Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 233–238

TETRAHEDRON: *ASYMMETRY*

Study of chiral β-enaminones prepared from pyrrolidine, cytisine, salsoline and 2-amino-1-(4-nitrophenyl)propane-1,3-diol: resolution of salsoline via diastereomeric modified carane-type β-enaminones

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Received 24 October 2002; revised 5 November 2002; accepted 13 November 2002

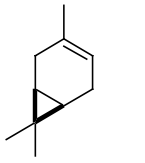
Abstract—A series of novel optically active β-enaminones have been prepared regio- and stereoselectively from primary and secondary amines (pyrrolidine, cytisine salsoline and 2-amino-1-(4-nitrophenyl)propane-1,3-diol) and (+)-3-carene-derived β-chlorovinylketone. Resolution of the isoquinoline alkaloid salsoline has been demonstrated as well as isolation of a single diastereomeric adduct from racemic 2-amino-1-(4-nitrophenyl)propane-1,3-diol.

1. Introduction

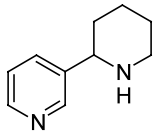
β-Enaminones are well established as versatile synthetic intermediates and their application as chelating ligands is also known.[1,2] Terpenoid-based chiral enaminones are considered to be potential biologically active compounds (enaminones comprising biologically active amines are regarded as prodrugs[2]) as well as ligands for diastereoselective synthesis. The only attempt to employ formyl camphor to resolve racemic amines via diastereomeric β-enaminones was reported several decades ago.[3] We have shown another chiral terpene-based enaminone—1-(3-amino-6,6-dimethylbicyclo-[3.1.0]hex-2-en-2-yl)ethanone to be an effective resolving agent for racemic cyclopropanecarboxylic acids.[4] Chiral *N*-substituted β-enaminones can be prepared not only from β-enaminones and acids (or their halogen anhydrides) but also by the reaction of amines with the corresponding β-diketones or chlorovinylketones, as it was shown previously for compounds **1** and **2**.[5] We wish to report herein the results of our studies on the preparation of chiral β-enaminones from β-chlorovinylketone **2**, their chemical structure and stereochemistry and their potential in the resolution of chiral amines.

2. Results and discussion

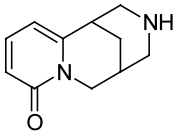
We studied the reaction of diketone **1** and β-chlorovinylketone **2**, which are readily accessible from the natural monoterpene hydrocarbon (+)-3-carene,[5] with racemic primary amine (±)-2-amino-1-(4-nitrophenyl)propane-1,3-diol and natural secondary amines anabasine, cytisine and salsoline (D/L ca. 2:1), as well as with pyrrolidine as a model compound.



