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Unprecedented Alkene Stereocontrol in the Claisen Rearrangement of Cyclic Bis-Allylic Esters

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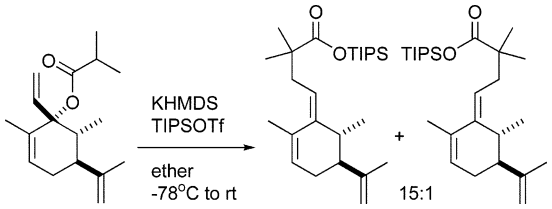
ABSTRACT



The Ireland and ester enolate Claisen rearrangements of tertiary substituted bis-allylic esters derived from cyclohexenones afford pentenoic acids that possess tri- and tetrasubstituted alkylidenes with unprecedented levels of stereoselectivity. In some cases the higher energy exocyclic alkene is the major product.

The stereoselective synthesis of tri- and tetrasubstituted alkenes is a long-standing goal of organic synthesis. Wittig-based and transition-metal-mediated strategies offer some of the more general strategies for stereoselective acyclic tri- and tetrasubstituted alkene synthesis.[1]

The Claisen rearrangement of allyl vinyl ethers, allylic esters, and related substrates has been employed to prepare trisubstituted alkenes in a stereoselective fashion.[2] One of the advantages of the rearrangement lies in its ability to concomitantly install a substituted alkene and one or two new stereogenic carbons. We have pursued Claisen rearrangement approaches to the preparation of alkylidenes derived from cycloalkenones.[3,4] Difunctionalization of the alkylidene double bond can be used for the installation of vicinal endo- and exocyclic stereocenters that would otherwise be difficult to access.[3c,5]

Because of the well-established propensity for the rearrangement to occur via a chairlike transition state in acyclic substrates, secondary carbinol-derived allyl vinyl ethers and related allyl ketene acetals almost invariably rearrange so as to provide the R_1-*trans*-isomer as the major product (Scheme 1) (R_1-*trans* and R_1-*cis* designate the isomers in which the R_1 group is *trans* or *cis* to the CH_2CH_2COX moiety, respectively).[2,6] The transition state leading to the R_1-*cis*-isomer suffers from 1,3-diaxial interactions between

(1) For concise summary of alkene synthesis references, see: Arefolov, A.; Langille, N. F.; Panek, J. S. *Org. Lett.* **2001**, *3*, 3281−4.

(2) For reviews, see: (a) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 1423−1452. (b) Bennett, G. B. *Synthesis* **1977**, *10*, 589−606. (c) Hill, R. K. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, pp 503−572. (d) Blechert, S. *Synthesis* **1989**, 71−82. (e) Wipf, P. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol 5, pp 827−873. (f) Tadano, K. *Studies in Natural Products Chemistry*; Rahman, A.-U., Ed.; Elsevier: Amsterdam, 1992; pp 405−455. (g) Pereira, S.; Srebnik, M. *Aldrichimica Acta* **1993**, *26*, 17−29. (h) Frauenrath, H. *Stereoselective Synthesis*; Helchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme: Stuttgart, 1995; Vol. E21d, pp 3301−3756. (i) Chai, Y.; Hong, S.-p.; Lindsay, H. A.; McFarland, C.; McIntosh, M. C. *Tetrahedron* **2002**, *58*, 2905−2928. (j) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939−3002.

(3) (a) Zhang, X.; McIntosh, M. C. *Tetrahedron Lett.* **1998**, *39*, 7043−7046. (b) McIntosh, M. C.; Hong, S.-p.; Lindsay, H. A.; Yaramasu, T.; Zhang, X. *J. Org. Chem.* **2002**, *67*, 2042−2055. (c) Hong, S.-p.; McIntosh, M. C. *Org. Lett.* **2002**, *4*, 19−21. Hutchison, J. M.; Hong, S.-p.; McIntosh, M. C. *J. Org. Chem.* **2004**, *69*, 4185−4191.

