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Highly Enantioselective Total Synthesis of (−)-(3′*S*)-Lomatin and (+)-(3′*S*,4′*R*)-*trans*-Khellactone

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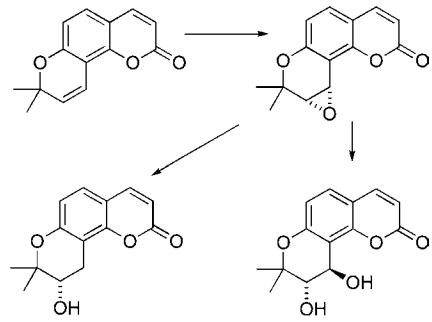
ABSTRACT



Concise highly enantioselective three-step syntheses are described for (−)-(3′*S*)-lomatin and (+)-(3′*S*,4′*R*)-*trans*-khellactone from 7-hydroxycoumarin in 97% ee and in 57% and 58% overall yields, respectively, using nonaqueous enantioselective epoxidation by an iminium salt as the key step.

Coumarins are widely distributed in nature, both in linear and nonlinear form, and have been shown to exhibit a broad range of pharmacological profiles,[1] including antibacterial,[2] anti-inflammatory,[3] anticancer,[4] and anti-HIV[5] activity. With cancer and HIV posing serious threats to public health, the need for new and better treatments is ever more important. Coumarins have been tested in industry and academia for bioactivity recently, where investigations have been undertaken to see how varying functional groups affect factors such as cytotoxic properties and therapeutic activity.[1]

Naturally occurring pyranocoumarins (Figure 1) include seselin **1**, predominantly isolated from *Plumbago zeylanica*, *Naucleopsis caloneura*, *Carum roxburghianum*, and *Citrus grandis*;[6] xanthyetin **2**, isolated from many sources including *Zanthoxylum americanum*;[7] selinidin **3**, isolated from *Angelica keiskei*;[3] both enantiomers of lomatin **4**, isolated from *Lomatium nutalli* and various Umbelliferae;[8] (+)-decursinol **5**, isolated from *Angelica gigas*;[9] and (+)-*trans*-khellactone

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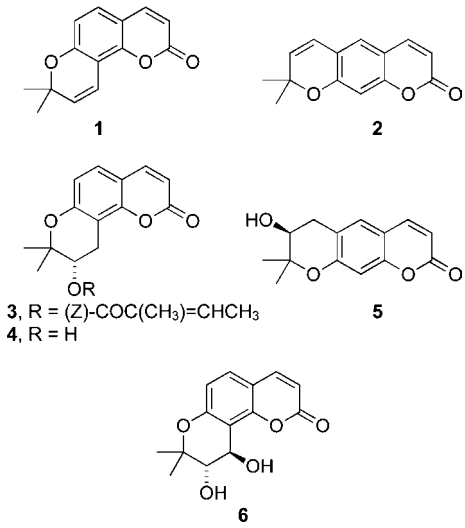

Figure 1. Naturally occurring pyranocoumarins.

6, isolated from the aerial parts of *Ligusticum elatum*[10] and *Peucedanum japonicum*.[11] Seselin **1** and xanthyetin **2** have shown cytotoxic activity against Vero monkey cells, with IC_{50} values of 12 μg/mL and >20 μg/mL,[12] while selenidin **3** has antisuppressant properties toward leukotriene C_4 production,[3] and (+)-decursinol **5** exerts anticancer activity against prostate cancer PC3 cells.[13] (+)-*trans*-Khellactone **6** has cytotoxic activity against P-388 lymphocytic leukemia systems (ED_{50} 2.8 μg/mL).[11]

To our knowledge, lomatin has been previously prepared only by achiral synthesis, using osthenol **7**,[14] 2,4-dihydroxybenzaldehyde,[15] visnadin (provismine) **8**,[16] and seselin **1**[8] as starting materials, although the enantiomers of lomatin have been resolved.[8] Racemic *trans*-khellactone has been prepared from seselin **1** using *m*-CPBA followed by saponification.[5] (+)-*trans*-Khellactone **6** has been isolated alongside the *cis* isomer in a 1:1 ratio from the alkaline hydrolysis of a number of dihydropyranocoumarins, such as peujaponisin **9**, (−)-visnadin **8**, and (+)-anomalin **10**, all diesters of (−)-*cis*-khellactone **11**, itself isolated from *Peucedanum japonicum*,[17] through epimerization at the benzylic position (Figure 2). We have shown that high levels of enantioselectivity can

