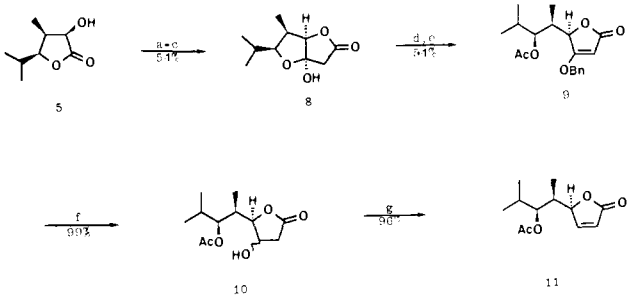
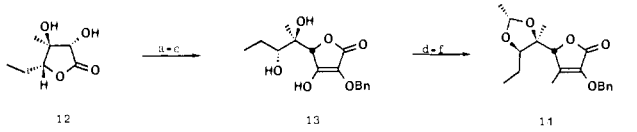
water by treatment with methanesulfonyl chloride and triethylamine then completed the construction of butenolide **11** (cf. **1**).



(a) Me_3SiNMe_2, THF; (b) $LiOC(OEt)CH_2$, THF, -78 °C; (c) K_2CO_3, MeOH; (d) $PhCH_2Br$, Na_2CO_3, Bu_4NBr, CH_2Cl_2/H_2O; (e) Ac_2O, Et_3N, DMAP; (f) 5% Rh/alumina, H_2, MeOH; (g) MsCl, Et_3N.

Conversion of **12** to **14** illustrates the "hydroxybutenolide elaboration". Protection of (+)-dihydroxyfuranone **12**[14] as the bis(trimethylsilyl) ether, addition of the anion of ethyl (benzyloxy)acetate,[15] and basic methanolysis gave tetronic acid **13**. The 4-methyl group was introduced by phase-transfer phosphorylation (diphenyl chlorophosphate) of the ethylidene acetal of **13**, followed by nickel acetylacetonate catalyzed coupling with dimethylzinc.[16] The resulting 3-hydroxybutenolide benzyl ether **14** is the operational equivalent of **4**.

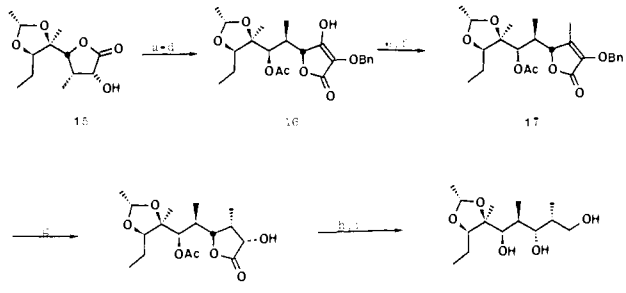


(a) Me_3SiCl, imidazole, DMF; (b) LiHMDS, $EtOC(O)CH_2OCH_2Ph$, THF, -50 °C; (c) K_2CO_3, MeOH; (d) acetal, CSA, CH_2Cl_2; (e) $(PhO)_2P(O)Cl$, Na_2CO_3, CH_2Cl_2/H_2O, Bu_4NBr; (f) Me_2Zn, $Ni(AcAc)_2$ Et_2O.

The successful conversions of **5** to **11** and of **12** to **14** complete the second stage of the general method. Every successive cycle produces butenolides which are identical with **1** or **4** except for the detailed structure of the side chains, and the method should therefore be generally applicable.

