Tetrahedron Letters,Vol.26,No.31,pp 3707-3710,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

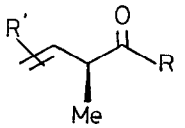
HIGHLY STEREOSELECTIVE APPROACH TO CHIRAL BUILDING BLOCK POSSESSING THREE CONTIGUOUS ASYMMETRIC CENTERS. PREPARATION OF FOUR POSSIBLE DIASTEREOMERS OF β,β'-DIMETHYL-BIS-HOMOALLYLIC ALCOHOL DERIVATIVE

Keisuke Suzuki*, Eiji Katayama, Katsuhiko Tomooka,
Takashi Matsumoto, and Gen-ichi Tsuchihashi*

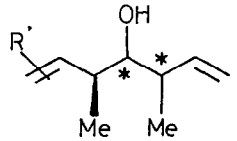
Department of Chemistry, Faculty of Science and Technology,
Keio University, Hiyoshi, Yokohama 223, Japan

Summary: *All four diastereomers of chiral alcohol 2 with three contiguous chiral centers were stereoselectively prepared via diastereoselective addition of nucleophiles (crotyl metal or H^-) to α-methyl-β,γ-unsaturated carbonyl compounds 1.*

Stereo-control of acyclic molecules, both in the enantio- and diastereomerical senses, is a significant problem in organic synthesis. Recently, the potential of the organoaluminum-promoted pinacol-type rearrangement has been demonstrated for the enantiospecific synthesis of chiral building blocks.[1] In connection with our research in the macrolide synthesis, our attention was focussed on the diastereoselective extention of the carbon framework of such chiral building blocks, which would lead to the advanced intermediates having multiple chiral centers. It is one of the common and essential problems in the macrolide synthesis where a wide variety of methods have been devised as exemplified in the "asymmetric aldol strategy" to overcome the so-called "Cram problem" of the chiral carbonyl compounds.[2] Our own clue to solve this problem is the exceptionally high diastereoselectivity in the nucleophilic addition to the α-methyl-β,γ-unsaturated carbonyl compounds 1.[3]



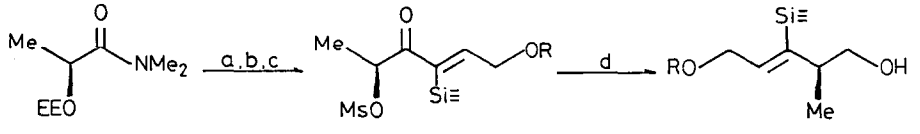
1



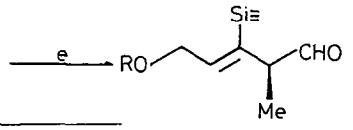
2

In this communication, we wish to describe a highly stereo-controlled approach to such advanced intermediates 2 possessing three contiguous chiral centers. By the full use of the aforementioned high diastereoselectivity, there was realized a stereoselective access to all the four possible isomers of the chiral β,β'-dimethyl-bis-homoallylic alcohol 2.[4]

The aldehyde 6 was prepared from the chiral amide 3 (available from (S)-ethyl lactate)[1] *via* the reductive pinacol-type rearrangement[1b] followed by oxidation.[5] The overall yield was 64% and the geometry of the migrating C-3 unit, 3-alkoxy-1-propenyl group, was retained throughout the process.



3 4 5

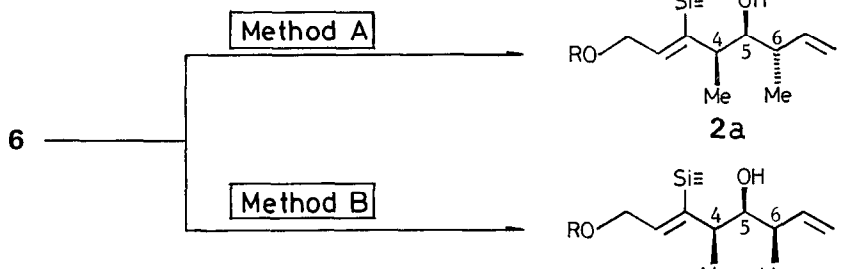


6

R = $PhCH_2OCH_2$-

a) (E)-$PhCH_2OCH_2OCH_2CH$=C($SiMe_3$)Br - BuLi / THF-Et_2O-hexane (4/1/1), -100°C, b) 1 N H_2SO_4 / dioxane, c) MsCl - Et_3N / CH_2Cl_2, -45°C, d) DIBAL / CH_2Cl_2, -78°C, then Et_3Al, e) $(COCl)_2$ - DMSO; Et_3N.

