HETEROCYCLES, Vol. 81, No. 11, 2010, pp. 2593 - 2598. © The Japan Institute of Heterocyclic Chemistry
Received, 29th July, 2010, Accepted, 31st August, 2010, Published online, 2nd September, 2010
DOI: 10.3987/COM-10-12030

TOTAL SYNTHESIS OF (±)-SCUTEFLORIN A

Fang Tan,[a] Liu-Lan Shen,[b] Young-Shin Kwak,[c]* and Jin-Hyun Jeong[a]*

[a]Department of Pharmaceutical Science, College of Pharmacy, Kyung Hee University, 1 Hoegi-dong, Dongdaemun-gu, Seoul 130-701, Republic of Korea, jeongjh@khu.ac.kr, [b]School of Pharmaceutical Engineering, ShenYang Pharmaceutical University, 103 WenHua Road, ShenHe District, ShenYang, LiaoNing 110016, P. R. China, liulanx@gmail.com, and [c]Bio Therapeutic Research Institute, Korea Research Institute of Bioscience & Biotechnology (KRIBB), 685-1 Yangcheong-ri, Ochang-eup, Cheongwon-gun, ChungBuk 363-883, Republic of Korea, yskwak@kribb.re.kr

Abstract – A highly efficient synthesis was developed for the first total synthesis of scuteflorin A.

Scutellaria lateriflora L. (also called "American skullcap") has long been used as an herbal medicine for treating neurological disorders such as anxiety, nervous tension, and convulsions in North America and Europe.[1] The therapeutic benefit of *S. lateriflora* has been validated by demonstrating significant anxiolytic effects of its aqueous extracts in rodent models and in healthy human volunteers.[2,3] In a recent study to reveal the chemical constituents of *S. lateriflora* extract, two new coumarins, scuteflorin A ((+)-**1**) and B ((+)-**2**), have been isolated and the fully characterized structures are shown in Figure 1.[4]

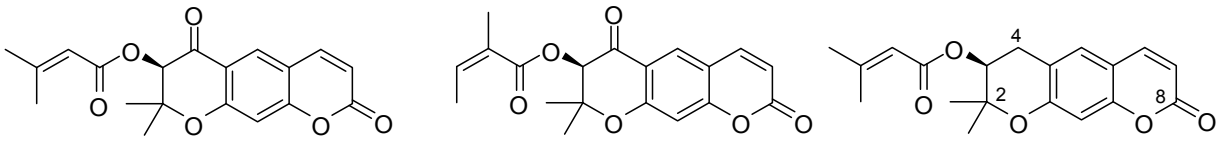
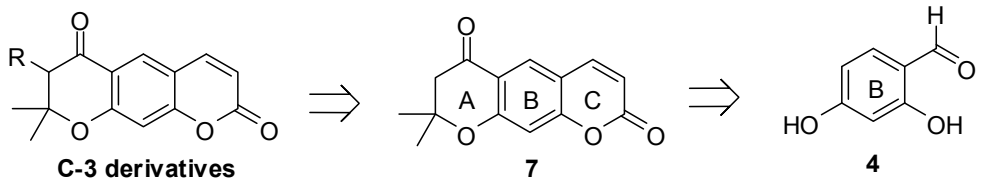


Figure 1

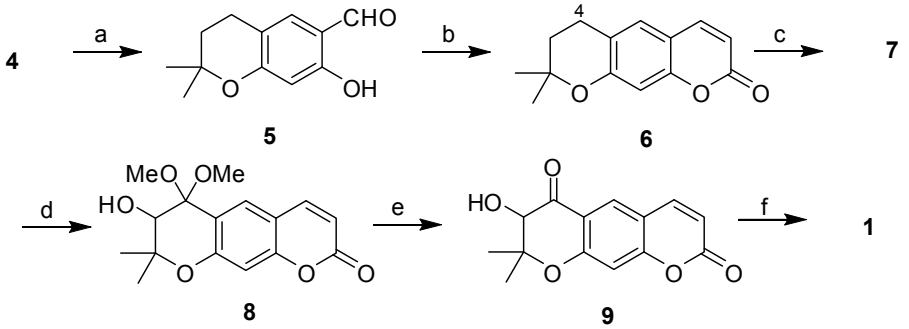
Scuteflorin A ((+)-**1**) is a very close analog of decursin (**3**),[5] differing from **3** only in C-4's oxidation state, and **3** therefore may be a precursor of (+)-**1** *via* a biotransformation. Decursin (**3**) is a well-known

