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Mechanistic Investigations of the Pd-Catalyzed Hydrogenolysis of Ketene Heterodimer *β*-Lactones

Manashi Panda,[a] Mukulesh Mondal,[a] Shi Chen,[a] Ahmad A. Ibrahim,[a] Dylan J. Twardy,[a] and Nessan J. Kerrigan[b],*

Abstract: Catalytic hydrogenolysis of the *Z*-isomer of a series of aryl-substituted ketene heterodimer *β*-lactones facilitated access to deoxypropionate derivatives with a dr ranging from 54:46 to 86:14, favoring the *anti*-isomer, and with excellent transfer of chirality (91->99% ee for 13 examples). Although X = 4-F was determined to provide optimal diastereoselectivity (dr 86:14), a non-linear relationship between diastereoselectivity and aryl substituent σ values was found. For cases where a *para*- or *ortho*-EWG was present on the aryl ring of the ketene heterodimer, formation of significant amounts of *β*-lactone (20-44%) as byproduct was observed. The results of a number of control reactions point to *anti*-*β*-elimination and an *anti*-selective hydrogenation of an *E*-isomer olefin intermediate being key steps in the reaction mechanism. The synthetic potential of the deoxypropionate derivative products was demonstrated by oxidative conversion into a 1,5-difunctionalized deoxypropionate motif.

Introduction

Deoxypropionates represent an important class of structural motif prevalent in many polyketide molecules exhibiting interesting biological activity. Some examples of those molecules include borrelidin, doliculide, mycocerosic acid, and mycolipanolic acid.[1] Stereoselective strategies for assembling these molecules have historically relied on chiral auxiliary-controlled methods.[2] Recently a number of catalytic asymmetric approaches for the construction of deoxypropionates have been developed.[3] Most notable among these are the chiral zirconocene (ZACA)-catalyzed method of Negishi, Feringa and Minnaard's Cu(I)-Josiphos-catalyzed conjugate addition of Grignard reagents to unsaturated thioesters and esters, and Burgess's Ir(I)-chiral NHC-oxazoline-catalyzed diastereoselective hydrogenation of alkenes bearing chiral centers.[4-6] Most approaches are iterative, with the notable exception of a recent convergent extension of the ZACA process by Negishi's group, and the strategy of the Schneider group involving an oxy-Cope rearrangement of an aldol product, iridium-catalyzed hydrogenation of enol esters, and a diastereoselective *α*-methylation.[7-9]

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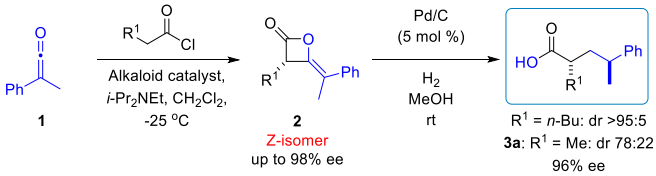
As part of our studies on the development of new reactions of ketenes, we recently introduced a catalytic ketene heterodimerization-hydrogenolysis process as a new method for the construction of deoxypropionate units.[10-15] This sequential process represents a very efficient, atom economical direction, as it entails the coupling of two catalytic processes, one of which is enantioselective, the second of which is diastereoselective.[12-15] The employment of just one chiral catalyst (an alkaloid derivative) for the overall creation of two stereocenters sets this process apart from other methodologies, which generally require two steps involving chiral catalysts/reagents/auxiliaries to establish the two asymmetric centers found in the deoxypropionate unit. The desired products were obtained in moderate to excellent diastereoselectivity (dr *ca.* 78:22 to >95:5), favoring the *anti*-diastereomer. The level of diastereoselectivity strongly depended upon the steric properties associated with the substituents on the ketene heterodimer, with long alkyl chains (*n*-Pr, *n*-Bu etc.) at R^1 (Scheme 1) giving best levels of diastereoselectivity (dr >95:5). Moderate diastereoselectivity (dr 78:22) was observed for the deoxypropionate unit **3a** (R^1 = Me) likely to have most applications in complex molecule synthesis. In addition, we had recently reported that when the *E*-isomer of ketene heterodimers was exposed to the same reaction conditions that a change in product selectivity to favor formation of 'fully reduced' *β*-lactone with generally high diastereoselectivity (dr ≥90:10 for most examples) was observed.[15] We were therefore motivated to investigate and gain an understanding of the underlying factors influencing product selectivity and diastereoselectivity. We hypothesised that the diastereoselectvity of the hydrogenolysis reaction was dependent upon the stereoselectivity of steps involving *β*-elimination and olefin intermediate hydrogenation, and that diastereoselectivity might be amplified to a useful level through appropriate electronic tuning of substrates. In this article, we report the synthesis of a series of ketene heterodimers and deoxypropionate derivatives of differing electronics with the goal of probing the reaction mechanism, and a general discussion of the results of those and related control experiments.



Scheme 1. Our previous work.

Results and Discussion

Preparation of substrates. To enable an exploration of electronic effects, the methylphenylketene-derived heterodimer **2a** was selected as the baseline substrate for catalytic hydrogenolysis studies. Substituent variation at the 4-position on the aryl ring of the ketene heterodimer was investigated. Both enantiomers of ketene heterodimers **2a**-**2n** were prepared in moderate to good yields through the alkaloid-catalyzed reaction of propionyl chloride (methylketene) with various methylarylketenes.[12,13] The desired ketene heterodimers were formed with excellent enantioselectivity (Table 1), and generally with excellent *Z*-isomer selectivity (entries 1-12). The only examples where poor *Z*:*E*-selectivity was observed was with examples bearing a 2-F substituent on the aryl ring of the methyl aryl ketene – in those cases, the desired heterodimers were obtained in poor to moderate yield (11-45%), albeit with excellent enantioselectivity (entries 13 and 14). A likely explanation for the poor *Z*:*E*-diastereoselectivity observed with those substrates is a retro-aldol-like process of enolate intermediate **II**, causing equilibration of enolate geometry (Scheme 2). Poor yields (14-17%) were also observed for examples bearing a strongly electron-donating group (X = OMe, entries 5 and 6), implicating reaction of ammonium enolate (Intermediate **I**) with alkylarylketene **1** as the slow step in the reaction (Scheme 2).[13]

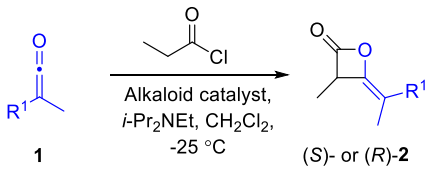
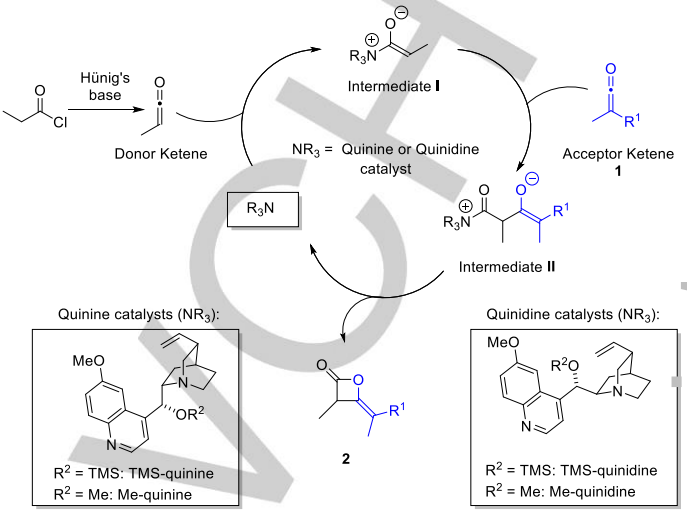


Table 1. Asymmetric synthesis of ketene heterodimers.

Entry	R^1	Catalyst	Yield [%][a]	*Z*:*E*[b]	ee [%][c]	**2**
1	Ph	MeQd	64	>95:5	95	(*S*)-**2a**
2	Ph	TMSQ	57	>95:5	93	(*R*)-**2b**
3	4-MeC_6H_4	MeQd	55	98:2	97	(*S*)-**2c**
4	4-MeC_6H_4	TMSQ	64	96.5:3.5	96	(*R*)-**2d**
5	4-$MeOC_6H_4$	MeQd	14	95:5	98	(*S*)-**2e**
6	4-$MeOC_6H_4$	TMSQ	17	93:7	95	(*R*)-**2f**
7	4-ClC_6H_4	MeQd	56	98:2	82	(*S*)-**2g**
8	4-ClC_6H_4	TMSQ	57	98:2	90	(*R*)-**2h**
9	4-FC_6H_4	MeQd	54	98:2	91	(*S*)-**2i**
10	4-FC_6H_4	TMSQ	58	95:5	88	(*R*)-**2j**
11	4-$F_3CC_6H_4$	MeQd	71	99:1	90	(*S*)-**2k**
12	4-$F_3CC_6H_4$	TMSQ	60	99:1	82	(*R*)-**2l**
13	2-FC_6H_4	MeQd	45	54:46	98/98	(*S*)-**2m**
14	2-FC_6H_4	TMSQ	11	48:52	93/96	(*R*)-**2n**

[a] % yield = isolated yield for both diastereomers. [b] *Z*:*E* determined by GC-MS or ^{1}H NMR analysis. [c] ee determined by chiral HPLC analysis.



Scheme 2. Proposed Mechanism for Alkaloid-catalyzed ketene heterodimerization.

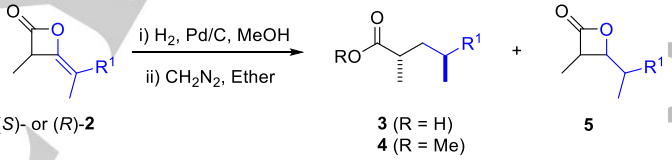
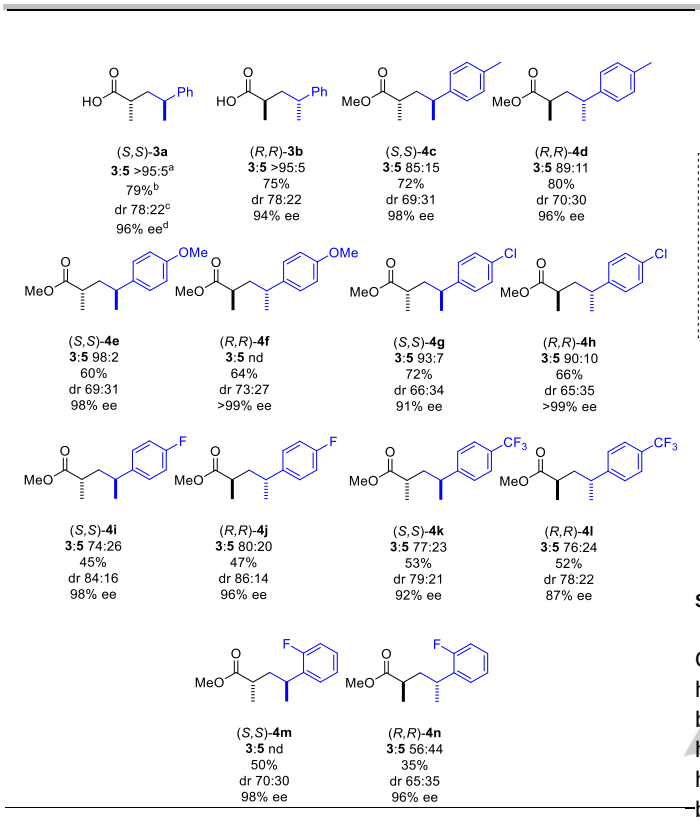


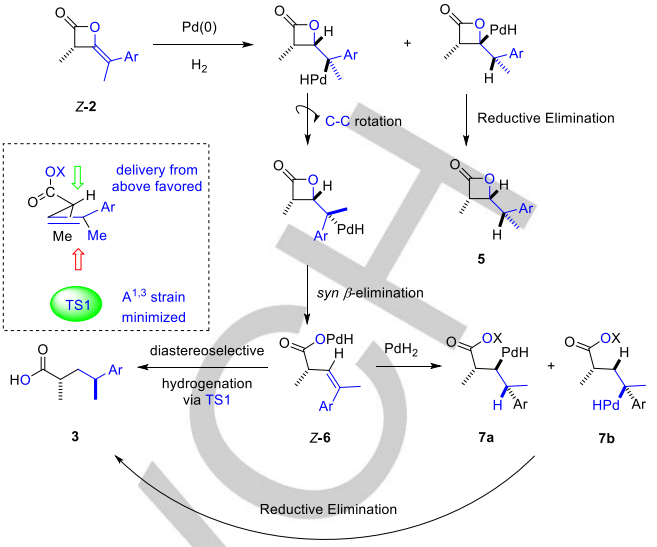
Table 2. Asymmetric synthesis of deoxypropionate derivatives.



