Practical, One-Step Synthesis of Optically Active β-Lactones via the Tandem Mukaiyama Aldol−Lactonization (TMAL) Reaction

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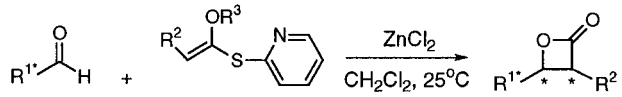
Introduction

The utility of β-lactones (2-oxetanones) continues to grow as additional novel transformations of these strained heterocycles are discovered.[1] The development of concise methods for the asymmetric synthesis of β-lactones will therefore further enhance their utility as intermediates in organic synthesis. Although several direct routes have been developed for the synthesis of β-lactones in racemic form,[2] relatively few general approaches for the concise synthesis of optically active β-lactones have been reported.[3] We recently described the development of a highly diastereoselective route to racemic trans-3,4-disubstituted β-lactones based on a tandem Mukaiyama aldol−lactonization (TMAL) reaction that builds on the work of Hirai.[4] Herein we describe the application of the TMAL reaction to a variety of optically active aldehydes including aldehydes bearing α-epimerizable centers (Scheme 1). Less than 2% racemization is observed with most epimerizable aldehydes studied. In most cases the degree of relative and internal stereoselection correlates with previously reported chelation-controlled Mukaiyama aldols resulting from either chelation or stereoelectronic control.[5] The derived β-lactones bear functionality which enables further functionalization of these useful intermediates.

Scheme 1



1 **2a**: R^2 = Me; R^3 = $SiEt_3$ **3**
2b: R^2 = Me; R^3 = Si*t*-BuMe_2
2c: R^2 = H; R^3 = Si*t*-BuMe_2

Results and Discussion

Our initial studies with optically active β-lactones began with the chiral aldehyde **1a**[6] bearing a β-stereocenter (Table 1). This aldehyde served as a model for our synthesis of (−)-panclicin D.[4a] Most of the TMAL reactions were performed using the triethylsilyl (TES) ketene acetal **2a** which we recently found provides higher yields of β-lactones as compared to the *tert*-butyldimethylsilyl (TBS) ketene acetals by minimizing formation of β-chlorosilyl ester side products.[4b] However, in some cases higher selectivities were observed using the TBS-ketene acetals (see entry 1, Table 1). Reaction of β-siloxy aldehyde **1a** under typical aldol−lactonization conditions with TBS-ketene acetal **2b** gave the β-lactone **3a** in 62% yield as a 1:9.1 ratio of syn/anti diastereomers. As in previous cases, the trans β-lactone is formed almost exclusively ($J_{3,4}$ = 4.0 Hz) while the minor diastereomer arises from incomplete relative stereoselection. The relative stereoselection observed is consistent with the model recently proposed by Evans.[7] Although slightly higher yields resulted when the TES-ketene acetal was employed, the relative stereoselectivity was diminished, leading to a 1:5.3 ratio of syn/anti diastereomers (entry 1). In a similar manner aldehyde **1b**[8] gave a 1:4.8 mixture of diastereomers using the TES ketene acetal **2a** along with ∼10−15% of diastereomeric tetrahydrofurans (entry 2).[9] The stereochemistry of the major diastereomer **3b** is based on analogy to β-lactone **3a** and comparison by ^{1}H NMR.

We then turned our attention to aldehydes that were capable of chelation-controlled additions and bearing α-epimerizable stereocenters. The latter feature would allow us to gauge the mildness of the TMAL reaction. The benzyloxy aldehyde **1c**[10] derived from ethyl (*S*)-lactate was studied first since it provided a model reaction for our synthesis of okinonellin B.[11] TMAL reaction with aldehyde **1c** provided the β-lactone **3c** in 69% yield with nearly complete relative and internal stereochemical control.[5b] Importantly, the enantiomeric purity of the derived β-lactone was determined to be 96% (chiral GC[12]), indicating that only slight epimerization

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(6) Aldehyde **1a** was obtained from ethyl acetoacetate by yeast reduction (85% ee) (a) Seebach, D.; Sutter, M. A.; Weber, R. H.; Zuger, M. F. *Org. Synth. VII*, 215−220. (b) Ireland, R. E.; Wardle, R. B. *J. Org. Chem.* **1987**, *52*, 1780−178] or by Noyori reduction (94% ee) (c) Taber, D. F.; Silverberg, L. J. *Tetrahedron Lett.* **1991**, *32*, 4227−4230. (d) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856−5858].

