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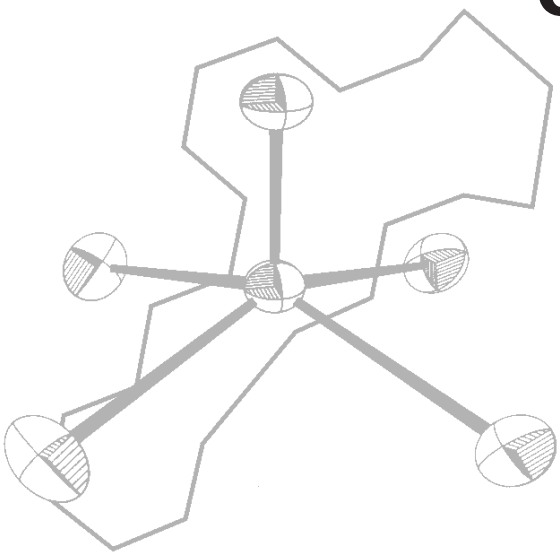

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Triacetic Acid Lactone Methyl Ether as a Natural Products Synthon

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Deprotonation at the 6-methyl group of 4-methoxy-6-methyl-3-trimethylsilyl-2*H*-pyran-2-one (1d) resulted in the formation of an extended enolate (1e) which was spectroscopically identified. The utility of this enolate towards the synthesis of some natural products of polyketide origin has been described, e.g. the synthesis of 4-methoxy-6-(2-oxopropyl)-2*H*-pyran-2-one (4) and 4-methoxy-6-phenacyl-2*H*-pyran-2-one (5), the former having been isolated from *Penicillium stipitatum* culture, and the synthesis of 5,6-dehydrokawain (6), a natural product extracted from the wood of *Aniba firmula* and from the seeds of *Alpina blepharocalyx*.

Keywords. Enolate; natural product synthesis; pyrone.

A number of pyrones have been used as protected β-polyketo acids in the biomimetic synthesis of natural products of polyketide origin,[1–7] one of which is triacetic acid lactone methyl ether* (1a) (Scheme 1), which is used in the present investigation. It has been used as a versatile synthon in polyketide-type biomimetic synthesis. In these earlier investigations pyrone (1a) was used as an electrophile[1–3] and it can also behave as a nucleophile.[4–7] The last reaction is presumably initiated by deprotonation.

There is no record in the literature in which the anion at C 7 of compound (1a) is generated by treatment with strong base in spite of the apparent stabilization available to the system by delocalization of the charge onto the carbonyl oxygen. This possibility was overlooked by Wachter and Harris[6] on the generation of the dianion and in exploratory works on the preparation of the ylide (1b) (Scheme 1), which was unable to be acylated with normal acylating agents.

A possible explanation for the difficulty in initiating reactivity at C 7 of compound (1a) emerged as a result of an observation that reaction of (1a) with lithium diisopropylamide in tetrahydrofuran at –78°C followed by quenching with deuterium oxide yielded the monodeuterated derivative (1c). It was found that the anion at C 3 of the pyrone (1a) could also be generated by treatment with either lithium diisopropylamide or butyllithium and could be made to react with chlorotrimethylsilane at –78°C to give the trimethylsilylpyrone (1d) in 45% yield.[8]

However, in the present investigation, when the pyrone (1a) was treated with methyllithium in tetrahydrofuran at –120°C, the anion at C 3 was generated in high yield. The anion was made to react with chlorotrimethylsilane affording the silylpyrone (1d) in higher than 92% yield. It was found that the yields were high even when the reaction was carried out on a large scale. This silylpyrone is of particular interest to us since it is a system in which ring deprotonation is blocked. It was, therefore, thought that deprotonation at other sites of the molecule, particularly at the 6-methyl group, would be easy. The trimethylsilyl group used for the protection is very easy to remove after it has accomplished its task.

