Pergamon

Tetrahedron Letters 39 (1998) 1937–1940

TETRAHEDRON LETTERS

# A Highly Convergent Synthesis of The Phytoalexin Elicitor Hexasaccharide

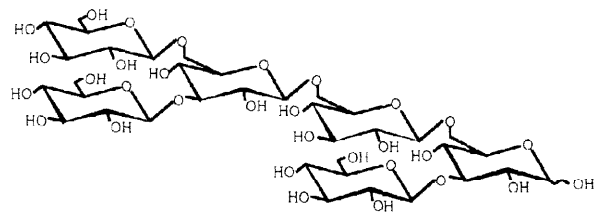
**Wei Wang, Fanzuo Kong***

Research Center for Eco-Environmental Sciences, Academia Sinica, P.O.Box 2871, Beijing 100085, P. R. China

Received 18 August 1997; revised 30 September 1997; accepted 20 November 1997

***Abstract***: A highly convergent synthesis of the elicitor-active D-glucohexatose **1** and its variant **19** was achieved via coupling of the trisaccharide donor **14** with the trisaccharide acceptor **15** followed by deprotection. **14** and **15** were obtained from rearrangement of the orthoesters **6** and **5** respectively which were prepared quantitatively from coupling of the disaccharide **4** with acetobromoglucose and 6-O-chloroacetylated acetobromoglucose respectively. © 1998 Elsevier Science Ltd. All rights reserved.

It is known that partial acid hydrolysis of mycelial walls of the fungus *Phytophthora megasperma f. sp. Glycinea* gives a mixture of oligosaccharides being capable of stimulating the formation of phytoalexins in soybean[1]. Biological assays of several oligosaccharides revealed that D-hexaglucoside is the minimum structural element required for high elicitor activity[2]. It is to be noted that the β-D-configuration at C-1 in the original elicitor hexasaccharide is not required for the elicitor-activity[3f], and this suggests that the hexasaccharide **1** and its variants can be used as valuable materials for biological investigation. The syntheses of heptasaccharide[3a,3b,3c,3d,3e,3g,3j] and methyl, allyl glycosides of the hexasaccharide[3f,3h,3i] have been reported. Almost all of the syntheses involved 2- or 3- regioselectivity of glucopyranoside with tedious separation, and the use of expensive reagents. Here we present a new strategy for the highly convergent and effective synthesis of the free hexasaccharide **1** and its 1,2-O-ethylidenated variant **19**.



**1**

As shown in the scheme, 1,2-O-(R,S)ethylidene-4,6-O-benzylidene- α -D-glucopyranoside (**2**) was used as the key starting material that was readily prepared from the conventional 4,6-O-benzylidenation[4,5] of 1,2-O-(R,S)ethylidene- α -D-glucopyranoside[6]. Coupling[7] of **2** with acetobromoglucose in the presence of AgOTf afforded unique 1,3-β-linked disaccharide **3** as crystals in a high yield (87%). Debenzylidenation[3h] with

0040-4039/98/$19.00 © 1998 Elsevier Science Ltd. All rights reserved.
*PII:* S0040-4039(98)00087-2

