dence). Thus some of the structure in the figure may be statistical, but most of the reactive trajectories come from the highest bound (v,j) states for each v, and so some of the maxima may be real; e.g., the large contributions from $v = 1, 6, 7$, and 12 are due to the particularly high reactivities of the (1,30), (6,22), (7,20), and (12,10) states, which are bound by just 0.52, 0.10, 0.61, and 0.02 kcal mol^{-1}, respectively. The decrease of $f(v)$ at high v is due to the low rotational partition functions for $v \leq 13$. These results show that the correct treatment of the equilibrium or nonequilibrium populations of low-v, high-j states as well as high vibrational levels is essential.[18a,b]

References and Notes

(1) H. Johnston and J. Birks, *Acc. Chem. Res.*, **5**, 327–335 (1972).
(2) H. O. Pritchard in "Specialist Periodical Reports, Reaction Kinetics", Vol. 1, The Chemical Society, London, 1975, pp 243–290.
(3) J. H. Kiefer, H. P. G. Joosten, and W. D. Breshears, *Chem. Phys. Lett.*, **30**, 424–428 (1975).
(4) (a) J. E. Dove and D. G. Jones, *J. Chem. Phys.*, **55**, 1531 (1971); (b) J. E. Dove and D. G. Jones, *Chem. Phys. Lett.*, **17**, 134 (1972).
(5) N. C. Blais and D. G. Truhlar in "State-to-State Chemistry", P. R. Brooks and E. F. Hayes, Ed., American Chemical Society, Washington, D.C., in press.
(6) (a) V. H. Shui, J. P. Appleton, and J. C. Keck, *Int. Symp. Combust., 13th, 1971*, 21–35 (1971); (b) V. H. Shui and J. P. Appleton, *J. Chem. Phys.*, **55**, 3126–3132 (1971).
(7) See also, e.g., (a) R. T. V. Kung and J. B. Anderson, *J. Chem. Phys.*, **60**, 3731–3743 (1974), (b) W. H. Wong and G. Burns, *Proc. R. Soc. London, Ser. A*, **341**, 105–119 (1974).
(8) M. Karplus, R. N. Porter, and R. D. Sharma, *J. Chem. Phys.*, **43**, 3259–3287 (1965). Quasi-classical trajectories are classical except for the assignment of quantal values to initial vibrational and rotational action values so that the trajectories correspond to real (v,j) states, where j is the initial rotational quantum number.
(9) N. C. Blais and D. G. Truhlar, *J. Chem. Phys.*, **65**, 5335–5356 (1976).
(10) This means that the (v,j) states of H_2 and the relative translational motion are assumed to be in thermal equilibrium but the overall concentration of reactants is not in equilibrium with that of products. See R. K. Boyd, *Chem. Rev.*, 77, 93–119 (1977).
(11) See, e.g., ref 1. We find, however, that their assumed dissociation rate coefficients from selected initial low-v levels are much too large compared with our calculated ones.
(12) For similar conclusions see (a) H. O. Pritchard, *Can. J. Chem.*, **51**, 3152–3155 (1973); (b) H. O. Pritchard, *Acc. Chem. Res.*, **9**, 99–105 (1976); (c) G. W. Tregay, W. G. Valance, and D. I. McLean, *J. Chem. Phys.*, **59**, 1634–1640 (1973). However, we disagree with their treatments. References a and b assume that *all* quasi-bound states are reactant states in local equilibrium and that dissociation rate constants from initial states with selected j values have a simple dependence on centrifugal barrier height. Reference c assumes that the dissociation probability depends on v and translational energy but not on j.
(13) This is essentially the same division into reactant and product states as used by R. E. Roberts, R. B. Bernstein, and C. F. Curtiss, *J. Chem. Phys.*, **50**, 5163–5176 (1969), to model the recombination of H atoms. We are presently studying the effect of considering the seven quasi-bound states with longest unimolecular lifetimes as reactant states.
(14) (a) R. C. Tolman, "Statistical Mechanics with Applications to Physics and Chemistry", Chemical Catalog Co., New York, N.Y., 1927, pp 266–270; (b) R. H. Fowler and E. A. Guggenheim, "Statistical Mechanics", Macmillan, New York, N.Y., 1939, pp 489–504; (c) H. S. Johnston, "Gas Phase Reaction Rate Theory", Ronald Press, New York, N.Y., 1966, pp 215–217; (d) D. G. Truhlar, *J. Chem. Educ.*, in press, and references therein.
(15) d. L. Baulch, D. D. Drysdale, D. G. Horne, and A. C. Lloyd, "Evaluated Kinetic Data for High Temperature Reactions", Vol. 1, CRC Press, Cleveland, Ohio, 1972, pp 309–323.
(16) W. D. Breshears and P. F. Bird, *Int. Symp. Combust., 14th, 1973*, 211–217 (1973).
(17) J. K. K. Ip and G. Burns, *J. Chem. Phys.*, **51**, 3425 (1969).
(18) (a) This work was performed under the auspices of the U.S. Energy Research and Development Administration and was supported in part by the National Science Foundation under Grant No. CHE-7506416. (b) Portions of this work have been presented at the Second Joint Conference of the Chemical Institute of Canada and the American Chemical Society, Montreal, Canada, June 1, 1977. (c) Alfred P. Sloan Research Fellow, 1973–1977.

