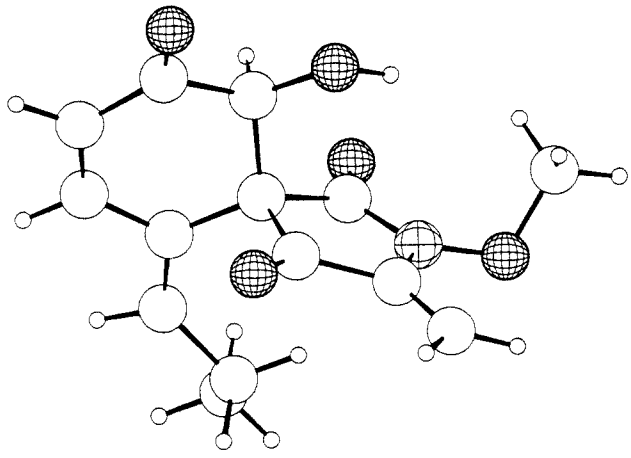
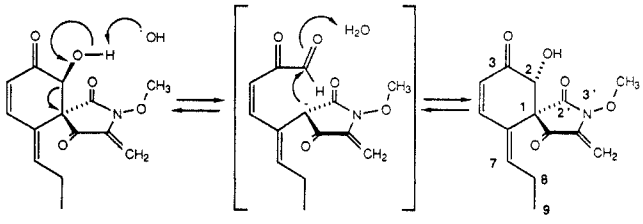


Figure 1. A computer-generated drawing of the final X-ray model of triticone A (**1**). No absolute configuration is implied (see text).

Scheme I



1 3 2

chemical studies have appeared. Our studies on *D. tritici-repentis*, the isolation and the characterization of unusual spirocyclic γ-lactams trivially named triticone A (**1**) and B (**2**), are the subject of this report.

D. tritici-repentis was grown in shake culture on a modified M-1-D medium for 3 weeks,[7] and a simple leaf puncture assay on wheat guided the toxin purification.[4] Extraction of the culture broth with ethyl acetate, flash chromatography, and chromatography on Sephadex LH-20 led to the isolation of the most active fraction as a mixture of triticones A and B (12 mg/L).[8] The mixture was active in a leaf assay at 10^{-5} M, and the assay symptoms closely resembled those of the natural infection.

Work on the active fraction was hampered by its ready decomposition; heating above 35 °C or silica gel TLC led to extensive decomposition. A fortuitous slow evaporation of an ethyl acetate solution in the cold led to the formation of crystals which belonged to space group $P2_12_12_1$ ($z = 8$) with $a = 9.026$ (2), $b = 13.387$ (3), and $c = 23.214$ (4) Å. The molecular structure was analyzed by single-crystal X-ray diffraction, and a drawing of the final X-ray model is shown in Figure 1. The molecule shown was called triticone A (**1**), and there were two independent enantiomeric molecules in the asymmetric unit.

The spectral data for the active fraction indicated the presence of two very similar molecules, which we were unable to separate chromatographically, in the approximate ratio of 10:9. The ^{1}H NMR signal for the proton on C2 was typical. It appeared as two doublets at δ 4.74 and 4.66 both with $J = 2.1$ Hz, and a 2-D NOESY spectrum indicated the cross peaks for interconversion between the two molecular forms. The optical rotation for the mixture varied from $[\alpha]_D$ of 0° to −9° depending on the sample's history. The most plausible interpretation of these and other observations is shown in Scheme I. Triticone A (**1**) could be converted to **3** in a retro-aldol type reaction. Intermediate **3** is achiral, so reversion to **1** would give racemization. Intermediate **3** could close in an alternate manner to generate **2**. Thus Scheme I interconverts **1** and **2** as well as racemizing both. Compound **1** is the diastereoisomer which crystallized and is trivially named triticone A; triticone B is **2**. The observed optical rotation indicates that *D. tritici-repentis* produces optically active **1** or **2** (or both) and that racemization or interconversion is an artifact of the isolation. The ultimate plant toxin may well be the putative intermediate **3**.

The triticones are new chemotypes, and no closely related molecules have been described. They are not only active in the leaf assay but also have an LD_{50} in a wheat protoplast assay 4.0 μM after 2 h.[9]

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Supplementary Material Available: Tables of fractional coordinates, thermal parameters, interatomic distances, interatomic and torsional angles for **1** and spectral data for **1** and **2** (8 pages). Ordering information is given on any current masthead page.

