ORGANIC LETTERS

2011
Vol. 13, No. 16
4224–4227

Syntheses of Chloroisosulochrin and Isosulochrin and Biomimetic Elaboration to Maldoxin, Maldoxone, Dihydromaldoxin, and Dechlorodihydromaldoxin

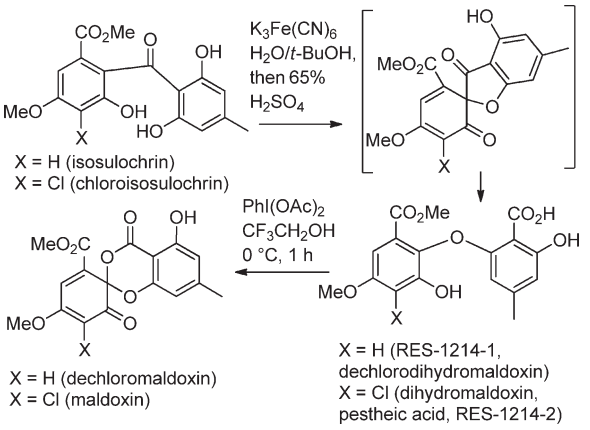
Min Yu and Barry B. Snider*

Department of Chemistry MS 015, Brandeis University, Waltham, Massachusetts 02454-9110, United States

snider@brandeis.edu

Received June 10, 2011

ABSTRACT



An efficient synthesis of chloroisosulochrin was accomplished using a novel ortho-selective chlorination of a phenol with sulfuryl chloride and 2,2,6,6-tetramethylpiperidine as the key step. Further elaboration by a biomimetic route converted chloroisosulochrin to dihydromaldoxin, maldoxone (lactone formed by dehydration of dihydromaldoxin), and maldoxin and isosulochrin to dechlorodihydromaldoxin and dechloromaldoxin.

Liu, Che, and co-workers recently reported the isolation of the cytotoxic natural product chloropestolide A (**3**) and several congeners from the fermentation of the plant endophytic fungus *Pestalotiopsis fici* .[1] These compounds were suggested to arise by an inverse electron demand Diels–Alder reaction between maldoxin (**1b**)[2] as the diene and isopropenylallene **2**, which was also isolated from *Pestalotiopsis fici*, as the dienophile (see Scheme 1).[1] We decided to synthesize maldoxin (**1b**) and then explore the regio- and stereoselectivity of the Diels–Alder reaction of maldoxin with a simpler isopropenylallene.[3]

The biosynthesis of maldoxin (**1b**) may proceed by oxidative cleavage of the anthraquinone fragilin (**4b**) and methylation of the carboxylic acid to give chloroisosulochrin (**5b**) (see Scheme 2).[4] Oxidative cyclization could give spirofuran-3-one **6b**, which could be hydrolyzed to give

(1) (a) Liu, L.; Liu, S.; Jiang, L.; Chen, X.; Guo, L.; Che, Y. *Org. Lett.* **2008**, *10*, 1397–1400. (b) Liu, L.; Li, Y.; Liu, S.; Zheng, Z.; Chen, X.; Zhang, H.; Guo, L.; Che, Y. *Org. Lett.* **2009**, *11*, 2836–2839. (c) Liu, L.; Bruhn, T.; Guo, L.; Götz, D. C. G.; Brun, R.; Stich, A.; Che, Y.; Bringmann, G. *Chem.—Eur. J.* **2011**, *17*, 2604–2613. (d) Liu, L. *Mycology* **2011**, *2*, 37–45.

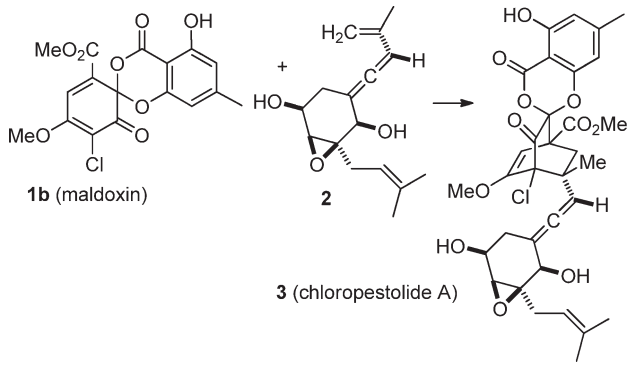
(2) Adeboya, M. O.; Edwards, R. L.; Lassøe, T.; Maitland, D. J.; Shields, L.; Whalley, A. J. S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1419–1425.

