Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 2875–2881

TETRAHEDRON: *ASYMMETRY*

Novel optically active pyrazole ligands derived from (+)-3-carene

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Received 19 October 2001; accepted 23 October 2001

Abstract—Reactions of chiral β-diketone with racemic hydrazines as well as reaction of chiral pyrazole with cyclohexene epoxide and *trans*-stilbene epoxide have been examined as the routes to optically active pyrazolylethanols. Diastereomerically pure products have been isolated by crystallization or column chromatography in good yields.

1. Introduction

Substituted pyrazole-*N*-alkanols are prospective agents for diastereoselective synthesis: optically active pyrazolylethanols were employed as chiral auxiliaries in the addition reaction of diethyl zinc to aldehydes,[1] whereas modified polydentate ligands obtained from pyrazolylethanols were used to synthesize complexes with Pd and Re.[2]

Optically active epoxides are known to be opened with pyrazoles at high pressure (10 kbar) to give diastereomerically pure products (regioisomers resulting from optically active pyrazoles are separated chromatographically).[1] Regioselective reactions of pyrazoles with cyclohexene epoxide at elevated temperatures providing chiral products have been described.[3,4] Kinetic resolution of racemic and diastereomeric adducts has been performed by immobilized lipase[3] to give diastereomerically pure (1*S*,2*S*)-derivatives. Pyrazole fused with a bornane framework has been reported to be alkylated with ethyl bromoacetate and reduced to give the regioisomeric pyrazole–ethanols.[1]

2. Results and discussion

We have studied the possibility of synthesizing new optically active pyrazole–*N*-ethanols starting from readily accessible derivatives of the natural monoterpene (+)-3-carene. We described earlier the reaction of optically active diketone **1** with monosubstituted hydrazines (hydrazino–ethanol and ethyl hydrazino–acetate) to proceed regioselectively providing substituted pyrazoles **3** in good yields.[5]

Racemic hydrazines **2a** and **2b** resulting from *trans*-stilbene oxide and cyclohexene oxide, respectively, were used in the reaction with diketone **1** to give pyrazoles **4** and **5** as ca. 1:1 (according to NMR) mixtures of diastereomers (Scheme 1). The reaction proceeds regioselectively to give only one positional isomer of the substituted pyrazoles.

The alternative route to substituted pyrazoles by opening of the epoxide ring in *trans*-stilbene oxide and cyclohexene oxide with pyrazole **3** (R = H)[6] was also studied (Scheme 2). Heating of equimolar mixture of pyrazole **3** (R = H) and *trans*-stilbene oxide in a sealed tube at 100–130°C resulted in poor regioselectivity affording mixtures of regioisomers **4** and **7** in ca. 4:1 ratio (NMR, GC–MS), whereas the reaction of the pyrazole **3** (R = H) with cyclohexene oxide gave ca. 10:1 mixture of **5** and **8**.

The mixture of diastereomers **4** can be separated easily by column chromatography to afford both isomers in quite good yields. The structure **4a** was established by X-ray crystallography (Fig. 1) showing the intermolecular hydrogen bonds between the hydroxyl hydrogen and

