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A New Alkenyl Ether Giving Acetal with Stereospecific Manner

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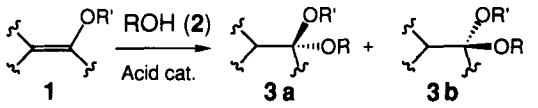
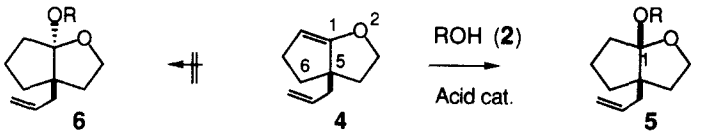
Abstract: A new alkenyl ether, bicyclo[3.3.0]-2-oxa-5-(2-propenyl)-1-octene, can stereospecifically produce cis-fused bicyclo[3.3.0]-2-oxa-(2-pentenyl)-1-alkoxyoctane and the stereochemistry was proved by X-ray analysis.

Alkenyl ethers (**1**) have frequently been used as a protecting reagent of alcohols (**2**) and playing an important role in organic synthesis[1] since protection of hydroxy group with the alkenyl ether and deprotection of the resulting acetal (**3**) can be carried out under the mild acidic conditions and the resulting acetals (**3**) are stable under both protic and aprotic basic conditions (Scheme 1). The serious drawback is, however, that the asymmetric center of the newly formed acetal carbon of **3** is generally *not* controlled *at all* to produce a futile mixture of enantiomers and/or diastereomers (**3a** and **3b**). Complete stereocontrol of asymmetric acetal is observed only when both of the ether linkages (both -OR and -OR' moieties of **3**) are incorporated in conformationally rigid ring system.[2] When the *intermolecular* reaction of **1** and **2** is carried out, OR group of **3** is located out of rigid ring. Thus, the alkenyl ether which produces asymmetric acetal with stereospecific form has not been developed until now.[3] To solve the problem, several alkenyl ethers which produce a symmetric acetal carbon have been reported.[4] In contrast, very few attempts for the stereospecific control of the asymmetric acetal have been accomplished.[5]



Scheme 1.

We report that a new alkenyl ether **4** stereospecifically produces an asymmetric acetal **5** (Scheme 2). Although the OR group of **5**, one of two ether linkages, is *not* incorporated in rigid cyclic system, the asymmetric center at C_1 is perfectly controlled since the *trans*-fused bicyclo[3.3.0]octane skeleton **6** is hardly formed.



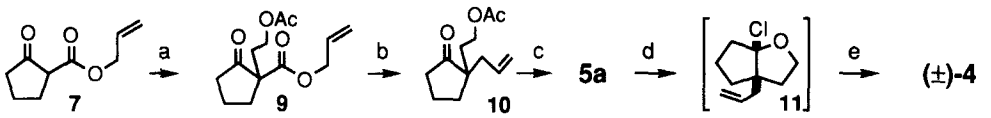
Scheme 2. a: R = -CH_3, b: R = -C_2H_5, c: R = -$CH(CH_3)_2$, d:R = -$C(CH_3)_3$, e:R = -$CH(CONH)_2$

The acetalization reaction from **4** to **5** is carried out using a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) or *p*-toluenesulfonic acid (*p*-TsOH) in either benzene or dichloromethane at a range

from 0°C to ambient temperature. The resulting acetal **5** is stable enough to purify on silica gel column without decomposition. Deprotection reaction is also accomplished with PPTS in methanol to give the free alcohol **2** along with **5a** in high yield.[6]

