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Re-visiting the diastereoselectivity of organocatalytic conjugate addition of 2-trimethylsiloxyfuran to *trans*-crotonaldehyde

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ABSTRACT

We describe the re-assignment of configuration previously ascribed to product diastereomers resultant from imidazolidinone-catalyzed conjugate addition of 2-trimethylsiloxyfuran to *trans*-crotonaldehyde. A modified procedure that uses a diphenylprolinol catalyst was subsequently developed to selectively provide the '*syn*' diastereomeric product in high enantiomeric excess on decagram scales.

The catalyzed conjugate addition of 2-siloxyfurans to Michael acceptors is a valuable method to prepare γ-substituted butenolides – a structural motif commonly observed in natural products and synthetic drug substances [1]. Studies by Brown and co-workers [2] demonstrated that chiral imidazolidinones could catalyze asymmetric conjugate addition of siloxyfurans to enal acceptors. Following that report, additional organocatalysts were shown effective for the transformation [3]. As part of studies aimed at synthesizing the pro-apoptotic natural product portimine [4], we required scalable access to the (3*S*, 5*R*) enantiomer of butenolide **1**, a '*syn*' diastereomer resultant from adding 2(5*H*)-furanone (or 2-trimethylsiloxyfuran) to *trans*-crotonaldehyde (Fig. 1A).

Of the known syntheses of **1** [3a-c], only Brown and co-workers reported [2] isolating the molecule in high diastereomeric and enantiomeric excess. In our hands, however, imidazolidinone catalyzed addition of 2-trimethylsiloxyfuran to *trans*-crotonaldehyde gave two isomeric butenolides in a ratio of ~2:1. Moreover, data originally reported for those products were inconsistent with that expected when using *trans*-crotonaldehyde. Instead, it appeared to reflect products derived from using 4-methyl-2-pentenal in the reaction [9]. Adding to this puzzle was the fact that ^{1}H NMR data for isomers **1** prepared by others were conflicting (Fig. 1B) [3a-c]. Lastly, related reactions of 2(5*H*)-furanone derivatives with (*E*)-β-methyl Michael acceptors gave mainly *anti* diastereomers [3a,5] or were non-selective [3b,3c]. For our own studies to progress, we needed to clarify these findings and develop an efficient, selective and scalable synthesis of (3*S*, 5*R*)-**1**.

We synthesized racemic **1** using a procedure developed by Yadav and co-workers for the addition of 2-trimethylsiloxyfuran to enones [6]. Stirring 2-trimethylsiloxyfuran with crotonaldehyde in the presence of catalytic I_2 gave (±)-**1** with exquisite stereocontrol (76%, *dr* > 20:1). When that material was reduced under Luche conditions and the incipient alcohol treated with NaH (THF, rt), one isomer of bicyclic tetrahydropyran **3** was isolated, albeit in low yield. *J*-couplings and NOE data (see ESI for details) obtained for **3** supported the stereochemistry drawn in Scheme 1, thereby implying precursor (±)-**1** was '*anti*' (as drawn). Further support for this assignment came from hydrogenating (±)-**1**, oxidizing the product under Pinnick conditions and coupling the resultant acid with 2-oxazolidone to afford imide (±)-**4**. NMR spectral data for (±)-**4** were identical to those reported by Katsuki [5a].

Having identified the *anti* diastereoisomer of **1**, we confirmed the identity of the *syn* diastereomer through regioselective Wacker–Tsuji oxidation [7] of (3*S*, 5*S*)-γ-butyrolactone **5** [8] to afford aldehyde **6**. The ^{1}H NMR spectrum of **6** was identical to that obtained by hydrogenating the minor isomer of **1** obtained from the Brown catalysis (Table 1, entry 1). Thus, the 2:1 mixture of isomers generated using the Brown procedure favors the *anti*-diastereomer, not the *syn* as reported. Our assignments are in agreement with those made by Yanai and co-workers [3a] and contrary to those made by Luo and co-workers. The major diastereomer isolated by Luo is *syn*, not *anti* as reported [3b].

Confident in our relative stereochemical assignments, we next sought to optimize the catalytic asymmetric synthesis of (3*S*, 5*R*)-**1**. We screened diastereoselectivity in the addition of 2-trimethylsiloxyfuran to *trans*-crotonaldehyde using several

