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(10) This approximation was successfully utilized in a similar system; see footnote 5 in ref 11.
(11) The assignment of the $C_{4,6}$ protons was made on the basis that the larger $^3J_{PSCH}$ value occurs with the equatorial protons (H_B). For example, see (a) L. D. Hall and R. B. Malcolm, *Chem. Ind. (London)*, 92 (1968); (b) J. R. Campbell and L. D. Hall, *ibid.*, 1138 (1971). Also note footnote 7 in ref 19e.
(12) In 2-phenyl-2-oxo-1,3,2-dioxaphosphorinanes, the P=O bond prefers an axial disposition vs. phenyl in $CDCl_3$ and CS_2. The preference varies with the polarity of the solvent and is ca. 250–700 cal/mol in nonpolar solvents; see J. P. Majoral, R. Pujol, and J. Navech, *C. R. Acad. Sci.*, **274**, 213 (1972).
(13) K. C. Yee and W. G. Bentrude, *Tetrahedron Lett.*, 2775 (1971).
(14) (a) W. G. Bentrude and J. H. Hargis, *Chem. Commun.*, 1113 (1969); (b) W. G. Bentrude, H. Tan, and K. C. Yee, *J. Am. Chem. Soc.*, **94**, 3264 (1972).
(15) (a) F. Ramirez, A. V. Patwardham, N. B. Desai, and S. R. Heller, *J. Am. Chem. Soc.*, **87**, 549 (1965); (b) Y. Kashman and O. Awerbouch, *Tetrahedron*, **27**, 5593 (1971).
(16) W. Wucherpfennig, *Justus Liebigs Ann. Chem.*, **737**, 144 (1970); J. G. Pritchard and P. C. Lauterbur, *J. Am. Chem. Soc.*, **83**, 2105 (1961); L. Cazaux and P. Maroni, *Tetrahedron Lett.*, 3667 (1969); C. H. Green and D. G. Hellier, *J. Chem. Soc., Perkin Trans. 2*, 458 (1972).
(17) Δ_{AB} values for **2** and **3** ($CDCl_3$) are −0.32 and 0.25, respectively. Bentrude and Yee have found Δ_{AB} values for *cis*- and *trans*-2-phenyl-2-oxo-5-*tert*-butyl-1,3,2-dioxaphosphorinanes (CCl_4) to be −0.40[14b] and 0.28,[18] respectively.
(18) W. G. Bentrude, private communication, 1972.
(19) Reports describing the use of NMR shift reagents with compounds containing the phosphoryl group include (a) ref 13; ref 14b; ref 15b; (b) T. M. Ward, I. L. Allcox, and G. H. Wahl, Jr., *Tetrahedron Lett.*, 4421 (1971); B. D. Cuddy, K. Treon, and B. J. Walker, *ibid.*, 4433 (1971); (c) J. K. M. Saunders and D. H. Williams, *ibid.*, 2813 (1971); (d) J. R. Corfield and S. Trippett, *Chem. Commun.*, 721 (1971); (e) W. G. Bentrude and H.-W. Tan, *J. Am. Chem. Soc.*, **95**, 4666 (1973); (f) J. A. Mosbo and J. G. Verkade, *ibid.*, **95**, 4659 (1973); (g) P. Finocchiaro, A. Recca, W. G. Bentrude, H.-W. Tan, and K. C. Yee, *J. Am. Chem. Soc.*, **98**, 3537 (1976). General references to the use of NMR shift reagents for assignment of molecular geometry may be found in J. R. Campbell, *Aldrichimica Acta*, **4**, 55 (1971); I. Y. Slonim and A. K. Bulai, *Russ. Chem. Rev. (Engl. Transl.)*, **42**, 904 (1973); R. E. Sievers, Ed., "Nuclear Magnetic Resonance Shift Reagents", Academic Press, New York, N. Y., 1973.
(20) Tris(dipivaloylmethanato)europium(III) gave poorly resolved, broad lines with **2** and **3** at high chelate to substrate ratios.
(21) The phosphoryl oxygen should be the preferential site of complexation for lanthanides; see (a) J. L. Burdett and L. L. Burger, *Can. J. Chem.*, **44**, 11 (1966); (b) S. C. Goodman and J. G. Verkade, *Inorg. Chem.*, **5**, 498 (1966); (c) ref 19g.
(22) (a) E. L. Eliel and R. O Hutchins, *J. Am. Chem. Soc.*, **91**, 2703 (1969); (b) E. L. Eliel, V. S. Rao, S. Smith, and R. O. Hutchins, *J. Org. Chem.*, **40**, 524 (1975).
(23) Introduction of sulfur atoms into a six-membered ring can significantly lower the chair–boat energy difference. For instance, 1,3-dioxane has an energy difference (ΔG°) of ca. 8.3 ± 0.5 kcal/mol [R. M. Clay, G. M. Kellie, and F. G. Riddell, *J. Am. Chem. Soc.*, **95**, 4632 (1973)], whereas 1,3-dithiane has a value of only ca. 1.7 kcal/mol.[22] The corresponding chair–boat energy difference for cyclohexane is ca. 5.3 kcal/mol [M. Squillacote, R. S. Sheridan, O. L. Chapman, and F. A. L. Anet, *J. Am. Chem. Soc.*, **97**, 3244 (1975)]; see also K. Pihlaja, *J. Chem. Soc., Perkin Trans. 2*, 890 (1974).
(24) The chair–boat energy difference for *cis*-2,5-di-*tert*-butyl-2-oxo-1,3,2-dioxaphosphorinane may be as low as ca. 1 kcal/mol [W. G. Bentrude and K. C. Yee, *J. Chem. Soc., Chem. Commun.*, 169 (1972); ref 19e], and the value for *trans*-2-methoxy-5-*tert*-butyl-1,3,2-dioxaphosphorinane is suggested to be 1.5–2.0 kcal/mol (see ref 2).
(25) There is precedent for an increase in ^{31}P–H coupling constants in phosphoryl compounds upon complexation with transition metals.[21a]
(26) The cis/trans designation may vary from compound to compound. In the discussion, we are comparing compounds correspondent by their alkyl/phenyl or alkyl/alkyl substitution.
(27) An example has been reported where a conformational equilibrium was not appreciably affected by europium chelates. See J. T. Groves and M. Van Der Puy, *Tetrahedron Lett.*, 1949 (1975).
(28) M. M. Crutchfield, C. H. Dungan, J. H. Letcher, V. Mark, and J. R. Van Wazer, *Top. Phosphorus Chem.*, **5**, 40–41 (1967).
(29) A. A. Bothner-by and S. M. Castellano in "Computer Programs for Chemistry", Vol. 1, D. F. Detar, Ed., W. A. Benjamin, New York, N.Y., 1968, Chapter 3.
(30) The program was first modified to operate on a Burroughs 5500 computer with the help of Mr. William Slegeir and was subsequently improved by Mr. Brandt Kramer. We are especially indebted to Mr. Kramer for carrying out spectral computations and for obtaining plots of calculated spectra.
(31) N. Bhacca and D. Williams, "Application of NMR Spectroscopy in Organic Chemistry", Holden-Day, San Francisco, Calif., 1964, p 43.