(7) Pinkerton, F.; Strobel, G. A. *Proc. Natl. Acad. Sci. U.S.A.* **1976**, *73*, 4007-11.

(8) The EIMS gave a m/z 277.0948 [$C_{14}H_{15}NO_5$ requires 277.0950]. Other spectral data for triticone A (**1**) and B (**2**) are given in the Supplementary Material.

(9) The protoplast assay was done by using a fluorescence activated cell sorter. Cells were stained with fluorescein diacetate according to the procedure of Strange et al.[10] A similar assay for animal cells is described in ref 11.

(10) Strange, R. N.; Pippard, D. J.; Strobel, G. A. *Physiol. Plant Pathology* **1982**, *20*, 359-364.

(11) Murphy, R. F.; Powers, S.; Cantor, C. R. *J. Cell. Biol.* **1984**, *98*, 1757-62.

Catalysis of Alkene Oxidation by Nickel Salen Complexes Using NaOCl under Phase-Transfer Conditions

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The selective oxidation of hydrocarbons by inexpensive oxidants is an area of intensive study. In particular, catalysis of alkene oxidation by soluble transition-metal complexes is of interest in both biomimetic and synthetic chemistry.[1] The use of hypochlorite ion for the epoxidation of alkenes was initially limited to the activated carbon–carbon double bonds of certain arenes[2] or α,β-unsaturated ketones.[3] More recently, OCl^- has been effectively used in the presence of manganese porphyrin catalysts to epoxidize a variety of olefins.[4] Only a few non-porphyrinic metal complexes have been studied; these reactions generally yield a large amount of C=C bond cleavage products when either OCl^- or IO_4^- is employed as oxidant.[5,6]

As part of our interest in hydrocarbon oxidation catalyzed by nickel^{II} complexes,[7] we report here the ability of Ni^{II}(salen)[8] and

(1) (a) Sheldon, R. A.; Kochi, J. K. *Metal-Catalyzed Oxidations of Organic Compounds*; Academic: New York, 1981. (b) Holm, R. H. *Chem. Rev.* **1987**, *87*, 1401-1449.

(2) (a) Krishnan, S.; Kuhn, D. G.; Hamilton, G. A. *J. Am. Chem. Soc.* **1977**, *99*, 8121-8123. (b) Fonouni, H. E.; Krishnan, S.; Kuhn, D. G.; Hamilton, G. A. *J. Am. Chem. Soc.* **1983**, *105*, 7672-7676.

(3) Reamonn, L. S. S.; O'Sullivan, W. I. *J. Chem. Soc., Chem. Commun.* **1976**, 1012-1013.

(4) (a) Guilmet, E.; Meunier, B. *Tetrahedron Lett.* **1980**, *21*, 4449-4450. (b) Guilmet, E.; Meunier, B. *Ibid.* **1982**, *23*, 2449-2452. (c) Guilmet, E.; Meunier, B. *Nouv J. Chim.* **1982**, *6*, 511-513. (d) Meunier, B.; Guilmet, E.; De Carvalho, M. E.; Poilblanc, R. *J. Am. Chem. Soc.* **1984**, *106*, 6668-6676.

(5) Eskenazi, C.; Balavoine, G.; Meunier, F.; Riviere, H. *J. Chem. Soc., Chem. Commun.* **1985**, 1111-1113.

(6) Dobson, J. C.; Seok, W. K.; Meyer, T. J. *Inorg. Chem.* **1986**, *25*, 1514-1515.

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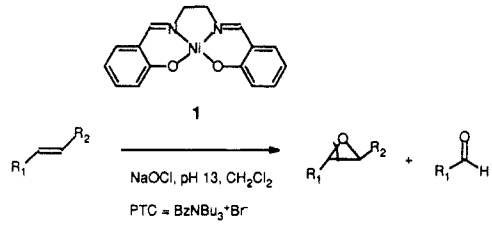
Table I. Percent Conversion and Yields of Products from Oxidation of Alkenes Using OCl^- Catalyzed by Ni^{II}(salen) (**1**)

substrate	% convsn[a]	epoxide[b]	PhCHO[c]	selectivity[d]
styrene	98	44	6	45
(*Z*)-β-methylstyrene	100	84[e]	10	84
(*E*)-β-methylstyrene	100	89[e]	0	89
(*Z*)-stilbene	45	12[e]	12	27
(*E*)-stilbene	80	46[e]	0	58
cyclohexene	87	23		26
norbornene	94	30[f]		32

[a] Disappearance of starting material after 5 h. [b] Based on starting alkene. [c] Remainder of product is $PhCO_2H$. [d] Epoxide yield/% conversion. [e] (*E*)-Epoxide only. [f] *exo*-Epoxide only.

