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MODELS OF FOLATE COENZYMES 14[1] AN ALTERNATE APPROACH TO THE YOHIMBANE SKELETON

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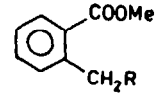
Abstract The anion of dimethyl homophthalate adds to imidazolinium and tetrahydropyrimidinium salts (2a,b) to yield imidazolidine and tetrahydropyrimidine adducts corresponding to methylenetetrahydrofolate models (3a,b) These models transfer the carbon fragment 2-(MeOOC)C_6H_4CH(COOMe)CH< to tryptamine to give an enamino ester intermediate which is cyclized, in two steps to the yohimboid skeleton

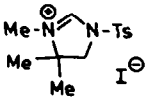
Our continued interest in the synthetic applications of models of methylenetetrahydrofolate (5,10-CH_2-THF) coenzyme has led us to consider facile routes to heterocyclic systems related to various classes of indole and isoquinoline alkaloids [3,4,5] In this connection we recently demonstrated that models derived from substituted benzaldehydes, as starting materials, provided a one-pot convenient synthesis of the 5-ring skeleton corresponding to yohimbane derivatives [5a] Since benzaldehydes, with desired substituents, are not always accessible with facility, we have turned our attention to other aryl derivatives from which "equivalent" 5,10-CHR-THF models can be derived In this paper we report the synthesis of models prepared from homophthalate ester and their utilization in the construction of the yohimbane skeleton Preliminary results of a part of this work have been communicated earlier [6]

In an orientation study, attempts were made to add the anion of 1a to salts 2a,b, to obtain adducts corresponding to folate models of type 3 (Scheme A) These, however, proved to be unsuccessful in our hands Presumably, delocalization of the negative charge over the benzoate moiety suppresses the nucleophilic character of the methylene anion In view of this, it was rationalized that introduction of an electron withdrawing group in the side chain methylene (CH_2R) might help to increase the nucleophilicity of the desired anion This expectation was borne out by reactions of the anion of homophthalate ester (1b) with salts 2a,b, whereupon, 3a,b were obtained as crystalline or amorphous products in good yields It was recognized that both 3a and 3b represent mixtures of diastereomers The structure of one of the diastereomers of 3a, m.p. 138-139°C, has been established as αR,2R by X-ray crystallography [7] In case of 3b, the formation of only one diastereomer was observed While its gross structure was attested by its spectral data (vide experimental), the stereochemistry of 3b has not been established.

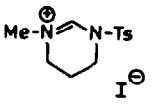
In the aforementioned reactions, varying amounts of enamine esters 4a,b were formed during the isolation of 3a,b The E-configuration of 4a and 4b is based upon Nuclear overhauser difference spectra, in both compounds the signals for the aromatic C(6) protons were enhanced upon irradiation of the relavent N-methyl groups The transfer of C(2)-fragment of 3a,b to tryptamine can be achieved by reacting either pure 3a or 3b or mixtures of 3a + 4a or 3b + 4b, with that amine, in the presence of acetic acid In all cases an isomeric mixture of 5 (E/Z ≈ 3/7) was obtained in



