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Synthesis of Reserpine-type Alkaloids, III[1)]

Synthesis of *rac*-Deserpidine and a *rac*-Raunescine Epimer

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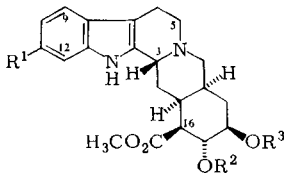
Starting from the key intermediate **2** previously used for the preparation of derivatives with a normal yohimbane skeleton, the synthesis of *rac*-deserpidine (**1b**) and the *rac*-raunescine epimer **9c**, having an *epi-allo* and *allo* skeleton, respectively, has been performed. In the course of the synthesis several stereoisomers of C-18-substituted *allo*-yohimbine have been prepared and characterized by spectroscopic and chemical means.

Synthese von Alkaloiden des Reserpin-Typs, III[1)]. – Synthese von *rac*-Deserpidin und einem *rac*-Raunescin-Epimer

Ausgehend von der in der vorausgehenden Mitteilung beschriebenen, zur Darstellung von Yohimbanen mit normalem Molekülgerüst verwendeten Schlüssel-Synthesevorstufe **2**, wurden *rac*-Deserpidin (**1b**) und das *rac*-Raunescin-Epimer **9c** mit *epi-allo*- bzw. *allo*-Gerüst hergestellt. Im Laufe der Synthese wurden einige Stereoisomere des in Position 18 substituierten *allo*-Yohimbins hergestellt und auf spektroskopischem und chemischem Wege charakterisiert.

The synthesis of reserpine (**1a**) and its derivatives, which are of great importance as anti-hypertensive medications, has been thoroughly investigated during the last twenty-five years. In principle, all synthetic approaches published up to now are based on the convergent model of *Woodward's* ingenious synthesis[3)], in which an appropriately substituted cyclohexane[4,5,6)] or *cis*-perhydroisoquinoline[7)] building block is connected with the indole part.



1

1	R^1	R^2	R^3	
a	OCH_3	CH_3	TMB	reserpine
b	H	CH_3	TMB	deserpidine
c	H	H	TMB	raunescine
d	OCH_3	H	TMB	pseudo-reserpine

TMB = 3,4,5-trimethoxybenzoyl

In the last paper of our series the conversion of the ketone **2** into *trans*-2,3-disubstituted derivatives had been discussed[1,2)]. The same intermediate **2** was expected

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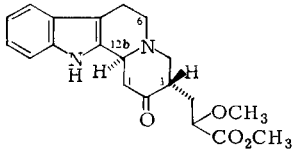
to be a proper starting material in producing *cis*-2,3-substituted derivatives which are suitable for the synthesis of reserpine-type alkaloids **1**, having D/E-*cis* ring fusion. The synthesis was planned *via allo* compounds, since the transformation of the *allo*-yohimbane skeleton into the *epi-allo* one is well known. The preparation of the respective *allo* compounds is based on our earlier work, where a similar problem had been solved during the total synthesis of *allo*-yohimbine[8].

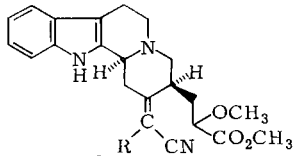
Our linear synthetic method appeared to be qualified for both forming *rac*-deserpidine (**1b**) itself and for obtaining different stereoisomers of the C-17 hydroxy substituted alkaloids with D/E-*cis* annulation, such as raunescine (**1c**) and pseudo-reserpine (**1d**).

A) Preparation of *cis*-2,3-substituted indolo[2,3-*a*]quinolizines

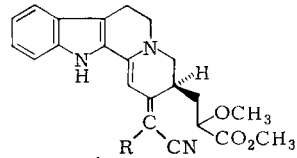
The reaction of **2** with malonodinitrile or methyl cyanoacetate gave condensation products **3a** and **3b**, respectively, in which the chiral center C-3 has been inverted during the procedure. Most probably the inversion at C-3 follows from the keto-enol equilibrium of **2** in which a small amount of the keto form containing the side chain at C-3 in pseudoaxial position is also present. Since the transition state of the Knoevenagel condensation derived from this form has lower energy than that derivable from the C-3 equatorially substituted epimer, the first form reacts faster. Consequently, derivatives of type **3** will be formed, the steric structure of which can be called as "pro-*allo* configuration".



2



3

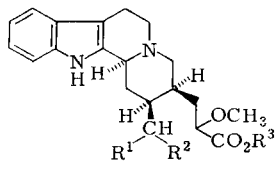


4

3-4	R
a	CN
b	CO_2CH_3

The realization of the condensation requires special circumspection due to possible side reactions. On the one hand the condensation products are easily oxidized into bright yellow substances of type **4** containing an extended conjugated system[8]. On the other hand the ester group of **2** hydrolizes easily by water formed in the reaction.

The most suitable conditions can be provided by using triethylammonium acetate as solvent in the presence of phosphorus pentoxide as dehydrating agent[8]. The reaction proceeds with malonodinitrile at room temperature in about 12 hours and affords the desired nitrile **3a** in a yield of 64%, while with methyl cyanoacetate as condensation partner the reaction rate as well as the yield are lower. The geometry of the C=C double bond of **3b** as well as the ratio of the possible isomers have not been investigated, as it was of no importance from the point of view of the synthesis.



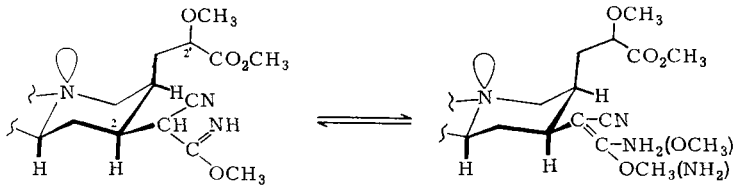
5

5	R^1	R^2	R^3
a	CN	CN	CH_3
b	CO_2CH_3	CN	CH_3
c	$C(=NH)OCH_3$	CN	CH_3
d	CO_2H	CN	H
e	H	CN	H
f	H	CN	CH_3
g	H	CO_2CH_3	CH_3

Reduction of the exocyclic double bond of **3a** and **3b** with sodium borohydride proceeded easily with complete stereoselectivity and furnished **5a** and **5b** having the *allo* arrangement. **5a** is a mixture of two diastereomeric racemates[1,2], while **5b** represents four stereoisomer racemates due to the additional chiral center in the C-2 side chain. The nitrile ester **5b** could also be obtained from **5a**. The base-catalyzed methanol addition of **5a** afforded the iminoether **5c** in crystalline form. In accordance with our earlier detailed study of this reaction[11], **5c** in solution is in equilibrium with its tautomeric enamine forms.

In the 250 MHz ^{1}H NMR spectrum of the tautomeric mixture four-four imine and enamine signals can be distinguished due to the four diastereomeric imine forms and the two-two diastereomeric *E* and *Z* enamines, respectively (see Scheme 1). The equilibrium of the four imine-enamine tautomers namely the relative concentration of each form depends both on the solvent and on the temperature.

Scheme 1



5c

The iminoether **5c** could be hydrolized in a well controllable reaction into the ester **5b**. The above route proved to be considerably more convenient, and resulted in higher yield of **5b** compared with condensation of **2** with methyl cyanoacetate followed by reduction.

Neither the additional chirality established in the C-2 side chain of **5b** and **5c** nor the imine-enamine tautomerism have any importance from the aspect of our synthesis, as they disappear in the course of further transformations.

Alkaline hydrolysis of both ester groups of **5b** is extremely rapid even at room temperature and furnishes the dicarboxylic acid **5d**. The unusually rapid hydrolysis can be attributed to neighbouring group participation studied earlier in connection with yohimbine alkaloids[8].

