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Stereodivergent Synthesis of Chiral Paraconic Acids via Dynamic Kinetic Resolution of 3-Acylsuccinimides

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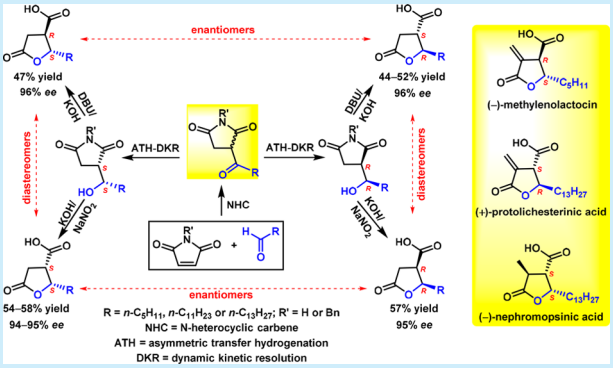
Supporting Information

ABSTRACT: A direct N-heterocyclic carbene (NHC) catalysis of maleimides with alkyl aldehydes is established for the synthesis of 3-acylsuccinimides. The first dynamic kinetic resolution of 3-acylsuccinimides is accomplished through asymmetric transfer hydrogenation. These two catalytic methodologies are utilized for the synthesis of each enantiomer of *trans*-paraconic acids in three steps and *cis*-paraconic acids in four steps with good yields and high stereoselectivities. This stereodivergent synthetic methodology is applied for the synthesis of seven bioactive paraconic acid natural products.



The stereoisomers of a drug exhibit a difference in their biological properties due to the building blocks such as amino acids and carbohydrates in the biological systems existing in homochiral forms. Hence, studying the structure–activity relationship of each stereoisomer of a drug in a specific target is an important area of research in medicinal chemistry.[1] Asymmetric synthesis of all the possible stereoisomers (stereodivergent synthesis) in pure form is a challenging task in synthetic organic chemistry.[2] Asymmetric catalysis has been developed as a modern tool for the stereodivergent synthesis of chiral molecules.[2b−f] But, direct application of the asymmetric catalysis for the stereodivergent synthesis of bioactive natural products is rarely studied in literature.[3]

On the other hand, stereodivergent paraconic acid natural products **1**–**7** show different biological properties,[4] such as antibiotic,[4a] anti-HIV-1,[4b,c] and antimicrobial,[4d] with respect to their substitution and stereochemistry (Figure 1). Some of these natural products have been synthesized using a chiral pool approach,[5] chiral auxiliaries,[6] chiral reagents,[7] and asymmetric catalysis.[8] To the best of our knowledge, there is no report in the literature for the stereodivergent synthesis of these natural products.

The α-methylene[8c] or α-methyl[5d] group could be conveniently installed at the later stage of the synthesis of these natural products. Hence, we envisaged a stereodivergent synthesis of the paraconic acids **12** and **13** and their enantiomers (*ent*-**12** and *ent*-**13**), as depicted in Scheme 1. *trans*-Paraconic acid **12** was synthesized from alcohol **11** through epimerization using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), followed by hydrolysis and cyclization.

The alcohol **11** was obtained through asymmetric transfer hydrogenation (ATH) accompanied by the dynamic kinetic resolution (DKR) of 3-acylsuccinimide **10**, which could be generated by the N-heterocyclic carbene (NHC) catalysis of maleimide **8** and alkyl aldehyde **9**. Synthesis of the other enantiomers of paraconic acids **12** (*ent*-**12**) was achieved through the alcohol *ent*-**11**, which could be obtained from **10** using the other enantiomer of a chiral catalyst in the ATH accompanied by DKR. Diastereomer **13** and its enantiomer (*ent*-**13**) could be accessed from alcohols **11** and *ent*-**11**, respectively, through hydrolysis, followed by cyclization without epimerization.

