Thiol/Diselenide Exchange for the Generation of Benzeneselenolate Ion. Catalytic Reductive Ring-Opening of α,β-Epoxy Ketones

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In the presence of *N*-acetylcysteine sodium salt, benzeneselenolate ion was generated *in situ* from diphenyl diselenide via thiol/diselenide and thiol/selenenyl sulfide exchange in aqueous methanol under mild conditions. Benzeneselenolate ion thus formed was efficiently alkylated and arylated to afford alkyl phenyl selenides and aryl phenyl selenides, respectively. α,β-Epoxy ketones were catalytically reduced by benzeneselenolate ion to afford β-hydroxy ketones (aldols) in good yields. The stereospecificity of the reaction was demonstrated in the preparation of optically active β-hydroxy ketones from chiral α,β-epoxy ketones.

Introduction

The kinetics and mechanisms of thiol/disulfide and selenol/diselenide exchange reactions (eq 1) have been the subject of a number of recent studies.[1] It has also been noted that selenols catalyze the interchange reaction of dithiols and disulfides.[2] On the other hand, the closely related thiol/diselenide (eq 2) and thiol/selenenyl sulfide (eq 3) equilibria have only received scant attention. Günther[3] reported in 1967 the stoichiometric quantitative reduction of a series of aliphatic diselenides to the corresponding alkaneselenols (eq 4) by dithiothreitol. It was also noted that less reducing monothiols (glutathione, cysteine) needed to be present approximately in a 1000-fold excess to shift equilibrium 4 completely to the right with selenocystine.[4]

$$RXH + RXXR' \rightleftharpoons RXXR' + R'XH \quad (1)$$

X = S, Se

$$RSH + R'SeSeR' \rightleftharpoons RSSeR' + R'SeH \quad (2)$$

$$RSH + RSSeR' \rightleftharpoons RSSR + R'SeH \quad (3)$$

$$2RSH + R'SeSeR' \rightleftharpoons RSSR + 2R'SeH \quad (4)$$

Selenols and selenolate ions are useful reagents for a variety of synthetic transformations[5] and intermediates in the preparation of organoselenium compounds.[6] It is therefore surprising to find that the thiol/diselenide exchange reaction has been so little explored. In the following we describe the generation and synthetic use of benzeneselenolate ion from diphenyl diselenide by using inexpensive *N*-acetylcysteine as a thiol reducing agent.

Results and Discussion

Initially, in order to find suitable reaction conditions for the generation of benzeneselenol according to eq 4, diphenyl diselenide was treated in a methanolic aqueous solution under argon with excess *N*-acetylcysteine in the presence of various alkyl or aryl halide trapping agents. The choice of *N*-acetylcysteine as a thiol reducing agent was based on the assumption that the high water solubility of the thiol, its corresponding disulfide, and any S-alkylated products formed would simplify extractive workup and purification of the reaction product. In order to obtain good yields of Se-alkylated/arylated products, it was found essential to have a slightly alkaline reaction medium. When diphenyl diselenide, dissolved in a 2:1 (by volume) mixture of methanol and water, was stirred at ambient temperature for 19 h with a 6-fold excess of *N*-acetylcysteine, sodium hydroxide and 1-iodododecane, dodecyl phenyl selenide (**1a**) was isolated in 83% yield. When 1-chloro-4-nitrobenzene and 1-chloro-2,4-dinitrobenzene were submitted to similar reaction conditions using buffered (pH = 9.2) aqueous methanol, diaryl selenides **1b** and **1c**, respectively, resulting from nucleophilic aromatic substitution, were isolated in 68 and 100% yield. 1,2-Dinitrobenzene turned out to be highly susceptible to nucleophilic substitution by the selenolate reagent. By using a slight excess of diphenyl diselenide, selenide **1d** was isolated in 99% yield. The quantitative or near quantitative isolated yields of compounds **1c** and **1d** indicate that thiolate anion derived from *N*-acetylcysteine

