Pergamon

Tetrahedron Letters 43 (2002) 673–675

TETRAHEDRON LETTERS

Facile syntheses of D-mannose hexa- and nonasaccharides: the di- and trimer of the trisaccharide repeating unit of the cell-wall mannans of *Epidermophyton floccosum*, *Trychophyton mentagrophytes*, *Microsporum canis* and related species of *Microsporum*

Jun Ning,[a] Linsen Heng[b] and Fanzuo Kong[a,*]

[a]*Research Center for Eco-Environmental Sciences, Academia Sinica, PO Box 2871, Beijing 100085, PR China*
[b]*Daxian Normal College, Department of Chemistry, Sichuan, PR China*

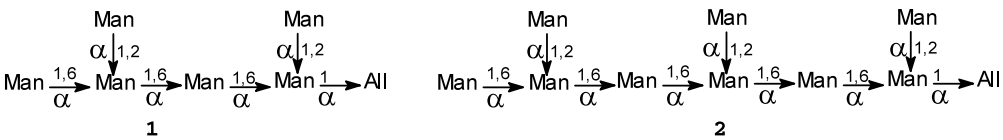
Received 25 October 2001; revised 15 November 2001; accepted 22 November 2001

Abstract—A highly efficient strategy for the preparation of D-mannose hexa- and nonasaccharides, the dimer and trimer of the α-D-Man*p*-(1→6)-[α-D-Man*p*-(1→2)-]D-Man*p* trisaccharide repeating unit of the cell-wall mannans from the fungi *Epidermophyton floccosum*, *Trychophyton mentagrophytes*, *Microsporum canis*, *M. cookei* and *M. racemosum*, has been developed using 1,2,6-tri-*O*-acetyl-3,4-di-*O*-benzoyl-α-D-mannopyranose (**6**) as the key synthon.

Facile, efficient and selective synthesis of oligosaccharides is a central problem in carbohydrate chemistry. For the past few years, considerable progress has been made in the oligosaccharide synthesis field. However, owing to their structural complexity, attempts to establish a general process for the construction of oligosaccharides is still impossible. More new and efficient strategies for the chemical synthesis of oligosaccharides having specific structures are needed.

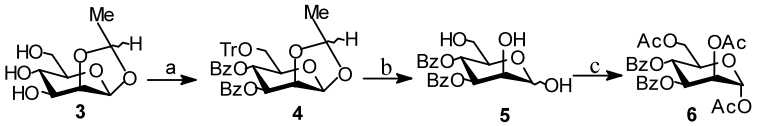
The 2,6-di-*O*-(α-D-mannopyranosyl)-D-mannopyranose structure is a common repeating unit of the cell-wall mannans of many fungi such as *Epidermophyton floccosum*, *Trychophyton mentagrophytes*, *Microsporum canis*, *M. cookei* and *M. racemosum*.[1–3] These fungi parasitize man and animals, and cause superficial cutaneous infections involving primarily the keratinized tissues of the epidermis, nails and pilosebaceous follicles.[4] Studies show that one of the causes of the infection resides in the immunosuppressive effects of the cell-wall mannans of these organisms.[5–7] To elucidate further the molecular structure responsible for this immunoinhibitory activity, it would be necessary to synthesize different fragments of these fungi mannans. So far there has been no general method for the construction of the fragments of these mannans.[2] Here we disclose a highly efficient strategy for the preparation of this kind of oligosaccharide using 1,2,6-tri-*O*-acetyl-3,4-di-*O*-benzoyl-α-D-mannopyranose (**6**) as a synthon. The syntheses of allyl-α-D-hexamannoside **1** and allyl-α-D-nonamannoside **2**, the dimer and the trimer of the trisaccharide repeating unit of these mannans, are presented as typical examples.

As shown in Scheme 1, tritylation of 1,2-*O*-ethylidene-β-D-mannopyranose[8] (**3**) followed by benzoylation in a one-pot manner gave the 3,4-di-*O*-benzoyl-6-*O*-trityl-1,2-*O*-ethylidene-D-mannopyranose (**4**) in 70% yield. Hydrolysis of **4** with 90% CF_3COOH afforded the 3,4-di-*O*-benzoyl-D-mannopyranose (**5**) in 88% yield. Subsequent acetylation with acetic anhydride in pyridine furnished 1,2,6-tri-*O*-acetyl-3,4-di-*O*-benzoyl-α-D-mannopyranose (**6**) as the key synthon (Scheme 1).



