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Asymmetric Synthesis of Dipropionate Derivatives through Catalytic Hydrogenation of Enantioenriched *E*-Ketene Heterodimers

Shi Chen^a, Mukulesh Mondal^a, Ahmad A. Ibrahim^a, Kraig A. Wheeler^b, and Nesson J. Kerrigan^a

Nesson J. Kerrigan: kerrigan@oakland.edu

^aDepartment of Chemistry, Oakland University, 2200 N. Squirrel Road, Rochester, MI 48309-4477, USA

^bDepartment of Chemistry, Eastern Illinois University, 600 Lincoln Avenue, Charleston, IL 61920-3099, USA

Abstract

A highly diastereoselective approach to dipropionate derivatives through Pd/C-catalyzed hydrogenation of enantioenriched *E*-ketene heterodimers is described. Catalytic hydrogenation of the *E*-isomer of ketene heterodimer β -lactones (12 examples) provides access to *syn,anti*- β -lactones (dipropionate derivatives) bearing up to three stereogenic centers (dr up to 49:1), and with excellent transfer of chirality (ee up to >99%).

Graphical abstract

Keywords

asymmetric synthesis; ketene heterodimer; diastereoselectivity; β -lactone; catalytic hydrogenation

Correspondence to: Nesson J. Kerrigan, kerrigan@oakland.edu.

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Dipropionate stereotriad units are compelling targets in synthesis as they are integral structural features of many biologically active molecules, such as (+)-discodermolide, pironetin, and mycolipanic acid.^{2,3} For dipropionate synthesis the best available methods are considered to be the aldol and crotylmatal reactions involving chiral aldehydes.^{4,5} The aldol methods of Evans and Patterson have mainly relied on the use of double diastereoselection, involving the reaction of chiral enolates with chiral aldehydes to provide access to the desired dipropionate unit, with good to excellent levels of diastereoselectivity.^{2,6,7} The sense of diastereoselectivity obtained depends upon the type of metal enolate chosen, and the nature of substituents present on the chiral aldehyde. However, the use of chiral auxiliaries with associated attachment/removal steps, is often required, and problems may also be encountered with sterically hindered enolates or chiral aldehydes.^{6c} Racemization of sensitive α -chiral aldehydes or epimerization of the final aldol product under the reaction conditions are other potential pitfalls. Crotylmatal reagents have been used extensively as an alternative strategy for the synthesis of dipropionates.⁵ Roush and others, have ably demonstrated that these reagents can be utilized to access all possible diastereomers of dipropionate stereotriad unit.^{5,8} Some of the disadvantages of this approach are that the crotylboron reagents have to be pre-prepared, and in many cases a stoichiometric amount of an enantioenriched crotylmatal reagent is necessary.

It is clear that there are few competent *catalytic* methods available for the construction of dipropionates with good diastereoselectivity and enantioselectivity.⁹ In 2006, Nelson and co-workers reported a catalytic approach to this problem through use of an alkaloid-Lewis acid catalytic system for the formal [2 + 2] cycloaddition of in situ-generated ketenes with chiral aldehydes.⁹ The resulting β -lactone products were easily ring-opened to reveal *syn,anti*- or *anti,anti*-dipropionate units. Calter's group had earlier developed a route to *syn, syn*-dipropionates through alkaloid-catalyzed homodimerization of in situ-generated methylketene followed by lithiated Weinreb amine ring-opening and tandem aldol reaction with an appropriate chiral aldehyde.¹⁰ Around that time Cordóva and co-workers demonstrated that polyketide sugars could be assembled through a proline-catalyzed two step process.¹¹ More recently, Yamamoto's group showed that polyols (polyketides) can be prepared through use of a catalytic supsilyl-directed reaction, albeit mainly restricted to racemic targets.¹²

In 2012 we reported the development of the alkaloid-catalyzed ketene heterodimerization reaction which facilitated an asymmetric synthesis of ketene heterodimer β -lactones.¹³ Recently, we adapted that process to the synthesis of deoxypropionate derivatives.¹⁴ We determined that Pd/C-catalyzed hydrogenolysis of *Z*-ketene heterodimers **1** in MeOH leads to the formation of *anti*-deoxypropionates (acids) **2** as the major product, e.g. formation of *anti*-**2a** from *Z*-**1a** (Scheme 1, eq 1). Previously, Romo's group had demonstrated that ketene homodimers could be subjected to Pd/C-catalyzed hydrogenation in CH₂Cl₂ to provide access to *cis*- β -lactones with high diastereoselectivity.¹⁵

In this paper we describe our studies involving catalytic hydrogenation of *E*-ketene heterodimer β -lactones (eq 2 and 3).¹⁶ When the *E*-isomer of **1a** (*E:Z* = 4:1) was exposed to our previously developed reaction conditions for *Z*-heterodimer hydrogenolysis, a switch in product selectivity was observed (Scheme 1, eq 3).¹⁴ Intriguingly, reduced β -lactone **3a** was

obtained as the major product and with very good diastereoselectivity (dr 19:1, Scheme 1) in MeOH. From these results it was evident that the catalytic hydrogenation reaction is largely stereodivergent in MeOH, in that the *E*-isomer of ketene heterodimer is converted to the reduced β -lactone **3** (just 2 diastereomers observed), while the *Z*-isomer is converted to mainly hydrogenolysis product **2** (*ca.* 15% observed for eq 3).

The use of other solvents (CH₂Cl₂, pentane, and EtOAc) led to lower levels of diastereoselectivity, with four diastereomers of **3a** being formed (dr ranged from 3.9:1 to 9.7:1, major: Σ all other diastereomers). In these other solvents, no hydrogenolysis product was formed despite the presence of *ca.* 20% *Z*-isomer in the starting material.

The scope of the β -lactone **3** forming reaction was then explored (Table 1). Consistently good levels of diastereoselectivity (7:1 to 49:1) were achieved with a variety of *E*-ketene heterodimers (entries 1-10). Interestingly, pentane proved to be a more effective solvent for facilitating the conversion of dimethyl-substituted **1f** to β -lactone **3f** (entries 11 and 12); in MeOH, a complex mixture of products was obtained. The high level of diastereoselection obtained in most cases may be interpreted in terms of a model where the large substituent at the stereogenic center on the ketene heterodimer blocks approach to one face of the exocyclic olefin, leading to formation of the *syn,anti*-diastereomer as the major isomer (Scheme 2). Occasionally poor diastereoselectivity was observed. For example, unsymmetrical dialkylketene-derived heterodimers (results not shown in Table 1), such as isobutylmethylketene-derived heterodimer, gave low diastereoselectivity (dr *ca.* 1:1) due to the heterodimer being composed of an equal mixture of olefin isomers (*Z:E* = *ca.* 1:1).

