# A Synthesis of the Carbon Skeleton of Maoecrystal V 

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An enantioselective synthesis of the maoecrystal V (1) carbon skeleton is described. The key transformations include arylation of a 1,3-dicarbonyl compound with a triarylbismuth(V)dichloride species, oxidative dearomatization of a phenol, and a subsequent intramolecular Diels-Alder reaction.

Maoecrystal V (1, Figure 1) was isolated and characterized in 2004 by Sun and coworkers from the Chinese medicinal herb Isodon Eriocalyx. ${ }^{1}$ It possesses an unusual architecture rendering it the most modified naturally occurring ent-kauranoid isolated to date. ${ }^{2}$ The structure was confirmed by X-ray crystallographic analysis to contain five highly congested rings and seven stereocenters, two of which are adjacent all carbon quaternary centers located in its interior. One of these all carbon quaternary centers is also the bridgehead carbon of the [2,2,2]bicyclooctanone moiety. This letter reports an early approach to $\mathbf{1}$ pursued in our laboratory from November 2007 to May 2008. ${ }^{3}$

Our initial retrosynthesis, shown in Scheme 1A, began by disconnecting the tetrahydrofuran ring and simplifying the enone of the A ring to an olefin leading to $\mathbf{2}$. Next, an intramolecular Diels-Alder ${ }^{4}$ disconnection of the bicyclic ring system would generate a cyclohexadiene/ acrylate conjugate $\mathbf{3}$. It was initially envisioned that silyl enol ether $\mathbf{3}$ could be used as the diene component in the Diels-Alder reaction. In order to construct this substrate via the corresponding enone 4 , an oxidative coupling of enolates or related substrates was proposed (i.e. $\mathbf{5}+\mathbf{6}$ ). ${ }^{5}$

Initial studies (Scheme 1B) with a model system using $\beta$-ketoaldehyde $\mathbf{7}$ and enol ether $\mathbf{8}$ led to the generation of the $\mathrm{C}-10$ quaternary center by treatment with cerium ammonium nitrate. ${ }^{6}$ Following reduction of the formyl group and esterification, silylation of the ketone under a variety of conditions led only to the undesired regioisomeric dienol ether 9 (presumably due to the sterically hindered $\alpha$-proton at C-9). To circumvent this problem, the diene was further dehydrogenated $\left(\mathrm{Pd} / \mathrm{C}, \mathrm{O}_{2}\right)$ and the resulting aromatic moiety was oxidized using a Wessely

[^0]Supporting Information Available: Detailed experimental procedures, copies of all spectral data, and full characterization. This material is available free of charge via the Internet at http://pubs.acs.org.
oxidation ${ }^{7}\left(\mathrm{~Pb}(\mathrm{OAc})_{4}\right)$ to furnish cyclohexadienone $\mathbf{1 0}$ in $59 \%$ yield. A Diels-Alder reaction delivered polycycle 11 in ca. $60 \%$ yield ( 3 mg scale) upon heating to $165^{\circ} \mathrm{C} .{ }^{8} \mathrm{X}$-ray crystallography confirmed the structure as that corresponding to the undesired regioisomeric outcome (based on the position of the geminal dimethyl group relative to the bicyclic portion of the molecule). Encouraged by the outcome of the intramolecular Diels-Alder, a revised route was devised to access the correct carbon framework found in $\mathbf{1}$ (Scheme 1C).

The sequence begins with $\beta$-ketoaldehyde 12, derived in three steps from a readily available symmetrical 1,3-diketone. ${ }^{9}$ Barton arylation ${ }^{10}$ of $\mathbf{1 2}$ with $\mathbf{1 3}^{9}$ led to $\mathbf{1 4}$ in $67 \%$ yield as a $7: 3$ readily separable mixture of diastereomers. In a similar fashion to the model study, reduction (to afford 15) and acylation led to $\mathbf{1 6}$. Removal of the MOM group with TFA and Wessely oxidation of the intermediate hemiketal 17 yielded an inconsequential mixture of diastereomeric acetates $\mathbf{1 8} / \mathbf{1 9}$ in 53\% yield over two steps.

