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Organocatalytic Asymmetric *Anti*-Selective Michael Reactions of Aldehydes and the Sequential Reduction/Lactonization/Pauson–Khand Reaction for the Enantioselective Synthesis of Highly Functionalized Hydropentalenes

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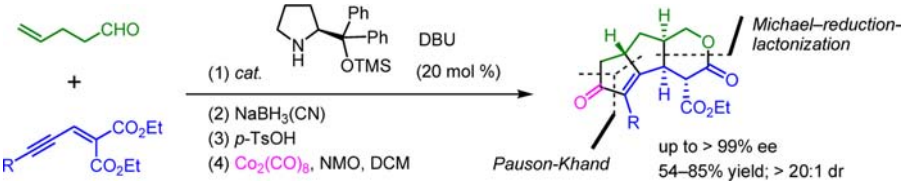
ABSTRACT



A new method has been developed for the enantioselective synthesis of highly functionalized hydropentalenes bearing up to four stereogenic centers with high stereoselectivity (up to 99% *ee*). This process combines an enantioselective organocatalytic *anti*-selective Michael addition with a highly efficient one-pot reduction/lactonization/Pauson–Khand reaction sequence. The structures and absolute configurations of the products were confirmed by X-ray analysis.

With high stereoselectivity and wide applications, organocatalyzed conjugate additions are finding increasing uses in synthetic chemistry.[1] Despite many successful *anti*-selective organocatalytic Michael reactions of ketones, numerous organocatalytic conjugate additions of aldehydes to nitroalkenes have been reported to be highly *syn*-selective (Scheme 1, eq 1).[2,3] Details of the reaction mechanism that account for this high *syn*-stereoselectivity have been advanced by a recent discovery.[4] Similarly, organocatalyzed Michael reactions of aldehydes to alkylidene malonates have been reported, as exemplified by the reactions with the Jørgensen–Hayashi catalyst,[5] which preferentially afforded the (2*R*,3*R*)-*syn*-adduct (Scheme 1, eq 2).[6] Nevertheless, efforts to obtain *anti*-selective conjugate additions of aldehydes have been elusive until a recent tactic

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(1) For recent reviews in organocatalyzed Michael reactions, see: (a) Sulzer-Mossé, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123–3135. (b) Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis* **2007**, 2065–2092.

(2) For a review: Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701–1716.

(3) For recent examples: (a) Belot, S.; Vogt, K. A.; Besnard, C.; Krause, N.; Alexakis, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 8923–8926. (b) Belot, S.; Massaro, A.; Tenti, A.; Mordini, A.; Alexakis, A. *Org. Lett.* **2008**, *10*, 4557–4560. (c) Hong, B.-C.; Nimje, R. Y.; Wu, M.-F.; Sadani, A. A. *Eur. J. Org. Chem.* **2008**, 1449–1457. (d) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212–4215.

(4) (a) Burés, J.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2011**, *133*, 8822–8825. (b) Patora-Komisarska, K.; Benohoud, M.; Ishikawa, H.; Seebach, D.; Hayashi, Y. *Helv. Chim. Acta* **2011**, *94*, 719–745. (c) Burés, J.; Armstrong, A.; Blackmond, D. G. *J. Am. Chem. Soc.* **2012**, *134*, 6741–6750.

(5) Jensen, K. L.; Ickmeiss, G.; Iang, H.; Albrecht, Ł.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248–264.

(6) (a) Zhao, G.-L.; Vesely, J.; Sun, J.; Christensen, K. E.; Bonneau, C.; Cørdova, A. *Adv. Synth. Catal.* **2008**, *350*, 657–661. (b) Sun, X.; Ma, D. *Chem.—Asian J.* **2011**, *6*, 2158–2165. (c) Wen, L.; Shen, Q.; Lu, L. *Org. Lett.* **2010**, *12*, 4655–4657.