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(1) (a) Pleasants, J. C.; Guo, W.; Rabenstein, D. L. *J. Am. Chem. Soc.* **1989**, *111*, 6553. (b) Rabenstein, D. L.; Theriault, Y. *J. Org. Chem.* **1984**, *62*, 1672. (c) Singh, R.; Whitesides, G. M. *J. Am. Chem. Soc.* **1990**, *112*, 1190.
(2) Singh, R.; Whitesides, G. M. *J. Org. Chem.* **1991**, *56*, 6931.
(3) Günther, W. H. H. *J. Org. Chem.* **1967**, *32*, 3931.
(4) Dickson, R. C.; Tappel, A. L. *Arch. Biochem. Biophys.* **1969**, *130*, 547.
(5) (a) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697. (b) Miyashita, M.; Suzuki, T.; Yoshikoshi, A. *J. Org. Chem.* **1985**, *50*, 3377. (c) Clive, D. L. J.; Manning, H. W.; Boivin, T. L. B.; Postema, M. H. D. *J. Org. Chem.* **1993**, *58*, 6857. (d) Inokuchi, T.; Sugimoto, T.; Kusumoto, M.; Torii, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 3200. (e) Francisco, C. G.; Freire, R.; Rodríguez, M. S.; Suárez, E. *Tetrahedron Lett.* **1991**, *32*, 3413. (f) Middleton, D. S.; Simpkins, N. S.; Terrett, N. K. *Tetrahedron* **1990**, *46*, 545. (g) Pedersen, M. L.; Berkowitz, D. B. *J. Org. Chem.* **1993**, *58*, 6966. (h) Paulmier, C. In *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon Press: Oxford, 1986; p 396.
(6) (a) Sakakibara, M.; Katsumata, K.; Watanabe, Y.; Toru, T.; Ueno, Y. *Synthesis* **1992**, 377. (b) Ku, B.; Chang, K.; Oh, D. Y. *Synthesis* **1988**, 899. (c) Masawaki, T.; Ogawa, A.; Kambe, N.; Ryu, I.; Sonoda, N. *Chem. Lett.* **1987**, 2407.

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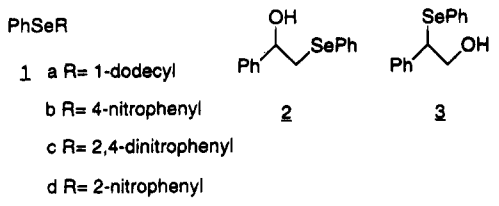
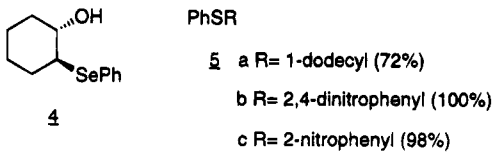


has a very low nucleophilic capacity under the conditions of the experiment. Styrene oxide was ring-opened by *in situ*-generated benzeneselenolate ion in high yield (87%) but with poor regioselectivity to afford a 4:6 mixture of the β-hydroxyselenides **2** and **3**. Cyclohexene oxide afforded the unsymmetrical selenide **4** in 88% yield when



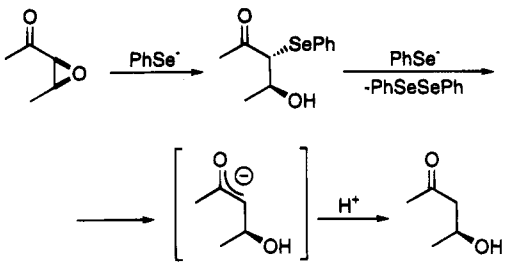
treated in methanol with the sodium salt of *N*-acetylcysteine in the presence of diphenyl diselenide.

For comparison, diphenyl diselenide was replaced by diphenyl disulfide in some of the above nucleophilic substitution reactions. As indicated by the high yields of compounds **5a–c**, the reaction conditions used are also suitable for the generation of benzenethiolate ion via thiol/disulfide exchange. However, as judged by the poor yields of the alkylation products, it was not possible to generate benzenetellurolate ion from diphenyl ditelluride by using the thiol/ditelluride exchange reaction.

With suitable reaction conditions at hand for the generation of highly nucleophilic benzeneselenolate ion via thiol/diselenide exchange, we next turned our attention to synthetic applications. Reductive ring-opening of α,β-epoxy ketones to the corresponding β-hydroxyketones (aldols) is of great interest in the synthesis of a variety of natural products. The method not only allows access to acyclic (intermolecular) aldols but also to a variety of cyclic (intramolecular) aldols which may be difficult to obtain by traditional methods. Several procedures, using such diverse reagents as samarium diiodide,[7] aluminium amalgam/ultrasound,[8] metallic lithium in liquid ammonia,[9] amine[10] /UV light, tributyltin hydride[11] /UV light, sodium hydrogen telluride,[12] benzeneselenolate ion[13] or its borate complex,[14] have been used for the reductive ring opening of α,β-epoxy ketones.

