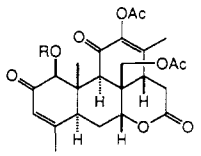
rise to 12 (R = H), mp 214–216 °C, in 82% yield. Jones oxidation of 12 (R = H) provided (74%) the α-diketone



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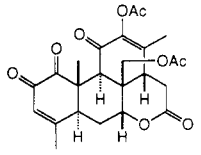

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13, which upon heating in pyridine at reflux gave rise in ca. 20% yield to the C(12), C(20) diacetate of shinjulactone C. Hydrolysis (KOMe, MeOH) of the acetates gave rise to crystalline (±)-shinjulactone C, mp 242.5–244.0 °C dec, whose ^{1}H NMR spectrum was not in complete agreement with the ^{1}H NMR data recorded in the literature.[1,9] That the structure of synthetic (±)-shinjulactone C was correct was unambiguously established by single-crystal X-ray analysis.

Acknowledgment. Generous support for this work from the National Cancer Institute, National Institutes of Health (Grant CA 28865), is gratefully acknowledged. The 500-MHz NMR instrument (Bruker 500) used in the above studies was purchased in part with funds provided by the National Institutes of Health (RR 02858) and the National Science Foundation (CHE 85-13707).

(9) During the tabulation of the ^{1}H NMR data for shinjulactone C,[1] the coupling constants for $J_{6\alpha,7}$ and $J_{6\beta,7}$ were interchanged. The C(6) α proton which appears as a doublet of doublets at δ 2.40 has coupling constants of 15.5 and 5.0 Hz, whereas the C(6) β proton (δ 2.70, dd) possesses J values of 15.5 and 10.0 Hz.

The Total Synthesis of Nikkomycin B

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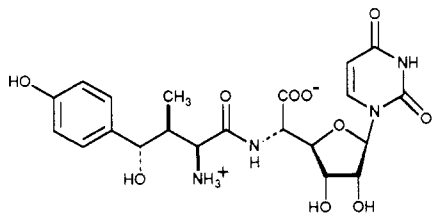
Received August 16, 1990

Summary: A highly stereoselective and general synthesis of the γ-hydroxy-β-methyl-α-aminobutanoic acid moiety, a common feature of the nikkomycin N-terminal amino acid is described and utilized in the total synthesis of nikkomycin B.

The nikkomycins[2] (neopolyoxins)[3] are a unique class of nucleoside peptide antibiotics isolated from the culture broths of *Streptomyces tendae* and *S. cacaoi* ssp. *asoensis*. Especially noteworthy is their effectiveness against the medically important human pathogen *Candida albicans*.[3b,c] This class of compounds has been shown to possess antifungal, insecticidal, and acaricidal activity[2-4] which render them particularly significant synthetic targets. Concurrent with the isolation and structure elucidation, König[2b,5] reported a nonstereoselective synthesis of the N-terminal amino acid residue of nikkomycin B (1) and B_x (2). More recently, they have reported the total syntheses of nikkomycin B_x (2) and related analogues.[6] Other syntheses of similar γ-hydroxy amino acid derivatives have been described in the literature.[5,7-9] We report a highly diastereo- and enantioselective synthesis of the N-terminal γ-hydroxy amino acid unit (3)[2b,5a,10] and the subsequent coupling to the C-terminal amino acid unit (4),[11] culminating in the total synthesis of nikkomycin B (1).



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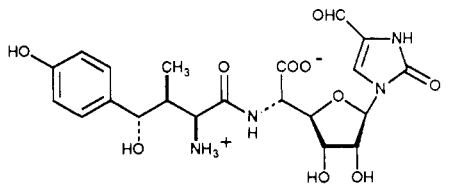


2

Recently a high degree of stereoselectivity has been achieved in the synthesis of β-methyl homoallylic alcohols

(1) Address correspondences to the author at Colorado State University, Fort Collins, CO 80523.

