Synthesis of Yohimbines. 4.† Synthesis of (±)-3-*epi*-α-Yohimbine and (±)-3,17-*epi*-α-Yohimbine. Carbon-13 Nuclear Magnetic Resonance Investigation of Yohimbine Stereoisomers

Katalin Honty, Eszter Baitz-Gács, Gábor Blaskó, and Csaba Szántay*

Institute of Organic Chemistry, Technical University, H-1521 Budapest, Gellért tér 4, Hungary, and Central Research Institute for Chemistry of the Hungarian Academy of Sciences, H-1525, Budapest, Pusztaszeri ut 59-67, Hungary

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By use of the method developed earlier for epimerization at C(3) and C(16) the first synthesis of (±)-3-*epi*-α-yohimbine (1) and (±)-3,17-*epi*-α-yohimbine (3) was accomplished. Comparative analysis of the carbon-13 chemical shift data for isomeric yohimbines with natural and nonnatural stereochemistry has provided the predominant conformations in the normal, allo, and epi-allo series.

Synthesis

Isorauhimbine isolated by Hofmann[1] from *Rauwolfia serpentina* Benth has been known since 1954 and was later found to be identical with 3-*epi*-α-yohimbine (1)[3] isolated by Schlittler.[2] In the past 2 decades several total sytheses leading to yohimbines were developed,[4-7] but none of them yielded isorauhimbine (1), including our attempt via reduction of 3-*epi*-alloyohimbinone (2).[8]

In previous parts of this series[5-8] we reported on the synthesis of nine isomeric yohimbines with natural and nonnatural stereochemistry. For completion of this work, we now report on the transformation of racemic allo- and *epi*-alloyohimbine stereoisomers **5**, **7**, and **9** (synthesized earlier in our laboratories[5-9]) into (±)-3-*epi*-α-yohimbine (**1**) by means of C(3) and C(16) epimerizations, respectively.

The C(3) epimerization of alloyohimbines into *epi*-allo stereoisomers by oxidation with mercury(II) acetate and subsequent reduction with zinc in glacial acetic acid is well-known and has been used for the transformation of natural (−)-α-yohimbine (**7**) into (−)-3-*epi*-α-yohimbine (**1**).[10a] We use this method for the total synthesis of racemic isorauhimbine (1) from (±)-**7**.

Seemingly the simplest way to obtain **7** is the reduction of alloyohimbinone (**6**). The sodium borohydride or catalytic reduction of **6** gave, however, only 6–8% of α-yohimbine (**7**) along with some alloyohimbine (**9**).[7,8] Epimerization of **9** at C(16) in 2 N sodium methoxide in methanol to **7** improved the yield only slightly (see Scheme I).

A more practical approach to **7** has been elaborated via 3-*epi*-alloyohimbine (**5**) which is the major product either of the sodium borohydride reduction of **2** or of the catalytic hydrogenation of $\Delta^{15,16}$-dehydroyohimbinone (**11**) in the presence of base[8] (Scheme II).

Synthesis of **1** from **5** by simple base-catalyzed C(16) epimerization could not be performed on a preparative scale as **5**, existing in the epi-allo trans (E_T) conformation, proved to be thermodynamically more stable than **1**, having a diequatorial substitution pattern and at the same time an epi-allo cis (E_{C_2}) skeletal conformation (see ^{13}C NMR studies). Accordingly, **5** predominates in the equilibrium[10b,6] (see Scheme I).

The **5** → **1** transformation, therefore, required an indirect path via the key intermediate **7**. The C(3) epimerization of **5** furnished alloyohimbine (**9**), which could be transformed into the thermodynamically more stable α-yohimbine (**7**) by C(16) epimerization.[6] The combined yield of the two steps was 20%.

