Synthesis of Dianhydrohexitole-based Benzamidines as Factor Xa Inhibitors Using Cross Couplings, Phenyl Ether and Amidine Formations as Key Steps

Marko Vogler,[a] Ulrich Koert,*[a] Dieter Dorsch,[b] Johannes Gleitz,[b] Peter Raddatz[b]

[a] Fachbereich Chemie, Philipps-Universität Marburg, Hans-Meerwein-Straße, 35043 Marburg, Germany

[b] Merck KgaA, Preclinical Research & Development, 64271 Darmstadt, Germany
Fax +49(6421)2825677; E-mail: koert@chemie.uni-marburg.de

Received 23 June 2003

Abstract: Starting with isosorbide or isomannide several dianhydrohexitole-based benzamidines were synthesized as potential factor Xa inhibitors. The key steps for the synthesis of the bisbenzamidines were nucleophilic aromatic substitutions and Mitsunobu reactions to build up phenylethers. Another type of monobenzamidines had *ortho*-substituted biphenyl groups. Their synthesis necessitated an optimization of cross coupling procedures due to the great sterical hindrance of the *ortho*-substituent. The benzamidines showed biological activity against factor Xa and selectivity against other serine proteases.

Key words: isosorbide, dianhydrohexitoles, amidines, Negishi reaction, factor Xa inhibitors

The serine protease factor Xa (fXa) plays a decisive role in the blood coagulation cascade.[1] Thus, it has emerged as a very attractive target to develop orally active antithrombotic agents.[2] Highly potent and specific inhibitors of fXa can effectively block both venous and arterial thrombosis formation.

We intended to use the dianhydrohexitoles isosorbide **1** (one *exo*-OH, one *endo*-OH, Figure 1) and isomannide **2** (two *endo*-OH) as molecular scaffolds linking two specific ligands for the S1 and S4 pockets of the fXa active site. **1** and **2** were already explored as successful templates for RGD-mimetics[3] in the development of integrin antagonists. They have the advantage of combining high rigidity with stereochemical bias.

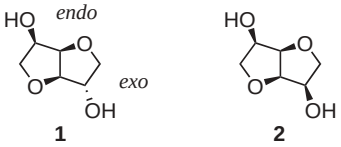


Figure 1

Here we present a novel synthetic approach to the phenylether benzamidines **3**–**6** with the isosorbide scaffold (Figure 2) and evaluate their potential as fXa inhibitors.

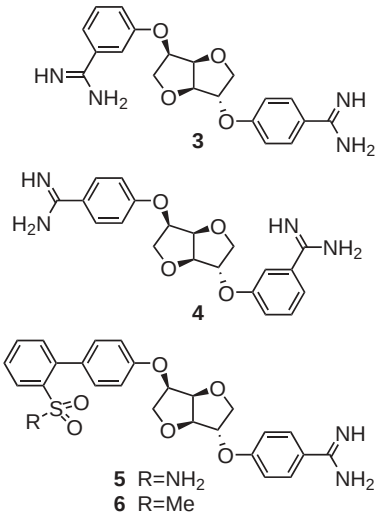
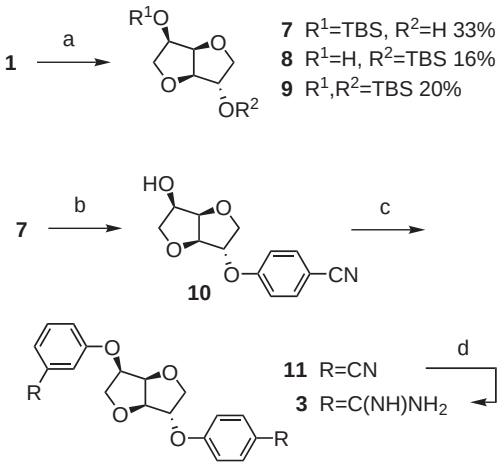


Figure 2



Scheme 1 a) TBS-Cl, Im, DMF, 40 °C, 3 h, **7** 33%, **8** 16%, **9** 20%. b) NaH, 4-FC_6H_4CN, DMF; TBAF, THF, 23 %. c) NaH, 3-FC_6H_4CN, DMF, 98%. d) LiHMDS, THF; HCl, EtOH/H_2O; prep. HPLC, 23%.