The formation of the *syn,anti*-isomer was confirmed by X-ray crystallographic analysis of the 3,5-dinitrobenzoate derivative (–)-**5a** from (–)-**4a** (see experimental section for details). In nearly every case examined, excellent transfer of chirality from ketene heterodimer to β -lactone **3** was observed (94-99% ee for 11 of 12 examples). It is also notable that both enantiomers of the dipropionate derivatives can be easily accessed from readily available antipodes of each ketene heterodimer.¹³

We propose that the formation of lactone **3** in most cases occurs through a mechanism involving hydropalladation of the exocyclic olefin of *E*-**1** to give a mixture of Regioisomers A and B (Scheme 2).¹⁷ Simple reductive elimination of both regioisomers leads to the observed β -lactone **3**, along with regeneration of the catalyst. This product selectivity contrasts with that observed when starting from the *Z*-ketene heterodimer (Scheme 1, eq 1), where acid **2** formation is preferred.¹⁴ We hypothesize that selectivity for formation of **3** over acid **2** from *E*-**1** is driven by developing *syn*-pentane-like interactions (e.g., between the Et and *i*-Bu groups for **3e**) experienced by Regioisomer A as it undergoes C-C bond rotation to the rotamer required for *syn* β -elimination.^{4a,14,18} Regioisomer A instead undergoes reductive elimination more quickly to give **3** as the major product. On the other hand, Regioisomer B has no option but to undergo reductive elimination to yield β -lactone **3**. As a result, acid **2** is formed from *E*-heterodimer only as a minor product, in addition to that produced from the minor *Z*-isomer of the heterodimer starting material.

Selectivity for β -lactone **3** formation observed for heterodimers bearing two methyl substituents on the exocyclic olefin (entries 11 and 12) is likely due to hydropalladation regioselectivity for Regioisomer B (Scheme 2). Dimethyl substitution on the exocyclic carbon would destabilize C(δ^-)-Pd(δ^+) formation at that carbon for electronic reasons (δ^- charge on C bearing electron donating Me groups), thus disfavoring formation of Regioisomer A, and hence acid **2**.¹⁷ It should be noted that the latter result was obtained when the reaction was performed in pentane, rather than the usually employed MeOH (the use of MeOH as solvent resulted in a complex mixture). The use of pentane presumably is also less stabilizing of the transition state leading to the putative Pd-carboxylate intermediate required for acid **2** formation. The observation of β -lactone **3** formation under these conditions contrasts with the result obtained when dimethyl substitution is replaced with diphenyl substitution at this position, where formation of hydrogenolysis product **2** is favored (albeit when the reaction is performed in MeOH).¹⁴

To demonstrate that β -lactones **3** can act as surrogates for *syn,anti*-aldol construction, (–)-**3a** was converted smoothly to Weinreb amide (+)-**4a** in 85% yield, with no loss of enantiomeric (95% ee) or diastereomeric (purified dr>99:1) integrity (Scheme 3).⁹ The opposite enantiomer [(–)-**4a**] was obtained with similar retention of chirality through the same treatment of (+)-**3a**. Thus, the catalytic asymmetric ketene heterodimerization–diastereoselective hydrogenation sequence has clear advantages over traditional aldol approaches in that it represents a catalytic alternative to the use of diastereoselective (double or otherwise) aldol reactions for *syn,anti*-aldol construction, and circumvents the need to use racemization-sensitive chiral aldehydes, and/or stoichiometric amounts of a chiral auxiliary.⁶

In summary, we have developed a catalytic asymmetric synthetic method of wide substrate scope that provides access to dipropionate derivatives with good to excellent diastereoselectivity from enantioenriched ketene heterodimers. The method exhibits interesting divergence in providing access to dipropionate derivatives (β -lactones) from the *E*-isomer of ketene heterodimers, while we have previously shown that deoxypropionate derivatives are furnished from the corresponding *Z*-isomer of ketene heterodimers. Dipropionate derivatives were formed with good to excellent diastereoselectivity (10 examples with dr 7:1, up to 49:1), and with excellent retention of chirality (11 examples with ee of 94 to >99%). Another advantage of the described method is that both enantiomers of the dipropionate units can be easily prepared from readily available antipodes of each ketene heterodimer.¹³ Studies are currently underway to develop double diastereoselective variants of the reported reaction through use of chiral homogeneous catalytic systems, and to examine applications in complex molecule synthesis.

General Information

THF was freshly distilled from benzophenone ketyl radical under nitrogen prior to use.

Hünig's base (diisopropylethylamine) was distilled from calcium hydride, and *N,N*-dimethylethylamine was distilled from potassium hydroxide under nitrogen.¹⁹

Dichloromethane and diethyl ether were dried by passing through activated alumina columns on a solvent purification system. Zinc dust (<10 μ m), lithium perchlorate, 2-phenylpropanoic acid and 2-phenylbutanoic acid were purchased from Aldrich Chemical Co. Propionyl

chloride and butyryl chloride were purchased from Aldrich Chemical Co. and distilled prior to use.¹⁹ Iatrobeds (Bioscan, 6RS-8060, 60 μ M particle size) as neutral silica gel, Silicycle (60-200 μ M particle size) as normal silica gel, and TLC plates (Sorbent Technologies, UV254, 250 μ M) were used as received. Methylphenylketene, ethylphenylketene, *n*-butylphenylketene, isobutylphenylketene, and dimethylketene were prepared according to literature procedures.²⁰ TMS-quinine, Me-quinidine and Me-quinine were synthesized according to literature procedures.²¹

NMR spectra were recorded on a Bruker Biospin AG 400 spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C). NMR chemical shifts were reported relative to TMS (0 ppm) for ^1H and to CDCl_3 (77.23 ppm) for ^{13}C spectra. High resolution mass spectra were obtained on an Agilent Technologies 6520 Accurate Mass Q-TOF LC-MS instrument (with ESI as the ionization method) at Oakland University. Low resolution mass spectra were recorded on a GC/MS Hewlett Packard HP 6890 GC instrument with a 5973 mass selective detector, and using a Restek Rtx-CL Pesticides2 GC column (30 m, 0.25 mm ID). Optical rotations were measured on Rudolph DigiPol 781 TDV automatic polarimeter. IR spectra were recorded on a Bio Rad FTS-175C spectrometer.

