Stereoselective Synthesis of β-D-Mannopyranosides with Reactive Mannopyranosyl Donors Possessing a Neighboring Electron-Withdrawing Group**

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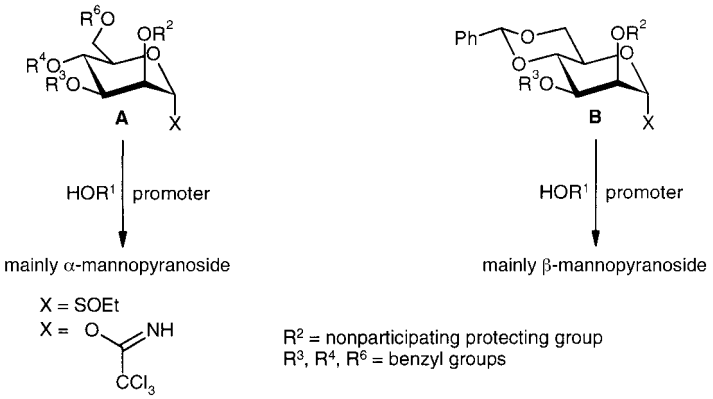
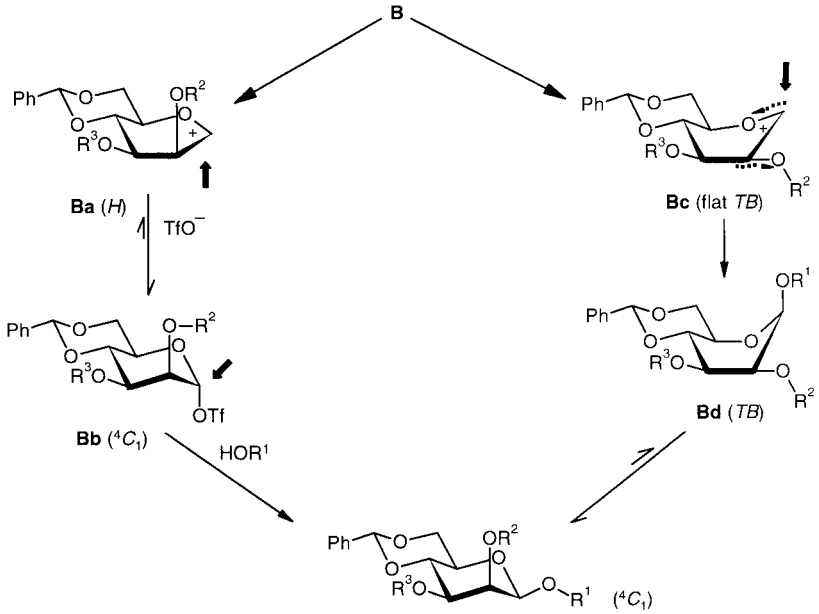
Dedicated to Professor Wolfgang Pfleiderer on the occasion of his 75th birthday

The presence of β-linked mannopyranosides in various natural products,[1] particularly in the N-glycan core structure of glycoproteins,[1,2] led to the search for efficient methodologies for producing this difficult target structure. Above all, mannopyranosyl donors **A** (Scheme 1), with nonparticipating protecting groups and different leaving groups X, were investigated for their β selectivity. However, in general, α products were obtained.[1,3–5] Several specific methods[6–12] have led to some success in this endeavour. Finally epimerization of β-glucopyranosides to β-mannopyranosides through an S_N2 reaction[12–16] and intramolecular aglycon delivery[17–19] appeared to be the method of choice.



Scheme 1. Preferred α- and β-mannopyranoside synthesis.

