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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 8567–8571

Preparation of enantiomerically pure 2-(1′-aminomethyl)furan derivatives and synthesis of an unnatural polyhydroxylated piperidine

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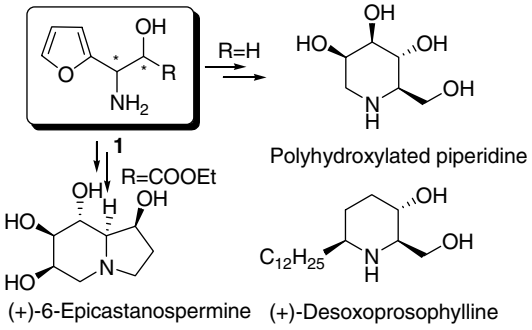
Received 15 August 2005; revised 28 September 2005; accepted 30 September 2005
Available online 14 October 2005

Abstract—Zinc-mediated propargylation of α-acylaminoaldehydes, and subsequent oxidative isomerization followed by Ag(I)-catalyzed cycloisomerization conveniently provides a new enantioselective route to the corresponding 2-aminoalkylfurans. One of these furans was successfully converted into an unnatural polyhydroxylated piperidine that efficiently incorporated structural features of the starting material. This represents a new entrance to biologically interesting polyhydroxylated piperidines having diverse substitutions.

Synthesis of furan derivatives has attracted tremendous interest over the past century, reflecting both the importance of these heterocycles in natural and synthetic substances and a requirement for more selective and versatile approaches for their syntheses.[1] Furthermore, optically active 2-(1′-amino-1′-substituent-methyl)furans serve as important synthetic building blocks for a variety of biologically important molecules. For example, 2-amino-2-(2-furyl)ethan-1-ol (**1**) is a critical intermediate for the synthesis of polyhydroxylated piperidines,[2] including (+)-desoxoprosophylline,[3] and (+)-6-epicastanospermine (Scheme 1).[4] Moreover, the furan moiety of 2-amino-2-(2-furyl)ethan-1-ol is also a more potent pharmacophore than the corresponding phenyl group in natural paclitaxel.[5]



Scheme 1. Several structures with 2-amino-2-(2-furyl)ethan-1-ol moiety.

Today, most synthetic approaches toward 2-(1′-amino-2′-hydroxyalkyl)furans (**1**, R = H) utilize materials containing functionalized furans. Among these, a variety of protocols to elaborate the side chains attached to the furan ring with the desired stereochemistry have been reported, including Sharpless asymmetric dihydroxylation[2,6] or aminohydroxylation[7] of vinylfuran; reduction of the carboxyl group from furyl glycine;[8] oxazaborolidine-catalyzed enantioselective reduction of oximes or oxime ethers,[9] and nucleophilic substitution of 2-furyl glycol leading to azides.[10] Vicinal amino alcohols are also very useful chiral building blocks for the syntheses of a variety of biologically active compounds,[11] and a number of synthetic methods have used these in the construction of chiral furans. For example, a one-pot reaction of aldehyde, amine, and furyl organoboronic acid directly furnished the corresponding chiral 2-amino-2-(2-furyl)ethan-1-ol derivatives.[12] Both *syn*- and *anti*-β-amino alcohols were achieved through catalytic diastereo- and enantioselective Mannich-type

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doi:10.1016/j.tetlet.2005.09.189

