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LETTERS

Titanium-mediated intramolecular cyclization of tethered propargyl alcohol derivatives. Access to exocyclic bis-allenes and cyclobutene derivatives

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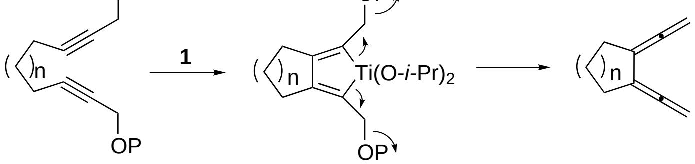
Abstract—Treatment of tethered bis-propargyl alcohol derivatives with (η^2-propene)Ti(O-*i*-Pr)$_2$ afforded four- and five-membered rings bearing conjugated exocyclic bis-allenes. In the case of six- and seven-membered rings, bicyclic cyclobutenes were obtained in the same pot most likely via the intermediate bis-allenes. © 2001 Elsevier Science Ltd. All rights reserved.

The titanium complex (η^2-propene)Ti(O-*i*-Pr)$_2$ (**1**), generated in situ by the treatment of Ti(O-*i*-Pr)$_4$ with 2 equiv. of *i*-PrMgCl, acts as a versatile titanium(II) equivalent to react with alkene or alkyne species.[1] From ene–enes, ene–ynes and yne–ynes, this easily obtained titanium reagent allows the formation of titanacycles via cyclometallation. Starting from tethered bis-propargyl alcohol derivatives, this coupling could afford the expected titanacycles via an intramolecular ring closure, which was followed by the elimination of the hydroxy-derived group acting as a leaving group[2] to provide the exocyclic conjugated bis-allenes as shown in Scheme 1. Quite recently, the same cyclization of bis-propargyl alcohol derivatives was attempted with Cp$_2$Zr reagent, but the preparation of bis-allenes proved to be difficult and only the transient formation of bis-allenes was alluded.[3]

Conjugated bis-allenes have been prepared by a few different routes: (i) treatment of the corresponding conjugated dienes with a dihalocarbene and then with methyllithium,[4a] or (ii) by the displacement of propargyl alcohol derivatives with organometallic reagents such as copper[4b] or aluminium.[4c] As described in Table 1, the coupling of tethered bis-propargyl alcohol derivatives provided conjugated exocyclic bis-allenes by the method shown in Scheme 1. This method appears reasonably general and can be applied to various substrates.

In contrast to the bis-allene structure of four- and five-membered cyclic products as shown above, the six-membered ring cyclization underwent a different reaction course which produced bicyclic cyclobutenes.[6] The formation of the cyclobutene derivatives may result from two consecutive reactions. The first step affords the exocyclic bis-allenes as previously described (see Scheme 1) and the second step involves a [2+2] electrocyclization of the bis-allenes (Scheme 2).[7] As summarized in Table 2, the preparation of this kind of com-



Scheme 1.

Keywords: cyclization; exocyclic bis-allenes; cyclobutenes; titanium.

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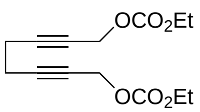
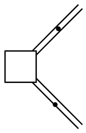
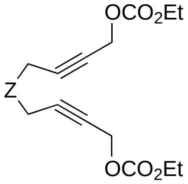
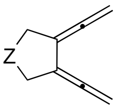
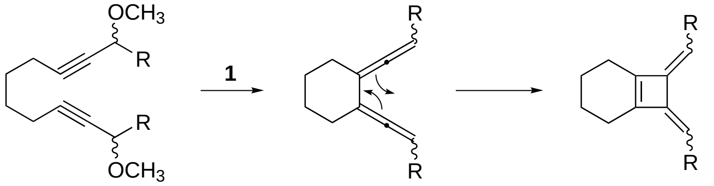
Table 1. Formation of four- and five-membered ring exocyclic conjugated bis-allenes[a]

Entry	Substrate		Product		Yield (%) by ^{1}H NMR[b] (Isolated yields)
1			2		10 (-)
2		Z=CH$_2$	3		60[c] (45)
3		Z=C(CH$_2$OBn)$_2$	4		30 (25)
4		Z=O	5		55 (45)
5		Z=N-Bn	6		45 (35)

[a] For a general procedure see Ref. 5.