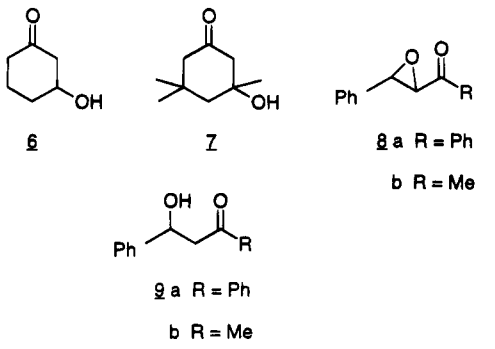
According to the proposed mechanism[13] for the benzeneselenolate-induced reduction, the epoxide ring is attacked by selenolate α to the carbonyl group, with formation of an α-(phenylselenenyl)-β-hydroxy ketone. In a following attack on selenium by benzeneselenolate ion, diphenyl diselenide is formed with the β-hydroxyketone

Scheme 1



enolate serving as the leaving group (Scheme 1). In support of the proposed mechanism, electrochemically generated benzeneselenolate ion[15] was shown to catalytically reduce α,β-epoxy ketones to β-hydroxy ketones.

It occurred to us that the thiol/diselenide exchange reaction may provide an even more convenient laboratory procedure for the continuous generation of benzeneselenolate ion from diphenyl diselenide. Therefore, a number of α,β-epoxy ketones were treated at ambient temperature under an inert atmosphere with the *in situ* generated sodium salt of *N*-acetylcysteine in the presence of 5 mol % of diphenyl diselenide. 2-Cyclohexen-1-one epoxide, when treated with 3 equiv of *N*-acetylcysteine in methanol/aqueous borax buffer, was readily ring-opened. However, the product **6** was partially dehydrated during

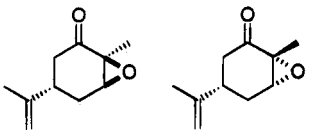


chromatographic purification, resulting in variable product yields (10–59%). A control experiment showed that *N*-acetylcysteine was unable to reduce the α,β-epoxy ketone in the absence of diphenyl diselenide. Isophorone oxide was catalytically reduced to afford 3-hydroxy-3,5,5-trimethylcyclohexanone (**7**) in 77% yield. By using the *in situ* generated sodium salt of *N*-acetylcysteine in methanol and a catalytic amount of diphenyl diselenide, 1,3-diphenyl-2-propen-1-one oxide (**8a**) and 4-phenyl-3-buten-2-one oxide (**8b**) were reduced to yield 1,3-diphenyl-3-hydroxypropan-1-one (**9a**) and 4-hydroxy-4-phenylbutan-2-one (**9b**) in 91 and 90% yields, respectively.

In order to define the scoop and limitations of the selenium-catalyzed ring-opening reaction, a series of chiral α,β-epoxy ketones were reduced. Such compounds can be obtained by epoxidation of chiral pool enones[16] or by Sharpless epoxidation of allylic alcohols, followed by transformation of the alcohol function to a ketone.[7a] A few examples of asymmetric epoxidation of enones are also known.[17,18]

(7) (a) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 2596. (b) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 4437.
(8) Miranda Moreno, M. J. S.; Sá e Melo, M. L.; Campos Neves, A. S. *Tetrahedron Lett.* **1993**, *34*, 353.
(9) McChesney, J. D.; Thompson, T. N. *J. Org. Chem.* **1985**, *50*, 3473.
(10) (a) Hasegawa, E.; Ishiyama, K.; Horaguchi, T.; Shimizu, T. *J. Org. Chem.* **1991**, *56*, 1631.
(11) Hasegawa, E.; Ishiyama, K.; Kato, T.; Horaguchi, T.; Shimizu, T; Tanaka, S.; Yamashita, Y. *J. Org. Chem.* **1992**, *57*, 5352.
(12) Osuka, A.; Taka-Oka, K.; Suzuki, H. *Chem. Lett.* **1984**, 271.
(13) Miyashita, M.; Suzuki, T.; Yoshikoshi, A. *Tetrahedron Lett.* **1987**, *28*, 4293.
(14) (a) Miyashita, M.; Hoshino, M.; Suzuki, T.; Yoshikoshi, A. *Chem. Lett.* **1988**, 507. (b) Miyashita, M.; Suzuki, T.; Yoshikoshi, A. *Chem. Lett.* **1987**, 2387.
(15) Inokuchi, T.; Kusumoto, M.; Torii, S. *J. Org. Chem.* **1990**, *55*, 1548.
(16) Hanessian, S. *Total synthesis of Natural Products: The "Chiron" Approach*; Pergamon Press: Oxford, 1983.
(17) Bolm, C. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 403 and references cited therein.
(18) Itsuno, S.; Sakakura, M.; Ito, K. *J. Org. Chem.* **1990**, *55*, 6047.

