isolated as its hydrochloride in 84%. Pure **5** was a colorless liquid which showed the expected 9-line ^{13}C NMR spectrum.[11] High-resolution mass spectrometry confirmed the formula $C_9H_{15}NO$.

That **5** did indeed possess the rearranged perhydroazaazulene skeleton[12] was demonstrated by hydrogenolysis (Zn dust, 80% aqueous acetic acid, 70 °C, 77%, mp 128–130 °C) to amino alcohol **12**, which was different from the educt **7**. Protection of the amine with the *t*-BOC group (di-*tert*-butyl carbonate, THF, H_2O, NaOH, 75%), followed by oxidation (PDC, CH_2Cl_2, 99%, mp 47–48 °C) gave the protected amino ketone **14**. The IR spectrum of **14** showed the ketone C=O stretching frequency at 1700 cm^{-1}. A similar protection–oxidation sequence applied to **7** gave the amido ketone **15** (oil, 92% from **7**), which showed the ketone C=O stretch at 1715 cm^{-1}.

We have established that nitrones can be prepared by heterolytic fragmentation of γ-*N*-hydroxyamino sulfonates under basic conditions and that these can be transformed into useful intra- and intermolecular 1,3-dipolar cycloadducts. We are continuing our examination of other suitable systems.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work.

(11) A stereochemical designation of **5** is (2*RS*,6*SR*,7*SR*)-1-aza-11-oxatricyclo[5.3.1.$0^{2,6}$]undecane: ^1H NMR ($CDCl_3$) δ 4.18 (dt, H_7, J_1 = 11.3 Hz, J_2 = 8.5 Hz), 4.1 (br t, H_2, J = 5.5 Hz), 3.6 (m, $H_{10\beta}$), 3.15 (m, H_6), 3.0 (dd, $H_{10\alpha}$, J_1 and $J_2 \simeq$ 6–7 Hz), 2.25 (m, H_3), 2.15 (m, H_3), 2.05–1.6 (m, 7 H), 1.35 (m, $H_{9\alpha}$); ^{13}C NMR ($CDCl_3$) 75.5, 72.0, 53.4, 49.8, 32.1, 25.53, 25.48, 24.4, 15.6 ppm; **5**-HCl, mp 204–206 °C dec.

(12) An examination of molecular models indicates that intramolecular cycloaddition of **4** in the other regiosense, i.e., to give 1-aza-11-oxatricyclo[4.4.1.$0^{2,7}$]undecane, is sterically constrained.

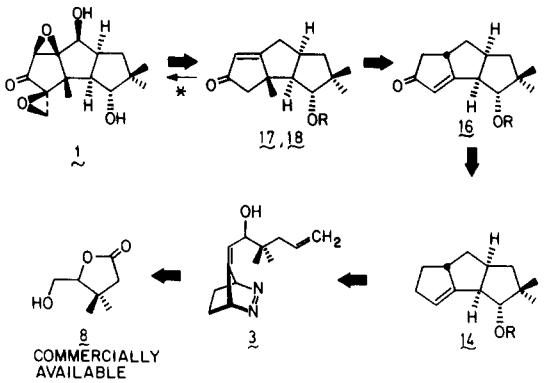
Norman A. LeBel,* Bradley W. Caprathe
Department of Chemistry
Wayne State University
Detroit, Michigan 48202
Received June 18, 1985

Intramolecular 1,3-Diyl Trapping Reactions. A Formal Total Synthesis of (±)-Coriolin

Summary: A formal total synthesis of racemic coriolin (**1**) from furanone **8** is described. An intramolecular 1,3-diyl trapping reaction served as the key step in the construction of the linearly fused tricyclopentanoid alcohol **14**.

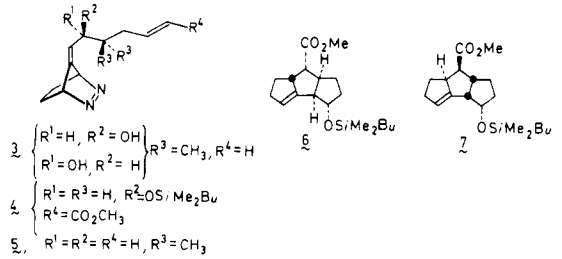
Sir: Coriolin (**1**) was first isolated in 1969 from fermentation broths of the Basidiomycete *Coriolus consors*.[2] By 1974, its structure had been firmly established through both chemical and X-ray crystallographic studies.[3] Attracted by reports of the antibiotic and antitumor activity of coriolin and diketocoriolin B (**2**), researchers have devised a number of elegant syntheses of coriolin, the first of which appeared in 1980.[4]

Scheme I. Retrosynthetic Analysis[a]



[a] * = convergent point.