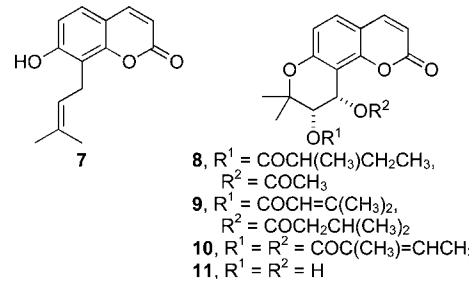

Figure 2. Known precursors of lomatin and khellactone.

be achieved in the epoxidation of *cis*-chromene structures using chiral iminium salt catalysts,[18] and we report herein the highly enantioselective synthesis of (−)-(3′*S*)-lomatin **4** and (+)-(3′*S*,4′*R*)-*trans*-khellactone **6** using such an enantioselective epoxidation of seselin, followed by reductive or hydrolytic ring opening of the resulting epoxide.

North has reported a simple synthesis of chromenes from commercially available starting materials, in which, for

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(21) **Seselin 1.**[28] Thermal method: 7-Hydroxycoumarin (1.0 g, 6.17 mmol) was dissolved in *p*-xylene (20 mL). 1,1-Diethoxy-3-methyl-2-butene (1.47 mL, 7.40 mmol) and 3-picoline (0.15 mL, 1.50 mmol) were added, and the reaction mixture was heated under reflux for 24 h. Dichloromethane (20 mL) was added to the reaction mixture, the solution was filtered through a pad of silica gel and Celite, and the pad was rinsed with ethyl acetate (3 × 20 mL). The combined organic solvents were removed under reduced pressure, and the residue was purified by column chromatography on silica gel using ethyl acetate/toluene (1:1) as eluent to give seselin **1** as a yellow solid (1.03 g, 73%). Microwave-assisted method: 7-Hydroxycoumarin (0.1 g, 0.62 mmol) and 1,1-diethoxy-3-methylbut-2-ene (0.13 mL, 0.74 mmol) were dissolved in 3-picoline (0.50 mL, 5.0 mmol). The mixture was submitted to microwave irradiation (300 W max, 100 °C, 2 × 10 min). Dichloromethane (5 mL) was added to the reaction mixture, the solution was filtered through a pad of silica gel and Celite, and the pad was rinsed with ethyl acetate (3 × 5 mL). The combined organic solvents were removed under reduced pressure, and the residue was purified by column chromatography on silica gel using ethyl acetate/toluene (1:1) as eluent to give seselin **1** as a yellow solid (0.132 g, 94%): mp 119−120 °C (lit.[28] 117−120 °C); ν_{max} (film/cm^{-1}) 2976, 2361, 1734, 1597, 1485, 1152; δ_H (400 MHz; $CDCl_3$) 1.45 (6H, s, 2 × CH_3), 5.71 (1H, d, J = 10 Hz), 6.20 (1H, d, J = 9.5 Hz), 6.70 (1H, d, J = 8.5 Hz), 6.86 (1H, d, J = 10 Hz), 7.20 (1H, d, J = 8.5 Hz), 7.59 (1H, d, J = 9.5 Hz); δ_C (100 MHz; $CDCl_3$) 28.3 (2 × CH_3), 53.4, 109.4, 112.7, 113.7, 115.1, 120.2, 127.9, 130.9, 144.1, 150.2, 156.4, 161.2.

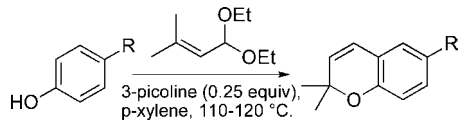
(22) Stereochemical assignment based on published structures of (−)-lomatin[8] and (+)-khellactone.[17,30]