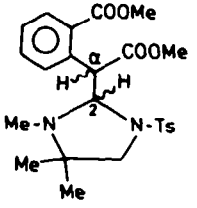
1a R = H
1b R = COOMe



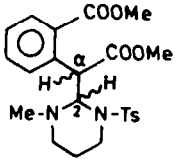
2a



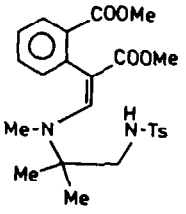
2b



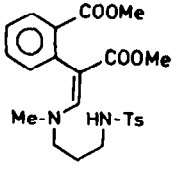
3a



3b

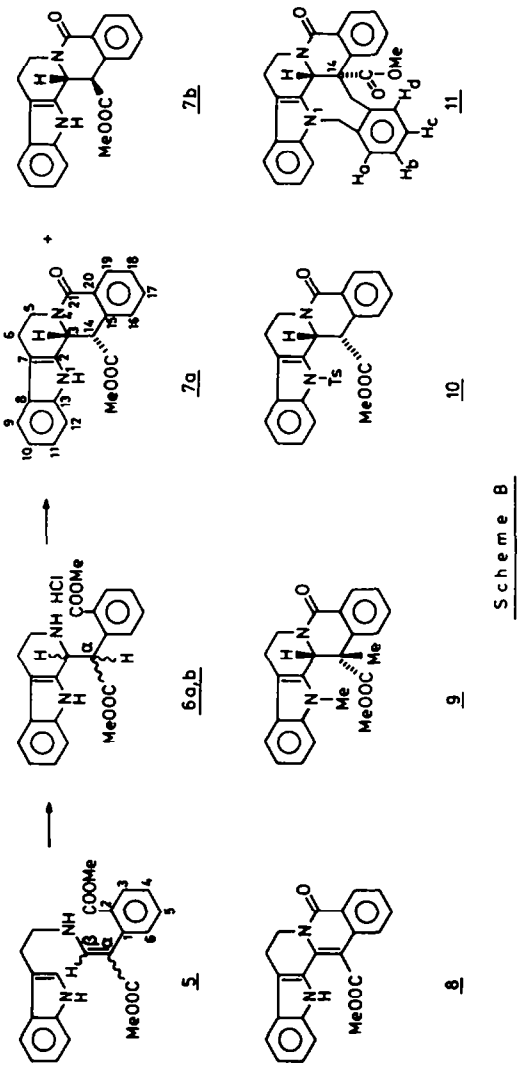


4a



4b

Scheme A



Scheme 8

yields varying from 60-90% It should be noted that 5 (Scheme B) contains all the atoms and suitable functional groups which are required for construction of the yohimbane skeleton In a previous communication[4] we have described the synthesis of the indoloquinolizidine skeleton employing the cyclization sequence AB → ABD → ABCD, starting out from an indole derivative
In the case of yohimbane skeleton, the preferred strategy - starting with "transfer product" 5 - followed the pathway AB → ABC → ABCDE Acid catalyzed cyclization of 5 (mixture) resulted in a diastereomic mixture of 6a and 6b in the ratio of 4 1, respectively. While the individual diastereomers could be recognized via the NMR spectra (vide experimental) of the mixture, the diastereomers have not been isolated in the pure state and their stereochemical assignments are not available at present The mixture of 6a and 6b was subsequently treated with triethylamine/acetic acid at room temperature, whereupon crystalline pentacyclic products 7a and 7b (7a m p 237°C dec , 7b m p 222°C dec , 7a/7b = 4/1 were formed in excellent yield The overall yield of the last two steps was 80% The stereochemistry of the predominant isomer 7a was established by Nuclear Overhauser difference spectroscopy Irradiation of C(14)-H results in positive signals for C(3), indole N-H and C(16)-H When the cyclization was carried out at higher temperature (~50°C), variable amounts of the pyridone 8 were found in the reaction mixture This reveals the sensitivity of 7a,b to oxidation

The facile access to 7a,b stimulated attempts to construct an additional ring between N(1) and C(14) Such a sequence could serve as a model study for the synthesis of the Eburnan or Vincan skeletons [7] Alkylation of 7a with excess of methyl iodide yielded, significantly, only one product (80%), whose structure and the assigned stereochemistry (9) is based on NMR spectral data Characteristic for the cis relationship between C(3)-H and C(14)-CH_3 was the enhancement of C(3)-H signal upon irradiation of C(14)-CH_3 Attempts to specifically alkylate C(14) with an acetate residue proved unsuccessful While 7a could be tosylated at N(1), the resulting amide 10 was inert to base-catalyzed alkylation with α-bromoacetate, at C(14) Models of 10 show that approach of a bulky electrophile at the C(14)-centre encounters considerable steric hindrance Reaction of 7a with bisalkylating agents has also been examined No reaction was, however, observed between the dianion of 7a and 1,2-dibromoethane It appears that a base-catalyzed dehydrohalogenation dominates this reaction To avoid this process, the same dianion was allowed to react with 1,2-(dibromomethyl)benzene In the latter case a crystalline product was obtained whose spectral data attests to the novel polycyclic compound 11

EXPERIMENTAL

All mps are uncorrected IR spectra were recorded on a Perkin Elmer 257 spectrometer The absorptions are given in cm^{-1} PMR spectra were run on a Bruker WM 250 instrument, using TMS as an internal standard Mass spectra were obtained with a Varian Matt 711 spectrometer Analyses were carried out at the microanalytical laboratory, Department of Physical Organic and Analytical Chemistry, Organic Chemistry institute, TNO, Zeist, The Netherlands THF was distilled from $LiAlH_4$ before use

