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Quinolizidines. XXXII.[1] A Chiral Synthesis of 3,4,5,6-Tetradehydro-17-hydroxycorynanium, the Zwitterionic Structure Assigned to an Alkaloid from *Aspidosperma marcgravianum*†

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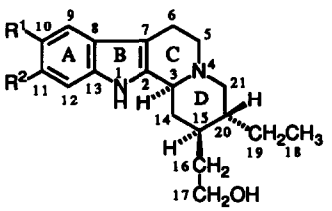
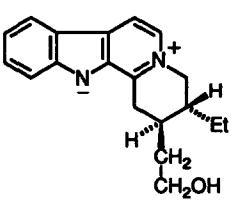
Abstract: The total synthesis of 3,4,5,6-tetradehydro-17-hydroxycorynanium [(+)-4], the zwitterionic structure assigned to an alkaloid from *Aspidosperma marcgravianum*, has been accomplished for the first time *via* a "lactim ether route". The route started with an initial condensation between the lactim ether [(+)-5] and 3-chloroacetylindole and proceeded through the lactam ester [(+)-23], lactam alcohol [(+)-24], acetoxylactam [(+)-26], quaternary iminium salt [(+)-25], and 3,4,5,6-tetradehydro-17-hydroxycorynanium perchlorate [(+)-27]. The ^{1}H NMR spectral data and the sign of specific rotation for the synthetic (+)-4 were in disagreement with those reported for a natural sample, leaving the chemistry of this *A. marcgravianum* alkaloid incomplete.

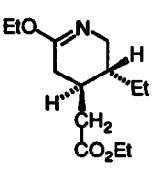
In 1983, Robert *et al.*[2] reported the isolation of 12 new alkaloids and 34 known alkaloids from the root bark, trunk bark, and leaves of *Aspidosperma marcgravianum* Woodson (family Apocynaceae). Most of them were indolo[2,3-*a*]quinolizidines and related alkaloids, including a zwitterionic dehydroindolo[2,3-*a*]quinolizidine alkaloid [amorphous, $[\alpha]_D$ −56° (*c* 0.57, MeOH)] isolated from the trunk bark. The French research group deduced the structure and absolute configuration of this zwitterionic alkaloid to be 3,4,5,6-tetradehydro-17-hydroxycorynanium (4)[3] on the basis of spectral analysis and of its identity with a semisynthetic sample prepared from corynan-17-ol (dihydrocorynantheol) [(−)-1] by lead tetraacetate oxidation.[2] As Gribble has recently reviewed,[4] structurally unique zwitterionic indolo[2,3-*a*]quinolizine alkaloids, of which 4 is an example, constitute only a small subfamily in the indoloquinolizidine family and have received less attention from the synthetic chemical community than have many other classes of alkaloids. This led us to investigate the chiral synthesis of 4 in the present study.



(−)-**1**: $R^1 = R^2 = H$
(−)-**2**: $R^1 = R^2 = MeO$
(−)-**3**: $R^1 = H$; $R^2 = MeO$

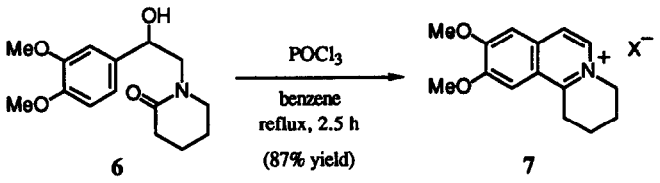


4



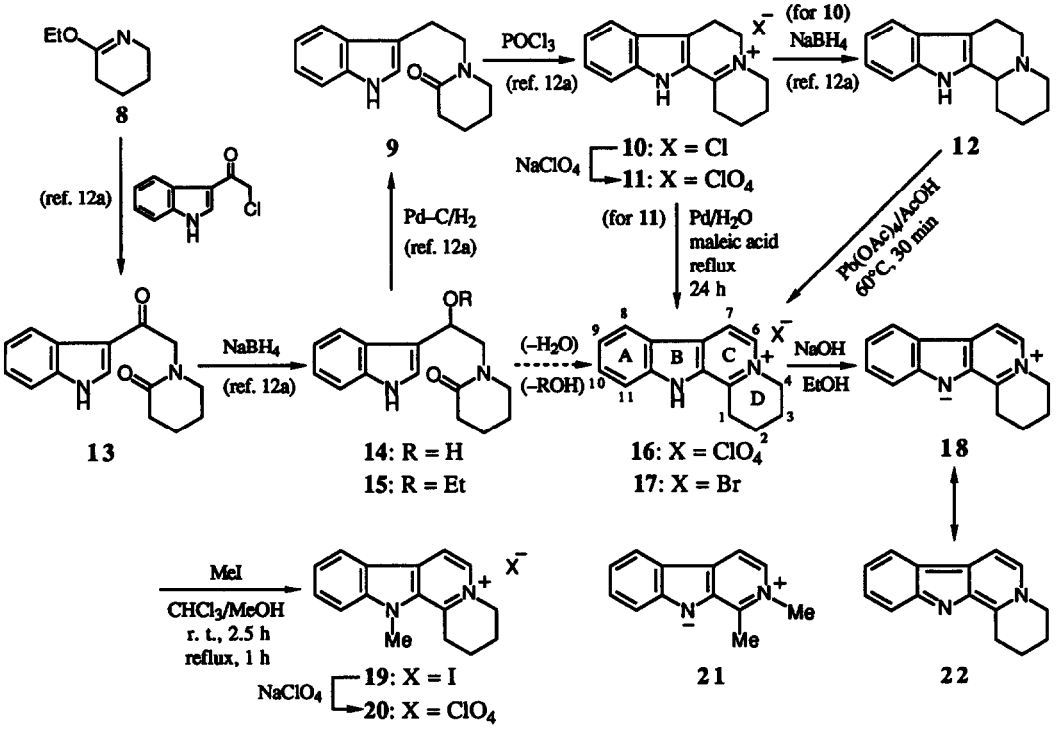
(+)-**5**

† Dedicated to Emeritus Professor Shun-ichi Yamada in recognition of his contribution to the chemistry of optically active compounds.