Analytical high performance liquid chromatography (HPLC) was performed using a Daicel Chiralpak AD column (0.46 cm $\times$ 25 cm), ODH column (0.46 cm $\times$ 25 cm), or an AS-H column (0.46 cm $\times$ 25 cm) (Daicel Chemical Ind., Ltd.) on a Perkin Elmer Flexar instrument attached with diode array detector (deuterium lamp, 190-600 nm) with HPLC-grade isopropanol and hexanes as the eluting solvents. Analytical gas chromatography (GC) was performed using an Astec CHIRALDEXTM B-DM column (30 m $\times$ 0.25 mm $\times$ 0.12 μ m) on a Perkin Elmer Clarus 500 instrument.

Compound Characterization and Determination of Diastereomeric Ratios and Enantiomeric Excesses

The enantioenriched ketene heterodimers **1a-1f** were synthesized as per previously reported procedures.^{13a} The β -lactones **3** were purified by plug column chromatography through neutral silica to provide samples of high purity (95%) for full characterization. Diastereomeric ratios were determined for the reduced β -lactones by GC-MS analysis. Enantiomeric excesses were determined by assaying reduced β -lactones **3a-3f** using chiral GC analysis. Racemic/scalemic samples for chiral GC analysis were generated through mixing of enantiomerically enriched samples.

Procedures

General procedure for catalytic hydrogenation

The ketene heterodimer (1 equiv) in methanol or pentane (0.1 M) was added via pasteur pipette to the pressure device containing the 10 wt% Pd/C catalyst (0.05 equiv). Hydrogen was supplied at the pressure of 225 psi (15 atm) rapidly while the outlet was closed, and the inlet was also closed immediately. The reaction mixture was stirred at 1150 rpm at room temperature for the specified time for each example. After the specified time (30 min-3h 15 min), the pressure device was vented, and the mixture was filtered through celite (10 g),

washing with dichloromethane (30-60 mL). The solvent was removed under reduced pressure, and product of high purity (95%) was isolated after plug column chromatography (using neutral silica for β -lactone **3** purification, details mentioned below).

(3*S*,4*R*)-3-Methyl-4-((*R*)-1-phenylpropyl)oxetan-2-one [(+)-3a**]**

Following general procedure, the (*S,E*)-**1a** heterodimer (175 mg, 0.86 mmol), of 94% ee and *Z:E*=1:7, in MeOH (8.6 mL) was added to the 10 wt% Pd/C catalyst (46 mg, 0.043 mmol) (reaction time: 35 min). Elution with 2%, 5%, and then 10% EtOAc/hexane through a plug column of silica gel afforded (+)-**3a** as a colorless gel-like liquid (135 mg, 76%), dr = 10:1 (by GC-MS); Chiral GC analysis: 80% ee [Supelco Chiraldex BDM column; GC Conditions: Split ratio: 1:20; make up flow: 25 mL/min; H₂ 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: 101.5 min (major), 102.2 min (minor)]; [α]_D²⁴ = 20.5 (c = 0.11, CH₂Cl₂); R_f = 0.15 (hexane-EtOAc, 9:1).

IR (CH₂Cl₂): 2986, 2970, 2902, 1821, 1452, 1407, 1393, 1382, 1251, 1230, 1146, 1075, 1066, 1056, 893, 865 cm⁻¹.

¹H NMR (400 MHz, CDCl₃, TMS): δ 7.41-7.32 (m, 2H, ArH), 7.32-7.19 (m, 3H, ArH), 4.70 (dd, *J* = 10.5, 6.2 Hz, 1H, H-4), 3.94-3.76 (m, 1H, H-3), 2.83 (td, *J* = 10.5, 3.7 Hz, 1H, CH), 1.73-1.45 (m, 2H, CH₂), 1.43 (d, *J* = 7.7 Hz, 3H, CH₃), 0.84 (t, *J* = 7.4 Hz, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃): δ 172.3, 139.6, 128.9, 128.6, 127.4, 77.9, 48.1, 47.4, 25.1, 11.6, 8.8.

(M + H)⁺ HRMS *m/z* calcd for (C₁₃H₁₇O₂)⁺: 205.1229; found: 205.1224.

(3*R*,4*S*)-3-Methyl-4-((*S*)-1-phenylpropyl)oxetan-2-one [(–)-3a**]**

Following general procedure, the heterodimer (*R,E*)-**1a** (94 mg, 0.46 mmol), of 85% ee and *Z:E*=1:4, in MeOH (4.6 mL) was added to the 10 wt% Pd/C catalyst (25 mg, 0.023 mmol) (reaction time: 30 min). Elution with 1%, 2%, and then 10% EtOAc/hexane through a plug column of neutral silica gel afforded (–)-**3a** as a colorless gel-like liquid (78 mg, 82%), dr = 19:1 (by GC-MS); Chiral GC analysis: 95% ee [Supelco Chiraldex BDM column; GC Conditions: Split ratio: 1:20; make up flow: 25 mL/min; H₂ 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: 101.3 min (minor), 102.2 min (major)]; [α]_D²⁴ = –46.4 (c = 0.06, CH₂Cl₂); R_f = 0.15 (hexane-EtOAc, 9:1).

IR (CH₂Cl₂): 3029, 2964, 2932, 2875, 1818, 1495, 1454, 1382, 1277, 1145, 1118, 1057, 1034, 1011, 893, 861, 757, 699, 555 cm⁻¹.

¹H NMR (400 MHz, CDCl₃, TMS): δ 7.40-7.27 (m, 2H, ArH), 7.27-7.14 (m, 3H, ArH), 4.63 (dd, *J* = 10.6, 6.2 Hz, 1H, H-4), 3.82-3.69 (m, 1H, H-3), 2.77 (td, *J* = 10.5, 3.8 Hz, 1H, CH), 1.66-1.45 (m, 2H, CH₂), 1.34 (d, *J* = 7.8 Hz, 3H, CH₃), 0.77 (t, *J* = 7.3 Hz, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃): δ 172.2, 139.6, 128.6, 128.4, 127.1, 77.7, 47.9, 47.1, 24.9, 11.3, 8.5.

(M + H)⁺ HRMS m/z calcd for (C₁₃H₁₇O₂)⁺: 205.1229; found: 205.1230.