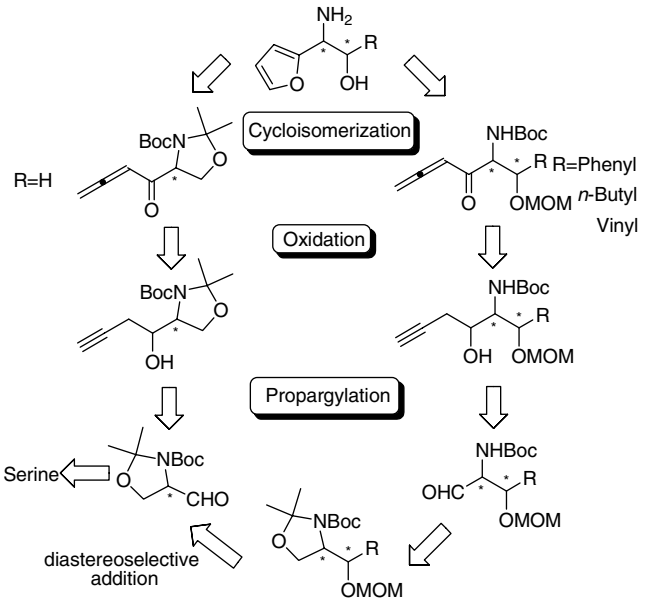


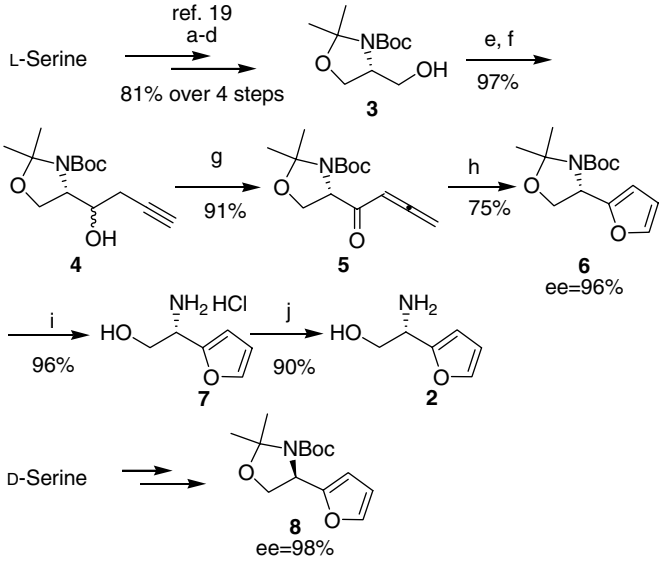
Figure 1. Retrosynthetic analysis of 2-amino-2-(furan-2′-yl)ethanols.

reactions.[13] Addition of racemic allylic stannanes to *N*-acyliminium precursors[14] or addition of the chlorotitanium enolate of methyl methoxyacetate to relatively unactivated aldimines[15] represent alternative approaches for these vicinal amino alcohols. Recently, interest in basic research and biomedical investigations has continued to mount in the area of new applications of natural and unnatural glycosidase inhibitors.[16] Many deoxy azasugars have been synthesized and shown to inhibit oligosaccharide processing enzymes selectively.[17] For these targets, including the polyhydroxylated piperidines and their derivatives, α-furfuryl amines are ideal starting materials.[4] In this report, we detail an efficient and enantioselective route for the synthesis of 2-amino-2-(furan-2′)-yl-ethanols using L- or D-serine as a common starting material. We include the application of these furan derivatives to the synthesis of diverse unnatural polyhydroxylated piperidines.

As illustrated in Figure 1, a pivotal transformation for furan formation is envisioned to be a cycloisomerization of α-allenylketones.[1,18] The requisite allenylketones can be synthesized by oxidation and subsequent in situ isomerization of the corresponding homopropargyl alcohols. Preparation of the homopropargyl alcohols can be carried out by propargylation of aldehyde precursor and/or diastereoselective addition of RMgBr (R = phenyl, *n*-butyl, vinyl) to Garner aldehyde.[19,20]

Our synthesis of (*S*)-2-amino-2-(furan-2′-yl)ethan-1-ol (**2**) started from commercially available L-serine, which gave the protected aminodiol **3** in high yield (Scheme 2). Swern oxidation gave the Garner aldehyde,[21] which was treated with propargyl bromide and zinc dust in DMF and Et_2O (1:1, v/v) to afford **4** in excellent yield. Dess–Martin oxidation of alcohol **4** and in situ isomerization furnished α-allenylketone **5** quantitively. Cycloisomerization of allenone **5** was achieved in the presence of catalytic $AgNO_3$ under an inert atmosphere to afford the furan derivative **6** (96% ee as measured by HPLC). Global deprotection of **6** with 3 N HCl in methanol followed by treatment with K_2CO_3 afforded (*S*)-2-amino-2-(furan-2′)yl-ethanol (**2**, $[\alpha]_D^{23}$ −10.9 (*c* 0.9, CH_3OH); Ref. 9: $[\alpha]_D^{20}$ −7.4 (*c* 0.8, CH_3OH)) in high yield after purification by silica gel flash column chromatography (ethyl acetate/hexane/methanol = 1:1:1).[9] This synthesis has the advantages of inexpensive materials, ease of operation, good overall yield, and high enantioselectivity.

