Synthetic Studies towards Mniopetals (I). A Short Synthesis of a Key Intermediate for the Total Synthesis of Mniopetals

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Abstract: A short and efficient synthesis of a tricyclic core structure of mniopetals based on a new, highly diastereoselective PhSeLi induced Baylis-Hillman reaction and an *endo*-selective Intramolecular Diels-Alder reaction (IMDA) as key steps is presented.

Key words: intramolecular Diels-Alder reaction, HIV, natural products, terpenoids, diastereoselective Baylis-Hillman reaction

In 1994, Anke and Steglich reported 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).[1]

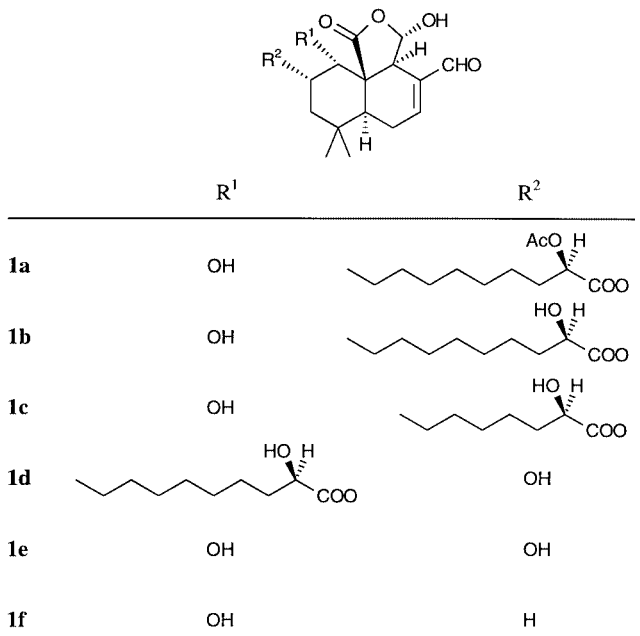
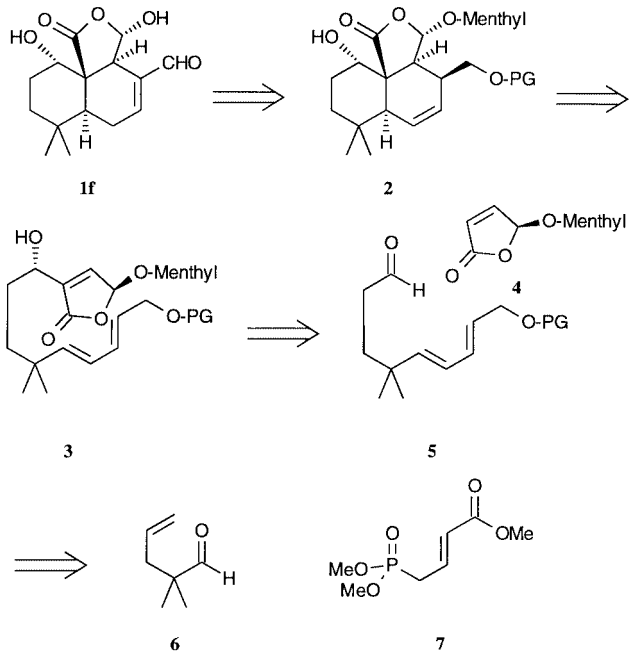


Figure 1 Structure of mniopetals A – F **1a** – **1f**.

It was shown that the mniopetals exhibit antibacterial and cytotoxic activity and are novel inhibitors of reverse transcriptase of several retroviruses, amongst them the HIV-1.[1] Therefore, the mniopetals are interesting targets for total synthesis.

