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7-*endo* Selective Friedel–Crafts type cyclization of vinyloxiranes linked to an ester group

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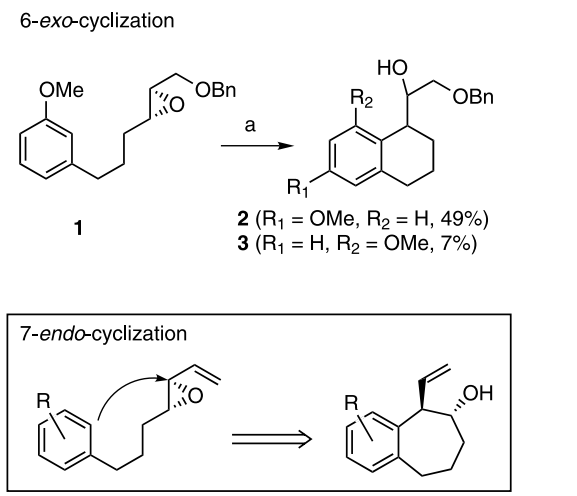
Abstract—Treatment of arylpropyl vinyloxiranes linked to ester with BF_3 was found to produce seven-membered ring products in excellent yields. This reaction proceeded in an inversion fashion.

Nature abounds with compounds containing seven-membered carbocycles as prominent structural features. Since many of these materials also show important biological activities, there is much interest in the development of new efficient methods for the construction of polyfunctional seven-membered carbon rings. Taylor et al. found that arylalkyl epoxides, as well as arylalkyl halides, olefins, and alcohols, are good substrates for intramolecular Friedel–Crafts (FC) reaction.[1] An intramolecular FC reaction of arylalkyl epoxide can be applied to the construction of seven-membered carbocycles. Distinct from other functional groups, epoxide can react in either of two directions. Consequently, regioselectivity is an important issue in this reaction. It should be noted that 7-*endo* cyclization by intramolecular FC reaction is generally difficult. Treatment of **1** with $BF_3{\cdot}Et_2O$ underwent only 6-*exo* cyclization to give **2** and **3** (Scheme 1).[2] It has been reported that the cyclization mode of epoxides with an internal nucleophilic moiety can be regulated by the π-orbital of a vinyl group linked to it under both acidic and alkaline conditions.[3] Such an effect of the π-orbital on the regioselectivity of intermolecular FC reaction has also been found.[4] It is thought that the effect of the π-orbital plays an important role in regioselectivity of the intramolecular FC reaction. We report here the development of 7-*endo* selective cyclization of arylalkyl vinyloxiranes, as shown in Scheme 1.

These vinyloxiranes were synthesized from aldehydes **4a**–**b** (Scheme 2). Wittig reaction of **4a**–**b**[5,6] followed by DIBAH reduction and epoxidation with *m*CPBA gave epoxyalcohols **5a**–**d**.[6] These compounds were converted into the vinyloxiranes **6a**–**d**[6] and **7**[6] by the sequence of Dess–Martin oxidation[7] and Wittig reaction.

At first, intramolecular FC reaction of vinyloxirane **7** was carried out upon treatment with $BF_3{\cdot}Et_2O$ (0.5 equiv.) at −30°C to give an inseparable mixture (ca. 1:1) of two seven-membered ring compounds **8**[6] in high yield (Scheme 3). Unfortunately, the cyclization proceeded non-stereoselectively. This stereochemical result can be rationalized by considering that an overly strong



Scheme 1. *Reagents and conditions*: (a) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −30°C.

