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CSIRO PUBLISHING

Aust. J. Chem. **2008**, *61*, 914–919

www.publish.csiro.au/journals/ajc

Synthesis of 2,5-Diazabicyclo[2.2.2]octanes by Dieckmann Analogous Cyclization

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Starting with (*S*)-aspartate, methyl (*S*)-2-[1-allyl-4-(4-methoxybenzyl)-3,6-dioxopiperazin-2-yl]acetate **10** was synthesized in a four-step synthesis. Deprotonation of **10** and subsequent trapping of the first cyclization product led to the bicyclic mixed acetal **13** in 15% yield. The low yield of **13**, compared with the yield of the corresponding glutamate derivatives, is explained by the higher energy (strain) of the bicyclo[2.2.2]octane system and the lower conformational flexibility of the shorter acetate side chain. The formation of a six-membered Na^+-chelate **12** as intermediate is responsible for the high diastereoselectivity of the cyclization step.

Manuscript received: 14 August 2008.
Final version: 29 September 2008.

Introduction

Recently we have described a new variation of the Dieckmann-type cyclization. This variation is based on a quantitative deprotonation of the starting compound with a strong base and trapping of the first cyclization product with trimethylsilyl chloride (TMSCl).[1,2] Whereas the driving force of the standard Dieckmann cyclization is the deprotonation of the finally formed β-dicarbonyl compound, the new variation allows the synthesis of cyclization products, which cannot form stabilized anions.

This method has been applied to the synthesis of bridged piperazines **3** which, because of the additional carbonyl moiety in position 2, serve as valuable starting compounds for the preparation of novel δ[3,4] and κ receptor agonists[5,6] as well as σ receptor ligands.[6–8] Generally, compounds with reduced conformational flexibility should lead to more potent receptor ligands as a result of favourable entropic factors.

Starting with (*S*)-glutamate, piperazinediones **1** with a propionate side chain were prepared first. In the key step of the synthesis, **1** was treated with lithium hexamethyldisilazane (LiHMDS) and subsequently with TMSCl to diastereoselectively provide the mixed methyl silyl acetal **2**.[1,2] The reaction sequence proceeded without racemization, as could be shown by various analytical methods (Scheme 1).[4]

In order to broaden the structure affinity relationships, piperazines with a substituted two-carbon bridge came into focus. Compounds with the 2,5-diazabicyclo[2.2.2]octane framework have been synthesized by a double cyclization of 2,5-dibromohexanediamide derivatives,[9] by a [4 + 2]cycloaddition of pyrazin-2(1*H*)-ones with ethene,[10] and by an intramolecular epoxide opening.[11] However, enantiomerically pure products are not accessible according to these methods. Furthermore, with exception of the third method, which results in two regioisomeric alcohols in the ratio of 2.7:1, the produced bicycles do not bear further substituents in the two-carbon bridge.

Therefore, we planned to synthesize enantiomerically pure 2,5-diazabicyclo[2.2.2]octanetriones **6** starting with the smaller homologue (*S*)-aspartate as outlined in Scheme 1. At first piperazinediones **4** with an acetate side chain should be synthesized. The establishment of the bicyclic structure will be realized as described for the glutamate derivatives **1**. However, the two-carbon acetate side chain of **4** comprises lower conformational flexibility than the propionate side chain of **1**, which could prevent cyclization.

Results and Discussion

In order to synthesize the piperazinedione **10** with an acetate side chain in position 2, (*S*)-aspartic acid was used as a starting compound (Scheme 2). After transformation of (*S*)-aspartate with TMSCl and methanol into the diester hydrochloride **7**·HCl the chloroacetamide **8** was prepared by acylation with chloroacetyl chloride. During the reaction of the chloroacetamide **8** with 4-methoxybenzylamine, an S_N2 reaction and intramolecular aminolysis took place consecutively, which directly provided the piperazinedione **9** in 85% yield. The orthogonal allyl protective group was attached by allylation with allyl bromide after deprotonation of the secondary amide **9** with NaHMDS to obtain the piperazinedione **10** in 52% yield.

