Synthetic Studies towards Mniopetals (II). A Short Synthesis of Mniopetal E

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Abstract: A short total synthesis of Mniopetal E in thirteen steps is reported. Key steps are a new and highly diastereoselective lithium phenylselenide induced Baylis-Hillman reaction with Feringa´s butenolide, an *endo*-selective intramolecular Diels-Alder reaction (IMDA) and a new variant of the Parikh-Doering oxidation.

Key words: Baylis-Hillman reactions, Diels-Alder reactions, furanones, natural products

Anke and Steglich[1] reported in 1994 the isolation, structure elucidation and determination of the absolute configuration of six new drimane type sesquiterpenes from *Mniopetalum* sp. 87256, the mniopetals A-F **1a**-**1f** (Figure 1).

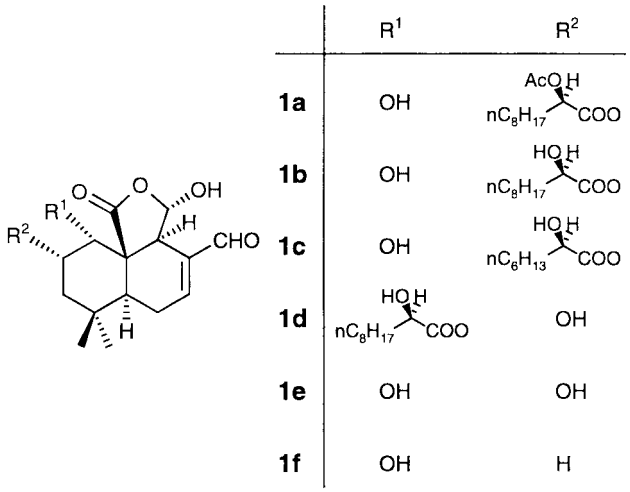
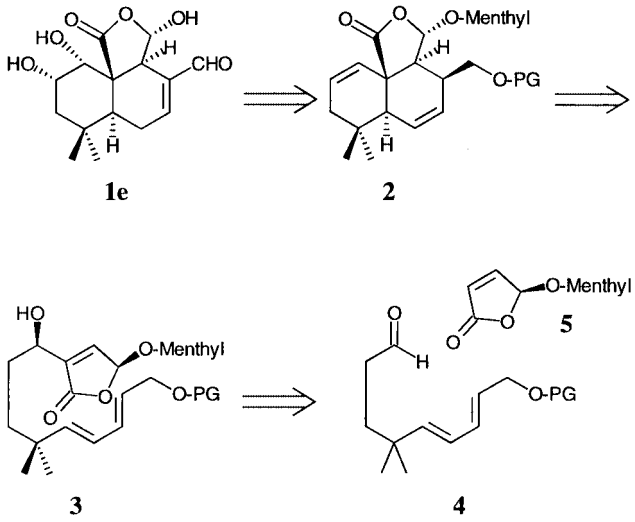


Figure 1 Structure of mniopetals A-F **1a**-**1f**.