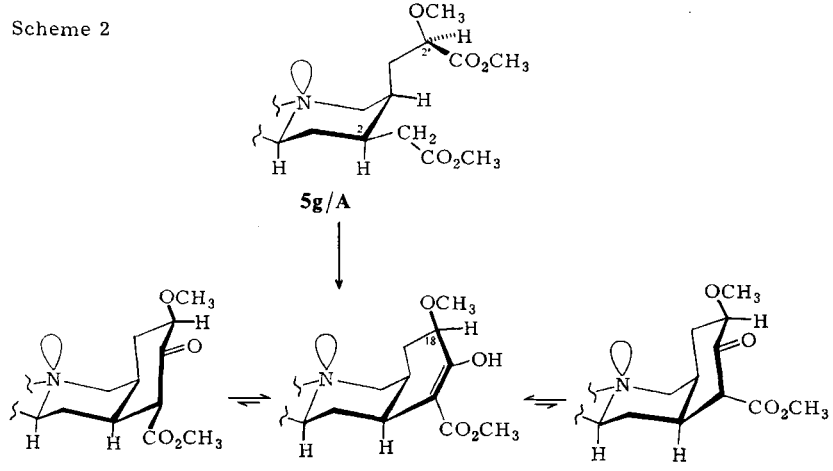
The dicarboxylic acid **5d** was decarboxylated by heating in DMF at 120°C and **5e** was formed. The latter without separation was esterified with diazomethane to obtain the nitrile ester **5f**. When esterification was carried out with 5 N hydrochloric acid in methanol, the nitrile group was also converted into an ester to yield the diester **5g**. It should be mentioned that most of the above conversions starting from **3a** can be drawn together and **5g** could be obtained in good yield without isolation of the single substances.

The diester **5g** could be separated into its diastereomeric components (**5g/A** and **5g/B** racemates) by preparative thin-layer chromatography. The two C-2′ epimers cannot be transformed into one another by the usual reversible epimerization method (2 N sodium methoxide/methanol). The relative configuration of the C-2′ chiral centers indicated in formulas **5g/A** and **5g/B** has been proved by ring closure experiments as follows.

B) Formation of the *allo* pentacycle 6 from the diester 5g

On performing the Dieckmann ring closure of **5g/A** with potassium *tert*-butoxide in boiling benzene the keto-enol tautomeric mixture **6** was obtained. The ^{1}H NMR spectrum gave basic information on the extent of enolization (about 40%) and on the steric arrangement of the C-18 methoxy substituent (pseudoequatorial β-position, see Scheme 2).

Scheme 2



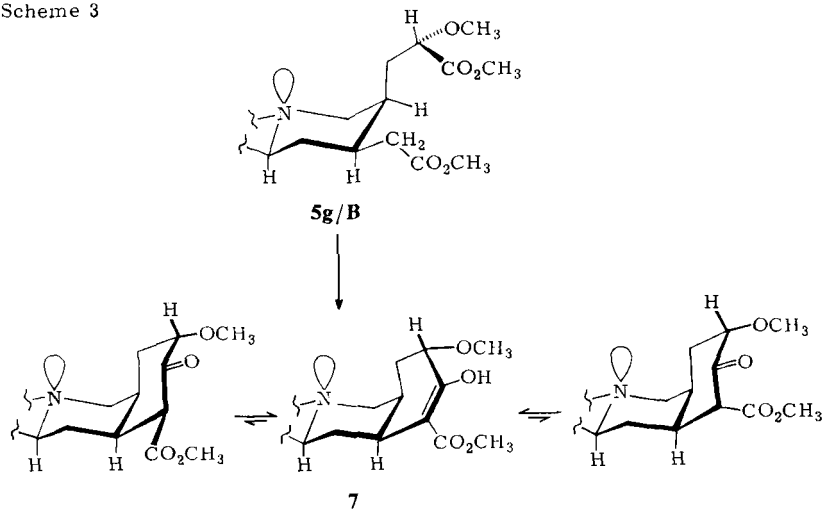
Thus it can be established that the ring closure of the diester **5g/A** is regioselective and yields the C-18 epimer-free product **6** uniformly.

The Dieckmann condensation of **5g/B** under the same conditions gave a complex mixture. In addition to the expected product **7** with C-18 axial (α) methoxy group its C-18 epimer **6**, a result of subsequent epimerization, was also formed in a quantity depending on processing conditions. The easily reversible C-18 epimerization of **6** and **7** was supported by the fact, that treating the separated β-keto esters with 0.5 N sodium

methoxide/methanol at room temperature yielded the same equilibrium mixture (7:3 in favour of **6**).

Epimer-free **7** could be separated only by preparative thin-layer chromatography. It is noteworthy that according to ^{1}H NMR the ratio of the enol form in **7** is considerably higher (about 80%) than in the case of **6** (see Experimental). The ^{1}H NMR spectrum also proves the presumed pseudoaxial (α) steric position of 18-OCH_3 in compound **7**.

Scheme 3



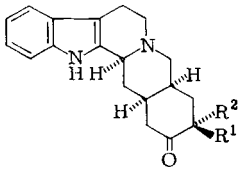
7

Hydrolysis and decarboxylation of **6** gave almost uniformly 18β-methoxy-*allo*-yohimbone (**8a**). The same process starting with **7** either in acidic or alkaline medium resulted only about 10% of the expected 18α-methoxy-*allo*-yohimbone (**8b**), the main product was **8a** again. The steric structure of the two *allo*-yohimbone derivatives **8a, b** has been elucidated by ^{1}H NMR spectroscopy (see Experimental). The reversibility of the C-18 epimerization of **8a** and **8b** was proved by separate experiments. Starting with either epimer **8a** or **8b** the same equilibrium mixture was obtained in 0.5 N sodium methoxide/methanol (**8a**:**8b** = 85:15).

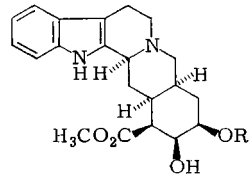
C) Preparation of 18-hydroxy-*allo*-yohimbines

To accomplish the proper substitution pattern of ring E the keto function of the *allo*-yohimbinone derivatives **6** and **7** was reduced with sodium borohydride. The reduction of **6** yielded the two alcohols **9a** and **10a** in a ratio of 6:4. Starting with either **9a** or **10a** the same equilibrium mixture could be achieved (**9a**:**10a** = 3:1) in 2 N sodium methoxide/methanol at room temperature. This fact, as well as the easy water elimination of both **9a** and **10a** yielding the same unsaturated ester **11a** unanimously proves that **9a** and **10a** are C-16 epimers in which the 17-OH is supposed to be axial. The final proof of the steric arrangement of **9a** and **10a** has been provided by spectroscopic methods. According to ^{1}H NMR[12,13] and IR[14] spectral data the yohimbane skeleton in both hydroxy esters **9a** and **10a** exists in A_T conformation[12], which is unexpected for

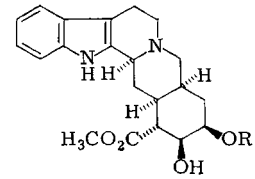
10a. The compound **10a** is the 18β-methoxy derivative of 17-*epi-allo*-yohimbine which is stable in an $A_T \rightleftharpoons A_{C2}$ conformational equilibrium at ambient temperature[16].



8	R^1	R^2
a	OCH_3	H
b	H	OCH_3



9	R
a	CH_3
b	H
c	TMB



10	R
a	CH_3
b	H

The probable cause of the preference of the A_T conformation in **10a** is that in an A_{C2} conformation the axial C-18 substituent would exert an unfavourable steric compression through its skew pentane interaction with the C-20 – C-21 bond.

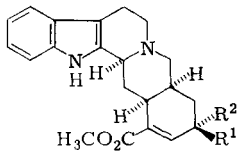
The difference of the orientation of the C-16 substituent in **9a** and **10a** is obvious from the ^{13}C chemical shifts of C-18, C-20, and C-14[15,16] (see Table 2). The γ *gauche* effect of the axial methoxycarbonyl group in **10a** shields both C-18 and C-20, while the equatorial methoxycarbonyl group in **9a** imposes a γ *peri* effect on C-14. The constancy of the C-19 shift proves that the stereochemistry at C-17 and C-18 is identical in both compounds.