Methyl 2(methoxycarbonyl)-α-[2-(1-tosyl-3,4,4-trimethyl)imidazolidinyl]-1-phenylacetate (3a) and 2-methoxycarbonyl-α-(methoxycarbonyl)-β-[2-(tosylamino-1,1-dimethyl]aminostyrene (4a)
To a solution 10 mmol LDA (lithiumdiisopropylamine) in 150 ml THF was added 2 08 g (10 mmol) of the homophtalic ester 1b dissolved in 5 ml/THF (-78°C, nitrogen) After an additional stirring for 20 min 3 94 g of 2a (10 mmol) was added to the reaction mixture The reaction mixture was vigorously stirred for 1 hr at -40°C and 2 hr at 0°C After evaporation of the solvent and chromatography on SiO_2/EtOAc two products could be recognized in the PMR spectrum a diastereomeric pair of compound 3a and some unreacted ester 1b The major diastereomer could be crystallized from MeOH (R,R) The resulting mixture contained besides the diastereomers of 3a some ring opened eneamine ester 4a The minor diastereomer of 3a could not be isolated as a pure material because of the strong tendency for this diastereomer to give the ring opened eneamine ester 4a Isolation of 4a from this mixture on SiO_2 using a gradient EtOAc/hexane (1 10) → (1 1) In neutral solutions (CH_2Cl_2, toluene) a mixture of 3a and 4a can be achieved at elevated temperatures
3a (R,R) + (S,S) Yield 1 85 g (39%), m p 138-139°C (from methanol) IR($CHCl_3$) 1735 (s), 1715 (s), 1599 (w), 1490 (w), 1365 (m), 1350 (s), 1260 (s), 1160 (vs) PMR($CDCl_3$) 3 0 21, 0 70 (2xs, 6H, 2xC^4CH_3), 1 85, 3 03 (ABq, J=11 1 Hz, 2H, C^5H_2), 2 10 (s, 3H, N-CH_3), 2 40 (s, 3H, $TOSCH_3$), 3 79, 3 82 (2xs, 6H, 2x$COOCH_3$), 4 85 (d, J=1 5 Hz, 1H, $C^{\alpha}H$), 5 32 (d, J=1 5 Hz, 1H, C^2H), 7 31 - 7 25 (m, 4H, $TOSC^3H$, $TOSC^5H$ and ArC^4H or ArC^5H), 7 48 (t, J=7 8 Hz, 1H, ArC^4H or ArC^5H), 7 65 (d, J=7 5 Hz, 1H, ArC^6H), 7 67 (d, J=8 2 Hz, 2H, $TOSC^2H$, $TOSC^6H$), 7 94 (d, J=7.3 Hz, 1H, ArC^3H) Irradiation of C^2H results in a positive NOE for $C^{\alpha}H$ and one of the C-CH_3 group at δ 0 70 In the mixture of the diastereomers of 3a some salients chemical shifts of the minor diastereomer were ($CDCl_3$, 250 MHz) 0 27 (s, 3H, C^4CH_3), 0 72 (s, 3H, C-CH_3), 4 92 (d, J=3 2 Hz, 1H, $C^{\alpha}H$), 5 28 (d, J=3 2 Hz, 1H, C^2H) MS Found 474 1824. Calc for $C_{24}H_{30}N_2O_6S_1$ = 474 1823 Found C, 60 55,

N, 5.84, H, 6.50, S, 6.65. Calc. for C, 60 75, N, 5 90, H, 6 32, S, 6.75.
4a Yield 400 mg (8.4%), isolated from the reaction mixture of 3a as white crystals, m.p. 135 - 136°C from EtOAc/hexane. IR($CHCl_3$) 3268 (s), 1715 (s), 1608 (s), 1597 (s), 1584 (vs), 1430 (m), 1380 (m), 1330 (m), 1160 (s). PMR(CD_3CN): 1.21, 1.25 (2xs, 6H, $C(CH_3)_2$), 2.16 (s, 3H, N-CH_3), 2.36 (s, 3H, TOSCH_3), 2.9-2.7 (m, 2H, CH_2NHTOS), 3.44 (s, 3H, $C^{\alpha}COOCH_3$), 3.73 (s, 3H, $C^{2}COOCH_3$), 5.08 (bt, 1H, NH), 7.18 (d, J=7,6 Hz, 1H, ArC^{6}H), 7.43-7.24 (m, 4H, TOSC^{3}H, TOSC^{5}H, ArC^{5}H and ArC^{4}H), 7 71-7.66 (m, 3H, TOSC^{2}H, TOSC^{6}H, ArC^{3}H), 7.75 (s, 1H, C=CH). Irradiation of N-CH_3 results in a positive NOE for ArC^{6}H at δ 7 18. Further, positive NOE for C-CH_3 and a small positive effect on C^{β}H, which is a result of rotation around the N-C^{β} bond MS Found 474 1824. Calc. for $C_{24}H_{30}N_2O_6S_1$= 474.1823

