Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 2153–2158

TETRAHEDRON: *ASYMMETRY*

Enantioselective synthesis of both enantiomers of vicinal norbornanediamines through the Leuckart reaction of 2-norbornanones

Antonio García Martínez,[a,*] Enrique Teso Vilar,[b,*] Amelia García Fraile[b] and Paloma Martínez-Ruiz[a]

[a]*Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense de Madrid, Ciudad Universitaria s/n, E-28040 Madrid, Spain*

[b]*Departamento de Química Orgánica y Biología, Facultad de Ciencias, UNED, c/Senda del Rey 9, E-28040 Madrid, Spain*

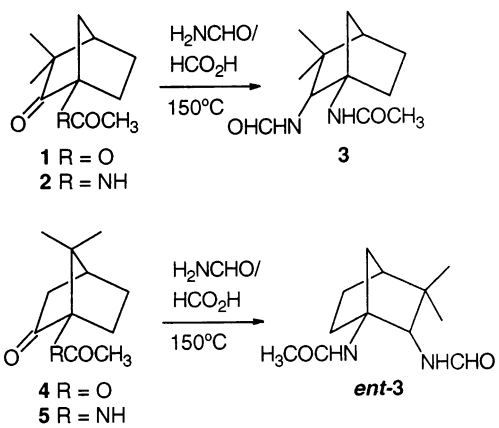
Received 20 July 2001; accepted 17 August 2001

Abstract—The reaction of 2-norbornanones bearing an amine derivative in the bridgehead position with formamide and formic acid yields enantiomerically pure 1,2-norbornane diamides. These compounds are excellent precursors of chiral vicinal diamines, which have been increasingly used due to their numerous applications in medicinal chemistry and asymmetric synthesis. The rigid structure of the norbornane framework allows the study of conformational equilibrium in the formamide groups and its dependence on other substituents in the molecule. © 2001 Published by Elsevier Science Ltd.

1. Introduction

Chiral, enantiomerically pure vicinal diamines and their derivatives[1] have been increasingly used in asymmetric catalysis for reactions including epoxidations,[2] aldol condensations,[3] nucleophilic additions to carbonyl compounds[4] and Diels–Alder cyclisations.[5] The 1,2-diamine functionality is also present in many natural products with biological properties such as biotin, cephalosporin or penicillins,[1] as well as in human pharmaceuticals such as antitumor agents, mainly in the form of diamine–metal complexes.[6,7] Over the past decades, a large number of chiral cisplatin analogues based on diaminocyclohexane derivatives, like oxaliplatin or ormaplatin, have been developed and high activities have been achieved with less toxicity.[6] In these molecules, control of the configuration of the stereogenic centres is extremely important, as it has been reported that the drugs prepared from the separated diastereoisomers have different antitumor activities.[8] The synthesis of chiral diamines with a norbornane framework is a topic of interest because they constitute rigid analogues of the diaminocyclohexane moiety. However, owing to their difficult preparation, only the synthesis and structural elucidation of 2,3-camphordiamine has been recently reported,[9] and no other chiral vicinal norbornanediamines have been described to date.

One of the classical procedures for the synthesis of amine derivatives is the Leuckart–Wallach reaction, based on the reductive amination of carbonyl compounds using mixtures of formamide, formic acid or ammonium formate as reagents.[10] The final product is in all cases a formamide derivative, which, after reduction or hydrolysis in basic or acid medium, gives the desired free amine.



Scheme 1.

* Corresponding authors. E-mail: palmarti@eucmax.sim.ucm.es

0957-4166/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0957-4166(01)00376-7

