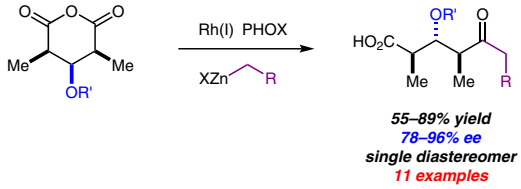
Synlett B. M. Cochran et al. Letter

Rhodium-Catalyzed Desymmetrization of *meso*-Glutaric Anhydrides to Access Enantioenriched *anti*,*anti*-Polypropionates

Brian M. Cochran[a]
Daniel D. Henderson[a]
Scott M. Thullen[a,b]
Tomislav Rovis*[a,b]

[a] Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, USA
[b] Department of Chemistry, Columbia University, New York, New York 10027, USA
tr2504@columbia.edu



Received: 22.08.2017
Accepted after revision: 13.09.2017
Published online: 17.10.2017
DOI: 10.1055/s-0036-1591488; Art ID: st-2017-b0639-l

Abstract An expedient desymmetrization of 3,5-dimethyl-4-alkoxyglutaric anhydrides to access *anti*,*anti*-polypropionates is described. The previously unknown anhydrides are rapidly assembled from readily available precursors. A Rh(I)·*t*-BuPHOX catalyst system was found to provide good yield and high selectivities. With these conditions, the trisubstituted anhydrides were desymmetrized with various alkyl zinc reagents to provide synthetically useful enantioenriched *anti*,*anti*-2,4-dimethyl-3-hydroxy-δ-ketoacids. An identical catalyst system also affords access to *syn*,*syn*-stereotriads as well as a partial kinetic resolution of a chiral anhydride.

Key words anhydride, desymmetrization, polypropionate, rhodium, zinc

Polypropionate natural products possess a daunting synthetic complexity that has long fascinated the synthetic community. The best known polypropionates are likely the macrolide antibiotics which possess distinctive 1,3-dimethyl moieties. Other polypropionates, such as dolabriferol,[1] ionomycin,[2] and zincophorin[3] also contain a similar *anti*,*anti*-1,3-dimethyl-2-hydroxy motif highlighted in Figure 1. Commonly utilized approaches to synthesize compounds like those shown in Figure 1 include aldol and crotylation reactions, although many strategies have been reported and reviewed.[4,5] In nature, these molecules are assembled from propionate and acetate monomers by the polyketide synthase (PKS) family of enzymes.[6,7] The almost limitless synthetic complexity arises from enzyme-promoted Claisen condensations, followed by partial or complete reduction of the resultant ketones. While nature can execute lengthy iterative syntheses with evolved efficiency, experimental syntheses of compounds containing several polypropionate segments can be lengthy and low-yielding ordeals.[8]

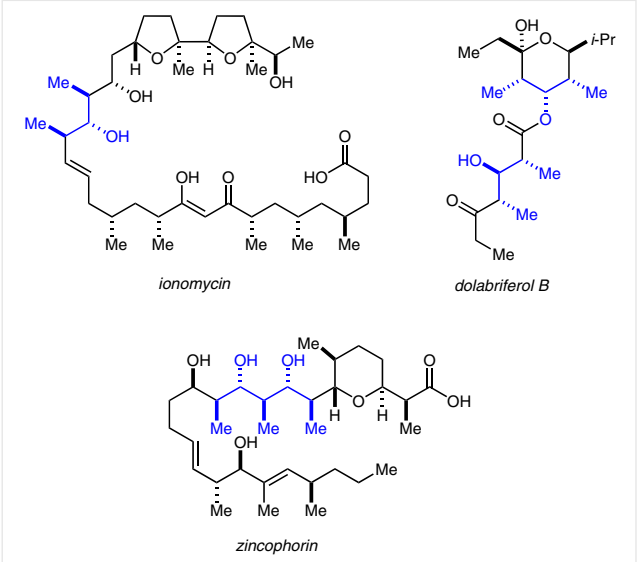
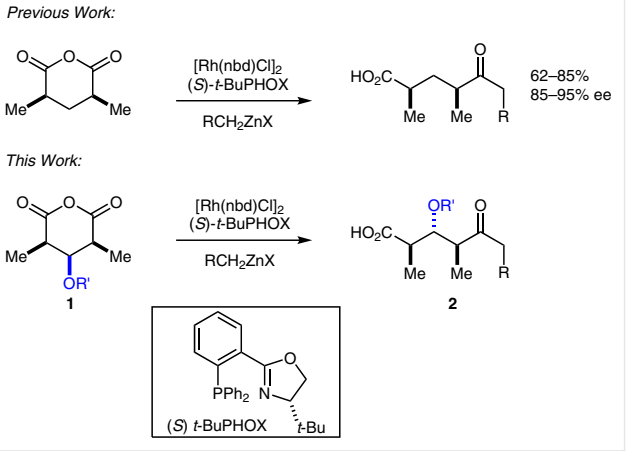


