A Short Synthesis of Mniopetal F[‡]

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Dedicated to Professor Wittko Francke on the occasion of his 60th birthday

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The first total synthesis of Mniopetal F in fourteen 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), inversion of a highly hindered secondary alcohol and a new variant of the Parikh–Doering oxidation.

Introduction

Anke and Steglich[1−4] 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).

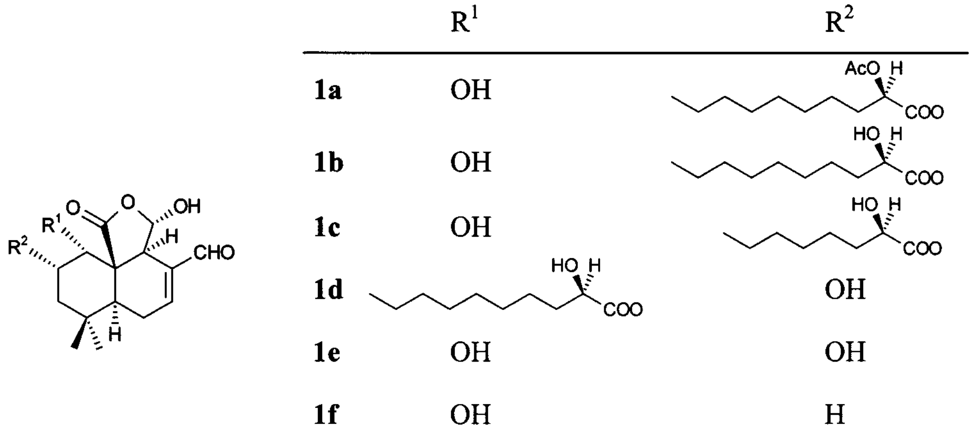

Figure 1. Structure of mniopetals A−F **1a−1f**

The mniopetals have gained considerable interest[5−8] since they act as inhibitors of HIV reverse transcriptase.[2,3] Here we wish to report our synthesis of mniopetal F **(1f)**.

Results and Discussion

According to our strategy[8] **1f** 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[9] **5**. Finally, aldehyde **4** can be synthesized from 2,2-dimethyl-4-pentenal[10,11] **(6)** and phosphonate **7**[12] (Scheme 1).

A Horner−Emmons reaction[13] of **6** and **7** leads to the *E*,*E*-triene ester **8** in 85% yield. DIBALH reduction[14] of the ester group followed by silylation with TBDPSCl/imidazole[15] results in triene **9**. Next, the mono-substituted double bond is regioselectively converted by a hydroboration-oxidation sequence[16,17] into a primary alcohol, which subsequently is oxidized to aldehyde **4** with TEMPO/diacetoxyiodobenzene.[18] At this point, we attempted the Baylis−Hillman reaction,[19] which is a domino Michael-aldol-elimination reaction, with Feringa's butenolide **5**. Since standard conditions with DABCO as nucleophile only work well with β-unsubstituted acrylic acid derivatives, and **5** is highly base sensitive, we had to develop a new variant of the Baylis−Hillman reaction.[20] Lithium phenylselenide[21,22] is the nucleophile of choice in this case because of its high nucleophilicity and very low basicity. Under these conditions, we isolated **3** as a single diastereomer. An intramolecular Diels−Alder reaction leads to **2** as previously reported[8] (Scheme 2).

The secondary alcohol in **2** has the opposite configuration with respect to **1f**. Therefore, this stereocenter has to

