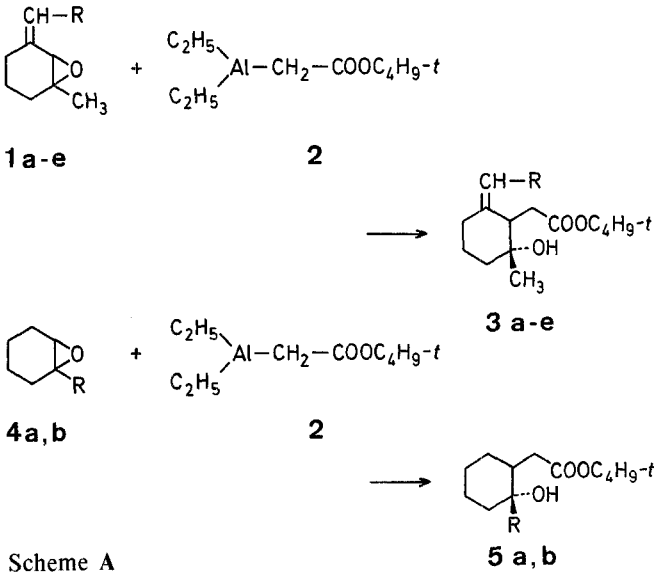
The Regio- and Stereoselective Addition of *t*-Butoxycarbonylmethyl-diethyl-alane to 1-Alkylidene-2,3-epoxy-3-methylcyclohexanes

Melean VISNICK, Lucjan STREKOWSKI, Merle A. BATTISTE*

Department of Chemistry, University of Florida, Gainesville, Florida 32611, U.S.A.

The synthetic value of the stereoselective ring-opening of oxiranes with nucleophiles, particularly organometallic reagents, is well recognized[1]. The mode of addition of organometallic reagents to vinyloxiranes, however, depends markedly on the nature of the metal species. Organolithium and Grignard reagents for the most part react randomly with vinyloxiranes, furnishing a mixture of 1,2- and 1,4-addition adducts[2–5]. Organocopper reagents, on the other hand, are more selective in their reactivity, affording 1,4-addition products preferentially and sometimes exclusively[6]. The exclusive conjugate alkylation of vinyloxiranes with dimethyl malonate, in the presence of palladium(0) catalysts, is of closely related synthetic interest[7].

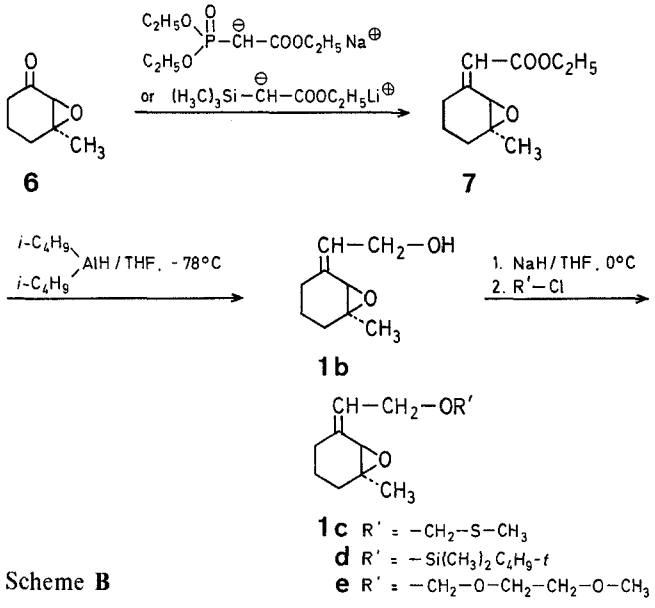
In this report we describe a highly efficient and general route to *trans*-2-hydroxy-6-alkylidenecyclohexane-acetate derivatives **3a–e** by the direct addition of *t*-butoxycarbonylmethyl-diethyl-alane **(2)** to the oxirane ring in compounds of general structure **1a–e** (Scheme **A**). Alane **2**, conveniently prepared *in situ* by the action of diethylaluminum chloride on *t*-butyl lithioacetate[8], has been used before with limited success in the opening of cyclohexene oxide **4a** (R = H) and similar saturated systems[9]. The hydroxy esters **3a–e** are important precursors to several substituted *trans*-7a-methyl-2(3*H*)-hexahydrobenzofuranone systems required for other purposes[10].



