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Asymmetric Synthesis of Deoxypropionate Derivatives via Catalytic Hydrogenolysis of Enantioenriched *Z*-Ketene Heterodimers

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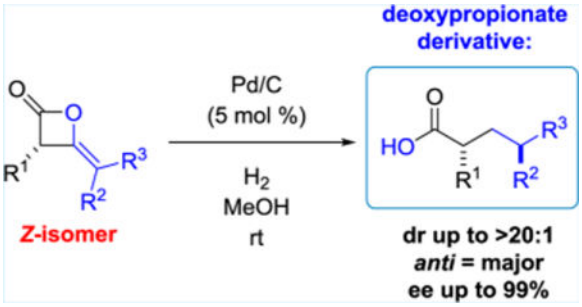
Abstract

A diastereoselective approach to deoxypropionate derivatives through Pd/C-catalyzed hydrogenolysis of enantioenriched ketene heterodimers is described. Catalytic hydrogenolysis of the *Z*-isomer of ketene heterodimers facilitates access to *anti*-deoxypropionate derivatives (10 examples with dr 7:1 to >20:1). Transfer of chirality from the *Z*-ketene heterodimer to an acid product was good to excellent in most cases (78–99% ee for 12 examples).



Deoxypropionate stereotriad units are compelling targets in synthesis, as they are integral structural features of many biologically active molecules (Figure 1).[1,2] Many of these molecules contain an *anti*-deoxypropionate unit, e.g. (−)-borrelidin, ionomycin, and 4,6,8,10,16,18-hexamethyldocosane.[1,2] Access to deoxypropionates has largely relied on methods involving chiral auxiliary-controlled enolate alkylations and conjugate additions, as well as substrate-controlled conjugate additions and allylic alkylations.[2] Feringa's and

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Supporting Information

Experimental procedures, spectroscopic data, and chromatograms for all new compounds, and CIF for derivative (+)-6. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.5b01391.

Notes

The authors declare no competing financial interest.

Negishi's groups have also reported catalytic asymmetric iterative approaches to deoxypropionates, although in Negishi's case with only moderate diastereoselectivity for *syn*-deoxypropionates.[3,4] In addition, Calter and co-workers have demonstrated that alkaloid-catalyzed asymmetric methylketene *homo*dimerization, coupled with diastereoselective aldol reactions, can be applied to the synthesis of deoxypropionate natural products, such as siphonarienal, siphonarienedione, and siphonarienolone.[5] However, Calter's elegant methodology for polypropionate synthesis requires additional deoxygenation steps in order to access deoxypropionate units.[5] Most synthetic strategies for deoxypolypropionates follow a linear-iterative concept, with new deoxypropionate units being successively added to a growing chain.[2,6] This approach, although conceptually simple, can lead to rather lengthy syntheses of complex molecules. Recently, some highly diastereoselective catalytic asymmetric approaches, which are not limited to iterative synthetic plans, have been introduced.[7–9] One especially noteworthy method was introduced by the Burgess group.[7] They demonstrated that a chiral Ir(I) complex could be used to catalyze the double diastereoselective hydrogenation of enantioenriched trisubstituted olefins, with good to excellent levels of diastereoselection being observed. However, Burgess's approach is dependent upon the availability of appropriate enantioenriched olefin substrates, which can often require lengthy multistep procedures to assemble (e.g., 6 steps for spongidepsin deoxypropionate unit).[9]

In contrast ketene *hetero*dimerization has remained a relatively unexplored field in the context of complex molecule synthesis.[10,11] Recently we reported the first catalytic asymmetric ketene heterodimerization reaction, which provided access to ketene heterodimer β-lactones with excellent enantio- and regioselectivity (Scheme 1).[12,13]

A fundamentally different approach to deoxypropionate synthesis would involve the use of an enantioselective ketene heterodimerization reaction followed by a diastereoselective catalytic hydrogenation reaction. Romo's group had previously demonstrated that the use of catalytic hydrogenation provided an efficient diastereoselective route for the synthesis of fully reduced *cis*-β-lactones from simple enantioenriched ketene homodimers.[14] We proposed a route whereby catalytic hydrogenation of a highly substituted ketene heterodimer **1** followed by regioselective ring opening of **2** would provide access to deoxypropionate unit **3** (Scheme 2).

