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Synthesis of Reserpine-type Alkaloids, II[1]

Synthesis of 18-Hydroxyyohimbine Stereoisomers and Raunescine Analogues with Normal Skeletons

Csaba Szántay *[a,b], *Katalin Honty*[a], *Gábor Blaskó*[b], *Eszter Baitz-Gács*[b], and *Pál Kolonits*[a]

Department of Organic Chemistry, Technical University[a], Gellért tér 4, H-1521 Budapest XI

Central Research Institute for Chemistry, Hungarian Academy of Sciences[b], Pusztaszeri ut 59 – 67, H-1525 Budapest II

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Starting from the previously described keto ester **2**, three raunescine analogues (**7c**, **9c**, **10c**) and one isoraunescine stereoisomer (**10d**) – all with a normal yohimbane skeleton – have been synthesized.

Synthese von Alkaloiden des Reserpin-Typs, II[1]. – Synthese von 18-Hydroxyyohimbin-Stereoisomeren und Raunescin-Derivaten mit normalem Molekülgerüst

Ausgehend von dem in der vorausgehenden Mitteilung beschriebenen Ketoester **2** wurden drei Raunescin-Derivate (**7c**, **9c**, **10c**) und ein Isoraunescin-Stereoisomer (**10d**) – alle mit normalem Yohimbangerüst – synthetisiert.

In our previous paper[1] we described the preparation of the keto ester **2** which can be used for the synthesis of 18-substituted yohimbine derivatives with D/E-*trans* as well as D/E-*cis* annulation. Proceeding with our studies in the field of reserpine-type alkaloids, we intended to convert **2** primarily into raunescine[2] analogues with a normal skeleton (**1a**-type compounds), so far unknown as natural substances.

Although *Potier*[3] and later *Court*[4] et al. reported the isolation of an "18-hydroxy-yohimbine fraction" (one of the **1b** stereoisomers) from various *Rauwolfia* species, however, the exact steric structure of this alkaloid has not been given.

Thus, compounds of type **1** might be interesting not only as potentially biologically active substances, but also because of their possible identity with natural compounds.

A) Preparation of *trans*-2,3-substituted indolo[2,3-*a*]quinolizidines

In order to build up ring E the first task is to convert the keto function of **2** into a (methoxycarbonyl)methyl group in a way that the C-2 and C-3 substituents of the quinolizidine ring come into relative *trans* position. For this purpose, ketone **2** was reacted with the anion of diethyl [(methoxycarbonyl)methyl]phosphonate in dimethylformamide. According to our previous experience[5] under such conditions

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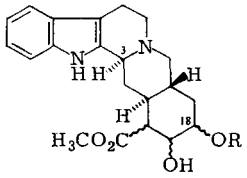
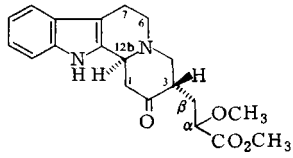
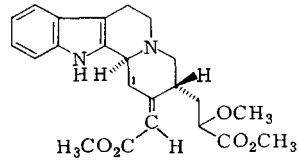
there is no significant epimerization at C-3. The reaction produced the unsaturated ester **3** in about 80% yield. Investigation on compounds with related structures in the emetine and despirroloyohimbane series[6] revealed that if the C-3 substituent is in equatorial position the *Z* isomer is sterically overcrowded to be formed in observable quantities. According to the chemical shift of 1-H_{eq} in the proton spectrum ($\delta \approx 3.9$)[6b], the exocyclic double bond has *E* geometry (see Experimental).



1



2



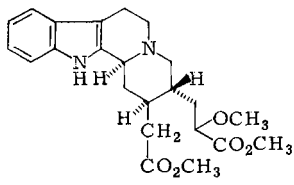
3

	R
a	TMB
b	H

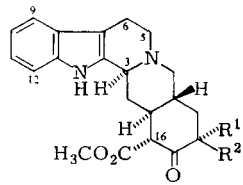
TMB = 3,4,5-trimethoxybenzoyl

The catalytic hydrogenation of **3** proceeds with high stereoselectivity, from the reaction mixture only the *trans*-2,3 diester **4** could be isolated. The steric structure is confirmed by both spectroscopic data and chemical transformations. Some of the characteristic peaks of **3** and **4** in their ^1H and ^{13}C NMR spectra appeared as doubled signals due to the fact that these products are mixtures of diastereomeric racemates.

The yohimbane skeleton was formed from **4** by Dieckmann ring closure carried out in benzene in the precence of potassium *tert*-butoxide. The resulting two diastereomers (**5** and **6**) could be separated by crystallization. NMR and mass spectrometric data indicated unambiguosly that the methoxycarbonyl group in both derivatives is in position 16, therefore the ring closure, as expected, took place with high regioselectivity.



4



	R^1	R^2
5	OCH_3	H
6	H	OCH_3

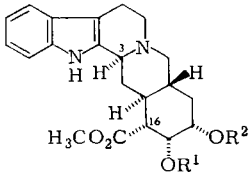
Although **5** and **6** have a β-keto carboxylate structure, none of them shows any enolization tendency which can be attributed to the "*peri* effect". This phenomenon was first observed by *Wenkert*[7] in the case of yohimbinone. The lack of enolization also supports the D/E-*trans* annulation in the skeleton of **5** and **6** because in the D/E-

cis fused *allo* and *epi-allo* series, enolization of the analogue β-keto esters is not hindered[8].

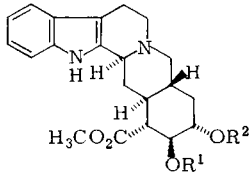
According to further information obtained from the ^{1}H NMR spectra, 18-OCH_3 is pseudoequatorial (α) in **5** and pseudoaxial (β) in **6** (see the respective coupling constants in Table 1). The stereochemistry at C-16 could not be deduced from the ^{1}H NMR spectra, since the signals of the protons in position 16 are overlapped by other signals. On the basis of the chemical shift values[9,10] of C-16 and C-20, the C-16 substituent in compounds **5** and **6** proved to be in the same steric position (pseudoequatorial, α) as in yohimbinone, a natural keto ester[9]. Since the additional substituent, the C-18 methoxy group in compound **5** is also pseudoequatorial, no considerable γ effects are observed on C-16 and C-20 (δ = 61.49 and 37.93) in comparison with those of yohimbinone (δ = 61.8 and 37.9)[9]. The upfield shift of these carbon signals in compound **6** (δ = 58.17 and 33.54) is the consequence of the γ *gauche* effects of the pseudoaxial C-18 methoxy group. This effect on C-16 indicates, that the 16-H is pseudoaxial, consequently the methoxycarbonyl group is pseudoequatorial in compound **6**, too.

The chiral center C-18 of **6** can be epimerized under mild conditions in 2 N sodium methoxide/methanol yielding the thermodynamically more stable compound **5**.

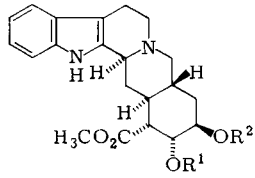
Reduction of the keto ester **6** with $NaBH_4$ yielded two alcohols, **9a** and **10a**, in approximately equal amounts, whereas the reduction of **5** furnished two stereoisomers, **7a** and **8a**, in a ratio of about 10:1.



