, m/z (relative intensity) 57 (100), 77 (46), 79 (46), 111 (50), 139 (73), 179 (11), 322 (25), 346 (12), 490 (3), 506 (<1).

(±)-N^a-Benzyl-16,17-dehydro-18-(phenylsulfonyl)kopsinine (21). Phenyl vinyl sulfone (100 mg, 0.60 mmol) was heated with the N^a-benzyl diene N-oxide **16** (50 mg, 0.12 mmol) in benzene (0.5 mL) at 100 °C under N_2. After 16 h, TLC (SiO_2, 1:9 MeOH–CH_2Cl_2) showed that the starting diene N-oxide had been consumed and the presence of a new product with R_f 0.52 (CAS, purple). Chromatography of the reaction mixture (1-mm SiO_2 chromatotron plate, 1:9 MeOH–CH_2Cl_2), concentration of the appropriate fractions, and crystallization from ethyl acetate gave 37 mg (57%) of the sulfone as a colorless powder: mp 231–232.5 °C; UV (ethanol) λ_{max} 223, 258, 300 nm; IR (KBr) ν_{max} 2933, 1718, 1601, 1479, 1448, 1304, 1277, 1254, 1154, 1138, 748 cm^{-1}; NMR ($CDCl_3$) δ 7.15–7.71 (m, 11 H), 7.08 (s, 1 H), 7.03 (t, J = 7.6 Hz, 1 H), 7.76 (t, J = 7.3 Hz, 1 H), 6.27 (d, J = 8.8 Hz, 1 H), 5.02 (dd, J = 70.9, 17.6 Hz, 2 H), 3.90 (t, J = 9.0 Hz, 1 H), 3.27 (s, 3 H), 2.98–3.21 (m, 2 H), 2.77–2.90 (m, 2 H), 2.59–2.66 (m, 1 H), 1.86–2.04 (m, 3 H), 1.22–1.51 (m, 3 H), 1.10 (d, J = 9.1 Hz, 2 H); mass spectrum, m/z (relative intensity) 566 (1), 398 (23), 339 (5), 307 (5), 168 (18), 125 (88), 91 (43), 77 (100), 65 (26), 51 (70).

(±)-16,17-Dehydro-18-(phenylsulfonyl)kopsinine (24). The diene **23** (183 mg, 0.594 mmol) and phenyl vinyl sulfone (200 mg, 1.19 mmol) in benzene (1 mL) was heated in a sealed tube at 120 °C for 16 h. TLC (SiO_2, 1:9 MeOH–CH_2Cl_2) of the reaction mixture showed a large amount of the starting diene (R_f 0.60; CAS, green, fading to yellow) and a new product (R_f 0.46; CAS, red-orange). Chromatography (2-mm SiO_2 chromatotron plate, 1:9 CH_3OH–CH_2Cl_2), concentration, and crystallization of the product from ethyl acetate gave 92 mg (33%) of the sulfone as a white powder: mp 228–229.5 °C; UV (ethanol) λ_{max} 227, 245, 292 nm; IR (KBr) ν_{max} 3399, 2942, 2855, 2819, 1713, 1608, 1447, 1302, 1274, 1254, 1153, 1140, 1080, 756, 742 cm^{-1}; NMR ($CDCl_3$) δ 7.47–7.71 (m, 5 H), 7.18 (s, 1 H), 7.12 (d, J = 7.2 Hz, 1 H), 7.02 (t, J = 7.6 Hz, 1 H), 6.76 (t, J = 7.4 Hz, 1 H), 6.45 (d, J = 7.7 Hz, 1 H), 5.46 (br s, 1 H), 3.89 (s, 3 H), 3.65 (t, J = 6.9 Hz, 1 H), 3.23 (s, 1 H), 3.01–3.05 (m, 2 H), 2.70–2.76 (m, 1 H), 2.53–2.64 (m, 1 H), 2.28–2.36 (m, 1 H), 1.89–2.13 (m, 2 H), 1.57–1.69 (m, 2 H), 1.35–1.48 (m, 3 H); mass spectrum, m/z (relative intensity) 476 (2), 308 (39), 168 (10), 125 (40), 84 (36), 77 (49), 57 (100). Note: This product could be obtained from the N-oxide **22** in slightly poorer yields, but contamination of the resulting crystals gave very poor yields on reduction with Raney Ni to kopsinine.

