JOC*Note*

Selective Synthesis of Chiral Dioxabicyclo[4.4.0]decane and Dioxabicyclo[5.3.0]decane from 3,4-Bisallyloxy-but-1-yne Derivatives via Ruthenium-Catalyzed En-yn-ene Metathesis

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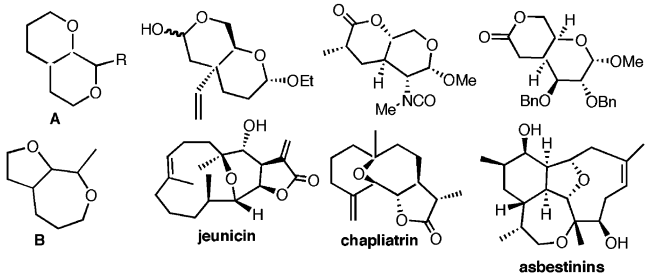
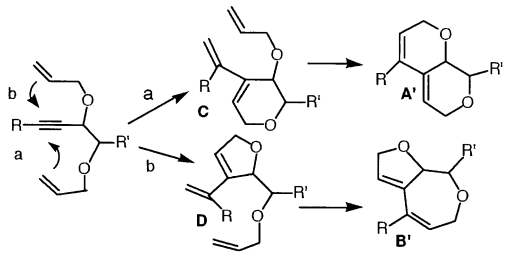
Abstract: We prepared a series of chiral 3,4-bisallyloxy-but-1-ynes having syn and anti configurations. Treatment of these substrates with Grubbs catalyst $Cl_2(PCy_3)_2Ru{=}CHPh$ (3 mol %) preferably gave chiral dioxabicyclo[4.4.0]-decane (yields > 55%) in addition to dioxabicyclo[5.3.0]-decane in minor proportions. On substitution of the 4-allyloxy group of these substrates with a 4-but-2-enyloxy group, the metathesis reactions produced only dioxabicyclo[5.3.0]decane in the presence of Grubbs ruthenium−imidazolidene carbene catalyst.

Enantiopure bicyclic ethers with frameworks **A** and **B** are often encountered in many naturally occurring compounds.[1−3] Scheme 1 shows several representatives[2,3] that exhibit interesting biological activities, including jeunicin,[3c] chapliatrin,[3d] asbestinins.[3e] These two bicyclic ethers are also useful building blocks for complex bioactive molecules.[1−3] A selective synthesis of these frameworks from one precursor is a challenging synthetic issue. Scheme 2 shows a protocol toward synthesis of enantiopure forms of frameworks **A** and **B** from chiral 3,4-bisallyloxy-but-1-yne via ruthenium-catalyzed en-yn-ene metathesis. Two pathways (a and b) are conceivable for such an en-yn-ene metathesis, via intermediate **C** or **D**, that ultimately lead to dioxabicyclo-[4.4.0]decane and dioxabicyclo[5.3.0]decane **A′** and **B′**, respectively. Synthesis of oxygenated molecules via enyne metathesis using Grubbs catalyst might encounter difficulties according to literature reports.[4] Functional groups such as alcohols, esters, or ethers may either not react or perform poorly in enyne metathesis. Chelation of an oxygen atom to a ruthenium carbene catalyst generally impedes catalytic reactivity.[4] The problem can be circumvented

SCHEME 1



SCHEME 2



with the use of ethylene gas or ruthenium−imidazolidene carbene catalyst.[5] Selective synthesis of bicyclic ethers **A′** or **B′** via tandem en-yn-ene metathesis of chiral 3,4-bisallyloxy-but-1-yne is therefore deemed an interesting synthetic approach to be studied.

The alkynyl 3,4-*anti*- and *syn*-diol precursors for the bis(allyloxy) derivatives **1**−**4** (Table 1) were prepared according to published methods.[6,7] As shown in Scheme 3, we also prepared (3*S*,4*S*)-3,4-di(allyloxy-1,5-hexadiyne) (**5**) in a few steps from a derivative of diethyl L-tartrate (eq 1).[8] Eqs 2 and 3 show the protocol[9] for synthesizing chiral *anti*-diol **6** and *syn*-diol **7**, respectively, both having a 4-but-2-enyloxy substituent.

