that spectrophotometry cannot be used for identification of the site of reduction in these synthetic chlorins and in those from natural sources.

Finally, it should be mentioned that this procedure offers access to a number of isomeric tetrapyrrole compounds suitable for spectroscopic study of model biological systems containing green hemes. Moreover, previous total syntheses of 2-vinylrhodoporphyrin XV[22] and 2,4-divinylrhodoporphyrin XV,[15] coupled with the published transformation of 2-vinylrhodochlorin into chlorophyll *a*,[14] open up a viable route for the efficient total synthesis of both chlorophyll *a* and 2,4-divinylchlorophyll *a*, the latter having been the topic of considerable attention in recent times.[23] This work is currently in progress.

Acknowledgment. This research was supported by grants from the National Science Foundation (CHE-81-20891) and the National Institutes of Health (HL 22252). We thank Frank Bobe for carrying out the NOE study.

Supplementary Material Available: Proton NMR spectra (360 MHz), melting points, and electronic absorption spectra of compounds **10** and **12-15** and the electronic absorption spectrum of the iron(III) chloride complex of **12** (typical example) (2 pages). Ordering information is given on any current masthead page.

(22) Howarth, T. T.; Jackson, A. H.; Kenner, G. W. *J. Chem. Soc., Perkin Trans. 1* **1974**, 502-511.
(23) Rebeiz, C. A. *Chem Tech*, **1982**, *12*, 52-63. Castelfranco, P. A.; Beale, S. *Annu. Rev. Plant Physiol.* **1983**, *34*, 241-278.

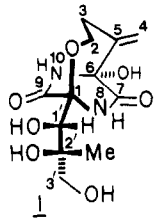
Stereocontrolled Total Synthesis of (±)- and (+)-Bicyclomycin: New Carbon-Carbon Bond-Forming Reactions on Electrophilic Glycine Anhydride Derivatives†

Robert M. Williams,*‡ Robert W. Armstrong, and Jen-Sen Dung

Department of Chemistry, Colorado State University Fort Collins, Colorado 80523

Received May 29, 1984

Bicyclomycin[1] (**1**) is a novel antibiotic that is biosynthetically derived[2] by the oxidative cyclodimerization of the amino acids leucine and isoleucine. Bicyclomycin has recently achieved



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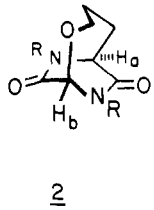

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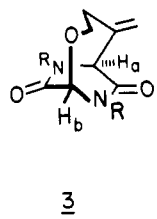

3

commerical stature[3] on a worldwide basis as a clinically useful antibiotic and is now produced on large scale from cultures of *Streptomyces sapporonensis*.

We have recently reported[4] the synthesis and regiocontrolled bridgehead carbanion elaboration of the 4-demethylene nucleus **2**. In order to reduce this efficient model study[5] to a total synthesis[6] of **1**, two difficult problems had to be addressed: (1) introduction of the C4-C5 *exo*-methylene moiety via a suitably oxidized isoleucine precursor and (2) selection of a suitable blocking group for the amides. In this paper, we wish to report a completely regio- and stereocontrolled total synthesis of bicyclomycin from the nucleus **3** that features a fundamentally new and generally useful C-C bond-forming reaction via *electrophilic* coupling to a glycine anhydride derivative.

As shown in Scheme I, 1,4-bis(*p*-methoxybenzyl)- and 1,4-dibenzyl-2,5-piperazinedione were brominated[7] and condensed with the sodium salt of 2-mercaptopyridine (THF, 25 °C, 30 min) to afford the crystalline *syn*-bis(sulfide) **5**. Precomplexation of **5** with 1 equiv of silver (I) triflate in THF at 25 °C for 10 min followed by addition of 1 equiv of butyrolactone trimethylsilyl enol ether (2 h, 25 °C) furnished the lactones **6** (1.3:1, syn:anti; 1.8:1 ratio, epimeric at the lactone α-carbon) in 71% yield.[8] It turned out to be critical to *precomplex* **5** with the silver salt before addition of the nucleophile to effect coupling. We were quite surprised to find that the silver complex of **5** is *indefinitely stable in solution* (THF, CH_2Cl_2, $CHCl_3$) and cleanly reacts, producing **6** upon addition of the trimethylsilyl ketene acetal. Additionally, the reaction proceeds predominantly with overall *retention* of stereochemistry with respect to the departing thiopyridyl residue and the newly attached lactone moiety. An X-ray crystallographic analysis[9] of the major syn diastereomer **6a** established the relative configuration (shown). Most importantly, we found that the *product* **6** *completely resists further C-C substitution at the remaining thiopyridyl residue* (excess AgOTf/ketene silyl acetal) at C-3 so that absolutely no 3,6-biscoupled products are observed. This remarkable chemoselectivity is highly significant since a major competing side reaction observed in the *nucleophilic* C-functionalization of N-substituted glycine anhydride enolates (i.e., of **4**) is 3,6-disubstitution.[4a]