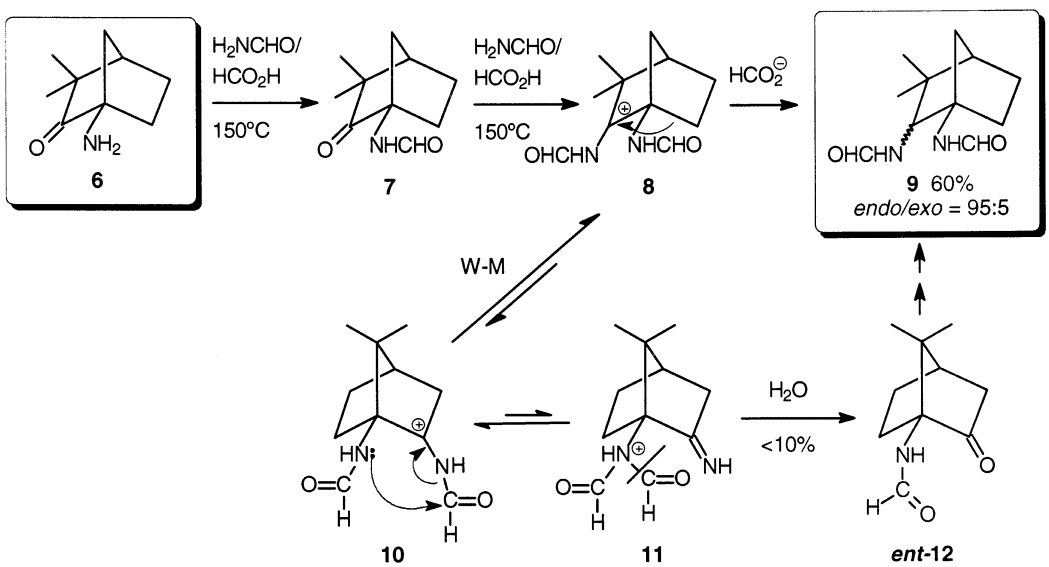
In the course of our research, we have studied the mechanism of the Leuckart reaction of 2-norbornanones, and its dependence on the substitution pattern of the substrate. In previous papers, we have described the synthesis of both enantiomers, (1*R*,2*R*)- and (1*S*,2*S*)-, of *N*-(3,3-dimethyl-2-formylamino-1-norbornyl)acetamide **3** and ***ent*-3**, respectively (Scheme 1)[11] through an ionic reaction pathway that includes skeleton rearrangements and intramolecular transamidations. This compound is the only product of the Leuckart reaction of bridgehead 2-oxo-1-norbornyl acetates[11,12] and acetamides **1**, **2**, **4** and **5** (see Scheme 1). Besides the mechanistic point of view, the relevance of this process is determined by the interest in these compounds as intermediates in the synthesis of chiral diamine derivatives.

2. Synthesis of vicinal diamines

Starting from diamide **3**, it should be possible to obtain in one step vicinal primary or secondary diamines through hydrolysis or reduction of this compound, respectively.[13] However, all attempts to hydrolyse the bridgehead acetamide group in acid or basic media were unsuccessful. This prompted us to attempt the synthesis of the title compounds through the Leuckart reaction of 3,3- and 7,7-dimethyl-2-oxo-1-norbornylamines **6** and **13**, respectively, that bear a free primary amine group at the bridgehead position. These substrates were prepared in four steps starting from naturally occurring (1*R*)-camphor and (1*R*)-fenchone, respectively.[14]

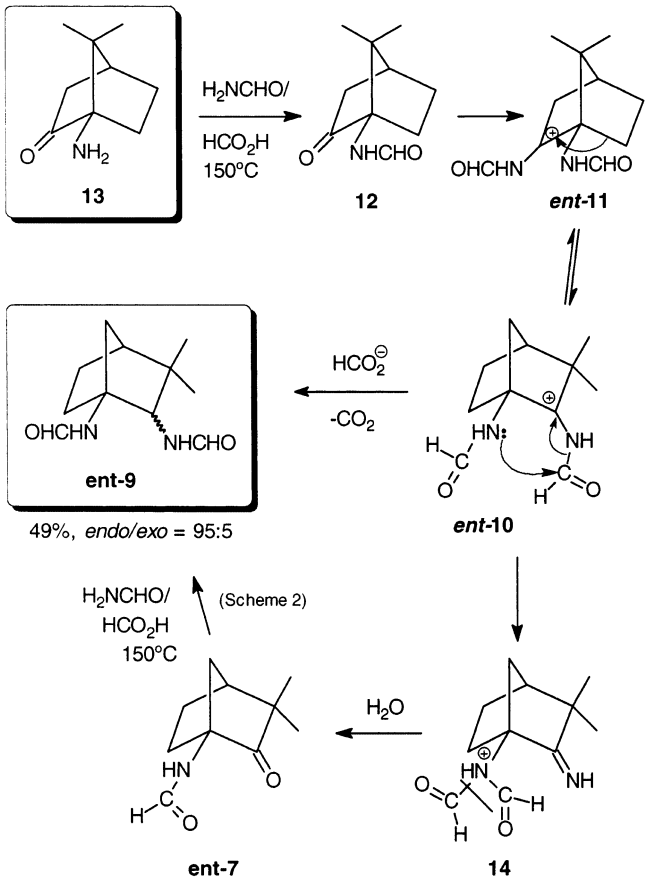
The Leuckart reaction of (1*R*)-(3,3)-dimethyl-2-oxo-1-norbornylamine **6** was carried out following the standard procedure ($HCO_2H/HCONH_2$, 150°C),[11] and monitored by GC/MS analysis. As shown in Scheme 2, the first step is the acylation of the amine group to give (1*R*)-*N*-(3,3-dimethyl-2-oxo-1-norbornyl)formamide **7**. This compound reacts with formamide in acid medium to give carbocation **8**; the reduction of this cation by formate ion yields (1*R*,2*R*)-*N*-(3,3-dimethyl-2-formylamino-1-norbornyl)formamide **9** as the sole final product. Together with 3,3-dimethyl-formamide **7**, a small amount (less than 10%) of (1*S*)-*N*-(7,7-dimethyl-2-oxo-1-norbornyl)formamide ***ent*-12**[†] is detected during the course of the reaction, which also gives the diformamide **9** as the final product. The appearance of ***ent*-12** can be explained in terms of an equilibrium between carbocations **8** and **10** (Scheme 2), that competes with the reduction of **8** by formate ion.