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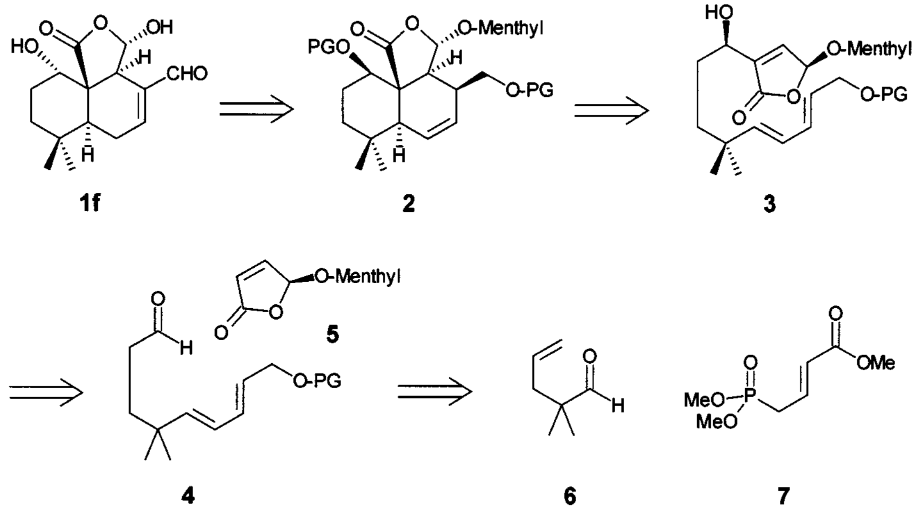
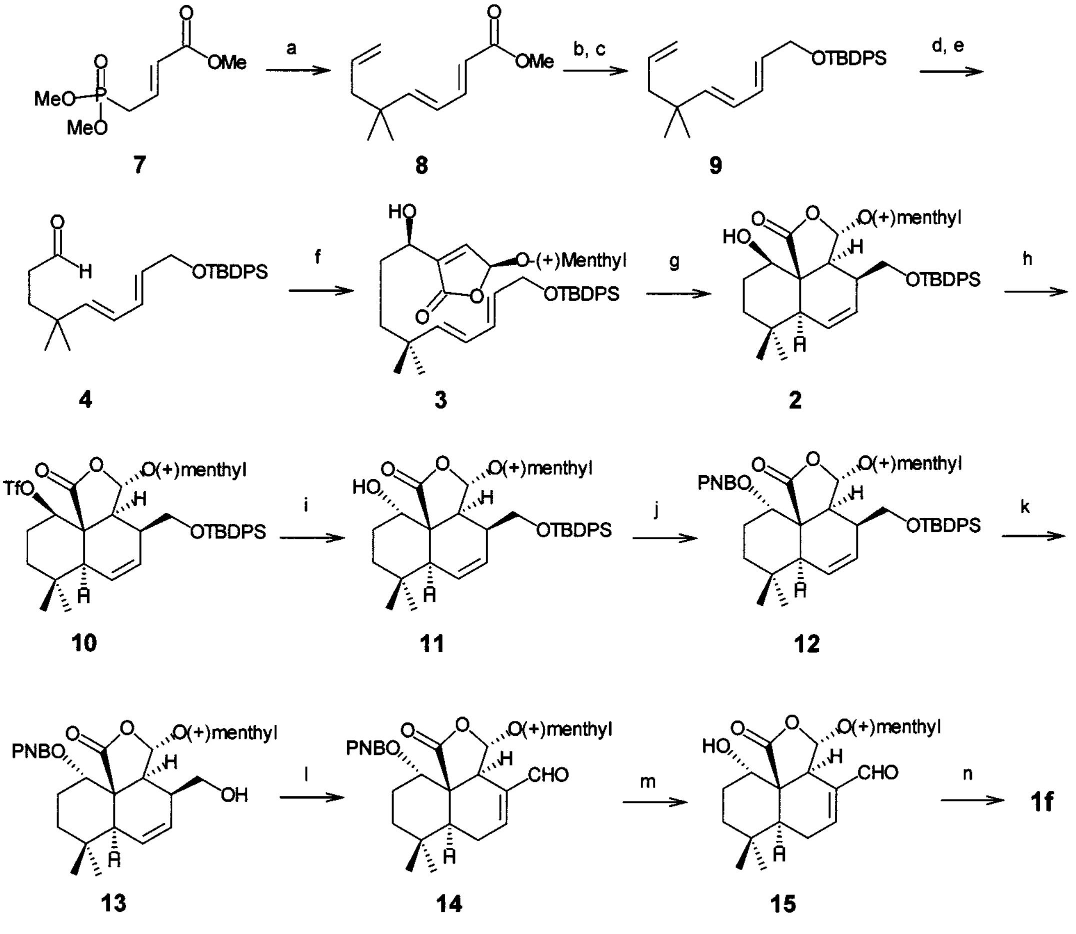


Scheme 1. Retrosynthetic analysis of **1f**



Scheme 2. Synthesis of mniopetal F **1f**: a) LiHMDS, **6**, THF, −40 °C, 85%, *trans:cis* > 20:1; b) DIBALH, Et_2O, 0 °C, 30 min., 98%; c) TBDPSCl, imidazole, DMF, room temp., 2 h, quant.; d) 9-BBN, THF, room temp., 4 h, H_2O_2, NaOH, EtOH, 0 °C, 4 h, 91%; e) TEMPO/$PhI(OAc)_2$, room temp., 2 h, 98%; f) Li(SePh), THF, **5**, −60 °C, 6 h, 88%; g) xylene, silylated flask, 140 °C, 60 h, 68%; h) Tf_2O/DMAP, room temp., 4 h, 95%; i) KNO_2/18-crown-6/DMF, 40 °C, 12 h, 66%; j) *p*-$O_2NC_6H_4COOH$, DCC, DMAP, room temp., 3 h, 98%; k) TBAF, THF, room temp., 2 h, 83%; l) $Py\cdot SO_3$/DMSO/Et_3N, 18 h, 62%; m) K_2CO_3, MeOH, room temp., 1 h, 72%; n) TFA/H_2O/acetone (1:1:1 v/v), room temp., 24 h, quant.