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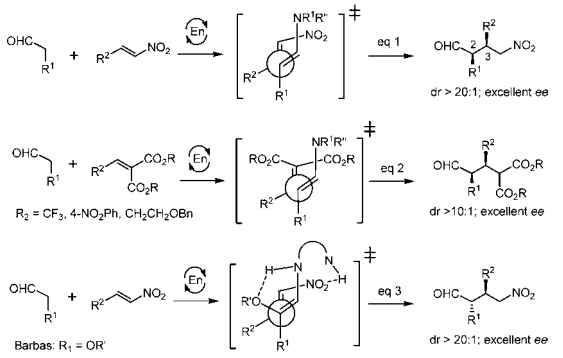
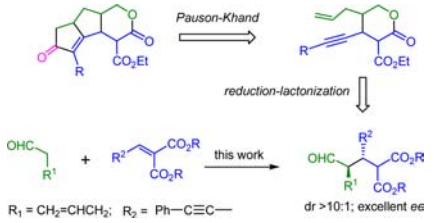
introduced by Barbas et al. which exploited the *anti*-selective Michael reaction of α-alkoxyaldehydes.[7] Inspired by the organocatalyzed *anti*-selective Michael reaction of ketones,[8] Barbas's strategy ingeniously employed an alkoxyacetaldehyde stabilized through intramolecular H-bonding throughout the synclinal transition state to furnish the *Z* enamine (Scheme 1, eq 3).

Scheme 1. Preferential Stereoselectivity of the Organocatalytic Michael Reaction of Aldehydes

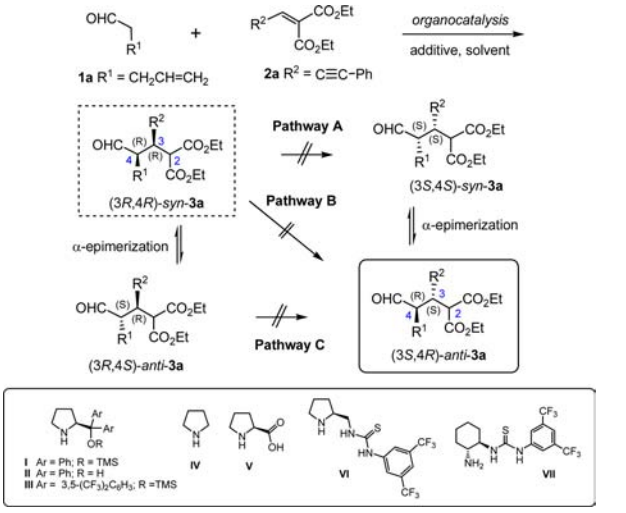


Scheme 2. Retrosynthetic Analysis



Nevertheless, a practical and expedient methodology for the *anti*-selective Michael reaction of regular aldehydes, e.g. nonalkoxy aldehydes, has yet to be achieved and is an attractive and compelling subject of exploration. However, recent advances in Pauson–Khand reactions (PKRs) have provided a versatile protocol for the synthesis of polycyclic complex molecules,[9] and the synergistic efforts of organocatalysis and metal catalysts also have recently received much attention with appealing outcomes. Considering the above background in the context of organocatalytic asymmetric annulations,[10] we envisioned an approach to cyclopenta[*g*]isochromen-3-one that could be accomplished by a sequence of organocatalytic asymmetric Michael reactions of aldehydes and reduction–lactonization–PKR (Scheme 2). Herein, we report details of the development of highly *anti*-selective asymmetric Michael reactions of aldehydes and alkylidene malonates, by a nucleophilic-catalysis strategy,[11] which affords

Table 1. Screening of Catalysts, Solvents, and Reaction Conditions for the Stereoselective Michael Reaction[a]



entry	cat.-additive	solvent	*t* (h)	yield[b] (%)	dr[c] *syn*/*anti*	*ee*[d,e] (%)
1	**I**–HOAc	$CHCl_3$	34	83	65:35	94[f]/26[g]
2	**I**	CH_3CN	20	80	52:48	99[f]/95[g]
3	**I**–DBU	CH_3CN	46	95	3:97	99[f]/96[g]
4	**I**–DBU	$CHCl_3$	64	94	7:93[h]	32[f]/99[g]
5	**I**–DBU	CH_2Cl_2	66	91	12:88	99[f]/97[g]
6	**I**–DBU	EtOH	20	68	19:81	91[f]/98[g]
7	**I**–DBU	DMF	23	87	34:66	89[f]/86[g]
8	**I**–DBU	THF	39	83	19:81	69[f]/99[g]
9	**I**–DBU	toluene	89	81	13:87	−73[i]/90[g]
10	**II**–DBU	CH_3CN	109	~0	na	na
11	**III**–DBU	CH_3CN	134	trace	nd	nd
12	**IV**–DBU	CH_3CN	62	80	17/83	0/0
13	**V**–DBU	CH_3CN	52	87	48/52	−13[i]/2
14	**VI**–DBU	CH_3CN	73	trace	nd	nd
15	**VII**–DBU	CH_3CN	60	trace	nd	nd
16	**I**–DBN	CH_3CN	85	87	25:75	−77[i]/95
17	**I**–DABCO	CH_3CN	19	83	41:59	86/15
18	**I**–TMG	CH_3CN	94	8[j]	18:82	−73[i]/86