As essential structural components of several biologically active compounds, β-amino alcohols have



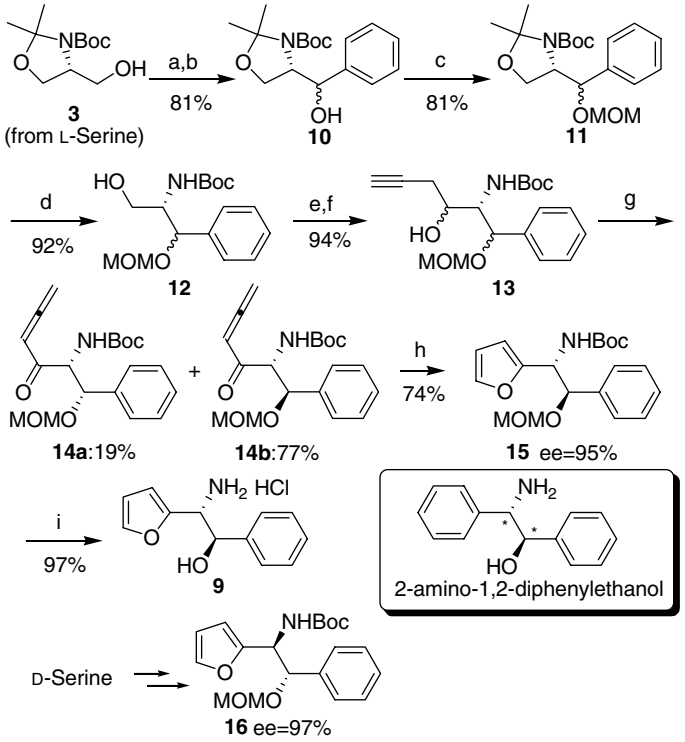
Scheme 2. Reagents and conditions: (a) HCl, MeOH, reflux; (b) Boc_2O, Et_3N, THF; (c) 2,2-DMOP, $BF_3{\cdot}Et_2O$, acetone; (d) LAH, anhydrous THF, −10 °C; (e) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C; (f) C_3H_3Br, Zn (dust), DMF/Et_2O (1:1, v/v); (g) Dess–Martin periodinane, CH_2Cl_2; (h) $AgNO_3$ (20 mol %), acetone, reflux; (i) 3 N HCl/CH_3OH; (j) K_2CO_3, CH_3OH. The ee values were determined by HPLC: Chiralpak OJ, eluent hexane/isopropanol 95:5, flow rate 0.7 mL/min.

attracted the attention of many synthetic chemists. Among recent literature,[11,22] 1,2-diphenyl-2-aminoethanols having both *syn*- and *anti*-configurations have shown great value because of their potential use in asymmetric synthesis as chiral auxiliaries or chiral ligands.[23] Utilizing the methodology outlined above, further development of general and efficient routes was desired to more diverse 1-aryl-2-amino-2-(furan-2-yl)ethanols, which would allow the asymmetric synthesis to exploit effects caused by the aromaticity of the furan moiety.

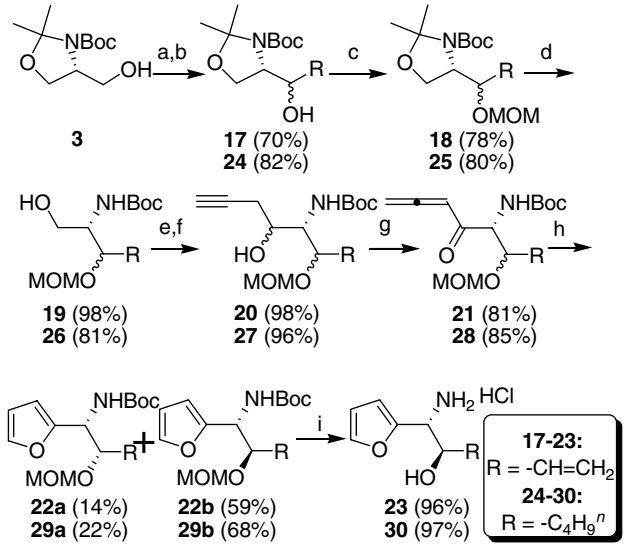
Accordingly, (1*R*,2*R*)-1-phenyl-2-amino-2-(furan-2-yl)-ethanol hydrochloride (**9**) was synthesized from Garner alcohol **3** (Scheme 3). Treatment of freshly prepared L-Garner aldehyde with phenylmagnesium bromide (3.0 equiv) in anhydrous THF at −70 to 0 °C gave **10** as a mixture of diastereoisomers.[24] The newly produced hydroxyl group was then protected as its MOM ether and the *N*,*O*-acetal was selectively deprotected with a catalytic amount of bismuth(III) bromide in acetonitrile.[25] Dess–Martin oxidation of the exposed primary alcohol **12** in CH_2Cl_2, followed by propargylation with zinc dust and propargyl bromide afforded homopropargyl alcohol **13**. Following Dess–Martin oxidation of the diastereomeric mixture **13**, *syn*-allenyl ketone **14a** and *anti*-allenyl ketone **14b** were easily separated by silica gel column chromatography in 19% and 77% yield, respectively. This indicated that the previous diastereoselective Grignard addition to the Garner aldehyde gave the *anti*-adduct predominantly (*anti*:*syn* = 77:19).[20,24] As before, cycloisomerization of the major product **14b** using $AgNO_3$ as a catalyst followed by global deprotection of the resulting furan **15** (95% ee, measured by HPLC) with 3 N HCl in methanol afforded (1*R*,2*R*)-1-phenyl-2-amino-2-(furan-2′)-yl-ethanol **9** in excellent overall yield.

