Organic Oxoammonium Salts. 3.[1] A New Convenient Method for the Oxidation of Alcohols to Aldehydes and Ketones

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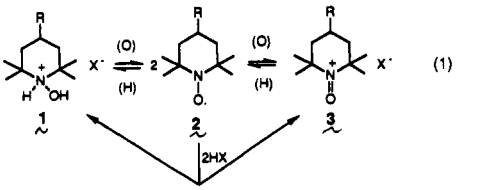
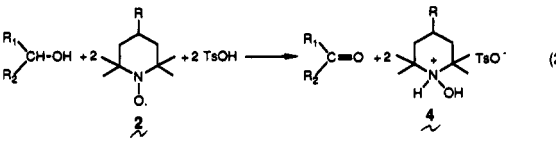
A new method for the selective oxidation of alcohols using organic oxoammonium salts generated by acid-promoted disproportionation of nitroxides in solution has been developed. Major advantages are high yields, ease of product isolation, and a high degree of selectivity in the presence of other functional groups.

Oxoammonium salts such as **3** have been used extensively for the oxidation of alcohols to aldehydes and ketones. The older literature has been summarized.[2] These reactions have been carried out in two modes. One is the use of synthetically prepared oxoammonium salts, and the other is the use of nitroxide catalysts (such as **2**) in the presence of a primary oxidant, which will oxidize the nitroxides to oxoammonium salts. Recent papers have appeared on the oxidation of difunctional alcohols,[3] ω-(benzoyloxy)alkanols,[4] *N,N*-dialkylanilines,[5] and poly(vinyl alcohol).[6] Nitroxide-catalyzed oxidations of alcohols with hypochlorite,[7,8] bromite,[9] or electrolytically generated Br^+[10] have been described. We have carried out the preparative oxidation of alcohols and thiols on graphite anodes coated with a nitroxide catalyst,[11] as have others.[12,13] The field has been reviewed recently.[14]

In this paper, we would like to describe a third mode based upon the known acid-promoted disproportionation of nitroxides **2** to oxoammonium salts **3** and hydroxyamine salts **1** (eq 1).[15-17] Thus, treatment of the alcohol to be



(1)



(2)

R = AcNH or H; R_1, R_2 = alkyl group or H;
X = *p*-toluenesulfonate (TsO) or
(*1S*)-(+)-10-Camphorsulfonate (CsO).

oxidized in an organic solvent with a slight excess of a mixture of 2 equiv of nitroxide and 2 equiv of *p*-toluenesulfonic acid gives essentially quantitative yields of aldehydes from primary alcohols and ketones from secondary alcohols. The oxoammonium salt formed during the disproportionation is reduced, in the oxidation, to the same hydroxyamine salt formed during the disproportionation. The overall reaction is shown in eq 2. The sulfonic acid promotes the disproportionation and pulls the reaction to completion by salt formation with the hydroxyamine product. The salt precipitates in high yield when the solvent is CH_2Cl_2. Product isolation involves the removal of the salt by filtration, washing of the CH_2Cl_2 with a small amount of water, drying, concentration, and distillation or crystallization of the essentially pure aldehyde or ketone.

It is quite possible that some of the earlier catalyzed work involving peracids goes by a similar mechanism since Cella[18] noted that his reaction required a strong acid such as HCl. The strong acid catalyzed the disproportionation, and the peracid reoxidizes the hydroxyamine to nitroxide. Such a mechanism was proposed by Aurich.[19] In support of this suggestion, there does not appear to be any report of the oxidation of nitroxide to oxoammonium salt with peracids, although the oxidation of hydroxyamines to nitroxides is well known.[19]

The advantages of this method are the high yields obtained and the convenience of the product isolation. It also avoids the presence of less selective oxidizing agents such as peracids and the halogen derivatives used in the various catalytic methods mentioned above[7-13] and elsewhere.[2]

(1) Paper 2: Bobbitt, J. M.; Guttermuth, M. C. F.; Ma, Z.; Tang, H. *Heterocycles* **1990**, *30*, 1131. Our previous papers have been published under the generic name "Nitrosonium Salts". At least five other names have been used; oxoammonium salts, oxoamminium salts, immonium salts, oxoiminium salts, and oxoazonium salts. "Oxoammonium Salts" seems to be used by most authors. We will use the modified term "organic oxoammonium salts".

