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Enantioselective Total Synthesis of (+)-Scuteflorin A Using Organocatalytic Asymmetric Epoxidation

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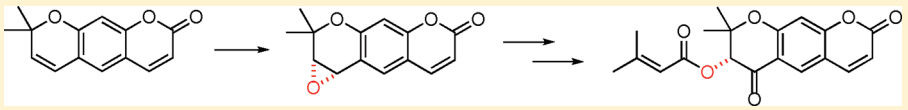
Supporting Information



ABSTRACT: We report the first enantioselective total synthesis of (+)-scuteflorin A in 14% overall yield, employing a chiral iminium salt to effect an organocatalytic asymmetric epoxidation of xanthyletin in >99% ee as the key step.

The *Scutellaria* genus, more commonly known as skullcaps, has been used in herbal remedies for many hundreds of years. To date, around 300 individual compounds have been isolated from *Scutellaria* species, and many of these have been shown to have pharmacological activities, including antibacterial, antiangiogenesis, antiviral, anticonvulsant, and anticancer activities.[1] *Scutellaria lateriflora* L., or the American skullcap, has demonstrated particular utility as a therapy for anxiety in a recent study of healthy subjects.[2]

During an investigation into the origin of the therapeutic activity of the American skullcap, Khan reported the isolation and characterization of two new dihydropyranocoumarins, scuteflorin A **1** and B **2** (Figure 1).[3]

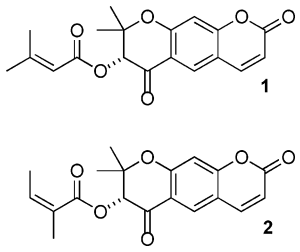
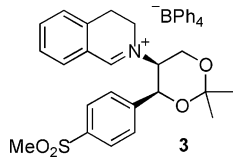


Figure 1. The recently isolated dihydropyranocoumarins, scuteflorin A **1** and B **2**.

Over the past decade, we have investigated the capacity of chiral iminium salts as organocatalysts for the asymmetric epoxidation of olefinic substrates.[4] We have previously reported the highly enantioselective epoxidation of *cis*-disubstituted alkenes with a preparatively simple dihydroisoquinolinium catalyst **3** under nonaqueous conditions, and recently we have described the enantioselective syntheses of (−)-(3*S*)-lomatin and (+)-(3*S*,4*R*)-*trans*-khellactone through a highly enantioselective epoxidation as the key step, using **3** as catalyst.[5]



To our knowledge, only a racemic synthesis of **1** has been reported to date.[6] We envisaged that the synthesis of (+)-**1** could be achieved by the asymmetric iminium salt-mediated epoxidation of xanthyletin **4**, which would install into **5** the stereochemistry and epoxide functionality required for further manipulation.

The synthesis of **4** was straightforward, following a route starting from 7-hydroxycoumarin outlined in the literature by Ahluwalia[7] and was achieved in our hands in an overall yield of 29%.

The enantioselective epoxidation of xanthyletin using Jacobsen's (*S*,*S*)-(+)-salen-Mn(III) catalyst has previously been reported by Kim and Jun to take place in 95% ee.[8] We have recently found that the (*S*,*S*)-acetonamine-derived biphenylazepinium catalyst **6** is superior to **3** for the epoxidation of *cis*-disubstituted alkenes, such as **4**, in terms of both reactivity and enantioselectivity.[4] We were pleased to observe that the epoxidation of **4**, employing catalyst **6** under our nonaqueous conditions together with tetraphenylphosphonium monoperoxysulfate (TPPP) as the stoichiometric oxidant

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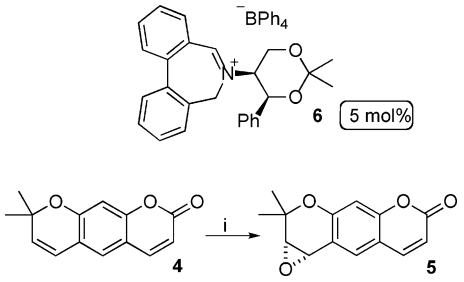
at −30 °C for 30 h, ran to full conversion to give **5** in ≥99% ee (Scheme 1).

