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Enantioselective Synthesis of Daurichromenic Acid and Confluentin

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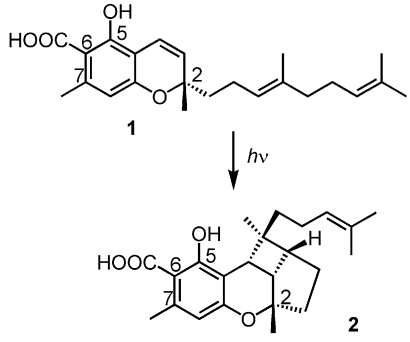
The first asymmetric synthesis of daurichromenic acid and confluentin is described. The key step of the sequence leading to both natural products is a highly enantioselective domino aldol/oxa Michael reaction (97 % *ee*) of farnesal and 2-methoxy-4-methylsalicylaldehyde.

Introduction

The MeOH extract of leaves and twigs of the asian plant *Rhododendron dauricum* contains several anti-HIV-active chromenes[1] which derive from the parent daurichromenic acid (**1**). This compound is the main component of the extract and its absolute configuration *S* at C2 was deduced by X-ray crystal structure determination of a derivative of the related chromane **2** (Scheme 1). **1** is the most potent anti-HIV component as demonstrated in experiments with acutely infected H9 cells (EC_{50} = 5.6 ng/mL).[1] Several short syntheses of racemic daurichromenic acid have already been published.[2–4] Here we wish to report the first enantioselective synthesis of natural **1**.



Scheme 1. Absolute configuration of daurichromenic acid (**1**) deduced by crystal structure determination of the *p*-bromophenacyl derivative of **2**.

Results and Discussion

The synthetic strategy employs the proline derivative **3** which catalyzes the domino aldol/oxa-Michael reaction of farnesal **4** and salicylaldehyde **5** to yield the chiral lactol **6** in acceptable yield and excellent enantioselectivity (Scheme 2).

This method was developed for the synthesis of *all-R*-configured α-tocopherol[5] and was subsequently also used for the preparation of chiral xanthones.[6] During the work on vitamin E[5] we had observed that the proline derivative **3**, derived from natural (*S*)-proline catalyzed the formation of a 2*S*-configured lactol, whereas the enantiomer of **3** gave the 2*R* configuration with high diastereoselectivity (*de* = 97%). Hence we anticipated that for the synthesis of **1** the organocatalyst **3** would be the ideal choice to generate **6** in high enantioselectivity. This was indeed the case, the *ee* value of lactol **6** (97%) was determined on the corresponding lactone **7**.

Though the lactol **6** is a versatile intermediate several problems *en route* to **1** were decisive for selecting the optimal reaction sequence and protecting groups. From lactol **6** one carbon has to be removed preferably by decarbonylation[7] at the aldehyde level (Scheme 3). This reaction, however, requires elevated temperatures and hence was unsuccessful using **8** for example. Further, it would have been of advantage to introduce the double bond in the chromane system at the final stage of the synthesis as it is known that chromenes can be rather unstable.[8,9] Conditions of chromane dehydrogenation using DDQ have been reported.[10] We have examined suitable intermediates of the synthesis such as **9** and **10** in the oxidation with DDQ in refluxing benzene,[11–12] however, the chromanes/chromenes did not survive these reaction conditions (Scheme 3).

Accordingly, we used a more elaborate sequence shown in Scheme 4. The lactol **6** was reduced quantitatively to the diol **11**, the primary alcohol was then selectively protected as the silyl ether and the resulting **12** reacted further with allyl bromide to yield **13**. Three different protecting groups are present in **13** for the following reasons i) the phenyl methyl ether was necessary to obtain high enantioselectivity in the domino aldol/oxa-Michael reaction (Scheme 2); ii) in contrast to a silyl protecting group (see **8** in Scheme 3) the allyl ether at C4 of the chromane system is stable under

