from incubation with enzymatically derived optically active MCPA-CoA.[15] This finding clearly indicates that both of the stereoisomers of MCPA-CoA are competent inhibitors for GACD, and therefore the inactivation is nonstereospecific.[16] Since the C_β–H cleavage of the trans dehydrogenation step is well established to be pro-*R* specific,[17] the lack of stereospecificity of bond rupture at C_β of MCPA-CoA found in our inactivation study strongly suggests that this ring-opening step leading to inactivation is not enzyme-controlled. Hence, such ring fragmentation is likely a spontaneous event, induced by an α-cyclopropyl radical.[18] Since the rearrangement of α-cyclopropyl radicals to the ring-opened alkyl radicals are extremely rapid,[9,19] the ring cleavage may bypass the chiral discrimination imposed by the enzyme.

Figure 1 also revealed that the extent of flavin modification parallels the loss of enzyme activity, although the rate of inactivation is slightly faster than that of bleaching. Furthermore, the bleaching of the flavin chromophore levels off first while small loss of enzyme activity continues. These phenomena may be ascribed to the existence of a minor inactivation pathway involving alkylation of the apoprotein as previously surmised.[1a,6b,20] Since none of the common amino acids possess an electrophilic center, such alkylation, if it indeed occurs concurrently with flavin modification, stands against the nucleophilic ring-opening mechanism.[21]

Thus, study of the MCPA-CoA-mediated mechanism-based inhibition of general acyl-CoA dehydrogenase seems to favor a radical-initiated process. Since this enzyme is expected to operate via a single mechanism, the mechanistic insights derived from the inhibition study provide compelling evidence arguing for a radical mechanism of general acyl-CoA dehydrogenase-catalyzed reaction. If the unusual structure of the inhibitor has led the enzyme to proceed through a different mechanism than it would normally follow, the aforementioned findings connote, at the very least, that general acyl-CoA dehydrogenase is capable of mediating one-electron oxidation–reduction.[22]

(15) MCPA-CoA was generally prepared from hypoglycin via L-amino acid oxidase mediated deamination and H_2O_2 induced decarboxylation to yield methylenecyclopropane acetic acid followed by thioester formation catalyzed by acyl-CoA synthetase.[6]

(16) However, this preliminary observation contradicts Baldwin's recent report (Baldwin, J. E.; Parker, D. W. *J. Org. Chem.* **1987**, *52*, 1475) in which they concluded that the C_1 epimer of MCPA-CoA shows no significant influence on the inactivation of enzyme by MCPA-CoA itself, and, thus, the inactivation is stereospecific. Since the MCPA-CoA used in our study was highly purified, quantitation of the inhibitor concentration was more accurate.

(17) (a) Biellmann, J. F.; Hirth, C. G. *FEBS Lett.* **1970**, *9*, 55. (b) Biellmann, J. F.; Hirth, C. G. *FEBS Lett.* **1970**, *9*, 335. (c) Bucklers, L.; Umani-Ronchi, A.; Retey, J.; Arigoni, D. *Experientia* **1970**, *26*, 931.

(18) The X-ray structure of this enzyme (Kim, J. P.; Wu, J. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 6677) has revealed that there is enough room for the acyl-CoA substrate at either side of the flavin ring. However, a recent stereochemical study showed that H transfer in this enzyme is via the *re* face of the flavin (Manstein, D. J.; Pai, E. F.; Schopfer, L. M.; Massey, V. *Biochemistry* **1986**, *25*, 6807) indicating that only *re* side binding is catalytically productive. This also excludes the possibility that enantiomers of MCPA-CoA could bind to opposite sides of the flavin to trigger the observed flavin modification since the initial binding and the subsequent α-proton abstraction shared by normal catalysis and MCPA-CoA-mediated inactivation should follow the same course.

(19) The additional ring strain imposed by the attached exocyclic double bond in MCPA-CoA and the capability of the product to stabilize the transient radical post ring cleavage may render the ring-opening step more rapid and apparently enzyme independent.

(20) Crane, F. L.; Mii, S.; Hauge, J. G.; Green, D. E.; Beinert, H. *J. Biol. Chem.* **1956**, *218*, 701.

(21) However, a report exists claiming no apoprotein modification during this inactivation (Zeller, H. D.; Ghisla, S. In *Flavins and Flavoproteins*; Edmondson, D. E., McCormick, D. B., Eds.; Walter de Gruyter: Berlin, 1987; p 161). Confirmation of our preliminary results would require the incubation of GACD with properly labeled [^{14}C]MCPA-CoA of high purity.

