Total Synthesis

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Total Syntheses of (±)-Dracocephalone A and (±)-Dracocequinones A and B

*Taehwan Hwang[+], Joseph P. Tuccinardi[+], Alexandra A. Beard, Amy C. Jackson, Min J. Jung, and John L. Wood**

Abstract: Described herein are the first total syntheses of (±)-dracocephalone A (**1**) and (±)-dracocequinones A (**4**) and B (**5**). The synthesis was initially envisioned as proceeding through an intramolecular isobenzofuran Diels–Alder reaction, a strategy that eventually evolved into a Lewis acid-promoted spirocyclization. This highly diastereoselective transformation set the stage for *trans*-decalin formation and a late-stage Suárez oxidation that produced a [3.2.1] oxabicycle suited for conversion to **1**. Brønsted acid-mediated aromatization, followed by a series of carefully choreographed oxidations, allowed for rearrangement to a [2.2.2] oxabicycle poised for conversion to **4** and **5**.

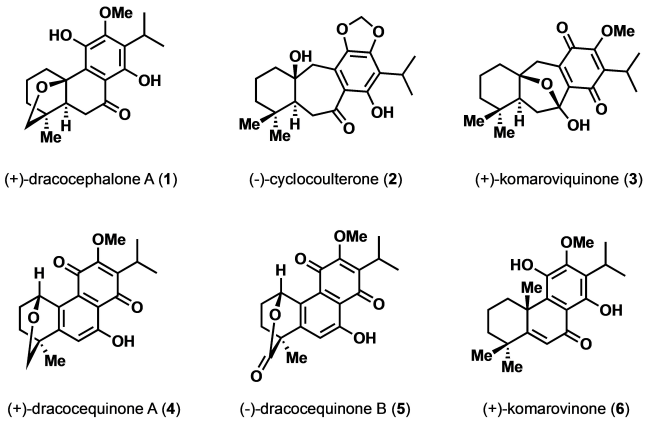

Figure 1. Representative diterpenoids from *Dracocephalum komarovi.*

Chagas disease (CD) is transmitted by the protozoan parasite *Trypanosoma cruzi* and, despite its prevalence and lethality across Central and South America, is considered to be a neglected disease.[1] Efforts to develop effective treatments for CD have proven problematic due to the necessity for prolonged drug regimens that result in associated adverse side-effects and the development of resistance.[2] Thus, effective therapeutic agents remain scarce and the treatment of CD presents an important unmet medical need.[3] In 2003, a 20-*nor*-abietane diterpenoid, (+)-dracocephalone A (**1**), along with (−)-cyclocoulterone (**2**) and (+)-komaroviquinone (**3**) (Figure 1), were isolated from the perennial semishrub *Dracocephalum komarovi*, a traditional medicine used for Inflammatory diseases and hypertony in Uzbekistan.[4]

In preliminary studies, extracts from *D. komarovi* showed strong in vitro trypanocidal activity against epimastigotes of *T. cruzi.* Inspired by these initial findings, further studies on the isolated components from the extracts revealed the minimum lethal concentrations (MLCs) of **1**, **2**, and **3** to be 200, 20, and 0.4 μM, respectively.[4] Several years later, three new structurally related diterpenoids, (+)-dracocequinone A (**4**), (−)-dracocequinone B (**5**), and (+)-komarovinone (**6**), were also isolated from *D. komarovi* (Figure 1) and the former two were found to exhibit trypanocidal activity (MLC = 12.5 and 25 μM, for **4** and **5**, respectively).[5] While the icetexane diterpenoids **2** and **3**, have been prepared by total synthesis, their corresponding *nor*-abietane congeners (**1**, **4**, and **5**) have not yet succumbed to total synthesis.[4–11] The scarcity of available methods for accessing *nor*-abietanoids, coupled with the interesting activity of **1**, **4**, and **5** against CD led us to develop the divergent synthetic strategy reported herein.

