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TETRAHEDRON: *ASYMMETRY*

Synthesis and separation of substituted cyclopropane carboxylic acid amide isomers

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Abstract—The phase-transfer-catalyzed cyclization of optically active malonic acid allylic ester amides yields bicyclic cyclopropane carboxamide lactone derivatives. The two diastereomers obtained could be separated in some cases by simple column chromatography yielding the pure isomers.

1. Introduction

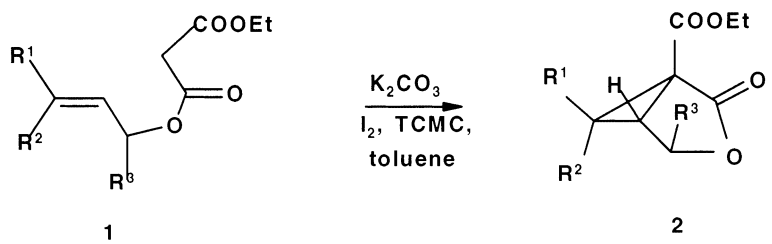
Cyclopropane carboxylic acid and a number of its derivatives are useful intermediates in the preparation of important natural and unnatural compounds having biological activity; for example, certain aminocyclopropane carboxylic acid derivatives and pyrethroid-type insecticides.[1–4] As in many cases, these compounds have several stereogenic centers and the stereoisomers have different biological activities; stereoselective synthesis of these compounds is therefore a useful exercise.

Recently a phase-transfer catalytic method was developed for the preparation of cyclopropane carboxylic acid lactones **2** from malonic acid allylic esters **1** using solid potassium carbonate, iodine and a lipophilic quaternary ammonium salt (Fig. 1). The reaction is diastereoselective, the two rings being *cis*-fused while the R^3 group is always in the *exo* position.[5]

2. Results and discussion

If R^1 and R^2 are different, a new stereogenic center is formed at C(6). The parameters of the reaction were studied including the effect of the R^1, R^2 and R^3 groups and the reaction temperature on the stereoselectivity.[6] The effect of hydrotalcite, a mineral-like solid base,[7] and microwave irradiation[8] on the *exo–endo* selectivity was discussed.

It seemed interesting to examine whether the introduction of a chiral auxiliary in the starting malonic acid derivative has any influence on the stereoselectivity of the reaction. For this purpose we synthesized the amide derivatives **5** by reacting (*R*)-(+)-1-phenylethylamine **4a** (Fig. 2, R = phenyl) or (*R*)-(+)-1-(1-naphthyl)-ethylamine **4b** (R = 1-naphthyl) with 6 molar excesses of diethyl malonate (Fig. 2). The ester-amides **5** thus obtained were hydrolyzed with aqueous sodium



1 2

Figure 1.

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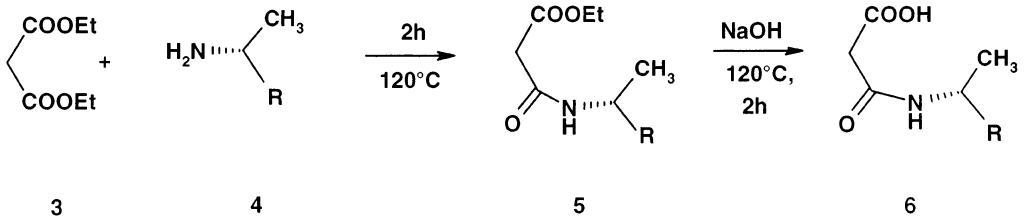


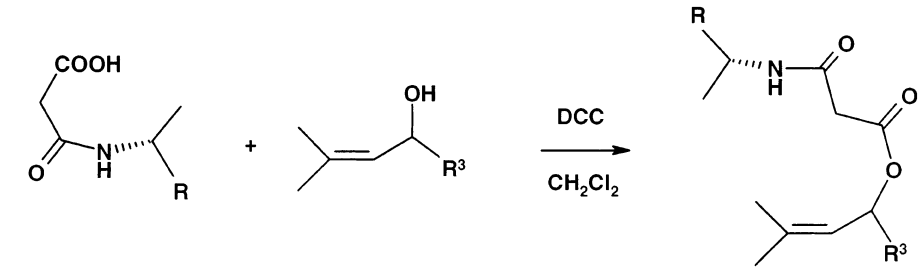
3 4 5 6

Figure 2.

