

Figure 2. Frozen aqueous X-band EPR spectrum of $\text{Ni}^{\text{III}}(^{13}\text{C})_6^{3-}$ prepared from 1.0×10^{-3} M $\text{Ni}^{\text{III}}(\text{CN})_4(\text{H}_2\text{O})_2^-$ and 7.4×10^{-2} M $^{13}\text{C}^-$; pH 10.5, $\mu = 0.10$ NaClO₄: (a) -190 °C; (b) -35 °C.

The frozen EPR spectrum of $\text{Ni}^{\text{III}}(\text{CN})_4(\text{H}_2\text{O})_2^-$ is similar to the spectra of nickel(III) peptide complexes where $g_{xx} \approx g_{yy} > g_{zz}$, and a tetragonally elongated geometry is assigned.^{11,14} The g values (Table I) agree with those obtained by γ -irradiation of $\text{Ni}(\text{CN})_4^{2-}$ in frozen aqueous solution.³ Isotopically enriched ^{61}Ni ($I = 3/2$) shows a quartet splitting in the g_{\parallel} region (Figure 1a), but there is no observable splitting in the g_{\perp} region. The axial spin coupling constant is 43.2 G. Thus, the unpaired electron is associated primarily with the nickel atom. This spin coupling constant is roughly twice the value for nickel(III) in biological molecules.^{15,16}

Solution and frozen EPR spectra of the ^{13}C ($I = 1/2$) (99% enriched) cyanide complex $\text{Ni}^{\text{III}}(^{13}\text{C})_4(\text{H}_2\text{O})_2^-$ are identical with the spectra for the ^{12}C cyanide complex. The lack of ^{13}C splitting from equatorial cyanides indicates that there is little interaction between their sp donor orbitals and the nickel(III) d_{z^2} orbital,

which contains the unpaired electron.

The frozen EPR spectrum for $\text{Ni}^{\text{III}}(\text{CN})_4(\text{NH}_3)_2^-$ (Figure 1b) shows intense hyperfine splitting in both the g_{\parallel} and g_{\perp} regions due to interaction of the unpaired electron in the d_{z^2} orbital with the two ^{14}N ($I = 1$) nuclei. There is also a characteristic shift of g_{\perp} to smaller values with stronger axial donors (Table I). Aqueous room-temperature EPR shows that the $\text{Ni}^{\text{III}}(\text{CN})_4(\text{imidazole})_2^-$ complex is fully formed with 2.5×10^{-2} M imidazole added to 1.0×10^{-3} M $\text{Ni}^{\text{III}}(\text{CN})_4(\text{H}_2\text{O})_2^-$. This indicates that the overall stability constant for this complex is greater than 1.6×10^5 M⁻².

Although the $\text{Ni}^{\text{III}}(\text{CN})_4(\text{H}_2\text{O})_2^-$ complex is a strong oxidizing agent, it coordinates excess CN^- to form $\text{Ni}^{\text{III}}(\text{CN})_6^{3-}$ rather than rapidly oxidizing cyanide ion. Hexacyanonickelate(III) gives an anisotropic EPR spectrum at -190 °C, with $g_{\perp} = 2.081$ and $g_{\parallel} = 2.010$ (Table I). At -35 °C the frozen spectrum collapses to an isotropic signal, $g_{\text{iso}} = 2.056$. Addition of excess $^{13}\text{C}^-$ (7.4×10^{-2} M) to $\text{Ni}^{\text{III}}(\text{CN})_4(\text{H}_2\text{O})_2^-$ (1.0×10^{-3} M) followed by a rapid freeze gives an anisotropic spectrum at -190 °C with 1:2:1 triplets in the g_{\perp} and g_{\parallel} regions (Figure 2a). This corresponds to two "EPR active" axial $^{13}\text{C}^-$ in a tetragonally elongated geometry. Once again the equatorial $^{13}\text{C}^-$ are "EPR silent". Figure 2b gives the frozen EPR spectrum of $\text{Ni}^{\text{III}}(^{13}\text{C})_6^{3-}$ at -35 °C. A rapid exchange of cyanide ions occurs and this seven-line spectrum, with intensity ratios of 1:6:15:20:15:6:1, corresponds to six equivalent $^{13}\text{C}^-$ bonded to nickel(III). The change between Figure 2 parts a and b is reversible with temperature. This is an example of dynamic Jahn-Teller distortion,¹⁷ where the six cyanides become equivalent, even in the frozen medium at -35 °C, due to vibrational interchange.

