Stereoselective Construction of Adjacent Quaternary Chiral Centers by the Ireland–Claisen Rearrangement: Stereoselection with Esters of Cyclic Alcohols

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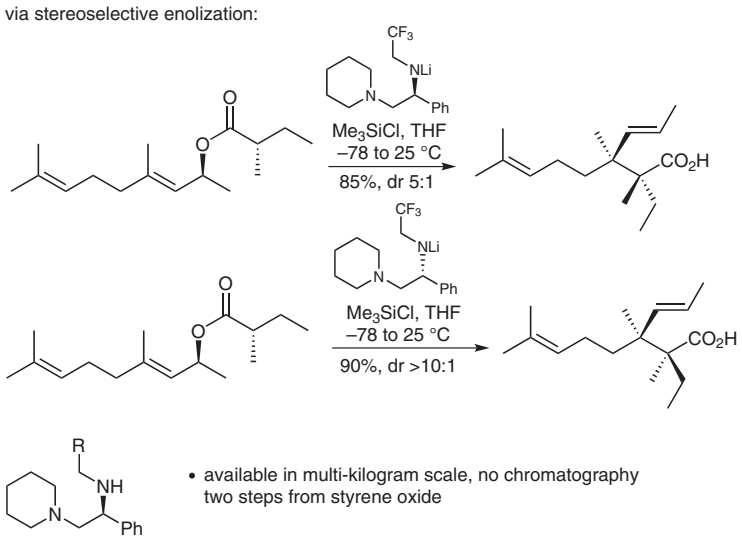
Abstract: This work describes a study of the Ireland–Claisen rearrangement of α,α-disubstituted enolates derived from esters of cyclic alcohols. Highly stereoselective enolizaitions could be generally achieved using *N*-benzyl Koga-type bases by matching chirality of the ester and the base. The [3,3]-sigmatropic rearrangement took place in good yields and moderate diastereoselectivity forming two adjacent quaternary stereogenic centers, and generally proceeding through a chairlike transition state.

Key words: diastereoselectivity, rearrangement, esters, sigmatropic, chirality, stereoselective synthesis

The widespread application of the Ireland–Claisen rearrangement in organic synthesis can be attributed to predictable relay of chirality in acyclic systems based on well-understood chairlike transition structures, generally high yields and stereoselectivities, and ready access to the starting materials by esterification.[1] Application of this powerful approach for the formation of adjacent quaternary stereogenic centers in acyclic systems has been precluded by the lack of methods for stereocontrolled formation of α,α-disubstituted enolates.[2] For the same reason, the rearrangement could not be reliably used to form defined quaternary stereogenic centers at the α-position to the carboxyl group in the products.

Recently, we described a new approach to stereoselective enolization of α-branched esters based on an unusual chirality match between a Koga-type base and an enolate precursor.[3] Although this method requires an investment in the synthesis of the chiral ester and chiral base counterparts, it provides direct and straightforward access to α,α-disubstituted enolates that are difficult to prepare otherwise. On the other hand, the starting materials can be readily prepared by well-established methods.[4,5] We have previously demonstrated that the enolization method can be effectively applied in the context of the Ireland–Claisen rearrangement. With esters of acyclic alcohols, high diastereoselectivities can be obtained for the assembly of adjacent stereogenic all-carbon quaternary centers (Scheme 1).[3] The utility and efficiency of the method has been demonstrated with a complex substrate on multigram scale during the course of the total synthesis of (+)-pinnatoxin A.[6] The goal of the study reported in this communication is to define the diastereoselectivity of the reaction with esters of chiral cyclic alcohols.



Scheme 1 Examples of the acyclic diastereoselective Ireland–Claisen rearrangement forming adjacent chiral quaternary centers

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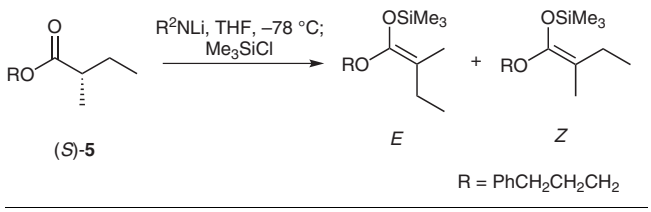
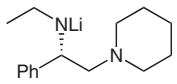
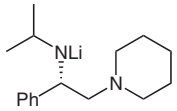
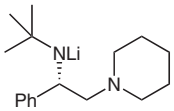
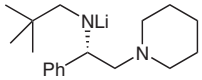
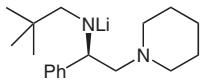
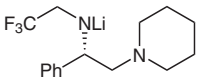
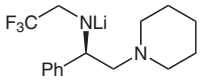
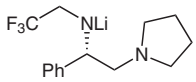
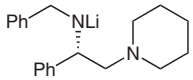
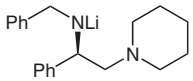
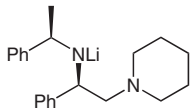
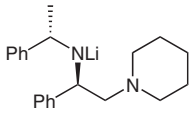
Table 1 Enolization of (*S*)-**5** with Koga Bases