(23) **(+)-(3′*S*,4′*S*)-Seselin Epoxide 12.**[6,29] Seselin **1** (0.50 g, 2.19 mmol) was dissolved in chloroform (30 mL) and the solution cooled to −30 °C. Sulfone catalyst **13** (0.16 g, 0.22 mmol) and TPPP (2.0 g, 4.38 mmol) were added, and the mixture was stirred at −30 °C for 24 h. Diethyl ether (50 mL) was added to the mixture and the resulting cloudy solution filtered through Celite. The solvents were removed under reduced pressure, and the residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate/triethylamine (3:1:0.1) as eluent to give (+)-(3′*S*,4′*S*)-seselin epoxide **12** as a colorless solid (0.348 g, 65%) of 97% ee (HPLC conditions/hexane/2-propanol (90:10), oven temp 20 °C, column Eurocel 01 250 × 4.6 mm, 5 μm particle size, flow rate 1 mL/min): mp 143−144 °C (lit.[29] mp 144−146 °C); α_D +7.2 (*c* 0.1 $CHCl_3$); ν_{max} (film/cm^{-1}) 2950, 2256, 1729, 1698, 1587, 1423, 1120; δ_H (400 MHz; $CDCl_3$) 1.24 (3H, s, CH_3), 1.53 (3H, s, CH_3), 3.49 (1H, d, J = 6.0 Hz), 4.53 (1H, d, J = 6.0 Hz), 6.19 (1H, d, J = 12.7 Hz), 6.65 (1H, d, J = 11.5 Hz), 7.24 (1H, d, J = 11.7 Hz), 7.55 (1H, d, J = 12.7 Hz); δ_C (100 MHz; $CDCl_3$) 23.1 (CH_3), 25.8 (CH_3), 44.2, 62.1, 75.0, 108.4, 113.1, 113.8, 115.8, 129.4, 144.2, 155.1, 156.2, 161.2.

(24) Optical rotation matched the known data for (−)-(3′*S*)-lomatin.[8]

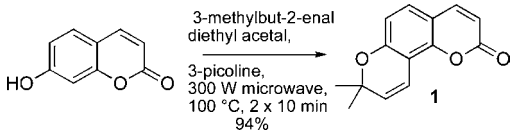
example, 3-methylbut-2-enal diethyl acetal was treated with phenols in the presence of 3-picoline in *p*-xylene solution at 110−120 °C to produce the corresponding chromenes in good yields (Scheme 1).[19]

Scheme 1. North's Chromene Synthesis



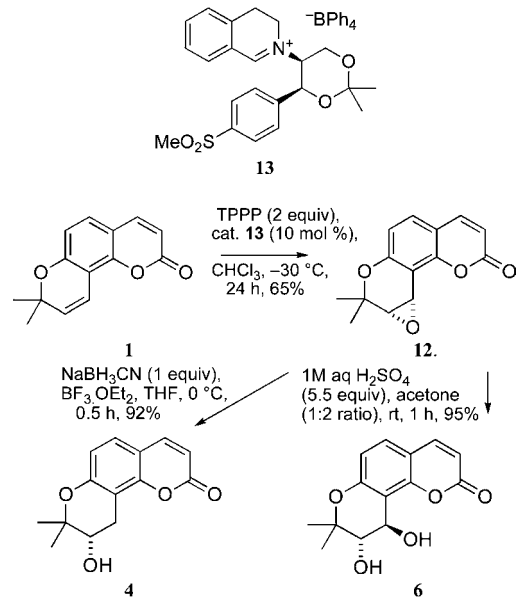
Using this procedure, we prepared seselin **1** from 7-hydroxycoumarin over 24 h in xylene under reflux, in 87% yield. The synthesis was also achieved more conveniently using microwave irradiation in neat 3-picoline in 94% yield (Scheme 2).[20,21]

Scheme 2. Preparation of Seselin



The epoxidation of seselin **1** to the chiral epoxide **12** was carried out under our nonaqueous conditions, using tetraphenylphosphonium monoperoxysulfate (TPPP) as stoichiometric oxidant together with the sulfone-containing iminium salt catalyst **13** at −30 °C for 24 h. (+)-(3′*S*,4′*S*)-Epoxide **12** was obtained in 97% ee.[22,23] Conversion of the epoxide into (−)-(3′*S*)-lomatin **4** was achieved by reductive cleavage with $NaBH_3CN$ at 0 °C in 92% yield and 97% ee.[24,25] Acid-catalyzed ring-opening of **12** yielded (+)-(3′*S*,4′*R*)-*trans*-khellactone **6** in 95% yield using an acetone/1 M H_2SO_4 mixture (Scheme 3).[26,27]

Scheme 3. Asymmetric Synthesis of (−)-(3′*S*)-Lomatin and (+)-(3′*S*,4′*R*)-*trans*-Khellactone