(4) For Claisen approaches to alkylidenes derived from cycloalkanones, see: (a) Cresson, P. *Bull. Soc. Chim. Fr.* **1964**, 2618−2628; 2629. (b) Chillous, S. E.; Hart, D. J.; Hutchinson, D. K. *J. Org. Chem.* **1982**, *47*, 5418−5420. (c) Dulcere, J. P. Rodriguez., J. *Synthesis* **1993**, 399−405. (d) Le Notre, J.; Brissieux, L.; Semeril, D.; Bruneau, C.; Dixneuf, P. H. *Chem. Commun.* **2002**, 1772−3.

(5) Hong, S.-p.; McIntosh, M. C.; Barclay, T.; Cordes, W. *Tetrahedron Lett.* **2000**, *41*, 155−159.

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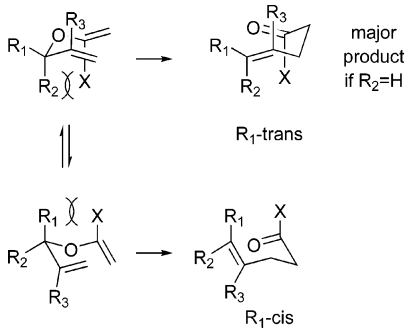
Scheme 1

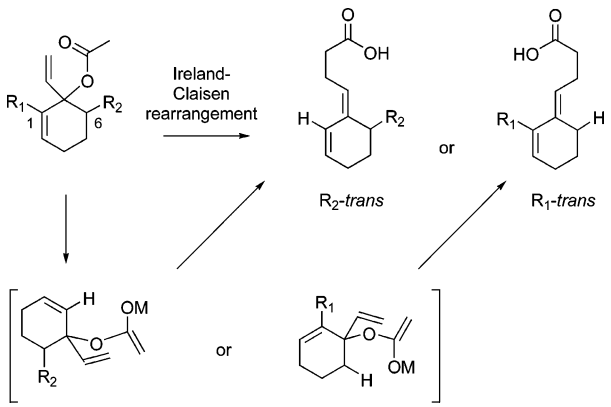


the R_1 and X groups. Claisen rearrangement of secondary carbinol derived allyl vinyl ethers or ketene acetals with substituents $R_3 \neq H$ have also stereoselectively provided trisubstituted *trans*-alkenes.[2] These examples can likewise be readily rationalized by a chairlike transition state in which the larger of the two carbinol substituents occupy the pseudoequatorial position. These features allow one to predict the alkene geometry of the product (as well as the relative stereochemistry at C2 and/or C3 of the pentenoic acid) by employing this straightforward steric analysis.

For tertiary carbinol-derived substrates (i.e., R_1, $R_2 \neq H$), the outcome becomes less obvious. Since both of the transition states leading to the R_1-*trans* and R_1-*cis* products suffer from 1,3-diaxial interactions, the major product will depend on which diaxial interaction is greater. There are scattered examples of stereoselective Claisen rearrangements of tertiary allylic esters for R_1, $R_2 \neq H$ for which there is a significant size difference between R_1 and R_2.[7] For substrates in which R_1 and R_2 are of similar size, the rearrangement would not be expected to be stereoselective. [8]

We have conducted extensive studies of the Ireland and ester enolate Claisen rearrangements of cycloalkenone-derived bis-allylic esters with a view toward their application in natural products synthesis (Scheme 2).[3]

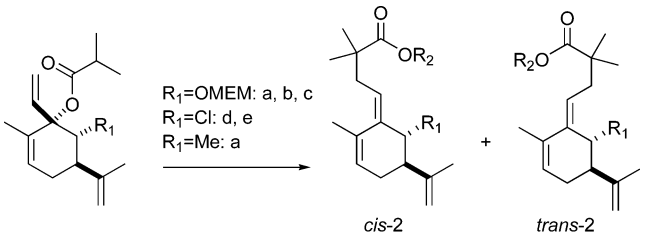
Scheme 2



We determined that monosubstitution at either of the carbons flanking the tertiary carbinol carbon (i.e., C1 or C6 for cyclohexenones) resulted in formation of solely the R_2-*trans* isomer for $R_1 = H$, $R_2 \neq H$ and solely the R_1-*trans* isomer for $R_1 \neq H$, $R_2 = H$. These results are fully consistent with the transition state model placing the larger substituent in the pseudoequatorial position.