The synthesis of **3** started with TBS-protection of isosorbide **1** (Scheme 1). Using the standard conditions (TBS-Cl, imidazole, DMF) both monoprotected isomers **7** (33%) and **8** (16%) as well as diprotected **9** (20%) were obtained besides 31% unreacted starting material. The structures of **7** and **8** could be assigned by NMR analysis

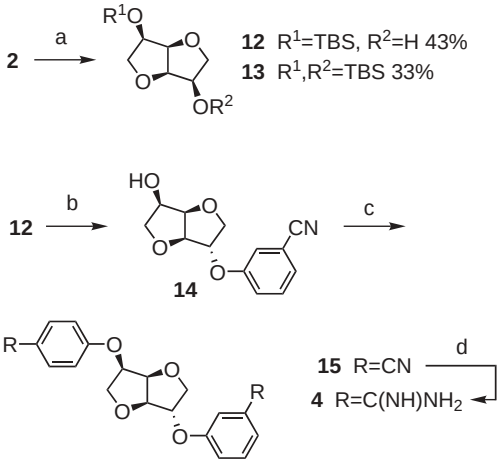
Synlett 2003, No. 11, Print: 02 09 2003. Web: 25 08 2003.
Art Id.1437-2096,E;2003,0,11,1683,1687,ftx,en;G14703ST.pdf.
DOI: 10.1055/s-2003-41426

and IR spectroscopy. Due to the intramolecular hydrogen bond of the *endo*-OH group with the ether oxygens, **8** shows a lower hydroxy IR absorption than **7** (diluted solution in CCl_4):[4] 3625 cm^{-1} for the *exo*-OH in **7**, but 3553 cm^{-1} for *endo*-OH in **8**. A comparing look at the NMR spectra of **1**, **2**, **7** and **8** in DMSO-d_6 reveals that the protons of *exo* hydroxy functions in dianhydrohexitoles are shifted down-field compared to the *endo* ones. Together with a precise analysis of the coupling constants[5] this NMR assignment is consistent with the IR data.

The *exo*-alcohol **7** was then converted to the phenylether **10** by nucleophilic substitution with 4-fluorobenzonitrile and subsequent TBAF-mediated deprotection. Unexpectedly, only 23% **10** were obtained, but 55% of 2,5-*O*,*O*-bis-(4-cyanophenyl)-isosorbide. Due to the lability of the *endo*-OTBS group in **7** under the reaction conditions of the aromatic substitution (NaH, DMF, 60 °C), silyl cleavage occurred already at this stage resulting in the formation of **10**. A nucleophilic aromatic substitution of alcohol **10** with 3-fluorobenzonitrile gave the bisnitrile (98%). Finally, the reaction of **11** in an one-pot procedure with LiHMDS[6,7] and a subsequent hydrolysis using ethanolic HCl led to the target bisamidine **3**. After purification by preparative HPLC (CH_3CN/H_2O + 0.1% TFA) and lyophilization **3** could be isolated as bisamidinium-trifluoroacetic salt.[7]

The synthesis of bisamidine **4** was accomplished as depicted in Scheme 2. First, one hydroxy function of isomannide **2** was TBS-protected to the monosilylether **12** (43% yield).[8] Since the *endo*-hydroxy group in isomannide **2** is intramolecularly hydrogen bound to the ether oxygens, the alcohol-alcoholate reactivity difference is low in this case. The free *endo*-OH in **12** was then inverted to the *exo*-phenylether by a Mitsunobu reaction with 3-hydroxybenzonitrile. After TBAF-mediated silyl ether cleavage isosorbide-based **14** was isolated in 79% yield. A detailed analysis of the NMR coupling constants[5] of **14** proved the inversion of the stereocenter. After nucleophilic aromatic substitution of **14** with 4-fluorobenzonitrile to the bisnitrile **15** (93%), a subsequent bisamidine formation led to the target compound **4**.

Since the in vitro data of the bisamidines **3** and **4** showed high potency against fXa, we intended to optimize the new dianhydrohexitole lead structure with regard to better pharmacokinetic properties. Thus, one benzamidine moiety was replaced by a less basic, more lipophilic *ortho*-SO_2NH_2-substituted biphenyl group (**5** and **6**, Figure 2).[9] The synthesis of **5** started with the monobenzylation of **2** to mono-benzyl-isomannide **16**, which was allowed to react with 4-fluoronitrobenzene to **17** in 95% yield. After reduction of the nitro group to an amine, the transformation into an aryl bromide or iodide was envisaged. Sandmeyer conditions with catalytic[10,11] or stochiometric[12] amounts of copper salts were unsatisfying (maximum 39% for the bromide and 64% for the iodide). Alternatively, we tried a new procedure[13] with KI, KNO_2 and HBr in DMSO. This gave reliably high yields of the iodide **18** of 80%. In the next step, **18** had to be cross-coupled to the biphenyl



