for conformational study,[13] and the glycal **4** could be converted to a number of sialyl Le^x derivatives on the basis of chemistry developed by Danishefsky and others.[14]

In summary, the recombinant α1,3FucT, like α(1,3/1,4)FucT,[3f] accepts a number of galactosides and sialosides as substrates and is useful for the synthesis of sialyl Le^x and related compounds. Coupled with in situ regeneration of UDP-Gal, CMP-NeuAc, and GDP-Fuc,[15] it is now possible to carry out large-scale enzymatic syntheses of sialyl Le^x and analogs. Work is in progress to investigate the synergistic inhibition of FucT with GDP and aza sugars.

Acknowledgment. Work at Scripps was supported by the NIH (GM44154) and Cytel and that at Michigan was supported by the NIH (DK38482). We thank Dr. J. C. Paulson at Cytel for helpful discussion and the kind gifts of α,1,3FucT and α2,3NeuT.

Supplementary Material Available: A listing of ^{1}H NMR spectral data for compounds **2**, **4**, and **6** (2 pages). Ordering information is given on any current masthead page.

† The Scripps Research Institute.
‡ Yale University.
§ University of Michigan Medical Center.

(1) (a) Kobata, A. *Biology of Carbohydrates*, Ginsburg, V., Robins, P. W., Eds.; John Wiley and Sons: New York, 1984; Vol. 2, p 87. (b) Feizi, T. *Nature* **1985**, *314*, 53. (c) Hakomori, S. *Adv. Cancer Res.* **1989**, *52*, 257.
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(8) The assay conditions were essentially the same as described previously.[3f] The specific activity of the enzyme was 2.6 U/mg (1 U = 1 μmol of GDP-Fuc consumed per hour).
(9) Hindsgaul, O.; Kaur, K. J.; Srivastava, G.; Blaszczyk-Thurin, M.; Crawley, S. C.; Leerze, L. D.; Palcic, M. M. *J. Biol. Chem.* **1991**, *266*, 17858.
(10) Compounds **1** and **3** were prepared from allyl βLacNAc and lactal, respectively, using a cloned Galβ1,3/4GlcNAc α-2,3-sialyltransferase (Ichikawa, Y.; Lin, Y.-C.; Dumas, D. P.; Shen, G.-J.; Garcia-Junceda, E.; Williams, M. A.; Bayer, R.; Ketcham, C.; Walker, S.; Paulson, J. C.; Wong, C.-H. *J. Am. Chem. Soc.*, submitted for publication). The glycals **3** and **4** were first prepared chemically by Danishefsky et al. (Danishefsky, S. J.; Gervay, J.; Peterson, J. M.; McDonald, F. E.; Koeski, K.; Oriyama, T.; Griffith, D. A.; Wong, C.-H.; Dumas, D. P. *J. Am. Chem. Soc.*, in press).
(11) Ichikawa, Y.; Sim, M. M.; Wong, C.-H. *J. Org. Chem.* **1992**, *57*, 2943.
(12) Compounds **2**, **4**, and **6** were characterized with ^{1}H NMR spectroscopy (see supplementary material)
(13) Lin, Y.-C.; Hummel, C. W.; Huang, D.-H.; Ichikawa, Y.; Nicolaou, K. C.; Wong, C.-H. *J. Am. Chem. Soc.* **1992**, *114*, 5452. Ichikawa, Y. et al. in ref 10.
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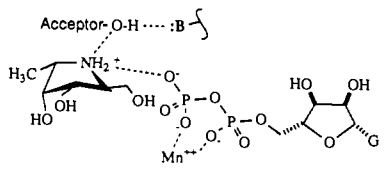
(15) For GDP-Fuc regeneration, see: Wong, C.-H.; Liu, K. K.-C.; Kajimoto, T.; Chen, L.; Zhong, Z.; Dumas, D. P.; Liu, J. L.-C.; Ichikawa, Y.; Shen, G.-J. *Pure Appl. Chem.* **1992**, *64*, 1197 and Ichikawa, Y. et al. in ref 10. For regeneration of CMP-NeuAc: Ichikawa, Y.; Shen, G.-J.; Wong, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 4698. For regeneration of UDP-Gal: Wong, C.-H.; Haynie, S. L.; Whitesides, G. M. *J. Org. Chem.* **1982**, *47*, 5416. Wong, C.-H.; Wang, R.; Ichikawa, Y. *J. Org. Chem.* **1992**, *16*, 4343.
(16) A possible complex in the active site is:



Model Studies on the Radical Induced DNA Strand Cleavage

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Diynene antitumor antibiotics like calicheamicin[1] or esperamicin[2] are radical generators that induce the cleavage of DNA **1** via hydrogen atom abstraction.[3] An important intermediate in this DNA strand scission is the deoxyribosyl radical **2** with the radical center at the 4'-position. This deoxyribosyl radical either reacts with oxygen[3] or decomposes directly.[4] Under anaerobic conditions ketoaldehydes **3a,b** are formed as the major products. To attain a deeper insight into the mechanism of this radical induced DNA strand cleavage under anaerobic conditions we selectively generated radicals **5a,b** by addition of benzenethiyl radicals to the dinucleotide derivatives **4a,b**.[5] Dinucleotide **4a** is cleaved quantitatively into fragments **6a** and **7a**.[6] Hydrolysis of **6a** exclusively yields ketoaldehyde **3c**.[7] It is therefore reasonable to assume that the anaerobic cleavage of DNA via deoxyribosyl radical **2** could initially lead to an enol ether of structure **6** which hydrolyzes to ketoaldehyde **3**. The rate of solvolysis depends upon the base. Thus radical addition to thymidine dimer **4b** in methanol/water (10:1) at 30 °C gives within 20 min directly the ketoaldehyde **3c** (45%) and the thymidine derivative **7b** (85%). Presumably, intermediate **6b** is hydrolyzed so rapidly that it is not built up during the reaction.

Kinetic experiments revealed that the fragmentation rate of **5a** is larger than 10^8 s^{-1} (30 °C). Using an excess of benzenethiol the mononucleotide derivative **8** yielded mainly fragment **6a** and a small amount of the addition product **10**. Under pseudo-first-order conditions a rate ratio $k_{6a}/k_{10} = 6.4$ was measured.[8] Thus, the rate coefficient of the fragmentation **9** → **6a** is larger than that of the hydrogen abstraction **9** → **10**. This is a remarkable result as benzenethiol is one of the most effective hydrogen donors, reacting with alkyl radicals with rate coefficients of about 10^8 M^{-1} s^{-1} (25 °C).[9]

The analogous benzoate **11** yielded only addition product **13**, the fragmentation product **6a** was not observed. This means that

(1) (a) Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461. (b) Golik, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3462. (c) De Voss, J. J.; Townsend, C. A.; Ding, W.-D.; Morton, G. O.; Ellestad, G. A.; Zein, N.; Tabor, A. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 9669.
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(3) For reviews, see: (a) Stubbe, J.; Kozarich, J. W. *Chem. Rev.* **1987**, *87*, 1107. (b) Nicolaou, K. C.; Dai, W.-M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1387.

