Synthetic Studies Toward Phenoxan Analogs

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We developed two reactions needed for a total synthesis of phenoxan, a naturally occurring compound with anti-HIV activity. In this Note, we further examined these two issues: metallation of a 2-methyloxazole and formation of a pyran-4-one. We employed these methods for the preparation of a phenoxan analog.

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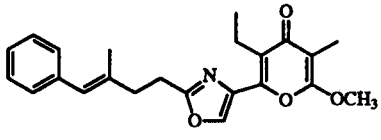
Introduction.

During the total synthesis of phenoxan [1], two challenges confronted us—the regioselective alkylation of a substituted oxazole [2] and the construction of a substituted pyran-4-one. There are a variety of methods for preparing substituted oxazoles [3], although, none were suitable for preparing a 2,4-disubstituted oxazole which would allow for further elaboration to phenoxan. We eventually adapted the metallation studies by Lipshutz and Hungate [4] who showed that 2,4,5-trimethyloxazole could be selectively metallated at the 2-methyl group, and following the addition of an electrophile, various alkylated oxazoles could be obtained. In contrast, Ganem and co-workers utilized an oxazole silylated at the 5-position in order to minimize alkylation on the ring [5]. This silyl group was later removed after alkylation at the 2-methyl group. In the total synthesis of phenoxan, we needed a mild conversion of a pyran-2-one to a pyran-4-one. Initially, we employed with good success a literature procedure on simple model systems. Application of this reaction for phenoxan resulted in the destruction of the intermediate pyran-2-one. We circumvented this problem by prior conversion to a silyl enol ether followed by treatment with Meerwein's reagent to give the desired pyran 4-one. This step was crucial as it took place in the presence of a fragil oxazole.

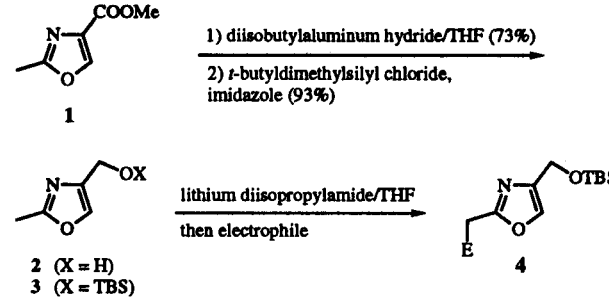


phenoxan

Results and Discussion.

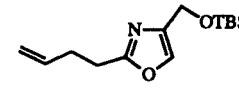
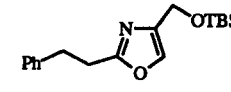
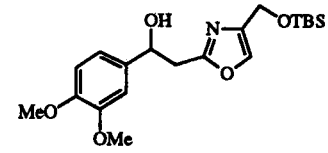
Alcohol **2** was initially obtained by the lithium alumimun hydride reduction of methyl 2-methyloxazolecarboxylate **1** [6]. A higher yield was afforded by diisobutylaluminum hydride reduction (Scheme 1). In the total synthesis of phenoxan [2] we treated the dianion of **2** with an allylic bromide which gave the desired product in 52% yield. We suspected the free hydroxyl group was interferring with the alkylation. Therefore, the alcohol was blocked as a *t*-butyldimethylsilyl ether **3**. We then examined the scope of the alkylation of **3** with other electrophiles (Table 1). The yields of all new compounds are based on pure isolated materials and are in good agreement with proton, carbon-nmr, mass spectrometry (low and high resolution), and elemental analysis.

