# Supplementary Information

# Synthetic and structural studies on macrocyclic amino cyclitols – conformational chameleons

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**1. 3,4-*O*-Isopropyliden-3(*R*),4(*S*),5(*R*)-trihydroxycyclohexaneoxime (9)**:

Ketone **8** (19.56 g, 105 mmol) was dissolved in 500 ml dry MeOH and a solution of ammonium hydrochloride (14.61 g, 210 mmol) and NaOAc (25.87 g, 315 mmol) in dry MeOH was added. The reaction mixture was stirred for 30 min, where after the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography using petroleum ether/ ethyl ether (1:3) as eluent. Oxime **9** (20.76 g, 103 mmol) was obtained as a colourless oil in 98 % yield. The product consists of two inseparable *E/Z*-isomers. Indices $_a$ and $_b$ therefore indicate the signals for the two isomers a and b.

$R_f$= 0.45 ($CH_2Cl_2$/MeOH= 9:1); $^1$H NMR (400 MHz; $CDCl_3$, TMS= 0 ppm): $\delta$= 1.34 (s, 3 H, $CH_{3a}$), 1.35 (s, 3 H, $CH_{3b}$), 1.41 (s, 3 H, $CH_{3a}$), 1.43 (s, 3 H, $CH_{3b}$), 2.40 (dd, *J*= 15.7, 5.0 Hz, 1 H, 6´$_b$-H), 2.55 (dd, *J*= 15.7, 4.5 Hz, 1 H, 6´$_a$-H), 2.60 (ddd, *J*= 19.1, 4.2, 1.5 Hz, 2 H, 2´-H), 2.67- 2.73 (m, 2 H, 6-H), 2.81 (dd, *J*= 15.7, 4.0 Hz, 1 H, 2$_b$-H), 3.13 (dd, *J*= 19.1, 2.5 Hz, 1 H, 2$_a$-H), 4.01 (ddd, *J*= 5.0, 2.4, 2.0 Hz, 1 H, 5$_b$-H), 4.08 (ddd, *J*= 4.5, 4.4, 4.2 Hz, 1 H, 5$_a$-H), 4.16 (dd, *J*= 7.1, 4.0 Hz, 1 H, 4$_b$-H), 4.20 (dd, *J*= 7.1, 4.2 Hz, 1 H, 4$_a$-H), 4.51- 4.57 (m, 2 H, 3-H) ppm; $^{13}$C NMR (100 MHz; $CDCl_3$, $CHDCl_3$= 77 ppm): $\delta$= 24.0 (q, $CH_{3b}$), 24.1 (q, $CH_{3a}$), 24.9 (t, C-2$_b$), 26.6 (q, $CH_{3b}$), 26.7 (q, $CH_{3a}$), 27.8 (t, C-6$_b$), 30.6 (t, C-2$_a$), 31.2 (t, C-6$_a$), 66.8 (d, C-5$_a$), 67.9 (d, C-5$_a$), 70.8 (d, C-3$_a$), 71.9 (d, C-3$_a$), 76.0 (d, C-4$_b$), 76.4 (d, C-4$_a$), 108.2 (s, $C_bMe_2$), 108.9 (s, $C_aMe_2$), 155.2 (s, C-1$_b$), 155.8 (s, C-1$_a$) ppm; LRMS: *m/z* (%): 201 (19.63); HRMS: (calculated: $M^+$, 201.1001; found: 201.0998).

**2. 3,4-*O*-Isopropyliden-3(*R*),4(*S*),5(*R*)-trihydroxy-1(R)-(2,2,2-trifluoroacetamido)-cyclohexane (10a)** and **3,4-*O*-isopropyliden-3(*R*),4(*S*),5(*R*)-trihydroxy-1(*S*)-(2,2,2-trifluoroacetamido)-cyclohexane (10b)**:

A solution of oxime **9** (20.76 g, 103 mmol) and $Ni(OAc)_2 \times 4\ H_2O$ (2.57 g, 10 mmol) as a catalyst in 700 ml MeOH was cooled to 0°C. After slow addition of $NaBH_4$ (19.53 g, 516 mmol) the catalyst turned black and strong formation of gas was noted. After 1 h, completion of the reaction was judged by TLC; otherwise additional 2 g of $NaBH_4$ and 0.05 g of $Ni(OAc)_2 \times 4\ H_2O$ were added. Without any workup $Et_3N$ (43.2 ml, 309.8 mmol) and $CF_3COOEt$ (61.6 ml, 513.6 mmol) were added and the colour changed from black to dark blue. After stirring for 18 h at RT, reaction was completed and the volatile compounds were removed under reduced pressure. The diastereomers **10a** and **10b** (2:1) could now be separated by flash column chromatography to yield both alcohols (26.75 g, 93.4 mmol; 92% yield).

**10a:** $R_f$= 0.60 ($CH_2Cl_2$ / MeOH= 9: 1); $[\alpha]^{20}_D$ = – 48.4 (*c*= 1.0, $CHCl_3$); $^1$H NMR (400 MHz; $CDCl_3$, TMS= 0 ppm): $\delta$= 1.32 (s, 3 H, $CH_3$), 1.47 (s, 3 H, $CH_3$), 1.50 (ddd, *J*= 14.1, 11.2, 3.4 Hz, 1 H, $6_{ax}$-H), 1.97 (ddd, *J*= 15.7, 4.1, 4.0 Hz, 1 H, $2_{ax}$-H), 2.11- 2.19 (m, 2 H, $2_{eq}$-H und $6_{eq}$-H), 2.41- 2.46 (s, 1 H, OH), 3.84 (ddd, *J*= 11.2, 6.3, 5.0 Hz, 1 H, 5-H), 3.89 (dd, *J*= 6.3, 4.7 Hz, 1 H, 4-H), 4.28 (ddddd, *J*= 7.5, 4.0, 3.8, 3.8, 3.4 Hz, 1 H, 1-H), 4.38 (ddd, *J*= 4.7, 4.1, 2.8 Hz, 1 H, 3-H), 7.40 (br d, *J*= 7.5 Hz, 1 H, NH) ppm; $^{13}$C NMR (100 MHz; $CDCl_3$, $CDCl_3$= 77 ppm): $\delta$= 25.8 (q, $CH_3$), 28.1 (q, $CH_3$), 29.6 (t, C-2), 33.6 (t, C-6), 44.5 (d, C-1), 68.3 (d, C-5), 74.0 (d, C-3), 80.2 (d, C-4), 109.3 (s, $CMe_2$), 115.8 (s, $CF_3$, $^1J_{C,F}$ = 287.7 Hz), 156.3 (s, $COCF_3$, $^2J_{C,F}$ = 36.9 Hz) ppm; LRMS: *m/z* (%): 268 (83.95) – $CH_3$ (15). HRMS: (calculated: $M^+$, 283.1008; found: 283.1008).

**10b:** $R_f$= 0.50 ($CH_2Cl_2$ / MeOH= 9: 1); $[\alpha]^{20}_D$ = –16.2 (*c*= 0.63, $CHCl_3$); $^1$H NMR (400 MHz; $CDCl_3$, TMS= 0 ppm): $\delta$= 1.36 (s, 3 H, $CH_3$), 1.49 (s, 3 H, $CH_3$), 1.50 (m, 1 H, $6_{ax}$-H), 1.82 (ddd, *J*= 14.4, 9.0, 4.4 Hz, 1 H, $2_{ax}$-H), 2.15 (ddd, *J*= 13.5, 4.5, 4.1 Hz, 1 H, $6_{eq}$-H), 2.31 (ddd, *J*= 14.4, 4.8, 4.4 Hz, 1 H, $2_{eq}$-H), 2.89 (s, 1 H, OH), 3.92- 4.00 (m, 2 H, 4-H, 5-H), 4.24 (ddddd, *J*= 9.0, 8.9, 8.2, 4.5, 4.4 Hz, 1 H, 1-H), 4.38 (ddd, *J*= 4.8, 4.4, 4.4 Hz, 1 H, 3-H), 6.96 (br d, *J*= 8.2 Hz, 1 H, NH) ppm; $^{13}$C NMR (100 MHz; $CDCl_3$, $CDCl_3$= 77 ppm): $\delta$= 25.7 (q, $CH_3$), 28.0 (q, $CH_3$), 31.6 (t, C-2), 33.8 (t, C-6), 43.4 (d, C-1), 70.0 (d, C-5), 72.2 (d, C-3), 78.7 (d, C-4), 109.1 (s, $CMe_2$), 115.7 (s, $CF_3$, $^1J_{C,F}$= 287.9 Hz), 156.5 (s, $COCF_3$, $^2J_{C,F}$= 37.1 Hz) ppm; LRMS: *m/z* (%): 283 (3.13); HRMS: (calculated: $M^+$, 283.1008; found: 283.1007).

