

Synthesis of Tetrasubstituted Ozonides by the Griesbaum Coozonolysis Reaction: Diastereoselectivity and Functional Group Transformations by Post-Ozonolysis Reactions

Yuanqing Tang,[†] Yuxiang Dong,[†] Jean M. Karle,[‡] Charles A. DiTusa,[‡] and Jonathan L. Vennerstrom^{*,†}

Department of Pharmaceutical Sciences, College of Pharmacy, University of Nebraska Medical Center, Omaha, Nebraska 68198-6025, and Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Silver Spring, Maryland 20910-7500

jvenners@unmc.edu

Received April 9, 2004

Abstract: The diastereoselectivity of the Griesbaum coozonolysis reaction with *O*-methyl 2-adamantanone oxime and 4-substituted cyclohexanones reveals that the major tetrasubstituted ozonide isomers possess *cis* configurations, suggesting a preferred axial attack of the carbonyl oxide on the cyclohexanone dipolarophiles. It is evident that these tetrasubstituted ozonides are quite stable to triphenylphosphine, borohydrides, hydrazine, alkyllithiums, Grignard reagents, mercaptides, and aqueous KOH as illustrated by the synthesis of amine, alcohol, acid, ester, ether, sulfide, sulfone, and heterocycle-functionalized ozonides by a wide range of post-ozonolysis transformations.

Griesbaum Coozonolysis. In 1995, Griesbaum et al.¹ reported a new type of cross-ozonolysis reaction (Scheme 1) in which an *O*-alkyl ketone oxime was ozonized in the presence of added carbonyl compounds such as acyl cyanides and activated esters to give cross-ozonides. Subsequently, they² found that this novel method could be efficiently applied to a number of unactivated ketones as exemplified by acetone or cyclohexanone. This provided for the first time a widely applicable synthesis of both symmetrical and unsymmetrical tetrasubstituted ozonides that are otherwise generally inaccessible by ozonolysis of a parent alkene³ or cross-ozonolysis of an alkene⁴ or enol ether⁵ in the presence of carbonyl compounds in solution. Another useful feature of the Griesbaum coozonolysis reaction is that it obviates the

SCHEME 1. Griesbaum Coozonolysis

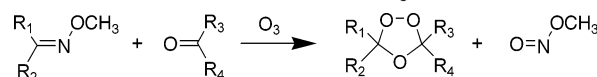


TABLE 1. Griesbaum Coozonolysis Diastereoselectivity

group	R	<i>cis</i> (3): <i>trans</i> (4)
I	C(CH ₃) ₃	3a:4a >20:1
	C ₆ H ₅	3b:4b >20:1
	<i>p</i> -C ₆ H ₄ OAc	3c:4c >20:1
	phthalimido	3d:4d >20:1
II	CH ₂ OAc	3e:4e 4.7:1
	CH ₂ COOEt	3f:4f 4.5:1
	CH ₂ SO ₂ C ₆ H ₅	3g:4g 4.9:1
	phthalimidomethyl	3h:4h 4.7:1
III	COOEt	3i:4i 2.5:1
	COOCH ₂ C(CH ₃) ₃	3j:4j 4:1
	CON(CH ₂ CH ₃) ₂	3k:4k 5:1

synthesis of parent tetrasubstituted olefins or enol ethers and instead requires only the straightforward synthesis of oxime ethers. The large number of commercially available ketones as both dipolarophile coupling partners and oxime ether precursors adds to the flexibility of this reaction.

Although the detailed mechanism⁶ for this cross-ozonolysis has not been well defined, the reaction outcome is consistent with the general pathway of the Criegee mechanism⁷ for ozonolysis of olefins, especially involving the key carbonyl oxide intermediate. This is evidenced by formation of 1,2,4,5-tetraoxanes⁸ in the absence of a ketone coupling partner and substantiated further by trapping experiments.^{1,2} In this paper, we report the diastereoselectivity of cycloadditions between the carbonyl oxide derived from the *O*-methyl 2-adamantanone oxime (**1**) and 4-substituted cyclohexanones (**2**) and functional group transformations of the tetrasubstituted ozonide products by post-ozonolysis reactions.

