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Diastereoselective synthesis of bis(3,5)pyrazolophanes by sequential inter- and intramolecular cycloadditions of homochiral nitrilimines

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Abstract

Starting from ethyl (*S*)-lactate as the chiral unit, we have developed the synthesis of the enantiopure bis(3,5)pyrazolophanes **9** and **19** by means of sequential inter- and intramolecular cycloadditions of nitrilimine intermediates.

1. Introduction

Intramolecular cycloadditions of homochiral nitrilimines have been recently brought to light by our group as a fruitful tool in the synthesis of a variety of enantiopure pyrazole derivatives.[1–4] On the other hand, the sequential inter- and intramolecular nitrilimine cycloaddition methodology was successfully exploited by us in the synthesis of macrocyclic (1,5)- and (3,5)pyrazolophanes.[5,6] Hence, we perceived the opportunity to join these research lines aimed at the first synthesis of enantiopure bis(3,5)pyrazolophanes, which may be of interest as non-conventional chiral ligands towards metal cations.[7–9] In doing so, we devised the cheaper ethyl (*S*)-lactate as the chiral building block.

2. Results and discussion

Enantiopure hydrazonoyl chlorides **5** and **16**, which were devised as the suitable precursors of the desired nitrilimines **6** and **17**, were synthesised through the sequences depicted in Schemes 1