Scheme 1



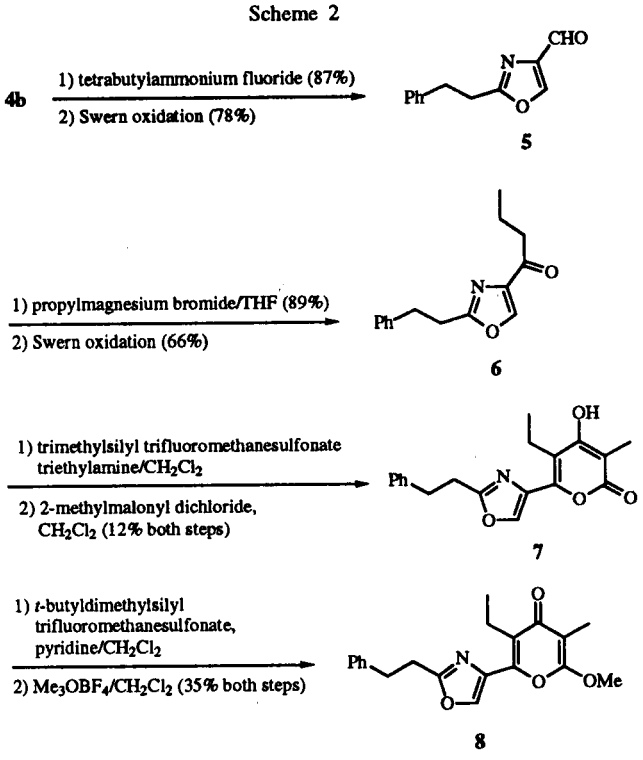
For construction of pyran-2-one **7** we employed a literature procedure [8] whereby a ketone can be indirectly transformed to a pyran-2-one by prior conversion to a silyl enol ether followed by treatment with malonyl dichloride

Table 1

electrophile	product
allyl bromide	 **4a** (41%)
benzyl bromide	 **4b** (60%)
benzyl methanesulfonate	**4b** (48%)
3,4-dimethoxybenzaldehyde	 **4c** (56%)

(Scheme 2). Desilylation and oxidation [9] of **4b** afforded **5** and following propylmagnesium bromide and Swern oxidation yielded **6**. Silylation of **6** to the silyl enol ether followed by acylation/cyclization with 2-methylmalonyl dichloride gave **7**. Silylation of the hindered enol and subsequent treatment with Meerwien's reagent gave phenoxan analog **8**. Spectral examination of **8** was consistent with the proposed strucutre. Future work will continue to examine the acylation-cylization reaction for preparing other pyran-2-ones.

Scheme 2



EXPERIMENTAL

General Methods.

All solvents were distilled from calcium hydride prior to use except for tetrahydrofuran (THF) which was distilled from molten potassium, and ethyl ether which was distilled from sodium-benzophenone. All reagents were used as obtained from commercial suppliers unless otherwise noted. Thin layer chromatography was performed with glass-backed precoated plates (Si-254F). Column chromatography utilized either silica gel 230-400 mesh, 60Å. The proton and carbon nmr spectra were recorded on a 300 MHz spectrometer (300 MHz ^{1}H, 75 MHz ^{13}C). Deuteriochloroform with tetramethylsilane (TMS) was referenced to TMS (0.000 ppm ^{1}H) or chloroform (77.00 ppm ^{13}C). Melting points are uncorrected. Elemental analysis were performed by Atlantic Microlab (Norcross, GA). High-resolution mass spectroscopic data were obtained by the Nebraska Center for Mass Spectrosopy.

2-Methyl-4-hydroxymethyloxazole (2).

To a solution of 2.53 g (17.8 mmoles) of **1** in 100 ml of dichloromethane chilled to -78° was added *via* syringe 40.2 ml (1 *M*, 2.3 equivalents) of diisobutylaluminum hydride. The reaction mixture was stirred at -78° for 2 hours and then quenched by addition of methanol. The reaction was poured into a separatory funnel containing water and ethyl acetate. The product was extracted with several portions of ethyl acetate. The organic layers were combined, washed with brine, and dried over magnesium sulfate. Filtration and evaporation of the solvent *in vacuo* left a yellow oil which was further purified by column chromatography (75% ethyl acetate/hexane) to give 1.37 g (68%) of **2** as a pale yellow oil which slowly crystallized upon standing, R_f = 0.11 (75% ethyl acetate/hexane); ^{1}H (deuteriochloroform): δ 2.4 (s, 3H), 4.5 (s, 3H), 7.4 (s, 1H); ^{13}C (deuteriochloroform): δ 162.2, 140.1, 134.9, 55.8, 13.7. This compound was identical to the material obtained by lithium aluminum hydride recduction of **1** [2].

