ORGANIC LETTERS

2006
Vol. 8, No. 1
95−98

Sequential Pericyclic Reaction of Ene-diallenes: An Efficient Approach to the Steroid Skeleton

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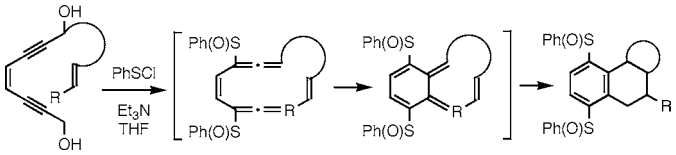
Received October 24, 2005

ABSTRACT

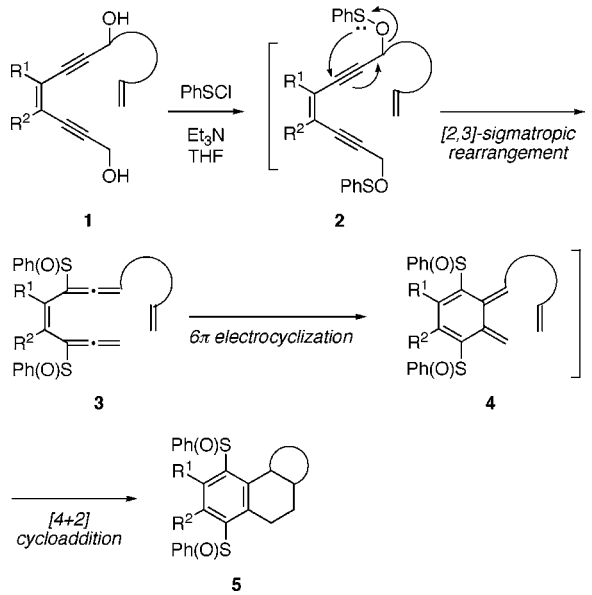


The one-pot construction of polycyclic aromatic systems from acyclic ene-bis(propargyl alcohols) was achieved through a tandem dual [2,3]-sigmatropic rearrangement/6π-electrocyclic reaction/intramolecular [4 + 2] cycloaddition sequence. A steroidal compound was conveniently synthesized using the present method.

o-Quinodimethane intermediates have been widely utilized as a powerful diene counterpart in the intramolecular [4 + 2] cycloaddition reaction for constructing complex polycyclic compounds such as steroids, alkaloids, terpenes, anthracyclins, and lignans.[1] The hitherto known methods for generation of *o*-quinodimethane species include the thermolysis of benzocyclobutenes, thermal cheletropic extrusion of small-sized molecules, and 1,4-elimination of α,α′-substituted *o*-xylenes. These procedures mostly require a considerably high temperature and/or multiple-step preparation of the substrates.

Despite their latent potential for the preparation of *o*-quinodimethanes from ene-diallenes via the 6π-electrocyclic reaction,[2] little attention has so far been paid to the chemistry of the ene-diallenes. We envisaged that the efficient generation of *o*-quinodimethane **4** would be attained under mild conditions starting from the ene-bis(propargyl alcohol) **1** by the consecutive sulfenic ester formation (first step), dual [2,3]-sigmatropic rearrangement of ene-bis(propargyl sulfenate) **2** (second step),[3,4] and 6π-electrocyclic reaction of ene-diallene **3** (third step) (Scheme 1). The sulfur-containing

Scheme 1. Construction of Polycyclic Skeleton Based on Ene-diallene Formation



groups on the benzene ring of the [4 + 2] cycloadduct **5** would further elaborate into other functionalities or hydro-

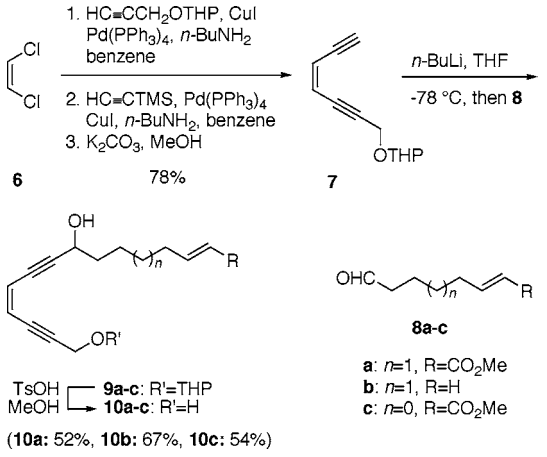
(1) (a) Segura, J. L.; Martin, N. *Chem. Rev.* **1999**, *99*, 3199−3246. (b) Martin, N.; Seoane, C.; Hanack, M. *Org. Prep. Proc. Int.* **1991**, *23*, 237−272. (c) Charlton, J. L.; Alauddin, M. M. *Tetrahedron* **1987**, *43*, 2873−2889. (d) Oppolzer, W. *Synthesis* **1978**, 793−802.

