Tetrahedron Letters, Vol.32, No.41, pp 5793-5796, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

Highly Efficient and General Method for Synthesis of Tertiary Allylic Alcohols in a Chiral Form. Synthesis of Arbaprostil

Sentaro Okamoto, Toshiharu Yoshino Hiromi Tsujiyama and Fumie Sato*

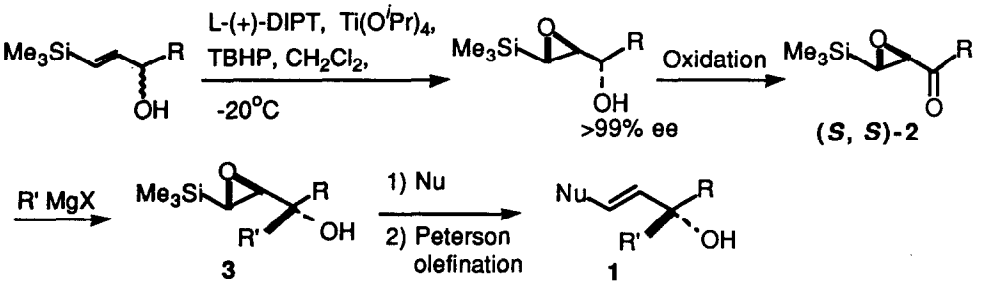
Department of Biomolecular Engineering, Tokyo Institute of Technology, Meguro, Tokyo 152, JAPAN

Key Words : optically active tertiary allylic alcohol; Peterson olefination reaction; prostaglandin; arbaprostil

***Summary** : Highly efficient and general method for synthesis of optically active tertiary allylic alcohols (1) starting from readily available optically active γ-trimethylsilyl-β,γ-epoxy tertiary alcohols (3), and the application of the reaction product to the synthesis of arbaprostil are described.*

The lack of a general synthetic method for preparation of optically active tertiary allylic alcohols (1), which are incorporated in the structures of a variety natural products and commercially important pharmaceuticals, has prompted us to synthesize **1** according to a series of the reactions shown in Scheme 1. In the

Scheme 1

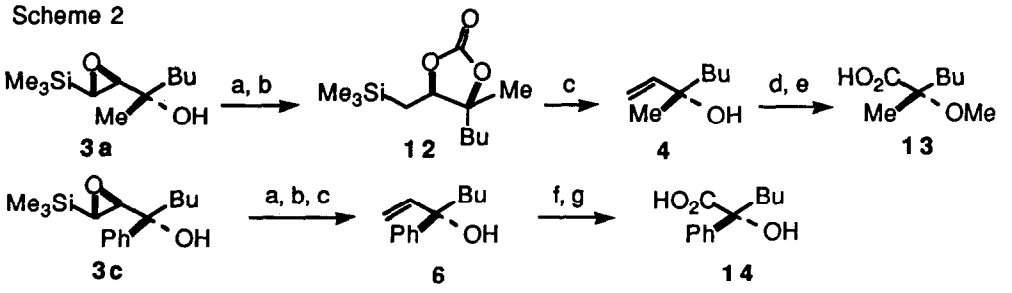


preceding paper[1] we reported the synthesis of both enantiomers of epoxy ketones **2** using the Sharpless kinetic resolution of racemic γ-trimethylsilyl allylic alcohols as the key reaction,[2] and their highly diastereoselective reaction with Grignard reagents, thus providing an efficient method for preparation of epoxy alcohols **3** with various substituents R and R', in which the chiral tertiary alcohol center is regulated stereospecifically (the structure of **3** was assigned as shown in Scheme 1 tentatively). Herein we report the conversion of **3** thus prepared into **1** by regiospecific epoxide ring opening with nucleophiles followed by Peterson

olefination reaction. We also report the synthesis of 15-epi-15-methyl prostaglandin E_2, arbaprostil, which has tertiary allylic alcohol moiety as ω side-chain unit.

