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New Methodology for the Stereoselective Synthesis of α-Furfurylamines from Sugars: Application to the Synthesis of Furyl Amino Acids and 3-Furylisoserines

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The synthesis of two new furyl amino acids as rigid isosteres of the dipeptides (D)-H-Ser-(D,L)-Thr-OH and (L)-H-Ser-(D,L)-Thr-OH is presented. The developed synthetic methodology starts from D-xylose and D-arabinose and makes use of trihydroxypropylfurans as intermediates. The key step of the strategy is the introduction of an amino function at the α-position of the adequate trihydroxypropylfuran derivative. This methodology was also applied to the synthesis of two new (2*R*,3*R*)-3-furylisoserines as analogues of the C-13 Taxol/Taxotere side chain.

Introduction

The area of peptidomimetics is of interest in the field of molecular diversity and drug discovery. The rational design of drugs based on peptides requires improving their stability against enzymatic hydrolysis by proteases and controlling the flexibility of the peptide chain towards the active conformation of a given receptor.[1] In this regard, the use of unnatural amino acids is of special interest for the generation of different molecular entities able to interact with biological targets, thus providing useful information about the corresponding biologically active protein conformation in structure–activity relationship studies. As an example, δ-amino acids that have structural analogy with dipeptides have been constructed to mimic dipeptide sequences with added structural constraints.[2] In recent years, unnatural amino acids incorporating heterocyclic moieties derived from thiazole, oxazole, imidazole, and furan have been assembled into peptidomimetics for the purpose of drug discovery.[3] These heterocyclic amino acids are also of importance, as they are part of biologically active products, both natural and synthetic.[4] Recently, they have also been used in macrocyclic peptides to create conformationally preorganized scaffolds.[5]

Among heterocyclic amino acids, furyl amino acids are of particular interest because they can also be considered as α-furfurylamines,[6] which are versatile intermediates for the synthesis of azasugar derivatives such as piperidine alkaloids, indolizidines, and quinolizidines through the aza-Achmatowicz rearrangement[6,7] (Figure 1). Other types of α-furfurylamines are the 3-furylisoserines. These compounds have gained a lot of interest since the discovery of Milataxel (**1**),[8] a taxane of a new generation that has a 3-furylisoserine moiety in the C-13 side chain of the baccatin skeleton. This taxane has shown better pharmacological properties than those of known antitumor agents such as Taxol (**2**, paclitaxel) and Taxotere (**3**, docetaxel) that incorporate 3-phenylisoserines as C-13 side chains.[8b] This fact makes the synthesis of (2*R*,3*R*)-furylisoserine derivatives an interesting goal to be achieved.

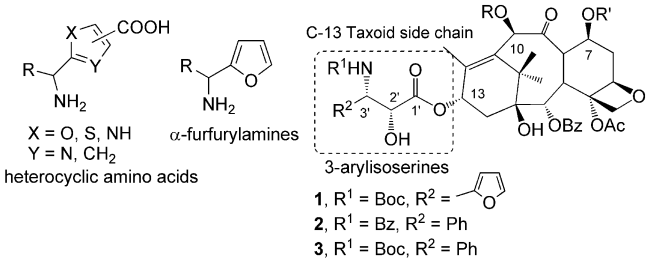

Figure 1. General structures for heterocyclic-based amino acids, α-furfurylamines, and 3-arylisoserines.

The synthesis of thiazole-, oxazole-, and imidazole-based amino acids is usually carried out through aromatization of the corresponding peptide derivative under different conditions (Scheme 1).[5] However, the syntheses of furyl-based amino acids are scarce.[9]

As part of our continuing interest in the synthesis and biological applications of chiral furan amino acids,[3c,10] we present a new strategy for the synthesis of constrained furyl amino acids **4** and *ent*-**4** starting from D-sugars (Scheme 2). The key step of the strategy is based on the stereoselective

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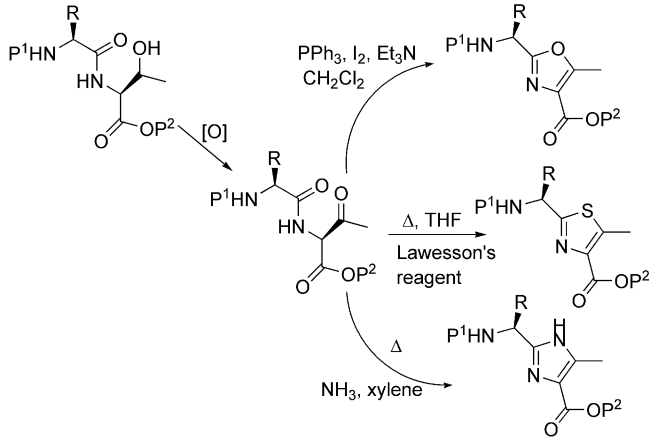
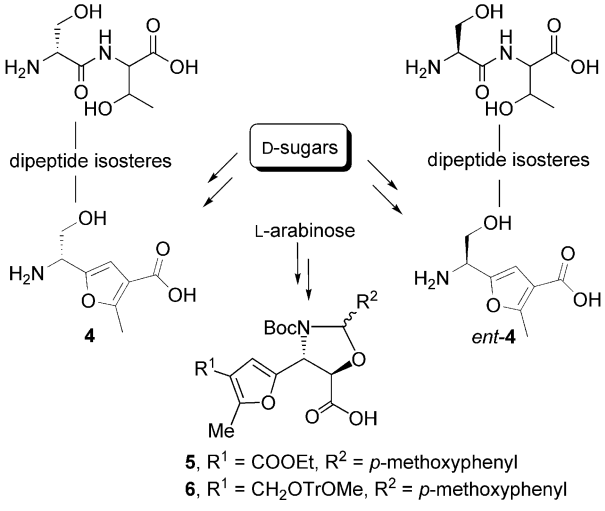


Scheme 1. General strategy for the synthesis of thiazole-, oxazole-, and imidazole-based amino acids.

introduction of an amino function at the α-position of a polyhydroxyalkylfuran moiety. These compounds can be envisaged as rigid isosteres of dipeptides (D)-H-Ser-(D,L)-Thr-OH and (L)-H-Ser-(D,L)-Thr-OH. These dipeptides are involved in the highly conserved peptide sequence of several serine/threonine protein kinases[11] found in many human malignancies and so have potential for the development of inhibitors. We also present the synthesis of new N,O-protected (2*R*,3*R*)-3-furylisoserines **5** and **6** by applying a similar methodology. These compounds are ready for the coupling to the baccatin skeleton for the preparation of new heteroaromatic taxoids, according to established methodologies.[12] New compounds **5** and **6** bear COOEt/CH_2O-TrOMe groups that will allow further derivatization.



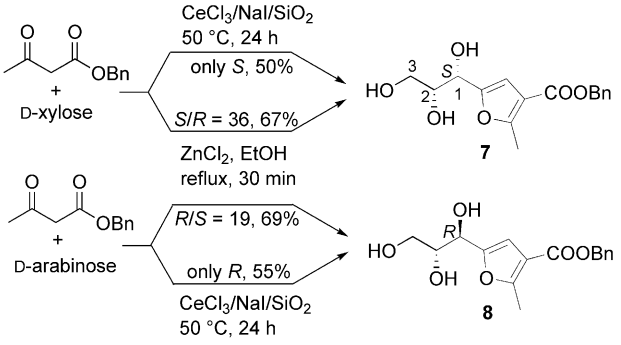
Scheme 2. Structure of the new furyl amino acids and furylisoserines.

Some of the results of this work have already been communicated in a preliminary form.[10c] We report herein details of the extended study.

Results and Discussion

Stereoselective Synthesis of Furyl Amino Acids from D-Sugars

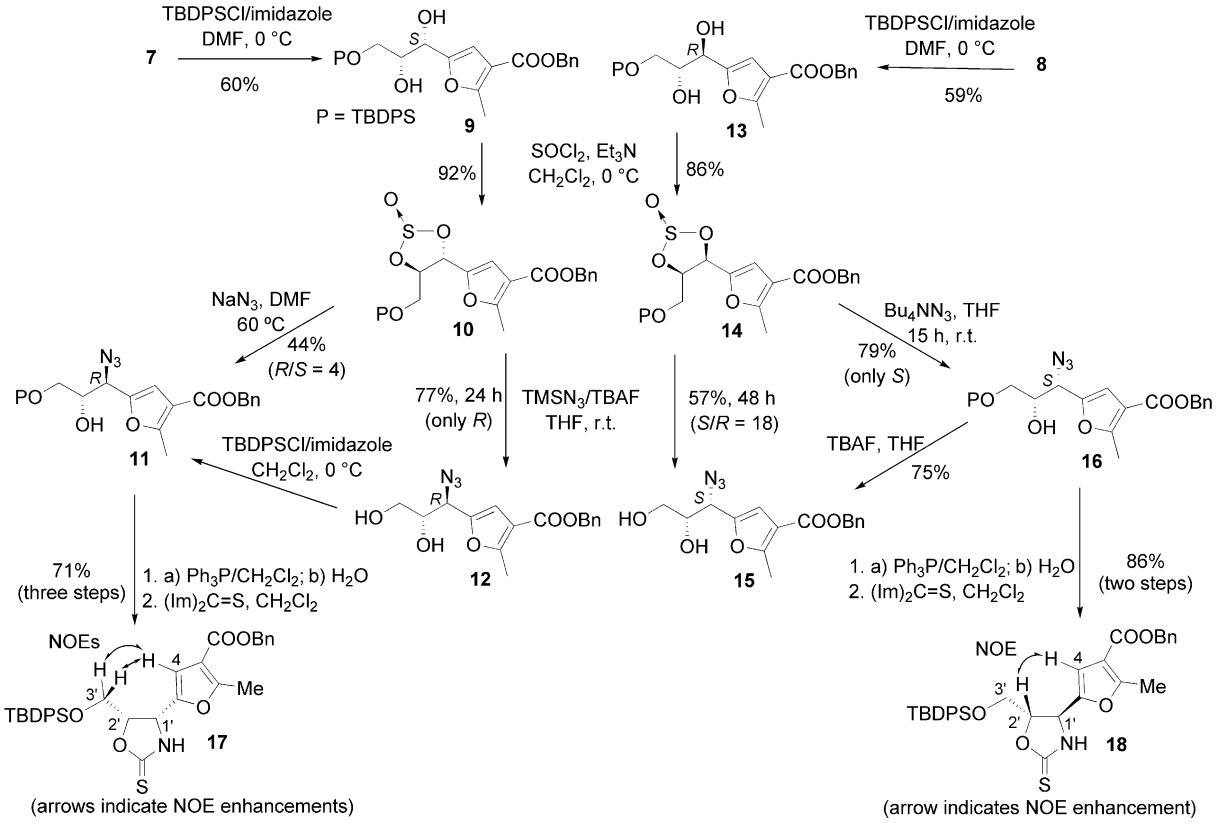
Recently, it has been described that condensation between hexoses and ethyl acetoacetate catalyzed by $CeCl_3$/NaI/SiO_2 under solvent-free conditions at 50 °C affords tetrahydroxybutylfurans in good yields.[13] This method is an efficient alternative to the classical García–González reaction, where this condensation is catalyzed by $ZnCl_2$ in EtOH as solvent.[14] We have successfully applied this methodology to the condensation of pentoses, D-xylose, and D-arabinose with benzyl acetoacetate for the synthesis of trihydroxypropylfurans **7** and **8** (Scheme 3). These compounds were obtained in moderate-to-good yields without epimerization at C-1 of the polyolic chain. A slight epimerization was observed when the experiment was carried out with the use of $ZnCl_2$ as catalyst.



