Synthesis of functionalized maoecrystal V core structures†

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Two strategies toward the total synthesis of maoecrystal V (1) culminating in the construction of core structures 2 and 3 are described.

Maoecrystal V (**1**, Fig. 1) is a recently reported terpenoid endowed with potent and selective cytotoxic properties and novel architectural motifs.[1] Isolated from the medicinally used Chinese herb *Isodon eriocalyx*, collected from the Jiangchuan prefecture of Yunnan province, this natural product exhibits selective cytotoxicity against HeLa cells (IC_{50} = 0.02 μg mL^{-1}) as compared to three other cell lines tested (K562, A549 and BGC-823). Its highly unusual structure was finally reported in 2004 after an X-ray crystallographic analysis, although it was suspected several years earlier on the basis of NMR spectroscopic and mass spectrometric experiments.[1] By virtue of its appealing molecular structure and antitumor properties, maoecrystal V attracted the attention of synthetic organic chemists and, thus, studies toward its synthesis already began to emerge.[2–4] In this communication, we report our early forays in this area that culminated in the construction of functionalized core structures **2** and **3** (Fig. 1) as well as preliminary biological evaluation of these compounds.

The striking molecular structure of maoecrystal V (**1**) is characterized by its compact polycyclic nature, unprecedented ring framework, and five stereogenic centers (of which three are quaternary). Our first approach to the pentacyclic framework of this molecule was based on the premise that it could be formed from a bicyclic precursor through an intramolecular [4 + 2] cycloaddition[5] that would introduce two additional rings, followed by an intramolecular cyclopropanation/dearomatization/ring opening cascade to forge the final ring (see Scheme 1). To this end, 2,6-dimethoxy benzoic acid (**4**)

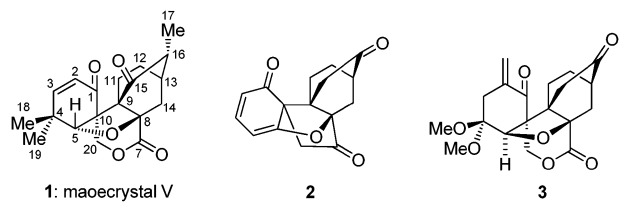
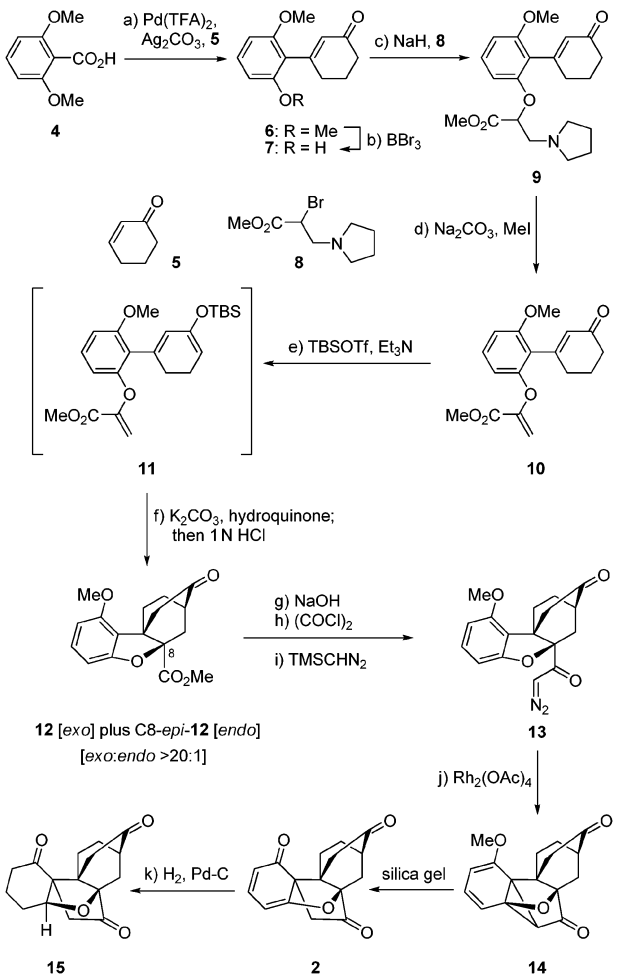


Fig. 1 Structures of maoecrystal V (**1**) and functionalized core structures **2** and **3**.



