Synthesis G.-Y. Luo et al. Special Topic

A Total Synthesis of (±)-Rhododaurichromanic Acid A via an Oxa-[3+3] Annulation of Resorcinols

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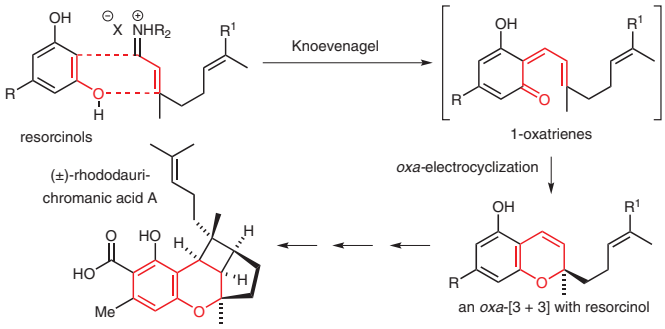

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Abstract Development of an oxa-[3+3] annulation of vinyliminium salts with resorcinols as a 1,3-diketo equivalent is described. This annulation constitutes a cascade of Knoevenagel condensation–oxa-electrocyclization leading to a direct access to chromenes. A series of attempts was made to demonstrate its synthetic utility in natural product synthesis, culminating in a total synthesis of (±)-rhododaurichromanic acid A that also featured an intramolecular Gassman-type cationic [2+2] cycloaddition.

Key words oxa-[3+3] annulation, resorcinol, bioinspired total synthesis, (±)-daurichromenic acid, (±)-rhododaurichromanic acid A

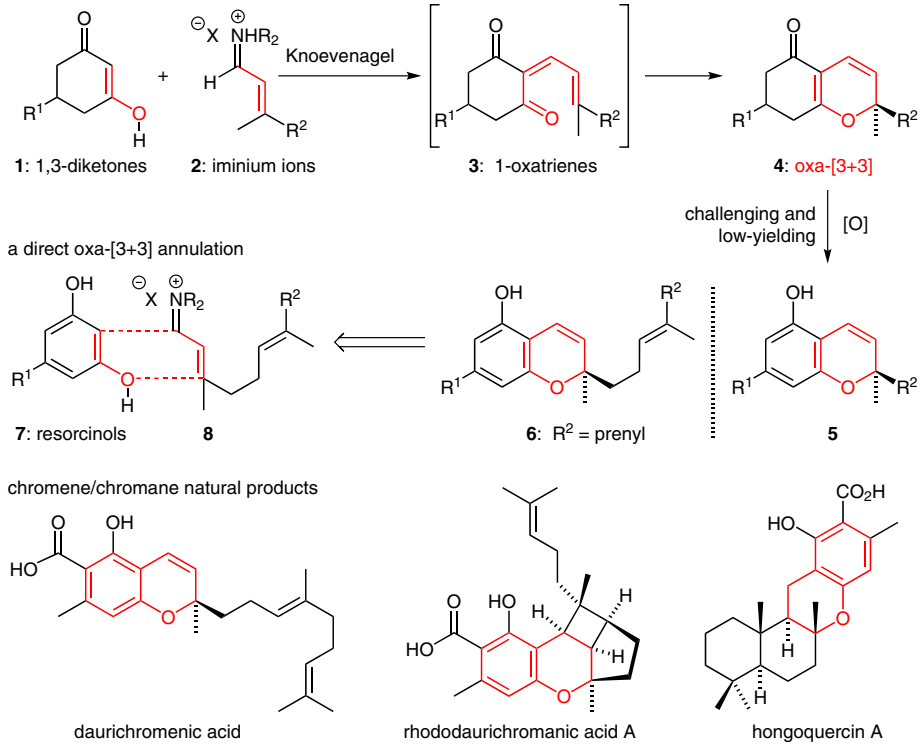
One of our longstanding research programs has been the development of an oxa-[3 + 3] annulation strategy and its applications.[1–4] In particular, annulations of cyclic 1,3-diketones with vinyliminium salts would lead to a facile construction of 1-oxadecalins[5] via a sequence of Knoevenagel condensation–oxa-electrocyclization (**1** + **2** → **3** → **4** in Scheme 1). This tandem sequence constitutes a powerful cascade[6] and represents a bioinspired approach[7,8] for natural product synthesis. While we recognized that an oxidative aromatization of **4**[9,10] would provide an entry into chromenes **5**,[11] a far more direct and attractive approach would be to employ resorcinols **7** in such annulation (**7** + **8** → **6**).

In addition, oxidative aromatization of **4** using reagents such as DDQ proved to be a low-yielding process.[9,10] While elegant reports by Jin[12] and later also by Lee,[13] Argade,[14a] and Zeng[14b] represent excellent precedents using resorcinols in related oxa-annulations, we were able to succeed such transformation only recently.[15] We wish to report here details of our studies and a concise total synthesis of (±)-rhododaurichromanic acid A.

We commenced our study by repeating the reaction that failed more than a decade earlier. Adding resorcinol **9** to a solution of the vinyliminium salt generated in situ from citral (**10**) using 2.0 equivalents of piperidine and 2.0 equivalents of Ac_2O followed by heating the mixture at 130 °C for 24 hours led to the desired chromene **11** in 75% isolated yield (Table 1, entry 1). This success is in direct contrast to our earlier efforts that somehow had focused on the use of supposedly more reactive amine salts such as L-proline,[16] piperidinium acetate,[17] piperidinium trifluoroacetate,[10c,18] and ethylenediamine diacetate[13] that had proven to be more successful and operatively versatile in these annulations. Instead, our very original reaction conditions[19] proved to be the most effective for this chromene construction as evident with other examples showcased in Table 1 including one-step syntheses of confluentin **17** (entry 4) and cannabichromeme **19**[20] from olivetol **18** (entry 5).