(±)-Pleiocarpinine (1, R = CH_3; X = H_2) and (±)-16,17-Didehydropleiocarpinine (25). The sulfone **20** (85 mg, 0.17 mmol) in ethanol (25 mL) was heated at reflux with freshly activated Raney nickel catalyst in water (0.5 g of the water suspension) under N_2. [For this purpose, commercial Raney Ni

(Aldrich) was stirred in 3 N NaOH at 60 °C for 30 min and then washed with water until the wash became neutral.] After 3 h, TLC (SiO_2, 1:9 MeOH–CH_2Cl_2) showed that the starting material had been almost completely converted to a major product with R_f 0.44 (CAS, red-orange) and a minor product with R_f 0.47 (CAS, red-orange). After filtration and concentration, chromatography (2-mm chromatotron plate, 1:9 MeOH–CH_2Cl_2), and concentration of the appropriate fractions gave 5 mg (8%) of (±)-didehydropleiocarpinine **25** as a foam and 42 mg (69%) of (±)-pleiocarpinine, which crystallized from ether–pentane as colorless prisms, mp 128–129 °C. (±)-16,17-Didehydropleiocarpinine (**25**): UV (ethanol) λ_{max} 227, 256, 299 nm; IR (KBr) ν_{max} 2927, 2860, 1718, 1608, 1477, 1268, 1245, 1208, 1140, 754, 740 cm^{-1}; NMR ($CDCl_3$) δ 7.08–7.20 (m, 1 H), 7.18 (s, 1 H), 7.11 (t, J = 7.8 Hz, 1 H), 6.76 (t, 7.3 Hz, 1 H), 6.55 (d, J = 7.8 Hz, 1 H), 3.82 (s, 3 H), 3.32 (s, 1 H), 3.06 (dd, J = 2.1, 8.8 Hz, 2 H), 2.85 (s, 3 H), 2.75 (t, J = 8.8 Hz, 1 H), 2.51–2.62 (m, 1 H), 2.41–2.45 (m, 1 H), 2.28 (m, 1 H), 1.91–2.05 (m, 2 H), 1.58–1.72 (m, 1 H), 1.26–1.50 (m, 4 H), 1.09–1.16 (m, 1 H); mass spectrum, m/z (relative intensity) 350 (0.75), 349 (1.5), 323 (24), 322 (100), 263 (29), 235 (13), 168 (17), 125 (66), 77 (51), 57 (31), 51 (35). (±)-Pleiocarpinine: UV (ethanol) λ_{max} 224, 259, 302 nm; IR (KBr) λ_{max} 2921, 2855, 2843, 1732, 1606, 1477, 1198, 1169, 1153, 741 cm^{-1}; NMR ($CDCl_3$) δ 7.20 (dd, J = 0.9, 7.2 Hz, 1 H), 7.05 (td, J = 1.2, 7.6 Hz, 1 H), 6.71 (td, J = 0.7, 7.4 Hz, 1 H), 6.44 (d, J = 7.7 Hz, 1 H), 3.75 (s, 3 H), 3.30–3.36 (m, 1 H), 2.83–3.12 (m, 6 H), 2.75 (s, 3 H), 2.55–2.67 (m, 1 H), 1.85–2.05 (m, 1 H), 1.21–1.64 (m, 9 H); mass spectrum, m/z (relative intensity) 352 (43), 324 (8), 293 (4), 132 (10), 124 (100), 109 (44), 91 (19), 86 (24), 84 (40). Anal. Calcd for $C_{22}H_{28}N_2O_2$: C, 74.97; H, 8.01; N, 7.95. Found: C, 75.17; H, 8.02; N, 7.83.