[a] **3**:**5** determined by GC-MS analysis of crude product. [b] % yield = isolated yield for both diastereomers of **3** or **4**. [c] dr determined by GC-MS analysis of crude **3** or **4**. [d] % ee for major diastereomer determined by chiral GC analysis.

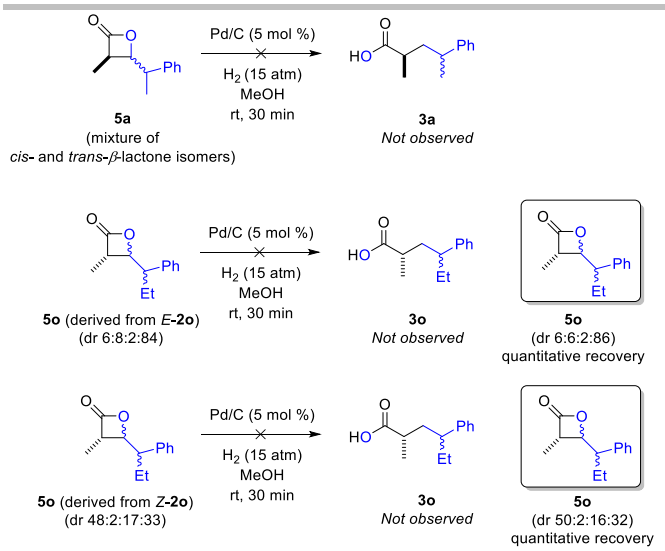
Ketene heterodimers **2a**-**2n** were then subjected to Pd/C-catalyzed hydrogenolysis, with the desired acid **3** or ester **4** products being obtained in acceptable to good yields in most cases (50-80% for 11 examples) and with moderate to good diastereoselectivity (Table 2).[14] In those cases where the yield of **3**/**4** was low (35-53%), *β*-lactone **5** was the major side-product and accounted for most of the remaining mass balance. An interesting trend in diastereoselectivity was observed, with electron donating substituents (X = Me, MeO vs H) on the aryl ring leading to a decrease in diastereoselectivity. In contrast, in a number of cases the presence of an electron withdrawing substituent (X = CF_3 or F), maintained or led to an increase in diastereoselectivity relative to X = H, with X = F providing the optimal diastereoselectivity (dr 86:14).

Reaction Mechanism. We had previously proposed a mechanism for the hydrogenolysis reaction, involving initial hydrometallation across the exocyclic double bond of the ketene heterodimer **2**.[14,15] The regioselectivity of hydrometallation, along with the ease of *β*-elimination, was proposed to be responsible for the formation of acid **3** rather than *β*-lactone **5** (Scheme 3). *Syn*-*β*-elimination was initially proposed to be a key step, as *syn*-*β*-eliminations tend to be more commonly observed for homogeneous Pd-catalyzed reactions than *anti*-eliminations.[16] Subsequent hydrogenation of *Z*-olefin **6** through an allylic-strain minimized transition state (inset of Scheme 3), where Me was regarded as the large substituent, predicted formation of acid **3** as the *anti*-diastereomer, which is the major isomer observed in experiments.[17] Delivery of hydrogen to the less sterically hindered face would provide access to the *anti*-isomer of **3**.[17]



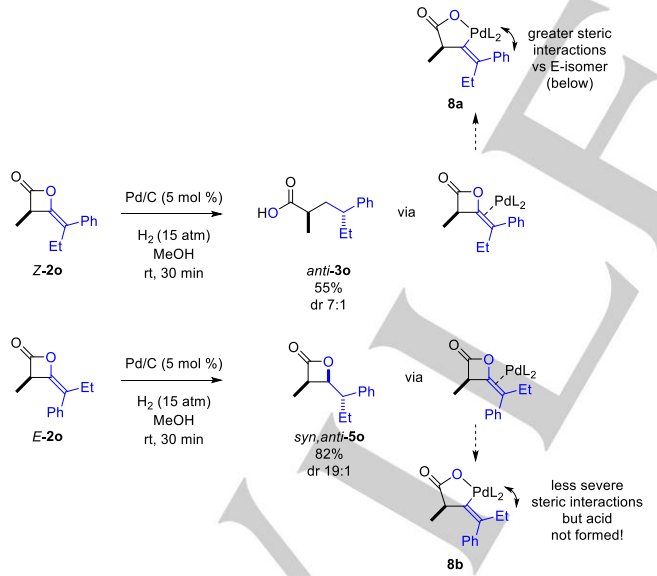
Scheme 3. Initially proposed reaction mechanism for hydrogenolysis reaction

Other possible mechanisms that were considered included hydrogenation of ketene heterodimer followed by ring insertion by Pd, or alternatively direct insertion by Pd into the ketene heterodimer ring, followed by reductive elimination and hydrogenation.[18] Hydrogenation of ketene heterodimer followed by ring insertion of Pd into the resultant *β*-lactone ring was probed by control experiments (Scheme 4). *β*-Lactone **5a** was prepared from ketene heterodimer *Z*-**2a**. This was done by carrying out the Pd/C-catalyzed hydrogenation in EtOAc. The desired *β*-lactone **5a** was obtained as a mixture of two diastereomers (30%, dr 1.3:1, *cis* and *trans* *β*-lactone isomers). The mixture, as well as each diastereomer separately, was exposed to the catalytic hydrogenolysis conditions (5 mol% Pd/C, MeOH, 30 min). **3a** was not formed from either of the two isolated diastereomers of *β*-lactone **5a**, and so we infer that **5a** does not function as an intermediate in the formation of acid **3a** (Scheme 4). To further explore this possibility, *β*-lactone **5o** (derived from *E*-**2o**, see Experimental), composed of a mixture of four diastereomers (dr 6:8:2:84 by GC-MS), was exposed to the standard hydrogenolysis reaction conditions, but no significant change in *β*-lactone dr was noted (dr 6:6:2:86 by GC-MS) and no acid formation was detected. Furthermore, *β*-lactone **5o** (derived from *Z*-**2o**, see Experimental), composed of a mixture of four diastereomers (dr 48:2:17:33 by GC-MS) was also exposed to the standard hydrogenolysis reaction conditions, and again no significant change in *β*-lactone dr was noted (dr 50:2:16:32 by GC-MS) and no acid formation was detected. We can therefore rule out the possibility that *β*-lactone **5** is an intermediate in the hydrogenolysis of ketene heterodimers **2** to acids **3**.



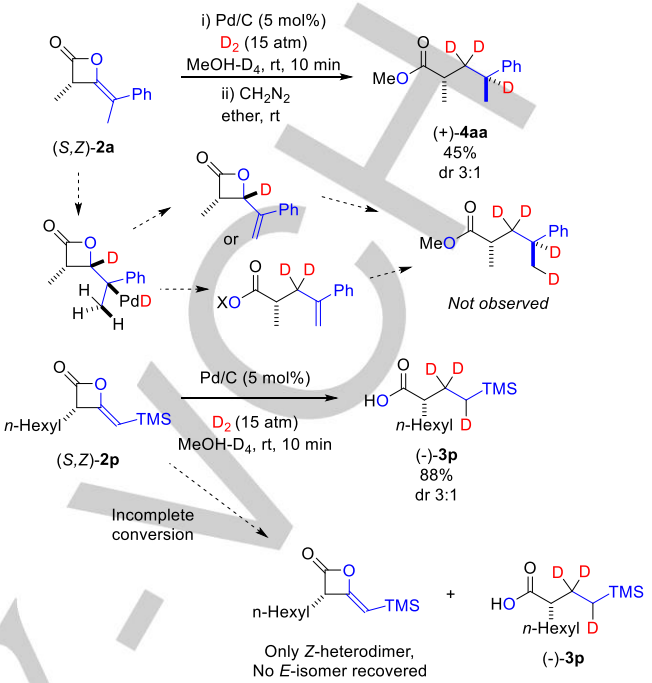
Scheme 4. Control experiments: exposure of *β*-lactones **5a** and **5o** to standard hydrogenolysis reaction conditions.

Direct insertion into the ketene heterodimer ring by Pd was also considered as a mechanism for hydrogenolysis. We have observed that ketene heterodimer *Z*-**2o** readily undergoes hydrogenolysis to afford acid **3o**. However, when *E*-**2o** was exposed to the same conditions, *β*-lactone **5o** was obtained as the major product with excellent diastereoselectivity (Scheme 5).[15]



Scheme 5. Comparison of hydrogenation of *Z*- and *E*-**2o**.

The latter result suggests that hydrogenolysis does not involve direct insertion into ketene heterodimer (to give **8a**/**8b**), as *E*-**2o** would be expected to undergo insertion more readily than Z-**2o** due to less steric incumbrance *cis* to the C-O bond proposed to undergo insertion, and yet *β*-lactone **5o** is preferred. *β*-Lactone **5o** would be most likely formed through hydropalladation of the exocyclic olefin followed by reductive elimination, but, in any case, not through direct insertion into the ketene heterodimer ring.



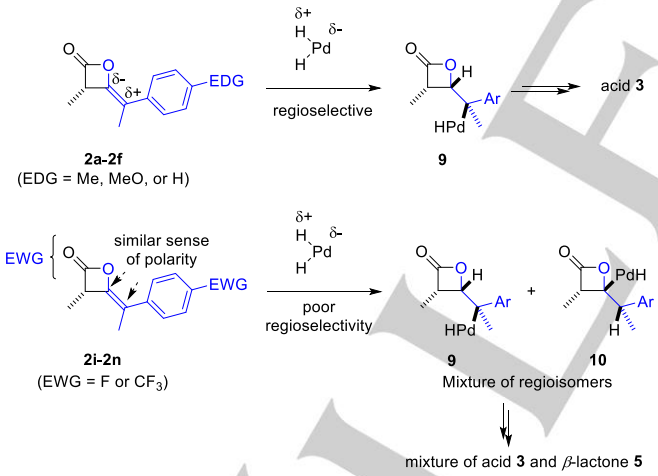
Scheme 6. Olefin migration/equilibration experiments.

In addition, the possibility of olefin migration through hydropalladation-*β*-hydride elimination was explored (Scheme 6).[14] An experiment involving Pd/C-catalyzed D_2 addition to methylphenylketene-derived heterodimer **2a** demonstrated that no olefin migration occurred (Scheme 6).[14] Interestingly, when deuteriolysis (15 atm D_2) of **2p** was stopped before all of the heterodimer had been consumed, no evidence for equilibration of olefin geometry in the starting heterodimer was observed (Scheme 6).[19] Therefore reversible hydropalladation-*β*-hydride elimination could be ruled out as a means of scrambling olefin geometry, and having an influence on diastereoselectivity.

This left hydropalladation, followed by *β*-elimination and then hydrogenation of olefin intermediate, as the most likely reaction mechanism (Scheme 3). To interrogate such a mechanism, we investigated a series of electronically differentiated ketene heterodimers **2a**-**2n** (Table 2) in the catalytic hydrogenolysis reaction, as well as carrying out control experiments with putative olefin intermediates **6** (Schemes 3 and 8). The results of our studies were then analyzed in order to gain insight into both mechanism and diastereoselectivity of the reaction.

Product profile. In all cases the acid product **3** was formed as the major product (yields of 35-80%) from the Pd/C-catalyzed hydrogenolysis of **2a**-**2n** (Table 2). In general, significant amounts of a competing *β*-lactone **5** product (20-44%) were observed when an electron withdrawing substituent (EWG) was introduced to the aryl ring (X = 4-F, 2-F, 4-CF_3). The change in product selectivity (acid **3** vs *β*-lactone **5**) with groups of differing electronic properties at the 2- or 4- position on the aryl ring of ketene heterodimer **2** is suggestive of hydrometallation regioselectivity being an important factor (Schemes 3 and 7).