Epoxidation of (*S*)-(+)-carvone according to a literature procedure,[19] occurred preferentially from the sterically least hindered side to afford a 97/3 mixture (NMR and GC) of compounds **10** and **11**. When the epoxidation was



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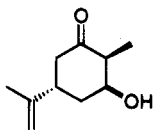

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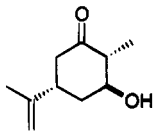

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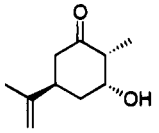
carried out at lower temperature (−20 °C) the selectivity was further improved to give isomer **10** as the only product. When compound **10** was treated in methanol with the sodium salt of *N*-acetylcysteine and diphenyl diselenide (catalytic conditions) two readily separated diastereoisomers **12** and **13** were isolated from the reaction mixture after aqueous workup in 86 and 10% yields, respectively, together with a small amount of dehydratation product (carvone). An X-ray structure determination of compound **12** is available.[20] The configurational assignment of compound **13** was based on ^{1}H NMR data in comparison with compound **12** ($^3J_{H,H}$ = 8.0 Hz and 2.6 Hz, respectively, for the vicinal methine protons of compounds **13** and **12**). (*R*)-(−)-Carvone epoxide was similarly ring-opened to give a mixture of alcohols **14** and **15**. Due to competing dehydratation, all



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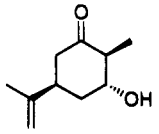

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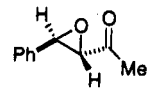
attempts to determine the optical purity of compounds **12**−**15** by converting them to Mosher's acid esters[21] failed. It is believed, though, that the chirality inherent in the commercially available (+)- and (−)-carvone is preserved throughout the epoxidation/ring-opening reaction sequence. Optical rotations of the compounds are reported in the Experimental Section.

In view of the enolate intermediate proposed in the mechanistic scheme (Figure 1), it is not surprising to find epimers at carbon 2 of the ring-opened α-substituted α,β-epoxy ketones. When compound **12** was stirred in methanolic aqueous borax buffer for 96 h, a thermodynamic 3/1 mixture of compounds **12** and **13** was obtained. The larger (9/1) product ratio obtained in the corresponding ring-opening experiment is suggesting that this reaction is kinetically controlled.

Reduction of optically pure (ee > 98%) α,β-epoxy ketone **16**[22] with the sodium salt of *N*-acetylcysteine/diphenyl diselenide afforded compound **17** with >95% ee, as determined by ^{1}H NMR spectroscopy of the corresponding Mosher's acid ester.[21]



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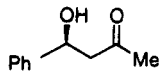

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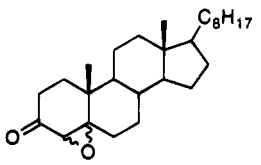
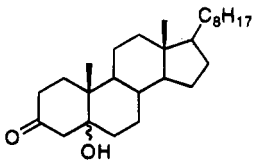
(4,5α)-Epoxy-5α-cholestan-3-one (**18a**)[23] and (4,5β)-epoxy-5β-cholestan-3-one (**18b**)[24] could not be reductively



18 a 4α,5α-epoxide
b 4β,5β-epoxide



19 a 5α-hydroxy
b 5β-hydroxy

ring-opened under our standard conditions at ambient or elevated temperature. When the catalytic reactions were run in dimethylformamide at ambient temperature, the compounds **19a** and **19b** were obtained in 72 and 52% yields, respectively. Whereas the optical rotation of compound **19a** showed good agreement with literature data, a significally lower rotation than reported was obtained for compound **19b**. Other sterically hindered α,β-epoxy ketones (pulegone epoxide and verbenone epoxide) could not be ring-opened at ambient temperature under similar conditions. At elevated temperatures the ring-opened products formed were readily dehydrated or polymerized.

By using *N*-acetylcysteine as a reducing agent, we have demonstrated, both in stoichiometric and catalytic applications, that thiol/diselenide and thiol/selenenyl sulfide exchange is useful for the generation of highly nucleophilic benzeneselenolate ion. As compared to other methods[7−15] for reductive ring-opening of α,β-epoxy ketones, the procedure described herein is probably the most convenient one.

