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A Modular and Concise Total Synthesis of (±)-Daurichromenic Acid and Analogues

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Received February 20, 2004

A modular and concise total synthesis of (±)-daurichromenic acid has been accomplished in four steps from ethyl acetoacetate, ethyl crotonate, and *trans,trans*-farnesal. A series of analogues of this natural product, which has potent anti-HIV activity, were also prepared from ethyl or methyl acetoacetate and a series of readily available α,β-unsaturated esters and aldehydes.

Introduction

Two novel chromane derivatives, rhododaurichromanic acid A (**1**) and B (**2**), as well as the known chromene derivative, daurichromenic acid (**3**), have been isolated recently from the leaves and twigs of *Rhododendron dauricum* (Figure 1).[1] The isolation of daurichromenic acid (**3**) has also been reported previously by other researchers.[2] The molecular structure and absolute stereochemistry of rhododaurichromanic acid A (**1**) was established by X-ray crystallography. The molecular structure and absolute stereochemistry of rhododaurichromanic acid B (**2**) and daurichromenic acid (**3**) were established indirectly as daurichromenic acid **(3)** can be converted to rhododaurichromanic acid A (**1**) and B (**2**) by photochemical methods.[1] It was assumed that the trans C11−C12 double bond of daurichromenic acid (**3**) was isomerized to cis under the reaction conditions prior to the photochemical cyclization reaction that afforded rhododaurichromanic acid B (**2**).

Daurichromenic acid (**3**) was shown to have potent anti-HIV activity [EC_{50} = 0.00567 μg/mL, therapeutic index (TI) of 3,710]. Rhododaurichromanic acid A (**1**) also showed relatively potent anti-HIV activity [EC_{50} = 0.37 μg/mL, TI = 91.9], whereas rhododaurichromanic acid B (**2**) was inactive.[1] Recently, the total syntheses of methyl (±)-daurichromenic ester (**8**) as well as (±)-rhododaurichromanic acid A (**1**) and B (**2**) have been reported by Hsung and co-workers (Scheme 1).[3] Condensation and concomitant electrocyclization of *trans,trans*-farnesal (**4**) with the symmetrical 1,3-cyclohexanedione **5** on heating with piperidine and acetic anhydride afforded the 2*H*-pyran **6**. The latter compound was converted to the methyl ester **7**, which in turn was dehydrogenated with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to afford methyl (±)-daurichromenic ester (**8**). Unfortunately, these researchers were not able to identify suitable reaction conditions to effect the hydrolysis of methyl ester **8** in order to complete a total synthesis of (±)-daurichromenic acid (**3**). Subsequent photochemical cyclization and saponification of methyl (±)-daurichromenic ester (**8**) afforded a mixture of (±)-rhododaurichromanic acid A (**1**) and B (**2**).

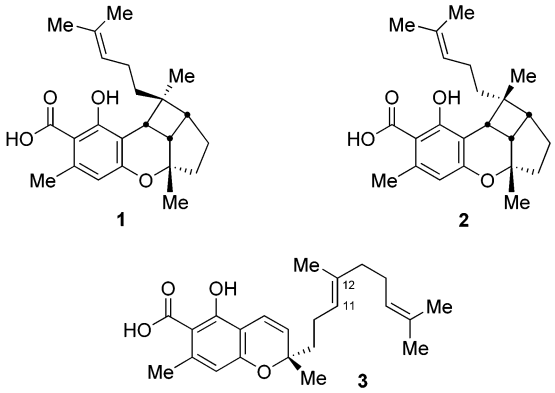


FIGURE 1. Molecular structures of rhododaurichromanic acid A (**1**), rhododaurichromanic acid B (**2**), and daurichromenic acid (**3**).

