Pergamon

Tetrahedron Letters, Vol. 36, No. 46, pp. 8461-8464, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01822-0

Synthesis of Various Model Compounds for the Conjugated Heterocyclic Ring System of Antibiotic Roseophilin

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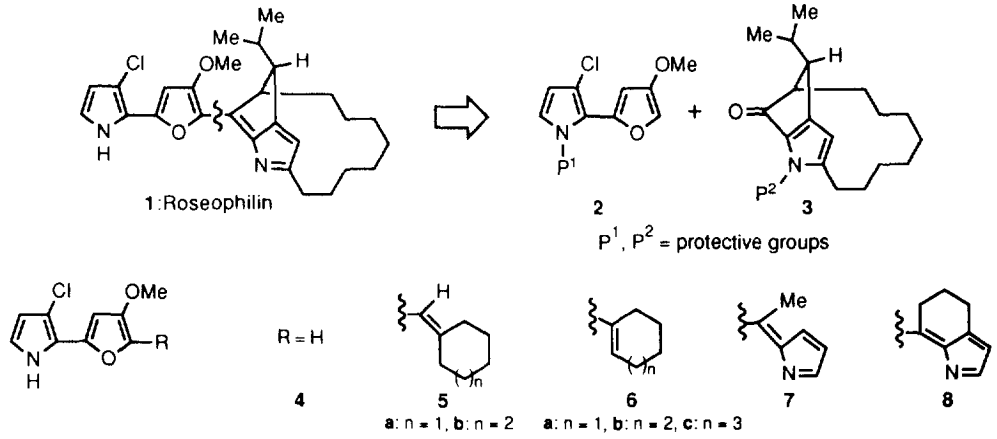
Abstract: The title synthesis was accomplished starting with 3-chloro-2-formylpyrrole. The synthetic scheme featured one-pot preparation of the 4-methoxy-2-(pyrrol-2-yl)furan from the 2-acetoacetylpyrrole and coupling reactions of the C_5-position of the 4-methoxy-2-(pyrrol-2-yl)furan with various types of aldehydes and ketones as key steps.

Roseophilin **1** isolated from *Streptomyces griseoviridis* by Seto *et al.*[1] in 1992 is a novel antibiotic which possesses a unique skeleton and a characteristic conjugated heterocyclic ring system containing furan and pyrrole rings. It is also reported that **1** showed strong cytotoxicity against K562 cells (IC_{50} 0.15 μg/mL) and KB cells (IC_{50} 0.40 μg/mL). The cytotoxicity observed for **1** is anticipated to be originated probably from the conjugated heterocyclic ring system which might interact with DNA. The intriguing structure and prominent cytotoxicity of **1** makes it as an attractive target of total synthesis.

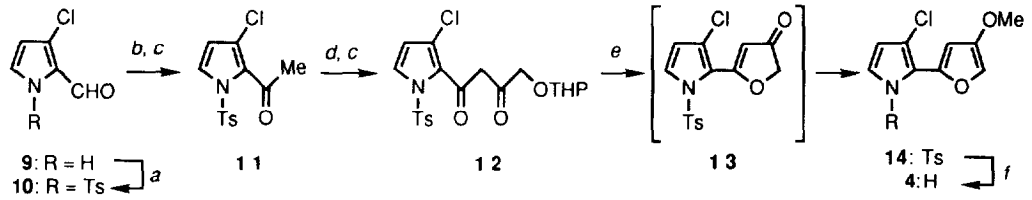
We embarked on the studies directed at the total synthesis of optically active **1** based on the synthetic strategy which features the coupling reaction of heterocyclic ring part **2** with carbocyclic ring part **3** as a key step. These synthetic studies were also commenced with an aim to elucidate the structure-activity relationships of **1** and to produce the congeners of **1** exhibiting the cytotoxicity superior to that of **1**. We wish to report here the synthesis of various types of the model compounds **4-8** having the conjugated heterocyclic ring systems similar to or the same as that of **1**. Successful synthesis of **5-8** accomplished by coupling **2** with various types of aldehydes and ketones, obviously suggests that optically active **1** could be produced following the proposed synthetic strategy.



