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Attempts To Improve the Overall Stereoselectivity of the Ireland−Claisen Rearrangement

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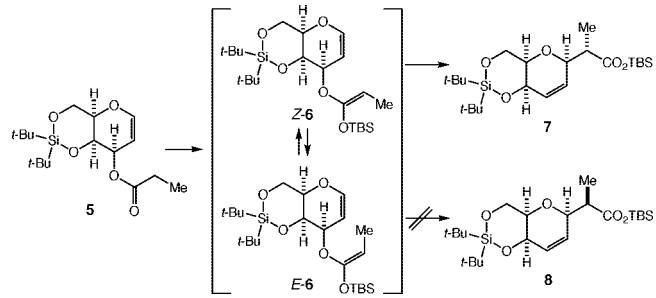
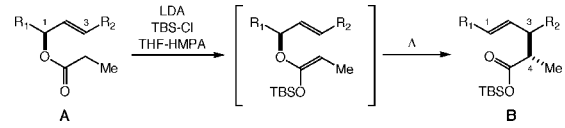
ABSTRACT



With focus on the steric effects present in the transition states for the [3,3]-sigmatropic rearrangement, the substrate 5 has been designed to improve the overall stereoselectivity of the Ireland−Claisen rearrangement. Experimentally, it has been found that (1) only *Z*-6 rearranges to 7 at 80 °C and (2) *E*-6 isomerizes to *Z*-6 at 80 °C, thereby allowing the transformation of 5 into 7 in an almost quantitative yield. To illustrate the usefulness of this approach, two additional examples are given.

The Ireland−Claisen rearrangement is a versatile method to transfer the stereochemistry of a C−O bond into a C−C bond.[1,2] As depicted in Scheme 1, this method consists of two synthetic operations, namely, *O*-silyl ketene acetal formation, followed by thermally induced [3,3]-sigmatropic rearrangement. Ireland demonstrated that *Z*- or *E*-selective *O*-silylation takes place on treatment of an ester with lithium-amide base in THF-HMPA or THF, respectively.[3] Upon heating, the *Z*- or *E*-stereochemistry is relayed to the C4-stereochemistry in the product. It is generally agreed that the [3,3]-rearrangement proceeds through a chairlike transition state for acyclic systems, whereas the rearrangement proceeds through a boatlike transition state for pyranoid- and furanoid-glucals.[2] Overall, the Ireland−Claisen rearrangement is effective to transform **A** into **B** in a stereocontrolled manner. However, it still remains a challenge to improve the overall stereoselectivity of this method.

Scheme 1. Ireland−Claisen Rearrangement Depicted for the Case Where the *O*-Silyl Ketene Acetal Is Formed under the *Z*-Selective Condition and the [3,3]-Sigmatropic Rearrangement Proceeds through a Chairlike Transition State



In the first generation synthesis of the marine natural products halichondrins (Scheme 2),[4] we relied on this synthetic method to construct the C27−C38 and C44−C53

(1) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897.
(2) For reviews, see: (a) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. (b) Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1847. (c) Chai, Y.; Hong, S.-P.; Lindsay, H. A.; McFarland, C.; Mclntosh, M. C. *Tetrahedron* **2002**, *58*, 2905. (d) Martin Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939.
(3) Ireland, R. E.; Wipf, P.; Armstrong, J. D., III *J. Org. Chem.* **1991**, *56*, 650.