More recently, an efficient and concise total synthesis of (±)-daurichromenic acid (**3**) has been reported by Jin and co-workers (Scheme 2).[4] The β-trimethylsilyl ethyl ester **10**, which was elaborated in three steps from orcinol (**9**), was condensed with *trans,trans*-farnesal (**4**) on heating in a microwave oven. Subsequent deprotection of the product of this reaction, the ester **11**, afforded (±)-daurichromenic acid (**3**). The corresponding ethyl ester of compound **10** was also condensed with *trans,trans*-farnesal (**4**) under these reaction conditions (70% yield). However, the hydrolysis (3 M NaOH, MeOH, H_2O, 40 °C) of the product of this reaction was slow and afforded (±)-daurichromenic acid (**3**) in relatively low yield (40%). (±)-Daurichromenic acid (**3**) was also converted photochem-

(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.

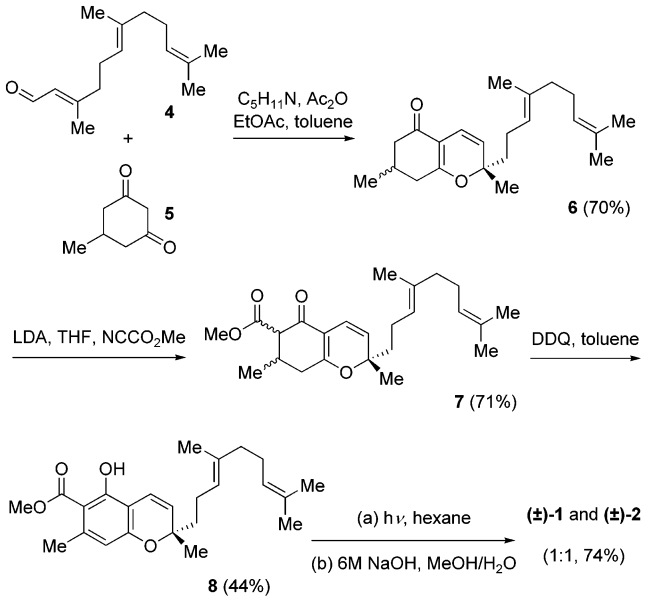
(2) Jpn. Kokai Tokkyo Koho, JP 82-28,080, 1982.

(3) Kurdyumov, A. V.; Hsung, R. P.; Ihlen, K.; Wang, J. *Org. Lett.* **2003**, *5*, 3935.

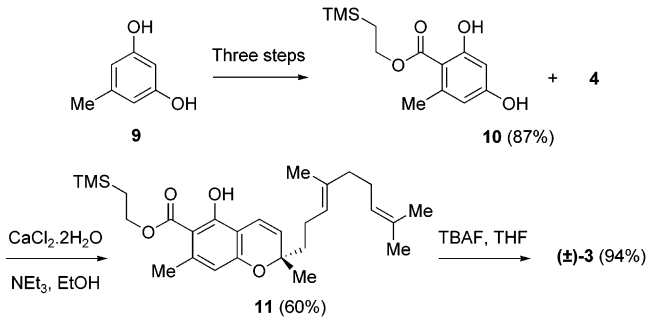
(4) Kang, Y.; Mei, Y.; Du, Y.; Jin, Z. *Org. Lett.* **2003**, *5*, 4481.

10.1021/jo049703f CCC: $27.50
Published on Web 04/24/2004

SCHEME 1. Synthesis of Methyl (±)-Daurichromenic Ester (8) and (±)-Rhododaurichromanic Acid A (1) and B (2) by Hsung et al.[3]



SCHEME 2. Synthesis of (±)-Daurichromenic Acid (3) by Jin et al.[4]



ically to (±)-rhododaurichromanic acid A (**1**) and B (**2**) (40 and 20% yield, respectively) by these researchers.