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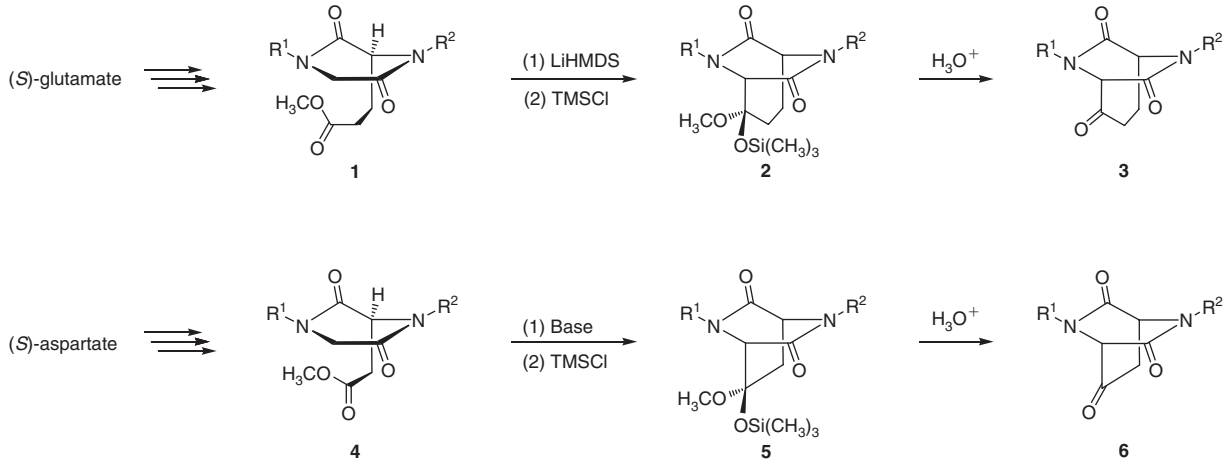
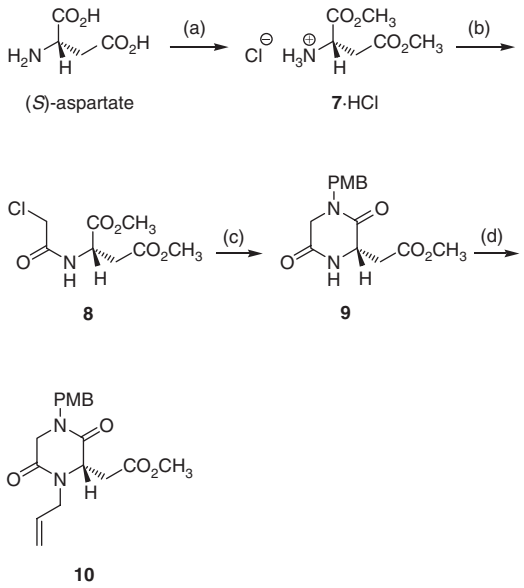
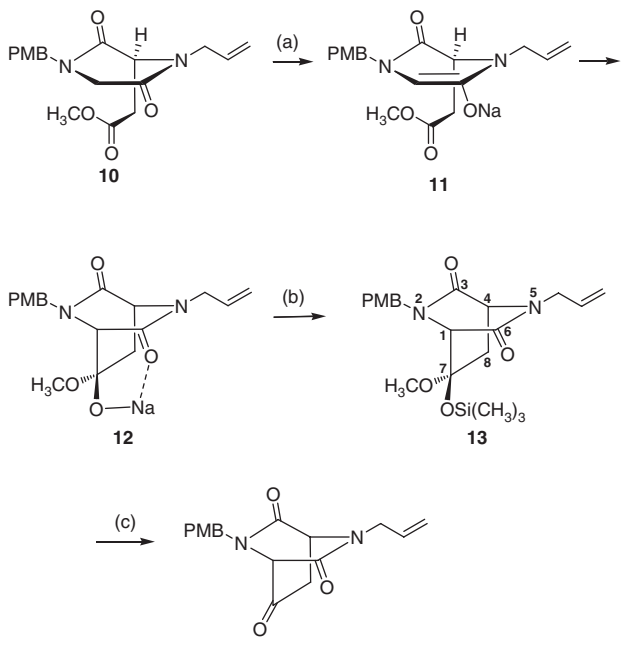


Scheme 1. Comparison of the cyclization strategy of piperazinediones with propionate and acetate side chains.



Scheme 2. (a) TMSCl, CH_3OH, room temp., 16 h, 99%; (b) $ClCH_2COCl$, CH_2Cl_2, $NaHCO_3$, room temp., 16 h, 67%; (c) 4-methoxybenzylamine, (PMB-NH_2), NEt_3, CH_3CN, Bu_4NI, reflux, 48 h, 85%; (d) NaHMDS, THF, −78°C, allyl bromide, Bu_4NI, −78°C, 1 h, room temp., 2 h, 52%.



Scheme 3. (a) NaHMDS, THF, −78°C, 40 min; (b) TMSCl, THF, −78°C, 1 h, then room temp., 2 h, 15%; (c) 0.5 M HCl, THF, room temp., 16 h, 95%.