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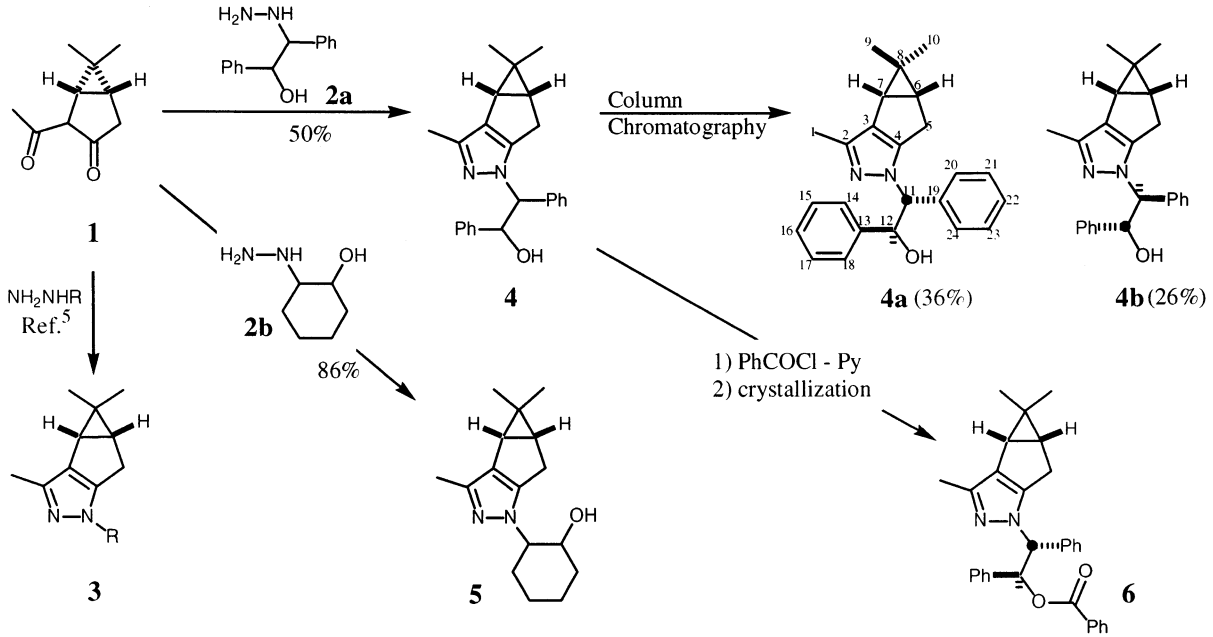
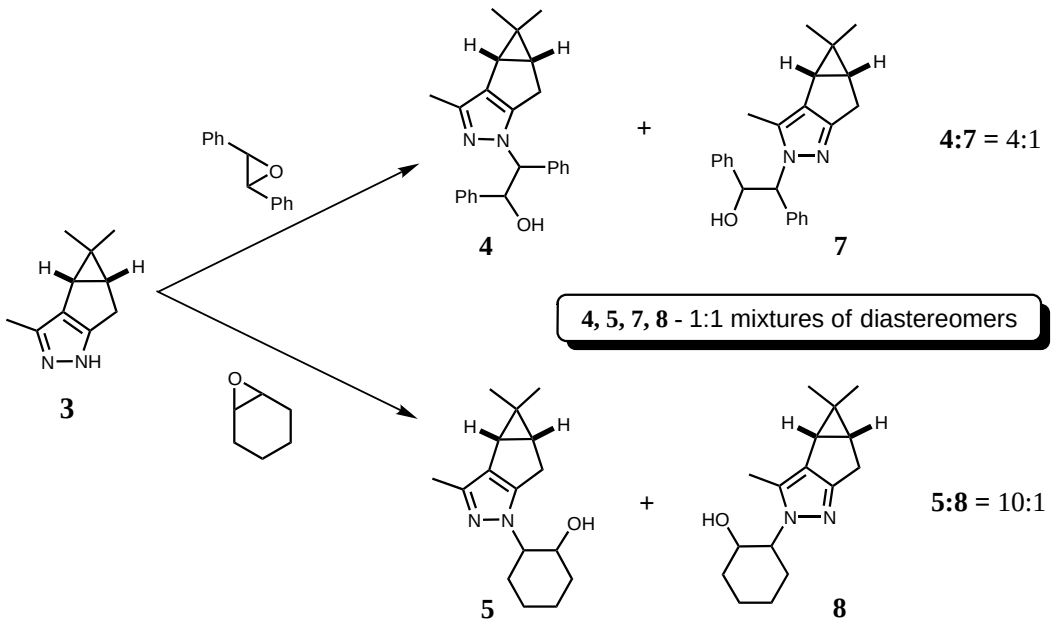
0957-4166/01/$ - see front matter
PII: S0957-4166(01)00477-3



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.



Scheme 2.

the non-substituted pyrazole nitrogen. When a solution of **4** in acetonitrile is seeded with the pure isomer **4a**, the isomer **4a** is isolated by crystallization in 11% yield.

Mixtures of isomers **5a** and **5b** are chromatographically homogeneous (TLC and GLC); moreover, attempts to separate **5a** and **5b** via crystallization failed (Scheme 3). Problems in separation of the simplest diastereomeric pyrazole–cyclohexanols have been documented,[4] and therefore we tried to separate their *O*-acylated derivatives. Treatment of **5** with AcCl resulted in the *O*-acetyl derivative, which was crystallized from MeCN to give a 2:1 mixture of diastereomers. On the other hand, crystallization of the *O*-benzoyl derivative **9** allowed us to prepare benzoate **9a** in diastereomerically pure form. The structure **9a** was established by X-ray analysis (Fig. 2). Bond lengths of the tetrahydrocyclopropa[3,4]cyclopenta[1,2-*c*]pyrazolyl fragment of compounds **4a** and **9a** are identical within experimental error. Overall, whole all bond lengths including that of pyrazole ring are close to the average ones.[7]

