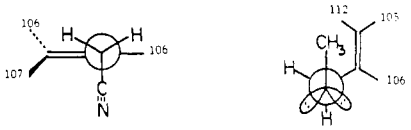
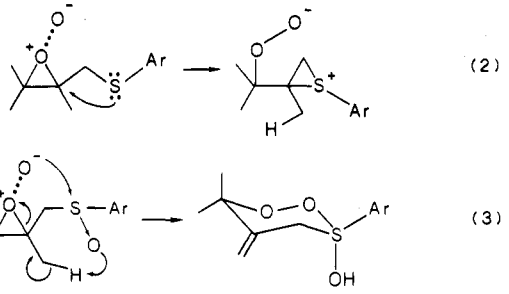


Figure 1. MM2[14] minimized structures for the cyano- and methoxy-substituted tetramethylethylenes. The dihedral angle relative to the olefinic plane for the most favorably aligned hydrogen on each methyl are given.

Anchimeric assistance from the allylic substituent resulting in regiochemically preferred opening of the perepoxide (eq 2 or 3) and subsequent, geminal hydrogen abstraction is an unlikely explanation for this phenomenon.



(2)

(3)

A change in the geminal selectivity, as the para substituent on the allylic phenyl sulfide or sulfoxide is varied, is not observed as anticipated for neighboring group assistance.

Two possible contributing factors to the geminal selectivity observed in these reactions are as follows.

(1) Electronic repulsion between lone pairs on the substituent and the pendant oxygen of the nascent perepoxide favors formation of the perepoxide on the distal side of the olefin. Eliel[12] and others have previously invoked a repulsive interaction between sulfur and oxygen in order to explain the greater equatorial preference in 5-(methylthio)-1,3-dioxane in comparison to (methylthio)cyclohexane. However, if the cis methyls on the distal side of the olefin are equally reactive exclusive formation of the distal perepoxide would result in 50% geminal hydrogen abstraction. The observation of 81% geminal selectivity (Table 1), although not excluding a role for electron repulsion, requires operation of an additional mechanism(s) enhancing the reactivity of the geminal methyls.

(2) The substituted tetramethylethylenes exist in conformations in which the geminal hydrogens are closer to and/or can reach the perpendicular geometry necessary for abstraction easier than the hydrogens on the cis and/or trans methyl groups. Houk[13] has previously utilized a very similar argument to explain the cis effect observed in the singlet oxygen ene reaction. Minor differences in conformational energetics are important because they contribute significantly to the near zero activation barriers for singlet oxygen reactions. Consistent with this explanation are MM2 calculations performed on the methoxy and cyano compounds. In the lowest energy conformation of the cyano compound (Figure 1) which exhibits no geminal selectivity the conformational dispositions of all three methyl groups are identical. In the lowest energy conformation of the methoxy compound, which does exhibit a moderate selectivity, the cis methyl is less favorably disposed for hydrogen abstraction.

Further work to delineate the factors which contribute to geminal selectivity, and additional attempts to trap a perepoxide are currently in progress and will be communicated in the near future.

Acknowledgment. We thank the National Science Foundation and the donors of the Petroleum Research Foundation, administered by the American Chemical Society, for their generous support of this research.