Preparation, Stereochemistry, and Nuclear Magnetic Resonance Spectroscopy of Methyl 1,3-Dimethyl-2-oxocyclohexaneacetates and Related Derivatives

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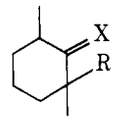
The two diastereomeric methyl 1,3-dimethyl-2-oxocyclohexaneacetates, **9b** and **10b**, as well as the related epimeric derivatives (**2–7**) have been prepared and their stereochemistry rigorously established via chemical correlation with the previously known enone **8**. During the correlation, oxidative cleavage of a variety of carbon–carbon double bonds was effected with $RuO_4/NaIO_4$ without concomitant epimerization either at incipient or remote ketone functionalities. Finally, the stereochemical assignments, in accord with the 60- and 220-MHz NMR spectral data, require reversal of the assignment previously made by Muller and Jeger[5] for diastereomers of **7**.

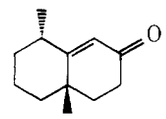
During the course of our studies on the thermal[1] and acid-catalyzed[2] decomposition of β,γ-unsaturated diazo ketones, we required an efficient approach to authentic samples of both diastereomers of methyl 1,3-dimethyl-2-oxocyclohexaneacetate (**1**). In this report we wish to document the preparation and rigorous stereochemical assignment of these esters as well as the related epimeric derivatives (**2–7**). Our stereochemical assignment involves a chemical correlation of **1–7** with the well-known enone (**8**) prepared first by the Marshall group[3] and improved several years later by Caine and co-workers.[4] Interestingly, the diastereomers of **7** were recently isolated and their structures defined employing NMR criteria.[5] The present chemical interrelationships require the reversal of these assignments. Finally, we note the synthetic utility of $RuO_4/NaIO_4$ in aqueous acetone for the oxidative cleavage of olefinic bonds without concomitant epimerization either at incipient or remote carbonyl functionalities.[6]

Our synthetic approach to the diastereomers of **1** involves the facile monoalkylation of 2,6-dimethylcyclohexanone with allyl bromide, utilizing lithium diisopropylamide as the base.[7] The resultant epimeric ketones **9a** and **10a**, produced in equal amounts, were each fully characterized after separation via vapor phase chromatography (VPC). Subsequent oxidation[6] of **9a** and **10a** with $RuO_4/NaIO_4$ in aqueous acetone followed by diazomethane esterification of the resultant acids provided **9b** and **10b**, the desired diastereomers of **1**. In each case, oxidation yielded only a single γ-keto ester, demonstrating that the oxidation conditions do not result in equilibration. On the

Chart I

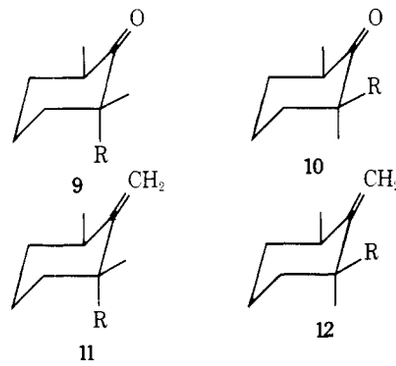


1, X = O; R = $CH_2CO_2CH_3$
2, X = O; R = $CH_2CH{=}CH_2$
3, X = O; R = $CH_2CH_2CO_2CH_3$
4, X = CH_2; R = $CH_2CO_2CH_3$
5, X = CH_2; R = $CH_2CH_2CO_2CH_3$
6, X = CH_2; R = CH_2COCH_3
7, X = O; R = CH_2COCH_3