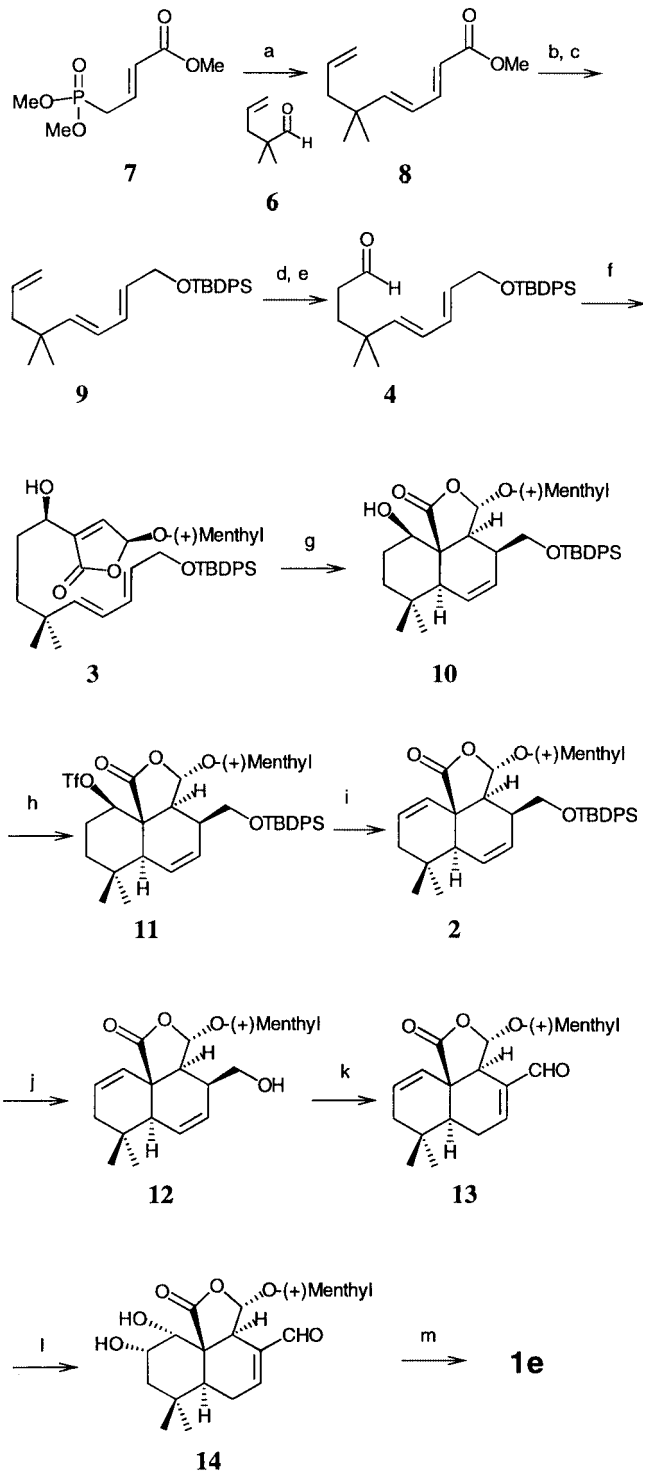
The mniopetals show various biological activities, among which the most important is the inhibition of HIV reverse transcriptase.[1] Therefore, the mniopetals are attractive targets for synthetic chemists. The mniopetals are related to kuehneromycin A,[2,3] which also inhibits reverse transcriptase of various retro viruses, and to the marasmanes.[4]

Tadano and coworkers[5] recently reported a total synthesis of mniopetal E using an intramolecular Diels-Alder reaction (IMDA reaction). Our strategy[6] is quite different and leads to mniopetal E in a total of thirteen steps from readily available starting materials. Here we wish to report our synthesis of mniopetal E **1e**. According to our strategy **1e** is derived from **2**, which is the result of an IMDA reaction of trienolide **3**. Compound **3** can be disconnected into aldehyde **4** and Feringa´s butenolide[7] **5** according to a Baylis-Hillman reaction. (Scheme 1).



Scheme 1 Retrosynthetic analysis of **1e**

Horner-Emmons reaction[8] of **7**[9] with aldehyde **6**[10] led to *E,E*-triene ester **8** in 85% yield. DIBALH reduction[11] of the ester group followed by silylation with TBDPSCl/imidazole[12] resulted in triene **9**. Next, the mono-substituted double bond was regioselectively converted by a hydroboration-oxidation sequence[13] into a primary alcohol, which subsequently was oxidized to aldehyde **4** with TEMPO/diacetoxyiodobenzene.[14] At this point, we wished to explore the Baylis-Hillman reaction[15] with Feringa´s butenolide **5**. Since standard conditions with DABCO as nucleophile only work well with β-unsubstituted acrylic acid derivatives and **5** and especially substituted Feringa-butenolides such as **3** are highly base sensitive, we had to develop a new variant of the Baylis-Hillman reaction.[16] Lithium phenylselenide[17] was the nucleophile of choice in that case because of its high nucleophilicity and very low basicity. Michael addition of PhSeLi at −60 °C was followed by highly diastereoselective aldol addition of the aldehyde **4** through a Zimmermann-Traxler transition state and subsequently PhSeLi was eliminated to rebuild the α,β-unsaturated lactone.



