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A Concise and Efficient Synthesis of Spiroketals – Application to the Synthesis of SPIKET-P and a Spiroketal from *Bactrocera* Species

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Keywords: Synthetic methods / Cyclization / Olefination / Spiro compounds / Natural products / Lactones / Enol ethers

We report the synthesis of spiroketals by sequence of enol ether synthesis and cyclization. The enol ethers were prepared from lactones by a Julia olefination reaction, and the starting chiral lactone was prepared from an industrial intermediate. This route is a concise and efficient way to synthesize naturally occurring and biologically interesting spiroketals. We used this sequence for the preparation of SPIKET-P and a spiroketal from *Bactrocera* species.

Introduction

Spiroketals are found in many natural products of biological interest such as marine macrolides, ionophores, and polyether antibiotics[1] (Figure 1). The synthesis of spiroketals has thus attracted considerable attention over the past decades.[2]

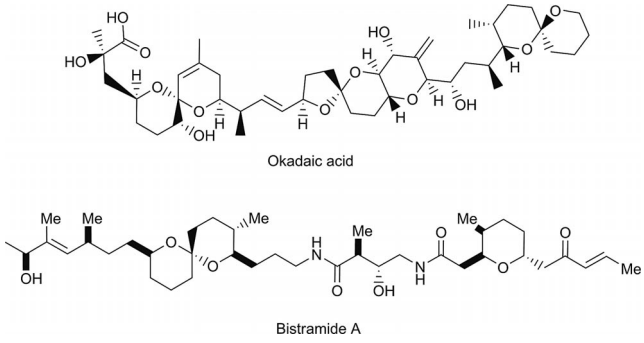

Figure 1. Structures of spiroketal-containing natural products.

We recently developed a short and convenient route to sugar-derived spiroketals using modified Julia reagents.[3] Starting from lactones, enol ethers were synthesized by treatment with a benzothiazolyl sulfone containing a protected alcohol. At this stage, the use of an acid-labile protecting group allowed us to prepare the spiroketals in a single step in acidic media (Figure 2).[4] We recently extended this methodology to non-carbohydrate lactones in the synthesis of the spiroketal fragment of bistramide A.[4b]

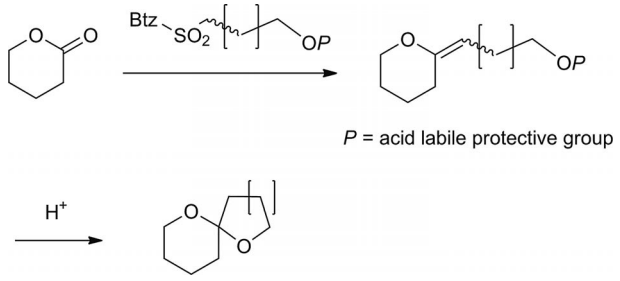

Figure 2. Synthetic route to spiroketals (Btz = benzothiazolyl).

In this paper, we describe how we have used this synthetic strategy for the preparation of two additional spiroketals of interest, and so tested the scope of the reaction with minimally substituted lactones. SPIKET-P (Figure 3) was rationally designed as a pharmacophore of spongistatin,[5] and has shown promising cytotoxicity against human breast cancer.[6] The second target is a component of the cephalic secretions of a cleptoparasitic bee.[7]

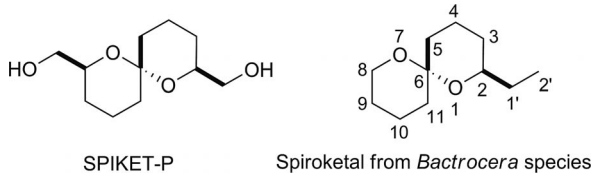

Figure 3. Structures of the two synthetic targets.

Results and Discussion

Optically active 2-hydroxymethyl lactones such as **4a** and **4b** are key intermediates for the synthesis of a large number

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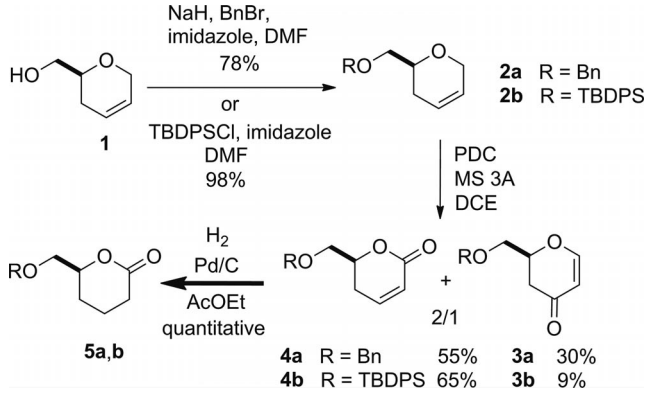
of natural products,[8] and we felt that it would be of interest to investigate their preparation from [(*S*)-3,6-dihydro-2*H*-pyran-2-yl]methanol (**1**), which was first synthesized as an intermediate for the synthesis of the protein kinase C inhibitor LY 333531.[9] Compound **1** was prepared by PPG on a large scale using a sequence of hetero-Diels–Alder reaction and enzymatic resolution.

Compound **1** was protected with a benzyl ether or a TBDPS (*tert*-butyldiphenylsilyl) ether protecting group (Scheme 1). Oxidation with PDC (pyridinium dichromate) in refluxing 1,2-dichloroethane (DCE) led to a separable mixture of the desired lactone (i.e., **4**) and enone **3**.[10] Finally, unsaturated lactones **4a** and **4b** were hydrogenated with Pd on charcoal to give lactones **5a** and **5b**, respectively, in quantitative yields.

