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Diastereoselective Oxidation of Sulfides to Sulfoxides. Synthesis of Novel C-6 Sulfoxy Tetrahydromevinic Acids.

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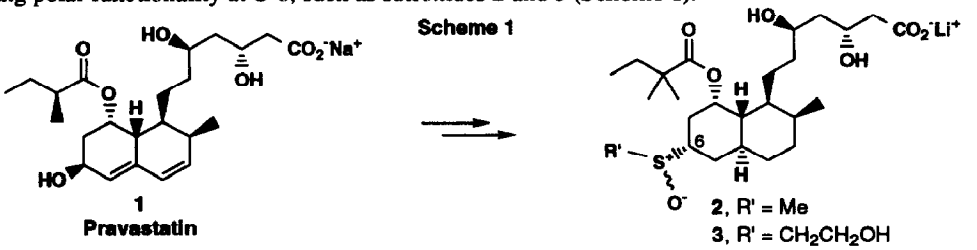
Abstract: *The synthesis and diastereoselective oxidation of novel tetrahydromevinic acid lactone sulfides to sulfoxides is described.*

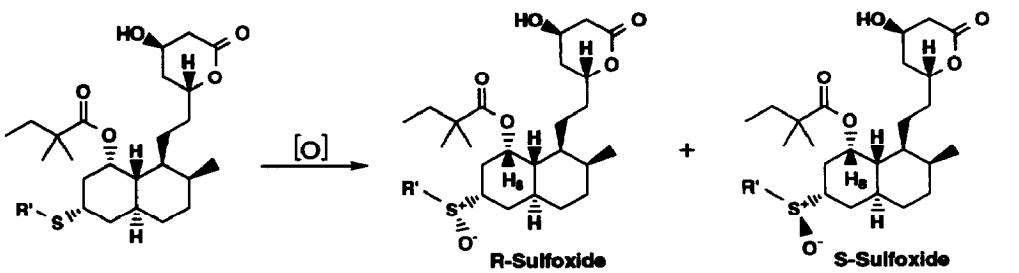
The enantio- and diastereoselective oxidation of sulfides to sulfoxides is an area of research currently under investigation in a number of laboratories.[1-4] As part of our program to identify a potent and hepato-selective HMG-CoA reductase inhibitor,[5] a series of tetrahydromevinic acid derivatives were prepared containing polar functionality at C-6, such as sulfoxides **2** and **3** (**Scheme 1**).

Scheme 1



The reductase inhibitory activity of **2** and **3** was identified as residing primarily with the **2R** and **3R** sulfoxide diastereomers. A synthetic effort to preferentially generate the desired R-sulfoxides was initiated. Reported herein are the results of our diastereoselective oxidation studies of sulfides **4**, **5**, and **6** to their corresponding sulfoxides (**Scheme 2**).

Scheme 2



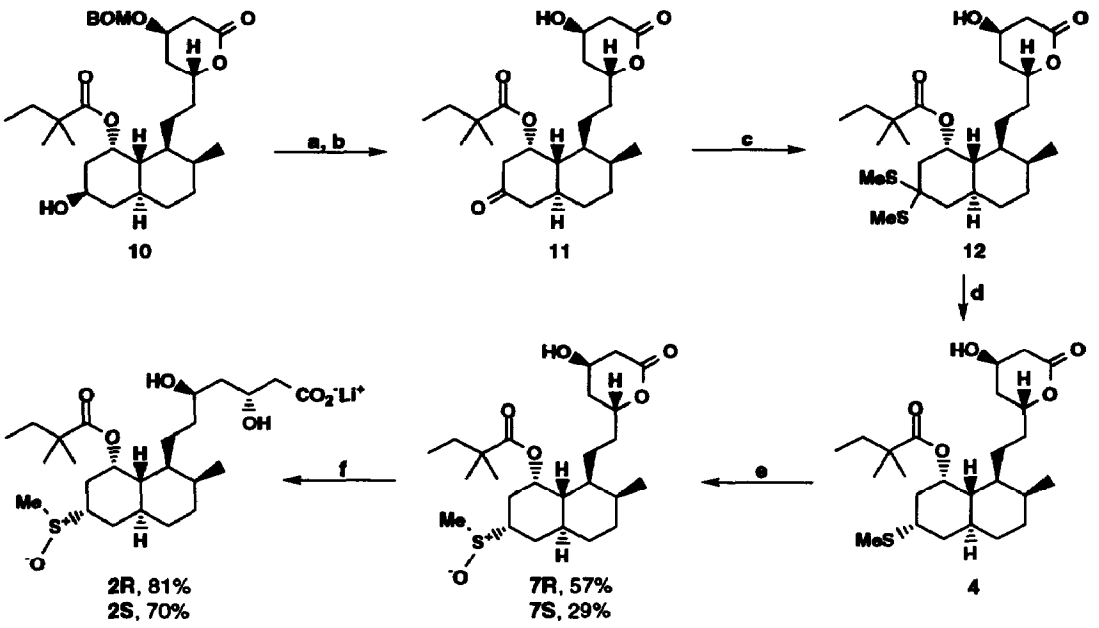
4, R' = Me
5, R' = CH_2CH_2OH
6, R' = CH_2CH_2OAc