Diastereoselectivity of the Griesbaum Coozonolysis Reaction. Because use of the symmetrical oxime ether avoids *syn-anti* isomerism of the resulting 2-adamantanone oxide, the stereochemistry of the cycloaddition products is only a function of the starting material cyclohexanones. For 4-substituted cyclohexanones, only two achiral diastereomers (*cis* and *trans*) are possible (Table 1). Preferably, the cozonolyses of **1** and **2** were carried out in pentane or cyclohexane at 0 °C, the conditions mostly suitable for ozonide formation as prescribed by Griesbaum.^{1,2} For more polar cyclohexanones, a mixed solvent system (hydrocarbon and dichlo-

* To whom correspondence should be addressed. Tel: 402-559-5362. Fax: 402-559-9543.

[†] University of Nebraska Medical Center.

[‡] Walter Reed Army Institute of Research.

(1) Griesbaum, K.; Övez, B.; Huh, T. S.; Dong, Y. *Liebigs Ann.* **1995**, 1571–1574.

(2) (a) Griesbaum, K.; Liu, X.; Kassiaris, A.; Scherer, M. *Liebigs Ann./Recl.* **1997**, 1381–1390. (b) Griesbaum, K.; Liu, X.; Dong, Y. *Tetrahedron* **1997**, 5463–5470. (c) Dong, Y.; Griesbaum, K.; McCullough, K. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1601–1604. (d) Griesbaum, K. *Trends Org. Chem.* **1997**, 6, 145–168.

(3) (a) Griesbaum, K.; Krieger-Beck, P.; Beck, J. *Chem. Ber.* **1991**, 124, 391–396. (b) Bunnelle, W. H. *Chem. Rev.* **1991**, 91, 335–362.

(4) (a) Criegee, R.; Blust, G.; Zinke, H. *Chem. Ber.* **1954**, 87, 766–768. (b) Keul, H. *Chem. Ber.* **1975**, 108, 1207–1217.

(5) (a) Keul, H.; Choi, H. S.; Kuczkowski, R. L. *J. Org. Chem.* **1985**, 50, 3365–3371. (b) Griesbaum, K.; Kim, W. S.; Nakamura, N.; Mori, M.; Nojima, M.; Kusabayashi, S. *J. Org. Chem.* **1990**, 55, 6153–6161. (c) Tabuchi, T.; Nojima, M. *J. Org. Chem.* **1991**, 56, 6591–6595. (d) Kuwabara, H.; Ushigoe, Y.; Nojima, M. *J. Chem. Soc., Perkin Trans. 1* **1996**, 871–874.

(6) Bailey, P. S. *Ozonation in Organic Chemistry*; Academic Press: New York, 1982; Vol. II, pp 231–235.

(7) Criegee, R. Mechanism of Ozonolysis. *Angew. Chem.* **1975**, 87, 765–771.

(8) (a) Ito, Y.; Konishi, M.; Matsuura, T. *Photochem. Photobiol.* **1979**, 30, 53–57. (b) Ito, Y.; Yokoya, H.; Umehara, Y.; Matsuura, T. *Bull. Chem. Soc. Jpn.* **1980**, 53, 2407–2408. (c) Dong, Y.; Vennerstrom, J. L. *J. Org. Chem.* **1998**, 63, 8582–8585.

romethane) was employed, with the proportion of dichloromethane minimized as less polar solvents favor ozonide formation. The oxime ether-to-ketone ratio varied between 1.5:1 and 1:2. Reaction yields of ozonides **3** + **4** ranged from 20% to 70%.

