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1,2-Dibromoalkanes into alkynes by elimination reaction under DBU conditions and their application to total synthesis of sapinofuranone B

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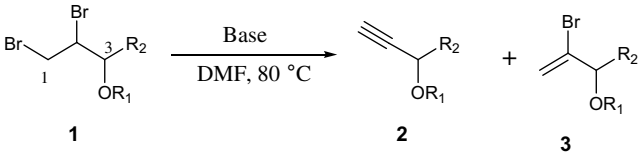
Abstract—Treatment of 1,2-dibromoalkanes with DBU effected an elimination reaction, leading to the alkynes. Oxygen substitution at the C3 position plays a critical role to abstract protons by inductive effects. By the application of this protocol, a total synthesis of sapinofuranone B **4** was accomplished.

In the previous papers, we investigated a facile synthesis of 2-bromo-1-alkenes carrying electron-withdrawing groups under the DBU conditions, which enabled the total synthesis of such natural products as 12-oxygenated-tremetones, tuliparin B, and tanikolide.[1] This elimination reaction might result from the inductive effects of the oxygen substituents, which induce high acidity of a hydrogen at the neighboring position, leading to the desired HBr abstraction. In addition, acidity enhancement of hydrogen at C1 was also observed during our extensive investigation.[1a]

This observation indicated a new prospective synthesis of alkynes from 1,2-dibromoalkanes under the DBU conditions (Scheme 1). Alkynes are one of the important functional groups in organic syntheses, which are employed as precursors of *cis*- and *trans*-1-iodo-1-alkenes,[2] 2-iodo-1-alkenes,[3] metalated alkenes,[2f] and alkynes,[4] as well as substrates of organometal-conducted coupling reactions.[5] HBr elimination reactions of 1,1-dibromo-1-alkenes,[6] and 1,2-dibromoalkanes using LiHMDS, $NaNH_2$, etc.,[7] as well as coupling of aldehydes with phosphonium diazomethanes[8] have been reported as synthetic methodologies of terminal alkynes. In addition



1 2 3

Scheme 1. Elimination reaction of 1,2-dibromoalkanes.

to conventional methods mentioned above, we describe herein our own DBU approach towards alkyne synthesis, and its application toward γ-lactone natural products synthesis (Fig. 1).

Elimination reaction of 1,2-dibromoalkanes carrying oxygen substituents at the C3 positions was undertaken by employing DBU as a base (Table 1).

General procedure (entry 3): To a solution of **1a** (186 mg, 0.5 mmol) in DMF (9.2 mL) was added 5 equiv of DBU at 0 °C; the mixture was stirred at 80 °C for 16 h. The reaction mixture was diluted with a 2:1 mixture of hexane and EtOAc, washed with 1 M aq HCl, H_2O, and brine. The organic layer was dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel column chromatography to yield **2a** (89 mg, 92%).

In contrast to the production of alkene **3a** by 2 or 3 equiv mol of DBU (entries 1 and 2), reaction with 5 equiv mol of the base (entry 3) produced the desired

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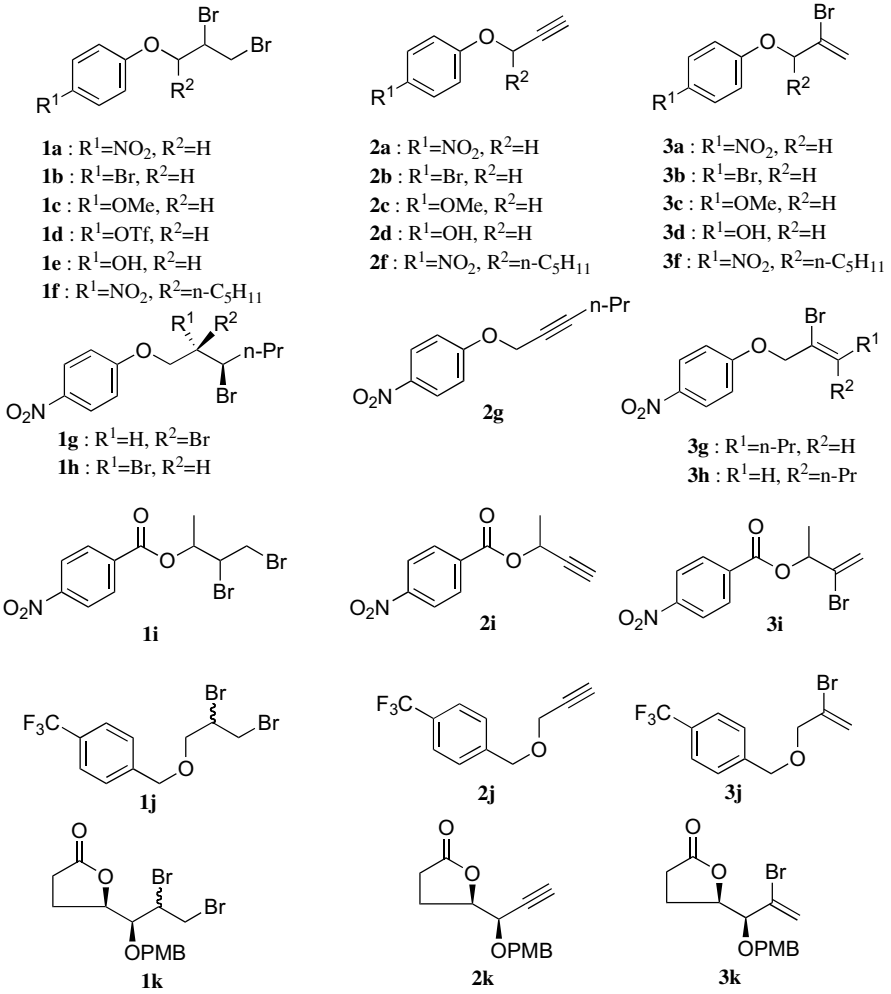


