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Towards EPC-syntheses of the structural class of cochleamycins and macquarimicins. Part 2: EPC-synthesis of the hydrindene subunit of the macquarimicins

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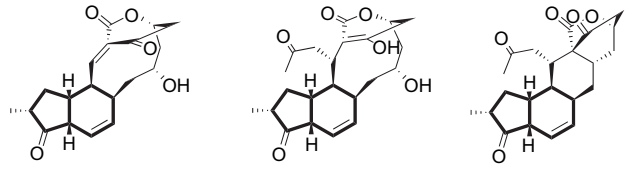
Abstract—The EPC-synthesis of the *cis*-hydrindene subunit of the macquarimicins, antibiotics with antitumour and anti-inflammatory activity, has been achieved. Desymmetrization of *cis*-1,4-cyclopent-2-enediol was succeeded by Diels–Alder reaction and functional group transformations to a tricyclic ketone. Regio- and stereoselective methylation via Claisen condensation and hydrogenation was followed by nucleophilic, intramolecular addition, reduction and acidic fragmentation. Further functional group transformations led to the target molecule.

1. Introduction

The macquarimicins, bacterial secondary metabolites from *Micromonospora chalcea*, were isolated by McAlpine et al.[1] This group also elucidated the structure of these tetra- and pentacyclic compounds[2] and demonstrated their antibacterial and antitumour activities.[1] Later on, Tanaka et al. detected the possible use of macquarimicin A as an anti-inflammatory therapeutic.[3] Recently, Tadano et al. succeeded in the syntheses of these structurally unusual acetogenic macrolides, which included structure revision of macquarimicin A (Scheme 1).[4]



Scheme 1.

2. Results and discussion

Here we want to present our own efforts to synthesize the enantiomerically pure hydrindene part of the macquarimicins.[5] As in the preceding paper, intermolecular neutral Diels–Alder reaction and mild acidic fragmentation were the key steps of our chosen strategy.[6] Again, ketone **1**[7] was the starting material. As demonstrated before, its highly shielded *endo*-face permitted exclusive attack from the *exo*-face.[6] Kinetic protonation via enolization of the thus produced *exo*-α-methyl ketone[6] to invert the methyl group failed.[8] Thus we decided to examine reduction of the corresponding α-methylene ketone **3** (Scheme 2).

Acid-catalyzed reaction of ketone **1** with Bredereck's reagent yielded enaminone **2** quantitatively.[9] According to literature reports we expected the α-methylene ketone as the product of the reduction of **2** with DIBAH at −78 °C.[10] However, we isolated heptacycle **4** resulting from dimerization of the α-methylene ketone **3** via hetero-Diels–Alder reaction. While hetero-Diels–Alder reactions of α-methylene ketones have been reported in the literature,[11] the very ease with which this bulky compound cyclized was surprising. We reasoned that the fast dimerization could be dependent on the Lewis acid activity of DIBAH. Using the conditions of Gras' protocol,[12] paraformaldehyde and *N*-methylanilinium trifluoroacetate as phase-transfer catalyst in THF at reflux, led again to dimerization. In this case working under 5-fold dilution permitted isolation of small amounts of the elusive α-methylene ketone **3**, which showed signals of the methylene protons at 5.94 and 5.28 ppm, but we failed to record satisfactory analytical data, because dimerization in $CDCl_3$ at room temperature was complete within 15 min.[5a] To circumvent this difficulty the methylene ketone was prepared in situ under hydrogenation conditions. To prevent deactivation of the heterogeneous catalyst by amines, the enaminone **2** was converted quantitatively into the methyl enol ether **6** with acidic methanol. The same

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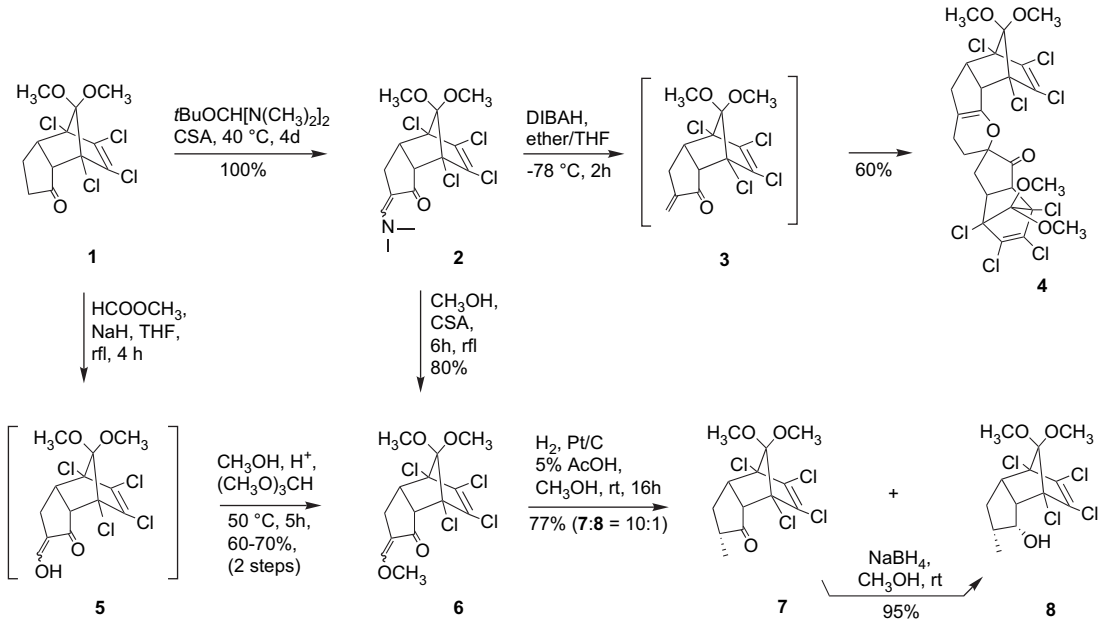
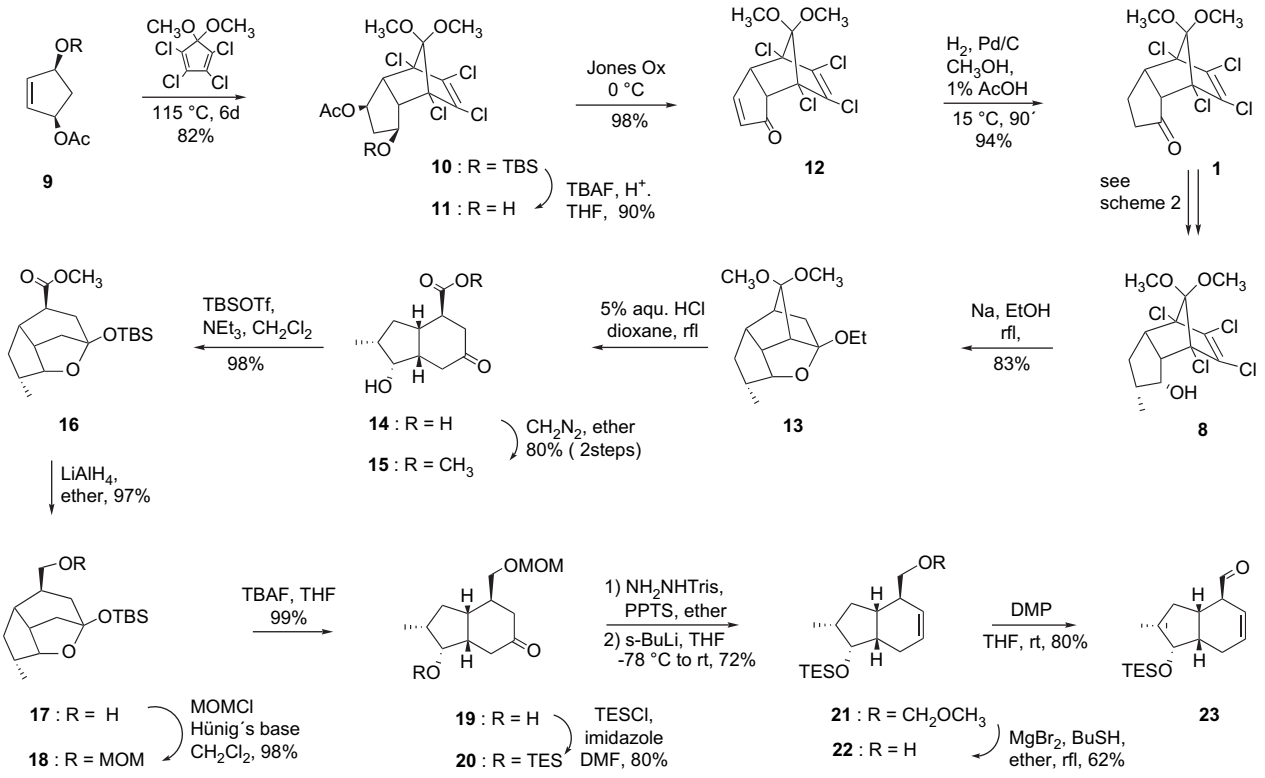


Scheme 2.

enol ether **6** was attained by Claisen condensation of **1** with methyl formate and NaH followed by treatment with acidic methanol. Hydrogenation of **6** with Adam's catalyst or platinum on charcoal in weakly acidic alcohol under 1 atm of hydrogen led mainly to the desired *endo*-methyl ketone **7** (70% yield) and to roughly 10% of the corresponding *endo*-alcohol **8**.[13] The *endo*-position of the methyl group in ketone **7** was ascertained by ^{1}H NMR spectroscopy and comparison with the spectra of its stereoisomer.[6] With this *endo*-methyl ketone in hand we approached the EPC-synthesis of ketone **1**.

Starting with a neutral Diels–Alder reaction permits the use of a wide variety of dienophiles because electron-withdrawing as well as electron-donating substituents increase the reaction rate.[14] By exchanging cyclopent-2-enone against cyclopent-2-enol or its derivatives, chirality is introduced and the loss of material by partial isomerization of cyclopent-2-enone to cyclopent-3-one is avoided.[6] Preliminary examinations[15] showed that cyclopent-2-enol itself is an unsuitable dienophile because the necessary reaction conditions for the cyclization led to consecutive partial dehydration of the tricyclic alcohol. Addition of (*tert*-butyldimethylsiloxy)cyclopent-2-ene[16] to 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene afforded exclusive *endo*-addition in good yields. However, the accompanying stereoisomer (<10%) generated due to incomplete face selectivity was difficult to separate. This fact combined with the laborious preparations of (*S*)-(*tert*-butyldimethylsilyl)-cyclopent-2-ene[17]and difficulties in scaling up led to the decision to use (1*S*,4*R*)-4-acetoxycyclopent-2-enol.[18] Its easy access and very high ee values as well as the hope of improving the face selectivity due to the bulk and polarity of the second substituent seemed to compensate the additional step in the following synthesis.[19] Again, the alcohol itself was unsuitable as dienophile due to consecutive dehydration (Scheme 3).