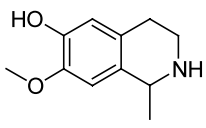
(+)-3-carene



anabasine



cytisine



salsoline

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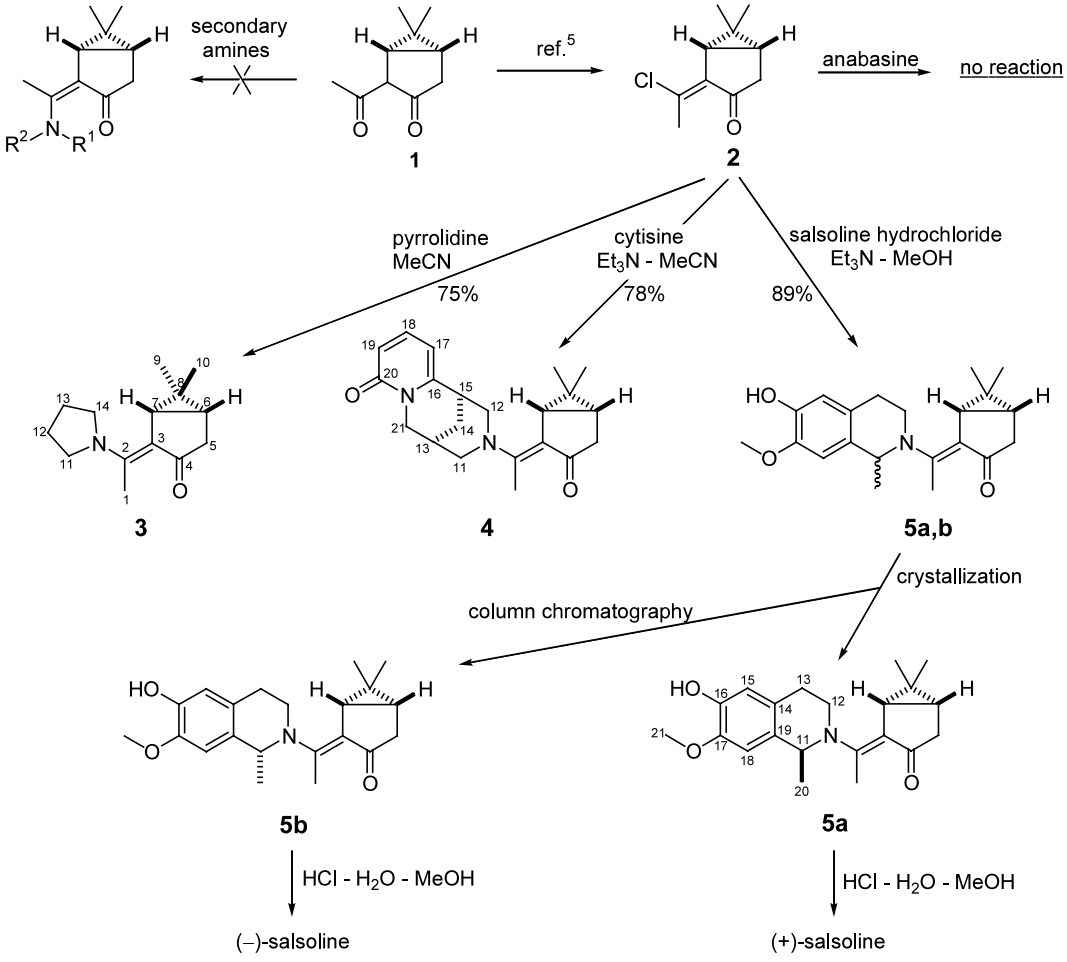
0957-4166/03/$ - see front matter
PII: S0957-4166(02)00781-4

Diketone **1** does not react with secondary amines at ambient temperature (Scheme 1) whereas boiling in benzene in the presence of acetic acid provides tar-like products.

The β-enaminones synthesized are crystalline compounds, which are quite stable in air, that prompted us to use the crystalline adducts of certain amines in the resolution processes. We found it possible to resolve the diastereomeric mixture of enaminones **5a** and **5b**. Thus, enaminone **5** resulting from salsoline was isolated as a mixture of two diastereomers **5a** and **5b** in the ratio ca. 2:1 corresponding to the enantiomeric composition of the starting amine.[8] The major diastereomer **5a** was isolated from the mixture by crystallization. Chromatography of the mother liquor and subsequent crystallization led to the minor isomer **5b**. According to the NMR data the diastereomeric purity of isomers were 97% for **5a** and 94% for **5b**. Treatment of diastereomers **5a** and **5b** with HCl in water–methanol solution at room temperature led to individual enantiomers of salsoline.

We found that the reaction of β-chlorovinylketone **2** with pyrrolidine, cytisine and racemic salsoline (as free bases or hydrochlorides) in the presence of triethylamine proceeds readily to give the corresponding β-enaminones in very good yields (Scheme 1). On the other hand we were unable to prepare the enaminone from anabasine: Treatment of chlorovinylketone **2** with anabasine at room temperature resulted in the starting compounds unchanged whereas completing the reaction in refluxing MeCN or MeOH led to tar-like products. The regio- and diastereoselectivity of the reactions of β-chlorovinylcarbonyl compounds with amines is often questionable.[6] Careful analysis of the NMR spectra of the products **3**–**5** (characteristic chemical shifts of the atoms C-4, C-7, 3H-1) demonstrated that all these compounds: (1) belong to one and the same structural type of cyclopentanone-type β-enaminone and (2) have the same configuration at the 2,3-carbon–carbon double bond. X-Ray analysis of the pyrrolidine derivative **3** proved the *E*-configuration of the 2,3-double bond (Fig. 1). According to the X-ray data, the fragment N–C=C–C=O in the molecule **3** is conjugated as evidenced by the bond length distribution. Similar bond length distribution was found in 1-((4-nitro-1*H*-inden-1-ylidene)methyl)pyrrolidine.[7]

Reaction of chlorovinylketone **2** with racemic 2-amino-1-(4-nitrophenyl)propane-1,3-diol in MeOH in the presence of Et-*i*-Pr_2N afforded a ca. 1:1 mixture of



Scheme 1. The numbering of the carbons shown does not coincide with the numbering of the system according to IUPAC and is given for NMR interpretation only.