Figure 1.

Table 1. Synthesis of 1-alkynes from 1,2-dibromoalkanes in DMF (80 °C)

Entry	Substrates	Bases (equiv)	Yields (%)	
			1-Alkynes	2-Bromo1-alkenes
1[a]	**1a**	DBU (2)	**2a** (—)	**3a** (100)
2	**1a**	DBU (3)	**2a** (trace)	**3a** (46)
3	**1a**	DBU (5)	**2a** (92)	**3a** (—)
4[b]	**1a**	NaOPiv (7)	**2a** (10)	**3a** (83)
5	**1b**	DBU (5)	**2b** (42)	**3b** (10)
6	**1c**	DBU (5)	**2c** (68)	**3c** (—)
7	**1d**	DBU (6)	**2d** (92)	**3d** (—)
8	**1e**	DBU (5)	**2e** (—)	**3d** (52)
9	**1f**	DBU (5)	**2f** (71)	**3f** (12)
10[c]	**1g**	DBU (5)	**2g** (95)	**3g** (—)
11[c]	**1h**	DBU (5)	**2g** (—)	**3h** (94)
12	**1i**	DBU (5)	**2i** (29)	**3i** (—)
13	**1j**	DBU (5)	**2j** (45)	**3j** (30)
14[d]	**1k**	DBU (5)	**2k** (73)	**3k** (—)

[a] 60 °C 1.5 h.
[b] 12 h.
[c] Racemic compound was used. Relative structure was shown.
[d] 85 h.

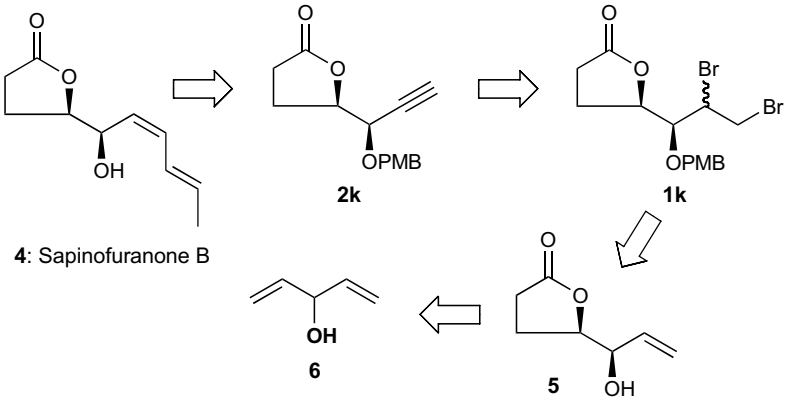
alkyne **2a** in 92% yield as the sole product. This observation indicated that **2a** is produced by a stepwise elimination through **3a**. Upon using NaOPiv, which successfully produced 2-bromo-1-alkenes in the previous investigation,[1a] even 7 equiv mol of the salt provided ca. 1:8 mixture of **2a** and **3a**. In comparison with the oxygen substituent at the C3 position, higher electron-withdrawing groups provided the corresponding alkynes in higher yields (entries 3, 5, and 6). Compound **1d**, possessing a TfO group, was converted with abstraction of the sulfonyl group to alkyne **2d** in 92% yield. Removal of the sulfonyl ester might take place after the construction of the alkyne moiety, because there was no acquisition of **2d**, but the corresponding alkene **3d** was obtained in moderate yield, from the phenolic dibromide **1e**. Upon introduction of an alkyl substituent at the C3 position (**1f**), the corresponding alkyne **2f** was obtained in lower yield than the intact substrate (**1a**), owing to the inductive effect of the alkyl group, which interfered in the electron-withdrawing effect of the oxygen function to lower the acidity of protons at the C1 and C2 positions (entry 9). When the internal dibromides, such as *syn*-**1g** and *anti*-**1h** were treated with DBU, **1g** quantitatively afforded the corresponding alkyne **2g**, in contrast to **1h** producing the bromo olefin **3h** (entries 10 and 11). While a combination of a methyl and an acyloxy group (**1i**) provided alkyne **2i** in low yield (entry 12), lactone **1k** carrying an additional oxygen substituent gave alkyne **2k** as the sole product in good yield (entry 14).

The two electron-withdrawing groups enhanced the desired alkyne synthesis, whereas considerable amounts of alkene **3j** were obtained in the case of the benzyloxy group (**1j**) even carrying a CF_3 group (entry 13).

