Synthesis of an Advanced Intermediate of the Macrotricyclic Core of Roseophilin

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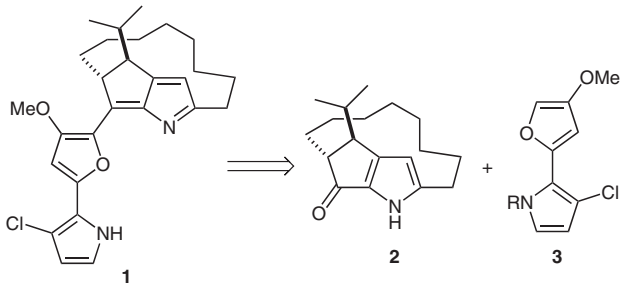
Abstract: A facile approach for the preparation of a cyclopenta[*b*]pyrrole derivative, the key precursor in Frontier's synthesis of the macrotricyclic core of roseophilin, was developed. The key steps involved two successive pyrrole acylations and a $Sc(OTf)_3$-catalyzed Nazarov cyclization reaction.

Key words: pyrrole acylation, Knoevenagel reaction, Nazarov cyclization, olefin cross-metathesis, scandium triflate

Roseophilin (**1**, Scheme 1), isolated from the culture broth of *Streptomyces griseoviridis* by Seto et al. in 1992, exhibits potent cytotoxicity against K562 human erythroid leukemia and KB human epidermoid carcinoma cell lines in the submicromolar range.[1] This alkaloid possesses a unique ansa-bridged cyclopenta[*b*]pyrrole skeleton incorporated with a conjugated pyrrolylfuran moiety. These properties render roseophilin an ideal target for total synthesis.[2,3] Quite unexpectedly, Boger's work showed that the unnatural enantiomer of roseophilin exhibits 2–10-fold higher cytotoxicity than the naturally occurring enantiomer.[2d]

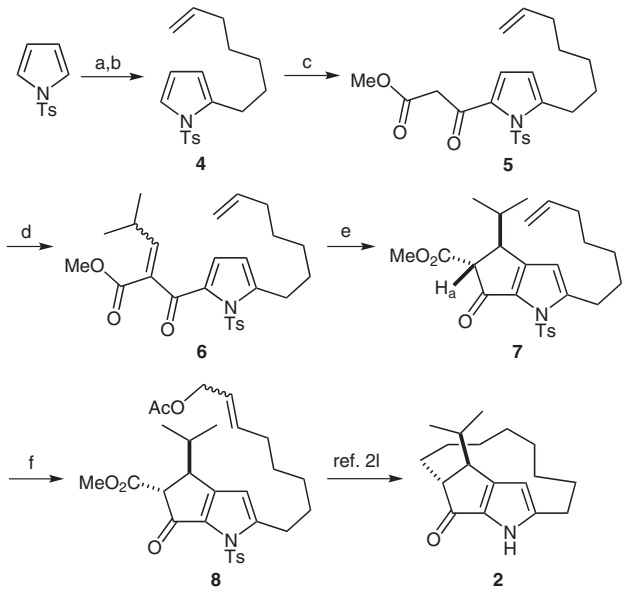


Scheme 1

The reported total syntheses of roseophilin to date[2a–d] are based on the same disconnection that includes the condensation of the macrotricyclic core **2** with the conjugated pyrrolylfuran portion **3**. Formal synthesis of roseophilin[2e–l] largely focused on development of new methodologies towards the construction of the tricyclic core **2**. Recently, Bitar and Frontier[2l] reported their synthesis of the tricyclic core **2**, and the precursor **8** for the palladium-catalyzed intramolecular Tsuji–Trost reaction[4] to form the 13-membered macrocyclic ring in 18 steps and <4% overall yield.

