+110° (c 3.1, $CDCl_3$)]. For ^1H and ^{13}C NMR data, see Table II and Figure 2, respectively.

Epoxide 23. Compound **22** (150 mg, 0.55 mmol) was dissolved in dichloromethane (5 mL) and cooled (ice bath). *m*-Chloroperbenzoic acid (150 mg, 0.65 mmol, 70%) was added and the mixture was left (ice bath) for 12 h and then chromatographed (Al_2O_3, CH_2Cl_2/EtOAc 1:1) to give **23** [oil, 68 mg, 43%; $[\alpha]^{23}_D$ +64° (c 1.35, $CDCl_3$)]. For ^1H and ^{13}C NMR data, see Table II and Figure 2, respectively.

(+)-(1*R*,2*S*,5*S*,6*S*,7*S*)-2-(Hydroxymethyl)-5-(benzyloxy)-4-oxatricyclo[5.2.1.0^{2,6}]dec-8-ene (24). The aldehyde **14** (123 mg, 0.45 mmol) was treated as in the preparation of **22** to give **24** [120 mg, 93%; $[\alpha]^{23}_D$ +92.5° (c 1.9, $CDCl_3$)]. For ^1H and ^{13}C NMR data, see Table II and Figure 2, respectively.

Alcohol 25. Compound **24** (100 mg, 0.37 mmol) was treated as in the preparation of **23** to give **25** [65 mg, 61%; mp 104–105 °C; $[\alpha]^{23}_D$ +96° (c 0.6, $CDCl_3$)]. For ^1H and ^{13}C NMR data, see Table II and Figure 2, respectively.

Acknowledgment. We thank Maria Levin for technical assistance. This work was supported by The Swedish Natural Science Research Council and The Swedish National Board for Technical Development.

Registry No. **1r**, 104322-41-0; **1s**, 104322-42-1; **2**, 128843-75-4; **3**, 128945-87-9; **6**, 128846-17-3; **7**, 128846-18-4; **8**, 128869-12-5; **9**, 128846-19-5; **10**, 104816-20-8; **11**, 104873-09-8; **12**, 104873-10-1; **13**, 104873-11-2; **14**, 104873-12-3; **15**, 104873-13-4; **16**, 128846-20-8; **17**, 128945-99-3; **18**, 128946-00-9; **19**, 128946-01-0; **20**, 128946-02-1; **21**, 128846-21-9; **22**, 104816-21-9; **23**, 104816-22-0; **24**, 104873-14-5; **25**, 104816-23-1; cyclopentadiene, 542-92-7.

Supplementary Material Available: ^1H and/or ^{13}C NMR spectra for compounds **10**, **11**, **15**, **18**, **20**, **21**, **22**, and **24** (15 pages). Ordering information is given on any current masthead page.

Total Synthesis of Indole Alkaloids. A New Strategy for (±)-19-Oxoaspidospermidine and (±)-19-Oxoaspidofractinine

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A synthesis for the preparation of 19-oxoaspidospermidine (1) and 19-oxoaspidofractinine (2) has been developed beginning with tetracyclic amido alcohol **9**. Dehydration of **9** gave enamide **10**. Reduction to the corresponding enamine followed by reaction with acetyl chloride afforded the tetracyclic enamino ketone **12**. Studies on the selective reduction of the olefinic bond of the enamino ketone moiety of **12** were carried out. Removal of N-4 protecting group and further alkylation with a three carbon atoms appendage gave compounds **17**. Cyclization to pentacyclic product **18** was achieved using NaH in a benzene/THF solution. After deprotection of the N-1 atom and oxidation to the unstable indolenine **22**, a biomimetic Mannich type cyclization led to 19-oxoaspidofractinine (**2**), a direct precursor of aspidofractinine **6**.

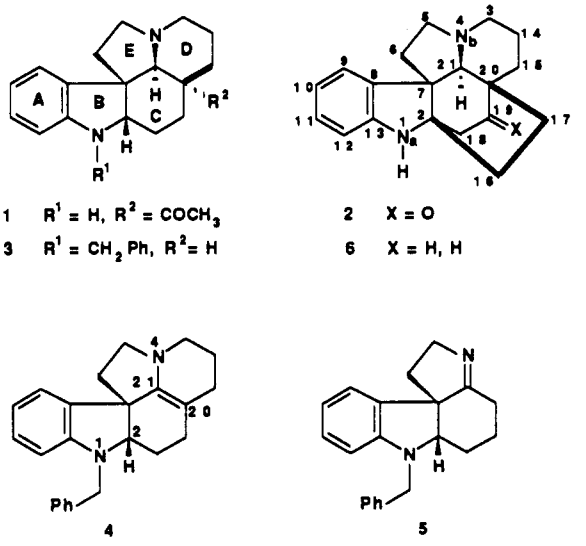
The *Aspidosperma* alkaloids belong to a series of natural products useful for the hemisynthesis of biologically active compounds (e.g. vincamine and antitumor dimeric alkaloids).[1] For these reasons increasing attention has been paid to their total synthesis.[2] In continuation of our program[3] aimed at the synthesis of the pentacyclic framework of these compounds, we report herein the synthesis of 19-oxoaspidospermidine (**1**) and 19-oxoaspidofractinine (**2**) (Chart I).

Our scheme is based on the fundamentally new approach we have described before for *N*-1-benzyldeethylaspidospermidine (**3**)[4] from *cis*-hexahydrocarbazol-4-ones.[5]

For the generality of this methodology it is necessary to be able to introduce a functionalized C-20[6] side chain often present in alkaloids of this group. The use of the previously described pentacyclic enamine **4**[4] failed due to its poor reactivity (no reaction occurred even with acetyl chloride). Starting from tetracyclic imine **5**[4] (Chart I), double alkylation at C-20 presented problems of reactivity and stereochemistry.

In order to circumvent these problems we thought that a tetracyclic enamine such as **11** (Scheme I) would be considerably more reactive than **4** and could be a useful synthetic intermediate.

Chart I



In our strategy the last stage of the synthesis is the formation of ring D. A C-20 acetyl chain would allow the

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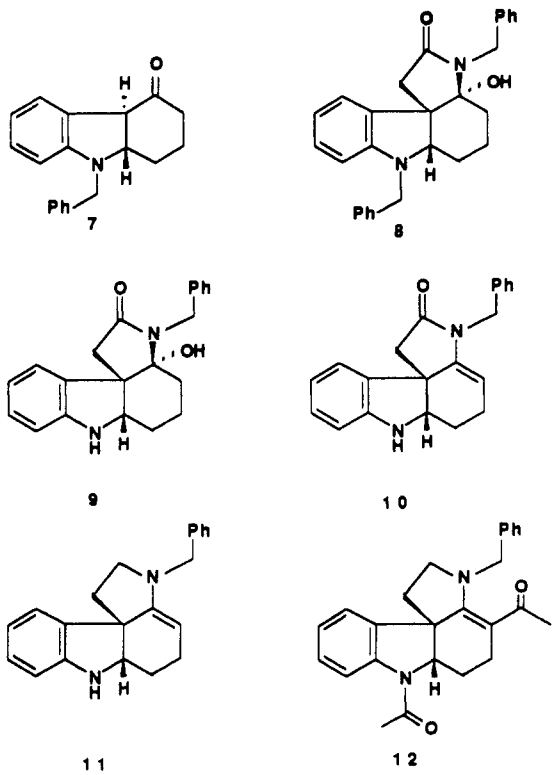
Scheme I



thermal cyclization of the enolate anion on the three-carbon chain situated on N-4. Such a final step was successfully used by Kuehne and Earley.[7] Moreover, this C-20 acetyl group could permit further modifications of the side chain[8] and biomimetic Mannich type cyclization to the hexacyclic structure of the aspidofractinine 6[9] (Chart I).