As illustrated retrosynthetically in Scheme 1, we envisioned **1**, **4**, and **5** as deriving from a common intermediate (**7**), which bears the requisite carbocyclic framework and oxidation patterns for diverging to each of the targets. We suspected the [3.2.1] oxabicycle embedded in **7** could be accessed via a late-stage Suárez oxidation, which would follow silyl ketal fragmentation and decarboalkoxylation of the [2.2.1] oxabicycle **8**. The latter oxabicycle would be assembled from lactone **9** via tandem isobenzofuran generation/Diels–Alder cycloaddition. Lactone **9** would arise from aldehyde **10** and benzamide **11** via a directed Snieckus *ortho*-metalation/nucleophilic addition sequence and subsequent lactonization.[12]

In accord with our synthetic plan, aldehyde **12** was first accessed by a known protocol reported by Frontier and coworkers (Scheme 2A) and advanced to the homologated

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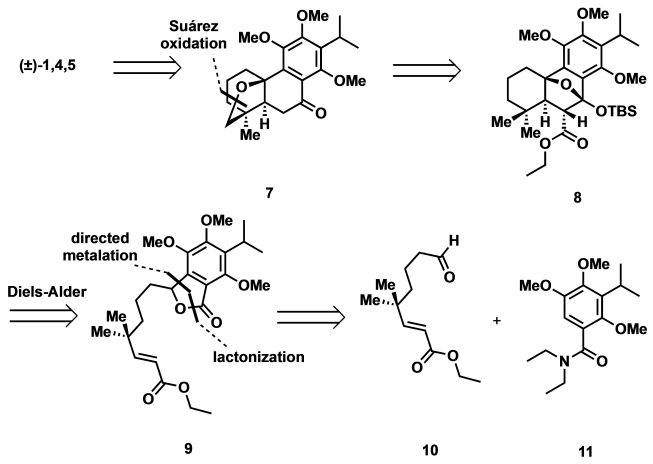
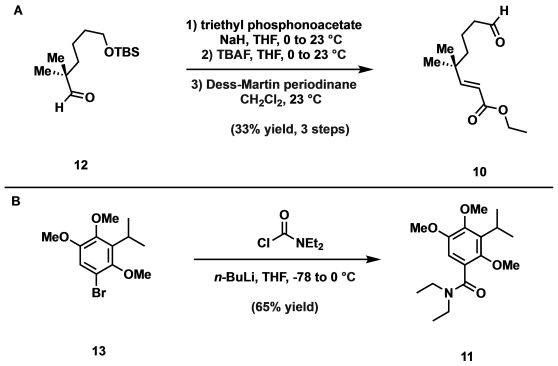
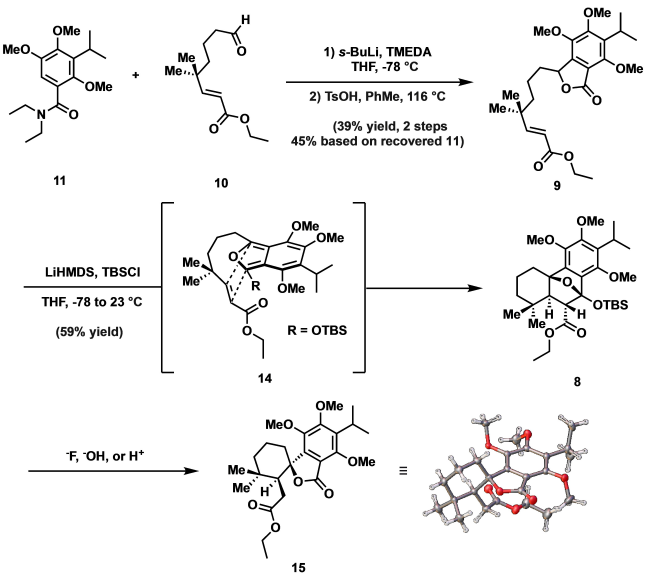


Scheme 1. Initial retrosynthetic analysis of (±)-dracocephalone A (**1**) and (±)-dracocequinone A (**4**) and B (**5**).



Scheme 2. A) Synthesis of aldehyde **10** and B) synthesis of benzamide **11**.