Dienes 18 and 19 were heated in a microwave reactor in $o-\mathrm{DCB}$ to $165^{\circ} \mathrm{C}$ for 1.5 hours in the presence of BHT, to give the expected endo-cycloadducts in $79 \%$ and $69 \%$ yields. The stereochemistry of the cycloadducts was verified by X-ray crystallographic analysis. ${ }^{11}$ Once the structures had been determined, both adducts were elaborated further towards $\mathbf{1}$ by hydrogenation of the bicyclic olefin $\left(\mathrm{H}_{2}, \mathrm{Pd} / \mathrm{C}\right)$. Next, the acetate group was excised using $\mathrm{SmI}_{2}$ to give an intermediate samarium enolate that was protonated by methanol to give the $\alpha$-methyl ketone as a mixture of diastereomers in $76 \%$ yield ( $\mathrm{dr}=17: 3$ with $\mathbf{2 5}$ as major). ${ }^{12}$ An X-ray crystal structure of $\mathbf{2 6}$ (C-16-epi-25) was obtained from the minor diasteromer as shown in Scheme 1C, establishing that the major isomer posseses the proper orientation of the $\mathrm{C}-16$ methyl group in $\mathbf{1}$.

Certain elements of the sequential Barton arylation/Wessely oxidation/Diels-Alder Strategy (i.e. $\mathbf{1 2} \rightarrow \mathbf{1 4}, \mathbf{1 7} \rightarrow \mathbf{1 8} / \mathbf{1 9}, \mathbf{1 8} / \mathbf{1 9} \rightarrow \mathbf{2 5}$ ) reported herein may well find use in an eventual synthesis of $\mathbf{1} .{ }^{13}$

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Representations of maoecrystal V.


C: Synthesis of the Carbon Skeleton








25 (major)


Scheme 1.
Maoecrystal V: (A) Retrosynthetic Analysis, (B) Model Study, and (C) Synthesis of the Complete Carbon Skeletona
${ }^{\text {a }}$ Details: reagents and conditions (a) $\mathrm{CAN}, \mathrm{NaHCO}_{3}, \mathrm{MeOH}, 0^{\circ} \mathrm{C}, 46 \%$, (b) $\mathrm{Li}(t-\mathrm{BuO})_{3} \mathrm{AlH}$, THF, $-78^{\circ} \mathrm{C}, 53 \%$, (c) acryloyl chloride, $\mathrm{Et}_{3} \mathrm{~N}, \mathrm{DMAP}, \mathrm{DCM}, 0^{\circ} \mathrm{C}, 36 \%$, (d) TBSOTf, $\mathrm{Et}_{3} \mathrm{~N}$, $\mathrm{DCM}, 63 \%$, (e) $\mathrm{Pd} / \mathrm{C}, \mathrm{O}_{2}, \mathrm{PhMe}, 110^{\circ} \mathrm{C}, 99 \%$, (f) $\mathrm{Pb}(\mathrm{OAc})_{4}, \mathrm{AcOH}, 59 \%$, (g) $165^{\circ} \mathrm{C}, o-\mathrm{DCB}$, $c a .60 \%$, (h) $\mathrm{Ar}_{3} \mathrm{BiCl}_{2}(\mathbf{1 3})$, DBU, $\mathrm{PhMe}, 67 \%$, (i) $\mathrm{Li}(t-\mathrm{BuO})_{3} \mathrm{AlH}, \mathrm{THF},-78^{\circ} \mathrm{C}, 72 \%$, (j) acryloyl chloride, DIEPA, DMAP, DCM, $-78^{\circ} \mathrm{C}, 69 \%$, (k) TFA, DCM, $0^{\circ} \mathrm{C}, 65 \%$, (l) Pb $(\mathrm{OAc})_{4}, \mathrm{AcOH}, 81 \%, \mathrm{dr}=3: 7,(\mathrm{~m}) 165^{\circ} \mathrm{C}, o-\mathrm{DCB}, \mathrm{BHT} 79 \%$ for 20, $69 \%$ for $21(\mathrm{n})$ $\mathrm{BF}_{3} \cdot \mathrm{OEt}_{2}, \mathrm{DCM}, 82 \%$, (o) $\mathrm{H}_{2}, \mathrm{Pd} / \mathrm{C}, \mathrm{EtOAc}, 97 \%$ for $\mathbf{2 3}, 99 \%$ for 24 (p) $\mathrm{SmI}_{2}, \mathrm{MeOH}, \mathrm{THF}$, $0^{\circ} \mathrm{C}, 76 \%, \mathrm{dr}=17: 3 . \mathrm{CAN}=$ cerium ammonium nitrate, $\mathrm{DMAP}=4$-dimethylaminopyridine, $\mathrm{DCM}=$ dichloromethane, $\mathrm{TBSOTf}=$ tert-butydimethylsilyl trifluoromethylsulfonate, $o-\mathrm{DCB}$ = ortho-dichlorobenzene, DIEPA $=$ diisopropylethylamine, $\mathrm{DBU}=1,8$-diazobicylco[5.4.0] undec-7-ene, TFA $=$ trifluoroacetic acid, BHT $=2,6$-di-tert-butyl- $p$-cresol.


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