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Enantioenriched Dihydropyrones from β-Lactone Templates

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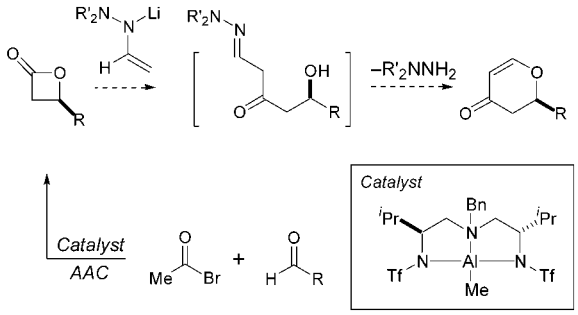
ABSTRACT



Optically active 4-substituted 2-oxetanones provide conduits for preparing 2,3-dihydro-4*H*-pyrone heterocycles. Enantioenriched β-lactones are prepared by asymmetric catalytic acyl halide-aldehyde cyclocondensation reactions. Hydrazone anion-mediated β-lactone ring opening and ensuing cyclization–dehydroamination of the derived β-ketohydrazone afford the desired dihydropyrones (68–81%). Optimized lactone ring-opening–cyclization reaction conditions render a variety of optically active 4-substituted-2-oxetanones as effective precursors to enantioenriched 2,3-dihydro-4*H*-pyrones.

Optically active dihydropyrones constitute generally useful building blocks for numerous synthesis activities, proving especially useful for accessing the structurally diverse pyran rings that characterize the ionophore family of natural products.[1,2] The chemotherapeutic potential of these pyran-containing natural products has inspired the development of numerous reaction technologies for preparing the dihydropyrone progenitors of the targeted pyran subunits. Hetero Diels−Alder (HDA) reactions stand out among these reaction technologies as affording the most direct entry to optically active 2,3-dihydro-4*H*-pyrones **1**.[3,4] Strategic decisions pursued within complex molecule syntheses ongoing in our group inspired us to investigate functional alternatives to HDA-based dihydropyrone syntheses that would, nonetheless, retain the considerable efficiency that characterizes these reactions (Figure 1). To this end, we have explored optically active 4-substituted 2-oxetanones **2** as conduits for preparing 2,3-dihydro-4*H*-pyrone heterocycles. Specifically, the β-keto aldehyde **3** emerging from acetaldehyde enolate-mediated ring opening of β-lactone **2** was anticipated to undergo facile lactol formation and ensuing dehydration to afford the corresponding enantioenriched dihydropyrone **1** (eq 1).

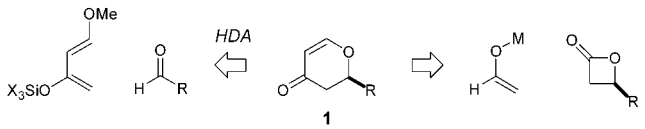


Figure 1. Synthesis of enantioenriched 2,3-dihydro-4*H*-pyrones.

(1) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407−2473.
(2) For reviews, see: (a) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380−1419. (b) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063-2192.
(3) (a) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1983**, *105*, 6968−6969. (b) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1986**, *108*, 7060−7067.