[a] Unless otherwise noted, the reactions were performed on a 0.2-mmol scale of **2a** and **1a** (2 equiv), using 20 mol % of the catalyst and additive at 0 °C in a vial containing the appropriate solvent. [b] Isolated yields of **3a**. [c] Determined by HPLC and ^{1}H NMR of the reaction mixture. [d] Determined by HPLC with chiral column Chiralpak AD. [e] Ee of *syn*-**3a** and *anti*-**3a**, respectively. [f] Major isomer (3*R*,4*R*)-*syn*-**3a**. [g] Major isomer (3*S*,4*R*)-*anti*-**3a**. [h] Direct concentration of the reaction mixture led to the isomerization of **3a**, *syn*/*anti* = 32/68; −99/85% *ee*, respectively, showing that some of the (3*S*,4*R*)-*anti*-**3a** was isomerized to (3*S*,4*S*)-*syn*-**3a** and some of the (3*R*,4*R*)-*syn*-**3a** was isomerized to (3*R*,4*S*)-*anti*-**3a**. [i] The opposite enantiomer, i.e. (3*S*,4*S*)-*syn*-**3a**, was obtained. [j] Slow conversion. nd = not determined. na = not available.

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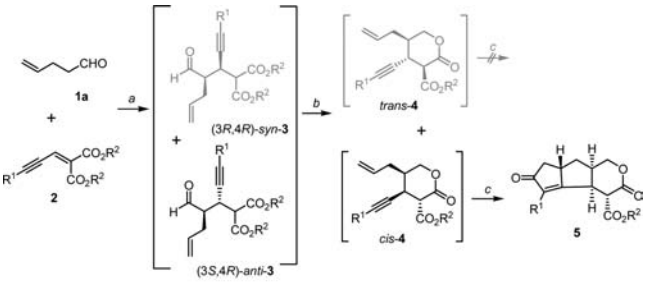
(9) For recent reviews, see: (a) Lee, H.-W.; Kwong, F.-Y. *Eur. J. Org. Chem.* **2010**, 789–811. (b) Takanori, S. *Adv. Synth. Catal.* **2006**, *348*, 2328–2336. (c) Gibson, S. E.; Mainolfi, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 3022–3037. (d) Bonaga, L. V. R.; Krafft, M. E. *Tetrahedron* **2004**, *60*, 9795–9833. (e) Gibson, S. E.; Stevenazzi, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1800–1810. (f) Blanco-Urgoiti, J.; Añorbe, L.; Pérez-Serrano, L.; Domínguez, G.; Pérez-Castells, J. *Chem. Soc . Rev.* **2004**, *33*, 32–42.

Table 2. Scope of Organocatalytic Sequential Michael Reduction Lactonization and Pauson–Khand Reaction[a]



a. cat. I–DBU (20 mol %), dry CH_3CN, 0 °C. *b.* (1) $NaBH_3CN$ (2.5 equiv), HOAc (20 equiv), rt, 3 h; (2) *p*-TSA (3.5 equiv), 2 h. *c.* $Co_2(CO)_8$ (1.2 equiv), CH_2Cl_2, 2 h; NMO (10 equiv), 12 h.