dichloroacetic acid-water (5:1 v/v) was carried out smoothly furnishing crystalline diol **4** in a satisfactory yield (90%). An attempt for selective 6-O-glycosylation of **4** with acetobromoglucose was not successful since a 4,6-di-O-glycosylated tetrasaccharide was the major product even at low temperature (-20 to -40°C) with a small quantity of the bromide donor (1 equiv). The high reactivity of the 4-OH of **4** was perhaps caused by the deformation of the 1,2-O-ethylidene-fused pyranose ring. However, we are gratified to find that coupling of **4** with acetobromoglucose at room temperature in the presence of 2,4-lutidine(1.5 equiv), gave orthoester **6** as crystals in a quantitative yield. TMSOTf catalyzed rearrangement[8] of **6** selectively offered the 1,6-linked trisaccharide **8** (76%), its acetylation gave **10**. To confirm the selectivity of rearrangement, **6** was acetylated first then isomerized with TMSOTf producing a compound the same as **10** (74%). **6** and **8** were easily identified from their $^1$H NMR spectra, the former showed seven acetyl methyl signals at δ1.99-2.11 and one upfield methyl of orthoester at δ1.74(S) or 1.75(R), but the latter gave all the eight methyl signals at the acetyl region (δ2.00-2.15). Deethylidenation with 90% $CF_3COOH$ was going smoothly giving crystalline 1,2-diol **11**. Acetylation of **11** followed by selective deacetylation at C-1, then treatment[9] with $CCl_3CN$ furnished the trisaccharide donor **14**. The synthesis of the trisaccharide acceptor **15** was accomplished by the same strategy as described for the synthesis of **8** except the use of 6-O-chloroacetylated acetobromoglucose instead of acetobromoglucose. The orthoester **5** was also crystalline, its isomerization, acetylation, followed by dechloroacetylation[10] gave the desired trisaccharide acceptor **15** as crystals. Coupling[11] of **14** with **15** using TMSOTf as the promoter afforded the acetylated hexasaccharide **16**, deacetylation of **16** gave a hexasaccharide variant **19**, while deethylidenation, acetylation, followed by deacetylation furnished the free hexasaccharide **1** as an amorphous solid. In all of the synthesis, very easily accessible materials and reagents were used and the reactions were carried out smoothly in high or good yield. Most of the intermediates involved in the synthesis were mixtures consisting of R and S isomers[12] which were well separated and had no difference in reactivity. Therefore here we present a highly convergent and effective synthesis of the title compound, suitable for a large scale preparation.

ACKNOWLEDGEMENT

Project 29672049 was supported by the National Natural Science Foundation of China.

