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Stereoselective synthesis of substituted dienes by the double *ortho* ester Claisen rearrangement

Suk-pyo Hong, Sung-jun Yoon and Byung-chan Yu*

Department of Chemistry, Mokwon University, Daejon, 302-729, Republic of Korea

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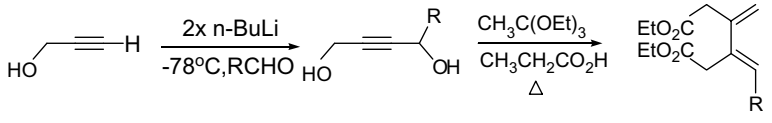
Abstract—This letter shows the highly stereoselective synthesis of substituted (*E*)-1,3-dienes from substituted propargylic diols via the double *ortho* ester Claisen rearrangement. The cyclohexyl-substituted diene undergoes thermal Diels–Alder cycloaddition with maleic anhydride to produce the corresponding bicyclic diester in highly stereoselective manner.

The *ortho* ester Claisen rearrangement[1] has been known as one of the major methodologies in organic synthesis because the methodology provides efficiency in conversion and predictable stereochemistry in carbon–carbon bond formations.[2] The general condition is that treatment of an allylic[3] or a propargylic alcohol[4] with an *ortho* ester in the presence of a catalytic amount of propionic acid gives rise to the corresponding olefinic ester or allenic ester upon heating within the range of 80–160 °C. The conversion is efficient due to the vinyl ether of the Claisen precursor could be generated in situ affording the corresponding ester in a good yield. The *ortho* ester Claisen rearrangement of allenols providing the 1,3-dienes has also been reported.[5] However, the yields of the resulting dienes are generally low or moderate. The stereoselectivity varies from low to high up to 95:5.

We have been interested in the stereoselective synthesis of 1,3-dienes by employing the double *ortho* ester Claisen rearrangement of the propargylic diol with various substituents. Although an example of the double *ortho* ester Claisen rearrangement of unsubstituted propargylic diol has been reported,[6] to the best of our knowledge, the stereoselectivity of the double Claisen rearrangement of substituted propargylic diols has not been utilized as a synthetic methodology for the stereodefined dienes in an efficient manner. We here report the efficient and concise syntheses of the substituted dienes employing the novel double *ortho* ester Claisen rearrangement. The substituted propargylic diols were prepared in moderate to good yields by the direct addition of lithiated dianion of propargylic alcohol (Scheme 1), or anion of THP protected propargylic alcohol[7] to the corresponding aldehydes at −78 °C.

The propargylic diols were treated with an excess triethylorthoacetate in the presence of a catalytic amount of propionic acid. The mixtures were heated at 130 °C for 3 to 24 h to afford the corresponding dienes in a highly stereoselective manner. The isolated yields and stereoselectivities are recorded in Table 1. The optimum yields were observed when the rearrangement proceeded without a high boiling solvent, such as toluene or xylene.



Scheme 1.

Keywords: The double *ortho* ester Claisen rearrangement; Substituted propargylic diols; (*E*)-1,3-dienes; Diels–Alder cycloaddition.
* Corresponding author. Tel.: +82 042 829 7565; fax: +82 042 822 7560; e-mail: chanyu@mokwon.ac.kr