In this paper, we report a modular and concise total synthesis of (±)-daurichromenic acid (**3**) and a series of structural analogues. Our retrosynthetic analysis of the target compounds **12** is illustrated below (Figure 2). It was conceived independently that (±)-daurichromenic acid and a series of analogues **12** could be prepared from the 2*H*-pyrans **13** by a dehydrogenation (oxidation/aromatization) reaction and a subsequent ester hydrolysis reaction. The 2*H*-pyrans **13** could be prepared in a convergent manner from the *unsymmetrical* 1,3-cyclohexanediones **14** and a series of α,*β*-unsaturated aldehydes **15** employing a condensation and concomitant electrocyclization reaction.[5,6] The 1,3-cyclohexanedione precursors **14** would in turn be available from the alkyl acetoacetates **16** and a series of α,*β*-unsaturated esters **17** employing a conjugate addition and concomitant intramolecular condensation reaction.

Results and Discussion

Two 1,3-cyclohexanediones **18** and **19** were prepared in the first instance (Figure 3). The 1,3-cyclohexanedione **18** was prepared from ethyl acetoacetate and ethyl

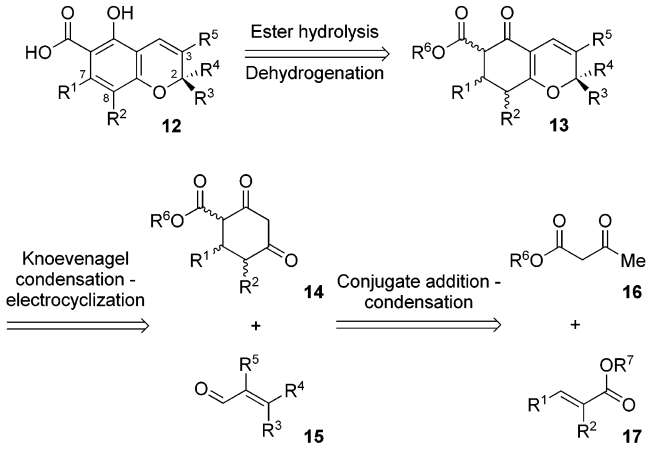


FIGURE 2. Retrosynthetic analysis of (±)-daurichromenic acid and analogues **12**.

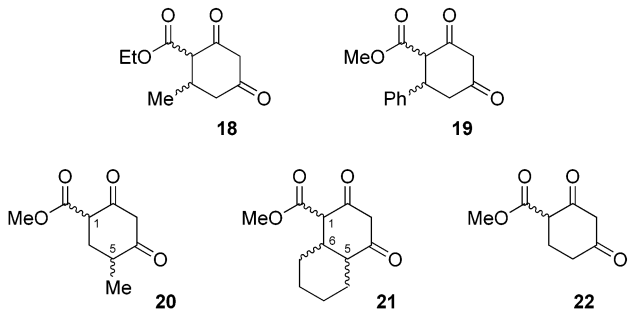


FIGURE 3. 1,3-Cyclohexanedione precursors **18**−**22**.

crotonate on reaction with sodium ethoxide in 81% yield.[7] The 1,3-cyclohexanedione **19** was prepared from methyl acetoacetate and methyl cinnamate on reaction with sodium methoxide in 61% yield.[7a,8] This demonstrated that a variety of substituents can potentially be introduced at C7 in the daurichromenic acid analogues. Unfortunately, it was not possible to prepare the C5-substituted, C5,C6-disubstituted, or the monosubstituted cyclohexanediones **20**−**22** from methyl acetoacetate and the corresponding commercially available α,*β*-unsaturated methyl esters by this direct one-pot procedure.

The α,*β*-unsaturated aldehydes selected for study included commercially available 3-methyl-2-butenal (senecialdehyde) (**23**), 3,7-dimethyl-2,6-octadienal (citral, *E*/*Z* = ∼2:1) (**24**), and cyclohexene-1-carboxaldehyde (**25**) (Figure 4). In addition, *trans*,*trans*-farnesal (**4**) was prepared from commercially available *trans*,*trans*-farne-

(5) The formation of 2*H*-pyrans from 1,3-dicarbonyl compounds and α,*β*-unsaturated aldehydes via the Knoevenagel condensation reaction is well established; see: (a) Tietze, L. F.; Beifuss, U. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Heathcock, C. H., Vol. Ed.; Pergamon Press: Oxford, 1992; Vol. 2, p 341. (b) Shen, H. C.; Wang, J.; Cole, K. P.; McLaughlin, M. J.; Morgan, C. D.; Douglas, C. J.; Hsung, R. P.; Coverdale, H. A.; Gerasyuto, A. I.; Hahn, J. M.; Liu, J.; Sklenicka, H. M.; Wei, L.-L.; Zehnder, L. R.; Zificsak, C. A. *J. Org. Chem*. **2003**, *68*, 1729 and references therein (see also ref 3).

