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Facial selectivity of the Ireland–Claisen rearrangement of allylic esters of 2-methyl and 2-methoxycyclopentanecarboxylic acids

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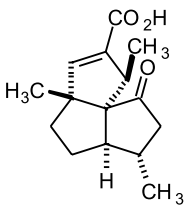
Abstract—Ketene silylacetals derived from prenyl and (*Z*)- and (*E*)-crotyl 2-methylcyclopentanecarboxylates (**9**) were subjected to the Ireland–Claisen rearrangement. All three substrates rearranged with complete facial selectivity, but the (*Z*)- and (*E*)-crotyl systems gave a mixture comprised of the same diastereomers of 1-(1-methyl-2-propenyl)-2-methylcyclopentanecarboxylic acid (**14**) in ratios of 2:1 and 1:2, respectively. In contrast, the ketene silylacetals prepared from allyl and prenyl 2-methoxycyclopentanecarboxylates (**22**) underwent rearrangements with both facial stereochemistries.

1. Introduction[1]

Organic chemists continue to be interested in developing new methodologies for synthesis of polyquinanes[2] due to the aesthetically appealing topologies of this class of compounds and the promising biological activities exhibited by some of its members. As part of a projected synthetic approach to subergorgic acid (**1**), a triquinane first isolated and characterized in 1982,[3,4] it was important to define the facial selectivity of the Ireland–Claisen rearrangement[5] of ketene silylacetals derived from allyl 2-methylcyclopentanecarboxylates (Eq. 1); such an isomerization was a key step for establishing certain stereochemical features in our planned approach to **1**.



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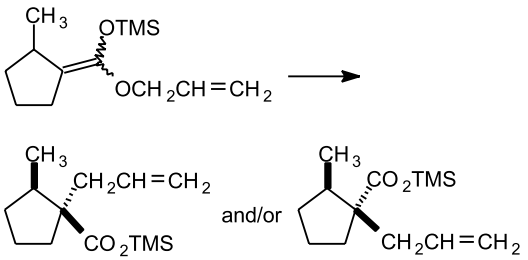
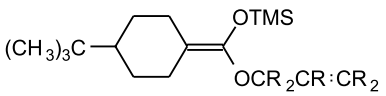
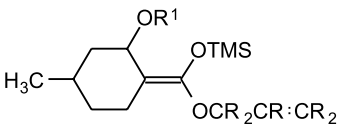


(1)

To our knowledge, there are no literature precedents for predicting the preferred facial selectivity of the Ireland–Claisen rearrangement in 2-substituted cyclopentanecarboxylate systems. The results of studies from our own group offer the closest analogies available, and extrapolating them to the present system is fraught with peril. For example, our previous work involved rearrangements of ketene silylacetals of allyl 4-alkyl and 2-alkoxy-4-alkylcyclohexanecarboxylates **2** and **3**, respectively,[6] so conformational differences between five and six-membered rings become an issue.



2
R = H or alkyl



3
R = H or alkyl, R^1 = alkyl

Keywords: Ireland–Claisen rearrangement; Sigmatropy; Facial selectivity; Diastereoselectivity.
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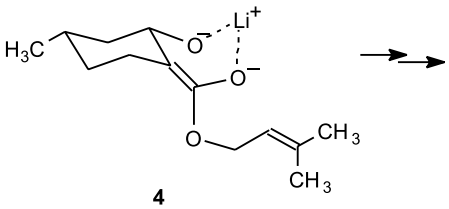
Moreover, although we found the preferred conformation for rearrangement to be chair-like and the orientation of attack of the allyl moiety to be equatorial in all cases, the facial selectivity of the process was dependent on the nature of substituents on the six-membered ring. Thus, the rearrangement of dianion **4** (Eq. 2) involved transfer of the allylic moiety *trans* to the alkoxide, whereas the opposite selectivity was observed with the ketene silylacetal **5** (Eq. 3).[6b–d] The possibility of chelation in **4** was invoked to rationalize the facial selectivity of its rearrangement. The reversal of facial selectivity with **5** presumably reflects operation of the Curtin–Hammett principle,[7] whereby $\Delta H^{\neq}$ to reach the transition state for rearrangement of the less thermodynamically stable conformer **5b** is less than that of **5a** owing to 1,3-interactions between the trimethylsiloxy and 2-alkoxy substituents that develop in the latter conformer during the course of the rearrangement.



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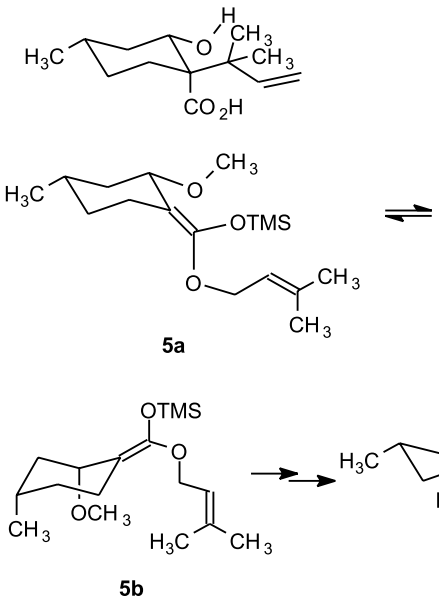
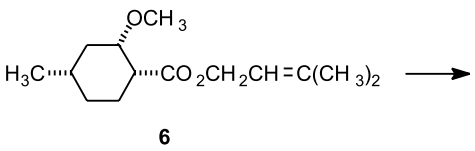


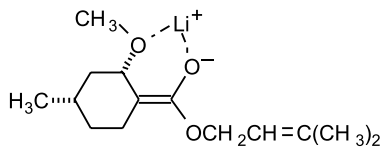
5a (3)

5b

Although the facial selectivity of the Ireland–Claisen rearrangement portrayed in Eq. 1 would presumably mimic that obtained with **5**, subtle conformational factors might well alter this outcome. Thus, whereas the chair conformation of six-membered rings has well-defined axial and equatorial positions, the five-membered analog does not.[8] In addition, the overall stereochemistry of the rearrangement depends not only on the [3,3] sigmatropic process itself, but also on the stereoselectivity for forming the ester enolate that is the precursor to the ketene silylacetal. The 2-methoxy substituent in **6** is available to foster formation of the (*E*)-enolate **7**, which affords **5** upon reaction with TMSCl (Eq. 4). An analogous stereoelectronic factor is unavailable in forming the enolate **8** (Eq. 5); rather, diastereoselectivity of enolate formation in this instance is dependent upon steric factors alone, and predictions of the control that such factors would provide are problematic at best. We, therefore, embarked upon model studies of the Ireland–Claisen rearrangement of allylic esters of 2-methylcyclopentanecarboxylates, and those of 2-methoxycyclopentanecarboxylates as well. The present paper describes the results of our investigations.