Thus silyl ether **9** (R=TBS)[20] and 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene were cyclized at 115 °C within six days to give an 80% yield of the desired cycloadduct **10**. Contrary to the above-mentioned expectations[19] but in accordance with the findings of Dols et al.,[21b] face selectivity was only slightly increased by the second substituent.[21] Fortunately the minor isomer of cycloadduct **10** with *endo*-positioned substituents (7%) was easily separated. After deprotection of the silyl ether **10** with tetrabutylammonium fluoride, the liberated alcohol **11** was oxidized at 0 °C with Jones' reagent leading via consecutive elimination of acetic acid directly to enone **12**. Careful hydrogenation of **12** at 15 °C with palladium on charcoal as catalyst and dry methanol containing less than 1% acetic acid as solvent under 1 atm of hydrogen afforded enantiomerically pure ketone **1**. Under these conditions partial overreduction by removal of the vinylic chlorides and subsequent reduction of the strained norbornene double bond was prevented.[5c] Enantiopure **1** was converted into the *endo*-methyl ketone **7** as described above. Highly selective reduction of the ketone with sodium borohydride preceded the treatment of the generated alcohol **8** with excess sodium in refluxing ethanol.[7] The thus obtained tetracyclic diketal **13** was converted into the hydrindanone carboxylic acid **14** by mild acidic fragmentation. Subsequent esterification with diazomethane led to methyl ester **15**. The alcohol as well as the keto group of **15** were protected as cyclic silyl ketal **16** by treatment with *tert*-butyldimethylsilyl triflate. Quantitative reduction of the ester group of **16** with lithium aluminium hydride was followed by protection of the primary alcohol **17** as methoxymethyl ether **18**. After cleaving the cyclic ketal with tetrabutylammonium fluoride the secondary alcohol **19** had to be protected. Contrary to our experience with the corresponding hydrindanone derivative containing the *exo*-methyl group at C(8),[6] *tert*-butyldimethylsilyl chloride as silylation reagent did not yield a single product but a mixture of the desired protected secondary alcohol and the cyclic silyl ketal



Scheme 3.

18. Consequently the slightly less bulky triethylsilyl chloride[22] was used, which indeed led to the desired protected secondary alcohol **20**. This compound represented the first possible candidate for the projected combination with the β-keto lactone unit (or its open-chained variant) to the macquarimicins. Further possible partners for the desired combination were achieved by transforming ketone **20** to the hydrindene derivative by Shapiro reaction.[23] Using trisylhydrazone as intermediate and *sec*-butyllithium as base yielded in good regioselectivity the desired Δ^3-hydrindene derivative **21**. Deprotection of the primary alcohol with magnesium dibromide[24] led to a further possible combination partner **22** as did oxidation of the primary alcohol to the β,γ-unsaturated aldehyde **23** with Dess–Martin periodinane.[25]

3. Experimental section

3.1. General

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Spectrospin AM 400-WB. Residual, non-deuterated solvent served as internal reference for ^{1}H spectra. For ^{13}C spectra, chemical shifts are given relative to the 77.00 ppm signal of $CDCl_3$. Coupling constants are given in hertz. Optical rotations were measured on a Perkin–Elmer 241 polarimeter with the Na D line. IR spectra were recorded on a Perkin–Elmer 1600 FTIR spectrometer and given in wave numbers (cm^{-1}). Melting points were obtained using a Reichert 'Kofler' hot-stage microscope and are uncorrected. EI mass spectra were recorded on a Finnigan 8230 spectrometer. Unless otherwise stated, starting materials were purchased from commercial suppliers and used without further purification. Dry dichloromethane was distilled from P_2O_5 and kept over 4 Å molecular sieves. Dry THF was distilled under argon from Na/benzophenone prior to use. Silica gel (230–400 mesh ASTM, Merck) was used for flash chromatography.

3.2. (±)-(1*R**,2*R**,6*R**,7*S**)-1,7,8,9-Tetrachloro-10,10-dimethoxy-4-[(dimethylamino)methylene]tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (2)

To (±)-**1**[7] (1 g, 2.89 mmol) dissolved in *tert*-butoxybis(dimethylamino)methane (Bredereck's reagent, 12 mL) was added a catalytic amount of camphorsulfonic acid. The reaction mixture was stirred at 40 °C under an argon atmosphere for four days. The reagent was then removed by bulb-to-bulb distillation under Hg diffusion vacuum at up to 80 °C. The residue was dissolved in diethyl ether and small amounts of dichloromethane, washed with satd aq $NaHCO_3$ and satd aq NH_4Cl, dried over $MgSO_4$ and the solvent was removed by rotary evaporation. This product **2** (1.18 g, 101%) can be used without further purification. To characterize this compound a small amount was purified by flash chromatography on silica gel (petroleum ether/diethyl ether 1:1) and isolated as yellow-brown crystals. Mp=182 °C. IR (cm^{-1}, film): 2950, 2872, 2846, 1751, 1576; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.70 (d, 1H, H(5α), $J_{5a,5\beta}$=15.6), 2.81 (dd, 1H, H(5β), $J_{5a,5\beta}$=15.5, $J_{5\beta,6}$=7.5), 3.03 (s, 6H, $N(CH_3)_2$), 3.16–3.23 (m, 2H, H(2,6)), 3.51 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 7.15 (t, 1H, H(1′), $J_{1',5\alpha}$=$J_{1',5\beta}$=1.2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 45.5, 51.6, 52.5, 57.7, 76.8, 78.3, 102.6, 114.0, 127.1, 129.2, 148.2, 196.9; MS (FI, 70 eV, 30 °C): *m*/*z* (%)=405 (8) M^+, 403 (46), 401 (100), 399 (80).

3.3. (±)-(3a′*R**,4′*R**,5a*R**,6*S**,7′*S**,7a′*R**,9*R**,9a*R**)-4′,5′,6,6′,7,7′,8,9-Octachloro-3,3a′,4,4′,5a,6,7′,7a′,9,9a-decahydro-8′,8′,10,10-tetramethoxy-6,9-methano-2*H*-indeno[1,2-*b*]pyrano[2-spiro-2′]-4′,7′-methanoindan-1′-one (4)

Enaminone **2** (100 mg, 0.25 mmol) was dissolved in dry diethyl ether (6 mL) and dry THF (4 mL) and cooled to −78 °C under an argon atmosphere. To this solution a 1.0 M solution of DIBAH in hexane (300 μL, 0.3 mmol) was added dropwise by syringe and the reaction mixture was stirred at −78 °C for 2 h. The reaction mixture was quenched with satd aq NH_4Cl and filtered. The residue was washed with diethyl ether. The organic layer was extracted with satd aq NH_4Cl (3×), dried over $MgSO_4$ and evaporated to dryness. Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate 10:1) afforded dimer (±)-**4** as white crystals (50 mg, 60%). Mp=177 °C. IR (cm^{-1}, film): 2983, 2950, 2845, 1757, 1697, 1603, 1485; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.35 (dd, 1H, H(3′), $J_{3',3a'}$=8, $J_{3',3'}$=15.1), 1.55 (ddd, 1H, H(3), $J_{3,3}$=14.2, $J_{3,4}$=7.8, $J_{3,4}$=6.3), 1.67 (ddd, 1H, H(3), $J_{3,3}$=14.2, $J_{3,4}$=5.2, $J_{3,4}$=6.3), 1.80 (dt, 1H, H(4), $J_{4,4}$=17.0, $J_{4,3}$=$J_{4,3}$=5.3), 1.99 (dq,1H, H(5), $J_{5,5}$=16.2, $J_{5,5a}$∼$J_{5,4}$∼$J_{5,9a}$∼2.1), 2.22 (ddd, 1H, H(5), $J_{11,10\alpha}$=16.0, $J_{5,5a}$=9.0, $J_{5,4}$=1.3), 2.30 (m, 1H, H(4)), 2.35 (dd, 1H, H(3′), $J_{3',3a'}$=8.9, $J_{3',3'}$=15.2), 3.1 (dt, 1H, H(5a), $J_{5a,5}$=$J_{5a,9a}$=9, $J_{5a,5}$=2.9), 3.49 (m, 1H, H(9a), $J_{9,5a}$=8.5), 3.53 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 3.60 (dt, 1H, H(3a′), $J_{3a',3'}$=$J_{3a',7a'}$=9.5, $J_{3a',3'}$=8.2), 3.61 (s, 3H, OCH_3), 3.70 (d, 1H, H(7a′), $J_{7a',3a'}$=10.0); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 24.3, 30.4, 33.3, 46.0, 46.3, 51.6, 51.9, 52.5, 52.7, 56.8, 57.0, 74.6, 76.7, 77.0, 77.8, 83.8, 112.7, 113.9, 115.3, 127.7, 128.8, 129.6, 130.2, 144.0, 206.0; MS (FI): *m*/*z* (%)=722 (6.4) M^+, 721 (6.5), 720 (22), 719 (18), 718 (66), 717 (30), 716 (100), 715 (24), 714 (77), 713 (6), 712 (32).

3.4. (±)-(1*R**,2*R**,6*R**,7*S**)-1,7,8,9-Tetrachloro-10,10-dimethoxy-4-(methoxymethylene)tricyclo[5.2.1.0^{2,6}]-dec-8-en-3-one (6)

To enaminone **2** (500 mg, 1.25 mmol) dissolved in dry methanol (60 mL) was added camphorsulfonic acid (290 mg, 1.25 mmol). The reaction mixture was stirred at reflux for 6 h. Addition of water (250 mL) was followed by extraction with ethyl acetate (3×). The combined organic layers were neutralized with satd aq $NaHCO_3$, washed with brine, dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The crude product **6** was purified by flash chromatography on silica gel (petroleum ether/acetone 6:1) and isolated as a colourless oil (380 mg, 80%). IR (cm^{-1}, film): 2950, 2848, 1706, 1626, 1450; UV (*c*=0.24 mmol/L in methanol): λ_{max1}=286 nm (ε_1=10,700 L mol^{-1} cm^{-1}, ε_2=4500 L mol^{-1} cm^{-1}); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.5–2.6 (m, 2H, H(5α, 5β)), 3.25 (d, 1H, H(2), $J_{2,6}$=9.0), 3.32 (dt, 1H, H(6), $J_{6,2}$=$J_{6,5\beta}$=8.8, $J_{6,5\alpha}$=3.5), 3.52 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.85 (s, 3H, C(1′)OCH_3), 7.17 (t, 1H, H(1′), $J_{1',5\alpha}$=$J_{1',5\beta}$=2.5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1, 46.2, 53.0, 53.1, 59.2, 62.6, 76.7, 78.4, 114.7, 115.9, 128.8, 129.4, 156.9; MS (FI): *m*/*z* (%)=392 (M^+, 4), 390 (M^+, 16), 388 (M^+, 100), 386 (M^+, 46).

