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Total Synthesis of Phenoxan and a Related Pyrone Derivative

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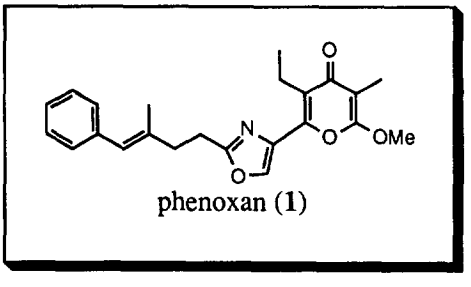
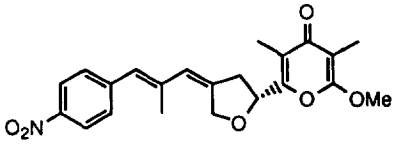
Abstract: Phenoxan, HIV-1 inhibitor isolated from the myxobacteria, has been synthesized in 16 steps starting from ethyl 2-methylacetoacetate. The related isomer corresponding to the oxazole part was also obtained via an orthoester-enediol rearrangement. Copyright © 1996 Elsevier Science Ltd

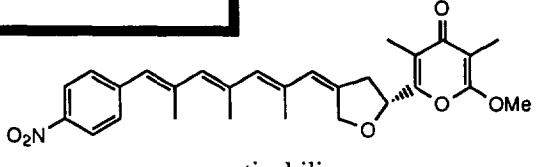
Phenoxan (**1**), isolated from *Poliangium spec.*, strain PL VO19, possesses potent inhibitory activity against HIV-1 infection at 6.6 nM as well as low cytotoxicity (>6600 nM)[1] in the MT-4 cell assay.[2] Although the mode of action has not been specified, **1** indicated moderate inhibition against HIV (ID_{50}=100 μg/ml) and Moloney murine leukemia virus (ID_{50} = 100 μg/ml) reverse transcriptase, like γ-pyrone natural products such as aureothin[3] (HIV-reverse transcriptase: ID_{50} =132 μg/ml) and spectinabilin (Rauscher leukemia virus: ID_{50} = 200 μg/ml). These findings open up the possibility that γ-pyrone natural products may be leads of new antiviral agents apart from AZT, DDI and other nucleoside analogs. Envisaging such potentiality, **1** was included as part of our synthetic investigation of aureothin-class natural products. We describe herein synthesis of **1** and a related substance.



phenoxan (**1**)