Mannopyranosyl donors with diol O-protecting groups, which lead to ring annelation, had already been investigated, but again with limited success.[20] However, the use of 2,3-di-*O*-alkyl-4,6-*O*-benzylidene-protected mannopyranosyl sulfoxides as donors (Scheme 1, **B**) gave preferentially β products with various acceptors at low temperatures.[21] The same result is more conveniently achieved with trichloroacetimidate leaving groups, because these mannopyranosyl donors are highly reactive and accessible to activation with catalytic amounts of trimethylsilyltrifluoromethanesulfonate (TMSOTf).[22] The results obtained on varying the reaction parameters in this reaction are not compatible with the reaction mechanism proposed for sulfoxide activation,[22] in which α-triflate intermediate **Bb**, formed via intermediate **Ba** (with a half-chair conformation), is thought to play a decisive role (Scheme 2).[21] Rather, the anomeric stereocontrol is caused by a conformational effect enforced by the 4,6-*O*-benzylidene group on the pyranosyl ring, which thus favors the generation of a flattened



Scheme 2. Mechanistic proposals for preferred β-mannopyranoside formation. *TB* = Twist–Boat conformation, *H* = half-chair conformation.

twist–boat conformation **Bc** as the intermediate.[22] For stereoelectronic and steric reasons, **Bc** will be preferentially attacked from the β side, which gives a twist–boat intermediate **Bd** that equilibrates to the $^4C_1$ conformer. This mechanistic proposal reconciles all results thus far found with different 4,6-*O*-benzylidene protected mannopyranosyl donors.

Based on these mechanistic considerations, β-mannopyranoside formation should be facilitated by nonparticipating, strongly electron-withdrawing groups R^2 at the 2-O atom (Scheme 2), because generation of the twist–boat intermediate **Bc** would gain from a strong dipole effect, as indicated by the dotted arrows in **Bc**. Earlier investigations with 2-*O*-mesyl- and 2-*O*-benzylsulfonyl-mannopyranosyl chlorides and tosylates as donors with some simple acceptors led to formation of the preferential β product,[23,24] which supports

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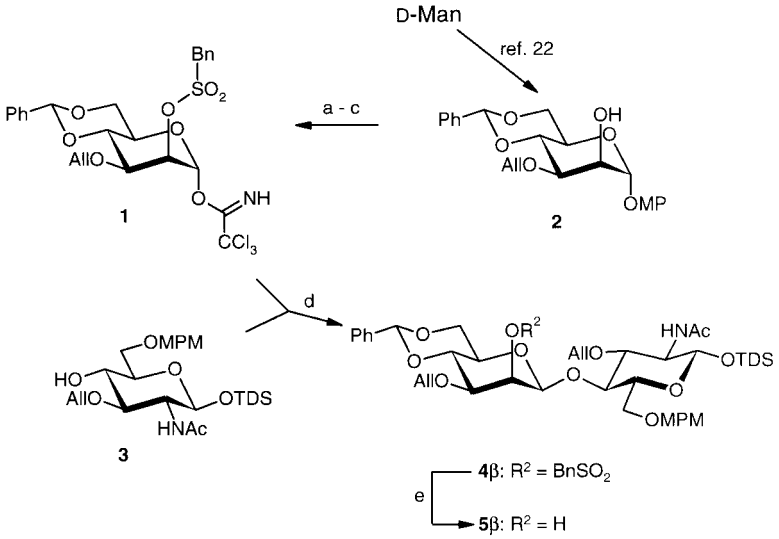
[**] This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and the European Community (Grant No. HPRN-CT-2000-00001/GLYCOTRAIN). A.A.H.A.R. and E. S. H. El Ashry are grateful to the Alexander von Humboldt Foundation for a fellowship and for the continued support, respectively.

