

Catalytic Asymmetric Assembly of Stereodefined Propionate Units: An Enantioselective Total Synthesis of (–)-Pironetin

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The importance of aldol-based bond constructions in modern asymmetric synthesis has generated considerable interest in developing catalytic asymmetric reaction variants. Catalyzed aldol additions eliminate the requirement for installing and recycling, or destroying, a chiral auxiliary used to affect asymmetric bond constructions. A number of highly successful catalytic asymmetric aldol addition reactions have been developed involving both direct aldol processes and additions of pregenerated latent enolates.¹ However, examples of these catalytic asymmetric aldol reactions being used in an iterative fashion to assemble repeating propionate or acetate networks are rare.² Herein, we describe the utility of alkaloid-catalyzed acyl halide–aldehyde cyclocondensation (AAC) reactions for the catalytic asymmetric synthesis of extended propionate networks (Figure 1).³ The utility of this reaction technology in synthesis activities is exemplified in a catalytic asymmetric total synthesis of (–)-pironetin.

As one solution to catalytic asymmetric aldol additions, we developed acyl halide–aldehyde cyclocondensations that provide enantioenriched β -lactones **1** as *syn* propionate aldol equivalents.⁴ Extending these reactions to AAC-based strategies for assembling repeating propionate units was predicated on engaging the enantioenriched β -lactone-derived *syn* aldehyde **2** in further AAC homologation (Figure 1). Ensuing AAC reactions of **2** with correct selection of alkaloid catalyst (**3** or **4**) would then deliver the stereochemically complementary propionate dimers **5** or **6**. A central issue to be addressed in this context would be the catalyst's ability to reliably and predictably complement or override the intrinsic facial bias expressed by the chiral aldehyde substrates.⁵

Iterative AAC homologation of α -substituted aldehyde **7** provided a representative test sequence for evaluating this polypropionate synthesis design (Scheme 1). Reacting (*S*) aldehyde **7** with propionyl chloride using 10 mol % of **4a** as catalyst (2 equiv of LiI, ^tPr₂NEt) afforded the anticipated *syn,anti* β -lactone **8** in 78% yield (*syn,anti*: Σ _{others} = 92:8).⁶ Reformating lactone **8** as the corresponding *syn* aldehyde **9** proceeded by amine-mediated lactone ring opening, alcohol silylation, and Weinreb amide reduction (55% yield for three steps). Ensuing TMSQd (*O*-trimethylsilylquinidine; **3a**)-catalyzed AAC homologation of **9** afforded β -lactone **10** (94% de, 84%) as a surrogate for the corresponding *syn,anti, syn* propionate trimer.⁷ The magnitude of double diastereoselection operative in these reactions became apparent upon AAC homologation of **9** employing the pseudoenantiomeric quinine-derived catalyst **4b** (10 mol %, EtCOCl, ^tPr₂NEt, 3 equiv of LiI) that afforded lactone **11** with excellent diastereoselection albeit with the unanticipated C₂–C₃/C₃–C₄ *anti,anti* stereochemistry. Our failure to isolate the all-*syn* lactone expected from catalyst-dominated stereocontrol suggested that mismatched substrate/catalyst chirality was responsible for the *anti* diastereoselection across the β -lactone, an observation previously unprecedented for the AAC reactions. Nevertheless, this observation suggested a strategy for realizing *syn*- or *anti*-selective-catalyzed aldol additions via the AAC reaction design.

Examining the generality of the AAC-based propionate synthesis revealed the conditions under which matched and mismatched diastereoselection was manifested. Under the ostensibly matched AAC reaction conditions, the β -lactone-derived *syn* aldehydes **12a/b**