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(8) Available in three steps from dimethyl (*S*)-malate (Aldrich), see: Saito, S.; Hasegawa, T.; Inaba, M.; Nishida, R.; Fujii, T.; Nomizu, S.; Moriwake, T. *Chem. Lett.* **1984**, 1389−1392.

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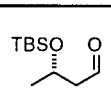
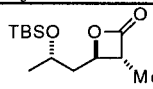
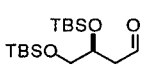
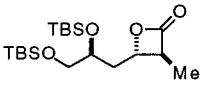
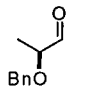
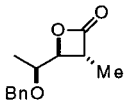
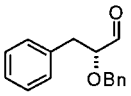
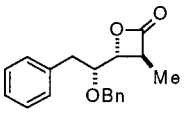
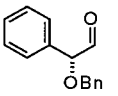
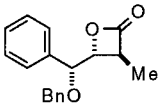
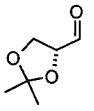
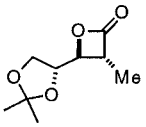
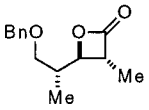
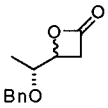
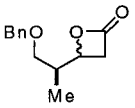
Table 1. Optically Active β-Lactones Obtained via the Tandem Mukaiyama Aldol-Lactonization Reaction

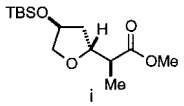
entry	Aldehydes	cmpd no.	β-lactone (major diastereomer)	cmpd no.	ketene acetal	time (h)	% yield[a]	trans/ cis[b]	syn/ anti[b]	% ee[c]
1		**1a**		**3a**	**2a**	24	69	>19:1	1:5.3	94[d]
					2b	22	62	>19:1	1:9.1	85[e]
2		**1b**		**3b**	**2a**	22	46[f]	>19:1	1:4.8	98[g]
3		**1c**[h]		**3c**	**2a**	24	69	>19:1	20:1[i]	96 (98)
4		**1d**[h]		**3d**	**2a**	24	63	>19:1	22:1[i]	98 (98)
5		**1e**[h]		**3e**	**2a**	24	50	>19:1	>19:1	69 (98)
6		**1f**		**3f**	**2a**	24	82 (63)[j]	3.6:1	<1:19	99 (99)
7		**1g**		**3g**	**2a**	67	29	>19:1	1:1.9	99 (99)
8		**1c**[h]		**3h**	**2c**	24	64	-	1:1.6	ND[k]
9		ent-**1g**		**3i**	**2c**	24	55	-	1:1.4	ND[k]

[a]Isolated yield of mixture of diastereomers. [b]Ratios determined on the crude reaction mixtures by GC or ^{1}H NMR (300 MHz). [c]%ee's of major diastereomer as determined by chiral HPLC (Chiralcel OD or OJ) or chiral GC (TBS-cyclodextrin, ref. 12). % ee's of starting material are given in parentheses. [d]Based on the %ee of methyl-β-hydroxybutyrate obtained by Taber's modified Noyori reduction (ref. 6c) of ethylacetoacetate as determined by chiral GC. [e]Based on the %ee of methyl-β-hydroxybutyrate obtained by yeast reduction (ref. 6a) of ethylacetoacetate as determined by Mosher ester analysis. [f]This β-lactone was accompanied by ~15% of a mixture of tetrahydrofuran acetic acids derived from TMAL reaction followed by intramolecular cyclization of the pendant silyl ether (see ref. 4a and 9). [g]Based on the %ee of the starting dimethyl (*S*)-malate (Aldrich). [h]These aldehydes were contaminated with ~5-10% of the corresponding alcohols resulting from over-reduction of the esters by DIBAl-H. [i]Determined after hydrogenolysis of the benzyl ether. [j]Isolated yield of the major anti-trans diastereomer (dr 24:1). [k]ND= not determined

