44. Preparation of a Key Intermediate for the Synthesis of the (±)-Pentalenolactone E Methyl Ester by Catalytic 'Palladium-Ene Cyclization'/Methoxycarbonylation

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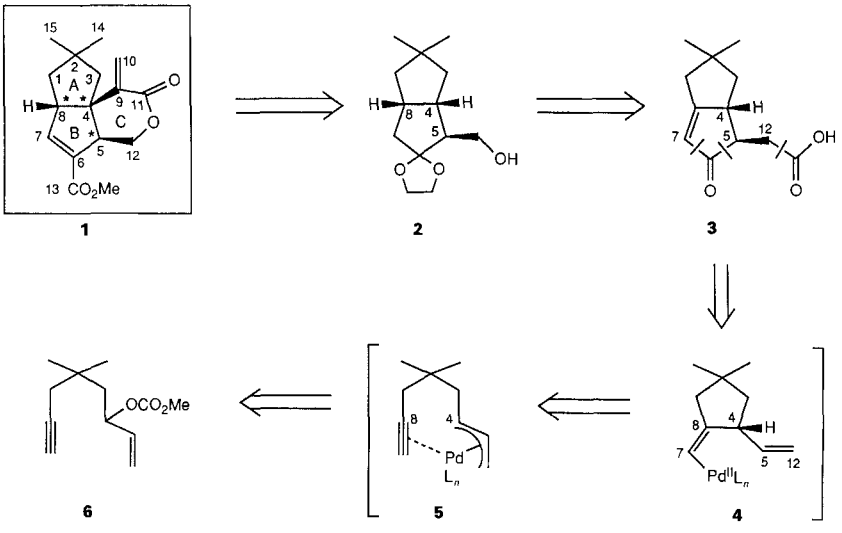
Bicyclic alcohol (±)-**2**, an advanced intermediate for the synthesis of the methyl ester **1** of pentalenolactone E, has been synthesized in nine operations starting from aldehyde **7**. The key step **6**→**9** is a Pd-catalyzed, tandem intramolecular alkyne allylation/carbonylation reaction.

Pentalenolactone E methyl ester, isolated after esterification of extracts of *Streptomyces UC 5319* and assigned structure **1** [1], has attracted considerable interest in organic synthesis [2]. Two syntheses, one of (±)-**1** (*Cane* and *Thomas* [2c]) and one of (−)-**1** (*Mori* and *Tsuji* [2g]) proceed *via* bicyclic alcohol **2** in its racemic or enantiomerically pure form.

We describe here a completely different approach to the key intermediate **2**, summarized by the disconnective analysis depicted in *Scheme 1*. Thus, formation of the C(4)–C(8) bond by Pd-catalyzed intramolecular alkyne allylation **6** → **5** → **4** would be coupled with subsequent CO insertions between C(7) and C(5) and at C(12)[1]). In view of previous model studies using Pd and Ni catalysis [3], we expected to obtain thereby bicyclic enone **3** in a diastereoselective manner[2]).

Scheme 1

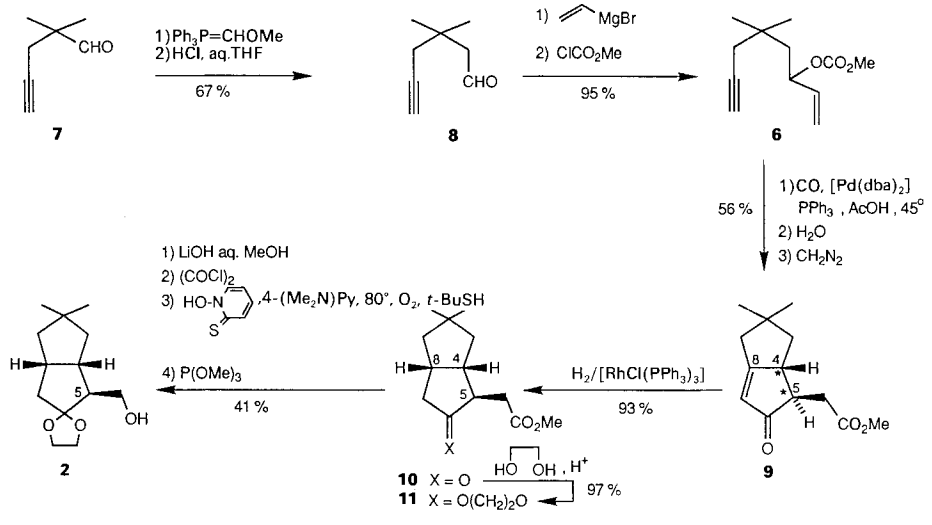


[1]) The numbering of **1** corresponds to [1] and is used also for all intermediates; systematic names are given in the *Exper. Part.*

[2]) For the Pd-catalyzed cyclization/carbonylation of octa-2,7-dien-1-yl acetate, see [4].

