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A new route to eremophilanes: synthesis of (±)-eremophilenolide, (±)-eremophiledinone, and (±)-deoxyeremopetasidione ☆

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ABSTRACT

A new and efficient route to the family of eremophilanes is reported. Key steps are the highly stereocontrolled Diels–Alder reaction and aldol condensation to furnish a *cis*-decalin system with the desired stereochemistry present in the eremophilane family of natural products. This approach is general and was utilized for the synthesis of (±)-eremophilenolide, (±)-eremophiledinone, and (±)-deoxyeremopetasidione.

A large variety of natural products of biological importance possess the decalin skeleton as an integral part of their structure. Functionalized decalins with suitable stereochemistry are possible intermediates for several terpenoids and related natural products.[1] The eremophilane group of sesquiterpene natural products is characterized by the *cis*-fused [4.4.0] decalin architecture with a *cis*-1,2-dimethyl substitution pattern.[2] The diverse biological properties of eremophilanes combined with the unique structural and conformational challenges have attracted considerable synthetic attention.[3] Despite their well known medical values (antioxidant, antiradical, and antifeedant properties), the eremophilenolides,[4] a subclass of eremophilane natural products, are believed to be interconnected biogenetically with furanoeremophilanes, and have received very little attention.[5] Deoxyeremopetasidione **4**, a derivative of (-)-eremopitasidione **3**,[6] which was isolated recently from the rhizome of *Petasites japonicus* MAXIM, a nor sesquiterpenoid possessing the same *cis*-fused [4.4.0] decalin architecture, has been used for the treatment of tonsillitis, contusion, and poisonous snake bites in Chinese medicine, but has received very little attention. The combination of novel structural features and promising biological activity prompted us to explore a general strategy for the synthesis of (±)-eremophilenolide **6**, (±)-eremophiledinone **5**, and (±)-deoxyeremopetasidione **4** (Fig. 1).

We herein report our efforts on the synthesis of these sesquiterpenes using a highly stereocontrolled Diels–Alder reaction and an aldol condensation as the key steps.

Retrosynthetically, we envisioned eremophilenolide **6** (Scheme 1) from eremophiledinone **5**, which is also a naturally occurring eremophilane through reduction of the carbonyl group followed by lactonization. The compound **5** could be prepared from the intermediate **7** using an intramolecular aldol condensation. The Diels–Alder adduct **9** obtained from diene **11** and tiglic aldehyde **10** would serve as a precursor for the synthesis of **7** through intermediate **8**.

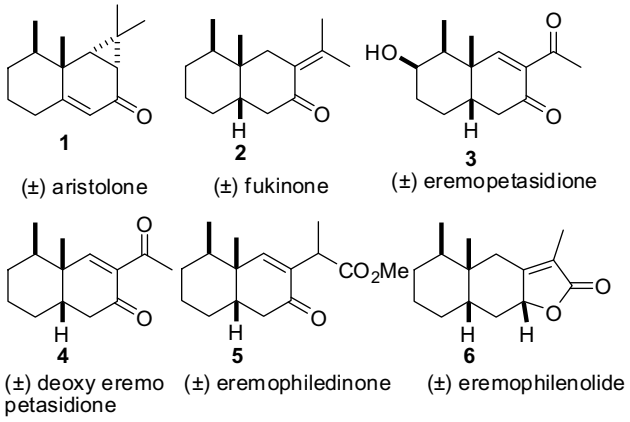

Figure 1. Selected eremophilanes possesing the *cis*-decalin system.

Our synthesis began with the Lewis acid ($BF_3{\cdot}Et_2O$)-mediated Diels–Alder reaction between known diene **11**[7] and commercially available tiglic aldehyde **10** to furnish the adduct **9**[8] with excellent stereoselectivity.[9] Protection of the aldehyde as an acetal followed by LiOH-mediated hydrolysis resulted in acid **12** in good yield. Weinreb amide formation with *N,O*-dimethyl hydroxylamine-hydrochloride followed by Grignard reaction between the resulting amide **8** and **13**[10] gave the desired carbon chain the elongated product **14**. Removal of the unwanted double bond and deprotection of the benzyl group were achieved in a single step in the