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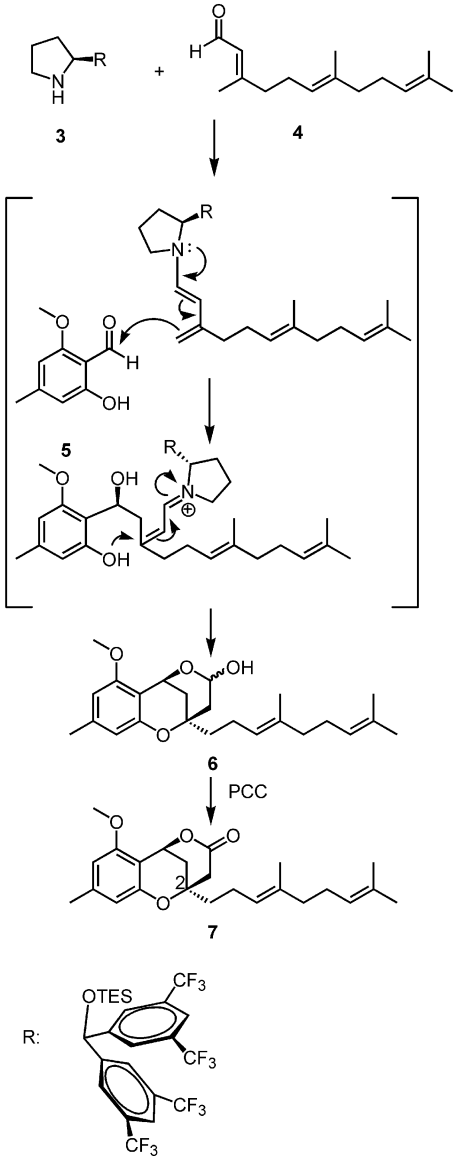
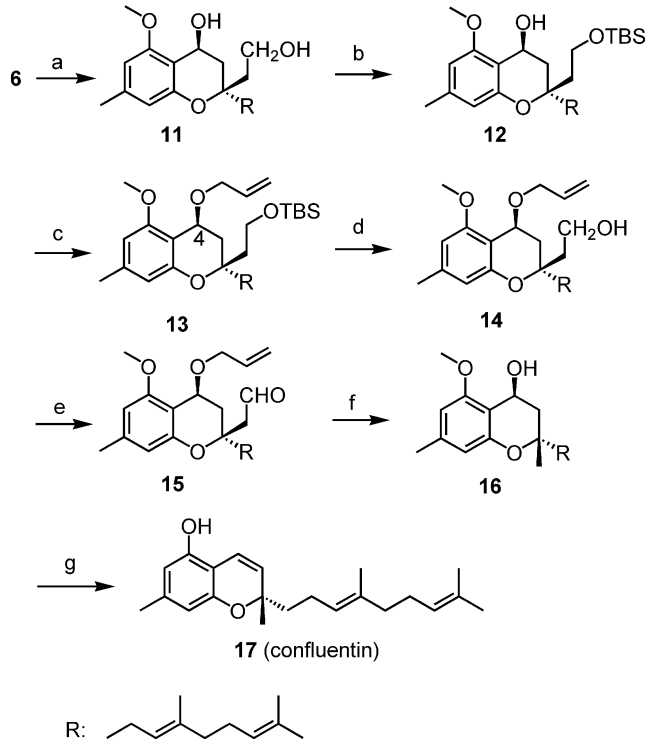


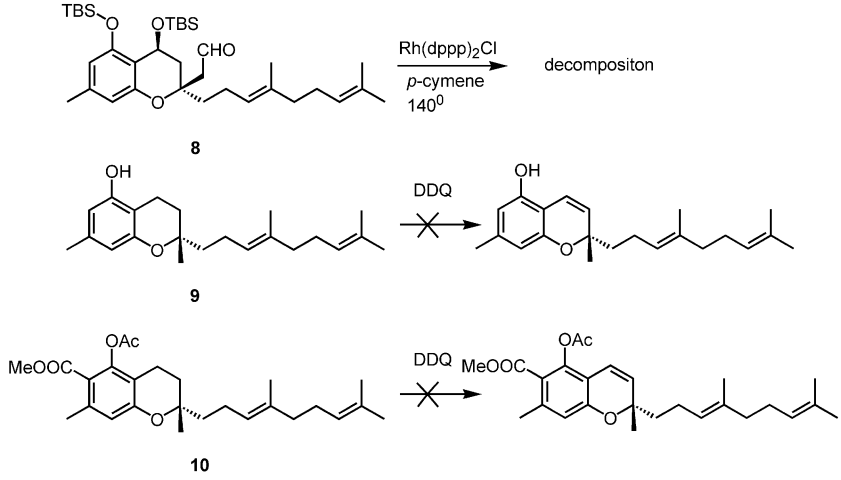
Scheme 2. Organocatalyzed domino aldol/oxa-Michael reaction to produce chiral lactol **6**. Experimental conditions: 30 mol-% **3**, benzoic acid, toluene, 76 h, room temp., 63%.

conditions of decarbonylation, *vide infra*; iii) the TBS group at the primary alcohol can be selectively removed in the presence of the other protecting groups.