The reactivity of ***ent*-12** with formamide/formic acid has been studied by carrying out the Leuckart reaction of (1*R*)-7,7-dimethyl-2-oxo-1-norbornylamine **13**. GC/MS monitoring of this process indicates that the first intermediate is the 7,7-dimethylformamide **12** (Scheme 3). The characterisation of **12** was completed by isolation from the reaction medium at low conversion ratios, because it rapidly isomerises to the (1*S*)-*N*-(3,3-dimethyl-2-oxo-1-norbornyl)formamide ***ent*-7** through a Wagner–Meerwein (W–M) rearrangement and an intramolecular transamidation. Subsequently, we detect an almost constant ratio between the two amides (***ent*-7**/**12** = 3:1), followed by the appearance of diformamide ***ent*-9** as the sole final product (Scheme 3). According to this, we can postulate two competitive reaction pathways starting from carbocation ***ent*-10**: one is the direct reduction by formate ion, that directly yields ***ent*-9**, and the other is the intramolecular transamidation to give cation **14**. The hydrolysis of one formyl group in this



Scheme 2.

[†] In those cases where the two enantiomers of the same structure are formulated, the prefix *ent*- is assigned to the (1*S*)-isomer.

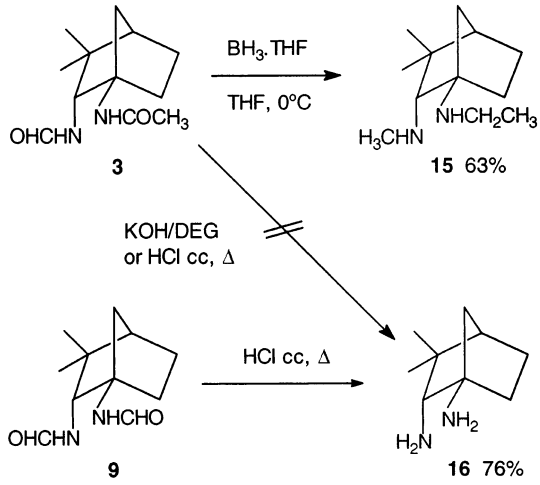


Scheme 3.

intermediate originates the formamide ***ent*-7**, whose reactivity under these conditions has been studied in Scheme 2. Using these two possible routes, (1*S*,2*S*)-diformamide ***ent*-9** is obtained as the only final product, with an overall yield of 49% (98 h) and an *endo*/*exo* ratio = 19:1 (^{1}H NMR 300 MHz).

As we have mentioned before, our strategy for the synthesis of enantiopure vicinal diamines is based on the transformation of 1,2-norbornanediamides **3** and **9**. Reduction of **3** was first attempted with $LiAlH_4$;[14] under various different conditions, a complex mixture was obtained in all cases, and no free diamine could be isolated. The reduction of the amide groups was then achieved by treatment of the substrate with BH_3·THF complex in THF, which afforded (1*R*,2*R*)-3,3-dimethyl-1-ethylamino-2-methylaminonorbornane **15** after 24 h (63%) (Scheme 4).