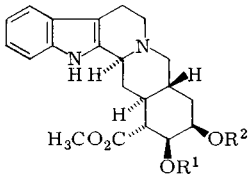
7a-c, f, g



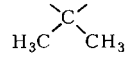
8a, b

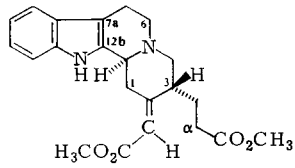


9a-c



10a-e

7-10	R^1	R^2
a	H	CH_3
b	H	H
c	H	TMB
d	TMB	H
e	TMB	TMB
f	$COCH_3$	CH_3
g		



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The ^{13}C NMR spectra show that the configurations at C-16 and C-18 of the β-keto esters **5** and **6** remained intact during reduction. An alteration of configuration at either C-16 or C-18 should modify the C-20 chemical shifts of the alcohols relative to the respective β-keto esters (see Table 2).

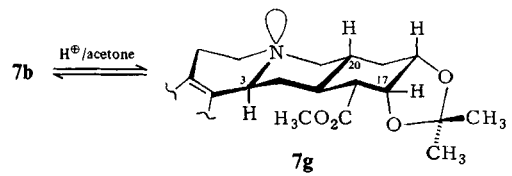
The coupling constants of 17-H in the proton spectra testify that the alcohols **9a** and **10a** formed from **6** are C-17 epimers. In **9a** – obtained in about 30% yield – the

hydroxy group is axial (α), whereas in its epimeric pair **10a** – formed in about 40% yield – it is in equatorial position. Comparison of the ^{13}C NMR spectrum of **9a** with that of **10a** shows the axial hydroxy group of the former to exert γ *gauche* effects on C-19 and C-15.

In the ^{1}H NMR spectrum of the alcohol **7a** obtained from the keto ester **5** the coupling constants of 17-H indicate its equatorial (β) position, while those of the minor isomer **8a** are characteristic for an axial proton. The ^{1}H NMR data of **7f**, an acetylated derivative[11-14] of **7a** is also in agreement with the stereochemical assignment of C-17 (17-H: δ = 5.80, both $J_{e,a}$ = 2.5 Hz). In the ^{13}C NMR spectrum of **7a** the γ *gauche* effect of the axial 17-OH, similary to that in **9a**, causes upfield shifts of the C-19 and C-15 resonances.

Furthermore, a pure chemical proof could also be found in verifying the steric arrangement of **7a**. *Weisenborn*[15] and later *Patterson*[16] reported on the microbiological hydroxylation of natural yohimbine. The relative *cis* configuration of the two vicinal hydroxy functions of the isolated 18-hydroxyyohimbine was proved by easy acetonide formation. Similarly, upon acid treatment of the acetone solution of the diol **7b** obtained by ether splitting of **7a** (see Section B), the acetonide **7g** was obtained. The success of the acetonide formation and the coupling constants of 17-H and 18-H in the proton spectrum of **7g** (see Experimental) unambigously proves the *cis* (α,α) positions of both 17-OH and 18-OH in **7b**. Similarly, acetonide formation could be performed with compound **10b**, which also contains the substituents in *cis* (β,β) position. No reaction could be observed, however, with the diol **9b**, indicating the *trans* diaxial position of its C-17 and C-18 substituents.

Scheme 1



7g

It should be noted that E2 elimination of water from **7a**, which appears to be very probable due to the favourable stereo-electronic position[17], cannot be accomplished. When **7a** was heated in 2 N sodium methoxide/methanol, instead of elimination, only fast ester hydrolysis could be observed.

This result is presumably due to the neighbouring group participation of 17-OH in accelerating the hydrolysis, which phenomenon has been already observed in the family of yohimbine alkaloids[18]. A similar failure was observed in the case of water elimination attempted with thionyl chloride, which was successful for yohimbine[19] and its analogues[14,21].

The obtained stereoselective formation of **7a** from **5** was rather surprising and in contradiction with our previous experience[5]: similar sodium borohydride reduction of yohimbinone yielded primarily β-yohimbine containing 17-OH in equatorial (β) position.

One of the probable explanations for the unexpected stereoselectivity is, that the attack of the $BH_4^{\ominus}$ anion on C-17 from the β side is preferred because of the steric hindrance caused by the α position of both C-16 and C-18 neighbouring substituents.

B) Synthesis of 18-hydroxyyohimbine stereoisomers

In the next step of the synthesis the C-18 methoxy groups of **7a – 10a** were demethylated to yield 18-hydroxyyohimbine stereoisomers. The reaction was first performed with 48-% hydrogen bromide. Under the reaction conditions applied the ester group also hydrolyzed, and thus to obtain the target diols **7b – 10b** subsequent esterification with diazomethane was required. According to ^1H and ^{13}C NMR spectra of the resulting compounds no epimerization took place at the chirality centers during hydrogen bromide treatment (see Tables 1 and 2). Characteristic changes in the C-17, C-18, and C-19 carbon resonances of **7b – 10b** in comparison with those of the respective 18-methoxy compounds **7a – 10a** are due to the difference in the α and β substituent effects between the hydroxy and methoxy groups.

A dealkylation method, which has always been found to lead to retention served as an independent chemical proof for the stereochemistry of the 18-hydroxy compounds. Using boron(III) bromide[20] reagent at 0 °C in dichloromethane, from **7a** uniformly **7b** was obtained. However, the boron(III) bromide demethylation of compounds **9a** and **10a** containing an axial (β) methoxy group at C-18 was slower by one order than in the case of **7a** with an equatorial (α) methoxy substituent. The reaction required larger excess of the reagent, proceeded with lower yield, and derivatives containing bromine in the aromatic nucleus were also formed. The difference observed between the rates of dealkylation of the epimers **7a – 10a** is in good correlation with the steric position assumed for the substituents of ring E.

As noted above at least one of the 18-hydroxy derivatives of yohimbine is a natural compound. The isolation of "18-hydroxy-yohimbine" was reported[3,4] without exact steric assignment of either the ring system or the substituents. Based upon the denomination between the quotation marks this alkaloid must have been assumed to be an 18-hydroxy derivative of yohimbine with known steric structure, and therefore it should be identical either with **7b** or **9b**. If the alkaloid in question were a derivative of β-yohimbine, its identification could be achieved by comparison with **8b** or **10b**. Thus our synthetic stereoisomers **7b – 10b** will be likely to help in solving this structure elucidation.

C) Formation of raunescine analogues with normal skeleton

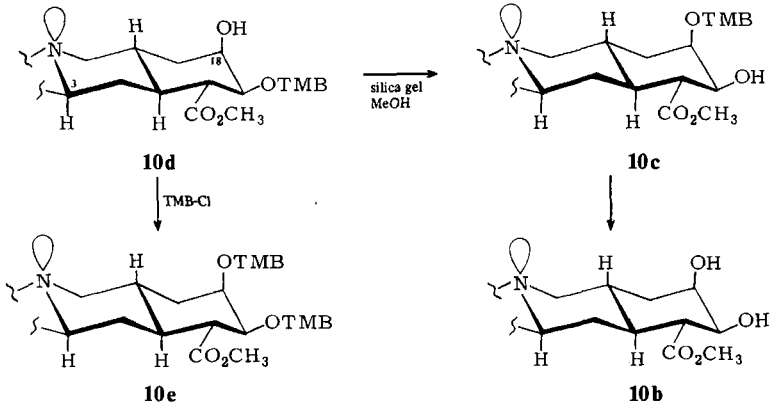
In order to prepare the raunescine stereoisomers with normal skeleton, the diols **7b**, **9b**, and **10b** were acylated with trimethoxybenzoyl chloride in pyridine.