(6) Recently, our research group has reported a related condensation reaction of a dibenzo-oxepinone with citral and senecialdehyde which was employed as a key step in the synthesis of the polycyclic ring systems of artocarpol A and D; see: Paduraru, M. P.; Wilson, P. D. *Org. Lett.* **2003**, *5*, 4911.

(7) (a) Gould, S. J.; Cheng, X.-C. *Tetrahedron* **1993**, *49*, 11135. (b) Gaucher, G. M.; Shepherd, M. G. *Biochem. Prepr.* **1971**, *13*, 70.

(8) Piskov, V. B.; Kasperovich, V. P. *J. Org. Chem. USSR* **1985**, *21*, 1088.

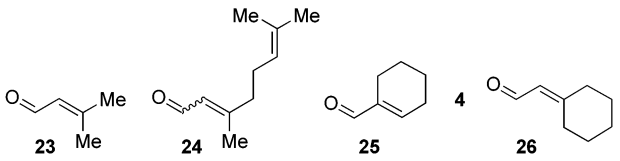
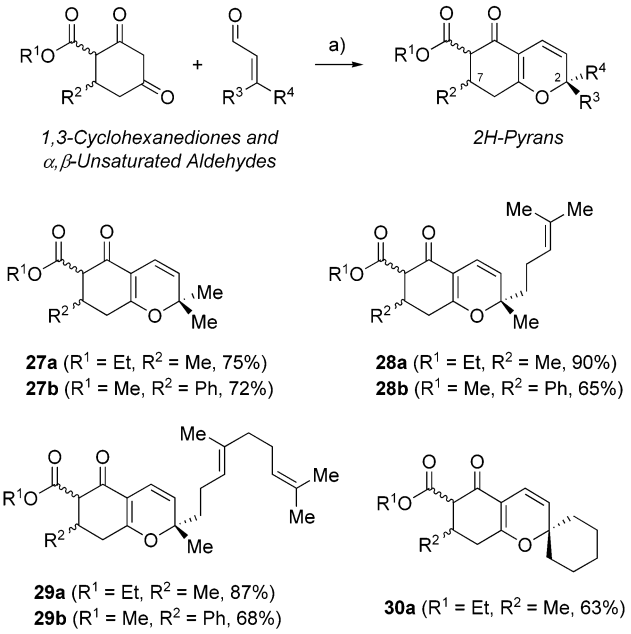


FIGURE 4. α,β-Unsaturated aldehyde precursors **23**−**25**, **4**, and **26**.

SCHEME 3. Knoevenagel Condensation−Electrocyclization Reaction Products 27a,b, 28a,b, 29a,b, and 30a[a]