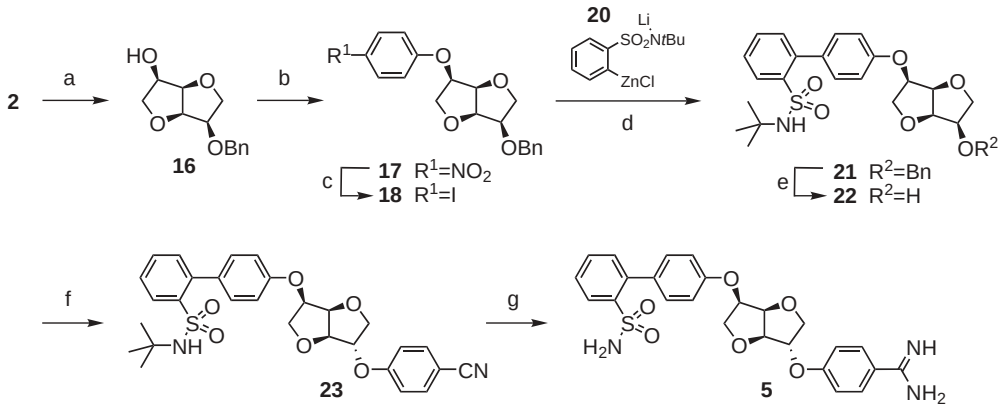
Scheme 2 a) TBS-Cl, Im, DMF, **12** 43%, **13** 33%. b) 3-HOC_6H_4CN, DEAD, PPh_3, THF; TBAF, THF, 79%. c) NaH, 4-FC_6H_4CN, DMF, **15** 93%. d) LiHMDS, THF; HCl, $EtOH/H_2O$, 48%.

compound **21**. A Suzuki protocol using standard conditions [$Pd(PPh_3)_4$, PhMe, aq. Na_2CO_3, reflux] with 2-(*tert*-butylaminosulfonyl)-phenylboronic acid (**19**) to build up the biphenyl moiety is described in the literature,[9a] but due to the great steric hindrance of the *ortho*-SO_2NH*t*Bu-substituent the yield was only 58%. We tried several Suzuki procedures[14] to optimize this coupling step. But none of these methods gave satisfying yields (maximum 44%). As a consequence we examined Negishi conditions[15] [$Pd_2(dba)_3$, PPh_3, LiCl, THF reflux] using the corresponding aryl zinc intermediate **20** (from $PhSO_2NH$*t*-Bu by *ortho*-lithiation and transmetallation). This worked well and produced the coupling product **21** in 83% yield. Hydrogenolysis of the benzylether provided the alcohol **22**.

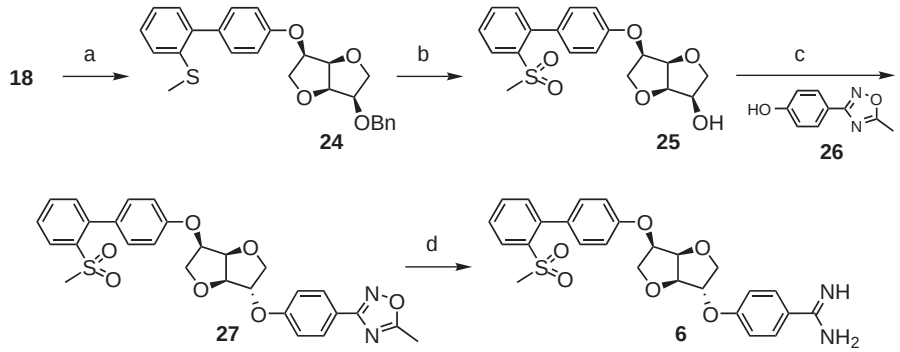
The synthesis of **5** continued with a Mitsunobu inversion using 3-hydroxybenzonitrile to yield the phenylether **23** (Scheme 3). For the conversion of the cyano function into an amidine group, a two-step procedure via amide oximes was most successful.[16] First, the benzonitrile was transformed via the amide oxime followed by acetylation and a heterogenous hydrogenation with palladium on charcoal or Raney-nickel[17] into the desired benzamidine. Finally, the *tert*-butyl protecting group was cleaved from the sulfone amide by treatment with a 10:1 mixture of TFA/anisole to produce **5**.[16b]

The synthesis of the sulfone **6** is summarized in Scheme 4. Suzuki coupling of commercially available 2-(methylthio)benzeneboronic acid with iodide **18** gave thioether **24** with 70% yield.[14e] Magnesium monoperoxo phthalate oxidation[18] to the sulfone and hydrogenolytic benzyl ether cleavage gave the alcohol **25** (86% for both steps). The Mitsunobu reaction using the oxadiazolylphenol **26**[19] led to an isosorbide-based precursor **27**, which could be converted to the amidine **6** by hydrogenolysis (96%).

