Synthesis of Enantiomerically Pure Cyclopentene Building Blocks

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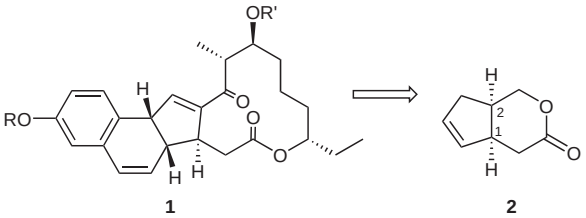
Received 23 November 2006

Abstract: An efficient synthesis of the enantiomerically pure *cis*-annulated cyclopentenes **2** and *ent*-**2** was established by the use of an enzymatic transesterification and hydrolysis, respectively, followed by an S_N2-type substitution with a benzyloxymethyl cuprate and a sigmatropic rearrangement. The advantage of this approach is the short sequence combined with an excellent overall yield and an enantiomeric excess of 99%.

Key words: cyclopentenes, enzymes, benzyloxymethyl cuprate, spinosyns, Claisen–Ireland rearrangement

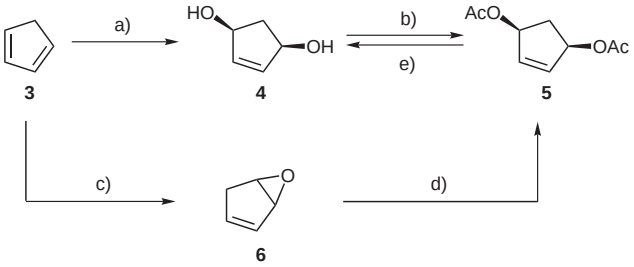
Cyclopentenes are important building blocks in organic synthesis due to their occurrence in a multitude of natural products such as the prostaglandines, the iridoids and the spinosyns, to name a few.[1] Recently we have developed an efficient approach to analogues of spinosyn A which is a highly potent insecticide. In the synthesis a two-fold palladium-catalyzed transformation of an 1,2-disubstituted cyclopentene derivative obtained from **2** was used (Scheme 1).[2]



Scheme 1 Spinosyn analogue **1** and starting material **2**.

Here we describe a novel and highly efficient synthesis of enantiopure **2** and *ent*-**2** starting from cyclopentadiene (**3**). So far only a few and rather long syntheses describing the preparation of this class of compounds have been published.[3]

At first, the known *meso*-compounds **4** and **5** were synthesized; diol **4** could be obtained from **3** by a photochemical reaction with Bengal rose as sensitizer followed by reduction of the primarily formed *endo*-peroxide.[4] The diacetate **5** was then produced from **4** by acetylation using acetic anhydride. For the synthesis of larger amounts of **4** and **5**, however, it is more appropriate to transform cyclopentadiene (**3**) into its epoxide **6** with peracetic acid in CH_2Cl_2, which is then treated without further purification with Ac_2O and $Pd(PPh_3)_4$ as catalyst to give **5** in a yield of 56% over two steps.[5,6] Solvolysis of the acetate groups with K_2CO_3 in methanol at 0 °C led to diol **4** in a yield of 94% (Scheme 2).

