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Efforts Toward a Synthesis of Crotogoudin and Crotobarin

Duy N. Mai◊
Dmitriy Uchenik◊
Christopher D. Vanderwal*

Department of Chemistry, 1102 Natural Sciences II, University of California, Irvine, CA 92697-2025, USA
cdv@uci.edu

◊ These authors contributed equally

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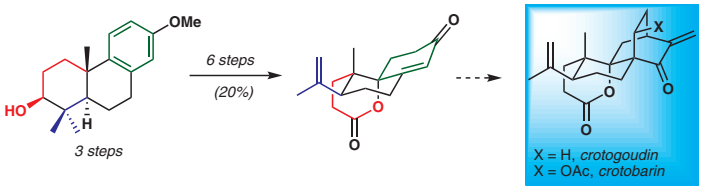

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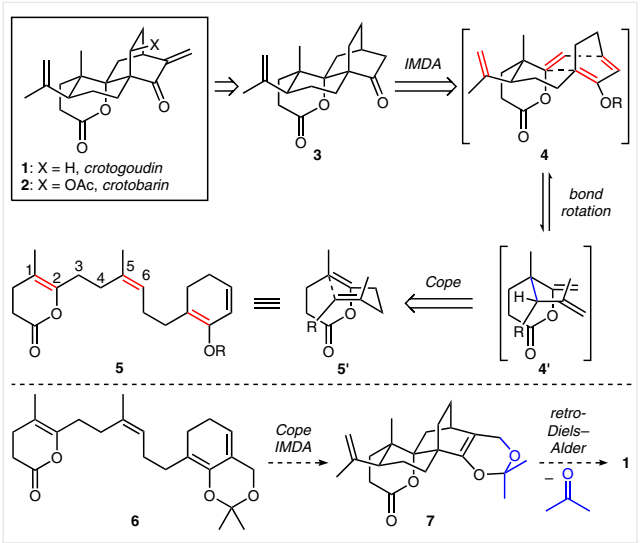
Abstract Two synthesis designs for the diterpenoid crotogoudin are discussed, and efforts to achieve each are described. First, a Cope rearrangement/intramolecular Diels–Alder cascade reaction was investigated. Second, a bioinspired sequence of cationic bicyclization and A-ring oxidative fragmentation set-up for a lactonization induced by a phenolic oxidation, ultimately providing a tricyclic intermediate that required only installation of the bridging ring of the salient bicyclo[2.2.2]octane system. This last endeavor was fraught with difficulty, but did lead to the development of conditions for cyclization of related keto-alkenes via manganese(III)-based radical chemistry.

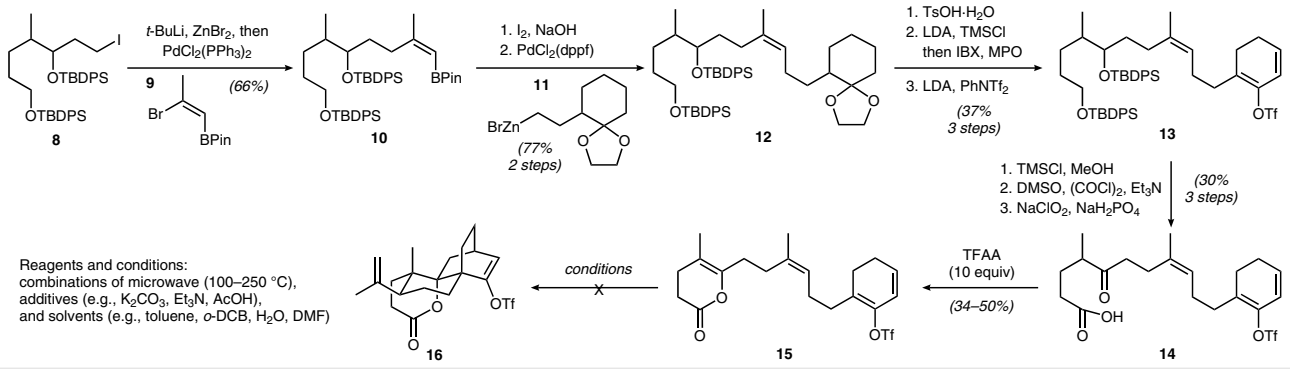
Key words diterpenoid, cascade, cationic cyclization, phenolic oxidation, dearomatization, Birch reduction, Diels–Alder cycloaddition, radical cyclization

