Carbohydrates as chiral starting compounds in synthetic organic chemistry

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Chapter 5

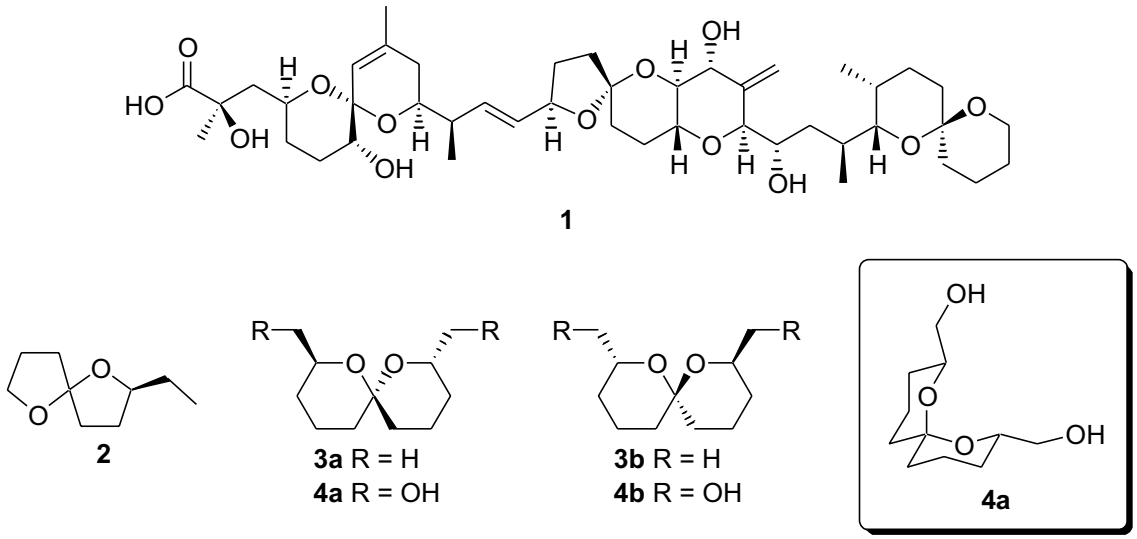
Claisen Self-Condensation/Decarboxylation as the Key Steps in the Synthesis of C_2-Symmetrical 1,7-Dioxaspiro[5.5]undecanes[1]

Introduction

Spiroketals are found as structural entities in many biologically active compounds isolated from a variety of natural sources, including insects, microbes, fungi, plants and marine organisms.[2] The vast majority of the spiroketal frameworks found in natural products are composed of spiro[5.5], spiro[4.5] and spiro[4.4] ring systems (see for representative examples Figure 1). The cytotoxic polyether okadaic acid (**1**) was isolated in 1981 from two marine sponges,[3] and is associated with diarrhetic shellfish poisoning.[4] It acts as an inhibitor of protein phosphatases.[5] The first total synthesis of okadaic acid, which contains two 1,7-dioxaspiro[5.5]undecane ring systems and one 1,6-dioxaspiro[4.5]decane fragment, was accomplished in 1986 by Isobe *et al*.[6] The first spiroketal identified from insects is chalcogran (2-ethyl-1,6-dioxaspiro[4.4]nonane, **2**). It was isolated as a mixture of isomers from the bark beetle *Pityogenes chalcographus* and found to be the principle component of the aggregation pheromone.[7] One of the most widespread spiroketal compounds found in nature is 2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (**3a,b**), present in several species of fruit flies, bees, wasps, ants

and beetles.[8] Several reports appeared in literature describing the synthesis of 2,8-dihydroxymethyl-1,7-dioxaspiro[5.5]undecanes (**4a,b**), versatile intermediates for the construction of 6,6-spiroketals as prevalent structural element in many natural products, but also as starting point for the development of natural product derived compound libraries.[9] For example, spiroketal **4b** has been evaluated on its biological activity such as inhibition of microtubule assembly and induction of apoptosis in human breast cancer cells.[10]

Figure 1



The conformational preference of substituted 1,7-dioxaspiro[5.5]undecane ring systems is influenced by stereoelectronic effects, steric interactions and, to a lesser extend, internal hydrogen bonding.[11] The thermodynamically most stable spiroketal will adopt a configuration in which substituents reside in equatorial positions and result in a ketal function with maximum stability (double anomeric effect). When both these stabilising factors are present a confident prediction of the molecular conformation can be made (e.g. **4a**), however there are numerous examples in which steric factors outweigh the anomeric effect and vise versa, resulting in mixtures of diastereomers at the spiro carbons. These stabilising factors are less consistent and predictable in the formation of dioxaspiro[4.4] (e.g. **2**) and dioxaspiro[4.5] ring systems.

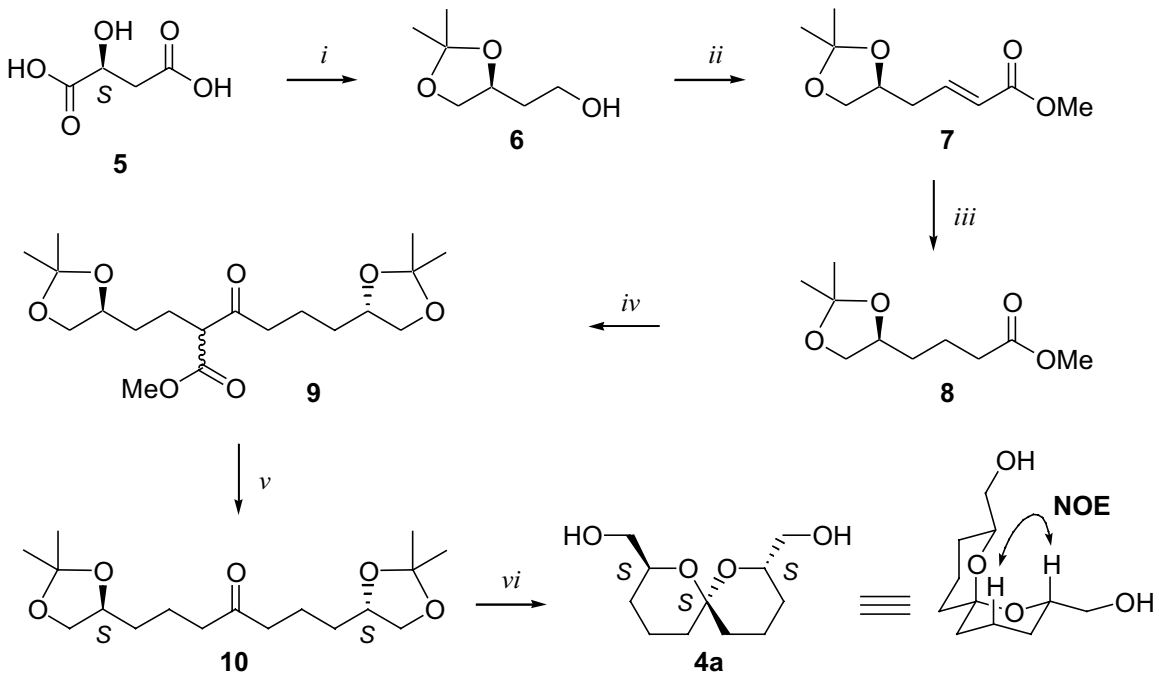
The vast majority of synthetic efforts in the preparation of spiroketal entities is focussed on the general ring systems depicted in Figure 1. Strategies towards spiroketal synthesis are based on two general approaches. The most common route is the intramolecular acid-catalysed ketalisation of dihydroxyketones or equivalents thereof. The second approach makes use of a preformed ring, followed by the addition of a carbon chain containing the necessary oxygen function to effect cyclisation. Main focus in all strategies concerns the installation of the spiro center from a ketone. Several representative examples to obtain the requisite carbonyl source, destined to be the spiro carbon, involve the use of nucleophilic additions to lactones,[12] 1,3-dithianes,[13] dimethylhydrazones,[14] nitroalkanes,[15] aldol condensation products[16] and hetero Diels-Alder reactions.[17] Claisen self-condensation of appropriately functionalised hydroxy esters, followed by decarboxylation and spiroketal formation, presents an efficient alternative for the preparation of C_2-symmetrical spiroketals, including **4a**. Rather surprisingly, this strategy has not been fully exploited to date.[18]