We first examined the metathesis on *anti*-diol derivative **1** using Grubbs catalysts **I**[10] and **II**[11] (Scheme 4). As shown in Table 1, treatment of the *anti*-diol derivative **1** with Grubbs catalyst $Cl_2(PCy_3)_2Ru{=}CHPh$ (**I**) (2 mol %)

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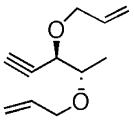
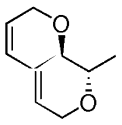
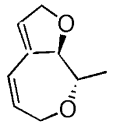
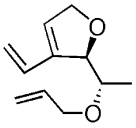
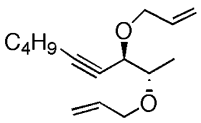
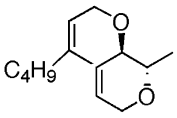
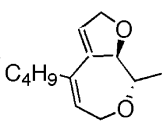
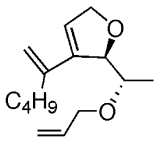
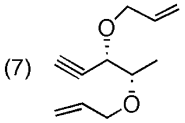
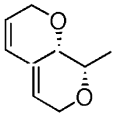
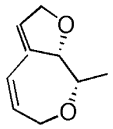
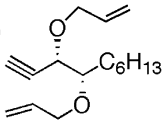
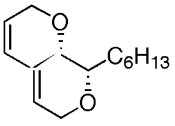
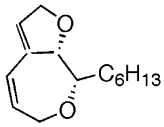
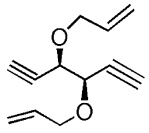
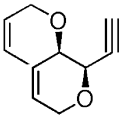
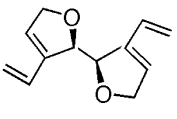
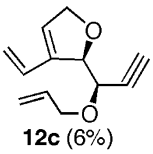
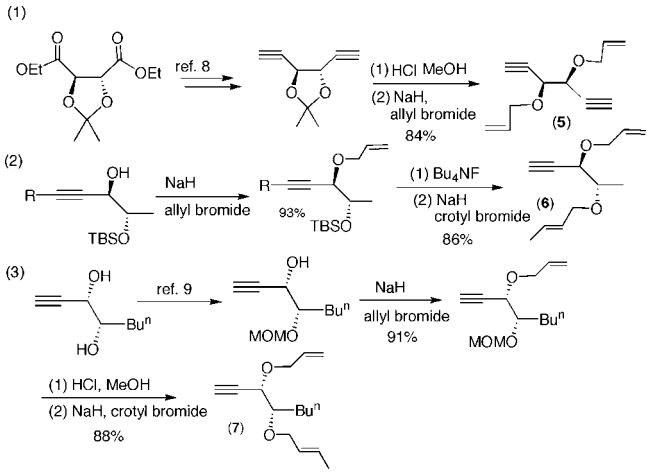
TABLE 1. Ruthenium-Catalyzed En-yn-ene Metathesis of Alkynyldiol Derivatives

	reactants	catalyst	products (yields)[a,c]		
					
(1)	**1**	I[b]	**8a** (trace)	**8b** (trace)	**8c** (trace)
(2)	**1**	I	**8a** (60%)	**8b** (8%)	**8c** (16%)
(3)	**1**	II[b]	**8a** (25%)	**8b** (8%)	**8c** (3%)
	1	II	**8a** (63%)	**8b** (19%)	**8c** (trace)
					
(5)	**2**	I	**9a** (62%)	**9b** (trace)	**9c** (23%)
(6)	**2**	II	**9a** (64%)	**9b** (21%)	**9c** (trace)
(7)	 **3**	I	 **10a** (63%)	 **10b** (15%)	
(8)	 **4**	I	 **11a** (65%)	 **11b** (13%)	
(9)	 **5**	I	 **12a** (56%)	 **12b** (23%)	 **12c** (6%)

[a] Unless specified, the reaction was carried out under ethylene gas (1.0 atm) in CH_2Cl_2 (0.15 M) in the presence of 2.0 mol % catalyst. [b] Under a N_2 atomsphere, 88 and 56% yields of compound **1** were recovered in entries 1 and 3, respectively. [c] Yields are reported after separation from column chromatography on silica gel.