The preferential α-side approach onto D/E-*cis* annulated yohimbinoids[17,18] as well as the β position of the C-18 methoxy group results in the exclusive α-side attack of the borohydride anion. These two factors together explain why only β-hydroxy derivatives **9a, 10a** are formed in the reaction.

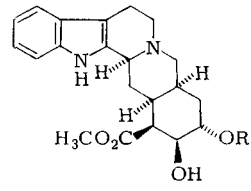
The steric approach control could be applied to the reduction of the β-keto ester **7**, too. The α orientation of 18-OCH_3 in **7** makes possible the β-side attack of $BH_4^{\ominus}$ anion as well. The ratio of the α and β attack is reflected in the composition of the product mixture. Accordingly, the reduction of **7** gave 47% of **12a**, 15% of **13a**, and 2% of **13b** in addition to **9a** and **10a** derivable from **6**, formed by previous C-18 epimerization of **7**.

The alcohol **12a** did not undergo epimerization in 2 N sodium methoxide/methanol at 25 °C, however, at higher temperature water elimination and formation of **11b** was observed. Neither epimerization nor water elimination could be achieved with **13a**. The elimination reaction failed also with **13b**, from the basic reaction mixture only **13a** could be isolated due to the easy C-16 epimerization into the thermodynamically more stable stereoisomer **13a**. These chemical results, together with spectral information, gave the complete stereoarrangement of the three new alcohols **12a**, **13a**, and **13b**. IR and NMR measurements showed that **12a** and **13a** are C-17 epimers, thus they can be considered as the axial (α) 18-OCH_3 derivatives of 17-*epi*-α-yohimbine and α-yohimbine, respectively. Accordingly, in comparison with the above substituted yohimbines, γ *gauche* effects are observed on C-20 (– 6.3 and – 6.4 ppm, respectively)

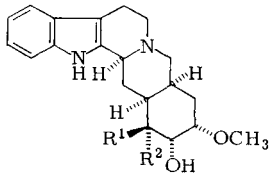
and on C-16 (−4.7 and −7.9 ppm, respectively)[16]. Inspection of the diagnostic C-3, C-6, and C-21 carbon shifts reveals that **12a** exists in an A_T conformation. The line broadening and slight upfield shift of C-3, C-6, and C-21 in the ^{13}C spectrum of **13a** indicate that the predominant A_T conformation is in equilibrium with the minor A_{C2} form. The proton spectrum of **13a** also supports the above observation. The rather low values of the 17-H couplings (2.5 and 5.5 Hz) reflect that the 17-OH is not purely equatorial. For **13b** a predominant A_{C2} conformation can be deduced from the C-3, C-6, and C-21 shifts of the ^{13}C NMR spectrum (δ = 51.47, 16.59, and 53.51, respectively).



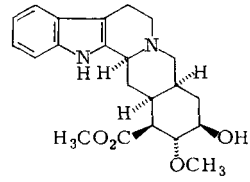
11	R^1	R^2
a	OCH_3	H
b	H	OCH_3
c	OH	H



12	R
a	CH_3
b	H



13	R^1	R^2
a	CO_2CH_3	H
b	H	CO_2CH_3

11c ⟶  ⟶⟶ **1b**

14

Thus, by the above reductions alcohols of five different steric structures have been obtained. By demethylating the three major products (**9a**, **10a**, **12a**) with 48-% hydrogen bromide, followed by re-esterification, furnished the corresponding diols **9b**, **10b**, and **12b**. Similarly to the case of their analogues with normal skeleton[1], the ether splitting can be performed with boron(III) tribromide in dichloromethane without the danger of epimerization (see Experimental). The resulted diols **9b**, **10b**, and **12b** with proved steric structure are stereoisomers of "18-hydroxy-α-yohimbine" having the *allo*-yohimbane skeleton and reported by *Iwu* and *Court*[19] as natural substance, moreover, they might as well prove to be alkaloids themselves.

D) Preparation of racemic deserpidine and a raunescine epimer

None of our synthetic products have the same ring E substitution pattern and stereoarrangement as the natural target compounds deserpidine (**1b**) and raunescine (**1c**).

The two major products **9b** and **10b**, however, contain the C-18 hydroxy group in the required orientation (β), so their utilization in the synthesis of deserpidine (**1b**) seemed reasonable.

Water elimination from **9b** and **10b** was performed in 2 N sodium methoxide/methanol, and from both stereoisomers 18β-hydroxy-*allo*-apoyohimbine (**11c**) was obtained in a good yield. Spectroscopic data of the product were found to be in full agreement with the conjugated ester structure. By this step the chiral centers at C-16 and C-17 were destroyed resulting in the key intermediate **11c** suitable to form **14** with appropriate stereochemistry of all asymmetry centers.

The α-side methanol addition to the α,β-unsaturated ester derivatives of *allo*-yohimbane is known[20,21] to proceed with complete stereoselectivity. Accordingly, **11c**, boiled 72 hours in dry methanol in the presence of 2.2 equivalents of sodium methoxide, furnished the expected **14** in 11% yield, and about 30% of the starting material **11c** could be recovered from the reaction mixture. With the exception of optical rotation all chromatographic and spectroscopic properties of racemic **14** were identical with those of an authentic sample prepared from natural deserpidine (**1b**) by deacylation[22] and C-3 epimerization[23]. This identity unambigously verifies the steric structure of synthetic **14**, *i.e.* the correctness of our stereochemical considerations in the course of the synthesis.

Esterification of the hydroxy group of **14** with trimethoxybenzoyl chloride, as well as oxidation of the product to the iminium salt and its subsequent reduction to racemic deserpidine (**1b**) have already been described in the literature[24]. Thus, by the preparation of racemic **14** our object, to synthesize deserpidine (**1b**) by a linear approach, has been attained.

For the preparation of raunescine stereoisomers from **9b**, **10b**, or **12b** our considerations were based upon our earlier experiments[1]. Regioselective C-18 trimethoxybenzoylation as well as formation of an epimer-free product can be expected only from the acylation reaction of the diol **9b**. The reaction was carried out in pyridine with trimethoxybenzoyl chloride at 100°C and resulted in 3-*epi*-17-*epi*-raunescine (**9c**) uniformly in rather good yield.

In this set of publications we extended our earlier results gathered during the synthesis of yohimbine alkaloids[8,9,10,16]. It has been demonstrated that a linear approach, starting with a properly substituted indolo[2,3-*a*]quinolizidin-2(1*H*)-one, is suitable for the synthesis of the target pentacyclic alkaloids with either five or six chiral centers, and gives a good opportunity to synthesize their stereoisomers at the same time.

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Experimental

Melting points are uncorrected. IR spectra were recorded in KBr with a Spectromom 2000 spectrophotometer. The ^1H and ^{13}C NMR spectra were collected on a Varian XL-100-15 and a Jeol FX-100 Fourier transform instrument operating at 100 MHz for ^1H and 25 MHz for ^{13}C NMR, using TMS as internal standard. Chemical shift values are given in δ values. Mass spectra (MS) were recorded with an AEI MS 902 double-focusing instrument (70 eV, ion source temp. 150 °C, direct insertion).

General procedures: All reactions were conducted under oxygen-free dry nitrogen and were monitored by tlc using Merck silica gel 60 F_{254} sheets and the following solvent systems: A = benzene-ethyl acetate (5:5), B = dichloromethane-methanol (10:0.5), C = dichloromethane-methanol (10:1), unless stated otherwise. For the quantitative separation Merck silica gel 60 $PF_{254+366}$, for column chromatography Merck silica gel 60 (70–230 mesh) adsorbent was used.

Usual workup of a reaction was carried out by extraction of an aqueous solution at pH 8.5–9 with ether or dichloromethane. The combined organic layer was washed with water, dried with anhydrous $MgSO_4$, and finally the solvent was evaporated *in vacuo*.