10.1021/ol0525720 CCC: $33.50
Published on Web 12/06/2005

gen.[5] In addition, the ene-bis(propargyl alcohol) **1** would be easily prepared by the Sonogashira coupling[6] of the suitable vinyl halide and the terminal alkynes. On the basis of these considerations, the sequential pericyclic reaction of ene-diallene, derived from ene-bis(propargyl alcohol), was investigated.[7] We describe herein the preliminary results of the one-pot synthesis of polycyclic aromatic compounds from acyclic ene-bis(propargyl alcohols) via the sequential ene-diallene−*o*-quinodimethane formation and intramolecular [4 + 2] cycloaddition and its application to the construction of the steroid skeleton.

The required ene-bis(propargyl alcohols) **10a**−**c** for the above sequential reaction were prepared by conventional methods as shown in Scheme 2. According to the literature

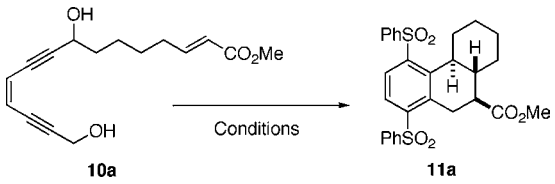
Scheme 2. Preparation of Ene-bis(propargyl alcohol) **10**



procedure, dichloroethylene (**6**) was transformed into **7**[8] via the two-step Sonogashira reaction. The acetylide, derived from **7**, was then added to the unsaturated aldehydes **8a**−**c**[9] to afford the **9a**−**c**, the THP protecting group of which was subsequently removed under acidic conditions to produce ene-bis(propargyl alcohols) **10a**−**c**.

With three ene-bis(propargyl alcohols) in hand, the first efforts focused on the construction of the octahydrophenanthrene skeleton from the ene-bis(propargyl alcohol) **10a** via the sequential pericyclic reaction. The ring-closing reaction was performed as follows. Benzenesulfenyl chloride was added to a solution of **10a** and triethylamine in THF at −78 °C and then warmed to room temperature. After *m*CPBA oxidation of the crude products, the phenanthrene derivative **11a** could be isolated in 30% yield from the reaction mixture. This result indicated that the expected sequential four-step reaction in one pot must have occurred (Table 1, entry 1).

Table 1. Sequential Pericyclic Reaction of **10a**[a]



entry	conditions	yield (%)
1	(1) PhSCl, Et_3N, THF, −78 °C, 1 h, then rt, 1 h (2) *m*CPBA, CH_2Cl_2	30
2	(1) PhSCl, Et_3N, THF, rt, 2 h (2) *m*CPBA, CH_2Cl_2	34
3	(1) PhSCl, Et_3N, THF, rt, 1 h, then reflux, 15 h (2) *m*CPBA, CH_2Cl_2	57
4	(1) PhSOCl, Et_3N, CH_2Cl_2, −78 °C, 1 h (2) toluene, reflux, 10 h	0[b]

[a] All reactions were performed on a 0.1 mmol scale (0.01 M), and 4−6 equivalents of $PhS(O)_mCl$ (m = 0, 1) and 5−7 equivalents of Et_3N were used. [b] Stylene **15a** was obtained in 84% yield.