Donald G. Truhlar*[18c]
Chemical Dynamics Laboratory
Department of Chemistry, University of Minnesota
Minneapolis, Minnesota 55455

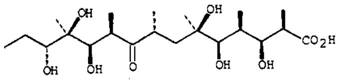
Normand C. Blais*
University of California
Los Alamos Scientific Laboratory
Los Alamos, New Mexico 87545

Received July 18, 1977

Acyclic Stereoselection. 2. Synthesis of 3-Hydroxy-2-methyl- and 3-Hydroxy-2,4-dimethylcarboxylic Acids

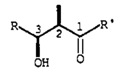
Sir:

One of the basic unsolved problems of organic synthesis is the stereoselective construction of acyclic compounds containing multiple chiral centers. This problem is best exemplified by the macrolide antibiotics as a whole and in particular by **1**, the open-chain form of the aglycone of the macrolide erythromycin A,[1] which has ten chiral centers. This polyhydroxy acid can be built up using a series of six aldol-type condensations, provided that sufficient control can be maintained over the stereochemical outcome of each condensation. This approach is similar to the biosynthesis of the macrolide aglycones in which the carbon skeleton is thought to originate from a series of condensations of acetyl- and propionyl-CoA units.[2]



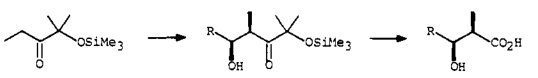
1

We[3] and others[4] have previously reported examples of aldol condensations which afford β-hydroxy ketones **2** (R, R′ = alkyl and/or aryl) in high diastereomeric purity.[5] We now report a simple modification which allows the production of β-hydroxycarboxylic acids **2** (R′ = OH).



2

The enolate[6] of 2-methyl-2-trimethylsilyloxy-3-pentanone (**3**)[7] was condensed[8] with aldehydes to give β-hydroxy ketones (**4**) which were converted to β-hydroxy acids (**5**) upon treatment with periodic acid. In each case, the relative stereochemistry about C-2 and C-3 has been assigned by consideration of the ^{1}H NMR coupling constant of the protons on these carbons.[9] We have not been able to detect any significant amounts of the other diastereomer in either the condensation or cleavage products (Table I). If the dianion of 2-hydroxy-2-methyl-3-pentanone is condensed with benzaldehyde, an 8:1 mixture of the two possible diastereomeric dihydroxy ketones is produced.

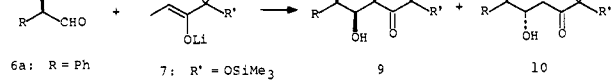


3

4a: R = Ph
4b: R = *i*-Pr
4c: R = $PhCH_2$

5a: R = Ph
5b: R = *i*-Pr
5c: R = $PhCH_2$

We have also examined the condensation of ketone enolates with aldehydes having a chiral center adjacent to the carbonyl group. For these condensations, there are four possible diastereomeric products,[11] but only **9** and **10** are detected. The relative configuration about the first two centers is determined by the factors we have discussed previously.[3] The relative configuration about the second and third centers is that predicted by Cram's rule[12] (Table II).