This plan was carried out as follows (*Scheme 2*). Homologation of known aldehyde **7** [5] by *Wittig* reaction with (methoxymethylidene)triphenylphosphane and hydrolysis (HCl, aq. THF) of the resulting enol ether furnished acetylenic aldehyde **8** (67% from **7**). Addition of vinylmagnesium bromide to **8** and trapping of the non-isolated alkoxymagnesium bromide with methyl chloroformate afforded carbonate **6** (95%). Now the stage was set for the crucial allylation/carbonylation step. Enyne **6** was stirred with $[Pd(dba)_2]$ (dba = dibenzylideneacetone = 1,5-diphenylpenta-1,4-dien-3-one; 0.1 mol-equiv.) and PPh_3 (0.3 mol-equiv.) in AcOH at 45° under CO (1 atm) for 72 h. Addition of H_2O, further stirring (0.5 h), and evaporation followed by esterification of the resulting crude acid **3** with CH_2N_2 in Et_2O and flash chromatography provided pure bicyclooctenone **9** (56% from **6**). The expected [3] *trans*-relation of H–C(4) H–C(5) in **9** was confirmed by its transformation to known compound **2**. Catalytic hydrogenation (*Wilkinson*'s catalyst, H_2) of **9** gave bicyclooctanone **10** (93%; admixed with 6% of a by-product, tentatively assigned as its C(5) epimer[1]). Acetalization (ethylene glycol, TsOH) afforded (ethylendioxy)bicyclooctane **11** in 97% yield.

Scheme 2



For the degradation of methyl ester **11** to nor-alcohol **2**, we chose *Barton*'s radical-chain method [6] which features thermolysis of an ester obtained with 1-hydroxypyridine-2(1*H*)-thione, trapping of the C-radical with O_2 in the presence of *t*-BuSH and reduction of the nor-hydroperoxide with $P(OMe)_3$ in a single operation. Thus, saponification of methyl ester **11** (LiOH, aq. MeOH), treatment of the resulting crude acid with oxalyl chloride, simultaneous addition of the resulting acyl chloride and of *t*-BuSH to a solution of 1-hydroxypyridine-2(1*H*)-thione/4-(dimethylamino)pyridine in toluene at 80° under a stream of O_2, then heating the mixture to 80° while passing through O_2 for 50 min, addition of $P(OMe)_3$, stirring for 3 h, and workup furnished crude nor-alcohol **2**. After chromatography, pure (±)-**2** was obtained in 41% overall yield from methyl ester **11**. The ^{1}H-NMR and ^{13}C-NMR spectra of (±)-**2** are identical to those of independently prepared (±)-**2** [2c] and (+)-**2** [2g].

In summary, we have prepared the key intermediate (±)-**2** for the synthesis of racemic pentalenolactone E methyl ester ((±)-**1**) from the simple aldehyde **7** *via* a sequence of nine steps in 13% overall yield. The crucial step **6** → **9** illustrates the potential of Pd- and Ni-catalyzed 'ene-type cyclizations', when combined with carbonylation reactions[3]).

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Experimental Part

General. All reactions were carried out under Ar or N_2 with magnetic stirring. Solvents were dried by distillation from drying agents as follows: Et_2O, THF, and PhH (Na metal); toluene (K metal); CH_2Cl_2 (CaH_2). 'Workup' denotes extraction with Et_2O, washing of the org. phase with sat. aq. NH_4Cl soln., drying ($MgSO_4$), and evaporation *in vacuo*. GC: *Hewlett-Packard 5790A*, integrator *HP 3390*, capillary column (fused silica, 0.2 mm i.d., 12 m), *OV-1*, 10 psi H_2, t_R in min (area-%). M.p.: *Kofler* hot stage; uncorrected. IR: *Polaris/Matteson*; in $CHCl_3$, unless otherwise specified. NMR: ^1H at 400 MHz, ^{13}C at 100 MHz; unless otherwise specified, in $CDCl_3$, standard $CHCl_3$ ($\delta = 7.27$ ppm), J in Hz. MS: m/z (rel. %).