Dihydroxyfuranone **12** was selected to illustrate the hydroxybutenolide elaboration because one more cycle, starting with butenolide **14**, leads to the C_7-C_{13} fragment of erythronolide A. Hydrogenation of **14** with rhodium on alumina removed the benzyl ether and saturated the double bond to give the 3-hydroxy-4-methyl-2-furanone **15**: mp 101-102 °C, $[\alpha]_D^{24}$ -33° (*c* 0.42, MeOH). A second hydroxybutenolide homologation sequence was applied to furanone **15**. Protection, butenolide elaboration, and hydrogenation, along the lines described for dihydroxyfuranone **12**, gave the 3-hydroxy-4-methyl-2-furanone **18**: mp 126-130 °C, $[\alpha]_D^{24}$ + 55° (*c* 0.32, MeOH). The hydroxybutenolide homologation and reduction sequences starting with dihydroxyfuranone **12** and with hydroxyfuranone **15** proceeded in 64% and 40% overall yields, respectively.

Further elaboration to erythronolide A, which is described in the following communication[17] in this issue, required triol **19** This was readily available from furanone **18** by lithium aluminum



(a) Me_3SiNMe_2, THF; (b) LiHMDS, $EtOC(O)CH_2OCH_2Ph$, THF, -50 °C; (c) K_2CO_3, MeOH; (d) Ac_2O, Et_3N, DMAP, CH_2Cl_2; (e) $(PhO)_2P(O)Cl$, Na_2CO_3, CH_2Cl_2/H_2O, Bu_4NBr; (f) Me_2Zn, $Ni(acac)_2$, Et_2O; (g) 5% Rh/alumina, H_2, MeOH; (h) LAH, THF, HOAc, H_2O, $NaIO_4$; (i) $NaBH_4$, EtOH.

hydride reduction, in situ sodium periodate oxidation, and sodium borohydride reduction. The resulting triol **19** has the correct stereochemistry of the C_7-C_{13} fragment of erythronolide A.[17]

Acknowledgment. We thank the National Institutes of Health and the National Science Foundation for the financial support of this work.

Supplementary Material Available: Experimental details for an iterative butenolide construction of polypropionate chains (30 pages). Ordering information is given on any current masthead page.

Concise Total Synthesis of (+)-(9*S*)-Dihydroerythronolide A

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Received August 12, 1986

We wish to report a total synthesis of (+)-(9*S*)-dihydroerythronolide A (**1**),[1] which also constitutes a formal total synthesis of erythromycin A (**2**).[2,3] The synthesis illustrates the usefulness

† National Science Foundation predoctoral fellow, 1981-1984.

(1) For the preparation of **1** [(+)-(9*S*)-9-deoxo-9-hydroxyerythronolide A] from erythromycin A, see: Jones, P. H.; Rowley, E. K. *J. Org. Chem.* **1968**, *33*, 665. Also see ref 2d, footnote 4.

(2) (a) For recent reviews of synthetic work in this area, see: Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569. Masamune, S.; McCarthy, P. A. In *Macrolide Antibiotics, Chemistry, Biology and Practice*; Academic: New York, 1984; Chapter 4. Total synthetic work directed toward erythronolide A and erythromycin: (b) Corey, E. J.; Hopkins, P. B.; Kim, S.; Yoo, S.; Nambiar, K. P.; Falck, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 7131. (c) Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B.-W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chenevert, R. B.; Fliri, A.; Frobel, K.; Gais, H.-J.; Garratt, D. G.; Hayakawa, K.; Heggei, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R. S.; Ong, B. S.; Press, J. B.; Rajan Babu, T. V.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, H. N.-C. *J. Am. Chem. Soc.* **1981**, *103*, 3210. (d) Woodward, R. B. et al. *J. Am. Chem. Soc.* **1981**, *103*, 3213. (e) Woodward, R. B. et al. *J. Am. Chem. Soc.* **1981**, *103*, 3215. (f) Hanessian, R.; Rancourt, G. *Can. J. Chem.* **1977**, *55*, 1111. (g) Hanessian, R.; Rancourt, G.; Guindon, Y. *Can. J. Chem.* **1978**, *56*, 1843. (h) Stork, G.; Paterson, I.; Lee, F. K. C. *J. Am. Chem. Soc.* **1982**, *104*, 4686. (i) Heathcock, C. H.; Hagan, J. P.; Young, S. D.; Pilli, R.; Bai, D.-L.; Märki, H.-P.; Kees, K.; Badertscher, U. *Chem. Scr.* **1985**, *25*, 39. (j) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pilli, R.; Badertscher, U. *J. Org. Chem.* **1985**, *50*, 2095. (k) Bernet, B.; Bishop, P. M.; Caron, M.; Kawamata, T.; Roy, B. L.; Ruest, L.; Sauve, G.; Soucy, P.; Deslongchamps, P. *Can. J. Chem.* **1985**, *63*, 2810. (l) Bernet, B.; Bishop, P. M.; Caron, M.; Kawamata, T.; Roy, B. L.; Ruest, L.; Sauve, G.; Soucy, P.; Deslongchamps, P. *Can. J. Chem.* **1985**, *63*, 2814. (m) Bernet, B.; Bishop, P. M.; Caron, M.; Kawamata, T.; Roy, B. L.; Ruest, L.; Sauve, G.; Soucy, P.; Deslongchamps, P. *Can. J. Chem.* **1985**, *63*, 2818.