Methyl 3-(2-dicyanomethylene-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-a]quinolizin-3β-yl)-2-methoxypropionate (**3a**): To a stirred solution of **2** · HCl (10.0 g, 25.3 mmol) in glacial acetic acid (30 ml) triethylamine (36 ml), phosphorus pentoxide (2.0 g, 14 mmol), and finally malononitrile (8.0 g, 121 mmol) was added. The reaction was monitored by tlc (system A, R_F **3a** > **2**). The mixture was diluted with ether (200 ml), then washed with 5-% sodium hydroxide to remove the acid, and the aqueous layer was re-extracted with ether (3 × 50 ml). The combined extracts were washed, dried, and evaporated under reduced pressure, giving an oil which was crystallized from methanol (10 ml) to supply **3a** (6.45 g, 64%); m.p. 201–202 °C (methanol). – IR (KBr): 1600 (C=C, conj.), 1730 (C=O), 2260 (C≡N, conj.), 2750–2950 (Bohlmann bands), 3300 cm^{-1} (NH). – ^1H NMR ([D_6]DMSO): δ = 3.22 (s, 3H, OCH_3), 3.54 (s, 3H, CO_2CH_3), 3.86 (m, 1H, 2'-H), 6.82–7.45 (m, 4H, aromatic protons), 11.18 (s, 1H, NH). – MS: *m/e* (rel. int.) = 404 ($M^{\oplus}$, 70), 403 (40), 389 (10), 345 (20), 313 (2.5), 301 (7), 288 (55), 209 (30), 170 (100).

$C_{23}H_{24}N_4O_3$ (404.5) Calc. C 68.30 H 5.98 N 13.85 Found C 68.36 H 6.06 N 13.83

Methyl 3-(2β-dicyanomethyl-1,2,3,4,6,7,17,12bα-octahydroindolo[2,3-a]quinolizin-3β-yl)-2-methoxypropionate (**5a**): To a stirred solution of **3a** (6.0 g, 14.85 mmol) in dichloromethane-methanol (1:1) mixture (50 ml) sodium borohydride was added in small portions. The reduction was followed by tlc (system A, R_F **3a** > **5a**). The mixture was acidified to pH 6 with acetic acid, and the solvent was removed *in vacuo*. The residue was treated with dichloromethane (100 ml), washed with water, dried, and evaporated under reduced pressure. The crude material (5.55 g, 92%) was treated with methanol (10 ml) and methanolic hydrogen chloride, yielding crystalline **5a** · HCl (5.16 g, 79%); m.p. 235–236 °C (methanol). – IR (KBr): 1740 (C=O), 2300 (C≡N), 2700–2900 (Bohlmann bands), 3300 cm^{-1} (NH). – ^1H NMR ($CDCl_3$): δ = 3.38 and 3.40 (s, s, 1.5H, 1.5H, OCH_3), 3.75 and 3.77 (s, s, 1.5H, 1.5H, CO_2CH_3), 3.82 (m, 1H, 2'-H), 7.07–7.60 (m, 4H, aromatic protons), 8.22 (s, 1H, NH). – MS: *m/e* (rel. int.) = 406 ($M^{\oplus}$, 8), 405 (6), 391 (3), 375 (20), 355 (8), 347 (30), 341 (100), 325 (3), 311 (25), 211 (20), 184 (10), 170 (15), 169 (20), 156 (15).

$C_{23}H_{26}N_4O_3$ · HCl (443.0) Calc. C 62.36 H 6.14 N 12.65 Found C 62.08 H 5.88 N 12.46

Methyl 3-{2β-[cyano(methoxycarbonyl)methyl]-1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-a]-quinolizin-3β-yl}-2-methoxypropionate (**5b**): To a solution of **2** · HCl (1.0 g, 2.53 mmol) in glacial acetic acid (5 ml) triethylamine (6 ml), phosphorus pentoxide (0.5 g, 3.5 mmol), and methyl

cyanoacetate (1 ml, 11.2 mmol) was added. The reaction mixture was kept at 50 °C for 72 h. The progress of the reaction was followed by tlc (system A, R_F **3b** > **2**). The mixture was diluted with ether (50 ml), then washed with 5-% sodium hydroxide. The aqueous phase was extracted with ether (3 × 10 ml). The combined organic layer was washed, dried, and evaporated *in vacuo* to give amorphous **3b** (0.7 g). – IR (KBr) 1610 (C=C, conj.), 1740 (C=O), 2300 (C≡N, conj.), 2750–2870 (Bohlmann bands), 3350 cm^{-1} (NH).

The crude **3b** was dissolved in methanol (20 ml) and treated with sodium borohydride. The reduction was followed by tlc [benzene-methanol (8.5:1.5), R_F **3b** > **5b**). The mixture was acidified to pH 6 with acetic acid and the solvent removed *in vacuo*. Workup including preparative tlc gave **5b** which was crystallized as hydrochloride (0.55 g, 46%, calc. for **2**); m.p. 185–187 °C (methanol). **5b**: IR (KBr): 1745 (C=O), 2770–2950 (Bohlmann bands), 3400 cm^{-1} (NH). – ^1H NMR ($CDCl_3$): δ = 3.28 and 3.31 (s, s, 1.5H, 1.5H, OCH_3), 3.65 and 3.72 (s, s, 1.5H, 1.5H, CO_2CH_3), 3.85 (m, 1H, 2'-H), 7.14–7.75 (m, 4H, aromatic protons), 8.15 (s, 1H, NH). – MS: *m/e* (rel. int.) = 439 ($M^{\oplus}$, 95), 438 (85), 424 (40), 408 (9), 380 (45), 341 (100), 313 (8), 225 (30), 211 (30), 184 (25), 171 (10), 170 (20), 169 (25), 156 (25).

Methyl 3-{2β-[cyano(methoxycarbonimidoyl)methyl]-1,2,3,4,6,7,12,12bα-octahydroindolo-[2,3-a]quinolizin-3β-yl}-2-methoxypropionate (**5c**): **5a** · HCl (10.5 g, 23.7 mmol) was dissolved in absol. methanol (160 ml) and sodium methoxide (1.62 g, 30 mmol) was added to the solution. The reaction mixture was kept at room temperature for about 12 h. The resulting crystals were filtered off to give **5c** (2.3 g, 22%); m.p. 215–216 °C (methanol). – IR (KBr): 1650 (C=N), 1725 (C=O), 2240 (C≡N), 2750–2860 (Bohlmann bands), 3280 cm^{-1} (NH). – IR (DMSO): 1600 (C=C, conj.), 1630–1660 (NH, deform.), 1740 (C=O), 2190 (C≡N, conj.). – ^1H NMR: see Table 1. – MS: *m/e* (rel. int.) = 438 ($M^{\oplus}$, 76), 423 (100), 406 (8), 380 (17), 341 (69), 339 (53), 325 (9), 234 (11), 226 (14), 223 (10), 211 (17), 184 (17), 169 (26), 156 (21), 143 (16).

$C_{24}H_{30}N_4O_4$ (438.5) Calc. C 65.73 H 6.90 N 12.78 Found C 65.79 H 6.79 N 12.85

The mother liquor of the above reaction was acidified to pH 3 with 18-% hydrochloric acid, and the mixture was kept at room temperature for 3 h. The transformation of **5c** into **5b** was monitored by tlc [dichloromethane-methanol (12:1), R_F **5b** > **5c**]. The reaction mixture was evaporated to dryness *in vacuo* and **5b** was isolated as hydrochloride (7.57 g, 67%).

