JOC Article

Carbocyclization Reaction of ω-Iodo- and 1,ω-Diiodo-1-alkynes without the Loss of Iodine Atoms through a Carbenoid-Chain Process

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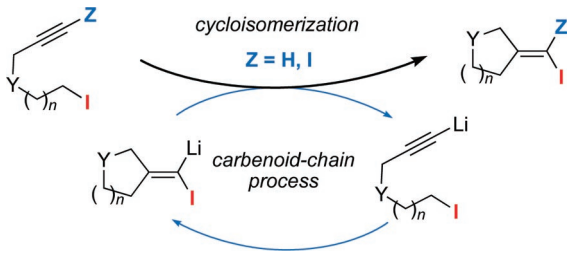
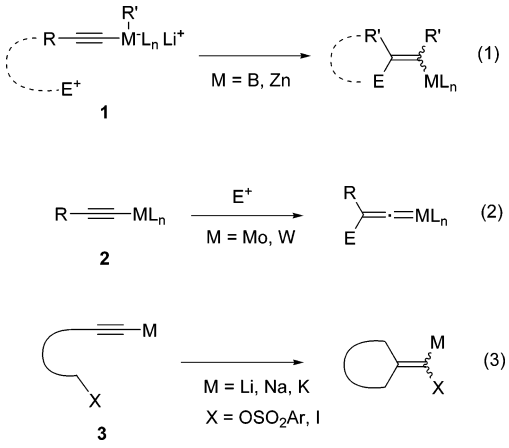
Received September 28, 2007



Atom-economical carbocyclization reactions of ω-iodo-1-alkynes and 1,ω-diiodo-1-alkynes to give products with incorporation of iodine atoms is described. Cycloisomerization of 2-(2-propynyloxy)ethyl iodides is initiated by a catalytic amount of LDA to give 3-(iodomethylene)tetrahydrofurans in high yields. Upon treatment of with a catalytic amount of 1-hexynyllithium, 1,ω-diiodo-1-alkynes efficiently undergo cycloisomerization to give (diiodomethylene)cycloalkanes. The diiodomethylene products are also obtained by iodine atom-transfer-type cyclization of ω-iodo-1-alkynes, using 1-iodo-1-hexyne as an external iodine atom source. Bromine atom-transfer and proton-transfer cyclization proceed as well by employing 1-bromo-1-octyne and 1-octyne, respectively. These reactions are proposed to proceed through a carbenoid-chain process involving *exo*-cyclization of the lithium acetylide intermediates to give Li,I-alkylidene carbenoids. It is shown that the *exo*-cyclization proceeded stereospecifically through inversion of the stereochemistry at the electrophilic carbon.

Introduction

1-Alkynyl organometallics, or acetylides, are efficient carbon nucleophiles, frequently used in organic syntheses. They react with a variety of electrophiles generally at the carbon α to the metal atom.[1] Although being less exploited in organic synthesis, some alkynylmetals are known to react at the β position. Alkynylmetal ate complexes **1** such as alkynylboronates[2,3] and -zincates[4] are known to react at the β position with simultaneous migration of the ate ligand to the α position (eq 1). Transition metal acetylides **2** such as M = Fe, W, Mo, and Rh are known to react with electrophiles at the β position to form vinylidene complexes (eq 2).[5]



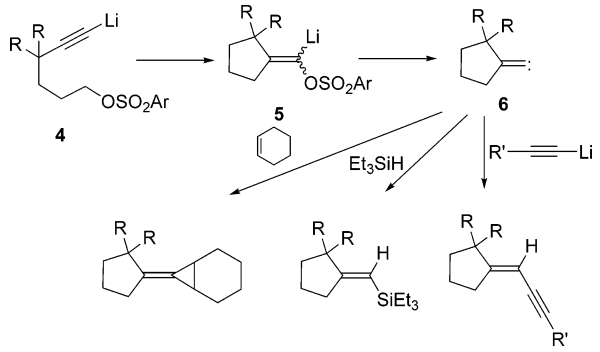
We have recently disclosed that alkaline metal acetylides **3** (M = Li, Na, K) also exhibit nucleophilic reactivity at the β

(1) (a) Pu, L. *Tetrahedron* **2003**, *59*, 9873. (b) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2004**, 4095. (c) Wei, C.; Li, Z.; Li, C.-J. *Synlett* **2004**, 1472.

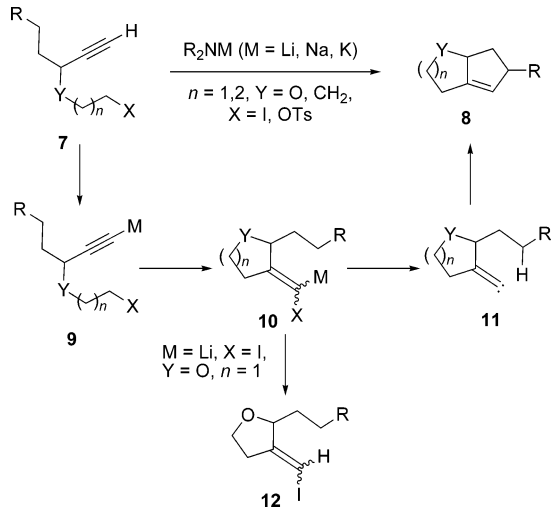
(2) Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*; Academic Press: London, UK, 1988; p 283.

10.1021/jo7021179 CCC: $40.75
Published on Web 12/04/2007

SCHEME 1

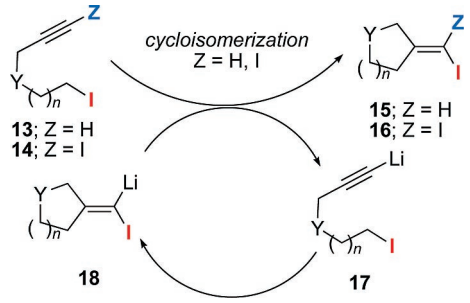


SCHEME 2



position in an intramolecular reaction (eq 3).[6−8] Lithium acetylides **4** bearing a remote leaving group undergo facile *exo*-cyclization at the β position to generate cycloalkylidene carbenoids **5**, which decompose to carbenes **6**, undergoing cyclopropanation, Si−H insertion, and addition by acetylides (Scheme 1).[6,9] A tandem cyclization of alkynes **7** leading to bicyclic products **8** was developed by the use of regioselective intramolecular C−H insertion of cycloalkylidene carbenes **11** generated by the *exo*-cyclization (Scheme 2).[7] Lithium, sodium, and potassium acetylides bearing tosyloxy and iodo leaving groups underwent the tandem cyclization. In the reaction of

SCHEME 3



iodo-acetylide **9** (M = Li, X = I, Y = O, n = 1), (iodomethylene)tetrahydrofuran **12** was obtained as a minor byproduct. The iodine-containing product was assumed to be formed by protonation of unstable Li,I-alkylidene carbenoid **10** before decomposing into reactive carbene **11**.

Organoiodine compounds are one of the most reliable electrophiles in organic synthesis. In their reactions, however, the iodine atom is usually not retained in the product but lost as an iodide salt, making them less attractive from an atom economy point of view.[10] Carbon−carbon bond-forming reactions that give products with incorporation of the iodine atom would provide a useful means for constructing complex carbon frameworks through a subsequent bond-forming reaction of the iodine-containing products.[11]

Byproduct formation of **12** in the tandem cyclization reaction suggested that, in spite of the notorious instability, carbenoids **10** can be trapped before decomposing into carbene **11**. The alkylidene carbenoids[12,13] generated through the *exo*-cyclization are more reactive as a nucleophile than the starting acetylides. We envisaged that the enhanced reactivity of the carbenoids can be exploited as a driving force in atom-economical cycloisomerization of iodoalkynes **13** and diiodoalkynes **14** to give methylene-cycloalkanes **15** and **16**, respectively (Scheme 3): Acetylides **17** would cyclize to form carbenoids **18**, which are reactive enough to be trapped by substrate **13** or **14** to give product **15** or **16**, respectively, with concurrent generation of the acetylides.

Herein, we wish to report cycloisomerization of iodoalkynes and diiodoalkynes to afford (iodomethylene)- and (diiodomethylene)cycloalkanes through a novel carbenoid-chain process

(3) (a) Merril, R. E.; Allen, J. L.; Abramovitch, A.; Negishi, E. *Tetrahedron Lett.* **1977**, 1019. (b) Corey, E. J.; Seibel, W. L. *Tetrahedron Lett.* **1986**, *27*, 909. (c) Negishi, E.; Nguyen, T.; Boardman, L. D.; Sawada, H.; Morrison, J. A. *Heteroatom Chem.* **1992**, *3*, 293.

(4) (a) Harada, T.; Wada, I.; Oku, A. *J. Org. Chem.* **1995**, *60*, 5370. (b) Harada, T.; Otani, T.; Oku, A. *Tetrahedron Lett.* **1997**, *38*, 2855.

(5) (a) Bruce, M. I. *Chem. Rev.* **1991**, *91*, 197. (b) Bruneau, C.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 2176. (c) Joo, J. M.; Yuan, Y.; Lee. C. *J. Am. Chem. Soc.* **2006**, *128*, 14818 and references cited therein.