Preparation of the 4-methoxy-2-(pyrrol-2-yl)furans **4** and **14** was first attempted as shown in **Scheme 1**. The synthesis commenced with the addition of methylmagnesium bromide to the 2-formyl-1-tosylpyrrole

10. The compound **10** was prepared from the 2-formylpyrrole **9** readily accessible from commercially available 4-nitropyridine *N*-oxide according to the literature.[2] Subsequent oxidation of the resulting carbinol afforded the 2-acetylpyrrole **11**. Aldol reaction of **11** with (tetrahydropyran-2-yloxy)acetaldehyde[3] followed by oxidation of the resulting carbinol produced the 2-acetoacetylpyrrole **12**. This was treated with a catalytic amount of acid in MeOH, giving rise to **14** in one pot reaction by sequential deprotection of the THP group, ring closure to the 3(2*H*)-furanone **13**,[4] and *O*-methylation of **13**. Further deprotection of **14** with K_2CO_3 /MeOH furnished **4**.

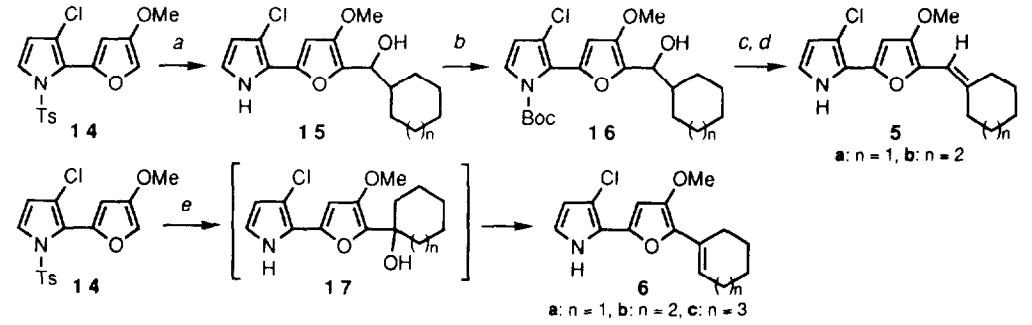
Scheme 1



Reagents: a, TsCl, Et_3N, MeCN, 98%; *b*, MeMgBr,THF, 84%; *c*, Dess-Martin periodinane, CH_2Cl_2, 95% for **11**, 60% for **12**; *d*, LDA, $THPOCH_2CHO$, THF, -78 °C, 54%; *e*, CSA, MeOH, 76%; *f*, K_2CO_3, MeOH, 71%.

With **4** and **14** in hand, the coupling reaction with various types of aldehydes or ketones and subsequent elaboration of the coupling products to **5**-**8** were next examined in order to explore the feasibility of the proposed synthetic strategy. Thus, the treatment of **14** with K_2CO_3/MeOH followed by the addition of cyclohexanecarboxaldehyde was found to undergo the coupling reaction of **4** *in situ* produced from **14**, affording the unstable coupling product **15a**. This was immediately protected with a Boc group to give the protected pyrrole **16a** (**Scheme 2**). Elimination of the hydroxyl group of **16a** followed by cleavage of the Boc group produced **5a**.[5] In a similar fashion, **5b** was prepared from **14** and cycloheptanecarboxaldehyde. Interestingly, the coupling reaction of **4** *in situ* produced from **14**, with cyclohexanone smoothly took place with K_2CO_3 in MeOH in a sealed tube, directly yielding **6a**.[6] Preparation of **6b**, **c** was similarly achieved by

