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Nazarov Cyclization Initiated by Peracid Oxidation. The Total Synthesis of (±)-Rocaglamide

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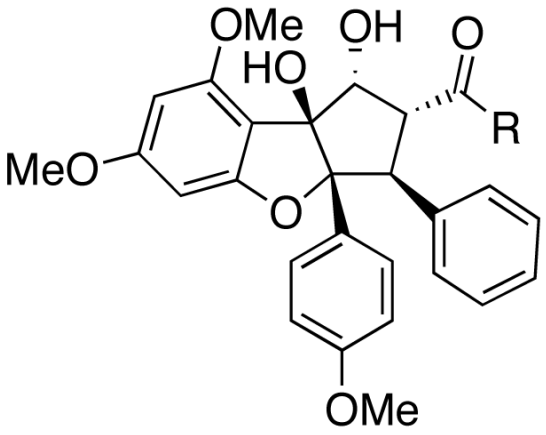
Indigenous to southeast Asia, the plant genus *Aglia* includes several species that produce a range of cyclopenta[b]tetrahydro-benzofuran-containing metabolites[1] including rocaglamide **1**, isolated from the roots and stems of *Aglia elliptifolia* by King.[2] King's initial report indicated that **1** showed significant *in vivo* activity in P388 lymphocytic leukemia-infected mice.[2] Since then, rocaglamide and related compounds have shown cytostatic and cytotoxic activity against a variety of human cancer cell lines with IC_{50} values ranging from 1.0–6.0 ng/mL.[3] Stereoselective synthesis of the dense substitution pattern of these targets is a formidable synthetic challenge: the molecules bear five contiguous stereocenters and *cis*-aryl groups on adjacent carbons. In 27 years of effort, only a handful of completed total syntheses have been reported, evidence of the difficulties associated with the synthesis of rocaglate natural products.[4]



1 R= NMe_2: rocaglamide
2 R=OMe: aglafolin

The original plan for the synthesis of rocaglamide focused on the Nazarov cyclization[5] of ketone **3**, a compound predicted to be reactive due to the juxtaposition of an electon-rich benzofuran and an electron-poor alkylidene β-ketoester.[6] Substrate polarization has proven successful in cyclizing a range of heteroaromatic compounds under mild Lewis acid catalysis.[7] It was hoped that Lewis acid activation of **3** would generate pentadienyl cation **4**, which would undergo conrotatory cyclization to give oxyallyl cation **5** (Scheme 1). It was hoped that the tertiary alcohol could be installed by trapping the cation with water (see **6**).[8]

Unfortunately, compound **3** failed to cyclize in the presence of any Lewis acid/trapping agent combination. Only products of hydrolysis were observed. The failure of our original model led to an alternative analysis of the pentadienyl cation, which suggested that intermediate **4** might

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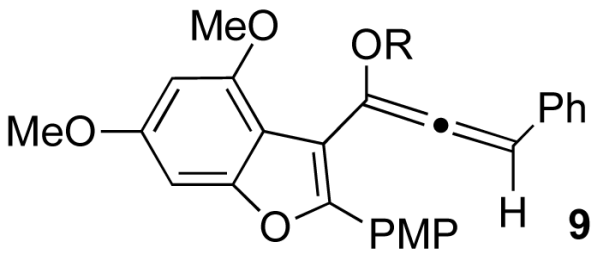
Supporting Information **Available:** Experimental procedures for the preparation of all compounds, characterization data, X-ray crystal structure data for compounds **15a** and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

have significant carbocation character at the 2-position of the benzofuran (Scheme 2).[9] Viewed this way, substrate **3** is not favorably polarized for cyclization, because both termini of the pentadienyl cation **4** are electron-deficient.

If this alternative analysis is correct, installing an electron-donating substituent in place of the ester should reestablish complementary polarization between the reacting termini of the pentadienyl cation (see **7**). The oxyallyl cation intermediate (**8**) is also stabilized in this scenario, which should improve cyclization efficiency.[6,10]

To test these ideas, we chose to explore the epoxidation of appropriately substituted alkoxyallenes **9**. Epoxide opening should give direct access to a pentadienyl cation of type **10** poised for cyclization. Similar transformations have been reported by Goré,[11] Corey,[12] and Cha,[13] and studied by De Lera.[14]