(±) Kopsinine (1, R = H; X = H_2) a. The N^a–H sulfone **24** (75 mg, 0.16 mmol) was dissolved in ethanol (50 mL) and heated at reflux with active Raney nickel catalyst in water (~1.0 g of the water suspension) under N_2. After 1 h, TLC (SiO_2, 1:9 MeOH–CH_2Cl_2) showed the starting material to be about half reacted and the presence of a major product with R_f 0.36 (CAS, faint orange) and a minor product with R_f 0.40 (CAS, orange) ((±)-16,17-didehydrokopsinine by mass spectrum). After 2 h the starting material and minor product had reacted completely and only the major product remained by TLC. After filtration and concentration, chromatography (1-mm chromatotron plate, 1:9 MeOH–CH_2Cl_2) afforded 35 mg (66%) of kopsinine. Crystallization from hexane gave colorless crystals: mp 145–149 °C; UV (ethanol) λ_{max} 222, 248, 296 nm; IR (KBr) λ_{max} 2923, 2858, 1729, 1608, 1461, 1205, 1180, 1154, 747 cm^{-1}; NMR ($CDCl_3$) δ 7.18 (d, J = 7.3 Hz, 1 H) 6.99 (td, J = 1.3, 7.6 Hz, 1 H), 6.75 (td, J = 0.9, 7.4 Hz, 1 H), 6.66 (d, J = 7.7 Hz, 1 H), 3.75–3.81 (m, 1 H), 3.76 (s, 3 H), 3.35 (q, J = 8.2 Hz, 1 H), 2.59–3.17 (m, 7 H), 1.87–1.99 (m, 2 H), 1.49–1.64 (m, 2 H), 1.17–1.45 (m, 6 H); mass spectrum, m/z (relative intensity) 338 (24), 310 (8), 169 (4), 153 (5), 136 (4), 124 (100), 109 (63), 84 (9), 57 (6).

b. The N^a-benzyl sulfone **21** (10 mg, 0.018 mmol) was similarly reduced by heating at reflux in ethanol (25 mL) with active Raney nickel catalyst (~0.5 g of the water suspension). After 1 h, TLC (SiO_2, 1:9 MeOH–CH_2Cl_2) showed starting material and the presence of five additional products, including kopsinine at R_f 0.36 (CAS, faint orange). After 3 h TLC of the reaction mixture showed kopsinine to be the major product. Filtration, concentration, and chromatography gave 4 mg (67%) of kopsinine as a colorless foam. Mass spectrometry showed this product to be identical with the (±)-kopsinine obtained from the N^a–H sulfone, m/z 109:124 (ratio = 62:100). Note: Kopsinine obtained from the N^a-benzyl sulfone **21** was difficult to purify because one of the minor products has an R_f value almost identical with that of kopsinine.

(±)-Aspidofractine (1, R = CHO; X = H_2) a. A solution of benzyltriethylammonium permanganate (126 mg, 0.4 mmol) in dichloromethane (10 mL) was added dropwise under N_2 to (±)-pleiocarpinine (38 mg, 0.011 mmol) in dichloromethane (20 mL) and acetic acid (1 mL) over 5 min at −78 °C. The reaction mixture was allowed to warm to 0 °C and saturated aqueous $NaHSO_3$ (10 mL) was added, followed by saturated aqueous $NaHCO_3$ (20 mL). TLC (SiO_2, 1:9 MeOH–CH_2Cl_2) of the organic phase showed a single major product with R_f 0.50 (UV, CAS, colorless). The organic phase was separated, and the aqueous phase was extracted twice with dichloromethane (20 mL). The combined organic solutions were dried ($MgSO_4$), concentrated under reduced pressure, and chromatographed (SiO_2, 1-mm chromatotron plate) to give 31 mg (78%) of (±)-aspidofractine, which crystallized from hexane: mp 154–157 °C; UV (ethanol) λ_{max} 220, 255, 290 nm; IR (KBr) λ_{max} 2951, 2875, 1727, 1674, 1594, 1481, 1382, 1221, 1212, 1084 cm^{-1}; NMR ($CDCl_3$) δ 8.97, 8.69 (2 s, 1 H rotational isomers), 7.04–8.14 (m, 4 H) 3.85 (t, J = 10.3 Hz, 1 H), 3.76, 3.70 (2 s, 3 H, rotational isomers), 2.62–3.30 (m, 6 H), 2.27–2.50 (m, 1 H), 1.75–2.02 (m, 2 H), 1.46–1.70 (m, 5 H), 1.26–1.40 (m, 3 H); mass spectrum, m/z (relative intensity) 366 (100), 351 (12), 336 (2), 307 (7), 180 (6), 167 (6), 154 (8), 124 (21), 109 (40). Note: m/z 109/124 = 1.9.

b. Kopsinine (11 mg, 0.033 mmol) was stirred in formic acid (1.0 mL) and acetic anhydride (0.1 mL) at 20 °C under N_2. After 2 h, dichloromethane (10 mL) was added, followed by dropwise addition of saturated aqueous $NaHCO_3$ to neutralize the acids. TLC (SiO_2, 1:9 MeOH–CH_2Cl_2) of the organic phase showed a single major product, which cospotted with (±)-aspidofractine, prepared above, at R_f 0.50. The organic phase was separated, and the aqueous phase was extracted twice with dichloromethane (2 × 10 mL). The organic solutions were combined, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography (SiO_2, 1-mm chromatotron plate) afforded 8.5 mg (71%) of (±)-aspidofractine. The NMR spectrum of this product matched that of the product prepared from (±)-pleiocarpine.

