

Tetrahedron Letters 39 (1998) 6911-6914

TETRAHEDRON LETTERS

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

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Received 1 June 1998; revised 2 July 1998; accepted 10 July 1998

## 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 thirteenmembered carbocycle and base-induced intramolecular acylation to construct the requisite pyrrole-fused cyclopentanone ring system as the key steps. © 1998 Elsevier Science Ltd. All rights reserved.

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 $\rightarrow$ 13) and the base-induced cyclization of the bromopyrrole 15 to construct the requisite pyrrole-fused cyclopentanone system 16 (15 $\rightarrow$ 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<sup>4</sup>) 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<sub>3</sub>, DMF, 0°C $\rightarrow$ rt; then AcONa in H<sub>2</sub>O, 60°C, 96%; (d) Boc<sub>2</sub>O, DMAP, MeCN, rt, 80%; (e) TrO(CH<sub>2</sub>)<sub>7</sub>P<sup>+</sup>Ph<sub>3</sub>Br<sup>-</sup>(10), NaHMDS, THF, -78°C  $\rightarrow$  rt, 88% (*cis:trans* = *ca.* 3:1); (f) *p*-TsOH, CHCl<sub>3</sub>-MeOH (2:1), rt; (g) MsCl, DMAP, pyridine, rt; (h) Nal, acetone, reflux, 81% (3 steps, *cis:trans* = *ca.* 3:1); Boc=*tert*-BuO<sub>2</sub>C; DMAP=4-(dimethyl-amino)pyridine; Tr=Ph<sub>3</sub>C; Ms=MeSO<sub>2</sub>

<sup>&</sup>lt;sup>4</sup> The isomeric ratio was estimated based on the 200 MHz <sup>1</sup>H-NMR spectrum.

converted to the iodide **12** (*cis:trans=ca.*3:1<sup>4</sup>), 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<sup>6</sup>. 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 *N*-H function with Boc<sub>2</sub>O, 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<sup>8</sup>. 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,  $CH_2CI_2$ , rt; (d) PyHBr•Br<sub>2</sub>, 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<sub>2</sub>O (10:1), 140°C, 81%; TFA=CF<sub>3</sub>CO<sub>2</sub>H; Boc=tert-BuO<sub>2</sub>C; DMAP=4-(dimethylamino)pyridine.

<sup>&</sup>lt;sup>5</sup> The spectral data for **13** are as follows: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  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, dd, 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<sup>+</sup>), 405 [(M-*tert*-Bu+1)<sup>+</sup>], 361 [(M-Boc+1)<sup>+</sup>], 346 [(M-*tert*-Bu-CO<sub>2</sub>Me+1)<sup>+</sup>], 302 [(M-Boc-CO<sub>2</sub>Me+1)<sup>+</sup>]; HREIMS calcd for C<sub>28</sub>H<sub>39</sub>NO<sub>6</sub>:461.2771. Found: 461.2764. <sup>6</sup> 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.

 $<sup>^{7}</sup>$  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<sub>2</sub>O (10:1) at 140°C, furnishing 3° in 81% yield. Spectral data (<sup>1</sup>H-NMR, MS) of 3 was found to be identical to those reported [6].





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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<sup>&</sup>lt;sup>8</sup> In this reaction, the N-Boc group was deleted simultaneously.

<sup>&</sup>lt;sup>9</sup> The spectral data for 3 are as follows: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) 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<sup>+</sup>), 258 [(M-Me)<sup>+</sup>], 230 [(M-*i*-Pr)<sup>+</sup>]; HREIMS calcd. for C<sub>18</sub>H<sub>27</sub>NO:273.2093. Found: 273.2064.