Methyl 2(methoxycarbonyl)-α-[2-(1-tosyl-3-methyl)-pyrimidinyl]-1-phenylacetate (3b) and 2-methoxycarbonyl-α-(methoxycarbonyl-β-(3-tosylaminopropylmethyl)aminostyrene (4b)

Procedure was identical with that of 3a. After column chromatography (SiO_2 EtOAc/hexane 1.10, to remove unreacted ester (1b), a mixture consisting of 3b and 4b was isolated. In the PMR of the crude reaction product only one diastereomer of 3b and a large amount of ring-opened eneamine ester 4b could be recognized. Yield 70-80%. Eneamine ester 4b was obtained by chromatography on SiO_2 EtOAc/hexane (1 1). When the reaction mixture was allowed to stand for 18 hr in CH_2Cl_2 at 20°C 3b gave a quantitative yield of ring-opened eneamine ester 4b. Crystallization of 3b from the reaction mixture (after chromatography) gave white crystals, m.p. 135-136°C (from MeOH). IR($CHCl_3$) 1730 (s), 1715 (s), 1330 (m), 1160 (s). PMR(CD_3CN) 1.08-1.00, 2.69-2.62 (2xm, 2H, $C^{5}H_2$), 2.26 (s, 3H, N-CH_3), 2.50 (s, 3H, TOSCH_3), 3.17-3.12, 3.41-3.29 (2xm, 4H, $C^{4}H_2$, $C^{6}H_2$), 3.55, 3.78 (2xs, 6H, 2x $COOCH_3$), 5.36 (d, J=11.3 Hz, 1H, C^{α}H), 5.86 (d, J=11.3 Hz, 1H, C^{2}H), 6.78 (d, J=8 Hz, 2H, TOSC^{3}H and TOSC^{5}H), 7.10 (d, J=8 Hz, 2H, TOSC^{2}H and TOSC^{6}H), 7 38 (t, J=7.6 Hz, 1H, ArC^{4}H), 7.52 (t, J=7 8 Hz, 1H, ArC^{5}H), 7.75 (d, J=7.8 Hz, 1H, ArC^{6}H), 7 84 (d, J=7 9 Hz, 1H, ArC^{3}H) MS Found· 460.1687 Calc for $C_{23}H_{28}N_2O_6S_1$= 460 1667

4b Recrystallized from EtOAc/hexane, m.p. 103°C. IR($CHCl_3$) 3400-3320 (w), 3320-3120 (w), 1721 (s), 1678 (s), 1616 (s), 1595 (s), 1494 (w), 1330 (m), 1160 (s). PMR(CD_3CN)· 1.60, 1.50 (m, 2H, $CH_2CH_2CH_2$), 2.29 (s, 3H, N-CH_3), 2.35 (s, 3H, TOSCH_3), 2.66 (dt, J=6.8 Hz, J=7.5 Hz, 2H, CH_2NH-TOS), 3.08-2.99 (m, 2H, MeN-CH_2), 3.43, 3.68 (2xs, 6H, 2x$COOCH_3$), 5.49 (bt, 1H, NH) 7.01 (d, J= 7 5 Hz, 1H, ArC^{6}H), 7.26 (d, J=7.5 Hz, 1H, ArC^{4}H), 7.32 (d, J=8.2 Hz, 2H, TOSC^{3}H and TOSC^{5}H), 7.37 (t, J=7.5 Hz, 1H, ArC^{5}H), 7.39 (s, 1H, C=CH), 7.65 (d, J=8 2 Hz, TOSC^{2}H and TOSC^{6}H), 7 69 (d, J= 7 5 Hz, 1H, ArC^{3}H) Irradiation of CH_3-N-CH_2 results in a positive NOE for ArC^{6}H MS Found 460 1687 Calc. for $C_{23}H_{28}N_2O_6S_1$= 460.1667