Selectivity for acid **3** over *β*-lactone **5** may be rationalized by invoking a mechanism involving reaction of the exocyclic olefin of ketene heterodimer **2** with PdH_2 (Scheme 7). The PdH_2 can interact with the ketene heterodimer through one of two competing bond polarity modes, with $Pd^{\delta-}$-$H^{\delta+}$ (Mode A) being favored over $Pd^{\delta+}$-$H^{\delta-}$ (Mode B), Scheme 7.[19] Such an argument has been previously advanced by Spencer's group to explain regioselectivity of hydrometallation in the heterogeneous catalytic hydrogenation of simple olefins.[19] In the case of ketene heterodimers bearing an aryl EDG or unsubstituted (EDG = H), regioselectivity of hydrometallation is high, with a preference for $Pd^{\delta-}$ adding to the olefin $C^{\delta+}$ furthest from the lactone ring (formation of intermediate **9**). The latter sense of regioselectivity enables *β*-elimination and hence the formation of acid **3** to dominate (for **3a**-**4h**). Thus, a matchup of electronics between the (H)Pd-H bond and the ketene heterodimer olefin is responsible for the high product selectivity observed. On the other hand, when the ketene heterodimer bears a stronger EWG (for **4i**-**4n**), the situation is more complicated as there is competition between the lactone-carboxy group and the EWG-bearing aryl ring for stabilization of partial negative charge on the exocyclic olefin carbons. Regioselectivity of $Pd^{\delta-}$-$H^{\delta+}$ attack (hydropalladation) suffers as a result, and hence a mixture of acid **3** (which was often subsequently derivatized as **4**) and *β*-lactone **5** is obtained, albeit with acid **3** always formed as the major product. Occasionally, a small difference in **3**:**5** ratio between enantiomeric examples (e.g. between **4c** and **4d**, and between **4i** and **4j**) was observed. This is due to differences in the isomeric composition (*Z*:*E*-isomer) of each enantiomer of heterodimer.



Scheme 7. Rationale for product selectivity (acid **3** vs β-lactone **5**).

Diastereoselectivity. While the presence of a *para*-F on the aryl ring (Table 2, **4i** and **4j**) was found to be beneficial to diastereoselectivity, there was a clear lack of consistency in the effect of EWGs on diastereoselectivity (e.g. **4k** and **4l** vs **4i** and **4j**). Hammett plots of diastereoselectivity (dr, % major diastereomer/ % minor diastereomer) versus aryl substituent σ values have been used by various groups to extract useful mechanistic information about a range of reactions (radical reactions, aminohydroxylations and Diels-Alder reactions).[20-22]

The non-linear relationship between diastereoselectivity (Table 2) and the aryl substituent σ values in our study was clear from the Hammett type plot shown in Figure 1. Such non-linearity may be suggestive of a change in reaction mechanism or a change in the rate determining step, on changing substituents (e.g. X = F to X = Cl).

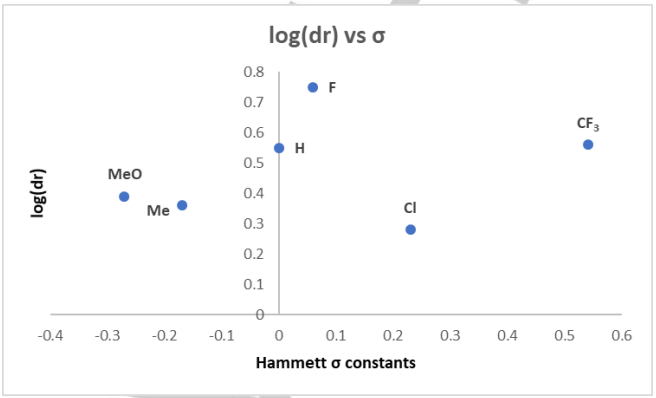
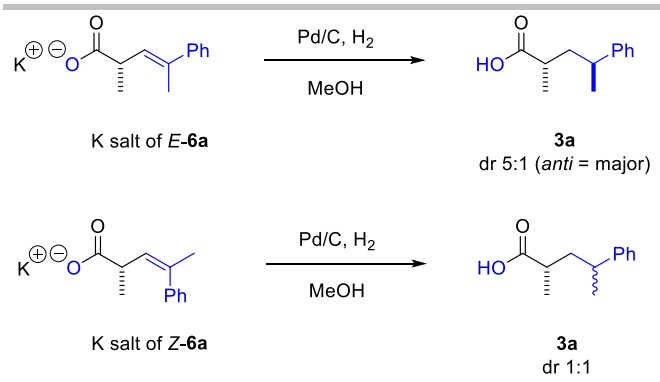


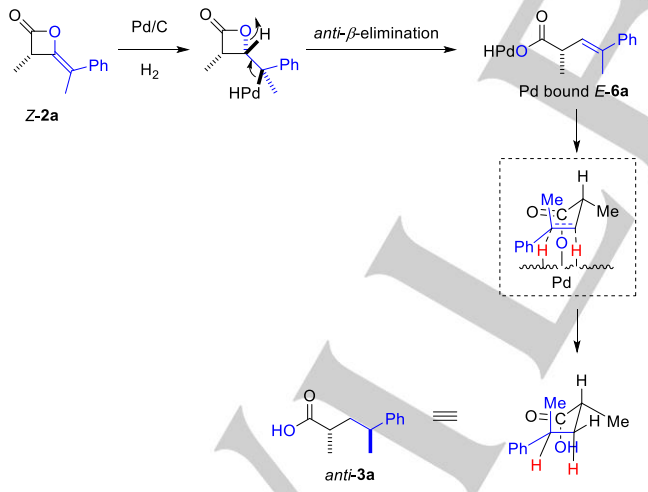
Figure 1. Hammett plot of log(dr) vs Hammett σ constants.[23]

To rationalize diastereoselectivity, we surmised that the Pd/C-catalyzed reaction involves a stereoselective *β*-elimination step, followed by a stereoselective hydrogenation of intermediate **6** (Scheme 3). Diastereoselectivity in acid formation would be established at the *β*-elimination-hydrogenation steps, with the mode of *β*-elimination (*anti* vs *syn*) being especially important. To test this proposal, we prepared the two putative olefin isomer intermediates *E*-**6a** and *Z*-**6a** as the neutral carboxylic acids and potassium carboxylates and exposed them to our standard hydrogenolysis reaction conditions (Scheme 8).[24,25] The neutral carboxylic acids were found to be unreactive under standard reaction conditions. However, it was found that the carboxylate of *E*-**6a** underwent hydrogenation to afford **3a** with a dr of 5:1, favoring the *anti*-diastereomer. On the other hand, the carboxylate of *Z*-**6a** underwent hydrogenation to afford **3a** with a dr of *ca*. 1:1. These results strongly suggest that the catalytic hydrogenolysis reaction involves a stereoselective *anti*-*β*-elimination to furnish *E*-**6a** as an intermediate, which subsequently undergoes a stereoselective hydrogenation process to access mainly *anti*-**3a** (Scheme 9). Indeed, although homogeneous palladium catalysis often involves *syn*-*β*-eliminations, there have been reports of *anti*-*β*-eliminations in molecules where a good leaving group is present.[16] As *syn*-*β*-elimination is a potentially competing process, we propose that the difference in diastereoselectivity observed in alkene hydrogenation (dr 5:1, 85:15) vs hydrogenolysis of ketene heterodimer **2a** (dr *ca*. 4:1, 78:22) is due to a competing, but minor, *syn*-*β*-elimination process, which would ultimately, after hydrogenation of *Z*-**6a**, lead to erosion of *anti*-acid selectivity.



Scheme 8. Control experiments: hydrogenation of putative olefin intermediates.

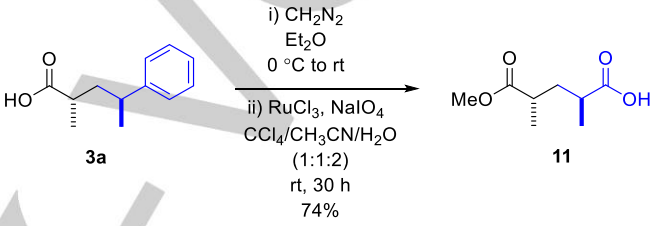
The results of our mechanistic experiments therefore point to diastereoselectivity arising out of, firstly, competing pathways for the proposed *β*-elimination step; *syn β*-elimination leading to the formation of the *Z*-isomer of olefin intermediate **6a**, while *anti β*-elimination leads to the formation of the *E*-isomer of olefin intermediate **6a** (Schemes 8 and 9). Subsequent hydrogenation of *Z*-**6a** would then afford acid **3a** as a stereorandom mixture, while hydrogenation of *E*-**6a** would afford **3a** predominately as the *anti*-diastereomer (Scheme 9). Formation of *anti*-**3a** as the major stereoisomeric product from *E*-**6a** can be explained as follows: bonding/coordination of the carboxylate group and olefin to the palladium surface, with a chair-like arrangement being adopted in the transition state, leads to the *α*-Me preferentially in a pseudoequatorial position (rather than pseudoaxial), to avoid 1,3-interactions with the (olefin) γ-Me (Scheme 9).[17]



Scheme 9. Stereoselectivity rationale.

With two distinct reaction steps (*anti- or syn β*-elimination and olefin hydrogenation) contributing to diastereoselectivity, each influenced by the nature of the substituent (electron donating or electron withdrawing group on the aryl ring of ketene heterodimer) to a differing degree, there would be no direct correlation between aryl substituent σ values and the diastereoselectivity (dr) of hydrogenolysis. This is borne out by the Hammett plot of log dr vs σ values of substituents, where the lack of a linear relationship is quite striking. What is clear is that hydrogenolysis diastereoselectivity is dependent upon which diastereomer of olefin intermediate **6** (*E* or *Z*) is produced during *β*-elimination, and upon the stereoselectivity of hydrogenation of the olefin intermediate.

Finally, the synthetic potential of the catalytic ketene heterodimerization-hydrogenolysis methodology was demonstrated by the facile conversion of enantioenriched **3a** into the corresponding 1,5-difunctionalized **11** through employment of a Ru-catalyzed oxidation procedure (Scheme 10).[26] Importantly this transformation demonstrates the potential utility of deoxypropionate derivatives (**3** and **4**) for bidirectional synthesis through availability of both carbonyl groups in **11**.



Scheme 10. Asymmetric synthesis of functionalized deoxypropionate derivative.

Conclusions

In conclusion, we report that diastereoselectivity in catalytic hydrogenolysis of ketene heterodimers may be mildly amplified in select cases through electronic tuning of ketene heterodimer substrates. Insight into the mechanism of catalytic hydrogenolysis was gained by an examination of the product distribution (acid vs *β*-lactone), where regioselectivity of hydrometallation was ascribed to be the key factor in determining whether acid formation was dominant or not. The proposed mechanism involving an *anti*-*β*-elimination to give an *E*-olefin isomer intermediate and an *anti*-selective hydrogenation of the *E*-olefin isomer intermediate, was supported by the results of a number of control experiments investigating putative intermediates of the reaction. The potential applicability of the methodology was examined by oxidative transformation into a 1,5-dicarbonyl substituted deoxypropionate building block. Future studies will involve exploration of the ketene heterodimerization-hydrogenolysis process in applications to deoxypropionate natural products.

Experimental Section

General

All reactions were carried out in flame-dried glassware under a nitrogen atmosphere using standard inert atmosphere techniques unless otherwise stated. THF was freshly distilled from a sodium benzophenone ketyl radical still under nitrogen prior to use. Hünig's base (diisopropylethylamine) and *N*,*N*-dimethylethylamine were distilled from calcium hydride under

nitrogen.[27] Dichloromethane and diethyl ether were dried by passing through activated alumina columns on a solvent purification system. *n*-Butyllithium (2.5 M in hexane), 2-phenylpropanoic acid, 4-methoxyphenylacetic acid, 4-fluorophenylacetic acid, 4-(trifluoromethyl)phenylacetic acid, 2-(4-methylphenyl)propanoic acid and 4-chloro-α-methylphenylacetic acid were purchased and used as received. Propionyl chloride was purchased and distilled prior to use.[27] Iatrobeads (neutral silica, 60μM particle size), normal silica gel (60-200 μM particle size), and TLC plates (UV254, 250μM) were used as received. Methylphenylketene, methyl 4-(trifluoromethyl)phenylketene, methyl 4-fluorophenylketene, methyl 2-fluorophenylketene, methyl 4-chlorophenylketene, methyl 4-methoxyphenylketene and methyl *p*-tolylketene were prepared according to literature procedures.[28] TMS-quinine and Me-quinidine were synthesized according to literature procedure.[29] Ketene heterodimers **2a**, **2b**, *Z*-**2o**, *E*-**2o** and **2p**, acids **3a** and **3b**, and *β*-lactone **5o** were prepared and characterized as previously described.[12-15]

NMR spectra were recorded on a 400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C). NMR chemical shifts were reported relative to TMS (0 ppm) for ^{1}H and to $CDCl_3$ (77.23 ppm) for ^{13}C spectra. High resolution mass spectra were obtained on an Accurate Mass Q-TOF LC-MS instrument (with ESI as the ionization method). Low resolution mass spectra were recorded on a GC-MS instrument equipped with a mass selective detector, and using a GC column (30 m, 0.25 mm ID). IR spectra were recorded on an IR spectrometer.