**3. 3,4-*O*-Isopropyliden-5-*O*-allyl-3(*R*),4(*S*),5(*R*)-trihydroxy-1(*R*)-(2,2,2-trifluoroacetamido)-cyclo-hexane (11a)** and **3,4-*O*-isopropyliden-5-*O*-allyl-3(*R*),4(*S*),5(*R*)-trihydroxy-1(*S*)-(2,2,2-trifluoroacetamido)-cyclohexane (11b)**:

A mixture of aminoalcohols **10a** and **10b** (26.44 g, 93.39 mmol) were dissolved in 300 ml MeCN and mixed with freshly prepared $Ag_2O$ (43.28 g, 186.78 mmol, 2 eq). After 15 min of stirring allyliodide (12.79 ml, 140.09 mmol, 1.5 eq) was added and the solution was stirred for 18 h at RT. The solution was filtered and the organic phase was evaporated in vacuum. The diastereomers could be separated by flash column chromatography utilising petroleum ether / ethyl acetate (2:1) as eluent to yield **11a** (15.08 g, 46.69 mmol; 50% yield) and the minor diastereomer **11b** (7.55 g, 23.35 mmol, 25% yield).

**11a:** $R_f$= 0.58 ($CH_2Cl_2$ / MeOH= 9: 1); $[\alpha]^{20}_D$ = – 99.4 (*c*= 1.0, $CHCl_3$); $^1$H NMR (400 MHz; $CDCl_3$, TMS= 0 ppm): $\delta$= 1.38 (s, 3 H, $CH_3$), 1.53 (s, 3 H, $CH_3$), 1.61 (ddd, *J*= 13.9, 10.2, 4.1 Hz, 1 H, $6_{ax}$-H), 2.04 (ddd, *J*= 15.5, 4.3, 3.3 Hz, 1 H, $2_{ax}$-H), 2.21 (m, 2 H, $2_{eq}$-H, $6_{eq}$-H), 3.61 (ddd, *J*= 10.2, 5.9, 4.1 Hz, 1 H, 5-H), 4.07 (dd, *J*= 5.9, 5.7 Hz, 1 H, 4-H), 4.10 (ddt, *J*= 12.7, 5.7, 1.4 Hz, 1 H, $7_b$-H), 4.14 (ddt, *J*= 12.7, 5.7, 1.4 Hz, 1 H, $7_a$-H), 4.32 (ddddd, *J*= 7.5, 4.3, 3.8, 3.8, 3.8 Hz, 1 H, 1-H), 4.45 (ddd, *J*= 5.7, 3.3, 2.9 Hz, 1 H, 3-H), 5.18 (ddd, *J*= 10.4, 3.1, 1.4 Hz, 1 H, $9_b$-H), 5.27 (ddd, *J*= 17.2, 3.1, 1.4 Hz, 1 H, $9_a$-H), 5.89 (dddd, *J*= 17.2, 10.4, 5.7, 5.7 Hz, 1 H, 8-H), 7.47 (br d, *J*= 7.5 Hz, 1 H, NH) ppm; $^{13}$C NMR (100 MHz; $CDCl_3$, $CDCl_3$= 77 ppm): $\delta$= 25.7 (q, $CH_3$), 27.9 (q, $CH_3$), 29.5 (t, C-2), 31.1 (t, C-6), 44.0 (d, C-1), 70.6 (t, C-7), 74.0 (d, C-5), 74.1 (d, C-3), 78.5 (d, C-4), 109.0 (s, $CMe_2$), 115.8 (s, $CF_3$, $^1J_{C,F}$ = 287.7 Hz), 117.4 (t, C-9), 134.6 (d, C-8), 156.2 (s, $COCF_3$, $^2J_{C,F}$ = 36.7 Hz) ppm; LRMS: *m/z* (%): 323 (7.95); HRMS: (calculated: $M^+$, 323.1344; found: 323.1339).

**11b:** $R_f$= 0.58 ($CH_2Cl_2$/ MeOH= 9: 1); $[\alpha]^{20}_D$ = – 99.4 (*c*= 1.0, $CHCl_3$); $^1$H NMR (400 MHz; $CDCl_3$, TMS= 0 ppm): $\delta$= 1.36 (s, 3 H, $CH_3$), 1.48 (s, 3 H, $CH_3$), 1.60 (ddd, *J*= 13.9, 6.7, 6.1 Hz, 1 H, $6_{ax}$-H), 1.85 (ddd, *J*= 14.4, 8.3, 4.8 Hz, 1 H, $2_{ax}$-H), 2.15 (ddd, *J*= 13.9, 5.0, 3.6 Hz, 1 H, $6_{eq}$-H), 2.20 (ddd, *J*= 14.4, 5.3, 5.0 Hz, 1 H, $2_{eq}$-H), 3.73 (ddd, *J*= 6.7, 4.5, 3.6 Hz, 1 H, 5-H), 4.09 (ddt, *J*= 12.7, 5.6, 1.5 Hz, 1 H, $7_b$-H), 4.10 (dd, *J*= 5.4, 4.5 Hz, 1 H, 4-H), 4.17 (ddt, *J*= 12.7, 5.6, 1.4 Hz, 1 H, $7_a$-H), 4.28 (ddddd, *J*= 8.3, 7.5, 6.1, 5.3, 5.0 Hz, 1 H, 1-H), 4.36 (ddd, *J*= 5.4, 5.0, 4.8 Hz, 1 H, 3-H), 5.22 (ddt, *J*= 10.4, 2.8, 1.4 Hz, 1 H, $9_b$-H), 5.29 (ddt, *J*= 17.2, 3.2, 1.5 Hz, 1 H, $9_a$-H), 5.90 (dddd, *J*= 17.2, 10.4, 5.6, 5.6 Hz, 1 H, 8-H), 6.97 (br d, *J*= 7.5 Hz, 1 H, NH) ppm; $^{13}$C NMR (100 MHz; $CDCl_3$, $CDCl_3$= 77 ppm): $\delta$= 25.7 (q, $CH_3$), 27.8 (q, $CH_3$), 30.7 (t, C-2), 31.4 (t, C-6), 43.0 (d, C-1), 70.9 (t, C-7), 71.6 (d, C-3), 75.5 (d, C-4), 76.0 (d, C-5), 108.9 (s, $CMe_2$), 115.8 (s, $CF_3$, $^1J_{C,F}$ = 287.9 Hz), 134.1 (d, C-8),

117.5 (t, C-9), 156.2 (s, $COCF_3$, $^2J_{C,F}$ = 36.7 Hz) ppm; LRMS: *m/z* (%): 323 (11.00); HRMS: (calculated: $M^+$, 323.1344; found: 323.1339).

**4. 5- *O*-Allyl-3(R), 4(S), 5(R)-trihydroxy-1(R)-(2,2,2-trifluoroacetamido)-cyclohexane (12a)**:

Acetonide **11a** (2.751 g, 8.513 mmol) was dissolved in a mixture of 22 ml MeOH/ $H_2O$ (10:1) and 0.2 ml concentrated $HCl_{(aq)}$. This solution was stirred for 1 h at RT. The solvents were evaporated in vacuum to yield product **12a** (2.332 g, 8.239 mmol) in 97% yield as a colourless solid without any further purification.

m.p.: 80-85°C; $[\alpha]^{20}_D$ = –120.1 (*c* = 1, MeOH); $^1$H NMR (400 MHz, $CDCl_3$, TMS = 0 ppm): $\delta$= 1.41 (ddd, *J*= 13.6, 11.2, 3.5 Hz, 1 H, $6_{ax}$H), 1.77 (ddd, *J*= 15.0, 4.1, 2.9 Hz, 1 H, $2_{ax}$-H), 2.08 (dddd, *J*= 15.0, 3.6, 3.0, 2.9 Hz, 1 H, $2_{eq}$-H), 2.40 (dddd, *J*= 13.6, 3.9, 3.6, 2.9 Hz, 1 H, $6_{eq}$-H), 3.15 (br s, 2 H, OH), 3.56 (dd, *J*= 9.1, 3.0 Hz, 1 H, 4-H), 3.67 (ddd, *J*= 11.2, 9.1, 3.9 Hz, 1 H, 5-H), 3.94 (ddt, *J*= 12.5, 6.2, 1.5 Hz, 1 H, 7′-H), 4.14 (ddt, *J*= 12.5, 5.5, 1.5, 1 H, 7-H), 4.29 (ddd, *J*= 3.0, 3.0, 2.9 Hz, 1 H, 3-H), 4.35 (ddddd, *J*= 7.2, 4.1, 3.6, 3.6, 3.5 Hz, 1 H, 1-H), 5.22 (ddd, *J*= 10.4, 2.8, 1.5 Hz, 1 H, 9′-H), 5.28 (ddd, *J*= 17.2, 3.1, 1.5 Hz, 1 H, 9-H), 5.90 (dddd, *J*= 17.2, 10.4, 6.2, 5.5 Hz, 1 H, 8-H), 8.11 (br s, 1 H, NH) ppm; $^1$H NMR (400 MHz, MeOH-$d_4$, MeOH-$d_3$ = 3.31 ppm): $\delta$= 1.72– 1.87 (m, 4 H, 2-H, 6-H), 3.69 (ddd, *J*= 3.7, 3.5, 3.5 Hz, 1 H, 5-H), 3.81 (dd, *J*= 3.5, 3.2 Hz, 1 H, 4-H), 3.89 (ddd, *J*= 10.7, 4.5, 3.2, 1 H, 3-H), 4.01 (ddt, *J*= 13.0, 5.4, 1.5 Hz, 1 H, 7′-H), 4.04– 4.08 (m, 1 H, 1-H), 4.09 (ddt, *J*= 13.0, 5.4, 1.5 Hz, 1 H, 7-H), 5.15 (ddd, *J*= 10.5, 3.3, 1.5 Hz, 1 H, 9′-H), 5.29 (ddd, *J*= 17.2, 3.3, 1.5 Hz, 1 H, 9-H), 5.92 (dddd, *J*= 17.2, 10.5, 5.4, 5.3 Hz, 1 H, 8-H) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, $CDCl_3$ = 77 ppm): $\delta_C$= 31.4 (t, C-2), 32.6 (t, C-6), 45.6 (d, C-1), 70.1 (t, C-7), 70.2 (d, C-3), 74.0 (d, C-5), 74.5 (d, C-4), 115.8 (s, $CF_3$, $^1J_{C,F}$ = 287.8 Hz), 117.9 (t, C-9), 134.3 (d, C-8), 156.2 (s, $COCF_3$, $^2J_{C,F}$ = 36.9 Hz) ppm; HRMS (ESI): *m/z* for negative ions; calculated: 283.1031 (282.0954 – $H^+$); found: 282.0953 (– $H^+$).

