Pergamon

Tetrahedron Letters 39 (1998) 7043–7046

TETRAHEDRON LETTERS

Intramolecularly Competitive Ireland Claisen Rearrangements: Stereoselective Synthesis of Alkylidene Cyclohexenes

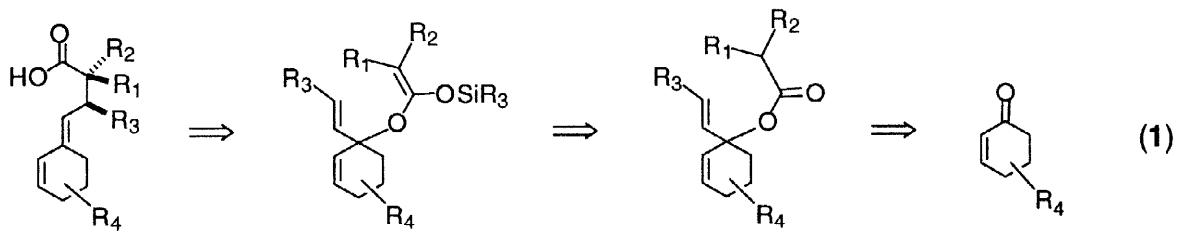
Xiaowei Zhang and Matthias C. McIntosh*

Department of Chemistry and Biochemistry, University of Arkansas, Fayetteville, AR 72701

Received 19 June 1998; revised 13 July 1998; accepted 17 July 1998

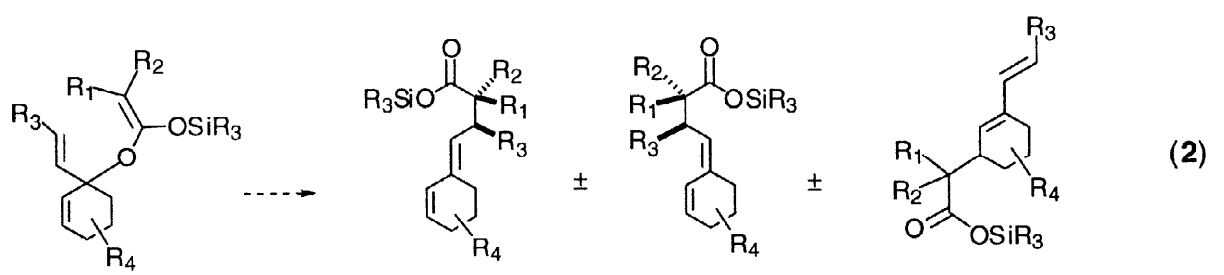
Abstract: Unsymmetrical bis-allyl silylketene acetals derived from cyclohexenones undergo regio- and stereoselective Ireland Claisen rearrangements to afford alkylidene cyclohexenes in good yield.

In the context of several total syntheses, we needed to develop a concise and stereoselective synthesis of alkylidene cyclohexenes **1** (**eq 1**). We considered the possibility that the Claisen rearrangement of bis-allyl silylketene acetals **2** derived from bis-allylic esters **3** might proceed regio- and stereoselectively to afford the desired alkylidene cyclohexenes.[1-4] Esters **3** are generally accessible in one or two steps via 1,2-addition of a vinyl metal nucleophile to cyclohexenones **4** followed by acylation with the appropriate acyl transfer reagent.[2]



1 **2** **3** **4** **(1)**

Several selectivity issues arise in considering the Claisen rearrangement of cyclic bis-allyl silylketene acetals **2**. Both exocyclic and endocyclic rearrangements are possible (**eq 2**). Claisen rearrangements of structurally similar allyl silylketene acetals or allyl vinyl ethers involving either endocyclic[1] or exocyclic[5] alkenes occur readily where no internal competition exists.[6] Furthermore, the desired exo Claisen rearrangement could afford diastereomeric mixtures of rearrangement products which possess opposite stereochemistry at the newly formed chiral centers and opposite alkene geometry.