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Furthermore, no metal ions are involved, as in oxidations with the various chromium or manganese reagents.[20] In contrast to the Moffatt and Swern oxidation and similar reactions,[21] anhydrous solvents are not required; the product isolation is simple; no dimethyl sulfide is given off. The main disadvantage is that 2 equiv of a, so far, noncommercially available nitroxide, **2**, R = NHAc, is required. However, the nitroxide can be prepared in 97% yield and recovered in yields of over 98%.

It would appear logical to explore the reactions of the oxoammonium salt, **3**, R = NHAc, itself rather than to prepare it as needed, and the reactions of many such compounds are known.[2] However, the salt did not precipitate under the various acid conditions normally used.[1] Since the nitroxides are much more stable than the oxoammonium salts, there seemed little reason to prepare **3**, R = NHAc.

We have used two nitroxides, the commercially available 2,2,6,6-tetramethylpiperidinyl-1-oxyl (**2**, R = H (TEMPO)) and 4-acetylamino-TEMPO (**2**, R = AcNH). (Acetylamino)-TEMPO[22] can be easily made in an overall yield of 97% by a modified two-step procedure, from the readily available and inexpensive 4-amino-2,2,6,6-tetramethylpiperidine. We prefer the acetylamino nitroxide for the following reason. The sulfonate salt of the hydroxyamine derived from TEMPO, **4**, R = H, is more soluble in CH_2Cl_2 than the salt of 4-(acetylamino)-TEMPO, **4**, R = AcNH. Thus, it is difficult to remove the TEMPO salt entirely, even with extensive water washing. The result is that there are nitroxide derived materials in the organic phase, which complicate the isolation procedure. If any TEMPO itself is present, it is volatile and distills with the products. In general, it was necessary to use short-column flash chromatography for product isolation when TEMPO was used (see entries 3, 7, 9, and 11 in Table I).

Two sulfonic acids were used to generate the oxoammonium salt, *p*-toluenesulfonic acid, and (1*S*)-(+)-camphor-10-sulfonic acid. The camphorsulfonic acid was used for several oxidations (entries 12, 14, and 22 in Table I) to see whether any enantioselectivity could be obtained, as has been noted in enzyme work (specifically for entry 22).[23] None was observed.

We have used two procedures for the oxidation. In the first procedure (method A), the alcohol to be oxidized is dissolved in CH_2Cl_2, and the *p*-toluenesulfonic acid is added as a solid (the solubility was determined to be less than 36 mg/100 mL). The nitroxide, dissolved in CH_2Cl_2, is added slowly to the ice-cooled alcohol–acid. The sulfonic acid slowly goes into solution, generating the oxoammonium ion. As the oxoammonium ion is used up, the color is dispatched. At the end of the reaction, the solution is almost colorless, and the hydroxyamine salt precipitates, sometimes after a short time. In the second procedure (method B), the sulfonic acid and nitroxide are mixed together to form the oxoammonium ion in solution, and this is slowly added to the cooled alcohol solution. Again, the color is dispatched, and the salt precipitates. In method A, the concentration of the oxidizing agent is kept low to enhance selectivity, but there is some acid present that might catalyze undesired reactions. In method B, the concentration of oxidant is high, but the acid is minimal. A real difference was noted only in the oxidation of nerol and geraniol to their respective aldehydes. Method B gave less isomerization around the 2,3 double bond than method A, although some was still observed.[24] Otherwise, there seem to be few differences between the methods.

The recovery of the nitroxide **2**, R = NHAc, from the hydroxyamine salt is quite simple. The salt is dissolved in water, basified with K_2CO_3, and treated with either H_2O_2 or sodium perborate ($NaBO_3$). After 24 h, the nitroxide crystallizes. The overall recovery is about 98%. The salt **4**, R = NHAc, is quite stable and can be stored for recovery at a later date.

The reaction has been investigated with a large array of alcohols as shown in Table I. Double bonds do not seem to interfere with the reaction, although there is some problem with entry 4 and cholesterol (not shown) in which there is a β–γ double bond. This is not understood and is under further study. Several diols were investigated in accord with previous studies,[8-10,25] pure products were not obtained. As pointed out by Endo,[4] alcohols having a β oxygen are not oxidized by oxoammonium salts, and those with a γ oxygen are slow. We have found that ethylene glycol is completely unreactive under our conditions, although 2,3-butanediol was found by Endo to give a poor yield of 3-hydroxy-2-butanone.[25] 5,6-Dodecanediol was oxidized in good yield by Torii using a similar method.[10] Under our conditions, 2-phenoxyethanol reacts slowly and incompletely. Acid groups do not interface with the reaction, although base groups should, due to the reversal of eq 2.