6 (4)



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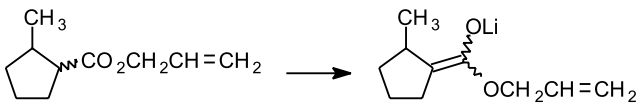


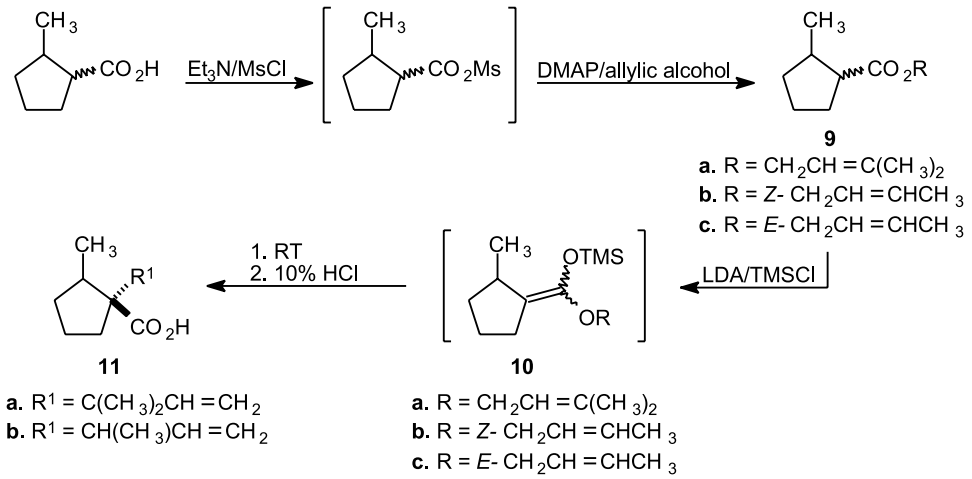
8 (5)

2. Results and discussion

The role of an alkyl group in defining the facial selectivity was explored with substrates **9** (Scheme 1), all of which were prepared in good yield (68–70%) by esterification of a mixture of the diastereomeric 2-methyl-cyclopentane-carboxylic acids[9] according to the unexceptional sequence of Scheme 1. ^{1}H NMR spectroscopic analysis of the esters revealed that each was a 2:1 mixture of diastereomers, a ratio corresponding to that of the mixture of precursor acids. Because the *trans*-isomer predominates in the starting acids, the major diastereomer of **9** is presumably *trans* as well, but since the stereochemistry at C(1) of the ring is destroyed upon formation of the ester enolate from which the ketene silylacetal is derived, separation of the diastereomers was not undertaken. Further conversion of the esters **9** to the ketene silylacetals **10** and rearrangement to the acids **11** were effected via the protocol developed by Ireland and Norbeck (Scheme 1).[10]

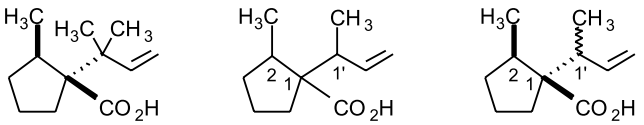
The prenyl ester **9a** afforded a 95% yield of a single carboxylic acid, as determined by ^{13}C and ^{1}H NMR spectral analyses (see Section 3). Through X-ray crystallographic analysis, the stereochemistry of the product was found to be that shown in **12**,[†] demonstrating that the rearrangement involves transfer of the allylic moiety *trans* to the methyl group of the acetal **10a** derived from **9a**. This stereo-chemical outcome suggests that the torsional factors believed to foster the opposite facial selectivity with **5** are not operating in the five-membered ring analog and

[†] Crystallographic data for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 218131. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].



Scheme 1.

bespeaks the subtle conformational effects that define the facial selectivity of the Ireland–Claisen rearrangement in such systems.

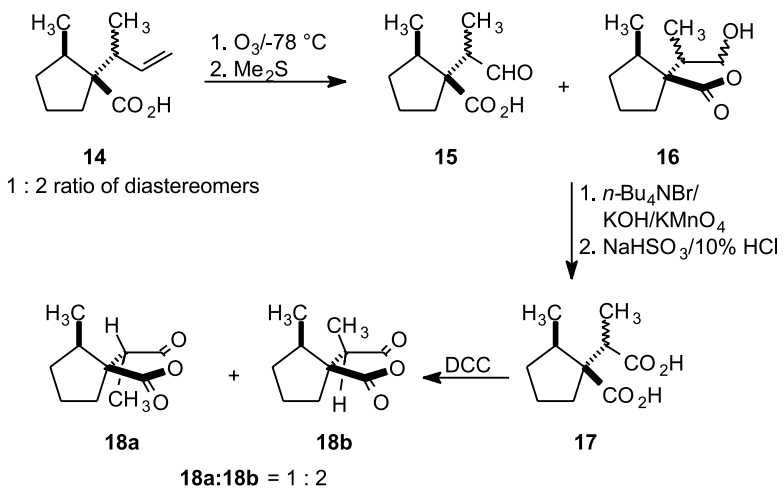


The corresponding rearrangements of **9b** and **c** were more complicated. Exposing **9b** to 2.2 equiv. of LDA according to the usual protocol for forming the ketene silylacetals resulted in the formation of a complex mixture. Decreasing the amount of LDA to 1.1 equiv. afforded a 45% yield of a 2:1 mixture of diastereomeric acids whose spectral properties (MS, IR, ^{13}C and ^{1}H NMR) were consistent with their having the expected carbon skeleton **13**. Subjecting **9c** to identical reaction conditions afforded the same two acids in a 45% yield, but now in a ratio of 1:2.

Either of the two stereocenters, namely C(1) and the allylic carbon atom C(1′), generated via the rearrangement could be the source of diastereomers, but it is the latter that accounts for this, as shown by NOE analyses. Thus, irradiating the allylic proton of the major isomer from both rearrangements provided the same enhancement of the ring methyl group, which suggests that the two diastereomers have the same relative stereochemistries at C(1) and C(2). Given the unambiguous facial selectivity with **9a** and the fact that **9b** and **c**, close steric analogs to **9a**, afford the same pair of diastereomers, the acids were tentatively assigned as having the *cis* stereochemistry shown in **14**.

Confirmation of this and assignment of the configurations of the diastereomers was obtained by converting the 1:2 mixture of the acids **14** to the spiroanhydrides **18** (Scheme 2), whose structural rigidity makes stereochemical definition possible through NMR techniques. Thus, ozonolysis[11] afforded a 1:38 ratio of aldehydes **15** and lactols **16**. Although attempted oxidation of this mixture using Jones reagent,[12] PCC,[13] or PDC[14] proved fruitless, use of basic aqueous potassium permanganate furnished a mixture of diacids **17**.[15] Treating this mixture with dicyclohexylcarbodiimide[16] effected cyclization to the spiroanhydrides **18**, the ratio of which was identical to that of the starting acids **14**.

As seen in Figure 1, there are four diastereomers of **18** that can be formed if no particular facial selectivity is assumed



Scheme 2.