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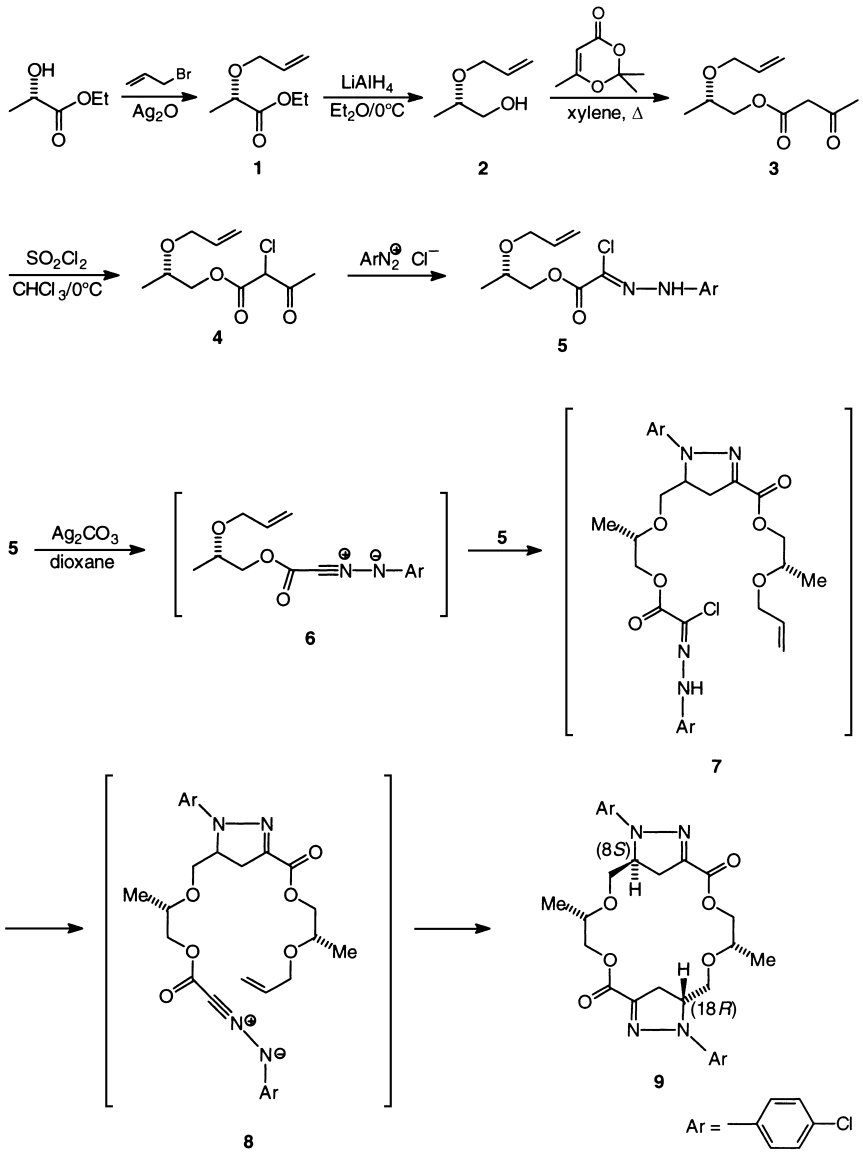
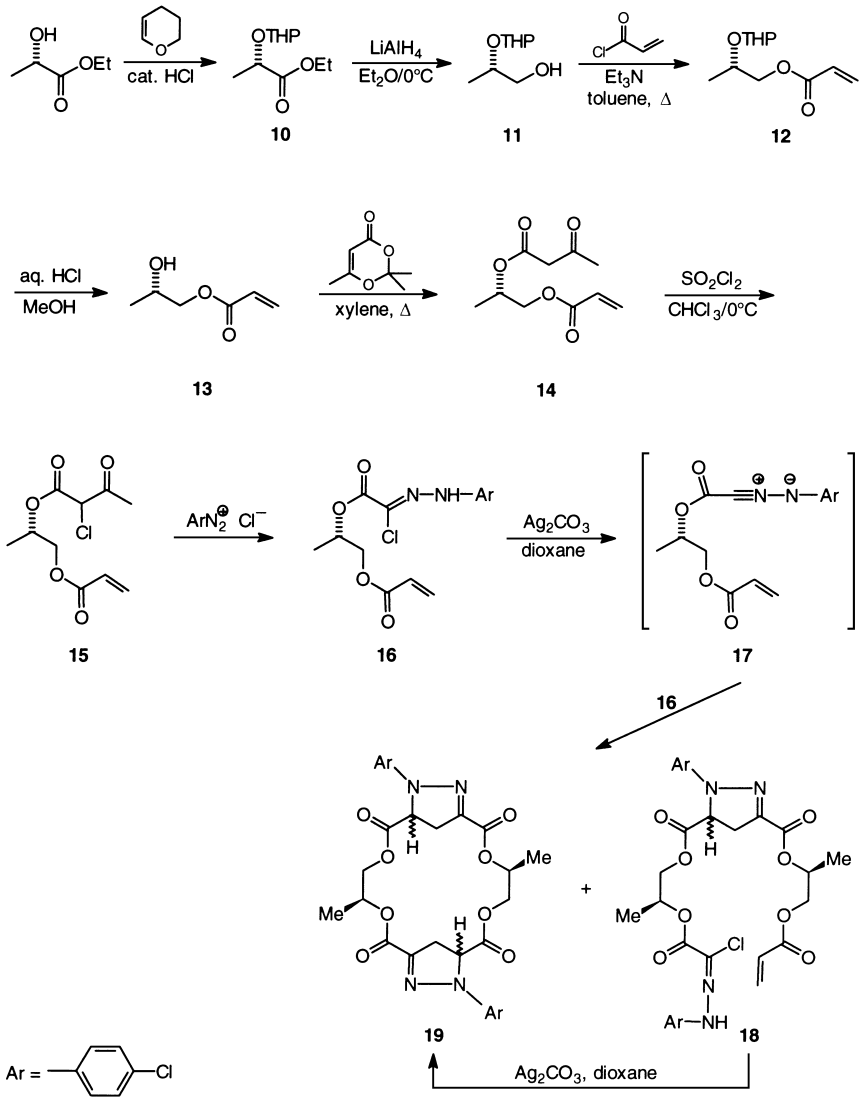
and 2. The in situ generation of the dipolar intermediates was accomplished by treating a 0.02 M solution of **5** or **15** with a twofold molar excess of silver carbonate in dry dioxane at room temperature. Column chromatography followed by crystallisation gave the pure macrocyclic compounds **9** or **19**, in 66 and 32% yield, respectively. The intermediate hydrazonoyl chloride **18** was also isolated, and its subsequent reaction with silver carbonate gave **19** in almost quantitative yield.



Scheme 1.

Both products **9** and **19** were fully characterised by analytical and spectroscopic data. In the case of **9**, X-ray diffractometric analysis elucidated unequivocally the absolute configurations of the newly formed stereocentres in the 5-position of the pyrazolinic rings as (8*S*,18*R*) (Fig. 1).



