Pergamon

Tetrahedron Letters 40 (1999) 5–8

TETRAHEDRON LETTERS

Expeditious Route to F unit Building Block of Moenomycin A

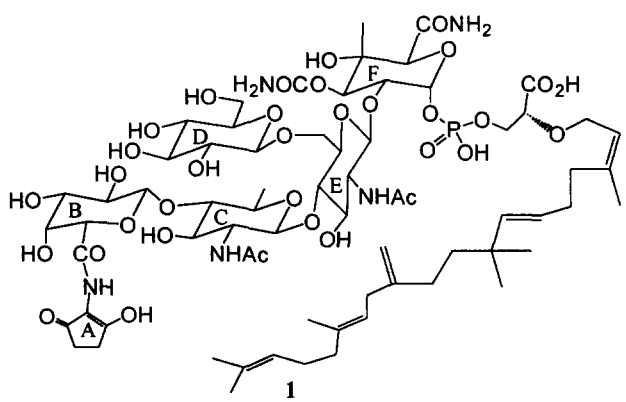
Ramesh Kakarla*, Manuka Ghosh, Jan A. Anderson, Richard G. Dulina and Michael J. Sofia

Intercardia Research Laboratories, 8 Cedar Brook Drive, Cranbury, NJ 08852

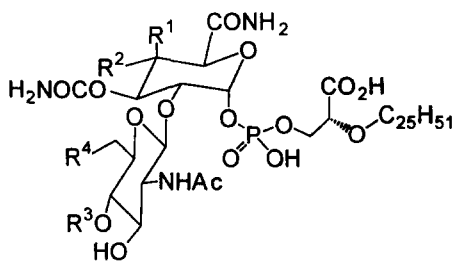
Received 18 September 1998; revised 13 October 1998; accepted 16 October 1998

Abstract: Synthesis of the versatile F sugar unit building block of moenomycin A, Phenyl 2-O-levulinoyl-4-C-methyl-1-thio-β-D-glucopyranosiduronic acid is described starting from phenyl 1-thio-β-D-galactopyranoside. The key synthetic steps included: (I) Regioselective protection of the 3-OH group of phenyl 6-O-trityl-1-thio-β-D-galactopyranoside as its TBDMS ether, (ii) TBAF mediated TBDMS group migration from the C-3 to C-2 position of phenyl 3-O-TBDMS-4-C-methyl-6-O-trityl-1-thio-β-D-galactopyranoside, and (iii) Selective deprotection of TBDMS and trityl groups in phenyl 2-O-levulinoyl-3-O-TBDMS-4-C-methyl-6-O-trityl-1-thio-β–D-glucopyranoside by DDQ.

Moenomycin A[1] (**1**, Figure 1) belongs to the moenomycin family of phosphoglycolipid antibiotics,[2] and is a potent inhibitor of bacterial cell wall peptidoglycan biosynthesis.[3] Moenomycin A is the major and most active constituent of animal nutritional product[2] Flavomycin[R]. The disaccharide **2**[4] (Figure 1) is the smallest fragment of moenomycin A, which retains the full biological activity of the parent compound. Further studies[5] on the degradation products of **1** revealed the moenuronamide part (F unit with phospholipid) shows some antibacterial activity. However, degradation products of moenomycin C_1 and A_{12}, which contain a galacturonamide moiety as the F unit, revealed that the trisaccharides **3**[6] and **4**[7] (Figure 1) were the minimum structures required for biological activity.



1



	R^1	R^2	R^3	R^4
2	CH_3	OH	H	OH
3	OH	H	β-Qui-NAc	OH
4	OH	H	β-Qui-NAc	H

Figure 1

0040-4039/99/$ - see front matter
PII: S0040-4039(98)02217-5

In order to probe the structure-activity relations of Moenomycin A degradation product **2** through a combinatorial library, we required a suitable protected F unit building block. We envisioned the moenuronamide compound **5** as a versatile building block to generate a three dimensional library. Diversity at C_1, C_2 and C_3 hydroxyl positions of compound **5** was expected to arise by introducing various phospholipids, monosaccharides and carbamate functionalities at respective positions (Figure 2). The existing synthetic methods[8] for the preparation of 4-C-methyl glucopyranosiduronic acid derivatives were not suitable to prepare the required building block **5**. In this communication, we present a novel and efficient method for the synthesis of compound **5** starting from phenyl 1-thio-β-D-galactopyranoside[9] (**6**).