We began our optimization of the proposed catalytic hydrogenation methodology with methylphenylketene-derived heterodimer *Z*-**1a** as the substrate (Scheme 3). Careful evaluation of a range of heterogeneous hydrogenation catalysts (Pd/C, Pt/C, Rh/C, Ru/C, PtO_2, Pd/alumina, $Pd/BaSO_4$, and Lindlar's catalyst among others) revealed that Pd/C was the optimal catalyst in terms of conversion of ketene heterodimer to reduction products (Scheme 3).[14] To our surprise, analysis of the reduction products revealed a mixture of fully reduced β-lactone **2a** and acid **3a** (formed through hydrogenolysis, Scheme 3).[15] Thereafter, we proceeded to optimize the process in order to favor direct formation of deoxypropionate **3a**. MeOH was found to be the best solvent for favoring formation of hydrogenolysis product **3a**, and with good diastereoselectivity (dr 4:1). We speculate that the use of a polar protic solvent allows for stabilization of the transition state leading to a palladium carboxylate intermediate to a greater extent than transition states containing just Pd–C

bonds, thus favoring formation of the carboxylic acid product. The *anti*-diastereomer was formed as the major diastereomer as determined by X-ray crystal structure analysis of a derivative of **3a** (see Supporting Information (SI) for details).

We then proceeded to evaluate the substrate scope of the reaction (Table 1). The ketene heterodimers examined had a *Z*/*E* ratio of 3:1 to >20:1 in most cases. In general it was found that when *Z*-ketene heterodimers were subjected to catalytic hydrogenolysis conditions, carboxylic acids **3** were formed as the major product, in good yield, and with moderate to excellent diastereoselectivity (Table 1). Minor amounts of reduced *β*-lactone 2 (typically 5–20%) were formed in most cases. Simple substrate modification (substituting Et for Me at R^3; **1b**) led to an improvement in diastereoselectivity (dr 7:1, entry 3, Table 1). The best levels of diastereoselectivity (dr >20:1) were observed when two moderately large alkyl substituents were employed (e.g., *n*-Pr and Et, entries 11 and 12, Table 1). We surmise that moderate diastereoselectivity for some examples (e.g., entries 1 and 2) may be due to equilibration of a *Z*-olefin intermediate (see Scheme 5). The ee of the acid was assayed for a selection of examples, and good to excellent transfer of chirality from ketene heterodimer to acid **3** was observed (78 to 99% ee for 12 examples analyzed).

It should be noted that the reaction is not strictly stereospecific; the minor *E*-isomer of ketene heterodimer does undergo hydrogenolysis to contribute the acid product as a mixture of *anti*- and *syn*-diastereomers. Occasional differences in diastereoselectivity resulting from enantiomeric ketene heterodimers were attributed to differing levels of *E*-ketene heterodimer in the starting material (e.g., for entry 9, dr 9:1 from (*S*)-**1e** with *Z*/*E* = 6:1 vs entry 10, dr 13:1 from (*R*)-**1e** with *Z*/*E* = 10:1).

From the data in Table 1, it is clear that an anion stabilizing group (e.g., Ph or $SiMe_3$) must be present at the olefin carbon furthest from the ring (the exocyclic olefin carbon) in order for the reaction to favor acid **3** rather than *β*-lactone **2**. When only alkyl substituents are present at this carbon, a complex product mixture containing none of **3** results (entry 19, Table 1). We hypothesize that hydropalladation regioselectivity is responsible for this divergency. Specifically, regioselective hydropalladation of the exocyclic olefin enabled by the presence of a Ph/$SiMe_3$ substituent would provide access to an intermediate with Pd bonded to the exocyclic carbon. This hydropalladated intermediate could subsequently undergo *β*-elimination and ultimately provide access to acid **3** (see Scheme 5).