entry	R	t^b (h)	dr[c] of **4**	yield of **5** (%)[d]	dr[e] of **5**	*Ee* (%)[f]
1	**a** R^1 = Ph; R^2 = Et	45	88:12	85	88:12	98
2	**b** R^1 = 4-MeC_6H_4; R^2 = Et	46	80:20	71	85:15	96
3	**c** R^1 = 4-CO_2Me-C_6H_4; R^2 = Et	26	80:20	67	86:14	99
4	**d** R^1 = 4-FC_6H_4; R^2 = Et	5	88:12	79	94:06	99
5	**e** R^1 = 4-ClC_6H_4; R^2 = Et	5	85:15	77	93:07	96
6	**f** R^1 = 3-ClC_6H_4; R^2 = Et	9	85:15	54	80:20	98
7	**g** R^1 = 4-BrC_6H_4; R^2 = Et	15	85:15	81	84:16	98
8	**h** R^1 = 4-IC_6H_4; R^2 = Et	15	84:16	62	76:24	99
9	**i** R^1 = *n*-C_5H_{11}; R^2 = Et	48	74:26	63	62:38	98
10	**j** R^1 = Ph; R^2 = Me	48	75:25	68	82:18	97
11	**k** R^1 = Ph; R^2 = *i*-Pr	40	68:32	65[g]	85:15	97
12	**l** R^1 = thiophen-2-yl; R^2 = Et	40	75:25	62	81:19	97[h]

[a] Unless otherwise noted, the reactions were performed on a 0.2-mmol scale of **1a** and **2**, in a ratio of 2:1, using 20 mol % of the catalyst **I** and DBU at 0 °C in a vial containing the appropriate solvent. [b] Time required for first Michael reaction. [c] Diastereomeric ratio of *cis*-/*trans*-**4**, determined by ^{1}H NMR of the crude reaction mixture after lactonization. [d] Isolated yield of **5** and its isomer after four steps. [e] Diastereomeric ratio determined by ^{1}H NMR of crude reaction mixture after Pauson–Khand reaction. [f] Ee of the major isomer of **5**, unless otherwise noted, determined by HPLC with Chiralpak IA. [g] 12 h reaction time was required for the lactonization. [h] Determined by HPLC with Chiralcel OD-H.

cyclopenta[*g*]isochromen-3-ones in good yields and excellent stereoselectivities up to 99% *ee*.

Initially, a solution of **1a** and **2a** in $CHCl_3$ was treated with Jørgensen–Hayashi catalyst **I**–HOAc (20 mol %), and an 83% yield of *syn*-**3**a and *anti*-**3**a was obtained in a ratio of 65/35 (Table 1, entry 1). To a certain extent, the *syn*-selectivity was diminished, as compared with other examples of alkylidene malonates (Scheme 1, eq 2),[6] probably due to the lesser steric bulk of the alkyne substituent (R_2), i.e., sp vs sp^3 and sp^2 in other literature examples. Additionally, the *syn*-**3a** was obtained with 94% *ee*, while a 26% *ee* was observed for *anti*-**3a** (Table 1, entry 1). Conducting the same reaction with the catalyst **I** in the absence of the acetic acid additive in CH_3CN did, however, afford a 52/48 ratio of *syn*- and *anti*-**3a**, with 99% *ee* and 95% *ee*, respectively (Table 1, entry 2).

Interestingly and notably, the reaction with catalyst **I** (20 mol %) and DBU (20 mol %) under the same reaction conditions in CH_3CN provided a 3/97 ratio of *syn*- and *anti*-**3a**, with 99% *ee* and 96% *ee*, respectively (Table 1, entry 3). A similar result was observed for the same reaction in $CHCl_3$ and CH_2Cl_2 albeit with a longer reaction time (Table 1, entries 4 and 5).[12] The highly *anti*-selective Michael reaction of aldehyde observed herein is remarkable and unusual, *vide supra*.[7] Moreover, during the isolation and purification process, direct concentration of the Michael adducts *in vacuo* caused a degree of epimerization and decreased the *syn*/*anti* ratio to ca. 32/68 with the inversion of *ee* of *syn*-**3a** (Table 1, entry 4, footnote h). It is noteworthy that the major enantiomeric *syn*-Michael adduct obtained, i.e., (3*S*,4*S*)-*syn*-**3a**, from this epimerization of the *cat*. **I**–DBU catalyzed product was found to be the enantiomer of the major *syn*-Michael adduct obtained, i.e., (3*R*,4*R*)-*syn*-**3a**, from the reaction with *cat*. **I**–HOAc. Notably, this epimerization could be circumvented by direct loading of the reaction mixture onto a silica gel column, thereby avoiding the direct concentration of the reaction mixture. Such prompt purification (EtOAc–hexane, 1:19) afforded the *anti*-Michael adduct in a 96:4 diastereomeric ratio. These observations led us to conclude that epimerization of acyclic *syn*- and *anti*-**3a** can occur under the harsh reaction conditions (e.g., concentrated under basic conditions) to produce the ~2:1 or 1:1 diastereomeric mixtures, depending on the time of exposure. However, *the highly diastereo- and enantioselective formation of anti-**3a** observed herein did not simply arise from the* α*-epimerization of syn-**3a*** since such an isomerization would not be able to drive all of the *syn*-/*anti*-**3a** mixture toward *anti*-**3a** and would lead to the opposite enantiomers and thereby decrease the enantioselectivities.