The final inversion at the C(3) chiral center of **7** was performed by the oxidation–reduction method[10a] resulting in racemic isorauhimbine (**1**). The physical and spectral (IR, ^{13}C NMR, and mass spectral) properties of the synthetic product were identical with those of the natural product.[10a,6,11]

To complete our work on the synthesis of yohimbine stereoisomers having an epi-allo skeleton, we have prepared the fourth unknown representative, the racemic 3,17-*epi*-α-yohimbine (**3**). **3** was obtained also from the corresponding allo isomer,[7] 17-*epi*-α-yohimbine (**8**) similarly by dehydrogenation with mercury(II) acetate and subsequent reduction with zinc in acetic acid. The stereostructure of **3** has been determined both by chemical and spectroscopic means. The configuration of the C(16) and C(17) substituents has been verified by C(16) epimerization of **3** in methanolic 2 N sodium methoxide, resulting in **4** as synthesized earlier.[6] The IR spectrum **3** exhibits no Bohlmann band, suggesting a cis C/D ring junction. This conclusion is supported by the characteristic chemical shift values for C(2), C(5), C(6), and C(21) in the ^{13}C NMR spectrum of **3** (see Table I). The axial orientation of the C(17) hydroxyl reflects in the chemical shifts of C(19) and C(14), effected by the γ-gauche and δ syn-diaxial steric interactions, respectively. These values are shifted upfield

* To whom correspondence should be addressed at the Central Research Institute for Chemistry.

† For part 3 see ref 8.

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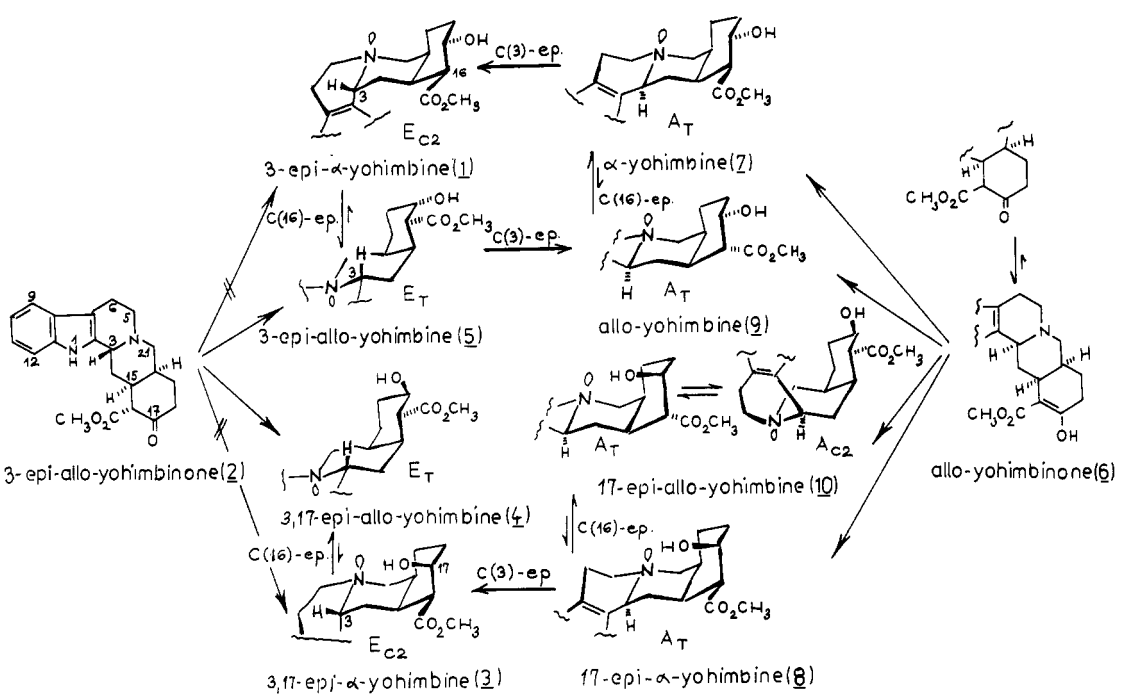
Table I. ^{13}C NMR Chemical Shifts of Yohimbine Stereoisomers[a]