cytotoxic PKC activator[5] and was also isolated from *S. lateriflora* extract in the same study. To unambiguously explain the mechanism of the *in vivo* pharmacology of **3**, profiling the biological activity and the toxicity of its potential metabolites is important, as in (+)-**1**. We thus sought to develop an efficient synthesis of **1**, and to assess its biological significance and its analogs to expedite the structure–activity relationship (SAR) study of scuteflorin and decursin analogs and to determine their therapeutic potential. We describe here the first total synthesis of (±)-scuteflorin A (**1**), with the aim of developing efficient syntheses of its analogs for biological evaluation.



Scheme 1. Retrosynthetic analysis of **1** from its C-3 derivatives

Our retrosynthetic analysis for **1** was developed with a view to designing a versatile synthetic route to **1** and its analogs, as depicted in Scheme 1. We envisioned that the advanced intermediate **7** should be a strategically convenient dividing point for approaching **1** and its C-3 derivatives. In turn, 2,4-dihydroxybenzaldehyde (**4**) would be a good motif for the B ring, potentially giving easy access to the formation of the A and C rings.



Scheme 2. Reagents and conditions: (a) 2-methyl-3-butene-2-ol, HCO_2H, reflux, 4h, 57%; (b) $Ph_3P{=}CHCO_2Et$, Et_2NPh, reflux, 0.5 h, 82%; (c) ceric ammonium nitrate, Et_2O–AcOH–H_2O, water bath, 30 min, 72%; (d) $PhI(OAc)_2$, KOH, MeOH, rt, 20 h; (e) 3 M HCl, MeOH, rt, 30 min, 64% for two steps; (f) senecioyl chloride, pyridine, CH_2Cl_2, rt, 3 h, 96%.

The synthesis of **1** is summarized in Scheme 2. In refluxing formic acid, 2,4-dihydroxybenzaldehyde (**4**) underwent an electrophilic alkylation with 2-methyl-3-buten-2-ol, followed by spontaneous cyclic ether

formation to afford **5** in a moderate 57% yield.[6] Wittig olefination of **5** in refluxing diethylaniline was accompanied by an intramolecular esterification to afford the unsaturated lactone **6** in 82% yield.[7] Oxidation of the methylene group (C-4) of **6** was achieved using ceric ammonium nitrate and provided the desired subtarget **7** in 72% yield.[8] C-3 hydroxylation of **6** by iodobenzene diacetate[9] in MeOH was accompanied by dimethylketal formation and produced **7**. The crude **7** was then immediately treated with 3 M HCl and transformed to the desired ketone **9** in 64% yield for the two steps. Finally, *O*-acylation of **9** with senecioyl chloride in the presence of pyridine provided racemic (±)-scuteflorin A (**1**), in an excellent yield. The spectral data of the synthetic racemic (±)-scuteflorin A (**1**) were identical to those reported for (+)-**1** from a natural source.[4]

In conclusion, we demonstrated the first total synthesis of racemic (±)-scuteflorin A (**1**) in a highly efficient manner, attesting to the viability of our synthetic strategy for the future SAR study of scuteflorin and decursin derivatives. Asymmetric synthesis of (+)-scuteflorin A ((+)-**1**) is currently under way. The biological activity of scuteflorin and its derivatives is under investigation and will be reported in due course.