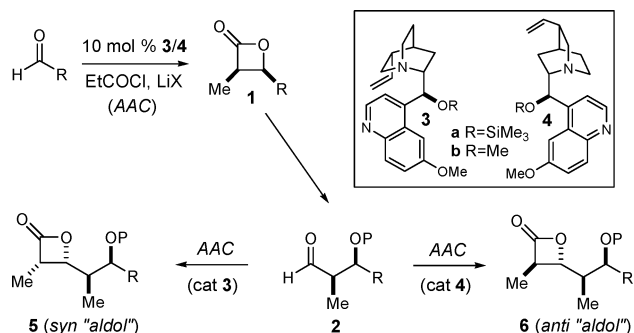
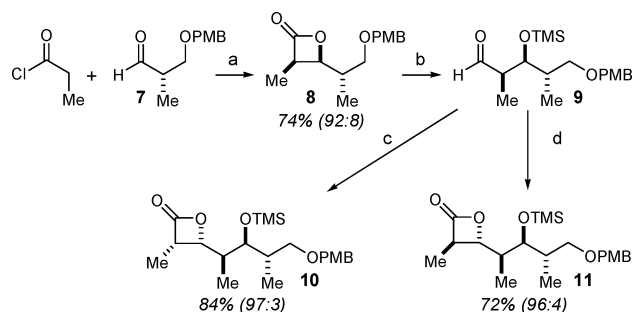


Figure 1. Iterative application of asymmetric catalytic AAC reactions.

Scheme 1^a



^a Conditions: (a) 10 mol % of **4a**, LiClO₄, ^tPr₂NEt, –78 °C (74%); (b) (i) (MeO)MeNH₂Cl, Me₂AlCl (80%); (ii) TMSOTf, 2,6-lutidine (86%); (iii) ^tBu₂AlH, THF (80%); (c) 10 mol % of **3a**, LiI, ^tPr₂NEt (84%); (d) 10 mol % of **4b**, LiI, ^tPr₂NEt (72%).

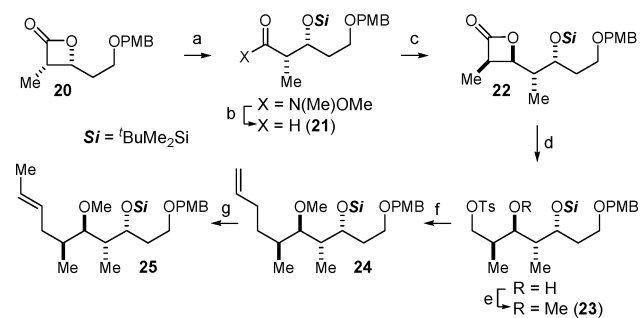
delivered the anticipated *syn,anti, syn* β -lactones **13a/b** with complete stereocontrol (Table 1, entries a and b). The mismatched quinine-catalyzed AAC homologations of *syn* aldehydes **12a/c** faithfully produced the *anti,anti, syn* β -lactones **14a/c** with high diastereoselectivity ($\geq 90\%$ de) (entries c and d). Matched AAC homologation (quinine catalyst) of *anti* aldehyde **15** afforded the *syn,anti,anti* β -lactone **16** with equally high diastereoselection (entry e).⁸ However, in contrast to the *syn* aldehyde electrophiles, the *anti* aldehyde **15** does not undergo the mismatched AAC reaction. To evaluate these reactions as potential conduits to extended propionate networks, the *syn,anti, syn* aldehyde **17**, obtained from β -lactone **13a**, was engaged in TMSQn (*O*-trimethylsilylquinine; **4a**)-catalyzed (matched) cyclocondensation with propionyl chloride to afford the propionate trimer equivalent **18** as a single diastereomer (entry f, 79% yield).

A catalytic asymmetric total synthesis of (–)-pironetin (**19**) highlights this reaction technology's utility in the context of a representative polyketide-derived target.^{9,10} The AAC-derived β -lactone **20** (99% ee, 89:11 *syn:anti*) was subjected to the three-step lactone-to-aldehyde conversion to afford *syn* aldehyde **21** (Scheme 2).¹¹ TMSQn-catalyzed (matched) homologation of **21** then provided the *syn,anti, syn* β -lactone **22** ($\geq 95\%$ de). Lactone reduction to the corresponding diol preceded selective primary alcohol tosylation and installation of the C₉ methyl ether to afford the protected tetraol **23**. Tosylate substitution by Cu(I)-mediated allyl Grignard addition