In this chapter the synthesis of a set of chiral C_2-symmetrical 1,7-dioxaspiro[5.5]undecane ring systems is reported. Key to this strategy is the realisation that suitable dihydroxyketone precursors amenable to acid-catalysed spiroketalisation are readily available via Claisen self-condensation of chiral, protected hydroxy-esters, followed by decarboxylation.

Results and discussion

As a first example, the synthesis of spiroketal **4a** commences with reduction of the carboxylate functions of (*S*)-malic acid (**5**) with borane-methyl sulfide complex followed by protection of the vicinal diol as the isopropylidene acetal, providing protected (*S*)-butanetriol derivative **6** in 83% over two steps (Scheme 1).[19] The requisite ester function was installed by a sequential Swern oxidation/Wittig olefination procedure. Treatment of **6** with oxalylchloride, dimethyl sulfoxide and diisopropylethylamine in dichloromethane followed by chain elongation of the crude aldehyde using methyl (triphenylphosphoranylidene)acetate in dichloromethane, resulted in the formation of *E*-

Scheme 1

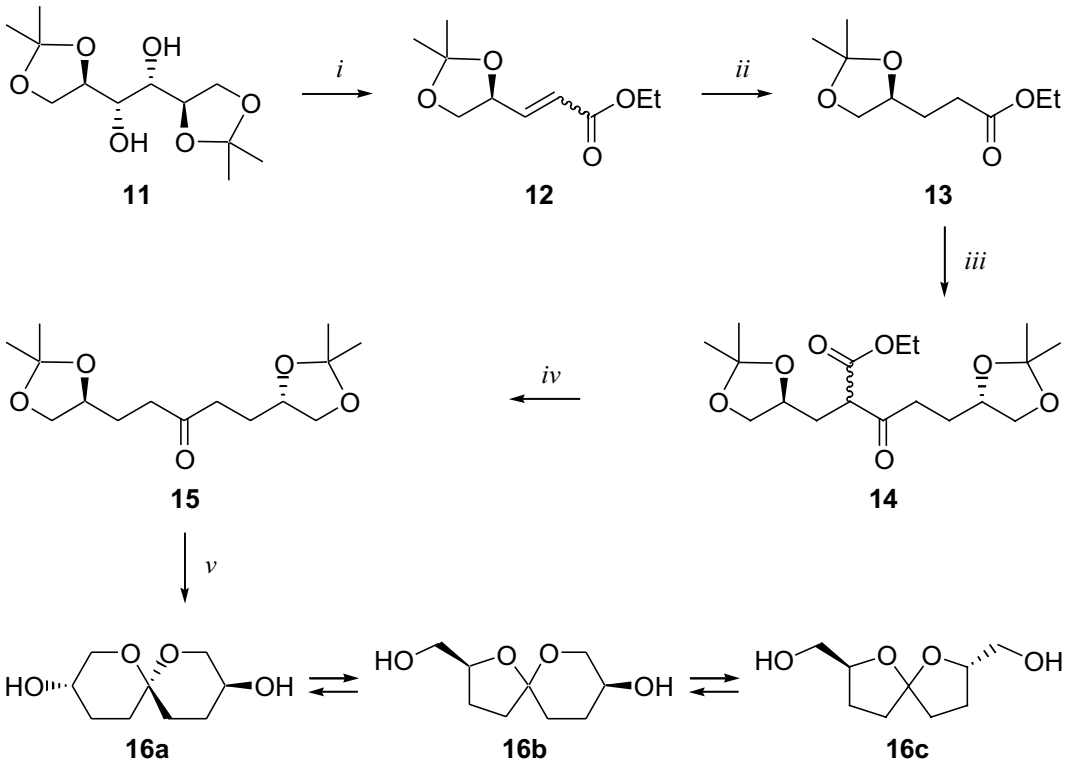


Reagents and conditions: *i*) a) $BH_3 \cdot Me_2S$, THF, 0 °C to rt, 15 h; b) acetone, *p*-TsOH, 17 h, rt, 83% (2 steps). *ii*) a) $(COCl)_2$, DMSO, DiPEA, CH_2Cl_2, -78 °C, 2 h; b) $Ph_3P{=}CHCO_2Me$ (1.4 equiv.), 0 °C to rt, 15 h, 81% (2 steps). *iii*) H_2, 10% Pd/C (cat.), EtOH, 24 h, rt, 88%. *iv*) LHMDS (1.0 M in hexanes, 2.5 equiv.), TMEDA (5.0 equiv.), THF, 0 °C, 2 h, 84%. *v*) LiCl (3.8 equiv.), DMSO, H_2O, reflux, 10 min, 94%. *vi*) HOAc/H_2O (3:2), rt, 90 min, quant.

alkene **7** in 81% yield. Hydrogenation of **7** over palladium on carbon afforded saturated ester **8** in 88%. Claisen self-condensation of **8** was effected by slow addition of excess lithium hexamethyldisilazane (LHMDS) and tetramethylethylenediamine (TMEDA) over a period of 2 hours at 0 °C, providing β-ketoester **9** in 84%.[18c] Decarboxylation of methyl ester **9** proceeded smoothly under the agency of lithium chloride and water in dimethyl sulfoxide[20] to give C_2-symmetrical ketone **10** in 94% yield. Unmasking of the diol functionalities by treatment with acid followed by intramolecular cyclisation led to the formation of spiroketal **4a** as the single isomer in quantitative yield. The conformation of **4a** was assigned based on NMR analysis through a NOE observed between the axial protons H2 and H4a.