3.5. (1*S*,2*S*,4*R*,6*S*,7*R*)-1,7,8,9-Tetrachloro-10,10-dimethoxy-4-methyltricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (7)

NaH (60% suspension in mineral oil, 3.0 g, 75 mmol) was washed with dry petroleum ether (3×), then added to a solution of (1*S*,2*S*,6*S*,7*R*)-1,7,8,9-tetrachloro-10,10-dimethoxytricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (+)-**1** (12.7 g, 36.9 mmol) in dry THF (50 mL) and methyl formate (200 mL) at 0 °C. The suspension was heated to reflux for 4 h and then cooled to room temperature. The mixture was quenched with satd aq NH_4Cl (130 mL) and extracted with ethyl acetate (4×60 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed by rotary evaporation to give a yellow residue, which was dissolved in dry methanol (300 mL) with camphorsulfonic acid (8.58 g, 36.9 mmol) and triethyl orthoformate (4.4 mL, 40.2 mmol). The solution was heated to 50 °C for 5 h, then cooled to room temperature and quenched with satd aq $NaHCO_3$ (150 mL). The mixture was reduced to approx. one third the volume by rotary evaporation and extracted with ethyl acetate (5×100 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to dryness to give a yellow residue. Crude **6** was used in the following reaction without further purification. Platinum on carbon (10%, 1.0 g) was placed in a 1 L three-necked flask under a stream of argon. Dry methanol (300 mL) and acetic acid (16 mL) were added. The vessel was sealed and evacuated and refilled with hydrogen (4×). After stirring for 1 h under hydrogen, a solution of the crude product from the previous reaction in dry methanol (100 mL) was added, and the mixture was stirred overnight. The flask was then evacuated and refilled with argon (4×). The solution was filtered through a plug of Celite and evaporated to dryness. The crude product (+)-**7** was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 4:1) and isolated as white crystals (6.2 g, 47% over three steps). $[\alpha]_D^{20}$ +10.3 (*c* 1.0, acetone). Mp=109 °C. IR (cm^{-1}, film): 2969, 2941, 2870, 2835, 1744, 1605, 1456, 1189, 1109; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.96 (d, 3H, C(4)CH_3, $J_{CH_3,4}$ = 6.4α); 1.20 (m, 1H, H(5β)), 2.39 (m, 2H, H(4, 5α)), 3.31 (dd, 1H, H(2), $J_{2,6}$=10, *J*=1.4), 3.38 (dt, 1H, H(6), $J_{6,2}$=$J_{6,5}$=10, $J_{6,5}$∼7), 3.52 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.76, 28.75, 45.41, 47.14, 52.21, 53.10, 57.91, 75.21, 78.50, 115.67, 129.92, 130.51, 213.40; MS (EI, 70 eV, 30 °C): *m*/*z* (%)=366 (2), 364 (14), 362 (42), 360 (100), 358 (65); HRMS (EI, 70 eV, 30 °C) calcd for $C_{13}H_{14}{}^{35}Cl_4O_3$: 357.9697, found 357.9704. Anal. Calcd for $C_{13}H_{14}Cl_4O_3$: C=43.37%, H=3.92%, found C=43.56%, H=3.83%.

3.6. (1*R*,2*R*,3*R*,5*S*,6*S*,7*S*)-3-Acetoxy-1,7,8,9-tetrachloro-10,10-dimethoxy-5-(*tert*-butyldimethylsiloxy)tricyclo[5.2.1.0^{2,6}]dec-8-ene (10)

Compound **9** (17.5 g, 68.3 mmol), 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene (19.3 g, 68.3 mmol), xylene (2 mL), crushed molecular sieves (4 Å, ca. 1.5 g) and a trace of hydroquinone were heated at 115 °C under an argon atmosphere in a sealed tube for six days. The mixture was cooled, then concentrated under reduced pressure and purified on silica gel (petroleum ether/diethyl ether 15:1) to give recovered diene (3.2 g, 12.1 mmol), one fraction of pure product and two other fractions containing product and a small amount of **9**, which may be purified further or used directly in the

next step. The product was isolated as a colourless oil (28.8 g, 81%). $[\alpha]_D^{20}$ +1.3 (*c* 0.7, $CHCl_3$). IR (cm^{-1}, film): 2954, 2895, 2856, 1744, 1602; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) −0.06 (s, 3H, $SiCH_3$), 0.00 (s, 3H, $SiCH_3$), 0.78 (s, 9H, $SiC(CH_3)_3$), 1.69 (m, 1H, H(4*exo*), $J_{4exo,4endo}$= 14.7, $J_{4exo,3}\sim J_{4exo,5}\sim$4.0, $J_{4,6}\sim J_{4,2}<1$), 1.79 (ddd, 1H, H(4*endo*), $J_{4endo,4exo}$=14.7, $J_{4endo,3}\sim J_{4endo,9}\approx$5.9), 1.93 (s, 3H, (CO)C$H_3$), 3.08 (dd, 1H, H(6), $J_{6,2}$=9.3, $J_{6,5}$=2.5, $J_{6,4}<1$), 3.20 (dd, 1H, H(2), $J_{2,6}$=9.3, $J_{2,3}$=2.7, $J_{2,4}<1$), 3.43 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 3.99 (ddd, 1H, CHOTBS, $J_{5,4exo}$=4.0, $J_{5,4endo}$=5.9, $J_{5,6}$=2.5), 4.86 (ddd, 1H, CHOAc, $J_{3,4exo}$=4.0, $J_{3,4endo}$=5.9, $J_{3,2}$=2.7); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.42, −4.39, 18.18, 21.50, 26.04, 43.67, 52.12, 52.96, 59.42, 62.92, 71.91, 74.12, 76.30, 76.58, 115.02, 129.40 (2C), 170.48; MS (EI, 70 eV, 50 °C): *m*/*z* (%)=485 (6), 483 (6), 117 (100), 75 (49), 73 (28); HRMS (EI, 70 eV, 50 °C) calcd for $C_{20}H_{30}{}^{35}Cl_3O_5Si$ $(M-{}^{35}Cl)^+$: 483.0928, found 483.0935.

3.7. (1*R*,2*R*,3*R*,5*S*,6*S*,7*S*)-3-Acetoxy-1,7,8,9-tetrachloro-10,10-dimethoxytricyclo[5.2.1.0^{2,6}]dec-8-en-5-ol (11)

Compound **10** (10.8 g, 20.7 mmol) was dissolved in dry THF (200 mL) containing AcOH (0.31 mL), and cooled to 10 °C. TBAF (1 M solution in THF, 41.4 mL, 41.4 mmol) was added by syringe. After 15 min, a solution of AcOH (0.92 mL) in dry THF (20 mL) was added dropwise over 0.5 h. After a further 1.5 h, the reaction was quenched with satd aq $NaHCO_3$ (50 mL) and concentrated under reduced pressure. The layers were separated and the aq phase was extracted with ethyl acetate (3×50 mL). The combined organic phases were washed with brine (100 mL), dried over $MgSO_4$ and evaporated to dryness. The product was purified on silica gel (petroleum ether/ethyl acetate 7:1, 1:1) affording **11** as a viscous, colourless oil (8.2 g, 97%). $[\alpha]_D^{20}$ −7.2 (*c* 1.0, $CHCl_3$). IR (cm^{-1}, film): 3437, 2952, 2846, 1742, 1602; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.82 (t, 2H, H(4*exo*), H(4*endo*), $J_{4,3}=J_{4,5}$=4.3), 1.84 (br m, 1H, OH), 2.00 (s, 3H, (CO)CH_3), 3.17 (dd, 1H, H(6), $J_{6,2}$=8.8, $J_{6,5}$=1.5); 3.22 (dd, 1H, H(2), $J_{2,6}$=8.8, $J_{2,3}$=1.5), 3.47 (s, 3H, OCH_3), 3.54 (s, 3H, OCH_3), 4.14 (m, 1H, H(5), $w_{1/2}$=10), 5.03 (td, 1H, H(3), $J_{3,4}$=4.3, $J_{3,2}$=1.5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.63, 43.17, 52.13, 53.01, 60.06, 62.85, 72.34, 74.82, 76.14, 76.33, 114.75, 129.15, 129.28, 170.07; MS (EI, 70 eV, 30 °C): *m*/*z* (%)=373 (32), 371 (89), 369 (100.0), 311 (38), 309 (41), 257 (19), 255 (54), 253 (60), 85 (30), 83 (45), 59 (26); HRMS (EI, 70 eV, 30 °C) calcd for $C_{14}H_{16}{}^{35}Cl_3O_5$ $(M-{}^{35}Cl)^+$: 369.0063, found 368.9. Anal. Calcd for $C_{14}H_{16}Cl_4O_5$: C=41.41%, H=3.97%, found C=41.13%, H=4.15%.