Similarly, two additional 2-aminoethanol derivatives, (1*R*,2*R*)-1-amino-1-(furan-2-yl)but-3-en-2-ol (**23**) and (1*R*,2*R*)-1-amino-1-(furan-2-yl)hexan-2-ol (**30**) were synthesized from alcohol **3**. The separation of diastereomers (**22a**/**22b** and **29a**/**29b**) was achieved by column chromatography following furan formation (ratio of **17**: *anti*:*syn* = 59:14; ratio of **24**: *anti*:*syn* = 68:22, respectively[26,27]) (Scheme 4). In theory, any 1-substituted-2-amino-2-(2′-furan)-yl-ethan-1-ol could be prepared by this general route.

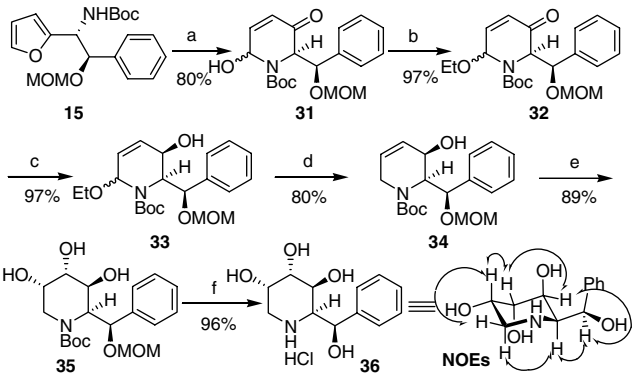
With the furan derivative **15** in hand, construction of unnatural piperidines was investigated next (Scheme 5). Oxidation of **15** using *m*-CPBA gave the dihydropyridone **31**, whose hemi-aminal hydroxyl group was immediately masked as an ethoxyl group using triethyl orthoformate and $BF_3{\cdot}OEt_2$. Ketone **32** was then reduced stereoselectively by $NaBH_4$ in the presence of $CeCl_3{\cdot}7H_2O$[4,28] to give **33** as the sole product, whose absolute configuration was confirmed by NOESY studies on the final target **36**. Reductive removal of ethoxyl group of **33** by $NaBH_4$ in formic acid provided compound **34**. Substrate-controlled dihydroxylation[29] of **34** with a catalytic amount of OsO_4 and NMO furnished triol **35** as a single diastereomer. Global deprotection of **35** using 3 N HCl/MeOH afforded the enantiopure



Scheme 3. Reagents and conditions: (a) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C; (b) PhMgBr, THF, −70 to 0 °C; (c) MOMCl, DIPEA, CH_2Cl_2; (d) $BiBr_3$ (20 mol %), CH_3CN; (e) Dess–Martin periodinane, CH_2Cl_2; (f) C_3H_3Br, Zn (dust), DMF/Et_2O (1:1, v/v); (g) Dess–Martin periodinane, CH_2Cl_2; (h) $AgNO_3$ (20 mol %), acetone, reflux; (i) 3 N HCl/CH_3OH. The ee values were determined by HPLC: Chiralpak AD, eluent hexane/isopropanol 90:10, flow rate 0.7 mL/min.



Scheme 4. Reagents and conditions: (a) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C; (b) vinylMgBr (for compound **17**) or *n*-butylMgBr (for compound **24**), THF, −70 to 0 °C; (c) MOMCl, DIPEA, CH_2Cl_2; (d) $BiBr_3$ (20 mol %), CH_3CN; (e) Dess–Martin periodinane, CH_2Cl_2; (f) C_3H_3Br, Zn (dust), DMF/Et_2O (1:1, v/v); (g) Dess–Martin periodinane, CH_2Cl_2; (h) $AgNO_3$ (20 mol %), acetone, reflux; (i) 3 N HCl/CH_3OH.