Scheme 1

In designing a synthetic route to **4**, our two previous synthetic studies were informative guides: (1) syntheses of (–)-**1**[5] and the *Neisosperma* alkaloids (–)-ochropposinine [(–)-**2**][6] and (–)-ochromianine [(–)-**3**][7] from the lactim ether [(+)-**5**][8,9] through the "lactim ether route"[9-12] and (2) synthesis of 9,10-dimethoxy-1,2,3,4-tetrahydrobenzo[*a*]quinolizinium salt (**7**), a tricyclic congener unsaturated in the quinolizidine moiety in a manner similar to that in **4**, from 1-[2-(3,4-dimethoxyphenyl)-2-hydroxyethyl]-2-piperidone (**6**)[13] (Scheme 1). Thus, a combination of the synthetic strategies employed in these studies generated a ring C-unsaturated version of our chiral synthesis of *Corynanthe*-type indoloquinolizidine alkaloids. The feasibility of this version was first tested in a synthesis of the parent skeleton **18**, as shown in Scheme 2.



Scheme 2

The key intermediate in the synthetic scheme was the known lactam alcohol **14**, which was prepared from the lactim ether **8** through the lactam ketone **13** according to our previous procedure.[12a] Cyclodehydration–dehydration of **14** in a one-step manner would provide a shortcut leading to the penultimate tetracyclic salt (type

16). However, treatment of **14** with $POCl_3$ in boiling benzene for 2 h gave a complex mixture, from which we were unable to isolate the desired tetracyclic salt. Applications of other dehydrating agents, such as $POCl_3$/pyridine (reflux, 10–15 min), polyphosphoric acid (140°C, 1 h), polyphosphate ester (PPE)[14] (120°C, 4 h; or in boiling $CHCl_3$, 2 h), PPE/$POCl_3$ (reflux, 5 min), P_2O_5/pyridine/sea sand[15] (reflux, 6 h), and $PCl_5/CHCl_3$ (reflux, 3 h), to **14** were also unsuccessful. Treatment of the *O*-ethyl derivative **15**[12a] with $POCl_3$ in boiling benzene for 3 h also failed to give the desired tetracyclic salt (type **16**). These difficulties are most likely due to

Table I. UV Spectral Data for Compounds **16**, **18**, **20**, (+)-**27**, and (+)-**4**

	UV spectra									
	16		**18**		**20**		(+)-**27**		(+)-**4**	
Solvent	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	λ_{max} (nm)	$\varepsilon \times 10^{-3}$	λ_{max} (nm)	$\varepsilon \times 10^{-3}$
0.1 N aq. HCl	248.5	33.5			254.5	31.0	249.5	32.4	249	32.3
	302.5	19.9			261.5	30.0	304	20.5	303.5	20.5
	361	4.9			306	17.5	360	5.5	360	5.3
					375	4.8				
H_2O	248.5	32.8			254.5	31.0	249	32.5	249	31.0
	302.5	19.3			261.5	29.9	303.5	20.7	303.5	19.8
	361	4.7			306	17.4	360	5.5	360	5.1
					375	4.8				
0.1 N aq. NaOH	247[a]	18.4			254.5	31.1	245[a]	17.9	245.5[a]	17.9
	276	45.1			261.5	30.2	276	46.5	276	46.3
	309.5[a]	9.0			306	17.6	308.5[a]	9.8	311.5[a]	10.3
	320.5	11.2			375	4.9	321	13.1	321	13.0
	400.5	3.5					404	3.4	403	3.3
A[b]	252	32.1	252	30.5	256.5	31.0	252.5	32.2	252.5	30.9
	305	20.8	305	19.7	263.5	31.0	306.5	22.2	306.5	21.3
	366	4.6	366	4.7	307.5	19.1	365	6.0	365	5.4
					378	5.0				
N[c]	252.5	32.5	252	29.9	256.5	30.5	252.5	30.9	252.5	30.4
	306	21.5	306	19.6	263.5	30.8	306.5	22.2	306.5	21.9
	366	4.9	366	4.6	307.5	19.1	365	5.2	365.5	4.8
					378	5.0				
B[d]	250[a]	14.1	249[a]	13.8	256.5	30.4	248.5[a]	14.2	248[a]	14.3
	282.5	51.2	283	48.2	263	30.7	282.5	50.7	282.5	50.3
	326.5	10.7	327	10.4	308	17.8	327	11.5	326.5	11.8
	418	3.0	418	3.2	382	4.6	418	2.9	420	3.0
C[e]	249[a]	14.1			256.5	29.5				
	283	51.3			263.5	29.8				
	327	10.7			308	18.1				
	420	3.1			380	4.7				

[a] Shoulder. [b] 95% (v/v) aqueous EtOH containing HCl at 0.1 N concentration. [c] 95% (v/v) aqueous EtOH. [d] 95% (v/v) aqueous EtOH containing NaOH at 0.1 N concentration. [e] 95% (v/v) aqueous EtOH containing NaOH at 0.015 N concentration.

the high reactivity at the indolylcarbinyl carbon atom under acidic conditions, as experienced previously[6,12a,16] under even milder conditions.

Thus, we switched to a bypass following the permutation **14**→**9**→**10**→**11**→**16**→**18** or **14**→**9**→**10**→**12**→**16**→**18**, in which the synthetic route to **12** from **14** through **9** and **10** had already been established in our laboratory.[12a] In the present study, the crystalline quaternary iminium perchlorate **11** was prepared from the crude chloride salt **10** in 93% overall yield (from **9**). On treatment with palladium black and maleic acid[17] in boiling H_2O for 24 h, **11** produced the ring C-dehydrogenated product **16** in 97% yield. The correctness of the assigned structure was supported by elemental analysis and the ^1H NMR spectrum of **16** in Me_2SO-d_6, which exhibited a pair of AB-type doublets (J = 6.5 Hz) at δ 8.50 and 8.60, assignable to C(7)-H and C(6)-H, respectively. The occurrence of dehydrogenation in ring C is in general agreement with what has been reported[17] for a similar structure. Meantime, dehydrogenation of the tetracyclic base **12** was also tried according to precedents. Oxidation of **12** with lead tetraacetate[18] in AcOH at 60°C for 30 min gave, after treatment of the product with $NaClO_4$, the quaternary perchlorate **16**, but in only 15% yield. On the other hand, dehydrogenation of **12** with palladium black and maleic acid[19] in boiling H_2O was too slow to complete within at least 48 h, hence rendering the permutation **14**→**9**→**10**→**11**→**16** most practical.