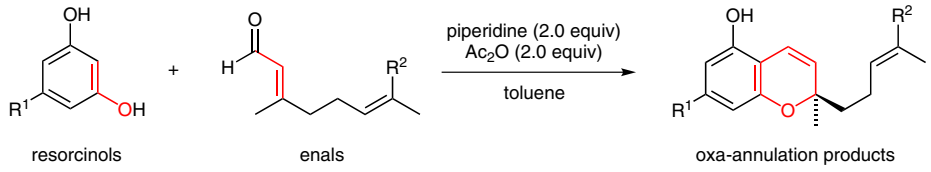
Armed with this success, we embarked on efforts that could lead to facile total syntheses of chromene natural products. As shown in Scheme 2, annulation of 6-hydroxyindole with citral (**10**) under the same reactions conditions leads to **20** in 30% yield. Although the yield is low, it demonstrates the feasibility of using 1,3-aminohydroxybenzene (masked here as indole) as a resorcinol equivalent for such annulation, and that it constitutes a potential facile approach toward (±)-murrayamine M.[21]

We next turned to the annulation of 5,7-dihydroxycoumarin (**21**), which could be prepared from a $ZnCl_2$-promoted oxa-[3+3] annulation[22] of phloglucinol (**12**) with ethyl propiolate.[23,24] Success here would lead to a facile total synthesis of eriobrucinol.[25,26] Instead, annulation of **21** with citral (**10**) afforded a complex mixture of double annulated



Scheme 1 A direct approach to chromenes and chromanes

Table 1 Oxa-[3+3] Annulation of Resorcinols



Entry	Resorcinol	R^1	Enal	R^2	Temp (°C)	Time (h)	Product	Yield (%)[a]
1	**9**	Me	**10**	Me[b]	130	24	**11**	75
2	**12**	OH[c]	**10**	Me[b]	90	18	**13**	93
3	**14**	H	**15**	prenyl[d]	120	24	**16**	48
4	**9**	Me	**15**	prenyl[d]	120	24	**17**[e]	72
5	**18**	*n*-C_5H_{11}[f]	**10**	Me[b]	130	40	**19**[g]	50

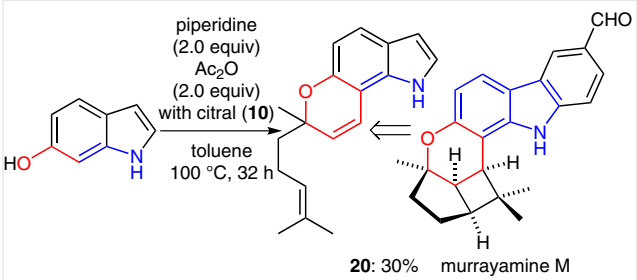
[a] All are isolated yields.
[b] **10**: citral.
[c] **12**: phologlucinol.
[d] **15**: *trans*,*trans*-farnesal.
[e] **17**: confluentin.
[f] **18**: olivetol.
[g] **19**: cannabichromeme.

product **22** as well as a mixture of single annulation products that we had hoped would include the desired tricycle **25**. However, upon treatment of this mixture with TFA at –30 °C for the ensuing intramolecular Gassman-type cationic [2+2] cycloaddition that was developed in our lab,[15,27,28] we managed to find only a mixture of iso-eriobrucinol A and B in 26% combined yield, and not eriobrucinol, thereby validating the presence of single annulation products **23** and **24** but not **25** (Scheme 3). A much more successful exercise is shown in a synthesis of (±)-daurichrome-

nic acid[29] from confluentin (**17**) via a short two-step sequence (Scheme 4): A regioselective formylation of **17**, which would give aldehyde **26**, and a subsequent standard Lindgren–Pinnick oxidation of **26**.