Figure 1 Natural products with the *anti*,*anti*-stereotriad

Desymmetrization of a *meso* starting material containing latent stereocenters establishes multiple stereocenters in a single operation,[9] but it is rarely used for the construction of polypropionate fragments.[10,2c] We have described Ni, Pd, and Rh catalysts for the cross-coupling of cyclic anhydrides, culminating in a Rh-catalyzed asymmetric desymmetrization of *meso*-3,5-dimethylglutaric anhydride with alkyl zinc reagents.[11–13] The valuable *syn*-1,3-dimethyl deoxypolypropionate stereodiad was thereby expeditiously accessed. Application of this methodology to hydroxylated glutaric anhydride **1** should result in access to polypropionates with oxygenation as shown in Scheme 1. However, the requisite anhydride **1** was not known, and the route used to access the deoxyanhydride was not amenable to substitution at that position. Furthermore, it was not obvi-

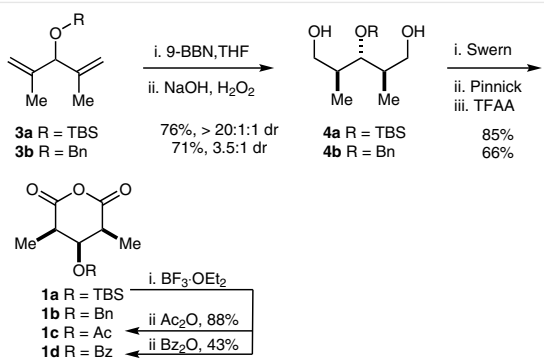
ous that additional steric bulk would be tolerated or the conditions mild enough to prevent elimination of the generated product. Herein, we disclose the successful realization of this goal.



Scheme 1 Extension of anhydride desymmetrization for *anti,anti* fragments

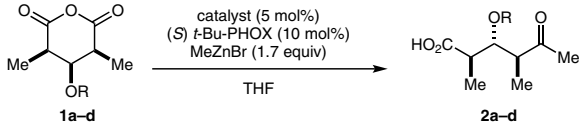
After surveying a number of approaches, we found that the 4-hydroxy-3,5-dimethyl glutaric anhydride desymmetrization precursor was readily accessed by a three-step process from dienes **3a**,**b** (Scheme 2). Utilizing hydroboration conditions developed by Harada,[14] *O*-TBS-protected diene **3a** was selectively oxidized to the *anti-anti*-diol using 9-BBN followed by hydrogen peroxide in >20:1:1 dr (Scheme 2). An *O*-Bn analogue **3b** was also oxidized to the diol under the same conditions with moderate selectivity (3.5:1 dr). Although accessing the anhydride from the diol appears trivial, the intermediacy of the lactol after the first oxidation and its inevitable oxidation to the lactone complicated the approach; the lactone proved resistant to further oxidation. Stepwise oxidation of the diol to the diacid was required to prevent lactol/lactone formation. To this end, a Swern followed by a Pinnick oxidation proceeded smoothly for both O-protected substrates. Cyclization of the diacid using trifluoroacetic anhydride gave the desired anhydrides in high yield over three steps. By this sequence, multigram quantities of anhydrides **1a** and **1b** were synthesized. Furthermore, the TBS group of **1a** was manipulated to an Ac (**1c**) or a Bz (**1d**) in a two-step process utilizing $BF_3{\cdot}OEt_2$ followed by the appropriate acylating agent.