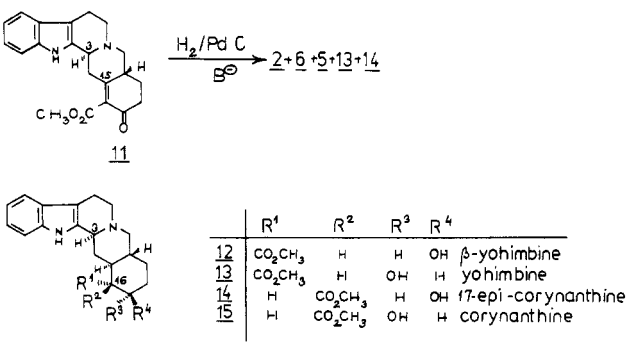
	7[b]	8[b]	9[b]	10[b,f]	1[c]	3[d]	4[d]	5[d]	12[b]	13[b]	14[b]	15[e]
C(2)	134.3	135.2	134.4	134.4	131.7	133.4	135.1	134.5	134.0	134.3	134.7	135.8
C(3)	60.1	61.6	60.1	56.9	53.7	54.4	54.4	54.3	59.0	59.8	59.9	60.5
C(5)	53.2	53.5	52.8	52.7	50.8	51.4	53.3	53.3	52.3	52.1	52.8	52.6
C(6)	21.7	21.9	21.3	19.6	16.5	17.0	21.7	21.6	21.3	21.5	21.7	21.6
C(7)	108.1	108.3	107.1	107.9	107.3	107.2	107.1	108.6	107.4	107.5	107.8	106.3
C(8)	127.1	127.6	126.8	127.8	127.2	127.7	127.1	127.6	126.9	127.0	127.3	127.0
C(9)	117.9	118.1	117.5	118.0	117.6	117.7	117.6	118.1	117.7	117.7	118.2	117.5
C(10)	119.1	119.3	118.6	119.5	118.9	118.8	118.6	119.5	118.8	118.8	119.3	118.4
C(11)	121.1	121.2	120.5	121.4	121.0	120.8	120.6	121.4	120.9	120.8	121.3	120.4
C(12)	110.6	110.8	110.6	111.2	110.8	111.1	111.0	110.8	110.7	110.6	111.0	111.1
C(13)	135.7	136.1	135.8	136.3	135.6	135.9	136.3	136.1	135.8	135.8	136.2	136.1
C(14)	27.6	29.4	31.0	30.2	23.6	25.9	32.5	32.7	33.8	33.8	33.9	33.6
C(15)	37.9	37.6	37.4	35.3	32.5	31.4	36.2	30.0	41.6	36.4	41.6	34.7
C(16)	54.6	49.8	50.6	51.8	54.1	49.4	50.6	45.2	57.1	52.6	51.7	51.1
C(17)	66.0	65.8	66.7	69.4	65.7	65.9	72.1	67.1	71.6	66.9	71.0	65.9
C(18)	33.2	31.9	30.2	31.1	33.5	31.9	30.3	27.3	33.5	31.4	29.5	28.2
C(19)	24.5	20.6	24.8	23.7	23.9	20.1	27.2	22.5	27.5	23.1	28.3	23.5
C(20)	36.4	36.9	32.0	33.5	35.6	36.7	33.6	33.9	39.1	40.2	33.9	36.5
C(21)	60.4	60.8	59.6	54.1	49.4	50.9	55.0	54.7	60.5	61.0	61.8	62.0
OMe	51.8	51.9	51.5	52.0	51.7	51.8	51.6	52.0	51.6	51.7	51.4	51.1
C=O	174.4	175.6	174.0	174.8	174.7	175.2	175.2	176.0	175.0	175.1	173.0	172.7

[a] The δ values are in parts per million from internal Me_4Si. Data for **1**, **7**, **9**, **12**, **13**, and **15** are taken from ref 11. [b] In $CDCl_3$ solution. [c] In $CDCl_3$ with a trace of ethanol. [d] In $CDCl_3$ + Me_2SO-d_6 (4:1). [e] In Me_2SO-d_6 solution. [f] Measured at elevated temperature (55 °C).

