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About the Leuckart reaction of chiral 2-norbornanones bearing electron-withdrawing groups: reaction of bridgehead triflates and triflamides

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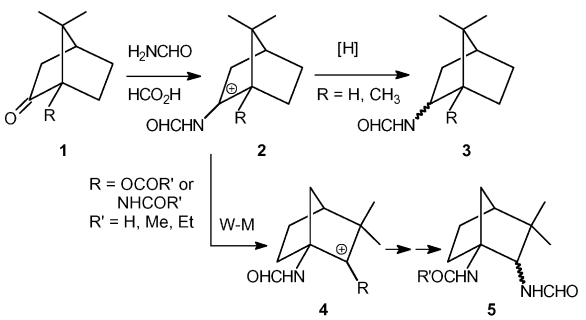
Abstract—The mechanism of the Leuckart reaction of 3,3- and 7,7-dimethyl-2-oxo-1-norbornyl triflates and triflamides, synthesised by us starting from (1*R*)-camphor and (1*R*)-fenchone, has been studied. Strikingly, the electron-withdrawing capacity of the bridgehead substituents has demonstrated not to be enough to control the Wagner–Meerwein rearrangement during the course of the reaction, so that only both enantiomers of a 3,3-dimethylnorbornanediamine derivative have been obtained as final products. As a result, the total synthesis of these interesting chiral compounds has been optimised and shortened until three overall steps starting from (1*R*)-fenchone.

1. Introduction

The synthesis of chiral, vicinal diamines is a topic of interest because of their potential applications in medicinal chemistry as antitumour agents[1,2] or as chiral ligands in asymmetric synthesis.[1,3] In the course of our research work about the chemistry of chiral norbornane derivatives, we have attempted the preparation of 1,2-norbornanediamines through different approaches.[4,5] Nevertheless, standard procedures such as the synthesis and reduction of 2-norbornanoximes, or the reductive amination of 2-norbornanones with ammonia or amines, have failed when applied to bridgehead amine derivatives.[4] Finally, the Leuckart reaction of different 7,7- or 3,3-dimethyl-2-norbornanones has allowed us to obtain for the first time both enantiomers of 3,3-dimethyl-1,2-norbornanediamines.[6] However, we have not been able to synthesise or even detect 7,7-dimethyl diamine precursors in any of the reactions essayed.

The mechanism proposed by us for the Leuckart reaction of 7,7-dimethyl-1-substituted-2-norbornanones **1**[6] implies an intermediate 2-formylamino-2-norbornyl cation **2**, which can either suffer a reduction by the formate ion to give a formamide **3**, or a W-M rearrangement to give a 2-acyloxy- or a 2-acylamino carbocation **4** (Scheme 1).[6b] According to it, an alternative way to obtain 7,7-dimethyl-1,2-norbornanediamine derivatives with structural retention could be the Leuckart reaction of substrates bearing electron-withdrawing bridgehead substituents that destabilise the rearranged 2-norbornyl cation **4**.

The trifluoromethanesulphonamido (triflamido) and trifluoromethanesulphonyloxy (trifliloxy) groups are well known by their high overall electron-withdrawing effect;[7] thus, it could be expected the Leuckart reaction of 2-oxo-1-norbornyltriflamides or triflates to take place without skeleton rearrangement. This would lead to the synthesis of amino alcohol or diamine precursors with structural retention, which is the main condition to obtain the desired 7,7-dimethylnorbornanediamine derivatives.



Scheme 1.

Keywords: Leuckart reaction; triflate; triflamide.

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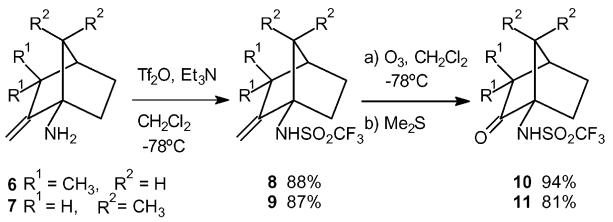


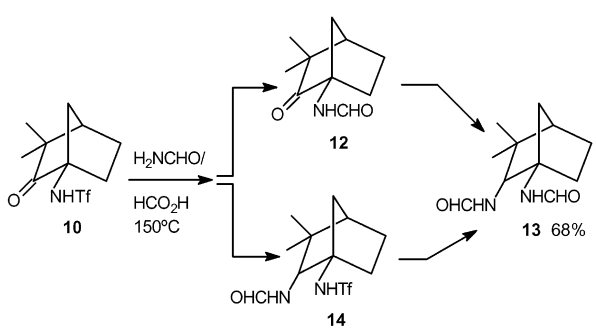
Scheme 2.