(14) Dihydroxyfuranone **12** was prepared in three steps and 43% overall yield from ethyl (4*R*)-4-hydroxy-2-hexynoate (available in 80% ee by Midland's procedure: Midland, M. M.; Tramontano, A. *Tetrahedron Lett.* **1980**, 3549) by the previously described method (Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, *24*, 3951). Dihydroxyfuranone **12** was recrystallized to optical purity: mp 76-77.5 °C, $[\alpha]_D^{22}$ +84.6° (*c* 1.36, methanol).

(15) Meinwald, J.; Dugan, A. J.; Adams, M. A. *Tetrahedron Lett.* **1978**, 4327.

(16) For a related transformation, see: Sum, F.-W.; Weiler, L. *Can. J. Chem.* **1979**, *61*, 2530. For a $Ni(acac)_2$-catalyzed conjugate addition of dimethylzinc to an unsaturated ketone, see: Greene, A. E.; Langard, J.-P.; Luche, J.-L.; Petrier, C. *J. Org. Chem.* **1984**, *40*, 931.

(17) Stork, G.; Rychnovsky, S. D., following paper in this issue.

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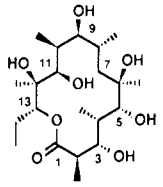
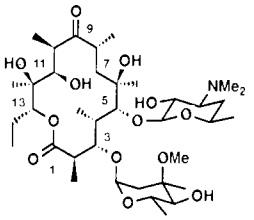
of the butenolide template route to "polypropionate" sequences.[4]



1



2

The route we selected involves using a C_7–C_{13} dihydroerythronolide A fragment with the 9*S* configuration.[4] The choice of the 9*S* configuration follows from the work of the Woodward group, who showed that cyclic 9,11 protecting groups lead to conformations that are much more favorable for the recyclization of the seco acid from **1** if the configuration of the 9-hydroxyl is 9*S* rather than 9*R*. A further requirement for efficient cyclization became apparent in the course of our own work: The solution conformation[5] of the C_8–C_{11} portion of (9*S*)-dihydroerythronolide A with a 9,11 cyclic protecting group is shown in Figure 1. A 1,3 diaxial interaction is present between R_2 and C_8, so that when R_2 is an alkyl group, the resulting severe interaction should make cyclization of the seco acid very unfavorable. In accord with this prediction, we found that a seco acid with a 9,11 cyclic *ketal* (R_1 and R_2 = methyl)[6] failed to cyclize.[7] We were similarly unable to cyclize a related 9,11 cyclic *acetal* in which R_1 = H and R_2 = methyl ("A-methylacetal").[8] Only those cyclic acetals in which R_1 = aryl or alkyl and R_2 = H ("B-methylacetals") can be expected to cyclize efficiently.[9]