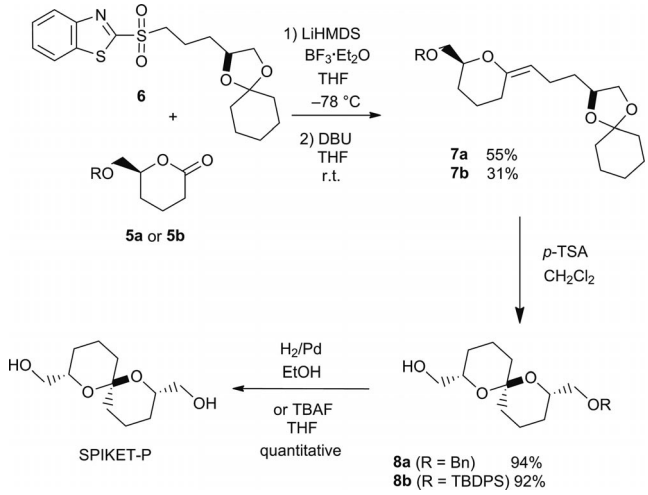


Scheme 1. Synthesis of lactones **5a** and **5b**.

SPIKET-P was prepared as shown in Scheme 2. The spiroketal was synthesized from lactone **5a** or **5b** and sulfone **6**[4b] in two steps using our methodology.[3,4] The enol ether was formed in the presence of LiHMDS and boron trifluoride–diethyl ether at low temperature, and was cyclized directly in acidic media (*p*-toluenesulfonic acid in dichloromethane) to give the thermodynamic spiroketals **8a** and **8b**. Not unexpectedly, the overall yield was higher with the less labile benzyl group. These compounds were deprotected to give SPIKET-P in six steps and overall yields of 18% (with TBDPS protection) and 22% (with benzyl protection) from (*S*)-(3,6-dihydro-2*H*-pyran-2-yl)methanol (**1**).

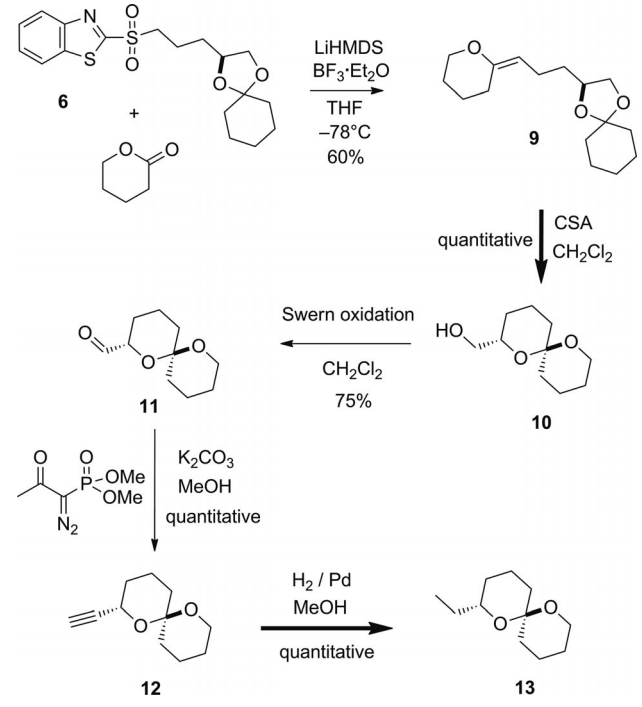
We then turned our attention to valerolactone, which was expected to be more challenging, due to the absence of either electronic or Thorpe–Ingold effects in the hemiketal anion intermediate.

Unexpectedly, treatment of a mixture of valerolactone, sulfone, and boron trifluoride–diethyl ether with LiHMDS at –78 °C gave the enol ether directly, and treatment with DBU was not required in this case (Scheme 3). The Julia olefination–cyclization sequence thus provided the thermodynamic spiroketal **10** in 60% yield. The homologation reaction was performed by oxidation of the primary alcohol, and reaction of the resulting aldehyde with the Ohira–Bestmann reagent to deliver the terminal alkyne **12**, which was hydrogenated to give the natural compound (i.e., **13**). The spiroketal from *Bactrocera* species was thus prepared in 12



Scheme 2. Synthesis of SPIKET-P (HMDS = hexamethyldisilazide; DBU = 1,8-diazabicycloundec-7-ene; *p*-TSA = *p*-toluenesulfonic acid; TBAF = tetrabutylammonium fluoride).

steps and 22% overall yield from dicyclohexylidene-D-mannitol. A wide range of natural and unnatural spiroketals can, in principle, be produced for diversity-orientated synthesis from a common Julia reagent following this approach.



Scheme 3. Synthesis of the spiroketal from *Bactrocera* species.

Conclusions

We have developed an original, general, and stereoselective route to spiroketals from lactones via an intermediate enol ether. We report the preparation of lactones **4** and **5** from an industrial intermediate, although additional in-

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vestigations into the control of the regiochemistry of the oxidation reaction are needed. We applied this methodology to the preparation of two spiroketals of interest: SPIKET-P, and a spiroketal from *Bactrocera* species.

Experimental Section

General Remarks: Reactions were carried out in dried glassware and under an argon atmosphere. All reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) on silica gel 60 F254 (Merck) plates using either UV light or 10% H_2SO_4 solution in ethanol to visualize the compounds. Solvents were distilled and dried from sodium benzophenone ketyl for tetrahydrofuran, and from calcium hydride for dichloromethane. Other dry solvents were purchased from commercial suppliers and used without further purification. Flash chromatography was performed on silica gel (40–60 μm) purchased from Acros Organics. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise noted. ^{1}H and ^{13}C NMR spectra were recorded at 23 °C with a Bruker Avance DRX300 spectrometer. Chemical shifts are referenced to the residual peaks of the solvent ($CDCl_3$: 7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C). The following abbreviations are used to denote the multiplicities: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, m = multiplet, and br. s = broad singlet. NMR solvents were purchased from Eurisotop (Saint Aubin, France). Low resolution mass spectra (ESI) and HRMS were recorded in positive ion mode using a Thermo Finnigan LCQ spectrometer.