7R, R' = Me
8R, R' = CH_2CH_2OH
9R, R' = CH_2CH_2OAc

7S, R' = Me
8S, R' = CH_2CH_2OH
9S, R' = CH_2CH_2OAc

The synthesis of **2** is outlined in **Scheme 3** and begins with compound **10** (prepared in 7 steps from pravastatin[5] **1**).[6] Jones oxidation of **10** followed by protecting group removal produced ketone **11**.[7] Ketalization with excess methanethiol afforded **12** which was then reduced with tin hydride to sulfide **4**. Oxidation of **4** with *m*-CPBA produced a mixture of sulfoxides **7R** and **7S** which were separated by chromatography. The assignments of the **7R** and **7S** sulfoxides were based on ^{1}H NMR chemical shifts which were consistent with the chemical shift patterns of analogous sulfoxides whose structures were confirmed by x-ray.[8] Sulfoxides **7R** and **7S** were saponified independently to afford dihydroxyheptanoic acids **2R** and **2S**. In an analogous fashion, sulfoxides **8R** and **8S** and **9R** and **9S** were prepared using 2-mercaptoethanol. Selective acylation of the hydroxyethyl sulfide **5** with acetyl chloride and pyridine in methylene chloride afforded the acetoxyethyl sulfide **6**.

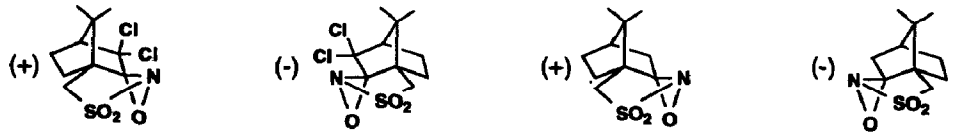
Scheme 3



Reagents and conditions: (a) CrO_3, H_2SO_4, H_2O, acetone, -40° to -10°C, 1 h; (b) $Pd(OH)_2$ on C, H_2, EtOAc, rt, 1 h, 87% over 2 steps; (c) MeSH (excess), BF_3•Et_2O (1 eq), CH_2Cl_2, HOAc, -50° to -25°C, 2.5 h, 95%; (d) *n*-Bu_3SnH (2 eq), C_6H_6, AIBN, reflux, 1.5 h, 74%; (e) *m*-CPBA (1.1 eq), CH_2Cl_2, 0°C-rt, 30 min, 86% (66R:34S); (f) 1 N LiOH, dioxane, 23° C, 1 h.

Oxidation of sulfides **4**, **5**, and **6**, using *m*-CPBA gave mixtures of the corresponding R and S sulfoxides in ratios of approximately 60:40 (**Table 1**, entry **A**).[8] To optimize the formation of the desired R-sulfoxides, alternative asymmetric oxidations were investigated. Modifications of the Sharpless epoxidation reaction were examined using (+) and (-)-diethyl tartrate (DET) in combination with titanium isopropoxide and cumene hydroperoxide (entries **B**, **C**, and **H**).[1,2] Additional oxidations using camphorsulfonyl oxaziridines, **13** and **14** (**Figure 1**), were also investigated (entries **D**, **E**, **F**, and **G**).[3]

Figure 1



(+)-13 (-)-13 (+)-14 (-)-14

Table 1

Oxidation of Sulfides to Sulfoxides

Reaction Conditions		Yield (%) 7	Ratio 7R:7S		Yield (%) 8	Ratio 8R:8S		Yield (%) 9	Ratio 9R:9S
A		86	66:34		70	57:43		84	60:40
B		87	82:18		93	49:51		82	78:22
C		45	22:78		93	49:51		91	41:59
D		100	26:74		99	27:73		94	36:64
E		100	68:32		95	80:20		98	87:13
F		96	26:74						
G		100	39:61						
H					59	68:32			

