Investigations on the Chemistry of Berbanes. 10.[1] Synthesis of Raunescinone Analogues with Hypotensive and Antihypertensive Activity

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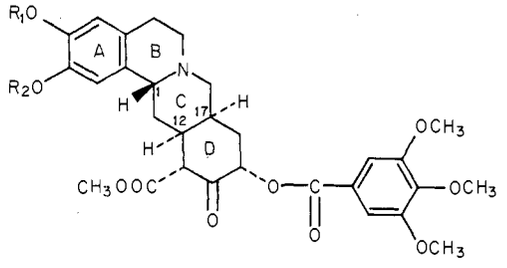
The pharmacologically active (methylenedioxy)- and diethoxyepialloberbane keto esters 1 have been synthesized with use of the readily available keto esters 2 as starting material. By choice of the appropriate reaction sequence both antipodes of keto ester **2a** can be employed to provide any enantiomer of the desired raunescinone analogue **1a**. Hypotensive, antihypertensive, and central depressant effects of **1a** are described. The principle effect observed for **1a** was a potent hypotensive and antihypertensive effect of long duration without depression of the central nervous system.

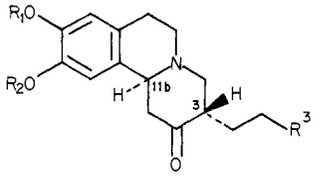
Among the berbane derivatives, which can be regarded as depyrrolo analogues of the well-known and biologically potent yohimbine and reserpine alkaloids,[2] many compounds show interesting pharmacological activity. According to our earlier investigations these types of compounds and certain intermediates encountered during their synthesis show antiinflammatory,[3] prostaglandin-like or antagonist,[4] as well as hypotensive and antihypertensive[5] effects.

Chemistry. After the successful construction of various depyrroloyohimbine and reserpine analogues, we report in this paper the total synthesis of racemic keto esters **1a** and **1b** as well as the preparation of both enantiomers of keto ester **1a**.[6]

The linear synthetic method[3,4,7a] developed earlier is flexible enough to build up either the *normal*, *allo*-, or *epiallo*berbane skeleton and permits the incorporation of a wide variation of substituents at rings A and D. Keto esters **2a** and **2b**, which were obtained by the cycloaddition of methyl 3-[(dimethylamino)methyl]-4-oxocapronate to 3,4-dihydro-6,7-(methylenedioxy)- or 6,7-diethoxyisoquinoline, are key intermediates in the synthesis of **1a** and **1b**, respectively.



1a, $R_1, R_2 = CH_2$
b, $R_1 = C_2H_5$; $R_2 = C_2H_5$



2a, $R_1, R_2 = CH_2$; $R_3 = COOCH_3$
b, $R_1 = C_2H_5$; $R_2 = C_2H_5$; $R_3 = COOCH_3$
c, $R_1 = CH_3$; $R_2 = CH_3$; $R_3 = H$

With **2a** as starting material, racemic bromo keto ester **9a** can be synthesized,[4] from which (±)-**1a** can be prepared by a reaction with potassium 3,4,5-trimethoxybenzoate.

In a similar manner, the racemic diethoxyepialloraunescinone analogue (±)-**1b** has also been produced. Since preliminary pharmacological examinations[5] indicated that **1a** possessed potent hypotensive and antihypertensive effects, synthesis of both of its enantiomers seemed desirable in order to investigate whether only one of the antipodes is responsible for the biological effect or whether both elicit this response. For this purpose, resolution at the stage of keto ester **2a** proved to be most suitable.

When racemic **2a** was treated with an equivalent amount of (+)-tartaric acid in ethyl acetate solution, the salt of the dextrorotatory keto ester was obtained in crystalline form. The keto ester recovered from the mother liquor, enriched in the levorotatory antipode, was then treated similarly with (−)-tartaric acid to produce pure (−)-**2a** after subsequent recrystallizations.

By comparison of the CD spectra of both keto ester antipodes with that of an intermediate employed for the synthesis of emetine [(−)-**2c**] with the known 3*S*,11b*S* configuration[7b] (see Figure 1), it was concluded that the levorotatory antipode of keto ester (−)-**2a** had the 3*S*,11b*S* configuration. Consequently, both chiral centers in (+)-**2a** can be characterized as *R*.

The synthetic pathway starting with (+)-**2a** and leading to epiallo keto ester (+)-**5** is given in Scheme I. The reaction of (+)-**2a** with [(methoxycarbonyl)methylene]-triphenylphosphorane takes place without epimerization at C-3 and results in the unsaturated diester (+)-(3*S*,11b*R*)-**3a**. Regioselective Dieckmann condensation of **3a** could be performed by refluxing in dry benzene in the presence of an equivalent amount of KOBu^t. This gave the tetracyclic keto ester (+)-(1*R*,17*S*)-**4a** as the sole product. Hydrogenation of the Δ^{12} double bond over Pd–C catalyst yielded the 4:1 mixture of epiallo and normal keto esters (+)-**5a** and (+)-**11a**. The two isomers, which differed only in the configuration at C-12, are separated by flash chromatography (R_f **11a** > R_f **5a**).