Chiral high performance liquid chromatography (chiral HPLC) was performed using an AD column (0.46 cm × 25 cm), OD-H column (0.46 cm × 25 cm), or an AS-H column (0.46 cm × 25 cm) on a HPLC instrument attached with diode array detector (deuterium lamp, 190-600 nm) with HPLC-grade isopropanol and hexanes as the eluting solvents. Chiral gas chromatography (chiral GC) was performed using a chiral B-DM column (30 m × 0.25 mm × 0.12 um) on a GC instrument. Optical rotations were measured on an automatic polarimeter in dichloromethane at 598 nm.

General procedure for ketene preparation: To an ice-cooled stirring solution of acid chloride (20 mmol) in THF (60 mL), *N*,*N*-dimethylethylamine (80 mmol) was added dropwise and stirring continued at 0 °C. After 4-5 h, the reaction mixture was filtered through a sintered funnel under nitrogen and the solvent was removed under vacuum. Finally, distillation of the crude reaction mixture under vacuum furnished the desired ketene.

General procedure for ketene heterodimerization[12,13]: Acyl chloride in dichloromethane was added over the indicated time via syringe pump to a solution of ketene, Hünig's base and alkaloid catalyst in dichloromethane at –25 °C, and stirred for the indicated time.

General procedure for catalytic hydrogenolysis[14]: The *Z*-ketene heterodimer (1 equiv) in methanol (0.1 M) was added via pasteur pipette to the pressure device containing the 10 wt% Pd/C catalyst (0.05 equiv). While the inlet to the pressure device was closed and stirring commenced, minimum vacuum was applied to remove air inside the pressure device through its outlet. Then the outlet was closed, and hydrogen was transferred to the pressure device at 50 psi. Minimum vacuum was applied again to remove hydrogen inside the pressure device through its outlet after the inlet was closed. This hydrogen flushing cycle was repeated twice to make sure that air was removed from the pressure device completely. Then, hydrogen pressure of 225 psi (15 atm) was applied under stirring (1150 rpm) and continued at room temperature for the specified time for each example.

After the specified time, the pressure device was vented, and the mixture was filtered through celite (10 g), washing with dichloromethane (50-60 mL/ 0.5 mmol). The solvent was removed under reduced pressure. Diastereomeric ratios were determined for the crude acids by GC-MS or ^{1}H NMR analysis. Then, the crude reaction mixture was treated with excess diazomethane solution in ether to convert the acid product into the corresponding non-polar ester. Evaporation of the solvent followed by regular silica gel column chromatographic purification afforded the desired ester.

Compound Characterization and Determination of Diastereomeric Ratios and Enantiomeric Excesses: *Z*:*E* ratios of ketene heterodimers **2** were determined by GC-MS analysis. Diastereomeric ratios were determined for the crude acids **3**/esters **4** by GC-MS or ^{1}H NMR analysis of the crude product. Enantiomeric excesses were determined by assaying ketene heterodimers **2** and the ester derivatives of acids **4** using chiral HPLC analysis (determined at λ = 254 or 225 nm, details given for each compound) or chiral GC analysis (details given for each compound). Racemic samples for chiral GC or HPLC analysis were generated through mixing of enantiomerically enriched samples.

Methyl *p*-tolylketene [1a][28]: Yellow, low melting solid (69%); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): *δ* 7.14-7.08 (m, 2H), 6.93-6.87 (m, 2H), 2.30 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 206.9, 133.9, 130.2, 129.8, 123.8, 33.5, 21.1, 8.9; MS (EI 70 eV): m/z 146.1.

(*S*,*Z*)-3-Methyl-4-(1-*p*-tolylethylidene)oxetan-2-one [(*S*,*Z*)-2c]: Following general procedure, propionyl chloride (0.65 mL, 7.41 mmol) in dichloromethane (2.0 mL) was added over 8 h to a solution of methyl *p*-tolylketene **1a** (542 mg, 3.70 mmol), Hünig's base (1.3 mL, 7.41 mmol) and Me-quinidine (125 mg, 0.37 mmol) in dichloromethane (10 mL) at –25 °C and stirred at this temperature for another 16 h. After 16 h the reaction was concentrated under reduced pressure to about 2 mL. The reaction was diluted with 1% EtOAc/hexane (30 mL) and passed through a plug of neutral silica (15 g), eluting with 1% EtOAc/hexane (500 mL). Removal of solvent under reduced pressure afforded **(*S*,*Z*)-2c** as a colorless oil (416 mg, 55%) with a *Z*:*E* ratio of 98:2 as determined by GC-MS analysis; R_f = 0.6 (EtOAc/hexane 1:9); HPLC analysis: 97% ee [Daicel Chiralpak OB-H column; 1 mL/min; solvent system: 2% isopropanol in hexane; retention times: 12.1 min (major), 33.1 min (minor)]; [*α*]D24 = –15.9 (c = 0.93, CH_2Cl_2); IR (thin film): 1745 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): *δ* 7.42-7.36 (m, 2H), 7.20-7.13 (m, 2H), 4.22 (q, *J* = 7.6 Hz, 1H), 2.34 (s, 3H), 1.98 (s, 3H), 1.57 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 170.1, 142.6, 137.2, 133.3, 129.2, 127.2, 108.1, 50.1, 21.3, 15.5, 12.5; $(M + H)^+$ HRMS m/z calcd for $(C_{13}H_{15}O_2)^+$: 203.1072; Found: 203.1067.

(*R*,*Z*)-3-Methyl-4-(1-*p*-tolylethylidene)oxetan-2-one [(*R*,*Z*)-2d]: Following general procedure, propionyl chloride (0.56 mL, 6.50 mmol) in dichloromethane (2.0 mL) was added over 8 h to a solution of methyl *p*-tolylketene **1a** (475 mg, 3.25 mmol), Hünig's base (1.13 mL, 6.50 mmol) and TMS-quinine (129 mg, 0.32 mmol) in dichloromethane (10.0 mL) at –25 °C and stirred at this temperature for another 16 h. After 16 h the reaction was

concentrated under reduced pressure to about 2 mL. The reaction was diluted with 1% EtOAc/hexane (30 mL) and passed through a plug of neutral silica (15 g), eluting with 1% EtOAc/hexane (500 mL). Removal of solvent under reduced pressure afforded **(*R*,*Z*)-2d** as a colorless oil (423 mg, 64%) with a *Z*:*E* ratio of 96.5:3.5 as determined by GC-MS analysis; R_f = 0.6 (EtOAc/hexane 1:9); HPLC analysis: 96% ee [Daicel Chiralpak OB-H column; 1 mL/min; solvent system: 2% isopropanol in hexane; retention times: 12.9 min (minor), 31.5 min (major)]; [*α*]D24 = 19.0 (c = 0.71, CH_2Cl_2); IR (thin film): 1747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): *δ* 7.42-7.36 (m, 2H), 7.20-7.13 (m, 2H), 4.23 (q, *J* = 7.6 Hz, 1H), 2.34 (s, 3H), 1.99 (d, *J* = 0.7 Hz, 3H), 1.58 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 170.2, 142.6, 137.2, 133.3, 129.2, 127.2, 108.2, 50.1, 21.3, 15.5, 12.6; (M + H)$^+$ HRMS m/z calcd for $(C_{13}H_{15}O_2)^+$: 203.1072; Found: 203.1066.

(2*S*,4*S*)-Methyl 2-methyl-4-*p*-tolylpentanoate [4c]: Following general procedure, the heterodimer (***S***,***Z***)-**2c** (51 mg, 0.25 mmol), of 97% ee and *Z*:*E* = 98:2, in MeOH (2.5 mL) was added to the 10 wt% Pd/C catalyst (13 mg, 0.012 mmol) (reaction time: 30 min). Crude GC-MS: acid:*β*-lactone = 85:15; Regular silica gel column purification of ester using 2% EtOAc/hexane afforded **4c** as a light yellow liquid (40 mg, 72% in two steps), dr = 69:31 (by GC-MS of crude ester); R_f = 0.5 (EtOAc/hexane 1:19); Chiral GC analysis: 98% ee [Supelco Chiraldex BDM column; GC Conditions: Split ratio: 1:20; make up flow: 25 mL/min; H_2 flow: 45 mL/min; air flow: 450 mL/min; injector temperature: 250 °C, pressure: 12.3-18.5 psi; oven temperature: 50-180 °C, 1 °C/min; detector temperature: 250 °C; retention times: 78.6 min (minor), 79.7 min (major)]; IR (thin film): 1750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS, Major isomer): *δ* 7.13-7.02 (m, 4H), 3.66 (s, 3H), 2.77-2.61 (m, 1H), 2.37-2.23 (m, 1H), 2.32 (s, 3H), 2.08-1.90 (m, 1H), 1.65-1.55 (m, 1H), 1.21 (d, *J* = 6.9 Hz, 3H), 1.09 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, Major isomer): *δ* 177.5, 144.0, 135.8, 129.3, 127.1, 51.7, 42.8, 37.9, 37.8, 22.8, 21.2, 18.1; (M + H)$^+$ HRMS m/z calcd for $(C_{14}H_{21}O_2)^+$: 221.1542; Found: 221.1535.

(2*R*,4*R*)-Methyl 2-methyl-4-*p*-tolylpentanoate [4d]: Following general procedure, the heterodimer (***R***,***Z***)-**2d** (60 mg, 0.29 mmol), of 96% ee and *Z*:*E* = 96.5:3.5, in MeOH (3.1 mL) was added to the 10 wt% Pd/C catalyst (15 mg, 0.014 mmol) (reaction time: 30 min). Crude GC-MS: acid:*β*-lactone = 89:11; Regular silica gel column purification of ester using 2% EtOAc/hexane afforded **4d** as a light yellow liquid (53 mg, 80% in two steps), dr = 70:30 (by GC-MS of crude ester); R_f = 0.5 (EtOAc/hexane 1:19); Chiral GC analysis: 96% ee [Supelco Chiraldex BDM column; GC Conditions: Split ratio: 1:20; make up flow: 25 mL/min; H_2 flow: 45 mL/min; air flow: 450 mL/min; injector temperature: 250 °C, pressure: 12.3-18.5 psi; oven temperature: 50-180 °C, 1 °C/min; detector temperature: 250 °C; retention times: 78.6 min (major), 79.3 min (minor)]; IR (thin film): 1750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS, Major isomer): *δ* 7.13-7.02 (m, 4H), 3.66 (s, 3H), 2.77-2.61 (m, 1H), 2.37-2.23 (m, 1H), 2.32 (s, 3H), 2.08-1.91 (m, 1H), 1.64-1.54 (m, 1H), 1.21 (d, *J* = 6.9 Hz, 3H), 1.09 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, Major isomer): *δ* 177.5, 143.9, 135.8, 129.3, 127.1, 51.7, 42.8, 37.9, 37.8, 22.8, 21.2, 18.1; (M + H)$^+$ HRMS m/z calcd for $(C_{14}H_{21}O_2)^+$: 221.1542; Found: 221.1537.

Methyl 4-methoxyphenylketene [1b][28]: Yellow low melting solid, purified by triturating with anhydrous pentane (62%); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): *δ* 6.97-6.85 (m, 4H), 3.77 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 208.0, 157.0, 125.0, 124.9, 114.9, 55.5, 32.8, 9.2; MS (EI 70 eV): m/z 162.1.

(*S*,*Z*)-4-(1-(4-Methoxyphenyl)ethylidene)-3-methyloxetan-2-one [(*S*,*Z*)-2e]: Following general procedure, propionyl chloride (0.65 mL, 7.39 mmol) in dichloromethane (2.0 mL) was added over 8 h to a solution of methyl 4-methoxyphenylketene **1b** (600 mg, 3.69 mmol), Hünig's base (1.28 mL, 7.39 mmol) and Me-quinidine (125 mg, 0.37 mmol) in dichloromethane (10.0 mL) at –25 °C and stirred at this temperature for another 16 h. After 16 h the reaction was concentrated under reduced pressure to about 2 mL. The reaction was diluted with 1% EtOAc/hexane (30 mL) and passed through a plug of neutral silica (15 g), eluting with 1% EtOAc/hexane (700 mL). Removal of solvent under reduced pressure afforded **(*S*,*Z*)-2e** as a sticky solid (95 mg, 14%) with a *Z*:*E* ratio of 95:5 as determined by GC-MS analysis; R_f = 0.5 (EtOAc/hexane 1:9); HPLC analysis: 98% ee [Daicel Chiralpak AD-H column; 1 mL/min; solvent system: 1% isopropanol in hexane; retention times: 12.2 min (minor), 12.9 min (major)]; [*α*]D24 = –14.0 (c = 0.6, CH_2Cl_2); IR (thin film): 1698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): *δ* 7.48-7.41 (m, 2H), 6.93-6.86 (m, 2H), 4.23 (q, *J* = 7.6 Hz, 1H), 3.82 (s, 3H), 1.98 (s, 3H), 1.58 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 170.2, 159.0, 142.1, 128.8, 128.5, 114.0, 107.8, 55.5, 50.1, 15.6, 12.6; (M + H)$^+$ HRMS m/z calcd for $(C_{13}H_{15}O_3)^+$: 219.1021; Found: 219.1013.

