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Stereoselective synthesis of 1,6-dioxaspiro[4.5]decane chiral spiroketal skeleton via C_2-symmetric approach using crossmetathesis

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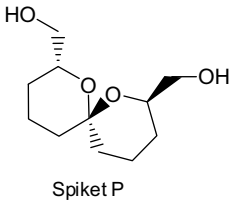
ABSTRACT

A common asymmetric approach for the synthesis of a 1,6-dioxaspiro[4.5]decane chiral spiroketal system, which is a subunit of various natural products, is described and the key aspects of the synthesis are self-crossmetathesis and exploitation of C_2-symmetric of the metathesis product **5** to obtain the required chiral spiroketal.

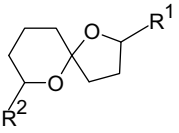
1. Introduction

Spiroketals are widely distributed in nature[1] and exist in a wide range of natural products of varying complexity. Spiroketals, particularly 1,7-dioxaspiro[5.5]undecane and the 1,6-dioxaspiro[4.5]decane systems, are subunits of many biologically active compounds such as polyether ionophores, insect pheromones, and antibiotic macrolides. The sources of these include insects, microbes, plants, fungi, and marine organisms.[2] The novel structural features of these spiroketals have attracted the attention of both biologists and synthetic organic chemists, and several approaches have been developed for their synthesis.[3] It was recently reported that even poorly substituted spiroketals exhibit biological effects such as tublin modulation[4] (Spiket P) and cytotoxicity against tumor cell lines[5] (Fig. 1).

Due to the wide occurrence of such structures, a rapid and reliable entry into spirocyclic structure is highly desirable. In continuation of our ongoing work in the synthesis of important acetals such as brevicomins,[6] spiroperoxides,[6e] and also in metathesis reaction,[7] we recently undertook the synthesis of (+)-spirolaxine

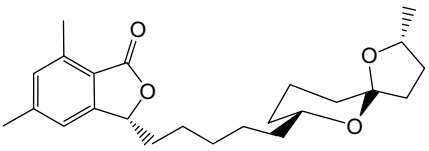


Spiket P



1,6-dioxaspiro[4,5]decane[3,10]

R^1	R^2
H	Me
Me	Me
Me	Et
Et	Me



(+)-spirolaxine methyl ether

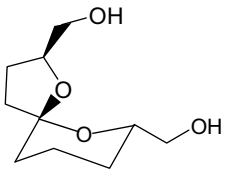


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Figure 1.

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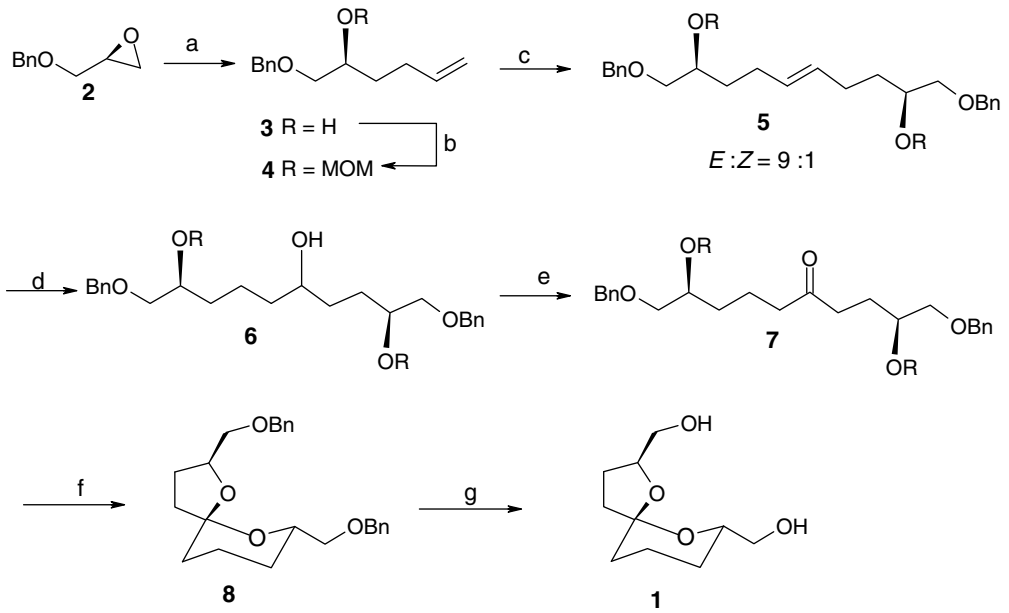
methyl ether (Fig. 1) an anti-helicobacter pylori agent,[8] which contains a 1,6-dioxaspiro[4.5]decane system. We envisaged that 1,6-dioxaspiro[4.5]decane unit **1**[9] can be a precursor of natural spiroketal class of compounds such as spirolaxine methyl ether and pheromones[3,10] and it could be synthesized from crossmetathesis[11] (self-metathesis of **4**) and acid-catalyzed cyclization reactions via C_2-symmetric substrate. This strategy of making C_2-symmetric compounds from a single substrate in a single step has an advantage over conventional approach, which requires more than one substrate thus leading to more manipulations.