Next, the use of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**11**) was investigated in the synthesis towards hydroxy substituted spiroketals **16** (Scheme 2). Periodate-assisted diol cleavage of **11**, immediately followed by Horner Wadsworth Emmons olefination, gave α,β-unsaturated ester **12** in 96% yield over two steps.[21] At this stage, in analogy with conditions described in Scheme 1, saturation of the double bond in **12** was achieved through palladium-catalysed hydrogenation (94%). Claisen self-condensation of the resulting ester **13** produced β-ketoester **14** in 58%. Decarboxylation of **14** with the LiCl/water/DMSO system furnished ketone **15** in a yield of 92%. Acid

Scheme 2

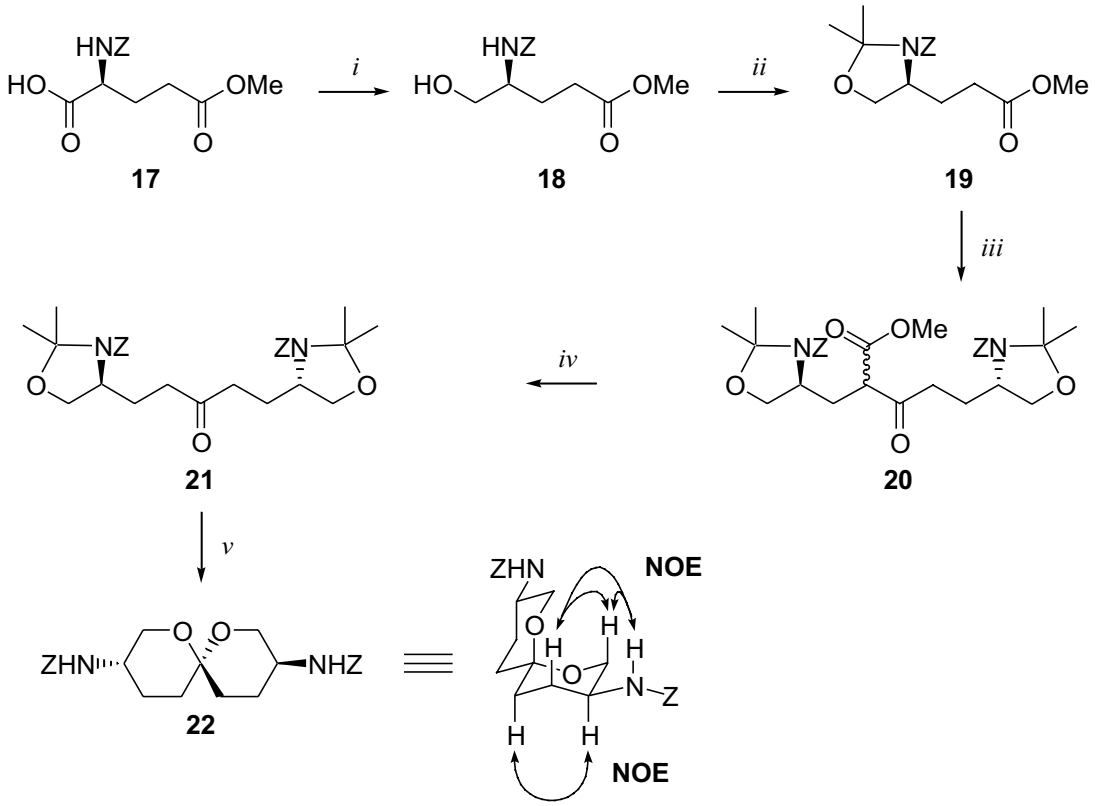


Reagents and conditions: *i*) a) $NaIO_4$ (1.2 equiv.), 5% aq. $NaHCO_3$, rt, 1 h; b) $(EtO)_2POCH_2COEt_2$ (4.2 equiv.), 6*M* aq. K_2CO_3, 0 °C to rt, 17 h, 96% (2 steps). *ii*) H_2, 10% Pd/C (cat.), EtOH, 45 min, 94%. *iii*) LHMDS (2.0 equiv.), TMEDA (4.0 equiv.), THF, 0 °C, 2.5 h, 58%. *iv*) LiCl (3.8 equiv.), DMSO, H_2O, reflux, 5 min, 92%. *v*) HOAc/H_2O (3:2), rt, 90 min, 76%.

mediated tandem deprotection/cyclisation resulted in the formation of a thermodynamic mixture of spiroketals (**16a-c**) in an overall yield of 76% (prolonged exposure to TFA did not result in a shift towards one of the individual spiroketals).

It was reasoned that replacement of the secondary hydroxyl groups in **15** with an amine functionality, as in **21**, would lead to 6,6-spiroketal **22** as the single product. In a two-step procedure the carboxylic acid moiety in glutamic acid derivative **17** was selectively reduced in the presence of the methyl ester (Scheme 3).[22] Treatment of **17**

Scheme 3



Reagents and conditions: *i*) a) NMM, $ClCO_2Et$, THF, -10 °C, 10 min; b) $NaBH_4$ (3.0 equiv.), 0 °C, 30 min, 83% (2 steps). *ii*) dimethoxypropane, acetone, *p*-TsOH, rt, 17 h, 94%. *iii*) LHMDS (1.0 M in hexanes, 2.5 equiv.), TMEDA (5.0 equiv.), THF, 0 °C, 3 h, 72%. *iv*) KOH (2.5 equiv.), MeOH/H_2O (1:1), reflux, 1 h, 79%. *v*) HOAc/H_2O (1:1), reflux, 3 h, 90%.