Scheme A

With the exception of *exo*-methyleneoxirane **1a** (R = H) which was prepared by the Wittig reaction of triphenylphosphonium methylid with 3-methyl-2,3-epoxycyclohexanone **(6)**[6], the remaining oxiranes **1b–e** were synthesized as outlined in Scheme **B**. Condensation of triethyl sodiophosphonoacetate or ethyl lithio-(trimethylsilyl)-acetate with ketone **6** furnished the ester **7** as a mixture of (*Z*)- and (*E*)-isomers. Interestingly, the Peterson olefination reagent affords predominantly the (*Z*)-isomer whereas the Wittig-Horner reagent is nonselective in its reactivity. This appears to be a general reaction for 2,3-epoxycyclohexanones[11]. Without separation, this mixture of esters **7** was reduced to the corresponding allylic alcohol **1b**

using diisobutylaluminum hydride. A small amount of one of the isomers of ester **7** was recovered from this reduction and assigned the (*Z*)-stereochemistry based on the 1.5 ppm lower field resonance for its oxirane proton, which is in agreement with published data for analogous systems[12]. As a result, the (*E*/*Z*)-stereochemistry for compounds **1b–e** and **3b–e** could be assigned unambiguously once samples of ester **7** enriched in the (*Z*)-isomer were carried through the reduction-protection sequence. Subsequent protection of the hydroxy function in **1b**, with groups commonly used in organic synthesis[13], afforded the allylic ethers **1c–e**.



Scheme **B**

The reaction of alkylideneoxiranes **1a–e** with alane **2** afforded hydroxy esters **3a–e** as the sole regio- and stereoisomeric products with no conjugate addition adducts, or products derived from *cis*-1,2-addition to the alkylideneoxiranes being detected. The stereochemistry of hydroxy esters **3a–e** was not readily established by their spectral properties; however, in each case the *trans*-stereochemistry was confirmed by subsequent conversion to a hexahydro-2(3*H*)-benzofuranone derivative of known configuration[10,14].

As revealed in Table 1 there is a remarkable solvent effect on the yield and facility of the alane-promoted oxirane ring-opening reaction for unsaturated oxiranes **1a** and **1e**. The effect of ether solvents was equally pronounced for the saturated oxirane **4b** although the reaction was considerably more sluggish. While the nature of this solvent effect is not clear, one would anticipate that in tetrahydrofuran and dimethoxyethane the aluminum reagent is monomeric and highly solvated, whereas in the hydrocarbon toluene an aggregated species is more likely[15]. The aggregated reagent could encounter steric difficulties in the delivery of the acetate group to the oxirane, thus allowing side-reactions, such as isomerization or polymerization of the oxirane, to compete with the Lewis acid-catalyzed *trans*-1,2-addition pathway. A related but less selective example of a solvent mediated ring-opening of a vinyloxirane by an alkynyl-dialkylalane has been previously reported[16].

(*Z*)- and (*E*)-1-(Ethoxycarbonylmethylene)-2,3-epoxy-3-methylcyclohexane (7):

Method A using triethyl sodiophosphonoacetate: Sodium hydride (50% dispersion in mineral oil, 700 mg, 15.2 mmol) is washed with *n*-pentane (3 × 10 ml), and dried under a stream of nitrogen. To the dry hydride slurried in tetrahydrofuran (20 ml) is added, dropwise, triethyl phosphonoacetate (3.02 ml, 15.2 mmol) in tetrahydrofuran (20 ml). During addition the reaction temperature is maintained at 10–20 °C and afterwards stirring is continued for an additional 15 min at 20 °C. 3-Methyl-2,3-epoxycyclohexanone (**6**; 1.02 g, 15.2 mmol) in tetrahydrofuran (15 ml) is added over the next 15 min while maintaining the reaction temperature just below 15 °C. The reaction mixture is warmed to room temperature, quenched with water (50 ml), and extracted with ether (4 × 100 ml). The combined ether extracts are dried with magnesium sulfate, filtered, and concentrated in vacuo. Distillation of the yellow residue affords a 55 : 45 mixture of (*Z*)-**7** and (*E*)-**7**; yield: 2.5 g (80%); b.p. 80–82 °C/0.2 torr.