The silylpyrone (1d) was shown to be deprotonated at the 6-methyl group, by treating with lithium diisopropylamide in tetrahydrofuran at –120°C to give the anion (1e). The ^{13}C n.m.r. spectrum of the parent silylpyrone and the anion derived from it provided experimental evidence for the formation of this enolate. The experiment consisted of cooling a solution of the silylpyrone (1d) in tetrahydrofuran to –120°C and adding 1 equiv. of lithium diisopropylamide. The solution was then brought to –70°C and the ^{13}C n.m.r. spectrum was recorded. No resonance due to the starting material could be observed. Furthermore, the lithium diisopropylamide was now present as diisopropylamine, indicating that deprotonation has occurred. It is interesting to note that deprotonation was observed to occur in less than 10 min.

The assignment of the ^{13}C n.m.r. spectrum of the anionic species was made on the basis of the chemical shift and the multiplicities in the proton-coupled spectrum. Thus it can be seen that the trimethylsilyl group in the anion spectrum is virtually unmoved (Table 1). C 7 is considerably deshielded and occurs as a triplet in the proton-coupled spectrum, while C 2 is shielded. Unfortunately, the very slowly relaxing quaternary C 3 does not appear under the rapid pulsing conditions employed, possibly due to saturation or accidental superposition with solvent resonance. Hence, it can be concluded that the anion is an extended enolate of the form (1e).

The synthetic utility of (1e) was tested by quenching with acetyl chloride and with benzoyl chloride, affording after alkaline workup compounds (2) and (3) in 63 and 81% yields

* 4-Methoxy-6-methyl-2*H*-pyran-2-one.

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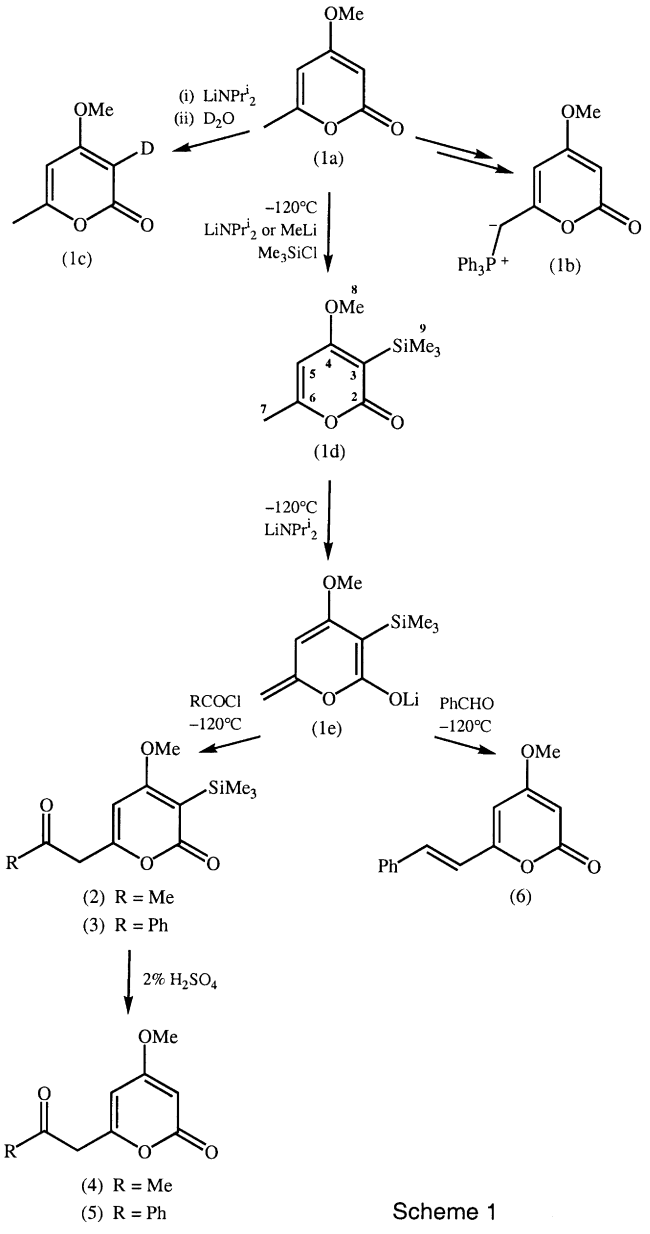
respectively (Scheme 1). On acidification, the silyl group is lost to give (4) and (5). Their ^{1}H n.m.r. spectra showed the presence of a methylene group and two vinylic protons (pyrone protons). The latter are coupled to each other with a coupling constant of 3 Hz. Compound (4) is the methyl ether of the natural product tetraacetic acid lactone. It has been isolated during studies on *Penicillium stipitatum* cultures.[9] The importance of compounds (4) and (5) in the biomimetic synthesis of polyketide-type aromatic compounds has also been mentioned in the literature.[9–11]