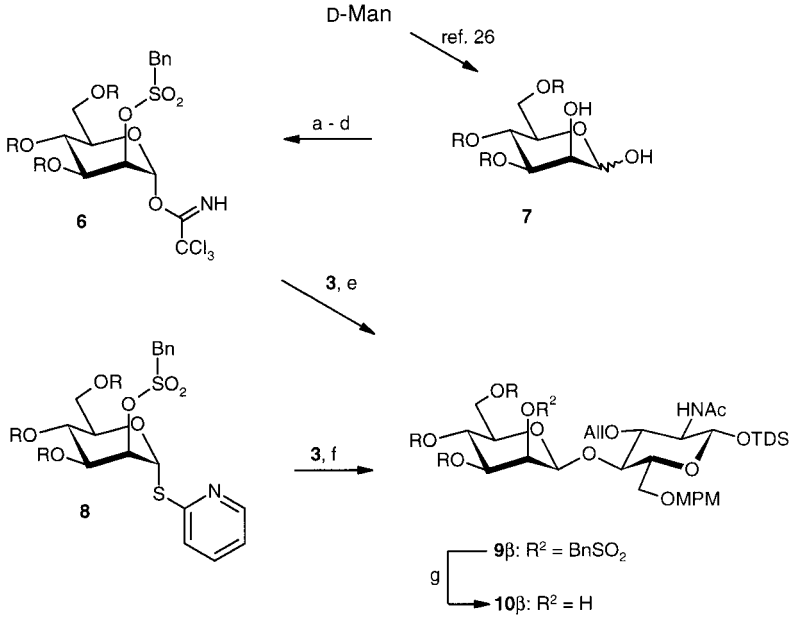
  0044-8249/02/4116-2972 $ 20.00+.50/0

our postulate. However, to demonstrate the potential of this direct approach to β-mannopyranoside synthesis 1) an excellent leaving group at the glycosyl donor, 2) success with an important acceptor, and 3) successful removal of the strong electron-withdrawing 2-*O*-protecting group are required. These preconditions are met by the method outlined herein.

For our study 3-*O*-allyl-2-*O*-benzylsulfonyl-4,6-*O*-benzylidene-protected mannopyranosyl trichloroacetimidate (**1**) was selected as the donor because this is a properly protected building block for the glycopeptide N-glycan synthesis[16] (Scheme 3). Compound **1** was synthesized from readily available methoxyphenyl (MP) mannopyranoside (**2**).[22] Treatment with benzylsulfonyl chloride in pyridine followed by removal of the MP group with ceric(III) ammonium nitrate (CAN) in a mixture of acetonitrile/water at 0 °C, and then reaction with trichloroacetonitile in the presence of DBU as the base afforded **1** in a high overall yield. Coupling of donor **1** (1.5 equiv) with 4-*O*-unprotected glucosamine derivative **3**[25] as the acceptor (1 equiv), in dichloromethane at −50 °C and in the presence of TMSOTf as the catalyst, under inverse conditions afforded, as hypothesized, mainly the β(1-4)-linked disaccharide **4β** (80% based on **3**, β:α = 8:1); the mixture of anomers could be readily separated by flash column chromatography. The benzylsulfonyl group was removed by treating **4β** with a solution of sodium amide in DMF at room temperature,[23f] which afforded 2-O-unprotected **5β** in 91% yield.



Scheme 3. Synthesis of **4** from **1**; a) $BnSO_2Cl$, pyr (91%); b) CAN, $MeCN/H_2O$ (4:1), O °C (82%); c) CCl_3CN, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (94%); d) TMSOTf, CH_2Cl_2, −50 °C (80% β:α = 8:1); e) $NaNH_2$, DMF, RT (91%). All = allyl; MPM = *para*-methoxybenzyl.



Scheme 4. Synthesis of Manβ(1-4)GlcNAc disaccharide from **6** and **8** (R = Bn); a) TDS-Cl, imidazole, DMF (95%); b) $BnSO_2Cl$, pyr (92%); c) TBAF, THF (90%); d) CCl_3CN, DBU, CH_2Cl_2 (97%); e) TMSOTf, CH_2Cl_2 (82%; β:α = 9:1); f) TMSOTf, CH_2Cl_2 (78%, β:α = 7.4:1); g) $NaNH_2$, DMF, RT (93%).