(*S*)-**5** *E* *Z*

R = $PhCH_2CH_2CH_2$

Entry	Base R_2NLi[a]	*Z*/*E* ratio[b]
1	*i*-Pr_2NLi	67:33
2		56:44
3		83:17
4		89:11
5		23:77
6		90:10
7		10:90
8		92:8
9		17:83
10		2:98
11		96:4
12		83:17
13		no reaction

[a] The lithium dialkylamides were generated by the treatment of a solution of corresponding amines in dry THF with *n*-BuLi (1 equiv, –78 °C to 0 °C, 1 h).

[b] Determined by 500 MHz NMR of the crude mixture of products.

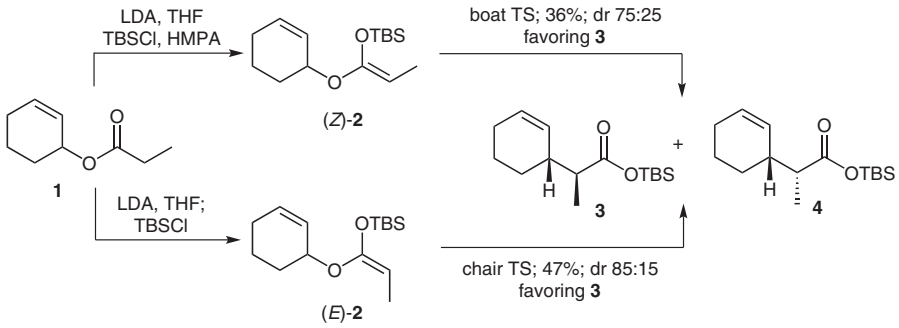
In contrast to acyclic esters, it has been demonstrated previously that esters of medium-size cyclic alcohols can preferentially undergo the Ireland–Claisen rearrangement through a boatlike transition state.[1,7] For example, the [3,3]-sigmatropic rearrangement of carbohydrate-derived pyranoid or furanoid substrates typically takes place through a boatlike transition state.[8] On the other hand, the rearrangement of other types of cyclic esters can be stereochemically more complex. As illustrated in Scheme 2, the major product in the transposition of both *E*- and *Z*-silyl enol ethers (*E*)-**2** and (*Z*)-**2** produced from 2-cyclohexen-1-yl propionate is diastereomer **3**, indicating that the *E*-isomer favors the chairlike transition state, while the boatlike transition state is preferred with the *Z*-isomer.[9]

α,α-Disubstituted enolates have *E* and *Z* substituents at the same time with unexplored preference for a chair or boat transition state in the Ireland–Claisen rearrangement of cyclic substrates, making them intriguing substrates for the [3,3]-sigmatropic process.

For the purposes of this study we carried out a screening of chiral Koga-type bases to investigate the effect of their structure on the stereoselectivity of enolization. The results are summarized in Table 1.

The base with a benzyl group as the achiral substituent on the nitrogen atom proved to have the highest stereodirecting power (entries 10 and 11). Perhaps the biggest surprise was that the achiral substituent on the nitrogen atom had a profound effect on the direction of *E*/*Z* selectivity. *N*-Ethyl base showed virtually no stereoselection (entry 2). The α-branched substituents in the *S* series, isopropyl and *tert*-butyl, favored the *Z*-enolate formation with up to 89% selectivity (entries 3 and 4). In the same *S* enantiomeric series, the β-branched achiral substituents on the nitrogen reversed selectivity now favoring the formation of the *E*-enolate, with the benzyl group giving the highest selectivity of 98% (entries 5, 7, and 10). As expected, opposite enantiomers favored different geometric isomers in the enolization process (cf. entries 6, 8, and 11). Replacement of the piperidine with pyrrolidine reduced stereoselection (entry 9). Introduction of an additional chiral center, as shown in entries 12 and 13, did not have a positive effect on selectivity, and in the mismatched case resulted in no deprotonation of the substrate.