The styrene derivative **15a** was obtained as the major byproduct (11%) as a result of the 1,5-hydrogen shift of the (*E*)-quinodimethane **12a** (Scheme 3).[10] Several conditions for improving the chemical yield of **11a** as well as the ratio of **11a** to **15a** were screened. Thus, the highest yield (**11a** 57%, **15a** 24%) was realized when a reaction mixture was heated under reflux for 15 h (Table 1, entry 3). The dual [2,3]-sigmatropic rearrangement of the bis(propargyl sulfinates) derived from the ene-bis(propargyl alcohol) **10a**, instead of the bis(propargyl sulfenates), in refluxing toluene was examined according to the literature precedent[11] but led

(2) (a) Sugimoto, Y.; Hanamoto, T.; Inanaga, J. *Appl. Organomet. Chem.* **1995**, *9*, 369−375. (b) Inanaga, J.; Sugimoto, Y.; Hanamoto, T. *Tetrahedron Lett.* **1992**, *33*, 7035−7038. (c) Bowes, C. M.; Montecalvo, D. F.; Sondheimer, F. *Tetrahedron Lett.* **1973**, 3181−3184. (d) Ben-Efraim, D. A.; Sondheimer, F. *Tetrahedron Lett.* **1963**, 313−315. (e) Tanaka, K.; Takamoto, N.; Tezuka, Y.; Kato, M.; Toda, F. *Tetrahedron* **2001**, *57*, 3761−3767. (f) Toda, F.; Tanaka, K.; Sano, I.; Isozaki, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1757−1758. (g) Ezcurra, J. E.; Moore, H. W. *Tetrahedron Lett.* **1993**, *34*, 6177−6180. (h) Braverman, S.; Duar, Y. *J. Am. Chem. Soc.* **1990**, *112*, 5830−5837. (i) Staab, H. A.; Draeger, B. *Chem. Ber.* **1972**, *105*, 2320−2333.

(3) Horner, L.; Binder, V. *Liebigs Ann. Chem.* **1972**, *757*, 33−68.

(4) The tandem formation and intramolecular [4 + 2] cycloaddition of 1-sulfinyl-1-vinylallenes, triggered by [2,3]-sigmatropic rearrangement of the corresponding propargyl sulfenates, has been reported: (a) Okamura, W. H.; Curtin, M. L. *Synlett* **1990**, 1−9. (b) Curtin, M. L.; Okamura, W. H. *J. Org. Chem.* **1990**, *55*, 5278−5287. (c) Gibbs, R. A.; Bartels, K.; Lee, R. W. K.; Okamura, W. H. *J. Am. Chem.* Soc. **1989**, *111*, 3717−3725. (d) Gibbs, R. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1988**, *110*, 4062−4063.

(5) (a) Nájera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547−10658. (b) Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press: Oxford, 1993.

(6) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467−4470.

(7) The intermolecular cycloaddition reaction of the *o*-quinodimethane, derived from *cis*-4-octene-2,6-diyne-1,8-diol and benzenesulfenyl chloride, was described in the review article by Grissom (Grissom, J. W.; Gunawardena, G. U.; Klingberg, D.; Huang, D. *Tetrahedron* **1996**, *52*, 6453−6518). However, no original manuscript dealing with the details of this reaction is available.

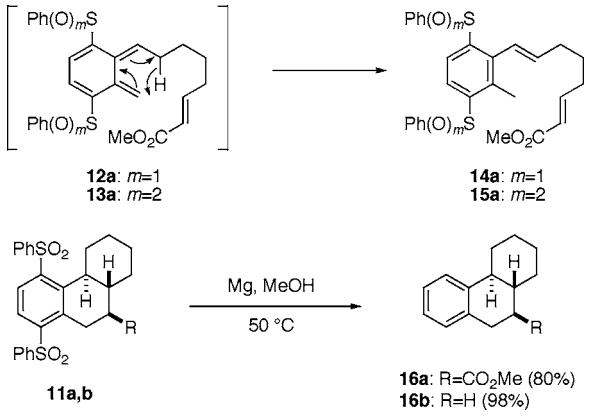
(8) (a) Lin, C.-F.; Wu, M.-J. *J. Org. Chem.* **1997**, *62*, 4546−4548. (b) Kadow, J. F.; Saulnier, M. G.; Tun, M. M.; Langley, D. R.; Vyas, D. M. *Tetrahedron Lett.* **1989**, *30*, 3499−3500.

(9) Little, R. D.; Fox, D. P.; Hijfte, L. V.; Dannecker, R.; Sowell, G.; Wolin, R. L.; Moëns, L.; Baizer, M. M. *J. Org. Chem.* **1988**, *53*, 2287−2294.