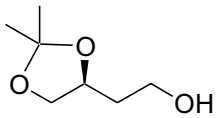
with *N*-methylmorpholine (NMM) and ethyl chloroformate yielded the corresponding mixed anhydride which was subsequently reduced with sodium borohydride furnishing alcohol **18** in 83%. Installation of the isopropylidene gave oxazolidine **19** (94%), of which Claisen self-condensation under the conditions previously described afforded β-ketoester **20** in a yield of 72%. Saponification of **20** at elevated temperature gave the corresponding β-ketoacid which immediately underwent decarboxylation yielding ketone **21** in 79% yield. Acidic removal of the isopropylidene protecting groups and concomitant cyclisation provided amine protected spiroketal **22** in a yield of 90%. The structure of compound **22** was established by NMR spectroscopy through observed NOEs indicated in Scheme 3.

Conclusion

In conclusion, a new route for the stereoselective synthesis of functionalised 1,7-dioxaspiro[5.5]undecane ring systems was developed. The C_2-symmetrical spiroketals were efficiently obtained via acid-catalysed cyclisation of different dihydroxyketones which are readily available from Claisen self-condensation of suitably substituted hydroxy esters.

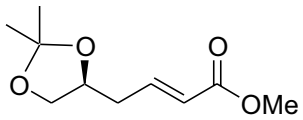
Experimental section

For general methods and materials see Chapter 2.

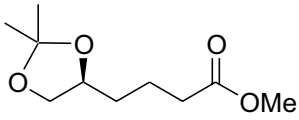


1,2-*O*-Isopropylidene-(*S*)-butane-1,2,4-triol (6): A solution of BH_3·DMS complex (58.6 mL, 0.610 mol, 3.05 equiv.) in freshly distilled THF (250 mL) was cooled to 0 °C. A solution of (*S*)-malic acid (26.82 g, 0.200 mol) in THF (150 mL) was added dropwise over 75 min to the borane mixture. After the addition was complete the cooling bath was removed and the reaction was stirred at rt for 15 h after which TLC analysis (MeOH/EtOAc 1:9) revealed complete consumption of starting material. Methanol (250 mL) was carefully added dropwise over 75 min and the solution was concentrated. The crude product was purified by flash chromatography (MeOH/EtOAc 1:9) to yield (*S*)-1,2,4-butanetriol (21.1 g, 0.199 mol). $[\alpha]_D^{20}$ –25.0 (*c* 1.0 MeOH). ^{13}C-NMR (50.0 MHz, MeOD): δ 70.4 (C-2), 67.3 (C-1), 59.7 (C-4), 36.8 (C-3). To a part of this triol (2.60 g, 24.50 mmol), dissolved in acetone (125 mL) was added *p*-TsOH (220 mg) and the solution was stirred overnight at rt. The mixture

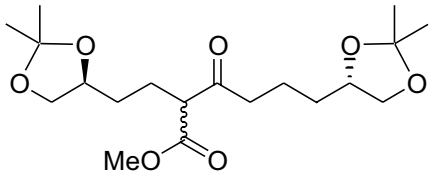
was neutralised with Et_3N and followed by concentration of the mixture. Purification by column chromatography (EtOAc/PE 1:3) gave **6** (2.96 g, 20.3 mmol, 83%). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.27 (m, 1H, H-2), 4.09 (dd, 1H, $J_{1a,2}$ = 6.2 Hz, $J_{1a,1b}$ = 7.7 Hz, H-1a), 3.87 (t, 1H, $J_{4,3}$ = 5.8 Hz, H-4), 3.59 (t, 1H, $J_{1b,1a}$ = 7.7 Hz, H-1b), 2.65 (bs, 1H, OH), 1.81 (m, 1H, H-3), 1.42 (s, 3H, Me), 1.37 (s, 3H, Me). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 108.1 (C_q *i*Pr), 73.9 (C-2), 69.1 (C-1), 59.2 (C-4), 35.6 (C-3), 26.5, 25.3 (2× CH_3, *i*Pr).



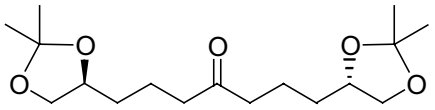
Methyl-(*S*)-(*E*)-5,6-isopropylidenedioxyhex-2-enoate (7): To a cold solution (-78 ºC) of oxalyl chloride (1.82 mL, 2.70 g, 21.2 mmol, 1.1 equiv.) in DCM (50 mL) was added dropwise a solution of DMSO (2.81 mL, 3.09 g, 39.6 mmol, 2.1 equiv.) in DCM (10 mL). After stirring for 10 min, a solution of **6** (2.82 g, 19.3 mmol) in DCM (15 mL) was added dropwise over 30 min. After stirring the resulting slurry for 40 min at –78 ºC, DiPEA (16.0 mL, 12.5 g, 96.6 mmol, 5.0 equiv.) was added slowely. The cooling bath was removed and the reaction mixture was stirred for 1 h. The yellow mixture was cooled to 0 ºC and treated with methyl (triphenylphosphoranylidene)acetate (9.03 g, 27.0 mmol, 1.4 equiv.). After stirring for 1 h the reaction mixture was allowed to reach rt overnight. The mixture was diluted with Et_2O and washed with water (three times). The organic phase was separated, washed with brine dried ($MgSO_4$) and concentrated. Purification by column chromatography (EtOAc/PE 1:6 to 1:3) gave alkene **7** (3.13 g, 15.6 mmol, 81% over two steps). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 6.78 (dt, 1H, $J_{3,4}$ = 7.3 Hz, $J_{3,2}$ = 15.3 Hz, H-3), 5.76 (dd, 1H, $J_{2,4}$ = 1.5 Hz, $J_{2,3}$ = 15.3 Hz, H-2), 4.06 (quintet, 1H, $J_{5,4}$ = $J_{5,6a}$ = $J_{5,6b}$ = 6.6 Hz, H-5), 3.90 (dd, 1H, $J_{6a,5}$ = 6.6 Hz, $J_{6a,6b}$ = 8.0 Hz, H-6a), 3.56 (s, 3H, CH_3 OMe), 3.42 (dd, 1H, $J_{6b,5}$ = 6.6 Hz, $J_{6b,6a}$ = 8.0 Hz, H-6b), 2.32 (m, 2H, H-4), 1.25 (s, 3H, CH_3 *i*Pr), 1.18 (s, 3H, CH_3 *i*Pr). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 166.0 (C-1), 143.8 (C-3), 123.0 (C-2), 108.8 (C_q *i*Pr), 73.8 (C-5), 68.4 (C-6), 51.0 (CH_3 OMe), 36.1 (C-4), 26.4, 25.1 (2× CH_3 *i*Pr).



