Formal [3 + 3] Cycloaddition Approach to Chromenes and Chromanes. Concise Total Syntheses of (±)-Rhododaurichromanic Acids A and B and Methyl (±)-Daurichromenic Ester
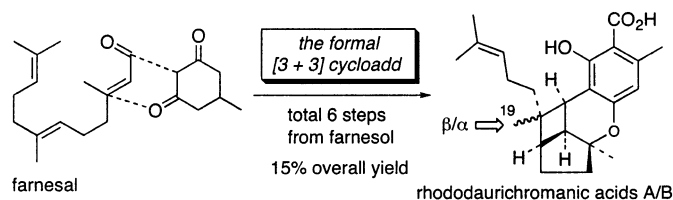
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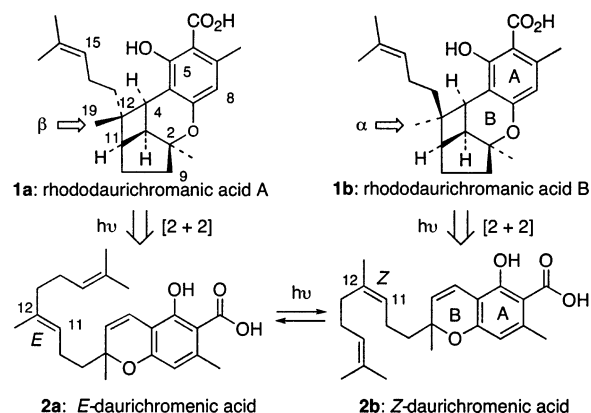*hsung@chem.umn.edu*

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ABSTRACT

Total syntheses of (±)-rhododaurichromanic acids A and B and methyl (±)-daurichromenic ester are described here. Despite the complex appearances of these compounds, their syntheses are completed in six steps with a 15% overall yield as a mixture by featuring our formal oxa-[3 + 3] cycloaddition methodology.

Rhododaurichromanic acids A and B (**1a** and **1b**, respectively) were isolated[1] from *Rhododendron dauricum*,[2] a plant known in areas of northern China, eastern Siberia, and Hokkaido, Japan. Also isolated from the same study was a known natural product, daurichromenic acid (**2a**).[3] While **2a** is a highly potent anti-HIV agent with an EC_{50} of 5.67 ng/mL and a TI (therapeutic index) of 3710,[3] rhododaurichromanic acid A (**1a**) also exhibits a relatively potent anti-HIV property with an EC_{50} of 0.37 µg/mL and a TI of 91.9. Although rhododaurichromanic acid B (**1b**) differs from **1a** only at the C12 stereocenter, it possesses no activity. The biosynthetic relationship between rhododaurichromanic acid A (**1a**) and daurichromenic acid (**2a**) is reported to be a photochemical [2 + 2] cycloaddition in conjunction with an

isomerization of the C11–C12 olefin from (*E*)- in **2a** to (*Z*)- in **2b** that could give **1b** upon cycloaddition.[1]

1a: rhododaurichromanic acid A   **1b**: rhododaurichromanic acid B

2a: *E*-daurichromenic acid   **2b**: *Z*-daurichromenic acid

Our efforts in developing a formal [3 + 3] cycloaddition reaction[4–6] for constructing 1-oxadecalins led us to these natural products. Annulation reaction of diketones **3** with

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(1) Kashiwada, Y.; Yamazaki, K.; Ikeshiro, Y.; Yamagishi, T.; Fujioka, T.; Mihashi, K.; Mizuki, K.; Cosentino, L. M.; Fowke, K.; Morris-Natschke, S. L.; Lee, K.-H. *Tetrahedron* **2001**, *57*, 1559.
(2) *Chinese Material Medica;* Edited by Jiangsu New Medical College; Shanghai People's Publishing House: Shanghai, 1997; p 2506.
(3) Jpn. Kokai Tokyo Koho JP 82-28080, 1982.