Experimental Section

Melting points were uncorrected. ^{1}H NMR spectra, obtained at 250 MHz, were recorded in $CDCl_3$ solutions containing tetramethylsilane as the internal standard. Optical rotations were measured in chloroform solutions at 25 °C. All *c*-values are given in g/mL. Visualization of TLC plates was accomplished by treatment with an acidic ethanolic solution of vanillin. Elemental analyses were performed by Analytical Laboratories, Engelskirchen, Germany. 2-Cyclohexen-1-one epoxide,[25] isophorone epoxide,[26] *trans*-chalcone epoxide,[10] *trans*-3,4-epoxy-4-phenyl-2-butanone,[22] (3*S*,4*R*)-(+)-*trans*-3,4-epoxy-4-phenyl-2-butanone,[22] (+)- and (−)-carvone epoxide,[19] (4,5α)-epoxy-5α-cholestan-3-one,[23,27] (4,5β)-epoxy-5β-cholestan-3-one[24,27] and pulegone epoxide[28] were prepared using literature procedures. (−)-*trans*-Verbenone epoxide was prepared in analogy

(19) Mascareñas, J. L.; Sarandeses, L. A.; Castedo, L.; Mouriño, A. *Tetrahedron* **1991**, *47*, 3485.
(20) Spek, A. L.; Duisenberg, A. J. M.; van den Heuvel, H. L. A.; Rookhuizen, R. B.; Bosch, R. *Acta Cryst.* **1990**, *C 46*, 630.
(21) Mulzer, J.; Scharp, M. *Synthesis* **1993**, 615.
(22) Takeshita, M.; Akutsu, N. *Tetrahedron: Asymmetry* **1992**, *3*, 1381.
(23) Bovicelli, P.; Lupattelli, P.; Mincione, E.; Prencipe, T.; Curci, R. *J. Org. Chem.* **1992**, *57*, 2182.
(24) Plattner, von Pl. A.; Heusser, H.; Kulkarni, A. B. *Helv. Chim. Acta* **1948**, *31*, 1822.
(25) Felix, D.; Wintner, C.; Eschenmoser, A. *Org. Synth. Coll. Vol. VI*, **1988**, 679.
(26) Wasson, R. L.; House, H. O. *Org. Synth. Coll. Vol. IV*, **1963**, 552.
(27) The product was isolated using a gradient chromatography technique. Baeckström, P.; Stridh, K.; Li, L.; Norin, T. *Acta Chem. Scand., Ser. B* **1987**, *41*, 442.
(28) Katsuhara, J. *J. Org. Chem.* **1967**, *32*, 797.

with a procedure reported in the literature.[29] *N*-acetylcysteine was kindly provided by Astra Draco AB, Lund, Sweden.

Dodecyl Phenyl Selenide (1a). To a stirred solution of diphenyl diselenide (0.050 g, 0.16 mmol) and 1-iodododecane (0.15 g, 0.51 mmol) in methanol (20 mL) under argon was added rapidly a solution of *N*-acetylcysteine (0.16 g, 0.98 mmol) and sodium hydroxide (0.085 g, 2.1 mmol) in water (10 mL). After 19 h, the reaction mixture was poured into a separatory funnel containing CH_2Cl_2 (200 mL) and water (200 mL). The organic phase was washed with water (2 × 100 mL), dried, evaporated, and subjected to flash chromatography (SiO_2, hexanes) to afford 0.086 g (83%) of dodecyl phenyl selenide, identical with an authentic sample prepared by a literature procedure.[30]

4-Nitrophenyl Phenyl Selenide (1b). To a stirred solution of diphenyl diselenide (0.050 g, 0.16 mmol) and 1-chloro-4-nitrobenzene (0.039 g, 0.25 mmol) in methanol (20 mL) under argon was added rapidly a solution of *N*-acetylcysteine (0.16 g, 0.98 mmol) and borax (0.40 g, 10.5 mmol) in water (10 mL). The reaction mixture was then heated at reflux for 4 h and the product isolated as described for the preparation of compound **1a** (SiO_2, CH_2Cl_2/hexanes = 1/4). The yield of 4-nitrophenyl phenyl selenide was 0.047 g (68%), mp 54 °C (lit.[31] mp 56–8 °C).

2,4-Dinitrophenyl Phenyl Selenide (1c) was isolated in 100% yield, mp 130–2 °C (lit.[31] mp 129–30 °C), from 1-chloro-2,4-dinitrobenzene by using the procedure for compound **1b** with some modifications: After mixing of the reactants, the reaction mixture was stirred for 1 h at ambient temperature before it was subject to workup (SiO_2, CH_2Cl_2/hexanes = 1/1).

2-Nitrophenyl Phenyl Selenide (1d) was isolated in 99% yield, mp 91 °C (lit.[32] mp 92 °C), from 1,2-dinitrobenzene by using the procedure for compound **1b** with some modifications: After mixing of the reactants, the reaction mixture was stirred for 2 h at ambient temperature before it was subject to workup.

