A FACILE CHEMOENZYMATIC ROUTE TO ENANTIOMERICALLY PURE 4,5-DISUBSTITUTED-2-HEXENOATE DERIVATIVES

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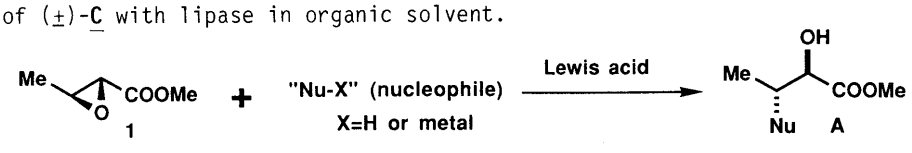
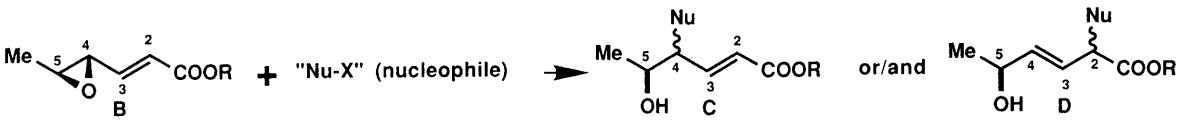
The reaction of 4,5-epoxy-2-hexenoate **2** and various nucleophiles in the presence of $BF_3.Et_2O$ predominantly gave the (4,5)-5-hydroxy-4-substituted compounds. Among them, (±)-(4,5)-anti-5-hydroxy-4-thiophenoxy ester **17** was enantioselectively esterified with acylating reagent in the presence of lipase "PL 266" from Alcaligenes sp. to provide the (4S,5R)-5-acetoxy ester **20** and the (4R,5S)-**17** quantitatively.

KEYWORDS 4,5-epoxy-2-hexenoate; epoxy ring opening; boron trifluoride etherate; lipase; enantioselective esterification

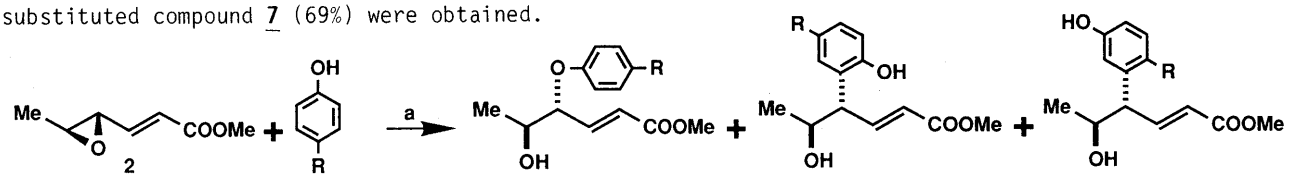
In connection with our work directed towards the synthesis of optically active 2,3-disubstituted butyrate derivatives **A** which were obtained by the reaction of an optically active 2,3-epoxy butyrate **1** and nucleophilic reagents in the presence of Lewis acid,[1] the reaction of 4,5-epoxy-2-hexenoate **B** having a vinylogous structure of **1** and various nucleophiles has aroused our interest. The reactions of **B** and alcohols[2] or acetoacetate[3] or methylcopper reagent,[4] producing the 4,5- or/and 2,5-disubstituted compounds (**C** or **D**), have been reported, but regio- and stereo-selectivities have not been thoroughly studied yet. Optically active 4,5-anti-disubstituted-2-hexenoate derivatives **C** are expected to be a chiral intermediate for the synthesis of biologically active compounds such as amino sugars or their related compounds.[2] We now report the regioselective synthesis of (±)-(4,5)-anti **C** and enantioselective esterification of (±)-**C** with lipase in organic solvent.



"Nu-X" ; O-nucleophile (alcohol, phenol), C-nucleophile (indol, $Et_2AlC{\equiv}CSiMe_3$)