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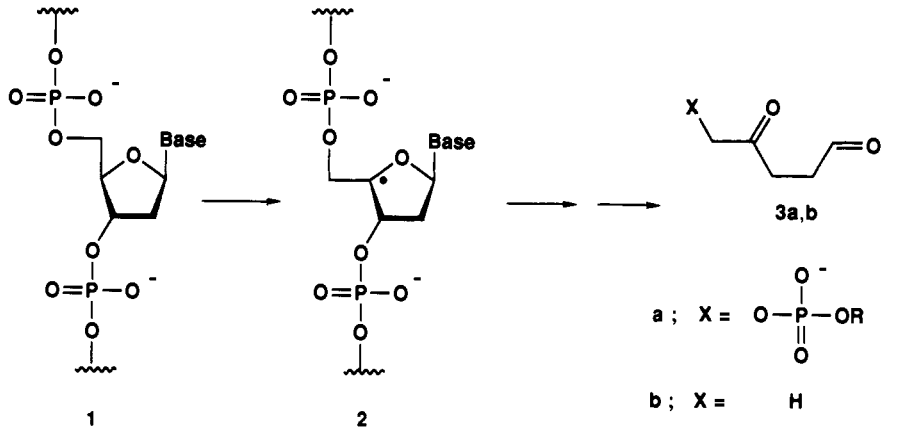
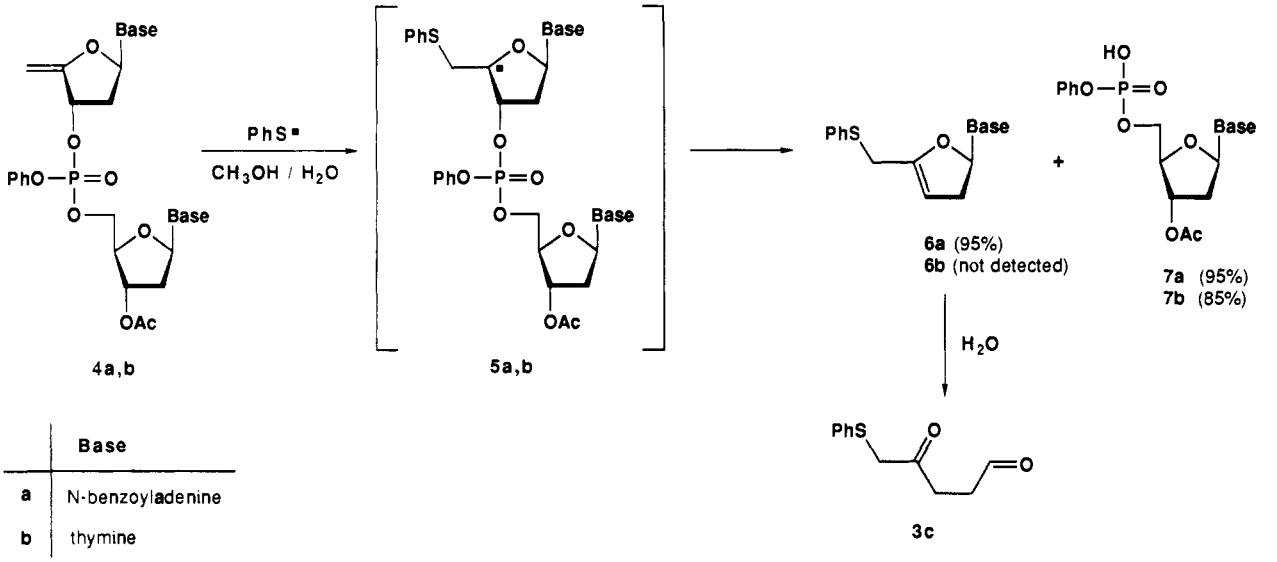
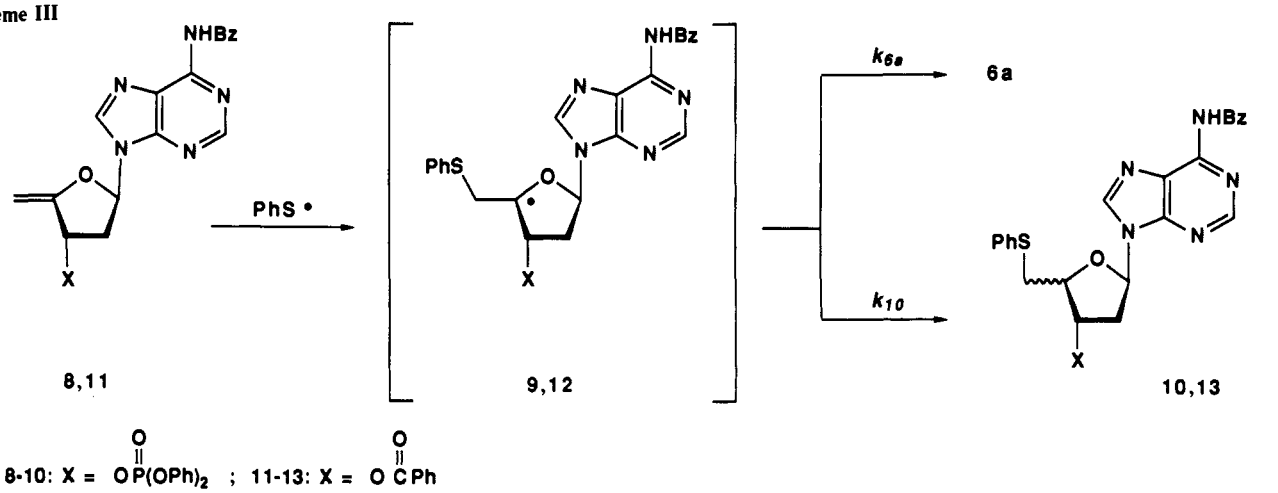
Scheme I