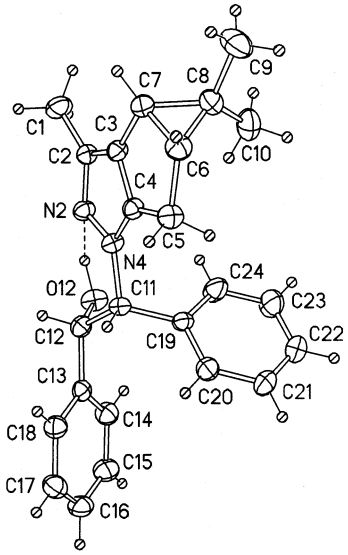


Figure 1. Molecular structure of compound **4a** according to X-ray crystallography. Thermal ellipsoids are shown at 30% probability level. Selected bond lengths (Å): C(2)–C(3) 1.387(4), C(3)=C(4) 1.361(4), C(4)–N(4) 1.345(4), N(4)–N(2) 1.372(3), N(2)=C(2) 1.359(4). Bicyclic system C(2)–C(7), N(2), N(4) is planar within ±0.032(3) Å. Parameters of the intramolecular hydrogen bond OH···N are as follows: O(12)···N(2) 2.704(4), O(12)–H 0.99(6), H···N(2) 1.93(6) Å, angle O(12)–H···N(2) 133(5)°.

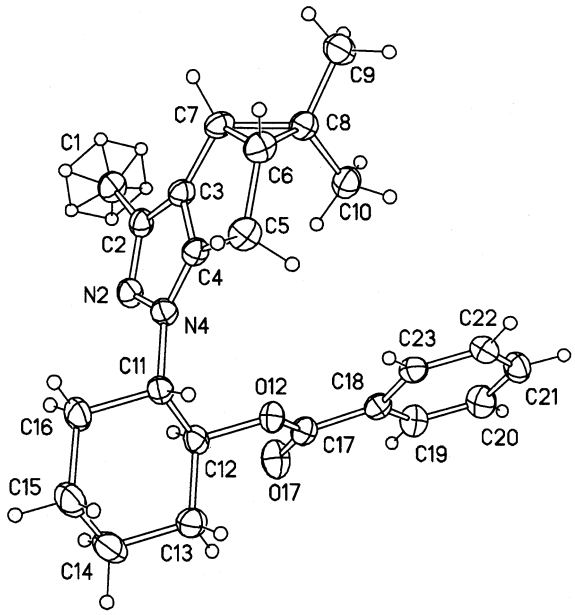
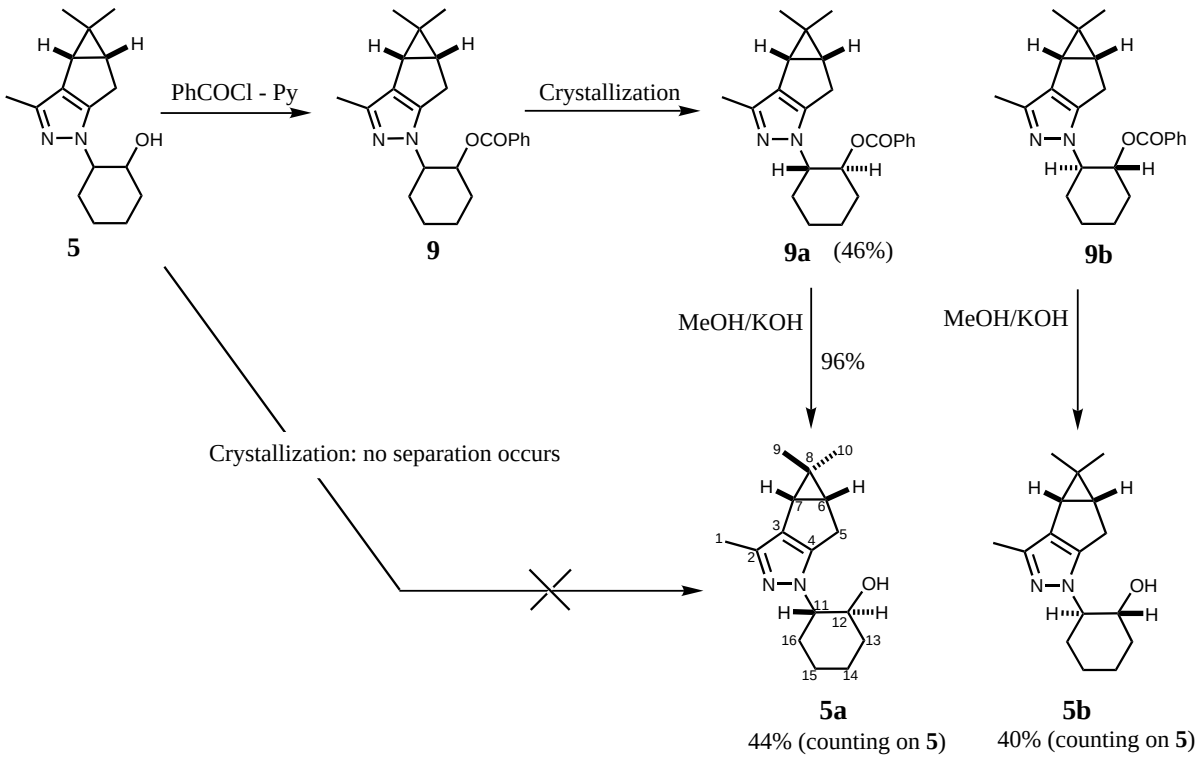


