Organic Process Research & Development **2007,** *11,* 972–980

Research and Development of an Efficient Synthesis of Hexahydrofuro[2,3-*b*]furan-3-ol Moiety—A Key Component of the HIV Protease Inhibitor Candidates

Richard H. Yu,* Richard P. Polniaszek, Mark W. Becker, Charles M. Cook, and Lok Him L. Yu

Process Research Department, Gilead Sciences, Inc., Foster City, California 94404

Abstract:

A highly efficient method for synthesizing racemic hexahydrofuro[2,3-*b*]furan-3-ol has been developed utilizing a lanthanide catalyst, such as Yb(fod)$_3$, to promote condensation of 2,3-dihydrofuran and glycolaldehyde dimer. Access to either optically enriched enantiomer of bisfuran alcohol can be obtained by using this method employing chiral ligands with the lanthanide catalyst. In support of Gilead Sciences' protease inhibitor project, this method has been demonstrated to be a robust and scalable process with potential application for the construction of a variety of furo[2,3-*b*]furan derivatives.

Introduction

The furo[2,3-*b*]furan structure, a fused cyclic acetal, exists in several biologically active natural products. Examples include aflatoxin, clerodin, asteltoxin, rhyacophiline, and acmimycin, among many others.[1–3] In particular, the (3a*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-ol moiety **1**, or "bisfuran alcohol", plays a significant role in the effectiveness of HIV protease inhibitor candidates[4] and is a key building block of Gilead Sciences' HIV protease inhibitor candidate GS-9005 (Scheme 1). The bisfuran alcohol **1** is also an integral component of Tibotec's PI TMC-114[5] and GSK's brecanavir (GW-0385).[6] Thus, considerable attention and numerous inquiries into novel synthetic methods to synthesize **1** have been reported.[5,7–12] Of particular note are efforts by Ghosh, and more recently, Quaedflieg. Ghosh and co-workers devised several approaches to (−)-**1**. One approach involved a radical cyclization[13] to the exocyclic alkene. Ozonolysis of the alkene to (±)-**1** followed by enzymatic resolution afforded (−)-**1**. Alternatively, Ghosh directly accessed (−)-**1** starting from isopropylidene-D-glyceraldehyde with a key photochemical step.[10] More recently, an *anti*-aldol strategy[12] was reported starting from an ester-derived titanium enolate to afford highly optically enriched **1**. Quaedflieg and co-workers demonstrated two routes to (−)-**1**, both based on diastereoselective Michael additions of nitromethane.[11] Of the two approaches, the route that utilized an initial Wittig reaction to the chiral enoate was proven on a multikiloscale. Other notable approaches included Pezechk's radical cyclization of bromoacetal[7] and Uchiyama's asymmetric oxyselenenylation of 2,3-dihydrofuran.[9] These varied approaches led to the desired optically enriched bisfuran alcohol; however, in all cases, drawbacks included multiple synthetic steps, ozonolytic cleavage, and photochemical transformation, which are not easily amenable to scale-up.

As previously indicated, the bisfuran moiety is a key component in Gilead Sciences' protease inhibitor GS-9005. To support the API needs for the development of the program, we have developed a direct and highly efficient pathway to construct the bisfuranyl system leading to the desired alcohol **1** (Scheme 2). With the use of enzymatic assistance, the enantiomerically pure compound can be obtained in good yields and high chemical and optical purities. The synthetic method described has been performed at the multikiloscale level in support of phase I clinical trials. As an extension of the methodology, results from evaluation in the use of chiral

* Corresponding author. E-mail: richard_yu@gilead.com.

(1) (a) Castellino, A. J.; Rapoport, H. *J. Org. Chem.* **1986**, *51*, 1006. (b) Merritt, A. T.; Ley, S. V. *Nat. Prod. Rep. Lett.* **1992**, 243. (c) Schreiber, S. L.; Satake, K. *J. Am. Chem. Soc.* **1984**, *106*, 4186.

(2) (a) Tadano, K.; Yamada, H.; Idogaki, Y.; Ogawa, S.; Suami, T. *Tetrahedron Lett.* **1988**, *29*, 655. (b) Fernandez, M. C.; Esquivel, B.; Cardenas, J.; Sanchez, A. A.; Toscano, R. A.; Rodriguez-Hahn, L. *Tetrahedron* **1991**, *47*, 7199. (c) Mellor, J. M.; Mohammed, S. *Tetrahedron* **1993**, *49*, 7557.

(3) (a) Enders, D.; Vázquez, J.; Raabe, G. *Chem. Commun.* **1999**, 701–702. (b) Petit, F.; Furstoss, R. *Synthesis* **1995**, 1517.

(4) (a) Ghosh, A. K.; Sridhar, P. R.; Kumaragurubaran, H.; Koh, Y.; Weber, I. T.; Mitsuya, H. *ChemMedChem* **2006**, *1* (9), 939–950. (b) Ghosh, A. K.; Schiltz, G.; Perali, R. S.; Leshchenko, S.; Kay, S.; Walters, D. E.; Koh, Y.; Maeda, K.; Mitsuya, H. *Bioorganic & Medicinal Chemistry Letters* **2006**, *16* (7), 1869–1873.

(5) (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-Jeyablaan, M.; Schiffer, C. A.; Wigerinck, P. B. T. P. *J. Med. Chem.* **2005**, *48*, 1813–1822. (b) Surleraux, D. L. N. G.; de Kock, H. A.; Verschueren, W. G.; Pille, G. M. E.; Maes, L. J. R.; Peeters, A.; Vendeville, S.; 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* (6), 1965–1973.

(6) (a) Ford, S.; Reddy, Y. S.; Anderson, M. T.; Murray, S. C.; Fernandez, P.; Stein, D. S.; Johnson, M. A. *Antimicrob. Agents Chemother.* **2006**, *50* (6), 2201–2206. (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*, 1788–1794.

(7) Pezechk, M.; Brunetiere, A. P.; Lallemand, J. Y. *Tetrahedron Lett.* **1986**, *27* (32), 3715–3718.

(8) Ghosh, A. K.; Chen, Y. *Tetrahedron Lett.* **1995**, *36* (4), 505–508.

(9) Uchiyama, M.; Hirai, M.; Nagata, M.; Katoh, R.; Ogawa, R.; Ohta, A. *Tetrahedron Lett.* **2001**, *42*, 4653–4656.

(10) Ghosh, A. K.; Leshchenko, S.; Noetzel, M. *J. Org. Chem.* **2004**, *69* (23), 7822–7829.