Introduction of this acetyl appendage could be easily obtained by acylation of tetracyclic enamine 11. Further chemo- and stereoselective reduction of the double bond of enamino ketone 12 thus obtained is the crucial step of the synthesis, since the stereochemistry of C-21 is definitively established at this stage.

Finally, 15 (Scheme III) could be transformed into target compound 17 by selective alkylation at N-4 with a three-carbon side chain unit bearing a leaving group. This approach requires a selective protection of N-1 and N-4 that is achieved with N-1 acetyl and N-4 benzyl substitutions.

Results and Discussion

I. Synthesis of Enamino Ketone 12. Nonoxidative photocyclization of tertiary enaminones led to the formation of *trans*-hexahydrocarbazol-4-one.[10] This reaction is efficient only if the nitrogen atom is substituted by an alkyl group: secondary (N-H) enaminones are photochemically unreactive as are enaminones in which the nitrogen atom is substituted by an electron-withdrawing group since the nitrogen lone pair involved in the photocyclization reaction is no longer available. Alkylation[5] of *trans*-hexahydrocarbazol-4-one 7 with *N*-benzyliodoacetamide in the presence of KH furnished the tetracyclic amido alcohol 8 in a 75% yield. Compound 8 is obtained as a single diastereoisomer with a cis B/C and C/E ring junction. Alkylation of 7 has already been shown to lead exclusively to the more stable B/C *cis*-hexahydrocarbazol-4-one.[5] The intramolecular cyclization of the hindered secondary amide function on the keto group is spontaneous and complete, as occurs in the case of iodoacetamide itself;[4] the C/E cis ring junction corresponds to the more favorable geometry as shown by examination of molecular models. Spectroscopic data were in accord with the proposed structure, i.e. strong IR absorptions at 3525 and 1705 cm^{-1} together with characteristic signals in the ^{13}C NMR spectrum for C-21 (δ 91.2) and C-5 (δ 171.8).

The selective protection of N-1 and N-4 which is necessary in the last steps of the synthesis is achieved at this stage. Treatment of 8 in hydrogenolysis conditions[11] should give only dihydroindole benzyl group cleavage since the N-4 benzyl group of the hydroxy amide 8 is expected to be insensitive.

In fact, the acidic conditions used for the hydrogenolysis of 8 led to partial dehydration of the tertiary hydroxyl group, giving a mixture of 9 (59%) and 10 (40%) which were separated by silica gel chromatography for characterization. In subsequent runs the mixture of 9 and 10 was treated in dehydrating conditions, leading quantitatively to 10.

Dehydration of carbinol amide 9 was performed in presence of *d,l*-10-camphorsulfonic acid in CH_2Cl_2 solution continuously dried by percolation over molecular sieves in a Soxhlet apparatus, to give, quantitatively, the enamide 10, which showed strong IR absorptions at 1675 and 1725 cm^{-1}. The ^1H and ^{13}C NMR spectra were straightforward: the ethylenic H-20 signal appeared at δ 5.1 (t, J = 4 Hz) and characteristic signals for C-20 (δ 101.5) and C-21 (δ 142.1) were observed. Selective reduction of the amide function of enamide 10 with lithium aluminum hydride[12] gave the corresponding enamine as an unstable oil (91%). Its N- and C-acylation with 2 equiv of acetyl chloride led to the corresponding enaminone 12 in which N-1 bore an acetyl group and N-4 a benzyl group. Compound 12 showed spectroscopic data in accord with the proposed

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(4) Gramain, J.-C.; Husson, H.-P.; Troin, Y. *J. Org. Chem.* **1985**, *50*, 5517.

(5) Gramain, J.-C.; Husson, H.-P.; Troin, Y. *J. Heterocycl. Chem.* **1988**, *25*, 201.

(6) The biogenetic numbering is used throughout this paper: Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508. The depicted absolute configuration is that of natural (−)-aspidofractinine.

(7) Kuehne, M. E.; Earley, W. G. *Tetrahedron* **1983**, *39*, 3707.

(8) Langlois, N.; Andriamialisoa, R. Z. *J. Org. Chem.* **1979**, *44*, 2468.

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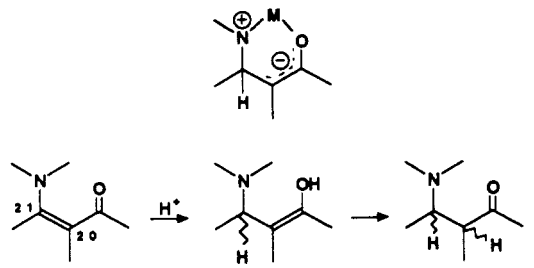
(10) Gramain, J.-C.; Husson, H.-P.; Troin, Y. *Tetrahedron Lett.* **1985**, *26*, 2323.

(11) Secrist, J. A. III; Logue, M. W. *J. Org. Chem.* **1972**, *37*, 335.

(12) Langlois, M.; Guillonneau, C.; Meingan, J.; Maillard, J. *Tetrahedron* **1971**, *27*, 5641.

Chart II



structure: strong IR absorptions at 1665 and 1630 cm^{-1}, two singlets at δ 2.25 and 2.0 for the N-1 acetyl group and the C-20 acetyl group, respectively, in the ^1H NMR spectrum, and signals at δ 193.9 (C-19), 168.1 (N-1 $COCH_3$), 158.2 (C-21), and 103.3 (C-20) in the ^{13}C NMR spectrum.

II. Reduction of Enamino Ketone 12. Crucial to the success of the synthesis is the stereoselective reduction of the double bond of the enamino ketone function since the stereochemistry of C-21 is fixed at this time and must correspond to a cis C/E ring junction as in the natural compounds of *Aspidosperma* series.

Chemoselectivity is also necessary because the reduction of the carbonyl group would give an alcohol which would be difficult to reoxidize in the presence of two nitrogen atoms.

At this step, two new asymmetric centers are introduced in the molecule and could lead to the formation of four diastereomers. It should be noticed that C-20 is epimerizable while C-21 is not.

While the reduction of enamines to amines is a well-known reaction, few methods for chemoselective reduction of the olefinic bond of an enamino ketone are described in the literature:

(1) $NaBH_3CN$ in acidic medium[13] is the most employed reagent. Langlois et al. have carried out a systematic study of reduction of the enamino ketone system in alkaloid synthesis,[14] and the best results were obtained in these conditions. In the first step the double bond is protonated to give an iminium ion which is further reduced by $NaBH_3CN$. The stereochemistry at C-20 depends on the stereochemistry of protonation and the stereochemistry at C-21 results from the approach of BH_3CN^- either on the α- or the β-face of the molecule.

(2) $LiAlH_4$ at low temperature[15] has been recently used in the chemoselective reduction of the double bond of Schiff's bases. The reduction mechanism proposed is analogous to those described earlier by Walker[16] and Martin:[17] it is a 1,4-reduction of the enamino ketone with the formation of cyclic complex. The first asymmetric center to be created is C-21 and the stereochemistry of C-20 depends on the stereochemistry of the protonation of the enol (Chart II).

(3) The treatment of enamino ketone with Meerwein's reagent leads to a conjugated iminium enol ether which is reduced by $NaBH_4$ to an amino enol ether. Final hydrogenolysis affords the desired β-amino ketone.[18] The stereochemistry at C-21 depends on the side of reduction of the iminium ion and the stereochemistry of C-20 is created during the hydrolysis of the enol ether (Chart III).