(*S*)-6-(Benzyloxymethyl)tetrahydro-2*H*-pyran-2-one (5a): [(*S*)-3,6-Dihydro-2*H*-pyran-2-yl]methanol (1 g, 8.77 mmol) was dissolved in anhydrous DMF (44 mL) under argon, and the solution was cooled to 0 °C. Imidazole (299 mg, 4.39 mmol, 0.5 equiv.) was added in portions, and then NaH (60% in mineral oil; 702 mg, 17.54 mmol, 2 equiv.) was added. After 20 min, benzyl bromide (2.16 mL, 13.16 mmol, 1.5 equiv.) was added, and the mixture was stirred at room temperature until complete conversion of the starting material was observed. The reaction was quenched by the addition of methanol (5 mL), and extracted with dichloromethane (3× 50 mL). The organic extracts were combined, washed with water (4× 50 mL) and brine (50 mL), and then dried with $MgSO_4$, and filtered. The solvents were evaporated in vacuo. After purification over silica gel (eluent petroleum ether/EtOAc, 9:1), **2a** (1.40 g, 6.86 mmol, 78%) was obtained, and the analytical data were identical to those described in the literature.[11]

Compound **2a** (2 g, 9.80 mmol) was dissolved in dichloroethane (33 mL) under argon, and molecular sieves (3 Å, 11 g) and PDC (11 g, 29.4 mmol, 3 equiv.) were added. The reaction mixture was stirred at reflux for 24 h. The crude mixture was cooled, diluted with diethyl ether (250 mL) and filtered through a pad of Celite. After evaporation under reduced pressure, the residue was purified over silica gel (eluent petroleum ether/EtOAc, 8:2 to 1:1) to give starting material (17%), **4a** (1.18 g, 5.40 mmol, 55%), and **3a** (642 mg, 2.90 mmol, 30%). The analytical data were identical to those reported in the literature.[12]

A solution of lactone **4a** (708 mg, 3.25 mmol) in ethyl acetate (13 mL) was stirred at room temperature for 45 min under a hydrogen atmosphere with palladium on charcoal. The reaction mixture was filtered to give compound **5a** (714 mg, 3.25 mmol, quantitative). The data were consistent with those reported in the literature.[13]

(*S*)-Dihydropyranylmethoxy(*tert*-butyl)diphenylsilane (2b): Imidazole (598 mg, 8.77 mmol, 2.0 equiv.) and *tert*-butyl(chloro)diphenylsilane (1.4 mL, 5.26 mmol, 1.2 equiv.) were added to a solution of (*S*)-dihydropyranylmethanol (500 mg, 4.39 mmol, 1 equiv.) in *N*,*N*-dimethylformamide (8 mL) at 0 °C. The resulting solution was stirred at room temperature for 12 h. The mixture was then poured into water and extracted with ethyl acetate. The combined organic extracts were washed with water and brine, and dried with anhydrous $MgSO_4$. After filtration and concentration in vacuo, the crude product was purified over silica gel (95:5 petroleum ether/ethyl acetate) to give **2b** (1.53 g, 4.35 mmol, 98%) as a slightly yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.09 (m, 9 H), 2.05–2.07 (m, 2 H, 4-H), 3.61–3.71 (m, 2 H, 6-H), 3.78–3.83 (m, 1 H, 5-H), 4.19–4.20 (m, 2 H, 1-H), 5.70–5.74 (m, 1 H, 2-H), 5.82–5.85 (m, 1 H, 3-H), 7.37–7.41 (m, 6 H), 7.69–7.71 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 135.60 (CH), 133.1 (C), 130.2 (CH), 128.1 (CH), 126.9 (CH, C-2), 124.4 (CH, C-3), 74.3 (CH, C-5), 67.2 (CH_2, C-6), 65.8 (CH_2, C-1), 27.5 (CH_2, C-4), 26.8 (CH_3), 19.7 (C) ppm.

(*S*)-5,6-Dihydro-6-[methoxy(*tert*-butyl)diphenylsilyl]pyran-2-one (4b) and (*S*)-2-{[(*tert*-Butyldiphenylsilyl)oxy]methyl}-2*H*-pyran-4(3*H*)-one (3b): A mixture of pyridinium dichromate (1.433 mg, 6.65 mmol, 3 equiv.) and powdered molecular sieves (3 Å) was added to a solution of compound **2b** (780 mg, 2.22 mmol, 1 equiv.) in freshly distilled dichloroethane (7 mL). The reaction mixture was stirred at reflux for 4 h, then diluted with diethyl ether (100 mL), and finally passed through a pad of silica gel, which was washed with diethyl ether. Removal of the solvent in vacuo and purification by flash chromatography over silica gel (8:2 petroleum ether/ethyl acetate) gave lactone **4b** (521 mg, 1.42 mmol, 65%) as a colorless oil and ketone **3b** (73 mg, 0.20 mmol, 9%)as a colorless oil.

Data for 4b: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.09 (m, 9 H), 2.43 (dddd, *J* = 1.1, 4.6, 5.6, 18.5 Hz, 1 H, 4-H), 2.59 (app ddt, *J* = 2.7, 2.7, 10.9, 18.5 Hz, 1 H, 4-H), 3.85 (d, *J* = 4.9 Hz, 2 H, 6-H), 4.52 (dddd, *J* = 4.7, 4.7, 4.7, 9.4 Hz, 1 H, 5-H), 6.01 (ddd, *J* = 1.1, 2.6, 9.7 Hz, 1 H, 2-H), 6.89 (ddd, *J* = 2.7, 5.7, 9.7 Hz, 1 H, 3-H), 7.34–7.52 (m, 6 H), 7.65–7.69 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 163.3 (C, C-1), 144.4 (CH, C-3), 136.0 (CH), 133.0 (C), 130.2 (CH), 128.2 (CH), 121.2 (CH, C-2), 74.3 (CH, C-5), 65.9 (CH_2, C-6), 27.8 (CH_2, C-4), 27.2 (CH_3), 19.7 (C) ppm.