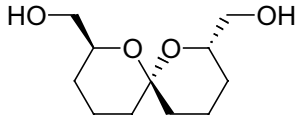
Methyl-(*S*)-5,6-isopropylidenedioxyhexanoate (8): A solution of alkene **7** (2.06 g, 10.3 mmol) dissolved in EtOAc (50 mL) was degassed. A catalytic ammount of Pd/C was added and after degassing the solution for a second time the reaction was stirred under a hydrogen atmosphere. After 24 h, TLC analysis (acetone/PE 1:9) showed complete conversion of starting material into a higher running spot. The mixture was filtered over Glass Fiber (GF/2A Whatman) and concentrated. The residue was filtered over a short plug of silica (acetone/PE 1:9) and the filtrate was concentrated to afford ester **8** (1.84 g, 9.11 mmol, 88%). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.07 (m, 2H, H-6), 3.67 (s, 3H, CH_3 OMe), 3.52 (m, 1H, H-5), 2.37 (t, 1H, $J_{2,3}$ = 7.0 Hz, H-2), 1.66 (m, 4H, H-3, H-4), 1.41 (s, 3H, CH_3 *i*Pr), 1.35 (s, 3H, CH_3 *i*Pr). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 173.0 (C-1), 108.1 (C_q *i*Pr), 75.1 (C-5), 68.8 (C-6), 50.8 (CH_3 OMe), 33.1, 32.5 (C-2, C-4), 26.4, 25.1 (2× CH_3 *i*Pr), 20.7 (C-3).



(2*S*, 5*R/S*, 10*S*)-1,2;10,11-Bis(isopropylidenedioxy)-5-methoxycarbonylundecan-6-one (9): Ester **8** (0.45 g, 2.23 mmol) was dissolved in THF (10 mL) and cooled to 0 °C under an argon atmosphere. A solution was prepared of LHMDS (5.57 mL, 5.57 mmol, 1.0 M in hexanes, 2.5 equiv.) and TMEDA (1.68 mL, 1.29 g, 11.1 mmol, 5.0 equiv) in THF (10 mL) and added dropwise to the cooled ester solution. After 2 h no starting material was present according to TLC analysis (EtOAc/PE 1:3). The reaction mixture was diluted with Et_2O and neutralised by addition of 1.0 M HCl. The layers were separated, the aqueous layer was washed with Et_2O. All organic layers were combined, washed against sat. aq. $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (EtOAc/PE 1:3) afforded an isomeric mixture of β-ketoester **9** (0.348 g, 0.935 mmol, 84%). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 204.0, 203.9 (C-6), 169.7, 169.6 (C=O CO_2Me), 108.4, 108.3 (C_q *i*Pr), 75.3 (C-2, C-10), 68.8 (C-1, C-11), 58.0, 57.7 (C-5), 51.9 (CH_3 OMe), 41.4, 41.0 (C-7), 32.3, 31.0, 30.7 (C-3, C-9), 26.5, 25.2 (CH_3 *i*Pr), 24.1 (C-4), 19.3 (C-8). IR (thin film): 1742, 1715 cm^{-1}. MS (ESI): *m/z* = 395.1 $[M+Na]^+$.

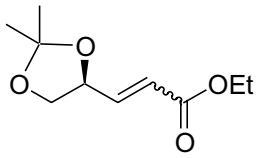


(2*S*, 10*S*)-1,2;10,11-Bis(isopropylidenedioxy)undecan-6-one (10): To a solution of β-ketoester **9** (0.215 g, 0.578 mmol) in DMSO (2.5 mL) were added two drops of water and LiCl (91.8 mg, 2.17 mmol, 3.75 equiv.). After 10 min heating under reflux, TLC analysis (acetone/PE 1:3) revealed complete consumption of starting material. The mixture was diluted with water followed by the addition of EtOAc and brine. The aqueous layer was separated and washed twice with EtOAc. All organic layers were combined, dried ($MgSO_4$), filtered and concentrated. Purification by silicagel column chromatography afforded ketone **10** (170 mg, 0.541 mmol, 94%). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.07 (m, 4H, H-1, H-11), 3.48 (m, 2H, H-2, H-10), 2.46 (m, 4H, H-5, H-7), 1.72-1.43 (m, 8H, H-3, H-4, H-8, H-9), 1.40 (s, 6H, 2× CH_3 *i*Pr), 1.35 (s, 6H, 2× CH_3 *i*Pr).^{13}C-NMR (50 MHz, $CDCl_3$): δ 209.7 (C-6), 108.4 (C_q *i*Pr), 75.5 (C-2, C-10), 69.0 (C-1, C-11), 42.1 (C-3, C-9), 32.7 (C-5, C-7), 26.7, 25.4 (CH_3 *i*Pr), 19.7 (C-4, C-8). IR (thin film): 3327, 2937, 2872, 2359, 2343, 1717, 1456, 1437, 1223, 1204, 1082, 1047, 1016, 980 cm^{-1}. MS (ESI): *m/z* = 337.2 $[M+Na]^+$.

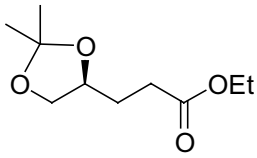


(2*S*, 6*S*, 8*S*) 2,8-Bishydroxymethyl-1,7-dioxaspiro[5.5]undecane (4a): Ketone **10** (0.163 g, 0.519 mmol) was dissolved in a 3:2 mixture of HOAc/water (3 mL) and stirred at rt for 90 min after which TLC analysis (1:1 EtOAc/PE) indicated complete consumption of starting material into a lower running spot. The reaction mixture was concentrated and traces of acid were coevaporated three times with toluene. The residue was purified by column chromatography (EtOAc/PE 1:3 to 1:1) to afford spiroketal **4a** (0.112 g, 0.518 mmol,

quantitative yield). $[\alpha]_D^{20}$ +59.0 (*c* = 0.8, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.75 (m, 2H, H-2, H-8), 3.60 (dd, 2H, *J* = 3.4 Hz, *J* = 11.4 Hz, 2× C*H*H CH_2OH), 3.51 (dd, 2H, *J* = 6.9 Hz, *J* = 11.4 Hz, 2× CH*H* CH_2OH), 2.54 (s, 2H, 2× OH), 1.99-1.82 (dddd, 2H, *J* = 4.2 Hz, *J* = 13.2 Hz, *J* = 26.4 Hz, H-4a, H-10a), 1.67-1.58 (m, 4H, H-4b, H-5a, H-10b, H-11a), 1.51 (m, 2H, H-3a, H-9a), 1.41 (m, 2H, H-5b, H-11b), 1.28 (ddd, 2H, *J* = 3.8 Hz, *J* = 12.8 Hz, *J* = 25.0 Hz, H-3b, H-9b). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 96.0 (C-6), 72.0 (C-2, C-8), 66.1 (2× CH_2OH), 35.1 (C-5, C-11), 26.4 (C-3, C-9), 18.2 (C-4, C-10). IR (thin film): 3377, 2937, 1225, 1082, 1045, 1014, 982 cm^{-1}. HRMS (ESI): calcd for $[C_{11}H_{20}O_4+H]^+$: 217.1434. Found: 217.1437.