Chart III

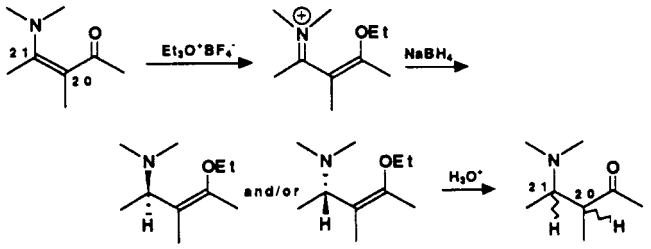
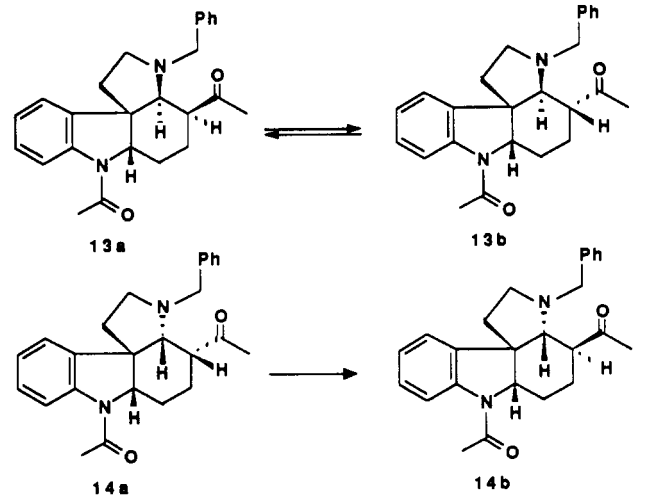


Table I. Reduction of Enamino Ketone 12. Product (Isolated Yield, %) and Stereochemistry of the Acetyl Side Chain

	$NaBH_3CN/H^+$	LAH	$Me_3O^+BF_4^-$ and then $NaBH_4$
21 nat	**13a** (20) ax	**13a** (42) ax **13b** (15) eq	
21 epi	**14a** (20) ax	**14a** (26) ax **14b** (5) eq	**14a** (80) ax

Scheme II



We have compared these three methods in order to obtain the best stereoselectivity. The results of the experiments are given in Table I.

(A) $NaBH_3CN/H^+$. Optimization of the experimental conditions ($NaBH_3CN$, 3 equiv; CF_3COOH, 1.5 equiv; MeOH; −30 °C; 5 min) gave with a moderate yield (40%) a mixture of amino ketones **13a** (20%) and **14a** (20%) (Scheme II), which were separated by silica gel chromatography. The reaction was very fast and was monitored by the disappearance of the yellow color of the starting material. Further reduction of the keto group to alcohol, which constituted most of the side products, could not be avoided even using the shortest reaction times.

Surprisingly the amino ketone **14a**, theoretically the least stable of the four possible isomers (with a C/E trans junction and an α-axial acetyl chain), is obtained in the same yield as the product with the natural stereochemistry at C-21, **13a**. Treatment in basic medium (NaH, THF, reflux) of **14a** afforded **14b** bearing the acetyl chain in a β-equatorial stereochemistry.

In fact, inspection of molecular models shows that the less hindered side of the molecule is the β-face. Therefore kinetic protonation of the enamino ketone from this side gives the observed stereochemistry at C-20 even though there is a strong steric interaction between the α-axial side chain and the dihydroindole nucleus. The α-face of the

(13) Lane, C. F. *Synthesis* **1975**, 135.
(14) Andriamialisoa, R. Z.; Langlois, N.; Langlois, Y. *Heterocycles* **1981**, *15*, 245.
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(17) Martin, J. C.; Barton, K. R.; Gott, P. G.; Meen, R. H. *J. Org. Chem.* **1966**, *31*, 943.
(18) Heathcock, C. H.; Davidsen, S. K.; Mills, S.; Sanner, M. A. *J. Am. Chem. Soc.* **1986**, *108*, 5650.

resulting iminium ion is even more crowded by the acetyl chain, and its reduction occurs only from the β-side, giving the enamino ketone **14a** of unnatural stereochemistry.

These considerations have only a qualitative value due to the great flexibility of ring C in these tetracyclic compounds as shown by molecular models and by the variation of the coupling constants of H-2 and H-21 with their neighbors. It should be noted that even with a short reaction time polar compounds (reduction of the carbonyl group) were obtained in nonnegligible amounts. All attempts to modify the experimental conditions (temperature, time of reaction) and especially by addition of zinc chloride in order to limit the carbonyl reduction[19] gave no improvement.

The low chemical yield, together with the formation of undesired products, led us to abandon this method.

(B) $LiAlH_4$ at Low Temperature. The reaction was carried on enamino ketone **12**, in the experimental conditions described by Schuda et al.[15] using 2.0 equiv of hydride ion and a short reaction time (30 s to 1 min). Usual treatment and purification by silica gel chromatography led to the four diastereoisomers, **13a** (42%), **13b** (15%), **14a** (26%), and **14b** (5%). The isomer with the desired C-21 configuration (**13a** + **13b**) (57%) can be used as a mixture in the following step.

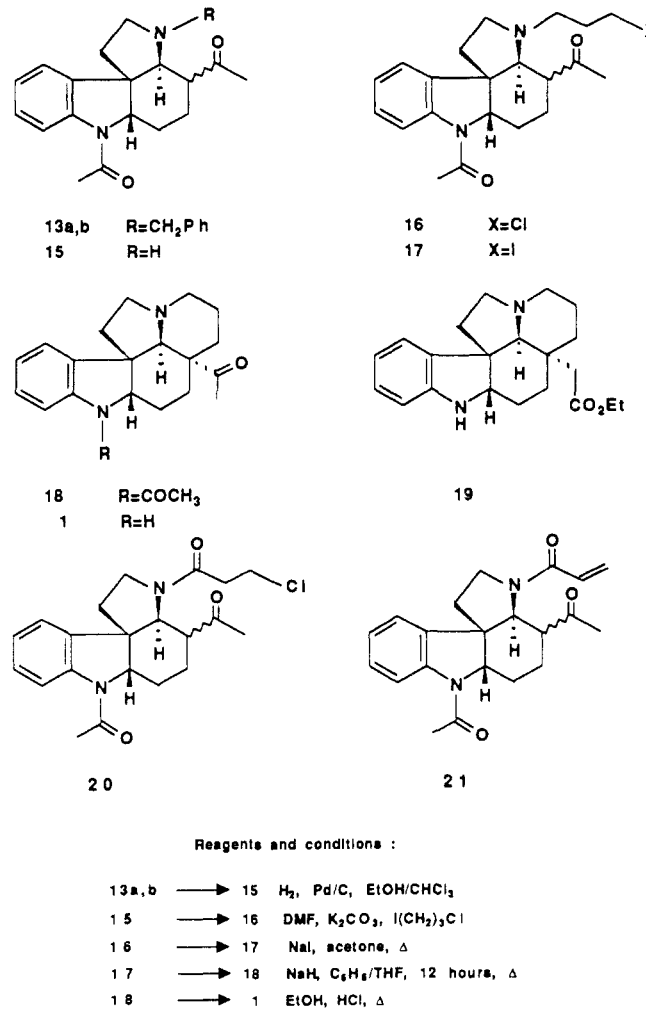
(C) Reduction of the Enol Ether by $NaBH_4$. Enamino ketone **12** was treated first with trimethyloxonium tetrafluoroborate in methylene chloride at 0 °C and then with sodium borohydride in methanol at 0 °C. After hydrolysis and purification **14a** is the only isomer obtained in a 80% yield. The obtention of the isomer of C/E trans configuration made this kind of reduction nonexploitable for our synthesis in spite of the good overall yield.

It is remarkable that the only product isolated is the kinetic one, **14a** being the less stable of the four diastereoisomers (vide supra). The reduction of the iminium occurs from the less hindered β-face, leading to C-21 epi stereochemistry and the subsequent protonation of the enol ether occurs also exclusively from the β-side leading to the α-axial acetyl chain.

The chemistry of the 1,4-reduction by $LiAlH_4$ (method B) is more difficult to rationalize: it is impossible that formation of a cyclic complex between the metal, the nitrogen atom, and the carbonyl group could make the α-attack more favorable.