(2) (a) Zähner, H.; Holst, H.; Zoebelein, G.; Keckeisen, A. U.S. Patent 4 287 186, 1981. (b) König, W. A.; Hass, W.; Dehler, W.; Fiedler, H.-P.; Zähner, H. *Liebigs Ann. Chem.* **1980**, 622. (c) Dähn, U.; Hagenmaier, H.; Höhne, H., König, W. A.; Wolf, G.; Zähner, H. *Arch. Microbiol.* **1976**, *107*, 143. (d) Hagenmaier, H.; Keckeisen, A.; Zähner, H.; König, W. A. *Liebigs Ann. Chem.* **1979**, 1494. (e) König, W. A.; Hahn, H.; Rathmann, R.; Hass, W.; Keckeisen, A.; Hagenmaier, H.; Bormann, C.; Dehler, W.; Kurth, R.; Zähner, H. *Liebigs Ann. Chem.* **1986**, 407. (f) Hagenmaier, H.; Keckeisen, A.; Dehler, W.; Fiedler, H.-P.; Zähner, H.; König, W. A. *Liebigs Ann. Chem.* **1981**, 1018. (g) Delzer, J.; Fiedler, H.-P.; Müller, H.; Zähner, H.; Rathmann, R.; Ernst, K.; König, W. A. *J. Antibiot.* **1984**, *37*, 80.

(3) (a) Uramoto, M.; Kobinata, K.; Isono, K.; Higashijima, T.; Miyazawa, T.; Jenkins, E. E.; McCloskey, J. A. *Tetrahedron Lett.* **1980**, *21*, 3395. (b) Kobinata, K.; Uramoto, M.; Nishii, M.; Kusakabe, H.; Nakamura, G.; Isono, K. *Agric. Biol. Chem.* **1980**, *44*, 1709. (c) Uramoto, M.; Kobinata, K.; Isono, K.; Higashijima, T.; Miyazawa, T.; Jenkins, E. E.; McCloskey, J. A. *Tetrahedron* **1982**, *38*, 1599.

(4) Fiedler, H.-P.; Kurth, R.; Langhärig, J.; Delzer, J.; Zähner, H. *J. Chem. Tech. Biotechnol.* **1982**, *32*, 271.

(5) (a) Zimmerman, G.; Hass, W.; Faasch, H.; Schmalle, H.; König, W. A.; *Liebigs Ann. Chem.* **1985**, 2165. (b) Hass, W.; König, W. A. *Liebigs Ann. Chem.* **1982**, 1615.

(6) Hahn, H.; Heitsch, H.; Rathmann, R.; Zimmerman, G.; Bormann, C.; Zähner, H.; König, W. A. *Liebigs Ann. Chem.* **1987**, 803.

(7) Jäger, V.; Grund, H.; Buss, V.; Schwab, W.; Müller, I.; Schohe, R.; Franz, R.; Ehrler, R. *Bull. Soc. Chim. Belg.* **1983**, *92*, 1039.

(8) Melnick, M. J.; Weinreb, S. M. *J. Org. Chem.* **1988**, *53*, 850.

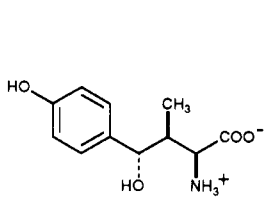
(9) (a) Banks, B. J.; Barrett, A. G. M.; Russell, M. A.; Williams, D. J. *J. Chem. Soc., Chem. Commun.* **1983**, 873. (b) Barrett, A. G. M.; Dhanak, D.; Lebold, S. A.; Russell, M. A., manuscript in preparation.

(10) König, W. A.; Pfaff, K.-P.; Bartsch, H.-H.; Schmalle, H.; Hagenmaier, H. *Liebigs Ann. Chem.* **1980**, 1728.

(11) (a) Isono, K.; Asahi, K.; Suzuki, S. *J. Am. Chem. Soc.* **1969**, *91*, 7490. (b) Damodaran, N. P.; Jones, G. H.; Moffatt, J. G. *J. Am. Chem. Soc.* **1971**, *93*, 3812. (c) Jones, G. H.; Moffatt, J. G.; Edge, M. D. U.S. Patent 3 935 184, 1976. (d) Rathmann, R.; König, W. A.; Schmalle, H.; Carlsson, G.; Bosch, R.; Hagenmaier, H.; Winter, W. *Liebigs Ann. Chem.* **1984**, 1216. (e) Barrett, A. G. M.; Lebold, S. A. *J. Org. Chem.* **1990**, *55*, 3853.