3,3-Dimethylhex-5-ynal (**8**). A 2M soln. of PhLi in cyclohexane/Et_2O 7:3 (30 ml, 60 mmol) was added dropwise to a stirred suspension of (methoxymethyl)triphenylphosphonium chloride (20.7 g, 60 mmol) in Et_2O (50 ml) at −5°. The red soln. was stirred at −5° for 30 min and then cooled to −70°. Addition of a soln. of aldehyde **7** [5] (3.3 g, 30 mmol) in Et_2O (10 ml) within 30 min, stirring of the mixture at −70° for 30 min, then at r.t. for 2 h, addition of sat. aq. NH_4Cl soln. and workup, followed by distillation afforded a (*Z*/*E*)-mixture of enol ethers (3.1 g, 75%; b.p. 64–66°/30 Torr). Stirring of this enol-ether mixture (300 mg, 2.2 mmol) with aq. 1N HCl (3 ml) and THF (2 ml) at r.t. for 4 h, addition of Et_2O, saturation of the aq. layer with NaCl, workup, and chromatography (hexane/Et_2O 97:3) furnished **8** (250 mg, 67% from **7**). IR: 3310, 3030–2835, 2735, 1720, 1470, 1430, 1390, 1235, 1175, 1055, 990, 650. ^1H-NMR: 1.17 (*s*, 6 H); 2.10 (*t*, $J = 2.8$, 1 H); 2.27 (*d*, $J = 2.8$, 2 H); 2.46 (*d*, $J = 2.8$, 2 H); 9.87 (*t*, $J = 2.8$, 1 H). ^{13}C-NMR: 201.9 (*d*); 81.2 (*d*); 70.9 (*s*); 53.6 (*t*); 33.3 (*s*); 32.0 (*t*); 26.9 (*q*, 2 C).

2,4-Dinitrophenylhydrazone of **8** (crystallized from Et_2O): m.p. 90.5–91°. Anal. calc. for $C_{14}H_{16}N_4O_4$: C 55.26, H 5.30, N 18.41; found: C 55.22, H 5.31, N 18.36.

1-Ethenyl-3,3-dimethylhex-5-ynyl Methyl Carbonate (**6**). A 1M soln. of vinylmagnesium bromide in THF (2.0 ml) was added slowly to a stirred soln. of **8** (130 mg, 1.05 mmol) in THF (2 ml) at 0°. Stirring at 0° for 30 min, then at r.t. for 30 min, addition of a soln. of methyl chloroformate (0.13 ml, 1.69 mmol) in THF (1 ml) over 30 min, quenching of the reaction with sat. aq. NH_4Cl soln., workup, and chromatography (hexane/Et_2O 9:1) afforded **6**. Colorless oil (210 mg, 95%). IR: 3320, 3010–2960, 1735, 1445, 1280, 935. ^1H-NMR: 1.04 (*s*, 6 H); 1.64 (*dd*, $J = 3.6$, 14, 1 H); 1.80 (*dd*, $J = 8$, 14, 1 H); 2.01 (*t*, $J = 2.8$, 1 H); 2.08–2.21 (2 H); 3.78 (*s*, 3 H); 5.18 (*d*, $J = 10$, 1 H); 5.21 (*m*, 1 H); 5.30 (*d*, $J = 17$, 1 H); 5.82 (*ddd*. $J = 7$, 10, 17, 1 H). ^{13}C-NMR: 155.0 (*s*); 137.2 (*d*); 116.7 (*t*); 81.9 (*d*); 76.7 (*q*); 70.3 (*s*); 54.6 (*d*); 44.8 (*t*); 32.9 (*s*); 32.3 (*t*); 27.2 (*q*); 27.0 (*q*). MS: 171 (3, $[M - MeO]^+$), 119 (17), 95 (100), 79 (60), 67 (34), 55 (45). Anal. calc. for $C_{12}H_{18}O_3$: C 68.55, H 8.63; found: C 67.82, H 8.55.