2. Results

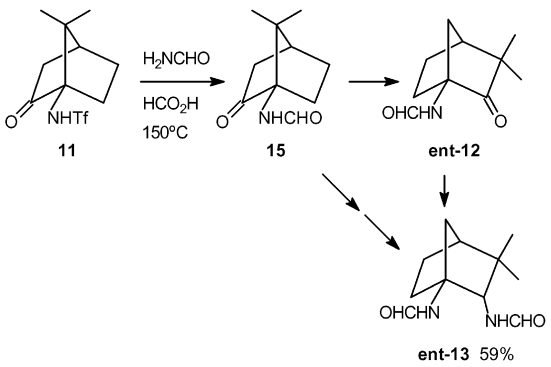
2.1. Leuckart reaction of *N*-(2-oxo-1-norbornyl)-triflamides

The triflamide moiety is well known as protecting group of primary and secondary amines,[8] mainly as a variant of the Gabriel synthesis,[9] but its reactivity as bridgehead substituent in rigid frameworks has not been studied to date. The synthesis of the new *N*-(2-oxo-1-norbornyl)triflamides **10** and **11**, starting from 2-methyliden-1-norbornylamines **6** and **7**,[10] is depicted in Scheme 2. The first step is the reaction of the primary amino group with triflic anhydride in the presence of triethylamine, at −78°C. The ozonolysis of **8** and **9** in CH_2Cl_2 at −78°C, followed by treatment with dimethyl sulphide, gives the desired enantiopure 2-oxo-1-norbornyltriflamides **10** and **11** with high yields.

The reaction of **10** with the formamide/formic acid couple was carried out following the standard procedure described in the literature.[6,11] According to the GC/MS monitoring, two different intermediates have been detected, that yield the same 3,3-dimethyl formamide as the only final product at the end of the process. The evolution of the reaction mixture is summarised in Scheme 3. By one side, the triflamide moiety suffers a N–S bond fission followed by N-formylation, to give the (1*R*)-*N*-(3,3-dimethyl-2-oxo-1-norbornyl)formamide **12**.[6c] On the other side, the other intermediate compound was also observed, which was identified as *N*-(3,3-dimethyl-2-formylamino-1-norbornyl)-triflamide **14** according to its mass spectrum fragmentation pattern.[12] However, all the attempts to isolate pure compound **14** from the reaction medium by means of column chromatography or recrystallisation were unsuccessful. Through a transacylation process at the bridgehead position, this triflamide also affords the (1*R*,2*R*)-*N*-(3,3-dimethyl-2-formylamino-1-norbornyl)-formamide **13** as final product (68% overall yield).



Scheme 3.

