bered ring and that nonbonded steric interactions in the transition state were responsible for the chiral recognition. Thus, oxidations of sulfides to sulfoxides using (−)-(*S*,*S*)-2-sulfonyloxaziridine, **4e**, afforded in every case the (−)-*S* sulfoxides.[9] Since the mechanism of chiral recognition for asymmetric oxidations using 2-sulfamyloxaziridines (eq 2) and 2-sulfonyloxaziridines is likely to be similar, the *S*,*S* and *R*,*R* configurations are tentatively assigned to the oxaziridine three-membered rings in (−)-**4a–d** and (+)-**5a–d**, respectively.[17] Note that like 2-sulfonyloxaziridines, the absolute configuration of the oxaziridine three-membered ring in **4** and **5** determines the product stereochemistry; i.e., (−)-**4a–d** and (+)-**5a–d** give the opposite sense of asymmetric induction, respectively (Table I).

The increased enantioselectivity exhibited by 2-sulfonyl- and 2-sulfamoyloxaziridines is likely a manifestation of the closer proximity of the oxaziridine substituents to the active site in comparison to peracids or hydroperoxides. In oxaziridines the active site oxygen is located in a rigid three-membered ring one bond removed from the carbon and nitrogen chiral centers. The group size difference (GSD) effect may be responsible for the higher asymmetric bias observed for oxidation of methyl 9-anthryl sulfide compared to isopropyl *p*-tolyl sulfide (53.0% vs. 38.0% ee at 25 °C).[9,16] As the GSD in the substrate increases, the asymmetric bias increases because attack of one of the enantiotopic sulfur electron pairs on the electrophilic oxaziridine oxygen is increasingly favored from the direction where there are the fewest nonbonding steric interactions.

Since the mechanism of chiral recognition is controlled by nonbonded steric interaction it is perhaps not surprising that the sulfamyl group in **4a–d** and **5a–d** has relatively little influence on the asymmetric bias because of its distance from the active site.[18] What is surprising is the effect of changing the aryl group from *p*-nitrophenyl to 2-chloro-5-nitrophenyl, nearly tripling the asymmetric bias (Table I, compare for example entries 1 and 2 with 3 and 4). While a definitive explanation of this effect is, at present, not possible, it may be related to greater system rigidity caused by the ortho substituent.[19] Rigidity in the oxaziridine would also be expected to increase on lowering the temperature. More conformational degrees of freedom available to isopropyl *p*-tolyl sulfide compared to methyl 9-anthryl sulfide may be reflected in the greater change in % ee on lowering the temperature of oxidation. System rigidity, caused by internal ligand chelation and/or rigid ring systems, is frequently associated with high stereoselectivities.[15,21] The relationship of the asymmetric bias to oxaziridine rigidity is currently under study.

In summary, chiral 2-sulfamyloxaziridines give the best results to date for the asymmetric oxidation of sulfides to sulfoxides. The great structural diversity conceivable for 2-sulfamyloxaziridines makes possible not only synthesis of more efficient asymmetric oxidizing reagents but also an increased understanding of the origins of asymmetric induction.

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An Efficient Synthesis of *N*-Bromoperhalo-1-alkanimines

Summary: Certain perhalogenated nitriles have been found to react readily with bromine and active cesium fluoride to afford high yields of *N*-bromoperhalo-1-alkanimines ($R_xFC{=}NBr$; R_x = CF_3, C_2F_5, n-C_3F_7, CF_2Cl, CCl_3). Photolysis of the perfluorinated *N*-bromo compounds affords the novel perfluoroazines $R_fFC{=}NN{=}CFR_f$.

Sir: A number of *N*-bromoperhalo-1-alkanimines ($R_xFC{=}NBr$) have long been known, but their chemistry has remained unexplored due to the inefficiency of the reported syntheses.[1] Here we report a simple, high-yield synthesis of five of these compounds by reaction of the corresponding perhalogenated nitriles with bromine and active cesium fluoride. These reactions probably proceed by initial formation of $R_xFC{=}N^-$, followed by oxidation of the intermediate anion by bromine to afford $R_xFC{=}NBr$. This postulate is supported by mechanistically similar chemistry reported for other unsaturated perfluorinated systems.[2]

The preparation of $CF_3FC{=}NBr$ (**1**) is described as a typical example. (*CAUTION*! Many *N*-halo compounds are known to be powerful explosives. We have experienced no explosions during the preparation and handling of the *N*-bromoperhalo-1-alkanimines, but the potential instability of these compounds and certain of their derivatives should be kept in mind. We advise that preparations and reactions of these materials be done on a small scale.) Trifluoroacetonitrile (15 mmol) and then bromine (30 mmol)[3] were condensed into a 100-mL Pyrex flask containing active cesium fluoride (35 mmol)[4] and fitted with

(17) Suitable crystals of **4** and **5** satisfactory for X-ray analysis have proven to be elusive to date.