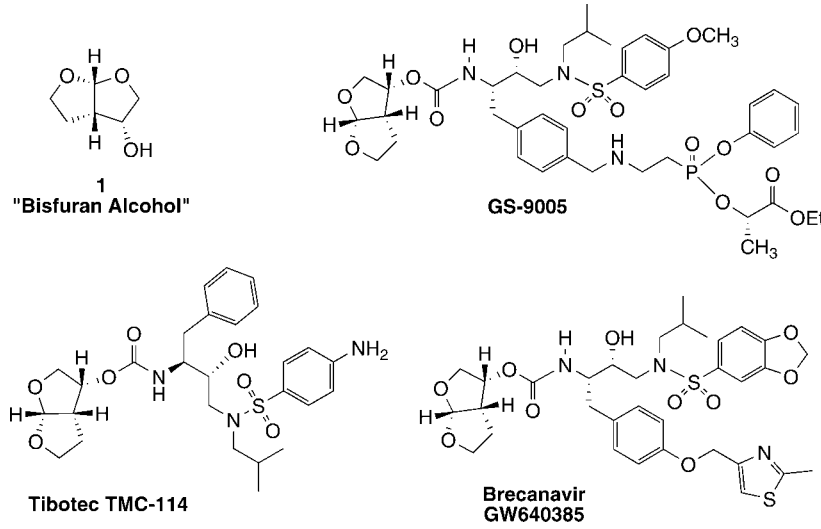
(11) Quaedflieg, P. J. L. M.; Kesteleyn, B. R. R.; Wigerinck, P. B. T. P.; Goyvaerts, N. M. F.; Vijn, R. J.; Liebregts, C. S. M.; Kooistra, J. H. M. H.; Cusan, C. *Org. Lett.* **2005**, *7* (26), 5917–5920.

(12) Ghosh, A. K.; Li, J.; Perali, R. S. *Synthesis* **2006**, *18*, 3015–3018.

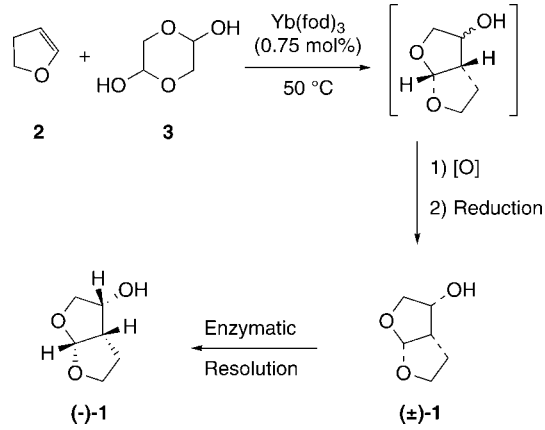
(13) (a) Ghosh, A. K.; Thompson, W. J.; Fitzgerald, P. M. D.; Culberson, C.; Axel, M. G.; McKee, S. P.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1994**, *37*, 2506–2508. (b) Ghosh, A. K.; Kincaid, J. F.; Walters, D. E.; Chen, Y.; Chaudhuri, N. C.; Thompson, W. J.; Culberson, C.; Fitzgerald, P. 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* (17), 3278–3290.

10.1021/op700160a CCC: $37.00
Published on Web 10/05/2007

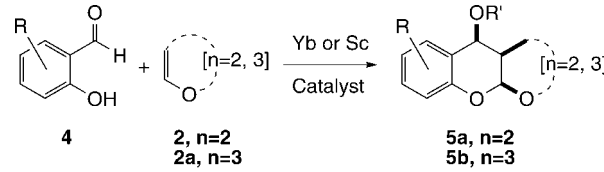
Scheme 1. **Bisfuran alcohol, 1, and drug candidates containing the hexahydrofuro[2,3-b]furan-3-ol moiety**



Scheme 2. **Gilead Sciences' direct approach to optically active bisfuran alcohol, (−)-1**



Scheme 3. **Lanthanide-catalyzed cyclization reactions**



catalysts to promote a one-pot synthesis and direct access to the enantiomeric enriched bisfuran alcohol **1** will be discussed.

Results and Discussion

Our proposed approach in the construction of **1** stemmed from the reported syntheses of ene products from enol ethers and aldehydes catalyzed by a Lewis acid[14] or, more specifically, ytterbium catalysts.[15] Yadav and co-workers[16] utilized ytterbium or scandium catalysts for the cyclization of 2,3-dihydrofuran **2** and 3,4-dihydro-2*H*-pyran **2a** with a series of *o*-hydroxybenzaldehydes **4** to afford furo-**5a** and pyranobenzopyrans **5b**, respectively (Scheme 3).

These literature precedents laid the foundation for our investigation into the construction of our target molecule **1** employing 2,3-dihydrofuran and an α-hydroxyaldehyde. In our approach, 2,3-dihydrofuran **2**, in theory, would attack the activated carbonyl of the α-hydroxyaldehyde **6** coordinated to the lanthanide catalyst to form the transient intermediate **7**. Subsequent attack of the alcohol to the oxonium ion intermediate would form the bicyclic, cis ring fused **1**. It was hypothesized that during ring formation, a mixture of the alcohol cis or trans to the ring configuration would be anticipated (Scheme 4).

In practice, to construct **1**, we used the commercially available glycolaldehyde dimer **3**, the dimeric form of hydroxyacetaldehyde **6**.[17] On initial screening of catalysts, the lanthanide catalyst, $Yb(fod)_3$ **8** (structure shown in Scheme 5) efficiently facilitated the cyclization and product formation was observed. A variety of lanthanide catalysts (structures shown in footnote section of Table 2), which included $Eu(fod)_3$, $Eu(hfc)_3$, $Eu(OTf)_3$, $Sc(OTf)_3$, $Yb(hfc)_3$ $Yt(hfc)_3$, $Yt(OTf)_3$, $Yb(OTf)_3$, and $Yb(fod)_3$ **8**,[18] were effective in our application. Among the list of lanthanide catalysts tested, $Yb(fod)_3$ was most effective in the formation of (±)-**1**. Thus, reaction of the glycolaldehyde dimer in 2,3-dihydrofuran (5 volumes) with 0.75 mol % $Yb(fod)_3$ heated at 50 °C for 5 h reproducibly afforded a diastereomeric mixture of 65:35 *cis*-**1** to *trans*-**1** in 60–65% isolated yields (Scheme 5). Although improved catalyst performance was observed with other systems using silica gel, a catalytic amount of acetic acid,[18] or triethylamine hydrochloride, negligible improvements in yield or diastereoselectivity were observed with our substrate using these additives. L-Phenylalanine hydrochloride and trifluoroacetic acid additives were too harsh, resulting in formation of complex mixtures. Solvents

(14) (a) Shoda, H.; Nakamura, T.; Tanino, K.; Kuwajima, I. *Tetrahedron Lett.* **1993**, *34* (39), 6281–6284. (b) Carreira, E. M.; Lee, W.; Singer, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 3649–3650.