REFERENCES AND NOTES

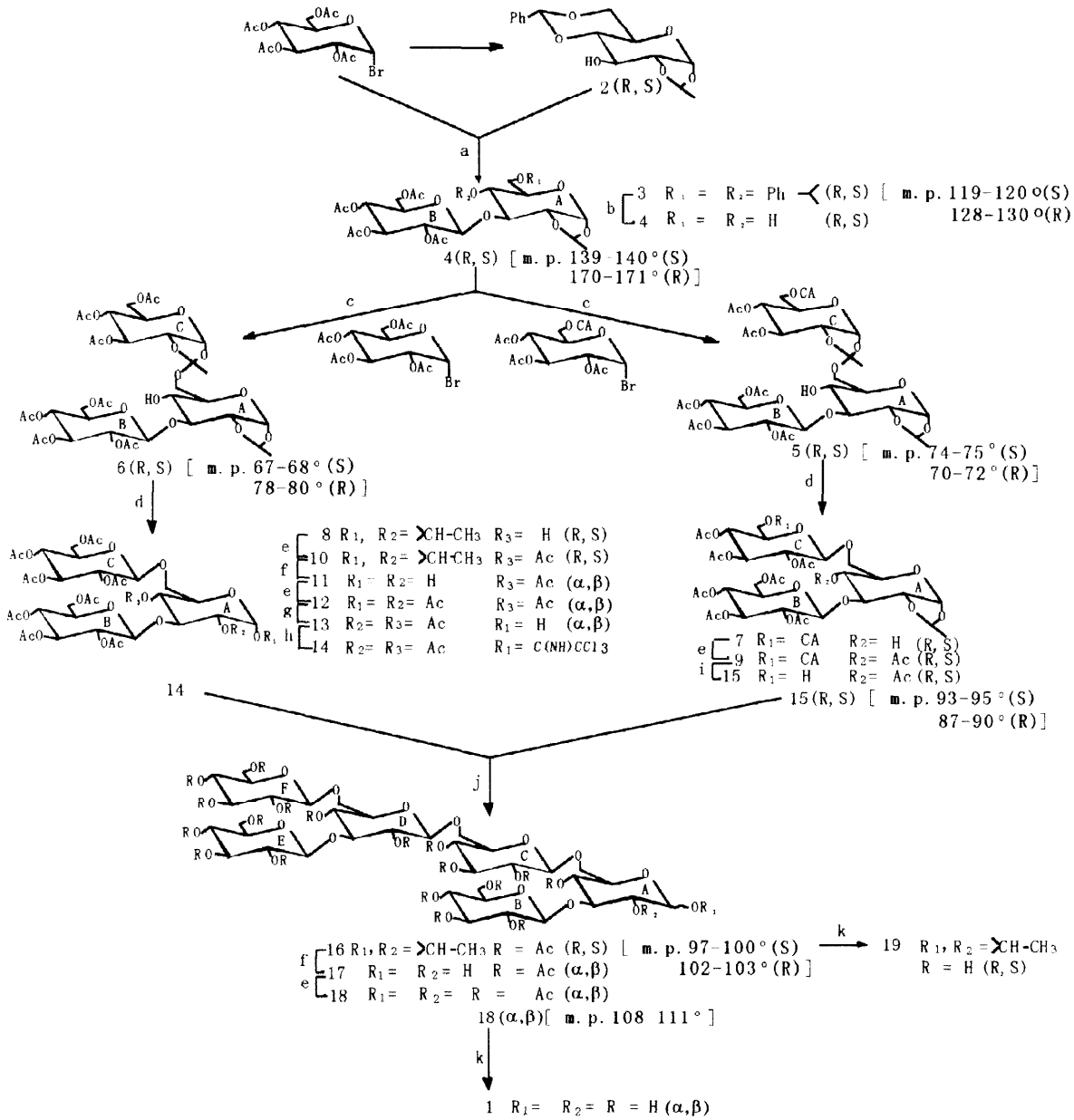
1. (a) Sharp, J.K.; Valent, B. and Albersheim, P. *J. Biol. Chem.*, **1984**, 259, 11312.
(b) Sharp, J.K.; McNeil, M. and Albersheim, P. *J. Biol. Chem.*, **1984**, 259, 11321.
(c) Sharp, J.K.; Albersheim, P. and Lindberg, B. *J. Biol. Chem.*, **1984**, 259, 11341.
2. Cheorg, J.J.; Birberg, W.; Ogawa, T. and Hahn, M.G. *Plant Cell.*, **1991**, 3, 127.
3. Synthesis: (a) Ossowski, P.; Pilotti, A.; Garegg, P.J. and indberg, B. *Angew. Chem., Int. Ed. Engl.*, **1983**, 22, 793. (b) Ossowski, P.; Pilotti, A.; Garegg, P.J. and indberg, B. *J. Biol. Chem.*, **1984**, 259, 11337. (c) Fugedi, P.; Birberg, W.; Garegg, P.J. and Pilotti, A. *Carbohydr. Res.*, **1987**, 164, 297. (d) Fugedi, P.; Garegg, P.J.; Kvarnstrom, I. and Pilotti, A. *J. Carbohydr. Chem.*, **1989**, 8, 47.(e)Fugedi, P.; Garegg, P.J.; Kvarnstrom, I. and Svansson, L. *J. Carbohydr. Chem.*, **1988**, 7, 389. (f) Hong, N. and Ogawa, T. *Tetrahedron Lett.*, **1990**, 31, 3179. (g) Lorentzen, P.J.; Helpap, B. and Lockhoff, O. *Angew. Chem., Int. Ed. Engl.*,**1991**, 30, 1681. (h) Hong, N.; Nakahara, Y. and Ogawa, T. *Proc. Jpn. Acad.*, **1993**, 698, 55. (i) Yamada, H.; Harad, T. and Takahashi, T. *J. Am. Chem. Soc.*, **1994**, 116, 7919. (j) Nicolaou, K.C.; Winssinger, N.; Pastor, J. and Derosse, F. *J. Am. Chem. Soc.*, **1997**, 119, 449.