The biological screening of the dianhydrosugar-based amidines **3**–**6** began with the potency determination against factor Xa. Subsequently, the activity against



Scheme 3 a) NaH, DMF, TBAI (cat.), BnBr, 48%. b) NaH, DMF, 4-$FC_6H_4NO_2$, 95%. c) H_2, MeOH/THF, Pd/C 100%; KI, KNO_2, DMSO, HBr, 81%. d) $PhSO_2NHtBu$, *n*-BuLi, THF; $ZnCl_2$; LiCl, $Pd_2(dba)_3$, PPh_3, 83%. e) H_2, $Pd(OH)_2$/C, THF/MeOH, 100%. f) DIAD, PPh_3, 4-HOC_6H_4CN, THF, 46%. g) $NH_2OH{\cdot}HCl$, Na_2CO_3, THF/EtOH/H_2O; MeOH/HOAc, Ac_2O; H_2, Pd/C; TFA, PhOMe, 53%.



Scheme 4 a) 2-$CH_3SC_6H_4B(OH)_2$, $Pd_2(dba)_3$, PPh_3, $Ba(OH)_2$, DME/H_2O, 70%. b) MMPP, CH_2Cl_2/EtOH/H_2O; H_2, $Pd(OH)_2$/C, MeOH/EtOAc, 86%. c) DIAD, PPh_3, THF, 92%. d) H_2, Pd/C, MeOH/HOAc, 96%.

thrombin, trypsin and plasmin were measured in order to get informations about the general specifity for serine proteases. The in vitro data were measured as IC_{50} values (Table 1).

Table 1 Biological Activity of the Dianhydrosugar-based Benzamidines **3**–**6** Against fXa, Thrombin, Trypsin and Plasmin

	IC_{50}/mM			
Compd.	**fXa**	Thrombin	Trypsin	Plasmin
3	**0.18**	>10	6.3	>10
4	**0.15**	>10	8.0	>10
5	**1.0**	>10	>10	>10
6	**1.3**	>10	>10	>10

The biological activities of the isosorbide-based bisamidines **3** and **4** with a substitution pattern 'inverse' to each other (*meta*-/*para*-benzamidine) are active against fXa and selective against thrombin and plasmin. But the trypsin-selectivity is low. Due to the favorable interactions of the biphenyl unit with the protein, the inhibitors **5** and **6** show not only high potency, but a better selectivity against trypsin. The reason might be, that the structural differences between the fXa and trypsin active sites play a greater role in the specific interactions with the biphenyl unit compared to a benzamidine.

In summary, a novel highly active and selective lead structure for fXa inhibitors was developed with rigid but stereodefined dianhydrohexitole scaffolds. A synthetic access to the class of isosorbide-based bisbenzamidines was developed with nucleophilic aromatic substitutions of fluorobenzonitriles, Mitsunobu reactions and amidine formation with LiHMDS as key steps. The biphenyl compounds **5** and **6** were synthesized from isomannide **2**. An optimized synthetic route to the aryl halide uses Suzuki and Negishi couplings to build up the biphenyl moiety. Despite a sterically demanding *ortho*-substituent an efficient novel Negishi protocol gave the target compound in very good yield. Current work is aimed to further optimize this lead structure in terms of higher biological activity and bioavailability.

Acknowledgment

This work was supported by Merck KgaA, Darmstadt, Germany.