All attempts to carry out the hydrolysis of **3** in basic or acid media were unsuccessful. Using diformamide **9** as starting compound, the treatment with concentrated KOH yields a complex mixture because of oxidation of the free amine in the reaction medium. Thus, we carried out the hydrolysis of **9** by reaction with boiling cc. HCl, where the deprotection of both formamide groups implies the stabilisation of the resulting diamine through the corresponding dihydrochloride salt. Finally, this procedure has allowed us to obtain



Scheme 4.

(1*R*,2*R*)-3,3-dimethyl-1,2-norbornanediamine **16** in 76% yield. The opposite enantiomer ***ent*-16** has also been synthesised starting from diformamide ***ent*-9**; the measurement of the $[\alpha]_D^{20}$ values of both compounds confirms the enantioselectivity of the global process.

3. Conformational equilibrium in norbornylformamides

One of the most studied properties of the formamide group is the conformational equilibrium between *trans* and *cis* isomers, because it constitutes the simplest model for the understanding of the structural properties of the peptide bond in proteins.[15,16] We have previously described the conformational equilibrium of 2-norbornylformamides in $CDCl_3$ and found different *trans*/*cis* ratios depending on the substituents linked to the norbornane framework.[11,12] In this paper, we have studied the behaviour of the synthesised 1-norbornylformamides **7** and **12** in solution, and we can confirm that the conformational equilibrium is strongly influenced by the shape of the norbornane moiety. Thus, in the case of 3,3-dimethylformamide **7**, we have only detected traces of the *cis* isomer in $CDCl_3$ solution, whereas the 7,7-dimethylformamide **12** shows a *trans*/*cis* ratio = 1.8:1. The introduction of a second formamide moiety complicates the ^{1}H NMR spectrum of diformamide **9**, and four conformers have been detected in $CDCl_3$ solution in a ratio of (*trans*,*trans*):(*trans*,*cis*):(*cis*,*trans*):(*cis*,*cis*) = 7.2:1.4:1.5:1, respectively. To identify these rotamers, we have considered the proton shift of the C(2) formyl groups, which must be very similar to that of 1-acetamide-2-formamide **3**, and the different $^3J_{\text{H-N-CO-H}}$ of the *cis* and *trans* isomers (10–13 and 0–2 Hz, respectively).[11] The ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of diformamide ***ent*-9**, with the assignment made through the formyl signals, is shown in Fig. 1.

In summary, we have developed an expeditious method for the enantioselective synthesis of new chiral 1,2-norbornanediamines. Starting from two different naturally occurring 2-norbornanones, we can obtain the two

