Chiral-Auxiliary-Induced Diastereoselectivity in the [4 + 2] Cycloadditions of Optically Active 2,2-Dimethyloxazolidine Derivatives of Sorbic Acid: A Model Study with Singlet Oxygen as the Smallest Dienophile

Waldemar Adam,[†] Markus Güthlein,[†] E.-M. Peters,[‡] Karl Peters,[‡] and Thomas Wirth*,[†]

Contribution from the Institut für Organische Chemie, Universität Würzburg, Am Hubland, D-97074 Würzburg, Germany, and Max-Planck-Institut für Festkörperforschung, Heisenbergstrasse 1, D-70506 Stuttgart, Germany

Received January 5, 1998

Abstract: Optically active 2,2-dimethyloxazolidines, conformationally controlled chiral auxiliaries, have been applied for the first time in the [4 + 2] cycloaddition of singlet oxygen, the smallest possible dienophile. High π-facial selectivity (diastereomeric ratio ≥ 95:5) has been achieved in the attack of singlet oxygen on the 1,3-diene moiety of the chiral amides **3** of sorbic acid. Expectedly, the sterically much more imposing 4-phenyl-1,2,4-triazoline-3,5-dione dienophile [4 + 2]-cycloadds with complete stereocontrol to the amide **3d**.

Introduction

Stereoselective [4 + 2] cycloadditions, controlled by chiral auxiliaries, are highly useful in organic synthesis, since the stereochemical information of the auxiliary can be used to generate selectively up to four new stereogenic centers in the cycloadduct in one step. This can be accomplished by using dienophiles or 1,3-dienes, appropriately attached to suitable chiral auxiliaries of the chiral pool or prepared specifically for this purpose.[1] The steering propensity of the chiral auxiliary derives from repulsive steric interactions between the auxiliary in the substrate and the attacking reaction partner.[2]

While such stereocontrol has been abundantly used with success for [4 + 2] cycloadditions of a variety of achiral dienophiles,[3−6] nothing is known to date for the smallest possible dienophile, namely, singlet oxygen. Therefore, the design of auxiliary-controlled 1,3-dienes for photooxygenation purposes presents a formidable challenge. Even more so, if it is realized that only modest success has been accomplished for ene reactions of singlet oxygen controlled by chiral auxiliaries.[7] Nevertheless, should one succeed, the resulting endoperoxides would serve as valuable building blocks for the synthesis of enantiomerically enriched, highly oxyfunctionalized target molecules.

In the present model study, we report the first-time use of chiral-auxiliary-controlled 1,3-dienes in [4 + 2] cycloaddition reactions with singlet oxygen, the smallest possible dienophile. As chiral auxiliaries we chose optically active 2,2-dimethyloxazolidines, recently developed by Kanemasa[8] and Porter.[9] Indeed, these auxiliaries, which operate both through steric and conformational control, turn out to be highly effective chiral inductors in the stereocontrolled [4 + 2] cycloaddition of singlet oxygen to the amides **3** of sorbic acid. Expectedly, for the sterically much more imposing PTAD (4-phenyl-1,2,4-triazoline-3,5-dione) as dienophile compared to singlet oxygen, the stereocontrol in such [4 + 2] cycloaddition is nearly perfect (diastereomeric ratio (dr) > 95:5).

[†] Universität Würzburg.

[‡] Max-Planck-Institut für Festkörperforschung.

[§] Undergraduate research participant, Spring 1997.

(1) *Stereoselective Synthesis, Methods of Organic Chemistry (Houben Weyl)*, 4th ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; G. Thieme: Stuttgart, New York, 1995; Vol. E 21.

(2) (a) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876. (b) Kim, B. H.; Curran, D. P. *Tetrahedron* **1993**, *49*, 293−318. (c) Jones, G. B.; Chapman, B. J. *Synthesis* **1995**, 475−497. (d) Studer, A. *Synthesis* **1996**, 793−815. (e) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835−875.

(3) For C═C dienophiles, see: Jurczak, J.; Bauer, T.; Chapuis, C. In *Methods of Organic Chemistry (Houben Weyl)*, 4th ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; G. Thieme: Stuttgart, New York, 1995; Vol. E 21, pp 2779−2798, 2853−2855, 2908−2910, 2937−2942.