Scheme 4. Synthesis of confluentin (**17**). Experimental conditions: a) LAH, THF, 0 °C to room temp., 100%; b) TBSCl, imidzole, DMF, 85%; c) allylic bromide, 60% NaH, THF, 97%; d) TBAF, THF, 97%; e) Dess–Martin periodinane, DCM, 87%; f) i. $Rh(dppp)_2Cl$, *p*-cymene, 140 °C, N_2, 75%; ii. $Ni(dppp)Cl_2$, DIBAL-H, toluene, 80%; g) i. PPh_2Li, THF, 40 °C, 12 h, 80%; ii. MsCl, Et_3N, THF, KHMDS, 50%.

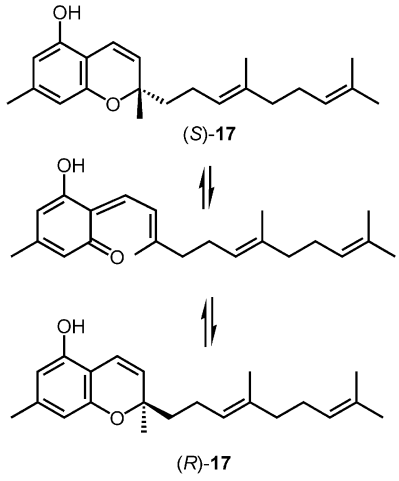
Hence, deprotection of the primary alcohol of **13** gave **14** which underwent a Dess–Martin oxidation to furnish the desired aldehyde **15** in overall excellent yield. In the presence of the allyl protecting group decarbonylation proceeded readily in 75% yield. Subsequent deallylation, how-



Scheme 3. Various unsuccessful attempts to generate the chromene system of **1**.

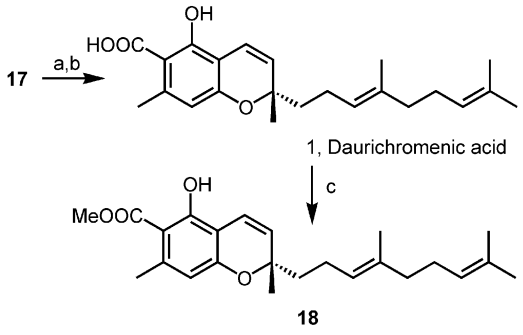
ever, was rather difficult; out of six different reaction conditions only Ni-catalyzed reduction was satisfactory and gave the benzylic alcohol **16** in 80% yield.[13] Demethylation of the phenol ether was accomplished under mild reductive conditions and the product immediately converted into the chromene **17** via mesylation/elimination in one pot. At this stage of the synthesis we were able to separate the enantiomers of the product and it was shown that **17** displayed an excellent enantiomeric excess of 97%, in agreement with **7**.

The chromene **17** is known as the natural product confluentin exhibiting weak antagonist activity at the human vanilloid receptor VR1. **17** was first isolated as a racemate from the fruitbodies of the fungi genus *Albatrellus spp.*[14] and more recently from the leaves *Rhododendron dauricum*.[15] In view of the facile ring opening of chromenes[8,9] (Scheme 5) racemization of natural **17** most likely occurred during isolation from the fungi.



Scheme 5. Racemization of **17**.

Assisted by the free phenol bromination of **17** occurred regioselectively in *ortho* position and subsequent carboxylation furnished the final target compound **1** with $[\alpha]_D^{20}$ = +30.0 ($CHCl_3$), in agreement with natural **1** within the experimental error: $[\alpha]_D^{20}$ = +30.4 ($CHCl_3$).[1] The enantiomeric excess of **1** was further confirmed at the derivative **18** (97% *ee*) being identical with **17** (Scheme 6).



Scheme 6. Synthesis of daurichromenic acid (**1**). Experimental conditions: a) NBS, DCM, 81%; b) *n*BuLi, CO_2, 60%; c) TMS-CH_2N_2, methanol, diethyl ether, 100%.

Conclusions

In conclusion, the synthesis of two physiologically significant natural chromenes confluentin (**17**) and daurichromenic acid (**1**) has been accomplished using an organocatalytic, highly enantioselective aldol/oxa-Michael reaction as a key step.