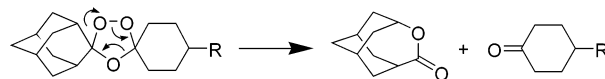
Product ratios were determined by integration of uniquely characteristic signals in the ^1H NMR spectra of unpurified reaction mixtures. In most cases, only the major isomers (**3**) were separated by flash chromatography or crystallization and individually characterized. The stereochemical assignments (*cis* or *trans*) are based on X-ray analyses and on the assumption that the stereochemical outcomes were consistent for all cycloaddition products (**3** and **4**) studied. No clear confirmation of stereochemistry could be derived from examination of chemical shifts and coupling constants or from elution rates on silica gel.

Acetoxy ozonide **3c**, a representative example from group I, was assigned a *cis* configuration on the basis of the X-ray crystallographic analysis of its phenol hydrolysis product **5** (Supporting Information). The data revealed a chair cyclohexane with the 4-hydroxyphenyl and peroxy groups at the equatorial and axial positions, respectively. In group II, structures (Supporting Information) for the major (**3h**) and minor (**4h**) isomers were confirmed to be *cis* and *trans*, respectively, again by X-ray crystallographic analysis. In *trans* isomer **4h**, the 4-phthalimido and peroxy groups were both equatorial. The *cis* configuration of the major isomer **3i** in group III was established by successfully transforming **3i** into **3h** (vide infra). These results also lend support to the conjecture that the major cycloaddition products share the same *cis* configuration and that the stereochemistry of the cycloaddition remains unchanged for 4-substituted cyclohexanones.

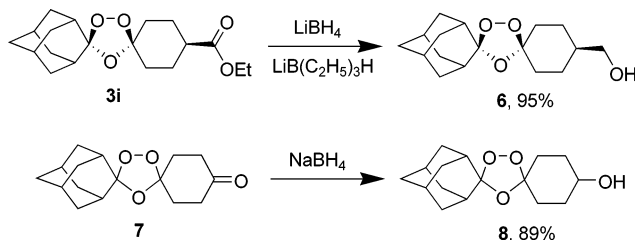
The results are compiled in Table 1. We found that diastereoselectivity is a function of the nature and size of the substituents at the 4-position of the cyclohexanone dipolarophile. Specifically, large groups (group I) such as *tert*-butyl, phenyl, and phthalimido gave exclusively one diastereomer with estimated *cis/trans* ratios greater than 20:1. 4-Substituted cyclohexanones with functional groups linked by a single methylene (group II) provided *cis/trans* ratios of approximately 5:1. The distal substituents attached to the methylene group apparently have no discernible directive effect on the cycloaddition reaction. Cyclohexanones with ester and amide groups at the 4-position (Group III) provided *cis/trans* ratios ranging from 2.5:1 to 5:1.

Post-Ozonolysis Reactions. With these ozonides in hand, we then turned our attention to ozonide-compatible synthetic transformations. Despite the utility of the Griesbaum cozonolysis reaction, the synthesis of functionalized tetrasubstituted ozonides is largely untested;^{2d,9} however, a limited number of post-ozonolysis reactions have been successfully employed for di-, tri-, and tetrasubstituted ozonides. For example, ozonide ketones¹⁰ and aldehydes^{11,12} have been reduced to ozonide alcohols with lithium and sodium borohydride. An ozonide alcohol was oxidized to the corresponding ozonide aldehyde by a Swern oxidation.¹³ Ozonide aldehydes were converted to their dimethyl and 1,3-dioxolane acetals^{11,12,14} and were successfully employed in several carbon-carbon bond-

SCHEME 2. Ozonide Decomposition



SCHEME 3. Reductive Reactions of Ozonides **3i** and **7**



forming reactions, including allylation with allylzinc bromide or allylsilanes and allylstannanes in the presence of TiCl_4 or SnCl_4 and Mukaiyama-type aldol condensations.