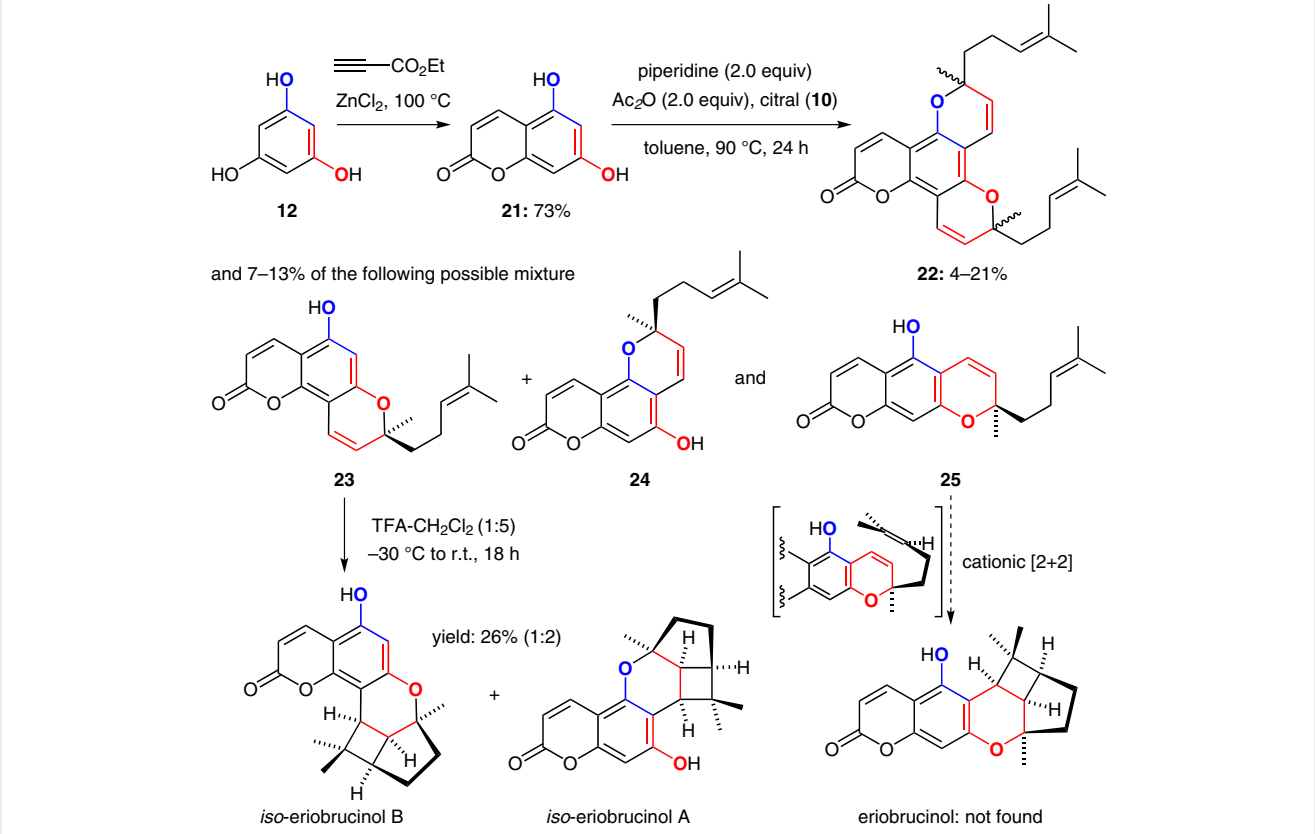
To ultimately demonstrate the power of this resorcinol oxa-[3+3] annulation, we put together a concise total synthesis of (±)-rhododaurichromanic acid A.[30,31] As shown in Scheme 5, under our cationic [2+2]-cycloaddition conditions, chromenes **26** and **17** underwent two completely different reaction pathways. Intriguingly, the former led to only the tetracyclic manifold **27** via a polyene cyclization process[32] with no observable cationic [2+2] cycloadduct **28**, while the latter gave only the cationic [2+2] cycloadduct **30**.

With the only difference between **26** and **17** being the formyl substitution, this unexpected diverging course actually sheds light on the mechanism of the cationic [2+2] cycloaddition. The formyl substitution in **26** renders the chromene oxygen atom (in blue) less Lewis basic than the corresponding oxygen atom (also in blue) in **17**. Consequently, protonation of this oxygen atom in **26** is likely slower than that in **17**, and that a slower protonation would allow the polyene-cyclization pathway to proceed more favorably as shown in **27**-TS. This outcome would then suggest that protonation of the chromene oxygen atom is essential for initiating the cationic [2+2] cycloaddition pathway as shown in **30**-TS because of the allyl cation formation needed for such cycloaddition.