To initiate the stereodivergent synthesis of paraconic acids, the existing methods for the synthesis of 3-acylsuccinimide **10** were explored. Unlike the synthesis of 3-aroylsuccinimide,[9] there are very few methodologies[9b,c] for the synthesis of 3-acylsuccinimide **10** reported in the literature. Moderate to poor

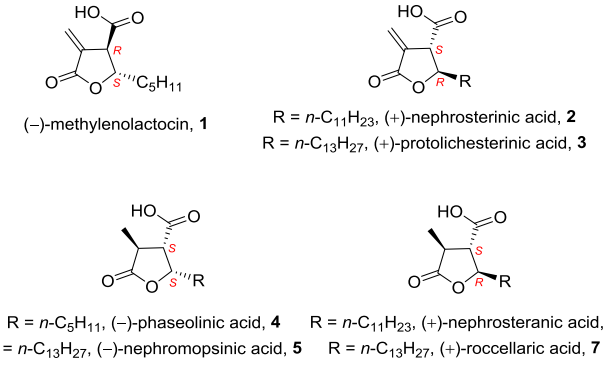


Figure 1. Bioactive paraconic acid natural products containing stereodivergent chiral centers.

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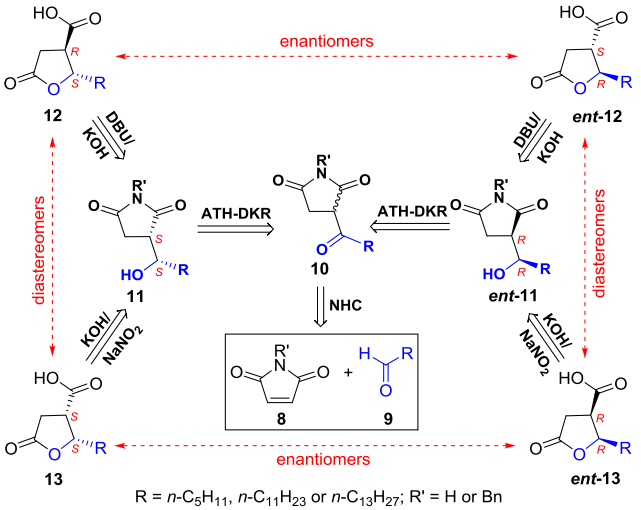
Scheme 1. Retrosynthetic Plan for the Stereodivergent Synthesis of Chiral Paraconic Acids



yields were reported for the direct acylation of succinimide.[9b,c] Very recently, 3-acylsuccinimide was synthesized in three steps starting from alkyl aldehyde.[9d] But, a NHC-catalyzed reaction of alkyl aldehyde with maleimide was found to be unsuccessful.[9a] Therefore, we attempted to develop a methodology for a one-step synthesis of 3-acylsuccinimide **10** starting from the alkyl aldehyde **9** and maleimide **8**.

Accordingly, hexanal **9a** and *N*-benzylmaleimide **8a** were treated with NHC precatalyst **cat-I** and K_2CO_3 in THF at rt, and no reaction was observed (Table 1, entry 1). When a precatalyst **cat-II** was used under similar reaction conditions, the product **14a** was isolated in 72% yield and 2:1 dr (entry 2). But, the expected 3-acylsuccinimide **10a** was not obtained even with the use of NaOAc or *N*,*N*-diisopropylethylamine (DIPEA) as the base additive (entries 2−5).

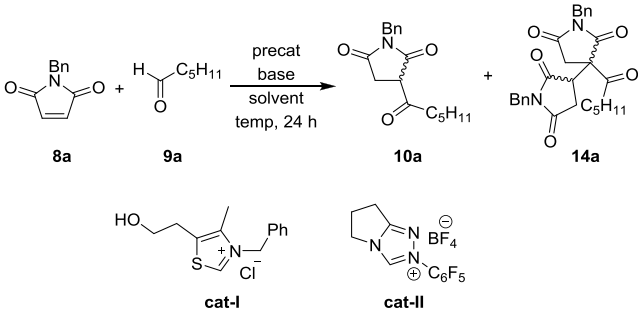
During the reaction at a higher catalytic loading (30 mol %) in toluene, the product **10a** was noticed in 25% yield along with **14a** (entry 6). The formation of **14a** was predicted to be an outcome of the Michael addition reaction of **10a** to **8a**. Therefore, the reaction was planned at a higher temperature to facilitate the retro-Michael reaction to obtain **10a** as the major product. Upon heating the reaction to reflux temperature in toluene, we were delighted to see the formation of 3-acylsuccinimide **10a** in 85% isolated yield (entry 7).