III. Structure and Stereochemistry of Amino Ketones 13a,b and 14a,b. Rigorous assignments of structure and stereochemistry of these compounds was possible through examination of spectra data, in particular ^1H NMR, ^{13}C NMR, and 2D NMR experiments (COSY), inspection of molecular models, and results of base-catalyzed equilibration of each compound. Thus, treatment of **13a** in methanolic potassium carbonate at room temperature gave an equilibrium mixture of **13a** and **13b** with a ratio of 25:75. The same ratio is obtained in the same conditions starting with pure **13b**. The equilibration of **14a** required more drastic conditions (NaH, THF, reflux) and furnished quantitatively **14b** whose spectroscopic data indicated that it was the fourth possible diastereoisomer. These results showed that **13a** and **13b** on the one hand and **14a** and **14b** on the other are epimers at C-20. The four isomers exhibited carbonyl absorption at 1705 cm^{-1} and Bohlmann–Wenkert bands[20] were observed for the pair **14a** and **14b**

Scheme III



indicating a trans disposition of H-21 and the lone pair of N-4.

Examinations of ^1H NMR spectra and especially the chemical shifts of H-9 and H-21 and the coupling constant of the latter with H-20 in each isomer indicated the relative stereochemistry of the four diastereomers. Thus, H-9 resonates at lower field in the 21 epi series (**14a**, δ 7.55; **14b**, δ 7.9) than in the 21 natural series (**13a**, δ 7.4; **13b**, δ 7.1) due to the relative proximity of the lone pair of N-4[3] in the C/D trans isomers. The H-21 appears at lower field in the natural series (**13a**, δ 3.9, broad singlet, $W_{1/2}$ = 7.5 Hz; **13b**, δ 3.7, broad singlet, $W_{1/2}$ = 8 Hz) than in the 21 epi series (**14a**, δ 3.1, d, J = 6 Hz; **14b**, δ 3.45, d, J = 10 Hz). The coupling constants are consistent with the geometry and with the H-20, H-21 dihedral angles expected for these products in which the C ring is flattened. The 10-Hz coupling constant in **14b** confirms the trans diaxial arrangement of H-20/H-21 and hence the equatorial position of the side chain.

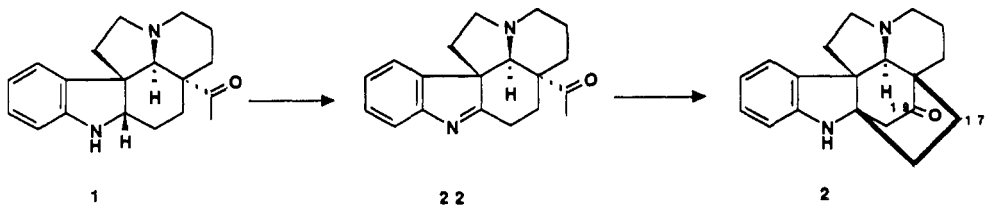
IV. Synthesis of 19-Oxoaspidospermidine (1). Starting from the mixture **13a,b** hydrogenolysis[11] of the benzyl group borne at N-4 led to the secondary amine **15** (Scheme III) in a quantitative yield. Alkylation of N-4 with 1-iodo-3-chloropropane gave **16** with an unoptimized yield of 53%. This alkylation step was very sluggish, and partial halogen exchange (Cl → I) was observed during this reaction. Treatment of **16** with NaI in acetone at reflux for 12 h furnished the iodo derivative **17**.

The latter was added to a suspension of sodium hydride in a mixture of benzene and THF and refluxed for 12 h

(19) Kim, S.; Oh Ho, C.; Suk Ko, J.; Han Ahn, K.; Jin Kim, Y. *J. Org. Chem.* **1985**, *50*, 1927.

(20) Wenkert, E.; Roychaudhuri, R. K. *J. Am. Chem. Soc.* **1956**, *78*, 6417. Gaudemer, A.; Golfier, M.; Mandelbaum, A.; Parthasaraty, R. In *Determination of configurations by spectrometric methods*; Kagan, Ed.; Georg Thieme Publishers: Stuttgart, 1977; Stereochemistry, Vol. I.

Scheme IV



1 22 2

1 ⟶ 22 $(COCl)_2$, DMSO, NEt_3, -60°C

22 ⟶ 2 MeOH, conc. HCl, Δ

to afford a single product 18 in 85% yield. The spectroscopic data confirmed the expected pentacyclic structure of 18: the IR spectrum shows the presence of Bohlmann–Wenkert bands at 2860, 2780, and 2720 cm^{-1} and absorption at 1700 and 1655 cm^{-1}. In the ^1H NMR spectrum the acetyl group at C-20 (δ 2.02) and H-21 as a singlet (δ 3.25) proved that cyclization had ocurred at C-20.

Finally characteristic fragmentations of the pentacyclic *Aspidosperma* alkaloids[21] are observed in mass spectrometry: main ions appear at *m/z* 166, 144, 138, 130, and 295 (M – 43) corresponding to the loss of the acetyl at C-20.[22]

The expected stereochemistry is that resulting from anionic cyclization on the β-face of the molecule and leading to an α-acetyl side chain. This process is by far more favorable than the cyclization leading to the epimer at C-20, as shown by examination of molecular models. The same stereochemistry has been observed by Kuehne and Earley[7] in the β-anilinoacrylate series. This analogy, the obtention of a unique compound with a good yield and finally the conversion into 19-oxoaspidofractinine, 2, confirm the pentacyclic structure and stereochemistry of 18.

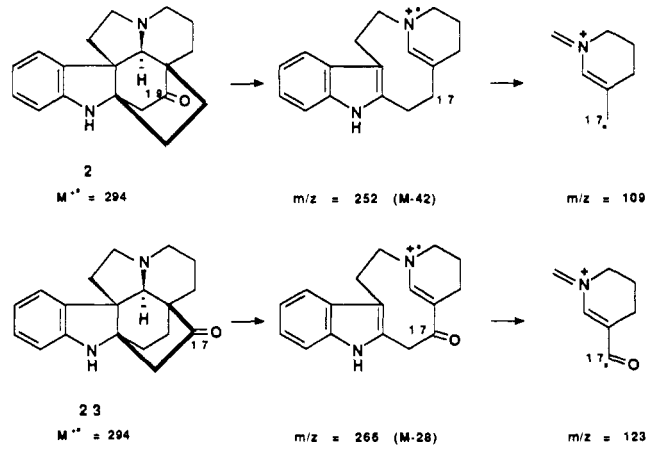
Deacetylation of 18 (concentrated HCl, MeOH, reflux) gives (±)-19-oxoaspidospermidine (1) in 90% yield. In the ^1H NMR spectrum the H-12 signal appears at δ 6.55 as expected, while H-2 resonates at δ 3.45 and couples with both C-16 protons (J = 5 and 10 Hz), characteristic of the cis B/C ring junction. The ^{13}C NMR spectrum of 1 is practically identical with that of 19[23] with the exception of C-20 which is differently substituted in the two compounds.

In view of the moderate yield (53%) of the alkylation step of 15, we introduced the three-carbon side chain by N-acylation of 15 with 3-chloropropionyl chloride. The acylated compound 20 was obtained with an excellent yield (95%). Unfortunately, although the stereochemistry of the compound is favorable for a ring closure of the side chain on carbon 20, basic treatment of 20 (KH/THF/reflux or NaH/THF/reflux) leads invariably to HCl elimination and formation of the acrylamide 21.

V. Synthesis of 19-Oxoaspidofractinine (2). The synthesis of 19-oxoaspidofractinine (2), a direct precursor of aspidofractinine itself,[9] was envisaged according to an intramolecular Mannich type cyclization.

Compound 1 was oxidized to indolenine 22 (Scheme IV) by Swern oxidation,[24] which gave better results than traditional methods using lead tetraacetate,[8] potassium permanganate,[25] or benzene selenic anhydride.[26] The nonisolated indolenine 22 was then refluxed with concentrated HCl in ethanol to give 2 in a 85% yield in two steps from 1.