2-Methyl-4-(*t*-butyldimethylsilyl)hydroxymethyloxazole (3).

To a solution of 5.15 g (45.6 mmoles) of **2** in 75 ml of dimethylformamide was added 7.54 g (50.0 mmoles, 1.1 equivalents) of *t*-butyldimethylsilyl chloride and 4.63 g (68.0 mmoles, 1.5 equivalents) of imidazole. The reaction mixture was stirred overnight at room temperature. It was then poured into a separatory funnel containing water and ethyl acetate and extracted several times with ethyl acetate. The organic layers were combined, washed with water, brine and dried over magnesium sulfate. Filtration and evaporation of the solvent *in vacuo* left a viscous oil which was further purified by column chromatography (75% ethyl acetate/hexane) to give 9.48 g (91%) of **3** as a pale yellow oil, R_f = 0.61 (50% ethyl acetate/hexane); ^{1}H (deuteriochloroform): δ 0.1 (s, 6H), 0.92 (s, 9H), 2.42 (s, 3H), 4.6 (s, 2H), 7.4 (s, 1H); ^{13}C (deuteriochloroform): δ 161.4, 141.1, 134.6, 58.6, 25.8, 18.3, 13.9, -5.4; ms: m/z 212 (M^+-CH_3), 170 (M^+-C_4H_9).

Anal. Calcd. for $C_{11}H_{21}NO_2Si$: C, 58.11; H, 9.31; N, 6.16. Found: C, 58.2; H, 9.34; N, 6.23.

2-(3-Butenyl)-4-(*t*-butyldimethylsilyl)hydroxymethyloxazole (4a).

General Procedure.

To a solution of 0.8 ml (5.7 mmoles, 1.3 equivalents) of diisopropylamine in 10 ml of tetrahydrofuran cooled to 0° was added 4.8 ml (4.8 mmoles, 1.1 equivalents) of *n*-butyllithium *via* syringe. The solution was stirred at 0° for 15 minutes and then chilled to -78° before adding 960 mg (4.20 mmoles) of **3** (dissolved in 4 ml of tetrahydrofuran) *via* cannula. The resulting orange-colored solution was stirred at -78° for 30 minutes and then 640 mg (5.2 mmoles, 1.2 equivalents) of allyl bromide (dissolved in 5 ml of tetrahydrofuran) was added *via* cannula. The reaction mixture was stirred at -78° for 2 hours and then allowed to warm to room temperature. The reaction mixture was quenched by the addition of saturated ammonium chloride and then extracted with several portions of ethyl acetate. The organic layers were combined, washed once with water, and then with brine. They were then dried over magnesium sulfate. Filtration and evaporation of solvent *in vacuo* left a viscous oil which was further purified by column chromatography (50% ethyl acetate/hexane) to give 480 mg (41%) of **4a**, R_f = 0.69 (50% ethyl acetate/hexane); ^{1}H (deuteriochloroform): δ 0.6 (s, 6H), 0.9 (s, 9H), 2.4-2.5 (q, 2H, J = 7.8 Hz), 2.7-2.8 (q, 2H, J = 7.8 Hz), 4.6 (s, 2H), 4.9-5.1 (m, 2H), 5.8-5.9 (m, 1H), 7.4 (s, 1H); ^{13}C (deuteriochloroform): δ 164.2, 141.1, 136.5, 134.6, 115.8,

58.7, 30.9, 27.7, 25.9, 25.7, 18.4, -5.4; ms: m/z 252 (M^+-CH_3), 210 (M^+-C_4H_9).

Anal. Calcd. for $C_{14}H_{25}NO_2Si$: C, 62.87; H, 9.42; N, 5.24. Found: C, 63.07; H, 9.52; N, 5.17.

2-(2-Phenylethyl)-4-(*t*-butyldimethylsilyl)hydroxymethyloxazole (**4b**).