Scheme 2

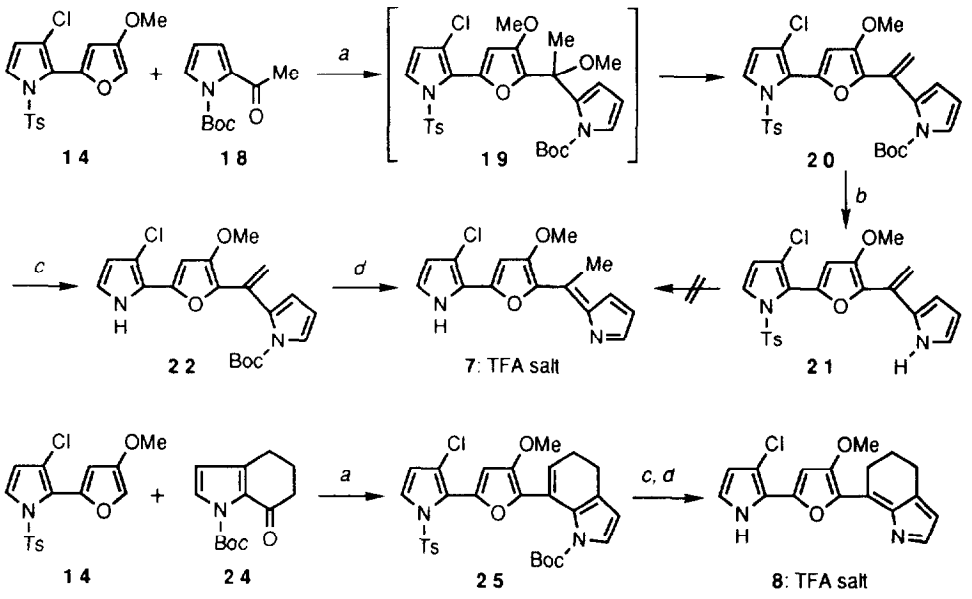


Reagents: *a*, K_2CO_3, MeOH, r.t. then aldehyde, 69% for **15a** ; *b*, Boc_2O, DMAP, MeCN, 54% for **16a**, 63% for **16b** (2steps from **14**); *c*, MsCl, Et_3N, CH_2Cl_2, 81% for **a** series, 55% for **b** series; *d*, K_2CO_3, MeOH, 76% for **5a**, 87% for **5b**; *e*, ketone, K_2CO_3, MeOH, sealed tube,100 °C (**a** and **b** series) or 120 °C (**c** series), 34% for **6a**,[7] 62% for **6b**, 37% for **6c**.

employing cycloheptanone and cyclooctanone. Probably, the unstable adducts **17** might be generated *in situ*, then dehydrated under the reaction conditions.

On the other hand, **4** appeared not to react with 2-acylpyrroles **18** and **24** under basic conditions. Even if *n*-butyllithium was used as a base to deprotonate **14**, no coupling reactions occurred. This is probably due to low electrophilicity of 2-acylpyrroles. Accordingly, acidic conditions were employed for the coupling reaction (**Scheme 3**). After experimentation, the coupling reaction of **14** with **18** was found to take place in the presence of trimethyl orthoformate and a catalytic amount of CSA, providing the coupling product **20**. Since trimethyl orthoformate was essential, the coupling reaction might proceed through the methyl ether **19** which can be generated from the acetal or the hemiacetal of **18**.[8] Sequential removals of both the Ts and Boc groups were required to obtain **7**. Towards this end, the Boc group was first removed to afford the unprotected pyrrole **21**.[9] However, under the basic conditions for cleaving the Ts group, **7** was found to be very unstable. Therefore, the Ts group of **20** was first removed to produce the unprotected pyrrole **22**, which in turn was exposed to TFA to furnish **7**[10] as a dark red TFA salt. The model compound **8**[11] was similarly synthesized as a dark red TFA salt by the coupling reaction of **14** with **24**[12] followed by sequential deprotections of the coupling product **25**.