Registry No. O_2, 7782-44-7; $Me_2C{=}C(Me)CH_2SO_2(p\text{-}MePh)$, 86925-63-5; $Me_2C(OOH)C(=CH_2)CH_2SO_2(p\text{-}MePh)$, 114597-44-3; $CH_2{=}C(Me)CMe(OOH)CH_2SO_2(p\text{-}MePh)$, 114597-45-4; $Me_2C{=}C(Me)CH_2SO(p\text{-}NO_2Ph)$, 114597-46-5; $Me_2C(OOH)C(=CH_2)CH_2SO(p\text{-}NO_2Ph)$, 114614-33-4; $CH_2{=}C(Me)CMe(OOH)CH_2SO\ (p\text{-}NO_2Ph)$, 114597-47-6; $Me_2C{=}C(Me)CH_2SOPh$, 101384-22-9; $Me_2C(OOH)C(=CH_2)CH_2SOPh$, 114597-48-7; $CH_2{=}C(Me)CMe(OOH)CH_2SOPh$, 114597-49-8; $Me_2C{=}C(Me)CH_2SO(p\text{-}MePh)$, 51954-48-4; $Me_2C(OOH)C(=CH_2)CH_2SO(o\text{-}MePh)$, 114597-50-1; $CH_2{=}C(Me)CMe(OOH)CH_2SO(p\text{-}MePh)$, 114597-51-2; $Me_2C{=}C(Me)CH_2SO(p\text{-}MeOPh)$, 114597-52-3; $Me_2C(OOH)C(=CH_2)CH_2SO(p\text{-}MeOPh)$, 114597-53-4; $CH_2{=}C(Me)CMe(OOH)CH_2SO(p\text{-}MeOPh)$, 114597-54-5; $Me_2C{=}C(Me)CH_2Br$, 5072-70-8; $Me_2C(OOH)C(=CH_2)CH_2Br$, 67228-75-5; $CH_2{=}C(Me)CMe(OOH)CH_2Br$, 114597-55-6; $Me_2C{=}C(Me)CH_2SPh$, 79597-54-9; $Me_2C(OOH)C(=CH_2)CH_2SPh$, 114597-56-7; $CH_2{=}C(Me)CMe(OOH)CH_2SPh$, 114597-57-8; $Me_2C{=}C(Me)CH_2S(p\text{-}NO_2Ph)$, 114597-58-9; $Me_2C(OOH)C(=CH_2)CH_2S(p\text{-}NO_2Ph)$, 114597-59-0; $CH_2{=}C(Me)CMe(OOH)CH_2S(p\text{-}NO_2Ph)$, 114597-60-3; $Me_2C{=}C(Me)CH_2OMe$, 20518-48-3; $Me_2C(OOH)C(=CH_2)CH_2OMe$, 114597-61-4; $CH_2{=}C(Me)CMe(OOH)CH_2OMe$, 114597-62-5; $Me_2C(OH)C(=CH_2)CHO$, 114597-67-0; $Me_2C{=}C(Me)CH_2OEt$, 20174-79-2; $Me_2C(OOH)C(=CH_2)CH_2OEt$, 114597-63-6; $CH_2{=}C(Me)CMe(OOH)CH_2OEt$, 114597-64-7; $Me_2C{=}C(Me)CH_2CN$, 4786-36-1; $Me_2C(OOH)C(=CH_2)CH_2CN$, 114597-65-8; $CH_2{=}C(Me)CMe(OOH)CH_2CN$, 114597-66-9.

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Received February 9, 1988

(12) (a) Eliel, E. L.; Juaristi, E. *J. Am. Chem. Soc.* **1978**, *100*, 6114. (b) Zefirov, N. S.; Gurvich, L. G.; Shashkov, A. S.; Krimer, M. Z.; Vorob'eva, E. A. *Tetrahedron* **1976**, *32*, 1211. (c) Juaristi, E.; Martinez, R.; Mendez, R.; Toscano, R. A.; Soriano-Garcia, M.; Eliel, E. L.; Petsom, A.; Glass, R. S. *J. Org. Chem.* **1987**, *52*, 3806.

(13) Houk, K. N.; Williams, J. C., Jr.; Mitchell, P. A.; Yamaguchi, K. *J. Am. Chem. Soc.* **1981**, *103*, 949.

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Nucleophilic and Electrophilic Mercaptanylations via 2-(Trimethylsilyl)ethanethiol-Derived Reagents[1]

Summary: 2-(Trimethylsilyl)ethanethiol reacts with carboxylic acids, alkyl halides, epoxides, and enones to provide acyl- and alkyl-substituted 2-(trimethylsilyl)ethyl sulfides. Electrophilic mercaptanylation is effected by a thiol-sulfonate reagent derived from 2-(trimethylsilyl)ethanethiol.

Sir: In conjunction with a pair of projects in our laboratory, we needed methods for nucleophilic and electrophilic introduction of the sulfhydryl moiety into highly functionalized substrates. The desired nucleophilic application required an efficient transformation of a carboxylic acid into a thiol acid. We anticipated that acylation of an alkyl mercaptan[2,3] followed by dealkylation of the resulting thiol

(1) Cytochalasin Support Studies. 10. For paper 9, see: Ranasinghe, M. G.; Fuchs, P. L. *Synth. Commun.* **1988**, *18*, 227.