According to our experiments these diols show different behaviour under the conditions of acylation. Whereas **7b** and **9b**, containing an axial (α) 17-OH group, could be transformed regioselectively into 18-monoacylated products **7c**, **9c**, in the case of **10b** with an equatorial (β) 17-OH function three trimethoxybenzoylated compounds **10c, d, e** were formed depending on the reaction conditions.

The differences observed in regioselectivity can be interpreted on the basis of the steric differences between the starting diols. In general, the acylation of an axial hydroxy group involves higher transition state energy than that of an equatorial one. This fact explains the selective trimethoxybenzoylation of **7b** into **7c**. The different reactivity of the two axial hydroxy groups in **9b** is due to the sterically more hindered position of the C-17 hydroxy substituent. The equatorial acylation could not predominate in **10b** because of the steric hindrance of the neighbouring ester group, and as a result the reactivity of the equatorial hydroxy function becomes comparable with that of the axial one. Accordingly, under mild conditions a mixture of monoacyl isomers **10c** and **10d** could be obtained, whereas under forced conditions (excess of reagent, longer reaction time) the diacylated compound **10e** was the main product.

The position of the acyl group was determined on the basis of the characteristic ^1H NMR shifts and the coupling constants of 17-H and 18-H[12,14,21] (see Table 1). The structure of **10d** is also supported by the possibility of transacylation into **10c**. Thus, when **10d** was heated in methanol in the presence of silica gel adsorbent (Kieselgel $PF_{254+366}$; Merck) as mild acidic catalyst, the C-17 equatorial acyl group migrated into the axial position C-18. The acyl migration was accompanied by a deacylation side reaction. If the reaction is performed in methanolic hydrochloric acid[14], the major product is the diol **10b**. Moreover, by trimethoxybenzoylation of **10d** the diacyl derivative **10e** can be obtained (see Scheme 2).

Scheme 2



10d **10c**

10e **10b**

TMB-Cl = 3,4,5-trimethoxybenzoyl chloride

As a result of the above trimethoxybenzoylation reactions three raunescine derivatives with normal yohimbane skeleton (**7c**, **9c**, **10c**) and one isoraunescine stereoisomer **10d** were obtained.

To the best of our knowledge, no other linear method is known for the synthesis of raunescine stereoisomers with normal skeleton up to now.

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Experimental

IR spectra were recorded in KBr with a Spectromom 2000 spectrophotometer. The ^1H and ^{13}C NMR spectra were obtained using 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. Chemical shifts are reported as δ values downfield from TMS as internal standard in both cases. Mass spectra (MS) were recorded with an AEI MS 902 double-focusing instrument (70 eV, ion source temp. 150 °C, direct insertion). Melting points are uncorrected.

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). Spots were visualized with an UV lamp or iodine vapor. For the quantitative separations (plc) Merck silica gel 60 $PF_{254+366}$, for column chromatography Merck silica gel 60 (70–230 mesh) adsorbent was used.

Usual workup of the reaction mixtures was carried out by extraction of an aqueos 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-{1,2,3,4,6,7,12,12bα-octahydro-2-[(methoxycarbonyl)methylene]indolo[2,3-a]quinolizin-3-yl}-2-methoxypropionate (**3**): To the stirred solution of a mixture of diethyl [(methoxycarbonyl)methyl]phosphonate (10 ml, 47 mmol) and sublimed potassium *tert*-butoxide (4.0 g, 35 mmol) in absol. DMF (50 ml) the ketone **2** (8.5 g, 24 mmol) in absol. DMF (40 ml) was added at 0 °C. The reaction mixture was allowed to stand for about 12 h in the refrigerator (at 10 °C), diluted with cold water (100 ml) and extracted with ether (3 × 200 ml) at pH 8.5–9. The combined organic layer was washed, dried, and evaporated *in vacuo*. The crude material (9.1 g, 92%) contained about 80% of **2** (based on tlc, system A, R_F **2** > **3**), and it was used without further purification for the next reaction step. An analytical sample was crystallized from methanol; m. p. 83–85 °C, hydrochloride m. p. 156–158 °C (methanol-ether). – IR: 1650 (C=C, conj.), 1712 (CO_2CH_3, conj.), 1750 (CO_2CH_3), 2750–2850 (Bohlmann bands), 3300 cm^{-1} (NH). – ^1H NMR ($CDCl_3$): δ = 3.37, 3.39 (2s, 3H, OCH_3), 3.5–4.1 (m, 2H, 1-H_{eq}, 12b-H), 3.73, 3.75, 3.77 (3s, 6H, CO_2CH_3), 5.67, 5.71 (2s, 1H, =CH–), 6.9–7.5 (m, 4H, aromatic protons), 8.76, 8.86 (2s, 1H, NH). – ^1H NMR (C_6D_6): δ = 3.14, 3.15 (2s, 3H, OCH_3), 3.2–4.1 (m, 3H, 1-H_{eq}, 12b-H + ?), 3.35, 3.36, 3.40 (3s, 6H, CO_2CH_3), 3.92 (dd, J_{gem} = 13, $J_{a,e}$ = 3 Hz, 1-H_{eq} of one diastereomer), 5.66, 5.75 (2s, 1H, =CH–), 7.2–7.5 (m, 4H, aromatic protons), 8.44, 8.63 (2s, 1H, NH). – ^{13}C NMR: see Table 3. – MS: *m/e* (rel. int.) = 412 ($M^{\oplus}$, 97), 411 (70), 397 (47), 381 (9), 353 (40), 309 (100), 296 (36), 295 (30), 184 (29), 183 (23), 182 (42), 171 (13), 170 (76), 169 (50), 156 (11), 144 (11), 130 (9).

Note: The geometry of the C=C bond in **3** was verified by comparison of its ^1H and ^{13}C NMR data with that of model compound **11**[5]. ^1H NMR of **11** in C_6D_6: δ = 3.36, 3.41 (2s, 6H, CO_2CH_3), 3.54 (m, 1H, 12b-H), 3.81 (dd, 1H, J_{gem} = 13, $J_{e,a}$ = 4 Hz, 1-H_{eq}), 5.61 (s, 1H, =CH–), 7.0–7.55 (m, 4H, aromatic protons), 8.27 (s, 1H, NH). – ^{13}C NMR of **11** see Table 3.