Chart IV



Compound 2 was obtained as a single diastereoisomer and the stereochemistry of the cyclization process depends upon that of the acetyl chain borne at C-20. Definitive confirmation is obtained by use of mass spectrometry. Mass fragmentation of hexacyclic alkaloids of this series has been extensively studied.[27-29] Initial fragmentation is via a retro Diels–Alder process which leads to loss of a fragment containing C-18 and C-19. In this way it is easy to distinguish between molecules substituted either on C-18/C-19 fragment or C-16/C-17 fragment.

In the case of compound 2 the principal ions are observed at *m/z* 252 (M – 42) and 109 as depicted for a C-19 carbonyl function. In contrast the same fragmentation leads to ions at *m/z* 266 (M – 28) and 123 for the recently synthesized 17-oxo isomer 23[30] (Chart IV).

This proof of stereochemistry for compound 2 also constitutes a confirmation of the stereochemistry attributed to 1 and its precursor 18. Since the reduction of the keto group has already been performed,[9] this work constitutes a formal total synthesis of (±)-aspidofractinine, 6.

In conclusion all these results illustrate the potential flexibility of our approach to the synthesis of indole alkaloids from the tetracyclic enamino ketone 12.

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Experimental Section

Infrared spectra (IR) were recorded in solution on a Perkin-Elmer 377 spectrophotometer. Infrared absorption bands are expressed in reciprocal centimeters with polystyrene calibration. Peaks yielding structural information are reported. ^1H nuclear magnetic resonance (NMR) spectra were recorded in $CDCl_3$ (tetramethylsilane as an internal standard) on a JEOL C60H, a Brucker WM 250, or a Brucker MSL 300 instrument. Chemical shift data are reported in parts per million downfield from tetramethylsilane, where s, d, dd, t, q, and m designate singlet, doublet, doublet of doublets, triplet, quadruplet, and multiplet, respectively. ^{13}C NMR spectra were recorded in $CDCl_3$ (TMS, $\delta = 0$) on a JEOL FX 60 or a Brucker MSL 300 instrument. Low-resolution (70 eV) and high-resolution mass spectrometries were performed on a Varian CH5 instrument.

All melting points were determined on a micro hot stage Reichert apparatus. Reagent-grade THF and ether were distilled from potassium benzophenone prior to use. All the samples used for spectroscopic measurements were obtained by flash chromatography[31] on silica gel. Irradiations were performed in a Pyrex glass vessel using a medium-pressure mercury lamp (Philips 400-W). Before irradiation the reaction mixture was flushed with a stream of argon for 10 min in order to remove oxygen. Potassium hydride was carefully washed with hexane before use and dried under argon.

Preparation of Amido Alcohol 8. A solution of **7** (1.4 g, 5.0 mmol) in THF (10 mL) was added to a suspension of potassium hydride (35% in oil; 0.63 g, 5.5 mmol) in THF (10 mL) and stirred at room temperature for 5 min under an atmosphere of argon. The resulting mixture was then added to a solution of *N*-benzyliodoacetamide (1.37 g, 5.5 mmol) in THF (20 mL). After the mixture had been stirred for an additional 10 min, water was added in order to solubilize the precipitate. The bulk of THF was distilled and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were washed with water, dried over sodium sulfate, and concentrated. The crude product was purified by filtration through a column of silica gel (elution with AcOEt–hexane, 1:1). The pure compound **8** (1.6 g, yield = 75%) was obtained: mp 155–156 °C (ether); IR (CCl_4) ν_{max} 3525, 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.1–2.3 (m, 6 H + 1 H exchangeable with D_2O), 2.7 (s, 2 H), 3.5–3.7 (m, 1 H), 4.3 (2 H, J_{AB} = 15 Hz, $\Delta\nu$ = 24 Hz), 4.5 (s, 2 H), 6.4–7.7 (m, 14 H); ^{13}C NMR ($CDCl_3$) δ 171.8, 153.3, 138.9, 138.4, 129.9, 127.4, 123.9, 118.9, 108.8, 91.2, 68.1, 52.9, 50.9, 42.4, 40.8, 34.4, 23.4, 16.7; MS *m/z* (relative intensity) 424 (18), 406 (34), 315 (27), 224 (4), 183 (7), 130 (6), 91 (100), 65 (11), 40 (9); exact mass *m/z* 424.2143 (calcd for $C_{28}H_{28}N_2O_2$ *m/z* 424.2144).

Preparation of Amido Alcohol 9 and Enamide 10. To a solution of amido alcohol **8** (1.0 g, 2.36 mmol) in $CHCl_3$ (25 mL) and ethanol (30 mL) was added concentrated hydrochloric acid (1.2 mL). The resulting mixture was hydrogenated for 20 h at 50 psi (Parr apparatus) and room temperature using 10% palladium on charcoal (50 mg) as catalyst. Water was added, and then the aqueous phase was extracted with CH_2Cl_2. The organic layer was washed with sodium carbonate solution (5%) and then with water and then dried over sodium sulfate, and the solvent was evaporated. The crude product was purified by flash chromatography on silica gel (elution with hexane–AcOEt, 1:1) to give successively **10** (0.3 g, yield = 40%) and **9** (0.47 g, yield = 59%). Compound **9** was dehydrated to enamide **10** using (±)-10-camphorsulfonic acid (0.0015 g) in CH_2Cl_2 in the presence of molecular sieves for 12 h. The reaction mixture was then neutralized at room temperature with anhydrous K_2CO_3. After filtration and concentration of the organic phase compound **10** (0.4 g) was obtained in quantitative yield.

9: mp 70–71 °C (ether); IR (CCl_4) ν_{max} 3530, 3390, 1695 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.2–2.0 (m, 6 H), 2.75 (s, 2 H), 2.5–3.5 (1 H, exchangeable with D_2O), 3.9 (m, 1 H), 4.5 (s, 2 H), 6.6–7.6 (m, 9 H + 1 H exchangeable with D_2O); ^{13}C NMR ($CDCl_3$) δ 172.2, 151.4, 138.8, 129.3, 129.0, 128.5, 128.4, 127.2, 124.4, 119.3, 110.3, 91.3, 63.3, 52.4, 42.2, 40.7, 33.8, 26.6, 16.5.

10: amorphous; IR (CCl_4) ν_{max} 3420, 1725, 1675 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.65 (m, 2 H), 1.95 (m, 2 H), 2.7 (s, 2 H), 3.25 (1 H exchangeable with D_2O), 4.0 (1 H, t, J = 4 Hz), 4.65 (2 H, J_{AB} = 15 Hz, $\Delta\nu$ = 43 Hz), 5.1 (1 H, t, J = 4 Hz), 6.5 (m, 2 H), 6.8 (d, 1 H, J = 7.5 Hz), 7.25 (t, 1 H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 172.6, 143.9, 142.1, 136.7, 136.2, 128.6, 128.4, 127.9, 127.6, 123.2, 122.1, 113.6, 101.5, 62.6, 58.3, 48.0, 43.8, 29.6, 19.7; MS *m/z* (relative intensity) 316 (16), 225 (19), 170 (28), 143 (10), 130 (20), 91 (100); exact mass *m/z* 316.1573 (calcd for $C_{21}H_{20}N_2O$ *m/z* 316.1575).