Table 1. Matched and Mismatched AAC Reactions

entry	aldehyde ^a	β -lactone ^b	% de (% yield) ^c
a			≥ 95 (83)
b	12b (R=Bn)	13b (R=Bn)	≥ 95 (78)
c	12a	14a (R=TMS)	91 (81)
d	12c (R=PMB)	14c (R=PMB)	92 (81)
e			≥ 95 (81)
f			≥ 95 (79)

^a Catalyst (10 mol %) **3a**, entries a, b; **4a**, entries c–f. ^b Stereochemical assignments based on X-ray structure determinations of derivatives of **14c** and **16** and comparison of ¹H coupling constants. ^c Diastereomeric ratios determined by HPLC or ¹H NMR analysis of crude reaction mixtures.

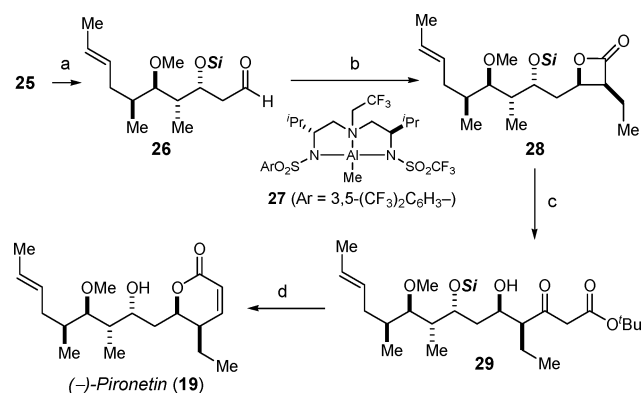
Scheme 2^a

^a Conditions: (a) (i) (MeO)MeNH₂Cl, Me₂AlCl; (ii) TBSCl, imidazole (97%); (b) ^tBu₂AlH (96%); (c) 10 mol % of **4a**, EtCOCl, LiI, ⁱPr₂NEt (91%); (d) ^tBu₂AlH, THF; (ii) TsCl, pyr (83%); (e) Me₃OBF₄, proton sponge (81%); (f) C₃H₅MgBr, CuBr (85%); (g) 2 mol % of Ir(PCy₃)₃⁺, 50:1 CH₂Cl₂:acetone (98%).

provided the terminal alkene **24** with ensuing Ir(I)-catalyzed olefin isomerization delivering the requisite *E* propenyl unit in the complete C₅–C₁₄ synthon **25**.¹²

From the C₅–C₁₄ synthon **25**, completing the pironetin synthesis proceeded by routine alcohol deprotection and oxidation to give aldehyde **26** (Scheme 3). Engaging **26** in Lewis acid-catalyzed AAC homologation (50 mol % of **27**) employing butyryl bromide as a butanoate enolate equivalent afforded β -lactone **28** ($\geq 95\%$ de, 65% yield) possessing all of the (–)-pironetin stereocenters.^{3b,13} β -Keto ester **29** emerged from ring opening **28** with the magnesium enolate of *tert*-butylacetate. Ketone reduction (NaBH₄) and reacting the resulting diol with TsOH elicited *tert*-butyl ester cleavage, lactonization, and dehydration to generate the requisite 2-pyranone unit, as well as silyl ether removal to directly furnish synthetic (–)-pironetin (**19**) (56% over two steps).

Alkaloid-catalyzed AAC reactions provide a uniform strategy for executing asymmetric *syn*- or *anti*-selective aldol additions on enantioenriched aldehyde substrates. Iterative application of these AAC reactions provides an entry to stereodefined polypropionate building blocks. The AAC-based catalytic asymmetric total synthesis of (–)-pironetin provides evidence for this methodology's

Scheme 3^a

^a Conditions: (a) (i) DDQ, aq. CH₂Cl₂ (81%); (ii) Swern (88%); (b) ^tPrCOBr, ⁱPr₂NEt, 50 mol % of **27**, BTF, –25 °C (65%); (c) *t*-BuOAc, KHMDS then MgBr₂ (66%); (d) (i) NaBH₄, EtOH; (ii) TsOH, toluene, 110 °C (56% for two steps).

utility in synthesis efforts directed toward polyketide-derived materials.