Scheme 3. Synthesis of trihydroxypropylfuran intermediates.

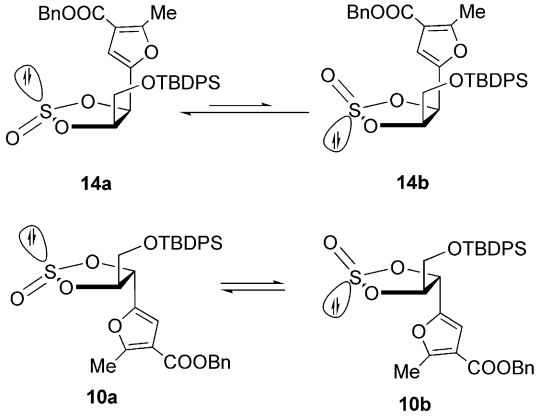
Protection of the primary alcohol in compound **7** afforded silyl derivative **9**. In order to introduce an azide function at C-1 of the polyolic chain, we carried out the reaction of **9** with thionyl chloride and triethylamine to obtain the corresponding cyclic sulfite **10** in 92% yield (Scheme 4). This compound was stable and could be purified by column chromatography and isolated as a diastereoisomeric mixture (1:1, epimers at sulfur). Although nucleophilic displacements are commonly performed on key sulfate intermediates,[15] the activated pseudo-benzylic position C-1 in sulfite **10** is thought to be reactive enough for nucleophilic ring opening. Treatment of sulfite **10** with NaN_3/DMF at 60 °C gave a mixture of azido derivatives **11**, epimers at C-1 (*anti*/*syn* = 4), indicating that S_N2 and S_N1-like mechanisms participated in the displacement. With the hope to avoid this epimerization, we decided to use the mixture $TMSN_3$/TBAF in THF as a source of azide anion with increased nucleophilicity. Thus, reaction under these conditions and at room temperature gave diastereomerically pure azido derivative **12** in 77% yield with concomitant removal of the protecting group.

The synthesis of diastereoisomeric azido derivative **15** was tried in a similar way but starting from trihydroxypropylfuran **8** (Scheme 4). Regioselective protection of **8**, followed by sulfite formation afforded compound **14**, which could be purified by column chromatography; it was iso-



Scheme 4.

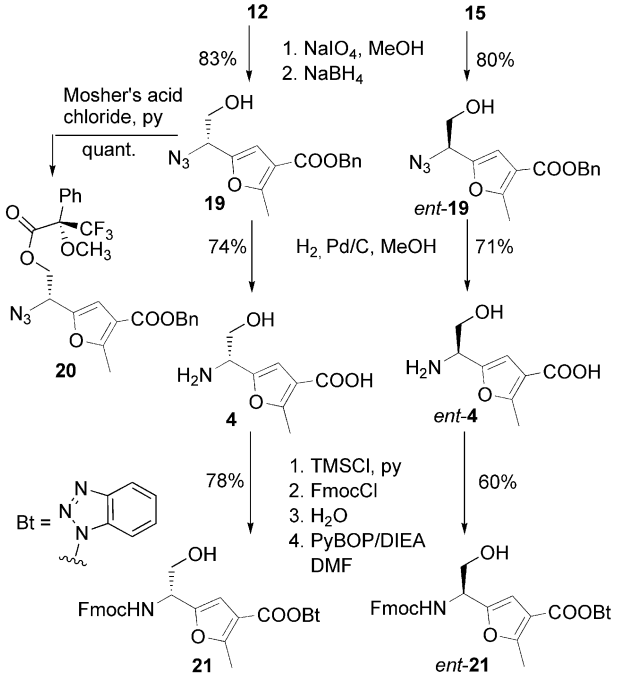
lated as a diastereoisomeric mixture (1:1, sulfur epimers) in 51% yield (two steps). ^{1}H NMR experiments showed that the initial ratio of sulfite epimers in **14** changed to a 10:1 ratio after 5 d in a $CDCl_3$ solution (Scheme 5). This epimerization was not observed in the diastereoisomeric mixture of cyclic sulfites **10** under a similar experiment. This indicates that the initial epimer ratio (*syn*/*anti* = **14a**/**14b** = 1) in sulfites **14** obtained under kinetic control changes as a result of the sulfur epimerization to give *anti* isomer **14b**, which is thermodynamically more stable. In the case of cyclic sulfites **10**, both stereoisomers, **10a** and **10b**, should have similar thermodynamic stability, explaining that no epimerization is observed in this case. Reaction of cyclic sulfites **14** with $TMSN_3$/TBAF in THF at room temperature afforded azido derivative **15** after 48 h (57%, Scheme 4). The displacement–deprotection step for compound **14** proved to be slower than for its isomer **10**. Besides, partial epimerization was detected (*syn*/*anti* = 18, measured by ^{1}H NMR spectroscopic analysis of the crude mixture), which is presumably due to the participation of an S_N1-like mechanism. Alternatively, treatment of **14** with an excess amount (3 equiv.) of tetrabutylammonium azide in THF afforded **16** in a shorter reaction and without epimerization at C-1′. Further treatment of **16** with TBAF/THF afforded **15** in 56% overall yield. To confirm the configuration of C-1′ in azido derivatives **12** and **15**, corresponding precursors **11** and **16** were transformed into their oxazolidine-2-thione derivatives **17** and **18**, respectively. These rigid structures showed unequivocal NOEs that confirmed the proposed structures (Scheme 4).



Scheme 5.

Oxidative cleavage of diol **12** followed by reduction of the resulting aldehyde afforded alcohol **19** in 83% yield. Mosher's ester of alcohol **19** confirmed that no epimerization at C-1′ occurred in the oxidative cleavage–reduction steps (Scheme 6). Hydrogenation of **19** with the use of Pd/C (10%) as catalyst afforded furyl amino acid **4** in good yield. Compound **15** was transformed into furyl amino acid *ent*-**4** by following the same way. Amino acid **4** and its enantiomer *ent*-**4** were transformed into activated protected amino acid derivatives **21** and *ent*-**21**, as suitable building blocks for their incorporation into peptides following both solid- and solution-phase peptide syntheses. Therefore, **4** and *ent*-**4** were *N*-protected following the procedure of

Koole.[16] The resulting Fmoc-amino acids were directly treated with PyBOP/DIPEA [(benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate/*N*,*N*-diisopropylethylamine] to afford the corresponding activated Fmoc-amino acids **21** and *ent*-**21** that could be isolated and purified by column chromatography.

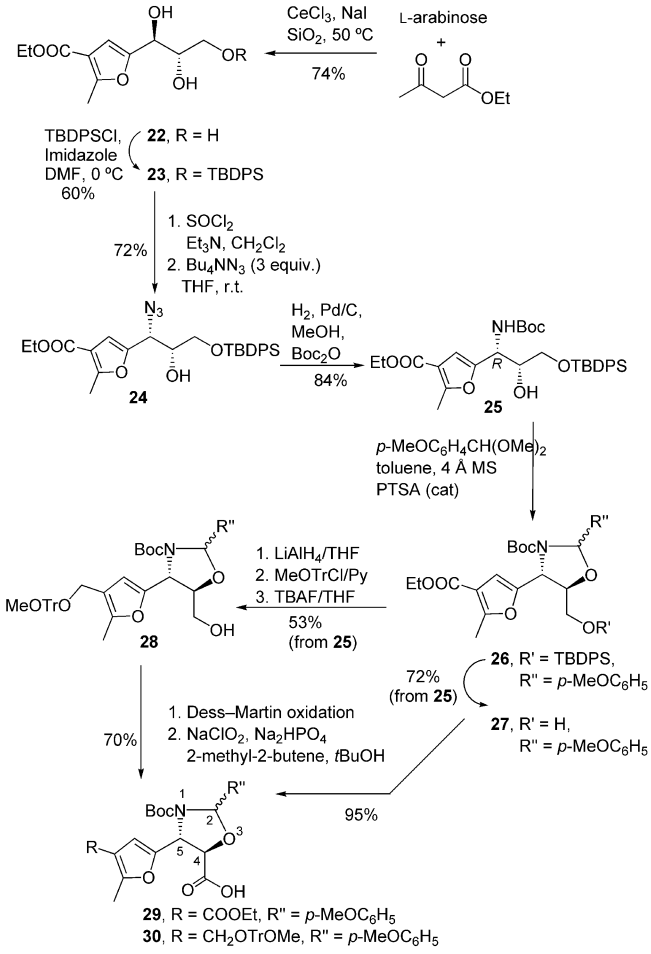


Scheme 6.