1-Phenyl-2-(phenylselenenyl)ethanol (2) and 2-phenyl-2-(phenylselenenyl)ethanol (3) were isolated in 36% and 51% yields, respectively, from styrene oxide by using the procedure for compound **1b** with some modifications: After mixing of the reactants [styrene oxide (0.050 g, 0.42 mmol)] the reaction mixture was stirred for 2 h at ambient temperature before it was subject to workup (SiO_2, CH_2Cl_2/hexanes = 1/1). The spectral characteristics of compounds **2** and **3** were in good agreement with literature data.[6a]

***trans*-2-Hydroxycyclohexyl phenyl selenide (4).** To a degassed solution of cyclohexene oxide (0.5 g, 5.1 mmol), borax (5.4 g, 14.2 mmol), and *N*-acetylcysteine (2.18 g, 13.4 mmol) in methanol/water (2/1, 180 mL) under argon was added diphenyl diselenide (0.83 g, 2.6 mmol) in one lot while a stream of argon was passed through the open system. After 24 h, the reaction mixture was diluted with water (50 mL), extracted with CH_2Cl_2 and dried over $MgSO_4$. Flash chromatography (SiO_2, EtOAc/hexanes = 1/4) afforded 1.14 g (88%) of the title compound. The spectral characteristics of the material were in good agreement with literature data.[6a]

Dodecyl phenyl sulfide (5a) was isolated in 72% yield, mp 33 °C (lit.[33] mp 33–4 °C), by using the procedure for compound **1a** with some modifications: Diphenyl diselenide was replaced by diphenyl disulfide (0.035 g, 0.16 mmol). The reaction mixture was heated at reflux for 22 h.

2,4-Dinitrophenyl phenyl sulfide (5b) was isolated in 100% yield, mp 121 °C (lit.[34] mp 121 °C), by using the procedure for the compound **1c** with some modifications: Diphenyl diselenide was replaced by diphenyl disulfide (0.035 g, 0.16 mmol).

2-Nitrophenyl phenyl sulfide (5c) was isolated in 98% yield, mp 76 °C (lit.[35] mp 80.5 °C), by using the procedure for compound **1d** with some modifications: Diphenyl diselenide was replaced by diphenyl disulfide (0.035 g, 0.16 mmol). The reaction mixture was stirred at ambient temperature for 5 h before it was subject to workup.

3-Hydroxycyclohexanone (6). To a stirred degassed solution of *N*-acetylcysteine (4.37 g, 26.8 mmol), borax (10.2 g, 26.8 mmol), and diphenyl diselenide (0.14 g, 0.45 mmol) in water (40 mL) under argon was added a solution of 2-cyclohexen-1-one epoxide (1.0 g, 8.93 mmol) in methanol (60 mL). After 10 min, the reaction mixture was saturated with NaCl, extracted with CH_2Cl_2 (3 × 50 mL), and dried over $MgSO_4$. Gradient chromatography[27] (SiO_2, hexanes/EtOAc) afforded 0.6 g (59%) of the title compound. ^1H NMR data were in good agreement with literature data.[7a]

3-Hydroxy-3,5,5-trimethylcyclohexanone (7). To a degassed solution of *N*-acetylcysteine (0.59 g, 3.6 mmol) and borax (1.45 g, 3.8 mmol) in water (15 mL) under argon was added a solution of isophorone oxide (0.19 g, 1.2 mmol) and diphenyl diselenide (0.019 g, 0.06 mmol) in methanol (20 mL) dropwise by syringe and stirring continued for 20 min. The reaction mixture was saturated with NaCl and extracted with CH_2Cl_2 and the extracts were dried over $MgSO_4$. After flash chromatography (SiO_2, CH_2Cl_2/MeOH = 19/1) 0.14 g (77%) of compound **7** was obtained as white crystals, mp 107 °C (hexanes) (lit.[15] mp 80 °C). Anal. Calcd for $C_9H_{16}O_2$: C, 69.34; H, 10.32. Found: C, 69.19; H, 10.32. ^1H NMR data were in good agreement with literature data.[7a]

1,3-Diphenyl-3-hydroxypropan-1-one (9a). To a stirred and degassed solution of *trans*-chalcone epoxide (0.45 g, 2.0 mmol), *N*-acetylcysteine (0.98 g, 6.0 mmol), and diphenyl diselenide (0.031 g, 0.1 mmol) in methanol (40 mL) under argon was added sodium hydroxide (1 mL, 6 M, 6.0 mmol) and stirring continued for 14 h. The reaction mixture was then diluted with water (20 mL), saturated with NaCl, and extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and evaporated, and the product was purified by gradient chromatography[27] (SiO_2,hexanes/EtOAc) to afford 0.41 g (90%) of compound **9a** as white crystals, mp 52 °C (hexanes) (lit.[10] mp 44–6 °C).