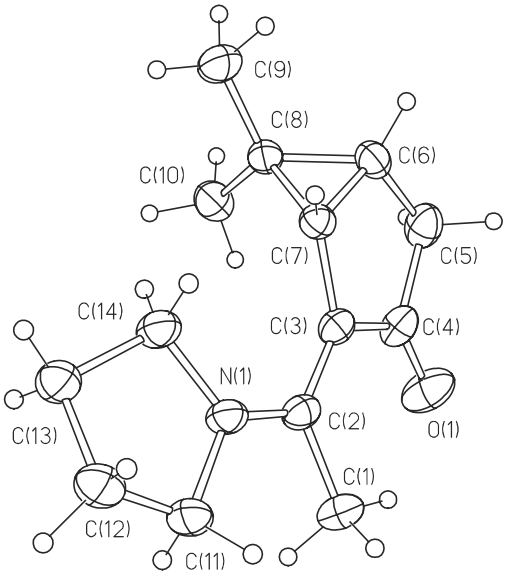


Figure 1. Molecular structure of compound **3** according to X-ray crystallography. Thermal ellipsoids are shown at the 30% probability level. Selected bond lengths (Å): N(1)–C(2) 1.352(3), C(2)=C(3) 1.379(3), C(3)–C(4) 1.456(3), C(4)=O(1) 1.226(3). The atoms O(1), N(1), C(1)–C(7), C(11) are in the same plane within ±0.112 Å. The pyrrolidine cycle has envelope conformation with the atom C(13) from plane deviation of 0.558(5) Å. There is a significant intermolecular contact C(12)–H···O(1): H···O 2.57(3) Å, C–H···O 134(2)°.

diastereomers **6** (according to NMR) in 81% yield (Scheme 2). Crystallization of **6** from MeCN gave diastereomer **6a** in 50% yield. The stereochemistry of **6a** was confirmed by the synthesis of the latter compound from **2** and (1*R*,2*R*)-2-amino-1-(4-nitrophenyl)propane-1,3-diol. In contrast to the β-enaminones **3**–**5**, which are derived from secondary amines, molecules of enaminones **6** have a *Z*-configured 2,3-carbon–carbon double bond (according to ^{1}H and ^{13}C NMR).

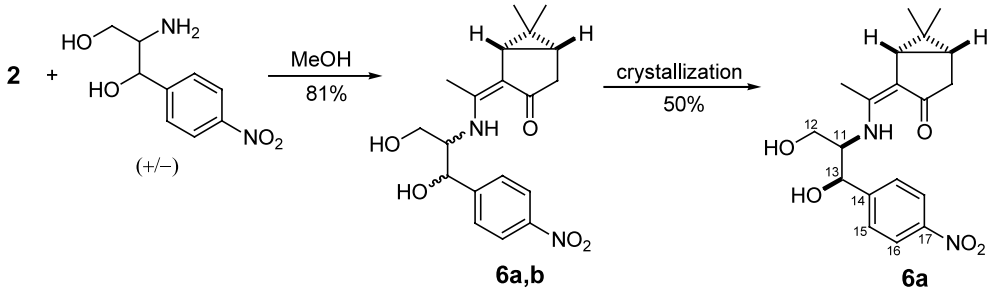
3. Conclusion

Optically active chlorovinylketone reacts regioselectively with a series of secondary and primary amines to give β-enaminones in good yields. In the case of racemic amines, separation of diastereomeric β-enaminones is possible by crystallization/column chromatography to demonstrate a new possibility for the resolution of racemic amines.