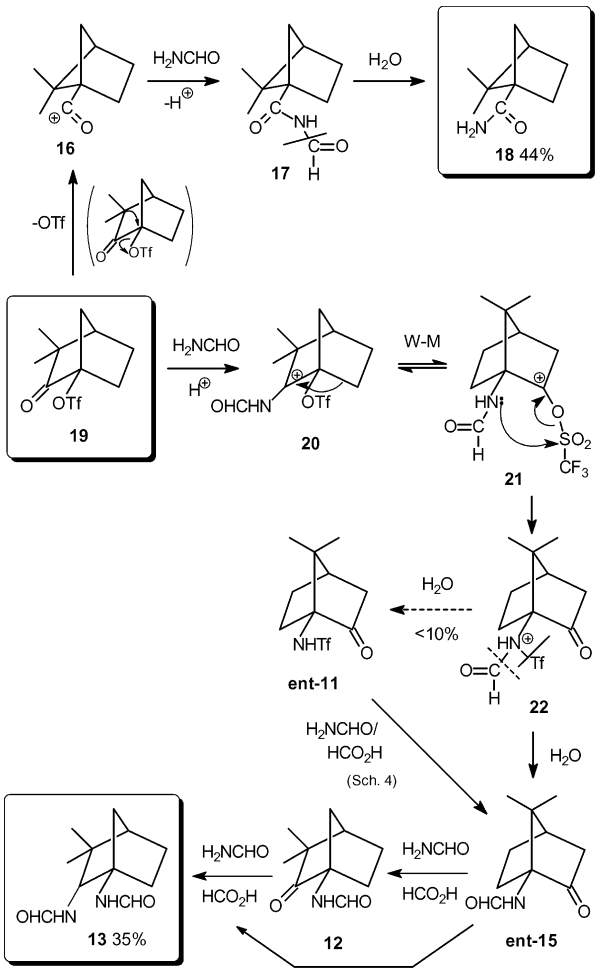


Scheme 4.

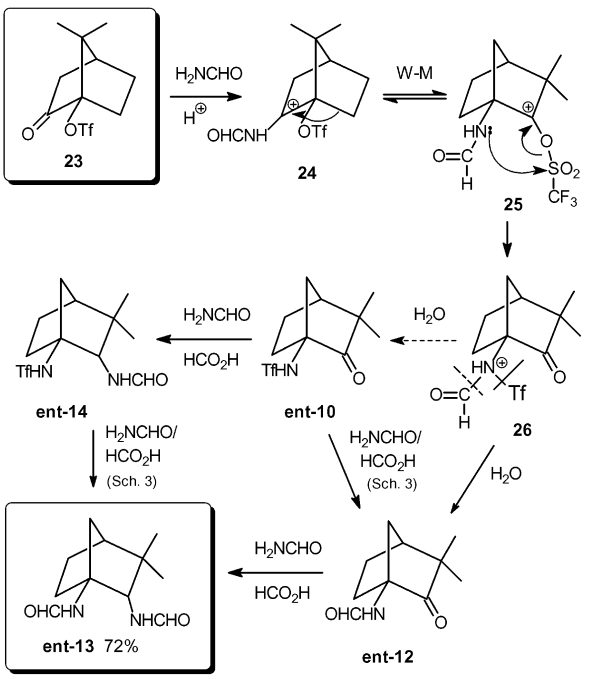
The GC/MS monitoring of the Leuckart reaction of 7,7-dimethyl triflamide **11** (Scheme 4) indicates that the first step is the transacylation at the bridgehead position, leading to the 7,7-dimethyl-2-norbornyl formamide **15** as first intermediate. The reactivity of this formamide has been studied by us,[6c] and explains the appearance of 3,3-dimethyl formamide **ent-12** as intermediate as well as the isolation of diformamide **ent-13** as only final product (59% yield). None intermediate similar to compound **14** (see Scheme 3) was detected in the course of the reaction, which means that the formamide addition to the carbonyl group to give a 2-formylamino-2-norbornyl cation is slower than the transamidation at the bridgehead position. Consequently, we were not able to study the effect of the triflamide group on the stability of adjacent 7,7- or 3,3-dimethyl-2-norbornyl cations. This fact prompted us to study the process starting from 2-oxo-1-norbornyl triflates, whose bridgehead group is not expected to suffer transacylation reactions in this medium.