Reduction of the major syn and anti lactones **6** afforded the diol **7**, which was cleanly cyclized[10] to the desired bicyclic alcohol **8** in the presence of silver(I) triflate in THF at 25 °C. Dehydration of **8** to the bicyclic olefin **9** was readily accomplished in three steps (Scheme I, steps e, f, g).

† Dedicated to the memory of the late Professor Kunio Sakan.
‡ NIH Research Career Development Awardee 1984-1989.
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(2) (a) Miyoshi, T.; Iseki, M.; Konomi, T.; Imanaka, H. *J. Antibiot.* **1980**, *33*, 480. (b) Miyoshi, T.; Iseki, M.; Konomi, T.; Imanaka, H. *Ibid.* **1980**, *33*, 488.
(3) "Merck Index", 10th Ed.; Merck: Rahway, NJ, 1983; no. 1213. Bicozamycin is the commercial synonym (Fujisawa Pharmaceutical Company, Ltd., Japan) for bicyclomycin (aizumycin).
(4) (a) Williams, R. M.; Anderson, O. P.; Armstrong, R. W.; Joey, J.; Meyers, H.; Eriksson, C. *J. Am. Chem. Soc.* **1982**, *104*, 6092. (b) Williams, R. M.; Dung, J.-S.; Josey, J.; Armstrong, R. W.; Meyers, H. *Ibid.* **1983**, *105*, 3214. (c) Armstrong, R. W.; Dung, J.-S.; Williams, R. M. "Abstracts of Papers", 185th National Meeting of the American Chemical Society, Seattle, WA, March 1983; American Chemical Society: Washington, DC, 1983; ORGN 10.
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(6) For a recent total synthesis, see: (a) Nakatsuka, S.; Yamada, K.; Yoshida, K.; Asano, O.; Murakami, Y.; Goto, T. *Tetrahedron Lett.* **1983**, *24*, 5627. (b) Nakatsuka, S.; Goto, T. *Heterocycles* **1984**, *21*, 61.
(7) Trown, P. W. *Biochem. Biophys. Res. Commun.* **1968**, *33*, 402.
(8) The coupling reaction of **5a** to afford **6a** proceeded to give a 2:1 ratio of syn lactones. The major syn diastereomer was directly converted to **8a** by $LiAlH_4$ reduction and cyclization. The minor syn lactone could either be epimerized to the major syn diastereomer or converted to **9a** as described in ref 10.
(9) Williams, R. M.; Armstrong, R. W.; Maruyama, L. K.; Dung, J.-S.; Anderson, O. P., unpublished results.
(10) The minor syn lactone **6b** could be epimerized to a 1:1 mixture of the two syn diastereomers (0.1 N NaOH, THF, 25 °C) or reduced to the corresponding diol ($LiAlH_4$). This diol was converted to the desired bicyclic system through (1) selective silylation at the 3″-hydroxyl (Me_2Bu^tSiCl, DMAP, Et_3N, CH_2Cl_2), (2) mesylation (MsCl, Et_3N, THF), and (3) cyclization with $Cu(ClO_4)_2$/THF, 25 °C, to afford the bicyclo[4.2.2] mesylate (epimeric at C-5, cf. structure **8**) which was directly converted to olefin **9** (Scheme I, steps f and g).