4. Experimental

4.1. General experimental procedures

All the solvents used were reagent quality. Removal of all solvents was carried out under reduced pressure and all commercial reagents were used without additional purification. Analytical TLC plates were Silufol® (Silpearl on aluminum foil, Czecho-Slovakia). Preparative column chromatography was performed on SiO_2 ('KSK', Russia, 0.04–0.07 mm, air dried and activated at 140°C for 5 h) or Al_2O_3 ('Reachim', Russia). Diketone **1** and chlorovinylketone **2** were prepared as described in Ref. 5. IR spectra were obtained using a Specord M-80 spectrometer. UV spectra were obtained for 1% solutions in EtOH using a Specord UV–vis spectrometer. A Polamat A polarimeter was used to measure optical rotation at 578 nm. Melting points were obtained using a Kofler melting point apparatus. Mass spectra were obtained on a Finnigan MAT 8200 instrument using the electron impact ionization technique (50–150°C, 70 eV). Purity was determined from constancy of melting point together with TLC and NMR data. ^{1}H and ^{13}C NMR spectra were recorded at room temperature for 5–10% solutions using a standard Bruker NMR Software System on a Bruker DRX-500 instrument (500 MHz for ^{1}H and 125 MHz for ^{13}C) locked to the deuterium resonance of the solvent ($CDCl_3$). The chemical shifts were calculated relative to the solvent signal used as the internal standard: δ_H 7.24 ppm and δ_C 76.90 ppm. The signs of the spin–spin coupling constants were not determined. The assignment of the signals was made using the ^{13}C NMR spectra recorded with the *J* modulation (proton-noise-decoupled spectra, the opposite phases for the signals of the atoms with the odd and even numbers of the attached protons, tuning to the constant $J=135$ Hz) and based on the data of the 2D spectra: (1) homonuclear ^{1}H–^{1}H correlation, (2) heteronuclear ^{13}C–^{1}H correlation at the direct spin–spin coupling constants ($J=135$ Hz), and (3) heteronuclear ^{13}C–^{1}H correlation at the long-range spin–spin coupling constants ($J=10$ Hz).



Scheme 2. The numbering of the carbons shown does not coincide with the numbering of the system according to IUPAC and is given for NMR interpretation only.

X-Ray data were measured at 296 K on a Bruker P4 diffractometer with graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å) using standard $\theta/2\theta$ scans. The structure was solved by direct methods using SHELXS-97 and refined by full matrix least squares method using SHELXL-97. Atomic coordinates, bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre.

4.2. General method for synthesis of enaminones 3–6

A solution of chlorovinylketone **2** (0.66 g, 3.6 mmol) in an appropriate solvent (3 ml),[†] was added at room temperature to a stirred solution of the corresponding amine or amine hydrochloride[‡] (3.6 mmol) and Et-*i*-Pr_2N (3.0 g, 23 mmol)[§] in 10 ml of the same solvent. The mixture was left for 24 h and concentrated under reduced pressure. The residue was extracted with $CHCl_3$ (2×30 ml), the combined organic extracts were washed with $NaHCO_3$ (1 M, 10 ml) and brine (20 ml) and dried over Na_2SO_4. Evaporation of the solvent left the crude enaminone.

4.3. (1*S*,5*R*)-6,6-Dimethyl-2-((*E*)-1-pyrrolidin-1-yl-ethylidene)bicyclo[3.1.0]hexan-3-one, 3

The title compound was prepared by the reaction of **2** with pyrrolidine as described above. Crystallization of the crude product gave **3** in 75% yield as pale yellow crystals with mp 76–77°C (hexane–MeO-*t*-Bu) and $[\alpha]_{578}^{22}$ −1020 (*c* 1.1, $CHCl_3$). MS (*m*/*z*, %): 219.1623 (M^+, 100%, $C_{14}H_{21}NO$, requires 219.1623), 204 (100), 190 (4), 176 (25), 162 (3), 148 (6), 135 (5), 122 (16), 107 (5), 96 (10), 79 (7), 70 (27), 55 (7). IR ($CHCl_3$) ν/cm^{-1}: 1628, 1521, 1482, 1415, 1374, 1337, 1300, 1250, 1214, 1177, 116, 1079, 1020, 950. UV (EtOH) λ_{max}/nm: 349 (ε 17900). ^1H NMR ($CDCl_3$): 2.34 (s, 3H-1), 2.52 (dd, $J = 18.4$, 7.7, H-5β), 2.12 (d, $J = 18.4$, H-5α), 1.06 (dd, $J = 8.0$, 7.7, H-6), 1.89 (d, $J = 8.0$, H-7), 1.04 (s, 3H-9), 0.84 (s, 3H-10), 3.60 and 3.43 (m, 2H-11, 2H-14), 1.96 and 1.76 (m, 2H-12, 2H-13). ^{13}C NMR ($CDCl_3$): 14.85 (C-1), 158.91 (C-2), 104.84 (C-3), 204.92 (C-4), 39.07 (C-5), 20.50 (C-6), 34.06 (C-7), 21.56 (C-8), 26.25 (C-9), 16.87 (C-10), 49.94 (C-11,14), 25.29 (C-12,13).

