Highly Enantioselective Oxidation of Sulfides to Sulfoxides by a New Oxaziridinium Salt
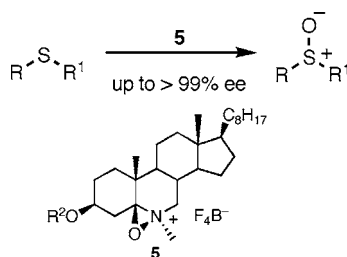
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ABSTRACT

The new oxaziridinium salt 5 (R² = TBDPS) is an effective reagent for the highly enantioselective oxidation of sulfides to sulfoxides with up to >99% ee and good yields. As such, it represents a new valuable nonmetallic alternative to the existing methods for asymmetric sulfoxidation.

Asymmetric sulfoxides are very useful as synthons and chiral auxiliaries in asymmetric synthesis[1] and also as biologically active compounds.[2] The asymmetric oxidation of sulfides is one of the most straightforward and convenient approaches to chiral sulfoxides. Biological and chemical processes may achieve this transformation.[1,2] Two main chemical methods have been shown to lead to specific sulfoxides with high enantioselectivity. They involve either an oxidant combined with a chiral transition metal complex or a nonmetallic chiral electrophilic oxidant. The area of metal-catalyzed sulfoxidations has been actively investigated since the outstanding results of Kagan[3] and Modena,[4] who obtained high enantioselectivities using modified versions of the Sharpless reagent.[5] Other metals (such as vanadium, manganese, and

more recently iron) as well as different chiral ligands have led to useful systems.[2b]

The area of nonmetallic electrophilic oxidants has known a breakthrough with the remarkable work of Davis on chiral sulfamyl- and sulfonyloxaziridines.[6] The latter are still the most efficient enantioselective nonmetallic reagents available for asymmetric sulfoxidation.

Oxaziridinium salts are also electrophilic oxygen transfer reagents, as established since Lusinchi first reported on the synthesis and the chemistry of oxaziridiniums.[7] Although the great majority of the reports concerning oxaziridiniums deals with the epoxidation of alkenes,[8,9] only few studies have been

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devoted to sulfide oxidation.[8e,10] The action of a racemic oxaziridinium on thioethers[10c] and the enantioselective sulfoxidation of *p*-tolyl methyl sulfide, with moderate enantioselectivity, by chiral oxaziridiniums have been described.[8e,10a,b] In a related but different reaction, the acid-promoted oxidation of sulfides to sulfoxides by unactivated oxaziridines,[10a,11] oxaziridinium-like intermediates are thought to be the active species. Moderate enantioselectivities also resulted when using chiral oxaziridines in this way.[10a,11b]

The development of new methods and reagents leading to chiral sulfoxides with high enantioselectivity remains a subject of both relevant synthetic and fundamental interest. Thus, as part of our interest in oxaziridinium chemistry and in the application of these reagents for asymmetric sulfoxidation, we report herein on the synthesis of a newly developed oxaziridinium salt and the oxidation of sulfides with high enantioselectivities by this reagent.

The oxaziridinium salt **5** was obtained in two steps from the protected 6-azacholesterol **3** (Scheme 1). The synthesis

Scheme 1
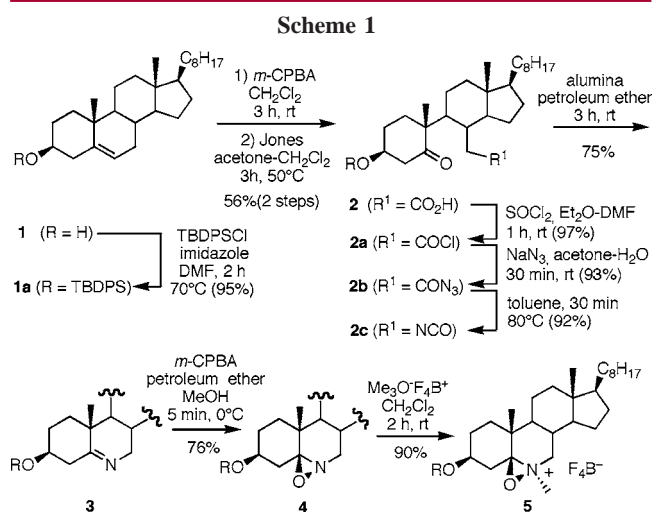
of **3** (R = TBDPS) was performed from cholesterol **1** following a strategy already described[12] for the synthesis of 6-azacholesterol and other 6-azasteroids but using where necessary different reagents and conditions to improve yields and essentially to overcome the elimination of the 3-oxy

substituent which is the weak point in this strategy. That problem we found using the originally described reaction conditions has also been pointed out by others.[13]