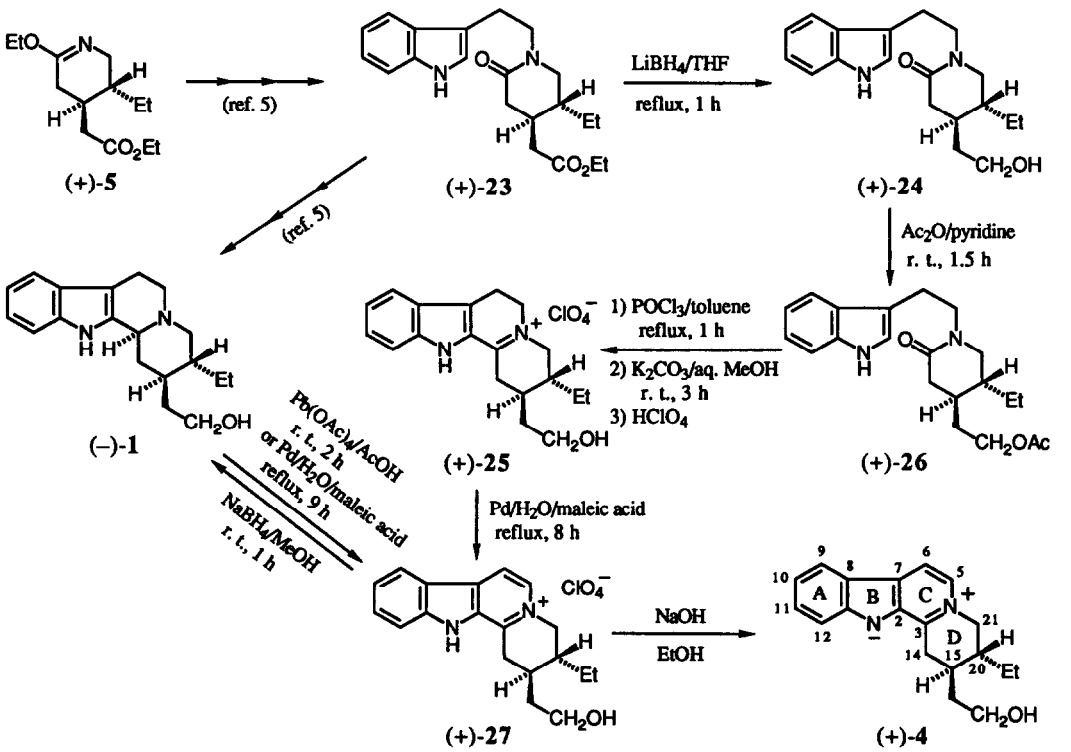
Table II. Chemical Shifts for Aromatic Protons of the Quaternary Perchlorates **16** and (+)-**27** and the Anhydronium Bases **18** and (+)-**4**

Solvent	Compound	Chemical shift (δ)[a]					
		Ring A				Ring C	
	16, **18**····· C(8 or 11)-H (+)-**27**, (+)-**4**·· C(9 or 12)-H	C(11 or 8)-H C(12 or 9)-H	C(9 or 10)-H C(10 or 11)-H	C(10 or 9)-H C(11 or 10)-H	C(6)-H C(5)-H	C(7)-H C(6)-H	
CD_3OD	**16**	7.74	8.35	7.44	7.78	8.45	8.32
	(+)-**27**	7.74	8.35	7.44	7.78	8.44	8.44
	18	7.74	8.16	7.18	7.55	8.14	7.82
	(+)-**4**	7.75	8.17	7.13	7.50	8.13	7.82
CD_3OD/NaOD[b]	**18**	7.76	8.14	7.10	7.48	8.08	7.68
	(+)-**4**	7.76	8.16	7.11	7.48	8.10	7.77
$CDCl_3$	**18**	7.94	8.09	7.13	7.51	7.86	7.16
	(+)-**4**	7.88	8.03	7.11	7.49	7.69	6.96
CD_3OD/D_2O[c]	**18**	7.72	8.18	7.24	7.59	8.17	7.88
	(+)-**4**	7.78	8.18	7.16	7.54	8.11	7.79
CD_3OD/DCl	**18**[d]	7.70	8.21	7.40	7.70	8.32	8.19
	(+)-**4**[e]	7.77	8.33	7.45	7.80	8.43	8.43

[a] Expressed in ppm downfield from internal Me_4Si. [b] Measured in CD_3OD (0.4 ml) containing a 40% solution (0.01 ml) of NaOD in D_2O. [c] Measured in CD_3OD–D_2O (10 : 1, v/v). [d] Measured in a mixture of CD_3OD (0.4 ml), D_2O (0.12 ml), and a 37% solution (0.04 ml) of DCl in D_2O. [e] Measured in a mixture of CD_3OD (0.4 ml), D_2O (0.04 ml), and a 37% solution (0.04 ml) of DCl in D_2O.

Groves and Swan[20] prepared the anhydronium base **18** by alkali-treatment of the bromide salt **17**, which they synthesized from tryptamine hydrochloride and 5-hydroxypentanal *via* a multi-step route. They methylated **18** with MeI to obtain the 12-methylated product **19**. In the present study, a parallel sequence of steps using the

perchlorate salt **16** instead of **17** was followed under slightly different conditions, affording **20** in 55% overall yield (from **16**) through **18** and **19**. Support for the correctness of the structure of the anhydronium base, represented by the two resonance structures **18** and **22**, came from the pH-dependent UV spectrum (Table I), as in the case of 1,2-dimethyl-β-carboline anhydronium base (**21**),[21] as well as from the ^{1}H NMR spectrum. It may be seen from Table II that in CD_3OD almost every aromatic proton of **18** resonates at higher field than does the corresponding proton in **16** and that this tendency is particularly remarkable for the ring C protons, reflecting a contribution of the resonance structure **22**. In CD_3OD/NaOD, almost every aromatic proton of **18** resonates at higher field than does in CD_3OD, and such an upfield shift is more marked in $CDCl_3$. On the other hand, the reverse is the case in CD_3OD/D_2O and CD_3OD/DCl. These results, together with the dullness of the aromatic proton signals observed for **18** in CD_3OD, suggest the existence of an equilibrium between **18** and its protonated form [*e. g.*, type **16** (X = OH)] in a protic solvent.