Experimental Section

Aldol/Oxa-Michael Reaction: To a solution of aldehyde **5** (294 mg, 1.8 mmol) and proline-catalyst **3** (345 mg, 0.54 mmol) in toluene (1.8 mL) was added solid benzoic acid (66 mg, 0.54 mmol) at room temp. under argon, then followed by addition of a solution of farnesal (**4**) (595 mg, 2.7 mmol) in toluene (3.6 mL) during 3 h by means of a syringe pump. The reaction mixture was stirred at room temp. for 3 d and directly purified by flash chromatography on silica gel, hexane/ethyl acetate (4:1, v/v) as an eluent to afford compound **6** (430 mg, yield 63%) as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.27 (s, 1 H), 6.14 (s, 1 H), 5.26 (m, 1 H), 5.07–5.15 (m, 2 H), 4.92 (m, 1 H), 3.71 (s, 3 H), 3.65 (d, J = 5.20 Hz, 1 H), 2.29 (s, 3 H), 1.96–2.20 (m, 8 H), 1.55–1.75 (m, 4 H), 1.68 (s, 3 H), 1.59 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 157.32, 156.57, 140.53, 135.82, 131.57, 124.46, 123.82, 108.81, 106.39, 103.04, 90.23, 76.02, 62.07, 55.61, 44.47, 41.64, 39.84, 32.91, 26.86, 25.88, 22.14, 21.45, 17.87, 16.18 ppm. ESI-MS: m/z = 409.2 [M + Na]$^+$, 795.1 [2M + 1]$^+$. $[\alpha]_D^{20}$ = +0.4 (c = 1.36, $CHCl_3$); elemental analysis calcd. (%) for $C_{24}H_{34}O_4 \cdot H_2O$ (404.26): C 71.26, H 8.97; found C 71.08, H 8.75.

Confluentin (17) from Alcohol 16: To a solution of diphenylphosphane (42 mg, 0.223 mmol) in THF (0.5 mL) was added a solution of *n*BuLi (0.21 mL, 0.335 mmol, 1.6 M in hexane) dropwise at 0 °C. The reaction mixture was stirred at room temp. for 20 min. Then a solution of alcohol **16** (20 mg, 0.056 mmol) in THF (1 mL) was added dropwise and heated to 40 °C overnight. The reaction was quenched with satd. aq. NH_4Cl and extracted three times with ethyl acetate. The combined organic phases were washed with water, brine and dried with Na_2SO_4. After concentration under vacuum, the residue was purified by flash chromatograph on silica gel using hexane/ethyl acetate (8:1, v/v) as an eluent to give the phenol (15.2 mg, yield 80%) as a yellowish very unstable oil. To a solution of the diol (19.26 mg, 0.056 mmol) in THF (1.5 mL) was added Et_3N (34 mg, 0.336 mmol) at –30 °C. Then a solution of MsCl (19.21 mg, 0.168 mmol) in THF (0.5 mL) was added dropwise at the same temperature. The reaction mixture was warmed to room temp. and stirred for 1 h. Then the solution was cooled down to 0 °C, and a solution of KHMDS in toluene (0.5 M, 0.5 mL, 0.25 mmol) was added dropwise. The resulting mixture was stirred for 20 min at the same temperature, quenched with satd. aq. NH_4Cl and extracted with diethyl ether. The combined organic phases were washed with brine, dried with Na_2SO_4. After concentration under vacuum, the residue was purified by flash chromatograph on silica gel using hexane/ethyl acetate (10:1, v/v) as an eluent and **17** (9.13 mg, yield 50%) was isolated as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.60 (d, J = 10.0 Hz, 1 H), 6.24 (s, 1 H), 6.11 (s, 1 H), 5.49 (d, J = 10.0 Hz, 1 H), 5.06–5.11 (m, 2 H), 4.62 (br., 1 H), 2.20 (s, 3 H), 2.01–2.13 (m, 4 H), 1.95 (m, 2 H), 1.65–1.78 (m, 2 H), 1.67 (s, 3 H), 1.59 (s, 3 H), 1.57 (s, 3 H), 1.37 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 154.32, 151.18, 139.73, 135.44, 131.51, 127.41, 124.54, 124.23, 116.86, 110.06, 108.45, 106.93, 78.39, 41.27, 39.86, 26.87, 26.46, 25.88, 22.81, 21.68, 17.86, 16.15 ppm. ESI-MS: m/z = 349.2 [M + Na]$^+$.