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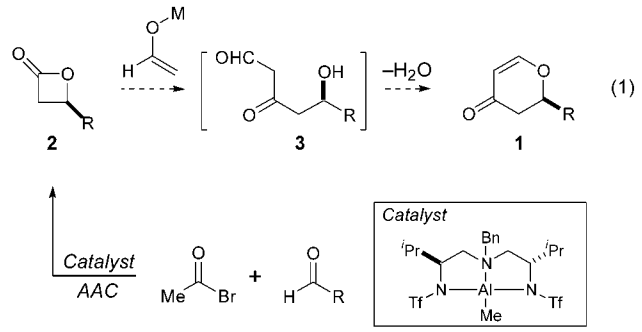
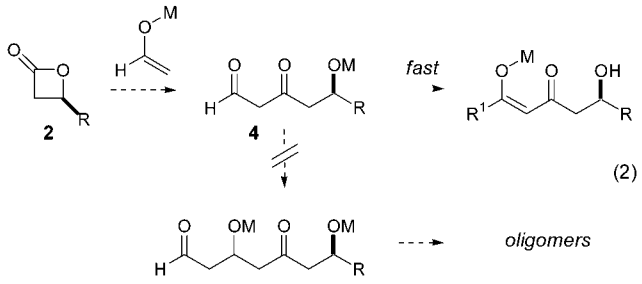
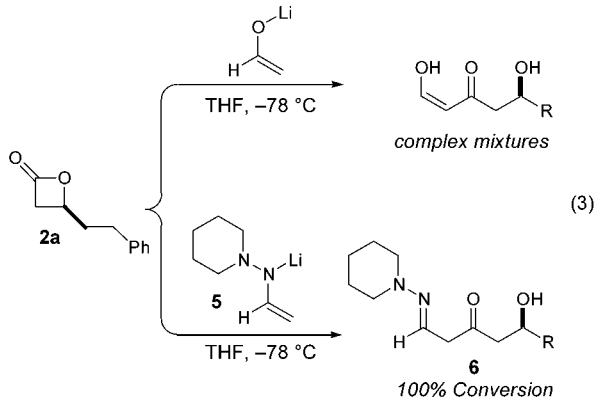
This report describes the successful implementation of this dihydropyrone synthesis relying on catalytic asymmetric acyl halide-aldehyde cyclocondensation (AAC) reactions as the source of the requisite β-lactone electrophiles.[5]



Ring strain imparts considerable activation to β-lactones toward nucleophile-mediated ring opening. Among several ring opening modes available to β-lactones, strongly basic nucleophiles promote ring opening derived from carbonyl addition−elimination.[6,7] Consistent with this observation, we anticipated that enolate nucleophiles would express similar regiochemical preferences in opening optically active 4-substituted 2-oxetanones **2** (eq 2). Furthermore, we expected the β-alkoxy ketone intermediate **4** emerging from this process to be protected from further carbonyl addition by rapid deprotonation of the transient β-dicarbonyl intermediate.[8]



Evaluating this hypothesis in the context of the proposed dihydropyrone synthesis led us to examine the reactivity of the acetaldehyde lithium enolate toward the hydrocinnamaldehyde-derived β-lactone **2a** (eq 3). Reacting **2a** with the lithium enolate of acetaldehyde (2 equiv) at temperatures ranging from −78 to 0 °C afforded complex product mixtures and only trace amounts of the desired β-keto aldehyde. Failure in these efforts was ultimately traced to our inability to rigorously control the quality and purity of the lithium enolate generated by the decomposition of 2-lithio tetrahydrofuran.[9]



These preliminary investigations focused our attention on identifying an actealdehyde enolate equivalent that could be generated under more carefully controlled reaction conditions. Alkanal hydrazones were thus selected as aldehyde surrogates, offering the advantage that the requisite anions could be generated under typical enolization conditions (LDA). Acetaldehyde hydrazone was conveniently prepared by condensing acetaldehyde with the appropriate *N*,*N*-dialkylhydrazine.[10] Reacting the lithiated hydrazone **5** with lactone **2a** at −78 °C provided regioselective carbonyl addition and ensuing ring opening to afford the β-keto hydrazone **6** as the only component in the crude product mixture (100% conversion) (eq 3).[11] The piperidine-derived hydrazone afforded a lithium anion **5** offering greater reproduciblity in the ring-opening reaction as compared to the *N*,*N*-dimethyl acetaldehyde hydrazone anion.

