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Bertozzi, F.; Crotti, P.; Macchia, F.; Pineschi, M.; Arnold, L.A.; Feringa, B.L.

Published in:
Organic letters

DOI:
[10.1021/ol005584o](https://doi.org/10.1021/ol005584o)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2000

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Citation for published version (APA):

Bertozzi, F., Crotti, P., Macchia, F., Pineschi, M., Arnold, L. A., & Feringa, B. L. (2000). A new catalytic and enantioselective desymmetrization of symmetrical methylenedicycloalkene oxides. *Organic letters*, 2(7), 933 - 936. <https://doi.org/10.1021/ol005584o>

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Supporting Information for

A New Catalytic and Enantioselective Desymmetrization of Symmetrical Methylidene Cycloalkene Oxides.

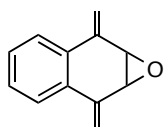
Fabio Bertozzi, Paolo Crotti, Franco Macchia, Mauro Pineschi*
*Dipartimento di Chimica Bioorganica e Biofarmacia, Università di Pisa,
Via Bonanno 33, 56126 Pisa, Italy*

Alexander Arnold and Ben L. Feringa*
*Department of Organic and Molecular Inorganic Chemistry, University of
Groningen, Nijenborgh 4, NL9747 AG Groningen, The Netherlands.*

General. All reactions were conducted in flame dried glassware with magnetic stirring under an atmosphere of argon. Toluene and diethyl ether were distilled from sodium/benzophenone ketyl and stored under argon. THF and Diisopropylamine were distilled from LiAlH₄ and CaH₂ respectively and stored under argon. Et₂Zn (1.1 M solution in toluene), EtMgCl (2.0 M solution in THF) and Butyllithium (1.6 M solution in hexanes) were purchased from Aldrich. Methyl-triphenyl-phosphonium-bromide (98%) and 2-Methyl-1,3-cyclopentanedione (99%) were purchased from Aldrich. Analytical TLC were performed on Alugram SIL G/UV254 silica gel sheets (Macherey-Nagel) with detection by 0.5% phosphomolybdic acid solution in 95% EtOH. Silica gel 60 (Macherey-Nagel 230-400 mesh) was used for flash chromatography. Solvents for extraction and chromatography were HPLC grade.

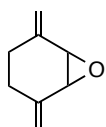
Optical rotation were measured on a Perkin-Elmer 241 digital polarimeter with a 1 dm cell. ¹H NMR spectra were recorded on a Bruker AC-200 spectrometer on CDCl₃ solution. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard (deuteriochloroform: δ 7.26). ¹³C NMR spectra were recorded on a Bruker AC-200 (50 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm downfield from tetramethylsilane with the solvent resonance as the internal standard (deuteriochloroform: δ 77.7). Gas chromatography was performed on a Perkin-Elmer 8420 apparatus (FI detector) using a Chromopak fused silica 25 m x 0.25 mm column, coated with CP-Cyclodextrin-B-236-M-19). In all cases, the

injector and detector temperature was 250°C and a 1.8 mL / min helium flow was employed. Analytical high performance liquid chromatography (HPLC) was performed on a Waters 600E equipped with a Waters 990 photodiode array detector using a Daicel Chiralcel OD-H column.



1,4-Dimethylidene-2,3-epoxy-2,3-dihydro-naphthalene (8).

Typical Procedure for Wittig Olefination. Accordingly to a previously described procedure,¹ to a stirring suspension of MePh₃PBr (8.21 g, 23 mmol) in anhydrous THF (20 ml) is added by a cannula at 0°C a solution of LDA (23 mmol) in anhydrous THF (10 ml). After the reaction mixture was stirred for 1.5 h at 0°C, 2,3-epoxy-2,3-dihydro-1,4-naphthoquinone² (1.0 g, 5.75 mmol) in anhydrous THF (5 ml) was added and the mixture was vigorously stirred for 1.5 h at room temperature. The mixture was quenched with saturated aqueous NH₄Cl and extracted with petroleum ether. Evaporation of the dried (MgSO₄) organic phase gave a crude product which was subjected to chromatography (SiO₂) with 20% EtOAc : hexanes to give 0.745 g (77%) of pure **8**, as a solid. M.p.=37-39°C. ¹H NMR δ 7.45-7.50 (m, 2H, Ar-H), 7.22-7.27 (m, 2H, Ar-H), 5.67 (s, 2H, methylidene-H), 5.45 (s, 2H, methylidene-H), 3.95 (s, 2H, C₂-H and C₃-H). ¹³C NMR δ 141.29, 131.81, 129.48, 126.04, 116.02, 57.98. Anal. Calcd. for C₁₂H₁₀O: C, 84.67; H, 5.93. Found : C, 84.38; H, 5.96.