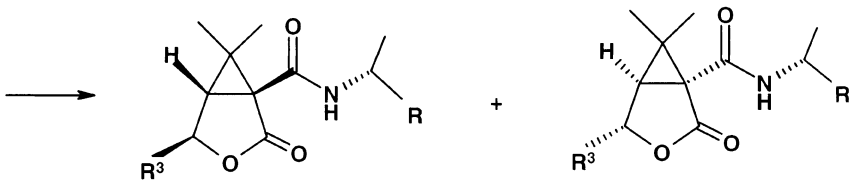
hydroxide to the corresponding acids **6**, which were coupled with 3-methyl-but-2-en-1-ol **7a**, 2-methyl-pent-2-en-4-ol **7b**, or 4-methyl-1,1,1-trichloro-pent-3-en-2-ol **7c** in dichloromethane in the presence of DCC, resulting in the desired ester-amides **8**, which are suitable starting materials for examination of the cyclization reaction. Due to the two methyl groups in the alcohols **7a**–**7c** and the diastereoselectivity of the reaction, only two diastereomers would be expected to form in the cyclization (Fig. 3).

Cyclization of the ester amides was effected[5] by stirring with iodine, solid potassium carbonate and TCMC, in refluxing toluene. ^{1}H NMR analysis of the crude product showed two singlets at 2.6–3.2 ppm and, when the R substituent was phenyl, two doublets were seen at ca. 7.2 ppm both in a 1:1 ratio, which were assigned as the C(5) proton and the amide NH, respectively, in the expected diastereomers **9** and **10**. This unambiguously showed that the chiral amide function had no effect on the stereoselectivity of the reaction.

Attempts were made to separate the obtained diastereomeric mixtures. Column chromatography of the crude **9e** and **10e** mixture using a hexane/ethyl acetate mixture (4:1) as the eluent yielded the pure diastereomers **9e** and **10e**. The absolute configuration of these isomers could not be determined by ^{1}H NMR experiments (Double Pulse Filtered Gradient Nuclear Overhauser Effect, DPFGNOE); there was no effect when the proton at the annelation point or the amide proton were irradiated. Since one of these diastereomers could be obtained in crystalline form, its absolute configuration was determined by X-ray crystallography. Crystals of **9e** suitable for the analysis were obtained by slow evaporation of the ethereal solution of the compound. The configuration of this isomer was (1*R*,4*R*,5*R*,α*R*) as shown in Fig. 4.



6 7 8



9 10

	R	R^3
a	phenyl	H
b	1-naphthyl	H
c	phenyl	CH_3
d	1-naphthyl	CH_3
e	phenyl	CCl_3
f	1-naphthyl	CCl_3

Figure 3.

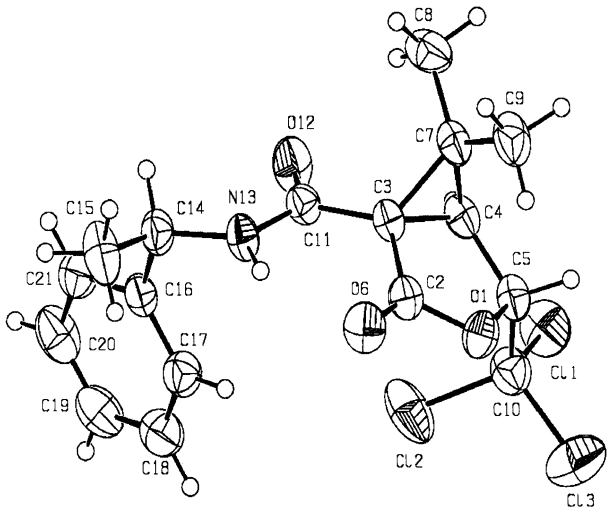


Figure 4.