The trisubstituted anhydrides **1a–d** were subjected to Rh(I)/PHOX/MeZnBr cross-coupling according to conditions previously developed for 3,5-dimethylgultaric anhydride (Table 1).[12] Anhydride **1a** failed to deliver ketoacid **2a** under these conditions and only decomposition products were detected (Table 1, entries 1 and 2). Presumably, the steric bulk of the TBS group on the anhydride prevents the oxidative insertion of the rhodium complex even when a sterically undemanding ligand is used (Table 1, entry 3). Gratifyingly, when the size of the protecting group on the alcohol was reduced to an acetate (**1c**), ketoacid **2c** was isolated in moderate yield and good enantioselectivity (Table 1, entry 3). Notably, when the diene ligand of the rhodium precatalyst was changed from cyclooctadiene to norbornadiene, the product yield and enantioselectivity increased (Table 1, entry 4).[15,16] Desymmetrization of anhydride **1d** and **1b** (Bz and Bn; Table 1, entries 5 and 6) also provides high yields and enantioselectivities of ketoacids **2d** and **2b**.[17] Due to the inherent stability of the Bn protecting group vs the Ac/Bz group,[18] anhydride **1b** was used to further explore the scope.



Scheme 2 Synthesis of *meso*-glutaric anhydrides

Table 1 Screen of O-Protecting Groups

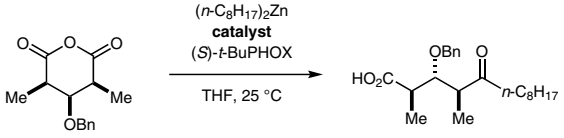


Entry	R	Catalyst	Yield (%)	ee (%)
1	**1a** TBS	$[Rh(COD)Cl]_2$	decomp.	–
2	**1a** TBS	$[Rh(nbd)Cl]_2$	decomp.	–
3	**1c** Ac	$[Rh(COD)Cl]_2$	47	84
4	**1c** Ac	$[Rh(nbd)Cl]_2$	90	91
5	**1d** Bz	$[Rh(nbd)Cl]_2$	50	86
6	**1b** Bn	$[Rh(nbd)Cl]_2$	98	91

An examination of the nucleophile scope beyond commercially available dialkyl zinc and alkyl zinc halide reagents was initially met with poor reactivity (Table 2). Dioctyl zinc was generated *in situ* from 1-iodooctane and diethyl zinc and when implemented using the above reaction conditions, ketoacid **5** was formed in 21% yield (Table 2, entry 1). Postulating that incomplete formation of the dioctyl zinc reagent results in the low yield, catalytic copper iodide was added during its formation[19] and the ketoacid yield increased to 47% (Table 2, entry 2). Concurrently with the de-

velopment of this methodology, our laboratory successfully explored hydroheteroarylation using rhodium(I) acetate complexes.[20] We envisioned a rhodium(I) acetate complex may undergo faster transmetalation with the dioctylzinc nucleophile as compared to a halogenated precatalyst. Adding 10 mol% $Zn(OAc)_2$ to the current reaction conditions drastically improved the yield of the ketoacid to 89% (Table 2, entry 3) presumably by making the rhodium acetate complex *in situ*. Indeed, when subjecting the isolated rhodium acetate norbornadiene complex to the reaction in the absence of $Zn(OAc)_2$ (Table 2, entry 4), the ketoacid was isolated with a comparable yield.