Acknowledgment. This work was supported by Public Health Service Grant GM-12152 from the National Institutes of General Medical Sciences and by National Science Foundation Grant CHE-8319935.

(17) Hathaway, B. J. *Struct. Bonding (Berlin)* 1984, 57, 55.

Stereospecific Synthesis of the Bicyclo[2.2.2] Portion of Granaticin: Synthesis of Sarubicin A

M. F. Semmelhack,* Yohini Appapillai, and Tadahisa Sato

Department of Chemistry, Princeton University
Princeton, New Jersey 08544

Received March 11, 1985

The naphthoquinone antibiotic granaticin (1)¹ and the benzoquinone antibiotic sarubicin A (2)² have in common the 2-oxabicyclo[2.2.2] ring system, derived from glucose.³ As part of our effort toward a synthesis of granaticin, we report here the stereospecific synthesis of compound 3, which comprises key features of granaticin (1) and constitutes a formal synthesis of sarubicin A (2).⁴ The general strategy is outlined in Scheme I. The key stages are (1) adding a formyl unit (or equivalent) to tetralone 4 trans to the hydroxyl, (2) diastereoselective addition of a methyl nucleophile to the aldehyde carbonyl in 5, and (3) closing the 2-oxabicyclo[2.2.2] ring from 6a.

The successful tactics are presented in Scheme II. The known⁴ bromotetralone 7 was converted to the silyl enol ether (lithium diisopropylamide, *t*-BuMe₂SiCl, THF/HMPA, -78 to 20 °C).

(1) (a) Carbaz, R.; Ettlinger, L.; Gaumann, E.; Kalvoda, J.; Keller-Schlierlein, W.; Kradolfer, F.; Maunkian, B. K.; Neipp, L.; Prelog, V.; Reusser, P.; Zähler, H. *Helv. Chim. Acta* 1957, 40, 1261. (b) Barcza, S.; Brufani, M.; Keller-Schlierlein, W.; Zähler, H. *Helv. Chim. Acta* 1966, 49, 1736. (c) Brufani, M.; Dobler, M. *Helv. Chim. Acta* 1968, 51, 1269-1275.

(2) (a) Slichta, L.; Chidester, C. G.; Reusser, F. *J. Antibiot.* 1980, 33, 919-923. (b) Reinhardt, G.; Bradler, G.; Eckardt, K.; Tresselt, D.; Ihn, W. *J. Antibiot.* 1980, 33, 787-790. (c) Tresselt, D.; Eckardt, K.; Ihn, W.; Radics, L.; Reinhardt, G. *Tetrahedron* 1981, 37, 1961-1965.

(3) Snipes, C. E.; Chang, C.; Floss, H. G. *J. Am. Chem. Soc.* 1979, 101, 701.

(4) Takeuchi, Y.; Sudani, M.; Yoshii, E. *J. Org. Chem.* 1983, 48, 4151.

(12) Subak, E. J.; Loyola, V. M.; Margerum, D. W., unpublished results.

