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Efficient Synthesis of (3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-3-ol from Glycolaldehyde

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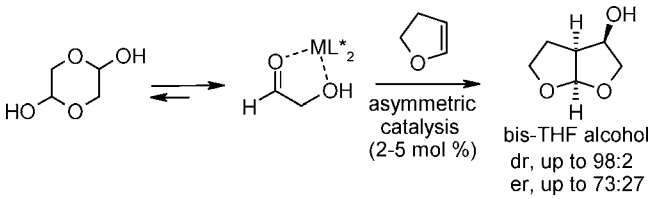
ABSTRACT



A one-step diastereoselective (up to 98:2) synthesis of the bis-furan alcohol of Darunavir and other HIV drug candidates has been achieved utilizing the novel cyclization of glycolaldehyde and 2,3-dihydrofuran. The cycloaddition was catalyzed by a variety of catalysts including those formed from tin(II) triflate and common chiral ligands such as BINAP and Evans's box ligands. An efficient and unique enzymatic process enhanced the enantiomeric purity to provide the target in optically pure form.

Despite the availability of more than 20 approved drugs for the treatment of human immunodeficiency virus (HIV) infection, many new compounds are in development in both new and existing classes of HIV inhibitors. This is driven in large part because of the development of drug resistance to current treatments in HIV-infected patients. Brecanavir or GW640385 (**1**, Figure 1) was a potent new protease inhibitor in phase 2 clinical trial for treatment of drug-resistant HIV. It has received Fast Track Designation from the U.S. Federal Drug Administration (FDA). The structure of **1** belongs to a novel class of sulfonamides that are aspartyl protease inhibitors.[1] Notable in the structure is the fused bicyclic tetrahydrofuran or bis-tetrahydrofuran (bis-THF) moiety, which has been described as a surrogate for the asparagines side chain in the design of HIV protease inhibitors.[2] The bis-THF unit is also present in the recently FDA approved Darunavir or TMC114 (**2**)[3a−c] and several other protease inhibitors reported in development as HIV drug candidates including UIC-94003[3c] and L-739,594.[3e]

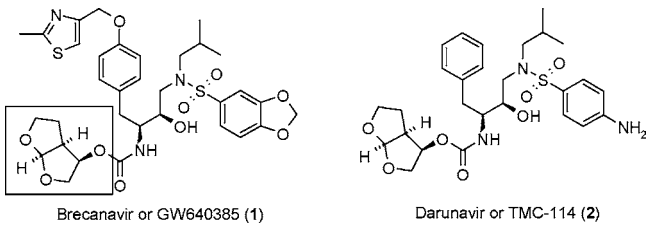


Figure 1. Structures of protease inhibitors **1** and **2** with bis-THF moiety.

(1) (a) Hanlon, M. H.; Porter, D. J. T.; Furfine, E. S.; Spaltenstein, A.; Carter, H. L.; Danger, D.; Shu, A. Y. L.; Kaldor, I. W.; Miller, J. F.; Samano, V. A. *Biochemistry* **2004**, *43*, 14500. (b) Miller, J. F.; Andrews, C. W.; Brieger, M.; Furfine, E. S.; Hale, M. R.; Hanlon, M. H; Hazen, R. J.; Kaldor, I.; McLean, E. W.; Reynolds, D.; Sammond, D. M.; Spaltenstein, A.; Tung, R.; Turner, E. M.; Xu, R. X.; Sherrill, R. G. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1788.

(2) (a) Thompson, W. J.; Ghosh, A. K.; Holloway, M. K.; Lee, H. Y.; Munson, P. M.; Schwering, J. E.; Wai, J.; Darke, P. L.; Zugay, J.; Emini, E. A.; Schleif, W. A.; Huff, J. R.; Anderson, P. S. *J. Am. Chem. Soc.* **1993**, *115*, 801. (b) Ghosh, A. K.; Thompson, W. J.; Holloway, M. K.; McKee, S. P.; Duong, T. T.; Lee, H. Y.; Munson, P. M.; Smith, A. M.; Wai, J. M.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 2300. (c) Ghosh, A. K.; Kincaid, J. F.; Cho, W.; Walters, D. E.; Krishnan K.; Hussain, K. A.; Koo, Y.; Cho, H.; Rudall, C.; Holland, L.; Buthod, J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 687.

