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Total Synthesis of (+)-Crotogoudin**

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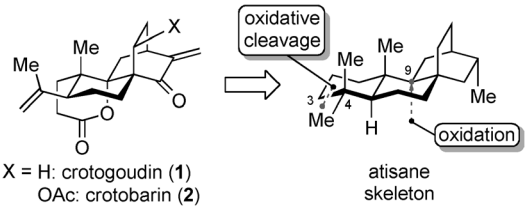
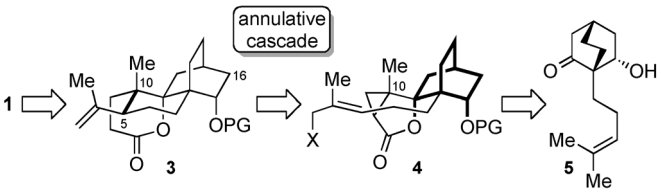
In 2010, a joint Madagascan–French research group reported the isolation of two closely related cytotoxic diterpenes, crotogoudin (**1**) and crotobarin (**2**), from indigenous *Croton* plants (Scheme 1).[1] Species of this genus have found widespread ethnomedical use around the globe and have proven to be a rich source of secondary metabolites, which exhibit a wide range of biological activity and have long served as inspiration for synthetic chemists.[2] Both **1** and **2** belong to the rare 3,4-*seco* atisane family of diterpenoids and feature unusual oxidation of the general skeleton at C(9).[3,4] The congested tetracyclic skeleton of crotogoudin contains four contiguous stereocenters, within which a tertiary alcohol from the corresponding *seco*-acid is flanked by two quaternary carbons.[5] This challenging motif, in combination with promising cytotoxic activity, attracted our interest. Herein, we describe the first total synthesis of (+)-crotogoudin (**1**) featuring a novel radical cyclopropane-opening/annulation/elimination cascade. Of added value, the synthesis permits assignment of the absolute configuration for this unusual natural product.



Scheme 1. Crotogoudin and crotobarin and their structural relationship to the atisane skeleton.

Structure-goal strategy-guided retrosynthetic analysis identified the embedded oxidized bicyclo[2.2.2]octane core as key (Scheme 2). It can be conveniently accessed from hydroxyketone **5**, itself available in enantiopure form by desymmetrization of the corresponding *meso*-diketone. We envisioned that the ketone in **5** could provide a handle for the concomitant construction of the δ-lactone and chair-cyclohexane ring in **1**. To this end, cyclopropane **4** could serve as a versatile intermediate to explore annulative cascade reactions because of its ambivalent character as a homoenolate or homo-Michael acceptor at C(10). In the pivotal step, regioselective cyclopropane opening in **4** would initiate a cyclization sequence engaging the isoprenyl side chain to form the key C(5)–C(10) bond and directly furnish the appropriately decorated tetracyclic carboskeleton of the *seco*-atisanes. Late-stage introduction of the enone at C(16) would complete the total synthesis.



Scheme 2. Retrosynthetic analysis of crotogoudin.

The synthesis commenced with the one-pot Michael addition/aldol condensation of ketoester **6**[6] with enal **7**[7] followed by Krapcho decarboxylation to furnish cyclohexenone **8** in 60% yield over two steps (Scheme 3). Concomitant debenzylation and conjugate reduction under Birch conditions[8] followed by Swern oxidation afforded ketoaldehyde **9**, which underwent acid-catalyzed intramolecular aldol addition.[9] Racemic hydroxyketone (±)-**5** was obtained as an inconsequential mixture of diastereomers and subsequently oxidized with Dess–Martin periodinane[10] to *meso*-diketone **10** in good yield over four steps (54%) without requiring purification of the intermediates. This sequence offers expedient and flexible access to bicyclo[2.2.2]octanones which are frequently encountered in terpenoid natural products and serve as precursors for ligands in asymmetric catalysis.[11,12]