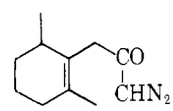
8

Chart II



9 10 11 12

a, R = $CH_2CH{=}CH_2$
b, R = $CH_2CO_2CH_3$
c, R = $CH_2CH_2CO_2CH_3$
d, R = CH_2COCH_3



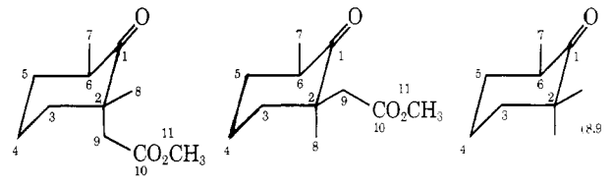
13

other hand, treatment of either **9b** or **10b** with $NaOCH_3$ in boiling methanol led to the same equilibrium mixture, i.e., 65:35, respectively.

A stereochemical assignment, albeit tentative, of diastereomers **1** and **2** based on the 220-MHz ^1H NMR data was possible at this point. For example, the resonance for the equatorial methyl substituent at C-1 in **9a** and **9b** experiences a small[8,9] upfield shift ($\Delta \sim 0.20$ ppm) relative to that of the C-1 axial methyls in **10a** and **10b.** Likewise, the equatorial methylene group at C-1 in **10b** appears upfield ($\Delta \sim 0.20$ ppm) compared to the axial counterpart in **9b.** We next turned to ^{13}C NMR to support these assignments. Table I records the carbon chemical shifts for **9b** and **10b** along with the multiplicity obtained during off-resonance decoupling. The carbon assignments were straightforward based on analogy with literature data for cyclohexane[10] and cyclohexanone[11] derivatives. For comparison we list the chemical shifts of 2,2,6-trimethylcyclohexanone.[11] Most noteworthy here is the lack of significant chemical shift differences between the respective carbons of **9b** and **10b,** thereby preventing verification by carbon NMR of the above stereochemical assignments.

With the ready availability of **9b** and **10b,** there remained only a chemical correlation with enone **8** to complete a rigorous stereochemical assignment. We envisioned here a simple

Table I. ^{13}C NMR Spectral Data of Diastereomers 9b and 10b



9b **10b**

Carbon assignments	Chemical shifts, ppm from Me_4Si		
	9b	10b	2,2,6-Trimethylcyclohexanone
1	214.6 (s)	215.0 (s)	216.4
10	171.5 (s)	172.5 (s)	
11	51.6 (q)	51.2 (q)	
2	47.6 (s)	47.3 (s)	45.0
9	42.7 (t)	42.6 (t)	(25.2 or 25.6)
6	41.2 (d)	41.1 (d)	40.6
3	40.6 (t)	38.7 (t)	41.8
5	36.6 (t)	35.9 (t(	36.7
8	22.9 (q)	23.7 (q)	(25.2 or 25.6)
4	21.0 (t)	21.4 (t)	21.6
7	15.1 (q)	15.0 (q)	15.0

Arndt–Eistert homologation of **9b** and **10b** to esters **9c** and **10c,** coupled with conversion of enone **8** to one of these esters. Approach to the desired δ-keto acid derivatives, **9c** and **10c,** from enone **8** has ample precedent. For example, Caspi[12] and Pelletier[13] reported recently the high-yield conversion of a variety of α,β-unsaturated steroidal ketones to δ-keto acid derivatives using ruthenium tetroxide oxidation. This strategy requires that both the oxidation of **8** and the homologation of **9b** and **10b** proceed without equilibration. Although our previous work indicates that $RuO_4/NaIO_4$ oxidation in aqueous acetone is sufficiently mild to avoid epimerization, prevention of equilibration in the chain homologation sequence, specifically ester hydrolysis preliminary to diazo ketone formation, appeared more difficult. This potential problem was circumvented by the availability in our laboratory of the epimeric esters **11b** and **12b,** the major and minor products, respectively, of the vinylogous Wolff rearrangement[1] of diazo ketone **13.** Correlation of these esters with **9b** and **10b** was effected without incident by oxidation with ruthenium tetroxide.

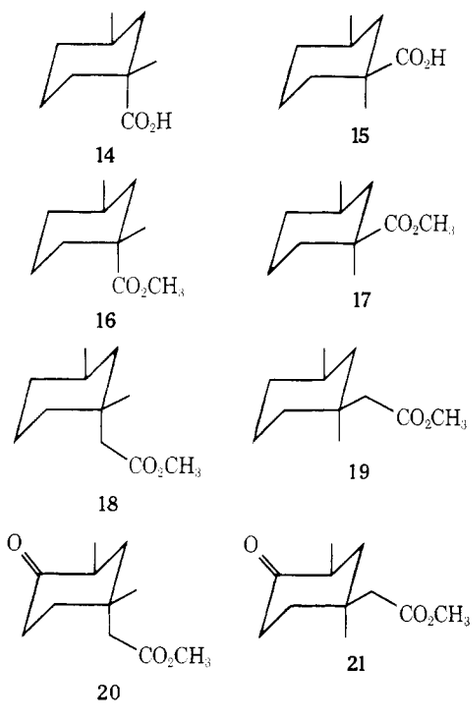
Employing esters **11b** and **12b,** side chain homologation followed by oxidative conversion of the methylene functionality to a carbonyl group without concomitant equilibration was now straightforward. To this end **11b** and **12b** were subjected to a photochemical[14] version of the Arndt–Eistert chain homologation. Each was transformed to the corresponding diazo ketone in the usual manner, and these in turn were irradiated in methanol through Pyrex ($\lambda > 280$ nm) to give **11c** and **12c** in 94 and 85% yield. Subsequent ruthenium tetroxide oxidation gave **9c** and **10c,** respectively. The final chemical correlation, completing the stereochemical assignment of diastereomers **1–5,** was effected by the successful conversion [(a) $RuO_4/NaIO_4$; (b) CH_2N_2] of enone **8**[4] to a single γ-keto ester which was identical in all respects (IR, 220-MHz NMR, and VPC data) with **10c.**