6a: R = Ph
6b: R = $MeO_2CCH_2CH_2$

7: R′ = $OSiMe_3$
8: R′ = CH_3

9

10

To prove the stereostructures of the products **9** and **10** from these condensations, the hydroxy ketones from **6b** and **8** were converted to the lactones **11** and **12**. These lactones were separated by column chromatography and examination of their

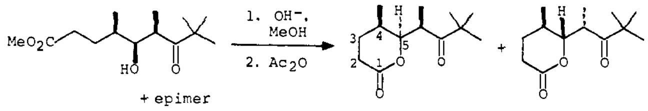
Table I

	4		5		
R	Yield, %[a]	$J_{2,3}$, Hz	Yield, %[d]	$J_{2,3}$, Hz	Mp, °C
Ph	86	5	77	4	Oil[b]
i-Pr	86	*c*	50	4	Oil
$PhCH_2$	90[d]	*c*	76	*c*	119-120

[a] Yields are crude and have not been optimized. [b] Lit.[10] mp 65-66 °C. Although this hydroxy acid has failed to crystallize in our hands, its stereostructure was determined by direct comparison with authentic **5a** and its threo diastereomer. [c] Splitting was complicated by other adjacent protons. [d] After hydrolysis of the trimethylsilyl group.

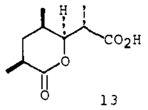
Table II

Aldehyde	Enolate	Ratio of **9**:**10**
6a	**8**	86:14
6b	**8**	74:26
6a	**7**	81:19



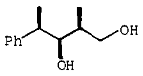
11 (74%) 12 (26%)

^1H NMR spectra shows that the signals for the C-5 protons appear as a triplet ($J = 7$ Hz) and a double doublet ($J = 10$ and 2 Hz) for the major and minor isomers, respectively. The analogous proton in the Prelog-Djerassi lactone (**13**) appears as a double doublet ($J = 9.5$ and 3.8 Hz).[13] Thus we assign the stereostructures for **11** and **12** as shown.

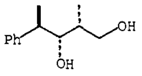


13

The hydroxy ketone mixture from the condensation of enolate **7** with aldehyde **6a** was cleaved by periodic acid in methanol and the mixture of β-hydroxy acids was esterified with diazomethane and separated by chromatography. The separated β-hydroxy esters were reduced using lithium aluminum hydride. The major hydroxy ester yielded diol **14** (mp 96.5-98 °C, lit.[11] mp 98-98.5 °C), and the minor hydroxy ester yielded diol **15** (mp 69-70.5 °C, lit.[11] mp 70.5-71 °C).

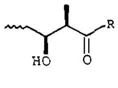


14

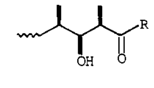


15

The results reported here provide the first steps toward our ultimate goal of constructing polyhydroxycarboxylic acids such as **1** by a series of stereoselective aldol condensations. At this point, we are able to introduce the three-carbon unit I with excellent selectivity and the four-carbon unit II in lower, but still acceptable, selectivity.



I



II

Acknowledgment. Support for this research was provided by the U.S. Public Health Service (Grant No. AI-11607) and the National Science Foundation (Grant No. GP-31321X).