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(1) L. Szabó, L. Dobay, L. Radics, and Cs. Szántay, *Nouv. J. Chim.*, **4**, 199 (1980).
(2) J. Jirkovsky and M. Protiva, *Coll. Czech. Chem. Commun.* **28**, 2577 (1963).
(3) L. Szabó, K. Nógrádi, I. Tóth, Cs. Szántay, L. Radics, S. Virág, and E. Kanyó, *Acta Chim. Acad. Sci. Hung.*, **100**, 1 (1979).
(4) L. Szabó, I. Tóth, L. Töke, P. Kolonits, and Cs. Szántay, *Chem. Ber.*, **109**, 3390 (1976).
(5) Cs. Szántay, L. Szabó, I. Tóth, I. Gy. Papp, and L. Szekeres, under patenting.
(6) Where compounds are optically active, the formulas depict their absolute configurations; for racemic compounds, only one enantiomer is represented except in the cases of formulas **2b**, **3b**, and **4b**, where both are shown.
(7) (a) L. Szabó, I. Tóth, K. Honty, L. Töke, J. Tamás, and Cs. Szántay, *Chem. Ber.*, **109**, 1724 (1976); (b) Cs. Szántay, L. Töke, and P. Kolonits, *J. Org. Chem.*, **31**, 1448 (1967).

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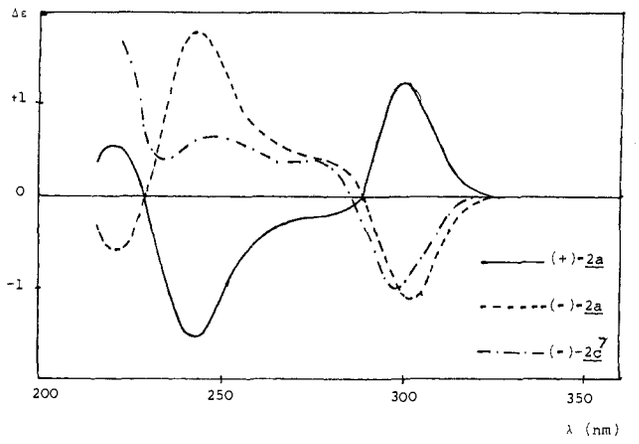
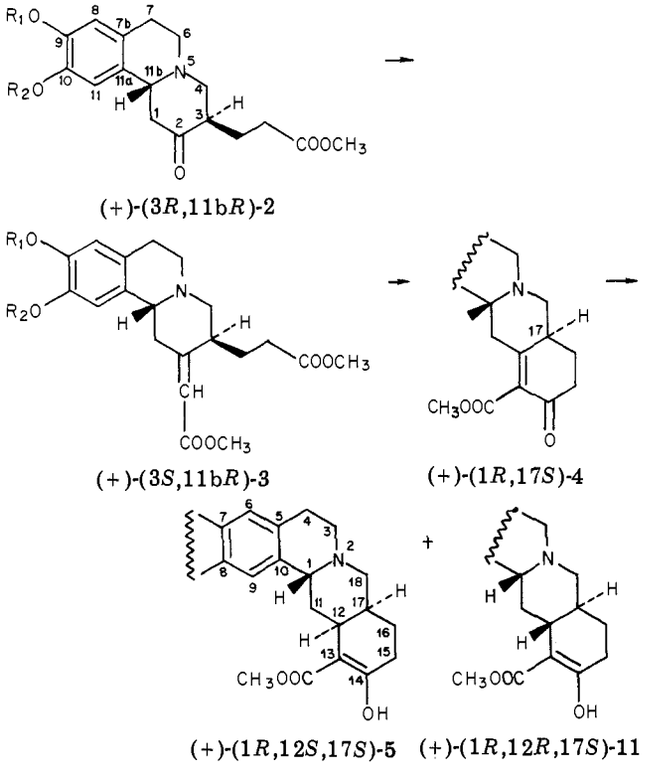


Figure 1.