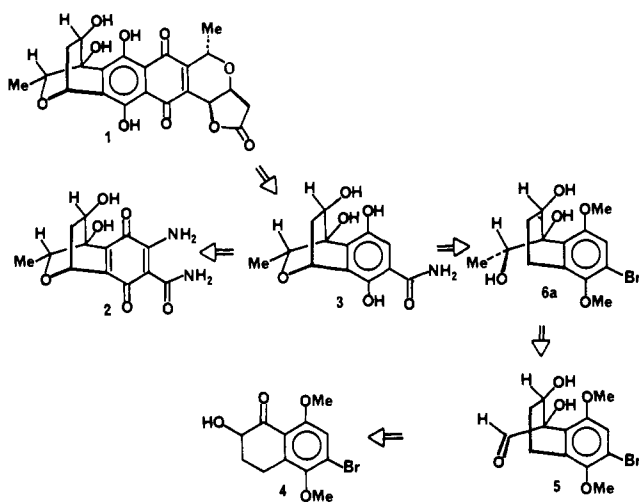
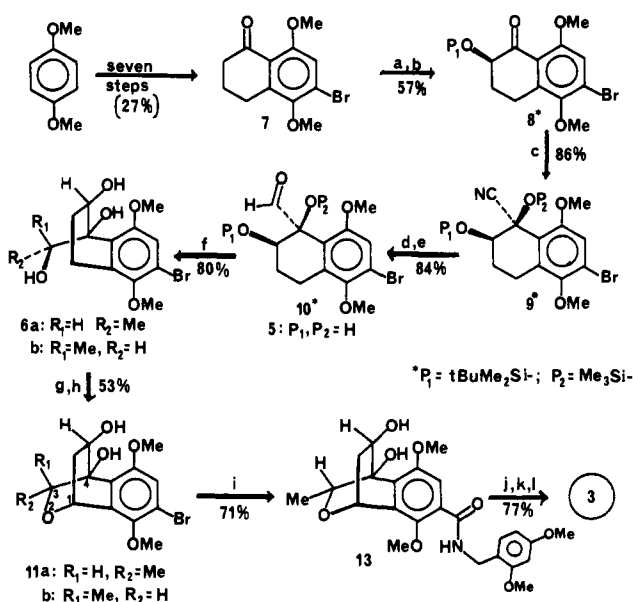
(13) Haines, R. I.; McAuley, A. *Inorg. Chem.* 1980, 19, 719.

(14) Jacobs, S. A.; Margerum, D. W. *Inorg. Chem.* 1984, 23, 1195.

(15) Kojima, N.; Fox, J. A.; Hausinger, R. P.; Daniels, L.; Orme-Johnson, W. H.; Walsh, C. *Proc. Natl. Acad. Sci. U.S.A.* 1983, 80, 378-382.

(16) Albracht, S. P. J.; Graf, E. G.; Thauer, R. K. *FEBS Lett.* 1982, 140, 311-313.

Scheme I

Scheme II^a

^a (a) $\text{LiN}(i\text{-Pr})_2$; $t\text{-BuMe}_2\text{SiCl}$. (b) $m\text{-ClC}_6\text{H}_4\text{CO}_2\text{H}$, CH_2Cl_2 , 0°C . (c) 18-O-6 crown/KCN (cat.), toluene, -30°C , Me_3SiCN . (d) $(i\text{-Bu})_2\text{AlH}$, toluene; stir with 2:1 mix saturated aq $\text{NH}_4\text{Cl}/2\text{H}_2\text{SO}_4$, 25°C . (e) HOAc , THF, H_2O , 12 M HCl (24:8:8:1 by volume), 65°C , 7 h. (f) $\text{TiMe}(\text{O}-i\text{-Pr})_3$, THF, 25°C , 16 h. (g) Cyclohexene oxide (3 \times), cat. AIBN and Br_2 , CCl_4 , NBS (2 \times), sun-lamp, 10°C , 45 min. (h) AgClO_4 , THF, 1 h, 0°C . (i) $(\text{Ph}_3\text{P})_2\text{Cl}_2\text{Pd}$, (0.1 mol equiv), (2,4-dimethoxybenzyl)amine (60 mol equiv), CO (1.1 atm), 90°C , 14 h. (j) (imidazole) $_2\text{CO}$, MeCOEt , K_2CO_3 , 105°C , 12 h. (k) $\text{Ce}(\text{IV})$, CH_3CN , H_2O , 12 h, 25°C . (l) 0.5 M NaOH , 50% aq dioxan, 25°C , 10 min.