0022-3263/90/1955-5818$02.50/0

by the addition of crotylmetal derivatives to aldehydes.[12,13] In particular, Brown and Bhat[13] have shown that crotyldiisopinocamphenylboranes react with aldehydes to yield the corresponding β-methyl homoallylic alcohols with excellent diastereoisomeric and enantiomeric control. We now report the application of this methodology to construct the 3*S*,4*S* stereogenic centers of the N-terminal amino acid (**3**). Reaction of 4-(pivaloyloxy)benzaldehyde (**5**)[14] with



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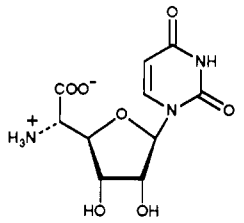

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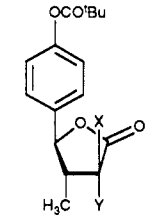
(−)-(*E*)-crotyldiisopinocamphenylborane followed by an alkaline hydrogen peroxide workup[13,15] gave the desired *anti*-β-methyl homoallylic alcohol **6** (82%) as a single diastereoisomer after chromatography (Scheme I).[16] Protection of alcohol **6** as the *tert*-butyldiphenylsilyl ether (97%)[17] followed by ozonolysis of the vinyl moiety afforded aldehyde **7** (84%). The last stereocenter was introduced by the Felkin Ahn controlled addition of lithiated ethyl vinyl ether[18] to aldehyde **7** at −100 °C. The corresponding vinyl ether was not isolated, but cleaved directly by reaction with ozone in situ, yielding a 6:1 mixture of α-hydroxy ethyl esters **8** and **9**. Flash chromatography on silica gave the pure major isomer **8** in a moderate yield overall (46%).

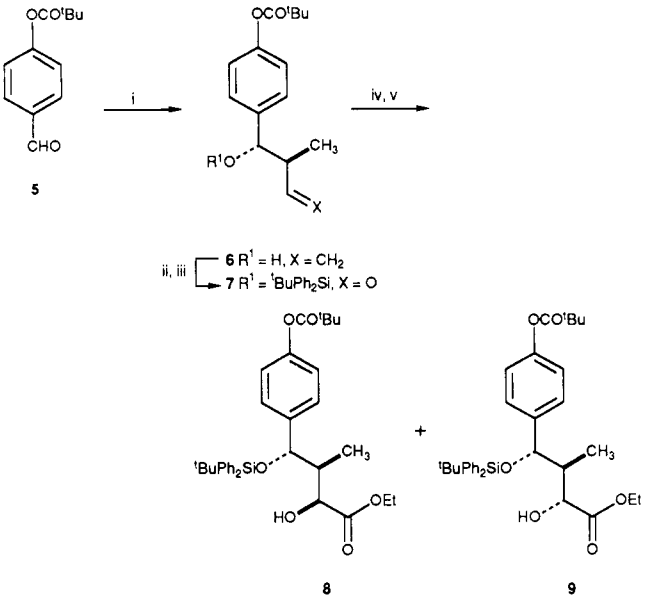
The C(2) stereochemistry of the α-hydroxy ethyl esters **8** and **9** was determined by conversion to the corresponding lactones **10** and **11**.[19] Through comparison of the H–C(3)–C(4)–H coupling constants, the trans stereochemistry was assigned to the major isomer,[8] which translates to the *S* configuration at C(2).



