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A tandem oxidative dearomatization/intramolecular Diels–Alder reaction: a short and efficient entry into tricyclic system of maoecrystal V

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ABSTRACT

A short and efficient route to tricyclic ring system containing bridged bicyclo[2.2.2]octanone annulated with a lactone ring present in the maoecrystal is described. In-situ generation of spiroepoxycyclohexa-2,4-dienone and intramolecular cycloaddition are the key features of our approach.

Recently maoecrystal V (1) (Fig. 1), a diterpene, was isolated from Chinese herb *Isodon eriocalyx* by Sun and co-workers.[1] It exhibits potent inhibitory activity against HeLa cells and thus appears to be a promising anticancer agent.[1] Maoecrystal V possess a highly complex and functionalized pentacyclic molecular architecture that contains a bridged bicyclo[2.2.2]octane framework annulated with a lactone ring and a spirocyclic six-membered ring along with a five-membered ring ether. The complex structure of **1** coupled with its biological potential has stimulated significant interest in its synthesis.[2] Though synthesis of maoecrystal V has not been achieved yet, several research groups have reported imaginative approaches towards its synthesis.[2]

Rapid generation of molecular complexity from simple precursors is one of the important features of synthesis design and development of methodology.[3] Tandem reactions and multicomponent reactions are often employed to achieve these objectives.[4] Recently, the reactive species derived from arenols such as cyclohexa-2,4-dienone ketals and congeners have proved to be an important tool and provided an efficient method for the synthesis of a diverse array of molecular structures and natural products.[5–7] We have a long standing interest in the chemistry of 6,6-spiroepoxycyclohexa-2,4-dienones, especially in its inverse demand $\pi^{4s} + \pi^{2s}$ cycloaddition and the chemistry of adducts in ground and excited states.[7]

In view of the contemporary interest in maoecrystal and our continuing interest in the creation of molecular complexity from aromatics,[7] we considered developing a simple, efficient and stereo-selective route to tricyclic compounds **2** (Fig. 1) containing a bridged bicyclo[2.2.2]octanone ring annulated with a lactone ring which comprises the structure of maoecrystal V. We wish to report our exploratory results herein.

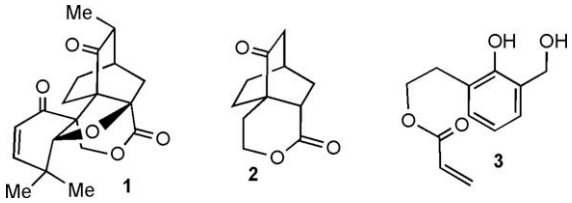

Figure 1. Structure of maoecrystal V (**1**) tricyclic compound **2** and the aromatic precursor **3**.

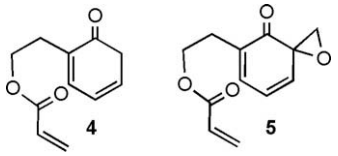

Figure 2. Cyclohexa-2,4-dienone **4** and spiroepoxycyclohexane-2,4-dienone **5**.

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Conceptually, the tricyclic lactone of type **2** may be directly obtained by intramolecular Diels–Alder reaction in the cyclohexa-2,4-dienone of type **4** (Fig. 2). However, compound **4** is inaccessible as it is a tautomer of the corresponding phenol.

Hence, we considered employing an equivalent of the dienone **4** especially the 6,6-spiroepoxycyclohexa-2,4-dienone **5**. We contemplated that intramolecular *endo*-cycloaddition in embellished spiroepoxycyclohexa-2,4-dienone **5** would provide tricyclic keto-epoxide **6** and that manipulation of the oxirane ring and reduction of the double bond would lead to desired tricyclic lactone **2** (Scheme 1). The spiroepoxycyclohexa-2,4-dienone **5** was thought to be generated by oxidative dearomatization of aromatic precursor **3**.

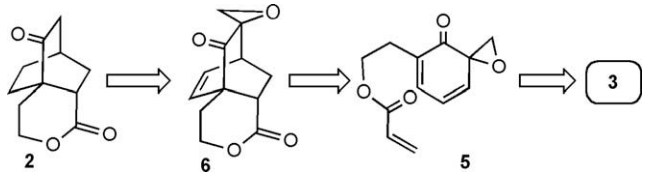
There are several key features of our strategy. For example, all the carbon atoms of the tricyclic intermediate **2** and the required functional groups are derived from the aromatic precursor **3**. Remarkably, the bridged bicyclic system annulated with the lactone ring required in the intermediate **2** is present in latent form in the precursor **3** and it is generated in a single stereo-selective step.