Table 2 Desymmetrization Optimization



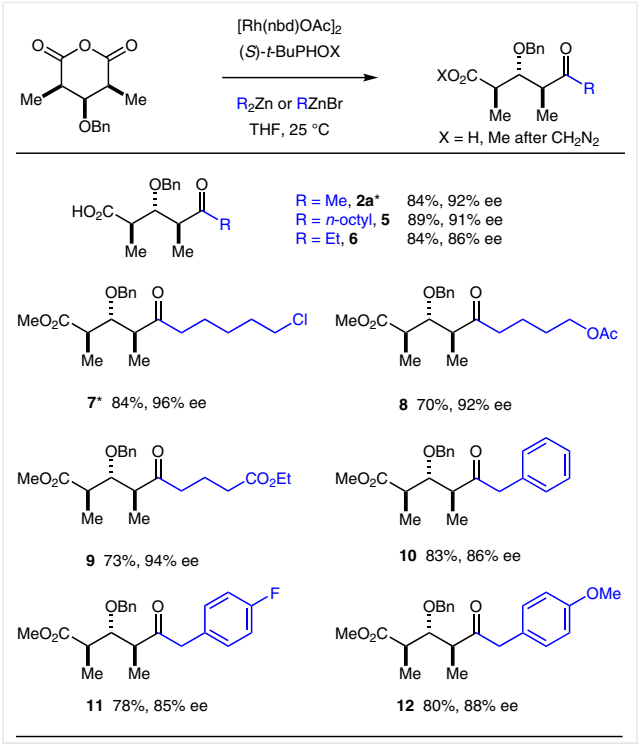
Entry[a]	Additive (mol%)[b]	Catalyst (mol%)	Yield (%)
1	none	$[Rh(nbd)Cl]_2$ (5)	21
2	CuI (0.3)	$[Rh(nbd)Cl]_2$ (5)	47
3	CuI (0.3)	$[Rh(nbd)Cl]_2$ (5) + $Zn(OAc)_2$ (10)	89
4	CuI (0.3)	$[Rh(nbd)OAc]_2$ (5)	83

[a] All reactions performed with 5 mol% [Rh], 10 mol% PHOX, and 1.7 equiv Oct_2Zn in THF (0.07 M) at 25 °C for 48 h.
[b] Additive used in formation of Oct_2Zn from OctI and Et_2Zn.

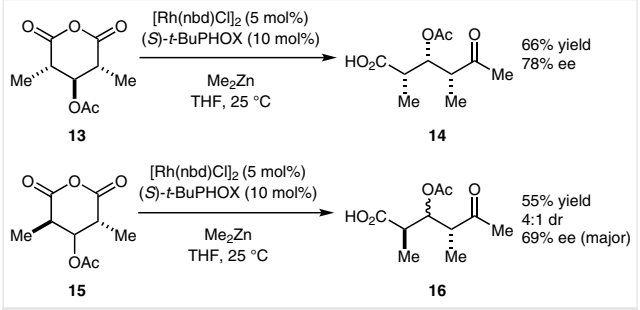
With these optimized conditions, an array of alkyl zinc reagents were effectively used in the desymmetrization of anhydride **1b** (Scheme 3). Small and long-chain alkyl groups were successfully added to give ketoacids **2a**, **5**, and **6** in good yield and good ee. The reaction tolerates chloride (**7**) and ester (**8** and **9**) functionalities having minimal impact on yield and ee. Benzyl groups with electron-donating and electron-withdrawing substituents (**10**–**12**) were also efficient in the desymmetrization reaction.

In addition to using this methodology to synthesize *anti,anti*-polypropionates, we briefly explored the desymmetrization of anhydrides to form *syn,syn*- and *syn,anti*-polypropionates with encouraging results (Scheme 4).[21] *meso*-Anhydride **13** successfully reacted with dimethylzinc utilizing early desymmetrization conditions to give ketoacid **14** in moderate yield and enantioselectivity. Additionally, racemic anhydride **15** was desymmetrized with dimethyl zinc in an enantio- and diastereoselective manner to give ketoacid **16** in 4:1 dr and 69% ee (major).[22] These unoptimized results are encouraging leads for further optimization.

In summary, we have demonstrated new methodology for the convergent synthesis of the *anti,anti*-polypropionate ketoacids utilizing a Rh(I)-catalyzed desymmetrization of anhydrides **1b–d** with primary alkyl zinc reagents and a *t*-Bu-PHOX ligand.[23,24] The anhydride precursors are readily accessed from a single diene. Through optimization, a Rh(I) acetate precatalyst was identified as superior vs a Rh(I) chloride precatalyst in the reaction. With this more reactive system, a variety of zinc nucleophiles were successfully used to desymmetrize anhydride **1b** in high yields and enantioselectivity to give synthetically useful *anti,anti*-polypropionates.