had occurred under the reaction conditions. Aldehydes **1d**[13] and **1e**[10] also led to high diastereoselectivity to deliver the β-lactones **3d** and **3e**, respectively. However partial racemization of aldehyde **1e** was observed and is presumably the result of the increased acidity of the α-protons due to the α-phenyl group. The stereochemistry of β-lactone **3c** was determined by conversion to the known, *all-syn*-butyrolactone **4**[14] via tandem transacylation−debenzylation with ferric chloride[1d] and is consistent with a chelation-controlled aldol reaction (Scheme 2). Conversion of β-lactone **3c** to hydroxy β-lactone **6** allowed more precise measurement of the diastereoselectivity due to interference at the β-lactone stage of a benzylation side product.[15]

In analogy to β-lactone **3c**, the stereochemistries of β-lactones **3d** and **3e** are assigned as that derived from chelation-controlled additions. Further evidence for the

(9) The stereochemistry of the major diastereomeric tetrahydrofuran **i** isolated after treatment with diazomethane has not been rigorously determined but is based on the β-lactone **3b** undergoing inversion during cyclization of the pendant silyl ether.



i

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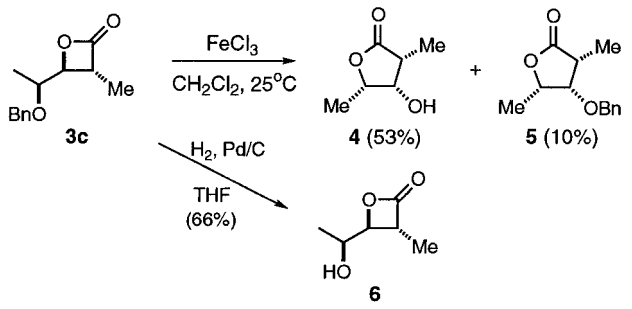
(11) Schmitz, W. D.; Messerschmidt, B.; Romo, D. Manuscript in preparation.

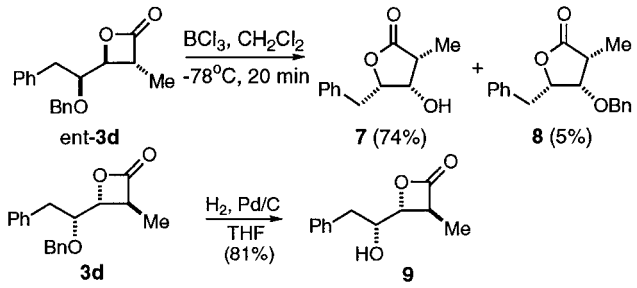
(12) Shitangkoon, A.; Vigh, G. *J. Chromatogr. A* **1996**, 31−42.

(13) Available in four steps from (*R*)-phenylalanine, see: Degerbeck, F.; Fransson, B.; Grehn, L.; Ragnarsson, U. *J. Chem. Soc., Perkin Trans. 1* **1993**, 11−14.