Ozonide ketones in which the ketone functional group was at the α -position (α -oxo ozonides) are transformed to α -diazonides by Griesbaum cozonolysis^{2c} and converted to ozonide *O*-methyl oximes and epoxides with *O*-methylhydroxylamine and diazomethane, respectively.¹⁵ α -Chloro ozonides, with¹⁶ or without¹³ AgBF_4 and α -acetoxy ozonides in the presence of NaHCO_3 ^{13,17} undergo displacement reactions with various alcohols to form ozonide ethers. Various post-ozonolysis chemistries have also been applied to unsaturated ozonides. Griesbaum and Zwick¹⁸ described the bromination of several vinyl and vinylidene ozonides to form ozonide dibromides. Several unsaturated bicyclic unsaturated ozonides were reduced by diimide to give saturated ozonides.¹⁹ Ozonolysis of a vinyl chloride ozonide in methanol afforded the corresponding methyl ester ozonide.²⁰ Successive treatment of another vinyl chloride ozonide with *m*-CPBA and AgBF_4 afforded an enone ozonide via an epoxy ozonide.²⁰

In post-ozonolysis transformations of these tetrasubstituted ozonides, we observed that reaction temperatures are best maintained below $60\text{ }^\circ\text{C}$ ³ to avoid decomposition of the ozonide heterocycle into adamantane lactone and the starting material cyclohexanones in Hock-type fragmentations (Scheme 2). As expected, these ozonides were quite stable to basic conditions as a result

(9) McCullough, K. J.; Nojima, M. *Peroxides from Ozonization*. In *Organic Peroxides*; Ando, W., Ed.; Wiley: Chichester, 1992; pp 661–728.

(10) Bunnelle, W. H.; Meyer, L. A.; Schlemper, E. O. *J. Am. Chem. Soc.* **1989**, *111*, 7612–7613.

(11) Hon, Y.-S.; Yan, S.-L. *Tetrahedron Lett.* **1993**, *34*, 6591–6594.

(12) Hon, Y.-S.; Yan, J.-L. *Tetrahedron* **1997**, *53*, 5217–5232.

(13) Griesbaum, K.; Quinkert, R. O. *Liebigs Ann./Recl.* **1997**, 2581–2585.

(14) Hon, Y.-S.; Yan, J.-L. *Tetrahedron Lett.* **1994**, *35*, 1743–1746.

(15) Griesbaum, K.; Dong, Y.; McCullough, K. J. *J. Org. Chem.* **1997**, *62*, 6129–6136.

(16) Griesbaum, K.; Schlindwein, K. *J. Org. Chem.* **1995**, *60*, 8062–8066.

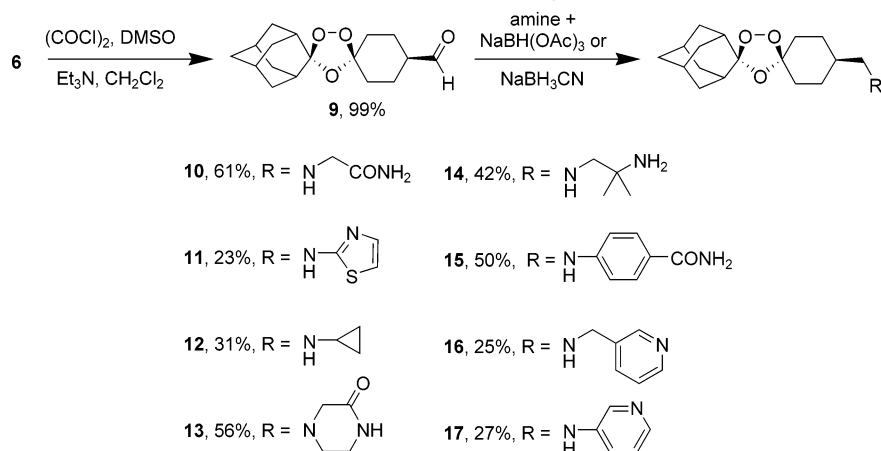
(17) Griesbaum, K.; Volpp, W.; Huh, T.-S. *Tetrahedron Lett.* **1989**, *30*, 1511–1512.