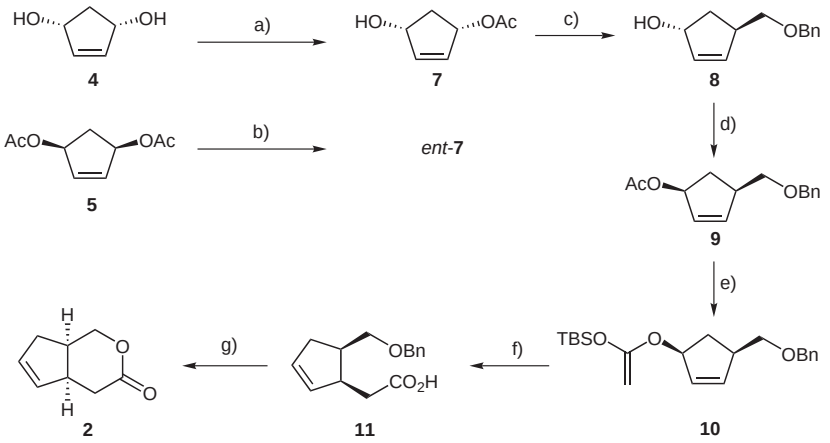


Scheme 2 Synthesis of *meso*-cyclopentenes **4** and **5**. *Reagents and conditions*: (a) *hν*, O_2, thiourea, cat. Bengal rose, MeOH, –35 °C, 6 h, r.t., 12 h, 65%; (b) Ac_2O, Et_3N, CH_2Cl_2, 3 h, 97%; (c) $MeCO_3H$, Na_2CO_3, CH_2Cl_2, 0 °C, 1.5 h, r.t., 3 h; (d) 5 mol% $Pd(PPh_3)_4$, Ac_2O, THF, 0 °C, 30 min, 56% (for two steps); (e) K_2CO_3, MeOH, 0 °C, 3 h, 94%.

The desymmetrization of **4** was performed by a monoacetylation using vinyl acetate and the enzyme pancreatin to give **7**.[7,8] On the other hand, *ent*-**7** was accessible by a partial hydrolysis of **5** using the enzyme Novozym 435.[9] Both procedures proceed with 99% ee and a yield of 96% and 72%, respectively.

Treatment of **7** and *ent*-**7** with a benzyloxymethyl cuprate, generated in situ from benzyloxymethyl chloride (BOMCl), led to **8** and *ent*-**8**, respectively, in 92% yield via a S_N2-type substitution of the acetate group.[10] The necessary *syn*-orientation of the substituents at the cyclopentene moiety could be re-established by a Mitsunobu inversion with acetic acid as a nucleophile to give acetate **9** and *ent*-**9**, respectively, as ideal precursors for the subsequent Claisen–Ireland rearrangement.[11] The required silyl enol ethers **10** and *ent*-**10** were prepared from **9** with in situ generated LDA and TBSCl.[12] For the rearrangement the crude materials were dissolved in xylene and heated in a sealed tube to 180 °C for 18 hours. After purification by column chromatography the acids **11** and *ent*-**11**, respectively, were isolated in a yield of 87% over two steps.[13] Cleavage of the benzyl ether moiety in **11** with boron trichloride and acidic work-up led to the desired annulated cyclopentenes **2** and *ent*-**2**, respectively, in 89% yield (Scheme 3).[14]

SYNLETT 2007, No. 3, pp 0485–0487
Advanced online publication: 07.02.2007
DOI: 10.1055/s-2007-967937; Art ID: G35406ST



Scheme 3 Syntheses of *cis*-annulated cyclopentenes **2** and *ent*-**2**. *Reagents and conditions*: (a) pancreatin, vinyl acetate, Et_3N, THF, 3 h; (b) Novozyme 435, buffer (pH 8), 18 h; (c) Mg turnings, $HgCl_2$, THF, BOMCl, 0 °C, 2.5 h, addition of CuCN and **7** in THF at –20 °C, 10 min; (d) DIAD, Ph_3P, AcOH, Et_2O, 0 °C, 30 min; (e) *n*-BuLi, $(i\text{-}Pr)_2NH$, THF, 0 °C, 5 min, addition of HMPA (1 equiv) at –78 °C, 10 min, addition of **9** in THF, 20 min, addition of TBSCl in THF, 5 min; (f) xylene, 180 °C, 18 h, sealed tube; (g) BCl_3, CH_2Cl_2, –40 °C to r.t., 2.5 h.

In summary, we have developed an efficient procedure to generate both enantiomers of the *cis*-annulated cyclopentene **2**, which are highly attractive precursors in natural product synthesis. In comparison to the published routes the described procedure has about half of the reaction steps and a much better overall yield.

