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Synthetic Approach to Malibatol A

George A. Kraus* and Ikyon Kim

Department of Chemistry, Iowa State University, Ames, Iowa 50011

gakraus@iastate.edu

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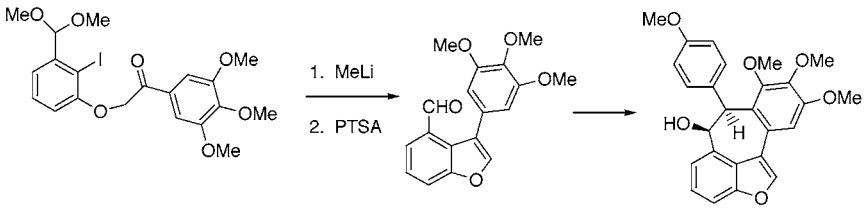
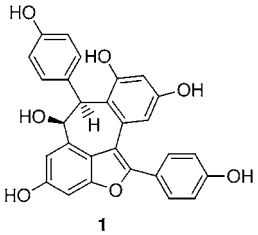
ABSTRACT



A synthetic approach to malibatol A featuring a novel benzofuran synthesis is described.

In 1998, Boyd and co-workers determined the structures of malibatol A (**1**) and balanocarpol (**2**).[1] These novel oligostilbenes exhibited cytotoxic activity and HIV-inhibitory activity.[2] No approaches to the synthesis of **1** or **2** have been reported. As part of a program to study terpene-based antiviral agents,[3] we developed a direct approach to these compounds.



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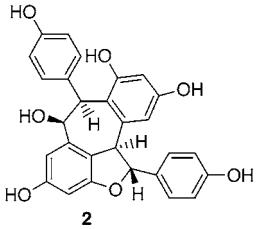

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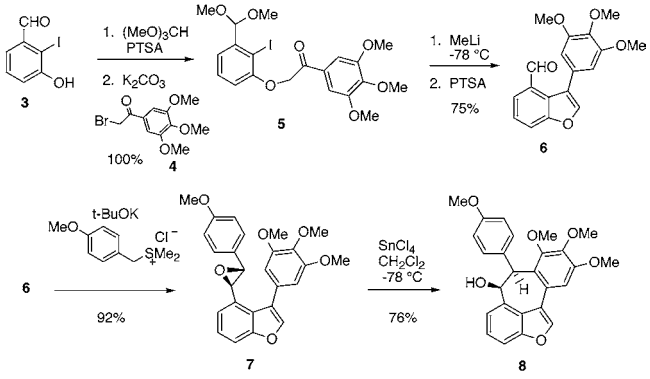
Our synthetic route began with iodo aldehyde **3**, which had been prepared by Lock from 3-hydroxybenzaldehyde in one step.[4] Protection of the aldehyde as the acetal with trimethylorthoformate and PTSA in methanol followed by alkylation of the phenol with potassium carbonate and bromo ketone **4** in boiling acetone afforded ketone **5** in quantitative yield.



Halogen−metal exchange using alkyllithium reagents can be faster than reaction with a carbonyl group.[5,6] We reacted iodo ketone **5** with 3 equiv of methyllithium at −78 °C and then treated the resulting compound with PTSA at ambient temperature. This two-step sequence produced benzofuran carboxaldehyde **6** in 75% yield from **5**. To the best of our knowledge, this is the first time this protocol has been applied to the synthesis of benzofurans.[7]

(1) Dai, J. R.; Hallock, Y. F.; Cardellina, J. H.; Boyd, M. *J. Nat. Prod.* **1998**, *61*, 351−3. Balanocarpol was also isolated: Diyasena, M. N. C.; Sotheeswaran, S.; Surendrakumar, S.; Balasubramanian, S.; Bokel, M.; Kraus, W. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1807−9.

(2) Dai, J. R.; Hallock, Y. F.; Cardellina, J. H., II; Boyd, M. *J. Nat. Prod* **1998**, *61*, 351−3.

(3) Kraus, G. A.; Ogutu, H. *Tetrahedron* **2002**, *58*, 7391.

(4) Lock, G. *Monatshefte* **1936**, 320.

(5) Kihara, M.; Iwai, Y.; Nagao, Y. *Heterocycles* **1995**, *41*, 2279.

(6) Cooke, M. P., Jr. *J. Org. Chem.* **1993**, *58*, 6833−7.

(7) Aoki, Y.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1995**, 463−4. The elegant 3 + 2 strategy developed by Wender for the synthesis of indoles is a related reaction (Wender, P. A.; White, A. W. *Tetrahedron Lett.* **1981**, *22*, 1475−8).

