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A Formal Total Synthesis of Roseophilin: Cyclopentannelation Approach to the Macrocyclic Core

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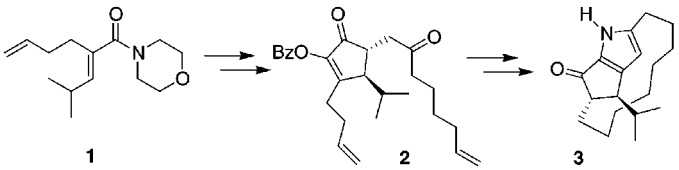
ABSTRACT

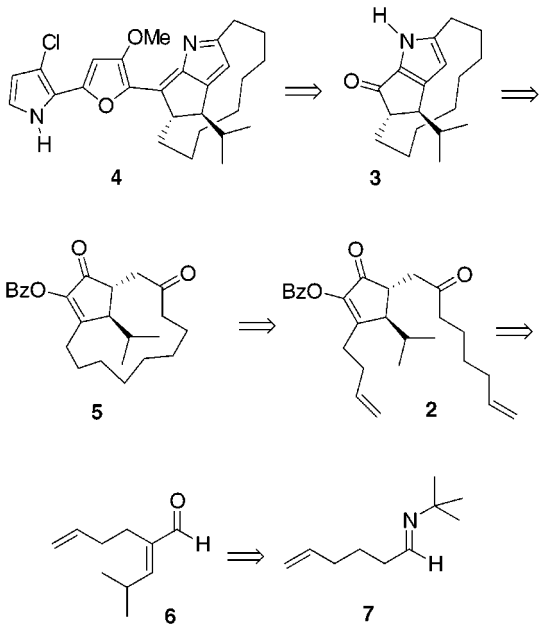


The formal total synthesis of the macrocyclic core of roseophilin 4 has been accomplished in 12 steps from 5-hexenal 8. The cyclopentannelation reaction was used to form the aliphatic five-membered ring of 3. Diene 2 was assembled by means of a Stetter reaction. Ring-closing metathesis of 2, reduction, and Knorr reaction of the 1,4-diketone 5 gave the ketopyrrole 3.

Roseophilin **4**, a structurally unique metabolite, was recently isolated from the culture broth of *Streptomyces griseoviridis* by Seto et al.[1] It shows high activity against K562 and KB cell lines in the sub-micromolar range. The high activity coupled with the unique structure has made roseophilin **4** a popular target for synthesis.[2] The first total synthesis was accomplished by Fürstner et al.[2f] Their concise synthesis utilized **3** as an advanced intermediate that, after protection of the pyrrole nitrogen atom with a SEM group, was coupled with the pyrrolylfuran side chain. Deprotection followed by loss of water gave racemic roseophilin **4**. During the same period, Fuchs reported a synthesis of the macrocyclic core via a difficult ring-closing metathesis reaction of a conformationally biased diene.[2c]

Our retrosynthetic approach to the roseophilin core **3** is shown in Scheme 1. A potentially challenging step in the synthesis, the macrocyclization via a ring-closing metathesis reaction,[3] was not envisioned to be problematic for the

Scheme 1



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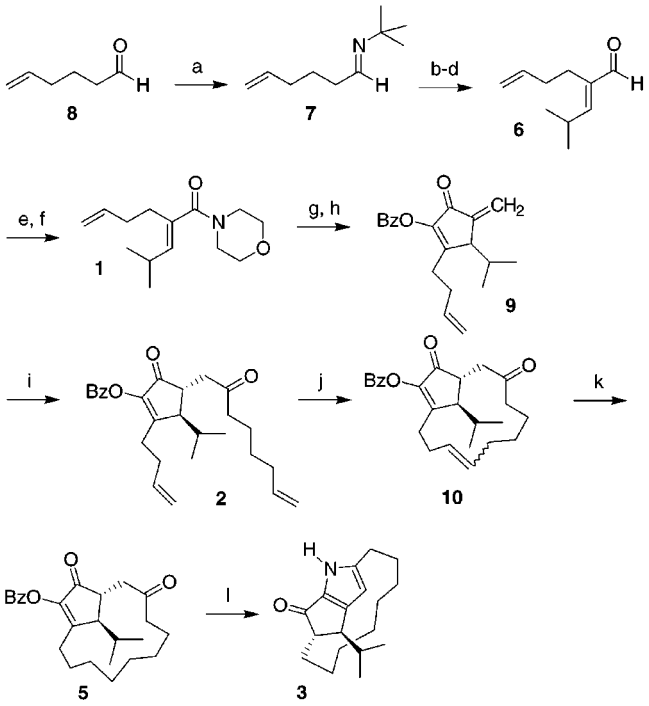
relatively unstrained, conformationally flexible diene **2**. Two key steps in the synthesis, the cyclopentannelation reaction and the attachment of the 7-carbon alkene fragment, provide diene **2**. The five-membered ring formation by the cyclopentannelation reaction,[4] a variant of the Nazarov cyclization, allows for the rapid assembly of the substituted α-methylenecyclopentenone. Peterson olefination provides the α,*β*-unsaturated aldehyde **6** with the desired *E* stereochemistry.