We then examined substrates that possessed substitutents at both the C2 and C6 positions to explore the feasibility of the rearrangement to more highly functionalized substrates that would be necessary for some prospective natural products applications. In the case of 6-OMEM ester **1a**, we found that Ireland−Claisen rearrangement afforded solely the alkene *cis*-**2a** after desilylation and esterification (for clarity, *cis* and *trans* are defined as having the carboxylic acid side chain either *cis* or *trans* to the endocyclic alkene) (Scheme 3).[3b] The 6-Cl ester **1b** behaved in an identical

Scheme 3 [a]



		cis/*trans*
1a R_1=OMEM	**2a** R_1=OMEM, R_2=Me, 60%	1:0
1b R_1=Cl	**2b** R_1=Cl, R_2=H, 77%	1:0
1c R_1=Me	**2c** R_1=Me, R_2=TIPS, 44% (see text)	15:1

[a] Reactions and conditions: (a) KHMDS, TIPSOTf, −78 °C to rt; (b) Bu_4NF, THF, rt; (c) CH_2N_2, ether, 0 °C; (d) LDA, TMSCl, −78 °C; (e) HCl.

fashion to give *cis*-**2b** after Ireland−Claisen rearrangement and desilylation. To probe whether the alkene stereoselectivity was due to an electronic effect (e.g., dipole/dipole repulsion between the OMEM or Cl and the $OSiR_3$ groups[9]), we next examined the Ireland−Claisen rearrangement of *trans*-6-methyl-substituted ester **1c**. Rearrangement of ester **1c** under identical conditions afforded diene *cis*-**1c** with the same sense of alkene stereoselectivity but in a 15:1 *cis*:*trans* ratio, which suggest that steric factors are the principal source of the observed selectivity.[10]

It was surprising to us that (i) such high alkene stereoselectivity was obtained, and (ii) the higher energy alkene isomer was the major product. This was demonstrated by

(6) For an exception, see: Fernandez de la Pradilla, R.; Montero, C.; Tortosa, M. *Org. Lett.* **2002**, *4*, 2373−6.

(7) (a. (b) Overman, L. E.; Lin, N.-H. *J. Org. Chem.* **1985**, *50*, 3669−3670. (c) Davidson, A. H.; Eggleton, N.; Wallace, I. H. *J. Chem. Soc., Chem. Commun.* **1991**, 378−380. (d) Enev, V.; Stojanova, D.; Bienz, S. *Helv. Chim. Acta* **1996**, *79*, 391−404.

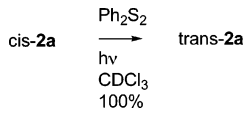
(8) Krafft has employed chelation to address this difficulty: Krafft, M. E.; Dasse, O. A.; Jarrett, S.; Fievre, A. *J. Org. Chem.* **1995**, *60*, 5093−5101.

(9) We thank David Birney, Texas Tech University, for suggesting this possibility.

(10) Alkene stereochemistry was confirmed by NOESY analysis for all alkenes.

quantitative isomerization of diene *cis*-**2a** to *trans*-**2a** under conditions known to afford the thermodynamic alkene isomer (Scheme 4).[3b,11] The more electron-rich diene *cis*-**2c** would

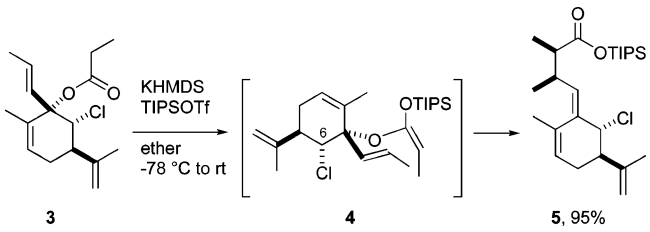
Scheme 4



undergo partial isomerization to *trans*-**2c** upon chromatography on silica gel. For characterization purposes, we converted the *cis/trans* mixture of diene-**2c** entirely to *trans*-**2c** under the same conditions (see Supporting Information).