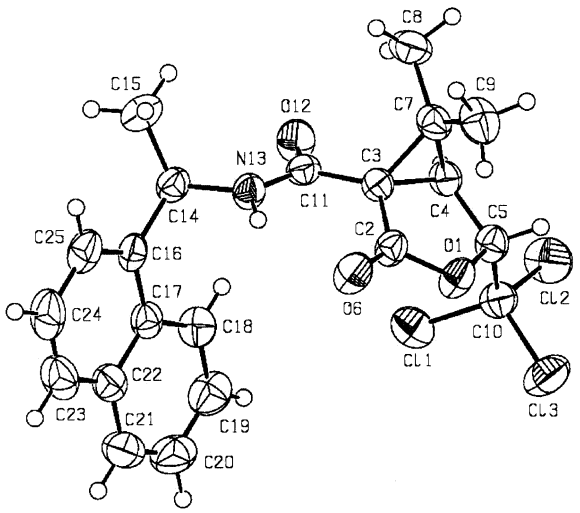


Figure 5.

Similarly, the pure isomers **9f** and **10f** could be separated by a simple column chromatography with excellent yield. One of these isomers was also crystalline; X-ray crystallographic data confirmed its (1*R*,4*R*,5*R*,α*R*) configuration (Fig. 5).

The ^{1}H NMR spectra of the crystalline isomers **9e** and **9f** showed that in both compounds the signals for the proton at the annelation point were seen at a lower chemical shift than in the equivalent isomers **10e** and **10f**, respectively (2.85 for **9e** and 2.93 for **10e**; while 2.92 for **9f** and 2.96 for **10f**). Taking this fact into account we could suppose that the chemical shift of the hydrogen at the annelation point in compounds **9** (having (*R*) configuration) always appeared at a lower δ value than in compounds **10** (having (*S*) configuration). In this way we could determine compounds **9** and **10** and their ratio from the ^{1}H NMR spectra.

Compounds **9c** and **10c** could be isolated by column chromatography; we obtained a 30% yield of both pure isomers (and a fraction of the diastereomeric mixture). In the case of **9a** and **10a** perfect separation could not be effected, only mixtures were obtained in which the isomeric ratio determined from the ^{1}H NMR spectra was 5:1 and 1:5, with 35 and 37% yield, respectively. The mixtures **9b**, **10b** and **9d**, **10d** were found to be inseparable.

By removing the chiral alkyl group from the amide function (by for example hydrogenolysis), pure enantiomers of substituted cyclopropane carboxylic acid lactones could be obtained, which are useful intermediates for substituted cyclopropane carboxylic acids or 1-aminocyclopropane carboxylic acids. As there was no possibility for the introduction of any functional group into the molecules **2** which would help to separate the isomers, simple resolution with diastereomeric salt formation could not be effected. Using our method the enantiomers of substituted cyclopropane carboxylic acids could be easily separated.

3. Experimental

Melting points were determined in a capillary and are uncorrected. IR spectra were recorded on a Perkin–Elmer Spectrum 1600 instrument. Optical rotations were determined on a Perkin–Elmer 241 polarimeter. ^{1}H NMR spectra were recorded on Bruker AW-250 (250 MHz) spectrometer; chemical shifts are given on the δ scale using TMS as internal standard. δ (TMS) = 0 ppm in $CDCl_3$. Thin-layer chromatography was carried out using Merck Kieselgel 60F plates with eluents hexane/acetone 4:1 or hexane/ethyl acetate 4:1. Column chromatography was carried out on Merck Kieselgel 60–200 mesh (25 g/0.1 g reaction mixture) with the same eluents.

3.1. Preparation of monoamides 6

Amine **4** (25 mmol) was added to diethyl malonate (24 g, 0.15 mol) at 120°C. The mixture was then stirred under reflux for 2 h. Excess diethyl malonate was distilled from the mixture under vacuum. A solution of sodium hydroxide (1.48 g, 0.037 mol) in water (20 mL) was added to the residue and the mixture was stirred under reflux for 2 h. The precipitate was removed by filtration, the filtrate was diluted with distilled water, acidified with conc. HCl (3.6 mL), the mixture was extracted with chloroform and the organic phase was dried over magnesium sulfate. The solvent was evaporated under vacuum and the solid thus obtained was recrystallized from toluene. The crystalline material was dissolved in a solution of sodium hydroxide (0.7 g, 18 mmol) in water (20 mL), extracted with chloroform, the aqueous layer was acidified with conc. HCl (2 mL), then extracted with chloroform, the organic layer was dried over magnesium sulfate and the solvent was evaporated.