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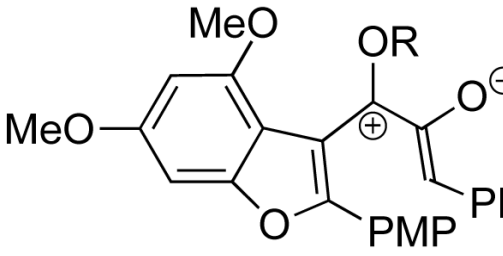

Synthesis began with alkylation of **11**[4b] with vinyl magnesium bromide, followed by osmylation and periodate cleavage of the resulting 3-vinyl benzofuran to give aldehyde **12** (Scheme 3). Alkylation with phenylacetylene and protection of the resultant propargyl alcohol with ethyl iodide or *p*-methoxy benzyl chloride gave propargyl ethers **13a** and **13b**, respectively.

Deprotonation at the propargylic position of **13** with *tert*-butyllithium gave rise to an allenyl anion, which was trapped with tri-*n*-butyltin chloride to give stannyl alkoxyallene **14**.[15] It was not possible to obtain the hydridoalkoxyallene using this protocol: if the allenyl anion was quenched with water, methanol, or imidazole, protonation occurred at the benzofuranylic position exclusively. Treatment of **14** with excess *m*-CPBA gave **15** (Scheme 4). This novel oxidation / Nazarov cyclization cascade is thought to commence with epoxidation of the allenol ether to generate allene oxide **16**. Epoxide opening, facilitated by both the furanyl and ether oxygen atoms and the acidic reaction conditions, unveils pentadienyl cation **17**, which cyclizes to form cyclopentenone **15**. Cleavage of the tributylstannyl group probably occurs prior to cyclization, but this has not been confirmed. Only one diastereomer was found in the reaction mixture, and its relative configuration was confirmed by X-ray analysis of **15a**.

All attempts to functionalize ethyl enol ether **15a** failed. The *p*-methoxybenzyl derivative **15b** was prepared to explore the possibility of effecting both enol ether cleavage and installation of the benzylic hydroxyl group under oxidative conditions. Indeed, treatment of **15b** with excess DDQ gave diosphenol **18** in excellent yield (Scheme 5). Enol **18** was converted to triflate **19** and then subjected to palladium-mediated carbonylation to install the final C-C linkage (see **20**).

The synthetic work of Trost guided the elaboration of **20** into the natural product **1**.[4a] Hydrogenation of **20** over PtO_2 gave **21** as a single diastereomer (Scheme 6). Templated reduction of the ketone afforded the natural product aglafolin (**2**), and saponification followed by amide formation furnished rocaglamide (**1**).

