Pergamon

Tetrahedron 56 (2000) 8173–8177

TETRAHEDRON

Reaction of 3-Methylamino-1,2-diols with Dihalomethanes. Synthesis of Chiral 4-Substituted 3-Methyltetrahydro-1,3-oxazin-5-ols

Chakib Hajji,[a] M[a] Luisa Testa,[a] Roberto de la Salud-Bea,[a] Elena Zaballos-García,[a] Juan Server-Carrió[b] and José Sepúlveda-Arques[a,*]

[a]*Departamento de Química Orgánica, Facultad de Farmacia, Universidad de Valencia, E-46100, Burjassot, Valencia, Spain*
[b]*Departamento de Química Inorgánica, Facultad de Farmacia, Universidad de Valencia, E-46100, Burjassot, Valencia, Spain*

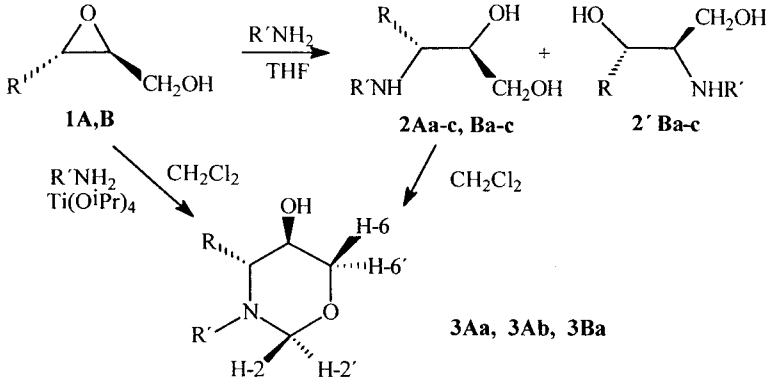
Received 25 May 2000; revised 31 July 2000; accepted 18 August 2000

Abstract—Enantiomerically pure 4,5-disubstituted 3-methyltetrahydro-1,3-oxazines have been obtained by reaction of 3-methylamino-1,2-diols with dichloromethane by regioselective differentiation of hydroxyl groups. © 2000 Published by Elsevier Science Ltd.

It has been established that although dichloromethane is a good solvent for organic reactions because of its low cost and solvating ability, it is not unreactive and with amines and diamines undergoes reactions leading to salts, aminals and Mannich adducts.[1] There are no reports in the literature concerning the formation of tetrahydro-1,3-oxazines or oxazolidines by reaction of dichloromethane with 1,3 or 1,2-amino alcohols. Here, as a continuation of our interest in the synthesis of amino alcohols,[2] we report some examples of reactions of 2,3-epoxyalcohols and 1,3 or 1,2-amino alcohols, where dichloromethane or dibromomethane can be used as C-1 synthon unit, for the preparation of tetrahydro-1,3-oxazines or oxazolidines with good yields.

It is known that ring opening of chiral 2,3-epoxyalcohols with secondary and primary amines in the presence of titanium tetraisopropoxide occurs with high regioselectivity affording regioisomers from C-3 attack.[3,4] When we studied the reaction of the primary amines, methyl, ethyl and propylamine with the epoxyalcohol **1A** (room temperature, THF, titanium tetraisopropoxide) we found that the alkylaminodiols **2Aa–c** were obtained as single regioisomers as a result of C-3 attack (Scheme 1, Table 1).

It is worth noting that it has been established[3,4] that in the absence of titanium(IV) the ring opening reactions of epoxyalcohols with primary amines at room temperature, proceed at slow rate and with low regioselectivity. However, we found that in the case of epoxyalcohol **1A**, the reaction with aqueous methylamine, aqueous ethylamine and



Scheme 1. A R=Ph, **B** R=C_3H_7; **a** R′=CH_3, **b** R′=CH_3, **b** R′=Et, **c** R′=Pr.