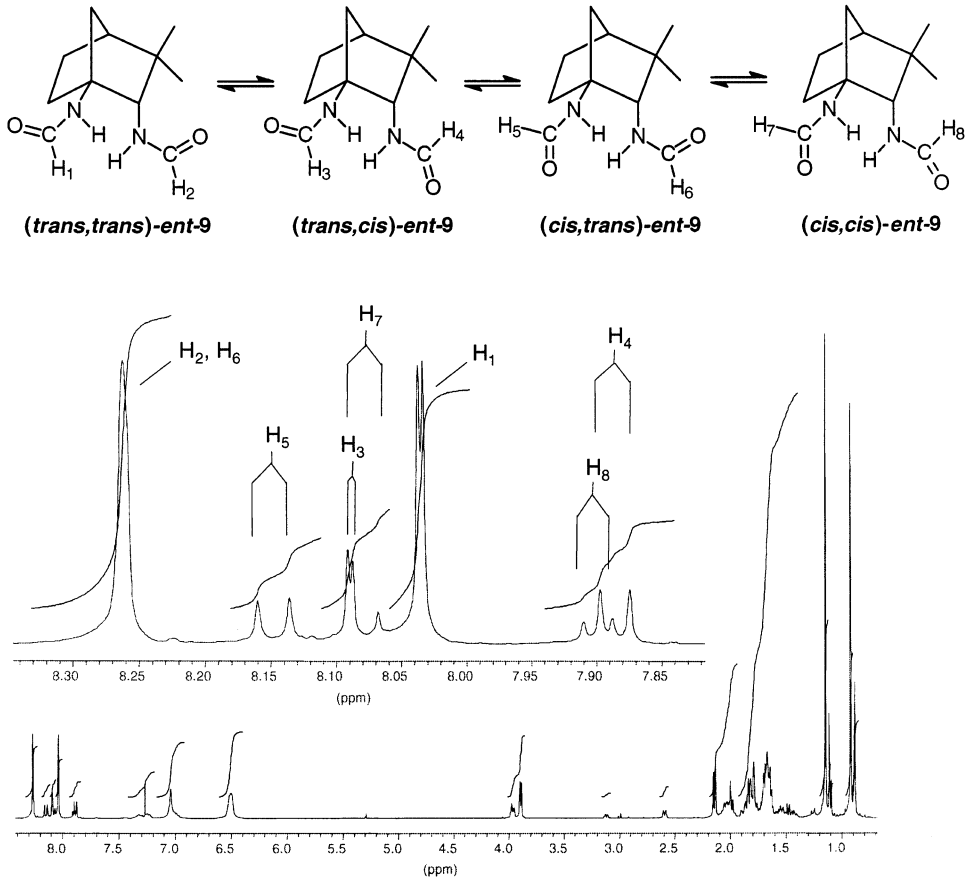


Figure 1.

enantiomers of the target molecules while controlling the configuration of the stereogenic centres.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were obtained using Varian VXR 300S, Brucker AMX500 and Brucker AC250 spectrometers, with tetramethylsilane as internal standard. Capillary GC/MS analyses were completed on a Shimadzu QP-17A (column type: TRB-1, 30 m) coupled to a Shimadzu QP-5000 mass spectrometer (EI, 60 eV). Melting points were recorded using a Gallenkamp apparatus; values are uncorrected. Molecular rotations were obtained using a Perkin–Elmer 241 spectropolarimeter. Elemental analysis was completed on a Perkin–Elmer 2400 CHN analyser. For the preparation of the amines **6** and **13** from (1*R*)-camphor and (1*R*)-fenchone, respectively, see Ref. 14. For the synthesis of compound **3**, see Refs. 11 and 12.

4.2. Leuckart reaction of 1-amino-2-norbornanones

A mixture of the corresponding 1-amino-2-norbornanone (2.0 mmol), formamide (32.2 mmol) and formic acid (17.9 mmol) was heated to 150°C. The reaction was monitored by GC/MS analysis until total disappearance of the starting ketone and intermediate compounds. Lower yields were observed after long reaction times due to formation of dark-coloured polymeric products. On completion of the reaction, a saturated aqueous $NaHCO_3$ solution (20 mL) was added and the mixture was extracted with CH_2Cl_2 (4×30 mL). The organic layer was washed with water (30 mL) and brine (20 mL), and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated in vacuo. The residue was analysed by GC/MS and NMR (*endo*/*exo* = 19:1, ^{1}H NMR 300 MHz, $CDCl_3$). The crude reaction mixture was decolourised with charcoal and recrystallised in MeOH/Et_2O; this procedure gave in all cases the pure *endo*-epimer. To isolate the *N*-(2-oxo-1-norbornyl)formamides **7** and **12**, the reaction was stopped at low conversion ratio (15–30 min). The mixture was hydrolysed with water (20 mL) and extracted with CH_2Cl_2 (3×20 mL), and the organic layer successively washed with 10% HCl solution (30 mL) and saturated $NaHCO_3$ (30 mL). After drying with $MgSO_4$ and removal of the solvent, the crude product was purified by column chromatography (silica gel, hexane:ethyl acetate, 1:1), followed by recrystallisation of the formamide in hexane.

4.3. (1*R*,2*R*)-*N*-(3,3-Dimethyl-2-formylamino-1-norbornyl)formamide 9

Following the procedure described above, the Leuckart reaction of (1*R*)-1-amino-3,3-dimethyl-2-norbornanone **6** gave 0.24 g of **9** (60% yield, white prisms) as the final

