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A Synthesis of the Carbon Skeleton of Maoecrystal V

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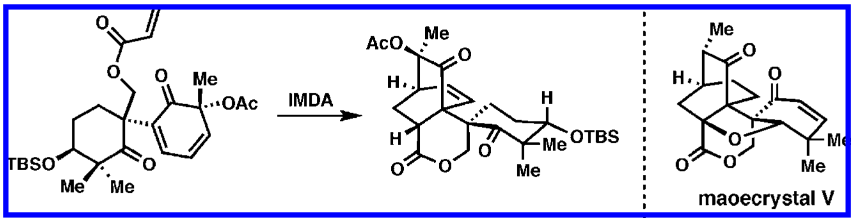
ABSTRACT



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 co-workers 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 paper reports an early approach to **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 **2**. Next, an intramolecular Diels−Alder[4] disconnection of the bicyclic ring system would generate a cyclohexadiene/acrylate conjugate **3**. It was initially envisioned that silyl enol ether **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., **5** + **6**).[5]

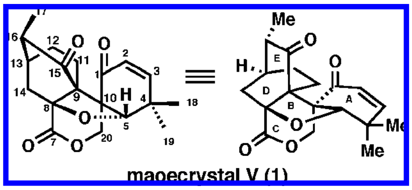


Figure 1. Representations of maoecrystal V.

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[1] Li, S.-H.; Wang, J.; Niu, X.-M.; Shen, Y.-H.; Zhang, H.-J.; Sun, H.-D.; Li, M.-L.; Tian, Q.-E.; Lu, Y.; Cao, P.; Zheng, Q.-T. *Org. Lett.* **2004**, *6*, 4327–4330.

[2] Sun, H.-D.; Huang, S.-X.; Han, Q.-B. *Nat. Prod. Rep.* **2006**, *23*, 673–698.

[3] During this period, one of the corresponding authors of the preceding paper was employed as a postdoctoral associate (C.-C. Li) in this laboratory: Gong, J.; Lin, G.; Li, C.-C.; Yang, Z. *Org. Lett.* **2009**, DOI: 10.1021/ol9014392. This work was reported in an NIH proposal (received 8/11/2008 and reviewed on 10/9/2008 by the BCMB-B study section) and a final report to the DFG (submitted 7/17/2009).

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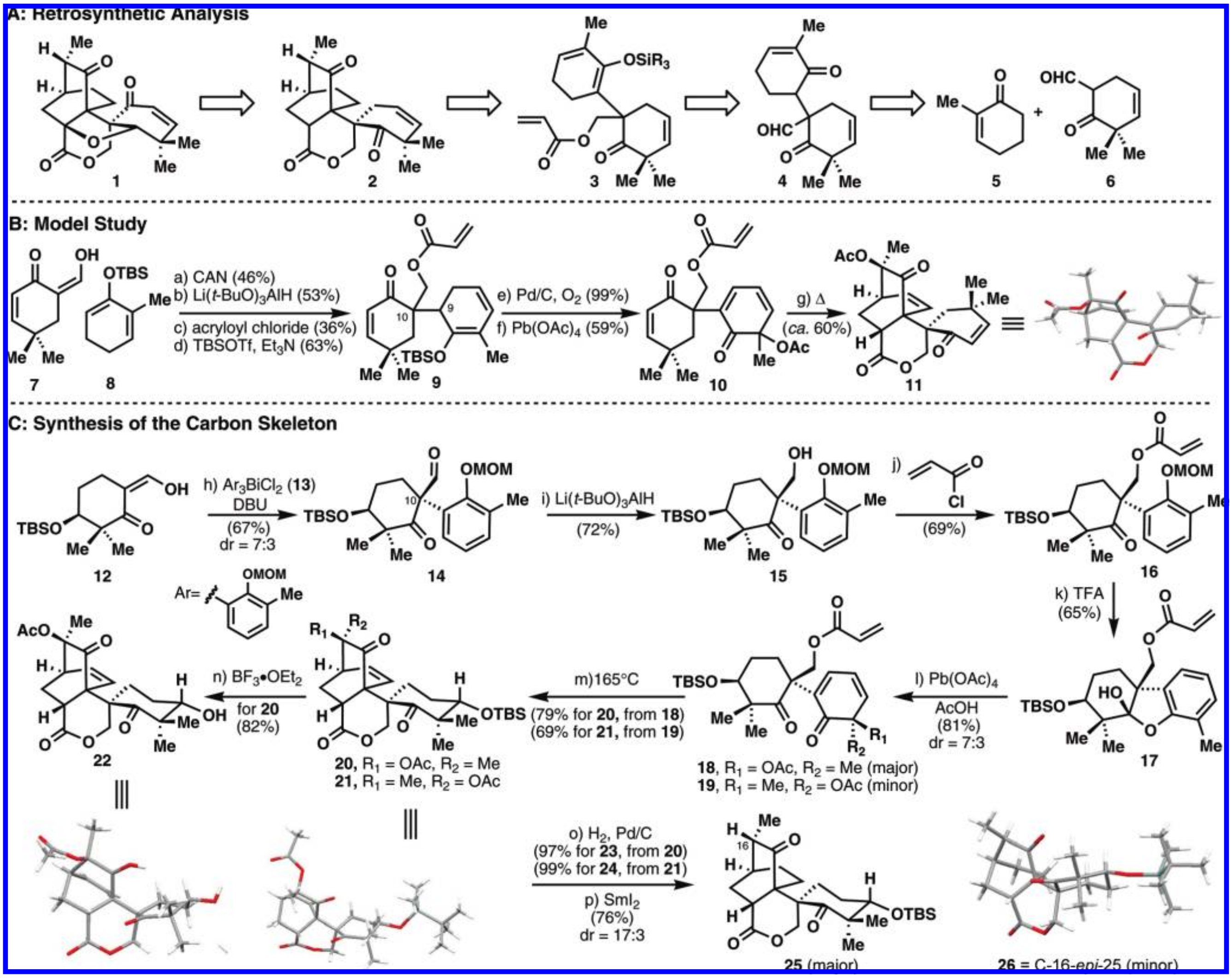
[5] (a) Baran, P. S.; DeMartino, M. P. *Angew. Chem., Int. Ed.* **2006**, *45*, 7083–7086. (b) DeMartino, M. P.; Chen, K.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 11546–11560.