A great advantage of the system is that both enantiomers of the deoxypropionate units can be readily obtained due to the availability of both antipodes of each ketene heterodimer (prepared through use of the appropriate pseudoenantiomer of a quinine/quinidine derivative in the alkaloid-catalyzed ketene heterodimerization reaction).[12]

The deoxypropionate derivatives **3** described here can be utilized effectively in the synthesis of natural products, as ably demonstrated by Negishi and co-workers.[4,16] The phenyl substituent of **3a**–**3h** can be treated as a protecting group and oxidized to a carboxyl group at an appropriate stage of a synthesis plan, allowing for extension of the deoxypropionate chain.[4] Aggarwal's group has also recently demonstrated how similar deoxypropionate units

may be incorporated via an iterative lithiation–borylation–protodeboronation strategy into a growing polydeoxypropionate chain.[6]

The formation of carboxylic acid **3a** from *Z*-ketene heterodimer **1a** could potentially be accomplished by a number of different mechanisms. To probe the mechanism of the hydrogenolysis reaction, we prepared *β*-lactone **2a** from ketene heterodimer *Z*-**1a**. This was done by carrying out the catalytic hydrogenation in EtOAc. The desired *β*-lactone **2a** 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 **2a**, and so we tentatively infer that **2a** does not function as an intermediate in the formation of acid **3a** (Scheme 4). However, at this point we cannot definitively rule out the possibility that another (unisolated) diastereomer of **2a** is an intermediate in the hydrogenolysis reaction. Subjecting heterodimer **1a** to deuteriolysis (15 atm D_2) revealed that no olefin migration occurs, as only the *β*- and *γ*-carbons (with respect to the carboxyl group) became labeled with D (Scheme 4).[17] In addition, when deuteriolysis (15 atm D_2) of **1i** was stopped before all of the heterodimer was consumed, no evidence for equilibration of olefin geometry in the starting heterodimer was observed (see SI for further details).[18]

Palladium catalysis typically involves *syn β*-eliminations, although there have been a few reports of *anti β*-eliminations in molecules where a good leaving group is present.[19] Hydrogenation of the *Z*-isomer of alkene **5** via TS1, in which the $A^{1,3}$ strain is minimized, predicts formation of the *anti*-isomer as the major diastereomer of **3a** (Scheme 5).[20,21] Alternatively, if *anti β*-elimination occurs, the *E*-isomer of alkene **5** would be formed. Hydrogenation of *E*-**5** would lead to formation of *anti*-**3a**, providing the carboxyl/carboxylate group (rather than Me) is the large substituent in an allylic strain-minimized conformation. Delivery of hydrogen to the less sterically hindered face would provide access to the *anti*-isomer of **3a**.[20] Mechanisms involving direct insertion into the heterodimer ring could also be possible.[22] Studies to distinguish between these mechanistic pathways are ongoing.