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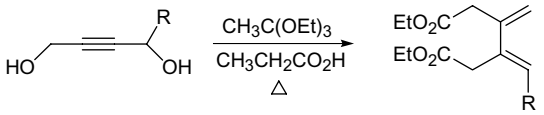
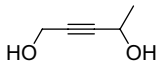
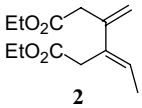
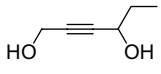
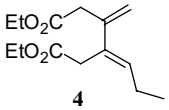
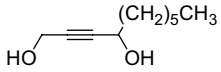
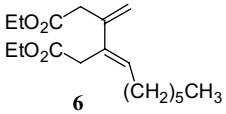
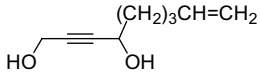
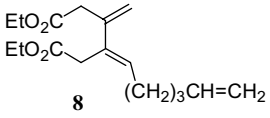
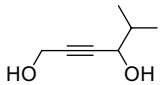
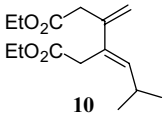
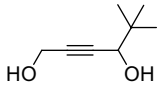
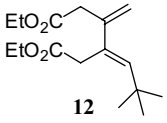
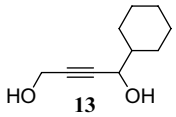
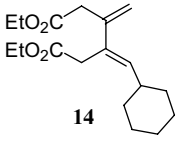
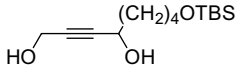
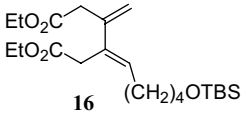
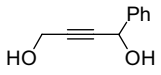
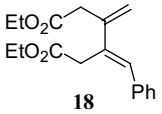
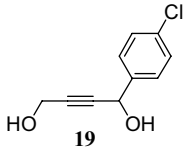
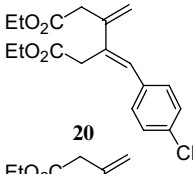
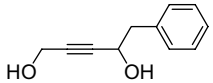
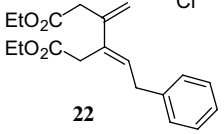
Table 1. The double *ortho* ester Claisen rearrangement of the substituted propargylic diols[a]



Entry	Substrate	Reaction time (h)	Product	Yield (%)[d]	*E*/*Z* ratio[b]
1	 **1**	20	 **2**	72	99:1
2	 **3**	19	 **4**	56	91:9[c]
3	 **5**	10	 **6**	84	83:17
4	 **7**	24	 **8**	58	95:5
5	 **9**	9	 **10**	72	97:3
6	 **11**	17	 **12**	63	>99:1
7	 **13**	17	 **14**	82	96:4
8	 **15**	15	 **16**	76	83:17[c]
9	 **17**	17	 **18**	66	90:10[c]
10	 **19**	13	 **20**	70	78:22[c]
11	 **21**	10	 **22**	22	79:21[c]

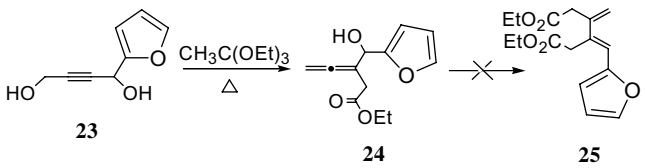
[a] Reaction conditions: 1 equiv of the propargylic diols, 5–7 equiv of triethylortho acetate, a catalytic amount of propionic acid at 120–130 °C.
[b] *E*/*Z* ratios were determined by capillary GC analysis.
[c] *E*/*Z* ratios were determined by ^{1}H NMR analysis.
[d] Isolated yields.

Propionic acid was used within 10 mol% of the diols. During the reaction we were able to observe the intermediate allenol according to TLC analysis.