(22) The flavin-MCPA-CoA adduct, upon the treatment of excess $Fe^{III}CN$ under anaerobic conditions, gave an absorbance maximum around 650 nm which is quite different from the original flavin semiquinone absorption at 560 nm of this protein.[1a] The fact that the inhibitor–flavin adduct can be reoxidized by $Fe^{III}CN$ strongly suggests that this adduct is a reduced flavin species and the observed absorption maximum should be informative in comparison with appropriate model systems. Since the modified flavin is known to be very unstable when isolated,[6,21] study of its spectroelectrochemical properties holds promise for directly deducing the general structural features of the modified cofactor in its intact form at the active site of the inactivated enzyme.

Acknowledgment. This work is supported by National Institute Health Grants GM 25344 (M.T.S.) and GM 35906/GM 40541 (H.W.L.). H.W.L. also thanks the Camille & Henry Dreyfus Foundation for a grant awarded to Distinguished New Faculty in Chemistry and the American Cancer Society for a Junior Faculty Research Award.

Role of Ring Strain and Steric Hindrance in a New Method for the Synthesis of Macrocyclic and High Polymeric Phosphazenes

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At present, the most general synthetic route to poly(organophosphazenes) **1** from small molecule cyclophosphazenes involves the ring-opening polymerization of the cyclic trimer $[NPCl_2]_3$ (**2**) to give the soluble high polymeric reactive intermediate $[NPCl_2]_n$ (**3**), which then functions as a substrate for chlorine atom replacement by a wide variety of organic nucleophiles (route A).[1-6] A second route to phosphazene polymers involves the condensation polymerization of *N*-silylphosphoranimines, a method that provides direct access to a range of alkyl- or arylpolyphosphazenes.[7] However, in principle, an alternative method of synthesis can be visualized that involves the introduction of organic and organometallic side groups at the cyclic trimer level (to give **4**)[8] followed by the ring-opening polymerization of these species (route B). The advantage of this route is that the substitution chemistry would be carried out on small molecule cyclic species rather than on the more sensitive macromolecular intermediates.[9]

Although many halogeno cyclic phosphazenes have been polymerized,[8,10] until now all attempts to polymerize fully substituted cyclic trimers of type **4** to high molecular weight materials have been unsuccessful.[11-13]

Recent synthetic advances have provided access to species in which strain is imparted to the phosphazene ring by means of transannular metallocenyl units.[14,15] Such ring strain is known to enhance the ease of polymerization of cyclophosphazenes that also bear halogen substituents.[16,17] We have now found that ring

(1) Allcock, H. R.; Kugel, R. L. *J. Am. Chem. Soc.* **1965**, *87*, 4216.
(2) Allcock, H. R.; Kugel, R. L.; Valan, K. J. *Inorg. Chem.* **1966**, *5*, 1709.
(3) Allcock, H. R.; Kugel, R. L. *Inorg. Chem.* **1966**, *5*, 1716.
(4) Allcock, H. R. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 147.
(5) Allcock, H. R. *Chem. Eng. News* **1985**, *63*(*11*), 22.
(6) *Inorganic and Organometallic Polymers*; Zeldin, M., Wynne, K. J., Allcock, H. R., Eds.; ACS Symposium Series; American Chemical Society: Washington, DC, 1988; Vol. 360, pp 250–282.
(7) Neilson, R. H.; Wisian-Neilson, P. *Chem. Rev.* **1988**, *88*, 541–562.
(8) Allcock, H. R.; Desorcie, J. L.; Riding, G. H. *Polyhedron* **1985**, *6*, 119.
(9) Allcock, H. R. *Acc. Chem. Res.* **1979**, *12*, 351.
(10) Allcock, H. R.; McDonnell, G. S.; Descorcie, J. L., manuscript in preparation.
(11) Allcock, H. R.; Schmutz, J. L.; Kosydar, K. M. *Macromolecules* **1978**, *11*, 179.
(12) Allcock, H. R.; Patterson, D. B. *Inorg. Chem.* **1977**, *16*, 197.
(13) Allcock, H. R.; Riding, G. H., unpublished results.
(14) Allcock, H. R.; Lavin, K. D.; Riding, G. H.; Susko, P. R.; Whittle, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 2337.
(15) Allcock, H. R.; Lavin, K. D.; Riding, G. H.; Whittle, R. R. *Organometallics* **1984**, *3*, 663.
(16) Allcock, H. R.; Lavin, K. D.; Riding, G. H. *Macromolecules* **1985**, *18*, 1340.
(17) Allcock, H. R.; Riding, G. H.; Lavin, K. D. *Macromolecules* **1987**, *20*, 6.