Acknowledgment

Generous financial support from the Deutsche Forschungsgemeinschaft (SFB 416) and the Fonds der Chemischen Industrie is gratefully acknowledged. We are also indebted to the BASF AG, the Bayer AG, the Degussa AG and the Wacker Chemie AG for generous gifts of chemicals.

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(7) For the preparation of **7** the following modified procedure was used. A mixture of diol **4** (8.0 g, 80 mmol), Et_3N (7.7 mL, 56 mmol), vinyl acetate (11 mL, 0.12 mol) and pancreatin (30 g) in THF (150 mL) was stirred at r.t. until complete consumption of **4** (TLC). The mixture was filtered, the filter pad of the residue washed with EtOAc (3 × 50 mL) and the solvent evaporated under reduced pressure. Purification of the residue by column chromatography (*n*-pentane–EtOAc, 3:1) afforded acetate **7** as white crystals (8.2 g, 58 mmol, 72%, 99% ee). The diacetate **5** was isolated as by-product in 22% yield; $[\alpha]_D^{20}$ –69.0 (*c* 1.00, $CHCl_3$); R_f = 0.4 (*n*-pentane–EtOAc, 1:1). IR (KBr): 3387, 2922, 1726, 1359, 1253, 1087, 1020, 968, 910, 880, 841, 794, 606 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.66 (dt, *J* = 14.7, 3.8 Hz, 1 H, H_B-2), 2.06 (s, 3 H, H-2′), 2.85 (dt, *J* = 14.7, 7.3 Hz, 1 H, H_A-2), 4.70–4.75 (m, 1 H, H-3), 5.47–5.53 (m, 1 H, H-1), 5.97–6.01 (m, 1 H, H-4), 6.10–6.14 (m, 1 H, H-5). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.16 ($COCH_3$), 40.46 (C-2), 74.80 (C-1), 77.03 (C-3), 132.60 (C-4), 138.47 (C-5), 170.76 ($OCOCH_3$). MS (EI): *m*/*z* (%) = 142.1 (1) [M^+], 99 (7) [$C_5H_7O_2^+$], 82 (100) [$C_5H_6O^+$], 43 (78) [$C_2H_3O^+$].

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(9) **Synthesis of *ent*-7.**
Novo sp 435 lipase (2.0 g) was added to a suspension of diacetate **5** (15.0 g, 81.5 mmol) in a buffer (pH 8, 400 mL) and the mixture was stirred for 18 h at r.t. After that, the reaction was filtered and washed with H_2O (100 mL) and EtOAc (2 × 200 mL). The aqueous layer was extracted with EtOAc (3 × 200 mL) and the combined organic fractions were dried (Na_2SO_4), filtered and concentrated under reduced pressure to afford monoacetate *ent*-**7** as white crystals (11.1 g, 78.1 mmol, 96%, 99% ee); $[\alpha]_D^{20}$ +66 (*c* 1.00, $CHCl_3$). IR (film): 3387, 2922, 1726, 1359, 1253, 1087, 1062, 1020, 968, 910, 880, 841, 794, 606 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.66 (dt, *J* = 14.7, 3.8 Hz, 1 H, 2-H_B), 2.06 (s, 3 H, 2′-H), 2.85 (quint, *J* = 7.3 Hz, 1 H, 2-H_A), 4.70–4.75 (m, 1 H, 3-H), 5.47–5.53 (m, 1 H, 1-H), 5.97–6.01 (m, 1 H, 4-H), 6.10–6.14 (m, 1 H, 5-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.16, 40.46, 74.80, 77.03, 132.60, 138.47, 170.76. MS (EI, 70 eV): *m*/*z* (%) = 142.1 (1) [M^+], 99 (7) [$C_5H_7O_2^+$], 82 (100) [$C_5H_6O^+$], 43 (78) [$C_2H_3O^+$].