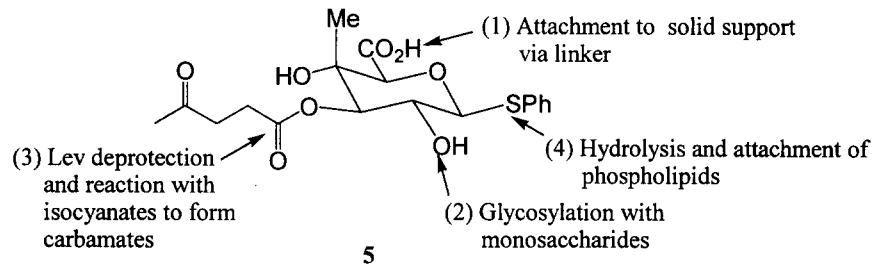
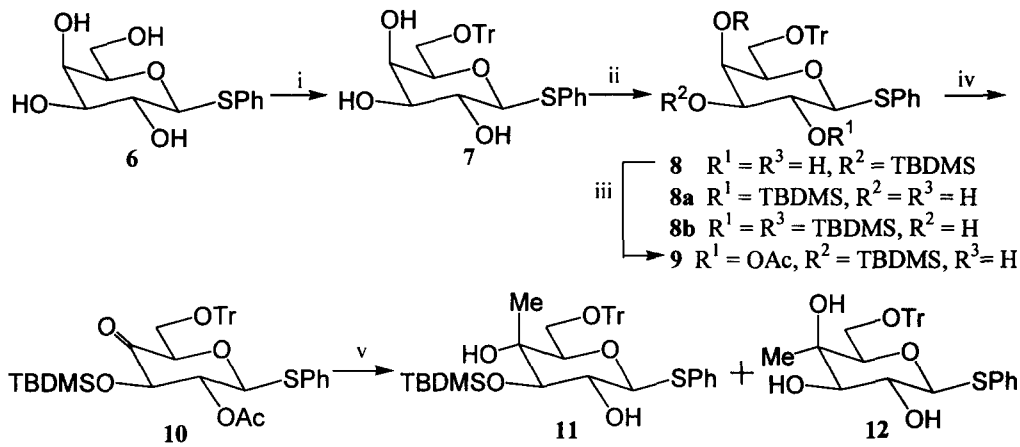


Figure 2

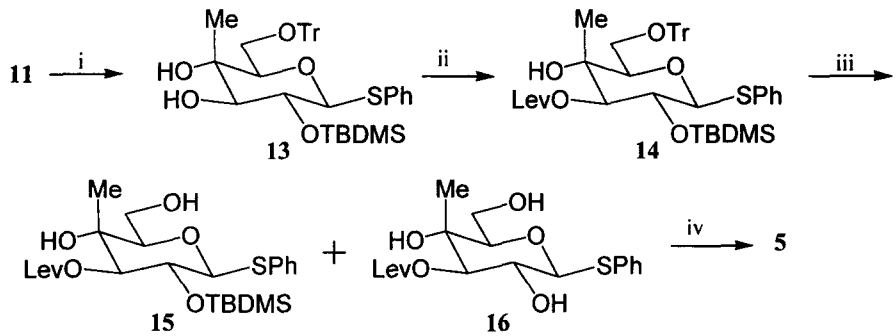
Tritylation of phenyl 1-thio-β-D-galactopyranoside (**6**) in pyridine and DMAP at 120 ^{0}C for 6h furnished 6-O-trityl compound **7** in quantitative yield. Selective protection of the 3-OH group in compound **7** as its TBDMS (tert-butyldimethylsilyl) ether using TBDMSCl and imidazole in DMF for 2h at rt afforded the 3-O-TBDMS derivative **8** in 80% yield along with 10% of the 2-O-TBDMS derivative **8a**, and trace amounts of the 2,4-di-O-TBDMS derivative **8b**. The structures of **8**, **8a** and **8b** were confirmed by conversion into their corresponding acetates. Regioselective acetylation of 3-O-TBDMS derivative **8** with Ac_2O and DMAP in pyridine at 0^{0}C to 10^{0}C gave us the 2-O-acetyl derivative **9** in quantitative yield. The structure of the 2-O-acetylated compound **9** was confirmed by its ^{1}H NMR,[10] which showed one $C\underline{H}_3$ signal at 2.10 ppm and a deshielded H-2 proton signal as a triplet at 5.16 ppm. PDC oxidation of the 4-OH group in compound **9** furnished the ulose derivative **10** in 75% yield. Grignard reaction of ulose derivative **10** with MeMgCl in the presence of $CeCl_3$ in toluene at -78^{0}C to rt resulted in 3:1 ratio (80% yield) of phenyl 3-O-TBDMS-4-C-methyl-6-O-trityl-1-thio-β-D-glucopyranoside (**11**) and phenyl 4-C-methyl-6-O-trityl-1-thio-β-D-galac-topyranoside (**12**) (Scheme 1). The stereochemical configuration at C-4 of 4-C-methyl-gluco derivative **11** and 4-C-methyl-galacto derivative **12** was confirmed by ^{13}C NMR,[11] which showed characteristic 4-C-Methyl carbon signals[12] at 15.77 and 20.65ppm, respectively.