Without purification, the silyl enol ether was immediately oxidized with *m*-chloroperoxybenzoic acid (NaHCO_3 , CH_2Cl_2 , 0°C)⁵ to produce the α -hydroxy ketone silyl ether **8** (57% yield for two steps, mp $83\text{--}84^\circ\text{C}$).

In various stages of the granaticin synthesis, we have studied addition of one-carbon nucleophiles to **8** and closely related compounds. In general, stereoselectivity is good, according to least hindered approach. For the present case, excellent results were obtained by addition of trimethylsilyl cyanide (catalytic 18-O-6 crown ether-KCN complex, toluene, -30°C , 3 h).⁶ A mixture of two epimeric cyanohydrin silyl ethers was obtained (100% yield)

(5) Hassner, A.; Reuss, R. H.; Pinnick, H. W. *J. Org. Chem.* **1975**, *40*, 3427.

(6) Evans, D. A.; Hoffman, J. M.; Truesdale, L. K. *J. Am. Chem. Soc.* **1973**, *95*, 5822.

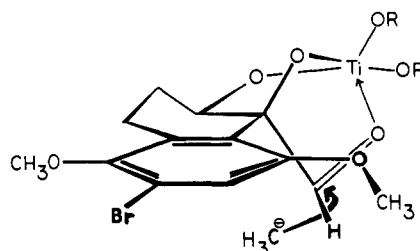


Figure 1.

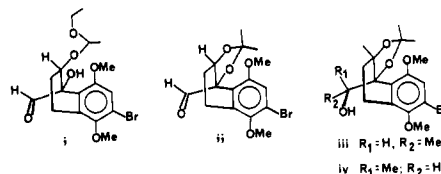
from which the desired isomer, **9**, was obtained by chromatography (86% yield, mp $81.5\text{--}82.5^\circ\text{C}$). The nitrile was converted to the formyl group following a general procedure⁷ (diisobutylaluminum hydride, toluene, -78 to 25°C , 4 h; imine hydrolysis with toluene/aqueous sulfuric acid, 3 h, 25°C). The resulting aldehyde **10** was obtained with the silyl groups intact. Since the hydroxyl groups (in **5**) were expected to play an important role ("chelation control")⁸ in the addition to the aldehyde, the silyl units were removed. This usually simple operation proved troublesome in this system. The diol-aldehyde **5** is sensitive, especially to base, and is converted to tetralone **4** (and, presumably, formaldehyde) under mild conditions such as the usual fluoride anion techniques for desilylation. Acidic cleavage under carefully controlled conditions ($\text{HOAc}/\text{THF}/\text{H}_2\text{O}/\text{concentrated HCl}$ in volume ratio 24:8:8:1; 60°C , 6 h) produced **5** in 84% yield.

Diastereoselective addition to the formyl group was analyzed in terms of coordination of one, both, or neither of the hydroxyl groups with the methyl delivery agent (e.g., MeMgBr). It appeared from models that chelation of the hydroxyls would lead to addition from the desired face of carbonyl group. Reaction of **5** and close analogues of **5** with excess methylmagnesium bromide in THF was very slow at -100°C and produced the desired isomer **6a** in good selectivity (4:1) but with disappointing conversion and yields. Higher temperatures gave lower selectivity, the mono- and di-protected analogues of **5** gave reverse selectivity.⁹ Recent reports suggest that $\text{Ti}(\text{IV})$ reagents are highly selective analogues of Grignard reagents¹⁰ and that diastereoselective addition to aldehydes with chiral α - and β -carbons can be effective with MeTiCl_3 and related agents based on TiCl_4 .^{8b} The same reagents are highly selective in additions to α -alkoxy, β -alkoxy, and α,β -dialkoxy aldehydes,¹¹ but little is reported about the reactivity and selectivity of the corresponding hydroxy aldehydes.¹²

(7) Corey, E. J.; Nicolau, K. C.; Toru, T. *J. Am. Chem. Soc.* **1975**, *97*, 2287.