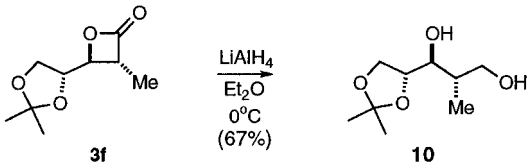
Scheme 2



Scheme 3



Scheme 4



assigned stereochemistry of β-lactone **3d** is based on coupling constant analysis[16] of the *all-syn*-butyrolactone **7** obtained using our recently improved conditions for the tandem debenzylation−transacylation reaction (Scheme 3).[11] Once again the diastereoselectivity was determined after hydrogenolysis which delivered the hydroxy β-lactone **9**.[15]

As previously reported, high trans selectivity (internal stereoselection) was observed with most aldehydes studied. An exception is β-lactone **3f** derived from glyceraldehyde **1f**[17] which gave a 3.6:1 ratio of trans/cis β-lactone diastereomers but gave excellent relative stereocontrol favoring the Felkin−Ahn product (entry 6).[5c] Importantly, the diastereomers could be readily separated by flash chromatography to give the major diastereomeric β-lactone **3f** with >99% ee in 63% isolated yield. The stereochemistry of β-lactone **3f** was determined by reduction to the known diol **10** (Scheme 4).[18]

TMAL reaction with α-methyl-β-benzyloxy aldehyde **1g**[19] (Table 1, entry 7) gave low yields even after prolonged reaction times which is consistent with our previous observations with α-alkyl-substituted aldehydes such as pivaldehyde.[4a,b] Interestingly, again no epimerization is observed even with this aldehyde which is known to be quite susceptible to epimerization.[19b] As expected, use of the acetic acid derived ketene acetal **2c** gave good yields but poor diastereoselectivity (entries 8 and 9).

In summary, the TMAL reaction provides a concise and direct route to optically active β-lactones from various chiral aldehydes under mild conditions. In most cases, less than 2% racemization of the α-chiral aldehyde substrates and high internal stereoselection is observed. In light of recently discovered, novel transformations of β-lactones, the optically active β-lactones described herein should prove to be useful synthetic intermediates. Ongoing mechanistic studies of this intriguing reaction have led to some interesting observations that will be the subject of future reports.

Experimental Section

General. Aldehydes were prepared according to literature procedures by DIBAl-H reduction of the corresponding ester (**1a**−**e**), by $NaIO_4$ cleavage of the corresponding diol (**1f**), or by Swern oxidation of the corresponding alcohol (**1g**) and were typically used directly in the TMAL reaction (especially α-epimerizable aldehydes) without purification to prevent potential racemization on silica gel.[19b] Solvent purification/drying, flash chromatography, thin-layer chromatography, and optical purity determination were performed as previously described.[4b]

General Procedure for TMAL Reaction as Described for β-Lactone 3a. Anhydrous $ZnCl_2$ (482 mg, 3.46 mmol, 1.4 equiv) was freshly fused at ~0.5 mmHg, and after cooling to ambient temperature, CH_2Cl_2 (appropriate volume to make the final concentration of aldehyde in CH_2Cl_2 ~0.15 M) was added. The aldehyde (527 mg, 2.47, 1.0 equiv) was then added neat or as a CH_2Cl_2 solution at room temperature, resulting in a cloudy, colorless solution. After 15 min of stirring, the thiopyridylketene acetal (847 mg, 2.86 mmol, 1.2 equiv) was added neat and the resulting yellow suspension was stirred vigorously for the time indicated in the table. As the reaction proceeded, the reaction solution typically went from a yellow suspension to a homogeneous yellow solution, and finally, an off-white precipitate formed.

