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Claisen self-condensation/decarboxylation as the key steps in the synthesis of C_2-symmetrical 1,7-dioxaspiro[5.5]undecanes

Bas Lastdrager, Mattie S. M. Timmer, Gijsbert A. van der Marel and Herman S. Overkleeft*

Leiden Institute of Chemistry, Leiden University, PO Box 9502, 2300 RA Leiden, The Netherlands

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Abstract—A convenient method for the synthesis of functionalised 1,7-dioxaspiro[5.5]undecanes using acid-catalysed spiroketalisations of substituted dihydroxyketones is described. The dihydroxyketones were readily prepared from appropriately substituted hydroxy esters via Claisen self-condensation followed by decarboxylation.

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.[1] 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 Fig. 1, for representative examples). The cytotoxic polyether okadaic acid (**1**) was isolated in 1981 from two marine sponges.[2] It acts as an inhibitor of protein phosphatases[3] and is associated with diarrhetic shellfish poisoning.[4] The first total synthesis of okadaic acid, containing 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.[5]

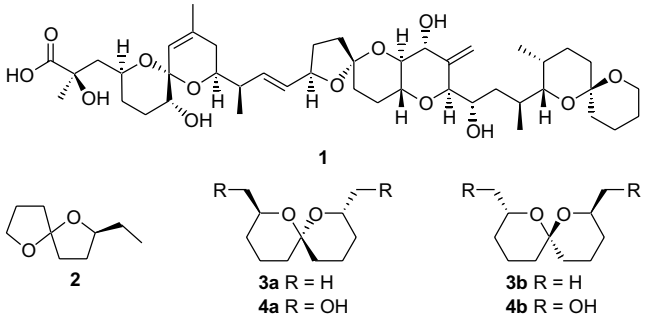

Figure 1.

The first spiroketal identified from insects was 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.[6] 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.[7] Several reports have appeared in the 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 elements in many natural products, and also as the starting point for the development of natural product derived compound libraries.[8] For example, spiroketal **4b** has been evaluated for its biological activities such as the inhibition of microtubule assembly and induction of apoptosis in human breast cancer cells.[9]

The vast majority of synthetic efforts in the preparation of spiroketal entities are 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. The main focus in all the strategies concerns the installation of the spiro centre from a ketone. Several representative examples to obtain the requisite carbonyl source, destined to be the spiro carbon, involve the use of

* Corresponding author. Tel.: +31 71 5274342; fax: +31 71 5274307; e-mail: h.s.overkleeft@chem.leidenuniv.nl

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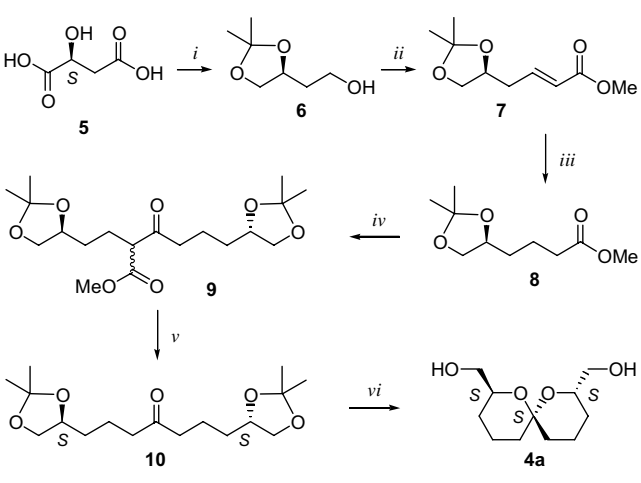
nucleophilic additions to lactones,[10] 1,3-dithianes,[11] dimethylhydrazones,[12] nitroalkanes,[13] aldol condensation products[14] and hetero Diels–Alder reactions.[15] Claisen self-condensation of appropriately functionalised hydroxy esters, followed by decarboxylation and spiroketal formation, presents an efficient alternative for the preparation of C_2-symmetrical spiroketals, including **4a**. Rather surprisingly, this strategy has not been fully exploited to date.[16]

Here, we report the synthesis of a set of chiral C_2-symmetrical 1,7-dioxaspiro[5.5]undecane ring systems. Key to our 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.

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).[17] The requisite ester function was installed by a sequential Swern oxidation/Wittig olefination procedure. Treatment of **6** with oxalyl chloride, dimethyl sulfoxide and diisopropylethylamine in dichloromethane followed by chain elongation of the crude aldehyde using triphenylphosphoranylidene acetate in dichloromethane, resulted in the formation of *E*-alkene **7** in 81% yield. Hydrogenation of **7** over palladium on carbon afforded saturated ester **8** in an 88% yield. Claisen self-condensation of **8** was effected by slow addition of excess lithium hexamethyldisilazane (LHMDS) and tetramethylethylenediamine (TMEDA) over a period of 2 h at 0 °C, providing β-ketoester **9** in an 84% yield.[16c] Decarboxylation of methyl ester **9** proceeded smoothly under the agency of lithium chloride and water in dimethyl sulfoxide[18] to give C_2-symmetrical ketone **10** in 94% yield.