The mechanisms of the reactions are not clear. Golubev suggested a mechanism for the acid-promoted disproportionation.[16b] A concerted cyclic mechanism for oxoammonium salt oxidations was suggested by Semmelhack[26] and is shown in Scheme I (**5** to **6** to **7**). An alternate mechanism with an acyclic transition state is shown as **5** to **8** to **7**. We favor the acyclic form for two reasons. First, it is probably less sterically confining than the cyclic form and there seem to be few steric effects in oxoammonium oxidations.[2] Second, the acyclic intermediate shows how a β oxygen may hinder the reaction by complexing with the positively charged nitrogen as shown in **9**. This is less likely to occur in **6** because of the negative oxygen. The complex formation as shown in **9** may hinder or slow the reaction in two ways. It may reduce the positive charge on nitrogen and therefore reduce the driving force of the reaction. Or, alternatively, complex formation may force the hydrogen being lost out of the planar conformation required for reaction.

Experimental Section

General Procedures. Gas chromatography–mass spectra were

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(22) Rozantsev, E. G.; Kokhanov, Y. V. *Bull Acad. Sci. U.S.S.R., Chem. Ser.* **1966**, *15*, 1422.
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(24) Such isomerization is normal in the oxidations of these compounds. In only one case has an oxidation been reported with no isomerization (Guziec, F. S., Jr.; Luzzio, F. A. *J. Org. Chem.* **1982**, *47*, 1787).
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Table I. Oxidation of Alcohols by Oxoammonium Salts 3 (R = H or AcNH, X = TsO or CsO)