The special stability of these benzotriazole-activated esters is due to the aromatic character of the furan-3-carboxylic acid moiety. This particular property makes these compounds attractive building blocks for peptide synthesis, especially in the solid phase where a high excess of activated amino acid is used for each coupling and the use of recovered amino acid needs further reactivation in situ.

Synthesis of (2*R*,3*R*)-3-Furylisoserines

The synthetic pathway for the preparation of new 3-furylisoserine derivatives involves the use of azido derivative **24** as the key intermediate. This compound was prepared in diastereoisomerically pure form[17] following the same methodology described for the synthesis of **16** but starting from L-arabinose and ethyl acetoacetate (Scheme 7).[18] Hydrogenation of compound **24** in the presence of Boc_2O afforded **25** in 84% yield. Cyclic N,O-acetalization of **25** with *p*-anisaldehyde dimethylacetal gave the corresponding 1,3-oxazolidine **27** as a mixture of diastereoisomers[19] in 72% yield, after standard removal of the silyl protecting group. Alternatively, reduction of the ethoxycarbonyl group in oxazolidine **26** with $LiAlH_4$ in THF at 0 °C followed by protection of the resulting alcohol with *p*-methoxytrityl chloride and desilylation under standard conditions gave alcohol **28** in 53% overall yield as a mixture of diastereoisomers. Oxidation of the free hydroxymethyl group on **27** and **28** was carried out by using Dess–Martin reagent followed by treatment of the resulting aldehyde with $NaClO_2$ and 2-methyl-2-butene in a buffered medium to afford **29** and **30** in moderate-to-good yields. Compounds **29** and **30** are ready to be coupled to baccatin under standard methods.[12]



Scheme 7.

Conclusions

The synthesis of two new chiral furyl amino acids was carried out by a stereoselective route starting from D-aldopentoses. These compounds are dipeptide isosteres and useful building blocks for the construction of peptidomimetics. They were transformed into stable activated Fmoc derivatives ready for peptide synthesis. Additionally, L-arabinose was effectively transformed into two different N,O-protected 3-furylisoserines, which are useful building blocks for coupling to baccatin. To the best of our knowledge, this is the first synthesis of 3-heteroarylisoserines that uses a sugar as starting material. The new compounds incorporate a substituent on the furan ring, which can improve the solubility of the targeted final taxoid and adds a new element of structural diversity to the previously described 3-furylisoserines.

Experimental Section

General Remarks: Optical rotations were measured in a 1.0-cm or 1.0-dm tube with a Perkin–Elmer 241MC spectropolarimeter. ^1H and ^{13}C NMR spectra were obtained for solutions in $CDCl_3$ and CD_3OD. All the assignments were confirmed by 2D NMR experiments. The NMR spectra for all compounds were performed in CITIUS (Research general service for the University of Seville). The FAB mass spectra were obtained by using glycerol or 3-nitrobenzyl alcohol as the matrix. TLC was performed on silica gel HF254 (Merck); detection was achieved by UV light and charring with H_2SO_4 or with Pancaldi reagent [$(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O]. Silica gel 60 (Merck, 230 mesh) was used for preparative chromatography.

Benzyl 2-Methyl-5-(D-*threo*-1,2,3-trihydroxyprop-1-yl)furan-3-carboxylate (7): Silica gel (2 g) was added to a mixture of $CeCl_3·7H_2O$ (0.452 g, 1.2 mmol) and NaI (56 mg, 1.2 mmol) in acetonitrile (28 mL), and the mixture was stirred overnight. Then, D-xylose (720 mg, 4 mmol) was added to the mixture, and the suspension was stirred for 1 h. The solvent was evaporated, benzyl acetoacetate (0.9 mL, 5.2 mmol) was added to the mixture, and the free solvent mixture was stirred for 24 h at 50 °C. After this period, MeOH was added to the mixture, the resulting suspension was filtered through Celite, and the solid residue was washed several times with MeOH. The filtered solution was evaporated to dryness, and the resulting crude was purified by column chromatography (CH_2Cl_2/MeOH, 12:1) to afford **7** (0.62 g, 50%) as a colorless oil. $[\alpha]_D^{22} = -11$ (c = 0.85, MeOH). IR: $\tilde{\nu}$ = 3430 (OH), 1697 (CO), 1429, 1227, 1090, 777 cm^{-1}. ^1H NMR (300 MHz, CD_3OD, 25 °C): δ = 2.53 (s, 3 H, CH_3), 3.46 (dd, $J_{3'b,2'}$ = 6.2 Hz, 1 H, 3′b-H), 3.59 (dd, $J_{3'a,3'b}$ = 11.3 Hz, $J_{3'a,2'}$ = 4.8 Hz, 1 H, 3′a-H), 3.84 (m, 1 H, 2′-H), 4.60 (d, $J_{1',2'}$ = 5.3 Hz, 1 H, 1′-H), 5.26 (s, 2 H, CH_2Ph), 6.59 (s, 1 H, 4-H), 7.40–7.31 (m, 5 H, Ar-H) ppm. ^{13}C NMR (7.4 MHz, CD_3OD, 25 °C): δ = 165.3 (*C*OOBn), 160.2 (C-2), 154.7 (C-5), 137.7, 129.6, 129.2, 129.1 (6 C, C-aromat.), 114.9 (C-3), 108.9 (C-4), 74.7 (C-2′), 68.6 (C-1′), 67.0 (*C*H_2Ph), 63.9 (C-3′), 13.8 (CH_3) ppm. MS (CI): m/z (%) = 306.1116 $[M]^+$, 288 (10) $[M - H_2O]^+$.

Benzyl 2-Methyl-5-(D-*erythro*-1,2,3-trihydroxyprop-1-yl)furan-3-carboxylate (8): This compound was prepared in a manner similar to that described for **7** except that D-arabinose was used as the starting material. Yield: 55%, colorless oil. $[\alpha]_D^{22} = +5$ (c = 1.0, MeOH). IR: $\tilde{\nu}$ = 3421 (OH), 1713 (CO), 1427, 1227, 1085, 698 cm^{-1}. ^1H NMR (300 MHz, CD_3OD, 25 °C): δ = 2.55 (s, 3 H, CH_3), 3.64 (dd, $J_{3'b,2'}$ = 6.1 Hz, 1 H, 3′b-H), 3.74 (dd, $J_{3'a,3'b}$ = 11.4 Hz, $J_{3'a,2'}$ = 3.6 Hz, 1 H, 3′a-H), 3.85 (m, 1 H, 2′-H), 4.53 (d, $J_{1',2'}$ = 7.3 Hz, 1 H, 1′-H), 5.26 (s, 2 H, CH_2Ph), 6.58 (s, 1 H, 4-H), 7.40–7.31 (m, 5 H, Ar-H) ppm. ^{13}C NMR (7.4 MHz, CD_3OD, 25 °C): δ = 165.4 (*C*OOBn), 160.2 (C-2), 154.9 (C-5), 137.8, 129.6, 129.5, 129.3, 129.2, 129.2 (6 C, C-aromat.), 114.8 (C-3), 109.2 (C-4), 74.5 (C-2′), 69.1 (C-1′), 67.0 (*C*H_2Ph), 64.4 (C-3′), 13.9 (CH_3) ppm. MS (CI): m/z (%) = 306.1093 $[M]^+$, 307 (7) $[M + H]^+$, 289 (49) $[M - OH]^+$.

Benzyl 5-(3-*O*-*tert*-Butyldiphenylsilyl-D-*threo*-1,2,3-trihydroxyprop-1-yl)-2-methylfuran-3-carboxylate (9): To a solution of **7** (4.75 g, 15.5 mmol) in dry DMF (15 mL) at 0 °C was added *tert*-butyldiphenylchlorosilane (TBDPSCl, 4.1 mL, 34.1 mmol) and imidazole (2.12 g, 31 mmol). The reaction mixture was stirred at 0 °C for 2 h, then water (0.1 mL) was added, and the mixture was stirred for 30 min. The solution was concentrated in vacuo, and the residue was dissolved in CH_2Cl_2 (100 mL) and washed with NH_4Cl, water, and brine. The organic layer was concentrated, and the resulting residue was purified by column chromatography (diethyl ether/petroleum ether, 1:3→2:1) to give **9** (5.18 g, 60%) as a colorless oil. $[\alpha]_D^{20} = -4$ (c = 2.45, CH_2Cl_2). IR: $\tilde{\nu}$ = 3442 (OH), 3070, 2930, 2857, 1715 (CO), 1427, 1112, 702 cm^{-1}. ^1H NMR (300 MHz, CD_3OD, 25 °C): δ = 1.01 [s, 9 H, $(CH_3)_3C$], 2.49 (s, 3 H, CH_3), 3.54 (dd, $J_{3'b,2'}$ = 4.9 Hz, 1 H, 3′b-H), 3.72 (dd, $J_{3'a,3'b}$ = 10.5 Hz, $J_{3'a,2'}$ = 5.3 Hz, 1 H, 3′a-H), 3.90 (m, 1 H, 2′-H), 4.74 (d, $J_{1',2'}$ = 5.8 Hz, 1 H, 1′-H), 5.24 (d, 1 H, CH_2Ph), 5.29 (d, 1 H, CH_2Ph), 6.55 (s, 1 H, 4-H), 7.68–7.28 (m, 15 H, Ar-H) ppm. ^{13}C NMR (75.4 MHz, CD_3OD, 25 °C): δ = 165.3 (*C*OOBn), 160.1 (C-2), 154.7 (C-5), 137.8, 136.7, 136.6, 134.5, 134.4, 130.8, 129.6, 129.2, 128.7 (18 C, C-aromat.), 115.0 (C-3), 109.0 (C-4), 74.8 (C-2′), 68.7 (C-1′), 67.0 (*C*H_2Ph), 66.0 (C-3′), 27.3 [$(CH_3)_3C$], 20.0 [$(CH_3)_3C$], 13.9 (CH_3) ppm. MS (FAB): m/z = 567.2186 $[M + Na]^+$.