(±)-Epikopsinine. (±)-Kopsinine (4.5 mg, 0.012 mmol) was heated at reflux with excess NaOMe in methanol (5 mL). After 16 h TLC (SiO_2, 1:9 MeOH–CH_2Cl_2) showed a single product, which cospotted with kopsinine. After cooling and concentration of the reaction mixture, chromatography (SiO_2, 1-mm chromatotron plate) afforded 4.0 mg (90%) of epikopsinine as a colorless oil: NMR ($CDCl_3$) δ 7.40, (d, J = 6.8 Hz, 1 H), 7.03 (td, J = 1.2, 7.6 Hz, 1 H), 6.80 (td, J = 0.8, 7.4 Hz, 1 H), 6.66 (d, J = 7.7 Hz, 1 H), 3.75–4.10 (m, 1 H), 3.81 (s, 3 H), 3.04–3.24 (m, 6 H), 2.62–2.72 (m, 1 H), 2.17–2.41 (m, 1 H), 1.60–1.87 (m, 4 H), 1.15–1.45 (m, 6 H); mass spectrum, m/z (relative intensity) 338 (31), 310 (22), 139 (12), 124 (37), 109 (100), 57 (22).

(±)-Epiaspidofractine. (±)-Epikopsinine (6 mg, 0.018 mmol) was stirred with formic acid (1 mL) and acetic anhydride (0.1 mL) at 20 °C under N_2 for 3 h. Dichloromethane (10 mL) and enough saturated $NaHCO_3$ to neutralize the acids were added, and the organic phase was separated. TLC (SiO_2, 1:9 MeOH–CH_2Cl_2) showed a product which cospotted with (±)-aspidofractine at R_f 0.50 and a small amount of starting material. Concentration and chromatography (SiO_2, 1-mm chromatotron plate, 1:9 MeOH–CH_2Cl_2) of the residue afforded 2.5 mg (42%) of (±)-epiaspidofractine as a colorless oil: NMR ($CDCl_3$) δ 8.82, 8.38 (2 s, 1 H), 6.84–8.04 (m, 4 H), 3.79 (s, 3 H), 3.47–3.65 (m, 2 H), 2.87–3.20 (m, 5 H), 2.35–2.66 (m, 3 H); mass spectrum, m/z (relative intensity) 366 (13), 310 (7), 277 (3), 154 (6), 139 (11), 124 (35), 109 (76), 81 (25), 69 (40), 57 (100).

(±)-Pleiocarpine (1, R = CO_2CH_3; X = H_2). (±)-Kopsinine (8 mg, 0.024 mmol) was stirred with methyl chloroformate (0.1 mL) and solid sodium carbonate (0.1 g) in dichloromethane (5 mL) at 20 °C under N_2. After 3 h, TLC (SiO_2, 1:9 MeOH–CH_2Cl_2) showed that the kopsinine had been converted to a new product at R_f 0.62 (CAS, purple). Filtration and concentration of the reaction mixture was followed by chromatography (SiO_2, 1-mm chromatotron plate, 1:9 MeOH–CH_2Cl_2) to give 6 mg (64%) of pleiocarpine, which crystallized from hexane: mp 144.5–145.5 °C; UV (ethanol) λ_{max} 215, 248, 235 nm; IR (KBr) ν_{max} 2925, 2848, 1707, 1478, 1275, 1218, 1201, 1088, 1044, 758 cm^{-1}; NMR (25 °C, $CDCl_3$) δ 7.82, 7.46 (br m, 1 H), 7.30–7.20 (m, 1 H), 7.16 (t, J = 7.7 Hz, 1 H), 7.00 (t, J = 7.4 Hz, 1 H), 3.82 (br s, 3 H), 3.69 (s, 3 H), 2.94–3.20 (m, 5 H), 2.40–2.54 (m, 2 H), 1.78–1.93 (m, 2 H), 1.42–1.69 (m, 6 H), 1.23–1.37 (m, 3 H) (50 °C) 7.60–7.70 (br m, 1 H), 7.20–7.30 (m, 1 H), 7.14 (t, 1 H), 6.96 (t, 1 H), 3.80 (s, 3 H), 3.68 (s, 3 H); (−50 °C) 7.84, 7.50 (2 d, 1 H), 7.20–7.30 (m, 1 H), 7.17 (t, 1 H), 7.02 (t, 1 H), 3.92, 3.79 (2 s, 4:5, 3 H), 3.74, 3.72 (2 s, 5:4, 3 H); mass spectrum, m/z (relative intensity) 396 (89), 395 (36), 381 (21), 368 (9), 337 (15), 295 (9), 182 (9), 124 (43), 109 (86), 59 (100).