(3) Yu, M.; Snider, B. B. Manuscript in preparation.

(4) Shimada, A.; Takahashi, I.; Kawano, T.; Kimura, Y. *Z. Naturforsch. B.* **2001**, *56*, 797–803.

10.1021/ol201561w
Published on Web 07/27/2011

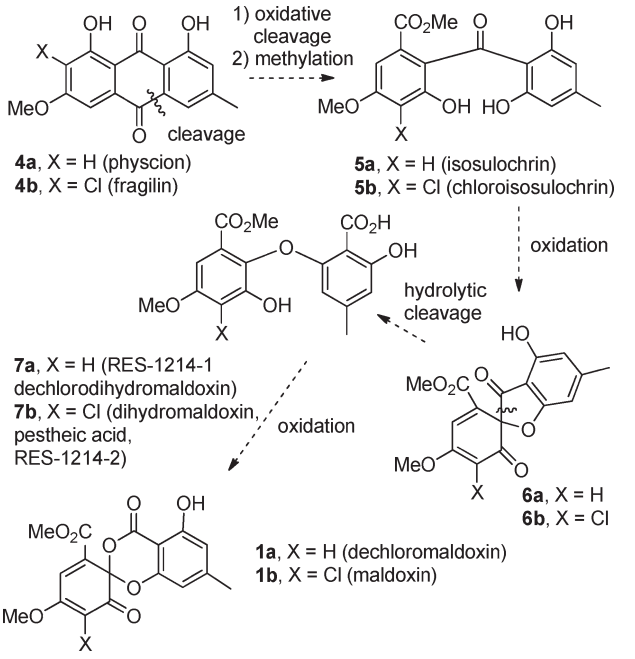
Scheme 1



dihydromaldoxin (RES-1214-2, pestheic acid, **7b**).[2,4,5] A second oxidative cyclization could then lead to maldoxin (**1b**).[2] A similar oxidative cleavage of physcion (**4a**) would give isosulochrin (**5a**),[4,6] which could be oxidatively cyclized to give dechlorodihydromaldoxin (RES-1214-1, **7a**).[2,5] Although only dihydromaldoxin was isolated by Liu and Che from *Pestalotiopsis fici*,[1] isosulochrin (**5a**), chloroisosulochrin (**5b**), and dihydromaldoxin (pestheic acid, **7b**) were all isolated from *Pestalotiopsis theae*,[4] both dechlorodihydromaldoxin (RES-1214-1, **7a**) and dihydromaldoxin (RES-1214-2, **7b**) were isolated from *Pestalotiopsis* sp. RES-1214,[5] and dechlorodihydromaldoxin (**7a**), dihydromaldoxin (**7b**), and maldoxin (**1b**) were all isolated from an unidentified *Xylaria* species.[2] The isolation of both chlorinated and unchlorinated **5** and **7** from the same source suggests that chlorination might occur after oxidative cleavage of anthraquinone **4**. RES-1214-1 (**7a**) and -2 (**7b**) selectively inhibit ET-1 binding to endothelin type A receptor (ET_A receptor) with IC_{50} values of 1.5 and 20 μM, respectively.[5] They also inhibit the increase in intracellular Ca^{2+} concentration elicited by 1 nM ET-1 in A10 cells.[5]

We planned to synthesize chloroisosulochrin (**5b**) and convert it to maldoxin (**1b**) by the biomimetic sequence shown in Scheme 2. The oxidative cyclization of 2,2′-dihydroxybenzophenones analogous to **5** to give spirofuranones analogous to **6** and acid-catalyzed hydrolysis of the spirofuranones to provide 2-(2-hydroxyphenoxy-)benzoic acids analogous to **7** are well precedented.[7] The oxidative cyclization of 2-(4-hydroxyphenoxy)benzoic acids to give benzo[*d*][1.3]dioxin-4-ones spiro fused at the 4-position to 2,5-cyclohexadienones is known,[8] but the