4. Buchanan, J.G. and Schwarz, J.C.P. *J. Chem. Soc.*, **1962**, 4770.
5. Evans, M.E. *Carbohydr. Res.*, **1972**, 21, 473.
6. Betaneli, V.I.; Ovchinnikov, M.V. and Kochetkov, N.K. *Carbohydr. Res.*, **1982,** 107, 285.
7. Garegg, P.J. and Hultberg, H. *Carbohydr. Res.*, **1982**, 110, 261.
8. Gass, J.; Strobl, M. and Kosma, P. *Carbohydr. Res.*, **1993,** 244, 69.
9. Schmidt, R.R. *Angew. Chem., Int. Ed. Engl.* **1986**, 25, 212.
10. Glaudemans, C.P.J. and Bertolini, M.J. *Methods in Carbohydr. Chem.* VIII, 271.
11. Sato, S.; Ito, Y.; Nukada, T.; Nakahara, Y. and Ogawa, T. *Carbohydr. Res.*, **1987**, 167, 197.

12. All of the new compounds (**3-19**) gave satisfactory elemental analysis results. Selected physical data are as follows: **1**. amorphous solid $[\alpha]_D$ -14.9° (c 0.1, MeOH); ESMS for $C_{36}O_{31}H_{62}$(990.87): 989.6$[M-H]^+$. **18.** $[\alpha]_D$ +16.0° (c 0.5, $CHCl_3$), m.p. 108-111°C; $^1H$ NMR ($CDCl_3$, 400MHz) $\delta_H$ 6.13(d, 2/3H, $J_{1,2}$ 3.1Hz,αH-1), 5.50(d, 1/3H, $J_{1,2}$ 9.3Hz,βH-1), 5.47-5.13(m, 16H, H-$2_{A\text{-}F}$,$3_{B,C,E,F}$,$4_{A\text{-}F}$), 4.85-4.45(m, 5H, $J_{1,2}$ 8.3Hz, H-$1_{B\text{-}F}$), 4.40-3.35(m, 20H, H-$3_{A,D}$,$5_{A\text{-}F}$,$6_{A\text{-}F}$), 2.04-1.88(m, 60H, 20C$H_3$CO). **16.** (R) $[\alpha]_D$ +15.9° (c 1.1, $CHCl_3$), m.p. 102-103°C; $^1H$ NMR ($CDCl_3$, 400MHz) $\delta_H$ 5.54(d, 1H, $J_{1,2}$ 4.6Hz, H-$1_A$), 5.45(q, 1H, J 4.4Hz, $CH_3CH$), 5.20-4.78(m, 15H, H-$2_{B\text{-}F}$,$3_{B,C,E,F}$,$4_{A\text{-}F}$), 4.74, 4.67, 4.60, 4.55, 4.49(5d, 5H, $J_{1,2}$ 8.2Hz, H-$1_{B\text{-}F}$), 4.31-3.41(m, 21H, H-2, $3_{A,C}$,$5_{A\text{-}F}$,$6_{A\text{-}F}$), 2.02-1.91(m, 54H, 18C$H_3$CO), 1.23(d, 3H, J 4.4Hz, C$H_3$CH). (S) $[\alpha]_D$ -8.6° (c 1.5, $CHCl_3$), m.p. 97-100°C; $^1H$ NMR ($CDCl_3$, 400MHz) $\delta_H$ 5.51(d, 1H, $J_{1,2}$ 4.1Hz, H-$1_A$), 5.25-4.83(m, 16H, H-$2_{B\text{-}F}$ ,$3_{B,C,E,F}$ ,$4_{A\text{-}F}$ , $CH_3CH$), 4.80, 4.73, 4.62, 4.58, 4.56(5d, 5H, $J_{1,2}$ 8.2Hz, H-$1_{B\text{-}F}$), 4.33-3.41(m, 21H, H-2, $3_{A,C}$ ,$5_{A\text{-}F}$ ,$6_{A\text{-}F}$), 2.13-1.93(m, 54H, 18C$H_3$CO), 1.47(d, 3H, J 4.9Hz, C$H_3$CH). **8**. (R) $[\alpha]_D$ +1.7° (c 0.4, $CHCl_3$), m.p. 77-78°C; $^1H$ NMR ($CDCl_3$, 400MHz) $\delta_H$ 5.63(d, 1H, $J_{1,2}$ 4.4 Hz, H-$1_A$), 5.50(q, 1H, J 4.7Hz, $CH_3CH$), 4.81(d, 1H, $J_{1,2}$ 7.9Hz, H-$1_C$), 4.54(d, 1H, $J_{1,2}$ 7.9Hz, H-$1_B$), 2.08-2.00(8s, 24H, 8C$H_3$CO), 1.36(d, 3H, J 4.7Hz, C$H_3$CH). (S) $[\alpha]_D$ -8.3° (c 0.4, $CHCl_3$), m.p. 87-88°C; $^1H$ NMR ($CDCl_3$, 400MHz) $\delta_H$ 5.56(d, 1H, $J_{1,2}$ 5.0 Hz, H-$1_A$), 5.21(q, 1H, J 5.2Hz, $CH_3CH$), 4.90(d, 1H, $J_{1,2}$ 8.0Hz, H-$1_C$), 4.73(d, 1H, $J_{1,2}$ 8.0Hz, H-$1_B$), 2.15-2.00(8s, 24H, 8C$H_3$CO), 1.48(d, 3H, J 5.2Hz, C$H_3$CH). 