Keywords: heterocycles; oxazines; oxazolidines; dichloromethane; amino alcohols.
* Corresponding author. Tel.: +96-3864938, fax: +96-3864939; e-mail: jose.sepulveda@uv.es

0040–4020/00/$ - see front matter © 2000 Published by Elsevier Science Ltd.
PII: S0040-4020(00)00744-4

Table 1. Reaction of epoxyalcohols **1A** and **1B** with $MeNH_2$, $EtNH_2$ and $PrNH_2$

	Epoxyalcohol **1A**				Epoxyalcohol **1B**	
$R'NH_2$	THF–Ti(IV) (25°C)	Cl_2CH_2–Ti(IV) (25°C)	Cl_2CH_2–Ti(IV) (60°C)	CH_3OH (100°C)	THF–Ti(IV) (25°C)	Cl_2CH_2–Ti(IV) (25°C)
$MeNH_2$	6 h **2Aa** 72%	17 h **3Aa** 18%+ **2Aa** 55%	48 h **3Aa** 78%	14 h **2Aa** 98%	168 h **2**+**2′Ba** (75:25) 79%	28 h **3Ba** 67% + **2**+**2′Ba** (60:40) 17%
$EtNH_2$	20 h **2Ab** 75%	24 h **3Ab** 6% + **2Ab** 70%	48 h **3Ab** 50%	14 h **2Ab** 95%	168 h **2**+**2′Bb** (75:25) 78%	168 h **2**+**2′Bb** (89:11) 78%
$PrNH_2$	24 h **2Ac** 64%	48 h **2Ac** 65%	48 h **2Ac** 64%	14 h **2Ac** 90%	168 h **2**+**2′Bc** (77:23) 76%	168 h **2**+**2′Bc** (97:3) 76%

Table 2. Reaction of aminodiols **2** with dichloromethane

	2Aa	2Ab	2Ac	2Ba	2Bb	2Bc
Cl_2CH_2 (100°C)	28 h **3Aa** 100%	108 h **3Ab** 70%	[a]	24 h **3Ba** 98%	[a]	[a]

[a] Tetrahydro-1,3-oxazines were not formed under similar reaction conditions.

propylamine took place in methanol at 100°C without catalyst, affording the single regioisomers **2Aa–c**, with similar rates and regioselectivity to reactions carried out in THF and with titanium tetraisopropoxide. However, the yields were higher because there was no need of the workup procedure for the removal of the catalyst.

When we studied the ring opening reactions of the epoxyalcohol **1B** with these primary amines (room temperature, THF, titanium tetraisopropoxide), we obtained different results. In contrast with the epoxyalcohol **1A** which afforded single regioisomers **2Aa–c**, the epoxyalcohol **1B** did not react with the amines with complete regioselectivity and mixtures of regioisomers from C_3/C_2 attack, **2Ba–c** and **2′Ba–c** were obtained.

The results were completely different when the solvent of the reaction was dichloromethane. The epoxyalcohol **1A** in the reaction with methyl and ethylamine (room temperature, titanium tetraisopropoxide), afforded the aminodiols **2Aa** and **2Ab**, but in addition the (4*R*,5*R*) 4-substituted tetrahydro-1,3-oxazin-5-ols **3Aa** and **3Ab**, were also obtained in low yields. In the reaction with propylamine no traces of the corresponding tetrahydro-1,3-oxazine was detected. The experiments were then attempted at 60°C in a pressure reactor and the tetrahydro-1,3-oxazines were obtained with better yields (**3Aa** 78%, **3Ab** 50%). In the reaction with propylamine at 60°C, the tetrahydro-1,3-oxazine was not detected.

In the reaction of **1B** with the mentioned primary amines, in dichloromethane, the alkylaminodiols **2Ba–c** and **2′Ba–c** were obtained with similar rates, but regioselectivities were much better than in experiments carried out in THF. With this epoxyalcohol **1B**, the tetrahydro-1,3-oxazine **3Ba** (67%) was obtained only in the case of the reaction with methylamine.

The best results in the preparation of the oxazines **3Aa** and **3Ab** occurred when the aminodiols **2Aa** and **2Ab**, were directly heated with dichloromethane at 100°C in a pressure reactor (**3Aa** 100%, **3Ab** 70%). With the aminodiol **2Ac** the formation of an oxazine was not detected (Table 2).

When the mixture of aminodiols **2Ba** and **2′Ba** was heated in dichloromethane (100°C, 24 h) the aminodiol **2Ba** was converted into the tetrahydro-1,3-oxazine **3Ba** (98% yield based on reacted **2Ba**) which was easily separated from the unreacted aminodiol **2′Ba**. Products from reaction with dichloromethane were not detected when the mixtures of aminodiols **2Bb**, **2′Bb** and **2Bc**, **2′Bc** were heated with this solvent (Table 2).