The unusual 3,4-*seco*-atisanes crotogoudin and crotobarin (**1** and **2**, Scheme 1) were recently reported by Rasoanaivo and co-workers.[1] These compounds were cytotoxic to the four human tumor cell lines tested (KB, HT29, A549, and HL60, IC_{50}values: 0.5–2.5 μM) with nearly equal potencies to docetaxel, the positive control, and induced cell-cycle arrest at the G2/M transition with apparent associated apoptosis. The underlying mechanism of activity is not known; however, as the isolation chemists suggest, it might well involve covalent modification of a biomolecule involved in the cell cycle, given the presence of the unsaturated ketone conjugate acceptor.[2,3] The Carreira group reported the first synthesis of crotogoudin via an elegant but lengthy route (>25 steps LLS)[4] that permitted the revision of the absolute configuration of the natural product, such that it fits into the large *ent*-atisane family. More recently, a concise synthesis of racemic crotogoudin was reported by Liu and co-workers.[5] Attractive approaches have also been published by the groups of Maier,[6] Singh,[7] and Jia.[8] Our goal was to obtain enough of these secondary metabolites to enable studies of their mechanism of action. We describe herein some efforts along these lines that permitted the assembly of advanced tricyclic intermediates.

Our first strategy involved a high-risk/high-reward cascade reaction of polyunsaturated precursors of type **5** (Scheme 1). We assumed that installation of the exocyclic alkene in **1** from **3**, the product of an intramolecular Diels–Alder reaction of **4**, would be straightforward.[4] Although the proposed cycloaddition involved electronically poorly matched components, the topologically similar substrate used in Peese and Gin's nominine synthesis gave credence to this idea.[9] The ene-lactone dienophile in **4**/**4′** was to arise from a (likely unfavorable) Cope rearrangement of **5** via conformation **5′**. The idea of heating this polyunsaturated, achiral intermediate to induce the establishment of a Cope equilibrium, which might be siphoned off via a productive intramolecular Diels–Alder cycloaddition, was provocative. We made and evaluated one such system, as described in Scheme 2.



Scheme 1 A cascade strategy toward crotogoudin; IMDA: intramolecular Diels–Alder reaction



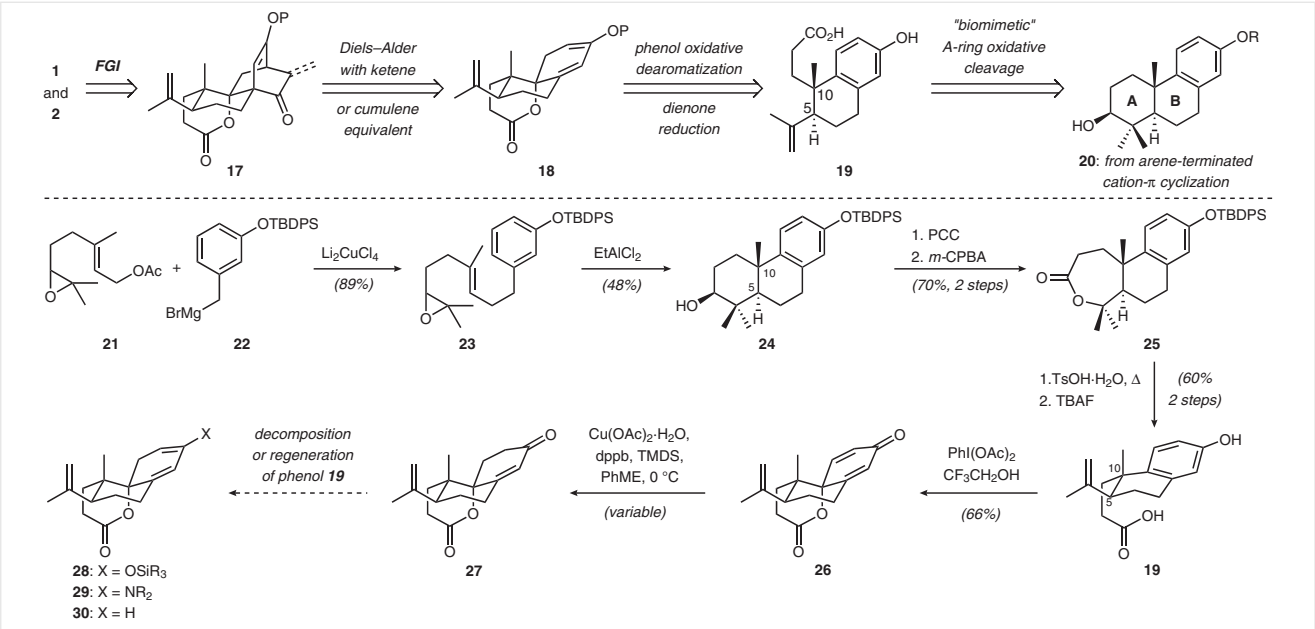
Scheme 2 Approach to crotogoudin based upon a pericyclic cascade sequence. .

