ORGANIC LETTERS

2000
Vol. 2, No. 22
3481−3484

A Facile Preparation of *exo*-Cyclic Conjugated Dienes Fused to Lactams or Lactones via Intramolecular Coupling of Acetylenes and Their Behavior in Diels–Alder Reactions

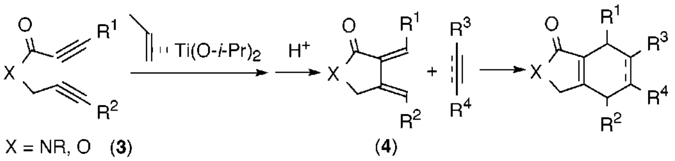
Hirokazu Urabe, Ryota Nakajima, and Fumie Sato*

Department of Biomolecular Engineering, Graduate School of Bioscience and Biotechnology, Tokyo Institute of Technology, 4259 Nagatsuta-cho, Midori-ku, Yokohama, Kanagawa 226-8501, Japan

fsato@bio.titech.ac.jp

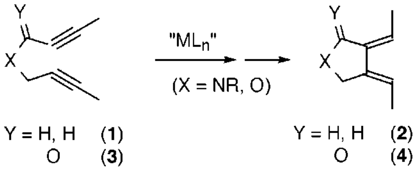
Received August 30, 2000

ABSTRACT



Treatment of bis-acetylenic amides or esters 3 with (η^2-propene)Ti(O-*i*-Pr)$_2$ generates functionalized titanacyclopentadienes which, upon hydrolytic workup, give *exo*,*exo*-cyclic conjugated dienes 4 in good yields. Some regio- and stereochemical aspects of their Diels–Alder reaction with dienophiles are also disclosed.

exo-Cyclic conjugated dienes **2** shown in eq 1 are useful intermediates in organic synthesis. Particularly, the characteristic structure of a diene fixed in a cisoid conformation is prone to undergo Diels−Alder and related reactions to enable convenient preparation of polycyclic compounds.[1] A recent and straightforward method to prepare dienes of type **2** is the transition metal-mediated cyclization of diynes **1** as formulated in eq 1.[2−4] Considering the synthetic flexibility,



(1)

we envisaged that the functionalized congener **4** having a carbonyl group would be a versatile compound as well. However, the method of eq 1 so far appears inapplicable to the synthesis of functionalized dienes **4** from **3**[2,3,5] due probably to the lack of compatibility of the carbonyl group.[6] We recently reported that the *intermolecular* coupling of functionalized acetylenes with titanium(II) alkoxide nicely

---

(1) (a) Desimoni, G.; Tacconi, G.; Barco, A.; Pollini, G. P. *Natural Products Synthesis through Pericyclic Reactions*; American Chemical Society: Washington, D.C., 1983. (b) Fringuelli, F.; Taticchi, A. *Dienes in the Diels−Alder Reaction*; Wiley: New York, 1990. (c) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1990. (d) Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 315−512. (e) Weinreb, S. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 401−449. (f) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 513−550. (g) Waldmann, H. *Synthesis* **1994**, 535−551.