3.2. Malonic acid (*R*)-(+)-1-phenylethylamide 6a

Yield: 76%, white crystals, mp: 69–71°C (toluene). IR (KBr): 3347, 3281, 1722, 1641, 1547; ^{1}H NMR (250

MHz, $CDCl_3$): 1.64 (d, 3H, *J* 6.33), 3.16 (s, 2H), 5.24 (m, 1H), 7.35–7.74 (m, 5H), 7.81 (d, 1H, *J* 8.16); $[\alpha]_D^{25}=+116.4$, $c=1$, methanol. Anal. found: C, 63.66; H, 6.28; N, 6.78%. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.28; N, 6.76%.

3.3. Malonic acid (*R*)-(+)-1-(1-naphthyl)ethylamide 6b

Yield: 88%, white crystals, mp: 125–127°C (toluene). IR (KBr): 3345.5, 3283.5, 1719, 1637, 1543; ^{1}H NMR (250 MHz, $CDCl_3$): 1.64 (d, 3H, *J* 6.33), 3.16 (s, 2H), 5.89 (m, 1H), 7.00 (s, 1H), 7.35–7.74 (m, 7H), 7.98 (d, 1H, *J* 8.16); $[\alpha]_D^{25}=+41.5$, $c=1$, methanol. Anal. found: C, 70.05; H, 5.89; N, 5.41%. Calcd for $C_{15}H_{15}NO_3$: C, 70.05; H, 5.83; N, 5.44%.

3.4. Esterification of carboxylic acids 6

To a solution of alcohol **7** (2.8 mmol) and acid monoamide **6** (2.83 mmol) in dichloromethane (15 mL) was added dicyclohexylcarbodiimide (0.69 g, 3 mmol) under stirring at 0°C. Then the mixture was further stirred at room temperature for 6 h. The mixture was filtered, the precipitate washed with dichloromethane and the organic phase washed with sodium hydrocarbonate solution; the organic layer was dried over magnesium sulfate and the solvent was evaporated. The residue was purified by column chromatography (with eluent hexane/acetone 4:1).

3.5. Malonic acid [(*R*)-(+)-1-phenylethylamide]-3-methyl-2-buten-1-yl ester 8a

Yield: 67%, colorless liquid. IR (film): 3293, 3068, 1749, 1657, 1551; ^{1}H NMR (250 MHz, $CDCl_3$): 1.49 (s, 3H), 1.52 (s, 3H), 1.73 (d, 3H, *J* 13.2), 3.31 (s, 2H), 4.63 (d, 2H, *J* 7.27), 5.13 (m, 1H), 5.35 (m, 1H), 7.1–7.4 (m, 5H), 7.5 (d, 1H, *J* 7.32); $[\alpha]_D^{25}=+85.8$, $c=1$, methanol. Anal. found C, 69.85; H, 7.69; N, 5.09%. Calcd for $C_{16}H_{21}NO_3$: C, 69.81; H, 7.63; N, 5.09%.

3.6. Malonic acid [(*R*)-(+)-1-(1-naphthyl)ethylamide]-3-methyl-2-buten-1-yl ester 8b

Yield: 68%, colorless liquid. IR (film): 3283, 3072, 1725, 1678, 1649, 1555; ^{1}H NMR (250 MHz, $CDCl_3$): 1.48 (s, 3H), 1.5 (s, 3H), 1.73 (d, 3H, *J* 7.71), 3.31 (s, 2H), 4.63 (d, 2H, *J* 7.27), 5.35 (m, 1H), 5.97 (m, 1H), 7.35–7.91 (m, 7H), 8.07 (d, 1H, *J* 7.71); $[\alpha]_D^{25}=+21.4$, $c=1$, methanol. Anal. found: C, 73.86; H, 7.09; N, 4.39%. Calcd for $C_{20}H_{23}NO_3$: C, 73.84; H, 7.07; N, 4.31%.

3.7. Malonic acid [(*R*)-(+)-1-phenylethylamide]-2-methyl-2-penten-4-yl ester 8c

Yield: 64%, colorless liquid. IR (film): 3284, 3057, 1745, 1655, 1550; ^{1}H NMR (250 MHz, $CDCl_3$): 1.27 (d, 3H, *J* 5.4 Hz) 1.51 (d, 3H, *J* 6.2), 1.71 (s, 6H), 3.27 (s, 2H), 5.12–5.18 (m, 2H), 5.71–5.86 (m, 1H), 7.2–7.5 (m, 5H), 7.6 (s, 1H); $[\alpha]_D^{25}=+57.7$, $c=1$, methanol. Anal. found: C, 70.51; H, 7.99; N, 4.85%. Calcd for $C_{17}H_{23}NO_3$: C, 0.58; H, 7.95; N, 4.84%.