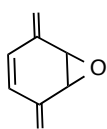
3,6-Dimethylidene-1,2-epoxy-cyclohexane (7).

Following the above described typical procedure 2,3-epoxy-cyclohexan-1,4-dione³ (0.160 g, 1.27 mmol) in anhydrous THF (3 ml) was added dropwise at 0°C to a suspension of Ph₃P=CH₂ (4.0 eq) in anhydrous THF (8 ml). After 1 h at room temperature the usual work-up afforded a crude product which was subjected to chromatography (SiO₂) with 8% diisopropyl ether: petroleum ether to give 72 mg of pure **7** (47%) as a liquid. ¹H NMR δ 5.26 (s, 2H, methylidene-H), 5.14 (s, 2H, methylidene-H), 3.64 (s, 2H, C₁-H and C₂-H), 2.32-2.47 (m, 2H, one of C₄-H₂ and one of C₅-H₂), 2.07-2.23 (m, 2H, one of C₄-H₂ and one of C₅-H₂). ¹³C NMR δ 142.65, 116.63, 58.18, 29.28. Anal. Calcd. for C₈H₁₀O: C, 78.64; H, 8.26. Found : C, 78.37; H, 8.39.

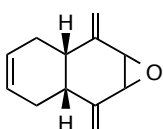
1) Marino, J.P.; Abe, H. *Synthesis*, **1980**, 872.

2) Alder, K.; Flock, F.H.; Beumling, H. *Chem. Ber.* **1960**, 93, 1896.

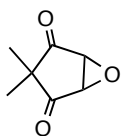
3) Abbulut, N.; Balci, M. *J. Org. Chem.* **1988**, 53, 3338.



3,6-Dimethylidene-1,2-epoxy-4-cyclohexene (6). Following the typical procedure, 2,3-epoxy-1,4-benzoquinone² (0.180 g, 1.47 mmol) in anhydrous THF (4 ml) was added dropwise at 0°C to a suspension of Ph₃P=CH₂ (4.0 eq) in anhydrous THF (10 ml). After 45 min at room temperature the usual work-up afforded a crude product which was subjected to chromatography (SiO₂) with 8% diisopropyl ether: petroleum ether to give 67 mg of pure **6** (39%), as a liquid. ¹H NMR δ 6.09 (s, 2H, C₄-H and C₅-H), 5.49 (s, 2H, methylidene-H), 5.38 (s, 2H, methylidene-H), 3.79 (s, 2H, C₁-H and C₂-H). ¹³C NMR δ 139.09, 127.02, 120.0, 56.01. Anal. Calcd. for C₈H₈O: C, 79.96; H, 6.72. Found : C, 79.77; H, 6.69.



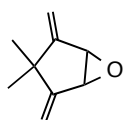
1,4-Dimethylidene-2,3-epoxy-cis-2,3,4a,5,8,8a-hexahydronaphthalene (9). Following the typical procedure 2,3-epoxy-2,3,4a,5,8,8a-hexahydro-1,4-naphtoquinone⁴ (0.712 g, 4.0 mmol) in anhydrous THF (15 ml) was added dropwise at 0°C to a suspension of Ph₃P=CH₂ (4.0 eq) in anhydrous THF (30 ml). After 1.5 h at room temperature the usual work-up afforded a crude product which was subjected to chromatography (SiO₂) with 8% diisopropyl ether: petroleum ether to give 397 mg of pure **9** (57%) as a liquid. ¹H NMR δ 5.52-5.58 (m, 2H, C₆-H and C₇-H), 5.37 (s, 2H, methylidene-H), 5.10 (s, 2H, methylidene-H), 3.67 (s, 2H, C₂-H and C₃-H), 2.66-2.72 (m, 2H, C_{4a}-H and C_{8a}-H), 1.94-2.04 (m, 4H, C₅-H₂ and C₈-H₂). ¹³C NMR δ 144.43, 125.46, 117.23, 58.00, 36.08, 28.87. Anal. Calcd. for C₁₂H₁₄O: C, 82.71; H, 8.1. Found : C, 82.93; H, 8.26.