Thus, cholesterol **1** was protected as the *tert*-butyldiphenylsilyl ether **1a**[14] using a standard protocol. The 5,6 double bond was then oxidized in two steps. It was first epoxidized at room temperature, and the resulting epoxides **1b** (not depicted in Scheme 1; mixture of diastereoisomers α/β in ca. 2.7:1 molar ratio) were oxidized with the Jones reagent at 50 °C.[15] The (5,6-*seco*)-ketoacid **2**, isolated in 60% yield (56% from **1a**), was converted to the acyl azide **2b** through the acid chloride **2a**. The acyl azide moiety smoothly rearranged into the isocyanate **2c** on moderate heating, in toluene. For the key step involving the cyclization of the intermediate **2c** leading to protected 6-azacholesterol **3**, we have established an alumina-promoted protocol. In our hands, it proved more efficient than the silica gel induced protocol developed by Frye et al.[13a] for the purpose of preventing the elimination of the 3-oxy substituent. Use of neutral alumina shortened the reaction time with no need of heating. Thus, the cyclization of **2c** was performed at room temperature, in 3 h, leading to **3**[16] in 75% yield (62% from **2**). Hence, **3** was prepared from cholesterol **1** in 32% overall yield.[17]

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(16) The formation of **3** from **2c** was characterized by an upfield shift in the ^{13}C NMR signal of C5 from 216.6 ppm in **2c** to 173.6 ppm in **3** indicating thereby the disappearance of the ketone and the formation of the imine bond.

(17) The overall yield is strongly dependent on the Jones oxidation step, in which yields ranging from 60 to 80% have been obtained mainly as a function of the efficiency of the workup, including chromatographic purification and subsequent crystallization of compound **2**.

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The peracid oxidation of **3** led stereospecifically to the β-oxaziridine **4** isolated in 76% yield. The NMR spectra of the crude product unambiguously indicated the formation of only one of the two possible diastereoisomers. On one hand, only one signal corresponding to C5, the quaternary carbon atom of the oxaziridine ring, was observed in the ^{13}C spectrum (at δ 87.7 ppm). On the other hand, the ^{1}H spectrum displayed a single set of signals for the protons in the neighborhood of the three-membered heterocyclic ring (i.e., on C4, C7, and C19). This was particularly apparent for the protons on C7, resonating at δ 3.40 ppm (dd, ^2J = 17.0 Hz, ^3J = 7.4 Hz) and δ 2.88 ppm (dd, ^2J = 17.0 Hz, ^3J = 9.9 Hz). Each signal integrated as much as the multiplet at δ 3.82 ppm corresponding to C3-H. The ^3J(H7,H8) coupling constants gave insight into the positions of both C7-H relative to the pseudoaxial C8-H. They were consistent with a pseudoaxial−pseudoequatorial coupling for the more deshielded proton at 3.40 ppm and with a pseudoaxial−pseudoaxial coupling for the more shielded proton at 2.88 ppm. Therefore, the first, *syn* to the pseudoaxial C8-H, was on the β face and pseudoequatorial whereas the second, *anti* to C8-H, was on the α face and pseudoaxial. From those relative positions, the β configuration of the oxaziridine ring naturally followed considering that the deshielding effect of the three-membered ring is stronger on the *cis*-vicinal protons than on the *trans*-disposed ones.[18] Accordingly, the chemical shifts of the protons on C4 were similarly affected. Although the α-proton resonated within the methyne region at δ 1.94 ppm (br d, ^2J = 12.4 Hz), the β-proton appeared more deshielded at δ 2.32 ppm (dd, ^2J = 12.4 Hz, ^3J = 11.3 Hz). This signal also integrated for one proton, as that of C3-H at δ 3.82 ppm, and showed a multiplicity consistent with a *trans*-pseudodiaxial arrangement with respect to the C3-H giving rise to a ^3J(H3−H4β) very close in value to the geminal H4β,H4α coupling constant.