4.3.1. Crystal data for 3. $C_{14}H_{21}NO$, $M = 219.32$, orthorhombic, space group $P2_12_12_1$, $a = 5.8185(4)$, $b = 8.5061(13)$, $c = 25.6803(15)$ Å, $V = 1271.0(2)$ Å^3, $Z = 4$, $D_{calcd} = 1.146$ g cm^{-3}, $\mu = 0.071$ mm^{-1}, $F(000) = 480$, crystal size 0.4×0.6×0.7 mm. Of 1330 measured intensities with $2\theta < 50°$ 1224 intensities were considered observed ($I > 2\sigma$). Absorption corrections were applied by psi-scans method, transmission 0.309–0.325. Goodness-of-fit on $F^2 = 1.101$. Final *R*-indices: (all data) $wR_2 = 0.0988$, $R_1 = 0.0376$; ($I > 2\sigma$) $wR_2 = 0.0951$, $R_1 = 0.0343$. Absolute structure parameter is equal to 0(3). Hydrogen atoms were located from D-maps and refined in isotropic approximation. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 189272 Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.4. 3-[(*E*)-1-((1*S*,5*R*)-6,6-Dimethyl-3-oxobicyclo[3.1.0]-hex-2-ylidene)ethyl]-(1*R*,5*S*)-1,2,3,4,5,6-hexahydro-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one, 4

Reaction of cytisine and **2** afforded the crude enaminone, which was crystallized to give **4** in 78% yield as pale yellow crystals with mp 207–209°C (MeCN–$CHCl_3$) and $[\alpha]_{578}^{22}$ −1470 (*c* 0.23, $CHCl_3$). MS (*m*/*z*, %): 338.1998 (M^+, 100%, $C_{21}H_{26}N_2O_2$ requires 338.1994), 323 (98), 295 (23), 241 (9), 193 (4), 189 (39), 177 (17), 164 (14), 146 (27), 135 (14), 130 (3), 121 (10), 117 (7), 105 (11), 96 (5), 91 (16), 77 (13), 67 (7), 55 (8), 44 (18). IR ($CHCl_3$) ν/cm^{-1}: 3671, 1655, 1549, 1448, 1426, 1344, 1305, 1211, 1144, 982. UV (EtOH) λ_{max}/nm: 231 (ε 9500), 318 (ε 15000), 350 (ε 18700). ^1H NMR (DMSO-d_6): 2.09 (s, 3H-1), 2.30 (dd, $J = 18.9$, 7.5, 1H-5β), 1.86 (d, $J = 18.9$, 1H-5α), 0.95 (dd, $J = 7.7$, 6.5, 1H-6), 1.17 (d, $J = 7.7$, 1H-7), 1.10 (s, 3H-9), 0.75 (s, 3H-10), 3.85 (dm, $J = 11.9$, $W_{1/2} = 8$ Hz, H-11a), 3.29 (dm, $J = 11.9$, $W_{1/2} = 7$ Hz, H-11b), 3.78 (dm, $J = 15.5$, $W_{1/2} = 5$ Hz, H-12a), 3.69 (ddm, $J = 15.5$, 6.5, $W_{1/2} = 5$ Hz, H-12b), 2.52 (m, $W_{1/2} = 16$ Hz, H-13), 1.92 (m, $W_{1/2} = 9$ Hz, 2H-14), 3.16 (m, $W_{1/2} = 9$ Hz, H-15), 6.19 (d, $J = 6.8$, H-17), 7.36 (dd, $J = 8.9$, 6.8, 1H-18), 6.24 (d, $J = 8.9$, H-19). ^{13}C NMR (DMSO-d_6): 14.08 (C-1), 162.18 (C-2 or C-20), 109.43 (C-3), 204.65 (C-4), 38.57 (C-5), 19.85 (C-6), 33.63 (C-7), 21.01 (C-8), 26.18 (C-9), 14.35 (C-10), 54.33 (C-11), 48.97 (C-12), 27.61 (C-13), 25.19 (C-14), 34.18 (C-15), 149.81 (C-16), 105.27 (C-17), 138.82 (C-18), 116.19 (C-19), 158.93 (C-20 or C-2), 53.09 (C-21).