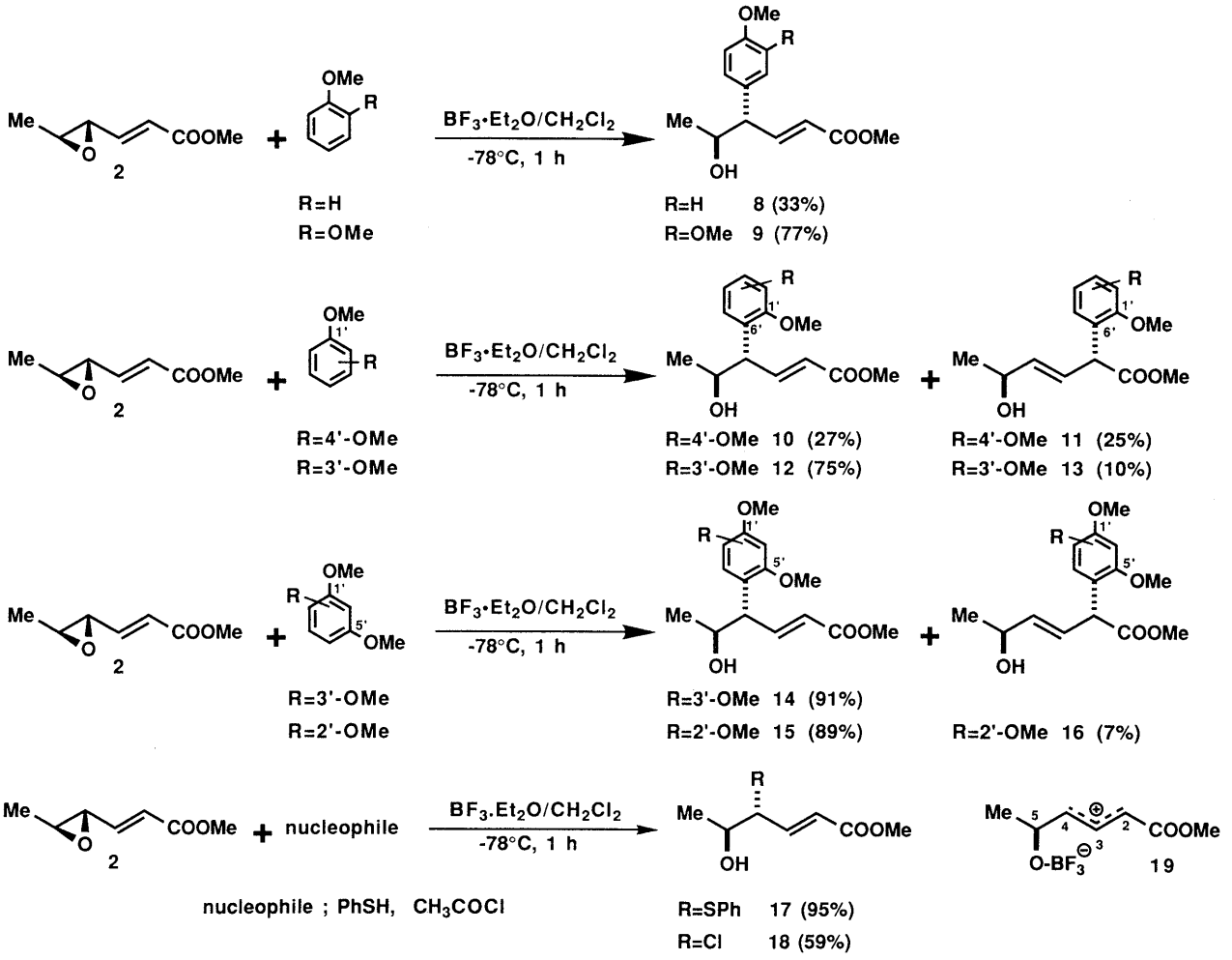
The Reaction of Methyl 4,5-Epoxy-2-hexenoate 2 with Various Nucleophiles The reaction of **2** (10 m mol) with p-methoxyphenol (5 m mol) in the presence of $BF_3.Et_2O$ (10 m mol) gave the 4,5-anti-4-aryl ether (O-substituted compound) **3** (25%)[5] and the 4,5-anti-4-aryl substitution products (C-substituted compounds **4** (48%)[6], **5** (6%)[6]. When p-cresol was used, the O-substituted compound **6** (17%) and the C-substituted compound **7** (69%) were obtained.



R=OMe R=OMe 3 (25%) R=OMe 4 (48%) R=OMe 5 (6%)
R=Me R=Me 6 (17%) R=Me 7 (69%)

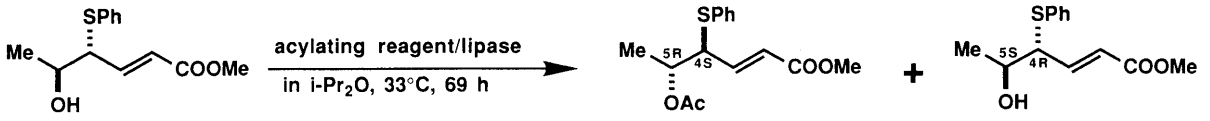
a; $BF_3.Et_2O/CH_2Cl_2$, -78°C, 1 h

For the purpose of obtaining selectively the C-substituted compounds, the reaction of 2 with various carbon nucleophiles was examined. When anisole, 1,2-dimethoxybenzene and 1,3,5-trimethoxybenzene were employed, the 4,5-anti-4-aryl substitution products (8 (33%), 9 (77%) and 14 (91%)) were predominantly obtained. The yield was found to rise as the nucleophilicity of aromatic ring increased. On the other hand, the reaction of 2 with other polymethoxybenzenes yielded the 2,5-anti-2-carbon substituted products[7] as well as the 4,5-anti-4-carbon substituted compounds. The reaction of 2 with thiophenol or with acetyl chloride afforded regioselectively the 4-substituted compounds (17 (95%) or 18 (59%)), respectively.