Methylation of the oxaziridine **4** with the Meerwein salt trimethyloxonium tetrafluoroborate led to oxaziridinium **5** isolated in high yield (90%). The configuration of the three-membered ring was obviously not affected on alkylation, but its deshielding effect was in turn increased as a consequence of the cationic nature of the oxaziridinium, which is far more electrophilic than the parent oxaziridine. Accordingly, the formation of the oxaziridinium salt **5** was characterized by a downfield shift of C5 in the ^{13}C spectrum to δ 102.0 ppm and deprotection of the vicinal protons in the ^{1}H spectrum with respect to oxaziridine **4**. Thus, C7-Hβ appeared at δ 4.19 ppm (dd, ^2J = 14.6 Hz, ^3J = 7.7 Hz) and C7-Hα appeared at δ 3.31 ppm (dd, ^2J = 14.6 Hz, ^3J = 10.8 Hz). The signals of the methyl-19 and C4-Hβ are also shifted downfield by ca. 0.3 ppm, appearing as a singlet at δ 1.41 ppm and a doublet of doublets at δ 2.60 ppm (^2J = 12.8 Hz, ^3J = 11.4 Hz). Moreover, the NOESY spectrum of **5** displayed correlations (Figure 1) in agreement with the previous structural assignments. Thus, the NMR data for oxaziridinium **5** suggested a nonsteroid-like predominant
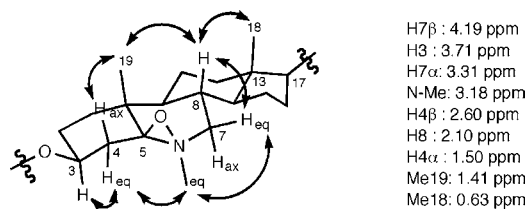

H7β : 4.19 ppm
H3 : 3.71 ppm
H7α : 3.31 ppm
N-Me: 3.18 ppm
H4β : 2.60 ppm
H8 : 2.10 ppm
H4α : 1.50 ppm
Me19: 1.41 ppm
Me18: 0.63 ppm

Figure 1. Selected NOESY correlations observed for **5**.[19]

conformation similar to those established for 5,6β-epoxides,[20] hence involving ring B in a half chair-like conformation (with C9 and C8, respectively, below and above the plane defined by C10−C5−N−C7) and ring A in a twist-like conformation, both leading to an A/B *cis* junction which allows the 3β-substituent to be equatorial[21] (Figure 1). The equatorial N−Me group, lying almost in the C10−C5−N−C7 (half chair) plane, showed NOE interactions with the equatorial protons on C4 and C7 (H4α and H7β) but not with the axial ones.

With the oxaziridinium salt **5** in hand, we explored the potential of this new reagent for asymmetric sulfoxidation. A series of sulfide oxidations were thus performed (Table 1). We first studied the action of **5** on methyl *p*-tolyl sulfide. Upon addition of 1 equiv of the oxaziridinium **5** to the sulfide, in dichloromethane at room temperature, the reaction was almost instantaneous,[22] complete, and quantitative. It led to the sulfoxide with high enantioselectivity (ee 92%, entry 1A). Interestingly, no overoxidation into sulfone could be detected by TLC and ^{1}H NMR in the crude reaction mixture. On lowering the reaction temperature, we found that the conversion remained quantitative while the enantioselectivity was improved to afford an almost enantiopure product (ee > 99%, entry 1B). The oxidation of a variety of sulfides involving different R^1 and R^2 residues was then examined. In all cases, no further oxidation of the sulfoxide was found.

With a few exceptions, the reactions proceeded with high to excellent enantioselectivities. Thus, a less efficient asymmetric induction resulted when the aryl group was a "bulky" *o*-disubstituted phenyl ring (entries 5 and 6). A similar trend, entailing lower enantioselectivities in the oxidation of sulfides exhibiting an apparent larger difference in size between the groups attached to the sulfur,[6a] has already been observed in the acid-promoted oxidation of a series of aryl methyl sulfides by a chiral oxaziridine.[10a] Once more, data in entries 1−6 indicate that the effective size of an aryl group in the transition state of this type of sulfoxidation reactions may be quite different from the apparent size.[23]

(18) See, for example, (a) the set: Dadoun, H.; Alazard, J.-P.; Lusinchi, X. *Tetrahedron* **1981**, *37*, 1525−1540. And: Jeanniot, J. P.; Lusinchi, X.; Milliet, P.; Parello, J. *Tetrahedron* **1971**, *27*, 401−410. (b) Ref 8f.