4.5. (1*S*,5*R*)-2-{(*E*)-1-[(1*R*)-6-Hydroxy-7-methoxy-1-methyl-3,4-dihydro-1*H*-isoquinolin-2-yl]ethylidene}-6,6-dimethylbicyclo[3.1.0]hexan-3-one, 5a and (1*S*,5*R*)-2-{(*E*)1-[(1*S*)-6-hydroxy-7-methoxy-1-methyl-3,4-dihydro-1*H*-isoquinolin-2-yl]ethylidene}-6,6-dimethylbicyclo-[3.1.0]hexan-3-one, 5b

The crude mixture of diastereomers **5a**,**b** (ca. 2:1) was prepared from salsoline hydrochloride and chlorovinylketone **2** in 89% yield as a yellow gum. The crude product was dissolved in boiling MeO-*t*-Bu (5 ml) and left at room temperature for 3 h and then at −10°C for 12 h. The crystalline precipitate was isolated by filtration, washed with MeO-*t*-Bu (2 ml) and dried in vacuum to give 0.61 g (ca. 84% counting on content of **5a** in the crude mixture) of diastereomer **5a** as pale yellow crystals. The mother liquor was concentrated at reduced pressure and chromatographed on a Al_2O_3 column (pentane–benzene) to afford pale yellow oil (0.31 g) which was then crystallized from a mixture of MeO-*t*-Bu and pentane to give **5b** (0.21 g, ca. 58% counting on the content of **5b** in the crude mixture of diastereomers) as pale yellow crystals.

[†] MeCN for the reactions with pyrrolidine, anabasine, cytisine; MeOH for the reactions with salsoline hydrochloride and (±)-2-amino-1-(4-nitrophenyl)propane-1,3-diol.

[‡] Hydrochloride was used only in the case of salsoline.

[§] In the case of pyrrolidine, 3 M excess of the reagent was used without any additional base.

4.5.1. Data for (1*S*,5*R*)-2-{(*E*)-1-[(1*R*)-6-hydroxy-7-methoxy - 1 - methyl - 3,4 - dihydro - 1*H* - isoquinolin - 2-yl]ethylidene}-6,6-dimethylbicyclo[3.1.0]hexan-3-one, 5a. Mp 163–165°C (MeO-*t*-Bu, dec.), $[\alpha]_{578}^{22}$ −934 (*c* 0.57, $CHCl_3$). MS (*m*/*z*, %): 341.1991 (M^+, 100%, $C_{21}H_{27}NO_3$ requires 341.1991), 326 (81), 313 (15), 298 (44), 286 (19), 272 (5), 256 (4), 244 (16), 230 (12), 218 (3), 192 (61), 178 (35), 150 (11), 145 (21), 121 (8), 117 (13), 105 (8), 91 (16), 77 (11), 67 (3), 55 (7), 41 (8). IR ($CHCl_3$) ν/cm^{-1}: 3545, 1635, 1515, 1465, 1420, 1377, 1332, 1278, 1248, 1211, 1157, 1129, 1050, 1015, 943, 877, 828. UV (EtOH) λ_{max}/nm: 288 (ε 3100), 352 (ε 18700). ^{1}H NMR ($CDCl_3$): 2.55 (s, 3H-1), 2.12 (d, *J*=18.9, 1H-5α), 2.51 (dd, *J*=18.9, 7.6, 1H-5β), 1.13 (dd, *J*=7.8, 7.6, 1H-6), 1.85 (d, *J*=7.8, 1H-7), 1.17 (s, 3H-9), 0.86 (s, 3H-10), 5.07 (q, *J*=6.7, 1H-11), 4.04 (dd, *J*=14.3, 5.5, 1H-12a), 3.40 (ddd, *J*=14.3, 13.4, 3.9, 1H-12b), 2.94 (ddd, *J*=15.7, 13.4, 5.5, H-13a), 2.64 (dd, *J*=15.7, 3.9, 1H-13b), 6.63 (s, 1H-15), 6.42 (s, 1H-18), 1.55 (d, *J*=6.7, 3H-20), 3.83 (s, 3H-21), 6.0 (br. $W_{1/2}$=300 Hz, Ar–OH). ^{13}C NMR ($CDCl_3$): 15.26 (C-1), 160.07 (C-2), 106.53 (C-3), 205.68 (C-4), 39.07 (C-5), 20.65 (C-6), 35.21 (C-7), 21.51 (C-8), 26.82 (C-9), 14.50 (C-10), 53.35 (C-11), 39.61 (C-12), 28.98 (C-13), 130.08 (C-14), 114.41 (C-15), 144.53 (C-16 or C-17), 145.35 (C-17 or C-16), 108.73 (C-18), 125.38 (C-19), 23.24 (C-20), 55.91 (C-21).