We now report a stereo- and regiocontrolled formal total synthesis of coriolin which further illustrates the versatility and synthetic utility of the intramolecular 1,3-diyl trapping reaction (note Schemes I and II). The selection of diazene **3** rather than any of several reasonable alternative diyl precursors was guided by our knowledge of the following principles. First, the intramolecular diyl trapping reaction is stereoselective and favors the formation of cis,anti ring-fused tricyclopentanoids.[5] It is reasonable to assume that this preference will again be observed, thereby leading to the establishment of the proper relative stereochemistries at C_1, C_6, and C_8 (coriolin numbering).[6] Second, photodeazetation (at 7 °C) of optically active diazene **4**



leads to the *cis,anti*-tricyclopentanoids **6** and **7** in a ratio of 26:1,[7] thereby suggesting that deazetation of **3** should lead to a large preference for the formation of the required

(1) Senior Research Assistant of the National Fund for Scientific Research (Belgium).

(2) Takeuchi, T.; Iinuma, H.; Iwanaga, J.; Takahashi, S.; Takita, T.; Umezawa, H. *J. Antibiot.* **1969**, *22*, 215.

(3) Takahashi, S.; Naganawa, H.; Iinuma, H.; Takita, T.; Maeda, K.; Umezawa, H. *Tetrahedron Lett.* **1971**, 1955. Nakamura, H.; Takita, T.; Umezawa, H.; Kunishita, M.; Nakayama, Y.; Iitaka, Y. *J. Antibiot.* **1974**, *27*, 301.

(4) Tatsuta, K.; Akimoto, K.; Kinoshita, M. *J. Antibiot.* **1980**, *33*, 4365. Danishefsky, S.; Zamboni, R.; Kahn, M.; Etheredge, S. J. *J. Am. Chem. Soc.* **1980**, *102*, 2097. Danishefsky, S.; Zamboni, R. *Tetrahedron Lett.* **1980**, *21*, 3439. Danishefsky, S.; Zamboni, R.; Kahn, M.; Etheredge, S. J. *J. Am. Chem. Soc.* **1981**, *103*, 3460. Shibasaki, M.; Iseki, K.; Ikegami, S. *Tetrahedron Lett.* **1980**, *21*, 2587. Iseki, K.; Yamazaki, M.; Shibasaki, M.; Ikegami, S. *Tetrahedron* **1981**, *37*, 4411. Tatsuta, K.; Akimoto, K.; Kinoshita, M. *Tetrahedron* **1981**, *37*, 4365. Mehta, G.; Reddy, A. V.; Murthy, A. N.; Reddy, D. S. *J. Chem. Soc., Chem. Commun.* **1982**, 540. Wender, P. A.; Howbert, J. J. *Tetrahedron Lett.* **1983**, *24*, 5325. Schuda, P. F.; Heimann, M. R. *Tetrahedron Lett.* **1983**, *24*, 4267. Funk, R. L.; Bolton, G. L. 189th National Meeting of the American Chemical Society, Miami Beach, FL, April 28–May 3, 1985, Organic Division; American Chemical Society: Washington, DC; Abstract 85. See also ref 10.

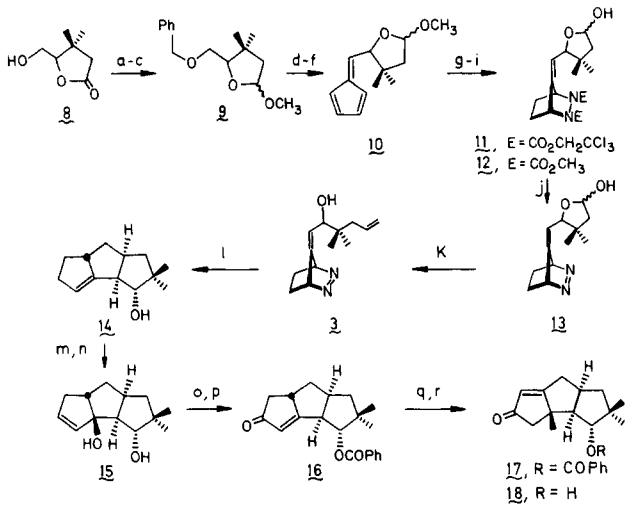
(5) Little, R. D.; Muller, G. W.; Venegas, M. G.; Carroll, G. L.; Bukhari, A.; Patton, L.; Stone, K. *Tetrahedron* **1981**, *37*, 4371.