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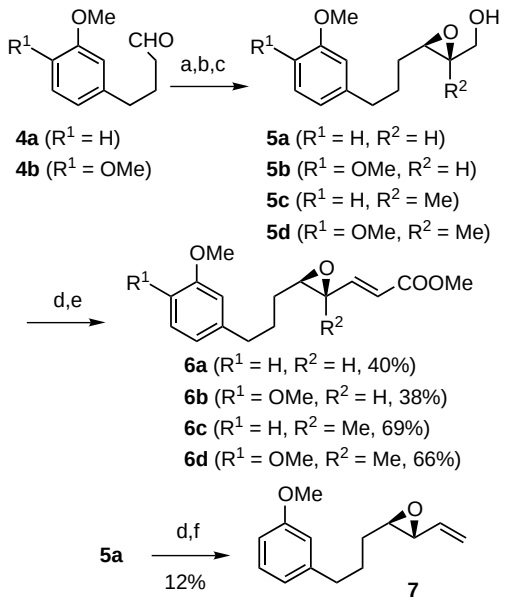
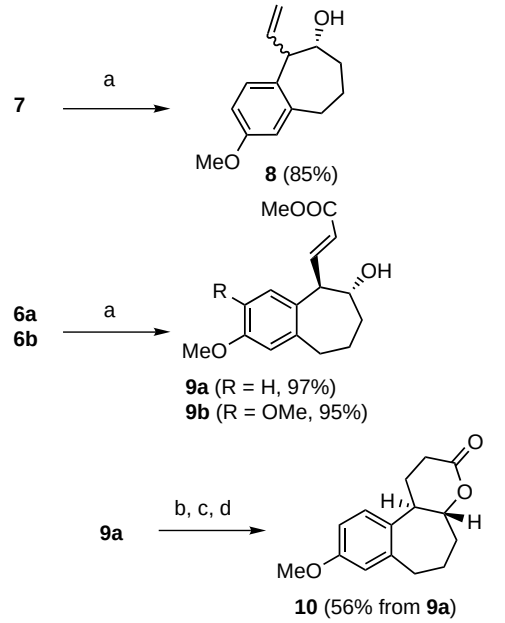


Scheme 2. *Reagents and conditions*: (a) Ph_3P=CHCOOMe or Ph_3P=CMeCOOEt, 60–79%; (b) DIBAH, −30°C, 86–100%; (c) *m*CPBA, 75–90%; (d) Dess–Martin oxd.; (e) Ph_3P=CHCOOMe; (f) Ph_3P=CH_2.



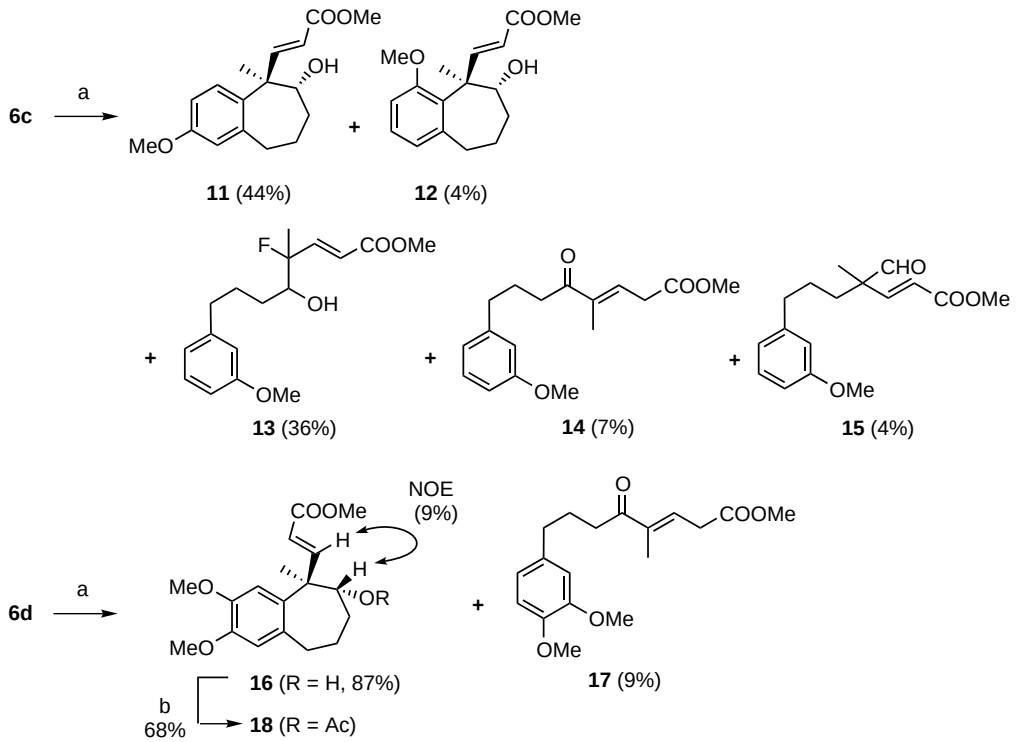
Scheme 3. *Reagents and conditions*: (a) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −30°C; (b) 20% $Pd(OH)_2$-C, H_2, MeOH; (c) K_2CO_3, MeOH, H_2O; (d) DCC, DMAP, toluene.