Scheme 3

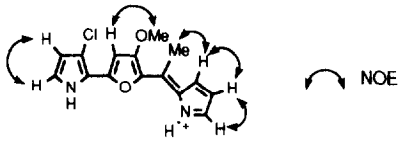


Reagents: a, $CH(OMe)_3$, CSA, MeOH, 44% for **20**, 25% for **25**; *b*, TFA, 72%; *c*, K_2CO_3, MeOH; *d*, TFA, $CHCl_3$, 41% for **7** (2steps), 28% for **8** (2steps).

In summary, we have succeeded in synthesizing **4-8** having the conjugated heterocyclic ring systems similar to or the same as that involved in **1**. These results obviously suggest that the total synthesis of **1** would be accomplished by employing the proposed synthetic strategy (*vide supra*). Studies on the total synthesis of optically active **1** are in progress and will be reported shortly.[13]

References and Notes

1. Hayakawa, Y.; Kawakami, K.; Seto, H.; Furihata, K. *Tetrahedron Lett.* **1992**, *33*, 2701.
2. (a) Bellamy, F.; Martz, P.; Streith, J. *Heterocycles* **1975**, *3*, 395. (b) Ochiai, E. *J. Org. Chem.* **1953**, *18*, 534.
3. Iwai, I.; Iwashige, T.; Asai, M.; Tomita, K.; Hiraoka, T.; Ide, J. *Chem. Pharm. Bull.* **1963**, *11*, 188.
4. The 3(2*H*)-furanone **13** could not be isolated under the condition directly producing **14** from **12**. However, treatment of **14** with a catalytic amount of CSA in MeOH-H_2O readily afforded **13** in 46% yield. Interestingly, **13** showed a strong cytotoxicity against P388 *Murine Leukemia* cells (IC_{50} 3.4 x 10^{-3} μg/mL).
5. Physical data for **5a**: ^{1}H NMR (200 MHz, C_6D_6) δ 1.44-1.73 (m, 6H), 2.23 (br t, *J* = 6 Hz, 2H), 2.76 (br t, *J* = 6 Hz, 2H), 3.33 (s, 3H), 5.88 (t, *J* = 3.0 Hz, 1H), 6.13 (t, *J* = 3.0 Hz, 1H), 6.31 (br s, 1H), 6.74 (s, 1H), 7.56 (br s, 1H). FTIR (neat, cm^{-1}) 3650-3050, 2920, 1615, 1565, 1455, 1380, 1105, 1060, 1015. LRMS *m/e* 293 (M^+, ^{37}Cl), 291 (M^+, ^{35}Cl). HRMS calcd for $C_{16}H_{18}{}^{35}ClNO_2$: 291.1024, found: 291.0992.
6. Physical data for **6a**: ^{1}H NMR (200 MHz, C_6D_6) δ 1.54-1.76 (m, 4H), 2.17-2.28 (m, 2H), 2.54-2.67 (m, 2H), 3.30 (s, 3H), 5.99 (t, *J* = 3.0 Hz, 1H), 6.15 (t, *J* = 3.0 Hz, 1H), 6.46 (tt, *J* = 4.2, 1.8 Hz, 1H), 6.79 (s, 1H), 7.56 (br, 1H). FTIR (neat, cm^{-1}) 3700-3050, 2925, 1615, 1570, 1380, 1095, 1065, 1020. LRMS *m/e* 279 (M^+, ^{37}Cl), 277 (M^+, ^{35}Cl). HRMS calcd for $C_{15}H_{16}{}^{35}ClNO_2$: 277.0868, found: 277.0846.
7. 5-[3-Chloro-1-(1-cyclohexen-1-yl)pyrrol-2-yl]-2-(1-cyclohexen-1-yl)-3-methoxyfuran was also produced in 17% yield.
8. Wenkert, E.; Goodwin, T. E. *Synth. Commun.* **1977**, *7*, 409.
9. Physical data for **21**: ^{1}H NMR (200 MHz, C_6D_6) δ 1.70 (s, 3H), 3.21 (s, 3H), 5.65 (d, *J* = 1.2 Hz, 1H), 5.82 (d, *J* = 1.2 Hz, 1H), 5.94 (d, *J* = 3.5 Hz, 1H), 6.28-6.32 (m, 1H), 6.29 (s, 1H), 6.48 (br d, *J* = 8.0 Hz, 2H), 6.50-6.55 (m, 1H), 6.71-6.75 (m, 1H), 7.23 (d, *J* = 3.5 Hz, 1H), 7.36 (br d, *J* = 8.5 Hz, 2H), 9.09 (br, 1H). FTIR (neat, cm^{-1}) 3430, 3160, 2950, 2870, 1640, 1600, 1530, 1465, 1380, 1180, 1140. LRMS *m/e* 444 (M^+, ^{37}Cl), 442 (M^+, ^{35}Cl). HRMS calcd for $C_{22}H_{19}{}^{35}ClN_2O_4S$: 442.0753, found: 442.0776.
10. The model compound **7** was obtained as a sole product probably due to thermodynamic control. A NOESY experiment showed that the stereochemistry of **7** was (*Z*)-configuration.