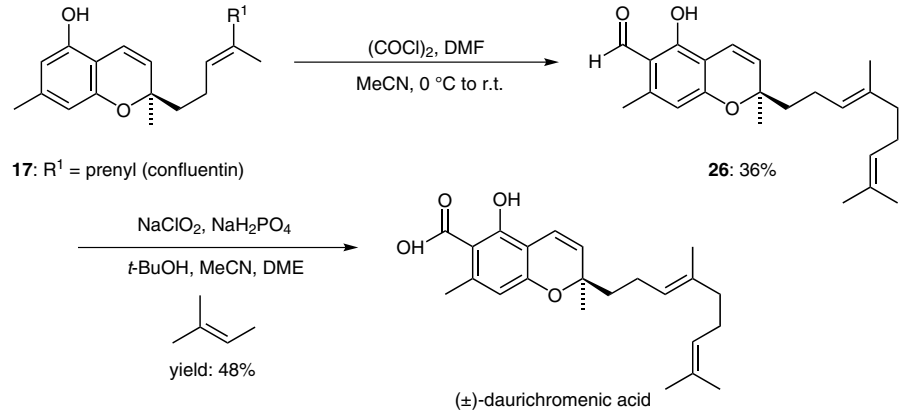


Scheme 2 A possible approach to (±)-murrayamine M

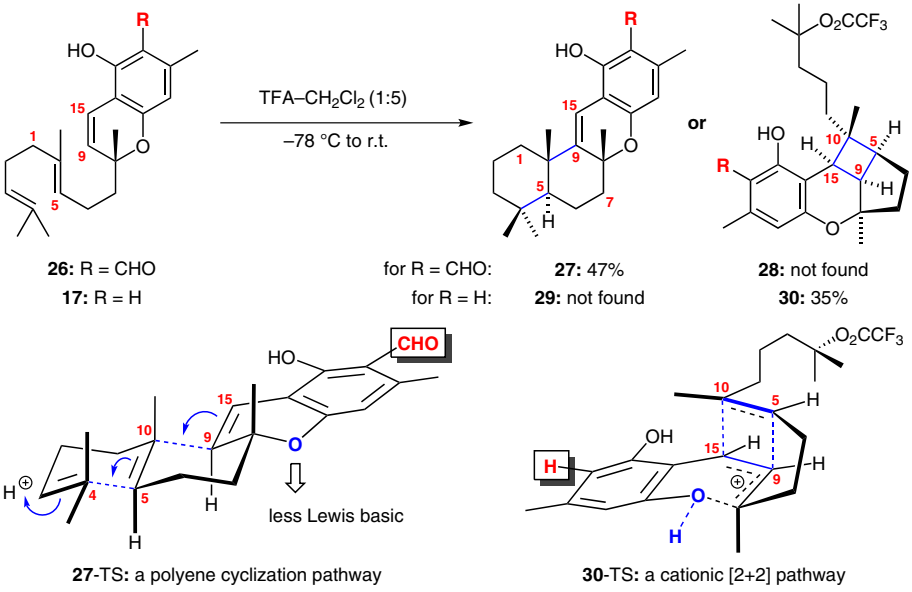
While tetracycle **27** should be very useful for a total synthesis (±)-hongoquercin A,[32–34] we focused on completing the synthesis of (±)-rhododaurichromanic acid A. As shown in Scheme 6, the use of $Fe(OTf)_3$ was even more useful for the cationic [2+2] cycloaddition,[28] as it does not suffer from the addition of TFA to the terminal prenyl double bond (see **30** in Scheme 5). Subsequent formylation of **31** and Lindgren–Pinnick oxidation would furnish (±)-rhododaurichromanic acid A.



Scheme 3 An attempt to synthesize (±)-eriobrucinol



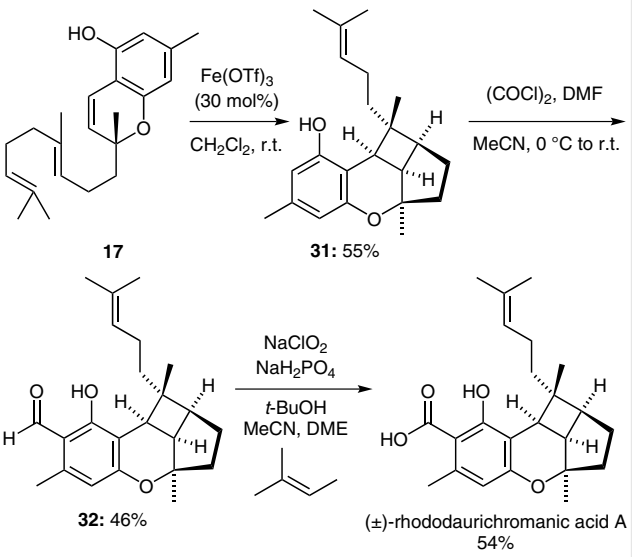
Scheme 4 Synthesis of (±)-daurichromenic acid



Scheme 5 A substrate dependent diverging cationic pathway

We have described here our efforts in developing an oxa-[3+3] annulation of vinyliminium salts with resorcinols as a 1,3-diketo equivalent. This annulation constitutes a powerful cascade of Knoevenagel condensation–oxa-electrocyclization to directly access chromenes. A series of attempts was made to demonstrate the synthetic utility of this new annulation in natural product synthesis. An ultimate total synthesis of (±)-rhododaurichromanic acid A was achieved and featured an intramolecular Gassman-type cationic [2+2] cycloaddition.

All reactions were performed in flame-dried glassware under N_2 atmosphere. Solvents were distilled prior to use. Reagents were used as purchased from J & K, Beijing Ouhe, Aldrich, Acros, Alfa Aesar, or TCI, unless otherwise noted. Petroleum ether (PE) used refers to the hydrocarbon mixture with a boiling range of 60–90 °C. Chromatographic separations were performed using Kangbino 48–75 Å SiO_2. ^1H and ^{13}C NMR spectra were recorded on 600 MHz Bruker Avance spectrometers using $CDCl_3$ with TMS or residual solvent as standard, unless otherwise noted. Melting points were determined using a Laboratory Devices MEL-TEMP and are uncorrected/calibrated. IR spectra were recorded on a Bruker TENSOR 27 spectrometer. TLC analysis was performed using Kangbino glass-backed plates (60 Å, 250 μm) and visu-



Scheme 6 A total synthesis of (±)-rhododaurichromanic acid A

alized using UV and $KMnO_4$ stains. Low-resolution mass spectra were obtained using an Agilent 1100 series LS/MSD. High-resolution mass spectra were obtained using a Q-TOF micro (Bruker) spectrometer.

Oxa-[3+3] Annulation; Typical Procedure

To a solution of citral (**10**; 1.70 mL, 10.0 mmol) and piperidine (2.17 mL, 22.0 mmol) in EtOAc (18 mL) was added Ac_2O (2.17 mL, 23.0 mmol) dropwise at 0 °C under a blanket of argon. After addition, the flask was sealed and the reaction mixture was heated in a 90 °C oil bath for 1 h. This iminium salt solution was then added to a solution of phloroglucinol (**12**; 1.89 g, 15.0 mmol) in toluene (41 mL) dropwise via cannula at r.t. under argon. The resulting mixture was stirred at 90 °C for 18 h before it was cooled to r.t. and concentrated under reduced pressure. The crude residue was purified using silica gel flash column chromatography (gradient eluent: 10–20% EtOAc in PE) to give chromene **13** (2.38 g, 93%) as a brown oil; yield: 2.38 g (93%); R_f = 0.50 (hexanes–EtOAc, 2:1) (Table 1).