EI 70 eV (m/e (%)) 460 (2,5), 429 (3,5), 262 (44), 253 (6,4), 230 (26,4), 212 (37), 177 (36,4), 176 (100), 148 (82,1), 91 (88,7). (4b)
EI 70 eV (m/e (%)) 472 (2,2), 267 (11,4), 176 (40,6), 149 (43,3), 148 (51,9), 133 (46,2), 105 (12,6), 97 (23,7), 91 (100). (4a)

2-Methoxycarbonyl-α-(methoxycarbonyl)-β-(tryptaminyl)styrene (Z/E (5)

From 3a + 4a a mixture of 3a (1 mmol, 474 mg) or 3a + 4a with a large excess of tryptamine (1.6 g, 10 mmol) was refluxed in acetonitrile (5 ml) and acetic acid (0.5 ml) After 1.5 hr the solvent was evaporated and the residue was chromatographed on SiO_2(EtOAc/hexane 1 10 → 1 2) Yield 240 mg (64%). According to PMR the mixture consisted of three products: Z and E conformers of the eneamine ester (5) and a small amount of the pyridone formed by intramolecular aminolysis of 5.
From 3b + 4b a mixture of 3b (1 mmol. 460 mg) or 3b + 4b with 320 mg tryptamine (2 mmol) in 5 ml acetonitrile containing 0.5 ml acetic acid was kept at 70°C for 2 hr (under nitrogen). (TLC EtOAc/hexane 1 2). After evaporation of the solvent and chromatography (SiO_2/EtOAc/hexane 1.10 → 1.2) the mixture consisted of the Z and E conformer (2 1). Yield 90% contaminated with 9% of the aforementioned pyridone
5 Yellow foam, IR($CHCl_3$) 3480 (s), 3420-3300 (w), 1730 (s), 1720 (s), 1674 (s), 1642 (s), 1612 (s), 1490 (w), 1452 (s), 1440 (s), 1370 (m) PMR(C_6D_6) 2.37 (t, J=6.6 Hz, 2H, $NHCH_2CH_2$,E), 2.57 (t, J=6.6 Hz, 2H, $NHCH_2CH_2$,Z), 2.70 (dt, J=6.4 Hz, J=6.5 Hz, 2H, $NHCH_2$,E), 2.88 (dt, J=6.4 Hz, J=6.5 Hz, 2H, $NHCH_2$,Z), 3.54, 3.52, 3.44 (3xs, 6H, $COOCH_3$,E and Z), 4.17-4.09 (m, 1H, NH,E), 6.35 (d, J=13.1 Hz, 1H, C^{β}H,Z), 6.6 (d, J=2.3 Hz, 1H, indole C^{4}H), 6.79 (d, J=7.6 Hz, 1H, C^{5}H), 6.92-7 45 (m, 1H, indole protons + indole N-H + C^{4}H and C^{5}H), 7.70 (d, J=13.5 Hz, 1H, C^{β}H,E), 7.93 (d, J=7.6 Hz, 1H, C^{3}H,Z) 8.01 (d, J=7,6 Hz, 1H, C^{3}H,E), 8.55-8 45 (m, 1H, NH-CH_2,Z) Double resonance was used for the assignment of C^{β}H, NH-CH_2CH_2, NH-CH_2CH_2 and NH-CH_2 MS Found 378 1599. Calc. for $C_{22}H_{22}N_2O_4$= 378 1579

Methyl-α-[1-(1,2,3,4-tetrahydro-β-carbonyl)]-2-methoxycarbonyl-1-phenylacetate. HCl salt (6a, 6b)

The diester 5 1 g (2.64 mmol) was dissolved in 25 ml of dry MeOH. To the solution was added 2.5 ml of a concentrated Et_2O/HCl soln. After 15 min at 20°C the solvent was evaporated under reduced pressure. The resulting brown crystals were recrystallized from EtOAc/Et_2O.
6a,b Yield 986 mg (90%) white crystals, m p. 140-170°C (diastereomeric mixture) IR($CHCl_3$): 3460 (m), 3455 (m), 2800-2250 (w), 1728 (s), 1720 (s), 1600 (w), 1580 (w), 1450 (m), 1436 (m), 1265 (s). PMR($CDCl_3$/NaOD/D_2O) 271-2 64 (m, 2H, NH-CH_2CH_2), 3 23-2 93 (m, 2H, NH-CH_2CH_2), 3 63, 3 69 (2xs, 6H, 2x$COOCH_3$), 4 72 (d, J=7 6 Hz, 1H, NH-CH_a), 4.79 (d, J=9.6 Hz, NH-CH_a), a/b· 4/1, 5.23 (d, J=9.6 Hz, 1H, $C^{\alpha}H_b$), 5.44 (d, J=7.6 Hz, 1H, $C^{\alpha}H_a$), 7.92-6.98 (m, 8H, aromatic protons). FD (m/e) 379 (MH^+).