(6) Harada, T.; Iwazaki, K.; Otani, T.; Oku, A. *J. Org. Chem.* **1998**, *63*, 9007.

(7) Harada, T.; Fujiwara, T.; Iwazaki, K.; Oku, A. *Org. Lett.* **2000**, *2*, 1855.

(8) Harada, T.; Oku, A. *J. Synth. Org. Chem. Jpn.* **2001**, *59*, 101.

(9) In contrast to the nucleophilic nature of acetylides in the *exo*-cyclization, addition of nucleophiles to the electrophilic β-carbon of alkynyliodonium salts has been exploited as a versatile and efficient method of generating alkylidene carbenes. For reviews with leading references, see: (a) Ochiai, M. *Reviews on Heteroatom Chemistry*; Oae, S., Ed.; MYU: Tokyo, Japan, 1989; Vol. 2, p 92. (b) Stang, P. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 274. (c) Varvoglis, A. *Tetrahedron* **1997**, *53*, 1179. (d) Stang, P. J.; Zhdankin, V. V. *Tetrahedron* **1998**, *54*, 10927. (e) Stang, P. J. *J. Org. Chem.* **2003**, *68*, 2997.

(10) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695.

(11) For iodine transfer radical cyclization of hex-5-enyl and hex-5-ynyl iodides, see: (a) Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1989**, *111*, 6265. (b) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140. (c) Ichinose, Y.; Matsunaga, S.; Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1989**, *30*, 3155. (d) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1998**, *63*, 8604. (e) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 11041. (f) Chakraborty, A.; Marek, I. *Chem. Commun.* **1999**, 2375. (g) Yanada, R.; Koh, Y.; Nishimori, N.; Matsumura, A.; Obika, S.; Mitsuya, H.; Fujii, N.; Takemoto, Y. *J. Org. Chem.* **2004**, *69*, 2417.

(12) (a) Köbrich, G. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 49. (b) Köbrich, G. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 41. (c) Köbrich, G. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 473. (d) Stang, P. J. *Chem. Rev.* **1978**, *78*, 383. (e) Taber, D. F. *Methods of Organic Chemistry* (*Houben Weyl*); Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: New York, 1995; Vol. E21a, p 1127. (f) Kirmse, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1164. (g) Braun, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 430. (h) Boche, G.; Lohrenz, J. C. W. *Chem. Rev.* **2001**, *101*, 697. (i) Knorr, R. *Chem. Rev.* **2004**, *104*, 3795.

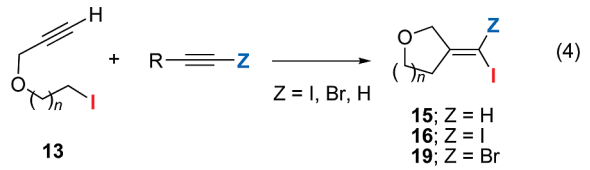
(13) For Li,I-alkylidene carbenoids, see: (a) Barluenga, J.; Rodriguez, M. A.; Campos, P. J.; Asensio, G. *J. Am. Chem. Soc.* **1988**, *110*, 5567−5568. (b) Barluenga, J.; Gonzalez, J. M.; Llorente, I.; Campos, P. J.; Rodriguez, M. A.; Thiel, W. *J. Organomet. Chem.* **1997**, *548*, 185−189.

TABLE 1. Cycloisomerization of Iodoalkyne 13a

entry	base	equiv	concn (M)	yield[a] (%)	*E*:*Z*[b]
1	LDA	0.2	0.1	30	10:1
2	LDA	0.2	0.5	74	9.1:1
3	LDA	0.2	1.0	70	9.0:1
4	LDA	0.1	0.5	30	8.1:1
5[c]	LDA	0.4	0.5	54	5.3:1
6	$NaN(TMS)_2$	0.2	0.5	10	4.2:1

[a] Isolated as an *E*−*Z* mixture after flash chromatography. [b] Determined by a capillary GC analysis. The structure of (*E*)-**15a** was determined by NOESY analysis. [c] **20** was also obtained in 10% yield.

involving *exo*-cyclization of the acetylide intermediate. The extension of the reactions to an atom-transfer-type cyclization of **13** (eq 4) as well as some mechanistic aspects in *exo*-cyclization of acetylides are also described.[14]

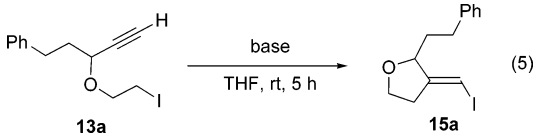


(4)

Results and Discussion

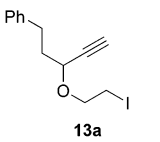
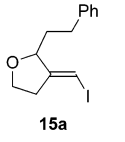
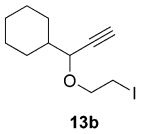
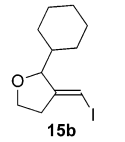
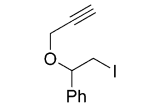
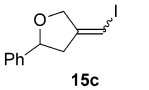
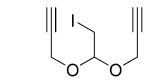
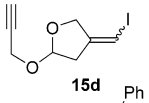
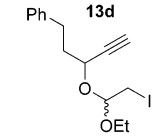
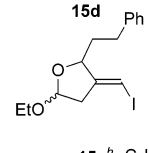
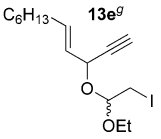
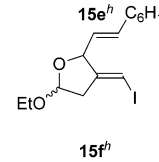
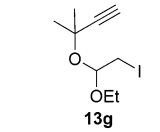
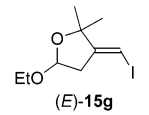
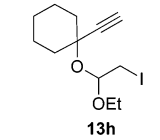
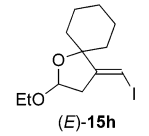
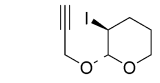
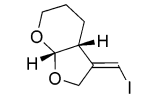
Cycloisomerization of Iodoalkynes. Treatment of iodoalkyne **13a** with 0.2 equiv of LDA in THF at 0.1 M for 5 h at room temperature gave cycloisomerization product (*E*)-**15a** stereoselectively in 30% yield together with the recovery of **13a** (60%) (Table 1, entry 1). Reactions at higher concentrations of 0.5 and 1.0 M gave (*E*)-**15a** in the improved yields of 74% and 70%, respectively, demonstrating the catalytic nature of the cycloisomerization reaction (entries 2 and 3). It should be noted that, in these reactions, any products derived from the intermolecular substitution reaction of an acetylide intermediate were not observed.[15] The use of a reduced amount of LDA gave rise to lower conversion of the reaction (entry 4), whereas an increased amount of the base did not give a better result and tandem-cyclization product **20** (10%) was obtained as a byproduct (entry 5). The formation of (*E*)-**15a**, albeit in low yield, was also observed with $NaN(TMS)_2$ (entry 6) but not with $KN(TMS)_2$. No reaction was observed when the reaction with LDA was carried out in ether. Bromoalkyne **21** did not undergo similar cyclization even at 65 °C.

The scope of LDA-initiated carbocyclization of iodoalkynes **13** is summarized in Table 2. The reaction of cyclohexyl derivative **13b** also proceeded with LDA (0.2 equiv) at room temperature to give (*E*)-**15b** stereoselectively (entry 2). On the other hand, iodoalkyne **13c** bearing phenyl group β to the iodine atom was found to be less reactive. The reaction with 0.4 equiv of LDA at 65 °C afforded **15c** as a mixture of stereoisomers in 30% yield (entry 3). The present cycloisomerization was successfully applied to acetal derivatives **13d**−**i**. Acetal **13d**, not bearing substituents at the propargylic position, was slightly less reactive but the corresponding cycloisomerization product



(5)

TABLE 2. LDA-Catalyzed Cycloisomeriztion of Iodoalkynes 13

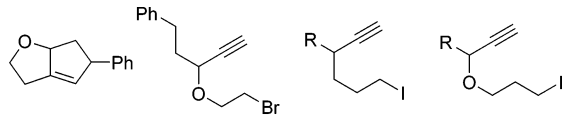
entry	iodoalkyne	product	yield[b] (%)	*E*:*Z*[c]
1	 **13a**	 **15a**	74	9.1:1
2	 **13b**	 **15b**	69	7.0:1
3[d,e]	 **13c**	 **15c**	30	1:1.3
4[f]	 **13d**	 **15d**	81	1:1.3
5	 **13e**[g]	 **15e**[h]	76	8.5:1[i]
6	 **13f**[g]	 **15f**[h]	62	5.5:1[i]
7	 **13g**	 (*E*)-**15g**	63	*j*
8[k]			62	*j*
9	 **13h**	 (*E*)-**15h**	81	*j*
10[d,e]	 **13i**	 (*Z*)-**15i**	7	*j*

[a] Unless otherwise noted, the reactions were carried out by using 0.2 equiv of LDA in THF at 25−30 °C for 4−7 h. [b] Isolated as an *E*,*Z* mixture after flash chromatography. [c] Unless otherwise noted, the *E*,*Z* ratio was determined by a capillary GC analysis. [d] The reaction was carried out at 65 °C. [e] LDA (0.4 equiv) was used. [f] The reaction was carried out at 40 °C for 18 h. [g] A 1:1 mixture of diastereomers. [h] *E* and *Z* isomers were obtained as a mixture of diastereomers. [i] Determined by ^1H NMR analysis. [j] The geometrical isomer was not detected by ^1H NMR analysis. [k] The reaction was carried out by using 0.1 equiv of LDA.