IR (thin film): 3414br s, 2960w, 2918w, 2855w, 1621m, 1580m, 1429m, 1370w, 1343w, 1141m, 1082m, 1048w, 831w cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.37 (s, 3 H), 1.58 (s, 3 H), 1.66 (s, 3 H), 1.54–1.78 (m, 2 H), 2.02–2.16 (m, 2 H), 4.90 (br s, 2 H), 5.09 (t quint, *J* = 7.2, 1.4 Hz, 1 H), 5.41 (d, *J* = 10.1 Hz, 1 H), 5.83 (d, *J* = 2.4 Hz, 1 H), 5.92 (d, *J* = 2.3 Hz, 1 H), 6.55 (d, *J* = 10.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.9, 25.9, 26.5, 41.2, 79.0, 95.6, 97.0, 103.4, 116.7, 124.3, 125.6, 131.9, 152.4, 155.6, 156.7.

MS (APCI): *m*/*z* (%) = 261.2 [100, $(M + H)^+$].

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{21}O_3$: 261.1485; found 261.1491.

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Yield: 390 mg (75%); brown oil; R_f = 0.51 (PE–EtOAc, 9:1).

IR (KBr): 3419br s, 2969m, 2923s, 1625s, 1579w, 1451s, 1142m, 1084s, 1058s, 990w cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.37 (s, 3 H), 1.57 (s, 3 H), 1.65 (s, 3 H), 1.67–1.78 (m, 2 H), 2.06–2.14 (m, 2 H), 2.18 (s, 3 H), 5.06–5.10 (m, 1 H), 5.14 (br s, 1 H), 5.47 (d, *J* = 9.9 Hz, 1 H), 6.09 (s, 1 H), 6.24 (s, 1 H), 6.61 (d, *J* = 9.9 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 17.7, 21.5, 22.8, 25.7, 26.2, 41.0, 78.3, 106.9, 108.5, 109.8, 116.9, 124.2, 127.2, 131.7, 139.6, 151.1, 154.0.

MS (APCI): *m*/*z* (%) = 281.1 [100, $(M + Na)^+$].

HRMS (ESI): *m*/*z* $(M - H)^-$ calcd for $C_{17}H_{21}O_2^-$: 257.1542; found: 257.1545.

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Yield: 280 mg (48%); yellow oil; R_f = 0.47 (PE–EtOAc, 9:1).

IR (KBr): 3408brs, 2968s, 2923s, 1618s, 1581w, 1505m, 1460m, 1377w, 1153s, 1117s, 988w cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.37 (s, 3 H), 1.57 (s, 3 H), 1.59 (s, 3 H), 1.67 (s, 3 H), 1.94–1.97 (m, 2 H), 2.04–2.08 (m, 3 H), 2.08–2.15 (m, 3 H), 5.08–5.11 (m, 3 H), 5.41 (d, *J* = 9.8 Hz, 1 H), 6.29 (s, 3 H), 6.80 (d, *J* = 7.7 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 16.0, 17.7, 22.6, 25.7, 26.7, 39.7, 41.3, 78.8, 103.5, 107.4, 107.5, 114.7, 116.8, 122.4, 124.0, 124.3, 127.2, 131.4, 135.3, 154.6, 156.5.

MS (APCI): *m*/*z* (%) = 335.2 [100, $(M + Na)^+$].

HRMS (ESI): *m*/*z* $(M + Na)^+$ calcd for $C_{21}H_{28}O_2Na^+$: 335.1987; found: 335.1994.

Confluentin (17)

Yield: 370 mg (72%); brown oil; R_f = 0.45 (PE–EtOAc, 9:1).

IR (KBr): 3410brs, 2968s, 2924s, 1626s, 1579s, 1451s, 1376m, 1142m, 1075s, 991w cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.37 (s, 3 H), 1.57 (s, 3 H), 1.59 (s, 3 H), 1.67 (s, 3 H), 1.70–1.78 (m, 2 H), 1.93–1.97 (m, 2 H), 2.02–2.06 (m, 2 H), 2.07–2.13 (m, 2 H), 2.19 (s, 3 H), 4.81 (br s, 1 H), 5.06–5.12 (m, 2 H), 5.49 (d, *J* = 10.0 Hz, 1 H), 6.10 (s, 1 H), 6.24 (s, 1 H), 6.61 (d, *J* = 10.1 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 16.0, 17.7, 21.5, 22.7, 25.7, 26.3, 26.7, 39.7, 41.1, 78.3, 106.9, 108.4, 109.8, 116.9, 124.1, 124.4, 127.1, 131.3, 135.3, 139.5, 151.2, 154.1.

MS (APCI): *m*/*z* (%) = 348.9 [100, $(M + Na)^+$].

HRMS (ESI): *m*/*z* $(M - H)^-$ calcd for $C_{22}H_{29}O_2^-$: 325.2162; found: 325.2155.

Cannabichromene (19)[20a]

Yield: 260 mg (50%); brown oil; R_f = 0.75 (hexanes–EtOAc, 4:1).