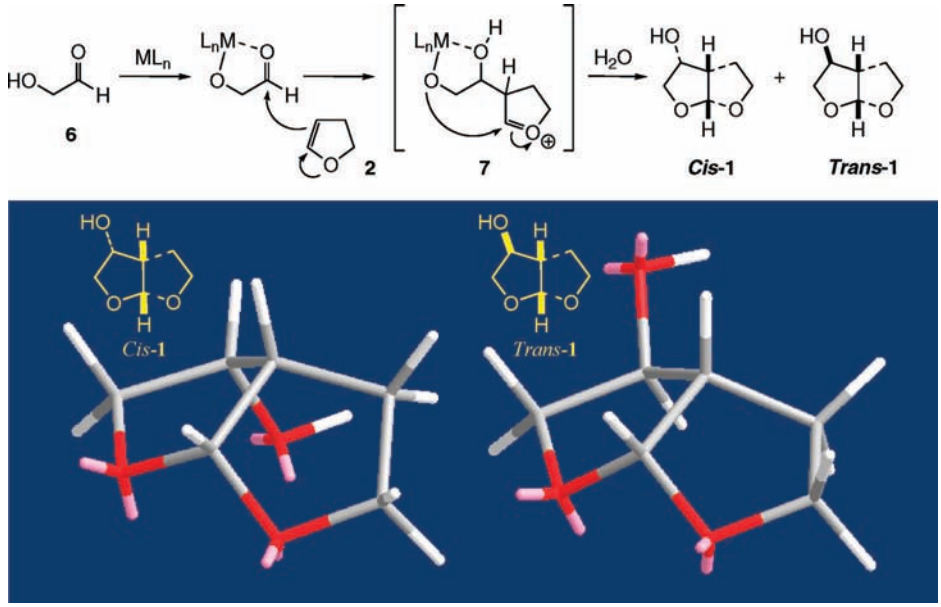
(15) Deaton, M.; Ciufolini, M. A. *Tetrahedron Lett.* **1993**, *34* (15), 2409–2412.

(16) Yadav, J.; Subba Reddy, B. V.; Aruna, M.; Venugopal, C.; Ramalingam, T.; Kiran Kumar, S.; Kunwar, A. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 165–171.

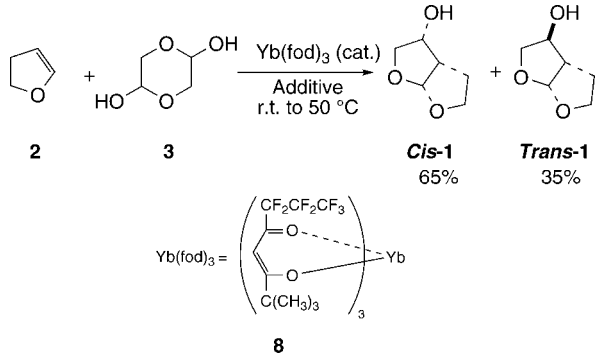
(17) (a) Yaylayan, V. A.; Harty-Majors, S.; Ismail, A. A. *Carbohydr. Res.* **1998**, *309* (1), 31–38. (b) Khomenko, T. I.; Lezina, V. P.; Stepanyants, A. U.; Sakharov, M. M.; Golovina, O. A.; Krylov, O. V. *Kinet. Katal.* **1976**, *17* (4), 911–15. (c) George, W. O.; Collins, G. C. S. *J. Chem. Soc., Perkin Trans. 2* **1971**, *7*, 1352–1355. (d) Stassinopoulou, C. I.; Zioudrou, C. *Tetrahedron* **1972**, *28*, 1257–1263. (e) Summerbell, R. K.; Rochen, L. K. *J. Am. Chem. Soc.* **1941**, *63* (12), 3241–3244.

(18) Deaton, M.; Ciufolini, M. A. *Tetrahedron Lett.* **1993**, *34* (15), 2409–2412.

Scheme 4. **Theoretical lanthanide-catalyst-promoted formation of *cis*-1 and *trans*-1 with 3D representation**



Scheme 5. **Condensation of glycolaldehyde dimer with 2,3-dihydrofuran**



such as tetrahydrofuran, dichloromethane, and acetonitrile were not only found to have no effect but were a detriment to the reaction progress with no detectable bisfuran alcohol product formation.

Overcoming Diastereoselectivity Issues. Commercially available $Yb(hfc)_3$, containing the chiral camphorate ligand, while able to aid in formation of (±)-**1**, did not promote any diastereomeric selectivity. Because the catalyst alone was unable to control diastereoselectivity, the sequence of oxidation to the ketone **9** followed by reduction back to (±)-**1** allowed us to overcome the observed *cis*-**1** to *trans*-**1** alcohol diastereomer distribution. This oxidation/reduction sequence improved the diastereomeric ratio from 65:35 to 95:5 in favor of the desired all-cis compound.

Of the several oxidation methods tested (Table 1), which included acetic anhydride in dimethyl sulfoxide,[19] Dess-Martin reagent, and trichloroisocyanuric acid and TEMPO,[20] sodium hypochlorite, and acetic acid,[21] sodium hypochlorite and TEMPO[22] proved superior and scalable. Although an exotherm was observed, it was easily controlled by the rate of addition of NaOCl, and cleanly furnished the bisfuran ketone.

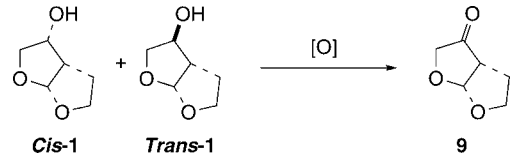
A drawback to the use of sodium hypochlorite, typically supplied at ~11–15% chloride content, was the large reaction volume limiting throughput. Although the ketone was isolable for analytical evaluation, facile degradation was observed when kept as a concentrated oil. No degradation was observed if the ketone was kept as a solution in dichloromethane and expeditiously carried forward to the reduction step. This allowed the oxidation and reduction steps to be incorporated into a "one-pot" synthesis (Scheme 6).

Selective reduction to the all-cis isomer was effected by using potassium triisopropoxyborohydride (KIPBH) in THF. However, on scale-up, sodium borohydride proved to be a more practical and suitable alternative even though diastereoselectivity was less than 100%. Thus, a freshly prepared ethanolic solution of sodium borohydride was added directly to a dichloromethane solution of the ketone at low temperature with near quantitative yield to (±)-**1**. Low reaction temperature (<5 °C) was required to ensure reduction selectivity (>95 % *cis*-(±)-**1**). The isolation, however, proved to be a challenge because of the high water solubility of **1**. Once dissolved into aqueous solutions, the bisfuran alcohol cannot be fully retrieved by extraction with organic solvents as (±)-**1** was equally distributed in both phases. Although an aqueous work-up was unavailable, removal of boron salts was necessary because, as expected, residual boron salts impeded the subsequent enzymatic resolution step. Thus, the isolation procedure involved an acetic acid quench of the hydride followed by organic solvent slurry to extract the alcohol from the salts. Alternatively, codistillation with methanol to remove boron as the trimethylborate was effective but tedious on large scale.