in CH_2Cl_2 (23 °C, 48 h) under nitrogen failed to give any cyclic product in significant amount. The metathesis, however, proceeded smoothly in the presence of ethylene gas, which was shown by Mori[12] to have an accelerating effect on en-yne metathesis. In the presence of catalyst (**I**), the products from substrate **1** consisted of dioxabicyclo-[4.4.0]decane (**8a**), dioxabicyclo[5.3.0]decane (**8b**), and furan derivative (**8c**); the isolated yields were 60, 8, and 16%, respectively. Structural assignment of bicyclic ethers **8a**−**c** are based on proton chemical shifts of the methylene OCH_2 protons, which have values of 4.58 and 4.25 ppm for five- and six-membered ether frameworks,[13] respectively. The corresponding olefinic protons =CH for five- and six-membered ethers occur at 5.80 and 5.42 ppm, respectively.[12] References for the NMR data of these oxacyclic frameworks are available from our previous investigation.[13]

SCHEME 3



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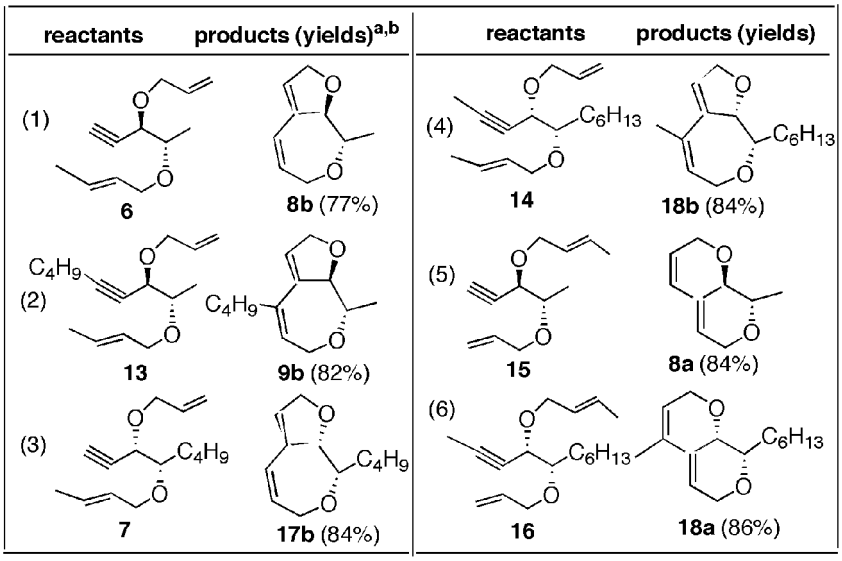
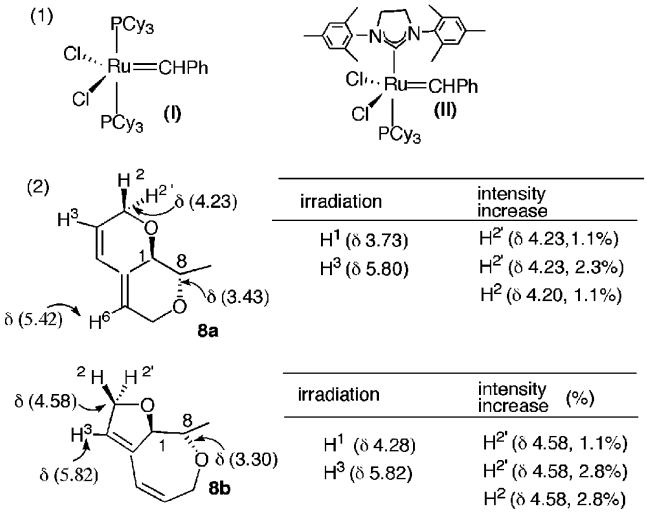
(12) (a) Kitamura, T.; Mori, M. *Org. Lett.* **2001**, 3, 1161. (b) Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082. (c) Kinoshita, A.; Sakakibara, N.; Mori, M. *Tetrahedron* **1999**, *55*, 8155.

TABLE 2. Selective Synthesis of Dioxabicyclo[5.3.0]decane via Tandem En-yn-ene Metathesis



[a] Unless specified, the reaction was carried out under ethylene gas (1.0 atm) in CH_2Cl_2 (0.15 M) in the presence of 2.0 mol % ruthenium−imidazolylidene catalyst **II**. [b] Yields are reported after separation from column chromatography on silica gel.