Method B using ethyl lithio-(trimethylsilyl)-acetate: To a solution of diisopropylamine (5.56 ml, 4.01 g, 39.7 mmol) in tetrahydrofuran (60 ml) is added a 2.1 molar solution of *n*-butyllithium in hexane (18.9 ml, 39.7 mmol) at 0 °C under a nitrogen atmosphere. The solution of lithium diisopropylamide is stirred at 0 °C for 10 min, cooled to −78 °C, and treated dropwise with ethyl (trimethylsilyl)-acetate. The resultant mixture is stirred at −78 °C for 30 min, treated dropwise with 3-methyl-2,3-epoxycyclohexanone (**6**; 5 g, 39.7 mmol), and then stirred for an additional 2 h at −78 °C. On warming to room temperature the reaction mixture is quenched with a saturated aqueous solution of ammonium chloride (200 ml) and extracted with ether (3 × 150 ml). Work-up, as described above, gives a 78 : 22 mixture of (*Z*)-**7** and (*E*)-**7**; yield: 6.04 g (78%).

Table 1. Reaction of Oxiranes **1a–e** and **4a, b** with *t*-Butoxycarbonylmethyl-diethyl-alane (**2**)[a]: Scheme **A**

Oxirane	R	Product	Reaction Conditions Solvent/Temperature/Time	Yield[b] [%]
1a	H	**3a**	toluene/+25 °C/2 h	24
			tetrahydrofuran/−55 °C/0.5 h	94
1b	$-CH_2OH$	**3b**	tetrahydrofuran/−40 °C/1 h	72
1c	$-CH_2OCH_2SCH_3$	**3c**	tetrahydrofuran/−55 °C/1 h	87
1d	$-CH_2OSi(CH_3)_2C_4H_9$-*t*	**3d**	tetrahydrofuran/−50 °C/1 h	82
			dimethoxyethane/−50 °C/1 h	84
1e	$-CH_2OCH_2OCH_2CH_2OCH_3$	**3e**	toluene/+25 °C/2 h	25
			dimethoxyethane/−45 °C/1 h	83
4a	H	**5a**	toluene/−30 °C/6 h	34[c]
			toluene/+25 °C/6 h	68[c]
4b	CH_3	**5b**	toluene/+25 °C/8 h	5
			dimethoxyethane/+25 °C/4 h	45

[a] The attempted condensation of *t*-butyl lithioacetate with **1a**, **1c**, and **4b** (tetrahydrofuran/−40 °C to +25 °C/8 h) afforded only recovered starting material.

[b] Yields of products isolated by flash chromatography[17].

[c] Data from Ref.[9].