Asymmetric Synthesis. Once the conditions to access (±)-**1** were established, modification to the lathanide catalyst to allow

(19) Albright, J. D.; Goldman, L. *J. Am. Chem. Soc.* **1965**, *87*, 4214–4216.
(20) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3* (19), 3041–3043.
(21) Stevens, R. V.; Chapman, K. T.; Weller, H. N. *J. Org. Chem.* **1980**, *45*, 2030–2032.
(22) Anelli, P. L.; Montanari, F.; Quici, S. *Org. Synth.* **1990**, *69*, 212–219; Coll. Vol.: **1993**, *8*, 367.

Table 1. **Screening of oxidation conditions for conversion of bisfuran alcohol, 1, to ketone, 9**

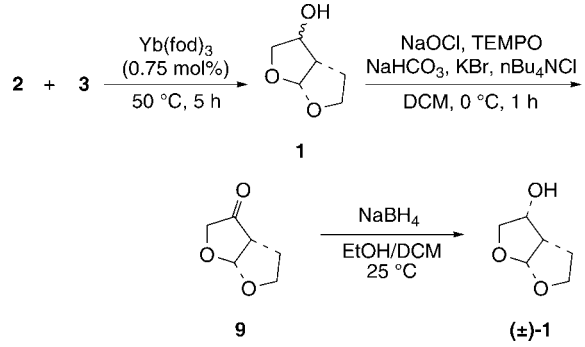


Cis-1 *Trans*-1 9

entry	oxidant	solvent	conditions	conversion (%)	yield[a] (%)
1	Ac_2O, DMSO	NA	r.t., 24 h	100	NA
2	Dess-Martin	DCM	r.t., 1 h	100	NA
3	NaOCl	HOAc	0 °C to r.t.	~5	NA
4	Trichloroiso-cyanuric acid, TEMPO	DCM	0 °C to r.t., 15 min	100	60–70
5	NaOCl, TEMPO, $NaHCO_3$, KBr, nBu$_4$NCl	DCM	0 °C	100	72–76

[a] Two-step yield. Isolated yield calculated from glycolaldehyde dimer.

Scheme 6. **One-pot synthesis to the (±)-bisfuran alcohol, 1**



9 (±)-1

direct asymmetric construction of either enantiomer of **1** was explored. As chiral ytterbium catalysts have been employed in stereoselective syntheses,[23] our effort focused on the use of commercially available chiral lanthanide catalysts possessing comparable properties to $Yb(fod)_3$ used in the racemic synthesis. Initial attempts using these chiral lanthanide catalysts (Table 2) in the condensation of **2** and **3** showed essentially no diastereoselectivity or significant asymmetric induction. Exchanging the fod ligands on the ytterbium with (*S*)-binaphthol was unsuccessful mostly because of a lack of ligand exchange rather than ineffectiveness of the potential chiral catalyst. In retrospect, the use of $Yb(OTf)_3$ may be more appropriate to promote ligand exchange. Some asymmetric induction was observed when Yb[(+)-tfc]$_3$ (Table 2, Entry 5) and Pr[(+)-tfc]$_3$ (Table 2, Entry 6) were used, resulting in a slight preference for the formation of the (–)-enantiomer.

Asymmetric induction was observed using Inanga's chiral ytterbium phosphate catalyst (Yb[(*R*)-(–)-BNP]$_3$)[24] and favored (–)-**1** at a modest 60:40 ratio employing 1.0 mol % catalyst whereas negligible improvement was observed by increasing the catalyst to 20 mol %.

Evans' pybox ligand,[25] the tridentate bis(oxazolinyl)pyridine copper (II) complex, proved too reactive in our bisfuran alcohol synthesis, resulting in polymerization products and decomposition with no product formation detected (Table 2). More appropriate for our application, scandium triflate[26] has been used in the same type of condensation reaction as ytterbium fod or ytterbium triflate in our bisfuran alcohol synthesis.[15] Thus, reaction of the preformed scandium triflate and (*S*)-pybox **10** complex in dichloromethane with **2** and **3** (Table 3, Entry 1) at room temperature afforded promising results of 79:21 favoring (–)-**1** after 5 h. At a minimum, 2 equiv of the ligand **10** to the catalyst were needed to achieve this ratio because reduction to 1.1 equiv of the ligand to the catalyst resulted in only a 62:38 ratio of (–)-**1** to (+)-**1** (Table 3, Entry 2). Three equivalents of ligand to catalyst were found to be optimal (Table 3, Entry 14) affording an 85:15 ratio of (–)-**1** to (+)-**1**. Using additional equivalents (for example, 6 equiv of ligand to catalyst) showed no improvement (Table 3, entry 12). In general, at room temperature, the reaction was judged completed in 5 h. Additional reaction time at room temperature resulted in mostly decomposition products (Table 3, entries 3 and 4; Table 4, entry 1). Higher temperature was detrimental to the reaction and resulted in no product detection (Table 3, entry 6). Temperatures below –5 °C retarded the reaction progress to <5% conversion (Table 3, Entries 16 and 17). Dichloromethane was the best solvent for the reaction. THF at 0 °C (Table 3, Entry 9) or acetonitrile (Table 3, Entry 10) afforded an ~75:25 ratio of (−)-**1** to (+)-**1**. Other solvents/conditions, such as THF at room temperature (Table 3, entry 7), chloroform (Table 3, entry 16), and MTBE/DME (Table 3, entry 8) resulted in complex reaction mixtures. The best results thus far were obtained using 6.7 mol % catalyst and 3 equiv of ligand **10** to the catalyst at –5 to 0 °C in dichloromethane (Table 3, entry 14), which achieved a (–)-**1** to (+)-**1** ratio of 85:15. One reaction was allowed to proceed for 68 h at 0 °C until all solids were dissolved into solution (Table 3, entry 18) affording an 82:18 ratio of (–)-**1** to (+)-**1** and a 33% isolated yield of the bisfuran alcohol. As expected, the use of the (*R*)-pybox ligand afforded the opposite ratio of similar selectivity, with a ratio of 23:77 favoring (+)-**1** (Table 4, Entry 4).

Changing the catalyst to $Yb(OTf)_3$ and the (*R*)-pybox ligand afforded a racemic mixture possibly due to inefficient complex

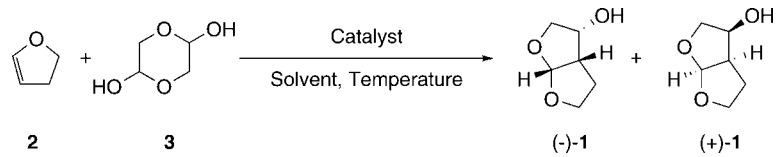
(23) (a) Kawamura, M.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40* (16), 3213–3216. (b) Quan, C.; Wang, L. *Tetrahedron: Asymmetry* **2000**, *11* (11), 2347–2357.