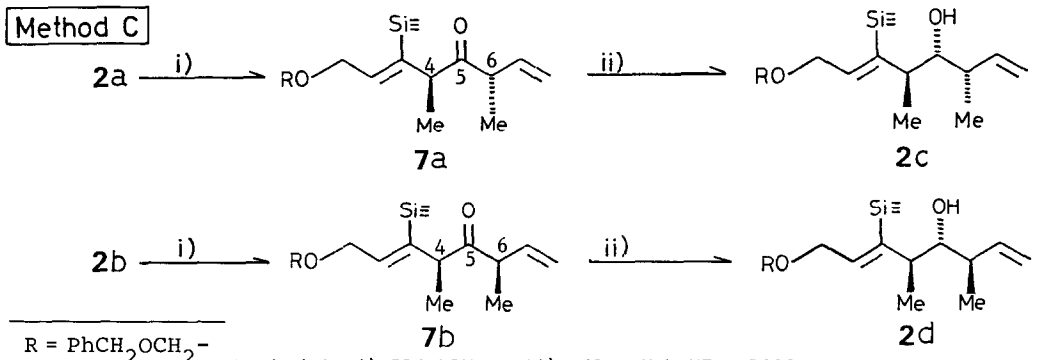
First, the stereoselectivity of the crotylation of 6 was examined: Crotylation of 6 with the Cr-mediated reagent ($CrCl_3$ - 1/2$LiAlH_4$, MeCH=$CHCH_2Br$ / THF, 0°C)[6b] gave the isomer 2a in a highly stereoselective manner. On the other hand, the reaction under the Lewis acid-mediated conditions (Bu_3SnCH_2CH=CHMe, $BF_3 \cdot OEt_2$ / CH_2Cl_2, -78°C)[6c] resulted in the predominant formation of the isomer 2b,[7] as shown in Table I.[8] These results reflect the following two features: (i) The C(4)-C(5) stereochemistry was controlled by the chirality of the aldehyde 6 (the Cram selectivity: 10/1, 12/1) as rationalized in terms of the Felkin-Anh's model,[3,9] and (ii) the C(5)-C(6) counterpart was controlled by the diastereoselectivity inherent in the crotyl metal reagent employed.[6] The stereochemistry of the adduct 2a was confirmed by converting it to the Prelog-Djerassi lactonic acid and the related compound.[10,11,12]



Method A: MeCH=$CHCH_2Br$, $CrCl_3$- 1/2 $LiAlH_4$ /THF, 0°C.
Method B: Bu_3SnCH_2CH=CHMe, $BF_3 \cdot OEt_2$ / CH_2Cl_2, -78°C.

R = $PhCH_2OCH_2$-

The other isomers, 2c and 2d, were also made accessible in highly stereoselective manner by the inversion of the C(5)-hydroxyl of 2a or 2b, efficiently achieved by the following oxidation-reduction sequence (method C): Oxidation of 2a or 2b gave the corresponding ketones 7a or 7b, without any epimerization or the conjugation. Subsequent reduction of these ketones with Super-Hydride ($LiBEt_3H$ / THF, -78°C) resulted in the exclusive formation of the alcohol 2c or



2d, respectively, and no trace of the parent alcohols, 2a and 2b, were detected in each of the cases.[8] Thus, the stereospecific conversion of the isomeric alcohols was realized, that is, from 2a to 2c, and from 2b to 2d.[7,12]

In addition to the apparent synthetic utility of the present reduction, it is also notable that the stereochemical outcome of the H^- attack totally depends on the chirality at C(4) irrespective of that at C(6). Thus, the stereochemical bias posed by the Me_3Si-substituted alkenyl group at C(4) greatly exceeds the non-substituted one at C(6), which could be well understood by our systematic investigation on the substituent dependence of the stereoselectivity in the reduction of the related model substrates as described earlier.[3a]

In Table I is summarized the whole feature of the present process, which depends on the highly diastereoselective attack of the nucleophilic species (crotyl metals or H^-) onto the α-methyl-β,γ-unsaturated carbonyl compounds. By way of these direct and indirect methods, all of the four possible isomers of the β,β'-dimethyl-bis-homoallylic alcohols 2a - 2d were synthesized with high stereochemical purities in a flexible manner.[13]

Application of the present method to the stereoselective synthesis of chiral natural products is now extensively studied in our laboratory.[11]

Table I. Stereoselective Synthesis of Alcohol 2

Starting Material	Method [a]	Ratio[b] 2a	2b	2c	2d
6	A[c]	>99	<1	———	
6	B[d]	4	96	———	
2a	C[f]	not detected		>99	<1
2b[e]	C[f]	not detected		4	96

a) See text. b) By HPLC, see ref 8). c) 78%; (2a+2b) / (2c+2d) = 10 / 1. d) 85%; (2a+2b) / (2c+2d) = 12 / 1. e) 2b containing 4% 2a was used, obtained by method B. f) Yield in two steps: >90%.

Acknowledgment

The present authors wish to express sincere gratitude to Professor Masaru Yamaguchi, Kyushu University, for kindly providing us with the spectral data of the intermediates in the synthesis of protomycinolide IV. Thanks are also due to Dr. Nobuharu Iwasawa, the University of Tokyo, for the measurement of ^{13}C NMR spectra.

References and Notes

1) a) K. Suzuki, E. Katayama, and G. Tsuchihashi, Tetrahedron Lett., 25, 1817 (1984).
b) K. Suzuki, E. Katayama, T. Matsumoto, and G. Tsuchihashi, ibid., 25, 3715 (1984).