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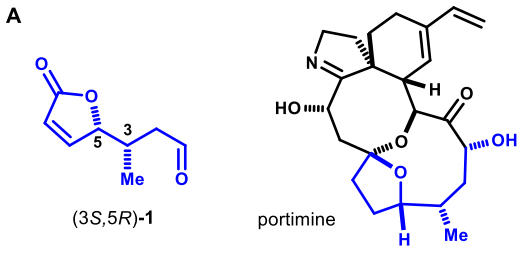
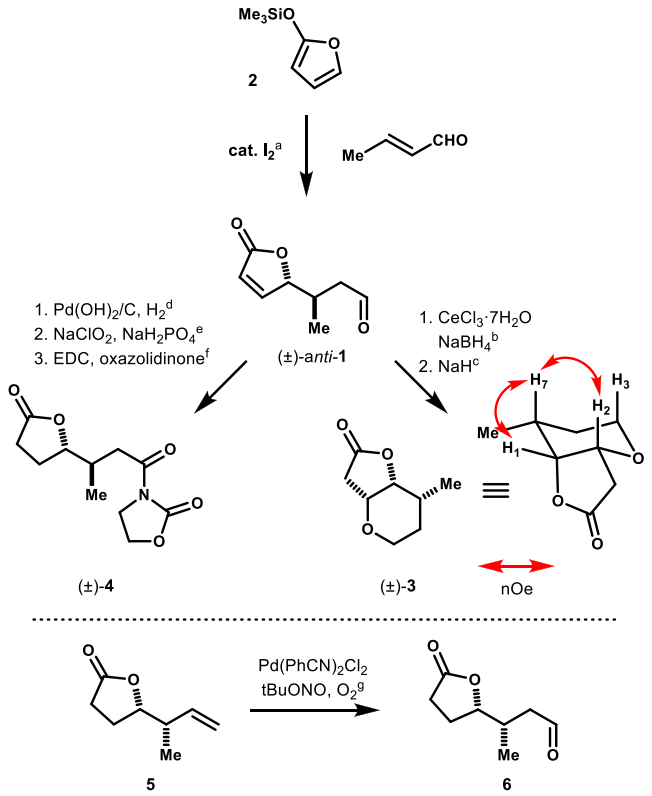


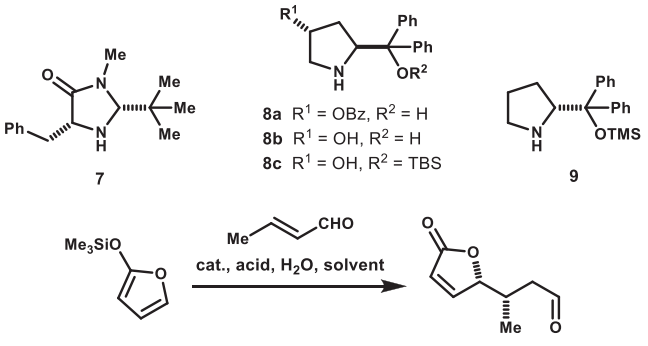
Ref	(*syn*:*anti*)	^{1}H NMR (δ CH$_3$)	
		syn	*anti*
2	8:1	-[b]	-[b]
3a	1:5.5	0.90	1.09
3b	1:2	-[b]	0.90
3c	42:58	1.11	0.87

Fig. 1. A) Butenolide **1** maps cleanly onto a segment of portimine. **B**) Data for isomers **1** synthesized by organocatalytic methods were missing and, in part, conflicting; [a]as originally assigned; [b]not reported.



Scheme 1. Syntheses of *syn* and *anti* **1** by non-organocatalyzed means.[a] Reagents and conditions: (a) *trans*-crotonaldehyde (0.7 eq.), I_2 (7 mol%), Et_2O (0.07 M), −78 °C, 76%, *dr* > 20:1; (b) $CeCl_3{\cdot}7H_2O$ (2.0 eq.), $NaBH_4$ (2.0 eq.), MeOH (0.05 M), 0 °C, 60%; (c) NaH (2.0 eq.), THF (0.05 M), rt, 25%; (d) $Pd(OH)_2/C$ (3 mol%), H_2 (balloon), MeOH (0.3 M), rt; (e) $NaClO_2$ (5.0 eq.), NaH_2PO_4 (6.0 eq.), *t*BuOH: amylene:H_2O (1.5:1:1, 0.05 M), rt; (f) EDCI·HCl (1.4 eq.), oxazolidinone (1.3 eq.), DMAP (1.15 eq.), CH_2Cl_2 (0.1 M), rt; 20% from (±)-*anti*-**1**; (g) $Pd(PhCN)_2Cl_2$ (7.5 mol %), *t*BuONO (20 mol%), O_2 (balloon), *t*BuOH (0.05 M), rt, 51% brsm.

Table 1
Optimization studies.[a]



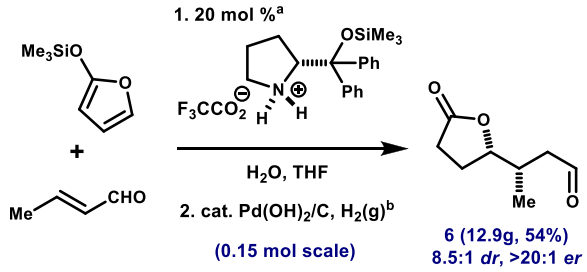
Entry	Catalyst	Acid	Solvent	*dr*[b] (*syn*:*anti*)
1[c]	**7**	DCA	$CHCl_3$	1.0:2.1
2[d]	**7**	DNBA	$CHCl_3$	1.0:3.3
3	**7**	TfOH	$CHCl_3$	1.0:5.2
4[e]	**7**	TFA	THF	2.5:1.0
5[f]	**8a**	DNBA	CH_2Cl_2	2.5:1.0
6[f]	**8a**	DNBA	THF	3.0:1.0
7[f,g]	**8a**	TFA	THF	4.0:1.0
8[f]	**8b**	TFA	THF	4.0:1.0
9[f]	**8c**	TFA	THF	4.3:1.0
10[g,h]	**9**	TFA	THF	5.0:1.0
11[g,i]	**9**	TFA	THF	5.5:1.0
12[g,j]	**9**	**TFA**	**THF**	**8.5:1.0**