(3*S*,4*R*)-3-methyl-4-((*R*)-1-phenylpentyl)oxetan-2-one [(+)-3b]

Following general procedure, the heterodimer (*S,E*)-**1b** (54 mg, 0.23 mmol), of 92% ee and *Z:E*=1:4, in MeOH (2.4 mL) was added to the 10 wt% Pd/C catalyst (13 mg, 0.012 mmol) (reaction time: 3 h 15 min). Elution with 1%, and 1.5% EtOAc/hexane through a plug column of neutral silica gel afforded (+)-**3b** as a colorless gel-like liquid (36 mg, 66%), dr = 15:1 (by GC-MS); Chiral GC analysis: >99% ee [Supelco Chiraldex BDM column; GC Conditions: Split ratio: 1:20; make up flow: 25 mL/min; H₂ 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: 116.4 min (major)]; [α]_D²⁴ = 28.0 (c = 0.084, CH₂Cl₂); R_f = 0.20 (hexane-EtOAc, 9:1).

IR (CH₂Cl₂): 2956, 2860, 1824, 1496, 1454, 1382, 1280, 1146, 1119, 1088, 1054, 1017, 899, 866, 754, 700, 574 cm⁻¹.

¹H NMR (400 MHz, CDCl₃, TMS): δ 7.38-7.30 (m, 2H, ArH), 7.30-7.18 (m, 3H, ArH), 4.64 (dd, *J* = 10.6, 6.2 Hz, 1H, H-4), 3.85-3.77 (m, 1H, H-3), 2.95-2.82 (m, 1H, PhCH), 1.65-1.50 (m, 2H, CH₂), 1.41 (d, *J* = 7.8 Hz, 3H, CH₃), 1.40-1.08 (m, 4H, 2 × CH₂), 0.82 (t, *J* = 7.1 Hz, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃): δ 172.3, 139.9, 128.9, 128.5, 127.4, 78.1, 47.4, 46.3, 31.6, 29.1, 22.8, 14.1, 8.8.

(M + H)⁺ HRMS m/z calcd for (C₁₅H₂₁O₂)⁺: 233.1542; Found: 233.1537.

(3*R*,4*S*)-3-methyl-4-((*S*)-1-phenylpentyl)oxetan-2-one [(−)-3b]

Following general procedure, the heterodimer (*R,E*)-**1b** (60 mg, 0.26 mmol), of 84% ee and *Z:E*=1:2.3, in MeOH (2.6 mL) was added to the 10 wt% Pd/C catalyst (14 mg, 0.013 mmol) (reaction time: 3 hrs). Elution with 1%, and 2% EtOAc/hexane through a plug column of neutral silica gel afforded (−)-**3b** as a colorless gel-like liquid (38 mg, 62%), dr = 12:1 (by GC-MS); Chiral GC analysis: 96% ee [Supelco Chiraldex BDM column; GC Conditions: Split ratio: 1:20; make up flow: 25 mL/min; H₂ 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: 115.8 min (minor), 116.8 min (major)]; [α]_D²⁴ = −24.7 (c = 0.154, CH₂Cl₂); R_f = 0.21 (hexane-EtOAc, 9:1).

IR (CH₂Cl₂): 2956, 2932, 2860, 1823, 1495, 1454, 1382, 1280, 1146, 1119, 1088, 1054, 1017, 898, 866, 753, 700, 574 cm⁻¹.

¹H NMR (400 MHz, CDCl₃, TMS): δ 7.38-7.30 (m, 2H, ArH), 7.29-7.18 (m, 3H, ArH), 4.65 (dd, *J* = 10.6, 6.2 Hz, 1H, H-4), 3.85-3.77 (m, 1H, H-3), 2.95-2.82 (m, 1H, PhCH), 1.65-1.50 (m, 2H, CH₂), 1.40 (d, *J* = 7.8 Hz, 3H, CH₃), 1.40-1.08 (m, 4H, 2 × CH₂), 0.82 (t, *J* = 7.1 Hz, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃): δ 172.2, 140.0, 128.9, 128.6, 127.4, 78.1, 47.4, 46.4, 31.7, 29.1, 22.8, 14.1, 8.8.

(M + H)⁺ HRMS m/z calcd for (C₁₅H₂₁O₂)⁺: 233.1542; Found: 233.1540.

(3*S*,4*R*)-3-Methyl-4-((*R*)-3-methyl-1-phenylbutyl)oxetan-2-one [(+)-3c]

Following general procedure, the heterodimer (*S,E*)-**1c** (35 mg, 0.15 mmol), of 98% ee and *Z:E*=1:32, in MeOH (1.5 mL) was added to the 10 wt% Pd/C catalyst (8 mg, 0.0075 mmol) (reaction time: 45 min). Elution with 2% EtOAc/hexane through a plug column of neutral silica gel afforded (+)-**3c** as a colorless gel-like liquid (20 mg, 58%), dr = 7:1 (by GC-MS); Chiral GC analysis: 96% ee [Supelco ChiralDEX BDM column; GC Conditions: Split ratio: 1:20; make up flow: 25 mL/min; H₂ 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: 111.4 min (minor), 112.5 min (major)]; [α]_D²⁴ = 63.0 (c = 0.076, CH₂Cl₂); R_f = 0.2 (hexane-EtOAc, 9:1).

IR (CH₂Cl₂): 2954, 2871, 1823, 1496, 1468, 1455, 1386, 1273, 1146, 1120, 1090, 1055, 1018, 897, 861, 751, 701, 579 cm⁻¹.

¹H NMR (400 MHz, CDCl₃, TMS): δ 7.40-7.33 (m, 2H, ArH), 7.32-7.22 (m, 3H, ArH), 4.63 (dd, *J* = 10.6, 6.2 Hz, 1H, H-4), 3.88-3.77 (m, 1H, H-3), 3.11-2.99 (m, 1H, PhCH), 1.74-1.63 (m, 1H, Me₂CH), 1.44 (d, *J* = 7.8 Hz, 3H, CH₃), 1.43-1.34 (m, 1H, CH₂), 1.32-1.21 (m, 1H, CH₂), 0.92 (d, *J* = 6.5 Hz, 3H, CH₃), 0.85 (d, *J* = 6.6 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 172.3, 139.8, 128.9, 128.5, 127.4, 78.4, 47.4, 44.3, 40.7, 25.1, 24.2, 21.3, 8.9.

(M + H)⁺ HRMS m/z calcd for (C₁₅H₂₁O₂)⁺: 233.1542; Found: 233.1546.