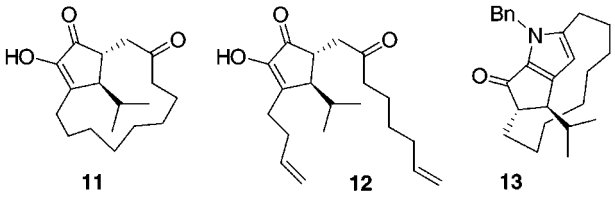
The synthesis starts with the formation of the *tert*-butylimine of 5-hexenal[5] **7** in 94% yield (Scheme 2).[6]

Scheme 2



(a) *t*-BuNH$_2$, rt, 94%; (b) LDA, TMSCl, THF, −78 to +10 °C; (c) LDA, *i*-PrCHO, −78 to +10 °C; (d) (COOH)$_2$, THF, H$_2$O, 71% (three steps); (e) NaClO$_2$, KH$_2$PO$_4$, 2-methyl-2-butene; (f) CBr$_4$, PPh$_3$, morpholine, 88% (two steps); (g) (i) α-(methoxy)methoxy-α-lithioallene, THF, −78 °C; (ii) AcOH; (h) BzCl, Et$_3$N, 49% (two steps); (i) 6-heptenal, Et$_3$N, 3-benzyl-5-(hydroxyethyl)-4-methylthiazolium chloride, 1,4-dioxane, 60%; (j) Grubbs' catalyst, 0.0005 M, 40 °C, 90%; (k) H$_2$, Pd/C, THF, 92%; (l) (NH$_4$)$_2$CO$_3$, propionic acid, 140 °C, 10 h, 52%.

Conversion of **7** to the α-TMS derivative was accomplished by deprotonation with LDA followed by addition of TMSCl.[7] The hydrolytically labile α-TMS imine of **7** was carried on without purification after aqueous workup. Deprotonation with LDA followed by addition of isobutyraldehyde gave the α,*β*-unsaturated imine after aqueous workup. Imine hydrolysis with oxalic acid in THF/H$_2$O (1:1) and column chromatography gave the aldehyde **6** in 71% yield as a single isomer following column chromatography. Oxidation of **6** under standard conditions[8] with NaClO$_2$ and 2-methyl-2-butene with a KH$_2$PO$_4$ buffer gave the α,*β*-unsaturated acid, which was used crude in the next step. Amide formation with CBr$_4$, PPh$_3$, and morpholine[9] gave **1** in 88% yield over two steps from aldehyde **6**. Formation of the protected α-methylenecyclopentenone **9** was accomplished via addition of α-(methoxy)methoxy-α-lithioallene at −78 °C to the morpholine amide[10] **1** followed by quenching with a solution of acetic acid in THF at −78 °C. Cyclization to the α-methylenecyclopentenone occurs spontaneously during workup without addition of strong acid.[11] Protection of the hydroxy group as the benzoate ester gave the α-methylenecyclopentenone **9** in 49% yield from morpholine amide **1**. Addition of the acyl carbanion equivalent of 6-heptenal to cyclopentenone **9** could have been accomplished in a number of different ways.[12] The addition was accomplished in a single step by means of the underutilized Stetter reaction.[13] Heating a mixture of **9** and 2 equiv of 6-heptenal[14] in the presence of catalytic Et$_3$N and 3-benzyl-5-(hydroxyethyl)-4-methylthiazolium chloride in 1,4-dioxane gave *trans*-diene **2**[15] in 60% yield.[16] It should be noted that loss of the benzoate under these conditions, which was envisioned to be a potential problem, did not occur to any appreciable extent. Diene **2** was accompanied by 9% of the cis isomer, which was easily separated by column chromatography. Additionally, no products arising from addition of 6-heptenal to the less reactive endocyclic *β*-carbon were isolated.



Two complementary strategies suggest themselves for the conversion of **2** to **3**: ring-closing metathesis, reduction,

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(11) Tius, M. A.; Kwok, C.-K.; Gu, X.-q.; Zhao, C. *Synth. Commun.* **1994**, *24*, 871−885.

(12) For a review of acyl anion equivalents, see: Albright, J. D. *Tetrahedron* **1983**, *39*, 3207−3233.