The piperazinedione **10** was treated with LiHMDS and subsequently with TMSCl in analogy to the propionate derivatives **1**.[1,2] However, in contrast to the analogous propionate derivatives **1**, which formed the bicyclic products **2** in more than 80% yield, the yield of the cyclization product **13** was only 5.3% (Scheme 3). In order to improve the reaction, the type of base (NaHMDS, LiHMDS, KHMDS), the amount of base (1.1–3.0 equiv.), the reaction temperature (−78 to 0°C), and the time between addition of the base and TMSCl (cyclization time: 40 min to 12 h) were systematically varied. In this series of experiments the best yield of **13** (15%) was achieved using 3.0 equivalents of NaHMDS instead of LiHMDS at −78°C and a cyclization time of 60 min. However, even under these optimized reaction conditions most of the starting material was recovered unchanged.

Careful hydrolysis of the mixed methyl silyl acetal **13** with 0.5 M HCl in tetrahydrofuran (THF) at ambient temperature gave the bicyclic ketone **14** in 95% yield. Under these very mild reaction conditions opening of the bicyclic system was not observed.

The cyclization of **10** to the mixed methyl silyl acetal **13** led stereoselectively to only one diastereomer. It was not possible to unequivocally determine the configuration of the newly formed stereocentre at position 7 of the bicyclic system. Therefore, an X-ray crystal structure analysis of **13** was envisaged. Recrystallization of **13** from diisopropyl ether gave colourless crystals that were suitable for X-ray crystal structure analysis. Since the configuration of the chiral centre in position 4 is given by the starting compound (*S*)-aspartate, the configuration of the mixed methyl silyl acetal **13** is proven by the X-ray structure to be (1*S*,4*S*,7*R*) (Fig. 1).

The (7*R*)-configuration supports the postulated reaction course of the Dieckmann-type cyclization. The enolate **11**

generated upon NaHMDS deprotonation of the acetate **10** stereoselectively attacks the Si-face of the ester moiety to form the hemiacetal anion **12**, which is trapped by TMSCl. In contrast to the diastereomeric hemiacetal anion with (7*S*)-configuration the (7*R*)-configured anion **12** is stabilized by a six-membered Na-chelate.

In order to evaluate possible reasons for the very different yields obtained for **2** and **13** in the cyclization reactions, we performed density functional theory (DFT) calculations of a series of model compounds. Besides the experimentally known 6,8-diazabicyclo[3.2.2]nonanes **2** and the 2,5-diazabicyclo [2.2.2]octane **13** we have also included the corresponding 7,9-diazabicyclo[4.2.2]decane system into this study, which would result from the next higher homologue of **1** (2-aminoadipic acid as starting compound). We used the *B3LYP/6-31G(d)* method for the geometry optimizations and the SCS-MP2/6-31G(d)//*B3LYP/6-31G(d)* method[12] for the energy determinations (including zero point correction) as implemented in the *GAUSSIAN03* package of programs.[13] In order to allow a direct comparison of the bicyclo-octane **13**, -nonane **2**, and -decane systems we have chosen a series of three model compounds with the same molecular formula ($C_{12}H_{20}N_2O_4$). These three isomeric model compounds differ in ring size and in the nature of the alkoxy groups being two propoxy groups for the bicyclooctane ring system, an ethoxy and a propoxy group for the bicyclononane system, and two ethoxy groups for the bicyclodecane system (Fig. 2). We assumed that ring strain energy contributions of the bicyclic systems were not severely falsified by the energy contribution of such varying alkoxy groups. The bicyclooctane system including the eight-membered ring came out best in energy (E_{rel} 0.00 kcal mol^{-1}), the bicyclononane system with the seven-membered ring, calculated in two isomeric forms, showed a relative energy of 1.09 and 1.16 kcal mol^{-1}, respectively, whereas the bicyclooctane system including the six-membered ring came out highest in energy (3.21 kcal mol^{-1}). Although the energy sequence obtained fits to chemical intuition, the relative differences between the isomeric model compounds are not very large. However, assuming a Hammond-postulate like reaction course with product-like transition states, kinetic barriers in the same sequence may well be reason for the different experimental yields obtained. Of course, such transition states are very strongly influenced by the nature of the counter ion and the chemical environment, which do not allow a serious attempt to model such a reaction computationally.