Methyl 2-methoxy-3-{1,2,3,4,6,7,12,12bα-octahydro-2β-[(methoxycarbonyl)methyl]indolo-[2,3-a]quinolizin-3β-yl}propionate (**5g**): The solution of **5b** · HCl (5.0 g, 10.5 mmol) in 5-% sodium hydroxide (100 ml) was allowed to stand for about 12 h at 5–10 °C. The reaction mixture was acidified with concentrated hydrochloric acid to pH 3, then evaporated to dryness *in vacuo*. The residue was dried by azeotropic destillation using benzene-ethanol (2:1) mixture (300 ml). The crude **5d** was immediately dissolved in dry DMF (80 ml) and heated at 120 °C under nitrogen for 2h. The decarboxylation was followed by tlc [isoamyl alcohol-methanol-20% ammonium hydroxide (5:4:2), R_F **5e** > **5d**]. The solvent was removed *in vacuo*, the residue treated with methanol (50 ml), and the inorganic salt was filtered off. The methanolic solution was saturated with hydrogen chloride gas, then refluxed for 1 h. This procedure was repeated several times until the esterification was complete. The reaction was monitored by tlc (system A, R_F **5g** > **5e**). After final removing of the solvent the residue was crystallized from methanol (5 ml) to supply **5g** · HCl (3.8 g, 80%); m.p. 196–197 °C (methanol). – IR (KBr): 1720 (C=O), 1725 (C=O), 2780–2900 (Bohlmann bands), 3300 cm^{-1} (NH). – ^1H NMR ($CDCl_3$): δ = 3.40 and 3.41 (s, s, 1.5H, 1.5H, OCH_3), 3.74 and 3.76 (s, s, 1.5H, 1.5H, CO_2CH_3), 3.82 (m, 1H, 2'-H), 7.00–7.65 (m, 4H, aromatic protons), 7.92 (s, 1H, NH). – MS: *m/e* (rel. int.) = 414 ($M^{\oplus}$, 95), 413 (100), 399 (90),

384 (30), 383 (50), 369 (20), 355 (35), 341 (20), 312 (20), 311 (10), 297 (12), 283 (12), 269 (10), 211 (50), 184 (50), 170 (50), 169 (40), 168 (20).

$C_{23}H_{30}N_2O_5$ (414.5) Calc. C 66.64 H 7.30 N 6.76 Found C 66.21 H 7.14 N 6.92

Separation of the diastereomers **5g/A** *and* **5g/B**: The mixture of the two diastereomeric **5g** racemates was separated by preparative tlc on freshly activated silica gel [Merck, $PF_{254+366}$, plates (1 mm)] using a dichloromethane-methanol (100:5) solvent system, R_F **5g/B** > **5g/A**.

5g/A: m.p. of the hydrochloride: salt 202–203 °C (methanol-ether). – ^{1}H NMR ($CDCl_3$): δ = 3.40 (s, 3H, OCH_3).

5g/B: m.p. of the hydrochloride: 198–199 °C (methanol-ether). – ^{1}H NMR ($CDCl_3$): δ = 3.41 (s, 3H, OCH_3).

Note: Under the following basic conditions neither **5g/A** nor **5g/B** could epimerize into each-other:

a) 2 N sodium methoxide in methanol, at room temperature for 1 week, or

b) in the same solvent at 60 °C for 5 h.

18β-Methoxy-allo-yohimbinone (**6**) *and 18α-methoxy-allo-yohimbinone* (**7**): A solution of **5g** (1.0 g, 2.4 mmol) (previously dried *in vacuo* at 80 °C over P_2O_5) in dry benzene (60 ml) was treated with potassium *tert*-butoxide (0.55 g, 5 mmol). To remove traces of water, benzene (15–20 ml) was distilled off, then the mixture was refluxed for 2–3 h. After cooling it was neutralized with acetic acid (0.3 ml) and evaporated *in vacuo*. Workup including preparative tlc [benzene-methanol (100:15), R_F **7** > **6**] supplied **6** and **7**.

Starting material	Crude product	Separated 6	and 7
5g	0.62 g (68%)	0.30 g (33%)	0.16 g (17%)
5g/A	0.64 g (70%)	0.51 g (56%)	–
5g/B	0.62 g (68%)	0.15 g (16%)	0.34 g (37%)

6: m.p. 183–185 °C (ether-petroleum ether) [m.p. of the hydrochloride: 222–223 °C (methanol)]. – IR ($CHCl_3$): 1620 and 1660 (enolic β-keto ester), 1720 (C=O), 1740 sh (CO_2CH_3), 2750–2900 (Bohlmann bands), 3470 cm^{-1} (NH). – ^{1}H NMR (C_6D_6); signals of the keto form: δ = 3.42 (s, 1.8H, CO_2CH_3), 3.52 (s, 1.8H, OCH_3), 3.95 (dd, $J_{a,e}$ = 7 Hz, $J_{a,a}$ = 10.5 Hz, 0.6H, 18-H); signals of the enol form: δ = 3.34 (s, 1.2H, OCH_3), 3.42 (s, 1.2H, CO_2CH_3), 4.08 (dd, $J_{a,e}$ = 6.5 Hz, $J_{a,a}$ = 12 Hz, 0.4H, 18-H), 12.8 (s, 0.4H, enol OH). – MS: *m/e* (rel. int.) = 382 ($M^{\oplus}$, 38), 381 (24), 367 (7), 365 (5), 355 (11), 351 (20), 350 (15), 349 (14), 338 (6), 337 (5), 335 (4), 325 (20), 324 (100), 323 (77), 309 (19), 307 (8), 293 (7), 281 (7), 235 (16), 221 (21), 211 (50), 184 (42), 170 (36), 169 (38), 156 (34).

7: m.p. 168–169 °C (ether-petroleum ether) [m.p. of the hydrochloride: 230–231 °C (methanol-ether)]. – IR ($CHCl_3$): 1620 and 1660 (enolic β-keto ester), 1720 (C=O), 2750–2870 (Bohlmann bands), 3470 cm^{-1} (NH). – ^{1}H NMR (C_6D_6); signals of the keto form: δ = 3.44 (s, 0.6H, CO_2CH_3), 3.62 (s, 0.6H, OCH_3); signals of the enol form: δ = 3.47 (s, 2.4H, CO_2CH_3), 3.58 (s, 2.4H, OCH_3), 3.68 (t, *J* = 3 Hz, 0.8H, 18-H), 12.7 (s, 0.8H, enol OH). – MS: *m/e* (rel. int.) = 382 ($M^{\oplus}$, 18), 381 (12), 367 (4), 365 (4), 351 (8), 350 (7), 349 (7), 338 (9), 337 (9), 336 (9), 335 (2), 325 (22), 324 (100), 323 (92), 309 (15), 307 (6), 293 (12), 281 (6), 235 (8), 221 (10), 211 (18), 184 (14), 170 (18), 169 (23), 156 (19).

Epimerization of **6** *and* **7**: a) 18α-Methoxy-*allo*-yohimbinone (**7**) (50 mg, 0.13 mmol) was kept at room temperature for one week in 0.5 N sodium methoxide in methanol solution. Workup including preparative tlc gave **6** (21 mg, 42%) and **7** (8 mg, 16%).

b) The same result was obtained starting from 18β-methoxy-*allo*-yohimbinone (**6**).

c) 18α-Methoxy-*allo*-yohimbinone (**7**) (10 mg) and potassium *tert*-butoxide (10 mg) were refluxed in benzene (10 ml) for 3 h. Analysis of the mixture by tlc showed that it consisted of **7** and **6** in a ratio of 3:7.

18β-Methoxy-allo-yohimbone (**8a**) *and 18α-methoxy-allo-yohimbone* (**8b**): To a solution of **6** (0.32 g, 0.84 mmol) in methanol-water (1:1) mixture (20 ml) potassium hydroxide (0.16 g, 2.8 mmol) was added. The reaction mixture was refluxed for 1 h and monitored by tlc [dichloromethane-methanol (12:1), R_F **6** > **8b** > **8a**]. Workup including preparative tlc supplied **8a** (170 mg, 63%) and **8b** (10 mg, 4%).