The synthetic strategy developed provides natural products aglafolin and rocaglamide can be prepared in 11 and 13 steps, respectively, from known benzofuranone **11**,[4b] and every step is highly diastereoselective. The key transformation is Nazarov cyclization of a pentadienyl cation generated in an unusual way: through peracid oxidation of an allenol ether. Development of an enantioselective approach to the rocaglate natural products using this oxidation / electrocyclization sequence is currently underway in the laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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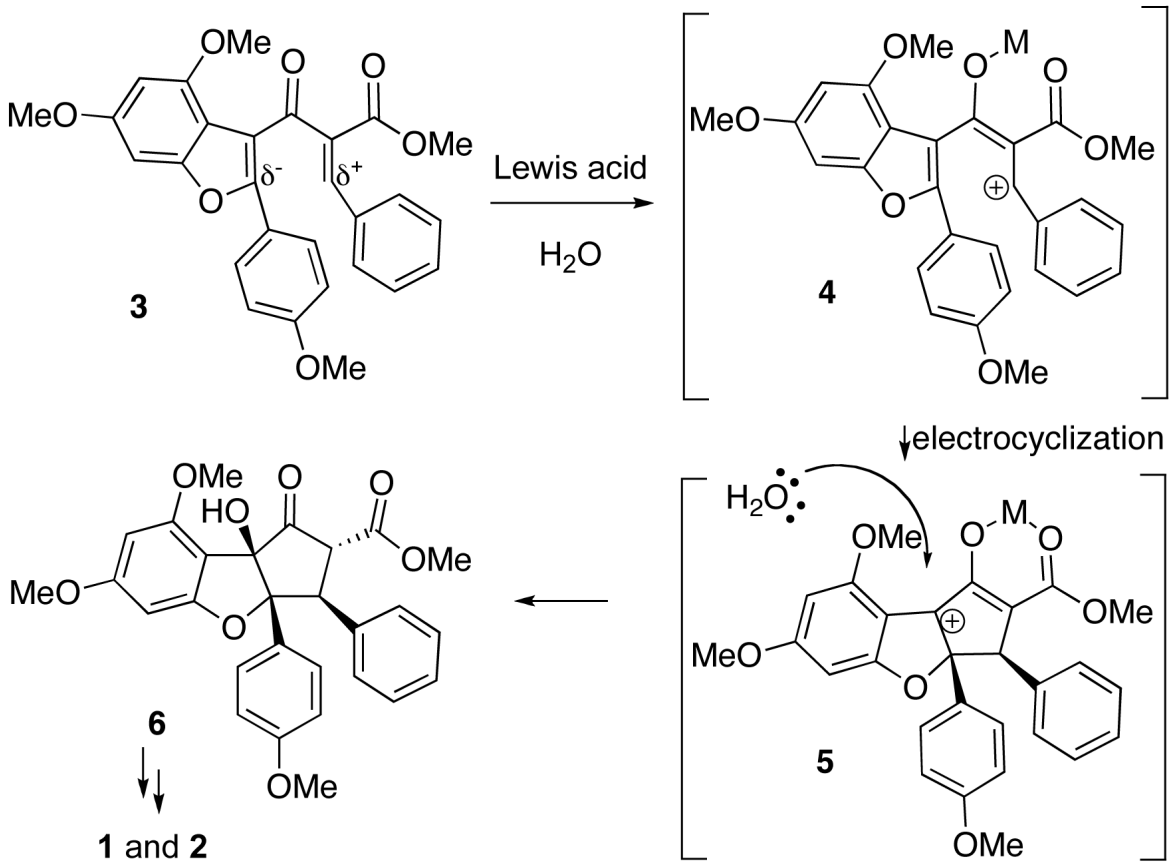
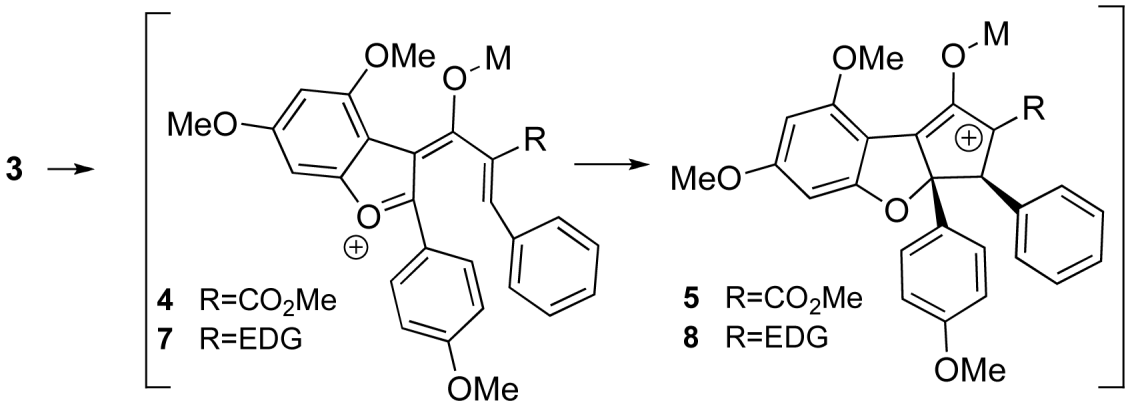
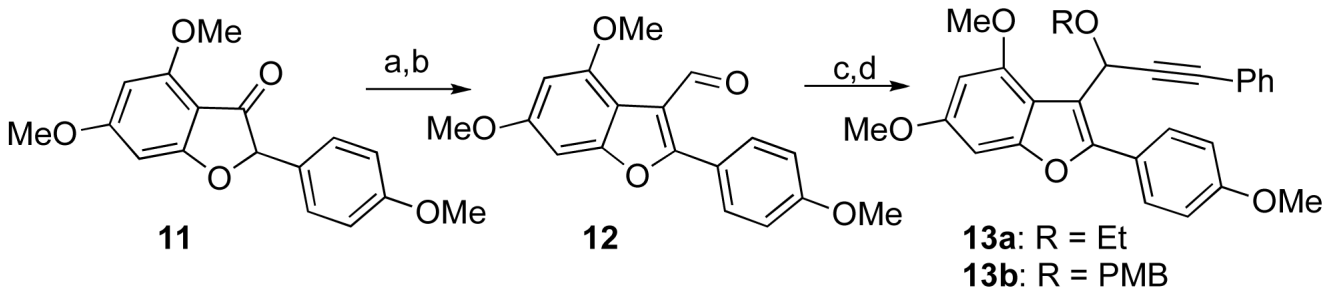