3.8. (1*S*,2*S*,6*S*,7*R*)-1,7,8,9-Tetrachloro-10,10-dimethoxytricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (12)

Compound **11** (7.89 g, 19.5 mmol) was dissolved in acetone (120 mL) and cooled to 0 °C. Jones' reagent was added dropwise until the solution remained yellow and no starting material was apparent on TLC. The reaction was quenched with satd aq NH_4OAc (60 mL) and the organic layer was separated. The aq layer was extracted with diethyl ether (4×40 mL) and the combined organic layers were washed with satd aq $NaHCO_3$ (60 mL). The aq layer was extracted with diethyl ether (2×15 mL) and the combined organic layers were dried over $MgSO_4$ and evaporated to dryness to give a white solid. The crude product was purified on silica gel (petroleum ether/ethyl acetate 4:1) to afford **12** (6.3 g, 94%) as white crystals. $[\alpha]_D^{20}$ +131.9 (*c* 1.0, $CHCl_3$). Mp= 74–77 °C. IR (cm^{-1}, film): 2953, 2924, 2848, 1714, 1603; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.14 (d, 1H, H(2), $J_{2,6}$=6.1), 3.58 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.84 (ddd, 1H, H(6), $J_{6,2}$=6.1, $J_{6,4}$=1.5, $J_{6,5}$=2.5), 6.26 (dd, 1H, H(4), $J_{4,5}$=5.8, $J_{4,6}$=1.5), 7.50 (dd, 1H, H(5), $J_{5,4}$=5.8, $J_{5,6}$=2.5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.28, 53.26, 54.02, 55.67, 75.53, 77.28, 115.68, 128.20, 128.53, 139.73, 158.65, 202.69; MS (EI, 70 eV, 70 °C): *m*/*z* (%)=311 (40), 310 (14), 309 (100), 308 (16), 307 (98), 271 (7), 255 (8), 253 (9), 249 (9), 247 (10), 235 (8), 233 (9), 213 (8), 209 (8), 207 (9), 170 (8), 109 (12), 75 (11), 59 (27); HRMS (EI, 70 eV, 20 °C) calcd for $C_{12}H_{10}{}^{35}Cl_3O_3$ $(M-{}^{35}Cl)^+$: 341.9384, found 341.9389. Anal. Calcd for $C_{12}H_{10}Cl_4O_3$: C=41.90%, H=2.93%, found C=42.17%, H=3.17%.

3.9. (1*S*,2*S*,6*S*,7*R*)-1,7,8,9-Tetrachloro-10,10-dimethoxytricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (1)

Palladium on carbon (10%, 4.45 g) was placed in a 1 L three-necked flask under a stream of argon. Dry methanol (150 mL) containing AcOH (3.3 mL) was added. The vessel was sealed and evacuated and refilled with hydrogen (5×). After stirring for 20 min under hydrogen, the solution was cooled to 15 °C and a solution of (+)-**12** (6.1 g, 17.7 mmol) in dry methanol (250 mL) was added over 30 min. The suspension was stirred rapidly for 60 min, while maintaining the temperature at 15 °C. The flask was then evacuated and refilled with argon (4×). The solution was filtered through a plug of Celite, reduced to approximately half the volume by rotary evaporation, neutralized with satd aq $NaHCO_3$, and extracted with diethyl ether (2×200 mL) and ethyl acetate (3×200 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to dryness. The crude product was purified on silica gel and obtained as white crystals (5.8 g, 94%). $[\alpha]_D^{20}$ +122.6 (*c* 1.0, $CHCl_3$). Mp=96–98 °C. IR (cm^{-1}, film): 2989, 2947, 2905, 2886, 2847, 1739, 1606, 1456, 1273, 1247; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.84–2.05 (m, 3H), 2.14–2.30 (m, 1H), 3.06 (br d, 1H, H(2), $J_{2,6}$=8.8), 3.34 (td, 1H, H(6), $J_{6,2}=J_{6,5exo}$=8.8, $J_{6,5endo}$=2.9), 3.48 (s, 3H, OCH_3), 3.53 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.37, 38.79, 49.15, 52.15, 53.05, 57.76, 76.28, 78.19, 114.79, 129.29, 129.51, 214.07; MS (EI, 70 eV, 50 °C): *m*/*z* (%)=347 (0.5), 313 (34), 311 (100), 309 (98), 255 (29), 253 (32), 75 (27), 59 (27); HRMS (EI, 70 eV, 60 °C) calcd for $C_{12}H_{12}{}^{35}Cl_4O_3$ $(M)^+$: 343.9541, found 343.9558. Anal. Calcd for $C_{12}H_{12}Cl_4O_3$: C=41.65%, H=3.50%, found C=41.73%, H=3.34%.

3.10. (1*S*,2*S*,3*R*,4*R*,6*S*,7*R*)-1,7,8,9-Tetrachloro-10,10-dimethoxy-4-methyltricyclo[5.2.1.0^{2,6}]dec-8-en-3-ol (8)

Compound (+)-**1** (6.27 g, 17.4 mmol) was dissolved in methanol (180 mL) and cooled to 0 °C. $NaBH_4$ (1.67 g, 44.1 mmol) was added, and the mixture allowed to warm to room temperature. After 80 min, the reaction was quenched with satd aq NH_4Cl (80 mL), reduced to approx. half the volume by rotary evaporation and extracted with dichloromethane (5×80 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to dryness to afford analytically pure product as

white crystals (6.15 g, 98%). $[\alpha]_D^{20}$ −12.3 (*c* 1.0, acetone). Mp=121–122 °C (racemic: 102 °C). IR (cm^{-1}, film): 3576, 2953, 1608, 1455, 1186, 1110, 991, 909, 751; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.97 (d, 3H, C(4)CH_3, $J_{CH_3,4}$ = 6.9), 1.07 (dt, 1H, H(5β) $J_{5\beta,6}$=10.9, $J_{5,5}$∼$J_{5\beta,4}$= 12.9), 1.28 (d, 1H, OH, $J_{OH,3}$=4.3), 1.74 (dt, 1H, H(5α), $J_{5,5}$=12.5, $J_{5\alpha,6}$∼$J_{5\alpha,4}$∼6.3), 1.88 (ddquin, 1H, H(4), $J_{4,3}$= 4.6, $J_{4,5\beta}$=13.1, $J_{4,5\alpha}$ = J_{4,CH_3} = 6.6), 3.03 (dt, 1H, H(6), $J_{6,2}$=$J_{6,5\beta}$=10.7, $J_{6,5\alpha}$=7), 3.12 (dd, 1H, H(2), $J_{2,6}$=10.6, $J_{2,3}$=5.8), 3.51 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 4.18 (q, 1H, H(3), $J_{3,OH}$∼$J_{3,4}$∼$J_{3,2}$∼5.0); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0, 31.0, 42.1, 52.0, 53.0, 54.9, 59.2, 73.8, 76.8, 78.1, 117.2, 126.8, 133.2; HRMS (EI, 70 eV, 70 °C) calcd for $C_{13}H_{16}{}^{35}Cl_4O_3$ $(M)^+$: 359.9854, found 359.9859.

3.11. (1*R*,3*S*,5*S*,7*S*,8*R*,9*S*,11*R*)-3-Ethoxy-6,6-dimethoxy-11-methyl-2-oxatetracyclo[6.3.0.0^{5,9}]undecane (13)

Sodium (2.0 g, 87 mmol) was added to dry ethanol (315 mL) and stirred until it was consumed. A solution of (−)-**8** (7.0 g, 19.3 mmol) in dry ethanol (110 mL) was then added slowly, and the mixture was heated to reflux for 1 h. More sodium (36.5 g, 1.59 mol) was added in small pieces over 2.5 h, while continuing to reflux. After a further 4 h, the mixture was cooled in ice and quenched with satd aq NH_4Cl (150 mL). The solution was reduced to half the volume by rotary evaporation, then extracted with dichloromethane (3×100 mL) and diethyl ether (3×100 mL). The combined organic layers were dried over $MgSO_4$ and evaporated to dryness. The product was separated by flash chromatography on silica gel (petroleum ether/diethyl ether 4:1) and isolated as a colourless oil (4.30 g, 83%). $[\alpha]_D^{20}$ −14.1 (*c* 1.0, acetone). IR (cm^{-1}, film): 2965, 1464, 1326, 1150, 1110; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.04 (d, 3H, C(11)CH_3, $J_{CH_3,4}$ = 6.8), 1.10 (ddd, 1H, H(10α), $J_{10,10}$=13.5, $J_{10\alpha,11}$= 10.6, $J_{10\alpha,9}$=5.1), 1.20 (t, 3H, H(2′), $J_{2',1'}$=7.1), 1.80 (dt, 1H, H(10β), $J_{10,10}$=13.5, $J_{10\beta,11}$=$J_{10\beta,9}$=9.1), 1.88 (dd, 1H, H(4α), $J_{4,4}$=13.9, $J_{4\alpha,5}$=2.4), 1.95 (dtq, 1H, H(11), $J_{11,10\alpha}$=$J_{11,10\beta}$= 10, J_{11,CH_3} = 6.8, $J_{11,1}$=3.3), 2.10 (m, 2H, H(4β,5)), 2.60 (d, 1H, H(7), $J_{7,8}$=4.7), 2.69 (m, 1H, H(9)), 2.73 (dt, 1H, H(8), $J_{8,9}$=9.5, $J_{8,1}$∼$J_{8,7}$=4–5), 3.51 (s, 3H, OCH_3), 3.52 (dq, 1H, H(1′), $J_{1',1'}$=9.1, $J_{1',2'}$=7.1), 3.56 (s, 3H, OCH_3), 3.69 (dq, 1H, H(1′), $J_{1',1'}$=9.1, $J_{1',2'}$=7.1), 4.12 (t, 1H, H(1), $J_{1,8}$=$J_{1,11}$= 3.3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 16.0, 31.6, 38.1, 41.6, 41.7, 43.0, 49.4, 50.4, 50.9, 52.0, 59.2, 83.9, 114.2, 116.5; MS (EI, 70 eV, 30 °C): *m/z* (%)=268 (100); HRMS (EI, 70 eV, 30 °C) calcd for $C_{15}H_{24}O_4$ $(M)^+$: 268.1675, found 268.1678.

3.12. (1*S*,2*S*,6*S*,7*R*,8*R*)-7-Hydroxy-8-methyl-4-oxobicyclo[4.3.0]non-2-yl-carboxylic acid (14)

Compound (−)-**13** (5.55 g, 20.7 mmol) was dissolved in a mixture of dioxane (95 mL) and 3% aq HCl (60 mL), and heated to reflux for 6 h. The solution was then diluted with water (100 mL) and extracted with ethyl acetate (5×110 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated to afford 4.85 g of a brown solid, which was usually used without further purification. Crude racemic product (±)-**14** was crystallized from petroleum ether/ether yielding colourless crystals. Mp=130–131 °C. IR (cm^{-1}, film): 3468, 2958, 2930, 1708, 1259, 1196; ^1H NMR (400 MHz, $(CD_3)_2SO$) δ (ppm) 0.95 (d, 3H, C(8)CH_3, $J_{CH_3,8}$ = 6.4), 1.25 (m, 1H, H(9β)), 1.83 (m, 2H, H(8,9α)), 2.14 (dd, 1H, H(5β), $J_{5,5}$=15.0, $J_{5\beta,6}$=5.9), 2.16 (dd, 1H, H(3β), $J_{3,3}$=17.5, $J_{3\beta,2}$=9.9), 2.34 (m, 3H, H(5α,6,1)), 2.42 (dd, 1H, H(3α), $J_{3,3}$=17.5, $J_{3\alpha,2}$=4.5), 2.68 (ddd, 1H, H(2), $J_{2,1}$=9.1, $J_{2,3\beta}$=9,8 $J_{2,3\alpha}$=4.3), 3.67 (m, 1H, H(7), $w_{1/2}$=8.4), 4.68 (br s, 1H, OH), 12.28 (br, 1H, COOH); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 14.4, 37.1, 38.2, 38.3, 39.2, 40.4, 41.6, 44.6, 73.8, 76.0, 176.2, 211.3; MS (EI, 70 eV, 30 °C): *m/z* (%)=212 (100), 168 (20); HRMS (EI, 70 eV, 80 °C) calcd for $C_{11}H_{16}O_4$ $(M)^+$: 212.1049, found 212.1052.