(14) For a preliminary report of the work described here, see: (a) Harada, T.; Muramatsu, K.; Fujiwara, T.; Kataoka, H.; Oku, A. *Org. Lett.* **2005**, *7*, 779. (b) Harada, T.; Mizunashi, K.; Muramatsu, K. *Chem. Commun.* **2006**, 638. (c) Harada, T.; Kitano, C.; Mizunashi, K. *Synlett* **2007**, 1130.

(15) Intermolecular reactions of lithium acetylides with primary iodoalkanes are slow in THF at room temperature and generally carried out in the presence of polar additives such as HMPA. (a) Fletcher, S.; Ahmad, A.; Perouzel, E.; Heron, A.; Miller, A. D.; Jorgensen, M. R. *J. Med. Chem.* **2006**, *49*, 349. (b) Fiandanese, V.; Bottalico, D.; Marchese, G.; Punzi, A. *Tetrahedron* **2006**, *62*, 5126. (c) Narayan, R. S.; Borhan, B. *J. Org. Chem.* **2006**, *71*, 1416.

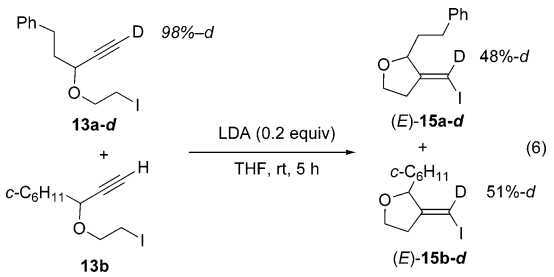
15d was obtained in 81% yield by carrying out the reaction at 40 °C (entry 4). *E*-selective cycloisomerization was observed for acetals **13e**−**h** bearing substituents at the propargylic position (entries 5−9). A smooth reaction took place for *gem*-disubstituted **13g** even with 0.1 equiv of LDA (entry 9). Although extremely sluggish even at 65 °C, the reaction of the transcyclic secondary iodide **13i** afforded cis-fused bicyclic product (*Z*)-**15i** (entry 10). The substrate for the LDA-initiated cycloisomerization is limited to 2-(2-propynyloxy)ethyl iodide derivatives **13** (Y = O, *n* = 1). Attempted reaction of iodoalkynes **22** and **23** did not give the anticipated cyclopentane and tetrahydropyran derivatives.



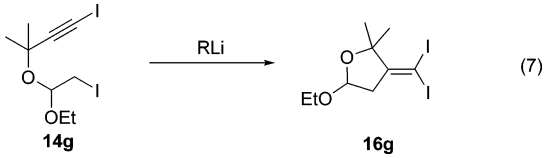
20 **21** **22** **23**

According to our supposition, the cycloisomerization reaction of iodoalkynes **13** proceeds through a chain mechanism depicted in Scheme 3 (Z = H). Thus, lithium acetylide **17**, generated by the lithiation of **13** with LDA, undergoes *exo*-cyclization to give alkylidene carbenoid **18**, which is basic enough to abstract the terminal acetylenic proton of **13** to give cycloisomerization product **15** with simultaneous generation of **17**. The atom transfer radical cyclization of analogous hex-5-ynyl iodides giving rise to cycloisomerization products has been reported.[11] Alternatively, the cycloisomerization reaction may proceed through the radical mechanism if LDA acts as a radical initiator.[16] However, such a mechanism is quite unlikely judging from the following observations. In the reaction of **13f** possessing both hex-5-ynyl and hex-5-enyl iodide structures (Table 2, entry 6), no product derived from cyclization on the olefinic moiety was formed. Low stereoselectivity has been reported for the radical cyclization of hex-5-hexynyl iodides.[11] Indeed, when **13a** was treated with radical initiator Et_3B in hexane at room temperature under air according to the procedure reported by Oshima et al.,[11c−e] **15a** was obtained with low stereoselectivity (*E*:*Z* = 2.7:1) in 49% yield. To the contrary, high *E* selectivity (9.1:1) was observed in the reaction with LDA (Table 1, entry 2).

A support for the proposed carbenoid-chain mechanism was provided by deuterium-labeling experiments. The reaction of **13a-*d*** (98% *d*) with LDA (0.2 equiv) gave (*E*)-**15a-*d*** (90% *d*) in 70% yield. When a 1:1 mixture of **13a-*d*** and **13b** was treated with LDA, deuterium incorporation was observed not only into (*E*)-**15a-*d*** (48%−*d*) (65% yield) but also into (*E*)-**15b-*d*** (51%−*d*) (58% yield) (eq 6). The observation of deuterium scrambling is well in accord with an intermolecular deuterium (and proton) transfer during the cycloisomerization process (Scheme 3).



Cycloisomerization of Diiodoalkynes. Treatment of diiodoalkyne **14g** with butyllithium (0.2 equiv) in THF at 40 °C for 2 h gave 3-(diiodomethylene)tetrahydrofuran **16g** in 69% (eq 7, Table 3, entry 1). An increase in the amount of



14g **16g**

butyllithium resulted in the lower yield of **16g** (entry 2). An improvement in the yield of **16g** was obtained by the use of 1-hexynyllithium as an initiator. Thus, in the presence of 0.2 equiv of 1-hexynyllithium in THF at 40 °C, **14g** cyclized to give **16g** in 85% yield (entry 3). Decreasing further the amount of the initiator decreased the product yield together with the recovery of the starting diiodide (16%) and formation of iodoalkyne **13g** (5%) (entry 3). At 0 °C, the cycloisomerization reaction proceeded slowly (33% conversion after 2 h) but steadily, reaching full conversion of **14g** after 22 h, to give **16g** in 86% yield (entry 5). The cycloisomerization proceeded also in DME with a slightly lower efficiency (entries 6 and 7). No reaction was observed in less polar diethyl ether (entry 8). However, in the presence of TMEDA (1.0 equiv), low-yield formation of **16g** was observed (entry 9). Neither 1-hexynylsodium nor EtMgCl was effective as an initiator (entries 10 and 11). In these reactions, the formation of iodoalkyne **13g** was observed, indicating generation of the corresponding sodium and magnesium acetylide intermediates.

The scope of the cycloisomerization was investigated for other diiodoalkynes (Table 4). A variety of 2-(3-iodo-2-propynyloxy)-ethyl iodides underwent cycloisomerization in the presence of 1-hexynyllithium (0.2 equiv) at 40 °C in THF to give 3-(diiodomethylene)tetrahydrofurans (entries 1−10). The efficiency of the reaction was influenced by substituents on a parent molecule. The reaction of *gem*-disubstituted derivatives **14g**,**h**,**j**−***l***, irrespective of the ethoxy group α to the oxygen atom, gave the corresponding cycloisomerization products **16g**,**h**,**j**−***l*** in high yield (entries 1−5). Parent nonsubstituted diiodoalkyne **14m** underwent cyclization to give **16m** in 50% yield (entry 8). While a relatively high yield formation of **16a**,**e** was observed for **14a**,**e** bearing a substituent at the propargylic position (entries 6 and 7), the reaction of 2-phenyl derivative **14c** resulted in low-yield formation of the corresponding product **16c** (entry 9). The reaction of secondary iodide **14n** took place at 60 °C to give **16n** in low yield (entry 10). With 0.2 equiv of 1-hexynyllithium,

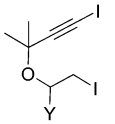
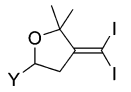
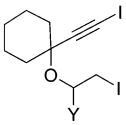
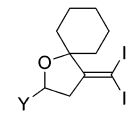
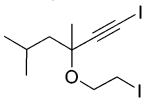
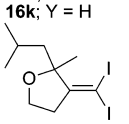
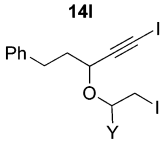
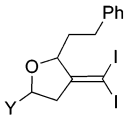
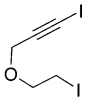
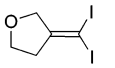
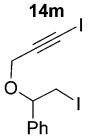
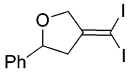
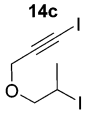
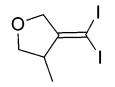
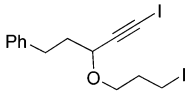
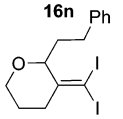
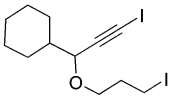
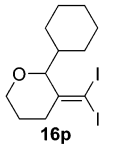
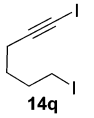
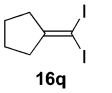
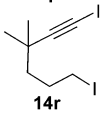
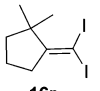
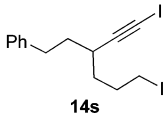
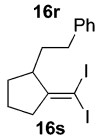
TABLE 3. Cycloisomerization of Diiodoalkyne 14g To Give 16g

entry	base	equiv	solvent	temp (°C)	time (h)	yield (%)	recovery (%)[a]
1	BuLi	0.2	THF	40	2	69	
2	BuLi	0.4	THF	40	2	48	
3	BuC≡CLi	0.1	THF	40	22	61	16 (5)
4	BuC≡CLi	0.2	THF	40	2	85	
5	BuC≡CLi	0.2	THF	0	22	86	
6	BuC≡CLi	0.2	DME	40	2	65	
7	BuC≡CLi	0.2	DME	0	22	80	
8	BuC≡CLi	0.2	Et_2O	30	4	0	90 (10)
9[b]	BuC≡CLi	0.2	Et_2O	30	4	13	43 (14)
10	BuC≡CNa	0.2	THF	0−40	4	0	42 (15)
11	EtMgCl	0.4	THF	0−40	4	0	66 (26)

[a] The yield of iodoalkyne **13g** is shown in parentheses. [b] The reaction was carried out in the presence of TMEDA (1.0 equiv).