Desymmetrization of *meso* compounds provides an efficient approach for the preparation of chiral organic molecules and has long been identified as a prime application of biocatalysis.[13] In this respect, the reduction of 1,3-dicarbonyl compounds with baker's yeast represents a striking example in terms of selectivity, preparative ease, and cost-effectiveness.[14] The research groups of Mori and Frejd showed that the reduction of bicyclo[2.2.2]octadi-2,6-ones proceeds with excellent enantio- and diastereoinduction, and substituents at the bridgehead carbon between the ketones were found to lead to increased selectivity, albeit for only two examples incorporating up to a two-carbon side chain.[11a,12a,b] Gratifyingly, when **10** was treated with a broth of baker's yeast and sugar in water, *endo*-alcohol (−)-**5** was obtained in 77% yield, as a single diastereomer and enantiomer, as determined by ^{1}H NMR and chiral SFC analysis.[15]

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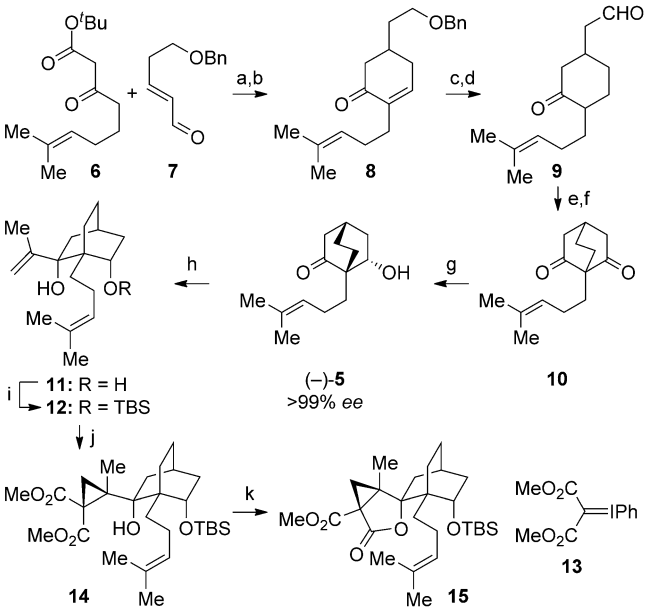


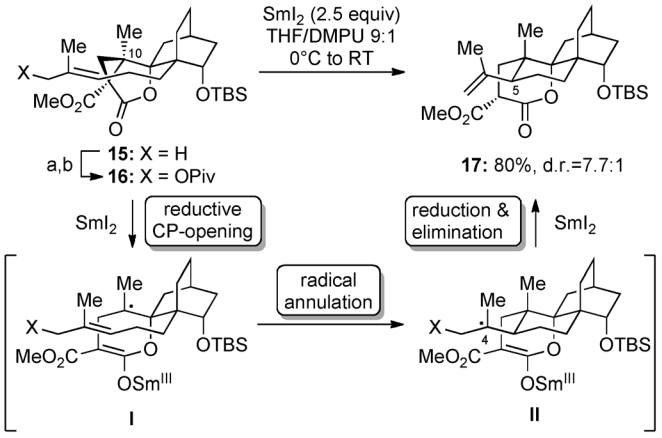
Scheme 3. Reagents and conditions: a) DBU (2 equiv), MeCN, 0 °C to 80 °C; b) LiCl (10 equiv), Me_2SO/H_2O (10:1), 160 °C, 60% over two steps; c) Na, NH_3 (l), EtOH, THF, −78 °C; d) $(COCl)_2$ (2.5 equiv), Me_2SO (5 equiv), NEt_3 (10 equiv), CH_2Cl_2, −78 °C to RT; e) 2 M HCl, acetone, 60 °C; f) Dess–Martin periodinane (1.1 equiv), $NaHCO_3$ (5 equiv), CH_2Cl_2, 54% over four steps; g) baker's yeast, sugar, EtOH, H_2O, 77% (87% brsm); h) 2-isopropenylMgBr (0.5 M in THF, 2.2 equiv), $LaCl_3{\cdot}2\,LiCl$ (0.5 M in THF, 1.1 equiv), THF, 0 °C, 88%; i) tBuMe$_2$SiOTf (1.1 equiv), 2,6-lutidine (4 equiv), CH_2Cl_2, −78 °C, 98%; j) **13** (2 equiv), $Rh_2(esp)_2$ (0.1 mol%), CH_2Cl_2, 0 °C, d.r. = 4.4:1, 66% (70% brsm); k) aq. sat. $NaHCO_3$, MeOH, RT, quantitative. brsm = based on recovered starting material, DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid.