We attempted the acetal formation using some alcohols to clarify whether the stereospecificity of the reaction from **4** to **5** is independent of the neighboring steric hindrance or not. To get precise information, the acetalization reactions with simple alcohols **2** like methanol, ethanol, 2-propanol and tert-butanol were effected. In each case, a single diastereomer **5a**, **5b**, **5c**, and **5d** was obtained in 92-99% yield. More importantly, no diastereomer **6** could be detected by either ^{1}H- or ^{13}C-NMR spectroscopy. To examine the reliability of stability of stereochemistry at C_1 of **5**, acidic treatment of **5** was also carried out under the condition where the alcohol exchange process is occurred. In the presence of *p*-TsOH at reflux, the four combinations, **5a** in ethanol, **5a** in 2-propanol, **5b** in methanol, and **5c** in methanol, were examined and no isomerization at C_1 was occurred in any case. General procedure for the acetalization reaction is as follows. To a solution of an alcohol (1 mmol) in benzene (5 mL) in the presence of *p*-TsOH (20 mg) or PPTS (20 mg) was added a solution of **4** (180 mg, 1.2 mmol) in benzene (3 mL) slowly at 0°C and the resulting solution was stirred for 20 min. The solution was poured into saturated aqueous solution of sodium hydrogen carbonate and extracted with three portions of ether. The combined organic layers were washed with brine, dried over sodium sulfate or potassium carbonate, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluted with hexane/ether=10/1 to give **5**.[7]

The alkenyl ether **4** was synthesized starting from 2-allyloxycarbonylated cyclopentan-1-one (**7**) in 5 steps (Scheme 3). The alkylation of **7** with **8** in dry acetone gave **9** in 89% yield. The allylic ß-ketoester **9** was converted to the allylic ketone **10** *via* Shimizu-Tsuji procedure[8], followed by treatment with a catalytic amount of *p*-TsOH in methanol to give the cyclic acetal **5a** in 74% overall yield. Treatment of **5a** with acetyl chloride for 20 hr in chloroform gave the chloride **11**, which was immediately converted to **4** using triethylamine in dichloromethane at reflux in 95% overall yield from **5a**. The alkenyl ether **4** was decomposed in silica gel but can be purified by alumina gel column chromatography. [9]



Scheme 3. a. I-CH_2CH_2-OAc (**8**)/K_2CO_3 in acetone: b. $Pd(OAc)_2$/PPh_3 in THF reflux: c. p-TsOH in CH_3OH:d. AcCl in $CHCl_3$ e. Et_3N/t-BuOH in CH_2Cl_2

The *cis*-fused stereochemistry of the 2-oxabicyclo[3.3.0]octane skeleton was confirmed by the X-ray analysis of **5e**[10] (Fig 1).

In conclusion, we have, for the first time, designed and prepared a new alkenyl ether having an asymmetric acetal carbon in stereospecific manner. Protection condition of alcohol using **4** and the chemical stability and deprotection condition of the acetal **5** are similar as the versatile protective reagents like ethyl vinyl ether (EVE) or 3,4-dihydro-2*H*-pyran (DHP). In contrast to EVE and DHP, however, the asymmetric center of acetal carbon is stable and its stereochemistry can be highly reliable and easily estimated. Preparation of optically active **4** is now in progress.

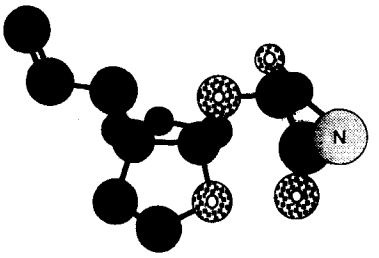


Fig. 1. Structure of 5e Analyzed by X-ray.

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References and Notes

1 Greene, T. W., *Protective Groups in Organic Synthesis*, John Wiley & Sons, New York, **1981**, p21 and p25.

2 Examples of stereospecifically controlled asymmetric acetals in rigid system: Pothier, N.; Goldstein, S.; Deslongchamps, P. *Helv. Chim. Acta.*, **1992**, 75, 604. Mori, K; *Tetrahedron*, **1975**, 43, 209.