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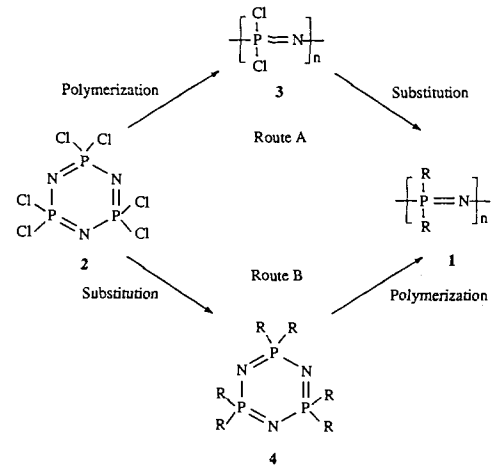
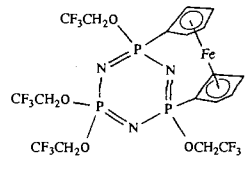
Scheme I

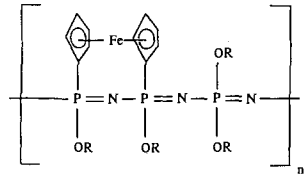


strain induces the ring-opening polymerization of phosphazene trimers that bear no halogen substituents. This is of considerable importance because it had previously been assumed that side group halogen atoms were a prerequisite for access to the ring-opening polymerization mechanism.

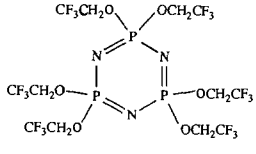
When the ferrocenylphosphazene **5**[18] was heated in the molten



5



6 R = CH_2CF_3

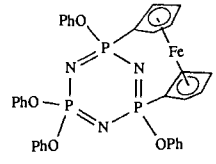


7

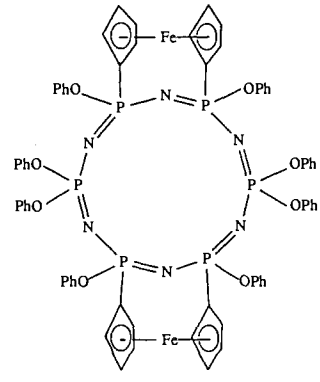
state at 250 °C in an evacuated Pyrex glass tube, virtually no change was detectable by ^{31}P NMR after 14 days.[19,20] However, when **5** was heated with a catalytic (1%) amount of **2** for 8 h under the same conditions, a marked increase in viscosity was apparent. Dissolution in THF followed by ^{31}P NMR analysis showed that the products consisted of a mixture of the poly(ferrocenylphosphazene) **6**[21] and unreacted **5**. Separation was achieved by precipitation from THF into hexanes three times, affording yellow polymeric **6** (yield, 35%). The molecular weight of **6** (by gel permeation chromatography (GPC) analysis) was 9.5×10^5.

The ring-opening polymerization of **5** in the presence of **2** is in marked contrast to the behavior of **7** in which the strain-imparting transannular ferrocenyl unit is absent.[22] Heating of **7** at 250 °C in either the presence or absence of a catalytic quantity of **2** leads only to ring–ring equilibration to higher cyclic species; no high polymer is found.[11,13] The observation that ring-opening polymerization of **5** requires the presence of catalytic amounts of **2** is consistent with a mechanism[23-25] for the *initiation* step of phosphazene polymerization which involves heterolysis of a phosphorus–chlorine bond. However, the need for only a *catalytic* quantity of **2** clearly indicates that the presence of phosphorus–chlorine bonds is not necessary for a cyclic trimer to participate in the *propagation* step.

We have also studied the effect of heating the phenoxy-substituted ferrocenylphosphazene **8**[26] under the same conditions as described for **5**. When **8** was heated at 250 °C in the presence of 1% **2** for 14 days, ^{31}P NMR showed that the major product formed was the cyclic hexamer **9**[27,28] (yield, 33%). The amount of high polymer formed was below the limit of detectability of the NMR analysis (ca 5%).