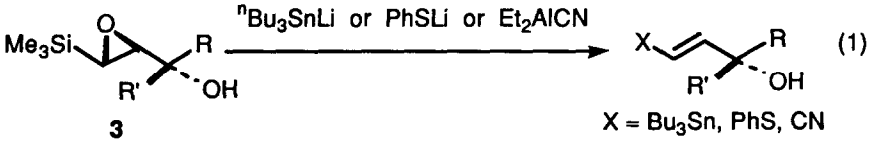
The results of the conversion of the compounds **3** into **1** are summarized in Table 1. Thus, as shown in Scheme 2, the reaction of **3a** with $LiAlH_4$ in THF afforded the ring opening product which was converted into the corresponding carbonate **12** by the reaction with $COCl_2$ and pyridine in THF. Treatment of **12** with Bu_4NF in THF afforded the tertiary allylic alcohol **4**. An identical synthetic procedure was applied to **3b** (the enantiomer of **3a**) to provide the antipodal alcohol **5**. The absolute configuration of the alcohol **4** was confirmed to be *S* by converting into 2-methyl-2-methoxyhexanoic acid **13** ($[\alpha]_D^{28}$ -12.5° (c 1.27, $CHCl_3$) (lit., [3] (*R*)-**13** ; $[\alpha]_D^{25}$ +12.9° (c 1.07, $CHCl_3$)). Similarly, the compound **3c** was converted into the tertiary allylic alcohol **6**, the absolute configuration of which was proven by correlation with (*R*)-2-phenyl-2-hydroxyhexanoic acid **14** ($[\alpha]_D^{20}$ -37.2° (c 11.3, $CHCl_3$) (lit., [4] (*S*)-**14** (43% ee) ; $[\alpha]_D^{20}$ +16.2° (c 11, $CHCl_3$)). The determination of the absolute configuration of **4** and **6** confirms the structure of **3** which was assigned tentatively in the preceding paper.[1]

Scheme 2



a) $LiAlH_4$, THF ; b) $COCl_2$, pyridine, THF ; c) $^nBu_4NF$, THF ; d) MeI, NaH, THF ; e)$NaIO_4$, cat. $RuCl_3$, CH_3CN-CCl_4-H_2O ; f) O_3 then Me_2S, MeOH ; g) $NaClO_3$, cyclohexene, NaH_2PO_4, ^tBuOH

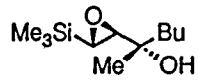
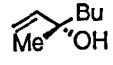
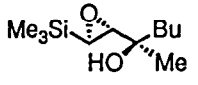
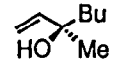
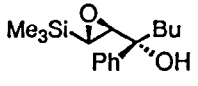
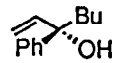
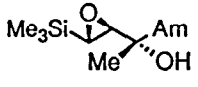
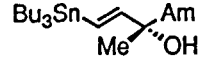
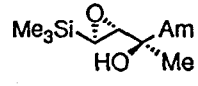
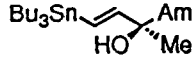
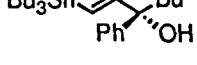
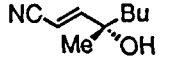
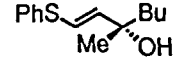
The reaction of **3** with Bu_3SnLi resulted in the regiospecific epoxide ring opening and *in situ* Peterson olefination reaction to afford the corresponding γ-tributylstannyl tertiary allylic alcohols directly (eq 1).[5] Similarly, the reaction of **3** with Et_2AlCN or PhSLi directly afforded the corresponding tertiary allylic alcohols. The easy access to these chiral tertiary allylic alcohols such as **7~11** shown in Table 1 is especially noteworthy because of the versatile reactivity of vinylstannane, vinylsulfide and α,β-unsaturated nitrile moiety presented in these alcohols.



(1)

Application of the chiral tertiary allylic alcohols obtained here in the synthesis of physiologically active compounds is in progress in our laboratory, and described next is the synthesis of 15-epi-15-methyl prostaglandin E_2, arbaprostil (an Upjohn

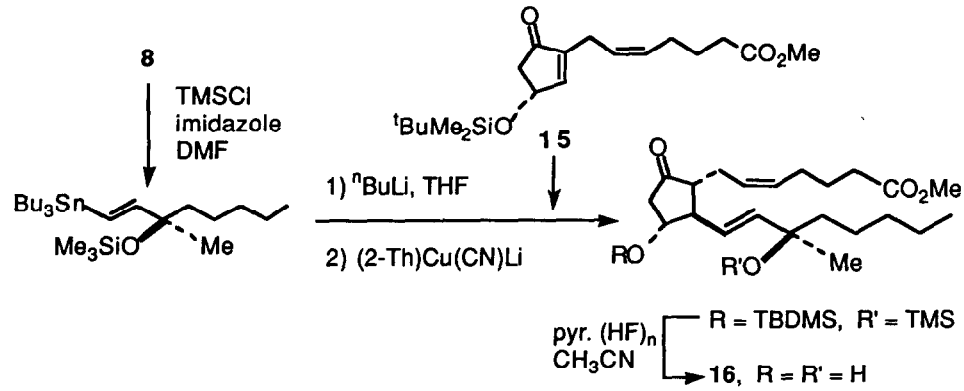
Table 1 Synthesis of chiral tertiary allylic alcohols by the reaction of **3** with nucleophiles.