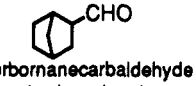
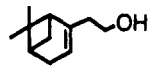
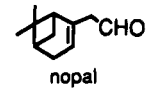
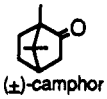
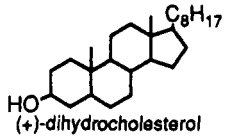
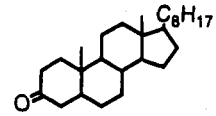
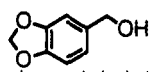
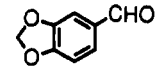
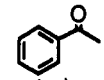
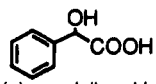
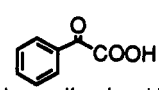
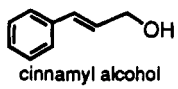
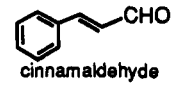
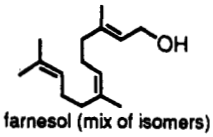
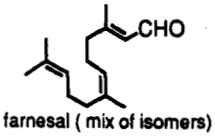
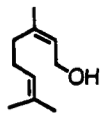
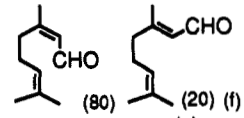
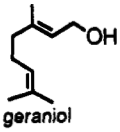
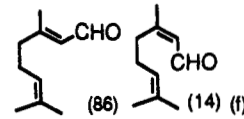
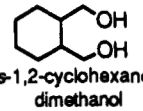
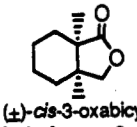
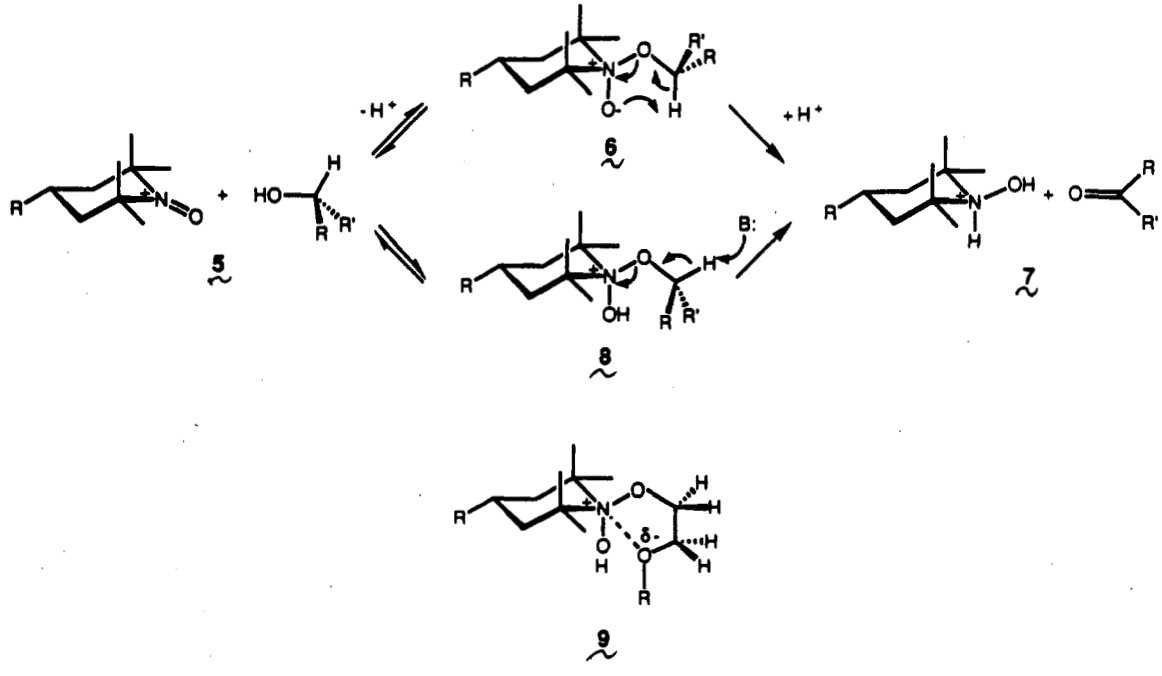
reaction number	substrate	oxidant	method (time)	product	yield, % [a] (purification method) [b]	bp, °C / mmHg or mp, °C (lit.)	ref.
1	$CH_3(CH_2)_{14}CH_2OH$ 1-hexadecanol	R = AcNH X = TsO	A (2.5 h)	$CH_3(CH_2)_{14}CHO$ hexadecanal	100 (FCC)	33-35 (34)	27
2	 (±)-2-norbornane-methanol	R = AcNH X = TsO	A (2 h)	 2-norbornanecarbaldehyde (endo and exo)	94 (Dis.)	36-38 /1.0 (69-70 / 13)	28
3	"	R = H X = TsO	A (2 h)	"	92 (FCC and Dis.)	36-38 / 1.0 (69-70 / 13)	28
4	 (1R)-(-)-nopol	R = AcNH X = TsO	A (2.5 h)	 nopal	76 (Dis.)	68-71 / 1.0 (94 / 10)	29
5	 (±)-isoborneol	R = AcNH X = TsO	A (1.5 h)	 (±)-camphor	97 (Rec., aq. EtOH)	177-178 (177-178)	30
6	 (+)-dihydrocholesterol	R = AcNH X = TsO	A (1 h)	 (5α)-cholestan-3-one	98 (Rec., EtOH)	130-131 (128-130)	31
7	"	R = H X = TsO	A (1 h)	"	100 (FCC)	128-130 (128-130)	31
8	 piperonyl alcohol	R = AcNH X = TsO	A (1 h)	 piperonal	99 (no purification)	34-36 (35-37)	32
9	"	R = H X = TsO	A (1 h)	"	90 (FCC)	34-37 (35-37)	32
10	 sec-phenethyl alcohol	R = AcNH X = TsO	A (2 h)	 acetophenone	100 (Dis.)	60-61 / 2.0 (88 / 16)	33
11	"	R = H X = TsO	A (1.5 h)	"	93 (FCC and Dis.)	82-84 / 13 (88 / 16)	33
12	"	R = AcNH (c) X = CsO	A (1.5 h)	"	83 (d) (FCC and Dis.)	60-62 / 2.0 (88 / 16)	33
13	 (±)-mandelic acid	R = AcNH X = TsO	A (6 h)	 benzoylformic acid	91 (Rec., CCl_4)	64-66 (65)	34
14	"	R = AcNH (c) X = CsO	A (6 h)	"	82 (d) (derivative) (e)	193-195 (196-197)	34
15	 cinnamyl alcohol	R = AcNH X = TsO	A (1 h)	 cinnamaldehyde	96 (Dis.)	88-92 / 1.2 (135-136 / 25)	35