In order to realize the aforementioned objective, the *o*-hydroxymethyl phenol **3** was easily prepared from the readily available[7c] compound **7** (Scheme 2). Thus, protection of 1,3-diol group as acetonide followed by oxidative cleavage of the double bond and reduction of the resulting aldehyde gave the compound **8** in excellent yield. Acylation of **8** with acrolyl chloride followed by hydrolysis of the acetonide efficiently furnished the desired precursor **3**.

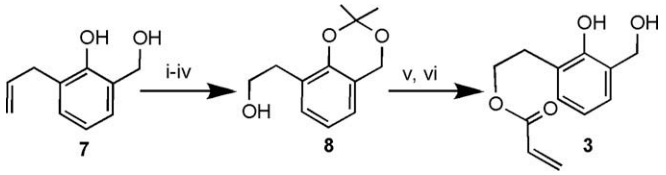
Towards the oxidative dearomatization and intramolecular cycloaddition, a solution of compound **3** in acetonitrile was oxidized with aq. $NaIO_4$ following a procedure developed earlier in our laboratory.[8] Chromatography of the product mixture furnished the tricyclic keto-epoxide **6** as a consequence of intramolecular cycloaddition along with the dimer **9**, the latter arising as a result of intermolecular cycloaddition between two moles of the cyclohexa-2,4-dienone **5** (Scheme 3).

It appeared that intermolecular cycloaddition between two moles of cyclohexa-2,4-dienone **5** is competing to a significant extent under the aforementioned mild reaction conditions. Therefore, it was thought that pyrolysis of **9** may also generate the species **5** which may undergo efficient intramolecular cycloaddition as a result of thermal activation. Indeed, heating the dimer **9** at 140 °C gave the desired adduct **6** in high yield as a consequence of retro-Diels–Alder/Diels–Alder cascade (Scheme 3).[9]

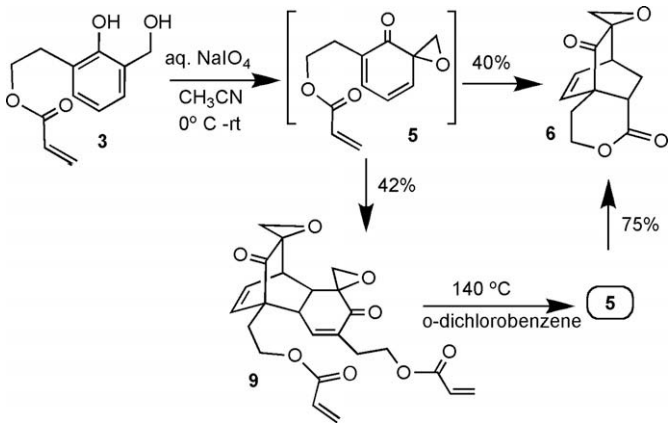
The structure of adduct **6** was deduced from the following spectral characteristics and further confirmed through single crystal X-ray analysis. Thus, the IR spectrum of **6** showed two absorption bands at 1744 and 1733 cm^{-1} for the carbonyl groups. The ^1H NMR spectrum (300 MHz) displayed characteristic signals at δ 6.65 (dd, J_1 = 8.1 Hz, J_2 = 6.9 Hz, 1H) and 5.84 (d, J = 8.1 Hz, 1H) for olefinic protons. The difference in the chemical shift of the olefinic protons is a manifestation of homoconjugation of the C=C π-bond with the carbonyl group in a bridged bicyclo[2.2.2]octane framework. This clearly indicated that cycloaddition had occurred. Similarly, the methylene group of spiro-oxirane ring appeared as part of AB pattern at distinct chemical shifts δ 3.20 (J_{AB} = 6.2 Hz, 1H) and 2.92 (part of AB system partly merged with another m, J_{AB} = 6.2 Hz, 1H). Further signals were observed at δ 4.47 (dd of part of an AB system, J_{AB} = 12.2 Hz, J_2 = 6.1 Hz, J_3 = 3 Hz, 1H), 4.30 (superimposed dd of part of an AB system, J_{AB} = 12.2 Hz, $J_2 = J_3$ = 4.5 Hz, 1H) for OCH_2 protons of the lactone ring. In addition, signals were observed at δ 3.06–2.90 (complex, m, 2H), 2.78–2.66 (m, 1H), 2.40–2.32 (merged m, 2H), 2.06–1.74 (complex m, 1H). ^{13}C NMR of adduct **6** also corroborated with its structure as it exhibited characteristic signals at δ 202.1, 172.2 and 137.4, 132.1 for the carbonyl carbons and olefinic carbons, respectively. Further signals were observed at δ 65.2, 57.1, 53.5, 51.0, 39.3, 37.8, 26.1 and 24.0 for other carbons. These spectral features suggested the gross structure of adduct. However, in order to ascertain the *endo*-stereochemistry and stereochemistry at the spiro-oxirane centre, X-ray crystal structure was undertaken which confirmed its structure (Fig. 3).



