Stereoselective Synthesis of Chiral Furan Amino Acid Analogues of D- and L-Serine from D-Sugars

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Abstract: The synthesis of chiral furan amino acid analogues of D- and L-serine is reported. The developed methodology starting from D-xylose affords the corresponding amino acid derivative analogue of D-serine enantiomerically pure. Starting from D-arabinose, the corresponding analogue of L-serine was isolated in 92.3% enantiomeric purity. The analogue of D-serine was transformed into a stable Fmoc activated derivative ready to be incorporated into peptides.

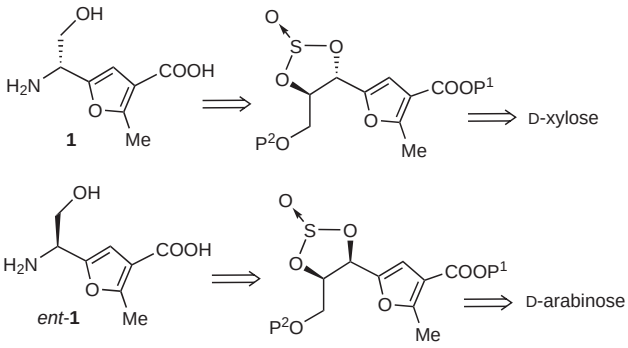
Key words: furan amino acids, cyclic sulfites, serine analogues, polyhydroxyalkyl furans, α-furfuryl amines

The rational design of new peptide-based drugs requires compounds with improved stability towards proteolytic cleavage on physiological systems, and a lessening of the peptide's intrinsic flexibility in order to obtain the effective conformation required for receptor binding. These requirements have been achieved by insertion of rigid non-peptide moieties into the appropriate site of the peptide backbone. This is a common approach to restrict the conformational degrees of freedom or stabilization of secondary structures that favors the binding to receptors.[1] In this context, many structurally rigid amino acids have been designed. Among them, heteroaromatic amino acids have recently attracted much attention,[2] and have been assembled into peptidomimetics for the purpose of drug discovery.[3]

As part of our continuing interest in the synthesis and biological applications of chiral furan amino acids,[4] we present the synthesis of constrained analogues of D- and L-serine (**1** and *ent*-**1**, Scheme 1) as novel scaffolds for the synthesis of non-proteinogenic peptides. Given that complex biochemical processes involve molecular recognition based not only on polar but also on hydrophobic interactions, the structure of our targets is of interest because they contain an alkyl furan moiety which increases the rigidity and hydrophobicity.[5] In addition, constrained serine analogues incorporated into peptides have been reported to clarify the conformational role of the hydroxymethyl group[6] and several serine analogues have been reported with this goal.[7]

The stereoselective introduction of an amino function into the α-position of a furan moiety has been widely studied[8] due to their interest as building blocks for the synthesis of azasugar derivatives[9] such as piperidine alkaloids, indolizidines and quinolizidines through the aza-Achmatowicz rearrangement.[10]

Here we report a novel stereoselective route for the synthesis of α-furfuryl amines and their transformation into D- and L-serine analogues. This methodology implies a nucleophilic displacement by azido anions on the intermediate sulfites that were obtained starting from D-xylose and D-arabinose, respectively (Scheme 1). Additionally, our target compounds are analogues of β-hydroxy-α-amino acids, which are constituents of many biologically active natural products and medicinally important compounds.[11]



Scheme 1

Thus, the reaction of D-xylose and D-arabinose with benzyl acetoacetate in the presence of $ZnCl_2$ as catalyst[12] afforded trihydroxypropyl furans **2** and **3**, respectively, in moderate to good yield (Scheme 2). The trihydroxypropyl derivatives were obtained with good stereoselectivities which implies almost no epimerization at C-1′ of the polyolic chain (*S*/*R* = 36 for **2** and *R*/*S* = 19 for **3**). Recently, it has been reported that the reaction of aldopentoses and other sugars including disaccharides with β-dicarbonyl compounds can be performed using $CeCl_3$ as catalyst.[13] In our hands, the condensation of D-xylose and D-arabinose with benzyl acetoacetate and $CeCl_3$ (25%), provoked the total epimerization at C-1′ after six hours of reaction, which is in contradiction with the results reported in the literature.[13]

Regioselective protection of the primary alcohol function in **2** afforded silyl derivative **4** after separation of the minor epimer by flash chromatography (Scheme 3). For the introduction of an azide function at C-1′ of the polyolic