With a route to enantiopure **5** established, nucleophilic addition of 2-isopropenyl magnesium bromide to the hindered ketone was investigated. Intriguingly, although initial tests with the corresponding TBS-protected hydroxyketone failed to give any product,[16] the use of free alcohol **5** with two equivalents of nucleophile afforded the tertiary alcohol with complete *exo*-diastereoselectivity,[17] albeit at low conversion owing to competing enolization of the starting ketone. This problem was circumvented by the use of soluble lanthanide salts ($LaCl_3{\cdot}2\,LiCl$ in THF),[18] yielding the monoprotected diol **12** in excellent yield after selective TBS-protection of the secondary alcohol (86% over two steps).

At this stage, the synthetic plan called for selective cyclopropanation of the newly introduced olefin. We were drawn to the use of phenyliodonium malonates such as **13** as a consequence of their reported selectivity for 1,1-disubstituted over trisubstituted olefins. Moreover, their use in Rh-catalyzed cyclopropanations enables the alkene to be the limiting reagent without the need for slow addition of the carbene precursor.[19] After preliminary experiments, we were pleased to observe that $[Rh_2(esp)_2]$[20] catalyzed the reaction efficiently to afford cyclopropane **14** as a separable 4.4:1 mixture of diastereomers in good yield (66%). The major diastereomer was subsequently converted to the corresponding lactone **15** under basic conditions, setting the stage for the key cascade transformation.

Initially, approaches were examined in which the trisubstituted olefin would serve as a nucleophile (e.g. X = H, $SiMe_3$) in the opening of the elecrophilic cyclopropane in **15** to deliver tetracyclic product **17** (Scheme 4).[21] However, no such reaction was observed despite extensive experimentation with various Lewis acids (e.g. $EtAlCl_2$, $TiCl_4$, $SnCl_4$). We then turned our attention towards a reversal of reactivity wherein the alkene would serve as an acceptor to a reactive, nucleophilic species at C(10) derived from reductive opening of the cyclopropane. Samarium(II) iodide[22] is known to promote the opening of acceptor-substituted cyclopropanes at room temperature or above. The resulting carbon-centered radicals have been exploited in simple systems for subsequent reactions, such as radical annulations or further reduction to form organosamarium species.[23]

Exposure of **15** to excess SmI_2 in refluxing THF afforded low yields (< 10%) of tetracyclic **17**. Interestingly, **17** was accompanied by equimolar amounts of reduction product bearing an isopropyl at C(5) with the remaining mass balance corresponding to polymeric material. This result was hypothesized to arise from a disproportionation reaction of tertiary radical **II** (X = H, Scheme 4), formed through cyclopropane-opening and subsequent radical olefin cyclization (**15**→**I**→**II**). We speculated that offering the radical at C(4) a suitable leaving group (X) would enable a favorable termination pathway, leading to increased product formation.