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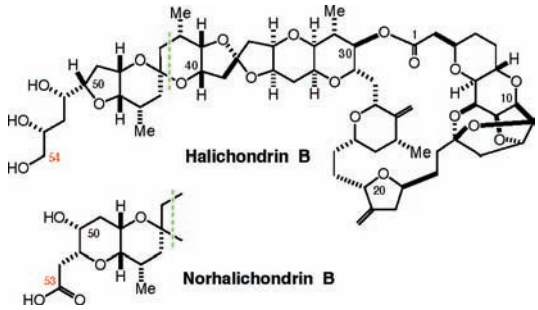
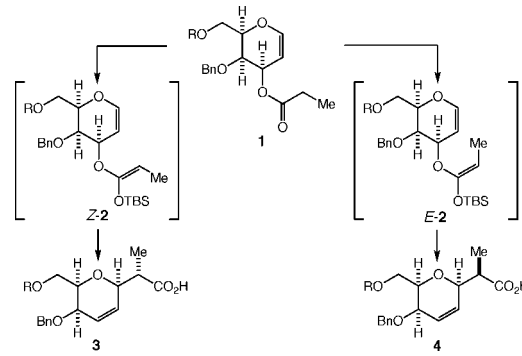
Scheme 2. Structure of Halichondrin B and Norhalichondrin B



building blocks of halichondrins (Scheme 3).[5−8] The overall stereoselectivity was approximately 8:1 for **1**→**3** and 5:1 for **1**→**4**, respectively. In this Letter, we report a new approach to perform this transformation in a completely stereocontrolled manner.

The overall stereoselectivity of **1**→**3** and **1**→**4** (Scheme 3) was found to match roughly with the *Z*/*E*-ratio of *O*-silyl ketene acetals subjected to the Claisen rearrangement,[7] indicating no obvious discrimination of the *Z*- over *E*-isomer at 80 °C in the step of [3,3]-sigmatropic rearrangement. However, we wondered whether the activation energy for the thermally induced [3,3]-sigmatropic rearrangements could be affected with steric factors, resulting in an improvement

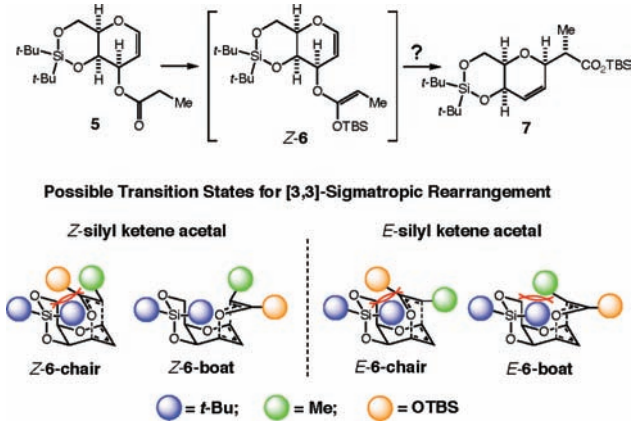
Scheme 3. Ireland−Claisen Rearrangements Used for the Stereoselective Construction of Two Building Blocks in the First Generation Synthesis of Halichondrins[a]



[a] Carboxylic acids **3** and **4** were converted to the C27−C38 building block of the halichondrins and the C44−C53 and C44−C55 building blocks of the nor- and homo-halichondrins, respectively.[7,8]

in the overall stereoselectivity of this process.[9] Specifically, we focused on the steric destabilization present in the transition state for the *Z*- or *E*-*O*-silyl ketene acetal shown in Scheme 4. The *E*-*O*-silyl ketene acetal could rearrange

Scheme 4. Analysis of Steric Destabilization in the Chairlike and Boatlike Transition States for the *Z*- and *E*-*O*-Silyl Ketene Acetals Derived from **5**[a]



[a] In this analysis, *t*-Bu, Me, and OTBS are considered as sterically demanding groups, but the size of the blue, green, or brown balls does not represent their relative steric size.

through, in principle, either a boatlike or chairlike transition state, but both transition states appear to have a severe steric destabilization. Similarly, the *Z*-*O*-silyl ketene acetal could rearrange through either a boatlike or chairlike transition state. Interestingly, the chairlike transition state appears to have a severe steric destabilization, whereas the boatlike transition state appears to be free from such a steric destabilization. Thus, there is a possibility that the [3,3]-