SCHEME 4. Catalysts, ^{1}H NMR Shifts, and NOE Maps



^{1}H NOE maps of compounds **8a** and **8b** shown in Scheme 4 are consistent with the proposed structure. Using Ru-imidazolylidene catalyst (**II**), only dioxabicyclo[4.4.0]decane (**8a**) and dioxabicyclo[5.3.0]decane (**8b**) were obtained in 63 and 19% yields, respectively, under ethylene gas (entry 4). If the reaction was carried out under nitrogen, the yields of compounds **8a**−**c** were 25, 8, and 3%, respectively, in addition to a 56% recovery yield of starting bisalloxy compound **1** (entry 3). This tandem en-yn-ene metathesis is also applicable to disubstituted alkyne **2** (entry 5), which gave dioxabicyclo[4.4.0]decane **9a** and furanyl diene **9c** in 62 and 23% yields, respectively. In the presence of ruthenium−imidazolylidene catalyst **II**, the minor product became dioxabicyclo[5.3.0]decane (**9b**) (entry 6). Entries 7 and 8 show catalytic transformations of *syn*-diol substrates **3** and **4** to give preferably dioxabicyclo[4.4.0]decane **10a** and **11a** (>63%) in addition to dioxabicyclo[5.3.0]decanes **10b** and **11b** (13−15%) in minor proportions. Evidentally, dioxabicyclo[5.3.0]decanes **10b** and **11b** with the syn configuration are more readily formed from metathesis than their anti analogues **8b** and **9b**. Although several cyclic products can result from highly functionalized dien-diyne **5** (entry 9), dioxabicyclo[4.4.0]decane (**12a**) is the preferable product (56%) accompanied by formation of bis-furan **12b** (23%) and furan **12c** (6%), respectively.

The results in Table 1 reveal that the preferential selectivity of dioxabicyclo[4.4.0]decane is attributed to a thermodynamic issue because a 2,5-dihydrofuran ring is more strained compared with a 3,6-dihydro-2*H*-pyran ring. On the basis of calculation,[14] *anti*-dioxabicyclo[4.4.0]-decane **8a** is ca. 5.9 kJ/mol lower in energy than *anti*-dioxabicyclo[5.3.0]decane **8b**, whereas *syn*-dioxa-bicyclo-[4.4.0]decane **11a** has an energy that is 10.2 kJ/mol smaller than that of *syn*-bicyclic dioxabicyclo[5.3.0]decane **11b**.

An approach for selective synthesis of *syn*- and *anti*-dioxabicyclo[5.3.0]decanes is shown in Table 2 in which the protocol is based on kinetic differentiation. Enyne metathesis of a 1,2-disubstituted olefin is known to proceed much more slowly than that of a vinyl group.[12] Substrates **6**, **7**, **13**, and **14** bear a 4-but-2-enyloxy group to inhibit the formation of a 3,6-dihydro-2*H*-pyran ring. Consistent with our expectation, tandem metathesis of these substrates using ruthenium−imidazolylidene catalyst (**II**) afforded only chiral dioxabicyclo[5.3.0]decanes in good yields (>77%). It worked well for not only both *syn*- and *anti*-diol derivatives but also terminal and disubstituted alkynes (entries 1−4). An alternative approach for selective synthesis of dioxabicyclo[4.4.0]decane is provided in entries 5 and 6, and substrates **15** and **16** have a 3-but-2-enyloxy group, which upon metathesis

(13) Guo, H.; Madhushaw, R. J.; Shen, F.-M.; Liu, R.-S. *Tetrahedron* **2002**, 58 5627.

(14) Calculation of relative energies of dioxabicyclo[4.4.0]decane and dioxabicyclo[5.3.0]decane were performed using the MM2 program (Pro. 6.0 edition).

gives only dioxabicyclo[4.4.0]decanes **8a** and **18a** with little byproducts (<1%).

In summary, we report a selective synthesis of enantiopure dioxabicyclo[4.4.0]decane and dioxabicyclo[5.3.0]-decane based on tandem en-yn-ene metathesis. Treatment of 3,4-bisallyloxy-but-1-yne derivatives with Grubbs catalysts preferably gave chiral dioxabicyclo[4.4.0]decane plus dioxabicyclo[5.3.0]decane in minor proportions. On substitution of the 4-allyloxy group of these substrates with a 4-but-2-enyloxy group, the catalytic reactions afforded only dioxabicyclo[5.3.0]decane in the presence of ruthenium−imidazolidene carbene catalyst.