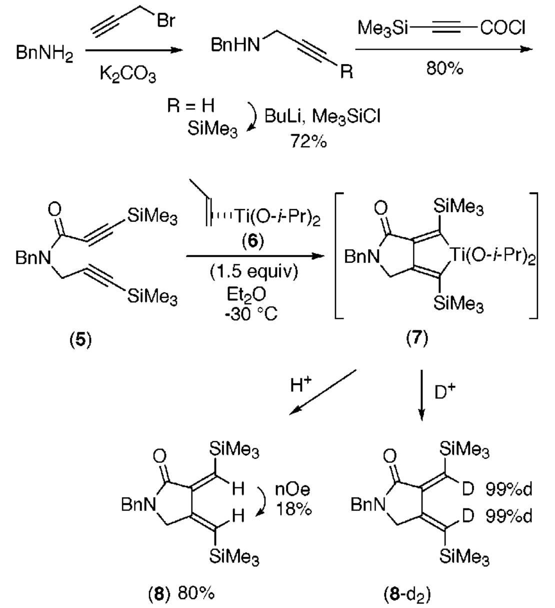
(2) For review on group 4 metal-mediated diyne cyclization, see: Buchwald, S. L.; Nielsen, R. B. *Chem. Rev.* **1988**, *88*, 1047−1058. Negishi, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 1163−1184. Broene, R. D.; Buchwald, S. L. *Science* **1993**, *261*, 1696−1701. Negishi, E.; Takahashi, T. *Acc. Chem. Res.* **1994**, *27*, 124−130. Maier, M. In *Organic Synthesis Highlights II*; Waldmann, H., Ed.; VCH: Weinheim, 1995; pp 99−113. Ohff, A.; Pulst, S.; Lefeber, C.; Peulecke, N.; Arndt, P.; Burlakov, V. V.; Rosenthal, U. *Synlett* **1996**, 111−118. Negishi, E.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 755−769.

10.1021/ol0065221 CCC: $19.00

took place to afford functionalized dienes.[7] As an intramolecular cyclization of diynes connected by an amide or an ester linkage such as **3** has not yet been investigated, we were interested in the viability of this mode of cyclization. Herein the preliminary results as well as the regio- and stereoselective Diels–Alder reaction of the resultant dienes of type **4** will be disclosed.

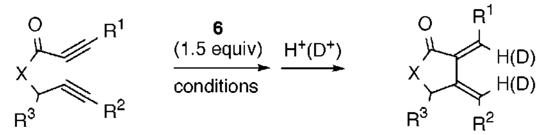
The starting materials **3** (X = NR) were prepared by standard methods involving acylation of propargylamines with a propiolic chloride as exemplified for **5** in Scheme 1.[7]

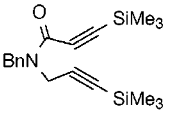
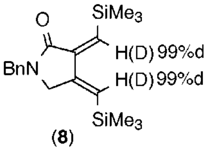
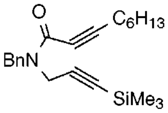
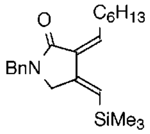
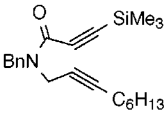
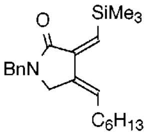
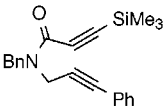
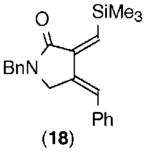
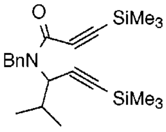
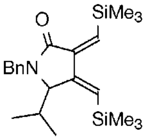
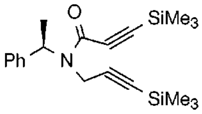
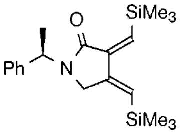
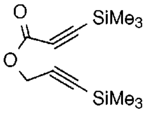
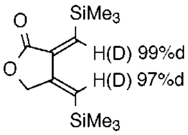
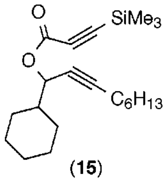
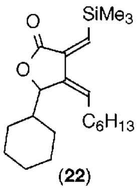
Scheme 1. Preparation and Cyclization of Amide-Tethered Diyne **5**



The cyclization was carried out by the treatment of the diyne with (η^2-propene)Ti(O-*i*-Pr)$_2$ (**6**) prepared in situ from Ti(O-*i*-Pr)$_4$ and *i*-PrMgCl.[8] Hydrolytic workup of the reaction mixture afforded the desired diene **8** having exclusively the *Z,Z* configuration (by NOE study of ^{1}H NMR spectroscopy) in good yield. Alternatively, deuteriolysis gave the bisdeuterated product **8**-d$_2$, confirming the presence of func-

