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THE CHEMISTRY OF ENOLATES DERIVED FROM 3,6-DIHYDROBENZOIC ACID ESTERS: A SYNTHESIS OF FUNCTIONALIZED 1,3-CYCLOHEXADIENES

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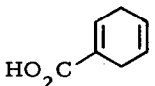
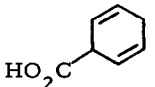
The chemistry of ester enolates and carboxylic acid dianions has rapidly developed since the initial work of Rathke[2] and Creger.[3] A wide variety of structural types have been studied including nonconjugated and conjugated acids[4] and esters.[5] The enolate species derived from 1,4-dihydrobenzoic acid is well known and has been shown to undergo alkylation.[6,7] However, the isomeric enolate species derived from 3,6-dihydrobenzoic acid and its esters have received comparatively little attention; one of the few examples being part of model studies directed toward Gibberellic Acid.[8]

In connection with our interest in the construction of substances leading to the cytotoxic sesquiterpenes,[9] we required methods for the stereospecific construction of functionalized 1,3-cyclohexadienes. We, therefore, have developed procedures for the generation and alkylation of the anions from 3,6-dihydrobenzoic acid esters which provides a general route to these interesting and potentially very useful synthetic intermediates.

Initially, we chose to study the dianion derived from 3,6-dihydrobenzoic acid (1)[10] since the isomeric dianion derived from (2) is well-behaved. We were unsuccessful, however, due to the remarkably rapid conversion of this carbanion to benzoic acid[11] (conditions:2 eq. LDA/THF/ -78°). We established that even at -78°, after careful exclusion of traces of oxygen, the dianion is still converted to benzoic acid. Attempts to trap the dianion with CH_3I or allyl bromide provided primarily benzoic acid with minor amounts of diene acid (3). However, the enolate


(1)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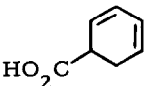
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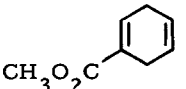
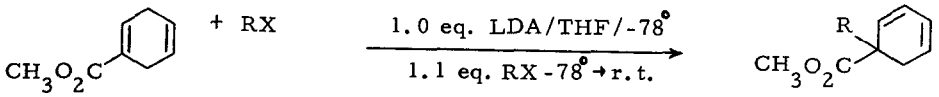
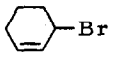

(4)

derived from the corresponding methyl ester (4) is rapidly and quantitatively generated (1.0 eq. LDA/-78°/THF) and is reasonably stable (oxygen or prolonged periods above -40° result in oxidation to methyl benzoate).

The anion derived from (4) reacts readily with 1° and 2° allylic bromides and iodides, and 1° iodides and bromides as is indicated in Table 1. The yields are uniformly high and the

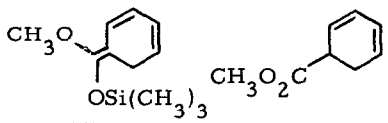
TABLE 1



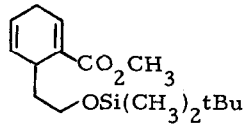
	Yield a, b
CH_3I	88%
CH_2=CH-CH_2Br	96%
$(CH_3)_2$C=CH-CH_2Br	52%
$CH_2(CH_2)_6CH_2I$	96%
$ClCH_2OC(=O)(CH_3)_3$	78%
$ClCH_2OCH_2Ph$	90%
	60%

a) Yields are reported for isolated materials purified by distillation or chromatography (SiO_2).
b) All new compounds exhibited spectral date (IR, NMR, and MS) consistant with the assigned structure. All new compounds provided correct combustion analytical data or high resolution mass spectra.

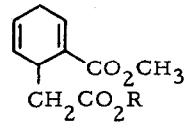
products easily isolated in high purity. Attempted alkylation with 2° aliphatic halides, aldehydes or ketones, or sulfenyation[12] with PhSSPh also provided only aromatized products. Deconjugation of methyl 3,6-dihydrobenzoate (4) could not be accomplished cleanly by direct quenching of the derived enolate with water, however quenching with $(CH_3)_3SiCl$ provides (5)(presumably) which is readily hydrolyzed to deconjugated ester (6)(~80%) during workup. We attempted to utilize the derived copper species to direct alkylation at a remote site[13] (δ,ϵ), but were only able to isolate products of α alkylation.[14]



(5) (6)

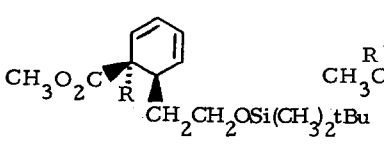


(7)

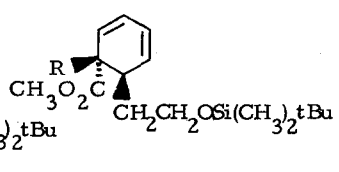


(8) R=H
(9) R=CH_3

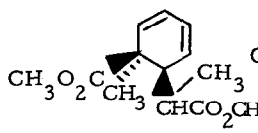
Substituted esters such as (7), (8), and (9)[15] undergo enolate formation in like manner. Treatment of the enolate derived from (7) (1.0 LDA/THF/-78°) with CH_3I provides esters (10)