Scheme I

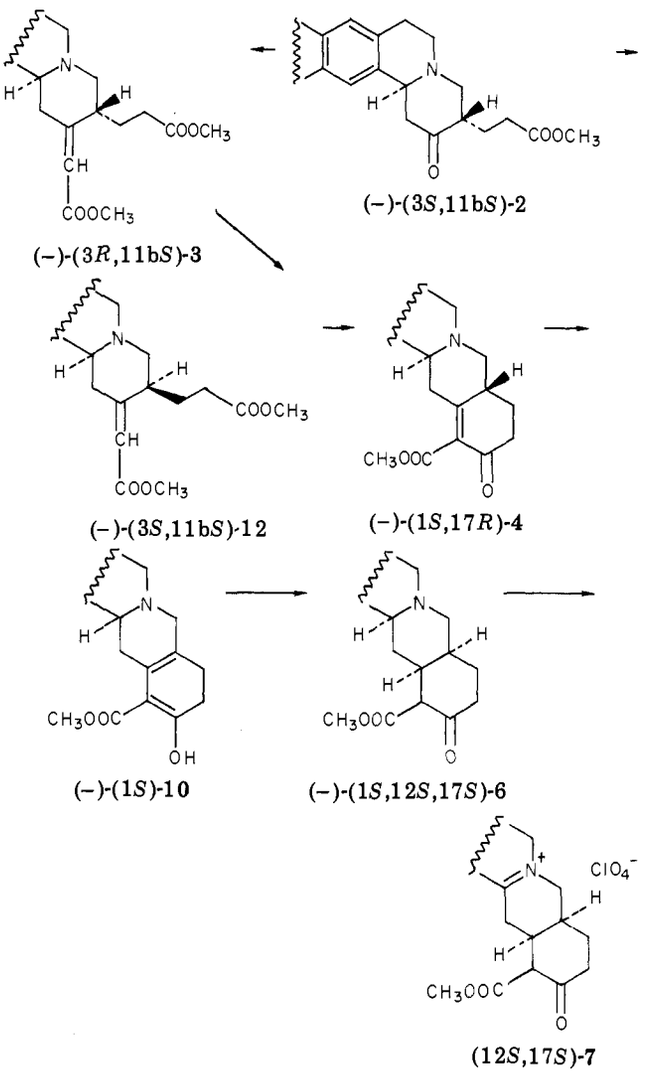


2-11
a, R_1, R_2 = CH_2
b, R_1 = C_2H_5; R_2 = C_2H_5

One of the most interesting features of the method was the synthesis of the same epiallo keto ester (+)-**5a** with the 1*R*,12*S*,17*S* absolute configuration from the other enantiomer of the key intermediate (-)-(3*S*,11b*S*)-**2a** (see Scheme II). In that case the condensation of the keto function of (-)-**2a** with methyl (diethoxyphosphinyl)acetate was accomplished in the presence of a base. In addition to the expected product (-)-**3a**, its C-3 epimer (-)-**12a** was also obtained as a mixture of *E* and *Z* isomers. The Dieckmann condensation of this mixture afforded enol ester (-)-**10a** regioselectively as a homogeneous product under these reaction conditions[6] (see Experimental Section). Compound (-)-**10a** can also be prepared from the corresponding keto ester (-)-**4a** by a treatment with strong bases.

Treatment of (-)-**10a** with hydrogen over Pd–C catalyst in the presence of a base yielded the allo isomer (-)-**6a** as the predominant product accompanied by the epiallo

Scheme II



stereoisomer (-)-**5a** as a minor product (ratio 7:1). They were separated by flash chromatography (R_f **6a** > R_f **5a**).

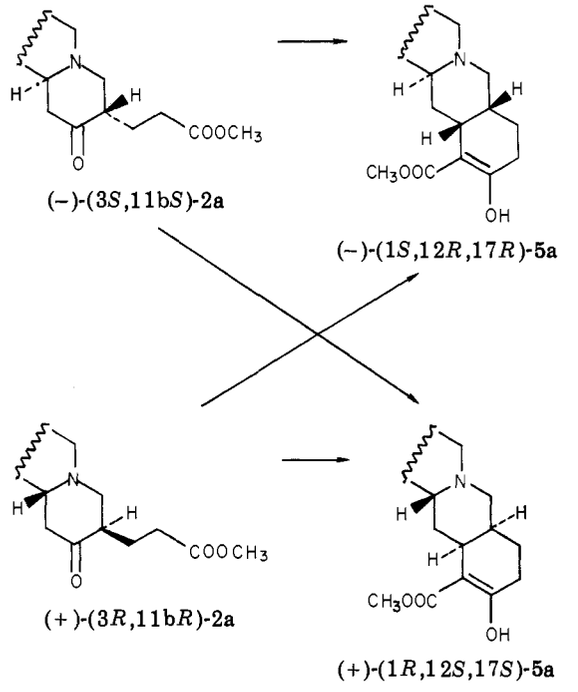
Transformation of allo keto ester (-)-**6a** into (+)-**5a** (epimeric at C-1) was accomplished by the well-known oxidation–reduction method[8,9] employed for the epimerization of the chiral center at C-1. This transformation provides an excellent opportunity to pass from the 1*R* to the 1*S* series. Consequently, (-)-**6a** was oxidized by mercury(II) acetate in glacial acetic acid to the iminium derivative (-)-**7a** (12*S*,17*S*) and was isolated in excellent yield. When the reduction of the C=N double bond was performed with activated zinc powder in an acidic medium, a mixture of (+)-(1*R*,12*S*,17*S*) epiallo **5a** and (-)-(1*S*,12*S*,17*S*) allo **6a** keto esters (ratio ~5:1) was obtained and separated by chromatography.

The two reaction sequences presented above supplied, therefore, an excellent and versatile method for the transformation of keto ester **2** into the epiallo compound **5**; moreover, from both enantiomers of keto ester **2** either of the desired antipodes of the epiallo keto ester **5** could be obtained by the proper choice between the two possible methods (see Scheme III).

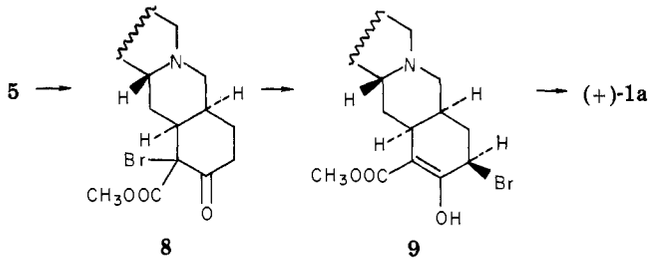
Consequently, an enantioselective total synthesis of both antipodes of the epiallo key intermediate **5** has been

(8) J. Ernest and, P. Protiva, *Naturwissenschaften* **47**, 156 (1960).
(9) I. Tôth, L. Szabó, M. Kajtár-Peredy, E. Baitz-Gács, L. Radics, and Cs. Szántay, *Tetrahedron*, **34**, 2113 (1978).

Scheme III



Scheme IV



achieved from the racemic keto ester **2**. Exploiting the experience gained during the preparation of racemic raunescinone analogues,[1,9] we completed the present synthesis on the methylenedioxy and diethoxy derivatives. This involved bromination, bromine transfer from C-13 to C-15, and subsequent treatment with potassium 3,4,5-trimethoxybenzoate. The chemical and stereochemical consequences of these transformations shown in Scheme IV have already been established.[4]

The hypotensive and antihypertensive effects of raunescinone analogues **1** were investigated, and data for the most effective methylenedioxy derivative (±)-, (+)-, and (−)-**1a** are summarized in the Pharmacological Section.

Pharmacological Section

Methods. Hypotensive activity was determined by indirect blood-pressure measurement on conscious normotensive male rats weighing 250–300 g. The animals were immobilized in Plexiglass tubes, which were kept at 37 °C. Systolic blood pressure was measured at the root of the tail, using a sphygmomanometer with a crystal microphone. The pressure cuff was pulled over the tail down to its base and the pulse pick-up device was placed behind it, as described earlier.[10] In these experiments the heart rate was also measured electronically via the blood-pressure recorder. The compounds were administered intraperitoneally.