References and Notes

(1) W. D. Celmer, *Pure Appl. Chem.*, **28**, 413 (1971).
(2) M. Berry, *Quart. Rev.*, **17**, 343 (1963).
(3) W. A. Kleschick, C. T. Buse, and C. H. Heathcock, *J. Am. Chem. Soc.*, **99**, 247 (1977).
(4) (a) J.-E. Dubois and M. Dubois, *Tetrahedron Lett.*, 4215 (1967); (b) J.-E. Dubois and P. Fellmann, *C.R. Hebd. Seances Acad. Sci., Ser. C*, **274**, 1307 (1972); (c) J.-E. Dubois and P. Fellmann, *Tetrahedron Lett.*, 1225 (1975); (d) W. Fenzel and R. Köster, *Justus Liebigs Ann. Chem.*, 1322 (1975).
(5) Although the structural formulas indicate one enantiomer, all substances are racemates.
(6) The enolate is prepared by the dropwise addition of the ketone to an ~0.6 M solution of lithium diisopropylamide in THF/hexane at −70 °C. After 20 min at this temperature, enolate formation was assumed to be complete.
(7) This was prepared from propionaldehyde via the protected cyanohydrin anion and acetone by the method of Stork (G. Stork and L. Maldonado, *J. Am. Chem. Soc.*, **93**, 5286 (1971)). The hydroxy ketone was silylated upon heating with bis(trimethylsilyl)acetamide. The overall yield from propionaldehyde cyanohydrin was 42%.
(8) The condensations were carried out as described in ref 3.
(9) H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Am. Chem. Soc.*, **95**, 3310 (1973).
(10) J. Canceill, J. Gabard, and J. Jacques, *Bull. Soc. Chim. Fr.*, 2653 (1966).
(11) T. Matsumoto, Y. Hosoda, K. Mori, and K. Fukui, *Bull. Chem. Soc. Jpn.*, **45**, 3156 (1972). These workers examined the Reformatsky reaction of methyl α-bromopropionate with α-phenylpropionaldehyde and obtained all four possible hydroxy esters in a ratio of 55:24:16:5.
(12) (a) D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952); (b) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, N.J., 1971, pp 41, 42.
(13) S. Masamune, C. U. Kim, K. E. Wilson, G. O. Spessard, P. E. Georghiou, and G. S. Bates, *J. Am. Chem. Soc.*, **97**, 3512 (1975).

Charles T. Buse, Clayton H. Heathcock*
Department of Chemistry, University of California
Berkeley, California 94720
Received August 29, 1977

Low-Temperature Nuclear Magnetic Resonance Evidence for Stereochemical Rigidity in Eight-Coordinate Metal β-Diketonates

Sir:

Until very recently,[1,2] NMR studies of eight-coordinate tetrakis chelates have failed to provide stereochemical and kinetic information because these chelates undergo very rapid stereochemical rearrangements. Previous low-temperature studies of tetrakis β-diketonates,[3,4] tropolonates,[5] and *N,N*-dialkyldithiocarbamates[6-8] have afforded only time-averaged NMR spectra. Only for the tetrakis(*N,N*-dimethyldithiocarbamato)tantalum(V) cation, $[Ta(S_2CNMe_2)_4]^+$,[1] and the heterochelate tris(5-methylpicolinato)(5,7-dichloro-8-quinolinolato)tungsten(IV), $W\overline{P}_3Q$,[2] have limiting slow-exchange spectra been reported. $[Ta(S_2CNMe_2)_4]^+$ exhibits two equally intense dithiocarbamate methyl resonances below the coalescence temperature of −62 °C,[1] consistent with the dodecahedral *mmmm*-D_{2d} stereoisomer found in the solid state.[9] $W\overline{P}_3Q$ displays two methyl resonances at room temperature.

Using the Freon solvent $CHClF_2$, we have investigated the ^1H NMR spectra of metal tetrakis(β-diketonates) at considerably lower temperatures than employed in earlier work,[3] and we have identified several zirconium(IV) and uranium(IV) β-diketonates which become stereochemically rigid on the NMR time scale at temperatures in the range of −100 to −170 °C. Typical spectra for tetrakis(acetylacetonato)zirconium(IV), $Zr(acac)_4$, are presented in Figure 1. The single, time-averaged methyl resonance characteristic of the higher temperatures splits into two lines of equal intensity below the coalescence temperature of −145 °C. The frequency separation in the slow-exchange limit is 11.1 Hz at 90 MHz (0.12 ppm), and the minimum line width below coalescence is ~6 Hz (at −163 °C); below −163 °C the line width increases owing to viscosity broadening. No splitting was observed for the ring proton resonance.

Low-temperature NMR spectra of $U(acac)_4$ (Figure 2) exhibit the same features found for $Zr(acac)_4$; however, the chemical shifts are appreciably larger and temperature dependent because of the paramagnetism of uranium(IV). The