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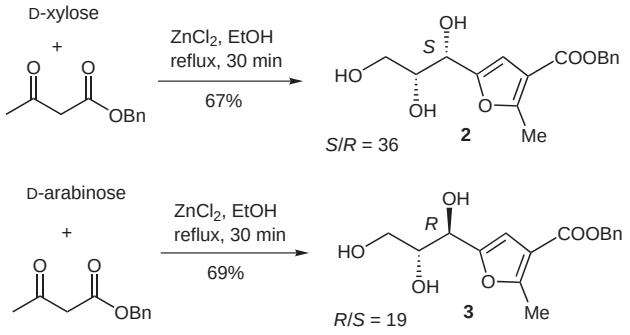


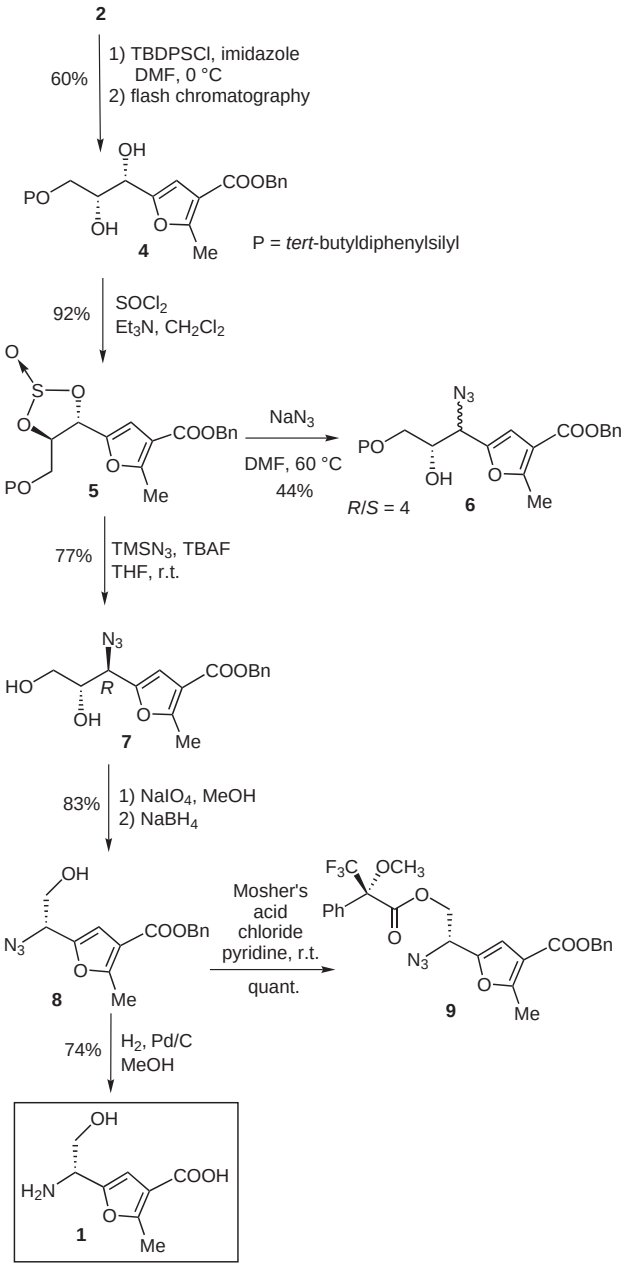
Scheme 2

chain of a tetrahydroxybutylfuran derivative, we have recently reported[14] on the regioselective chlorination at C-1′ followed by nucleophilic displacement with an azido anion. However, this procedure is poorly stereoselective giving a mixture of epimers at C-1′ in a 2:1 ratio.

We present in this letter a methodology that improves this functionalization in order to obtain α-furfuryl amino derivatives with high stereoselectivity and good yield. Reaction of **4** with thionyl chloride and triethylamine afforded the stable cyclic sulfite **5** in 92% yield, which could be even purified by column chromatography. Although nucleophilic displacements are commonly performed on key sulfate intermediates, the activated benzylic position C-1′ in sulfite **5** is thought to be reactive enough for nucleophilic ring-opening. Treatment of **5** with NaN_3/DMF at 60 °C gave a mixture of azido derivatives **6**,[15,16] epimers at C-1′, in a ratio *R*/*S* = 4, indicating that S_N2 and S_N1-like mechanisms participated in the displacement. In order to avoid epimerization, we decided to use the mixture $TMSN_3$/TBAF with increased nucleophilicity and solubility of the azide anion in organic solvents. Thus, the reaction of **5** with $TMSN_3$/TBAF in THF at room temperature gave the azido derivative **7**[17] as unique compound in 77% yield with the concomitant removal of the silyl protecting group. This fact indicates that the reaction occurred through an S_N2 mechanism allowing the total stereoselective introduction of the azide function. Oxidative cleavage of diol **7** followed by reduction of the aldehyde function with $NaBH_4$ afforded alcohol **8** in 83% overall yield. In order to confirm that no epimerization at C-1′ occurred in the reduction, Mosher's ester of compound **8** was prepared. ^{1}H NMR and ^{13}C NMR experiments showed that only diastereomer **9**[18] was present and no signals for the epimerized derivative could be found. Finally, hydrogenation of **8** using Pd/C (10%) as catalyst afforded the furan amino acid **1** in good yield.