(2) For leading references on the acylation of mercaptans, see: (a) Ohta, S.; Okamoto, M. *Tetrahedron Lett.* **1981**, *22*, 3245. (b) Kertesz, D. J.; Marx, M. *J. Org. Chem.* **1986**, *51*, 2315. (c) Arrieta, A.; Garcia, T.; Lago, J. M.; Palomo, C. *Synth. Commun.* **1983**, *13*, 471 and references cited therein.

0022-3263/88/1953-3125$01.50/0

Scheme I

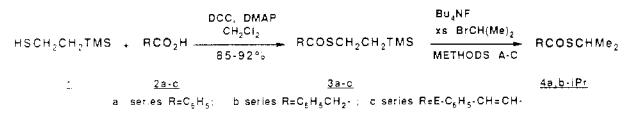


Table I

product	method[a] A	B	C
4a-*i*-Pr	61%	69%	99%
4b-*i*-Pr	50%	87%	92%

[a] A: Thiolesters **3a,b**, powdered 4A molecular sieves (Lancaster), and 4.0 equiv of TBAF (1.0 M Lancaster) were stirred in THF (0.11 M) at 25 °C for 13 h and then quenched with 10.0 equiv of isopropyl bromide and stirred for 4 h. B: Identical with method A, except the isopropyl bromide was added at the beginning of the reaction. C: Same as method A, except the cleavage was conducted at 25 °C for 3 h with sonication prior to adding the isopropyl bromide. Note: In all methods, the powdered 4A molecular sieves, THF, and TBAF were combined prior to the addition of the thiolester substrate.

ester would afford thiolcarboxylate anions which could be subsequently alkylated. The alkyl mercaptan selected for this task was 2-(trimethylsilyl)ethanethiol (BEST[4a]) **1**[4b,5] since the fluoride-mediated cleavage of 2-(trimethylsilyl)ethyl esters,[6a] carbonates,[6b] urethanes,[6c,d] and phosphates[6e] have been shown to be efficient reactions. Recently Weinreb reported that fluoride treatment of 2-(trimethylsilyl)ethyl sulfonamides[7] effects fragmentation to the corresponding amino derivatives; this example represents the only 2-silyl-substituted sulfur derivative that has been shown to undergo this mode of cleavage.

Reaction of BEST (**1**)[4,5] with carboxylic acids **2a–c** in methylene chloride containing DCC and DMAP[8] affords BEST esters **3a–c**[9,10] in 85–92% yield (Scheme I). A comparison of fluoride-mediated dealkylation methods with BEST esters **3a,b** is presented in Table I; the yields are for isolated, purified isopropyl thiol esters **4a,b**.[9a,11,12]

Table II

substrate	alkylating agent[a]/product[b] MeI	$BrCHMe_2$	$BrCH_2Ph$
3a	**4a**-Me	**4a**-*i*-Pr	**4a**-Bz
	43,[c] 95%	75, 99%	91, 99%
3b	**4b**-Me	**4b**-*i*-Pr	**4b**-Bz
	78%,[d] NA[f]	76,[d] 92%	71%,[d] NA
3c	**4c**-Me	**4c**-*i*-Pr	**4c**-Bz
	97%,[e] 99%	83%, NA	89%, NA

[a] General method C, Table I. [b] Product yields isolated when employing 1.05 equiv and 10.0 equiv of alkylating agent, respectively. [c] 27–31% of methyl benzoate (duplicate) was also isolated (controls indicate that methyl thiolbenzoate is not an intermediate in this reaction). [d] 4.0 equiv of glacial acetic acid was added prior to 1.05 equiv of alkyl halide (omission of the HOAc gave the bis-alkylated adducts in 56–62% due to fluoride-catylized enolization at the benzylic position). [e] 2% of methyl cinnamate isolated. [f] NA denotes not applied.

Once having settled on the ultrasound cleavage/in situ alkylation method (method C), we examined this procedure for the cleavage/alkylation reactions of BEST esters **3a–c** with both 1 equiv and an excess of three common alkylating agents (Table II).