7. (R) $[\alpha]_D$ +1.7° (c 0.4, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400MHz) $\delta_H$ 5.62(d, 1H, $J_{1,2}$ 4.4 Hz, H-$1_A$), 5.50(q, 1H, J 4.4Hz, $CH_3CH$), 4.79(d, 1H, $J_{1,2}$ 7.8 Hz, H-$1_C$), 4.55(d, 1H, $J_{1,2}$ 7.8Hz, H-$1_B$), 4.10(s, 2H, C$H_2$ClCO), 2.07-1.98(7s, 21H, 7C$H_3$CO), 1.35(d, 3H, J 4.4Hz, C$H_3$CH). (S) $[\alpha]_D$ -8.3° (c 0.4, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400MHz) $\delta_H$ 5.50(d, 1H, $J_{1,2}$ 4.7 Hz, H-$1_A$), 5.20(q, 1H, J 4.7Hz, $CH_3CH$), 4.80(d, 1H, $J_{1,2}$ 8.0Hz, H-$1_C$), 4.64(d, 1H, $J_{1,2}$ 8.0Hz, H-$1_B$), 4.11(s, 2H, C$H_2$ClCO), 2.07-1.99 (7s, 21H, 7C$H_3$CO), 1.47(d, 3H, J 4.7Hz, C$H_3$CH ). **6**. (R) $[\alpha]_D$ +49.3° (c 0.8, $CHCl_3$), m.p. 78-80°C; $^1H$ NMR ($CDCl_3$, 400MHz) $\delta_H$ 5.74(d, 1H, $J_{1,2}$ 5.1Hz, H-$1_C$), 5.50(d, 1H, $J_{1,2}$ 4.7 Hz, H-$1_A$), 5.41(q, 1H, J 4.9Hz, $CH_3CH$), 4.63(d, 1H, $J_{1,2}$ 7.8 Hz, H-$1_B$), 2.09-1.99(7s, 21H, 7C$H_3$CO), 1.75(s, 3H, C$H_3CO_3$), 1.35 (d, 3H, J 4.9Hz, C$H_3$CH). (S) $[\alpha]_D$ +43.7° (c 1.3, $CHCl_3$), m.p. 67-68°C; $^1H$ NMR ($CDCl_3$, 400MHz) $\delta_H$ 5.73(d, 1H, $J_{1,2}$ 5.1Hz, H-$1_C$), 5.49 (d, 1H, $J_{1,2}$ 4.9 Hz, H-$1_A$), 5.40(q, 1H, J 4.9Hz, $CH_3CH$), 4.64(d, 1H, $J_{1,2}$ 7.8 Hz, H-$1_B$), 2.11-2.03(7s, 21H, 7C$H_3$CO), 1.74(s, 3H, C$H_3CO_3$), 1.36 (d, 3H, J 4.9Hz, C$H_3$CH). **5**. (R) $[\alpha]_D$ +4.5° (c 1.5, $CHCl_3$), m.p. 70-72°C; $^1H$ NMR ($CDCl_3$, 400MHz) $\delta_H$ 5.73(d, 1H, $J_{1,2}$ 5.1Hz, H-$1_C$), 5.51 (d, 1H, $J_{1,2}$ 4.6 Hz, H-$1_A$), 5.42(q, 1H, J 4.6Hz, $CH_3CH$), 4.66(d, 1H, $J_{1,2}$ 8.0 Hz, H-$1_B$), 4.10(s, 2H, C$H_2$ClCO), 2.12-2.04(6s, 18H, 6C$H_3$CO), 1.74(s, 3H, C$H_3CO_3$), 1.39 (d, 3H, J 4.6Hz, C$H_3$CH). (S) $[\alpha]_D$ -3.5° (c 1.1, $CHCl_3$), m.p. 74-75°C; $^1H$ NMR ($CDCl_3$, 400MHz) $\delta_H$ 5.72(d, 1H, $J_{1,2}$ 5.8Hz, H-$1_C$), 5.57(q, 1H, J 5.2Hz, $CH_3CH$), 5.53(d, 1H, $J_{1,2}$ 5.2 Hz, H-$1_A$), 4.68(d, 1H, $J_{1,2}$ 7.9 Hz, H-$1_B$), 4.13(s, 2H, C$H_2$ClCO), 2.13-2.04(6s, 18H, 6C$H_3$CO), 1.75(s, 3H, C$H_3CO_3$), 1.48(d, 3H, J 5.2Hz, C$H_3$CH). **3**. (R) $[\alpha]_D$ 66.8° (c 1.7, $CHCl_3$), m.p. 128-130°C; $^1H$ NMR ($CDCl_3$, 200MHz) $\delta_H$ 5.57(s, 1H, PhC$H$), 5.50(d, 1H, $J_{1,2}$