Antihypertensive effects were determined similarly by indirect blood-pressure measurement on conscious, spontaneously hypertensive male rats weighing 250–300 g.[10] Test compounds were given intraperitoneally.

The depressant effect of 1a on the central nervous system was determined by measurement of the forced coordinated motor activity[11,12] on female mice weighing 20–25 g. The animals were divided in groups of 10 and trained by conducting several trials on a rod of 3 cm in diameter at a speed of 15 rpm. The mice were forced to walk the rotating rod without side excursions to keep from falling off. The compounds were injected intraperitoneally, and the time each of the 10 animals remained on the rod ("group performance time") was recorded, up to a limit of 120. Under these conditions, depressant effect is indicated by a reduction in the group performance time.

Results and Conclusion

The results summarized in Table I demonstrate that **1a** possessed a significant and lasting hypotensive activity. Blood-pressure reduction of about the same intensity and duration can be achieved by administering 20 mg/kg of this compound and 5 mg/kg of reserpine, respectively. The reduction in blood pressure induced by **4a** is associated with a biphasic change in heart rate: an initial tachycardia followed by bradycardia. Similar results were obtained with derivatives containing two alkoxy groups in the place of the methylenedioxy group.

The data given in Table II indicate that the (+)-(1*R*,12*S*,17*S*) and (−)-(1*S*,12*R*,17*R*) enantiomers of **1a** have antihypertensive activity. Furthermore, the degree of antihypertensive effect is the same with both enantiomers.

The results are illustrated in Table III show that at the time of the maximum blood-pressure lowering effect, **1a**, unlike reserpine, does not induce depression of the central nervous system as measured by the forced coordinated motor activity. Consequently, the berbane derivative **1a** possesses particularly durable hypotensive and antihypertensive activity. Unlike with reserpine, this effect is exerted without depressing the central nervous system.

Experimental Section

The IR spectra were recorded on Spectromom 2000, Unicam SP 200, and Perkin-Elmer spectrophotometers. The NMR spectra were obtained with a Perkin-Elmer and a Varian XL-100-15 Fourier-transform instrument, and chemical shifts are reported as ppm (δ) downfield from Me_4Si. Mass spectra were run on an AEI MS902 instrument (70 eV, ion source temperature 150 °C, direct insertion). The reactions were checked by qualitative TLC (KG-PF_{254}, benzene:methanol (14:2)). For the quantitative separation, Kieselgel $PF_{254-366}$ absorbent (20 × 20 cm, layer 1.5 mm, benzene:MeOH (14:2)) or flash chromatography (Kieselgel G, benzene:MeOH (14:1), 1.6 atm) were used.

The reactions were carried out under argon, and melting points are uncorrected. Solvents were evaporated under reduced pressure with a rotary evaporator.

Optical rotations were measured with an automatic polarimeter Model Polamat A (c = 1.00). CD curves were recorded with Roussel-Jouan Model III dichrograph, in EtOH solution (c = 10^{-4} to 10^{-3} M), in 1–5-mm cells at room temperature.

(+)-(3*R*,11b*R*)- and (−)-(3*S*,11b*S*)-Methyl 3-[9,10-(Methylenedioxy)-2-oxo-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]-quinolizin-3-yl]propionate [(+)- and (−)-2a]. Racemic keto ester (**2a**)[3] (10.0 g) was dissolved in EtOAc (300 mL), and a solution of (+)-tartaric acid (4.789 g) in MeOH (30 mL) was added. After the mixture stood at room temperature for 24 h, the crystals were filtered off and washed with EtOAc. After recrystallization from

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(11) W. J. Kinnard and C. J. Carr: *J. Pharm. Exp. Ther.*, 121, 354 (1957).

(12) W. Cutting, H. Parkman, G. Read, D. Read, J. Cutting, and A. Fürst, *Arch. Int. Pharmacodyn.*, 121, 14 (1959).

Table I. Effects of (±)-**1a** on Blood Pressure (BP)[a] and Heart Rate (HR)[a] of Conscious Normotensive Rats

compd, mg/kg[b]	n	BP (mmHg) and HR (beats/min) prior to dosing	change in BP (mmHg) or HR (beats/min) after dosing					
			3 h	6 h	12 h	18 h	24 h	48 h
(±)-**1a**								
10	5	BP 115 ± 2	−5 ± 2	−16 ± 2[c]	−14 ± 2[c]	−11 ± 2[c]	−11 ± 2[c]	−11 ± 4
		HR 364 ± 10	+6 ± 7	+40 ± 1[c]	+14 ± 6	+4 ± 3	−34 ± 8[c]	−78 ± 5[c]
20	5	BP 116 ± 2	−9 ± 2[c]	−23 ± 2[c]	−20 ± 2[c]	−15 ± 3[c]	−11 ± 2[c]	−5 ± 1[c]
		HR 368 ± 14	+8 ± 6	+60 ± 13[c]	+42 ± 8[c]	+26 ± 2[c]	−2 ± 1	−10 ± 2[c]
reserpine								
5	5	BP 117 ± 2	−18 ± 5[c]	−23 ± 7[c]	−16 ± 1[c]	−10 ± 2[c]	−12 ± 3[c]	−7 ± 3
		HR 364 ± 5	−34 ± 5[c]	−44 ± 5[c]	−40 ± 6[c]	−40 ± 4[c]	−32 ± 5[c]	−10 ± 7

[a] All values are given as mean ± SEM. [b] Administered intraperitoneally as HCl salt [(±)-**1a**] or base (reserpine). [c] $p < 0.05$ (Student's t test).