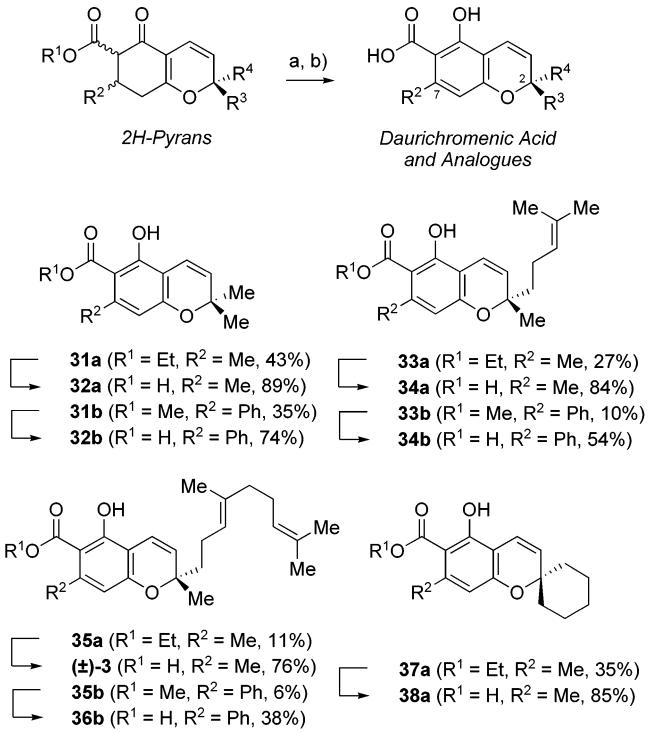
[a] Reagents and conditions: (a) 5 mol % $H_2NCH_2CH_2NH_2$, 10 mol % AcOH, MeOH, rt, 3−16 h.

sol on oxidation with pyridinium dichromate (buffered with sodium bicarbonate) in 96% yield.[3,4] Cyclohexylideneacetaldehyde (**26**) was also prepared in 39% overall yield from cyclohexanone on addition of vinylmagnesium bromide and subsequent oxidation of the resultant tertiary allylic alcohol with pyridinium chlorochromate.[9]

Condensation of 1,3-cyclohexanedione **18** in methanol with senecialdehyde (**23**), citral (**24**), *trans,trans*-farnesal (**4**), and cyclohexylideneacetaldehyde (**26**), at room temperature in the presence of 5 mol % of 1,2-ethylenediammonium diacetate for ∼3 h, afforded the expected substituted 2*H*-pyrans **27a**−**29a** and the spirocyclic 2*H*-pyran **30a** (Scheme 3).[10,11]

The tandem Knoevenagel condensation−electrocyclization reaction was also used to prepare three phenyl-substituted derivatives **27b**−**29b** from 1,3-cyclohexanedione **19** and senecialdehyde (**23**), citral (**24**), and *trans, trans*-farnesal (**4**) (at room temperature for ∼16 h). All of the 2*H*-pyran derivatives were isolated as inseparable

SCHEME 4. Total Synthesis of (±)-Daurichromenic Acid (3) and Analogues, 32a,b, 34a,b, 36b, and 38a[a]



[a] Reagents and conditions: (a) DDQ, benzene, reflux, 4−16 h; (b) 5 M NaOH (aq), DMSO, 80 °C, ∼16 h.

mixtures of diastereoisomers in good to excellent yield (63−90%). The 2*H*-pyran **29a**, which is a precursor of (±)-daurichromenic acid (**3**), was isolated in 87% yield. This series of efficient reactions demonstrated that a variety of substituents can be introduced at C2 and C7 in the daurichromenic acid analogues. However, the condensation reaction of 1,3-cyclohexanedione **18** with cyclohexene-1-carboxaldehyde **25**, under these reaction conditions, afforded a complex mixture of products from which it was not possible to isolate the corresponding tricyclic (C2,C3-disubstituted) analogue.

A broad spectrum of reagents and reaction conditions were screened in order to effect the dehydrogenation reaction of the products of the latter reactions (the 2*H*-pyrans **27a**,**b**, **28a**,**b**, **29a**,**b**, and **30a**).[12,13] It was found independently that heating these esters with DDQ at reflux in benzene for 4−16 h afforded the desired aromatized reaction products in low to moderate yield (6−43%) (Scheme 4). However, these reactions can be performed on a relatively large scale, and significant quantities of the desired analytically pure reaction

(9) (a) Mason, T. L.; Harrison, M. J.; Hall, J. A.; Sargent, G. D. *J. Am. Chem. Soc.* **1973**, *95*, 1849. (b) Dauben W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682.

(10) Tietze, L. F.; von Kiedrowski, G.; Berger, B. *Synthesis* **1982**, 683.