(10) Kametani, T.; Tsubuki, M.; Shiratori, Y.; Kato, Y.; Nemoto, H.; Ihara, M.; Fukumoto, K.; Satoh, F.; Inoue, H. *J. Org. Chem.* **1977**, *42*, 2672−2676.

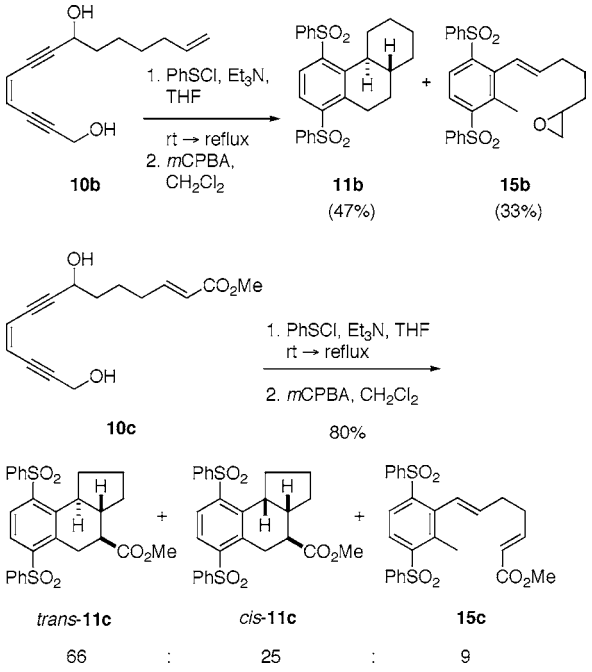
(11) (a) Saalfrank, R. W.; Welch, A.; Haubner, M.; Bauer, U. *Liebigs Ann.* **1996**, 171−181. (b) Stirling, C. J. M. *Chem. Commun.* **1967**, 131.

Scheme 3



to the exclusive production of styrene **15a** via **13a** (Table 1, entry 4). The cycloadduct **11a** was obtained as a single diastereomer, whose relative stereochemistry between C_{4b}-H and C_{8a}-H was unambiguously established to be *trans* by the chemical transformation (desulfonylation)[12] to the known compound **16a**.[13] Compound **10b** without the methoxycarbonyl group at the olefin terminus also underwent a similar sequential reaction under the optimized conditions to afford **11b**[14] as a single diastereomer (Scheme 4).[15] Interestingly,

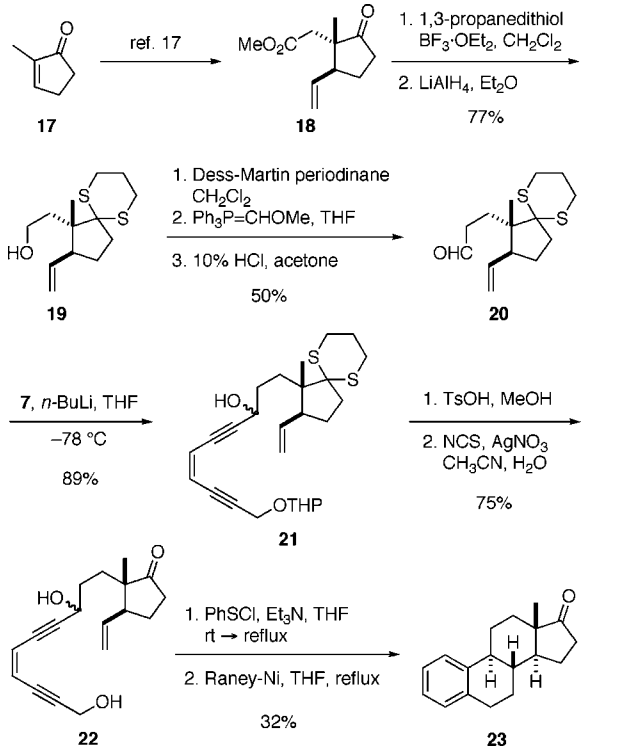
Scheme 4



the ring-closing reaction of the one-carbon shorter **10c** gave an unseparable mixture of two cycloadducts, *trans*-**11c** and *cis*-**11c**, and the 1,5-hydrogen shift product **15c** in a ratio of 66:25:9 for a 80% combined yield.[16]