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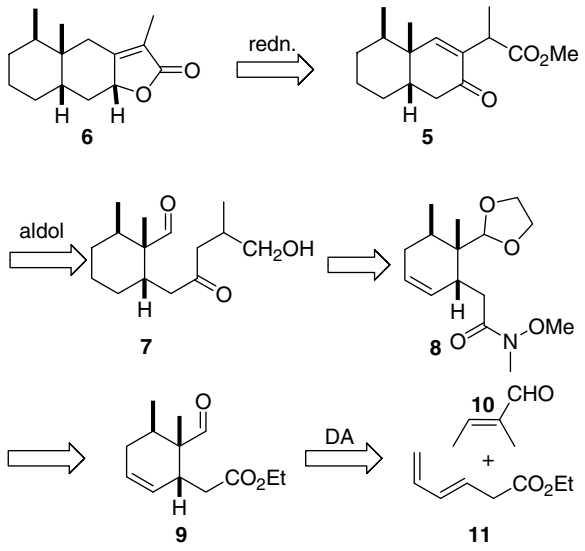
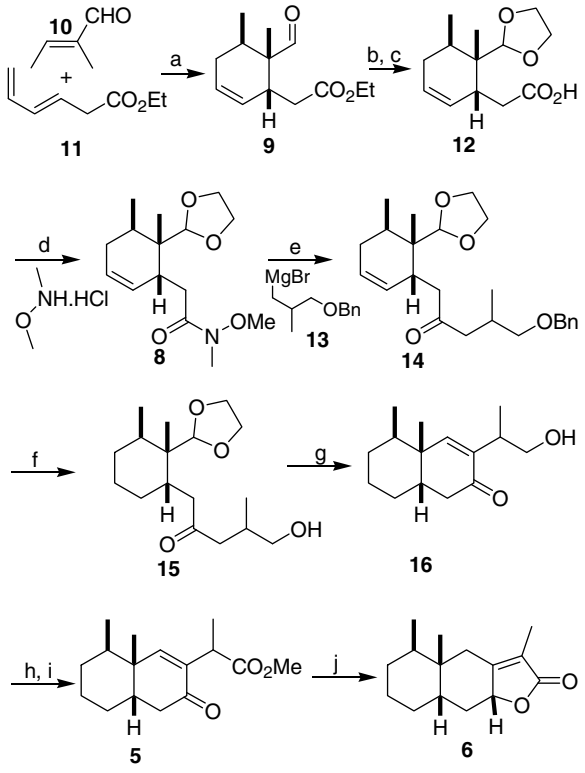


Scheme 1.

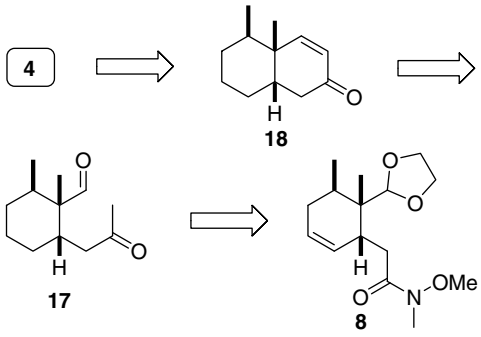
presence of the 10% Pd/C, $HCOONH_4$ to give alcohol **15** in 92% yield. As expected, when we treated **15** with 6 N HCl in DCM in order to deprotect the aldehyde group, the *cis*-decalin derivative **16** was isolated in 80% yield as a result of an in situ acid-mediated aldol condensation. Oxidation of the primary alcohol in **16** using Jone's reagent followed by esterification with diazomethane resulted in the (±)-eremophiledinone **5**. Stereoselective reduction of the carbonyl group in **5** using $NaBH_4$ followed by heating the product with DBU in benzene furnished the natural product (±)-eremophilenolide **6** in 70% isolated yield over two steps (Scheme 2).[11] The spectral data of both natural products **5**[12] and **6**[13] are compared well with those of the literature values.[4] We have accomplished the total synthesis of (±) eremophilenolide **6** in eleven steps and in 15% overall yield.