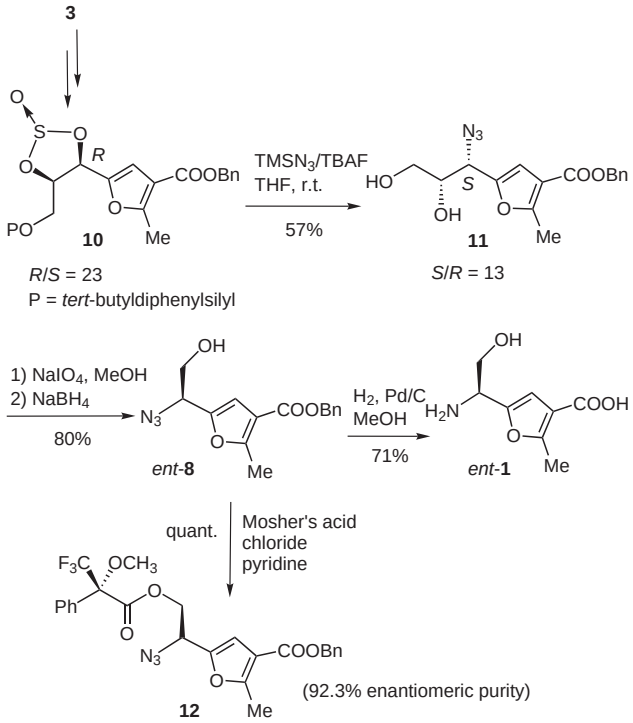
In a similar way, the synthesis of *ent*-**1** was carried out starting from trihydroxypropyl furan **3** (C-1′, *R*/*S* = 19) that was obtained from D-arabinose in 69% yield (Scheme 4).

tert-Butyldiphenylsilyl protection followed by sulfite formation afforded **10** (C-1′, *R*/*S* = 23) after purification by column chromatography (Scheme 4). Displacement reaction of **10** using the mixture $TMSN_3$/TBAF in THF at

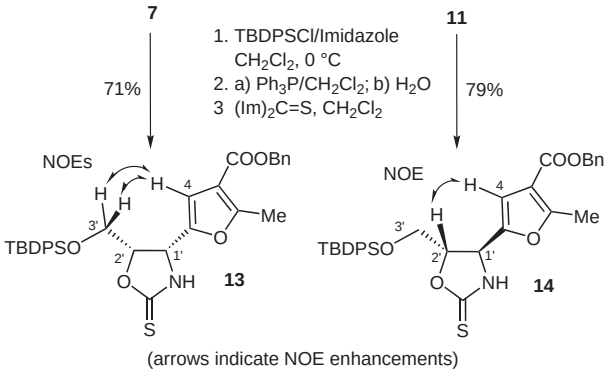


Scheme 3

room temperature gave the azido derivative **11** (57% after 48 h of reaction). The displacement–deprotection step for compound **10** proved to be slower than for its epimer **5**. Besides, partial epimerization was detected (ratio on C-1′, *S*/*R* = 13 = **11**/**7** measured by ^{1}H NMR in the crude mixture) which is presumably due to the participation of an S_N1-like mechanism. Attempts to improve the stereoselectivity of the displacement using DMF as solvent or lower temperatures were not successful. Oxidative cleavage of **11** followed by reduction with $NaBH_4$ afforded alcohol *ent*-**8**, that was reduced to give the amino acid derivative *ent*-**1** in good-to-moderate yield (Scheme 4). The enantiomeric purity (92.3%) of *ent*-**8** was determined by formation of the corresponding Mosher's ester.