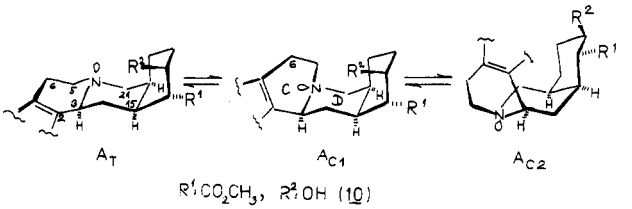
Scheme I



Scheme II



Scheme III



by 3.8 ppm for C(19) and downfield by 2.3 ppm for C(14) compared with the corresponding data of **1** containing the C(17) hydroxyl group in an equatorial position.

^{13}C NMR Studies

It is well-known that yohimbine alkaloids are classified on the basis of the relative configurations of the C(3), C(15), and C(20) chiral centers into four main types: normal, pseudo, allo, and epi-allo. While normal and pseudoyohimbines have rigid ring systems (N_T, P_{C2}), the allo and epi-allo compounds are able to exist in three possible conformers (see Scheme III for an allo compound),

one of them having *trans*- (A_T, E_T) while the other two *cis*-quinolizidine ring conformations (A_{C1}, A_{C2}, E_{C1}, E_{C2}).[12]

One can rely on several physical methods (e.g., IR and ^1H, ^{13}C, and ^{15}N NMR spectroscopies[13-18]) to decide whether the quinolizidine ring conformation of a given isomer is cis or trans. Of all these methods ^{13}C NMR spectroscopy excels, since on the basis of the different chemical shift values of the C(5), C(6), and the C(21) carbon atoms even the two cis conformers can be unequivocally distinguished.[11,15-17]

With hydroxy ester **3** in hand, all the four possible *epi*-alloyohimbine stereoisomers (i.e., **1** and **3–5**) became available. These, together with the racemic normal and allo isomers, synthesized earlier by us, render the set of the yohimbine stereoisomers complete. Carbon-13 NMR has been shown to provide useful information on the conformations of these polycyclic systems. In their pioneering work, Wenkert et al.[11] carried out the ^{13}C NMR analysis of the natural yohimbine stereoisomers. A similar study on isomers with nonnatural substitution pattern is of interest because the new ^{13}C data may further our understanding of factors which affect the conformational properties of the yohimbane skeleton.

The carbon-13 chemical shift data of the synthetic isomers (**3–5**, **8**, **10**, and **14**), together with literature values for the natural products (**1**, **7**, **9**, **12**, **13**, and **15**),[11] are summarized in Table I. The assignment of the spectra was derived by means of standard FT NMR methods (SFORD, SFSD) and was assisted by spectral comparison with mono-, di-, and trisubstituted depyrroloyohimbanes, studied by us[19] in detail.

The orientations of substituents were either known or were assumed on the basis of selective chemical reactions (epimerization, elimination).[6,7] The assumed orientations were corroborated by ^{13}C NMR analysis, taking into account the substituent effects of the methoxycarbonyl and hydroxyl groups. With multiple substitution, the usual substituent shifts of the α- and β-carbon resonances may be considerably modified by substituent–substituent and substituent–skeleton interactions.[19,20] These interactions are, for instance, responsible for the fact that the chemical shifts of C(17) in hydroxy esters with an axial C(17) hydroxyl group (**3** and **8**) are nearly equal to the corresponding values of isomers with an equatorial C(17) OH (**1** and **7**, respectively; see Table I). Thus, information regarding the steric position of ring E substituents were generally inferred from their steric effects on γ-carbon atoms and/or from their δ syn-diaxial interactions[21] with C(14) (isomers **3** and **8**) and C(21) (**14** and **15**).

While ring E carbon resonances are informative on the substitution pattern of yohimbine stereoisomers, the actual conformational state (cis or trans C/D ring junction) of a given isomer can be inferred from the chemical shift values of the ring C and D carbon atoms.