Table 2. Spectral Data of Compounds 7 and **1b–e**

Compound No.	Molecular[a] formula	b.p. [°C]/ torr	I.R. (film)[b] ν [cm^{-1}]	Isomer	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm][c]
7	$C_{11}H_{16}O_3$ (196.1)	80–82°/0.13	1720, 1645	(*E*)	1.30 (t, 3H, J=7 Hz); 1.42 (s, 3H); 1.45–3.0 (m, 6H); 3.20 (s, 1H, oxirane-H); 4.21 (q, 2H, J=7 Hz); 5.97 (br. s, 1H)
				(*Z*)	1.30 (t, 3H, J=7 Hz); 1.42 (s, 3H); 1.45–3.0 (m, 6H); 4.24 (q, 2H, J=7 Hz); 4.57 (s, 1H, oxirane-H); 5.97 (br. s, 1H)
1b	$C_9H_{14}O_2$[d] (154.0)	98–102°/0.20	3400, 1665	(*E*)	5.80 (t, J=7 Hz, 1H); 4.20 (d, J=7 Hz, 2H); 3.22 (s, 1H); 3.45 (s, 1H); 1.75 (m, 6H); 1.39 (s, 3H)
				(*Z*)	5.80 (t, J=7 Hz, 1H); 4.32 (d, J=7 Hz, 2H); 3.58 (s, 1H); 3.45 (s, 1H); 1.75 (m, 6H); 1.39 (s, 3H)
1c	$C_{11}H_{18}O_2S$ (214.3)	102–105°/0.03	1660	(*E*)	5.78 (t, J=7 Hz, 1H); 4.67 (s, 2H); 4.17 (d, J=7 Hz, 2H); 3.20 (s, 1H); 2.13 (s, 3H); 2.10–1.40 (m, 6H); 1.37 (s, 3H)
				(*Z*)	5.77 (t, J=7 Hz, 1H); 4.68 (s, 2H); 4.30 (dd, J=7 Hz, 2H); 3.55 (s, 1H); 2.15 (s, 3H); 3.10–1.20 (m, 6H); 1.35 (s, 3H)
1d	$C_{15}H_{28}O_2Si$ (268.4)	98–102°/0.35	1665	(*E*)	5.70 (t, J=7 Hz, 1H); 4.37 (d, J=7 Hz, 2H); 3.13 (s, 1H); 1.30–2.15 (m, 6H); 1.28 (s, 3H); 0.85 (s, 9H); 0.05 (s, 6H)
				(*Z*)	5.67 (t, J=7 Hz, 1H); 4.22 (d, J=7 Hz, 2H); 3.47 (s, 1H); 1.30–2.15 (m, 6H); 1.28 (s, 3H); 0.85 (s, 9H); 0.05 (s, 6H)
1e	$C_{13}H_{22}O_4$ (242.3)	—	1660	(*E*)	5.80 (t, J=7 Hz, 1H); 4.80 (s, 2H); 4.35 (d, J=7 Hz, 2H); 3.70 (m, 4H); 3.40 (s, 3H); 3.20 (s, 1H); 1.40–2.20 (m, 6H); 1.37 (s, 3H)
				(*Z*)	5.77 (t, J=7 Hz, 1H); 4.72 (s, 2H); 4.25 (d, J=7 Hz, 2H); 3.70 (m, 5H); 3.40 (s, 3H); 1.40–2.20 (m, 6H); 1.37 (s, 3H)

[a] Satisfactory microanalyses were obtained (C, ±0.30; H, ±0.13).
[b] Perkin-Elmer 283B spectrophotometer.
[c] Varian EM-360 spectrometer.
[d] Compound was uniform on TLC and gave good high resolution MS data for the molecular ion.

Table 3. Spectral Data for Hydroxy Esters **5b** and **3a–e** (for R, see Table 1)

Compound No.	Molecular[a] formula	m.p. [°C]	I.R. (film)[b] ν [cm^{-1}]	Isomer[e]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm][c]
5b	$C_{13}H_{24}O_3$[d] (228.3)	61–63°	3455, 1730	(*E*)	1.10 (s, 3H); 1.45 (s, 9H); 1.2–2.9 (m, 12H)
3a	$C_{14}H_{24}O_3$ (240.3)	127–128°	3460, 1735		1.07 (s, 3H); 1.4 (s, 9H); 1.4–3.0 (m, 10H); 4.7 (br. s, 1H); 4.85 (br. s, 1H)
3b	$C_{15}H_{26}O_4$ (270.3)	(*E*) 96–97° (*Z*) 82–84°	3400, 1720	(*E*)	1.08 (s, 3H); 1.32 (s, 9H); 1.50–2.60 (m, 11H); 4.20 (br. s, J=7 Hz, 2H); 5.48 (t, J=7 Hz, 1H)
				(*Z*)	0.90 (s, 3H); 1.45 (s, 9H); 1.60–2.60 (m, 11H); 4.22 (8 line ABXm, 2H); 5.68 (t, J=7 Hz, 1H)
3c	$C_{17}H_{30}O_4S$ (330.5)	(*E*) 54–56° (*Z*) oil	3400, 1720	(*E*)	1.13 (s, 3H); 1.45 (s, 9H); 2.17 (s, 3H); 1.3–2.8 (m, 10H); 4.18 (A_2Xd, J=7 Hz, 2H); 4.66 (s, 2H); 5.43 (t, J=7 Hz, 1H)
				(*Z*)	1.2 (s, 3H); 1.42 (s, 9H); 2.2 (s, 3H); 1.3–3.3 (m, 10H); 3.6–4.6 (8 line ABXm, 2H); 4.71 (s, 2H); 5.7 (t, J=7 Hz, 1H)
3d	$C_{21}H_{40}O_4Si$ (384.6)	(*E*) 67–69° (*Z*) oil	3480, 1732	(*E*)	0.05 (s, 6H); 0.9 (s, 9H); 1.08 (s, 3H); 1.44 (s, 9H); 1.2–2.8 (m, 10H); 4.24 (A_2Xd, J=7 Hz, 2H); 5.38 (t, J=7 Hz, 1H)
				(*Z*)	0.10 (s, 6H); 0.91 (s, 9H); 1.18 (s, 3H); 1.4 (s, 9H); 1.2–3.2 (m, 10H); 3.8–4.5 (8 line ABXm, 2H); 5.66 (t, J=7 Hz, 1H)
3e	$C_{19}H_{34}O_6$ (358.4)	(*E*) oil (*Z*) oil	3460, 1730	(*E*)	1.09 (s, 3H); 1.42 (s, 9H); 1.2–2.9 (m, 10H); 3.40 (s, 3H); 3.45–3.85 (m, 4H); 4.13 (A_2Xd, J=7 Hz, 2H); 4.70 (s, 2H); 5.37 (t, J=7 Hz, 1H)
				(*Z*)	1.19 (s, 3H); 1.40 (s, 9H); 1.3–3.2 (m, 10H); 3.40 (s, 3H); 3.45–3.70 (m, 4H); 3.75–4.50 (8 line ABXm, 2H); 4.69, 4.80 (dd, J=7.0 Hz, 2H); 5.30 (m, 1H)