Scheme 2. Biosynthesis of Maldoxin



analogous preparation of benzo[*d*][1.3]dioxin-4-ones such as maldoxin that are spiro fused at the 6-position to 2,4-cyclohexadienones is unknown, possibly because of the susceptibility of such dienones to dimerization.[9]

We started with resorcinol **8**,[10] an intermediate in Katoh's synthesis of geodin. Selective methylation of the less hindered hydroxy group of **8** provided phenol **9a** in 92% yield (see Scheme 3). We needed to selectively chlorinate **9a** ortho to the phenol. Unfortunately, ortho chlorination of complex phenols has proved to be very challenging.[11] Our initial attempt with NCS and benzoyl peroxide in CCl_4 provided a disappointing 1:8 mixture of the desired ortho chlorophenol **9b** and the para chlorophenol **10**. Gnaim and Sheldon reported that phenol can be selectively ortho chlorinated with SO_2Cl_2 and primary or secondary amines in toluene.[12] They suggested that the high regioselectivity with phenol results from the *in situ* formation of an *N*-chloroamine, which hydrogen bonds to the phenol forming a complex that delivers chlorine intramolecularly to the ortho position. We were disappointed to find that chlorination of **9a** with SO_2Cl_2 and *tert*-butylamine in toluene provided only a 1:2.6 mixture of **9b** and **10**, although these conditions provide an 11.4:1 ortho/para mixture from phenol itself.[12b] Presumably,

(5) Ogawa, T.; Ando, K.; Aotani, Y.; Shinoda, K.; Tanaka, T.; Tsukuda, E.; Yoshida, M.; Matsuda, Y. *J. Antibiot.* **1995**, *48*, 1401–1406.

(6) (a) Assante, G.; Camarda, L.; Nasini, G. *Gazz. Chim. Ital.* **1980**, *110*, 629–631. (b) Hamasaki, T.; Kimura, Y. *Agric. Biol. Chem.* **1983**, *47*, 163–165.

(7) (a) Hendrickson, J. B.; Ramsay, M. V. J.; Kelly, T. R. *J. Am. Chem. Soc.* **1972**, *94*, 6834–6843. (b) Sala, T.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1981**, 855–869. (c) Sala, T.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1981**, 877–882. (d) Coomber, M. F.; Sargent, M. V.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Perkin Trans 1* **1989**, 441–448. (e) Pulgarin, C.; Tabbachi, R. *Helv. Chim. Acta* **1989**, *72*, 1061–1065 and references cited therein.

(8) Hassall, C. H.; Lewis, J. R. *J. Chem. Soc.* **1961**, 2312–2315.

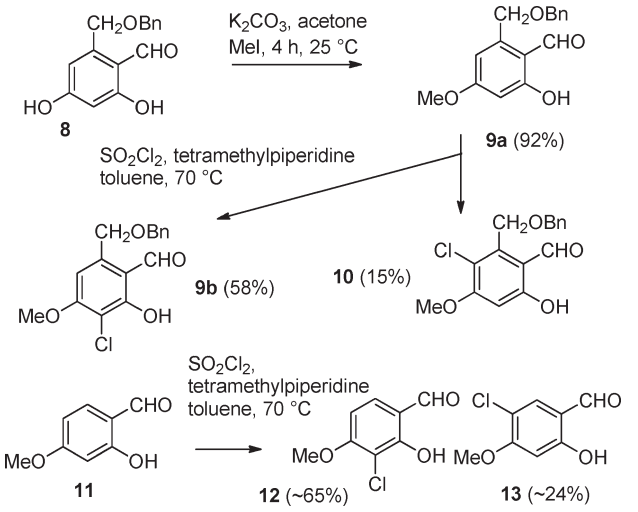
(9) (a) Quideau, S.; Pouységu, L. *Org. Prep. Proc. Int.* **1999**, *31*, 617–680. (b) Gagnepain, J.; Méreau, R.; Dejugnac, D.; Léger, J.-M.; Castet, F.; Deffieux, D.; Pouységu, L.; Quideau, S. *Tetrahedron* **2007**, *63*, 6493–6505. (c) Dory, Y. L.; Roy, A.-L.; Soucy, P.; Deslongchamps, P. *Org. Lett.* **2009**, *11*, 1197–1200.

(10) Katoh, T.; Ohmuri, O.; Iwasaki, K.; Inoue, M. *Tetrahedron* **2002**, *58*, 1289–1299.

