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SYNTHESIS OF GAMMA-HYDROXY ENONES VIA PERSULFATE OXIDATION OF DIENYL ETHERS[1].

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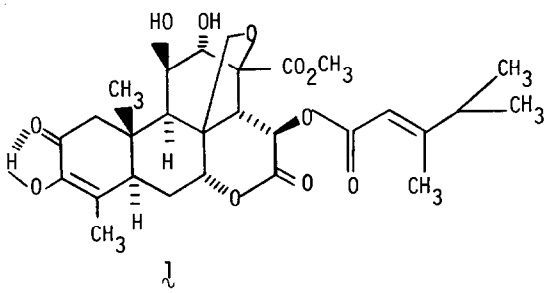
Summary: The commercial oxidant "oxone" ($2KHSO_4 \cdot K_2SO_4 \cdot KHSO_4$) has been found to be a superior reagent for the gamma oxidation of dienyl ethers to axial gamma-hydroxy enones.

In connection with our program directed toward the total synthesis of the antileukemia agent bruceantin (1),[1] we required an effective method for the conversion of the readily available tricyclic ketal 2[3] to the axial gamma-hydroxy enone 6.



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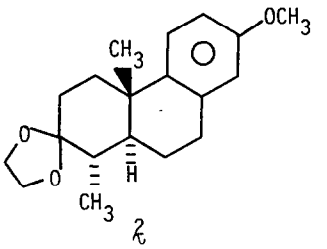
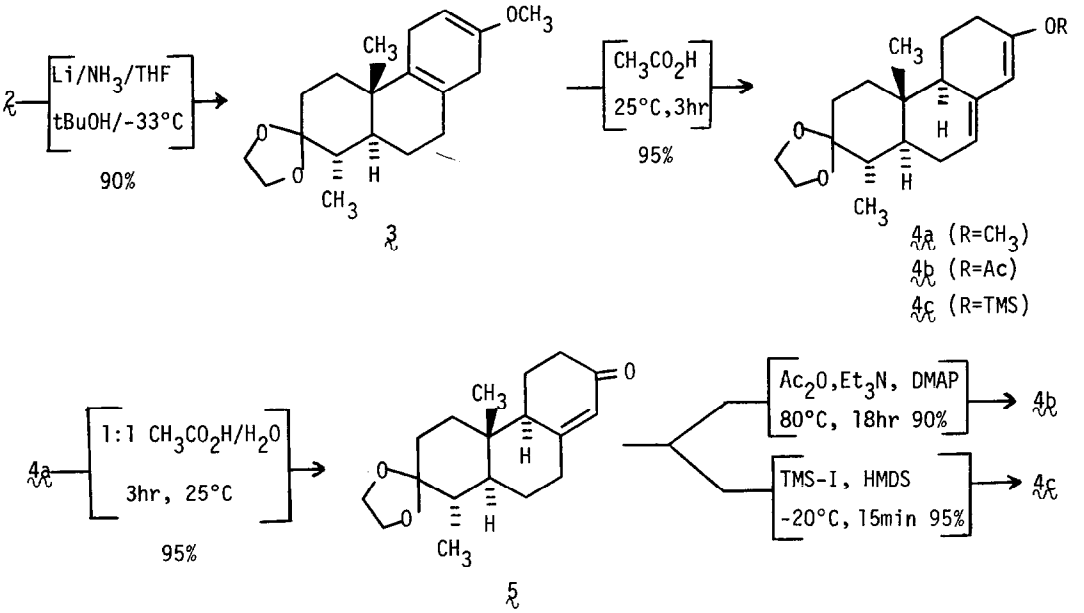


2

Reduction of ketal 2 with excess lithium metal in the presence of t-butanol smoothly affords enol ether 3[4]. Isomerization of 3 to the through-conjugated isomer 4a[4] was best accomplished by standing in neat glacial acetic acid.[5] Hydrolysis of 4a to enone 5[4] is effected in >95% yield by treatment with 1:1 50% aquenous acetic acid.[4,6] Conversion of enone 5 to dienyl acetate 4b[4] and silyldienyl ether 4c was efficiently accomplished by the methods of Secrist and Miller, respectively.[7]



Oxidation of dienyl ethers 4a-c was investigated based upon the known propensity of this moiety to afford gamma-functionalized enones with high axial stereospecificity.[8]

It was found (Table I) that for the 4→6 transformation, oxone[9] was a mild, rapid, economical, and substantially higher yielding alternative to other oxidizing reagents examined for this transformation.[8,10]