[a] Reagents and conditions: **2** (1.0 eq.), crotonaldehyde (3.0 eq.), cat. (20 mol%), acid (20 mol%), H_2O (2.0 eq.), solvent (0.1 M), −10 °C.
[b] *dr* measured by ^{1}H NMR.
[c] DCA: dichloroacetic acid, reaction was performed with 5.0 eq. of H_2O in 0.5 M of $CHCl_3$ at −78 °C.
[d] DNBA: 2,4-dinitrobenzoic acid.
[e] Parallel reactions were carried out at −10 °C and 50 °C. Both resulted in similar selectivity.
[f] (3*R*, 5*S*)-**1** was the major product.
[g] crotonaldehyde (5.0 eq.), H_2O (3.0 eq.).
[h] The reaction was left at −20 °C overnight after 1 h at −10 °C.
[i] 10 mol% of **9** and 13 mol% of TFA was used.
[j] TFA (26 mol%), **2** was added over 7 h at −15 °C, *er* > 20:1, measured on a chiral amine derivative by ^{1}H NMR.

organocatalysts under varied conditions (see Table 1). Imidazolidinone catalyst **7** [2] in the presence of co-catalytic protic acids uniformly gave poor diastereoselectivities, although the major isomer did switch from *anti* to *syn* when TFA in THF was used (Entry 4).

A set of hydroxyproline-derived catalysts **8a-c** were then synthesized and their performance were examined. Under the conditions shown in Table 1, each formed *syn*-**1** as the major diastereomer, although selectivities were modest (Entries 5–9). Improvements came when simpler diphenylprolinol catalyst **9** was employed. At −20 °C in THF, 20 mol% **9** and TFA catalyzed formation of *syn* and *anti* **1** in a 5:1 ratio (Entry 10). Selectivity was not diminished when the catalyst loading was reduced to 10 mol % (Entry 11). When siloxyfuran **2** was added slowly (7 h) to a stirred THF solution of crotonaldehyde containing catalyst **9** and TFA at −15 °C, diastereoselectivity increased to 8.5:1 (Entry 12) [9].

This last procedure could be scaled to support our total synthesis studies (Scheme 2). On 0.15 mol scale (0.1 M in THF), the reaction was stirred at −15 °C for 1 h after the addition of **2** was complete. The reaction was filtered through a pad of silica gel and concentrated. The crude material was dissolved in MeOH and hydrogenated over $Pd(OH)_2/C$ to give γ-butyrolactone **6** (12.9 g, 54%, *dr* = 8.5:1) following chromatography. Isolated **6** showed $[\alpha]_D^{23}$ = +30.8 (*c* = 0.1, $CHCl_3$) and material synthesized previously from alkene **5** (Scheme 1) gave $[\alpha]_D^{24}$ = +26.7 (*c* = 0.1, $CHCl_3$), confirming absolute stereochemistry as (3*S*, 5*S*). An enan-



Scheme 2. Scalable asymmetric synthesis of butyrolactone **6**.[a] [a]Reagents and conditions: (a) **2** (1.0 eq.), crotonaldehyde (5.0 eq.), cat. (20 mol%), acid (26 mol%), H_2O (3.0 eq.), THF (0.1 M), −15 °C; (b) $Pd(OH)_2/C$ (3 mol%), H_2 (balloon), MeOH (0.3 M), rt; 54% over 2 steps.

tiomeric ratio of >20:1 in **6** was inferred from ^{1}H NMR analysis of the diastereomeric products derived from reductive amination with (*S*)-α-methylbenzylamine (see ESI).

In summary, we have firmly assigned relative stereochemistry to diastereomeric products derived from conjugate addition of 2-trimethylsiloxyfuran to *trans*-crotonaldehyde. We have developed an iodine catalyzed version of the reaction that provides the racemic *anti* diastereomer with high selectivity (*dr* > 20:1). The optically active *syn* diastereomer is produced selectively on scale using a diphenylprolinol catalyst. Attempts to elaborate (+)-**6** to portimine are ongoing and will be reported shortly.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Experimental procedures and spectral data can be found in ESI. Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153056.

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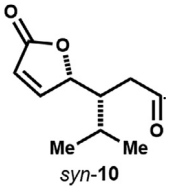
[9] Under the conditions shown in Table 1 entry 12, the reaction of 2-trimethylsiloxyfuran and 4-methyl-2-pentenal gave a 6:1 mixture of diastereomeric butenolides. The ^{1}H NMR spectrum of the major isomeric product (*syn*-**10**) corresponded to the major isomer reported by Luo (ref. 3b), whereas the ^{1}H NMR spectrum of the minor isomeric product (*anti*-**10**) matched the data reported for *syn*-**1** in ref 2



syn-**10**