In summary, we have developed a catalytic asymmetric synthetic method of wide substrate scope that provides access to deoxypropionate derivatives with moderate to excellent diastereoselectivity (10 examples with dr ≥7:1, up to >20:1) from enantioenriched ketene heterodimers. Studies are currently underway to examine other hydrometalation technologies and to examine applications in complex molecule synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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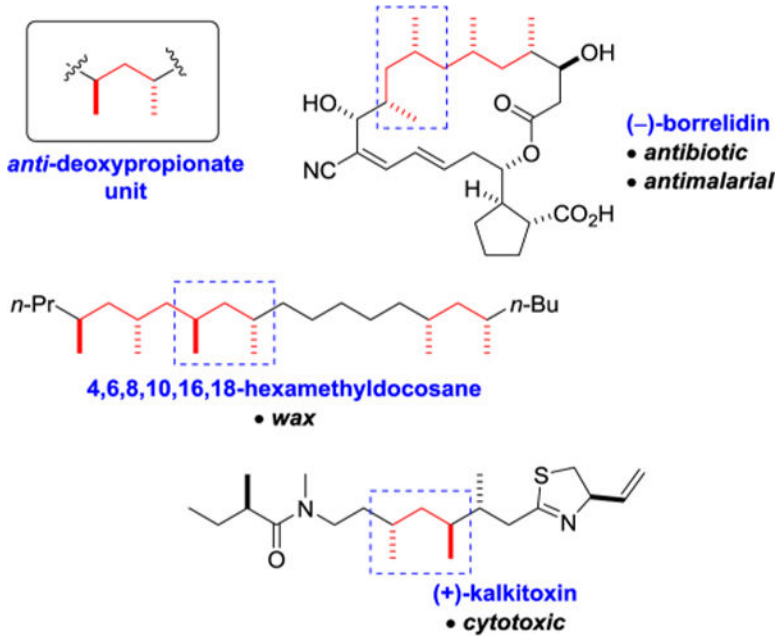
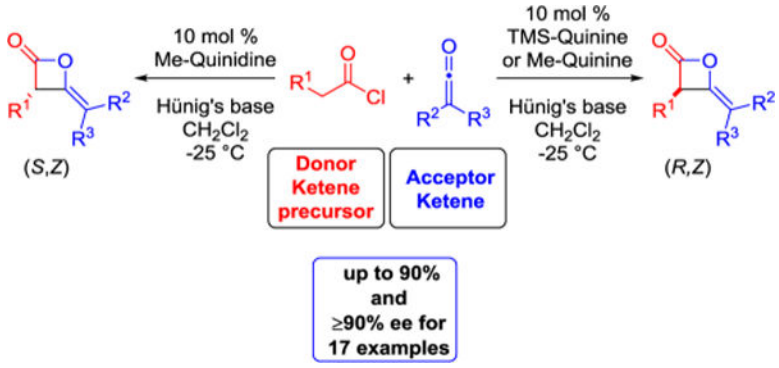
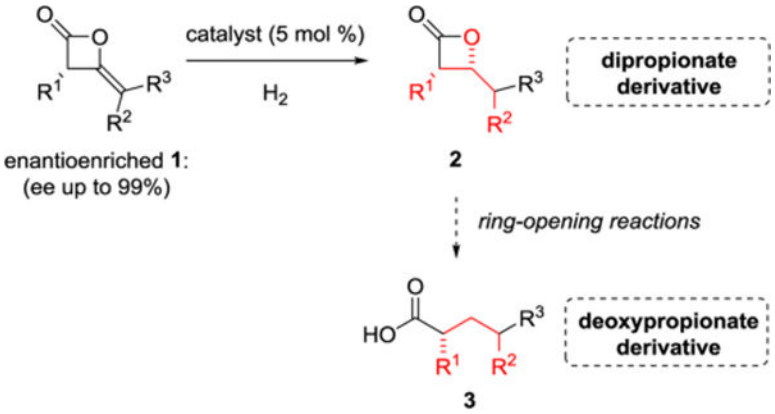


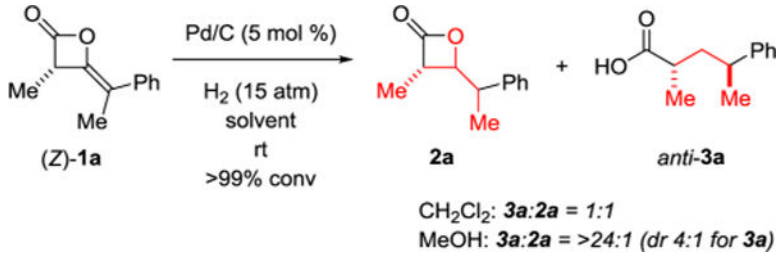
Figure 1.
Deoxypropionate natural products.