The natural yohimbines of normal type, yohimbine (**13**), corynanthine (**15**), and β-yohimbine (**12**), possess a *trans*-quinolizidine (N_T) conformation.[11] Examination of the shift values for ring C and D carbons reveals that the same also holds for the synthetic 17-*epi*-corynanthine (**14**).

Of the four epi-allo isomers, the natural 3-*epi*-α-yohimbine (**1**) has been shown to occur in a *cis*-quinolizidine conformation (E_{C2}).[11] On the basis of the ^{13}C NMR data in Table I, the same conclusion can be made for the synthetic 3,17-*epi*-α-yohimbine (**3**).

In alkaloids of epi-allo type, the equilibrium between the *trans*- and *cis*-quinolizidine conformations depends on the configuration of the ring E substituents.[22] Di- and trisubstituted natural epi-allo alkaloids (see, e.g., **1** or reserpine) possess *cis*-quinolizidine structures, since in the trans conformation all of their ring E substituents would be constrained to an axial position.[11] In such an arrangement, the substituent at C(16) is expected to exert substantial steric compression through its skew-pentane interactions with the C(14)–C(3) and C(20)–C(21) bonds. In fact, we have found that epi-allo yohimbans (as well as *epi*-depyrroloalloyohimbans)[19] featuring a C(16) substituent in the β configuration occurred always in a predominantly cis form, whereas both α and β configurations for C(17) and C(18) substituents proved to be allowed in either conformation. The role of the configuration of C(16) substituent in determining the preferred conformational state of yohimbine alkaloids is further evidenced by the finding that both synthetic epi-allo isomers **4** and **5**, having the C(16) methoxycarbonyl group in an α orientation, assume a *trans*-quinolizidine (E_T) form. (This follows from the increased chemical shift values for C(2), C(6), C(14), and C(21) relative to those in the cis isomers).

Unlike natural alloyohimbines (**7**, **9**), occurring in the preferred trans (A_T) form,[11] synthetic 17-*epi*-α-yohimbine (**8**) has its C(17) hydroxyl substituent in an axial position. Nevertheless, carbon-13 data attest that the latter molecule also assumes a trans conformation. This suggests that the skew-pentane interaction between the C(17) OH and the C(14)–C(15) bond alone is insufficient to destabilize significantly the A_T form. According to the ^{13}C NMR data, however, destabilization of the allo trans conformation does occur with isomer **10** in which the substitution pattern would require both ring E substituents to assume an axial steric position in the trans form.[7] The carbon-13 spectrum recorded at ambient temperature disclosed substantial line broadenings (up to disappearance of the resonances) for signals due to C(3), C(6), and C(21). The line widths decreased at elevated temperature (55 °C). The data in Table I show that the chemical shift values obtained under fast-exchange conditions for these carbon atoms are considerably lower than those observed with other allo isomers existing in a preferred A_T state. This indicates that the equilibrium mixture contains the cis isomer in significant amounts. Carbon-13 chemical shift data for related synthetic yohimbanes occuring predominantly in the A_{C2}[23] form suggest that the conformational equilibrium observed for isomer **10** corresponds to an $A_T \rightleftharpoons A_{C2}$ transition[24] (see Scheme III).

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(24) Similar conformation behavior has been noted for *epi*-alloakuammigine, a natural heteroyohimbane, the low temperature ^{13}C spectrum of which shows the presence of two conformers.[11]

To the best of our knowledge, except for rauniticine,[25] a heteroyohimboid natural product, no yohimbine alkaloid or synthetic isomers possessing an A_{C2} conformation has been reported as yet in the literature.

Experimental Section

IR spectra were recorded in KBr with a Spectromom 2000 spectrophotometer. Mass spectra were obtained with an AEI MS 902 double-focusing instrument (70 eV, ion source temperature 150 °C, direct insertion). The ^1H and ^{13}C NMR spectra were recorded on a Varian XL-100 Fourier transform spectrometer operating at 100.1 and 25.16 MHz, respectively. Chemical shifts are reported as parts per million (δ) downfield from Me_4Si as an internal standard in both cases. The course of the reactions was checked by qualitative TLC, for which DC-Alufolien Kieselgel 60 F_{254} (Merck) adsorbent was used. The quantitative separation (PLC) was done with Kieselgel 60 $PF_{254+366}$ (Merck) adsorbent. The developing systems used in the experiments are as follows: system A, dichloromethane–methanol (100:10); system B, dichloromethane–methanol (100:16); system C, benzene–methanol (40:10).