(11) The ^{1}H NMR spectrum (see the Supporting Information) of the *trans,trans*-farnesal-derived 2*H*-pyran **29a** was very similar to the related compound **7** (see Scheme 1) prepared by Hsung and co-workers; see ref 3 (Supporting Information).

(12) Various dehydrogenation reaction conditions (employing for example: Pd/C, chloranil, NCS, NBS, TEMPO, Br_2, *o*-iodoxybenzoic acid, $Pd(OAc)_2$, $CuCl_2$, MnO_2, SeO_2, ceric ammonium nitrate, peroxides, molecular oxygen, and vitamin B_2 as reagents) either proved to be unreactive, caused extensive decomposition of the starting materials, or resulted in isolation of the desired reaction products in low yield. Similarly, attempted oxidation of the corresponding silyl enol ether derivatives of these substrates was low yielding.

(13) Tietze has commented that related 2*H*-pyrans that have substituents incorporating carbon−carbon double bonds are difficult to dehydrogenate selectively. He developed a two-step procedure to effect this transformation (LDA, THF, then PhSeCl; *m*-CPBA then 3,5-dimethoxyaniline; see ref 10). In this instance, these reaction conditions proved to be less than satisfactory.

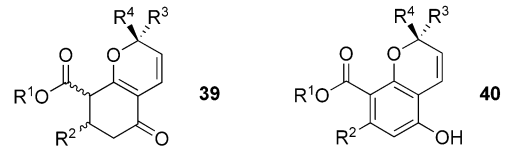


FIGURE 5. Regioisomeric Knoevenagel condensation−electrocyclization reaction products **39** and dehydrogenation products **40**.

products **31a**,**b**, **33a**,**b**, **35a**,**b**, and **37a** were isolated chromatographically. The aromatic ethyl ester **35a**, which is the direct precursor of (±)-daurichromenic acid (**3**), was isolated in 11% yield.[14,15] Following considerable experimentation, it was found that all of these aromatic *o*-hydroxy esters could be saponified with an aqueous 5 M solution of sodium hydroxide (∼10 equiv) in dimethyl sulfoxide (DMSO) on heating at 80 °C for ∼16 h.[16]

The latter procedure afforded significant quantities of the desired target compounds, (±)-daurichromenic acid (**3**) and the analogues **32a**,**b**, **34a**,**b**, **36b**, and **38a**, in moderate to high yield (38−89%). The saponification reactions of the methyl and ethyl esters of (±)-daurichromenic acid have been reported to be problematic (due to a facile decarboxylation reaction of the product).[3,4] In this instance, (±)-daurichromenic acid (**3**) was isolated in good yield (76%). The spectroscopic data for (±)-daurichromenic acid (**3**) were in full agreement with those reported for the natural product.[1] Of note and in regard to the regioselectivity of the Knoevenagel condensation−electrocyclization reaction, we have not isolated nor do we have any spectroscopic data of crude reaction products to indicate that the regioisomeric products **39** were formed (Figure 5). Similarly, the regioisomeric dehydrogenation products **40** were not isolated from any of the reactions.

Conclusion

A modular and concise total synthesis of (±)-daurichromenic acid **3** has been accomplished in four steps from *trans*,*trans*-farnesal (**4**) and readily available starting materials (ethyl acetoacetate and ethyl crotonate). The synthetic route was adapted to prepare a series of daurichromenic acid analogues in which a variety of substituents were introduced at C2 and C7. Although the overall yield of the route is relatively low (in the case of derivatives that have substituents that incorporate carbon−carbon double bonds), significant quantities of analytically pure materials have been prepared for subsequent biological evaluation. The results of these investigations will be reported in due course. It is hoped that these studies will provide insight into the structure−activity relationships of this potent anti-HIV lead compound. Further synthetic studies are in progress to improve the yield of the dehydrogenation step and additional structural analogues are being prepared by this method. In addition, the synthetic route is being adapted for use in polymer-supported synthesis and alternative modular and concise syntheses of daurichromenic acid analogues are under active investigation.

