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SYNTHESIS OF BICYCLO[4.3.0]NONENONE AND BICYCLO[3.3.0]OCTENONE DERIVATIVES BY INTRAMOLECULAR WADSWORTH-EMMONS REACTION: FORMAL SYNTHESIS OF THE SESQUITERPENE CEDRENE

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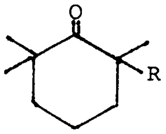
Annulation by the intramolecular Wadsworth-Emmons reaction for constructing bicyclo[4.3.0]nonenone and bicyclo[3.3.0]octenone is described. As an application of the reaction, the formal synthesis of the sesquiterpene cedrene was accomplished.

KEYWORDS———intramolecular Wadsworth-Emmons reaction; bicyclo[4.3.0]nonenone; bicyclo[3.3.0]octenone; sesquiterpene; cedrene

There have been several reports concerning annulation for the preparation of bicyclo[4.3.0]nonenone and bicyclo[3.3.0]octenone structure. Of these the intramolecular Wadsworth-Emmons reaction (W-E reaction)1) is one of the attractive methods for constructing the bicyclic compounds. In 1973, Grieco and Pogonowski2) reported cyclization of 2,6-diketo-phosphonate to produce a cyclohexenone derivative. Following that report, Heathcock and his co-workers3) reported an application of the reaction for constructing a bicyclic compound. However, there are few reports indicating the application of the reaction between $\alpha,\alpha,\alpha',\alpha'$-tetra-substituted ketone and acyl phosphonate in the same molecule. We report here our investigation on construction of some bicyclic compounds by the intramolecular W-E reaction of the tetra-substituted ketone and the phosphonate.

Alkylation of 2,2,6-trimethylcyclohexanone with methyl bromoacetate gave the acetate (1a), which was smoothly converted to the Wadsworth-Emmons type compound (2a) with lithium dimethyl methylphosphonate4) (LDMP). Treatment of (2a) with NaH in benzene gave the bicyclononenone (3) in 75% yield. However, the phosphonate (2b), prepared from the cyclohexanone-propionate (1b), gave no annulation product even after several attempts. We have no explanation for this.

Next, we focused our attention on the synthesis of bicyclo[3.3.0]octenone by the intramolecular W-E reaction. Alkylation of the enolate derived from the Dieckmann reaction of dimethyl adipate with methyl bromoacetate gave the methyl ester (4a), methylation (NaH and MeI) of which yielded the dimethyl-diester (5a). Treatment of (5a) with LDMP gave a mixture of the diketone (6) (40%)5) and the diketo-ester (7a) (2%). The reaction mechanism for the loss of methoxycarbonyl group is not clear at present.

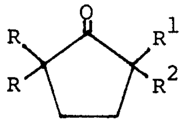


(1a) R=CH_2CO_2Me

(1b) R=$CH_2CH_2CO_2Me$

(2a) R=CH_2COCH_2DMP

(2b) R=$CH_2CH_2COCH_2DMP$



(4a) R=H; $R^1=CO_2Me$; $R^2=CH_2CO_2Me$

(4b) R=H; $R^1=CO_2Bu^t$; $R^2=CH_2CO_2Me$

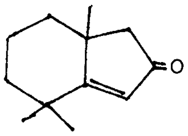
(5a) R=Me; $R^1=CO_2Me$; $R^2=CH_2CO_2Me$

(5b) R=Me; $R^1=CO_2Bu^t$; $R^2=CH_2CO_2Me$

(6) R=Me; $R^1=H$; $R^2=CH_2COCH_2DMP$

(7a) R=Me; $R^1=CO_2Me$; $R^2=CH_2COCH_2DMP$

(7b) R=Me; $R^1=CO_2Bu^t$; $R^2=CH_2COCH_2DMP$



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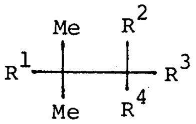


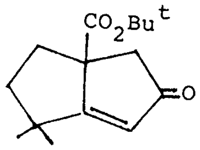
$$R^1-\underset{Me}{\overset{Me}{C}}-\underset{R^4}{\overset{R^2}{C}}-R^3$$

(9) $R^1=CN$; $R^2=R^3=CO_2Me$; $R^4=H$

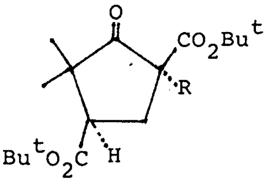
(10) $R^1=CN$; $R^2=R^3=CO_2Me$; $R^4=CH_2CH_2CO_2Me$

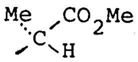
(11) $R^1=R^2=CO_2H$; $R^3=H$; $R^4=CH_2CH_2CO_2H$

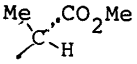
(12) $R^1=R^2=CO_2Bu^t$; $R^3=H$; $R^4=CH_2CH_2CO_2Bu^t$

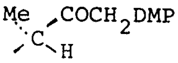


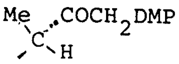
(8)