Scheme 5. Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2; (b) $HC(OEt)_3$, $BF_3{\cdot}Et_2O$, 4 Å MS, THF, 0 °C; (c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −78 °C; (d) $NaBH_4$, HCO_2H, 0 °C; (e) OsO_4(cat.), NMO, acetone/H_2O 9:1 (v/v), rt; (f) 3 N HCl/CH_3OH.

3,4,5-trihydroxypiperidine derivative **36**, which is structurally similar to 1-deoxygalactonojirimycin (a strong inhibitor of α-glycosidase A in preclinical trials as potential therapy for Farby's Disease[16b]) and deoxygulonojirimycin (DGJ, fucosidase inhibitor[29a]). The absolute configuration of piperidine **36** was unambiguously confirmed by NOESY experiments.[30]

In conclusion, disclosed herein is a new and effective access to the enantiomerically pure 2-amino-2-(furan-2-yl)ethan-1-ols and derivatives using L- or D-serine as common starting materials. Zinc-mediated propargylation of aldehydes, oxidative isomerization of homopropargyl alcohols, and Ag(I)-catalyzed cycloisomerization of α-allenylketones served as key steps. Advantages of this approach include inexpensive materials and reagents, ease of operation, excellent overall yields, and excellent enantio purity of products. These optically pure furyl aminoethanols may potentially serve as chiral ligand or chiral auxiliary in asymmetric synthesis, and as intermediates for the syntheses of diverse unnatural polyhydroxylated alkaloids.

Acknowledgments

This work was financially supported in part by the Major State Basic Research and Development Program (G2000077500), NSFC (20425205 and 20321202), the Chinese Academy of Sciences (KGCX2-SW-209) and Shanghai Municipal Commission of Science and Technology (03DZ19203 and 04DZ14901).

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30. Data for the key target compounds: **23**: $[\alpha]_D^{19}$ 21.3 (*c* 1.5, CH_3OH). IR (KBr): 3327, 2945, 2836, 1606, 1505, 1152, 1023 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ 4.40–4.41 (m, 1H), 4.46–4.49 (m, 1H), 5.16 (d, $J = 10.2$ Hz, 1H), 5.33 (d, $J = 17.1$ Hz, 1H), 5.63–5.74 (m, 1H), 6.36–6.37 (m, 1H), 6.48–6.49 (m, 1H), 7.47 (s, 1H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ 54.5, 73.0, 111.8, 112.1, 119.3, 136.8, 144.9, 148.6 ppm. ESIMS (*m*/*z*, %): 137.2 ($M-NH_2^+$, 75%), 154.2 ($M+H^+$, 100%). HRMS (MALDI) calcd for $C_8H_{11}NO_2Na$ ($M+Na^+$): 176.0687; Found: 176.0683. **30**: $[\alpha]_D^{19}$ −4.5 (*c* 1.4, CH_3OH). IR (KBr): 3339, 2957, 2932, 2873, 2622, 1604, 1519, 1496, 1158, 1012 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ 0.89 (t, $J = 6.6$ Hz, 3H), 1.29–1.46 (m, 6H), 3.96–3.98 (m, 1H), 4.45 (br s, 1H), 6.48 (s, 1H), 6.59 (d, $J = 2.7$ Hz, 1H), 7.58 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.5, 23.8, 29.1, 34.3, 54.7, 71.8, 111.8, 112.1, 144.9, 148.9 ppm. ESIMS (*m*/*z*, %): 167.3 ($M-NH_2^+$, 100%), 184.2 ($M+H^+$, 40%). HRMS (ESI) calcd for $C_{10}H_{18}NO_2$ ($M+H^+$): 184.1338; Found: 184.1328. **36**: $[\alpha]_D^{27}$ −22.7 (*c* 0.7, CH_3OH). IR (KBr): 3384, 2950, 2839, 1638, 1456, 1205, 1021, 703 cm^{-1}. ^1H NMR (500 MHz, CD_3OD): δ 3.06 (br s, 1H), 3.09 (br s, 1H), 3.55 (dd, $J = 6.3$, 1.5 Hz, 1H), 3.87 (dd, $J = 4.2$, 3.0 Hz, 1H), 4.06–4.07 (m, 1H), 4.16–4.23 (m, 1H), 5.06 (d, $J = 6.3$ Hz, 1H), 7.34–7.52 (m, 5H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 45.1, 59.0, 63.9, 68.8, 70.4, 73.2, 127.8, 130.0 (2C), 130.3 (2C), 141.3 ppm. ESIMS (*m*/*z*, %): 240.1 ($M+Na^+$, 100%). HRMS (MALDI) calcd for $C_{12}H_{18}NO_4$ ($M+H^+$): 240.1236; Found: 240.1231.