Benzyl 5-(3-*O*-*tert*-Butyldiphenylsilyl-1,2-di-*O*-sulfinyl-D-*threo*-1,2,3-trihydroxyprop-1-yl)-2-methylfuran-3-carboxylate (10): To a solution of **9** (4.66 g, 8.5 mmol) and triethylamine (5.24 mL, 37.4 mmol) in dry CH_2Cl_2 (15 mL) cooled to 0 °C was dropwise added a solution of thionyl chloride (1.56 mL, 21.3 mmol) in dry CH_2Cl_2 (2 mL). The mixture was stirred at 0 °C for 30 min, then diluted with cooled ether (400 mL) and washed with water and brine. The organic phase was dried (Na_2SO_4), filtered, and concentrated. The resulting residue was purified by column chromatography (diethyl ether/petroleum ether, 1:3) to give **10** (4.61 g, 92%, 1:1 mixture of diastereoisomers) as a yellow oil. IR: $\tilde{\nu}$ = 2931, 2858, 1719 (CO), 1428, 1218 (SO), 1113, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C, mixture of diastereoisomers a and b): δ = 1.04, 1.02 [2 s, 9 H each, $(CH_3)_3C$ (a, b)], 2.60 [s, 6 H, CH_3 (a, b)], 3.87 [dd, 1 H, 3′b-H (b)], 3.93 [dd, $J_{3'b,2'}$ = 4.3 Hz, 1 H, 3′b-H (a)], 4.02 [dd, $J_{3'a,3'b}$ = 11.9 Hz, 1 H, 3′a-H (b)], 4.03 [dd, $J_{3'a,3'b}$ = 11.3 Hz, $J_{3'a,2'}$ = 5.5 Hz, 1 H, 3′a-H (a)], 4.67 [m, 1 H, 2′-H (a)], 5.17 [dt, $J_{2',3'a} = J_{2',3'b}$ = 3.5 Hz, 1 H, 2′-H (b)], 5.28 [d, 1 H, CH_2Ph (a or b)], 5.29 [s, 2 H, CH_2Ph (a or b)], 5.32 [d, $^2J_{H,H}$ = 12.6 Hz, 1 H, CH_2Ph (a or b)], 5.47 [d, $J_{1',2'}$ = 8.7 Hz, 1 H, 1′-H (b)], 5.88 [d, $J_{1',2'}$ = 8.7 Hz, 1 H, 1′-H (a)], 6.79, 6.78 [2 s, 1 H each, 4-H (a, b)], 7.63–7.32 [m, 30 H, Ar-H (a, b)] ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 163.2, 163.1 [*C*OOBn (a, b)], 161.6, 161.5 [C-2 (a, b)], 145.3, 144.2 [C-5 (a, b)], 136.1, 135.7, 135.6, 132.7, 132.6, 132.5, 132.4, 130.2, 130.1, 128.8, 128.5, 128.4, 128.1, 128.0 [18 C, C-aromat. (a, b)], 114.8 [2 C, C-3 (a, b)], 113.3, 112.9 [C-4 (a, b)], 84.0 [C-2′ (a)], 80.9 [C-2′ (b)], 78.1 [C-1′ (a)], 75.9 [C-1′ (b)], 66.4, 66.3 [*C*H_2Ph (a, b)], 62.8 [C-3′ (a)], 61.2 [C-3′ (b)], 26.8, 26.7 [$(CH_3)_3C$ (a, b)], 19.4, 19.3 [$(CH_3)_3C$ (a, b)], 14.2, 14.1 [CH_3 (a, b)] ppm. MS (FAB): m/z = 549.2054 $[M - SO_2 + Na]^+$.

Benzyl 5-(1-Azido-1-deoxy-D-*erythro*-1,2,3-trihydroxyprop-1-yl)-2-methylfuran-3-carboxylate (12): To a solution of **10** (4.61 g, 7.8 mmol) in THF (15 mL) was added $TMSN_3$ (3.24 mL, 23.4 mmol) and TBAF (1 M in THF, 1.6 mL), and the mixture was stirred 24 h at room temperature. Then, the solution was concentrated, and the resulting residue was purified by chromatography column (diethyl ether/petroleum ether, 5:1) to give **12** (1.98 g, 77%) as a colorless oil. $[\alpha]_D^{20} = +99$ (c = 0.87, CH_2Cl_2). IR: $\tilde{\nu}$ = 3449 (OH), 2924, 2104 (N_3), 1715 (CO), 1225 (N_3) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.60 (s, 3 H, CH_3); 3.72 (dd, $J_{3'b,2'}$ = 5.2 Hz, 1 H, 3′b-H), 3.76 (dd, $J_{3'a,3'b}$ = 11.5 Hz, $J_{3'a,2'}$ = 3.4 Hz, 1 H, 3′a-H), 4.02 (m, 1 H, 2′-H), 4.56 (d, $J_{1',2'}$ = 7.3 Hz, 1 H, 1′-H), 5.29 (s, 2 H, CH_2Ph), 6.75 (s, 1 H, 4-H), 7.40–7.28 (m, 5 H, Ar-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 163.5 (*C*OOBn), 160.4 (C-2), 147.5 (C-5), 135.9, 128.6, 128.3, 128.2 (6 C, C-aromat.), 114.2 (C-3), 110.9 (C-4), 71.9 (C-2′), 66.2 (*C*H_2Ph), 62.9 (C-3′), 59.9 (C-1′), 14.3 (CH_3) ppm. MS (CI): m/z = 332.1236 $[M + H]^+$.

Benzyl 5-(3-*O*-*tert*-Butyldiphenylsilyl-D-*erythro*-1,2,3-trihydroxyprop-1-yl)-2-methylfuran-3-carboxylate (13): This compound was

prepared in a manner similar to that described for **9** except that compound **8** was initially used. Yield: 59%, colorless oil. $C_{32}H_{36}O_6Si$ (544.22): calcd. C 70.56, H 6.66; found C 70.37, H 6.74. $[\alpha]_D^{20}$ = +1 (*c* = 0.71, CH_2Cl_2). IR: $\tilde{\nu}$ = 3464 (OH), 3070, 2931, 2858, 1715 (CO), 1427, 1113, 701 cm^{-1}. ^1H NMR (300 MHz, CD_3OD, 25 °C): δ = 1.04 [s, 9 H, $(CH_3)_3C$], 2.51 (s, 3 H, CH_3), 3.76 (dd, 1 H, 3′b-H), 3.80 (dd, $J_{3'a,3'b}$ = 10.5 Hz, 1 H, 3′a-H), 3.99 (dt, $J_{2',3'a} = J_{2',3'b}$ = 5.3 Hz, 1 H, 2′-H), 4.73 (d, $J_{1',2'}$ = 5.9 Hz, 1 H, 1′-H), 5.26 (s, 2 H, CH_2Ph), 6.56 (s, 1 H, 4-H), 7.65–7.31 (m, 15 H, Ar-H) ppm. ^{13}C NMR (75.4 MHz, CD_3OD, 25 °C): δ = 165.4 (*C*OOBn), 160.1 (C-2), 154.7 (C-5), 137.8, 136.7, 136.7, 134.6, 130.8, 129.6, 129.2, 128.8, 128.7 (18 C, C-aromat.), 114.9 (C-3), 109.2 (C-4), 74.9 (C-2′), 69.2 (C-1′), 66.9 (*C*H_2Ph), 66.2 (C-3′), 27.3 [(*C*H_3)$_3$C], 20.0 [(CH$_3$)$_3$*C*], 13.9 (CH_3) ppm. MS (FAB): *m*/*z* = 567.2183 $[M + Na]^+$.

Benzyl 5-(3-*O*-*tert*-Butyldiphenylsilyl-1,2-di-*O*-sulfinyl-D-*erythro*-1,2,3-trihydroxyprop-1-yl)-2-methylfuran-3-carboxylate (14): This compound was prepared in a manner similar to that described for **12** except that compound **13** was initially used. Yield: 86% (1:1 mixture of diastereoisomers that isomerize after 5 d to a major isomer), colorless oil. IR: $\tilde{\nu}$ = 2932, 2858, 1718 (CO), 1428, 1218 (SO), 1113, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C, major stereoisomer): δ = 0.99 [s, 9 H, $(CH_3)_3C$], 2.47 (s, 3 H, CH_3), 3.61 (dd, $J_{3'b,2'}$ = 6.5 Hz, 1 H, 3′b-H), 3.76 (dd, $J_{3'a,3'b}$ = 11.0 Hz, $J_{3'a,2'}$ = 5.4 Hz, 1 H, 3′a-H), 5.18 (m, 1 H, 2′-H), 5.26 (d, 1 H, CH*H*Ph), 5.28 (d, $^2J_{H,H}$ = 12.3 Hz, 1 H, C*H*HPh), 5.85 (d, $J_{1',2'}$ = 6.2 Hz, 1 H, 1′-H-), 6.71 (s, 1 H, 4-H), 7.46–7.28 (m, 15 H, Ar-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C, major stereoisomer): δ = 163.2 (*C*OOBn), 160.9 (C-2), 144.7 (C-5), 136.0, 135.6, 135.6, 135.5, 132.5, 132.4, 130.2, 130.1, 128.8, 128.5, 128.4, 128.0, 127.9 (18 C, C-aromat.), 114.4 (C-3), 112.4 (C-4), 80.5 (C-2′), 78.3 (C-1′), 66.3 (*C*H_2Ph), 61.5 (C-3′), 26.7 [(*C*H_3)$_3$C], 19.2 [(CH$_3$)$_3$*C*], 14.0 (CH_3) ppm. MS (FAB): *m*/*z* = 549.2073 $[M - SO_2 + Na]^+$.