Scheme 1.
Initial approach: Interrupted Nazarov Cyclization



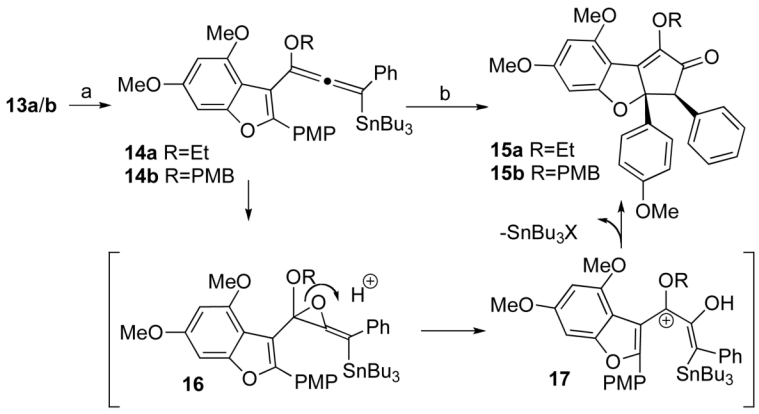
Scheme 2.
Alternative analysis of pentadienyl cation polarization



Scheme 3.

Synthesis of propargyl ethers **13**[a]

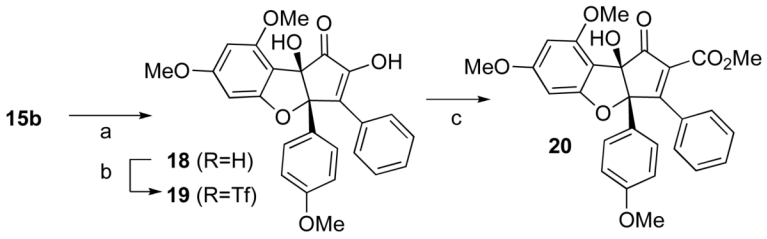
Reagents and conditions: (a) $CeCl_3$, vinyl magnesium bromide, then HCl 1M, 65%; (b) (i) OsO_4 (4 mol%), NMO (1.2 equiv.), acetone/*t*-BuOH/H_2O; (ii) $NaIO_4$, THF/H_2O; (c) phenylacetylene, n-BuLi, THF; (d) KH, EtI, THF, 64% or KH, NaI, PMBCl, THF, 69% (over three steps).



Scheme 4.

Nazarov cyclization initiated by epoxide opening[a]

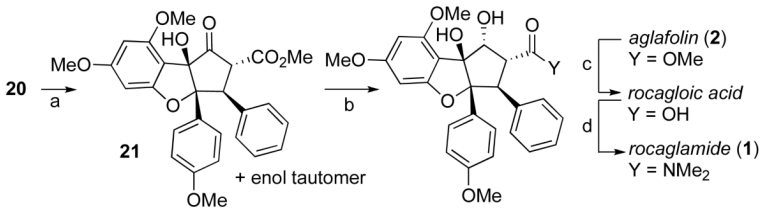
Reagents and conditions: (a) *t*-BuLi, Bu_3SnCl, Et_2O, −40°C (b) *m*-CPBA (4 equiv.), DMF, rt, 40–50% over two steps.



Scheme 5.

Completion of the rocaglamide skeleton

Reagents and conditions: (a) DDQ (4 equiv.), DCM, 71% (b) KHMDS, $PhNTf_2$, THF, 0°C, 83% (c) $Pd(PPh_3)_4$, CO, MeOH, Hünig's base, THF, 65°C, 79%.



Scheme 6.

Completion of the synthesis[a]

Reagents and conditions: (a) PtO_2, H_2, EtOH, rt, 65% (b) $NaHB(OAc)_3$, MeCN/AcOH, 56% (c) LiOH, THF/H_2O, 82%; (d) $Me_2NH{\bullet}HCl$, DCC, DMAP, 60%.