(4) For C═O dienophiles, see: Jurczak, J.; Bauer, T.; Chapuis, C. In *Methods of Organic Chemistry (Houben Weyl)*, 4th ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; G. Thieme: Stuttgart, New York, 1995; Vol. E 21, pp 2919−2921.

(5) For N═N dienophiles, see: (a) Orena, M. In *Methods of Organic Chemistry (Houben Weyl)*, 4th ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E. Eds.; G. Thieme: Stuttgart, New York, 1995; Vol. E 21, pp 5538−5542. (b) Thiem, R.; Rotscheidt, K. Breitmaier, E. *Synthesis* **1989**, 836−843.

(6) For N═O Dienophiles, see: Orena, M. In *Methods of Organic Chemistry (Houben Weyl)*, 4th ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; G. Thieme: Stuttgart, New York, 1995; Vol. E 21, pp 5581−5582.

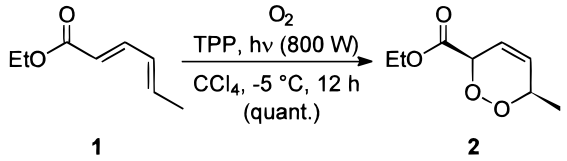
(7) (a) Adam, W.; Brünker, H.-G.; Nestler, B. *Tetrahedron Lett.* **1991**, *32*, 1957−1960. (b) Adam, W.; Griesbeck, A. *Synthesis* **1986**, 1050−1052. (c) Adam, W.; Prein, M. *Angew. Chem.* **1996**, *108*, 519−538. (d) Dussault, P. H.; Woller, K. R.; Hillier, M. C. *Tetrahedron* **1994**, *50*, 8929−8940.

(8) (a) Kanemasa, S.; Onimura, K.; Tanaka, J. *Tetrahedron: Asymmetry* **1991**, *2*, 1185−1188. (b) Kanemasa, S.; Onimura, K. *Tetrahedron* **1992**, *48*, 8631−8644. (c) Kanemasa, S.; Onimura, K. *Tetrahedron* **1992**, *48*, 8645−8658. (d) Kanemasa, S.; Suenaga, H.; Onimura, K. *J. Org. Chem.* **1994**, *59*, 6949−6954. (e) Kanemasa, S.; Ueno, K.; Onimura, K.; Kikukawa, T.; Yamamoto, H. *Tetrahedron* **1995**, *51*, 10453−10462. (f) Kanemasa, S.; Nomura, M.; Yoshinaga, S.; Yamamoto, H. *Tetrahedron* **1995**, *51*, 10463−10476.

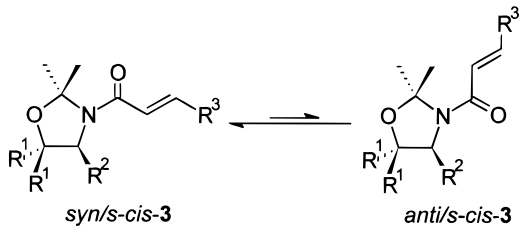
(9) (a) Porter, N. A.; Bruhnke, J. D.; Wu, W.-X.; Rosenstein, I. J.; Breyer, R. A. *J. Am. Chem. Soc.* **1991**, *113*, 7788−7790. (b) Porter, N. A.; Rosenstein, I. J.; Breyer, R. A.; Bruhnke, J. D.; Wu, W.-X.; McPhail, A. T. *J. Am. Chem. Soc.* **1992**, *114*, 7664−7676. (c) Porter, N. A.; Allen, T. R.; Breyer, R. A. *J. Am. Chem. Soc.* **1992**, *114*, 7676−7683. (d) Scott, D. M.; McPhail, A. T.; Porter, N. A. *J. Org. Chem.* **1993**, *58*, 1178−1186. (e) Narukawa, Y.; Juneau, K. N.; Snustad, D.; Miller, D. B.; Hegedus, L. S. *J. Org. Chem.* **1992**, *57*, 5453−5462.