a) LiHMDS, THF, -40 °C, 85%, *trans:cis* > 20:1; b) DIBALH, Et_2O, 0 °C, 30 min, 98%; c) TBDPSCl, Imidazole, DMF, RT, 2 h, quant.; d) 9-BBN, THF, RT, 4 h, H_2O_2, NaOH, EtOH, 0 °C, 1 h, 91%; e) TEMPO/PhI$(OAc)_2$, RT, 2h, 98%; f) Ph-Se-Li, THF, **5**, -60 °C, 6 h, 88%; g) Xylene, silylated flask, 140 °C, 60 h, 69%; h) Tf_2O, DMAP, 0 °C, 2 h, 98%; i) 2,6-lutidine, 100 °C, 4 h, 84%; j) TBAF, THF, RT, 2 h, 90%; k) DMSO, NEt_3, RT, add pyridine-SO_3 in DMSO via syringe pump during 16 h, 79%; l) cat. OsO_4, NMO, THF/H_2O, 0 °C, 168 h, 62%; m) TFA/H_2O/acetone 1:1:1, RT, 24 h, quant.

Scheme 2 Synthesis of mniopetal E **1e**.

Thus, we arrived at trienolide **3**, which was the starting material for the IMDA reaction.[18] Cyclization of **3** to form **10** proceeded smoothly at 140 °C in xylene in a silylated flask to reduce epimerization at the acetal center. In the following steps **10** was transformed into mniopetal E **1e**. First, the secondary alcohol (which has the opposite configuration at C1 in comparison to the mniopetals) was transformed into triflate **11** using trifluoromethanesulfonic anhydride and DMAP as base. Elimination of the triflate group was accomplished in 2,6-lutidine at 100 °C leading to **2**. Removal of the silyl protecting group with TBAF[12] was straightforward leading to the β,γ-unsaturated alcohol **12** which had to be converted into an α,β-unsaturated aldehyde **13**. This oxidation was best carried out with pyridine-SO_3 complex in DMSO with NEt_3 as base (Parikh-Doering oxidation[19]). To obtain reproducible good results it was important to run the reaction under inert atmosphere and to add the pyridine-SO_3 complex dissolved in DMSO very slowly via syringe pump overnight. Now, the two double bonds had different electronic properties and it was possible to transform the more electron-rich double bond between C1 and C2 stereoselectively from the *si*-face into the *cis*-diol **14** (the only stereoisomer found) with OsO_4/NMO.[20] In the final step, the menthyl residue was removed by action of TFA/H_2O/acetone (1:1:1) overnight. The product obtained was identical in all respects with the natural mniopetal E.[21] The complete synthesis is shown in Scheme 2. Starting from aldehyde **6** and phosphonate **7**, we were able to synthesize mniopetal E **1e** in only thirteen steps in a total yield of 16% through efficient combination of a new variant of the Baylis-Hillman reaction, the powerful IMDA reaction, a new variant of the Parikh-Doering oxidation and a chemo- and stereoselective *cis*-hydroxylation.

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For details of the described IMDA reaction of **3** see Reiser, U.; Jauch, J.; Herdtweck, E. *Tetrahedron: Asymmetry* **2000**, *11*, 3345.
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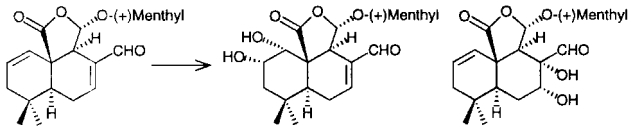
First, we studied the *cis*-hydroxylation with OsO_4 cat./NMO, THF/water, 18 h, r.t. However, under these conditions **13** gave a mixture of **14** (35%) and the regio-isomer **15** (35%).