With these facts in mind, the goal became the conversion of triol **3** to the B-methylacetal (cf. **5**). Triol **3**, prepared via the butenolide template method,[4] was first converted to the primary alkyl phenyl sulfide which, under acid-catalyzed acetalization conditions (Scheme I), largely gave, not unexpectedly, the more stable but undesirable A-methylacetal **4** (4:5 = 8:1).[10] A stereospecific construction of the required less stable B-methylacetal **5** was, therefore, required. This was achieved via the orthoacetate **6**, easily obtained from triol **3**. Eliel's classical demonstration of stereoelectronic control in the reduction of cyclic orthoacetates[11] suggested that treatment of the orthoacetate **6** with diborane should cleave the less hindered[12] C_7 oxygen–carbon bond with

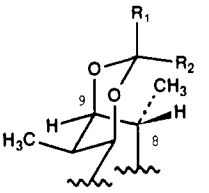
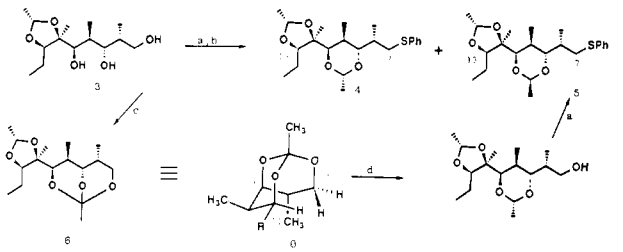


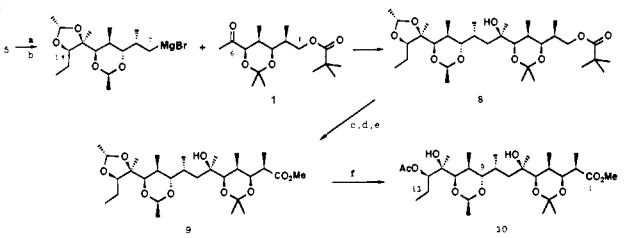
Figure 1.

Scheme I[a]



[a] (a) $(PhS)_2$, Bu_3P, CH_3CN; (b) $CH_3CH(OEt)_2$, CSA, CH_2Cl_2; (c) $CH_3C(OEt)_3$, PPTS; (d) BH_3, THF.

Scheme II[a]



[a] (a) 4,4′-di-*tert*-butylbiphenyl, Li, THF; (b) $MgBr_2$, Et_2O; (c) CH_3Li, Et_2O; (d) PDC, DMF; (e) Me_2SO_4, Na_2CO_3, Bu_4NBR; (f) O_3, CH_2Cl_2.

retention of configuration at the ortho ester carbon atom. This expectation was realized: reduction of **6** with diborane gave the B-methylacetal precursor of **5** as a single isomer. The primary alcohol was subsequently converted to the phenyl sulfide **5**, identical with the minor isomer from direct acetal formation. The necessary B-methylacetal **5** was thus prepared stereospecifically, in three steps and 72% overall yield, from triol **3**.

We were now ready to add the C_7–C_{13} fragment represented by the phenyl sulfide **5** to the C_1–C_6 ketone **7** (Scheme II).[13] We had previously[2h] effected a related coupling by adding a C_7 sulfoxide anion to a C_1–C_6 ketone. The anticipated chelation control had indeed favored the desired epimer (5:1) at the newly formed C_6 center. Since there was good reason to expect that better chelation control in the desired direction would result from the reaction of a grignard-type reagent[14] rather than of a sulfoxide anion, we devised a method which should be especially useful with the usually troublesome polyoxygenated systems: The phenyl sulfide **5** was converted to the corresponding alkyllithium reagent by addition to 3 equiv of LiDBB (lithium 4,4′-di-*tert*-butylbiphenylide)[15] in THF at −78 °C. Addition of anhydrous magnesium bromide, followed by addition of ketone **7**, now gave the required coupled product **8**, apparently *as a single isomer*, in 73% yield.