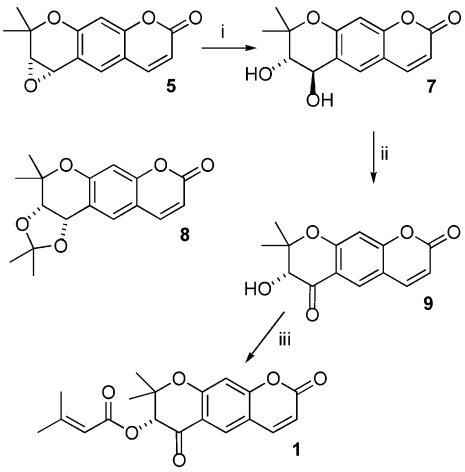
Scheme 1. [a]



[a](i) Catalyst **6**, TPPP, $CHCl_3$, −30 °C, 30 h, 97%.

The acid-catalyzed epoxide ring-opening procedure previously used by us in the synthesis of (+)-(3*S*,4*R*)-*trans*-khellactone,[5,8b] in this instance, yielded (+)-*trans*-decursidinol **7** in 60% yield after chromatography. Interestingly, we also isolated a product **8** in 8% yield that appeared to result from the incorporation of acetone by a Ritter-type reaction with **5**. We utilized Dess−Martin periodinane to achieve the mild selective oxidation of the benzylic hydroxyl group of **7** to yield keto-alcohol **9** in 95% yield. The introduction of the 3,3-dimethyl acryloyl side chain and completion of the synthesis of **1** were accomplished by the coupling of the appropriate acyl chloride with **9** (Scheme 2). The optical rotation for the synthetic material matched that reported by Khan for the authentic sample of **1**.[3]

Scheme 2. [a]



[a](i) acetone/1 M H_2SO_4 (2:1), rt, 10 min, 60%; (ii) DMP (1 equiv), $CHCl_3$, RT, 95%; (iii) 3,3-dimethyl acryloyl chloride (5 equiv), $NaHCO_3$ (1.1 equiv), THF, rt, 4 h, 88%.

In conclusion, we have completed the first enantioselective total synthesis of (+)-scuteflorin A, in very high ee, in seven linear steps and a 14% overall yield, via (+)-*trans*-decursidinol. Our enantioselective epoxidation of xanthyletin also offers a potential route to the asymmetric synthesis of decursin, which inhibits the estrogen-stimulated andestrogen-independent growth and survival of breast cancer cells,[9] and related analogues such as dihydropyranocoumarin D2, which has been shown to be a MITF-degrading agent, inhibiting the synthesis of melanin at the transcription level.[10]

EXPERIMENTAL SECTION

Xanthyletin Oxide 5.[8] Xanthyletin **4** (24 mg, 0.11 mmol) was dissolved in $CHCl_3$ (2.5 mL) and cooled to −30 °C. TPPP (96 mg, 0.22 mmol) was added in one portion followed by catalyst **6** (3.7 mg, 0.0053 mmol). The reaction was stirred at −30 °C until **4** had been consumed, at which time Et_2O (20 mL), cooled to the reaction temperature, was added to precipitate the TPPP and its reduced byproduct. The suspension was filtered through Celite, and solvents were removed in vacuo. The epoxide **5** was isolated cleanly, and no further purification was required prior to the subsequent synthetic steps (26 mg, 97%); a small sample was purified for analysis, giving a colorless crystalline solid: mp 157−158 °C; $[\alpha]^{18}_D$ +280.1 (c = 1.23, $CHCl_3$); ν_{max} (neat)/cm^{-1} 2984, 2961, 2928, 1730, 1627, 1562, 1496, 1459, 1435, 1390, 1367, 1348, 1333, 1282, 1271, 1235, 1207, 1189, 1144, 1103, 1035, 1001, 981, 948, 915, 894, 852, 834, 819, 755, 717; δ_H (300 MHz; $CDCl_3$) 1.29 (3H, s) 1.59 (3H, s), 3.53 (1H, d, *J* = 4.4 Hz), 3.96 (1H, d, *J* = 4.4 Hz), 6.26 (1H, d, *J* = 9.5 Hz), 6.75 (1H, s), 7.45 (1H, d, *J* = 9.5 Hz), 7.62 (1H, s); δ_C (75 MHz; $CDCl_3$) 22.9, 25.3, 50.1, 61.9, 74.6, 106.1, 113.1, 113.9, 117.3, 128.9, 142.9, 156.2, 160.9.