Data for 3b: ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.07 (s, 9 H), 2.44 (ddd, *J* = 1.1, 3.7, 16.9 Hz, 1 H, 4-H), 2.82 (app dd, *J* = 13.9, 16.9 Hz, 1 H, 4-H), 3.82 (dd, *J* = 11.4, 4.5 Hz, 1 H, 6-H), 3.92 (dd, *J* = 11.4, 3.9 Hz, 1 H, 6-H), 4.49 (dddd, *J* = 4.0, 4.1, 4.1, 13.5 Hz, 1 H, 5-H), 5.41 (dd, *J* = 6.0, 1.1 Hz, 1 H, 2-H), 7.50–7.32 (m, 7 H, 1-H), 7.70–7.61 (m, 4 H) ppm.

(*S*)-(*tert*-Butyldiphenylsiloxymethyl)tetrahydro-2*H*-pyran-2-one (5b): A solution of **14** (634 mg, 1.73 mmol, 1 equiv.) and Pd-C (10%; 10 mg, 0.08 mmol, 0.05 equiv.) in ethyl acetate (7 mL) was stirred under a positive pressure of H_2 for 24 h. The mixture was then diluted with diethyl ether, and passed through a pad (5 cm) of Celite, which was then washed with ethyl acetate. Removal of the solvent in vacuo and purification by flash chromatography over silica gel (8:2 petroleum ether/ethyl acetate) gave lactone **5b** (623 mg, 1.69 mmol, quantitative) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.07 (m, 9 H), 1.67–1.70 (m, 2 H, 3-H), 1.91–2.00 (m, 2 H, 4-H), 2.39–2.50 (m, 1 H, 2-H), 2.55–2.65 (m, 1 H, 2-H), 3.75 (dd, *J* = 4.0, 9.6 Hz, 1 H, 6-H), 3.80 (dd, *J* = 3.2, 9.6 Hz, 1 H, 6-H), 4.36–4.43 (m, 1 H, 5-H), 7.37–7.47 (m, 6 H), 7.65–7.69 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.6 (C, C-1), 135.6 (CH), 133.5 (C), 135.8 (CH), 128.2 (CH), 80.4 (CH, C-5), 65.7 (CH_2, C-6), 30.0 (CH_2, C-2), 26.9 (CH_3), 24.6 (CH_2, C-4), 19.4 (C), 18.5 (CH_2, C-3) ppm. MS (ESI): *m*/*z* = 391 $[M + Na]^+$. HRMS (ESI): calcd. for $[M + Na]^+$ 391.1700; found 391.1699.

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2-{3-[(*S*)-6-(Benzyloxymethyl)tetrahydro-2*H*-pyran-2-ylidene]-propyl}-1,4-dioxaspiro[4.5]decane (7a): Benzothiazolyl sulfone **6** (250 mg, 0.65 mmol, 1.2 equiv.) was added to a solution of lactone **5a** (119 mg, 0.54 mmol, 1 equiv.) and $BF_3{\cdot}Et_2O$ (68 μL, 0.54 mmol, 1 equiv.) in THF (1 mL) at room temperature . The mixture was cooled to –78 °C, and lithium hexamethyldisilazide (1 M in THF; 1 mL, 1.00 mmol, 2 equiv.) was added dropwise. The reaction mixture was stirred at –78 °C for 30 min, quenched by the addition of water at –78 °C, diluted with ethyl acetate, stirred at room temperature for 15 min, and extracted with ethyl acetate. The organic extracts were combined, washed with brine, and dried with anhydrous sodium sulfate. After filtration and evaporation in vacuo, the residue was dissolved in THF (5 mL), and 1,8-diazabicyclo[5.4.0]undec-7-ene (161 μL, 1.08 mmol, 2 equiv.) was added over 10 min. The reaction mixture was stirred at room temperature for 30 min, then it was concentrated in vacuo and the residue was purified by flash chromatography over alumina (9:1 petroleum ether/ethyl acetate) to give compound **7a** (114.6 mg, 0.30 mmol, 55%) as a colorless oil. IR: $\tilde{\nu}$ = 2933, 2860, 1722, 1676, 1497, 1450, 1364, 1331, 1279, 1233, 1163, 1099, 1069, 1041, 1028, 929, 908, 847, 828, 735, 697 cm^{-1}. $[\alpha]_D^{25}$ = +27.4 (*c* = 1.0, $CHCl_3$). ^1H NMR ([D]$_6$acetone, 300 MHz): δ = 1.38 (m, 2 H), 1.45–1.65 (m, 13 H), 1.83–1.93 (m, 1 H), 1.95–2.07 (m, 4 H), 3.44 (dd, *J* = 7.2, 7.2 Hz, 1 H, 10-H), 3.57 (dd, *J* = 4.8, 10.4 Hz, 1 H, 6-H), 3.63 (dd, *J* = 5.4, 10.2 Hz, 1 H, 6-H), 3.96–4.01 (m, 3 H, 5-H and 11-H), 4.49 (m, 1 H, 7-H), 4.58 (s, 2 H), 7.25–7.38 (m, 5 H) ppm. ^{13}C NMR ([D]$_6$acetone, 75 MHz): δ = 154.8 (C, C-1), 140.2 (C), 129.5 (CH), 128.7 (CH), 128.6 (CH), 109.8 (C), 96.2 (CH, C-7), 76.7 (CH, C-5), 75.7 (CH, C-10), 74.1 (CH_2, C-11), 73.6 (CH_2, C-6), 70.1 (CH_2), 37.9 (CH_2), 36.5 (CH_2), 35.2 (CH_2), 34.4 (CH_2), 26.4 (CH_2), 25.5 (CH_2), 25.1 (CH_2), 25.0 (CH_2), 24.5 (CH_2), 20.9 (CH_2) ppm. MS (ESI): *m*/*z* = 409 $[M + Na]^+$. HRMS (ESI): calcd. for $[M + Na]^+$ 409.2355; found 409.2357.