	3[a]	Nucleophile	Reaction conditions	Tertiary allylic alcohols		(yield, %)[b]	$[\alpha]_D$ (c)[c]
a		H	see the text		**4**	(88),	+9.5° (c 0.76)[d]
b		H	see the text		**5**	(90),	-9.4° (c 0.62)[d]
c		H	see the text		**6**	(81),	-70.4° (c 0.48)
d		$^nBu_3Sn$	LDA (2.5 equiv), Bu_3SnH (1.5 equiv) THF, room temp., 2h		**7**	(95),	-3.8° (c 2.28)
e		$^nBu_3Sn$	LDA (2.5 equiv), Bu_3SnH (1.5 equiv) THF, room temp., 2h		**8**	(97),	+4.2° (c 2.56)
	3c	$^nBu_3Sn$	LDA (2.5 equiv), Bu_3SnH (1.5 equiv) THF, room temp., 2h		**9**	(87),	-9.2° (c 0.79)
	3a	CN	Et_2AlCN (2 equiv) THF, reflux, 2h		**10**	(99),	-6.3°(c 0.82)
	3a	SPh	PhSLi (1.5 equiv) THF, room temp., 1h		**11**	(85),	+17.7° (c 0.95)

[a] Prepared according to the procedure described in ref. 1. [b] Isolated yield. [c] Unless otherwise indicated, in $CHCl_3$ at 25 °C. [d] In Et_2O at 25 °C.

compound). Arbaprostil inhibits gastric acid secretion and protects the gastric mucosa, and thus has deserved particular attention as promising therapeutic agents.[6] The reported synthetic method of arbaprostil, however, suffers from the need of tedious separation of the stereoisomers at C-15 (PG numbering).[7] With the compound **8**, which is corresponding to arbaprostil ω side-chain unit, we carried out the synthesis of methyl ester of arbaprostil via two component coupling process (Scheme 3). After protection of the hydroxyl group of **8** as trimethylsilyl ether it was converted into the higher ordered cyano mixed cuprate by subsequent reaction with ^{n}BuLi (1.0 eq) and (2-thienyl)Cu(CN)Li[8] (1.2 eq) in tetrahydrofuran. The reaction of the enone **15** [9] (1.0 eq) with this cuprate (-78°C to 0°C, 1h) afforded a 1,4-addition product which was desilylated to give methyl ester of arbaprostil **16** ($[\alpha]_D^{18}$ -75.3° (c 1.10, $CHCl_3$), lit.,[7] $[\alpha]_D^{18}$ -74°(c 1.0, $CHCl_3$)) in 77% overall yield.

Scheme 3



References and Notes

1) S. Okamoto, H. Tsujiyama, T. Yoshino, and F. Sato, *Tetrahedron Lett.*, preceding paper. 2) Y. Kitano, T. Matsumoto, and F. Sato, *J. Chem. Soc. Chem. Commun.*, 1323 (1986). *idem, Tetrahedron*, **44**, 4073 (1988). 3) U. Guzzi, R. Ciabatti, G. Parova, F. Battaglia, M. Cellentani, A. Depaoli, G. Galliani, P. Schiatti, and G. Spina, *J. Med. Chem.*, **29**, 1826 (1986). 4) D. Abenhaim, G. Boireau, and B. Sabourault, *Tetrahedron Lett.*, **21**, 3043 (1980). D. Abenhaim, G. Boireau, and A. Deberly, *J. Org. Chem.*, **50**, 4045 (1985). 5) S. Okamoto, T. Shimazaki, Y. Kobayashi, and F. Sato, *Tetrahedron Lett.*, **28** 2033.(1987) 6) A. Robert, and E. W. Yankee, *Proc. Soc. Exp. Biol. Med.*, **148**, 1155 (1975). G. Vantrappen, J. Jansses, T. Popiela, J. Kulig, G. N. J. Tytgat, K. Huibregtse, R. Lambert, J. P. Pauchard, and A. Robert, *Gastroenterology*, **83**, 357 (1982). W. P. Fung, and M. M. Karim, *Med. J. Aust.*, **2**, 127 (1976). 7) E. W. Yankee, U. Axen, and G. L. Bundy, *J. Am. Chem. Soc.*, **96**, 5865 (1974). E. L. Cooper, and E. W. Yankee, *ibid*, **96**, 5876 (1974). 8) B. H. Lipshutz, *Synthesis*, 325 (1987). 9) Prepared according to the procedure reported by us : S. Okamoto, Y. Kobayashi, H. Kato, K. Hori, T. Takahashi, J. Tsuji, and F. Sato, *J. Org. Chem.*, **53**, 5590 (1988).

(Received in Japan 22 May 1991)