The above stereochemical assignments are in complete accord with the 60- and 220-MHz ^1H NMR spectra. Table II lists the observed chemical shifts of the axial and equatorial C-1 methyl and methylene groups obtained for diastereomers **1–7** as well as the related epimeric derivatives (**14–21**) recently assigned by Wolff and Agosta.[15] Evident here is the generalization, observed originally by Johnson[8] and later by Musher[9] and Grant[10] that proton resonances for equatorial methyl and

Table II. ^{1}H NMR Data for Diastereomers 1–11

Diastereomer	Isomer	Registry no.	Chemical shifts, δ C-1 CH_3	Chemical shifts, δ C-1 CH_2
1	**9b**	61140-22-5	1.05	2.57
	10b	61140-23-6	1.23	2.42
2	**9a**	61140-24-7	0.97	
	10a	61140-25-8	1.13	
3	**9c**	61140-26-9	0.98	
	10c	61140-27-0	1.17	
4	**11b**	61140-28-1	1.20	2.42
	12b	61140-29-2	1.20	2.43
5	**11c**	61140-30-5	1.02	
	12c	61140-31-6	1.05	
6	**11d**	61140-32-7	1.17	2.52
	12d	61140-33-8	1.20	2.55
7	**9d**	58254-23-2	1.02	2.70
	10d	58254-24-3	1.18	2.48
	14	38864-02-7	1.20	
	15	38864-08-3	1.23	
	16	38864-04-9	1.09	
	17	38864-09-4	1.17	
	18	60415-83-0	0.96	2.21
	19	38864-10-7	0.98	2.06
	20	23733-86-0	1.08	2.58
	21	23733-85-9	1.32	2.24

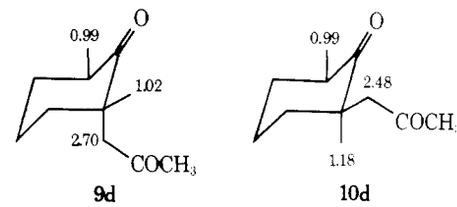
Chart III



methylene substituents experience a small upfield shift (~0.02–0.25 ppm) relative to that of the corresponding C-1 axial substituents. Exceptions occur for diastereomers **4** and **6** where the shifts are either extremely small or nonexistent. Interestingly, the magnitude of the observed shifts are somewhat larger when the ring contains a carbonyl group. This augmentation in effect appears to be independent of location of the carbonyl group on the ring. Finally, it should be noted that this generalization is the exact reverse of the well-known empirical correlation that equatorial cyclohexyl protons appear at lower field relative to axial protons.[16]

While this work was in progress, Muller and Jeger[5] reported the isolation and stereochemical assignment of the related 1,4-diketones, **9d** and **10d.** However, their stereochemical assignments did not conform with the reported NMR observations. To clarify this discrepancy, we transformed esters **11b** and **12b,** now of known stereochemistry, to **9d** and **10d,** respectively. Each ester was first hydrolyzed to the corresponding carboxylic acid and then treated in ether with 2 equiv of methyllithium to yield **11d** and **12d.**[17] All attempts at this point to transform these unsaturated ketones to **9d** and **10d** with ruthenium tetroxide lead to overoxidation. Successful conversion was finally accomplished via microozonolysis at −78 °C, followed by reductive workup with triphenylphosphine.[18] Gas chromatography revealed in each case the formation of a single 1,4-diketone. The spectral data for **9d** and **10d,** as shown in Chart IV, were in complete agreement

Chart IV



9d **10d**

with the data reported by Muller and Jeger[5] upon reversal of their stereochemical assignments.

Experimental Section

Materials and Equipment. All VPC separations were accomplished on a Varian Aerograph Model 920 gas chromatograph employing one of the following columns: A, 25% QF-1, 10 ft × 0.375 in.; B, 25% QF-1, 50 ft × 0.25 in.; C, 25% DEGS, 10 ft × 0.375 in. The column oven was operated at 140–190 °C and the helium carrier gas flow rate was 100–120 ml/min. Compounds purified by VPC were obtained as colorless liquids. IR and NMR spectra were obtained for CCl_4 solutions, the former on a Perkin-Elmer Model 337 spectrophotometer and the latter on a Varian A-60 (60 MHz) or HR-220 (220 MHz) spectrometer. ^{13}C NMR spectra were obtained in $CDCl_3$ on a JEOL PS-100 spectrometer. The internal standard for both ^{1}H and ^{13}C NMR spectroscopy was Me_4Si. Solutions were dried over $MgSO_4$; melting points are corrected; boiling points are uncorrected. Photochemical experiments were carried out with a Hanovia Model L mercury lamp (no. 679A-36) in a quartz immersion well using Pyrex 7740 as filter. Ruthenium dioxide ($RuO_2 \cdot x H_2O$, 57.95%) was obtained from Englehard Laboratories.