Figure 2. Molecular structure of compound **9a** according to X-ray crystallography. Thermal ellipsoids are shown at 30% probability level. Selected bond lengths (Å): C(2)–C(3) 1.409(5), C(3)=C(4) 1.375(5), C(4)–N(4) 1.340(5), N(4)–N(2) 1.376(4), N(2)=C(2) 1.335(5). Bicyclic system C(2)–C(7), N(2), N(4) is planar within ±0.028(3) Å.



Scheme 3. 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.

Saponification of **9a** with methanolic KOH provided isomer **5a**, whereas the saponification of the mother liquor (after separation of the isomer **9a**) resulted in the second diastereomer **5b**.

Analyses of mixtures of diastereomers in all the cases were carried out using GC–MS as well as high-field NMR spectroscopy. NMR parameters for the terpenic fragments in pyrazolyl cyclohexanols **5a** and **5b** are close to those for corresponding *N*-unsubstituted pyrazoles **3** described earlier.[5,6]

Introduction of the 1,2-diphenylethanol moiety gives rise to substantial discrepancy of ^{1}H NMR parameters between compounds **4a**, **4b**, and **6** and known *N*-unsubstituted pyrazole **3**,[5,6] the protons at C-10 being especially sensitive to remote chiral environment. Thus, chemical shifts of the H-10 atoms are 0.59, 0.36 and −0.01 ppm for compounds **4b**, **4a**, and **6**, respectively: This could be the result of the strong anisotropic effects caused by the constrained phenyl moieties.

3. Conclusion

Thus, pyrazole–*N*-alkanols derived from (+)-3-carene and cyclohexene oxide and stilbene oxide were prepared in preparative yields and in diastereomerically pure form. Preliminary studies have shown the new pyrazole–*N*-alkanols to form complexes with transition metal ions allowing one to consider them as new potential chiral ligands for enantioselective catalysis.

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, Czechoslovakia). 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 pyrazole **3** (R = H) were prepared as described in Ref. [6]. 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). GC–MS data were obtained on a quadrupole MS (Hewlett–Packard MSD 5971) coupled to a HP 5890/II GC fitted with an HP-5 fused silica column, injector and detector (MSD) temperature were 280 and 170°C, respectively. MSD was operated at 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 standard Bruker NMR Software System on a Bruker AC 200 instrument (200 MHz for ^{1}H and 50.32 MHz for ^{13}C) and 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.

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

4.2. Synthesis of substituted hydrazines 2a and 2b from oxides of *trans*-stilbene and cyclohexene

A solution of epoxide (0.1 M) in methanol (40 ml) was added dropwise to a stirred solution of hydrazine hydrate (15 ml) in methanol (30 ml) at ambient temperature. The mixture was refluxed for 2 h and then concentrated at reduced pressure. The resulting product was washed with MeCN (10 ml), dried in vacuum over concentrated H_2SO_4 for 2 h and was used immediately in the reaction with diketone **1** without any additional purification.

4.3. Synthesis of 4 and 5 from diketone 1 and substituted hydrazines

A solution of a substituted hydrazine (1,2-diphenyl-2-hydroxyethyl hydrazine or 2-hydrazinocyclohexanol, 6.0 mmol) in methanol (10 ml) was added dropwise to a stirred ice-cooled solution of diketone **1** (1.00 g, 6 mmol) in a mixture of methanol (15 ml) and AcOH (1 ml). The mixture was kept at ambient temperature overnight and then stirred at reflux for 0.5 h. The solvent was removed under reduced pressure, and the residue was treated with water (100 ml) and extracted with benzene (50 ml). The organic phase was washed with $NaHCO_3$ (0.5 M, 50 ml), dried (Na_2SO_4) and evaporated at reduced pressure to give the crude product, which was chromatographed on a short alumina column (benzene) and crystallized (MeCN) to give the pure pyrazoles **4** or **5** as 1:1 mixtures of diastereomers.

