skeleton from 1. The biogenic carbamoylating agent could be carbamoyl phosphate.[5]

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(5) (a) Jones, M. E. *Science (Washington, D.C.)* **1963**, *140*, 1373. For general discussions of carbamoyl phosphate, see: (b) Stryer, L. *Biochemistry*; Freeman: San Francisco, 1981; pp 411–414. (c) Brucie, T. C.; Benkovic, S. J. *Bioorganic Mechanisms, Vol II*; Benjamin: New York, 1966; pp 84–88.

Supplementary Material Available: Experimental procedure for the conversion of 3 into 7 and ^{1}H NMR spectra of synthetic and natural methyl homodaphniphyllate (4 pages). Ordering information is given on any current masthead page.

Enantioselective Synthesis of Tertiary α-Hydroxy Carbonyl Compounds Using ((8,8-Dichlorocamphoryl)sulfonyl)oxaziridine

Franklin A. Davis* and Michael C. Weismiller

Department of Chemistry, Drexel University, Philadelphia, Pennsylvania 19104

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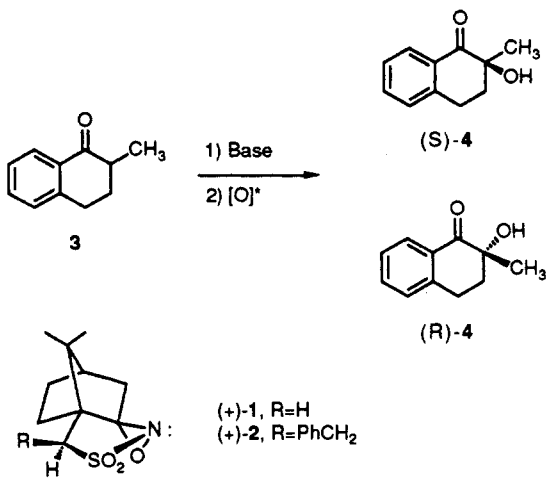
Summary: Very high stereoinduction, generally 90–95% ee, is observed for the asymmetric oxidation of 2-substituted-1-tetralone enolates to 2-hydroxy-2-substituted-1-tetralones by chiral nonracemic oxaziridine (+)-7. Not only are these α-hydroxy carbonyl compounds difficult to prepare enantiomerically pure via other methods, but they are also models for several biologically active compounds.

The development of highly enantioselective methods for the construction of tertiary α-hydroxy carbonyl compounds is of current interest because such compounds are common to many biologically active natural products. This is particularly true of the tetralin(tetralone) ring system where this structural unit is featured in the anthracycline antitumor antibiotics,[1] the phytoalexin lacinilene C,[2] the antitumor alkaloid campthothecin,[3] and the homoisoflavanone eucomol.[4]

Efforts in our laboratory have been directed toward developing methodology for the reagent controlled asymmetric oxidation of enolates to α-hydroxy carbonyl compounds using chiral nonracemic *N*-sulfonyloxaziridines such as 1 and 2.[5,6] These reagents afforded synthetically useful enantioselectivities, 60–95% ee, for the asymmetric oxidation of prochiral acyclic ketone,[6,7] ester,[8] amide,[8] and α-keto ester[9] enolates to the corresponding α-hydroxy carbonyl compounds. However, the stereoselectivity for the asymmetric oxidation of the tetrasubstituted enolate of 2-methyl-1-tetralone (3) to 2-hydroxy-2-methyl-1-tetralone (4), a model for the aforementioned tetralin ring system, is only 16–30% ee using (+)-1.[6,7]

Scheme I



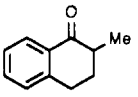
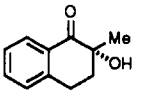
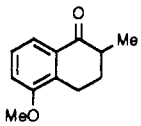
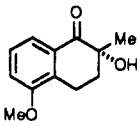
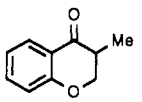
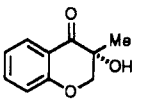
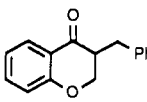
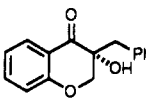
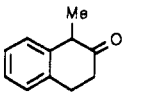
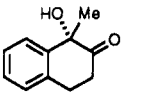
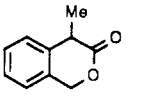
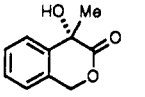
Studies of the oxidation of ketone enolate anions by (+)-1 suggest that the enolate geometry, the enolate substitution pattern, and the enolate solution structure strongly influence the product stereochemistry.[6,10] To explain the chiral recognition a mechanism involving an S_N2 type substitution of the enolate on (+)-1 via an "open" transition controlled by nonbond steric interactions was formulated.[6] In cyclic systems control of enolate geometry is unimportant and options for improving reaction stereoselectivities by varying the enolate substitution pattern are limited. While there are greater opportunities for increasing the stereoinduction by altering counterion and solvent, i.e. the enolate solution structure, this approach also appears limited. For example, optimization of the reaction conditions resulted in only a modest improvement in the stereoinduction of 4 when the solvent was changed from THF to toluene, i.e. 30–60% ee, respectively.[6]

