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

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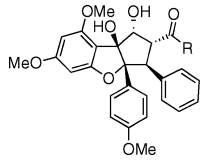
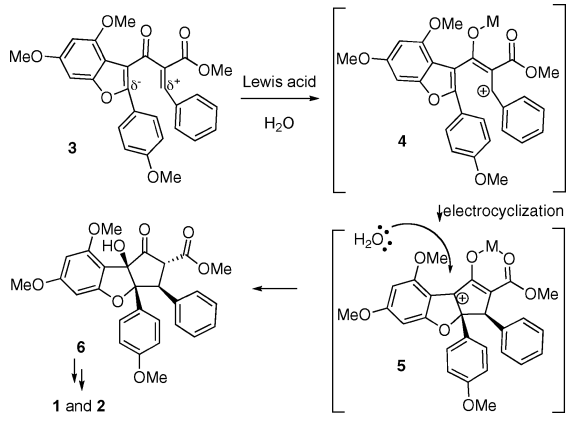
Indigenous to southeast Asia, the plant genus *Aglia* includes several species that produce a range of cyclopenta[*b*]tetrahydrobenzofuran-containing metabolites,[1] including rocaglamide (**1**), isolated from the roots and stems of *Aglia elliptifolia* by King.[2] King's initial report indicated that **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 in the range 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

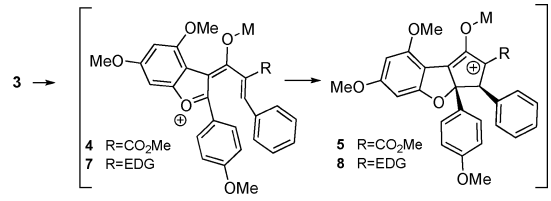
The original plan for the synthesis of rocaglamide focused on Nazarov cyclization[5] of ketone **3**, a compound predicted to be reactive because of the juxtaposition of an electron-rich benzofuran and an electron-poor alkylidene *β*-ketoester.[6] Substrate polarization has proven successful in cyclizing 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). Also, we hoped to install the tertiary alcohol by trapping the cation with water (see **6**).[8]

Scheme 1. Initial Approach: Interrupted Nazarov Cyclization



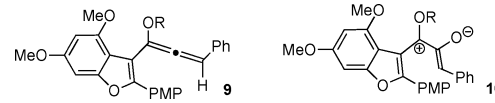
Unfortunately, compound **3** failed to cyclize in the presence of any Lewis acid/trapping agent combination. Only products of hydrolysis were observed. The failure of our original model led to an alternative analysis of the pentadienyl cation, which suggested that intermediate **4** might have significant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

Scheme 2. Alternative Analysis of Pentadienyl Cation Polarization



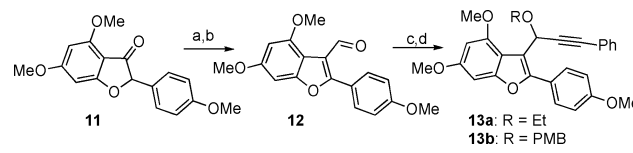
If this alternative analysis is correct, installing an electron-donating substituent in place of the ester should reestablish complementary polarization between the reacting termini of the pentadienyl cation (see **7**). The oxyallyl cation intermediate (**8**) would also be stabilized in this scenario,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

To test these ideas, we chose to explore the epoxidation of appropriately substituted alkoxyallenes **9**. Epoxide opening was expected to 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]



The synthesis began with alkylation of **11**[4b] using vinyl magnesium bromide, which was 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 and *p*-methoxybenzyl chloride gave propargyl ethers **13a** and **13b**, respectively.

Scheme 3. Synthesis of Propargyl Ethers **13**[a]



[a] Reagents and conditions: (a) $CeCl_3$, vinyl magnesium bromide, then HCl (1 M), 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.

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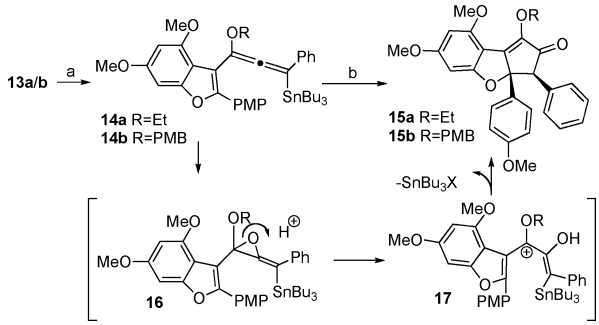
Deprotonation at the propargylic position of **13** with *tert*-butyllithium gave rise to an allenyl anion, which was trapped with tri-*n*-butyltin chloride to give stannyl alkoxyallene **14**.[15] It was not possible to obtain the hydridoalkoxyallene using this protocol: when the allenyl anion was quenched with water, methanol, or imidazole, protonation occurred at the benzofuranylic position exclusively. Treatment of **14** with excess *m*-CPBA gave **15** (Scheme 4). This interesting 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, unveiled pentadienyl cation **17**, which cyclized to form cyclopentenone **15**. Cleavage of the tributylstannyl group probably occurred 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**.

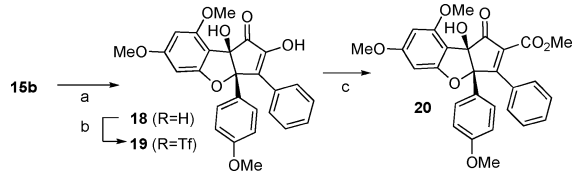
Scheme 4. Nazarov Cyclization Initiated by Epoxide Opening[a]



[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.

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**).

Scheme 5. Completion of the Rocaglamide Skeleton[a]

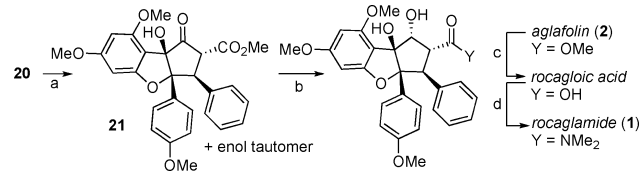


[a] Reagents and conditions: (a) DDQ (4 equiv), DCM, 71%; (b) KHMDS, $PhNTf_2$, THF, 0°C, 83%; (c) $Pd(PPh_3)_4$, CO, MeOH, Hünig's base, THF, 65°C, 79%.

The synthetic work of Trost[4a] guided the elaboration of **20** into natural product **1**. 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 in this work provides the natural products aglafolin and rocaglamide 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 our laboratory.

Scheme 6. Completion of the Synthesis[a]



[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) $Me_2NH\cdot HCl$, DCC, DMAP, 60%.

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

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