IR (thin film): 3416brs, 2963s, 2928w, 2859w, 1624s, 1576s, 1431m, 1377m, 1343w, 1144w, 1084m, 1053w, 833w cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.0 Hz, 3 H), 1.20–1.36 (m, 4 H), 1.38 (s, 3 H), 1.48–1.62 (m, 2 H), 1.57 (s, 3 H), 1.62–1.83 (m, 2 H), 1.65 (s, 3 H), 2.00–2.21 (m, 2 H), 2.43 (t, *J* = 7.6 Hz, 2 H), 4.79 (br s, 1 H), 5.00–5.18 (m, 1 H), 5.49 (d, *J* = 10.0 Hz, 1 H), 6.11 (d, *J* = 1.0 Hz, 1 H), 6.25 (s, 1 H), 6.61 (d, *J* = 10.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 17.7, 22.7, 22.8, 25.8, 26.4, 30.8, 31.6, 36.0, 41.2, 78.3, 107.1, 107.8, 109.3, 116.9, 124.3, 127.4, 131.8, 144.9, 151.1, 154.2.

MS (APCI): *m*/*z* (%) = 315.3 [100, $(M + H)^+$].

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{31}O_2$: 315.2319; found: 315.2320.

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Yield: 12 mg (30%); yellow oil; R_f = 0.43 (PE–EtOAc, 9:1).

IR (KBr): 3422brs, 2967s, 2923s, 1641s, 1436s, 1376m, 1173w, 803s, 717s cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.42 (s, 3 H), 1.57 (s, 3 H), 1.65 (s, 3 H), 1.71–1.76 (m, 2 H), 2.10–2.18 (m, 2 H), 5.08–5.10 (m, 1 H), 5.62 (d, *J* = 9.8 Hz, 1 H), 6.46 (s, 1 H), 6.59 (d, *J* = 9.7 Hz, 1 H), 6.67 (d, *J* = 8.3 Hz, 1 H), 7.08 (s, 1 H), 7.36 (d, *J* = 8.3 Hz, 1 H), 8.00 (br s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 16.6, 21.7, 24.6, 24.7, 39.5, 76.9, 102.1, 103.7, 109.8, 116.3, 119.7, 121.4, 121.8, 123.2, 127.6, 130.6, 131.3, 147.9.

MS (APCI): *m*/*z* (%) = 268.2 [100, $(M + Na)^+$].

HRMS (ESI): *m*/*z* $(M + H)^+$ calcd for $C_{18}H_{22}NO^+$: 268.1701; found: 268.1701.

Aldehyde 26

To a solution of DMF (1.0 mL, 5.0 mmol) in MeCN (5 mL) was added oxalyl chloride (0.50 mL, 4.5 mmol) under a blanket of N_2 at 0 °C. The resulting mixture was stirred for an additional 30 min at 0 °C. A solution of **17** in MeCN (0.50 mL) was then added dropwise a 0 °C. After stirring overnight at r.t., the reaction mixture was quenched with 10% aq NaOH (30 mL) and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 1% EtOAc in PE) to provide the aldehyde **26** as a yellow oil; yield: 35 mg (36%); R_f = 0.75 (PE–EtOAc, 9:1).

IR (KBr): 2970s, 2925m, 1633s, 1568m, 1483m, 1451m, 1385m, 1292s, 1252s, 1158s, 839w cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 3 H), 1.56 (s, 3 H), 1.59 (s, 3 H), 1.67 (s, 3 H), 1.74–1.79 (m, 2 H), 1.93–1.97 (m, 2 H), 2.01–2.05 (m, 2 H), 2.06–2.10 (m, 2 H), 2.48 (s, 3 H), 5.06–5.11 (m, 2 H), 5.48 (d, *J* = 10.1 Hz, 1 H), 6.16 (s, 1 H), 6.69 (d, *J* = 10.2 Hz, 1 H), 10.03 (s, 1 H), 12.64 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0, 17.7, 18.3, 22.6, 25.7, 26.7, 27.3, 39.7, 41.8, 80.7, 107.0, 111.0, 113.2, 115.8, 123.6, 124.3, 126.3, 131.3, 135.6, 143.7, 160.6, 160.9, 192.8.

MS (APCI): *m*/*z* (%) = 377.0 [100, $(M + Na)^+$].

HRMS (ESI): *m*/*z* $(M + Na)^+$ calcd for $C_{23}H_{30}O_3Na^+$: 377.2093; found: 377.2096.

(±)-Daurichomenic Acid

To a solution of the above aldehyde **26** (17.0 mg, 0.050 mmol) in *t*-BuOH (0.6 mL), MeCN (0.6 mL), 2-methylbut-2-ene (0.40 mL), and 1,2-dimethoyethane (0.20 mL) were added NaH_2PO_4 (28.0 mg, 0.25 mmol) and $NaClO_2$ (22.0 mg, 0.25 mmol, dissolved in 0.2 mL H_2O) at –20 °C. After stirring for an additional 2 h at –20 °C, the mixture was warmed up slowly to r.t. and stirred overnight. Then, brine (3 mL) was added and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified via flash column chromatography (SiO_2, gradient eluent: 10–40% EtOAc in PE) to provide (±)-daurichromenic acid as a yellow oil; yield: 8 mg (48%); R_f = 0.15 (PE–EtOAc, 1:1).