(18) Griesbaum, K.; Zwick, G. *Chem. Ber.* **1985**, *118*, 3041–57.

(19) Adam, W.; Eggelte, H. J.; Rodriguez, A. *Synthesis* **1979**, 383–384.

(20) Griesbaum, K.; Bandyopadhyay, A. R.; Meister, M. *Can. J. Chem.* **1986**, *64*, 1553–1559.

SCHEME 4. Reductive Amination Reactions of Ozonide Aldehyde 9



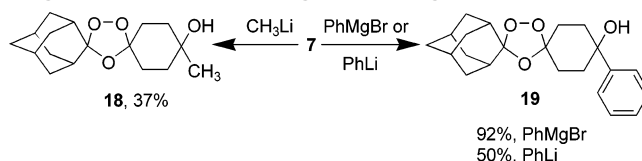
of their lack of α -hydrogen atoms that precluded Kornblum–DeLaMare fragmentation.^{11,21} The ozonides were also stable to mild acid treatment such as that required for Boc deprotection.

X-ray data for **3h** and **5** permit us to assign the stereochemistry of ozonides **3c**, **32**, and **33** as *cis*. Although **3h** is customarily synthesized directly via the cozonolysis reaction, it was also synthesized in a Mitsunobu reaction between ozonide alcohol **6** and phthalimide (vide infra), establishing the stereochemistry of **6** as *cis*. Ozonide ester **3i**, the precursor of **6**, and the aldehyde (**9**) and mesylate (**25**) ozonides derived from **6** also share its *cis* stereochemistry. Ozonide acid **20**, derived from **3i**, is similarly *cis*. With the exception of ozonide carbinols **8**, **18**, and **19**, these data permit us to assign the stereochemistry of the remaining ozonides reported herein as *cis*.

Reductive reactions with borohydride reagents are depicted in Scheme 3. Treatment of ozonide ester **3i** with a combination of lithium borohydride and 10 mol % of lithium triethylborohydride²² afforded ozonide alcohol **6** in nearly quantitative yield. Reduction of ozonide ketone **7**²³ with sodium borohydride gave ozonide alcohol **8** as a 1:1 mixture of *cis* and *trans* diastereomers in high yield.

Reductive amination reactions are depicted in Scheme 4. Ozonide aldehyde **9** was prepared in quantitative yield by Swern oxidation of ozonide alcohol **6**. Reductive amination of **9** with primary, secondary, and aromatic amines using $\text{NaBH}(\text{OAc})_3/\text{AcOH}/\text{DCE}$ afforded the corresponding ozonide amines **10**–**17** in poor to good yields along with various proportions of ozonide alcohol **6**. Reductive amination of **9** with cyclopropylamine gave, in addition to **12**, the corresponding diozonide tertiary amine in 37% yield. Although anilines worked well in this reaction (**15**), less nucleophilic heterocyclic aromatic amines were not as efficient (**11** and **17**). Because glycineamide hydrochloride was only sparingly soluble in DCE, it was used in large excess in a reductive amination reaction with NaBH_3CN in MeOH to afford **10**.

SCHEME 5. Reaction of Ozonide Ketone 7 with Organolithium and Grignard Reagents



Reactions with carbon nucleophiles are depicted in Scheme 5. Treatment of ozonide ketone **7** with methyl-lithium in ether at -78°C formed ozonide carbinol **18** as a 1.4:1 mixture of diastereomers along with 2-methyl-2-adamantanone (6%), the methyl-lithium addition product of 2-adamantanone, produced in turn from decomposition of ozonide ketone **7**. Treatment of **7** with either phenyl-lithium or phenylmagnesium bromide followed a parallel course with formation of ozonide carbinol **19** as a 1:1 mixture of *cis* and *trans* diastereomers. For the latter reactions, no 2-phenyl-2-adamantanone was detected. These results demonstrate that the 1,2,4-trioxolane heterocycle in ozonide ketone **7** is quite stable to Grignard reagents at low temperatures and fairly stable to aryl- and alkyl-lithium reagents.

