Mendeleev Commun., 1997, 7(4), 139–141

Synthesis of chiral *N*-acyl-2-pyrazolin-5-ols with a modified carane carbon frame

Sergey A. Popov and Alexey V. Tkachev*

Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 630090 Novosibirsk, Russian Federation. Fax: +7 3832 35 4752; e-mail: atkachev@lfmi.nioch.nsc.ru

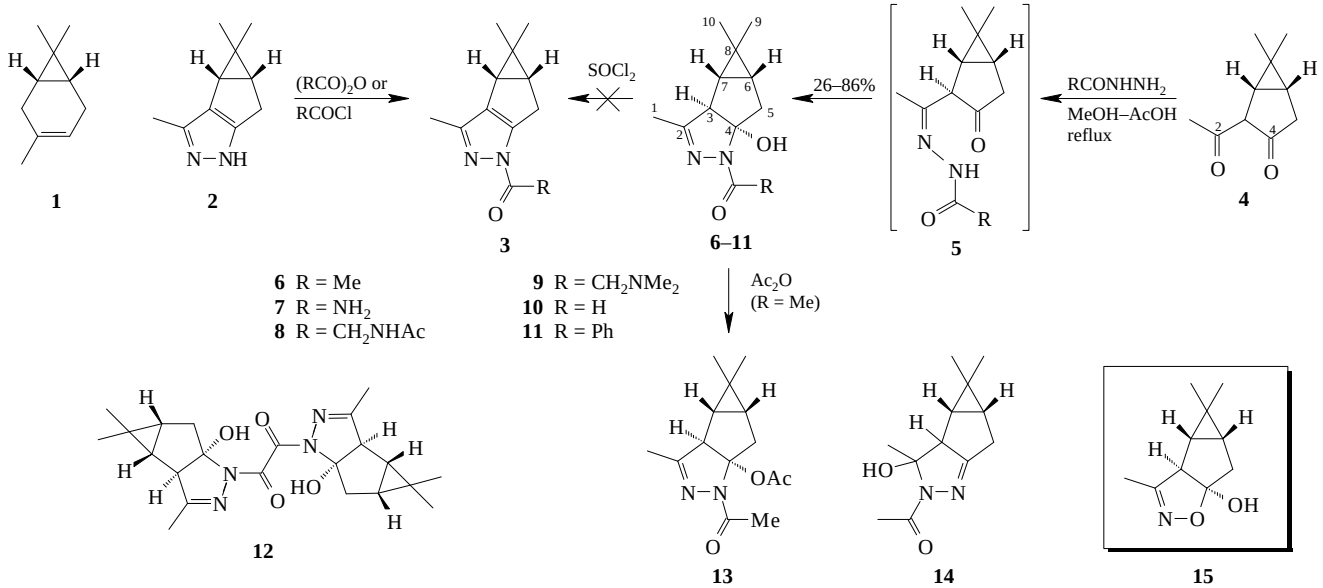
Treatment of bicyclic monoterpene diketone with a modified carane skeleton with acylhydrazines results in stable *N*-acylpyrazolinols in 26–86% yield.

N-Acylpyrazoles have drawn considerable attention as compounds possessing biological activities of various types.[1,2] The successful application of optically active pyrazolides as chiral auxiliaries in diasteroselective synthesis has been demonstrated recently.[3] Reactions of pyrazoles with acyl halides and anhydrides as well as reaction of 1,3-diketones with acylhydrazines are the most common synthetic routes to *N*-acylpyrazoles;[4–6] different positional isomers (R-N^1 or R-N^2) being often obtained in the reactions of non-symmetric substituted pyrazoles. Treatment of pyrazole **2**, derived from natural (+)-3-carene **1**, with acetic anhydride or acetyl chloride proceeded regioselectively to form the only positional isomer **3**.[7] In order to study the possibility of formation of another positional isomer of acylated pyrazoles and to obtain *N*-acyl derivatives which are not accessible by direct acylation, we have involved diketone **4** in the reaction with a number of acylhydrazines.