2,*t*-6- and 2,*c*-6-Dimethyl-*r*-2-allylcyclohexan-1-one[19] (9a and 10a). To a solution containing 25 ml of dry THF and 5.3 g (1.2 equiv) of diisopropylamine distilled from KOH and cooled under N_2 to 0–5 °C was added with stirring 21 ml (1.2 equiv, 2.5 M) of *n*-BuLi. After the addition was complete the solution was cooled to −78 °C and 9.4 g (1.2 equiv) of HMPA distilled from CaH_2 was added. Approximately 30 min later a solution containing 5.5 g (44 mmol) of 2,6-dimethylcyclohexanone and 20 ml of THF was added slowly followed 45 min later by the addition of 8.7 g (1.2 equiv) of allyl bromide. The resulting solution was stirred for 1 h at −78 °C and then overnight at room temperature. The reaction mixture was then poured into 80 ml of saturated aqueous NH_4Cl and extracted with ether; the combined organic phases were washed with H_2O and brine and dried. Removal of the solvent in vacuo followed by distillation afforded 4.4 g (63%) of a 1:1 mixture of **9a** and **10a.** Preparative VPC on column B gave pure **9a** and **10a.** The first was **10a:** IR 3075 (w), 2975 (s), 2940 (s), 1705 (s), 1640 (w), 995 (s), 905 cm^{-1} (s); NMR (220 MHz) δ 0.95, 1.13 (d, s, J = 6 Hz, 6 H), 1.16–2.36 (m, 8 H), 2.55 (m, 1 H), 4.98 (m, 2 H), 5.75 (m, 1 H); mass spectrum *m/e* 166.1361 (M^+, calcd for $C_{11}H_{18}O$, 166.1357). The second was **9a:** IR 3075 (w), 2975 (s), 2940 (s), 1705 (s), 1640 (w), 915 cm^{-1} (s); NMR (220 MHz) δ 0.92, 0.97 (d, s, J = 6 Hz, 6 H), 1.05–2.54 (m, 9 H), 5.00 (m, 2 H), 5.55 (m, 1 H); mass spectrum *m/e* 166.1347 (M^+, calcd for $C_{11}H_{18}O$, 166.1357).

Methyl 1,*t*-3-Dimethyl-2-oxo-*r*-1-cyclohexaneacetate (9b). A solution containing 80 mg of RuO_2, 500 mg of $NaIO_4$, 20 ml of H_2O, and 35 ml of reagent acetone was stirred (ca. 1 h) at room temperature until the organic phase assumed a distinct yellow coloration (RuO_4). To this mixture was added a solution containing 50 mg (0.30 mmol)

of pure **9a** in 10 ml of acetone. The resultant mixture was then stirred at room temperature for 4 h, whereupon 500 μl of 2-propanol was added and the black precipitate filtered after 15 min. The filtrate was poured into 60 ml of H_2O and extracted with ether. The combined organic phases were washed with H_2O and brine and dried. Removal of the solvent in vacuo gave 51.5 mg (93%) of acid [IR 3600–2500 (s, br), 1710 cm^{-1} (s)] which was esterified with excess ethereal diazomethane (CH_2N_2). After 60 min the excess CH_2N_2 was removed on a steam bath and the solution dried. Removal of the solvent in vacuo gave 80 mg of crude **9b**. An analytical sample was obtained by VPC on column A: IR 2975 (s), 2943 (s), 1749 (s), 1723 (s), 1207 cm^{-1} (s); NMR (60 MHz) δ 0.98, 1.05 (d, s, J = 6 Hz, 6 H), 1.13–3.03, 2.57 (m, dd, J = 14 Hz, 9 H), 3.57 (s, 3 H).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.88; H, 9.08.

Methyl 1,*c*-3-Dimethyl-2-oxo-*r*-1-cyclohexaneacetate (10b). By a procedure similar to that listed for **9b,** 35 mg (0.21 mmol) of **10a** was oxidized and esterified to afford 39 mg (93%) of **10b.** An analytical sample was obtained by VPC on column B: IR 2970 (s), 2940 (s), 2875 (s), 1740 (s), 1708 (s), 1171 (s), 1004 cm^{-1} (s); NMR (60 MHz) δ 1.00 (d, J = 7 Hz, 3 H), 1.23 (s, 3 H), 1.33–2.83, 2.42 (m, dd, J = 16 Hz, 9 H), 3.59 (s, 3 H).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.89; H, 9.17.

Equilibration of Diastereomers 9b and 10b. On a 50-mg scale, pure keto ester **10b** was dissolved in 6 ml of a freshly prepared solution of NaOMe in MeOH (~0.6 M) and heated at reflux under N_2 for 16 h. After workup vapor phase chromatography on column A indicated a mixture of keto esters **9b** and **10b** in a ratio of 65:35, respectively. Keto ester **9b** isolated from this mixture by preparative VPC on column A was identical (VPC retention time, 60-MHz NMR) with keto ester **9b** prepared previously.