Scheme 1.
Catalytic Asymmetric Heterodimerization of Ketenes



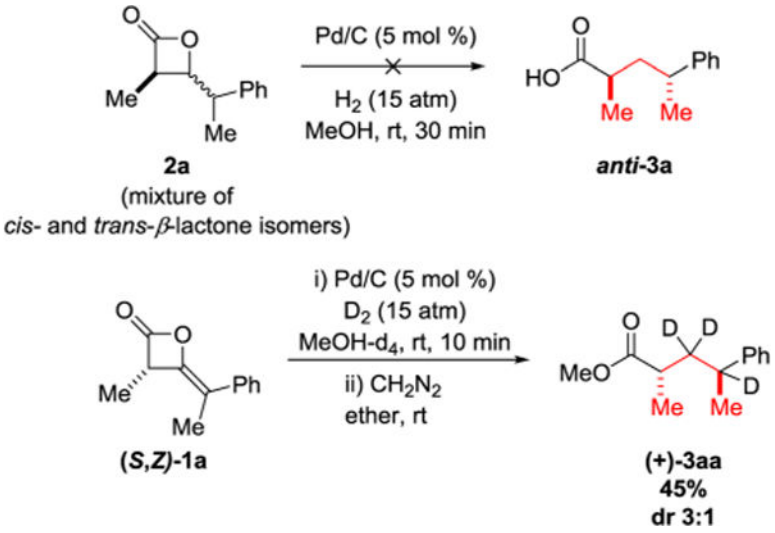
Scheme 2.
Initial Plan for the Catalytic Synthesis of Deoxypropionate Molecules



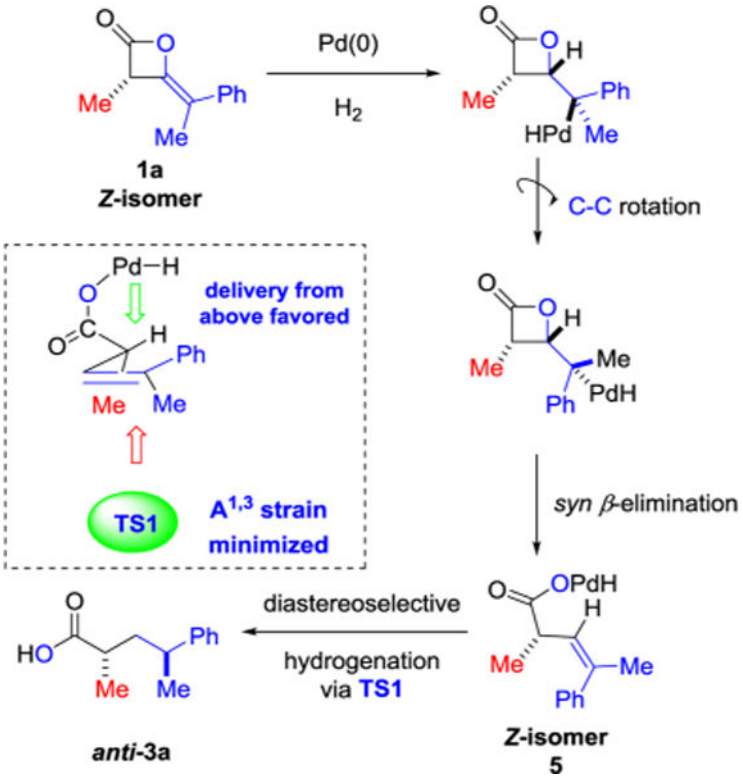
Scheme 3.

Optimization of Catalytic Hydrogenolysis of Ketene Heterodimers[a]

[a]conv = conversion, determined by GC-MS analysis of crude product; dr determined by GC-MS and corroborated by ^{1}H NMR analysis.