The coupled product **8** was now elaborated to the seco acid **11**. Deprotection of the primary alcohol, PDC oxidation, and in situ methylation gave methyl ester **9** in 82% yield. Selective depro-

(3) Woodward et al. have reported the conversion of (9*S*)-dihydroerythronolide A to erythromycin A by way of **1**; see ref 2e (footnote 22).

(4) See structure **19** in the preceding paper in this issue.

(5) (a) Celmer, W. D. *Pure Appl. Chem.* **1971**, *28*, 413. (b) Egan, S.; Perun, T. J.; Martin, J. R.; Mitscher, L. A. *Tetrahedron* **1973**, *29*, 2525.

(6) The 3,5/9,11-bisacetonide of **1** was prepared (ref 2l) and hydrolyzed to the corresponding seco acid. An indirect hydrolysis procedure proved to be much more effective than the previously reported lactone hydrolysis conditions (ref 2d): The lactone was heated at 150 °C in a sealed tube for 3 h with hydrazine containing 10% water. Aqueous workup gave the acyl hydrazide, which was oxidized with NaOCl solution (bleach) in aqueous THF to give a 93% yield of the desired seco acid.

(7) Under the conditions of: Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394.

(8) The 9,11-acetaldehyde A-acetal of the 3,5-isopropylidene seco acid of **1** was prepared from **4** by a procedure analogous to that reported here for the conversion of **5** to **11**.

(9) As a corollary, type B acetals of the 9,11-glycol system can easily be made from (9*S*)-dihydroerythronolide A because, in contrast to the situation with the corresponding seco acids, they are more stable than the A isomers. Thus, the 3,5/9,11-bismesitaldehyde acetal obtained from **1** by Woodward et al. (ref 2d) is a 9,11-acetal of the B type and can, therefore, be hydrolyzed to a seco acid with a B type acetal. Although this method of preparation is obviously irrelevant to our synthetic route, it served to confirm our anticipations since we found that the seco acid from Woodward's diacetal cyclizes efficiently under Keck's conditions (ref 7).

(10) Assignment of acetal stereochemistry is based on correlation of **5** with the acetal **12** prepared from naturally derived **1**. The proton NMR spectrum of **5** is consistent with this assignment. When the C_8 proton (2.37 ppm, m) was irradiated, the C_9 proton (3.32 ppm, J = 10.2 Hz) collapsed to a singlet, so $J(8,9)$ = 10.2 Hz and $J(9,10)$ = 0 Hz, in agreement with the conformation depicted in Figure 1.

(11) Eliel, E. L.; Nader, F. *J. Am. Chem. Soc.* **1970**, *92*, 3045.

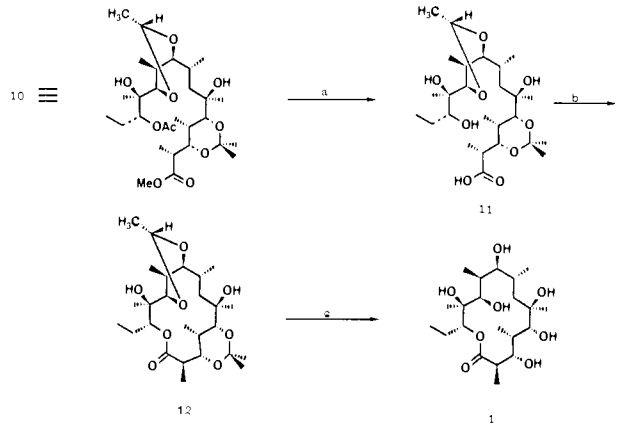
(12) Fleming, B.; Bolker, H. I. *Can. J. Chem.* **1974**, *52*, 888.

(13) Ketone **7** was prepared by the procedure described in ref 2h, except for the substitution of a pivaloyl protecting group for a *tert*-butyldiphenylsilyl ether protecting group.

(14) Still, W. C.; McDonald, J. H., III. *Tetrahedron Lett.* **1980**, 1031.