An approach that offers much greater flexibility and promise for improving enolate oxidation stereoselectivities

(1) Krohn, K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 790. Krohn, K. *Foretschr. Chem. Org. Naturst.* **1989**, *55*, 37.
(2) Stipanovic, R. D.; McCormick, J. P.; Schlemper, E. O.; Hamper, B. C.; Shinmyozu, T.; Pirkle, W. H. *J. Org. Chem.* **1986**, *51*, 2500.
(3) Schultz, A. G. *Chem. Rev.* **1973**, *73*, 385.
(4) Tamm, C. *Foretschr. Chem. Org. Naturst.* **1981**, *40*, 105.
(5) For a review on the chemistry of *N*-sulfonyloxaziridines, see: Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703.
(6) Davis, F. A.; Sheppard, A. C.; Chen, B. C.; Haque, M. S. *J. Am. Chem. Soc.* In press.
(7) (a) Davis, F. A.; Haque, M. S. *J. Org. Chem.* **1986**, *51*, 4083. (b) Davis, F. A.; Haque, M. S.; Prezeslawski, R. M. *J. Org. Chem.* **1989**, *54*, 2021.
(8) Davis, F. A.; Haque, M. S.; Ulatowski, T. G.; Towson, T. G. *J. Org. Chem.* **1986**, *51*, 4083.
(9) Chen, B. C.; Davis, F. A.; Boschelli, D.; Empfield, J. R.; Smith, A. B., III Submitted.
(10) Davis, F. A.; Weismiller, M. C.; Lal, G. S.; Chen, B. C.; Przeslawski, R. M. *Tetrahedron Lett.* **1989**, 1613.

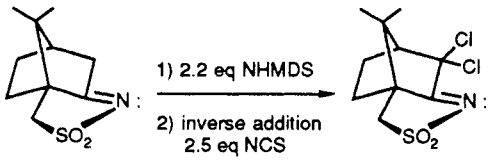
0022-3263/90/1955-3715$02.50/0

Table I. Asymmetric Oxidation of Enolates Using (Camphorylsulfonyl)oxaziridines 1 and 7 at −78 °C in THF

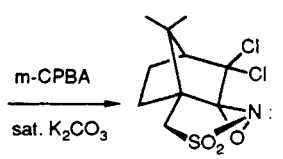
entry	oxaziridine	substrate	conditions base/additive [h]	product	% ee (config)[a]	% isolated yield	$[\alpha]^{20}_D$ ($CHCl_3$)
1	(+)-1		NHMDS [0.25]		16 (*R*)	90	
2			NHMDS[c] [0.25]		20 (*R*)	71	
3			NHMDS/HMPA[c,d] [0.25]		22 (*R*)	70	
4			LDA[e,c] [0.25]		30 (*R*)	90	
5	(+)-7	**3**[b]	NHMDS [1]	**4**	≥95 (*R*)	66	+17.3° (*c* = 2.0)
6			NHMDS[c] [1]		56 (*R*)	68	
7			NHMDS/HMPA[d] [1]		91 (*R*)	60	
8			LDA[e] [1]		≥95 (*R*)	60	
9	(+)-1		NHMDS [1]		14 (*R*)	68	
10	(+)-7	**8**[f]	NHMDS [1]	**9**	≥95 (*R*)	62	+7.0° (*c* = 1.8)
11	(+)-1		NHMDS [0.5]		71 (*R*)	80	
12			LDA[e] [1]		30 (*S*)	56	
13	(+)-7		NHMDS [0.5]		≥96 (*R*)	77	−9.4° (*c* = 1.8)
14		**10**	LDA[e] [1]	**11**	64 (*S*)	70	+6.4° (*c* = 1.1)
15	(+)-1		NHMDS [1]		15 (*R*)	70	
16	(+)-7		NHMDS [0.5]		91 (*R*)	71	−10.0° (*c* = 3.0)
17	(−)-7[g]	**12**	NHMDS [0.5]	**13**	92 (*S*)	67	+9.0° (*c* = 2.2)
18	(+)-1		NHMDS [0.5]		76 (*S*)	60	+77.0° (*c* = 4.2)
19			NHMDS/HMPA[d] [0.5]		65 (*S*)	70	
20			LDA[e] [1]		10 (*S*)	58	
21	(+)-7		NHMDS [3]		16 (*S*)	55	
22		**14**[b]	LDA[e] [1]	**15**[h]	54 (*S*)	56	
23	(+)-1		NHMDS [1]		77 (*S*)	40	+36.0° (*c* = 1.4)
24			LDA[e] [1]		23 (*S*)	45	
25	(+)-7		NHMDS [3]		45 (*S*)	60	
26		**16**	LDA[e] [1]	**17**[h]	17 (*S*)	55	