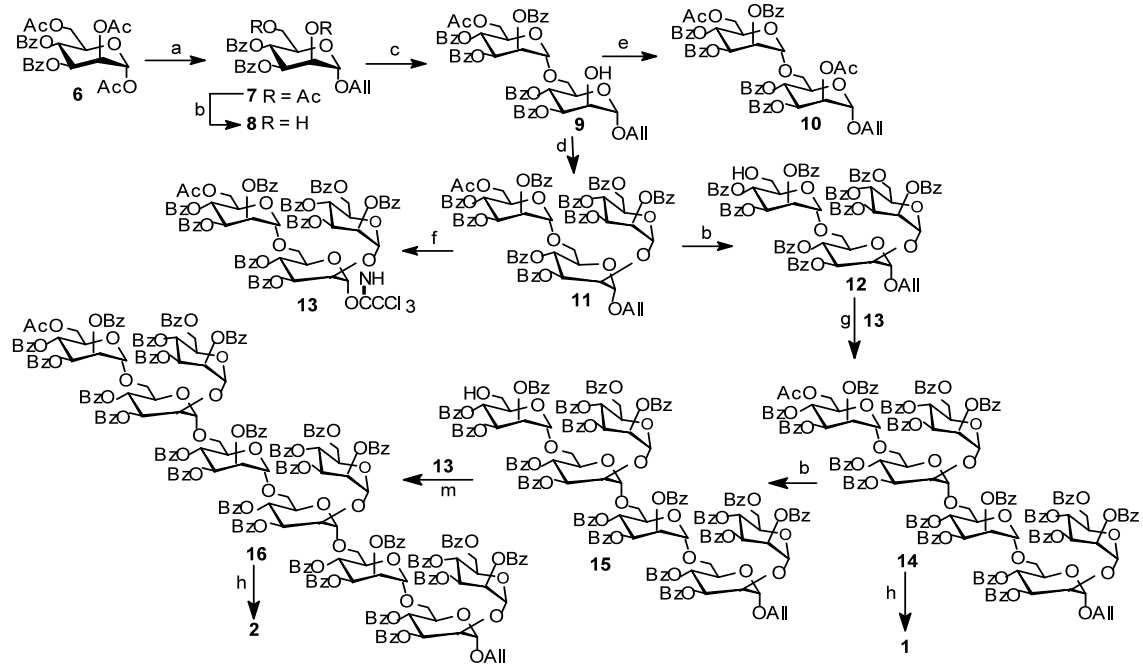
* Corresponding author.

0040-4039/02/$ - see front matter
PII: S0040-4039(01)02232-8



Scheme 1. *Reagents and conditions*: (a) i. trityl chloride (1.2 equiv.), pyridine, 50°C, 32 h, ii. PhCOCl (4.8 equiv.), <40°C, 24 h; 70% (for two steps); (b) F_3CCOOH (90%), rt, 4 h, 88%; (c) Ac_2O, pyridine, rt, 5 h, 100%.

