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Convergent Formal Synthesis of (±)-Roseophilin

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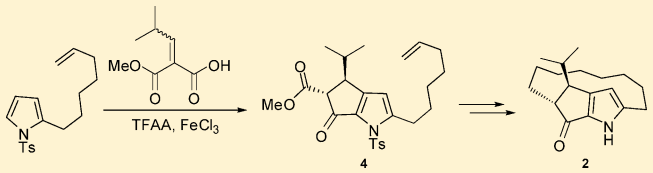
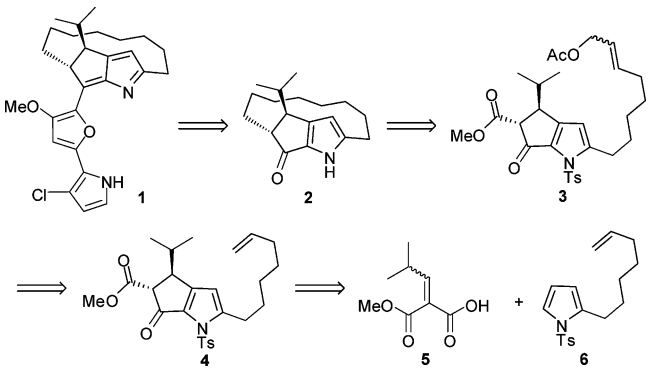
Supporting Information

ABSTRACT: A facile convergent synthesis of the tricyclic core **2** of roseophilin is described, which represents the shortest route so far for the formal synthesis of roseophilin. The key step was a tandem pyrrole acylation-Nazarov cyclization reaction to form the cyclopenta[*b*]pyrrole moiety **4**.



Roseophilin (**1**, Scheme 1), isolated from the culture broth of *Streptomyces griseoviridis* by Seto et al. in 1992,[1] has

Scheme 1. Retrosynthetic Analysis of Roseophilin



stimulated the synthetic effort of several research groups[2−17] because of its highly promising antitumor property and topologically interesting ansa-bridged azafulvene macrocyclic core structural unit. Remarkably, Boger's work indicated that the unnatural enantiomer of roseophilin exhibits 2−10-fold higher cytotoxicity than the naturally occurring enantiomer.[11]

There are three reported total syntheses of roseophilin to date. Since Fürstner reported the first total synthesis of racemic roseophilin,[2,6] Boger[11] and Tius[12] have described the asymmetric synthesis of *ent*-(−)-roseophilin and the natural enantiomer, respectively. Formal synthesis of roseophilin[3−5,7−10,13−16] largely focused on the development of new methodologies toward the construction of the macrotricyclic core **2**. Recently, Bitar and Frontier described a scandium(III) triflate-catalyzed Nazarov cyclization reaction of pyrrolyl vinyl ketone derivative to form the cyclopenta[*b*]pyrrole moiety as a key step in their synthesis of **2**.[16,18] However, this otherwise valuable approach required 17 steps to prepare the precursor required for Nazarov cyclization. Herein, we report our strategy to the synthesis of **2** featuring a tandem pyrrole acylation−Nazarov cyclization reaction[15] as the key step to form the cyclopenta[*b*]pyrrole moiety (i.e., **5** + **6** → **4**), and the retrosynthetic analysis is shown in Scheme 1. A late-stage intramolecular Tsuji−Trost reaction of **3** would eventually close the 13-membered ring.

As shown in Scheme 2, 2-methoxycarbonyl-4-methylpentenoic acid **5** was obtained in 92% overall yield as a mixture of *Z*/*E* isomers in 3:2 ratio via Knoevenagel condensation[19] between *tert*-butyl methyl malonate and isobutyraldehyde, followed by removal of the *tert*-butyl group with TFA.