These results indicate that the reaction of the aminodiols **2** with dichloromethane affording the (4*R*,5*R*)-4-substituted tetrahydro-1,3-oxazin-5-ols **3**, takes place with excellent yields only in the case of the *N*-methyl derivatives. Agami et al.[5,6] have reported examples of cyclization reactions where the presence of a *N*-methyl substituent enhances the cyclization rate in *N*-Boc aminoalcohols.

An X-ray crystallographic analysis of **3Aa** confirmed unequivocally the structure and stereochemistry. The X-ray study was made with a single crystal of **3Aa**, obtained

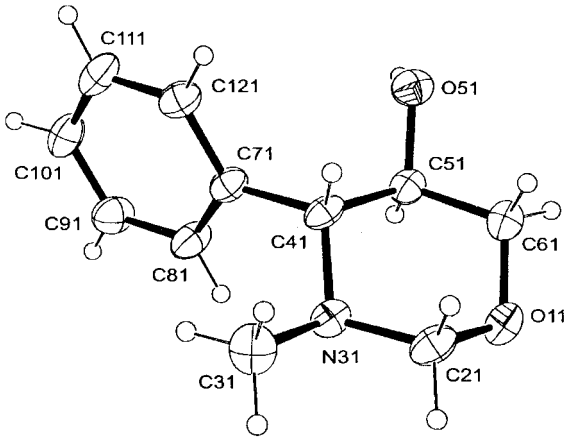
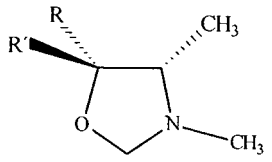


Figure 1.



4 R = C_6H_5 R′ = H

5 R = H R′ = C_6H_5

Figure 2.

from an experiment with racemic phenylglycidol as starting material and revealed the presence of two molecules in the asymmetric unit, one of each enantiomer. Fig. 1, shows one molecule of the 4*R*,5*R*-enantiomer with the numbering scheme used in the crystal study.

The most similar example to the selective differentiation of hydroxyl groups here described, has been reported for chiral 3-amino-4-phenyl-1,2-butanediol.[7] In this work the reaction of the 3-amino-1,2-diols with trichloromethylchloroformate affords oxazolidinones or oxazinones under kinetic or thermodinamic control respectively. 1,3-Oxazolidines, tetrahydro-1,3-oxazines and their derivatives are in equilibrium[8] and in the case of compounds **3** the equilibrium appears to be completely shifted to the six-membered ring.

The cyclization reaction involving the methylamino and the primary hydroxyl groups in the case of methyl aminodiols **2** suggested we attempt a similar cyclization with natural methylamino alcohols. Ephedrine and pseudoephedrine, which contain a methylamino group and a vecinal secondary alcohol, would afford with dichloromethane the formation of five membered rings by similar cyclization reactions. When (−)-ephedrine and (+)-pseudoephedrine were heated in dichloromethane at 100°C for 12 h the corresponding 1,3-oxazolidines **4**, (4*S*,5*R*)-3,4-dimethyl-5-phenyl-1,3-oxazolidine and **5**, (4*S*,5*S*)-3,4-dimethyl-5-phenyl-1,3-oxazolidine, were obtained with 37 and 41% yields, respectively. When we used dibromomethane, lower temperatures (50°C) were needed and the 1,3-oxazolidines were obtained with better yields (**4**, 49%, **5**, 51%)[9] (Fig. 2).

In conclusion, we have demonstrated the synthetic utility of dichloromethane and dibromomethane as very useful C-1 synthon units for the preparation of tetrahydro-1,3-oxazines and 1,3-oxazolidines with 1,3 and 1,2-methylamino alcohols as starting materials.

Experimental

Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. THF was distilled from Na/benzophenone immediately prior to use. CH_2Cl_2 was distilled from calcium hydride under argon. Analytical thin layer chromatography was performed on Merck pre-coated silica gel (60 F_{254}) plates and flash column chromatography was accomplished on Merck Kieselgel 60 (230–240 mesh). Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured at room temperature in a Perkin–Elmer 241 polarimeter. ^{1}H and ^{13}C NMR spectra were measured for $CDCl_3$ solutions at 250 and 62.9 MHz, respectively, using a Bruker AC-250 spectrometer and chemical shifts are recorded relative to Me_4Si. High-resolution mass spectral data were obtained with a VG Autospec spectrometer.