(±)-N^a-Methylkopsanone (2, R = CH_3; X = H_2). (±)-Pleiocarpinine (15 mg, 0.29 mmol) was heated in methanol (0.5 mL) in a sealed tube at 190 °C. After 12 h, TLC (SiO_2, 5% methanol in CH_2Cl_2) showed that most of the (±)-pleiocarpinine

(R_f 0.11) had been converted to a new product at R_f 0.30 (CAS, orange). Chromatography (1-mm SiO_2 chromatotron plate; 5% methanol in CH_2Cl_2) and concentration of the appropriate fractions gave 8 mg (59%) of (±)-N^a-methylkopsanone, which crystallized from pentane; mp 151–153.8 °C; UV (ethanol) λ_{max} 223, 256, 299 nm; IR (KBr) ν_{max} 2947, 2859, 1739, 1478, 1300, 1119, 891, 743 cm^{-1}; NMR ($CDCl_3$) δ 7.26 (dd, J = 0.7, 7.3 Hz, 1 H), 7.13 (td, J = 1.4, 7.6 Hz, 1 H), 6.75 (td, J = 0.7, 7.4 Hz, 1 H), 6.48 (d, J = 7.7 Hz, 1 H), 3.48 (t, J = 9.9 Hz, 1 H), 3.35 (d, J = 1.8 Hz, 1 H), 3.12 (dd, J = 4.8, 9.5 Hz, 1 H), 3.00–3.06 (m, 2 H), 2.78 (d, J = 10.9 Hz, 1 H), 2.60 (s, 3 H), 2.51–2.58 (m, 1 H), 2.05 (d, J = 14.7 Hz, 1 H), 1.70–1.78 (m, 2 H), 1.45–1.65 (m, 3 H), 1.21–1.40 (m, 4 H); mass spectrum, m/z (relative intensity) 321 (39), 320 (100), 277 (6), 264 (5), 242 (11), 210 (5), 169 (17), 129 (12), 109 (26), 69 (17), 55 (42).

(±)-Kopsanone (2, R = H; X = H_2). (±)-Kopsinine (15 mg, 0.044 mmol) was heated in methanol (0.5 mL) in a sealed tube at 210 °C. After 36 h TLC (SiO_2, 5% MeOH in CH_2Cl_2) showed that almost all of the (±)-kopsinine (R_f 0.20) had been converted to a single product with R_f 0.36 (CAS, orange). Chromatography (SiO_2, 1-mm chromatotron plate, 5% MeOH in CH_2Cl_2) afforded 12 mg (88%) of (±)-kopsanone, which crystallized from hexane as colorless crystals: mp 156–157 °C; UV (ethanol) λ_{max} 227, 249, 297 nm; IR (KBr) ν_{max} 3355, 2927, 2841, 1743, 1604, 1475, 1459, 1221, 1091, 759, 746 cm^{-1}; NMR ($CDCl_3$) δ 7.29 (d, J = 7.3 Hz, 1 H), 7.06 (t, J = 7.6 Hz, 1 H), 6.79 (t, J = 7.4 Hz, 1 H), 6.67 (d, J = 7.8 Hz, 1 H) 3.46–3.58 (m, 2 H), 3.37 (s, 1 H), 3.10–3.16 (m, 1 H), 3.02–3.06 (dd, J = 2.2, 7.5 Hz, 2 H), 2.69 (d, J = 10.8 Hz, 1 H), 2.57 (dd, J = 4.7, 10.4 Hz, 1 H), 2.03 (d, J = 15 Hz, 1 H), 1.48–1.87 (m, 5 H), 1.22–1.40 (m, 4 H); mass spectrum, m/z (relative intensity) 306 (100), 305 (81), 277 (8), 183 (18), 153 (20), 109 (25), 96 (17), 84 (34), 55 (24).

