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Enantiodivergent synthesis of *trans*-3,4-disubstituted succinimides by SmI_2-mediated Reformatsky-type reaction

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Abstract

An enantiodivergent strategy for the synthesis of *trans*-3,4-disubstituted succinimides is reported. The key step is a highly trans-stereoselective SmI_2-induced Reformatsky-type reaction of 4-substituted-O-benzoylated malimides with carbonyl compounds. Double chirality transmissions were performed with good to excellent diastereoselectivities.

Keywords: Succinimides; Reformatsky-type reaction; Samarium diiodide; Chiral relay; Enantioselective synthesis

Since the report of Komura and co-workers in 1987 on the isolation of andrimid as a new and highly specific antibiotic,[1] 3-substituted and 3,4-disubstituted succinimide substructure-containing compounds are emerging as a new class of natural products possessing important bioactivities. In addition to its original isolation from the culture broth of an intracellular symbiont of *Nilaparvata lugens* (brown planthopper), in 1994, andrimid has also been isolated along with moiramides A, B (**2**), and C from the marine bacterium *Pseudomonas fluorescens*.[2] Andrimid[3] (**1**) and moiramide B (**2**) (Fig. 1) were found to exhibit potent in vitro antibacterial activity against methicillin resistant *Staphylococcus aureus* and a range of other antibiotic resistant human pathogens.[1,2] The 3,4-disubstituted succinimide subunit was shown to be the key structural feature for efficient target binding.[1–4] More recently, hirsutellones A–E were isolated from the insect pathogenic fungus *Hirsutella nivea* BCC 2594, which display a significant growth inhibitory activity against *Mycobacterium tuberculosis* H37Ra;[5] while haterumaimides A–Q are cytotoxic labdane alkaloids isolated from an ascidian *Lissoclinum* sp.,[6] which have attracted considerable interest because of their potential use as protein synthesis inhibitors,[7] and as antitumor drugs.[8]

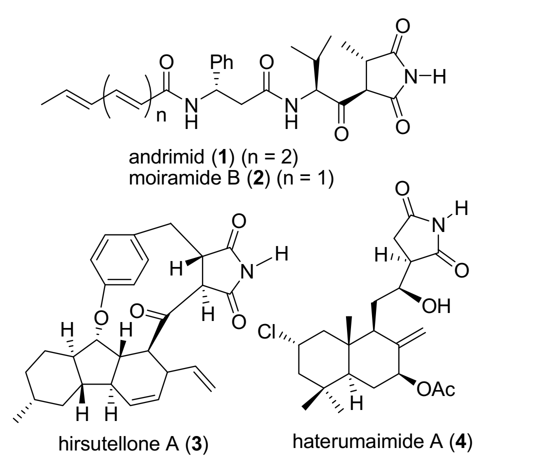

Fig. 1. Structure of some 3,4-disubstituted succinimide subunit containing natural products.

In continuation of our efforts toward the development of synthetic methodologies based on cheap and easily available optically active α-hydroxy acids[9] and considering the

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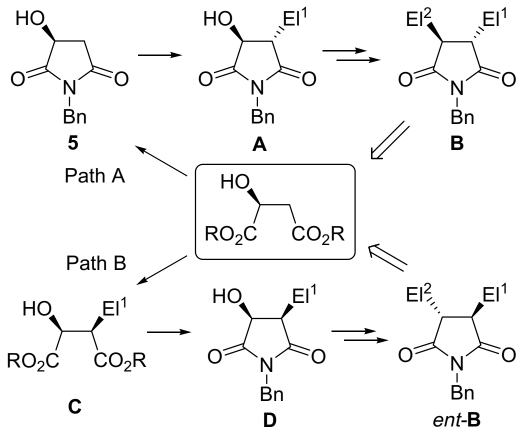


Scheme 1. Enantiodivergent approach to **B** or *ent*-**B** based on double chirality relay method.

substituent diversity of succinimide-type natural products, we envisioned the development of a chirality relay-based approach to 3,4-disubstituted succinimides by exploring an SmI_2-mediated Reformatsky-type reaction. The results of these investigations are described herein.