$C_{23}H_{28}N_2O_5$ (412.5) Calc. C 66.96 H 6.84 N 6.79 Found C 66.93 H 6.82 N 6.84

Methyl 3-{1,2,3,4,6,7,12,12bα-octahydro-2β-[(methoxycarbonyl)methyl]indolo-[2,3-a]quinolizin-3α-yl}-2-methoxypropionate (**4**): Crude **3** (9.1 g) was hydrogenated in methanol (250 ml) in

the presence of 10-% palladium on carbon to yield **4** which was isolated as hydrochloride (6.1 g, 67%); tlc: system A, R_F **3** > **4**. Hydrochloride: m. p. 186–187 °C (methanol-ether). – IR 1740 (CO_2CH_3), 3200 cm^{-1} (NH). – Base **4**: ^1H NMR ($CDCl_3$): δ = 3.39, 3.40 (2s, 3H, OCH_3), 3.72, 3.78 (2s, 6H, 2 CO_2CH_3), 7.05–7.55 (m, 4H, aromatic protons), 8.02 (s, 1H, NH). – MS: *m/e* (rel. int.) = 414 ($M^{\oplus}$, 100), 413 (90), 339 (40), 355 (20), 341 (14), 340 (6), 313 (20), 298 (4), 297 (7), 269 (5), 211 (30), 198 (7), 184 (15), 170 (30), 169 (30), 156 (20), 144 (20), 143 (15).

$C_{23}H_{30}N_2O_5 \cdot HCl$ (451.0) Calc. C 61.25 H 6.93 N 6.21 Found C 61.15 H 6.79 N 6.29

18α-Methoxyyohimbinone (**5**) *and 18β-Methoxyyohimbinone* (**6**): Compound **4** (7.4 g, 18 mmol) was dissolved in absol. benzene (200 ml) and dried by azeotropic distillation. Sublimed potassium *tert*-butoxide (3.0 g, 27 mmol) was added to the stirred reaction mixture and refluxed for 2 h, protected from air and light. Then the reaction mixture was neutralized with an equivalent amount of glacial acetic acid (1.6 ml, 27 mmol), evaporated to dryness, and the residue was extracted with dichloromethane (5 × 50 ml) at pH 8.5. The combined organic extract was washed, dried, and evaporated *in vacuo*. The amorphous residue (5.7 g, 84%) was treated with methanol (40 ml) and the crystalline **5** (1.6 g, 23%), separated. The evaporated mother liquor was purified by column chromatography on silica gel with ethyl acetate to supply **6** (1.6 g, 23%) and an additional amount of 1.1 g (total 2.7 g, 39%) **5**; tlc: system A, R_F **6** > **4** > **5**.

5: m. p. 163–165 °C (methanol). – IR: 1730, 1750 (CO_2CH_3, CO), 2730–2870 (Bohlmann bands), 3150, 3450 cm^{-1} (NH). – ^1H NMR ($CDCl_3$): δ = 3.48 (s, 3H, OCH_3), 3.87 (dd, 1H, $J_{a,e}$ = 5.5, $J_{a,a}$ = 12 Hz, 18-H), 3.85 (s, 3H, CO_2CO_3), 7.05–7.55 (m, 4H, aromatic protons), 7.85 (s, 1H, NH). – MS: *m/e* (rel. int.) = 382 ($M^{\oplus}$, 100), 381 (7), 367 (5), 351 (7), 324 (2), 323 (3.3), 237 (4.3), 235 (4), 224 (5.7), 223 (4), 211 (12), 184 (20), 170 (33), 169 (27), 150 (14), 144 (10), 143 (9.3).

$C_{22}H_{26}N_2O_4$ (382.5) Calc. C 69.08 H 6.85 N 7.32 Found C 68.92 H 6.95 N 7.15

6: m. p. 125–127 °C (methanol). – IR: 1700, 1740 (CO_2CH_3, CO), 2750–2870 (Bohlmann bands), 3150, 3500 cm^{-1} (NH). – ^1H NMR ($CDCl_3$): δ = 3.32 (s, 3H, OCH_3), 3.66 (t, 1H, $J_{e,a}$ = $J_{e,e}$ = 3 Hz, 18-H), 3.82 (s, 3H, CO_2CH_3), 7.05–7.55 (m, 4H, aromatic protons), 7.98 (s, 1H, NH).

$C_{22}H_{26}N_2O_4$ (382.5) Calc. C 69.08 H 6.85 N 7.32 Found C 68.85 H 7.01 N 7.34

Epimerization of **6** *to* **5**: Compound **6** (40 mg, 0.1 mmol) was dissolved in 2 N methanolic sodium methoxide (5 ml) at –10 °C, and the solution was kept at the same temperature for 72 h. Epimerization was monitored by tlc (system A, R_F **6** > **5**). The resulting crystalline material was filtered off and recrystallized from methanol; m. p. 163–165 °C. According to spectral and chromatographic data the product was identical with compound **5** obtained from the ring closure of **4**.

Note: Epimerization could not be accomplished at room temperature due to ring opening of **5** (→ **4**).

18α-Methoxyyohimbine (**7a**) *and 18α-Methoxy-β-yohimbine* (**8a**): To a stirred solution of **5** (1.2 g, 3.1 mmol) in methanol (80 ml) and dichloromethane (20 ml) sodium borohydride was added in small portions at 0 °C. The reduction was followed by tlc (system B, R_F **5** > **7a** > **8a**). Subsequent to evaporation of the solvent *in vacuo* the residue was dissolved in a minimal amount of water and extracted with dichloromethane (4 × 20 ml) at pH 9.5. The combined organic layer was washed, dried, and evaporated *in vacuo*. The remaining material (1.15 g) was treated with methanol (50 ml) and the crystalline **7a** (0.66 g, 55%) was separated. The evaporated mother liquor was purified by plc (system C, pretreated with ammonia, R_F **7a** > **8a**) to yield an additional amount of 0.18 g **7a** (total 70%) and **8a** (90 mg, 8%); tlc on alumina typ E: benzene-methanol (10:0.2), R_F **7a** > **8a**.

Note: The same ratio of **7a** and **8a** was obtained *via* catalytic (Pt/C) hydrogenation in glacial acetic acid (0.20 g of **5** and 0.20 g of Pt-C (10%) in 20 ml of solvent, 17 h).

7a: m. p. 210 – 212 °C (methanol). – IR: 1730 (CO_2CH_3), 2750 – 2850 (Bohlmann bands), 3200, 3350 cm^{-1} (OH, NH). – ^1H NMR (C_6D_6 + [D$_6$]DMSO): δ = 3.28 (s, 3H, OCH_3), 3.45 (m, 1H, $J_{a,e} = J_{a,e} = 2.5$ Hz, $J_{a,a} = 10$ Hz, 18-H_{ax}), 3.72 (s, 3H, CO_2CH_3), 4.25 (m, 1H, 17-OH), 4.43 (m, 1H, $J_{c,a} = J_{e,a} = 2.5$ Hz, 17-H_{eq}), 7.05 – 7.65 (m, 4H, aromatic protons), 10.70 (s, 1H, NH). – MS: *m/e* (rel. int.) = 384 ($M^{\oplus}$, 100), 383 (100), 369 (2), 353 (4), 352 (2), 321 (2), 184 (25), 170 (25), 169 (30), 156 (20), 144 (15).