**5- *O*-Allyl-3(R), 4(S), 5(R)-trihydroxy-1(S)-(2,2,2-trifluoroacetamido)-cyclohexane (12b)**:

Acetonide **11b** (232 mg, 0.715 mmol) was dissolved in a mixture of 3 ml MeOH/ $H_2O$ (10:1) and 0.05 ml concentrated $HCl_{(aq)}$. This solution was stirred for 1 h at rt. The solvents were evaporated in vacuum to yield product **12b** (194 mg, 0.686 mmol) in 96% yield as a colourless solid without any further purification.

m.p.: 148-149°C; $[\alpha]^{20}_D$ = –20.6 (*c* = 1, MeOH); $^1$H NMR (400 MHz, MeOH-$d_4$, MeOH-$d_3$ = 3.31 ppm): $\delta$= 1.38 (ddd, *J*= 11.6, 11.2, 10.5 Hz, 1 H, $6_{ax}$-H), 1.63 (ddd, *J*= 12.5, 11.5, 3.5 Hz,

1 H, $2_{ax}$-H), 1.99 (ddd, *J*= 12.5, 4.5, 3.9 Hz, 1 H, $2_{eq}$-H), 2.23 (ddd, *J*= 11.6, 4.9, 3.9 Hz, 1 H, $6_{eq}$-H), 3.46– 3.54 (m, 1 H, 4-H), 3.67 (ddd, *J*= 10.5, 9.1, 4.9 Hz, 1 H, 5-H), 4.08– 4.01 (m, 1 H, 3-H), 4.14 (dt, *J*= 5.8, 1.0 Hz, 2 H, 7-H), 4.23 (dddd, *J*= 11.5, 11.2, 3.9, 3.9 Hz, 1 H, 1-H), 5.15 (ddd, *J*= 10.8, 2.0, 1.0 Hz, 1 H, 9´-H), 5.30 (ddd, *J*= 17.0, 2.0, 1.0 Hz, 1 H, 9-H), 5.96 (dddd, *J*= 17.0, 10.8, 5.8, 5.8 Hz, 1 H, 8-H) ppm; $^{13}$C NMR (100 MHz, MeOH-$d_4$, MeOH-$d_4$ = 49 ppm): $\delta_C$= 35.3 (t, C-6), 36.7 (t, C-2), 44.7 (d, C-1), 69.5 (d, C-3), 72.0 (t, C-7), 75.4 (d, C-4), 77.6 (d, C-5), 117.1 (t, C-9), 117.4 (s, $CF_3$, $^1J_{C,F}$ = 286.9 Hz), 136.5 (d, C-8), 158.0 (s, $COCF_3$, $^2J_{C,F}$ = 36.7 Hz) ppm; HRMS (ESI): *m/z* for negative ions; calculated: 283.1031 (282.0954 – $H^+$); found: 282.0963 (– $H^+$).

**6. 1´,4´-*O*-Di-(3,4-*O*-isopropyliden-1(*R*)-(trifluoroacetamido)-3(*R*),4(*S*),5(*R*)-trihydroxycyclo-hexane-1,4-butane (14)**:

L-Allylether **10a** (75 mg, 0.232 mmol) was dissolved in 1 ml $CH_2Cl_2$ under argon-atmosphere. Grubbs I catalyst **13** (16 mg, 0.02 mmol, 0.085 eq.) was added and the solution was heated under reflux for 52 h. After 18 h as well as 24 h small portions (each time 2 mg, 3 µmol) of catalyst **13** were added. The solvent was evaporated and the residue was purified by flash column chromatography (petroleum ether / ethyl acetate= 4:1) to yield recovered **11a** (17 mg, 0.053 mmol; 23%) and **18** (55 mg, 0.178 mmol; 77%) as colourless oils. This product was directly employed in the next step without any further purification by dissolving them in a mixture of ethyl acetate / $CH_2Cl_2$ / MeOH (16:8:1; 2 ml). Then it was treated with a catalytic amount of $PtO_2$ (27.5 mg, 0.121 mmol) under a $H_2$-atmosphere for 24 h. The solution was filtered through a pad of Celite$^{TM}$, washed with MeOH and evaporated in vacuum. The residue was purified by flash column chromatography (petroleum ether / ethyl acetate= 3:1) to yield the reduction product (44 mg, 0.071 mmol; 73% yield; 61% for two steps) as a colourless oil.

$R_f$= 0.63 ($CH_2Cl_2$: MeOH= 9: 1); $[\alpha]^{20}_D$ = – 80.0° (c= 1.0, $CHCl_3$); $^1$H NMR (400 MHz; $CDCl_3$, TMS= 0 ppm): $\delta_H$= 1.37 (s, 6 H, $CH_3$), 1.53 (s, 6 H, $CH_3$), 1.59– 1.63 (m, 4 H, 8-H), 1.66 (ddd, *J*= 14.0, 9.8, 4.2 Hz, 2 H, $6_{ax}$-H), 2.05 (ddd, *J*= 15.4, 4.5, 3.4 Hz, 2 H, $2_{ax}$-H), 2.08– 2.16 (m, 4 H, $2_{eq}$-H, $6_{eq}$-H) 3.50 (ddd, *J*= 9.8, 5.6, 4.4 Hz, 2 H, 5-H), 3.51– 3.55 (m, 2 H, $7_b$-H), 3.56– 3.63 (m, 2 H, $7_a$-H), 4.04 (dd, *J*= 5.6, 5.5 Hz, 2 H, 4-H), 4.31 (ddddd, *J*= 8.1, 4.5, 4.2, 4.1, 4.0 Hz, 2 H, 1-H), 4.44 (ddd, *J*= 5.5, 3.4, 3.0 Hz, 2 H, 3-H), 7.44 (br d, *J*= 8.1 Hz, 2 H, NH) ppm; $^{13}$C NMR (100 MHz; $CDCl_3$, $CDCl_3$= 77 ppm): $\delta_C$= 25.5 (q, $CH_3$), 26.7 (t, C-8), 27.8 (q, $CH_3$), 29.5 (t, C-$6_{eq}$, C-2), 31.1 (t, C-$6_{ax}$), 43.7 (d, C-1), 69.7 (t, C-7), 73.9 (d, C-3), 75.2 (d, C-5), 78.1 (d, C-4), 108.9 (s, $CMe_2$), 115.9 (s, $CF_3$, $^1J_{C,F}$ = 288.1 Hz), 156.2 (s,

$COCF_3$, $^2J_{C,F}$ = 36.7 Hz) ppm; LRMS: *m/z* (%): 620 (2.54); HRMS: (calculated: $M^+$, 620.2531; found: 620.2532).

**7. 1´,4´-*O*-Di-(3,4-*O*-isopropyliden-1(*S*)-(trifluoroacetamido)-3(*R*),4(*S*),5(*R*)-trihydroxycyclo-hexane-1,4-butane (15)**:

Based on the general procedure for compound **14** D-allyl ether **11b** (2.706 g, 8.37 mmol) was treated with the Grubbs catalyst **13** (0.345 g, 0.42 mmol). After purification by column chromatography over silica gel (petroleum ether / ethyl acetate= 4:1) D-allylether **11b** (1.343 g, 4.15 mmol; 50% yield) was reisolated as well as the corresponding homodimer (1.184 g, 1.92 mmol; 46% yield) as colourless oils. The crude product was treated with $PtO_2$ under $H_2$ atmosphere as described before and purified by column chromatography (petroleum ether / ethyl acetate= 5:1→1:3) to yield the reduction product **15** (1.028 g, 1.656 mmol, 86% yield, 40 % for two steps) as a white solid.