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The importance of the bis-THF alcohol in drug discovery has generated a significant interest in the synthesis.[3] One approach utilized substrate-controlled synthesis starting from a chiral pool material like D-glyceraldehyde derivatives.[3b−d] The most notable synthesis along this approach is the recently reported synthesis by Quaedflieg and co-workers starting from *S*-2,3-*O*-isopropylideneglyceraldehyde.[3b] Generally, good stereochemical control was reported with this approach. Another approach involved the synthesis of the racemic form of bis-THF alcohol followed by enzymatic resolution.[3a,e−g] Despite the need for multiple steps to establish the relative stereochemistry of the bicyclic structure prior to the enzymatic resolution, this synthetic approach has been demonstrated to be highly practical. One such synthesis has been scaled up to tonnage quantity in production of **1**.[3g] Recently, Ghosh reported an asymmetric synthesis based on an anti-aldol reaction of an ester-derived titanium enolate.[3i] However, this is still a substrate-controlled synthesis requiring a stoichiometric amount of a chiral indanol.

Our goal was to achieve an efficient synthesis of the bis-THF alcohol **3** in high optical purity through a short and stereoselective synthesis employing catalytic reagent control as shown in Figure 2. The bicyclic [2.2.0] ring structure of

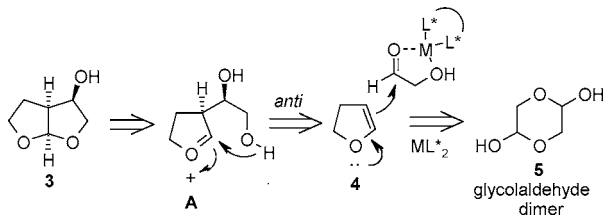
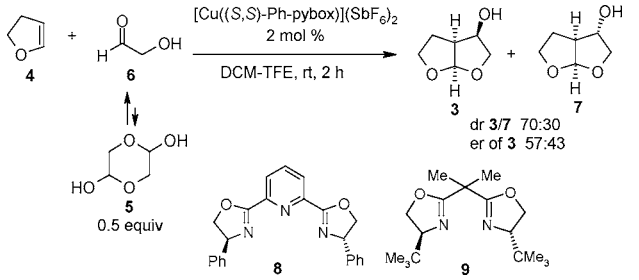


Figure 2. Strategy for asymmetric synthesis of bis-tetrahydrofuran alcohol **3**.

3 means that only one of the two bridge-head stereocenters needs to be controlled, and the other stereocenter is formed in the cyclization. This line of thinking led to postulation of an oxonium-like intermediate **A**. The two stereocenters in **A** would require the addition of 2,3-dihydrofuran (2,3-DHF, **4**) to a complex of glycolaldehyde and the chiral catalyst (ML^*_2) in the anti fashion. The commercially available glycolaldehyde dimer (**5**) would serve as the ultimate electrophile for the catalyzed reaction.[4] In an ideal case, this would give the target bis-THF alcohol (**3**) in a single step from the most simple carbohydrate and 2,3-DHF.[5]

The equilibrium of glycolaldehyde (**6**) and its dimer (**5**) has been a subject for several reports (Scheme 1).[6] We

Scheme 1



anticipated that the cycloaddition would drive the equilibrium from **5** to **6**. The desired product **3** and diastereomeric compound **7** correspond to the anti and syn additions of **4** to **6**, respectively, prior to the ring closure.