The reactions with catalyst **I**–DBU in other solvents produced lesser yields, dr's, and/or *ee*'s (Table 1, entries 5–9). In addition, a series of organocatalysts were screened in the reactions (Table 1, entries 10–15). Among them, most reactions did not proceed or gave a reduced dr and *ee*. Moreover, the product obtained from the pyrrolidine (**IV**)–DBU was used as a racemic standard for the HPLC analysis (Table 1, entry 12). Some amine bases, e.g., DBN, DABCO, and tetramethylguanidine, were tested with catalyst **I** in the reactions, but the results were not as promising as the outcome of the reactions with DBU (Table 1,

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(11) An interesting and creative diastereodivergent asymmetric sulfa-Michael addition of α-branched enones with the choice of acidic additives and reaction media has been reported; however, its detailed reaction mechanism remains unclear; see: Tian, X.; Cassani, C.; Liu, Y.; Moran, A.; Urakawa, A.; Galzerano, P.; Arceo, E.; Melchiorre, P. *J. Am. Chem. Soc.* **2011**, *133*, 17934–17941.

(12) For the reaction in $CHCl_3$, Table 1 entry 4, a certain amount of α-epimerization of (3*S*,4*R*)-*anti*-**3a** might have occurred and reduced the *ee* of *syn*-**3a**.

entries 16–18). For the reaction in toluene, Table 1 entry 9, a longer reaction time was required for completion of the reaction, and a certain amount of α-epimerization of (3*S*,4*R*)-*anti*-**3a** to (3*S*,4*S*)-*syn*-**3a** might have occurred. As a result, reverse enantioselectivity was observed.

To shed light on the mechanism of isomerization, a solution of **3a** (*syn*/*anti* = 4:96) was stirred in $CDCl_3$–D_2O in the presence of silica gel. Subsequent ^1H NMR analysis of the diastereomers of **3a** showed a change of *syn*/*anti* ratio (25:75 after 12 h; 34:66 after 66 h). In addition, deuteration of the C_2–H took place after a few minutes of the reaction, while C_4–H, the methine adjacent to the aldehyde, was deuterated after prolonged exposure, and the C_3–H remained untouched. Alternatively, freshly prepared **3a** (*anti*/*syn* = 95:5) in the same reaction medium (*cat*. **I**–DBU) with a few drops of D_2O was concentrated *in vacuo* to yield **3a** with a decreased *anti*/*syn* ratio, and the same deuteration phenomenon was observed but in a more facilitated process. These observations point to the fact that the highly selective *anti*-adduct (3*S*,4*R*)-**3a** obtained in the *cat*. **I**–DBU reaction is not produced in a straightforward process through the DBU epimerization of the C_3–H on *syn*-adduct (3*R*,4*R*)-**3a** (β-epimerization, Pathway B, or A, and C, Table 1).[13]