EtOAc, 6.72 g (91%) of (+)-**2a** salt was obtained: $[\alpha]^{25}_D$ +76.8° (MeOH); mp 155–157 °C (EtOAc).

The salt was dissolved in water (300 mL), basified with 5% $NaHCO_3$, and extracted with CH_2Cl_2. After drying on $MgSO_4$, the solvent was evaporated and the residue was crystallized from MeOH to yield 4.0 g (86%) of (+)-(3*R*,11b*R*)-**2a**: mp 116–118 °C (MeOH); $[\alpha]^{25}_D$ +127° (CH_2Cl_2); CD (EtOH) λ, nm (Δ) 300 (+1.22), 275 (−0.23), 242 (−1.54), 220 (+0.52).

The first mother liquor was concentrated, water (300 mL) was added, and the solution was alkalinated with 5% $NaHCO_3$ and extracted with CH_2Cl_2. After drying on $MgSO_4$, the solution was evaporated and the residue was crystallized from MeOH to yield 4.0 g (80%) of (−)-**2a**. These crystals (4.0 g) were dissolved in EtOAc (150 mL) and a solution of (−)-tartaric acid (1.916 g) in MeOH (12 mL) was added. After the mixture stood overnight at room temperature, the crystals were separated and recrystallized from EtOAc to yield 0.36 g of (−)-**2a** salt: $[\alpha]^{25}_D$ −51.6°.

The same procedure as for (+)-**2a** yielded 0.25 g (62.5%) of (−)-(3*S*,11b*S*)-**2a**: mp 117–118 °C (MeOH); $[\alpha]^{25}_D$ −119°; CD (EtOH) λ, nm (Δ) 302.5 (−1.16), 275 (+0.41), 243.5 (+1.79), 220 (−0.49).

Synthesis of (+)-(3*S*,11b*R*)- and (−)-(3*R*,11b*S*)-Methyl 3-[9,10-(Methylenedioxy)-2-[(methoxycarbonyl)-methylene]-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizin-3-yl]propionate [(+)- and (−)-3a] and Methyl 3-[9,10-Diethoxy-2-[(methoxycarbonyl)methylene]-1,3,4,5,6,11bα-hexahydro-2*H*-benzo[*a*]quinolizin-3α-yl]propionate (3b). A mixture of keto ester **2** (13.3 mmol) and [(methoxycarbonyl)-methylene]triphenylphosphorane (5.3 g, 15.2 mmol) was stirred at 160 °C for 5 h, ether (100 mL) was added, and the reaction mixture was filtered. The ethereal solution was evaporated, the residue was treated with 5% HCl (100 mL), and the yellow precipitate was filtered off. The acidic solution was basified to pH 9 and then extracted with ether. The ethereal solution, after drying on $MgSO_4$, was evaporated and the crude residue crystallized from MeOH to yield **3**.

(+)-(3*S*,11b*R*)-**3a** (41%): mp 91–92 °C (MeOH); $[\alpha]^{25}_D$ +15° (CH_2Cl_2).

(−)-(3*R*,11b*S*)-**3a** (46%): mp 90 °C (MeOH); $[\alpha]^{25}_D$ −15° (CH_2Cl_2).

3b (61%): mp 81–84 °C; IR (KBr) 2750–2800 (Bohlmann (bands), 1705, 1715 ($COOCH_3$), 1630 cm^{-1} (C=C); NMR ($CDCl_3$) δ 6.65, 6.55 (2 H, s, C_8-H, C_{11}-H), 4.0 (4 H, q, OCH_2CH_3), 3.65 (6 H, s, $COOCH_3$), 1.45 (6 H, t, OCH_2CH_3). Anal. ($C_{24}H_{33}NO_6$) C; calcd, 66.79; found, 66.12; H; N.

Synthesis of (+)-(3*R*,11b*R*)- and (−)-(3*S*,11b*S*)-Methyl 3-[9,10-(Methylenedioxy)-2(*E*)- and -(*Z*)-[(methoxycarbonyl)methylene]-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]-quinolizin-3-yl]propionate [(+)- and (−)-12a] and Methyl 3-[9,10-Diethoxy-2(*E*)- and -(*Z*)-[(methoxycarbonyl)-methylene]-1,3,4,6,7,11bα-hexahydro-2*H*-benzo[*a*]-quinolizin-3β-yl]propionate (12b). A solution of keto ester **2** (5 mmol) was added to the solution of $KOBu^t$ (0.86 g, 7.6 mmol) and methyl (diethoxyphosphinyl)acetate (2.0 g, 9.43 mmol) in DMF (3 mL). After standing for 2 days at room temperature, the mixture was poured into ice water (100 mL) and extracted with ether. After evaporation of the solvent, the crude product was separated by flash chromatography to yield **12**.

(*E*)- and (*Z*)-(+)-(3*R*,11b*R*)-**12a** (37%), oil.

(*E*)- and (*Z*)-(−)-(3*S*,11b*S*)-**12a** (33%), oil.

(*E*)-**12b**[13] (12%): mp 93–95 °C (MeOH); IR (KBr) 2750–2850 (Bohlmann bands), 1735, 1725 ($COOCH_3$), 1640 cm^{-1} (C=C). Anal. ($C_{24}H_{33}NO_5$) C: calcd, 66.79; found, 67.91; H; N. (*Z*)-**12b**[13] (13%): mp 98 °C (MeOH); IR (KBr) 2750–2850 (Bohlmann bands), 1730, 1710 ($COOCH_3$), 1640 cm^{-1} (C=C). Anal. ($C_{24}H_{33}NO_6$) C, H, N.