(16) Ashby, E. C.; Sun, X.; Duff, J. L. *J. Org. Chem.* **1994**, *59*, 1270.

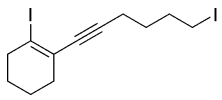
TABLE 4. Cycloisomerization of Diiodoalkynes 14 with Hexynyllithium[a]

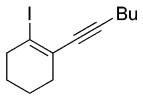
entry	diiodide	product	yield
1	 **14g**; Y = OEt	 **16g**; Y = OEt	85%
2	**14j**; Y = H	**16j**; Y = H	86%
3	 **14h**; Y = OEt	 **16h**; Y = OEt	80%
4	**14k**; Y = H	**16k**; Y = H	87%
5	 **14l**	 **16l**	87%
6	 **14e**; Y = OEt	 **16e**; Y = OEt	68%
7	**14a**; Y = H	**16a**; Y = H	81%
8[b]	 **14m**	 **16m**	50%
9[c]	 **14c**	 **16c**	20%
10[c]	 **14n**	 **16n**	25%
11[b]	 **14o**	 **16o**	42%
12[b]	 **14p**	 **16p**	42%
13[d]	 **14q**	 **16q**	11%
14[d,e]			33%
15[b,d,f]			45%
16[b]	 **14r**	 **16r**	45%
17[b]	 **14s**	 **16s**	42%

[a] Unless otherwise noted, the reactions were carried out with 0.2 equiv of 1-hexynyllithium in THF at 40 °C for 2−4 h. [b] 0.4 equiv of 1-hexynyllithium was used. [c] The reaction was carried out at 60 °C. [d] Enyne **24** was obtained in 11% (entry 13), 33% (entry 14), and 36% yield (entry 15).[e] 0.3 equiv of 1-hexynyllithium was used. [f] Enyne **25** was obtained in 21% yield.

the reaction of homologous 2-(3-iodo-2-propynyloxy)propyl iodides **14o**,**p** was sluggish at 40 °C. However, by using 0.4 equiv of the initiator, 3-(diiodomethylene)tetrahydropyrans **16o**,**p** were obtained in moderate yields (entries 11 and 12).

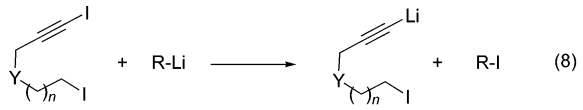
Treatment of 1,6-diiodo-1-hexyne (**14q**) with 1-hexynyllithium (0.2 equiv) at 40 °C gave cycloisomerization product **16q** in 11% yield (entry 13). Again, an improvement in the product yield was obtained by the increase of the amount of the initiator (entries 14 and 15). In these reactions, byproduct formation of enyne **24** and/or **25** was observed.[17] By using 0.4 equiv of 1-hexynyllithium, (diiodomethylene)cyclopentanes **16r**,**s** were obtained in moderate yield in the reaction of the substituted derivatives **14r**,**s** (entries 16 and 17).

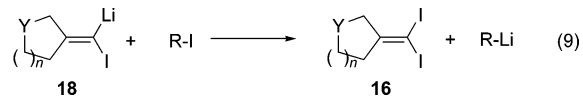

24


25

It should be noted that the cycloisomerization of diiodoalkynes **14** could not be achieved through a radical chain reaction. Thus, for example, treatment of **14g** with radical initiator Et_3B (0.2 equiv) in hexane at room temperature for 8 h resulted in the recovery of **14g** (69%) without the formation of cycloisomerization product **16g**.

The cycloisomerization of diiodoalkynes **14** is rationalized by a carbenoid-chain mechanism analogous to that proposed for the reaction of iodoalkyne **13** (Scheme 3, Z = I). The initiation step involves selective iodine/lithium exchange of diiodoalkyne **14** at the acetylenic carbon by the organolithium compounds (RLi) (eq 8). Lithium acetylide **17**, thus generated, undergoes *exo*-cyclization to give carbenoid **18**, which, in turn, undergoes iodine/lithium exchange with **14** to give product **16** with concurrent generation of **17**. According to this chain mechanism, stoichiometric conversion of **14** into the product would be achieved only when carbenoid **18** undergoes iodination not only by **14** but also by RI, which is formed in the initiation step (eq 9). The observation that the yield of **16g** decreased



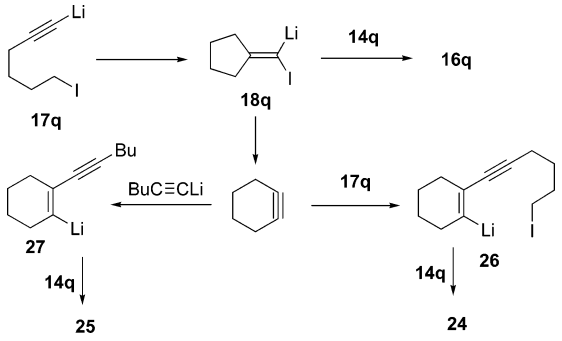


with the increase of the amount of butyllithium (Table 3, entries 1 and 2) implies that 1-iodobutane (R = Bu) does not serve as an iodine donor toward carbenoid **20**. On the other hand, when 1-hexynyllithium was employed as an initiator, 1-iodo-1-hexyne (R = BuC≡C) could participate in iodination of carbenoid **4**, thus leading to the high-yield formation of **16g**.

In comparison with the cycloisomerization reaction of iodoalkynes **13**, the reaction of diiodoalkynes **14** proceeded more efficiently, realizing higher yields of the products. The less efficient nature of the reaction of iodoalkynes **13** is most probably owing to the competing decomposition of carbenoid

(17) Boatman, R. J.; Whitlock, B. J.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1977**, *99*, 4822.

SCHEME 4



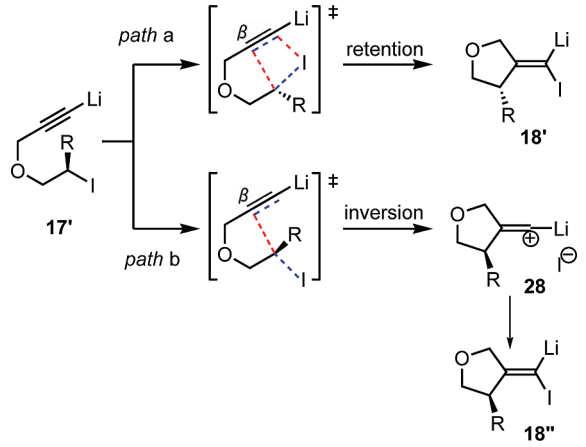
intermediate **18** before undergoing proton abstraction to form the cycloisomerization product **15**. Halogen/lithium exchange by organolithium compounds is known to be much faster than proton abstraction.[17] A rapid transformation of labile carbenoid **18** by iodine/lithium exchange to the product might be responsible for the higher efficiency of the cycloisomerization reaction of diiodoalkynes.

It is most probable that the *exo*-cyclization of acetylide **17** is a rate-determining step of the cycloisomerization reaction, considering from a fast rate of iodine/lithium exchange to generate **17** and high reactivity of the resulting carbenoid **18**. The advantageous effect of *gem*-disubstitution[18] observed in tetrahydrofuran-ring formation (Table 4, entries 1−5) is rationalized by the acceleration of the *exo*-cyclization step. The *exo*-cyclization to form a tetrahydropyran ring was slower and required a prolonged reaction at 40 °C, resulting in the chain termination through the decomposition of the corresponding carbenoid with elimination of LiI. This might be the reason why a larger amount of the initiator was required in the reaction of 2-(3-iodo-2-propynyloxy)propyl iodides **14o**,**p**.

In the cycloisomerization reaction of 1,6-diiodo-1-hexyne (**14q**), formation of enyne **24** and/or **25** was also observed. Cyclopentylidene carbenoid **18q** is prone to undergo Fritsch−Buttenberg−Wiechell rearrangement[19] to form cyclohexyne (Scheme 4).[20,12i,] Enynes **24** and **25** were most probably produced through carbolithiation of thus generated cyclohexyne with lithium acetylide **17q** and 1-hexynyllithium[6a,21] followed by iodination of the resulting alkenyllithium **26** and **27**, respectively. In the reaction of oxa-derivatives **14a**−**n**, no such byproduct was detected. The result implies that the rearrangement of cyclopentylidene carbenoids to cyclohexynes, which proceeds fast enough to complete the rapid lithium/iodine exchange reaction, is considerably retarded by the introduction of the oxygen atom in the ring.