Scheme 4

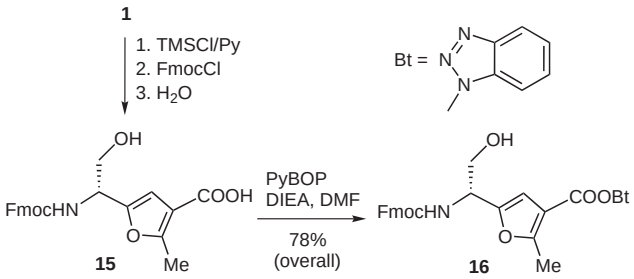


Scheme 5

The absolute configuration of C-1′ in **1** and *ent*-**1** was confirmed in the corresponding precursors **7** and **11** by transformation into their corresponding oxazolidine-2-thione derivatives **13** and **14** (Scheme 5). Appropriate NOEs confirmed the proposed structures.

Amino acid derivative **1** is a suitable scaffold for its incorporation into peptides through the Fmoc solid-phase methodology. For this purpose, Fmoc derivative **15** was prepared starting from **1** following Koole's methodology[19] (Scheme 6). Moreover, reaction of **15** with PyBOP/DIEA afforded the activated ester **16**[20] that could be isolated by chromatography column.

In summary, the synthesis of new chiral furan amino acid analogues of D- and L-serine is described starting from D-aldopentoses. In the case of the D-serine analogue **1** the method proved to be very efficient as the final product was obtained enantiomerically pure. For the L-serine analogue *ent*-**1**, the method provides the target compound with 92.3% of enantiomeric purity. Compound **1** was easily transformed into the corresponding Fmoc-activated derivative ready to be incorporated into a peptide or peptidomimetic following the Fmoc strategy for solid-phase peptide synthesis. Due to the aromatic character of the furan-3-carboxylic acid, compound **16** is stable which makes it an attractive building block for solid phase peptide synthesis as compared to most OBt esters[21] of Fmoc-amino acids which are not stable enough and need to be generated in situ. Work is in progress to prepare peptidomimetics with conformational bias by solid phase synthesis using the new scaffold, and to extend this methodology to other constrained hetaryl amino acids.



Scheme 6

Acknowledgment

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References and Notes

(1) (a) Recent Advances in Peptidomimetics; *Tetrahedron Symposia-in-Print*, No. 83; Aubé, J., Ed.; *Tetrahedron*; **2000**, 56, 50. (b) Robinson, J. A. *Synlett* **2000**, 429. (c) Smith, A. B. III; Favor, D. A.; Sprengeler, P. A.; Guzman, M. C.; Carrol, P. J.; Furst, G. T.; Hirschmann, R. *Bioorg. Med. Chem.* **1999**, *7*, 9. (d) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789. (e) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244. (f) Kinshenbaum, K.; Zuckerman, R. N.; Dill, K. A. *Curr. Opin. Struct. Biol.* **1999**, *9*, 530. (g) Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173.

(2) (a) Singh, R. K.; Sinha, N.; Jain, S.; Salman, M.; Nazqui, F.; Anand, N. *Tetrahedron* **2005**, *61*, 8868. (b) You, S.-L.; Razavi, H.; Kelly, J. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 83. (c) You, S.-L.; Kelly, J. W. *J. Org. Chem.* **2003**, *68*, 9506. (d) You, S.-L.; Kelly, J. W. *Chem. Eur. J.* **2004**, *10*, 71. (e) Davidson, B. S. *Chem. Rev.* **1993**, *93*, 1771. (f) Wipf, P. *Chem. Rev.* **1993**, *95*, 2115. (g) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165.

(3) (a) Bertran, A.; Pattendem, G. *Heterocycles* **2002**, *58*, 521. (b) Wang, W.; Nan, F. *J. Org. Chem.* **2003**, *68*, 1636. (c) You, S.-L. i.; Deechongkit, S.; Kelly, J. W. *Org. Lett.* **2004**, *6*, 2627. (d) Pattenden, G.; Thompson, T. *Tetrahedron Lett.* **2002**, *43*, 2459. (e) Deeley, J.; Pattenden, G. *Chem. Commun.* **2005**, 797.