Synthesis of aminodiols 2

Procedure a. Titanium tetraisopropoxide (3.5 mmol) was added to a solution of 2,3-epoxyalcohols (**1A**, **1B**)[10] (1.73 mmol) and the corresponding alkylamine (2 mmol) in dry tetrahydrofuran (20 mL). The mixture was heated in a pressure reactor at the temperature and time indicated. Then a solution of 10% NaOH in saturated brine (10 mL) was added and the suspension stirred for an additional period of 12 h. The solution was filtered through a short pad of celite. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3×10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo and chromatographed on silica gel NEt_3 pre-treated (2.5% v/v). Eluting with hexane/ethyl acetate mixtures provided the amino alcohols **2Aa–c** and **2+2′Ba–c**.

Procedure b. A solution of the 2,3-epoxyalcohol **1A** (6.6 mmol) in methanol (20 mL) and a solution of aqueous methylamine (40%), aqueous ethylamine (70%) or propylamine (17.4 mmol) was heated in a pressure reactor at 100°C for 14 h. After cooling, the mixture was concentrated in vacuo affording the amino alcohols **2Aa–c**.

(2*R*,3*R*)-3-Methylamino-3-phenyl-1,2-propanediol (2Aa). *a*. 72% (25°C, 6 h), *b*. 98%. White solid. Mp 105–106°C. $[\alpha]_D^{20}=-71$ (*c* 0.52, $CHCl_3$). ν_{max} (Nujol) 3335 (br), 1659, 1485, 1308, 1224, 1107, 894. ^{1}H NMR ($CDCl_3$): δ=2.26 (s, 3H), 3.17 (br, 3H), 3.53 (d, *J*=4.7 Hz, 2H), 3.70 (d, *J*=5.5 Hz, 1H), 3.84 (m, 1H), 7.32 (m, 5H). ^{13}C NMR ($CDCl_3$): δ=34.2 (q), 64.5 (d), 68.4 (t), 73.3 (d), 127.7 (d), 128.2 (d), 128.6 (d), 138.9 (s). *m/z* (CI) 182 (1, MH^+), 164 (1), 150 (2), 134 (1), 120 (100), 107 (4), 91 (5). HRMS (CI): MH^+, found 182.1188. $C_{10}H_{16}NO_2$ requires 182.1181.

(2*R*,3*R*)-3-Ethylamino-3-phenyl-1,2-propanediol (2Ab). *a*. 75% (25°C, 20 h), *b*. 95%. White solid. Mp 98–99°C. $[\alpha]_D^{20}=-47$ (*c* 0.03, $CHCl_3$). ν_{max} (Nujol) 3415 (br), 1636, 1495, 1425, 1329, 1098. ^{1}H NMR ($CDCl_3$): δ=0.98 (t, *J*=7.0 Hz, 3H), 2.40 (dq, *J*=17.5, 7.0 Hz, 2H), 3.41 (m, 2H), 3.73 (d, *J*=4.7 Hz, 1H), 3.86 (m, 1H), 7.25 (m, 5H). ^{13}C NMR ($CDCl_3$): δ=14.5 (q), 41.2 (t), 64.2 (t), 65.3 (d), 73.4 (d), 127.4 (d), 127.9 (d), 128.3 (d), 138.7 (s). *m/z* (FAB) 196 (100, MH^+), 177 (11), 165 (4), 154 (70), 134 (50). HRMS (FAB) MH^+, found 196.1331. $C_{11}H_{18}NO_2$ requires 196.1337.

(2*R*,3*R*)-3-Propylamino-3-phenyl-1,2-propanediol (2Ac). *a*. 64% (25°C, 24 h), *b*. 90%. White solid. Mp 107–108°C. $[\alpha]_D^{20}=-63$ (*c* 0.12, $CHCl_3$). ν_{max} (Nujol) 3402 (br), 1642, 1495, 1408, 1358, 1092, 1034. ^{1}H NMR ($CDCl_3$): δ=0.78 (t, *J*=7.0 Hz, 3H), 1.36 (m, 2H), 2.27 (m, 2H), 3.37 (m, 2H), 3.70 (d, *J*=5.0 Hz, 1H), 3.82 (m, 1H), 7.22 (m, 5H). ^{13}C NMR ($CDCl_3$): δ=11.4 (q), 22.5 (t), 48.8 (t), 63.9 (t), 65.5 (d), 73.3 (d), 127.1 (d), 127.7 (d), 128.1 (d), 139.0 (s). *m/z* (FAB) 210 (100, MH^+), 195 (5), 177 (3), 165 (2).