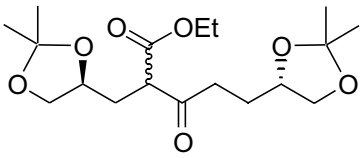


Ethyl-(*S*)-(*E/Z*)-4,5-isopropylidenedioxypent-2-enoate (12): A 5% aqueous $NaHCO_3$ solution (50 mL) was added to 1,2:5,6 diisopropylidenemannitol **11** (6.30 g, 24.02 mmol) and the resulting suspension was cooled to 0 °C. A solution of $NaIO_4$ (6.3 g, 29.45 mmol, 1.2 equiv.) dissolved in water (50 mL) was added to the cooled mannitol suspension, stirred for 90 min at rt and cooled again at 0 °C. To this slurry was added triethylphosphonoacetate (19.84 mL, 22.4 g, 100 mmol, 4.2 equiv.). A solution of K_2CO_3 (150 mL, 6M) was added slowly (CAUTION! Exothermic reaction) and the reaction was stirred overnight at rt. The mixture was diluted with DCM and extracted three times with DCM and the combined organic layers were dried ($MgSO_4$), filtered and concentrated. Column chromatography (EtOAc/PE 1:9) of the residue afforded **12** as an E/Z mixture of alkenes in a combined yield (9.21 g, 46.0 mmol, 96%). *E*-isomer: ^{1}H-NMR (200 MHz, $CDCl_3$): δ 6.88 (dd, 1H, $J_{3,4}$ = 5.8 Hz, $J_{3,2}$ = 15.3 Hz, H-3), 6.09 (dd, $J_{2,4}$ = 1.5 Hz, $J_{2,3}$ = 15.3 Hz, H-2), 4.65 (m, 1H, H-4), 4.20 (q, 2H, *J* = 7.3 Hz, CH_2 Et), 4.14 (m, 1H, H-5a), 3.67 (dd, 1H, *J* = 7.3 Hz, *J* = 8.0 Hz, H-5b), 1.44 (s, 3H, CH_3 *i*Pr), 1.40 (s, 3H, CH_3 *i*Pr), 1.29 (t, 3H, *J* = 7.3 Hz, CH_3 Et). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 165.5 (C-1), 144.4 (C-3), 122.0 (C-2), 109.7 (C_q *i*Pr), 74.6 (C-4), 68.4 (C-5), 60.1 (CH_2 Et), 26.1, 25.4 (2× CH_3 *i*Pr), 13.8 (CH_3 Et). *Z*-isomer: ^{1}H-NMR (200 MHz, $CDCl_3$): δ 6.37 (dd, 1H, $J_{3,4}$ = 6.6 Hz, $J_{3,2}$ = 11.7 Hz, H-3), 5.85 (dd, 1H, $J_{2,4}$ = 2.2 Hz, $J_{2,3}$ = 11.7 Hz, H-2), 5.49 (m, 1H, H-4), 4.38 (dd, 1H, *J* = 6.9 Hz, *J* = 8.4 Hz, H-5a), 4.18 (q, 2H, *J* = 7.3 Hz, CH_2 Et), 3.63 (dd, 1H, *J* = 6.9 Hz, *J* = 8.4 Hz, H-5b), 1.46 (s, 3H, CH_3 *i*Pr), 1.40 (s, 3H, CH_3 *i*Pr), 1.30 (t, 3H, *J* = 7.3 Hz, CH_3 Et). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 164.9 (C-1), 149.1 (C-3), 120.1 (C-2), 109.0 (C_q *i*Pr), 73.1 (C-4), 68.8 (C-5), 59.7 (CH_2 Et), 26.0, 24.8 (2× CH_3 *i*Pr), 13.6 (CH_3 Et).

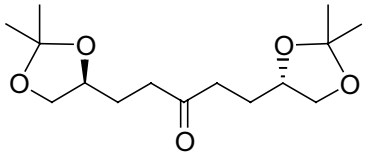


Ethyl-(*S*)-4,5-isopropylidenedioxypentanoate (13): A mixture of *E/Z* alkenes **12** (0.218 g, 1.09 mmol) dissolved in EtOH (8 mL) was degassed. A catalytic ammount of Pd/C was added and after degassing the solution for a second time the reaction was stirred under a hydrogen atmosphere. After 45 min TLC analysis (EtOAc/PE 1:3) showed complete conversion of starting material into a lower running spot. The mixture was filtered over Glass Fiber (GF/2A Whatman) and concentrated. The residue was filtered over a short plug of silica (EtOAc/PE 1:3) and the filtrate was concentrated to afford ester **13** (0.208 g, 1.03 mmol,

94%). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 4.13 (q, 2H, *J* = 7.3 Hz, CH_2 Et), 4.08 (m, 2H, H-4, H-5a), 3.54 (m, 1H, H-5b), 2.42 (m, 2H, H-2), 1.85 (m, 2H, H-3), 1.40 (s, 3H, CH_3 *i*Pr), 1.33 (s, 3H, CH_3 *i*Pr), 1.26 (t, 3H, *J* = 7.3 Hz, CH_3 Et). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 172.8 (C-1), 108.6 (C_q *i*Pr), 74.7 (C-4), 68.8 (C-5), 60.0 (CH_2 Et), 30.1, 28.5 (C-2, C-3), 26.6, 25.3 (2× CH_3 *i*Pr), 13.9 (CH_3 Et).