2.2. Leuckart reaction of 2-oxo-1-norbornyl triflates

We have described in previous papers the synthesis and reactivity in solvolytic media of chiral 2-oxo-1-norbornyl triflates starting from naturally occurring 2-norbornanones,[13] as well as their application to the synthesis of β-amino alcohols[10] and diols.[14] To study the behaviour of these substrates with the $HCOOH/HCONH_2$ couple, the Leuckart reaction of (1*R*)-3,3-dimethyl-2-oxo-1-norbornyl triflate **19**[13] was carried out. The results are shown in Scheme 5: two different final products **18** and **13** were obtained, resulting from two competitive reaction pathways. After purification by column chromatography (silica gel, AcOEt/MeOH), these compounds were characterised as (1*R*)-5,5-dimethyl-1-bicyclo[2.1.1]hexanecarboxamide **18** (44% yield), and (1*R*,2*R*)-*N*-(3,3-dimethyl-2-formylamino-1-norbornyl)formamide **13** (35% yield). According to our experience about the reactivity of ketotriflate **19** in solvolytic media,[13b,15] we can conclude that a ring contraction process favoured by the nucleofugacity of the triflate group and the σ-participation of the C2–C3 bond originates the formation of carboxamide **18**. The other reaction pathway constitutes the proper Leuckart reaction of the 2-oxo-1-norbornyl triflate that yields again diformamide **13** at the end of the process. As intermediates in this route, we have detected the 7,7-dimethyl-2-oxo-1-norbornyl triflamide **ent-11** (less than 10%), and the bridgehead formamides **ent-15** and **12** (Scheme 5).



Scheme 5.



Scheme 6.

As shown in Scheme 5, the mechanism proposed implies the formamide addition to the carbonyl group of **19** to give the 2-formylamino-2-norbornylcation **20**. Owing to the electron-withdrawing effect of the trifluoromethanesulphonyl group, this cation should be more stable than the triflyloxycarbenium ion **21**, originated after a Wagner–Meerwein rearrangement. Nevertheless, by monitoring the process we have not detected in the reaction medium any 2-formylamino-1-norbornyl triflate resulting from the reduction of cation **20**. It means that carbocation **21** suffers an intramolecular transamidation that shifts the equilibrium to the right, in a similar way to the Leuckart reaction of 2-oxo-1-norbornyl acetates or propionates.[6b] The competitive hydrolysis of the N–S or N–C bond in the intermediate **22** explains both formamide **ent-15** and triflamide **ent-11** to appear simultaneously in the reaction medium. The later evolution of the intermediates follows the mechanism described before (see Schemes 2–4), and finally diformamide **13** is obtained as the only product of this reaction pathway.

The last substrate tested for the Leuckart reaction was the (1*R*)-7,7-dimethyl-2-oxo-1-norbornyl triflate **23**[14] (Scheme 6). As in the case of 3,3-dimethyl triflate **19**, the reaction pathway is consistent with consecutive Wagner–Meerwein rearrangements and intramolecular transacylations.

The first intermediate detected is the (1*S*)-*N*-(3,3-dimethyl-2-oxo-1-norbornyl)triflamide **ent-10**, together with a little amount of (1*S*)-*N*-(3,3-dimethyl-2-oxo-1-norbornyl)formamide **ent-12**. The appearance of the intermediate (1*S*)-*N*-(3,3-dimethyl-2-formylamino-1-norbornyl)triflamide **ent-14** was also observed, coming from the formamide addition to ketone **ent-10**. All the intermediates give finally diformamide **ent-13** as the only final product with an overall yield of 72%. Consequently, this route is the shortest way (three overall steps starting from (1*R*)-fenchone) to access to the synthesis of 1,2-norbanediamine derivatives. The mechanism proposed in Scheme 6 involves a Wagner–Meerwein rearrangement of carbocation **24** to give a triflyloxycarbenium ion **25**. In a similar way to cation **21** (see Scheme 5), it suffers an intramolecular transacylation to give **26**. The N–C bond hydrolysis in **26** gives triflamide **ent-10**, which reacts with formamide and formic acid to yield finally diformamide **ent-13** through the triflamide **ent-14** or the formamide **ent-12** (see Scheme 3). This last compound can also be originated through the N–S bond hydrolysis in the intermediate **26**. None ring contraction product was detected in the crude reaction, in agreement with the different behaviour of triflates **19** and **23** observed in solvolytic media.[13b]