S0002-7863(98)00059-6 CCC: $15.00
Published on Web 04/17/1998

Scheme 1



Scheme 2



a: R^1 = H, R^2 = CH_2Ph, R^3 = CH=$CHCH_3$
b: R^1 = H, R^2 = CH_2Nph, R^3 = CH=$CHCH_3$
c: R^1 = H, R^2 = *i*-Pr, R^3 = CH=$CHCH_3$
d: R^1 = H, R^2 = Ph, R^3 = CH=$CHCH_3$
e: R^1 = CH_3, R^2 = CH_2Ph, R^3 = CH=$CHCH_3$

Results and Discussion

The photooxygenation of ethyl sorbate **1** in carbon tetrachloride (Scheme 1), the solvent of choice since singlet oxygen possesses in it one of the longest lifetimes,[10] afforded the labile endoperoxide **2** as only detectable reaction product, formed by [4 + 2] cycloaddition of singlet oxygen to the diene moiety. Thus, contrary to previous findings, ethyl sorbate **1** is *not* inert toward singlet oxygen.[11,12]

In view of this unexpected result, it was of interest to test the optically active 2,2-dimethyloxazolidines recently developed as chiral auxiliaries by Kanemasa[8] and Porter[9] as a stereochemical probe in the [4 + 2] cycloaddition of the smallest possible singlet-oxygen dienophile. For this purpose, the optically active sorbic acid amides **3** (Scheme 2) were prepared analogously to the known crotonic acid amides (Scheme 2, $R^3 = CH_3$).[8d] NMR studies have shown that the amides **3a**−**e** exist mostly as *syn*/*s-cis* conformers with respect to the α,*β* double bond in chloroform solution at room temperature. This is akin to the *N*-acryloyl ($R^3 = H$)[8b] or *N*-crotonoyl ($R^3 = CH_3$) derivatives,[8d] as expected from their vinylogous relationship.

The photooxygenations of the optically active amides **3** (Scheme 3) afforded the labile endoperoxides **4** as only detectable reaction products. The diastereoselectivities (Table 1) depend on the substitution pattern of the oxazolidinyl auxiliary and increase in the same order as observed for the benzonitrile oxide addition to *N*-acryloyl derivatives ($R^3 = H$).[8c] For example, increased branching at the α-carbon atom of the R^2 substituent raises the diastereoselectivity in the order $CH_2Ph \approx CH_2Nph$ < *i*-Pr < Ph. This would be expected from the increasing steric interactions between R^2 and the incoming singlet-oxygen dienophile in the *ul* transition state (Scheme 4). Indeed, complete stereochemical control is achieved in the special case of amide **3e**. In this case, the two methyl groups adjacent to the C-4 position of the oxazolidine ring force the phenyl group of the benzyl R^2 substituent to be placed directly over the reacting diene moiety.[8c] The resulting massive steric repulsion with singlet oxygen suppresses the *ul* attack completely.

Scheme 3

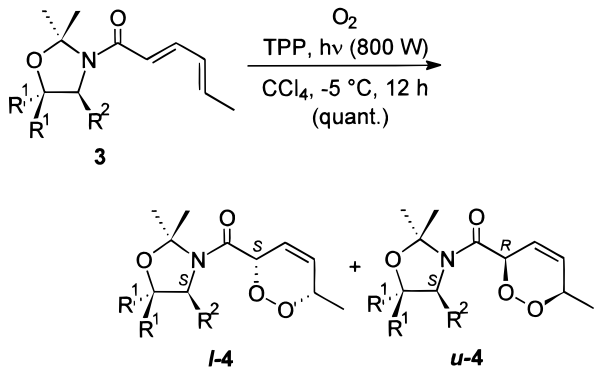
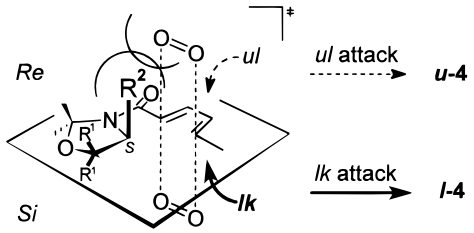


Table 1: Diastereoselectivities in the Photooxygenation of Optically Active Sorbic Acid Amides **3**

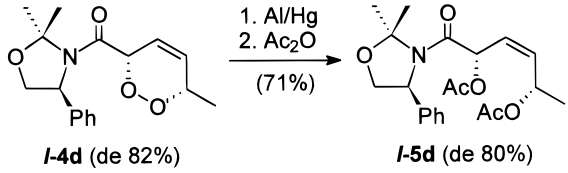
entry	amide	R^1	R^2	dr[a] ***l*-4**:***u*-4**
1	**3a**	H	CH_2Ph	68:32
2	**3b**[b]	H	CH_2Nph[c]	67:33
3	**3c**	H	*i*-Pr	76:24
4	**3d**	H	Ph	91:9
5	**3e**	Me	CH_2Ph	≥95:5

[a] Diastereomeric ratios determined by ^1H or ^{13}C NMR analysis directly on the crude reaction mixtures, error ±5% of the stated values. [b] Other enantiomer was used. [c] Nph = 2-naphthyl.