The efficiency of the hydrazone-mediated lactone openings presented the cyclization−dehydroamination sequence as the

(4) (a) Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, *33*, 6907−6910. (b) Keck, G. E.; Li, X.-Y.; Krishnamurthy, D. *J. Org. Chem.* **1995**, *60*, 5998−5999. (c) Ghosh, A. K.; Mathivanan, P.; Cappiello, J.; Krishnan, K. *Tetrahedron: Asymmetry* **1996**, *7*, 2165−2168. (d) Schaus, S. E.; Brånalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403−405. (e) Yao, S.; Johannsen, M.; Audrain, H.; Hazell, R. G.; Jorgensen, K. A. *J. Am. Chem. Soc.* **1998**, *120*, 8599−8605. (f) Dossetter, A. G.; Jamison, J. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398−2400. (g) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335 and references therein. (h) Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558−3588 and references therein. (i) Qian, C.; Wang, L. *Tetrahedron Lett.* **2000**, *41*, 2203−2206. (j) Aikawa, K.; Irie, R.; Katsuki, T. *Tetrahedron* **2001**, *57*, 845−851. (k) Huang, Y.; Rawal, V. *Org. Lett.* **2000**, *2*, 3321−3323.

(5) (a) Nelson, S. G.; Peelen, T. J.; Wan. Z. *J. Am. Chem. Soc.* **1999**, *121*, 9742−9743. (b) Nelson, S. G.; Wan, Z. *Org. Lett.* **2000**, *2*, 1883−1886. See also: (c) Nelson, S. G.; Spencer, K. L. *J. Org. Chem.* **2000**, *65*, 1227. (d) Nelson, S. G.; Wan. Z.; Peelen, T. J.; Spencer, K. L. *Tetrahedron Lett.* **1999**, *40*, 6535−6540.

(6) Pommier, A.; Pons, J.-M. *Synthesis* **1993**, 441−459.

(7) (a) Arnold, L. D.; Kalantar, T. H.; Vederas, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 7105. (b) Griesbeck, A.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1326. (c) Arnold, L. D.; May, R. G.; Vederas, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 2237. (d) Castagnani, R.; De Angelis, F.; De Fusco, E.; Giannessi, F.; Misiti, D.; Meloni, D.; Tinti, M. O. *J. Org. Chem.* **1995**, *60*, 8318. (e) Bernabei, I.; Castagnani, R.; De Angelis, F.; De Fusco, E.; Giannessi, F.; Misiti, D.; Muck, S.; Scafetta, N.; Tinti, M. O. *Chem. Eur. J.* **1996**, *2*, 826. (f) Nelson, S. G.; Spencer, K. L. *Angew. Chem.* **2000**, *39*, 1323. (g) Wan, Z.; Nelson, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 10470−10471. (h) Ref 5b.

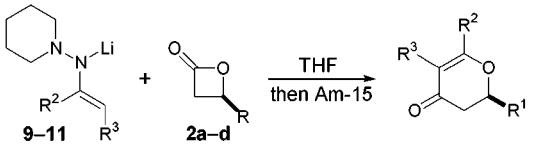
(8) For the aldol polymerization of acetaldehyde enolate equivalents, see: (a) Murahashi, S.; Nozakura, S.; Sumi, M. *J. Polym. Sci., Polym. Lett.* **1965**, *3*, 245−249. (b) Nozakura, S.-I.; Ishihara, S.; Inaba, Y.; Matsumura, K.; Murahashi, S. *J. Polym. Sci.* **1973**, *11*, 1053−1067. (c) Sogah, D. Y.; Webster, O. W. In *Recent Advances in Mechanistic and Synthetic Aspects of Polymerization*; Fontanille, M., Guyot, A., Eds.; D. Reidel: Dordrecht, The Netherlands, 1987; pp 61−72. (d) Charleux, B.; Pichot, C. *Polymer* **1993**, *34*, 195−203.

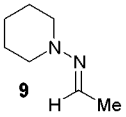
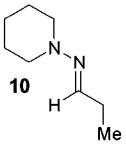
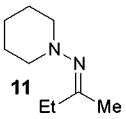
(9) Bates, R. B.; Kroposki, L. M.; Potter, D. E. *J. Org. Chem.* **1972**, *37*, 560.