(6) The numbering system shown in structure **1** is used throughout.

(7) Stone, K. J.; Little, R. D. *J. Am. Chem. Soc.* **1985**, *107*, 2495.

0022-3263/85/1950-3940$01.50/0

Scheme II[a]



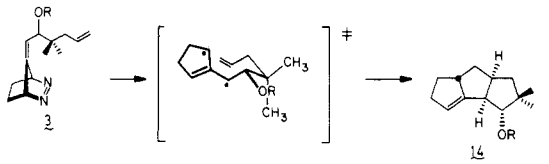
[a] (a) $PhCH_2Br$, Ag_2O, DMF, room temperature, 48 h, 76%; (b) DIBAL-H, Et_2O, −60 °C, 20 min; (c) 0.05% *p*-TsOH in MeOH, 3 h, room temperature, yield for steps b and c 95%; (d) H_2, $Pd(OH)_2$ on carbon, MeOH, 1 atm, room temperature, 3 h, 94%; (e) $(COCl)_2$, Me_2SO, CH_2Cl_2, −60 °C, 15 min, then Et_3N, −60 °C, 5 min; (f) CpH (2.5 equiv), pyrrolidine (2.0 equiv), AcOH (1.0 equiv), MeOH, room temperature, 15 h, yield for steps e and f 53%; (g) $RO_2CN{=}NCO_2R$, Et_2O, 4 °C, 1 h when R = CH_2CCl_3, or 5 days when R = CH_3; (h) $KO_2CN{=}NCO_2K$, CH_2Cl_2, AcOH, 0 °C, 3 h; (i) AcOH, H_2O, THF (7:2:1), 50–60 °C, 5 days, yield for steps g, h, and i 65% when R = CH_2CCl_3 and 81% when R = CH_3; (j) e^- (Hg), −1.7 V (SCE), DMF, room temperature, then $K_3Fe(CN)_6$, H_2O, 0 °C, 1 h, 72% when R = CH_2CCl_3, or KOH, EtOH, reflux, 1 h, then $K_3Fe(CN)_6$, H_2O, 0 °C, 1 h, 76% when R = CH_3; (k) $Ph_3P{=}CH_2$ (from Ph_3PCH_3Br and *n*-BuLi), THF, room temperature, 2 h, 70–80%; (l) *hν* (450-*W* Hanovia with a Pyrex filter), CH_3CN, 4–6 °C, 3 h, 84%; (m) MCPBA, $CHCl_3$, Na_2CO_3, 0 °C, 10 min; (n) LDA or *n*-Bu_2NLi, THF, reflux, 2 h, yield for steps m and n 52%; (o) PhCOCl, CH_2Cl_2, pyridine, room temperature, 4 h; (p) PCC, CH_2Cl_2, room temperature, 3 h, yield for steps o and p 78%. (q) $Me_2Cu(CN)Li_2$, THF, −50 °C, 3 h, 80%; (r) LDA, THF, −78 °C, Me_3SiCl; $Pd(OAc)_2$, benzoquinone, CH_3CN, 10 h, room temperature, 40% product and 50% recovered starting material (see ref 17).

relative and, if desired, absolute stereochemistry at C_{11}. Finally, while the use of an unactivated diylophile has on rare occasion led to the formation of diyl dimer,[8] we elected to use an unactivated diylophile in the present instance based upon prior experience with diazene **5**.[9] Thus, we reasoned that like the diyl derived from **5**, dimerization of the diyl derived from **3** would not compete successfully with the desired intramolecular cycloaddition. Enones **17** and **18** have previously been converted to coriolin and were selected as our target molecules.[10] Commercially available dihydro-5-(hydroxymethyl)-4,4-dimethyl-2(3*H*)-furanone (**8**) was chosen as the starting material since it incorporates all of the essential structural features which are present in the acyclic chain of diazene **3**.[11]