As can be seen from Scheme 1, the aim of our research was to develop an enantiodivergent and stepwise chirality relay-based concept that differs from Seebach's well-known SRS (self-regeneration of stereocenters) methodology[10] in that the original chirality is also the temporary one, and both enantiomers are accessible from the same chiron via two variants.

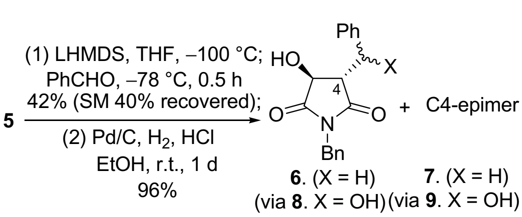
To validate this concept, we first investigated the installation of the alkyl group at C-4 of malimide **5**. Because initial attempts to perform a direct alkylation[3,11,12] of malimide **5** yielded a mixture of two inseparable diastereomers **6/7**, we explored a two-step procedure. Thus, treatment of the dianion generated from malimide **5** (LHMDS 2.2 equiv, −100 °C, 0.5 h) with benzaldehyde gave the desired aldol-type products **8** and **9** as a mixture of four diastereomers in 42% yield (69% based on the recovered starting material) (Scheme 2). Subjection of the diastereomeric mixture of benzylic alcohols **8/9** to hydrogenolysis (H_2, Pd/C. EtOH, HCl, rt, 1 d) led to the deoxygenated products **6** and **7** in 6:1 ratio with a combined yield of 96%. This result showed that the stereoselectivity of the imide aldol-type reaction at the malimide ring (C-3/C-4) was 6:1 in favor of trans-diastereomer **8**. Similar deoxygenation of the major diastereomers **8** afforded the benzylated diastereomer **6** as the sole diastereomer. These results imply that compounds **8/9**, and thus **6/7** are diastereomers at C-4. The trans-stereochemistry of compounds **6** and **8** was assigned according to the observed characteristic vicinal coupling constants ($J_{3,4} = 3.9$–4.0 Hz).

After securing access to 4-benzylmalimide **6** in substantial amount, we turned our attention to the key issue of the strategy, namely the dehydroxylative enolate formation-nucleophilic reaction with an aldehyde (**A**→**B**; **D**→*ent*-**B**) (Scheme 1). Although a stepwise SmI_2-induced deoxygenation[13] and enolate formation followed by an aldol-type reaction can be envisioned, there exist several drawbacks in such an approach, for example, low chemical yields, low diastereoselectivity,[14] as well as possible epimerization or racemization of the aldol-type reaction due to the high basicity of the enolates. To tackle these problems, SmI_2-mediated tandem deoxygenation-nucleophilic addition, namely a Reformatsky-type reaction, was envisioned.

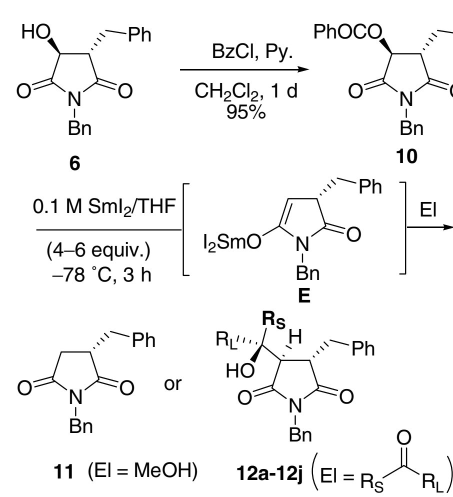
Several SmI_2-mediated Reformatsky-type reactions[15–18] have been reported; however, most of them involve α-bromo-, α-phenylthio-, or α-pyridinylthio-substituted ketones, imide, or carboxylic acid derivatives.[15,17] The most attractive method is the SmI_2-promoted Reformatsky-type reaction of α-benzoyloxy lactone derivatives developed by Enholm.[16]