HRMS (FAB): MH^+, found 210.1503. $C_{12}H_{20}NO_2$ requires 210.1494.

(2*R*,3*R*)-3-Methylamino-1,2-hexanediol (2Ba). *a*. **2**+**2′Ba** 79% (C_3/C_2, 75:25, 25°C, 168 h). White solid. ν_{max} (Nujol) 3415 (br), 1655, 1470, 1273, 1073. ^{1}H NMR ($CDCl_3$): δ=0.87 (t, J=6.5 Hz, 3H), 1.33 (m, 2H), 1.47 (m, 2H), 2.41 (s, 3H), 2.86 (m, 1H), 3.72 (m, 3H). ^{13}C NMR ($CDCl_3$): δ=14.2 (q), 19.4 (t), 31.8 (t), 34.7 (q), 63.1 (d), 63.9 (t), 71.1(d). *m/z* (EI) 148 (4, MH^+), 116 (16), 86 (100), 74 (42). HRMS (EI): MH^+, found 148.1334. $C_7H_{18}NO_2$ requires148.1337.

(2*R*,3*R*)-3-Ethylamino-1,2-hexanediol (2Bb). *a*. **2**+**2′Bb** 78% (C_3/C_2, 75:25, 25°C, 168 h). White solid. ν_{max} (Nujol) 3421 (br), 1655, 1463, 1293, 1078. ^{1}H NMR ($CDCl_3$): δ=0.86 (t, J=6.5 Hz, 3H), 1.01 (t, J=7.0 Hz, 3H), 1.33 (m, 2H), 1.42 (m, 2H), 2.56 (m, 1H), 2.64 (m, 2H), 3.56 (m, 2H), 3.64 (m, 1H). ^{13}C NMR ($CDCl_3$): δ= 13.8 (q), 15.5 (t), 19.3 (t), 32.9 (t), 42.8 (t), 61.1 (d), 64.2 (t), 71.3 (d). *m/z* (EI) 162 (1, MH^+), 144 (1), 130 (10), 118 (4), 100 (100), 88 (13). HRMS (EI): MH^+, found 162.1497. $C_8H_{20}NO_2$ requires162.1494.

(2*R*,3*R*)-3-Propylamino-1,2-hexanediol (2Bc). *a*. **2**+**2′Bc** 76% (C_3/C_2, 77:23, 25°C, 168 h). White solid. ν_{max} (Nujol) 3351 (br), 1655, 1469, 1308, 1073. ^{1}H NMR ($CDCl_3$): δ=0.87 (m, 6H), 1.36 (m, 6H), 2.48 (m, 1H), 2.61 (m, 2H), 3.53 (m, 1H), 3.55 (m, 2H), 3.67 (m, 1H). ^{13}C NMR ($CDCl_3$): δ=11.7 (q), 14.2 (q), 19.4 (t), 23.6 (t), 33.4 (t), 50.8 (t), 61.6 (d), 64.3 (t), 71.4 (d). *m/z* (EI) 176 (1, MH^+), 158 (1), 144 (10), 132 (4), 115 (8), 114 (100), 102 (4), 72 (10). HRMS (EI): MH^+, found 176.1642. $C_9H_{22}NO_2$ requires 176.1650.

Synthesis of tetrahydro-1,3-oxazines 3

Procedure a. The corresponding alkylamine (3.9 mmol) was added to a solution of the 2,3-epoxyalcohols **1A**, **1B** (3.3 mmol) and titanium tetraisopropoxide (6.6 mmol) in dichloromethane (40 mL). The mixture was heated in the pressure reactor at the temperature and times indicated. Then a solution of 10% NaOH in saturated brine (30 mL) was added and the suspension stirred for an additional period of 12 h. The solution was filtered through a short pad of celite. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3×10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo. The crude product was purified by chromatography on silica gel eluting with hexane/ethyl acetate mixtures affording the oxazines **3Aa**, **3Ab** and **3Ba**.