3. Conclusions

In summary, we have shown that a cascade of Wagner–Meerwein transpositions and intramolecular transacylations dominates the Leuckart reaction of 7,7-dimethyl-2-norbornanones bearing *N*- or *O*-trifluoromethanesulphonyl substituents at the bridgehead position. These rearrangements that had been previously described by us for the analogous amides and esters, cannot be avoided by increasing the electron-withdrawing capacity of the bridgehead groups, and the only products of the process

are 1,2-diamides having a *gem*-dimethyl group attached to the C3 centre. Therefore, the $-I$ effect of both triflamide and trifliloxy groups seems to be compensated by their electron donating $+M$ effect[7b,16] towards an adjacent cationic centre. Besides the mechanistic relevance of the process, the employment of 2-oxo-1-norbornyl triflates as substrates for the Leuckart reaction has resulted in an optimisation of the stereoselective synthesis of enantiopure 1,2-norbornanediamine precursors, that can be obtained in three steps, with an overall yield of 53%, starting from (1*R*)-fenchone.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra: Varian VXR 300S and Brucker AC250 spectrometers, with tetramethylsilane as internal standard. Capillary GC/MS: Shimadzu QP-17A (column type: TRB-1, 30 m) coupled to a Shimadzu QP-5000 Mass-spectrometer (EI, 60 eV). Exact mass: VG AutoSpec mass spectrometer. Melting points: Gallenkamp apparatus; values are uncorrected. Molecular rotations: Perkin–Elmer 241 spectropolarimeter. For the preparation of **6** and **7** from (1*R*)-camphor and (1*R*)-fenchone, respectively, see Ref. 10. For the synthesis of compounds **19** and **23**, see Ref. 13.

4.2. Synthesis of *N*-(2-methyliden-1-norbornyl)-triflamides

In a typical procedure, a solution of trifluoromethanesulphonic anhydride (1.1 mL, 6.6 mmol) in 10 mL of CH_2Cl_2 was added at −78°C over a solution of the corresponding 2-methylyden-1-norbornylamine (1.00 g, 6.6 mmol) and triethylamine (2.7 mL, 19.7 mmol) in 20 mL of CH_2Cl_2. When the hydrochloride of the amine was used as starting compound, 26.5 mmol of triethylamine were added, with similar final yield. The reaction was maintained under stirring 30 min at −78°C, and 30 min at room temperature. Then the mixture was hydrolysed with 30 mL of water, and extracted with CH_2Cl_2 (2×30 mL). The organic layer was washed with 10% HCl solution (2×20 mL) and brine (2×30 mL), and dried over $MgSO_4$. After solvent elimination, the obtained triflamides were very pure; nevertheless, purification can be made through recrystallisation in hexane at −25°C.

4.2.1. (1*R*)-*N*-(3,3-Dimethyl-2-methyliden-1-norbornyl)-triflamide 8. According to the procedure described above, 1.00 g of (1*R*)-3,3-dimethyl-2-methyliden-1-norbornylamine **6** gave 1.65 g of triflamide **8**. Yield: 88% (colourless syrup), $[\alpha]_D^{20}=+9.7$ (*c* 1.01, CH_2Cl_2). IR (CCl_4) ν 3385, 2980, 1430, 1380, 1230, 1200, 1150 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.51 (br. s, 1H), 4.90 (s, 1H), 4.78 (s, 1H), 2.20–1.50 (m, 7H), 1.11 (s, 3H), 1.09 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.1, 119.1 (q, *J*=318.0 Hz), 99.8, 69.4, 44.6, 42.1, 41.1, 33.6, 29.2, 25.8, 24.0 ppm. MS (%B): 283 ($M^{+\cdot}$, 4), 254 (3), 240 (100), 214 (2), 150 (10), 134 (4), 121 (6), 106 (13), 91 (12), 69 (43), 41 (42). Exact mass calcd: 283.0854; found: 283.0844.