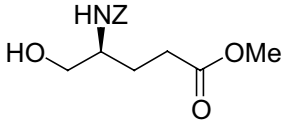


(2*S*, 4*R/S*, 8*S*)-1,2;8,9-Bis(isopropylidenedioxy)-4-ethoxycarbonylnonan-5-one (14): A solution of ester **13** (0.404 g, 1.998 mmol) in freshly distilled THF (10 mL) was cooled to 0 °C. A solution of LHMDS (0.668 g, 4.00 mmol, 2.0 equiv.) in freshly distilled THF (5 mL) and TMEDA (1.21 mL, 0.929 g, 7.99 mmol, 4.0 equiv.) was added to the chilled ester solution. After 2.5 h of stirring at 0 °C TLC analysis (EtOAc/PE 1:3) indicated complete consumption of starting material. The reaction mixture was neutralised by addition of HCl (25 mL, 1.0 M) and diluted with Et_2O. The aqueous phase was separated and extracted twice with Et_2O. All organic layers were combined, dried ($MgSO_4$) and concentrated. Purification of the residue by column chromatography (EtOAc/PE 1:9) afforded β-ketoester **14** (0.208 g, 0.581 mmol, 58%) as an isomeric mixture. ^{13}C-NMR (50 MHz, $CDCl_3$): δ 203.8 (C-5), 169.0, 168.8 (C=O CO_2Et), 108.7, 108.4 (C_q *i*Pr), 74.5, 74.4, 73.4, 72.9 (C-2, C-8), 68.8 (C-1, C-9), 61.0 (CH_2 Et), 55.3, 54.6 (C-4), 38.5, 37.7 (C-6), 31.8, 31.4 (C-3), 26.9 (C-7), 26.5, 25.2 (4× CH_3 *i*Pr), 13.6 (CH_3 Et). MS (ESI): *m/z* = 381.1 $[M+Na]^+$, 739.6 $[2M+Na]^+$.



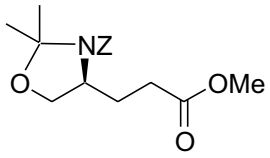
(2*S*, 8*S*)-1,2;8,9-Bis(isopropylidenedioxy)nonan-5-one (15): Decarboxylation of **14** (0.117 g, 0.327 mmol) using the procedure described going from **9** to **10**, gave after refluxing for 5 min, ketone **15** (86 mg, 0.301 mmol, 92%). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.99 (m, 4H, H-1, H-9), 3.44 (m, 2H, H-2, H-8), 2.47 (m, 4H, H-4, H-6), 1.74 (m, 4H, H-3, H-7), 1.32 (s, 6H, 2× CH_3 *i*Pr), 1.25 (s, 6H, 2× CH_3 *i*Pr). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 209.2 (C-5), 108.7 (C_q *i*Pr), 74.8 (C-2, C-8), 69.0 (C-1, C-9), 38.5 (C-4, C-6), 27.2 (C-3, C-7), 26.7, 25.4 (4× CH_3 *i*Pr). MS (ESI): *m/z* = 309.1 $[M+Na]^+$.

Spiroketals (16 a-c): According to the procedure described going from **10** to **4**, ketone **15** (60.0 mg, 0.210 mmol) was dissolved in a mixture of (1.5 mL HOAc/water 3:2). After stirring for 90 min at rt, TLC analysis (MeOH/EtOAc 1:19) revealed complete consumption of starting material also indicating the formation of three lower running spots. Work up as described for **4a** resulted in the formation of compounds **16a**, **16b**, **16c** (30 mg, 0.159 mmol, 76%).

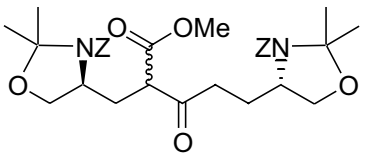


Methyl-(*S*)-4-[(benzyloxycarbonyl)amino]-5-hydroxypentanoate (18): Z-Glu(OMe)-OH, **17**, (1.48 g, 5.00 mmol) was dissolved in THF (25 mL) and cooled to –10 °C. To this solution were added NMM (0.550 mL, 0.506 g, 5.00

mmol) and ethyl chloroformate (0.478 mL, 0.543 g, 5.00 mmol). After stirring this mixture for 10 min at –10 °C, $NaBH_4$ (0.567 g, 15.0 mmol, 3.0 equiv.) was added in one portion, followed by slow addition of MeOH (50 mL). The reaction mixture was stirred and allowed to reach 0 °C. After 30 min, the reaction was quenched by the addition of 1.0 M HCl (11 mL, pH 5). After addition of water, brine and EtOAc, the organic phase was separated, dried ($MgSO_4$) and concentrated. Purification by column chromatography (EtOAc/PE 2:1 to 3:1) gave title compound **18** (1.17 g, 4.15 mmol, 83%) as a white solid. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.36 (m, 5H, CH_{arom}), 5.10 (s, 2H, CH_2 Z), 3.65 (m, 6H, H-4, H-5, CH_3 Me), 2.43 (m, 2H, H-2), 1.88 (m, 2H, H-3). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 173.7 (C=O CO_2Me), 156.3 (C=O Z), 136.0 (C_q Z), 127.9, 127.5 (CH_{arom}), 66.1, 63.9 (C-5, CH_2 Z), 52.0, 51.1 (C-4, CH_3 OMe), 30.0, 25.9 (C-2, C-3).). IR (thin film): 3315, 1693, 1529, 1439, 1242, 1172, 1059, 1028 cm^{-1}. MS (ESI): *m/z* = 282.3 $[M+H]^+$, 304.0 $[M+Na]^+$, 585.2 $[2M+Na]^+$.

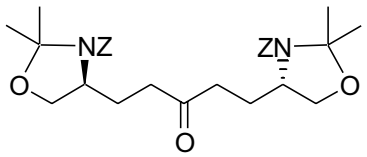


Methyl 3-[(4*S*)-3-(benzyloxycarbonyl)-2,2-dimethyl-1,3-oxazolidin-4-yl]-propanoate (19): Alcohol **18** (0.640 g, 2.28 mmol) was dissolved in dry acetone (20 mL). Dimethoxypropane (3.0 mL, 24.2 mmol) and a catalytic ammount of *p*-TsOH (65 mg) were added and the mixture was stirred overnight at rt. After 18 h, TLC analysis revealed complete consumption of starting material. Pyridine (0.1 mL) was added and the organic solvents were removed under reduced pressure. The residue was dissolved in EtOAc, washed against sat. aq. $NaHCO_3$, water and brine. The separated organic layer was dried ($MgSO_4$) and purified by column chromatography (EtOAc/PE 1:6 to 1:3) to give oxazolidine **19** (0.689 g, 2.15 mmol, 94%). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.36 (m, 5H, CH_{arom}), 5.13 (m, 2H, CH_2 Z), 4.03 (m, 2H, H-5), 3.70 (m, 4H, H-4, CH_3 Me), 2.31 (m, 2H, H-2), 1.98 (m, 2H, H-3), 1.55 (m, 6H, 2× CH_3 *i*Pr). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 172.3 (C=O CO_2Me), 151.5 (C=O Z), 136.0 (C_q Z), 127.7, 127.2 (CH_{arom}), 93.4, 92.9 (C_q *i*Pr), 66.4, 65.7 (C-5, CH_2 Z), 56.6, 55.6, 50.6 (C-4, CH_3 OMe), 29.7, 28.2, 27.7 (C-2, C-3), 26.8, 25.8, 23.7, 22.2 (CH_3 *i*Pr). IR (thin film): 2951, 1736, 1697, 1404, 1348, 1252, 1070 cm^{-1}. MS (ESI): *m/z* = 344.2 $[M+Na]^+$, 360.0 $[M+K]^+$, 665.3 $[2M+Na]^+$.