(24) (a) Hanamoto, T.; Furuno, H.; Sugimoto, Y.; Inanaga, J. *Synlett* **1997**, 79–80. (b) Hanamoto, T.; Furuno, H.; Sugimoto, Y.; Inanaga, J. *Org. Lett.* **2000**, *2* (1), 49–52.

(25) (a) Evans, D. A.; Scheidt, K. A.; Johnston, J. N.; Willis, M. C *J. Am. Chem. Soc.* **2001**, *123*, 4480–4491. (b) Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893–7894.

(26) (a) Evans, D. A.; Sweeney, Z. K.; Rovis, T.; Tedrow, J. S. *J. Am. Chem. Soc.* **2001**, *123*, 12095–12096. (b) Evans, D. A.; Masse, C. E.; Wu, J. *Organic Lett.* **2002**, *4*, 3375–3378.

Table 2. **Chiral lanthanide camphorate catalysts in bisfuran alcohol formation**[a]



2 **3** **(-)-1** **(+)-1**

entry	conditions	catalyst	solvent	conversion (%)	GC analysis[b] [(–)-1 to (+)-1]
1	50 °C, 5 h	Yb(hfc)$_3$ (+)	DHF	100	49:51
2	50 °C, 5 h	Yb(hfc)$_3$ (−)	DHF	100	50:50
3	50 °C, 5 h	Eu(hfc)$_3$ (+)	DHF	100	48:52
4	r.t., 20 h	Yb(fod)$_3$, *S*-binaphthol	MTBE	100	50:50
5	50 °C, 5 h	Yb(tfc)$_3$ (+)	DHF	100	52:48
6	50 °C, 5 h	Pr(tfc)$_3$ (+)	DHF	100	56:44
7	50 °C, 2.5 h	Yb[(R)-(−)-BNP]$_3$	DHF	100	60:40
8	30 °C, 12 h	Yb[(R)-(−)-BNP]$_3$	DHF	100	59:41
9	50 °C, 5 h	Yb[(R)-(−)-BNP]$_3$	DHF	100	65:35
10	r.t., 5 h	Cu[Pybox]	DHF	polymerized	DNA
11	50 °C, 5 h	Cu[Pybox]	DHF	polymerized	DNA
12	r.t., 5 h	Cu[Pybox]	DCM	<5	DNA
13	50 °C, 5 h	Cu[Pybox]	DCM	0	DNA
14	r.t., 20 h	Cu[Pybox]	DHF/DCM	0	DNA

[a] DHF = dihydrofuran, DCM = dichloromethane, MTBE = methyl-t-butylether, DNA = did not analyze. [b] GC analyses were performed by derivatizing bisfuran alcohol to the trifluoroacetate with trifluoroacetic anhydride in DCM.

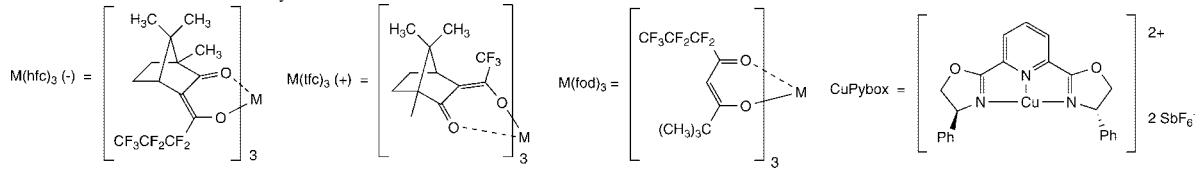
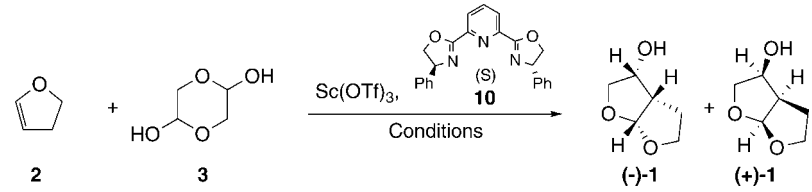


Table 3. **Use of scandium (III) catalyst and chiral ligand, 10, to directly access (–)-1**[a]



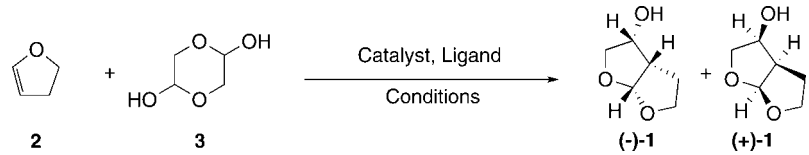
2 **3** **(-)-1** **(+)-1**

entry	**3**:catalyst ratio (mol %)	catalyst:ligand **10** ratio	temp (°C)	time (h)	solvent	conversion (%)	GC analysis[b] [(–) to (+)]
1	100:3.4	1:2.2	r.t.	(3)5	DCM	100	79:21
2	100:3.4	1:1.1	–10 to r.t.	(3)5	DCM	100	62:38
3	100:20.0	1:1.1	r.t.	(3)24	DCM	<10	NA
4	100:3.4	1:2.2	r.t.	(3)24	DCM	<10	NA
5	100:3.4	1:2.2	r.t.	(3)5	DCM	100	78:22
6	100:3.4	1:3	50	(3)5	DCM	<10	NA
7	100:3.4	1:3	r.t.	(3)5	THF	<10	NA
8	100:3.4	1:3	r.t.	(3)5	MTBE/DME	<10	NA
9	100:3.4	1:3	0	(3)5	THF	100	75:25
10	100:3.4	1:3	r.t.	(3)5	MeCN	100	74:26
11	100:6.7	1:3	r.t.	(3)5	DCM	100	82:18
12	100:10.0	1:6	r.t.	(3)5	DCM	100	82:18
13	100:6.7	1:3	r.t.	(3)5	TFT	<5	NA
14	100:6.7	1:3	0	(3)5	DCM	100	85:15
15	100:6.7	1:3	0	(3)6	$CHCl_3$	>10	NA
16	100:6.7	1:3	–78	(3)6	DCM	0	NA
17	100:6.7	1:3	–20	(3)6	DCM	<5	NA
18	100:6.7	1:3	0 to –5	(5)68	DCM	100	82:18

[a] TFT = trifluorotoluene, DME = dimethoxyethane, DCM = dichloromethane, MTBE = methyl-t-butylether, THF = tetrahydrofuran. [b] GC analyses were performed by derivatizing bisfuran alcohol to the trifluoroacetate with trifluoroacetic anhydride in DCM.

formation (Table 4, entry 3). Increasing the catalyst loading and using **11** afforded a slight preference for the (–)-enantiomer (Table 4, entry 9). Surprisingly, using alternative "pybox" ligands afforded no selectivity (Table 4, entry 5) or a very small

