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Studies Toward the Total Synthesis of Antibiotic Roseophilin : A Novel Synthesis of the Macrotricyclic Part

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Abstract

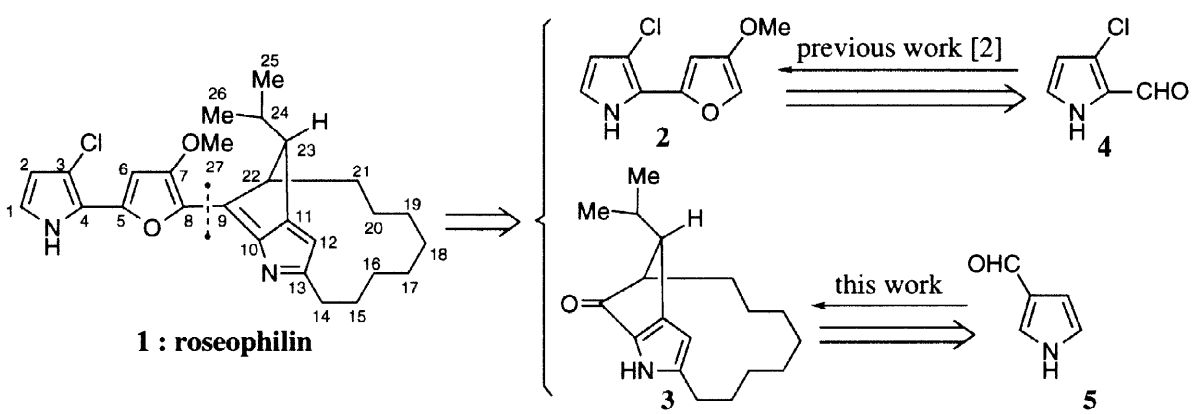
The macrotricyclic part of roseophilin, a novel cytotoxic antibiotic, was efficiently synthesized starting with the known 3-formylpyrrole; the method features intramolecular alkylation to form the desired thirteen-membered carbocycle and base-induced intramolecular acylation to construct the requisite pyrrole-fused cyclopentanone ring system as the key steps.

Keyword: natural product; antibiotic; macrocycles; pyrroles

Roseophilin (**1**) isolated from *Streptomyces griseoviridis* by Seto *et al.* in 1992, exhibits potent cytotoxicity against human cancer cell lines [1]. The structure of **1** was revealed by extensive spectroscopic studies to have a unique ansa-bridged cyclopenta[*b*]pyrrole skeleton incorporated with a characteristic conjugated heterocyclic ring system containing furan and pyrrole moieties [1]. Its remarkable biological properties as well as its novel structural features make **1** an exceptionally intriguing and timely target for total synthesis.

Our synthetic strategy for **1** was designed as outlined in **Scheme 1**, which features the

Scheme 1. Retrosynthetic analysis for roseophilin (**1**)