Scheme 2.

Unfortunately, the macrocycle **19** was obtained as an amorphous solid which precluded its diffractometric analysis, and the absolute configurations of the newly formed stereocentres may only be tentatively assigned by analogy with **9**. Such analogy is reinforced by the lack of symmetry as evidenced by the NMR data for **19**. This means that the intermolecular cycloaddition leading to the intermediate **7** is fully diastereoselective, although we are not able to determine whether the formation of the (8*S*) or the (18*R*) stereocentre occurs in this step. This behaviour could arise from the asymmetric induction due to the pre-existing stereocentres reinforced by some kind of coordination between the silver ion and the ethereal oxygens of the reactants. Analogous considerations could also be applied to the subsequent intramolecular cycloaddition leading from **8** to **9**. The replacement of the allylic dipolarophile of **6** with the more reactive acrylic one of **17** (Scheme 2) did not produce better results since, despite a single diastereoisomer again being

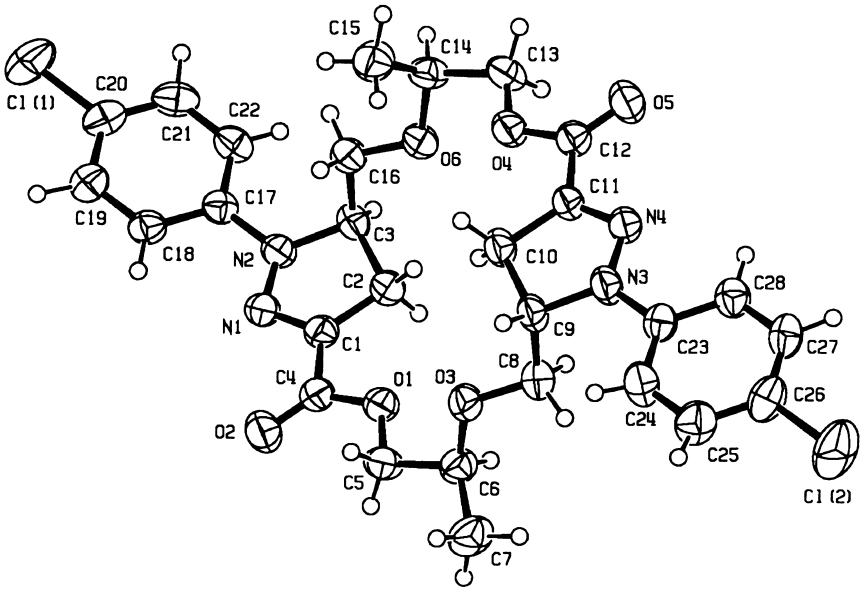


Figure 1. ORTEPIII[16] projection of **9**, with the crystallographic numbering scheme. Ellipsoids at 50% probability level. H atoms not to scale

obtained, the extent of the double cycloaddition process was far less effective. It may be that the ester oxygens of **17** and **18** are less prone to coordination with the silver ion in comparison to the ether oxygens of **6** and **7**.

3. Experimental

Melting points were determined with a Büchi apparatus and are uncorrected. IR spectra were recorded with a Perkin–Elmer 1725X spectrophotometer. Mass spectra were determined with a VG-70EQ apparatus. ^{1}H NMR and ^{13}C NMR spectra were taken with a Bruker AC 300 or a Bruker AMX 300 instrument (in $CDCl_3$ solutions). Chemical shifts are given as ppm from tetramethylsilane and J values are given in hertz. Optical rotations were recorded on a Perkin–Elmer Model 241 polarimeter at the sodium D line at 25°C. Compound **11**[10] was prepared according to the literature method.