For an initial study of the Ireland–Claisen rearrangement we selected ester **6** prepared from (*S*)-3-methyl-2-cyclohexenol-1 and commercially available (*S*)-2-methylbutyric acid (Scheme 3).[10,11] Enolization with the lithium amides derived from *N*-benzyl amines (*S*)- and (*R*)-**7**, which showed the highest selectivity in the preceding study, followed by silylation with TMSCl, thermal rearrangement at 70 °C, and mild hydrolysis of the silyl esters afforded a mixture of **9** and **10** in good yields and moderate diastereocontrol in favor of **9**.[12,13] Analysis of the products indicates that both (*E*)- and (*Z*)-**8** undergo the [3,3]-sigmatropic rearrangement through the chairlike transition state preferentially, although for (*Z*)-**8** this preference appears to be less pronounced. Surprisingly, the corresponding *t*-$BuMe_2Si$ (TBS) ketene acetals could not be formed when the lithium amide of amine **7** was used for enolization even under forcing conditions. Remarkably, when $TBSOSO_2CF_3$ was employed, only C-silylation



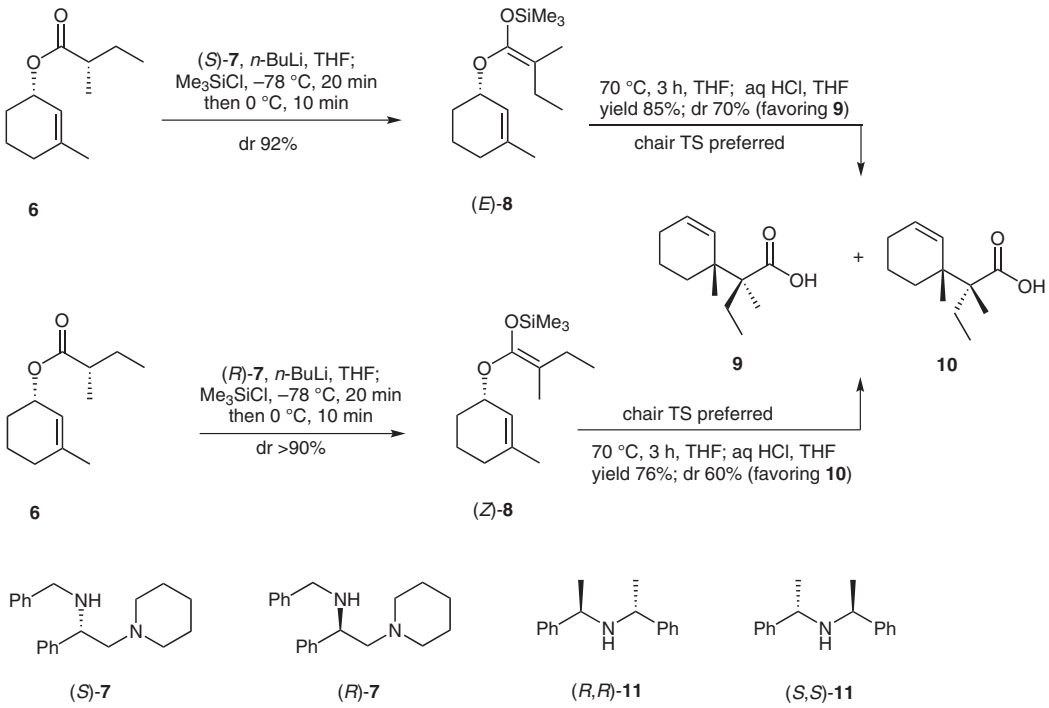
Scheme 2 Influence of the substrate on the boat/chair transition-state preference

forming a hindered silane was observed. This problem could be readily overcome by switching to (*R*)-bis[(*R*)-1-phenylethyl]amine (*R*,*R*)-**11** or (*S*)-bis[(*S*)-1-phenylethyl]amine (*S*,*S*)-**11**, which also induce highly selective enolizations. This is an indication that the lithium enolates generated from ester **6** and bases **7** exist as a congested aggregate that prevents O-silylation with TBSCl or $TBSOSO_2CF_3$.[14] With the TBS ketene acetals, a slight reduction in selectivity was noted [88% yield, dr 68% for TBS-(*E*)-**8**; 80% yield, dr 55% for TBS-(*Z*)-**8**], but the preference for the chairlike transition state was maintained.