IR (KBr): 2927s, 1619s, 1454s, 1381w, 1264s, 1177s, 1010m cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 1.41 (s, 3 H), 1.57 (s, 3 H), 1.59 (s, 3 H), 1.67 (s, 3 H), 1.75–1.78 (m, 2 H), 1.94–1.96 (m, 2 H), 2.02–2.06 (m, 2 H), 2.08–2.11 (m, 2 H), 2.53 (s, 3 H), 5.08–5.12 (m, 2 H), 5.48 (d, *J* = 9.9 Hz, 1 H), 6.23 (s, 1 H), 6.73 (d, *J* = 9.9 Hz, 1H), 11.71 (s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 16.0, 17.7, 22.6, 24.5, 25.7, 26.7, 27.2, 39.7, 41.7, 80.1, 103.5, 107.0, 112.2, 116.7, 123.7, 124.3, 126.3, 131.4, 135.5, 144.4, 159.0, 160.7, 175.8.

MS (APCI): *m*/*z* (%) = 393.1 [100, $(M + Na)^+$].

HRMS (ESI): *m*/*z* $(M - H)^-$ calcd for $C_{23}H_{29}O_4^-$: 369.2066; found: 369.2062.

Aldehyde 27

To a solution of the aldehyde **26** (18.0 mg, 0.053 mmol) in CH_2Cl_2 (5 mL) at –78 °C was added TFA (1 mL, 15 mmol) dropwise. The mixture was stirred at –78 °C for 1 h and then at r.t. for 2 h. The reaction was then quenched by pouring the mixture to sat aq $NaHCO_3$ (2 mL) and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (2 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 2% EtOAc in PE) to provide the aldehyde **27** as a yellow oil; yield: 8.2 mg (47%); R_f = 0.70 (PE–EtOAc, 9:1).

IR (KBr): 2930s, 1777s, 1632s, 1370m, 1262m, 1219s, 1014m cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 0.86 (s, 3 H), 0.92 (s, 3 H), 1.09 (d, *J* = 12.2 Hz, 1 H), 1.16 (s, 3 H), 1.25–1.28 (m, 2 H), 1.45 (s, 3 H), 1.56–1.60 (m, 2 H), 1.68 (t, *J* = 12.8 Hz, 2 H), 1.79 (d, *J* = 13.5 Hz, 1 H), 1.91 (td, *J* = 4.2, 9.4 Hz, 1 H), 2.03 (d, *J* = 12.1 Hz, 1 H), 2.19 (d, *J* = 12.6 Hz, 1 H), 2.49 (s, 3 H), 6.18 (s, 1 H), 6.46 (s, 1 H), 10.06 (s, 1 H), 12.66 (s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 18.3, 18.8, 19.3, 21.7, 23.5, 27.3, 33.3, 33.7, 38.0, 39.4, 41.4, 41.5, 52.2, 80.2, 107.4, 109.0, 110.9, 113.3, 142.7, 149.0, 159.4, 160.4, 193.0.

MS (APCI): *m*/*z* (%) = 376.9 [100, $(M + Na)^+$].

HRMS (ESI): *m*/*z* $(M - H)^-$ calcd for $C_{23}H_{29}O_3^-$: 353.2117; found: 353.2121.

30

To a solution of confluentin (**17**; 20.0 mg, 0.072 mmol) in CH_2Cl_2 (1.2 mL) at –78 °C was added TFA (0.23 mL, 3.00 mmol) dropwise. The mixture was stirred at –78 °C for 1 h and then at r.t. for 1.5 h. The reaction was then quenched by pouring the mixture to sat aq $NaHCO_3$ (2 mL) and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic phases were washed with brine (2 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 2% EtOAc in PE) to provide compound **30** as a yellow oil; yield: 7 mg (35%); R_f = 0.4 (PE–EtOAc, 9:1).

IR (KBr): 2962s, 1777s, 1585w, 1372m, 1261m, 1218s, 1017s cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 0.73 (s, 3 H), 1.36 (s, 3 H), 1.56 (s, 3 H), 1.57 (s, 3 H), 1.62–1.66 (m, 5 H), 1.75 (td, *J* = 6.9, 18.1 Hz, 2 H), 1.86 (dd, *J* = 7.6, 8.0 Hz, 2 H), 1.96–1.99 (m, 1 H), 2.22 (s, 3 H), 2.38–2.40 (m, 1 H), 2.56 (t, *J* = 8.7 Hz, 1 H) 3.04 (d, *J* = 9.4 Hz, 1 H), 4.48 (br m, 1 H), 6.15 (s, 1 H), 6.32 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.9, 18.2, 21.2, 25.5, 25.6, 25.7, 27.2, 35.4, 38.5, 39.0, 41.0, 42.4, 44.4, 46.5, 83.4, 89.4, 108.0, 108.4, 111.4, 114.5 (q, *J* = 427.9 Hz), 137.5, 153.9, 154.5, 156.3 (q, *J* = 61.2 Hz).

^{19}F NMR (564 MHz, $CDCl_3$): δ = –75.73.

MS (APCI): *m*/*z* (%) = 463.6 [100, $(M + Na)^+$].

HRMS (ESI): m/z (M – H)$^-$ calcd for $C_{24}H_{30}F_3O_4^-$: 439.2090; found: 439.2089.

Alkene 31

To a solution of confluentin (**17**; 50.0 mg, 0.17 mmol) in CH_2Cl_2 (2 mL) was added $Fe(OTf)_3$ (25.0 mg, 0.005 mmol) at r.t. under a blanket of N_2. After stirring for 6 h, the reaction mixture was quenched with sat aq $NaHCO_3$ (2 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (2 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 2% EtOAc in PE) to provide the alkene **31** as white solid; yield: 36 mg (55%); R_f = 0.40 (PE–EtOAc, 9:1); mp 136–138 °C.

