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A General Method for the Enantioselective Synthesis of Pantolactone Derivatives

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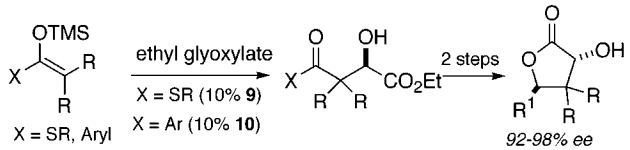
ABSTRACT



An efficient enantioselective synthesis of β,β-dialkyl-γ-substituted pantolactones has been achieved utilizing the cationic [Sc((*S*,*S*)-R-pybox)](Cl)$_2^+$, R = Ph (9), *t*-Bu (10), complex in a catalyzed aldol reaction as the key step. The pantolactone derivatives are isolated in high enantiomeric excesses.

The asymmetric synthesis of pantolactone (**1a**), pantothenic acid (**2a**), and their derivatives (Figure 1) continue to be of

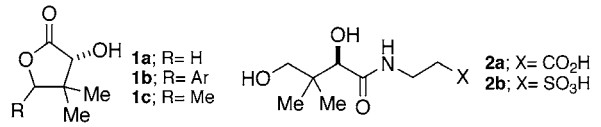


Figure 1. Biologically active pantolactone and pantothenic acid derivatives.

interest to organic chemists as a consequence of their biological activity and utility as a secondary alcohol derived chiral auxiliary. The taurine derivative of panthothenic acid (pantoyltaurine, **2b**) has been shown to inhibit the growth of streptococci, pneumococci, plasmodium relictum,[1] and certain strains of diphtheria bacilli.[2] γ-Methylpantolactone and its open-chain derivative, as well as a variety of related γ-substituted pantolactone analogues (**1a**−**c**), all possess inhibitory properties toward lactic acid bacteria and malaria.[3] The purpose of this Letter is to describe a catalytic enantioselective approach to the synthesis of this family of lactone targets and their γ-substituted analogues.

Since racemic, unsubstituted pantolactone (**1a**) is readily prepared in a "one-pot" reaction from hydroxypivalaldehyde, sodium cyanide, hydrochloric acid, and calcium chloride,[4] various methods for its chemical[5] and enzymatic[6] resolution have been developed.

Direct access to enantiopure pantolactone may also be achieved by enantioselective hydrogenation of 3,3-dimethyl-2-oxobutyrolactone with a variety of different metal catalyst systems.[7] Recently, Upadhya has also reported that Sharpless's asymmetric dihydroxylation of the corresponding cyclic silylketene acetal pantolactone precursor affords the desired pantolactone in high enantiomeric excess.[8]

(1) Winterbottom, R.; Clapp, J. W.; Miller, W. H.; English, J. P.; Roblin, R. O., Jr. *J. Am. Chem. Soc*. **1947**, *69*, 1393−1401.
(2) Roblin, R. O., Jr. Chem. Rev. **1946**, *38*, 255−367.
(3) (a) Drell, W.; Dunn, M. S. *J. Am. Chem. Soc*. **1948**, *70*, 2057−2063. Drell, W.; Dunn, M. S. *J. Am. Chem. Soc*. **1954**, *76*, 2804−2808.
(4) Ford, J. H. *J. Am. Chem. Soc*. **1944**, *66*, 20−21.
(5) (a) Stiller, E. T.; Harris, S. A.; Finkelstein, J.; Keresztesy, J. C.; Folkers, K. *J. Am. Chem. Soc*. **1940**, *62*, 1785−1790. (b) Fuji, K.; Node, M.; Murata, M. *Tetrahedron Lett*. **1986**, *27*, 5381−5382. (c) Bevinakatti, H. S.; Banerji, A. A.; Newadkar, R. V. *J. Org. Chem*. **1989**, *54*, 2453−2455. (d) Kagan, F.; Heinzelman, R. V.; Weisblat, D. I.; Greiner, W. *J. Am. Chem. Soc*. **1957**, *79*, 3545−3549.
(6) (a) Baumann, M.; Hauer, B. H.; Bornscheuer, U. T. *Tetrahedron: Asymmetry* **2000**, *11*, 4781−4790.