The synthesis began with benzylation of **8** followed by reduction and masking of the resulting lactol as a methyl ether to afford **9** in 72% yield. The benzyl group was removed by hydrogenolysis over Pearlman's catalyst (94%), and the resulting primary alcohol was subjected to a Swern oxidation, thereby affording an aldehyde suitable for conversion to the desired fulvene **10**. After considerable effort, it was discovered that the latter transformation could best be achieved by adding an equivalent amount of acetic acid to the reaction mixture consisting of 1 equiv of the aldehyde, 2.5 equiv of cyclopentadiene, and 2.0 equiv of pyrrolidine in methyl alcohol at room temperature.[12]

The dicarbamates **11** (E = $CO_2CH_2CCl_3$) and **12** (E = CO_2CH_3) were prepared by treatment of fulvene **10** with the appropriate azo dicarboxylate, followed by selective reduction of the endocyclic π bond of the resulting Diels–Alder cycloadduct, and hydrolytic cleavage of the methyl ether. Both carbamates served as useful intermediates for the construction of diazene **3**. Attempts to introduce the diylophile at this stage of the sequence (E = $CO_2CH_2CCl_3$) by using the simple methylene ylide, $Ph_3P{=}CH_2$, met with failure; in contrast, the same lactol readily undergoes opening when $Ph_3P{=}CHCO_2CH_3$ is utilized. To circumvent this problem, the vicinal dicarbamate unit was converted to a diazene linkage. Once this maneuver was accomplished, the resulting diazene lactol **13** could be opened by using $Ph_3P{=}CH_2$ and was converted to the desired diazene **3** in yields ranging from 70% to 80%.

Once again, the synthesis utility of the intramolecular diyl trapping reaction was clearly demonstrated by the facile conversion of diazene **3** to the linearly fused tricyclopentanoid alcohol **14** (*hν*, CH_3CN, 6 °C, 84%). We were assured that the proper stereochemical assignments had been made on the basis of the conversion of compound **14** to the desired target molecule (vide infra).



All attempts to introduce the carbonyl unit at C_4 by using a variety of allylic oxidation methods were unsuccessful;[13] at best less than 10% of the desired enone could be obtained. This temporary impasse was circumvented by a four-step sequence involving epoxidation, Rickborn–Crandall ring-opening initiated with either (*n*-Bu)$_2$NLi or LDA,[14] protection of the secondary alcohol as a benzoate ester, and conversion of the A-ring tertiary allylic alcohol to the desired enone **16** by using PCC.[15]

Despite severe crowding at the β carbon, conjugate addition of the required C_2 methyl group was readily achieved by using the recently developed method of Lipshutz and co-workers calling for the use of boron trifluoride etherate in conjunction with the higher order cuprate $Me_2Cu(CN)Li_2$.[16] Introduction of the final π bond was achieved

(8) Little, R. D.; Carroll, G. L.; Petersen, J. L. *J. Am. Chem. Soc.* **1983**, *105*, 928.
(9) Little, R. D.; Higby, R. G.; Moeller, K. D. *J. Org. Chem.* **1983**, *48*, 3139.
(10) (a) Koreeda, M.; Mislankar, S. G. *J. Am. Chem. Soc.* **1983**, *105*, 7203. (b) Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1981**, *103*, 7380. (c) Demuth, M.; Ritterskamp, P.; Schaffner, K. *Helv. Chim. Acta* **1984**, *67*, 2023. (d) Exon, C.; Magnus, P. *J. Am. Chem. Soc.* **1983**, *105*, 2477. (e) Ito, T.; Tomiyoshi, N.; Nakamura, K.; Azuma, S.; Izawa, M.; Maruyama, F.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1982**, *23*, 1721; (f) **1984**, *40*, 241–255. (g) Schuda, P. F.; Heimann, M. R. *Tetrahedron* **1984**, *40*, 2365.
(11) Available from Dynamit Nobel Aktiengesellschaft, D-5210 Troisdorf, Federal Republic of Germany.
(12) Stone, K. J.; Little, R. D. *J. Org. Chem.* **1984**, *49*, 1849.
(13) (a) Dauben, W. G.; Lorber, M.; Fullerton, D. S. *J. Org. Chem.* **1969**, *34*, 3587. (b) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057. (c) Van Hijfte, L.; Vandewalle, M. *Tetrahedron* **1984**, *40*, 4371. (d) Pearson, A. J.; Chen, Y.-S.; Hsu, S.-Y.; Ray, T. *Tetrahedron Lett.* **1984**, *25*, 1235.
(14) Kissel, C. L.; Rickborn, B. *J. Org. Chem.* **1972**, *37*, 2060 and references cited therein.
(15) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682.