4.5.2. Data for (1*S*,5*R*)-2-[(*E*)-1-((1*S*)-6-hydroxy-7-methoxy - 1 - methyl - 3,4 - dihydro - 1*H* - isoquinolin - 2-yl)ethylidene]-6,6-dimethylbicyclo[3.1.0]hexan-3-one, 5b. Mp 158–165°C (MeO-*t*-Bu, dec.), $[\alpha]_{578}^{22}$ −725 (*c* 0.26, $CHCl_3$). MS, IR and UV spectra of the compound are identical to those of diastereomer **5a**. ^{1}H NMR ($CDCl_3$): 2.47 (s, 3H-1), 2.14 (d, *J*=18.9, 1H-5α), 2.51 (dd, *J*=18.9, 7.4, 1H-5β), 1.11 (dd, *J*=7.8, 7.4, 1H-6), 1.61 (d, *J*=7.8, 1H-7), 1.14 (s, 3H-9), 0.94 (s, 3H-10), 5.29 (q, *J*=6.5, 1H-11), 3.98 (dd, *J*=12.6, 5.5, 1H-12a), 3.43 (ddd, *J*=12.6, 12.6, 3.7, 1H-12b), 2.77 (ddd, *J*=15.7, 12.6, 5.5, H-13a), 2.60 (dm, *J*=15.7, $W_{1/2}$=8 Hz, 1H-13b), 6.62 (s, 1H-15), 6.48 (s, 1H-18), 1.39 (d, *J*=6.7, 3H-20), 3.83 (s, 3H-21), 5.7 (br. $W_{1/2}$=340 Hz, Ar–OH). ^{13}C NMR ($CDCl_3$): 15.98 (C-1), 158.83 (C-2), 110.62 (C-3), 206.45 (C-4), 39.07 (C-5), 21.25 (C-6), 35.60 (C-7), 21.81 (C-8), 26.54 (C-9), 14.48 (C-10), 52.56 (C-11), 40.30 (C-12), 28.99 (C-13), 129.76 (C-14), 114.27 (C-15), 144.37 (C-16 or C-17), 145.29 (C-17 or C-16), 108.71 (C-18), 126.37 (C-19), 22.62 (C-20), 55.90 (C-21).

4.6. Salsoline recovery

To an ice-cooled solution of diastereomer **5a** (200 mg, 0.59 mmol) in MeOH (5 ml) a solution of concentrated aqueous HCl in MeOH (ca. 15% w/w, 5 ml) was added. The mixture was left at room temperature for 14 h and concentrated under reduced pressure at the bath temperature 40°C. The residue was stirred with MeO-*t*-Bu (5 ml), the crystals were filtered, washed with MeO-*t*-Bu (2×2 ml) and dried in vacuum to afford 123 mg (92%) of (+)-salsoline hydrochloride as pale yellow crystals with mp 169–172°C (lit. 171–172°C) and $[\alpha]_{578}^{22}$ +42.1 (*c* 3.1, H_2O) (lit. $[\alpha]_D$ +40.1). Diastereomer **5b** (100 mg, 0.62 mmol) was worked up as described above for diastereomer **5a** to give (−)-salsoline hydrochloride (50 mg) as pale yellow crystals with mp 168–170°C and $[\alpha]_{578}^{25}$ −41.9 (*c* 2.9, H_2O).

