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Novel Synthesis of a Mixed Phosphonic Anhydride. A route to Carboxylic Acid Derivatives from a Methyl Ketone

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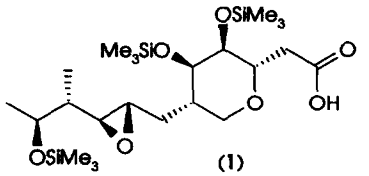
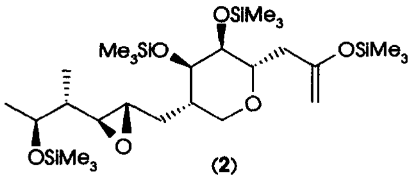
Abstract: Conversion of a methyl ketone to the kinetic enol phosphate followed by ozonolysis provides a novel synthesis of a mixed phosphonic anhydride. This can either be isolated, or reacted *in situ* with nucleophiles to afford the corresponding acid derivatives.

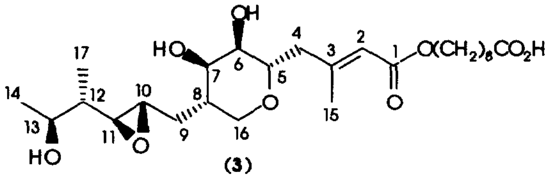
Oxidative cleavage of silyl enol ethers by ozonolysis has been reported to afford the corresponding carboxylic acids[1]. We wished to utilise this in the synthesis of the acid (**1**) and its derivatives, from the enol ether (**2**). However, problems were encountered due to the instability of the acid (**1**) and its readiness to undergo deprotection.



(1)



(2)

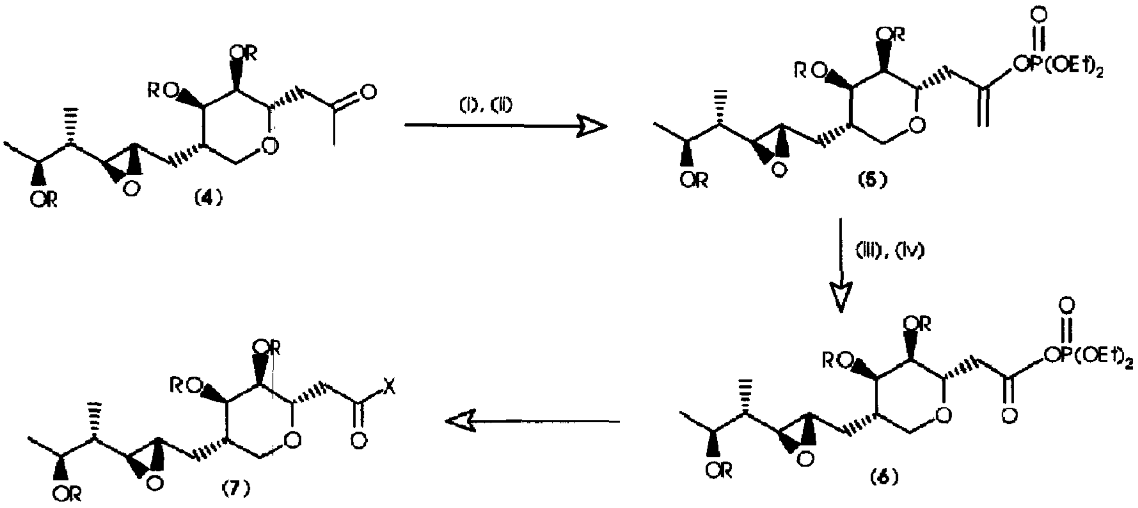


(3)

We report here a direct synthesis of carboxylic acid derivatives *via* the mixed phosphonic anhydride (**6**), obtained by ozonolysis of the enol phosphate (**5**). This avoids formation and isolation of the acid (**1**).

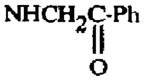
The *tris*-trimethylsilyl protected ketone (**4**), which is readily accessible from pseudomonic acid (**3**)[2], is converted to the enol phosphate (**5**) under kinetic conditions. This key intermediate can be cleaved by ozone, followed by reductive work-up to the mixed phosphonic anhydride (**6**), thus providing an activated acid directly, under conditions compatible with the sensitive protecting groups.

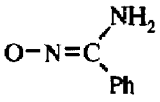
The trimethylsilyl protected mixed phosphonic anhydride (**6**) can be reacted *in situ* with nucleophiles to afford the corresponding acid derivatives. However, when the more stable triethylsilyl protecting group is used, it is possible to isolate and characterise the mixed phosphonic anhydride[3].