Stereochemistry. A major difficulty in a detailed study on the unprecedented *exo*-cyclization of acetylides is the instability

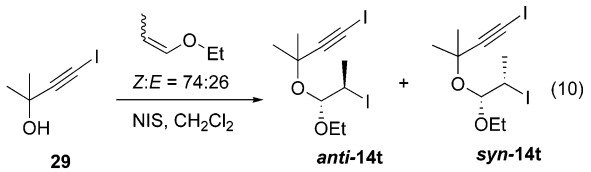
SCHEME 5

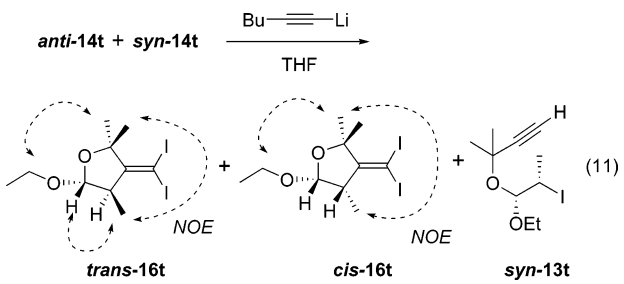


of the resulting cycloalkylidene carbenoids. The cycloisomerization of diiodoalkynes, especially that of 2-(3-iodo-2-propynyloxy)ethyl iodides, would afford us indirect but reliable information on the *exo*-cyclization judging from the observed high efficiency in trapping the carbenoid intermediate through the facile lithium/iodine exchange reaction.

There are two plausible pathways for the *exo*-cyclization (Scheme 5). π-Electrons of acetylide **17′** attack on the electrophilic carbon (π-type cyclization)[22] with simultaneous transfer of the departed iodide anion to the carbon bearing the lithium atom, leading to the formation of carbenoid **18′** in a concerted manner (path a). Alternatively, the *exo*-cyclization proceeds through a stepwise mechanism involving initial π-type cyclization followed by the internal return of the resulting intimate ion pair **28** (path b). The two pathways could be discriminated by the stereochemistry of the reaction: Cyclization through concerted path a and stepwise path b would give retention product **18′** and inversion product **18″**, respectively.

Although inversion product (*Z*)-**15i** was obtained in the cycloisomerization of secondary iodide **13i** (Table 2, entry 10), the reaction was extremely sluggish and the structures of the substrate and the product were relatively constrained. We therefore examined the cycloisomerization of diiodoalkyne *anti*-**14t** and *syn*-**14t** (eq 11). Iodoetherification of 1-ethoxy-1-





propene (*Z*:*E* = 74:26) with iodoalkynol **29** and NIS gave *anti*- and *syn*-**14t** as an inseparable 25:75 mixture (eq 10). Treatment of the mixture at 40 °C for 21 h in the presence of 1-hexynyl-

(18) (a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc.* **1915**, *107*, 1080. (b) Lightstone, F. C.; Bruice, T. C. *J. Am. Chem. Soc.* **1994**, *116*, 10789. (c) Schleyer, P. v. R. *J. Am. Chem. Soc.* **1961**, *83*, 1368. (d) Milstein, S.; Cohan, L. A. *J. Am. Chem. Soc.* **1972**, *94*, 9166.

(19) (a) Fritsch, P. *Liebigs Ann. Chem.* **1894**, *279*, 319. (b) Buttenberg, W. P. *Liebigs Ann. Chem.* **1894**, *279*, 324. (c) Wiechell, H. *Liebigs Ann. Chem.* **1894**, *279*, 337. (d) Rezaei, H.; Yamanoi, S.; Chemla, F.; Normant, J. F. *Org. Lett.* **2000**, *2*, 419. (e) Luu, T.; Tykwinski, R. R. *J. Org. Chem.* **2006**, *71*, 8982 and references cited therein.

(20) (a) Meier, H. *Adv. Strain Org. Chem.* **1991**, *1*, 215. (b) Erickson, K. L.; Wolinsky, J. *J. Am. Chem. Soc.* **1965**, *87*, 1143. (c) Fitjer, L.; Kliebisch, U.; Wehle, D.; Modaressi, S. *Tetrahedron Lett.* **1982**, *23*, 1661. (d) Gilbert, J. C.; Baze, M. E. *J. Am. Chem. Soc.* **1983**, *105*, 664. (e) Gilbert, J. C.; Baze, M. E. *J. Am. Chem. Soc.* **1984**, *106*, 1885. (f) Tseng, J.; McKee, M. L.; Shevlin, P. B. *J. Am. Chem. Soc.* **1987**, *109*, 5474.

TABLE 5. Cycloisomerization of *anti*- and *syn*-14t

entry	**14t** *anti*:*syn*	BuC≡CLi (equiv)	temp (°C)	time (h)	products yield (%)[a] *trans*-**16t**	*cis*-**16t**	*syn*-**13t**	*syn*-**14t**
1	25:75	0.2	40	21	15 (60)	trace	7 (9)	47 (63)[b]
2	38:62	0.3	40	2	32 (84)	7 (11)	20 (32)	23 (37)
3	2:98	0.3	50	22	2 (100)	18 (18)	3 (3)	16 (16)

[a] Determined by ^{1}H NMR analysis. Yields based on *anti*- and *syn*-**14t** are shown in parentheses. [b] *anti*-**14t** was recovered in 3% yield.

lithium (0.2 equiv) gave cycloisomerization product *trans*-**16t** in 15% yield together with a trace amount of *cis*-**16t** (Table 5, entry 1). Stereochemistry of the cycloisomerization products was determined by ^{1}H NMR NOESY analysis. In this reaction, *anti*-**14t** was almost consumed while *syn*-**14t** was recovered in 47% yield and iodoalkyne *syn*-**13t** was formed in 7% yield. The result suggests that *anti*-**14t** reacted smoothly to give *trans*-**16t** (60% yield based on the *anti*-**14t**) and that *syn*-**14t** is less reactive resulting in the recovery (63% based on the *syn*-**14t**) and in the formation of *syn*-**13t** (9% yield based on the *syn*-**14t**).

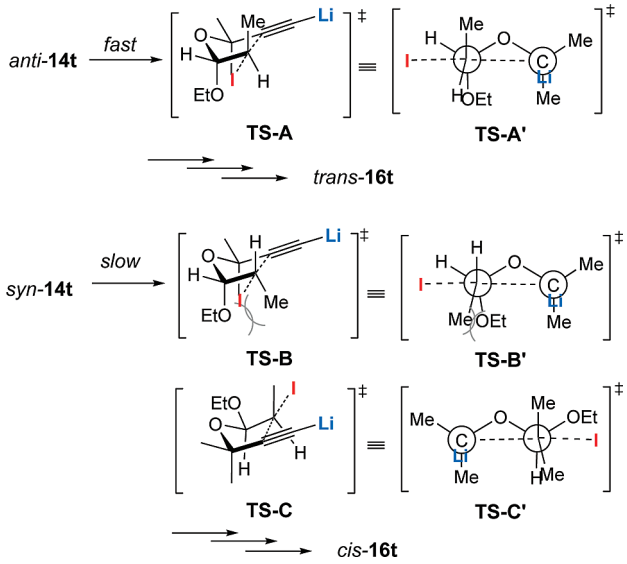
When a 38:62 mixture of *anti*- and *syn*-**14t** was treated with 0.3 equiv of 1-hexynyllithium at 40 °C for 2 h, a product distribution similar to that in the previous experiment was observed with an increased yield of minor *cis*-**16t** (7%) (entry 2). Taking advantage of the less reactive nature of *syn*-**14t**, we could obtain a *syn*-enriched 2:98 mixture of the diiodoalkyne by recovering the starting material from the reaction mixture of the cycloisomerization. Upon treatment with 0.3 equiv of 1-hexynyllithium at 50 °C, for 22 h, *syn*-**14t** underwent slow cyclization to give *cis*-**16t** in 18% yield (entry 3).

The cycloisomerization of *anti*-**14t** proceeded rapidly and efficiently to give *trans*-**16t**. On the other hand, the reaction of *syn*-**14t** was slower and less efficient to give *cis*-**16t**. These stereochemical results clearly showed that the *exo*-cyclization proceeded stereospecifically through inversion of the stereochemistry at the electrophilic carbon. Accordingly, the stepwise mechanism (path b), involving a π-type cyclization and the internal return of the resulting intimate ion pair **28**, is most probable for the *exo*-cyclization of lithium acetylides **17**.