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Supporting Information Available: Experimental procedures, stereochemical proofs, and representative ¹H and ¹³C spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) For recent reviews, see: (a) Alcaide, B.; Almendros, P. *Eur. J. Org. Chem.* **2002**, 1595. (b) Silvestri, M. G.; Desantis, G.; Mitchell, M.; Wong, C.-H. *Top. Stereochem.* **2003**, 23, 267. (c) Shibasaki, M.; Yoshikawa, N.; Matsunaga, S. In *Comprehensive Asymmetric Catalysis, Supplement*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Heidelberg, Germany, 2004; p 135. (d) Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Soc. Rev.* **2004**, 33, 65. (e) Notz, W.; Tanaka, F.; Barbas, C. F., III. *Acc. Chem. Res.* **2004**, 37, 580.
- (2) (a) Gijzen, H. J. M.; Wong, C.-H. *J. Am. Chem. Soc.* **1995**, 117, 7585. (b) Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, 305, 1752. (c) Casas, J.; Engqvist, M.; Ibrahim, I.; Kaynak, B.; Córdova, A. *Angew. Chem., Int. Ed.* **2005**, 44, 1343.
- (3) (a) Nelson, S. G.; Peelen, T. J.; Wan, Z. *J. Am. Chem. Soc.* **1999**, 121, 9742. (b) Nelson, S. G.; Zhu, C.; Shen, X. *J. Am. Chem. Soc.* **2004**, 126, 14.
- (4) Zhu, C.; Shen, X.; Nelson, S. G. *J. Am. Chem. Soc.* **2004**, 126, 5352.
- (5) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, 24, 1.
- (6) α -Branched aldehydes generally require 1.5–3 equiv of lithium salt (LiClO₄ or LiI) for complete conversion. See ref 4.
- (7) Control experiments confirmed that α -substituted aldehydes are not subject to epimerization under the AAC reaction conditions.
- (8) For *anti* aldehyde substrates, a solvent system composed of 10:1 CH₂Cl₂/DMF provided superior reaction rates and yields as compared to the standard CH₂Cl₂/Et₂O system.
- (9) (a) Yoshida, T.; Koizumi, K.; Kawamura, Y.; Matsumoto, K.; Itazaki, H. Japanese Patent Kokai 5-310726, 1993; European Patent 60389 A1, 1993. (b) Kobayashi, S.; Tsochia, K.; Harada, T.; Nishide, M.; Kurokawa, T.; Nakagawa, T.; Shimada, N.; Kobayashi, K. *J. Antibiot.* **1994**, 47, 697.
- (10) Previous syntheses: (a) Yasui, K.; Tamura, Y.; Nakatani, T.; Kawada, K.; Ohtani, M. *J. Org. Chem.* **1995**, 60, 7567. (b) Gurjar, M. K.; Chakrabarti, A.; Rao, A. V. R. *Heterocycles* **1997**, 45, 7 and references therein. (c) Chida, N.; Yoshinaga, M.; Tobe, T.; Ogawa, S. *Chem. Commun.* **1997**, 1043. (d) Watanabe, H.; Watanabe, H.; Usui, T.; Kondoh, M.; Osada, H.; Kitahara, T. *J. Antibiot.* **2000**, 53, 540 and references therein. (e) Keck, G. E.; Knutson, C. E.; Wiles, S. A. *Org. Lett.* **2001**, 3, 707. (f) Dias, L. C.; de Oliveira, L. G.; de Sousa, M. A. *Org. Lett.* **2003**, 5, 265.
- (11) Lactone **20** was prepared as described in ref 4 from 3-*p*-methoxybenzyl-oxypropanal.
- (12) Nelson, S. G.; Bungard, C. J.; Wang, K. *J. Am. Chem. Soc.* **2003**, 125, 13000.
- (13) The alkaloid-catalyzed AAC variant failed for this transformation, a result attesting to the complementary nature of the Lewis acid- and alkaloid-catalyzed AAC reactions.

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