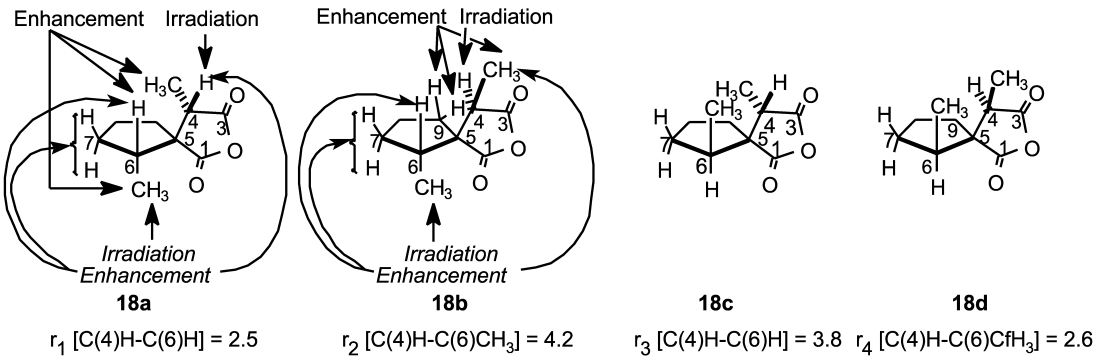


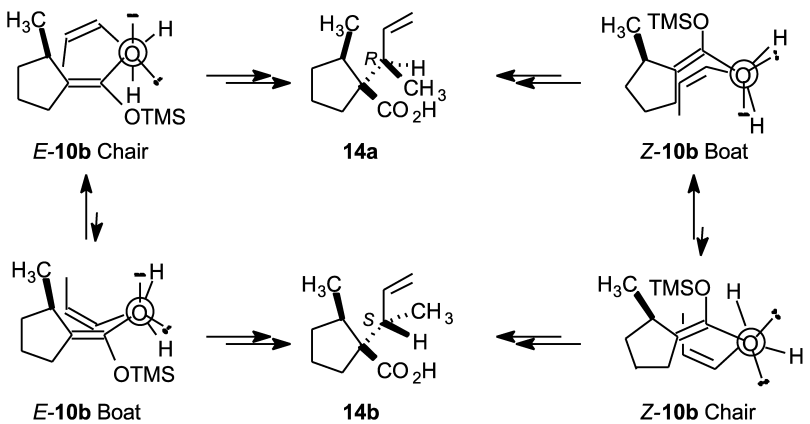
Figure 1. Enhancements from GOESY NMR experiment; r_1 and r_3 are distances (Å) between protons at C(4) and C(6) for **18a** and **18c**, respectively; r_2 and r_4 are distances (Å) for closest approach between proton at C(4) and proton of C(6) methyl group for **18b** and **18d**, respectively.

for the rearrangement of **9bc**. Application of a variety of 1D and 2D NMR spectroscopic techniques, viz. GOESY, ^{1}H–^{1}H COSY, ^{13}C–^{1}H COSY, and NOESY allowed definitive assignment of stereochemistry to the two diastereomers obtained experimentally. With respect to making a structural assignment for the minor isomer, irradiating the C(4) proton enhanced the resonances for that at C(6) and those of the methyl groups at C(4) and C(6), whereas irradiating the protons of the C(6) methyl group enhanced the absorptions for the C(4), C(6), and C(7) protons. These observations remove **18b** and **18d** as possibilities. Excluding **18c** as the minor isomer is based on data from a NOESY experiment in which no interaction was observed between the proton at C(4) and those of the C(6) methyl group; were the minor isomer **18c**, an interaction would be expected. Thus, a molecular mechanics calculation using the SYBYL force field showed that the most stable conformer for both **18a** and **18c** has the C(4) and C(6) methyl groups quasi-axial and quasi-equatorial, respectively. The distance between the C(4) and C(6) protons in these conformers is 2.5 Å in **18a** and 3.8 Å in **18c** (Fig. 1). These relative distances are consistent with the enhancement of the C(6) proton observed when irradiating that at C(4) in the GOESY experiment if the minor isomer is **18a** rather than **18c**. Assigning **18a** for the structure of the minor isomer is therefore consistent with all the data.

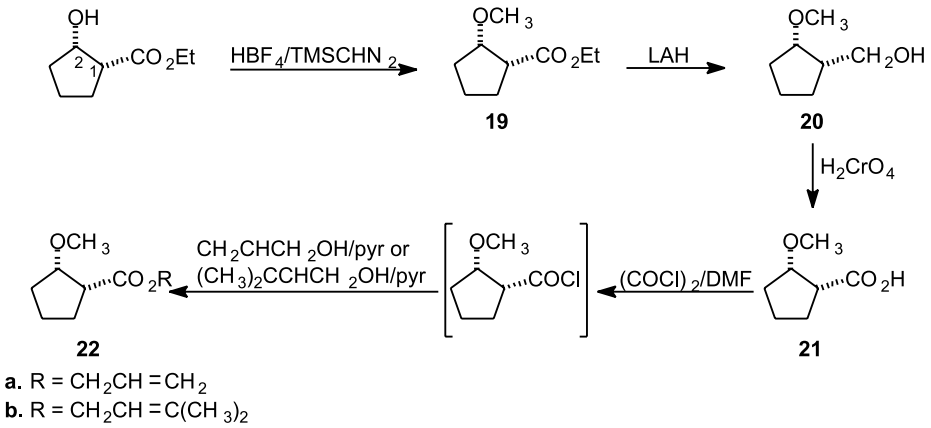
As for the major isomer, irradiating the C(4) proton enhanced the absorptions for the C(9) protons and those of the C(4) methyl group and irradiating the C(6) methyl group enhanced the resonances for the C(6) and C(7) protons and the C(4) methyl protons. Structure **18c** (and **18a**) is thereby eliminated from consideration. Differentiation between **18b** and **18d** as the major isomer comes from the NOESY experiment, wherein a stronger interaction is seen between the C(6) proton and those of the C(4) methyl group than between the protons of the two methyl groups. If the major isomer were **18d**, exactly the reverse would be expected. Applying molecular mechanics calculations to **18b** and **18d** shows that the most stable conformer for **18b** is the one having both methyl groups quasi-equatorial and that for **18d** is that having both methyl groups quasi-axially oriented. The distance between the C(4) proton and those of the C(6) methyl group is computed as 4.2 Å in **18b** and 2.6 Å in **18d**. The distance predicted for **18b** is consistent with the absence of enhancement of the C(4) proton when the C(6) methyl group is irradiated, as seen in the GOESY data; in contrast, enhancement would have been seen if the major isomer were **18d**.

It is highly improbable that epimerization in the step involving formation of **17** would have precisely inverted the ratio of diastereomers **18ab** relative to that of acids **14**. Thus, it is possible to conclude that the major isomer derived from Ireland–Claisen rearrangement of **9c** is **14b** whereas that from **9b** is **14a** (Scheme 3).

There are two obvious ways to rationalize formation of **14ab** from **9bc**. One approach is to assume that a single diastereomer of the ketene silylacetal **10b** is produced from **9b** and that it undergoes the rearrangement through a combination of chair- and boat-like conformations



Scheme 3.



Scheme 4.

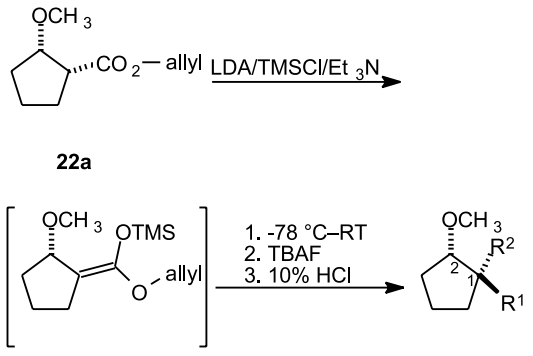
(Scheme 3). For the (*E*)-diastereomer, the two conformations afford the (*R*)- and (*S*)-diastereomers, respectively, at the allylic carbon atom C(1′), whereas in the case of the (*Z*)-diastereomer, the chair- and boat-like conformations yield the (*S*)- and (*R*)-diastereomers, respectively. A comparable analysis can be applied to **10c**.