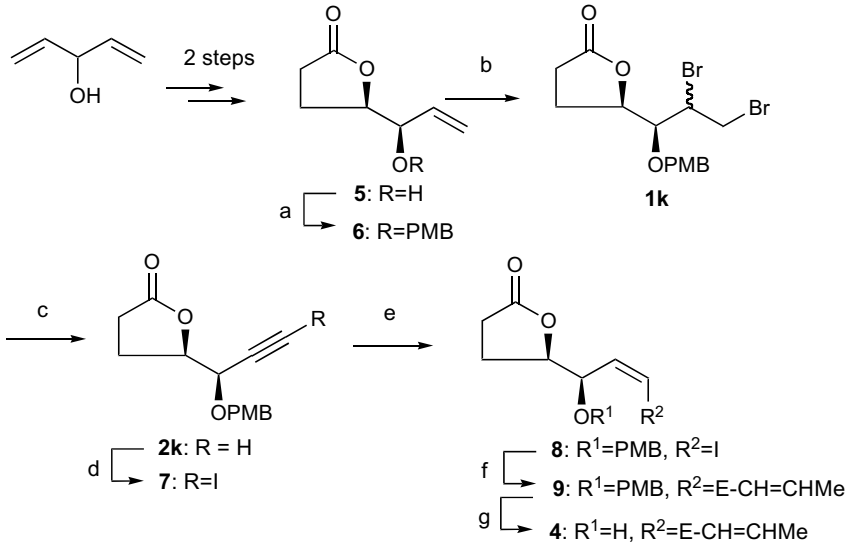
With the observation mentioned above, the alkyne-synthesis protocol was applied to the total synthesis of phytotoxic sapinofuranone B **4**, isolated from *Saphaeropsis sapinea*.[9] Until now, its enantiomer, isolated from *Acremonium strictum*, has been synthesized by two groups.[10] As can be seen in the retrosynthetic analysis (Scheme 2), **4** might be produced by conversion of the alkyne moiety of **2k** to the corresponding diene. Substrate **1k** of the elimination would be obtained by successive *p*-methoxybenzylation and bromination of allyl alcohol **5**.[11]

Along this line, synthesis of **4** was commenced with *p*-methoxybenzylation of **5** to give the PMB ether **6** in quantitative yield, which was submitted to bromination with Py–HBr_3 to yield dibromide **1k**, as a diastereomeric mixture in 93% yield (Scheme 3), which was converted as depicted in Table 1 to **2k** under the DBU conditions. Introduction of iodine into the terminal alkyne moiety[12] in **2k** gave **7** in 80% yield, which was submitted to the diimide reduction[2c,d] with NBSH (*o*-nitrophenylsulfonylhydrazide),[13] leading to the *cis*-iodoalkene **8** in quantitative yield. The Suzuki–Miyaura coupling[14] of **8** with *E*-1-propeneboronic acid provided **9** in 87% yield, which upon deprotection of a *p*-methoxybenzyl group with DDQ gave the expected **4** in 89% yield,[15] spectroscopic data of which was identical with that reported. In this synthesis, the two asymmetric centers were introduced by the Sharpless dihydroxylation protocol,[16] which will enable a synthesis of its enantiomeric form.

In conclusion, our elimination reaction methodology of 3-O-substituted 1,2-dibromoalkanes proposed a new



Scheme 2. Retrosynthetic analysis of sapinofuranone B **4**.



Scheme 3. Reagents and conditions: (a) *p*-methoxybenzyl trichloroacetimidate, TfOH/Et_2O (100%); (b) Py–HBr_3/CH_2Cl_2 (93%); (c) DBU (5 equiv)/DMF, 80 °C (73%); (d) NIS, $AgNO_3$/acetone (80%); (e) NBSH, Et_3N/THF-*i*PrOH (100%); (f) $PdCl_2$(dppf), *E*-1-propeneboronic acid, CsF/PhMe (87%); and (g) DDQ/CH_2Cl_2–H_2O (89%).

synthesis of alkynes under the DBU conditions. As a demonstration of the versatile availability of the reaction, sapinofuranone B **4** was successfully synthesized.

Acknowledgments

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15. $[\alpha]_D^{25}$ −12.6 (*c* 0.50, $CHCl_3$) (optical purity: based on 90% ee); IR: 3421, 1772 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.82 (3H, dd, $J = 0.8$, 6.8 Hz), 2.03–2.12 (2H, complex), 2.19–2.28 (1 H, m), 2.49–2.67 (2H, complex), 4.47 (1H, m), 4.58 (1H, m), 5.32 (1H, m), 5.86 (1H, m), 6.20 (1H, t, $J = 11.7$ Hz), 6.36 (1H, m); ^{13}C NMR ($CDCl_3$) δ 18.5, 23.8, 28.5, 70.1, 82.8, 123.8, 125.9, 133.88, 133.94, 176.8; HRMS calcd for $C_{10}H_{13}O_2$ (M−OH) 165.09145. Found *m*/*z* 165.0901.
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