(1RS,2RS)-Methyl 7,7-Dimethyl-3-oxobicyclo[3.3.0]oct-4-ene-2-acetate (**9**). Bis(dibenzylideneacetone)palladium (120 mg, 0.21 mmol) and PPh_3 (165 mg, 0.62 mmol) were added to a soln. of **6** (440 mg, 2.10 mmol) in degassed AcOH (15 ml). Heating of the mixture at 45° under CO (1 atm) for 72 h, addition of H_2O (2 ml), stirring for 30 min at 45°, evaporation, treatment of the residue with Et_2O/CH_2N_2 for 30 min, evaporation, and chromatography of the residue (hexane/AcOEt 9:1) furnished pure **9** (260 mg, 56%). IR: 3030–2890, 1735, 1700, 1630, 1465, 1440, 1370, 920, 650. ^1H-NMR: 1.13 (*s*, 3 H); 1.19 (*s*, 3 H); 1.23 (*t*, $J = 12$, 1 H); 1.98 (*dd*, $J = 8$, 12, 1 H); 2.36–2.5 (4 H); 2.91 (*dd*, $J = 3$, 16, 1 H); 2.93 (*m*, 1 H); 3.69 (*s*, 3 H); 5.88 (*m*, 1 H). ^{13}C-NMR: 209.6 (*s*); 189.1 (*s*); 172.8 (*s*); 123.7 (*d*); 52.1 (*d*); 51.6 (*q*); 51.2 (*d*); 46.0 (*t*); 42.1 (*t*); 41.0 (*s*); 33.5 (*t*); 30.6 (*q*); 30.4 (*q*). HR-MS: 222.1250 ($C_{13}H_{18}O_3^+$, calc. 222.1256).

(1RS,2SR,5RS)-Methyl 7,7-Dimethyl-3-oxobicyclo[3.3.0]octane-2-acetate (**10**). H_2 was passed through a soln. of **9** (500 mg, 2.25 mmol) in dry toluene (15 ml). Then tris(triphenylphosphine)rhodium(I) chloride (10 mg, 0.01 mmol) was added. Stirring of the mixture under H_2 (1 atm) at r.t. for 20 h, filtration (*Florisil*), evaporation, and FC (hexane/Et_2O 5:1) yielded **10**. Colorless oil (500 mg, 99%; containing 6% of a by-product). GC (150°):

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[3]) For reviews, see [7].

2.56 (94%), 2.84 (6%). IR: 3050–2870, 1738, 1440, 1370, 1180. ^{1}H-NMR: 0.99 (*s*, 3 H); 1.11 (*s*, 3 H); 1.27 (br. *t*, *J* = 12, 1 H); 1.38 (*dd*, *J* = 6.5, 13.0, 1 H); 1.83 (*ddd*, *J* = 1.5, 7.5, 12.5, 1 H); 1.92 (*ddd*, *J* = 1.5, 7.5, 13.0, 1 H); 2.21 (*ddd*, *J* = 1, 5, 19, 1 H); 2.35 (*m*, 1 H); 2.4–2.6 (3 H); 2.68 (*dd*, *J* = 5, 16.5, 1 H); 2.8 (*m*, 1 H); 3.68 (*s*, 3 H). ^{13}C-NMR: 219.9 (*s*); 172.6 (*s*); 52.0 (*d*); 51.7 (*q*); 49.0 (*t*); 48.2 (*t*); 45.4 (*d*); 43.4 (*t*); 41.5 (*s*); 36.9 (*d*); 34.2 (*t*); 29.8 (*q*); 28.5 (*q*). MS: 225 (5, $[M+1]^+$), 224 (3, $M^{+\cdot}$), 193 (14), 167 (20), 151 (84), 135 (24), 107 (31), 95 (57), 81 (33), 67 (38), 55 (100). HR-MS: 224.1390 ($C_{13}H_{20}O_3^{+\cdot}$, calc. 224.1412).

The minor by-product was tentatively assigned as the (1*RS*,2*RS*,5*RS*)-epimer of **10** based on the following acid-catalyzed interconversion studies. Partial separation of the hydrogenation products by HPLC (*Merck Lichrosorb*, hexane/AcOEt 7:1) gave a fraction containing 99% of **10** (GC) and another fraction containing **10** and the more polar by-product in a ratio of 33:67 (GC). Treatment of each fraction with TsOH · H_2O in Et_2O at r.t. for 48 h provided the same 74:26 mixture (GC).