***trans*-Decursidinol 7.**[8b] Xanthyletin oxide **5** (0.20 g, 8.92 mmol) was dissolved in acetone (10 mL), and 1 M HCl (aq) (5 mL) was added in one portion. The reaction was stirred until it was judged by TLC that the starting material had been completely consumed (ca. 5 min). The solution was neutralized to pH 7 with saturated aqueous $NaHCO_3$ and diluted with CH_2Cl_2 (30 mL) and water (30 mL). The aqueous layer was extracted further with CH_2Cl_2 (2 × 30 mL), and the combined organic extracts were washed with brine (15 mL) and dried over $MgSO_4$. The solvents were removed in vacuo to leave a white oily residue which was purified by column chromatography, eluting with 1:1 light petroleum/EtOAc to yield **7** as a stiff white foam (0.14 g, 60%): mp 147−148 °C (dec.); $[\alpha]^{18}_D$ +146.1 (c = 0.33, MeOH); ν_{max} (neat)/cm^{-1} 3422, 3057, 2983, 2918, 1694, 1289, 1263, 1074, 1063, 1024, 976, 862, 762, 743; δ_H (300 MHz; $CDCl_3$) 1.16 (3H, s) 1.43 (3H, s), 3.58 (1H, d, *J* = 9.0 Hz), 3.87 (1H, br s), 4.17 (1H, br s), 4.52 (1H, d, *J* = 8.6 Hz), 6.05 (1H, d, *J* = 9.5 Hz), 6.53 (1H, s), 7.46 (1H, d, *J* = 9.5 Hz), 7.47 (1H, s); δ_C (75 MHz; acetone-d_6) 19.0, 26.2, 68.2, 75.2, 80.2, 103.2, 112.9, 123.0, 128.5, 143.9, 155.1, 156.2, 160.3; *m*/*z* 263.0911, $C_{14}H_{15}O_5$ [M + H^+] requires 263.0919.

(3a*S*, 11b*S*)-2,2,4,4-Tetramethyl-3a,4-dihydro[1,3] dioxolo-[4,5-*c*]pyrano[3,2-*g*]chromen-8(11b*H*)-one 8.[11] This minor product was isolated as a colorless crystalline solid upon column chromatography from the preparation of **7** (19 mg, 8%): ν_{max} (neat)/cm^{-1} 2984, 2931, 1725, 1622, 1564, 1494, 1461, 1391, 1371, 1334, 1298, 1263, 1221, 1161, 1134, 1081, 1022, 967, 946, 922, 899, 865, 850, 821, 785, 751, 731; δ_H (300 MHz; $CDCl_3$) 1.16 (3H, s), 1.25 (3H, s), 1.42 (3H, s), 1.52 (3H, s), 3.71 (1H, d, *J* = 2.4 Hz), 4.45 (1H, d, *J* = 6.0 Hz), 5.16 (1H, d, *J* = 6.0 Hz), 6.25 (1H, d, *J* = 9.5 Hz), 6.78 (1H, s), 7.48 (1H, s), 7.62 (1H, d, *J* = 9.3 Hz); *m*/*z* 303.1226, $C_{17}H_{19}O_5$ [M + H^+] requires 303.1232.

(+)-(*R*)-7-Hydroxy-8,8-dimethyl-7,8-dihydropyrano[3,2-*g*]-chromene-2,6-dione 9. *Trans*-decursidinol **7** (0.055 g, 0.21 mmol) was dissolved in $CHCl_3$ (4 mL). Dess−Martin periodinane (0.89 g, 0.21 mmol) was added in two equal portions with an hour between additions. After the reaction was judged to have run to completion by TLC, the reaction was transferred to a separating funnel and washed with aqueous $NaHCO_3$ (15 mL). The aqueous phase was extracted with $CHCl_3$ (3 × 10 mL), the combined organic extracts were dried over $MgSO_4$, and the solvents were removed under reduced pressure. The crude yellow oil was purified by column chromatography, eluting with light petroleum/EtOAc (8:5) to give a colorless oil (0.52 g, 95%): $[\alpha]^{16}_D$ +31.4 (c = 0.51, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3289, 3062, 2984, 1736, 1698, 1610, 1560, 1483, 1445, 1389, 1372, 1336, 1284, 1201, 1140, 1101, 1018, 978, 905, 843, 826, 801, 764, 740, 657; δ_H (300 MHz; $CDCl_3$) 1.25 (3H, s) 1.68 (3H, s), 3.71 (1H, d, *J* = 2.4 Hz), 4.45 (1H, d, *J* = 2.3 Hz), 6.33 (1H, d, *J* = 9.3 Hz), 6.85 (1H, s), 7.67 (1H, d,