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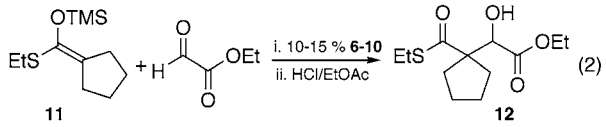
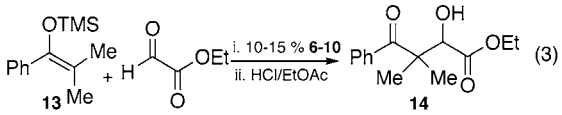
Table 1. Catalyst Survey for Silylketene Acetals and Ketone Enolsilane Additions to Ethyl Glyoxylate (eqs 2, 3)[a]



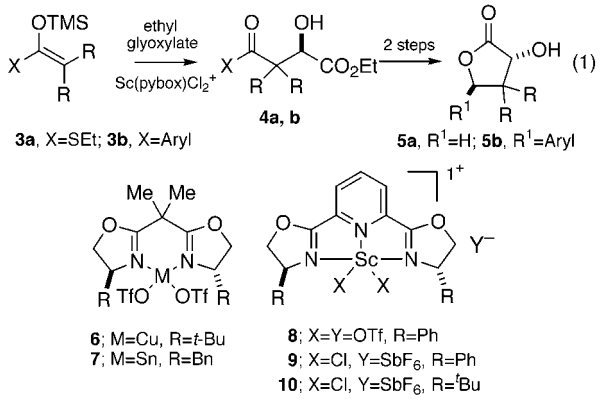


catalyst	% ee[b]	config[c]	conv%	catalyst	% ee[b]	config[c]	conv %
[Cu((*S*,*S*)-*t*-Bu-box)](OTf)$_2$ (**6**)	98	(*S*)	61	[Cu((*S*,*S*)-*t*-Bu-box)](OTf)$_2$ (**6**)	95	(*S*)	<5
[Sn((*S*,*S*)-Bn-box)](OTf)$_2$ (**7**)	95	(*S*)	89	[Sn((*S*,*S*)-Bn-box)](OTf)$_2$ (**7**)	76	(*S*)	<5
[Sc((*S*,*S*)-Ph-pybox)](OTf)$_3$ (**8**)	6	(*R*)	87	[Sc((*S*,*S*)-Ph-pybox)](OTf)$_3$ (**8**)	4	(*R*)	90
[Sc((*S*,*S*)-Ph-pybox)](Cl$_2$)(SbF$_6$) (**9**)	95	(*R*)	90	[Sc((*S*,*S*)-Ph-pybox)](Cl$_2$)(SbF$_6$) (**9**)	32	(*R*)	70
[Sc((*S*,*S*)-*t*-Bu-pybox)](Cl$_2$)(SbF$_6$) (**10**)	62	(*S*)	45	[Sc((*S*,*S*)-*t*-Bu-pybox)](Cl$_2$)SbF$_6$) (**10**)	95	(*S*)	85[d]

[a] All reactions were carried out in CH_2Cl_2 for 16 h at −78 °C. [b] Enantiomeric excess determined by HPLC using Chiracel AD or OD-H columns. [c] See Supporting Information for absolute configuration assignments. [d] Reaction was run at −35 °C with 2 equiv of TMS−Cl.