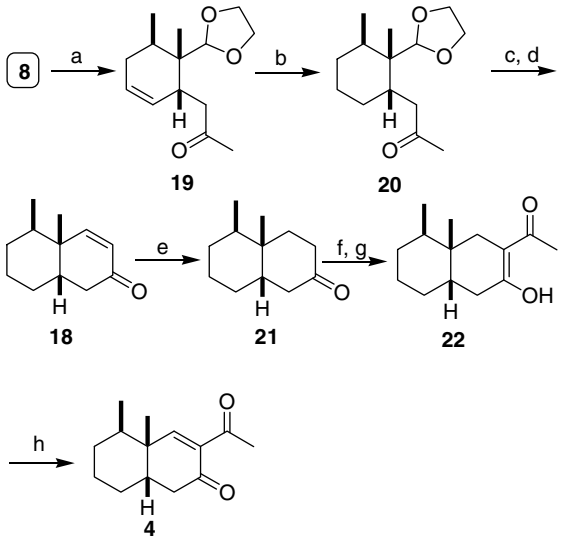
Scheme 2. Reagents and conditions: (a) $BF_3{\cdot}Et_2O$, DCM, −78 °C to rt, 75%; (b) $(CH_2OH)_2$, cat. PTSA, benzene, 81%, (c) LiOH, MeOH, H_2O, 85%; (d) EDC, HOBt, Et_3N, DCM, 90%; (e) **13**, THF, 0 °C, 90%; (f) 10% Pd/C, HCO_2NH_4, MeOH, reflux, 92%; (g) 6N HCl, DCM, reflux, 80%; (h) Jone's reagent, acetone, rt, 70%; (i) CH_2N_2, ether, 68%; and (j) $NaBH_4$, MeOH, rt, DBU, benzene, reflux, 70% in two steps.

Retrosynthetically, (±)-deoxyeremopetasidione **4** (Scheme 3) can be prepared from an intermediate *cis*-decalin **18**. The compound **18** could be prepared from **17** using an intramolecular aldol condensation. The common intermediate **8** would serve as a precursor for the synthesis of **17**.

Our synthesis began with the conversion of Weinreb amide **8** into ketone **19** through a Grignard reaction with methyl magnesium chloride followed by removal of the double bond with 10% Pd/C in methanol to give **20**. Subsequent deprotection of the aldehyde group with 6 N HCl in DCM followed by intramolecular condensation with 15% KOH in methanol furnished the desired key intermediate *cis*-decalin derivative **18**[14] in 90% isolated yield (Scheme 4). Hydrogenation of enone **18** in the presence of 10% Pd/C in methanol produced decalin **21** in 90% yield. The C-acylation[15] of the enolate derived from **21** with pyruvonitrile, and subsequent treatment with NaOH produced **22**. Finally, dehydrogenation[16] of the enol was performed with DDQ to accomplish the total synthesis of (±)-deoxyeremopetasidione **4**[17] (Scheme 4). Here, we have accomplished the total synthesis of (±)-deoxyeremopetasidione in eight synthetic steps from intermediate **8** in 44% overall yield.



Scheme 3.



Scheme 4. Reagents and conditions: (a) MeMgCl, THF, 0 °C, 90%; (b) 10% Pd/C, MeOH, 90%; (c) 6 N HCl, reflux; (d) 15% KOH, MeOH, 85%; (e) 10% Pd/C, MeOH, 90%; (f) LiHMDS, CH_3COCN, THF, −78 °C, 84%; (g) NaOH, THF, 85%; and (h) DDQ, dioxane, 85%.

In summary, we have developed an efficient, short, and highly stereocontrolled route to the synthesis of (±)-deoxyeremopetasidione **4**, (±)-eremophiledinone **5** and (±)-eremophilenolide **6**. Novel application of a Lewis acid mediated Diels-Alder reaction and aldol condensation strategy to construct the *cis*-decalin system and further synthetic manipulation to the natural products was carried out in a planned and optimized sequence. This approach is general, and uses inexpensive and commercially available starting materials to generate various structural analogs of eremophilanes for biological investigation.