In a similar manner pure keto ester **9b** (40 mg) was dissolved in 6 ml of a freshly prepared solution of NaOMe in MeOH and heated to reflux under N_2 for 16 h. After workup VPC on column A indicated a mixture of keto esters **9b** and **10b** in a ratio of 65:35, respectively.

Oxidation of Methyl 1,*t*-3-Dimethyl-2-methylene-*r*-1-cyclohexaneacetate (11b). A suspension containing 104 mg of RuO_2, 580 mg of $NaIO_4$, 20 ml of H_2O, and 35 ml of acetone was stirred for 1 h at room temperature until the organic phase assumed a distinct yellow coloration (i.e., RuO_4). To this mixture was added a solution containing 54 mg (0.28 mmol) of ester **11b** in 10 ml of acetone. The resultant mixture was then stirred at room temperature for 4 h, whereupon 500 μl of 2-propanol was added and the black RuO_2 filtered after 15 min. The filtrate was poured into H_2O and extracted with ether. The organic phase was washed and dried. Removal of the solvent in vacuo gave 50.3 mg (91%) of a γ-keto ester which, after VPC purification on column A, was identical in all respects (i.e., IR, 220-MHz NMR, and VPC retention properties) with ester **9b.**

Oxidation of Methyl 1,*c*-3-Dimethyl-2-methylene-*r*-1-cyclohexaneacetate (12b). In a manner similar to the above, 33 mg (0.17 mmol) of ester **12b** was oxidized (RuO_2, $NaIO_4$, aqueous acetone) yielding 26 mg (79%) of a γ-keto ester which, after VPC purification of column A, was identical in all respects (i.e., IR, 220-MHz NMR, and VPC retention properties) with ester **10b.**

Methyl 1,*t*-3- and 1,*c*-3-Dimethyl-2-methylene-*r*-1-cyclohexaneacetate (11b and 12b). A solution consisting of 358.6 mg (1.88 mmol) of diazo ketone **13,** 27.1 mg of $Cu(AcAc)_2$, 123 μl of MeOH (1.5 equiv), and 100 ml of cyclohexane was heated at reflux for 60 min. After cooling the reaction mixture was washed successively with 1 N HCl, H_2O, and brine, and dried. Removal of the solvent in vacuo afforded 344 mg of an oily residue containing 150 mg (41%, by VPC calibration) of a 9:1 mixture of **11b** and **12b,** respectively. Preparative VPC on column C gave pure **11b** and **12b.** The first was **11b:** IR 3110 (w), 2930 (s), 1740 (s), 1640 (w), 1475 (m), 1212 (s), 1181 (s), 898 cm^{-1} (s); NMR (60 MHz) δ 0.87, 1.20, 1.29–2.06 (d, s, m, J = 7 Hz, 13 H), 2.42 (dd, J = 13 Hz, 2 H), 3.53 (s, 3 H), 4.75 (m, 2 H).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.34; H, 10.13.

The second was **12b:** IR 3110 (w), 2930 (s), 1740 (s), 1640 (w), 1470 (m), 1210 (s), 1115 (s), 1007 (s), 890 cm^{-1} (s); NMR (60 MHz) δ 1.05, 1.20, 1.26–2.03 (d, s, m, J = 7 Hz, 13 H), 2.43 (s, 2 H), 3.60 (s, 3 H), 4.67 (m, 2 H); mass spectrum m/e 196.1472 (M^+, calcd for $C_{12}H_{20}O_2$, 196.1462).

Methyl 1,*t*-3-Dimethyl-2-methylene-*r*-1-cyclohexanepropionate (11c). A solution containing 360 mg (1.84 mmol) of ester **11b,** 12 ml of MeOH, and 4.4 ml of 5% (w/v) aqueous NaOH was heated at reflux under nitrogen for 2 h, yielding upon workup 324 mg (97%) of the corresponding acid [IR 3400–2600 (s, broad), 1700 (s), 1640 (w), 900 cm^{-1} (s)].

A solution containing 324 mg (1.78 mmol) of this acid in 2 ml of benzene was treated with 300 μl (2.0 equiv) of oxalyl chloride and stirred for 4 h at room temperature. Distillation (Kuglerohr) of the residue after removal in vacuo of the benzene and excess oxalyl chloride afforded 334 mg (94%) of the corresponding acid chloride [IR 2940 (s), 1800 (s), 1640 (w), 900 cm^{-1} (s)]. This acid chloride was dissolved in 20 ml of ether and added dropwise with stirring to an ethereal solution of CH_2N_2 (3.5 equiv) yielding 360 mg (100%) of the corresponding diazo ketone [IR 3100 (w), 2940 (s), 2100 (s), 1645 (s), 900 cm^{-1} (s)]. The diazo ketone was dissolved in 70 ml of MeOH and irradiated for 90 min. The photolysate was poured into 50 ml of H_2O and extracted with ether and the organic phase washed with H_2O and brine and dried. Removal of the solvent in vacuo gave 328 mg (94%) of **11c.** An analytical sample was obtained by VPC on column C: IR 3110 (w), 2940 (s), 1740 (s), 1640 (w), 1195 (s), 1173 (s), 895 cm^{-1} (s); NMR (60 MHz) δ 0.93–2.5, 1.02, 1.04 (m, s, d, J = 6 Hz, 17 H), 3.58 (s, 3 H), 4.75 (m, 2 H).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H 10.54. Found: C, 74.20; H, 10.57.