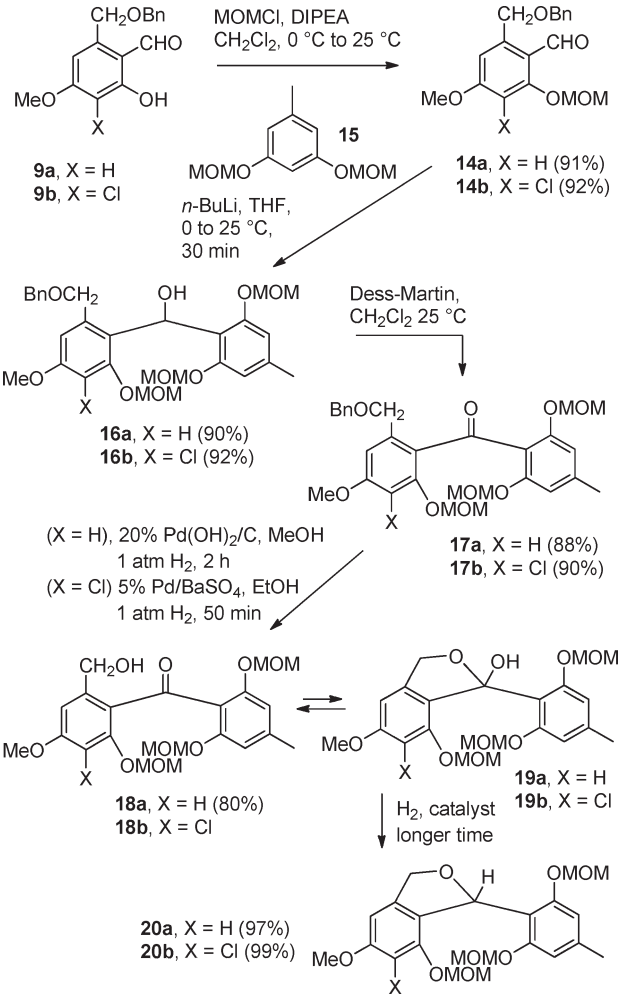
(11) Mal, D.; Dey, S. *Tetrahedron* **2006**, *62*, 9589–9602.

(12) (a) Smith, K.; Butters, M.; Nay, B. *Tetrahedron Lett.* **1988**, *29*, 1319–1322. (b) Gnaim, J. M.; Sheldon, R. A. *Tetrahedron Lett.* **1995**, *36*, 3893–3896. (c) Gnaim, J. M.; Sheldon, R. A. *Tetrahedron Lett.* **2004**, *45*, 8471–8473.

Scheme 3. Selective Ortho Chlorination



Scheme 4. Preparation of Hydroxymethyl Ketone **18**



intermolecular chlorination to give **10** occurs more rapidly with the more nucleophilic aromatic ring of **9a**. We reasoned that hindered secondary amines would form a more hindered and therefore less reactive *N*-chloroamine that would favor chlorination via the hydrogen bonded complex that leads to **9b**. We were pleased to find that the selectivity increased as we changed to more hindered secondary amines, increasing to 1.8:1 with dipropylamine, to 3.3:1 with diisopropylamine, and to 3.9:1 with 2,2,6,6-tetramethylpiperidine. Fortunately the products are easily separated so that using the latter amine we were able to obtain **9b** (58%) and **10** (15%) on a gram scale. We observed a similar effect of amine bulk on the chlorination selectivity with phenol **11**, which gave a 0.8:1, 1.8:1, 2.4:1, or 2.6:1 mixture of **12**[13] and **13**[14] with sulfuryl chloride and *tert*-butylamine, dipropylamine, diisopropylamine, or 2,2,6,6-tetramethylpiperidine, respectively.

We proceeded in parallel with both maldoxin precursor **9b** and the unchlorinated phenol **9a**, which should give rise to dechloromaldoxin and allow us to explore the effect of the chlorine atom on the Diels–Alder reaction. Protection of phenols **9a/b** with MOMCl and DIPEA afforded MOM ethers **14a** (91%) and **14b** (92%) (see Scheme 4). Deprotonation[15] of bis MOM ether **15** with *n*-BuLi and addition of the aryllithium to **14a/b** afforded alcohols **16a** (90%) and **16b** (92%), which were oxidized by Dess–Martin periodinane to give benzophenones **17a** (88%) and **17b** (90%).