After the successful reaction optimization for the synthesis of 3-acylsuccinimide **10a**, the reaction of aliphatic aldehyde **9a−c** with maleimide **8a−b** to form 3-acylsuccinimides **10a−e** was achieved in excellent isolated yields under the optimized reaction conditions (Scheme 2).

As 3-acylsuccinimide **10** possesses an easily epimerizable chiral center, the DKR was envisaged during the reduction of **10** using ATH. The DKR of ketones,[10] imines,[11] keto esters,[12] keto amides,[13] and keto phosphonates[14] has been reported using ATH. To the best of our knowledge, there is no report in the literature for the DKR of keto imides (3-acylsuccinimides **10**). Hence, we initiated the reaction optimization for the ATH accompanied by DKR of 3-acylsuccinimides **10** (Table 2).

During the catalyst screening for the ATH of **10a** in CH_2Cl_2, an alcohol **15a** was observed as a major diastereomer (Table 2, entries 1−3) but with a lower ee (61% ee with the precatalyst

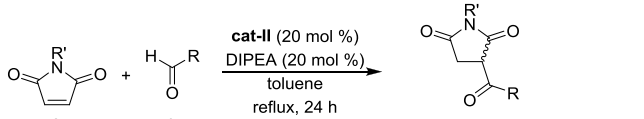
Table 1. Reaction Optimization for the Synthesis of 3-Acylsuccinimide 10a[a]



					yield (%)[b]	
entry	precat	base	solvent	temp	**10a**	**14a**
1	**cat-I**	K_2CO_3	THF	rt	–	–
2	**cat-II**	K_2CO_3	THF	rt	0	72[c]
3	**cat-II**	NaOAc	THF	rt	0	60
4	**cat-II**	DIPEA	THF	rt	0	76
5	**cat-II**	DIPEA	toluene	rt	0	86
6[d]	**cat-II**	DIPEA	toluene	rt	25	60
7[e]	**cat-II**	DIPEA	toluene	reflux	85[c]	0

[a]Reactions were performed with **8a** (38 mg, 0.2 mmol, 1.0 equiv), **9a** (74 μL, 0.6 mmol, 3.0 equiv), NHC precatalyst (0.02 mmol, 10 mol %), and base (0.02 mmol, 10 mol %) in solvent (2 mL) unless otherwise mentioned. [b]Determined by ^{1}H NMR analysis using 1,3-dinitrobenzene as an internal standard. [c]Isolated yield after column chromatography. [d]Catalyst (30 mol %) and DIPEA (30 mol %) were used. [e]Catalyst (20 mol %) and DIPEA (20 mol %) were used.

Scheme 2. Synthesis of 3-Acylsuccinimides 10a−e



10a, R = *n*-C_5H_{11}, R' = Bn, 87%
10b, R = *n*-$C_{11}H_{23}$, R' = Bn, 90%
10c, R = *n*-$C_{13}H_{27}$, R' = Bn, 89%
10d, R = *n*-C_5H_{11}, R' = H, 91%
10e, R = *n*-$C_{13}H_{27}$, R' = H, 80%

cat-IV). On the other hand, an alcohol **11a** was obtained in 70% ee but with a lower dr (Table 2, entry 3). Further reaction optimization with the precatalyst **cat-IV** in different solvents did not improve the stereoselectivities (dr and ee) of the alcohol **15a** (entries 4−6). However, a reversal of diastereoselectivity (3:1) was noticed in EtOAc to form **11a** as a major diastereomer with 81% ee (entry 6). As the precatalyst **cat-V** produced the alcohol **11a** with a higher ee in CH_2Cl_2 (entry 3), it was tested again in EtOAc, and **11a** was obtained in 95% yield with 3:1 dr and 94% ee (entry 7).