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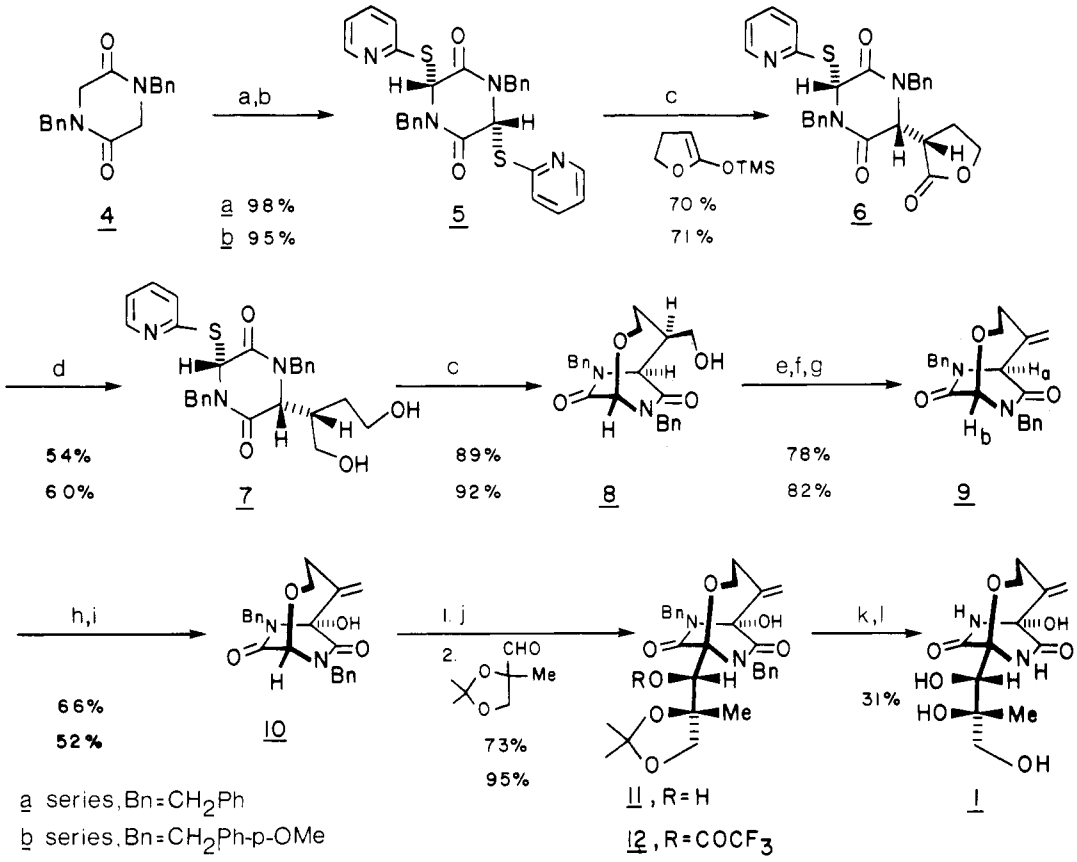
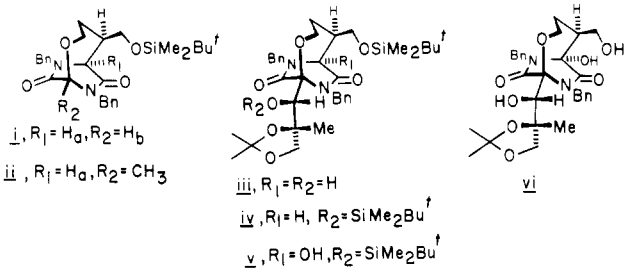
Scheme I[a]



[a] Reagents and Conditions: (a) 2 equiv of *N*-bromosuccinimide, catalytic benzoyl peroxide, CCl_4, reflux, 30 min; (b) 2.0 equiv of NaS(py), THF, 25 °C, 30 min; (c) 1 equiv of AgOTf, THF, 25 °C; (d) 1 equiv of $LiAlH_4$, THF, 25 °C, 1 min then, $Na_2SO_4 \cdot 10H_2O$; (e) 2.5 equiv of methanesulfonyl chloride, Et_3N (2.5 equiv), THF, 25 °C, 12 h; (f) 2.2 equiv of $NaBH_3SePh$, THF, reflux, 2.2 h; (g) 30% H_2O_2 (5 equiv) THF, reflux, 20 min; (h) 1.5 equiv of *n*-BuLi, HMPA (2 equiv), $(Me_2N)_3P$ (2 equiv), THF, −78 °C, 1 min; (i) O_2 (gas) 15 min, −100 °C; (j) 2.3 equiv of *n*-BuLi, THF, −100 °C; (k) 10 equiv of $(F_3CCO)_2O$, 15 equiv of DMAP, CH_2Cl_2, 25 °C, 20 min; (l) 4 equiv of ceric ammonium nitrate, CH_3CN/H_2O (4:1, 0.2 M), 25 °C, 35 min, then silica gel PTLC (20% MeOH in $CHCl_3$).