Preparation of Enamino Ketone 12. A solution of crude enamide **10** (2.25 g, 7.12 mmol) in THF (100 mL) was added to a suspension of $LiAlH_4$ (21.5 mL of a 1.0 M solution in THF, 21.5 mmol). The resultant mixture was then refluxed for 12 h. After addition of water and filtration of inorganic salts, the filtrate was concentrated to give **11** as a crude product which could be used without purification in the next step. To a solution of enamine **11** (1.96 g, 6.5 mmol) in anhydrous CH_2Cl_2 (50 mL) at 0 °C and under argon were added successively triethylamine (2.3 mL, 16.5 mmol) and acetyl chloride (0.97 mL, 13.6 mmol). The mixture was stirred for an additional 15 min at 0 °C, water was then added, and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were washed with water and dried over sodium sulfate, and the solvent was evaporated. The crude product was purified by flash chromatography on silica gel (elution with AcOEt) to give **12** (1.89 g, yield = 75%): mp 159–160 °C (ether); IR (CCl_4) ν_{max} 1665, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.6–2.4 (m, 6 H), 2.0 (s, 3 H), 2.25 (s, 3 H), 3.35 (m, 1 H), 3.65 (m, 1 H), 4.35 (m, 1 H), 4.85 (s, 2 H), 6.55 (d, 1 H, J = 7.5 Hz), 6.85 (t, 1 H, J = 7.5 Hz), 7.15 (t, 1 H, J = 7.5 Hz), 7.3 (m, 5 H), 8.1 (d, 1 H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 193.9, 168.1, 158.2, 142.2, 137.1, 135.0, 129.4, 128.4, 127.4, 124.2, 122.1, 116.8, 113.5, 103.3, 68.3, 54.8, 51.4, 51.1, 37.7, 33.0, 28.9, 23.7, 23.3; MS *m/z* (relative intensity) 386 (24), 371 (6), 369 (5), 343 (32), 295 (8), 143 (16), 130 (10), 91 (100); exact mass *m/z* 386.1990 (calcd for $C_{25}H_{26}N_2O_2$ *m/z* 386.1994).

Reduction of Tetracyclic Enamino Ketone 12. Method A. To a solution of sodium cyanoborohydride (0.044 g, 0.70 mmol) and trifluoroacetic acid (0.027 mL, 0.35 mmol) in methanol (5 mL) at −25 °C under argon was added a solution of enamino ketone **12** (0.09 g, 0.23 mmol) in methanol (5 mL). The end of the reaction was checked by the disappearance of the yellow color of the starting enamino ketone. The mixture was then poured into a 10% aqueous sodium carbonate solution, and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were washed with water and dried over sodium sulfate, and the solvent was evaporated. After purification by flash chromatography on silica gel (elution with hexane–AcOEt, 1:1), **13a** (0.018 g, yield = 20%) and **14a** (0.020 g, yield = 22%) were separated.

13a: amorphous; IR (CCl_4) ν_{max} 1705, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.65–1.75 (m, 2 H), 1.9–2.05 (m, 4 H), 2.15 (s, 3 H), 2.28 (s, 3 H), 2.5 (m, 1 H), 2.8 (m, 1 H), 3.05 (m, 1 H), 3.7 (1 H, broad singlet, $\Delta\nu$ = 8 Hz), 3.85 (2 H, J_{AB} = 13.5 Hz, $\Delta\nu$ = 170 Hz), 4.05 (m, 1 H), 7.05 (t, 1 H), 7.1 (m, 2 H), 7.2–7.4 (m, 5 H), 8.1 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 209.2, 167.9, 144.3, 139.2, 129.7, 128.3, 127.9, 126.9, 123.8, 118.1, 115.5, 66.5, 64.3, 58.9, 53.0, 50.6, 49.9, 39.4, 37.4, 29.1, 23.4, 20.1; MS *m/z* (relative intensity) 388 (4), 345 (5), 343 (6), 297 (17), 212 (7), 170 (7), 168 (9), 146 (14), 107 (15), 106 (16), 91 (100); exact mass *m/z* 388.2152 (calcd for $C_{25}H_{28}N_2O_2$ *m/z* 388.2151).

14a: mp 187–189 °C (ether); IR (CCl_4) ν_{max} 2870, 2810, 1705, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.4 (m, 1 H), 1.65 (m, 1 H), 1.8–2.0 (m, 3 H), 2.1 (m, 1 H), 2.28 (s, 3 H), 2.35 (s, 3 H), 2.4 (m, 1 H), 3.05 (m, 1 H), 3.1 (d, 1 H, J = 6 Hz), 3.2 (m, 1 H), 3.35 (d, 1 H, J = 13 Hz), 4.05 (dd, 1 H, J = 6 and 8 Hz), 4.65 (d, 1 H, J = 13 Hz), 6.95–7.5 (m, 7 H), 7.55 (d, 1 H, J = 8 Hz), 8.15 (d, 1 H, J = 8 Hz); ^{13}C NMR ($CDCl_3$) δ 207.3, 167.6, 140.8, 138.6, 135.5, 128.5, 128.1, 127.0, 125.1, 123.5, 118.1, 115.2, 69.2, 67.0, 59.5, 53.1, 50.0, 45.3, 38.6, 31.7, 26.5, 23.8, 23.2; MS *m/z* (relative intensity) 388 (7), 345 (15), 297 (13), 212 (6), 146 (12), 144 (13), 130 (13), 91 (100); exact mass *m/z* 388.2149 (calcd for $C_{25}H_{28}N_2O_2$ *m/z* 388.2151).

Method B. To a suspension of $LiAlH_4$ (0.65 mL of 1.0 M solution in THF, 0.65 mmol) in THF was added rapidly, under argon and at −25 °C, a solution of enamino ketone **12** (0.5 g, 1.3 mmol) in THF (20 mL). After 1 min ethyl acetate (0.170 mL) and then water (0.420 mL) were added successively. The resultant solution was warmed to room temperature and stirred for an

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additional 30 min. The mixture was dried over sodium sulfate; the inorganic salts were washed with CH_2Cl_2 and concentrated. After purification by flash chromatography on silica gel **13a** (0.075 g, yield = 15%), **13b** (0.21 g, yield = 42%), **14a** (0.13 g, yield = 26%), and **14b** (0.025 g, yield = 5%) were obtained.

13b: mp 144–145 °C (ether); IR (CCl_4) ν_{max} 1705, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (m, 1 H), 1.55–1.75 (m, 2 H), 1.9 (m, 1 H), 2.15 (m, 1 H), 2.2 (m, 1 H), 2.25 (s, 6 H), 2.4 (m, 1 H), 2.5 (m, 1 H), 3.05 (m, 1 H), 3.55 (2 H, J_{AB} = 12.5 Hz, $\Delta\nu$ = 137 Hz), 3.9 (1 H, broad singlet, $\Delta\nu$ = 7.5 Hz), 4.05 (dd, 1 H, J = 6 and 11 Hz), 7.15 (t, 1 H, J = 7.5 Hz), 7.2–7.4 (m, 7 H), 8.15 (d, 1 H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 210.4, 168.2, 141.6, 139.3, 134.5, 128.3, 127.1, 124.5, 121.4, 118.8, 115.9, 65.8, 65.1, 59.5, 54.3, 51.7, 51.3, 37.6, 29.2, 28.6, 23.2, 18.1; MS exact mass m/z 388.2152 (calcd for $C_{25}H_{28}N_2O_2$ m/z 388.2151).

14b: mp 120–122 °C (ether); IR (CCl_4) ν_{max} 2870, 2810, 1710, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.2 (m, 1 H), 1.4–1.6 (m, 3 H), 1.85 (m, 1 H), 1.9 (s, 3 H), 2.0 (m, 1 H), 2.3 (s, 3 H), 2.45 (m, 1 H), 2.7 (m, 1 H), 3.1 (m, 1 H), 3.45 (d, 1 H, J = 10 Hz), 3.5 (2 H, J_{AB} = 13 Hz, $\Delta\nu$ = 98 Hz), 4.3 (m, 1 H), 7.1 (t, 1 H, J = 8 Hz), 7.25 (t, 1 H, J = 8 Hz), 7.3–7.4 (m, 5 H), 7.9 (d, 1 H, J = 8 Hz), 8.2 (d, 1 H, J = 8 Hz); ^{13}C NMR ($CDCl_3$) δ 209.9, 168.2, 142.7, 139.7, 137.3, 129.5, 128.4, 128.0, 127.0, 125.2, 124.1, 117.0, 113.8, 66.1, 64.1, 59.4, 52.7, 51.0, 47.2, 38.5, 29.4, 26.9, 23.6, 21.5; MS exact mass m/z 388.2154 (calcd for $C_{25}H_{28}N_2O_2$ m/z 388.2151).