Upon further solvent screening, DMF was found to be a suitable solvent to form **11a** in 98% yield with 9:1 dr and 97% ee (entry 9). A lower catalytic loading (2 mol % of **cat-V**) at the higher reaction concentration in DMF (0.4 M) was successfully employed to achieve the alcohol **11a** in 97% yield with 9:1 dr and 97% ee through the ATH accompanied by DKR (entry 10). A further attempt to decrease the catalytic loading (1 mol % of **cat-V**) was not fruitful (entry 11).

Using **cat-V** under the optimized reaction conditions (Table 2, entry 10), 3-acylsuccinimides **10a** and **10c** were converted to the corresponding alcohols **11a** (78%) and **11c** (80%), respectively, as the major diastereomers with 9:1 dr and 97%

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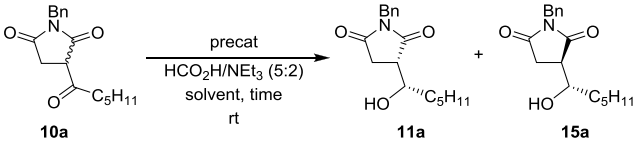
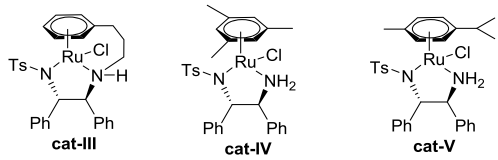
Table 2. Reaction Optimization for the Asymmetric Transfer Hydrogenation of 3-Acylsuccinimide 10a[a]





entry	solvent	precat (mol %)	time (h)	yield (%)[b]	dr[c] 11a:15a	ee (%)[d] 11a	ee (%)[d] 15a
1	CH_2Cl_2	**cat-III** (5)	24	93	1:3	9	41
2	CH_2Cl_2	**cat-IV** (5)	24	95	1:2	49	61
3	CH_2Cl_2	**cat-V** (5)	24	94	1:2	70	36
4	DCE	**cat-IV** (5)	24	86	1:2	57	52
5	$CHCl_3$	**cat-IV** (5)	24	–	–	–	–
6	EtOAc	**cat-IV** (5)	24	89	3:1	81	27
7	EtOAc	**cat-V** (5)	12	95	3:1	94	60
8	CH_3CN	**cat-V** (5)	12	92	3:1	91	18
9	DMF	**cat-V** (5)	24	98	9:1	97	20
10[e]	DMF	**cat-V** (2)	18	97	9:1	97	20
11[f]	DMF	**cat-V** (1)	40	86	5:1	97	nd

[a]Reactions were performed with **10a** (58 mg, 0.2 mmol), HCO_2H:NEt_3 (188 μL, 5:2), and precatalyst in solvent (2 mL, 0.1 M) unless otherwise mentioned. [b]Determined by ^1H NMR analysis using 1,3-dinitrobenzene as an internal standard. [c]Determined by ^1H NMR analysis of the crude reaction mixture. [d]Determined by HPLC analysis on a chiral stationary phase. [e]DMF (0.5 mL, 0.4 M) was used. [f]DMF (0.2 mL, 1M) was used.