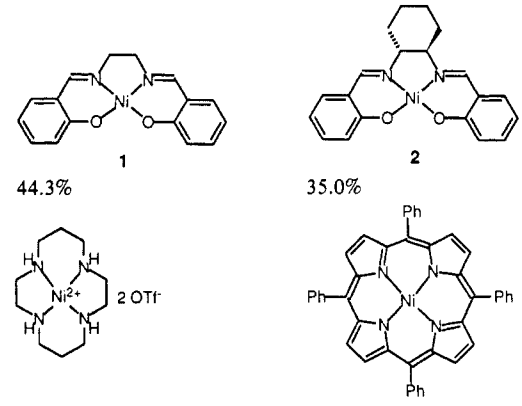
Ni^{II}(cyclam) complexes to facilitate oxygen atom transfer from OCl^- to alkenes. These complexes were recently shown to be the first examples of Ni^{II} catalysts for olefin epoxidation and were effective when iodosylbenzene was used in very large excess as the terminal oxidant.[9,10] In addition, Mn^{III}- and Cr^{III}(salen) complexes are also catalytically active in PhIO epoxidation reactions.[11] It was therefore a great interest to ascertain how effective Ni^{II}(salen) might be with OCl^-, a far more convenient oxidant, and to compare its reactivity to oxidations using PhIO.



In a typical experiment, 4.0 mmol alkene, 0.1 mmol nickel catalyst, and 0.15 mmol benzyltributylammonium bromide (phase-transfer catalyst, PTC) in 10 mL of CH_2Cl_2 were stirred vigorously with 20 mL of 0.77 M NaOCl (domestic bleach, pH 13) at room temperature. A fine black precipitate formed slowly in the reaction mixture upon addition of NaOCl but sometimes disappeared after all of the substrate was consumed, typically 2–6 h. Aliquots of the CH_2Cl_2 layer were analyzed by gas chromatography and compared to an internal standard. Turnover rates for reactive substrates (β-methylstyrenes) were as high as 65 h^{-1}.

Table I lists the yields of epoxidation and C=C bond cleavage products for a variety of substrates. Overall, the selectivity for epoxidation by OCl^- with respect to other oxidation pathways was higher for Ni^{II}(salen) than for other non-porphyrin complexes.[5,6] Electron-rich β-methylstyrenes were converted to epoxides in excellent yield. From other aromatic olefins, epoxides were less selectively produced, and further oxidation to benzaldehyde and benzoic acid was competitive. (*Z*)-Stilbene was less reactive than its *E* isomer. This selectivity is opposite that of metal–porphyrin catalysts[4] but similar to that observed for the Ni^{II}(cyclam)/PhIO system.[10] Aliphatic olefins were very reactive but gave only moderate yields of the simple epoxides and substantial amounts of products containing both chlorine and oxygen. This was surprising since the pH 13 medium should suppress the concentration of HOCl and therefore free-radical chlorination. In another experiment, the epoxidation of norbornene was investigated and found to give exclusively the exo epoxide. This result suggests that the reaction mechanism does not involve the intermediacy of chlorohydrins.[4,12]

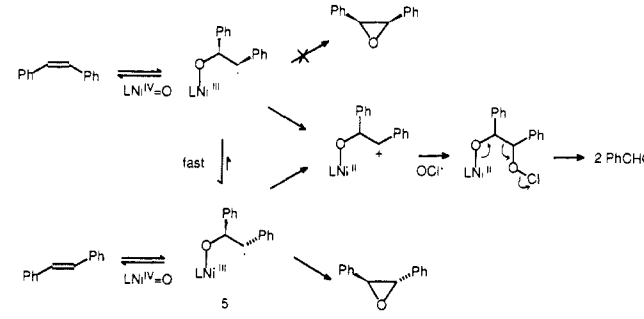
Table II. Yields of Styrene Oxide as a Function of Catalyst[a]



1	2	3	4	$Ni(OCOCH_3)$	no catalyst[b]
44.3%	35.0%	4.7%	0%	trace	0.7%

[a] Reaction time (6 h); see text for standard reaction conditions. [b] Reaction time (18 h).