After the extended enolate (1e) was quenched with benzaldehyde at –120°C and the reaction worked up in acid medium, a crystalline compound (6) was obtained in 52% yield. The ^{1}H n.m.r. spectrum of this compound showed, beside the aromatic protons, vinylic hydrogens at δ 6.95, 1H, d, and 7.40, 1H, d, the coupling constant being 15 Hz, indicating that the two hydrogens are *trans* oriented. The n.m.r. spectrum also showed pyrone protons at typical chemical shifts, i.e., δ 5.55, 1H, d, and 6.15, 1H, d, coupled to each other with a coupling constant of 3 Hz. Hence the structure was assigned as 5,6-dehydrokawain (6). Further evidence came from the infrared spectral frequencies of 1400, 1585, 1605, 1645 and 1710 cm^{-1}. Compound (6) was first isolated from the wood of *Aniba firmula*.[12] It was, recently, isolated from the seeds of *Alpina blepharocalyx* and reported to strongly inhibit platelet aggregation induced by collagen arachidonic acid.[13,14]



Scheme 1

Table 1. ^{13}C n.m.r. spectral data, recorded at –70°C, of compound (1d) and the extended enolate (1e)

Cpd	C2	C4	C6	C3	C5	C8	C7	C9
(1d)	175.2	164.5	164.4	96.4	93.6	54.8	19.0	–1.1
(1e)	169.2	168.0	161.2	—	75.2	52.8	68.9	0.2

In conclusion, this investigation has solved the following chemical problems. Firstly an understanding of the relative activities of the various sites of triacetic acid lactone methyl ether (1a) towards strong bases is now established, particularly at C3 and C7. Secondly, the reaction conditions employed for the preparation of the silylpyrone (1d) in high yields have been improved. Thirdly, and more importantly, this work has established a new and easy method for the generation and synthetic use of the extended enolate (1e).

Experimental

Melting points were recorded on a Kofler hot-stage apparatus and are uncorrected. Infrared spectra (KBr) were measured on a Perkin–Elmer 297 instrument. ^{1}H and ^{13}C n.m.r. spectra were recorded on a Varian EM-360, CFT20, or XL-100 spectrometer. Chemical shifts are expressed in δ values (ppm) relative to tetramethylsilane as the internal reference standard; coupling constants (*J*) are given in Hz. Mass spectra were recorded on AEI MS 50 and MS 30 spectrometers. Ultraviolet spectra were recorded on a Pye Unicam SP-8-100 spectrophotometer. Tetrahydrofuran was refluxed over and distilled from lithium aluminium hydride and stored over sodium wire, under an atmosphere of argon. Chlorotrimethylsilane was distilled twice and then treated with triethylamine and centrifuged. It was stored over lithium hydride under an atmosphere of nitrogen. Acetyl chloride was refluxed with phosphorus pentachloride for several hours and distilled. It was then distilled from 1/10 its volume of dimethylamine. Benzoyl chloride in benzene solution was washed several times with cold aqueous potassium carbonate solution. The solution was then dried over calcium chloride and distilled. Benzaldehyde was washed several times with 10% aqueous sodium carbonate, then with saturated sodium sulfite solution and then with water. It was dried over magnesium sulfate and distilled under reduced pressure under an atmosphere of nitrogen. Sodium hydride and potassium hydride were obtained as 50% suspensions in oil, and were washed with n-hexane and tetrahydrofuran to remove the oil prior to use. Preparative thin-layer chromatography (p.l.c.) was carried out on 1 mm silica plates (Merck 60 PF254). The following mixtures were used for cooling: 0°C, ice and water; –4°C, salted ice/water; from –10 to –15°C, ice/methanol; –78°C, dry ice/acetone; –120°C, liquid nitrogen/diethyl ether.