3 Examples of the recent reports for the stereoselectivity of the reaction between alkenyl ether and alcohol: 5-Isopropyl-substituted DHP gave 3:1 mixture. Wuts, P. G. M.; Bigelow, S. S. *J. Chem. Soc., Chem. Commun.*, **1984**, 736. Ethyl lactate and DHP gave 1:1 mixture. Mash, E. A.; Fryling, J. A. *J. Org. Chem.*, **1991**, 56, 1094. Mash, E. A. *Synlett*, **1991**, 529.

4 Reese, C. B.; Saffhill, R.; Sulston, J. E. *J. Am. Chem. Soc.*, **1967**, 89, 3366.: van Boom, J. H.; van Deursen, P.; Meeuwse, J.; Reese, C. B. *J. Chem. Soc., Chem. Commun.*, **1972**, 766. Klug, A. F.; Untch, K. G.; Fried, J. H. *J. Am. Chem. Soc.*, **1972**, 94, 7827.

5 Although very high intermolecular stereoselective control was observed in the following papers, the obtained asymmetric centers were kinetically controlled and reliability of the thermodynamic stability was not discussed. Charette, A. B.; Marcoux, J.-F.; Côté, B. *Tetrahedron Lett.*, **1991**, 32, 7215. Noe, C. R.; Knollmüller, M.; Steinbauer, G.; Jangg, E.; Völlenkle, H. *Chem. Ber.*, **1988**, 121, 1231. Ferrier, R. J. *Methods Carbohydr. Chem.*, **1972**, 6, 307.

6 Example of the deprotection procedure: The protected 10-undecen-1-ol (64.0 mg, 0.20 mmol) was treated with PPTS (9 mg) at 35°C for 2 hr in anhydrous methanol (5 ml). The resulting mixture was poured into saturated aqueous solution of $NaHCO_3$ and extracted with three portions of ether. The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluted with hexane/ether=10/1 to give 10-undecen-1-ol (30.7 mg, 0.18 mmol, 90% yield) and **5a** (28.5 mg, 0.19 mmol, 95% recovered).

7 **5a:** IR (neat) 3075, 2974, 2872, 1736, 1639, 1437, 1390, 1325, 1120, 1100, 1060, 912 cm^{-1}; ^1H-NMR (270 MHz), 5.83 (ddd, J = 7.0, 10.0, 16.5 Hz, 1H, CH_2=C***H***-), 5.11 ~ 4.99 (m, 2H, C***H*****$_2$**=CH-), 3.85 (dt, J = 4.5, 8.0 Hz, 1H, -O-C***H*****$_2$**-), 3.76 (dt, J = 7.0, 8.0 Hz, 1H, -O-C***H*****$_2$**-), 3.30 (s, 3H, C***H*****$_3$**O-), 2.33 (ddt, J = 13.0, 7.0, 1.0 Hz, 1H, CH_2=CH-C***H*****$_2$**-), 2.17 (ddt, J = 13.0, 7.0, 1.0 Hz, 1H, CH_2=CH-C***H*****$_2$**-), 2.13 ~ 2.05 (m, 1H), 1.93 (ddd, J = 4.5, 7.0, 12.0 Hz, 1H, -OCH_2-C***H*****$_2$**-C-), 1.71 (dt, J = 12.0, 8.0 Hz, 1H, -OCH_2-C***H*****$_2$**-C-), 1.67 ~ 1.50 (m, 5H). ; ^{13}C-NMR (67.75 MHz) 136.59

117.88, 116.74, 65.91, 53.88, 50.69, 40.11, 38.20, 36.86, 33.80, 21.31, Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.72; H, 9.92.