The synthesis of oligosaccharides from **6** is shown in Scheme 2. Thus, allyl 2,6-di-*O*-acetyl-3,4-di-*O*-benzoyl-α-D-mannopyranoside (**7**) was prepared using **6** as the glycosyl donor and allyl alcohol as the acceptor in 87% yield.[9] Selective removal of the acetyl groups of **7** in methanol containing 0.5% HCl gave the glycosyl acceptor **8** in 96% yield.[10] Selective 6-*O*-glycosylation of **8** with 6-*O*-acetyl-2,3,4-tri-*O*-benzoyl-α-D-mannopyranosyl trichloroacetimidate[10] as the glycosyl donor gave the disaccharide **9** in 86% yield. Acetylation of **9** confirmed 6-*O*-glycosylation as the ^{1}H NMR spectrum of acetylated disaccharide **10** showed a newly emerged doublet of doublets at δ 5.52 ppm for H-2. Coupling **9** with 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl trichloroacetimidate[10] afforded the trisaccharide **11** in 85% yield. For accumulation of **11**, a one-pot manner was used. Thus, selective coupling of **8** with 6-*O*-acetyl-2,3,4-tri-*O*-benzoyl-α-D-mannopyranosyl trichloroacetimidate, followed by condensation with 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl trichloroacetimidate afforded **11** readily. The ^{1}H NMR spectrum of **11** showed one acetyl signal (δ 1.99), allyl signals (δ 5.47–5.33) and three H-1 signals (δ 5.32, 5.27, 5.18), confirming the structure of **11**. Selective removal of the 6-*O*-acetyl group of the trisaccharide **11** gave the glycosyl acceptor **12** in 93% yield. Deallylation[11] of **11** with $PdCl_2$ followed by activation with CCl_3CN in the presence of K_2CO_3 or DBU gave the trisaccharide donor **13** in 71% yield (for two steps). The fully protected hexasaccharide **14** was smoothly obtained by coupling **12** with **13** in 84% yield. The ^{1}H NMR spectrum of **14** showed one acetyl signals (δ 2.04), allyl signals (δ 5.44–5.28) and six H-1 signals (δ 5.34, 5.34, 5.31, 5.19, 5.03 and 4.80), characteristic of the structure of the hexasaccharide **14**.[12] Selective removal of the 6-*O*-acetyl group of the hexasaccharide **14** followed by coupling with **13** gave the nonasaccharide **16** in 81% yield. The ^{1}H NMR data of **16** contained structurally characteristic information, i.e. one acetyl signals (δ 2.35), allyl signals (δ 5.42–5.25) and nine H-1 signals (δ 5.40, 5.34, 5.29, 5.29, 5.22, 5.18, 5.17, 4.99 and 4.85). Deprotection of **14** and **16** in ammonia-saturated methanol gave the title allyl-α-D-hexamannoside **1** and allyl-α-D-nonamannoside **2**. A bioassay of **1** and **2** is in progress.



Scheme 2. *Reagents and conditions*: (a) allyl alcohol (2 equiv.), TMSOTf (0.26 equiv.), CH_2Cl_2, rt, 3 h, 87%; (b) methanol/0.5% HCl, rt, 12–14 h, 93–96%; (c) 6-*O*-acetyl-2,3,4-tri-*O*-benzoyl-α-D-mannopyranosyl trichloroacetimidate (1.0 equiv.), CH_2Cl_2, TMSOTf (0.08 equiv.), rt, 3 h, 86%; (d) 2,3,4,6-tetra-*O*-benzoyl-α-D-mannopyranosyl trichloroacetimidate (1.4 equiv.), CH_2Cl_2, TMSOTf (0.16 equiv.), rt, 3 h, 85%; (e) Ac_2O, pyridine, rt, 5 h, 100%; (f) i. $PdCl_2$, CH_3OH–CH_2Cl_2, 2 h, ii. CCl_3CN, DBU, CH_2Cl_2, 8 h, 71% (two steps); (g) **13** (1.2 equiv.), CH_2Cl_2, TMSOTf (0.3 equiv.), rt, 3 h, 84%; (h) CH_3OH satd with dry NH_3, rt, 72 h, 95–98%; (m) **13** (1.2 equiv.), CH_2Cl_2, TMSOTf (0.3 equiv.), rt, 3 h, 81%.

In summary, we have successfully developed a highly efficient strategy for the preparation of mannose oligosaccharides found in many fungi cell-wall mannans with the α-D-mannopyranosyl-(1→6)-[α-D-mannopyranosyl-(1→2)-]D-mannopyranose trisaccharide repeating unit as a feature. The sole use of acyl groups in the synthesis substantially simplified the procedure.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (59973026 and 29905004).