Because of the principal importance, 2-*O*-benzylsulfonyl-3,4,6-tri-*O*-benzyl-protected mannopyranosyl trichloroacetimidate (**6**) (Scheme 4) was also investigated in β-mannopyranoside synthesis. The strong dipole effect enforced by the benzylsulfonyl group should favor formation of the twist–boat intermediate of type **Bc** (Scheme 2) even in the absence of the 4,6-*O*-benzylidene ring, and thus lead to β product formation. The required donor **6** was prepared from 3,4,6-tri-*O*-benzyl-D-mannose (**7**)[26] by regioselective anomeric-O-silylation[11] with thexyldimethylsilyl (TDS) chloride in the presence of imidazole; the ensuing reaction with benzylsulfonyl chloride in pyridine, removal of the TDS group with tetrabutylammonium fluoride (TBAF) in THF, and then treatment with trichloroacetonitrile in the presence of DBU afforded the donor **6** in high overall yield. Coupling **6** with acceptor **3** under the above-described conditions led to even better results than **1**, and mainly afforded β-linked disaccharide **9β** (82%, **9β**:**9α** 9:1). Similar results were obtained with the corresponding mannopyranosyl donor **8**;[27] presumably, because of the lower reactivity, the β:α-ratio was somewhat decreased (78%, **9β**:**9α** 7:1). The 2-*O*-benzylsulfonyl group (→**10β**) was again removed in high yield.[28]

The α and β configuration of the disaccharides **4α**,**β**, **5α**,**β**, **9α**,**β**, and **10α**,**β**, could be assigned with the $^1J_{1C,1H}$ coupling constants of the anomeric protons. As expected,[29] these values are 174.1–175.7 Hz for the α anomers and 162.3–163.6 Hz for the β anomers.

In conclusion, a convenient and highly efficient method for the synthesis of β-mannopyranosides is introduced. The mannopyranosyl donors possess a strongly electron-withdrawing 2-*O*-benzylsulfonyl group and a trichloroacetimidate or pyridylthio group, respectively, as the leaving group at the anomeric center. The deprotection of the 2-*O*-benzylsulfonyl group was readily performed; thus, in addition, an often

  0044-8249/02/4116-2973 $ 20.00+.50/0

advantageous selective access to the 2-hydroxy group of the mannose residue is provided.

Received: March 6, 2002 [Z18837]

[1] J. J. Gridley, H. M. I. Osborn, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1471 – 1491, and references therein.

[2] a) A. Kobata, *Acc. Chem. Res.* **1993**, *26*, 319 – 324; b) R. A. Dwek, *Chem. Rev.* **1996**, *96*, 683 – 720; c) J. Montreuil, *Adv. Carbohydr. Chem. Biochem.* **1980**, *37*, 157 – 223; d) R. Kornfeld, S. Kornfeld, *Annu. Rev. Biochem.* **1985**, *54*, 631 – 644.

[3] H. Paulsen, *Angew. Chem.* **1982**, *94*, 184 – 201; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 155 – 173.

[4] a) R. R. Schmidt, *Angew. Chem.* **1986**, *98*, 213 – 236; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 212 – 235; b) R. R. Schmidt, W. Kinzy, *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21 – 123.

[5] F. Barresi, O. Hindsgaul in *Modern Methods in Carbohydrate Synthesis* (Eds.: S. H. Khan, R. A. O'Neill), Harwood Academic Publishers, Amsterdam, **1996**, pp. 251 – 276.

[6] a) H. Paulsen, O. Lockhoff, *Chem. Ber.* **1981**, *114*, 3102 – 3114; b) H. Paulsen, R. Lebhuhn, *Liebigs Ann. Chem.* **1983**, 1047 – 1072.

[7] P. J. Garegg, P. Ossowski, *Acta Chem. Scand.* **1983**, *337*, 249 – 258.

[8] R. R. Schmidt, M. Behrendt, A. Toepfer, *Synlett* **1990**, 694 – 696.