3.8. Malonic acid [(*R*)-(+)-1-(1-naphthyl)ethylamide]-2-methyl-2-penten-4-yl ester 8d

Yield: 68%, colorless liquid. IR (film): 3284, 3057, 1745, 1655, 1550; ^{1}H NMR (250 MHz, $CDCl_3$): 1.27 (d, 3H, *J* 5.4 Hz) 1.51 (d, 3H, *J* 6.2), 1.71 (s, 6H), 3.27 (s, 2H), 5.12–5.24 (m, 2H), 5.97 (m, 1H), 7.2–7.6 (m, 7H), 8.06 (s, 1H); $[\alpha]_D^{25}=+24.7$, $c=1$, methanol. Anal. found: C, 74.41; H, 7.38; N, 4.15%. Calcd for $C_{21}H_{25}NO_3$: C, 74.33; H, 7.37; N, 4.12%.

3.9. Malonic acid [(*R*)-(+)-1-phenylethylamide]-4-methyl-1,1,1-trichloro-3-penten-2-yl ester 8e

Yield: 68%, colorless liquid. IR (film): 3291, 3065, 1755, 1650, 1553; ^{1}H NMR (250 MHz, $CDCl_3$): 1.48 (s, 3H), 1.51 (s, 3H), 1.86 (d, 3H, *J* 6.97), 3.43 (s, 2H), 5.13 (m, 1H), 5.31 (d, 1H, *J* 9.24), 6.08 (d, 1H, *J* 9.24), 7.2–7.5 (m, 6H); $[\alpha]_D^{25}=+64.7$, $c=1$, methanol. Anal. found: C, 51.92; H, 5.02; N, 3.59%. Calcd for $C_{17}H_{20}Cl_3NO_3$: C, 51.97; H, 5.09; N, 3.56%.

3.10. Malonic acid [(*R*)-(+)-1-(1-naphthyl)ethylamide]-4-methyl-1,1,1-trichloro-3-penten-2-yl ester 8f

Yield: 59%, colorless liquid. IR: 3324, 3054, 1753, 1647, 1557; ^{1}H NMR (250 MHz, $CDCl_3$): 1.61 (s, 3H), 1.64 (s, 3H), 1.75 (d, 3H, *J* 7.71), 3.4 (s, 2H), 5.24 (d, 1H, *J* 9.27), 5.97 (m, 1H), 6.03 (d, 1H, *J* 9.27), 7.3–7.7 (m, 7H), 8.07 (d, 1H, *J* 7.71); $[\alpha]_D^{25}=+35.7$, $c=1$, methanol. Anal. found: C, 56.91; H, 4.92; N, 3.19%. Calcd for $C_{21}H_{22}Cl_3NO_3$: C, 56.94; H, 4.97; N, 3.16%.

3.11. General procedure for cyclization of compounds 8

To a mixture of potassium carbonate (3.3 g), iodine (3.0 g) and one drop of TCMC in toluene (30 mL), a solution of esters **8** (5 mmol) in toluene (10 mL) was added dropwise at 110°C with vigorous stirring. The mixture was stirred until **8** was completely consumed (monitored by TLC analysis). The mixture was cooled and filtered, the solid was washed with toluene, the filtrate washed with sodium thiosulfate solution then further washed with water, dried over magnesium sulfate and the solvent was evaporated. The oily residue was purified by column chromatography (with eluent hexane/ethyl acetate 4:1).