Oxidation Conditions: A: *m*-CPBA (1.2 eq), CH_2Cl_2, 0°C-rt, 30 min; B: (+)-DET (4 eq), Ti(O-*i*-Pr)$_4$ (1 eq), $PhC(CH_3)_2OOH$ (2 eq), CH_2Cl_2, -20° C, 24 h; C: (-)-DET (4 eq), Ti(O-*i*-Pr)$_4$ (1 eq), $PhC(CH_3)_2OOH$ (2 eq), CH_2Cl_2, -20° C, 24 h; D: (+)-13 (1.2 eq), CCl_4, CH_2Cl_2, -20° C to rt, 24-48 h; E: (-)-13 (1.2 eq), CCl_4, CH_2Cl_2, -20° C to rt, 24-48 h; F: (+)-14 (2 eq), CCl_4, CH_2Cl_2, -20° C, 72 h, rt, 12 h; G: (-)-14 (1.2 eq), CH_2Cl_2, -20° C to rt, 48 h; H: (+)-DET (2 eq), Ti(O-*i*-Pr)$_4$ (1 eq), H_2O (1 eq), CH_2Cl_2, $PhC(CH_3)_2OOH$ (1.1 eq), -20° C, 27 h.

With sulfides **4** and **6**, formation of R-sulfoxides **7R** and **9R** was favored (~80R:20S) using (+)-DET in the modified Sharpless conditions (entry **B**). Oxidation of hydroxyethyl sulfide **5** to sulfoxides **8** using (+) or (-)-DET (entries **B** and **C**), however, produced equal amounts of diastereomers **8R** and **8S**. Presumably, complexation of the alcohol moiety with the titanium reagent precludes chirality transfer during the oxidation. Further modification of the Sharpless reaction conditions using (+)-DET for the oxidation of **5** to **8** again favored R-sulfoxide formation (68R:32S) (entry **H**).

Optimal results for R-sulfoxide formation were achieved using 8,8-dichlorocamphorsulfonyl oxaziridine, (-)-**13** (entry **E**). Oxidation of acetoxyethyl sulfide **6** with this reagent produced an 87R:13S ratio of sulfoxides **9** in 98% yield. The best results for S-sulfoxide formation were achieved using 8,8-dichlorocamphorsulfonyl oxaziridine (+)-**13** (entry **D**). Oxidation of methyl sulfide **4** with oxaziridine (+)-**13** produced a 26R:74S ratio of sulfoxides **7** in quantitative yield (entry **D**).

Oxidation of methyl sulfide **4** to methyl sulfoxides **7R/7S** with oxaziridine (+)-**14** produced the S-sulfoxide preferentially as expected (26R:74S, entry **F**). Oxidation of **4** with (-)-**14**, however, did not preferentially form the R-sulfoxide as anticipated but favored the S-sulfoxide (39R:61S, entry **G**). This

anomalous result was not investigated further due to the superior selectivity demonstrated by the dichlorooxaziridines **13**.

In summary, the R-sulfoxides of **2** and **3** were prepared with high diastereoselectivity using (+)-diethyl tartrate in modified Sharpless epoxidation conditions or using (-)-8,8-dichlorocamphorsulfonyl-oxaziridine (-)-**13**. Similarly, the S-sulfoxides of **2** and **3** could be preferentially prepared using (-)-DET or oxaziridine (+)-**13**.

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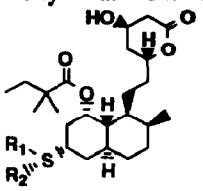

15, R_1=Ph R_2= O
16, R_1=CH_2F R_2= O
17, R_1=O R_2=cyclopentyl

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7. Yields are for pure products or mixtures of pure diastereomers obtained after silica gel chromatography. All new compounds exhibited ^1H NMR (300 or 400 MHz) and mass spectral data consistent with their assigned structures. Most compounds were also characterized by ^{13}C NMR (100 MHz). The ratio of sulfoxides was determined by HPLC.
8. The ^1H chemical shift for H_8 (**Scheme 2**) in the major diastereomer (R-sulfoxide) produced in the *m*-CPBA oxidation appears at a lower field than the chemical shift for H_8 in the corresponding minor diastereomer (S-sulfoxide). Representative chemical shifts for H_8 ($CDCl_3$, 300 or 400 MHz) are: **7R**, δ 5.27; **7S**, δ 5.12; **8R**, δ 5.24; **8S**, δ 5.13; **9R** δ 5.28; **9S**, δ 5.15.

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