(±)-Alloyohimbine (9). 3-*epi*-Alloyohimbine (**5**; 0.17 g, 0.48 mmol) was dissolved in glacial acetic acid (4 mL) and treated with lead tetraacetate (0.42 g, 0.95 mmol) at 50 °C for 10 min. The reaction mixture was evaporated in vacuo, and the residue was diluted with dichloromethane (10 mL), cooled to 0 °C, and treated with an excess of sodium borohydride. The reaction was monitored by TLC (system B; R_f of **9** was greater than that of **5**). After the complete reduction, the solvent was removed, and the residue was basified with aqueous ammonium hydroxide to pH 9 and extracted with dichloromethane (3 × 15 mL). The organic layer was washed with water, dried, and evaporated. The residue was purified by PLC (system B) to supply **9** (80 mg, 47%). The product was in all respects identical with the substance prepared by us earlier in independent ways.[6,7]

(±)-α-Yohimbine (7). Alloyohimbine (**9**; 100 mg, 0.28 mmol) was dissolved in 2 N methanolic sodium methoxide solution (5 mL) and was kept for 4 days at room temperature under a nitrogen atmosphere. The epimerization was followed by TLC (system A, R_f of **7** > R_f of **9**). The reaction mixture was neutralized with glacial acetic acid (0.6 mL) and treated with an excess of etheral diazomethane. After evaporation in vacuo, the residue was taken up in dichloromethane (30 mL) and then basified (pH 9.5) with aqueous ammonium hydroxide. The organic layer after the usual workup, including PLC (system A), gave 42 mg of **7**.[6,7]

(±)-3-*epi*-α-Yohimbine (1). α-Yohimbine (**7**; 24 mg, 0.067 mmol) was dissolved in glacial acetic acid (3 mL) and treated with mercury(II) acetate (85 mg 0.27 mmol) at 60 °C for 2 h. The course of the oxidation was monitored by TLC (system B). The reaction mixture was saturated with hydrogen sulfide gas at 70 °C and then filtered, and the precipitate was washed with warm acetic acid (3 mL). To the vigorously stirred acetic acid solution was added zinc powder (0.15 g) at 120 °C. One hour later the solvent was removed in vacuo, and the residue was diluted with dichloromethane (20 mL) and treated with aqueous ammonium hydroxide at pH 9.5. The organic layer was washed with water, dried, and evaporated. The remaining material was separated by PLC (system B R_f of **7** > R_f of **1**) to give 2 mg of **7** and 5 mg (21%) of racemic 3-*epi*-α-yohimbine (**1**) which upon recrystallization from ethyl acetate afforded colorless needles: mp 229–230 °C; IR 3480 (NH), 1725 (CO_2CH_3), 1060 cm^{-1} (COH); ^{13}C NMR ($CDCl_3$ with trace of ethanol) δ 175.0 (COO), 121.7 (C11), 119.5 (C10), 118.0 (C9), 111.3 (C12), 65.8 (C17), 54.4 (C3, C16), 52.0 (OCH_3), 51.2 (C5), 49.7 (C21), 35.7 (C20), 33.7 (C18), 32.4 (C15), 24.0 (C19), 23.8 (C14), 16.6 (C6); MS, *m/e* (relative intensity) 354 (100, M), 353 (93), 339 (10), 337 (3.2), 336 (1.6), 335 (2.5), 325 (4.4), 323 (6.1), 297 (6.3), 295 (8.7), 219 (11), 188 (3.2), 184 (16), 170 (13), 169 (15).