product. ^{1}H NMR analysis in $CDCl_3$ solution showed four conformational isomers whose relative ratios (*trans*,*trans*):(*trans*,*cis*):(*cis*,*trans*):(*cis*,*cis*) were 7.2:1.4:1.5:1, respectively. Owing to the complexity of the spectrum, not all the signals were assigned. Mp 142.9–145.3°C. $[\alpha]_D^{20}$ −58.8 (*c* 0.50, MeOH). IR (KBr) *v* 3260, 3050, 2990, 2950, 1670, 1650, 1550, 1390 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1H *trans*,*trans*, 1H *cis*,*trans*), 8.15 (d, J=12.3 Hz, 1H *cis*,*trans*), 8.09 (d, J=1.8 Hz, 1H *trans*,*cis*), 8.08 (d, J=12.0 Hz, 1H *cis*,*cis*), 8.04 (d, J=1.5 Hz, 1H *trans*,*trans*), 7.90 (d, J=11.4 Hz, 1H *cis*,*cis*), 7.89 (d, J=11.4 Hz, 1H *trans*,*cis*), 7.50–6.80 (m, 1H), 6.50 (br. s, 1H), 3.98 (dm, J=9.0 Hz, 1H *trans*,*cis*, 1H *cis*,*cis*), 3.90 (dd, J=7.3 Hz, J=1.5 Hz, 1H *trans*,*trans*, 1H *cis*,*trans*), 3.13 (dm, J=11.1 Hz, 1H *cis*,*cis*), 2.61 (dm, J=10.2 Hz, 1H *trans*,*cis*), 2.17 (dd, J=9.9 Hz, J=1.5 Hz, 1H *trans*,*trans*, 1H *cis*,*trans*), 2.10–1.40 (m, 6H), 1.16 (s, 3H *trans*,*trans*, 3H *cis*,*trans*), 1.13 (s, 3H *trans*,*cis*), 1.11 (s, 3H *cis*,*cis*), 0.93 (s, 3H *trans*,*trans*), 0.90 (s, 3H *cis*,*cis*), 0.89 (s, 3H *trans*,*cis*, 3H *cis*,*trans*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$). δ *trans*,*trans*-*Conformer*: 163.3, 161.5, 66.7, 62.8, 45.9, 38.8, 38.0, 30.8, 25.3, 22.8, 21.0 ppm. *trans*,*cis*-, *cis*,*trans*- *and cis*,*cis*-*Conformers*: 165.8, 165.7, 163.7, 163.4, 162.6, 161.2, 65.5, 65.3, 65.0, 67.8, 61.7, 61.6, 45.6, 45.5, 45.2, 40.4, 39.8, 38.3, 38.1, 38.0, 37.9, 30.7, 26.2, 25.8, 25.4, 25.1, 25.0, 24.2, 21.5, 21.4, 21.2 ppm. MS (%B): 152 ($M^{+\bullet}$−NHCOH, 2), 150 (3), 110 (100), 82 (29), 68 (8), 55 (10), 41 (20). Exact mass calcd 210.1368. Found 210.1360. Anal. calcd for $C_{11}H_{18}N_2O_2$.: C, 62.83; H, 8.63; N, 13.32. Found C, 62.27; H, 8.28; N, 13.11%.

4.4. (1*R*)-*N*-(3,3-Dimethyl-2-oxo-1-norbornyl)formamide 7

Following the procedure described above, formamide **7** was isolated from the reaction medium as an intermediate of the Leuckart reaction of (1*R*)-1-amino-3,3-dimethyl-2-norbornanone **6**. Mp 72.4–75.4°C (white crystals). $[\alpha]_D^{20}$ −8.6 (*c* 0.97, MeOH). IR ($CHCl_3$) *v* 3400, 2990, 2740, 1750, 1700, 1520, 1390 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, J=2.2 Hz, 1H), 6.20 (br. s, 1H), 2.60 (dd, J=10.5 Hz, J=2.0 Hz, 1H), 2.57–2.43 (m, 1H), 2.30–2.05 (m, 1H), 2.00–1.80 (m, 3H), 1.44–1.24 (m, 1H), 1.12 (s, 3H), 1.11 (s, 3H) ppm. The formyl group signals showed traces of the *cis*-isomer in $CDCl_3$, but no other signals were located. ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 217.3, 160.8, 68.0, 46.1, 43.4, 38.6, 26.6, 24.4, 23.6, 21.7 ppm. MS m/e (%B): 153 ($M^{+\bullet}$–C_2H_4, 9). 138 (4), 124 (4), 110 (100), 108 (20), 93 (11), 85 (32), 69 (51), 57 (20), 41 (85). Anal. calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.55; H, 8.36; N, 7.69%.

4.5. (1*S*,2*S*)-*N*-(3,3-Dimethyl-2-formylamino-1-norbornyl)formamide *ent*-9

Following the procedure described above, the Leuckart reaction of (1*R*)-1-amino-7,7-dimethyl-2-norbornanone **13** gave 0.20 g of ***ent*-9** (49% yield, white prisms) as final product. $[\alpha]_D^{20}$ +57.9 (*c* 0.64, MeOH).