14-(Methoxycarbonyl-21-oxo-Δ15,17,19-Yohimbane (7a, 7b)

To a suspension of 1 g (2.41 mmol) of 6a,6b in 30 ml dry benzene was added 0.25 ml triethylamine and 1 ml acetic acid. The reaction mixture was stirred for 18 hr at 20°C under nitrogen. After evaporation of the solvent and chromatography on SiO_2(EtOAc) a mixture of 7a,7b was obtained as light yellow crystals Yield 710 mg (85%) According to the PMR the ratio of 7a/7b was 4 1 From this mixture of 7a/7b, 7a could be recrystallized from MeOH. The resulting mother liquid contained predominantly 7b, a small amount of 7a and 8. The aromatic pyridone 8 is a result of oxidation during the purification. When solutions of 7a/b were allowed to stand at 20°C for several days,

a large amount of oxidation product 8 could be obtained.

7a: m.p 237° dec. (from MeOH). IR($CHCl_3$) 3465 (m), 1728 (s), 1642 (s), 1600 (w), 1585 (w), 1488 (w), 1460 (m), 1410 (m), 1305 (s), 1165 (s). PMR(DMSO-d_6) 2 72-2 65 (m, 1H, C^6H), 3.04-2.87 (m, 2H, C^6H and C^5H_{ax}), 3 19 (s, 3H, $COOCH_3$), 4.66 (d, J=4 1 Hz, 1H, $C^{14}H$), 5 01-4.94 (m, 1H, C^6H_{eq}), 5.45-5.43 (m, 1H, C^3H), 7 02 (t, J=7.2 Hz, $C^{10}H$), 7.10 (t, J=7,9 Hz, 1H, $C^{11}H$), 7 63-7 39 (m, 4H, C^9H, $C^{12}H$, $C^{17}H$, $C^{18}H$), 7.49 (d, J=8.2 Hz, 1H, $C^{16}H$), 8 04 (d, J=7.5 Hz, 1H, $C^{19}H$), 11.14 (bs, 1H, N-H. Double resonance result: Irradiation of C^6H (2 72-2 65) gives a doublet J=4 1 Hz for C^3H (loss of homoallylic coupling). Irradiation of $C^{14}H$ results in a positive NOE for C^3H, $C^{16}H$ and N^1H MS Found 346 1312 Calc for $C_{21}H_{18}N_2O_3$= 346 1317

7b: m p 220-222° dec , recrystallized from Et_2O/hexane after column chromatography (on SiO_2/EtOAc/hexane 1 5 → 1 1) of the mother liquid IR($CHCl_3$) 3458 (s), 1729 (s), 1643 (s), 1600 (m), 1580 (m), 1460 (s), 1411 (s), 1300 (s), 1165 (s). PMR(CD_3CN): 3.06-2.79 (3H, 2H, C^6H_{eq}, C^6H_{ax}, C^5H_{ax}), 3.86 (s, 3H, $COOCH_3$), 4.25 (d, J=7.9 Hz, 1H, $C^{14}H$), 5.02-4.94 (m, 1H, C^5H_{eq}), 5.44-5.39 (m, 1H, C^3H), 7.01 (t, J=7.9 Hz, 1H, $C^{10}H$), 7.09 (t, J=7.9 Hz, 1H, $C^{11}H$), 7.22 (d, J=7.6 Hz, 1H, $C^{16}H$), 7.53-7 34 (m, 4H, C^9H, $C^{12}H$, $C^{17}H$ and $C^{18}H$), 8.02 (d, J=7.7 Hz, 1H, $C^{19}H$), 8.71 (bs, 1H, N^1H). MS Found 346.1312 Calc. for $C_{21}H_{18}N_2O_3$= 346.1317

14-(Methoxycarbonyl)-21-oxo-3,14-dehydro-Δ15,17,19-Yohimbane (8)