The 4-C-methyl-gluco derivative **11** when treated with TBAF[13] at rt for 15 min resulted in TBDMS group migration to give compound **13** in 90% yield. The 3-OH group in compound **13** was converted in 85% yield to its levulinoyl ester **14** by treatment with levulinic acid, DCC and DMAP in dichloromethane at refluxing conditions for 10 h. Simulta-



Scheme 1: (i) TrCl, Py, DMAP, 120 ^{0}C, 6 h; (ii) TBDMSCl, imidazole, DMF, rt, 2 h; (iii) Ac_2O, Py, DMAP, 0 ^{0}C to 10 ^{0}C, 1 h; (iv) PDC, Ac_2O, CH_2Cl_2, reflux, 2 h; (v) MeMgCl, $CeCl_3$, Toluene, -76 ^{0}C to rt, 14h

neous deprotection of trityl and TBDMS protecting groups in compound **14** was achieved by modifying the existing DDQ catalyzed TBDMS deprotection protocol.[14] Refluxing compound **14** with 0.5 equivalents of DDQ in 90% aqueous acetonitrile for 4 h gave compound **16** in 70% yield along with a 15% yield of phenyl 2-O-TBDMS-3-O-Levu-linoyl-4-C-methyl-1-thio-β-D-glucopyranoside (**15**). Jones oxidation[15] of 3-O-levulinoyl-4-C-methyl-glucopyranoside derivative **16** furnished **5** in 65% yield (Scheme 2). The structure of compound **5** was confirmed by ^{1}H NMR, ^{13}C NMR, MS and elemental analysis.[16]



Scheme 2: (i) TBAF, THF, rt, 15 min; (ii) Levulinic acid, DCC, DMAP, CH_2Cl_2, reflux, 24 h; (iii) 90% aq. CH_3CN, DDQ, 90 ^{0}C, 4 h; (iv) Jones reagent, acetone, sonication, 30 ^{0}C, 1 h

In conclusion, we developed an expeditious (17% overall yield) route to F Unit building block (**5**) of Moenomycin A. This versatile building block **5** will be used as an acceptor in the construction of a combinatorial library based on the disaccharide phosphoglycolipid **2**. The selective protection of compounds **8** and **9** with TBDMS and acetate groups should find general utility for carbohydrate building block synthesis. We have also demonstrated for the first time that in the presence of a thiophenyl group and a levulinoyl ester, DDQ is useful in deprotecting TBDMS and trityl groups from carbohydrate molecules.