Surprisingly, treatment of diketone **4** with aliphatic acylhydrazines and semi-carbazide in boiling methanol in the presence of acetic acid results in good yields of 1-acylpyrazolin-5-ols **6**–**10**, **12** shown in the scheme. (The numbering scheme of the carbon frame does not coincide with the numbering of the system according to IUPAC and is given for NMR interpretation only). No pyrazolides were detected in the crude products. Reaction of diketone **4** with formyl hydrazine yields unsubstituted pyrazole **2** as one of the main products. In contrast to aliphatic acyl hydrazines, reaction of diketone **4** with aromatic acid derivatives (benzoyl, salicyl and anthranil hydrazines) led to complex mixtures of unidentified products under the same reaction conditions. Only in the case of benzoyl hydrazine was 1-benzoylpyrazolin-5-ol **11** derivative isolated in moderate yield.

4*H*-Pyrazolin-5-ols are believed to be labile intermediates and are not isolated in the normal manner. The known example of pyrazolin-5-ol – 1-phenyl-4-dialkylpyrazolin-5-ol – was obtained by reduction of the corresponding pyrazol-5-one.[8] The carane-type 1-acylpyrazolin-5-ols **6**–**12** are stable compounds and are not transformed to the corresponding acylpyrazoles **3** by dehydration. Thus, treatment of *N*-acylpyrazolinol with acetic anhydride resulted in *O*-acylation and formation of the corresponding *N*-acyl-*O*-acetyl derivative **13**, and only traces of acylpyrazole **3** (R=Me) were detected. Reaction of 1-acylpyrazolin-5-ols **6**–**12** with $SOCl_2$ gave a complex mixture of products. Analysis of the ^1H and ^{13}C NMR spectra of the 1-acylpyrazolin-5-ols **6**–**12** and *O*-acyl derivative **13** shows that these compounds are stereochemical analogues of isoxazolin-5-ol **15** whose formation and stability has been already discussed.[9] All the compounds **6**–**13** show strong intramolecular hydrogen bonding (ν_{O-H} 3525–3550 cm^{-1}) in contrast to isoxazolin-5-ol **15** (ν_{O-H} 3590 cm^{-1}).[9] This is due to the most stable conformation with a synclinal alignment of the hydroxyl and carbonyl oxygen (according to molecular mechanics calculations: $\phi_{C4-N-C-O}$ = 0–5°, $\phi_{O-C4-N-C}$ = 40–45°). Reaction of diketone **4** with acylhydrazines proceeds highly regioselectively, and formation of the isomeric pyrazolinol **14** was not detected. The high regioselectivity of the reaction is explained in terms of primary attack of the least hindered carbonyl (C-2 atom of the substrate) by the terminal nitrogen of the *N*-acylhydrazines and intermediate formation of hydrazone **5**. The reason for the tolerance of the 1-acylpyrazolin-5-ols **6**–**12** to dehydration is probably the same as in the case of isoxazolin-5-ol **15**: unfavourable relative position of the hydroxyl and adjacent C–H bonds (according to molecular mechanics calculations: $\phi_{H-C3-C4-O}$ = 5°, $\phi_{H5\alpha-C5-C4-O}$ = 6°, $\phi_{H5\beta-C3-C4-O}$ = 112°) makes bimolecular elimination (dehydration) extremely difficult. Monomolecular elimination (protonation of the hydroxyl followed by removal of the water molecule and intermediate formation of the C-4-cation) is also unfavourable because of the presence of an electron acceptor at the neighbouring position (acyl group).