(4) (a) Moreno-Vargas, A. J.; Fernández-Bolaños, J. G.; Fuentes, J.; Robina, I. *Tetrahedron Lett.* **2001**, *42*, 1283. (b) Moreno-Vargas, A. J.; Jiménez-Barbero, J.; Robina, I. *J. Org. Chem.* **2003**, *68*, 4138.
(5) (a) Silverman, D. N.; Lindskog, S. *Acc. Chem. Res.* **1988**, *21*, 30. (b) Greener, B.; Rose, J. *Chem. Commun.* **1999**, 2361. (c) Lehn, J. M. *Supramolecular Chemistry: Concepts and Perspectives*; VCH: Weinheim, **1995**.
(6) Cleland, W. W.; Kreevoy, M. M. *Science* **1994**, *264*, 1887.
(7) (a) Clerici, F.; Gelmi, M. L.; Gambini, A. *J. Org. Chem.* **1999**, *64*, 5764. (b) Clerici, F.; Gelmi, M. L.; Gambini, A. *J. Org. Chem.* **2000**, *65*, 6138. (c) Clerici, F.; Gelmi, M. L.; Gambini, A.; Nava, D. *Tetrahedron* **2001**, *57*, 6429. (d) Avenoza, A.; Busto, J. H.; Canal, N.; Peregrina, J. M. *J. Org. Chem.* **2005**, *70*, 330. (e) Avenoza, A.; Busto, J. H.; Canal, N.; Peregrina, J. M.; Pérez-Fernández, M. *Org. Lett.* **2005**, *7*, 3597.
(8) (a) Sun, X.-L.; Kai, T.; Takayanagi, H.; Furuhata, K. *Synlett* **1999**, 1399. (b) Bushey, M. L.; Haukaas, M. H.; O'Doherty, G. A. *J. Org. Chem.* **1999**, *64*, 2984. (c) Saaby, S.; Bayón, P.; Aburel, P. S.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4352. (d) Miyata, O.; Iba, R.; Hashimoto, J.; Naito, T. *Org. Biomol. Chem.* **2003**, *1*, 772.
(9) For a review on α-furfuryl amine derivatives, see: Zhou, W.-S.; Lu, Z.-H.; Xu, Y.-M.; Liao, L.-X.; Wang, Z.-M. *Tetrahedron* **1999**, *55*, 11959.
(10) (a) Ciufolini, M. A.; Wood, C. W. *Tetrahedron Lett.* **1986**, *27*, 5085. (b) Ciufolini, M. A.; Hermann, C. Y. W.; Dong, Q.; Shimizu, T.; Swaminathan, S.; Xi, N. *Synlett* **1998**, 105.
(11) (a) McMillan, J. B.; Molinski, T. F. *Org. Lett.* **2002**, *4*, 1883. (b) Willis, M. C.; Cutting, G. A.; Piccio, V. J.-D.; Durbin, M. J.; John, M. P. *Angew. Chem. Int. Ed.* **2005**, *44*, 1543. (c) *Amino Acids, Peptides and Proteins*, Vol.1-28; Special Periodical Reports, Chemistry Society: London, **1968-1995**.
(12) For similar condensations between aldohexoses and ketohexoses with β-dicarbonyl compounds see: García-González, F. *Adv. Carbohydr. Chem.* **1956**, *11*, 97.
(13) Misra, A. K.; Agnihotri, G. *Carbohydr. Res.* **2004**, *339*, 1381.
(14) (a) Moreno-Vargas, A. J.; Robina, I.; Demange, R.; Vogel, P. *Helv. Chim. Acta* **2003**, *86*, 1894. (b) Robina, I.; Moreno-Vargas, A. J.; Fernández-Bolaños, J. G.; Fuentes, J.; Demange, R.; Vogel, P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2555.
(15) (a) For the same reaction on a similar but unstable cyclic sulfite giving only one diasteroisomer, see ref. 8d. (b) Seki, M.; Mori, K. *Eur. J. Org. Chem.* **1999**, 2965.
(16) For reviews on cyclic sulfite reactivity, see: (a) Lohray, B. B. *Synthesis* **1992**, 1035. (b) Byun, H.-S.; He, L.; Bittman, R. *Tetrahedron* **2000**, *56*, 7051.