[a] The % ee's determined by the chiral shift reagent $Eu(hfc)_3$. [b] Aldrich Chemical Co. [c] Oxidation at 0 °C. [d] Ratio of THF/HMPA, 20:1. [e] Enolate generated at 0 °C for 30 min. [f] Hattersley, P. J.; Lockhart, I. M.; Wright, M. *J. Chem. Soc. C* **1969**, 217. [g] Oxidation using (−)-((8,8-dichlorocamphoryl)sulfonyl)oxaziridine (**7**) see ref 14. [h] Reaction quenched using 1.0 N HCl.

is modification of the oxidizing reagent. Indeed oxidation of the enolate anion of **3** with oxaziridine (+)-**2** gave (*R*)-**4** in 67% ee.[10] In this context we describe preliminary results of a study of the asymmetric oxidation of 2-substituted tetralone derived enolate anions and the synthesis of (+)-((8,8-dichlorocamphoryl)sulfonyl)oxaziridine (**7**), a new reagent, which affords exceptional ee's in these oxidations.



(−)-**5** (+)-**6**



(+)-**7**

(+)-((8,8-Dichlorocamphoryl)sulfonyl)imine (**6**) was prepared by treating (camphorylsulfonyl)imine (**5**)[11] with sodium bis(trimethylsilyl)amide (NHMDS) at −78 °C in THF to generate the azaenolate followed by its addition, via a cannula tube, to 2.5 equiv of *N*-chlorosuccinimide (NCS) at −78 °C. After being warmed to 0 °C for 3 h the reaction mixture was quenched with water. An ^1H NMR spectra of the crude reaction mixture indicated the formation of a 75:10:15 mixture of (+)-**6** and the mono- and dichlorination products of **6** at the α-sulfonyl carbon. Imine **6** was isolated in 64% yield by flash chromatography (silica gel; 6:4 CH_2Cl_2–*n*-hexane).[12,13] It is interesting to note that the azaenolate of **5**, in contrast to its reactions with NCS to give (+)-**6**, reacts with carbon electrophiles at nitrogen affording the corresponding enamines.[10] Biphasic oxidation of **6** in CH_2Cl_2 with 1.5 equiv of >95% *m*-CPBA saturated with K_2CO_3 for 18 h gave, after crystallization from ethanol, (+)-**7** in greater than 90% isolated yield.[12,14]

The asymmetric oxidation of enolate anions derived from the ketones and lactone listed in Table I were chosen for study because they simulate similar functionalities in natural products. Compounds **10** and **12** and **16** were prepared in moderate to good yields by alkylation of the enolates of 4-chromanone and 3-isochromanone, respec-

(11) Davis, F. A.; Towson, J. C.; Weismiller, M. C.; Lal, S. G.; Carroll, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 8477.

(12) All new compounds gave satisfactory elemental analysis and had spectral properties consistent with their structures.

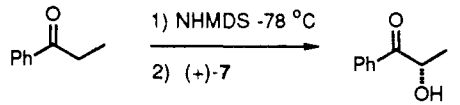
(13) Sulfonimine (+)-**6**: mp 174 °C; $[\alpha]^{20}_D$ +7.9° (*c* 1.0 $CHCl_3$). Sulfonimine (−)-**6**: mp 174 °C; $[\alpha]^{20}_D$ −8.6° (*c* 1.3 $CHCl_3$).

(14) Oxaziridine (+)-**7**: mp 178–80 °C; $[\alpha]^{20}_D$ +89.4° (*c* 1.0 $CHCl_3$). Oxaziridine (−)-**7**: mp 178–80 °C; $[\alpha]^{20}_D$ −88.3° (*c* 1.3 $CHCl_3$).

tively. The enolates were generated, as previously described,[6,7] by treatment of the corresponding ketones with 1.2 equiv of the appropriate base at −78 °C followed, after 30 min, by addition of 1.2 equiv of (+)-**1** or (+)-**7**. When oxidation was complete, as determined by TLC analysis (typically 0.5–3 h), the reaction mixture was quenched at −78 °C by addition of aqueous NH_4Cl or, in the case of **14** and **16**, with 1.0 N HCl. The α-hydroxy carbonyl compounds were isolated by preparative TLC (silica gel) and/or flash chromatography, and the enantiomeric purity was determined using the chiral shift reagent $Eu(hfc)_3$.[6] The absolute configurations were assigned by comparisons of the sign of rotation and the CD spectra with known values and application of the CD octet rule.[15] These results are summarized in Table I.