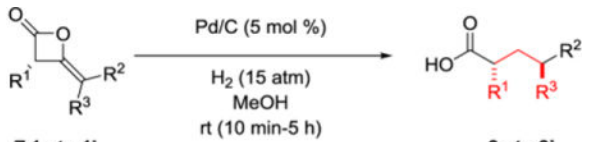
Scheme 4.
Mechanistic Experiments



Scheme 5.
Possible Mechanism for Catalytic Hydrogenolysis of Ketene Heterodimer

Table 1

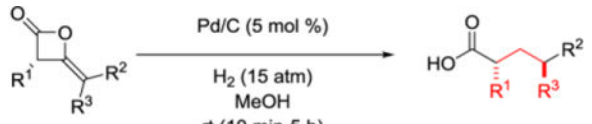
Substrate Scope of Catalytic Hydrogenolysis of *Z*-Ketene Heterodimers[a]



Z-1a to 1j (S) and (R) → **3a to 3j (+) and (–)**

R^2 = Ph except for
entry 17 and 18: R^2 = TMS (1i,3i)
entry 19: R^2 = Me (1j,3j)

entry ((*S*)- or (*R*)-1)[b]	R^1	R^3	% ee *Z*-1	yield[c] (%)	ee[d] (%)	dr[e]	3
1 (*S*)-**1a**	Me	Me	95	79	96	4:1	(+)-**3a**[f]
2 (*R*)-**1a**	Me	Me	93	75	94	4:1	(−)-**3a**
3 (*S*)-**1b**	Me	Et	98	73	79	7:1	(+)-**3b**
4 (*R*)-**1b**	Me	Et	73	55	92	7:1	(−)-**3b**
5 (*S*)-**1c**	Me	Ph	96	92	94		(+)-**3c**
6 (*R*)-**1c**	Me	Ph	96	73	86		(−)-**3c**
7 (*S*)-**1d**	Et	Me	99	98	96	4:1	(+)-**3d**
8 (*R*)-**1d**	Et	Me	99	87	95	4:1	(−)-**3d**
9 (*S*)-**1e**	Et	Et	95	84	86	9:1	(+)-**3e**
10 (*R*)-**1e**	Et	Et	70	83	78	13:1	(−)-**3e**
11 (*S*)-**1f**	*n*-Pr	Et	95	45[g]	99	>20:1	(+)-**3f**
12 (*R*)-**1f**	*n*-Pr	Et	72	66	80	>20:1	(−)-**3f**
13 (*S*)-**1g**	*n*-Bu	Me	94	79		>20:1	(+)-**3g**[h]
14 (*R*)-**1g**	*n*-Bu	Me	74	72		>20:1	(−)-**3g**
15 (*S*)-**1h**	*n*-Bu	Et	95	68		>20:1	(+)-**3h**
16 (*R*)-**1h**	*n*-Bu	Et	76	54[g]		>20:1	(−)-**3h**
17 (*S*)-**1i**	*n*-Hex	H	95	71			(−)-**3i**
18 (*R*)-**1i**	*n*-Hex	H	97	70			(+)-3i



Z-1a to 1j
(*S*) and (*R*)

3a to 3j
(+) and (–)

R^2 = Ph except for
entry 17 and 18: R^2 = TMS (1i,3i)
entry 19: R^2 = Me (1j,3j)

entry ((*S*)- or (*R*)-1)[b]	R^1	R^3	% ee *Z*-1	yield[c] (%)	ee[d] (%)	dr[e]	3
19 (*S*)-**1j**	Me	Me	95	0[i]			**3j**

[a] *Z*/*E* = 3:1 to >20:1 (see SI for individual details).

[b] Absolute configuration of heterodimer.

[c] Isolated yield for both diastereomers of **3**.

[d] ee of major diastereomer of **3**, determined by chiral GC of methyl ester derivative in most cases (by chiral HPLC for entries 5 and 6).

[e] dr determined by GC-MS or by ^{1}H NMR analysis of crudes.

[f] Sign of specific rotation.

[g] 15–20% of 2 as well.

[h] ee not determined for entries 13–18.

[i] Complex mixture with no acid **3**.