References

(1) Davie, E. W.; Fujikawa, K.; Kisiel, W. *Biochemistry* **1991**, *30*, 10363.
(2) (a) Rai, R.; Sprengeler, P. A.; Elrod, K. C.; Young, W. B. *Curr. Med. Chem.* **2001**, *8*, 101. (b) Samama, M. M. *Thromb. Res.* **2002**, *106*, V267. (c) Kaiser, B. *Cell. Mol. Life Sci.* **2002**, *59*, 189. (d) Leadley, R. J. Jr. *Curr. Top. Med. Chem.* **2001**, *1*, 151.
(3) Osterkamp, F.; Wehlan, H.; Koert, U.; Wiesner, M.; Raddatz, P.; Goodman, S. L. *Tetrahedron* **1999**, *55*, 10713.
(4) Brimacombe, J. S.; Foster, A. B.; Stacey, M.; Whiffen, D. H. *Tetrahedron* **1958**, *4*, 351.
(5) Hopton, F. J.; Thomas, G. H. S. *Can. J. Chem.* **1969**, *47*, 2395.
(6) Boeré, R. T.; Oakley, R. T.; Reed, R. W. *J. Orgmet. Chem.* **1987**, *331*, 161.
(7) (a) General procedure for the preparation of bisamidines **3** and **4** from bisnitriles by the LiHMDS[6] method: A oven-dried Schlenck-flask equipped with a rubber septum is charged with HMDS (2.6 mmol) in THF (3 mL) under argon atmosphere and cooled by an ice bath. After addition of *n*-BuLi (3.0 mmol, 2.5 M in hexane) and stirring for 1 h a solution of the bisnitrile (0.52 mmol) in THF (3 mL) was added. The reaction mixture turned dark red or brown. It was stirred for 24 h at room temperature and then quenched with 6 M HCl in ethanol (2 mL). After 1 h the solvents were removed in vacuo. The residue was solved in few MeOH and purified by preparative HPLC (Rainin RP18, H_2O/CH_3CN mixtures with 0.1% TFA). The bisamidine was isolated as a TFA salt by lyophilization resulting in a colorless powder. (b) Analytical data of **3** and **4**: 2-*O*-(4′-Amidinophenyl)-5-*O*-(3′′-amidinophenyl)-1,4:3,6-dianhydro-D-sorbitol trifluoroacetic acid salt (**3**): $[\alpha]_D^{20}$ = +49, $[\alpha]_{578}^{20}$ = +51, $[\alpha]_{546}^{20}$ = +58, $[\alpha]_{436}^{20}$ = +100, $[\alpha]_{365}^{20}$ = +160 (*c* 0.099, H_2O); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 3.87–4.05 (m, 4 H, 1-H_2, 6-H_2), 4.61 (d, *J* = 4.1 Hz, 1 H, 3-H), 5.02–5.13 (m, 3 H, 2-H, 4-H, 5-H), 7.19–7.44 (m, 5 H, 2′-H, 6′-H, 2′′-H, 4′′-H, 6′′-H), 7.55 (t, *J* = 7.9 Hz, 1 H, 5′′-H), 7.79 (pd, *J* = 9.0 Hz, 2 H, 3′-H, 5′-H), 8.88–9.29 [m, 8 H, 2 × $C(NH_2)_2$]. ^{13}C NMR (75 MHz, DMSO-d_6) δ = 71.2, 72.7 (C-1, C-6), 77.4, 81.1, 81.5, 86.0 (C-2, C-3, C-4, C-5), 115.1 (C-2′′), 115.4 (C-2′, C-6′), 120.1 (C-4′), 120.8, 121.1 (C-4′′, C-6′′), 129.9 (C-3′′), 130.3 (C-3′, C-5′), 130.8 (C-5′′), 156.9 (C-1′′), 162.5 (C-1′), 164.9, 165.4 [2 × *C*$(NH_2)_2$]; HRMS (FAB): *m/z* calcd 383.1719, found 383.1717 ($C_{20}H_{23}N_4O_4$, M + H^+). 2-*O*-(3′-Amidinophenyl)-5-*O*-(4′′-amidinophenyl)-1,4:3,6-dianhydro-D-sorbitol trifluoroacetic acid salt (**4**): $[\alpha]_D^{21}$ = +46, $[\alpha]_{578}^{21}$ = +49, $[\alpha]_{546}^{21}$ = +55, $[\alpha]_{436}^{21}$ = +94, $[\alpha]_{365}^{21}$ = +157 (*c* 0.267, H_2O); ^{1}H NMR (300 MHz, DMSO-d_6) δ = 3.86–4.10 (m, 4 H, 1-H_2, 6-H_2), 4.60 (d, *J* = 4.7 Hz, 1 H, 3-H), 5.00–5.15 (m, 3 H, 2-H, 4-H, 5-H), 7.18 (pd, *J* = 9.0 Hz, 2H, 2′′-H, 6′′-H), 7.34–7.45 (m, 3 H, 2′-H, 4′-H, 6′-H), 7.53 (t, *J* = 7.9 Hz, 1 H, 5′-H), 7.83 (pd, *J* = 8.9 Hz, 2 H, 3′′-H, 5′′-H), 9.00–9.35 [m, 8 H, 2 × $C(NH_2)_2$]; ^{13}C NMR (75 MHz, DMSO-d_6) δ = 70.9, 72.8 (C-1, C-6), 77.3, 80.8, 81.6, 86.0 (C-2, C-3, C-4, C-5), 114.6 (C-2′), 115.7 (C-2′′, C-6′′), 120.5, 120.7 (C-4′, C-6′), 120.6 (C-4′′), 129.6 (C-3′), 130.6 (C-3′′, C-5′′), 158.0 (C-1′), 161.1 (C-1′′), 164.9, 165.5 [2 × $C(NH_2)_2$]; HRMS (FAB): *m/z* calcd. 383.1719, found 383.1715 ($C_{20}H_{23}N_4O_4$, M + H^+).
(8) McDougal, P. G.; Rico, J. G.; Oh, Y.-I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388.