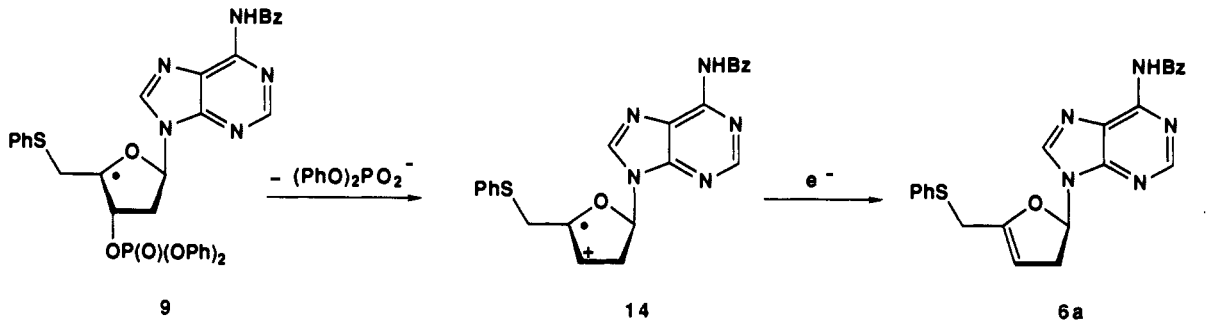


Scheme II



Scheme III





only in radicals like **9**, where phosphate is a good ionic leaving group, the C,O bond cleavage can compete with the hydrogen abstraction from benzenethiol. In radical **12**, with benzoate as a less effective ionic leaving group, cleavage of the C,O bond was not observed. This is in accord with the suggestion by Schulte-Frohlinde[4,10] that a phosphate group β to a radical center is cleaved off via a heterolytic C,O bond dissociation. Radicals **5a** and **9** should then lead to radical cation **14** that yields enol ether **6a** via a single electron transfer[11] from benzenethiol.[12]

Acknowledgment. This work was supported by the Swiss National Foundation.

Supplementary Material Available: Characterization data (^{1}H and ^{13}C NMR, MS, elementary analysis) for **3c**, **4a,b**, **6a**, **7a,b**, **8**, **10**, **11**, and **13a,b** and pseudo-first-order plot of the product ratio **6a**/**10** against 1/[PhSH] (5 pages). Ordering information is given on any current masthead page.

(4) For a review, see: Von Sonntag, C.; Hagen, U.; Schön-Bopp, A.; Schulte-Frohlinde, D. *Adv. Rad. Biol.* **1981**, *9*, 109.

(5) The 5′-deoxy-4′,5′-didehydronucleosides **4a,b**, **8**, and **11** were synthesized from their 5′-arylselenides via oxidative elimination using the following procedure: Takaku, H.; Nomoto, T.; Kimura, K. *Chem. Lett.* **1981**, 1221.