Table II. Effects of the Enantiomers of **1a** on Blood Pressure (BP)[a] on Conscious Spontaneously Hypertensive Rats

compd (mg/kg)[b]	n	BP (mmHg) prior to dosing	change in BP mmHg after dosing		
			6 h	18 h	24 h
(+)-(1*R*,12*S*, 17*S*)-**1a** (10)	6	175 ± 2	−16 ± 3[c]	−7 ± 2[c]	−5 ± 3
(−)-(1*S*,12*R*, 17*R*)-**1a** (10)	6	176 ± 3	−15 ± 3[c]	−8 ± 1[c]	−2 ± 3

[a] All values are given as mean ± SEM. [b] Administered intraperitoneally as HCl salt. [c] $p < 0.05$ (Student's t test).

Table III. Lack of Depressant Effect on **1a** on the Central Nervous System as Measured by the Forced Coordinated Motor Activity on Mice

compd (mg/kg)[a]	n[b]	time of performance test after dosing, h	group performance time,[c] s	act. ratio[d]
control	10		98 ± 9	1.00
(±)-**1a** (20)	10	6[e]	102 ± 12	1.04
control	10		117 ± 3	1.00
reserpine (5)	10	6[e]	9 ± 3[f]	<0.08

[a] Administered intraperitoneally as HCl salt (**1a**) or base (reserpine). [b] Number of groups of 10 mice used in test. [c] Mean ± SEM. [d] Performance time under the effect of drug divided by the corresponding control performance time. [e] The time elapsed from dosing required to obtain maximum hypotensive or antihypertensive effect (see Tables I and II). [f] $p < 0.05$ (Student's t test).

Synthesis of (+)-(1*R*,17*S*)-Methyl 7,8-(Methylenedioxy)-14-oxo-12,13-didehydro-13-berbanecarboxylate [(+)-4a] and Methyl 7,8-Diethoxy-14-oxo-12,13-didehydro-13-berbanecarboxylate (4b). Dimethyl ester **3** (10 mmol) in benzene (60 mL) was refluxed for 20 min with $KOBu^t$ (1.12 g, 10 mmol). The cold reaction mixture was extracted with saturated aqueous NaCl solution (40 mL). After drying on $MgSO_4$, the organic phase was evaporated and the residue was crystallized from MeOH to yield **4**.

(+)-(1*R*,17*S*)-**4a** (47%): mp 174–177 °C (MeOH); $[\alpha]^{25}_D$ +28° (CH_2Cl_2); MS, m/e 355 (M^+); IR (KBr) 2750–2800 (Bohlmann bands), 1730 ($COOCH_3$), 1660 (C=O conj), 1620 cm^{-1} (C=C); UV (MeOH) λ_{max} (log ε) 230 (3.8), 292 nm (3.7); NMR ($CDCl_3$) δ 6.2 (2 H, s, C_6-H, C_9-H), 5.94 (2 H, s, OCH_2O), 3.92 (3 H, s, $COOCH_3$). Anal. ($C_{20}H_{21}NO_5$) C, H, N.

4b (73.4%): mp 126 °C; MS, m/e 399 (M^+); IR (KBr) 2750–2800 (Bohlmann bands), 1710 ($COOCH_3$), 1760 (C=O), 1610 cm^{-1} (C=C); NMR ($CDCl_3$) δ 6.6, 6.58 (2 H, s, C_6-H, C_9-H), 4.15 (4 H, q, OCH_2CH_3), 3.95 (3 H, s, $COOCH_3$), 1.4 (6 H, t, OCH_2CH_3). Anal. ($C_{23}H_{29}NO_5$) C, H, N.

Synthesis of (−)-(1*S*)-Methyl 7,8-(Methylenedioxy)-14-

(13) Determination of the configuration of C=C based on the analogy. See: L. Szabó, K. Honty, L. Töke, and Cs. Szántay, *Chem. Ber.*, **105**, 3231 (1972).

oxo-12,17-didehydro-13-berbanecarboxylate [(−)-10a] and Methyl 7,8-Diethoxy-14-oxo-12,17-didehydro-13-berbanecarboxylate (10b). (a) A mixture of $NaOCH_3$ (250 mmol) in MeOH (200 mL) and the unsaturated keto ester **4b** (10 g, 25 mmol) was allowed to stand at room temperature for 3 h, neutralized with CH_3COOH, and evaporated. The residue was treated with water, basified with 5% Na_2CO_3 (pH 8), and extracted with CH_2Cl_2. After drying on $MgSO_4$, the organic phase was evaporated and the residue crystallized from MeOH to yield 6.2 g (62%) of **10b**: mp 164–166 °C (MeOH); MS, *m/e* 399 (M^+); IR (KBr) 2730–2800 (Bohlmann bands), 1660 ($COOCH_3$), 1620 cm^{-1} (C=C); NMR ($CDCl_3$) δ 6.6 (2 H, s, C_6-H, C_9-H), 4.1 (4 H, q, OCH_2CH_3), 3.8 (1.3 H, s, $COOCH_3$ equatorial), 3.75 (0.5 H, s, $COOCH_3$ enol), 3.65 (1.2 H, s, $COOCH_3$ axial), 1.35 (6 H, t, OCH_2CH_3). Anal. ($C_{23}H_{29}NO_5$) C; calcd, 69.15; found, 69.90; H; N.

(b) A mixture of (−)-(1*S*,17*R*)-**12a** dimethyl ester (1.8 g, 4.66 mmol), benzene (18 mL), and $KOBu^t$ (1.0 g, 8.9 mmol) was refluxed for 4 h and processed similarly to yield 64% of (−)-(1*S*)-**10a**: mp 135 °C (MeOH); $[\alpha]^{25}_D$ −7.1° (CH_2Cl_2).