10.1021/ol901963v CCC: $40.75

Scheme 1. Maoecrystal V: (A) Retrosynthetic Analysis, (B) Model Study, and (C) Synthesis of the Complete Carbon Skeleton[a]



[a] Reagents and conditions: (a) CAN, $NaHCO_3$, MeOH, 0 °C, 46%; (b) Li(t-BuO)$_3$AlH, THF, −78 °C, 53%; (c) acryloyl chloride, Et_3N, DMAP, DCM, 0 °C, 36%; (d) TBSOTf, Et_3N, DCM, 63%; (e) Pd/C, O_2, PhMe, 110 °C, 99%; (f) $Pb(OAc)_4$, AcOH, 59%; (g) 165 °C, *o*-DCB, ca. 60%; (h) Ar_3BiCl_2(**13**), DBU, PhMe, 67%; (i) Li(t-BuO)$_3$AlH, THF, −78 °C, 72%; (j) acryloyl chloride, DIEPA, DMAP, DCM, −78 °C, 69%; (k) TFA, DCM, 0 °C, 65%; (l) $Pb(OAc)_4$, AcOH, 81%, dr = 3:7; (m) 165 °C, *o*-DCB, BHT 79% for **20**, 69% for **21**; (n) $BF_3{\cdot}OEt_2$, DCM, 82%; (o) H_2, Pd/C, EtOAc, 97% for **23**, 99% for **24**; (p) SmI_2, MeOH, THF, 0 °C, 76%, dr = 17:3. CAN = cerium ammonium nitrate, DMAP = 4-dimethylaminopyridine, DCM = dichloromethane, TBSOTf = *tert*-butydimethylsilyl trifluoromethylsulfonate, *o*-DCB = *o*-dichlorobenzene, DIEPA = diisopropylethylamine, DBU = 1,8-diazobicylco[5.4.0]undec-7-ene, TFA = trifluoroacetic acid, BHT = 2,6-di-*tert*-butyl-*p*-cresol.

Initial studies (Scheme 1B) with a model system using β-keto aldehyde **7** and enol ether **8** led to the generation of the 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 α-proton at C-9). To circumvent this problem, the diene was further dehydrogenated (Pd/C, O_2) and the resulting aromatic moiety was oxidized using a Wessely oxidation[7] ($Pb(OAc)_4$) to furnish cyclohexadienone **10** in 59% yield. A Diels−Alder reaction delivered polycycle **11** in ca. 60% yield (3 mg scale) upon heating to 165 °C.[8] 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

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(6) Nair, V.; Mathew, J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 187–188.