We were initially drawn to the Evans pybox (**8**) and box (**9**) ligands because of their wide use in a variety of reactions involving (benzyloxy)acetaldehyde.[7] We were delighted to find that a mixture of 2,3-DHF (**4**) and half equivalent of glycolaldehyde dimer (**5**) in the presence of 2 mol % of [Cu((*S*,*S*)-Ph-pybox)]$(SbF_6)_2$ gave rise to a mixture of cycloadducts **3** and **7** at ambient temperature. Both diastereo and enantio selectivities were obtained by analysis of the crude reaction mixture in a chiral GC with a racemic reference as well as an enantiomerically pure sample of **3**.[3g] In ^{1}H NMR analysis, the doublets for the acetal H of **3** and **7** were well separated and highly diagnostic at 5.7 and 5.9 ppm, respectively. Although the diastereo (70:30 for **3**/**7**) and enantio (57:43 for **3** favoring the desired 3*R*-alcohol as shown) selectivities were modest, the observation that the skeleton of the bis-THF alcohols was established in a single step prompted us to further examine the reaction. Also, the desired diastereomer **3** resulting from anti addition of **4** to **6** was favored over the syn adduct **7**, albeit in modest ratio. This is in contrast with the extremely high syn selectivity

(3) (a) Surleraux, D. L. N. G.; Tahri, A.; Verschueren, W. G.; Pille, G. M. E.; de Kock, H. A.; Jonckers, T. H. M.; Peeters, A.; De Meyer, S.; Azijn, H.; Pauwels, R.; de Bethune, M.-P.; King, N. M.; Prabu-Jeyabalan, M.; Schiffer, C. A.; Wigerinck, P. B. T. P. *J. Med. Chem.* **2005**, *48*, 1813. (b) Quaedflieg, P. J. L. M.; Kesteleyn, B. R. R.; Wigerinck, P. B. T. P.; Goyvaerts, N. M. F.; Vijn, R. J.; Liebregts, C. S. M.; Kooistra, J. H. M. H.; Cusan, C. *Org. Lett.* **2005**, *7*, 5917. (c) Ghosh, A. K.; Leshchenko, S.; Noetzel, M. *J. Org. Chem.* **2004**, *69*, 7822. (d) Ghosh, A. K.; Kincaid, J. F.; Walters, D. E.; Chen Y.; Chaudhuri, N. C.; Thompson, W. J.; Culberson, C.; Fitzgerald, P. M. D.; Lee, H. Y.; McKee, S. P.; Munson, P. M.; Duong, T. T.; Darke, P. L.; Zugay, J. A.; Schleif, W. A.; Axel, M. G.; Lin, J.; Huff, J. R. *J. Med. Chem.* **1996**, *39*, 3278. (e) Ghosh, A. K.; Chen. Y. *Tetrahedron Lett.* **1995**, *36*, 505. (f) Ghosh, A. K.; Thompson, W. J.; Fitzgerald, P. M. D.; Culberson, J. C.; Axel, M. G.; McKee, S. P.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1994**, *37*, 2506. (g) Roberts, J. C.; Toczko, J. F. PCT/US2004/020353, WO 2005/000249 A2. (h) Uchiyama, M.; Hirai, M.; Nagata, M.; Katoh, R.; Ogawa, R.; Ohta, A. *Tetrahedron Lett.* **2001**, *42*, 4653. (i) Ghosh, A. K.; Li, J.; Perali, R. S. *Synthesis* **2006**, 3015.

(4) Glycolaldehyde dimer, commercially available from Sigma-Aldrich, is used in food industry as a flavoring and browning agent and was reportedly produced in large scale from the pyrolysis of sawdust: Stradal, J. A.; Underwood, G. L. US Patent 5,393,542, 1995.

(5) During the preparation of this manuscript, we noted a publication by Yu and co-workers in November 2007 using the same strategy: Yu, R. H.; Polniaszek, R. P.; Becker, M. W.; Cook, C. M.; Yu, L. H. L. *Org. Process Res. Dev.* **2007**, *11*, 972. Our work with a much higher anti diastereoselectivity to avoid the need of oxidation-reduction for OH inversion was independently conceived and presented in ACS ProSpectives Symposium on Process Chemistry, Boston, MA, in September, 2007.