(18) Note that replacement of the sulfamyl group by a camphorsulfonyl group has a major influence on the asymmetric bias particularly for oxidation of isopropyl *p*-tolyl sulfide (Table I: compare entries 3 and 4 with 8).

(19) An X-ray structure of (−)-(*S*,*S*)-2-[(*d*-α-bromo-π-camphoryl)-sulfonyl]-2-chloro-5-nitrophenyl)oxaziridine (**4e**, Z* = *d*-α-bromo-π-camphoryl)[9] reveals, that in the solid state, the oxaziridine aryl and C–N bonds are nearly coplanar and that there is some interaction between the nitrogen lone pair and an aromatic ortho proton.[9] In 2-sulfonyloxaziridines lacking an ortho substituent the aryl groups are slightly twisted out of coplanarity with the oxaziridine C–N bond.[20] The *o*-chloro substituent may inhibit rotation about the C-aryl oxaziridine bond resulting in greater system rigidity.

(20) Chen, J. S.; Watson, W. H.; Davis, F. A.; Lamendola, J. F., Jr.; Nadir, U. K. *Acta Crystallogr., Sect. B* **1978**, *B34*, 2861. Kimura, M.; Watson, W. H.; Davis, F. A.; Lamendola, J. F., Jr.; Nadir, U. K. *Ibid.* **1979**, *B35*, 234.

(21) (a) Heathcock, C. H. *ACS Symp. Ser.* **1982**, *185*, 55. (b) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23. (c) Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S.; Druelinger, M. *J. Am. Chem. Soc.* **1981**, *103*, 3081.

(1) (a) Tullock, C. W. Brit. Pat. 870328, 1968. See also: *Chem. Abstr.* **1962**, *56*, 8561*f*. (b) Chambers, W. J.; Coffman, D. D. U.S. Pat. 3023208, 1962. See also: *Chem. Abstr.* **1962**, *57*, 11215. (c) Tullock, C. W. U.S. Pat. 3057849, 1962. See also: *Chem. Abstr.* **1963**, *58*, 3315*b*. (d) Chambers, W. J.; Tullock, C. W.; Coffman, D. D. *J. Am. Chem. Soc.* **1962**, *84*, 2337.

(2) Chambers, R. D. "Fluorine in Organic Chemistry"; Wiley: New York, 1973.

(3) The excess bromine is eventually absorbed by the solid phase. Presumably, $CsBr_3$ and higher cesium polybromides are formed.

(4) The cesium fluoride was activated by fusion in a platinum dish, followed by grinding to a fine powder in a ball mill under dry nitrogen.

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Table I. Spectral Data for *N*-Bromoperhalo-1-alkanimines

compound	^{19}F NMR;[a] solvent	IR ($\nu_{C=N}$, cm^{-1})
1, $CF_3{}^AF^MC{=}NBr$	F^A −71.8; F^M −27.5; J_{AM} 5.5 Hz; $CFCl_3$	1705[b]
2, $CF_3{}^BCF_2{}^AF^MC{=}NBr$	F^A −118.7; F^B −83.55; F^M −21.76; J_{AB} 2, J_{AM} 16, J_{BM} 5 Hz; $CDCl_3$	1695
3, $CF_3{}^CCF_2{}^BCF_2{}^AF^MC{=}NBr$	F^A −116.2; F^B − 127.3; F^C −81.23; F^M −19.95; J_{AM} 13, J_{BM} 6.5, J_{AC} 8, others $\leq$ 2 Hz; CCl_4/$CDCl_3$ (9:1)	1690
4, $CClF_2{}^AF^MC{=}NBr$	^AF −60.02; ^MF −26.70; J_{AM} 11 Hz; $CDCl_3$	1695
5, $CCl_3F^MC{=}NBr$	F^M −24.32; acetone-d_6	1670

[a] 90-MHz NMR in ppm; $CFCl_3$ internal reference. [b] Chang, S.-C.; DesMarteau, D. D. *Inorg. Chem.* **1983**, *22*, 805.