3.1. Preparation of ethyl [2-(S)-allyloxy]propanoate *1*

Ag_2O (6.96 g, 30.0 mmol) was added portionwise, under vigorous stirring, to a solution of ethyl 2-(*S*)-lactate (3.50 g, 30.0 mmol) and allyl bromide (5.45 g, 45.0 mmol) in anhydrous diethyl ether (60 mL) at room temperature. The mixture was refluxed for 2 h, then it was cooled and filtered over Celite. The organic layer was dried over sodium sulfate, the solvent was evaporated and the residue was distilled in vacuo giving **1** (4.30 g, 93%): bp 50–53°C (15 mmHg); $[\alpha]_D^{25} = -70.7$ (*c* 2.68, MeOH); ^{1}H NMR δ: 1.23 (3H, t, $J = 6.7$), 1.35 (3H, d, $J = 6.7$), 3.41–3.97 (2H, m), 4.05 (1H, q, $J = 6.7$), 4.17 (2H, q, $J = 6.7$), 5.12–6.12 (3H, m). IR (neat) 1750 cm^{-1}. MS *m*/*z*: 158 (M^+). Anal. calcd for $C_8H_{14}O_3$: C, 60.72; H, 8.92. Found: C, 60.77; H, 8.94.

3.2. Preparation of 2-(S)-allyloxypropan-1-ol **2**

A solution of **1** (4.00 g, 25.3 mmol) in anhydrous diethyl ether (25 mL) was added dropwise to a suspension of $LiAlH_4$ (1.40 g, 35.4 mmol) in anhydrous diethyl ether (35 mL) at 0°C under a nitrogen atmosphere and vigorous stirring. The mixture was allowed to warm to room temperature; after 2 h it was poured onto crushed ice (120 mL) and 2.5 M sodium hydroxide (60 mL) was added. The bulky precipitate was filtered off over Celite and washed with diethyl ether (50 mL). The organic layer was dried over sodium sulfate and evaporated. Distillation of the residue under reduced pressure gave **2** (1.70 g, 58%): bp 78–80°C (30 mmHg); $[\alpha]_D^{25} = +32.2$ (*c* 0.50, MeOH); ^{1}H NMR δ: 1.05 (3H, d, $J = 6.0$), 2.46 (1H, br s), 3.42–3.49 (1H, m), 3.54–3.62 (2H, m), 3.96 (1H, dd, $J = 13.0$, 6.0), 4.10 (1H, dd, $J = 13.0$, 6.0), 5.15–5.98 (3H, m). IR (neat) 3400 cm^{-1}. MS *m*/*z*: 116 (M^+). Anal. calcd for $C_6H_{12}O_2$: C, 62.02; H, 10.42. Found: C, 62.10; H, 10.46.

3.3. Preparation of 2-(S)-allyloxypropyl 3-oxobutanoate **3**

A solution of **2** (1.60 g, 13.8 mmol) in xylene (5 mL) was treated with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one[11] (1.90 g, 13.8 mmol). The mixture was refluxed for 1 h. Evaporation of the solvent under reduced pressure and subsequent in vacuo distillation of the residue gave **3** (2.50 g, 92%): bp 75–77°C (0.1 mmHg); $[\alpha]_D^{25} = +8.6$ (*c* 1.75, MeOH); ^{1}H NMR δ: 1.12 (3H, d, $J = 5.7$), 2.25 (3H, s), 3.45 (2H, s), 3.66–3.74 (1H, m), 4.02–4.17 (4H, m), 5.18–5.92 (3H, m). IR (neat) 1750, 1720 cm^{-1}. MS *m*/*z*: 200 (M^+). Anal. calcd for $C_{10}H_{16}O_4$: C, 59.97; H, 8.06. Found: C, 60.03; H, 8.02.

3.4. Preparation of 2-(S)-allyloxypropyl 2-chloro-3-oxobutanoate **4**

A solution of sulfuryl chloride (1.60 g, 12.0 mmol) in dry dichloromethane (8 mL) was slowly added (1 h) to a solution of **3** (2.40 g, 12.0 mmol) in dry dichloromethane (15 mL), while keeping the temperature in the range 0–5°C. After 1 h at room temperature, dichloromethane (75 mL) was added and the organic solution was washed with 5% aqueous sodium hydrogencarbonate (25 mL). The organic layer was then washed with water (100 mL) and dried over sodium sulfate. Evaporation of the solvent gave **4** (2.80 g, 99%) as a thick oil not analytically pure: $[\alpha]_D^{25} = +8.8$ (*c* 2.50, MeOH); ^{1}H NMR δ: 1.16 (3H, d, $J = 5.8$), 2.36 (3H, s), 3.52–3.72 (1H, m), 3.95–4.20 (4H, m), 4.78 (1H, s), 5.18–6.03 (3H, m). IR (neat) 1760, 1735 cm^{-1}. MS *m*/*z*: 234 (M^+).