An alternate approach is to posit that formation of the enolate from **9bc** is not completely diastereoselective, so that an *E*/*Z* mixture of acetals **10** is generated. In this event, even exclusive rearrangement through either a chair- or boat-like conformation is destined to afford **14** as a mixture of diastereomers.

If our earlier results[6b–d] with six-membered ring analogs of **10** serve as a guide, the preference for its rearrangement through a chair-like conformation should be about 9:1. The experimentally observed ratios of 2:1 and 1:2 for **14a/14b** from **9b** and **9c**, respectively, are then clearly less than those that would be expected. This may reflect a differing selectivity between the two reactive conformers for rearrangement, of course, but it may also be the consequence of the ratio of diastereomeric acetals *E*- and *Z*-**10** produced.

To assess the latter possibility, we next explored the Ireland–Claisen rearrangement in a system where it was hoped that chelation would control the selectivity of enolate formation from the starting ester, and thus of the ketene silylacetals as well. Given the apparent success of a 2-methoxy group to control enolate formation in **6** (Eq. 4) cyclopentyl analogs **22** were prepared (Scheme 4). Methylation[17] of ethyl *cis*-2-hydroxy-1-cyclopentane-carboxylate under acidic conditions gave rise to **19**. Reduction[18] to alcohol **20** followed by oxidation[12] afforded carboxylic acid **21**. Its conversion to esters **22ab** was unexceptional,[19] and the products had the expected spectral characteristics (see Section 3). Epimerization at C(1) was not observed for any of the steps in Scheme 4.

Subjecting allyl ester **22a** to the Ireland–Claisen rearrangement, followed by hydrolysis, produced a 53% isolated yield of a mixture of carboxylic acids, whose spectral characteristics were consistent with their being the isomers **24** (Eq. 6). Of particular note were a pair of multiplets at δ 3.92 and 3.60, corresponding to the protons at C(2) of the two isomers, and a pair of doublets of doublets associated with the downfield portions of two AB quartets at δ 2.62 and 2.45 (the centers for each of the doublets of doublets) that were assigned to the diastereotopic allylic protons of the two isomers.[‡] The ratio of the lower field to upper field multiplets of each set of resonances was 1.0:1.1, a result demonstrating that the same diastereomer accounted for the resonances and that the overall course of the rearrangement of **22a** is essentially non-facioselective, that is, the effect of a methoxy group on the facial selectivity of the Ireland–Claisen rearrangement in the six-membered ring system **6** is lost in the five-membered analog.



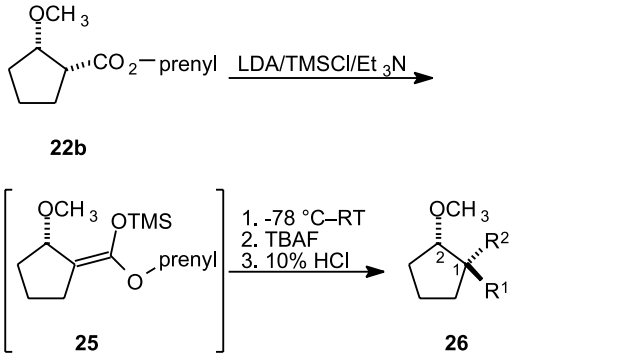
(6)

The major isomer from Ireland–Claisen rearrangement of **22a** was found to be **24b**: Separation of the isomers through column chromatography and GOESY NMR (500 MHz) analyses showed that the lower-field resonances at δ 3.92 and 2.62 are due to the minor isomer **24a**. This assignment was made through the irradiation of the C(2) proton in both the major and minor isomers: In addition to the strong enhancement of the resonance for the methoxy protons in both isomers, the allylic protons of the minor isomer are negligibly enhanced, whereas those of the major isomer are strongly increased. An assignment of the relative stereochemistry of the isomers solely by considering steric compression[20] would have been incorrect because **24b**

[‡] First order splitting patterns were observed for the ABX spin systems in both **24** and **26** based on their $\Delta\nu/J$ values (see Section 3).

would be expected to have resonances for the protons at C(2) and the allylic position at lower field; anisotropic factors associated with the methoxy and carboxy functions account for the observed result.

We had hoped that the increased steric demands of the prenyl moiety in **22b** might improve the facial selectivity in the rearrangement, but this was not to be the case. Treating this ester in the same way as **22a** afforded a 57% isolated yield of a 1.0:1.0 mixture of the carboxylic acids **26**, based on ^{1}H NMR analysis (Eq. 7).



a. $R^1 = CO_2H$, $R^2 = C(CH_3)_2CH=CH_2$
b. $R^1 = C(CH_3)_2CH=CH_2$, $R^2 = CO_2H$

(7)

Particularly diagnostic resonances in this mixture were those of the internal vinylic proton, which appeared as a pair of doublets of doublets centered near δ 6.13 and 5.93, and the C(2) proton, which provided two multiplets at δ 4.09 and 3.88, respectively. One isomer provided the more deshielded resonances of both sets of multiplets, and NMR techniques (GOESY, 500 MHz) on the pure isomers of **26** showed that the lower-field sets of resonances are those of **26a**. Thus, the spectroscopic data for **26** are entirely consistent with those obtained on **24**.[§]

The absence of diastereoselectivity in the overall transformation of **22a** and **22b** to **24** and **26**, respectively, could be associated with the selectivity in forming the ketene silylacetals **23** and **25**, in the faciality of the rearrangement, or with a combination of both factors. An effort to examine these possibilities was undertaken by preparing a sample of **25** and monitoring its rearrangement by NMR spectroscopy. A 5:1 *trans*/*cis* mixture of **22b** afforded a 3:1 mixture of acetals **25** using the conditions shown in Eq. 7, with the exception that the ester enolate was formed and trapped at −110 °C. It appears that there may be some loss of diastereoselectivity in forming **25**, although its lability precludes determining its yield and thereby makes a conclusion on this point ambiguous. By following the disappearance of the resonances at δ 3.19 and 3.21 for the methoxy protons of **25** as a function of time and the concomitant appearance of the corresponding resonances for **26**, it was found that both diastereomers rearranged at the same rate and provided **26** in an unchanging ratio of 55:45 (Table 1). This constancy proves that both diastereomers of **25** have identical and non-discriminant facial selectivity in the rearrangement.

Table 1. Study of rearrangement of **25** at 25 °C as function of time

Time (min)	Ratio of isomers of **25**	Ratio of **25**/**26**	Ratio of **26b**/**26a** (*cis*/*trans*)
30	3:1	95:5	60:40
85	3:1	87:13	55:45
135	3:1	79:21	55:45
195	3:1	70:30	55:45
255	3:1	62:38	55:45
375	3:1	47:53	55:45
2880	N/A	<5:95	55:45

Our observations with the esters **22** clearly show that a 2-methoxy group in the five-membered ring system does not exercise the level of control of enolate diastereoselectivity as it did in the six-membered analog **6**. Even if it is assumed that the major isomer of **25** produced has the *Z*-configuration, the influence of the methoxy group on deprotonation is modest. The reason for this is not particularly obvious and merits further investigation. Moreover, the methoxy group fails to foster the level of facial selectivity that the methyl group in **9** does. This may be due to subtle conformational factors, or may simply reflect the greater steric bulk of a methyl group as compared to a methoxy function.[21]

The generation of isomeric ketene silylacetals from **22b** strongly implies that the formation of diastereomers **14** from **9b** and **9c** results from the formation of a mixture of acetals rather than from competition between chair- and boat-like conformations for the rearrangement. Although the latter may be a factor, we believe it to play a minor role compared to that associated with poor selectivity in forming acetals **10bc**. Whether or not greater diastereoselectivity in keteneacetal formation can be achieved is a subject for future investigations.

