Tetrahedron Letters No. 27, pp 2371 - 2374, 1978. 0040-4039/78/0701-2371$02.00/0

A NEW β-ACYL VINYL ANION EQUIVALENT. SYNTHESIS OF PYRENOPHORIN

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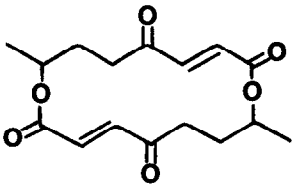
(Received in USA 22 March 1978; received in UK for publication 4 May 1978)

γ- and ε-oxygenated acrylates and enones are important features of many natural products, including macrocyclic antibiotics such as pyrenophorin (1) and brefeldin A (2), cytochalasin B, and the prostaglandin family. While multiple step processes for the preparation of the acrylates,[2] the enones,[3] and the C-8 side chain of prostaglandins[4] are available, almost all of them require the use of anhydrous solvents, strong bases, and low temperatures in one or more steps. We would like to report a one pot sequence of reactions that does not require anhydrous conditions, takes place at room temperature or above, and leads to the desired functional groups in moderate to good yields.



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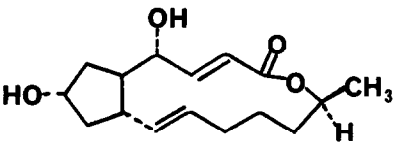

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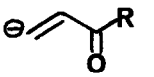

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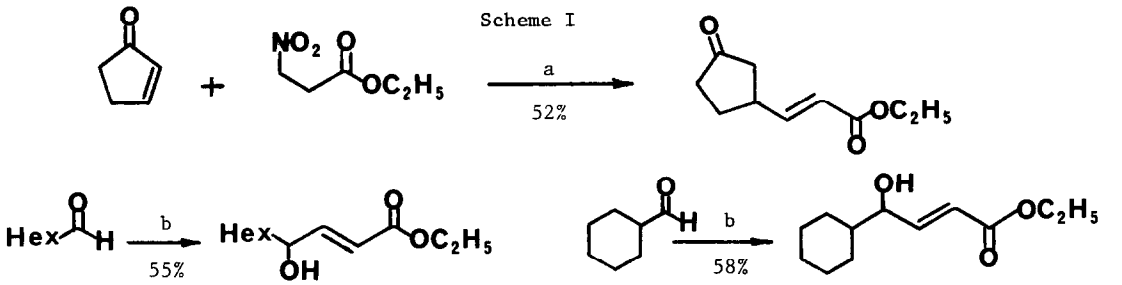
Retrosynthetic analysis readily points to the β-acyl vinyl anion equivalent 3 as a promising synthon,[5] since its reaction with aldehydes would lead to γ-hydroxy acrylates or enones while Michael addition to α,β-unsaturated ketones would lead to ε-ketoenones. Nitro compounds are known to add readily to aldehydes and reactive enones under mild basic conditions.[6] β-nitro esters, lactones, ketones, and phosphonates,[7] under similar conditions, eliminate nitrous acid with the formation of the respective α,β-unsaturated compounds. Thus, we sought to combine these two modes of reaction to see if carbon-carbon bond formation could precede the elimination step.[8]

Treatment of cyclopentenone and ethyl β-nitropropionate with diisopropylamine in chloroform, or with tetramethyl guanidine (TMG) in methanol, gave ethyl acrylate along with recovered cyclopentenone. Evidently, elimination under these conditions proceeds faster than carbon-carbon bond formation. However, diisopropylamine in commercial, unpurified, dimethyl

formamide (DMF) at room temperature, or in slightly better isolated yield, potassium t-butoxide in THF followed by addition of methanol and overnight standing, gave the desired acrylate in 52% isolated yield. This, and similar reactions with aldehydes, are shown in Scheme I.

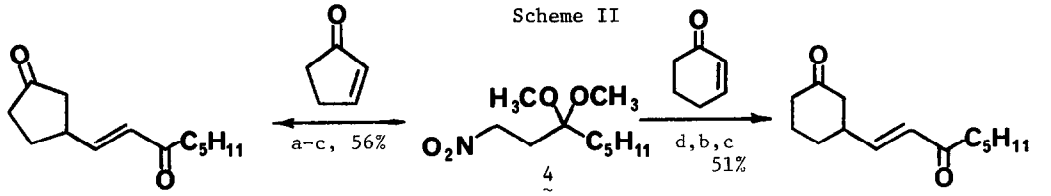
Scheme I



a) t-BuOK/THF/-20° to R.T., then add CH_3OH, stir 16 hrs R.T.; b) $EtO_2CCH_2CH_2NO_2/HN(CHMe_2)_2$/DMSO/RT 24 hrs.