Table II. Spectral Data for Perfluoroazines

compound	^{19}F NMR;[a] solvent	IR ($\nu_{C=N}$, cm^{-1})
6, $(CF_3{}^AF^MC{=}N\text{-})_2$	F^A −72.70; F^M −62.22; J_{AM} 11 Hz; CCl_4 $CCl_4/CDCl_3$ (9:1)	1720
7, $(CF_3{}^BCF_2{}^AF^MC{=}N\text{-})_2$	F^A −120.2; F^b − 83.14; F^M −55.94; J_{AB} 2, J_{AM} 14.5, J_{BM} 4.5 Hz; $CDCl_3$	1710
8, $(CF_3{}^CCF_2{}^BCF_2{}^AF^MC{=}N\text{-})_2$	F^A −118.4; F^B −127.3; F^C − 81.01; F^M − 55.46; J_{AC} 9, J_{AM} 13, J_{BM} 10, others $\leq$ 2 Hz; $CDCl_3$	1710

[a] 90-MHz NMR in ppm; $CFCl_3$ internal reference.

a glass-Teflon stopcock. As the bromine melted, the flask was rotated so as to distribute the Br_2/CsF in a thin layer. The reaction became mildly exothermic, and most of the free bromine appeared to have been consumed within 5 min. The mixture was left in darkness for 16 h at 23 °C. Trap-to-trap fractionation (−93, −196 °C) gave $CF_3FC{=}NBr$, slightly contaminated with bromine, in the −93 °C trap. Unreacted CF_3CN collected in the −196 °C trap. The bromine was removed by brief exposure of the mixture to an excess (~8 mmol) of ethylene, followed by trap-to-trap fractionation: −54 °C ($C_2H_4Br_2$), −90 °C ($CF_3FC{=}NBr$; 11.8 mmol, 79% yield), −196 °C (C_2H_4). The compounds $C_2F_5FC{=}NBr$ (**2**), n-$C_3F_7FC{=}NBr$ (**3**), $CClF_2FC{=}NBr$ (**4**), and $CCl_3FC{=}NBr$ (**5**) were obtained in a similar fashion (eq 1).

$$R_xC{\equiv}N + CsF + 2Br_2 \longrightarrow \begin{matrix} R_x \\ \diagdown \\ C{=}N \\ \diagup \\ F \end{matrix}\!\!\begin{matrix} \\ \\ \\ \\ Br \end{matrix} + CsBr_3 \quad (1)$$

R_X = CF_3, C_2F_5, n-C_3F_7, $CClF_2$, CCl_3

We attempted to prepare $CH_3FC{=}NBr$ and $C_6F_5FC{=}NBr$ from CH_3CN and C_6F_5CN, respectively, without success. These results indicate that a highly halogenated aliphatic group, R_x, is necessary for preparation of $R_xFC{=}NBr$ under our conditions.

The *N*-bromoperhalo-1-alkanimines were readily characterized by their ^{19}F NMR and IR spectra (Table I). The fluoroalkyl NMR absorptions all appear as simple first-order patterns. The "vinylic" fluorines (F^M) characteristically give rise to broad peaks near δ −20 ($R_xF^MC{=}NBr$). The NMR spectra indicate that imines **1–5** exist in only one of two possible isomeric forms. We assume, on steric grounds, that the observed isomer is, in each case, the one with the bromine atom anti to the perhaloalkyl group. Compounds **1–5** are thermally stable ($CF_3FC{=}NBr$ survives prolonged heating at 200 °C). Pyrolysis at higher temperatures (450–500 °C, Pyrex flow system) affords a mixture of perhaloalkyl bromide and cyanogen fluoride (eq 2).

$$\begin{matrix} R_x \\ \diagdown \\ C{=}N \\ \diagup \\ F \end{matrix}\!\!\begin{matrix} \\ \\ \\ \\ Br \end{matrix} \xrightarrow[\text{Pyrex}]{450\text{–}500\ ^\circ C} R_xBr + FCN \quad (2)$$

R_X = CCl_3, CF_3, C_2F_5, n-C_3F_7

The *N*-bromo imines are moderately light-sensitive. The light-sensitivity of compounds **1–3** was exploited in the preparation of the perfluorinated azines **6–8**.[5] Ultraviolet photolysis (250-W medium-pressure mercury lamp) of the bromo imines affords a mixture consisting primarily of azine, bromine, and starting materials (eq 3). This be-

$$2\ \begin{matrix} R_f \\ \diagdown \\ C{=}N \\ \diagup \\ F \end{matrix}\!\!\begin{matrix} \\ \\ \\ \\ Br \end{matrix} \xrightarrow[\text{Pyrex}]{h\nu} \begin{matrix} F \\ \diagdown \\ NN \\ \diagup \\ R_f \end{matrix}\!\!\begin{matrix} R_f \\ \diagup \\ C{=}N \\ \diagdown \\ F \end{matrix} + Br_2 \quad (3)$$