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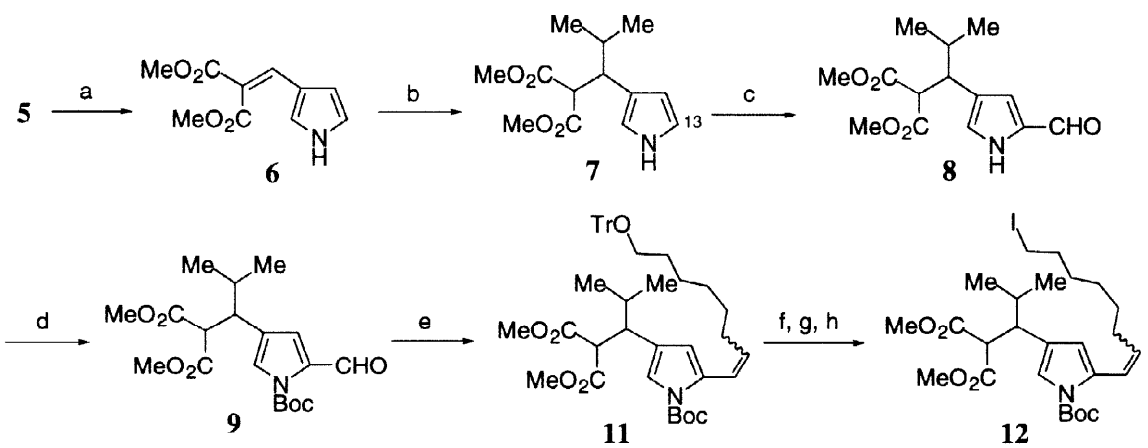
coupling reaction of the heterobiaryl part **2** with the macrotricyclic part **3** as the key step [2]. Based on this, we have already developed a method for the preparation of **2** starting with 3-chloro-2-formylpyrrole (**4**) [2]. Furthermore, we have demonstrated the utility of **2** in the synthesis of various model compounds for the conjugated heterocyclic ring system of **1** [2]. The synthesis of the macrocyclic part **3** and its *N*-protected form has been reported by Fuchs *et al.* [3,4] and Fürstner *et al.* [5], respectively. Quite recently, the first total synthesis of **1** by the coupling reaction of **2** and **3** was accomplished by Fürstner *et al.* [6]. In this communication, we wish to report a novel synthetic pathway to **3**, starting with the known 3-formylpyrrole (**5**) [7,8]. The sequence involves the macrocyclization of the iodide **12** to elaborate the desired thirteen-membered carbocycle **13** (**12**→**13**) and the base-induced cyclization of the bromopyrrole **15** to construct the requisite pyrrole-fused cyclopentanone system **16** (**15**→**16**) as the key steps (**Scheme 3**).

As shown in **Scheme 2**, the synthesis commenced with Knoevenagel reaction of **5** with dimethyl malonate, affording the condensation product **6** in 70% yield. Subsequent Michael reaction of **6** with isopropylmagnesium bromide cleanly took place to provide the addition product **7** in 81% yield. Regioselective formylation at the C-13 position (roseophilin numbering) in **7** was performed by reaction with phosphorous oxychloride in *N*,*N*-dimethylformamide (DMF) followed by treatment with aqueous sodium acetate solution, giving rise to the formylpyrrole **8** in 96% yield. After protection of the *N*-H function in **8**, Wittig reaction of the resulting *N*-Boc-pyrrole **9** with the phosphorane generated *in situ* from the phosphonium bromide **10** proceeded smoothly, resulting in the formation of the olefin **11** as a hardly separable mixture (*cis*:*trans*=*ca.* 3:1[4]) in 88% yield. Without separation, **11** was

Scheme 2. Synthesis of the iodide **12** for macrocyclization



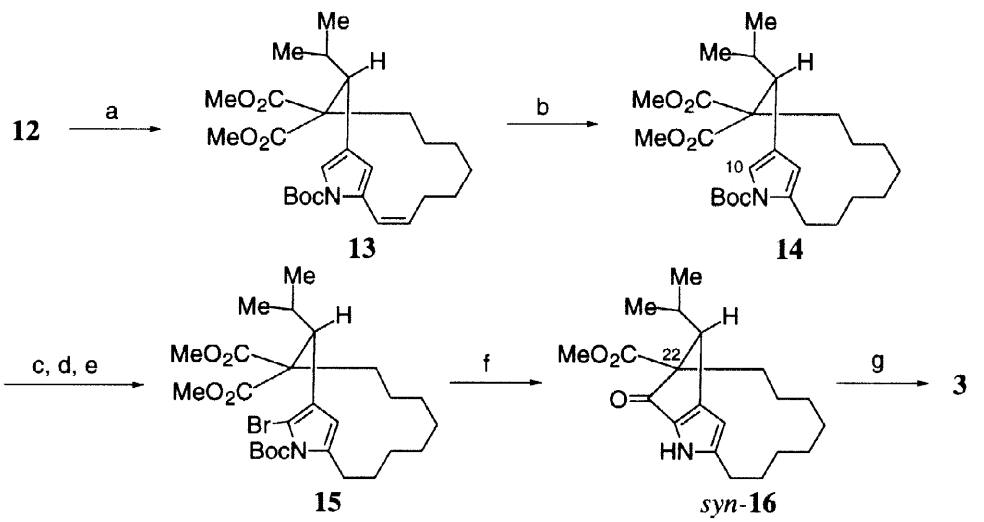
(a) $MeO_2CCH_2CO_2Me$, piperidine, pyridine, 70°C, 70% ; (b) *i*-PrMgBr, THF, -78°C, 81% ; (c) $POCl_3$, DMF, 0°C→rt ; then AcONa in H_2O, 60°C, 96% ; (d) Boc_2O, DMAP, MeCN, rt, 80% ; (e) $TrO(CH_2)_7P^+Ph_3Br^-$ (**10**), NaHMDS, THF, -78°C → rt, 88% (*cis*:*trans* =*ca.* 3:1) ; (f) *p*-TsOH, $CHCl_3$-MeOH (2:1), rt ; (g) MsCl, DMAP, pyridine, rt ; (h) NaI, acetone, reflux, 81% (3 steps, *cis*:*trans* = *ca.* 3:1) ; Boc=*tert*-BuO_2C ; DMAP=4-(dimethylamino)pyridine; Tr=Ph_3C; Ms=$MeSO_2$