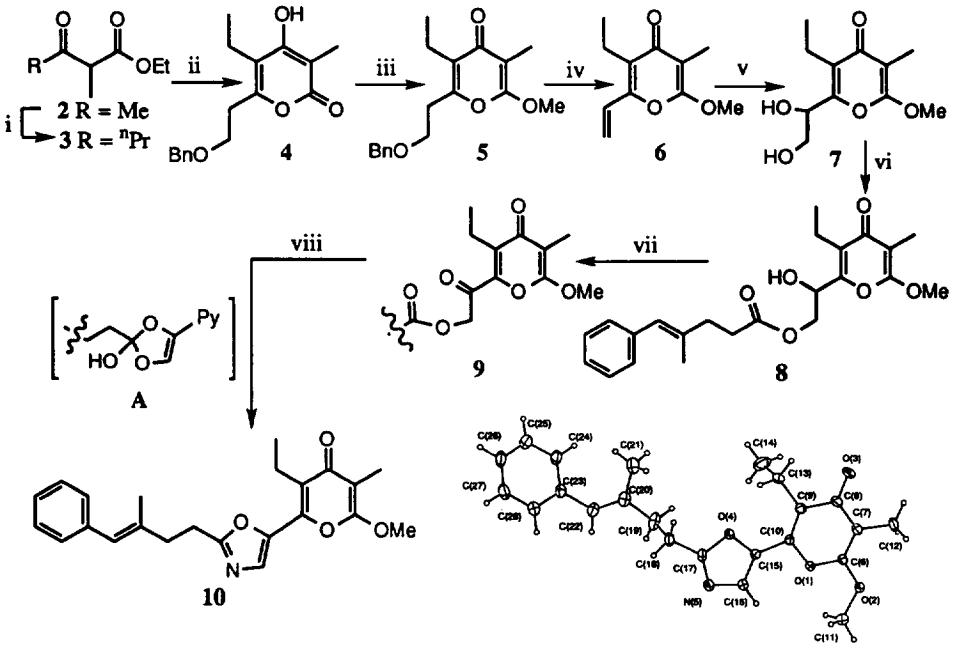


aureothin



spectinabilin

As can be seen in Scheme 1, our synthesis was commenced by alkylation of the commercially available ethyl 2-methylacetoacetate (**2**) under Weiler's conditions to give β-ketoester **3**[4] in good yield. Cyclization of **3** was effected by a 2-step procedure via the corresponding diketoester, leading to α-pyrone **4** . Methylation of **4** with methyl fluorosulfonate underwent the desired isomerization to γ-pyrone **5**[5] in 61% yield. In the next stage, the allylic position was oxidized to construct an oxazole ring. Thus, **5** was converted in 3 steps into olefin **6**

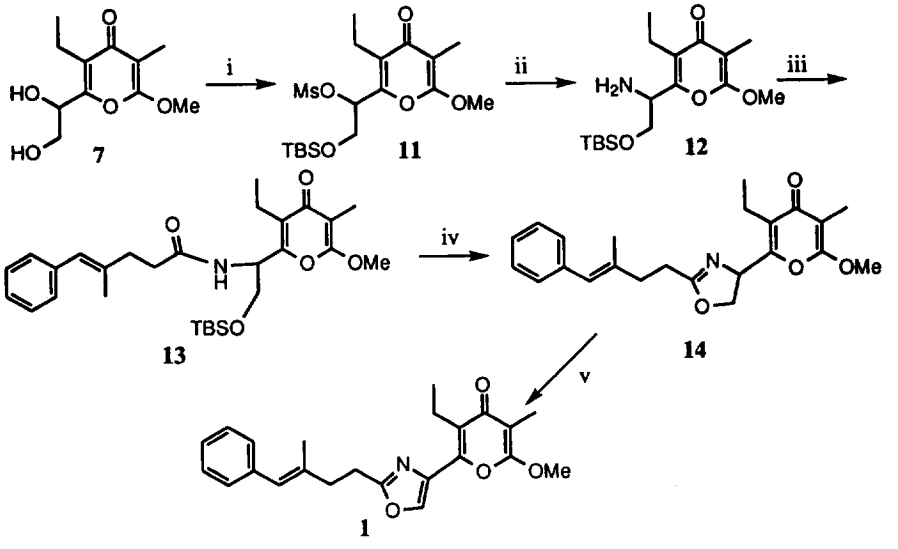


Scheme 1. i. NaH, then ^{n}BuLi, EtI / THF (0°C, 1 h) (72%). ii. a) NaH, then LDA (0°C, 30 min); $BnO(CH_2)_2COImd$ / THF (-78°C, 1 h); b) DBU / benzene (60°C, 3 h) (68%). iii. $MeOSO_2F$ / CH_2Cl_2 (room temp., 4 h) (61%). iv. a) H_2, Pd-C / MeOH (50°C, 3 h); b) MsCl / pyr.-CH_2Cl_2 (room temp., 2 h); c) K_2CO_3 / MeOH (room temp., 30 min) (89% in 3 steps). v. OsO_4, NMO / CH_3CN-H_2O (3 : 1) (room temp., 12 h) (100%). vi. $PhCH{=}C(Me)(CH_2)_2CO_2H$, DCC, DMAP / CH_2Cl_2 (0°C, 30 min) (67%). vii. Dess-Martin reagent / CH_2Cl_2 (room temp., 1 h) (59%). viii. NH_4OAc / AcOH (70°C, 1 day) (42%).

which was oxidized with OsO_4 to give diol **7** in 89% yield from **5**. The primary hydroxyl group of **7** was selectively acylated with the known 4-methyl-5-phenyl-4-(*E*)-pentenoic acid[6] to afford the monoacylate (**8**), followed by Dess-Martin oxidation to give the ketone (**9**) in 40% yield from **7**. Upon treatment of **9** with ammonium acetate, the reaction involving the unexpected enediol-orthoester rearrangement (**A**) afforded the regio isomer of **1** (**10**) in 42% yield, whose structure was unambiguously confirmed by X-ray crystallographic analysis.[7] From the NMR data reported, this structure could not be ruled out; however, comparison of both data indicated that **1** has the structure as to be depicted.