The surprisingly difficult fluoride-mediated cleavage observed with *acyl*-substituted 2-(trimethylsilyl)ethanethiols **3a–c**[12] combined with the previously reported reluctance for fluoride cleavage of 2-(trimethylsilyl)ethyl ethers[13] did not portend well for the prospect of cleavage of 2-(trimethylsilyl)ethyl sulfides. This pessimism proved well-founded in the laboratory since model sulfide **5** (prepared in 90% from **1** and 3-(bromopropyl)benzene) was quantitatively recovered by using the methodology described above. After investigating a number of unsuccessful fluoride-based reagent combinations (including the addition of various Lewis Acids), we discovered an effective two-step procedure for the conversion of 2-(trimethylsilyl)ethyl sulfides to mercaptans.

Treatment of sulfide **5** with 1.1 equiv of (methylthio)-dimethylsulfonium tetrafluoroborate (**6**)[14] and 5 equiv of dimethyl disulfide in methylene chloride at 0 °C for 4 h affords a 92% yield of unsymmetrical disulfide **7** along with 3–4% of symmetrical disulfide **8** (Scheme II). Repetition of the same reaction without the inclusion of the dimethyl disulfide provides approximately a 1:1 mixture of **7** and **8** in near-quantitative yield. Control studies reveal that excess dimethyl disulfide will react with **8** in the presence of a 0.1 equiv of **6** to establish the observed 92:4 ratio.[15] Cleavage of disulfide **7** to mercaptan **9** is smoothly accomplished by reaction with tri-*n*-butylphosphine in aqueous methanol.[16] For preparative purposes, mixtures of symmetrical and unsymmetrical disulfides pose no problem since a purified sample of **8** is also converted to **9** (83%) under identical conditions used for **7**.

Application of this chemistry to ω-bromo sulfides **10a,b**[9,17] afforded ca. 10:1 mixtures of unsymmetrical and

(3) For synthetic application of thiolesters, see: (a) Liu, H.-J.; Bukownik, R. R.; Pednekar, P. R. *Synth. Commun.* **1981**, *11*, 599 and references cited therein. (b) Gauthier, J. Y.; Bourdon, F.; Young, R. N. *Tetrahedron Lett.* **1986**, *27*, 15 and references cited therein. (c) Douglas, K. T. *Acc. Chem. Res.* **1986**, *19*, 186 and references cited therein.

(4) (a) The acronym BEST refers to β-ethylsilyl thiol. The IUPAC name is 2-(trimethylsilyl)ethanethiol. (b) Ito, T. I.; Weber, W. P. *J. Org. Chem.* **1974**, *39*, 1694.

(5) Two experimental modifications facilitated the synthesis of the 2-(trimethylsilyl)ethanethiol in 71% overall yield on a 30-g scale. The basic method of Gornowicz et al. (Gornowicz, G. A.; Ryan, J. W.; Speier, J. L. *J. Org. Chem.* **1968**, *33*, 2918) was adjusted to include a second addition of the *tert*-butylperoxy pivalate (Pennwalt) catalyst at the halfway point of the reaction to afford 2-(trimethylsilyl)ethyl thiolacetate in 82% yield after distillation (ca. 5% of the secondary thiolacetate is contained in the for run). The second modification employed LAH cleavage (86% after distillation at 52–54 °C/25 mmHg) of the thiolacetate (cf. Ambasht, S.; Chiu, S. K.; Peterson P. E.; Queen, J. *Synthesis* **1980**, 318) rather than the methanolysis employed in ref 4.

(6) (a) Gerlach, H. *Helv. Chim. Acta* **1977**, *60*, 3039. (b) Gioeli, C.; Balgobin, N.; Josephson, S.; Chattopadhyaya, J. B. *Tetrahedron Lett.* **1981**, *22*, 969. (c) Capson, T. L.; Poulter, C. D. *Tetrahedron Lett.* **1984**, *25*, 3515. (d) Meyers, A. I.; Roland, D. M.; Comins, D. L.; Henning, R.; Fleming, M. P.; Shimizu, K. *J. Am. Chem. Soc.* **1979**, *101*, 4732. (e) Honda, S.; Hata, T. *Tetrahedron Lett.* **1981**, *22*, 2096.

(7) Weinreb, S. M.; Demko, D. M.; Lessen, T. A. *Tetrahedron Lett.* **1986**, *27*, 2099.

(8) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.

(9) (a) All new compounds exhibit satisfactory spectral and physical data. (b) Wood, K. V.; Rothwell, A. P.; Anderson, M. B.; Fuchs, P. L. *Rapid Commun. Mass Spectrom.* **1988**, *2*, 38.