3. Experimental

3.1. General information

Unless otherwise stated, ^{1}H and ^{13}C NMR spectra were recorded using spectrometers operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C and $CDCl_3$ served as solvent and internal reference. Chemical shifts (δ) are reported in ppm from TMS. Ratios of isomers were determined from integrated ^{1}H NMR spectra. Infrared spectra were recorded on a Nicolet 510 FT-IR instrument, and were obtained as samples prepared as solutions or thin films between NaCl plates. Low resolution MS measurements were obtained in the chemical ionization mode with a Finnegan-MAT TSQ-70 spectrometer operating at 70 eV with 4 Torr methane gas pressure. High resolution MS measurements were obtained in the chemical ionization mode on a VG ZAB2-E

[§] A shift reagent study using EuFOD was originally applied to define the stereochemistry of **26a** and **26b**. The more upfield of the two methoxy resonances of isomers **26** was shifted downfield faster (see Section 3). Although this result might be interpreted as placing the carboxylic acid and methoxy moieties *cis* to one another as in **26b**, such a conclusion rests on considering only the dependence of lanthanide-induced shifts on distance and neglects that of angle. The upfield methoxy resonance is actually that of **26a**, as determined by GOESY experiments, demonstrating the critical role that angular depenence can play in the interpretation of shift data.

instrument. X-ray structure analysis was carried out by Dr. Vincent Lynch at the Department of Chemistry and Biochemistry at the University of Texas at Austin. Melting ranges were uncorrected. Chromatographic purification of product mixtures refers to purification by flash column chromatography on silica gel, according to the procedure described by Still, et al.[22] All anhydrous reactions were run under a positive pressure of Ar or N_2. All syringes, and hypodermic needles, cannulae, and reaction flasks required for anhydrous reactions were dried for at least 12 h in an oven at 120 °C and cooled under a N_2 atmosphere or in a desiccator. THF was distilled from benzophenone ketyl, under a N_2 atmosphere, just prior to use. Dichloromethane (CH_2Cl_2), *N*,*N*′-dimethylformamide (DMF), pyridine (pyr) and triethylamine (Et_3N) were distilled from CaH_2 under a N_2 atmosphere immediately before use. Benzene (C_6H_6), diisopropylamine (DIPA), and trimethylsilyl chloride (TMSCl) were distilled from CaH_2 and stored over molecular 4 Å sieves. All other reagents and solvents were purified, as necessary, according to standard procedures.[23] Unless noted otherwise, concentration of solutions was accomplished by rotary evaporation at water aspirator pressures.

3.2. Esterification

In a modification of the procedure developed by Chandresekaren and Turner,[24] the diastereomeric 2-methylcyclopentanecarboxylic acids[9] (1 equiv.), CH_2Cl_2, and Et_3N (2 equiv.) were combined in a flask equipped for magnetic stirring under an atmosphere of Ar, and the solution was cooled to 0 °C. Freshly distilled methanesulfonyl chloride (1 equiv.) was added dropwise via syringe to the stirred solution, which was stirred for 1 h at 0 °C. DMAP (0.1 equiv.) and the allylic alcohol (2–4 equiv.) were added to CH_2Cl_2 under an Ar atmosphere, and the solution was cooled to 0 °C. It was then added via syringe to the solution of acid and Et_3N solution. The resulting mixture was held at 0 °C for 1 h. The solution was then stirred for 16 h at room temperature, transferred to a separatory funnel, and diluted with Et_2O. The ethereal solution was sequentially washed with 10% aq. HCl, water, saturated aq. $NaHCO_3$, and dried (Na_2SO_4). Concentration and flash chromatography of the residue afforded the ester as a colorless oil.

3.2.1. 3-Methyl-2-butenyl 2-methylcyclopentanecarboxylate (9a). Flash chromatography (20% EtOAc, 80% hexanes, R_f=0.48) afforded **9a** (414.4 mg, 70% yield), starting with 384.5 mg (3.000 mmol) of acid and 258.4 mg (6.000 mmol) of alcohol. Spectral data (mixture of *trans*/*cis*=2:1): IR ($CHCl_3$): 1722 cm^{-1}; ^1H NMR: δ 5.31 (m, 1H), 4.54 (m, 2H), 2.75 (q, *J*=7.2 Hz, 0.33H, *cis*-isomer), 2.34–1.08 (m, 13.67H, including peaks for two methyls at 1.73 (s, 1H, *cis*-isomer), 1.68 (s, 2H, *trans*-isomer)), 1.02 (d, *J*=6.5 Hz, 2H, *trans*-isomer), 0.87 (d, *J*=7.1 Hz, 1H, *cis*-isomer); ^{13}C NMR (short of two olefinic carbon resonances due to degeneracy): δ 176.5, 175.3, 138.7, 118.9, 61.2, 60.9, 52.0, 48.3, 39.4, 37.4, 34.8, 33.8, 30.1, 29.7, 27.5, 25.8, 24.4, 23.8, 19.6, 18.0, 16.2, 14.1; HRMS (CI): *m*/*z* calcd for $C_{12}H_{21}O_2$ $(M+H)^+$ 197.1541; found 197.1551.

3.2.2. (*Z*)-2-Butenyl 2-methylcyclopentanecarboxylate (9b). Flash chromatography (2.5% EtOAc, 97.5% hexanes, R_f=0.3) afforded **9b** (372.9 mg, 68% yield), starting with 384.5 mg (3.000 mmol) of acid and 865.4 mg (12.00 mmol) of alcohol. Spectral data (2:1 mixture of *trans*/*cis*): IR ($CHCl_3$): 1722 cm^{-1}; ^1H NMR: δ 5.68 (m, 1H), 5.52 (m, 1H), 4.61 (d, *J*=6.9 Hz, 2H), 2.76 (q, *J*=7.5 Hz, 0.33H, *cis*-isomer), 2.23 (q, *J*=8.4 Hz, 0.67H, *trans*-isomer), 2.16–0.80 (m, 13H, including peaks for three methyls at 1.68 (d, *J*=6.9 Hz, 3H), 1.03 (d, *J*=6.3 Hz, 2H, *trans*-isomer), 0.86 (d, *J*=6.5 Hz, 1H, *cis*-isomer)); ^{13}C NMR (lacking two olefinic carbon resonances due to degeneracy): δ 176.1, 175.0, 129.1, 124.6, 59.8, 59.4, 51.8, 48.2, 39.3, 37.4, 34.7, 33.7, 30.0, 27.4, 24.4, 23.7, 21.0, 19.5, 16.1, 13.0; HRMS (CI): *m*/*z* calcd for $(M+H)^+$ $C_{11}H_{19}O_2$ 183.1385; found 183.1383.

