Pergamon

Tetrahedron Letters 39 (1998) 3775–3778

TETRAHEDRON LETTERS

Efficient and Stereospecific Construction of Asymmetric Quaternary Carbons via γ-Alkyl-γ,δ-epoxy Acrylates

Naoki Ishibashi, Masahiro Miyazawa, and Masaaki Miyashita*

Division of Chemistry, Graduate School of Science, Hokkaido University, Sapporo 060, Japan

Received 12 February 1998; revised 18 March 1998; accepted 20 March 1998

Abstract: Highly efficient and stereospecific construction of asymmetric quaternary carbons via the alkylation of γ-alkyl-γ,δ-epoxy acrylates with $(CH_3)_3Al$ is described.

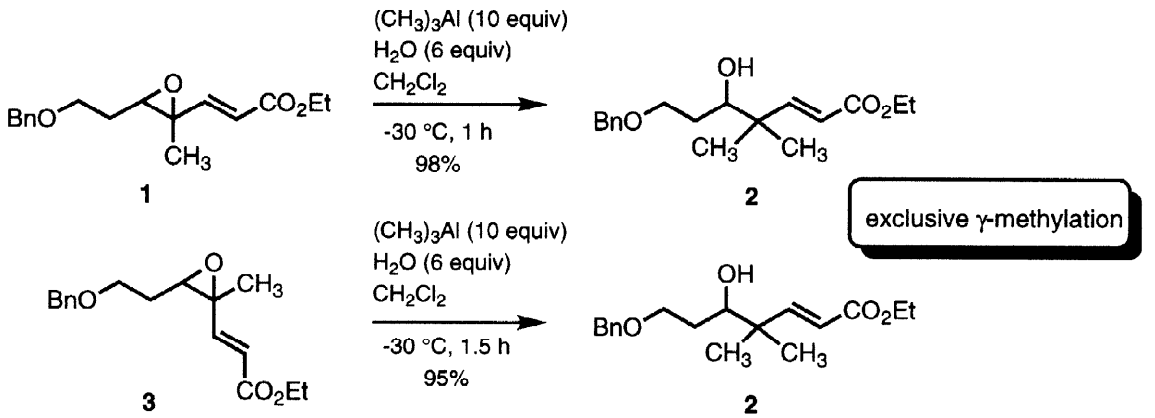
Stereoselective construction of asymmetric quaternary carbon atoms is not only challenging but also very important in organic synthesis, particularly in natural product synthesis since a variety of biologically active natural products containing quaternary carbon atom(s) have been found in nature and in most cases only one enantiomer of them has been known to exhibit biological activity. Much efforts have been devoted in this decade to development for the stereoselective construction of quaternary carbon atoms including asymmetric and chiral ones.[1]

We have reported the regio- and stereo-specific methylation of γ,δ-epoxy acrylates with $(CH_3)_3Al$ in the presence of water[2] and recently developed the methodology to the stereospecific internal alkylation of terminal γ,δ-epoxy acrylates with trialkylaluminum.[3] We have also demonstrated the usefulness of the new methodology in the synthesis of biologically active natural products, *inter alia* polypropionate-derived antibiotics.[4] In connection with acyclic stereocontrol by the use of γ,δ-epoxy acrylates, we anticipated that the reaction of γ-alkyl-γ,δ-epoxy acrylates with trialkylaluminum in the presence of water should occur regio- and stereo-specifically at the γ-position as well yielding an asymmetric quaternary carbon at the γ-position. We report here an efficient and stereospecific method for construction of asymmetric quaternary carbons by using the alkylation of γ-alkyl-γ,δ-epoxy acrylates with $(CH_3)_3Al$ in the presence of water.

Initially we prepared ethyl *trans*-7-benzyloxy-4,5-epoxy-4-methyl-2-heptenoate (**1**) as a model compound and investigated its methylation reaction with $(CH_3)_3Al$. Thus, treatment of **1** with $(CH_3)_3Al$ (2 M solution in hexane, 10 equiv.) in CH_2Cl_2 in the presence of water (6 equiv.) at -30 °C for 1 h, followed by aqueous workup, gave the expected compound **2** as a single product, in which a methyl group was regioselectively introduced at the γ-position, in 98% isolated yield (Scheme 1). Similarly, the reaction of the analogous *cis*-epoxy unsaturated ester **3** with $(CH_3)_3Al$ under the similar conditions (-30 °C, 1.5 h) gave exclusively the same product **2** in 95% yield. No any other product was detected in these reactions.[5] These results demonstrate that the methylation of γ-alkyl-γ,δ-epoxy acrylates with $(CH_3)_3Al$ proceeds cleanly and regioselectively at the γ-position as well as those of γ,δ-epoxy acrylates,[2, 3] even faster than the latters.