4.4. Synthesis of mixtures 4/7 and 5/8

An equimolar mixture of pyrazole **3** (R = H) and epoxide of cyclohexene or epoxide of *trans*-stilbene was heated in a sealed tube at 130°C for 6–10 h to give mixtures **4**/**7** or **5**/**8** in 95–98% yield (purity was established by NMR and GC–MS data).

4.5. Chromatographic separation of diastereomeric mixture 4

A mixture of diastereomers **4** (0.700 g, 1.95 mmol) was chromatographed on a silica gel column ($l = 230$ mm,

$\varnothing = 20$ mm, eluent CCl_4, CCl_4–EtOAc) to give **4a** 250 mg (0.70 mmol, 36%) and **4b** 180 mg (0.50 mmol, 26%).

4.6. Synthesis of benzoate of pyrazole–cyclohexanol 9 and separation of the diastereomers

Benzoyl chloride 5.0 g (36 mmol) was added to a stirred mixture of pyrazole **5** (4.3 g, 17 mmol) in CH_2Cl_2 (30 ml) and pyridine (10 g) and the mixture was allowed to stay for 48 h. The mixture was sequentially washed with satd aq. $NaHCO_3$ (100 ml), 1.0 M H_2SO_4 (100 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The resulting light brown viscous oil was dissolved in MeCN (50 ml) and left in refrigerator. After 24 h benzoate **9a** (3.0 g, 45%) was separated as white crystals. The mother liquor was evaporated to afford a brownish oil, which contained benzoates **9b** and **9a** (10:1 according to NMR) together with impurities.

4.7. Saponification of benzoates 9a and 9b

A solution of **9a** (1.0 g, 2.7 mmol) or solution of the mother liquor (1.0 g) in MeOH (10 ml) and KOH (1 g, 17.8 mmol) were heated at 70°C for 1 h. The mixture was evaporated at reduced pressure. Water (40 ml) was added to the residue and the mixture was extracted with CCl_4 (2×20 ml). The combined organic extracts were washed with 1 M aq. H_2SO_4 (3×15 ml). The combined aqueous extracts were neutralized with conc. aq. NH_3 (20 ml) and extracted with CH_2Cl_2 (3×15 ml) to afford a solid, which was crystallized from MeCN to give pyrazolocyclohexanol as pale yellow crystals.

4.8.(1*S*,2*S*)-2-((3b*S*,4a*R*)-3,4,4-Trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-*c*]pyrazol-1-yl)cyclohexanol and (1*R*,2*R*)-2-((3b*S*,4a*R*)3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-*c*]-pyrazol-1-yl)cyclohexanol 5

Reaction of diketone **1** (1.65 g, 10.0 mmol) with 2-hydrazinocyclohexanol led to a mixture of diastereomers **5** (2.20 g, 84%) as yellow crystals. Heating a mixture of pyrazole **3** (R = H) (3.6 g, 2.2 mmol) and cyclohexene oxide led to a mixture of pyrazoles **5** and **8** (5.44 g, 95%, **5**:**8** = 10:1 according to NMR and GC–MS).

4.9. (1*S*,2*S*)-2-((3b*S*,4a*R*)-3,4,4-Trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-*c*]pyrazol-1-yl)-cyclohexanol 5a

Saponification of benzoate **9a** (2.9 g, 8.0 mmol) led to **5a** (2.0 g, 96%) as white crystals with mp 138–140°C (MeCN). $[\alpha]_D^{25} = +102$ (*c* 1.0, $CHCl_3$). MS (*m*/*z*, %): 260.18886 (M^+, 35%, $C_{16}H_{24}N_2O$, requires 260.18885); 245 (73), 227 (28), 217 (3), 189 (3), 175 (30), 163 (55), 147 (100), 133 (7), 120 (3), 106 (8), 91 (7), 81 (9), 65 (3), 55 (3), 45 (4). IR ($CHCl_3$) ν/cm^{-1} 3592, 3346, 1551, 1518; 1485, 1451; 1432, 1373, 1333, 1291, 1262, 1215; 1173, 1121, 1072, 1045, 982. IR ($CHCl_3$) ν/cm^{-1} 3592 (O–H). UV (EtOH) λ_{max}/nm 238 (ε 5300). ^{1}H NMR (500 MHz, $CDCl_3$): 2.14 (s, 3H-1), 2.52 (ddd, J = 16.8, 1.1, 1.1, 1H-5α), 2.75 (dd, J = 16.8, 7.0, 1H-5β), 1.67 (ddd, J = 7.0, 6.6, 1.1, 1H-6), 1.74 (dd, J = 6.6, 1.1, 1H-7), 1.03 (s, 3H-9); 0.61 (s, 3H-10), 3.79 (ddd, J = 9.9, 9.9, 4.7, 1H-11), 3.58 (ddd, J = 12.5, 9.4, 4.2, 1H-12), 2.06 (m, 1H-13a); 1.70–1.80 (m, 2H-15a, 14a), 1.25–1.37 (m, 3H-15b, 14b, 13b), 1.65 (m, 1H-16a), 1.99 (m, 1H-16b), 3.53 (br.s, 1H-OH). ^{13}C NMR (125 MHz): 12.38 (C-1), 150.48 (C-2), 125.59 (C-3), 142.19 (C-4), 24.68 (C-5), 34.02 (C-6), 25.74 (C-7), 22.21 (C-8), 26.18 (C-9), 13.60 (C-10), 65.64 (C-11), 72.61 (C-12), 33.02 (C-13), 23.89 (C-14), 24.702 (C-15), 30.39 (C-16).