(*R*,*Z*)-4-(1-(4-Methoxyphenyl)ethylidene)-3-methyloxetan-2-one [(*R*,*Z*)-2f]: Following general procedure, propionyl chloride (0.65 mL, 7.39 mmol) in dichloromethane (2.0 mL) was added over 8 h to a solution of methyl 4-methoxyphenylketene **1b** (600 mg, 3.69 mmol), Hünig's base (1.28 mL, 7.39 mmol) and TMS-quinine (146 mg, 0.36 mmol) in dichloromethane (10.0 mL) at –25 °C and stirred at this temperature for another 16 h. After 16 h the reaction was concentrated under reduced pressure to about 2 mL. The reaction was diluted with 1% EtOAc/hexane (30 mL) and passed through a plug of neutral silica (15 g), eluting with 1% EtOAc/hexane (700 mL). Removal of solvent under reduced pressure afforded **(*R*,*Z*)-2f** as a sticky solid (138 mg, 17%) with a *Z*:*E* ratio of 93:7 as determined by GC-MS analysis; R_f = 0.5 (EtOAc/hexanes 1:9); HPLC analysis: 95% ee [Daicel Chiralpak AD-H column; 1 mL/min; solvent system: 1% isopropanol in hexane; retention times: 12.2 min (major), 13.0 min (minor)]; [*α*]D24 = 18.6 (c = 0.72, CH_2Cl_2); IR (thin film): 1701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): *δ* 7.48-7.41 (m, 2H), 6.93-6.85 (m, 2H), 4.23 (q, *J* = 7.6 Hz, 1H), 3.82 (s, 3H), 1.97 (s, 3H), 1.57 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 170.2, 158.9, 142.0, 128.8, 128.5, 114.0, 107.8, 55.5, 50.1, 15.6, 12.6; (M + H)$^+$ HRMS m/z calcd for $(C_{13}H_{15}O_3)^+$: 219.1021; Found: 219.1017.

(2*S*,4*S*)-Methyl 4-(4-methoxyphenyl)-2-methylpentanoate [4e]: Following general procedure, the heterodimer (***S***,***Z***)-**2e** (60 mg, 0.27 mmol), of 98% ee and *Z*:*E* = 95:5, in MeOH (3 mL) was added to the 10 wt% Pd/C catalyst (15 mg, 0.013 mmol) (reaction time:3h). Crude GC-MS: acid:*β*-lactone = 98:2; Regular silica gel column purification of ester using 2% EtOAc/hexane afforded **4e** as a light yellow liquid (39 mg, 60% in two steps), dr = 69:31 (by GC-MS of crude ester); R_f = 0.4 (EtOAc/hexane 1:19); Chiral GC analysis: 98% ee [Supelco Chiraldex BDM column; GC Conditions: Split ratio: 1:20; make up flow: 25 mL/min; H_2 flow: 45 mL/min; air flow: 450 mL/min; injector temperature: 250 °C, pressure: 12.3-18.5 psi; oven temperature: 50-180 °C, 1 °C/min; detector temperature: 250 °C; retention

times: 96.7 min (minor), 97.4 min (major)]; IR (thin film): 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS, Major isomer): δ 7.12-7.04 (m, 2H), 6.87-6.80 (m, 2H), 3.78 (s, 3H), 3.66 (s, 3H), 2.76-2.60 (m, 1H), 2.36-2.24 (m, 1H), 2.06-1.90 (m, 1H), 1.65-1.51 (m, 1H), 1.20 (d, J = 6.9 Hz, 3H), 1.09 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, Major isomer): δ 177.5, 158.2, 139.0, 128.1, 114.1, 55.5, 51.6, 43.0, 37.9, 37.4, 22.9, 18.1; $(M + H)^+$ HRMS m/z calcd for $(C_{14}H_{21}O_3)^+$: 237.1491; Found: 237.1482.

(2*R*,4*R*)-Methyl 4-(4-methoxyphenyl)-2-methylpentanoate [4f]: Following general procedure, the heterodimer (***R*,*Z***)-**2f** (49 mg, 0.22 mmol), of 95% ee and *Z*:*E* = 93:7, in MeOH (3.0 mL) was added to the 10 wt% Pd/C catalyst (12 mg, 0.011 mmol) (reaction time: 3 h). Regular silica gel column purification of ester using 2% EtOAc/hexane afforded **4f** as a light yellow liquid (34 mg, 64% in two steps), dr = 73:27 (by GC-MS of crude ester); R_f = 0.4 (EtOAc/hexane 1:19); Chiral GC analysis: 99% ee [Supelco Chiraldex BDM column; GC Conditions: Split ratio: 1:20; make up flow: 25 mL/min; H_2 flow: 45 mL/min; air flow: 450 mL/min; injector temperature: 250 °C, pressure: 12.3-18.5 psi ; oven temperature: 50-180 °C, 1 °C/min; detector temperature: 250 °C; retention times: 97.1 min (major), 97.2 min (minor)]; IR (thin film): 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS, Major isomer): δ 7.12-7.04 (m, 2H), 6.87-6.80 (m, 2H), 3.78 (s, 3H), 3.66 (s, 3H), 2.75-2.60 (m, 1H), 2.36-2.23 (m, 1H), 2.06-1.90 (m, 1H), 1.65-1.51 (m, 1H), 1.20 (d, J = 6.9 Hz, 3H), 1.09 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, Major isomer): δ 177.5, 158.2, 139.0, 128.1, 114.1, 55.4, 51.6, 43.0, 37.9, 37.4, 22.9, 18.1; $(M + H)^+$ HRMS m/z calcd for $(C_{14}H_{21}O_3)^+$: 237.1491; Found: 237.1483.

Methyl 4-chlorophenylketene [1c][28]: Yellow oil (64%); ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 7.29-7.23 (m, 2H), 6.95-6.88 (m, 2H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.9, 132.2, 129.8, 129.2, 125.0, 33.7, 8.9; MS (EI 70 eV): m/z 166.0.

(*S*,*Z*)-4-(1-(4-Chlorophenyl)ethylidene)-3-methyloxetan-2-one [(*S*,*Z*)-2g]: Following general procedure, propionyl chloride (0.65 mL, 7.35 mmol) in dichloromethane (2.0 mL) was added over 8 h to a solution of methyl 4-chlorophenylketene **1c** (612 mg, 3.68 mmol), Hünig's base (1.28 mL, 7.35 mmol) and Me-quinidine (124 mg, 0.37 mmol) in dichloromethane (10.0 mL) at –25 °C and stirred at this temperature for another 16 h. After 16 h the reaction was concentrated under reduced pressure to about 2 mL. The reaction was diluted with 1% EtOAc/hexane (30 mL) and passed through a plug of neutral silica (15 g), eluting with 1% EtOAc/hexane (500 mL). Removal of solvent under reduced pressure afforded **(*S*,*Z*)-2g** as a low melting white solid (461 mg, 56%) with a *Z*:*E* ratio of 98:2 as determined by GC-MS analysis; R_f = 0.6 (EtOAc/hexane 1:9); HPLC analysis: 82% ee [Daicel Chiralpak OB-H column; 1 mL/min; solvent system: 2% isopropanol in hexane; retention times: 11.6 min (major), 16.0 min (minor)]; [α]D24 = –13.2 (c = 1.02, CH_2Cl_2); IR (thin film): 1701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 7.46-7.40 (m, 2H), 7.35-7.29 (m, 2H), 4.25 (q, J = 7.6 Hz, 1H), 1.98 (s, 3H), 1.58 (d, J = 7.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 143.8, 134.7, 133.2, 128.7, 128.6, 107.2, 50.4, 15.4, 12.5; $(M + H)^+$ HRMS m/z calcd for $(C_{12}H_{12}ClO_2)^+$: 223.0526; Found: 223.0521.

(*R*,*Z*)-4-(1-(4-Chlorophenyl)ethylidene)-3-methyloxetan-2-one [(*R*,*Z*)-2h]: Following general procedure, propionyl chloride (0.65 mL, 7.35 mmol) in dichloromethane (2.0 mL) was added over 8 h to a solution of methyl 4-chlorophenylketene **1c** (612 mg, 3.68 mmol), Hünig's base (1.28 mL, 7.35 mmol) and TMS-quinine (146 mg, 0.36 mmol) in dichloromethane (10.0 mL) at –25 °C and stirred at this temperature for another 16 h. After 16 h the reaction was concentrated under reduced pressure to about 2 mL. The reaction was diluted with 1% EtOAc/hexane (30 mL) and passed through a plug of neutral silica (15 g), eluting with 1% EtOAc/hexane (500 mL). Removal of solvent under reduced pressure afforded **(*R*,*Z*)-2h** as a low melting white solid (467 mg, 57%) with a *Z*:*E* ratio of 98:2 as determined by GC-MS analysis; R_f = 0.6 (EtOAc/hexane 1:9); HPLC analysis: 90% ee [Daicel Chiralpak OB-H column; 1 mL/min; solvent system: 2% isopropanol in hexane; retention times: 12.1 min (minor), 15.1 min (major)]; [α]D24 = 16.7 (c = 1.04, CH_2Cl_2); IR (thin film): 1700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS): δ 7.47-7.39 (m, 2H), 7.35-7.28 (m, 2H), 4.24 (q, J = 7.6 Hz, 1H), 1.98 (s, 3H), 1.58 (d, J = 7.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 143.7, 134.7, 133.1, 128.7, 128.6, 107.2, 50.3, 15.4, 12.4; $(M + H)^+$ HRMS m/z calcd for $(C_{12}H_{12}ClO_2)^+$: 223.0526; Found: 223.0522.

(2*S*,4*S*)-Methyl 4-(4-chlorophenyl)-2-methylpentanoate [4g]: Following general procedure, the heterodimer (***S*,*Z***)-**2g** (81 mg, 0.36 mmol), of 82% ee and *Z*:*E* = 98:2, in MeOH (5 mL) was added to the 10 wt% Pd/C catalyst (19 mg, 0.018 mmol) (reaction time: 10 min). Crude GC-MS: acid:β-lactone = 93:7; Regular silica gel column purification of ester using 2% EtOAc/hexane afforded **4g** as a light yellow liquid (63 mg, 72% in two steps), dr = 66:34 (by GC-MS of crude ester); R_f = 0.5 (EtOAc/hexane 1:19); Chiral GC analysis: 91% ee [Supelco Chiraldex BDM column; GC Conditions: Split ratio: 1:20; make up flow: 25 mL/min; H_2 flow: 45 mL/min; air flow: 450 mL/min; injector temperature: 250 °C, pressure: 12.3-18.5 psi; oven temperature: 50-180 °C, 1 °C/min; detector temperature: 250 °C; retention times: 91.2 min (minor), 91.6 min (major)]; IR (thin film): 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS, Major isomer): δ 7.30-7.23 (m, 2H), 7.14-7.06 (m, 2H), 3.66 (s, 3H), 2.79-2.64 (m, 1H), 2.35-2.20 (m, 1H), 2.10-1.91 (m, 1H), 1.67-1.52 (m, 1H), 1.21 (d, J = 6.9 Hz, 3H), 1.09 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, Major isomer): δ 177.2, 145.3, 128.8, 128.6, 127.3, 51.7, 42.6, 37.8, 37.7, 22.7, 18.1; $(M + H)^+$ HRMS m/z calcd for $(C_{13}H_{18}ClO_2)^+$: 241.0995; Found: 241.0991.