4-Hydroxy-4-phenylbutan-2-one (9b). Reduction of *trans*-3,4-epoxy-4-phenylbutan-2-one (**8b**) using the procedure for compound **9a** afforded the title compound in 91% yield as an oil. ^1H and ^{13}C NMR data were in good agreement with data reported in the literature.[36]

(2*S*,3*S*,5*S*)-3-Hydroxy-2-methyl-5-(1-methylethenyl)-cyclohexanone (12) and (2*R*,3*S*,5*S*)-3-hydroxy-2-methyl-5-(1-methylethenyl)cyclohexanone (13). (*S*)-(+)-Carvone epoxide **10** (0.20 g, 1.2 mmol) was ring-opened using the procedure for compound **9a** (reaction time 1.5 h). Gradient chromatography[27] (SiO_2, hexanes/EtOAc) afforded 0.18 g (86%) of compound **12**: $[\alpha]^{25}_D$ +18.5 ° (*c* = 0.01) (lit.[37] $[\alpha]^{25}_D$ +15.7 ° (*c* = 0.01)); mp 68 °C (hexanes) (lit.[37] mp 79–80 °C); ^1H NMR δ 4.80 (s, 1H), 4.78 (d, 1H), 4.32 (m, 1H), 2.88 (m, 1H), 2.47–2.58 (several peaks, 2H), 2.24–2.31 (t, 1H), 2.12–2.16 (d, 1H), 1.76 (s, 3H), 1.55 (m, 1H), 1.12 (d, 3H); ^{13}C NMR δ 210.8, 147.2, 110.0, 73.6, 49.2, 46.5, 39.9, 37.6, 20.6, 10.7. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39 H, 9.59. Found: C, 71.30; H, 9.47. Compound **13**: 0.020 g (10%) was obtained as an oil; $[\alpha]^{25}_D$ −40.8 ° (*c* = 0.01); ^1H NMR δ 4.79 (d, 1H, *J* = 0.7 Hz), 4.68 (s, 1H), 3.86 (m, 1H), 2.80 (m, 1H), 2.49–2.55 (several peaks, 1H), 2.36–2.43 (several peaks, 2H), 2.05–2.11 (several peaks, 1H), 1.90–1.94 (m, 1H), 1.74 (s, 3H), 1.15 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR δ 212.6, 146.7, 111.1, 72.7, 52.9, 43.0, 38.4, 33.8, 21.3, 13.3. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.30; H, 9.46.

(29) Klein, E; Ohloff, G. *Tetrahedron* **1963**, *19*, 1091.
(30) Detty, M. R. *J. Org. Chem.* **1980**, *45*, 274.
(31) Back, T. G.; Collins, S.; Kerr, R. G. *J. Org. Chem.* **1981**, *46*, 1564.
(32) Cullinane, N. M.; Rees, A. G.; Plummer, C. A. J. *J. Chem. Soc.* **1939**, 151.
(33) Adams, R.; Ferretti, A. *J. Am. Chem. Soc.* **1959**, *81*, 4927.
(34) Cullinane, N. M.; Davies, C. G.; Davies, G. I. *J. Chem. Soc.* **1936**, 1435.
(35) Gilman, H.; Broadbent, H. S. *J. Am. Chem. Soc.* **1947**, *69*, 2053.
(36) Hegedus, L. S.; Stiverson, R. K. *J. Am. Chem. Soc.* **1974**, *96*, 3250.
(37) Personal communication, Dr. R. B. Rookhuizen, Department of Geriatrics, Akademisch Ziekenhuis, Utrecht, Holland. Our ^1H and ^{13}C NMR data were in good agreement with those reported in the literature.[9] See also ref 20.

(2*R*,3*R*,5*R*)-3-Hydroxy-2-methyl-5-(1-methylethenyl)-cyclohexanone (14): [$[\alpha]^{25}_D$ −16.3° (*c* = 0.01); mp 68 °C (hexanes)] and **(2*S*,3*R*,5*R*)-3-Hydroxy-2-methyl-5-(1-methylethenyl)cyclohexanone (15)** [oil, $[\alpha]^{25}_D$ +40.5° (*c* = 0.01)] were obtained from (*R*)-(−)-carvone epoxide, using the procedure for compound **12**.