10 X = OH, Y = H
11 X = H, Y = OH

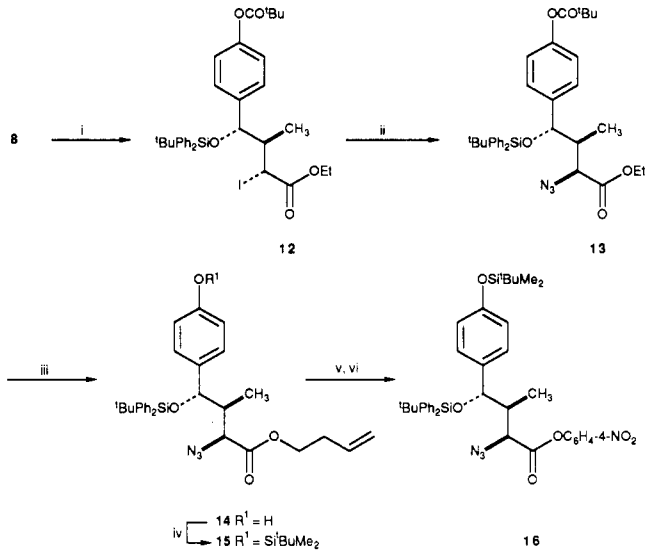
Introduction of the α-amino functionality was achieved by conversion of the hydroxy ester **8** to the iodide **12**

Scheme I[a]



[a] Reagents: (i) (−)-$(Ipc)_2BCH_2CH{=}CH_2CH_3$ (from (+)-pinene), THF/Et_2O, −78 °C, 4.5 h; H_2O_2, NaOH, reflux, 12 h, 82%; (ii) $BuPh_2SiCl$, DMF, imidazole, cat. DMAP, 60 °C, 12 h, 97%; (iii) O_3, 1:1 CH_2Cl_2–MeOH, −78 °C; DMS, 25 °C, 12 h, 84%; (iv) $CH_2{=}C(Li)OEt$, THF, −100 °C; (v) O_3, CH_2Cl_2, −78 °C; DMS, 25 °C, 18 h, 46%. Ipc = isopinocamphenyl.

Scheme II[a]



[a] Reagents: (i) $[Me(OPh)_3P^+]I^-$, DMF, 25 °C, 18 h, 85%; (ii) NaN_3, DMF, 60 °C, 30 min, 91%; (iii) 0.3 equiv of $Ti(O^iPr)_4$, 20 equiv of $CH_2{=}CHCH_2CH_2OH$, PhH, reflux 6 h, 91%; (iv) TBDMSOTf, 2,6-lutidine, THF, −78 °C to 25 °C, 95%; (v) O_3, 1:1 CH_2Cl_2–MeOH, −78 °C; DMS, 25 °C, 4 h; DBU, 25 °C, 2 h; (vi) DCC, 4-O_2N-C_6H_4OH, THF, 25 °C, 12 h, 61%.

(85%)[20] followed by nucleophilic displacement with sodium azide in DMF,[21] affording the desired 2(*S*)-α-azido ethyl ester **13** (91%) as a single diastereoisomer (Scheme II).

(12) For examples, see: (a) Buse, C. T.; Heathcock, C. H. *Tetrahedron Lett.* **1978**, 1685. (b) Hoffmann, R. W.; Zeiss, H.-J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 218. (c) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 555. (d) Yamamoto, Y.; Maruyama, K. *Heterocycles* **1982**, *18*, 357. (e) Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243. (f) Garcia, J.; Kim, B.-M.; Masamune, S. J. *J. Org. Chem.* **1987**, *52*, 4831. (g) Roush, W. R.; Halterman, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 294. (h) Roush, W. R.; Palkowitz, A. D.; Palmer, M. A. J. *J. Org. Chem.* **1987**, *52*, 316. (i) Martin, S. F.; Li, W. *J. Org. Chem.* **1989**, *54*, 6129.

(13) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293, 5919.

(14) Bender, M. L.; Nakamura, K. *J. Am. Chem. Soc.* **1962**, *84*, 2577.

(15) It is noteworthy to mention the use of sodium perborate as a convenient alternative to the basic peroxide workup described by Brown and Bhat (ref 13), see: Kabalka, G. W.; Shoup, T. M.; Goudgaon, N. M. *Tetrahedron Lett.* **1989**, *30*, 1483; *J. Org. Chem.* **1989**, *54*, 5930.