3.2.3. (*E*)-2-Butenyl 2-methylcyclopentanecarboxylate (9c). Flash chromatography (2.5% EtOAc, 97.5% hexanes, R_f=0.3) afforded **9c** (383.8 mg, 70% yield), starting with 384.5 mg (3.000 mmol) of acid and 865.4 mg (12.00 mmol) of alcohol. Spectral data (2:1 mixture of *trans*/*cis*): IR ($CHCl_3$): 1722 cm^{-1}; ^1H NMR: δ 5.74 (m, 1H), 5.57 (m, 1H), 4.48 (m, 2H), 2.76 (q, *J*=8.1 Hz, 0.33H, *cis*-isomer), 2.23 (q, *J*=8.4 Hz, 0.67H, *trans*-isomer), 2.16–0.80 (m, 13H, including peaks for three methyls at 1.70 (d, *J*=5.4 Hz, 3H), 1.03 (d, *J*=6.6 Hz, 2H, *trans*-isomer), 0.86 (d, *J*=6.3 Hz, 1H, *cis*-isomer); ^{13}C NMR (lacking one olefinic carbon resonance due to degeneracy): δ 176.1, 174.9, 130.9, 130.7, 125.4, 64.8, 64.6, 51.9, 48.3, 39.3, 37.4, 34.8, 33.7, 30.0, 27.4, 24.4, 23.7, 22.0, 19.6, 17.6, 16.2; HRMS (CI): *m*/*z* calcd for $(M+H)^+$ $C_{11}H_{19}O_2$ 183.1385; found 183.1383.

3.3. General procedure for Ireland–Claisen rearrangements of 9

All rearrangements were run under strictly anhydrous conditions according to procedures developed by Ireland et al.[10] A solution of LDA[25] in THF was prepared in a round-bottomed flask and cooled to −78 °C under a positive pressure of Ar. A dry centrifuge tube was charged with TMSCl/Et_3N/THF (volume ratio of 2.0:0.5:3.7), centrifuged for 10 min, then cooled to −78 °C, and kept under a positive pressure of Ar. The supernatant of the centrifugate (3.0 mL) was transferred via cannula to the LDA solution. The resulting mixture was stirred at −78 °C for 5 min. A solution of the ester in THF, which had been precooled to −78 °C under a positive pressure of Ar, was added dropwise via cannula. This mixture was maintained at −78 °C for 30 min, at which time the solution was allowed to warm to room temperature and stirred at this temperature for 18–48 h. The resulting heterogeneous mixture was diluted with Et_2O (25 mL) and stirred with 10% aq. HCl for 45 min to effect hydrolysis. The resulting biphasic mixture was separated, and the aqueous layer was extracted with Et_2O (3×10 mL). The ethereal solutions were combined, washed sequentially with 10 mL each of 10% aq. HCl solution and brine acidified to pH 2, and dried (Na_2SO_4). Concentration afforded a yellow oil that was purified by flash chromatography.

3.3.1. (1*S,2*R**)-1-(1,1-Dimethyl-2-propenyl)-2-methylcyclopentanecarboxylic acid (12).** Following the general procedure and using 196.3 mg (1.000 mmol) of ester **9a**,

2.2 mmol of LDA and an 18-h period of stirring afforded acid **12** (187.1 mg, 95% yield) after flash chromatography (25% EtOAc/hexanes, R_f=0.17). The initially isolated colorless oil solidified to provide X-ray quality crystals: mp 52–53 °C. Spectral data: IR 1691 cm^{-1}; ^1H NMR: δ 6.13 (dd, J=17.7, 10.5 Hz, 1H), 4.99 (m, 2H), 2.40–1.00 (m, 16H, including peaks for three methyl groups at 1.17 (s, 3H), 1.13 (s, 3H), 1.06 (d, J=7.2 Hz, 3H)); ^{13}C NMR: δ 182.2, 146.0, 112.2, 61.8, 41.9, 40.2, 35.9, 33.6, 24.6, 24.1, 23.9, 18.0; HRMS (CI): m/z calcd for $C_{12}H_{21}O_2$ $(M+H)^+$ 197.1541; found 197.1534.

3.3.2. (1*S* *,2*R* *)-1-(1-Methyl-2-propenyl)-2-methylcyclopentanecarboxylic acids (14). Following the general procedure and using 182.3 mg (1.000 mmol) of ester **9b**, 1.1 mmol of LDA and a 48-h period of stirring afforded a 2:1 ratio of the acids **14** as a colorless oil (82.6 mg, 45% yield) after flash chromatography (15% EtOAc/hexanes, R_f=0.33). Spectral data (mixture of *trans*/*cis*=2:1): IR 1693 cm^{-1}; ^1H NMR: δ 5.91 (m, 0.67H, *trans*-isomer), 5.67 (m, 0.33H, *cis*-isomer), 5.05 (m, 2H), 2.75 (m, 0.33H, *cis*-isomer), 2.47 (m, 0.67H, *trans*-isomer), 2.30–1.05 (m, 7H), 1.01 (d, J=7.0 Hz, 1H, *cis*-isomer), 1.00 (d, J=6.8 Hz, 2H, *trans*-isomer), 0.95 (d, J=7.0 Hz, 1H, *cis*-isomer), 0.93 (d, J=6.9 Hz, 2H, *trans*-isomer); ^{13}C NMR δ 182.1, 181.7, 141.5, 139.7, 116.3, 114.7, 60.2, 60.1, 42.9, 41.8, 41.1, 41.0, 33.2, 33.1, 30.8, 28.8, 22.4, 22.2, 17.8, 16.3, 15.5, 15.0; HRMS (CI): m/z calcd for $(M+H)^+$ $C_{11}H_{19}O_2$ 183.1385; found 183.1382. The rearrangement of ester **9c** (182.3 mg, 1.000 mmol) was accomplished according to the same procedure used for **9b** to provide the diastereomeric acids **14** (81.8 mg, 45% yield) in a 1:2 ratio.