(3*R*,4*S*)-3-Methyl-4-((*S*)-3-methyl-1-phenylbutyl)oxetan-2-one [(−)-3c]

Following general procedure, the heterodimer (*R,E*)-**1c** (30 mg, 0.13 mmol), of 96% ee and *Z:E*=1:24, in MeOH (1.3 mL) was added to the 10 wt% Pd/C catalyst (7 mg, 0.0066 mmol) (reaction time: 2 h). Elution with 2% EtOAc/hexane through a plug column of neutral silica gel afforded (−)-**3c** as a colorless gel-like liquid (18 mg, 58%), dr = 16:1 (by GC-MS); Chiral GC analysis: >=99% ee [Supelco ChiralDEX BDM column; GC Conditions: Split ratio: 1:20; make up flow: 25 mL/min; H₂ 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: 112.2 min (major)]; [α]_D²⁴ = −50.0 (c = 0.014, CH₂Cl₂); R_f = 0.2 (hexane-EtOAc, 9:1).

IR (CH₂Cl₂): 2968, 2958, 2925, 2902, 1823, 1495, 1467, 1453, 1407, 1383, 1272, 1251, 1229, 1146, 1120, 1075, 1066, 1056, 896, 862, 831, 751, 700, 577 cm⁻¹.

¹H NMR (400 MHz, CDCl₃, TMS): δ 7.40-7.32 (m, 2H, ArH), 7.32-7.22 (m, 3H, ArH), 4.63 (dd, *J* = 10.6, 6.2 Hz, 1H, H-4), 3.87-3.77 (m, 1H, H-3), 3.13-2.99 (m, 1H, PhCH), 1.75-1.62 (m, 1H, Me₂CH), 1.44 (d, *J* = 7.8 Hz, 3H, CH₃), 1.43-1.34 (m, 1H, CH₂), 1.32-1.22 (m, 1H, CH₂), 0.92 (d, *J* = 6.5 Hz, 3H, CH₃), 0.85 (d, *J* = 6.6 Hz, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃): δ 172.3, 139.8, 128.9, 128.5, 127.4, 78.4, 47.4, 44.3, 40.7, 25.1, 24.2, 21.3, 8.9.

(M + H)⁺ HRMS m/z calcd for (C₁₅H₂₁O₂)⁺: 233.1542; Found: 233.1542.

(3*S*,4*R*)-3-Ethyl-4-((*R*)-1-phenylpropyl)oxetan-2-one [(+)-3d]

Replace Following general procedure, the heterodimer (*S,E*)-**1d** (30 mg, 0.14 mmol), of 88% ee and *Z:E*=1:3, in MeOH (1.4 mL) was added to the 10 wt% Pd/C catalyst (7 mg, 0.007 mmol) (reaction time: 70 min). Elution with 2% EtOAc/hexane through a plug column of neutral silica gel afforded (+)-**3d** as a colorless gel-like liquid (20 mg, 65%), dr = 49:1 (by GC-MS); Chiral GC analysis: 99% ee [Supelco Chiraldex BDM column; GC Conditions: Split ratio: 1:20; make up flow: 25 mL/min; H₂ 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: 105.3 min (minor), 107.0 min (major)]; [α]_D²⁴ = 40.8 (c = 0.24, CH₂Cl₂); R_f = 0.11 (hexane-EtOAc, 9:1).

IR (CH₂Cl₂): 2964, 2933, 2875, 1810, 1494, 1454, 1381, 1266, 1203, 1164, 1129, 1071, 1026, 877, 758, 737, 699, 568 cm⁻¹.

¹H NMR (400 MHz, CDCl₃, TMS): δ 7.40-7.14 (m, 5H, ArH), 4.69 (dd, *J* = 10.0, 6.2 Hz, 1H, H-4), 3.70-3.59 (m, 1H, H-3), 2.83 (td, *J* = 10.3, 3.6 Hz, 1H, CH), 1.99-1.84 (m, 1H, CH₂), 1.84-1.74 (m, 1H, CH₂), 1.74-1.53 (m, 2H, CH₂), 1.18 (t, *J* = 7.4 Hz, 3H, CH₃), 0.83 (t, *J* = 7.3 Hz, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃): δ 171.7, 139.8, 128.9, 128.6, 127.4, 77.7, 54.4, 48.4, 25.4, 17.9, 12.4, 11.7.

(M + H)⁺ HRMS m/z calcd for (C₁₄H₁₉O₂)⁺: 219.1385; Found: 219.1384.

(3*R*,4*S*)-3-Ethyl-4-((*S*)-1-phenylpropyl)oxetan-2-one [(−)-3d]

Following general procedure, the heterodimer (*R,E*)-**1d** (30 mg, 0.14 mmol), of 93% ee and *Z:E*=1:3, in MeOH (1.4 mL) was added to the 10 wt% Pd/C catalyst (7 mg, 0.0067 mmol) (reaction time: 1 h). Elution with 2% EtOAc/hexane through a plug column of neutral silica gel afforded (−)-**3d** as a colorless gel-like liquid (26 mg, 85%), dr = 13:1 (by GC-MS); Chiral GC analysis: 97% ee [Supelco Chiraldex BDM column; GC Conditions: Split ratio: 1:20; make up flow: 25 mL/min; H₂ 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: 105.5 min (major), 106.1 min (minor)]; [α]_D²⁴ = −20.7 (c = 0.07, CH₂Cl₂); R_f = 0.11 (hexane-EtOAc, 9:1).

IR (CH₂Cl₂): 2966, 2936, 2876, 1818, 1495, 1455, 1381, 1274, 1152, 1121, 1074, 1042, 874, 701, 558 cm⁻¹.

¹H NMR (400 MHz, CDCl₃, TMS): δ 7.40-7.14 (m, 5H, ArH), 4.69 (dd, *J* = 10.0, 6.2 Hz, 1H, H-4), 3.70-3.59 (m, 1H, H-3), 2.83 (td, *J* = 10.3, 3.5 Hz, 1H, CH), 1.98-1.85 (m, 1H, CH₂), 1.85-1.74 (m, 1H, CH₂), 1.74-1.54 (m, 2H, CH₂), 1.18 (t, *J* = 7.4 Hz, 3H, CH₃), 0.83 (t, *J* = 7.4 Hz, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃): δ 171.7, 139.8, 128.8, 128.6, 127.4, 77.7, 54.3, 48.3, 25.4, 17.9, 12.3, 11.6.

(M + H)⁺ HRMS m/z calcd for (C₁₄H₁₉O₂)⁺: 219.1385; Found: 219.1380.