$R_f$= 0.31 (petroleum ether / ethyl acetate= 1:1); m.p.= 46°C; $[\alpha]^{20}_D$ = – 19.9 (*c*= 1, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$, TMS = 0 ppm): $\delta$= 1.35 (s, 6 H, $CH_3$), 1.49 (s, 6 H, $CH_3$), 1.57 (ddd, *J*= 13.9, 6.2, 5.5 Hz, 2 H, $2_{ax}$-H), 1.63 (m, 4 H, 8-H), 1.86 (ddd, *J*= 14.0, 8.2, 4.8 Hz, 2 H, $6_{ax}$-H), 2.13 (ddd, *J*= 13.9, 4.9, 4.2 Hz, 2 H, $2_{eq}$-H), 2.15 (ddd, *J*= 14.0, 5.2, 5.1 Hz, 2 H, $6_{eq}$-H), 3.56 (ddd, *J*= 11.6, 5.5, 2.9 Hz, 2 H, $7_b$-H), 3.67 (m, 2 H, $7_a$-H), 3.66 (m, 2 H, 5-H), 4.07 (dd, *J*= 5.0, 4.9 Hz, 2 H, 4-H), 4.26 (ddddd, *J*= 8.3, 8.2, 5.5, 5.2, 4.9 Hz, 2 H, 1-H), 4.34 (ddd, *J*= 6.2, 5.0, 4.2 Hz, 2 H, 3-H), 7.11 (br d, *J*= 8.3 Hz, 2 H, NH) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, $CDCl_3$ = 77 ppm): $\delta$= 25.7 (q, $CH_3$), 26.7 (t, C-8), 27.9 (q, $CH_3$), 30.9 (t, C-2), 31.5 (t, C-6), 43.2 (d, C-1), 70.0 (t, C-7), 71.6 (d, C-5), 75.5 (d, C-3), 76.7 (d, C-4), 108.9 (s, $CMe_2$), 115.8 (s, $CF_3$, $^1J_{C,F}$ = 287.9 Hz), 156.2 (s, $COCF_3$, $^2J_{C,F}$ = 36.8 Hz) ppm; HRMS (ESI): *m/z* for positive ions; calculated: 620.2531 (643.2430 + $Na^+$) ; found: 643.2188 (+ $Na^+$).

**8. Macrocycle (29)**:

Bisallylether **22** (63 mg, 0.089 mmol) and Grubbs catalyst **13** (7.4 mg, 0.010 mmol) were dissolved in 60 ml degassed benzene under an argon atmosphere and heated at 40°C for 36h. After completion of the reaction air was bubbled through the solution for at least 10 min. Then, all volatile compounds were removed under reduced pressure and the residue was filtered over silica gel (ethyl acetate / petroleum ether= 2:1) to yield an inseparable mixture of two products (30.2 mg, 0.045 mmol; 50%) as a colourless oil. A major portion (25 mg, 0.037 mmol) was dissolved in 2.5 ml ethyl acetate/$CH_2Cl_2$/MeOH and was treated with $Pt_2O$ (3.3 mg, 0.015 mmol) under hydrogen atmosphere to furnish product **29** (21.6 mg, 0.032 mmol;

86%) as an inseparable mixture (1:1) conformers. In conformer **29a** both cyclohexane rings adopt a different chair conformation, while in conformer **29b** both rings have the same conformational orientation. This leads to three sets of different signals for cyclohexane rings in a ratio of 1:2:1, which is indicated with the capital letters A and C for **29a** and B for **29b**.
$R_f$= 0.66, 0.58 and 0.48 ($CH_2Cl_2$ / MeOH= 9:1); $^1$H NMR (500 MHz, $CDCl_3$, $CHCl_3$ = 7.26 ppm): $\delta$= 1.42– 1.49 (m, 2 H), 1.50– 1.68 (m, 22 H, 6-H$^A$), 1.69– 1.79 (m, 10 H, 2-H$^A$), 1.82– 1.90 (m, 1 H), 2.09 (s, $COCH_3$), 2.12 (s, $COCH_3$), 2.06– 2.12 (m, 18 H, 2-H$^A$), 2.23 (s, $COCH_3$), 2.14– 2.24 (m, 6 H), 2.38 (dm, *J*= 13.9, 1 H, 6-H$^A$), 3.37– 3.43 (m, 3 H, 7-H), 3.45– 3.81 (m, 27 H, 3-H 5-H, 7-H, 10-H), 3.94 (br s, 1 H, 3-H$^A$), 4.11– 4.26 (m, 3 H, 1-H$^{B,C}$), 4.40 (br s, 1 H, 1-H$^A$), 4.75 (dd, *J*= 10.0, 2.7 Hz, 1 H, 4-H$^A$), 5.29 (dd, *J*= 2.6, 2.6 Hz, 2 H, 4-H$^B$), 5.31 (dd, *J*= 2.7, 2.7 Hz, 1 H, 4-H$^C$), 6.17– 6.23 (m, 3 H, NH$^{B,C}$), 8.07 (br d, *J*= 7.8 Hz, 1 H, NH$^A$) ppm; TOCSY 29a/A (500 MHz, $CDCl_3$, 4-H$^A$ = 4.75 ppm): δ= 1.54 (ddd), 1.73 (ddd), 1.46 (ddd), 2.03 (dd), 2.38 (br d), 3.73 (ddd), 3.94 (br s), 4.40 (br s), 4.75 (dd), 8.07 (d) ppm; TOCSY 29a/B (500 MHz, $CDCl_3$, 4-H$^B$ = 5.29 ppm): $\delta$= 1.55 (ddd), 1.62 (q), 2.07 (br d), 2.18 (br d), 3.65 (dd), 3.77 (ddd), 4.21 (dt), 5.29 (t), 6.21 (d) ppm; TOCSY 29a/C (500 MHz, $CDCl_3$, 4-H$^C$ = 5.31 ppm): δ=1.66 (q), 2.09 (br d), 2.20 (br d), 3.65 (dd), 3.79 (ddd), 4.16 (ddt), 5.31 (t), 6.19 (d) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, $CDCl_3$ = 77 ppm): $\delta$= 21.1 (q, $COCH_3$), 21.1 (q, $COCH_3$), 21.2 (q, $COCH_3$), 25.5 (t), 25.5 (t), 26.1 (t), 27.3 (t), 27.3 (t), 27.8 (t), 29.7 (t), 31.3 (t), 31.5 (t), 32.2 (t), 32.6 (t), 35.1 (t, C-6$^A$), 43.6 (d, C-1), 44.0 (d, C-1), 45.3 (d, C-1), 68.0 (d, C-4$^B$), 68.1 (d), 68.5 (t), 69.0 (t), 70.0 (t), 70.1 (t), 70.3 (t), 71.5 (d, C-5$^A$), 72.2 (d), 72.3 (t, C-7), 73.0 (d), 74.5 (d), 74.7 (d), 76.8 (d, C-4$^A$), 77.2 (d), 78.3 (d, C-3$^A$), 115.7 (s, $CF_3$, $^1J_{C,F}$ = 288.1 Hz), 115.8 (s, $CF_3$, $^1J_{C,F}$ = 288.1 Hz), 116.0 (s, $CF_3$, $^1J_{C,F}$ = 288.1 Hz), 156.3 (s, $COCF_3$, $^2J_{C,F}$ = 36.7 Hz), 156.3 (s, $COCF_3$, $^2J_{C,F}$ = 36.7 Hz), 156.4 (s, $COCF_3$, $^2J_{C,F}$ = 36.9 Hz), 169.9 (q, $COCH_3$), 169.9 (q, $COCH_3$), 170.6 (q, $COCH_3$) ppm; HRMS (ESI): *m/z* for positive ions: calculated: 678.2587 (701.2485 + $Na^+$); found: 701.2507 (+ $Na^+$).

**9. Amino alcohol (30)**:

The protected amino alcohol **29** (26 mg, 0.038 mmol) and NaOH (18.4 mg, 0.460 mmol) were dissolved in a mixture of water and methanol (1:1; 2 ml). The solution was allowed to stir for 2h at rt and was then neutralised with dry ice. After evaporation of all volatile compounds the resulting crude material was purified by reverse phase chromatography (RP18; $H_2O \rightarrow H_2O$ / MeOH= 4:1 → 3:2 → 1:1) which yielded amino alcohol **30** (10.4 mg, 0.026 mmol; 67%) as a colourless sticky solid.