Herein, we report our approach to the synthesis of **8**, which was realized in six steps and >10% overall yield starting from a TFAA-mediated regioselective acylation of *N*-tosylpyrrole previously developed by one of us.[5]

As shown in Scheme 2, acylation of *N*-tosylpyrrole with 6-heptenoic acid[6] in the presence of TFAA, followed by reduction of the carbonyl group in the acylation product with borane-*tert*-butylamine complex in the presence of aluminum trichloride[7] delivered **4** in 37% isolated yield over two steps. A second acylation with monomethyl malonate and TFAA gave acylpyrrole **5**[8] in 61% yield. Knoevenagel condensation[9] between **5** and isobutyraldehyde provided **6**[10] as a mixture of *Z*- and *E*-isomers in a ratio of 1.7:1. Scandium(III)-catalyzed Nazarov cyclization[2l] of compound **6** gave cyclopenta[*b*]pyrrole **7**[11] in good yield, solely as the *trans* isomer. The stereochemical assignment of **7** was made on the basis of NOE correlations of H^a with both the methine and the methyl protons of the isopropyl group. Finally, cross olefin metathesis reaction[12] of **7** with allyl acetate gave **8**[13] in 79% isolated yield, as a mixture of *E*- and *Z*-isomers in a ratio of 6.4:1. Compound **8** could then be converted into **2** fol-



Scheme 2 *Reagents and conditions*: (a) 6-heptenoic acid, TFAA, DCE, 80 °C, 24 h, 56%; (b) BH_3·*t*-$BuNH_2$, $AlCl_3$, CH_2Cl_2, r.t., 15 min, 66%; (c) monomethyl malonate, TFAA, CH_2Cl_2, r.t., 30 h, 61%; (d) pyrrolidine, AcOH, 4 Å MS, CH_2Cl_2, 0 °C, 5 min, then isobutyraldehyde, 0 °C to r.t., 16 h, 73%; (e) $Sc(OTf)_3$, $LiClO_4$, DCE, reflux, 1 h, 81%; (f) Grubbs II catalyst, CH_2Cl_2, 40 °C, 24 h, 79%.

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lowing Frontier's procedure by palladium-catalyzed intramolecular Tsuji–Trost reaction to close the 13-membered macrocyclic ring, followed by double bond reduction, detosylation and Krapcho dealkoxycarbonylation.[21]

In summary, we have developed a facile synthesis of cyclopenta[*b*]pyrrole moiety **8**, which represents a valuable approach for the formal synthesis of roseophilin.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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References

(1) Hayakawa, Y.; Kawakami, K.; Seto, H. *Tetrahedron Lett.* **1992**, *33*, 2701.

(2) For total synthesis, see: (a) Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817. (b) Fürstner, A.; Gastner, T.; Weintritt, H. *J. Org. Chem.* **1999**, *64*, 2361. (c) Harrington, P. E.; Tius, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 8509. (d) Boger, D. L.; Hong, J. *J. Am. Chem. Soc.* **2001**, *123*, 8515. For formal synthesis, see: (e) Kim, S. H.; Figueroa, I.; Fuchs, P. L. *Tetrahedron Lett.* **1997**, *38*, 2601. (f) Mochizuki, T.; Itoh, E.; Shibata, N.; Nakatani, S.; Katoh, T.; Terashima, S. *Tetrahedron Lett.* **1998**, *39*, 6911. (g) Harrington, P. E.; Tius, M. A. *Org. Lett.* **1999**, *1*, 649. (h) Bamford, S. J.; Luker, T.; Speckamp, W. N.; Hiemstra, H. *Org. Lett.* **2000**, *2*, 1157. (i) Trost, B. M.; Doherty, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 3801. (j) Robertson, J.; Hatley, R. J. D.; Watkin, D. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3389. (k) Occhiato, E. G.; Prandi, C.; Ferrali, A.; Guarna, A. *J. Org. Chem.* **2005**, *70*, 4542. (l) Bitar, A. Y.; Frontier, A. J. *Org. Lett.* **2009**, *11*, 49. For synthetic studies, see: (m) Luker, T.; Koot, W.-J.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1998**, *63*, 220. (n) Fagan, M. A.; Knight, D. W. *Tetrahedron Lett.* **1999**, *40*, 6117. (o) Salamone, S. G.; Dudley, G. B. *Org. Lett.* **2005**, *7*, 4443. (p) Song, C.; Knight, D. W.; Whatton, M. A. *Org. Lett.* **2006**, *8*, 163.