*(1*RS,*2*SR,*5RS)-Methyl 3,3-(Ethylenedioxy)-7,7-dimethylbicyclo[3.3.0]octane-2-acetate* (**11**). A mixture of **10** (490 mg, 2.18 mmol), ethylene glycol (2 ml), TsOH · H_2O (17 mg), and benzene (30 ml), was stirred under reflux with azeotropic removal of H_2O (*Dean-Stark* trap) for 18 h. Washing of the soln. with sat. aq. $NaHCO_3$ and sat. aq. NaCl soln., drying (Na_2SO_4), evaporation, and chromatography (hexane/AcOEt 5:1) gave **11** (570 mg, 97%). GC (150°): 5.26 (92%), 5.48 (8%). IR: 3050–2990, 1735, 1430, 1285, 1155, 1105, 1030. ^{1}H-NMR: 0.86 (*s*, 3 H); 1.03 (*s*, 3 H); 1.16 (*dd*, *J* = 10, 12.5, 1 H); 1.23 (*dd*, *J* = 8.5, 12.5, 1 H); 1.43 (*dd*, *J* = 8.5, 13.5, 1 H); 1.64–1.72 (2 H); 2.04 (*dd*, *J* = 8.5, 13.5, 1 H); 2.15–2.65 (5 H); 3.66 (*s*, 3 H); 3.86–3.91 (4 H). ^{13}C-NMR (50 MHz): 173.7 (*s*); 119.4 (*s*); 65.1 (*t*); 64.3 (*t*); 51.4 (*q*); 49.4 (*d*); 48.8 (*t*); 47.8 (*t*); 46.3 (*d*); 42.9 (*s*); 41.4 (*t*); 38.2 (*d*); 33.8 (*t*); 28.8 (*q*); 26.9 (*q*). MS: 268 (13, $M^{+\cdot}$), 253 (7), 237 (6), 225 (6), 211 (5), 209 (5), 197 (7), 195 (10), 181 (21), 153 (100), 139 (19), 113 (46). HR-MS: 268.1643 ($C_{15}H_{24}O_4^{+\cdot}$, calc. 268.1675).

*(1*RS,*2*RS,*5*RS)-3,3-(Ethylenedioxy)-7,7-dimethylbicyclo[3.3.0]octane-2-ethanol* (**2**). A mixture of **11** (170 mg, 0.67 mmol), LiOH · H_2O (140 mg, 3.35 mmol), and MeOH/H_2O 2:1 (9 ml) was stirred at r.t. for 18 h, then acidified to pH 1 with aq. 0.5N HCl at 0° and saturated with solid NaCl. Extraction of the aq. layer (Et_2O), washing (sat. aq. NaCl soln.), drying ($MgSO_4$) and evaporation gave the corresponding crude acid (155 mg, 97%) which was directly submitted to the following degradation protocol [6]. Freshly distilled oxalyl chloride (0.2 ml) was added to a soln. of this acid (75 mg, 0.295 mmol) in benzene (1 ml) at r.t. Stirring of the mixture at r.t. for 1.7 h and repeated coevaporation with benzene gave crude acyl chloride which was injected simultaneously with *t*-BuSH (0.3 ml), both in toluene (3 ml), over 10 min to a stirred soln. of 1-hydroxypyridine-2(1*H*)-thione (45 mg, 0.32 mmol) and 4-(dimethylamino)pyridine (40 mg, 0.32 mmol) in toluene at 80° through which O_2 was passed *via* a sinter plate. Then, the mixture was stirred at 80° under a continuous stream of O_2 for 50 min. Subsequent addition of $P(OMe)_3$ (0.1 ml, 0.85 mmol), stirring of the mixture at r.t. for 3 h, workup, and chromatography (hexane/AcOEt 3:1) gave pure **2** (28 mg, 41% from **11**). M.p. 51.5–52.5° (hexane). IR: 3510 (br.), 3010–2890, 1465, 1360, 1295, 1285, 1150, 1105, 1040, 1020. ^{1}H-NMR: 0.90 (*s*, 3 H); 1.05 (*s*, 3 H); 1.17–1.29 (2 H); 1.47 (*ddd*, *J* = 0.5, 6.2, 13.2, 1 H); 1.65–1.78 (2 H); 1.94 (*m*, 1 H); 2.08 (*dd*, *J* = 8.5, 13.2, 1 H); 2.41–2.6 (2 H); 2.66 (*t*, *J* = 6, 1 H, disappears on exchange with D_2O); 3.62–3.74 (2 H, multiplicity simplified on exchange with D_2O); 3.87–4.0 (4 H). ^{13}C-NMR: 120.9 (*s*); 64.6 (*t*); 64.1 (*t*); 61.9 (*t*); 53.5 (*d*); 48.8 (*t*); 47.8 (*t*); 42.7 (*s*); 42.0 (*d*); 41.5 (*t*); 38.3 (*d*); 28.9 (*q*); 27.1 (*q*). MS: 226 (25, $M^{+\cdot}$), 211 (12), 183 (7), 181 (15), 153 (100), 139 (27), 113 (42). HR-MS: 226.1549 ($C_{13}H_{22}O_3^{+\cdot}$, calc. 226.1569). Anal. calc. for $C_{13}H_{22}O_3$: C 68.99, H 9.80; found: C 68.83, H 9.71.

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