$[\alpha]^{20}_D$ = – 8.0 (*c*= 1, MeOH); $^1$H-NMR (400 MHz, MeOH-$d_4$, MeOH-$d_3$ = 3.31 ppm): $\delta$= 1.50– 1.87 (m, 8 H, 2-H, 6-H, 8-H, 11-H), 1.89 (s, $CH_3COOH$), 2.92 (dddd, *J*= 10.0, 9.9, 4.2, 4.2 Hz, 1 H, 1-H), 3.47– 3.73 (m, 6 H, 3-H, 5-H, 7-H, 10-H), 3.79 (br s, minor conformer), 3.86– 3.95 (br s, 1 H, 4-H), 3.98 (br s, minor conformer), 4.05 (br s, minor conformer) ppm; $^{13}$C NMR (100 MHz, MeOH-$d_4$, MeOH-$d_4$ = 49 ppm): $\delta$= 24.2 (q, $CH_3COR$), 27.2 and 28.3 (t, C-8, C-11), 35.4 and 35.9 (t, C-2, C-6), 45.9 (d, C-1), 69.3 and 70.9 (t, C-7, C-10), 69.4 (d, C-4), 77.4 and 78.8 (d, C-3, C-5), 180.4 (s, $RCOCH_3$) ppm. HRMS (ESI): *m/z* for positive ions: calculated: 402.2730 (403.2808 + $H^+$); found: 403.2804 (+ $H^+$).

**10. Macrocycle (33)**:

According to the procedure described for the preparation of macrocycle **29**, bisallylether **24** (115 mg, 0.163 mmol) and Grubbs catalyst **13** (13.2 mg, 0.016 mmol) were dissolved in 15 ml degassed benzene. The resulting crude product purified by column chromatography over silica gel (ethyl acetate / petroleum ether= 3:1) to yield a mixture of two products (74 mg, 0.109 mmol; 67%) as a colourless oil. A portion of this mixture (52 mg, 0.077 mmol) was dissolved in 5 ml ethyl acetate / $CH_2Cl_2$ / MeOH and treated with $Pt_2O$ (7.0 mg, 0.031 mmol) under a hydrogen atmosphere to furnish macrocycle **33** as a colourless (33.1 mg, 0.049 mmol; 64%).

$R_f$= 0.57 and $R_f$= 0.47 ($CH_2Cl_2$: MeOH= 9:1); $[\alpha]^{20}_D$ = – 31.5 (*c*= 1, $CHCl_3$); $^1$H NMR (500 MHz, $CDCl_3$, TMS = 0 ppm): $\delta$= 1.55– 1.75 (m, 10 H, 8-H, 10-H, $6_b$-H), 1.91 (m, 4 H, $2_a$-H, $2_b$-H), 2.12 (s, 6 H, $COCH_3$), 2.12- 2.19 (m, 2 H, $6_a$-H), 3.35 (dd, *J*= 7.8, 3.4 Hz, 2 H, 4-H), 3.39 (ddd, *J*= 10.0, 6.3, 6.1 Hz, 2 H, $10_b$-H), 3.46 (ddd, *J*= 9.8, 6.2, 5.8 Hz, 2 H, $10_a$-H), 3.58 (ddd, *J*= 8.9, 7.8, 4.2 Hz, 2 H, 5-H), 3.67 (dt, *J*= 9.7, 5.7 Hz, 2 H, $7_b$-H), 3.73 (dt, *J*= 9.5, 5.8 Hz, 2 H, $7_a$-H), 4.35 (ddddd, *J*= 8.6, 4.4, 4.4, 4.4, 4.3 Hz, 2 H, 1-H), 5.51 (ddd, *J*= 4.0, 3.8, 3.4 Hz, 2 H, 3-H), 7.05 (br d, *J*= 7.4 Hz, 2 H, NH) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$, $CDCl_3$ = 77 ppm): $\delta$= 21.0 (t, $COCH_3$), 26.4 (t, C-8, C-11), 31.7 (t, C-2), 33.3 (t, C-6), 44.5 (d, C-1), 69.5 (d, C-3), 69.6 (t, C-10), 70.4 (t, C-7), 73.4 (d, C-5), 79.2 (d, C-4), 115.8 (s, $CF_3$, $^1J_{C,F}$ = 288.2 Hz), 156.0 (s, $COCF_3$, $^2J_{C,F}$ = 36.7 Hz), 169.1 (s, $COCH_3$) ppm. HRMS (ESI): *m/z* for positive ions; calculated: 678.2587 (701.2485 + $Na^+$); found: 701.2451 (+ $Na^+$).

**11. Amino alcohol (34)**:

Based on the procedure for the preparation of amino alcohol **30**, the protected amino alcohol **33** (6.2 mg, 9 μmol) and NaOH (4.4 mg, 0.110 mmol) were dissolved in a mixture of water and methanol (1:1; 1.5 ml). The resulting crude material was purified by reverse phase

chromatography (RP18; $H_2O \rightarrow H_2O$ / MeOH= 4:1 $\rightarrow$ 3:2 $\rightarrow$ 1:1) to yield product **34** (3.0 mg, 7 µmol; 83%) as a colourless sticky solid.

$R_f$= 0 ($CH_2Cl_2$ / MeOH= 9:1); $[\alpha]^{20}_D$ = – 17.9 (*c*= 0.29, MeOH); $^1$H NMR (400 MHz, MeOH-$d_4$, MeOH-$d_3$ = 3.31 ppm): $\delta$= 1.36– 1.29 (m, 2 H, $CH_2$), 1.54– 1.63 (m, 2 H, $CH_2$), 1.64– 1.82 (m, 12 H, $CH_2$), 3.03 (br ddd, *J*= 11.8, 5.9, 5.6 Hz, 2 H, 1-H), 3.41 (dd, *J*= 5.6, 3.2 Hz, 2 H, 4-H), 3.54 (ddd, 4 H, $CH_2$), 3.68 (ddd, *J*= 10.4, 5.8, 5.8 Hz, 2 H, $CH_2$), 3.78– 3.87 (m, 4 H, 5-H, $CH_2$), 3.99 (ddd, *J*= 8.4, 3.5, 3.2 Hz, 2 H, 3-H) ppm; $^{13}$C NMR (125 MHz, $CDCl_3$, $CDCl_3$ = 77 ppm): $\delta$= 27.5 (t), 27.8 (t), 36.2 (t), 38.0 (t), 46.3 (d, C-1), 69.1 (t), 69.3 (d, C-3), 71.3 (t), 75.4 (d, C-5), 81.2 (d, C-4) ppm. HRMS (ESI): *m/z* for positive ions: calculated: 402.2730 (403.2808 + $H^+$); found: 403.2816 (+ $H^+$).

**12. Macrocycle (37)**:

According to the procedure described for the preparation of macrocycle **29**, bisallylether **28** (67.6 mg, 0.095 mmol) and Grubbs catalyst **13** (8 mg, 0.010 mmol) were dissolved in 27 ml degassed $CH_2Cl_2$. The resulting crude material was subjected to flash column chromatographic purification over silica gel (ethyl acetate / petroleum ether= 3:1) to yield a mixture of three products (51.7 mg, 0.076 mmol; 80%) as a colourles oil. A portion of this mixture (25.5 mg, 0.038 mmol) was dissolved in 2.5 ml ethyl acetate/$CH_2Cl_2$/MeOH and treated with $Pt_2O$ (4 mg, 0.015 mmol) under hydrogen atmosphere to furnish macrocycle **37** (24.4 mg, 0.036 mmol; 94%) as a colourless oil. To a minor degree (> 10%) this product is present in another chair conformation that could not be structurally characterised.

$R_f$= 0.50 and $R_f$= 0.44 ($CH_2Cl_2$: MeOH= 9:1); $[\alpha]^{20}_D$ = – 55.0 (*c*= 1, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$, TMS = 0 ppm): $\delta$= 1.44– 1.52 (m, 2 H, $CH_2$), 1.53– 1.60 (m, 2 H), 1.61– 1.77 (m, 7 H, $CH_2$), 1.78– 1.85 (m, 2 H), 1.89 (ddd, *J*= 15.0, 4.0, 3.2 Hz, 1 H, $CH_2$), 2.08 (s, 3 H, t, $COCH_3$), 2.10 (s, 3 H, t, $COCH_3$), 2.11– 2.14 (m, 1 H, $CH_2$), 2.26– 2.34 (m, 1 H, $CH_2$), 3.40 (ddd, *J*= 10.1, 7.5, 3.4 Hz, 1 H, $CH_2$), 3.45– 3.52 (m, 2 H, 4´-H, $CH_2$), 3.55– 3.63 (m, 3 H, 5´-H, $CH_2$), 3.64– 3.70 (m, 1 H, $CH_2$), 3.70– 3.83 (m, 5 H, 3-H, 5-H, $CH_2$), 4.24 (ddddd, *J*= 8.9, 8.7, 8.5, 4.4, 4.1 Hz, 1 H, 1´-H), 4.37 (ddddd, *J*= 7.0, 3.8, 3.5, 3.5, 3.0 Hz, 1 H, 1-H), 5.39 (br s, 1 H, 3´-H), 5.46 (dd, *J*= 3.3, 3.3 Hz, 1 H, 4-H), 6.68– 6.95 (br s, 1 H, NH´), 7.97 (br d, *J*= 7.0 Hz, 1 H, NH) ppm; $^{13}$C NMR (100 MHz, $CDCl_3$, $CDCl_3$ = 77 ppm): $\delta$= 21.0 (t, $COCH_3$), 21.1 (t, $COCH_3$), 25.7 (t), 26.1 (t), 26.3 (t), 27.2 (t), 28.6 (t), 30.2 (t), 44.1 (d, C-1´), 45.7 (d, C-1), 67.2 (d, C-3´), 68.0 (d, C-4), 68.6 (t), 69.0 (d), 69.5 (t), 70.5 (t), 71.0 (t), 76.1 (d), 77.6 (d), 115.7 (s, $CF_3$, $^1J_{C,F}$ = 287.5 Hz), 116.0 (s, $CF_3$, $^1J_{C,F}$ = 288.7 Hz), 155.9 (s, $COCF_3$, $^2J_{C,F}$

= 36.5 Hz), 156.4 (s, $COCF_3$, $^2J_{C,F}$ = 37.0 Hz), 170.2 (q, $COCH_3$) ppm. HRMS (ESI): *m/z* for positive ions: calculated: 678.2587 (701.2485 + $Na^+$); found: 701.2498 (+ $Na^+$).

