Selective conversion of bromo oxirane into tetrahydropyranylacrylate by epoxide ring opening

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In order to construct the tetrahydropyran ring of rhopaloic acid A and hippospongic acid A, the ring-expansion of methyl 2-bromomethyl-6,7-epoxyhept-2-enoate with various acids was studied; treatment of the bromo oxirane with Lewis acids ($TiBr_4$, $MgBr_2$ and $ZnBr_2$) afforded a tetrahydrofuran derivative as the major product, while reaction of the oxirane with silver salt ($AgNO_3$/KPF_6) gave a tetrahydropyran derivative as the major product.

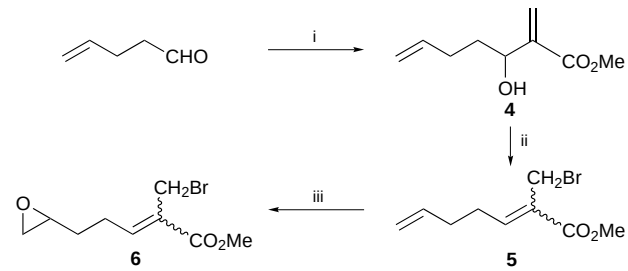
Marine sponges are known to produce structurally and bioactively interesting terpenoids such as rhopaloic acid A (**1**) and hippospongic acid A (**2**) which exhibit potent inhibition in gastrulation of starfish (*Asterina pectinifera*) embryos.[1,2] In particular, rhopaloic acid A, which was isolated from a marine sponge, *Rhopaloeides sp*., exhibited potent cytotoxicities *in vitro* against human myeloid cells, human leukemia cells, *etc*.[1] The interesting structure of these compounds consists of a hydrophilic pyranylacrylic acid moiety and a hydrophobic isoprenoid part. The interest in the structural features and potential of **1** and **2** and their analogues as probes of biological activities prompted us to undertake the selective synthesis of the pyranylacrylate moiety, 2-(1-methoxycarbonylvinyl)tetrahydropyran derivative **3**.

Our synthetic strategy consists of ring-expansion of oxiranes into tetrahydropyran rings followed by connection of various hydrophobic aliphatic chains (Scheme 1). The conversion of oxirane compounds to cyclic ethers is an interesting and useful synthetic methodology. Although extensive work has been reported on *endo*-cyclization of epoxy alcohols,[3] the ring expansion reaction of the epoxy group has hardly been investigated.[4] Recently, Murai and co-workers reported a method for the synthesis of the tetrahydropyran ring by the selective opening of the oxirane ring without directing groups by utilizing the epoxy group as a nucleophile.[4b] Here we describe the selective expansion of the oxirane ring into the tetrahydropyran ring along with simultaneous formation of an acrylate moiety.

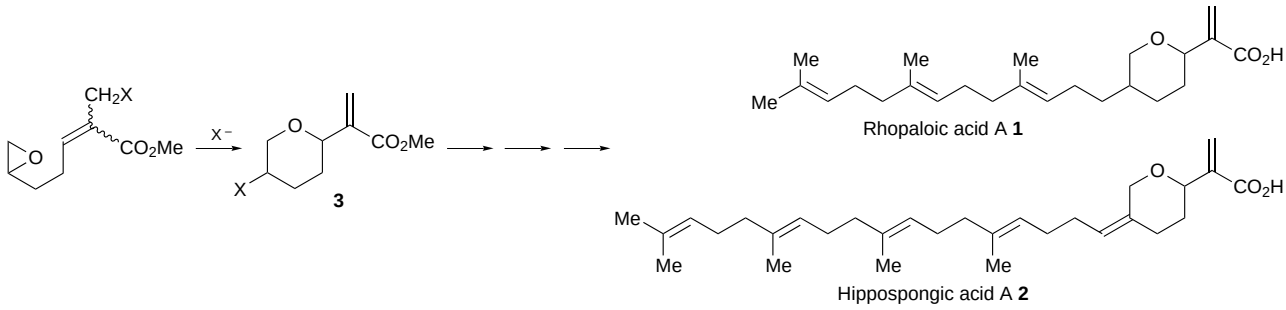
Baylis–Hillman reaction of pent-4-enal with methyl acrylate afforded the corresponding ester **4** in 79% yield. Bromination of **4** with CBr_4–PPh_3 gave bromo ester **5** as a 1 : 1 mixture of geometric isomers in 52% yield. Epoxidation of **5** with MCPBA furnished epoxy bromo ester **6** in 85% yield (Scheme 2).