Experimental Sections

Unless otherwise noted, all reactions were carried out under a nitrogen atmosphere in oven-dried glassware using standard syringe, cannula, and septa apparatus. Benzene, diethyl ether, tetrahydrofuran, and hexane were dried with sodium benzophenone and distilled before use. Dichloromethane was dried over CaH_2 and distilled before use. Chiral diol derivatives **1**−**4** were prepared according to literature procedures.[6−7,15] The ee values of compounds **1**−**4** exceeded 97% on the basis of HPLC analysis (Chiralcel OD, diisopropyl ether/hexane = 1/50). Synthetic procedures and spectral data of compounds **1**−**7** and **9**−**18** are provided in Supporting Information. All NMR spectra were run at 400 MHz (^{1}H NMR) or 100 MHz (^{13}C NMR) in $CDCl_3$ solution.

General Procedure for the Catalytic En-yn-ene Metathesis. To a 25 mL flask were added ruthenium catalyst $(PCy_3)_2Cl_2$-Ru=CHPh **I** (18.1 mg, 0.022 mmol, 2.0 mol %) in CH_2Cl_2 (7.39 mL, 0.15 M) via a syringe and then a CH_2Cl_2 solution (0.50 mL) of *anti*-diol derivative **1** (200 mg, 1.10 mmol) under an atmosphere of ethylene gas (1.0 atm). The resulting light brown solution was allowed to stir at 23 °C for 48 h. The solution was filtered over a short silica bed and chromatographed over a preparative silica plate (diethyl ether/hexane = 1/5) to afford fused dioxabicyclo[4.4.0]decane **8a** (100 mg, 0.65 mmol, 60%), dioxabicyclo[5.3.0]decane **8b** (13.3 mg, 0.087 mmol, 8%), and furan derivative **8c** (31.0 mg, 0.172 mmol, 16.0%), respectively.

Spectral Data for (8*S*,8*aR*)-8-Methyl-2,6,8,8a-tetrahyropyrano[3,4-b]-pyran (8a): $[\alpha]^{23}_D$ +46.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (ppm) δ 6.14 (d, J = 10.4 Hz, 1 H), 5.80 (d, J = 12.4 Hz, 1 H), 5.42 (s, 1 H), 4.30−4.18 (m, 4 H), 3.72 (d, J = 8.8 Hz, 1 H), 3.44−3.40 (m, 1 H), 1.20 (d, J = 6.8 Hz, 3 H); ^{13}C NMR δ 130.5, 127.2, 124.3, 121.1, 74.4, 72.5, 65.9, 65.5, 18.4; HRMS calcd for $C_9H_{12}O_2$ 152.0854, found 152.0859.

Spectral Data for (8*S*,8*aR*)-8-Methyl-2,6,8,8a-tetrahydrofuro[2,3-c]oxepine (8b): $[\alpha]^{23}_D$ +10.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 6.28 (d, J = 11.6 Hz, 1 H), 5.82 (s, 1 H), 5.63 (dd, J = 12.0, 4.4 Hz, 1 H), 4.62−4.58 (m, 2 H), 4.35 (dd, J = 14.0, 5.2 Hz, 1 H), 4.32−4.31 (m, 1 H), 4.26 (d, J = 17.6 Hz, 1 H), 3.34−3.31 (m, 1 H), 1.32 (d, J = 3.8 Hz, 3 H); ^{13}C NMR δ 139.5, 130.5, 125.9, 120.6, 88.6, 79.1, 74.0, 69.4, 19.1; HRMS calcd for $C_9H_{12}O_2$: 152.0164, Found 152.0167.

Spectral Data for (2*R*)-2-[(1*S*)-1-(Allyloxy-ethyl)-3-vinyl-2,5-dihydro-furan (8c): $[\alpha]^{23}_D$ −12.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 6.41 (dd, J = 18.0, 11.2 Hz, 1 H), 5.99−5.95 (m, 1 H), 5.90 (s, 1 H), 5.31 (dd, J = 16.0, 1.6 Hz, 1 H), 5.20−5.14 (m, 4 H), 4.74−4.69 (m, 2 H), 4.12 (dd, J = 12.8, 2.8 Hz, 1 H), 4.05 (dd, J = 12.8, 2.8 Hz, 1 H), 3.80−3.77 (m, 1 H), 1.04 (d, J = 6.4 Hz, 3 H); ^{13}C NMR δ 139.1, 135.4, 129.4, 126.7, 116.7, 116.2, 86.2, 75.7, 75.6, 69.7, 12.7; HRMS calcd for $C_{11}H_{16}O_2$ 180.1257, found 180.1252.

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Supporting Information Available: Spectral data of compounds **1**−**7** and **9**−**18** in repetitive experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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