Scheme 4



Scheme 5



To assign the absolute configuration of the new [4 + 2] cycloadducts **4**, a 91:9 mixture of the labile endoperoxides **4d** was directly reduced with aluminum amalgam.[13] Subsequent double acetylation yielded the diacetate **5d** as a 90:10 mixture of diastereomers (Scheme 5). The major diastereomer ***l*-5d** was isolated by fractional crystallization and its absolute configuration was determined to be *like* by X-ray analysis (cf. the Supporting Information). Moreover, in view of the paralleling diasteroeselectivities in the [4 + 2] cycloadditions of sorbic acid amides **3** and in the 1,3-dipolar cycloaddition of benzonitrile oxide to analogous *N*-acryloyl derivatives,[8c] the major diastereomers ***l*-4** were assigned to be *like*-configured. The same sense in the cycloadditions for the corresponding phenylglycinol-

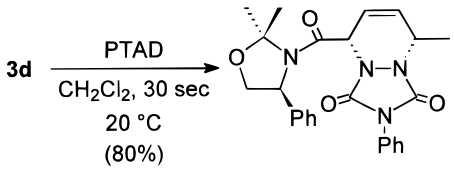
(10) Aubry, J.-M.; Mandard-Cazin, B.; Rougee, M.; Bensasson, R. V. *J. Am. Chem. Soc.* **1995**, *117*, 9159−9164.

(11) Matsumoto, M.; Kuroda, K. *Tetrahedron Lett.* **1982**, *12*, 1285−1288.

(12) The formation of carbonyl compounds was observed in the photooxygenation of methyl sorbate in ethanol: Gollnick, K. *Adv. Photochem.* **1968**, *6*, 89−94.

(13) Corey, E. J.; Da Silva Jardin, P.; Rohloff, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 3672−3673.

Scheme 6



***l*-6d** (d.r. > 95 : 5)

derived amides **3** (R^3 = CH=CHCH$_3$ and R^3 = H) also substantiates this assignment.

In addition the [4 + 2] cycloaddition of PTAD (*N*-phenyl-1,2,4-triazoline-3,5-dione) with amide **3d** was examined. Since PTAD and singlet oxygen display similar reactivities toward dienes and follow the same mechanism,[14] but the former is much bigger, a higher extent of diastereoselection was expected for PTAD. Indeed, the reaction of PTAD with **3d** afforded only one diastereomeric [4 + 2] cycloadduct **6d** (Scheme 6), for which the *like* configuration was assigned, as in the singlet-oxygen [4 + 2] cycloaddition.

These novel results demonstrate that for dienophiles larger than singlet oxygen, namely, triazolinediones (TADs), the phenylglycinol-derived Kanemasa−Porter auxiliary in **3d** is already efficient enough to induce complete diastereoselection in their [4 + 2] cycloaddition with the sorbic acid amides **3**. Furthermore, phenylglycinol is more readily available than 3-amino-2-methyl-4-phenybutan-2-ol,[8b] the amino alcohol necessary for the preparation of amide **3e**, which constitutes another reason why phenylglycinol is the amino alcohol of choice for [4 + 2] cycloadditions controlled by 2,2-dimethyloxazolidine auxiliaries.

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft (Schwerpunktprogramm: Sauerstofftransfer/Peroxidchemie) and the Fonds der Chemischen Industrie (doctoral fellowship for T.W. during 1996−1998) for financial support and Prof. K.-H. Drauz and Dr. M. Schwarm (Degussa AG, Hanau) for generous gifts of optically active amino alcohols. We are also grateful to Prof. S. Hünig for helpful discussions and to C. Wolz for her skillful assistance in the synthesis of starting materials.

Supporting Information Available: Experimental details (30 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA980059U

(14) Radl, S. *Adv. Heterocycl. Chem.* **1997**, *67*, 189−190.