Experimental Section

2,7-Dimethyl-2-(4,8-dimethyl-3*E*,7-nonadienyl)-5-oxo-5,6,7,8-tetrahydro-2*H*-chromene-6-carboxylic Acid Ethyl Ester (29a). Representative Procedure for the Formation of 2*H*-Pyrans (27a,b, 28a,b, 29b, and 30a). To a mixture of 1,2-ethylenediamine (20 μL, 0.30 mmol) and acetic acid (34 μL, 0.59 mmol) in dry methanol (10 mL) was added the ester **18** (1.16 g, 5.83 mmol) at room temperature. After 30 min, *trans*,*trans*-farnesal (**4**) (1.17 g, 5.30 mmol) was added. After 3 h, the solvent was removed in vacuo, and the yellow residue was dissolved in ethyl acetate (20 mL) and washed with water (2 × 10 mL), a saturated aqueous solution of sodium bicarbonate (2 × 10 mL), and then brine (10 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo, and the resultant residue was purified by flash chromatography using ethyl acetate/hexanes (4%) as the eluant to afford the *title compound* **29a** (1.85 g, 87%) as a pale yellow oil: ^{1}H NMR (400 MHz, C_6D_6) δ 0.72 (d, J = 6.4 Hz, 3H), 1.02 (t, J = 7.1 Hz, 3H), 1.10 (s, 3H), 1.57 (apparent s, 6H), 1.63 (m, 2H), 1.67 (s, 3H), 2.02 (m, 2H), 2.08 (m, 4H), 2.17 (m, 2H), 2.38 (m, 1H), 2.88 (d, J = 11.6 Hz, 1H), 4.09 (m, 2H), 4.80 (d, J = 10.1 Hz, 1H), 5.20 (m, 2H), 6.73 (d, J = 10.1 Hz, 1H); ^{13}C NMR (101 MHz, C_6D_6) δ (mixture of isomers, major signals reported) 14.3, 16.0, 17.7, 19.5, 22.7, 23.0, 27.1, 30.8, 35.2, 40.1, 60.6, 60.8, 82.4, 82.5, 109.6, 109.7, 117.0, 117.1, 124.07, 124.11, 124.7, 124.8, 131.31, 131.34, 135.7, 169.8, 170.0, 170.08, 170.13, 188.9, 190.0; IR (ef) 2967, 1739, 1655, 1597, 1415, 1326, 1254, 1157 cm^{-1}; MS (CI) *m*/*z* (rel intensity) 401 (M + H, 100); FAB HRMS calcd for $C_{25}H_{36}O_4$ *m*/*z* 400.2614, found *m*/*z* 400.2611.

5-Hydroxy-2,7-dimethyl-2-(4,8-dimethyl-3*E*,7-nonadienyl)-2*H*-chromene-6-carboxylic Acid Ethyl Ester (35a). Representative Procedure for the Formation of Esters (31a,b, 33a,b, 35b, and 37a). To a solution of the ester **29a** (580.0 mg, 1.46 mmol) in benzene (16 mL) was added DDQ (497.2 mg, 2.20 mmol) at room temperature. The reaction mixture was then heated at reflux for 16 h. On cooling, the resultant mixture was filtered through a pad of basic alumina with ethyl acetate (160 mL). The solvent was removed in vacuo, and the dark red residue was purified by flash chromatography using ethyl acetate/hexanes (2%) as the eluant to afford the *title compound* **35a** (63.4 mg, 11%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 3H), 1.40 (t, J = 7.1 Hz, 3H), 1.56 (s, 3H), 1.59 (s, 3H), 1.67 (s, 3H), 1.65−1.75 (m, 2H), 1.95 (m, 2H), 2.03 (m, 2H), 2.09 (m, 2H), 2.47 (s, 3H), 4.38 (q, J = 7.1 Hz, 2H), 5.09 (m, 2H), 5.47 (d, J = 10.1 Hz, 1H), 6.18 (s, 1H), 6.73 (d, J = 10.1 Hz, 1H), 12.07 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.4, 16.1, 17.8, 22.7, 24.7, 25.8, 26.8, 27.1, 39.8, 41.7, 61.3, 79.8, 105.2, 107.2, 111.8, 117.0, 123.9, 124.5, 126.4, 131.5, 135.6, 142.9, 157.9, 159.9, 172.1; IR (ef) 3316, 2971, 1650, 1566, 1453, 1377, 1270, 1174 cm^{-1}; MS (CI) *m*/*z* 399 (M + H, 100), 353 (38), 249 (14), 209 (5). Anal. Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 75.16; H, 8.61.