To probe the geometry of the transition state, we treated *E*-propenyl propionate **3** under the same reaction conditions (Scheme 5). The product was isolated as a single *anti*-

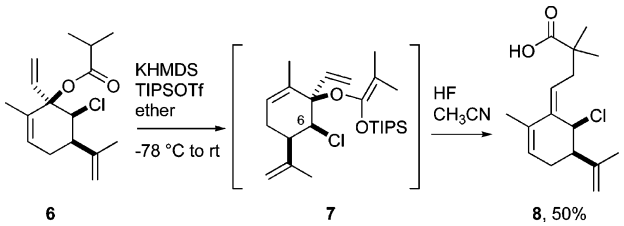
Scheme 5



C2/C3 *cis*-alkene isomer **5** (*anti* refers to the C2/C3 stereochemistry in the extended conformation of the pentenoic acid).[12,13] The *anti* stereochemistry coupled with the *trans*-alkene geometry necessitates a chairlike transition state **4** with the C6 carbon of the cyclohexenone occupying a pseudoequatorial position.

In contrast to β-alkenyl-α-Cl ester **1b**, the doubly epimeric α-alkenyl-β-Cl ester **6** underwent Ireland−Claisen rearrangement to afford solely *trans*-alkene **8** (Scheme 6). In this case

Scheme 6



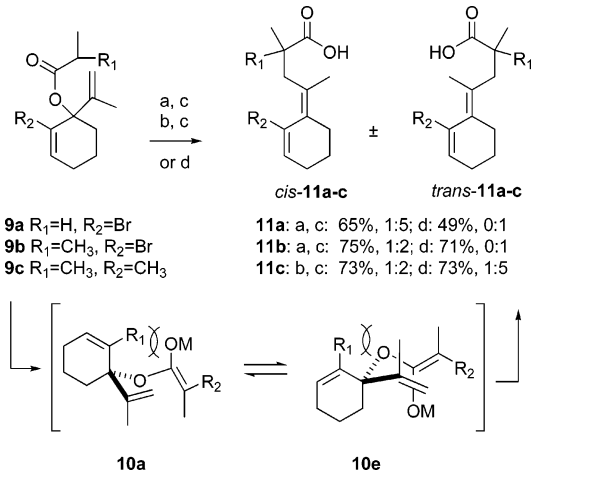
the C6 carbon occupied the pseudoaxial position. The results make clear that high stereoselectivity can be obtained in Ireland−Claisen rearrangements in which the outcome is not a priori obvious.

(11) Moussebois, C.; Dale, J. *J. Chem. Soc. C* **1966**, 260−264.

These results prompted us to consider whether tetrasubstituted alkenes could be prepared stereoselectively via the Claisen rearrangement. There is a single report of a Claisen rearrangement being used to form an unsymmetrical tetrasubstituted alkene by Johnson, although in that case one of the alkene substituents was fluorine.[14] We are unaware of any reports of a Claisen rearrangement being used to form a tetrasubstituted alkene in which all of the alkene substituents are carbon.

Bis-allylic esters **9a**−**c** possessing a 2-propenyl group would have unfavorable steric interactions in either chair transition state **10a** or **10e** (Scheme 7). In **10a** there is a

Scheme 7 [a]



[a] Reactions and conditions: (a) KHMDS, TIPSOTf, ether, −78 °C to rt; (b) KHMDS, TMSCl, −78 °C to rt; (c) HF/CH_3CN; (d) LDA, THF, −78 °C to rt.