3.4. Additional experimental information

3.4.1. (4*R* *,5*S* *,6*R* *)- and (4*S* *,5*S* *,6*R* *)-1,3-Dioxo-2-oxa-4,6-dimethylspiro[4.4]nonane (18ab). A 25-mL two-neck round-bottomed flask, equipped for magnetic stirring, was charged with a solution of **14** (39.4 mg, 0.216 mmol, 1:2 ratio of diastereomers) in CH_2Cl_2 (15 mL) under an N_2 atmosphere. The solution was stirred and cooled to −78 °C and then ozone was bubbled into this solution until it turned a faint blue color, at which time oxygen was bubbled into it to expel excess ozone. Dimethyl sulfide (0.16 mL, 2.18 mmol) was added to the reaction mixture, which was allowed to warm slowly to rt over 3 h with stirring. The mixture was transferred to a 50-mL round-bottomed flask and concentrated to give a pale yellow residue. ^1H NMR spectroscopy indicated that the residue was a mixture of **15** and **16** in a ratio of 1:38. The residue was subjected to the oxidation using a modified procedure as follows.[15] The residue was diluted with CH_2Cl_2 (2.0 mL) in a 10-mL round-bottomed flask and tetrabutylammonium bromide (35.2 mg, 0.108 mmol), 0.10 M aq. KOH (2.8 mL, 0.28 mmol), and $KMnO_4$ (93.5 mg, 0.592 mmol) were added with stirring. The mixture was stirred at rt for 3 h and then cooled in an ice–water bath before slow addition of solid sodium bisulfite (198.0 mg, 1.90 mmol). Aqueous 10% HCl was added dropwise to dissolve MnO_2, then the mixture was further acidified to pH 3 and transferred to a separatory funnel. Diethyl ether (10 mL) and H_2O (2 mL) were added, and the aqueous layer was separated and extracted with Et_2O (3×10 mL). The combined organic layers were washed with brine (3×10 mL), dried (Na_2SO_4), and concentrated to furnish a pale yellow oil. ^1H NMR spectroscopy of this residue indicated formation of diacids **17**. The crude oil in CH_2Cl_2 (3.0 mL) contained in a 10-mL round-bottomed flask was stirred in the presence of dicyclohexylcarbodiimide (22.5 mg, 0.108 mmol) at rt for 1 h. Water (3 mL) was added, and the mixture was acidified to pH 3 using aq. 10% HCl before being transferred to a separatory funnel. The aqueous layer was separated and extracted with Et_2O (3×10 mL), and the combined organic layers were washed with brine (3×10 mL) and dried (Na_2SO_4). Concentration gave a mixture containing solid and oil, which was washed with hexanes (3×4 mL). The combined washes were concentrated and chromatographed to give anhydrides **18ab** in a ratio of 1:2 as a colorless oil (23.5 mg, 60% for the three steps). ^1H NMR (500 MHz): δ 3.06 (q, J=7.5 Hz, 0.67H), 2.86 (q, J=7.5 Hz, 0.33H), 2.32–1.40 (m, 7H), 1.27 (d, J=7.5 Hz, 1H, CH_3 of **18a**), 1.24 (d, J=7.2 Hz, 2H, CH_3 of **18b**), 1.03 (d, J=6.3 Hz, 1H, CH_3 of **18a**), 0.93 (d, J=6.9 Hz, 2H, CH_3 of **18b**); ^{13}C NMR (125 MHz): δ 175.2, 174.7, 174.0, 173.4, 58.6, 58.4, 44.4, 42.9, 42.6, 39.6, 34.0, 32.4, 32.0, 31.0, 22.0, 21.9, 15.0, 14.3, 12.0, 7.9; HRMS (CI): m/z calcd for $(M+H)^+$ $C_{10}H_{15}O_3$ 183.1022; found 183.1028, 183.1040.

3.4.2. Ethyl *cis*-2-methoxycyclopentanecarboxylate (19). Methylation of ethyl *cis*-2-hydroxycyclopentane-carboxylate (635.6 mg, 3.940 mmol) followed the reported procedure[17] except that $TMSCHN_2$ was added dropwise at 30- rather than 20-min intervals. This afforded **19** (577.2 mg) as a colorless oil in 85% isolated yield. It's spectral data agree with what has been reported in the literature.[26,¶] ^1H NMR: δ 4.24–4.04 (m, 2H), 3.94 (m, 1H), 3.26 (s, 3H), 2.81 (m, 1H), 2.16–1.42 (m, 6H), 1.24 (t, J=7.2 Hz, 3H); ^{13}C NMR: δ 172.8, 84.1, 60.1, 57.1, 49.4, 30.4, 25.2, 21.9, 14.3; HRMS (CI): m/z calcd for $(M+H)^+$ $C_9H_{17}O_3$ 173.1178; found 173.1175.

3.4.3. *cis*-2-Methoxycyclopentanemethanol (20). Reduction of **19** (250.0 mg, 1.452 mmol) followed the reported procedure[18] except that the reaction was performed in THF instead of diethyl ether and afforded **20** (165.1 mg) as a colorless oil in 87% isolated yield. Spectral data: ^1H NMR: δ 3.86 (m, 1H), 3.70 (m, 2H), 3.28 (s, 3H), 2.79 (s, broad, 1H), 2.09 (m, 1H), 1.80–1.40 (m, 6H); ^{13}C NMR: δ 85.3, 63.1, 56.5, 44.7, 30.3, 25.6, 22.2; HRMS (CI): m/z calcd for $(M+H)^+$ $C_7H_{15}O_2$ 131.1072; found 131.1069.

3.4.4. *cis*-2-Methoxycyclopentanecarboxylic acid (21). Oxidation of **20** (165.1 mg, 1.268 mmol) followed the reported procedure[12] except that the reaction mixture was stirred for 5 instead of 2 h and gave **21** (155.6 mg) as a white solid in 85% isolated yield: mp 61–63 °C. Spectral data:[26,‖] ^1H NMR: δ 11.32 (s, broad, 1H), 3.98 (m, 1H), 3.28 (s, 3H), 2.83 (m, 1H), 2.16–1.46 (m, 6H); ^{13}C NMR: δ 178.2, 83.8, 56.9, 49.3, 30.2, 25.4, 21.7; HRMS (CI): m/z calcd for $(M+H)^+$ $C_7H_{13}O_3$ 145.0865; found 145.0859.

¶ The spectral data of ethyl (1*R*,2*S*)-2-methoxycyclopentanecarboxylate previously reported had an additional ^{13}C resonance at δ 22.5 ppm.[26]

‖ The reported[26] spectral data of a 3.4:1 mixture of (1*R*,2*S*) and (1*S*,2*S*)-2-methoxycyclopentanecarboxylic acids are consistent with ours except that the responses at δ 56.9 and 60.0 ppm were assigned to the *trans*- and *cis*-isomers, respectively; this is opposite to our own assignment.

3.4.5. 2-Propenyl *cis*-2-methoxycyclopentanecarboxylate (22a). Esterification of **21** (144.2 mg, 1.000 mmol) followed the reported procedure[19] except that the reagents were mixed at 8–10 °C instead of rt. The reaction mixture was stirred at rt for 16 h to afford **22a** (136.0 mg) as a colorless oil in 74% isolated yield. Spectral data: ^{1}H NMR: δ 5.98–5.82 (m, 1H), 5.36–5.14 (m, 2H), 4.38–4.50 (m, 2H), 3.96 (m, 1H), 3.25 (s, 3H), 2.86 (m, 1H), 2.10 (m, 1H), 1.82–1.46 (m, 5H); ^{13}C NMR: δ 172.4, 132.5, 117.7, 84.0, 64.9, 57.0, 49.5, 30.4, 25.2, 21.9; HRMS (CI): *m/z* calcd for $(M+H)^+$ $C_{10}H_{17}O_3$ 185.1177; found 185.1180.

3.4.6. 3-Methyl-2-butenyl *cis*-2-methoxycyclopentanecarboxylate (22b). Esterification of **21** (144.2 mg, 1.000 mmol) followed the same procedure as was used to prepare **22a** and gave **22b** (165.2 mg) as a colorless oil in 78% isolated yield. Spectral data: ^{1}H NMR: δ 5.32 (m, 1H), 4.57 (m, 2H), 3.93 (m, 1H), 3.24 (s, 3H), 2.81 (m, 1H), 2.07 (m, 1H), 1.90–1.44 (m, 11H, including peaks for two methyls at 1.72(s, 3H), 1.67 (s, 3H)); ^{13}C NMR: δ 172.8, 138.6, 118.9, 84.1, 61.2, 57.1, 49.5, 30.5, 25.7, 25.3, 22.0, 18.0; HRMS (CI): *m/z* calcd for $(M+H)^+$ $C_{12}H_{21}O_3$ 213.1491; found 213.1489.