*4-Methoxy-6-methyl-3-trimethylsilyl-2*H*-pyran-2-one (1d)*

Method A. Triacetic acid lactone methyl ether (1a) (140 mg, 1 mmol) in tetrahydrofuran (10 ml) in a flask fitted with a serum cap, flushed with nitrogen and cooled to –120°C, was transferred by means of a double-ended needle to a flask containing lithium diisopropylamide (1 mmol) in tetrahydrofuran (10 ml) cooled to –120°C. After a few minutes, chlorotrimethylsilane (0.20 ml, excess) was added and the reaction mixture left to warm to room temperature. Saturated potassium

hydrogen carbonate (10 ml) was then added and the reaction mixture extracted with ether. The ethereal solution was dried over sodium sulfate and evaporated to dryness in vacuum. P.l.c. (ether/light petroleum 1 : 1) afforded, beside unreacted (1a), a colourless crystalline solid (1d) (84 mg, 40%), m.p. 77°C (lit.[8] 76–78°C). ^{1}H n.m.r. ($CDCl_3$) δ 0.02, s, 9H; 2.25, s, 3H; 3.90, s, 3H; 5.80, s, 1H. I.r. (cm^{-1}) 1695, 1645, 1565.

Method B. Triacetic acid lactone methyl ether (1) (140 mg, 1 mmol) was dissolved in tetrahydrofuran (100 ml) in a flask flushed with nitrogen and cooled to –120°C. Methyllithium (0.60 ml, 1 mmol) was added and the reaction mixture instantly turned a faint yellow colour. After 1–2 min chlorotrimethylsilane (0.20 ml, excess) was injected. The reaction mixture was then maintained at –78°C. A saturated solution of potassium bicarbonate was added and the reaction mixture left to warm to room temperature. It was then extracted into ether (3×15 ml) and the ethereal solution dried over sodium sulfate and decolorized by charcoal. The solvent was then evaporated in vacuum and purified by p.l.c. (same solvent mixture as before) to give colourless needles of (1d) (184 mg, 92%), m.p. 77°C (lit.[8] 76–78°C). Spectral data were the same as those recorded for this compound in the previous experiment.

*4-Methoxy-6-(2-oxopropyl)-2*H*-pyran-2-one (4)*

A solution of lithium diisopropylamide (0.50 mmol) was cooled to –78°C and transferred by means of a double-ended needle to a flask containing a solution of the silylpyrone (1d) (106 mg, 0.50 mmol) in tetrahydrofuran (5 ml) at –120°C and kept under a nitrogen atmosphere. After a few minutes dry acetyl chloride (0.1 ml, excess) was injected. The reaction mixture was left to stir for 10 min at –120°C and then warmed to –78°C. Dilute sulfuric acid solution (2%, 10 ml) was then added. The reaction mixture was then extracted with ethyl acetate (3×15 ml); the solution was dried over anhydrous magnesium sulfate and evaporated in vacuum. Recrystallization from methanol gave colourless crystals (58 mg, 64%), m.p. 80–83°C (lit.[9] 83°C). ^{1}H n.m.r., δ 2.20, 3H, s; 3.45, 2H, s; 3.70, 3H, s; 5.40, 1H, d, *J* 3 Hz; 5.58, 1H, d, *J* 3 Hz. I.r. (cm^{-1}) 1720, 1710, 1415. U.v. λ_{max} 282 nm.