Alkyl iodide **8** was prepared in six steps from δ-valerolactone.[10] It was coupled via a Negishi reaction[11] with bifunctional reagent **9**,[12] affording boronic ester **10**. After stereospecific iododeborylation,[12] a second Negishi coupling with **11** (precursor halide made in four steps from cyclohexanone[10]) provided **12**. The careful orchestration of steps shown was needed to generate compounds of type **5** because of the reactivity of the ene-lactone; further, we found that most 2-oxygenated 1,3-cyclohexadienes were unstable, and we could only handle the corresponding triflate.

As a result, the generation of triflate **15** from **12** was challenging, and **15** was the only compound of general type **5** that we were able to access. The successful sequence from **12** involved ketal hydrolysis, selective ketone dehydrogenation,[13] and O-triflation of the cross-conjugated enolate to afford **13**. Desilylation under acidic conditions and two-step oxidation to keto-acid **14** preceded dehydration to the sensitive ene-lactone **15**. Although lengthy, this sequence provided tens of milligrams of **15** for a range of attempts to thermally isomerize it into crotogoudin-like compound **16** (conditions shown in Scheme 2).[10] Unfortunately, in all cases wherein reactions occurred, extensive decomposition was observed. Wary of the many possible side reactions, including Cope reaction with the other 1,5-diene system, and other cycloaddition possibilities, we turned to computation to assess the likelihood of success. Computed barriers for both key reactions were prohibitively high, and those computed for undesired pathways were lower. Had this cascade to convert polyunsaturated, achiral intermediate **15** (or more stable derivatives) into the polycyclic architecture of crotogoudin succeeded, we would have attempted the reaction of **6** (Scheme 1), a precursor with all of the carbon atoms of crotogoudin; after the Cope/IMDA cascade, a cycloreversion to expel acetone might directly give crotogoudin. Still, our synthesis would have remained lengthy, because of the difficulties in installing the orthogonal functional-group arrangements in these types of cascade precursor, and preliminary computational and experimental results were not encouraging. Enamored with the attractive structure and properties of the targets, we sought a much more direct route.

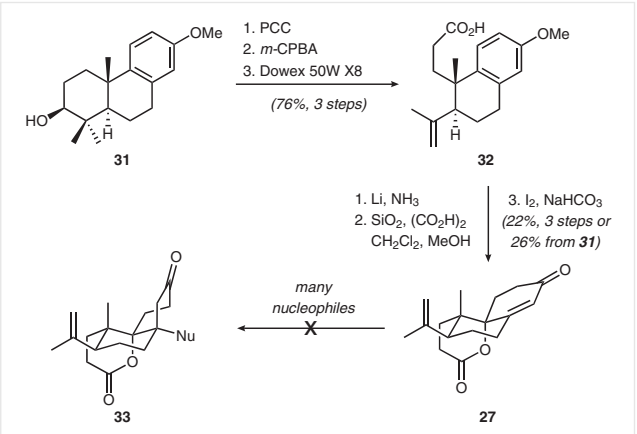
Our second approach (Scheme 3) features steps that are likely relevant to the biogenesis of atisane and *seco*-atisane diterpenoids: a cation-π cyclization to forge the B-ring and an A-ring oxidative cleavage, which would establish the C5–C10 stereorelationship with perfect stereochemical control (see **19**).[14,15] Formation of the δ-lactone would arise from carboxylate addition to an electron-deficient carbon center generated in the course of a phenolic oxidation. The endgame, with introduction of the bridging ring, would call for intermolecular Diels–Alder reactivity using a suitable ketene or cumulene equivalent diene.[16] Recently, a related strategy was successfully implemented by Liu and co-workers.[5]