After addition of pH 7 buffer, the mixture was stirred vigorously for 10 min and filtered through Celite with CH_2Cl_2. The organic layer was separated, dried over $MgSO_4$, filtered, taken up in CH_2Cl_2 (appropriate volume to make the final concentration ~0.15 M), and directly treated with $CuBr_2$ (1.3 equiv relative to ketene acetal) to remove excess thiopyridylketene acetal and any thioester formed. The resulting suspension was stirred for 1.5 h, filtered through Celite, and washed with 10% aqueous K_2CO_3 and brine. The organic layer was dried over $MgSO_4$, filtered, concentrated in vacuo to afford the crude product, and purified by flash chromatography (silica gel) to give 444 mg (69%) of β-lactone **3a** as a colorless oil with the following physical and spectral characteristics. The following data were obtained for β-lactone **3a** using aldehyde **1a** derived from yeast reduction of ethyl acetoacetate: R_f 0.44 (10:90 EtOAc:hexanes); $[\alpha]^{26}_D$ 72.8 (*c* 1.05, $CHCl_3$);^{1}H NMR (200 MHz, $CDCl_3$) δ 4.36 (ddd, J = 4.2, 4.2, 8.7 Hz, 1H), 3.92−4.07 (m, 1H), 3.23 (dq, J = 4.0, 7.5 Hz, 1H), 1.73−1.96 (m, 2H), 1.39 (d, J = 7.5 Hz, 3H), 1.18 (d, J = 6.1 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.1, 76.8, 64.9, 50.7, 44.2, 25.7, 24.3, 17.9, 12.3, −4.3, −4.9; IR (thin film) 1832 cm^{-1}; FAB HRMS calcd for [M + H] 259.1729, found 259.1719. Anal. Calcd for $C_{13}H_{26}O_3Si$: C, 60.42; H, 10.14. Found: C, 60.27; H, 10.16.

(14) Chiarello, J.; Joullie, M. M. *Synth. Commun.* **1989**, *19*, 3379−3383.

(15) After hydrogenolysis, *p*-tolyltoluene was isolated indicating that the benzylation leading to aldehyde **1c** and **1d** led to Friedel−Crafts alkylation of the benzyl ether. This byproduct was obtained regardless of the source of benzyltricholoracetimidate (Lancaster, Aldrich, or freshly prepared). The presence of ~10% of this *p*-tolylbenzyl-protected material was readily apparent by ^{1}H NMR in the starting aldehydes **1c** and **1d** and in the β-lactones **3c** and **3d**. See spectral data in Supporting Information.

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Using the general procedure described above, β-lactones **3a**−**g** were prepared in the reaction times and diastereo- and enantioselectivities indicated in the table. Characterization data for β-lactones **3b**−**g** can be found in the Supporting Information.

γ-Lactone 4 was prepared according to the method described previously. Data not previously reported or different from that previously reported follow: R_f 0.07 (10:90 EtOAc:hexanes); mp 57−58 °C, lit.[14] mp 51−53 °C; $[\alpha]^{26}_D$ −45.6 (*c* 0.92, $CHCl_3$), lit.[14] $[\alpha]^{25}_D$ −48.0 (c 1.13, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.49 (dq, *J* = 3.0, 6.6 Hz, 1H), 4.28 (br s, 1H), 2.75 (dq, *J* = 5.1, 7.5 Hz, 1H), 2.10 (br s, 1H), 1.44 (d, *J* = 6.6 Hz, 3H), 1.28 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 78.9, 72.4, 42.4, 13.7, 8.0; IR (KBr) 3130−3610, 1752 cm^{-1}.

Hydroxy β-lactone 6 was prepared as described below for hydroxy β-lactone **9**: R_f 0.2 (1:2 EtOAc:hexanes); $[\alpha]^{26}_D$ 67.6 (*c* 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (dd, *J* = 3.9, 5.4 Hz, 1H), 3.92−4.00 (m, 1H), 3.48 (dq, *J* = 3.9, 7.5 Hz, 1H), 2.05 (br s, 1H), 1.41 (d, *J* = 7.5 Hz, 3H), 1.29 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 81.9, 67.9, 47.1, 18.3, 12.1; IR (thin film) 3050−3720, 1822 cm^{-1}; FAB HRMS calcd for [M + Na] 153.0528, found 153.0525.