[9] a) J. Kerékgyárto, J. G. M. van der Ven, J. P. Kamerling, A. Liptak, J. F. G. Vliegenthart, *Carbohydr. Res.* **1993**, *238*, 135 – 145; b) K. K.-C. Liu, S. J. Danishefsky, *J. Org. Chem.* **1994**, *59*, 1892 – 1894; c) S. J. Danishefsky, S. Hu, P. F. Cirillo, M. Eckhardt, P. H. Seeberger, *Chem. Eur. J.* **1997**, *3*, 1617 – 1628.

[10] a) E. Kaji, F. W. Lichtenthaler, *Trends Glycosci. Glycotechnol.* **1993**, *5*, 121 – 142; b) F. W. Lichtenthaler, T. Schneider-Adams, *J. Org. Chem.* **1994**, *59*, 6728 – 6734.

[11] a) R. R. Schmidt, U. Moering, M. Reichrath, *Chem. Ber.* **1982**, *115*, 39 – 49; b) J. Tamura, R. R. Schmidt, *J. Carbohydr. Chem.* **1995**, *14*, 895 – 911.

[12] a) G. Hodosi, P. Kovác, *J. Am. Chem. Soc.* **1997**, *119*, 2335 – 2336; G. Hodosi, P. Kovác, *Carbohydr. Res.* **1997**, *303*, 239 – 243; **1998**, *308*, 63 – 75; b) V. K. Srivastava, C. Schuerch, *Tetrahedron Lett.* **1979**, *20*, 3269 – 3272; c) K. C. Nicolaou, F. L. von Delft, S. R. Conley, H. J. Mitchell, Z. Jin, R. M. Rodriguez, *J. Am. Chem. Soc.* **1997**, *119*, 9057 – 9058.

[13] a) O. Théander, *Acta Chem. Scand.* **1958**, *12*, 1883 – 1885; b) G. Ekborg, B. Lindberg, J. Lonngren, *Acta Chem. Scand. B* **1972**, *26*, 3287 – 3292; c) K. K.-C. Liu, S. J. Danishefsky, *J. Org Chem.* **1994**, *59*, 1892 – 1894.

[14] a) M. Miljkovic, M. Gligorijevic, D. Glisin, *J. Org. Chem.* **1974**, *39*, 3223 – 3226; b) R. Albert, K. Dax, R. W. Link, A. E. Stütz, *Carbohydr. Res.* **1983**, *118*, C5-C6; c) S. David, A. Molleron, C. Dini, *Carbohydr. Res.* **1989**, *188*, 193 – 200; d) J. Alais, S. David, *Carbohydr. Res.* **1990**, *201*, 69 – 77; e) I. Matsuo, M. Isomura, R. Walton, K. Ajisaka, *Tetrahedron Lett.* **1996**, *37*, 8795 – 8798.

[15] a) H. Kunz, W. Günther, *Angew. Chem.* **1988**, *100*, 1118 – 1119; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1086 – 1087; b) H. Kunz, M. Schultz in *Glycopeptides and Related Compounds* (Eds.: D. G. Large, C. D. Warren), Marcel Dekker, New York, **1997**, pp. 23 – 78.

[16] a) S. Weiler, R. R. Schmidt, *Tetrahedron Lett.* **1998**, *39*, 2299 – 2302; b) M. V. Chiesa, R. R. Schmidt, *Eur. J. Org. Chem.* **2000**, 3541 – 3554.

[17] a) F. Barresi, O. Hindsgaul, *J. Am. Chem. Soc.* **1991**, *113*, 9376 – 9377; F. Barresi, O. Hindsgaul, *Synlett* **1992**, 759 – 761; F. Barresi, O. Hindsgaul, *Can. J. Chem.* **1994**, *72*, 1447 – 1465; b) G. Stork, G. Kim, *J. Am. Chem. Soc.* **1992**, *114*, 1087 – 1088; c) G. Stork, J. J. LaClair, *J. Am. Chem. Soc.* **1996**, *118*, 247 – 248; d) Y. Ito, T. Ogawa, *Angew. Chem.* **1994**, *106*, 1843 – 1845; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1765 – 1767; e) Y. Ito, T. Ogawa, *J. Am. Chem. Soc.* **1997**, *119*, 5562 – 5566.