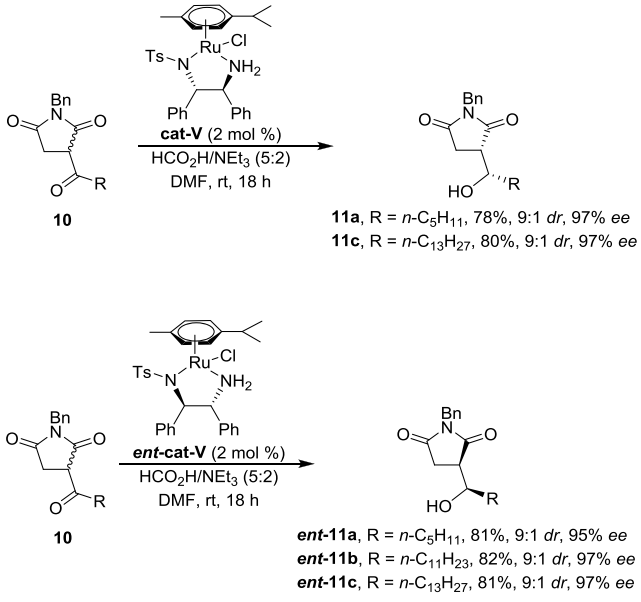
ee. On the other hand, the enantiomer of **cat-V** (*ent*-**cat-V**) was used for the synthesis of other enantiomers of alcohols **11a–c** (*ent*-**11a–c**) under the optimized reaction conditions in excellent isolated yields and stereoselectivities (Scheme 3). When 3-acylsuccinimides **10d** or **10e** were subjected to the ATH using **cat-V**, an inseparable diastereomeric mixture (9:1 dr) of alcohols was observed.

Once the alcohols **11** were synthesized from the ATH accompanied by DKR of **10**, we turned our attention toward the conversion of **11** to paraconic acids **12** or **13** with or without epimerization of the chiral center at the 3-position.

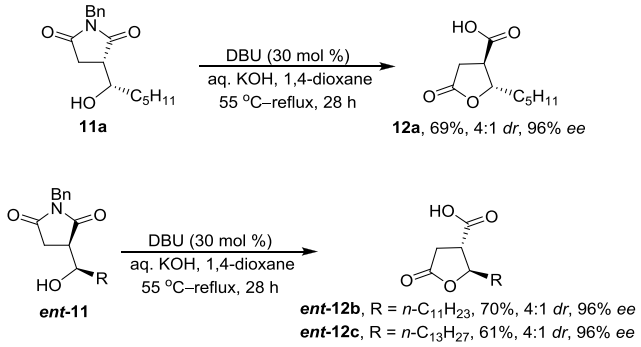
When the alcohol **11a** was heated in acidic (conc. HCl) or basic conditions (aq. KOH), a diastereomeric mixture of paraconic acids **12a** and **13a** was noticed (see the Supporting Information). Hence, the alcohol **11a** was epimerized to its diastereomer **15a** (4:1 dr) using DBU (30 mol %) in 1,4-dioxane at 55 °C, followed by the treatment with 10% aqueous KOH and then 30% aqueous KOH at reflux temperature to obtain *trans*-paraconic acid **12a** as the major diastereomer in 69% isolated yield and 4:1 dr (Scheme 4). Similarly, *ent*-**12b** (70%) and *ent*-**12c** (61%) were synthesized from *ent*-**11b** and *ent*-**11c**, respectively. The enantiomeric excess of *trans*-paraconic acids **12** was determined after converting them into the corresponding benzyl esters (see the Supporting Information).

For the synthesis of *cis*-paraconic acid **13a** as the major diastereomer, an alternate method was considered in two steps.

Scheme 3. ATH of 3-Acylsuccinimides 10a–c Using Precatalyst cat-V or *ent*-cat-V



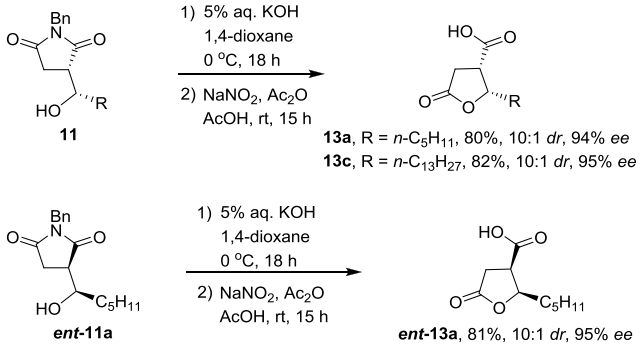
Scheme 4. Synthesis of *trans*-Paraconic Acids 12



Accordingly, the alcohol **11a** was treated with 5% aqueous KOH at 0 °C to facilitate hydrolysis of imide, and the crude reaction mixture was further treated with $NaNO_2$ and Ac_2O in AcOH to achieve the *cis*-paraconic acid **13a** as a major diastereomer in 80% isolated yield with 10:1 dr and 94% ee (Scheme 5). Similarly, the alcohols **11c** and *ent*-**11a** were converted to **13c** and *ent*-**13a**, respectively, in excellent isolated yields and stereoselectivities.