Mitsunobu reactions using diisopropyl azodicarboxylate/triphenylphosphine as coupling reagents are depicted in Scheme 6. Ozonide acid **20**, prepared by aqueous KOH hydrolysis of its corresponding ester **3i**, reacted with 1-(2-hydroxyethyl)imidazole to form ozonide imidazole ester **21**. Similarly, ozonide phenyl ethers **22** and **23** were prepared by Mitsunobu reactions of ozonide phenol **5** and ozonide alcohol **6**, respectively. In the preparation of **22**, addition of triethylamine improved the yield from 20% to 80%. Ozonide phenol **5** was obtained by aqueous KOH hydrolysis of the corresponding ozonide acetate **3c**. Phthalimide and hydantoin ozonides **3h** and **24** were synthesized by Mitsunobu reactions of ozonide alcohol **6** with phthalimide and hydantoin, respectively.

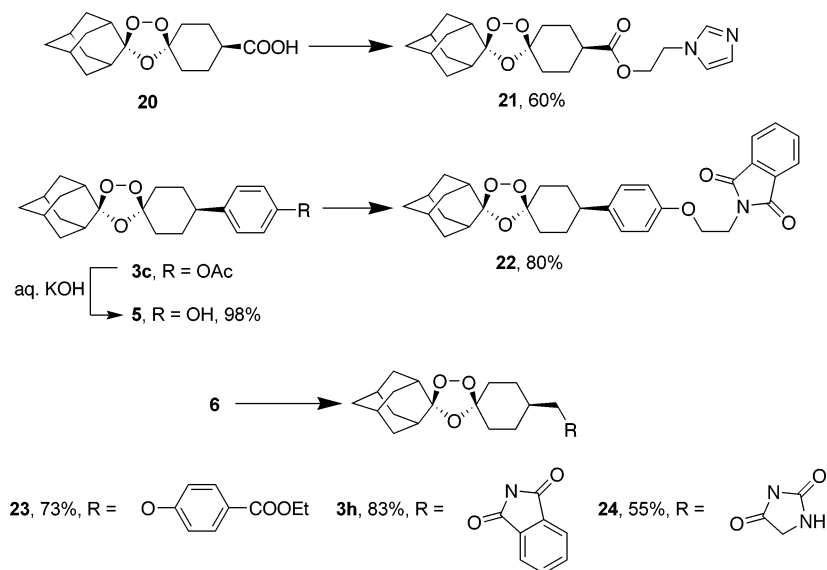
The syntheses of azoles, sulfides, and sulfones are depicted in Scheme 7. Ozonide imidazole **26** and ozonide triazole **27** were synthesized by nucleophilic displacement reactions of ozonide mesylate **25** with the NaH-generated anions of imidazole and triazole, respectively. Reaction of ozonide mesylate **25** with 2-mercaptopyridine-*N*-oxide sodium salt hydrate and 1-methyl-5-mercaptotetrazole sodium salt dihydrate afforded the respective ozonide

(21) Kornblum, N.; DeLaMare, H. E. *J. Am. Chem. Soc.* **1951**, *73*, 880–881.

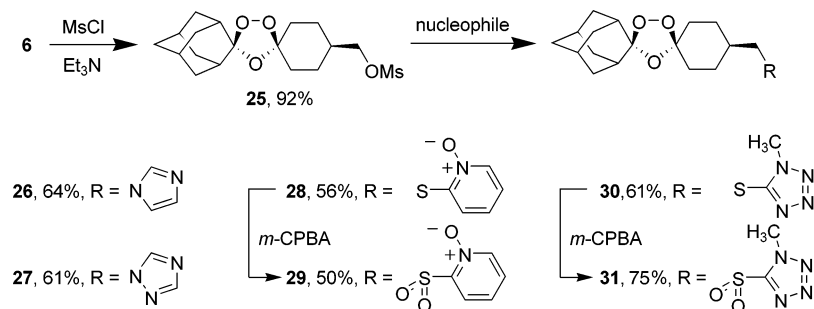
(22) Brown, H. C.; Narasimhan, S. *J. Org. Chem.* **1982**, *47*, 1604–1606.