(7) (a) Wessely, F.; Sinwel, F. *Monatsh. Chem.* **1950**, *81*, 1055–1070. (b) Barnes-Seeman, D.; Corey, E. J. *Org. Lett.* **1999**, *1*, 1503–1504. (c) Nicolaou, K. C.; Simonsen, K. B.; Vassilikogiannakis, G.; Baran, P. S.; Vidali, V. P.; Pitsinos, E. N.; Couladouros, E. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3555–3559. (d) Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004**, *104*, 1383–1429.

(8) For recent examples using *o*-quinols as dienophiles, see: (a) Nicolaou, K. C.; Toh, Q.-Y.; Chen, D. Y.-K. *J. Am. Chem. Soc.* **2008**, *130*, 11292–11293. (b) Gao, S.-Y.; Chittimalla, S. K.; Chuang, G. J.; Liao, C.-C. *J. Org. Chem.* **2009**, *74*, 1632–1639. (c) Dory, Y. L.; Roy, A.-L.; Soucy, P.; Deslongchamps, P. *Org. Lett.* **2009**, *11*, 1197–1200. (d) Snyder, S. A.; Kontes, F. *J. Am. Chem. Soc.* **2009**, *131*, 1745–1752.

Diels−Alder, a revised route was devised to access the correct carbon framework found in **1** (Scheme 1C).

The sequence begins with β-keto aldehyde **12**, derived in three steps from a readily available symmetrical 1,3-diketone.[9] Barton arylation[10] of **12** with **13**[9] led to **14** in 67% yield as a 7:3 readily separable mixture of diastereomers. In a fashion similar to that of the model study, reduction (to afford **15**) and acylation led to **16**. Removal of the MOM group with TFA and Wessely oxidation of the intermediate hemiketal **17** yielded an inconsequential mixture of diastereomeric acetates **18**/**19** in 53% yield over two steps.

Dienes **18** and **19** were heated in a microwave reactor in *o*-DCB to 165 °C for 1.5 h 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 toward **1** by hydrogenation of the bicyclic olefin (H_2, Pd/C). Next, the acetate group was excised using SmI_2 to give an intermediate samarium enolate that was protonated by methanol to give the α-methyl ketone as a mixture of diastereomers in 76% yield (dr = 17:3 with **25** as major).[12] An X-ray crystal structure of **26** (C-16-*epi*-**25**) was obtained from the minor diasteromer as shown in Scheme 1C, establishing that the major isomer possesses the proper orientation of the C-16 methyl group in **1**.

Certain elements of the sequential Barton arylation/Wessely oxidation/Diels−Alder Strategy (i.e., **12**→**14**, **17**→**18**/**19**, **18**/**19**→**25**) reported herein may well find use in an eventual synthesis of **1**.[13]

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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.

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[9] See the Supporting Information for details.

[10] (a) Barton, D. H. R.; Lester, D. J.; Motherwell, W. B.; Papoula, M. T. B. *J. Chem. Soc., Chem. Commun.* **1980**, 246–247. (b) Barton, D. H. R.; Blazejewski, J.-C.; Charpiot, B.; Finet, J.-P.; Motherwell, W. B.; Papoula, M. T. B.; Stanforth, S. P. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2667–2675. (c) Barton, D. H. R.; Finet, J.-P.; Giannotti, C.; Halley, F. *J. Chem. Soc., Perkin Trans. 1* **1987**, 241–249. (d) Combes, S.; Finet, J.-P. *Tetrahedron* **1999**, *55*, 3377–3386. (e) Fedorov, A. Y.; Finet, J.-P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3775–3778. (f) Finet, J.-P.; Fedorov, A. Y. *J. Organomet. Chem.* **2006**, *691*, 2386–2393.

[11] For adduct **21**, a crystal was grown directly, whereas adduct **20** was crystallized after removal of the TBS group as alcohol **22**.

[12] Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135–1138.

[13] While this paper was in review, two other groups reported progress toward **1**: (a) Peng, F. Yu, M. Danishefsky, S. J. *Tetrahedron Lett.*, **2009**, DOI: 10.1016/j.tetlet.2009.09.050. (b) Nicolaou, K. C.; Dong, L.; Deng, L.; Talbot, A. C.; Chen, D. Y.-K. *Chem. Commun.* **2009**, in press.