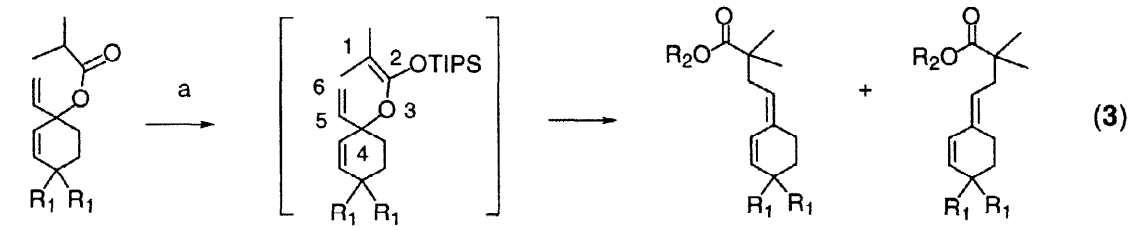


2 (E)-exo (Z)-exo endo **(2)**

email: mcintosh@comp.uark.edu

PII: S0040-4039(98)01525-1

In our initial investigations, we chose to probe only the endo/exo selectivity of the Claisen rearrangement and the stereoselectivity of alkene formation. For this reason, substrates bearing identical substituents at C_1 and C_6 were employed (**eq 3**). Esters **5a,b** were prepared in one step in good yield via vinyl MgBr addition to the corresponding cyclohexenone, followed by in situ acylation with isobutyric anhydride. Sequential treatment of esters **5a,b** with two equivalents each of potassium bis(trimethylsilyl)amide (KHMDS) and triisopropylsilyltrifluoromethane sulfonate (TIPSOTf) in ether at -78°C, followed by warming of the reaction mixture to rt, yielded exclusively the exo Claisen rearrangement products **7a,b** as 2.5:1 and 3:1 mixtures of Z/E stereoisomers, respectively.[7] For ease of purification, the silyl esters were hydrolyzed to carboxylic acids **8a,b** with no change in the isomeric ratio and with overall yields of 60% and 69%, respectively, from esters **5a,b**.



5a R_1 = H
5b R_1 = CH_3

6a R_1 = H
6b R_1 = CH_3

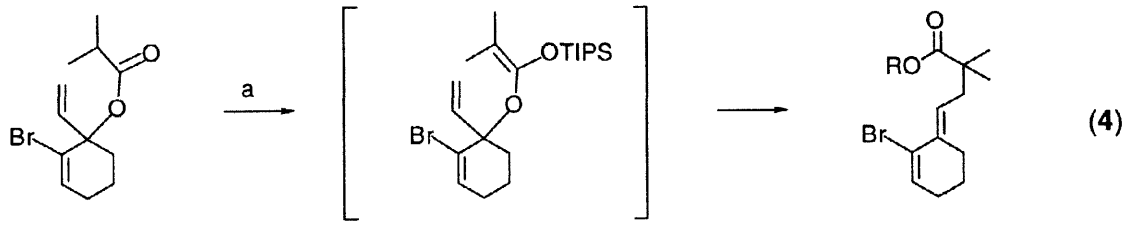
b

7a R_2 = TIPS, R_1 = H, Z:E = 2.5:1
7b R_2 = TIPS, R_1 = CH_3, Z:E = 3:1

8a R_2 = H, R_1 = H, Z:E = 2.5:1 (60%)
8b R_2 = H, R_1 = CH_3, Z:E = 3:1 (69%)

(a) KHMDS, TIPSOTf, ether, -78°C to rt.
(b) K_2CO_3, THF/MeOH/H_2O, 1N HCl.

We expected that introduction of a substituent on the endo double bond proximal to C_4 of the allyl silylketene acetal would reverse the stereoselectivity of the rearrangement (vide infra).[2,5b] In the event, treatment of ester **9**[2] as described above afforded exclusively E-diene **12** (**eq 4**).[7,8]