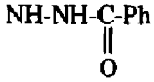


R = SiMe$_3$ or SiEt$_3$

(a) X = NHCH$_2$Ph

(b) X =

$NHCH_2C(=O)Ph$

(c) X =

$O{-}N{=}C(NH_2)Ph$

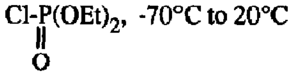
(d) X =

$NH{-}NH{-}C(=O)Ph$

(e) X = OMe

(f) X = SEt

Reagents:

(i) LDA, -70°C, THF

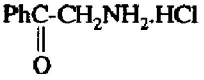
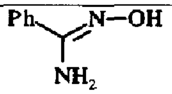
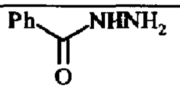
(ii)

$Cl{-}P(=O)(OEt)_2$, -70°C to 20°C

(iii) O$_3$, CH$_2$Cl$_2$, -70°C

(iv) Me$_2$S, -70°C to -30°C

For example, addition of the *tris*-trimethylsilyl protected ketone (4) to a solution of excess lithium diisopropylamide in THF at -70°C, followed by quenching the anion with diethylchlorophosphate afforded solely the kinetic enol phosphate (5) in 63% yield. This was dissolved in dichloromethane, and ozone bubbled through at -70°C until the solution became blue in colour. Argon was bubbled through to remove excess ozone, followed by treatment with dimethyl sulphide at -70° to -30°C. After 30 minutes at -30°C, the reaction mixture was treated with the corresponding nucleophile (1.1 equivalent) under the conditions shown in the table, and allowed to warm to room temperature. In general it was necessary to employ excess base, to prevent the reaction mixture from becoming acidic. After 1 hour the reaction mixture was washed with water and brine. The crude products were chromatographed on Kieselgel 60 eluting with ethyl acetate/hexane mixtures to afford **7(a)-(f)** in the yields shown.

REACTION CONDITIONS FOR THE CONVERSION OF (6) - (7)

	Protecting group R	Conditions			Yield of (7) from (6)
(a)	$SiMe_3$	NH_2CH_2Ph (4 equiv)		CH_2Cl_2	49%
(b)	$SiMe_3$	 $PhC(=O)CH_2NH_2.HCl$	NEt_3 (2.2 equiv)	MeOH	76%
(c)	$SiMe_3$		NEt_3 (1.1 equiv)	CH_2Cl_2	76%
(d)	$SiMe_3$		NEt_3 (1.1 equiv)	CH_2Cl_2	69%
(e)	$SiMe_3$	NaOMe	CH_2Cl_2/MeOH 30 : 1		24%
(f)	$SiEt_3$	EtSH	NEt_3 (1.1 equiv) DMAP (0.1 equiv)	CH_2Cl_2	32%

Thus we have shown a facile route to carboxylic acid derivatives, compatible with a highly functionalised system, from the corresponding methyl ketone.

REFERENCES AND NOTES

1. R.D. Clark and C.H. Heathcock, *Tetrahedron Lett.*, **1974**, *23*, 2027.
2. M.J. Crimmin, P.J. O'Hanlon and N.H. Rogers, *J. Chem. Soc., Perkin Trans I*, **1985**, 541.

3. All compounds were characterised by infra-red and 250MHz ^{1}H nmr data plus mass spectral evidence. Some selected physical data for the *tris*-trimethylsilyl protected enol phosphate (**5**), the *tris*-triethylsilyl protected mixed phosphonic anhydride (**6**) and the *tris*-trimethylsilyl protected amide (**7a**) are as follows:

   (**5**); υ_{max} (CH_2Cl_2) 3671, 1655, 1449 and 1372cm^{-1}. δ_H ($CDCl_3$) *inter alia* 0.91 (3H, d, *J* 7.1Hz, 17-H_3), 1.20 (3H, d, *J* 6.4Hz, 14-H_3), 1.36 (6H, dt, *J* 0.73, 6.9Hz, CH_3), 4.16 (2H, dq, appears as 5 lines, *J* 7.3Hz, CH_2) and 4.77 (2H, d, *J* 74.5Hz, =CH_2); *m/z* 654 (*M*H$^+$, 1%). (Found *M*H$^+$ 654.3218. $C_{28}H_{59}O_9PSi_3$ requires 654.3205).

   (**6**); υ_{max} (CH_2Cl_2) 1824, 1774 and 1645cm^{-1}; δ_H ($CDCl_3$) *inter alia* 1.21 (3H, d, *J* 7.1Hz, 14-H_3), 1.40 (6H, dt, *J* 0.9, 6.9Hz, OCH_2CH_3), 2.62-2.72 (3H, m, 10-H, 11-H and 4-H), 2.85 (1H, dd, *J* 2.7, 15.6Hz, 4'-H), 4.28 (4H, dq, appears as 5 lines *J* 7.1Hz, OCH_2CH_3).

   (**7a**); υ_{max} (CH_2Cl_2) 3445, 3380, 1675 and 1540cm^{-1}; δ_H ($[CD_3]_2$ C=O) *inter alia* 0.81 (3H, d, *J* 7.1Hz, 17-H_3), 1.08 (3H, d, *J* 6.4Hz, 14-H_3), 2.15 (1H, dd, *J* 9.5, 14.3Hz, 4-H), 2.45 (1H, dd, *J* 2.8, 14.3Hz, 4'-H), 2.58 (1H, dd, *J* 2.0, 7.5Hz, 11-H), 2.63 (1H, dt, *J* 2.2, 5.7Hz, 10-H), 3.97 (1H, dt, *J* 2.7, 9.4Hz, 5-H), 4.30 (2H, dd, *J* 1.4, 6.1Hz, CH_2Ar), 7.09-7.20 (5H, m, Ar-H), 7.35 (1H, br.t, N-H); *m/z* (+ve ion FAB, 3-NOBA-Na) 632 (*M*Na$^+$, 100%).

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