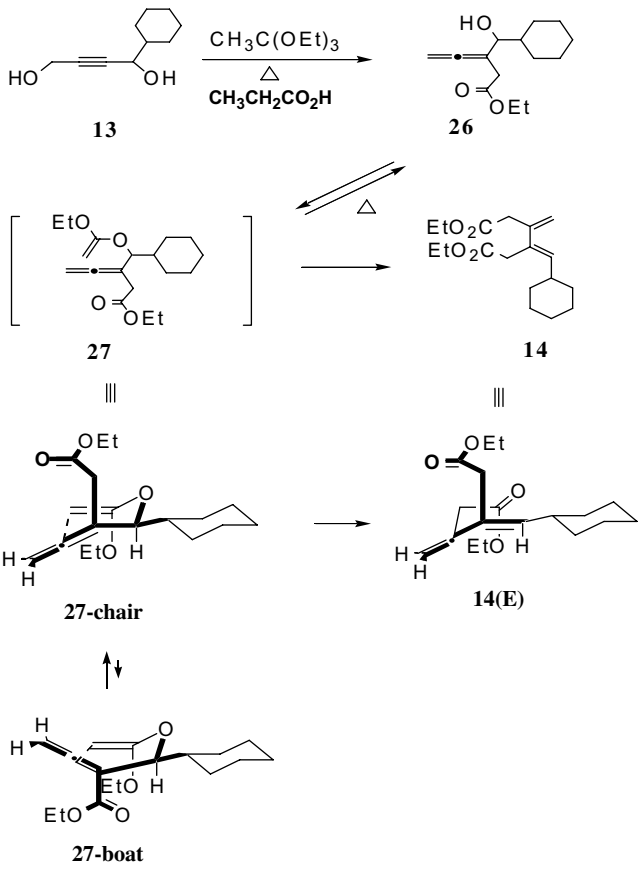
The rearrangement of methyl-substituted propargylic diol **1** gave the corresponding (*E*)-diene diethylester **2** in 72% yield with a 99:1 *E*/*Z* ratio according to capillary GC and ^{1}H NMR analysis. Chain elongation from ethyl to pentyl causes slightly decreasing selectivity, as shown in entries 2 and 3. In the case of the rearrangement of propargylic diol with pentenyl group bearing a terminal olefin, an increase of stereoselectivity to 95:5 was observed. An attempt to effect the novel double Claisen-intramolecular Diels–Alder reaction with the terminal olefinic diol in one pot has not been successful, but resulted in decomposition after several attempts, probably due to the presence of propionic acid during the Diels–Alder reaction at a high temperature.

As expected, an increase of the bulkiness of the substituent by employing isopropyl, *tert*-butyl and cyclohexyl groups also gave great stereoselectivities of the dienes **10**, **12** and **14**, respectively, as shown in entries 5, 6 and 7. Use of 4-(*t*-butyldimethylsilyloxy)butyl substituent caused a decreasing selectivity to 83:17 ratio according to ^{1}H NMR analysis. Although the stereoselectivity of the rearrangement in entry 8 is not as great as in the case of entry 1, this resulting diene is considered to be attractive because the protected alcohol functionality of diene **16** could be utilized to manipulate further chain elongation, such as the incorporation of a dienophile to effect the intramolecular Diels–Alder cycloaddition afterward. The reaction of the diols bearing a phenyl substituent gave the diene **18** with a selectivity of 90:10 in 66% yield. However, the presence of a *para*-substituted electron-withdrawing group leads to decreasing selectivity, down to 78:22 as shown in entry 10. When the benzyl group was substituted, the selectivity decreased to 79:21 as shown in entry 11, with a low yield. The low yield might be caused from the elimination of the starting benzyl-substituted propargylic diol. In the case of the furan-substituted propargylic diol **23**, we obtained only the first Claisen adduct (an allenol) **24** in a low yield (Scheme 2).

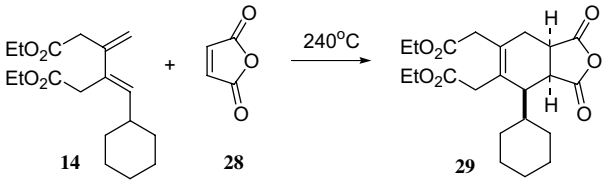
The mechanism of the double *ortho* ester Claisen rearrangement of cyclohexyl substituted propargylic alcohol as an exemplary reaction could be postulated as follows (Scheme 3): The diols would be converted to the allenol **26** which undergoes the second rearrangement to give the corresponding diene **14**. The high stereoselectivity probably comes from a chair transition state of the second Claisen rearrangement which should be more stable than the boat transition state of **27**. The substituent in the chair transition state is disposed as equatorial position resulting the (*E*)-diene products exclusively.



Scheme 2.



Scheme 3. Proposed mechanism of the double *ortho* ester Claisen rearrangement of the cyclohexyl substituted propargylic diol **13**.