3.4.7. (1*R,2*R**)- and (1*S**,2*R**)-1-(2-Propenyl)-2-methoxycyclopentanecarboxylic acid (24a and 24b).** Ester **22a** (93.2 mg, 0.506 mmol), 2.2 equiv. of LDA, and 4.6 equiv. of TMSCl were used in the general procedure for Ireland–Claisen rearrangement. After the reaction mixture had been stirred for 48 h, TBAF (2.33 mL, 1 M solution in THF, 4.6 equiv.) was added at 0 °C, and stirring was continued at rt for 3 h. Water (3.0 mL) was added dropwise at 0 °C, and the pH of the resulting mixture was adjusted to 3–5 by dropwise addition of 10% aq. HCl solution at 0 °C. Normal workup and flash chromatography of the residue afforded a 1.0:1.1 ratio of diastereomers **24** (49.6 mg, 0.269 mmol, 53% yield) as a colorless oil. Further purification by column chromatography (20% EtOAc/hexanes, R_f=0.40, 0.27) effected separation of the isomers. Spectral data for **24a**: ^{1}H NMR: δ 10.40 (s, broad, 1H), 5.77 (m, 1H), 5.04 (m, 2H), 3.92 (m, 1H), 3.32 (s, 3H), 2.62 (dd of downfield portions of AB quartet, *J*=6.3, 13.8 Hz, 1H), 2.28 (dd of upper portions of AB quartet, *J*=7.8, 14.0 Hz, 1H), 2.14–1.52 (m, 6H); ^{13}C NMR: δ 182.3, 134.8, 117.5, 86.0, 57.5, 57.4, 36.3, 32.6, 29.7, 20.7; HRMS (CI): *m/z* calcd for $(M+H)^+$ $C_{10}H_{17}O_3$ 185.1177; found 185.1186; spectral data for **24b**: ^{1}H NMR: δ 10.20 (s, broad, 1H), 5.80–5.64 (m, 1H), 5.07 (d, *J*=1.2 Hz, 1H), 5.03 (d, *J*=1.2 Hz, 1H), 3.60 (m, 1H), 3.32 (s, 3H), 2.45 (dd of downfield portions of AB quartet, *J*=7.2, 13.6 Hz, 1H), 2.13 (dd of upper portions of AB quartet, *J*=7.2, 14.0 Hz, 1H), 2.32–1.52 (m, 7H, including doublet of upper portions of AB quartet); ^{13}C NMR: δ 178.7, 133.4, 118.3, 88.4, 58.0, 57.3, 40.0, 30.0, 28.4, 20.3; HRMS (CI): *m/z* calcd for $(M+H)^+$ $C_{10}H_{17}O_3$ 185.1177; found 185.1168.

3.4.8. (1*R,2*R**) and (1*S**,2*R**)-1-(1,1-Dimethyl-2-propenyl)-2-methoxycyclopentanecarboxylic acid (26a and 26b).** Following the same procedure as with **22a**, **22b** (143.1 mg, 0.674 mmol) afforded a 1.0:1.0 ratio of diastereomers **26** (81.9 mg, 0.386 mmol, 57%) as a colorless oil. Further purification by column chromatography (20% EtOAc/hexanes, R_f=0.53, 0.42) effected separation of the isomers. Spectral data for **26a**: ^{1}H NMR: δ 10.88 (s, broad, 1H), 6.13 (dd, *J*=18.0, 10.5 Hz, 1H), 4.94–4.84 (m, 2H), 4.09 (d, *J*=4.2 Hz, 1H), 3.24 (s, 3H), 2.18–1.32 (m, 6H), 1.17 (s, 3H), 1.16 (s, 3H); ^{13}C NMR: δ 181.1, 146.8, 110.6, 86.8, 65.7, 55.8, 40.0, 27.7, 27.1, 25.9, 23.9, 20.4; HRMS (CI): *m/z* calcd for $(M+H)^+$ $C_{12}H_{21}O_3$ 213.1491; found 213.1497; spectral data for **26b**: ^{1}H NMR: δ 10.73 (s, broad, 1H), 5.93 (dd, *J*=17.2, 11.1 Hz, 1H), 5.10–5.00 (m, 2H), 3.88 (dd, *J*=9.6, 7.5 Hz, 1H), 3.46 (s, 3H), 2.38–1.40 (m, 6H), 1.14 (s, 3H), 1.08 (s, 3H); ^{13}C NMR: δ 174.6, 143.9, 113.4, 83.8, 62.5, 57.7, 39.6, 29.2, 27.8, 24.6, 23.8, 17.4; HRMS (CI): *m/z* calcd for $(M+H)^+$ $C_{12}H_{21}O_3$ 213.1491; found 213.1501.

3.5. Shift reagent study of 26[27]

A 1-dram vial was charged with the mixture of acids **26** (80 mg, 0.40 mmol). Deuteriochloroform (1.5 mL) was added to the vial and the solution was thoroughly shaken. Resolve-Al^{TM} EuFOD (100 mg, 0.100 mmol) was dissolved in $CDCl_3$ (1.0 mL) in a second 1-dram vial. Approximately 0.8 mL of the solution containing **26** was transferred to a 5-mm NMR tube, and a ^{1}H NMR spectrum was obtained. One drop of the EuFOD solution was added to the NMR tube, and another spectrum was obtained. This process was repeated until 15 spectra had been taken. Representative data points for the methoxy resonances are: (1) δ 3.46 (*cis*-isomer), 3.24 (*trans*-isomer); no EuFOD solution; (2) δ 3.46 (*cis*-isomer), 3.37 (*trans*-isomer); two drops of EuFOD solution; (3) δ 3.48 (*cis*-isomer), 3.71 (*trans*-isomer); four drops of EuFOD solution.

3.6. Formation and trapping of the ketene silylacetal intermediate (25)

THF (16 mL) contained in a round-bottomed flask equipped with a stirbar was cooled to −110 °C under Ar and 2 M LDA (0.40 mL) in THF/heptanes was added via syringe and stirred. To this was added 1 mL of the supernatant centrifugate of a solution of TMSCl (2 mL), Et_3N (0.5 mL) and THF (4 mL). The resulting solution was stirred at −110 °C for 3 min. A solution of ester **22b** (80 mg, 0.37 mmol) in THF (1 mL) was cooled to −78 °C and added via cannula to the LDA solution. The mixture was stirred and allowed to warm slowly to −20 °C. At this point, the crude ketene silylacetal could be isolated as a solution in toluene-d_8, in the following manner. The solvents were removed under vacuum (0.5 Torr) at −20 °C, and the residue was suspended in toluene-d_8 (1 mL). The suspension was then quickly passed through a cotton plug into an NMR tube under Ar for immediate analysis by ^{1}H NMR spectroscopy. The *E* and *Z* diastereomers of the ketene silylacetal were observed in approximately a 1:3 ratio. Partial ^{1}H NMR of **25**: δ 5.3–5.4 (m, 1H), 3.21 (s, 3H, −OMe of one acetal), 3.19 (s, 3H, −OMe of other acetal).

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