3.5. Preparation of hydrazonoyl chloride **5**

A cold aqueous solution of 4-chlorobenzenediazonium chloride (10.7 mmol) was added dropwise to a solution of **4** (2.50 g, 10.7 mmol) in tetrahydrofuran (70 mL) under vigorous stirring and ice-cooling. During the addition, the pH was adjusted to 5 by adding sodium acetate. The mixture was stirred for 2 h at 0°C, then 2 h at room temperature. The solvent was partly removed under reduced pressure and the resulting mixture was extracted with diethyl ether (100 mL). The organic layer was washed firstly with 5% aqueous sodium hydrogencarbonate (25 mL), then with water (100 mL), and dried over sodium sulfate. Evaporation of the solvent gave **5** (2.30 g, 65%): mp 87°C (from diisopropyl ether); $[\alpha]_D^{25} = +16.6$ (*c* 0.40, MeOH); ^{1}H NMR δ: 1.25 (3H, d, $J = 6.1$), 3.78–3.89 (1H, m), 4.13 (2H, d, $J = 6.4$), 4.22–4.35 (2H, m), 5.17 (1H, dd, $J = 10.8$, 2.0), 5.31 (1H, dd, $J = 16.5$, 10.8), 5.93 (1H, dd, $J = 16.5$, 10.8), 7.12–7.35 (4H, m), 8.32 (1H, br s). IR (nujol) 3270,

1730 cm^{-1}. MS *m/z*: 330 (M^+). Anal. calcd for $C_{14}H_{16}Cl_2N_2O_3$: C, 50.90; H, 4.89; N, 8.49. Found: C, 50.93; H, 4.93; N, 8.44.

3.6. Treatment of **5** with silver carbonate

A solution of **5** (2.00 g, 6.0 mmol) in dry dioxane (120 mL) was treated with silver carbonate (3.31 g, 12.0 mmol) and stirred in the dark at room temperature for 30 h. The undissolved material was filtered off, the solvent was evaporated, and then the residue was chromatographed on a silica gel column with diethyl ether:hexane (4:1). The first fraction contained unreacted **5** (0.30 g, 15%). Further elution gave 9,19-bis-(4-chlorophenyl)-5,15-bis-(*S*)-methyl-8-(*S*)-18-(*R*)-3,6,13,16-tetraoxa-9,10,19,20-tetraaza-tricyclo[16.2.1.$1^{8,11}$]docosa-1(20),10-diene-2,12-dione **9** (0.84 g, 66%): mp 121°C (from diisopropyl ether–dichloromethane); $[\alpha]_D^{25} = -310.0$ (*c* 0.16, $CHCl_3$); ^{1}H NMR δ: 1.06 (3H, d, $J = 6.7$), 1.18 (3H, d, $J = 6.7$), 3.19–3.38 (5H, m), 3.53 (1H, dd, $J = 9.9$, 2.8), 3.63–3.78 (3H, m), 3.82 (1H, dd, $J = 8.9$, 3.4), 3.99 (1H, dd, $J = 11.8$, 6.3), 4.08 (1H, dd, $J = 12.0$, 8.4), 4.18 (1H, dd, $J = 11.9$, 2.4), 4.31 (1H, dd, $J = 11.7$, 2.4), 4.66–4.75 (2H, m), 7.05–7.30 (8H, m); ^{13}C NMR δ: 16.3 (q), 16.6 (q), 35.0 (t), 35.9 (t), 60.9 (d), 61.2 (d), 66.0 (t), 66.9 (t), 67.2 (t), 68.7 (t), 72.9 (d), 74.7 (d), 116.0–129.9, 139.7 (s), 140.3 (s), 141.1 (s), 141.2 (s), 162.4 (s), 162.6 (s). IR (nujol) 1725 cm^{-1}. MS *m/z*: 588 (M^+). Anal. calcd for $C_{28}H_{30}Cl_2N_4O_6$: C, 57.13; H, 5.14; N, 9.52; Cl, 11.89. Found: C, 57.17; H, 5.11; N, 9.49; Cl, 11.95.