Synthesis of (+)-Methyl 7,8-(Methylenedioxy)-14-oxo-13-epiallo- and -(normal)berbanecarboxylate [(+)-(1*R*,12*S*,17*S*)-5a, (+)-(1*R*,12*R*,17*S*)-11a] and Methyl 7,8-Diethoxy-14-oxo-13-epialloberbanecarboxylate (5b) and -berbanecarboxylate (11b). A solution of keto ester **4** (2.5 mmol) in MeOH (50 mL) was hydrogenated over Pd–C catalyst. After removal of the catalyst, the solvent was evaporated and the residue was separated by flash chromatography (R_f **11** > R_f **5**) to yield **11** and **5**.

(+)-(1*R*,12*R*,17*S*)-**11a** (13%): mp 171 °C (MeOH); $[\alpha]^{25}_D$ +108° (CH_2Cl_2).

(+)-(1*R*,12*S*,17*S*)-**5a** (50%): mp 160–161 °C (MeOH); $[\alpha]^{25}_D$ +126° (CH_2Cl_2).

5b (18%): mp 119–121 °C (MeOH); HCl salt, mp 205–207 °C (MeOH); MS, *m/e* 401 (M^+); IR (KBr) 2750–2800 (Bohlmann bands), 1725, 1705 ($COOCH_3$, C=O), 1610 cm^{-1} (aromatic); NMR (C_6D_6) δ 6.96, 6.58 (2 H, s, C_6-H, C_9-H), 3.90 (4 H, q, OCH_2CH_3), 3.48 (3 H, s, $COOCH_3$), 1.28 (6 H, t, OCH_2CH_3). Anal. ($C_{23}H_{31}NO_5$) C, H, N.

11b (60%): mp 160.5–162 °C (MeOH); MS, *m/e* 401 (M^+); IR (KBr) 2750–2800 (Bohlmann bands), 1720, 1705 ($COOCH_3$, C=O), 1610 cm^{-1} (aromatic); NMR ($CDCl_3$) δ 6.65, 6.55 (2 H, s, C_6-H, C_9-H), 4.1 (4 H, q, OCH_2CH_3), 3.50 (3 H, s, $COOCH_3$), 1.31 (6 H, t, OCH_2CH_3). Anal. ($C_{23}H_{31}NO_5$) C, H, N.

Synthesis of (−)-Methyl 7,8-(Methylenedioxy)-14-oxo-13-allo- and -epialloberbanecarboxylate [(−)-(1*S*,12*S*,17*S*)-6a, (−)-(1*S*,12*R*,17*R*)-5a] and Methyl 7,8-Diethoxy-14-oxo-13-allo- and -epialloberbanecarboxylate (6b, 5b). A mixture of keto ester **10** (3 mmol) and $NaOCH_3$ (20 mmol) in MeOH (20 mL) was hydrogenated over Pd–C (1.0 g) for 24 h. After removal of the catalyst and evaporation of the MeOH, water (50 mL) and CH_3COOH (20 mmol) were added to the residue and extracted with CH_2Cl_2. After drying on $MgSO_4$, the organic phase was evaporated, and keto esters **5** and **6** were separated by flash chromatography (R_f **6** > R_f **5**).

(−)-(1*S*,12*S*,17*S*)-**6a** (51%): mp 135–138 °C (MeOH); $[\alpha]^{25}_D$ −98° (CH_2Cl_2).

(−)-(1*S*,12*R*,17*R*)-**5a** (7%): mp 160–161 °C (MeOH); $[\alpha]^{25}_D$ −126° (CH_2Cl_2).

6b (52%): mp 102–103 °C (MeOH); MS, *m/e* 401 (M^+); IR (KBr) 2750–2820 (Bohlmann bands), 1660 ($COOCH_3$ conj), 1620 cm^{-1} (aromatic); NMR ($CDCl_3$) 12.55 (1 H, s, OH), 6.7, 6.55 (2 H, s, C_6-H, C_9-H), 3.05 (4 H, q, OCH_2CH_3), 3.85 (3 H, s, $COOCH_3$), 1.35 (6 H, t, OCH_2CH_3). Anal. ($C_{23}H_{31}NO_5$) C, H, N.

5b (8%).

Racemic and (12*S*,17*S*)-7,8-(Methylenedioxy)-13-(methoxycarbonyl)-14-oxo-Δ^1-berbenium Perchlorate [(±)-7a, (12*S*,17*S*)-7a] and 7,8-Diethoxy-13-(methoxycarbonyl)-14-oxo-Δ^1-berbenium Perchlorate (7b). To a solution of keto ester **6** (1.4 mmol) in CH_3COOH (2 mL) was added $Hg(OAc)_2$ (0.7 g, 2.2 mmol). After stirring at 100 °C for 3 h, the reaction mixture was poured into ice–water, basified to pH 9 with NH_4OH, and extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was evaporated, the residue was dissolved in MeOH (2 mL) and $HClO_4$ (0.5 mL) was added. The crystals were filtered off and washed with ether to yield **7**.

7a (82%): mp 220 °C dec.

(12*S*,17*S*)-**7a** (78.7%): mp 218–220 °C dec; IR (KBr) 1720, 1660 ($COOCH_3$ conj), 1640, 1570 (C=N), 1605 (aromatic), 1110–1090 cm^{-1} (perchlorate). Anal. ($C_{20}H_{22}NO_9Cl$) C; calcd, 52.69; found, 51.90; H; N.

7b (84.9%): mp 205–207 °C dec; IR (KBr) 1660 ($COOCH_3$ conj), 1640, 1575 (C=N), 1610 (aromatic), 1110–1090 cm^{-1} (perchlorate). Anal. ($C_{23}H_{30}NO_9Cl$) C; H; calcd, 6.04; found, 6.55; N; Cl.