(8) (a) Still, W. C.; McDonald, J. H., III. *Tetrahedron Lett.* **1980**, *21*, 1031. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556-569.

(9) With the mono-protected version, i, addition of excess methyl mag-



nesium bromide at at -100°C for 2 h gave the adduct in 40% yield (74% conversion) as a mixture of four diastereomers. After removal of the protecting group, the ratio **6a:6b** was determined by $^1\text{H NMR}$ to be 1:3:8. A parallel sequence with acetonide ii gave the adducts iii and iv in 70% yield (66% conversion) in a ratio of 1:9.

(10) (a) Reetz, M. T.; Steinbach, R.; Westermann, J.; Peter, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 1011. (b) Weidmann, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 31. (c) General review: Reetz, M. T. *Top. Curr. Chem.* **1982**, *106*, 1.

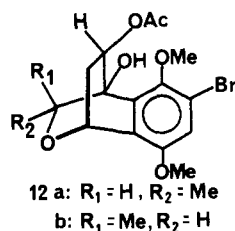
(11) (a) Mulzer, J.; Angermann, A. *Tetrahedron Lett.* **1983**, 2843. (b) See reference to unpublished work in ref 8b. (c) Reetz, M. T.; Kessler, K.; Schmidtberger, S.; Wenderoth, B.; Steinbach, R. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 989. (d) Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833.

(12) The addition of $\text{MeTi}(\text{O}-i\text{-Pr})_3$ to benzoin gives very high diastereoselectivity, and a chelated five-coordinate $\text{Ti}(\text{IV})$ intermediate is postulated.¹³ The reaction of β -hydroxybutanal with $\text{MeTi}(\text{O}-i\text{-Pr})_3$ affords a 55:45 mixture of *meso*- and *d,l*-2,4-pentanediois.¹³

(13) Reetz, M. T.; Steinbach, R.; Westermann, J.; Urz, R.; Wenderoth, B.; Peter, R. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 135; *Angew. Chem. Suppl.* **1982**, 257.

We postulated strong chelation of Ti(IV) to **5** by deprotonation and alkoxy exchange with MeTi(OiPr)₃, and then external delivery of the methyl nucleophile from the least hindered face (Figure 1). On treatment of **5** with methyltriisopropoxytitanium (3 mol equiv, THF, 25 °C, 16 h) the desired triol **6a** was produced as a single diastereoisomer, in 80% yield. This procedure is more selective than any MeMgBr additions we have attempted and readily gives complete conversion.

The third critical stage of the synthesis, oxidative cyclization to **11a**, was accomplished in two steps. First a crude benzylic bromination product was prepared (*N*-bromosuccinimide, cyclohexene oxide as acid scavenger, azoisobutyronitrile, sunlamp for 0.5 h at 10 °C in CCl₄), and then ring closure was induced by treatment with silver ion (silver perchlorate, THF, 0–20 °C over 0.5 h). Chromatography gave pure **11a** in 53% yield. The configuration of C-3 in **11a** was clear from the ¹H NMR spectrum, in which the C-3 methyl group appears as a doublet at δ 0.86, reflecting a strong upfield shift due to proximity to the face of the arene ring. In the epimeric series (e.g., **11b**) the C-3 methyl generally appears at δ 1.3. This is consistent with the data for the natural products, **1** and **2**.^{1,2} In addition, in related studies, we prepared the isomers **12a** and **12b** by a similar sequence and



observed the parallel differences in the ¹H NMR spectral data. The structure of **12a** was confirmed by X-ray diffraction analysis.¹⁴