Scheme 1 Construction of dienone **2**. Reagents and conditions: (a) **5** (1.6 equiv.), $Pd(TFA)_2$ (0.2 equiv.), Ag_2CO_3 (2.0 equiv.), DMF/DMSO (20 : 1), 80 °C, 3 h, 89%; (b) BBr_3 (1.8 equiv.), CH_2Cl_2, −15 °C, 2.5 h, 70%; (c) NaH (2.1 equiv.), THF, 0 → 23 °C, 1 h; then **8** (5.0 equiv.) 0 → 23 °C, 16 h; (d) Na_2CO_3 (5.0 equiv.), MeI (10.0 equiv.), MeOH, reflux, 2 h, 80% over the two steps; (e) TBSOTf (1.5 equiv.), Et_3N (3.0 equiv.), CH_2Cl_2, 0 °C, 1.5 h; (f) K_2CO_3 (4.8 equiv.), hydroquinone (1.2 equiv.), toluene, reflux, 16 h; then 1.0 N aq. HCl, 1 h, 23 °C, 64% over the two steps; (g) NaOH (1.0 N aq.)/EtOH (1 : 1), 60 °C, 5 h; (h) $(COCl)_2$ (5.0 equiv.), DMF (1 drop), CH_2Cl_2, reflux, 1 h; (i) $TMSCHN_2$ (5.0 equiv.), THF–CH_3CN (1 : 1), 0 °C, 2 h, 79% over the three steps; (j) $Rh_2(OAc)_4$ (0.1 equiv.), CH_2Cl_2, 23 °C, 1 h, 75%; (k) 10% Pd/C (0.26 equiv.), H_2, EtOAc, 23 °C, 24 h, 87%.

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was reacted with cyclohexenone (**5**) in the presence of $Pd(OCOCF_3)_2$ catalyst and Ag_2CO_3 to afford arylated enone **6** through a decarboxylative Heck process,[6] in 89% yield. Mono-demethylation of dimethoxy enone **6** (BBr_3, 70% yield) followed by *O*-alkylation of the resulting phenol (**7**) with bromide **8**[7] resulted in the formation of pyrrolidine derivate **9**, whose conversion to the desired alkenyl methyl ester **10** required quaternization and extrusion of its nitrogen moiety (Na_2CO_3–MeI, 80% overall yield from **7**). Subsequent reaction of enone **10** with TBSOTf–Et_3N furnished TBS enol ether **11**, which was subjected to the intended intramolecular [4 + 2] cycloaddition reaction directly and without purification in the presence of K_2CO_3 and hydroquinone (toluene, reflux). Upon exposure of the resulting cycloadducts to aq. HCl, the *exo* (major) Diels–Alder product **12** (64% yield from **10**) and its *endo* isomer (C8-*epi*-**12**, not shown, 1.7% yield from **10**) were obtained and chromatographically separated. The structural identity of **12** (m.p. 200–201 °C, EtOAc/hexanes) was unambiguously assigned through X-ray crystallographic analysis[8] (see ORTEP, Fig. 2).[9] The second of the two contiguous all carbon quaternary centers was fabricated through an intramolecular, carbene-mediated cyclopropanation/fragmentation process inspired by the work of Mander,[10] as shown in Scheme 1. Thus, saponification of the methyl ester within **12** (1 N aq. NaOH/EtOH 1 : 1, 60 °C), followed by acid chloride formation [$(COCl)_2$] and exposure to $TMSCHN_2$, led to α-diazo ketone **13** in 79% overall yield for the three steps. Treatment of diazo ketone **13** with $Rh_2(OAc)_4$ catalyst in CH_2Cl_2 at ambient temperature resulted, upon exposure of the resulting cyclopropane (**14**) to silica gel, in the formation of pentacyclic dienone maoecrystal V core **2** in 75% overall yield from **13**. Assigned by NMR spectroscopic and mass spectrometric techniques, the structure of **2** was unambiguously confirmed through X-ray crystallographic analysis of its fully hydrogenated product [**15**, H_2, Pd–C (cat), 87% yield] (m.p. 237–238 °C, EtOAc, see ORTEP,[11] Fig. 2). Compound **2** holds promise as a possible precursor to maoecrystal V (**1**).