8a: m.p. 248–249 °C (methanol-water). – IR (KBr): 1710 (C=O), 2750–2970 (Bohlmann bands), 3320 cm^{-1} (NH). – ^1H NMR ($CDCl_3$ + [D_6]DMSO): δ = 3.35 (s, 3H, OCH_3), 3.92 (dd, 1H, $J_{a,e}$ = 8 Hz, $J_{a,a}$ = 10 Hz, 18-H), 6.90–7.43 (m, 4H, aromatic protons), 11.53 (s, 1H, NH). – MS: *m/e* (rel. int.) = 324 ($M^{\oplus}$, 100), 323 (98), 309 (6), 294 (50), 293 (70), 281 (3), 279 (3), 265 (4), 235 (8), 233 (9), 223 (10), 221 (8), 211 (25), 184 (14), 170 (25), 169 (30), 155 (20).

8b: m.p. 192–195 °C (methanol-water). – IR (KBr): 1700 (C=O), 2750–2900 (Bohlmann bands), 3400 cm^{-1} (NH). – ^1H NMR ($CDCl_3$): δ = 3.32 (s, 3H, OCH_3), 3.45 (t, J = 3 Hz, 1H, 18-H), 7.05–7.50 (m, 4H, aromatic protons), 7.66 (s, 1H, NH). – MS: *m/e* (rel. int.) = 324 ($M^{\oplus}$, 100), 323 (84), 309 (25), 293 (12), 211 (13), 193 (10), 169 (18), 156 (15), 143 (10).

Following the above procedure starting from **7** (0.35 g, 0.91 mmol) the separation of the reaction mixture by tlc resulted **8a** (155 mg, 52%) and **8b** (28 mg, 9%).

Refluxing of **6** (100 mg, 0.26 mmol) in methanol (10 ml) and 10-% hydrochloric acid (10 ml) for 5 h supplied **8a** (30 mg, 35%) and **8b** (4 mg, 5%).

Epimerization of **8a** *and* **8b**: a) 18β-Methoxy-*allo*-yohimbone (**8a**) (50 mg, 0.15 mmol) was dissolved in 0.5 N sodium methoxide in methanol solution (15 ml) and refluxed for 1 h. Workup including preparative tlc gave **8a** (34 mg, 68%) and **8b** (5.5 mg, 11%).

b) The above ratio was obtained keeping the reaction mixture at room temperature for 24 h.

c) Starting from 18α-methoxy-*allo*-yohimbone (**8b**) (10 mg) the analysis of the epimerization mixture by tlc showed that it consisted of **8a** and **8b** in a ratio of 8.5:1.5.

Methyl 17β-hydroxy-18β-methoxy-allo-yohimbane-16β-carboxylate (**9a**), *methyl 17β-hydroxy-18β-methoxy-allo-yohimbane-16α-carboxylate* (**10a**), *methyl 17β-hydroxy-18α-methoxy-allo-yohimbane-16β-carboxylate* (**12a**), *methyl 17α-hydroxy-18α-methoxy-allo-yohimbane-16β-carboxylate* (**13a**), *and methyl 17α-hydroxy-18α-methoxy-allo-yohimbane-16α-carboxylate* (**13b**). – *General procedure for the reduction:* The appropriate β-keto ester (60 mg, 0.16 mmol) was dissolved in methanol (10 ml) and dichloromethane (5 ml). Sodium borohydride was added over a 1-h period to the stirred solution, and the reaction was monitored by tlc [cyclohexane-ether-methanol (5:10:1.5), R_F **12a** ≫ **9a** > **10a** ≫ **13a** = **13b**, or chloroform-methanol (12:1), R_F **12a** > **9a** ≫ **10a** > **13a** > **13b**]. The reaction mixture was neutralized with acetic acid and the solvent removed *in vacuo*. The residue was triturated with chloroform (3 × 30 ml), filtered, washed with water (2 × 10 ml), dried, and evaporated to give a solid mixture (45–50 mg, 75–83%) which was submitted to subsequent preparative tlc.

9a: m.p. 243–245 °C (methanol). – IR (KBr): 1735 (C=O), 2750–2850 (Bohlmann bands), 3420 (NH), 3580 cm^{-1} (OH). – ^1H NMR ($CDCl_3$): δ = 3.41 (s, 3H, OCH_3), 3.84 (s, 3H,

CO_2CH_3), 3.32 (m, $J_{a,a}$ = 12 Hz, $J_{a,e} + J_{a,e}$ = 3 + 4 Hz, 1H, 18-H), 4.50 (t, $J_{e,a} \approx J_{e,a} \approx$ 3 Hz, 1H, 17-H), 6.97–7.50 (m, 4H, aromatic protons), 8.74 (s, 1H, NH). – ^{13}C NMR: see Table 2. – MS: see Table 3.

10a: m.p. 166–168°C (methanol). – IR (KBr): 1735 (C=O), 2780–2850 (Bohlmann bands), 3200–3340 cm^{-1} (NH, OH). – ^{1}H NMR ($CDCl_3$): δ = 3.38 (s, 3H, OCH_3), 3.76 (s, 3H, CO_2CH_3), 3.51 (m, $J_{a,a}$ = 11 Hz, $J_{a,e} + J_{a,e}$ = 3 + 4 Hz, 1H, 18-H), 4.32 (t, $J_{ee} \approx J_{e,a} \approx$ 3 Hz, 1H, 17-H), 6.95–7.47 (m, 4H, aromatic protons), 9.13 (s, 1H, NH). – ^{13}C NMR: see Table 2. – MS: see Table 3.

12a: m.p. 230–232°C (methanol). – IR (KBr): 1730 (C=O), 2780–2850 (Bohlmann bands), 3280–3480 cm^{-1} (NH, OH). – ^{1}H NMR ($CDCl_3$): δ = 3.36 (s, 3H, OCH_3), 3.85 (s, 3H, CO_2CH_3), 3.48 (q, $J_{e,e} \approx J_{e,e} \approx J_{e,a} \approx$ 3 Hz, 1H, 18-H), 4.26 (t, $J_{e,a} \approx J_{e,e} \approx$ 3 Hz, 1H, 17-H), 6.96–7.50 (m, 4H, aromatic protons), 9.60 (s, 1H, NH). – ^{13}C NMR: see Table 2. – MS: see Table 3.

13a: m.p. 210–212°C (methanol). – IR (KBr): 1735 (C=O), 2750–2850 (Bohlmann bands), 3430–3560 cm^{-1} (NH, OH). – ^{1}H NMR ($CDCl_3$): δ = 3.32 (s, 3H, OCH_3), 3.75 (s, 3H, CO_2CH_3), 3.52 (br m, 1H, 18-H), 3.87 (dd, $2 \times J$ = 5 + 2.5 Hz, 1H, 17-H), 6.95–7.45 (m, 4H, aromatic protons), 9.65 (s, 1H, NH). – ^{13}C NMR: see Table 2. – MS: see Table 3.

13b: m.p. 155–158°C (methanol-ether). – IR (KBr): 1735 (C=O), 3250–3550 cm^{-1} (NH, OH). – ^{1}H NMR ($CDCl_3$ + [D_6]DMSO): δ = 3.35 (s, 3H, OCH_3), 3.82 (s, 3H, CO_2CH_3), 3.52 (br, 1H, 18-H), 4.50 (br, 1H, 17-H), 7.00–7.52 (m, 4H, aromatic protons), 8.52 (s, 1H, NH). – ^{13}C NMR: see Table 2. – MS: see Table 3.

Starting material	**9a**		**10a**		**12a**		**13a**		**13b**	
	mg	%	mg	%	mg	%	mg	% [e]	mg	% [e]
6 [a]	28	47	19	32	–	–	–	–	–	–
7 [b]	4	7	3	5	28	47	9	15	1	2
6 + **7** [c]	19	32	13	22	12	20	4	7	<1	
6 + **7** [d]	22	37	14	23	8	13	2	3	1.5	2.5

[a] pH = 8; 0.5 h. – [b] pH = 8; 2 h. – [c] pH = 8; 1 h. – [d] pH > 9; 4 h. – [e] Approximate yields because of the repeated preparative tlc purification.
In the case of **6** + **7** the epimerization was done with the crude reaction mixture resulted in the Dieckmann ring closure of **5g**.