(10) Corey, E. J.; Enders, D. *Chem. Ber.* **1978**, *111*, 1337−1339.

(11) β-Keto hydrazone intermediates **6** can be isolated and purified by column chromatography; however, crude β-keto hydrazones emerging from the β-lactone ring openings were routinely used in the subsequent cyclization reactions.

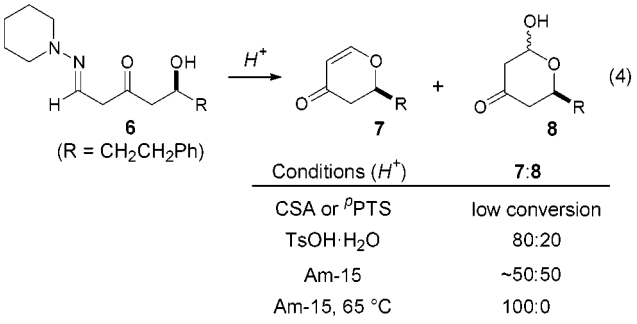
Table 1. β-Lactone-to-Dihydropyrone Interconversion



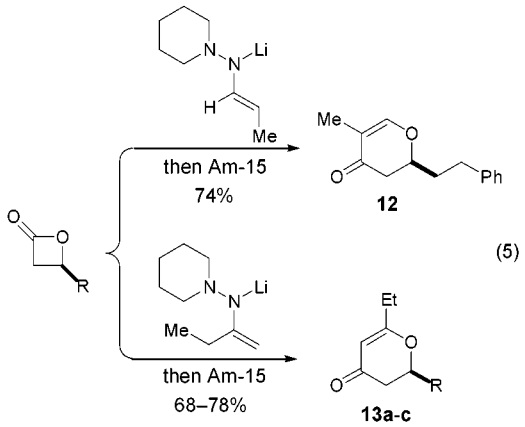
entry	Hydrazone	Lactone **2** (R)[a]	% Yield[b]
a	 **9**	–CH_2CH_2Ph (**2a**, 91% ee)	78 (**7a**)
b	**9**	–C≡C–$SiMe_3$ (**2b**, 90% ee)	72 (**7b**)
c	**9**	–$(CH_2)_8CHCH_2$ (**2c**, 90% ee)	81 (**7c**)
d	**9**	–CH_2OBn (**2d**, 91% ee)	75 (**7d**)
e	 **10**	–CH_2CH_2Ph (**2a**, 91% ee)	74 (**12**)
f	 **11**	–CH_2CH_2Ph (**2a**, 91% ee)	78 (**13a**)
g	**11**	–C≡C–$SiMe_3$ (**2b**, 90% ee)	68 (**13b**)
h	**11**	–CH_2OBn (**2d**, 91% ee)	76 (**13c**)

[a] Lactones **2** were prepared as described in ref 5a. [b] The absolute configuration of dihydropyrones **7a** and **7d** was unambiguously established; see ref 4a and b. The configuration of the remaining dihydropyrones was assigned by analogy to these determinations.