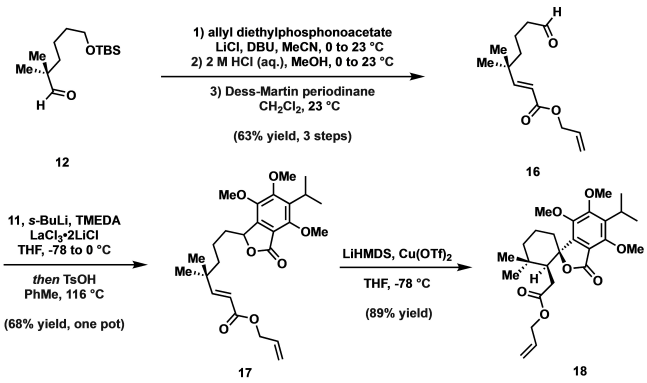
aldehyde **10** via a 3-step sequence involving Horner–Wadsworth–Emmons olefination, desilylation with tetra-n-butylammonium fluoride, and Dess–Martin oxidation.[13] Having prepared the requisite electrophile **10**, we turned our attention to the preparation of benzamide **11** (Scheme 2B). The latter was accessed in short order by subjecting known bromide **13** to metal-halogen exchange (*n*-BuLi), followed by addition of the resultant organolithium to *N*,*N*-diethylcarbamoyl chloride.[14] With the coupling fragments in hand, the directed *ortho*-metalation was effected under conditions developed by Snieckus and the derived anion exposed to aldehyde **10** (Scheme 3).[12] Following work-up, exposure of the intermediate alcohol (not shown) to *p*-toluenesulfonic acid then afforded lactone **9** in modest yield. We were pleased to find that upon treatment with lithium hexamethyldisilazide (LiHMDS) and *tert*-butyldimethylsilyl chloride (TBSCl), **9** was converted to the corresponding siloxyisobenzofuran **14** which, upon warming to room temperature, smoothly underwent the desired Diels–Alder cycloaddition to deliver the sensitive silyl acetal **8** as the only isolable product.[15] With **8** in hand, we screened a number of conditions to effect opening of the silyl acetal to the requisite decalin. To our dismay, no products corresponding to the desired C–O cleavage were ever detected. Instead, under all conditions tested, cleavage of the C–C bond outpaced that of the C–O bond thereby giving rise to a spirolactone, the structure of which was unambiguously defined as illustrated (**15**) by single crystal X-ray analysis.



Scheme 3. Syntheses of Diels–Alder cycloadduct **8** and undesired lactone **15**.

Given the sensitivity of the silyl acetal moiety of **8** coupled with its propensity to undergo an undesired *retro*-Dieckmann reaction, it was clear that an alternative route was needed. However, given its accessibility, **15** remained an attractive intermediate for constructing the decalin. In considering potential deviations from our initial synthetic strategy, we envisioned that decarboxylative formation of an alkyl anion from the ester moiety present in **15** would set the stage for reforming the pivotal C–C bond and deliver the required decalin. To this end, preliminary studies were conducted to convert **15** into its corresponding carboxylic acid. Unfortunately, all attempts to affect selective hydrolysis of the ethyl ester moiety failed. Accordingly, we sought access to a more malleable allyl ester **18**.

By utilizing a similar sequence, illustrated in Scheme 4, efforts to prepare **18** were accompanied with optimization studies and commenced with subjection of aldehyde **12** to Masamune-Roush modified Horner–Wadsworth–Emmons olefination conditions. Subsequent aqueous HCl-mediated deprotection and Dess–Martin oxidation furnished **16** in a greatly improved yield relative to that observed for **10**. Turning next to the coupling event, we found that the *ortho*-metalation/lactonization sequence could be significantly improved by the addition of lanthanum(III) chloride bis-lithium chloride complex followed by direct exposure to *p*-toluenesulfonic acid. These conditions efficiently delivered lactone **17**. In further optimization efforts designed to bypass the intermediate siloxybenzofuran, we discovered that exposure of **18** to LiHMDS and catalytic quantities of copper(II) trifluoromethanesulfonate resulted in excellent



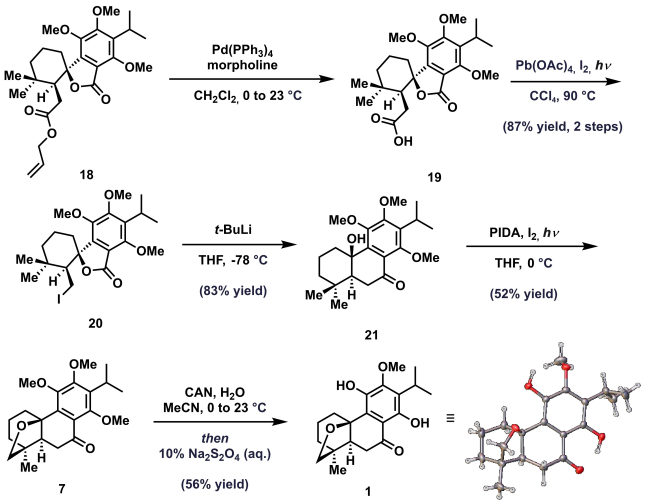
Scheme 4. Modified synthetic route to allyl ester **18**.

yields of **18**.[16] Clearly, the exclusion of TBSCl circumvented formation of an isolable Diels–Alder adduct, thereby resulting in net spirocyclization to **18**.