9

10

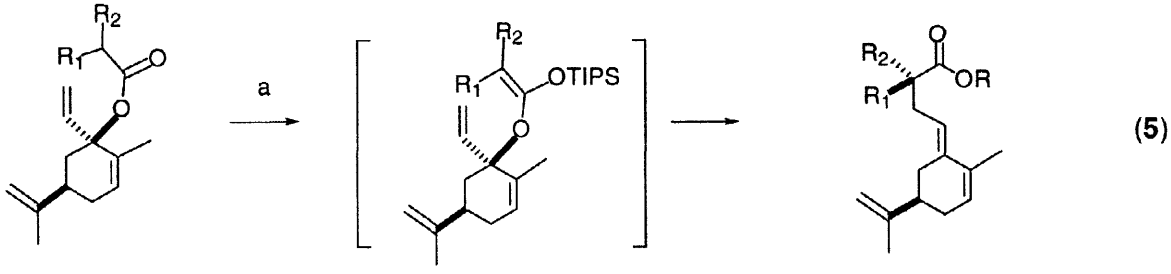
b

R = TIPS **11**

R = H **12**, 63% from **9**

(a) KHMDS, TIPSOTf, ether, -78°C to rt; (b) K_2CO_3, THF/MeOH/H_2O, 1N HCl

Similarly, rearrangement of ester **11a** (prepared in one step from (R)-carvone) afforded only E-diene **14a** (**eq 5**).[7,9] We then examined the issue of chirality transfer using propionate ester **11b**. To our satisfaction, rearrangement of ester **11b** as described above afforded E-diene **14b** with >10:1 de based on ^{1}H-NMR analysis of the crude reaction mixture.[10] The latter rearrangement is particularly noteworthy in that the stereochemistry of the isopropenyl group is ultimately responsible for 1,6-asymmetric induction in the two-step conversion of (R)-carvone to diene **13b**.



11a R_1, $R_2 = CH_3$
11b R_1, R_2 = H, CH_3

12a R_1, $R_2 = CH_3$
12b $R_1 = CH_3$, R_2 = H

b

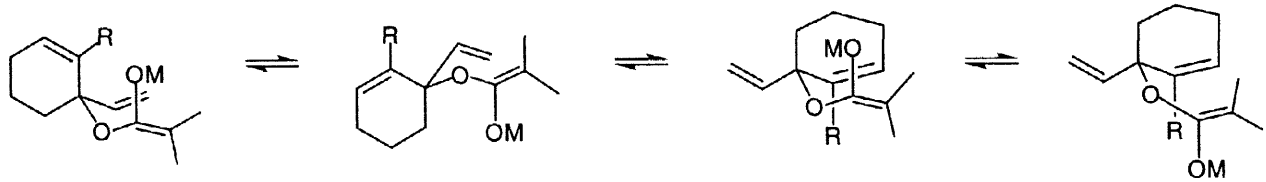
13a R = TIPS, R_1, $R_2 = CH_3$
13b R = TIPS, R_1 = H, $R_2 = CH_3$

14a R = H, R_1, $R_2 = CH_3$ 58%
14b R = H, R_1 = H, $R_2 = CH_3$ 65%

(a) KHMDS, TIPSOTf, ether, -78°C to rt; (b) K_2CO_3, THF/MeOH/H_2O, 1N HCl

The exo Claisen rearrangement pathway is presumably preferred because either chair or boat transition states **iii** or **iv** for the endo pathway would have developing 1,3-diaxial and/or eclipsing interactions which are not present in exo transition states **i** or **ii** (**Scheme**).[1] The E/Z stereoselectivity of the newly formed alkene is likely due to higher 1,3-diaxial strain in transition state **i** leading to the Z-alkene for silylketene acetals **10** and **12** (R = Br or CH_3). Applications of the exo-selective Ireland Claisen rearrangement to the synthesis of natural products will be reported in due course.

Scheme



i (Z)-exo

ii (E)-exo

iii endo

iv endo

Acknowledgments

Support for this work was provided in part by the American Chemical Society Petroleum Research Fund (32150-G1). The X-ray crystal structure of the (S)-α-methylbenzylamide of diene **14b** was solved by Tosha Barclay and Wally Cordes, University of Arkansas. Thanks to Harriet A. Lindsay, University of Arkansas, for confirmation of selected results, and to Raymond L. Funk, Pennsylvania State University, for helpful discussions.

References and Footnotes

(1) For reviews of the Claisen rearrangement, see: Wipf, P. in *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 5, pp 827-873; Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423; Pereira, S.; Srebnik, M. *Aldrichimica Acta* **1993**, *26*, 17 and references cited therein.

(2) Spino, C.; Liu, G.; Tu, N.; Girard, S. *J. Org. Chem.* **1994**, *59*, 5596.

(3) For intramolecularly competitive Claisen rearrangements of bis-allyl vinyl ethers in acyclic systems, see: Cresson, P.; Bancel, S. *C. R. Acad. Sc., Ser. C.* **1968**, *266*, 409; Parker, K. A.; Farmar, J. G. *J. Org. Chem.* **1986**, *51*, 4023; Nonoshita, K.; Banno, H.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 316.