α,β-unsaturated iminium salts **4**[6] involves a Knoevenagel condensation followed by a 6π-electron electrocyclic ring-closure of 1-oxatrienes **5**, providing a convergent synthesis of 1-oxadecalins **6** (Scheme 1).[7] This sequential anionic-

Scheme 1
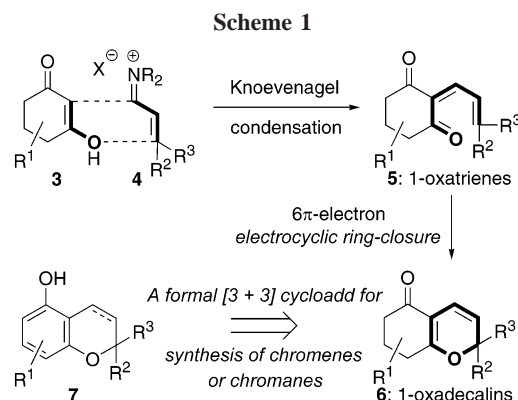
pericyclic strategy[8] constitutes a stepwise formal [3 + 3] cycloaddition[9,10] in which two σ-bonds are constructed in addition to a new stereocenter adjacent to the oxygen atom.[11] More recently, we demonstrated that this methodology can serve as a useful entry to chromenes **7** via oxidative aromatization of **6**,[6b,12] thereby allowing us to explore syntheses of those natural chromenes and chromanes with important medicinal values.[13,14] We report here concise total syntheses of (±)-rhododaurichromanic acids A and B and methyl (±)-daurichromenic ester.

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The synthesis of daurichromenic acid **2a** is outlined in Scheme 2. Aldehyde **8**,[15] the precursor for preparing the

Scheme 2[a]
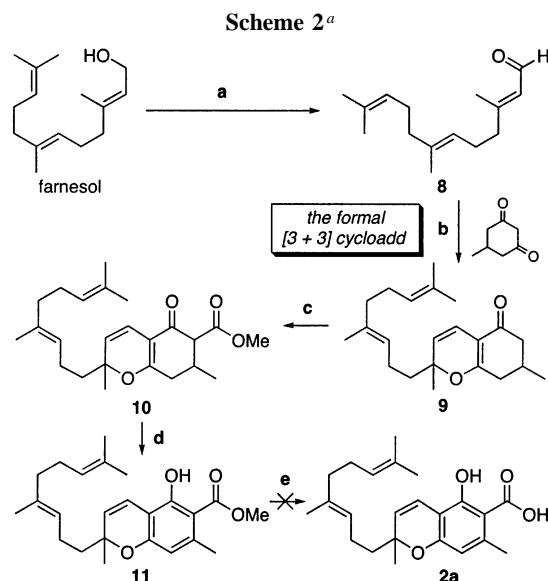
[a] Reaction conditions: (a) DMSO, CH₂Cl₂, SO₃-pyridine, Et₃N (94%). (b) Piperidine, Ac₂O, 90 °C, EtOAc, 1 h; this mixture was then added to 5-methyl-1,3-cyclohexanedione in toluene, 90 °C, 12−18 h (70%). (c) LDA, THF, −78 °C; this was then added to NCCO₂Me (71%). (d) DDQ, toluene, reflux (44%). (e) KOH, NaOH, LiOH, AlCl₃, or BBr₃; decarboxylation occurred.

appropriate α,β-unsaturated iminium salt, was obtained nearly quatitatively via SO₃-pyridine oxidation of (*E,E*)-

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(15) All new compounds are characterized by ¹H NMR, ¹³C NMR, FTIR, and LRMS.

farnesol. An α,β-unsaturated iminium salt was then generated via heating **8** in the presence of piperidine and Ac₂O in EtOAc using a sealed tube at 90 °C.[4,6] The iminium salt's subsequent formal cycloaddition with 5-methyl-1,3-cyclohexanedione was also accomplished using a sealed tube at 90 °C for 12−18 h providing the desired adduct **9** as a 1:1 mixture of two diastereomers in 70% yield. This key cycloaddition could be carried out on multigram scale.