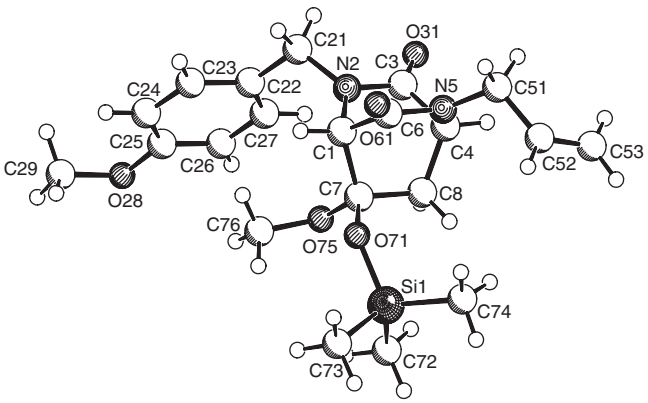
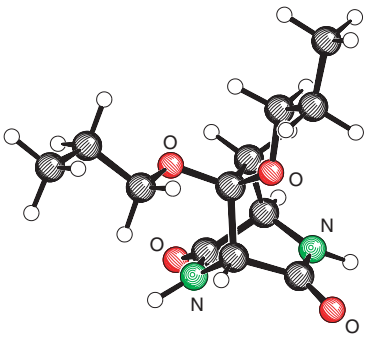


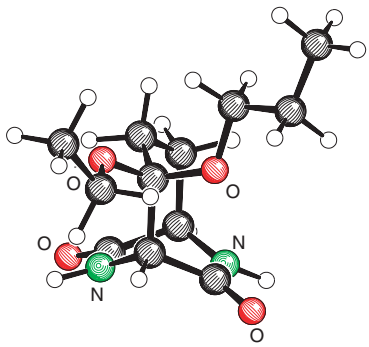
Fig. 1. X-Ray crystal structure analysis of the mixed methyl silyl acetal **13**.

Conclusions

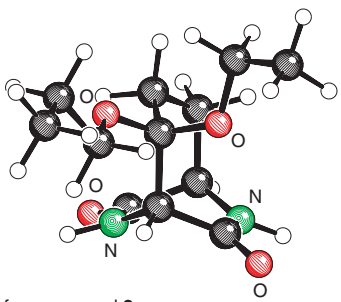
We have shown that the piperazinedione **10** bearing an acetate side chain can be cyclized according to our recently described



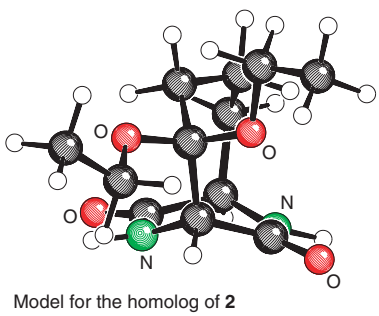
Model for compound **13**
2,5-Diazabicyclo[2.2.2]octane: E_{rel} = 3.21 kcal mol^{-1}



Model for compound **2**
6,8-Diazabicyclo[3.2.2]nonane, diast. 1: E_{rel} = 1.16 kcal mol^{-1}



Model for compound **2**
6,8-Diazabicyclo[3.2.2]nonane, diast. 2: E_{rel} = 1.09 kcal mol^{-1}



Model for the homolog of **2**
7,9-Diazabicyclo[4.2.2]decane: E_{rel} = 0.0 kcal mol^{-1}

Fig. 2. Determination of the relative energy of the bicyclic compounds by DFT calculations: Model compounds with the same molecular formula ($C_{12}H_{20}N_2O_4$) are chosen for the three bicyclic systems. SCS-MP2/6-31G(d)//B3 LYP/6-31G(d) including zero-point correction.

Dieckmann-type cyclization protocol to form piperazine derivatives with a C-2 bridge. In contrast to the glutamate derivatives **3** the yield of **13** is rather low, which is explained by the higher energy (ring strain) of the more constrained system **13** and the reduced conformational flexibility of the shorter acetate side chain of **10**. The high diastereoselectivity of the cyclization supports the hypothesis that the six-membered metal-chelate **12** is the driving force of the cyclization.