8a: m. p. 236 – 237 °C (methanol). – IR: 1730 (CO_2CH_3), 2750 – 2850 (Bohlmann bands), 3350, 3400 cm^{-1} (OH, NH). – ^1H NMR ($CDCl_3$): δ = 3.45 (s, 3H, OCH_3), 3.75 (m, 1H, 17-H_{ax}), 3.84 (s, 3H, CO_2CO_3), 7.05 – 7.45 (m, 4H, aromatic protons), 7.76 (s, 1H, NH). ^1H NMR (C_6D_6 + [D$_6$]DMSO): δ = 3.39 (s, 3H, OCH_3), 3.77 (s, 3H, CO_2CH_3), 3.95 (m, 1H, $J_{a,a} = J_{a,a} =$ 10 Hz, 17-H_{ax}), 5.10 (m, 1H, 17-OH), 7.12 – 7.57 (m, 4H, aromatic protons), 10.92 (s, 1H, NH). – MS: *m/e* (rel. int.) = 384 ($M^{\oplus}$, 34), 383 (100), 369 (5.8), 367 (1.7), 353 (3.3), 211 (5), 184 (17), 169 (18.3).

O-Acetyl-18α-methoxyyohimbine (**7f**): To a solution of **7a** (126 mg, 0.33 mmol) in dry pyridine (3 ml) freshly distilled acetic anhydride (0.3 ml, 2.9 mmol) was added. After standing for about 12 h the crystalline product **7f** (90 mg, 64%) was filtered off; m. p. 266 – 268 °C (pyridine). – IR: 1230 ($OCOCH_3$), 1700 – 1735 (CO_2CH_3), 2780 – 2850 (Bohlmann bands), 3350 cm^{-1} (NH). – ^1H NMR (C_6D_6 + [D$_6$]DMSO): δ = 1.97 (s, 3H, $OCOCH_3$), 3.28 (s, 3H, OCH_3), 3.72 (s, 3H, CO_2CH_3), 5.80 (t, 1H, $J_{c,a} + J_{e,a} = 6$ Hz, 17-H_{eq}), 7.05 – 7.60 (m, 4H, aromatic protons), 10.75 (s, 1H, NH). – MS: *m/e* (rel. int.) = 426 ($M^{\oplus}$, 100), 425 (78), 411 (0.6), 397 (1.3), 395 (2.1), 384 (9), 383 (8.4), 367 (3.6), 307 (1.4), 184 (10), 170 (9.6), 169 (10), 156 (7.8), 144 (6).

$C_{24}H_{30}N_2O_5$ (426.5) Calc. C 67.58 H 7.09 N 6.57 Found C 67.46 H 6.95 N 6.27

18β-Methoxyyohimbine (**9a**) *and 18β-Methoxy-β-yohimbine* (**10a**): The keto ester **6** (2.3 g, 6 mmol) was dissolved in methanol (10 ml) and dichloromethane (40 ml). Sodium borohydride was added in small portions to the stirred reaction mixture at 0 °C, and it was monitored by tlc (system B, R_F **10a** > **9a**). Workup including preparative tlc (cyclohexane-ether-methanol, 30:50:6, R_F **9a** > **10a**) supplied **9a** (0.7 g, 30%) and **10a** (1.1 g, 43%).

9a: m. p. 204 – 205 °C (ether-petroleum ether) [**9a** · HCl: m. p. 253 – 255 °C (methanol-ether)]. – IR: 1080 (C – OH), 1710 (CO_2CH_3), 2750 – 2850 (Bohlmann bands), 3200 – 3400 cm^{-1} (OH, NH). – ^1H NMR (C_6D_6 + [D$_6$]DMSO): δ = 3.21 (s, 3H, OCH_3), 3.59 (q, 1H, $J_{e,a} = J_{e,e} = J_{e,e} =$ 3 Hz, 18-H_{eq}), 3.70 (s, 3H, CO_2CH_3), 4.41 (t, 1H, $J_{e,a} = J_{e,e} = 3$ Hz, 17-H_{eq}), 7.13 – 7.65 (m, 4H, aromatic protons), 10.30 (s, 1H, NH). – MS: *m/e* (rel. int.) = 384 ($M^{\oplus}$, 100), 383 (100), 369 (1), 353 (2), 325 (4), 323 (1), 184 (10), 170 (10), 169 (15), 156 (10), 144 (8).

10a: m. p. 225 – 228 °C (dichloromethane-petroleum ether) [**10a** · HCl: 241 – 242 °C (methanol-ether)].– IR: 1725 (CO_2CH_3), 2780 – 2850 (Bohlmann bands), 3200 – 3400 cm^{-1} (OH, NH). – ^1H NMR (C_6D_6 + [D$_6$]DMSO): δ = 3.23 (s, 3H, OCH_3), 3.46 (q, 1H, $J_{e,e} = J_{e,a} = J_{e,a} = 3$ Hz, 18-H_{eq}), 3.77 (s, 3H, CO_2CH_3), 3.97 (dd, 1H, $J_{a,e} = 3$ Hz, $J_{a,a} = 11$ Hz, 17-H_{ax}), 7.12 – 7.65 (m, 4H, aromatic protons), 10.60 (s, 1H, NH). – MS: *m/e* (rel. int.) = 384 ($M^{\oplus}$, 100), 383 (100), 369 (2), 353 (5), 325 (5), 323 (1), 184 (10), 170 (15), 169 (25), 156 (15), 144 (8).

18α-Hydroxyyohimbine (**7b**): a) Compound **7a** (0.5 g, 13 mmol) was dissolved in 48-% aqueous hydrogen bromide solution (20 ml) and kept at 100 °C for 3 h. The solvent was removed under reduced pressure and the dried (over P_2O_5 *in vacuo*) residue refluxed in absol. methanol (50 ml). After evaporation the remaining material was treated with a minimal amount of water and extracted with dichloromethane (2 × 20 ml) at pH 9.5. The combined organic layer was

washed, dried, and evaporated *in vacuo*, and the crude material obtained was purified by plc (system C, pretreated with ammonia) to give **7b** (0.3 g, 62%).

b) To a solution of **7a** (0.25 g, 0.65 mmol) in absol. dichloromethane (100 ml) boron tribromide (0.90 g, 0.34 ml, 3.6 mmol) was added at 0 °C. The reaction mixture was stirred for 4 h at 0 °C and kept in a refrigerator for about 12 h. Then the solution was treated with 10-% ammonium hydroxide solution, the organic phase was separated, washed, dried, and evaporated *in vacuo*. The crude material (0.17 g) was purified by plc (system C, R_F **7a** > **7b**) to supply **7b** (0.13 g, 54%).

7b: m. p. 221 – 223 °C (ethyl acetate). – IR: 1020 (C – OH), 1720 (CO_2CH_3), 3250 cm^{-1} (OH, NH). – ^1H NMR ($CDCl_3$): δ = 3.65 (br. m, 1H, $J_{a,a} + J_{a,e} + J_{a,e}$ = 16 Hz, 18-H_{ax}), 3.78 (s, 3H, CO_2CH_3), 4.18 (t, 1H, $J_{e,a} = J_{e,a}$ = 2 Hz, 17-H_{eq}), 6.95 – 7.45 (m, 4H, aromatic protons), 9.05 (s, 1H, NH). – MS: *m/e* (rel. int.) = 370 ($M^{\oplus}$, 100), 369 (97), 353 (3), 352 (4), 351 (4), 339 (6), 338 (8), 337 (7), 321 (4), 311 (5), 211 (8), 184 (21), 170 (7), 169 (22), 156 (15).

18α-Hydroxy-β-yohimbine (**8b**), *18β-Hydroxyyohimbine* (**9b**), *and 18β-Hydroxy-β-yohimbine* (**10b**): **8b**, **9b**, and **10b** were obtained according to method a); **7b**: 55 – 60% yield; tlc: system C, R_F **10b** > **9b**; **7b** > **8b**.