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Supporting Information Available: Full experimental details, HPLC traces, and ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) **(−)-(3′*S*)-Lomatin 4.**[8] Seselin epoxide (20 mg, 0.08 mmol) was dissolved in tetrahydrofuran (3 mL) and the solution cooled to 0 °C. Boron trifluoride etherate (7 μL, 0.12 mmol) was added. Sodium cyanoborohydride (0.005 g, 0.12 mmol) was added in one portion and the mixture stirred for 30 min. Water (1 mL) and dichloromethane (3 mL) were added to the reaction mixture, and the organic phase was separated. The aqueous layer was extracted with dichloromethane (2 × 3 mL), and the organic layers were combined and dried over magnesium sulfate. The solvents were removed under reduced pressure, and the residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (7:3) as eluent to give to give (−)-(3′*S*)-lomatin **4** as a yellow solid (19 mg, 94%) of 97% ee (HPLC conditions: hexane/2-propanol (99:1), oven temp 20 °C, column Eurocel 01 250 × 4.6 mm, 5 μm particle size, flow rate 0.5 mL/min): mp 164−165 °C (lit.[8] mp 163−165 °C); α_D −52 (*c* 0.4, EtOH), lit.[8] α_D −51 (*c* 0.5, EtOH); ν_{max} (film/cm^{-1}) 3452, 2935, 1723, 1604, 1405, 1117; δ_H (400 MHz; $CDCl_3$) 1.32 (3H, s, CH_3), 1.38 (3H, s, CH_3), 2.94 (1H, dd, *J* = 5.2, 17.6 Hz), 3.11 (1H, dd, *J* = 5.0, 17.6 Hz), 3.88 (1H, t, *J* = 5.0 Hz), 6.19 (1H, d, *J* = 9.4 Hz), 6.75 (1H, d, *J* = 8.6 Hz), 7.22 (1H, d, *J* = 8.6 Hz), 7.59 (1H, d, *J* = 9.4 Hz); δ_C (100 MHz; $CDCl_3$) 22.3, 24.8, 25.9, 68.5, 78.3 (quat), 107.6 (quat), 112.3 (quat), 112.5, 114.5, 126.8, 144.2, 153.7 (quat), 156.5 (quat), 161.6 (quat).

(26) Optical rotation matched the known data for (−)-(3′*S*,4′*R*)-khellactone.[17,30]

(27) **(+)-(3′*S*,4′*R*)-*trans*-Khellactone 6.**[17,30] Seselin epoxide (20 mg, 0.08 mmol) was dissolved in acetone (1 mL) at room temperature. Aqueous sulfuric acid (1M, 0.5 mL) was added to the solution, and the mixture was stirred for 1 h. The reaction mixture was neutralized to pH 7 using sodium hydrogen carbonate. Dichloromethane (3 mL) was added to the reaction mixture and the organic phase separated. The aqueous layer was extracted with dichloromethane (2 × 3 mL), and the organic layers were combined and dried over magnesium sulfate. The solvents were removed under reduced pressure, and the residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (2:1) as eluent to give to give (+)-(3′*S*,4′*R*)-*trans*-khellactone **6** as a colorless solid (20 mg, 95%) of 97% ee (HPLC conditions: hexane/2-propanol (99.5:0.5), oven temp 20 °C, column Eurocel 01 250 × 4.6 mm, 5 μm particle size, flow rate 1 mL/min): mp 182−184 °C (lit.[30] mp 181−185 °C); α_D +19 (*c* 1.7, $CHCl_3$), lit.[30] +19.6 (*c* 0.6, $CHCl_3$); ν_{max} (film/cm^{-1}) 3418, 1715, 1605, 1491, 1245; δ_H (300 MHz; $CDCl_3$) 1.30 (3H, s, CH_3), 1.51 (3H, s, CH_3), 3.08−3.35 (1H, s, OH), 3.85 (1H, d, *J* = 6.9 Hz, C*H*OH), 4.09−4.46 (1H, br s, OH), 5.00 (1H, d, *J* = 6.9 Hz, C*H*OH), 6.25 (1H, d, *J* = 9.3 Hz, C*H*=), 6.78 (1H, d, *J* = 8.4 Hz, CH_{ar}), 7.32 (1H, d, *J* = 8.7 Hz, CH_{ar}), 7.66 (1H, d, *J* = 9.6 Hz, C*H*=); δ_C (75 MHz; $CDCl_3$) 161.2, 156.3, 154.4, 144.4, 128.6, 114.8, 112.5, 112.2, 111.6, 79.3, 74.8, 66.5, 25.4, 19.9.

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