Experimental

General Methods

Unless otherwise noted, moisture sensitive reactions were conducted under dry nitrogen. THF was dried with sodium/benzophenone and was freshly distilled before use. TLC used silica gel 60 F_{254} plates (Merck). Flash chromatography used silica gel 60, 40–64 μm (Merck); parentheses include: diameter of the column, eluent, fraction size, R_F value. Melting points were determined on a SMP 3 (Stuart Scientific) melting point apparatus, and were uncorrected. Mass spectrometry was performed on a MAT GCQ (Thermo-Finnigan). A 480Plus FT-ATR-IR (Jasco) IR spectrophotometer was employed. ^{1}H NMR (400 MHz) spectra were acquired on a Unity Mercury Plus 400 spectrometer (Varian). Signals are reported in δ (ppm) relative to tetramethylsilane. Coupling constants are given with 0.5 Hz resolution. HPLC was performed with a Merck Hitachi Equipment equipped with a UV detector (L-7400), an autosampler (L-7200), a pump (L-7100), degasser (L-7614), using a LiChrospher 60 RP-select B (5 μm) column, and a LiCroCART 250-4 mm cartridge. The flow rate was 1.000 mL min^{-1} with an injection volume of 5.0 μL and detection at λ 210 nm. The solvents used were: A) water with 0.05% (v/v) trifluoroacetic acid and B) acetonitrile with 0.05% (v/v) trifluoroacetic acid. Experiments were performed with a gradient elution: 0.0 min: 90.0% of A, 10.0% of B; 4.0 min: 90.0% of A, 10.0% of B; 29.0 min: 0.0% of A, 100.0% of B; 31.0 min: 0.0% of A, 100.0% of B; 31.5 min: 90.0% of A, 10.0% of B; 40.0 min: 90.0% of A, 10.0% of B.

*(+)-Dimethyl (S)-Aspartate Hydrochloride **7**·HCl*

(*S*)-Aspartic acid (10.0 g, 75.1 mmol) was suspended in methanol (150 mL). Under ice-cooling chlorotrimethylsilane (33.5 mL, 262 mmol) was added dropwise. The mixture was stirred for 16 h at room temperature. The volatiles were then removed under vacuum. The residue was dissolved in methanol and the mixture was concentrated under vacuum. Diethyl ether was then added (×3) and the mixture was concentrated under vacuum. The product was obtained as a colourless solid, mp 112°C, yield 14.7 g (99%). $[\alpha]_D^{20}$ +10.2 (*c* 0.65, H_2O). $C_6H_{12}ClNO_4$ (197.6). *m/z* (EI) 162 (M − Cl, 70%). δ_H ($CDCl_3$) 3.25 (dd, *J* 18.0/5.5, 1H, CH_2CO$_2$CH$_3$), 3.35 (dd, *J* 18.0/5.5, 1H, CH_2CO$_2$CH$_3$), 3.75 (s, 3H, CO$_2$CH_3), 3.84 (s, 3H, CO$_2$CH_3), 4.59–4.66 (m, 1H, C*H*CH$_2$CO$_2$CH$_3$), 8.73 (s, 3H, NH_3^+). ν_{max}/cm^{-1} 2865 (m, $\nu_{C-H\ aliph.}$), 1766 (m), 1732 (s, $\nu_{C=O\ ester}$).

*(+)-Dimethyl (S)-2-(2-Chloroacetylamino)succinate **8***

Compound **7**·HCl (10.2 g, 51.6 mmol) was dissolved in CH_2Cl_2 (300 mL). Under ice-cooling a solution of chloroacetyl chloride (12.7 mL, 18.1 g, 160 mmol) in CH_2Cl_2 (80 mL) was added dropwise. After 40 min a saturated aqueous solution of $NaHCO_3$ (100 mL) was added and the mixture was stirred at room temperature for 16 h. The organic layer was separated and washed with 0.5 M NaOH (×2). The aqueous layer was extracted with CH_2Cl_2 (×2) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue was purified by flash chromatography (8 cm, cyclohexane/ethyl acetate = 1/1, 30 mL, R_f = 0.41) to give a colourless oil, yield 8.24 g (67%). HPLC: t_R 10.4 min, purity 99.8%. $[\alpha]_D^{20}$ +50.7 (*c* 0.43, CH_2Cl_2). $C_8H_{12}ClNO_5$ (237.6). *m/z* (EI) 240 (MH (Cl^{37}), 41%), 238 (MH (Cl^{35}), 100). δ_H ($CDCl_3$) 2.85 (dd, *J* 17.2/4.7, 1H, CH_2CO$_2$CH$_3$), 3.08 (dd, *J* 17.2/4.7, 1H, CH_2CO$_2$CH$_3$), 3.71 (s, 3H, CO$_2$CH_3), 3.78 (s, 3H, CO$_2$CH_3), 4.05 (d, *J* 14.9, 1H, ClCH_2CO), 4.10 (d, *J* 14.9, 1H, ClCH_2CO), 4.85 (dt, *J* 8.6/4.7, 1H, C*H*CH$_2$CO$_2$CH$_3$), 7.57 (d, *J* 8.6, 1H, N*H*). ν_{max}/cm^{-1} 3319 (m br, ν_{N-H}), 2956 (m, $\nu_{C-H\ aliph.}$), 1735 (s, $\nu_{C=O\ ester}$), 1670 (s, $\nu_{C=O\ amide}$), 1523 (m, δ_{N-H}).