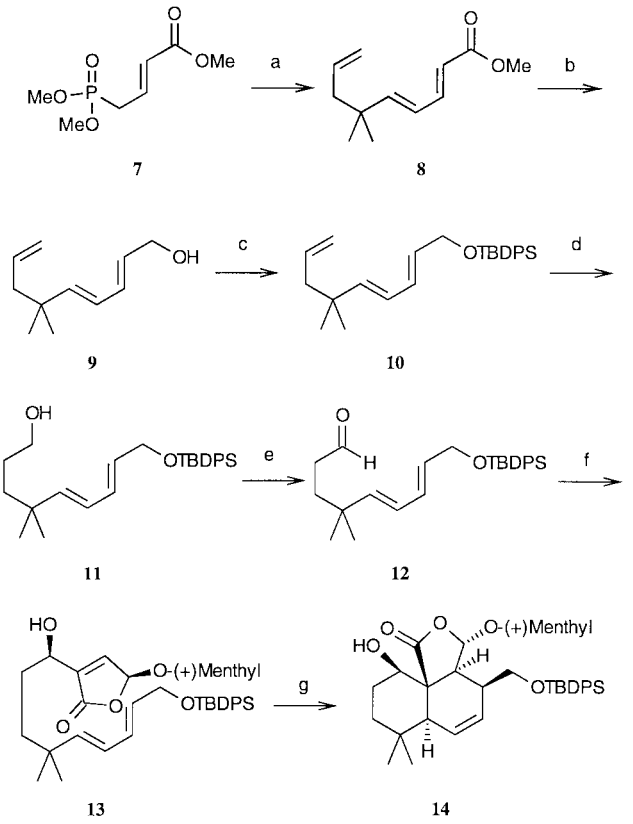
Recently, Tadano and coworkers[2] published their synthesis of a tricyclic key intermediate for the total synthesis of the mniopetals, which is based on an Intramolecular Diels-Alder reaction (IMDA) as a central step. Although we too use an Intramolecular Diels-Alder approach, our strategy is quite different and reaches the tricyclic core structure of the mniopetals after only seven steps from readily available starting materials. We wish to report our synthesis of an advanced key intermediate for the total synthesis of mniopetals.

Our retrosynthetic strategy (Scheme 1) focuses on mniopetal F **1f**. Key steps are a diastereoselective IMDA reaction[3] and a diastereoselective Baylis-Hillman reaction.[4] Retrosynthetic transformation of the hemi acetal of **1f** from an acetal using (+)-menthol and deconjugation of the α,β-unsaturated aldehyde followed by aldehyde reduction led to **2**, which originated from trienolide **3** after IMDA reaction. Disconnection of **3** according to the Baylis-Hillman reaction led to Feringa´s butenolide **4** and dienal **5**. Dienal **5** is retrosynthetically further simplified by Horner-Wadsworth-Emmons reaction using thereadily available starting materials **6** and **7**.



Scheme 1 Retrosynthetic analysis of mniopetals

a) LiHMDS, **6**, THF, -40 °C, 85%, *trans:cis* > 20:1; b) DIBALH, Et_2O, 0 °C, 30 min, 98%; c) TBDPSCl, Imidazole, DMF, RT, 2 h, 87%; d) 9-BBN, THF, r.t., 4 h, H_2O_2, NaOH, EtOH, 0 °C, 1 h, 83%; e) PDC, MS 3 Å, CH_2Cl_2, r.t., 45 min, 67%; f) Ph-Se-Li, THF, **4**, -40 °C to 0 °C, 8 h, 53%; g) Xylene, silylated flask, 140 °C, 60 h, 50%.



Scheme 2 Synthesis of an advanced key intermediate **14** in the total synthesis of mniopetals.