3.12. 6,6-Dimethyl-3-oxa-bicyclo[3.1.0]hexan-2-on-1-carboxylic acid (*R*)-(+)-1-phenylethylamide 9a, 10a

Yield: 67%, colorless liquid. IR (film): 3295, 1782, 1654, 1552; ^{1}H NMR (250 MHz, $CDCl_3$): 1.31, (s, 3H), 1.34 (s 3H), 1.51 (d, 3H, *J* 7.15), 2.63, 2.66 (d,d, 1H, *J* 4.94), 4.13 (d, 2H, *J* 5.38), 5.14 (m, 1H), 7.1–7.35 (m, 5H), 7.98, 7.99 (d, 1H, *J* 7.32). Anal. found: C, 70.38; H, 6.98; N, 5.19%. Calcd for $C_{16}H_{19}NO_3$: C, 70.32; H, 6.95; N, 5.12%.

(1*R*,4*S*,5*R*,α*R*)-**9a**/(1*S*,4*R*,5*S*,α*R*)-**10a** 1:5 mixture: $[\alpha]_D^{25}=+62.4$, $c=1$, methanol.

(1*R*,4*S*,5*R*,α*R*)-**9a**/(1*S*,4*R*,5*S*,α*R*)-**10a** 5:1 mixture: $[\alpha]_D^{25}=+56.5$, $c=1$, methanol.

3.13. 6,6-Dimethyl-3-oxa-bicyclo[3.1.0]hexan-2-on-1-carboxylic acid (*R*)-(+)-1-(1-naphthyl)ethylamide 9b, 10b

Mixture of diastereomers, yield: 54%, yellow oil. IR (film): 3361, 1781, 1666, 1529; ^{1}H NMR (250 MHz, $CDCl_3$): 1.15 (s, 3H), 1.29 (s, 3H), 1.16 (d, 3H, *J* 5.49), 2.62, 2.7 (d,d, 2H, *J* 5.38), 4.13 (d, 2H, *J* 5.38), 5.96 (m, 1H), 7.6–8.2 (m, 8H); $[\alpha]_D^{25}=-0.53$, $c=1$, methanol. Anal. found: C, 74.33; H, 6.55; N, 4.39%. Calcd for $C_{20}H_{21}NO_3$: C, 74.31; H, 6.50; N, 4.33%.

3.14. 6,6-Dimethyl-4-methyl-3-oxa-bicyclo[3.1.0]hexan-2-on-1-carboxylic acid (*R*)-(+)-1-phenylethylamide 9c, 10c

(1*R*,4*S*,5*R*,α*R*)-**9c**: yield 32%, $[\alpha]_D^{25}=+35.5$, $c=1$, methanol; (1*S*,4*R*,5*S*,α*R*)-**10c**: yield 30%, $[\alpha]_D^{25}=+60.4$, $c=1$, methanol; spectroscopic data of the diastereomeric mixture: IR (film): 3296, 1788, 1653, 1550; ^{1}H NMR (250 MHz, $CDCl_3$): 1.31, (s, 3H), 1.34 (s, 3H), 1.51–1.87 (m, 6H), 2.61, 2.69 (s, s, 1H, *J* 4.91), 4.12–4.23 (m, 1H), 4.45–4.53 (m, 1H), 5.14 (m, 1H), 7.1–7.41 (m, 5H), 8.02, 8.11 (d, 1H, *J* 7.32). Anal. found: C, 71.05; H, 7.39; N, 4.85%. Calcd for $C_{17}H_{21}NO_3$: C, 71.08; H, 7.31; N, 4.87%.

3.15. 6,6-Dimethyl-4-methyl-3-oxa-bicyclo[3.1.0]hexan-2-on-1-carboxylic acid (*R*)-(+)-1-(1-naphthyl)ethylamide 9d, 10d

Mixture of diastereomers, yield: 51%, colorless liquid. IR (film): 3293, 1792, 1655, 1559; ^{1}H NMR (400 MHz, $CDCl_3$): 1.31, (s, 3H), 1.34 (s, 3H), 1.51–1.87 (m, 6H), 2.63, 2.65 (s, s, 1H, *J* 4.91), 4.12–4.23 (m, 1H), 4.45–4.53 (m, 1H) 5.14 (m, 1H), 7.3–8.12 (m, 8H); $[\alpha]_D^{25}=+13.7$, $c=1$, methanol. Anal. found: C, 71.27; H, 6.83; N, 4.15%. Calcd for $C_{21}H_{23}NO_3$: C, 71.21; H, 6.82; N, 4.15%.

