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The first synthesis of a noreremophilane isolated from the roots of *Ligularia przewalskii* ☆

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Abstract—The total synthesis of a natural product noreremophilane has been achieved in just three steps from readily available starting materials. A highly stereo- and regio-selective Diels–Alder reaction was the key step in our synthesis.

Recently, Jia and his group isolated 10 structurally unrelated eremophilane derivatives from the roots of *Ligularia przewalskii* (Maxim.) Diels (comopsitae).[1] This plant has been used traditionally for the treatment of asthma, hemoptysis, hepatitis, and pulmonary tuberculosis in Chinese folk medicine. These compounds are closely related to the biologically important eremophilane/bakkane family and selected members **1**–**4** are shown in Figure 1. The interesting biological profiles and structural features present in these molecules have generated significant interest from the synthetic community.[2] In this letter, we disclose the first synthesis of noreremophilane **1**,[1] which further confirms the structure assigned on the basis of spectral data.

Initially, we targeted noreremophilane **1**, the simplest member of this group utilizing a Diels–Alder/aldol sequence,[3] which was recently developed by one of us (DSR). Retrosynthetically, it was hoped that the noreremophilane skeleton could be constructed using a Diels–Alder/aldol sequence starting from dienophile **5** and diene **6** (disconnections are shown in Scheme 1). To execute the plan, we synthesized the dienophile **5** with the desired substitution pattern starting from dimethyl tartrate via periodate cleavage followed by a Wittig olefination.[4] The diene **6** was prepared from divinyl carbinol using a Claisen rearrangement as described in a previous communication (Scheme 2).[3]

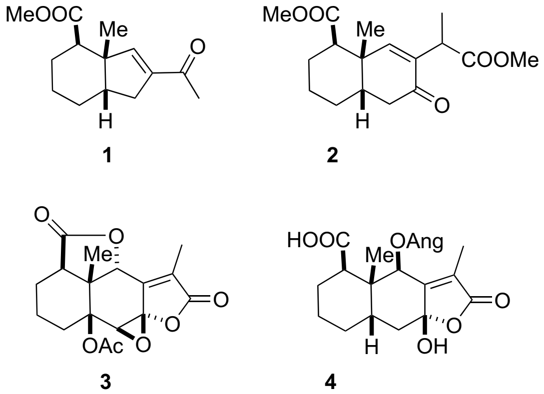
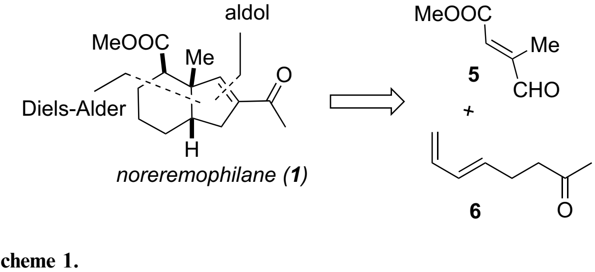


Figure 1. Selected natural products isolated from the roots of *Ligularia przewalskii.*



Scheme 1.

Keywords: Noreremophilane; Diels–Alder; Aldol.

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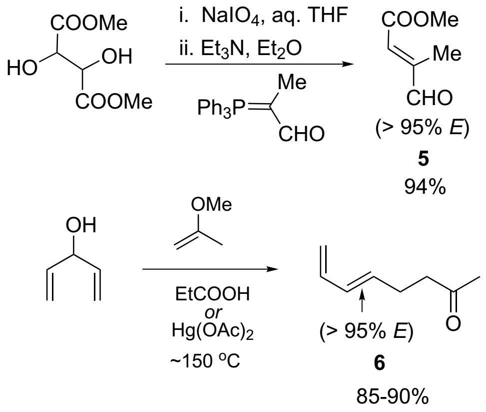
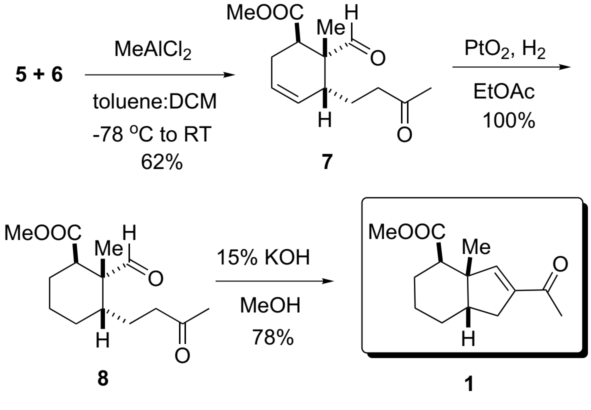


Scheme 2.