[4] The isomeric ratio was estimated based on the 200 MHz ^{1}H-NMR spectrum.

converted to the iodide **12** (*cis*:*trans*=*ca.*3:1[4]), the substrate for macrocyclization, in 81% overall yield through a three-step sequence involving deprotection of the triphenylmethyl(Tr) group, mesylation of the resulting alcohol, and iodination of the mesylate.

With **12** in hand, the construction of the macrocyclic part **3** was next investigated as shown in **Scheme 3**. Thus, the crucial macrocyclization was found to be effected by treating **12** with cesium carbonate in DMF at 80°C under a diluted condition (5 mM), providing the *cis*-macrocyclic olefin **13**[5] as the sole product in 38% yield. In this reaction, the corresponding *trans*-olefinic macrocycle was not isolated at all. This observation suggests that the *cis*-olefinic double bond may shorten the distance between the reaction sites in **12** for the macrocyclization[6]. Hydrogenation of the double bond in **13** under conventional conditions provided the *N*-Boc-pyrrole **14** in 90% yield. A three-step sequence involving deprotection of the *N*-Boc group in **14** under acidic conditions, bromination of the C-10 (roseophilin numbering) with pyridinium bromide perbromide, and reprotection of the *N*-H function with Boc_2O, provided the bromopyrrole **15**, the second key cyclization precursor, in 63% overall yield. Lithiation of **15** with *n*-BuLi at -78°C underwent the cyclization, affording the desired pyrrole-fused cyclopentanone system **16**[7] as the sole *syn*-isomer in 39% yield[8]. This complete

Scheme 3. Synthesis of the macrocyclic part **3**



(a) Cs_2CO_3, DMF, 80°C, 38%; (b) H_2 (1 atm), 10%Pd-C, toluene, rt, 90%; (c) TFA, CH_2Cl_2, rt; (d) PyHBr•Br_2, THF, -78°C; (e) Boc_2O, DMAP, CH_3CN, rt, 63% (3 steps); (f) *n*-BuLi, THF-HMPA (10:1), -78°C, 39%; (g) NaCN, DMSO-H_2O (10:1), 140°C, 81%; TFA=CF_3CO_2H; Boc=*tert*-BuO_2C; DMAP=4-(dimethylamino)pyridine.