2) For example: see S. Masamune, M. Hirama, S. Mori, S. A. Ali, and D. S. Garvey, J. Am. Chem. Soc., 103, 1568 (1981); D. A. Evans and J. Bartroli, Tetrahedron Lett., 23, 807 (1982).

3) a) K. Suzuki, E. Katayama, and G. Tsuchihashi, Tetrahedron Lett., 25, 2479 (1984).
b) Y. Kobayashi, Y. Kitano, and F. Sato, J. Chem. Soc., Chem. Commun., 1984, 1329.

4) Several approaches to the four isomers of the related building unit, R-CHMe-CHOH-CHMe-R', have been reported where R and R' were properly discriminated, see the following;
a) M. R. Johnson, T. Nakata, and Y. Kishi, Tetrahedron Lett., 1979, 4343.
b) H. Nagaoka and Y. Kishi, Tetrahedron, 37, 3873 (1981).
c) T. Nakata, M. Fukui, H. Ohtsuka, and T. Oishi, Tetrahedron Lett., 24, 2661 (1983).
d) Y. Oikawa, T. Nishi, H. Itaya, and O. Yonemitsu, ibid., 24, 1987 (1983).

5) A. J. Mancuso, S.-L. Huang, and D. Swern, J. Org. Chem., 43, 2480 (1978).

6) a) Review: R. W. Hoffmann, Angew. Chem., Int. Ed. Engl., 21, 555 (1982).
b) T. Hiyama, Y. Okude, K. Kimura, and H. Nozaki, Bull. Chem. Soc. Jpn., 55, 561 (1982).
c) Y. Yamamoto, H. Yatagai, Y. Naruta, and K. Maruyama, J. Am. Chem. Soc., 102, 7107 (1980).

7) The $[\alpha]_D$ values and ^{13}C NMR spectra of isomers 2a - 2d are as follows;

Isomer	$[\alpha]_D$ in $CHCl_3$	^{13}C NMR (δ, $CDCl_3$)
2a	$[\alpha]_D^{25}$ -2.5° (c 2.5).	0.76, 14.6, 16.9, 40.8, 41.3, 67.2, 69.5, 76.2, 94.2, 115.3, 127.6, 127.8, 128.4, 138.0, 138.6, 140.8, 147.3
2b	$[\alpha]_D^{24}$ -2.6° (c 2.6).	0.73, 13.4, 16.1, 40.8, 41.3, 67.3, 69.5, 75.7, 94.2, 114.6, 127.7, 127.9, 128.4, 137.9, 138.6, 141.4, 147.6
2c	$[\alpha]_D^{23}$ -20° (c 0.86).	0.60, 11.1, 18.4, 39.4, 41.6, 67.3, 69.6, 78.3, 94.3, 113.9, 127.7, 127.9, 128.4, 138.0, 138.1, 142.9, 148.2
2d	$[\alpha]_D^{23}$ -32° (c 0.94).	0.57, 18.3, 18.4, 40.4, 42.6, 67.3, 69.6, 78.8, 94.3, 115.4, 127.7, 127.9, 128.4, 137.9, 138.4, 139.2, 148.0

8) On SiO_2 TLC (hexane/Et_2O = 7/3), a mixture of 2a - 2d was easily separated into two spots, where the lower spot (Rf 0.29) consisted of 2a and 2b, and the higher one (Rf 0.43) consisted of 2c and 2d. Ratio of 2a/2b, and that of 2c/2d were determined by the HPLC analysis of the separated spots stated above. HPLC conditions are as follows;
2a / 2b: Develosil ODS-5 (4.6/250, Nomura Chem., Co.), MeOH / H_2O = 4 / 1.
2c / 2d: ZORBAX SIL (4.6/250, Du Pont Instruments), hexane / AcOEt = 20 / 1.

9) M. Chérest, H. Felkin, and N. Prudent, Tetrahedron Lett., 1968, 2199; N. T. Anh and O. Eisenstein, Nouv. J. Chim., 1, 61 (1977).

10) M. Honda, T. Katsuki, and M. Yamaguchi, Tetrahedron Lett., 25, 3857 (1984).

11) Intensive work is now under way directed toword the asymmetric total synthesis of the 16-membered macrolide, protomycinolide IV. On the preliminary results of the work, see the accompanying paper in this issue.

12) The stereochemistry of 2b and 2d was determined by ^1H NMR data after conversion to meso-2,4-dimethylpentyl 1,3,5-triacetates according to Oikawa and Yonemitsu et al., (ref. 4d).

13) It is obvious that each antipode of these four isomeric alcohols is accessible, if desired, starting from (R)-methyl lactate; G. Tsuchihashi, K. Tomooka, and K. Suzuki, Tetrahedron Lett., 25, 4253 (1984); K. Suzuki, T. Ohkuma, and G. Tsuchihashi, ibid., 26, 861 (1985).

(Received in Japan 16 April 1985)