**13. Amino alcohol (38)**:

Based on the general procedure described for preparation of amino alcohol **30**, the protected amino alcohol **37** (20 mg, 0.029 mmol) and NaOH (14 mg, 0.354 mmol) were dissolved in a mixture of water and methanol (1:1; 2 ml). The resulting residue was purified by reverse phase chromatography (RP18; $H_2O \rightarrow H_2O$ / MeOH= 4:1 $\rightarrow$ 3:2 $\rightarrow$ 1:1) to afford amino alcohol **38** (10.1 mg, 0.025 mmol, 86%) as a colourless sticky solid. The signals for the cyclohexane ring with the *exo* alcohol group (´) could be assigned and the coupling constants could be determined, while signals for the *endo* cyclohexane ring appeared as broad multipletts.

$[\alpha]^{20}_D$ = – 61.8 (*c*= 1, MeOH); $^1$H NMR (400 MHz, MeOH-$d_4$, MeOH-$d_3$ = 3.31 ppm): δ =1.10 (ddd, *J*= 11.7, 11.4, 11.2 Hz, 1 H, $6_b$-H), 1.26– 1.37 (m, 2 H, $2_b$-H), 1.43– 1.56 (m, 1 H), 1.57– 1.86 (m, 7 H), 2.00 (ddd, *J*= 13.6, 6.6, 4.0 Hz, 1 H, $2_a$-H), 1.95– 2.04 (m, 1 H), 2.04 – 2.18 (m, 1 H), 2.19– 2.27 (m, 1 H, $6_a$-H), 3.07 (dddd, *J*= 11.2, 11.1, 4.0, 3.9 Hz, 1 H, 1-H), 2.99 – 3.11 (m, 1 H, 1-H), 3.14 (dd, *J*= 8.8, 2.5 Hz, 1 H, 4-H), 3.44– 3.53 (m, 2 H), 3.54– 3.64 (m, 3 H, 5-H), 3.64 – 3.80 (m, 7 H), 4.12– 4.18 (m, 1 H, 3-H) ppm; $^{13}$C NMR (100 MHz, MeOH-$d_4$, MeOH-$d_4$ = 49 ppm): δ = 27.6 (t), 40.8 (t, C-2, C-6), 44.6 (d, C-1), 67.5 (d, C-3), 70.0 (t, broad signal), 77.0 (d, C-5), 84.9 (d, C-4) ppm. HRMS (ESI): *m/z* for positive ions: calculated: 402.2730 (403.2808 + $H^+$); found: 403.2818 (+ $H^+$).

**14. Determination of *E/Z*-ratio after cross olefin metathesis** (Figures 1 and 2).

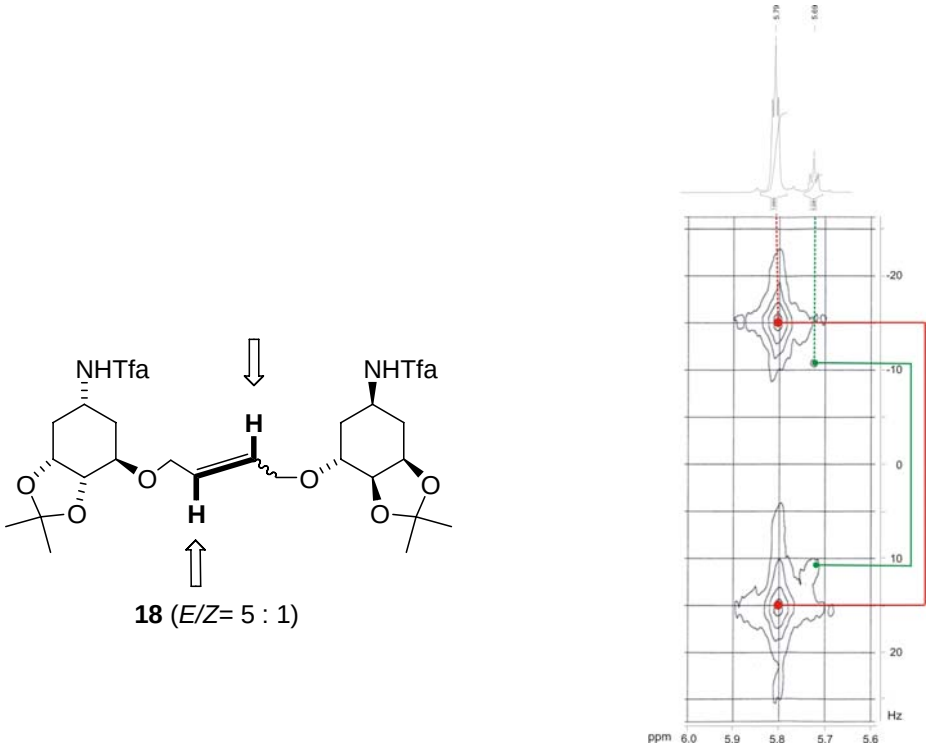



**Figure 1**. Determination of the double bond configuration of the homodimeric metathesis product **18** by NMR-spectroscopy.

The *E*-selectivity of this process is in full accordance with most intermolecular metathesis olefinations for which formation of *trans*-α,β-disubstituted metallocyclobutane intermediates has to be made responsible.[1] The ratios of the inseparable *E/Z*-mixtures were assigned by $^{1}H$ and $^{13}C$ NMR spectroscopy and the correlation spectra derived there from.[2] Nevertheless, precise assignment of the coupling constants is not possible due to their $C_2$-symmetry. In conjunction with our synthetic efforts in this field, Glaser et al. recently improved an NMR-technique which allows to distinguish vicinal protons as found in $C_2$-symmetrical *E*- and *Z*-alkenes, respectively. In this two dimensional experiment the $^{3}J_{(H,H)}$-coupling of interest is evolved under selective isotopic mixing conditions and the proton signal is acquired. This occurs via selective detection of $^{13}C$-bound protons which causes a break of symmetry.[3] We used this improved NMR-tool for determining the *E/Z*-ratio of the metathesis products as exemplified for homodimer **18** (Figure 1).

The RCM products for the macrocycles **29**, **31**, **33**, **35** and **37** are also *E/Z* mixtures of $C_2$-symmetric alkenes which can be analysed by the NMR method described above (Figure 3). An illustrative example is macrocycle **39** (Figure 4) which demonstrates that this 2D NMR technique allows to resolve and read out the coupling constants for totally overlapping double

bond protons while the protons next to the OAc group are not affected and therefore show no coupling in the NMR spectrum.