3.7. Preparation of 2-(S)-hydroxypropyl propenoate **13**

Propenoyl chloride (2.30 g, 25.0 mmol) in anhydrous toluene (15 mL) was added dropwise to a solution of **11** (4.00 g, 25.0 mmol) and triethylamine (5.10 g, 50.0 mmol) in anhydrous toluene (80 mL) under vigorous stirring and ice-cooling. The mixture was stirred for 1 h at 0°C, then for 3 h at room temperature. Water (200 mL) was added, the organic layer was dried over sodium sulfate and the solvent was evaporated giving crude 2-(*S*)-(tetrahydropyranyl)oxypropyl propenoate **12** (3.2 g, 78%) as a thick oil which was used without any further purification: ^{1}H NMR δ: 1.21 (3H, d, $J = 6.3$), 1.42–1.80 (6H, m), 3.96–4.11 (5H, m), 5.78 (1H, d, $J = 10.1$), 6.08 (1H, dd, $J = 17.2$, 10.1), 6.36 (1H, d, $J = 17.2$). IR (neat) 1730 cm^{-1}.

A solution of **12** (3.00 g, 14.0 mmol) in methanol (15 mL) and water (5 mL) was added with 37% aqueous hydrochloric acid (0.05 mL) and stirred for 0.5 h at room temperature. The mixture was poured into water-ice (50 mL) and extracted with dichloromethane (2×50 mL). The organic layer was washed with 5% aqueous sodium hydrogencarbonate (25 mL), then with water (25 mL), and dried over sodium sulfate. The solvent was evaporated and subsequent in vacuo distillation of the residue gave **13** (1.62 g, 90%): bp 50–52°C (3.0 mmHg); $[\alpha]_D^{25} = +18.8$ (*c* 1.96, MeOH); ^{1}H NMR δ: 1.18 (3H, d, $J = 6.0$), 2.25 (1H, br s), 3.96–4.14 (3H, m), 5.82 (1H, d, $J = 10.4$), 6.12 (1H, d, $J = 17.3$, 10.4), 6.40 (1H, d, $J = 17.3$). IR (neat) 3435, 1725 cm^{-1}. MS *m/z*: 130 (M^+). Anal. calcd for $C_6H_{10}O_3$: C, 55.36; H, 7.75. Found: C, 55.40; H, 7.79.

3.8. Preparation of 2-(S)-(1,3-dioxobutyl)oxypropyl propenoate **14**

A solution of **13** (0.75 g, 4.7 mmol) in xylene (5 mL) was treated with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one[11] (0.67 g, 4.7 mmol). The mixture was refluxed for 2 h. Evaporation of the solvent under reduced pressure and subsequent in vacuo distillation of the residue gave **14** (0.90 g, 89%): bp 70–72°C (0.1 mmHg); $[\alpha]_D^{25} = +10.2$ (*c* 1.40, CH_3OH); ^{1}H NMR δ: 1.05 (3H, d, $J = 7.0$), 2.00

(3H, s), 3.22 (2H, s), 3.80–4.20 (3H, m), 5.58 (1H, dd, $J=8.3$, 3.0), 5.96 (1H, dd, $J=16.8$, 3.0), 6.28 (1H, dd, $J=16.8$, 8.3). IR (neat) 1750, 1720 cm^{-1}. MS m/z: 214 (M^+). Anal. calcd for $C_{10}H_{14}O_5$: C, 56.05; H, 6.59. Found: C, 55.99; H, 6.56.