Our second foray toward maoecrystal V (**1**) involved the same type of intramolecular Diels–Alder reaction but a different dearomatization process to arrive at the even more advanced intermediate **3**, as shown in Scheme 2. Thus, bis-demethylation of intermediate **6** (BBr_3) followed by mono-protection of the resulting diphenol (**16**) as a MOM ether (NaH–MOMCl), afforded phenolic enone **17** in 55% overall yield. Attachment of the dienophile moiety onto **17** was carried out through the same sequence as described above

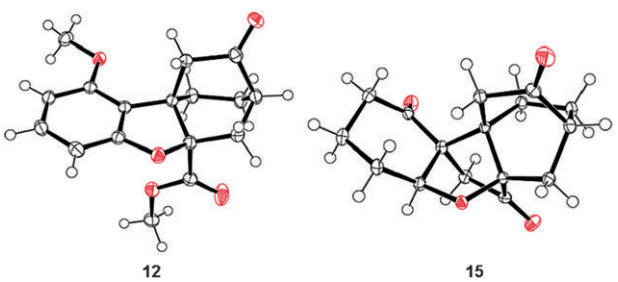
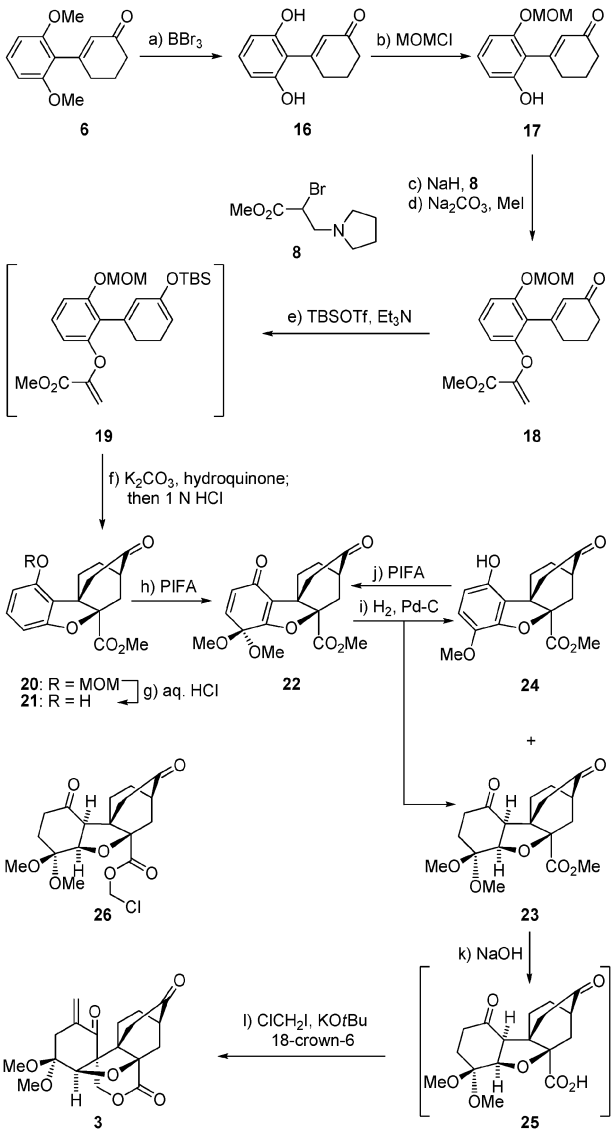


Fig. 2 X-ray derived ORTEP of intramolecular Diels–Alder product **12** and triketone **15** with thermal ellipsoids shown at the 50% probability level.