5b: IR (neat) 3075, 2974, 2872, 1736, 1639, 1437, 1390, 1325, 1120, 1060, 913 cm^{-1}; ^{1}H-NMR (400 MHz) 5.86 (ddt, J = 18.0, 10.0, 7.0 Hz, 1H, CH_2=C***H***-), 5.09 ~ 4.99 (m, 2H, C***H₂***=CH-), 3.82 (ddd, J = 4.0, 8.0, 8.0 Hz, 1H, -OC***H₂***-CH_2-), 3.77 (ddd, J = 7.0, 8.0, 8.0 Hz, 1H, -O-C***H₂***-CH_2-), 3.66 (dq, J = 9.0, 7.0 Hz, 1H, -O-C***H₂***-CH_3), 3.46 (dq, J = 9.0, 7.0 Hz, 1H, -O-C***H₂***-CH_3), 2.26 (ddt, J = 14.0, 7.0, 1.0 Hz, 1H, CH_2=CH-C***H₂***-), 2.10 ~ 2.04 (m, 1H), 2.09 (ddt, J = 14.0, 7.0, 1.0 Hz, 1H, CH_2=CH-C***H₂***-), 1.94 (ddd, J = 4.0, 7.0, 12.0 Hz, 1H, -OCH_2-C***H₂***-), 1.69 (ddd, J = 8.0, 8.0, 12.0 Hz, 1H, -OCH_2-C***H₂***-), 1.65 ~ 1.49 (m, 5H), 1.16 (t, J = 7.0 Hz, 3H, -OCH_2-C***H₃***). ; ^{13}C-NMR (100MHz) 136.90, 117.48, 116.60, 65.80, 58.53, 53.90, 40.27, 38.40, 36.93, 34.53, 21.51, 15.84. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.33; H, 10.25.

5c: IR (neat) 3075, 2974, 2872, 1639, 1437, 1390, 1325, 1120, 1060, 912 cm^{-1}; ^{1}H-NMR (400MHz) 5.86 (ddt, J = 17.0, 10.0, 7.0 Hz, 1H, CH_2=C***H***-), 5.07 ~ 4.99 (m, 2H, C***H₂***=CH-), 3.99 (quintet, J = 6.0 Hz, 1H, $(CH_3)_2$-C***H***-), 3.81 (ddd, J = 4.0, 8.0, 8.0 Hz, 1H, -O-C***H₂***-), 3.77 (ddd, J = 7.0, 8.0, 8.0 Hz, 1H, -O-C***H₂***-), 2.24 (ddt, J = 7.0, 14.0, 1.0 Hz, 1H, CH_2=CH-C***H₂***-), 2.07 (ddt, J = 7.0, 14.0, 1.0 Hz, 1H, CH_2=CH-C***H₂***-), 2.14 ~ 2.07 (m, 1H), 1.92 (ddd, J = 4.0, 7.0, 12.0 Hz, 1H, -OCH_2-C***H₂***-), 1.69 (ddd, J = 12.0, 8.0, 8.0 Hz, 1H, -OCH_2-C***H₂***-), 1.65 ~ 1.45 (m, 5H), 1.15 (d, J = 6.0 Hz, 3H, $(CH_3)_2$-CH-), 1.11 (d, J = 6.0 Hz, 3H, $(CH_3)_2$-CH-). ; ^{13}C-NMR (100MHz) 137.07, 117.69, 116.53, 66.28, 65.59, 54.24, 40.42, 38.55, 36.69, 34.89, 24.72, 24.14, 21.53. Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.23; H, 10.47

5d: IR (neat) 3075, 2974, 2871, 1827, 1731, 1637, 1437, 1371, 1325, 1120, 1060, 912 cm^{-1}; ^{1}H-NMR (400MHz) 5.86 (ddt, J = 17.0, 10.0, 7.0 Hz, 1H, CH_2=C***H***-), 5.07 ~ 4.98 (m, 2H, C***H₂***=CH-), 3.81 (dd, J = 6.0, 7.0 Hz, 2H, -O-C***H₂***-), 2.23 (ddt, J = 7.0, 14.0, 1.0 Hz, 1H, CH_2=CH-C***H₂***-), 2.18 ~ 2.12 (m, 1H), 2.06 (ddt, J = 7.0, 14.0, 1.0 Hz, 1H, CH_2=CH-C***H₂***-), 1.69 ~ 1.50 (m, 5H), 1.44 ~ 1.37 (m, 1H), 1.27 (s, 9H, -C(C***H₃***)₃). ; ^{13}C-NMR (100MHz) 137.38, 117.04, 116.33, 74.28, 65.84, 56.51, 40.66, 38.01, 37.78, 34.88, 30.60, 22.03. Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.67; H, 10.77.