Not surprisingly, the hydrogenolysis of the benzyl ether of **17a/b** proved to be challenging. Product **18a/b** is a hydroxy ketone that can cyclize to form hemiketal **19a/b**, which is readily hydrogenolyzed to form dihydroisobenzofuran **20a/b**, which still has two benzylic oxygen substituents that are susceptible to hydrogenolysis. Hydrogenolysis of **17a** was best accomplished over 20% $Pd(OH)_2/C$ with 1 atm of H_2 in MeOH for 2 h to give **18a** (80%). However, **20a** was isolated in 97% yield when the reaction was run for 5 h. Hydrogenation of chloride **17b** over 20% $Pd(OH)_2/C$ afforded a mixture of hydroxy ketone **18b** and hemiketal **19b**, which was rapidly reduced to **20b**. The effect of substituents on the equilibration of related hydroxy ketones and hemiketals has been previously noted.[16] Chloride **17b** was best hydrogenolyzed over 5% $Pd/BaSO_4$[17] with 1 atm of H_2 in EtOH for 50 min to give **18b**. However, **20b** was isolated when the reaction was run for 2 h. Replacing the benzyl protecting group with a 2-naphthylmethyl group should solve the overreduction problem because hydrogenolysis of the 2-naphthylmethyl group is much faster than that of a benzyl group.[18]

(13) Plattner, J. J.; Fung, A. K. L.; Parks, J. A.; Pariza, R. J.; Crowley, S. R.; Pernet, A. G.; Bunnell, P. R.; Dodge, P. W. *J. Med. Chem.* **1984**, *27*, 1016–1026.

(14) Akselson, Ø. W.; Skattebøl, L.; Hansen, T. V. *Tetrahedron Lett.* **2009**, *50*, 6339–6341.

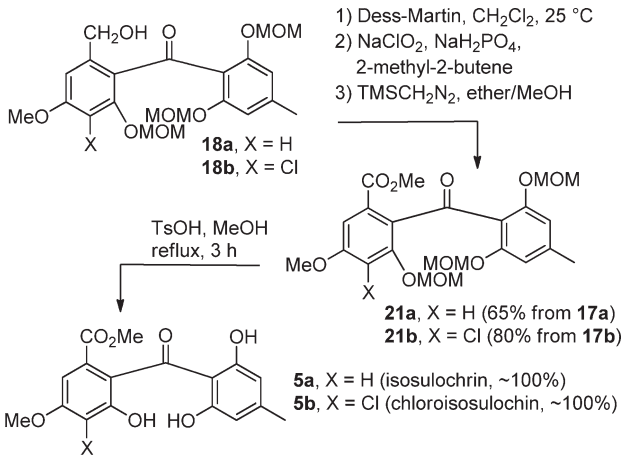
(15) Lambert, G. J.; Duffley, R. P.; Dalzell, H. C.; Razdan, R. K. *J. Org. Chem.* **1982**, *47*, 3350–3353.

(16) (a) Smith, J. G.; Fogg, D. E.; Munday, I. J.; Sandborn, R. E.; Dibble, P. W. *J. Org. Chem.* **1988**, *53*, 2942–2953. (b) Epsztajn, J.; Jóźwiak, A.; Szcześniak, A. K. *Tetrahedron* **1993**, *49*, 929–938.