Scheme 3

With the above pilot experiment completed, we now followed a parallel sequence of reactions, as delineated in Scheme 3, for the chiral synthesis of the target anhydronium base **4**. The first half [(+)-**5**→→→(+)-**23**→→→(–)-**1**] of this synthetic scheme was a mere repetition of our recent synthesis[5] of (–)-dihydrocorynantheol [(–)-**1**],[22] but on a gram-size scale. Selective reduction of the lactam ester (+)-**23** with $LiBH_4$ in boiling tetrahydrofuran (THF)[23] for 1 h produced the lactam alcohol (+)-**24** (84% yield), which was then converted into the acetate (+)-**26** (100% yield) by treatment with acetic anhydride in pyridine at room temperature for 1.5 h. Bischler–Napieralski cyclization of (+)-**26** with $POCl_3$ in boiling toluene for 1 h, followed by hydrolysis of the ester group

with K_2CO_3 in aqueous MeOH at room temperature for 3 h, gave a tetracyclic alcohol, which was isolated in the form of the perchlorate salt (+)-**25** (86% yield). On treatment with palladium black and maleic acid in boiling H_2O for 8 h, (+)-**25** afforded the dehydrogenated product (+)-**27** in 91% yield. Unsaturation of (+)-**27** in ring C was assignable on the basis of the similarities to the model compound **16** in the mode of formation (*vide supra*), in the chemical shift values for the ring C protons (see Table II), and in the UV spectrum as shown in Table I. Furthermore, the same unsaturated tetracyclic alcohol [(+)-**27**] was obtained from synthetic (–)-**1**[5] by dehydrogenation with lead tetraacetate in AcOH at room temperature[24] for 2 h or by dehydrogenation using palladium black and maleic acid in boiling H_2O[25] for 9 h in 8% or 72% yield, respectively. In addition, (+)-**27** reverted to (–)-**1** in quantitative yield when reduced with $NaBH_4$ in MeOH at room temperature for 1 h.

Finally, treatment of (+)-**27** with aqueous NaOH in EtOH furnished the ultimate anhydronium base (+)-**4**, which was characterized as a hydrate [(+)-**4**•2/5H_2O] [mp 161–162.5°C (dec.); $[\alpha]_D^{18}$ +50.0° (*c* 0.53, MeOH)]. The correctness of structure (+)-**4** was supported by elemental analysis and by the similarities to the model **18** in the chemical shift values for the ring C protons (see Table II) and in the UV spectrum (see Table I). Although the UV (in EtOH and EtOH/NaOH), IR (KBr), and mass spectral data for the synthetic (+)-**4** were closely similar to those reported[2] for a sample of the natural anhydronium base, the ^1H NMR spectral data for both samples were not identical and, to our surprise, the signs of specific rotation (in MeOH) for both samples were opposite. Unfortunately, no sample of the alkaloid, to which structure **4** was assigned,[2] was available for detailed and direct comparison with the synthetic (+)-**4**, and thus its chemistry is incompletely understood.

In conclusion, the above synthesis of (+)-**4** represents a new addition to the range[12] of chiral syntheses of the indolo[2,3-*a*]quinolizidine system by the "lactim ether route",[9-11] which remains the best available vehicle for unified racemic and chiral syntheses of benzo[*a*]quinolizidine-type *Alangium* alkaloids.[10] It is hoped that the knowledge obtained on the synthetic (+)-**4** will be of great help toward further isolation of this anhydronium base, if it is present, from natural sources.

EXPERIMENTAL

General Notes

All melting points were taken on a Yamato MP-1 capillary melting point apparatus and are corrected. Unless otherwise noted, the organic solutions obtained after extraction were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. See refs. 6 and 7 for details of chromatography, instrumentation, and measurements. Elemental analyses were performed by Mr. Y. Itatani and his associates at Kanazawa University. The following abbreviations are used: br = broad, d = doublet, dd = doublet-of-doublets, ddd = doublet-of-doublets-of-doublets, m = multiplet, s = singlet, sh = shoulder, t = triplet.

1,2,3,4,6,7-*Hexahydro*-12H-*indolo*[2,3-a]*quinolizin*-5-*ium Perchlorate* (11)

A solution of **9**[12a] (1.15 g, 4.75 mmol) and $POCl_3$ (2.7 ml, 29 mmol) in dry benzene (9 ml) was heated under reflux in an atmosphere of N_2 for 1.5 h. After cooling, the reaction mixture was kept in a refrigerator overnight, and the orangy-yellow solid (presumed to be **10**) that deposited was filtered off, washed with benzene (10 ml), and dissolved in MeOH (7 ml). To the resulting methanolic solution was added a solution of $NaClO_4$•H_2O (2.00 g, 14.2 mmol) in MeOH (4 ml). The precipitate that resulted was filtered off, washed successively with MeOH (1 ml) and H_2O (2 ml), and dried to give **11** (1.43 g, 93%) as orangy-yellow needles, mp 220–222°C (dec.). Recrystallization from MeOH afforded an analytical sample as yellow needles, mp 222.5–

224.5°C (dec.) [lit.[17] mp 223–227°C (dec.)]; UV $\lambda_{max}^{95\%\ (v/v)\ aq.\ EtOH}$ 246 nm (ε 11000), 251.5 (sh) (10500), 351.5 (21400); IR ν_{max}^{Nujol} cm^{-1}: 3290 (NH), 1627 (C=N$^+$); ^{1}H NMR (Me_2SO-d_6) δ: 1.75–2.15 [4H, m, C(2)-H's and C(3)-H's], 3.1–3.4 [4H, m, C(1)-H's and C(7)-H's], 3.7–4.15 [4H, m, C(4)-H's and C(6)-H's], 7.18 [1H, ddd, J = 2, 6.5, and 8 Hz, C(9)-H or C(10)-H], 7.3–7.6 [2H, m, C(10)-H or C(9)-H and C(8)-H or C(11)-H], 7.76 [1H, dull d, J = 8 Hz, C(11)-H or C(8)-H], 12.18 (1H, br, NH). *Anal.* Calcd for $C_{15}H_{17}ClN_2O_4$: C, 55.48; H, 5.28; N, 8.63. Found: C, 55.33; H, 5.24; N, 8.34. The UV spectral data for this sample were in agreement with those[17] reported in the literature.