Regioselective[11] bridgehead hydroxylation of **9** (Scheme I, steps h and i) afforded the desired bridgehead alcohol **10** (55%). Formation of the dianion[4] of **10** followed by aldol condensation with (±)-2,2,4-trimethyl-1,3-dioxolane-4-carboxaldehyde[12] afforded a *single* diastereomer **11** (95%); no evidence for the formation of any of the other three possible diastereoisomers on many trials could be obtained under these conditions.[13] We found it necessary to block the secondary hydroxyl group of **11b** to effect the clean removal[14] of the *p*-methoxybenzyl residues and preclude a competing rearrangement similar to that recently reported by Wacker.[15] Thus, treatment of **11b** with TFAA/DMAP in CH_2Cl_2 afforded the corresponding 1′-*O*-trifluoroacetate **12**. Reaction of this material with 4 equiv of ceric ammonium nitrate[16] in acetonitrile/H_2O (0.2 M) followed by PTLC on silica gel *directly* furnished totally synthetic bicyclomycin (31% overall from **11b**). The synthetic material was identical with the natural sample[17] by ^1H NMR, ^{13}C NMR, IR, MS, and TLC behavior. By carrying out the aldol condensation of racemic **10** with *optically active* (−)-2,2,4-trimethyl-1,3-dioxolane-4-carboxaldehyde[12b] (83% ee) and following exactly the same procedure as above, *optically active* bicyclomycin, $[\alpha]^{25}_D$ +50.8° (MeOH, 78% ee), was obtained; this constitutes the *first* total synthesis of bicyclomycin in optically active form. Thus, the total synthesis of bicyclomycin has been achieved in only 12 chemical steps with *complete* regio- and stereocontrol (4.6% yield overall). In addition, the new C–C

(11) We initally investigated the bridgehead functionalization of the *tert*-butyldimethylsilyl ether *i* obtained from **8a** ($ClSiMe_2Bu^t$, Et_3N, CH_2Cl_2, DMAP). Treatment of i with *n*-BuLi in THF/HMPA at −100 °C followed by quenching with CH_3I afforded *exclusively* the methylated derivative ii. This regioselectivity is in contradistinction with that we have observed[4] for **2**. Regio- and stereoselective aldol condensation of the bridgehead carbanion of i (LDA/THF, −100 °C) as described for **10** → **11** afforded a *single* diastereomer iii (80%). Silylation (Bu^tMe_2SiOTf, 2,6-lutidine, CH_2Cl_2, 25 °C) of the secondary alcohol followed by hydroxylation (*t*-BuLi/THF −100 °C, O_2 quenching) afforded the alcohol v (78%).



(12) (a) Maag, H.; Blount, J. F.; Coffen, D. L.; Steppe, T. V.; Wong, F. *J. Am. Chem. Soc.* **1978**, *100*, 6786. (b) See also: Dung, J.-S.; Armstrong, R. W.; Anderson, O. P.; Williams, R. M. *J. Org. Chem.* **1983**,, *48*, 3592.

(13) At −78 °C, a small amount of the C-2′ diastereomer can be isolated. The related aldol condensation in the Goto synthesis[6] exhibited relatively poor diastereoselectivity (3:1:1:0 ratio, 41% yield).

(14) The *N*-benzyl series was terminated at this junction since all attempts to reductively remove the *N*-benzyl groups on any bicyclic derivative (i–vi, **8a**, **2**) failed to produce any quantity of the desired deprotected compounds; reductive cleavage of the C_1–O ether linkage and saturation of the aromatic benzylic rings were the *only* types of reactivity observed. Conditions examined: 20% Pd/C, H_2, 1 atm, EtOH, 80 °C; 20% PtO_2, H_2; 20% $Pd(OH)_2/H_2$; a range of solvents, temperatures, and H_2 pressures were examined for each catalyst; see also, ref 6.

(15) Wacker, O.; Kump, W.; Muller, B. W. *Tetrahedron Lett.* **1983**, *24*, 5607.