*(−)-Methyl (S)-2-[4-(4-Methoxybenzyl)-3,6-dioxopiperazin-2-yl]acetate **9***

Compound **8** (7.13 g, 30.0 mmol) was dissolved in acetonitrile (230 mL) and 4-methoxybenzylamine (5.88 mL, 6.17 g, 45.0 mmol), triethylamine (6.38 mL, 4.64 g, 45.9 mmol), and tetrabutylammonium iodide (1.11 g, 3.00 mmol) were added. The mixture was heated to reflux for 48 h. The volume of solvent was then reduced by two thirds under vacuum. The residue was filtered and poured into 0.5 M HCl. The mixture was extracted with CH_2Cl_2 (×3), the combined organic layers were dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue was purified by flash chromatography (8 cm, petroleum ether/acetone = 1/1, 30 mL, R_f = 0.42) to give a yellow oil, yield 7.82 g (85%). $[\alpha]_D^{20}$ −12.6 (*c* 0.49, CH_2Cl_2). $C_{15}H_{18}N_2O_5$ (306.3). *m/z* (EI) 306 (M, 38%), 185 (M − CH_2PhOCH_3, 18), 121 (CH_2PhOCH_3, 100). δ_H ($CDCl_3$) 2.82 (dd, *J* 17.2/8.6, 1H, CH_2CO$_2$CH$_3$), 3.10 (dd, *J* 17.2/3.1, 1H, CH_2CO$_2$CH$_3$), 3.70 (s, 3H, CO$_2$CH_3), 3.80 (s, 3H, ArOCH_3), 3.81 (d, *J* 18.0, 1H, O=CCH_2N), 3.88 (d, *J* 18.0, 1H, O=CCH_2N), 4.37–4.42 (m, 1H, C*H*CH$_2$CO$_2$CH$_3$), 4.53 (s, 2H, NCH_2Ar), 6.67 (s, 1H, N*H*), 6.87 (d, *J* 8.6, 2H, 3′-$H_{4\text{-methoxybenzyl}}$, 5′-$H_{4\text{-methoxybenzyl}}$), 7.19 (d, *J* 8.6, 2H, 2′-$H_{4\text{-methoxybenzyl}}$, 6′-$H_{4\text{-methoxybenzyl}}$). ν_{max}/cm^{-1} 3241 (m br, ν_{N-H}), 2953 (w, $\nu_{C-H\ aliph.}$), 1734 (m, $\nu_{C=O\ ester}$), 1656 (s, $\nu_{C=O\ amide}$), 1611 (m), 1512 (m, $\nu_{C=C\ arom.}$).

*(+)-Methyl (S)-2-[1-Allyl-4-(4-methoxybenzyl)-3,6-dioxopiperazin-2-yl]acetate **10***

Under an N_2 atmosphere a solution of **9** (6.24 g, 20.4 mmol) and tetrabutylammonium iodide (1.50 g, 4.07 mmol) in THF (150 mL) was cooled to −78°C. A 2.0 M solution of sodium hexamethyldisilazane (NaHMDS) in THF (11.2 mL, 22.4 mmol) was then added dropwise. After stirring the mixture at −78°C for 40 min allyl bromide (8.9 mL, 12.3 g, 102 mmol) was added. The mixture was stirred at −78°C for 1 h and was then allowed to warm to room temperature. After stirring the mixture at room temperature for 2 h, water was added and the mixture was extracted with CH_2Cl_2 (×3). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed under vacuum. The residue was purified by flash chromatography (8 cm, cyclohexane/ethyl acetate = 1/2, 30 mL, R_f = 0.20) to give a colourless solid, mp 89°C, yield 3.64 g (52%). HPLC: t_R = 17.3 min, purity 98.2%. $[\alpha]_D^{20}$ +57.1 (*c* 0.33, CH_2Cl_2). $C_{18}H_{22}N_2O_5$ (346.4). *m/z* (EI) 346 (M, 39%), 225 (M − CH_2PhOCH_3, 10), 121 (CH_2PhOCH_3, 100). δ_H ($CDCl_3$) 2.88 (dd, *J* 17.2/4.7, 1H, CH_2CO$_2$CH$_3$), 3.13 (dd, *J* 17.2/3.1, 1H, CH_2CO$_2$CH$_3$), 3.60 (s, 3H, CO$_2$CH_3), 3.63 (dd, *J* 15.7/7.0,