3.13. Methyl (1*S*,2*S*,6*S*,7*R*,8*R*)-7-hydroxy-8-methyl-4-oxobicyclo[4.3.0]non-2-yl-carboxylate (15)

Crude **14** (ca. 20 mmol) was dissolved in diethyl ether (80 mL) at 0 °C. Diazomethane solution was added dropwise until the reaction mixture remained yellow, whereupon it was allowed to stir for a further 1 h, while warming to room temperature. A few drops of AcOH were added to destroy any remaining diazomethane, then the solvent was removed by rotary evaporation. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 3:1) to give the product as an oil, which slowly solidified on standing (3.56 g, 76% over two steps). $[\alpha]_D^{20}$ +160.2 (*c* 1.0, acetone). Mp=114 °C (racemic: 85 °C). IR (cm^{-1}, film): 3523, 2954, 1733, 1715, 1198; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.02 (d, 3H, C(8)CH_3, $J_{CH_3,8}$ = 6.5), 1.34 (dt, 1H, H(9β), $J_{9,9}$=$J_{9\beta,8}$=11.8, $J_{9\beta,1}$=7.8), 1.74 (d, 1H, OH, $J_{OH,7}$=3.3), 1.91 (m, 1H, H(8)), 1.99 (dt, 1H, H(9a), $J_{9,9}$=11.8, $J_{9a,8}$∼ $J_{9a,1}$∼7.2), 2.32 (dd, 1H, H(5α), $J_{5,5}$=15.0, $J_{5\alpha,6}$=6.4), 2.34 (dd, 1H, H(3β), $J_{3,3}$=18.0, $J_{3\beta,2}$=10.3), 2.38–2.52 (m, 2H, H(1,6)), 2.55 (dd, 1H, H(3a), $J_{3,3}$=18.0, $J_{3a,2}$=4.6), 2.65 (dd, 1H, H(5β), $J_{5,5}$=15.5, $J_{5\beta,6}$=7.2), 2.85 (ddd, 1H, H(2), $J_{2,1}$=8.9, $J_{2,3\beta}$=10.5, $J_{2,3\alpha}$=4.6), 3.66 (s, 3H, $COOCH_3$), 3.86 (q, 1H, H(7), $J_{7,6}$=$J_{7,8}$=$J_{7,OH}$=3.1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 37.0, 38.4, 38.7, 39.8, 40.8, 42.1, 45.3, 52.3, 73.8, 77.9, 175.2; MS (EI, 70 eV, 30 °C): *m/z* (%)=226 (100); HRMS (EI, 70 eV, 50 °C) calcd for $C_{12}H_{18}O_4$ $(M)^+$: 226.1205, found 226.1209.

3.14. Methyl (1*S*,3*S*,4*S*,6*R*,7*R*,8*S*)-1-(*tert*-butyldimethylsiloxy)-6-methyl-10-oxatricyclo[5.2.1.0^{4,8}]-dec-3-yl-carboxylate (16)

Compound (+)-**15** (3.38 g, 14.9 mmol) was dissolved in dry dichloromethane (400 mL) containing triethylamine (6.4 mL) and the solution was cooled to −50 °C. TBSOTf (4.5 mL, 18 mmol) was added slowly by syringe. After 30 min, the reaction was quenched with satd aq NH_4Cl (150 mL). The aq layer was extracted with diethyl ether (4×90 mL) and the combined organic layers were washed with satd aq $NaHCO_3$ (150 mL) and brine (100 mL), and dried over $MgSO_4$. The solvent was removed by rotary evaporation to give a pale yellow oil that slowly crystallized on standing. It may be purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 30:1) or used directly in the next step. $[\alpha]_D^{20}$ −25.1 (*c* 1.0, acetone). Mp=62–64 °C. IR (cm^{-1}, film): 2954, 2893, 2857, 1735, 1194, 1178; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.00 (s, 3H, $SiCH_3$), 0.02 (s, 3H, $SiCH_3$), 0.78 (s, 9H, Si*t*-Bu), 0.93 (d, 3H, C(6)CH_3, $J_{CH_3,6}$ = 6.8), 1.07 (ddd, 1H, H(5), $J_{5,5}$=12.9, $J_{5,6}$=10.8, $J_{5,4}$=6.3), 1.56 (ddd, 1H, H(9), $J_{9,9}$=12.1, $J_{9,8}$=3.3, J_{lr}=2.53), 1.64 (m, 1H, H(9), $J_{9,9}$=12.1, $J_{9,8}$∼J_{lr}∼ 1–2), 1.76 (m, 1H, H(6), $J_{6,5}$=10.9, $J_{6,5}$∼9.6, J_{6,CH_3} = 6.8,

$J_{6,7}$=2.5), 2.06 (dt, 1H, H(5) $J_{5,5}$=12.9, $J_{5,6}$~$J_{4,5}$~9.2), 2.06–2.13 (m 1H, H(2), $J_{2,2}$=14.4, $J_{2,3}$=9.6, J~1.5), 2.27 (m, 1H, H(3) $J_{3,2}$=9.6, $J_{3,4}$~$J_{3,2}$~1–2), 2.38 (m, 1H, H(2), $J_{2,2}$=14.4, $J_{2,3}$~J_{lr}~1–3), 2.47 (m, 1H, H(8), $J_{8,4}$=9.6, $J_{8,9}$~3.5, $J_{8,7}$=2.5, $J_{8,9}$~1.3), 2.79 (m, 1H, H(4), $J_{4,5}$~$J_{4,8}$~9.6, $J_{4,5}$=6.32, $J_{4,3}$~J_{lr}~1–2), 3.60 (s, 3H, OCH_3), 3.96 (t, 1H, H(7), $J_{7,6}$~$J_{7,8}$~2.5); ^{13}C NMR (100 MHz, $CDCl_3$) δ −2.9, −2.8, 14.7, 17.9, 26.05, 36.7, 37.4, 38.3, 38.9, 39.9, 43.3, 45.5, 52.0, 86.25, 106.3, 176.8; MS (EI, 70 eV, 30 °C): *m/z* (%)=340 (30), 284 (22), 283 (100), 255 (10), 225 (30), 223 (36), 151 (14), 131 (14), 115 (11), 91 (11), 89 (12), 77 (11), 75 (46), 73 (54), 59 (17); HRMS (EI, 70 eV, 30 °C) calcd for $C_{18}H_{32}O_4Si$ $(M)^+$: 340.2070, found 340.2077. Anal. Calcd for $C_{18}H_{32}O_4Si$: C=63.49%, H=9.47%, found C=63.68%, H=9.29%.

3.15. (1*R*,3*S*,4*R*,6*R*,7*R*,8*S*)-3-(Hydroxymethyl)-6-methyl-1-(*tert*-butyldimethylsiloxy)-10-oxatricyclo-[5.2.1.0^{4,8}]decane (17)

$LiAlH_4$ (0.70 g, 18.5 mmol) was suspended in dry diethyl ether (45 mL). A solution of (−)-**16** (crude product from previous reaction ca. 14.9 mmol) in dry diethyl ether (8 mL) was added slowly by syringe, and the mixture stirred at room temperature. After 3 h, satd aq NH_4Cl (50 mL) was added, and the phases separated. The aq layer was extracted with diethyl ether (4×40 mL). The combined organic layers were washed with brine (50 mL) and dried over $MgSO_4$. The solution was then evaporated to dryness to give the analytically pure product as a colourless, highly viscous oil (4.28 g, 92% over two steps). IR (cm^{-1}, film): 3306 (br), 2952, 2894; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.10 (s, 3H, $SiCH_3$), 0.12 (s, 3H, $SiCH_3$), 0.90 (s, 9H, Si*t*-Bu), 1.05 (d, 3H, C(6)CH_3, $J_{CH_3,6}$ = 7.1), 1.21 (m, 1H, H(5)), 1.38 (m, 1H, OH), 1.77–1.69 (m, 3H, H(9), H(3), H(2)), 1.86 (m, 1H, H(9), $J_{9,9}$=11.6, $J_{9,8}$~J_{lr}~1–2), 1.91 (m, 1H, H(6)), 2.11 (m, 1H, H(2), $J_{2,2}$=14.4, $J_{2,3}$=10.6, J_{lr}=2.5), 2.27–2.17 (m, 2H, H(4), H(5)), 2.50 (m, 1H, H(8), $J_{8,4}$=8.3, $J_{8,9}$~$J_{8,9}$~4.2, J>1), 3.55 (m, 2H, CH_2O), 4.12 (t, 1H, H(7), $J_{7,6}$~$J_{7,8}$~2.9); ^{13}C NMR (100 MHz, $CDCl_3$) δ −2.9, −2.8, 15.1, 17.9, 26.1, 36.65, 38.2, 38.3, 40.7, 41.7, 43.4, 46.5, 68.8, 87.1, 106.7; HRMS (EI, 70 eV, 30 °C) calcd for $C_{17}H_{32}O_3Si$ $(M)^+$: 312.2121, found 312.2116. Anal. Calcd for $C_{17}H_{32}O_3Si$: C=65.33%, H=10.32%, found C=65.34%, H=10.24%.