The intermediate **11a** is an obvious precursor of sarubicin A (**2**). The bromide substituent was first replaced by an acyl amide unit using the Pd(0)-catalyzed carbonylation procedure of Heck.¹⁵ For our purposes ammonia would be the ideal nucleophilic trapping agent for the expected acylpalladium intermediate, but ammonia itself was not successful. A primary amine was chosen with a removable carbon substituent. Several candidates, such as benzylamine, performed well in the amido carbonylation, but we were less successful in cleaving the benzyl substituent.¹⁶ The best solution is (2,4-dimethoxybenzyl)amine [with 10 mol % (Ph₃P)₂PdCl₂, Ph₃P, CO at 1.1 atm, 90 °C, 14 h] which produced **13** in 71% yield (60% after one recrystallization, mp 175–177 °C). Protection of the diol unit as the carbonate (*N,N'*-carbonyldiimidazole, methyl ethyl ketone, K₂CO₃, 105 °C) allowed oxidative removal of the 2,4-dimethoxybenzyl group [Ce(IV), CH₃CN, water, 0 °C, 0.5 h] and hydrolysis of the carbonate (0.5 M NaOH in 50% aqueous dioxan, 10 min, 25 °C) gave the key intermediate **3** in high purity, 77%. Recrystallization gave colorless plates (56% yield) with mp 207–209 °C. This compound has been converted to sarubicin A in one step (two operations),⁴ and preparation of **3** provides a formal total synthesis of sarubicin A. The overall synthesis (Scheme II) is highly stereoselective and requires minimal use of protecting groups. We expect these procedures will make available useful quantities of intermediate **11a** for conversion to granaticin.

Acknowledgment. We are pleased to acknowledge support of this work through NIH Grant GM 31352.

Registry No. **1**, 19879-06-2; **2**, 75533-14-1; **3**, 96866-91-0; (±)-**5** (P₁ = P₂ = H), 96866-92-1; (±)-**6a** (R₁ = H; R₂ = Me), 96866-93-2; (±)-**6b** (R₁ = Me; R₂ = H), 96866-94-3; **7**, 87338-27-0; (±)-**8** (P₁ = *t*-BuMe₂Si), 96866-96-5; (±)-*cis*-**9** (P₁ = *t*-BuMe₂Si; P₂ = Me₃Si),

96866-97-6; (±)-*trans*-**9** (P₁ = *t*-BuMe₂Si; P₂ = Me₃Si), 96866-98-7; (±)-**10** (P₁ = *t*-BuMe₂Si; P₂ = Me₃Si), 96867-00-4; **11a**, 96867-01-5; **13**, 96867-02-6; (±)-*i*, 96867-03-7; (±)-*i*-MeMgBr adduct (isomer 1), 96867-04-8; (±)-*i*-MeMgBr adduct (isomer 2), 96867-05-9; (±)-*i*-MeMgBr adduct (isomer 3), 96867-06-0; (±)-*i*-MeMgBr adduct (isomer 4), 96896-73-0; (±)-*ii*, 96867-07-1; (±)-*iii*, 96867-08-2; (±)-*iv*, 96947-22-7; 1-(*tert*-butyldimethylsiloxy)-6-bromo-5,8-dimethyl-3,4-dihydronaphthalene, 96866-95-4; (±)-*cis*-6-bromo-2-[[[(1,1-dimethylethyl)dimethylsilyloxy]-1,2,3,4-tetrahydro-5,8-dimethoxy-1-[(trimethylsilyloxy)-1-(iminomethyl)naphthalene, 96866-99-8; (2,4-dimethoxybenzyl)amine, 20781-20-8.

Supplementary Material Available: Characterization data for **5**, **6a**, **8**, **9**, **11a**, **13**, and **3** (5 pages). Ordering information is given on any current masthead page.