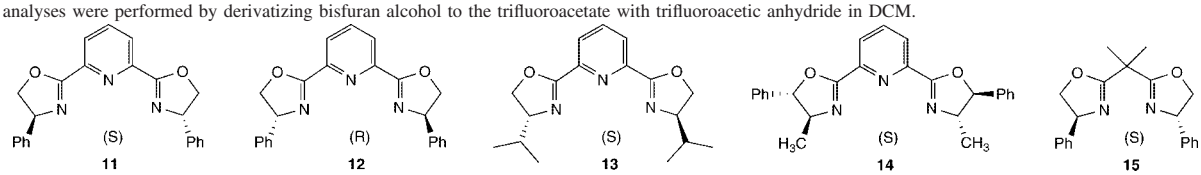
Table 4. **Direct synthesis of (–)-1 utilizing chiral ligands and catalysts**



2 **3** **(-)-1** **(+)-1**

entry	catalyst used	**3**:catalyst ratio (mol %)	ligand used	catalyst:ligand ratio	temp (°C)	time (h)	solvent	GC analysis[a] [(–) to (+)]
1	$Sc(OTf)_3$	100:3.4	**12**	1:2	r.t.	(3)24	DCM	complex mixture
2	$Sc(OTf)_3$	100:3.4	**12**	1:2	r.t.	(3)5	DCM	26:74
3	$Yb(OTf)_3$	100:3.4	**12**	1:2	r.t.	(3)3	DCM	50:50
4	$Sc(OTf)_3$	100:3.4	**12**	1:3.5	r.t.	(3)5	DCM	23:77
5	$Sc(OTf)_3$	100:3.4	**13**	1:2	r.t.	(3)5	DCM	51:49
6	$Sc(OTf)_3$	100:3.5	**14**	1:2	r.t.	(3)5	DCM	57:43
7	$Cu(OTf)_2$	100:4.8	**15**	1:1	r.t.	(0.5)3	DCM	52:48
8	$Cu(OTf)_2$	100:5.6	**15**	1:2.5	r.t.	(3)5	DCM	52:48
9	$Yb(OTf)_3$	100:6.7	**11**	1:3	r.t.	(3)5	DCM	61:39

[a] GC analyses were performed by derivatizing bisfuran alcohol to the trifluoroacetate with trifluoroacetic anhydride in DCM.



selectivity (Table 4, entry 6). Two attempts at using a bidentate ligand with $Cu(OTf)_3$ showed no observation of selectivity (Table 4, entries 7 and 8). In the cases involving the use of catalysts with chiral ligands as described in Tables 2, –4, 100 diastereoselectivity for the cis isomer was observed. Further screening of potential ligands or other catalytic complexes are on-going to improve the selectivity.

Pilot Plant Campaign. To aggressively and rapidly move forward the process development of GS-9005, a quick resolution for the asymmetric preparation of (−)-**1** had to be implemented. Because the preparation of (±)-**1** had been optimized and perceived to be scalable, access to (−)-**1** could come by way of enzymatic resolution rather than direct synthesis, which would require more development time and resources. Thus, racemic bisfuran alcohol (±)-**1** was resolved using immobilized lipase PS-C "amano" I enzyme in 1,2-dimethoxyethane (DME). Under optimized conditions, the ceramic bound lipase efficiently converted (+)-**1** to the acetate **16**, whereas the desired (–)-**1** remained as the alcohol. The enantiomeric resolution efficiency was affected by the enzyme quality and activity and varied from lot to lot, which necessitated optimization of the parameters for each lot of enzyme employed. In general, on laboratory scales, the resolution performed robustly and afforded (–)-**1** in 28–35% overall yield from **3** and an optical purity of >99% ee. The amount of enzyme used ranged from 20 to 37 U per mmol of **3** and usually required 6–16 h for completion of resolution, which was dictated by enantiomeric excess rather than percent conversion of the alcohol to the acetate. These enzymatic resolution reactions performed well in laboratory experiments, which employed magnetic stir bars or overhead stirring mechanisms. Typically, the enzyme has a good correlation of activity to selectivity. At slightly beyond 50% conversion, or nearly a 1:1 ratio of bisfuran acetate **16** to bisfuran alcohol **1** (determined by ^{1}H NMR), the enantiomeric excess showed >98% ee by GC analysis.

However, in the pilot plant, the enzymatic resolution performed in the reactors and in large glassware afforded poorly resolved material (~70% ee at 50% conversion). Although the use tests showed efficient resolution of the enantiomers, the poor enzyme performance on large scale was attributed to loose enzyme produced from agitator shearing of the bound enzyme. Experimentally, loose enzyme was observed to acetylate (±)-**1** slowly and without preference. Conversion to 50% acetylation was extremely slow but analysis of the "resolved" bisfuran alcohol revealed only racemic product. This indicated that the slow conversion observed was due to only the minute amount of unbound enzyme present in the DME. The loose enzyme embodied hyperactivity, which severely minimized or nullified enantioselectivity.

As part of the critical parameter investigation, water content was found to be an important factor on reaction progress and efficiency. As DME is highly hygroscopic, nonrigorous exclusion of atmospheric moisture may result in possible uptake of water and, in the presence of the enzyme, may promote hydrolysis of the acetate back to the alcohol. In one experiment, water spiked to a 1.3:1.0 mixture of **16** to (–)-**1** ((–)-**1** @ 98% ee) reversed the observed ratio to 1.0:1.2 (**16** to (–)-**1** and 64% ee) after 8 h. Further, spiking water in at the beginning of a typical reaction setup severely stalled to only a trace amount of conversion (1:10 of **16** to (–)-**1**) and afforded a mere 12% ee for (–)-**1**. Although the tolerable amount of water to effectively perform a successful resolution has not been determined, it was clear that in the presence of active enzyme, water presented detrimental effects in the reaction progress as well as resolution outcome. Maintaining anhydrous conditions for the enzymatic transformation was a critical parameter.

To overcome the inefficiencies and detrimental effects of a stirred reactor, we tested a loop reactor system (Scheme 7). The system began from the reactor to the lipase/sand-packed column input via a circulating pump and the column output return to

Scheme 7. **Column method setup for enantiomeric resolution of (±)-bisfuran alcohol**