(6) In a typical procedure 1 mmol of the 5′-deoxy-4′,5′-didehydronucleoside **4a,b** or **8** in 10 mL of degassed (3 freeze–thaw cycles) methanol/water (10:1) was treated with 2–20 mmol of benzenethiol at 30 °C under irradiation (UV, Hanovia lamp) for 1 h. Alternatively di-*tert*-butyl hyponitrite was used as a thermal radical initiator at 30 °C. In the absence of light or di-*tert*-butyl hyponitrite no reaction occurred with **4a** or **8** within 20 h. This is a strong indication that benzenethiyl radicals are involved. An alternative source of these radicals is photolysis of diphenyl disulfide. In the absence of light this disulfide did not react with nucleotides **4a** and **8**. But under photolytic conditions product **6a** was formed in 50% yield.

(7) A heterogeneous mixture of 8.6 mg of enol ether **6a** and 1.0 mL water was stirred at 30 °C for 24 h. This led to ketoaldehyde **3c** in 95% yield. The structure of **3c** was proved by independent synthesis. A homogeneous solution of **6a** in methanol/water (10:1) under slightly acidic conditions (pH = 3) led to solvolysis product **3c** with a half-life time of 15 min.

(8) A toluene solution (1.0 mL) of 0.1 mmol of **8** and 0.5–5.0 mmol of benzenethiol was irradiated at 30 °C for 1 h under nitrogen. The product ratio **6a**/**10** was determined by HPLC with a reproducibility of ±10%. The plot of **6a**/**10** against 1/[PhSH] gave a linear correlation with a correlation coefficient r = 0.986.

(9) (a) Franz, J. A.; Bushaw, B. A.; Alnajjar, M. S. *J. Am. Chem. Soc.* **1989**, *111*, 268. (b) Newcomb, M.; Glenn, A. G.; Manek, M. B. *J. Org. Chem.* **1989**, *54*, 4603.

(10) Methoxyalkyl radicals with a neutral β-phosphate group cleave the β-C,O-bond with rates of about 10^6 (20 °C, H_2O). The respective phosphate monoanion is cleaved 10^3 times slower: Behrens, G.; Koltzenburg, G.; Ritter, A.; Schulte-Frohlinde, D. *Int. J. Radiat. Biol.* **1978**, *33*, 163. See, also: Koltzenburg, G.; Behrens, G.; Schulte-Frohlinde, D. *J. Am. Chem. Soc.* **1982**, *104*, 7311.

(11) Cyclic voltammetry of the enol ether **6a** [5 mM in acetonitrile/0.1 M $(n\text{-Bu})_4NBF_4$] gave a redox potential on a platinum electrode of 1.54 V (vs Ag/AgCl, 20 °C, scan rate 0.2 V s^{-1}).

(12) An alternative route, that is reduction of radicals **9** and **12**, respectively, to anions by benzenethiol can be excluded, because this should also lead to C,O-bond cleavage of the benzoylated radical **12**.

Synthesis of Nitrogen Heterocycles via Catalytic Ring-Closing Metathesis of Dienes

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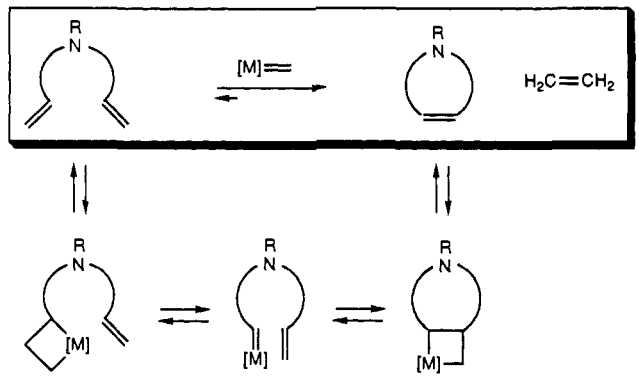
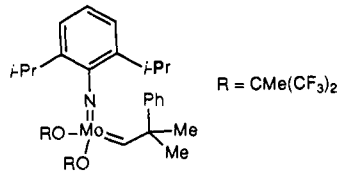
Because alkaloids represent a significant subset of all biologically-active compounds,[2] the development of general new methods for their construction remains an important goal of organic synthesis. We have recently described an approach to the generation of unsaturated ethers based upon transition metal alkylidene-catalyzed ring-closing olefin metathesis.[3-5] In this communication, we report the surprisingly successful application of this cyclization process to the synthesis of a variety of nitrogen heterocycles.