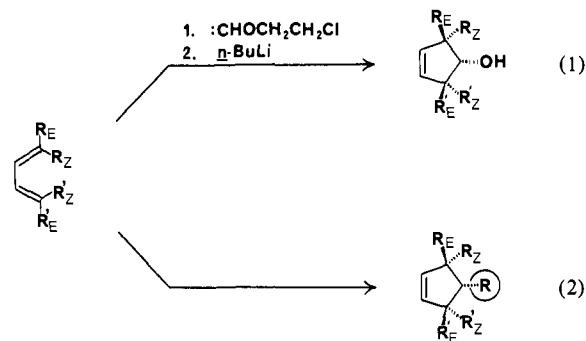
Carbanion-Accelerated Vinylcyclopropane Rearrangement. Application in a General, Stereocontrolled Annulation Approach to Cyclopentene Derivatives

Rick L. Danheiser,*¹ Joanne J. Bronson, and Kazuo Okano

Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139

Received March 28, 1985

In the field of cyclopentanoid synthesis,² a problem of continuing interest is the development of a general method, analogous to the Diels–Alder reaction, for the conversion of conjugated dienes to cyclopentene derivatives. Toward this end, we have recently devised a highly stereoselective [4 + 1] annulation approach to substituted cyclopentenols.³ As outlined in eq 1, this method



features an alkoxy-accelerated vinylcyclopropane rearrangement as a key step and results in the effective 1,4-addition of hydroxycarbene about the termini of a 1,3-diene. In this paper, we now report a second-generation version of our strategy, which extends this methodology to include the synthesis of cyclopentene derivatives bearing a variety of functionalized substituents in place of the hydroxyl group on the new five-membered ring (eq 2).

The pivotal step in our new annulation strategy is a *carbanion-accelerated vinylcyclopropane rearrangement*.⁴ α -Sulfonyl carbanions have proved to be the most effective activating groups

(1) Fellow of the Alfred P. Sloan Foundation, 1981–1985.

(2) (a) Ramaiah, M. *Synthesis* **1984**, 529. (b) Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1. (c) Paquette, L. A. *Ibid.* **1979**, *79*, 49.

(3) (a) Danheiser, R. L.; Martinez-Davila, C.; Auchus, R. J.; Kadonaga, J. T. *J. Am. Chem. Soc.* **1981**, *103*, 2443. (b) Danheiser, R. L.; Martinez-Davila, C.; Morin, J. M. *J. Org. Chem.* **1980**, *45*, 1340.

(4) For previous examples of carbanion-accelerated pericyclic reactions, see: (a) Comber, R. N.; Swenton, J. S.; Wexler, A. J. *J. Am. Chem. Soc.* **1979**, *101*, 5411. (b) Kametani, T.; Tsubuki, M.; Nemoto, H.; Suzuki, K. *Ibid.* **1981**, *103*, 1256. (c) Cooper, D.; Trippet, S. J. *Chem. Soc., Perkin Trans I* **1981**, 2127. (d) Denmark, S. E.; Harmata, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 4972. (e) Denmark, S. E.; Harmata, M. A. *J. Org. Chem.* **1983**, *48*, 3369. (f) Nemoto, H.; Suzuki, K.; Tsubuki, M.; Minemura, K.; Fukumoto, K.; Kametani, T.; Furuyama, H. *Tetrahedron* **1983**, *39*, 1123. (g) Denmark, S. E.; Harmata, M. A. *Tetrahedron Lett.* **1984**, *25*, 1543. (h) Blechert, S. *Tetrahedron Lett.* **1984**, *25*, 1547.

(14) We are grateful for assistance from Professor Jon Clardy and the Cornell X-ray facility for these data.

(15) Heck, R. F.; Schoenberg, A. *J. Org. Chem.* **1974**, *39*, 3327.

(16) Attempts to remove the *N*-benzyl group by catalytic hydrogenation led to saturation of the aromatic ring in the benzyl group. See also ref 14 in: Williams, R. M.; Armstrong, R. W.; Dung, J. S. *J. Am. Chem. Soc.* **1984**, *106*, 5748–5750.