Epimerization experiments

The solution of **9a** (70 mg, 0.18 mmol) in 2 N sodium methoxide in methanol (10 ml) was refluxed for 2 h or was left standing for about 12 h at room temperature. The reaction was monitored by tlc [chloroform-methanol (12:1), R_F **9a** > **10a**]. Workup including preparative tlc supplied **10a** (9.1 mg, 13%) and **9a** (28 mg, 40%).

The above ratio of **9a** and **10a** was also obtained starting from **10a**.

12a does not epimerize under the same conditions.

The solution of **13b** (40 mg, 0.1 mmol) in 2 N sodium methoxide in methanol (5 ml) was refluxed for 2 h. Workup including preparative tlc gave only **13a** (23 mg, 72%).

13a does not epimerize under the same conditions.

Methyl 18β-methoxy-apo-allo-yohimbane-16-carboxylate (**11a**) *and methyl 18α-methoxy-apo-allo-yohimbane-16-carboxylate* (**11b**): The solution of **9a** (115 mg, 0.3 mmol) in 2 N sodium

methoxide in methanol (10 ml) was refluxed for 6 h and followed by tlc [chloroform-methanol (12:1), R_F **11a** > **9a** > **10a**]. Then the reaction mixture was neutralized with acetic acid and evaporated to dryness. The residue was treated with dichloromethane (30 ml) and washed with water, the organic layer was dried and evaporated *in vacuo*. The crude material (84 mg, 73%) was purified by preparative tlc to give **11a** (68 mg, 59%).

11a: m.p. 161 – 163 °C (ether) [m.p. of the hydrochloride: 231 – 233 °C (methanol-ether)]. – IR (KBr): 1640 (C = C), 1710 (C = O), 2800 – 2900 (Bohlmann bands), 3350 cm^{-1} (NH). – ^1H NMR ($CDCl_3$): δ = 3.38 (s, 3H, OCH_3), 3.81 (s, 3H, CO_2CH_3), 4.10 (m, 1H, 18-H), 6.92 (d, *J* = 2.5 Hz, 1H, C = C – H), 6.90 – 7.45 (m, 4H, aromatic protons), 7.80 (s, 1H, NH). – MS: *m/e* (rel. int.) = 366 ($M^{\oplus}$, 100), 365 (90), 351 (60), 335 (25), 334 (30), 333 (32), 307 (4), 184 (30), 170 (20), 169 (30), 156 (60).

Following the above procedure **11b** could be obtained from **12a** with a yield of 57%; m.p. 150 – 152 °C (ether) [m.p. of the hydrochloride: 224 – 226 °C (methanol-ether)]. – IR (KBr): 1640 (C = C), 1710 (CO_2CH_3), 2720 – 2850 (Bohlmann bands), 3400 cm^{-1} (NH). – ^1H NMR ($CDCl_3$): δ = 3.42 (s, 3H, OCH_3), 3.82 (s, 3H, CO_2CH_3), 3.85 (m, 1H, 18-H), 7.02 (d, *J* = 4 Hz, 1H, C = C – H), 6.95 – 7.50 (m, 4H, aromatic protons), 7.78 (s, 1H, NH). – MS: *m/e* (rel. int.) = 366 ($M^{\oplus}$, 8), 365 (6), 334 (95), 333 (100), 319 (80), 303 (30), 302 (40), 291 (12), 235 (30), 223 (40), 221 (30), 184 (25), 170 (35), 169 (30), 156 (20).

Methyl 17β,18β-dihydroxy-allo-yohimbane-16β-carboxylate (**9b**), *methyl 17β,18β-dihydroxy-allo-yohimbane-16α-carboxylate* (**10b**), *and methyl 17β,18α-dihydroxy-allo-yohimbane-16β-carboxylate* (**12b**). – a) *General procedure for the demethylation of* **9a**, **10a**, *and* **12a** *with hydrogen bromide:* The solution of the appropriate hydroxy ester (**9a**, **10a**, or **12a**) (200 mg, 0.53 mmol) in 48-% aqueous hydrogen bromide (10 ml) was heated at 100 °C for 2 h. The solvent was removed *in vacuo*, then the residue was dissolved in methanol (5 ml) and ethereal diazomethane was added to the solution. The reaction mixture was evaporated *in vacuo* and the crude dihydroxy ester (**9b**, **10b**, or **12b**) was purified by preparative tlc [dichloromethane-methanol (120:15)].

Starting material	Product mg	yield	
9a	102	53%	**9b**
10a	77	40%	**10b**
	21	11%	**9b**
12a	104	54%	**12b**

b) *General procedure for the demethylation of* **9a**, **10a**, *and* **12a** *with boron tribromide:* To a solution of the hydroxy ester (**9a**, **10a**, or **12a**) (100 mg, 0.26 mmol) in absol. dichloromethane (100 ml) boron tribromide (0.35 g, 0.13 ml, 1.4 mmol) was added at 0 °C. The reaction mixture was stirred at 0 °C for 5 h, then kept for about 12 h in the refrigerator. The dichloromethane solution was extracted with 10-% ammonium hydroxide, then washed with water, dried, and evaporated *in vacuo*. The crude dihydroxy ester (**9b**, **10b**, or **12b**) was purified by preparative tlc.

Starting material	Product mg	yield	
9a	58	61%	**9b**
10a	44	46%	**10b**
12a	31	30%	**12b**

9b: m.p. 266–270 °C (methanol). – IR (KBr): 1735 (C=O), 2750–2850 (Bohlmann bands), 3150–3600 cm^{-1} (NH, OH). – ^1H NMR ($CDCl_3$ + [D_6]DMSO): δ = 3.85 (s, 3H, CO_2CH_3), 3.56 (m, $J_{a,a}$ = 13 Hz, $J_{a,e}$ + $J_{a,e}$ = 3 + 4 Hz, 1H, 18-H), 4.30 (t, J = 3 Hz, 1H, 17-H), 6.95–7.45 (m, 4H, aromatic protons), 9.32 (s, 1H, NH).

10b: m.p. 242–244 °C (methanol). – IR (KBr): 1735 (C=O), 2750–2850 (Bohlmann bands), 3170–3500 cm^{-1} (NH, OH). – ^1H NMR ($CDCl_3$ + [D_6]DMSO): δ = 3.82 (s, 3H, CO_2CH_3),

Table 1. 250 MHz ^1H NMR data of **5c** ($CDCl_3$ solution, δ values) Σ = sum of signal intensities

indole NH	H–N=	NH_2	CO_2CH_3	OCH_3
10.55	8.38	6.12	3.78	3.30
10.37	8.36	6.11	3.75	3.28
10.33	8.31	5.89	3.74	3.25
10.30	8.26	5.87	3.70	3.23
Σ = 1H	Σ = 0.25H	Σ = 1.5H	3.66	3.14
			3.63	3.13
			3.62	Σ = 3H
			3.61	
			Σ = 3H	

Table 2. ^{13}C NMR chemical shifts of 18-methoxy-*allo*-yohimbines ($CDCl_3$/[D_6]DMSO solutions, δ values)