Treatment of **6** with various acids afforded ring expansion products (tetrahydropyran and tetrahydrofuran derivatives **7a**–**c** and **8a**–**c**) and ring-opened products (**9a**,**b** and **10a**,**b**), Scheme 3 and Table 1. The product distribution was dependent upon the ring-opening reagents. Reaction of **6** (*E*/*Z*, 1 : 1 mixture) with 47% aqueous HBr in THF afforded a mixture of ring-opened products **9b** (11%) and **10b** (57%). Treatment of **6** with $TiCl_4$ gave the analogous chlorides **9a** (47%) and **10a** (44%), while reaction of **6** with $TiBr_4$ gave **8b** (46%), **9b** (14%) and **10b** (32%). Reactions of **6** with $MgBr_2$ and $ZnBr_2$ gave tetrahydrofuran derivative **8b** as a mixture of *cis*/*trans* isomers in 52 and 64% yields, respectively. The *cis*/*trans* ratio of the furan derivatives varied slightly depending on the Lewis acid used.

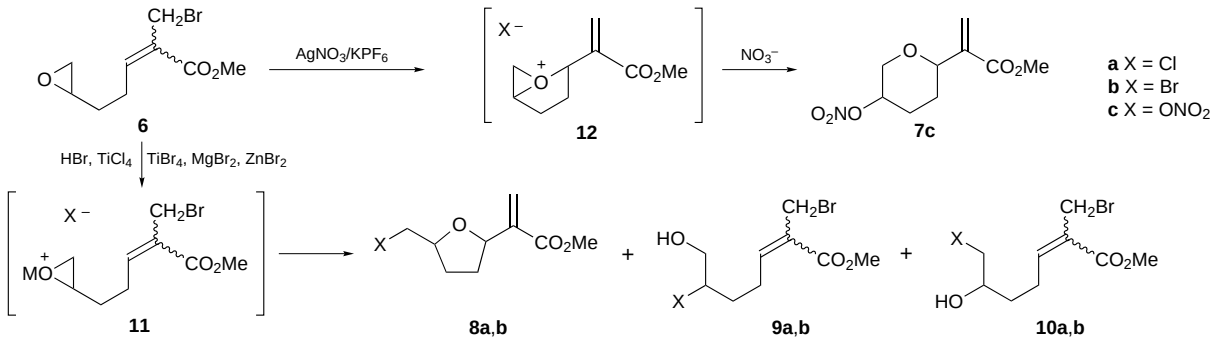
Since proton acid (HBr) and Lewis acids such as $TiCl_4$, $TiBr_4$, $MgBr_2$ and $ZnBr_2$ are considered to be oxophilic, it is reasonable to assume that the acids reacted with the epoxy group to give the intermediate **11**, followed by inter- or intramolecular nucleophilic attack to give **8a**,**b**, **9a**,**b** and **10a**,**b** (Scheme 3). On the other hand, the silver salt, which is known to have a high halide affinity, might be expected to eliminate bromide ion together with concomitant opening of the epoxy group in **6**. In fact, treatment of **6** with a mixed reagent ($AgNO_3$–KPF_6) in Et_2O–H_2O (100 : 1) selectively gave tetrahydropyran derivative **7c** (11%; *cis*/*trans* = 0.4 : 1). The use of CH_2Cl_2 as solvent resulted in an increase in yield. The relative stereochemistry of the diastereoisomers was determined by the vicinal coupling patterns.‡§ In the silver-promoted reaction, the



Scheme 2 *Reagents and conditions*: i, methyl acrylate, DABCO, room temp., 2 weeks, 79%; ii, PPh_3, CBr_4, CH_2Cl_2, room temp., 30 min, 52%; iii, MCPBA, CH_2Cl_2, room temp., 48 h, 85%



Scheme 1



Scheme 3

Table 1 Reaction of bromo epoxide **6** with HBr and Lewis acids

					Product yield (%) (*cis*/*trans* ratio)[a]			
Entry	Reagent	Solvent	Conditions	X	**7**	**8**	**9**	**10**
1	47% aq HBr	THF	25 °C, 6 h	Br	0	0	11	57
2	$TiCl_4$	CH_2Cl_2	−78 °C, 6 h/25 °C, 6 h	Cl	0	0	47	44
3	$TiBr_4$	CH_2Cl_2	−78 °C, 3 h/25 °C, 10 h	Br	0	46 (5 : 1)	14	32
4	$MgBr_2$	Et_2O	−78 °C, 3 h/25 °C, 8 h	Br	0	52 (1 : 1)	12	15
5	$ZnBr_2$	CH_2Cl_2	−78 °C, 6 h/25 °C, 6 h	Br	0	64 (0.4 : 1)	10	9
6	$AgNO_3/KPF_6$	Et_2O–H_2O (100 : 1)	25 °C, 18 h	ONO_2	11 (0.4 : 1)	0	0	0
7	$AgNO_3/KPF_6$	CH_2Cl_2	25 °C, 6 h	ONO_2	56 (0.5 : 1)	0	0	0