To circumvent such an undesired process, it was necessary to introduce a nitrogen atom at an early stage of the synthesis. Thus, the primary hydroxyl group of **7** was protected as a siloxy ether, followed by mesylation to provide mesylate **11** in 80% (Scheme 2). Compound **11** was converted in two steps into the primary amine (**12**), which was immediately acylated with the above mentioned pentenoic acid to give amide **13** in 86% yield from **11**. After deprotection of **13** with a fluoride anion, the resulting alcohol was subjected to mesylation to effect a spontaneous cyclization to **14**[8] (68% from **13**). Finally, effective oxidation of **14** was accomplished with excess amounts of MnO_2 to give phenoxan (**1**)[9] in 75% yield. The spectral data (IR, HRMS, ^{1}H and ^{13}C NMR) of synthetic sample (**1**) was in good accordance with those reported for the natural product.[1a]

Synthesis of related pyrone derivatives and their biological evaluation will be published elsewhere.



Scheme 2. i. a) TBSCl, Imd. / DMF (0°C, 4 h) (84%); b) MsCl / pyr. (0 °C, 1 h) (95%). ii. a) NaN_3 DMF (room temp., 4 h) (93%); b) Pd-C, H_2 / MeOH (100%). iii. $PhCH{=}C(Me)(CH_2)_2CO_2H$, DCC, HOBt, Et_3N / THF (room temp., 5 h) (93%). iv. a) TBAF / THF (0 °C, 30 min) (88%); b) MsCl, Et_3N / CH_2Cl_2 (0 °C, 2 h → room temp., 16 h) (77%). v. MnO_2 / $CHCl_3$ (refluxing temp., 6 h) (75%).

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6. 4-Methyl-5-phenyl-4-(*E*)-pentenoic acid was prepared from α-methyl-cinnamaldehyde in five steps through a π–allyl-palladium complex. The *E* : Z ratio on the double-bond was determined to be 97 : 3 based on the ^1H NMR spectra. a) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730 - 4743. b) Frenking, G.; Hülskämper, L.; Weyerstahl, P. *Chem. Ber.* **1982**, *115*, 2826 - 2835.