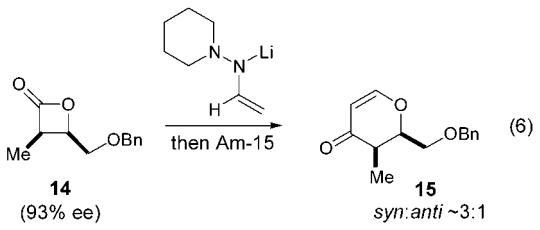
last barrier to completing the envisioned dihydropyrone synthesis. Hydrazone protonation was expected to elicit facile cyclic aminal formation upon subjecting the β-keto hydrazone to simple acids. In practice, the efficiency of the cyclization−dehydroamination sequence proved to be particularly sensitive to the nature of the acid reagent (eq 4). Relatively weak acids (^{p}TsOH, CSA, ^{p}PTS) at ambient temperatures (~23 °C) afforded mixtures of the desired pyranone **7** and the lactol **8**. While **8** was considered a precursor to the desired unsaturated pyranone **7**, effecting dehydration of **8** without isolation and resubmission to the reaction conditions resulted in partial decomposition of the dihydropyrone **7** and commensurately low isolated yields. These results suggested that extended reaction times under even mildly acidic conditions were detrimental to reaction efficiency. Thus, reaction conditions that would shorten reaction times, including more strongly acidic media and elevated temperatures, were next evaluated. These investigations led to amberlyst-15 acidic resin (Am-15) and refluxing THF solvent being identified as the reaction conditions affording maximum yields in the cyclization−dehydroamination sequence. Thus, treating the crude β-ketohydrazone **6** with Am-15 resin in refluxing THF afforded the desired dihydropyrone **7**, uncontaminated with the lactol, in consistently good yields.



Merging the optimized lactone ring opening and cyclization−dehydroamination reaction conditions rendered a variety of optically active 4-substituted-2-oxetanones **2a**−**d** as effective precursors to enantioenriched 2,3-dihydro-4*H*-pyrones (Table 1). Acetaldehyde hydrazone anion reacts with β-lactones incorporating simple alkyl chains, ether functionality, as well as unsaturated alkyl groups to effect the lactone-to-pyranone conversion in good yields (68−81%). We anticipated that these reaction conditions would have no effect on the resident stereogenic center and would proceed with complete stereochemical integrity; the veracity of this prediction was unambiguously confirmed for the known pyranones **7a**[4a] and **7d**.[4b] Differentially substituted dihydropyrones were prepared by analogous heterocycle interconversion employing other aldehyde and ketone hydrazone anions to effect β-lactone ring opening; lithium anions



derived from hydrazones **10** and **11** provided the enantioenriched 2,5- or 2,6-disubstituted dihydropyrones **12** and **13a**−**c**, respectively (eq 5, Table 1). The optically active 3,4-disubstituted 2-oxetanone **14** also undergoes analogous lactone-to-dihydropyrone interconversion to afford the 2,3-disubstituted dihydropyrone **15** (eq 6); however, partial epimerization of the C_3 stereocenter during pyranone formation led to **15** being obtained as ~3:1 (*syn*:*anti*) diastereomeric mixture.[12]



Despite the power of asymmetric catalyzed bond constructions, rigorous uncoupling of reaction enantioselection and substrate structure cannot always be assured. Thus, multiple strategies for accessing target synthons are often desirable. The β-lactone-to-dihydropyrone interconversions provide convenient access to structurally diverse, enantioenriched dihydropyrone synthons. As a result, these transformations are expected to complement the highly efficient hetero Diels−Alder-based routes widely employed in preparing these versatile synthons.

(12) A representative experimental procedure for converting optically active β-lactones to the corresponding 2,3-dihydro-4*H*-pyrones involved adding the hydrazone (1.5 mmol) to a 0 °C solution of lithium diisopropylamide (1.5 mmol) in THF (7 mL) and stirring for 1 h. The resulting heterogeneous mixture was cooled to −78 °C; a solution of β-lactone **2** (1.0 mmol) in THF (1 mL) was added, and the resulting solution was maintained at −78 °C for 3 h before warming to ambient temperature and stirring for 12 h. The reaction was quenched with H_2O (0.5 mL), and the mixture was diluted with Et_2O (20 mL), dried ($MgSO_4$), filtered, and concentrated. The resulting residue was dissolved in THF (10 mL), and amberlyst-15 acidic resin (500 mg) was added; the reaction was heated at reflux for 3 h. Upon cooling to ambient temperature, the mixture was filtered, concentrated, and purified by flash chromatography.

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Supporting Information Available: Experimental procedures, compound characterization data, and representative spectra are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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