The formation of the β-ketoester **10** as a mixture of isomers was best accomplished via addition of the lithium enloate derived from **9** to Mander's reagent. Additives such as HMPA provided a comparable outcome. Stereoselectivity of this acylation is also inconsequential, as DDQ oxidation of **10** led to the racemic methyl daurichromenic ester **11** in 44% yield. We were surprised to discover that numerous attempts to saponify ester **11** failed to give (±)-daurichromenic acid **2a**. In most cases, decarboxylation occurred readily in addition to decomposition.

To circumvent this problem, we examined photochemical [2 + 2] cycloaddition of ester **11**. As shown in Scheme 3,

Scheme 3
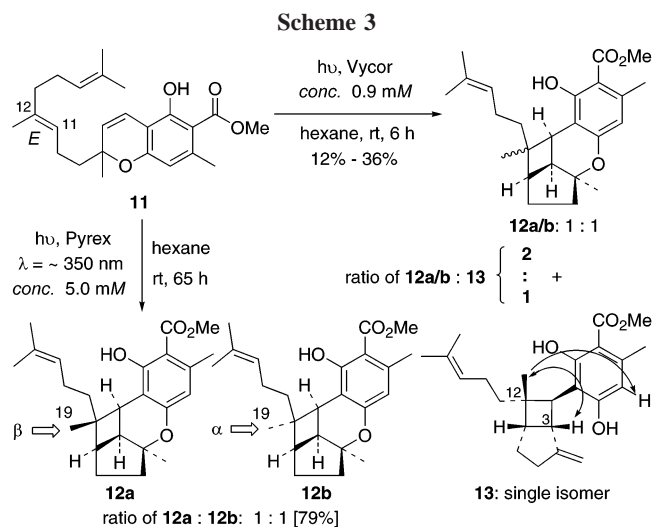
irradiation of **11** in hexane (concentration = 0.9 mM) using a medium-pressure mercury lamp with a Vycor filter led to rapid disappearance of the starting material and afforded the desired cycloadducts **12a** and **12b** in 1:1 ratio with an overall yield varying between 12 and 36%. Formation of the cycloadduct **12b** is a direct result of photochemical isomerization of the C11−C12 olefin in **11** from (E)- to (Z)- prior to [2 + 2] cycloaddition. This isomerization was also observed in LCMS analysis.

Also isolated was the [3.2.0] bicycloheptane **13** as a single isomer, its relative stereochemistry was assigned according to NOE experiments (arrows are shown). The relative stereochemistry at the ring junction is assigned on the basis of the notion that the [3.2.0] bicycloheptane **13** should be cis-fused. Irradiation of **11** in hexane (concentration = 5.0 mM) using Pyrex as a cutoff filter provided a cleaner outcome, affording cycloadducts **12a** and **12b** in 79% yield

Scheme 4
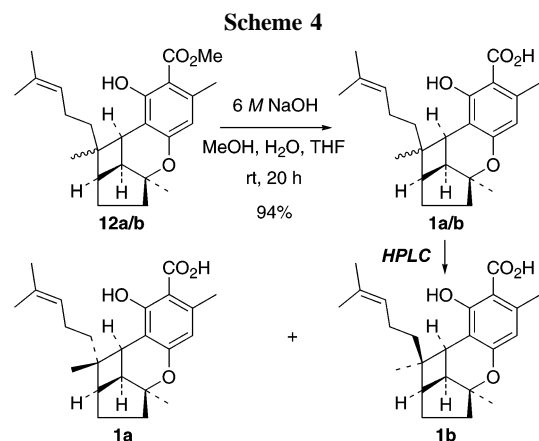
as a 1:1 isomeric mixture, although the reaction took a much longer time.