({(2*S*)-6-[3-(1,4-Dioxaspiro[4.5]decan-2-yl)propylidene]tetrahydro-2*H*-pyran-2-yl}methoxy)(*tert*-butyl)diphenylsilane (7b): Following the same procedure as for **7a**, the crude mixture was purified over basic alumina (eluent petroleum ether/EtOAc, 95:5) to obtain **7b** (224 mg, 0.42 mmol, 31%) as a colorless oil. R_f (SiO_2, petroleum ether/EtOAc, 8:2) = 0.90. IR: $\tilde{\nu}_{max}$ = 2932, 2857, 1741, 1676, 1473, 1462, 1448, 1428, 1390, 1363, 1332, 1280, 1235, 1163, 1104, 1069, 1044, 1006, 976, 930, 908, 848, 823, 796, 739, 700 cm^{-1}. $[\alpha]_D$ = +18.2 (*c* = 1.0, $CHCl_3$). ^1H NMR ([D]$_6$acetone, 300 MHz): δ = 7.79–7.75 (m, 4 H, H-Ar), 7.49–7.45 (m, 6 H, H-Ar), 4.49 (m, 1 H, 7-H), 4.09–3.92 (m, 3 H), 3.84 (dd, *J* = 10.6, 4.9 Hz, 1 H, 6a-H), 3.80 (dd, *J* = 10.6, 5.1 Hz, 1 H, 6b-H), 3.44 (t, *J* = 7.2 Hz, 1 H, 10-H), 2.14–1.98 (m, 6 H), 1.72–1.47 (m, 12 H), 1.38 (m, 2 H), 1.08 [s, 9 H C(CH_3)$_3$] ppm. ^{13}C NMR ([D]$_6$acetone, 75 MHz): δ = 154.0 (C), 135.9 (CH), 133.9 (C), 130.1 (CH), 128.1 (CH), 108.9 (C), 95.2 (CH), 76.2 (CH), 75.8 (CH), 69.2 (CH_2), 66.7 (CH_2), 37.0 (CH_2), 35.6 (CH_2), 34.4 (CH_2), 33.5 (CH_2), 26.7 [(CH_3)$_3$], 25.2 (CH_2), 24.2 (CH_2), 24.2 (CH_2), 24.1 (CH_2), 23.7 (CH_2), 20.1 (CH_2), 19.4 (C) ppm. MS (ESI^+): *m*/*z* = 557.3 $[M + Na]^+$. HRMS (ESI^+): calcd. for $[M + Na]^+$ 557.3063; found 557.3062.

[(2*S*,6*S*,8*S*)-8-(Benzyloxymethyl)-1,7-dioxaspiro[5.5]undecan-2-yl]-methanol (8a): *para*-Toluenesulfonic acid (21 mg, 0.11 mmol, 0.5 equiv.) was added to the mixture of enol ethers **7a** (83.5 mg, 0.22 mmol, 1 equiv.) in dichloromethane (3 mL). The reaction mixture was stirred at room temperature for 25 min, then the solvent was evaporated in vacuo, and the crude product was purified by flash chromatography over silica gel (70:30 petroleum ether/ethyl acetate) to give spiroketal **8a** (61.2 mg, 0.20 mmol, 94%) as a colorless oil. R_f (SiO_2, petroleum ether/EtOAc, 7:3) = 0.32. IR: $\tilde{\nu}_{max}$ = 3446, 2937, 2868, 1721, 1497, 1454, 1365, 1280, 1225, 1204, 1166, 1090, 1045, 1018, 984, 950, 923, 907, 841, 820, 734, 697 cm^{-1}. $[\alpha]_D$ = +32.3 (*c* = 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.35–7.25 (m, 5 H, H Ar), 4.60 (s, 2 H, PhCH_2O), 3.88–3.74 (m, 2 H, 2-H and 8-H), 3.60 (m, 1 H, 1′a-H), 3.52–3.42 (m, 1 H, 1′b-H), 3.50 (dd, *J* = 10.2, 5.7 Hz, 1 H, 1′′a-H), 3.44 (dd, *J* = 10.2, 4.8 Hz, 1 H, 1′′b-H), 2.01 (br. s, 1 H, OH), 2.03–1.81 (m, 2 H), 1.68–1.54 (m, 5 H), 1.51–1.21 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 139.0 (C), 128.7 (CH), 127.9 (CH), 127.8 (CH), 96.5 (C), 74.0 (CH_2), 73.7 (CH_2), 70.0 (CH), 69.2 (CH), 66.6 (CH_2), 35.7 (CH_2), 35.5 (CH_2), 27.8 (CH_2), 26.9 (CH_2), 18.9 (CH_2), 18.6 (CH_2) ppm. MS (ESI^+): *m*/*z* = 329.1 $[M + Na]^+$, 307.0 $[M + H]^+$. HRMS (ESI^+): calcd. for $[M + Na]^+$ 329.1729; found 329.1729.

