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Intramolecularly Competitive Ireland Claisen Rearrangements: Stereoselective Synthesis of Alkylidene Cyclohexenes

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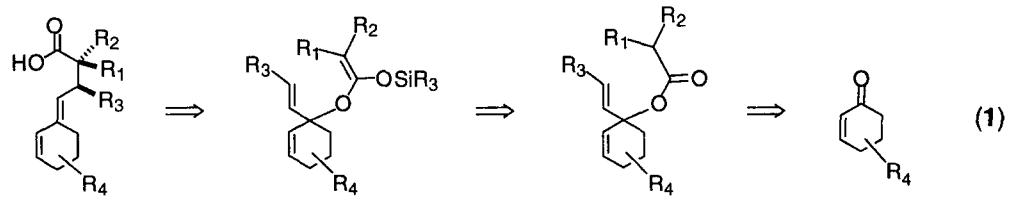
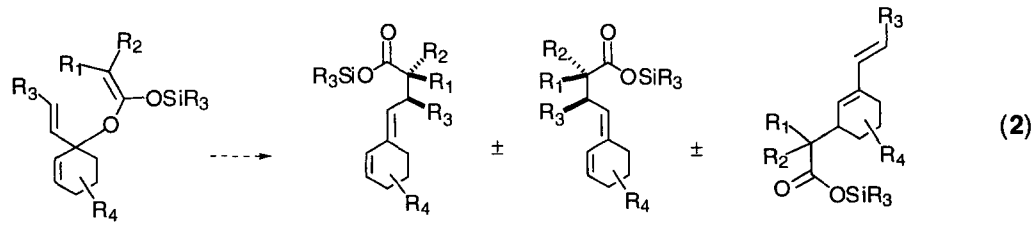
Abstract: Unsymmetrical bis-allyl silylketene acetals derived from cyclohexenones undergo regio- and stereoselective Ireland Claisen rearrangements to afford alkylidene cyclohexenes in good yield.

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)**

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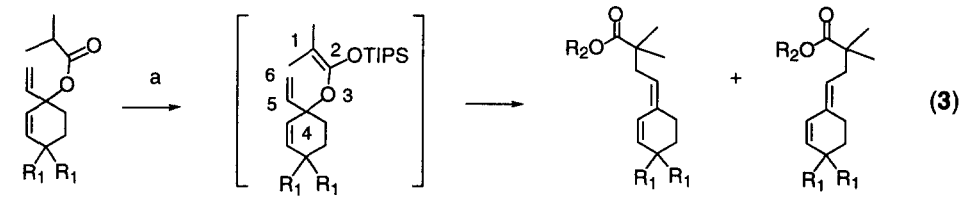
In our initial investigations, we chose to probe only the endo/exo selectivity of the Claisen rearrangement and the stereoselectivity of alkene formation. For this reason, substrates bearing identical substituents at C_1 and C_6 were employed (**eq 3**). Esters **5a,b** were prepared in one step in good 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

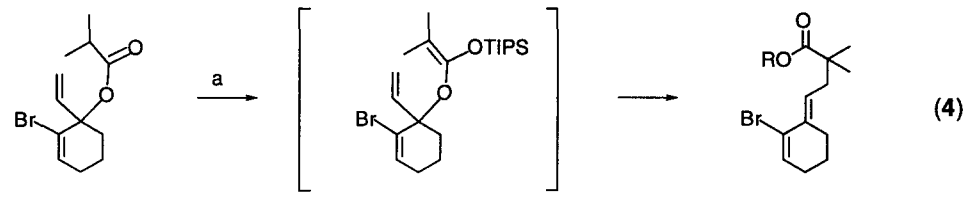
b

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

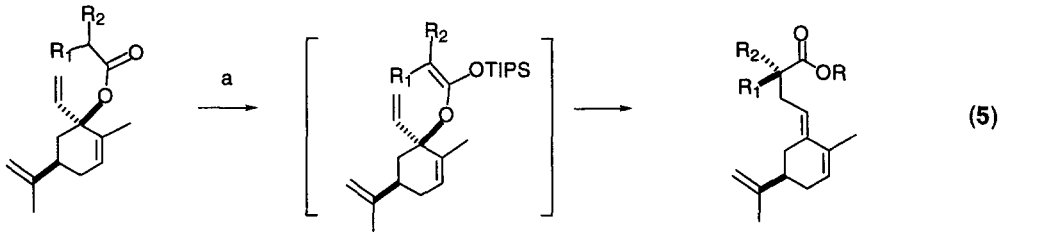
b

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

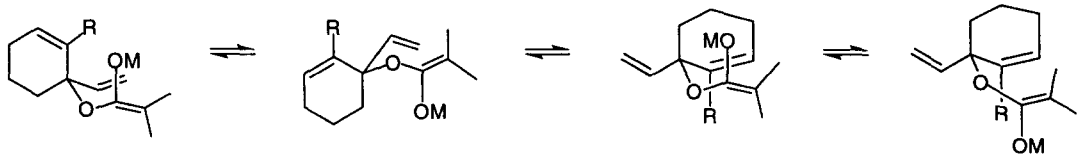
13a R = TIPS, R_1, $R_2 = CH_3$
13b R = TIPS, R_1 = H, $R_2 = CH_3$

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

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References and Footnotes

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(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.