A typical synthesis was carried out as follows. Acylhydrazine (4 mmol, prepared by treatment of the



corresponding methyl ester with hydrazine hydrate) was added to a stirred solution of diketone **4** (0.33 g, 2 mmol, prepared as described earlier[9]) in a mixture of methanol (15 ml) and AcOH (0.5 ml). The reaction mixture was heated to reflux and allowed to stay at this temperature for 3–4 h. The solvent was distilled off at reduced pressure, the residue was treated with water (20 ml) and extracted with CH_2Cl_2 (2×20 ml). The combined extracts were dried (Na_2SO_4) and concentrated to give the crude product that was then purified by column chromatography or crystallization from the appropriate solvent to give an analytical sample of acylpyrazolinol. The yields were 75% (**6**),† 86% (**7**),‡ 77% (**8**),§ 58% (**9**),¶ 36% (**10**),†† 26% (**11**).‡‡ In case of oxalyl hydrazide, dipyrazolide **12**§§ was obtained in 56% yield. *O*-Acylation was carried out as follows. Acetic anhydride (10 g, 98 mmol) was added dropwise at 0 °C to a stirred solution of *N*-acylpyrazolinol **7** (3.0 g, 13 mmol) in Et_3N (10 ml) and the reaction mixture was allowed to stay at room temperature for 48 h. The resulting solution was diluted with water and extracted with ether. The ethereal extract was washed with water and 0.5 M aqueous $NaHCO_3$, dried and concentrated at reduced pressure. The crude product was percolated through a silica gel column (Et_2O–pentane) and crystallized from toluene–pentane to give white crystals of acylated derivative **13** (1.8 g, 52%).¶¶

The research described in this publication was made possible in part by grant no. INTAS-93-1588-EXT.

References

1 J. B. Wright, W. E. Dullin and J. H. Markillie, *J. Med. Chem.*, 1964, **7**, 102.

2 C. Kashima, I. Fukuchi, K. Takahashi and A. Hosomi, *Tetrahedron Lett.*, 1993, **34**, 8305.

† (3a*R*,3b*R*,4a*R*,5a*R*)-{5a-*Hydroxy*-3,4,4-*trimethyl*-3a,3b,4,4a,5,5a-*hexahydrocyclopropa*[3,4]*cyclopenta*[1,2-*c*]*pyrazol*-1-*yl*}*ethanone* **6**. Colourless oil with $[\alpha]^{21}$ –150 (*c* 11.4, $CHCl_3$). IR (ν/cm^{-1}, $CHCl_3$) 3525 (O–H), 1640 (C=O), 1620 sh., 1450. UV (λ/nm, EtOH): 233 (ε 16400). MS (*m*/*z*, %): 222.13681 (M^+, 12, $C_{12}H_{18}N_2O_2$ requires 222.13682), 207 (2), 180 (2), 179 (1), 165 (12), 163 (4), 140 (20), 123 (5), 111 (22), 109 (6), 99 (22), 98 (41), 91 (4), 83 (21), 82 (100). ^{1}H NMR (200 MHz, $CDCl_3$–CCl_4) δ: 0.93 (s, 3H-10), 0.92 (dd, *J* = 7.3 and 1.3 Hz, H-7), 1.06 (s, 3H-9), 1.10 (dd, *J* = 7.3 and 7.3 Hz, $w_{1/2}$ = 3.0 Hz, H-6), 1.95 (s, 3H-1), 1.97 (dd, *J* = 15.5 and 1.3 Hz, H-5a), 2.12 (s, $NCOCH_3$), 2.77 (dd, *J* = 15.5 and 7.3 Hz, H-5b), 2.93 (br. s, $w_{1/2}$ = 3.5 Hz, H-3), 4.9 (br., $w_{1/2}$ = 37 Hz, OH). ^{13}C NMR (50 MHz) δ: 14.46 (C-1), 156.23 (C-2), 61.97 (C-3), 107.01 (C-4), 40.38 (C-5), 30.75 (C-6), 32.34 (C-7), 20.51 (C-8), 26.64 (C-9), 14.06 (C-10), 168.94 ($NCOCH_3$), 21.83 ($NCOCH_3$).