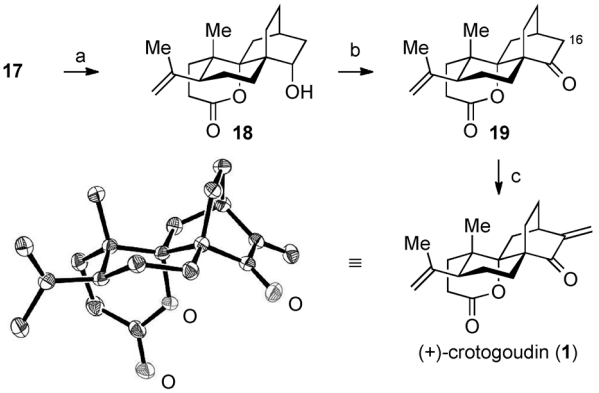


Scheme 4. Radical cyclopropane-opening/annulation/elimination cascade. Reagents and conditions: a) SeO_2 (50 mol%), tBuO$_2$H (5 M in n-C_9H_{17}, 2 equiv), CH_2Cl_2, 0 °C to RT; then $NaBH_4$ (1.0 equiv), MeOH, 0 °C, 74% over two steps; b) Me_3COCl (1.2 equiv), 4-dimethylamino-pyridine (5 mol%), pyridine, 0 °C to RT, 95%. DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, TBS = *tert*-butyldimethylsilyl.

Inanata and co-workers showed that allylic acetates can afford terminal olefins in the cyclization of ketyl or aryl radicals.[24] This was proposed to occur by a second single-electron reduction of the resulting carbon-centered radical and subsequent anionic β-elimination. More recently, Nicolaou and co-workers made use of an allylic carbonate as a leaving group in the application of a ketyl radical cyclization in their synthesis of vannusal B.[25]

A variety of allylic acetates and carbonates were prepared by stereoselective allylic oxidation and functionalization of the resulting (*E*)-allylic alcohol (Scheme 4). We were delighted to observe that both acetates and carbonates participate in the key cyclopropane-opening/annulation/elimination cascade in dramatically improved yield. Sterically demanding allylic leaving groups were found to offer higher diastereomeric ratios at C(5), and optimization of the reaction conditions (THF/DMPU 9:1, 0 °C to RT) led to the isolation of tetracyclic product **17** in 80% yield and high diastereoselectivity (d.r. = 7.7:1) from pivaloate **16**.

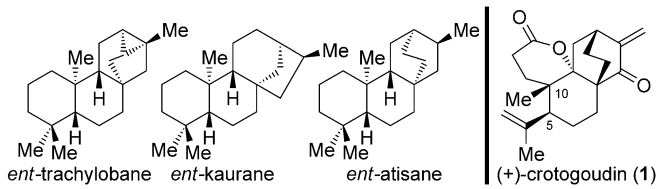
Having successfully constructed the tetracyclic core of crotogoudin, decarboxylation, alcohol deprotection, and oxidation to arrive at ketolactone **19** proceeded uneventfully in high yield (Scheme 5). The α-methenylation of ketone **19** required protection of the lactone, as the latter was found to undergo preferential reaction with electrophiles compared to the ketone. We consequently devised a procedure involving transient masking of the lactone in **19** as the corresponding silyl ketene acetal. This enabled subsequent generation of the ketone enolate and its participation in chemoselective reaction at C(16) with Eschenmoser's salt (CH_2=$NMe_2^+I^-$).[26] In the experiment, after formation of the triisopropylsilyl ketene acetal (TIPSOTf, NEt_3), the ketone was deprotonated (LiHMDS) and quenched with CH_2=$NMe_2^+I^-$. Careful control of the reaction temperature (≤ -50 °C) was necessary to minimize formation of byproducts.[27] Hofmann elimination (MeI, then basic Al_2O_3) then afforded (+)-crotogoudin (**1**) as a white, crystalline solid in 54% yield over four steps.