3.16. (1*R*,3*S*,4*R*,6*R*,7*R*,8*S*)-1-(*tert*-Butyldimethylsiloxy)-3-(2,4-dioxapentyl)-6-methyl-10-oxatricyclo[5.2.1.0^{4,8}]-decane (18)

Compound **17** (4.27 g, 13.7 mmol) was dissolved in dry dichloromethane (360 mL). Hünig's base (11.9 mL, 68.4 mmol) was added, followed by MOMCl (3.1 mL, 41.1 mmol). After 3 h, the reaction was quenched with satd aq NH_4Cl (100 mL). The aq phase was extracted with dichloromethane (4×45 mL) and the combined organic layers were washed with satd aq $NaHCO_3$ (60 mL) and brine (60 mL). The solvent was removed and the resulting yellow residue was purified on a short column of silica gel (petroleum ether/ethyl acetate 10:1) to give the product as a colourless oil (4.8 g, 98%). $[\alpha]_D^{20}$ −6.0 (*c* 1.0, acetone). IR (cm^{-1}, film): 2929, 1461, 1344, 1247, 1168, 1110, 986; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) −0.02 (s, 3H, $SiCH_3$), 0.00 (s, 3H, $SiCH_3$), 0.76 (s, 9H, Si*t*-Bu), 0.94 (d, 3H, C(6)CH_3, $J_{CH_3,6}$ = 6.8), 1.11 (m, 1H, H(5)), 1.62 (ddd, 1H, H(9), $J_{9,9}$=11.6, $J_{9,8}$=3.5, J_{lr}=2.5), 1.63 (dd, 1H, H(2), $J_{2,2}$=14.3, $J_{2,3}$=2.4), 1.73 (m, 1H, H(3), $J_{3,2}$=9.5, $J_{3,1'}$=7.8, $J_{3,1'}$=7.6, $J_{3,2}$=2.3, J_{lr}=2.5), 1.78 (d, 1H, H(9), $J_{9,9}$=11.1), 1.79 (m, 1H, H(6), J_{6,CH_3} = 6.8, $J_{6,5}$~9, $J_{6,7}$=3), 2.00 (m, 1H, H(2) $J_{2,2}$=14.4, $J_{2,3}$=10.1, J_{lr}=2.3), ~2.07 (m, 1H, H(4)), 2.09 (m, 1H, H(5), $J_{5,5}$~$J_{5,6}$~$J_{5,4}$~9–10), 2.38 (m, 1H, H(8), $J_{8,4}$=8.6, $J_{8,9}$~3, $J_{8,7}$=3, $J_{8,9}$~1), 3.25 (s, 3H, OCH_3), 3.30 (ABX-system, 1H, H(1′), $J_{1',1'}$=9.35, $J_{1',3}$=7.6), 3.35 (ABX, 1H, H(1′), $J_{1',1'}$=9.35, $J_{1',3}$=7.8), 4.00 (t, 1H, H(7), $J_{7,6}$~$J_{7,8}$~2.9), 4.50 (s, 2H, OCH_2O); ^{13}C NMR (100 MHz, $CDCl_3$) δ −2.9, −2.8, 15.1, 17.9, 26.1, 37.2, 38.15, 38.3, 40.3, 41.1, 41.6, 46.4, 55.2, 73.95, 87.1, 96.5, 106.7; MS (EI, 70 eV, 30 °C): *m/z* (%)=356, 299 (73), 281 (41), 267 (27), 253 (44), 239 (21), 237 (34), 225 (55), 175 (38), 147 (26), 145 (33), 121 (33), 93 (34), 75 (68), 73 (100); HRMS (EI, 70 eV, 40 °C) calcd for $C_{19}H_{36}O_4Si$ $(M)^+$: 356.2383, found 356.2397.

3.17. (1*R*,2*S*,6*S*,7*R*,8*S*)-2-(2,4-Dioxapentyl)-8-methylbicyclo[4.3.0]nonan-4-on-7-ol (19)

Compound (−)-**18** (4.77 g, 13.38 mmol) was dissolved in dry THF (200 mL) and TBAF (26 mL, 1 M solution in THF, 26 mmol) was added. After 1 h, the solution was diluted with water (150 mL), and the layers were separated. The aq layer was extracted with diethyl ether (4×100 mL) and ethyl acetate (100 mL), and the combined organic layers were washed with satd aq $NaHCO_3$ (180 mL) and brine (120 mL) and dried over $MgSO_4$. The product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 2:1) to give a colourless oil (3.21 g, 99%). $[\alpha]_D^{20}$ +190 (*c* 1.0, acetone). IR (cm^{-1}, film): 3473, 2926, 1713, 1455, 1040; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.04 (d, 1H, CH_3(8)), 1.3 (m, 1H, H(9)), 1.80–2.04 (m, 4H, H(1,3,8,9)), 2.1 (m, 1H, H(2)), 2.28 (dd, 1H, H(5), $J_{5,5}$=14.65, $J_{5,6}$=6.8), 2.36 (tdd, 1H, H(6), $J_{6,5}$=$J_{6,1}$=9.8, $J_{6,5}$=6.8, $J_{6,7}$=3.3), 2.49 (dd,1H, H(3), $J_{3,3}$=17.0, $J_{3,2}$=3.2), 2.74 (dd, 1H, H(5), $J_{5,5}$=14.6, $J_{5,6}$=9.8), 3.31 (3H, s, CH_3O), 3.34 (dd, 1H, H(1′), $J_{1',1'}$=9.6, $J_{1',2}$=6.2), 3.49 (dd, 1H, H(1′), $J_{1',1'}$=9.6, $J_{1',2}$=3.3), 3.86 (t, 1H, H(7), $J_{7,8}$=$J_{7,6}$=3.3), 4.54 (AB-system, 1H, H(1′), J_{AB}=6.75), 4.57 (AB-system, 1H, H(1′), J_{AB}=6.75); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 36.6, 38.1, 38.5, 39.6, 40.2, 42.1, 42.4, 55.2, 70.0, 77.2, 96.5, 214.4; MS (EI, 70 eV, 30 °C): *m/z* (%)=242 (<1), 224 (4), 211 (7), 197 (6), 180 (83), 167 (65), 149 (47), 139 (30), 137 (21), 129 (47), 121 (67), 107 (100), 95 (33), 93 (47), 84 (39), 79 (35); HRMS (EI, 70 eV, 70 °C) calcd for $C_{13}H_{22}O_4$ $(M)^+$: 242.1518, found 242.1521. Anal. Calcd for $C_{13}H_{22}O_4$: C=64.43%, H=9.13%, found C=64.44%, H=9.15%.

3.18. (1*R*,2*S*,6*S*,7*R*,8*R*)-2-(2,4-Dioxapentyl)-8-methyl-7-(triethylsiloxy)bicyclo[4.3.0]nonan-4-one (20)

Compound (+)-**19** (2.2 g, 9.1 mmol) and imidazole (1.23 g, 18 mmol) were dissolved in dry DMF (160 mL). Fresh TESCl (2.3 mL, 13.6 mmol) was added by syringe, and the solution was stirred under nitrogen at room temperature. After 2.5 h, the solution was diluted with water (200 mL) and extracted with toluene (3×200 mL). The combined organic layers were washed with brine (200 mL) and dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The crude product was purified by flash chromatography on

silica gel (petroleum ether/ethyl acetate 10:1) to give a colourless oil (2.9 g, 90%). $[\alpha]_D^{20}$ +124.5 (*c* 1.0, acetone). IR (cm^{-1}, film): 2955, 2877, 2823, 1715; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.98 (q, 6H, Si(CH_2CH_3)$_3$, *J*=8.0), 0.98 (t, 9H, Si(CH_2CH_3)$_3$, *J*=8.0), 1.04 (d, 3H, C(8)CH_3, $J_{CH_3,8}$ = 6.3), 1.35 (ddd, 1H, H(9*endo*), J_{gem}= 14.5, *J*=13.3, *J*=8.1), 1.84–2.06 (m, 3H, H(1,8,9*exo*)), ≈2.03 (d, 1H, H(3*endo*), J_{gem}∼17, $J_{3endo,2}$∼4.7), ≈2.08 (m, 1H, H(2), $J_{2,1'}$≈3.3, $J_{2,1'}$=6.3, $J_{2,3exo}$=2.8, $J_{2,3}$=4.7), 2.24 (dd, 1H, H(5*exo*), J_{gem}=14.4, $J_{5exo,6}$=6.6), 2.35 (tdd, 1H, H(6), $J_{6,5endo}$=10.9, $J_{6,1}$=10.6, $J_{6,5exo}$=6.5, $J_{6,7}$∼4.3), 2.56 (dd, 1H, H(3*exo*), J_{gem}=17.2, $J_{3exo,2}$=2.8), 2.69 (dd, 1H, H(5*endo*), J_{gem}=14.4, $J_{5endo,6}$=11.1), 3.36 (s, 3H, OCH_3), 3.36 (dd, 1H, H(1′), J_{gem}=9.6, $J_{2,1'}$=6.3), 3.55 (dd, 1H, H(1′), J_{gem}=9.6, $J_{2,1'}$=3.3), 3.98 (dd, 1H, H(7), $J_{6,7}$∼ $J_{7,8}$∼3.7), 4.60 (A-part of AB-system, 1H, OCH_2O, J_{gem}= 6.6), 4.62 (B-part of AB-system, 1H, OCH_2O, J_{gem}=6.6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.2, 7.05, 14.6, 36.6, 38.1, 39.4, 40.3, 42.3, 42.6, 55.2, 70.1, 78.0, 96.5, 214.7; MS (EI, 70 eV, 30 °C): *m*/*z* (%)=327 (100), 295 (36), 175 (19), 145 (24), 103 (25), 75 (22); HRMS (EI, 70 eV, 60 °C) calcd for $C_{17}H_{31}O_4Si$ $(M-C_2H_5)^+$: 327.1992, found 327.1998.