‡ (3a*R*,3b*R*,4a*R*,5a*R*)-{5a-*Hydroxy*-3,4,4-*trimethyl*-3a,3b,4,4a,5,5a-*hexahydrocyclopropa*[3,4]*cyclopenta*[1,2-*c*]pyrazole-1}*carboxylic acid amide* **7**. Mp ≈140 °C (decomp., EtOAc–EtOH), $[\alpha]^{21}$ –132 (*c* 2.56, EtOH). IR (ν/cm^{-1}, $CHCl_3$) 3530 (O–H), 3410 (N–H), 1695, 1675, 1655, 1640, 1570, 1465, 1455. UV (λ/nm, EtOH): 233 (ε 12200). MS (*m*/*z*, %): 223.13261 (M^+, 8, $C_{11}H_{17}N_3O_2$ requires 223.13207), 205 (1), 180 (2), 165 (10), 163 (5), 162 (6), 147 (21), 141 (62), 111 (16), 109 (6), 99 (18), 98 (100), 83 (21), 82 (69). ^{1}H NMR (200 MHz, $CDCl_3$–CCl_4) δ: 0.97 (s, 3H-10), 0.95 (d, *J* = 7.3 Hz, H-7), 1.09 (s, 3H-9), 1.16 (dd, *J* = 7.3 and 7.3 Hz, $w_{1/2}$ = 3.0 Hz, H-6), 1.98 (s, 3H-1), ≈1.96 (H-5a), 2.77 (dd, *J* = 15.3 and 7.3 Hz, H-5b), 2.97 (br. s, $w_{1/2}$ = 3.5 Hz, H-3), 5.1 (br., $w_{1/2}$ = 33 Hz, OH), 5.69 (br. s, $w_{1/2}$ = 11 Hz, NH_2). ^{13}C NMR (50 MHz) δ: 14.57 (C-1), 62.33 (C-3), 107.45 (C-4), 40.35 (C-5), 30.75 (C-6), 32.14 (C-7), 20.52 (C-8), 26.66 (C-9), 14.20 (C-10), 154.45 and 155.59 (C-2 and $NCONH_2$).

§ (3a*R*,3b*R*,4a*R*,5a*R*)-*N*-{2-(5a-*Hydroxy*-3,4,4-*trimethyl*-3a,3b,4,4a,5,5a-*hexahydrocyclopropa*[3,4]*cyclopenta*[1,2-*c*]*pyrazol*-1-*yl*)-2-*oxoethylacetamide* **8**. Mp 158–160 °C (decomp., toluene–$CHCl_3$), $[\alpha]^{21}$ –126 (*c* 2.63, $CHCl_3$). IR (ν/cm^{-1}, $CHCl_3$) 3545 (O–H), 3420 (N–H), 1660, 1645, 1515, 1460, 1430. UV (λ/nm, EtOH): 233 (ε 12200). MS (*m*/*z*, %): 279.1577 (M^+, 10, $C_{14}H_{21}N_3O_3$ requires 279.1582), 207 (7), 180 (100), 165 (41), 163 (11), 156 (22), 147 (4), 111 (41), 99 (97). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.97 (s, 3H-10), 0.99 (d, *J* = 7.3 Hz, H-7), 1.09 (s, 3H-9), 1.16 (dd, *J* = 7.3 and 7.3 Hz, $w_{1/2}$ = 3.0 Hz, H-6), 1.96 (s, CH_3CON), 2.00 (s, 3H-1), ≈2.03 (H-5a), 2.83 (dd, *J* = 15.3 and 7.3 Hz, H-5b), 3.00 (br. s, $w_{1/2}$ = 3.5 Hz, H-3), 4.24 (AB-part of ABX-system, J_{AB} = 19 Hz, J_{AX} = J_{BX} = 5 Hz, $COCH_2NH$), 4.7 (br., $w_{1/2}$ = 18 Hz, OH), 5.5 (br., $w_{1/2}$ = 14 Hz, CH_2NHCO). ^{13}C NMR (50 MHz) δ: 14.54 (C-1), 158.42 (C-2), 62.07 (C-3), 107.45 (C-4), 39.87 (C-5), 30.61 (C-6), 32.37 (C-7), 20.62 (C-8), 26.49 (C-9), 14.00 (C-10), 166.71 and 170.06 ($NCOCH_2$ and CH_3CONH), 42.01 ($COCH_2NH$), 22.75 ($HNCOCH_3$).