Our synthesis is shown in Scheme 2. First, 2,2-dimethyl-4-pentenal[5] **6** is coupled with 4-(dimethylphosphono)methylcrotonate[6] **7** providing triene **8** (*trans:cis* > 20:1), which is reduced to alcohol **9** with DIBALH.[7] Protection of the hydroxyl group as a TBDPS ether[8] **10** is followed by a hydroboration/oxidation[9] sequence under standard conditions leading to dienol **11**. Oxidation of the unprotected primary alcohol with PDC in presence of molecular sieves 3Å gives aldehyde **12**. Next, we planned to couple **12** with Feringa´s butenolide[10] **4** in a Baylis-Hillman reaction.[4] Since Feringa´s butenolide **4** is highly base sensitive and Baylis-Hillman coupling under standard conditions using DABCO as nucleophile only works well with *β*-unsubstituted derivatives of acrylic acid, the original Baylis-Hillman protocol could not be applied. Thus, we developed a new and highly diastereoselective variant[11] of the Baylis-Hillman reaction using lithium phenylselenide[12] as nucleophile. PhSeLi is readily prepared from PhSeSePh through reductive cleavage by elemental lithium or by BuLi and is a very weak base and a very good nucleophile. Reaction of PhSeLi in THF with a mixture of aldehyde **12** and Feringa´s butenolide **4** at –40 °C to 0 °C during 8 h gives trienolide **13**[13] in a highly diastereoselective tandem-Michael-aldol-retro-Michael reaction.[14] Subsequently **13** is cyclized in an *endo* selective thermal IMDA reaction providing the 1-epimer **14**[15,16] of the core structure **2** of mniopetal F **1f** in only seven steps with a total yield of 11%.

The IMDA reaction in this letter is the first one using a substituted Feringa-butenolide as dienophile. The absolute configuration of **2** is determined by the chiral auxilliary (+)-menthol, which functions as a control element to establish the correct configuration of the acetal carbon in **2** and in the mniopetals A-F **1a**-**1f** as well as the correct absolute configuration of the tricyclic core of the mniopetals. A possible transition state is shown in Fig. 2.

Figure 2 Transition state of the IMDA reaction and selected NOEs in **14**.

In summary, we developed a short and efficient synthesis of an advanced intermediate in the total synthesis of the mniopetals. Transformation of this key intermediate into the natural products is currently under way and will be published in due course.

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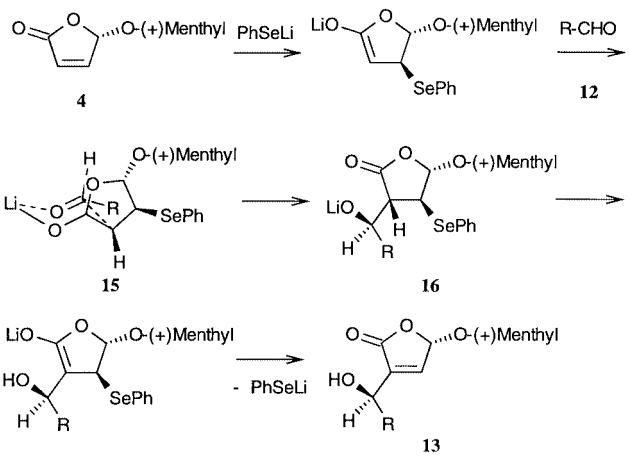
(13) **13**: 374.5 mg diphenyldiselenide (1.20 mmol) are dissolved in 3.5 mL anhyd THF under nitrogen and cooled to –10 °C. 0.75 mL of 1.5 M BuLi in hexanes (1.12 mmol) are added dropwise with stirring. After 5 min the solution is cooled to –40 °C and a mixture of 238.8 mg **4** (1.00 mmol) and 504.8 mg **12** (1.20 mmol) in 10 mL THF is added dropwise. The reaction mixture is stirred at this temperature for 4 h and then warmed to 0 °C during 4 h. Then the reaction mixture is quenched with sat. aq NH_4Cl and extracted with diethyl ether. The combined extracts are dried over $MgSO_4$ and after evaporation of the solvent the product is purified by flash chromatography (pentane/diethyl ether 2:1). Yield: 349.0 mg (53%). ^{1}H-NMR (360 MHz, $CDCl_3$): 7.68 (m, 4H); 7.39 (m, 6H); 6,90 (s, 1H); 6,24 (dd, 14.9 Hz, 10.4 Hz, 1H); 6.00 (s, 1H); 5.96 (dd, 15.6 Hz, 10.4 Hz, 1H); 5.69 (dt, 15.6 Hz, 4.9 Hz, 1H); 5.58 (d, 14.9 Hz, 1H); 4.46 (br s, 1H); 4.23 (d, 5.2 Hz, 2H); 3.64 (td, 4.6 Hz, 10.8 Hz, 1H); 2.12 (m, 2 H); 1.80-1.20 (m, 11H); 1.06 (s, 9H); 1.02 (s, 6H); 0.94 (d, 6.5 Hz, 3H); 0.87 (d, 7.1 Hz, 3H); 0.80 (d, 7.1 Hz, 3H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 170.6; 143.3; 142.9; 139.8; 135.5; 133.6; 130.3; 130.2; 129.6; 127.6; 126.3; 99.1; 79.1; 67.1; 64.2; 47.7; 40.3; 38.1; 35.7; 34.1; 31.4; 30.5; 27.2; 27.0; 26.8; 25.3; 23.1; 22.2; 20.8; 19.2; 15.8 .