4.10. (1*R*,2*R*)-2-((3b*S*,4a*R*)-3,4,4-Trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-*c*]pyrazol-1-yl)-cyclohexanol 5b

Treatment of **5** (4.5 g, 17 mmol) with benzoyl chloride followed by separation of **9a** (crystallization) resulted in the mother liquor, which was concentrated and saponified to give **5b** (1.8 g, 40%) as white needles with mp 131–133°C(MeCN) and $[\alpha]_D^{25} = +66$ (*c* 1.25, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): 2.14 (s, 3H-1), 2.50 (ddd, J = 16.6, 1.3, 1.6, 1H-5α), 2.80 (dd, J = 16.6, 7.0, 1H-5β), 1.68 (ddd, J = 7.0, 6.5, 1.3, 1H-6), 1.75 (dd, J = 6.5, 1.6, 1H-7), 1.07 (s, 3H-9), 0.63 (s, 3H-10), 3.80 (ddd, J = 10.5, 9.5, 4.8, 1H-11), 3.56 (ddd, J = 12.3, 9.4, 4.2, 1H-12), 1.35 (m, 1H-13a), 2.08 (m, 1H-13b), 1.32 (m, 1H-14a), 1.77 (m, 1H-14b), 1.30 (m, 1H-15a), 1.78 (m, 1H-15b), 1.66 (dddd, J = 12.5, 12.5, 12.5, 3.9, 1H-16ax), 1.99 (m, 1H-16eq), 3.36 (br.s, $W_{1/2}$ = 90, 1H-OH). ^{13}C NMR (125 MHz): 12.45 (C-1), 150.58 (C-2), 125.50 (C-3), 142.14 (C-4), 24.66 (C-5), 34.11 (C-6), 25.95 (C-7), 22.27 (C-8), 26.31 (C-9), 13.68 (C-10), 65.68 (C-11), 72.52 (C-12), 33.15 (C-13), 24.05 (C-14), 24.90 (C-15), 30.47 (C-16). IR, UV, and MS data were identical to those of **5a**.

4.11. (1*S*,2*S*)-Benzoic acid-2-((3b*S*,4a*R*)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-*c*]-pyrazol-1-yl)cyclohexyl ester 9a

Treatment of **5** (4.5 g, 17 mmol) with benzoyl chloride followed by crystallization of the crude product **9** from MeCN led to **9a** (2.9 g, 46%) as white needles with mp 167–169°C (MeCN, dec.) and $[\alpha]_D^{21} = +179$ (*c* 1.7, $CHCl_3$). UV (EtOH) λ_{max}/nm 231 (ε 17000); 269 (ε 900). IR ($CHCl_3$) ν/cm^{-1} 1716 (C=O). MS (*m*/*z*, %): 364.2143 (M^+, 45%, $C_{23}H_{28}N_2O_2$, requires 364.2151), 349 (79), 259 (28), 242 (11), 227 (93), 201 (10), 173 (4), 161 (24), 147 (98), 132 (7), 105 (100), 77 (54), 41 (13). ^{1}H NMR (CCl_4–$CDCl_3$, 200 MHz): 2.05 s (3H-1), 2.48 d (J = 16.0, 1H-5α), 2.77 dd (J = 16.0, 7.0, 1H-5β), 2.32 m (1H), 1.1–1.71 m (5H), 1.75–2.1 m (4H), 3.96 m (1H-11), 5.22 m (1H-12); aromatic protons: 7.25–7.50 m (3H), 7.80–7.90 m (2H). ^{13}C NMR (50 MHz): 12.28 (C-1), 149.34 (C-2), 124.72 (C-3), 141.33 (C-4), 23.69 (C-5), 33.77 (C-6), 25.99 (C-7), 21.98 (C-8), 26.11 (C-9), 13.33 (C-10), 62.06 (C-11), 74.49 (C-12), 31.41 (C-13), 23.69 (C-14), 24.61 (C-15), 31.20 (C-16), 164.55 (C=O), aromatic carbons: 127.67 d (2C), 129.34 d (2C), 130.20 s (1C), 132.15 d (1C).