1,2,3,4-*Tetrahydro*-12H-*indolo*[2,3-a]*quinolizin*-5-*ium Perchlorate* (16)

(i) *Dehydrogenation of* **11** *with Palladium Black and Maleic Acid.* A stirred mixture of **11** (1.17 g, 3.6 mmol), maleic acid (1.25 g, 10.8 mmol), and palladium black[26] (450 mg) in H_2O (70 ml) was heated under reflux in an atmosphere of N_2 for 24 h. After cooling, the catalyst was removed by filtration and washed with five 100-ml portions of hot MeOH. The filtrate and washings were combined and concentrated *in vacuo* to leave a yellowish solid, which was mixed with H_2O (30 ml). The resulting aqueous mixture was neutralized with saturated aqueous $NaHCO_3$, and then a solution of $NaClO_4 \cdot H_2O$ (506 mg, 3.6 mmol) in H_2O (3 ml) was added. The precipitate that resulted was filtered off, washed with H_2O (6 ml), and dried to give **16** (1.13 g, 97%) as a yellow solid, mp 239–240°C (dec.). Recrystallization from MeOH and drying over P_2O_5 at 1 mmHg and 75°C for 8 h provided an analytical sample of **16** as yellowish fluffy needles, mp 229.5–233.5°C (dec.); UV (Table I); IR ν_{max}^{Nujol} cm^{-1}: 3295 (NH), 1637 (C=N$^+$); ^{1}H NMR (Me_2SO-d_6) δ: 1.95–2.3 [4H, m, C(2)-H's and C(3)-H's], 3.4–3.65 [2H, m, C(1)-H's], 4.55–4.8 [2H, m, C(4)-H's], 7.3–7.55 [1H, m, C(9)-H or C(10)-H], 7.65–7.85 [2H, m, C(10)-H or C(9)-H and C(8)-H or C(11)-H], 8.45 [1H, d, J = 8 Hz, C(11)-H or C(8)-H], 8.50 [1H, d, J = 6.5 Hz, C(7)-H], 8.60 [1H, d, J = 6.5 Hz, C(6)-H], 12.76 (1H, br, NH); ^{1}H NMR (CD_3OD) (Table II). *Anal.* Calcd for $C_{15}H_{15}ClN_2O_4$: C, 55.82; H, 4.68; N, 8.68. Found: C, 56.05; H, 4.57; N, 8.74.

(ii) *Dehydrogenation of* **12** *with Lead Tetraacetate.* The tetracyclic base **12**[12a] (226 mg, 1 mmol) was dissolved in AcOH (2 ml) at 60°C. After addition of lead tetraacetate (of 90% purity[27]) (1.48 g, 3 mmol), the solution was stirred at 60°C in an atmosphere of N_2 for 30 min. The reaction mixture was concentrated *in vacuo*, and the residue was mixed with H_2O (2 ml). The aqueous mixture was made alkaline by addition of 10% aqueous NaOH, the inorganic precipitate that resulted was filtered off and washed with $CHCl_3$ (15 ml), and the aqueous filtrate was extracted with $CHCl_3$ (4 × 10 ml). The $CHCl_3$ extracts were combined with the above $CHCl_3$ washings, washed with saturated aqueous NaCl (2 × 10 ml), dried, and concentrated to leave a black glass. The glass was triturated with 10% aqueous HCl (5 ml), and the insoluble tarry substance that resulted was removed by filtration. To the filtrate was added a solution of $NaClO_4 \cdot H_2O$ (421 mg, 3 mmol) in H_2O (2 ml), and the precipitate that resulted was filtered off, washed with H_2O (2 ml), and dried to give a brown solid (146 mg). Two recrystallizations of the solid from MeOH, including decoloration with activated charcoal powder, yielded **16** (49 mg, 15%) as brownish yellow needles, mp 231–233°C (dec.). This sample was identical (by comparison of the IR spectrum) with the one obtained by method (i).

1,2,3,4-*Tetrahydroindolo*[2,3-a]*quinolizine* (18)

To a solution of **16** (115 mg, 0.36 mmol) in EtOH (2 ml) was added 10% aqueous NaOH (2 ml). The yellow needles that resulted were filtered off, washed with H_2O (2 ml), and dissolved in EtOH (2 ml). To the resulting ethanolic solution was added 10% aqueous NaOH (2 ml), and the yellow needles [mp 80.5–85°C (dec.)] that deposited were filtered off and washed with H_2O. Repeated recrystallization in the same manner and drying over KOH at atmospheric pressure and room temperature for 7 days produced an analytical sample of **18**•1/5H_2O as yellow needles, mp 167.5–170°C (dec.); MS *m/z*: 222 (M$^+$); UV (Table I); IR ν_{max}^{Nujol} cm^{-1}: 1616 (C=N); ^{1}H

NMR ($CDCl_3$) δ: 1.85–2.25 [4H, m, C(2)-H's and C(3)-H's], 3.4–3.8 [2H, m, C(1)-H's], 4.05–4.35 [2H, m, C(4)-H's], 7.13 [1H, t, J = 8 Hz, C(9)-H or C(10)-H], 7.16 [1H, d, J = 6.5 Hz, C(7)-H], 7.51 [1H, t, J = 8 Hz, C(10)-H or C(9)-H], 7.86 [1H, d, J = 6.5 Hz, C(6)-H], 7.94 [1H, d, J = 8 Hz, C(8)-H or C(11)-H], 8.09 [1H, d, J = 8 Hz, C(11)-H or C(8)-H]; ^1H NMR (other solvents) (see Table II). *Anal.* Calcd for $C_{15}H_{14}N_2 \cdot 1/5H_2O$: C, 79.76; H, 6.43; N, 12.40. Found: C, 79.62; H, 6.21; N, 12.15.