Scheme 2 Construction of pentacyclic lactone **3**. Reagents and conditions: (a) BBr_3 (3.5 equiv.), CH_2Cl_2, −78 → 0 °C, 2 h, 98%; (b) NaH (1.1 equiv.), MOMCl (1.2 equiv.), THF, 0 °C, 2 h, 56%; (c) NaH (2.1 equiv.), THF, 0 → 23 °C, 1 h; then **8** (4.0 equiv.), THF, 0 → 23 °C, 8 h; (d) Na_2CO_3 (2.6 equiv.), MeI (11 equiv.), MeOH, reflux, 2 h, 57% over the two steps; (e) TBSOTf (1.5 equiv.), Et_3N (3.0 equiv.), CH_2Cl_2, 0 °C, 2 h; (f) K_2CO_3 (4.8 equiv.), hydroquinone (1.2 equiv.), toluene, reflux , 18 h; then 1.0 N aq. HCl, 23 °C, 1 h, 50% over the two steps; (g) HCl (6.0 N aq.)/EtOH–$CHCl_3$ (1 : 1 : 1), reflux, 3 h, 83%; (h) PIFA (2.0 equiv.), $KHCO_3$ (2.2 equiv.), MeOH, 0 → 23 °C, 0.5 h, 83%; (i) 10% Pd/C (0.33 equiv.), H_2, EtOH, 23 °C, 10 h, **23**: 66%, **24**: 33%; (j) PIFA (2.0 equiv.), $KHCO_3$ (2.2 equiv.), MeOH, 0 → 23 °C, 0.5 h, 70%; (k) 1.0 N aq. NaOH (7.0 equiv.), EtOH, reflux, 5 h; then 1.0 N aq. HCl; (l) $ClCH_2I$ (11 equiv.), KO*t*Bu (5.0 equiv.), 18-crown-6 (5.5 equiv.), THF, 23 °C, 3 h, 42% over the two steps.

for **7** → **10** (Scheme 1) (NaH, **8**; Na_2CO_3, MeI),[7] leading to enone alkenyl ester **18** in 57% overall yield. Silyl enol ether formation within the latter compound (TBSOTf–Et_3N) then provided the desired Diels–Alder substrate **19**, which was used without purification in the following steps as described above for the related substrate **11**. In this instance, heating **19** in refluxing toluene in the presence of K_2CO_3 and hydroquinone

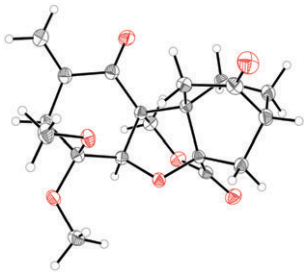


Fig. 3 X-ray derived ORTEP of enone lactone **3** with thermal ellipsoids shown at the 50% probability level.