On the other hand, regioselective acylation of *N*-tosylpyrrole with 6-heptenoic acid[20] in the presence of TFAA delivered acylpyrrole **8** in 56% isolated yield (Scheme 3).[21] Reduction of the carbonyl group in **8** with borane-*t*-butylamine complex in the presence of aluminum trichloride[22] gave 2-(6′-heptenyl)-pyrrole **6**. Longer reaction times or use of excess of the borane complex resulted in the double bond being destroyed. After some experiments, it was found that the optimized reaction condition was to treat acylpyrrole **8** with 1.5 equiv of the borane complex and 1 equiv of aluminum trichloride for 15 min at 0 °C, which resulted in the formation of pyrrole **6** in 66% isolated yield. With **5** and **6** in hand, we then attempted the key tandem pyrrole acylation−Nazarov cyclization reaction. When **6** was subjected to **5** and TFAA, the reaction proceeded very slowly and gave a variety of products. The desired cyclopenta-[*b*]pyrrole derivative **4** could only be isolated in low yield after prolonged reflux in DCE. Presumably, the inefficiency of the acylation and subsequent Nazarov cyclization reaction was due to the electron-withdrawing as well as the cation-destabilizing nature of the methoxycarbonyl group at C-2 of **5**.[21,23,15] That both pyrrole acylation and Nazarov cyclization reactions could be catalyzed by Lewis acids promoted us to investigate their effect in our tandem reaction. However, when $Ti(O^iPr)_4$ or $AlCl_3$ was used, little improvement was observed. Use of $Sc(OTf)_3$, which was found by Frontier to be the most reactive catalyst for the Nazarov cyclization of pyrrolyl vinyl ketones,[24,16] resulted in hydration of the double bond. To our delight, when $FeCl_3$ was applied, the tandem pyrrole acylation−Nazarov cyclization reaction proceeded smoothly

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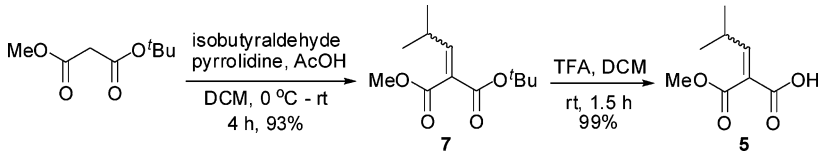
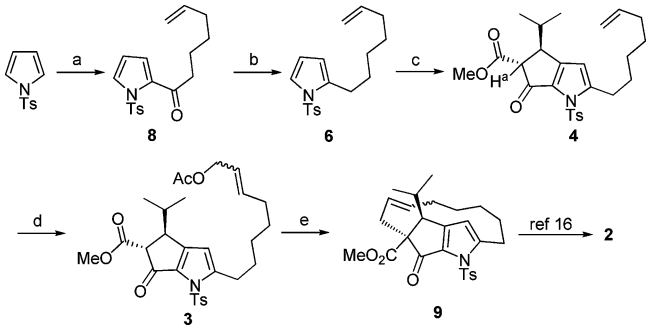
Scheme 2. Synthesis of Compound 5



Scheme 3. [a]



[a]Reagents and conditions: (a) 6-heptenoic acid, TFAA, DCE, 80 °C, 24 h, 56%; (b) BH_3·*t*-$BuNH_2$, $AlCl_3$, DCM, 0 °C, 15 min, 66%; (c) **5**, TFAA, $FeCl_3$, DCE, 80 °C, 10 h, 75%; (d) allyl acetate, Grubbs 2nd generation catalyst, DCM, 40 °C, 24 h, 79%; (e) NaH, $Pd(OAc)_2$, dppe, THF, reflux, 24 h, 38%.

and resulted in the formation of **4** in 75% isolated yield, solely as the trans isomer. The stereochemical assignment was made on the basis of NOE correlations of H^a with the methine as well as the methyl protons of the isopropyl group. Next, cross olefin metathesis reaction[25] of **4** with allyl acetate gave **3** in 79% isolated yield as a mixture of *E*/*Z* isomers in a ratio of 6.4:1. Finally, a palladium-catalyzed intramolecular Tsuji–Trost reaction[26,27] delivered **9** in moderate yield, which could be converted into **2** following known literature procedures by hydrogenation of the double bond, detosylation, and Krapcho dealkoxycarbonylation reaction.[16]

In summary, we have developed an eight-step synthesis of the macrotricyclic core **2** of roseophilin starting from acylation of *N*-tosylpyrrole with 6-heptenoic acid and TFAA. This approach represents the shortest route so far for the formal total synthesis of (±)-roseophilin. Future work will focus on development of an asymmetric version of the tandem pyrrole acylation–Nazarov cyclization reaction.