Procedure b. The aminodiols **2Aa**, **2Ab** and a mixture of **2Ba** and **2′Ba** (6 mmol) in CH_2Cl_2 (50 mL) were heated to temperature and the time indicated. The solvent was evaporated in vacuo and the residue was purified by chromatography on silica gel eluting with hexane/ethyl acetate mixtures affording the oxazines **3Aa**, **3Ab** and **3Ba**.

(4*R*,5*R*)-3-Methyl-4-phenyltetrahydro-1,3-oxazin-5-ol (3Aa). *a*. 78% (60°C, 48 h). *b*. 100%. (100°C, 28 h). White crystals. Mp 142°C. $[\alpha]_D^{20}$=−43.75 (*c* 0.032, $CHCl_3$). ν_{max} (Nujol) 3472 (br), 1642, 1418, 1354, 1041. ^{1}H NMR ($CDCl_3$): δ=1.92 (s, 3H), 2.25 (br, 1H), 2.85 (d, J= 8.7 Hz, 1H, H-4), 3.31 (t, J=10.6 Hz, 1H, H-6), 3.71 (d, J=8.0 Hz, 1H, H-2), 3.75 (m, 1H, H-5), 4.17 (dd, J=10.6, 5.1 Hz, 1H, H-6′), 4.41 (d, J=8.0 Hz, 1H, H-2′), 7.35 (m, 5H). ^{13}C NMR ($CDCl_3$): δ=36.7 (q), 68.0 (d), 71.6 (t), 75.3 (d), 87.0 (t), 128.1 (d), 128.5 (d), 128.7 (d), 138.4 (s). *m/z* (CI) 193 (M^+, 100), 176 (75), 149 (90), 133 (84), 118 (47), 91 (24). HRMS (CI): MH^+, found 194.1187. $C_{11}H_{16}NO_2$ requires 194.1181.

(4*R*,5*R*)-3-Ethyl-4-phenyltetrahydro-1,3-oxazin-5-ol (3Ab). *a*. 50% (60°C, 48 h). *b*. 70% (100°C, 108 h). Colourless oil. ν_{max} (Nujol) 3427 (br), 1655, 1448, 1169, 1073, 1048. ^{1}H NMR ($CDCl_3$): δ=0.70 (t, J=7.3 Hz, 3H), 2.37 (m, 2H), 3.01 (d, J=8.7 Hz, 1H, H-4), 3.21 (t, J=10.6 Hz, 1H, H-6), 3.65 (m, 1H, H-5), 3.72 (d, J=8.0 Hz, 1H, H-2), 4.05 (dd, J=10.6, 4.7 Hz, 1H, H-6′), 4.51 (d, J=8.0 Hz, 1H, H-2′), 7.24 (m, 5H). ^{13}C NMR ($CDCl_3$): δ=11.7 (q), 42.7 (t), 68.1 (d), 71.6 (t), 73.1 (d), 84.1 (t), 127.9 (d), 128.6 (d), 128.7 (d), 138.6 (s). *m/z* (EI) 207 (32, M^+), 192 (8), 164 (14), 162 (100), 149 (16), 146 (52), 132 (37), 118 (47), 107 (30), 91 (50). HRMS (EI): M^+, found 207.1262. $C_{12}H_{17}NO_2$ requires 207.1259.

(4*R*,5*R*)-3-Methyl-4-propyltetrahydro-1,3-oxazin-5-ol (3Ba). *a*. 67% (25°C, 28 h). *b*. 98% calculated on reacted **2B**a (100°C, 24 h). White crystals. Mp 77°C. ν_{max} (Nujol) 3402 (br), 1655, 1558, 1470, 1194, 1066, 1015. ^{1}H NMR ($CDCl_3$): δ=0.90 (t, J=7.0 Hz, 3H), 1.40 (m, 3H), 1.51 (m, 1H), 2.32 (s, 3H), 2.40 (dt, J=8.7, 4.4 Hz, 1H, H-4), 3.31 (dd, J=10.6, 8.9 Hz, 1H, H-6), 3.50 (ddd, J=8.7, 8.9, 4.6 Hz, 1H, H-5), 3.95 (dd, J=10.6, 4.6 Hz, 1H, H-6′), 4.10 (d, J=10.0 Hz, 1H, H-2), 4.34 (d, J=10.0 Hz, 1H, H-2′). ^{13}C NMR ($CDCl_3$): δ=14.0 (q), 18.5 (t), 29.9 (t), 34.6 (q), 63.4 (d), 64.3 (d), 71.6 (t), 85.7 (t). *m/z*(EI) 159 (75, M^+), 128 (8), 116 (100), 114 (79), 100 (45), 70 (54). HRMS (EI): M^+, found 159.1253. $C_8H_{17}NO_2$ requires 159.1259.