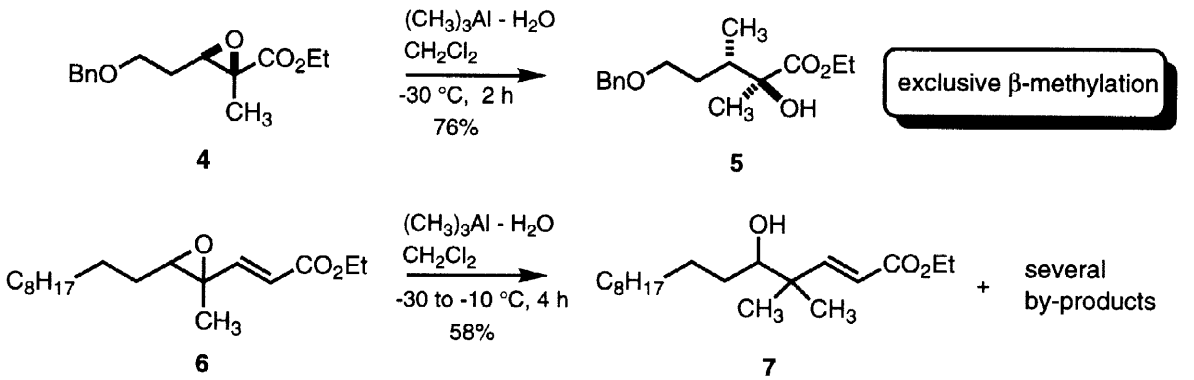
On the contrary, it was found that the reaction of ethyl *trans*-5-benzyloxy-2,3-epoxy-2-methylpentanoate (**4**), the compound lacking a double bond of **1**, with $(CH_3)_3Al$ under the similar

0040-4039/98/$19.00
PII: S0040-4039(98)00614-5



Scheme 1

conditions (-30 °C, 2 h) produced exclusively the compound **5**, in which a methyl group was regioselectively introduced at the less-substituted carbon atom of the epoxide with inversion of configuration, in 76% yield (Scheme 2). We also examined the reaction of ethyl *trans*-4,5-epoxy-4-methyl-2-pentadecenoate (**6**), a substrate that bears no ether oxygen atom in the left chain of the epoxide function, with $(CH_3)_3Al$ and found that **6** required longer reaction time and resulted in formation of **7** in lower yield (58%), along with several by-products (Scheme 2).



Scheme 2

These results unambigously demonstrate that an acrylate moiety is critical for the control of the regioselectivity in the reaction and the chelation of the aluminum reagent by the oxygen atoms of the epoxide and the ether moiety plays key roles for the achievement of extremely high γ-regioselectivity (Fig.1), as is

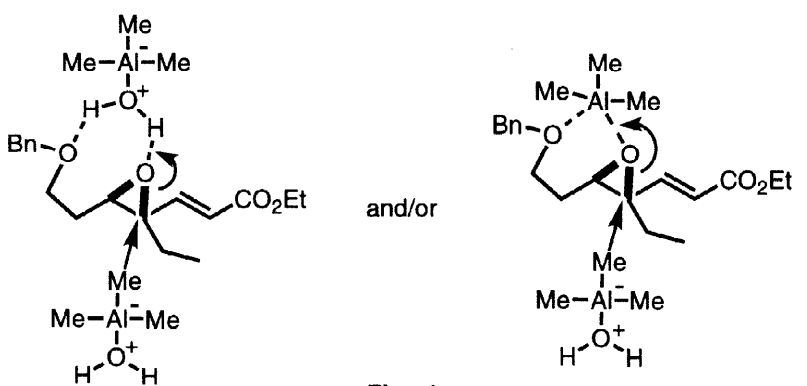
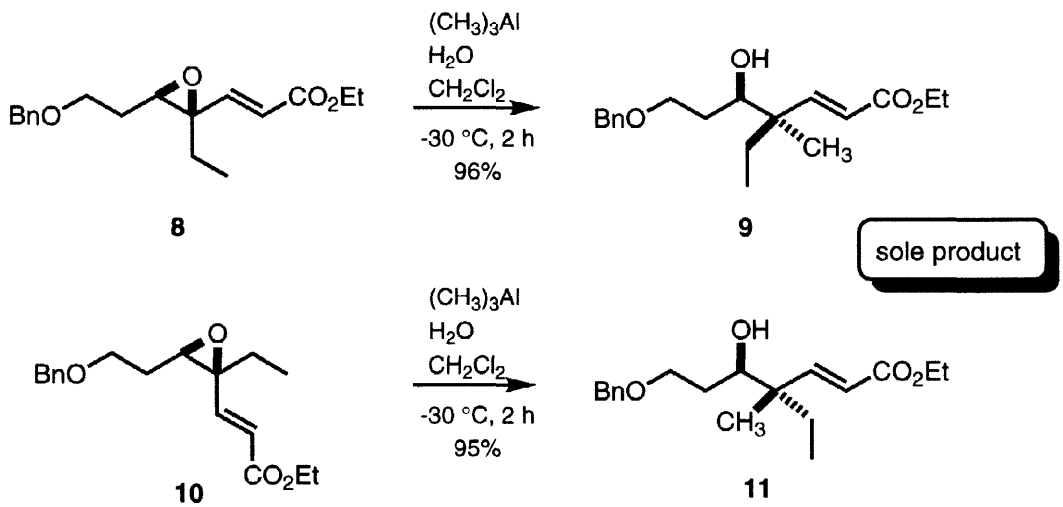