Methyl 1,*c*-3-Dimethyl-2-methylene-*r*-1-cyclohexanepropionate (12c). By a similar procedure ester **12b** was homologated to ester **12c** in 87% overall yield. Preparative VPC on column C gave pure **12c:** IR 3100 (w), 2940 (s), 1740 (s), 1640 (w), 1198 (s), 1170 (s), 895 cm^{-1} (s); NMR (60 MHz) δ 0.96–2.67, 1.05, 1.06 (m, s, d, J = 7 Hz, 17 H), 3.65 (s, 3 H), 4.78 (s, 2 H).

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.23; H, 10.46.

Methyl 1,*t*-3-Dimethyl-2-oxo-*r*-1-cyclohexanepropionate (9c). A mixture of 80 mg of RuO_2, 450 mg of $NaIO_4$, 20 ml of H_2O, and 35 ml of acetone was stirred at room temperature for 60 min followed by dropwise addition of 49.2 mg (0.23 mmol) of ester **11c** in 10 ml of acetone. After stirring for 4.5 h at room temperature, 500 μl of 2-propanol was added and the RuO_2 was removed by filtration. The filtrate was poured into H_2O and extracted with ether; the combined organic phases were washed with H_2O and brine and dried. Removal of the solvent in vacuo afforded 34 mg (70%) of crude **9c.** After purification by VPC on column C, **9c** had the following spectral data: IR 2970 (s), 2940 (s), 1740 (s), 1710 (s), 1255 cm^{-1} (s); NMR (60 MHz) δ 0.96, 0.98 (d, s, J = 6 Hz, 6 H), 1.05–2.66 (m, 11 H), 3.63 (s, 3 H); mass spectrum m/e 212.1425 (M^+, calcd for $C_{12}H_{20}O_3$, 212.1411).

Methyl 1,*c*-3-Dimethyl-2-oxo-*r*-1-cyclohexanepropionate (10c). In a manner similar to that listed for ester **9c,** 27.6 mg (0.13 mmol) of ester **12c** was oxidized (80 mg of RuO_2, 253 mg of $NaIO_4$, aqueous acetone, 4 h) affording 20 mg (71%) of crude **10c.** After purification by VPC on column C, **10c** had the following spectral data: IR 2940 (s), 1740 (s), 1715 (s), 1200 (s), 1170 cm^{-1} (s); NMR (220 MHz) δ 0.96 (d, J = 6 Hz, 3 H), 1.17 (s, 3 H), 1.24–2.41 (m, 10 H), 2.42–2.73 (m, 1 H), 3.66 (s, 3 H); mass spectrum m/e 212.1412 (M^+, calcd for $C_{12}H_{20}O_3$, 212.1411).

Oxidation of 4,4a,5,6,7,8-Hexahydro-4aβ,8α-dimethyl-2(3*H*)-naphthalenone (8). In a manner similar to the previously listed oxidations, 70.5 mg (0.4 mmol) of enone **8** was oxidized to the corresponding keto acid which was then esterified with excess CH_2N_2 for 60 min to yield 75 mg (88%) of a keto ester (**10c**). After VPC purification on column C this keto ester was identical in all respects (IR, 220-MHz NMR, and VPC retention properties) with **10c** prepared from ester **12c.**

2,*t*-6-Dimethyl-*r*-2-(2′-oxoprop-1′-yl)-1-methylenecyclohexane (11d). A solution containing 360 mg (1.8 mmol) of pure **11b,** 12 ml of MeOH, and 4.4 ml of 5% (w/v) aqueous NaOH was heated at reflux under nitrogen for 2 h. The reaction mixture was then cooled, poured into water, and extracted with ether. Acidification of the aqueous phase, extraction with ether, drying, and removal of the solvent in vacuo gave as an oil 324 mg (97%) of the corresponding carboxylic acid.

A solution containing 142 mg (0.78 mmol) of this acid and 10 ml of anhydrous ether was treated at 0 °C under N_2 with 950 μl (2.5 equiv) of MeLi (2.06 M). The resulting solution was stirred at room temperature for 13 h, and then added dropwise to a stirred saturated aqueous solution of NH_4Cl. The reaction mixture was extracted with ether and the combined organic phases washed with H_2O and brine and then dried. Removal of the solvent in vacuo gave 137.2 mg (93%) of **11d.** An analytical sample was prepared by VPC on column C: IR 3110 (w), 2970 (s), 2940 (s), 1710 (s), 1640 (w), 900 cm^{-1} (s); NMR (60 MHz) δ 1.00–1.92, 1.08, 1.17 (m, d, s, J = 6 Hz, 12 H), 1.93–2.98, 1.97, 2.52 (m, s, d, J = 14 Hz, 6 H), 4.97 (m, 2 H); mass spectrum m/e 180.1498 (M^+, calcd for $C_{12}H_{20}O$, 180.1513).