Similar reactions with β-nitroketones did not lead to carbon-carbon bond formation before elimination of the nitro group. Accordingly, we chose to protect the carbonyl group as the dimethyl ketal and, after hydrolysis of the product, eliminate the nitro group under mild basic conditions. The three step sequence could be performed in a variety of solvents without isolation of intermediates. Two examples using a readily prepared β-nitro ketal 4[9] are shown in Scheme II.

Scheme II

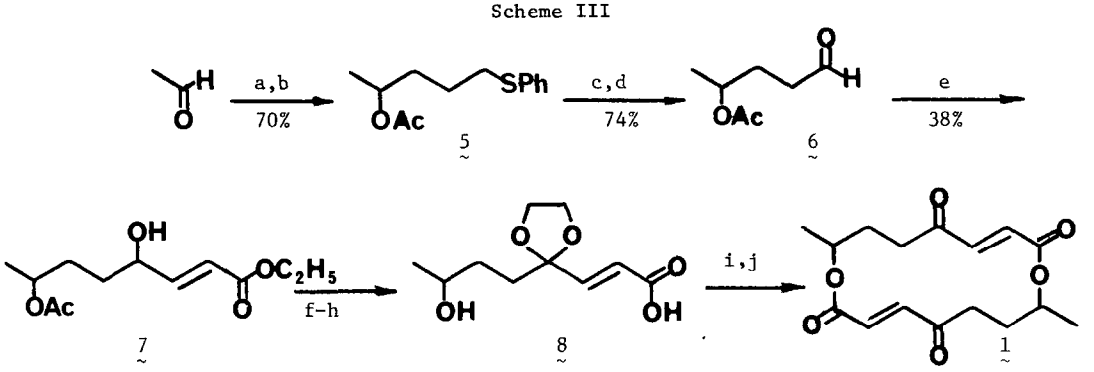


a) $HN(CHMe_2)_2/CH_3OH$/RT 20 hrs; b) $H_3O^{\oplus}/CH_3OH/H_2O$; c) $HN(CHMe_2)_2/CH_3OH/H_2O$/R.T. 12 hrs; d) TMG, CH_3OH, Δ 4.5 hrs.

Finally, we would like to report an application of this strategy to the synthesis of pyrenophorin (1) (see Scheme III). Treatment of acetaldehyde with the Grignard reagent prepared from 3-bromopropyl phenyl sulfide[10] followed by acylation gave the sulfide 5.[11] Oxidation with N-chlorosuccinimide (NCS) followed by hydrolysis[10,12] of the alkyl chlorosulfide produced the aldehyde 6 in 52% yield, previously prepared in low yield by a multistep sequence.[13] Reaction of aldehyde 6 with 1.2 equivalents of ethyl β-nitropropionate, and 1.3 equivalents of diisopropylamine in DMF at room temperature for 40 hrs. gave the hydroxy acrylate 7 in 38% yield. Oxidation of the alcohol followed by protection of the carbonyl group and hydrolysis of the two ester groups gave the hydroxy acid 8. Dimerization of the compound 8 was achieved in 23% yield[14] by stirring a dilute toluene solution of the hydroxy acid with dimethyl azodicarboxylate and triphenylphosphine[15] at -5°C to room temperature for

two days. Hydrolysis of the ketal gave d,ℓ- and meso-pyrenophorin (1) in 70% yield.

Scheme III



a) $BrMgCH_2CH_2CH_2SPh$; b) AcCl/Py; c) NCS; d) $Cu(II)/H_2O/(CH_3)_2CO$; e) $O_2NCH_2CH_2CO_2Et/HN(CHMe_2)_2/DMF/RT$; f) $PyHCrO_3Cl$; g) $HOCH_2CH_2OH/H^{\oplus}$; h) $LiOMe/CH_3OH/RT$; i) $MeO_2C-N=N-CO_2Me/Ph_3P/PhCH_3$ -5°C to RT; j) $(CH_3)_2CO/H^{\oplus}$.

Synthesis of prostaglandins and brefeldin A are underway and will be reported in due course.

Acknowledgment. We would like to thank Rice University, and particularly Professor Wenkert, for providing facilities where part of this work was done. Special thanks are due to Professor Colvin for spectral data on pyrenophorin and Professor Baker for mass spectral determinations. The partial support of this work by CNPq and CAPES is gratefully acknowledged.

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