(±)-3,17-*epi*-α-Yohimbine (3). The above process was repeated by starting from **8**[7] (100 mg, 0.28 mmol) in glacial acetic acid (4 mL) and using mercury(II) acetate (360 mg, 1.1 mmol) for the oxidation. After the reduction with zinc dust (200 mg) in glacial acetic acid (6 mL) at 100 °C for 2 h, the mixture was worked up, including PLC (system C, R_f of **8** > R_f of **3**) to give 30 mg of **8** and 15 mg of **3**: mp 195–200 °C (amorphous substance); IR 3450, 3250 (OH, NH), 1710 (CO_2CH_3), 1080 cm^{-1} (COH); MS, *m/e* (relative intensity) 354 (100, M), 353 (78), 339 (6.7), 337 (3.3), 323 (5.4), 295 (4.6), 278 (1.8), 223 (7.5), 221 (5.4), 184 (11.2), 170 (11.7), 169 (13.5), 156 (10.9), 144 (7.3).

On heating **3** in 2 N methanolic sodium methoxide solution at 70 °C for 2 h, it was completely converted into **4**. (During the epimerization a slight elimination took place.) TLC with system C showed the R_f of **4** to be greater than that of **3**.

TLC Chromatographic Behavior of Hydroxy Esters with the *epi*-Alloyohimban Skeleton. TLC with DC-Alufolien Kieselgel 60 F_{254} and heptane–ethyl methyl ketone–methanol (20:10:3) gave the following compounds in order of decreasing R_f: **5** > **4** > **1** > **3**.

NMR spectra of 3-*epi*-alloyohimbinone (2): ^1H NMR ($CDCl_3$ + Me_2SO-d_6) δ 9.78 (s, 1 H, NH), 7.50–6.98 (m, 4 H, aromatic H), 3.82 (s, 3 H, CO_2CH_3), 3.60 (br m, 1 H, C3 H); ^{13}C NMR ($CDCl_3$ + Me_2SO-d_6) δ 134.91 (C2), 54.16 (C3), 53.67 (C5), 21.50 (C6), 107.03 (C7), 127.01 (C8), 117.39 (C9), 118.37 (C10), 120.39 (C11), 110.96 (C12), 136.33 (C13), 32.65 (C14), 37.07 (C15), 56.85 (C16), 205.94 (C17), 38.20 (C18), 28.50 (C19), 33.25 (C20), 52.87 (C21), 51.70 (OCH_3), 169.67 (COO).

NMR spectra of alloyohimbinone (6): ^1H NMR ($CDCl_3$) δ 12.15 (br s, ~0.8 H, enolic OH), 7.72 (s, 1 H, NH), 7.52–7.05 (m, 4 H, aromatic H), 3.83, 3.78 (2 s, 0.83 and 0.17 H, CO_2CH_3), 3.30 (br m, 1 H, C3 H); ^{13}C NMR ($CDCl_3$ + Me_2SO-d_6) for enolic form δ 134.59 (C2), 60.25 (C3), 53.25 (C5), 21.29 (C6), 106.77 (C7), 126.98 (C8), 117.67 (C9), 118.70 (C10), 120.74 (C11), 111.05 (C12), 136.36 (C13), 29.31 (C14), 32.82 (C15), 101.30 (C16), 173.04 (C17), 32.54 (C18), 22.13 (C19), 33.85 (C20), 60.36 (C21), 51.41 (OCH_3), 172.60 (COO); for keto form δ 61.2 (C16), 205.8 (C17), 40.3 (C18), 52.4 (OCH_3), 169.5 (COO).

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Registry No. (±)-**1**, 83540-86-7; (±)-**2**, 83540-87-8; (±)-**3**, 83540-88-9; (±)-**4**, 40085-30-1; (±)-**5**, 40085-29-8; (±)-**6**, 83476-37-3; (±)-**7**, 40088-25-3; (±)-**8**, 40088-19-5; (±)-**9**, 40085-32-3; (±)-**10**, 40088-20-8; (±)-**14**, 59952-53-3.

(25) See ref 47 in ref 11.