1,2,3,4-*Tetrahydro*-12-*methyl*-12H-*indolo*[2,3-a]*quinolizin*-5-*ium Perchlorate* (20)

To a solution of **16** (323 mg, 1 mmol) in EtOH (2 ml) was added 10% aqueous NaOH (6 ml), and the yellow needles that deposited were filtered off, washed with H_2O (2 ml), dried, and dissolved in a mixture of $CHCl_3$ (3 ml) and MeOH (0.5 ml). To the resulting solution was added MeI (2 ml), and the mixture was stirred at room temperature for 2.5 h and then heated under reflux for 1 h. The reaction mixture was concentrated *in vacuo*, and the residue was dissolved in MeOH (10 ml). To the resulting methanolic solution was added a solution of $NaClO_4 \cdot H_2O$ (281 mg, 2 mmol) in MeOH (1 ml), and the precipitate that resulted was filtered off, washed with H_2O (2 ml), and recrystallized from MeOH, giving **20** (184 mg, 55% yield from **16**) as brownish prisms, mp 238–240°C (dec.). Recrystallization from MeOH, including decoloration with activated charcoal powder, yielded an analytical sample as yellow needles, mp 241.5–243°C (dec.); UV (Table I); IR ν_{max}^{Nujol} cm^{-1}: 1627 (C=N$^+$); ^1H NMR (Me_2SO-d_6) δ: 1.95–2.25 [4H, m, C(2)-H's and C(3)-H's], 3.92 [2H, dull t, J = 6 Hz, C(1)-H's], 4.30 [3H, s, N(12)-Me], 4.75 [2H, dull t, J = 6 Hz, C(4)-H's], 7.47 [1H, ddd, J = 2, 6.5, and 8 Hz, C(9)-H or C(10)-H], 7.7–8.0 [2H, m, C(10)-H or C(9)-H and C(8)-H or C(11)-H], 8.47 [1H, dull d, J = 8 Hz, C(11)-H or C(8)-H], 8.52 [1H, d, J = 6.5 Hz, C(7)-H], 8.65 [1H, d, J = 6.5 Hz, C(6)-H]. *Anal.* Calcd for $C_{16}H_{17}ClN_2O_4$: C, 57.06; H, 5.09; N, 8.32. Found: C, 56.88; H, 5.13; N, 8.28.

(4S,5R)-5-*Ethyl*-4-(2-*hydroxyethyl*)-1-[2-(1H-*indol*-3-*yl*)*ethyl*]-2-*piperidone* [(+)-24]

To a stirred, ice-cooled solution of the lactam ester (+)-**23**[5] (285 mg, 0.8 mmol) in dry tetrahydrofuran (THF) (5 ml) was added $LiBH_4$ (105 mg, 4.8 mmol) by portions, and the mixture was heated under reflux for 1 h. The reaction mixture was then cooled in an ice bath, acidified with 10% aqueous HCl, and concentrated *in vacuo*. The residue was partitioned by extraction with a mixture of H_2O (8 ml) and CH_2Cl_2 (45 ml). The CH_2Cl_2 extracts were washed with saturated aqueous NaCl (2 × 10 ml), dried, and concentrated to leave a yellow, hard oil (257 mg). Purification of the oil by means of flash chromatography[28] [silica gel, $CHCl_3$–EtOH (20 : 1, v/v)] yielded (+)-**24** (211 mg, 84%) as a colorless solid, mp 143.5–145.5°C. Recrystallization from $CHCl_3$–hexane (2 : 1, v/v) furnished an analytical sample as colorless needles, mp 145–146.5°C; $[\alpha]_D^{25}$ +85.4° (*c* 0.50, EtOH)]; MS *m/z*: 314 (M$^+$); UV $\lambda_{max}^{99\%\,(v/v)\,aq.\,EtOH}$ 222.5 nm (ε 37000), 274 (sh) (5400), 282.5 (6100), 291 (5200); IR ν_{max}^{Nujol} cm^{-1}: 3460 (OH), 3215 (NH), 1604 (lactam CO); ^1H NMR ($CDCl_3$) δ: 0.76 (3H, t, J = 7 Hz, CH_2*Me*), 0.95–3.25 (12H, m, C*H*$_2$Me, C*H*$_2$Ar, C(3)-H's, C(4)-H, C(5)-H, C(6)-H's, and C*H*$_2$CH$_2$OH), 1.85 (1H, s, CH$_2$O*H*), 3.4–3.85 (4H, m, C*H*$_2$CH$_2$Ar, C*H*$_2$OH), 6.95–7.7 (5H, m, aromatic protons), 8.22 (1H, br, NH). *Anal.* Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.33; N, 8.91. Found: C, 72.29; H, 8.39; N, 8.73.

(4S,5R)-5-*Ethyl*-4-(2-*acetoxyethyl*)-1-[2-(1H-*indol*-3-*yl*)*ethyl*]-2-*piperidone* [(+)-26]

A mixture of (+)-**24** (285 mg, 0.91 mmol) and Ac_2O (0.26 ml, 2.8 mmol) in dry pyridine (2 ml) was stirred at room temperature for 1.5 h. The reaction mixture was concentrated *in vacuo*, and the residue was partitioned by extraction with a mixture of H_2O (10 ml) and $CHCl_3$ (60 ml). The $CHCl_3$ extracts were washed with saturated aqueous NaCl (2 × 10 ml), dried, and concentrated to leave a slightly brownish solid (328 mg). Purification of the solid by means of flash chromatography[28] [silica gel, AcOEt–$CHCl_3$ (1 : 3, v/v)] gave (+)-**26** (322 mg, 100%) as a slightly pinkish solid, mp 141.5–144°C. Recrystallization from AcOEt–hexane (1 : 1, v/v)

afforded an analytical sample as colorless scales, mp 144–145°C; $[\alpha]_D^{25}$ +77.0° (*c* 0.50, EtOH)]; MS *m/z*: 356 (M^+); UV $\lambda_{max}^{99\%\ (v/v)\ aq.\ EtOH}$ 222.5 nm (ε 36500), 274.5 (sh) (5300), 282 (5900), 291 (5100); IR ν_{max}^{Nujol} cm^{-1}: 3225 (NH), 1745 (ester CO), 1613 (lactam CO); ^1H NMR ($CDCl_3$) δ: 0.75 (3H, t, *J* = 7 Hz, CH_2*Me*), 0.95–3.25 [12H, m, C*H*$_2$Me, C*H*$_2$Ar, C(3)-H's, C(4)-H, C(5)-H, C(6)-H's, and C*H*$_2$CH$_2$OAc], 2.04 (3H, s, CH_2OCO*Me*), 3.4–3.85 (2H, m, C*H*$_2$CH$_2$Ar), 4.07 (2H, t, *J* = 6 Hz, C*H*$_2$OAc), 6.95–7.7 (5H, m, aromatic protons), 8.12 (1H, br, NH). *Anal.* Calcd for $C_{21}H_{28}N_2O_3$: C, 70.76; H, 7.92; N, 7.86. Found: C, 70.60; H, 7.90; N, 7.71.