4.2.2. (1*S*)-*N*-(7,7-Dimethyl-2-methyliden-1-norbornyl)-triflamide 9. According to the procedure described above, 1.00 g of (1*R*)-7,7-dimethyl-2-methyliden-1-norbornylamine **7** gave 1.63 g of triflamide **9** (87% yield, white crystals). Mp: 115.9–118.0°C. $[\alpha]_D^{20}=+2.8$ (*c* 1.03, CH_2Cl_2). IR (KBr) ν 3270, 2960, 1440, 1370, 1240, 1210, 1200, 1150 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06 (t, *J*=2.6 Hz, 1H), 4.89 (t, *J*=2.0 Hz, 1H), 4.77 (br. s, 1H), 2.50 (m, 2H), 2.06 (dt, *J*=16.5, 2.0 Hz, 1H), 1.97 (m, 1H), 1.78 (m, 2H), 1.39 (m, 1H), 1.02 (s, 3H), 0.88 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.4, 119.5 (q, *J*=318.0 Hz), 104.4, 73.5, 48.4, 41.1, 35.7, 28.2, 27.2, 18.7, 18.3 ppm. MS (%B): 283 ($M^{+\cdot}$, 3), 268 (2), 254 (4), 240 (10), 228 (22), 214 (4), 150 (41), 134 (8), 106 (30), 94 (39), 81 (21), 69 (50), 53 (30), 41 (100). Exact mass calcd: 283.0854; found: 283.0863.

4.3. Synthesis of *N*-(2-oxo-1-norbornyl)triflamides

In a typical procedure, a solution of 2-methyliden-1-norbornylamine (1.00 g, 3.5 mmol) in 40 mL of CH_2Cl_2 at −78°C was submitted to ozonolysis and monitored by GC until disappearance of the starting material. After treatment with SMe_2, water (30 mL) was added, and the organic phase separated. The aqueous layer was extracted again with CH_2Cl_2 (3×20 mL), and the combined organic extracts dried with $MgSO_4$. After filtration and solvent elimination, the obtained ketones were very pure; nevertheless, purification can be made through recrystallisation in hexane at −25°C.

4.3.1. (1*R*)-*N*-(3,3-Dimethyl-2-oxo-1-norbornyl)triflamide 10. According to the procedure described above, 1.00 g of (1*R*)-*N*-(3,3-dimethyl-2-methyliden-1-norbornyl)-triflamide **8** gave 0.95 g of ketone **10**. Yield: 94% (colourless syrup), $[\alpha]_D^{20}=+19.5$ (*c* 0.88, CH_2Cl_2). IR (CCl_4) ν 3150, 2970, 1750, 1715, 1420, 1380, 1355, 1230, 1200, 1150, 1030 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.75 (br. s, 1H), 2.35–1.80 (m, 6H), 1.55 (m, 1H), 1.10 (s, 3H), 1.09 (s, 3H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 215.3, 118.9 (q, *J*=319 Hz), 70.6, 46.2, 42.6, 38.6, 29.1, 23.7, 23.4, 21.3 ppm. MS (%B): 257 ($M^{+\cdot}-C_2H_4$, 1), 242 (1), 214 (64), 136 (1), 124 (11), 108 (8), 83 (13), 69 (100), 55 (28), 41 (65). Exact mass calcd: 285.0646; found: 285.0644.

4.3.2. (1*R*)-*N*-(7,7-Dimethyl-2-oxo-1-norbornyl)triflamide 11. According to the procedure described above, 1.00 g of (1*R*)-*N*-(3,3-dimethyl-2-methyliden-1-norbornyl)-triflamide **9** gave 0.82 g of ketone **11**. Yield: 81% (white crystals), mp: 95.7–98.2°C, $[\alpha]_D^{20}=-46.8$ (*c* 0.80, CH_2Cl_2). IR (CCl_4) ν 3100, 2960, 2900, 1750, 1420, 1380, 1370, 1220, 1200, 1140, 1070 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.60 (br. s, 1H), 2.66 (m, 1H), 2.48 (dt, *J*=18.6, 3.9 Hz, 1H), 2.20–2.02 (m, 3H), 1.68–1.46 (m, 2H), 1.19 (s, 3H), 0.90 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.3, 119.3 (q, *J*=319.1 Hz), 75.9, 47.5, 40.9, 39.8, 26.3, 23.1, 19.5, 18.6 ppm. MS (%B): 257 ($M^{+\cdot}-C_2H_4$, 14), 241 (23), 228 (1), 216 (23), 201 (3), 188 (3), 146 (1), 136 (3), 124 (51), 108 (21), 97 (19), 83 (23), 69 (46), 55 (61), 41 (100). Exact mass calcd: 285.0646; found: 285.0638.