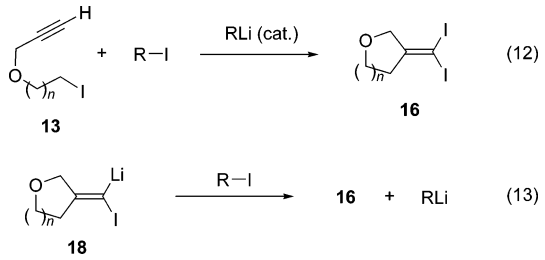
The likely origin of difference in reactivity between the *anti* and *syn* isomers can be seen by comparing S_N2-type trigonal-bipyramidal transition state structures **TS-A** and **-B** (Scheme 6). Assuming the pseudoaxial orientation of the ethoxy group by anomeric effect, *anti*-**14t** cyclized through **TS-A** (=**TS-A′**). Note that the reaction of *syn*-**14t** leads to an eclipsing interaction in **TS-B** (=**TS-B′**) between the ethoxy group and the methyl group adjacent to the reacting center, which is absent in **TS-A**. To circumvent the eclipsing interaction, *anti*-**14t** is required to cyclize through **TS-C** (=**TS-C′**) with the sacrifice of the anomeric stabilization.[23]

Atom-Transfer-Type Carbocyclization. Since mono-iodoalkynes **13** are synthetically more accessible than diiodides **14**,[24] the reaction of **13** leading to the same diiodo products **16** by using an external iodine atom source would be more useful (eq 12). Such iodine atom-transfer-type cyclization can be realized through iodination of the carbenoid intermediate **18** with an

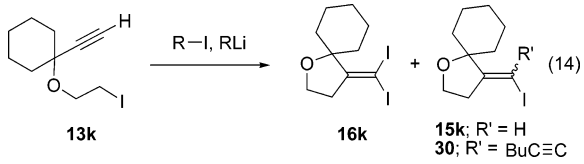
SCHEME 6



iodide (R-I), which affords **16** together with RLi, the latter serving as a base to undergo lithiation of **13** (eq 13).



Indeed, treatment of iodoalkyne **13k** with 1-iodo-1-hexyne (1.1 equiv) in the presence of 1-hexynyllithium (0.4 equiv) in THF at 40 °C for 2 h gave anticipated diiodo product **16k** in 80% yield (eq 14) (entry 2 in Table 6). When an amount of



1-hexynyllithium was reduced to 0.2 equiv, essentially no cyclization was observed (entry 1). With 1.0 equiv of 1-hexynyllithium, the yield of **16k** was decreased and byproduct formation of enyne **30** (8%) was observed (entry 3). When iodobenzene or 2-iodothiophene was employed as an iodine atom source in combination with phenyllithium or 2-thienyllithium, respectively, monoiodo product **15k** was obtained in moderate yield without formation of diiodo product **16k** (entries 4 and 5).

(21) (a) Nakagawa, M. Cyclic Acetylenes. In *The Chemistry of Carbon-Carbon Triple Bond*; Patai, S., Ed.; J. Wiley & Sons: New York, 1978; p 635. (b) Roberts, J. D. *J. Am. Chem. Soc.* **1960**, *82*, 4750. (c) Wittig, G.; Pohlke, R. *Chem. Ber.* **1961**, *94*, 3276. (d) Gassman, P. G.; Valcho, J. J. *J. Am. Chem. Soc.* **1975**, *97*, 4768.

(22) (a) Negishi, E.; Boardman, L. D.; Sawada, H.; Bagheri, V.; Stoll, A. T.; Tour, J. M.; Rand, C. L. *J. Am. Chem. Soc.* **1988**, *110*, 5383. (b) Liu, F.; Negishi, E. *Tetrahedron Lett.* **1997**, *38*, 1149.

TABLE 6. Iodine Atom-Transfer-Type Cyclization of 13k with RI/RLi[a]

entry	R−I	R−Li (equiv)	yield (%) 16k	yield (%) 15k
1	BuC≡CI	0.2	trace	0
2		0.4	80	0
3[b]		1.0	69	0
4	C_6H_5I	0.4	0	43
5	2-ThI[c]	0.2	0	30

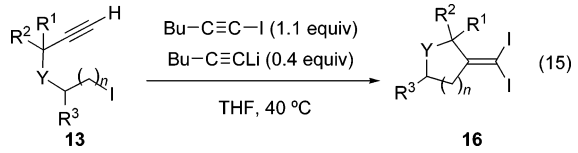
[a] Unless otherwise noted, reactions were carried out in THF (0.5 M) at 40 °C for 2−6 h. [b] Enyne **30** was obtained in 8% yield. [c] 2-Iodothiophene.

TABLE 7. Iodine Atom-Transfer-Type Carbocyclization of Iodoalkynes 13[a]

entry	iodoalkyne	Y	n	R^1	R^2	R^3	product	yield (%)[b]
1	**13k**	O	1	$-(CH_2)_5-$		H	**16k**	80
2	**13h**	O	1	$-(CH_2)_5-$		EtO	**16h**	77
3	**13j**	O	1	Me	Me	H	**16j**	78
4	**13g**	O	1	Me	Me	EtO	**16g**	81
5	**13*l***	O	1	*i*-Bu	Me	H	**16*l***	78
6	**13a**	O	1	$PhCH_2CH_2$	H	H	**16a**	71
7	**13m**	O	1	H	H	H	**16m**	55
8	**13q**	CH_2	1	H	H	H	**16q**	13[c]
9	**13o**	O	2	$PhCH_2CH_2$	H	H	**16o**	20[c]

[a] Reactions were carried out with 1-iodo-1-hexyne (1.1 equiv) and 1-hexynyllithium (0.4 equiv) in THF (0.5 M) at 40 °C in for 1−2 h. [b] Isolated yield unless otherwise noted. [c] Yields were determined by ^{1}H NMR.

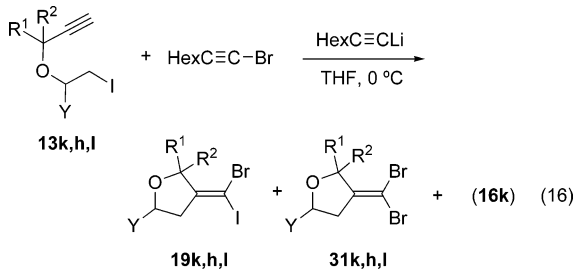
The scope of the iodine atom-transfer-type carbocyclization was investigated under the conditions using 1-iodo-1-hexyne (1.1 equiv) with 1-hexynyllithium (0.4 equiv) at 40 °C (eq 15,



(15)

Table 7). 2-(2-Propynyloxy)ethyl iodides **13a**−**m** underwent a smooth cyclization to give the corresponding 3-(diiodomethylene)tetrahydrofurans **16a**−**m**. Of these, 4,4′-disubstituted derivatives **13g**,**h**,**j**,**k**,***l***, irrespective of the ethoxy substitution *β* to the iodine atom, gave the corresponding products in high yields (entries 1−5). On the other hand, the efficiency of the reaction was steadily lowered for monosubstituted derivative **13a** (entry 6) and for nonsubstituted derivative **13m** (entry 7). Cyclopentane ring-formation of 6-iodo-1-hexyne (**13q**) as well as tetrahydropyran ring-formation of the homologous substrate **13o** also proceeded under these conditions, albeit with low product yields (entries 8 and 9).

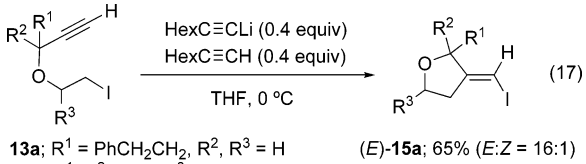
When 1-bromo-1-octyne was used instead of 1-iodo-1-hexyne, the corresponding 3-(bromoiodomethylene)tetrahydrofurans **19** were obtained along with 3-(dibromomethylene)-tetrahydrofurans **31** (eq 16). Thus, treatment of iodoalkyne **13k**



(16)

with 1-bromo-1-octyne (1.7 equiv) in the presence of 0.4 equiv of 1-octynyllithium (0.4 equiv) at 0 °C for 14 h gave **19k** and **31k** in 45% and 40% yield, respectively (Table 8, entry 1). Bromoiodo product **19k** was obtained as a single diastereomer, whose *E* geometry was assigned tentatively by analogy to the selective formation of *E*-cycloisomerization products in the reaction of iodoalkynes **13** (Table 2). When a limited amount of 1-bromo-1-octyne (0.9 equiv) was used under otherwise the same conditions, byproduct formation of dibromo product **31k** was reduced (entry 2). However, diiodo product **16k** was also produced in 26% yield. No improvement was observed for the yield of **19k**. The reaction of iodoalkyne **13h** and **13*l*** with 1-bromo-1-octyne also gave a mixture of the corresponding bromoiodomethylene products **19h**,***l*** and dibromomethylene products **31h**,***l*** in comparable yields (entries 3 and 4).