Scheme 1. Strategy for the synthesis of compound **2**.



Scheme 2. Synthesis of aromatic precursor **3**. Reagents and conditions: (i) *p*-TsOH, dimethoxypropane, acetone, rt, 72.5%; (ii) OsO_4, NMO, aq. acetone, 90%; (iii) $NaIO_4$, aq. MeCN, 0 °C, 2 h, 81%; (iv) $NaBH_4$, aq. MeOH, 99%; (v) acrolyl chloride, CH_2Cl_2, diisopropyl ethyl amine, DMAP, 95%; (vi) aq. HCl, THF, rt, 91.8%.



Scheme 3. Synthesis of tricyclic keto-epoxide **6**.

It may be worth noting the stereoselectivity during the aforementioned cycloaddition as well as rapid generation of complex and functionalized molecular structure from a simple aromatic precursor. Further the presence of α-keto-epoxide functionality in the adduct **6** provided a unique opportunity for further manipulation.

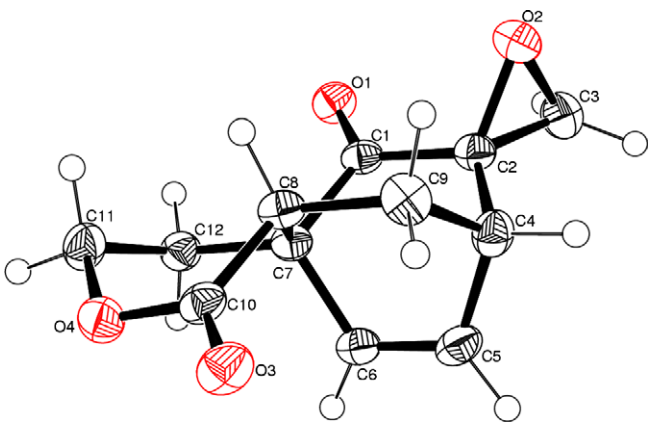
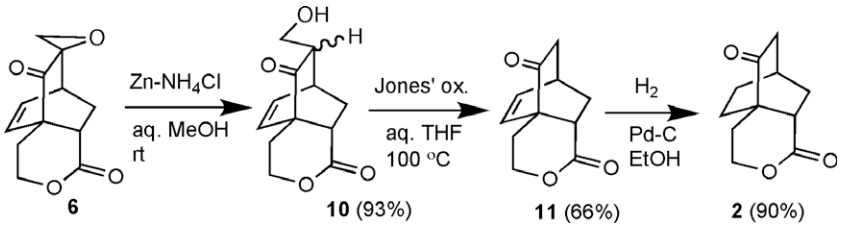


Figure 3. X-ray crystal structure of adduct **6**.



Scheme 4. Synthesis of tricyclic intermediate **2**.