This compound was prepared according to the general procedure from oxazole **3** and benzyl bromide, R_f = 0.75 (75% ethyl acetate/hexane); ^1H (deuteriochloroform): δ 0.1 (s, 6H), 0.9 (s, 9H), 3.0-3.1 (m, 4H), 4.6 (d, 2H, J ~ 0.9 Hz), 7.1-7.2 (m, 5H), 7.4 (s, 1H); ^{13}C (deuteriochloroform): δ 164.0, 141.1, 140.4, 134.6, 128.5, 128.2, 126.3, 58.7, 33.1, 30.1, 25.9, 18.4, -5.3; ms: m/z 260 (M^+-C_4H_9).

Anal. Calcd. for $C_{18}H_{27}NO_2Si$: C, 68.09; H, 8.57; N, 4.41. Found: C, 68.32; H, 8.61; N, 4.26.

The above compound was also prepared from oxazole **3** and benzyl methanesulfonate.

Alcohol **4d**.

The compound was prepared according to the general procedure from oxazole **3** and 3,4-dimethoxybenzaldehyde, R_f = 0.10 (50% ethyl acetate/hexane); ^1H (deuteriochloroform): δ 0.09 (s, 6H), 0.9 (s, 9H), 3.0-3.1 (m, 2H), 3.85 (2s, 6H), 4.6 (s, 2H), 5.1 (t, 1H, J = 6.3 Hz), 6.8-7.0 (m, 3H), 7.4 (s, 1H); ^{13}C (deuteriochloroform): δ 162.6, 149.0, 148.6, 141.0, 135.3, 134.8, 117.9, 111.0, 108.8, 71.1, 58.4, 55.9, 55.8, 37.7, 25.8, 18.3, -5.3; ms: m/z 393 (M^+), 336 (M^+-C_4H_9).

Anal. Calcd. for $C_{20}H_{31}NO_5Si$: C, 61.04; H, 7.94; N, 3.56. Found: C, 60.79; H, 7.91; N, 3.53.

2-(2-Phenylethyl)oxazole-4-carboxaldehyde (**5**).

This compound was prepared in two steps from **4b**. To a solution of **4b** (2.0 g, 6.3 mmoles) in 60 ml of tetrahydrofuran was added 15.5 ml of tetrabutylammonium fluoride (1*M*, 2.5 equivalents) and stirred at room temperature for 1 hour. The reaction mixture was quenched by the addition of 20 ml water. The solution was reduced in volume *in vacuo* and then extracted with several portions of ethyl acetate. The organic layers were combined, washed with brine, and dried over magnesium sulfate. Filtration and evaporation of solvent *in vacuo* left an oil which was purified by column chromatography (75% ethyl acetate/hexane) to give 1.1 g (86%) of the primary alcohol as a viscous oil, R_f = 0.17 (75% ethyl acetate/hexane); ^1H (deuteriochloroform): δ 3.0 (br s, 4H), 4.5 (s, 2H), 7.2-7.3 (m, 5H), 7.5 (s, 1H); ^{13}C (deuteriochloroform): δ 164.8, 140.3, 140.2, 134.9, 128.6, 128.3, 126.4, 56.1, 33.0, 30.0; ms: m/z 203 (M^+), 91 (M^+-$C_5H_6NO_2$).

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.44; N, 6.89. Found: C, 70.79; H, 6.48; N, 6.78.