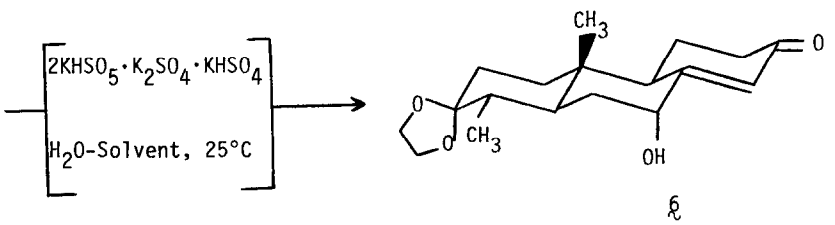


Table I

ENTRY	SUBSTRATE	REAGENT	SOLVENT	BUFFER	TIME (hr)	YIELD of 6	REF.
1	4a	MCPBA	aq.THF	-	2	49%	8a
2	4b	MCPBA	aq.Dioxane	-	2	43%	8a
3	4c	MCPBA	aq.THF	-	2	48%	8a
4	4a	MCPBA	C_2H_5OH	-	2	57%	8b
5	4b	MCPBA	C_2H_5OH	-	12	93%	8b
6	4a	O_2,hν	CH_3OH	-	24	40%	8e
7	4a	C_6H_5I=O	aq.CH_3OH	$NaHCO_3$	12	66%	10
8	4a	C_6H_5I=O	aq.CH_3OH	NaOH	24	52%	10
9	4a	C_6H_5I=O	aq.C_2H_5OH	$NaHCO_3$	24	40%	10
10	4b	C_6H_5I=O	aq.CH_3OH	$NaHCO_3$	12	75%	10
11	4c	C_6H_5I=O	aq.CH_3OH	$NaHCO_3$	3	25%[a]	10
12	4a	oxone	aq.CH_3OH	$NaHCO_3$	1	75%	-
13	4a	oxone	aq.THF	$NaHCO_3$	1	97%	-
14	4b	oxone	aq.CH_3OH	$NaHCO_3$	1	93%	-
15	4c	oxone	aq.THF	$NaHCO_3$	1	25%	-

a. Extensive silyl either hydrolysis.

Acknowledgement

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References and Notes

1. Bruceantin support studies 2. For paper 1 in this series see O.D. Dailey, Jr., P.L. Fuchs, J. Org. Chem., 45, 216 (1980).
2. Postdoctoral Research Associate.
3. Racemic ketal 2 can be easily prepared in 37% overall yield (6 steps) from para-methoxy phenyl acetic acid by optemization of the existing methodology: (a) G. Stork, A. Meisels, J.E. Davies, J. Amer. Chem. Soc., 85, 3419 (1963); (b) H. Hauth, D. Stauffacher, Helv. Chim. Acta., 55, 1532 (1972); (c) J.W. Apsimon, P. Baker, J.W. Hooper, S. Macaulay, Can. J. Chem., 50, 1944 (1972).
4. All new compounds had spectra (IR, ^{1}H NMR, and ^{13}C NMR spectra as well as low- and high-resolution mass spectra in accord with the assigned structures. Yields refer to isolated material of >95% purity.
5. This method of dienyl ether isomerization has been previously employed in our laboratories: D.M. Hedstrand, P.L. Fuchs unpublished results; c.f. A.W. Burgstahler, L.R. Worden, J. Amer. Chem. Soc., 86, 96 (1964).
6. In this instance, the overall yield of enone 5 (>90%) produced via the isomerization-hydrolysis route (3→4a→5) compares very favorably with the more traditional procedure (R.B. Turner, O. Buchardt, E. Herzog, R.B. Morin, A. Riebel, J.M. Sanders, J. Amer. Chem. Soc., 88, 1766 (1966)) of hydrolysis to the β,γ unsaturated ketone followed by isomerization to enone 5 (66%).
7. (a) T.J. Cousineau, S.L. Cook, J.A. Secrist, III, Syn. Comm., 9, 157 (1979); (b) R. D. Miller, D.R. McKean, Synthesis 730 (1979).
8. (a) D.N. Kirk, J.M. Wiles, Chem. Comm., 1015 (1970); (b) P.M. Wege, R.D. Clark, C.H. Heathcock, J. Org. Chem., 41, 3144 (1976); (c) R.E. Ireland, P. Beslin, R. Giger, U. Hengartner, H.A. Kirst, H. Maag, J. Org. Chem., 42, 1267 (1977); (d) H.L. Holland, P.R.P. Diakow, Can. J. Chem., 56, 694 (1978); (e) R. Gardi, A. Lusignani, J. Org. Chem., 32, 2647 (1967).
9. (a) B.M. Trost, D.P. Curran, Tet. Lett. 1287 (1981). (b) R.J. Kennedy, A.M. Stock, J. Org. Chem., 25, 1901 (1960).
10. R.M. Moriarty, H. Hu, S.C. Gupta, Tet. Lett. 1283 (1981).

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