8



9

The lower polymerizability of **8** compared to **5** may be attributed to the presence of the more sterically demanding phenoxy substituents. Intramolecular steric repulsions are more severe in linear poly(organophosphazenes) than in their cyclic oligomeric counterparts.[23,24] Bulkier substituents would therefore be expected to lead to a destabilization of the high polymer relative to small or medium molecular weight rings. Interestingly, the formation of **9** from **8** as the major cyclic oligomeric product represents the first example of ring–ring equilibration of a cyclotriphosphazene almost exclusively[29] to a cyclic hexamer: usually a range of cyclic species is formed with the cyclic tetramer predominating. This observation is strongly supportive of the results of recent studies[10] which indicate that ring–ring equilibration reactions involving cyclotriphosphazenes proceed via an initial coupling of two trimer molecules to give a cyclic hexamer.

This use of transannular ring strain to favor polymerization of a cyclic phosphazene may be of wider significance, since

(18) Compound **5** was prepared by refluxing a dioxane solution of $[N_3P_3F_4(\eta\text{-}C_5H_4)_2Fe]$[16] and 8 equiv of $Na[OCH_2CF_3]$ (prepared from Na and excess trifluoroethanol in dioxane) for 24 h. Purification by column chromatography followed by recrystallization from CH_2Cl_2–hexane at −20 °C gave **5** as orange-yellow crystals (yield 89%). For characterization see ref 16.

(19) ^{31}P and ^1H NMR spectra were recorded in $CDCl_3$ on either a Bruker WP-360 or a JEOL FX-90 Q spectrometer. Chemical shifts are relative to aqueous 85% H_3PO_4 (^{31}P) or TMS (^1H).

(20) A small amount (ca. 3%) of other products is formed which consists mainly of the cyclic hexamer $[N_6P_6(OCH_2CF_3)_8\{(\eta\text{-}C_5H_4)_2Fe\}_2]$: ^{31}P NMR δ 32.7 d, 13.9 t, $^2J_{PNP}$ = 46 Hz; MS theory 1430, found 1430.

(21) Polymer **6** has been previously prepared via the thermal ring-opening polymerization of $[N_3P_3F_4(\eta\text{-}C_5H_4)_2Fe]$ followed by treatment of the resulting polymer with sodium trifluoroethoxide.[16]

(22) The X-ray crystal structure of **5** has been determined. The presence of ring strain is indicated by the nonplanarity, bond angles, and bond lengths of the phosphazene ring: Allcock, H. R.; Dodge, J. A.; Manners, I.; Parvez, M.; Riding, G. H., unpublished results.

(23) Allcock, H. R. *Phosphorus–Nitrogen Compounds*; Academic Press: New York, 1972.

(24) Allcock, H. R. *Chem. Rev.* **1972**, *72*, 315.

(25) Allcock, H. R.; Gardner, J. E.; Smeltz, K. M. *Macromolecules* **1975**, *8*, 36.

(26) Compound **8** was prepared by heating a mixture of $[N_3P_3F_4(\eta\text{-}C_5H_4)_2Fe]$[16] and 10 equiv of Na[OPh] in dioxane at 200 °C in a stainless steel high-pressure reactor for 7 days. **NOTE**: Although this reaction has been carried out many times without incident, on one occasion an explosive build up of pressure occurred; extreme caution should therefore be exercised. Purification by column chromatography and recrystallization from CH_2Cl_2–hexane at −20 °C gave **8** as yellow-orange crystals (yield 70%). For **8**: ^{31}P NMR δ 35.3 d, 11.4 t, $^2J_{PNP}$ = 60 Hz; ^1H NMR δ 7.57, 7.49, 7.26, 7.10, 6.87, all m (20 H), 4.91 m (2 H), 4.87 m (2 H), 4.66 m (2 H), 4.31 m (2 H); MS theory 691, found 691.

(27) Compound **9** was separated from unreacted **8** by column chromatography. Multiple recrystallization from THF–diethyl ether afforded **9** as a yellow-orange solid. For **9**: ^{31}P NMR δ 27.5 d, 5.9 t, $^2J_{PNP}$ = 48 Hz; ^1H NMR δ 7.13, 7.04, 6.86 all m (40 H), 4.36, 4.26 both m (16 H); MS theory 1382, found 1382.

(28) Heating **8** alone at 250 °C for 14 days led to a lower conversion to **9** (10%).