[18] a) K.-H. Jung, M. Müller, R. R. Schmidt, *Chem. Rev.* **2000**, *100*, 4423 – 4442, and references therein; b) A. A.-H. Abdel Rahman, E. S. H. El Ashry, R. R. Schmidt, *Carbohydr. Res.* **2002**, *337*, 195 – 206.

[19] a) T. Ziegler, G. Lemanski, A. Rakoczy, *Tetrahedron Lett.* **1995**, *36*, 8973 – 8976; b) T. Ziegler, G. Lemanski, *Angew. Chem.* **1998**, *110*, 3367 – 3369; *Angew. Chem. Int. Ed.* **1998**, *37*, 3129 – 3132.

[20] a) P. A. Gorin, A. S. Perlin, *Can. J. Chem.* **1961**, *39*, 2474 – 2485; b) P. J. Caregg, T. Iversen, R. Johansson, *Acta Chem. Scand. B* **1980**, *34*, 505 – 508.

[21] a) D. Crich, S. Sun, *J. Org. Chem.* **1996**, *61*, 4506 – 4507; b) D. Crich, S. Sun, *J. Org. Chem.* **1997**, *62*, 1198 – 1199; c) D. Crich, S. Sun, *J. Am. Chem. Soc.* **1997**, *119*, 11 217 – 11 223; d) D. Crich, S. Sun, *J. Am. Chem. Soc.* **1998**, *120*, 435 – 436; e) D. Crich, S. Sun, *Tetrahedron* **1998**, *54*, 8321 – 8348; f) D. Crich, W. Cai, Z. Dai, *J. Org. Chem.* **2000**, *65*, 1291 – 1297; g) D. Crich, M. Smith, *J. Am. Chem. Soc.* **2001**, *123*, 9015 – 9020.

[22] R. Weingart, R. R. Schmidt, *Tetrahedron Lett.* **2000**, *41*, 8753 – 8758.

[23] a) V. K. Srivastava, C. Schuerch, *Carbohydr. Res.* **1980**, *79*, C13; b) V. K. Srivastava, C. Schuerch, *J. Org. Chem.* **1981**, *46*, 1121 – 1126; c) V. K. Srivastava, C. Schuerch, *Carbohydr. Res.* **1982**, *100*, 411 – 417; d) E. S. H. El Ashry, C. Schuerch, *Carbohydr. Res.* **1982**, *105*, 33 – 43; e) E. S. H. El Ashry, C. Schuerch, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1581 – 1586; f) L. F. Awad, E. S. H. El Ashry, C. Schuerch, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1587 – 1592.

[24] These results have had little attention; in some reviews on β-mannopyranoside formation they are not even mentioned.

[25] **3**: TLC (petroleum ether:ethyl acetate, 2:1) $R_f = 0.54$; $[\alpha]_D = -6.5°$ ($c = 1.0$, chloroform); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 0.02$ (s, 3H; CH_3), 0.09 (s, 3H; CH_3), 0.80, 0.82, 0.84, 0.86 (4s, 12H; 4 CH_3), 1.20–1.34 (m, 1H; CH), 1.98 (s, 3 H $COCH_3$), 3.21 (m, 1H; 2-H), 3.45 (m, 1H; 4-H), 3.56 (m, 1H; 5-H), 3.73–3.81 (m, 4H; 6-H, OCH_3), 4.10–4.21 (m, 3H; 6′-H, $CH_2CH{=}CH_2$), 4.35–4.40 (m, 3H; 3-H, $CH_2CH{=}CH_2$), 5.28 (d, $J = 7.8$ Hz, 1H; 1-H), 5.48 (s, 1H; CH_2Ar), 5.56–5.63 (m, 2H; NH, $CH_2CH{=}CH_2$), 7.03 (d, $J = 7.5$ Hz, 2H; Ar-H), 7.34 ppm (d, $J = 7.4$ Hz, 2H; Ar-H); FAB-MS: (positive mode, NBOH/NaI-matrix); *m*/*z*: 524 [*M*H$^+$], 546 [*M*Na$^+$].