3.19. (1*R*,2*S*,6*S*,7*R*,8*R*)-2-(2,4-Dioxapentyl)-8-methyl-7-(triethylsiloxy)bicyclo[4.3.0]non-3-ene (21)

Compound (+)-**20** (0.48 g, 1.35 mmol) and freshly prepared [(2,4,6-triisopropylphenyl)sulfonyl]hydrazide (trisylhydrazine) (0.45 g, 1.5 mmol) were dissolved in dry diethyl ether (6 mL) at 0 °C. The solution was stirred at 0 °C for 1 h, then at room temperature in the dark overnight. The solvent was then removed by rotary evaporation at room temperature, and the resulting foam was dried under vacuum for 1 h. The residue was then dissolved in dry THF (6 mL) and cooled to −78 °C. *s*-BuLi (3.1 mL, 1.3 M solution in cyclohexane, 4.05 mmol) was added, producing a bright orange colour. The solution was stirred at −78 °C for 1 h, then allowed to warm to room temperature and stirred for a further 0.5 h, before being quenched with satd aq NH_4Cl (8 mL). The mixture was extracted with ethyl acetate (4×10 mL) and the combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$. The crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 10:1) to give a colourless oil (0.33 g, 72%). $[\alpha]_D^{20}$ +90.6 (*c* 1.035, acetone). IR (cm^{-1}, film): 2954, 2876, 1458, 1150, 1112, 1047; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.52 (q, 6H, Si(CH_2CH_3), *J*=8.0), 0.89 (t, 9H, Si(CH_2CH_3)$_3$, *J*=8.0), 0.90 (d, 3H, C(8)CH_3, $J_{CH_3,8}$ = 7.1), 1.14 (ddd, 1H, H(9), J_{gem}=11.6, *J*=10.9, *J*=9.6), 1.78 (m, 1H, H(1)), 1.83 (ddd, 1H, H(9), J_{gem}=11.6, *J*=8.0, *J*=7.3), 1.90–2.02 (m, 4H, H(5,5,6,8)), 2.06 (m, 1H, H(2), $w_{1/2}$= 15), 3.30 (s, 3H, OCH_3), 3.37 (d, 2H, H(1′), $J_{1',2}$=6.1), 4.01 (dd, 1H, H(7), *J*=6.8, *J*=4.5), 4.57 (s, 2H, OCH_2O), 5.60 (ddt, 1H, H(3), $J_{3,4}$=10.1, *J*∼3, *J*=*J*=1.5), 5.75 (dddd, 1H, H(4), $J_{4,3}$=10.1, *J*=4.5, *J*=3, *J*∼2.4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.1, 7.0, 16.6, 22.6, 36.4, 37.4, 37.9, 39.8, 40.2, 55.1, 71.4, 77.5, 96.5, 127.6, 127.7; MS (EI, 70 eV, 30 °C): *m*/*z* (%)=311 (6), 250 (16), 249 (77), 205 (21), 147 (51), 146 (100), 145 (50), 133 (42), 131 (41), 117 (39), 115 (22), 105 (44), 103 (47), 91 (80), 87 (33), 75 (48); HRMS (EI, 70 eV, 30 °C) calcd for $C_{19}H_{36}O_3Si$ (M^+): 340.2434, found 340.2437. Anal. Calcd for $C_{19}H_{36}O_3Si$: C=67.01%, H= 10.65%, found C=67.25%, H=10.70%.

3.20. (1*R*,2*S*,6*S*,7*R*,8*R*)-2-(Hydroxymethyl)-8-methyl-7-(triethylsiloxy)bicyclo[4.3.0]non-3-ene (22)

Compound (+)-**21** (1.3 g, 3.8 mmol), $MgBr_2$ (3.5 g, 19 mmol; prepared from 1,2-dibromoethane and magnesium in dry ether) and BuSH (1.0 mL, 9.5 mmol) were dissolved in dry diethyl ether (50 mL) and stirred rapidly for 6 h at room temperature. The mixture was then quenched with ice-cold water (40 mL). The separated aq layer was extracted with ethyl acetate (4×40 mL) and the combined organic layers were dried over $MgSO_4$. The residue was separated by flash chromatography on silica gel (petroleum ether/ethyl acetate 8:1) to give the product as a colourless oil (0.70 g, 62%) and a small amount of recovered starting material (0.13 g, 10%). $[\alpha]_D^{20}$ +63.7 (*c* 0.3, $CHCl_3$). IR (cm^{-1}, film): 3350, 3017, 2876; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.59 (q, 6H, SiCH_2CH_3, *J*=7.9), 1.01 (t, 9H, $SiCH_2CH_3$, *J*=7.9), 1.25 (br, 1H, H(9)), 1.80–1.96 (m, 2H, H(9,1)), 2.00–2.12 (m, 5H, H(2,5,5,6,8)), 3.55 (m, 2H, H(1′,1′)), 4.12 (dd, 1H, H(7), *J*=7.3, *J*=5), 5.66 (m, 1H, H(3)), 5.84 (m, 1H, H(4)); ^1H NMR (400 MHz, C_6D_6) δ (ppm) 0.58 (q, 6H, SiCH_2CH_3, *J*=7.94), 1.00 (t, 9H, $SiCH_2CH_3$, *J*=7.94), 1.06 (d, 3H, CH_3(8), $J_{CH_3,8}$ = 6.8), 1.24 (m, 1H, H(9), $J_{9,9}$∼$J_{9,8}$∼$J_{9,1}$∼9–11.7), 1.77–1.84 (m, 2H, H(9,1)), 1.91 (m, 1H, H(8), $J_{8,9}$=10.2, $J_{8,9}$=7.55, $J_{8,7}$= 7.17, J_{8,CH_3} = 6.8), 1.97 (m, 1H, H(2), $w_{1/2}$=15.8), 2.00–2.06 (m, 2H, H(5,6)), 2.115 (m, 1H, H(5), $J_{5,5}$∼20, $J_{5,6}$∼10.95, $J_{5,4}$∼$J_{5,3}$∼$J_{5,2}$∼2.65), 3.345 (d, 2H, H(1′,1′), $J_{1',2}$=5.67), 3.975 (dd, 1H, H(7), $J_{7,8}$=7.17, $J_{7,6}$=4.53), 5.645 (m, 1H, H(3), $J_{3,4}$∼10.19, J_3∼3.78, J_3∼2.65, J_3∼1.13), 5.83 (m, 1H, H(4), $J_{4,3}$∼9.82, $J_{4,5}$∼$J_{4,5}$∼$J_{4,2}$∼$J_{4,6}$∼2.26–2.55); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.4, 7.4, 17.3, 22.9, 36.5, 37.3, 38.6, 40.5, 42.4, 67.0, 77.7, 126.9, 129.2; MS (EI, 70 eV, 30 °C): *m*/*z* (%)=296 (3), 278 (1), 267 (25), 249 (50), 147 (61), 146 (75), 133 (69), 131 (39), 105 (79), 103 (47), 91 (100), 79 (45); HRMS (EI, 70 eV, 30 °C) calcd for $C_{17}H_{30}O_2Si$ $(M)^+$: 296.2172, found 296.2168. NOESY crosspeak 1′/6 confirms the *exo*-position of the hydroxymethyl group.

3.21. (1*R*,2*S*,6*S*,7*R*,8*R*)-2-Formyl-8-methyl-7-(triethylsiloxy)bicyclo[4.3.0]non-3-ene (23)

Freshly prepared Dess–Martin periodinane (300 mg, 0.71 mmol) was added to a solution of **22** (60 mg, 0.2 mmol) in dry dichloromethane (6 mL) and stirred rapidly at room temperature. After starting material was consumed (usually <1 h), the reaction was quenched with a 3:1 mixture (10 mL) of satd aq $Na_2S_2O_3$ and satd aq $NaHCO_3$. The mixture was extracted with diethyl ether (3×10 mL), and the combined organic layers were dried over $MgSO_4$. The solvent was removed by rotary evaporation and the residue was dried under vacuum and used without further purification. $[\alpha]_D^{20}$ +74.4 (*c* 0.35, $CHCl_3$). IR (cm^{-1}, film): 2938, 2730, 1725, 1691, 1585sh; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.55 (q, 6H, SiCH_2CH_3, *J*=8), 0.97 (t, 9H, $SiCH_2CH_3$, *J*=8), 0.99 (d, 3H, CH_3(8), $J_{CH_3,8}$ = 6.9), 1.1 (dt, 1H, H(9), $J_{9,9}$=12.5, $J_{9,8}$∼$J_{9,1}$∼9.8), 1.77 (ddd, 1H, H(9), $J_{9,9}$=12.2, *J*∼8.3, *J*∼7.2), 1.78–2.05 (m, 4H, H(5,5,6,8)), 2.07 (m, 1H, H(1), $J_{1,9}$=9.9, $J_{1,9}$∼*J*∼7.5, *J*∼5), 2.59 (m, 1H, H(2), $w_{1/2}$=10.1), 3.89 (dd, 1H, H(7), *J*=6.85, *J*=4.75), 5.67 (m, 1H, H(3), $J_{3,4}$=9.9), 5.81 (m, 1H, H(4), $J_{4,3}$=9.9, $J_{4,5}$=4.6, $J_{4,5}$=$J_{4,2}$=2.7), 9.41 (s, 1H, H(1′), $J_{1',2}$=1.5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.8, 7.4, 17.0, 22.9, 34.0, 37.7,

38.1, 40.6, 53.7, 78.0, 121.0, 130.6, 202.4; MS (EI, 70 eV, 30 °C): *m/z* (%)=294 (6.6) [M^+], 265 (32) [M^+-HCO], 162 (20) [$M^+-OSiEt_3$], 145 (65.5), 131 (39), 103 (100), 75 (80), 59 (52); HRMS (EI, 70 eV, 30 °C) calcd for $C_{17}H_{28}O_2Si$ $(M)^+$: 294.2015, found 294.2007.