by using the well-established method of Saegusa.[17] Comparison of material prepared in this way with an authentic sample of **17** generously supplied to us by Professor Koreeda indicated that the formal synthesis was complete and our objectives had been achieved.

Efforts are underway to prepare biologically active analogues of coriolin and to utilize the diyl trapping reaction in the construction of other natural products. The results of these studies will be reported in due course.

Acknowledgment. We gratefully acknowledge the continued support of the Public Health Service (National Cancer Institute). L.V.H. thanks the Belgian National Fund for Scientific Research for a Senior Research Assistantship. The initial synthetic efforts to prepare coriolin by Dr. Olof Wallquist are acknowledged with pleasure. Finally, both of us thank Professors Koreeda, Trost, Danishefsky, and Mehta for copies of spectral data and/or authentic samples which were used for comparison purposes.

(16) (a) Lipshutz, B. H.; Parker, D. A.; Kozlowski, J. A.; Nguyen, S. L. *Tetrahedron Lett.* **1984**, *25*, 5959. (b) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. *Tetrahedron* **1984**, *40*, 5005.

(17) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011. Lithium diisopropylamide (LDA) provided ca. a 3:2 mixture of silyl enol ethers while lithium tetramethylpiperidide affords the same enol ethers in a 6:1 ratio (personal communication from Professor Raymond Funk, University of Nebraska). The major product in each case results from enolate formation toward C_5. The minor product is converted back to the starting ketone after being treated with palladium acetate and workup.

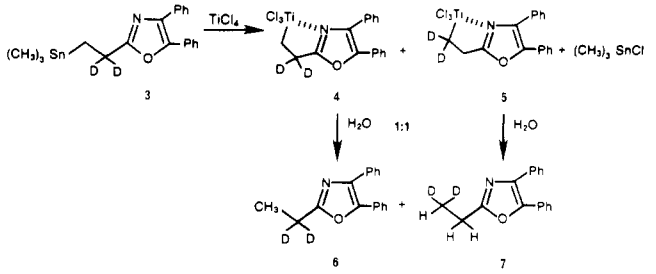
Luc Van Hijfte,[1] R. Daniel Little*
Department of Chemistry
University of California, Santa Barbara
Santa Barbara, California 93106
Received May 28, 1985

Metalation of 4,5-Diphenyl-2-[2-(trimethylstannyl)ethyl]oxazole with Titanium Tetrachloride. A New Carbon–Carbon Bond Forming Methodology Based on Organotitanium Reagents[1]

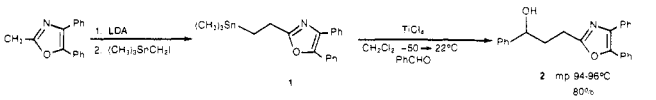
Summary: The reaction of 4,5-diphenyl-2-[2-(trimethylstannyl)ethyl]oxazole (**1**) with titanium tetrachloride produces, by a chelation controlled mechanism, a trichlorotitanium intermediate which reacts with benzaldehyde to afford a secondary alcohol.

Sir: In connection with a program directed toward the preparation of new pharmaceuticals, we required a synthesis of γ-hydroxy carboxylic acids. A proposed entry into these types of molecules was the addition of a propionate homoenolate equivalent to an aldehyde.[2,3] 4,5-Diphenyl-2-[2-(trimethylstannyl)ethyl]oxazole (**1**)[4] was developed as a homoenolate equivalent. In this communication we report the first example of a metalation reaction of an alkyl carbon–tin σ bond with titanium tetrachloride. A mechanistic interpretation of this novel reaction will be presented.