4.6. (1*R*)-*N*-(7,7-Dimethyl-2-oxo-1-norbornyl)formamide 12

Following the procedure described above, formamide **12** was isolated from the reaction medium as intermediate of the Leuckart reaction of (1*R*)-1-amino-7,7-dimethyl-2-norbornanone **13**. *trans*/*cis* ($CDCl_3$)=1.8:1. Mp 150.5–153.0°C (white crystals). $[\alpha]_D^{20}$ −40.2 (*c* 0.49, MeOH). IR ($CHCl_3$) *v* 3450, 2980, 1750, 1510, 1390 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (d, J=1.8 Hz, 1H *trans*), 8.25 (d, J=13.2 Hz, 1H *cis*), 5.90 (br. s, 1H), 3.19 (td, J=12.3 Hz, J=3.6 Hz, 1H), 2.55–2.40 (m, 1H), 2.22–2.00 (m, 3H), 1.56–1.32 (m, 2H), 1.27 (s, 3H *trans*), 1.12 (s, 3H *cis*), 0.91 (s, 3H *cis*), 0.86 (s, 3H *trans*) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$) δ *trans*-*Conformer*: 213.3, 161.2, 72.9, 48.4, 41.2, 40.4, 26.6, 21.6, 19.1, 18.9 ppm. *cis*-*Conformer:* 211.9, 163.7, 71.9, 47.3, 41.7, 40.6, 27.7, 22.4, 19.1, 18.9 ppm. MS m/e (%B) 181 ($M^{+\bullet}$, 12), 153 (59), 137 (21), 112 (54), 108 (27), 84 (38), 69 (25), 55 (24), 41 (100). Anal. calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73. Found: C, 66.13; H, 7.94; N, 7.59%.

4.7. (1*R*,2*R*)-3,3-Dimethyl-1-ethylamino-2-methylaminonorbornane 15

A solution of (1*R*,2*R*)-*N*-3,3-dimethyl-2-formylamino-1-norbornyl)acetamide **3**[11] (0.40 g, 2.0 mmol) in THF (20 mL) was slowly added to a BH_3·THF solution (1 M, 12 mL, 12 mmol) at 0°C under Argon. The mixture was heated under reflux and monitored by GC until disappearance of the starting material, then cooled to 0°C and carefully hydrolysed with cc. HCl (20 mL). After washing with diethyl ether (2×20 mL), the aqueous layer was basified with NaOH solution (30%) and extracted with diethyl ether (4×30 mL). The organic layer was washed with brine (30 mL) and dried over KOH, and the solvent evaporated in vacuo. Yield: 0.21 g, 63% (colourless liquid). The obtained diamine was very pure, but oxidises readily in air. Thus, the characterisation was carried out on the corresponding hydrochloride, prepared by bubbling gaseous HCl through a solution of diamine in Et_2O, filtration and recrystallisation from MeOH/Et_2O. Mp >170°C (decomp). $[\alpha]_D^{20}$ −1.6 (*c* 1.47, MeOH). IR (KBr) *v* 3020, 2740, 1620, 1515, 1490, 1350 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD) δ 3.55 (s, 1H), 3.30–3.18 (m, 2H), 2.88 (s, 3H), 2.25 (dm, J=10.3 Hz, 1H), 2.0–1.8 (m, 6H), 1.47 (t, J=7 Hz, 3H), 1.31 (s, 3H), 1.25 (s, 3H) ppm. ^{13}C NMR (75 MHz, CD_3OD) δ 68.7, 67.2, 44.7, 39.1, 38.5, 35.0, 32.4, 29.4, 23.0, 21.0, 18.4, 9.8 ppm. MS m/e (%B): 165 ($M^{+\bullet}$–C_2H_5, 6), 110 (100), 94 (3), 82 (6), 42 (17). Anal. calcd for $C_{12}H_{26}Cl_2N_2$: C, 53.53; H, 9.73; N, 10.40. Found: C, 52.99; H, 9.75; N, 10.39.