(9) (a) Quan, M. L.; Liauw, A. Y.; Ellis, C. D.; Pruitt, J. R.; Carini, D. J.; Bostrom, L. L.; Huang, P. P.; Harrison, K.; Knabb, R. M.; Thoolen, M. J.; Wong, P. C.; Wexler, R. R. *J. Med. Chem.* **1999**, *42*, 2752. (b) Quan, M. L.; Ellis, C. D.; Liauw, A. Y.; Alexander, R. S.; Knabb, R. M.; Lam, G.; Wright, M. R.; Wong, P. C.; Wexler, R. R. *J. Med. Chem.* **1999**, *42*, 2760. (c) Fevig, J. M.; Pinto, D. J.; Han, Q.; Quan, M. L.; Pruitt, J. R.; Jacobson, I. C.; Galemmo, R. A.; Wang, S. A.; Orwat, M. J.; Bostrom, L. L.; Wong, P. C.; Lam, P. Y. S.; Wexler, R. R. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 641. (d) Jia, Z. J.; Wu, Y.; Huang, W.; Goldman, E.; Zhang, P.; Woolfrey, J.; Wong, P.; Huang, B.; Sinha, U.; Park, G.; Reed, A.; Scarborough, R. M.; Zhu, B.-Y. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1651. (e) Su, T.; Wu, Y.; Doughan, B.; Jia, Z. J.; Woolfrey, J.; Huang, B.; Park, G.; Sinha, U.; Scarborough, R. M.; Zhu, B.-Y. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2947. (f) Pruitt, J. R.; Pinto, D. J.; Estrella, M. J.; Bostrom, L. L.; Knabb, R. M.; Wong, P. C.; Wright, M. R.; Wexler, R. R. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 685.
(10) Courtin, A. *Helv. Chim. Acta* **1983**, *66*, 68.
(11) Dains, F. B.; Eberly, F. *Org. Synth., Coll. Vol. II*; Wiley: New York, **1943**, 355.
(12) Doyle, M. P.; Siegfried, B.; Dellaria, J. F. *J. Org. Chem.* **1977**, *42*, 2426.
(13) Baik, W.; Kim, J. M.; Kim, Y. S.; Lee, S. W. *European Symposium on Organic Chemistry 12*; Poster presentation: Groningen Netherlands, **2001**.
(14) Coupling of boronic acid **19** using several Suzuki methods: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457; standard conditions: $PdCl_2(PPh_3)_2$, Bu_4NBr (cat.), aq. Na_2CO_3, PhMe reflux, 44%. (b) Wallow, T. I.; Novak, B. M. *J. Org. Chem.* **1994**, *59*, 5034; $Pd(OAc)_2$, aq. Na_2CO_3, THF reflux, 0%. (c) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550; $Pd(OAc)_2$, 2-(di-*tert*-butylphosphino)-biphenyl, KF, THF reflux, 0%. (d) Alo, B. I.; Kandil, A.; Patil, P. A.; Sharp, M. J.; Siddiqui, M. A.; Snieckus, V. *J. Org. Chem.* **1991**, *56*, 3763; $Pd_2(dba)_3$, PPh_3, aq. Na_2CO_3, DME reflux, 35%. (e) Watanabe, T.; Miyaura, N.; Suzuki, A. *Synlett* **1992**, 207; $Pd_2(dba)_3$, PPh_3, $Ba(OH)_2$, DME/H_2O reflux, 39%.
(15) (a) Savage, S. A.; Smith, A. P.; Fraser, C. L. *J. Org. Chem.* **1998**, *63*, 10048. (b) Negishi coupling of aryl iodide **18**: An oven-dried Schlenk-flask equipped with a rubber septum was charged with 1.29 g (6.0 mmol) $PhSO_2NH$*t*-Bu in 15 mL THF under an argon atmosphere and cooled in an ice bath. After addition of 8.2 mL *n*-BuLi (1.6 M in hexanes) the solution was stirred for 2 h. A thick, pale yellow precipitate formed. 1.82 g (13.4 mmol) $ZnCl_2$ beads were added (the precipitate dissolves) and 1 h later a solution of 2.19 g (5.0 mmol) **18**, 185 mg (0.2 mmol) $Pd_2(dba)_3$ and 262 mg (1.0 mmol) PPh_3 in 10 mL THF was transferred into the reaction mixture. After addition of 424 mg (10.0 mmol) dried LiCl the reaction mixture was refluxed for 70 h. 100 mL sat. aq. NH_4Cl and 100 mL MTBE were added and the aqueous layer was extracted three times with MTBE. The combined organic fractions were washed with brine and dried over $MgSO_4$. Purification by flash chromatography (pentane/MTBE 2:1→1:1) yielded 2.18 g (4.2 mmol, 83%) pure **21**. (c) Analytical data of 2-*O*-benzyl-5-*O*-[4′-(2′′-*tert*-butylamino-sulfonylphenyl)-phenyl]-1,4:3,6-dianhydro-D-mannitol (**21**): colorless solid; Mp 62 °C; $[\alpha]_D^{20}$ = +128, $[\alpha]_{578}^{20}$ = +133, $[\alpha]_{546}^{20}$ = +152 (*c* 1.008, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ = 0.98 [s, 9 H, $C(CH_3)_3$], 3.58 (s, 1 H, NH), 3.78 (t, *J* = 8.7 Hz, 1H, 1-H), 3.94 (dd, *J* = 8.6 Hz, 7.0 Hz, 1H, 1-H), 4.06–4.12 (m, 2 H, 2-H, 6-H), 4.20 (dd, *J* = 9.4