Synthesis of 1,3-oxazolidines (4, 5)

A solution of (−)ephedrine *o*-(+)pseudoephedrine (3 mmol) in (a) CH_2Cl_2 (20 mL) or (b) CH_2Br_2 (4 mL) was heated to temperature and the time indicated. After cooling, the crystalline precipitate (the corresponding salt hydrochloride or hydrobromide) was filtered off and washed with dichloromethane. The filtrate was evaporated in vacuo and the residue was purified by chromatography on silica gel eluting with hexane/ethyl acetate mixtures affording the corresponding oxazolidines **4** and **5**.

(4*S*,5*R*)-3,4-Dimethyl-5-phenyl-1,3-oxazolidine (4). *a*. 37% (100°C, 4 h). *b*. 49% (50°C, 7 h). Colourless oil. $[\alpha]_D^{20}$=+12.13 (*c* 1.04, $CHCl_3$). ν_{max} (Nujol) 3427 (br), 1661, 1502, 1457, 1386, 1239, 1054. ^{1}H NMR ($CDCl_3$): δ=0.55 (d, J=6.6 Hz, 3H), 2.23 (s, 3H), 2.73 (dq, J=6.9, 6.6 Hz, 1H, H-4), 3.93 (d, J=3.3 Hz, 1H, H-2), 4.74 (d, J=3.3 Hz, 1H, H-2′), 4.97 (d, J=6.9 Hz, 1H, H-5), 7.19 (m, 5H). ^{13}C NMR ($CDCl_3$): δ=14.0 (q), 37.4 (q), 63.1 (d), 81.7 (d), 87.9 (t), 126.6 (d), 127.0 (d), 127.6 (d),139.7 (s). *m/z* (CI) 178 (11, MH^+), 176 (100), 162 (11), 148 (78),

146 (13), 132 (6), 118 (14), 105 (14), 91 (16). HRMS (CI): M^+, found 178.1225. $C_{11}H_{16}NO$ requires 178.1231.

(4*S*,5*S*)-3,4-Dimethyl-5-phenyl-1,3-oxazolidine (5). *a*. 41% (100°C, 14 h). *b*. 49%, (50°C, 14 h). Colourless oil. $[\alpha]_D^{20}=+59.37$ (*c*0.48, $CHCl_3$). ν_{max} (Nujol) 3434 (br), 1636, 1493, 1470, 1386, 1239, 1066. ^1H NMR ($CDCl_3$): $\delta=1.15$ (d, $J=6.2$ Hz, 3H), 2.39 (s, 3H), 2.53 (dq, $J=8.7$, 6.2 Hz, 1H, H-4), 4.33 (d, $J=3.6$ Hz, 1H, H-2), 4.46 (d, $J=8.7$ Hz, 1H, H-5), 4.75 (d, $J=3.6$ Hz, 1H, H-2′), 7.24 (m, 5H). ^{13}C NMR ($CDCl_3$): $\delta=13.0$ (q), 37.0 (q), 67.8 (d), 85.8 (d), 87.4 (t), 126.0 (d), 128.1 (d), 128.4 (d),138.3 (s). *m*/*z* (EI) 177 (1, M^+), 148 (7), 132 (5), 117 (5), 105 (7), 91 (10), 86 (19), 71 (90), 58 (100). HRMS (EI): M^+, found 177.1145. $C_{11}H_{15}NO$ requires 177.1153.