[a] The *cis*/*trans* ratio was determined by ^{1}H NMR spectroscopy.

bridged oxonium ion **12** can be considered to form in the initial step by the intramolecular nucleophilic attack of the epoxy group. Then, the *endo*-attack to the intermediate **12** by nucleophile (NO_3^-) would produce 2-tetrahydropyranylacrylate derivative **7c**.[4–6]

The synthetic methodology shown above could be applied to synthesis of not only rhopaloic acid A (**1**), hippospongic acid A (**2**) and their analogues, but also to other natural products containing 5- and 6-membered oxygen heterocycles.[3]

NMR and MS measurements were made using JEOL GSX-270 and SX-102A spectrometers, respectively, at the Instrument Center for Chemical Analysis, Hiroshima University.

Footnotes

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‡ Typical experimental procedure: to a suspension of $AgNO_3$ (70 mg, 0.4 mmol) and KPF_6 (80 mg, 0.4 mmol) in CH_2Cl_2 (10 ml) was added **6** (10 mg, 0.04 mmol). After stirring for 6 h at room temperature, the reaction mixture was filtered. The filtrate was poured into 5% aq. $NaHCO_3$ and extracted with CH_2Cl_2. The extracts were dried and evaporated and the residue was then purified by preparative TLC on silica gel (EtOAc–hexane, 3 : 7 v/v). Each geometric isomer, *trans*-**7c** and *cis*-**7c**, was obtained by recycle HPLC [Japan Analytical Industry Co., Ltd., JAIGEL-H ($CHCl_3$)].

All new compounds were fully characterized by ^{1}H NMR spectroscopy and gave satisfactory high resolution mass spectra. Correct elemental analyses were also obtained for selected compounds. *Selected spectroscopic data* for *trans*-**7c**: ν(neat)/cm^{-1} 1717 (CO_2Me), 1625, 1277 (NO_2); δ_H(270 MHz, $CDCl_3$) 6.31 (dd, *J* 1.5, 1.0, 1 H), 5.98 (t, *J* 1.5, 1 H), 5.00 (m, 1 H), 4.29 (ddd, *J* 13.2, 2.5, 2.0, 1 H), 4.28 (dddd, *J* 9.3, 2.0, 1.5, 1.0, 1 H), 3.80 (dd, *J* 13.2, 1.5, 1 H), 3.77 (s, 3 H), 2.25-2.15 (m, 1 H), 2.09–1.85 (m, 2 H), 1.66–1.51 (m, 1 H); δ_C(270 MHz, $CDCl_3$) 166.1, 140.9, 124.0, 78.0, 75.4, 74.3, 51.8, 31.8, 27.8 (HRMS: found, 185.0815 [M − NO_2]$^+$. Calc. for $C_9H_{13}O_4$, 185.0814). For *cis*-**7c**: ν(neat)/cm^{-1} 1720 (CO_2Me), 1637, 1280 (NO_2); δ_H(270 MHz, $CDCl_3$) 6.25 (t, *J* 1.5, 1 H), 5.94 (dd, *J* 1.5, 1.0, 1 H), 4.75 (tdd, *J* 6.8, 1.5, 1.0, 1 H), 4.61 (dd, *J* 11.7, 3.9, 1 H), 4.50 (dd, *J* 11.7, 5.9, 1 H), 4.29 (m, 1 H), 3.77 (s, 3 H), 2.41–2.31 (m, 1 H), 2.15–2.05 (m, 1 H), 1.81–1.67 (m, 2 H); δ_C(270 MHz, $CDCl_3$) 166.0, 140.6, 125.3, 76.1, 74.9, 68.2, 51.8, 26.8, 26.3 (HRMS: found, 185.0820 [M − NO_2]$^+$. Calc. for $C_9H_{13}O_4$, 185.0814).

§ It is considered that the *cis* isomer exists as a nearly equimolar mixture of two indistinguishable conformers, whereas the *trans* isomer consists of two unequally populated conformers, the predominant e,e conformer and the much less abundant a,a conformer which has axial vinyl and nitro groups. The methine proton at C-2 of the tetrahydropyran ring shows a distinct difference in pattern between *cis*- and *trans*-**7c**. The axial disposition of a methine proton of *trans*-**7c** (δ 4.28) is clearly indicated by its coupling constants, which consist of an axial–axial (*J* 9.3), an axial–equatorial (*J* 2.0) and two allyl ^4J couplings (*J* 1.5 and 1.0). On the other hand, the coupling constants of the methine proton of *cis*-**7c** (δ 4.75) consist of an averaged vicinal (t, *J* 6.8) and two allyl ^4J couplings (*J* 1.5 and 1.0) since the tetrahydropyran ring of *cis*-**7c** is more flexible compared with that of *trans*-**7c**.

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