(4) For the isolation of the halichondrins from a marine sponge *Halichondria okadai* Kadota, see: (a) Uemura, D.; Takahashi, K.; Yamamoto, T.; Katayama, C.; Tanaka, J.; Okumura, Y.; Hirata, Y. *J. Am. Chem. Soc.* **1985**, *107*, 4796. (b) Hirata, Y.; Uemura, D. *Pure Appl. Chem.* **1986**, *58*, 701. For isolation of the halichondrins from different species of sponges, see: (c) Pettit, G. R.; Herald, C. L.; Boyd, M. R.; Leet, J. E.; Dufresne, C.; Doubek, D. L.; Schmidt, J. M.; Cerny, R. L.; Hooper, J. N. A.; Rützler, K. C. *J. Med. Chem.* **1991**, *34*, 3339. (d) Pettit, G. R.; Tan, R.; Gao, F.; Williams, M. D.; Doubek, D. L.; Boyd, M. R.; Schmidt, J. M.; Chapuis, J.-C.; Hamel, E.; Bai, R.; Hooper, J. N. A.; Tackett, L. P. *J. Org. Chem.* **1993**, *58*, 2538. (e) Litaudon, M.; Hart, J. B.; Blunt, J. W.; Lake, R. J.; Munro, M. H. G. *Tetrahedron Lett.* **1994**, *35*, 9435. (f) Litaudon, M.; Hickford, S. J. H.; Lill, R. E.; Lake, R. J.; Blunt, J. W.; Munro, M. H. G. *J. Org. Chem.* **1997**, *62*, 1868.

(5) For the synthetic work on the marine natural product halichondrins from this laboratory, see: (a) Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Matelich, M. C.; Scola, P. M.; Spero, D. M.; Yoon, S. K. *J. Am. Chem. Soc.* **1992**, *114*, 3162. (b) Choi, H.-w.; Demeke, D.; Kang, F.-A.; Kishi, Y.; Nakajima, K.; Nowak, P.; Wan, Z.-K.; Xie, C *Pure Appl. Chem.* **2003**, *75*, 1. (c) Namba, K.; Jun, H.-S.; Kishi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7770. (d) Namba, K.; Kishi, Y. *J. Am. Chem. Soc.* **2005**, *127*, 15382. (e) Kaburagi, Y.; Kishi, Y. *Org. Lett.* **2007**, *9*, 723. (f) Zhang, Z.; Huang, J.; Ma, B.; Kishi, Y. *Org. Lett.* **2008**, *10*, 3073, and references therein.

(6) For synthetic work by Salomon, Burke, Yonemitsu, and Phillips, see: (a) Kim, S.; Salomon, R. G. *Tetrahedron Lett.* **1989**, *30*, 6279. Cooper, A. J.; Pan, W.; Salomon, R. G. *Tetrahedron Lett.* **1993**, *34*, 8193, and references therein. (b) Burke, S. D.; Buckanan, J. L.; Rovin, J. D. *Tetrahedron Lett.* **1991**, *32*, 3961. Lambert, W. T.; Hanson, G. H.; Benayoud, F.; Burke, S. D. *J. Org. Chem.* **2005**, *70*, 9382, and references therein. (c) Horita, K.; Hachiya, S.; Nagasawa, M.; Hikota, M.; Yonemitsu, O. *Synlett* **1994**, 38. Horita, K.; Nishibe, S.; Yonemitsu, O. *Phytochem. Phytopharm.* **2000**, 386, and references therein. (d) Henderson, J. A.; Jackson, K. L.; Phillips, A. J. *Org. Lett.* **2007**, *9*, 5299.

(7) (a) Aicher, T. D.; Buszek, K. R.; Fang, F. G.; Forsyth, C. J.; Jung, S. H.; Kishi, Y.; Scola, P. M. *Tetrahedron Lett.* **1992**, *33*, 1549. (b) Fang, F. G.; Kishi, Y.; Matelich, M. C.; Scola, P. M. *Tetrahedron Lett.* **1992**, *33*, 1557.