Hz, 6.0 Hz, 1 H, 6-H), 4.60 (d, *J* = 11.9 Hz, 1 H, CH*H*Ph), 4.62 (t, *J* = 4.7 Hz, 1 H, 3-H), 4.78 (d, *J* = 11.9 Hz, 1 H, C*H*HPh), 4.79–4.85 (m, 2 H, 4-H, 5-H), 7.04 (pd, *J* = 8.7 Hz, 2H, 2′-H, 6′-H), 7.29 (dd, *J* = 7.7 Hz, 1.0 Hz, 1 H, 6‴-H), 7.29–7.40 (m, 5 H, Ph-H), 7.43–7.47 (m, 3 H, 3′-H, 5′-H, 4‴-H), 7.53 (td, *J* = 7.6 Hz, 1.2 Hz, 1H, 5‴-H), 8.15 (dd, *J* = 7.9 Hz, 1.0 Hz, 1H, 3‴-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 29.7 [C(CH_3)$_3$], 54.3 [C(CH_3)$_3$], 71.0, 71.6, 72.6 (C-1, C-6, CH_2Ph), 77.9, 78.9, 80.6, 80.8 (C-2, C-3, C-4, C-5), 114.9 (C-2′, C-6′), 127.6, 128.1 (C-3″, C-6″), 127.9, 128.4 (Ph-C), 131.1 (C-3′, C-5′), 131.7, 132.4 (C-4″, C-5″), 132.2 (C-4′), 137.6 (Ph-C_q), 139.4 (C-1″), 142.2 (C-2″), 158.1 (C-1′); IR(film): 3371, 2973, 2876, 1607, 1514, 1467, 1324, 1245, 1152, 1128, 1076, 988, 834, 765 cm^{-1}; Anal. calcd. for $C_{29}H_{33}NO_6S$ (523.65) C 66.52, H 6.35, N 2.68, found C 66.41, H 6.01, N 2.48.