[a] Satisfactory microanalyses were obtained (C, ±0.28; H, ±0.14).
[b] Perkin-Elmer 283B spectrophotometer.
[c] Varian EM-360 spectrometer.
[d] Hydroxy ester **5b** (R = CH_3) was hydrolyzed to the known *trans*-2-hydroxy-2-methylcyclohexane-acetic acid[18].
[e] The isomers were separated by flash chromatography[17].

(*Z*)- and (*E*)-1-(2-hydroxyethylidene)-2,3-epoxy-3-methylcyclohexane (1b):

A solution of ester 7 (4.71 g, 24 mmol) in tetrahydrofuran (25 ml) is cooled to −78 °C and treated dropwise with a 1 molar solution of diisobutylaluminum hydride (50 ml, 50 mmol) under a nitrogen atmosphere at such a rate that the temperature of the reaction mixture does not exceed −70 °C. After the addition is complete (1 h), the mixture is warmed to −50 °C, and quenched with methanol (60 ml). Filtration of the solution through Celite, followed by washing of the Celite cake with hot methanol (3 × 125 ml) and concentration of the methanol filtrate in vacuo yields a slightly yellow, viscous oil. Flash chromatography on silica gel[17] eluting with 22:78 acetone/dichloromethane, affords recovered ester (*Z*)-7 (378 mg) and a 50:50 mixture of (*Z*)-**1b** and (*E*)-**1b** as a colorless oil; yield: 3.13 g [92% based on recovered (*Z*)-7].

Allylic Ethers 1c-e; General Procedure:
Sodium hydride (50% dispersion, 880 mg, 18.4 mmol) is washed with *n*-pentane (3 × 3 ml), dried under a nitrogen stream, and slurried with tetrahydrofuran (15 ml). The hydride suspension is cooled to −5 °C and alcohol **1b** (1.42 g, 9.21 mmol) in tetrahydrofuran (10 ml) is added dropwise so as to avoid a vigorous reaction. The reaction mixture is warmed to 0 °C, stirred for 15 min, and methoxyethoxymethyl chloride (1.57 ml, 13.8 mmol) added while maintaining the temperature at 0 °C. The reaction mixture is allowed to warm to room temperature and stirred for an additional 12 h before quenching with 5% aqueous sodium hydrogen carbonate (30 ml). Extraction with ether (3 × 75 ml), filtration through magnesium sulfate, and evaporation of the volatiles yields a yellow oil. Flash chromatography on silica gel[17] eluting with 30:70 ethyl acetate/hexanes, affords product **1e** as a colorless oil; yield: 1.8 g (81%).