Scheme I



A comparison of the effectiveness of various ligands in Ni^{II} complexes is shown in Table II. The salen ligand prepared from *trans*-1,2-diaminocyclohexane (**2**) was similar to **1** in its reactivity toward epoxidation. Surprisingly, the cyclam complex **3** was significantly less effective than salen complexes, while the reverse was found for the catalysis of epoxidation using PhIO.[9] Complex **1** is a diamagnetic species with square-planar structure, while **3** is a mixture of square-planar and octahedral forms in halocarbon solvents. (Tetraphenylporphyrinato)nickel^{II} (**4**) was completely inactive, as it is, too, in PhIO reactions. Thus, there exist very specific ligand requirements in order for Ni^{II} to participate in catalysis of epoxidation with OCl^-.

The appearance of a fine black suspension in the reaction mixture implied that nickel peroxide, $NiO(OH)_2$,[13] a species known to be formed upon addition of OCl^- to Ni^{2+} salts,[14] might be the active oxidant in the reaction. This proposal was ruled out by the observation of only trace amounts of epoxidation when nickel peroxide was generated from $Ni(OCOCH_3)_2$ and used as catalyst. Furthermore, when the black precipitate was isolated and added to a reaction mixture containing only substrate or substrate plus nickel(salen) but no OCl^-, no epoxidation was detected. Thus, small amounts of nickel peroxide that may indeed be formed in the reaction mixture are not responsible for epoxidation. In addition, it was found that O_2 and $NaIO_4$ were unreactive toward Ni^{II}salen complexes, although persulfate ($KHSO_5$, pH 8 buffer) could be substituted for OCl^-. We propose that complexes **1** and **2** are able to react efficiently with hypochlorite to yield a high valent nickel–oxo species capable of oxygen atom transfer to

(7) Kinneary, J. F.; Albert, J. S.; Burrows, C. J. *J. Am. Chem. Soc.*, accepted for publication.
(8) Abbreviations used: salen, *N*,*N*′-ethylenebis(salicylideneamine); cyclam, 1,4,8,11-tetraazacyclotetradecane; TPP, 5,10,15,20-tetraphenylporphyrin.
(9) Koola, J. D.; Kochi, J. K. *Inorg. Chem.* **1987**, *26*, 908–916.
(10) Kinneary, J. F.; Wagler, T. R.; Burrows, C. J. *Tetrahedron Lett.* **1988**, *29*, 877–880.
(11) (a) Samsel, E. G.; Srinivasan, K.; Kochi, J. K. *J. Am. Chem. Soc.* **1985**, *107*, 7606–7617. (b) Srinivasan, K.; Michaud, P.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309–2320.
(12) (a) Kwart, H.; Wosburg, W. G. *J. Am. Chem. Soc.* **1954**, *76*, 5400–5403. (b) For further discussion of *endo*- versus *exo*-epoxynorbornane, see ref 4d and Traylor et al. (Traylor, T. G.; Nakano, T.; Dunlap, B. E.; Traylor, P. S.; Dolphin, D. *J. Am. Chem. Soc.* **1986**, *108*, 2782–2784).
(13) $NiO(OH)_2$ is an approximate formula. See ref 14.
(14) George, M. V.; Balachandran, K. S. *Chem. Rev.* **1975**, *75*, 491–519.

alkenes as well as hydrogen atom abstraction.

A mechanistic pathway is suggested in Scheme I. Ni^{IV}–oxo intermediates have been proposed for the cyclam complexes responsible for epoxidation with PhIO,[7,9] and a similar mechanism may be occurring with the salen complex. Because of higher d orbital occupancy however, a Ni^{IV}–oxo complex of salen might not have a structure strictly analogous to the known (salen)-$Cr^{V}{=}O^{+}$ complex[15] or the proposed square pyramidal (TPP)-$Fe^{IV}{=}O^{+}$,[16] although it would be expected to be highly reactive toward olefins. The lack of stereospecificity in the epoxidation pathway is consistent with the subsequent nickel–oxo–olefin intermediate existing as an open chain radical with rapid rotation possible before reductive elimination to yield epoxides. Trapping of this intermediate **5** by OCl^{-} provides an explanation for the appearance of benzaldehyde in the reactions of phenyl-substituted alkenes. Subsequent oxidation of PhCHO to $PhCO_2H$ is well-known with NaOCl. Rigorous degassing of the solutions to remove O_2 prior to the reaction had little effect on the composition of the products. However, bubbling O_2 through the reaction mixture markedly increased the amount of PhCHO + $PhCO_2H$ formed. This further suggests that intermediate **5** may be trapped by dissolved O_2. Further work in this area is in progress to determine more precisely the structure of the proposed intermediates.