1H, NCH_2CH=CH_2), 3.78 (d, *J* 17.2, 1H, O=CCH_2N), 3.80 (s, 3H, ArOCH_3), 4.03 (d, *J* 17.2, 1H, O=CCH_2N), 4.23–4.27 (m, 1H, C*H*CH_2CO_2CH_3), 4.43 (ddt, *J* 15.7/5.5/1.6, 1H, NCH_2CH=CH_2), 4.50 (d, *J* 14.9, 1H, NCH_2Ar), 4.59 (d, *J* 14.9, 1H, NCH_2Ar), 5.20–5.27 (m, 2H, NCH_2CH=CH_2), 5.67–5.78 (m, 1H, NCH_2C*H*=CH_2), 6.86 (d, *J* 8.6, 2H, 3′-$H_{4\text{-methoxybenzyl}}$, 5′-$H_{4\text{-methoxybenzyl}}$), 7.21 (d, *J* 8.6, 2H, 2′-$H_{4\text{-methoxybenzyl}}$, 6′-$H_{4\text{-methoxybenzyl}}$). ν_{max}/cm^{-1} 3080 (w, $\nu_{C-H\ arom.}$), 2924 (m, $\nu_{C-H\ aliph.}$), 1735 (m, $\nu_{C=O\ ester}$), 1660 (s, $\nu_{C=O\ amide}$), 1611 (m), 1512 (m, $\nu_{C=C\ arom.}$).

(+)-(1S,4S,7R)-5-Allyl-7-methoxy-2-(4-methoxybenzyl)-7-(trimethylsiloxy)-2,5-diazabicyclo[2.2.2]octane-3,6-dione ***13***

Under an N_2 atmosphere **10** (485 mg, 1.40 mmol) was dissolved in THF (30 mL) and cooled to −78°C. A 2 M solution of sodium hexamethyldisilazane (NaHMDS) in THF (2.1 mL, 4.20 mmol) was then added dropwise. After stirring at −78°C for 40 min, chlorotrimethylsilane (0.45 mL, 380 mg, 3.50 mmol) was slowly added. The mixture was stirred at −78°C for 1 h and at room temperature for 2 h. A saturated solution of $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2 (×3). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed under vacuum. The residue was purified by flash chromatography (3 cm, cyclohexane/ethyl acetate = 2/1, 20 mL, $R_f = 0.18$) to give a colourless solid, mp 103°C, yield 84 mg (15%). HPLC: $t_R = 21.5$ min, purity 96.1%. $[\alpha]_D^{20}$ +6.5 (*c* 0.13, CH_2Cl_2). $C_{21}H_{30}N_2O_5Si$ (418.6). *m/z* (EI) 418 (M, 8%), 297 (M − CH_2PhOCH_3, 32), 121 (CH_2PhOCH_3, 100). δ_H ($CDCl_3$) 0.15 (s, 9H, OSi(CH_3)$_3$), 2.17 (dd, *J* 14.1/3.9, 1H, 8-H), 2.22 (dd, *J* 14.1/2.3, 1H, 8-H), 3.02 (s, 3H, OCH_3), 3.79 (s, 3H, ArOCH_3), 3.86–3.95 (m, 3H, 1-H, 4-H, NCH_2CH=CH_2 (1H)), 4.06 (dd, *J* 14.9/5.5, 1H, NCH_2CH=CH_2), 4.21 (d, *J* 14.9, 1H, NCH_2Ar), 4.76 (d, *J* 14.9, 1H, NCH_2Ar), 5.22–5.30 (m, 2H, NCH_2CH=CH_2), 5.71 (ddt, *J* 17.2/10.2/6.3, 1H, NCH_2C*H*=CH_2), 6.86 (d, *J* 8.6, 2H, 3′-$H_{4\text{-methoxybenzyl}}$, 5′-$H_{4\text{-methoxybenzyl}}$), 7.14 (d, *J* 8.6, 2H, 2′-$H_{4\text{-methoxybenzyl}}$, 6′-$H_{4\text{-methoxybenzyl}}$). ν_{max}/cm^{-1} 3016 (w, $\nu_{C-H\ arom.}$), 2962 (m, $\nu_{C-H\ aliph.}$), 1685 (s, $\nu_{C=O\ amide}$), 1612 (m), 1586 (m), 1508 (m, $\nu_{C=C\ arom.}$).

X-Ray Crystal Structure Analysis of ***13***

Further recrystallization from diisopropyl ether gave colourless crystals that were suitable for X-ray crystal structure analysis.