Benzyl 5-(1-Azido-1-deoxy-D-*threo*-1,2,3-trihydroxyprop-1-yl)-2-methylfuran-3-carboxylate (15): This compound was prepared in a manner similar to that described for **12** except that compound **14** was initially used. Yield: 79% (*S*/*R* = 18), colorless oil. $[\alpha]_D^{24}$ = –95 (*c* = 0.56, CH_2Cl_2). IR: $\tilde{\nu}$ = 3418 (OH), 2104 (N_3), 1714 (CO), 1227 (N_3) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.97 (br. s, 1 H, OH), 2.59 (s, 3 H, CH_3), 2.67 (br. s, 1 H, OH), 3.49 (dd, $J_{3'b,2'}$ = 5.4 Hz, 1 H, 3′b-H), 3.67 (dd, $J_{3'a,3'b}$ = 11.6 Hz, $J_{3'a,2'}$ = 3.6 Hz, 1 H, 3′a-H), 4.02 (m, 1 H, 2′-H), 4.57 (d, $J_{1',2'}$ = 7.5 Hz, 1 H, 1′-H), 5.28 (s, 2 H, CH_2Ph), 6.73 (s, 1 H, 4-H), 7.43–7.34 (m, 5 H, Ar-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 163.4 (*C*OOBn), 160.6 (C-2), 147.2 (C-5), 136.0, 128.8, 128.5, 128.4 (6 C, C-aromat.), 114.3 (C-3), 110.9 (C-4), 72.5 (C-2′), 66.3 (*C*H_2Ph), 63.1 (C-3′), 60.8 (C-1′), 14.1 (CH_3) ppm. MS (FAB): *m*/*z* = 354.1083 $[M + Na]^+$.

Benzyl 5-(1-Azido-3-*O*-*tert*-butyldiphenylsilyl-1-deoxy-D-*threo*-1,2,3-trihydroxyprop-1-yl)-2-methylfuran-3-carboxylate (16): To a solution of compound **14** (173 mg, 0.29 mmol) in THF (3 mL) was added Bu_4NN_3 (247 mg, 0.87 mmol). The mixture was stirred at room temperature overnight. The solvent was evaporated, and the resulting residue was purified by column chromatography (diethyl ether/petroleum ether, 1:5) to give **16** (130 mg, 79%) as a colorless oil. $[\alpha]_D^{24}$ = –49 (*c* = 0.56, CH_2Cl_2). IR: $\tilde{\nu}$ = 3440 (OH), 2929, 2103 (N_3), 1717 (CO), 1613, 1427, 1227 (N_3), 1113, 1076, 823, 741, 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.06 [s, 9 H, $(CH_3)_3C$], 2.54 (s, 3 H, CH_3), 2.56 (s, 1 H, OH), 3.58 (dd, $J_{3'b,2'}$ = 5.2 Hz, 1 H, 3′b-H), 3.68 (dd, $J_{3'a,3'b}$ = 10.6 Hz, $J_{3'a,2'}$ = 4.7 Hz, 1 H, 3′a-H), 4.04 (m, 1 H, 2′-H), 4.59 (d, $J_{1',2'}$ = 6.5 Hz, 1 H, 1′-H), 5.29 (s, 2 H, CH_2Ph), 6.65 (s, 1 H, 4-H), 7.64–7.31 (m, 10 H, Ar-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 163.5 (*C*OOBn), 160.2 (C-2), 147.9 (C-5), 136.2, 135.7, 135.6, 132.8, 132.7, 130.1, 128.8, 128.4, 128.0, 128.0 (12 C, C-aromat.), 114.2 (C-3), 110.4 (C-4), 72.9 (C-2′), 66.2 (*C*H_2Ph), 64.4 (C-3′), 60.3 (C-1′), 27.0 [(*C*H_3)$_3$C], 19.4 [(CH$_3$)$_3$*C*], 14.0 (CH_3) ppm. MS (FAB): *m*/*z* (%) = 570.2441 $[M + H]^+$, 527 (5) $[M - N_3]^+$.

Benzyl 5-[(4*R*,5*S*)-5-(*tert*-Butyldiphenylsilyloxy)methyl-2-thioxazolidin-4-yl]-2-methylfuran-3-carboxylate (17): To a solution of **11** (157 mg, 0.47 mmol) in dry DMF (5 mL) at 0 °C was added *tert*-butyldiphenylchlorosilane (282 μL, 1.04 mmol) and imidazole (71 mg, 1.04 mmol). The reaction mixture was stirred at 0 °C for 1.5 h, water (0.1 mL) was then added, and the mixture was stirred for 30 min. The solution was concentrated in vacuo, and the residue was dissolved in CH_2Cl_2 (100 mL) and washed with NH_4Cl, water, and brine. The organic layer was concentrated, and the resulting residue was purified by column chromatography (diethyl ether/petroleum ether, 1:4→1:1) to give the corresponding silyl derivative (218 mg, 85%) as a colorless oil that was not characterized. Silyl derivative (170 mg, 0.298 mmol) was dissolved in dry THF (3.5 mL) and Ph_3P (96 mg, 0.366 mmol) was added. The mixture was stirred for 12 h at room temperature. Then, water (0.3 mL) was added, and the mixture was stirred for 1 h at room temperature. The mixture was concentrated and coevaporated with toluene. The resulting crude was dissolved in CH_2Cl_2 (2 mL), and a solution of 1,1′-thiocarbonyldiimidazole (53 mg, 0.298 mmol) in CH_2Cl_2 (2 mL) was added under an atmosphere of argon. The mixture was stirred at room temperature for 24 h. Then, the solution was diluted with CH_2Cl_2 and washed with brine. The organic phase was dried (Na_2SO_4), filtered, and concentrated to dryness. The resulting crude was purified by column chromatography (diethyl ether/petroleum ether, 1:2) to give **17** (150 mg, 84%) as a white foam. $[\alpha]_D^{20}$ = +37 (*c* = 0.85, CH_2Cl_2). IR: $\tilde{\nu}$ = 3304 (NH), 1716 (CO), 1496, 1112 (CS), 702 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 0.97 [s, 9 H, $(CH_3)_3C$], 2.44 (s, 3 H, CH_3), 3.62 (dd, $J_{1''b,5'}$ = 6.8 Hz, 1 H, 1′′b-H), 3.80 (dd, $J_{1''a,1''b}$ = 11.2 Hz, $J_{1''a,5'}$ = 4.8 Hz, 1 H, 1′′a-H), 5.07 (m, 1 H, 5′-H), 5.13 (d, $J_{4',5'}$ = 8.6 Hz, 1 H, 4′-H-), 5.28 (s, 2 H, CH_2Ph), 6.64 (s, 1 H, 4-H), 7.55–7.30 (m, 15 H, Ar-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 189.7 (C-2′), 163.2 (*C*OOBn), 161.0 (C-2), 146.0 (C-5), 136.0, 135.6, 132.5, 132.4, 130.2, 130.1, 128.8, 128.5, 128.4, 128.0, 127.9 (18 C, C-aromat.), 114.5 (C-3), 111.1 (C-4), 84.5 (C-5′), 66.4 (*C*H_2Ph), 61.3 (C-1′′), 55.9 (C-4′), 26.8 [(*C*H_3)$_3$C], 19.2 [(CH$_3$)$_3$*C*], 14.0 (CH_3) ppm. MS (FAB): *m*/*z* = 608.1928 $[M + Na]^+$.

Benzyl 5-[(4*S*,5*S*)-5-(*tert*-Butyldiphenylsilyloxy)methyl-2-thioxazolidin-4-yl]-2-methylfuran-3-carboxylate (18): This compound was prepared in a manner similar to that described for **17** except that compound **16** was initially used. Yield: 86%, colorless oil. IR: $\tilde{\nu}$ = 3408 (NH), 1638 (CO), 1497, 1113 (CS), 701 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.56 (s, 3 H, CH_3), 1.07 [s, 9 H, $(CH_3)_3C$], 3.82 (dd, $J_{1''b,5'}$ = 3.9 Hz, 1 H, 1′′b-H), 3.99 (dd, $J_{1''a,1''b}$ = 11.7 Hz, $J_{1''a,5'}$ = 4.2 Hz, 1 H, 1′′a-H), 4.86 (m, 1 H, 5′-H), 5.04 (d, $J_{4',5'}$ = 6.3 Hz, 1 H, 4′-H), 5.27 (s, 2 H, CH_2Ph), 6.57 (s, 1 H, 4-H), 7.73–7.36 (m, 15 H, Ar-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 189.3 (C-2′), 163.2 (*C*OOBn), 161.0 (C-2), 147.6 (C-5), 136.0, 135.8, 135.7, 135.0, 132.8, 132.3, 130.3, 129.8, 128.8, 128.5, 128.3,128.1, 127.9 (18 C, C-aromat.), 114.5 (C-3), 110.0 (C-4), 86.6 (C-5′), 66.4 (*C*H_2Ph), 62.9 (C-1′′), 55.0 (C-4′), 26.8 [(*C*H_3)$_3$C], 19.4 [(CH$_3$)$_3$*C*], 14.0 (CH_3) ppm. MS (FAB): *m*/*z* = 608.1885 $[M + Na]^+$.