2. Results and discussions

The synthesis of **1** was initiated from the known epoxide **2**, which is commercially available. The regioselective opening of epoxide **2** using allylmagnesiumbromide gave alcohol **3**; the alcohol functionality was protected as methoxymethyl ether to get the olefin precursor **4** using methoxymethyl chloride and diisopropylethylamine in dichloromethane. The key crossmetathesis reaction of olefin **4** using Grubbs' first generation olefin metathesis catalyst (10 mol %) afforded the C_2-symmetric dimer compound **5** as an inseparable *E*, *Z* mixture with a ratio of *E*:*Z* = 9:1, which was identified by proton integration values in ^{1}H NMR and was used in the next step without their separation. Hydroboration of olefin **5** yielded alcohol **6**. This was converted to keto compound **7** using Dess–Martin periodinane. The spiroketalization of ketone **7** by treatment with concd HCl in MeOH gave cyclized compound **8**. Finally, the deprotection of benzyl group was achieved by Na/liq. NH_3 to afford the desired compound **1**, as a colorless liquid in 90% yield, whose physical and spectroscopic data were in good agreement with the reported values.[9]



Reagents and conditions: (a) CH_2=CH-CH_2MgBr, CuI, Ether, -20 °C, 12 h, 87%; (b) MOM-Cl, DIPEA, DMAP, DCM, 0 °C to rt, 4 h, 90%; (c) 10 mol% Grubbs 1st generation catalyst, DCM, 40 °C, 12 h, 94%; (d) BH_3-DMS, H_2O_2, NaOH, THF, 0 °C to rt, 8 h, 85%; (e) Dess-Martin periodinane, DCM, 0 °C to rt, 3 h, 88%; (f) Conc. HCl, MeOH, 40 °C, 10 min 92%; (g) Na in liq. NH_3, THF, -78 °C, 5 h, 85%.

3. Conclusions

In conclusion, we have demonstrated a short asymmetric and versatile approach for the synthesis of 1,6-dioxaspiro[4.5]decane chiral spiroketal system from only one starting material using self-metathesis and acid-catalyzed cyclization. Extention studies for the synthesis of natural spiroketals are under progress.

4. Experimental

TLC was performed on Merck Kiesel Gel 60, F254 plates (layer thickness 0.25 mm). Column chromatography was performed on silica gel (60–120 mesh) using ethyl acetate and hexane mixture as eluent. Melting points were determined on a Fisher John's melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer RX-1 FT-IR system. ^{1}H NMR and ^{13}C NMR spectra were recorded using Varian Gemini-200 MHz or Bruker Avance-300 MHz spectrometer.^{1}H NMR data are expressed as chemical shifts in ppm followed by multiplicity (s-singlet; d-doublet; t-triplet; q-quartet; m-multiplet), number of proton(s) and coupling constant(s) *J* (Hz). ^{13}C NMR chemical shifts are expressed in ppm. Optical rotations were measured with Horiba-SEPA-300 digital polarimeter. Accurate mass measurement was performed on Q STAR mass spectrometer (Applied Biosystems, USA).

4.1. (*S*)-((2-(Methoxymethoxy)hex-5-enyloxy)methyl)benzene 4

To an ice-cooled stirred solution of alcohol **3** (2 g, 9.7 mmol) in DCM (20 mL) were added DIPEA (6.6 mL, 38.8 mmol), MOMCl (1.5 mL, 19.4 mmol), and DMAP (5 mg). The reaction mixture was allowed to warm to room temperature, then stirred for 4 h. The reaction mixture was extracted with DCM (3 × 30 mL) and water (30 mL). The combined organic layers were washed with brine dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate: petroleum ether (1:7) to afford compound **4** (2.2 g, 91%) as a liquid. $[\alpha]_D^{32} = -42$ (*c* 1, $CHCl_3$); IR ν_{max} 2926, 1639, 1450, 1364, 1211, 1101, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.3 (m, 5H),

5.8 (m, 1H), 5 (m, 2H), 4.72 (d, H, J = 7.2 Hz), 4.62 (d, H, J = 7.2 Hz) 4.52 (s, 2H), 3.72 (m, 1H), 3.47 (m, 2H), 3.35 (s, 3H), 2.13 (m, 2H), 1.65 (m, 2H); ^{13}C NMR (75 MHz) in $CDCl_3$: δ 138.1, 128.2, 127.4, 114.6, 95.9, 75.6, 73.1, 72.4, 55.3, 31.1, 29.5; LC–MS: 273 $[M+Na]^+$.