EXPERIMENTAL SECTION

Solvents were dried according to standard procedures where needed. IR spectra were obtained using an IFS25 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were obtained on a Bruker AV400 instrument. Mass spectra were recorded on a Micromass Q-TOF mass spectrometer.

2-(6′-Heptenoyl)-*N*-tosylpyrrole 8. To a solution of *N*-tosylpyrrole (5.0 g, 22.6 mmol) in DCE (50 mL) were added 6-heptenoic acid (8.0 g, 62.4 mmol) and TFAA (14.2 mL). The resulting mixture was refluxed for 24 h and cooled. Water was added carefully until no bubbling was observed. The mixture was washed successively with water (50 mL), saturated aqueous sodium bicarbonate (50 mL), and brine (50 mL). The separated organic phase was dried (Na_2SO_4), filtered, and evaporated. The residue was purified by column chromatography on silica gel (10% ethyl acetate in petroleum ether) to give acylpyrrole **8** (4.2 g, 56%) as a colorless oil: ν_{max}/cm^{-1} 1677, 1640, 1596, 1440, 1401, 1367, 1174, and 1145; δ_H (400 MHz, $CDCl_3$) 7.88 (2H, d, *J* = 8.2 Hz), 7.78 (1H, dd, *J* = 2.8 and 1.6 Hz), 7.28 (2H, d, *J* = 8.2 Hz), 7.03 (1H, dd, *J* = 3.6 and 1.6 Hz), 6.31 (1H, t, *J* = 3.2 Hz), 5.74 (1H, ddt, *J* = 17.2, 10.4, and 7.2 Hz), 4.96 (1H, dd, *J* = 17.2 and 1.6 Hz), 4.91 (1H, d, *J* = 10.4 Hz), 2.66 (2H, t, *J* = 7.2 Hz), 2.37 (3H, s), 2.00 (2H, q, *J* = 7.2 Hz), 1.60 (2H, quint, *J* = 7.2 Hz), and 1.34 (2H, quint, J = 7.2 Hz); δ_C (100 MHz, $CDCl_3$) 188.2, 144.7, 138.4, 135.9, 133.3, 130.0, 129.3, 128.3, 123.4, 114.6, 110.3, 39.2, 33.5, 28.3, 24.3, and 21.6; *m*/*z* (ESI) 354 ([M + Na]$^+$, 100%) and 332 ([M + H]$^+$, 10) [found [M + Na]$^+$ 354.1160, $C_{18}H_{21}NNaO_3S$ requires 354.1140].

2-(6′-Heptenyl)-*N*-tosylpyrrole 6. A mixture of borane-*tert*-butylamine complex (1.0 g, 11.76 mmol) and aluminum trichloride (1.0 g, 7.84 mmol) in dry DCM (100 mL) was stirred at rt for 30 min before being cooled to 0 °C. A solution of 2-(6′-heptenoyl)-*N*-tosylpyrrole **8** (2.6 g, 7.84 mmol) dissolved in 80 mL of dry DCM was added dropwise over 10 min. After addition, the resulting mixture was stirred for a further 5 min and then quenched with ice water. The separated aqueous phase was extracted with DCM (50 mL). The combined organic phase was dried (Na_2SO_4), filtered, and evaporated. The residue was purified by column chromatography on silica gel (5% ethyl acetate in petroleum ether) to give pyrrole **6** (1.7 g, 66%) as a colorless oil: ν_{max}/cm^{-1} 1597, 1367, 1175, and 1154; δ_H (400 MHz, $CDCl_3$) 7.66 (2H, d, *J* = 8.4 Hz), 7.31–7.29 (3H, m), 6.22 (1H, t, *J* = 3.4 Hz), 6.02 (1H, m), 5.82 (1H, ddt, *J* = 17.0, 10.0, and 6.8 Hz), 5.02 (1H, dd, *J* = 17.0 and 1.4 Hz), 4.97 (1H, d, *J* = 10.0 Hz), 2.69 (2H, t, *J* = 7.6 Hz), 2.41 (3H, s), 2.05 (2H, q, *J* = 6.8 Hz), 1.58 (2H, quint, *J* = 7.4 Hz), and 1.43–1.34 (4H, m); δ_C (100 MHz, $CDCl_3$) 144.8, 138.9, 136.6, 135.9, 130.0, 126.7, 122.2, 114.4, 111.8, 111.3, 33.7, 28.8, 28.7, 28.5, 27.1, and 21.6; *m*/*z* (ESI) 340 ([M + Na]$^+$, 100%) [found [M + Na]$^+$ 340.1338, $C_{18}H_{23}NNaO_2S$ requires 340.1347].