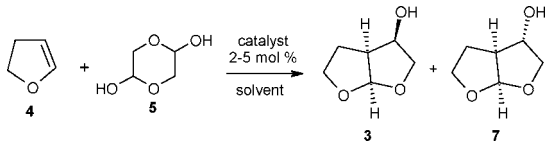
(6) (a) George, W. O.; Collins, G. C. S. *J. Chem. Soc, Phys. Org.* **1971**, 1352. (b) Stassinopoulou, C. I.; Zioudrou, C. *Tetrahedron* **1972**, *28*, 1257. (c) Wolfe, J.; Nemeth, D.; Costero, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 983. (d) Gennari, C.; Molinari, F.; Bartoletti, M.; Piarulli, U.; Potenza, D. *J. Org. Chem.* **1991**, *56*, 3201.

(7) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669.

reported by Evans in the use of the same catalyst in addition of (benzyloxy)acetaldehyde to silyketene acetals.[7]

In the search for a better catalyst, we noted the significant variability in both reactivity and selectivity reported by Evans group on box and pybox catalysts of Sc^{3+}, Cu^{2+}, and Sn^{2+}.[8] Complexes from Sc^{3+} and Cu^{2+} favor the syn selectivity, and complexes from Sn^{2+} favor the anti selectivity. In a communication on use of [Sc((*S*,*S*)-Ph-pybox)](OTf)$_3$ in reactions of allenylsilanes with ethyl glyoxylate, Evans described hexafluoroisopropanol (HFIP) as an additive that slightly improved the reaction yields.[8a] Accordingly, our screening started with Sn, Cu, and Sc salts and ligands **8** and **9** in solvents including 2,2,2-trifluoroethanol (TFE) and HFIP. Results are shown in Table 1.[9,10] The trend of favoring

Table 1. Catalysis by Sn^{2+}, Cu^{2+}, and Sc^{3+} with Box and Pybox Ligands



entry	catalyst[a]	solvent	dr[10] **3/7**	er[10] **3**
1	$Sn(OTf)_2$+**9**	DCM-TFE	95:5	50:50
2	$Sn(OTf)_2$+**9**	DCM−HFIP	98:2	49:51
3	$Sn(OTf)_2$+**8**	DCM	49:51	49:51
4	$Sn(OTf)_2$+**8**	DCM-TFE	85:15	54:46
5	$Sn(OTf)_2$+**8**	DCM−HFIP	93:7	51:49
6	$Sn(OTf)_2$+**8**	TFE	86:14	64:36
7	$Sn(OTf)_2$+**8**	HFIP	93:7	58:42
8	[Cu((*S*,*S*)-Ph-pybox)]$(SbF_6)_2$[a]	DCM	66:34	60:40
9	[Cu((*S*,*S*)-Ph-pybox)]$(SbF_6)_2$[a]	DCM-TFE	70:30	57:43
10	$Sc(OTf)_3$+**8**	DCM-TFE	56:44	56:44
11	$Sc(OTf)_3$+**8**	DCM−HFIP	55:45	60:40

[a] Cu catalyst (2 mol %) was prepared following ref 7. All other catalysts (5 mol %) were prepared as described in ref 9.

anti selectivity (**3**) for Sn^{2+} (entries 1−2, and 4−7), Cu^{2+} (entries 8 and 9), and Sc^{3+} (entries 10−11) in the descending order was evident. This was in line with the observations by the Evans group on use of those metals with the pybox ligands.[7,8]

(8) (a) Evans, D. A.; Zachary, K.; Sweeney. T. R.; Jason, S. T. *J. Am. Chem. Soc.* **2001**, *123*, 12095. (b) Evans, D. A.; MacMillan, D. W. C.; Campos *J. Am. Chem. Soc.* **1997**, *119*, 10859. (c) Evans, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **1998**, *120*, 4895. (d) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325. (e) Evans, D. A.; Masse, C. E.; Wu, J. *Org. Lett.* **2002**, *4*, 3375.

(9) Typical procedure for screening reactions: a catalyst, 5 mol % relative to 2,3-DHF unless otherwise noted, was prepared by mixing a metal salt (0.068 mmol) and a ligand (0.071 mmol) in 1.5 mL of solvent (2:1 of DCM and another solvent when mixture used) at ambient temperature for 40 min. Glycolaldehyde dimer (86 mg, 0.71 mmol) was added in one portion. The resultant solution was cooled with an ice bath, followed by addition of 2,3-DHF (100 mg, 1.43 mmol). The reaction was warmed to ambient temperature over about one hour and sampled for analysis upon completion, typically within 5 h.