4.2. (5*R*,12*S*,*E*)-5,12-Bis(benzyloxymethyl)-2,4,13,15-tetraoxahexadec-8-ene 5

The olefin **4** (1 g, 3.75 mmol) was dissolved in dry CH_2Cl_2 (10 mL). Grubbs' 1st generation catalyst (0.15 g, 0.18 mmol) was added. The reaction mixture was stirred at 40 °C temperature for 12 h, and then concentrated under reduced pressure after which the residue was purified by column chromatography using ethyl acetate–petroleum ether (1:6) to afford the compound **5** (0.89 g, 94%) as a viscous liquid (*cis*–*trans* mixture, 9:1). $[\alpha]_D^{32} = -9.2$ (c 1.25, $CHCl_3$); IR ν_{max} 2926, 2855, 1619, 1451, 1304, 1146, 1103, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.28 (m, 10H), 5.4-5.32 (m, 2H), 4.7 (d, 2H, J = 6.8 Hz), 4.6 (d, 2H, J = 6.8 Hz) 4.5 (s, 4H), 3.7 (m, 2H), 3.44 (m, 4H), 3.34 (s, 6H), 2.05 (m, 4H), 1.58 (q, 4H, J = 7.5 and 11.4 Hz); ^{13}C NMR (75 MHz) in $CDCl_3$: δ 137.9, 129.7, 129.2, 127.9, 127.1, 95.6, 75.5, 75.3, 72.8, 72.2, 54.9, 31.6, 31.5, 22.8; LC–MS: 495 $[M+Na]^+$; HRMS: calcd For $C_{28}H_{40}O_6$ $[M+Na]^+$ 495.2722, found 495.2703.

4.3. (5*R*,12*S*)-5,12-Bis(benzyloxymethyl)-2,4,13,15-tetraoxahexadecan-8-ol 6

To a solution of **5** (0.8 g, 1.58 mmol) in THF (10 mL), $BH_3{\cdot}Me_2S$ (1.6 mL, 1.58 mmol) was added dropwise at −10 °C. Stirring continued for 8 h at room temperature. The reaction mixture was quenched by the addition of 10% NaOH (2 mL) followed by 30% H_2O_2 (4 mL) at 0 °C and allowed to warm to room temperature, stirring continued for another 2 h. The reaction mixture was extracted with ethyl acetate (2 × 50 mL) and water (50 mL). The combined organic layers were washed with brine dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate–petroleum ether (2:5) to afford compound **6** (0.7 g, 85%) as a syrup. $[\alpha]_D^{32} = -7.6$ (c 1.2, $CHCl_3$); IR ν_{max} 3482, 2906, 1613, 1501, 1451, 1300, 1142, 1037 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32–7.23 (m, 10H), 4.73 (d, 1H, J = 7.1 Hz), 4.71 (d, 1H, J = 7 Hz), 4.62 (d, 1H, J = 7.1 Hz),4.61 (d, 1H, J = 7.0 Hz), 4.51 (s, 4H), 3.71 (m, 2H), 3.6–3.4 (m, 5H), 3.3 (s, 6H), 1.7–1.3 (m, 10H); ^{13}C NMR (75 MHz) in $CDCl_3$: δ 138.4, 138.3, 128.2, 127.5, 96., 76.4, 76.3, 73.2, 72.8, 71.3, 71.1, 55.4, 37.5, 33.1, 32.9, 32, 28.3, 28.21, 21.4; LC–MS: 513 $[M+Na]^+$; HRMS: calcd For $C_{28}H_{42}O_7$ $[M+Na]^+$ 513.2828, found 513.2852.