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References and notes

1. Jackson, M.; Karwowski, J. P.; Theriault, R. J.; Rasmussen, R. R.; Hensey, D. M.; Humphrey, P. E.; Swanson, S. J.; Barlow, G. J.; Premachandran, U.; McAlpine, J. B. *J. Antibiot.* **1995**, *48*, 462–466.
2. Hochlowski, J. L.; Mullaly, M. M.; Henry, R.; Whittern, D. M.; McAlpine, J. B. *J. Antibiot.* **1995**, *48*, 467–470.
3. Tanaka, M.; Nara, F.; Yamasato, Y.; Masuda-Inoue, S.; Doi-Yoshioka, H.; Kumakura, S.; Enokita, R.; Ogita, T. *J. Antibiot.* **1999**, *52*, 670–673.
4. Munakata, R.; Katakai, H.; Ueki, T.; Kurosaka, J.; Takao, K.; Tadano, K. *J. Am. Chem. Soc.* **2003**, *125*, 14722–14723; Munakata, R.; Katakai, H.; Ueki, T.; Kurosaka, J.; Takao, K.; Tadano, K. *J. Am. Chem. Soc.* **2004**, *126*, 11254–11267; Takao, K.-i.; Munakata, R.; Tadano, K.-i. *Chem. Rev.* **2005**, *105*, 4779–4807, esp. 4800–4801.
5. Preliminary publication of the hydrindene part of the macquarimicins: (a) Kalb, R. Versuche zur Synthese der Macquarimicine. Diploma Work, Universität Wien, 1998; (b) Schwaiger, J.; Pflugseder, K.; Grünberger, K.; Gössinger, E., 37th IUPAC Congress, Frontiers in Chemistry, Berlin, 1999; (c) Orglmeister, E. Versuche zur Synthese des Cochleamycin B. Diploma Work, Universität Wien, 2002.
6. Preceding paper: Chrobok, A.; Gössinger, E.; Orglmeister, E.; Pflugseder, K.; Schwaiger, J.; Wuggenig, F. *Tetrahedron* **2007**, *63*, 8311–8325.
7. Böhm, K.; Gössinger, E.; Müller, R. *Tetrahedron* **1989**, *45*, 1391–1408.
8. Zimmerman, H. E.; Cheng, J. *Org. Lett.* **2005**, *7*, 2595–2597 and literature cited therein; Zimmerman, H. E. *Acc. Chem. Res.* **1987**, *20*, 263–268.
9. Bredereck, H.; Jaus, H.; Kantlehner, W.; Kienitz, L. *Liebigs Ann. Chem.* **1979**, 2096–2113; Bredereck, H.; Wagner, F.; Kantlehner, W. *Liebigs Ann. Chem.* **1980**, 344–357; Uskokovic, M. R.; Lewis, R. L.; Partridge, J. J.; Despreaux, C. W.; Pruess, D. L. *J. Am. Chem. Soc.* **1979**, *101*, 6742–6744; Lögers, M.; Overman, L. E.; Welmaker, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 9139–9150; Bredereck, H.; Simchen, G.; Wahl, R. *Chem. Ber.* **1968**, *101*, 4048–4056.
10. Ziegler, F. E.; Fang, J. M. *J. Org. Chem.* **1981**, *46*, 825–827; Kakiuchi, K.; Nakamura, I.; Matsuo, F. *J. Org. Chem.* **1995**, *60*, 3318–3333.
11. Desimoni, G.; Tacconi, G. *Chem. Rev.* **1975**, *75*, 651–692; Desimoni, G.; Astolfi, L.; Cambieri, M.; Gamba, A.; Tacconi, G. *Tetrahedron* **1973**, *29*, 2627–2634; Colonge, J.; Descotes, G. *Organic Chemistry*; Hamer, J., Ed.; Academic: New York, NY, 1967; Vol. 8; Chapter 8, pp 217–224; Bolon, D. A. *J. Org. Chem.* **1970**, *35*, 715–717; McRae, K. J.; Rizzacasa, M. A. *J. Org. Chem.* **1997**, *62*, 1196–1197; Mühlstädt, M.; Gensrich, H.-J. *J. Prakt. Chem.* **1966**, *34*, 139–144; Winterfeldt, E. *Liebigs Ann. Chem.* **1986**, 465–478; Caine, D.; Stanhope, B. *Tetrahedron* **1992**, *48*, 33–44; Letulle, M.; Guenot, P.; Ripoll, J. L. *Tetrahedron Lett.* **1991**, *32*, 2013–2016; Gardner, P. D.; Sarrafizadeh, R. H.; Brandon, R. L. *J. Am. Chem. Soc.* **1959**, *81*, 5515; Mao, Y. L.; Boekelheide, V. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 1732–1735; Keiko, N. A.; Stepanova, L. G.; Vainberg, N. N.; Bannikova, O. B.; Voronkov, M. G. *J. Org. Chem. USSR (Engl. Transl.)* **1983**, 419–423; Keiko, N. A.; Stepanova, L. G.; Sarapulova, G. I.; Vashchenko, A. V.; Larina, L. I.; Funtikova, E. A.; Voronkov, M. G. *Russ. Chem. Bull.* **1999**, *48*, 1997–1998; *Russ. Chem. Bull.* **2000**, *49*, 1977–1980; *Izv. Akad. Nauk, Ser. Khim.* **1999**, *10*, 2020–2021; *Izv. Akad. Nauk, Ser. Khim.* **2000**, *12*, 2009–2013; Laitalainen, T.; Kuronen, P.; Hesso, A. *Org. Prep. Proced. Int.* **1993**, *25*, 597–599; Berthelette, C.; McCooye, C.; Leblanc, Y.; Trimble, L. A.; Tsou, N. N. *J. Org. Chem.* **1997**, *62*, 4339–4342; Jorgensen, K. A. *J. Org. Chem.* **2004**, *62*, 2093–2102; Thongsornkleeb, C.; Danheiser, R. L. *J. Org. Chem.* **2005**, *62*, 2364–2367; Biosynthetic examples: Oikawa, H.; Tokiwano, T. *Nat. Prod. Rep.* **2004**, *21*, 328–330; Huang, S.-X.; Xiao, W. L.; Li, L.-M.; Li, S.-H.; Zhou, Y.; Ding, L.-S.; Lou, L.-G.; Sun, H.-D. *Org. Lett.* **2006**, *8*, 1157–1160, here the authors demonstrated that the biosynthetic hetero-Diels–Alder reaction forming a dihydropyrane cannot be repeated biomimetically without enzymatic catalysis!
12. Gras, J. L. *Tetrahedron Lett.* **1978**, *24*, 2111–2114; 2955–2958; Gras, J. L. *Org. Synth., Coll. Vol. VII* **1990**, 332–334; Disanayaka, B. W.; Weedon, A. C. *Synthesis* **1983**, 952.
13. Balko, T. W.; Fields, S. C.; Webster, J. D. *Tetrahedron Lett.* **1999**, *24*, 6347–6350; Waring, A. J.; Zaidi, J. H.; Pilkington, J. W. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1454–1459.
14. Konovalov, A. J.; Samuilov, Y. D.; Slepova, L. F.; Breus, V. A. *J. Org. Chem. USSR* **1973**, *9*, 2539–2541; Schuhbauer, H. Reaktivitäts-Studien an polyhalogenierten Cyclopentadienen: Übergänge von normalen über neutrale zu inversen Diels–Alder-Reaktionen. Ph.D. thesis, Universität Regensburg, 1995.
15. (a) Weber, K. Versuche zur Synthese der Coronafacinsäure. Diploma Work, Universität Wien, 1995; (b) See Ref. 5a; (c) Schwaiger, J. Towards EPC-syntheses of the structural class of Cochleamycins and Macquarimicins. Planned Ph.D. thesis, Universität Wien.
16. Livinghouse, T.; Stevens, R. V. *J. Am. Chem. Soc.* **1978**, *100*, 6479–6482; Bunnelle, W. H.; Isbell, T. A. *J. Org. Chem.* **1992**, *57*, 729–740.
17. Of the many preparations described in the literature we examined the following: Fukazawa, T.; Hashimoto, T. *Tetrahedron: Asymmetry* **1993**, *4*, 2323–2326; Fukazawa, T.; Shimoji, T.; Hashimoto, T. *Tetrahedron: Asymmetry* **1996**, *7*, 1649–1658; Kabat, M. M.; Kiegiel, J.; Cohen, N.; Toth, K.; Wovkulich, P. M.; Uskokovic, M. R. *J. Org. Chem.* **1996**, *62*, 118–124; Schinzer, D.; Bärmann, H. *Angew. Chem.* **1996**, *108*, 1825–1827.
18. (1*S*,4*R*)-4-Acetoxycyclopent-2-enol is commercially available and can be easily prepared: (a) Kaneko, C.; Sugimoto, A.; Tanaka, S. *Synthesis* **1974**, 876–877; (b) Dols, P. M. A.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron* **1994**, *28*, 8515–8538; (c) Theil, F.; Ballschuh, S.; Schick, H.; Haupt, M.; Häfner, B.; Schwarz, S. *Synthesis* **1988**, 540–541; (d) Johnson, C. R.; Bis, S. J. *Tetrahedron Lett.* **1992**, *33*, 7287–7290; (e) Zürcher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem.*

Soc. **1996**, *118*, 6634–6640; (f) Kalkote, U. R.; Ghorpade, S. R.; Joshi, R. R.; Ravindranathan, T.; Bastawade, K. B.; Gokhale, D. V. *Tetrahedron: Asymmetry* **2000**, *11*, 2965–2970; (g) Ghorpade, S. R.; Kharul, R. K.; Joshi, R. R.; Kalkote, U. R.; Ravindranathan, T. *Tetrahedron: Asymmetry* **1999**, *10*, 891–899.

19. Curran, T. T.; Hay, D. A.; Koegel, C. P. *Tetrahedron* **1994**, *28*, 8515–8538; Curran, T. T.; Hay, D. A.; Koegel, C. P. *Tetrahedron* **1997**, *53*, 1983–2004.
20. Haller, J.; Niwayama, S.; Duh, H. Y.; Houk, K. N. *J. Org. Chem.* **1997**, *62*, 5728–5731.
21. (a) Recent reviews about diastereofacial selectivity in Diels–Alder reaction: Coxon, J. M.; Froese, R. D. J.; Ganguly, B.; Marchand, A. P.; Morokuma, K. *Synlett* **1999**, 1681–1703; Marchand, A. P.; Coxon, J. M. *Acc. Chem. Res.* **2002**, *35*, 271–277; Mehta, G.; Uma, R. *Acc. Chem. Res.* **2000**, *33*, 278–286; (b) See Ref. 18b; The authors described dienophiles similar to ours in normal Diels–Alder reaction and the high influence of the vicinal silylether function.
22. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: Chichester, UK, 1991; p 73; Roush, W. R.; Russo-Rodriquez, S. *J. Org. Chem.* **1987**, *52*, 598–603.
23. Cusack, N. J.; Reese, C. B.; Risius, A. C.; Roozepeikar, B. *Tetrahedron* **1976**, *32*, 2157–2160; Shapiro, R. H. *Org. React.* **1976**, *23*, 405–507; Shapiro, R. H.; Heath, M. J. *J. Am. Chem. Soc.* **1967**, *89*, 5734–5735; Roy, O.; Pattenden, G.; Pryde, D. C.; Wilson, C. *Tetrahedron* **2003**, *59*, 5115–5121; Regiochemistry: Chamberlin, A. R.; Blum, S. H. *Org. React.* **1990**, *39*, 1–83; Corey, E. J.; Enders, D. *Chem. Ber.* **1978**, *111*, 1337–1361; Hydrazone derivatives with high structural tolerance: Kolonko, K. J.; Shapiro, R. H. *J. Org. Chem.* **1978**, *43*, 1404–1408; Mohamadi, F.; Collum, D. B. *Tetrahedron Lett.* **1984**, *25*, 271–274; Sarkar, T. K.; Ghorai, B. K. *J. Chem. Soc., Chem. Commun.* **1992**, 1184–1185; Maruoka, K.; Oishi, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 2289–2290.
24. Kim, S.; Kee, I. S.; Park, Y. H.; Park, J. H. *Synlett* **1991**, 183–184; *Tetrahedron Lett.* **1991**, *32*, 3099–3102.
25. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156; Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.