Conversion of 3-*O*-Substituted 1,2-Dibromoalkanes into 2-Bromo-1-alkenes by the Selective Elimination: Its Application to Total Synthesis of 12-Oxygenated Tremetones

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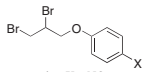
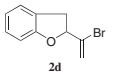
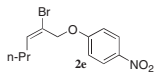
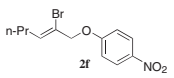
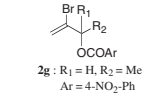
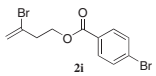
2-Bromo-1-alkenes were efficiently synthesized in good yields by the regioselective HBr-elimination reaction of 3-aryloxy- or 3-acyloxy-1,2-dibromoalkanes. Total synthesis of several oxygenated tremetones has been accomplished by using the 2-bromo-1-alkene derivative produced by this elimination reaction.

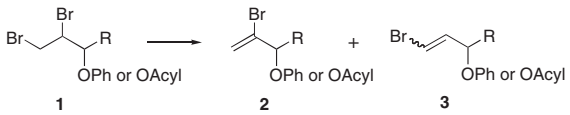
2-Bromo-1-alkenes[1] have been recognized as one of important functional groups for preparation of vinyl lithium[2] and vinyl Grignard reagents,[3] coupling partners in a wide range of transition metal-mediated coupling reactions,[3,4] substrates of radical reaction,[5] and precursors of α-haloketones.[6] Synthesis of 2-bromo-1-alkenes has been achieved by the bromo-boration of terminal alkynes with 9-bromo-9-borabicyclo[3.3.1]nonane (9-Br-9-BBN)[1a] or regioselective addition of hydrogen bromide to alkyne systems.[1b,1c] In our synthetic investigation of biologically active compounds, we unexpectedly found that the selective elimination of 3-aryloxy- or 3-acyloxy-1,2-dibromoalkanes **1** provided the corresponding alkenyl bromide **2** (major product) and **3** (minor product). We disclose herein the investigation of the novel synthesis of 2-bromo-1-alkenes, and its application to natural products synthesis.

Conversion of 3-aryloxy-1,2-dibromoalkanes **1a**–**1f** including the benzofuran-type compound **1d** into the corresponding 3-aryloxy-2-bromo-1-alkenes **2a**–**2f** was investigated (Table 1). Elimination reaction of **1a**–**1f**, synthesized by bromination of the corresponding olefin,[7] provided **2a**–**2f** under basic conditions such as DBU, NaOAc, and NaOPiv in DMF. Characteristically, this method required no extra-dry conditions, as well as expensive reagents. Regioselectivity and yields of the reaction were regulated by the electron-withdrawing effect of *O*-functional groups at the C-3 position of **1** (Entries 1–6). Interestingly, when using weak bases, such as NaOAc and NaOPiv, the desired eliminations preferentially proceeded in good yields, rather than usual substitution reactions of the alkyl bromide into the corresponding acylates. Upon comparison of bases used, good regioselectivity was obtained in the order of DBU > NaOPiv > NaOAc. Even **1d**, carrying a dihydrobenzofuran, underwent the desired HBr-elimination selectively to produce **2d** in good yield (Entries 7, 8). In the case of 3-*O*-substituted-1-alkyl-1,2-dibromoalkane derivatives **1e** and **1f**, both of the *syn*- and *anti*-dibromides underwent the regioselective elimination to provide the corresponding alkenes, **2e** and **2f** (Entries 9, 10). The 1,3-acyl migration by the attack of acyloxy group to the vicinal dibromide was not observed in 3-acyloxy-1,2-dibromoalkanes **1g** and **1h**[7] (Entries 11, 12). On the other hand, regioselectivity and yield of the reaction were decreased in the dibromoalkane **1i**[7] carrying the electron-withdrawing group at the C-4 position of the dibromoalkane chain, effects of which were lowered by insertion of a methylene group (Entry 13). Thus, the merit of our method are as follows; (i) in contrast to precedented method, which employed terminal acetylide precursors, our approach with the bromo-alkene intermediate would provide an entirely different synthetic pathway, for instance, production of **2d** via a terminal acetylene would need long steps more than our method, (ii) our method required no extra-dry conditions, as well as expensive reagents (NaOAc and DBU), (iii) our method is applicable to synthesis of bromoalkenes even at internal position, as depicted in Entries 9, 10.

Table 1. Synthesis of 2-bromo-1-alkenes from 1,2-dibromides

Entry	1,2-Dibroalkane (**1**)	Method[a]	Temp / °C	2-Broalkene (**2**)	Yield / %[b]	Ratio[c] (**2** and **3**[d])
1	**1a**	A	60		**2a** + **3a**: 96	17 : 1
2	**1a**	B	60		**2a** + **3a**: 96	20 : 1
3	**1a**	C	60		**2a** + **3a**: 98	26 : 1
4	**1b**	A	60		**2b** + **3b**: 60	10 : 1[d]
5	**1b**	C	60		**2b** + **3b**: 96	18 : 1
6	**1c**	A	60		**2c** + **3c**: 67	12 : 1
7	**1d**	B	80		**2d** + **3d**: 92	40 : 1
8	**1d**	C	80		**2d** + **3d**: 97	>99 : 1
9[e]	**1e**	C	60		**2e** + **2f** + **3e**: 97 (**2e**:**2f** = 60:1)	40 : 1
10[e]	**1f**	C	60		**2f** + **2g** + **3e**: 99 (**2e**:**2f** = 1:60)	40 : 1
11	**1g**	A	60		**2g** + **3g**: 94	40 : 1
12	**1h**	A	60		**2h** + **3h**: 98	75 : 1
13	**1i**	C	60		**2i** + **3i**: 76	1.5 : 1

[a]Method A; 2 equiv. of NaOAc in DMF, Method B; 2 equiv. of NaOPiv in DMF, Method C; 1.05 equiv. of DBU in DMF. [b]Yield of a mixture of **2** and **3**. [c]Ratio of **2** and **3** was determined by ^{1}H NMR. [d]Starting material was recovered (13%). [e]Racemic compound was used.