(10) **Synthesis of 8.**
Magnesia turnings (575 mg, 23.6 mmol) were dried in vacuo at r.t. for 12 h. After activation with bromine and $HgCl_2$ a solution of benzyl chloromethyl ether (0.5 mL, 0.55 g, 3.5 mmol) in THF (2 mL) was added, whereupon the reaction started. The reaction mixture was then cooled immediately to –5 °C and more benzyl chloromethyl ether (1.5 mL, 1.65 g, 10.5 mmol) was added carefully as a solution in THF (20 mL). After additional stirring for 2.5 h at –5 °C the mixture was transferred into a suspension of CuCN (35 mg,

10 mol%) in THF (20 mL) at –20 °C and stirred for 5 min. Monoacetate **7** (550 mg, 3.90 mmol) was added and the reaction stirred for further 15 min. After addition of sat. NH_4Cl (20 mL) and aq NH_3 (20 mL) the aqueous layer was separated and extracted with EtOAc (3 × 70 mL). The combined organic layers were dried (Na_2SO_4) and the solvent removed under reduced pressure. Purification of the residue by column chromatography (*n*-pentane–EtOAc, 3:1) afforded benzyl ether **8** as a clear liquid (732 mg, 3.59 mmol, 92%); $[\alpha]_D^{20}$ +146.3 (*c* 1.00, $CHCl_3$); R_f = 0.17 (*n*-pentane–EtOAc, 3:1). IR (KBr): 3380, 3060, 2856, 1651, 1496, 1453, 1361, 1074, 1028, 738, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.75 (s, 1 H, OH), 1.81–2.01 (m, 2 H, H_2-5), 3.12–3.24 (m, 1 H, H-4), 3.29–3.41 (m, 2 H, CH_2OBn), 4.51 (s, 2 H, CH_2Ph), 4.84–4.91 (m, 1 H, H-1), 5.89 (dt, *J* = 5.6, 2.2 Hz, 1 H, H-2), 5.97–6.01 (m, 1 H, H-3), 7.24–7.38 (m, 5 H, PhH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.3, 44.8, 73.0, 73.9, 76.9, 127.5, 128.3, 134.3, 136.8, 138.3. MS (EI, 70 eV): *m*/*z* = 204.1 $[M^+]$. HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{16}O_2$: 204.2649; found: 204.2649.

(11) **Synthesis of 9.**

DIAD (3.94 g, 19.5 mmol) was added dropwise to a stirred solution of benzyl ether **8** (1.98 g, 9.74 mmol), Ph_3P (5.12 g, 19.5 mmol) and AcOH (2.23 mL, 2.34 g, 39.0 mmol) in Et_2O (60 mL) at 0 °C. After stirring for 30 min at 0 °C the reaction was filtered and the filtrate was washed with cold pentane (4 × 100 mL). The combined extracts were washed with sat. $NaHCO_3$ (100 mL) and the aqueous layer was separated and extracted with pentane (2 × 100 mL). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the residue by column chromatography (PE–EtOAc, 20:1) gave acetate **9** as a colorless oil (4.56 g, 18.5 mmol, 95%); $[\alpha]_D^{20}$ –1.10 (*c* 1.00, $CHCl_3$); R_f = 0.24 (*n*-pentane–EtOAc, 15:1). UV/Vis (MeOH): λ_{max} (lg ε) = 204.5 (3.926), 251.0 (2.324), 257.0 (2.304), 263.0 (2.140) nm. IR (film): 3391, 3064, 2857, 1732, 1496, 1454, 1364, 1243, 1202, 1092, 1025, 907, 740, 708 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.54 (dt, *J* = 14.3, 4.1 Hz, 1 H, H_A-5), 1.99 (s, 3 H, CH_3), 2.46 (dt, *J* = 14.3, 7.9 Hz, 1 H, H_B-5), 2.92 (m_c, 1 H, H-4), 3.33–3.46 (m, 2 H, CH_2OBn), 4.52 (s, 2 H, CH_2Ph), 5.59–5.66 (m, 1 H, H-1), 5.84 (dt, *J* = 5.7, 2.3 Hz, 1 H, H-2), 6.03–6.07 (m, 1 H, H-3), 7.25–7.37 (m, 5 H, PhH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.26, 33.59, 44.79, 73.08, 74.05, 79.47, 127.55, 127.57, 128.33, 130.49, 138.13, 138.30, 170.85. MS (EI, 70 eV): *m*/*z* (%) = 246.2 (1) $[M^+]$, 203.1 (4) $[M - C_2H_3O^+]$, 186.1 (12) $[M - C_2H_4O_2^+]$, 91 (100) $[C_7H_7^+]$. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_8H_{10}NaO_2$: 269.11482; found: 269.11473.