***trans*-2-(6′-Heptenyl)-4-isopropyl-5-methoxycarbonyl-1-tosylcyclopenta[*b*]pyrrol-6-one 4.** To a solution of heptenylpyrrole **6** (214 mg, 0.67 mmol), 2-methoxycarbonyl-4-methylpentenoic acid **5** (230 mg, 1.35 mmol), and TFAA (0.3 mL) in dry DCE (30 mL) was added ferric trichloride (33 mg, 0.20 mmol). The resulting mixture was heated to reflux for 10 h and then cooled to rt. The bulk of solvent was evaporated in vacuo. The residue was partitioned between ethyl acetate (50 mL) and water (50 mL). The separated organic phase was dried (Na_2SO_4), filtered, and evaporated. The residue was purified by column chromatography on silica gel (15% ethyl acetate in petroleum ether) to give the title compound **4** (237 mg, 75%) as an orange oil: ν_{max}/cm^{-1} 1743, 1704, 1440, 1380, 1366, and 1229; δ_H (400 MHz, $CDCl_3$) 8.01 (2H, d, *J* = 8.4 Hz), 7.31 (2H, d, *J* = 8.4 Hz), 6.08 (1H, s), 5.82 (1H, ddt, *J* = 17.2, 10.4, and 6.8 Hz), 5.03 (1H, dd, *J* = 17.2 and 1.6 Hz), 4.97 (1H, d, *J* = 10.4 Hz), 3.77 (3H, s), 3.57 (1H, d, *J* = 3.2 Hz), 3.26 (1H, dd, *J* = 5.8 and 3.2 Hz), 3.06–2.92 (2H, m), 2.42 (3H, s), 2.10–2.06 (2H, m), 1.92 (1H, m), 1.72–1.69 (2H, m), 1.46–1.44 (4H, m), 0.94 (3H, d, *J* = 6.6 Hz), and 0.89 (3H, d, *J* = 6.6 Hz); δ_C (100 MHz, $CDCl_3$) 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, 28.8, 28.7, 28.6, 21.7, 19.8, and 19.7; *m*/*z* (ESI) 494 ([M + Na]$^+$, 100%) and 472 ([M + H]$^+$, 75) [found [M + Na]$^+$ 494.1980, $C_{26}H_{33}NNaO_5S$ requires 494.1977].

***trans*-2-(8′-Acetoxy-6′-octenyl)-4-isopropyl-5-methoxycarbonyl-1-tosylcyclopenta[*b*]pyrrol-6-one 3.** A mixture of **4** (110 mg, 0.23 mmol), allyl acetate (233 mg, 2.33 mmol), and Grubbs second generation catalyst (20 mg, 0.02 mmol) in DCM (250 mL) under nitrogen was refluxed for 24 h and cooled. The bulk of DCM was removed in vacuo. The residue was purified by column chromatography on silica gel (15% ethyl acetate in petroleum ether) to give the title compound **3** (99 mg, 79%) as an orange oil: ν_{max}/cm^{-1} 1736, 1702, 1597, 1483, 1438, 1380, 1321, 1229, 1181, 1134, 1089, and 1026; δ_H (400 MHz, $CDCl_3$) 8.01 (2H, d, *J* = 8.4 Hz), 7.32 (2H, d, *J* = 8.4 Hz), 6.08 (1H, s), 5.83–5.57 (2H, m), 4.65 (0.28H, d, *J* =