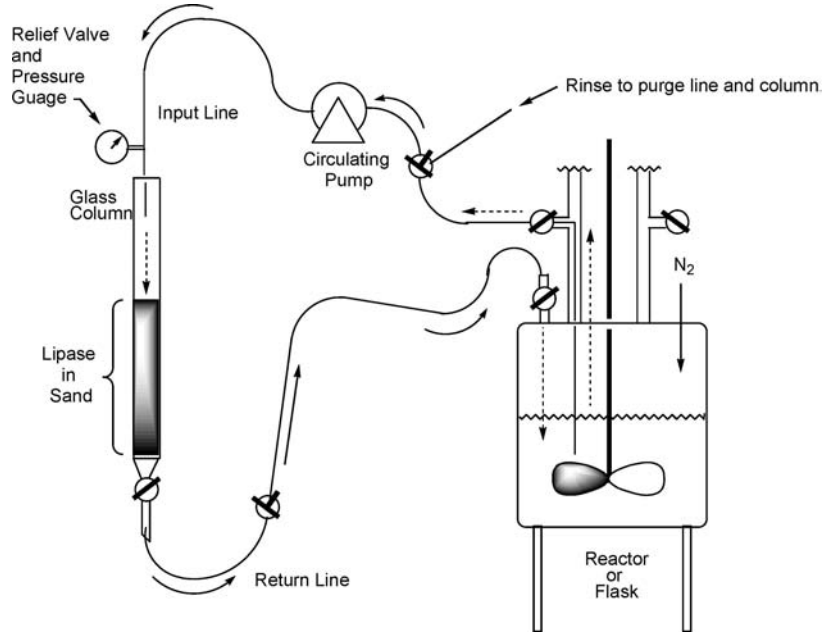
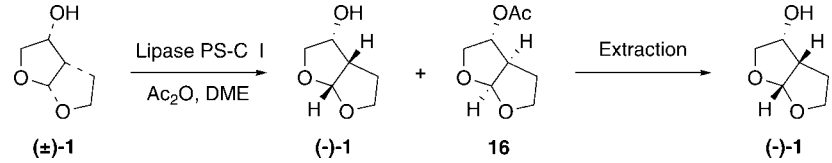


Table 5. **Use of column method for enantiomeric resolution of (±)-bisfuran alcohol**



entry	lipase activity (U/g)	amount of lipase (g)	flow rate (mL/min)	residence time (min)	total time (hrs)	conversion[a] (ROAc to ROH) (10:1)	optical purity (% ee)	yield (%)
1	1925	18.6	17	1.8	10.5	1.5:1.0	97.2	32
2	1925	22.7	164	0.52	19.0	NA	98.2	42
3	1925	275.6	2000	0.8	14.5	1.2:1.0	97.2	33

[a] Conversion determined by ^{1}H NMR analysis.

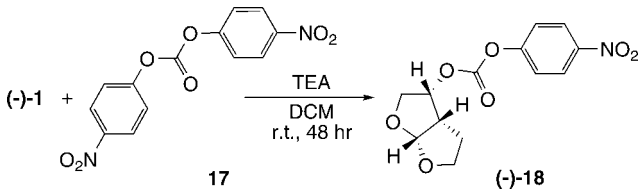
the reactor to complete the loop. An agitated solution of (±)-**1**, acetic anhydride, and DME in the reactor was paced through the lipase/sand column at an optimized rate. The resolution took place during the residence time when the portion of (±)-**1** in DME was in contact with the lipase/sand layer. The clear advantage of the loop system was the control of the exposure or residence time of the substrate to the enzyme and elimination of the shearing of the bound enzyme. Smaller, laboratory-scale tests of the loop reactor system were successful and the results were equivalent to the batch method. On scale up (Table 5), the residence time was optimized at 0.52 min and afforded 50% conversion and an isolated yield of (–)-**1** in 42% yield at 98.2% ee after 19.0 h. An increase in residence time to 1.8 min accelerated conversion (1.5:1 of **16** to (–)-**1** @ 10.5 h) but lowered selectivity, resulting in 97.2% ee and a 32% isolated yield of (–)-**1**. On a 4 kg pilot plant scale, the flow rate was limited by equipment configuration to 2 L/min, which translated to a residence time of 0.8 min. As expected, the conversion was less efficient than the optimized parameters required a total conversion time of 14.5 h to achieve a conversion of 1.2:1.0 **16** to (–)-**1** to acquire an optical purity of 97.2% ee. Because this material was to be used in a toxicology batch, the lower optical purity was quite acceptable. The isolated yield of the batch was 33%.

The use of the column and the loop reactor system improved the enzymatic resolution step compared to the use of stirred reactors, and the proof of concept was made.

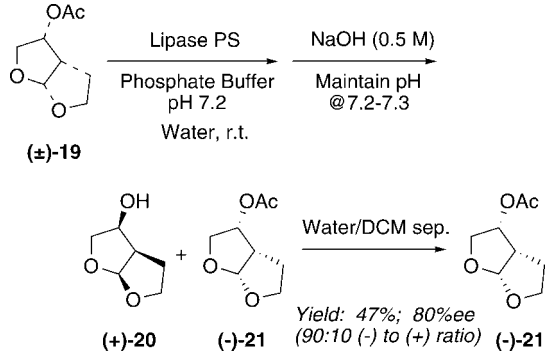
Isolation of the (–)-bisfuran alcohol again proved to be a challenge because of the high water solubility of both (–)-**1** and **16**. However, extractions between dichloroethane, ethyl acetate, chlorobenzene, xylenes or toluene and aqueous solutions were effective in removing a majority of **16** away from (–)-**1**. In all cases, the alcohol was retained in the water layer. Toluene exhibited a fair balance between efficiency in the removal of **16** while minimizing the loss of (–)-**1** from the aqueous layer. Additionally, toluene, being less dense than water, simplified the handling of the back extraction procedure.

Entirely separating **16** from (–)-**1** was not necessary. Because both compounds are liquids, (–)-**1** can be selectively converted to a carbonate solid. Thus, (–)-**1** was converted to the (*p*-nitrophenyl)carbonate **18** and, upon isolation, **16** was removed (Scheme 8). This method tolerated up to ~35% acetate in the mixture. Isolation of the (–)-**1** as the succinimidyl carbonate

Scheme 8. **Formation of bisfuran-(*p*-nitrophenyl)carbonate, 18**



Scheme 9. **Kinetic lipase-induced hydrolysis of bisfuran acetate**



has also shown to be effective. However, formation of the imidazole carboxylate was unsuccessful.

An alternative method of resolution by a kinetically controlled lipase-induced hydrolysis was attempted (Scheme 9).[27,28] (±)-**1** was quantitatively converted to the acetate **19** and treated with lipase PS in a phosphate buffer. Sodium hydroxide was added at a rate to maintain the pH at 7.2–7.3. Addition of the base required more than 6 days to complete, resulting in only an ~80% ee for the isolated (–)-bisfuran acetate, **21**. Although process optimization may improve the resolution results, further pursuit and investigation of this process was deferred.

Conclusions

We have described a direct and efficient pathway to the hexahydrofuro[2,3-*b*]furan-3-ol system by condensation of 2,3-dihydrofuran and glycolaldehyde dimer mediated by a series of lanthanide catalysts. Under the optimized mild conditions, the ytterbium catalyst, $Yb(fod)_3$, effectively promoted the formation of the cis-fused ring system. Utilizing enzymatic assistance, the optically pure (–)-bisfuran alcohol **1** was obtained. This method has been demonstrated on the multikiloscale in support of Gilead Sciences' protease inhibitor candidate GS-9005. Significant progress has been made in the direct asymmetric synthesis of the (–)-**1** by modifying the catalyst to scandium complexes containing chiral ligands. Varying the chiral ligand, this method has shown that both enantiomers of the bisfuran alcohol can be obtained. In general, this process has been demonstrated to be more efficient than the existing methods to construct the bisfuranyl system. Additionally, this method has the advantage in its simplicity, mild conditions, and the ability to directly access not only the racemic but also optically enriched hexahydrofuro[2,3-*b*]furan derivatives.