(3*S*,4*R*)-3-Ethyl-4-((*R*)-3-methyl-1-phenylbutyl)oxetan-2-one [(+)-3e]

Following general procedure, the heterodimer (*S,E*)-**1e** (33 mg, 0.14 mmol), of 98% ee and *Z:E*=1:19, in MeOH (1.4 mL) was added to the 10 wt% Pd/C catalyst (7 mg, 0.0066 mmol) (reaction time: 3 h). Elution with 2.5%, 5%, and then 10% EtOAc/hexane through a plug column of neutral silica gel afforded (+)-**3e** as a colorless gel-like liquid (21 mg, 63%), dr = 13:1 (by GC-MS); Chiral GC analysis: 99% ee [Supelco Chiraldex BDM column; GC Conditions: Split ratio: 1:20; make up flow: 25 mL/min; H₂ 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: 114.7 min (minor), 116.8 min (major)]; [α]_D²⁴ = 20.7 (c = 0.38, CH₂Cl₂); R_f = 0.25 (hexane-EtOAc, 9:1).

IR (CH₂Cl₂): 2956, 2928, 2870, 1821, 1496, 1455, 1385, 1271, 1148, 1123, 1093, 1042, 901, 878, 753, 700, 581 cm⁻¹.

¹H NMR (400 MHz, CDCl₃, TMS): δ 7.39-7.31 (m, 2H, ArH), 7.31-7.21 (m, 3H, ArH), 4.62 (dd, *J* = 10.1, 6.2 Hz, 1H, H-4), 3.68-3.58 (m, 1H, H-3), 3.11-3.00 (m, 1H, PhCH), 2.00-1.75 (m, 2H, CH₂), 1.75-1.63 (m, 1H, Me₂CH), 1.45-1.25 (m, 2H, CH₂), 1.19 (t, *J* = 7.4 Hz, 3H, CH₃), 0.92 (d, *J* = 6.3 Hz, 3H, CH₃), 0.85 (d, *J* = 6.4 Hz, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃): δ 171.7, 139.9, 128.9, 128.5, 127.4, 78.2, 54.3, 44.5, 40.9, 25.1, 24.2, 21.3, 18.0, 12.4.

(M + H)⁺ HRMS m/z calcd for (C₁₆H₂₃O₂)⁺: 247.1698; Found: 247.1697.

(3*R*,4*S*)-3-Ethyl-4-((*S*)-3-methyl-1-phenylbutyl)oxetan-2-one [(−)-3e]

Following general procedure, the heterodimer (*R,E*)-**1e** (32 mg, 0.13 mmol), of 97% ee and *Z:E*=1:16, in MeOH (1.3 mL) was added to the 10 wt% Pd/C catalyst (7 mg, 0.0066 mmol) (reaction time: 2 h 30 min). Elution with 2.5% EtOAc/hexane through a plug column of neutral silica gel afforded (−)-**3e** as a colorless gel-like liquid (22 mg, 68%), dr = 12:1 (by GC-MS); Chiral GC analysis: 97% ee [Supelco Chiraldex BDM column; GC Conditions: Split ratio: 1:20; make up flow: 25 mL/min; H₂ 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: 115.4 min (major), 116.3 min (minor)]; [α]_D²⁴ = −5.8 (c = 0.06, CH₂Cl₂); R_f = 0.25 (hexane-EtOAc, 9:1).

IR (CH₂Cl₂): 2954, 2925, 2868, 1823, 1494, 1466, 1455, 1384, 1200, 1170, 1123, 1073, 1055, 877, 754, 700 cm⁻¹.

¹H NMR (400 MHz, CDCl₃, TMS): δ 7.39-7.31 (m, 2H, ArH), 7.31-7.21 (m, 3H, ArH), 4.62 (dd, *J* = 10.1, 6.2 Hz, 1H, H-4), 3.68-3.58 (m, 1H, H-3), 3.11-3.00 (m, 1H, PhCH), 2.00-1.75 (m, 2H, CH₂), 1.75-1.62 (m, 1H, Me₂CH), 1.44-1.25 (m, 2H, CH₂), 1.19 (t, *J* = 7.4 Hz, 3H, CH₃), 0.92 (d, *J* = 6.3 Hz, 3H, CH₃), 0.85 (d, *J* = 6.4 Hz, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃): δ 171.7, 140.0, 128.9, 128.5, 127.4, 78.2, 54.3, 44.5, 40.9, 25.1, 24.2, 21.4, 18.0, 12.4.

(M + H)⁺ HRMS m/z calcd for (C₁₆H₂₃O₂)⁺: 247.1698; Found: 247.1695.

(3*S*,4*R*)-4-Isopropyl-3-methyloxetan-2-one [(–)-3f]

Following general procedure, the heterodimer (*S*)-**1f** (36 mg, 0.28 mmol) of 95% ee, in pentane (2.8 mL) was added to the 10 wt% Pd/C catalyst (15 mg, 0.014 mmol) (reaction time: 2 h 30 min). Elution with 1%, 2%, 3%, 4%, and then 5% EtOAc/hexane through a plug column of neutral silica gel afforded (–)-**3f** as a colorless liquid (20 mg, 54%), dr = 3:1 (by NMR); Chiral GC analysis: 98% ee [Supelco Chiraldex BDM column; GC Conditions: Split ratio: 1:20; make up flow: 25 mL/min; H₂ flow: 45 mL/min; air flow: 450 mL/min; injector temperature: 250 °C, pressure: 15 psi; oven temperature: 50–180 °C, 2 °C/min; detector temperature: 250 °C; retention times: 24.1 min (major), 26.2 min (minor)]; [α]_D²⁴ = –16.9 (c = 0.06, CH₂Cl₂); R_f = 0.24 (hexane–EtOAc, 9:1).

IR (CH₂Cl₂): 2961, 2929, 2855, 1728, 1463, 1407, 1393, 1381, 1259, 1075, 1066, 1057, 869 cm^{–1}.

¹H NMR (400 MHz, CDCl₃, TMS): δ 4.13 (dd, *J* = 10.6, 6.2 Hz, 1H, H-4), 3.79–3.69 (m, 1H, H-3), 2.09–1.93 (m, 1H, Me₂CH), 1.35 (d, *J* = 7.8 Hz, 3H, CH₃), 1.10 (d, *J* = 6.5 Hz, 3H, CH₃), 0.94 (d, *J* = 6.6 Hz, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃): δ 172.9, 80.7, 47.0, 28.8, 19.3, 18.0, 8.8.

(M + H)⁺ HRMS m/z calcd for (C₇H₁₃O₂)⁺: 129.0916; Found: 129.0911.