To a solution of oxalyl chloride (0.3 ml, 3.4 mmoles) in 4 ml of dichloromethane, cooled to -78°, was added over 5 minutes, 1.1 ml (15.2 mmoles) of dimethyl sulphoxide dissolved in 4 ml of dichloromethane. The solution was stirred at -78° for 25 minutes and then the alcohol (500 mg, 2.5 mmoles), dissolved in 3 ml of dichloromethane, was added to the reaction mixture *via* cannula. The reaction mixture was stirred at -78° for 1 hour and then quenched by the addition of 9 ml of triethylamine. The solution was poured into a separatory funnel containing diluted aqueous sodium bicarbonate. The organic layer was washed once with water, and then with brine. It was then dried over sodium sulfate. Filtration and evaporation of the solvent *in vacuo* left a pale yellow oil which was further purified by column chromatography (75% ethyl acetate/hexane) and gave 393 mg (78%) of **5**, R_f = 0.42 (25% ethyl acetate/hexane); ^1H (deuteriochloroform): δ 3.14 (br s, 4H), 7.2-7.3 (m, 5H), 8.2 (s, 1H), 9.9 (s, 1H). This compound was not fully characterized but carried on to the next step, as it was prone to further oxidation.

2-(2-Phenylethyl)oxazole-4-butanoyloxazole (**6**).

This compound was prepared in two steps from **5**. To a solution of **5** (800 mg, 4.0 mmoles) in 20 ml of tetrahydrofuran was added 8.2 ml of 1*M* (8.2 mmoles) propylmagnesium bromide at 0° for 2 hours. The reaction mixture was quenched by the addition of aqueous ammonium chloride and then extracted from ethyl acetate and water. The organic layers were washed with water, brine, and then dried over magnesium sulfate. Filtration and evaporation of the solvent *in vacuo* left a pale yellow oil which was further purified by column chromatography (50% ethyl acetate/hexane) to give 873 mg (89%) of a viscous oil, R_f = 0.35 (50% ethyl acetate/hexane); ^1H (deuteriochloroform): δ 1.0 (t, 3H, J = 7.5 Hz), 1.2-1.5 (m, 2H), 1.8 (m, 2H), 3.06 (m, 4H), 4.8 (q, 1H), 7.1-7.3 (m, 5H), 7.4 (s, 1H); ^{13}C (deuteriochloroform): δ 164.3, 143.6, 140.3, 133.6, 128.6, 128.3, 126.4, 66.9, 38.4, 33.2, 30.1, 18.7, 13.9; ms: m/z 245 (M^+), 227 (M^+-H_2O), 202 (M^+-C_3H_7). The sensitive alcohol was quickly carried on to the next step. To a solution of oxalyl chloride (1.2 ml, 13.6 mmoles) in 8 ml of dichloromethane, cooled to -78°, was added for over 5 minutes, 2.0 ml (27.9 mmoles) of dimethyl sulphoxide dissolved in 8 ml of dichloromethane. The solution was stirred at -78° for 25 minutes and then 820 mg (3.3 mmoles) of the secondary alcohol, dissolved in 6 ml of dichloromethane, was added to the reaction mixture *via* cannula. The reaction mixture was stirred at -78° for 1 hour, and then quenched by the addition of 8 ml of triethylamine. The reaction was poured into a separatory funnel containing dilute aqueous sodium bicarbonate. The organic layer was washed once with water, brine and then dried over sodium sulfate. Filtration and evaporation of solvent *in vacuo* left a pale yellow oil which was further purified by column chromatography (75% ethyl acetate/hexane) and gave 660 mg (82%) of **6** as a white solid, mp 62-64°, R_f = 0.70 (50% ethyl acetate/hexane); ^1H (deuteriochloroform): δ 0.1 (t, 3H, J = 7.8 Hz), 1.7 (sext, 2H), 2.8 (t, 2H, J = 7.0 Hz), 3.1 (br s, 4H), 7.2-7.3 (m, 5H), 8.1 (s, 1H); ^{13}C (deuteriochloroform): δ 195.3, 164.5, 141.8, 140.7, 139.9, 128.6, 128.3, 126.5, 41.8, 33.0, 30.0, 17.3, 13.8; ms: m/z 243 (M^+), 91 (M^+-$C_5H_6NO_2$).

Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.97; H, 7.07; N, 5.76.

Pyran-2-one **7**.