provided, upon treatment with 1 N aq. HCl at ambient temperature, *exo* Diels–Alder product **20** as a single diastereoisomer in 50% overall yield from **18**. The desired dearomatization of the benzenoid ring of **20** was performed, this time, through a sequence involving deprotection of its phenolic group (6 N aq. HCl/EtOH–$CHCl_3$, 1 : 1 : 1, reflux) and subsequent treatment of the resulting phenol (**21**) with PIFA–$KHCO_3$ in MeOH, furnishing dimethoxy dienone derivative **22** in 69% overall yield for the two steps. Hydrogenation of the latter compound [H_2, 10% Pd–C (cat)] afforded a mixture of the desired diketone **23** (epimeric to **1** at C5) and aromatized product **24** (**24** : **23** *ca.* 1 : 3 ratio, 99% combined yield). Chromatographic separation of **24** and **23** allowed recycling of the former to dienone **22** (PIFA-$KHCO_3$, MeOH, 70% yield), and saponification of the latter to carboxylic acid **25** (aq. NaOH, EtOH, reflux). On exposure to KO*t*Bu and $ClCH_2I$ in the presence of 18-crown-6 at ambient temperature, diketone carboxylic acid **25** underwent triple alkylation (two intermolecular and one intramolecular) to afford enone lactone **3** in 42% overall yield from methyl ester **23**. Supported by NMR spectroscopic and mass spectrometric data, the structure of **3** (m.p. 173–175 °C, EtOAc/hexanes) was unambiguously proven by X-ray crystallographic analysis (see ORTEP,[12] Fig. 3). The precise sequence of events in the cascade leading from **25** to **3** has not been established as yet. Worthy of note, however, is the failure of chloroester **26**[13] to afford **3** (or any other γ-lactone product) under the conditions employed to convert **25** to **3**, suggesting that *C*-alkylation may precede *O*-alkylation in this process.[14] Containing the entire ring framework of maoecrystal V (**1**), core structure **3** (epimeric to **1** at C-5) may prove a viable precursor to this natural product.

Compounds **2**, **3**, and **15** were tested against a panel of cancer cells, including breast (MCF-7), CNS (SF268), lung (NCI-H460), and cervical (HeLa), using doxorubicin and Taxol® as standards, and the results are summarized in Table 1. While compounds **2** and **15** exhibited no significant cytotoxicity below 10 μM, the more advanced intermediate **3** showed moderate activity (3.6–6.7 μM) against these tumor cell lines (see Table 1).

The described chemistry is expected to facilitate the total synthesis of maoecrystal V (**1**) and related compounds for chemical and biological studies.

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Table 1 Cytotoxicity of compounds **2**, **3**, and **15** against selected cancer cell lines. (GI_{50} values in μM)[a]

		Cell line			
Entry	Compound	MCF-7[b]	SF268[b]	NCI-H460[b]	HeLa[b]
1	**2**	>10	>10	>10	>10
2	**3**	3.6 ± 0.3	5.3 ± 0.1	5.6 ± 0.1	6.7 ± 0.2
3	**15**	>10	>10	>10	>10
4	Doxorubicin	0.089 ± 0.011	0.468 ± 0.003	0.054 ± 0.003	0.965 ± 0.002
5	Taxol®	0.007 ± 0.000	0.033 ± 0.000	0.0065 ± 0.001	0.008 ± 0.000

[a] Antiproliferative effects of tested compounds against human tumor cell lines and drug-resistant cell lines in a 48 h growth inhibition assay using the sulforhodamine B staining methods. Human cancer cell lines: breast (MCF-7), lung (NCI-H460), CNS (SF268), and cervical (HeLa). Growth inhibition of 50% (GI_{50}) is calculated as the drug concentration which caused a 50% reduction in the net protein increase in control cells during drug incubation.[15] GI_{50} values for each compound are given in μM and represent the mean of two independent experiments ± standard error of the mean. [b] These cell lines were provided by the National Cancer Institute (NCI), Division of Cancer Treatment and Diagnosis (DCTD).

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8 CCDC 748550 contains the supplementary crystallographic data for compound **12**. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif or in the ESI†.
9 The minor isomer (C8-*epi*-**12**) (m.p. 182–183 °C, EtOAc/hexanes) was also subjected to X-ray crystallographic analysis that confirmed its structure. CCDC 742701 contains the supplementary crystallographic data for compound C8-*epi*-**12**†.
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11 CCDC 748551 contains the supplementary crystallographic data for compound **15**†.
12 CCDC 742693 contains the supplementary crystallographic data for compound **3**†.
13 Chloroester **26** was prepared from **25** by reaction with K_2CO_3 (1.0 equiv.) and $ClCH_2I$ (11 equiv., DMF, 23 °C, 8 h) in 82% yield.
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