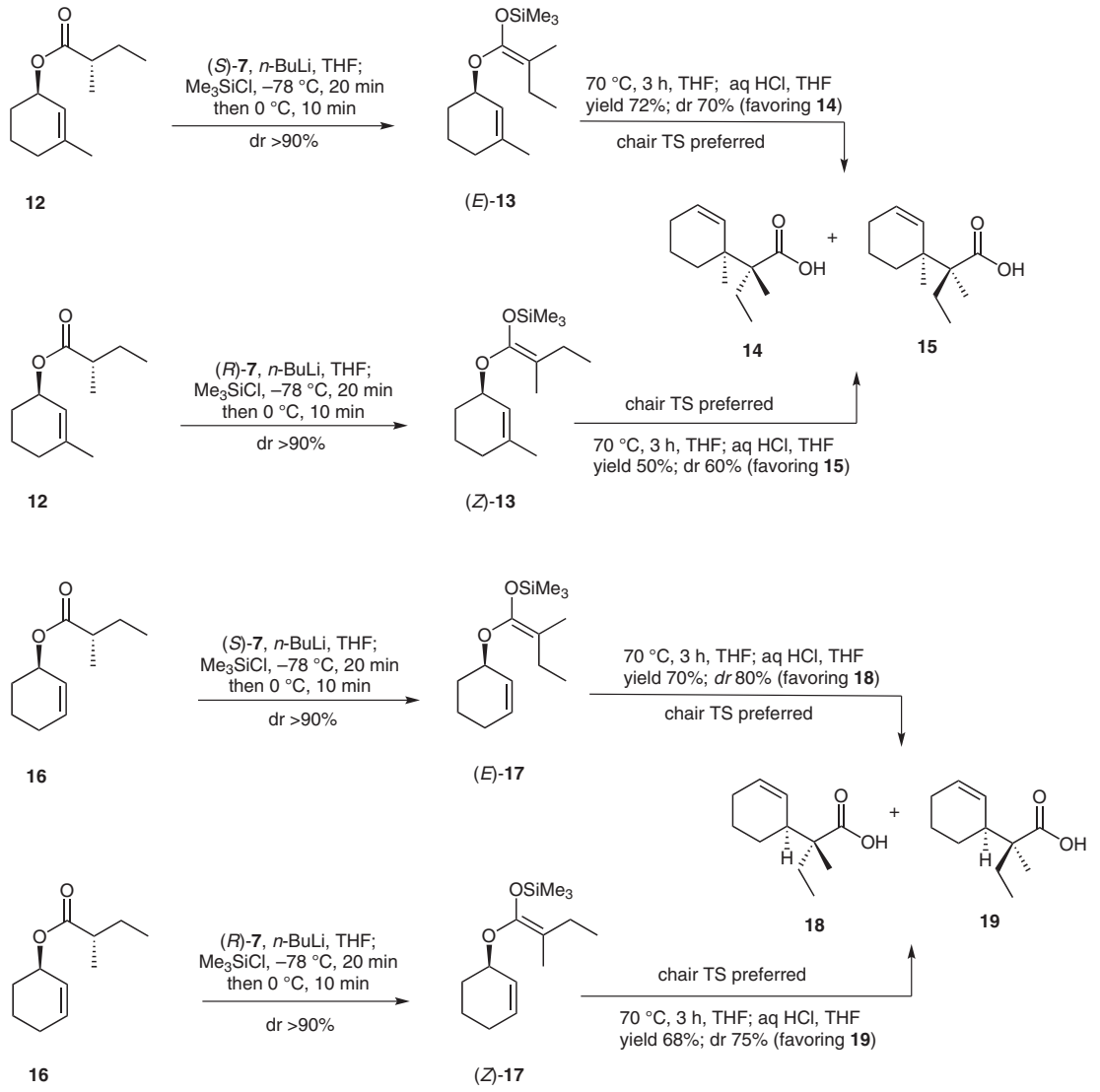
Stereocontrol in both enolization and the [3,3]-sigmatropic rearrangement with diastereomeric ester **12** was nearly identical, as expected (Scheme 4). An important conclusion in this case is that the stereochemistry of the allylic alcohol exerts no influence on the enolization process, which appears to be controlled entirely by chirality of the ester and the base.

The Ireland–Claisen rearrangement of ester **16** displayed increased diastereoselectivity in favor of the chairlike transition state. Analysis of the transition structures presented in Scheme 5 reveals a gauche interaction between both substituents of the enolate and the R group in the chair transition states, while in the boat transition states there is an eclipsing interaction between R and only the *Z*-substituent. When R = Me, the chair transition state experiences higher destabilization compared to when R = H, thus decreasing selectivity favoring products resulting from the chairlike transition state.