(3) For a review, see: Fürstner, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 3582.

(4) Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, 4387.

(5) Song, C.; Knight, D. W.; Whatton, M. A. *Tetrahedron Lett.* **2004**, *45*, 9573.

(6) Starostin, E. K.; Furman, D. B.; Ignatenko, A. V.; Barkova, A. P.; Nikishin, G. I. *Russ. Chem. Bull. Int. Ed.* **2006**, *55*, 2016.

(7) Ketcha, D. M.; Carpenter, K. P.; Atkinson, S. T.; Rajagopalan, H. R. *Synth. Commun.* **1990**, *20*, 1647.

(8) Mp 75–77 °C. IR (KBr): 1743, 1678, 1643, 1594, 1488, 1358, 1258, 1172, 1110 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.0 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 6.94 (d, *J* = 3.6 Hz, 1 H), 6.08 (d, *J* = 3.6 Hz, 1 H), 5.81 (ddt, *J* = 17.2, 10.4, 6.8 Hz, 1 H), 5.01 (d, *J* = 17.2 Hz, 1 H), 4.96 (d, *J* = 10.4 Hz, 1 H), 3.82 (s, 2 H), 3.72 (s, 3 H), 2.92 (t, *J* = 7.8 Hz, 2 H), 2.43 (s, 3 H), 2.05 (m, 2 H), 1.65 (m, 2 H), 1.41 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.8, 167.8, 147.2, 144.9, 138.8, 136.5, 135.1, 129.6, 127.6, 123.5, 114.5, 111.5, 52.4, 47.3, 33.6, 28.9, 28.8, 28.6, 21.7. MS (ESI): *m/z* (%) = 440 (100) $[M + Na]^+$, 424 (5), 418 (6) $[M + H]^+$. HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{22}H_{27}NNaO_5S$: 440.1508; found: 440.1521.

(9) Ranu, B. C.; Jana, R. *Eur. J. Org. Chem.* **2006**, 3767; and references cited therein.

(10) IR (neat): 1724, 1662, 1597, 1557, 1480, 1435, 1371, 1330, 1294, 1247, 1191, 1175, 1103. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.04 (m, 2 H), 7.34 (d, *J* = 8.0 Hz, 2 H), 6.84 (d, *J* = 11.2 Hz, 0.63 H), 6.78 (d, *J* = 3.6 Hz, 0.63 H), 6.62 (d, *J* = 3.6 Hz, 0.37 H), 6.60 (d, *J* = 10.4 Hz, 0.37 H), 6.08 (d, *J* = 3.6 Hz, 0.63 H), 6.02 (d, *J* = 3.6 Hz, 0.37 H), 5.80 (ddt, *J* = 16.8, 10.4, 6.4 Hz, 1 H), 5.01 (d, *J* = 16.8 Hz, 1 H), 4.95 (d, *J* = 10.4 Hz, 1 H), 3.80 (s, 1.11 H), 3.68 (s, 1.89 H), 3.01 (t, *J* = 7.6 Hz, 1.26 H), 2.84 (t, *J* = 7.6 Hz, 0.74 H), 2.51 (m, 1 H), 2.43 (s, 3 H), 2.05 (m, 2 H), 1.68 (m, 1.26 H), 1.59 (m, 0.74 H), 1.36–1.44 (m, 4 H), 1.10 (d, *J* = 6.4 Hz, 2.22 H), 0.96 (d, *J* = 6.4 Hz, 3.78 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 182.5, 180.5, 166.3, 165.5, 157.5, 154.7, 148.3, 145.0, 144.9, 144.8, 138.8, 136.8, 136.3, 135.8, 134.8, 133.9, 131.3, 129.7, 129.5, 125.7, 122.3, 114.5, 114.4, 111.1, 110.9, 52.2, 52.1, 33.6, 29.5, 29.2, 28.9, 28.9, 28.7, 28.6, 28.3, 22.0, 21.8, 21.7. MS (ESI): *m/z* (%) = 494 (100) $[M + Na]^+$, 472 (10) $[M + H]^+$. HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{26}H_{33}NNaO_5S$: 494.1977; found: 494.1986.

