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INTRAMOLECULAR ENE APPROACH TO STEREOCONTROL OVER THREE CONTIGUOUS CHIRAL CENTERS

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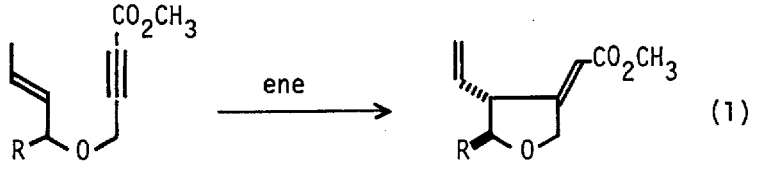
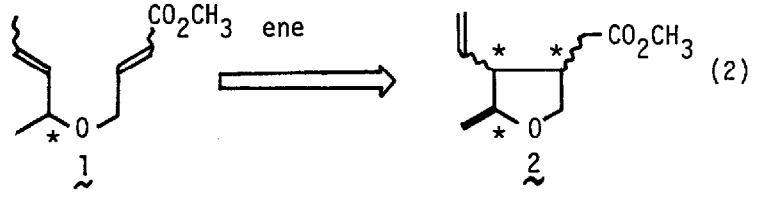
SUMMARY: An intramolecular ene approach to stereocontrol over contiguous chiral centers is described, where three centers can be created with remarkably high level of both diastereofacial selectivity and diastereoselectivity by virtue of the preexisting chiral center in the ene component.

The intramolecular ene reaction has been one of the potentially efficient methods for carbocyclization. However, a previous study on its stereochemistry has been limited on the simple diastereoselection over adjacent two chiral centers.[1] As part of a program designed to develop the intramolecular ene reaction into a new and stereoselective methodology for carbocyclization, we have recently reported the high trans diastereofacial selectivity in the ene cyclization involving an acetylenic enophile (eq 1).[2] As the continuation of our program, we have now investigated the stereochemistry of the ene cyclization involving an olefinic enophile as formulated in eq 2, where three contiguous chiral centers are created by virtue of the preexisting chiral center in the ene component.[3] Disclosed herein is a remarkably high level of stereocontrol, which is dictated by the olefinic geometry of the ene and/or enophile components.





1 2

Substrate ethers (1) with different olefinic geometries, prepared by the standard method via Williamson etherification,[2] were heated at 200 °C[4] in toluene (0.3 M) under argon atmosphere in sealed tubes (Scheme 1). Table 1 summarizes the stereochemical results, which

scheme 1

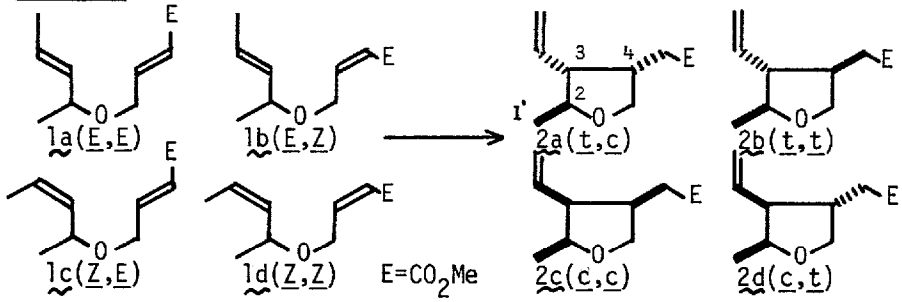


Table 1. Stereocontrol over Three Contiguous Chiral Centers[a]

run	diene 1 (ene, enophile)	ene-product 2a : 2b : 2c : 2d[b]	diastereoselectivity / diastereofacial selectivity
1	**1a** (E, E)	45 : 41 : 10 : 4	55% cis / 86% trans
2	**1b** (E, Z)	65 : 20 : 9 : 6	74% cis / 85% trans
3	**1c** (Z, E)	97 : 0 : 3 : 0	100% cis / 97% trans
4	**1d** (Z, Z)	97 : 0 : 3 : 0	100% cis / 97% trans