In the cycloisomerization of iodoalkynes **13** initiated by LDA, unstable carbenoid intermediate is trapped with the terminal acetylenic proton of the substrates (Scheme 3, Z = H). The use of alkynyllithium, instead of LDA, as an initiator, in combination with the corresponding terminal alkyne, would improve the efficiency of the cycloisomerization by an increased rate in protonation of the unstable carbenoid intermediate. When iodoalkynes **13a**,**g**,**k** were treated with 1-octynyllithium (0.4 equiv) and 1-octyne (0.4 equiv) at 0 °C for 12 h, the anticipated cycloisomerization reaction proceeded to give cycloisomerization products **15a**,**g**,**k** (eq 17). However, the product yields were



(17)

13a; R^1 = $PhCH_2CH_2$, R^2, R^3 = H (*E*)-**15a**; 65% (*E*:*Z* = 16:1)
13g; R^1, R^2 = Me, R^3 = OEt (*E*)-**15g**; 77%
13k; R^1, R^2 = -$(CH_2)_5$-, R^2 = H (*E*)-**15k**; 77%

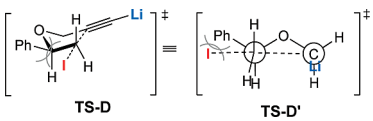
not much improved, being comparable to those in the LDA-initiated reactions (entries 1 and 7 in Table 2).

TABLE 8. Bromine Atom-Transfer-Type Carbocyclization of Iodoalkynes 13[a]

entry	iodoalkyne	R^1	R^2	Y	products: yield[b] (%) 19	31
1	**13k**	$-(CH_2)_5-$		H	**19k**: 45	**31k**: 40
2[c]					**19k**: 46	**31k**: 17
3	**13h**	$-(CH_2)_5-$		OEt	**19h**: 42	**31h**: 46
4	**13*l***	*i*-Bu	Me	OEt	**19*l***: 36	**31*l***: 47

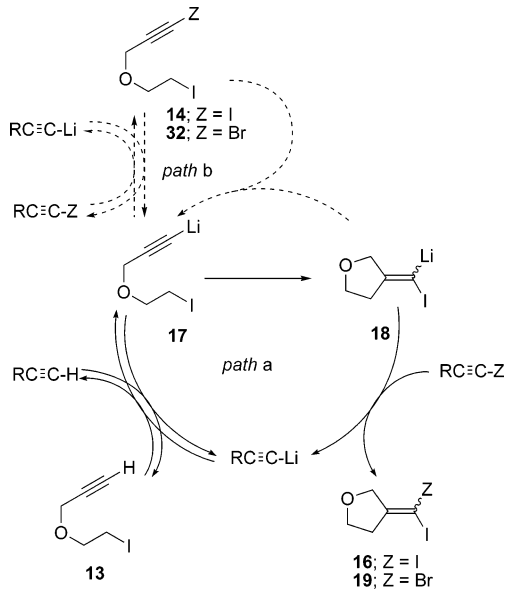
[a] Reactions were carried out with 1-bromo-1-octyne (1.7 equiv) and 1-octynyllithium (0.4 equiv) in THF (0.5 M) at 0 °C for 14−20 h. [b] The yield was based on a ^{1}H NMR analysis of a mixture of **31** and **32** obtained by column chromatography. [c] Diiodo product **16k** was obtained in 26%.

(23) Low yields of cycloisomerization products were observed in the reaction of **13c** and **14c**, bearing a phenyl group *β* to the leaving iodine atom (entry 2 in Table 2 and entry 9 in Table 4). The observation is also rationalized by the S_N2-type transition state (**TS-D**), where unfavorable interaction exists between the iodine atom and the phenyl group.



(24) For the preparation of **13** and **14**, see the Supporting Information.

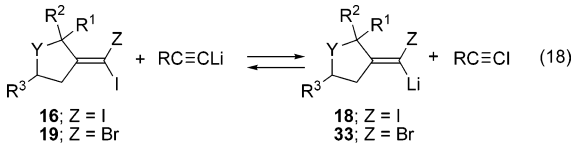
SCHEME 7

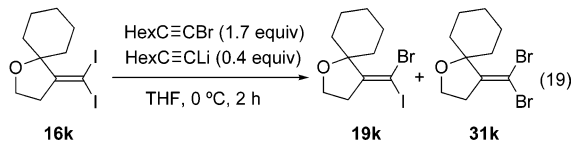


According to our initial supposition, the iodine and bromine atom-transfer-type cyclization might proceed through a chain mechanism in which alkylidene carbenoid **18** is trapped by 1-halo-1-alkynes (RC≡CZ; Z = I, Br) with concurrent formation of the 1-alkynyllithium (RC≡CLi), serving as a base to generate acetylide **17** under equilibrium conditions (Scheme 7, path a). When **13k** was treated at −20 °C with 1-iodohexyne (1.1 equiv) and 1-hexynyllithium (0.4 equiv) for 2 h, a 39:61 mixture of diiodoalkyne **14k** and **13k** was obtained without the formation of **16k**. The observation suggests an alternative mechanism (path b) for the cyclization: The starting alkyne **13** is first converted into diiodoalkyne **14** or bromoiodoalkyne **32** via lithium/halogen exchange of acetylide **17** with RC≡CZ (Z = I, Br) and then undergoes cycloisomerization through a carbenoid chain mechanism. It is most probable that both pathways are operating concurrently in the present cyclization.

In the iodine atom-transfer-type cyclization of **13k** with 1.0 equiv of 1-hexynyllithium, enyne **30** was obtained as a minor byproduct (Table 6, entry 3). The enyne might be formed by the addition of 1-hexynyllithium to carbenoid intermediate **18** followed by iodination of the resulting alkenyllithium.[6] The cyclization reaction leading to diiodo product **16** did not occur with iodobenzene/phenyllithium or 2-iodothiophene/2-thienyllithium (Table 6, entries 4 and 5). It has been shown, by a combination of theoretical studies with NMR and crystal structure investigations, that the C−Li bonds of lithium carbenoids have high s-character, causing a higher p-character of the C−X bond.[12h,25] The C−Li bond of alkylidene carbenoids is close to sp hybridized and stabilized.[25c] Accordingly, the reaction of the iodoarenes either with carbenoid **18** (path a) or with acetylide **17** (path b) to form relatively unstable sp^2-hybridized aryllithiums is an unfavorable process. Under these conditions, carbenoid **18** rather underwent proton abstraction from **13** leading to the formation of cycloisomerization product **15**.

Considering the relatively high s-character of the C−Li bond of alkylidene carbenoids and its stability, diiodo products **16** and bromoiodo products **19** may undergo iodine/lithium exchange reaction with 1-alkynyllithiums in a reversible manner (eq 18). Indeed, when 3-(diiodomethylene)tetrahydrofuran **16k** was treated with 1-bromo-1-octyne (1.7 equiv) in the presence of 1-octynyllithium (0.4 equiv) at 0 °C for 2 h, bromoiodomethylene derivative **19k** was obtained in 72% yield along with **31k** (10%) and **16k** (7%) (eq 19). The result indicates that **16k**





underwent the iodine/lithium exchange reaction with 1-octynyllithium to give carbenoid **18**, which reacted with 1-bromo-1-octyne to give **19k**. Minor formation of dibromomethylene derivative **31k** is rationalized by the iodine/lithium exchange of **19k** followed by bromination of the resulting Li,Br carbenoid **33**.

In the cycloisomerization of diiodoalkynes **14** (eq 4, Z = I) and the iodine atom-transfer-type cyclization of iodoalkynes **13** (eq 15), it is very likely that the iodine/lithium exchange reaction of the product **16** with alkynyllithiums (eq 18, Z = I) takes place reversibly as a nonproductive pathway. The reversible exchange reaction (eq 18, Z = Br) is responsible for the formation of dibromo derivative **31** in the reaction of **13** with 1-bromo-1-octyne (eq 16). 1-Iodo-1-octyne concurrently produced in this reaction may serve as an iodine atom donor to give diiodo derivative **16k** as another byproduct in the reaction with 0.9 equiv of 1-bromo-1-octyne (Table 8, entry 2).

Conclusion

We have described new carbocyclization reactions of iodo- and diiodoalkynes to give products with incorporation of iodine atoms through a novel carbenoid-chain process. In the presence of a catalytic amount of LDA, 2-(2-propynyloxy)ethyl iodides **13** underwent cycloisomerization to give 3-(iodomethylene)-tetrahydrofurans **15** in high yields. By the use of 1-hexynyllithium as an initiator, cycloisomerization of 1,ω-diiodo-1-alkynes **14** proceeded in an efficient manner to furnish diiodomethylene products **16**. Diiodomethylene products **16** were also obtained in high yield by the reaction of iodoalkynes **13** and 1-iodo-1-hexyne in the presence of a catalytic amount of the corresponding 1-alkynyllithium. A relevant bromine atom- and proton-transfer-type cyclization proceeded as well by employing 1-bromo-1-octyne and 1-octyne, respectively, in place of 1-iodo-1-hexyne. The stereochemical outcome in the cycloisomerization of secondary diiodoalkyne **14t** clearly showed that the *exo*-cyclization proceeded stereospecifically through inversion of the stereochemistry at the electrophilic carbon, providing support for a stepwise mechanism involving a π-type cyclization of the acetylide moiety followed by the internal return of the resulting intimate ion pair. The enhanced reactivity of the lithium alkylidene carbenoids generated by the *exo*-cyclization of the lithium acetylide serves as a driving force

(25) (a) Seebach, D.; Hässig, R.; Gabriel, J. *Helv. Chim. Acta* **1983**, *66*, 308. (b) Boche, G.; Marsch, M.; Müller, A.; Harms, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1032. (c) Boche, G.; Bosold, F.; Hermann, H.; Marsch, M.; Harms, K.; Lohrenz, J. C. W. *Chem. Eur. J.* **1998**, *4*, 814.

in the present carbenoid-chain reactions and can be exploited further in the development of atom-economical carbon−carbon bond-forming reactions.