(15) (a) Rücker, C. *Tetrahedron Lett.* **1984**, 4349. (b) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924. (c) Screttas, C. G.; Screttas, M. M. *J. Org. Chem.* **1978**, *43*, 1064. (d) Cohen, T.; Matz, J. R. *J. Am. Chem. Soc.* **1980**, *102*, 6900.

Scheme III[a]



[a] (a) KOH, aqueous MeOH; (b) see text; (c) HCl, aqueous MeOH, 50 °C.

tection of the five-membered acetal was now required to set the stage for the final cyclization. This was accomplished by selective ozonolysis of the methyl ester **9** with ozone,[16,17] which gave the monoacetate **10** in 75% yield. Subsequent hydrolysis gave the seco acid **11** in quantitative yield.

The simple protection and deprotection sequence described here greatly simplified the selective protection problems which had to be solved in the construction of **11**. Cyclization of seco acid **11** was achieved by using the conditions recently reported by Keck (Scheme III).[7] Seco acid **11** was added to a refluxing chloroform solution of dicyclohexylcarbodiimide, 4-(dimethylamino)pyridine, and its trifluoroacetate salt, via a syringe pump, to give macrocyclic lactone **12**, which was isolated in 64% yield. It was shown to be identical with an authentic sample, prepared from natural erythromycin A,[18] by ^{1}H NMR, IR, MS, TLC in two different solvent systems, and optical rotation ($[\alpha]^{25}_{265}$ +54° (*c* 0.2, methanol). Treatment of macrocyclic lactone **12** with acidic methanol removed (56%) the protecting groups to give (9*S*)-dihydroerythronolide A, identical with an authentic sample[1] by ^{1}H NMR, IR, and TLC.

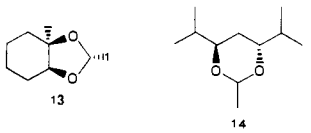
The synthesis we have just described leads in 26 steps and 1.3% overall yield[19] from optically pure ethyl (4*R*)-4-hydroxy-2-hexynoate to (9*S*)-dihydroerythronolide A. Since the latter has previously been converted to erythromycin A,[3] this work also constitutes a formal total synthesis of antibiotic.

Acknowledgment. We thank the National Institutes of Health and the National Science Foundation for their financial support of this work.

Supplementary Material Available: Experimental details for the synthesis of (+)-(9*S*)-dihydroerythronolide A (23 pages). Ordering information is given on any current masthead page.

(16) Deslongchamps, P.; Atlani, P.; Frehel, D.; Malaval, A.; Moreau, C. *Can. J. Chem.* **1974**, *52*, 3651. Deslongchamps, P.; Moreau, C. *Can. J. Chem.* **1971**, *49*, 2465.

(17) (a) The ozonolysis reactions were run in a Rubin apparatus by adding a large excess of ozone-saturated dichloromethane to a −78 °C solution of the acetal and quenching with excess dimethyl sulfide after the alloted time. (b) Rubin, M. *J. Chem. Educ.* **1964**, *41*, 388. Under these conditions, the five-membered acetal **13** showed 90% oxidation after 3 min but acetal **14** showed only 5% oxidation after 15 min.



(18) The preparation of **12** from naturally derived **1** (ref 1) is described in the supplementary material.

(19) Previous syntheses have led to ~0.01 to 0.04% overall yields.

The First Magic Angle Spinning NMR Spectrum of a Captive Intermediate: Direct Observation of a Singlet Ground State Biradical, 3,4-Dimethylenefuran

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Immobilization in matrices or rigid glasses, in combination with modern spectroscopic methods, has become an invaluable technique for the study of reactive intermediates. This has been particularly useful in the study of paramagnetic species such as radicals and triplet carbenes, as they can be readily observed by ESR spectroscopy in rigid glasses.[1-3] On the other hand, characterization of singlet ground state intermediates under these conditions has been difficult. Most investigations have relied on solution-phase chemical trapping, structurally nonspecific time-resolved optical spectroscopy, and negative results from ESR.[4,5] The study of important reactive intermediates such as singlet carbenes,[5] biradicals,[4] and silylenes[6] has been impeded by this lack of suitable spectroscopic tools.