Fig. 1

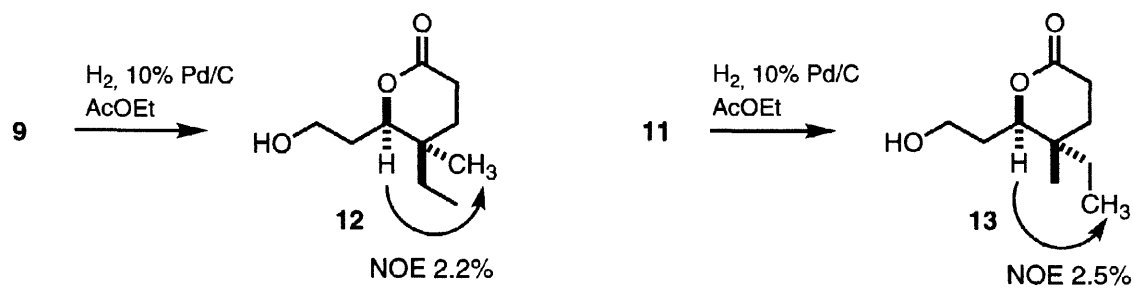
seen in the reactions of **1**, **3**, and the previous examples.[2]

In turn, we investigated the stereoselectivity in the reactions of γ-alkyl-γ,δ-epoxy acrylates with $(CH_3)_3Al$, namely whether those reactions occur stereospecifically at the γ-position with net inversion of configuration, as the reactions of γ,δ-epoxy acrylates with $(CH_3)_3Al$,[2, 3] or not. To this end, treatment of ethyl *trans*-7-benzyloxy-4,5-epoxy-4-ethyl-2-heptenoate (**8**) with $(CH_3)_3Al$ (10 equiv.) in CH_2Cl_2 in the presence of water (6 equiv.) at -30 °C for 2 h, gave the syn compound **9**[6] as a single product, in which a methyl group was stereospecifically introduced at the γ-position with net inversion of configuration, in 96% yield (Scheme 3). Similarly, the reaction of the analogous *cis*-epoxy unsaturated ester **10** with $(CH_3)_3Al$ under the same conditions gave solely the anti compound **11**[7] in 95% yield. The stereochemistry of the products was confirmed by ^1H NMR analysis including NOE measurement of the hydroxy δ-lactones **12** and **13** which were derived from **9** and **11** by catalytic hydrogenation, respectively (Scheme 4).



Scheme 3

Thus the reactions of γ-alkyl-γ,δ-epoxy acrylates with $(CH_3)_3Al$ in the presence of water were demonstrated to proceed regio- and stereo-specifically at the γ-position with net inversion of configuration as those of γ,δ-epoxy acrylates with trialkylaluminum.[2, 3]



Scheme 4

The major advantage of the method described here is that alkylation occurs stereospecifically and with complete diastereoselectivity at the γ-position and not to produce any stereoisomer concerning an asymmetric quaternary carbon atom whose separation may be extremely difficult. The present method should provide a powerful tool in organic synthesis including natural product synthesis. Further studies of

the alkylation of γ,δ-epoxy acrylates and the application of these methodologies to the synthesis of natural products are in progress.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (No. 08245101) and a Grant-in-Aid for Exploratory Research (No. 09874149) from the Ministry of Education, Science, Sports and Culture of Japan.