(8) Strictly speaking, **3** was converted to the C27−C38 building block of halichondrin B as well as homo- and nor-halichondrin Bs, whereas **4** was converted to the C44−C53 and C44−C55 building blocks of nor- and homo-halichondrin Bs, respectively.

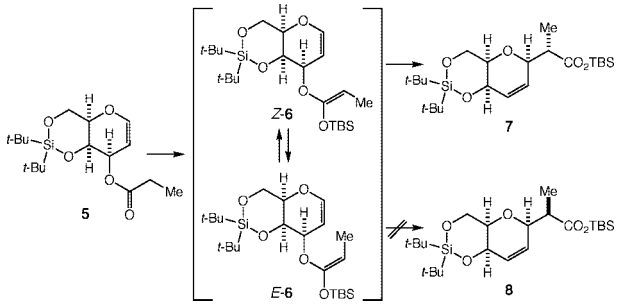
(9) For a relevant study, for example see: Wilcox, C. S.; Babston, R. E. *J. Am. Chem. Soc.* **1986**, *108*, 6636.

sigmatropic process might take place preferentially for the *Z*-*O*-silyl ketene acetal through the boatlike transition state, thereby resulting in an improvement in the overall stereoselectivity of this process.

To test this possibility, we synthesized the silylene **5** from commercially available D-galactal in two steps, (1) $(t\text{-Bu})_2Si(OTf)_2$, py and (2) $(EtCO)_2O$, DMAP, Et_3N, in 91% overall yields on a 10-g scale. It is worthwhile to note that, unlike the acetonide case,[10] the silylene formation is completely selective for the C4 and C6 hydroxyl groups.

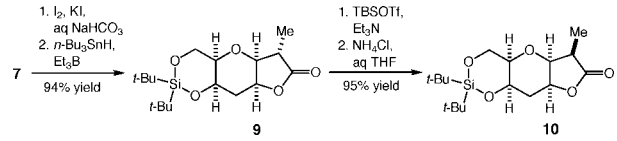
Under the conditions reported by Ireland (LHMDS, TBSCl, HMPA, THF, −78 °C), **5** was converted to the corresponding *O*-silyl ketene acetal **6**, which was estimated as a 7.3:1 mixture of ***Z*-6** and ***E*-6** via ^{1}H NMR analysis (Scheme 5). Upon heating at 80 °C in benzene for 1 day,

Scheme 5. Stereospecific Ireland−Claisen Rearrangement To Transform **5** to **7**



this mixture furnished the carboxylate **7** as a *single diastereomer* in >85% yield, along with **5** and ***E*-6** in a ca. 12% combined yield. The stereochemistry of **7** was unambiguously established via X-ray analysis on a derivative of the γ-lactone **9** shown in Scheme 6.[11] We should make a comment on two experimental observations. First, the *O*-silyl ketene acetal recovered from the reaction was ***E*-6**, thereby indicating that the Claisen rearrangement took place through ***Z*-6**, but not through ***E*-6**. Second, the Me-stereochemistry

Scheme 6. Inversion of the Stereogenic Center of Secondary Methyl Group



of **7** indicated that the Claisen rearrangement proceeded exclusively via the boatlike transition state ***Z*-6**.[12]

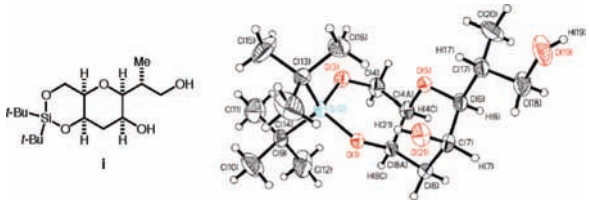
We then examined the possibility to isomerize ***E*-6** into ***Z*-6**, desirably under the rearrangement condition. Wilcox and Babston reported a facile geometrical isomerism of *O*-silyl ketene acetals in the presence of trialkylammonium perchlorate in $CDCl_3$.[13,14] Being encouraged with this, we heated a 7.3:1 mixture of ***Z*-6** and ***E*-6** at 80 °C in benzene for 3 days and obtained virtually pure **7** in an almost quantitative yield, thereby demonstrating that ***E*-6** did isomerize into ***Z*-6** under the rearrangement condition. The *O*-silyl ketene acetal used was the crude product obtained via a standard aqueous workup of the silylation reaction.[15] Thus, we speculate that the observed isomerization is thermally induced, although there is the possibility that a salt(s) contaminated in the crude silyl ketene acetal might have catalyzed the isomerization. For preparative purposes, this procedure now allows us to stereospecifically convert **5** into **7** in an almost quantitative yield.[16]