In summary, Ni^{II}(salen) complexes are unusually active as catalysts for olefin oxidation in the presence of hypochlorite. In view of nature's ability to use nickel-containing enzymes in redox processes[17] and chemists' ability to create new ligands, the future of nickel complexes in catalysis of hydrocarbon transformations is quite attractive.

Acknowledgment. We gratefully acknowledge a grant from the National Science Foundation (CHE-8706616) in support of this work.

(15) Srinivasan, K.; Kochi, J. K. *Inorg. Chem.* **1985**, *24*, 4671–4679.
(16) We also cannot rule out the possibility that Cl^{-} is still bound to the oxygen atom in the nickel–oxo catalytic intermediate.
(17) Walsh, C. T.; Orme-Johnson, W. H. *Biochemistry* **1987**, *26*, 4901–4906.

Observations on the Activation of Bicyclomycin

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The mode of action of the antibiotic, bicyclomycin (**1**), remains enigmatic. Proposals have appeared suggesting that the biological process entails the binding of nucleophilic species (i.e., sulfhydryl proteins) to the exomethylene group in **1**[1-4] within the peptidoglycan assembly of Gram-negative bacterial cell walls.[3,4] Recently, Vasquez[3] and Williams[4] have both proposed that drug activation is initiated by enzymatic cleavage of the C_9–N_{10} bond of the piperazinedione ring in bicylomycin. Adequate support for these hypotheses is lacking. Progress has been hampered by the inability to activate the drug under conditions which approximate the biological process. In all previous cases, use of either highly basic[1a,4,5] or acidic[6] conditions were required to functionalize the exomethylene group in **1**. In this communication, we report the *binding of bicyclomycin to thiols at room temperature at near neutral "pH"*. Evidence is provided that functionalization of the exomethylene group in bicyclomycin is accompanied by an extraordinary mixed-Claisen condensation.

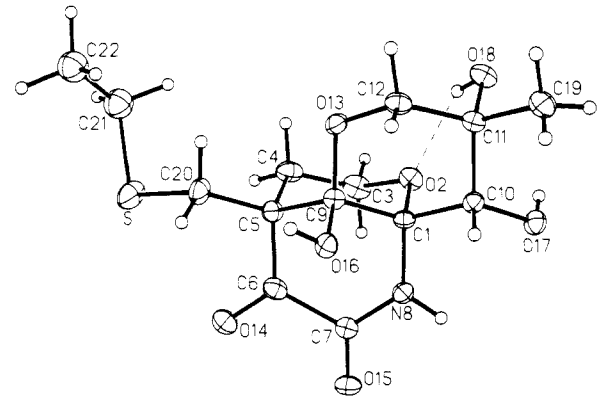
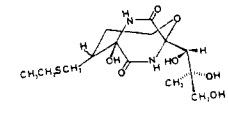


Figure 1. View of compound **2** showing the atom labeling scheme. The thermal ellipsoids are 30% equiprobability envelopes, with hydrogens as spheres of arbitrary diameter.

Treatment of a 3:1 tetrahydrofuran–aqueous Tris-HCl mixture[7] containing bicyclomycin (0.8 mM) and 16 equiv of ethyl mercaptan (room temperature, 20 h, final "pH" 8.1) gave 45% of **2**[8] along with starting material and a trace amount of two additional compounds.[9] High resolution mass spectral analysis of the major product showed a molecular ion at m/e 347.1053 (calcd for $C_{14}H_{21}NO_7S$, 347.1039) compatible with the formation of a 1:1 adduct between **1** and ethyl mercaptan and the loss of ammonia. Inspection of both the ^1H and ^{13}C NMR spectra indicated that a single diastereomer was generated in the reaction. Evidence that the thioethoxy group was bound to the exomethylene group in **1** was furnished by the appearance of an AB quartet at δ 2.96 for the C_{5a} methylene protons.[1a,5] The ^{13}C NMR spectrum for **2** displayed two carbonyl carbon resonances at 160.0 and 195.2 ppm. The latter signal was considerably downfield from the corresponding resonances in **1**[10] and suggested the presence of an α,β-unsaturated carbonyl system.[11] In agreement with this proposal, the IR spectrum exhibited carbonyl absorption bands at 1730 and 1670 cm^{-1}.[12] Verification of these spectral assignments was provided by the X-ray crystallographic analysis of **2** (Figure 1).[13]