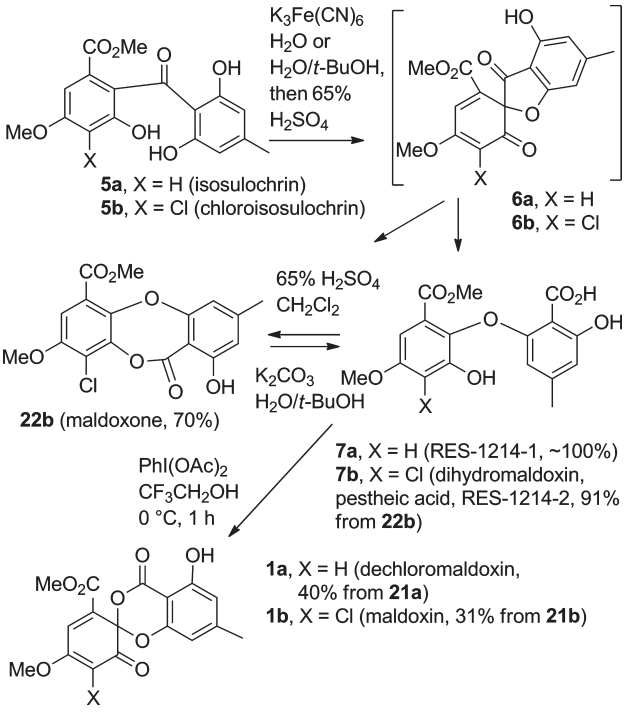
(17) Nikam, S. S.; Kornberg, B. E.; Johnson, D. R.; Doherty, A. M. *Tetrahedron Lett.* **1995**, *36*, 197–200.

(18) Gaunt, M. J.; Yu, J.; Spencer, J. B. *J. Org. Chem.* **1998**, *63*, 4172–4173.

Scheme 5. Completion of the Chloroisosulochrin Synthesis



Scheme 6. Biomimetic Conversion of Chloroisosulochrin to Maldoxin



Unfortunately, chlorination of the 2-naphthylmethyl analog of **9a** proceeded in only 40% yield with only 1.6:1 ortho/para selectivity and addition of the lithium reagent prepared from **15** to the 2-naphthylmethyl analog of **14b** proceeded in only 68% yield.

The standard three-step sequence shown in Scheme 5 converted hydroxy ketones **18a** and **18b** to keto esters **21a** (65% from **17a**) and **21b** (80% from **17b**). The four-step conversion of the benzyl ethers of **17a/b** to the methyl esters of **21a/b** is cumbersome but was used because we were unable to add the aryllithium reagent prepared from **15** to the aldehyde analogous to **14a** with a CO_2Me instead of a CH_2OBn group. Deprotection of all three MOM ethers of **21a/b** with TsOH in MeOH at reflux cleanly afforded isosulochrin (**5a**)[6] and chloroisosulochrin (**5b**).[4]

Oxidation[7] of **5a** with potassium ferricyanide in water afforded spirofuranone **6a**, which was hydrolyzed[7] with 65% sulfuric acid to give diaryl ether dechlorodihydromaldoxin[2,4] (**7a**) in quantitative yield (see Scheme 6). A similar oxidation of **5b** in aqueous *tert*-butanol afforded spirofuranone **6b**, but hydrolysis of **6b** with 65% sulfuric acid initially gave a mixture of maldoxone[2] (**22b**) and dihydromaldoxin (**7b**) that was converted to maldoxone in 70% yield at longer reaction times. Hydrolysis of maldoxone with K_2CO_3 in aqueous *tert*-butanol afforded dihydromaldoxin[2,4,5] (**7b**) in 91% yield. Oxidative cyclization of **7a** with $PhI(OAc)_2$ in CF_3CH_2OH at 0 °C afforded dechloromaldoxin (**1a**) in 40% overall yield for the four-step sequence from **21a**. The structure of **1a** was confirmed by X-ray crystallography. A similar oxidative cyclization of **7b** afforded maldoxin (**1b**) in 31% overall yield for the five-step sequence from **21b**. The Diels–Alder reactions of both dihydromaldoxin (**1a**) and maldoxin (**1b**) with an isopropenylallene will be described elsewhere.[3]

In conclusion, an efficient synthesis of chloroisosulochrin (**5b**) was accomplished using a novel ortho-selective chlorination of a phenol with sulfuryl chloride and 2,2,6,6-tetramethylpiperidine as the key step. Further elaboration by a biomimetic route converted chloroisosulochrin to dihydromaldoxin, maldoxone, and maldoxin and isosulochrin to dechlorodihydromaldoxin and dechloromaldoxin.

Acknowledgment. We are grateful to the National Institutes of Health (GM-50151) for support of this work. We thank the National Science Foundation for Grant CHE-0521047 for a new X-ray diffractometer.

Supporting Information Available. Complete experimental procedures, copies of ^1H and ^{13}C NMR spectral data, and CIF file and drawing of X-ray crystal structure of **1a**. This material is available free of charge via the Internet at http://pubs.acs.org.