One-step Synthesis of Tyromycin A and Analogues

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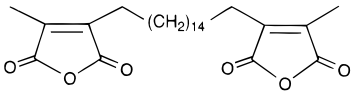
Among the enzymes bound to surfaces of mammalian cells, aminopeptidases have been recognized as potential target for immunomodulating drugs.[1] Among inhibitors of this class of enzymes, tyromycin A, an inhibitor of leucine and cysteine aminopeptidases, was isolated from mycelial cultures of the basidiomycete *Tyromyces lacteus* (Fr.) Murr.[2] Tyromycin A is the first naturally occurring natural product containing two citraconic anhydride units. Tyromycin A was found to inhibit the leucine and cysteine aminopeptidases bound to the outer surface of HeLa S3 cells and therefore may possess cytostatic activity. Synthesis of this promising compound has not been reported to date.



Tyromycin **1a**

We recently reported [3] an efficient one-step synthesis of chaetomellic anhydride A, using Barton radical decarboxylation [4,5] In this paper we report further extension of this reaction to total synthesis of tyromycin A and some analogues using a double radical decarboxylation. Thus, the readily available diacids **2** were converted to their thiohydroxamic diesters **3**, using Ph_3P/2,2′-dithiobis-(pyridine *N*-oxide) **5** coupling method [6] (Scheme 1). Irradiation in situ of the thiohydroxamic diesters **3**, in the presence of 10 equiv of citraconic anhydride, with a tungsten light (500 W), during 30 min, gave the intermediate addition products **4**, which upon purification on silica gel afforded the elimination products **1**. The nonisolable intermediate **4** could be observed by NMR analysis of the crude mixture of the reaction run in $CDCl_3$. After 30 min irradiation, characteristic signals for the presence of addition product **4** (δ 3.2 ppm, t, CH-3′) and elimination product **1** (δ 2.5 ppm, t, CH_2-1) were seen, in a ratio 3:1. After 48 h stirring at room temperature, complete disappearance of addition product **4** and presence of the only signals corresponding to the elimination product **1**, as the sole isomer, were observed in the NMR spectrum. In agreement with our previous work, the facile syn elimination of the 2-pyridylthio group of the intermidiate **4** on silica established the trans stereochemical relationship of the 2-pyridylthio group and the alkyl substituents, which is the result of a trans addition of radical to citraconic anhydride.[7,8] Tyromycin A was obtained in 79% yield after irradiation of the thiohydroxamic ester **3a** and stirring for 48 h to ensure complete elimination of the 2-pyridylthio group followed by purification over C-18 reverse-phase.[9] The other diacids **2b**−**e** were successfully decarboxylated in the presence of citraconic anhydride to furnish the desired tyromycin analogues **1b**−**e** in good yield. The results are summarized in Table 1.

In conclusion, we have described the first total synthesis of tyromycin and their analogues, in one step, from readily available dicarboxylic acids. The facile elimination of the pyridylthio group, which avoids further reactions (e.g., oxidation to sulfoxide and elimination), and exceptionally mild reaction conditions offer a rapid synthetic access to tyromycin analogues and will allow further exploration of structure−activity relationships in this area.

Experimental Section

All the reactions were carried out under an argon atmosphere. All reagents were obtained from commercial suppliers and used without purification. Methylene chloride was distilled from CaH_2. Flash chromatography was effected on silica (Merck Kieselgel 60, 230−400 mesh) with mixtures of ethyl acetate and hexane as eluent. TLC analyses were performed on thin-layer analytical plates 60 F254 (Merck). Elementary analyses were carried out at the Institut de Chimie des Substances Naturelles, Gif-sur-Yvette, France.

General Procedure. Note: The *N*-hydroxy-2-thiopyridone derivatives are somewhat sensitive to daylight. It is advisable to cover the reaction flask with an aluminum foil.