Scheme I



The catalytic ring-closing olefin metathesis strategy is illustrated in Scheme I for the synthesis of unsaturated nitrogen heterocycles from acyclic diene–amines. To the best of our knowledge, there is no precedent for this transformation, perhaps due in part to the fact that the metathesis of olefinic amines has been problematic; the few systems that are known to metathesize this class of compounds are characterized by low yields (<60%), low turnovers (≤5), and limited scope.[6] Attempts to metathesize olefinic amides have been even less successful.[7] In contrast, we have found that $Mo(CHCMe_2Ph)(NAr)(OCMe(CF_3)_2)_2$ (Ar = 2,6-(i-Pr)$_2$C$_6$H$_3$, **1**)[8,9] efficiently catalyzes the cyclization of a range of dienes to afford the desired nitrogen heterocycles.



1

The generality of the catalytic ring-closing metathesis reaction is illustrated in Table I.[10,11] Pyrrolines in which the olefin is either di- or trisubstituted form readily upon treatment of diallylamines with 4 mol % **1** at 20 °C (entries 1 and 2). Tetrahydropyridines

(1) National Science Foundation Postdoctoral Fellow.

(2) For leading references to the synthesis and structure of natural products containing nitrogen heterocycles, see: (a) *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Cordell, G. A., Eds.; Academic: New York, 1992. (b) *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley-Interscience: New York, 1988. (c) Belen'kii, L. I. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic: New York, 1988; Vol. 44, Chapter 4. (d) *Comprehensive Heterocyclic Chemistry*; Meth-Cohn, O., Ed.; Pergamon: New York, 1984.

(3) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426-5427.

(4) Reviews of olefin metathesis: (a) Feldman, J.; Schrock, R. R. *Prog. Inorg. Chem.* **1991**, *39*, 1-74. (b) Grubbs, R. H.; Tumas, W. *Science* **1989**, *243*, 907-915. (c) Ivin, K. J. *Olefin Metathesis*; Academic: New York, 1983.

(5) Review of applications of olefin metathesis in organic synthesis: Grubbs, R. H.; Pine, S. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 5, Chapter 9.3.

(6) For an overview, see: Edwige, C.; Lattes, A.; Laval, J. P.; Mutin, R.; Basset, J. M.; Nouguier, R. *J. Mol. Catal.* **1980**, *8*, 297-311.

(7) For example, see: Levisalles, J.; Rudler, H.; Cuzin, D.; Rull, T. *J. Mol. Catal.* **1984**, *26*, 231-238.

(8) (a) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875-3886. (b) Bazan, G. C.; Oskam, J. H.; Cho, H.-N.; Park, L. Y.; Schrock, R. R. *J. Am. Chem. Soc.* **1991**, *113*, 6899-6907. (c) Bazan, G. C.; Schrock, R. R.; Cho, H.-N.; Gibson, V. C. *Macromolecules* **1991**, *24*, 4495-4502. (d) Wagener, K. B.; Brzezinska, K.; Bauch, C. G. *Makromol. Chem., Rapid Commun.* **1992**, *13*, 75-81.

(9) Catalyst **1** is both air- and moisture-sensitive. For details regarding its preparation, see: (a) Reference 8. (b) Fox, H. H.; Yap, K. B.; Robbins, J.; Cai, S.; Schrock, R. R. *Inorg. Chem.* **1992**, *31*, 2287-2289.

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