Table I (Continued)

reaction number	substrate	oxidant	method (time)	product	yield, % [a] (purification method) [b]	bp, °C / mmHg or mp, °C (lit.)	ref.
16	 farnesol (mix of isomers)	R = AcNH X = TsO	A (1 h)	 farnesal (mix of isomers)	86 (Dis.)	126-134 / 1.0 (135-155 / 2)	36
17	 nerol	R = AcNH X = TsO	A (2 h)	 neral (80) geranial (20) (f)	91 (Dis.)	73-74 / 1.2 (84-85 / 2)	37
18	•	R = AcNH X = TsO	B (1:5 h)	• (92) • (8) (f)	91 (Dis.)	73-75 / 1.2 (84-85 / 2)	37
19	 geraniol	R = AcNH X = TsO	A (2 h)	 geranial (86) neral (14) (f)	90 (Dis.)	70-72 /1.2 (84-85 / 2)	38
20	•	R = AcNH X = TsO	B (1.5 h)	• (94) • (6) (f)	95 (Dis.)	74-75 /1.4 (84-85 / 2)	38
21	 *cis*-1,2-cyclohexane-dimethanol	R = AcNH (g) X = TsO	A (2 h)	 (±)-*cis*-3-oxabicyclo-[4.3.0]nonan-2-one	89 (Dis.)	88-90 / 1.2 (72-77 / 0.5)	23
22	•	R = AcNH (g) X = CsO	A (2 h)	•	90 (Dis.)	90-93 /1.5 (72-77 / 0.5)	23

[a] Isolated yield of purified product. [b] FCC: flash column chromatography on silica gel. Dis.: distillation. Rec.: recrystallization. [c] Half amount of oxidants used to check for enantioselectivity. [d] Yield based on 4-(acetylamino)-TEMPO. [e] (2,4-Dinitrophenyl)hydrazone derivative. [f] The ratios were estimated by gas chromatography and ^{1}H NMR spectroscopy. [g] Two equivalents of oxidant used to produce lactone.

Scheme I



obtained on a Hewlett Packard 5970G system equipped with a 12 M HP-1 capillary column. Elemental analyses were performed by Galbraith Laboratories, Inc., Memphis, TN.

The 4-amino-2,2,6,6-tetramethylpiperidine was obtained from Fluka Chemical Co., Ronkonkoma, NY, and the various alcohols were all commercial samples used without purification.

4-(Acetylamino)-TEMPO (2, R = NHAc). Acetic anhydride (70.0 g, 0.686 mol) was added, dropwise, to a solution of 34.6 g (0.221 mol) of 4-amino-2,2,6,6-tetramethylpiperidine dissolved in 100 mL of anhydrous ether that had been cooled to 0 °C. After addition was complete (about 1 h), the solution was stirred for 30 min at room temperature. The precipitate was removed by filtration and washed with 20 mL of ether to give 55.6 g (98%) of 4-(acetylamino)-2,2,6,6-tetramethylpiperidinium acetate, mp 175 °C subl.

The acetate was dissolved in 400 mL of water and basified with 50.0 g of $K_2CO_3 \cdot 1.5\ H_2O$ (0.303 mol). To this solution was added 80 mL of 30% H_2O_2, 4.00 g of sodium tungstate, and 4.00 g of ethylenediaminetetracetic acid, tetrasodium salt. The mixture was stirred at room temperature for 72 h. The red precipitate was removed by filtration and washed with 20 mL of H_2O to give 38.6 g of product, which melted at 146–147 °C, lit.[22] mp 147.5 °C. The filtrate was saturated with solid K_2CO_3 and extracted with two 100-mL portions of CH_2Cl_2. The organic phase was washed with saturated aqueous sodium chloride, dried over Na_2SO_4, and evaporated to give 7.1 g more of product, mp 145–147 °C. The combined yield was 45.7 g (overall yield for the two steps, 97%).