(4*S*)-Hydroxy-4-phenylbutan-2-one (17). Reduction of chiral epoxy ketone **16** [$[\alpha]^{25}_D$ +82.8° (*c* = 0.049), lit.[22] $[\alpha]^{25}_D$ +77.5° (*c* = 0.022; 98% ee)] using the procedure for compound **12** afforded the title compound as a colorless oil $[\alpha]^{25}_D$ −71.8° (*c* = 0.033) (lit.[38] $[\alpha]^{20}_D$ −76.4° (*c* = 0.003)]. ^{1}H NMR data were in good agreement with data reported in literature.[38] The ee (95%) was determined by preparation of the diastereomeric ester with (*R*)-(+)-MTPA-Cl.[21] [^{1}H NMR of (*R*)-(+)-MTPA-**12**: δ 7.28−7.41 (several peaks, 10H), 6.46 (dd, 1H, *J* = 9.3, 4.2 Hz), 3.42 (d, 3H), 3.21 (dd, 1H, *J* = 17.5, 9.3 Hz), 2.78 (dd, 1H, *J* = 17.4, 4.1 Hz), 2.05 (s, 3H)) and integration of the peaks at 3.50 ppm (corresponding to (*R*,*R*)-isomer) and 3.42 ppm ((*R*,*S*)-isomer)].

5α-Hydroxy-5α-cholestan-3-one (19a). To a stirred and degassed solution of (4,5α)-epoxy-5α-cholestan-3-one (**18a**) (0.203 g, 0.5 mmol), *N*-acetylcysteine (0.25 g, 1.52 mmol), and diphenyl diselenide (0.008 g, 0.026 mmol) in DMF (40 mL) under argon was added sodium hydroxide (0.25 mL 6M, 1.52 mmol) in one lot and stirring continued for 72 h. The solvents were evaporated under vacuo and the residue was subject to gradient chromatography[27] (SiO_2, hexanes/EtOAc) to afford 0.105 g (52%) of compound **19a** as white crystals: $[\alpha]^{25}_D$ +42.6° (*c* = 0.053) (lit.[39] $[\alpha]^{25}_D$ +41.4° (*c* = 0.034)); mp 222−7 °C (hexanes) (lit.[39] mp 219−23 °C); ^{1}H NMR δ 2.67(d, 1H, *J* = 15.1 Hz), 2.36 (m, 2H), 2.15−0.85 (several peaks, 40H), 0.68 (s, 3H); ^{13}C NMR δ 210.9, 56.2, 56.0, 51.9, 46.0, 42.6, 39.9, 39.5, 39.2, 37.9, 36.1, 35.8, 34.8, 34.4, 32.7, 28.2, 28.0, 26.2, 24.2, 23.9, 22.8, 22.6, 21.5, 18.5, 15.8, 12.1.

5β-Hydroxy-5β-cholestan-3-one (19b). To a stirred and degassed solution of (4,5β)-epoxy-5β-cholestan-3-one (**18b**) (0.2 g, 0.50 mmol), *N*-acetylcysteine (0.24 g, 1.5 mmol) and diphenyl diselenide (0.0077 g, 0.025 mmol) in DMF (25 mL) under argon was added sodium hydroxide (0.25 mL, 6 M, 1.5 mmol) in one lot and stirring continued for 20 h. Workup as described for compound **19a**, followed by gradient chromatography[27] (SiO_2, hexanes/EtOAc), afforded 0.144 g (72%) of compound **19b** as white crystals, $[\alpha]^{25}_D$ +46° (*c* = 0.029) (lit.[24] $[\alpha]^{25}_D$ +63.1° (*c* = 0.011)); mp 154−5 °C (hexanes) (lit.[24] mp 151−2 °C); ^{1}H NMR δ 3.05 (d, 1H, *J* = 15.1 Hz), 2.4−0.85 (several peaks, 42 H), 0.68 (s, 3H); ^{13}C NMR δ 211.5, 78.6, 56.5, 56.1, 49.3, 43.8, 42.5, 40.1, 39.8, 39.5, 37.3, 36.3, 36.1, 35.7, 34.7, 31.1, 29.1, 28.2, 28.0, 24.1, 23.8, 22.8, 22.5, 21.7, 18.6, 16.1, 12.0. Anal. Calcd for $C_{27}H_{46}O_2$: C, 80.54; H, 11.51. Found: C, 80.31; H, 11.60.

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(38) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663.

(39) Plattner, von Pl. A.; Fürst, A.; Koller, F.; Lang, W. *Helv. Chim. Acta* **1948**, *31*, 1455.