Significantly, oxidation of the sodium or lithium enolates of 2-methyl-1-tetralone (**3**) by (+)-((8,8-dichlorocamphoryl)sulfonyl)oxaziridine (**7**) afforded (+)-(*R*)-2-hydroxy-2-methyl-1-tetralone (**4**) in greater than 95% ee (entry 5 and 8). Similar high enantioselectivities, 92–95%, are observed with this reagent for the oxidation of enolate derivatives of this ring system (Table I). For example, introduction of a 5-methoxy group **8**, the 3-isochromanone ring system **10**, or a 3-benzyl substituent **12** had little effect on the high stereoselectivities (entries 10, 13, 16). By contrast the ee's for similar oxidations employing oxaziridine (+)-**1** were much lower, i.e. 14–71% (entries 4, 9, 11, and 15). On the other hand oxaziridine (+)-**1** gave better ee's than (+)-**7** for oxidation of enolate species of 1-methyl-2-tetralone (**14**) and 4-methyl-2-benzopyran-3-one (**16**), 76–77 and 54–45%, respectively (compare entries 18 and 23 with 22 and 25).

Oxaziridine (+)-**7** is also useful for the preparation of acyclic α-hydroxy ketones of high enantiomeric purity, which are difficult to prepare in other ways.[16] For example, (*S*)-2-hydroxy-1-phenyl-1-propanone (**19**) was obtained in greater than 95% ee and 61% isolated yield by oxidation of the sodium enolate of propiophenone (**18**) at −78 °C by (+)-**7**. Oxidation of this enolate species with (+)-(camphorylsulfonyl)oxaziridine (**1**) resulted in **19** in only 62% ee.[6]



18 (S)-**19** (95% ee)

(15) Kirk, D. N. *Tetrahedron* **1986**, *42*, 777.

(16) For examples of chiral auxiliary based asymmetric synthesis of α-hydroxy ketones, see: Enders, D.; Bhushan, V. *Tetrahedron Lett.* **1988**, *29*, 2437. Lohray, B. B.; Enders, D. *Helv. Chim. Acta* **1989**, *72*, 980.

In these oxidations we have generally argued that the enantioselection is controlled by steric forces and the transition-state geometry predicted by evaluation of nonbonded interactions. Based on these considerations it is difficult to see why replacing hydrogen by a larger chlorine atom, (+)-**1** to (+)-**7**, should have such a dramatic effect on the stereoinduction. Furthermore, (+)-**7** is more reactive than (+)-**1**, being able to oxidize **3** to **4** at −78 °C vs 0 °C, respectively (compare entries 2 and 5). These effects, which cannot be readily accommodated by our simple steric model,[6] suggests that stereoelectronic factors and/or metal chelation effects caused by the presence of the electronegative chlorine atoms play some role in determining the transition-state topology. While it is well established that enolates exist and react as aggregate molecules in solution, our knowledge of the structure of the actual reacting species remains sketchy.[6,17] Thus additional studies are necessary to provide a useful rationale for the reactivity of this new asymmetric oxidizing reagent.

In summary, (+)-((8,8-dichlorocamphoryl)sulfonyl)oxaziridine (**7**) gives high stereoinduction, generally 90–95% ee, for the enantioselective oxidation of tetrasubstituted enolates to tertiary α-hydroxy carbonyl compounds. These compounds are models for natural products and are difficult to prepare enantiomerically pure in other ways. The fact that the configuration of the oxaziridine controls the product stereochemistry means that either enantiomer is readily available by choice of the appropriate oxidizing reagent (compare entries 16 and 17). Finally, modification of the oxaziridine oxidizing reagent, as an efficient method for improving enolate oxidation stereoselectivities, is demonstrated by these results.

Acknowledgment. The financial support of the National Institutes of Health (Institute of General Medical Sciences) through Grant GM 34014 is gratefully acknowledged.

Supplementary Material Available: Detailed procedures for the synthesis of starting materials and physical constants (yields, melting points, IR, ^1H NMR, CD spectra) for all compounds (6 pages). Ordering information is given on any current masthead page.

(17) (a) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624 and references cited therein. (b) Arnett, E. M.; Fisher, F. J.; Nichols, M. A.; Ribeiro, A. A. *J. Am. Chem. Soc.* **1990**, *112*, 801. (c) Williard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 462. (d) Williard, P. G.; Hintze, M. J. *J. Am. Chem. Soc.* **1987**, *109*, 5539. (e) Williard, P. G.; MacEwan, G. J. *J. Am. Chem. Soc.* **1989**, *111*, 7671. (f) Amstuz, R.; Schweizer, W. B.; Seebach, D.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2617. (g) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, *33*, 2737.