(16) The ^1H NMR spectrum of **6** indicated the material to be at least 96% diastereoisomerically pure. The enantiomeric purity of alcohol **6** was determined by conversion to the correspoding (*R*)-Mosher ester. Analysis of the crude ester by 400-MHz ^1H NMR showed the presence of a single diastereoisomer (>96% ee), see: Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(17) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975; **1977**, *55*, 562.

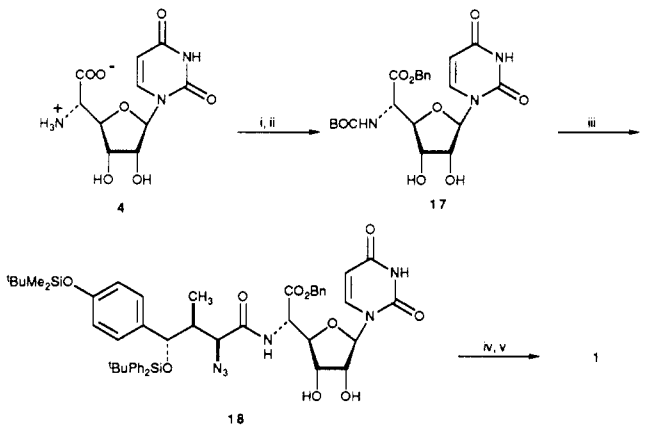
(18) Baldwin, J. E.; Höfle, G. A.; Lever, O. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7125.

(19) Reaction of **8** with HF/pyridine in CH_2Cl_2 at 0 °C gave **10** (27%) whereas reaction of **9** with BuNF in THF at 25 °C gave **11** (25%) (yields not optimized).

(20) Verheyden, J. P. H.; Moffatt, J. G. *J. Org. Chem.* **1970**, *35*, 2319.

(21) Boyer, J. H.; Canter, F. C. *Chem. Rev.* **1954**, *54*, 1 and references therein.

Scheme III[a]



[a] Reagents: (i) 1:1 dioxane-H_2O, K_2CO_3, BOC anhydride, 25 °C, 3.5 h; (ii) MeOH, $PhCHN_2$, 25 °C, 72%; (iii) TFA, EtOAc, 0 °C to 25 °C, 30 min, evaporate; 2 equiv of *N*-methylmorpholine, DMF, **16**, 25 °C, 72 h, 53%; (iv) TBAF, THF, 25 °C, 30 min; (v) 10% $Pd/BaSO_4$ (prehydrogenated overnight), $MeOH/H_2O$, H_2, 25 °C, 30 min, 39%.

Although saponification of the ester **13** led to undesired desilylation and lactonization, ester **13** could be hydrolyzed under nonaqueous conditions developed in this laboratory.[22] Transesterification of **13** in the presence of 3-buten-1-ol and $Ti(Oi\text{-}Pr)_4$[23] gave the ester **14** (91%), which was protected as the *tert*-butyldimethylsilyl ether **15** (95%).[24] Ozonolysis of the butene residue afforded the aldehyde which, after treatment with DBU[22] in situ, gave the α-azido acid. Without isolation, treatment of the acid with *p*-nitrophenol and DCC in THF[25] afforded the activated ester **16** (61%) as a single diastereoisomer.

p-Nitrophenyl esters are widely used to facilitate peptide bond formation.[25,26] In fact, a variety of *p*-nitrophenyl esters of N-protected α-amino acids have been utilized in the peptide-coupling reaction with α-amino nucleosides including the C-terminal amino acid, uracil polyoxin C (**4**).[27] Unfortunately, reaction of the C-terminal amino acid **4** with the activated ester **16** in DMF[27b] failed to afford any coupled product. However, after protecting nucleoside **4**, formation of the amide bond was achieved. The α-amino acid was first protected as the BOC derivative[28] followed by formation of the benzyl ester **17** using $PhCHN_2$,[29] (72% over 2 steps) (Scheme III). Liberation of the amine moiety by treatment with trifluoroacetic acid[26] gave the corresponding ammonium trifluoroacetate which was used directly in the peptide coupling reaction in DMF using N-methylmorpholine,[27] affording amide **18** (53%). Desilylation[17] of **18** and subsequent chemoselective hydrogenation over 10% $Pd/BaSO_4$ in aqueous methanol[11c] afforded the nucleoside dipeptide amino acid nikkomycin B (**1**) (39%).[30]

In conclusion, a potentially general route to the (2*S*,3*S*,4*S*)-γ-hydroxy-β-methyl-α-aminobutanoic acid moiety, a common feature of the nikkomycin N-terminal amino acid residues, has been described. The protected α-amino nucleoside fragment **17** has been successfully coupled with the activated *p*-nitrophenyl ester **16**, completing the total synthesis of nikkomycin B (**1**).