To a stirred solution of sodium hydride (60% in mineral oil; 0.011 g, 0.283 mmol) in THF (5 mL) was added, under nitrogen, a solution of **14a** (0.1 g, 0.257 mmol) in THF (2 mL). The resulting mixture was refluxed for 1 h. After cooling, water was added, and the aqueous phase was extracted with CH_2Cl_2. The organic layer was washed with water and dried over sodium sulfate, and the solvent was evaporated to give **14b** in quantitative yield.

Preparation of Amine 15. A solution of amino ketones **13a** and **13b** (0.96 g, 2.47 mmol) in chloroform (20 mL) and ethanol (30 mL), made pH 4 with concentrated hydrochloric acid, was hydrogenated for 8 h at 50 psi (Parr apparatus) and room temperature using 10% palladium on charcoal (50 mg) as catalyst. The reaction mixture was filtered through a Celite bed and neutralized with a 5% aqueous sodium carbonate solution. The aqueous phase was extracted with CH_2Cl_2; the organic layer was washed with water, dried over sodium sulfate, and concentrated to gave the nearly pure amine **15** (0.7 g, yield = 95%), which was used directly in the next step: IR (CCl_4) ν_{max} 3380, 1710, 1665 cm^{-1}.

Preparation of Amine 16. A solution of **15** (0.7 g, 2.35 mmol) and 1-iodo-3-chloropropane (0.3 mL, 2.8 mmol) in DMF (5 mL) was stirred at room temperature under nitrogen for 4 days. The solvent was evaporated and the crude residue was chromatographed on silica gel (elution hexane–AcOEt, 1:1, then AcOEt) to give **16** as two diastereoisomers.

16a (0.32 g, yield = 36%): amorphous; IR (CCl_4) ν_{max} 2850, 2800, 1710, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (m, 1 H), 1.65 (m, 2 H), 1.95 (m, 3 H), 2.22 (s, 3 H), 2.25 (s, 3 H), 2.15–2.45 (m, 5 H), 2.55 (m, 1 H), 3.25 (m, 1 H), 3.55 (m, 2 H), 3.75 (m, 1 H), 4.0 (m, 1 H), 7.1 (t, 1 H, J = 8 Hz), 7.25 (m, 2 H), 8.15 (d, 1 H, J = 8 Hz), MS m/z (relative intensity) 376 (25), 374 (75), 339 (29), 331 (42), 311 (100), 297 (91), 269 (35), 251 (29).

16b (0.14 g, yield = 16%): amorphous; IR (CCl_4) ν_{max} 2860, 2800, 1710, 1660 cm^{-1}; MS m/z (relative intensity) 376 (11), 374 (33), 338 (53), 331 (21), 311 (64), 297 (53), 295 (100), 149 (74).

Preparation of Compound 17. A solution of **16a,b** (0.225 g, 0.6 mmol) in acetone (10 mL) was added to a solution of sodium iodide (0.9 g, 6 mmol) in acetone (15 mL). The resultant mixture was heated at reflux for 2 days. After cooling the bulk of the acetone was evaporated. Water (20 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with a 5% sodium thiosulfate solution, dried over sodium sulfate, and concentrated to give compounds **17** (0.28 g, quantitative yield) as amorphous products.

Cyclization of 17: *N*-Acetyl-19-oxoaspidospermidine (18). To a suspension of sodium hydride (60% in oil; 0.026 g, 0.66 mmol) in benzene (10 mL) was added a solution of **17** (0.28 g, 0.6 mmol) in THF (10 mL). The resulting mixture was stirred under nitrogen at reflux for 12 h. After cooling, the bulk of solvent was evaporated. Water was then added, and the aqueous phase was extracted with CH_2Cl_2. The organic layer was washed with a saturated solution of ammonium chloride, dried over sodium sulfate, and concentrated.

The crude product was purified by flash chromatography on alumina (elution with hexane–AcOEt, 1:1) and gave **18** (0.172 g, yield = 85%): amorphous; IR ($CHCl_3$) ν_{max} 2860, 2780, 2720, 1700, 1655 cm^{-1}; UV (EtOH) λ_{max} nm (log ϵ) 250 (4.1), 210 (4.4); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.3–1.8 (m, 8 H), 2.02 (s, 3 H), 2.25 (s, 3 H), 1.95–2.4 (m, 4 H), 3.0–3.2 (m, 2 H), 3.25 (s, 1 H), 4.0 (dd, 1 H, J = 5 and 11 Hz), 7.05 (t, 1 H, J = 7.5 Hz), 7.15 (t, 1 H, J = 7.5 Hz), 7.3 (d, 1 H, J = 7.5 Hz), 8.05 (d, 1 H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 210.4, 168.2, 140.9, 135.6, 127.8, 124.3, 124.2, 117.9, 67.5, 64.4, 53.7, 53.1, 52.3, 51.4, 39.4, 33.9, 27.6, 25.0, 23.7, 23.3, 21.4; MS m/z (relative intensity) 338 (39), 323 (16), 295 (65), 267 (8), 166 (16), 149 (16), 144 (7), 143 (6), 138 (35), 130 (9), 94 (100); exact mass m/z 338.1990 (calcd for $C_{21}H_{26}N_2O_2$ m/z 338.1994).

Compound 20. To a solution of **15** (0.209 g, 0.70 mmol) and triethylamine (0.107 mL, 0.77 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 °C was added dropwise under nitrogen 3-chloropropionyl chloride (0.070 mL, 0.735 mmol). After stirring an additional 15 min at 0 °C, the resulting mixture was allowed to warm to room temperature. Water was added, and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were dried over sodium sulfate, and the solvent was evaporated to give **20** (0.256 g, yield = 95%): mp 124–125 °C (ether); IR ($CHCl_3$) ν_{max} 1705, 1655, and 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 1.2–2.5 (9 H, m), 2.28 (3 H, s, $COCH_3$), 2.38 (3 H, s, $NCOCH_3$), 2.7–3.1 (2 H, m), 3.6–4.1 (4 H, m), 7.0–7.5 (3 H, m), 8.0–8.2 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 209.7, 170.2, 168.3, 140.7 135.4, 129.0, 124.7, 122.0, 65.2, 60.5, 53.1, 49.4, 49.0, 46.3, 39.8, 37.9, 30.3, 26.9, 23.6, 19.0.

Compound 21. A solution of **20** (0.020 g, 0.05 mmol) in anhydrous THF (10 mL) was added dropwise to a suspension of potassium hydride (35% dispersion in oil; 0.006 g, 0.055 mmol) in THF (2 mL) under argon. The mixture was stirred for 2 h at room temperature. A 5% aqueous sodium bicarbonate solution (5 mL) was added, and the resulting mixture was extracted with CH_2Cl_2. The organic layer was dried over sodium sulfate, and the solvent was evaporated to give **21** (0.018 g, yield = 99%): amorphous; IR ($CHCl_3$) ν_{max} 1705, 1650, and 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.6–2.0 (5 H, m), 2.25 (3 H, s, $COCH_3$), 2.4 (3 H, s, $NCOCH_3$), 2.3–2.6 (2 H, m), 3.5–3.7 (4 H, m), 4.85 (1 H, d, J = 10 Hz), 7.1 (2 H, m), 7.15–7.4 (3 H, m), 8.1 (1 H, d, J = 8 Hz); MS m/z (relative intensity) 352 (39), 310 (31), 309 (100), 267 (39), 244 (39), 241 (31), 218 (19), 164 (96), 163 (100), 149 (31), 143 (31), 135 (31), 132 (26), 130 (26).

