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STEREOSPECIFIC INTERNAL ALKYLATION OF TERMINAL γ,δ-EPOXY ACRYLATES

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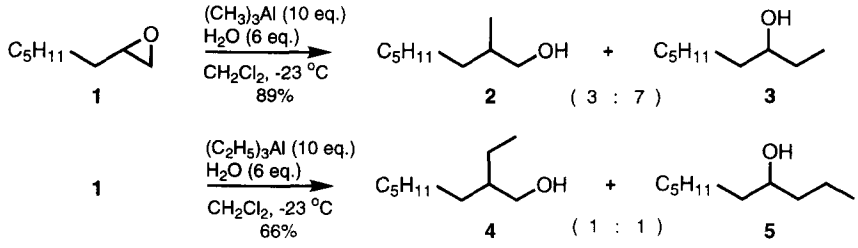
Abstract: The alkylation of ethyl (*S*)- and (*R*)-4,5-epoxy-2-pentenoates (**11**) and (**12**), chiral terminal γ,δ-epoxy acrylates prepared from D-mannitol, by trialkylaluminum in the presence of water occurs regioselectively at the γ position, i.e., at the internal position, to yield a sole product respectively with net inversion of configuration. The method provides useful chiral synthons for natural product synthesis. © 1997 Elsevier Science Ltd.

It is well-known that the nucleophilic opening of terminal epoxides by organocopper reagents or alkyllithiums occurs regioselectively at the terminal position to give the corresponding secondary alcohols.[1] On the contrary, regio- and stereo-selective internal alkylation of terminal epoxides is rather exceptional, although a few examples have been reported.[2]

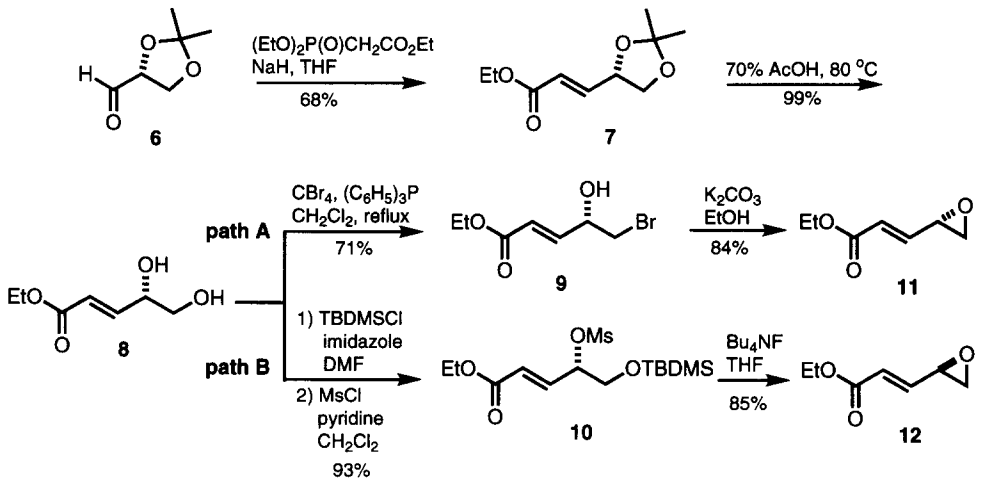
Recently we developed the stereospecific methylation of γ,δ-epoxy acrylates by trimethylaluminum ($(CH_3)_3Al$) *in the presence of water* which occurs exclusively at the γ position[3] and demonstrated the synthetic potential of the new methodology by stereoselective synthesis of several natural products.[4] On the other hand, from inspection of the above reactions, it was anticipated that the alkylation of terminal γ,δ-epoxy acrylates by trialkylaluminum would occur regioselectively at the γ position as well, i.e., internally. We report here the stereospecific internal alkylation of terminal epoxides by the use of chiral γ,δ-epoxy acrylates and trialkylaluminum.