(29) The fast atom bombardment (FAB) mass spectrum of the product formed on heating **8** with 1% **2** also showed evidence for the formation of small amounts of the cyclic nonamer $[N_9P_9(OPh)_{12}\{(\eta\text{-}C_5H_4)_2Fe\}_3]$ and cyclic dodecamer $[N_{12}P_{12}(OPh)_{16}\{(\eta\text{-}C_5H_4)_2Fe\}_4]$.

considerable interest exists in the formation of polymers from other ring systems that have so far resisted polymerization.

Acknowledgment. We thank the U.S. Army Research Office for financial support and A. A. Dembek for obtaining high field ^{31}P and ^{1}H NMR spectra.

Oxidative Decarboxylation-Deoxygenation of 3-Hydroxycarboxylic Acids via Vanadium(V) Complexes: A New Route to Tri- and Tetrasubstituted Olefins

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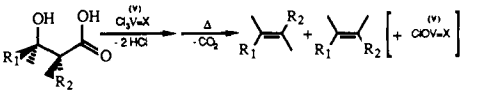
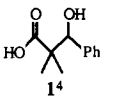
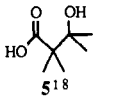
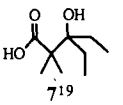
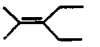
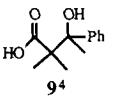
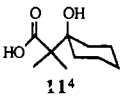
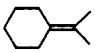
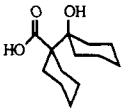
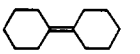
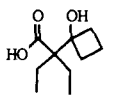
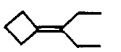
Oxidative decarboxylation of carboxylic acids is a "classical" procedure in synthetic organic chemistry which is well known in scope and mechanism. Surprisingly, whereas 2-hydroxycarboxylic acids have been studied in detail,[1] no similar investigations of 3-hydroxycarboxylic acids have appeared although these compounds are readily prepared by "aldol-type" condensation procedures.[2] We have now found that 3-hydroxycarboxylic acids readily undergo not only oxidative decarboxylation but also an unprecedented deoxygenation to yield olefins in the presence of an oxophilic metal species. This chemistry thus represents a direct route from aldol products to olefins.

Vanadium(V) is active for oxidative decarboxylation of 2-hydroxycarboxylic acids, but it is usually used in perchloric or sulfuric acid media, conditions which limit its scope of utility.[1] We find that readily available $VOCl_3$ is a convenient alternative source of reactive V(V) which can be used in the absence of added acid and which is comparable to aqueous V(V) compounds in its ability to oxidize carboxylic acids.[3] When $VOCl_3$ (0.5 mmol) was added to a suspension of 2,2-dimethyl-3-hydroxy-3-phenylpropanoic acid (**1**)[4] (0.5 mmol) in anhydrous chlorobenzene (5 mL) at room temperature, a homogeneous orange-red solution was obtained. Analysis by ^{1}H NMR and IR suggested the formation of a chelated vanadyl carboxylate.[5] When the solution of the adduct was heated to reflux, it became dark greenish-brown. After 30 min the reaction mixture was cooled, a few drops of water were added, and evaporative distillation yielded 2-methyl-1-phenyl-1-propene (**2**) (61%) and benzaldehyde (37%). No 2-methylpropanoic acid was produced; therefore, benzaldehyde is not formed by a "retro-aldol" reaction. Double bond isomerization products were observed in decarboxylation of several acids such as **3**, **7**, or **9** (see Table I). Such double bond isomerization could result from acid catalysis ($VOCl_3$ is a Lewis acid, and 2 equiv of HCl are generated overall in olefin formation). For example, treating 2-ethyl-3-hydroxy-2-methyl-3-phenylpropanoic acid (**3**) or the pure erythro diastereomer (**3a**) with $VOCl_3$ gave (*E*)- and (*Z*)-2-methyl-1-phenyl-1-butene (**4E** (26%) and **4Z** (14%)) as well as double bond isomers (27%); however, when **3a** was reacted with $VOCl_3$ in the presence of 1 equiv of Proton Sponge, only **4E** (27%) and **4Z** (20%) were formed. (Proton Sponge forms a complex with $VOCl_3$ which is only slightly soluble in chlorobenzene; longer reaction times are also needed to effect olefin synthesis when it is used.) Therefore, *E*/*Z* product formation, in contrast to double bond isomerization, need not be caused by proton catalysis.