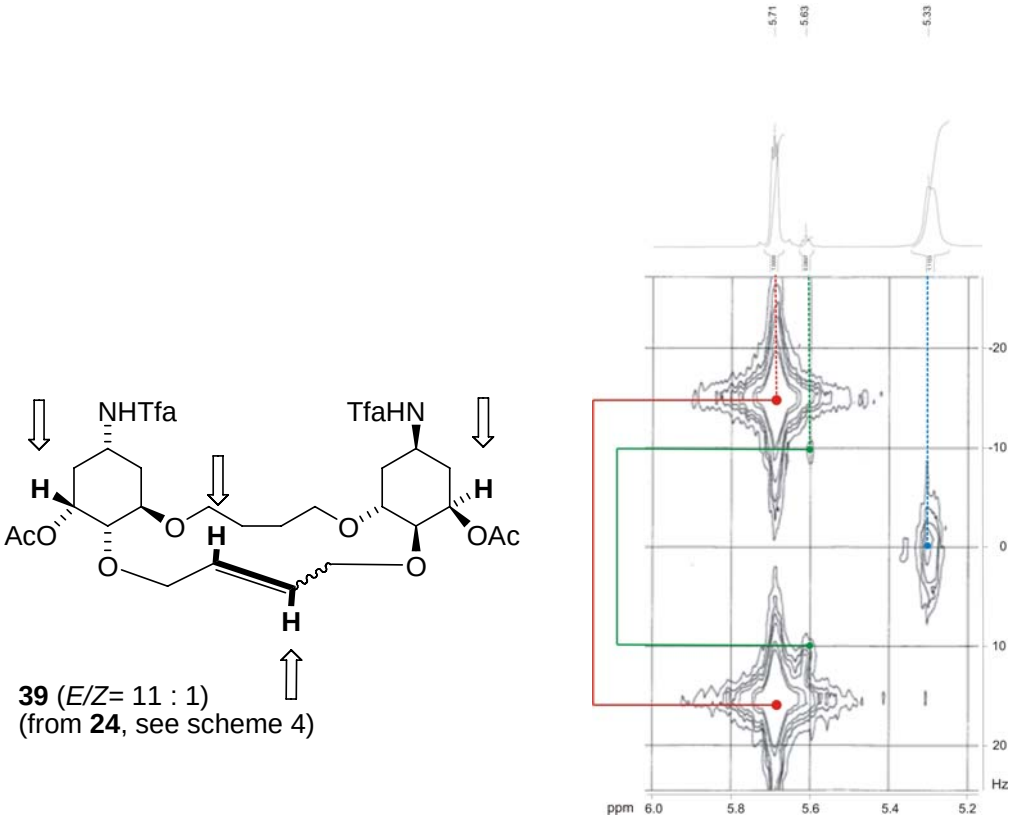


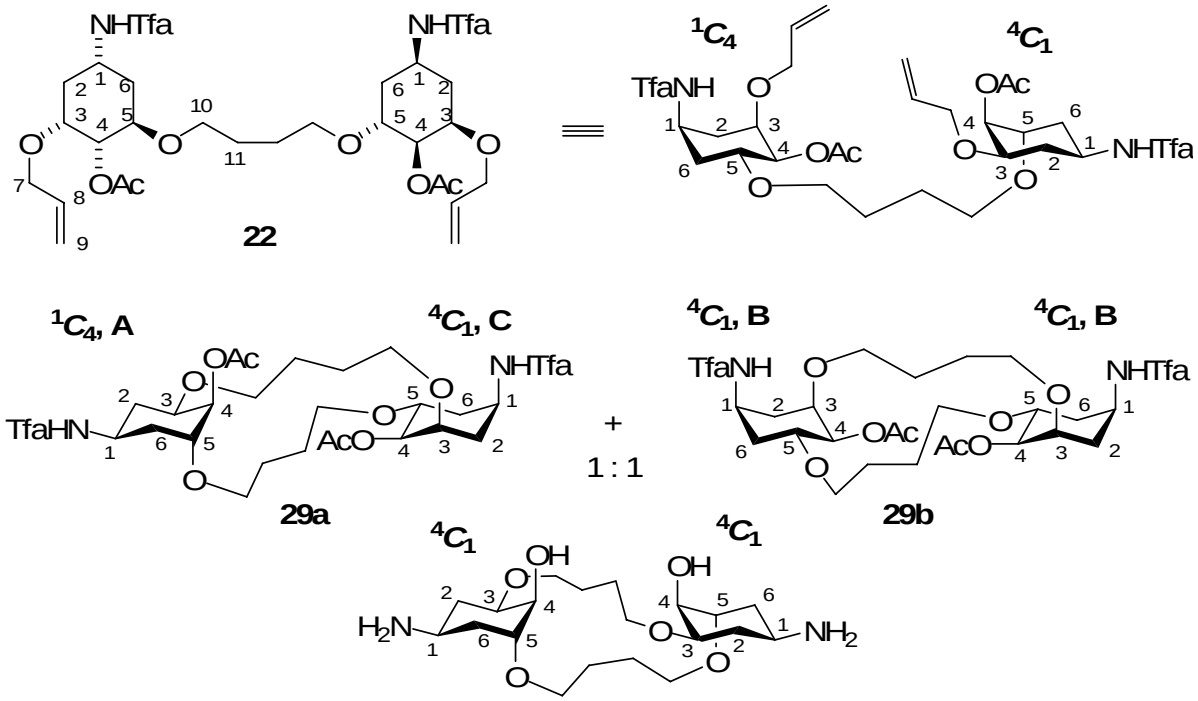

**Figure 2**: Determination of the double bond configuration of macrocyclic RCM product **39** by NMR-spectroscopy.

**15. RCM products 29a/b**

In contrast to **23** the dimer **22** has two *endo*-acetyl cyclohexane rings. Theoretically three different conformations could be obtained after ring closure. However, only two conformers (1:1 ratio) **29a** ($^{1}C_4$ labeled **A** and $^{4}C_1$ labelled **C**) and **29b** (both $^{4}C_1$ labelled **B**) were detected by NMR-spectroscopy (selective TOCSY) and could not be separated by chromatography. These are stable conformers and do not interconvert (Table 2). After removal of the protective groups only homogeneous product **30** was formed as demonstrated by the $^{1}$H and $^{13}$C NMR spectra.

It is interesting to note that the overall ratio of $^{1}C_4$ to $^{4}C_1$ conformations of the *endo*-acetyl cyclohexane ring in macrocycles **31a** and **31b** as well as **29a** and **29b** are about 1:3. The free amino alcohol **30** does not gives well resolved NMR spectra. Only coupling constants for H-1 could be determined. The information collected indicate a flexible conformation with some dominance for the $^{4}C_1$ conformation.

**Table 3**. Preferred conformations of diene **22** as well as macrocycles **29** and **30**.




| | $^3J$ coupling constants [Hz] [a] | | | | | | | | $\delta$ [ppm][b] |
|---|---|---|---|---|---|---|---|---|---|
| | 1-H | $2_{ax}$-H | $2_{eq}$-H | 3-H | 4-H | 5-H | $6_{ax}$-H | $6_{eq}$-H | **H**NTfa |
| **22** $CDCl_3$ | 4.8, 4.8, 4.6, 4.5 | m | m | 4.4, 4.3, 3.2 | 8.1, 2.4 | 8.3, 8.1, 4.0 | m | m | 7.54 |
| **29a** (**A**) $CDCl_3$ | m | m | m | br s | 10.0, 2.7 | M | m | m | 8.07 |
| **29a** (**C**) $CDCl_3$ | m | m | m | m | 2.7, 2.7 | M | m | m | 6.17- 6.23 |
| **29b** (**B**) $CDCl_3$ | m | m | m | m | 2.6, 2.6 | M | m | m | 6.17- 6.23 |
| **30** $CD_3OD$ | 10.0, 9.9, 4.2, 4.2 | m | m | m | br s | M | m | m | n.d. |

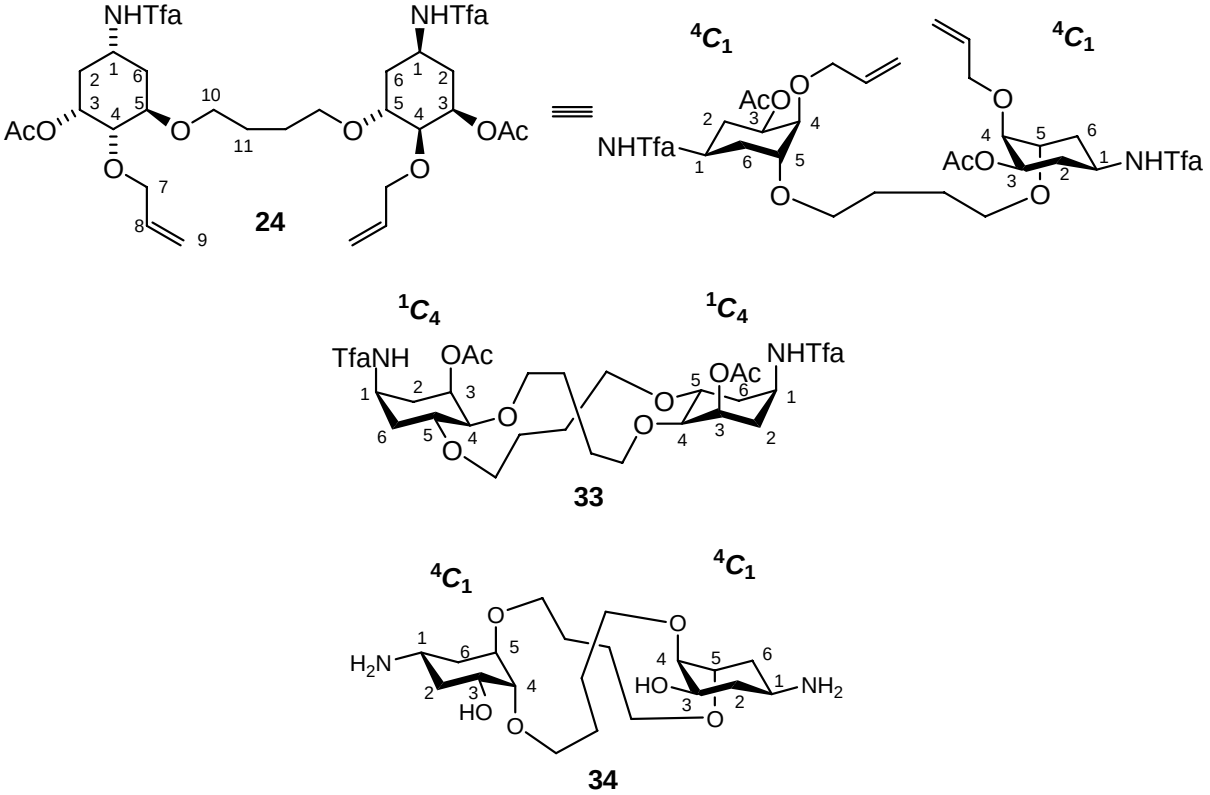
m= multiplett, caused by overlapping of signals, higher order signals or broad signals; n.d.= not detectable because of use of $CD_3OD$ as solvent; [a] coupling from 1-H to NH (around 8.0 Hz) is not mentioned for clarity reasons also as large geminal $^2J$ couplings of 2-H and 6-H (around 12 Hz); [b] at 295 K.