To a solution of **6** (970 mg, 4.0 mmoles) in 6 ml of dichloromethane at 0° was added 0.60 ml (4.4 mmoles) of triethylamine and 0.90 ml (4.4 mmoles) of trimethylsilyl trifluoromethansulfonate *via* syringe. The resulting yellow solution was stirred at 0° for 4 hours. The solvent was removed *in vacuo* and the residue extracted with dry ether. Removal of the solvent *in vacuo* afforded the silyl enol ether which was quickly carried on to the next step. The silyl enol ether was dissovled in 4 ml of dichloromethane and then 2-methylmalonyl dichloride (0.23 g, 1.52 mmoles) was added *via* syringe at 0°. The reaction mixture was stirred at 0° for 4 hours. The reaction was warmed to room temperature and quenched by the addition of dilute aqueous sodium carbonate. The product was extracted with several portions of ethyl acetate. The organic layers were combined and washed with water, and then with brine. It was then dried over

sodium sulfate. Filtration and evaporation of the solvent *in vacuo* left a viscous oil which was further purified by column chromatography (50% ethyl acetate/hexane) to give 115 mg (24% from **6**) of **7** as a viscous oil, R_f = 0.27 (50% ethyl acetate/hexane), ^1H (deuteriochloroform): δ 1.16 (t, 3H, J = 7.35 Hz), 2.03 (s, 3H), 3.0 (q, 2H, J = 7.35 Hz), 3.11 (s, 4H), 5.9 (s, 1H), 7.3-7.35 (m, 5H), 8.04 (s, 1H); ^{13}C (deuteriochloroform): δ 186.2, 164.2, 164.0, 163.7, 140.1, 139.0, 135.1, 128.6, 128.3, 126.5, 113.6, 100.2, 32.8, 29.8, 16.9, 14.1, 8.6; hrms Calcd. for $C_{19}H_{19}NO_4$: 325.1314. Found: 325.13196 (1.68 ppm deviation).

Pyran-4-one **8**.

To a solution of 34 mg, 0.11 mmole of **7** dissolved in 5 ml of dichloromethane was added 0.05 ml (0.66 mmole, 6 equivalents) of pyridine and 0.1 ml (0.44 mmoles, 4 equivalents) of *t*-butyldimethylsilyl trifluoromethanesulfonate *via* microsyringe. The reaction mixture was stirred at room temperature for 2 hours. The reaction was quenched by pouring into a separatory funnel containing ethyl acetate and aqueous sodium bicarbonate. The organic layer was washed once with water, and then with brine. It was then dried over sodium sulfate. Filtration and evaporation of the solvent *in vacuo* left a viscous oil which was carried on to the last step. The crude silyl enol ether was placed in a small round bottomed flask containing 42 mg (0.28 mmole, 2.6 equivalents) of trimethyloxonium tetrafluoroborate dissolved in 5 ml of dichloromethane. The reaction mixture was stirred at room temperature for 2 hours. The reaction was quenched by pouring into a separatory funnel containing ethyl acetate and saturated sodium bicarbonate. The product was extracted with several portions of ethyl acetate. The organic layers were combined, washed once with water, and then with brine. It was then dried over sodium sulfate. Filtration and evaporation of solvent *in vacuo* gave a viscous oil which was further purified by preparative thin layer chromatography (33% ethyl acetate/hexane) to give 12 mg (34% from **7**) of **8** as a white solid, mp 84-87°, R_f = 0.41 (50% ethyl acetate/hexane); ^1H (deuteriochloroform): δ 1.12 (t, 3H, J = 7.5 Hz), 1.89 (s, 3H), 2.8 (q, 2H, J = 7.5 Hz), 3.14 (s, 4H), 4.01 (s, 3H), 7.2-7.3 (m, 5H), 7.86 (s, 1H); ^{13}C (deuteriochloroform): δ 180.4, 164.6, 159.8, 147.2, 140.0, 137.4, 134.4, 128.6, 128.4, 126.5, 125.8, 100.3, 55.5, 32.8, 29.8, 17.7, 13.4, 6.8; hrms Calcd. for $C_{20}H_{21}O_4N$: 339.1470. Found: 339.1478 (2.18 ppm deviation).

Anal. Calcd. for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.88; H, 6.20; N, 3.76.

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