resonance effect induces the formation of a fully open cation intermediate. Since an ester group was expected to lower the resonance effect of the vinyl group toward epoxide, we next carried out the intramolecular FC reaction of vinyloxiranes **6a**–**b** linked to the ester group. As our expectation, 7-*endo*-cyclization proceeded stereoselectively to afford only **9a**–**b** in almost quantitative yield (Scheme 3). The structure of **9a**–**b** has been identified by ^1H and ^{13}C NMR and HRMS.[8] As a further confirmation, **9a** was converted to a six-membered lactone **10**,[8] whose IR spectrum showed a peak at 1725 cm^{-1}. The stereochemistry of **9a** was determined to be *trans* by a coupling constant (10.3 Hz) between two ring juncture protons in **10**.

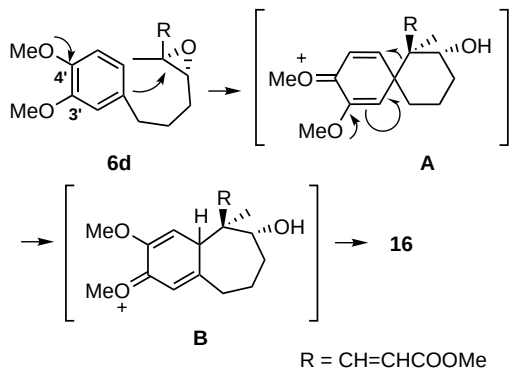
This reaction would be more useful if seven-membered ring compounds possessing quarternal carbon are prepared from trisubstituted epoxide. However, it has been reported by Jung et al. that treatment of 2-methyl-2-vinyl-3-alkyloxiranes with Lewis acid undergoes facile 1,2-alkyl or 1,2-hydride migration.[9,10] We thus thought that such migrations would be a problem in the intramolecular FC reaction of three substituted epoxides. When vinyloxirane **6c** was subjected to the FC reaction, the desired 7-*endo* cyclization took place to provide **11**[6] (44%) and **12**[6] (4%) (Scheme 4). Unfortunately, the success of this cyclization was diminished to some extent by the formation of fluorohydrin **13**[6] (36%), ketone **14**[6] (7%) and aldehyde **15**[6] (4%). It should be noted that a fluorohydrin product was not obtained in Jung's rearrangement of vinyloxiranes.[9,11] Formation of **13** is thought to be due to the presence of a conjugated ester group.

On the other hand, the intramolecular FC reaction of vinyloxirane **6d** proceeded smoothly to provide **16**[6] in high yield along with a small amount of ketone **17**[6] (Scheme 4). Fluorohydrine and aldehyde compounds were not obtained in the reaction of **6d**. The stereochemistry of **16** was determined by NOE correlation of the corresponding acetate **18**[6] as shown. The remarkable improvement of 7-*endo* cyclization by the methoxy group at the C4′ position surprised us because the methoxy group has no resonance effect on alkylation at C2′ or C6′ positions. As an alternative possibility, the mechanistic route including the *ipso*-cyclization of vinyloxirane and the subsequent skeletal rearrangement can also be considered (Scheme 5). If so, the methoxy group at the C4′ position might strongly accelerate the *ipso*-cyclization, and the methoxy group at the C3′ position might be essential for the skeletal rearrangement of spirobenzenium ion **A** into **B** in the sequential process.

In conclusion, we have developed an intramolecular FC reaction of arylalkyl vinyloxiranes showing a selective 7-*endo* cyclization mode. An α,β-unsaturated ester group was found to be the best activator of the C–O bond of epoxide adjacent to it. Di- and tri-substituted epoxides were acceptable for this new reaction. In both cases, excellent yields and high regio- and stereoselectivities were achieved. Obtained seven-membered ring products having polyfunctional groups should be useful for synthetic applications. Mechanistic studies and possible synthetic applications of this reaction are in progress.