Thus 3-*O*-benzoylmalimide derivative **10** was selected as our starting material, which was prepared from **6**. Treatment of a THF solution of malimide 3-*O*-benzoate **10**[20a] with 4.0 mol equiv of a 0.1 M THF solution of SmI_2[19] at −78 °C and in situ quenching of the organosamarium(III) intermediate **E** with methanol gave the desired deoxygenated product 3-benzylsuccinimide **11** in quantitative yield (Scheme 3, Table 1, entry 1). The formation of **11** in high yield implied that the reductive samariation of **10** occurred smoothly. The optical rotation for 3-benzylsuccinimide **11** $\{[\alpha]_D^{17}$ 81.1 (*c* 0.95, $CHCl_3$)$\}$ consists with those of the *S*-enantiomers of its N-substituted analogs.[3c,24b]

Next, the SmI_2-mediated Reformatsky-type reaction of malimide derivative **10** with a variety of ketones or



Scheme 2. Synthesis of 1,4-dibenzylmalimide.



Scheme 3. SmI_2-promoted deoxygenation-coupling reactions of **10**.

Table 1
SmI_2-mediated Reformatsky-type reaction of malimide derivative **10** with electrophiles

Entry	Electrophile	Product[a] (yield, %)	Diastereoselectivity at C-1′[d] (%)
1	CH_3OH	**11** (100)[b]	—
2	MeCOMe	**12a** (92)[b]	Single diastereomer
3	MeCOEt	**12b** (94)[b]	1:5.2
4	*n*-PrCOEt	**12c** (90)[b]	1:2.7
5	*t*-BuCOMe	**12d** (82)[b]	Single diastereomer
6	$(CH_2)_4CO$	**12e** (90)[b]	Single diastereomer
7	$(CH_2)_5CO$	**12f** (94)[b]	Single diastereomer
8	*n*-$C_5H_{11}CHO$	**12g** (94)[c]	1:6.5[e]
9	*n*-$C_7H_{15}CHO$	**12h** (90)[c]	1:4[e]
10	*i*-PrCHO	**12i** (92)[c]	Single diastereomer
11	*t*-BuCHO[f]	**12j** (91)[c]	Single diastereomer

[a] Isolated yield, only the trans-diastereomers were obtained.
[b] 4.0 mol equiv of SmI_2.
[c] 6.0 mol equiv of SmI_2.
[d] Diastereoselectivity (at the carbinolic center) determined by ^{1}H NMR.
[e] Diastereoselectivity determined by HPLC.
[f] A solution of 75% pivalaldehyde in *t*-BuOH was used.

aldehydes was investigated under Barbier-type conditions[20b] and the results are summarized in Table 1. As can be seen from the table, all the reactions gave the desired Reformatsky-type products **12a**–**12j** in excellent yields. What is surprising is that not only did the reactions with symmetric ketones give a single diastereomer in each case (Table 1, entries 2, 6, and 7), but coupling with sterically hindered pinacolone, *i*-butanal, and pivalaldehyde (Table 1, entries 5, 10, and 11) also resulted in a single diastereomer in each case. The reactions with 2-butanone and *n*-hexanal also afforded good diastereoselectivities (Table 1, entries 3 and 8).

The stereochemistry of compound **12d** was determined by single crystal X-ray crystallographic analysis,[20c] which shows that the stereochemistry at the C-1′ is *R* and the relative stereochemistry is trans-*threo*. The stereoselectivity of the reaction can therefore be rationalized with the favored transition state **F** (Fig. 2), which implies that carbonyl compounds approach trans to the alkyl group of enolate **E** (Scheme 3) and with the *si*-face of the approaching carbonyl group.

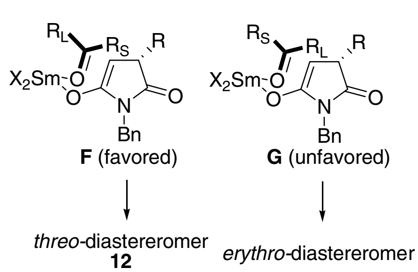
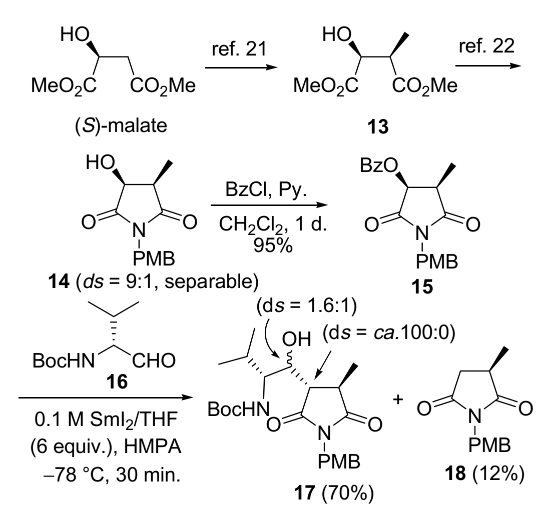