(16) The excellent procedure reported by Yoshimura was utilized: Yoshimura, J.; Yamaura, M.; Suzuki, T.; Hashimoto, H. *Chem. Lett.* **1983**, 1001.

coupling reaction we have developed for this synthesis represents a highly useful chemoselective method for preparing hitherto inaccessible α-C-homologated piperazinediones and, potentially, other α-amino acid derivatives.[9] The methodology described herein is *uniquely* adaptable to the preparation of many structurally diverse bicyclomycin analogues that cannot be prepared by modification of the abundantly available natural product nor from any of the other published[5,6] synthetic efforts. Finally, we have found that the *p*-methoxybenzyl groups can be cleanly and *reliably* removed from any of these bicyclic structures[17] (i.e., **2** (R = CH_2Ph-*p*-OCH_3), **8b**, **9b**, and **10b**) to afford the hydrophilic "free" amides. Biological and mechanistic studies utilizing this chemistry shall be reported in due course from these laboratories.

Acknowledgment. We gratefully acknowledge the National Institutes of Health Grant RO1AIGM 18957 for financial support of this work. We thank Fujisawa Pharmaceutical Co., Ltd., Japan, for the generous gift of natural bicyclomycin used for comparison. NMR measurements at 360 MHz were obtained at the Colorado State University Regional NMR Center, funded by the National Science Foundation Grant CHE 78-18581.

Supplementary Material Available: Complete spectroscopic and analytical data for all new compounds (12 pages). Ordering information is given on any current masthead page.

(17) Preliminary antimicrobial assays of totally synthetic (±)-bicyclomycin against *E. coli 94* and *Klebsiella pneumoniae 369* show that the racemic material exhibits half the activity of the natural compound; numerous N-deprotected bicyclic analogues have been evaluated for antimicrobial activity: Williams, R. M.; Armstrong, R. W.; Dung, J.-S., unpublished results. We thank Drs. Hans Maag and David Pruess of Hoffman La-Roche, Inc., for performing the assay.

Fast Atom Bombardment Mass Spectroscopy (FABMS) of Polyoxoanions

Richard G. Finke,*[1] Michael W. Droege,[1] J. Carter Cook,[2] and Kenneth S. Suslick*[2]

Department of Chemistry, University of Oregon
Eugene, Oregon 97403
School of Chemical Sciences
University of Illinois at Urbana-Champaign
Urbana, Illinois 61801

Received May 3, 1984

Polyoxoanion chemistry[3] is a field poised for a rapid development with a wide range of potential applications.[3a,c,4-7] Hampering this development, however, are well-known difficulties in obtaining accurate analytical[8] and molecular weight data,[3a] problems that

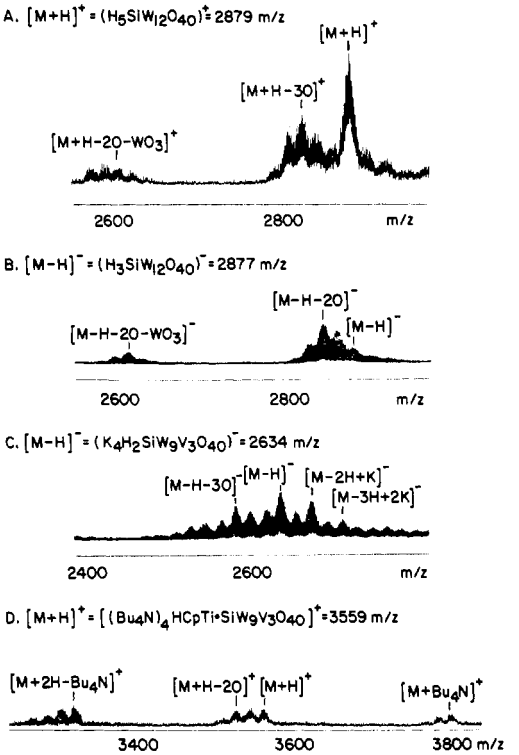


Figure 1. (A) Positive-ion spectrum of $H_4SiW_{12}O_{40}$. (B) Negative-ion spectrum of $H_4SiW_{12}O_{40}$. Note that molecular ion and the loss of O and WO_3 are observed in both spectra A and B. Not shown are the sequential losses of WO_3 in both spectra and much smaller peaks above 3000 m/z due to the attachment of WO_3 fragments or of thioglycerol in the negative-ion spectrum. (C) Negative-ion spectrum of $K_4H_3SiW_9V_3O_{40}$. Extensive exchange of cations (cationization) is observed. Sequential loss of O and WO_3 (not shown) is also observed. (D) Positive-ion spectrum of $(Bu_4N)_4CpTi{\cdot}SiW_9V_3O_{40}$. Only peaks corresponding to cation exchange and loss of O are observed. The sequential loss of WO_3 is not observed.