IR (KBr): 1450w, 1260s, 1089m, 1017s cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.76 (s, 3 H), 1.36 (s, 3 H), 1.63 (s, 3 H), 1.58–1.63 (m, 2 H), 1.66 (d, J = 5.6 Hz, 1 H), 1.70 (s, 3 H), 1.71–1.76 (m, 2 H), 1.93–1.99 (m, 2 H), 2.03–2.07 (m, 1 H), 2.22 (s, 3 H), 2.47 (t, J = 6.5 Hz, 1 H), 2.56 (t, J = 7.9 Hz, 1 H), 3.05 (d, J = 9.5 Hz, 1 H), 4.43 (br s, 1 H), 5.17 (t, J = 6.8 Hz, 1 H), 6.17 (s, 1 H,), 6.32 (s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.9, 17.6, 21.2, 22.8, 25.5, 25.8, 27.3, 35.4, 38.4, 38.9, 42.3, 44.3, 46.7, 83.4, 108.0, 108.4, 111.3, 124.9, 131.3, 137.5, 153.9, 154.4.

MS (APCI): m/z (%) = 349.7 [100, (M + Na)$^+$].

HRMS (ESI): m/z (M – H)$^-$ calcd for $C_{22}H_{29}O_2^-$: 325.2162; found: 325.2161.

Aldehyde 32

To a solution of DMF (0.70 mL, 8.69 mmol) in MeCN (20 mL) was added oxalyl chloride (0.60 mL, 7.10 mmol) under a blanket of N_2 and stirred for 30 min at 0 °C. A solution of alkene **31** (255.0 mg, 0.79 mmol) in MeCN (10 mL) was then added dropwise at 0 °C. After stirring overnight at r.t., the reaction mixture was quenched with 10% aq NaOH (20 mL) and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 2% EtOAc in PE) to provide the aldehyde **32** as a white solid; yield: 113 mg (46%); R_f = 0.78 (PE–EtOAc, 9:1); mp 118–120 °C.

IR (KBr): 2962w, 1625s, 1578m, 1489m, 1371s, 1261s, 1017s cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.76 (s, 3 H), 1.39 (s, 3 H), 1.57–1.63 (m, 2 H), 1.64 (s, 3 H), 1.65–1.69 (m, 2 H), 1.71 (s, 3 H), 1.72–1.76 (m, 1 H), 1.85 (t, J = 11.6 Hz, 1 H), 1.89–1.93 (m, 2 H), 2.07–2.16 (m, 1 H), 2.48 (s, 3 H), 2.57 (t, J = 6.8 Hz, 1 H), 3.09 (d, J = 9.2 Hz, 1 H), 5.18 (t, J = 7.62 Hz, 1 H), 6.23 (s, 1 H), 10.05 (s, 1 H), 12.59 (s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.7, 17.7, 18.0, 22.7, 25.7, 25.8, 27.4, 34.8, 38.4, 39.3, 42.3, 44.6, 46.3, 85.0, 109.8, 112.6, 112.8, 125.0, 131.1, 141.0, 161.3, 164.2, 192.9.

MS (APCI): m/z (%) = 376.9 [100, (M + Na)$^+$].

HRMS (ESI): m/z (M – H)$^-$ calcd for $C_{23}H_{29}O_3^-$: 353.2111; found: 353.2116.

(±)-Rhododaurichomanic Acid A

To a solution of the aldehyde **32** (20.0 mg, 0.050 mmol) in *t*-BuOH (0.5 mL), MeCN (0.5 mL), 2-methylbut-2-ene (0.30 mL), and 1,2-dimethoxyethane (0.20 mL) were added NaH_2PO_4 (28.0 mg, 0.25 mmol) and $NaClO_2$ (22.0 mg, 0.25 mmol, dissolved in 0.2 mL H_2O) at –20 °C. After stirring for an additional 2 h at –20 °C, the mixture was warmed up slowly to r.t. and stirred overnight. Sat. aq NaCl (2 mL) was added and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO_2, 10–40% EtOAc in PE) to afford (±)-rhododaurichomanic acid A as a white solid; yield: 8 mg (54%); mp 168–170 °C; R_f = 0.12 (PE–EtOAc, 1:1).

IR (KBr): 3410brs, 2962w, 2930m, 1620m, 1572w, 1460s, 1365m cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.76 (s, 3 H), 1.40 (s, 3 H), 1.65 (s, 3 H), 1.65–1.69 (m, 3 H), 1.71 (s, 3 H), 1.86 (t, J = 6.9 Hz, 1 H), 1.89–1.95 (m, 2 H), 1.99–2.14 (m, 2 H), 2.50 (m, 1 H), 2.53 (s, 3 H), 2.58 (t, J = 4.9 Hz, 1 H), 3.11 (d, J = 6.0 Hz, 1 H), 5.18 (t, J = 4.0 Hz, 1 H), 6.30 (s, 1 H), 11.66 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7, 17.6, 22.7, 24.5, 25.7, 25.8, 27.5, 35.5, 38.5, 39.1, 42.3, 44.5, 46.2, 84.5, 103.1, 109.6, 113.7, 125.1, 131.0, 141.7, 159.3, 164.3, 176.2.

MS (APCI): m/z (%) = 392.9 [100, (M + Na)$^+$].

HRMS (ESI): m/z (M – H)$^-$ calcd for $C_{23}H_{29}O_4^-$: 369.2066; found: 369.2069.

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Supporting Information

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