(4) For intramolecularly competitive Claisen rearrangements of bis-allyl vinyl ethers derived from 1-cycloalkene carboxaldehydes, see: Bancel, S.; Cresson, P. *C. R. Acad. Sc., Ser. C.* **1969**, *268*, 1535; Hudlicky, T.; Kwart, L. D.; Tiedje, M. H.; Ranu, B. C.; Short, R. P.; Frazier, J. O.; Rigby, H. L. *Synthesis* **1986**, 716; Tanis, S.; McMills, M. C.; Scahill, T. A.; Kloosterman, D. A. *Tetrahedron Lett.* **1990**, *31*, 1977.

(5) (a) Cresson, P. *Bull. Soc. Chim. Fr.* **1964**, 2618; *ibid*, 2629; Marbet, R.; Saucy, G. *Helv. Chim. Acta* **1967**, *50*, 218; (b) Chillous, S. E.; Hart, D. J.; Hutchinson, D. K. *J. Org. Chem.* **1982**, *47*, 5420.

(6) For intramolecularly competitive anionic oxy-Cope rearrangements, see: Paquette, L. A.; Guevel, R.; Sauer, D. R. *Tetrahedron Lett.* **1992**, *33*, 923; Still, W. C.; Murata, S.; Revial, G.; Yoshihara, K. *J. Am. Chem. Soc.* **1983**, *105*, 625 and references cited therein.

(7) All new compounds have been characterized by ^{1}H-NMR, ^{13}C-NMR, HRMS and IR. Alkene geometries were determined by NOE experiments and/or X-ray crystallography (ref 10).

(8) For some alternative approaches to stereoselective preparation of alkylidene cycloalkenes, see: Larock, R. C.; He, Y.; Leong, W. W.; Han, X.; Refvik, M. D.; Zenner, J. M. *J. Org. Chem.* **1998**, *63*, 2154; Chamakh, A.; Amri, H. *Tetrahedron Lett.* **1998**, *39*, 375; Ahmar, M.; Antras, F.; Cazes, B. *Tetrahedron Lett.* **1998**, *39*, 4417; Murakami, M., Itami, K.; Ito, Y. *J. Am. Chem. Soc.* **1997**, *119*, 716; Terakado, M.; Miyazawa, M.; Yamamoto, K. *Synlett* **1994**, 134; Nuss, J. M.; Rennels, R. A., Levine, B.H. *J. Am. Chem. Soc.* **1993**, *115*, 6991; Brown, S.; Clarkson, S.; Grigg, R.; Sridharan, V. *Tetrahedron Lett.* **1993**, *34*, 157; Trost, B. M.; Dumas, J. *Tetrahedron Lett.* **1993**, *34*, 19; Owczarczyk, Z.; Lamaty, F.; Vawter, E. J.; Negishi, E.-i. *J. Am. Chem. Soc.* **1992**, *114*, 10091; Reich, H. J.; Eisenhart, E. K.; Whipple, W. L.; Kelly, M. J. *J. Am. Chem. Soc.* **1988**, *110*, 6432; Okamura, W. H.; Peter, R.; Reischl, W. *J. Am. Chem. Soc.* **1985**, *107*, 1034; Paquette, L. A.; Yan, T.-H.; Wells, G. J. *J. Org. Chem.* **1984**, *49*, 3610. See also ref 2.

(9) Data for compound **14a**: ^{1}H NMR (270 MHz, $CDCl_3$): δ 5.6 (s, 1H), 5.4 (t, J = 7.7 Hz, 1H), 4.7 (s, 2 H), 2.7 (d, J = 14.2 Hz, 1H), 2.45 (dd, J = 7.7 Hz, 14.4 Hz, 1H), 2.35 (dd, J = 7.7 Hz, 14.4 Hz, 1H), 1.8-2.2 (m, 4H), 1.78 (s, 3H), 1. 74 (s, 3H), 1.20 (s, 6H); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 184.8, 149.6, 138.6, 133.1, 126.2, 118.8, 109.1, 43.0, 41.8, 37.9, 31.4, 31.2, 24.8, 24.6, 20.8, 19.9; HRMS calc'd for $C_{16}H_{24}O_2$ 248.1776; found 248.1784.

(10) The structure of diene **14b** was determined unambiguously by X-ray crystallography of the corresponding (S)-α-methylbenzamide.