4.7. (1*S*,5*R*)-2-{(*Z*)-1-[(1*R*,2*R*)-2-Hydroxy-1-hydroxymethyl-2-(4-nitrophenyl)ethylamino]ethylidene}-6,6-dimethylbicyclo[3.1.0]hexan-3-one, 6a and (1*S*,5*R*)-2-{(*Z*)-1-[(1*S*,2*S*)-2-hydroxy-1-hydroxymethyl-2-(4-nitrophenyl)ethylamino]ethylidene}-6,6-dimethylbicyclo[3.1.0]hexan-3-one, 6b

The crude mixture of diastereomers **6a** and **6b** (ca. 1:1 according to NMR data) was prepared in 81% yield as a yellow gum from (±)-2-amino-1-(4-nitrophenyl)propane-1,3-diol and chlorovinylketone **2**.

4.7.1. (1*S*,5*R*)-2-{(*Z*)-1-[(1*R*,2*R*)-2-Hydroxy-1-hydroxymethyl - 2 - (4 - nitrophenyl)ethylamino]ethylidene} - 6,6-dimethylbicyclo[3.1.0]hexan-3-one, 6a. The mixture of diastereomers **6a**,**b** (1.46 g, 4.1 mmol) was crystallized from MeCN (5 ml) to give pure diastereomer **6a** (0.45 g, 63%) as yellow crystals. Reaction of **2** with (1*R*,2*R*) - 2 - amino - 1 - (4 - nitrophenyl)propane - 1,3 - diol afforded **6a** in 78% yield. Mp 177–183°C (MeCN, dec.). $[\alpha]_{578}^{19}$ +642 (*c* 0.33, $CHCl_3$). MS (*m*/*z*, %): 360.1701 (M^+, 8%, $C_{19}H_{24}N_2O_5$ requires 360.1685), 345 (2), 208 (100), 165 (6), 148 (9), 121 (4), 91 (7), 84 (46), 60 (6), 42 (8). IR (KBr) ν/cm^{-1}: 3346, 3151, 1619, 1578, 1516, 1486, 1456, 1383, 1349, 13232, 1308, 1264, 1225, 1199, 1168, 1105, 1085, 1043, 1014, 969, 927, 880, 865, 814. UV (EtOH) λ_{max}/nm: 204 (ε 15300), 273 (ε 9600), 346 (ε 15000). ^{1}H NMR (DMSO-d_6–$CDCl_3$): 1.60 (s, 3H-1), 0.99 (s, 3H-9), 1.96 (d, *J*=18.5, 1H-5α), 2.41 (dd, *J*=18.5, 7.7, 1H-5β), 0.94 (dd, *J*=7.9, 7.7, 1H-6), 1.47 (d, *J*=7.9, 1H-7), 0.94 (s, 3H-9), 0.66 (s, 3H-10), 3.57 (m, $W_{1/2}$=22 Hz, H-11), 3.61 (m, $W_{1/2}$= 32 Hz, H-12a), 3.42 (ddd, *J*=10.0, 4.8, 4.4, H-12b), 5.02 (dd, *J*=2.4, 2.4, H-13), 7.52 (d, *J*=8.7, 2H-15), 8.06 (d, *J*=8.7, 2H-16), 10.13 (d, *J*=9.7, NH), 4.47 (dd, *J*=4.4, 4.4, CH_2–OH), 5.61 (d, *J*=2.4, CH–OH). ^{13}C NMR (DMSO-d_6–$CDCl_3$): 15.78 (C-1), 157.46 (C-2), 103.83 (C-3), 201.47 (C-4), 37.57 (C-5), 20.28 (C-6), 30.26 (C-7), 20.89 (C-8), 25.87 (C-9), 13.69 (C-10), 59.90 (C-11), 61.71 (C-12), 69.85 (C-13), 150.91 (C-14), 126.73 (2C-15), 122.43 (2C-16), 146.26 (C-17).

Acknowledgements

The authors thank the Russian Foundation for Basic Research (Grant No. 01-03-32369) and INTAS (Grant No. 97-0217) for the financial support of this work. The samples of natural alkaloids salsoline (D/L ca. 2:1), cytisine and anabasine were provided by Inter-BioScreen Ltd. (Moscow).

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