Thus, the adduct **6** was treated with Zn in the presence of NH_4Cl in aq. MeOH at ambient temperature (~30 °C) which gave the β-hydroxyketone **10** in excellent yield (93%) which upon Jones' oxidation and decarboxylation furnished the keto-lactone **11** (Scheme 4). Catalytic hydrogenation of **11** readily gave the desired compound **2** which represents the tricyclic core of maoecrystal V. The structure of all the compounds was clearly revealed from their spectral data.[9]

In summary, we have presented an efficient and stereo-selective route to tricyclic core structure of maoecrystal V from a simple aromatic precursor. A tandem oxidative dearomatization of appropriately appended *o*-hydroxymethylphenol and intramolecular cycloaddition gave a tricyclic adduct having bridged bicyclo[2.2.2]octanone framework annulated with the lactone ring. Manipulation of the oxirane ring and the double bond furnished the desired intermediate. The present methodology constitutes a nice example of creation of molecular complexity from aromatics which is an important aspect of synthesis design.[3]

Acknowledgement

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9. All the compounds were thoroughly characterized with the help of spectral data. *Data for adduct* **6**: mp 139–140 °C. IR ν_{max} (KBr): 1744, 1731 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.65 (dd, J_1 = 8.1 Hz, J_2 = 6.9 Hz, 1H) and 5. 84 (d, J = 8.1 Hz, 1H), 4.47 (dd of part of an AB system, J_{AB} = 12.2 Hz, J_2 = 6.1 Hz, J_3 = 3 Hz, 1H), 4.30 (superimposed dd of part of an AB system, J_{AB} = 12.2 Hz, J_2 = J_3 = 4.5 Hz, 1H), 3.20 (part of an AB system J_{AB} = 6.2 Hz, 1H) and 2.92 (part of AB system partly merged with another m, J_{AB} = 6.2 Hz, 1H), 3.06–2.90 (complex, m, 2H), 2.78–2.66 (m, 1H), 2.40–2.32 (merged m, 2H), 2.06–1.74 (complex m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.1, 172.2 (CO groups) and 137.4, 132.1 (olefinic carbons), 65.2, 57.1, 53.5, 51.0, 39.3, 37.8, 26.1, and 24.0 for other carbons. HRMS (ESI) *m*/*z*: 221.0808 $(M+H)^+$; $C_{12}H_{13}O_4$ requires 221.0814.
Crystal data: $C_{12}H_{12}O_4$, Mol. Wt. 220.22. Crystal size = 0.23 × 0.18 × 0.13 mm. Space group: Triclinic $P\bar{1}$, Z = 2, a = 6.5009(5), b = 8.2023 (5), c = 9. 5100 (8) Å, α = 102. 097(6), β = 97.030(7), γ = 93.250 (6)°. Dc: 1.492 mg/m^3, crystal volume = 490.33 (6) $Å^3$, T = 150(2) K, γ = 0.71073 Å F (000) = 232. Reflections collected/unique 3382/1723, [R(int) = 0.0258], final R indices [I >2σ (I)], R_1 = 0.0404, wR_2 = 0.1144. R indices all data = R_1 = 0.0499, wR_2 = 0.1183. Crystallographic data has been deposited with Cambridge Crystallographic data Centre, CCDC No. 771301. Copy of the data can be obtained, free of charge, on application to CCDC. E-mail. Deposit@ccdc.cam.ac.uk.
Data for compound **11**: mp 92–93 °C. IR ν_{max} (KBr): 1731, 1715 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.63 (dd, J_1 = 8 Hz, J_2 = 7 Hz, 1H), 5.73 (d, J = 7 Hz, 1H), 4.46–4.40 (complex m, 1H), 4.28–4.20 (complex m, 1H), 3.14–3.08 (br m, 1H), 2.98 (t of d, J_1 = 15 Hz, J_2 = 4.2 Hz, 1H), 2.30–2.22 (complex m, 1H), 2.20–2.16 (m, 2H), 2.06–1.88 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.9, 172.9, 140.0, 130.5, 65.5, 50.8, 38.8, 38.4, 31.7, 27.8, 26.3. HRMS (ESI) *m*/*z*: 193.0861 $(M+H)^+$; $C_{11}H_{13}O_3$ requires 193.0865.
Data for compound **2**: mp 104–105 °C. IR ν_{max} (KBr): 1742, 1723 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.40–4.29 (m, 1H), 4.15–4.00 (m, 1H), 2.85–2.80 (m, 1H), 2.74–2.70 (m, 1H), 2.50–2.20 (m, 4H), 2.00–1.60 (m, 5H), 1.45–1.30 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.2, 173.7, 65.4, 44.3, 43.5, 38.4, 29.3, 27.2, 26.4, 25.94, 25.90. HRMS (ESI) *m*/*z*: 195.1022 $(M+H)^+$; $C_{11}H_{15}O_3$ requires 195.1021.