Additional examples of the diastereoselective Ireland–Claisen rearrangement performed within the scope of this study are enunciated in Scheme 6. With cyclic esters of a number of α,α-disubstituted esters, the yields are generally very good, and the stereoselectivities are comparable to our previous examples in the range of about 70%. Diastereoselectivity in the rearrangement of ester **24**, derived from 3-methylcyclopenten-1-ol, was nearly identical to the previous examples.



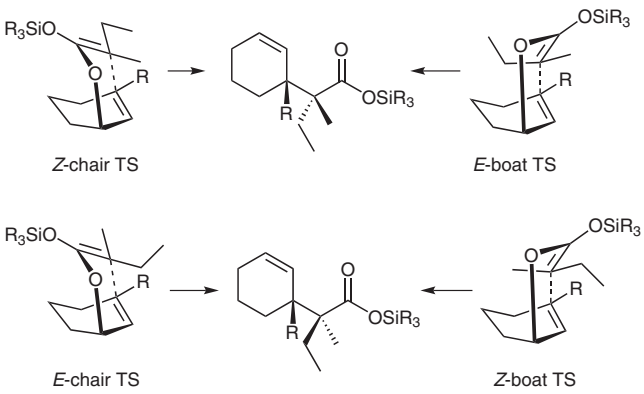
Scheme 3



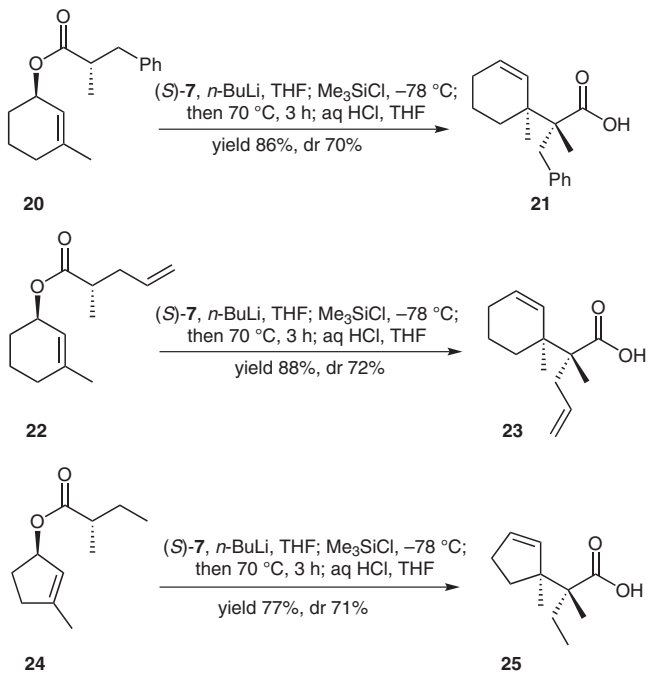
Scheme 4

The relative stereochemistry of carboxylic acids **9** and **10** was established by a series of experiments shown in Scheme 7. Iodolactonization followed by deiodination under radical conditions provided a mixture of lactones **26** and **27**. NOE enhancements observed with **26** and **27** confirmed the assigned configuration. The assignment of **25** was confirmed by conversion of known acid **28** to methyl ester **29** in two steps involving esterification and ring-closing metathesis. After methyl ester formation, the NMR data for the major product of the Ireland–Claisen rearrangement of **24** performed with (*S*)-**7** correlated to those of **29**.

In conclusion, the Ireland–Claisen rearrangement of α,α-disubstituted esters of carbocyclic alcohols can be carried out with moderate diastereoselectivity using highly stereoselective enolizations with Koga-type bases, and the products resulting from chairlike transitions states are generally preferred. This observation is in contrast with the rearrangements of unbranched cyclic esters, where the boat versus chair selectivity demonstrates a higher dependence on the enolate geometry.