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J = 9.6 Hz), 7.99 (1H, s); δ_C (75 MHz; $CDCl_3$) 17.6, 26.6, 76.9, 84.7, 105.9, 113.7, 115.0, 116.2, 127.4, 143.0, 159.7, 159.8, 162.2, 193.1; m/z 261.0759, $C_{14}H_{13}O_5$ [M + H^+] requires 261.0763.

(+)-Scuteflorin A 1.[3] Oxalyl chloride (2.83 mL, 3.3 mmol) was added dropwise over a period of 5 min to a solution of 3,3-dimethyl acrylic acid (3.0 g, 30 mmol) in CH_2Cl_2 (25 mL). The reaction was stirred at room temperature for a further 1 h after the initial effervescence had ceased. Solvents were removed in vacuo without the use of a heated water bath. The excess oxalyl chloride was removed by three cycles of dissolution of the residue in chloroform and subsequent concentration in vacuo. 3,3-Dimethylacryloyl chloride was isolated as a pale-yellow oil (3.57 g, 99%): ν_{max} (neat)/cm^{-1} 2254, 1753, 1617, 1444, 1377, 1205, 1091, 1011, 904, 831, 764, 723, 650; δ_H (400 MHz; $CHCl_3$) 1.92 (3H, s), 2.11 (3H, s), 5.71 (1H, s); δ_C (75 MHz; $CHCl_3$) 21.5, 27.2, 122.6, 163.7, 164.3.[12] The α-hydroxy ketone **9** (0.041 g, 0.15 mmol) and $NaHCO_3$ (0.014 g, 0.17 mmol) were added to THF (2.0 mL), and the resulting suspension was stirred for 2 min prior to the addition of 3,3-dimethyl acryloyl chloride (0.087 mL, 0.75 mmol). The reaction was stirred until the consumption of the starting material had been observed by TLC (ca. 4 h). The reaction mixture was filtered and concentrated in vacuo. The crude oil was purified by column chromatography, eluting with petroleum ether/EtOAc (3.5:1). (+)-Scuteflorin A was isolated as a colorless amorphous solid (0.045 g, 88%): mp 139−140 °C; $[\alpha]^{22}_D$ +27.0 (c 0.38, MeOH); ν_{max} (neat)/cm^{-1} 2985, 2906, 1749, 1728, 1699, 1647, 1626, 1611, 1562, 1486, 1443, 1389, 1354, 1342, 1287, 1260, 1221, 1201, 1168, 1128, 1095, 1084, 1070, 1029, 913, 840, 823, 752, 740, 701, 655, 620, 600; δ_H (400 MHz; CD_3OD) 1.35 (3H, s), 1.53 (3H, s), 1.96 (3H, s), 2.18 (3H, s), 5.69 (1H, s), 5.82 (1H, s), 6.31 (1H, d, J = 9.6 Hz) 6.89 (1H, s), 7.91 (1H, d, J = 9.4 Hz), 8.06 (1H, s); δ_C (75 MHz; CD_3OD) 20.0, 20.7, 26.4, 27.7, 77.3, 84.2, 106.6, 115.76, 115.80, 118.9, 129.3, 145.4, 161.2, 161.7, 161.8, 163.1, 166.5, 189.3; m/z 343.1180, $C_{19}H_{19}O_6$ [M + H^+] requires 343.1182.

■ ASSOCIATED CONTENT

Supporting Information

General experimental methods, ^1H and ^{13}C NMR spectra, HPLC traces for xanthyletin oxide, and X-ray crystallographic analysis of **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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