3,4-*Didehydro*-17-*hydroxycorynanium Perchlorate* [(+)-25]

A mixture of (+)-**26** (865 mg, 2.43 mmol) and $POCl_3$ (2.24 g, 14.6 mmol) in dry toluene (9 ml) was heated under reflux in an atmosphere of N_2 for 1 h. The reaction mixture was concentrated *in vacuo*, and the residue was partitioned between H_2O (15 ml) and $CHCl_3$ (200 ml). The $CHCl_3$ extracts were washed with saturated aqueous NaCl (50 ml), dried, and concentrated to leave a yellow glass. The glass was dissolved in MeOH (20 ml), and the methanolic solution was stirred at room temperature for 3 h after addition of a solution of K_2CO_3 (672 mg, 4.86 mmol) in H_2O (2 ml) and then concentrated *in vacuo*. The residue was acidified with 10% aqueous HCl in a mixture of H_2O (20 ml) and MeOH (5 ml), and a solution of $NaClO_4 \cdot H_2O$ (1.02 g, 7.3 mmol) in H_2O (1 ml) was added. The crystals that deposited were filtered off, washed with H_2O (3 ml), and recrystallized from MeOH–ether (1 : 1, v/v), giving (+)-**25** (827 mg, 86%) as yellow needles, mp 192.5–194°C (dec.). Further recrystallization in the same manner provided an analytical sample as yellow needles, mp 193.5–195°C (dec.); $[\alpha]_D^{31}$ +108.8° (*c* 0.50, EtOH)]; UV $\lambda_{max}^{99\%\ (v/v)\ aq.\ EtOH}$ 248 nm (sh) (ε 11100), 295 (sh) (4700), 306.5 (sh) (7200), 322 (sh) (10800), 353 (18300); IR ν_{max}^{Nujol} cm^{-1}: 3535 (OH), 3320 (NH), 1645 (C=N^+); ^1H NMR (Me_2SO-d_6) δ: 0.93 (3H, t, *J* = 7 Hz, CH_2*Me*), 1.05–4.2 [17H, m, C*H*$_2$Me, C*H*$_2$C*H*$_2$O*H*, C(14)-H's, C(15)-H, C(20)-H, C(21)-H's, C(5)-H's, and C(6)-H's], 7.19 [1H, ddd, *J* = 2, 6.5, and 8 Hz, C(10)-H or C(11)-H], 7.35–7.6 [2H, m, C(11)-H or C(10)-H and C(9)-H or C(12)-H], 7.76 [1H, dull d, *J* = 8 Hz, C(12)-H or C(9)-H], 12.24 (1H, br, NH). *Anal.* Calcd for $C_{19}H_{25}ClN_2O_5$: C, 57.50; H, 6.35; N, 7.06. Found: C, 57.50; H, 6.46; N, 6.79.

3,4,5,6-*Tetradehydro*-17-*hydroxycorynanium Perchlorate* (3,4,5,6-*Tetradehydrodihydrocorynantheol Perchlorate*) [(+)-27]

(i) *From* (+)-**25**. A stirred mixture of (+)-**25** (124 mg, 0.31 mmol), maleic acid (72.4 mg, 0.62 mmol), and palladium black[26] (60 mg) in H_2O (12 ml) was heated under reflux in an atmosphere of N_2 for 8 h. After cooling, the catalyst was filtered off and washed with hot MeOH (5 × 15 ml). The filtrate and washings were combined and concentrated *in vacuo*, and the residue was mixed with a solution of $NaClO_4 \cdot H_2O$ (87.6 mg, 0.62 mmol) in H_2O (1.5 ml). The yellow precipitate that resulted was filtered off, washed with H_2O (1 ml), and recrystallized from EtOH–ether (2 : 1, v/v) to afford (+)-**27** (112 mg, 91%) as yellow needles, mp 153–155°C. Further recrystallization from EtOH–ether (1 : 1, v/v) yielded an analytical sample as yellow needles, mp 155–156°C; $[\alpha]_D^{27}$ +46.6° (*c* 0.50, MeOH)]; UV (Table I); IR ν_{max}^{KBr} cm^{-1}: 3505–3090 (OH, NH), 1635 (C=N^+); ^1H NMR (Me_2SO-d_6) δ: 0.98 (3H, t, *J* = 7 Hz, CH_2*Me*), 1.1–3.9 [9H, m, C*H*$_2$Me, C*H*$_2$C*H*$_2$O*H*, C(14)-H's, C(15)-H, and C(20)-H], 4.3–4.9 [4H, m, CH$_2$C*H*$_2$OH and C(21)-H's], 7.35–7.6 [1H, m, C(10)-H or C(11)-H], 7.65–7.85 [2H, m, C(11)-H or C(10)-H and C(9)-H or C(12)-H], 8.46 [1H, d, *J* = 8 Hz, C(12)-H or C(9)-H], 8.63 [2H, s, C(5)-H and C(6)-H], 12.85 (1H, br, NH); ^1H NMR (CD_3OD) δ: 1.07 (3H, t, *J* = 7 Hz, CH_2*Me*), 1.15–2.35 [6H, m, C*H*$_2$Me, C*H*$_2$CH$_2$OH, C(15)-H, and C(20)-H], 3.1–3.9 [4H, m, C(14)-H's and C(21)-H's], 4.48 (1H, dd, *J* = 7.5 and 13.5 Hz) and 4.81 (1H, dd, *J* = 4.5 and 13.5 Hz) (CH$_2$C*H*$_2$OH), 7.35–7.55 [1H, m, C(10)-H or C(11)-H], 7.65–7.9 [2H, m, C(11)-H or C(10)-H and C(9)-H or C(12)-H], 8.35 [1H,

d, J = 8 Hz, C(12)-H or C(9)-H], 8.44 [2H, s, C(5)-H and C(6)-H]. *Anal.* Calcd for $C_{19}H_{23}ClN_2O_5$: C, 57.80; H, 5.87; N, 7.09. Found: C, 57.64; H, 6.00; N, 7.05.