¶ (3a*R*,3b*R*,4a*R*,5a*R*)-2-*Dimethylamino*-1-{5a-*hydroxy*-3,4,4-*trimethyl*-3a,3b,4,4a,5,5a-*hexahydrocyclopropa*[3,4]*cyclopenta*[1,2-*c*]*pyrazol*-1-*yl*}-*ethanone* **9**. Mp 91–93 °C (hexane–toluene), $[\alpha]^{15}$ –122 (*c* 1.05, $CHCl_3$). IR (ν/cm^{-1}, $CHCl_3$) 3525 (O–H), 1645 (C=O), 1625 sh., 1455. UV (λ/nm, EtOH): 238 (ε 13200). MS (*m*/*z*, %): 265.1792 (M^+, 4, $C_{14}H_{23}N_3O_2$ requires 265.1790), 247 (9), 163 (2), 165 (41), 85 (2), 58 (100). ^{1}H NMR (200 MHz, $CDCl_3$–CCl_4) δ: 0.95 (s, 3H-10), 0.94 (dd, *J* = 5.7 and 1.2 Hz, H-7), 1.08 (s, 3H-9), 1.15 (dd, *J* = 7.2 and 5.7 Hz, H-6), 1.98 (s, $w_{1/2}$ = 2.3 Hz, 3H-1), 2.02 (dd, *J* = 15.2 and 1.7 Hz, H-5a), 2.30 (s, Me_2NCO), 2.80 (dd, *J* = 15.2 and 7.2 Hz, H-5b), 2.94 (br. s, $w_{1/2}$ = 3.5 Hz, H-3), 3.34 (br. s, $w_{1/2}$ = 3.0 Hz, $NCOCH_2N$), 4.55 (br., $w_{1/2}$ = 32 Hz, OH). ^{13}C NMR (50 MHz) δ: 14.57 (C-1), 156.77 (C-2), 61.60 (C-3), 107.39 (C-4), 40.69 (C-5), 30.81 (C-6), 32.45 (C-7), 20.66 (C-8), 26.66 (C-9), 14.06 (C-10), 168.44 ($NCOCH_2$), 45.57 (Me_2N), 59.92 ($COCH_2N$).

†† (3a*R*,3b*R*,4a*R*,5a*R*)-{5a-*Hydroxy*-3,4,4-*trimethyl*-3a,3b,4,4a,5,5a-*hexahydrocyclopropa*[3,4]*cyclopenta*[1,2-*c*]*pyrazol*-1-*yl*}*carboxaldehyde* **10**. Mp 96–97 °C (hexane–toluene), $[\alpha]^{21}$ –143 (*c* 3.10, $CHCl_3$). IR (ν/cm^{-1}, $CHCl_3$) 3545 (O–H), 2725 (H–CO), 1655 (C=O), 1630, 1430. UV (λ/nm, EtOH): 230 (ε 15000). MS (*m*/*z*, %) δ 208.1219 (M^+, 39, $C_{11}H_{16}N_2O_2$ requires 208.1211), 193 (7), 165 (14), 164 (16), 163 (11), 162 (13), 148 (15), 147 (37), 109 (22), 99 (8), 98 (11), 82 (100), 79 (14), 67 (52). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.97 (s, 3H-10), 0.98 (dd, *J* = 7.4 and 1.1 Hz, H-7), 1.09 (s, 3H-9), 1.17 (ddd, *J* = 7.4, 7.4 and 1.6 Hz, H-6), 2.01 (s, 3H-1), 2.03 (dd, *J* = 15.1 and 1.5 Hz, H-5a), 2.89 (dd, *J* = 15.1 and 7.3 Hz, H-5b), 3.03 (br. s, $w_{1/2}$ = 4.5 Hz, H-3), 4.75 (br., $w_{1/2}$ = 28 Hz, OH), 8.57 (s, NCHO). ^{13}C NMR (50 MHz) δ: 14.45 (C-1), 159.25 (C-2), 62.76 (C-3), 106.43 (C-4), 39.27 (C-5), 30.56 (C-6), 32.26 (C-7), 20.72 (C-8), 26.49 (C-9), 14.03 (C-10), 159.98 (NCHO).