(16) (a) Judkins, B. D.; Allen, D. G.; Cook, T. A.; Evans, B.; Sardharwala, T. E. *Synth. Commun.* **1996**, *26*, 4351. (b) Preparation of benzamidine **5** via amide oxime: Benzonitrile **23** (1 mmol) was dissolved in 10 mL THF/EtOH (1:1). After addition of NH_2OH·HCl (3 mmol), Na_2CO_3 (2 mmol) and 10 mL water the mixture was heated to 80 °C and stirred for 20 h (TLC monitoring). After cooling 20 mL water was added and the aqueous layer was extracted three times each with 20 mL CH_2Cl_2. The combined organic fractions were dried over $MgSO_4$ and the solvents were removed in vacuo. The crude amide oxime was then dissolved in 30 mL MeOH/HOAc (1:1) and Ac_2O (2 mmol) was added. After 30 min Pd/C was added and the reaction mixture was vigorously stirred under hydrogen atmosphere (HPLC monitoring, Rainin RP18, H_2O/CH_3CN mixtures + 0.1% TFA). Finally, the solution was filtrated over a pad of celite and the solvents were completely removed in vacuo. The crude bezamidine was then stirred under an argon atmosphere in dry TFA/anisole (10:1) for 24 h. Purification by flash chromatography (CH_2Cl_2/MeOH/TFA, 100:2:1 → 100:5:1), concentration of all product fractions and subsequent precipitation with MTBE/hexane gave **5** as TFA salt. (c) Analytical data of 2-*O*-(4′-amidinophenyl)-5-*O*-[4″-(2‴-aminosulfonylphenyl)-phenyl]-1,4:3,6-dianhydro-D-sorbitol trifluoroacetic acid salt (**5**): colorless solid; $[\alpha]_D^{20}$ = +51, $[\alpha]_{578}^{20}$ = +54, $[\alpha]_{546}^{20}$ = +61, $[\alpha]_{436}^{20}$ = +108, $[\alpha]_{365}^{20}$ = +174 (*c* 0.407, CH_2Cl_2/MeOH, 1:1); ^{1}H NMR (500 MHz, DMSO-d_6) δ = 3.56 (d, *J* = 10.4 Hz, 1 H, 1-H), 3.89 (dd, *J* = 9.4 Hz, 5.4 Hz, 1 H, 6-H), 4.07 (dd, *J* = 9.4 Hz, 5.7 Hz, 1 H, 6-H), 4.11 (dd, *J* = 10.4 Hz, 3.8 Hz, 1 H, 1-H), 4.62 (d, *J* = 5.1 Hz, 1 H, 3-H), 4.97 (q, *J* = 5.5 Hz, 1 H, 5-H), 5.04 (t, *J* = 5.0 Hz, 1 H, 4-H), 5.11 (d, *J* = 3.3 Hz, 1 H, 2-H), 7.02 (pd, *J* = 8.7 Hz, 2 H, 2″-H, 6″-H), 7.13 (s, 2 H, SO_2NH_2), 7.20 (pd, *J* = 8.9 Hz, 2 H, 2′-H, 6′-H), 7.29 (d, *J* = 7.5 Hz, 1 H, 6‴-H), 7.32 (pd, *J* = 8.7 Hz, 2 H, 3″-H, 5″-H), 7.53 (t, *J* = 7.5 Hz, 1 H), 7.59 (t, *J* = 7.4 Hz, 1 H, 4‴-H, 5‴-H), 7.83 (pd, *J* = 8.8 Hz, 2 H, 3′-H, 5′-H), 8.01 (d, *J* = 7.8 Hz, 1 H, 3‴-H), 9.01/9.15 [s/s, 4 H, C(NH_2)$_2$]; ^{13}C NMR (75 MHz, DMSO-d_6) δ = 70.9, 71.7 (C-1, C-6), 77.1, 80.7, 81.8, 86.0 (C-2, C-3, C-4, C-5), 114.3 (C-2″, C-6″), 115.7 (C-2′, C-6′), 120.6 (C-4′), 127.4 (C-3‴, C-6‴), 130.5, 130.6 (C-3′, C-5′, C-3″, C-5″), 131.6, 132.7 (C-4″, C-4‴, C-5‴), 139.8 (C-1‴), 142.4 (C-2‴), 157.3 (C-1″), 161.2 (C-1′), 164.9 [C(NH_2)$_2$]; HRMS (ESI) *m/z* calcd. 496.1542, found 496.1544 ($C_{25}H_{26}N_3O_6S$, M + H$^+$).

(17) Pd/C is preferred, since the use of Raney-nickel in MeOH/AcOH leads to the formation of minor amounts of Ni(OAc)$_2$, which is difficult to remove by chromatography.

(18) Brougham, P.; Cooper, M. S.; Cummerson, D. A.; Heaney, H.; Thompson, N. *Synthesis* **1987**, 1015.

(19) Krone, W. *Chem. Ber.* **1891**, *24*, 834.