R_f = CF_3, C_2F_5, n-C_3F_7

havior parallels that seen for $(CF_3)_2C{=}NBr$, which, upon photolysis, affords $(CF_3)_2C{=}NN{=}C(CF_3)_2$ and Br_2.[6] In the cases described here, however, the photolytic conversion is not as efficient as that reported for the preparation of $(CF_3)_2C{=}NN{=}C(CF_3)_2$. In this work, as the concentrations of azine and bromine build up, significant competing reactions begin to occur.[7] These competitive processes can be partly overcome by periodic removal of the bromine, using either ethylene or propylene, but complete conversion of bromo imine to azine is never achieved. Removal of unreacted bromo imine is done by reaction with mercury (to yield the corresponding nitrile); the nitrile and azine are then separable by vacuum-line fractionation or by preparative GLC. The purified products were readily characterized by their ^{19}F NMR and IR spectra (Table II).

Further studies of the reactions of the *N*-bromoperhalo-1-alkanimines (such as those with olefins, to yield $R_xFC{=}NCYY'CZZ'Br$, and with CO, to yield 1-bromoperhaloalkyl isocyanates), and of the products derived from them, are in progress.

(5) Some of these azines have been prepared by reaction of appropriate perfluorinated diazenes with metal carbonyls: (a) Chambers, W. J. U.S. Pat. 3 117 996, 1964. See also: ref 1d and *Chem. Abstr.* **1964**, *60*, 6745e. (b) Compound **6** has recently been prepared from $CF_3ClC{=}NN{=}CClCF_3$ and KF: Barlow, M. J.; Bell, D.; O'Reilly, N. J.; Tipping, A. E. *J. Fluorine Chem.* **1983**, *23*, 293.

(6) Middleton, W. J.; Krespan, C. G. *J. Org. Chem.* **1965**, *30*, 1398.

(7) The competing reactions yield colorless, crystalline solids of slight volatility. The structures of these products are unclear at present, but we have determined that, in the case where R_f = CF_3, the material contains both bromine (produced by slow decomposition of the material at 23 °C in room light) and the $CF_3FC{=}N$ group (observed in the mass spectrum of the vapor).

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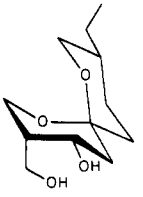
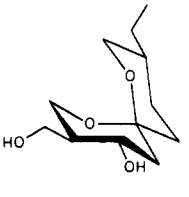
An Enantioselective Total Synthesis of (–)-Talaromycins A and B

Summary: The first enantioselective total synthesis of (–)-talaromycin A and B from a common advanced intermediate is described.

Sir: The talaromycins (A and B), two novel toxins, were isolated by Lynn and co-workers[2] in 1982 from *Talaromyces stripitatas*, a fungus known to grow on animal feed produced from chicken litter, and which renders the feed toxic to mammals. Structural assignments (**1** and **2**, respectively) were based in large part on two-dimensional



Talaromycin A
(1)

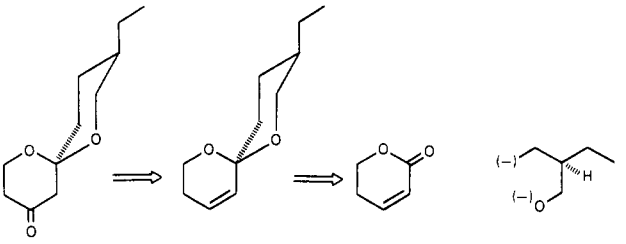


Talaromycin B
(2)

proton NMR correlation spectra (2D COSY) of a 1:1 mixture.[2] Tentative assignment of absolute configuration rests on application of the ORD-benzoate sector rule to the dibenzoate of talaromycin A (**1**).[2,3] Of particular interest from a synthetic point of view was the quantitative conversion of talaromycin A to B upon treatment with acid.[2,4]

Our interest in the talaromycins as synthetic targets stemmed directly from the spiroketal moiety central to the milbemycin–avermectin family of macrolide antibiotics.[5] In this communication we record the first enantioselective total synthesis of both (–)-talaromycin A and B. We note in advance that this work confirms the structure of talaromycin A as well as the absolute configurations of both isomers. Furthermore, the synthesis is economic (i.e., short, 10 steps), affording both talaromycins A and B from a common advanced intermediate.