2,2-Dimethyl-4,5-epoxy-cyclopentan-1,3-dione (16). Typical Procedure for Alkaline Epoxidation. According to a previously described procedure,² to a solution of 2,2-dimethyl-4-cyclopenten-1,3-dione⁵ (400 mg, 3.22 mmol) in acetone (10 ml), at 0°C, under vigorous stirring, were added Na₂CO₃ (20%) (120 mg, 1.12 mmol) and H₂O₂ (30%) (1.1 ml, 9.67 mmol). After 1.5 h at room temperature the reaction was quenched with Na₂S₂O₃ (10%) and H₂O (reaction kept cold with ice-water bath), and gave 348 mg of pure **16** (78%), as a pale yellow solid. M.p.= 37-39°C. ¹H NMR δ 3.94 (s, 2H, C₄-H and C₅-H), 1.27 (s, 3H, one of C₂-CH₃), 1.11 (s, 3H, one of C₂-CH₃). ¹³C NMR δ 207.57, 57.52, 48.31, 24.05, 20.53. Anal. Calcd. for C₇H₈O₃: C, 59.98; H, 5.76. Found : C, 59.74; H, 5.59.

4) Herz, W.; Iyer, V.S.; Nair, M.G. *J. Org. Chem.* **1975**, *40*, 3519.

5) Agosta, W.C.; Smith, A.B. III. *J. Org. Chem.* **1970**, *35*, 3856.



4,4-Dimethyl-1,2-epoxy-3,5-dimethylidene-cyclopentane (10).

Following the typical procedure for Wittig olefination, 5,5-Dimethyl-2,3-epoxy-cyclopentan-1,4-dione **16** (0.348 g, 2.48 mmol) in anhydrous THF (10 ml) was added dropwise at 0°C to a suspension of Ph₃P=CH₂ (4.0 eq) in anhydrous THF (20 ml). After 1 h at room temperature the reaction was quenched with H₂O and the usual work-up afforded a crude product which was subjected to chromatography (SiO₂) with petroleum ether:diethyl ether:Et₃N (95:5:1) to give 158 mg of **10** (47%), as an oil (contaminated with 4% PPh₃). ¹H NMR δ 5.32 (s, 2H, methylidene-H), 5.12 (s, 2H, methylidene-H), 3.91 (s, 2H, C₁-H and C₂-H), 1.17 (s, 3H, one of C₄-CH₃), 1.15 (s, 3H, one of C₄-CH₃). ¹³C NMR δ 156.57, 110.71, 61.36, 42.96, 33.66, 28.61. Anal. Calcd. for C₉H₁₂O: C, 79.36; H, 8.89. Found : C, 79.55; H, 8.81.

Determination of Absolute Configurations. The absolute configurations of all 1,4-addition products **4**, **17-20** were determined on compound **4** by means of the known diastereofacial selectivity of 1-substituted allylic alcohols with titanium/tartrate/TBHP (Sharpless kinetic resolution AE).⁶ This inherently reliable procedure had been applied quite recently to the related (±)-3-methyl-2-cyclohexen-1-ol to give optically active products with a known absolute configuration.⁷ Also the comparison of the optical rotation of optically active seudenol [*R*-(+) and *S*-(-)-3-methyl-2-cyclohexen-1-ol],⁸ an aggregation pheromone from *Dendroctonus pseudotsugae*, bearing a methyl instead of propyl in the 3 position of compound **4**, gave us the same indication obtained with the kinetic resolution strategy (see below).

Titanium Tartrate Catalytic Asymmetric Epoxidation of 4. Following the original procedure,⁹ an oven-dried 25 mL two-necked round-bottomed flask was charged with 30 mg of 4 Å powdered activated molecular sieves and with 2 mL of dry CH₂Cl₂ under an argon atmosphere. The flask was cooled to -20°C and *D*-(-)-DIPT (10 mg dissolved in a minimum amount of CH₂Cl₂, 6 mol%), Ti(*O-i*-Pr)₄ (10.6 μl, 5 mol%) and anhydrous TBHP (0.47 mL of a 3.0 M solution in isooctane, 2 eq.) were added sequentially with stirring. The resulting mixture was stirred at -20°C for 30 min. and (±)-3-propyl-2-cyclohexen-1-ol (**4**) (100 mg, 0.714 mmol) dissolved in 0.5 mL of CH₂Cl₂ was then added dropwise and the reaction temperature was maintained between -20°C and -25°C. The reaction was monitored by GC and quenched (Ferrous sulfate/tartaric acid work-up) after 2 h (60% conversion). The

6) Johnson, R.A.; Sharpless, K.B. In *Catalytic Asymmetric Synthesis*; Ojima, I, Ed.; VCH: New York, **1993**; pp 104-108.