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6.6 Hz), 4.54 (1.72H, d, J = 6.6 Hz), 3.78 (3H, s), 3.58 (1H, d, J = 3.0 Hz), 3.26 (1H, dd, J = 6.0 and 3.0 Hz), 3.06−2.92 (2H, m), 2.43 (3H, s), 2.09 (5H, m), 1.92 (1H, m), 1.72 (2H, m), 1.46 (4H, m), 0.94 (3H, d, J = 6.8 Hz), and 0.90 (3H, d, J = 6.8 Hz); m/z (ESI) 566 ([M + Na]$^+$, 100%), 552 (12) and 544 ([M + H]$^+$, 10) [found [M + Na]$^+$ 566.2201, $C_{29}H_{37}NNaO_7S$ requires 566.2188].

Synthesis of Macrocycle 9. To a solution of **3** (529 mg, 0.97 mmol) in dry THF (10 mL) was added sodium hydride (60% w/w dispersion in mineral oil; 50 mg, 1.17 mmol). The resulting mixture (solution A) was stirred at ambient temperature for 0.5 h. A separate flask was charged with palladium acetate (44 mg, 0.19 mmol), dppe (194 mg, 0.49 mmol), and dry THF (30 mL). The mixture was heated to reflux. Solution A was added dropwise over a period of 1 h. After addition, the reaction was allowed to reflux for 23 h and then cooled and quenched with water (60 mL). The separated aqueous phase was extracted with ethyl acetate (60 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was dissolved in DCM (20 mL), which was added dropwise to a solution of dimethyl maleate (100 mg) and aluminum trichloride (10 mg) in DCM (10 mL). The resulting mixture was stirred at ambient temperature for 6 h. Water (20 mL) was added. The separated organic phase was dried ($MgSO_4$), filtered, and evaporated in vacuo. The residue was purified by column chromatography on silica gel (15% ethyl acetate in petroleum ether) to give macrocycle **9** (178 mg, 38%) as an orange oil: ν_{max}/cm^{-1} 1736, 1701, 1640, 1597, 1484, 1433, 1386, 1214, 1192, and 1182; δ_H (400 MHz, $CDCl_3$) 8.07 (2H, d, J = 8.0 Hz), 7.30 (2H, d, J = 8.0 Hz), 5.98 (1H, s), 5.21 (1H, dt, J = 15.6 and 6.4 Hz), 4.75 (1H, dt, J = 15.6 and 7.6 Hz), 3.77 (3H, s), 3.40 (1H, dt, J = 14.4 and 5.2 Hz), 2.76 (1H, d, J = 4.4 Hz), 2.75−2.57 (3H, m), 2.41 (3H, s), 1.99 (3H, m), 1.57 (1H, m), 1.07 (1H, m), 0.97 (3H, d, J = 6.8 Hz), 0.83 (2H, m), 0.64 (2H, m), and 0.57 (3H, d, J = 6.8 Hz); δ_C (100 MHz, $CDCl_3$) 185.5, 172.1, 158.2, 152.2, 145.7, 136.5, 136.3, 134.2, 130.0, 128.4, 124.3, 115.1, 70.2, 52.4, 51.0, 41.3, 30.7, 29.2, 28.9, 28.2, 27.7, 24.6, 23.1, 22.0, and 19.5; m/z (ESI) 506 ([M + Na]$^+$, 100%) and 484 ([M + H]$^+$, 40) [found [M + Na]$^+$ 506.1979, $C_{27}H_{33}NNaO_5S$ requires 506.1977].

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra for compounds **3**, **4**, **6**, **8**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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