The novel *o*-quinodimethane formation reaction from the ene-bis(propargyl alcohol) via the ene-diallene could be developed. The next phase of this investigation involved the application of the newly developed method for the synthesis of biologically important frameworks. Thus, a steroid skeleton was chosen as the target molecule. Preparation of the quinodimethane precursor, namely, the ene-bis(propargyl alcohol) **22**, was made in a straightforward manner (Scheme 5). 2-Methylcyclopentenone (**17**) was stereoselectively con-

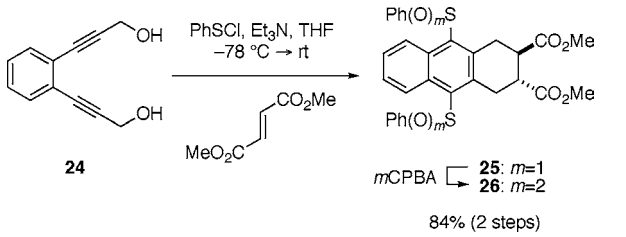
Scheme 5. Synthesis of Steroid **23**



verted into the trisubstituted cyclopentanone **18** according to the literature procedures.[17] The ketalization of **18** with 1,3-propanedithiol and subsequent reduction with $LiAlH_4$ afforded the cyclopentanethanol **19** (77%, 2 steps). The one-carbon homologation of **19** was realized by the successive Dess−Martin oxidation, Wittig olefination, and acid hydrolysis to furnish the aldehyde **20** (50%, 3 steps). Addition of the acetylide, derived from **7**, to the aldehyde **20** provided the monoprotected ene-bis(propargyl alcohol) **21** in 89% yield. Compound **21** was then converted into the ene-bis(propargyl alcohol) **22** by exposure to acid conditions and silver nitrate. Simple treatment of **22** with benzenesulfenyl

(12) Brown, A. C.; Carpino, L. A. *J. Org. Chem.* **1985**, *50*, 1749−1750.
(13) Sato, H.; Isono, N.; Miyoshi, I.; Mori, M. *Tetrahedron* **1996**, *52*, 8143−8158.
(14) Cycloadduct **11b** was converted into **16b**, and the stereochemistry of **16b** was confirmed by comparison of its ^{13}C NMR spectrum with that reported: (a) Nicolaou, K. C.; Barnette, W. E.; Ma, P. *J. Org. Chem.* **1980**, *45*, 1463−1470. (b) Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 863−865.
(15) In this case, the styrene derivative, a 1,5-hydrogen-shifted product, underwent epoxidation with *m*CPBA to give **15b**.
(16) For determination of the product ratio and the stereochemistries of the cycloadducts, see Supporting Information.
(17) Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1982**, *104*, 7609−7622.

Scheme 6



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chloride effected the consecutive four-step conversion in one operation (ester formation, [2,3]-sigmatropic rearrangement, 6π-electrocyclic reaction, and [4 + 2] cycloaddition) to provide the steroid framework. The bis(sulfinyl group) of the resulting compound was subsequently removed with Raney nickel to afford the desired estra-1,3,5(10)-trien-17-one (**23**)[14a] in a 32% yield.

In summary, we have developed a new method for the construction of polycyclic aromatic systems based on the sequential formation of the ene-bis(propargyl sulfenates)/ene-diallenes/*o*-quinodimethanes, followed by [4 + 2] cycloaddition. The characteristic feature of this unique method is that *o*-quinodimethanes can be directly prepared from acyclic compounds under very mild conditions in one operation. The efficiency of the present method has been verified by a convenient synthesis of the estra-1,3,5(10)-trien-17-one. The intermolecular version of this methodology could be successfully applied to the preparation of tetrahydroanthracene derivative **25** as depicted in Scheme 6. Further studies of the development of a more efficient way for the preparation of ene-diallene species and the total synthesis of natural products based on the present protocol are currently in progress.

Acknowledgment. This work was supported in part by a Grant-in Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan, for which we are thankful.

Supporting Information Available: Experimental procedure for the sequential pericyclic reaction and characterization data for compounds **11a**−**c**, **15a**−**c**, **23**, and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0525720