Acknowledgment. We thank the National Institutes of Health (AI-22252) for the support of this program and for the purchase of a 400-MHz NMR spectrometer (RR-01672) and a high-resolution mass spectrometer (RR-03245) used in these studies. We additionally thank Dr. Colin Smith of Glaxo Research Group, Greenford, Middlesex, U.K., for most generously providing authentic uracil polyoxin C (**4**) for studies on the peptide coupling reaction, G. D. Searle and Co., Skokie, IL, for microanalytical services, and Dr. Xiao-an Zhang for preliminary studies.

Supplementary Material Available: Experimental procedure for the conversion of **18** into nikkomycin B (**1**) and spectroscopic data for **1** (2 pages). Ordering information is given on any current masthead page.

(22) Barrett, A. G. M.; Lebold, S. A.; Zhang, X.-A. *Tetrahedron Lett.* **1989**, *30*, 7317.
(23) Seebach, D.; Hungerbühler, E.; Naef, R.; Schnurrenberger, P.; Weidmann, B.; Züger, M. *Synthesis* **1982**, 138.
(24) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.
(25) Bodansky, M.; du Vigneaud, V. *J. Am. Chem. Soc.* **1959**, *81*, 5688.
(26) (a) Bodansky, M.; Klausner, Y. S.; Ondetti, M. A. *Peptide Synthesis*; John Wiley: New York, 1976; pp 102-106. (b) Bodansky, M. *Principles of Peptide Synthesis*; Springer, Verlag: New York, 1984; p 30.
(27) (a) Azuma, T.; Saita, T.; Isono, K. *Chem. Pharm. Bull.* **1977**, *25*, 1740. (b) Khare, R. K.; Becker, J. M.; Naider, F. R. *J. Med. Chem.* **1988**, *31*, 650.
(28) Moroder, L.; Hallett, A.; Wünsch, E.; Keller, O.; Wersin, G. *Hoppe-Seyler's Z. Physiol. Chem.* **1976**, *357*, 1651.
(29) Adamson, J. R.; Bywood, R.; Eastlick, D. T.; Gallagher, R.; Walker, D.; Wilson, E. M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2030.
(30) We have been unable to obtain an authentic sample of nikkomycin B (**1**). Our structural assignment is based upon comparison of spectroscopic data for our synthetic material with the data reported by Konig for nikkomycin B_x (**2**). See ref 6 and the supplementary material.

Short Synthesis of (±)-Sterpurene

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Summary: The tricyclic fungal metabolite sterpurene (**1**) has been synthesized by a very short route employing a cyclopentane annulation as the key transformation.

Sterpurene (**1**) was first reported by Ayer in 1981 as a metabolite of *Stereum purpureum*, a fungus that is responsible for silver leaf disease.[1] Syntheses of racemic and nonracemic sterpurene have been reported by Murata, Little, and Okamura.[2] Herein we report our synthesis of (±)-sterpurene.

(1) Ayer, W. A.; Saeedi-Ghomi, M. H. *Can. J. Chem.* **1981**, *59*, 2536.
(2) (a) Murata, Y.; Ohtsuka, T.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1981**, *22*, 4313. (b) Moëns, L.; Baizer, M. M.; Little, R. D. *J. Org. Chem.* **1986**, *51*, 4497. (c) Gibbs, R. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1988**, *110*, 4062. (d) Gibbs, R. A.; Bartels, K.; Lee, R. W. K.; Okamura, W. H. *Ibid.* **1989**, *111*, 3717.

0022-3263/90/1955-5820$02.50/0