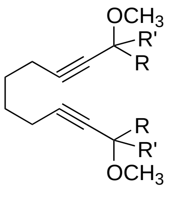
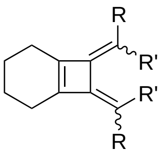
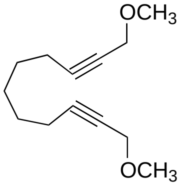
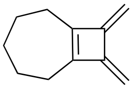
[b] Reference to an internal standard.

[c] Compound **3** was provided in a 45% yield under the same reaction conditions except for the use of a catalytic amount of Ti(O-*i*-Pr)$_4$ (20 mol%).



Scheme 2.

Table 2. Formation of bicyclic cyclobutene derivatives[a]

Entry	Substrate			Product	Yield (%) by ^{1}H NMR[b] (Isolated Yield)
1		R=R'=H	7		85 (80)
2		R=Ph, R'=H	8		80 (75)[c]
3		R=n-C$_5$H$_{11}$, R'=H	9		45 (40)[c]
4		R=R'=CH$_3$	10		65 (60)
5		R=Ph, R'=CH$_3$	11		20 (15)[d]
6			12		15 (10)

[a] For a general procedure see Ref. 9.

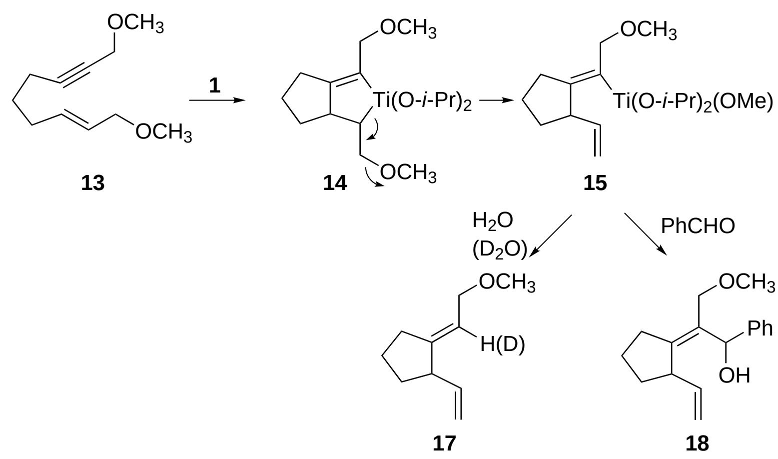
[b] Reference to an internal standard.

[c] In each case, two isomers were provided in almost equal amounts.

[d] Only one isomer was formed.

pounds can be achieved from a variety of substituted substrates. These results suggest that our method should be a good alternative to the previously reported preparations.[8]

The cyclization of the tethered ene–yne **13** (Scheme 3), under the same conditions as in Table 1, did not provide the expected exocyclic en–allene **16** (Fig. 1). Anyway, one single product **17** was afforded in a 80% yield. The presence of the intermediate **15** was ascertained by treatment with D$_2$O affording the corresponding deuterated compound in 75% yield (>97% D) and by trapping by benzaldehyde producing the alcohol **18** as one single diastereomer in 50% yield, even though



Scheme 3.

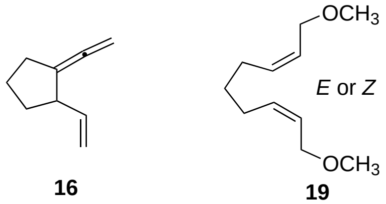


Figure 1.

the relative stereochemistry has not yet been clarified. Attempted coupling of the tethered bis-allylic alcohol derivative **19** (Fig. 1) by **1** proved unsuccessful.

The titanium-mediated intramolecular cyclization of bis-propargyl alcohol derivatives allowed the formation of two kinds of compounds dependent on the starting material: (i) four- and five-membered exocyclic bis-allenes (compounds **3**–**6**, hitherto unknown in the literature) and (ii) bicyclic cyclobutenes bearing a six- or seven-membered ring (compounds **8**–**12**, hitherto unknown in the literature).