For comparison, the reaction of simple 1,2-epoxyalkanes with $(CH_3)_3Al$ was initially examined. Thus, treatment of 1,2-epoxyoctane (**1**) with $(CH_3)_3Al$ (2 M solution in hexane, 10 equiv) in CH_2Cl_2 in the presence of water (6 equiv) at -23 °C for 1 h gave a 3 : 7 mixture of the internal alkylation product **2** and the external alkylation product **3** in 89% combined yield (**Scheme 1**).[5] On the other hand, the reaction of **1** with $(C_2H_5)_3Al$ under the same conditions produced a ca. 1 : 1 mixture of **4** and **5** in 66% yield. Consequently, the reaction of 1,2-epoxyalkanes with trialkylaluminum in the presence of water proved to give a mixture of regioisomers in a variable ratio depending on trialkylaluminum used.



Scheme 1

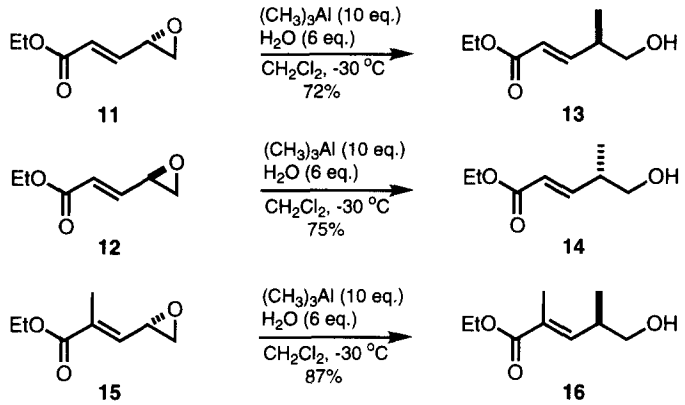
In turn, the reaction of terminal γ,δ-epoxy acrylates with trialkylaluminum was investigated. Initially, two enantiomeric epoxides, ethyl (*S*)- and (*R*)-4,5-epoxy-2-pentenoates (**11**) and (**12**) were prepared as substrates from D-glyceraldehyde acetonide (**6**) (**Scheme 2**). Thus **6** readily available from D-mannitol[6] was subjected to the Horner-Emmons reaction with triethyl phosphonoacetate to give the (*E*)-unsaturated ester **7** in 68% yield after purification by silica gel chromatography. Subsequent treatment of **7** with aqueous AcOH at 80 °C afforded the diol **8** in nearly quantitative yield. The diol **8** thus obtained was used as the common key intermediate for the synthesis of **11** and **12**. At first (*S*)-4,5-epoxy-2-pentenoate (**11**) was synthesized from **8** according to path A. Bromination of **8** with CBr_4 and $(C_6H_5)_3P$ in CH_2Cl_2 at reflux afforded the bromohydrin **9** in 71% yield along with 15% of secondary bromide. These bromides were easily separated by silica gel column chromatography. The bromohydrin **9** was then treated with K_2CO_3 in EtOH to give the desired (*S*)-epoxy acrylate **11**[7] ($[\alpha]_D^{18}$ + 33.4 (*c* 1.04, $CHCl_3$)) in 84% yield. On the other hand, (*R*)-4,5-epoxy-2-pentenoate (**12**) was synthesized from **8** according to path B. Selective protection of the primary hydroxyl group of **8** with *tert*-butyldimethylchlorosilane followed by mesylation gave the mesylate **10** in 93% yield which was subsequently treated with tetrabutylammonium fluoride (Bu_4NF) in THF at room temperature to produce the desired (*R*)-epoxy acrylate **12** in 85% yield. The specific rotation of **12** ($[\alpha]_D^{18}$ - 27.6 (*c* 1.42, $CHCl_3$)) was found, however, to be somewhat lower (ca. 83% e.e., *vide post*) in comparison with that of **11**. This is presumably due to partial epimerization of the labile allyl mesylate **10** by treatment with Bu_4NF.