The synthesis commenced with the pivotal Diels–Alder reaction between dienophile **5** and diene **6** using $MeAlCl_2$ in a toluene–dichloromethane mixture.[5] To our delight, we obtained the desired transformation to furnish **7**[6] in 62% isolated yield with excellent *endo* selectivity and regioselectivity (dr > 9:1). The highly selective intermolecular Diels–Alder reaction established the requisite stereochemistry of the three contiguous stereogenic centers of this group of natural products. The diastereo- and regioselectivity of the DA reaction is in agreement with the literature precedence.[7] The unwanted double bond was removed from **7** using Adam's catalyst under hydrogen atmosphere to provide **8**[6] in quantitative yield, which on aldol condensation using 15% KOH in methanol furnished the target compound **1** in 78% isolated yield. It is also interesting to note that we did not see any epimerization at the center bearing the carboxylic ester group under basic conditions (Scheme 3). The spectral data of **1** were compared with those of the natural product[1] and they were found to be identical.[8] It is also noteworthy to mention that we have prepared the natural product noreremophilane **1** in good quantity (~0.2 g) using this route, which can be used for biological assays.

In conclusion, the first synthesis of racemic noreremophilane **1** was achieved in 48% overall yield starting from readily available precursors **5** and **6** in just three steps. Key to the overall efficiency of this approach was the use of a highly diasteroselective and regioselective Diels–Alder/aldol sequence. The synthesis confirms the structural assignment of **1**. The inherent flexibility of this approach is that by changing the diene one can synthesize other members of this group and related compounds. The synthesis of other members and adaptation to an asymmetric version will be the subject of future work from our group.



Scheme 3.

Acknowledgements

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6. Spectral data of **7**: IR (Neat): 1722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.69 (s, 1H), 5.70 (m, 2H), 3.68 (s, 3H), 3.03 (m, 1H), 2.54–2.39 (m, 4H), 2.21 (m, 1H), 2.13 (s, 3H), 1.76 (m, 1H), 1.52 (m, 1H), 1.25 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 207.5, 204.9, 174.1, 126.9, 125.3, 51.4, 49.2, 44.9, 42.0, 40.9, 38.8, 29.6, 25.8, 15.6; MS (CI): 253 (M^++1); **8**: IR (Neat): 1720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.67 (s, 1H), 3.65 (s, 3H), 2.98 (m, 1H), 2.47 (m, 1H), 2.39 (m, 1H), 2.13 (s, 3H), 1.85 (m, 1H), 1.79–1.61 (m, 6H), 1.53 (m, 1H), 1.33 (m, 1H), 1.23 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 207.9, 205.5, 174.2, 50.3, 42.2, 41.4, 40.6, 39.4, 29.5, 24.3, 21.8, 19.8, 17.0; MS (CI): 255 (M^++1).

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8. Spectral data for the synthetic natural product noreremophilane **1**: IR (Neat): 1732, 1669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.84 (d, 1H, $J = 1.6$ Hz), 3.69 (s, 3H), 2.51 (dd, 1H, $J = 15.9$, 8.1), 2.42 (m, 1H), 2.32 (dd, 1H, $J = 12.0$, 3.2 Hz), 2.33 (s, 3H), 2.03 (m, 1H), 1.73 (m, 1H), 1.64 (m, 2H), 1.58 (m, 1H), 1.52 (m, 1H), 1.41 (m, 1H), 1.12 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 197.8, 174.8, 154.1, 142.7, 51.4, 48.7, 48.5, 46.4, 33.1, 26.3, 23.8, 23.0, 20.7, 19.2; MS (CI): 237 (M^{+}+1).