(2*R*,4*R*)-Methyl 4-(4-chlorophenyl)-2-methylpentanoate [4h]: Following general procedure, the heterodimer (***R*,*Z***)-**2h** (77 mg, 0.34 mmol), of 90% ee and *Z*:*E* = 98:2, in MeOH (3.5 mL) was added to the 10 wt% Pd/C catalyst (18 mg, 0.017 mmol) (reaction time: 10 min). Crude GC-MS: acid:β-lactone = 90:10; Regular silica gel column purification of ester using 2% EtOAc/hexane afforded **4h** as a light yellow liquid (55 mg, 66% in two steps), dr = 65:35 (by GC-MS of crude ester); R_f = 0.5 (EtOAc/hexanes 1:19); Chiral GC analysis: 99% ee [Supelco Chiraldex BDM column; GC Conditions: Split ratio: 1:20; make up flow: 25 mL/min; H_2 flow: 45 mL/min; air flow: 450 mL/min; injector temperature: 250 °C, pressure: 12.3-18.5 psi; oven temperature: 50-180 °C, 1 °C/min; detector temperature: 250 °C; retention times: 91.2 min (major), 91.7 min (minor)]; IR (thin film): 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS, Major isomer): δ 7.30-7.23 (m, 2H), 7.14-7.06 (m, 2H), 3.66 (s, 3H), 2.79-2.64 (m, 1H), 2.37-2.20 (m, 1H), 2.10-1.91 (m, 1H), 1.67-1.53 (m, 1H), 1.21 (d, J = 6.9 Hz, 3H), 1.09 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, Major isomer): δ 177.2, 145.3, 128.8, 128.6, 127.2, 51.7, 42.6, 37.8, 37.7, 22.7, 18.1; $(M + H)^+$ HRMS m/z calcd for $(C_{13}H_{18}ClO_2)^+$: 241.0995; Found: 241.0992.

Methyl 4-fluorophenylketene [1d]: Yellow oil (71%); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.04-6.90 (m, 4H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 206.0, 160.3 (d, J = 243 Hz), 129.1 (d, J = 3 Hz), 125.1 (d, J = 8 Hz), 116.1 (d, J = 22 Hz), 33.2, 9.1; MS (EI 70 eV): m/z 150.0.

(*S*,*Z*)-4-(1-(4-Fluorophenyl)ethylidene)-3-methyloxetan-2-one [(*S*,*Z*)-2i]: Following general procedure, propionyl chloride (0.65 mL, 7.39 mmol) in dichloromethane (1.0 mL) was added over 8 h to a solution of methyl 4-fluorophenylketene **1d** (555 mg, 3.69 mmol), Hünig's base (1.28 mL, 7.39 mmol) and Me-quinidine (125 mg, 0.37 mmol) in dichloromethane (11.0 mL) at –25 °C and stirred at this temperature for another 16 h. After 16 h the reaction was concentrated under reduced pressure to about 2 mL. The reaction was diluted with 1% EtOAc/hexane (30 mL) and passed through a plug of neutral silica (15 g), eluting with 1% EtOAc/hexane (500 mL). Removal of solvent under reduced pressure afforded **(*S*,*Z*)-2i** as a colorless oil (408 mg, 54%) with a *Z*:*E* ratio of 98:2 as determined by GC-MS analysis; R_f = 0.6 (EtOAc/hexane 1:9); HPLC analysis: 91% ee [Daicel Chiralpak OB-H column; 1 mL/min; solvent system: 2% isopropanol in hexane; retention times: 11.9 min (major), 16.7 min (minor)]; [α]D24 = –24.2 (c = 0.67, CH_2Cl_2); IR (thin film): 1704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.50-7.44 (m, 2H), 7.08-7.00 (m, 2H), 4.25 (q, J = 7.6 Hz, 1H), 1.99 (d, J = 0.8 Hz, 3H), 1.58 (d, J = 7.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 162.0 (d, J = 247 Hz), 143.0, 132.3, 129.0 (d, J = 8 Hz), 115.4 (d, J = 21 Hz), 107.3, 50.2, 15.6, 12.5; (M + H)$^+$ HRMS m/z calcd for $(C_{12}H_{12}FO_2)^+$: 207.0821; Found: 207.0816.

(*R*,*Z*)-4-(1-(4-Fluorophenyl)ethylidene)-3-methyloxetan-2-one [(*R*,*Z*)-2j]: Following general procedure, propionyl chloride (0.76 mL, 8.68 mmol) in dichloromethane (1.0 mL) was added over 8 h to a solution of methyl 4-fluorophenylketene **1d** (652 mg, 4.34 mmol), Hünig's base (1.51 mL, 8.68 mmol) and TMS-quinine (172 mg, 0.43 mmol) in dichloromethane (11.0 mL) at –25 °C and stirred at this temperature for another 16 h. After 16 h the reaction was concentrated under reduced pressure to about 2 mL. The reaction was diluted with 1% EtOAc/hexane (30 mL) and passed through a plug of neutral silica (15 g), eluting with 1% EtOAc/hexane (500 mL). Removal of solvent under reduced pressure afforded **(*R*,*Z*)-2j** as a colorless oil (517 mg, 58%) with a *Z*:*E* ratio of 95:5 as determined by GC-MS analysis; R_f = 0.6 (EtOAc/hexane 1:9); HPLC analysis: 88% ee [Daicel Chiralpak OB-H column; 1 mL/min; solvent system: 2% isopropanol in hexane; retention times: 12.2 min (minor), 15.8 min (major)]; [α]D24 = 23.7 (c = 0.84, CH_2Cl_2); IR (thin film): 1705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.50-7.44 (m, 2H), 7.08-7.00 (m, 2H), 4.24 (q, J = 7.5 Hz, 1H), 1.98 (d, J = 0.7 Hz, 3H), 1.58 (d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 162.0 (d, J = 247 Hz), 143.0, 132.3, 129.0 (d, J = 8 Hz), 115.4 (d, J = 21 Hz), 107.3, 50.2, 15.6, 12.5; (M + H)$^+$ HRMS m/z calcd for $(C_{12}H_{12}FO_2)^+$: 207.0821; Found: 207.0814.

(2*S*,4*S*)-Methyl 4-(4-fluorophenyl)-2-methylpentanoate [4i]: Following general procedure, the heterodimer (***S***,***Z***)-**2i** (106 mg, 0.52 mmol), of 91% ee and *Z*:*E* = 98:2, in MeOH (5 mL) was added to the 10 wt% Pd/C catalyst (28 mg, 0.026 mmol) (reaction time: 30 min). Crude GC-MS: acid:β-lactone = 74:26; Regular silica gel column purification of ester using 2% EtOAc/hexane afforded **4i** as a light yellow liquid (52 mg, 45% in two steps), dr = 84:16 (by GC-MS of crude ester); R_f = 0.5 (EtOAc/hexanes 1:19); Chiral GC analysis: 93% ee [Supelco Chiraldex BDM column; GC Conditions: Split ratio: 1:20; make up flow: 25 mL/min; H_2 flow: 45 mL/min; air flow: 450 mL/min; injector temperature: 250 °C, pressure: 12.3-18.5 psi; oven temperature: 50-180 °C, 1 °C/min; detector temperature: 250 °C; retention times: 69.5 min (minor), 69.9 min (major)]; IR (thin film): 1733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS, Major isomer): δ 7.15-7.08 (m, 2H), 7.01-6.93 (m, 2H), 3.66 (s, 3H), 2.79-2.65 (m, 1H), 2.35-2.21 (m, 1H), 2.04-1.91 (m, 1H), 1.64-1.52 (m, 1H), 1.21 (d, J = 6.9 Hz, 3H), 1.09 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, Major isomer): δ 177.4, 161.5 (d, J = 244 Hz), 142.5 (d, J = 3 Hz), 128.6 (d, J = 8 Hz), 115.3 (d, J = 21 Hz), 51.7, 42.8, 37.8, 37.5, 22.9, 18.1; (M + H)$^+$ HRMS m/z calcd for $(C_{13}H_{18}FO_2)^+$: 225.1291; Found: 225.1284.

(2*R*,4*R*)-Methyl 4-(4-fluorophenyl)-2-methylpentanoate [4j]: Following general procedure, the heterodimer (***R***,***Z***)-**2j** (61 mg, 0.29 mmol), of 88% ee and *Z*:*E* = 95:5, in MeOH (3 mL) was added to the 10 wt% Pd/C catalyst (16 mg, 0.015 mmol) (reaction time: 30 min). Crude GC-MS: acid:β-lactone = 80:20; Regular silica gel column purification of ester using 2% EtOAc/hexane afforded **4j** as a light yellow liquid (31 mg, 47% in two steps), dr = 86:14 (by crude GC-MS of crude acid); R_f = 0.5 (EtOAc/hexane 1:19); Chiral GC analysis: 96% ee [Supelco Chiraldex BDM column; GC Conditions: Split ratio: 1:20; make up flow: 25 mL/min; H_2 flow: 45 mL/min; air flow: 450 mL/min; injector temperature: 250 °C, pressure: 12.3-18.5 psi; oven temperature: 50-180 °C, 1 °C/min; detector temperature: 250 °C; retention times: 69.6 min (major), 70.0 min (minor)]; IR (thin film): 1733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS, Major isomer): δ 7.16-7.07 (m, 2H), 7.01-6.93 (m, 2H), 3.66 (s, 3H), 2.79-2.64 (m, 1H), 2.35-2.21 (m, 1H), 2.05-1.91 (m, 1H), 1.64-1.52 (m, 1H), 1.21 (d, J = 6.9 Hz, 3H), 1.09 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, Major isomer): δ 177.4, 161.5 (d, J = 244 Hz), 142.5 (d, J = 3 Hz), 128.6 (d, J = 8 Hz), 115.3 (d, J = 21 Hz), 51.7, 42.8, 37.8, 37.5, 22.9, 18.1; (M + H)$^+$ HRMS m/z calcd for $(C_{13}H_{18}FO_2)^+$: 225.1291; Found: 225.1285.

Methyl 4-(trifluoromethyl)phenylketene [1e]: Yellow oil (60%); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.54 (d, J = 8.2 Hz, 2H), 7.08 (d, J = 8.2 Hz, 2H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.7, 138.4,128.1 (d, J = 8.0 Hz), 126.0 (q, J = 3 Hz), 124.8 (d, J = 326 Hz), 123.6, 34.6, 8.7; MS (EI 70 eV): m/z 200.0.

(*S*,*Z*)-4-(1-(4-(Trifluoromethyl)phenyl)ethylidene)-3-methyloxetan-2-one [(*S*,*Z*)-2k]: Following general procedure, propionyl chloride (0.49 mL, 5.60 mmol) in dichloromethane (1.0 mL) was added over 8 h to a solution of methyl 4-(trifluoromethyl)phenylketene **1e** (560 mg, 2.8 mmol), Hünig's base (0.98 mL, 5.6 mmol) and Me-quinidine (95 mg, 0.28 mmol) in dichloromethane (11.0 mL) at –25 °C and stirred at this temperature for another 16 h. After 16 h the reaction was concentrated under reduced pressure to about 2 mL. The reaction was diluted with 1% EtOAc/hexane (30 mL) and passed through a plug of neutral silica (15 g), eluting with 1% EtOAc/hexane (500 mL). Removal of solvent under reduced pressure afforded **(*S*,*Z*)-2k** as a colorless oil (510 mg, 71%) with a *Z*:*E* ratio of 99:1 as determined by GC-MS analysis; R_f = 0.6 (EtOAc/hexane 1:9); HPLC analysis: 90% ee [Daicel Chiralpak OB-H column; 1 mL/min; solvent system: 2% isopropanol in hexane; retention times: 7.8 min (major), 10.2 min (minor)]; [α]D24 = –16.3 (c = 0.93, CH_2Cl_2); IR (thin film): 1701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ 7.60 (bs, 4H), 4.29 (q, J = 7.7 Hz, 1H), 2.03 (d, J = 0.7 Hz, 3H), 1.60 (d, J = 7.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 145.0, 139.9, 129.3 (q, J = 32 Hz), 127.6, 125.4 (q, J = 4 Hz), 124.4 (d, J = 272 Hz), 107.1,

50.6, 15.4, 12.4; (M + H)$^+$ HRMS m/z calcd for ($C_{13}H_{12}F_3O_2$)$^+$: 257.0789; Found: 257.0783.