be inverted. This task is complicated by four facts. First, the quaternary C on the right side is a neopentyl-like C which sterically shields the stereocenter at C1. This is most probably the reason why Mitsunobu reactions[23] under different conditions did not work. Second, the α-oriented methyl group on C4 prevents nucleophilic attack of large nucleophiles at C1 from the axial direction. Third, the lactone group electronically shields attack of Lewis-basic reducing agents ($NaBH_4/CeCl_3$, $ZnBH_4$, L-Selectride) from the β-direction. This is why an oxidation/reduction sequence also did not give the inverted alcohol. Fourth, inversion of the secondary alcohol by a retro-Aldol/Aldol sequence could not be applied to **2**, since the equatorial OH group at C1 is more stable in principle than an axial OH group, and, additionally in our case, is further stabilized by an intramolecular hydrogen bond[24] to *O*-menthyl in the acetal substructure.

From these points, it follows that inversion should be possible if the OH group is converted into a good leaving group and a small nucleophile is used for inversion by an S_N2 mechanism. The method of Moriarty[25] gave the best results. Thus, converting **2** into triflate **10** and warming this in the presence of KNO_2/18-crown-6/traces of water to 40 °C for 12 h gives 49.8% of the inverted alcohol **11** together with ca. 25% recovered starting material (66% corrected yield), along with some unidentified side products.

Transformation of **11** into **1f** is straightforward. Protection of the axial OH group as its *p*-nitrobenzoic ester gives **12** in 98% yield. Cleavage of the silyl protecting group with TBAF results in a primary β,γ-unsaturated alcohol (**13**, 83%), which is transformed into the α,β-unsaturated aldehyde **14** by Parikh−Doering oxidation (62%). Removal of the *p*-nitro benzoyl group (1% K_2CO_3 in MeOH; 72%) and the menthyl group (TFA/H_2O/acetone; quant.) leads to mniopetal F **1f** in 14 steps and 10.1% yield, spectroscopically identical in all respects with the natural product (Scheme 2). However, we found a specific optical rotation of $[\alpha]_D^{20} = -63$ ($c = 0.65$, methanol) whereas Steglich et al.[3] reported $[\alpha]_D^{23} = -29$ ($c = 0.22$, methanol).

Conclusion

In summary, we were able to synthesize mniopetal F in 14 steps and 10.1% yield by a strategy employing a new variant of the Baylis−Hillman reaction, an IMDA reaction and a new variant of the Parikh−Doering oxidation.

Synthesis of the naturally occurring mniopetals A−D is currently under way and will be published in due course.

Experimental Section

General Remarks: All reactions were run under an atmosphere of dry nitrogen in dried glassware, except where water is used as a reagent. DMF was distilled from P_2O_5 under nitrogen and stored over 3 Å molecular sieves. Solvents for chromatography were freshly distilled. NMR spectra were obtained on a Bruker AM 360 operating at 360 MHz (^{1}H) or 90.6 MHz (^{13}C).

Inverted Alcohol 11: Triflate **10** (1.31 g, 1.67 mmol) was dissolved in 25 mL dry DMF under nitrogen. KNO_2 (2.3 g, 27 mmol, 16 equiv.) and 18-crown-6 (0.5 g, 1.85 mmol, 1.1 equiv.) were then added and the reaction mixture was stirred at 40−50 °C for 12 h. The mixture was then diluted with 50 mL diethyl ether and washed with water. After drying with $MgSO_4$ the product was purified by flash chromatography with pentane/diethyl ether (8:1, v/v). Yield: 0.5478 g (49.8%). Additionally, unreacted starting material (0.32 g, ca. 25%) was recovered. − ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.67 and 7.41 (m, 10 H), 6.00 (m, 1 H), 5.73 (dt, *J* = 9.1, 2.9 Hz, 1 H), 5.44 (s, 1 H), 4.08 (br s, 1 H), 3.93 (d, *J* = 7.1 Hz, 2 H), 3.42 (td, *J* = 10.4, 3.9 Hz, 1 H), 3.07 (d, *J* = 7.1 Hz, 1 H), 2.52 (m 2 H), 2.15 (m, 2 H), 1.99 (m, 2 H), 1.73−1.53 (m, 9 H), 1.27 (s, 3 H), 1.08 (s, 9 H), 0.97 (s, 3 H), 0.86 (d, *J* = 7.1 Hz, 3 H), 0.80 (d, *J* = 6.5 Hz, 3 H), 0.72 (d, *J* = 7.1 Hz, 3 H). − ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 177.27, 135.63, 135.60, 133.45, 131.39, 129.79, 128.92, 127.75, 98.30, 76.23, 68.86, 63.74, 56.98, 48.84, 47.71, 43.75, 39.54, 39.04, 34.61, 34.36, 33.20, 31.97, 31.30, 30.89, 26.97, 25.87, 25.53, 22.86, 22.20, 21.85, 21.02, 19.34, 15.30