Cation-π cyclization precursor **23** was made by copper-catalyzed coupling[17] of allylic acetate and benzylic Grignard precursors. Lewis acid catalyzed bicyclization provided **24** (along with some *ortho* product), which was subjected to a bioinspired A-ring cleavage[18] followed by liberation of the phenol in **19**. Oxidative dearomatization[19] provided gram quantities of tricyclic dienone **26**. At this stage, monoreduction was required to afford enone **27**. This reaction proved incredibly challenging owing to competing overreduction or rearomatization to regenerate **19**. Our best results were obtained using the procedure of Lipshutz and co-workers,[20] which were still rather capricious. We uncovered a possible dependence on oxygen for this reduction, and investigated the relevance of dppb-monooxide[21] as the key ligand for conjugate reduction, but this approach never led to reproducibility.[10] Owing to these problems, we could at best accumulate ca. 50 mg of **27**, which was still enough to learn of the tremendous challenges associated with generating reactive Diels–Alder dienes of types **28**–**30**. All attempts to make enol/enamine derivatives of **27** led either to ejection of the bridging carboxylate to reform phenol **19**, or to decomposition. These outcomes were unchanged even when the operations were performed in the presence of model dienophiles. The poor material throughput associated with



Scheme 3 Approach to crotogoudin based upon a bioinspired polyene cyclization and A-ring oxidative cleavage; TBDPS: *tert*-butyldiphenylsilyl; PCC: pyridinium dichromate; *m*-CPBA: *meta*-chloroperbenzoic acid; TBAF: tetra-*n*-butylammonium fluoride; TMDS: tetramethyldisilazane

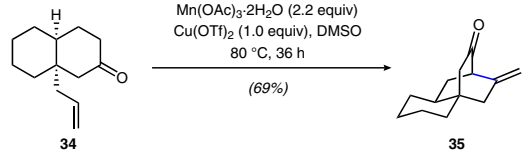
this sequence limited our studies of this and related endgames, and therefore led us to consider a revised approach that might be more scalable.



Scheme 4 A more robust approach to tricyclic enone intermediate **27**

An adjustment in strategy, wherein the order of oxidation/reduction operations on the arene was changed, led to the sequence shown in Scheme 4. Known cationic cyclization product **31**[22] was made in a very similar manner to **24**, but in much higher overall throughput.[10] Oxidative A-ring cleavage of **31** proceeded uneventfully to afford **32**. The key conceptual reversal of the oxidation and reduction steps from Scheme 3 led to the successful formation of **27** via (1) Birch reduction, (2) careful enol ether hydrolysis to avoid enone conjugation, and (3) iodolactonization with spontaneous β-elimination of hydroiodic acid. With compound **27** in hand in larger quantities, further explorations of Diels–Alder reactivity (as shown in Scheme 3) as well as conjugate addition chemistry were undertaken, without success. Conjugate allylation (Hosomi–Sakurai and copper-mediated), vinylation, propargylation, allenylation, and more were uniformly met with failure. Closely related systems have been shown to be particularly poor participants in functionalizations of the enone β-position.[23] No doubt, the developing 1,3-diaxial interaction in such reactions (see desired product **33**) is at least partly responsible for this lack of reactivity.

This impasse was unfortunate, because in the model system shown in Equation 1, we have set a reasonable precedent for completion of the tetracyclic ring system of crotogoudin via oxidative radical cyclization. This example of a manganese(III)-mediated ketone alkene cyclization[24] is remarkable, because the vast majority of such reaction types appear to require doubly activated (very acidic) carbonyl systems, such as malonates and β-keto-esters.[25] Although we have not evaluated this reaction type extensively, we believe that these conditions could prove general for the cyclization of alkenes onto otherwise unactivated ketones. The rapid synthesis of **35** from inexpensive materials (Robinson annulation of cyclohexanone, Hosomi–Sakurai conjugate allylation[26] to give **34**,[27] radical cyclization to **35**) shows a rather rapid increase in complexity, and it is unfortunate that we were never able to effect conjugate allylation of enone **27** to study this radical cyclization as a means to complete a synthesis of crotogoudin.