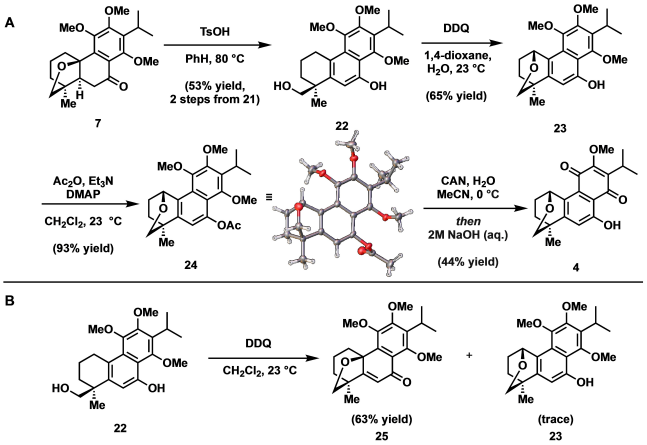
It is worth noting that the highly diastereoselective spirocyclization could arise via two distinct mechanistic pathways: either an anionic Diels–Alder/*retro*-Dieckmann cascade or an intramolecular Michael cyclization.[17] Given that the sense and extent of diastereoselectivity very closely matched the outcome of the *endo* selective siloxyisobenzofuran Diels–Alder (see above, cf. Scheme 3), we hypothesize that the former is at play. Further, examples of anion-assisted furanone Diels–Alder reactions in the literature support the feasibility of such a process.[18,19]

Having optimized the route, we set the stage for the endgame by preparing decagram quantities of **18** and then began advancing by subjecting the ester to palladium-mediated deallylation to furnish the corresponding carboxylic acid **19** (Scheme 5). Subsequent exposure of **19** to modified Hunsdiecker conditions smoothly induced decarboxylative iodination to furnish alkyl iodide **20**.[20,21] Metal-halogen exchange using *t*-BuLi then initiated a rapid intramolecular nucleophilic acyl substitution reaction that produced *trans*-decalin **21** which,[22] upon treatment with phenyl iodide diacetate (PIDA) and I_2 under Suárez conditions, undergoes a diastereotopic group selective transannular oxidation of the syn-methyl group to furnish ether **7**, thus completing construction of the [3.2.1] oxabicyclic ring system.[23] At this point, all that remained was regioselective double demethylation to the hydroquinone, a transformation that in practice proved to be a considerable challenge due to the lability of **7** under acidic conditions. After considerable experimentation, it was eventually determined that cerium (IV) ammonium nitrate (CAN) can be employed to convert **7** to a transient quinone intermediate which, upon reduction with sodium dithionite, gives rise to dracocephalone A (**1**).[6,24] Notably, this efficient synthetic approach provided quantities sufficient for crystallization of **1** and further structural confirmation via single crystal X-Ray analysis.

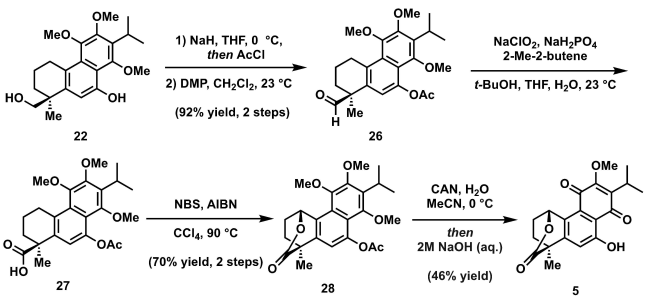
Having accessed **1**, we next sought to extend this strategy to the aromatized and further oxidized congeners **4** and **5**. In accord with our retrosynthetic plan, our intent was to employ **7** (trivially *O,O*-dimethyldracocephalone A) as the point of divergence. Toward this end, aromatization of the central ring was most efficiently accomplished by treating **7** with catalytic *p*-toluenesulfonic acid in hot benzene to give naphthol **22** (Scheme 6A). A number of oxidants were screened in hope of effecting conversion of **22** to an intermediate quinone methide (not shown) from which transannular etherification would deliver **23**. Although these efforts revealed 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)-mediated oxidations to be the most promising, they were initially found to be poorly reproducible.[25] In anhydrous CH_2Cl_2, trapping of the aryl oxidation intermediate to deliver **25** was observed as the predominant event, with only traces of **23** being detected (Scheme 6B). Switching solvents to 1,4-dioxane gave improved but variable yields of **23** along with **25**. Eventually, we discovered the course of this reaction to be reliant on water content of the solvent. Interestingly, the addition of superstoichiometric water was found to completely suppress formation of **25**, thereby enabling isolation of **23** in good yield. At this stage, to