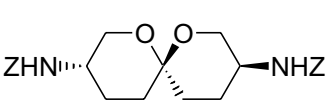


(2*R/S*)-1,5-Bis((4S)-3-(benzyloxycarbonyl)-2,2-dimethyl-1,3-oxazolidin-4-yl)-2-methoxycarbonyl-pentan-3-one (20): Condensation of ester **19** (0.304 g, 0.95 mmol), as described for the synthesis of **9**, gave after 3 h and purification by column chromatography (EtOAc/PE 1:3 to 1:1), β-ketoester **20** (0.208 g, 0.341 mmol, 72%). ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.35 (m, 10H, CH_{arom}), 5.11 (m, 4H, 2× CH_2 Z), 3.92 (m, 4H, H-1, H-9), 3.64 (m, 6H, H-2, H-4, H-8, CH_3 OMe), 2.59 (m, 2H, H-6), 2.14 (m, 2H, H-3), 1.87 (m, 2H, H-7), 1.62-1.43 (m, 12H, 4× CH_3 *i*Pr). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 203.0 (C-5), 169.5 (C=O CO_2Me), 152.0 (C=O Z), 136.1 (C_q Z), 128.2, 127.7 (CH_{arom}), 93.9 (C_q *i*Pr), 67.4, 66.9, 66.3, 65.5 (C-1, C-9, 2× CH_2 Z), 56.0, 55.4 (C-2, C-4, C-8), 52.1 (CH_3 OMe), 37.7 (C-6), 32.6 (C-3),

27.0 (C-7), 27.6, 26.3, 24.1, 22.7 (CH_3 *i*Pr). IR (thin film): 1744, 1697, 1404, 1350, 1251, 1207, 1072 cm^{-1}. MS (ESI): *m/z* = 611.4 $[M+H]^+$, 633.4 $[M+Na]^+$, 1221.9 $[2M+H]^+$, 1243.6 $2M+Na]^+$.



1,5-Bis((4S)-3-(benzyloxycarbonyl)-2,2-dimethyl-1,3-oxazolidin-4-yl)-pentan-3-one (21): To a solution of β-ketoester **20** (73.0 mg, 0.120 mmol), dissolved in MeOH/water (1:1, 3.0 mL), was added KOH (16.8 mg, 0.299 mmol, 2.5 equiv.). The reaction mixture was heated till reflux and after 1 h TLC analysis (EtOAc/toluene 1:3) indicated complete disappearance of starting material. The mixture was concentrated and the residue dissolved in Et_2O and washed against water and brine. The organic phase was dried ($MgSO_4$), concentrated and purified by column chromatography (EtOAc/toluene 1:3) to yield ketone **21** (52.0 mg, 0.094 mmol) in 79%. ^{1}H-NMR (200 MHz, $CDCl_3$): δ 7.35 (m, 10H, CH_{arom}), 5.12 (s, 4H, 2× CH_2 Z), 3.94 (m, 4H, H-1, H-9), 3.70 (m, 2H, H-2, H-8), 2.36 (m, 4H, H-4, H-60, 1.87 (m, H-3, H-7), 1.63-1.43 (m, 12H, 4× CH_3 *i*Pr). ^{13}C-NMR (50 MHz, $CDCl_3$): δ 208.7 (C-5), 152.3 (C=O Z), 136.5 (C_q Z), 128.5, 128.0, 127.9 (CH_{arom}), 94.2, 93.7 (C_q *i*Pr), 67.2, 66.5 (C-1, C-9, 2× CH_2 Z), 57.1, 56.3 (C-2, C-8), 38.7 (C-2, C-6), 27.4 (C-3, C-7), 26.5, 24.5, 23.0 (CH_3 *i*Pr). IR (thin film): 1699, 1406, 1352, 1074 cm^{-1}. MS (ESI): *m/z* = 553.5 $[M+H]^+$, 575.6 $[M+Na]^+$, 591.2 $[M+K]^+$.



(3*S*, 6*S*, 9*S*)-3,9-Bis((benzyloxycarbonyl)amino)-1,7-dioxaspiro[5.5] undecane (22): Ketone **21** (38 mg, 0.069 mmol) was dissolved in HOAc/water (3mL 1:1) and heated till reflux. After 3 h, TLC analysis (EtOAc/toluene 1:1) showed complete conversion of starting material into a lower running spot. The mixture was concentarted under reduced pressure and purified over a small plug of silica (EtOAc/toluene 1:1) to give spiroketal **22** (29 mg, 0.064 mmol, 90%). $[\alpha]_D^{20}$ +12.0 (*c* = 0.1, $CHCl_3$). ^{1}H-NMR (400 MHz, DMSO-d_6, 333K): δ 7.40-7.27 (m, 10H, CH_{arom}), 7.05 (2H, 2× NH), 5.01 (m, 4H, 2× CH_2 Z), 3.51 (dd, 2H, *J* = 4.6 Hz, *J* = 9.8 Hz, H-2a, H-8a), 3.44 (m, 2H, H-3, H-9), 3.18 (m, 2H, H-2b, H-8b), 1.64 (m, 6H, H-4a, H-4b, H-5a, H-10a, H-10b, H-11a), 1.50 (dd, 2H, *J* = 4.6 Hz, *J* = 13.0 Hz, H-5b, H-11b). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 155.5 (C=O Z), 137.0 (C_q Z), 128.3, 127.8 (CH_{arom}), 93.2 (C-6), 65.3 (CH_2 Z), 62.1 (C-2, C-8), 46.3 (C-3, C-9), 33.7 (C-5, C-11), 24.7 (C-4, C-10). IR (thin film): 3300, 2953, 1684, 1545, 1439, 1312, 1292, 1084, 1024, 964 cm^{-1}. HRMS (ESI): calcd for $[C_{25}H_{30}N_2O_6+H]^+$: 455.2177. Found: 455.2175.

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