(12) **Synthesis of 10.**

n-BuLi (2.5 M in hexane, 12.0 mL, 29.9 mmol) was added dropwise to a stirred solution of DIPA (4.33 mL, 3.10 g, 31.0 mmol) in THF (20 mL) at 0 °C. After 5 min HMPA (5 mL) was added and the reaction was cooled to –78 °C and stirred for further 10 min whereupon a solution of acetate **9** (5.08 g, 20.7 mmol) in THF (35 mL) was added dropwise. The reaction was maintained at –78 °C for additional 20 min. A solution of TBSCl (4.07 g, 27.0 mmol) in THF (5 mL) was added and the reaction was stirred at –78 °C for 5 min before warming to r.t. Then pentane (150 mL) and aq NaOH (0.1 M, 150 mL) were added. The aqueous layer was separated and extracted with pentane (2 × 150 ml). The combined pentane extracts were washed with aq NaOH (0.1 M, 2 × 100 mL), H_2O (100 mL), dried (Na_2SO_4) and the solvent evaporated to give the title compound as a yellow oil (7.45 g, 20.7 mmol, quant.) which was used without further purification steps for the next reaction; $[\alpha]_D^{20}$ +18.5 (*c* 1.00, $CHCl_3$). UV/Vis (MeOH): λ_{max} (lg ε) = 251.5 (2.728), 257.5 (2.734), 263.0 (2.666) nm. IR (film): 3426, 3063, 2929, 2855, 1734, 1496, 1454, 1363, 1244, 1093, 1026, 937, 873, 835, 770, 737, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.24 [s, 6 H, $Si(CH_3)_2$], 0.89 [s, 9 H, $(SiC(CH_3)_3]$], 1.57–1.60 (m, 1 H, H_A-5), 2.40–2.52 (m, 1 H, H_B-5), 2.80–2.96 (m, 1 H, H-4), 3.25–3.60 (m, 4 H, CH_2OBn, H_2-2′) 4.51 (s, 2 H, CH_2Ph), 5.59–5.65 (m, 1 H, H-1), 5.80–6.08 (m, 2 H, H-2, H-3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –3.62, 17.94, 25.60, 33.57, 44.78, 69.40 73.08, 74.04, 79.49, 127.56, 128.33, 130.48, 138.13, 138.27, 160.51. MS (DCI): *m*/*z* (%) = 378.4 (12) $[M + NH_4^+]$, 361.4 (4) $[M + H^+]$, 264.2 (100) $[C_{15}H_{18}O_3 + NH_4^+]$.