Scheme 2

With the chiral substrates **11** and **12** in hand, the key reactions with trialkylaluminum were examined (**Scheme 3**). By employing the similar reaction conditions for **1**, **11** and **12** were treated with $(CH_3)_3Al$ (10 equiv) in CH_2Cl_2 in the presence of water (6 equiv) at -30 °C for 2 h to give solely **13**[8] and **14** in 72% and 75% yields, respectively. The presence of water is critical because in its absence reaction does not occur to any extent. The enantiomeric purity of the products was examined by comparison with an authentic sample[9] and analysis of ^1H NMR spectra of the corresponding (*S*)-α-methoxyphenylacetic acid esters.[10] As a consequence, the enantiomeric excess of **13** ($[\alpha]_D^{21}$ + 28.0 (*c* 0.97, $CHCl_3$)) and **14** ($[\alpha]_D^{21}$ = -21.6 (*c* 1.08, $CHCl_3$)) was found to be >99% and 83%, respectively. These results clearly demonstrate that both the

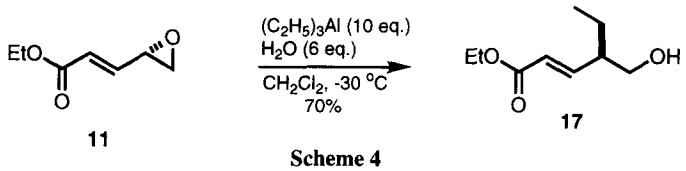
reactions proceeded regiospecifically at the γ position with net inversion of configuration. Similarly, the reaction of **15** prepared from **6** via an analogous synthetic route with $(CH_3)_3Al$ also occurred regioselectively at the γ position to give **16** in 87% yield (**Scheme 3**). The enantiomeric purity of **16** ($[\alpha]_D^{22}$ + 13.9 (*c* 1.16, $CHCl_3$)) was found to be 78% by ^1H NMR analysis of the corresponding (*S*)-α-methoxyphenylacetic acid esters.[11]



Scheme 3

On the other hand, the reaction of **11** with $(C_2H_5)_3Al$ under the same conditions afforded the compound **17**[12] as a sole product in 70% yield (**Scheme 4**). The enantiomeric purity of **17** was determined in a similar manner for the compounds **13** and **14**, and found to be greater than 99%. Thus ethylation was also shown to proceed stereospecifically at the γ position, with net inversion of configuration.

These outcomes demonstrate that the alkylation of terminal γ,δ-epoxy acrylates by trialkylaluminum-water occurrs regiospecifically at the γ position, i. e., internally, with maintenance of optical integrity. Since the compounds **13**, **14**, **16** and **17** possess a variety of functional groups in a compact molecule such as an ester group, a hydroxyl group, a conjugated double bond as well as a chiral center which are useful for further transformation, they serve as versatile chiral synthons for natural product synthesis.



Scheme 4

In summary, we demonstrated that the alkylation of terminal γ,δ-epoxy acrylates with trialkylaluminum in the presence of water proceeds regio- and stereo-specifically at the γ position, i. e., internally, with net inversion of configuration.