(*R*,*Z*)-4-(1-(4-(Trifluoromethyl)phenyl)ethylidene)-3-methyloxetan-2-one [(*R*,*Z*)-2l]: Following general procedure, propionyl chloride (0.49 mL, 5.60 mmol) in dichloromethane (1.0 mL) was added over 8 h to a solution of methyl 4-(trifluoromethyl)phenylketene **1e** (560 mg, 2.8 mmol), Hünig's base (0.98 mL, 5.6 mmol) and TMS-quinine (111 mg, 0.28 mmol) in dichloromethane (11.0 mL) at –25 °C and stirred at this temperature for another 16 h. After 16 h the reaction was concentrated under reduced pressure to about 2 mL. The reaction was diluted with 1% EtOAc/hexane (30 mL) and passed through a plug of neutral silica (15 g), eluting with 1% EtOAc/hexane (500 mL). Removal of solvent under reduced pressure afforded **(*R*,*Z*)-2l** as a colorless oil (428 mg, 60%) with a *Z*:*E* ratio of 99:1 as determined by GC-MS analysis; R_f = 0.6 (EtOAc/hexane 1:9); HPLC analysis: 82% ee [Daicel Chiralpak OB-H column; 1 mL/min; solvent system: 2% isopropanol in hexane; retention times: 7.9 min (minor), 9.4 min (major)]; [*α*]D24 = 15.9 (c = 0.99, CH_2Cl_2); IR (thin film): 1702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): *δ* 7.60 (s, 4H), 4.29 (q, *J* = 7.7, 1H), 2.02 (d, *J* = 0.7, 3H), 1.60 (d, *J* = 7.6, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 169.2, 145.0, 139.9, 129.2 (q, *J* = 32 Hz), 127.6, 125.4 (q, *J* = 4 Hz), 124.4 (d, *J* = 272 Hz), 107.1, 50.6, 15.3, 12.4; (M + H)$^+$ HRMS m/z calcd for ($C_{13}H_{12}F_3O_2$)$^+$: 257.0789; Found: 257.0785.

(2*S*,4*S*)-Methyl 4-(4-(trifluoromethyl)phenyl)-2-methylpentanoate [4k]: Following general procedure, the heterodimer (***S***,***Z***)-**2k** (77 mg, 0.30 mmol), of 90% ee and *Z*:*E* = 99:1, in MeOH (3 mL) was added to the 10 wt% Pd/C catalyst (16 mg, 0.015 mmol) (reaction time: 30 min). Crude GC-MS: acid:*β*-lactone = 77:23; Regular silica gel column purification of ester using 2% EtOAc/hexane afforded **4k** as a light yellow liquid (43 mg, 53% in two steps), dr = 79:21 (by GC-MS of crude ester); R_f = 0.5 (EtOAc/hexane 1:19); Chiral GC analysis: 94% ee [Supelco Chiraldex BDM column; GC Conditions: Split ratio: 1:20; make up flow: 25 mL/min; H_2 flow: 45 mL/min; air flow: 450 mL/min; injector temperature: 250 °C, pressure: 12.3-18.5 psi; oven temperature: 50-180 °C, 1 °C/min; detector temperature: 250 °C; retention times: 71.3 min (minor), 72.2 min (major)]; IR (thin film): 1734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS, Major isomer): *δ* 7.60-7.51 (m, 2H), 7.32-7.24 (m, 2H), 3.66 (s, 3H), 2.87-2.74 (m, 1H), 2.36-2.21 (m, 1H), 2.07-1.96 (m, 1H), 1.69-1.57 (m, 1H), 1.25 (d, *J* = 6.9 Hz, 3H), 1.11 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, Major isomer): *δ* 177.1, 151.0, 128.8 (q, *J* = 32 Hz), 127.6, 125.6 (q, *J* = 4 Hz), 124.5 (d, *J* = 272 Hz), 51.7, 42.5, 38.2, 37.8, 22.5, 18.1; (M + H)$^+$ HRMS m/z calcd for ($C_{14}H_{18}F_3O_2$)$^+$: 275.1259; Found: 275.1253.

(2*R*,4*R*)-Methyl 4-(4-(trifluoromethyl)phenyl)-2-methylpentanoate [4l]: Following general procedure, the heterodimer (***R***,***Z***)-**2l** (77 mg, 0.30 mmol), of 82% ee and *Z*:*E* = 99:1, in MeOH (3 mL) was added to the 10 wt% Pd/C catalyst (16 mg, 0.015 mmol) (reaction time: 30 min). Crude GC-MS: acid:*β*-lactone = 76:24; Regular silica gel column purification of ester using 2% EtOAc/hexane afforded **4l** as a light yellow liquid (43 mg, 53% in two steps), dr = 78:22 (by GC-MS of crude ester); R_f = 0.5 (EtOAc/hexane 1:19); Chiral GC analysis: 87% ee [Supelco Chiraldex BDM column; GC Conditions: Split ratio: 1:20; make up flow: 25 mL/min; H_2 flow: 45 mL/min; air flow: 450 mL/min; injector temperature: 250 °C, pressure: 12.3-18.5 psi; oven temperature: 50-180 °C, 1 °C/min; detector temperature: 250 °C; retention times: 71.2 min (major), 72.5 min (minor)]; IR (thin film): 1734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS, Major isomer): *δ* 7.60-7.51 (m, 2H), 7.32-7.24 (m, 2H), 3.66 (s, 3H), 2.88-2.74 (m, 1H), 2.36-2.20 (m, 1H), 2.07-1.96 (m, 1H), 1.69-1.57 (m, 1H), 1.25 (d, *J* = 7.0 Hz, 3H), 1.11 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, Major isomer): *δ* 177.1, 151.0, 128.8 (q, *J* = 32 Hz), 127.6, 125.6 (q, *J* = 4 Hz), 124.5 (d, *J* = 272 Hz), 51.7, 42.5, 38.2, 37.8, 22.5, 18.1; (M + H)$^+$ HRMS m/z calcd for ($C_{14}H_{18}F_3O_2$)$^+$: 275.1259; Found: 275.1256.

Methyl 2-fluorophenylketene [1f]: Yellow oil (86%); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): *δ* 7.13-7.07 (m, 1H), 7.06-6.87 (m, 3H), 1.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 200.4, 158.5 (d, *J* = 244 Hz), 125.1 (d, *J* = 8 Hz), 124.9 (d, *J* = 3 Hz), 124.1 (d, *J* = 3 Hz), 122.6 (d, *J* = 15 Hz), 114.5 (d, *J* = 21 Hz), 28.2, 9.4; MS (EI 70 eV): m/z 150.1.

(*S*,*Z*)-4-(1-(2-Fluorophenyl)ethylidene)-3-methyloxetan-2-one [(*S*,*Z*)-2m]: Following general procedure, propionyl chloride (0.71 mL, 8.11 mmol) in dichloromethane (1.0 mL) was added over 8 h to a solution of methyl 2-fluorophenylketene **1f** (609 mg, 4.05 mmol), Hünig's base (1.41 mL, 8.11 mmol) and Me-quinidine (137 mg, 0.41 mmol) in dichloromethane (12.0 mL) at –25 °C and stirred at this temperature for another 16 h. After 16 h the reaction was concentrated under reduced pressure to about 2 mL. The reaction was diluted with 1% EtOAc/hexane (30 mL) and passed through a plug of neutral silica (15 g), eluting with 1% EtOAc/hexane (500 mL). Removal of solvent under reduced pressure afforded **(*S*,*Z*)-2m** as a colorless oil (379 mg, 45%) with a *Z*:*E* ratio of 54:46 as determined by GC-MS analysis; R_f = 0.5 (EtOAc/hexane 1:9); HPLC analysis: 98% ee (*Z*-isomer), 98% ee (*E*-isomer), [Daicel Chiralpak AS-H column; 1 mL/min; solvent system: 1% isopropanol in hexane; retention times: 5.5 min (major *E*), 6.8 min (minor *E*), 9.6 min (minor *Z*), 11.2 min (major *Z*)]; IR (thin film): 1718 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS, ~1:1 mixture of diastereomers): *δ* 7.34-7.20 (m, 4H), 7.17-7.02 (m, 4H), 4.20 (q, *J* = 7.6 Hz, 1H), 4.12 (q, *J* = 7.6 Hz, 1H), 2.06 (s, 3H), 2.00 (s, 3H), 1.59 (d, *J* = 7.6 Hz, 3H), 1.13 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ~1:1 mixture of diastereomers): *δ* 169.8, 169.4, 161.2, 161.2, 158.8, 158.7, 145.6, 143.9, 130.7, 130.6, 130.2, 130.1, 129.5, 129.5, 129.4, 129.4, 124.5, 124.4, 124.1, 124.1, 116.2, 116.0, 105.5, 105.0, 49.3, 49.3, 49.1, 16.4, 16.3, 15.6, 15.6, 12.3, 11.5; (M + H)$^+$ HRMS m/z calcd for ($C_{12}H_{12}FO_2$)$^+$: 207.0821; Found: 207.0815.

(*R*,*Z*)-4-(1-(2-Fluorophenyl)ethylidene)-3-methyloxetan-2-one [(*R*,*Z*)-2n]: Following general procedure, propionyl chloride (0.71 mL, 8.11 mmol) in dichloromethane (1.0 mL) was added over 8 h to a solution of methyl 2-fluorophenylketene (609 mg, 4.05 mmol), Hünig's base (1.41 mL, 8.11 mmol) and TMS-quinine (161 mg, 0.41 mmol) in dichloromethane (12.0 mL) at –25 °C and stirred at this temperature for another 16 h. After 16 h the reaction was concentrated under reduced pressure to about 2 mL. The reaction was diluted with 1% EtOAc/hexane (30 mL) and passed through a plug of neutral silica (15 g), eluting with 1% EtOAc/hexane (500 mL). Removal of solvent under reduced pressure afforded **(*R*,*Z*)-2n** as a colorless oil (92 mg, 11%) with a *Z*:*E* ratio of 48:52 as determined by GC-MS analysis; R_f = 0.5 (EtOAc/hexane 1:9); HPLC analysis: 93% ee (*Z*-isomer), 96% ee (*E*-isomer), [Daicel Chiralpak AS-H column; 1 mL/min; solvent system: 1% isopropanol in hexane; retention times: 5.5 min (minor *E*), 6.7 min (major *E*), 9.3 min (major *Z*), 11.3 min (minor *Z*)]; IR (thin film): 1720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$,

TMS, ~1:1 mixture of diastereomers): δ 7.34-7.20 (m, 4H), 7.17-7.02 (m, 4H), 4.20 (q, J = 7.6 Hz, 1H), 4.12 (q, J = 7.6 Hz, 1H), 2.06 (s, 3H), 2.00 (s, 3H), 1.59 (d, J = 7.6 Hz, 3H), 1.13 (d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ~1:1 mixture of diastereomers): δ 169.8, 169.4, 161.3, 161.2, 158.8, 158.8, 145.8, 144.0, 130.7, 130.6, 130.2, 130.1, 129.6, 129.5, 129.5, 129.4, 124.5, 124.4, 124.2, 124.1, 116.3, 116.0, 105.5, 105.0, 49.4, 49.3, 49.1, 16.4, 16.4, 15.7, 15.6, 12.3, 11.5; $(M + H)^+$ HRMS m/z calcd for $(C_{12}H_{12}FO_2)^+$: 207.0821; Found: 207.0813.

(2*S*,4*S*)-Methyl 4-(2-fluorophenyl)-2-methylpentanoate [4m]: Following general procedure, the heterodimer (***S***,***Z***)-**2m** (78 mg, 0.38 mmol), of 98% ee (*Z*-isomer), 98% ee (*E*-isomer) and *Z*:*E* = 54:46, in MeOH (4 mL) was added to the 10 wt% Pd/C catalyst (20 mg, 0.019 mmol) (reaction time: 30 min). Regular silica gel column purification of ester using 2% EtOAc/hexane afforded **4m** as a light yellow liquid (42 mg, 50% in two steps), dr = 70:30 (by GC-MS of crude ester); R_f = 0.4 (EtOAc/hexane 1:19); Chiral GC analysis: 98% ee (major), >99% ee (minor) [Supelco Chiraldex BDM column; GC Conditions: Split ratio: 1:20; make up flow: 25 mL/min; H_2 flow: 45 mL/min; air flow: 450 mL/min; injector temperature: 250 °C, pressure: 12.3-18.5 psi; oven temperature: 50-180 °C, 1 °C/min; detector temperature: 250 °C; retention times: 66.5 min (minor enantiomer of major diastereomer), 67.4 min (major enantiomer of major diastereomer), 69.1 min (major enantiomer of minor diastereomer)]; IR (thin film): 1734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS, major diastereomer): δ 7.30-6.95 (m, 4H), 3.64 (s, 3H), 3.17-3.05 (m, 1H), 2.36-2.25 (m, 1H), 2.04-1.94 (m, 1H), 1.76-1.61 (m, 1H), 1.24 (d, J = 7.0 Hz, 3H), 1.12 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, major diastereomer): δ 177.2, 161.1 (d, J = 245 Hz), 133.3 (d, J = 19 Hz), 128.3 (d, J = 5 Hz), 127.7 (d, J = 8 Hz), 124.3 (d, J = 3 Hz), 115.6 (d, J = 23 Hz), 51.6, 41.1, 37.9, 31.2, 21.3, 18.0; $(M + H)^+$ HRMS m/z calcd for $(C_{13}H_{18}FO_2)^+$: 225.1291; Found: 225.1285.