**16. RCM product 33**

The $C_2$ symmetric diene **24** has two *exo*-acetate cyclohexane rings with a $^4C_1$ chair conformation. Upon formation of the macrocycle **33** a ring flip to the $^1C_4$ conformation takes place in both cyclohexanes. The macrocycle **33** bears two *exo*-acetate groups that do not restrict the conformational space or flexibility of the molecule as in **31a/b** and **29a/b**. The

deprotected amino alcohol **34** showed ambiguous conformational behaviour because of broadened NMR signals. The dominating conformation seems to be $^4C_1$ which in fact is opposite to the one determined for **33**.

**Table 4**. Preferred conformations of diene **24** and macrocycle **33**.



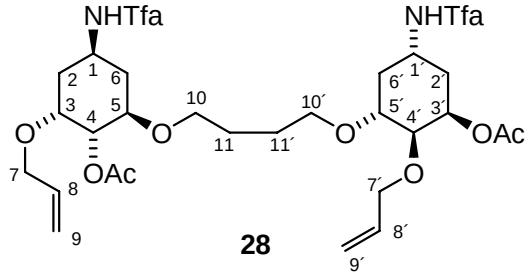

| | $^3J$ coupling constants [Hz] [a] | | | | | | | | $\delta$ [ppm][b] |
|---|---|---|---|---|---|---|---|---|---|
| | 1-H | $2_{ax}$-H | $2_{eq}$-H | 3-H | 4-H | 5-H | $6_{ax}$-H | $6_{eq}$-H | **H**NTfa |
| **24** | 10.5, | 10.7, | M | m | m | m | 10.2, | m | 6.48 |
| $CDCl_3$ | 10.2, | 10.5 | | | | | 2.4 | | |
| | 4.7, 4.7 | | | | | | | | |
| **33** | 4.4, | m | M | 4.0, | 7.8, | 8.9, | m | m | 7.05 |
| $CDCl_3$ | 4.4, | | | 3.8, | 3.4 | 7.8, | | | |
| | 4.4, 4.3 | | | 3.4 | | 4.2 | | | |
| **34** | br s, | m | M | 8.4, 3.5, | 5.6, 3.2 | m | m | m | n.d. |
| MeOD | 11.8, | | | 3.2 | | | | | |
| | 5.9, 5.6 | | | | | | | | |

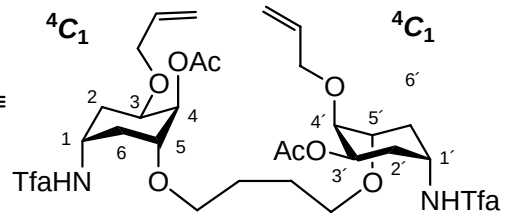
m= multiplett, caused by overlapping of signals, higher order signals or broad signals; n.d.= not detectable because of use of $CD_3OD$ as solvent; br s= broad signal; [a] coupling from 1-H to NH (around 8.0 Hz) is not mentioned for clarity reasons also as large geminal $^2J$ couplings of 2-H and 6-H (around 12 Hz); [b] at 295K.

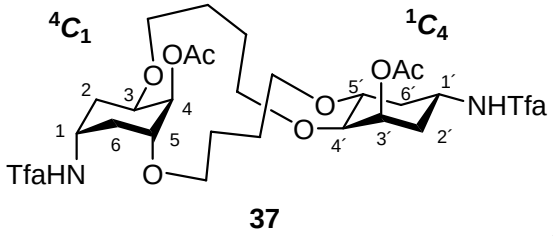
**17. RCM product 37**

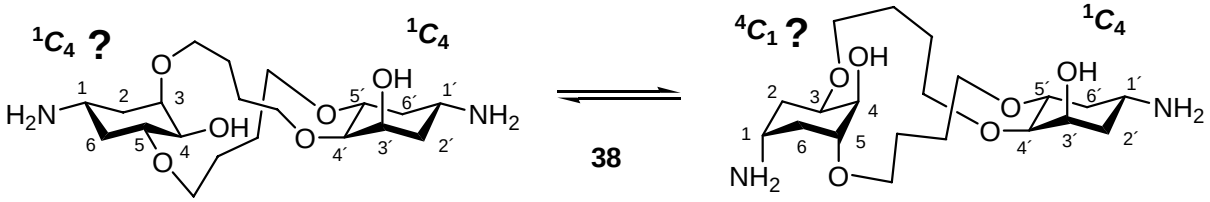
The C-1 epimer of diene **23** is diene **28**. In $CDCl_3$ the cyclohexane rings of diene **28** adopt an axial-rich $^4C_1$ conformation[36] with three substituents in an axial and one in an equatorial position. The energetically disfavoured axial-rich conformations seem to be stabilised by intramolecular H-bonds as indicated by the pronounced downfield chemical shifts of NH (see Table 5). For the unprotected amino alcohol **38** the conformational analysis was also difficult. Some signals of the *exo* ring could be resolved and suggest a $^1C_4$ conformation, while the *endo* ring gives only broad signals.

**Table 5**. Preferred conformations of diene **28** and macrocycle **37**.




| | $^3J$ coupling constants [Hz] [a] | | | | | | | | $\delta$ [ppm] [b] |
|---|---|---|---|---|---|---|---|---|---|
| | 1-H | $2_{ax}$-H | $2_{eq}$-H | 3-H | 4-H | 5-H | $6_{ax}$-H | $6_{eq}$-H | **H**NTfa |
| **28** (*endo)* $CDCl_3$ | 4.0, 4.0, 4.0, 4.0 | m | m | m | br s | m | m | m | 7.68 |
| **28** (*exo)* $CDCl_3$ | 4.0, 4.0, 4.0, 4.0 | m | br dd 4.1, 0.9 | 11.6, 4.1, 2.6 | br s | m | m | m | 7.77 |
| **37** (*endo)* $CDCl_3$ | 3.8, 3.5, 3.5, 3.0 | m | m | m | 3.3, 3.3 | m | m | m | 7.97 |
| **37** *(exo)* $CDCl_3$ | 8.9, 8.7, 4.4, 4.1 | m | m | br s | m | m | m | m | 6.68- 6.95 |
| **38** (*endo)* MeOD | m | m | m | m | m | m | m | m | n.d. |
| **38** (*exo)* MeOD | 11.2, 11.1, | m | 6.6, 4.0 | m | 8.8, 2.5 | m | 11.4, 11.2 | m | n.d. |

4.0, 3.9

m= multiplett, caused by overlapping of signals, higher order signals or broad signals; n.d.= not detectable because of use of $CD_3OD$ as solvent; br s= broad signal; [a] coupling constants between 1-H and NH (around 8.0 Hz) not listed; large geminal $^2J$ couplings at positions 2 and 6 (around 12 Hz) not listed; [b] at 295K.

Ring closure afforded macrocycle **37** along with a minor component ($R_f$= 0.50 and $R_f$= 0.44 in $CH_2Cl_2$ : MeOH = 9:1). However, only the major component **37** could be analysed by NMR spectroscopy. The *endo*-acetate cyclohexane ring has a $^4C_1$-conformation while the cyclohexane with the *exo*-acetate group adopts mainly the $^1C_4$-conformation. An H-bond between the amide group NH and O-5 can again stabilise the axial-rich $^4C_1$-conformation of the *endo*-acetate cyclohexane ring. The deprotected amino alcohol **38** stayed ambiguous in its conformational behaviour and was not further analysed.

**References:**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2. a) E. Breitmaier, W. Voelter, In *Carbon-* $^{13}$*NMR Spectroscopy. High Resolution Methods and Applications in Organic Chemistry and Biochemistry*; VCH: New York **1987**; p 192; b) S. T. Diver and S. L. Schreiber, *J. Am. Chem. Soc*. 1997, **119**, 5106–5109.

3. While simultaneously suppressing the signals of $^{12}$C-bound protons the experiment delivers clear spectra. Besides a significant sensitivity gain the experiment permits a straightforward interpretation, since only the desired $^3J_{(H,H)}$-coupling gives rise to an observable splitting. The advantages of this method are i) short recording time and ii) direct determination of coupling constants *J* of the central vicinal alkenic hydrogens in $C_2$-symmetric compounds. B. Luy, G. Hauser, A. Kirschning and S. J. Glaser, *Angew. Chem.* 2003, **115**, 1338–1341; *Angew. Chem. Int. Ed*. 2003, **42**, 1125–1132.