Physical data for **7**: mp 174-176 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.68 (s, 3H), 4.22 (s, 3H), 6.43 (br t, *J* = 2.2 Hz, 1H), 6.53 (quint, *J* = 2.1 Hz, 1H), 7.10 (s, 1H), 7.23-7.28 (m, 1H), 7.49 (br t, *J* = 3.0 Hz, 1H), 8.04-8.09 (m, 1H), 12.40 (br, 1H), 14.57 (br, 1H). FTIR (neat, cm^{-1}) 3620-3030, 2930, 1700, 1685, 1590, 1550, 1210, 1130. LRMS *m/e* 290 (M^+-CF_3CO_2H, ^{37}Cl), 288 (M^+-CF_3CO_2H, ^{35}Cl). HRMS calcd for $C_{15}H_{13}{}^{35}ClN_2O_2$ (M^+-CF_3CO_2H): 288.0664, found: 288.0656. Anal. Calcd for $C_{17}H_{14}ClF_3N_2O_4$: C; 50.70, H; 3.50, N; 6.96, Found: C; 50.56, H; 3.44, N; 6.74.
11. Physical data for **8**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.04 (quint, *J* = 6.3 Hz, 2H), 2.85 (t, *J* = 6.3 Hz, 2H), 3.13 (t, *J* = 6.1 Hz, 2H), 4.19 (s, 3H), 6.33 (br s, 1H), 6.40 (t, *J* = 2.4 Hz, 1H), 7.06 (s, 1H), 7.38-7.42 (m, 1H), 8.15-8.18 (m, 1H), 12.79 (br, 1H), 14.30 (br, 1H). FTIR (neat, cm^{-1}) 3600-3050, 2940, 1690, 1550, 1465, 1130. LRMS *m/e* 316 (M^+-CF_3CO_2H, ^{37}Cl), 314 (M^+-CF_3CO_2H, ^{35}Cl). HRMS calcd for $C_{17}H_{15}{}^{35}ClN_2O_2$ (M^+-CF_3CO_2H): 314.0820, found: 314.0817.
12. Kakushima, M.; Hamel, P.; Frenette, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 3214.
13. *In vitro* cytotoxicity of **4-8** against P388 *Murine Leukemia* cells was as follows: (IC_{50} μg/mL) **4**, >100; **5a**, 23; **5b**, 10; **6a**, 37; **6b**, 35; **6c**, 3.6; **7**, 3.2; **8**, 3.5. These results are not enough to confirm the proposed hypothesis (*vide supra*), but indicate that the carbocyclic part in **1** plays some important roles in its strong cytotoxicity. *In vivo* experiments using these compounds are in progress.

(*Received in Japan* 11 *August* 1995; *revised* 20 *September* 1995; *accepted* 22 *September* 1995)