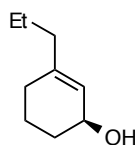
7) Brown, S.M.; Davies, S.G.; Sousa, J.A.A. *Tetrahedron: Asymm.* **1991**, *2*, 511.

8) Mori, K.; Tamada, S.; Uchida, M.; Mizumachi, N.; Tachibana, Y.; Matsui, M. *Tetrahedron* **1978**, *34*, 1901.

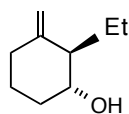
9) Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H.; Sharpless, K.B. *J. Am. Chem. Soc.* **1988**, *109*, 5765.

enantiomeric excess of unreacted **4** (35%) was determined by chiral GC (CP-cyclodex- β -column), programmed temperature rate: 100°C/ 7.0 min + 3°/min up to 120°C, *S*-(-) (major) t_R 17.79 min, *R*-(+) (minor) t_R 18.36 min. The same reaction was also carried out with enantiomeric *L*-(+)-DIPT, affording *R*-(+) as the major enantiomer of the unreacted substrate **4**.

General Procedure for the Enantioselective Ring-Opening of Vinyloxiranes **3 and **6-10** with Et₂Zn.** A solution of Cu(OTf)₂ (2.70 mg, 0.0075 mmol) and chiral ligand (*S,S,S*)-**1** or (*S,R,R*)-**2** (8.1 mg, 0.015 mmol) in anhydrous toluene (1.5 mL) was stirred at r.t. for 40 min. The colorless solution was cooled to -70 °C, additioned with a solution of the epoxide (0.5 mmol) in toluene (0.5 mL) and then with 0.68 mL (0.75 mmol) of a 1.1M solution of Et₂Zn in toluene (0.23 mL for the **kinetic resolution protocol**, see Table 1). For all reactions, the temperature was allowed to warm slowly to 0°C (3 h) and the mixture was quenched with saturated aqueous NH₄Cl (3.0 mL). Extraction with Et₂O (2 x 20 mL) and evaporation of the dried (MgSO₄) organic phase gave a crude product which was subjected to chromatography (SiO₂).



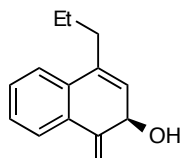
***S*-(*-*)-3-Propyl-2-cyclohexen-1-ol (**4**).** The general procedure was followed, in accordance with a kinetic resolution protocol, employing 55 mg of racemic vinyloxirane **3**¹⁰ (0.5 mmol), Cu(OTf)₂ (2.70 mg, 0.0075 mmol), chiral ligand **2** (8.1 mg, 0.015 mmol) and Et₂Zn (0.23 mL). The usual work-up afforded a crude reaction mixture which was subjected to chromatography (SiO₂) with 10% EtOAc: hexanes to give 18 mg of pure **4** (76% based on unreacted **3**), as a liquid. TLC (15% EtOAc/hexanes) R_f =0.14. $[\alpha]_D$ =-45.9 (c =1.08, CHCl₃). ¹H NMR δ 5.41-5.49 (m, 1H, C₂-H), 4.15-4.22 (m, 1H, CH-OH), 1.90-1.98 (m, 4H), 1.37-1.84 (m, 6H), 0.88 (t, 3H, J =7.32 Hz, C₃-H₃). ¹³C NMR δ 143.15, 124.47, 66.69, 40.41, 32.73, 29.20, 21.35, 19.84, 14.53. Anal. Calcd. for C₉H₁₆O: C, 77.08; H, 11.51. Found : C, 77.29; H, 11.62. The enantiomeric excess of **4** (85%) was determined by chiral GC (CP-cyclodex- β -column), programmed temperature rate: 100°C/ 7.0 min + 3°/min up to 120°C, *S*-(-) (major) t_R 17.79 min, *R*-(+) (minor) t_R 18.36 min.



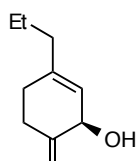
3-Methylidene-2-ethyl-1-cyclohexanol (5**).** The first eluting fractions of the above flash chromatography afforded 3 mg of pure **5** (9% based on unreacted **3**). TLC (15% EtOAc/hexanes) R_f =0.20. ¹H NMR δ 4.83-4.87 (m, 1H, methylidene-H), 4.69-4.74 (m, 1H, methylidene-H), 3.65-3.74 (m, 1H, CH-

10) Tanis, S.P.; Herrinton, P.M. *J. Org. Chem.* **1985**, *50*, 3988.