After column chromatography on SiO_2 (EtOAc/hexane 1.5 → 1 1) of the mother liquid of 7a/7b, m p. 233-235°C (from EtOAc/hexane) Yellow crystals. IR($CHCl_3$) 3430 (m), 1714 (s), 1648 (s), 1609 (s), 1598 (s), 1588 (s), 1563 (m), 1488 (s), 1342 (s), 1314 (s). PMR(DMSO-d_6, 250 MHz) 3.19-3.08 (m, 2H, C^6H), 3.98 (s, 3H, $COOCH_3$), 4 41-4.36 (m, 2H, C^5H), 7.12 (t, J=7.5 Hz, 1H, $C^{10}H$), 7.26 (t, J=7 5 Hz, 1H, $C^{11}H$), 7 83-7.54 (m, 5H, $C^{16}H$, $C^{17}H$, $C^{18}H$, C^9H and $C^{12}H$), 8.33 (d, J=7.9 Hz, 1H, $C^{19}H$), 10 46 (bs, 1H, N^1H) MS FD (m/e): 344 (M^+).

14-(Methoxycarbonyl)-14-methyl-1-methyl-21-oxo-Δ15,17,19-Yohimbane (9)

To a stirred solution of 100 mg (0 289 mmol) of 7a/7b was added 2 25 eq NaH and 2 5 eq freshly distilled CH_3J (102 mg 0.722 mmol). Temperature was slowly raised from -78°C to 5°C in 18 hr under nitrogen The resulting mixture was brought in a concentrated NH_4Cl/H_2O soln extracted with Et_2O and the organic layer treated with $NaCl/H_2O$ soln. After drying over Na_2SO_4 and evaporation of the solvent, the crude product was chromatographed on SiO_2 (EtOAc/hexane 1 4). Yield 86.5 mg (80%), m.p. 251-253°C (from MeOH) IR($CHCl_3$) 1731 (s), 1645 (s), 1602 (m), 1581 (w), 1465 (m), 1410 (m). PMR (DMSO-d_6, 250 MHz): 3,01-2 74 (m, 3H), C^6H_{eq} C^6H_{ax} and C^5H_{ax}), 3.38 (s, 3H, $COOCH_3$), 2.10 (s, 3H, N^1CH_3), 3.69 (s, 3H, $C^{14}CH_3$), 4 79-4 71 (m, 1H, C^5H_{eq}), 5 45 (bs, 1H, C^3H), 7 11 (t, J=7.9 Hz, 1H, $C^{10}H$), 7.23 (t, J=8 1 Hz, 1H, $C^{11}H$), 7 47 (d, J=8.1 Hz, 1H, $C^{16}H$), 7.63-7.45 (m, 4H, $C^{17}H$, $C^{18}H$, C^9H and $C^{12}H$), 8 02 (d, J=7.5 Hz, 1H, $C^{19}H$) MS Found 374 1632 Calc for $C_{23}H_{22}O_3N_2$= 374 1630 Irradiation of $C^{14}CH_3$ at δ 3.69 results in a positive NOE for C^3H at δ 5.45 and $C^{16}H$ at δ 7 47. It should be mentioned that the signal for C^{14}-CH_3 appears at low field due to deshielding by the aromatic ring and the ester carbonyl, whose conformational mobility is restricted

14-(Methoxycarbonyl)-1-(Tosyl)-21-oxo-Δ15,17,19-Yohimbane (10)