4.8. (1*R*,2*R*)- and (1*S*,2*S*)-3,3-Dimethyl-1,2-norbornanediamine 16

(1*R*,2*R*)-*N*-(3,3-Dimethyl-2-formylamino-1-norbornyl)-formamide **9** (0.30 g, 1.4 mmol) was suspended in cc. HCl (15 mL) and heated at 100°C for 12 h. After cooling and washing with diethyl ether (2×20 mL), the

aqueous layer was basified and continuously extracted with diethyl ether (24 h). The organic layer was dried over KOH, filtered and the solvent was evaporated in vacuo. Yield: 0.16 g, 76% (colourless liquid). The obtained diamine was very pure, but oxidises readily in air. Thus, characterisation was carried out on the corresponding hydrochloride, prepared by bubbling gaseous HCl through a solution of diamine in Et_2O, filtration and recrystallisation from $MeOH/Et_2O$. Mp >250°C (decomp). $[\alpha]_D^{20}$ +1.5 (*c* 0.67, MeOH). IR (KBr) *v* 3500–2500, 1600, 1565, 1515, 1480, 1340, 1060 cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ 3.35 (d, $J=1.8$ Hz, 1H), 2.19 (dm, $J=10.3$ Hz, 1H), 2.05–1.65 (m, 6H), 1.22 (s, 3H), 1.09 (s, 3H) ppm. ^{13}C NMR (75 MHz, CD_3OD) δ 64.9, 63.0, 46.6, 40.8, 40.0, 30.6, 25.4, 24.3, 20.3 ppm. MS m/e (%B): 137 ($M^{+\bullet}-NH_3$, 5), 122 (7), 82 (100), 56 (7), 41 (8). Anal. calcd for $C_9H_{20}Cl_2N_2$: C, 47.58; H, 8.87; N, 12.33. Found: C, 47.88; H, 9.05; N, 12.30%.

The same procedure was applied in the hydrolysis of ***ent*-9** to obtain ***ent*-16**, $[\alpha]_D^{20}$ −1.2 (*c* 1.39, MeOH).

Acknowledgements

We thank the DGCYT (Spain) for financial supports of this work (Grant PB 97-0264).

References

1. Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580–2627.
2. Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, J. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801–2803.
3. Kobayashi, S.; Uchiro, H.; Fujishita, Y.; Shiina, T.; Mukaiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 4247–4252.
4. Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833–856.
5. (a) Evans, D. A.; Lectka, T.; Miller, S. J. *Tetrahedron Lett.* **1993**, *34*, 7027–7030; (b) Corey, E. J.; Sarshar, S.; Bordner, J. *J. Am. Chem. Soc.* **1992**, *114*, 7938–7939.
6. Reedijk, J. *Chem. Commun.* **1996**, 801–806.
7. Wong, E.; Giandomenico, C. M. *Chem. Rev.* **1999**, *99*, 2451–2466.
8. (a) Kidani, Y.; Inagaki, K.; Tsukagoshi, S. *Gann* **1976**, *67*, 923; (b) Kidani, Y.; Inagaki, K.; Saito, R.; Tsukagoshi, S. *J. Clin. Hematol. Oncol.* **1977**, *7*, 197.
9. Busacca, C. A.; Campbell, S.; Dong, Y.; Grossbach, D.; Ridges, M.; Smith, L.; Spinelli, E. *J. Org. Chem.* **2000**, *65*, 4753–4755.
10. Moore, M. L. *Org. React.* **1949**, *5*, 301–330.
11. Martínez, A. G.; Teso Vilar, E.; García Fraile, A.; Martínez, P.; Macías San Antonio, R.; Martínez-Alcázar, M. P. *Tetrahedron: Asymmetry* **1999**, *10*, 1499–1505.
12. Martínez, A. G.; Teso Vilar, E.; García Fraile, A.; Martínez-Ruiz, P. *Eur. J. Org. Chem.* **2001**, *15*, in press.
13. Martínez, A. G.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Rodríguez Herrero, E.; Martínez Ruiz, P.; Subramanian, L. R.; García Gancedo, A. *J. Med. Chem.* **1995**, *38*, 4474–4477.
14. Martínez, A. G.; Teso Vilar, E.; García Fraile, A.; de la Moya Cerero, S.; Martínez Ruiz, P.; Subramanian, L. R. *Tetrahedron: Asymmetry* **1996**, *7*, 1257–1260.
15. Radzicka, A.; Pedersen, L.; Wolfenden, R. *Biochemistry* **1988**, *27*, 4538–4541.
16. Axe, F. U.; Renugopalakrishnan, V.; Hagler, T. *J. Chem. Res. (M)* **1998**, 242–264.