*4-Methoxy-6-phenacyl-2*H*-pyran-2-one (5)*

A solution of lithium diisopropylamide (0.50 mmol) was cooled to –78°C and then transferred by means of a double-ended needle to a flask containing a solution of the silylpyrone (1d) (106 mg, 0.50 mmol) in tetrahydrofuran (5 ml) at –120°C kept under a nitrogen atmosphere. After a few minutes benzoyl chloride (0.1 ml, excess) was added. The reaction mixture was left to stir for 5–10 min at –120°C and for 5 min at –78°C and then left to warm to room temperature. Dilute sulfuric acid (2%, 10 ml) was then added. The reaction mixture was extracted with ether; the ethereal solution was dried over anhydrous magnesium sulfate and evaporated in vacuum. The product was recrystallized from methanol to give yellow crystals of (5) (98 mg, 80%), m.p. 136°C (lit.[11] 135–137°C). ^{1}H n.m.r. δ 3.75, 3H, s; 3.80, 2H, s; 5.40, 1H, d, *J* 3 Hz; 5.45, 1H, d, *J* 3 Hz; 7.90, 3H, m; 7.95, 2H, m. I.r. (cm^{-1}) 1650, 1600, 1570, 1450, 1400. U.v. λ_{max} 280, 245 nm.

5,6-Dehydrokawain (6)

Lithium diisopropylamide (1 mmol) in tetrahydrofuran was cooled to –78°C and transferred by means of a double-ended needle to a solution of the silylpyrone (1d) (212 mg, 1 mmol) in tetrahydrofuran (10 ml) in a flask fitted with a serum cap and cooled to –120°C under a nitrogen atmosphere. After a few minutes dry benzaldehyde (0.1 ml, excess) was injected. The reaction mixture was left to warm slowly to room temperature over 3 h. Dilute sulfuric acid (5%, 20 ml) was added and the reaction mixture was extracted with ethyl acetate (3×20 ml). The combined organic extracts were dried over anhydrous magnesium sulfate and the solvent was evaporated in vacuum. The product was purified by p.l.c. (ether/light petroleum 1 : 1), affording colourless needles of (6) (118 mg, 51%), m.p. 139°C (lit.[12] 140°C). ^{1}H n.m.r. δ 3.75, 3H, s; 5.55, 1H, d, *J* 3 Hz; 6.15, 1H, d, *J* 3 Hz; 6.95, 1H, d, *J* 15 Hz; 7.40, 1H, d, *J* 15 Hz; 7.37–7.66, 5H, m. I.r. (cm^{-1}) 1710, 1645, 1605, 1585, 1455, 1400. U.v. λ_{max} 343, 255, 230 nm.

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References

[1] Leeper, F. J., and Staunton, J., *J. Chem. Soc., Chem. Commun.,* 1975, 675.
[2] Evans, G. E., Leeper, F. J., Murphy, F. J., and Staunton, J., *J. Chem. Soc., Chem. Commun*., 1979, 205.
[3] Builock, J. D., and Smith, H. G., *J. Chem. Soc*., 1960, 502.
[4] Douglas, J. L., and Money, T., *Can. J. Chem.,* 1968, **46**, 695.
[5] Harris, T. M., and Wachter, M. P., *Tetrahedron,* 1970, **26**, 5255.
[6] Wachter, M. P., and Harris, T. M., *Tetrahedron*, 1970, **26**, 1685.
[7] Bloomer, J. L., Zaidi, S. M. H., Strupczewski, J. T., Brosz, C. S., and Gudzyk, L. A., *J. Org. Chem.*, 1974, **39**, 3615.
[8] Carpenter, T. A., Jenner, P. J., Leeper, F. J., and Staunton, J., *J. Chem. Soc., Chem. Commun*., 1980, 1227.
[9] Bentley, R., and Zwitkowits, P. M., *J. Am. Chem. Soc.,* 1967, **89**, 676; Yamamura, S., *J. Chem. Soc., Chem. Commun*., 1961, 1580.
[10] Guilford, H., Scott, A. I., Skingle, D., and Yalpani, M., *J. Chem. Soc., Chem. Commun*., 1968, 1127.
[11] Harris, T. M., Watcher, M. P., and Wiseman, G. A., *J. Chem. Soc., Chem. Commun.,* 1969, 177.
[12] Gottleib, O. R., and Mors, W. B., *J. Org. Chem.,* 1959, **24**, 17.
[13] Teng, C. M., Lin, C. H., Yu, S. M., Wang, K. J., Li, M. H., and Chin, C. F., *China J. Physiol.*, 1990, **20**, 41.
[14] Dongand, S. H., and Chin, S. X., *J. Nat. Prod.,* 1998, **61**, 142.