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Registry No. (±)-**1** (R = CH_3, X = H_2), 98737-04-3; (±)-**1** (R = H, X = H_2), 98737-06-5; (±)-**1** (R = CHO, X = H_2), 98737-07-6; (±)-**1** (R = CO_2CH_3, X = H_2), 98737-08-7; (±)-**2** (R = CH_3, X = H_2), 98759-80-9; (±)-**2** (R = H, X = H_2), 84960-64-5; **8**, 57584-86-8; (±)-**9**, 98736-98-2; (±)-**10**, 66859-22-1; **11**, 98759-97-8; (±)-**12**, 98759-74-1; (±)-**13**, 98736-99-3; (±)-**14**, 98737-00-9; (±)-**15**, 98737-01-0; (±)-**16**, 98759-98-9; (±)-**17**, 98737-02-1; (±)-**18**, 98737-03-2; (±)-**19**, 98776-94-4; (±)-**20**, 98759-76-3; (±)-**21**, 98759-77-4; (±)-**22**, 98759-75-2; (±)-**23**, 98777-02-7; (±)-**24**, 98776-95-5; (±)-**25**, 98737-05-4; (±)-epikopsinine, 98759-78-5; (±)-epiaspidofractine, 98759-79-6; 5-chloropentanal, 20074-80-0; benzeneselenenyl chloride, 5707-04-0; diethylamine, 109-89-7; phenyl vinyl sulfone, 5535-48-8.

Stereochemistry of Cyclic Dipeptides. Assignment of the Prochiral Methylenes of 1-Aminocyclopropane-1-carboxylic Acid

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The two enantiomeric methylene carbons of 1-aminocyclopropane-1-carboxcylic acid (ACC) were differentiated by an NMR study. Several amino acids such as L-alanine, D-alanine, and 2-aminoisobutyric acid as well as ACC were condensed with L- and/or D-phenylalanine to form their corresponding 2,5-diketopiperazines. The measurement of the ^1H NMR signal of these model compounds indicates that the benzyl in the 6-position of these diketopiperazines exerts a shielding effect on the β-carbon of the various amino acids causing an upfield shift in their ^1H resonances. Conversely, the shielding effect of the benzyl results in a downfield shift in the ^{13}C resonance. Although the assignment of the proton resonances of the ACC portion of cyclo[ACC-L-Phe] was more complex, a combination of homonuclear and heteronuclear experiments allowed the proton signals at δ 1.4 and 0.98 to be assigned to the trans methylene group, the one not being shielded by the 6-benzyl group (^{13}C, δ 17.02), and the proton signals at δ 0.74 and 0.36 to be assigned to the cis methylene (^{13}C, δ 19.46). This assignment allows for the nondestructive, nonisotopic diluting analysis of various biosynthetically derived deuterated ACC's formed from the corresponding deuterated *S*-adenosylmethionines.

Our studies on the mechanism of the biosynthesis of 1-aminocyclopropane-1-carboxylic acid (ACC) from *S*-adenosyl-L-methionine (SAM) by 1-aminocyclopropane-1-carboxylic acid synthase[1-3] and our interest in the synthesis of regio- and stereospecifically deuterium-labeled 1-aminocyclopropane-1-carboxylic acid[4] for the study of the mechanism of the biosynthesis of ethylene by plants has made it necessary to distinguish between the enantiotopic methylene groups of ACC. The limited amounts of compounds and our desire to analyze in a nondestructive and nonisotopic diluting technique suggested the use of nuclear magnetic resonance. Since the two methylene carbons of ACC are enantiotopic, they are isochronous and cannot be distinguished by NMR.[5] However, enantiotopic groups can be rendered diastereotopic and thus anisochronous by several techniques: (1) use of a chiral solvent, (2) use of a chiral lanthanide shift reagent, and (3) derivatization with a chiral reagent.[6] The last procedure has

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