(10) The ^{13}C NMR carbonyl resonance of the 2-(trimethylsilyl)ethyl thiolester is typically 25 ppm downfield of the corresponding 2-(trimethylsilyl)ethyl ester.

(11) Omission of the alkylation reagent allows isolation of thiolbenzoic acid (82%) and thiolphenylacetic acid (89%). Attempts to isolate thiolcinnamic acid were unsuccessful.

(12) The cleavage of 2-(trimethylsilyl)ethyl oxyesters[6] appears to be a factor of 3–4 times faster than the corresponding BEST ester as revealed by direct competition studies with the benzoic acid derivatives.

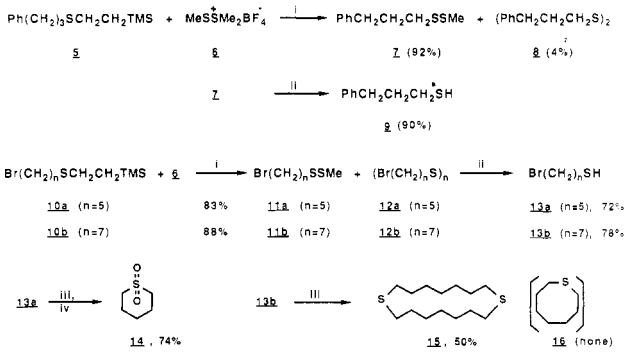
(13) (a) Lipshutz, B. H.; Pegram, J. J.; Morey, M. C. *Tetrahedron Lett.* **1981**, *22*, 4603. (b) Trost, B. M.; Quayle, P. *J. Am. Chem. Soc.* **1984**, *106*, 2469. (c) Burke, S. D.; Pacofsky, G. J. *Tetrahedron Lett.* **1986**, *27*, 445.

(14) (a) Smallcombe, S. H.; Caserio, M. C. *J. Am. Chem. Soc.* **1971**, *93*, 5826. (b) Trost, B. M.; Murayama, E. *J. Am. Chem. Soc.* **1981**, *103*, 6529.

(15) While the mechanism of this reaction must involve sulfenylation of **5** followed by fluoride-promoted cleavage of the resulting thiosulfonium salt (to afford **7**, BF_3, TMSF, and ethylene), it is clear that numerous thiosulfonium salts, disulfides, and sulfenylated disulfides must be present in this complex equilibrium reaction. Examination of the crude reaction mixture by 470-MHz NMR fails to reveal the presence of methyl 3-phenylpropyl sulfide or bis(3-phenylpropyl) sulfide.

(16) Humphrey, R. E.; Potter, J. L. *Anal. Chem.* **1965**, *37*, 165.

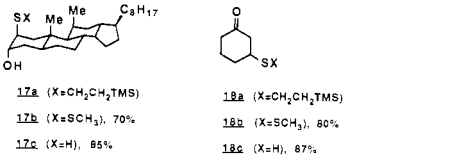
Scheme II[a]



[a] (i) MeSSMe (5 equiv), CH_2Cl_2, 0 °C, 4 h; (ii) *n*-Bu_3P, 10% aqueous CH_3OH, 25 °C, 1 h; (iii) NaH, THF; (iv) MCPBA, CH_2Cl_2, 0 °C, 30 min.

symmetrical disulfides **11a/12a** and **11b/12b** which were separated for characterization purposes. Cleavage of **11a** and **11b** with tri-*n*-butylphosphine in aqueous methanol provides ω-bromo mercaptans **13a,b** in 72% and 78% yield, respectively. Treatment of **13a** with sodium hydride in THF at room temperature provides the pentamethylene sulfide which was not purified but directly oxidized with MCPBA to give sulfone **14** in 74% overall yield. Repetition of the cyclization procedure with the 7-bromo-1-mercaptoheptane (**13b**) (even using extremely slow addition of a 0.005 M solution of the bromo mercaptan to a large volume of THF containing excess NaH) afforded only the 16-membered disulfide **15** (50%) with no indication for the presence of the monomeric sulfide **16** as assayed by mass spectrometry.

The same cleavage protocol was applied to two additional 2-(trimethylsilyl)ethyl sulfides: steroidal sulfide-alcohol **17a** (98% yield from 2α,3α-cholestane oxide and mercaptan **1**) and β-substituted ketone **18a** (85% yield from cyclohexenone and **1**). These substrates are sequentially transformed to disulfides **17b,18b** and the mercaptans **17c,18c** in the yields indicated.