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8. *Experimental procedure and spectral data for* **9**: To a solution of diene **11** (7.5 g, 53.57 mmol) and tiglic aldehyde **10** (11.2 g, 134 mmol) in dry DCM (265 ml) was added $BF_3{\cdot}Et_2O$ (15.5 g, 107.14 mmol) dropwise at −78 °C. The reaction was allowed to warm to rt and stirred overnight. The DCM layer was washed with 10% $NaHCO_3$ followed by water and brine, then dried over Na_2SO_4, and evaporated in vacuum. The residue was purified by flash column chromatography over silica gel (ethyl acetate/hexane, 0.2:99.8) to afford 9 g (75%) of **9** as a light brown colored oil. IR (neat, cm^{-1}) 2978, 1732, 1174; ^1H NMR (400 MHz, $CDCl_3$) δ = 9.60 (s, 1H), 5.71–5.66 (m, 1H), 5.64–5.97 (m 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 2.65–2.59 (m, 1H), 2.45 (dd, *J* = 5.4 Hz, 15.8 Hz, 1H), 2.37–2.30 (m, 1H), 2.25–2.18 (m, 1H), 2.17–2.05 (m, 1H), 1.79–1.72 (m, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.08 (s, 3H), 0.93 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 206.6, 172.6, 127.4, 126.1, 60.4, 49.6, 37.6, 35.6, 30.65, 29.5, 15.7, 15.6, 13.9; Mass (ESI): 225 $[M+H]^+$.
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12. *Spectral data of* **5**: IR (neat, cm^{-1}): 2993, 1737, 1676; ^1H NMR (400 MHz; $CDCl_3$): δ = 6.63 (br s, 1H), 3.67–3.62 (m, 1H), 3.65 (s, 3H), 2.68–2.61 (m, 1H), 2.32–2.26 (m, 1H), 2.09–2.04 (m, 1H), 1.82–1.70 (m, 2H), 1.57–1.43 (m, 3H,), 1.39–1.23 (m, 2H), 1.27 (d, *J* = 7.3 Hz, 3H), 1.12 (s, 3H), 0.92 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (50 MHz; $CDCl_3$) δ = 198.4, 175.0, 156.4, 136.6, 51.8, 39.4, 38.9, 38.2, 37.9, 36.1, 30.2, 27.0, 20.8, 20.4, 16.5, 15.8; HRMS calculated for $C_{16}H_{25}O_3$ $[M+H]^+$ 265.1804, found 265.1801.
13. *Spectral data of* **6**: IR (neat, cm^{-1}): 2932, 1738; ^1H NMR (400 MHz; $CDCl_3$): δ = 4.66–4.61 (m, 1H), 2.89 (d, *J* = 15 Hz, 1H,), 2.01–2.05 (m, 1H), 1.89–1.64 (m, 4H), 1.80 (s, 3H), 1.48–1.33 (m, 5H), 1.28–1.20 (m, 1H), 1.03 (s, 3H), 0.88 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (50 MHz; $CDCl_3$) δ = 174.9, 161.1, 120.5, 80.4, 40.2, 39.8, 36.4, 35.2, 30.6, 30.0, 26.7, 21.6, 20.6, 15.9, 8.2; HRMS calculated for $C_{15}H_{23}O_2[M+H]^+$ 235.1698, found 235.1700.
14. *Spectral data of* **18**: IR (neat, cm^{-1}): 2925, 1680, 1375; ^1H NMR (400 MHz; $CDCl_3$): δ = 6.81 (d, *J* = 10.2 Hz, 1H), 5.91 (d, *J* = 10.2 Hz, 1H), 2.65 (dd, *J* = 12.7, 17 Hz, 1H), 2.20 (dd, *J* = 4.4, 17 Hz, 1H), 2.09–2.03 (m, 1H), 1.84–1.72 (m, 2H), 1.57–1.40 (m, 3H), 1.39–1.24 (m, 2H), 1.21 (s, 3H), 0.92 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (50 MHz; $CDCl_3$) δ = 200.6, 161.3, 127.1, 39.8, 39.3, 38.8, 35.65, 30.1, 27.1, 20.4, 20.2, 15.9; mass (ESI): 179 $[M+H]^+$.
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17. *Spectral data of* **4**: IR (neat, cm^{-1}): 2930, 1691, 1680, 1357, 1250; ^1H NMR (400 MHz; $CDCl_3$): δ = 7.49 (s, 1H), 2.73 (dd, *J* = 12.4, 16.6 Hz, 1H), 2.46 (s, 3H), 2.32 (dd, *J* = 4.4, 16.6 Hz, 1H), 2.15–2.06 (m, 1H), 1.87–1.82 (m, 1H), 1.78–1.72 (m, 1H), 1.59–1.55 (m, 1H), 1.54–1.40 (m, 2H), 1.39–1.33 (m, 2H), 1.18 (s, 3H), 0.95 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz; $CDCl_3$) δ = 198.4, 197.6, 166.5, 136.9, 40.4, 39.6, 39.4, 35.5, 30.7, 30.2, 26.8, 20.2, 20.1, 15.9; HRMS calculated for $C_{14}H_{21}O_2$ $[M+H]^+$ 221.1547, found 221.1551.