8b: m. p. 185 – 187 °C (dec., amorphous). – IR: 1050 (C – OH), 1710 (CO_2CH_3), 3350 cm^{-1} (br., OH, NH). – ^1H NMR ($CDCl_3$): δ = 3.80 (s, 1H, CO_2CH_3). – MS: *m/e* (rel. int.) = 370 ($M^{\oplus}$, 96), 369 (100), 355 (4), 353 (4), 337 (5), 311 (7), 309 (6), 293 (4), 240 (8), 184 (20), 169 (31), 156 (23).

9b: m. p. 174 – 176 °C (dec., ethyl acetate). – IR: 1030 (C – OH), 1715 (CO_2CH_3), 3350 cm^{-1} (br., OH, NH). – ^1H NMR ($CDCl_3$ + [D_6]DMSO): δ = 3.78 (s, 3H, CO_2CH_3), 3.98 (q, 1H, $J_{e,a} = J_{e,e} = J_{e,e}$ = 3 Hz, 18-H_{eq}), 4.02 (t, 1H, $J_{e,a} = J_{e,e}$ = 3 Hz, 17-H_{eq}), 7.0 – 7.45 (m, 4H, aromatic protons), 8.73 (s, 1H, NH). – MS: *m/e* (rel. int.) = 370 ($M^{\oplus}$, 99), 369 (100), 355 (2), 353 (2), 315 (2), 311 (8), 240 (4), 184 (20), 170 (22), 169 (26), 156 (16).

10b: m. p. 182 – 184 °C (dec., ethyl acetate). – IR: 1710 (CO_2CH_3), 3350 cm^{-1} (br., OH, NH). – ^1H NMR ($CDCl_3$): δ = 3.76 (dd, 1H, $J_{a,e}$ = 2.5 Hz, $J_{a,a}$ = 10.5 Hz, 17-H_{ax}), 4.04 (q, 1H, $J_{e,e} = J_{e,a} = J_{e,a}$ = 3 Hz, 18-H_{eq}), 7.0 – 7.5 (m, 4H, aromatic protons), 7.90 (s, 1H, NH). – MS: *m/e* (rel. int.) = 370 ($M^{\oplus}$, 99), 369 (100), 355 (2), 353 (3), 351 (4), 311 (6), 240 (7), 184 (11), 170 (14), 169 (15), 156 (10).

Note: If the ether cleavage starting from **9a** or **10a** was carried out by method b) **9b** or **10b** could be isolated in a yield of 15% besides other products brominated at the indole part.

Spectral data of brominated diol side-products

Product from **9a** *(24%):* IR: 710, 770, 1715 (CO_2CH_3), 3400 cm^{-1} (br., OH, NH). – MS: *m/e* (rel. int.) = 450 (91), 449 (92), 448 ($M^{\oplus}$, 100), 447 (77), 410 (16), 409 (18), 391 (4.6), 389 (6), 384 (22), 383 (20), 341 (5), 264 (8), 262 (8), 250 (8), 249 (11), 248 (9), 247 (8).

Product from **10a** *(10%):* IR: 720, 760, 1710 (CO_2CH_3), 3350 cm^{-1} (br., OH, NH). – MS: *m/e* (rel. int.) = 450 (91), 449 (97), 448 ($M^{\oplus}$, 100), 447 (82), 410 (13), 409 (16), 391 (5.5), 389 (7), 384 (6), 383 (5.5), 341 (5.5), 264 (12), 262 (12), 250 (12), 249 (15), 248 (13), 247 (12).

18α-(3,4,5-Trimethoxybenzoyloxy)yohimbine (**7c**): To the solution of **7b** (0.74 g, 1.9 mmol) in absol. pyridine (30 ml) 3,4,5-trimethoxybenzoyl chloride (1.33 g, 5.7 mmol) was added. The reaction mixture was kept at 100 °C for 1 h and the acylation monitored by tlc (system C, R_F **7c** > **7b**). After removing the solvent *in vacuo* the residue was dissolved in dichloromethane (70 ml) and stirred with saturated aqueous K_2CO_3 solution for 20 min. The organic layer was separated, washed, dried, and evaporated *in vacuo*. The crude material (0.74 g) was purified by column chromatography on silica gel with dichloromethane-methanol (100:2) to yield **7c**

(350 mg, 31%); m. p. 168–169 °C (ethyl acetate). – IR: 1710–1730 (ester CO), 2760, 2810, 2840 (Bohlmann bands), 3480 (NH), 3520 cm^{-1} (OH). – ^1H NMR ($CDCl_3$): δ = 3.81, 3.90 (2s, 3H, 9H, CO_2CH_3, OCH_3), 4.50 (t, 1H, $J_{e,a} = J_{e,a}$ = 2.5 Hz, 17-H_{eq}), 5.11 (m, 1H, $J_{a,e} = J_{a,e}$ = 2.5 Hz, $J_{a,a}$ = 12 Hz, 18-H_{ax}), 7.05–7.55 (m, 6H, aromatic protons), 7.94 (s, 1H, NH). – MS: *m/e* (rel. int.) = 564 ($M^{\oplus}$, 33), 563 (18), 549 (1), 547 (1), 533 (1), 505 (0.5), 370 (2), 369 (2), 366 (10), 365 (9), 352 (40), 351 (40), 294 (1.6), 293 (4), 281.5 (3), 226 (70), 212 (90), 211 (40), 197 (80), 195 (55), 186 (8), 184 (45), 170 (16), 169 (42), 167 (7), 157 (9), 156 (30), 154 (100).

$C_{31}H_{36}N_2O_8$ (564.6) Calc. C 65.94 H 6.43 N 4.96 Found C 65.62 H 6.27 N 5.11

18β-(3,4,5-Trimethoxybenzoyloxy)yohimbine (**9c**): Starting with **9b** (50 mg, 0.14 mmol) in absol. pyridine (5 ml) using trimethoxybenzoyl chloride (92 mg, 0.4 mmol) the above mentioned sequence afforded 90 mg of crude **9c** which was purified by preparative tlc (system C, R_F **9c** > **9b**) to give **9c** (25 mg, 34%); m. p. 165–166 °C (ethyl acetate-petroleum ether). – IR: 1715 (ester CO), 3200–3400 cm^{-1} (OH, NH). – ^1H NMR ($CDCl_3$): δ = 3.80, 3.87, 3.89 (3s, 12H, CO_2CH_3, OCH_3), 4.26 (dd, 1H, $J_{e,a} = J_{e,e}$ = 3 Hz, 17-H_{eq}), 5.29 (q, 1H, $J_{e,a} = J_{e,e} = J_{e,e}$ = 3 Hz, 18-H_{eq}), 7.0–7.50 (m, 6H, aromatic protons), 7.88 (s, 1H, NH). – MS: *m/e* (rel. int.) = 564 ($M^{\oplus}$, 100), 563 (60), 549 (3), 533 (3), 434 (2), 352 (30), 351 (30), 293 (4), 281.5 (4), 226 (20), 212 (60), 195 (30), 184 (20), 170 (20), 169 (20), 156 (20), 144 (10).