GENERAL EXPERIMENTAL

Preparation of **5**: 2-Methyl-3-butene-2-ol (0.70 mL, 6.7 mmol) was added to a solution of **4** (1.38 g, 10.0 mmol) in 10 mL of 95% HCO_2H and stirred. The mixture was heated at reflux for 4 h and then cooled to room temperature. The reaction mixture was then poured into water (100 mL) with stirring and neutralized with solid $NaHCO_3$ to pH 7–8. The aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ and the volatiles were removed *in vacuo*. The crude product was purified by flash column chromatography using hexanes and EtOAc to afford **5** (0.76 g, 57%) as a white solid. Mp 97-98 °C. FT-IR (KBr): 1648 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ ppm: 1.36 (s, 6H), 1.83 (t, 2H, J = 6.6 Hz), 2.75 (t, 2H, J = 6.6 Hz), 6.32 (s, 1H), 7.21 (s, 1H), 9.66 (s, 1H), 11.06 (s, 1H). ^{13}C-NMR ($CDCl_3$) δ ppm: 21.45, 26.98, 26.98, 32.57, 76.27, 104.38, 113.78, 115.23, 135.30, 162.04, 162.14, 194.19. MS (ESI): $C_{12}H_{15}O_3$, 207.1 m/z, found 207.1 m/z $(M+H)^+$.

Preparation of **6**: Carbethoxynethylenetriphenylphosphorane (1.15 g, 3.3 mmol) was added to a solution of **5** (0.62 g, 3 mmol) in 12 mL of Et_2NPh and stirred. The stirred mixture was heated at reflux for 30 min. The reaction mixture was then cooled and diluted with water, and extracted with EtOAc. The organic extract was washed with 5% HCl, brine, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to provide **6** (0.57 g, 82%) as a white solid. Mp 122-123 °C. FT-IR (KBr): 1724 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ ppm: 1.57 (s, 6H), 1.85 (t, 1H), 2.82 (t, 1H),

6.19 (d, 1H, *J* = 9.5 Hz), 6.72 (s, 1H), 7.15 (s, 1H), 7.57 (d, 1H, *J* = 9.5 Hz). ^{13}C-NMR ($CDCl_3$) δ ppm: 21.91, 26.90, 26.90, 32.42, 75.78, 104.64, 112.20, 112.82, 118.41, 128.24, 143.36, 154.04, 157.76, 161.56. HRMS (ESI): calcd for $C_{14}H_{15}O_3$, 231.1021 m/z $(M+H)^+$, found 231.1024 m/z $(M+H)^+$.

Preparation of **7**: A solution of **6** (0.44 g, 1.8 mmol) in Et_2O (10 mL) was added to a well stirred solution of acetic acid (10 mL) in water (10 mL). Ceric ammonium nitrate (1.97 g, 3.6 mmol) was added in small portions to this stirred biphasic mixture. The reaction mixture was then heated in a water bath (20–30 min) with stirring. The reaction mixture was allowed to cool to room temperature and then diluted with water. The precipitate was filtered and purified by flash column chromatography on silica gel using hexane-EtOAc as the eluent to provide **7** (0.32 g, 72% yield). FT-IR (KBr): 1741, 1694 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ ppm: 1.50 (s, 6H), 2.78 (s, 2H), 6.31 (d, 1H, *J* = 9.6 Hz), 6.84 (s, 1H), 7.67 (d, 1H, *J* = 9.6 Hz), 8.03 (s, 1H). ^{13}C-NMR ($CDCl_3$), δ ppm: 26.72, 26.72, 48.65, 80.76, 105.61, 113.32, 114.04, 117.64, 127.37, 143.33, 159.27, 159.92, 162.39, 190.83. HRMS (ESI): calcd for $C_{14}H_{13}O_4$, 245.0814 m/z $(M+H)^+$, found 245.0814 m/z $(M+H)^+$.