γ-Lactone 7. To a solution of β-lactone **ent-3d** (79.9 mg, 0.27 mmol) in 1.5 mL of CH_2Cl_2 was added 0.28 mL of BCl_3 (1 M solution in hexane, 0.28 mmol) at −78 °C. After 20 min, 1 mL of pH 7 buffer was added. To the resulting mixture was added 3 mL of CH_2Cl_2. The organic phase was washed with brine, dried over $MgSO_4$, filtered, concentrated in vacuo, and purified by flash chromatography (1:4 → 1:3 → 1:2 EtOAc:hexanes) to give 41.4 mg (74%) of γ-lactone **7** as a white solid: R_f 0.09 (20:80 EtOAc:hexanes); $[\alpha]^{26}_D$ −34.9 (*c* 1.06, $CHCl_3$); mp 109−111 °C; ^{1}H NMR (300 MHz, $CDCl_3$−D_2O) δ 7.12−7.31 (m, 5H), 4.79 (br s, 1H), 4.52 (ddd, *J* = 3.0, 7.2, 7.5 Hz, 1H), 4.25 (dd, *J* = 3.0, 4.8 Hz, 1H), 3.21 (dd, *J* = 7.2, 13.8 Hz, 1H), 3.11 (dd, *J* = 7.5, 13.8 Hz, 1H), 2.70 (dq, *J* = 4.8, 7.0 Hz, 1H), 1.26 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3, 136.4, 129.2, 128.6, 126.8, 83.3, 71.2, 42.1, 34.5, 8.0; IR (KBr) 3250−3610, 1756 cm^{-1}; FAB HRMS calcd for [M + H] 207.1021, found 207.1021.

Hydroxy β-Lactone 9. To a solution of β-lactone **3d** (12.7 mg, 0.043 mmol) in 3 mL of THF was added 15 mg of Pd/C. After being stirred overnight under a H_2 atmosphere at ambient temperature, the reaction mixture was filtered through Celite, concentrated, and purified by flash chromatography (1:6 → 1:4 → 1:2 EtOAc:hexanes) to give 7.1 mg (81%) of hydroxy β-lactone **9**: $[\alpha]^{26}_D$−67.8 (*c* 2.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23−7.37 (m, 5H), 4.11 (dd, *J* = 3.9, 4.2 Hz, 1H), 3.97−4.04 (m, 1H), 3.51 (dq, *J* = 3.9, 7.8 Hz, 1H), 2.96 (dd, *J* = 7.5, 13.5 Hz, 1H), 2.84 (dd, *J* = 6.3, 13.5 Hz, 1H), 2.15 (br s, 1H), 1.30 (d, *J* = 7.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 136.3, 129.3, 128.8, 127.0, 80.0, 72.0, 46.9, 39.5, 12.0; IR (thin film) 3120−3710, 1814 cm^{-1}; EI HRMS calcd for [M^+] 206.0943, found 206.0945.

Tetrahydrofuran i: R_f 0.43 (10:90 EtOAc:hexanes); $[\alpha]^{26}_D$ +13.2 (*c* 0.68, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.42 (dddd, *J* = 2.4, 2.4, 4.8, 5.7 Hz, 1H), 4.23 (ddd, *J* = 6.3, 6.9, 9.3 Hz, 1H), 3.93 (dd, *J* = 4.8, 9.3 Hz, 1H), 3.69 (s, 3H), 3.62 (ddd, *J* = 0.6, 2.4, 9.3 Hz, 1H), 2.58 (dq, *J* = 6.9, 6.9 Hz, 1H), 1.90 (dddd, *J* = 0.6, 2.4, 6.3, 12.9 Hz, 1H), 1.80 (ddd, *J* = 5.7, 9.3, 12.9 Hz, 1H), 1.23 (d, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.058 (s, 3H), 0.050 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 79.2, 76.0, 72.6, 51.7, 44.2, 39.5, 25.8, 18.0, 13.7, −4.76, −4.83; IR (thin film) 1741 cm^{-1}; FAB HRMS calcd for [M + H] 289.1835, found 289.1850.

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Supporting Information Available: Characterization data for β-lactones **3b**−**g**. ^{1}H and ^{13}C NMR spectra of β-lactones **3a**−**d,f** γ-lactone **7**, hydroxy β-lactones **6** and **9**, and tetrahydrofuran **i**. Representative GC traces (for β-lactone **3f**) for enantiomeric purity determination (21 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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