While there have been numerous reports on the asymmetric synthesis of pantolactone **1a**, to the best of our knowledge, only one paper has been published concerning the stereoselective synthesis of γ-substituted pantolactones. This synthesis employed a diastereoselective enzymatic reduction of the corresponding ketone precursor.[9] Herein, we report an efficient method for the asymmetric synthesis of differentially substituted β,β-dialkyl pantolactones and a general method for the diastereo- and enantioselective preparation of β,β-dialkyl-γ-aryl-substituted pantolactone derivatives. The key step in the preparation of these analogues is an enantioselective scandium-catalyzed aldol reaction of either thiosilylketene acetal **3a** or enolsilane **3b** nucleophiles with ethyl glyoxylate to give **4a**,**b** (Scheme 1). Raney nickel

Scheme 1



reduction of thioester **4a** or directed reduction[10] of hydroxy ketone **4b** affords pantolactones **5a**,**b**, respectively.

Table 1 documents the relative effectiveness of these metal complexes in promoting the additions of silylketene acetal and ketone enolsilane nucleophiles to ethyl glyoxylate.

In several recent studies, we have reported that [Sc((*S*,*S*)-Ph-pybox)](OTf)$_3$ (**8**), catalyzes the enantioselective addition of allenylsilanes to ethyl glyoxylate,[11] while [Sc((*S*,*S*)-Ph-pybox)](Cl$_2$)(SbF$_6$) (**9**) is an effective catalyst for syn-selective aldol reactions between thiosilylketene acetals and enolsilanes with ethyl glyoxylate.[12] In complementary studies, we have shown that [Cu((*S*,*S*)-t-Bu-box)](OTf)$_2$ (**6**) also catalyzes enolsilane aldol additions to pyruvate esters,[13] while [Sn((*S*,*S*)-Bn-box](OTf)$_2$ catalyzes the addition of thiosilylketene acetals to both glyoxylate and pyruvate esters.[14] A survey of ligand−metal complexes **6**−**10** revealed that [Cu((*S*,*S*)-t-Bu-box)](OTf)$_2$ (**6**), [Cu((*S*,*S*)-(Bn-box)](OTf)$_2$ (**7**), and [Sc((*S*,*S*)-Ph-pybox)](Cl$_2$)(SbF$_6$) (**9**) mediated the aldol reaction between thiosilylketene acetal **11** and ethyl glyoxolate to give the malate derivative **12** in high enantiomeric excesses and conversions (Table 1, eq 2).[14b] A catalyst survey was also conducted to determine the best complex for the additions of enolsilanes to ethyl glyoxylate (Table 2, eq 3). Initially, complex **10** afforded the desired product in excellent enantioselectivity (92%), albeit in low conversion (27%). When the temperature was elevated from −78 °C to −25 °C, increased conversion (69%) was observed with an attendant decrease in enantiomeric excess (86% ee). When a stoichiometric amount of complex **10** was employed, complete conversion was achieved in less than 0.5 h with increased enantiomeric excess (>99% ee). These experiments

(7) (a) Ojima, I.; Kogure, T.; Terasaki, T. *J. Org. Chem.* **1978**, *43*, 3444−3446. (b) Kagan, H. B.; Tahar, M.; Fiaud, J.-C. *Tetrahedron Lett.* **1991**, *32*, 5959−5962. (c) Genet, J.-P.; Pinel, C.; Mallart, S.; Juge, S.; Cailhol, H.; Laffitte, J. A. *Tetrahedron Lett.* **1992**, *33*, 5343−5346. (d) Takahashi, H.; Hattori, M.; Chiba, M.; Morimoto, T.; Achiwa, K. *Tetrahedron Lett.* **1986**, *37*, 4477−4480. (e) Roucoux, A.; Agbossou, F.; Mortreux, A.; Petit, F. *Tetrahedron: Asymmetry* **1993**, *4*, 2279−2282. (f) Chiba, M.; Takahashi, H.; Morimoto, T. Achiwa, K. *Tetrahedron Lett.* **1987**, *28*, 3675−3678.

(8) Upadhya, T. T.; Gurunath, S.; Sudalai, A. *Tetrahedron: Asymmetry* **1999**, *10*, 2899−2904.