4.4. General procedure for the Leuckart reaction of 2-norbornanones

A mixture of 2.0 mmol of the corresponding 2-norbornanone,

formamide (32.2 mmol) and formic acid (17.9 mmol) was heated to 150°C. The reaction progress was monitored by GC/MS until total disappearance of starting ketone and intermediate compounds. Lower yields were observed after long reaction times due to formation of dark-coloured polymeric products. After completion of the reaction, 20 mL of saturated aqueous solution of $NaHCO_3$ were 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*=95:5, ^{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.

4.4.1. Leuckart reaction of (1*R*)-*N*-(3,3-dimethyl-2-oxo-1-norbornyl)triflamide 10. Following the procedure described above, 0.30 g (1.05 mmol), of (1*R*)-*N*-(3,3-dimethyl-2-oxo-1-norbornyl)triflamide **10** gave 0.15 g of (1*R*,2*R*)-*N*-(3,3-dimethyl-2-formylamine-1-norbornyl)formamide **13**, 68% yield. $[\alpha]_D^{20}=-58.5$ (*c* 0.98, MeOH). As intermediate of the reaction we detected by GC/MS the (1*R*,2*R*)-*N*-(3,3-dimethyl-2-formylamine-1-norbornyl)triflamide **14**: MS (%B): 214 ($M^{+\cdot}-C_5H_{11}NO$, 5), 181 (13), 163 (3), 136 (3), 100 (8), 82 (100), 55 (18), 46 (20), 41 (18).

4.4.2. Leuckart reaction of (1*R*)-*N*-(7,7-dimethyl-2-oxo-1-norbornyl)triflamide 11. Following the procedure described above, 0.30 g (1.05 mmol) of (1*R*)-*N*-(7,7-dimethyl-2-oxo-1-norbornyl)triflamide **11** gave 0.13 g of (1*S*,2*S*)-*N*-(3,3-dimethyl-2-formylamine-1-norbornyl)formamide **ent-13**, 59% yield. $[\alpha]_D^{20}=+57.6$ (*c* 1.03, MeOH).

4.4.3. Leuckart reaction of (1*R*)-3,3-dimethyl-2-oxo-norbornyl triflate 19. Following the procedure described above, the reaction was carried out starting from 0.30 g (1.04 mmol) of (1*R*)-3,3-dimethyl-2-oxo-norbornyl triflate. The crude reaction was purified by column chromatography (silica gel, AcOEt/MeOH, 4:1) gave a mixture of 0.08 g of diformamide **13** (35% yield), $[\alpha]_D^{20}=-56.8$ (*c* 0.72, MeOH), and 0.07 g (44% yield) of (1*R*)-5,5-dimethyl-1-bicycle[2.1.1]hexanecarboxamide **18**.

4.4.4. (1*R*)-5,5-Dimethyl-1-bicycle[2.1.1]hexanecarboxamide 18. $[\alpha]_D^{20}=+6.45$ (*c* 0.77 MeOH). Mp: 82.8–84.6°C. IR ($CHCl_3$) *ν*: 3420, 2980, 2970, 1680, 1590, 1400 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.25 (br. s, 1H), 5.45 (br. s, 1H), 2.22 (m, 1H), 2.07 (m, 1H), 1.92 (m, 1H), 1.78 (m, 2H), 1.65 (m, 1H), 1.25 (s, 3H), 1.16 (d, *J*=7.2 Hz, 1H), 0.93 (s, 3H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 176.2, 56.6, 48.6, 43.5, 37.5, 29.5, 26.0, 19.6, 19.3 ppm. MS (%B): 153 (M^+, 3), 138 (23), 124 (13), 112 (25), 109 (17), 85 (52), 69 (49), 67 (55), 58 (47), 41 (100). Exact mass calcd: 153.1154; found: 153.1159.

4.4.5. Leuckart reaction of (1*R*)-7,7-dimethyl-2-oxo-norbornyl triflate 23. Following the procedure described above, 0.30 g (1.04 mmol) of triflate **23** gave 0.16 g (72% yield) of (1*S*,2*S*)-*N*-(3,3-dimethyl-2-formylamine-1-norbornyl)formamide **ent-13**. $[\alpha]_D^{20}=+58.1$ (*c* 0.71, MeOH).

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