To a stirred solution of 120 mg of 7a/7b (0 346 mmol) was added 1.05 eq NaH and 1 eq p-toluene-sulfonylchloride (66.12 mg) The temperature was slowly raised from -78°C to 5°C in 18 hr, under nitrogen. (TLC EtOAc/hexane 2 3 gives 4 products). After evaporation of the solvent and chromatography on SiO_2 (EtOAc/hexane 1 4), two oily products were collected. The first product (22.13 mg) was a very unstable product. According to the IR spectrum this product was the C^{14}-tosylated product. IR($CHCl_3$) 3470 (s), 1755 (s), 1655 (s), 1645 (s), 1460 (s), 1310 (s), 1160 (m). The second oily product (83.7 mg) could be crystallized from EtOAc/hexane giving 54 6 mg (31.5%) of the N^1-tosylated product (10), m.p. 108° dec. IR($CHCl_3$) 1735 (s), 1642 (s), 1602 (w), 1582 (w), 1460 (m), 1370 (s), 1305 (m), 1170 (vs), 810 (w). PMR(DMSO-d_6 2.26 (s, 3H, $ArCH_3$), 3.0-2.84 (3H + H_2O, m, C^6H_{eq}, C^6H_{ax} and C^5H_{ax}), 3 15 (s, 3H, $COOCH_3$), 4.78 (d, J=3 5 Hz, 1H, $C^{14}H$), 4.98-4.90 (m, 1H, C^5H_{eq}), 5 92 (m, 1H, C^3H), 7.23 (d, J=8 4 Hz, 2H, TOS-C^3H, C^5H), 7 44-7.27 (m, 2H, $C^{10}H$ and $C^{11}H$), 7.61-7.50 (m, 4H, $C^{12}H$, $C^{17}H$, $C^{18}H$ and $C^{16}H$), 7 74 (d, J=8 4 Hz, 2H, TOS-C^2H, C^6H), 8.10-8.03 (m, 2H, C^9H and $C^{19}H$). Irradiation of $C^{14}H$ resulting in a positive NOE for C^3H and $C^{16}H$. MS Found: 500.1405. Calc. for $C_{28}H_{24}N_2O_5S_1$= 500 1405. EI 70 eV (m/e. (%)) 500 (71,7), 4.98 (24,6), 441 (18,9), 440 (13,4), 346 (100), 345 (100), 344 (100), 324 (100), 286 (43,7), 285 (64,1), 256 (16,6), 176 (46,6), 170 (30,8), 169 (100), 148 (41,3), 142 (23,8), 133 (44,3), 115(13), 108 (14,3), 94 (36,8), 91 (28,4) Attempts to alkylate C^{14} with methyl-bromo-acetate proved unsuccessfull After work-up the mixture consisted predominantly of starting material (10)

14-(Methoxycarbonyl)-1,14-(O-xylyl)-21-oxo-Δ15,17,19-Yohimbane (11)

To a stirred solution of 100 mg (0.288 mmol) of 7a in 20 ml THF was added 0.59 mmol NaH and 0.288 mmol of α,α-dibromo-ortho-xylene (mw 263.97; m.p. 92-94°C). The resulting mixture was stirred at 0°C for 2 hr (under nitrogen). After an additional stirring for 6 hr at 20°C all starting material had disappeared (TLC EtOAc/hexane/CH_2Cl_2 1.3 0 5). A concentrated NH_4Cl/H_2O soln was added to the mixture, followed by CH_2Cl_2 extraction and $NaHCO_3/H_2O$, $NaCl/H_2O$ treatment. Drying over Na_2SO_4 followed by evaporation of the solvent and chromatography on SiO_2 (EtOAc/hexane 1 1) gave yellow crystals which were recrystallized from EtOAc/hexane. Yield 98 mg (75.9%), m.p. 295° dec. white crystals. IR($CHCl_3$): 1729 (s), 1642 (s), 1600 (m), 1578 (m), 1458 (s), 1418 (s) PMR($CDCl_3$, 250 MHz) 2 96-2 64 (m, 3H, C^6H_{eq}, C^6H_{ax}, C^5H_{ax}), 3 94 (d, J=14 7 Hz, 1H, $C^{14}CH$), 4.02 (d, J=14 7 Hz, 1H, $C^{14}CH$), 4.75 (bs, 1H, C^3H), 5.02-4.96 (m, 1H, C^5H_{eq}), 5.19 (d, J=13.7 Hz, 1H, N^1CH), 5.65 (d, J=13,7 Hz, 1H, N^1CH), 6.88 (d, J=7.5 Hz, 1H, CHd), 7.68-7.05 (m, 9H, C^9H, $C^{10}H$, $C^{11}H$ $C^{12}H$, $C^{17}H$, $C^{18}H$ + Ha, Hb, Hc), 7.79 (d, J=7.9 Hz, 1H, $C^{16}H$), 8.21 (d, J=6 4 Hz, 1H, $C^{19}H$). Irradiation of the A/B system of the $C^{14}CH_2$ protons results in a positive NOE for C^3H, $C^{16}H$, CHd and one of the N^1CH protons EI 70 eV (m/e (%)) 448 (100), 433 (6,3), 389 (38,4), 390 (11,9), 344 (9), 59 (15) MS Found 448 1780. Calc. for $C_{29}H_{24}N_2O_3$= 448 1786.

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