3.16. 6,6-Dimethyl-4-trichloromethyl-3-oxa-bicyclo[3.1.0]hexan-2-on-1-carboxylic acid (*R*)-(+)-1-phenylethylamide 9e, 10e

(1*R*,4*R*,5*R*,α*R*)-**9e**: yield: 30%, white crystals, mp: 121.5°C. IR (KBr): 3291, 1785, 1650, 1553; ^{1}H NMR (400 MHz, $CDCl_3$): 1.33 (s, 3H), 1.34 (s, 3H), 1.5 (d, 3H, *J* 8.24), 2.85 (s, 2H), 4.62 (s, 1H), 5.14 (m, 1H), 7.3–7.7 (m, 5H), 7.73 (d, 1H, *J* 7.69), 7.84 (d, 1H, *J* 7.69); $[\alpha]_D^{25}=+22.8$, $c=1$, methanol. Anal. found: C, 52.28; H, 4.65; N, 3.59%. Calcd for $C_{17}H_{18}Cl_3NO_3$: C, 52.24; H, 4.60; N, 3.58%.

(1*S*,4*S*,5*S*,α*R*)-**10e**: yield: 30%, yellow oil. IR (film): 3291, 1785, 1650, 1553; ^{1}H NMR (400 MHz, $CDCl_3$): 1.33 (s, 3H), 1.34 (s, 3H), 1.5 (d, 3H, *J* 8.24), 2.93 (s, 2H), 4.62 (s, 1H), 5.14 (m, 1H), 7.3–7.7 (m, 5H), 7.73 (d, 1H, *J* 7.69), 7.84 (d, 1H, *J* 7.69); $[\alpha]_D^{25}=+71.0$, $c=1$, methanol. Anal. found: C, 52.28; H, 4.65; N, 3.59%. Calcd for $C_{17}H_{18}Cl_3NO_3$: C, 52.24; H, 4.60; N 3.58%.

3.17. 6,6-Dimethyl-4-trichloromethyl-3-oxa-bicyclo[3.1.0]hexan-2-on-1-carboxylic acid (*R*)-(+)-1-(1-naphthyl)ethylamide 9f, 10f

(1*R*,4*R*,5*R*,α*R*)-**9f**: Yield: 25%, white crystals, mp: 190.5°C. IR (KBr): 3304, 1782, 1653, 1540; ^{1}H NMR (400 MHz): 1.41 (s, 3H), 1.43 (s, 3H), 1.67 (d, 3H, *J* 6.82), 2.92 (s, 1H), 4.6 (s, 1H), 5.95 (m, 1H), 7.3–8.13 (m, 8H); $[\alpha]_D^{25}=-6.7$, $c=1$, methanol. Anal. found: C, 57.21; H, 4.52; N, 3.19%. Calcd for $C_{21}H_{20}Cl_3NO_3$: C, 57.20; H, 4.54; N, 3.17%.

(1*S*,4*S*,5*S*,α*R*)-**10f**: Yield: 25%, yellow oil. IR (film): 3304, 1782, 1653, 1540; ^{1}H NMR (400 MHz, $CDCl_3$): 1.41 (s, 3H), 1.43 (s, 3H), 1.67 (d, 3H, *J* 6.82), 2.96 (s, 1H), 4.6 (s, 1H), 5.95 (m, 1H), 7.3–8.13 (m, 8H); $[\alpha]_D^{25}=+13.8$, $c=1$, methanol. Anal. found: C, 57.21; H, 4.52; N, 3.19%. Calcd for $C_{21}H_{20}Cl_3NO_3$: C, 57.20; H, 4.54; N, 3.17%.

3.18. X-Ray diffraction studies

Crystal data for compound **9e**: $C_{17}H_{18}Cl_3NO_3$, Fwt: 390.67, colorless prism, size: 0.60×0.60×0.35 mm, orthorhombic, space group $P2_12_12_1$, $a=8.156(1)$, $b=11.207(1)$, $c=20.600(3)$ Å, $V=1882.9(4)$ Å^3, $T=293(2)$ K, $Z=4$, $F(000)=808$, $D_x=1.378$ Mg m^{-3}, $m=0.501$ mm^{-1}.

Cell parameters were determined by least-squares of the setting angles of 25 ($15.03\leq\theta\leq16.96°$) reflections.