3.9. Preparation of 2-(S)-(1,3-dioxo-2-chlorobutyl)oxypropyl propenoate **15**

A solution of sulfuryl chloride (0.60 g, 4.4 mmol) in dry dichloromethane (2 mL) was slowly added (1 h) to a solution of **14** (0.96 g, 4.4 mmol) in dry dichloromethane (8 mL), while keeping the temperature in the range 0–5°C. After 1.5 h at room temperature, dichloromethane (50 mL) was added and the organic solution was washed with 5% aqueous sodium hydrogencarbonate (30 mL). The organic layer was then washed with water (80 mL) and dried over sodium sulfate. Evaporation of the solvent gave **15** (1.10 g, 99%) as a thick oil not analytically pure: $[\alpha]_D^{25}=+12.4$ (c 1.50, MeOH); ^1H NMR δ: 1.25 (3H, d, $J=6.5$), 2.30 (3H, s), 4.10 (2H, d, $J=6.7$), 4.70 (1H, s), 4.70–4.76 (1H, m), 5.50 (1H, dd, $J=8.5$, 2.8), 6.00 (1H, dd, $J=16.6$, 2.8), 6.48 (1H, dd, $J=16.6$, 2.8). IR (neat) 1750, 1735, 1730 cm^{-1}. MS m/z: 248 (M^+).

3.10. Preparation of hydrazonoyl chloride **16**

A cold aqueous solution of 4-chlorobenzene diazonium chloride (4.4 mmol) was added dropwise to a solution of **15** (1.08 g, 4.4 mmol) in tetrahydrofuran (20 mL) under vigorous stirring and ice-cooling. During the addition, the pH was adjusted to 5 by adding sodium acetate. The mixture was stirred for 1 h at 0°C, then 0.5 h at room temperature. The solvent was partly removed under reduced pressure and the resulting mixture was extracted with diethyl ether (80 mL). The organic layer was washed firstly with 5% aqueous sodium hydrogencarbonate (25 mL), then with water (100 mL), and dried over sodium sulfate. Evaporation of the solvent gave **16** (1.27 g, 84%): mp 94°C (from diisopropyl ether); $[\alpha]_D^{25}=+93.4$ (c 0.22, MeOH); ^1H NMR δ: 1.40 (3H, d, $J=6.5$), 4.26 (2H, d, $J=6.7$), 4.30–4.38 (1H, m), 5.85 (1H, dd, $J=10.5$, 1.4), 6.11 (1H, dd, $J=17.2$, 10.5), 6.64 (1H, dd, $J=17.2$, 1.4), 7.13–7.30 (4H, m), 8.33 (1H, br s). IR (nujol) 3250, 1720 cm^{-1}. MS m/z: 344 (M^+). Anal. calcd for $C_{14}H_{14}Cl_2N_2O_4$: C, 48.83; H, 4.10; N, 8.14. Found: C, 48.85; H, 4.07; N, 8.14.

3.11. Treatment of **16** with silver carbonate

A solution of **16** (1.20 g, 3.0 mmol) in dry dioxane (60 mL) was treated with silver carbonate (1.66 g, 6.0 mmol) and stirred in the dark at room temperature for 48 h. The undissolved material was filtered off, the solvent was evaporated, and then the residue was chromatographed on a silica gel column with diethylether:toluene (7:1). The first fraction contained unreacted **16** (0.24 g, 20%). The second fraction contained 9,19-bis-(4-chlorophenyl)-4,14-bis-(*S*)-methyl-3,6,13,16-tetraoxa-9,10,19,20-tetraaza-tricyclo[16.2.1.1^{8,11}]docosa-1(20),10-diene-2,7,12,17-dione **19** (0.18 g, 32%): mp 130°C (from diisopropyl ether–methanol); $[\alpha]_D^{25}=-424.4$ (c 0.20, $CHCl_3$); ^1H NMR δ: 1.25 (6H, d, $J=6.4$), 3.43 (2H, dd, $J=18.3$, 13.2), 3.59 (2H, dd, $J=18.3$, 4.8), 3.82 (2H, dd, $J=12.0$, 9.9), 4.47 (2H, dd, $J=12.0$, 2.1), 4.91 (2H, dd, $J=13.2$, 4.8), 5.56–5.60 (2H, m), 7.00–7.25 (8H, m); ^{13}C NMR δ: 16.2 (q), 16.5 (q), 36.0 (t), 36.9 (t), 61.9 (d), 67.8 (d), 68.0 (d), 68.0 (d), 68.5 (t), 69.2 (t), 106.0 (s), 115.0–118.0, 127.3 (s), 128.0–130.2, 139.1 (s), 140.0 (s), 141.1 (s), 162.2 (s), 169.5 (s). IR (nujol) 1740, 1725 cm^{-1}. MS m/z: 616 (M^+). Anal. calcd for $C_{28}H_{26}Cl_2N_4O_8$: C, 54.54; H, 4.25; N, 9.09; Cl, 11.35. Found: C, 54.60; H, 4.28; N, 9.12; Cl, 11.41.