Scheme 4. *Reagents and conditions*: (a) $BF_3{\cdot}Et_2O$, CH_2Cl_2, −30°C; (b) Ac_2O, Py.



Scheme 5.

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8. **9a** (colorless oil): IR (neat) 3462, 1721, 1649 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 7.20 (dd, $J=15.6$, 5.6 Hz, 1H), 7.05 (d, $J=9.0$ Hz, 1H), 7.04–6.67 (m, 2H), 5.60 (dd, $J=15.6$, 2.1 Hz, 1H), 4.20 (br, 1H), 3.88 (td, $J=5.6$, 2.1 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 2.85–2.74 (m, 1H), 2.69–2.60 (m, 1H), 2.05–1.86 (m, 2H), 1.75–1.65 (m, 2H), 1.58 (br, 1H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 166.9, 159.1, 147.8, 144.1, 133.3, 127.6, 122.0, 116.6, 111.1, 70.5, 55.4, 55.2, 51.5, 35.8, 34.7, 21.6. HR-MS (EI) calcd for $C_{16}H_{20}O_4$ (M^+) 276.1360. Found 276.1383. **9b** (white needles): mp 144°C (toluene). IR (neat) 3498, 1717, 1653 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$) δ 7.18 (dd, $J=15.5$, 5.3 Hz, 1H), 6.66 (s, 1H), 6.64 (s, 1H), 5.60 (dd, $J=15.5$,

2.0 Hz, 1H), 4.23 (br, 1H), 3.87 (s, 3H), 3.86 (br, 1H), 3.85 (s, 3H), 3.72 (s, 3H), 2.78 (m, 1H), 2.61 (m, 1H), 2.04–1.86 (m, 2H), 1.74–1.63 (m, 2H), 1.57 (s, 1H). ^{1}H NMR (270 MHz, C_6D_6) δ 7.30 (dd, J=15.7, 5.6 Hz, 1H), 6.47 (s, 1H), 6.40 (s, 1H), 5.77 (dd, J=15.7, 2.0 Hz, 1H), 3.91–3.84 (m, 1H), 3.55–3.50 (m, 1H), 3.43 (s, 3H), 3.41 (s, 3H), 3.40 (s, 3H), 2.58 (dd, J=14.3, 11.0 Hz, 1H), 2.27 (dd, J=14.3, 6.3 Hz, 1H), 1.78–1.51 (m, 3H), 1.46–1.33 (m, 1H), 1.26–1.18 (m, 1H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 166.8, 147.8, 147.4, 147.0, 134.9, 127.3, 121.9, 115.8, 114.1, 70.4, 55.9 (×2), 55.8, 51.4, 35.3, 34.5, 21.6. HR-MS (EI) calcd for $C_{17}H_{22}O_5$ (M^+) 306.1466. Found 306.1445. Anal. calcd for $C_{17}H_{22}O_5$ C, 66.65; H, 7.24. Found C, 66.71; H, 7.37%. **10** (white needles): mp 104°C (*n*-hexane:toluene=2:1). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.15 (d, J=8.3 Hz, 1H), 6.76 (dd, J=8.3, 2.7 Hz, 1H), 6.71 (d, J=2.7 Hz, 1H), 4.04 (td, J=10.3, 3.7 Hz, 1H), 3.80 (s, 3H), 3.11 (td, J=10.3, 4.7 Hz, 1H), 2.91–2.67 (m, 3H), 2.53 (ddd, J=5.0, 11.2, 17.2 Hz, 1H), 2.40–2.24 (m, 2H), 2.20–2.04 (m, 2H), 1.95–1.80 (m, 1H), 1.51–1.37 (m, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 171.2, 158.6, 144.7, 130.1, 125.9, 115.4, 111.2, 83.4, 55.2, 41.6, 39.0, 34.8, 30.5, 25.5, 24.1. IR ($CHCl_3$) 1725 cm^{-1}. Anal. calcd for $C_{15}H_{18}O_3$ C, 73.15; H, 7.37. Found: C, 73.30; H, 7.49%.

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