2,*c*-6-Dimethyl-*r*-2-(2′-oxoprop-1′-yl)-1-methylenecyclohexane (12d). A solution containing 147 mg (0.75 mmol) of pure **12b,** 12 ml of MeOH, and 2 ml of 5% (w/v) aqueous NaOH was heated at reflux

under nitrogen for 3 h. The reaction mixture was then cooled, poured into water, and extracted with ether. Acidification of the aqueous phases, extraction with ether, drying, and removal of the solvent in vacuo gave as an oil 126 mg (93%) of the corresponding carboxylic acid.

A solution containing 74 mg (0.41 mmol) of this acid and 10 ml of anhydrous ether was treated at 0 °C under nitrogen with 0.63 ml (3.2 equiv) of MeLi (2.06 M). The resulting solution was stirred at room temperature for 19 h and then worked up as above to give 68 mg (93%) of **12d**. An analytical sample was obtained by VPC on column C: IR 3110 (w), 2970 (s), 2930 (s), 1710 (s), 1640 (w), 890 cm^{-1} (s); NMR (60 MHz) δ 1.07, 1.20 (d, s, J = 7 Hz, 6 H), 1.23–2.06 (m, 7 H), 2.08 (s, 3 H), 2.55 (s, 2 H), 4.62 (m, 2 H); mass spectrum m/e 180.1497 (M^+, calcd for $C_{12}H_{20}O$, 180.1513).

2,*t*-6-Dimethyl-*r*-2-(2′-oxoprop-1′-yl)-1-cyclohexanone (9d). A solution containing 55 mg (0.31 mmol) of ketone **11d** and 6 ml of spectroquality hexane was cooled to −78 °C. Ozone was then passed slowly through the solution for 75 min after which 95 mg of triphenylphosphine was added. After warming to room temperature the resulting suspension was filtered and the filtrate chromatographed on silica gel. Elution with ether–hexane (1:1) gave 46 mg (82%) of **9d**. A pure sample prepared by VPC on column C possessed the IR and NMR data listed below, which were identical with those reported for *trans*-2,6-dimethyl-2-(2-oxoprop-1-yl)cyclohexan-1-one by Muller and Jager:[5] IR 2975 (s), 2940 (s), 1720 (s, br), 1360 (s), 1015 (s), 975 (w), 950 cm^{-1} (w); NMR (60 MHz) δ 0.99, 1.02 (d, s, J = 6 Hz, 6 H), 1.13–2.67, 2.04 (m, s, 10 H), 2.70 (s, 2 H); (220 MHz) δ 0.98–1.91, 0.99, 1.02 (m, d, s, J = 6 Hz, 10 H), 1.92–2.36, 2.05 (m, s, 5 H), 2.56–2.82, 2.70 (m, dd, J = 16 Hz, 3 H).

2,*c*-6-Dimethyl-*r*-2-(2′-oxoprop-1′-yl)-1-cyclohexanone (10d). In a manner similar to the above, 29 mg (0.16 mmol) of **12d** was ozonized to give 29 mg (94%) of **10d**. A pure sample of **10d** prepared by VPC on column C possessed the IR and NMR data listed below which were identical with those reported for *cis*-2,6-dimethyl-2-(2-oxoprop-1-yl)cyclohexan-1-one by Muller and Jager:[5] IR 2975 (s), 2940 (s), 1710 (s, br), 1360 (s), 1168 (s), 1142 (s), 1125 (s), 1000 (s), 978 (m), 955 cm^{-1} (w); NMR (60 MHz) δ 1.02 (d, J = 6 Hz, 3 H), 1.20 (s, 3 H), 1.50–2.16, 2.09 (m, s, 9 H), 2.16–2.75, 2.51 (m, dd, J = 17 Hz, 3 H); (220 MHz) δ 0.99 (d, J = 6 Hz, 3 H), 1.18 (s, 3 H), 1.20–2.13, 2.09 (m, s, 9 H), 2.42, 2.48 (m, dd, J = 17 Hz, 3 H).

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Registry No.—**8**, 17990-00-0; **10c** free acid, 61140-34-9; **11b** free acid, 61140-35-0; **11b** acid chloride, 61140-36-1; **12b** free acid, 61140-37-2; **12b** acid chloride, 61140-38-3; **13**, 61140-39-4; 2,6-dimethylcyclohexanone, 2816-57-1; allyl bromide, 106-95-6.

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Analogues of Phosphoenol Pyruvate. 3.[1] New Synthetic Approaches to α-(Dihydroxyphosphinylmethyl)acrylic acid and Unequivocal Assignments of the Vinyl Protons in Its Nuclear Magnetic Resonance Spectrum

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Three new synthetic routes to α-(dihydroxyphosphinylmethyl)acrylic acid (**1**), the phosphonic acid analogue of phosphoenolpyruvic acid, have been developed. One of these routes was devised so that a carbon-13 label could be introduced specifically in the carboxylate carbon position of **1**. By measurement of $^3J_{^1H-^{13}C}$ coupling constants in the NMR spectrum of **1**, unequivocal assignments for the vinyl protons have been made.

Phosphoenolpyruvic acid (PEP) is one of the most important biological substances with a high phosphate group-transfer potential.[4] In 1972, Stubbe and Kenyon reported the synthesis of the nonhydrolyzable phosphonate analogue of PEP, α-(dihydroxyphosphinylmethyl)acrylic acid (**1**). This analogue has been found to replace PEP as a substrate in the enolase reaction[1,5] and to serve as a weak competitive inhibitor of rabbit muscle pyruvate kinase.[6] In the case of both enzymes,