(ii) *From* (–)-**1** *by Dehydrogenation with Palladium Black/Maleic Acid.* A stirred mixture of (–)-**1**[5] (44.8 mg, 0.15 mmol), maleic acid (87.1 mg, 0.75 mmol), and palladium black[26] (60 mg) in H_2O (5 ml) was heated under reflux in an atmosphere of N_2 for 9 h. Work-up of the reaction mixture in a manner similar to that described above under method (i) gave (+)-**27** (42.5 mg, 72%) as yellow needles, mp 154.5–155.5°C; $[\alpha]_D^{21}$ +45.9° (*c* 0.48, MeOH)]. This sample was identical (by comparison of the IR spectrum) with the one obtained by method (i).

(iii) *From* (–)-**1** *by Dehydrogenation with Lead Tetraacetate.* Synthetic dihydrocorynantheol [(–)-**1**][5] (29.8 mg, 0.1 mmol) was dissolved in AcOH (0.5 ml) at 60°C. After addition of lead tetraacetate (of 90% purity[27]) (148 mg, 0.3 mmol), the solution was stirred at room temperature in an atmosphere of N_2 for 2 h. The reaction mixture was concentrated *in vacuo*, and the residue was mixed with H_2O (1 ml). The aqueous mixture was made alkaline with 10% aqueous Na_2CO_3 and extracted with $CHCl_3$ (5 × 3 ml) in a manner similar to that described above for **16** under item (ii). The $CHCl_3$ extracts were dried and concentrated to leave a reddish brown glass, which was dissolved in MeOH (0.5 ml). To the resulting methanolic solution was added a mixture of 70% aqueous $HClO_4$ (0.1 ml) and H_2O (0.5 ml), and the precipitate that resulted was collected by filtration, washed with H_2O (1 ml), and recrystallized from MeOH, giving (+)-**27** (3.3 mg, 8%) as yellow needles, mp 152.5–154.5°C; $[\alpha]_D^{18}$ +45° (*c* 0.10, MeOH)]. This sample was identical (by comparison of the IR spectrum) with the one prepared by method (i).

Conversion of (+)-27 *into Corynan*-17-*ol* [(–)-1]

To a stirred, ice-cooled solution of (+)-**27** (79 mg, 0.2 mmol) in MeOH (3 ml) was added $NaBH_4$ (113 mg, 3 mmol) by portions. The mixture was stirred at room temperature for 1 h and then concentrated *in vacuo*. The residue was partitioned between H_2O (3 ml) and $CHCl_3$ (20 ml). The $CHCl_3$ extracts were washed with saturated aqueous NaCl (2 × 6 ml), dried, and concentrated to leave (–)-**1** (59.5 mg, 100%) as a yellowish solid, mp 180–182°C. Recrystallization from AcOEt–hexane (1 : 1, v/v) furnished a pure sample as colorless needles, mp 183–185°C; $[\alpha]_D^{19}$ –32.8° (*c* 0.47, pyridine)]. This product was identical (by comparison of the IR spectrum) with authentic (–)-**1**.[5]

3,4,5,6-*Tetradehydro*-17-*hydroxycorynanium* [(+)-4]

To a solution of (+)-**27** (300 mg, 0.76 mmol) in EtOH (2 ml) was added 10% aqueous NaOH (2 ml). The yellow needles that resulted were filtered off, washed with H_2O (3 ml), and dissolved in EtOH (3 ml). To the resulting ethanolic solution was added 10% aqueous NaOH (3 ml), and the yellow needles that deposited were filtered off and washed with H_2O (3 ml). Repeated recrystallization in the same manner and drying over P_2O_5 at 2 mmHg and room temperature for 20 h and then at 50°C for 7 h provided (+)-**4**•2/5H_2O as yellow needles, mp 161–162.5°C (dec.); $[\alpha]_D^{18}$ +50.0° (*c* 0.53, MeOH)]; MS *m/z* (relative intensity): 294 (M^+) (39), 250 (20), 249 (100), 235 (19), 222 (16), 221 (73), 219 (31), 207 (24), 193 (15), 182 (18); UV (Table I); IR ν_{max}^{KBr} cm^{-1}: 3410 (OH), 1620 (C=N); ^1H NMR ($CDCl_3$) δ: 0.87 [3H, t, J = 6.5 Hz, C(18)-H's], 0.95–2.1 [6H, m, C(15)-H, C(16)-H's, C(19)-H's, and C(20)-H], 2.9–4.05 [6H, m, C(14)-H's, C(17)-H's, and C(21)-H's], 4.97 (*ca.* 1.7H, br, OH and H_2O), 6.96 [1H, d, J = 6 Hz, C(6)-H], 7.11 [1H, ddd, J = 1, 7, and 8 Hz, C(10)-H or C(11)-H], 7.49 [1H, ddd, J = 1.2, 7, and 8 Hz, C(11)-H or C(10)-H], 7.69 [1H, d, J = 6 Hz, C(5)-H], 7.88 [1H, d, J = 8 Hz, C(9)-H or C(12)-H], 8.03 [1H, d, J = 8 Hz, C(12)-H or C(9)-H]; ^1H NMR (CD_3OD) δ: 1.02 [3H, t, J = 7 Hz, C(18)-H's], 1.1–2.15 [6H, m, C(15)-H, C(16)-H's, C(19)-H's, and C(20)-H], 3.6–3.95 [2H, m, C(21)-H's], 4.23 (1H, dd, J = 7 and 13.5 Hz) and 4.54 (1H, dd, J = 4.5 and 13.5 Hz) [C(17)-H's],

7.13 [1H, ddd, J = 1, 7, and 8 Hz, C(10)-H or C(11)-H], 7.50 [1H, ddd, J = 1.2, 7, and 8 Hz, C(11)-H or C(10)-H], 7.75 [1H, d, J = 8 Hz, C(9)-H or C(12)-H], 7.82 [1H, d, J = 6.5 Hz, C(6)-H], 8.13 [1H, d, J = 6.5 Hz, C(5)-H], 8.17 [1H, d, J = 8 Hz, C(12)-H or C(9)-H]; ^{1}H NMR (other solvents) (see Table II). *Anal.* Calcd for $C_{19}H_{22}N_2O \cdot 2/5H_2O$: C, 75.67; H, 7.62; N, 9.29. Found: C, 75.56; H, 7.52; N, 9.27.

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