(27) Lord, M. D.; Negri, J. T.; Paquette, L. A. *J. Org. Chem.* **1995**, *60*, 191–195.
(28) Schwartz, A.; Madan, P.; Whitesell, J. K.; Lawrence, R. M. *Org. Synth.* **1990**, *69*, 1–9; Coll. Vol.: **1993**, *8*, 516.

Experimental Section

Immobilized lipase PS-C "amano" I (*Pseudomonas cepacia*) was purchased from Amano Enzyme U.S.A. Co., Ltd. 2,3-Dihydrofuran and glycolaldehyde dimer were purchased from Aldrich Chemicals, Inc. Gas chromatography analyses were performed on a Hewlett Packard 5890 GC with a flame ionization detector using a Chiraldex B-DM* column. Samples of **1** were derivatized by treatment with trifluoroacetic anhydride before injection. NaOCl (11–15% chloride) is commercially available from local pool supply vendors and was analyzed for chloride content before use. All reactions were performed under a dry nitrogen atmosphere. Proton nuclear magnetic resonance spectra were obtained on a Varian spectrometer (300 MHz). The ^1H NMR shifts are expressed in parts per million (δ).

Preparation of (3a*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-3-ol (1). To a reaction vessel, charge glycolaldehyde dimer (4.45 kg), $Yb(fod)_3$ catalyst (0.29 kg), and 2,3-dihydrofuran (20.5 kg). Agitate contents to mix and heat to 50 ° for ~5 h. Concentrate reaction content to a crude oil, dissolve in saturated aqueous $NaHCO_3$ solution (60 kg), and wash with dichloromethane (6 kg). Charge dichloromethane (58 kg), KBr (0.89 kg), and TEMPO (0.116 kg) to the aqueous layer and cool the mixture to 0 °C. Slowly add sodium hypochlorite (NaOCl, ~11% Cl, 55 kg) to this mixture. Upon completion of reaction, allow the organic and aqueous layers to separate. Wash the aqueous layer with dichloromethane (29 kg). Combine the organic layers and wash with water, 10% HCl with KI, and 10% sodium thiosulfate. Dry the organic layer over sodium sulfate, filter the solids, and cool the filtrate to below 0 °C. Add a freshly prepared solution of sodium borohydride (0.36 kg) in ethanol (7.1 kg) while maintaining the reaction content temperature below 0 °C. Upon completion of the reaction, add acetic acid (1.4 kg) and water (13.4 kg) to quench. Concentrate the mixture by vacuum distillation. To the resulting crude oil/semisolid mixture add ethyl acetate (31 kg). Dry organic layer over sodium sulfate, filter solids, and concentrate via vacuum distillation to isolate (±)-**1** as an oil.

Enzymatic Resolution. Charge ethylene glycol dimethyl ether (DME, 14.7 kg) and acetic anhydride (4.6 kg) to the crude product oil. Circulate this solution through a column packed with a mixture of lipase PS-C "amano I" (0.36 kg) and sand (6 kg). Upon completion of the enantiomeric resolution, concentrate the solution via vacuum distillation. Add water (18 kg) to dissolve the product and wash the solution with dichloromethane (28 kg). Concentrate the product containing aqueous layer via vacuum distillation. Dissolve the resulting oil in ethyl acetate (16 kg) and dry over sodium sulfate. Additional product can be isolated by back extracting the dichloromethane layer with water several times. Concentrate the combined water layers via vacuum distillation. Dissolve the resulting oil in ethyl acetate, dry over sodium sulfate, and filter solids. Concentrate the combined ethyl acetate layers via vacuum distillation to afford the product (3a*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-ol, (–)-**1**, as an oil (1.6 kg, 97 % ee, 33% yield) contaminated with a approximately 15 wt% of the corresponding acetate. Analytical data: ^1H NMR (DMSO-d6, 300 MHz) δ 5.52 (dd, 1 H),

4.25–4.15 (m, 1 H), 3.85–3.75 (m, 2 H), 3.7–3.6 (m, 1 H), 3.3 (t, 1 H), 2.75–2.65 (m, 1 H), 2.23–2.13 (m, 1 H), 1.75–1.6 (m, 1 H).

Preparation of (3a*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-*b*]furan-3-yl 4-Nitrophenyl Carbonate, (18). Charge to a reaction vessel with bis(4-nitrophenyl)carbonate (2.85 kg) and dichloromethane (33.4 kg). Add to this solution with (3a*R*,3a*S*,6a*R*)-hexahydrofuro[2,3-*b*]furan-3-ol, (–)-**1** (1.2 kg, 98.5% ee, contaminated with ~36% acetate) dissolved in dichloromethane (6.7 kg). Charge triethylamine (1.6 kg) and agitate the resulting reaction contents at 20–25 °C. Upon completion of reaction, wash the contents with water (16.8 kg). Separate the layers and concentrate the dichloromethane layer via vacuum distillation. Dissolve the product containing oil in ethyl acetate (21.2 kg) and sequentially wash with water, aqueous potassium carbonate solution, and brine. Dry the ethyl acetate layer over sodium sulfate, filter solids, and concentrate via vacuum distillation. Dissolve the concentrated product mixture in ethyl acetate (9.3 kg) and heat to 45 °C. Charge hexanes (6.7 kg) slowly and cool the final mixture slowly to 0 °C. Filter the resulting slurry to isolate **12**. Wash the solid cake with a solution of ethyl acetate and hexanes (1:1 v/v, 5.3 kg). Dry the product to constant weight, affording 1.5 kg of **12** (55%) as an off-white solid. Additional product may be obtained by concentrating the mother liquor via vacuum distillation and repeating the crystallization procedure. Analytical data: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.3 (d, 2 H), 7.4 (d, 2 H), 5.8 (d, 1 H) 5.3–5.2 (m, 1 H), 4.2–4.1 (m, 1 H), 4.1–3.9 (m, 3 H), 3.25–3.1 (m, 1 H), 2.3–2.1 (m, 1 H), 2.1–1.9 (m, 1 H); HPLC AN = 98.5%.

Acknowledgement

The authors gratefully thank Mr. Harlan Chapman, Mr. Kenneth Kent, Dr. Regan Shea, Dr. Duong Tran, Dr. Keiko Sujino, Dr. Jinyu Shen, and Dr. Zhongxin Zhou for their valuable discussions, technical contributions, and suggestions. We thank the Process Development staff members for support during the pilot plant campaign. Collaboration and cooperation from Theresa Lynch, Mark Sparacino, and colleagues from the analytical research development group are highly appreciated.

Received for review July 11, 2007.

OP700160A