α,β-Unsaturated Aldehyde 14: Alcohol **13** (0.25 g, 0.43 mmol) was dissolved in dry DMSO under nitrogen. Triethyl amine (435 mg, 0.6 ml, 4.3 mmol, 10 equiv.) was added at room temperature. Then, a solution prepared from pyridine sulfur trioxide complex (0.55 g; 3.44 mmol, 8 equiv.) in 3.2 mL dry DMSO was added very slowly with a syringe pump during 18 h. Next, the reaction mixture was cooled with cold water, quenched with saturated $NaHCO_3$ solution and extracted with diethyl ether (5 × 30 mL). The combined extracts were washed with 1% H_2SO_4 in water, saturated $NaHCO_3$ and brine, and dried with $MgSO_4$. After removal of the solvent the crude product was purified by flash chromatography with pentane/diethyl ether (4:1, v/v). Yield: 0.155 g (62%). − ^{1}H NMR (360 MHz, $CDCl_3$): δ = 9.48 (s, 1 H), 8.29 and 8.14 (m, 4 H), 7.19 (br d, *J* = 6.5 Hz, 1 H), 5.80 (br s, 1 H) 5.27 (s, 1 H), 3.44 (td, *J* = 11.1, 4.5 Hz, 1 H), 3.39 (m, 1 H), 2.59 (ddd, *J* = 19.5, 6.5, 3.2 Hz, 1 H), 2.35 (dddd, *J* = 19.5, 12.4, 3.3, 1.9 Hz, 1 H), 2.25−2.15 (m, 2 H), 2.08−2.00 (m, 2 H), 1.85 (dd, *J* = 12.6, 3.2 Hz, 1 H), 1.66−1.59 (m, 3 H), 1.41 (dt, *J* = 13.6, 3.2 Hz, 1 H), 1.32 (s, 3 H), 1.09 (s, 3 H), 0.95 (d, *J* = 7.2 Hz, 3 H), 0.85 (d, *J* = 6.5 Hz, 3 H), 0.75 (d, *J* = 7.2 Hz, 3 H). − ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 192.96, 174.82, 162.66, 154.86, 150.58, 138.11, 135.64, 130.52, 123.72, 102.19, 79.17, 72.65, 51.08, 47.17, 46.86, 41.89, 39.76, 34.15, 33.82, 33.59, 32.36, 31.41, 25.47, 25.10, 22.57, 22.47, 22.29, 22.13, 21.01, 15.10.

Mniopetal F (1f): Compound **15** (20 mg, 0.047 mmol) was dissolved in 2 mL of a mixture of equal volumes of trifluoroacetic acid, water and acetone and was stirred at room temperature for 24 h. Evaporation of the solvent under high vacuum gave the crude product, which was purified by preparative TLC [toluene/acetone/acetic acid, 70:30:1 (v/v); $R_f = 0.25$]. Yield: 13.3 mg (quant.). − ^{1}H NMR (360 MHz, [D_4]methanol): δ = 9.43 (s, 1 H), 7.21 (d, *J* = 6.8 Hz, 1 H), 5.38 (s, 1 H), 4.36 (s, 1 H), 3.68 (s, 1 H), 2.50 (ddd, *J* = 18.9, 6.8, 3.2 Hz, 1 H), 2.15 (m, 1 H), 2.08 (m, 1 H), 1.85 (ddd, *J* = 14.2, 13.6 Hz, 3.1 Hz, 1 H), 1.69 (dd, *J* = 12.6, 3.1 Hz, 1 H), 1.62 (ddd, *J* = 14.0, 6.8, 3.4 Hz, 1 H), 1.24 (m, 1 H), 1.23 (s, 3 H), 0.99 (s, 3 H). − ^{13}C NMR (90.6 MHz, [D_4]methanol): δ = 195.25, 179.12, 156.53, 140.38, 101.53, 68.55, 54.14, 47.96, 41.57, 34.14, 33.74, 33.11, 26.40, 26.11, 23.15. − $[\alpha]_D^{20} = -63$ ($c = 0.65$, methanol).

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