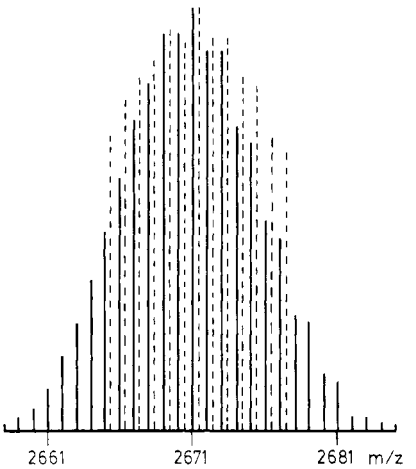


Figure 2. Calculated (solid line) vs. observed (dotted line) isotopic distribution patterns for the $[M - 2H + K]^-$ (= $K_5HSiW_9V_3O_{40}^-$) ion at m/z 2671. Only the centermost lines of the two patterns are directly comparable due to the presence of overlapping patterns in the observed FABMS for the $K_5HSiW_9V_3O_{40}^-$ ion.

(1) University of Oregon.
(2) University of Illinois.
(3) (a) Pope, M. T. In "Heteropoly and Isopoly Oxometalates"; Springer-Verlag: New York, 1983; Inorganic Chemistry Concepts. (b) Weakley, T. J. R. *Struct. Bonding* **1974**, *18*, 131. (c) Tsigdinos, G. *Topics Curr. Chem.* **1978**, *76*, 1. (d) Evans, H. T., Jr. *Perspect. Struct. Chem.* **1971**, *4*, 1. (e) Kepert, D. L. *Prog. Inorg. Chem.* **1962**, *4*, 199. (f) Tytko, K.-H., Glemser, O. *Adv. Inorg. Chem. Radiochem.* **1976**, *19*, 239.
(4) A large number of examples of polyoxoanions in catalysis, largely heterogeneous catalysis, exist. A few references in acid catalysis,[4a-d] oxidation catalysis,[4e-h] homogeneous Wacker-type[4i,j] chemistry, and recent reviews[4k] are provided below. (a) Onoue, Y.; Mizutani, Y.; Akiyama, S.; Izumi, Y. CHEMTECH **1978**, 432 (b) Ono, Y.; Baba, T.; Sakai, J.; Keii, T. *J. Chem. Soc., Chem. Commun.* **1981**, 400. Baba, T.; Sakai, J.; Ono, Y. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2657. (c) Okuhara, T.; Kasai, A.; Hayakawa, N.; Yoneda, Y.; Misono, M. *J. Catal.* **1983**, *83*, 121. (d) Hayashi, H.; Moffat, J. B. *J. Catal.* **1983**, *83*, 192; *Ibid.* **1983**, *81*, 61. (e) Konishi, Y.; Sakata, K.; Misono, M.; Yoneda, Y. *J. Catal.* **1982**, *77*, 169. (f) Ai, M. *J. Catal.* **1981**, *71*, 88. (g) Akimoto, M.; Tsuchida, Y.; Echigoya, E. *Chem. Lett.* **1980**, 1205. (h) Akimoto, M.; Tsuchida, Y.; Sato, K.; Echigoya, E. *J. Catal.* **1981**, *72*, 83. (i) Ogawa, H.; Fujinami, H.; Taya, K. *J. Chem. Soc., Chem. Commun.* **1981**, 1274. (j) Taraban'ko, V. E.; Kozhevenikov, I. V.; Matreev, K. I. *Kinet. Katal.* **1978**, *19*, 1160. (k) Kozhevnikov, I. V.; Matveev, K. I. *Appl. Catal.* **1983**, *5*, 135; *Russ. Chem. Rev. (Engl. Transl.)* **1982**, *51*, 1075.
(5) For photochemical applications, see: (a) Papaconstantinou, E. *J. Chem. Soc., Chem. Commun.* **1982**, 12. (b) Yamase, T. *Inorg. Chim. Acta* **1983**, *76*, L25; *Ibid.* **1981**, *54*, L207. (c) Yamase, T.; Sasaki, R.; Ikawa, T. *J. Chem. Soc., Dalton Trans.* **1981**, 628. (d) Hill, C. L., unpublished results. Cited at the Proceedings of the Joint NSF-CNRS Polyoxoanion Workshop, St. Lambert des Bois, France, July 11-13, 1983.

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