Carbon	**9a**	**10a**	**12a**	**13a**	**13b**
C-2	135.98	135.44	136.03	136.38	132.90
C-3	60.90	60.56	60.91	59.17	51.47
C-5	53.20	53.22	53.19	52.81	51.28
C-6	21.74	21.54	21.67	20.83	16.59
C-7	106.25	107.17	106.23	106.58	106.41
C-8	126.83	127.23	126.79	126.94	127.32
C-9	117.28	117.75	117.27	117.65	117.49
C-10	118.25	119.79	118.26	118.69	118.54
C-11	120.17	120.73	120.18	120.74	120.58
C-12	110.95	111.01	110.99	111.10	111.15
C-13	136.18	136.27	136.18	136.38	135.96
C-14	28.42	32.86	28.17	28.33	31.78
C-15	35.30	35.52	35.42	33.64	36.91
C-16	48.48	50.25	45.15	46.53	50.88
C-17	65.48	67.11	66.42	68.82	72.74
C-18	80.77	78.69	79.29	79.65	78.25
C-19	26.44	26.02	24.63	27.62	30.63
C-20	35.43	32.00	30.63	29.99	33.00
C-21	60.90	60.35	60.91	59.41	53.51
–CO–	172.47	174.00	173.59	173.79	174.14
$-CO_2CH_3$	51.37	51.91	51.32	51.62	51.76
$-OCH_3$	55.25	55.79	56.00	56.59	56.69

Table 3. Relative peak intensities in the mass spectra of 18-methoxy-*allo*-yohimbines

m/e	**9a**	**10a**	**12a**	**13a**	**13b**	M – X
384	100	100	100	100	100	M
383	92	80	95	81	93	M – 1
369	6.6	5.9	6.8	12	1.5	M – 15
367	1.1	1.0	1.4	3.9	0.8	M – 17
365	1.1	0.8	1.0	1.0	0.5	M – 1 – 18
353	6.7	5.6	7.2	9.6	2.7	M – 31
351	1.8	22	–	4.0	5.7	M – 33
350	–	–	–	1.0	4.7	M – 34
335	–	1.2	1.5	–	–	M – 49
326	–	1.0	–	4.2	2.1	M – 58
325	1.3	2.4	–	5.7	4.1	M – 59
254	3.3	7.3	–	4.3	–	M – 130
237	4.8	3.3	4.2	1.2	2.2	M – 147
235	1.4	2.4	1.5	1.0	1.0	M – 149
224	4.2	3.3	4.2	1.2	–	M – 160
223	4.0	3.9	4.1	1.3	–	M – 161
211	3.6	4.3	–	1.8	–	M – 163
184	5.8	7.4	7.5	3.9	7.8	
170	7.1	9.3	9.2	7.9	9.1	
169	10.0	12.0	12.2	9.3	11.0	
156	7.2	8.9	9.2	7.1	8.6	

3.70 (m, $J_{a,a}$ = 11 Hz, $J_{a,e}$ + $J_{a,e}$ = 3 + 4 Hz, 1H, 18-H), 4.32 (t, J = 3 Hz, 1H, 17-H), 6.95 – 7.50 (m, 4H, aromatic protons), 9.50 (s, 1H, NH).

12b: m.p. 232 – 235 °C (methanol). – IR (KBr): 1735 (C=O), 2700 – 2850 (Bohlmann bands), 3170 – 3550 cm^{-1} (NH, OH). – ^1H NMR ($CDCl_3$ + [D_6]DMSO): δ = 3.82 (s, 3H, CO_2CH_3), 3.90 (q, J = 3 Hz, 1H, 18-H), 4.10 (t, J = 3 Hz, 1H, 17-H), 6.92 – 7.45 (m, 4H, aromatic protons), 9.80 (s, 1H, NH).

Methyl 18β-hydroxy-apo-allo-yohimbane-16-carboxylate (**11c**): The solution of **9b** (0.26 g, 0.7 mmol) in 2 N sodium methoxide in methanol (20 ml) was refluxed for 5 h. The reaction was monitored by tlc [dichloromethane-methanol (10:1), R_F **11c** > **9b**]. The reaction mixture was neutralized with hydrochloric acid and evaporated to dryness *in vacuo*. The residue was treated with dichloromethane at pH 8.5, the organic layer separated, washed with water, dried, and evaporated. The crude material (190 mg, 77%) was purified by preparative tlc to supply **11c** (150 mg, 61%); m.p. 183 – 185 °C (ether). – IR (KBr): 1630 (C=C), 1715 (C=O), 2750 – 2860 (Bohlmann bands), 3350 cm^{-1} (NH). – MS: *m/e* (rel. int.): 352 ($M^{\oplus}$, 100), 351 (100), 340 (1), 337 (3), 335 (1), 321 (4), 293 (4), 284 (5), 279 (5), 244 (5), 235 (14), 221 (5), 211 (10), 185 (10), 184 (12), 170 (10), 169 (12), 168 (5), 156 (14), 149 (40), 144 (10).

$C_{21}H_{24}N_2O_3$ (352.4) Calc. C 71.57 H 6.86 N 7.95 Found C 71.24 H 6.68 N 8.10

Methyl 3-isodeserpate (**14**): To a solution of **11c** (100 mg, 0.28 mmol) in absol. methanol (10 ml) sodium methoxide (35.4 mg, 0.65 mmol) was added. The reaction mixture was refluxed for 72 h under previously dried nitrogen and followed by tlc [chloroform-methanol (15:0.5), R_F **14** > **11c**]. Workup including preparative tlc on silica gel ("DC Fertigplatte", Merck) supplied **14** (12.7 mg, 11%) and unreacted **11c** (31 mg, 31%); m.p. 206 – 208 °C (methanol). – IR (KBr): 1740 (C=O), 2750 – 2850 (Bohlmann bands), 3200 – 3450 (NH, OH). – ^1H NMR ($CDCl_3$):

$\delta = 3.54$ (s, 3H, OCH_3), 3.81 (s, 3H, CO_2CH_3), 3.68 (m, 1H, 18-H), 3.43 (t, J = 10 Hz, 1H, 17-H), 7.05 – 7.50 (m, 4H, aromatic protons), 7.80 (s, 1H, NH). – MS: *m/e* (rel. int.): 384 ($M^{\oplus}$, 100), 383 (92), 369 (18), 367 (4), 353 (10), 351 (11), 341 (4), 337 (4), 325 (2), 295 (6), 237 (7), 231 (13), 224 (6), 223 (5), 221 (27), 211 (6), 184 (12), 170 (9), 169 (13), 156 (10), 144 (9).

$C_{22}H_{28}N_2O_4$ (384.4) Calc. C 68.72 H 7.34 N 7.29 Found C 68.52 H 7.21 N 7.34

3-Epi-17-epi-raunescine (**9c**): To a solution of **9b** (120 mg, 0.32 mmol) in absol. pyridine (5 ml) trimethoxybenzoyl chloride (350 mg, 1.5 mmol) was added. The reaction mixture was heated at 100 °C for 2 h and monitored by tlc [dichloromethane-methanol (12:1), R_F **9c** > **9b**]. The solvent was removed *in vacuo*, the residue was treated with dichloromethane at pH 8.5. The organic layer was washed twice with water and evaporated *in vacuo*. The remaining material was purified by preparative tlc to give **9c** (116 mg, 63%); m.p. 196 – 198 °C (methanol-ether). – IR (KBr): 1595 (Ar), 1720 (C=O), 2750 – 2870 (Bohlmann bands), 3480 cm^{-1} (NH). – ^1H NMR (C_6D_6): δ = 3.44 (s, 9H, 3 × OCH_3), 3.80 (s, 3H, CO_2CH_3), 4.64 (t, J = 3 Hz, 1H, 17-H), 5.04 (m, $J_{a,a}$ = 12.5 Hz, $J_{a,e}$ + $J_{a,e}$ = 3 + 4 Hz, 1H, 18-H), 6.70 – 7.65 (m, 6H, aromatic protons). – MS: *m/e* (rel. int.): 564 ($M^{\oplus}$, 6), 563 (4), 352 (16), 351 (45), 227 (13), 226 (100), 212 (50), 211 (30), 198 (50), 197 (65), 195 (40), 184 (23), 183 (13), 182 (25), 181 (15), 170 (9), 169 (30).

$C_{31}H_{36}N_2O_8$ (564.6) Calc. C 65.94 H 6.43 N 4.96 Found C 65.57 H 6.21 N 5.09

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