Scheme 5. Completion and crystal structure of (+)-crotogoudin (**1**); Thermal ellipsoids are set at 50% probability. Reagents and conditions: a) LiCl (10 equiv), Me_2SO/H_2O (9:1), 130 °C; then 5 M HCl, MeOH, 0 °C, 96% over two steps; b) Dess–Martin periodinane (1.2 equiv), CH_2Cl_2, 0 °C to RT, 93%; c) iPr_3SiOTf (1.3 equiv), NEt_3 (4.3 equiv), MeCN, 0 °C to RT; then $LiN(SiMe_3)_2$ (2.0 equiv), CH_2=$NMe_2^+I^-$ (4.0 equiv), THF, −78 °C to −50 °C; then MeI (10 equiv), Et_2O/CH_2Cl_2 (3:1), RT; then basic Al_2O_3, CH_2Cl_2, RT, 54% over four steps.

1D/2D NMR data for synthetic **1** was in full agreement with that reported for the natural product.[1] Additionally, recrystallization of the synthetic material (hexane/CH_2Cl_2) afforded crystals suitable for X-ray diffractometry (mp 170–171 °C), providing further structural conformation.[28] Comparison of the optical rotation revealed matching signs for both synthetic and natural material, although a significant deviation in magnitude was noted (synthetic: $[\alpha]_D^{20} = +29.6$ ($c = 0.4$, $CHCl_3$); reported: $[\alpha]_D^{20} = +7$ ($c = 0.4$, $CHCl_3$)).

Intriguingly, the absolute configuration determined for (+)-**1** that follows from the synthesis is noteworthy when compared to that implicated by the original publication. To the best of our knowledge it would represent the first example of an atisane-type natural product that is not in the *ent*-configurational series (compare structures in Scheme 6).[29] Although their absolute configuration has not always been rigorously established, the vast majority of tetracyclic diterpenoids, such as atisanes, trachylobanes, or kauranes, belong to the *ent*-series. These findings prompted us to examine possible explanations for the anomaly. Discussions with the team responsible for the isolation and structural characterization culminated in re-measurement of the optical rotations.[1] Accordingly, the values for natural crotogoudin (**1**) and crotobarin (**2**) should be revised to (**1**): $[\alpha]_D^{20} = -25.2$ ($c = 0.4$, $CHCl_3$) and (**2**): $[\alpha]_D^{20} = -23.8$ ($c = 0.4$, $CHCl_3$) respectively.[30] Therefore, natural (−)-crotogoudin (*ent*-**1**) is assigned the absolute configuration (5*R*,10*R*) and belongs to the expected *ent*-atisane family.



Scheme 6. Skeletons of naturally occurring tetracyclic diterpenoids and (+)-crotogoudin illustrating the absolute configuration.

In conclusion, we have reported a total synthesis of *ent*-crotogoudin (**1**). The synthesis relies on a key radical cyclopropane-opening/annulation/elimination cascade to diastereoselectively access the tetracyclic carbon skeleton. Additional salient features of the route include versatile and efficient access to 1-substituted bicyclo[2.2.2]octa-2,6-diones for desymmetrization by baker's yeast reduction and the application of a selective rhodium-catalyzed cyclopropanation of phenyliodonium malonates in a complex setting. Additional efforts to gain insight into the bioactivity of **1** and to expand the strategy to crotobarin (**2**) along with other related natural products are the subject of current research in our laboratories and will be reported in due course.

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[28] CCDC 943670 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Additionally, the absolute stereochemistry was unambiguously determined by X-ray diffractometry (CCDC 946770) of the Mosher's ester derived from alcohol **18** (Scheme 5); see the Supporting Information for details.

[29] a) C. Demetzos, K. S. Dimas in *Studies in Natural Products Chemistry*, *Vol. 25* (Ed.: Atta-ur-Rahman), Elsevier, New York, **2001**, pp. 235 – 292; b) J. M. Finefield, D. H. Sherman, M. Kreitman, R. M. Williams, *Angew. Chem.* **2012**, *124*, 4886 – 4920; *Angew. Chem. Int. Ed.* **2012**, *51*, 4802 – 4836.

[30] Dr. V. Dumontet (ICSN-CNRS, France) and Prof. P. Rasoanaivo (University of Antananarivo, Madagascar), private communication. We are grateful for their efforts and assistance in this matter.