Unlike the case outlined in Scheme 3, the Ireland−Claisen rearrangement of **5** does not give a direct access to the Me-diastereomer of **7**. Therefore, we studied a method to convert **7** into its Me-diastereomer **8**. With use of two standard synthetic operations, **7** was converted to the γ-lactone **9** in 94% overall yield (Scheme 6). Considering its cagelike structure, we anticipated that the protonation on the enolate of **9** should take place preferentially from its convex face. In practice, the enolate of **9** was first trapped as its TBS-silyl ether, and desilylation in the presence of aqueous ammonium chloride yielded exclusively **10** in 95% overall yield.

The example summarized in Scheme 5 demonstrates that the overall stereoselectivity of the Ireland−Claisen rearrangement can be improved by modulating sterically the activation energy for the [3,3]-sigmatropic rearrangement. Naturally, we were curious in testing this notion on other substrates. In this respect, the following two examples are instructive.

(10) Acetonization of D-galactal ($(MeO)_2C(Me)_2$/PPTS) gave a 2:1 mixture of C4/C6- and C3/C4-acetonides.

(11) An X-ray analysis was conducted on crystalline diol **i** (mp 143 °C) obtained on $LiBH_4$-reduction of **9**. X-ray crystal data for compound **i**: $C_{17}H_{34}O_5Si$; MW = 346.53; monoclinic, space group $P2_1$ (No. 4), a = 9.1476(2) Å, b = 8.6362(1) Å, c = 12.8960(2) Å; α = 90°, β = 105.592(1)°, γ = 90°, V = 981.30(3) Å^3, Z = 2, D_{cal} = 1.173 Mg/m^3; independent reflections [R(int) = 0.0337]; refinement method, full-matrix least-squares refinement on F^2; Goodness-of-fit on F^2 = 1.020; final R indices [$I > 2\sigma(I)$] $R1$ = 0.0359, $wR2$ = 0.0857.



(12) Strictly speaking, **7** could arise through the chairlike transition state of ***E*-6**. However, this possibility is very unlikely, because ***E*-6** was recovered and also because the *E*-enriched silyl ketene acetal did not give a higher yield of **7**.

(13) Wilcox, C. S.; Babston, R. E. *J. Org. Chem.* **1984**, *49*, 1451.

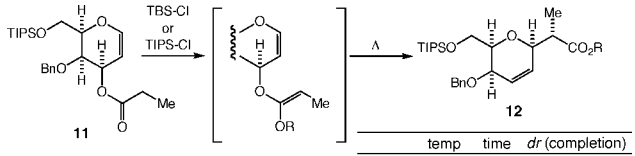
(14) For some relevant examples, see: (a) Adam, W.; Wang, X. *J. Org. Chem.* **1991**, *56*, 7244. (b) Tanaka, F.; Node, M.; Tanaka, K.; Mizuchi, M.; Hosoi, S.; Nakayama, M.; Taga, T.; Fuji, K. *J. Am. Chem. Soc.* **1995**, *117*, 12159.

(15) After *O*-silylation completed, the reaction mixture was poured onto hexanes. The organic layer was washed with water (5 times) and brine, dried (Na_2SO_4), and concentrated to afford the crude *O*-silyl ketene acetal.

(16) This transformation was repeated on 20-g scales by Dr. Chengguo Dong and Mr. Atsushi Ueda in this laboratories.