$C_{31}H_{36}N_2O_8$ (564.6) Calc. C 65.94 H 6.43 N 4.96 Found C 65.48 H 6.17 N 5.12

18β-(3,4,-5-Trimethoxybenzoyloxy)-β-yohimbine (**10c**) *and Methyl 18β-hydroxy-17β-(3,4,5-trimethoxybenzoyloxy)yohimban-16α-carboxylate* (**10d**): a) The solution of **10b** (0.30 g, 0.8 mmol) in absol. pyridine (20 ml) was treated with trimethoxybenzoyl chloride (0.54 g, 2.4 mmol) at 100 °C for 1 h. The reaction was followed by tlc (system C, R_F **10c** > **10d** > **10b**). After evaporation of the solvent *in vacuo* the residue was dissolved in dichloromethane (30 ml) and stirred with saturated aqueous K_2CO_3 solution for 20 min. The organic phase was separated, washed, dried, and evaporated *in vacuo*. The residue was purified by plc (system C) to supply **10d** (50 mg, 11%) and **10c** (125 mg, 26%).

10c: m. p. 153–156 °C (ethyl acetate-petroleum ether). – IR: 1710–1730 (ester CO), 2750 bis 2800 (Bohlmann bands), 3300–3400 (OH, NH). – ^1H NMR ($CDCl_3$): δ = 3.83, 3.88 (2s, 3H, 9H, CO_2CH_3, OCH_3), 4.08 (dd, 1H, $J_{a,e}$ = 3, $J_{a,a}$ = 11 Hz, 17-H_{ax}), 5.52 q, 1H, $J_{e,e} = J_{e,a} = J_{e,a}$ = 3 Hz, 18-H_{eq}), 7.0–7.54 (m, 6H, aromatic protons), 7.85 (s, 1H, NH). – MS: *m/e* (rel. int.) = 564 ($M^{\oplus}$, 100), 563 (58), 549 (2), 547 (1), 533 (1.4), 505 (1.5), 370 (5), 369 (6), 366 (1.5), 365 (1), 352 (30), 351 (30), 294 (6), 293 (8), 281.5 (6), 226 (23), 212 (35), 211 (16), 197 (16), 195 (50), 186 (25), 184 (20), 170 (24), 169 (25), 167 (40), 157 (40), 156 (30), 154 (10).

$C_{31}H_{36}N_2O_8$ (564.6) Calc. C 65.94 H 6.43 N 4.96 Found C 65.54 H 6.21 N 5.18

10d: m. p. 217–218 °C (ethyl acetate). – 1710–1730 (ester CO), 2750–2800 (Bohlmann bands), 3300–3450 cm^{-1} (OH, NH). – ^1H NMR ($CDCl_3$): δ = 3.67, 3.88 (2s, 3H, 9H, CO_2CH_3, OCH_3), 4.38 (q, 1H, $J_{e,e} = J_{e,a} = J_{e,a}$ = 3 Hz, 18-H_{eq}), 5.22 (dd, 1H, $J_{a,e}$ = 3 Hz, $J_{a,a}$ = 10 Hz, 17-H_{ax}), 7.0–7.5 (m, 6H, aromatic protons), 8.05 (s, 1H, NH). – MS: *m/e* (rel. int.) = 564 ($M^{\oplus}$, 100), 563 (55), 549 (1.8), 547 (0.9), 533 (1.6), 505 (1.4), 370 (8), 369 (14), 366 (1.5), 365 (0.8), 352 (23), 351 (26), 294 (7), 293 (8), 281.5 (6), 226 (40), 212 (35), 211 (30), 197 (20), 195 (40), 186 (3), 184 (25), 170 (20), 169 (25), 167 (6), 157 (8), 156 (22), 154 (7).

$C_{31}H_{36}N_2O_8$ (564.6) Calc. C 65.94 H 6.43 N 4.96 Found C 65.72 H 6.34 N 5.21

b) Compound **10d** (15 mg) in dry methanol (5 ml) was refluxed in the presence of silica gel $PF_{254+366}$ (30 mg) for 4 h. After filtration the solvent was evaporated *in vacuo* and the residue separated by tlc (system C, R_F **10c** > **10d** > **10b**) to give **10c** (3.5 mg), **10b** (5 mg), and unreacted **10d** (2 mg).

Table 1. Characteristic ^{1}H NMR data[a]

	17-H	18-H
5	–	3.87 (ax), $J_{a,c}$ = 5.5, $J_{a,a}$ = 12
6	–	3.66 (eq), $J_{e,e}$ = $J_{e,a}$ = 3
7a	4.43[c] (eq), $J_{e,a}$ = $J_{e,a}$ = 2.5	3.45 (ax), $J_{a,a}$ = 10, $J_{a,e}$ = $J_{a,e}$ = 2.5
8a	3.95[e] (ax), $J_{a,a}$ = $J_{,aa}$ = 10	– [b]
9a	4.41[e] (eq), $J_{e,a}$ = $J_{e,e}$ = 3	3.59 (eq), $J_{e,a}$ = $J_{e,e}$ = $J_{e,e}$ = 3
10a	3.97[c] (ax), $J_{a,e}$ = 3, $J_{a,a}$ = 11	3.46 (eq), $J_{e,e}$ = $J_{e,a}$ = $J_{e,a}$ = 3
7b	4.18[c] (eq), $J_{e,a}$ = $J_{e,a}$ = 2	3.65 (ax), $J_{a,a}$ + $J_{a,e}$ + $J_{a,e}$ = 16
9b	4.02[d] (eq), $J_{e,a}$ = $J_{e,e}$ = 3	3.98 (eq), $J_{e,a}$ = $J_{e,e}$ = $J_{e,e}$ = 3
10b	3.76[c] (ax), $J_{a,e}$ = 2.5, $J_{a,a}$ = 10.5	4.04 (eq), $J_{e,e}$ = $J_{e,a}$ = $J_{e,a}$ = 3
7c	4.50[c] (eq), $J_{e,a}$ = $J_{e,a}$ = 2.5	5.11 (ax), $J_{a,a}$ = 12, $J_{a,e}$ = $J_{a,e}$ = 2.5
9c	4.26[c] (eq), $J_{e,a}$ = $J_{e,e}$ = 3	5.29 (eq), $J_{e,a}$ = $J_{e,e}$ = $J_{c,e}$ = 3
10c	4.08[c] (ax), $J_{a,e}$ = 3, $J_{a,a}$ = 11	5.52 (eq), $J_{e,e}$ = $J_{e,a}$ = $J_{e,a}$ = 3
10d	5.22[c] (ax), $J_{a,e}$ = 3, $J_{a,a}$ = 10	4.38 (eq), $J_{e,e}$ = $J_{e,a}$ = $J_{c,a}$ = 3
10e	5.47[d] (ax), $J_{a,e}$ = 3, $J_{a,a}$ = 10	5.82 (eq), $J_{e,e}$ = $J_{e,a}$ = $J_{c,a}$ = 3

[a] Shifts are given in δ values relative to Me_4Si and J values in hertz. – [b] Overlapped. – [c] In $CDCl_3$ solution. – [d] In $CDCl_3$ + [D_6]DMSO solution. – [e] In C_6D_6 + [D_6]DMSO solution.