19-Oxoaspidospermidine (1). To a solution of **18** (0.054 g, 0.16 mmol) in ethanol (25 mL) was added concentrated hydrochloric acid (1 mL). The resulting mixture was stirred at reflux for 48 h. After cooling, the solvent was evaporated. CH_2Cl_2 was added, and the crude mixture was basified with a 5% sodium carbonate solution. The organic layers were dried over sodium sulfate, and the solvent was evaporated. The crude mixture was purified by chromatography on alumina (elution with hexane–AcOEt, 1:1) and gave **1** (0.043 g, yield = 90%).

1: mp 146–148 °C (ether); IR ($CHCl_3$) ν_{max} 3390, 2860, 2780, 2720, 1700, 1655 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.2–1.9 (m, 10 H), 1.95 (s, 3 H), 2.1–2.5 (m, 2 H + 1 H exchangeable with D_2O), 3.05 (s, 1 H), 3.05–3.2 (m, 2 H), 3.45 (dd, 1 H, J = 5 and 10 Hz), 6.55 (d, 1 H, J = 8.5 Hz), 6.70 (t, 1 H, J = 8.5 Hz), 6.95 (t, 1 H, J = 8.5 Hz), 7.15 (d, 1 H, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 210.8, 149.8, 133.1, 127.7, 124.4, 119.0, 110,2, 66.2, 65.0, 54.0, 53.1, 51.5, 38.3, 34.1, 28.4, 25.1, 22.9, 21.6; MS m/z (relative intensity) 296 (52), 253 (100), 225 (10), 204 (10), 138 (42), 134 (16), 130 (28); exact mass m/z 296.1886 (calcd for $C_{19}H_{24}N_2O$ m/z 296.1888).

19-Oxoaspidofractinine (2). A mixture of dimethyl sulfoxide (0.010 mL, 0.141 mmol) and methylene chloride (0.5 mL) was added, under argon, at −60 °C, to a solution of oxalyl chloride (0.007 mL, 0.08 mmol) in methylene chloride (2 mL). After stirring for 3 min, a solution of compound **1** (0.020 g, 0.067 mmol) in CH_2Cl_2 (0.5 mL) was added. Stirring was continued for a further 10 min, and then triethylamine (0.047 mL, 0.337 mmol) was added. The resultant solution was warmed to room temperature, water (5 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The organic layer was washed with saturated aqueous sodium chloride solution and dried over sodium sulfate,

and the solvent was evaporated to gave the unstable indolenine **22**, which was used directly in the next step: IR ($CHCl_3$) ν_{max} 2860, 2790, 2730, 1695, 1600, and 1575 cm^{-1}.

Compound **22** (0.020 g, 0.068 mmol) was dissolved in ethanol (10 mL). Concentrated hydrochloric acid (1 mL) was added, and the resulting mixture was stirred at reflux for 12 h. After cooling, the solvent was evaporated, 5% sodium carbonate solution was added, and the mixture was extracted three times with CH_2Cl_2. The organic extract was dried over sodium sulfate and concentrated. The crude product was purified by flash chromatography on silica gel (elution with AcOEt–MeOH, 95:5) and gave compound **2** (0.017 g, yield = 85%): amorphous; IR ($CHCl_3$) ν_{max} 3350, 2850, 2780, 2720, 1705, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.2–2.0 (m, 10 H), 2.2–3.3 (m, 7 H + 1 H exchangeable with D_2O), 6.7 (d, 1 H, J = 7.5 Hz), 6.8 (t, 1 H, J = 7.5 Hz), 7.05 (t, 1 H, J = 7.5 Hz), 7.18 (d, 1 H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 216.6, 149.2, 143.5, 127.6, 122.2, 120.6, 111.3, 67.2, 65.2, 57.1, 51.2, 48.5, 47.8, 46.9, 35.4, 27.1, 26.2, 23.9, 17.3; MS m/z (relative intensity) 294 (100), 279 (10), 266 (12), 252 (45), 238 (20), 166 (10), 144 (12), 143 (12), 138 (40), 130 (10), 123 (10), 109 (60); exact mass m/z 294.1729 (calcd for $C_{19}H_{22}N_2O$ m/z 294.1732).

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Preparation of 4- and 10-Fluorobenzo[*j*]fluoranthene via Cyclodehydration of Acetals and Cyclopropanecarboxaldehydes

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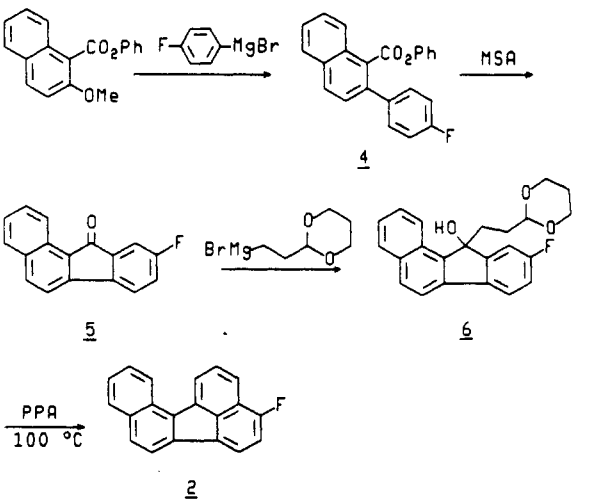
Two procedures have been developed for the synthesis of 4-fluorobenzo[*j*]fluoranthene (4-fluoroBjF) and 10-fluoroBjF. Reaction of 9-fluoro-11*H*-benzo[*a*]fluoren-11-one (**5**) with the Grignard reagent prepared from 2-(2-bromoethyl)-1,3-dioxane provided hydroxy acetal **6** in quantitative yield. Cyclodehydration with polyphosphoric acid (PPA) at 110 °C gave 4-fluoroBjF in 35% yield. This represents an improvement over previous methods for preparing BjF derivatives substituted in the B ring. The preparation of 10-fluoroBjF represents a new synthetic entry into the BjF ring system. 1-(4-Fluorophenyl)acenaphthylene (**8**) was treated with ethyl diazoacetate in the presence of copper bronze to give a mixture of *anti*- and *syn*-cyclopropanecarboxylates **9** and **10** in the ratio of 2:1. Reaction with iodotrimethylsilane gave the ring-opened ester attached at the 2-position of the substituted acenaphthylene. Reduction to the aldehyde followed by cyclodehydration with PPA at 100 °C gave 10-fluoroBjF in 58% yield. Alternatively, the cyclopropyl esters could be reduced directly to the aldehydes, which underwent efficient ring opening and cyclodehydration in PPA at 100 °C to 10-fluoroBjF in 53–57% yield.

Introduction

Benzo[*j*]fluoranthene (**1**) (BjF) (Figure 1) is a nonalternant polycyclic aromatic hydrocarbon that is tumorigenic to mice when applied topically and is carcinogenic when administered ip to newborn mice.[1] Studies in our laboratory have shown that two dihydrodiol metabolites, BjF-4,5-diol and BjF-9,10-diol, have tumorigenic activity under these bioassay conditions. While BjF-4,5-diol is more tumorigenic than BjF-9,10-diol, the latter is formed to a greater extent in vivo in mouse skin.[1a,c] The effect of fluorine substitution on biological activity will be evaluated to ascertain the relative contribution of these two major sites of metabolic activation of BjF to its overall tumorigenic activity. Fluorine frequently inhibits metabolism at the bond to which it is attached. In this report we describe the synthesis of 4-fluoroBjF (**2**) and 10-fluoroBjF (**3**) via cyclodehydration of acetals and cyclopropanecarboxaldehydes. The synthesis of **3** represents a new entry into the BjF ring system.

Scheme I. Synthesis of 4-Fluorobenzo[*j*]fluoranthene



Results and Discussion

9-Fluoro-11*H*-benzo[*a*]fluoren-11-one (**5**) was judged to be a suitable starting material for the synthesis of **2** (Scheme I). Previous syntheses of BjF derivatives substituted in either the A or B ring relied on alkylation of benzo[*a*]fluorene derivatives and required a total of nine steps.[2] It was envisioned that a much more concise synthesis could be devised by reacting a three-carbon nu-

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