Scheme 3 Scope of alkyl zinc reagents. All reactions performed on 0.2 mmol scale with 5 mol% [Rh] dimer, 10 mol% *t*-BuPHOX and 1.7 equiv R_2Zn or RZnX in THF (0.07 M) at r.t. for 48 h. *$[Rh(nbd)Cl]_2$ used in place of $[Rh(nbd)OAc]_2$.



Scheme 4 Accessing *syn,syn*- and *syn,anti*-adducts

Funding Information

We thank the National Science Foundation for support of this work.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591488.

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(17) Absolute stereochemistry was determined by single crystal analysis of a sulfoxide derivative of **2b**. See Supporting Information.

(18) Over long reaction times or higher temperatures, the acetate and benzoate groups eliminate.

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(21) Anhydrides **13** and **15** were synthesized in a similar manner as **1c** and **1d** utilizing alternative hydroboration conditions developed by Harada (see ref. 14). See Supporting Information.

(22) Determination of a k_{rel} selectivity factor in this reaction was frustrated by anhydride hydrolysis and decomposition on workup.

(23) **General Procedure**

To a 5 mL flask was added $[Rh(nbd)Cl]_2$ (5 mol%) and (*S*)-*t*-BuPHOX (10 mol%). In some cases, $Zn(OAc)_2$(10 mol%) was also added. The flask was capped with a septum, placed under vacuum, and the atmosphere was replaced with argon. The solids were dissolved in THF (0.4 M vs anhydride) and freshly prepared organozinc reagent (see below; 0.2 M in THF, 1.7 equiv) was added by syringe producing a deep red solution. The appropriate anhydride (1 equiv) was dissolved in THF (0.25 M) and was added to the reaction by syringe taking care to remove all air from the headspace. The reaction was stirred at r.t. for 16–24 h, quenched with 1 M HCl and extracted in to EtOAc (3×).

(24) **Representative Example**

(2*R*,3*R*,4*S*)-3-(Benzyloxy)-2,4-dimethyl-5-oxohexanoic Acid (2b)

Following the general procedure on 1 g scale of the anhydride and using MeZnBr, a colorless oil was isolated (0.91 g, 87%). Conversion into the methyl ester utilizing diazomethane allowed for enantiomeric excess determination: Chiralpak IA column eluting with 99:1 hexanes/isopropanol, eluting at 1.0 mL/min, showing 92% ee, with the major enantiomer eluting at 19.26 min and the minor at 22.74 min. R_f = 0.26 (59:40:1, hexane/EtOAc/AcOH). $[\alpha]_D^{20}$ = –6.5 (*c* 0.011 g/mL, CH_2Cl_2). IR (thin film): ν_{max} = 3090, 3032, 2982, 2886, 1738, 1711, 1456, 1379, 1190, 1067, 738, 699 cm^{-1}. ^1H NMR: (300 MHz, $CDCl_3$): δ = 11.12 (br, 1 H), 7.24–7.18 (5 H, m), 4.53 (1 H, d, J = 11.2 Hz), 4.45 (1 H, d, *J* = 11.2 Hz), 3.96 (1 H, dd, *J* = 4.0, 8.0 Hz), 2.90 (1 H, quint, *J* = 7.2 Hz), 2.78 (1 H, dq, *J* = 4.4, 7.2 Hz), 2.17 (3 H, s), 1.25 (3 H, d, *J* = 7.2 Hz), 1.07 (3 H, d, *J* = 7.2 Hz). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 211.1, 179.1, 137.6, 128.4, 127.8, 82.7, 74.4, 49.2, 41.6, 30.3, 12.9, 12.6. LRMS (ESI, pos.): *m/z* calcd for $C_{15}H_{20}O_4Na$ $[M + Na]^+$: 287.30; found: 287.1.