[26] N. E. Franks, R. Montgomery, *Carbohydr. Res.* **1968**, *3*, 286 – 298; T. G. Mayer, R. R. Schmidt, *Eur. J. Org. Chem.* **1999**, 1153 – 1165.

[27] **8**: TLC (petroleum ether:ethyl acetate, 3:1) $R_f = 0.53$; $[\alpha]_D = +111°$ ($c = 0.2$, chloroform); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 3.70$ (d, $J =$ 11.0 Hz, 1H; 6-H), 3.85 (dd, $J = 4.0$, 11.2 Hz, 1H; 6-H), 3.99 (dd, $J_{3,2} =$ 3.2 Hz, $J_{3,4} = 9.3$ Hz, 1H; 3-H), 4.15 (t, $J = 9.6$ Hz, 1H; 4-H), 4.16 (m, 1H; 5-H), 4.45 (d, $J = 11.9$ Hz, 1H; CH_2), 4.53 (d, $J = 10.7$ Hz, 1H; CH_2), 4,55 (d, $J = 11.2$ Hz, 1H; CH_2), 4.59 (s, 2H; SO_2CH_2), 4.66 (d, $J = 11.9$ Hz, 1H; CH_2) 4.75 (d, $J = 11.2$ Hz, 1H; CH_2), 4.80 (d, $J =$ 10.9 Hz, 1H; CH_2), 5.66 (m, 1H; 2-H), 6.45 (d, $J = 1.8$ Hz, 1H; 1-H), 7.19 (d, $J = 7.0$ Hz, 1H; Ar-H), 7.23 (d, $J = 7.1$ Hz, 1H; Ar-H), 7.25–7.33 (m, 20H; 4 Ph), 7.50 (d, $J = 7.1$ Hz, 1H; Ar-H), 8.50 ppm (d, $J = 6.0$ Hz, 1H; Ar-H); MALDI-MS: *m*/*z*: 720 [*M*Na$^+$].

[28] **10β**: TLC (petroleum ether:ethyl acetate, 5:1) $R_f = 0.34$; $[\alpha]_D = +$ 53.1° ($c = 0.1$, chloroform); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 0.12$ (s, 3H; CH_3), 0.23 (s, 3H; CH_3), 0.85–0.89 (m, 12H; 4CH_3), 1.64–1.71 (m, 1H; CH), 1.98 (s, 3H; $COCH_3$), 3.31 (m, 1H; 2_a-H), 3.50 (m, 1H; 4_a-H), 3.56 (m, 1H; 5_a-H), 3.66—3.71 (m, 10H; 2_b-H, 3_b-H, 4_b-H, 2 6_a-H, 2 6_b-H, OCH_3), 4.01–4.19 (m, 4H; 3_a-H, 5_b-H, $CH_2CH = CH_2$), 4.48 (m, 2H; CH_2), 4.52–4.68 (m, 9H; 1_b-H, $3CH_2$, $CH_2CH = CH_2$), 5.44–5.58 (m, 3H; 1_a-H, NH, $CH_2CH = CH_2$), 7.09 (d, $J = 7.5$ Hz, 2H; Ar-H), 7.16 (d, $J = 7.5$ Hz, 2H; Ar-H), 7.22–7.33 ppm (m, 15H; 3Ph); MALDI-MS: *m*/*z*: 979 [*M*–Na$^+$].

[29] K. Bock, C. Pedersen, *J. Chem. Soc. Perkin Trans. 2* **1974**, 293 – 297.

  0044-8249/02/4116-2974 $ 20.00+.50/0