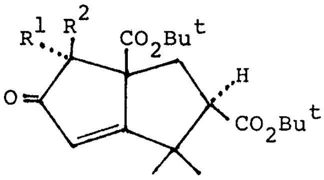


(13a) R= 

(13b) R= 

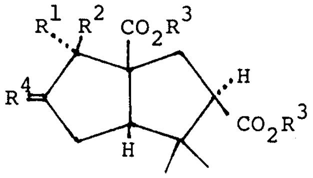
(14a) R= 

(14b) R= 



(15a) $R^1=Me$; $R^2=H$

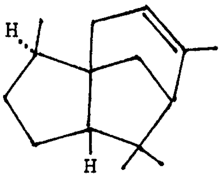
(15b) $R^1=H$; $R^2=Me$



(16a) $R^1=Me$; $R^2=R^3=H$; $R^4=H_2$

(16b) $R^1=R^3=H$; $R^2=Me$; $R^4=H_2$

(17) $R^1=H$; $R^2=Me$; $R^3=Bu^t$; $R^4=O$



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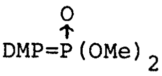

$$DMP=\overset{\overset{O}{\uparrow}}{P}(OMe)_2$$

As a trial to avoid the loss of the methoxycarbonyl group of (5a), *tert*-butyl-β-ketoester (7b) was prepared as follows. The Dieckmann reaction of di-*tert*-butyl adipate followed by alkylation with methyl bromoacetate gave the diketo-diester (4b), methylation of which gave the diester (5b). Treatment of (5b) with LDMP afforded the diketo-ester (7b) in 60% yield without an observable amount of product losing the *tert*-butoxycarbonyl group. Cyclization of (7b) with NaH gave the bicyclo-octenone (8) in 60% isolated yield.

Based on these results, we aimed at the synthesis of cedrene (18), the first synthesis of which was accomplished by Prof. G. Stork,$^{6)}$ by replacing the aldol condensation in Stork's synthesis with the intramolecular W-E reaction to make the bicyclo[3.3.0]octane structure of cedrene.

Michael addition of the nitrile-diester (9) on methyl acrylate (Triton B in DMF, 5 min) gave the nitrile-triester (10) in 55% yield. Hydrolysis of (10) with conc. HCl in acetic acid gave the tri-acid (11) (mp 163-165°C) in 85% yield. Esterification of (11) with isobutylene and a few drops of H_2SO_4 resulted in a mixture of the mono- and di- *tert*-butyl-ester of (11) in low yield. Eventually, we found that tri-*tert*-butyl-ester (12) was obtained in 55% yield by using CF_3SO_3H in place of H_2SO_4. Dieckmann reaction of (12) with KH in benzene followed by alkylation with methyl α-bromopropionate afforded two tri-esters, (13a) (mp 98-100°C) and (13b) (oil) in 35% and 10% isolated yield, respectively. The stereostructures of these products were not elucidated at this stage, but each was converted to its respective bicyclic compound by the intramolecular W-E reaction and the bicyclic compounds were subjected to X-ray crystallography. Thus treatment of (13a) with LDMP in DME gave the phosphonate (14a) in 70% yield which was smoothly cyclized to the bicyclo-octenone (15a) with NaH in 85% yield. (15a) was transformed to epi-norcedrenedicarboxylic acid (16a) by the following reaction sequences: hydrogenation (H_2-Pd), thioketalization ($HSCH_2CH_2SH$ + BF_3-etherate, concomitant cleavage of *tert*-butyl ester), methylation (CH_2N_2), desulfurization (Raney Ni in MeOH), and hydrolysis of methyl ester (KOH in EtOH). The structure of the latter (16a) (mp 221-223°C) was firmly established by X-ray crystallography. Crystal data: monoclinic prisms from hexane-ether, space group P21/c, a=7.153, b=14.361, c=13.734Å, β=113.44°, Z=4, R-factor=4.6% for 1839 reflections.

The oily tri-ester (13b) was subjected to the reaction sequence (LDMP treatment, NaH in benzene, and hydrogenation) to give the keto-diester (17) (mp 75-76°C), the structure of which was revealed by X-ray crystallography. Crystal data: monoclinic prisms from hexane, space group P21/c, a=12.738, b=15.192, c=11.659Å, β=109.33°, Z=4, R-factor=6.2% for 2804 reflections.

The keto-diester (17) was transformed to dl-norcedrenedicarboxylic acid (16b) (mp 221-223°C) by the reaction sequence ($HSCH_2CH_2SH$ + BF_3-etherate, CH_2N_2, Raney Ni, and methionine + $CH_3SO_3H^{7)}$). Its IR spectrum (KBr-disc) was identical with that of dl-norcedrenedicarboxylic acid,$^{8)}$ indicating the accomplishment of a formal synthesis of a sesquiterpene, cedrene, since dl-norcedrenedicarboxylic acid has been transformed to cedrene.$^{6)}$

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5) ^{1}H-NMR spectrum of the diketone (6) exhibited the signals of two methoxyl groups (δ, ($CDCl_3$) 3.78, d, J=11.5 Hz) assigned to the methyl phosphonate group and its mass spectrum showed the parent ion at m/z 276, suggesting the structure.

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8) Mixed mp showed no depression.

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