4.11.1. Crystal data for 9a. $C_{23}H_{28}N_2O_2$, M = 364.47, monoclinic, space group $P2_1$, a = 5.8010(8), b =

18.834(2), $c=9.541(1)$ Å, $\beta=95.77(1)°$, $V=1037.1(2)$ Å^3, $Z=2$, $D_{calcd}=1.167$ g cm^{-3}, $\mu=0.074$ mm^{-1}, $F(000)=392$, crystal size 0.19×0.38×1.10 mm. Absorption corrections were applied by integration method (min. and max. transmission 0.93–0.99) for 1859 measured intensities ($\theta<25°$) of which 1581 were considered as observed ($I>2\sigma$). Data/restraints/parameters: 1859/1/246. Goodness-of-fit on F^2: 1.028. Final R indices [$I>2\sigma(I)$]: $R_1=0.0469$, $wR_2=0.1254$. R indices (all data): $R_1=0.0558$, $wR_2=0.1344$. Absolute structure parameter: 2(2). Extinction coefficient: 0.004(4). The positions of hydrogen atoms were refined using riding model. C(1) methyl group is disordered with occupation factors 40:60. Crystallographic data (excluding structure factors) for the structure **9a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 172663. 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].

4.12. Diastereomeric mixture of (1*R*,2*S*)-1,2-diphenyl-2-((3b*S*,4a*R*)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-*c*]pyrazol-1-yl)ethanol and (1*S*,2*R*)-1,2-diphenyl-2-((3b*S*,4a*R*)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-*c*]pyrazol-1-yl)ethanol 4

Treatment of diketone **1** (1.3 g, 7.9 mmol) with 1,2-diphenyl-2-hydroxyethyl hydrazine **2a** resulted in a mixture of diastereomers **4** (1.4 g, 50%, **4a**:**4b**=1:1 according to NMR and GC–MS) as pale yellow crystals. IR ($CHCl_3$) ν/cm^{-1} 3327 (OH). UV (EtOH) λ_{max}/nm 240 (ε 4360). MS (m/z, %): 358.20457 (M$^+$, 2%, $C_{24}H_{26}N_2O$, requires 358.20450), 325 (10), 308 (2), 284 (2), 251 (100), 237 (4), 221 (5), 209 (6), 194 (3), 175 (33), 147 (13), 117 (4), 105 (11), 91 (15), 77 (15), 65 (3), 51 (2).

Double crystallization of **4** (100 mg, 0.28 mmol) resulted in **4a** (11 mg, 11%) as white crystals, while column chromatography of **4** gave **4a** (36% yield) and **4b** (26%).

4.13. (1*S*,2*R*)-1,2-Diphenyl-2-((3b*S*,4a*R*)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-*c*]-pyrazol-1-yl)ethanol 4a

Mp 159–160°C (MeCN), $[\alpha]_D^{21}=+298$ (c 1.34, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 2.24 (s, 3H-1), 1.87 (d, $J=17.0$, 1H-5α), 2.47 (dd, $J=17.0$, 7.0 1H-5β), 1.56 (dd, $J=7.0$, 7.0, 1H-6), 1.75 (dd, $J=7.0$, 1.3, 1H-7), 0.97 (s, 3H-9), 0.36 (s, 3H-10), 4.92 (d, $J=3.0$, 1H-11), 5.69 (d, $J=3.0$, 1H-12); aromatic protons: 6.66–6.79 2H, 6.95–7.15 (m, 8H). ^{13}C NMR (100 MHz): 12.71 (C-1), 151.41 (C-2), 125.49 (C-3), 141.63 (C-4), 23.62 (C-5), 26.27 (C-6), 34.13 (C-7), 21.95 (C-8), 26.40 (C-9), 13.48 (C-10), 68.77 (C-11), 74.83 (C-12), aromatic carbons: 126.70 d (2C), 127.28 d (3C), 127.47 d (1C), 127.71 d (2C), 128.55 d (2C), 135.50 s (1C), 139.98 s (1C). IR, UV, and MS data were identical to those of **4**.