General Procedure for Alcohol Oxidation. Method A. *p*-Toluenesulfonic acid monohydrate (4.00 g, 21 mmol) was suspended in 30 mL of CH_2Cl_2 containing 10 mmol of the alcohol to be oxidized and cooled to 0 °C. A solution of 4.47 g (21 mmol) of nitroxide **2**, R = NHAc, in 30 mL of CH_2Cl_2 was added dropwise over 30 min. This addition could be much slower if there were a problem with selectivity. The solution was stirred at 0 °C for 1 h and then at room temperature until it was almost completely decolorized. During the last of the reaction or sometimes after color was gone, a heavy white precipitate formed. The mixture was cooled in ice, and the precipitate was removed by filtration and washed with 10 mL of cold CH_2Cl_2 to give the salt **4** in essentially quantitative yield. The filtrate was washed with 50 mL of H_2O and 50 mL of saturated aqueous NaCl and dried over Na_2SO_4. After removal of the solvent, the product was purified by distillation or crystallization. The products were identified by MS, IR, and NMR spectroscopy, and in some cases by derivative formation (Table I).

General Procedure for Alcohol Oxidation. Method B. A solution of oxoammonium salt **3**, R = NHAc, was prepared by stirring a suspension of 4.00 g (21.0 mmol) of *p*-toluenesulfonic acid monohydrate with 4.47 g (21.0 mmol) of nitroxide **2**, R = NHAc, in 30 mL of CH_2Cl_2 for 20 min at 0 °C. An intense red color developed from the oxoammonium salt. This solution was added dropwise to 10 mmol of the alcohol to be oxidized in 30 mL of cold CH_2Cl_2 over 30 min. The orange solution was then stirred at room temperature until the color was essentially gone and a dense white precipitate formed. The reaction mixture was then processed as described in method A.

4-(Acetylamino)-2,2,6,6-tetramethyl-1-hydroxypiperidinium *p*-Toluenesulfonate (4). The salt, as recovered from the oxidation reactions, melted at 169–171 °C when the temperature was slowly raised. When the temperature was raised quickly, a second melting point at about 145 °C was observed, almost surely corresponding to a loss of water. The compound was recrystallized from water with no change in mp. Anal. Calcd for $C_{18}H_{30}N_2O_4S \cdot H_2O$: C, 53.44; H, 7.97; N, 6.97. Found: C, 53.72; H, 8.05; N, 6.89.

Recovery of Nitroxide 2, R = NHAc, from Salt 4, R = NHAc. A solution of 22.8 g (60 mmol) of **4** in 300 mL of H_2O was made basic with 19.8 g of $K_2CO_3 \cdot 1.5\ H_2O$ (120 mmol). Hydrogen peroxide, 20 mL of 30% (170 mmol), *or* 27.3 g of sodium perborate tetrahydrate (170 mmol) was added, and the solution was stirred at room temperature for 24 h to give an intense red solution. The solution was saturated with solid K_2CO_3, and a red precipitate formed. The precipitate was removed by filtration to give 11.99 g (98%) of **2**, R = NHAc, mp 146–147 °C. The purity was sufficient for use in further oxidations.

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Direct Conversion of (1*S*,2*S*)-2-Amino-1-[(4-methylthio)phenyl]-1,3-propanediol into Its Enantiomer for Efficient Synthesis of Thiamphenicol and Florfenicol

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The usual synthesis of thiamphenicol and florfenicol involves the resolution of racemic *threo*-2-amino-1-[(4-methylthio)phenyl]-1,3-propanediol into its 1*S*,2*S* and 1*R*,2*R* isomers ((+)-**3** and (−)-**3**), of which only the latter is a useful precursor. An efficient conversion of the 1*S*,2*S* isomer into the 1*R*,2*R* enantiomer in high yield, is described.

Thiamphenicol, *threo*-(1*R*,2*R*)-2-(dichloroacetamido)-1-[(4-methylsulfonyl)phenyl]-1,3-propanediol (**1**),[1] and florfenicol (**2**),[2] the 3-fluoro derivative of **1**, are broad-spectrum antibiotics (Figure 1).

Current manufacturing processes for **1** and **2** involve an optical resolution at some stage of the synthesis. In most cases, entrainment resolution[3] is performed on racemic *threo*-2-amino-1-[(4-methylthio)phenyl]-1,3-propanediol[4] to afford the 1*R*,2*R* isomer (−)-**3** (the precursor of **1** and

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