Further elution gave the intermediate hydrazonoyl chloride **18** (0.16 g, 26%) as a thick oil not analytically pure: $[\alpha]_D^{25} = -216.2$ (*c* 0.28, $CHCl_3$); ^{1}H NMR δ: 1.25 (6H, d, $J = 6.5$), 3.42 (1H, dd, $J = 18.6$, 13.5), 3.59 (1H, dd, $J = 18.6$, 5.0), 3.81 (1H, dd, $J = 11.8$, 9.8), 4.29 (1H, dd, $J = 12.0$, 6.5), 4.37 (1H, dd, $J = 12.0$, 3.8), 4.47 (1H, dd, $J = 11.8$, 2.0), 4.90 (1H, dd, $J = 13.5$, 5.0), 5.31–5.39 (1H, m), 5.50–5.60 (1H, m), 5.84 (1H, dd, $J = 10.4$, 1.3), 6.12 (1H, dd, $J = 17.3$, 10.4), 6.42 (1H, dd, $J = 17.3$, 1.3), 7.00–7.30 (8H, m), 8.30 (1H, br s); ^{13}C NMR δ: 16.2 (q), 16.5 (q), 36.0 (t), 36.9 (t), 60.9 (d), 61.2 (d), 66.0 (t), 66.9 (t), 67.2 (t), 68.7 (t), 72.9 (d), 74.7 (d), 116.0–129.9, 139.7 (s), 140.3 (s), 141.1 (s), 141.2 (s), 162.4 (s), 162.6 (s). IR (nujol) 3160, 1740, 1730 cm^{-1}. MS *m*/*z*: 652 (M^+).

3.12. Treatment of *18* with silver carbonate

A solution of **18** (0.10 g, 0.15 mmol) in dry dioxane (15 mL) was treated with silver carbonate (83 mg, 0.30 mmol) and stirred in the dark at room temperature for 96 h. The undissolved material was filtered off, the solvent was evaporated, and then the residue was chromatographed on a silica gel column with diethyl ether. The first fraction contained the macrocyclic compound **19** (85 mg, 90%).

3.13. X-Ray structure determination of *9*

$C_{28}H_{30}Cl_2N_4O_6 \cdot 1/2(CH_2Cl_2)$, $M_r = 631.92$, monoclinic, $a = 14.553(2)$, $b = 11.776(2)$, $c = 17.699(2)$ Å, $\beta = 92.699(11)^\circ$, $V = 3029.8(7)$ Å^3, space group *C*2, $T = 291(1)$ K, $Z = 4$, $d_{calc} = 1.385$ gcm^{-1}, μ(Mo-*K*α) = 0.350 mm^{-1}. Crystal data were collected with a Bruker P4 diffractometer, using graphite monochromated Mo-*K*α radiation $\lambda = 0.71073$ Å; $\omega/2\theta$ scans, $4 < 2\theta < 55^\circ$; $0 < h < 18$, $-15 < k < 15$, $-22 < l < 22$; data corrected for absorption on the basis of ψ-scan data[12]; 6963 unique reflections collected were used for all calculations [5742 with $I > \sigma(I)$]. The structure was solved by *SIR*92,[13] and refined on *F*2 by full-matrix least-squares by using SHELX97.[14] Heavy atoms were anisotropic, H atoms isotropic; H atoms of methyl groups were fixed in calculated positions. Final discrepancy index on all reflections $R = 0.0554$ and $wR(F2) = 0.1164$, g.o.f. 1.015, $-0.26 < \Delta\rho < 0.20$ eÅ^{-3}. The (*S*) configuration at atoms C6 and C14, known on the basis of the reactants knowledge, was confirmed by Flack[15] parameter [0.04(5)]; the configuration at atoms C3 is (*R*) while at C9 is (*S*). The dichloromethane molecule lies on a crystallographic C_2 axis. Bond distances and bond angles are in the expected range. Crystallographic data of **9** have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication no. 138143.

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