4.9Hz, H-$1_A$), 5.45(q, 1H, J 5.3Hz, $CH_3CH$), 4.76(d, 1H, $J_{1,2}$ 7.8 Hz, H-$1_B$), 2.06, 2.01, 2.01, 2.00(4s, 12H, $4CH_3CO$), 1.41(d, 3H, J 5.3Hz, $CH_3CH$). (S) $[\alpha]_D$ -45.4° (c 1.6, $CHCl_3$), m.p.119-120°C; $^1H$ NMR ($CDCl_3$, 400MHz) $\delta_H$ 5.58(s, 1H, PhCH), 5.48(d, 1H, $J_{1,2}$ 5.1Hz, H-$1_A$), 5.44-4.72(m, 4H, H-$2_B$,$3_B$,$4_B$, $CH_3CH$), 4.70(d, 1H, $J_{1,2}$ 8.0 Hz, H-$1_B$), 2.09, 2.06, 2.03, 2.01(4s, 12H, $4CH_3CO$), 1.50 (d, 3H, J 5.1Hz, $CH_3CH$).

Scheme *Synthesis of Phytoalexin Accumulation Elicitors*




Reagents and conditions: a. AgOTf, MS 4A in $CH_2Cl_2$, 5 °C (87%). b. 5/1 $Cl_2CHCOOH/H_2O$, 50 °C (90%). c. AgOTf, 2,4- lutidine, MS 4A in $CH_2Cl_2$, RT(100%). d. TMSOTf, MS 4A in $CH_2Cl_2$(76%) e. $Ac_2O$, Pyridine. f. 90% $F_3CCOOH$, RT (>85%). g. $NH_2NH_2$·AcOH in DMF, RT(96%). h. $CCl_3CN$, DBU in $CH_2Cl_2$, 0 °C (91%). i. $NH_2CSNH_2$ in EtOH, 50 °C (89%). j. TMSOTf, MS 4A in $CH_2Cl_2$, -30 °C (86%). k. NaOMe—MeOH .