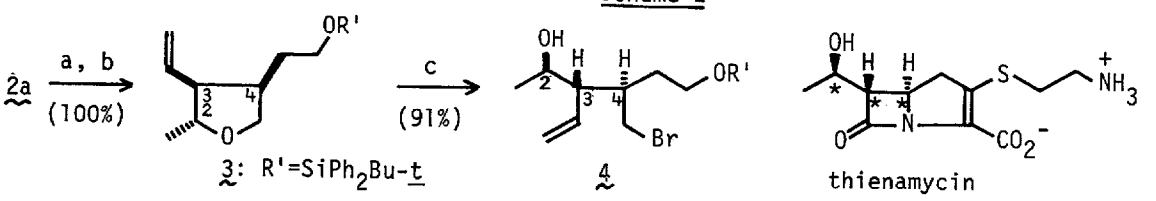
a A 0.3 M solution of the diene (**1**) in toluene was heated at 200 °C for 20 h using a sealed Pyrex tube to give the ene product (**2**) in 60-95% isolated yield after column chromatography. b Determined by capillary GLC (ULBON HR-20M, 50 m), HPLC (Zorbax SIL, hexane/ethyl acetate = 10 : 1) and/or 500 MHz ^{1}H NMR analyses.

reveal the following significant features of the present ene cyclizations. The ene cyclizations involving the E-ene component exhibit a low-to-moderate level of simple diastereoselection (55-74% cis) and diastereofacial selection (85-86% trans); the diastereoselection depends on the enophile geometry, while the diastereofacial selection does not. In marked contrast, the ene cyclizations involving the Z-ene component show a remarkably high level of both diastereofacial selection (97% trans) and diastereoselection (100% cis) irrespective of the enophile geometry; this finding is rather surprising because the acetylenic counterpart involving the Z-ene component do not proceed under similar conditions.[2] It should be emphasized here that the key to the high stereoselective ene-cyclization is the establishment of the olefinic reaction involving the Z-ene component.

The stereochemical assignment of the three contiguous chiral centers deserves special comments. The 2,3-trans configuration of the major stereoisomers (**2a** and **2b**) was determined by ^{1}H- and ^{13}C-NMR, and capillary GLC analyses;[5] the 2,3-trans isomers show the 2-methyl protons[6] and C2/C1'-carbons[7] at lower fields in their ^{1}H- and ^{13}C-NMR and shorter GLC retention time.[8] The 3,4-cis relationship of **2a** was assigned by 500 MHz 2-D NOE spectroscopy (NOESY); a strong cross-peak between the methylene protons alpha to the ester and the vinylic proton was observed.[9]

The three contiguous chiral centers thus controlled can be converted to those in the acyclic system of which the stereochemical relationships are consistent with those of the thienamycin frameworks (Scheme 2).[10] Thus, the reduction of the ester with DIBAH followed by silylation with tert-butyldiphenylsilyl chloride gave the siloxy oxolane (**3**) in almost quantitative yield from **2a**. Treatment of 3 with dimethylboron bromide[11,12] gave the acyclic bromide (**4**) in 91% isolated yield based on the reacted oxolane (**3**).[13]