X-Ray crystal data

$C_{11}H_{15}NO_2$, $M=193.245$, triclinic $P\bar{1}$, $a=6.5003(4)$, $b=10.230(2)$, $c=16.108(1)$ Å, $\alpha=72.86(1)$, $\beta=78.35(1)$, $\gamma=89.98(1)°$, $U=1000.5(2)$ Å^3, $D_c=1.28$ g cm^{-3}, $Z=4$, MoKα ($\lambda=0.7107$ Å), $\mu=0.88$ cm^{-1}. Data reduction with XRAY 76 System.[11] From the 3508 independent reflections 1923 were considered observed with the $I > 2\sigma(I)$ criterion. The structure was solved by direct methods using the program SIR 92.10.[12] Refinement by least-squares on F^2 with SHELXL 97.[13] (256 parameters). All non-hydrogen atoms were anisotropically refined. Hydrogens bonded to C atoms were placed at calculated positions. Fourier difference maps detected the hydrogens of the hydroxyl groups that were treated with a riding model in which the torsion angle of hydrogen atom was refined. Extinction coefficient= 0.014(7). Weighting scheme $w=1/[\sigma^2(F_o^2)+(0.1359P)^2]$ were $P=(F_o^2+2F_c^2)/3$. Final values: $R_1=0.062$, $wR_2=0.143$, $S=1.032$ and $\Delta\rho_{max}=0.25$, $\Delta\rho_{min}=-0.30e$ Å^{-3}. Molecular graphics were done with ORTEP3 for Windows.[14]

Acknowledgements

We are indebted to Dirección General de Investigación Científico y Técnica, for project PB98-1451. M[a] Luisa Testa thanks Generalitat Valenciana for a grant.

References

1. Claramunt, R. M.; Elguero, J.; Meco, J. *J. Heterocycl. Chem.* **1983**, 1245–1249; Mills, J. E.; Maryanoff, C. A.; Cosgrove, R. M.; Scott, L.; McComsey, D. F. *Org. Prep. Proced. Int.* **1984**, *16*, 97–114; Nevstad, G. O.; Songstad, J. *Acta Chem. Scand.* **1984**, *38*, 469–477; Mills, J. E.; Maryanoff, C. A.; McComsey, D. F.; Stanzione, R. C.; Scott, L. *J. Org. Chem.* **1987**, *52*, 1857–1859; Federsel, H. J.; Könberg, E.; Lilljequist, L.; Swahm, B. M. *J. Org. Chem.* **1990**, *55*, 2254–2256; Souquet, F.; Martens, T.; Fleury, M. B. *Synth. Commun.* **1993**, *23*, 817–828; Matsumoto, K.; Uchida, T.; Hashimoto, S.; Yonezawa, Y.; Iida, H.; Kakehi, A.; Otani, S. *Heterocycles* **1993**, *36*, 2215–2219; Hon, Y. S.; Chang, F. J.; Lu, L. J. *Chem. Soc., Chem. Commun.* **1994**, 2041–2042; Gonzalez, C.; Greenhouse, R. *Heterocycles* **1985**, *23*, 1127–1130.

2. Sepúlveda-Arques, J.; Armero-Alarte, T.; Acero-Alarcón, A.; Zaballos-García, E.; Yruretagoyena–Solesio, B.; Ezquerra-Carrera, J. *Tetrahedron* **1996**, *52*, 2097–2102.

3. Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1557–1560.

4. Canas, M.; Poch, M.; Verdaguer, X.; Moyano, A.; Pericás, A.; Riera, A. *Tetrahedron Lett.* **1991**, *32*, 6931–6934.

5. Agami, C.; Couty, F.; Hamon, L.; Venier, O. *Tetrahedron Lett.* **1993**, *34*, 4509–4512.

6. Agami, C.; Couty, F.; Hamon, L.; Venier, O. *Bull. Chem. Soc. Fr.* **1995**, *132*, 808–814.

7. Melon, C.; Gravier-Pelletier, C.; Merrer, Y. L.; Depezay, J. C. *Bull. Chem. Soc. Fr.* **1992**, *129*, 585–593.

8. László, L.; Lakatos, A. G.; Fülop, F.; Bernáth, G.; Riddell, F. G. *Tetrahedron* **1997**, *53*, 1081–1088.

9. Gelbcke, M.; Baudet, M.; Hoyois, J.; Van De Vliedt, G.; Deleers, M. *Nov. J. Chim.* **1983**, *7*, 41–47.

10. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.

11. Stewart, J. M.; Machin, P. A.; Dickinson, C. W.; Ammon, H. L.; Heck, H.; Flack, H. *The X-RAY76 System*, Technical report TR-446; Computer Science Center, University of Maryland, College Park, Maryland, 1976.

12. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G.; Giacovazzo, G.; Guagliardi, A.; Polidori, G. *J. Appl. Crystallogr.* **1994**, *27*, 435.

13. Sheldrick, G.M., SHELXL 97, Programme for the refinement of crystal structures. University of Göttingen, Germany, 1997.

14. Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30*, 565.