References and Notes

1 S. F. Martin, *Tetrahedron*, **1980**, *36*, 419-460; K. Fuji, *Chem. Rev.*, **1993**, *93*, 2037-2066; D. Desmaële and J. d'Angelo, *J. Org. Chem.*, **1994**, *59*, 2292-2303; N. Watanabe, Y. Ohtake, S. Hashimoto, M. Shiro, and S. Ikegami, *Tetrahedron Lett.*, **1995**, *36*, 1491-1494; T. Takemoto, M. Sodeoka, and M. Shibasaki, Tennen Yuki Kagoubutu Toronkai Koen Yoshisyu, 36th, 220-227 (1994); Y. Kataoka, I. Makihira, H. Akiyama, and K. Tani, *Tetrahedron Lett.*, **1995**, *36*, 6495-6498; T. Fosaka, T. Ueda, Y. Fujiwara, Y. Miki, O. Iire, T. Omodani, and K. Shishido, Tennen Yuki Kagoubutu Toronkai Koen Yoshisyu, 37th, 379-384 (1995); T. Saito, M. Morimoto, C. Akiyama, T. Matsumoto, and K. Suzuki, *J. Am. Chem. Soc.*, **1995**, *117*, 10757-10758; Y. Yamamoto, S. Hara, and A. Suzuki, *Synlett*, **1996**, 883-884; C. Palomo, J. M. Aizpurua, J. M. García, R. Galarza, M. Legido, R. Urchegui, P. Román, A. Luque, J. Server-Carrió, and A. Linden, *J. Org. Chem.*, **1997**, *62*, 2070-2079; S. E. Denmark and L. R. Marcin, *ibid.*, **1997**, *62*, 1675-1686; J. C. F. Alves, A. B. C. Simas, P. R. R. Costa, and J. d'Angelo, *Tetrahedron: Asymmetry*, **1997**, *8*, 1963-1966; M. Murakata, T. Jono, Y. Mizuno, and O. Hoshino, *J. Am. Chem. Soc.*, **1997**, *119*, 11713-11714.

2 M. Miyashita, M. Hoshino, and A. Yoshikoshi, *J. Org. Chem.*, **1991**, *56*, 6483-6485.

3 M. Miyazawa, N. Ishibashi, S. Oonuma, and M. Miyashita, *Tetrahedron Lett.*, **1997**, *38*, 3419-3422.

4 M. Miyashita, K. Yoshihara, K. Kawamine, M. Hoshino, and H. Irie, *Tetrahedron Lett.*, **1993**, *34*, 6285-6288; T. Shiratani, K. Kimura, K. Yoshihara, S. Hatakeyama, H. Irie, and M. Miyashita, *J. Chem. Soc. Chem. Commun.*, **1996**, 21-22; M. Miyashita, T. Shiratani, K. Kawamine, S. Hatakeyama, and H. Irie, *ibid.*, **1996**, 1027-1028; M. Miyazawa, S. Oonuma, K. Maruyama, and M. Miyashita, *Chem. Lett.*, **1997**, 1191-1192; M. Miyazawa, S. Oonuma, K. Maruyama, and M. Miyashita, *ibid.*, **1997**, 1193-1194.

5 The reaction of **1** with $(C_2H_5)_3Al$ under similar conditions gave the corresponding γ-ethylated compound in 61% yield, along with a S_N2' product (8%) and a rearranged 5-keto compound (7%).

6 ^1H NMR (270 MHz, $CDCl_3$) δ 7.28-7.37 (m, 5H), 6.88 (d, *J* = 16.1 Hz, 1H), 5.78 (d, *J* = 16.1 Hz, 1H), 4.53 (d, *J* = 11.9 Hz, 1H), 4.48 (d, *J* = 11.9 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.59-3.76 (m, 3H), 1.62-1.78 (m, 2H), 1.55 (q, *J* = 7.5 Hz, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.03 (s, 3H), 0.80 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 166.5, 154.0, 137.4, 128.3, 127.6, 127.5, 120.5, 76.9, 73.3, 70.1, 60.2, 44.8, 31.5, 29.7, 16.5, 14.3, 8.3; IR (neat) 3500, 2970, 2937, 2877, 1739, 1718, 1647, 1496, 1454, 1369, 1309, 1269, 1242, 1184, 1095, 1043, 995, 950, 736, 698 cm^{-1}.

7 ^1H NMR (270 MHz, $CDCl_3$) δ 7.28-7.37 (m, 5H), 7.02 (d, *J* = 16.2 Hz, 1H), 5.78 (d, *J* = 16.2 Hz, 1H), 4.51 (s, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.59-3.77 (m, 3H), 1.60-1.76 (m, 2H), 1.53 (q, *J* = 7.5 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H), 0.99 (s, 3H), 0.81 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 166.5, 154.1, 137.5, 128.3, 127.6, 127.5, 120.6, 76.9, 73.3, 69.9, 60.1, 44.7, 31.1, 29.1, 17.6, 14.3, 8.3; IR (neat) 3500, 2970, 2937, 2879, 1735, 1718, 1647, 1496, 1454, 1367, 1309, 1271, 1244, 1184, 1095, 1039, 999, 952, 736, 698 cm^{-1}.