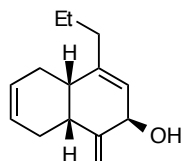
OH), 2.02-2.13 (m, 1H, C₂-H), 1.44-1.85 (m, 8H, -CH₂-), 0.86 (t, 3H, *J*=7.3 Hz, -CH₃). ¹³C NMR δ 148.5, 111.6, 73.1, 54.1, 32.5, 30.4, 23.5, 23.3, 12.7.



R-(-)-4-propyl-1-methylidene-(2H)-2-naphthol (17) The general procedure was followed employing 85 mg of symmetrical vinyloxirane **8** (2.0 mmol), Cu(OTf)₂ (10.8 mg, 0.03 mmol), chiral ligand **1** (32.4 mg, 0.06 mmol) and Et₂Zn (2.70 mL). The usual work-up afforded a crude reaction mixture which was subjected to chromatography (SiO₂) with 20% EtOAc: hexanes, to give 366 mg of pure **17** (92%), as a liquid. [α]_D²⁰ = -172.8 (*c* = 1.31, CHCl₃). ¹H NMR δ 7.47-7.51 (m, 1H, Ar-H), 7.11-7.21 (m, 3H, Ar-H), 5.86 (d, 1H, *J* = 4.4 Hz, C₃-H), 5.48 (s, 1H, methylidene-H), 5.34 (s, 1H, methylidene-H), 4.63-4.75 (m, 1H, CH-OH), 2.28-2.38 (m, 2H, C₁-H₂), 1.34-1.53 (m, 2H, C₂-H₂), 0.87 (t, 3H, *J* = 7.32 Hz, C₃-H₃). ¹³C NMR δ 138.43, 133.40, 129.01, 128.26, 126.79, 125.86, 124.13, 114.80, 107.44, 69.29, 35.25, 21.85, 14.57. Anal. Calcd. for C₁₄H₁₆O: C, 83.95; H, 8.06. Found: C, 83.77; H, 8.04. The enantiomeric excess (66%) was determined on the purified product (SiO₂) by chiral HPLC (Daicel Chiralcel OD-H column), hexanes / 2-propanol 97:3, flow rate 0.5 mL/min, *R*-(-) t_R 19.98, *S*-(+) t_R 20.94 min.

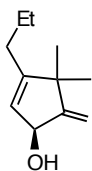


R-(-)-3-propyl-6-methylidene-2-cyclohexen-1-ol (19) The general procedure was followed employing 56 mg of symmetrical vinyloxirane **7** (0.46 mmol), Cu(OTf)₂ (2.49 mg, 0.0069 mmol), chiral ligand **1** (7.5 mg, 0.0138 mmol) and Et₂Zn (0.63 mL). The usual work-up afforded a crude reaction mixture which was subjected to chromatography (SiO₂) with 20% EtOAc: hexanes, to give 63 mg of pure **19** (90%), as a liquid. [α]_D²⁰ = -110 (*c* = 0.96, CHCl₃). ¹H NMR δ 5.47-5.51 (m, 1H, C₂-H), 5.01 (s, 1H, methylidene-H), 4.89 (s, 1H, methylidene-H), 4.48-4.55 (m, 1H, CH-OH), 2.40-2.53 (m, 1H), 2.21-2.33 (m, 1H), 1.92-2.17 (m, 4H), 1.34-1.52 (m, 2H, C₂-H₂), 0.88 (t, 3H, *J* = 7.32 Hz, C₃-H₃). ¹³C NMR δ 149.41, 143.63, 124.11, 109.06, 69.85, 40.02, 31.76, 29.82, 21.37, 14.52. Anal. Calcd. for C₁₀H₁₆O: C, 78.89; H, 10.6. Found: C, 78.56; H, 10.48. The enantiomeric excess (97%) was determined by chiral GC (CP-cyclodex-β-column), programmed temperature rate: 100°C/3.0 min + 3°/min up to 120°C, *S*(+) t_R 17.89, *R*(-) t_R 18.09 min.