‡‡ (3a*R*,3b*R*,4a*R*,5a*R*)-{5a-*Hydroxy*-3,4,4-*trimethyl*-3a,3b,4,4a,5,5a-*hexahydrocyclopropa*[3,4]*cyclopenta*[1,2-*c*]*pyrazol*-1-*yl*}*phenylmethanone* **11**. Mp 106–108 °C (hexane–toluene), $[\alpha]^{15}$ –183 (*c* 0.47, $CHCl_3$). IR (ν/cm^{-1}, $CHCl_3$) 3512 (O–H), 1615 (C=O), 1450, 1440. UV (λ/nm, EtOH): 230 (ε 9800). MS (*m*/*z*, %): 284.1518 (M^+, 3, $C_{17}H_{20}N_2O_2$ requires 284.15247), 202 (27), 106 (11), 105 (100), 82 (11), 77 (27). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.06 (s, 3H-10), 1.10 (dd, *J* = 7.3 and 1.0 Hz, H-7), 1.21 (s, 3H-9), 1.30 (ddd, *J* = 7.3, 7.3 and 1.4 Hz, H-6), 2.08 (s, 3H-1), 2.21 (dd, *J* = 15.2 and 1.4 Hz, H-5a), 2.99 (dd, *J* = 15.2 and 7.3 Hz, H-5b), 3.11 (br. s, $w_{1/2}$ = 3.5 Hz, H-3), 4.8 (br. s, $w_{1/2}$ = 26 Hz, OH), 7.3–7.5 (m, 3H) and 7.8–8.0 (m, 2H, PhCO). ^{13}C NMR (50 MHz) δ: 14.81 (C-1), 158.08 (C-2), 61.23 (C-3), 108.81 (C-4), 40.93 (C-5), 30.90 (C-6), 32.55 (C-7), 20.78 (C-8), 26.69 (C-9), 14.18 (C-10), 167.31 (PhCO), aromatic carbons: 127.58 (d, 2C), 129.89 (d, 2C), 131.13 (d), 133.94 (s).

§§ (3a*R*,3b*R*,4a*R*,5a*R*)-1,2-*Bis*{5a-*hydroxy*-3,4,4-*trimethyl*-3a,3b,4,4a,5,5a-*hexahydrocyclopropa*[3,4]*cyclopenta*[1,2-*c*]*pyrazol*-1-*yl*}*ethane*-1,2-*dione* **12**. Mp 126–127 °C (hexane–toluene), $[\alpha]^{16}$ –93.2 (*c* 1.30, $CHCl_3$). IR (ν/cm^{-1}, $CHCl_3$) 3550 (O–H), 1670, 1650, 1500, 1430. UV (λ/nm, EtOH): 236 (ε 21400). MS (*m*/*z*, %): 414.2260 (M^+, 14, $C_{22}H_{30}N_4O_4$ requires 414.2267), 317 (21), 299 (14), 207 (69), 191 (22), 179 (20), 164 (37), 163 (100), 147 (45), 136 (12), 121 (15), 111 (25), 109 (18), 106 (13). ^{1}H NMR (200 MHz, $CDCl_3$–[$^2H_6$]acetone) δ: 1.00 (s, 3H-10), 1.09 (dd, *J* = 7.1 and 1.1 Hz, H-7), 1.15 (s, 3H-9), 1.21 (ddd, *J* = 7.1, 7.1 and 1.6 Hz, H-6), 1.99 (s, 3H-1), 2.05 (dd, *J* = 15.2 and 1.6 Hz, H-5a), 3.03 (dd, *J* = 15.2 and 7.1 Hz, H-5b), 3.01 (br. s, $w_{1/2}$ = 4.5 Hz, H-3), 5.50 (br. s, $w_{1/2}$ = 5 Hz, O*H*). ^{13}C NMR (50 MHz) δ: 13.24 (C-1), 61.85 (C-3), 106.34 (C-4), 37.42 (C-5), 29.53 (C-6), 31.55 (C-7), 19.43 (C-8), 25.32 (C-9), 12.90 (C-10), 157.57 and 159.87 (C-2 and NCOCON).