Table 1. Preparation of *exo*-Cyclic Conjugated Dienes Fused to Lactams or Lactones



entry	substrate	conditions	workup	product	yield (%)
1	 **(5)**	-30 °C, 4 h	H$^+$(D$^+$)	 **(8)**	80
2	 **(9)**	-50 °C, 8 h	H$^+$	 **(16)**	51
3	 **(10)**	-50 °C, 8 h	H$^+$	 **(17)**	52
4	 **(11)**	-50 °C, 4 h	H$^+$	 **(18)**	67
5	 **(12)**	-20 °C, 4 h	H$^+$	 **(19)**	83
6	 **(13)**	-20 °C, 4 h	H$^+$	 **(20)**	79
7	 **(14)**	-50 °C, 5 h	H$^+$(D$^+$)	 **(21)**	50
8	 **(15)**	-50 °C, 5 h	H$^+$	 **(22)**	53

---

(3) For the preparation of dienes via diyne cyclization mediated by transition metals other than group 4, see: Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1–16. Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635–662. Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49–92. Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259–281. Tamao, K.; Kobayashi, K.; Ito, Y. *Synlett* **1992**, 539–546. Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34–42.

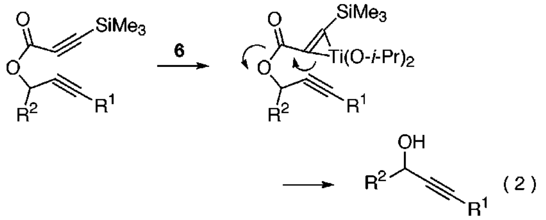
(4) A preparation of polycyclic compounds based on the cyclization of diyne **1** with a group 4 metalocene reagent followed by Diels–Alder reaction was reported; see: Nugent, W. A.; Calabrese, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 6422–6424.

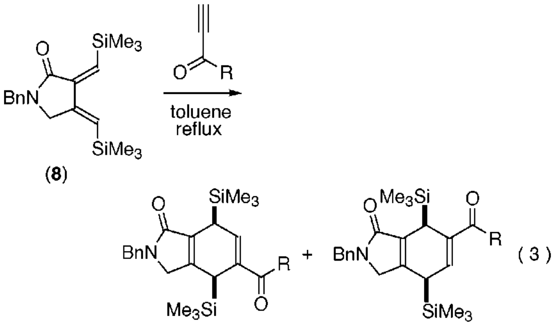
(5) Formation of functionalized rhodacycles similar to **7** in Scheme 1 is known, but its conversion to diene upon hydrolysis is not clear. Müller, E. *Synthesis* **1974**, 761–774.

(6) Some attempts to promote the cyclization of similar functionalized *enynes* were unsuccessful. An enyne tethered by an ester analogous to **14** in Table 1 failed in the titanocene-mediated cyclization. Zhao, Z.; Ding, Y.; Zhao, G. *J. Org. Chem.* **1998**, *63*, 9285–9291. Berk, S. C.; Grossman, R. B.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 8593–8601. Palladium-catalyzed arylative cyclization of an enyne tethered by amide afforded a product similar to **17** only in a low yield. Xie, X.; Lu, X. *Tetrahedron Lett.* **1999**, *40*, 8415–8418. See also: Lu, X.; Zhu, G.; Wang, Z. *Synlett* **1998**, 115–121.

(7) Hamada, T.; Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 7342–7344.