For the first example, we chose to use again the galactal template, but with a pattern of protecting groups different from that of **5**. Upon heating at 80 °C in benzene, the *O*-silyl ketene acetal prepared with treatment of **11** with TBS-Cl gave a 11:1 mixture of **12** and its Me-diastereomer (Scheme 7). Interestingly, the *O*-silyl ketene acetal prepared by

Scheme 7. Ireland−Claisen Rearrangement of the Galactal with a Pattern of Protecting Groups Different from that of **5**



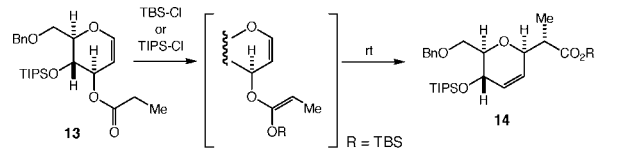
	temp	time	*dr* (completion)
R = TBS	80 °C	1 D	11 : 1 (100%)
R = TIPS	80 °C	1 D	14 : 1 (100%)
	40 °C	1 D	ca. 30 : 1 (55%)
	40 °C	2 D	ca. 23 : 1 (80%)
	40 °C	4 D	19 : 1 (96%)

treatment of **11** with TIPS-Cl gave a 14:1 mixture of the two diastereomers, thereby showing that the steric bulkiness of the silyloxy group also has a noticeable effect. We then studied the rearrangement at a lower temperature (40 °C) and found that the diastereomeric ratio declined gradually from day 1 to day 4. This time-course study suggested that (1) activation energy from the *Z*-isomer to the product is smaller than that from the *E*-isomer and (2) [3,3]-sigmatropic rearrangement proceeds via a boatlike transition state from the stereochemistry of **12**. In addition, the observed overall stereoselectivity at 80 °C (14:1) versus 40 °C (19:1) indicated that the *E*→*Z* isomerization takes place under the rearrangement condition at 40 °C.

For the second example, we chose to use a substrate in the glucal series (Scheme 8).[17] Unlike the galactal series, the *Z*/*E*-ratio at *O*-silylation was not reliably estimated,

(17) Several cases were reported of the Ireland−Claisen rearrangement of D-glucal derivatives, with the overall stereoselectivity varying from 2:1 to 6:1; see: (a) Ireland, R. E.; Wuts, P. G. M.; Ernst, B. *J. Am. Chem. Soc.* **1981**, *103*, 3205. (b) Wallace, G. A.; Scott, R. W.; Heathcock, C. H. *J. Org. Chem.* **2000**, *65*, 4145.

Scheme 8. Ireland−Claisen Rearrangement of a Glucal



because the [3,3]-sigmatropic rearrangement occurred even at room temperature. The overall stereoselectivity from **13** to **14** was 14:1 via *O*-silylation with TBS-Cl. As noticed in the **11**→**12** case, the stereoselectivity was vastly improved via *O*-silylation with TIPS-Cl. Speculating that **11** and **13** may share the overall profiles of reactivity, i.e., (1) the *Z*-isomer rearranges more quickly than the *E*-isomer and (2) the *E*-isomer isomerizes to the *Z* isomer, we examined the possibility to improve the stereoselectivity by keeping the crude *O*-silyl ketene acetals at 0 °C; indeed, the transformation of **13** into **14** was achieved in 91% overall yield with ca. 43:1 stereoselectivity.

In summary, we have demonstrated a valid approach to improve the overall stereoselectivity of the Ireland−Claisen rearrangement by sterically modulating the activation energy for the [3,3]-sigmatropic process. With this, the transformation of **5** into **7** was realized in a stereospecific manner in an almost quantitative yield. Following the routes previously established, **7** was converted into the two building blocks of halichondrins.

Acknowledgment. We are grateful to the National Institutes of Health (CA 22215) and to the Eisai Research Institute for generous financial support.

Supporting Information Available: Experimental details, data of X-ray analysis, and ^{1}H and ^{13}C NMR spectra of key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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