(9) Hata, H.; Shimizu, S.; Hattori, S.; Yamada, H. *J. Org. Chem.* **1990**, *55*, 4377−4380.

(10) (a) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155−158. (b) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.

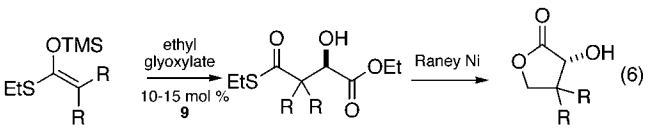
(11) Evans, D. A.; Sweeney, Z. K.; Rovis, T.; Tedrow, J. S. *J. Am. Chem. Soc.* **2001**, *123*, 12095−12096.

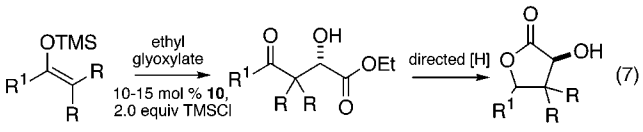
(12) (a) See preceding paper in this issue. (b) For assignment of absolute stereochemistry, also see preceding paper in this issue.

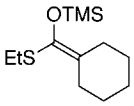
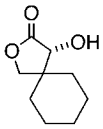
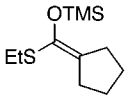
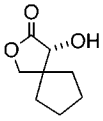
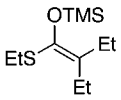
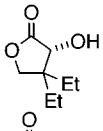
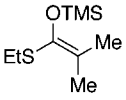
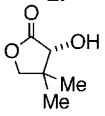
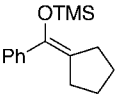
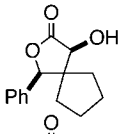
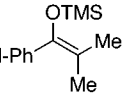
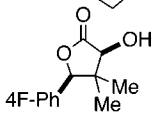
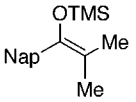
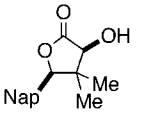
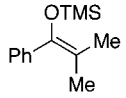
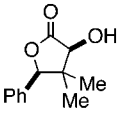
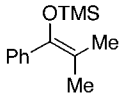
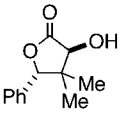
(13) (a) Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936−7943. (b) Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893−7894.

(14) Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859−10860.

Table 2. Reaction Scope of Pantolactone Synthesis[a]



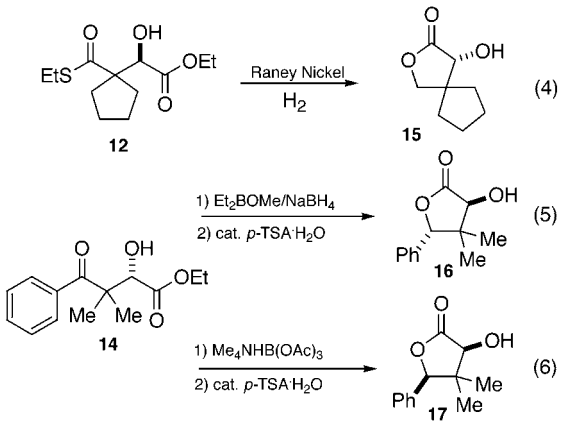


entry	substrate	product	ee,%[b]	yield,%[c]
1			92	88
2			95	80
3			95	76
4[d]			94	60
5[e]			98[f]	65
6			95	60
7			98	49
8			95	60
9			95	62

[a] See Supporting Information for detailed procedures on aldol addition and reduction/cyclization sequence. [b] Enantiomeric excesses were determined from the aldol product by HPLC using either Chiracel AD or OD-H column [c] Isolated yield over two and three steps for thiosilylketene acetal and enolsilane nucleophiles, respectively). [d] Because complex **9** afforded aldol production poor selectivities, this reaction was run using (*R*,*R*)-**7**, which mediated the aldol reaction 94% ee and 60% yield. [e] Relative stereochemistry was confirmed by single-crystal X-ray analysis of the pantolactone product. [f] Enantiomeric excess was determined again after cyclization and found to be within experimental error of the initial measurement. Unless otherwise noted, relative stereochemistry was determined by analogue via ^{1}H NMR.