This paper reports on the first solid-state ^{13}C NMR study of a *captive intermediate*, i.e., an intermediate whose persistence requires matrix isolation. The species is 3,4-dimethylenefuran (**1**), a π-conjugated non-Kekulé biradical which has been tentatively assigned a singlet ground state on the basis of previous experimental[4] and computational[12] criteria. Given the strong correlation between ^{13}C chemical shifts and structure, matrix-isolation ^{13}C NMR studies of ESR-silent intermediates such as **1** should be especially informative. The feasibility of matrix-isolation NMR has been previously demonstrated in a variety of circumstances.[7-10] The most promising technique is the combination of cross polarization with magic angle spinning (CP/MAS) as it avoids the problems with overlap of powder patterns encountered in static measurements.[8,9] Yannoni, Reisenauer, and Maier[10] have shown that ^{13}C CP/MAS NMR can be used to follow photochemistry at low temperatures in rigid glasses. While these preliminary experiments have been encouraging, no solid-state NMR studies have yet been reported on a captive intermediate due to the difficulties encountered in combining CP/MAS with matrix-isolation conditions. As Yannoni and co-workers[10] point out, their particular methodology is not applicable to most matrix problems. The species to be studied, including the precursor, must be sufficiently stable to permit exposure of the matrix to the atmosphere as their samples are not sealed, and irradiation is difficult as light can only enter the top of the sample cell. This also makes it difficult to use any matrices that must be deposited onto a cold surface as when gas-phase pyrolysis of precursors is used.

In order to make matrix-isolation NMR more generally applicable, CP/MAS hardware was specifically designed in this work

(1) Perutz, R. N. *Chem. Rev.* **1985**, *85*, 77–128.
(2) McGlynn, S. P.; Azumi, T.; Kinoshita, M. *Molecular Spectroscopy of the Triplet State*; Prentice-Hall: Englewood Cliffs, NJ, 1969; pp 369–402.
(3) Weltner, W., Jr. *Magnetic Atoms and Molecules*; Van Nostrand Reinhold: New York, 1983.
(4) Stone, K. J.; Greenberg, M. M.; Goodman, J. L.; Peters, K. S.; Berson, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 8088–8089.
(5) Lapin, S. C.; Schuster, G. B. *J. Am. Chem. Soc.* **1985**, *107*, 4243–4248.
(6) (a) Gaspar, P. P. *React. Intermed. (Plenum)* **1981**, *2*, 335–387. (b) Nefedov, O. M.; Kolesnikov, S. P.; Ioffe, A. I. *J. Organomet. Chem. Libr.* **1981**, *5*; *Organomet. Chem. Rev.*
(7) Kohl, J. E.; Semack, M. G.; White D. *J. Chem. Phys.* **1978**, *69*, 5378–5385.
(8) Zilm, K. W.; Grant, D. M. *J. Am. Chem. Soc.* **1981**, *103*, 2913–2922.
(9) Zilm, K. W.; Conlin, R. T.; Grant, D. M.; Michl, J. *J. Am. Chem. Soc.* **1978**, *100*, 8083.
(10) Yannoni, C. S.; Reisenauer, H. P.; Maier, G. *J. Am. Chem. Soc.* **1983**, *105*, 6181–6182.
(11) Gay, I. D. *J. Magn. Reson.* **1984**, *58*, 413–420.
(12) (a) Lahti, P. M.; Rossi, A. R.; Berson, J. A. *J. Am. Chem. Soc.* **1985**, *107*, 2273. (b) Lahti, P. M. Ph.D. Dissertation, Yale University, New Haven, CT. (c) Du, P.; Hrovat, D. A.; Borden, W. T. *J. Am. Chem. Soc.* **1986**, *108*, 8086–8087.

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