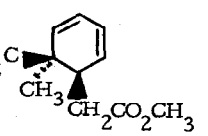
(10) R=CH_3
(12) R=CH_2OCH_2Ph



(11) R=CH_3
(13) R=CH_2OCH_2Ph

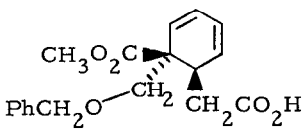


(14)

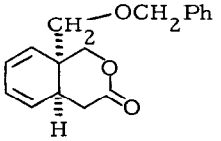


(15)

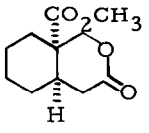
and (11) (60%) (4.8:1).[16] The bulk of the alkyl group has little effect upon the stereoselectivity as is shown by formation of (12) and (13) (4.5:1)[16] upon treatment with $ClCH_2OCH_2Ph$. These stereoselective alkylations allow the synthesis of stereochemically defined cyclohexadiene derivatives. Attempted formation of the presumed more stable conjugated enolate from ester (9) (1 eq. LDA/-78°/THF) provided mixtures of products upon quenching with CH_3I. Use of two equivalents of LDA allowed production of the dienolate and derived dimethylated ester (14). To enhance formation of the desired enolate, the more slowly formed acid dianions were studied. Acid (8) upon treatment with LDA (two equivalents) in THF and quenching with CH_3I (XS) afforded diester (15) (6:1, t/c, 63%) plus ~17% homophthalic acid dimethyl ester. Treatment of (8) as above with 1.1 eq. $ClCH_2OCH_2Ph$ gave (16) in 64% yield.[16] In this case, alkylation of the carboxylate could be controlled and only the trans ester was detected. This appears to be a general device for achieving regiospecific deprotonation of diacid derivatives.



(16)



(17)

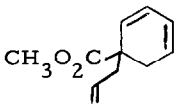


(18)

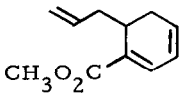
Acid (16) can be converted to cis lactone (17) by reduction (DIBAL/toluene) and lactonization on workup (10% HCl/H_2O). The structure of (17) was verified by conversion to (18) which had been prepared previously.[17] Lactones of these types have served as intermediates in the synthesis of vernolepin[18] and the required modifications are presently under investigation in our laboratories.

The cyclohexadienes which are made available by the foregoing route are quite easily functionalized. In particular, use of sequential Cope rearrangements could provide potential access to a variety of trans fused, angularly substituted decalin derivatives stereospecifically, by final ring closure of ϵ substituted derivatives.

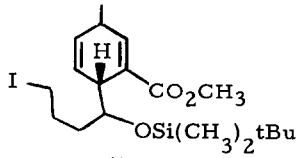
We have tested the feasibility of the functionalization at the ϵ position via sequential Cope rearrangements. Thermolysis of (19) (Table 1) at 150° in toluene (sealed tube/Ar/120 h) provides



(19)



(20)



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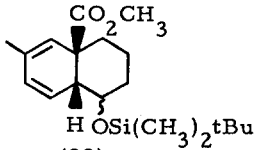

(22)

the conjugated diene (20) in 54% yield[20] as a viable alternative to the copper mediated alkylation which failed in this system. The utility of cis or trans fused bicyclic dienes such as (22) for the preparation of germacrane systems has been documented previously.[20] The general route outlined previously allows the rapid assembly of such ring systems. Iodide (21) prepared from sorbaldehyde[22] undergoes cyclization to (22) stereospecifically under the usual conditions

(51%).[22,23] We are presently exploring applications of this chemistry to terpene synthesis.

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11. The deep red color characteristic of these carbanions is observed, however, on standing at -78° then quenching with aq. NH_4Cl, mainly aromatized products are obtained.
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14. The major products in these cases were aromatized materials.
15. Prepared as above from reaction of 1.1 eq. methyl propiolate and 1.0 eq. diene at 150° for 4 hours, yields generally 80-90%.
16. Spectral Data: (10) NMR (δ): 0.05(s, 6H), 0.9(s, 9H), 1.4(s, 3H), 1.4-2.0(m, 2H), 2.6(m, 1H), 3.7(m, 2H), 3.8(m, 3H), 5.8-6.2(m, 4H); (16): 2.45(m, 2H), 3.0(m, 1H), 3.75(s[br]; 5H) 4.55 (s, 2H), 5.95(m, 2H), 6.1(m, 2H), 7.35(s, 5H), 10.0(s, 1H); (17): 2.6(m, 2H), 2.8(m, 1H), 3.45(s, 2H), 4.15(d, J=12Hz, 1H), 4.50(d, J=12Hz, 1H), 4.6(s, 2H), 4.5-6.3(m, 4H), 7.35(s, 5H); (22) NMR (δ): 0.05(s, 6H, 0.9(s, 9H), 1.75(s[br], 3H), 1.0-2.4(m, 6H), 3.1(m, 1H), 3.75-3.85 (s, 3H total), 3.8-3.9(m, 1H), 5.5-6.3(m, 3H).
The stereochemical assignments are based upon expected steric preferences cf. G. Stork, R. L. Danheiser, and B. Ganem, J. Am. Chem. Soc., 95, 3414 (1973).
17. Prepared by the sequence beginning with the Diels Alder reaction of methyl 3,5-hexadienoate and α-acetoxymethyl methyl acrylate.
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23. The structure of (22) was confirmed by conversion to a mixture of γ lactone and hydroxy acid, cf. J. A. Marshall and P. Wuts, J. Org. Chem., 42, 1794 (1977).