Regular tungsten lamps or weak UV lamps were not useful for this photochemical cycloaddition. Irradiations at low temperature were also examined. However, the irradiation was best carried out without using a standard reaction vessel or cooling bath but employing just the standard photochemical emersion well with a mercury lamp situated within the filter inside the well and a regular sealed reaction flask or vial being held next to the emersion well. Therefore, the reaction formally proceeded at room temperature, and there was no observable rise in temperature due to the irradiation.

To complete the total synthesis, cycloadducts **12a** and **12b** were successfully saponified using 6 M aqueous NaOH in THF/MeOH without any complication to give rhododaurichromanic acids A and B (**1a** and **1b**, respectively) in 94% overall yield (Scheme 4). Final separation using HPLC

Scheme 5
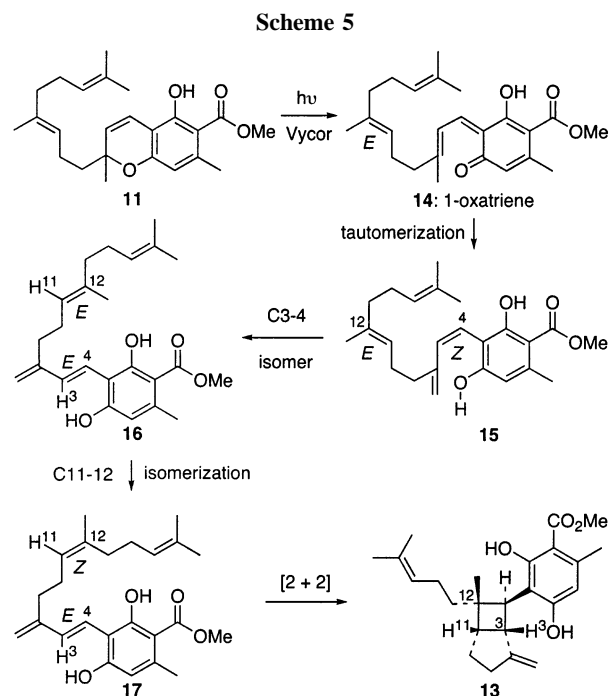
(eluent = 1% aqueous acetic acid/CH$_3$CN with a ratio of 20:80) led to both **1a** and **1b** as individual isomers that gave spectroscopic data identical with reported values.[1]

Isolation of the byproduct **13** was intriguing, and its formation is postulated in Scheme 5. Since this occurred only when irradiation was done at a shorter wavelength, a photochemical electrocyclic ring opening could occur competitively to give 1-oxatriene **14**.[16] A tautomerization/rearomatization would lead to the styrene derivative **15**. On the basis of stereochemical assignment, it appears that two olefinic isomerizations would have to occurr, although the order of the two isomerizations is unknown at this point, with one of them being drawn here. Isomerizations at C3−C4 from (*Z*)- to (*E*)- and at C11−C12 from (*E*)- to (*Z*)- would lead to the cycloaddition precursor **17**. The subsequent [2 + 2] cycloaddition between C3−C4 and C11−C12 olefins should lead to **13** with the assigned relative stereochemistry. We are currently examining why we did not observe the corresponding isomeric cycloadducts derived from **15** and **16** prior to isomerizations at C3−C4 and C11−C12 olefins, repsectively.

We have described here concise total syntheses of (±)-rhododaurichromanic acids A and B and the methyl ester of (±)-daurichromenic acid. Despite the complex appearance of (±)-rhododaurichromanic acids A and B, their syntheses were accomplished in six steps (excluding HPLC separation) featuring our methodology with a 15% overall yield for the mixture of A and B. These efforts represent the first applications of our formal [3 + 3] cycloaddition approach in the synthesis of natural chromenes and chromanes.

Supporting Information Available: Experimental and ^{1}H NMR spectral and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL030100K

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