Scheme 4.

To demonstrate the novel Diels–Alder cycloaddition with the diene the corresponding diene **14** was subjected to thermal Diels–Alder cycloaddition reaction with maleic anhydride to afford the bicyclic diester **29** in 78% yield with the selectivity of ca. >99:1(*endo*:*exo*) (Scheme 4).[8,9]

In conclusion, we were able to synthesize the stereodefined 1,3-dienes starting from propargylic alcohol in a two step sequence involving the double *ortho* ester Claisen rearrangement in a high stereoselective manner. The substituted dienes could be useful precursors for the Diels–Alder reactions. Currently, we are investigating the use of the dienes as key intermediates toward synthesis of biologically interesting natural products.

Acknowledgments

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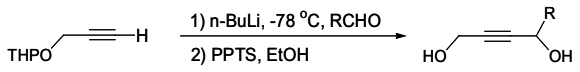
References and notes

1. Johnson, W. S.; Werthmann, L.; Bartlett, W. R.; Brockson, T. J.; Li, T. T.; Faulkner, D. J.; Peterson, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.
2. For review articles on the Claisen rearrangement: (a) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423; (b) Lutz, R. *Chem. Rev.* **1984**, *84*, 206; (c) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227; (d) Bennett, G. B. *Synthesis* **1977**, 589.
3. (a) Stork, G.; Raucher, S. *J. Am. Chem. Soc.* **1976**, *98*, 1583; (b) Daub, G. W.; Edwards, J. P.; Okada, C. R.; Allen, J. W.; Maxey, C. T.; Wells, M. S.; Goldstein, A. S.; Dibley, M. J.; Wang, C. J.; Ostercamp, D. P.; Chung, S.; Cunningham, P. S.; Berliner, M. A. *J. Org. Chem.* **1997**, *62*, 1976, and references therein.
4. (a) Handerson, M. A.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 4736; (b) Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1999**, *121*, 10012.
5. (a) Bertrand, M.; Viala, J. *Tetrahedron Lett.* **1978**, *19*, 2575; (b) Egert, E.; Schumidt, D.; Gonschorreck, C.; Hoppe, D. *Tetrahedron Lett.* **1987**, *28*, 789; (c) Behrens, U.; Wolff, D.; Hoppe, D. *Synthesis* **1991**, 644.
6. Ishino, Y.; Nishiguchi, I.; Kim, K.; Hirashima, T. *Synthesis* **1982**, 740.
7. The diols **3**, **7** and **17** were prepared by the following steps:



8. For other examples of the *endo* Diels–Alder adducts using maleic anhydride as dienophile, see: *Stereoselective Synthesis*; Helmchen, G., Ed.; Georg Thieme: Stuttgart: New York, 1996; Vol. 5, p 2802.
9. The representative procedure of the cyclohexyl propargylic diol, the following double *ortho* ester Claisen rearrangement and the Diels–Alder cycloaddition reaction:
1-Cyclohexylbut-2-yne-1,4-diol (13) To a solution 2.0 g (36 mmol) of the propargylic alcohol in 20 mL of THF was added 30 mL (75 mmol) of 2.5 M solution *n*-BuLi in hexanes dropwise at −78 °C. The solution was stirred for 1 h and then added 4.3 mL (36 mmol) of freshly distilled cyclohexanealdehyde in a portion. The mixture was allowed to warm to room temperature. Water was added. The organic layer was separated and extracted with ether three times. The extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with 80% ether in hexanes gave 5.5 g (91%) of the diol: IR (neat) 3305, 2924, 2242, 1450, 1006 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.31 (2H, s, $-CH_2OH$), 4.19 (1H, d, J = 6.1 Hz, methine), 1.81–1.17 (13H, m, –OH and cyclohexyl Hs) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) 85.5, 83.7, 77.4, 66.8, 50.5, 43.8, 28.5, 28.1, 26.2, 25.8 ppm; EI+ mass spectrum *m*/*z* (%): 137 (M-CH_2OH, 9), 121 (8), 108 (9), 95 (11), 91 (9), 86 (12), 83 (68), 68 (100), 55 (85).
3-Cyclohexylmethylene-4-methylenehexanedioic acid diethyl ester (14). The mixture of 500 mg (3.0 mmol) of the propargylic diol, 2.7 mL (15 mmol) of triethylorthoacetate and 11 mg (0.15 mmol) of propionic acid was stirred for 17 h at 130 °C. The mixture was chromatographed on silica gel. Elution with 10% ether in hexanes gave 750 mg (82%) of the diene **14**. The stereoselectivity of the ester was observed to be 96:4 (*E*:*Z*) according to the analysis of gas chromatography: IR (neat) 3085, 2925, 1738, 1631, 1447, 1366, 1034, 979, 900 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.23 (1H, d, J = 9.8 Hz, vinyl H), 5.14 and 4.97 (2H, d and d, J = 1.6 Hz, terminal olefinic Hs), 4.10 (4H, q, J = 7.3 Hz, $-OCH_2CH_3$), 3.16 and 3.08 (4H, s and s, methylenes), 2.30 (1H, m, methine of cyclohexyl group), 1.80–1.40 (10H, m, cyclohexyl Hs), 1.23 (6H, t, J = 7.3 Hz, $-OCH_2CH_3$) ppm; ^{13}C NMR (125 Hz, $CDCl_3$) 171.1, 170.5, 139.7, 138.3, 131.2, 117.6, 60.4, 60.1, 42.0, 41.3, 37.7, 33.1, 25.8, 25.4, 13.9 ppm; EI+ mass spectrum *m*/*z* (%): 308 (M, 7), 263 (62), 234 (66), 220 (44), 205 (6), 188 (47), 175 (40), 161 (58), 147 (100), 133 (27), 119 (40), 105 (58), 91 (57), 79 (36), 67 (27), 55 (32).
***Rel*-(3a*R*,7*R*,7a*S*)-(7-Cyclohexyl-6-ethoxycarbonyl methyl-1,3-dioxo-1,3,3a,4,7,7a-hexahydroisobenzofuran-5-yl) acetic acid ethyl ester (29).** The mixture of 300 mg (1.0 mmol) of the diene, 470 mg (4.8 mmol) of maleic anhydride was stirred for 5 h at 240 °C. Water was added. The aqueous layer was separated and extracted with ether three times. The extracts were washed with brine, dried over $MgSO_4$ and concentrated under reduce pressure. The residue was chromatographed on silica gel. Elution with 50% ether in hexanes gave 310 mg (78%) of the ester (*endo*:*exo* = 99:1): IR (neat) 2928, 1851, 1778, 1731, 1447, 1368, 1244, 1159, 1030 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.10 (4H, q, J = 7.2 Hz, $-OCH_2CH_3$), 3.44–3.41(2H, m, angular methine Hs), 3.33 and 2.91 (2H, AB, J_{AB} = 15.5 Hz, $-CH_2CO_2Et$), 3.75 and 3.05 (2H, AB, J_{AB} = 16.8 Hz, $-CH_2CO_2Et$), 2.61 (2H, m, allylic methylene), 2.54 (1H, d, J = 8.4 Hz, allylic methylene), 1.90–1.14 (17H, m, cyclohexyl Hs, $-OCH_2CH_3$) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) 174.5, 174.1, 170.2, 170.1, 132.2, 128.9, 61.1, 61.0, 60.9, 48.0, 42.0, 40.2, 40.1, 39.9, 31.2, 31.2, 28.9, 26.4, 26.2, 26.1, 14.1, 13.9; EI+ mass spectrum, *m*/*z* (%): 406 (M^+, 12), 361 (25), 333 (100), 304 (6), 287 (55), 277 (11), 259 (87), 221 (7), 205 (65), 177 (71), 165 (25), 149 (30), 132 (18), 121 (22), 105 (93), 93 (17), 83 (40), 67 (13).