(1) Someya, A.; Iseki, M.; Tanaka, N. *J. Antibiot.* **1979**, *32*, 402. (b) Tanaka, N.; Iseki, M.; Miyoshi, T.; Aoki, H.; Imanaka, H. *Ibid.* **1976**, *29*, 155. (c) Someya, A.; Iseki, M.; Tanaka, N. *Ibid.* **1978**, *31*, 712.
(2) Williams, R. M.; Armstrong, R. W.; Dung, J.-S. *J. Med. Chem.* **1985**, *28*, 733.
(3) Pisabarro, A. G.; Canada, F. J.; Vasquez, D.; Arriaga, P.; Rodriguez-Tebar, A. J. *J. Antibiot.* **1986**, *34*, 914.
(4) (a) Williams, R. M.; Tomizawa, K.; Armstrong, R. W.; Dung, J.-S. *J. Am. Chem. Soc.* **1985**, *107*, 6419. (b) Williams, R. M.; Tomizawa, K.; Armstrong, R. W.; Dung, J.-S. *Ibid.* **1987**, *109*, 4028.
(5) Kohn, H.; Abuzar, S. *J. Am. Chem. Soc.*, in press.
(6) Kohn, H.; Abuzar, S. *J. Org. Chem.*, in press.
(7) The reaction is biphasic at the onset but within a few hours becomes homogeneous.
(8) Select data for compound **2**: mp 216–218 °C; R_f 0.70 (10% methanol–chloroform); $[\alpha]^{25}D$ + 51.7° (c1, CH_3OH); IR 1730, 1670 cm^{-1}; ^1H NMR (CD_3OD) δ 1.15 (s, 3 H), 1.25 (t, 3 H, J = 7.3 Hz), 1.91 (d, 1 H, J = 14.0 Hz), 2.31 (ca. dt, 1 H, J = 6.3, 14.0 Hz), 2.58 (q, 2 H, J = 7.3 Hz), 2.90 (1/2 AB_q, 1 H, J = 13.9 Hz), 3.02 (1/2 AB_q, 1 H, J = 13.9 Hz), 3.63 (d, 1 H, J = 12.3 Hz), 3.76 (ca. dt, 1 H, J = 2.1, 14.0 Hz), 3.92 (s, 1 H), 4.03 (dd, 1 H, J = 6.3, 14.0 Hz), 4.04 (d, 1 H, J = 12.3 Hz); ^{13}C NMR (CD_3OD) 15.1, 21.2, 29.6, 32.4, 33.1, 56.7, 58.7, 70.9, 71.9, 72.4, 85.3, 96.1, 160.0, 195.2 ppm.
(9) One of the two minor products has been tentatively identified as the bicyclomycin–ethyl mercaptan adduct on the basis of the observed ^1H NMR spectra data.[5]



(10) Kohn, H.; Abuzar, S.; Korp, J. D.; Zektzer, A. S.; Martin, G. E. *J. Heterocycl. Chem.*, in press.
(11) Stothers, J. B. *Carbon-13 NMR Spectroscopy*; Academic: New York, 1972; p 282.
(12) Nakanishi, K.; Solomon, P. M. *Infrared Absorption Spectroscopy*; 2nd ed.; Holden-Day: San Francisco, 1977; p 38.
(13) Crystal data for **2**: $C_{14}H_{21}NO_7S$, M = 347.4, orthorhombic, space group $P2_12_12_1$, a = 6.714 (1) Å, b = 10.379 (2) Å, c = 22.181 (4) Å, V = 1546 Å^3, Z = 4, Nicolet R_{3m}/V diffractometer, Mo Kα (λ = 0.71073 Å), μ = 2.35 cm^{-1}, 2581 reflections $I > 3\sigma(I)$ refined to R = 0.039 (R_w = 0.027).

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