Scheme 5. Completed synthesis of (±)-dracocephalone A (**1**).



Scheme 6. A) Total synthesis of (±)-dracocequinone A (**4**) and B) solvent/water-induced reversal of oxidation selectivity.



Scheme 7. Total synthesis of (±)-dracocequinone B (**5**).

complete the syntheses of **4** and **5**, we hoped to apply the oxidative demethylation conditions that proved effective in the completion of **1**. However, recognizing the potential for complications arising from the free phenol we opted to mask **23** as its corresponding acetate. To this end, acylation of **23** gave the crystalline naphthol acetate **24**; the structure of which was confirmed via single crystal X-Ray analysis. Finally, oxidation of the trimethoxyarene to its corresponding *para*-quinone using CAN was followed by in situ removal of the naphthol acetate to furnish dracocequinone A (**4**).

Turning to the completion of **5**, a slightly modified course of events was required to access the requisite lactone **28** (Scheme 7). Specifically, selective protection of the naphthol **22** as the corresponding acetate (NaH/AcCl) was required since the free hydroxyl moiety was found to preclude selective oxidation of the primary alcohol. Subsequent Dess–Martin oxidation of the intermediate acetate proceeded to give aldehyde **26** in excellent yield over the two steps. Oxidation of **26** under standard Pinnick conditions resulted in smooth conversion to carboxylic acid **27**. Much to our chagrin, efforts to advance **27** via the previously developed DDQ/water-mediated protocol failed and returned only starting material. Fortunately, we found that the desired lactone **28** could be prepared under Wohl-Ziegler bromination conditions, presumably via an S_N1-type displacement of the transient benzylic bromide. Finally, CAN oxidation and removal of the naphthol acetate in the same pot secured access to dracocequinone B (**5**).

In summary, we have completed the first total synthesis of (±)-dracocephalone A (**1**) in 10-steps and 8% overall yield from known materials. The developed synthetic strategy was successfully extended to the first total syntheses of (±)-dracocequinones A (**4**) and B (**5**), in 13 and 15 steps, respectively, from known materials. To the best of our knowledge, these represent the first total syntheses of C-20 *nor*-abietane natural products. The efficiency of the approach and ability to prepare intermediates on gram scale has greatly facilitated ongoing investigations into the trypanocidal activity of late-stage intermediates and simple variants,[27] as well as the syntheses of other *nor*-abietanoids and related *trans*-decalin natural products.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Chagas Disease · Diels–Alder · Oxidation · Synthesis · Terpenoids

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[27] Notably, intermediate **21** was prepared in multigram quantities, only a fraction of which was required to complete the syntheses of **1**, **4**, and **5**. In addition to scale, the steps leading to **21** and those employed in the end-game have proven robust in terms of reproducibility.

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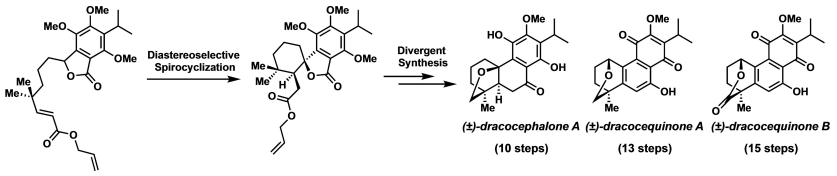

Described herein are the first total syntheses of (±)-dracocephalone A (**1**) and (±)-dracocequinones A (**4**) and B (**5**). An initially-envisioned intramolecular isobenzofuran Diels–Alder strategy guided the evolution of a Lewis acid-promoted spirocyclization approach that allowed for access to the carbocyclic core of **1**. Further advancement by a series of carefully choreographed oxidations and rearrangements allowed for conversion to **1**, **4**, and **5**.