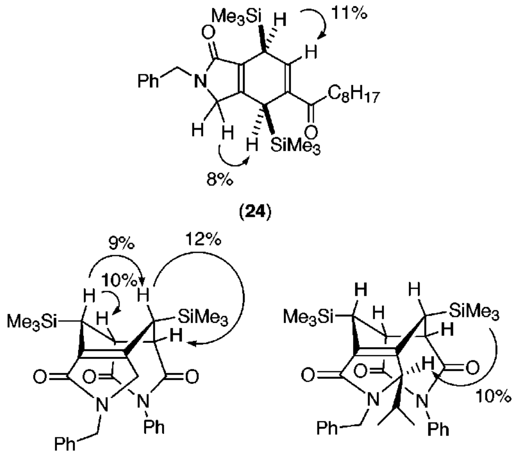
tionalized titanacyclopentadiene **7** before the workup. A variety of *N*-hetereocyclic dienes were prepared by this method, the results of which are summarized in entries 1−6 of Table 1. The reaction proceeded in good yield to give relatively strained five-membered lactams having two *exo*-methylene substituents. A bulky substituent close to the reaction center in substrate **12** (entry 5) did not retard the cyclization at all. Even when the regiochemistry of the cyclization (entry 2) is not in accord with the intrinsic preference observed in the intermolecular coupling reaction,[7,9] the desired product **16** was successfully obtained. Bis-acetylenic esters **14** and **15**, prepared from the corresponding propargyl alcohols and the propiolic chloride, afforded *exo*-cyclic conjugated dienes **21** and **22** fused to butyrolactone as well (entries 7 and 8). The lower yields recorded for these lactones as compared to the aforementioned lactams are most likely attributable to the ester cleavage by the elimination reaction as shown in eq 2 or, possibly, by the nucleophilic attack of the Grignard reagent or **6** to the carbonyl group. In fact, the released propargyl alcohol was detected in 12−25% yield in these cases.





R = OEt (**23**) 66% 85 : 15
C_8H_{17} (**24**) 63% 93 : 7

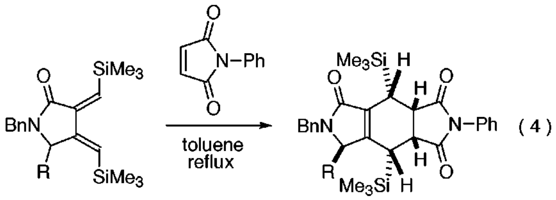
With the desired dienes **4** (eq 1) in hand, we proceeded to the next stage to see their behavior in Diels−Alder reaction. The reaction of diene **8**, having equal substituents (Me_3Si) at both terminal carbons, with ethyl propiolate or an alkynone provided an answer to the regiochemical issue (eq 3). The diene exhibited good regiochemical control with ethyl propiolate, which was further improved by acetylenic ketone to be 93:7. In both cases, the major adduct **23** or **24** has two acyl groups in the *para*-position,[10] which was established through NOE correlation of their protons (for example, **24** in Figure 1). The carbonyl group conjugated to the diene moiety apparently contributed to the regioselective reaction with the above unsymmetrical dienophiles. Besides the regioselectivity, diene **8** showed very high stereoselectivity, *endo* preference, in the reaction with *N*-phenylmaleimide to give a single adduct, **25** (eq 4). More importantly, a proximate substituent (*i*-Pr) to the reacting center in **12** showed efficient chiral induction to form again an almost single adduct, **26**, out of the four possible stereoisomers. The structures of **25** and **26** were verified by ^{1}H NMR spectros-



(24)

(25) **(26)**

Figure 1. Values in % refer to selected NOE enhancements.

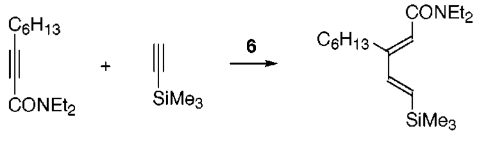


R = H (**8**) R = H (**25**) 83% single adduct
i-Pr (**12**) *i*-Pr (**26**) 95% d.s. = >95:<5

---

(8) Sato, F.; Urabe, H.; Okamoto, S. *Pure Appl. Chem.* **1999**, *71*, 1511−1519. Sato, F.; Urabe, H.; Okamoto, S. *Synlett* **2000**, 753−775. Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835−2886.

(9) In an intermolecular cyclization where no positional bias exists, a nonsilylated propiolic amide **29** was incorporated into the diene **30** exclusively with its amide group being placed at the terminal position of the diene system, which is not the case in **16** of entry 2, Table 1.