After the stereodivergent syntheses of paraconic acids (**12**, *ent*-**12**, **13**, and *ent*-**13**), their application to the syntheses of

Scheme 5. Synthesis of *cis*-Paraconic Acids 13



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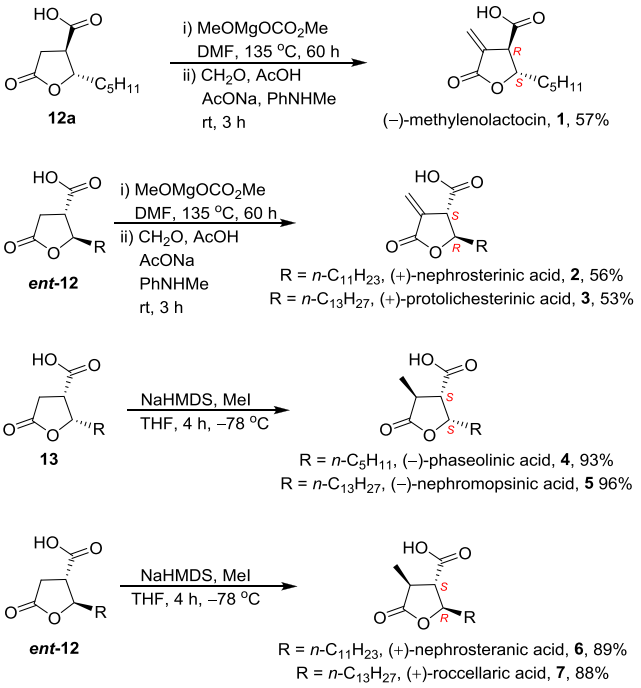
bioactive natural products **1**−**7** was planned (Scheme 6). Accordingly, the natural products **1**−**3** were synthesized by the

Scheme 6. Syntheses of Bioactive Paraconic Acid Natural Products 1−**7**



α-methylenation of **12a**, *ent*-**12b**, and *ent*-**12c**, respectively, using the literature procedure.[8c] The natural products **4**−**7** were synthesized by the α-methylation of **13a**, **13c**, *ent*-**12b**, and *ent*-**12c**, respectively, using the reported procedure.[5d]

In summary, we have developed an efficient and short synthetic route for the stereodivergent synthesis of substituted paraconic acids starting from commercially available maleimides **8** and alkyl aldehydes **9**. NHC catalysis is established for a one-step synthesis of 3-acylsuccinimides **10**. The first DKR of 3-acylsuccinimides **10** is accomplished through ATH to achieve the alcohols **11** or *ent*-**11** in good yields and high stereoselectivities. Synthesis of *trans*-paraconic acids **12** or *ent*-**12** is realized by DBU catalyzed epimerization of the alcohols **11** or *ent*-**11** followed by hydrolysis and cyclization under the basic conditions. Conversely, synthesis of *cis*-paraconic acids **13** or *ent*-**13** is achieved from the alcohols **11** or *ent*-**11** by mild hydrolysis followed by cyclization. Using this stereodivergent synthetic methodology, both the enantiomers of *trans*-paraconic acids (**12** and *ent*-**12**) are synthesized in three steps with 44−52% overall yield and 96% ee. On the other hand, both the enantiomers of *cis*-paraconic acids **13** and *ent*-**13** are obtained in four steps with 54−58% overall yield and 94−95% ee. This stereodivergent synthetic methodology is successfully applied for the synthesis of stereoisomeric bioactive paraconic acid natural products **1**−**7**. Further applications of this NHC catalysis and the ATH of 3-acylsuccinimides for the synthesis of other bioactive butyrolactone natural products are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01445.

Complete experimental procedures and characterization of new products, NMR spectra, and HPLC chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

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