{(2*S*,6*S*,8*S*)-8-[(*tert*-Butyldiphenylsilyloxy)methyl]-1,7-dioxaspiro-[5.5]undecan-2-yl}methanol (8b): Following the same procedure as for **8a**, the crude mixture was purified over silica gel (eluent petroleum ether/EtOAc, 8:2) to give spiroketal **8b** (180 mg, 0.40 mmol, 92%) as a pale yellow oil. R_f (SiO_2, petroleum ether/EtOAc, 8:2) = 0.53. IR: $\tilde{\nu}$ = 3485, 2934, 2858, 1741, 1590, 1473, 1458, 1428, 1373, 1239, 1226, 1112, 1089, 1074, 1045, 982, 949, 922, 840, 823, 802, 739, 701, 690 cm^{-1}. $[\alpha]_D$ = +9.5 (*c* = 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 7.75–7.71 (m, 4 H), 7.40–7.32 (m, 6 H), 3.87–3.73 (m, 2 H, 2-H and 8-H), 3.68 (dd, *J* = 10.3, 6.2 Hz, 1 H), 3.60 (dd, *J* = 11.3, 3.4 Hz, 1 H), 3.58 (dd, *J* = 10.4, 4.5 Hz, 1 H), 3.49 (dd, *J* = 11.1, 6.8 Hz, 1 H), 2.17 (br. s, 1 H, OH), 1.93 (m, 1 H), 1.68–1.57 (m, 5 H), 1.48–1.25 (m, 6 H), 1.07 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 135.8 (CH), 134.0 (C), 129.7 (C), 127.7 (CH), 127.7 (CH), 96.1 (C), 70.4 (CH), 69.5 (CH), 67.5 (CH_2), 66.4 (CH_2), 35.5 (CH_2), 35.3 (CH_2), 27.1 (CH_2), 26.9 [(CH_3)$_3$], 26.6 (CH_2), 19.7 (C), 19.4 (CH_2), 18.7 (CH_2) ppm. MS (ESI^+): *m*/*z* = 477.2 $[M + Na]^+$. HRMS (ESI^+): calcd. for $[M + Na]^+$ 477.2437; found 477.2437.

[(2*S*,8*S*)-8-(Hydroxymethyl)-1,7-dioxaspiro[5.5]undec-2-yl]methanol (SPIKET-P): A mixture of spiroketal **8a** (23.5 mg, 0.08 mmol, 1 equiv.) and $Pd(OH)_2$ (20 mg) in ethanol (4 mL) was stirred under a positive pressure of H_2 for 16 h. The mixture was diluted with diethyl ether, and passed through a pad (5 cm) of Celite, which was washed with ethyl acetate. The solvent was evaporated in vacuo, and the crude product was purified by flash chromatography over silica gel (70:30 petroleum ether/ethyl acetate) to give SPIKET-P (14.7 mg, 0.07 mmol, 90%) as a colorless oil. IR: $\tilde{\nu}$ = 3380, 2931, 1463, 1454, 980 cm^{-1}. $[\alpha]_D^{25}$ = +62.9 (*c* = 0.9, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.19–1.54 (m, 6 H, 2-H, 4-H, 7-H, and 9-H), 1.54–1.68 (m, 4 H, 2-H, 3-H, 7-H, and 8-H), 1.89 (qt, *J* = 4.2, 13.0 Hz, 2 H, 3-H and 8-H), 2.18 (br. s, 2 H, OH), 3.50 (dd, *J* = 6.9, 11.3 Hz, 2 H, 6-H and 11-H), 3.50 (dd, *J* = 6.9, 11.3 Hz, 2 H, 6-H and 11-H), 3.78–3.69 (m, 2 H, 5-H and 10-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 96.2 (C, C-1), 69.9 (CH, C-5 and C-10), 66.3 (CH_2, C-6 and C-11), 35.4 (CH_2, C-2 and C-7), 26.5 (CH_2, C-4 and C-9), 18.4 (CH_2, C-3 and C-8) ppm. MS (CI): *m*/*z* = 217 $[M + H]^+$. Analytical data consistent with those reported in the literature.[14]

2-[3-(Tetrahydro-2*H*-pyran-2-ylidene)propyl]-1,4-dioxaspiro[4.5]-decane (9): $BF_3{\cdot}Et_2O$ (279 μL, 2.20 mmol, 1 equiv.) was added to a solution of *δ*-valerolactone (200 μL, 220 mg, 2.20 mmol) and 2-[3′-(1,4-dioxaspiro[4.5]decan-2-yl)propylsulfonyl]benzo[*d*]thiazole (**6**) (1.00 g, 2.64 mmol, 1.2 equiv.) in distilled THF (11 mL) under argon. The mixture was cooled to –78 °C, and LiHMDS (1 M in THF; 4.39 mL, 4.39 mmol, 2 equiv.) was added. After 30 min at –78 °C, the reaction mixture was quenched by the addition of water (500 μL), and diluted with ethyl acetate. The solution was dried with sodium sulfate, filtered, and evaporated to give a pale yellow solid. This residue was purified by flash chromatography over basic

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alumina (eluent petroleum ether/EtOAc, 95:5) to give enol ether **9** (348 mg, 1.31 mmol, 60%) as a colorless oil. R_f (SiO_2, petroleum ether/EtOAc, 8:2) = 0.71 and 0.76. IR: $\tilde{\nu}_{max}$ = 2932, 2862, 1675, 1449, 1389, 1364, 1347, 1280, 1233, 1163, 1143, 1102, 1064, 1042, 978, 929, 909, 848, 827, 814, 761, 658 cm^{-1}. $[\alpha]_D$ = +7.1 (c = 1.0, $CHCl_3$). ^1H NMR ([D$_6$]acetone, 300 MHz): δ = 4.50 (t, J = 3.5 Hz, 1 H, 5-H), 4.13–4.02 (m, 2 H), 3.97 (dd, J = 5.1, 5.1 Hz, 2 H), 3.48 (dd, J = 7.2, 6.6 Hz, 1 H, 8-H), 2.04–1.98 (m, 4 H), 1.82–1.74 (m, 2 H), 1.65–1.51 (m, 12 H), 1.45–1.39 (m, 2 H) ppm. ^{13}C NMR ([D$_6$]acetone, 75 MHz): δ = 155.1 (C), 109.5 (C), 96.0 (CH), 76.4 (CH), 69.9 (CH_2), 66.7 (CH_2), 37.6 (CH_2), 36.2 (CH_2), 35.1 (CH_2), 34.1 (CH_2), 26.1 (CH_2), 24.9 (CH_2), 24.7 (CH_2), 24.2 (CH_2), 23.4 (CH_2), 21.0 (CH_2) ppm. MS (CI): m/z = 267.2 $[M + H]^+$ HRMS (ESI^+): calcd. for $[M + H]^+$ 267.1960; found 267.1960.