suggest that the addition step may be fast and that a relatively slow silyl transfer and subsequent turnover of the metal-aldolate adduct might be the cause of incomplete conversion at lower temperatures. [15] Indeed, when the reaction was conducted at −35 °C, in the presence of 15 mol % of [Sc((*S*,*S*)-t-Bu-pybox)](Cl$_2$)(SbF$_6$) (**10**) and 2 equiv of chlorotrimethylsilane (TMS-Cl) to facilitate catalyst turnover,[16] aldol adduct **14** was isolated in 85% yield and 95% enantiomeric excess.

With the desired α-hydroxyesters in hand, attention was directed to the reduction/cyclization sequence. Hydrogenation of thioester **12** to the derived primary alcohol and spontaneous lactonization afforded the pantolactone derivative 15 in 95% enantioselectivity and 80% yield over two steps (eq 4). Hydroxyl-directed syn reduction of **14** with diethylmethoxyborane and sodium borohydride,[10a] followed by cyclization promoted by catalytic p-TSA yielded **16** as a 20:1 mixture of diastereomers (eq 5).[10a] Diastereomer separation



by column chromatography afforded the desired trans pantolactone **16** in 62% isolated yield over three steps (Table 2, entry 9). Similarly, the cis pantolactone derivative **17** was isolated as a single diastereomer in 60% yield after anti reduction of hydroxyester **14** with Me$_4$NHB(OAc)$_3$ followed by treatment with catalytic *p*-TSA (eq 6).[10b] Thus, with the appropriate choice of scandium catalyst, it is possible to

(15) Other aldol processes that have utilized silylation as the turnover event: (a) Evans, D. A.; Tedrow, J. S.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2002**, *124*, 392−393. (b) Chini. M.: Crotti, P.; Gardelli, C.; Minutolo, F.; Pineschi, M. *Gazz. Chim. Ital.* **1993**, *123*, 673−676. (c) Kiyooka, S.-I.; Tsutsui, T.; Maeda, H.; Kaneko, Y.; Isobe, K. *Tetrahedron Lett.* **1995**, *36*, 6531−6534.

(16) The sense of asymmetric induction is opposite to that of thiosilylketene acetal addition to ethyl glyoxylate. See preceding paper in this issue for assignment of absolute stereochemistry as well as stereochemical rationale.

acccess all four diastereomers of β,β,γ-substituted pantolactones.

The scope of this methodology is summarized in Table 2. This sequence afforded the pantolactones in high enantioselectivities and yields for a variety of cyclic and acylic substitution patterns on the thiosilylketene acetal nucleophiles (entries 1−4). When enolsilanes are used as the nucleophile, a wide array of aromatic groups can be present, including phenyl, 4-fluorophenyl, and naphthyl (entries 6−8). Furthermore, both dimethyl and cyclopentyl substituents on the enolsilanes are also well tolerated (entries 5, 8).

In conclusion, we have developed a highly efficient, catalytic, asymmetric process for the synthesis of substituted and unsubstituted pantolactones. This process represents a general method for the efficient synthesis of differentially substituted β,β-dialkyl pantolactones and the diastereo- and enantioselective preparation of β,β-dialkyl-γ-aryl-substituted pantolactones.

Acknowledgment. We acknowledge the National Science Foundation for generous financial support of this research. J.W. gratefully thanks the American Society for Engineering Education for a predoctoral NDSEG Fellowship.

Supporting Information Available: Representative experimental procedures and analytical data for all pantolactones prepared. Details of the X-ray diffraction data and structure for Table 2, entry 5. This material is available free of charge via the Internet at http://pubs.acs.org.

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