Similar alkylations of **1b** with chloromethyl methyl sulfide (1 equivalent of sodium iodide added) or with *t*-butyldimethylsilyl chloride furnish products **1c** or **1d**, respectively; yields: 80–90%.

Reactions of *t*-Butoxycarbonylmethyl-diethyl-alane (2) with Compounds 1; General Procedure:
To a solution of lithium diisopropylamide (10 mmol) in hexane (~30 ml) under nitrogen at −78 °C is added dropwise *t*-butyl acetate (1.35 ml, 10 mmol). The resultant slurry of *t*-butyl lithioacetate is stirred for 20 min at −78 °C, allowed to warm to 0 °C, and evaporated to dryness under reduced pressure. After the flask is flushed with argon, a solvent (toluene, tetrahydrofuran or dimethoxyethane; 50 ml) is added at −40 °C and the reaction mixture treated with a 1.83 molar solution of diethylaluminum chloride in toluene (5.0 ml, 9.2 mmol). The resultant solution of reagent **2** is stirred at −30 °C for 30 min, cooled to −60 °C, and treated dropwise with alkylideneoxiranes **1a–e** or **4b** (3.5 mmol). The reaction mixture is quenched at −40 °C with 3% aqueous hydrochloric acid (25 ml) and extracted with ether (4 × 40 ml). The combined ether extracts are washed successively with 5% sodium hydrogen carbonate (20 ml) and saturated sodium chloride solutions (20 ml), and then dried with magnesium sulfate. Products **5b** and **3a–e** are isolated by flash chromatography[17], eluting typically with an 80:20 hexanes/ether mixture. The reaction conditions and yields of the hydroxy esters are summarized in Table 1.

Financial support of this research by the Department of Citrus, State of Florida, and the Institute of Food and Agricultural Sciences, University of Florida, is gratefully acknowledged.

Received: November 23, 1982

[1] W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Dryer, W. R. Hubbard, *J. Am. Chem. Soc.* **83,** 606 (1961).
E. J. Corey, K. C. Nicolaou, D. J. Beames, *Tetrahedron Lett.* **1974,** 2439.
J. P. Marino, H. Abe, *J. Am. Chem. Soc.* **103,** 2907 (1981).
[2] R. J. Anderson, *J. Am. Chem. Soc.* **92,** 4978 (1970).
[3] R. W. Herr, C. R. Johnson, *J. Am. Chem. Soc.* **92,** 4979 (1970).
[4] J. Staroscik, B. Rickborn, *J. Am. Chem. Soc.* **93,** 3046 (1971).
[5] D. M. Wieland, C. R. Johnson, *J. Am. Chem. Soc.* **93,** 3047 (1971).
[6] J. P. Marino, H. Abe, *Synthesis* **1980,** 872.
[7] B. M. Trost, G. A. Molander, *J. Am. Chem. Soc.* **103,** 5969 (1981).
[8] M. W. Rathke, D. F. Sullivan, *J. Am. Chem. Soc.* **95,** 3050 (1972).
[9] S. Danishefsky, T. Kitahara, M. Tsai, J. Dynak, *J. Org. Chem.* **41,** 1669 (1976).
[10] *Cf.* L. Strekowski, M. A. Battiste, *Tetrahedron Lett.* **22,** 279 (1981).
[11] M. Visnick, R. Bradley, M. A. Battiste, unpublished results.
[12] M. Rouillard, S. Geribaldi, M. Azzaro, *Org. Mag. Res.* **16,** 94 (1981).
[13] T. W. Greene, *Protective Groups in Organic Synthesis,* Wiley-Interscience, New York, 1981.
[14] M. Visnick, L. Strekowski, M. A. Battiste, manuscript in preparation.
[15] K. Ziegler, in *Organometallic Chemistry,* ACS Monograph No. 147, H. Zeiss, Ed., Reinhold, New York, 1960, pp. 194–269.
[16] G. A. Crosby, R. A. Stephenson, *J. Chem. Soc. Chem. Commun.* **1975,** 287.
[17] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **43,** 2923 (1978).
[18] J. Ficini, A. Maugean, *Bull. Soc. Chim. Fr.* **1971,** 219.