{(2*S*,6*S*)-1,7-Dioxaspiro[5.5]undecan-2-yl}methanol (10): Following the same procedure as for compound **8a**, the crude mixture was purified over silica gel (eluent petroleum ether/EtOAc, 8:2). Spiroketal **10** (301 mg, 1.62 mmol, quantitative) was obtained as a colorless oil. R_f (SiO_2, petroleum ether/EtOAc, 8:2) = 0.23. IR: $\tilde{\nu}_{max}$ = 3436, 2938, 2870, 1439, 1383, 1280, 1258, 1227, 1210, 1182, 1146, 1119, 1092, 1076, 1059, 1046, 1021, 988, 949, 919, 894, 875, 862, 847, 806, 734 cm^{-1}. $[\alpha]_D$ = +77.4 (c = 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 3.71 (m, 1 H, 8a-H), 3.64–3.52 (m, 2 H, 2-H and 8b-H), 3.58 (dd, J = 11.2, 3.5 Hz, 1 H, 1′a-H), 3.47 (dd, J = 7.0, 11.3 Hz, 1 H, 1′b-H), 2.43 (br. s, 1 H, OH), 1.91–1.71 (m, 2 H), 1.60 (m, 1 H), 1.57–1.16 (m, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 95.9 (C), 70.1 (CH_2), 66.6 (CH_2), 60.8 (CH_2), 35.9 (CH_2), 35.7 (CH_2), 26.8 (CH), 25.6 (CH_2), 18.9 (CH_2), 18.5 (CH_2) ppm. MS (CI): m/z = 187 $[M + H]^+$. HRMS (CI): calcd. for $[M + H]^+$ 187.1333; found 187.1334.

(2*S*,6*S*)-1,7-Dioxaspiro[5.5]undecane-2-carbaldehyde (11): Oxalyl chloride (2 M in dichloromethane; 1.44 mmol, 2 equiv.) was cooled to –78 °C under argon. A solution of anhydrous DMSO (205 μL, 2.88 mmol, 4 equiv.) in dichloromethane (600 μL) was added dropwise. Then alcohol **10** (134 mg, 0.72 mmol, 1 equiv.) in dichloromethane was added. After 15 min at –78 °C, Et_3N (600 μL, 4.32 mmol, 6 equiv.) was added, and the reaction mixture was warmed to room temperature. The mixture was extracted with diethyl ether (3× 25 mL). The organic extracts were combined, washed with brine (20 mL), dried with Na_2SO_4, and filtered, and the solvents were evaporated in vacuo. Purification of the residue on silica gel (eluent petroleum ether/EtOAc, 8:2) gave aldehyde **11** (99 mg, 75%) as a colorless oil. The aldehyde could also be used without further purification. ^1H NMR ($CDCl_3$, 300 MHz): δ = 9.67 (s, 1 H, 1′-H), 4.03 (d, J = 12.1 Hz, 1 H), 3.59 (d, J = 6.4 Hz, 2 H), 1.85–1.21 (m, 12 H) ppm.

(2*S*,6*S*)-2-Ethynyl-1,7-dioxaspiro[5.5]undecane (12): K_2CO_3 (150 mg, 1.09 mmol, 2 equiv.) and dimethyl 1-diazo-(2-oxopropyl)-phosphonate (118 mg, 0.61 mmol, 1.2 equiv.) in methanol (1 mL) were added to a solution of (2*S*,6*S*)-1,7-dioxaspiro[5.5]undecane-2-carbaldehyde (**11**) (100 mg, 0.51 mmol) in methanol (8 mL) under argon. The reaction mixture was stirred at room temperature for 2 h. The mixture was extracted with ether (2× 50 mL), and the combined organic extracts were washed with $NaHCO_3$ (sat. aq.; 25 mL), then brine (25 mL). The organic phase was dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent petroleum ether/EtOAc, 95:5) to give **12** (98 mg, 0.51 mmol, quantitative) as white needles, m.p. 64–66 °C. R_f (SiO_2, petroleum ether/EtOAc, 95:5) = 0.39. IR: $\tilde{\nu}_{max}$ = 3217, 2944, 2877, 2115, 1451, 1438, 1384, 1355, 1301, 1281, 1254, 1231, 1209, 1181, 1143, 1111, 1091, 1064, 1052, 1043, 1031, 979, 947, 932, 909, 891, 865, 849, 814, 740, 721 cm^{-1}. $[\alpha]_D$ = +52.7 (c = 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ = 4.42 (dt, J = 11.3, 2.2 Hz, 1 H, 2-H), 3.71 (m, 1 H, 8a-H), 3.65–3.59 (m, 1 H, 8b-H), 2.42 (d, J = 2.2 Hz, 1 H, 1′-H), 2.01–1.78 (m, 3 H), 1.73–1.65 (m, 1 H), 1.63–1.37 (m, 8 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 96.5 (C), 84.3 (C), 72.2 (CH), 61.0 (CH_2), 60.3 (CH), 35.8 (CH_2), 35.1 (CH_2), 32.1 (CH_2), 25.5 (CH_2), 18.8 (CH_2), 18.7 (CH_2) ppm. MS (CI): m/z = 181.2 $[M + H]^+$. HRMS (CI): calcd. for $[M + H]^+$ 181.1229; found 181.1230.