Equation 1

We have examined two distinct approaches to the synthesis of crotogoudin and crotobarin. The first pericyclic cascade strategy was certainly undermined by the instability of key intermediates, but computational studies suggested that poor selectivity for the desired pathway would also have plagued this approach. A bioinspired approach led to advanced tricyclic intermediates; unfortunately, the inability to manipulate enone **27** prevented further forward progress toward these targets. In this study, we have shown the strategic equivalence of dearomatizing oxidative heterocyclizations of phenols/dienone reduction and Birch reduction/halocyclization. Furthermore, we provide a rare example of a manganese(III)-mediated keto-alkene cyclization wherein the ketone is not further activated.[28]

Funding Information

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Acknowledgment

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Supporting Information

Supporting information for this article (Experimental procedures for the synthesis of new compounds from Schemes 2, 3, and 4, and from Equation 1, and their characterization data, are provided) is available online at https://doi.org/10.1055/s-0036-1588560.

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(28) **Representative Experimental Procedure and Characterization Data**
Compound **26**: Phenol **19** (1.48 g, 5.39 mmol) was dissolved in CF_3CH_2OH (50 mL) assisted by sonication. The open flask was cooled to 0 °C. A solution of diacetoxyiodobenzene (1.82 g, 5.66 mmol) in CF_3CH_2OH (4 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 2 h, diluted with water (100 mL), and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and concentrated in vacuo. The resultant crude dark red oil was purified by column chromatography (20% EtOAc in hexanes) to give **26** as a white solid (0.96 g, 66% yield; mp 105–107 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.86 (d, *J* = 10.2 Hz, 1 H), 6.33 (d, *J* = 10.2 Hz, 1 H), 6.16 (s, 1 H), 5.02 (s, 1 H), 4.82 (s, 1 H), 2.88–2.71 (m, 4 H), 2.42 (d, *J* = 13.3 Hz, 1 H), 2.02–1.83 (m, 4 H), 1.77 (s, 3 H), 0.89 (s, 3 H).^{13}C NMR (125 MHz, $CDCl_3$): δ = 184.8, 169.9, 156.7, 144.1, 143.6, 131.1, 126.2, 116.3, 82.8, 44.0, 41.1, 31.8, 28.6, 28.0, 26.0, 23.3, 17.5. IR (thin film): 3077, 3053, 2969, 2949, 1741, 1674, 1640, 1615 cm^{-1}. ESI-HRMS (MeOH): *m*/*z* calcd for $C_{17}H_{20}O_3Na$ [M + Na]$^+$: 295.1310; found: 295.1311.
Compound **35**: $Mn(OAc)_3{\cdot}2H_2O$ (0.316 g, 1.18 mmol) and $Cu(OTf)_2$ (0.195 g, 0.539 mmol) were added to a flame-dried vial, degassed in triplicate (backfilling with argon), and suspended in DMSO (5.4 mL). Ketone **34** (0.103 g, 0.533 mmol) was added neat, via syringe, and the reaction mixture was heated to 80 °C in a preheated aluminum block for 36 h. The brown suspension was cooled to r.t., diluted with water (2 mL), extracted with CH_2Cl_2 and Et_2O (2 × 2 mL). The combined organic extracts

were washed with $NaHCO_3$, water, brine, dried over Na_2SO_4, filtered through SiO_2, and concentrated in vacuo. The resultant crude material was purified by column chromatography (1–3% EtOAc in hexanes) to give **35** as a yellow oil (0.070 g, 69% yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 4.92 (d, *J* = 0.7 Hz, 1 H), 4.81 (d, *J* = 1.0 Hz, 1 H), 2.85 (dd, *J* = 3.6, 2.2 Hz, 1 H), 2.69 (dd, *J* = 19.1, 3.2 Hz, 1 H), 2.23 (dd, *J* = 17.1, 2.3 Hz, 1 H), 2.18–2.12 (m, 2 H), 1.74 (dd, *J* = 19.2, 1.4 Hz, 1 H), 1.73–1.62 (m, 2 H), 1.60–1.48 (m, 3 H), 1.37–1.16 (m, 4 H), 1.08 (ddd, *J* = 35.7, 13.0, 3.5 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 212.7, 143.3, 110.6, 55.0, 44.0, 42.9, 37.5, 36.3, 36.1, 32.9, 31.2, 26.2, 21.8. HRMS (CI/CH_2Cl_2): *m*/*z* calcd for $C_{13}H_{18}ONH_4$ $[M + NH_4]^+$: 208.1701; found: 208.1703.