In the reaction of 2 with nucleophiles in the presence of $BF_3.Et_2O$, the possibility of forming oxo-π-allyl complex 19 from 2 are considered. If the complex formation takes place, then the nucleophilic attack from the less hindered side (anti-direction) should give the 4,5-anti-4-substituted compounds or the 2,5-anti-2-substitution products. In the reaction of 2 and the methylcopper reagents, it was reported that the harder nucleophiles attack predominantly the C_4-position while the softer reagents react predominantly at the C_2-position.[4] In the present case, it is difficult to explain the regioselectivity quantitatively on the basis of a delicate difference in softness among the used nucleophiles.

Enantioselective Esterification of (±)-4-Thiophenoxy Ester 17 with Lipase The treatment of (±)-17 and acylating reagents (isopropenyl acetate or phenylthioacetate) with lipase "PL 266" from Alcaligenes sp. in isopropyl ether provided quantitatively the (4S,5R)-5-acetoxy ester 20 (98-99% ee) and the (4R,5S)-5-hydroxy ester 17 (97-99% ee). The stereochemistry of (4R,5S)-17 was determined by comparison with authentic sample (4S,5R)-17, prepared by the reaction of the known (4R,5R)-2[8] and thiophenol in the presence of $BF_3.Et_2O$.

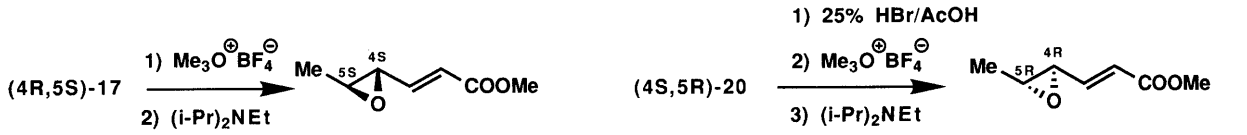


(±)-17 (4S,5R)-20 (4R,5S)-17

Entry	substrate (mg)	Lipase	Acylating reagent	Product (yield, %; optical purity, % ee)	
1	(103)	PL 266 (*Alcaligenes* sp.)	A	(4S,5R)-20 (50.2%, 98% ee)	(4R,5S)-17 (49.7%, >99% ee)
2	(97)	PL 679 (*Alcaligenes* sp.)	A	(4S,5R)-20 (61.1%, 58% ee)	(4R,5S)-17 (34.6%, 90% ee)
3	(107)	PL 266 (*Alcaligenes* sp.)	B	(4S,5R)-20 (49.5%, 99% ee)	(4R,5S)-17 (49.8%, 97% ee)
4	(109)	PL 679 (*Alcaligenes* sp.)	B	(4S,5R)-20 (41.5%, 95% ee)	(4R,5S)-17 (57.8%, 67% ee)

A ; isopropenyl acetate B ; PhSAc

Treatment of (4R,5S)-17 with $Me_3O^+BF_4^-$ was followed by epoxy formation with $(i\text{-}Pr)_2NEt$ to afford the (4S,5S)-2 in 58% overall yield. In this process, the isomerization to the undesired cis epoxy ester was partly observed, but no loss of optical purity was detected. The (4S,5R)-5-acetoxy ester 20 was also converted into the (4R,5R)-2. These conversions mean that chiral synthesis of the 4,5-disubstituted-2-hexenoate derivatives is achieved by applying the reaction of (±)-2 and various nucleophiles to the reaction using the chiral 4,5-epoxy-2-hexenoate 2.



58% (*trans*-epoxy : *cis*-epoxy = 4 : 1)

51% (*trans*-epoxy : *cis*-epoxy = 4.5 : 1)

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REFERENCES AND NOTES

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2) a) Chemical Abstract, 81, 266 (1974);
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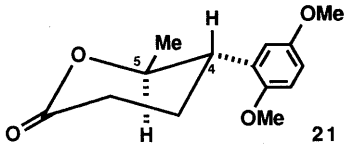
5) Satisfactory analytical data were obtained for all new compounds.
6) The structure of 4 and 5 were determined by NMR analysis (NOE experiment) and chemical correlation. Methylation of 4 and 5 provided the same dimethoxy compound 10 which was converted in the δ-lactone 21.
The coupling constant of C_4-axial proton and C_5-axial proton of 21 was 10 Hz, clearly indicating that the starting 4 or 5 possessed anti-configuration.



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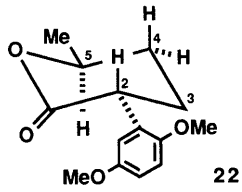
7) In order to determine the structure of this type compound, for example, compound 11 was converted into the δ-lactone 22. The coupling constants due to the C_2-axial proton and C_5-axial proton were $J_{2a,3a}$= 11 Hz , $J_{2a,3e}$=7 Hz and $J_{5a,4a}$=11 Hz, $J_{5a,4e}$=2 Hz, respectively.
These data clearly indicate that the starting 11 possessed 2,5-anti-configuration.
8) I. Dyong, R. Knollmann, and N. Jersch, Angew. Chem. Int. Ed. Engl., 15, 302 (1976).



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