Fig. 2. Proposed transition state for the SmI_2-mediated Reformatsky-type reaction of **10** with carbonyl compounds. R_S = smaller alkyl groups; R_L = larger alkyl groups.

After accomplishing the synthesis of *trans*-3,4-disubstituted succinimides of type **B** via route A (Scheme 1), we next turned our attention to explore the synthesis of succinimides of type *ent*-**B**. To avoid the use of the more expensive (*R*)-malic acid for establishing 4*R*-chirality, an alternative route (route B, Scheme 1) was investigated. To this end, methyl (*S*)-3-methylmalate **13** was prepared according to Seebach's method,[21] and then converted successively into the known 4-methylmalimide **14**[22] and benzoate **15** (Scheme 4). The latter was subjected to an SmI_2-mediated Reformatsky-type reaction with α-aminoaldehyde **16**,[23] which afforded **17** as a mixture of two diastereomers in 1:1.6 ratio along with 12% of the reduced product **18**.[24] In the light of the high level of stereochemical transmission observed in the SmI_2-mediated Reformatsky-type reaction of **10** (Table 1), the two diastereomers obtained from the reaction of **15** were assigned as diastereomeric **17**, which may be used as key intermediates for the synthesis of andrimid. More importantly, this result implies that even with the small methyl group, the SmI_2-mediated Reformatsky-type reaction still provides excellent diastereoselectivity. Comparison of the optical rotation of succinimide **18** {$[\alpha]_D^{25}$ +17.8 (*c* 1.13, $CHCl_3$)} with that reported for its antipode {$[\alpha]_D^{23}$ −17.3 (*c* 1.10, $CHCl_3$)}[24b] allowed us to conclude that no appreciable racemization or epimerization occurred in the synthetic sequence. The low diastereoselectivity at C-1′ might be attributed to the presence of a chelating group in **16**, and/or a mismatched situation.

In summary, by combining different chirality relay strategies (alicyclic chelation control and cyclic steric control) and a synthetic methodology (SmI_2-induced Reformatsky-type reaction of succinimide derivatives), we have established an enantiodivergent approach to 3,4-disubstituted succinimides. The highly diastereoselective SmI_2-induced Reformatsky-type reaction of α-benzoyloxy imides (4-substituted-O-benzoylated malimides) will find applications in organic synthesis.



Scheme 4. An access to *ent*-**B** via an alternative double chirality relay method.

Acknowledgments

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20. (a) All the new compounds gave satisfied analytical and spectroscopic data; (b) *General procedure for the synthesis of succinimide derivatives* **12** *by SmI_2-mediated Reformatsky-type reaction of malimide derivative* **10**: To a cooled solution (−78 °C) of malimide derivative **10** (100 mg, 0.25 mmol) in anhydrous THF (2.50 mL) were added successively and under an atmosphere of argon, a carbonyl compound (0.50 mmol) and a 0.1 M THF solution of SmI_2 (40 mL, 4.0 mmol). The mixture was stirred at −78 °C until the dark blue color disappeared (for aldehyde, addition of another 2 equiv of SmI_2 is necessary). The reaction was quenched with 20 mL of saturated aqueous NH_4Cl solution and 5 mL of 1 M hydrochloric acid. The resulting mixture was extracted with EtOAc (3 × 40 mL). The organic layers were washed successively with a saturated aqueous $NaHCO_3$ solution, a $Na_2S_2O_3$ solution, and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (EtOAc/PE = 1:5) afforded the corresponding Reformatsky-type products **12**; (c) Crystallographic data for the structure of **12d** have been deposited in Cambridge Crystallographic Data Centre with the number CCDC-659938. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
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