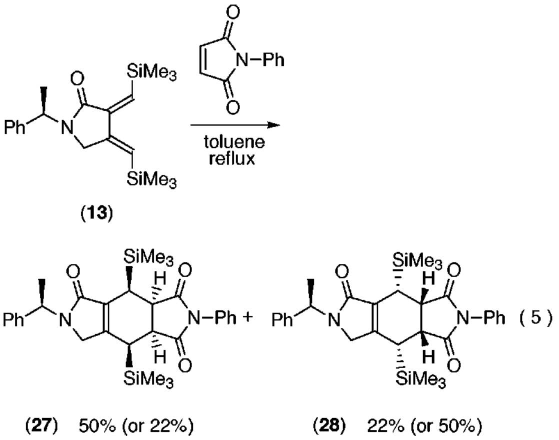


(29) **(30)**

(10) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: London, 1976; pp 132−136.

(11) Juaristi, E.; León-Romo, J. L.; Reyes, A.; Escalante, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2441−2495. Bloch, R. *Chem. Rev.* **1998**, *98*, 1407−1438. Enders, D.; Reinhold: U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895−1946.

copy as shown in Figure 1. It is interesting to note that the *N*-phenethyl group in **13** (eq 5),[11] the chiral carbon of which is the fifth atom from the reacting center, still showed appreciable chiral induction (better than 2:1) to give two separable stereoisomers **27** and **28**. This nontrivial remote chiral induction should be attributable to the flat and rigid shape of diene **13**.



In conclusion, titanium-mediated intramolecular cyclization of an amide- or ester-tethered diyne afforded *exo*-cyclic dienes incorporated in lactams or lactones in good yields.[12] These dienes proved to be versatile substrates for the Diels–Alder reaction with electron-deficient acetylenes or olefins to give heteropolycyclic compounds in a regio- and stereoselective manner.[13,14]

Acknowledgment. We thank the Ministry of Education, Science, Sports and Culture (Japan) for financial support.

OL0065221

---

(12) **Representative procedure for the preparation of 8:** To a stirred solution of bis-acetylenic amide **5** (40 mg, 0.117 mmol) and Ti(O-*i*-Pr)$_4$ (0.052 mL, 0.176 mmol) in 3 mL of Et$_2$O was added a 1.35 M solution of *i*-PrMgCl in ether (0.260 mL, 0.351 mmol) at −78 °C under argon to give a yellow homogeneous solution. The solution was warmed to −30 °C over 60 min, during which period its color turned brown. After stirring at −30 °C for an additional 4 h, the reaction was terminated by the addition of 1 N HCl, and the organic products were extracted with ether. The combined organic layers were washed with an aqueous solution of NaHCO$_3$, dried over MgSO$_4$, and concentrated in vacuo to give a crude oil, which was chromatographed on silica gel (hexanes−ether) to afford the title compound (32 mg, 80%) as an oil.

(13) The nitrogen heterocycles obtained herein will be useful intermediates for the synthesis of both pyrrolidine and isoindoline derivatives. Cordell, G. A., Saxton, J. E., Shamma, M., Smith, G. F., Eds. *Dictionary of Alkaloids*; Chapman and Hall: London, 1989. Glasby, J. S., Ed. *Encyclopedia of the Alkaloids*; Plenum Press: New York, 1975.

(14) For further elaboration based on the silylated diene and allylsilane moieties in the products, see: Luh, T.-Y.; Wong, K.-T. *Synthesis* **1993**, 349−370. Weber, W. P. In *Silicon Reagents for Organic Synthesis*; Springer-Verlag: Berlin, 1983. Colvin, E. W. In *Silicon in Organic Synthesis*; Butterworth: London, 1981. Fleming, I.; Dunogués, J.; Smithers, R. In *Organic Reactions*; Kende, A. S., Ed.; Wiley: New York, 1989; Vol. 37, pp 57−575. Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063-2192.