Benzyl 5-[(*R*)-1-Azido-2-hydroxyethyl]-2-methylfuran-3-carboxylate (19): To a solution of **12** (113 mg, 0.342 mmol) in MeOH (5 mL) cooled to 0 °C was dropwise added a solution of $NaIO_4$ (146 mg,

0.68 mmol) in H_2O (1 mL), and the mixture was stirred for 1 h. Then, the solution was filtered, and $NaBH_4$ (27 mg, 0.68 mmol) was added to the filtrate. After 15 min, the solution was neutralize with citric acid (pH 7) and concentrated in vacuo. The crude was dissolved in CH_2Cl_2 (60 mL) and washed with water (30 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting residue was purified by chromatography column (diethyl ether/petroleum ether, 1:3) to give **19** (84 mg, 83%) as a colorless oil. $[\alpha]_D^{20}$ = +101 (c = 1.96, CH_2Cl_2). IR: $\tilde{\nu}$ = 3414 (OH), 2921, 2104 (N_3), 1715 (CO), 1408, 1227 (N_3), 1076 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.94 (t, $J_{OH,2'}$ = 6.5 Hz, 1 H, OH), 2.59 (s, 3 H, CH_3), 3.91–3.87 (m, 2 H, 2′-H), 4.58 (t, $J_{1',2'}$ = 6.3 Hz, 1 H, 1′-H), 5.28 (s, 2 H, CH_2Ph), 6.68 (s, 1 H, 4-H), 7.41–7.36 (m, 5 H, Ar-H) ppm. ^{13}C NMR (7.4 MHz, $CDCl_3$, 25 °C): δ = 163.5 (*C*OOBn), 160.3 (C-2), 147.7 (C-5), 136.1, 128.8, 128.4, 128.3 (6 C, C-aromat.), 114.3 (C-3), 110.0 (C-4), 66.3 (*C*H_2Ph), 63.5 (C-2′), 60.4 (C-1′), 14.0 (CH_3) ppm. MS (CI): m/z (%) = 301.1063 $[M]^+$, 259 (51) $[M - N_3]^+$.

Benzyl 5-[(*R*)-1-Azido-2-hydroxyethyl]-2-methylfuran-3-carboxylate (*ent*-19): This compound was prepared in a manner similar to that described for **19** except that compound **15** was initially used. Yield: 80%, colorless oil. $[\alpha]_D^{27}$ = –108 (c = 0.93, CH_2Cl_2).

Benzyl 5-{(*R*)-1-Azido-2-[(*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyloxy]ethyl}-2-methylfuran-3-carboxylate (20): To a solution of **19** (20 mg, 0.066 mmol) in dry pyridine (1.5 mL) cooled to 0 °C was added Mosher's acid chloride (12.3 μL, 0.066 mmol). The reaction was stirred at room temperature for 4 h, and then the solvent was evaporated to give pure **20** (34 mg, quant.). $[\alpha]_D^{20}$ = +25 (c = 2.62, CH_2Cl_2). IR: $\tilde{\nu}$ = 2953, 2107 (N_3), 1756 (CO), 1717 (CO), 1227 (N_3), 1171, 721, 698 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.59 (s, 3 H, CH_3), 3.53 (q, $J_{CH,F}$ = 1.2 Hz, 3 H, OCH_3), 4.53 (dd, 1 H, 2′b-H), 4.57 (dd, $J_{2'a,2'b}$ = 11.4 Hz, 1 H, 2′a-H), 4.73 (t, $J_{1',2a'}$ = $J_{1',2'b}$ = 6.5 Hz, 1 H, 1′-H), 5.28 (s, 2 H, CH_2Ph), 6.65 (s, 1 H, 4-H), 7.42–7.33 (m, 10 H, Ar-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 166.4 (CO), 163.3 (*C*OOBn), 160.7 (C-2), 146.1 (C-5), 136.1–127.3 (12 C, C-aromat.), 123.1 (q, $^1J_{C,F}$ = 288 Hz, CF_3), 114.4 (C-3), 110.7 (C-4), 84.7 [q, $^2J_{C,F}$ = 28.2 Hz, *C*$(OCH_3)(CF_3)$Ph], 66.3 (*C*H_2Ph), 65.2 (C-2′), 56.7 (C-1′), 55.7 (OCH_3), 14.0 (CH_3) ppm. MS (CI): m/z (%) = 517.1445 $[M]^+$, 475 (6) $[M - N_3]^+$.

5-[(*R*)-1-Amino-2-hydroxyethyl]-2-methylfuran-3-carboxylic Acid (4): A solution of **19** (65 mg, 0.216 mmol) in MeOH (3 mL) was hydrogenated under atmospheric pressure for 3 h by using Pd/C (10%) as catalyst. Then, the solution was filtered through Celite, and the catalyst was washed with MeOH. The filtered solution was concentrated in vacuo to give pure **4** (30 mg, 74%) as a colorless syrup. ^1H NMR (300 MHz, CD_3OD, 25 °C): δ = 2.52 (s, 3 H, CH_3), 3.82 (dd, 1 H, 2′b-H), 3.90 (dd, $J_{2'a,2'b}$ = 11.5 Hz, 1 H, 2′a-H), 4.27 (dd, $J_{1',2'a}$ = 8.0 Hz, $J_{1',2'b}$ = 4.7 Hz, 1 H, 1′-H), 6.61 (s, 1 H, 4-H) ppm. ^{13}C NMR (75.4 MHz, D_2O, 25 °C): δ = 161.5 (*C*OOH), 158.3 (C-2), 144.4 (C-5), 119.7 (C-3), 111.9 (C-4), 60.7 (C-2′), 50.4 (C-1′), 13.3 (CH_3) ppm.

5-[(*S*)-1-Amino-2-hydroxyethyl]-2-methylfuran-3-carboxylic Acid (*ent*-4): This compound was prepared in a manner similar to that described for **4** except that compound *ent*-**19** was initially used. Yield: 71%, colorless oil.

Benzotriazol-1-yl 5-[(*R*)-1-(9-Fluorenylmethoxycarbonyl)amino-2-hydroxyethyl]-2-methylfuran-3-carboxylate (21): To a stirred mixture of **4** (26 mg, 0.138 mmol) in dry pyridine (2 mL) at 0 °C was added trimethylsilyl chloride (54 μL, 0.414 mmol), and the reaction mixture was stirred for 45 min at room temperature. Then, the reaction mixture was cooled to 0 °C and 9-fluorenylmethoxycarbonyl chloride (46 mg, 0.18 mmol) was added; the mixture was then stirred for 1.5 h at room temperature. Water (0.1 mL) was added, and the reaction mixture was stirred for 1 h and then evaporated to give the *N*-protected amino acid that was used in the next step without any purification. The crude *N*-protected amino acid was dissolved in DMF and DIEA (53 μL, 0.3 mmol) and PyBOP (88 mg, 0.168 mmol) were then added. The mixture was stirred for 1 h at room temperature, and then the solution was evaporated in vacuo. The resulting residue was purified by column chromatography (AcOEt/petroleum ether, 1:1) to give **21** (57 mg, 78%) as a white solid. $[\alpha]_D^{20}$ = +38 (c = 0.84, CH_2Cl_2). IR: $\tilde{\nu}$ = 3320 (OH), 3065, 2950, 1793 (CO), 1711 (CO), 1266, 960, 740 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.60 (s, 3 H, CH_3), 4.04–3.91 (m, 2 H, 2′-H), 4.22 (t, 1 H, CH of Fmoc), 4.49 (d, J = 6.5 Hz, 2 H, CH_2 of Fmoc), 4.94 (br. s, 1 H, 1′-H), 5.75 (d, $J_{NH,1'}$ = 7.5 Hz, 1 H, NH), 8.08–7.27 (m, 12 H, Ar-H), 6.76 (s, 1 H, 4-H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 163.6 (*C*OOBt), 159.6 (C-2), 156.3 (CO of Fmoc), 152.4 (C-5), 143.8, 143.6, 141.5, 129.0, 127.9, 127.2, 125.1, 120.6, 120.2, 107.4 (18 C, C-aromat.), 109.0 (C-3), 108.5 (C-4), 67.2 (CH_2 of Fmoc), 63.4 (C-2′), 51.0 (C-1′), 47.4 (CH of Fmoc), 14.3 (CH_3) ppm. MS (FAB): m/z = 547.1581 $[M + Na]^+$.

Benzotriazol-1-yl 5-[(*R*)-1-(9-Fluorenylmethoxycarbonyl)amino-2-hydroxyethyl]-2-methylfuran-3-carboxylate (*ent*-21): This compound was prepared in a manner similar to that described for **21** except that compound *ent*-**4** was initially used. Yield: 60%, colorless oil. $[\alpha]_D^{25}$ = –35 (c = 0.79, CH_2Cl_2).

Ethyl 2-Methyl-5-(L-*erythro*-1,2,3-trihydroxyprop-1-yl)furan-3-carboxylate (22): Compound **22** was obtained according to the general procedure described for **7** and **8** except that L-arabinose (2 g, 13.3 mmol) was used as the starting sugar. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH, 15:1→5:1) afforded **22** (2.4 g, 74%) as a white solid. $[\alpha]_D^{21}$ = –13 (c = 0.97, CH_2Cl_2). ^1H NMR (300 MHz, CD_3OD, 25 °C): δ = 6.56 (s, 1 H, 4-H), 4.53 (d, J = 7.3 Hz, 1 H, 3′-H), 4.27 (q, J = 7.1 Hz, 2 H, C$H_2$$CH_3$), 3.86 (ddd, 1 H, 2′-H), 3.75 (dd, J = 11.4 Hz, J = 3.7 Hz, 1 H, 1′a-H), 3.65 (dd, J = 6.1 Hz, 1 H, 1′b-H), 2.55 (s, 3 H, CH_3), 1.33 (t, 3 H, CH_2CH_3) ppm. ^{13}C NMR (75.4 MHz, CD_3OD, 25 °C): δ = 165.7 (*C*OOEt), 159.9, 154.8 (C-2, C-5), 115.1 (C-3), 109.2 (C-4), 74.6 (C-2′), 69.2 (C-3′), 64.4 (C-1′), 61.3 (*C*H_2CH_3), 14.7 (CH_2*C*H_3), 13.9 (CH_3) ppm. MS (CI): m/z = 245.1013 $[M + H]^+$.