(10) All reactions were sampled by evaporation to remove solvents, diluted with MeCN and directly injected to chiral GC for ratio analysis.

Table 2. Catalysis by (*S*,*S*)-Ph-Pybox **8** with Various Salts[a]

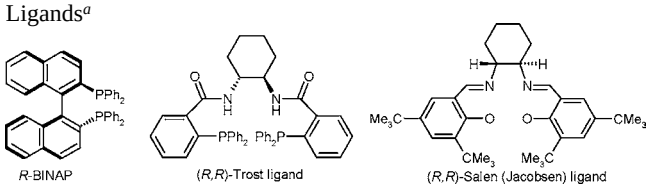
entry	metal salt	dr[10] **3/7**	er[10] **3**	er[10] **7**
1	$MnBr_2$	58:42	27:73	40:60
2	$InCl_3$	78:22	36:64	70:30
3	$Zn(OTf)_2$	81:19	49:51	51:49
4	$Mg(OTf)_2$	72:28	48:52	50:50
5	$MgBr_2$	74:26	48:52	48:52
6	$Yb(OTf)_2$	73:27	49:51	50:50
7	$CoBr_2$	64:36	46:54	42:58
8	$Cu(OTf)_2$	40:60	61:39	43:57
9	AgOAc	73:27	51:49	51:49

[a] General procedure described in ref 9 was followed.

Significant enhancement of diastereoselectivity (dr, **3**/**7**) was observed when the fluoro alcohol solvents were used alone or in combination with DCM. This enhancement was most evident for the Sn catalysts as the ratios shown in entries 1, 2, and 4−7 (85:15−98:2) in comparison with entry 3 with DCM (49:51). Other alcohols such as EtOH and *t*-BuOH did not have the same impact as the fluoro alcohols. Whenever TFE or HFIP was used, regardless of the metal, the reaction was much faster and cleaner. In the case of Sn-catalyzed reactions, glycolaldehyde was nearly completely consumed within 1 h as monitored by silica gel TLC and GC. Unfortunately, the impact of TFE and HFIP on the enantioselectivities of either **3** or **7** was quite limited, similar to Evans's observation for his aldol reactions.[8a] The best enantioselectivity for the desired bis-THF alcohol **3** was only 64:36 (entry 6), but the diastereoselectivity (86:14) was somewhat lower in this case.

The DCM−HFIP (2:1) cosolvent and the (*S*,*S*)-Ph-pybox ligand were then used to screen other metal salts. The results are shown in Table 2. With regard to the enantioselectivity of **3**, $MnBr_2$ and $InCl_3$ provided the highest enantio ratio, 27:73 and 36:64, respectively (entries 1 and 2). However,

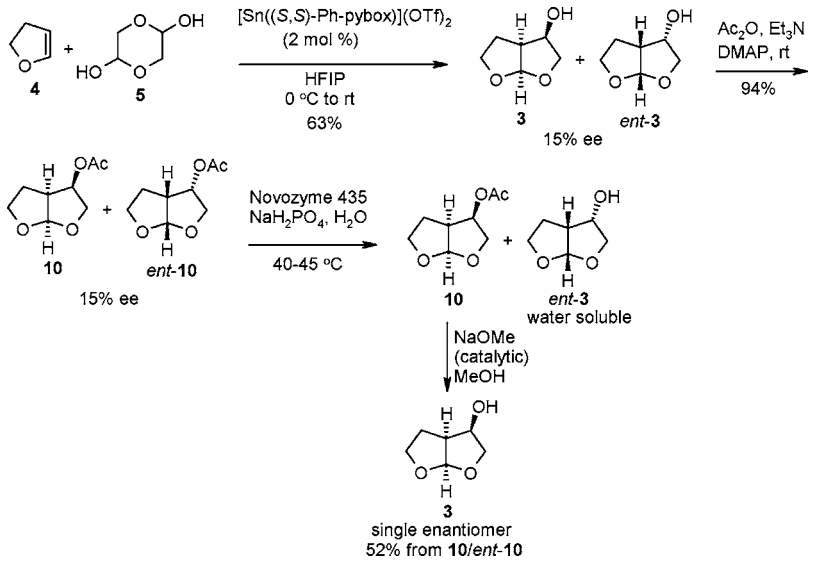
Table 3. Cycloaddition with Catalysts from Non-Oxazoline Ligands[a]