Acknowledgements

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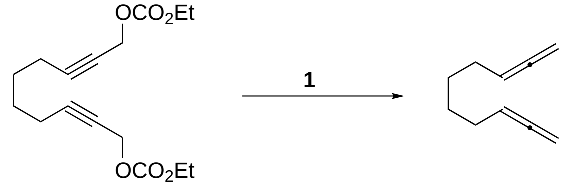
3. (a) Hara, R.; Ura, Y.; Huo, S.; Kasai, K.; Suzuki, N.; Takahashi, T. *Inorg. Chim. Acta* **2000**, *300–302*, 741–748. For a relevant olefinic case, see: (b) de Meijere, A.; Stecker, B.; Kourdioukov, A.; Williams, C. M. *Synthesis* **2000**, *7*, 929–934.
4. (a) Heldeweg, R. F.; Hogeveen, H. *J. Org. Chem.* **1978**, *43*, 1916–1920; (b) Toda, F.; Takehira, Y. *J. Chem. Soc., Chem. Commun.* **1975**, 174; (c) Tolstikov, G. A.; Romanova, T. Y.; Kuchin, A. V. *J. Organomet. Chem.* **1985**, *285*, 71–82.
5. General procedure for the preparation of bis-allenes **2**–**6**: To a mixture of Ti(O-*i*-Pr)$_4$ (1.25 equiv.) and bis-propargyl carbonate (1.00 equiv.) in Et$_2$O (0.2 M) was added *i*-PrMgCl (2.5 equiv., 1.4 M in Et$_2$O) dropwise at −50°C. The solution was warmed to −20°C during 5 h. The reaction mixture was quenched at −20°C with a small amount of water (2 mL/mmol of titanium), filtered through a short pad of Celite and concentrated. The crude product was purified by flash chromatography (silica gel, pentane). Representative spectral data are as follows: Compound **3**: colorless oil; ^{1}H NMR (CDCl$_3$, 300 MHz): δ 4.96 (s, 4H), 2.51 (br.s, 4H), 1.77 (br.s, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz): δ 204.0, 102.9, 78.4, 32.1, 26.0. Compound **5**: colorless oil; ^{1}H NMR (CDCl$_3$, 300 MHz, rt): δ 5.14 (s, 4H), 4.50 (s, 4H); ^{13}C NMR (CDCl$_3$, 75 MHz, rt): δ 201.2, 100.7, 81.4, 70.4.

6. Our attempt to provide a six-membered ring from propargyl carbonates rather than methyl ethers was unsuccessful. The intramolecular cyclization did not occur, only giving the open-chain bis-allene:



7. As far as the compound **7** (Table 2, entry 1) is concerned, it was produced in the Cp_2Zr-mediated cyclization (see Ref. 3a), where, however, the intramolecular vinylzirconation to an allene bond was proposed as a most likely mechanism. Contrarily, in our case, we consider that the [2+2] electrocyclization of the bis-allene should be a reasonable path, because the bis-allene intermediates were, in fact, obtained in other cases (Table 1).
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9. General procedure for the preparation of cyclobutenes **7**–**12**: To a mixture of $Ti(O\text{-}i\text{-}Pr)_4$ (1.25 equiv.) and bis-propargyl methyl ether (1.00 equiv.) in Et_2O (0.2 M) was added *i*-PrMgCl (2.5 equiv., 1.4 M in Et_2O) dropwise at −50°C. The solution was warmed to room temperature overnight. The reaction mixture was quenched at rt with a small amount of water (2 mL/mmol of titanium), filtered through a short pad of Celite and concentrated. The crude product was purified by flash chromatography (silica gel, pentane). Representative spectral data are as follows: Compound **7**: Spectral data in good agreement with those reported in Ref. 3a. Compound **10**: colorless oil; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.38 (br.s, 4H), 1.90 (s, 6H), 1.79 (s, 6H), 1.69 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 150.4, 138.1, 112.9, 24.6, 22.9, 22.2, 21.7.