Preparation of **9**: A solution of **7** (0.24 g; 1.0 mmol) in 10 mL of absolute MeOH was added to a stirred solution of KOH (0.17 g, 3.0 mmol) in MeOH (5 mL) over a period of 5 min at 0 °C. The stirring was continued and solid iodobenzene diacetate (0.39 g, 1.2 mmol) was added in three portions during 2 min period. The resulting mixture was stirred for an additional hour at 0 °C and then overnight at room temperature. Most of the MeOH was evaporated in vacuo and then water (20 mL) was added. After saturating the mixture with K_2CO_3, it was extracted with EtOAc (3 × 20 mL). The combined EtOAc extracts were dried with anhydrous $MgSO_4$ and concentrated *in vacuo*. This crude product suggested dimethyl acetal, **8**. FT-IR (KBr): 1737 cm^{-1}. ^{1}H-NMR ($CDCl_3$), δ ppm: 1.41 (s, 3H), 1.53 (s, 3H), 3.25 (s, 3H), 3.45 (s, 3H), 3.84 (s, 1H), 6.25 (d, 1H, *J* = 9.6 Hz), 6.79 (s, 1H), 7.65 (d, 1H, *J* = 9.6 Hz), 7.68 (s, 1H). ^{13}C-NMR (MeOH-d_4), δ ppm: 26.26, 26.66, 49.02, 49.35, 71.42, 81.90, 97.44, 104.99, 113.22, 113.44, 118.11, 131.10, 145.99, 156.75, 158.72, 163.16. HRMS (ESI): calcd for $C_{16}H_{19}O_6$, 307.1182 m/z $(M+H)^+$, found 307.1180 m/z $(M+H)^+$. The crude product was dissolved in 5 mL of 3 N HCl and stirred for 30 min at room temperature. Water (20 mL) was added and the mixture was stirred for a further 10 min. The pH of the mixture was adjusted to basic with solid K_2CO_3 and then the basic mixture was extracted with EtOAc (3 × 20 mL). The combined EtOAc extracts were dried with $MgSO_4$ and concentrated *in vacuo* to give a solid crude product. The crude product was purified by silica gel column chromatography using hexane and EtOAc to afford **9** (0.19 mg, 64%) as a white solid. Mp 144-145 °C. FT-IR (KBr): 1743, 1698 cm^{-1}. ^{1}H-NMR ($CDCl_3$), δ ppm: 1.26 (s, 3H), 1.69 (s, 3H), 3.76 (s, 1H), 4.47 (s, 1H), 6.34 (d, 1H, *J* = 9.6 Hz), 6.86 (s, 1H), 7.69 (d, 1H, *J* = 9.6 Hz), 8.00 (s, 1H). ^{13}C-NMR ($CDCl_3$), δ ppm: 17.74, 26.70, 76.91, 84.78, 105.83, 113.69, 114.96, 116.15, 127.44, 143.05, 159.68, 159.70, 162.03,