Ethyl 5-(1-Azido-3-*O*-*tert*-butyldiphenylsilyl-1-deoxy-L-*threo*-1,2,3-trihydroxyprop-1-yl)-2-methylfuran-3-carboxylate (24): To a solution of compound **22** (1.12 g, 4.6 mmol) in dry DMF (8 mL) cooled to 0 °C was added imidazole (377 mg, 5.52 mmol) and TBDPSCl (0.66 mL, 5.52 mmol), and the mixture was stirred at 0 °C for 2 h. Then, water was added (0.5 mL), and the mixture was stirred for 15 min. The mixture was evaporated to dryness, and the resulting crude was diluted with CH_2Cl_2 and washed with a saturated aqueous solution of NH_4Cl, water, and brine. The organic layer was dried with Na_2SO_4 and filtered, and the solvent was evaporated to give **23**, which was employed in the following step without purification. To a cooled solution of crude **23** (≈4.6 mmol) in dry CH_2Cl_2 (10 mL) was added Et_3N (2.6 mL, 18.4 mmol) and a solution of $SOCl_2$ (0.68 mL, 9.2 mmol) in CH_2Cl_2 (10 mL). After 30 min at 0 °C, cold Et_2O was added, and the mixture was washed with water and brine. The organic phase was then dried (Na_2SO_4), filtered, and concentrated. The mixture of epimeric cyclic sulfites (≈4.6 mmol) thus obtained was dissolved in THF (25 mL) and Bu_4NN_3 (3.92 g, 13.8 mmol) was added. After 24 h at room temperature, the solvent was evaporated, and the residue was purified by flash chromatography on silica gel (Et_2O/petroleum ether, 1:4→1:2) to afford **24** (1.05 g, 45%) as a colorless oil. $[\alpha]_D^{24}$ = +57

(c = 0.86, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.65–7.36 (m, 10 H, Ar-H), 6.64 (s, 1 H, 4-H), 4.59 (d, J = 6.3 Hz, 1 H, 3′-H), 4.29 (q, J = 7.1 Hz, 2 H, CH_2CH_3), 4.09–4.01 (m, 1 H, 2′-H), 3.68 (dd, J = 10.5 Hz, J = 4.7 Hz, 1 H, 1′a-H), 3.59 (dd, J = 5.2 Hz, 1 H, 1′b-H), 2.57 (d, J = 5.7 Hz, 1 H, OH), 2.54 (s, 3 H, CH_3), 1.35 (t, 3 H, CH_2CH_3), 1.06 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 163.8 (*C*OOEt), 159.8, 147.8 (C-2, C-5), 135.7, 135.6, 132.8, 132.8, 130.1, 128.0, 128.0 (12 C-aromat.), 114.5 (C-3), 110.4 (C-4), 72.9 (C-2′), 64.4 (C-1′), 66.4 (CH_2CH_3), 60.3 (C-3′), 27.0 [$(CH_3)_3C$], 19.4 [$(CH_3)_3C$], 14.5 (CH_2CH_3), 13.9 (CH_3) ppm. MS (CI): m/z = 465.2088 $[M - N_3]^+$.

Ethyl 5-[1-(*tert*-Butoxycarbonylamino)-3-*O*-*tert*-butyldiphenylsilyl-1-deoxy-L-*threo*-1,2,3-trihydroxyprop-1-yl]-2-methylfuran-3-carboxylate (25): A solution of **24** (1.9 g, 3.74 mmol) and $(Boc)_2O$ (978 mg, 4.5 mmol) in MeOH (60 mL) was hydrogenated under atmospheric pressure for 1.5 h by using Pd/C (10%) as catalyst. Then, the solution was filtered through Celite, and the catalyst was washed with MeOH. Pd/C (10%) and Et_3N (0.6 mL) were added, and the mixture was hydrogenated again for 2 h. Then, the solution was filtered through Celite, and the catalyst was washed with EtOH. The filtered solution was evaporated to dryness, and the resulting residue was purified by flash chromatography to give pure **25** (1.78 g, 84%) as a colorless oil. $[\alpha]_D^{22}$ = +22 (c = 0.45, CH_2Cl_2). IR: $\tilde{\nu}$ = 3437 (OH), 2931, 1717 (CO), 1585 (NH), 1497, 1428, 1366, 1229, 1168, 1113, 824, 779, 741, 704 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.66–7.36 (m, 10 H, Ar-H), 6.49 (s, 1 H, 4-H), 5.23 (br. s, 1 H, NH), 4.80 (dd, $J_{3',NH}$ = 8.5 Hz, $J_{2',3'}$ = 2.5 Hz, 1 H, 3′-H), 4.27 (q, $^3J_{H,H}$ = 7.2 Hz, 2 H, CH_2CH_3), 4.11–4.05 (m, 1 H, 2′-H), 3.72 (dd, $J_{1'a,1'b}$ = 10.3 Hz, $J_{1'a,2'}$ = 4.9 Hz, 1 H, 1′a-H), 3.60 (dd, $J_{1'b,2'}$ = 7.0 Hz, 1 H, 1′b-H), 2.64 (br. s, 1 H, OH), 2.53 (s, 3 H, CH_3), 1.41 [s, 9 H, $(CH_3)_3C$], 1.33 (t, 3 H, CH_2CH_3), 1.07 [s, 9 H, $(CH_3)_3C$] ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ = 164.1 (*C*OOEt), 158.8, 155.7 (C-2, C-5), 151.4 (CO of Boc), 135.7, 133.0, 130.1, 128.0 (12 C, C-aromat.), 114.4 (C-3), 107.9 (C-4), 80.2 [$(CH_3)_3C$], 72.4 (C-2′), 64.8 (C-1′), 60.2 (CH_2CH_3), 50.0 (C-3′), 28.5 [$(CH_3)_3C$], 27.0 [$(CH_3)_3C$], 19.4 [$(CH_3)_3C$], 14.5 (CH_2CH_3), 13.9 (CH_3) ppm. MS (FAB): m/z = 604.2733 $[M + Na]^+$.

(4*R*,5*R*)-*N*-(*tert*-Butoxycarbonyl)-4-(4-ethoxycarbonyl-5-methylfuran-2-yl)-5-hydroxymethyl-2-(*p*-methoxyphenyl)oxazolidine (27):[20] To a solution of compound **25** (193 mg, 0.33 mmol) in dry toluene (6 mL) containing 4 Å MS was added a catalytic amount of *p*-toluenesulfonic acid (PTSA; 5 mol-%, 4 mg) and *p*-anisaldehyde dimethylacetal (63 μL, 0.36 mmol). The reaction mixture was stirred for 2 h at room temperature. Then, the mixture was diluted with AcOEt and washed with a saturated aqueous solution of $NaHCO_3$ and brine. The organic phase was dried (Na_2SO_4) and filtered, and the solvents were evaporated to dryness to give crude compound **26**. The resulting residue was dissolved in THF (4 mL) and TBAF (1 M in THF, 561 μL, 0.561 mmol) was added. The mixture was stirred for 1 h at room temperature. The solvent was evaporated, and the crude product was purified by flash chromatography on silica gel (Et_2O/petroleum ether, 1:1) to give compound **27** (109 mg, 72%, 1.1:1 mixture of diastereoisomers) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, mixture of diastereoisomers a and b): δ = 7.43 [d, J = 8.6 Hz, 2 H, Ar-H (b)], 7.36 [d, J = 8.6 Hz, 2 H, Ar-H (a)], 6.91 [d, 2 H, Ar-H (a)], 6.90 [d, 2 H, Ar-H (b)], 6.61 [s, 1 H, 3′-H (a)], 6.49 [s, 1 H, 3′-H (b)], 6.33 [s, 1 H, 2-H (b)], 6.08 [s, 1 H, 2-H (a)], 4.95 [d, $J_{4,5}$ = 7.8 Hz, 1 H, 4-H (a)], 4.89 [d, $J_{4,5}$ = 7.2 Hz, 1 H, 4-H (b)], 4.35–4.23 [m, 6 H, 5-H (a), 5-H (b), CH_2CH_3 (a, b)], 3.91–3.85 [m, 2 H, CH*H*OH (a, b)], 3.82 [s, 6 H, OCH_3 (a, b)], 3.76–3.63 [m, 2 H, C*H*HOH (a, b)], 2.58 [s, 3 H, CH_3 (a)], 2.51 [s, 3 H, CH_3 (b)], 1.92 [br. s, 2 H, OH (a, b)], 1.39 [s, 9 H, $(CH_3)_3C$ (b)], 1.36–1.30 [m, 6 H, CH_2CH_3 (a, b)], 1.07 [s, 9 H, $(CH_3)_3C$ (a)] ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C, mixture of diastereoisomers a and b): δ = 164.1 (*C*OOEt), 160.5, 160.0, 159.1, 153.9, 151.9, 149.9 [6 C, CO of Boc (a, b), C-2′ (a, b), C-5′ (a, b)], 131.6, 128.5, 128.2, 114.1, 113.7 [12 C, C-aromat. (a, b)], 114.6 [C-4′ (a, b)], 109.5 [C-3′ (a)], 109.2 [C-3′ (b)], 91.1 [C-2 (a)], 90.3 [C-2 (b)], 82.3 [C-5 (a or b)], 81.4 [$(CH_3)_3C$ (a or b)], 81.2 [C-5 (a or b)], 80.7 [$(CH_3)_3C$ (a or b)], 60.9 [2 C, CH_2OH (a, b)], 60.3 [2 C, CH_2CH_3(a, b)], 55.5 [2 C, OCH_3 (a, b)], 55.4 [C-4 (a)], 55.2 [C-4 (b)], 28.4 [$(CH_3)_3C$ (b)], 28.0 [$(CH_3)_3C$ (a)], 14.5 [2 C, CH_2CH_3 (a, b)], 14.0 [2 C, CH_3 (a, b)] ppm. MS (CI): m/z = 462.2122 $[M + H]^+$.