Formula $C_{21}H_{30}N_2O_5Si$, *M* 418.6, *T* 223 K, colourless crystal, crystal size 0.30 × 0.06 × 0.03 mm^3, *a* 6.3562(4), *b* 8.3604(4), *c* 41.7503(17) Å, *V* 2218.6(2) $Å^3$, ρ_{calc} 1.253 g cm^{-3}, μ 1.216 mm^{-1}, empirical absorption correction ($0.712 \leq T \leq 0.964$), *Z* 4, orthorhombic, space group $P2_12_12_1$ (no. 19), λ 1.54178 Å, ω and φ scans, 9554 reflections collected (±*h*, ±*k*, ±*l*), [$(\sin\theta)/\lambda_{max}$] 0.59 $Å^{-1}$, 3523 independent ($R_{int} = 0.069$) and 2780 observed reflections [$I \geq 2\sigma(I)$], 267 refined parameters, *R* 0.053, wR^2 0.124, max. residual electron density 0.26 (−0.22) e $Å^{-3}$, Flack parameter −0.04(5), hydrogen atoms on calculated positions and refined as riding atoms. The dataset was collected with a Nonius Kappa CCD diffractometer. Programs used: data collection COLLECT,[14] data reduction Denzo-SMN,[15] absorption correction Denzo,[16] structure solution *SHELXS-97*,[17] structure refinement *SHELXL-97*,[18] and graphics *SCHAKAL*.[16,19]

CCDC-676280 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44(1223)336-033, Email: deposit@ccdc.cam.ac.uk].

(+)-(1S,4S)-5-Allyl-2-(4-methoxybenzyl)-2,5-diazabicyclo[2.2.2]octane-3,6,7-trione ***14***

Under an N_2 atmosphere the mixed methyl silyl acetal **13** (42 mg, 0.10 mmol) was dissolved in a degassed mixture of THF/0.5 M HCl (9/1, 20 mL) and the mixture was stirred at room temperature for 16 h. Water was then added and the mixture was extracted with CH_2Cl_2 (×3). The organic layer was dried (Na_2SO_4), filtered, and the solvent was removed under vacuum. The residue was purified by flash chromatography (1 cm, 1/2 cyclohexane/ethyl acetate, 5 mL, R_f 0.25) to give a colourless solid, mp 149°C, yield 30 g (95%). HPLC: t_R 13.7 min, purity 97.1%. $[\alpha]_D^{20}$ +34.6 (*c* 0.10, CH_2Cl_2). $C_{17}H_{18}N_2O_4$ (314.3). *m/z* (EI) 314 (M, 9%), 121 (CH_2PhOCH_3, 100). δ_H ($CDCl_3$) 2.47 (dd, *J* 18.8/3.1, 1H, 8-H), 2.61 (dd, *J* 18.8/1.6, 1H, 8-H), 3.78 (s, 3H, ArOCH_3), 4.00 (ddt, *J* 14.9/6.3/1.6, 1H, NCH_2CH=CH_2), 4.09 (ddt, *J* 14.9/6.3/1.6, 1H, NCH_2CH=CH_2), 4.16 (s, 1H, 1-H), 4.18 (dd, *J* 3.1/1.6, 1H, 4-H), 4.47 (d, *J* 14.9, 1H, NCH_2Ar), 4.60 (d, *J* 14.9, 1H, NCH_2Ar), 5.26–5.33 (m, 2H, NCH_2CH=CH_2), 5.69 (ddt, *J* 17.2/10.2/6.3, 1H, NCH_2C*H*=CH_2), 6.84 (d, *J* 8.6, 2H, 3′-$H_{4\text{-methoxybenzyl}}$, 5′-$H_{4\text{-methoxybenzyl}}$), 7.10 (d, *J* 8.6, 2H, 2′-$H_{4\text{-methoxybenzyl}}$, 6′-$H_{4\text{-methoxybenzyl}}$). ν_{max}/cm^{-1} 3005 (w, $\nu_{C-H\ arom.}$), 2959 (w, $\nu_{C-H\ aliph.}$), 1752 (m, $\nu_{C=O\ ketone}$), 1676 (s, $\nu_{C=O\ amide}$), 1613 (m), 1510 (m, $\nu_{C=C\ arom.}$).

Acknowledgements

This work was performed within the International Research Training Group 'Complex Functional Systems in Chemistry: Design, Synthesis and Applications' in collaboration with the University of Nagoya. Financial support of this IRTG by the *Deutsche Forschungsgemeinschaft* is gratefully acknowledged.

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