(2*R*,4*R*)-Methyl 4-(2-fluorophenyl)-2-methylpentanoate [4n]: Following general procedure, the heterodimer (***R***,***Z***)-**2n** (37 mg, 0.18 mmol), of 93% ee (*Z*-isomer), 96% ee (*E*-isomer) and *Z*:*E* = 48:52, in MeOH (2 mL) was added to the 10 wt% Pd/C catalyst (10 mg, 0.009 mmol) (reaction time: 30 min). Crude GC-MS: acid:*β*-lactone = 56:44; Regular silica gel column purification of ester using 2% EtOAc/hexane afforded **4n** as a light yellow liquid (14 mg, 35% in two steps), dr = 65:35 (by GC-MS of crude acid); R_f = 0.4 (EtOAc/hexane 1:19); Chiral GC analysis: 96% ee (major) [Supelco Chiraldex BDM column; GC Conditions: Split ratio: 1:20; make up flow: 25 mL/min; H_2 flow: 45 mL/min; air flow: 450 mL/min; injector temperature: 250 °C, pressure: 12.3-18.5 psi; oven temperature: 50-180 °C, 1 °C/min; detector temperature: 250 °C; retention times: 66.6 min (major enantiomer of major diastereomer), 67.5 min (minor enantiomer of major diastereomer), 68.9 min (minor diastereomer)]; IR (thin film): 1735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS, ~1:1 mixture of isomers): δ 7.30-6.95 (m, 8H), 3.65 (s, 3H), 3.58 (s, 3H), 3.17-3.05 (m, 2H), 2.36-2.25 (m, 2H), 2.15-2.05 (m, 1H), 2.04-1.94 (m, 1H), 1.76-1.61 (m, 2H), 1.29-1.22 (m, 3H), 1.17-1.10 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ~1:1 mixture of isomers): δ 177.3, 177.2, 162.31, 162.27, 159.88, 159.84, 133.44, 133.30, 133.05, 132.91, 128.38, 128.33, 128.30, 127.74, 127.73, 127.65, 124.42, 124.39, 124.36, 124.32, 115.79, 115.56, 115.55, 51.7, 41.18, 41.17, 40.9, 37.91, 37.87, 31.23, 31.21, 30.73, 30.71, 21.69, 21.35, 18.0, 17.2; $(M + H)^+$ HRMS m/z calcd for $(C_{13}H_{18}FO_2)^+$: 225.1291; Found: 225.1286.

(2*S*,4*S*)-4-(Methoxycarbonyl)-2-methylpentanoic acid [11][30]**:** To an ice-cold stirred solution of acid **(*S*,*S*)-3a**[14] with dr = 75:25 (81 mg, 0.42 mmol) in diethyl ether, excess diazomethane solution in diethyl ether was added, and the reaction was allowed to warm to room temperature. After reaction completion, as determined by GCMS and TLC analysis, removal of solvent under reduced pressure afforded crude ester **4a** (86 mg, 0.42 mmol) which was used without further purification. To a vigorously stirred solution of crude ester **4a** (86 mg, 0.42 mmol) in a mixture of carbon tetrachloride (2 ml), acetonitrile (2 ml) and water (4 ml) at room temperature, $RuCl_3$ (8.65g, 0.04 mmol) and $NaIO_4$ (1.36 g, 6.34 mmol) were added, and stirring was continued for 48 h. The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic phases were washed with brine (20 mL) and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure followed by column chromatographic purification using EtOAc/hexane (0-30%) furnished the desired acid **11**[30] (53.5 mg, 74%) as a colorless oil, dr = 75:25 (by crude ^{1}H NMR); R_f = 0.6 (EtOAc/hexane 1:2); IR (thin film): 1734, 1702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS, major isomer): δ 11.29 (bs, 1H), 3.68 (s, 3H), 2.63-2.46 (m, 2H), 1.78 (t, J = 7.3 Hz, 2H), 1.25-1.14 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$, major isomer): δ 182.6, 176.9, 51.8, 37.7, 37.4, 37.2, 17.9, 17.8; $(M + H)^+$ HRMS m/z calcd for $(C_8H_{15}O_4)^+$: 175.0970; Found: 175.0958.

Determination of relative and absolute stereochemistry: The relative stereochemistry of a derivative of **3a** was determined by X-ray structure analysis to be the *anti*-isomer, and hence the absolute configuration was assigned to be (2*S*,4*S*) as previously described.[14] By analogy, all acids **3** (and ester derivatives **4**) synthesized from (*S*,*Z*)-heterodimers **2** were assigned the (2*S*,4*S*)-*anti* configuration. Similarly, all acids **3** (and ester derivatives **4**) synthesized from (*R*,*Z*)-heterodimers **2** were assigned the (2*R*,4*R*)-*anti* configuration.

Control experiments:

Attempted synthesis of 3o from 5o (starting from *E*-2o). A solution of heterodimer *E*-**2o**[12,13] (72 mg, 0.36 mmol) in dichloromethane (3.6 mL) was added to a pressure device containing 10 wt% of Pd/C catalyst (19 mg, 0.02 mmol). The stirred (1150 rpm) reaction mixture was subjected to hydrogenation under 15 atm pressure for 30 min. The reaction mixture was filtered through celite and washed with dichloromethane (50 mL). Removal of the solvent in vacuo followed by neutral silica gel column chromatographic purification afforded *β*-lactone **5o** (49 mg, 67%), dr 6:8:2:84 (by GC-MS), and no acid formation observed by crude GC-MS analysis of the crude. Spectroscopic data agreed with that for previously reported **5o**.[15]

A solution of *β*-lactone **5o** (49 mg, 0.24 mmol) in methanol (2.4 mL) was added to a pressure device containing 10 wt% of Pd/C catalyst (13 mg, 0.012 mmol). The stirred (1150 rpm) reaction mixture was subjected to hydrogenation under 15 atm pressure for 30 min. The reaction mixture was diluted with dichloromethane (20 mL), filtered through celite, and washed with dichloromethane (30 mL). After removal of the solvent in vacuo, crude GC-MS analysis of the crude showed no acid formation. *β*-Lactone **5o** (49 mg, quantitative), dr 6:6:2:86 (by GC-MS), was recovered.

Attempted synthesis of 3o from 5o (starting from *Z*-2o). A solution of heterodimer *Z*-**2o** (179 mg, 0.89 mmol) in dichloromethane (8.9 mL) was added to a pressure device

containing 10 wt% of Pd/C catalyst (47 mg, 0.044 mmol). The stirred (1150 rpm) reaction mixture was subjected to hydrogenation under 15 atm pressure for 30 min. The reaction mixture was filtered through celite and washed with dichloromethane (50 mL). After removal of the solvent in vacuo, GC-MS analysis of the crude showed formation of a mixture of acid **3o** (dr 2.4:1) and *β*-lactone **5o** (dr 32:1:10:20). The crude reaction mixture was treated with diazomethane solution in ether (10 mL) at 0 °C for 30 min to convert acids into non-polar ester for easy separation. Removal of the solvent in vacuo followed by neutral silica gel column chromatographic purification afforded *β*-lactone **5o** (87 mg, 48%), dr 48:2:17:33 (by GC-MS analysis).

A solution of *β*-lactone **5o** (87 mg, 0.43 mmol) in methanol (4.3 mL) was added to a pressure device containing 10 wt% of Pd/C catalyst (23 mg, 0.021 mmol). The stirred (1150 rpm) reaction mixture was subjected to hydrogenation under 15 atm pressure for 30 min. The reaction mixture was diluted with dichloromethane (30 mL), filtered through celite, and washed with dichloromethane (40 mL). After removal of the solvent in vacuo, GC-MS analysis of the crude showed no acid formation. *β*-Lactone **5o** (86 mg, quantitative), dr 50:2:16:32 (by GC-MS analysis), was recovered.

Synthesis of 3a from *E*-6a. (*E*)-2-Methyl-4-phenylpent-3-enoic acid (*E*-**6a**) was synthesized following a literature procedure.[24] Potassium hydride (13 mg, 0.32 mmol) was washed with pentane and then placed under vacuum. THF (1 mL) was added and the suspension cooled to 0 °C. A solution of *E*-**6a** (51 mg, 0.27 mmol) in THF (1 mL) was added dropwise to the stirring suspension. After a further 15 min of stirring at 0 °C, the reaction mixture was removed from ice and stirred at room temperature for 30 min. THF was then removed in vacuo, and the crude product was re-dissolved in methanol (2.7 mL) and subjected to hydrogenation following the general hydrogenolysis procedure with Pd/C (14 mg, 0.013 mmol) as catalyst. After 90 min, the reaction mixture was filtered through celite, and the solution was concentrated in vacuo. Crude GC-MS analysis of the crude showed that the reaction had proceeded to ~40% conversion, with formation of the desired acid product **3a** with dr 85:15, favoring the *anti*-diastereomer, and found to be identical to the major product **3a** formed from standard catalytic hydrogenolysis of ketene heterodimer *Z*-**2a**. ^{1}H NMR analysis of the crude showed 50% conversion and that the major product was *anti*-**3a** (dr 5:1).

Synthesis of 3a from *Z*-6a. (*Z*)-2-Methyl-4-phenylpent-3-enoic acid (*Z*-**6a**) was synthesized following literature procedures.[25] To a stirring solution of (*Z*)-4-phenylpent-3-enoic acid (430 mg, 2.44 mmol) in THF (36 mL) at −78 °C, a solution of LDA (2.0 mL, 5.008 mmol) was added dropwise.[25a] After 45 min stirring at −78 °C, methyl iodide (0.23 mL, 3.66 mmol) was added to the reaction mixture and it was allowed to gradually warm to room temperature. The solvent was removed in vacuo, and the crude mixture was dissolved in 2N NaOH solution (20 mL), and washed with dichloromethane (20 mL × 3). The basic layer was acidified using 20% hydrochloric acid and extracted using dichloromethane (25 mL × 3). The combined organic layers were washed with brine and dried over sodium sulfate. Removal of the solvent in vacuo afforded the desired product *Z*-**6a** as an oil (440 mg, 95%); R_f = 0.4 (EtOAc/hexane 1:5); IR (thin film): 1701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): *δ* 10.36 (bs, 1H), 7.38-7.31 (m, 2H), 7.29-7.23 (m, 1H), 7.23-7.17 (m, 2H), 5.49 (dd, *J* = 10.2, 1.4 Hz, 1H), 3.28-3.14 (m, 1H), 2.05 (d, *J* = 1.5 Hz, 3H), 1.19 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 181.8, 141.5, 139.6, 128.5, 128.0, 127.2, 125.7, 39.9, 26.0, 18.5; $(M + H)^+$ HRMS m/z calcd for $(C_{12}H_{15}O_2)^+$: 191.1072; Found: 191.1065.

Potassium hydride (13 mg, 0.32 mmol) was washed with pentane (2 mL × 3) and subjected to vacuum. The reaction vessel was cooled to 0 °C and THF (1.0 mL) was added. To the stirred suspension a solution of *Z*-**6a** (51 mg, 0.27 mmol) in THF (1.0 mL) was added slowly. After 15 min, the reaction was removed from ice and stirring at room temperature was continued for another 30 min. The solvent was removed in vacuo, and the crude was re-dissolved in methanol (2.7 mL) and subjected to hydrogenation using Pd/C catalyst (14 mg, 0.013 mmol) under 15 atm hydrogen pressure. After 90 min, crude GC-MS analysis showed ~50% conversion and formation of acid as 31:69 diastereomeric mixture. After 240 min, crude GC-MS analysis showed ~95% conversion and formation of acid as 33:67 diastereomeric mixture. After 360 min, the reaction was almost complete. The reaction was diluted with dichloromethane (20 mL), filtered through celite, and washed with dichloromethane (40 mL). Removal of solvent in vacuo afforded the desired acid **3a** (50 mg, quantitative, dr ~1:1).

Other control experiments detailed in Scheme 6 were carried out as previously described.[14]

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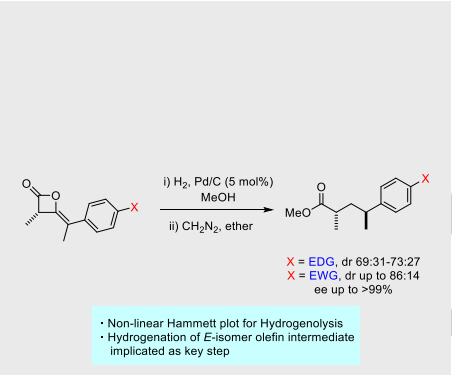

Asymmetric Synthesis, Deoxypropionate Synthesis*

*Manashi Panda, Mukulesh Mondal, Shi Chen, Ahmad A. Ibrahim, Dylan J. Twardy, and Nessan J. Kerrigan**

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