(3*R*,4*S*)-4-Isopropyl-3-methyloxetan-2-one [(+)-3f]

Following general procedure, the heterodimer (*R*)-**1f** (37 mg, 0.29 mmol) of 91% ee, in pentane (2.9 mL) was added to the 10 wt% Pd/C catalyst (16 mg, 0.015 mmol) (reaction time: 2 h 30 min). Elution with 1%, 2%, 3%, 4%, and then 5% EtOAc/hexane through a plug column of neutral silica gel afforded (+)-**3f** as a colorless liquid (18 mg, 49%), dr = 4:1 (by NMR); Chiral GC analysis: 94% ee [Supelco Chiraldex BDM column; GC Conditions: Split ratio: 1:20; make up flow: 25 mL/min; H₂ flow: 45 mL/min; air flow: 450 mL/min; injector temperature: 250 °C, pressure: 15 psi; oven temperature: 50–180 °C, 2 °C/min; detector temperature: 250 °C; retention times: 24.3 min (minor), 25.9 min (major)]; [α]_D²⁴ = 21.4 (c = 0.10, CH₂Cl₂); R_f = 0.24 (hexane–EtOAc, 9:1).

IR (CH₂Cl₂): 2959, 2924, 2854, 1732, 1458, 1379, 1260, 1114, 1075, 1046 cm^{–1}.

¹H NMR (400 MHz, CDCl₃, TMS): δ 4.13 (dd, *J* = 10.6, 6.2 Hz, 1H, H-4), 3.79–3.69 (m, 1H, H-3), 2.08–1.93 (m, 1H, Me₂CH), 1.35 (d, *J* = 7.8 Hz, 3H, CH₃), 1.09 (d, *J* = 6.4 Hz, 3H, CH₃), 0.94 (d, *J* = 6.6 Hz, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃): δ 172.9, 80.7, 47.0, 28.8, 19.3, 18.0, 8.7.

(M + H)⁺ HRMS m/z calcd for (C₇H₁₃O₂)⁺: 129.0916; Found: 129.0914.

(2S,3R,4R)-3-Hydroxy-N-methoxy-N,2-dimethyl-4-phenylhexanamide [(-)-4a]

Dimethylaluminium chloride (0.98 mL, 0.98 mmol) solution (1M in hexane) was added dropwise to an ice-cooled stirring mixture of N,O-dimethylhydroxylamine hydrochloride (96 mg, 0.98 mmol) in CH₂Cl₂ (4 mL). After 10 min the reaction was removed from the ice bath and stirring was continued at room temperature. After 2 h stirring at room temperature, the clear solution was cooled to -25 °C and a solution of (+)-**3a** (100 mg, 0.49 mmol, 80% ee and dr = 10:1) in CH₂Cl₂ (2 mL) was added and stirring was continued at -25 °C for 16 h. The reaction was quenched with a saturated aqueous solution of potassium sodium tartrate (2 mL), diluted with water (25 mL), acidified with 2N HCl to pH ~7, and extracted with CH₂Cl₂ (25 mL × 3). The combined organic layers were washed with water, and brine, and dried over sodium sulfate. Removal of the solvent under reduced pressure followed by silica gel column chromatographic purification using 25% EtOAc/hexane afforded (-)-**4a** as a thick oil (113 mg, 87%), dr>99:1 (by ¹H NMR); Chiral HPLC analysis: 80% ee [Daicel Chiralpak OD-H column; 1.0 mL/min; solvent system: 10% isopropanol in hexane; retention time: 4.92 min (minor), 6.18 min (major)]; [α]_D²⁴ = -20.8 (c = 0.75, CH₂Cl₂); R_f = 0.3 (hexane-EtOAc, 2:1).

IR (CH₂Cl₂): 3448, 2962, 2936, 2874, 1637, 1455, 1387, 993, 706 cm⁻¹;

¹H NMR (400 MHz, CDCl₃, TMS): δ 7.33-7.27 (m, 2H, ArH), 7.26-7.17 (m, 3H, ArH), 4.07 (dd, *J* = 6.5, 4.6 Hz, 1H, H-3), 3.54 (s, 3H, OCH₃), 3.17 (s, 3H, NCH₃), 2.96 (bs, 1H, H-4), 2.71-2.61 (m, 1H, H-2), 1.82-1.70 (m, 1H, CH₂), 1.70-1.57 (m, 1H, CH₂), 1.18 (d, *J* = 7.0 Hz, 3H, 2-CH₃), 0.75 (t, *J* = 7.3 Hz, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃): δ 178.0, 142.2, 129.2, 128.4, 126.6, 75.1, 61.4, 50.7, 38.0, 32.4, 25.6, 12.2, 11.9.

(M + H)⁺ HRMS *m/z* calcd for (C₁₅H₂₄NO₃)⁺: 266.1756; Found: 266.1759.

(2R,3S,4S)-3-Hydroxy-N-methoxy-N,2-dimethyl-4-phenylhexanamide [(+)-4a]

Dimethylaluminium chloride (0.59 mL, 0.59 mmol) solution (1M in hexane) was added dropwise to an ice-cooled stirring mixture of N,O-dimethylhydroxylamine hydrochloride (57 mg, 0.59 mmol) in CH₂Cl₂ (3 mL). After 10 min, the reaction was removed from the ice bath and stirring continued at room temperature. After 2 h stirring at room temperature, the clear solution was cooled to -25 °C and a solution of (-)-**3a** (60mg, 0.29 mmol, 95% ee and dr = 19:1) in CH₂Cl₂ (2 mL) was added and stirring continued at -25 °C for 16 h. The reaction was quenched with a saturated aqueous solution of potassium sodium tartrate (2 mL), diluted with water (25 mL), acidified with 2N HCl to pH ~7, and extracted with CH₂Cl₂ (25 mL × 3). The combined organic layers were washed with water, and brine, and dried over sodium sulfate. Removal of the solvent under reduced pressure followed by silica gel column chromatographic purification using 25% EtOAc/hexane afforded (+)-**4a** as a thick oil (66 mg, 85%), dr>99:1 (by ¹H NMR); Chiral HPLC analysis: 95% ee [Daicel Chiralpak OD-H column; 1.0 mL/min; solvent system: 10% isopropanol in hexane; retention time: 4.88 min (major), 6.22 min (minor)]; [α]_D²⁴ = 22.8 (c = 0.5, CH₂Cl₂); R_f = 0.3 (hexane-EtOAc, 2:1).

IR (CH₂Cl₂): 3448, 2962, 2936, 2874, 1636, 1456, 993, 707 cm⁻¹.