(13) For a review of the Stetter reaction, see: Stetter, H.; Kuhlmann, H. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1991; Vol. 40, pp 407−496. See also: Stetter, H.; Haese, W. *Chem. Ber.* **1984**, *117*, 682−693.

followed by Knorr reaction, or the reverse sequence. Fuchs has observed the exclusive formation of dimeric products from the ring-closing metathesis reaction of an intermediate in which the bicyclic core structure is present.[2c] To circumvent the problem, Fuchs performed the ring-closing metathesis reaction on a conformationally biased diene. The control was achieved by the use of a strategically placed OTIPS group. In view of Fuchs' result, performing the ring-closing metathesis reaction on the more conformationally mobile **2** seemed the more attractive approach. In the event, heating a 0.0005 M solution of **2** with 30 mol % of Grubbs' catalyst gave macrocycle **10** in 90% yield as a cis,trans mixture.[17] Catalytic hydrogenation of the mixture gave the 1,4-diketone **5** in 92% yield. Formation of the ketopyrrole **3**, the intermediate in Fürstner's synthesis,[2f] was accomplished by heating a 0.04 M solution of **5** and 35 equiv of ammonium carbonate in propionic acid in a sealed tube.[18] The ketopyrrole **3** was isolated in 52% yield after 10 h at 140 °C. The first step in this process is loss of the benzoate ester function from **5**. When the reaction was sampled prior to completion, only benzamide and ketoenol **11** were present. That ketoenol **11** has the structure shown was proven by isolation, followed by benzoylation, which returned **5** as the exclusive product. It was subsequently determined that hydrolysis of the benzoate group in **2** led to ketoenol **12**. In both cases, ketoenols **11** and **12** were strongly favored (>95%) as evidenced by ^{1}H NMR. The reason for the preferential enolization of one of the two keto groups in **11** and **12** is not obvious. In the case of **11**, it is likely that the regiochemistry for the enolization is critical for the success of the Knorr reaction.

Exposure of **5** to benzylamine in propionic acid at 200 °C for 10 d produced *N*-benzylpyrrole **13**, an intermediate in the Fürstner synthesis of roseophilin, in 34% yield. At the end of the reaction, only a small amount (<5%) of **11** remained in the mixture. Lower temperatures and longer reaction times did not improve the yield of **13**. Additionally, the use of Lewis acids or high pressure (13 kbar) did not result in an improvement in the yield. The stark difference between the two reactions leading to **3** and **13**, respectively, will be discussed in a future publication.

In conclusion, we have completed a convergent 12 step synthesis of the macrocyclic core of roseophilin. The ketopyrrole **3** junctions with Fürstner's synthesis; therefore, this work represents a formal total synthesis of racemic roseophilin **4**. The overall yield of **3**, 7.4%, is comparable to Fürstner's overall yield of 6.6%.[2h] Work in progress is directed toward the development of an enantioselective synthesis of **3**.

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Supporting Information Available: Experimental procedures for compounds **1**−**3**, **5**−**7**, **9**, **10**, and **13**. IR, ^{1}H NMR, ^{13}C NMR, and mass spectra and full characterization for compounds **1**−**3**, **5**−**7**, **9**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) 6-Heptenal was prepared in 65% yield by reduction of commercially available 6-cyano-1-hexene with DIBAL.

(15) Stereochemistry was determined by NOE.

(16) **Diene 2.** To a mixture of cyclopentenone **9** (150 mg, 0.483 mmol) and 6-heptenal (120 mg, 1.07 mmol) was added 1.0 mL of a solution of 3-benzyl-5-(hydroxyethyl)-4-methylthiazolium chloride (42 mg, 0.16 mmol) and triethylamine (100 μL, 72.6 mg, 0.717 mmol) in 1,4-dioxane (2.9 mL). The reaction mixture was heated to 70 °C in a sealed tube. After 18 h, the reaction mixture was diluted with Et_2O and water. The aqueous phase was extracted with ether (3×), and the combined organic extracts were washed with brine (1×) and dried over $MgSO_4$. Purification by flash column chromatography on silica (EtOAc gradient in hexanes) gave the *trans*-diene **2** (123 mg, 60% yield) as a colorless oil: R_f = 0.16 (10% EtOAc in hexanes); IR (neat) 2975, 2945, 1750, 1725, 1665, 1265, 1100, 1070, 715 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (dm, J = 7.1 Hz, 2H), 7.62 (tt, J = 7.4, 1.2 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 5.87−5.72 (m, 2H), 5.09−4.92 (m, 4H), 2.80−2.73 (m, 2H), 2.69−2.57 (m, 3H), 2.43 (t, J = 7.3 Hz, 2H), 2.38−2.18 (m, 4H), 2.05 (q br, J = 7.2 Hz, 2H), 1.59 (quint br, J = 7.6 Hz, 2H), 1.43−1.33 (m, 2H), 1.06 (d, J = 6.8 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.0, 200.8, 164.2, 163.3, 145.6, 138.4, 136.8, 133.6, 130.3, 128.6, 128.5, 115.8, 114.6, 49.7, 44.3, 43.0, 40.7, 33.5, 30.6, 28.44, 28.41, 26.7, 23.2, 21.1, 16.3; mass spectrum *m*/*z* 190 (20), 106 (15), 105 (100), 77 (45); exact mass calcd for $C_{27}H_{34}O_4$ 422.2457, found 422.2467.

(17) Ring-closing metathesis of the cis isomer of **2** proceeded in much lower yield (ca. 10%) under the same conditions.

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