In the next stage, the bromoalkene derivative **2d** produced by our effective elimination reaction, was utilized to the total synthesis of several (±)-12-oxygenated tremetones. Tremetone (−)-**4**[8] is the principal toxic ketone of white snakeroot (*Eupato-*

rium urticaefolium) extensively growing in damp area of the central United States. In addition, several tremetone derivatives, possessing the (*R*)- and (*S*)-stereoisomers, were isolated from natural source (Figure 1).[9–12] For instance, methyl (+)-2-(5-acetyl-2,3-dihydrobenzofuran-2-yl)propenoate (**5**) was isolated by Hildebrand et al.[9] from the roots of *Microglossa pyrifolia*, which is used as a traditional medicine both in Africa and in tropical Asia. The first total synthesis of (±)-**6** was achieved by the Nickl reaction,[13] followed by selenium-oxidation (5–16%).[14] (−)-**6**, (−)-**7**, and (±)-**7** were synthesized by using diverse synthetic approaches.[10a,14,15] Although (+)-**5** is an ingredient of esteemed traditional medicine, its biological activity have been uncovered, probably owing to insufficient supplying from natural source. In spite of biological expectation, synthesis of **5** to supply sufficient amounts, has not been reported to our knowledge. Additionally, (−)-**6** was observed to possess inhibitory activity against myeloperoxidase.[10b] With such motivation, total synthesis of **5**, **6**, and **7** in their racemic forms using our regioselective elimination reaction was started.

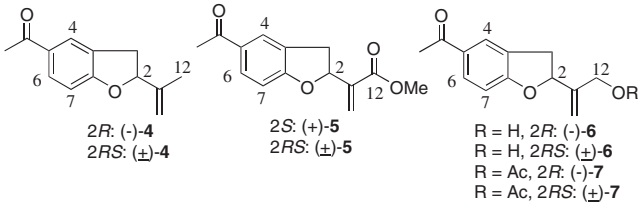
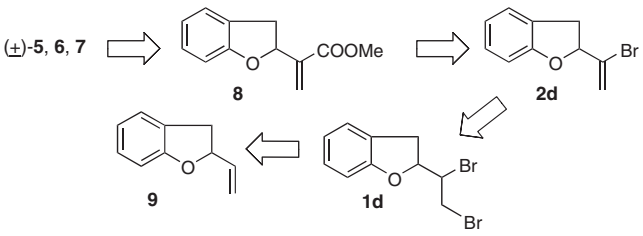


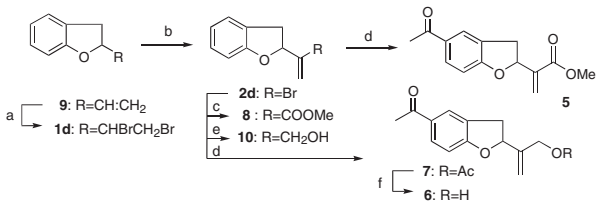
Figure 1. Structure of tremetone and 12-oxygenated tremetones.



Scheme 1. Retrosynthesis of 12-oxygenated-tremetones.

In our retrosynthetic analysis (Scheme 1), **5**, **6**, and **7** would be constructed from the α,β-unsaturated ester **8**, which would be produced from bromoalkene **2d** by using the Pd-catalyzed carbonyl insertion. The bromoalkene system of **2d** would be produced from **9** through intermediate **1d**. Synthesis of the oxygenated tremetones **5**, **6**, and **7** commenced with bromination of **9** to give dibromide **1d** in 95% yield (Scheme 2). The vicinal dibromide possessing a aryloxy group at the adjacent position was regioselectively eliminated with DBU to yield the key 2-bromo-1-alkene derivative **2d** in 97% yield (**2d**:**3d** = >99:1). The Pd-catalyzed carbonyl insertion of **2d** led to methyl ester **8** in 62% yield, followed by acetylation afforded **5** in 91% yield. In addition, the α,β-unsaturated ester **8** was converted into allyl alcohol **10** in 99% yield, and the following acetylation, afforded **7** in 91% yield. Finally, hydrolysis of **7** led to **6** in 99% yield. All of the synthetic **5**, **6**, and **7** were identical to the natural products under the full range of spectroscopic data.[10,11,13]

In conclusion, synthesis of 2-bromo-1-alkene systems has been accomplished in good yields from 3-aryloxy- or 3-acyloxy-1,2-dibromoalkane derivatives **1** by regioselective elimination reactions. Natural tremetone derivatives **5**, **6**, and **7** were successfully synthesized in racemic forms by employing our 2-bromo-1-alkene derivative.



Scheme 2. Reagent and conditions: a. Pyr.-HBr_3, DMF, rt (95%). b. DBU, DMF, 80 °C (97%). c. CO, 10 mol % $PdCl_2(Ph_3P)_2$, Cs_2CO_3, MeOH-PhMe-THF, 60 °C (62%). d. Ac_2O, $SnCl_4$, $(CH_2C1)_2$, 0 °C. (91%). e. DIBAL-H, THF, 0 °C (99%). f. NH_3, MeOH, rt (99%).

References and Notes

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