To a solution of dicarboxylic acid **2a**−**e** (1 mmol) and 2,2′-dithiobis(pyridine *N*-oxide) (2.2 mmol) in dry CH_2Cl_2 (10 mL) was added Ph_3P (2.2 mmol) under argon. The mixture was stirred at room temperature for 30 min. Citraconic anhydride (10 mmol) was then added, the aluminum foil removed, and the mixture irradiated with a tungsten lamp (500 W) at 10−15 °C for 30 min. The mixture was concentrated, and the residue was dissolved in ether (100 mL), washed with 5% $NaHCO_3$ (50 mL), water (50 mL), and brine (50 mL), and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, the excess of citraconic anhydride removed in high vacuum, and the residue subjected to flash chromatography on silica with hexanes−ethyl acetate (9:1) as the eluent yielded the compounds **1c**−**e**. In the case of tyromycin **1a**, and **1b**, after 30 min of irradiation, the mixture was stirred for 48 h at room temperature. Usual workup as described for **1c**−**e**, the residue was purified over C-18 reverse phase, using MeOH−H_2O (9:1) as eluent.

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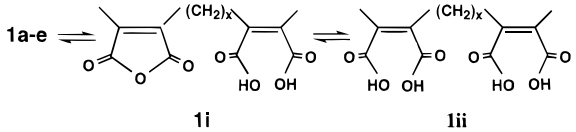
(9) Purification of tyromycin A **1a** (n = 14), and its analogue **1b** (n = 12) over standard silica gel gave 48 and 46% yield, respectively. We believe that an amount of dimaleic anhydrides **1a**−**e** opened to their dicarboxylic (**1i**) or tetracarboxylic (**1ii**) derivatives, particularly in the case of tyromycin **1a** and analogue **1b** (n = 12).



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Scheme 1

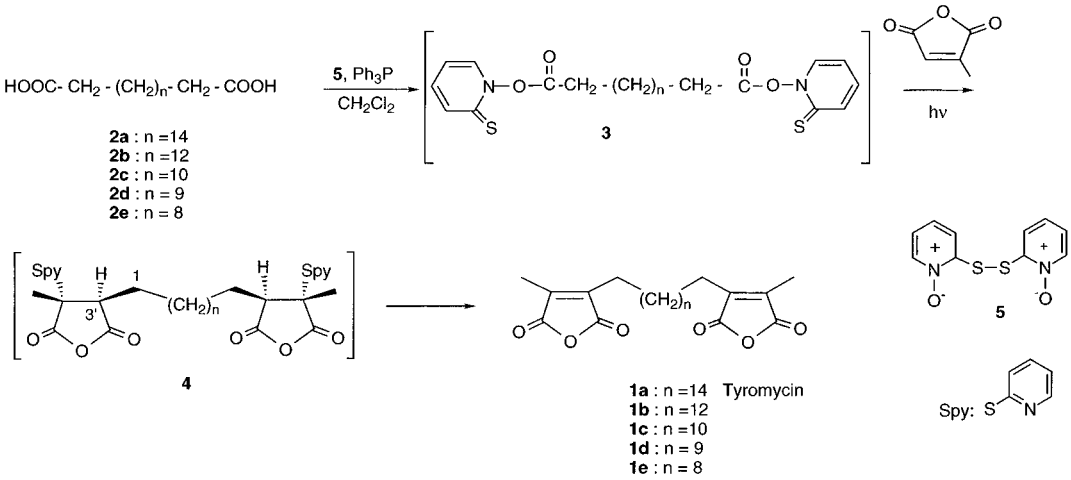

Table 1

entry	diacids	% product (yields)
1	**2a**	Tyromycin A **1a** (74)
2	**2b**	**1b** (75)
3	**2c**	**1c** (78)
4	**2d**	**1d** (65)
5	**2e**	**1e** (72)

Tyromycin A: 1,16-Bis[4-methyl-2,5-dioxo-3-furyl]hexadecane (1a). R_f 0.73 (Hex:AcOEt, 7:3); *m/z* (CI) 447 (MH^+); ν_{max} (neat)/cm^{-1} 1859, 1769, 1670, 1278, 920, 734; ^1H NMR ($CDCl_3$) 2.41 (4 H, t), 2.03 (6 H, s), 1.54 (4 H, m), 1.30−1.15 (24 H, m); ^{13}C NMR ($CDCl_3$) 166.2 (C), 165.8 (C), 144.7 (C), 140.4 (C), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 27.6 (CH_2), 24.4 (CH_2), 9.5 (CH_3). Anal. Calcd for $C_{26}H_{38}O_6$: C, 69.95; H, 8.52. Found: C, 69.68; H, 8.57; mp 58 °C (lit.[1] mp 59−60 °C).