(13) **Synthesis of 11.**

A solution of crude silyl ketene acetal **10** (7.45 g, 20.7 mmol) in dry xylene (50 mL) was heated in a sealed tube to 180 °C for 18 h. After cooling to ambient temperature the solvent was removed under reduced pressure and the residue dissolved in THF (60 mL). Then, aq NaOH (2 M, 60 mL) was added and the reaction stirred vigorously for 2 h. Pentane was then added (100 mL) and the mixture extracted with aq NaOH (2 M, 3 × 150 mL). The combined aqueous layers were acidified to pH 1 with HCl (6 M) and extracted with EtOAc (3 × 200 mL). The combined organic layers were dried over Na_2SO_4 and the solvent evaporated under reduced pressure. Purification of the residue by column chromatography (pentane–EtOAc, 6:1 + 0.5% AcOH) gave acid **11** as a pale yellow oil (4.43 g, 18.0 mmol, 87%); $[\alpha]_D^{20}$ +76.1 (*c* 1.00, $CHCl_3$); R_f = 0.34 (*n*-pentane–EtOAc, 5:1, 6% AcOH). UV/Vis (MeOH): λ_{max} (lg ε) = 251.5 (2.265), 257.5 (2.321), 263.5 (2.201) nm. IR (film): 3060, 2926, 1706, 1496, 1453, 1410, 1364, 1276, 1200, 1098, 1028, 935, 735, 698 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.04–2.14 (m, 1 H, H_B-4′), 2.21 (dd, *J* = 15.6, 9.0 Hz, 1 H, H_B-2), 2.32–2.46 (m, 1 H, H_A-4′), 2.58 (dd, *J* = 15.6, 6.5 Hz, 1 H, H_A-2), 2.70 (m_c, 1 H, H-5′), 3.13–3.24 (m, 1 H, H-1′), 3.42–3.52 (m, 2 H, CH_2OBn), 4.49 (s, 2 H, CH_2Ph), 5.72–5.75 (m, 2 H, H-2′, H-3′), 7.24–7.38 (m, 5 H, Ph-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 34.60, 34.89, 40.01, 42.32, 70.58, 73.01, 127.55, 127.65, 128.33, 130.38, 133.71, 138.10, 179.39. MS (EI, 70 eV): *m*/*z* (%) = 246.2 (4) $[M^+]$, 91 (100) $[C_7H_7^+]$. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{18}NaO_3$: 269.11482; found: 269.11487.

(14) **Synthesis of 2.**

BCl_3 (ca. 1 M in CH_2Cl_2, 2.0 mL, 2.0 mmol) was added dropwise to a solution of acid **11** (246 mg, 1.00 mmol) in CH_2Cl_2 (10 mL) at –40 °C. The reaction was allowed to warm to 0 °C while being continuously stirred for 2 h. After being stirred for a further 15 min at 0 °C sat. NH_4Cl (5 mL) was added, the aqueous layer was separated and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated under reduced pressure. After purification of the residue by column chromatography (*n*-pentane–Et_2O, 1:1) **2** was obtained as a white solid (124 mg, 890 μmol, 89%); $[\alpha]_D^{20}$ +51.0 (*c* 0.30, CH_2Cl_2); R_f = 0.22 (*n*-pentane–Et_2O, 1:1). IR (KBr): 3444, 3052, 2994, 2900, 2854, 1742, 1484, 1435, 1386, 1358, 1340, 1280, 1232, 1078, 991, 950, 861, 758, 724 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.21–2.31 (m, 1 H, H_B-7), 2.25 (dd, *J* = 15.0, 7.2 Hz, 1 H, H_B-4), 2.62–2.86 (m, 2 H, 7-H_A, H-7a), 2.66 (dd, *J* = 15.0, 6.4 Hz, 1 H, H_A-4), 3.26–3.40 (m, 1 H, H-4a), 4.10 (dd, *J* = 11.3, 6.4 Hz, 1 H, H_A-1) 4.30 (dd, *J* = 11.3, 4.3 Hz, 1 H, H_B-1), 5.56 and 5.76 (2 × m_c, 2 × 1 H, H-5, H-6). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 33.79, 33.87, 41.84, 70.27, 130.88, 131.79, 173.37. MS (EI, 70 eV): *m*/*z* = 138 (6) $[M^+]$, 66.0(100) $[C_6H_6]^+$. HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_8H_{10}O_2$: 138.0681; found: 138.0681.