entry	catalysts[b]	dr[10] **3/7**	er[10] **3**	er[10] **7**
1	$Sn(OTf)_2$+(*R*)-BINAP	96:4	43:57	48:52
2	$Sn(OTf)_2$+(*R*,*R*)-Trost ligand	95:5	48:52	52:48
3	(*S*,*S*)-Jacobsen Co(II) catalyst[b]	65:35	36:64	33:67
4	(*R*,*R*)-Jacobsen Cr(III)Cl[b] catalyst	56:44	67:33	67:33

[a] General procedure described in ref 9 was followed. [b] Salen catalysts were purchased ready for use as ligand−metal complex.

Scheme 2



in all cases, the diastereo ratio was lower than that achieved when using $Sn(OTf)_2$. While there was some difference between the er of the anti adduct **3** and the syn adduct **7**, they followed the same trend for the level of er. The highest er for **7** was obtained with $MnBr_2$ and $InCl_3$ as in the case with **3**.

In an effort to optimize the cycladdition, we examined some catalysts derived from non-bisoxazoline ligands as shown in Table 3.

The major finding from the ligand screening was that the (*R*)-BINAP (entry 1) and the (*R*,*R*)-Trost ligands (entry 2) both gave high diastereoselectivity when used with $Sn(OTf)_2$, albeit in modest enantioselectivity. The Jacobsen salen catalysts on the other hand delivered better enantio ratio (entries 3 and 4). For the sake of practicality, we preferred the higher diastereo ratio to the higher enantio ratio.

An example illustrating the synthetic sequence for preparation of bis-THF alcohol **3** is shown in Scheme 2. The cycloaddition provided 63% isolated yield of **3** in 15% ee (favoring **3** over its enantiomer *ent*-**3**) with the pybox and $Sn(OTf)_2$. Although the undesired *ent*-**3** can be removed by direct enzymatic acetylation for a two-step synthesis of **3**,[3d] we chose the three-step ee enhancement for better practicality. Acetylation gave in 94% yield the corresponding acetates **10**, which were subjected to an enzymatic process with lipase Novozyme 435.[3g] With NaH_2PO_4 buffer at 40−45 °C, the undesired acetate (*ent*-**10**) was selectively hydrolyzed back to the corresponding alcohol (*ent*-**3**). This alcohol was highly water soluble and was removed from acetate **10** by aqueous wash of the DCM extract. Deacetylation of acetate **10** with 2 mol % NaOMe in MeOH provided a 52% yield (90% of theory) of enantiomerically pure alcohol **3**.[11]

In summary, a novel synthesis of (3*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-ol has been achieved utilizing the catalyzed cyclization of readily available 2,3-DHF and glycolaldehyde dimer to set the relative stereochemistry of the bis-THF alcohol in a single step with up to 98:2 diastereoselectivity. The best enantio selectivity (73:27) was obtained with $MnBr_2$ and (*S*,*S*)-Ph-pybox ligand. The cycloadduct from catalysis with [Sn((*S*,*S*)-Ph-pybox)]$(OTf)_2$, obtained in 15% ee, was acetylated and enzymatically enhanced to provide the optically pure bis-THF alcohol. The synthesis of four simple steps including the three steps for enantio enhancement represents an efficient synthesis of the bis-THF alcohol. The method is a two-step synthesis if the one-step enzymatic acetylation is to be applied instead.[3d]

Acknowledgment. We thank Dr. Thomas M. O'Connell (University of North Carolina at Chapel Hill) for the NMR studies on a reaction intermediate.

Supporting Information Available: Detailed experimental procedure and analysis for compounds **3**, **7**, and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The optical rotation and the ^{13}C and ^{1}H NMR spectra matched those reported in the literature.[3c]