(4*R*,5*R*)-*N*-(*tert*-Butoxycarbonyl)-5-hydroxymethyl-2-(*p*-methoxyphenyl)-4-(4-*p*-methoxytrityloxymethyl-5-methylfuran-2-yl)oxazolidine (28):[20] To a solution of crude compound **26** (≈2.58 mmol) in dry THF (14 mL) cooled to 0 °C was slowly added (over 5 min) $LiAlH_4$ (2 M in THF, 2.58 mL, 5.16 mmol), and the reaction mixture was stirred for 30 min at 0 °C. Then, the mixture was diluted with Et_2O and a saturated aqueous solution of Na_2SO_4 was added in small portions. The reaction mixture was filtered through Celite, the filtrate was washed with water, the organic phase was dried (Na_2SO_4), and the solvents were evaporated to dryness. The crude product thus obtained was dissolved in dry pyridine (20 mL) and MeOTrCl (1.19 g, 3.87 mmol) was added. The reaction mixture was stirred overnight at room temperature. Then, MeOH (2 mL) was added, and the reaction mixture was stirred for 30 min. The solvent was evaporated to dryness, and the resulting crude was dissolved in THF (20 mL); TBAF (1 M in THF, 5.16 mL, 5.16 mmol) was added in one portion. The mixture was stirred for 2 h at room temperature. The solvent was evaporated, and the resulting residue was purified by flash chromatography (AcOEt/petroleum ether, 1:3) to give compound **28** (0.94 g, 53% from **25**, mixture of diastereoisomers 4.4:1) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, major diastereoisomer): δ = 7.37–6.83 (m, 18 H, Ar-H), 6.34 (s, 1 H, 2-H), 6.25 (s, 1 H, 3′-H), 4.90 (d, J = 6.9, 1 H, 4-H), 4.40 (m, 1 H, 5-H), 3.91–3.71 (m, 10 H, CH_2OAr, $CH_2OTrOMe$, CH_3OPh, CH_3OTr), 2.10 (s, 3 H, CH_3), 1.41 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C, major diastereoisomer): δ = 159.9, 158.7, 153.9, 149.4, 148.6, 144.8, 136.0, 131.9 (CO of Boc, C-2′, C-5′, 6 C_q-aromat.), 130.5, 128.6, 128.4, 127.9 (14 C-aromat.), 117.8 (C-4′) 113.7, 113.2 (4 C-aromat.), 110.2 (C-3′), 90.3 (C-2), 86.6 [$C(CH_3)_3$], 81.3, 81.0 (C-5, rotamers), 61.6 (CH_2OH), 58.0 (CH_2TrOMe), 55.5 (C-4), 55.4, 55.4 (CH_3OPh, CH_3OTr), 28.4 [$(CH_3)_3C$], 12.0 (CH_3 of furan) ppm. MS (ESI): m/z = 714 $[M + Na]^+$.

(4*R*,5*R*)-*N*-(*tert*-Butoxycarbonyl)-5-carboxy-4-(4-ethoxycarbonyl-5-methylfuran-2-yl)-2-(*p*-methoxyphenyl)oxazolidine (29):[20] To a solution of alcohol **27** (260 mg, 0.56 mmol) in CH_2Cl_2 (9 mL) was added Dess Martin periodinane (367 mg, 0.84 mmol), and the reaction mixture was stirred for 1.5 h at room temperature. The mixture was diluted with CH_2Cl_2 (60 mL), and a saturated aqueous solution of $NaHCO_3$ and $Na_2S_2O_3{\cdot}5H_2O$ was added; the mixture was stirred for 5 min. The organic phase was separated, washed with a saturated aqueous solution of $NaHCO_3$ and brine, and dried with Na_2SO_4, and the solvents were evaporated to dryness. The resulting residue was dissolved in *t*BuOH (8 mL), and then 2-methyl-2-butene (0.4 mL) and an aqueous solution (4 mL) of $NaClO_2$ (640 mg, 5.64 mmol) and NaH_2PO_4 (880 mg, 5.64 mmol) were added. The reaction mixture was stirred for 2 h at room temperature. The residue was diluted with AcOEt and washed with water. The organic phase was dried with Na_2SO_4, filtered, and concentrated. The resulting residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 15:1) to give acid **29** (254 mg, 95%, 1.2:1 mixture of diastereoisomers) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$,

25 °C, mixture of diastereoisomers a and b): δ =7.40 [d, J = 8.6, 2 H, Ar-H (b)], 7.36 [d, J = 8.6, 2 H, Ar-H (a)], 6.91 [d, 2 H, Ar-H (a)], 6.88 [d, 2 H, Ar-H (b)], 6.66 [s, 1 H, 3′-H (a)], 6.57 [s, 1 H, 4′-H (b)], 6.34 [s, 1 H, 2-H (b)], 6.19 [s, 1 H, 2-H (a)], 5.41 [d, $J_{4,5}$ = 4.0, 1 H, 4-H (a)], 5.32 [br. s, 1 H, 4-H (b)], 4.94 [d, $J_{4,5}$ = 3.4, 1 H, 5-H (b)], 4.74 [d, 1 H, 5-H (a)], 4.32–4.24 [m, 4 H, CH_2CH_3 (a and b)], 3.81 [s, 6 H, OCH_3 (a and b)], 2.60 [s, 3 H, CH_3 (a)], 2.56 [s, 3 H, CH_3 (b)], 1.35–1.31 [m, 15 H, $(CH_3)_3C$ (b), CH_2CH_3 (a and b)], 1.16 [s, 9 H, $(CH_3)_3C$ (a)] ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C mixture of diastereoisomers a and b): δ = 171.3 (*C*OOH), 164.0 (*C*OOEt), 160.7, 160.3, 159.2, 151.7, 150.6, 149.6 [6 C, CO of Boc (a and b), C-2′ (a and b), C-5′ (a and b)], 130.4, 128.8, 128.6, 114.2, 113.7 [12 C, C-aromat. (a and b)], 114.7 [C-4′ (a, b)], 109.6 [C-3′ (b)], 109.5 [C-3′ (a)], 92.0 [C-2 (a)], 91.4 [C-2 (b)], 81.9 [$(CH_3)_3C$ (a or b)], 81.6[$(CH_3)_3C$ (a or b)], 79.2 [C-5 (a or b)], 78.4 [C-5 (a or b)], 60.3 [2 C, CH_2CH_3 (a and b)], 57.4 [C-4 (a)], 57.2 [C-4 (b)], 55.5 [2 C, OCH_3 (a and b)], 28.4 [$(CH_3)_3C$ (b)], 28.0 [$(CH_3)_3C$ (a)], 14.5 [2 C, CH_2CH_3 (a and b)], 14.0 [2 C, CH_3 (a and b)] ppm. MS (CI): m/z = 476.1941 $[M + H]^+$.

(4*R*,5*R*)-*N*-(*tert*-Butoxycarbonyl)-5-carboxy-2-(*p*-methoxyphenyl)-4-(4-*p*-methoxytrityloxymethyl-5-methylfuran-2-yl)oxazolidine (30):[20] To a solution of alcohol **28** (280 mg, 0.41 mmol) in CH_2Cl_2 (5 mL) was added Dess Martin periodinane (259 mg, 0.61 mmol), and the reaction mixture was stirred for 2 h at room temperature. The mixture was diluted with CH_2Cl_2 (40 mL), a saturated aqueous solution of $NaHCO_3$ and $Na_2S_2O_3{\cdot}5H_2O$ was added; the mixture was stirred for 5 min. The organic phase was separated, washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried with Na_2SO_4, and concentrated. The resulting residue was dissolved in *tert*-butyl alcohol (6 mL) and 2-methyl-2-butene (0.3 mL) was added, followed by an aqueous solution (3 mL) of $NaClO_2$ (369 mg, 4.0 mmol) and NaH_2PO_4 (554 mg, 4.0 mmol). The reaction mixture was stirred for 2 h at room temperature. The residue was diluted with AcOEt and washed with water. The organic phase was dried with Na_2SO_4, filtered, and concentrated. The resulting residue was purified by flash chromatography (CH_2Cl_2/MeOH, 50:1→10:1, 1% of Et_3N) to give the triethylammonium salt of acid **30** (225 mg, 70%, 4:1 mixture of diastereoisomers) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$, 25 °C, major diastereoisomer): δ = 7.47–6.79 (m, 18 H, H-aromat.), 6.32 (s, 1 H, H-3′), 6.27 (s, 1 H, H-2), 5.32 (br. s, 1 H, H-5), 4.85 (d, $J_{4,5}$ = 2.9, 1 H, H-4), 3.83 (s, 2 H, $CH_2OTrOMe$), 3.76, 3.69 (2 s, 3 H each, MeOTr, MeOPh), 3.06 [q, J = 7.3, 6 H, $HN(CH_2CH_3)_3$], 2.09 (s, 3 H, CH_3 of furan), 2.02 [s, 9 H, $(CH_3)_3C$], 1.23 [t, 9 H, $HN(CH_2CH_3)_3$] ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C, major diastereoisomer): δ = 174.9 (COO), 159.7, 158.5, 153.4, 150.9, 148.2, 144.7, 136.0, 131.7, 130.3, 129.1, 128.5, 127.8, 127.7, 126.8, 117.5, 113.4, 113.2, 113.1 (27 C, C-aromat. of MeOTr and MeOPh, C-2′, C-4′, C-5′), 109.6 (C-3′), 90.5 (C-2), 86.4 [$(CH_3)C$], 80.5, 80.2 (mixture of rotamers, C-4), 58.0 (C-5), 57.9 ($CH_2OTrOMe$), 55.2, 55.1 (CH_3OPh, CH_3OTr), 45.3 [$N(CH_2CH_3)_3$] 28.3 [$(CH_3)_3C$], 11.9 (CH_3 of furan), 8.6 [$N(CH_2CH_3)_3$] ppm. MS (FAB): m/z = 750 $[M - Et_3NH + 2Na]^+$, 728.2859 $[M - Et_3N + Na]^+$.

Supporting Information (see footnote on the first page of this article): NMR spectra for all new compounds.

Acknowledgments

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[18] Alternatively, compound **24** could be obtained from **22** without purification of intermediates **22** and **23** in 45% overall yield.

[19] The mixture of diastereoisomeric oxazolidines could not be separated either by crystallization or flash chromatography.

[20] The nomenclature used for compounds **27**–**30** is different to the rest of the compounds due to the presence of the oxazolidine ring and do not correspond with that normally employed for (2*R*,3*R*)-3-arylisoserines.

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