rt, 18 h	35%	35%
0 °C, 7 d	62%	20%

To run the reaction with acceptable chemoselectivity, we had to decrease the reaction temperature to 0 °C.
A typical procedure is as follows: 20 mg **13** (50 μmol) were dissolved in 0.4 mL THF and 0.1 mL water. The solution was cooled to 0 °C and 3 μL of a 1 M solution of OsO_4 (3 μmol) in acetone and 7 mg NMO (50 μmol) were added. The reaction mixture was stirred at 0 °C for one week, then saturated aqueous $NaHCO_3$ solution (2 mL) and saturated aqueous $Na_2S_2O_3$ solution (1 mL) was added and the reaction mixture was allowed to reach room temperature. Extraction with AcOEt, drying with $MgSO_4$ and purification by preparative TLC (diethyl ether/pentane 2:1 (v:v), silica, R_f = 0.2) gave 13 mg (62%) of **14**. ^{1}H NMR (360 MHz, $CDCl_3$, δ rel. to TMS): 9.48 (s, 1H); 7.12 (d, br, 6.6 Hz, 1H); 5.28 (s, 1H); 4.32 (d, br, 2.2 Hz, 1H); 4.18 (ddd, 12.4 Hz, 4.4 Hz, 2.6 Hz, 1H); 3.72 (s, br, 1H); 3.47 (td, 10.6 Hz, 4.0 Hz, 1H); 2.47 (ddd, 18.6 Hz, 7.5 Hz, 4.0 Hz, 1H); 2.28-2.17 (m, 3H); 2.06 (septd, 7.1 Hz, 3.1 Hz, 1H); 1.79 (t, 12.8 Hz, 1H); 1.67 (dm, 12.8 Hz, 2H); 1.53 (dd, 12.4 Hz, 4.0 Hz, 1H); 1.28 (s, 3H); 1.10-0.8 (m, 7H, superimposed by the following signals); 1.03 (s, 3H); 0.95 (d, 6.6 Hz, 3H); 0.90 (d, 7.1 Hz, 3H); 0.76 (d, 7.1 Hz, 3H). ^{13}C NMR (90.3 MHz, $CDCl_3$, δ rel. to TMS): 193.0; 176.0; 154.7; 138.7; 102.3; 79.0; 71.0; 65.9; 53.4; 47.6; 46.2; 41.6; 39.8; 39.6; 34.3; 33.6; 33.4; 31.5; 25.8; 24.7; 23.3; 22.7; 22.2; 21.1; 15.2; $[\alpha]_D^{20}$ = +27 (c = 0.8, $CHCl_3$).

(21) A typical procedure is as follows: To 10 mg of **14** (23 μmol) was added a mixture of TFA and water (1:1 v/v, 2 mL). Then 1 mL of acetone was added to dissolve **14** and the mixture was stirred at room temperature overnight. Then the mixture was evaporated to dryness at reduced pressure and the residue was purified by preparative TLC (toluene/acetone/acetic acid 70:30:1 (v/v), silica, R_f = 0.25). Yield: 6.8 mg (quant.). ^{1}H NMR (360 MHz, D_4-methanol, δ rel. to TMS): 9.49 (s, 1H); 7.26 (d, br, J = 6.6 Hz, 1H); 5.44 (s, 1H); 4.39 (s, br, 1H); 4.14 (dd, J = 12.4Hz, 2.9 Hz, 1H); 3.77 (s, br, 1H); 2.55 (dm, J = 17.7 Hz, 1H); 2.17 (m, 1H); 1.92 (t, J = 12.4, 1H); 1.69 (dd. J = 12.8 Hz, 3.5 Hz, 1H); 1.45 (dd, J = 12.8 Hz, 4.0 Hz, 1H); 1.31 (s, 3H); 1.07 (s, 3H). ^{13}C NMR (90.3 MHz, D_4-methanol, δ rel. to TMS): 195.1; 178.9; 156.3; 140.3; 101.8; 72.3; 66.8; 55.5; 47.9; 42.2; 41.0; 34.4; 33.9; 25.9; 24.0. $[\delta]_D^{20}$ = − 59 (c = 0.1, CH_3OH); Lit.[1b]: $[\delta]_D^{20}$ = –57 (c = 0.1, CH_3OH).

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