¶¶ (3a*R*,3b*R*,4a*R*,5a*R*) *acetic acid* {1-*acetyl*-3,4,4-*trimethyl*-1,3a,3b,4,4a,5-*hexahydrocyclopropa*[3,4]*cyclopenta*[1,2-*c*]*pyrazol*-5a-*yl*} *ester* **13**. Mp 126–127 °C (hexane–toluene), $[\alpha]^{20}$ –153 (*c* 2.83, $CHCl_3$). IR (ν/cm^{-1}, $CHCl_3$) 1740 (C=O), 1660 (C=O), 1435, 1370. UV (λ/nm, EtOH): 230 (ε 14400), MS (*m*/*z*, %): 264.14760 (M^+, 9, $C_{14}H_{20}N_2O_3$ requires 264.14738), 222 (3), 207 (2), 205 (6), 204 (23), 189 (11), 166 (6), 163 (18), 162 (34), 148 (13), 147 (100), 111 (8), 106 (7), 99(13). ^{1}H NMR (200 MHz, $CDCl_3$–CCl_4) δ: 0.96 (s, 3H-10), 1.03 (dd, *J* = 7.4 and 1.0 Hz, H-7), 0.97 (s, 3H-9), 1.07 (ddd, *J* = 7.4, 6.7 and 1.6 Hz, H-6), 1.92 (s, $OCOCH_3$), 2.02 (d, *J* = 0.8 Hz, 3H-1), 2.14 (s, $NCOCH_3$), 2.19 (dd, *J* = 16.0 and 1.7 Hz, H-5a), 2.99 (dd, *J* = 16.0 and 6.7 Hz, H-5b), 3.15 (br. s, $w_{1/2}$ = 3.3 Hz, H-3). ^{13}C NMR (50 MHz) δ: 14.17 (C-1), 155.12 (C-2), 60.53 (C-3), 107.97 (C-4), 38.36 (C-5), 28.34 (C-6), 33.04 (C-7), 20.33 (C-8), 26.52 (C-9), 14.03 (C-10), 167.78 and 168.52 ($OCOCH_3$ and $NCOCH_3$), 20.87 and 22.56 ($NCOCH_3$ and $OCOCH_3$).

3 (*a*) C. Kashima, K. Takahashi and K. Fukusaka, in *Abstracts of 15th International Congress on Heterocyclic Chemistry*, Taipey, 1995, PO2-180; (*b*) C. Kashima, I. Fukuchi, K. Takahashi and A. Hosomi, *Tetrahedron*, 1996, **52** ,10335.
4 K. von Auwers and K. Dietrich, *J. Pract. Chem.*, 1934, **139**, 65.
5 C. Kashima, H. Harada, I. Kita, I. Fukuchi and A. Hosomi, *Synthesis*, 1994, 61.
6 E. Luboch and J. F. Biernat, *Pol. J. Chem.*, 1981, **55**, 2183.
7 S. A. Popov and A. V. Tkachev, *Tetrahedron: Asymmetry*, 1995, **6**, 1013.
8 K. von Auwers and F. Dersch, *Liebigs Ann. Chem.*, 1928, **462**, 104.
9 S. A. Popov, A. Yu. Denisov, Yu. V. Gatilov, I. Yu. Bagryanskaya and A. V. Tkachev, *Tetrahedron: Asymmetry*, 1994, **5**, 479.

Received: Moscow, 10th January 1997
Cambridge, 8th May 1997; Com. 7/00348J