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References and Notes

1. Yamaguchi, M.; *Comprehensive Organic Synthesis*; Trost, B.; Ed., Pergamon Press, Oxford, **1991**, Vol. 1, pp 342-345; Lipshuts, B. H.; Sengupta, S.; *Organic Reactions*, John Wiley & Son, New York, **1992**, Vol. 41, p152.
2. (a) Isobe, M.; Ichikawa, Y.; Funabashi, Y.; Mio, S.; Goto, T.; *Tetrahedron*, **1986**, *42*, 2863; (b) Fukumasa, M.; Furuhashi, K.; Umezawa, J.; Takahashi, O.; Hirai, T.; *Tetrahedron Lett.*, **1991**, *32*, 1059.
3. Miyashita, M.; Hoshino, M.; Yoshikoshi, A.; *J. Org. Chem.*, **1991**, *56*, 6483.
4. Miyashita, M.; Toshimitsu, Y.; Shiratani, T.; Irie, H.; *Tetrahedron: Asymmetry*, **1993**, *4*, 1573; Miyashita, M.; Yoshihara, K.; Kawamine, K.; Hoshino, M.; Irie, H.; *Tetrahedron Lett.*, **1993**, *34*, 6285; Shiratani, T.; Kimura, K.; Yoshihara, K.; Hatakeyama, S.; Irie, H.; Miyashita, M.; *J. Chem. Soc., Chem. Commun.*, **1996**, 21; Miyashita, M., Shiratani, T.; Kawamine, K.; Hatakeyama, S.; Irie, H.; *ibid*, **1996**, 1027.
5. It has been reported that the reaction of some 1,2-epoxyalkanes with $(CH_3)_3Al$ (1. 5 equiv) in hexane (0 °C, 2 h) produced the corresponding internal alkylation products with 92-96% inversion of configuration.[2b]
6. Schmid, C. R.; Bryant, J. D.; *Org. Synth.*, **1995**, *72*, 6.
7. ^1H NMR (250 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.2 Hz, 3H), 2.73 (dd, *J* = 2.2, 5.5 Hz, 1H), 3.06 (dd, *J* = 4.2, 5.5 Hz, 1H), 3.40-3.52 (br, 1H), 4.21 (q, *J* = 7.2 Hz, 2H), 6.18 (d, *J* = 15.9 Hz, 1H), 6.63 (dd, *J* = 7.4, 15.9 Hz, 1H); ^{13}C NMR(67.5 MHz, $CDCl_3$) d 14.2, 49.2, 50.3, 60.6, 124.3, 144.6, 165.4; IR (neat) 2986, 2910, 1720, 1659, 1468, 1448, 1398, 1389, 1367, 1308, 1259, 1242, 1194, 1161, 1136, 1096, 1035, 978, 928, 860, 841, 796, 785, 719 (cm^{-1}); $[\alpha]_D^{18}$ + 33.4 (*c* 1.04, $CHCl_3$); EI-MS *m/z* 143 (M^++1, 0.7%), 142 (M^+, 0.5), 114 (4), 112(11), 97 (56), 84 (81), 69 (100); HR-MS: Calcd for $C_7H_{10}O_3$ (M^+): 142.0630. Found: 142.0621.
8. ^1H NMR (250 MHz, $CDCl_3$) δ 1.09 (d, *J* = 7.2 H, 3H), 1.29 (t, *J* = 7.0 Hz, 3H), 2.50-2.61 (br, 1H), 3.54-3.64 (br, 2H), 4.20 (q, *J* = 7.0 Hz, 2H), 5.90 (dd, *J* = 1.2, 15.9 Hz, 1H), 6.91 (dd, *J* = 8.0, 15.9 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 14.2, 15.5, 39.2, 60.4, 66.4, 121.6, 150.9, 166.6; IR (neat) 3433, 2980, 2936, 2876, 1718, 1655, 1369, 1306, 1273, 1225, 1182, 1148, 1096, 1038, 984, 945, 920, 862, 725 (cm^{-1}); $[\alpha]_D^{21}$ + 28.0 (*c* 0.97, $CHCl_3$); EI-MS *m/z* 159 (M^++1, 0.8%), 128 (100), 113 (43), 100 (90), 82 (65), 55 (64).
9. An authentic sample **13** ($[\alpha]_D^{24}$ + 26.8 (*c* 0.83, $CHCl_3$)) was prepared from methyl (*S*)-(+)-3-hydroxy-2-methylpropionate.
10. Trost, B. M.; Belletire, J. L.; Godleski, S.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E., Ponticello, G. S.; Varga, S. L.; Springer, J. P.; *J. Org. Chem.*, **1986**, *51*, 2370.
11. The value is presumably due to the purity of the substrate.
12. ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.7 Hz, 3H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.20-1.48 (m, 1H), 1.50-1.64 (m, 1H), 2.25-2.40 (m, 1H), 3.58 (dd, *J* = 7.7, 10.6 Hz, 1H), 3.65 (dd, *J* = 5.5, 10.6 Hz, 1H), 4.19 (q, *J* = 7.0 Hz, 2H), 5.91 (d, *J* = 16.1 Hz, 1H), 6.80 (dd, *J* = 8.8, 16.1 Hz, 1H); ^{13}C NMR (100.4 MHz, $CDCl_3$) δ 11.6, 14.3, 23.4, 47.1, 60.5, 65.1, 123.3, 150.0, 166.6; IR (neat) 3440, 2964, 2935, 2877, 1720, 1655, 1649, 1460, 1371, 1310, 1269, 1240, 1180, 1141, 1042, 986, 864 (cm^{-1}); $[\alpha]_D^{23}$ - 4.8 (*c* 1.68, $CHCl_3$).

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