(17) Selected data for compound **7**: $[\alpha]_D^{20}$ +99 (*c* 0.98, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 7.40–7.28 (m, 5 H, H-arom.), 6.75 (s, 1 H, H-4), 5.29 (s, 2 H, CH_2Ph), 4.56 (d, 1 H, $J_{1',2'}$ = 7.3 Hz, H-1′), 4.02 (m, 1 H, H-2′), 3.76 (dd, 1 H, $J_{3'a,3'b}$ = 11.5 Hz, $J_{3'a,2'}$ = 3.4 Hz, H-3′a), 3.72 (dd, 1 H, $J_{3'b,2'}$ = 5.2 Hz, H-3′b), 2.60 (s, 3 H, CH_3) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 298 K): δ = 163.5 (CO), 160.4, 147.5 (C-2, C-5), 135.9, 128.6, 128.3, 128.2 (6 C-arom.), 114.2 (C-3), 110.9 (C-4), 71.9 (C-2′), 66.2 (CH_2Ph), 62.9 (C-3′), 59.9 (C-1′), 14.3 (CH_3) ppm. HRMS (CI): *m/z* calcd for $C_{16}H_{18}N_3O_5 + H^+$: 332.1246; found: 332.1236.
(18) Selected data for compound **9**: $[\alpha]_D^{20}$ +25 (*c* 2.62, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 7.42–7.36 (m, 10 H, H-arom.), 6.67 (s, 1 H, H-4), 5.30 (s, 2 H, CH_2Ph), 4.75 (t, 1 H, $J_{1',2'a} = J_{1',2'b}$ = 6.5 Hz, H-1′), 4.56 (d, 2 H, H-2′a and H-2′b), 3.55 (q, 3 H, $J_{CH,F}$ = 1.2 Hz, CH_3O), 2.58 (s, 3 H, CH_3) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 298 K): δ = 166.2 (CO), 163.1 (CO), 160.5, 146.0 (C-2, C-5), 131.8–127.2 (12 C, C-arom.), 123.1 (q, 1 C, $^1J_{C,F}$ = 288, CF_3), 114.2 (C-3), 110.5 (C-4), 84.7 [q, 1 C, $^2J_{C,F}$ = 28.2 Hz, (*C*(OMe)(CF_3)Ph], 66.2 (CH_2Ph), 65.0 (C-2′), 56.5 (C-1′), 55.5 (OCH_3), 13.9 (CH_3) ppm.
(19) Koole, L. H.; Moody, H. M.; Broeders, N. L. H. L.; Quaedflieg, P. J. L. M.; Kuijpers, W. H. A.; van Genderen, M. H. P.; Coenen, A. J. J. M.; van der Wal, S.; Buck, H. M. *J. Org. Chem.* **1989**, *54*, 1657.
(20) **Experimental Procedure for the Preparation of Fmoc-Activated Amino Acid Derivative 16 from 1.** To a stirred mixture of **1** (26 mg, 0.138 mmol) in dry pyridine (2 mL) at 0 °C, TMSCl (54 μL, 0.414 mmol) was dropped and the reaction mixture stirred for 45 min at r.t. Then the reaction mixture was cooled to 0 °C, 9-fluorenylmethoxycarbonyl chloride (46 mg, 0.18 mmol) was added and the mixture stirred for 1.5 h at r.t. Afterwards, H_2O (0.1 mL) was added, the mixture stirred for 1 h at r.t., and then evaporated to give **15** that was used in the next step without any purification. Crude **15** was dissolved in DMF, then DIEA (53 μL, 0.3 mmol) and PyBOP (88 mg, 0.168 mmol) were added. The mixture was stirred for 1 h at r.t., then the solution was evaporated in vacuo. The resulting residue was purified by column chromatography (EtOAc–PE, 1:1) to give **16** (57 mg, 0.108 mmol, 78%) as a white solid. $[\alpha]_D^{20}$ +38 (*c* 0.84, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 7.57–7.27 (m, 12 H, H-arom.), 6.74 (s, 1 H, H-4), 5.56 (d, 1 H, $J_{NH,1'}$ = 7.5 Hz, N*H*Fmoc) 4.90 (br s, 1 H, H-1′), 4.51 (d, 2 H, *J* = 6.5 Hz, CH_2 of Fmoc), 4.22 (t, 1 H, CH of Fmoc), 3.94 (br m, 2 H, H-2′a and H-2′b), 2.62 (CH_3) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$, 298 K): δ = 163.4 (CO), 159.5 (C-2), 156.1 (CO of Fmoc), 152.3 (C-5), 143.7, 143.4, 141.4, 128.8, 127.8, 127.1, 124.9, 120.4, 120.0, 107.3 (18 C, C-arom.), 108.8 (C-3), 108.4 (C-4), 67.0 (CH_2 of Fmoc), 63.3 (C-2′), 50.9 (C-1′), 47.2 (CH of Fmoc), 14.2 (CH_3).
(21) The OBt esters of protected amino acids are not isolable and must be generated in situ. Only less reactive OPfp esters are commercially available, see: Novabiochem,® 2004/5 catalogue.