References

1. Kawarasaki, I.; Takeda, T.; Shimonaka, H.; Nozawa, Y. *Chem. Pharm. Bull.* **1979**, *27*, 2073–2075.
2. Takeda, T.; Kawarasaki, I.; Ogihara, Y. *Carbohydr. Res.* **1981**, *89*, 301–308.
3. Jiménez-Barbero, J.; Prieto, A.; Gómez-Miranda, B.; Bernabé, M. *Carbohydr. Res.* **1995**, *272*, 121–128.
4. Wu-yuan, C. D.; Hashimoto, T. *J. Bacteriol.* **1977**, *129*, 1584–1592.
5. Blake, J. S.; Dahl, M. V.; Herron, M. J.; Nelson, R. D. *J. Invest. Dermatol.* **1991**, *96*, 657–661.
6. Grando, S. A.; Hostager, B. S.; Dahl, M. V.; Nelson, R. D. *J. Invest. Dermatol.* **1992**, *98*, 876–880.
7. Grando, S. A.; Hostager, B. S.; Dahl, M. V.; Nelson, R. D. *Acta Derm. Venereol.* **1992**, *72*, 273–276.
8. Betaneli, V. I.; Backinowsky, L. V.; Kochetkov, N. K. A. *Carbohydr. Res.* **1982**, *107*, 285–291.
9. Liao, W.; Lu, D. *Carbohydr. Res.* **1996**, *296*, 171–182.
10. Heng, L.; Ning, J.; Kong, F. *J. Carbohyr. Chem.* **2001**, *20*, 285–296.
11. Boss, R.; Scheffold, R. *Angew. Chem.* **1976**, *88*, 578–579.
12. All new compounds gave satisfactory elemental analysis results. Selected physical data for some key compounds are as follows, for **6**: mp 142–144°C; $[\alpha]_D$ −28.2° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 6.21 (d, 1H, $J_{2,1}=1.9$ Hz, H-1), 5.84 (dd, 1H, $J_{3,4}=J_{5,4}=9.9$ Hz, H-4), 5.75 (dd, 1H, $J_{2,3}=4.7$ Hz, $J_{4,3}=10.1$ Hz, H-3), 5.48 (dd, 1H, $J_{1,2}=1.9$ Hz, $J_{3,2}=4.7$ Hz, H-2), 4.36–4.20 (m, 3H, H-5, H-6a, H-6b), 2.24, 2.18, 2.05 (3s, 9H, $3COCH_3$). Anal. calcd for $C_{26}H_{26}O_{11}$: C, 60.70; H, 5.09. Found: C, 60.45; H, 5.06. For **8**: $[\alpha]_D$ −18.6° (*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.00–7.32 (m, 10H, 2Ph*H*), 5.97 (m, 1H, C*H*=CH_2), 5.82–5.75 (m, 2H, H-3, 4), 5.39–5.27 (m, 2H, CH=CH_2), 5.05 (d, 1H, $J_{2,1}=1.6$ Hz, H-1). For **9**: $[\alpha]_D$ −50.0° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 6.04 (m, 1H, C*H*=CH_2), 5.49–5.33 (m, 2H, CH=CH_2), 5.16 (d, 1H, $J_{2',1'}=1.3$ Hz, H-1′), 5.08 (d, 1H, $J_{2,1}=1.0$ Hz, H-1), 2.01 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 170.4 (1C, *C*OCH_3), 165.5, 165.4, 165.3, 165.1, 165.0 (5C, 5*C*OPh), 117.9 (1C, CH_2CH=CH_2), 98.7, 97.0 (2 C-1), 20.4 (CO*C*H_3). Anal. calcd for $C_{52}H_{48}O_{17}$: C, 66.10; H, 5.12. Found: C, 66.27; H, 5.05. For **10**: $[\alpha]_D$ −35.7° (*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 6.05 (m, 1H, C*H*=CH_2), 5.52 (dd, 1H, $J_{1,2}=1.8$ Hz, $J_{3,2}=4.6$ Hz, H-2), 5.48–5.34 (2H, CH=CH_2), 5.14 (d, 1H, $J_{2',1'}=1.2$ Hz, H-1′), 5.04 (d, 1H, $J_{2,1}=1.1$ Hz, H-1), 2.21, 1.98 (2s, 6H, $2COCH_3$). For **11**: $[\alpha]_D$ −87.1° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 5.47–5.33 (m, 2H, CH=CH_2), 5.32 (d, 1H, $J=1.2$ Hz, H-1), 5.27 (d, 1H, $J=1.3$ Hz, H-1), 5.18 (d, 1H, $J=1.5$ Hz, H-1), 1.99 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 170.4 (*C*OCH_3), 118.1 ($1CH_2CH$=CH_2), 99.7, 97.8, 97.4 (3C-1), 20.5 (CO*C*H_3). Anal. calcd for $C_{86}H_{74}O_{26}$: C, 67.80; H, 4.90. Found: C, 67.61; H, 4.93. For **13**: $[\alpha]_D$ −49.3° (*c* 2.