Intensity data were collected on an Enraf–Nonius CAD4 diffractometer (graphite monochromator; Mo-Kα radiation, $\lambda=0.710730$ Å) at 293(2) K in the range $2.69\leq\theta\leq29.95°$ using $\omega/2\theta$ scans. The intensities of three standard reflections were monitored regularly (every 60 min). The intensities of the standard reflections indicated a crystal decay of 10% (the data were corrected for decay).

A total of 6293 reflections were collected of which 5423 were unique [$R_{int}=0.0132$, $R(\sigma)=0.0404$]; intensities of 3200 reflections were greater than $2\sigma(I)$.[9] Completeness to $\theta=0.991$.

A psi-scan absorption correction[10] was applied to the data (the minimum and maximum transmission factors were 0.9145 and 0.9944).

The structure was solved by direct methods[11] (and subsequent difference syntheses). Anisotropic full-matrix least-squares refinement[12] on F^2 for all non-hydrogen atoms yielded $R_1=0.0392$ and $wR_2=0.0931$ for 3200 [$I>2\sigma(I)$] and $R_1=0.0806$ and $wR_2=0.1022$ for all (5423) intensity data (number of parameters=220, goodness-of-fit=0.934, absolute structure parameter $x=0.00(5)$, the maximum and mean shift/esd is 0.000 and 0.000).

The maximum and minimum residual electron density in the final difference map was 0.160 and −0.272 e Å^{-3}.

The weighting scheme applied was $w=1/[\sigma^2(F_o^2)+(0.0583P)^2]$ where $P=(F_o^2+2F_c^2)/3$.

Hydrogen atomic positions were calculated from assumed geometries except H13 that was located in difference maps. Hydrogen atoms were included in structure factor calculations but they were not refined. The isotropic displacement parameters of the hydrogen atoms were approximated from the U_{eq} value of the atom they were bonded to.

Crystal data for compound **9f**: $C_{21}H_{19}Cl_3NO_3$, Fwt: 439.72, colorless prism, size: 0.60×0.50×0.35 mm, orthorhombic, space group $P2_12_12_1$, $a=9.405(1)$, $b=10.996(1)$, $c=20.138(2)$ Å, $V=2082.6(4)$ Å^3, $T=293(2)$ K, $Z=4$, $F(000)=908$, $D_x=1.402$ Mg m^{-3}, $m=0.462$ mm^{-1}.

Cell parameters were determined by least-squares of the setting angles of 25 ($15.05\leq\theta\leq16.90°$) reflections.

Intensity data were collected on an Enraf–Nonius CAD4 diffractometer (graphite monochromator; Mo-Kα radiation, $\lambda=0.710730$ Å) at 293(2) K in the range $2.39\leq\theta\leq31.96°$ using $\omega/2\theta$ scans. The intensities of three standard reflections were monitored regularly (every 60 min). The intensities of the standard reflections indicated a crystal decay of 4% (the data were corrected for decay).

A total of 8210 reflections were collected of which 7161 were unique [$R_{int}=0.0141$, $R(\sigma)=0.0490$]; intensities of 4093 reflections were greater than $2\sigma(I)$.[9] Completeness to $\theta=0.993$.

A psi-scan absorption correction[10] was applied to the data (the minimum and maximum transmission factors were 0.9947 and 0.9747).

The structure was solved by direct methods[11] (and subsequent difference syntheses). Anisotropic full-matrix least-squares refinement[12] on F^2 for all non-hydrogen atoms yielded $R_1=0.0421$ and $wR_2=0.0932$ for 4093 [$I>2\sigma(I)$] and $R_1=0.0872$ and $wR_2=0.1034$ for all (7161) intensity data (number of parameters = 256, goodness-of-fit = 0.883, absolute structure parameter $x=-0.08(5)$, the maximum and mean shift/esd is 0.001 and 0.000).

The maximum and minimum residual electron density in the final difference map was 0.374 and –0.209 e Å^{-3}. The weighting scheme applied was $w=1/[\sigma^2(F_o^2)+(0.0606P)^2]$ where $P=(F_o^2+2F_c^2)/3$.

Hydrogen atomic positions were calculated from assumed geometries. Hydrogen atoms were included in structure factor calculations but they were not refined. The isotropic displacement parameters of the hydrogen atoms were approximated from the U_{eq} value of the atom they were bonded to. Scattering factors,[13] molecular graphics.[14]

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