Experimental Section

3-Iodomethylene-2-phenylethyltetrahydrofuran (15a): Typical Procedure for Cycloisomerization of Iodoalkynes 13. To a solution of iodoalkyne **13a** (157 mg, 0.5 mmol) in THF (1 mL) under argon atmosphere at 0 °C was added LDA (1 M solution in THF, 0.10 mL, 0.1 mmol). The resulting solution was stirred at room temperature for 5 h. The mixture was poured into water and extracted twice with ether. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 2−3% ether in hexane) to afford 116 mg (74% yield) of **15a** (*E*:*Z* = 9.0:1) as an oil. (*E*)-**15a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.85−2.00 (2H, m), 2.56−2.66 (2H, m), 2.73 (1H, ddd, J = 6.9, 10.0, and 13.8 Hz), 2.82 (1H, ddd, J = 5.2, 10.2, and 13.8 Hz), 3.86 (1H, dt, J = 7.2 and 8.1 Hz), 4.11 (1H, ddd, J = 5.1, 7.1, and 8.7 Hz), 4.29 (1H, m), 6.00 (1H, q, J = 2.7 Hz), 7.20−7.36 (5H, m); NOESY experiment showed a cross-peak between H_a (δ 6.00) and H_b (δ 1.9); ^{13}C NMR (125.8 MHz) δ 31.5, 36.1, 38.3, 65.6, 68.4, 80.6, 125.9, 128.35, 128.38, 141.6, 155.5. (*Z*)-**15a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.91 (1H, m), 2.15 (1H, m), 2.65 (2H, m), 2.70−2.82 (2H, m), 3.87 (1H, q, J = 7.4 Hz), 4.12 (1H, m), 4.35 (1H, br d, J = 8.7 Hz), 6.06 (1H, q, J = 1.7 Hz), 7.17−7.30 (5H, m); NOESY experiment showed a cross-peak between H_a (δ 6.06) and H_b (δ 2.65); ^{13}C NMR (125.8 MHz) δ 31.5, 33.8, 36.1, 67.3, 67.5, 82.7, 125.8, 128.3, 128.5, 141.8, 153.3. (*E*)- and (*Z*)-**15a**: IR (liquid film) 3050, 1640, 1250, 740, 700 cm^{-1}. Anal. Calcd for $C_{13}H_{15}IO$: C, 49.70; H, 4.81. Found: C, 49.78; H, 4.82.

5-Ethoxy-3-diiodomethylene-2,2-dimethyltetrahydrofuran (16g): Typical Procedure for Cycloisomerization of Diiodoalkynes 14. To a solution of 1-hexyne (23 μL, 0.20 mmol) in THF (2 mL) under argon atmosphere at 0 °C was added BuLi (1.6 M solution in hexane) (0.14 mL, 0.22 mmol). The resulting solution was stirred at 0 °C for 30 min. To the resulting solution of 1-hexynyllithium in THF was added diiodoalkyne **14g** (0.408 g, 1.00 mmol). The resulting solution was stirred at 40 °C for 4 h. The mixture was poured into water and extracted three times with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 2−5% ethyl acetate in hexane) to give 0.346 g (85% yield) of **16g**: ^{1}H NMR (500 MHz, C_6D_6) δ 1.11 (3H, t, J = 7.0 Hz), 1.54 (1H, s), 1.71 (1H, s), 2.62 (1H, dd, J = 5.5 and 17.4 Hz), 2.88 (1H, d, J = 17.4 Hz), 3.24 (1H, qd, J = 7.1 and 9.4 Hz), 3.75 (1H, qd, J = 7.1 and 9.4 Hz), 4.76 (1H, d, J = 5.4 Hz); ^{13}C NMR (125.8 MHz, C_6D_6) δ −2.6, 15.2, 26.7, 27.0, 52.5, 62.4, 85.2, 99.0, 161.3. Anal. Calcd for $C_9H_{14}O_2I_2$: C, 26.49; H, 3.46. Found: C, 26.53; H, 3.59.

Preparation of (Diiodomethylene)tetrahydrofuran 16g from Iodoalkyne 13g: Typical Procedure for Iodine Atom-Transfer-Type Cyclization of Iodoalkynes 13. To a solution of 1-iodo-1-hexyne (0.12 mL, 0.75 mmol) in THF (1 mL) under argon atmosphere at 0 °C was added BuLi (1.6 M solution in hexane) (0.13 mL, 0.20 mmol). The resulting solution was stirred at 0 °C for 30 min. To the resulting solution of 1-hexynyllithium (0.2 mmol) and 1-iodo-1-hexyne (0.55 mmol) in THF was added iodoalkyne **13g** (0.141 g, 0.50 mmol). The resulting solution was stirred at 40 °C for 1.5 h. The mixture was poured into water and extracted twice with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 7% ethyl acetate in hexane) to give 0.165 g (81% yield) of **16g**.

4-Bromoiodomethylene-1-oxaspiro[4.5]decane (19k) and 4-Dibromomethylene-1-oxaspiro[4.5]decane (31k): Typical Procedure for Bromine Atom-Transfer-Type Cyclization of Iodoalkynes 13. To a solution of 1-octyne (0.030 mL, 0.20 mmol) in THF (1 mL) under argon atmosphere at 0 °C was added BuLi (1.6 M solution in hexane) (0.125 mL, 0.200 mmol). The resulting solution was stirred at 0 °C for 30 min. To the resulting solution of 1-octynyllithium in THF was added 1-bromo-1-octyne (0.160 g, 0.846 mmol). The resulting solution was stirred at 0 °C for 30 min. To this was then added iodoalkyne **13k** (0.139 g, 0.500 mmol). The resulting solution was stirred at 0 °C for 14 h. The mixture was poured into water and extracted three times with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 4% ethyl acetate in hexane) to give 0.142 g of a mixture of **19k** (45% yield) and **31k** (40% yield). The products were isolated by a preparative recycling GPC (JAI LC-908 equipped with JAIGEL-1H and -2H columns, chloroform as an eluent). **19k**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (1H, m), 1.50−1.67 (8H, m), 2.16−2.25 (2H, m), 2.66 (2H, t, J = 6.8 Hz), 3.82 (2H, t, J = 6.8 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 22.0, 25.0, 30.8, 39.7, 45.1, 62.4, 85.6, 157.5; MS (EI), *m*/*z* (rel intensity) 358, 356 (M^+, 27, 28), 315, 313 (100, 98), 231, 229 (76, 78); HRMS (EI) calcd for $C_{10}H_{14}O^{81}BrI$ 357.9252, found 357.9261, calcd for $C_{10}H_{14}O^{79}BrI$ 355.9273, found 355.9282. **31k**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21 (1H, m), 1.52−1.69 (8H, m), 2.09−2.18 (2H, m), 2.71 (2H, t, J = 6.8 Hz), 3.83 (2H, t, J = 6.8 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 22.0, 25.0, 30.7, 40.3, 62.9, 78.4, 85.4, 151.9; MS (EI), *m*/*z* (rel intensity) 312, 310, 308 (M^+, 13, 28, 15), 269, 267, 265 (54, 100, 52), 231, 229 (54, 57); HRMS (EI) calcd for $C_{10}H_{14}O^{81}Br_2$ 311.9370, found 311.9395, calcd for $C_{10}H_{14}O^{81}Br^{79}Br$ 307.9411, found 309.9399, calcd for $C_{10}H_{14}O^{79}Br_2$ 307.9411, found 307.9413.

4-Iodomethylene-1-oxaspiro[4.5]decane (15k): Typical Procedure for Proton Transfer-Type Cyclization of Iodoalkynes 13. To a solution of 1-octyne (0.059 mL, 0.40 mmol) in THF (1 mL) under argon atmosphere at 0 °C was added BuLi (1.6 M solution in hexane) (0.13 mL, 0.20 mmol). The resulting solution was stirred at 0 °C for 30 min. To the resulting solution of 1-octynyllithium (0.20 mmol) and 1-octyne (0.20 mmol) in THF was added iodoalkyne **13k** (0.139 g, 0.50 mmol). The resulting solution was stirred at 0 °C for 12 h. The mixture was poured into water and extracted twice with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 3% ethyl acetate in hexane) to give 0.107 g (77% yield) of **15k**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (1H, m), 1.32 (2H, m), 1.53−1.61 (4H, m), 1.67 (1H, m), 1.73 (2H, m), 2.61 (2H, dt, J = 2.6 and 7.0 Hz), 3.91 (2H, t, J = 7.0 Hz), 5.93 (1H, t, J = 2.6 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 22.3, 25.3, 35.6, 38.2, 63.1, 68.8, 84.2, 160.2; MS (EI), *m*/*z* (rel intensity) 278 (M^+, 12), 235 (36), 151 (100); HRMS calcd for $C_{10}H_{15}OI$ 278.0168, found 278.0174.

Supporting Information Available: Preparation of starting materials **13** and **14**, experimental procedure, and spectra data for carbocyclization products **15**, **16**, **19**, and **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO7021179