(14) The configuration of the newly formed secundary alcohol is the result of chirality transfer from the acetal carbon to the new hydroxyl center via the sequence depicted below. The configuration of this center is determined in the aldol step in a Zimmermann-Traxler-like transition state and turns out to be (*R*) which is epimeric to the corresponding configuration in the natural product. This could be derived from coupling constants in **16** (OH instead of OLi) if the reaction mixture is quenched prior to PhSeLi elimination. It is consistent with the configuration of the secondary hydroxyl group in **14** and is in accordance with an X-ray structure obtained for the reaction with benzaldehyde.[11]



(15) **14**: 296.5 mg **13** (0.45 mmol) are dissolved in anhydrous xylene under nitrogen in a silylated flask and heated to 140 °C for 60 h. After cooling to room temperature the solvent is evaporated under reduced pressure and the residue is purified by flash chromatography (pentane/diethyl ether 7:1). Yield: 148.0 mg (50%). It is important to use a silylated flask for the IMDA reaction, since the glass surface catalyzes the epimerization of the acetal carbon of **13**. Higher temperatures than 140 °C increases the amount of decomposition products. The yield given corresponds to ca. 80% conversion. ^{1}H-NMR (360 MHz, $CDCl_3$): 7.68 (m, 4H); 7.40 (m, 6H); 6,00 (m, 1H); 5.73 (dt, 8.6 Hz, 3.0 Hz, 1H); 5.43 (s, 1H); 3.96 (d, 7.3 Hz, 2H); 3.93-3.80 (m, 1H); 3.69 (dd, 11.0 Hz, 3.6 Hz, 1H); 3.50 (td, 10.4 Hz, 4.3 Hz, 1H); 3.20 (m, 1H); 2.64 (d, 6.7 Hz, 1H); 2.50-1.50 (m, 10 H); 1.40-1.00 (m, 3H); 1.29 (s, 3H); 1.09 (s, 9H); 0.92 (s, 3H); 0.85 (d,7.1 Hz, 3H); 0.80 (d, 6.5 Hz, 3H); 0.74 (d, 6.5 Hz, 3H). ^{13}C-NMR (90.6 MHz, $CDCl_3$): 175.7; 135.6; 135.5; 133.4; 133.3; 131.6; 129.9; 128.6; 127.8; 97.7; 77.8; 76.0; 63.4; 58.4; 52.0; 48.6; 47.6; 39.8; 38.9; 38.8; 34.2; 34.1; 32.0; 31.3; 27.0; 26.6; 25.0; 22.6; 22.2; 21.7; 21.1; 19.3; 15.1.

(16) Together with **14** we found small quantities of two other products which have not yet been structurally fully characterized.

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