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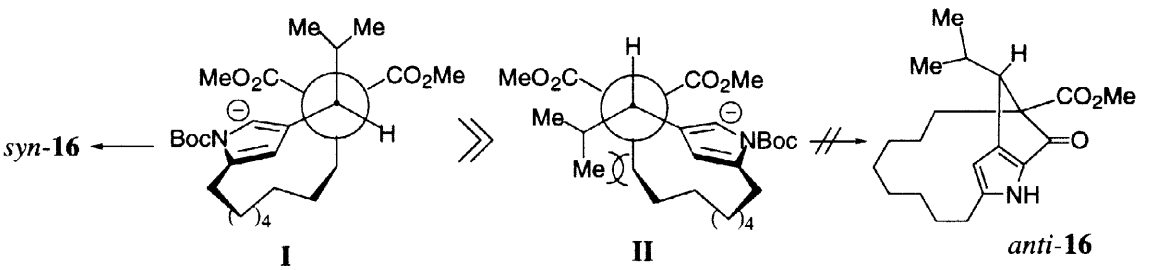
[5] The spectral data for **13** are as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.66-0.76 (1H, m), 0.85 (3H, d, *J* = 6.7 Hz), 0.91 (3H, d, *J* = 6.7 Hz), 0.98-1.07 (1H, m), 1.21-1.49 (6H, m), 1.54 (9H, s), 1.56-1.63 (1H, m), 1.73 (1H, td, *J* = 3.1, 13.5 Hz), 1.92 (1H, td, *J* = 4.9 Hz, 13.5 Hz), 1.95-2.02 (1H, m), 2.06-2.12 (1H, m), 3.36 (1H, d, *J* = 4.1 Hz), 3.72 (3H, s), 3.76 (3H, s), 5.90 (1H, ddd, *J* = 6.8, 8.8, 10.7 Hz), 6.09 (1H, br s), 6.49 (1H, d, *J* = 10.7 Hz), 7.06 (1H, d, *J* = 1.4 Hz); EIMS *m/e* 461 (M^+), 405 [(M-*tert*-Bu+1)$^+$], 361 [(M-Boc+1)$^+$], 346 [(M-*tert*-Bu-CO_2Me+1)$^+$], 302 [(M-Boc-CO_2Me+1)$^+$]; HREIMS calcd. for $C_{26}H_{39}NO_6$:461.2771. Found: 461.2764.

[6] When the dihydro-derivative of **12** produced by hydrogenation was used as the substrate for the macrocyclization, only 21% yield of the cyclized product was obtained. This observation also supports that the *cis*-olefinic double bond in **12** plays an important role in this macrocyclization reaction.

[7] The stereostructure of **16** was assigned based on the fact that the demethoxycarbonylation of **16** proceeds with retention of the C-22 configuration (roseophilin numbering) due to the rigid tricyclic system, giving rise to **3** as the sole product.

stereoselectivity could be explained by the conformational preference of the lithiopyrrole generated *in situ* from **15** (**Figure 1**). Thus, the two conformations **I** and **II** in which the pyrrole group and one of the two methoxycarbonyl groups occupy the syn-periplanar position, are possible for the cyclization of the lithiopyrrole. The conformation **I** in which the isopropyl group and the macrocyclic methylene chain are an anti form, should be sterically more favored than **II** bearing the aforementioned two groups in a gauche conformation, leading to the complete stereoselective formation of *syn*-**16**. Finally, demethoxycarbonylation of **16** was carried out by treatment with sodium cyanide in DMSO-H_2O (10:1) at 140°C, furnishing **3**[9] in 81% yield. Spectral data (^{1}H-NMR, MS) of **3** was found to be identical to those reported [6].

Figure 1. Possible conformations for the cyclization of the lithiopyrrole generated from **15**



In summary, we have succeeded in developing a novel synthetic pathway to the macrotricyclic part **3** of roseophilin (**1**) starting with 3-formylpyrrole (**5**). Since the total synthesis of **1** by the coupling reaction of **2** and **3** has been achieved [6], our successful synthesis of **3** constitutes the formal total synthesis of **1**.

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[8] In this reaction, the *N*-Boc group was deleted simultaneously.

[9] The spectral data for **3** are as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.39-0.48 (2H, m), 0.83-1.32 (10H, m), 0.89 (3H, d, J=6.6 Hz), 1.00 (3H, d, J = 6.6 Hz), 1.75-1.85 (2H, m), 1.90-1.97 (1H, m), 2.43 (1H, ddd, J = 5.8, 10.5, 14.0 Hz), 2.61 (1H, d, J=6.7 Hz), 2.75 (1H, dd, J = 3.5, 4.8 Hz), 2.88 (1H, dt, J = 5.0, 14.0 Hz), 5.99 (1H, d, J = 1.7 Hz), 8.90 (1H, br s); EIMS *m/e* 273 (M^+), 258 [(M-Me)$^+$], 230 [(M-*i*-Pr)$^+$]; HREIMS calcd. for $C_{18}H_{27}NO$:273.2093. Found: 273.2064.