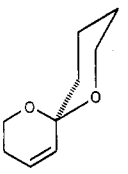
Scheme I



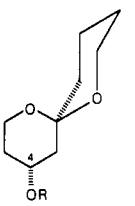
3 4 5 6

At the outset, we set as overall goal the development of a synthetic strategy that would not only lead to the talaromycins but would also provide access to a number of simple structural derivatives for biological testing. Our synthetic analysis is illustrated in Scheme I. Removal of the hydroxymethyl substituent leads to the first synthetic subtarget (**3**). We anticipated that regioselective hydroxymethylation would yield a mixture of epimers, which, after carbonyl reduction, would lead to both talaromycin A and B. In this regard, Lynn[2] reported that while the talaromycins are not readily separable, esterification with phenylboronic acid yields a seperable mixture. Basic hydrolysis then gives the talaromycins in pure form.

Continuing with this analysis, ketone **3** was anticipated to derive from regioselective hydration of olefin **4**, the latter envisioned to arise via addition of dianion **6** or its equivalent to lactone **5**. To examine the feasibility of this strategy, in particular, construction of olefin **4** and its conversion to ketone **5**, we explored the synthesis of the norethyl derivative **7**.[6] Toward this end, addition of the



7



8: R = $CH_2CH{=}CH_2$
9: R = H

Normant[7] Grignard derived from 4-chloro-1-butanol to lactone **5**[8] gave, after acidic workup, spiroketal **7** albeit in poor yield (ca. 15%). After considerable experimentation a modest improvement was obtained when the Grignard derived from the ethoxyethyl ether of 4-bromo-1-butanol was employed. The yield in this case, while still modest (ca. 35%), allowed rapid construction of the spiropyrano skeleton.

Turning next to hydration of the C(3,4) olefinic bond, reaction of **7** with allyl alcohol (TsOH) afforded **8**[9,10] in near

(1) Camille and Henry Dreyfus Teacher–Scholar, 1978–1983; National Institutes of Health (National Cancer Institute) Career Development Award, 1980–1985.

(2) Lynn, D. G.; Phillips, N. J.; Hutton, W. C.; Shabanowitz, J.; Fennel, D. I.; Cole, R. J. *J. Am. Chem. Soc.* **1982**, *104*, 7319.

(3) Nakanishi, K.; Harada, N. "Circular Dichroic Spectroscopy-Exiton Coupling in Organic Stereochemistry"; University Science Books: Mill Valley, CA, 1983; Chapter 3.

(4) This observation led to an elegant synthesis of talaromycin B by Schreiber; see: Schreiber, S. L.; Sommer, T. J. *Tetrahedron Lett.* **1983**, *24*, 4781. After completion of our work two additional syntheses of talaromycin B appeared. See: Kocienski, P.; Yeates, C. *J. Chem. Soc., Chem. Commun.* **1984**, 151. Kozikowski, A. P.; Scripko, J. G. *J. Am. Chem. Soc.* **1984**, *106*, 343.

(5) (a) Milbemycin: Mishima, H.; Kurabayashi, M.; Tamura, C. *Tetrahedrn Lett.* **1975**, 711. Also see: Takiguchi, Y.; Mishima, H.; Okuda, M.; Terao, M.; Aoki, A.; Fukuda, R. *J. Antibiotics* **1980**, *33*, 1120. (b) Avermectin: Albers-Schonberg, G.; Arison, B. H.; Chabala, J. C.; Douglas, A. W.; Eskola, P.; Fisher, M. H.; Lusi, A.; Mrozik, H.; Smith, J. L.; Tolman, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 4216. Springer, J. P.; Arison, B. H.; Hirshfield, J. M.; Hoogsteen, K. *Ibid.* **1981**, *103*, 4221. (c) Milbemycin synthesis: Smith, A. B., III; Schow, S. R.; Bloom, J. D.; Thompson, A. S.; Winzenberg, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 4015. Williams, D. R.; Barner, B. A.; Nishitani, K.; Phillips, J. G. *Ibid.* **1982**, *104*, 4708.

(6) Construction of the norethyl and other closely related derivatives of the talaromycins for biological testing is underway in our laboratory.

(7) Cahiez, G.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1978**, 3013.

(8) This lactone is readily available from vinyl acetic acid and paraformaldehyde; see: Nakagawa, M.; Saegusa, J.; Tonozuka, M.; Obi, M.; Kiuchi, M.; Hino, T.; Ban, Y. *Org. Synth.* **1976**, *56*, 49.

(9) The regioselective introduction of oxygen was anticipated on the basis of work in the avermectin area, see: Mrozik, H.; Eskola, P.; Arison, B. H.; Albers-Schonberg, G.; Fisher, M. H. *J. Org. Chem.* **1982**, *47*, 489. Also see, ref 11.

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