(±)-Daurichromenic Acid (3). Representative Procedure for the Formation of Daurichromenic Acid Analogues (32a,b, 34a,b, 36b, and 38a). To a solution of the ester **35a** (200.0 mg, 0.503 mmol) in DMSO (3 mL) was added an aqueous solution of sodium hydroxide (20% w/v, 1.0 mL, 5.0 mmol) at room temperature. The reaction was then heated at 80 °C for 16 h. On cooling, water (2 mL) was added, and the resultant solution was washed with ether (5 mL). The aqueous

(14) Hsung and co-workers have reported that the 2*H*-pyran methyl ester **7** can be dehydrogenated with DDQ on heating at reflux in toluene (see Scheme 1). In our hands, these reaction conditions caused extensive decomposition of the corresponding 2*H*-pyran ethyl ester **29a** and only a trace amount of the desired aromatic ethyl ester **35a** was isolated; see ref 3.

(15) The aromatic ethyl ester **35a** has been prepared previously by Jin and co-workers. Our NMR data (see the Supporting Information) was completely consistent with the data reported for this compound; see ref 4 (Supporting Information).

(16) Elix, J. A.; Whitton, A. A. *Aust. J. Chem.* **1989**, *42*, 1969.

layer was acidified with hydrochloric acid (6 M) to pH ~2 and extracted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with water (2 × 5 mL) and brine (10 mL), dried over anhydrous sodium sulfate, and concentrated in vacuo. The dark brown crude product was then purified by flash chromatography using methanol/dichloromethane (3%) as the eluant to afford the *title compound* **(±)-3** (140.4 mg, 76%) as a light brown syrup: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 3H), 1.57 (s, 3H), 1.59 (s, 3H), 1.67 (s, 3H), 1.66−1.77 (m, 2H), 1.95 (m, 2H), 1.97 (m, 2H), 2.04−2.12 (m, 2H), 2.54 (s, 3H), 5.09 (m, 2H), 5.48 (d, J = 10.1 Hz, 1H), 6.24 (s, 1H), 6.74 (d, J = 10.1 Hz, 1H), 11.66 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 16.1, 17.8, 22.7, 24.6, 25.8, 26.8, 27.3, 39.8, 41.8, 80.3, 103.7, 107.2, 112.4, 116.8, 123.9, 124.5, 126.5, 131.5, 135.7, 144.7, 159.2, 160.8, 176.4; IR (ef) 2966, 1621, 1455, 1268, 1177 cm^{-1}; MS (CI) m/z 327 (M + H, − CO_2, 100), 175 (9). Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.30; H, 8.18.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada (NSERC) and Simon Fraser University (SFU) for financial support. We also wish to acknowledge the Canadian Foundation for Innovation (CFI) for support of our research program. H.H. thanks SFU for graduate research fellowships. T.J.H. thanks NSERC for an undergraduate summer research award (USRA). We are also grateful to Professor Y. Kashiwada for kindly providing copies of the ^{1}H and ^{13}C NMR spectra of daurichromenic acid **3** as well as a sample of the natural product for comparison purposes.

Supporting Information Available: Detailed experimental procedures and complete product characterization data for all of the additional compounds synthesized as well as ^{1}H and ^{13}C NMR spectra for compounds **(±)-3**, **27a**,**b**, **28a**,**b**, **29a**,**b**, **30a**, **32a**,**b**, **34a**,**b**, **35a**, **36b**, and **38a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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