1,14-Bis[4-methyl-2,5-dioxo-3-furyl]tetradecane (1b). R_f 0.68 (Hex:AcOEt, 7:3); *m/z* (CI) 419 (MH^+); ν_{max} (neat)/cm^{-1} 1860, 1769, 1671, 1278, 921, 734; ^1H NMR ($CDCl_3$) 2.43 (4 H, t), 2.02 (6 H, s,), 1.53 (4 H, m), 1.30−1.15 (20 H, m); ^{13}C NMR ($CDCl_3$) 166.2 (C), 165.9 (C), 144.7 (C), 140.4 (C), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 27.6 (CH_2), 24.4 (CH_2), 9.5 (CH_3). Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.9; H, 8.13. Found: C, 68.79; H, 8.38; mp 47 °C.

1,12-Bis[4-methyl-2,5-dioxo-3-furyl]dodecane (1c). R_f 0.64 (Hex:AcOEt, 7:3); *m/z* (CI) 391 (MH^+); ν_{max} (neat)/cm^{-1} 1859, 1770, 1670, 1278, 920, 734; ^1H NMR ($CDCl_3$) 2.44 (4 H, t), 2.02 (6 H, s), 1.55 (4 H, m, 2,11-CH_2), 1.30−1.15 (16 H, m); ^{13}C NMR ($CDCl_3$) 166.2 (C), 165.9 (C), 144.7 (C), 140.4 (C), 29.5 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 27.6 (CH_2), 24.4 (CH_2), 9.5 (CH_3). Anal. Calcd for $C_{22}H_{30}O_6$: C, 67.69; H, 7.69. Found: C, 67.79; H, 7.74. Colorless oil.

1,11-Bis[4-methyl-2,5-dioxo-3-furyl]undecane (1d). R_f 0.60 (Hex:AcOEt, 7:3); *m/z* (CI) 377 (MH^+); ν_{max} (neat)/cm^{-1} 1859, 1770, 1670, 1278, 920, 734; ^1H NMR ($CDCl_3$) 2.43 (4 H, t, 1,11-CH_2), 2.02 (6 H, s, 2-CH_3), 1.55 (4 H, m, 2,10-CH_2), 1.30−1.15 (14 H, m, CH_2); ^{13}C NMR ($CDCl_3$) 166.2 (C), 165.9 (C), 144.7 (C), 140.4 (C), 29.4 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 27.5 (CH_2), 24.4 (CH_2), 9.5 (CH_3). Anal. Calcd for $C_{21}H_{28}O_6$: C, 67.02; H, 7.44. Found: C, 67.12; H, 7.56. Colorless oil.

1,10-Bis[4-methyl-2,5-dioxo-3-furyl]decane (1e). R_f 0.58 (Hex:AcOEt, 7:3); *m/z* (CI) 363 (MH^+); ν_{max} (neat)/cm^{-1} 1859, 1770, 1670, 1278, 920, 734; ^1H NMR ($CDCl_3$)) 2.42 (4 H, t), 2.02 (6 H, s), 1.55 (4 H, m), 1.30−1.15 (12 H, m); ^{13}C NMR ($CDCl_3$) 166.2 (C), 165.9 (C), 144.7 (C), 140.4 (C), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 27.5 (CH_2), 24.4 (CH_2), 9.5 (CH_3). Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.30; H, 7.18. Found: C, 66.17; H, 7.31. Colorless oil.

Supporting Information Available: ^1H and ^{13}C NMR spectra of tyromycin A and analogues (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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