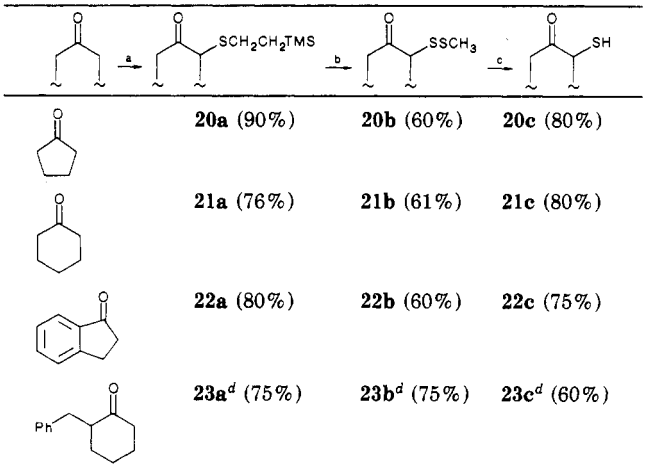


Electrophilic introduction of the mercaptan moiety can be effected by a sulfenylation/cleavage sequence. Treatment of a variety of ketone enolates (Table III) under standard conditions[18] with the thiolsulfonate reagent (**19**[19]) derived from **1** affords the α-sulfenylated ketones **20–25a** in very good yield. Conversion of these materials to the disulfides **20–23b** and then to the α-mercapto ketones **20–23c** proceeds smoothly.

A final example of the versatility of this methodology is shown in Scheme III. Metalation of cyclohexyl sulfone **24** followed by sulfenylation with thiolsulfonate **19** affords α-sulfenylated sulfone **25** in 83% yield. Chemospecific reductive cleavage of the *arylsulfonyl* moiety[20] of both **25** and **26** affords the 2-(trimethylsilyl)ethyl-substituted sulfide **27** and sulfone **28** without any trace of the aryl sulfone **24** which would have resulted from the alternative

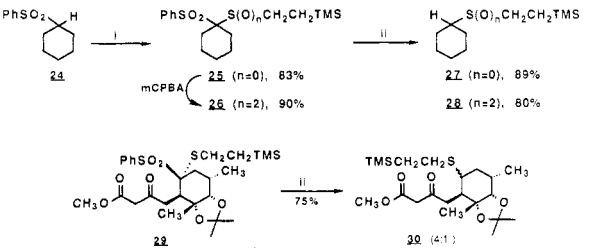
(17) Compounds **10a,b** were prepared from 5-acetoxy-1-chloropentane and methyl 7-bromoheptanoate via (i) reaction with **1**, (ii) LAH reduction, and triphenyl phosphine/CBr_4 reaction in 48% and 64% overall yield, respectively.
(18) Trost, B. M. *Chem. Rev.* **1978**, *78*, 363.
(19) See ref 1 for further elucidation.
(20) Trost, B. M.; Arndt, H. C.; Strenge, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.

Table III



[a] (a) i. LDA, −78 °C, THF; ii. $TMSCH_2CH_2STs$ (**19**); (b) $MeS^+SMe_2BF_4^-$, MeSSMe, CH_2Cl_2, 0 °C; (c) *n*-Bu_3P, 10% aqueous CH_3OH, 25 °C, 2 h; (d) ~1:1 mixture of diastereomers.

Scheme III



[a] (i) a, *n*-BuLi, THF, −30 °C; (b) $TMSCH_2CH_2STs$ (**19**); (ii) Na-(Hg), 1:1 THF/CH_3OH.

mode of cleavage. Application of this strategy to the more highly functionalized sulfone **29** provides desulfonylated β-keto ester **30** in 75% yield as a 4:1 mixture of diastereomers.

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Supplementary Material Available: Experimental procedures along with NMR, IR, and mass spectroscopy data (19 pages). Ordering information is given on any current masthead page.

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Lipase-Catalyzed Irreversible Transesterification for Preparative Synthesis of Chiral Glycerol Derivatives[1]

Summary: An irreversible, lipase-catalyzed transesterification using enol ester as an acylating agent has been developed for preparative enantioselective acylation of *meso*-1,3-diols.