(11) IR (neat): 1743, 1704, 1639, 1597, 1483, 1440, 1380, 1366, 1229, 1192, 1182, 1133, 1087, 1027, 970 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.4 Hz, 2 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 6.08 (s, 1 H), 5.82 (ddt, *J* = 17.2, 10.4, 6.8 Hz, 1 H), 5.03 (dd, *J* = 17.2, 1.6 Hz, 1 H), 4.97 (d, *J* = 10.4 Hz, 1 H), 3.77 (s, 3 H), 3.57 (d, *J* = 3.2 Hz, 1 H), 3.26 (dd, *J* = 5.8, 3.2 Hz, 1 H), 2.99 (m, 2 H), 2.42 (s, 3 H), 2.08 (m, 2 H), 1.92 (m, 1 H), 1.69–1.72 (m, 2 H), 1.44–1.46 (m, 4 H), 0.94 (d, *J* = 6.6 Hz, 3 H), 0.89 (d, *J* = 6.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.7, 170.3, 159.3, 152.2, 145.5, 138.8, 135.8, 132.5, 130.0, 127.8, 114.5, 109.0, 61.8, 52.6, 44.4, 33.6, 31.2, 28.8, 28.7, 28.6, 28.5, 21.7, 19.8, 19.7. MS (ESI): *m/z* (%) = 494 (100) $[M + Na]^+$, 472 (75) $[M + H]^+$. HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{26}H_{33}NNaO_5S$: 494.1977; found: 494.1980.

(12) (a) Schuster, M.; Blechert, S. *Angew. Chem. Int. Ed.* **1997**, *36*, 2036. (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (c) Connon, S. J.; Blechert, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 1900. (d) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4592. (e) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360. (f) Hoveyda, A. H.; Zhugralin, A. R. *Nature (London)* **2007**, *450*, 243.

(13) IR (neat): 1736, 1702, 1597, 1483, 1438, 1380, 1321, 1229, 1181, 1134, 1089, 1026 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.4 Hz, 2 H), 7.32 (d, *J* = 8.4 Hz, 2 H), 6.08 (s, 1 H), 5.57–5.83 (m, 2 H), 4.65 (d, *J* = 6.6 Hz, 0.28 H), 4.54 (d, *J* = 6.6 Hz, 1.72 H), 3.78 (s, 3 H), 3.58 (d, *J* = 3.0 Hz, 1 H), 3.26 (dd, *J* = 6.0, 3.0 Hz, 1 H), 2.99 (m, 2 H), 2.43 (s, 3 H), 2.09 (m, 5 H), 1.92 (m, 1 H), 1.72 (m, 2 H), 1.46 (m, 4 H), 0.94 (d, *J* = 6.8 Hz, 3 H), 0.90 (d, *J* = 6.8 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.7, 170.9, 170.3, 159.4, 152.1, 145.5, 136.1, 135.7, 132.5, 129.9, 127.7, 124.0, 109.1, 65.2, 61.7, 52.6, 44.4, 32.0, 31.2, 28.8, 28.8, 28.6, 28.5, 21.7, 21.0, 19.8, 19.6. MS (ESI): *m/z* (%) = 566 (100) $[M + Na]^+$, 552 (12), 544 (10) $[M + H]^+$. HRMS-ESI: *m/z* $[M + Na]^+$ calcd for $C_{29}H_{37}NNaO_7S$: 566.2188; found: 566.2201.