$[\alpha]_D^{20}$ = +71.0 (c = 0.5, $CHCl_3$); enantiomeric excess: 97%, determined by HPLC on Chrialpak AD-H column (*n*-hexane/2-propanol, 90:10), 20 °C, UV 220 nm, 0.5 mL/min; major enantiomer t_R = 10.50 min, minor enantiomer t_R = 9.37 min.

Daurichromenic Acid (1): To a solution of **17** (10 mg, 0.031 mmol) in DCM (1 mL) was added a solution of NBS (6 mg, 0.034 mmol) in DCM (1 mL) very slowly at 30 °C. After addition, the reaction was stirred at 20 °C for 30 min when TLC showed that **17** was consumed. The reaction was quenched with silica gel and directly purified by flash chromatograph on silica gel using hexane/ethyl acetate (20:1v/v) as an eluent to give crude bromide (10 mg, yield 81%) as yellowish oil. To a solution of the bromide (10 mg, 0.025 mmol) in THF (1 mL) was added a solution of *n*BuLi (1.6 M, 62.5 μL) in hexane dropwise at –30 °C. The reaction was stirred for 1.5 h between –30 and –15 °C. When all bromide was consumed, the reaction was cooled down to –70 °C, and bubbled with CO_2 for 3 h at –70 °C to –50 °C. The reaction was quenched with water, adjusted to pH 7 using 1 N HCl, then extracted three times with ethyl acetate. The combined organic phases were washed with brine and dried with Na_2SO_4. After concentration under vacuum the residue was purified by flash chromatograph on silica gel using hexane/ethyl acetate (1:1 to 0:100, v/v) as an eluent to give **1** (5.56 mg, 60%) as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.73 (d, J = 10.0 Hz, 1 H), 6.23 (s, 1 H), 5.48 (d, J = 10.0 Hz, 1 H), 5.07–5.11 (m, 2 H), 2.52 (s, 3 H), 1.95–2.09 (m, 6 H), 1.65–1.77 (m, 2 H), 1.67 (s, 3 H), 1.59 (s, 3 H), 1.57 (s, 3 H), 1.40 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 175.17, 160.82, 159.00, 144.38, 135.69, 131.55, 126.47, 124.50, 123.90, 116.87, 112.22, 107.21, 103.76, 80.21, 41.86, 39.85, 27.34, 26.85, 25.88, 24.64, 22.76, 17.87, 16.16 ppm. ESI-MS: 369.2 $[M - H]^-$. $[\alpha]_D^{20}$ = +30.0 (c = 0.25, $CHCl_3$).

Methyl Ester of Daurichromenic Acid 18: To a solution of **1** (5.0 mg, 0.135 mmol) in methanol (0.5 mL) and diethyl ether (0.5 mL) was added a solution of TMS-CH_2N_2 in hexane until the color of the solution became yellow at 0 °C. The reaction mixture was stirred at same temperature for 0.5 h. The reaction was quenched with acetic acid and concentrated under vacuum to afford a residue that was purified by flash chromatography on silica gel using hexane/ethyl acetate (40:1, v/v) as an eluent to give the ester **18** (5.2 mg, 100%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 11.97 (s, 1 H), 6.72 (d, J = 10.0 Hz, 1 H), 6.19 (s, 1 H), 5.47 (d, J = 10.0 Hz, 1 H), 5.05–5.11 (m, 2 H), 3.91 (s, 3 H), 2.45 (s, 3 H), 1.92–2.13 (m, 6 H), 1.62–1.78 (m, 2 H), 1.67 (s, 3 H), 1.59 (s, 3 H), 1.56 (s, 3 H), 1.39 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.56, 159.94, 158.04, 142.92, 135.63, 131.53, 126.46, 124.50, 123.96, 117.01, 111.84, 107.23, 105.09, 79.90, 51.98, 41.78, 39.85, 27.21, 26.85, 25.88, 24.62, 22.75, 17.86, 16.15 ppm. ESI-MS: 407.2 $[M + Na]^+$. $[\alpha]_D^{20}$ = +31.5 (c = 0.38, $CHCl_3$); enantiomeric excess: 97%, determined by HPLC on Chrialpak AD-H column (*n*-hexane/2-propanol, 98:2), 20 °C, UV 250 nm, 0.5 mL/min, major enantiomer t_R = 8.45 min, minor enantiomer t_R = 9.57 min.

Supporting Information (see also the footnote on the first page of this article): Experimental procedures and analytical data for compounds **1**, **6**, **7**, **11**–**18**, are provided with copies of the respective ^{1}H NMR and ^{13}C NMR spectra and HPLC chromatograms of **17** and **18**.

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