(19) NOESY experiment carried out in CDCl$_3$ at 400 MHz using a mixing time of 0.6 s.
(20) See, for example: (a) Tavarès, M.; Ramasseul, R.; Marchon, J.-C.; Bachet, B.; Brassy, C.; Mornon, J.-P. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1321−1329. (b) Anta, C.; Gonzalez, N.; Rodriguez, J.; Jimenez, C. *J. Nat. Prod.* **2002**, *65*, 1357−1359.
(21) A 3β-substituent is axial in a 5β-steroid with the normal steroidal A/B cis junction.
(22) Actually too fast to be monitored by ^{1}H NMR.

Table 1. Sulfoxidations with Oxaziridinium **5**

Entry	Sulfoxide	Cond[a]	Yield %[b]	ee %[c] (config.)
1		A	69	92 (R)[d, 3b]
		B	88	>99 (R)[d, 3b]
2		A	87	92 (R)[e, 24]
		B	85	98 (R)[e, 24]
3		A	80	92 (R)[e, 25]
		B	70	97 (R)[e, 25]
4		A	78	92 (R)[e, 25]
		B	70	95 (R)[e, 25]
5		B	71	60 (R)[e, 25]
6		B	62	64 (R)[d, 26]
7		B	73	84 (R)[d, 3b]
8		B	86	88 (R)[d, 3b]
9		B	63	90 (R)[d, 3b]
10		B	76	90 (R)[e, 27]
11		B	76	94 (R)[e, 27]
12		B	67	84 (R)[d, 28]
13		B	48	6 (R)[d, 3b]
14		B	83	85 (R)[d, 26]
15		B	57	98 (R)[d, 24]

[a] Conditions. A: CH_2Cl_2, rt. B: CH_2Cl_2, −70 °C to rt. [b] Not optimized; sulfoxides isolated by CC. [c] Determined by HPLC using a chiral OD CHIRALCEL column. [d] Absolute configuration assigned by comparing HPLC elution order with known literature data. [e] Absolute configuration established by comparison of the sign of $[\alpha]_D$ to literature data.

The results for entries 7−9, 12, and 15[29] suggested that electronic effects play minor roles in the asymmetric induction. The oxidations of entries 9−11 suggested that for primary and secondary alkyl residues the asymmetric induction is almost unaffected by the size of the group.

The ee values depicted in Table 1 strongly suggested that satisfactory results could also be expected from the action of **5** on more challenging sulfides. With this idea in mind, we applied the new reagent to the asymmetric synthesis of the biologically active chiral sulfoxide lansoprazole,[1a,2b] a member of the well-known family of sulfinyl-substituted benzimidazoles that behave as proton pump inhibitors and are efficient antiulcer agents.[30] Thus, the oxidation of sulfide **6**[31] by oxaziridinium **5** led to (R)-lansoprazole[32] **7** with excellent enantioselectivity (ee 97%) in good yield (Scheme 2). Moreover, the reaction was chemoselective.

Scheme 2
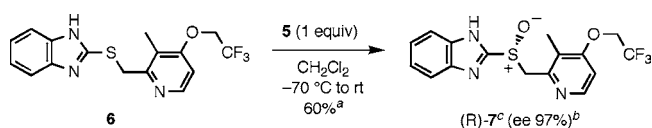
[a−c] See footnotes b, c, and d in Table 1.

In conclusion, we have completed the first synthesis of a new oxaziridinium salt (**5**) starting from cholesterol. Compound **5** turned out to be a very effective reagent for the highly enantioselective oxidation of sulfides to sulfoxides (ee up to >99%). As such, it does represent a new valuable nonmetallic alternative to the existing methods for asymmetric sulfoxidation. Studies on the reactivity of **5** toward other nucleophiles and the synthesis of new steroidal oxaziridiniums displaying different substitution patterns or bearing the oxaziridinium function upon other cycles of the steroidal framework are underway.

Supporting Information Available: Experimental procedures and spectral data for new compouds. General procedure for sulfide oxidation and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) The difference between effective and apparent size has been rationalized[10a] assuming a product-like TS where the preferred orientation of the aromatic ring may vary from almost coplanar to the incoming SO bond for unhindered phenyl rings to almost coplanar to the orbital containing the lone electron pair for the ortho-disubstituted phenyl rings.

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