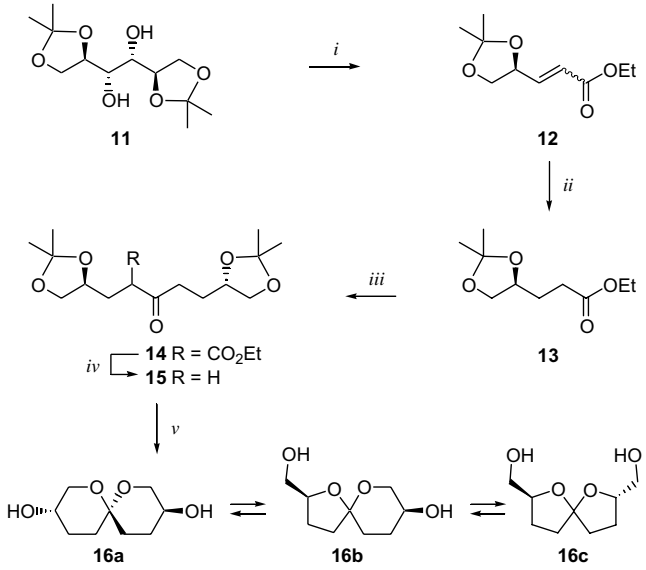


Scheme 1. Reagents and conditions: (i) (a) $BH_3{\cdot}Me_2S$, THF, 0 °C to rt, 15 h; (b) acetone, *p*-TsOH, 17 h, rt, 83% (2 steps); (ii) (a) $(COCl)_2$, DMSO, DiPEA, DCM, −78 °C, 2 h; (b) $Ph_3P{=}CHCO_2Me$ (1.4 equiv), DCM, 0 °C to rt, 15 h, 81% (2 steps); (iii) H_2, 10% Pd–C (cat.), EtOH, 24 h, rt, 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.

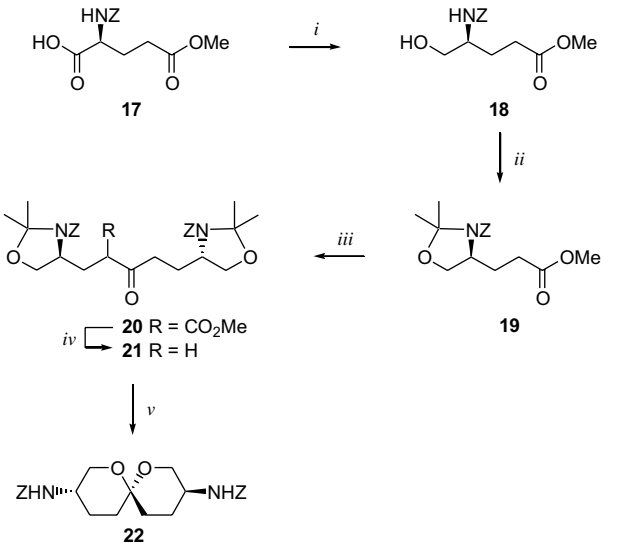
Unmasking of the diol functionalities by treatment with acid followed by intramolecular cyclisation led to the formation of spiroketal **4a** as a single isomer in quantitative yield.[19]

Next, the use of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (**11**) was investigated in the synthesis of 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.[20] At this stage, by analogy with the conditions described in Scheme 1, saturation of the double bond in **12** was achieved through palladium-catalysed hydrogenation leading to the formation of ester **13** (94%). Claisen self-condensation of ester **13** produced β-ketoester **14** in 58% yield. Decarboxylation of **14** with the LiCl/H_2O/DMSO system furnished ketone **15** in a yield of 92%. Acid 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).[21] Treatment of **17** with *N*-methylmorpholine (NMM) and ethyl chloroformate yielded the corresponding mixed anhydride



Scheme 2. Reagents and conditions: (i) (a) $NaIO_4$ (1.2 equiv), 5% aq $NaHCO_3$, rt, 1 h; (b) $(EtO)_2POCH_2CO_2Et$, 6 M aq K_2CO_3, 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%.



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%.

which was subsequently reduced with sodium borohydride furnishing alcohol **18** in 83% yield. Installation of the isopropylidene group 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%. Acidic removal of the isopropylidene protecting groups and concomitant cyclisation provided amine protected spiroketal **22** in a yield of 90%.[22]

In conclusion, we have presented a new route for the stereoselective synthesis of functionalised 1,7-dioxaspiro[5.5]undecane ring systems. These C_2-symmetrical spiroketals were efficiently obtained via acid-catalysed cyclisation of dihydroxyketones which are readily available from the Claisen self-condensation of suitably substituted hydroxy esters. The scope of our strategy in the preparation of unsymmetrical spiroketals and their implementation as chiral scaffolds is currently under investigation.

Acknowledgement

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19. All analytical data of compound **4a** are in full agreement with those reported in the literature (see Refs. 8b,f). $[\alpha]_D^{20}$ +59.0 (*c* 0.8, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 3.75 (m, 2H, H-2, H-7), 3.60 (dd, 2H, $J = 3.4$ Hz, $J = 11.4$ Hz, $2 \times CHCH_2OH$), 3.51 (dd, 2H, $J = 6.9$ Hz, $J = 11.4$ Hz, $2 \times CHCH_2OH$), 2.54 (s, 2H, $2 \times OH$), 1.99–1.82 (qt, 2H, $J = 4.2$ Hz, $J = 13.2$ 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 (dq, 2H, $J = 3.8$ Hz, $J = 12.8$ 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 ($2 \times CH_2OH$), 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.

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22. Analytical data of compound **22**: amorphous white solid. $[\alpha]_D^{20}$ +12.0 (*c* 0.1, $CHCl_3$). ^1H NMR (400 MHz, DMSO-d_6, 333 K): δ 7.40–7.27 (m, 10H, CH_{arom}), 7.05 (2H, $2\times NH$), 5.01 (m, 4H, $2\times CH_2Bn$), 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=OCBz), 137.0 (C_qCBz), 128.3, 127.8 (CH_{arom}), 93.2 (C-6), 65.3 (CH_2CBz), 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: 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.