scheme 2



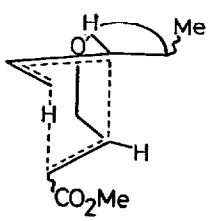
3: R'=$SiPh_2Bu$-t

4

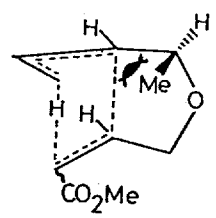
thienamycin

a: DIBAH, b: t-$BuPh_2SiCl$, c: Me_2BBr

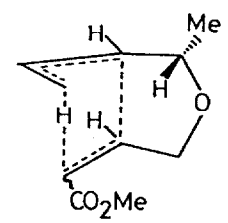
The extremely high diastereoselection and diastereofacial selection are reasonably explicable on the basis of the bicylic transition state model.[1,2] In the cyclization of the Z-ene, the endo transition state (**A**) appears to be highly strained. Therefore, the 3,4-cis product would be formed via the relatively unstrained exo transition states (**B** and **C**). Of the two exo transition states, **B** leading to the 2,3-cis relationship would suffer a large $A^{1,3}$-steric repulsion as shown. Thus, the 2,3-trans, 3,4-cis product (**2a**) is exclusively obtained via the transition state (**C**). In the cyclization of the E-ene, the steric interactions are relatively subtle, and therefore the diastereoselection and diastereofacial selection are only low to moderate.



A → 3,4-trans



B → 2,3-cis
3,4-cis



C → 2,3-trans
3,4-cis

In summary, we have demonstrated a new and efficient intramolecular ene approach to stereocontrol over three contiguous chiral centers, where an extremely high level of both diastereo- and diastereofacial selectivities are obtained. We are currently investigating applications of this methodology to natural product synthesis.

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References and Notes

1 Review: W. Oppolzer and V. Snieckus, Angew. Chem. Int. Ed. Engl., 1978, **17**, 476.

2 K. Mikami, K. Takahashi, and T. Nakai, Chem. Lett., 1987, 2347.

3 Oppolzer et al. have reported an example of the stereocontrol over three contiguous chiral centers in the context of the total synthesis of (-)-α-kainic acid, where 83% stereoselectivity was attained by the preexisting chiral center in the enophile component: W. Oppolzer and K. Thirring, J. Am. Chem. Soc., 1982, **104**, 4978. There is no report, however, on the stereocontrol over three contiguous chiral centers by the preexisting chiral center on an ene component.

4 Up to 170 °C, no ene cyclization was observed.

5 ^{1}H NMR $\delta_{2\text{-Me}}$ **2a**: 1.223 ppm; **2b**: 1.216 ppm; **2c**: 1.128 ppm; **2d**: 1.105 ppm.
^{13}C NMR δ_{C2}/δ_{C1}, **2a**: 79/19 ppm; **2b**: 80/19 ppm; **2c**: 78/17 ppm; **2d**: 77/17 ppm.
GLC R_t **2a**: 23.61 min; **2b**: 19.34 min; **2c**: 25.05 min; **2d**: 24.43 min.
HPLC R_t **2a**: 17.7 min; **2b**: 18.5 min; **2c**: 19.7 min; **2d**: 21.7 min.

6 The 2-methyl protons of 2,3-cis isomers must be shielded by the vinyl groups: D. Kim, Y. M. Jang, I. O. Kim, and S. W. Park, J. Chem. Soc., Chem. Commun., 1988, 760, and references cited therein

7 E. L. Eliel, V. S. Rao, and K. M. Dietrusiewicz, Org. Magn. Reson., 1979, **12**, 461.

8 The 2,3-trans series of oxolanes have been reported to show shorter retention times in GLC: M. L. Mihailovic, S. Gojkovic, and S. Konstantinovic, Tetrahedron, 1973, **29**, 3675.

9 The 3,4-cis relationships of **2a** and **2c** were confirmed through their upfield shifts of C3 and C4 as compared with those of **2b** and **2d**: ^{13}C NMR δ_{C3}/δ_{C4} **2a**: 38.2/32.7 ppm; **2b**: 41.3/35.6 ppm; **2c**: 38.6/33.0 ppm; **2d**: 39.7/35.4 ppm.

10 Review: T. Nagahara and T. Kametani, Heterocycle, 1987, **25**, 729.

11 Direct treatment of **2a** with dimethylboron bromide gave the unexpected lactone.

12 For regiocontrolled opening of cyclic ethers using dimethylboron bromide, see: Y. Guidon, M. Therien, Y. Girard, and C. Yoakim, J. Org. Chem., 1987, **52**, 1680.

13 On treatment with Ag_2O, **4** was converted to **3** in quantitative yield.

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