4.13.1. Crystal data for 4a. $C_{24}H_{26}N_2O$, $M=358.47$, orthorhombic, space group $P2_12_12_1$, $a=5.867(1)$, $b=13.713(2)$, $c=25.385(4)$ Å, $V=2042.5(6)$ Å^3, $Z=4$, $D_{calcd}=1.166$ g cm^{-3}, $\mu=0.071$ mm^{-1}, $F(000)=768$, crystal size 0.08×0.09×2.30 mm. Of 2081 measured intensities with $\theta<25°$ 1510 were considered observed ($I>2\sigma$). No absorption corrections were applied, min. and max. transmission 0.85–0.99. Data/restraints/parameters: 2081/0/251. Goodness-of-fit on F^2: 1.040. Final R indices [$I>2\sigma(I)$]: $R_1=0.0451$, $wR_2=0.1073$. R indices (all data): $R_1=0.0688$, $wR_2=0.1224$. Absolute structure parameter: 1(3). Extinction coefficient: 0.0079(17). The positions of hydrogen atoms were refined using riding model. Crystallographic data (excluding structure factors) for the structure **4a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 172662. 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].

4.14. (1*R*,2*S*)-1,2-Diphenyl-2-((3b*S*,4a*R*)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-*c*]-pyrazol-1-yl)ethanol 4b

Mp 109–111°C (MeCN). $[\alpha]_D^{21}=-39$ (c 1.59, $CHCl_3$); ^{1}H NMR (CCl_4–$CDCl_3$, 200 MHz): 2.23 (s, 3H-1), 2.17–2.24 (m, 2H-5), 1.53 (m, 1H-6), 1.69 (d, $J=7.0$, 1H-7), 1.02 (s, 3H-9), 0.59 (s, 3H-10), 4.84 (d, $J=3.5$, 1H-11), 5.63 (d, $J=3.5$, 1H-12), 5.55 (br.s (OH)); aromatic protons: 6.74–6.79 (m, 2H), 7.04–7.16 (m, 8H). ^{13}C NMR (50 MHz): 12.70 (C-1), 151.68 (C-2), 125.43 (C-3), 142.03 (C-4), 23.65 (C-5), 26.72 (C-6), 34.50 (C-7), 22.31 (C-8), 26.52 (C-9), 13.90 (C-10), 69.39 (C-11), 75.13 (C-12), aromatic carbons: 126.82 d (2C), 127.28 d (1C), 127.56 d (3C), 127.74 d (2C), 128.69 d (2C), 136.13 s (1C), 140.41 s (1C). IR, UV and MS data were identical to those of **4**.

4.15. (1*S*,2*R*)-Benzoic acid-1,2-diphenyl-2-((3b*S*,4a*R*)-3,4,4-trimethyl-3b,4,4a,5-tetrahydrocyclopropa[3,4]cyclopenta[1,2-*c*]pyrazol-2-yl)ethyl ester 6

Treatment of **4** (100 mg, 0.28 mmol) with benzoyl chloride followed by crystallization of the crude product from MeCN led to **6** (36 mg, 28%) as white crystals with mp 155°C (MeCN, dec.) and $[\alpha]_D^{21}=+119$ (c 0.5, $CHCl_3$). MS (m/z, %): 462.2313 (M$^+$, 3%, $C_{31}H_{30}N_2O_2$, requires 462.2307), 447 (2), 325 (10), 284 (2), 251 (100), 235 (4), 209 (4), 179 (4), 146 (5), 105 (40), 77 (20), 57 (4). IR ($CHCl_3$) ν/cm^{-1} 1723 (C=O). ^{1}H NMR (400 MHZ, $CDCl_3$): 2.13 (s, 3H-1), 2.03 (ddd, $J=16.5$, 1.3, 1.3, 1H-5α), 2.56 (dd, $J=7.0$, 16.2, 1H-5β), 1.48 (ddd, $J=7.0$, 6.3, 1.3, 1H-6), 1.58 (dd, $J=6.3$, 1.3, 1H-7), 0.92 (s, 3H-9), –0.01 (s, 3H-10), 5.25 (d, $J=10.0$, 1H-11), 6.86 (d, $J=10.0$, 1H-12); aromatic protons: 7.11–7.22 (m, 4H), 7.24–7.32 (m, 4 H), 7.38–

7.45 (m, 3H), 7.76 (m, 2H). ^{13}C NMR (100 MHz): 12.70 (C-1), 150.61 (C-2), 124.90 (C-3), 142.70 (C-4), 23.35 (C-5), 26.30 (C-6), 33.93 (C-7), 22.04 (C-8), 26.31 (C-9), 13.20 (C-10), 68.10 (C-11), 75.98 (C-12), 164.43 (C=O), aromatic carbons: 127.12 d (2C), 128.05 d (1C), 128.09 d (2C), 128.17 d (2C), 128.27 d (3C), 128.31 d (2C), 129.46 d (2C), 130.08 s (1C), 132.65 d (1C), 137.58 s (1C), 138.39 s (1C).

Acknowledgements

The authors thank the Russian Foundation for Basic Research (Grant No. 01-03-32369) and INTAS (Grant No. 97-0217) for financial support of this work.

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