192.95. HRMS (ESI): calcd for $C_{14}H_{13}O_5$, 261.0763 m/z $(M+H)^+$, found 261.0763 m/z $(M+H)^+$.

Synthesis of **1**: A solution of **9** (0.26 g, 1.0 mmol) and pyridine (0.08 mL, 1.0 mmol) in anhydrous CH_2Cl_2 (15 mL) was stirred in an ice bath. Senecioyl chloride (0.12 mL) was added slowly and the reaction was stirred for 3 h. The reaction produced crystalline precipitates and was extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with water and brine, and then dried with $MgSO_4$. The volatiles were removed under reduced pressure and the crude product was purified by silica gel column chromatography using hexane and EtOAc to afford **1** as a white solid (0.33 g, 96.5%). Mp 139-140 °C. FT-IR (KBr): 1747, 1708 cm^{-1}. HRMS (ESI): calcd for $C_{19}H_{18}NaO_6$, 365.1001 m/z $(M+Na)^+$, found 365.1004 m/z $(M+Na)^+$. ^{1}H-NMR (MeOH-d_4), δ ppm: 1.39 (s, 3H), 1.57 (s, 3H), 2.00 (d, 3H, J = 1.2 Hz), 2.22 (d, 3H, J = 1.2 Hz), 5.73 (s, 1H), 5.86 (br, 1H), 6.35 (d,1H, J = 9.6 Hz), 6.93 (s, 1H), 7.95 (d, 1H, J = 9.6 Hz), 8.10 (s, 1H). ^{13}C-NMR (MeOH-d_4), δ ppm: 18.70, 19.42, 25.09, 26.38, 75.90, 82.77, 105.20, 114.32, 114.33, 114.36, 117.46, 127.80, 143.92, 159.69, 160.18, 160.31, 161.58, 164.93, 187.71. Comparison with natural product[4]: FT-IR: 2924, 1732, 1623$cm^{-1.}$ HRMS (ESI): *m/z* 365.1013 ($(M+Na)^+$, calcd for 365.1001). ^{1}H-NMR (MeOH-d_4), δ ppm: 1.39 (s, 3H), 1.58 (s, 3H), 1.97 (d, 3H, J = 1.2 Hz), 2.20 (d, 3H, J = 1.1 Hz), 5.71 (s, 1H), 5.85 (br, 1H), 6.36 (d,1H, J = 9.6 Hz), 6.90 (s, 1H), 8.04 (d, 1H, J = 9.6 Hz), 8.11 (s, 1H). ^{13}C-NMR (MeOH-d_4), δ ppm: 20.1, 20.5, 26.2, 27.5, 76.5, 83.6, 106.0, 115.1, 115.5, 115.6, 118.2, 128.7, 144.5, 159.9, 160.5, 160.6, 162.2, 165.23, 187.8.

ACKNOWLEDGMENT

This work was supported by a Korea Research Foundation grant funded by the Korean government (MOEHRD; KRF-2005-041-E00499).

REFERENCES (AND NOTES)

1. S. Foster, *Bus. Herbs*, 1996, **May/June**, 14.
2. R. Awad, J. T. Arnason, V. Trudeau, C. Bergeron, J. W. Budzinski, B. C. Foster, and Z. Merali, *Phytomedicine*, 2003, **10**, 640.
3. P. Wolfson and D. L. Hoffmann, *Altern. Ther. Health Med.*, 2003, **9**, 74.
4. J. Li, Y. Ding, X.-C. Li, D. Ferreira, S. Khan, T. Smillie, and I. A. Khan, *J. Nat. Prod.*, 2009, **72**, 983.
5. K. Hata and K. Sano, *Yakugaku Zasshi*, 1969, **89**, 549; K. Sano, I. Yosioka, and I. Kitagawa, *Chem. Pharm. Bull.*, 1973, **21**, 2095; K.-S. Ahn, W.-S. Sim, and I.-H. Kim, *Planta Med.*, 1996, **62**, 7; K.-S. Ahn, W-S. Sim, I.-K. Lee, Y.-B. Seu, and I.-H. Kim, *Planta Med.*, 1997, **63**, 360; For racemic syntheses of **1** and related natural coumarins, see: W. Steck, *Can. J. Chem.*, 1971, **49**, 2297; R. D.

Murray, M. Sutcliffe, and P. H. McCabe, *Tetrahedron*, 1971, **27**, 4901.

6. Q. Wang, X. She, X. Ren, J. Ma, and X. Pan, *Tetrahedron: Asymmetry*, 2004, **15**, 29.
7. S. Ray, A. Patra, and D. Mal, *Tetrahedron*, 2008, **64**, 3253.
8. M. N. Kanvinde, S. A. Kulkarni, and M. V. Paradkar, *Synth. Commun.*, 1990, **20**, 3259.
9. R. M. Moriarty, O. Praksh, and C. T. Thachet, *Synth. Commun.*, 1984, **14**, 1373.