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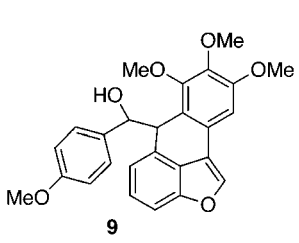
Treatment of aldehyde **6** with dimethyl(*p*-methoxybenzyl)-sulfonium chloride[8] and potassium *tert*-butoxide in THF at 25 °C gave a 92% yield of epoxide **7** as a single isomer as evidenced by proton NMR. The small coupling constant of the hydrogens attached to the epoxide ring (1.8 Hz) supports the assigned structure. The epoxide reacted rapidly with stannic chloride at −78 °C to give a single compound **8** in 76% yield.[9] The coupling constant between the two methine protons in **8** was 2.7 Hz, compared to 2.5 Hz in malibatol. Two-dimensional NMR analysis supported a trans relationship between the methine proton and the hydroxyl group.[10]

We expected that the *para*-methoxyphenyl group would direct the epoxide opening. However, we could not rule out the isomeric alcohol **9**. Oxidation of the alcohol with the Dess−Martin periodinane reagent gave a ketone that we assigned as **10** on the basis of the deshielding of the hydrogen at C-5 of the benzofuran. The chemical shifts of the hydrogens on the *para*-methoxyphenyl group were not deshielded after the oxidation. Moreover, the mass spectra did not exhibit fragmentations that one would expect for alcohol **9** ($M^+ - 137$) or the ketone derived from oxidation of **9** ($M^+ - 135$). Reduction of ketone **10** with either sodium borohydride in methanol or DIBAL in THF provided only alcohol **8**. The tetracyclic ring system in **10** is flat with the *p*-methoxyphenyl group approximately perpendicular to the ring system. Hydride attack opposite to the *p*-methoxyphenyl group would explain the production of **8**.



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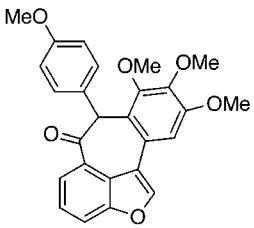

10

This concise synthetic route features a novel construction of a benzofuran ring and an efficient generation of a seven-membered ring by regioselective epoxide opening. This route should enable us to construct malibatol A as well as several analogues.

Acknowledgment. We thank Iowa State University for partial support of this research.

OL027574O

(8) Buckley, N.; Oppenheimer, N. J. *J. Org. Chem.* **1994**, *59*, 5717.

(9) Compound **7**: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 7.93 (1H, s), 7.27 (3H, m), 7.05 (1H, s), 6.94 (2H, d, $J = 9.0$ Hz), 6.48 (2H, d, $J = 8.7$ Hz), 5.49 (1H, br s), 5.45 (1H, d, $J = 2.7$ Hz), 3.96 (3H, s), 3.92 (3H, s), 3.71 (3H, s), 3.60 (3H, s), 2.55 (1H, br s); ^{13}C NMR ($CDCl_3$ 75 MHz) δ 158.0, 155.2, 153.0, 152.7, 142.3, 140.6, 137.0, 131.7, 130.1, 127.1, 126.8, 125.0, 123.1, 121.9, 119.0, 113.4, 110.1, 105.8, 73.8, 61.8, 61.2, 56.3, 55.1, 49.8; HRMS *m*/*z* calcd for $C_{26}H_{24}O_6$ 432.1573, found 432.1580. Compound **10**: ^{1}H NMR ($CDCl_3$ 300 MHz) δ 8.03 (1H, s), 7.79 (1H, d, $J = 7.5$ Hz), 7.52 (1H, d, $J = 8.1$ Hz), 7.33 (1H, t, $J = 8.1$, 7.5 Hz), 7.03 (1H, s), 6.74 (2H, d, $J = 9.0$ Hz), 6.51 (2H, d, $J = 8.7$ Hz), 6.06 (1H, s), 3.98 (3H, s), 3.95 (3H, s), 3.85 (3H, s), 3.60 (3H, s); ^{13}C NMR ($CDCl_3$ 75 MHz) δ 196.8, 158.1, 155.2, 153.7, 153.1, 143.0, 141.8, 131.2, 130.5, 128.1, 126.7, 125.2, 124.9, 123.7, 123.0, 121.7, 115.6, 113.8, 106.5, 62.2, 61.3, 56.8, 56.3, 55.2; HRMS *m*/*z* Calcd for $C_{26}H_{22}O_6$ 430.1416, found 430.1424.

(10) In compound **8**, the two-dimensional NOESY spectrum showed a strong interaction between the two methine hydrogens. The benzylic alcohol methine proton showed a NOE interaction only with the adjacent methine. If the stereochemistry were reversed, molecular models indicate that there would almost certainly be a strong NOE interaction with the hydrogen on C-5 of the benzofuran.