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.82 (s, 1H, OC(N*H*)CCl_3), 6.67 (d, 1H, $J=1.1$ Hz, H-1), 5.38 (d, 1H, $J=1.0$ Hz, H-1), 5.19 (d, 1H, $J=1.2$ Hz, H-1), 1.96 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 170.3 (*C*OCH_3), 159.8 (O*C*(NH)CCl_3), 99.5, 97.4, 96.1 (3C-1), 90.5 (OC(NH)*C*Cl_3), 20.4 (CO*C*H_3). Anal. calcd for $C_{85}H_{70}O_{26}NCl_3$: C, 62.72; H, 4.33. Found: C, 62.90; H, 4.39. For **14**: $[\alpha]_D$ −55.6° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 5.44 (dd, 1H, $^2J=1.3$ Hz, $^3J_{trans}=17.1$ Hz, CH=CH_2), 5.34 (m, 2H, 2H-1), 5.31 (d, 1H, H-1), 5.28 (dd, 1H, $^2J=1.3$ Hz, $^3J_{cis}=10.4$ Hz, CH=CH_2), 5.19 (d, 1H, H-1), 5.03 (d, 1H, H-1), 4.80 (d, 1H, H-1), 2.04 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 170.4 (*C*OCH_3), 118.1 (CH_2CH=CH_2), 100.0, 99.8, 98.5, 97.9, 97.9, 97.6 (6C-1), 78.0, 77.3 (2C-2), 20.4 (CO*C*H_3). Anal. calcd for $C_{167}H_{140}O_{50}$: C, 68.07; H, 4.79. Found: C, 68.19; H, 4.87. For **1**: $[\alpha]_D$ +49.2° (*c* 1.0, H_2O); ^1H NMR (D_2O, 400 MHz): δ 5.86 (m, 1H, *C*H=CH_2), 5.27–5.17 (m, 2H, CH=CH_2), 5.03 (m, 2H, 2H-1), 4.94 (d, 1H, H-1), 4.92 (d, 1H, H-1), 4.83 (d, 1H, H-1), 4.81 (d, 1H, H-1); ^{13}C NMR (100 MHz, D_2O): 119.4 (CH_2CH=CH_2), 103.1, 103.0, 100.3, 100.1, 98.8, 98.3 (6C-1), 79.7, 79.6 (2C-2). HRMS. calcd for $C_{39}H_{66}O_{31}$: 1030.93 [M]. found: 1053.4 $(M+Na)^+$. For **16**: $[\alpha]_D$ −59.5° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 5.42 (dd, 1H, $^2J=1.2$ Hz, $^3J_{trans}=15.7$ Hz, CH=CH_2), 5.40 (d, 1H, H-1), 5.34 (d, 1H, H-1), 5.29 (m, 2H, 2H-1), 5.25 (dd, 1H, $^2J=1.2$ Hz, $^3J_{cis}=10.4$ Hz, CH=CH_2), 5.22 (d, 1H, H-1), 5.18 (d, 1H, H-1), 5.17 (d, 1H, H-1), 4.99 (d, 1H, H-1), 4.85 (d, 1H, H-1), 2.35 (s, 3H, $COCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$): 118.0 (CH_2CH=CH_2), 100.1, 100.1, 99.9, 98.8, 98.6, 98.0, 97.9, 97.9, 97.6 (9C-1), 78.2, 78.0, 77.2 (3C-2). Anal. calcd for $C_{248}H_{206}O_{74}$: C, 68.16; H, 4.75. Found: C, 68.01; H, 4.81. For **2**: $[\alpha]_D$ +37.2° (*c* 1.0, H_2O); ^1H NMR (400 MHz, D_2O): δ 5.84 (m, 1H, C*H*=CH_2), 5.24–5.14 (2H, CH=CH_2), 4.98–4.97 (m, 3H, 3H-1), 4.93–4.89 (m, 3H, H-1), 4.79–4.77 (m, 3H, H-1); ^{13}C NMR (100 MHz, D_2O): 114.7 (CH_2CH=CH_2), 98.5, 98.4, 98.4, 95.8, 95.7, 95.7, 94.4, 94.4, 93.9 (9C-1), 75.0, 74.9, 74.9 (3C-2). HRMS. calcd for $C_{57}H_{96}O_{46}$: 1517.34 [M]. Found: 1540.1 $(M+Na)^+$.