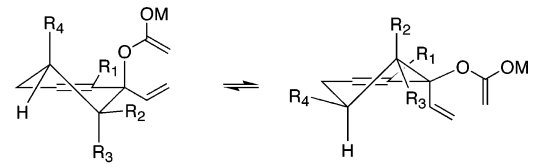
diaxial-like interaction between the R_1 and OM substituents, whereas in **10e** there is a diaxial-like interaction between R_1 and the propenyl methyl group. The products themselves would differ little in energy, so only a kinetically controlled reaction could result in high alkene stereoselectivity.

In the event, treatment of esters **9a**,**b** with KHMDS/TIPSOTf resulted in formation of the pentenoic acids in high yield, albeit with only modest alkene stereoselectivity favoring *cis* **11a** and low stereoselectivity for **11b**,**c** (Scheme 7).[15] Use of the ester enolate variant of the rearrangement, however, resulted in exclusive formation of the *trans*-alkenes for esters **11a**,**b** (R_2 = Br), although in somewhat reduced yield in the case of ester **11a**.[16] Rearrangement of 2-methyl substituted ester **11c** gave lower stereoselectivity (1:5 *cis:trans*).

(12) Hong, S.-p.; McIntosh, M. C. *Tetrahedron* **2001**, *57*, 5055−5060.
(13) The *E*-stereochemistry of the silyl ketene acetal of intermediate **4** is assumed based on extensive prior studies; see refs 3 and 12.
(14) Johnson, W. S.; Buchanan, R. A.; Bartlett, W. R.; Tham, F. S.; Kullnigt, R. K. *J. Am. Chem. Soc.* **1993**, *115*, 504−515. A 4:1 *cis*/*trans* ratio was observed when Ireland−Claisen conditions were employed.
(15) Yields determined after desilylation of the TIPS ester with HF/CH_3CN.
(16) Proton NMR analysis of the crude product indicated a 2:1 mixture of acid to allyl alcohol (the ketene elimination product).

The bis-allyl ketene acetals described herein possess an additional degree of complexity not found in most Claisen rearrangement substrates. Because the carbinol carbon is contained within a ring, the ring conformation itself may play a critical role in the outcome of the rearrangement. For each of the two chair transition states of the allyl ketene acetal, it will also be necessary to consider both half-chair conformations of the cyclohexenyl ring (Scheme 8). In the absence of other steric considerations, it seems likely that the cyclohexene conformation in which the breaking C−O bond is pseudoaxial would be the lowest energy. In that conformation, the breaking C−O σ-bond can overlap with the π-system of the endocyclic alkene. The weakening of allylic C−X bonds as a result of overlap with the alkene is a well-established phenomenon.[17] In the case of ester **6**, however, such a conformation would not be favored, since that would result in diaxial strain between the isopropenyl group (i.e., R_4) and the ketene acetal group.

Scheme 8



pseudo-axial C-O bond pseudo-equatorial C-O bond

In conclusion, we have found that the Ireland−Claisen rearrangement can give high alkene stereoselectivity in cases where the accepted transition state model does not allow for ready prediction of the outcome. We have reported the first examples of the stereoselective preparation of the higher energy alkene isomer for some trisubstituted alkenes. We also reported the first examples of stereoselective synthesis of unsymmetrically substituted tetrasubstituted alkenes possessing all carbon substituents. We are currently investigating these rearrangements computationally in the hopes of shedding light on the reasons for the observed stereoselectivites.

Acknowledgment. We thank NIH (GM59406 and RR15569) and the Arkansas Biosciences Institute for support of this work.

Supporting Information Available: Experimental procedures and characterization data for all new compounds; ^{1}H and ^{13}C NMR spectra for dienes *cis*-**2b**, *trans*-**2c**, **5**, **8**, *trans*-**11a**, *trans*-**11b**, and *cis/trans*-**11c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) See, for example: Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255−263.