We then undertook a one-pot strategy in the reduction–lactonization reaction sequence. Reduction of **3a** ($NaBH_3CN$, HOAc, 25 °C, 3 h), followed by the addition of *p*-TsOH, with stirring for an additional 3 h, gave the *cis*- and *trans*-lactone **4a** in a ratio of 88:12 (Schemes in Table 2). These lactones were somewhat unstable during the silica-gel chromatography purification process and so were subjected to the PKR without purification. A solution of crude **4a** and $Co_2(CO)_8$ in CH_2Cl_2 was stirred at ambient temperature for 2 h until completion of the reaction, as monitored by TLC. To this dark-red solution was added *N*-methylmorpholine *N*-oxide (NMO), and the dark-purple reaction mixture was then stirred for 12 h at rt. After filtration through a pad of Celite, the solution was concentrated *in vacuo* and purified by SiO_2 flash column chromatography to give **5a** (85% yield), in a diastereomeric ratio of 88:12.[14] It is worth noting that the three-step reaction sequence from **1a** and **2a** to **4a** proceeded in one pot, with only regular extraction and concentrative work-up, without purification of **4a**. The PKR afforded lactone **5a** in 85% overall yield, from the four-step reaction sequence. With this protocol in hand, we applied the method to a series of **1a** and **2** derivatives. The reaction is general with respect to the substrates tested, providing the desired adducts with excellent enantioselectivities (95 to >99% *ee*) (Table 2). In general, the Michael reaction of **1a** and **2** was completed in a short period of time when electron-withdrawing substituents were present in the R_1 phenyl group (Table 2, entries 3–8). In the case of (±)-**5a** and (−)-**5l** the structures were assigned by X-ray crystallography (see Supporting Information).[15] In addition, extending the protocol to other substituted aldehydes was also realized.[16]

In summary, we have elucidated an unusual organocatalytic *anti*-selective asymmetric Michael addition of aldehydes to alkylidene malonates.[17] The introductory reaction along with the subsequent one-pot reduction–lactonization–PKR provides an efficient protocol for the enantioselective synthesis of highly functionalized hydropentalenes containing four stereogenic centers. The reaction not only adds to the limited repertoire of organocatalysis with metal catalyzed cyclization reactions but also demonstrates for the first time the utilization of nucleophilic catalysts in the stereodivergent asymmetric Michael reaction. The strategy focused on solving the intractable problem of *anti*-selective Michael addition of aldehydes, and with the appropriate selection of nucleophilic catalysts and organocatalysts, this strategy could provide a venue for wide applications in asymmetric synthesis. The benign reaction conditions and the efficient construction of complex products confirm the merit of this strategy. The structures and the absolute configurations of the products were verified by X-ray analysis of the appropriate adducts. Further work is underway to elaborate the detailed mechanism, as well as the synthetic applications of this strategy.

Acknowledgment. We acknowledge financial support for this study from the National Science Council, Taiwan, ROC and are thankful to the instrument center of the National Science Council for compound analyses.

Supporting Information Available. Experimental procedures and characterization data for the new compounds and X-ray crystallographic data for (±)-**5a** and (−)-**5l** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

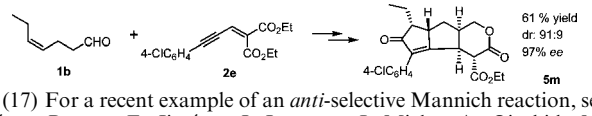
The authors declare no competing financial interest.

(13) For a proposed mechanism, see Supporting Information.

(14) *trans*-**4a** was unable to undergo a Pauson–Khand reaction and was decomposed during recovery purification by silica-gel chromatography. A sample with a ca. 1:1 ratio of *cis*- and *trans*-**4a** was subjected to the same reaction conditions affording only a 40% yield of **5a** with the same 88:12 diastereomeric ratio.

(15) X-ray crystal structure analysis of (±)-**5a**: Formula $C_{20}H_{20}O_5$, weight 340.36 g mol^{-1}, colorless crystal. CCDC-893145; X-ray crystal structure analysis of (−)-**5l**: Formula $C_{18}H_{18}O_5S$, weight 346.38 g mol^{-1}, colorless crystal. CCDC-893205, CCDC-893206, CCDC-893207, and CCDC-893208 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(16) For an example, see:



(17) For a recent example of an *anti*-selective Mannich reaction, see: Gómez-Bengoa, E.; Jiménez, J.; Lapuerta, I.; Mielgo, A.; Oiarbide, M.; Otazo, I.; Velilla, I.; Vera, S.; Palomo, C. *Chem. Sci.* **2012**, *3*, 2949–2957.