Reduction of Iminium Salt 7. Iminium salt **7** (1.8 mmol) was stirred in a mixture of acetone (20 mL), water (4 mL), 10% HCl (6 mL), $FeCl_3$ (5 mg), and $HgCl_2$ (5 mg), and zinc powder (2.5 g) was added in small portions for 3 h. The reaction mixture was filtered, concentrated to 5–7 mL, basified with concentrated NH_4OH to pH 9, and extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was evaporated and the residue separated by flash chromatography to yield **5** and **6**. (+)-(1*R*,12*S*,17*S*)-**5a** (56%); (−)-(1*S*,12*S*,17*S*)-**6a** (20%) (starting compound).

We obtained from **7b** in a similar manner **5b** (47%) and **6b** (13%) (starting compound).

Racemic and (+)-(1*R*,12*S*,17*S*)-Methyl 7,8-(Methylenedioxy)-14-oxo-15-bromo-13-epialloberbanecarboxylate [(±)-9a, (+)-9a] and Methyl 7,8-Diethoxy-14-oxo-15-bromo-13-epialloberbanecarboxylate (9b). Epiallo keto ester **5** (2.8 mmol) was dissolved in CH_3COOH (10 mL), and Br_2 (0.47 g, 2.8 mmol) was added dropwise at 5 °C for 1 h. The mixture was stirred at room temperature for 3 h and at 95 °C for 5 h. The cold reaction mixture was poured into ether (50 mL) and filtered, and the precipitate was washed with ether to yield **9**·HBr.

9a·HBr (70%): mp 230 °C; IR (KBr) 1665 ($COOCH_3$ conj), 1620 cm^{-1} (C=C); NMR ($CDCl_3$) δ 12.5 (1 H, m, enol OH), 6.76, 6.52 (2 H, s, C_6-H, C_9-H), 5.85 (2 H, s, OCH_2O), 4.75 (1 H, m, C_{15}-H eq), 3.85 (3 H, s, $COOCH_3$). Anal. ($C_{20}H_{33}NO_5Br_2$) C, H, N, Br.

(+)-(1*R*,12*S*,17*S*)-**9a**·HBr (76%): mp 228–230 °C; $[\alpha]^{25}_D$ +42°.

9b·HBr (78%): mp 173–177 °C dec; IR (KBr) 1660 ($COOCH_3$, conj), 1620 cm^{-1} (C=C), NMR (C_6D_6) 6.90, 6.58 (2 H, s, C_6-H, C_9-H), 4.60 (1 H, dd, C_{15}-H eq), 3.95 (4 H, q, OCH_2CH_3), 3.50 (1 H, d, C_1-H), 3.38 (3 H, s, $COOCH_3$), 1.30 (6 H, t, OCH_2CH_3). Anal. ($C_{23}H_{31}NO_5Br_2$) C, H, N, Br.

Racemic and (+)-(1*R*,12*S*,17*S*)-Methyl 7,8-(Methylenedioxy)-14-oxo-15-[(3,4,5-trimethoxybenzoyl)oxy]-13-epialloberbanecarboxylate [(±)-1a, (+)-1a] and Methyl 7,8-Diethoxy-14-oxo-15-[(3,4,5-trimethoxybenzoyl)oxy]-13-epialloberbanecarboxylate (1b). A mixture of bromo keto ester **9** (0.9 mmol) and potassium 3,4,5-trimethoxybenzoate (0.5 g, 2.8 mmol) in DMF (5 mL) was stirred for 20 min at 100 °C. The reaction mixture was poured into ice–water (100 mL), basified with 2.5% Na_2CO_3 to pH 8, and filtered, and the precipitate was washed with water and purified by chromatography to yield **1**.

(±)-**1a** (82%): mp 186 °C (MeOH); MS, *m/e* 567 (M^+); IR (KBr) 2750–2800 (Bohlmann bands), 1715, 1705 (OTMB, CO, $COOCH_3$), 1670 ($COOCH_3$ conj), 1620 (C=C), 1590 cm^{-1} (aromatic); NMR (C_6D_6 + Me_2SO) 7.68 (2 H, s, C′$_2$-H, C′$_6$-H), 6.86, 6.57 (2 H, s, C_6-H, C_9-H), 6.20 (1 H, m, J_{aa} = 11 Hz, J_{ae} = 7.5 Hz, C_{15}-H), 5.53 (2 H, s, OCH_2O), 3.90, 3.48, 3.46, 3.44, 3.43 (12 H, s, OCH_3, $COOCH_3$). Anal. ($C_{30}H_{33}NO_{10}$) C, H, N.

(+)-(1*R*,12*S*,17*S*)-**1a** (82%): mp 186 °C (MeOH); $[\alpha]^{25}_D$ +15° (CH_2Cl_2).

1b·HCl (56%): mp 226–228 °C (MeOH); IR (KBr) 2750–2800 (Bohlmann bands), 1760, 1720, 1705 ($COOCH_3$, CO, OCO), 1600, 1590 (aromatic) cm^{-1}; NMR ($CDCl_3$) δ 7.3 (2 H, s, C′$_2$-H, C′$_6$-H), 6.60, 6.50 (2 H, s, C_6-H, C_9-H), 5.60 (1 H, m, J = 22 Hz, C_{15}-H), 3.90 (4 H, q, OCH_2CH_3), 3.80 (12 H, s, OCH_3, $COOCH_3$), 1.45 (6 H, t, OCH_2CH_3). Anal. ($C_{33}H_{41}NO_{10}$·HCl) C, H, N.

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