Scheme I



4,5-Diphenyl-2-[2-(trimethylstannyl)ethyl]oxazole (**1**) was prepared in 70% yield by alkylation of 4,5-diphenyl-2-methyloxazole[5] (LDA, 1 equiv, THF −50 °C, 30 min) with (iodomethyl)trimethyltin[6] (1 equiv, −50 °C to 0 °C). When titanium tetrachloride (1 equiv) was added to a solution containing benzaldehyde (1.1 equiv) and tin-oxazole **1** (1 equiv) in dry dichloromethane at −50 °C and the resulting red wine colored reaction mixture was warmed to 22 °C for 2 h, only the crystalline hydroxy oxazole **2** (mp 94–96 °C) was isolated in 80% yield (eq 1).



(1)

The high-field (360 MHz) proton magnetic resonance spectrum of **1** in CD_2Cl_2 exhibited a pair of A_2X_2 triplets. Absorptions for the major isotope (^{118}Sn) and the minor isotopes (^{117}Sn and ^{119}Sn) of oxazole **1** were observed. The methylene protons adjacent to tin and the oxazole ring appeared at 1.27 and 3.05 ppm, respectively. The low-temperature proton spectrum of oxazole **1** and titanium tetrachloride showed dramatic changes in the methylene proton region.[7] Two A_2M_2 triplets were found at 3.12 and 3.50 ppm (J = 6.8 Hz) without the associated coupling to the isotopes of tin. A new singlet appeared at 0.69 ppm. When a solution of trimethyltin chloride was added, a new singlet did not appear and only the peak at 0.69 ppm became enhanced. When the sample was warmed to 22 °C, the proton spectrum remained unchanged. These results indicated that titanium tetrachloride had reacted with oxazole **1** between −60 °C to −1 °C and formed trimethyltin chloride and an organotitanium species. The proton signals at 3.12 and 3.50 ppm were consistent with values cited in the literature for the methylene protons of (trichloroethyl)titanium.[8] When the metalation reaction was repeated and monitored by TLC (1:3 ethyl acetate/hexane), the addition of the organotitanium species to benzaldehyde occurred between 0 °C to 22 °C. We con-

(1) Dedicated to Professor Robert M. Coates on the occasion of his 20th anniversary at the University of Illinois, Champaign–Urbana.

(2) For some recent examples of propionate homoenolate equivalents, see: (a) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1977**, *99*, 7360. (b) Caine, D.; Frobese, A. S. *Tetrahedron Lett.* **1978**, 883. (c) Jacobson, R. M.; Lahm, G. P. *J. Org. Chem.* **1980**, *45*, 395. (d) Goswami, R.; Corcoran, D. E. *Tetrahedron Lett.* **1982**, *23*, 1463. (e) Hoppe, D.; Bronneke, A. *Tetrahedron Lett.* **1983**, *24*, 1687. (f) Taylor, E. C.; Davies, H. M. L. *Tetrahedron Lett* **1983**, *24*, 5453. (g) Nakamura, F.; Kuwajima, I. *J. Am. Chem. Soc.* **1983**, *105*, 651. (h) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 3368.

(3) For a general review of homoenolate anions and homoenolate anion equivalents, see: Werstiuk, N. H. *Tetrahedron* **1983**, *39*, 205.

(4) All isolated compounds have yielded spectral and analytical data consistent with the assigned structures.

(5) 4,5-Diphenyl-2-methyloxazole was prepared by two procedures: (a) Davidson, D.; Weiss, M.; Jelling, M. *J. Org. Chem.* **1937**, *2*, 328. (b) Jeffreys, R. A. *J. Chem. Soc.* **1952**, 4823. Alternatively, 4,5-diphenyl-2-methyloxazole can be obtained from the Aldrich Chemical Co.

(6) Seyferth, D.; Andrews, B. *J. Organomet. Chem.* **1971**, *30*, 151.

(7) The low-temperature ^1H NMR (360 MHz) experiment was performed as follows: a solution of oxazole **1** in CD_2Cl_2 (CH_2Cl_2 internal standard) was placed in an NMR tube and cooled to −60 °C (dry ice–acetone bath). Excess titanium tetrachloride (neat liquid) was added to the NMR tube. A red wine colored solution appeared immediately. The tube was quickly transferred to a cooled probe (−1 °C) and the low-temperature spectrum was obtained.

(8) Hanlan, J.; McCorvan, J. D. *Can. J. Chem.* **1972**, *50*, 747.

0022-3263/85/1950-3942$01.50/0