Scheme 5



Scheme 6

Acknowledgment

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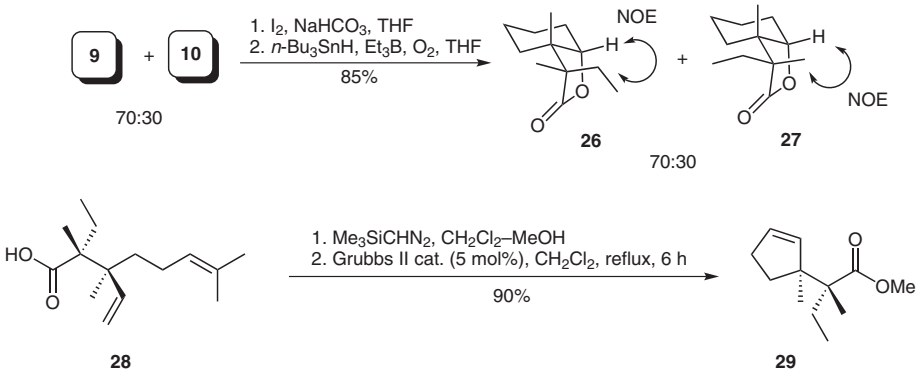
(11) **General Procedure for Esterification – Synthesis of (*S*)-[(*S*)-3-Methylcyclohex-2-enyl] 2-Methylbutanoate (6)**

EDCI (0.345 g, 1.80 mmol) was added to a mixture of (*S*)-3-methyl-2-cyclohexen-1-ol (0.100 g, 0.89 mmol), (*S*)-2-methylbutyric acid (0.153 g, 1.50 mmol) in CH_2Cl_2 (4.0 mL), and the resultant mixture was stirred at r.t. for 2 h. After evaporation, the residue was purified by column chromatography (3% EtOAc–hexanes) to give the ester **6** (0.143 g, 82%); $[\alpha]_D^{22}$ –112 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.44 (s, 1 H), 5.25 (s, 1 H), 2.40–2.28 (m, 1 H), 2.06–1.84 (m, 2 H), 1.82–1.58 (m, 8 H), 1.52–1.39 (m, 1 H), 1.13 (d, *J* = 6.8 Hz, 3 H), 0.90 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.5, 140.7, 120.2, 68.3, 41.2, 29.9, 28.0, 26.8, 23.7, 19.1, 16.7, 11.6 ppm. HRMS (FI): *m/z* calcd for $C_{12}H_{20}O_2$ [M^+]: 196.1463; found: 196.1455.



Scheme 7

(12) **General Procedure for the Ireland–Claisen Rearrangement – (*S*)-2-Methyl-2-[(*R*)-1-Methylcyclohex-2-enyl]butanoic acid (9)**
n-BuLi (1.96 M in hexanes, 0.105 mL, 0.20 mmol) was added to a solution of (*S*)-**7** (60 mg, 0.20 mmol) in THF (0.25 mL) at –78 °C. After 5 min, the flask was removed from the ice bath and stirring was continued at r.t. The solution was allowed to stir for 20 min before being cooled down to –78 °C, at which point a solution of **6** (19.6 mg, 0.10 mmol) in THF (0.50 mL) was added dropwise to the reaction vessel. After 1.5 h, TMSCl (25 μL, 0.20 mmol) was added. The mixture was stirred at –78 °C for 20 min, then at 0 °C for 10 min. The reaction mixture was diluted with hexanes (20 mL). The organic layer was washed with 1 M HCl (2 × 2 mL), followed immediately by sat. aq $NaHCO_3$ (10 mL), dried with Na_2SO_4, and concentrated. The residue was dissolved in THF (1.0 mL) and heated in a sealed flask at 70 °C. After 3 h, the reaction vessel was cooled to r.t. and THF (2.0 mL) was added followed by the addition of 1 M HCl (3.0 mL). The progress of the silyl ester hydrolysis was monitored by TLC. After dilution with CH_2Cl_2 and H_2O, the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were dried with Na_2SO_4, concentrated, and the residue was purified by column chromatography (silica, 10% EtOAc–hexanes w/0.1% AcOH then 40% EtOAc–hexanes w/0.1% AcOH) delivering a 70:30 mixture of carboxylic acids **9** and **10** (16.7 mg, 85 μmol, 85%), respectively. ^{1}H NMR (300 MHz, $CDCl_3$): δ (major isomer) = 5.66 (dd, J_1 = 10.8 Hz, J_2 = 0.8 Hz, 1 H), 5.61 (ddd, J_1 = 10.4 Hz, $J_2 = J_3$ = 3.2 Hz, 1 H), 2.10–2.10 (m, 1 H), 1.75–1.68 (m, 3 H), 1.51–1.40 (m, 3 H), 1.34–1.27 (m, 1 H), 1.14 (s, 3 H), 1.09 (s, 3 H), 0.87 (dd, $J_1 = J_2$ = 7.6 Hz, 3 H) ppm.

(13) Lithium diisopropylamide gives an equimolar ration of **9** and **10**.

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