8 Shimizu, I; Tsuji, J. *J. Am. Chem. Soc.*, **1982**, 104, 5844.

9 **4**: IR (neat) 3080, 2980, 2955, 2910, 2860, 1680, 1640, 1455, 1445, 1375, 1230, 1215, 1180, 1170, 995, 925 cm^{-1}; ^{1}H-NMR (270 MHz) 5.87 (dddd, J = 7.0, 7.5, 10.0, 16.5 Hz, 1H, CH_2=C***H***-), 5.15 ~ 5.06 (m, 2H, C***H₂***=CH-), 4.50 (dddd, J = 0.0, 2.0, 9.0, 10.0 Hz, 1H, -O-C***H₂***-), 4.48 (ddd, J = 5.0, 8.5, 10.0 Hz, 1H, -O-C***H₂***-), 4.38 (brdd, J = 3.5, 1.5 Hz, 1H, -C***H***=C-O-), 2.69 (dddd, J = 1.5, 6.0, 9.5, 15.5 Hz, 1H, -C***H₂***-CH=C-O-), 2.39 (dddd, J = 0.0, 3.5, 8.5, 15.5 Hz, 1H, -C***H₂***-CH=C-O-), 2.26 (brdd, J = 7.0, 15.0 Hz, 1H, -C***H₂***-CH=CH_2), 2.19 (brdd, J = 7.5, 15.0 Hz, 1H, -C***H₂***-CH=CH_2), 1.96 (ddd, J = 0.0, 6.0, 12.0 Hz, 1H, -C***H₂***-CH_2CH=C-O-), 1.96 (ddd, J = 0.0, 5.0, 11.5 Hz, 1H, -C***H₂***-CH_2-O-), 1.71 (brddd, J = 8.5, 9.0, 11.5 Hz, 1H, -C***H₂***-CH_2-O-), 1.66 (ddd, J = 8.5, 9.5, 12.0 Hz, 1H, -C***H₂***-CH_2CH=C-O-), ^{13}C-NMR (67.75 MHz) 168.52 (s), 135.82 (d), 117.65 (t), 88.90 (d), 76.91 (t), 54.46 (s), 38.69 (t), 35.74 (t), 35.02 (t), 33.18 (t), (in parenthesis: result by off-resonance measurement). Anal. Calcd for $C_{10}H_{14}O_1$: C, 79.96; H, 9.39. Found: C,79.69; H, 9.37.

10 **X-ray Crystallography of 5e** Crystal data: M.F.=$C_{13}H_{20}N_2O_4(CHCl_3)_{1/2}$, M.W.=328.0, Colorless Prisms, Crystal Sizes = 0.30 x 0.25 x 0.3 mm, Triclinic, spacing group = $P_{\bar{1}}$, a = 11.864(2), b = 13.993(4), c = 11.191(3)Å, α = 102.42(2), β = 114.80(1), γ = 89.16(2)°, V = 1633.9(8)Å^3, Z = 4, Dcalcd = 1.333 g/cm^{-3}, A total of 4169 reflections (2θ > 50°) were measured using ω-2σ scan method, from which 2001 reflections with (|Fo|>3σ|Fo|) were used in the block-diagonal least squares refinement. Intensity data gradually dropped because of an escape of solvent molecule. The ***R*** factor was 0.18 with isotopic temperature factors for non-hydrogen atoms. Further refinement was impossible for the measured data. However, no further experiment was made since the stereochemistry of **5e** was determined unambiguously at this point.

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