4.4. (5*R*,12*S*)-5,12-Bis(benzyloxymethyl)-2,4,13,15-tetraoxahexadecan-8-one 7

To a stirred solution of alcohol **6** (0.6 g, 1.14 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added Dess–Martin periodinane (0.63 g, 1.49 mmol) and stirred for 3 h. The reaction mixture was diluted with ether (20 mL) followed by washing with saturated $NaHCO_3$ solution (2 × 25 mL) and brine (2 × 25 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate–petroleum ether (2:11) to afford compound **7** (0.52 g, 88%) as a syrup. $[\alpha]_D^{32} = -21.4$ (c 1.3, CH_2Cl_2); IR ν_{max} 3030, 2916, 1712, 1614, 1500, 1452, 1303, 1107, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.35–7.25 (m, 10H), 4.8–4.65 (m, 4H), 4.53 (s, 4H), 3.75–3.72 (m, 2H), 3.5–3.48 (m, 4H), 3.36 (s, 6H), 2.45 (m, 5H), 1.9–1.65 (m, 6H), ^{13}C NMR (75 MHz) in $CDCl_3$: δ 208.8, 138.2, 128.2, 127.4, 95.9, 95.8, 75.6, 75.3, 73.1, 72.6, 55.2, 42.3, 38.0, 31.5, 25.9, 19.5; LC–MS: 511 $[M+Na]^+$; HRMS: calcd for $C_{28}H_{40}O_7$ $[M+Na]^+$ 511.2671, found 511.2670.

4.5. (2*S*,5*R*,7*S*)-2,7-Bis(benzyloxymethyl)-1,6-dioxaspiro[4.5]-decane 8

To a stirred solution of ketone **7** (0.5 g, 0.96 mmol) in methanol was added two drops of concd HCl, then the reaction mixture was heated to 40 °C. Stirring was continued for another 10 min after which methanol was removed under reduced pressure. The mixture was extracted with ethyl acetate (2 × 25 mL) and water (25 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography using ethyl acetate–petroleum ether (1:6) to afford the compound **8** (0.33 g, 92%) as a colorless liquid. $[\alpha]_D^{32} = +18.2$ (c 1.1, $CHCl_3$); IR ν_{max} 3029, 2866, 1612, 1501, 1304, 1113 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.3–7.25 (m, 10H), 4.55 (s, 2H), 4.53 (s, 2H), 4.25 (m, 1H), 3.99 (m, 1H), 3.48–3.32 (m, 4H), 2.18–2.07 (m, 1H), 1.95–1.83 (m, 2H), 1.73–1.56 (m, 5H), 1.36–1.21 (m, 2H); ^{13}C NMR (75 MHz) in $CDCl_3$: δ 138.7, 138.6, 128.3, 127.6, 127.57, 127.51, 127.4, 106.6, 77.1, 73.7, 73.2, 73.1, 72.7, 69.6, 37.4, 33.1, 27.5, 26.5, 20; LC–MS: 405 $[M+Na]^+$; HRMS: calcd for $C_{24}H_{30}O_7$ $[M+Na]^+$ 405.2041, found 405.2032.

4.6. (2*S*,5*R*,7*S*)-1,6-Dioxaspiro[4.5]decane-2,7-diyldimethanol 1

A solution of compound **8** (0.2 g, 0.52 mmol) in THF (10 mL) was added to a solution of liq. ammonia (20 mL) and sodium (0.25 g, 10.47 mmol) at −78 °C. The reaction was then stirred for 5 h. After evaporation of ammonia, the reaction mixture was neutralized with saturated aqueous NH_4Cl solution and extracted with ethyl acetate (2 × 25 mL). The combined organic layers were washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and residue was purified by column chromatography using ethyl acetate–petroleum ether (2:3) to afford the desired compound **1** (0.08 g, 85%) as a colorless liquid. $[\alpha]_D^{27} = +70.0$ (c 1.25, $CHCl_3$), {lit.,[9] $[\alpha]_D$ = +70.9 (c 1.38, $CHCl_3$)}; IR ν_{max} cm^{-1} (neat): 3447, 2927, 1450, 1123, 1141, 968; ^{1}H NMR (300 MHz) in $CDCl_3$: δ 4.2 (dtd, 1H, J = 8.7, 5.5, 3.1 Hz), 3.9 (ddt, 1H, J = 11.9, 6.3, 3.1 Hz), 3.72 (dd, 1H, J = 11.1, 3.1 Hz), 3.58 (dd, 1H, J = 11.9, 3.9 Hz), 3.53 (dd, 1H, J = 12.7, 7.9 Hz), 3.49 (dd, 1H, J = 12.8, 7.9 Hz), 2.3 (br s), 2.1 (m, 1H), 1.96 (m, 1H), 1.82 (m, 1H), 1.7 (m, 5H), 1.5 (dq, 1H, J = 16.6, 3.1 Hz), 1.3 (qd, 1H, J = 16.6, 3.9 Hz), ^{13}C NMR (75 MHz) in $CDCl_3$: δ 106.6, 78.3, 71.0, 66.0, 64.8, 37.7, 33.05, 26.3, 25.3, 19.6; FABMS: 203 $[M+1]^+$; HRMS: calcd for $C_{10}H_{18}O_4$ $[M+Na]^+$ 225.1102, found 225.1099.

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