7. Colourless prisms were grown from ^{t}BuOMe - hexane. Crystallographic data: $C_{23}H_{25}NO_4$, MW 379.46, monoclinic, space group $P2_1/n$, a=8.123 (5), b=18.683 (3), c=13.816 (2) Å, β=93.49 (2)°, V=2092.9 (11) Å^3, Z=4, Dx=1.204 g cm^{-3}, μ (Mo $K\alpha$)=0.077 mm^{-1}. The X-ray intensities up to 2θ=50° were measured on Rigaku AFC-5 four-circle diffractometer with graphite-monochromatized Mo K α radiation. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were introduced. Final R is 0.073 for 1719 reflections. The assignment of N and O atoms in the oxazole ring was based on their thermal parameters, and is supported by the bond lengths of 1.276 (9) and 1.380 (9) Å for N=C and N-C, respectively.
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10. The spectral data for the new compounds were in accord with the structures assigned, and only selected data are cited: **5** as an oil: $C_{18}H_{22}O_4$ [m/z 302.1502 (M^+)]; IR (film) 1670 cm^{-1}; δ_H ($CDCl_3$) 1.07 (3H, t, J= 7.59 Hz), 1.87 (3H, s), 2.46 (2H, q, J= 7.59 Hz), 2.89 (2H, t, J= 6.60Hz), 3.74 (2H, t, J= 6.60Hz), 3.80 (s), 4.52 (2H, s), 7.27 - 7.35 (5H, complex); δ_C ($CDCl_3$) 6.76, 13.61, 18.01, 31.22, 55.08, 66.67, 72.98, 99.79, 125.25, 127.53x2, 127.73, 128.37x2, 137.81, 155.40, 161.98, 180.23. **9** as an oil: $C_{23}H_{26}O_6$ [m/z 398.1703 (M^+)]; IR (film) 1755, 1730 and 1630 cm^{-1}; δ_H ($CDCl_3$) 1.08 (3H, t, J= 7.59 Hz), 1.90 (6H, s), 2.58 (2H, t, J= 7.92 Hz), 2.74 (2H, t, J= 7.92 Hz), 2.86 (2H, q, J= 7.59 Hz), 4.06 (3H, s), 5.20 (2H, s), 6.34 (1H, br. s), 7.16 - 7.35 (5H, complex); δ_C ($CDCl_3$) 7.15, 12.94, 17.22, 17.67, 32.53, 35.31, 55.73, 66.34, 102.89, 125.84, 126.13, 128.01x2, 128.79x2, 133.55, 136.53, 138.04, 147.19, 161.17, 172.40, 179.08, 187.37. **10** as prisms: mp 82 - 83 °C (from ^{t}BuOMe - hexane); $C_{23}H_{25}O_4N$ [m/z 379.1743 (M^+)]; IR (film) 1660 cm^{-1}; δ_H (CD_3OD) 1.10 (3H, t, J= 7.51 Hz), 1.84 (3H, s), 1.89 (3H, d, J= 1.47 Hz), 2.69 (2H, t, J= 7.32 Hz), 2.69 (2H, q, J= 7.51 Hz), 3.16 (2H, t, J= 7.32 Hz), 4.06 (3H, s), 6.25 (1H, br. s), 7.11 - 7.16 (3H, complex), 7.23 - 7.27 (2H, complex), 7.62 (1H, s); δ_C (CD_3OD) 7.15, 13.68, 17.55, 18.69, 27.84, 38.78, 56.79, 101.17, 125.44, 127.33, 127.74, 129.07, 129.60, 129.78, 137.47, 139.23, 144.95, 146.31, 164.16, 168.06, 181.80. **14** as an oil: $C_{23}H_{27}NO_4$ [m/z 366.1712 (M^+-CH_3)]; IR (film) 1670 cm^{-1}; δ_H ($CDCl_3$) 1.11 (3H, t, J= 7.59 Hz), 1.83 (3H, s), 1.90 (3H, s), 2.50 - 2.63 (6H, complex), 3.85 (3H, s), 4.36 (1H, dd, J= 7.26, 8.74 Hz), 4.49 (1H, dd, J= 8.74, 9.90 Hz), 5.30 (1H, br. q, J= 5.60 Hz), 6.33 (1H, br. s), 7.17 - 7.22 (3H, complex), 7.28 - 7.35 (2H, complex); δ_C ($CDCl_3$) 6.72, 14.23, 17.47, 17.54, 26.72, 36.66, 55.01, 64.33, 69.96, 100.05, 125.27, 125.82, 126.15, 128.01x2, 128.68x2, 136.64, 137.83, 154.09, 161.92, 170.10, 179.82. **phenoxan (1)** as prisms: mp 87 - 88 °C (from hexane - EtOAc); $C_{23}H_{25}NO_4$ [m/z 364.1536 (M^+-CH_3)]; IR (nujol) 1665 cm^{-1}; δ_H (CD_3OD) 1.06 (3H, t, J= 7.59 Hz), 1.82 (3H, s), 1.87 (3H, d, J= 1.25 Hz), 2.65 (2H, t, 7.59 Hz), 2.83 (2H, q, J= 7.59 Hz), 3.08 (2H, t, J= 7.59 Hz), 4.03 (3H, s), 6.27 (1H, br. s), 7.11 - 7.14 (3H, complex), 7.22 - 7.27 (2H, complex), 8.32 (1H, s); δ_C (CD_3OD) 7.13, 13.82, 17.59, 18.36, 27.64, 38.61, 56.60, 100.84, 126.07, 127.20, 127.56, 129.02x2, 129.79x2, 135.14, 137.59, 139.33, 140.48, 149.48, 164.16, 166.63, 182.39.

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