Table 2. ^{13}C NMR chemical shifts[a,b]

Carbon	**6**	**9a**	**10a**	**9b**	**10b**	**5**	**7a**	**7b**
C-2	134.08	135.49	135.29	134.86	134.96	134.03	135.36	135.37
C-3	58.94	60.30	59.47	60.24	59.77	58.94	60.07	60.19
C-5	52.75	52.89	52.57	52.86	52.86	52.86	52.73	52.86
C-6	21.82	21.75	21.64	21.64	21.66	21.93	21.70	21.77
C-7	108.32	106.48	106.32	107.21	106.77	108.61	106.47	106.47
C-8	127.32	126.94	126.74	127.13	127.00	127.50	126.89	126.99
C-9	118.11	117.40	117.35	117.81	117.59	118.21	117.38	117.48
C-10	119.39	118.35	118.24	118.84	118.52	119.60	118.32	118.44
C-11	121.44	120.29	120.24	120.84	120.54	121.66	120.28	120.43
C-12	110.91	111.03	110.85	111.01	111.03	110.94	111.03	111.06
C-13	136.19	136.28	136.04	136.11	136.00	136.37	136.25	136.35
C-14	35.04	33.97	33.72	33.76	33.56	35.22	33.73	33.86
C-15	44.23	35.78	42.13	36.31	42.20	44.12	35.43	35.35
C-16	58.17	48.14	51.52	47.48	51.19	61.49	51.42	51.43
C-17	205.36	68.25	72.84	70.62	73.24	202.40	67.02	70.69
C-18	82.86	78.14	78.45	68.37	68.46	83.43	80.11	70.69
C-19	36.08	26.88	30.67	30.91	34.79	37.04	28.52	31.78
C-20	33.54	33.79	33.41	33.61	33.03	37.93	38.24	38.47
C-21	60.50	61.36	60.67	61.30	61.03	60.39	61.08	61.19
–CO–	170.00	173.69	174.34	175.34	175.02	169.02	172.41	172.71
$-CO_2Me$	52.18	51.22	51.22	51.72	51.61	52.21	51.32	51.64
$-OCH_3$	57.18	55.94	56.83	–	–	58.26	55.49	–

[a] Chemical shifts (ppm) are relative to internal TMS in $CDCl_3$ solutions. – [b] The small amounts of **8a** and **8b** were not sufficient to take their ^{13}C NMR spectra.

Table 3. ^{13}C NMR chemical shifts (δ values, $CDCl_3$, internal TMS)

	11	**3**
C-1	31.21	27.92 + 31.24
C-2	160.56	159.83 + 161.00
C-3	43.73	40.37 + 41.22
C-4	57.98	56.37 + 57.51
C-6	51.63	51.28 + 51.66
C-7	20.15	19.13 + 20.15
C-7a	107.56	107.26 + 107.44
C-7b	127.24	127.27
C-8	117.97	118.00
C-9	119.20	119.20
C-10	121.28	121.28
C-11	111.01	111.09
C-11a	135.09	136.05
C-12a	133.44	133.09 + 133.44
C-12b	59.18	58.39 + 59.18
$-CO-$	173.46	172.99
C(α)	31.61	78.13 + 78.54
C(β)	24.81	33.08 + 33.90
$-CO-$	167.61	167.76 + 167.84
$=C-H$	113.35	113.03 + 114.72
$-OCH_3$	–	52.07 + 58.39
$-CO_2CH_3$	51.22	51.28
$-CO_2CH_3$	51.63	51.66

Methyl 17β,18β-bis(3,4,5-trimethoxybenzoyloxy)yohimban-16α-carboxylate (**10e**): a) The solution of **10b** (0.38 g, 1 mmol) in absol. pyridine (10 ml) was treated with trimethoxybenzoyl chloride (1.3 g, 5.6 mmol) at 100 °C for 2 h. Similar workup including preparative tlc (system B, R_F **10e** > **10b**) gave **10e** (0.15 g, 33%); m. p. 223–224 °C (ethyl acetate). – IR: 1710–1730 (CO_2CH_3), 2750–2850 (Bohlmann bands), 3200–3400 cm^{-1} (NH). – ^1H NMR ($CDCl_3$ + [D_6]DMSO): δ = 3.66, 3.74, 3.84, 3.86, 388, (5s, 6H, 3H, 12H, CO_2CH_3, OCH_3), 5.47 (dd, 1H, $J_{a,e}$ = 3 Hz, $J_{a,a}$ = 10 Hz, 17-H_{ax}), 5.82 (q, 1H, $J_{e,e} = J_{e,a}$ = 3 Hz, 18-H_{eq}), 6.95–7.45 (m, 8H, aromatic H), 9.42 (s, 1H, NH). – MS: *m/e* (rel. int.) = 758 ($M^{\oplus}$, 25), 757 (8), 658 (1), 656 (1.3), 578 (11), 563 (1), 560 (1.4), 547 (15), 546 (40), 545 (19), 531 (1.5), 515 (1.1), 487 (0.7), 378.5 (2), 366 (2), 365 (2.2), 352 (8), 351 (18), 336 (14), 335 (22), 334 (8), 333 (8), 273 (4), 226 (38), 212 (100), 197 (47), 195 (42), 185 (10), 184 (25), 170 (13), 169 (19), 156 (25).

b) Compound **10d** (10 mg, 0.02 mmol) in absol. pyridine (3 ml) was heated with trimethoxybenzoyl chloride (17 mg, 0.07 mmol) at 100 °C for 4 h. Workup including plc yielded **10e** (6 mg).

Acetonide of 18α-Hydroxyyohimbine (**7g**): To the solution of **7b** (80 mg, 0.2 mmol) in dry acetone (8 ml) a few drops of perchloric acid and 1 g of molecular sieves (3 Å) were added. The reaction mixture was stirred at room temperature and monitored by tlc (system C, R_F **7g** > **7b**). At about 80-% conversion (≈ 4 h) solid potassium carbonate was added to neutralize, the salt filtered off, and the solvent evaporated *in vacuo*. The residue, after separation by plc (system C), gave **7g** (40 mg, 35%); m. p. 236–237 °C (ethyl acetate). – IR: 1040, 1140, 1210 (characteristic bands), 1725 (CO_2CH_3), 2750–2850 (Bohlmann bands), 3350 cm^{-1} (NH). – ^1H NMR ($CDCl_3$): δ = 1.34, 1.51 (2s, 3H, 3H, CH_3), 3.35 (d, 1H, 12b-H), 3.79 (s, 3H, CO_2CH_3), 4.16 [m, 1H,

$J_{18,19}$ = 12 Hz (a,a), $J_{18,19}$ = 7 Hz (a,e), $J_{18,17}$ = 4 Hz (a,e), 18-H_{ax}], 4.42 (t, 1H, $J_{e,a}$ = $J_{e,a}$ = 4 Hz, 17-H_{eq}), 7.0–7.5 (m, 4H, aromatic protons), 8.03 (s, 1H, NH). – MS: *m/e* (rel. int.) = 410 ($M^{\oplus}$, 100), 409 (91.2), 395 (10.6), 351 (5.8), 349 (4.6), 197 (5.9), 194 (10.6), 170 (8.7), 169 (9.5), 156 (8.2), 144 (5.9), 70 (5.9), 61 (8.7), 45 (5.9), 43 (50.7).

Note: The acetonide of **10b** could be obtained by a similar process, however, no acetonide formation could be detected in the case of **9b**.

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