¹H NMR (400 MHz, CDCl₃, TMS): δ 7.33-7.26 (m, 2H, ArH), 7.26-7.17 (m, 3H, ArH), 4.11-4.03 (m, 1H, H-3), 3.53 (s, 3H, OCH₃), 3.16 (s, 3H, NCH₃), 3.11 (bs, 1H, OH), 2.94 (bs, 1H, H-4), 2.71-2.62 (m, 1H, H-2), 1.82-1.70 (m, 1H, CH₂), 1.70-1.57 (m, 1H, CH₂), 1.18 (d, J = 6.9 Hz, 3H, 2-CH₃), 0.75 (t, J = 7.5 Hz, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃): δ 177.8, 142.2, 129.2, 128.4, 126.5, 75.0, 61.3, 50.7, 38.0, 32.3, 25.6, 12.1, 12.0.

(M + H)⁺ HRMS m/z calcd for (C₁₅H₂₄NO₃)⁺: 266.1756; Found: 266.1756.

(2*S*,3*R*,4*R*)-1-(Methoxy(methyl)amino)-2-methyl-1-oxo-4-phenylhexan-3-yl-3,5-dinitrobenzoate [(*-*)-5a]

3,5-Dinitrobenzoyl chloride (94 mg, 0.41 mmol) solution in CH₂Cl₂ (2 mL) and Et₃N (0.14 mL, 1.01 mmol) were added to an ice-cooled stirring solution of (*-*)-**4a** (90 mg, 0.34 mmol, 80% ee and dr = >99:1) in CH₂Cl₂ (4 mL). After 10 min, DMAP (4 mg, 0.03 mmol) was added to the reaction mixture, the reaction was removed from the ice bath, and stirring was continued at room temperature for 24 h. Water (30 mL) was added, the layers separated, and the aqueous layer extracted with CH₂Cl₂ (30 mL $\times$ 2). The combined organic layers were washed with water, and brine, and dried over sodium sulfate. Removal of the solvent followed by silica gel column chromatographic purification using 12% EtOAc/hexane afforded (*-*)-**5a** as a light yellow solid (103 mg, 66%), dr>99:1 (by ¹H NMR); Mp: 154-157 °C; [α]_D²⁴ = -20.8 (c = 2, CH₂Cl₂); R_f = 0.5 (hexane-EtOAc, 3:1). IR (CH₂Cl₂): 3104, 2967, 2937, 2876, 1733, 1655, 1545, 1345, 1272, 1075 cm⁻¹.

¹H NMR (400 MHz, CDCl₃, TMS): δ 9.19 (t, J = 2.1 Hz, 1H, NO₂ArH), 9.03 (d, J = 1.7 Hz, 2H, NO₂ArH), 7.34-7.27 (m, 2H, ArH), 7.26-7.16 (m, 3H, ArH), 5.90 (t, J = 6.4 Hz, 1H, H-3), 3.54 (s, 3H, OCH₃), 3.18 (s, 3H, NCH₃), 3.13 (t, J = 7.8 Hz, 1H, H-4), 3.10-3.02 (m, 1H, H-2), 1.88-1.77 (m, 1H, CH₂), 1.72-1.61 (m, 1H, CH₂), 1.17 (d, J = 6.8 Hz, 3H, 2-CH₃), 0.81 (t, J = 7.2 Hz, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃): δ 174.8, 162.2, 148.9, 140.4, 134.2, 129.6, 129.2, 128.7, 127.3, 122.5, 79.6, 61.4, 49.7, 38.3, 32.8, 25.8, 12.7, 12.1.

(M + H)⁺ HRMS m/z calcd for (C₂₂H₂₆N₃O₈)⁺: 460.1720; Found: 460.1727.

Assignment of relative stereochemistry

A colorless solution of pure (*-*)-**5a** in acetone/hexane (1:6) was prepared. Crystals suitable for X-ray structure analysis were obtained from this on standing. The relative stereochemistry of (*-*)-**5a** was determined by X-ray structure analysis to be *syn,anti*, and hence the absolute configuration was assigned to be (2*S*,3*R*,4*R*).²² By analogy, all β -lactones synthesized from (*S,E*)-heterodimers were assigned the (2*S*,3*R*,4*R*)-*syn,anti* configuration. Similarly, all β -lactones synthesized from (*R,E*)-heterodimers were assigned the (2*R*,3*S*,4*S*)-*syn,anti* configuration.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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22. Crystallographic data (excluding structure factors) for (–)-**5a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 1442759.

Our Previous work: **This work:** **Scheme 1.**Optimization of Catalytic Hydrogenation of *E*-Ketene Heterodimers.

Scheme 2.
Mechanistic Rationale for Formation of β -Lactones through Hydrogenation of *E*-Ketene Heterodimers.

Scheme 3.

Access to Dipropionate synthon **(+)-4a** from *syn,anti*- β -lactone **(-)-3a**.

Table 1

Substrate Scope of Catalytic Hydrogenation of *E*-Ketene Heterodimers.^a

Entry	Dimer (<i>E</i>)-1 (% ee)	R ¹	R ²	R ³	% Yield ^{b,c}	% ee ^d	dr ^e	Product
1	(<i>S</i>)-1a (94%)	Me	Et	Ph	76	80	10:1	(+)-3a
2	(<i>R</i>)-1a (85%)	Me	Et	Ph	82	95	19:1	(-)-3a
3	(<i>S</i>)-1b (92%)	Me	<i>n</i> -Bu	Ph	66	>99	15:1	(+)-3b
4	(<i>R</i>)-1b (84%)	Me	<i>n</i> -Bu	Ph	62	96	12:1	(-)-3b
5	(<i>S</i>)-1c (98%)	Me	<i>i</i> -Bu	Ph	58	96	7:1	(+)-3c
6	(<i>R</i>)-1c (96%)	Me	<i>i</i> -Bu	Ph	58	>99	16:1	(-)-3c
7	(<i>S</i>)-1d (88%)	Et	Et	Ph	65	99	49:1	(+)-3d
8	(<i>R</i>)-1d (93%)	Et	Et	Ph	85	97	13:1	(-)-3d
9	(<i>S</i>)-1e (98%)	Et	<i>i</i> -Bu	Ph	63	99	13:1	(+)-3e
10	(<i>R</i>)-1e (97%)	Et	<i>i</i> -Bu	Ph	68	97	12:1	(-)-3e
11 ^f	(<i>S</i>)-1f (95%)	Me	Me	Me	54	98	3:1	(-)-3f
12 ^f	(<i>R</i>)-1f (91%)	Me	Me	Me	49	94	4:1	(+)-3f

^a *E*:*Z* 4:1 in most cases (see procedures for individual details).^b Isolated yield for both diastereomers.^c Acid **2** also formed (ca. 15-40%, dr 1:1-2:1).^d ee of major diastereomer, determined by chiral GC analysis.^e dr determined by GC-MS analysis in most cases (by ¹H NMR for entries 11 and 12).^f Pentane used as solvent.