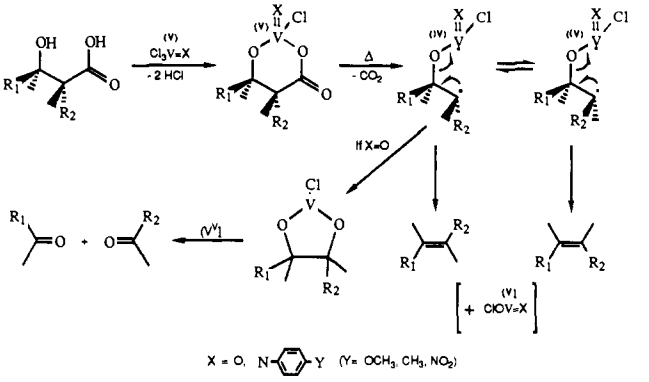
Table I



X	acid	conditions[a]	olefins[b]
O	 **1**[4]	+1 equiv of Proton Sponge 70 h	 **2** (73%)
$NC_6H_4CH_3$	**1**	24 h	**2** (72%)
$NC_6H_4CH_3$	 **5**[18]	19 h	 **6** (89%)
$NC_6H_4CH_3$	 **7**[19]	1,2,4-$C_6H_3Cl_3$; +1 equiv of Proton Sponge; 48 h, 132-4 °C	 **8** (80%)
$NC_6H_4CH_3$	 **9**[4]	+1 equiv of Proton Sponge; 49 h	 **10**[4] (>95%)
$NC_6H_4CH_3$	 **11**[4]	1,2,4-$C_6H_3Cl_3$; +1 equiv of Proton Sponge 70 h, 160 °C	 **12**[4] (77%)
$NC_6H_4CH_3$	 **13**[10b]	+1 equiv of Proton Sponge 68 h	 **14**[10b] (48%)[20]
$NC_6H_4CH_3$	 **15**[21]	+1 equiv of Proton Sponge 53 h	 **16**[21] (88%)

[a] Reactions were run in chlorobenzene unless otherwise stated. [b] Yields were determined by gas chromatography; all products were confirmed by GC/MS analysis comparison with actual samples.

Scheme I



(1) For examples of oxidative decarboxylation of 2-hydroxycarboxylic acids with V(V), see: (a) Jones, J. R.; Waters, W. A.; Littler, J. S. *J. Chem. Soc., London* **1961**, 630-2. (b) Mehrotra, R. N. *J. Chem. Soc. B* **1968**, 642-4. (c) Paul, S. D.; Pradhan, D. G. *Indian J. Chem.* **1972**, *10*, 562-3. (d) Virtanen, P. O. I.; Karppinen, S. *Finn. Chem. Lett.* **1984**, 34-7. (e) Kalidoss, P.; Srinivasan, V. S. *J. Chem. Soc., Dalton Trans.* **1984**, 2631-5. (f) Micera, G.; Deiana, S.; Dessi, A.; Pusino, A.; Gessa, C. *Inorg. Chim. Acta* **1986**, *120*, 49-51.

(2) For examples of aldol and "aldol-type" condensation reactions, see: (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. Stereoselective Aldol Condensations. In *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Wilen, S. H., Eds.; John Wiley and Sons: New York, 1982; Vol. 13; pp 1-115. (b) Mukaiyama, T. *Org. React.* **1982**, *28*, 203-331. (c) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066-81. (d) Heathcock, C. H.; Jarvi, E. T. *Tetrahedron Lett.* **1982**, *23*, 2825-8. (e) Davies, S. G.; Dordor-Hedgecock, I. M.; Warner, P. *Tetrahedron Lett.* **1985**, *26*, 2125-8.

(3) Vanadium oxytrichloride (1.5 mmol) was added by syringe to a suspension of D-mandelic acid (1.5 mmol) in anhydrous chlorobenzene (5 mL), and the resultant solution was heated to reflux. Benzaldehyde was obtained (50%, 2 h).

(4) Adam, W.; Baeza, J.; Liu, J.-C. *J. Am. Chem. Soc.* **1972**, *94*, 2000-6.

(5) 2,2-Dimethyl-3-hydroxy-3-phenylpropanoic acid (**1**): δ 4.68 (s, 1 H, C*H*Ph); vanadyl carboxylate, δ 7.36 (s, 1 H, C*H*Ph).

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