(4a*S*, 8a*R*, 2*R*)-(+)-4-propyl-1-methylidene-*cis*-,5,4a,8,8a-tetrahydro-(2H)-naphthalen-2-ol (18) The general procedure was followed employing 87 mg of symmetrical vinyloxirane **9** (0.5 mmol), Cu(OTf)₂ (2.70 mg, 0.0075 mmol), chiral ligand **1** (8.1 mg, 0.015 mmol) and Et₂Zn (0.68 mL). The usual work-up afforded a crude reaction mixture

which was subjected to chromatography (SiO₂) with 20% EtOAc: hexanes, to give 80 mg of pure **18** (78%), a solid. M.p.= 35-38°C. [α]_D=+20.96 (*c*=1.04, CHCl₃). ¹H NMR δ 5.52-5.75 (m, 2H, C₆-H and C₇-H), 5.48 (d, 1H, *J*= 4.0 Hz, C₃-H), 5.15 (s, 1H, methylenide-H), 4.84 (s, 1H, methylenide-H), 4.44 (d, 1H, *J*= 3.9 Hz, CH-OH), 2.82-2.92 (m, 1H), 1.93-2.42 (m, 7H), 1.33-1.55 (m, 2H, C₂'-H₂), 0.91 (t, 3H, *J*= 7.33 Hz, C₃'-H₃). ¹³C NMR δ 149.69, 149.08, 125.89, 125.17, 122.08, 111.51, 70.74, 39.14, 37.76, 34.32, 28.37, 27.07, 21.38, 14.48. Anal. Calcd. for C₁₄H₂₀O: C, 82.29; H, 9.87. Found : C, 82.12; H, 9.86. The enantiomeric excess of **18** (71%) was determined by chiral HPLC analysis (Daicel Chiralcel OD-H column), hexanes / 2-propanol 99:1, flow rate 0.5 mL/min, t_R 7.14 min (major), t_R 8.89 min (minor) on the corresponding (*R*)-MTPA ester obtained using a three fold excess of the corresponding (*R*)-MTPA chloride in anhydrous pyridine in the presence of catalytic amounts of DMAP.



***R*-(-)-4,4-Dimethyl-3-propyl-5-methylenide-2-cyclopenten-1-ol (20)** The general procedure was followed employing 34 mg of symmetrical vinyloxirane **10** (0.25 mmol), Cu(OTf)₂ (1.35 mg, 0.0037 mmol), chiral ligand **1** (4.1 mg, 0.0075 mmol) and Et₂Zn (0.34 mL). Usual work-up afforded a crude reaction mixture which was subjected to chromatography (SiO₂) with 10% EtOAc: hexanes, to give 33 mg of pure **20** (80%), as a liquid. [α]_D=-125.9 (*c*=0.52, CHCl₃). ¹H NMR δ 5.44-5.49 (m, 1H, C₂-H), 5.28 (d, 1H, *J*=1.71 Hz, methylenide-H), 5.09 (d, 1H, *J*=1.71 Hz, methylenide-H), 4.96-5.04 (m, 1H, CH-OH), 1.92-2.02 (m, 2H, C₁'-H₂), 1.47-1.65 (m, 2H, C₂'-H₂), 1.16 (s, 3H, one of C₄-CH₃), 1.08 (s, 3H, one of C₄-CH₃), 0.96 (t, 3H, *J*=7.32 Hz, C₃'-H₃). ¹³C NMR δ 164.42, 156.73, 123.96, 107.93, 48.73, 30.39, 29.30, 28.49, 28.35, 21.39, 14.92. Anal. Calcd. for C₁₁H₁₈O: C, 79.45; H, 10.92. Found : C, 79.28; H, 10.98. The enantiomeric excess (85%) was determined after chromatography (SiO₂) by chiral GC (CP-cyclodex- β -column), isothermal 110°C, *R*-(-) t_R 33.55, *S*-(+) t_R 35.44 min.

Synthesis of Racemic S_N2' (Conjugate) Adducts 4, 17-20. To a stirring suspension of CuCN (9.0 mg, 0.1 mmol) in anhydrous Et₂O (0.5 mL), at -40°C, was added dropwise EtMgCl (2.0 M in THF) (0.38 mL, 0.75 mmol). The heterogeneous mixture was allowed to stir for 30 min at the same temperature and was then cooled up to -65°C. A solution of the vinyloxirane (0.5 mmol) in Et₂O (0.5 mL) was slowly added and the resulting mixture was allowed to warm to 0°C. The reaction was followed with analytical TLC and was quenched at 0°C with saturated aqueous NH₄Cl. Extraction with Et₂O and evaporation of the dried (MgSO₄) organic phase gave almost exclusively the corresponding racemic S_N2' adduct **4, 17-20** for all the employed vinyloxiranes.