(23) Vennerstrom, J. L.; Dong, Y.; Chollet, J.; Matile, H. Spiro and Dispiro 1,2,4-Trioxolane Antimalarials. U.S. Patent 6,486,199, November 2002.

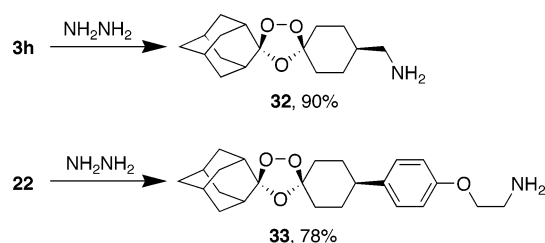
SCHEME 6. Ozonide Mitsunobu Reactions



SCHEME 7. Synthesis of Ozonide Azoles, Sulfides, and Sulfones from Ozonide Mesylate 25



SCHEME 8. Hydrazine Deprotection of Ozonide Phthalimides 3h and 22



sulfides **28** and **30**, which were further oxidized to the corresponding ozonide sulfones **29** and **31**.

Phthalimide deprotection using hydrazine is depicted in Scheme 8. When ozonide phthalimides **3h** and **22** were treated with hydrazine in $\text{CHCl}_3/\text{EtOH}$ (7:3) at 60 °C, ozonide primary amines **32** and **33** were formed in high yields and isolated as their mesylate salts. The deprotection reactions were completed without effect on the trioxolane ring. An array of reaction conditions for the deprotection of ozonide phthalimide **3h** was investigated, and it was found that the optimal reaction was 5–6 equiv of hydrazine in $\text{CHCl}_3/\text{EtOH}$ at 60 °C for 12 h.

Summary. The diastereoselectivity of the Griesbaum cozonolysis reaction reveals that attack of the carbonyl oxide from the axial side²⁴ is strongly favored. The product ratio is mainly a reflection of the conformational rigidity of the cyclohexanones, although electronic contributions by the 4-substituent cannot be ruled out. These findings suggest that the stereochemistry of cycloaddition (preferred axial attack) is controlled mainly by kinetic (transition-state hyperconjugation) factors. This work has also expanded the range of ozonide-compatible synthetic transformations to include ester to alcohol reductions, reductive aminations, various Mitsunobu reactions, displacement reactions with mercaptides and imidazole/triazole anions, addition reactions with organolithium and Grignard reagents, and phthalimide deprotections with hydrazine. Although it is unknown whether di-, tri-, or other tetrasubstituted ozonides are similarly unaltered by these chemical transformations, the wide range of applicable post-ozonolysis chemistry for these tetrasubstituted ozonides parallels that seen in the preparation of the many semisynthetic artemisinin derivatives.^{25,26}

Acknowledgment. We thank the Medicines for Malaria Venture (MMV) for generous support of this research.

Supporting Information Available: Synthesis and characterization data for **2a–k**, **3a–k**, **4h**, **4i**, and **5–33** and X-ray structural data for **3h**, **4h**, and **5**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO040171C

(24) Gung, B. W. *Chem. Rev.* **1999**, *99*, 1377–1386.
 (25) Vroman, J. A.; Alvim-Gaston, M.; Avery, M. A. *Curr. Pharm. Des.* **1999**, *5*, 101–138.
 (26) G. Bez.; Kalita, B.; Sarmah, P.; Barua, N. C.; Dutta, D. K. *Curr. Org. Chem.* **2003**, *7*, 1231–1255.