(2*S*,6*S*)-2-Ethyl-1,7-dioxaspiro[5.5]undecane (13): Pd on charcoal (7 mg) was added to a solution of compound **12** (50 mg, 0.39 mmol) in methanol (1.3 mL), and the mixture was stirred under a hydrogen atmosphere overnight at room temperature. After filtration through Celite, the pad was washed with dichloromethane. The filtrates were combined, and the solvent was evaporated under reduced pressure to give compound **13** (51 mg, 0.39 mmol, quantitative) as a colorless oil. ^1H NMR ($CDCl_3$): δ = 3.72–3.34 (m, 3 H), 1.93–1.75 (m, 2 H), 1.64–1.32 (m, 11 H), 1.22–1.08 (m, 1 H), 0.98 (t, J = 6.0 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 95.3 (C), 70.4 (CH), 60.4 (CH_2), 35.9 (CH_2), 35.4 (CH), 30.9 (CH_2), 29.3 (CH_2), 25.5 (CH_2), 18.8 (CH_2), 18.6 (CH_2), 10.3 (CH_3) ppm. HRMS (EI): calcd. for $[M]^+$ 184.1463; found 184.1458.

Supporting Information (see footnote on the first page of this article): ^1H NMR spectra of compounds **4a**, **4b**, **5a**, **5b**, **7b**, **9**, and **11**, and ^1H and ^{13}C NMR spectra of compounds **7a**, **8a**, **8b**, SPIKET-P, **10**, **12** and **13** are available.

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[1] a) W. Francke, W. Kitching, *Curr. Org. Chem.* **2001**, *5*, 233–251; b) J. E. Aho, P. M. Pihko, T. K. Rissa, *Chem. Rev.* **2005**, *105*, 4406–4440.

[2] a) F. Perron, K. F. Albizati, *Chem. Rev.* **1989**, *89*, 1617–1661; b) K. T. Mead, B. N. Brewer, *Curr. Org. Chem.* **2003**, *7*, 227–256; c) S. Favre, P. Vogel, S. Gerber-Lemaire, *Molecules* **2008**, *13*, 2570–2600; d) M. C. Mc Leod, M. A. Brimble, D. C. K. Rathwell, Z. E. Wilson, T. Y. Yuen, *Pure Appl. Chem.* **2012**, *84*, 1379–1390.

[3] a) D. Gueyrard, R. Haddoub, A. Salem, N. Said Bacar, P. G. Goekjian, *Synlett* **2005**, 520–522; b) B. Bourdon, M. Corbet, P. Fontaine, P. G. Goekjian, D. Gueyrard, *Tetrahedron Lett.* **2008**, *49*, 747–749.

[4] a) M. Corbet, B. Bourdon, D. Gueyrard, P. G. Goekjian, *Tetrahedron Lett.* **2008**, *49*, 750–754; b) L. Tomas, D. Gueyrard, P. G. Goekjian, *Tetrahedron Lett.* **2010**, *51*, 4599–4601; c) L. Tomas, G. Boije af Gennas, M. A. Hiebel, P. Hampson, D. Gueyrard, B. Pelotier, J. Yli-Kauhaluoma, O. Piva, J. M. Lord, P. G. Goekjian, *Chem. Eur. J.* **2012**, *18*, 7452–7466.

[5] H. Huang, C. Mao, S. T. Jan, F. M. Uckun, *Tetrahedron Lett.* **2000**, *41*, 1699–1702.

[6] F. M. Uckun, C. Mao, A. O. Vassilev, H. Huang, S. T. Jan, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 541–545.

[7] a) J. Tengo, G. Bergstrom, A. K. Borg-Karlson, I. Groth, W. Francke, *Z. Naturforsch. C* **1982**, *37*, 376–380; b) J. E. Stok, C. S. Lang, B. D. Schwartz, M. T. Fletcher, W. Kitching, J. J. De Voss, *Org. Lett.* **2001**, *3*, 397–400.

[8] a) J. Mulzer, E. Oehler, *Angew. Chem.* **2001**, *113*, 3961–3964; *Angew. Chem. Int. Ed.* **2001**, *40*, 3842–3846; b) L. C. Dias, P. R. R. Meira, *Tetrahedron Lett.* **2002**, *43*, 8883–8885; c) J. Pospisil, I. E. Marko, *Tetrahedron Lett.* **2006**, *47*, 5933–5937; d)

 © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

M. Kanematsu, M. Yoshida, K. Shishido, *Tetrahedron Lett.* **2011**, *52*, 1372–1374.
[9] J. C. Caille, C. K. Govindan, H. Junga, J. Lalonde, Y. Yao, *Org. Process Res. Dev.* **2002**, *6*, 471–476.
[10] F. Bonadies, R. Di Fabio, C. Bonini, *J. Org. Chem.* **1984**, *49*, 1647–1649.
[11] S. Aragonès, F. Bravo, Y. Diaz, M. I. Matheu, S. Castillon, *Tetrahedron: Asymmetry* **2003**, *14*, 1847–1856.
[12] G. E. Keck, X.-Y. Li, C. E. Knutson, *Org. Lett.* **1999**, *1*, 411–413.
[13] N. C. Barua, R. R. Schmidt, *Synthesis* **1986**, 1067–1070.
[14] a) S. Sauret, A. Cuer, J. Gourcy, G. Jeminet, *Tetrahedron: Asymmetry* **1995**, *6*, 1995–2000; b) M. T. Crimmins, S. W. Rafferty, *Tetrahedron Lett.* **1996**, *37*, 5649–5652; c) X. Fan, G. R. Flentke, D. H. Rich, *J. Am. Chem. Soc.* **1998**, *120*, 8893–8894; d) P. Hayes, B. D. Suthers, W. Kitching, *Tetrahedron Lett.* **2000**, *41*, 6175–6179; e) A. B. Smith, R. M. Corbett, G. R. Pettit, J. C. Chapuis, J. M. Schmidt, E. Hamel, M. K. Jung, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2039–2042; f) A. Sharma, P. Iyer, S. Gamre, S. Chattopadhyay, *Synthesis* **2004**, 1037–1040; g) B. Lastdrager, M. S. M. Timmer, G. A. Van der Marel, H. S. Overkleeft, *Tetrahedron Lett.* **2005**, *46*, 6195–6198; h) N. Ardes-Guisot, B. Ouled-Lahoucine, I. Canet, M. E. Sinibaldi, *Tetrahedron Lett.* **2007**, *48*, 8511–8513.

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