References and notes

1. a) Welzel, P.; Witteler, F.-J.; Muller, D.; Riemer, W. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 121-123. b) Welzel, P.;Wietfeld, B.; Kunisch, F.; Schubert, T.; Hobert, K.; Duddeck, H.; Muller, D.; Huber, G.; Maggio, J. E.; Williams, D. H. *Tetrahedron* **1983**, 39, 1583-1591, and references cited therein.
2. Huber, G. *Antibiotics*; (Ed.) Hahn, F. E.; Springer: Berlin; **1979**, vol 5, 135-153.
3. van Heijenoort, J.; van Heijenoort, Y.; Welzel, P. Antibiotic Inhibition of Bacterial Cell Wall Surface Assembely and Function; (Eds.) Actor, P.; Danco-Moore, L.; Higgins, M. L.; Salton, M. R. J.; Shockman, G. D.; *American Society for Microbiology*: Washington, **1988**, 549-557.
4. Welzel, P.; Kunisch, F.; Kruggel, F.; Stein, H.; Scherkenbeck, J.; Hiltmann, A.; Duddeck, H.; Muller, D.; Maggio, J. E.;Fehlhaber, H. -W.; Siebert, G.; van Heijenoort, Y.; van Heijenoort, J. *Tetrahedron* **1987**, *43*, 585-598.
5. Fehlhaber, H.-W.; Girg, M.; Seibert, G.; Hobert, K.; Welzel, P.; van Heijenoort, Y.; van Heijenoort, J. *Tetrahedron* **1990**, *46*, 1557-1568.
6. Hebler-Klintg, M; Hobert, K.; Biallab, A.; Siegels, T.; Hiegemann, M.; Maulshagen, A.; Muller, D.; Welzel, P.; Huber, G.; Bottger, D.; Markus, A.; Seibert, G.; Stark, A.; Fehlhaber, H.-F.; van Heijenoort, Y.; van Heijenoort, J. *Tetrahedron* **1993**, *49*, 7667-7678.
7. Donnerstag, A.; Marzian, S.; Muller, D.; Welzel, P. *Tetrahedron* **1995**, *51*, 1931-1940.
8. a) Sato, K.-I.; Kubo, K.; Hong, N.; Kodama, H.; Yoshimura, J. J. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 938-942. b) Welzel, P.; Bulian, H.-P.; Maulshagen, A.; Muller, D.; Snatzke, G. *Tetrahedron* **1984**, *40*, 3657-3666. c) Plewe, M.; Sandhoff, K.; Schmidt, R. R. *Carbohydrate Res.* **1992**, *235*, 151-161. d) Hansson, T. G.; Plobeck, N. A. *Tetrahedron* **1995**, *51*, 11319-11326.
9. a) Ferrier, R. J.; Furneaux, R. H. *Carbohydrate Res.* **1976**, *52*, 63-68. b) Sarkar, A. K.; Matta, K. L. *Carbohydrate Res.* **1992**, *233*, 245-250.
10. Compound **9**: ^{1}H NMR ($CDCl_3$ + 2 drops D_2O): δ 7.60-7.10 (m, 5H), 5.16 (t, J = 9.6Hz, 1H), 4.54 (d, J = 9.6Hz, 1H), 3.75-3.50 (m, 4H), 3.28-3.22 (m, 1H), 2.10 (s, 3H), 0.85 (s, 9H), 0.06 and 0.05 (each s, 6H).
11. a) Compound **11**: ^{1}H NMR ($CDCl_3$ + 2 drops D_2O) δ 7.70-7.20 (m, 5H), 4.61 (d, J = 9.6Hz, 1H), 3.52-3.40 (m, 3H), 3.26-3.16 (m, 2H), 0.90 (s, 3H), 0.85 (s, 9H), 0.09 and 0.07 (each s, 6H). Selected peaks in ^{13}C NMR ($CDCl_3$) δ 88.89, 87.05, 81.51, 81.1973.09, 71.70, 62.66, 25.93, 18.34, 15.77 (4-C-Me), -4.40 and -4.73. b) Compound **12**: ^{1}H NMR ($CDCl_3$ + 2 drops D_2O) δ 7.69-7.22 (m, 5H), 4.56 (d, J = 9.6Hz, 1H), 3.65 (t, J = 9.6Hz), 3.57-3.25 (m, 3H), 3.17 (d, J = 9.6Hz, 1H), and 0.95 (s, 3H). Selected peaks in ^{13}C NMR ($CDCl_3$ + 2 drops D_2O) δ 88.20, 87.12, 81.34, 78.08, 73.14, 70.35, 62.95, 20.65 (4-C-Me).
12. a) Miljkovic, M.; Gligorijevic, M. Satoh, T.; Miljkovc, D. *J. Org. Chem.* **1974**, *10*, 1379-1384. b) Miljkovic, M.; Gligorijevic, M. Satoh, T.; Glisin, D. *J. Org. Chem.* **1974**, *26*, 3847-3850.
13. a) Wuts, P. G. M.; Bigelow, S. S. *J. Org. Chem.* **1988**, *53*, 5023-5034. b) Franke, F.; Guthrie, R. D. *Aust. J. Chem.* **1978**, *31*, 1285-1290. c) Torisawa, Y.; Shibasaki, M.; Ikegami, S. *Tetrahedron Lett.* **1979**, 21, 1865-1868. d) Ogilvie, K. K.; Beaucage, S. L.; Schifman, A. L.; Theriault, N. Y.; Sadana, K. L. *Can. J. Chem.* **1978**, *56*, 2768-2780. e) Jones, S. S.; Reese, C. B. *J. Chem. Soc., Perkin Trans. I* **1979**, 2762-2764. f) Ogilvie, K. K.; Entwistle, D. W. *Carbohydrate Res.* **1981**, *89*, 203-210.
14. Tanemura, K.; Suzuki, T.; Horaguchi, T. *J. Chem. Soc. Perkin Trans. I* **1992**, 2997-2998.
15. Allanson, N. A.; Liu, D.; Chi, F.; Jain, R. K.; Chen, A.; Ghosh, M.; Hong, L.; Sofia, M. J. *Tetrahedron Lett.* **1998**, 39, 1889-1892.
16. Compound **5**: mp, 60-62 ^{0}C; TLC (CH_2Cl_2 / MeOH, 4:1) R_f = 0.2.; MS (EI): 416 $(M+NH_4)^+$; Elemental analysis, Calc: C, 54.26; H, 5.57; S, 8.05. Found: C, 54.45; H, 5.68; S, 7.98. ^{1}H NMR (CD_3OD) δ 7.53-7.18 (m, 5H), 4.95 (d, J = 9.6Hz, 1H), 4.62 (d, J = 9.6Hz, 1H), 3.85 (br s, 1H), 3.21 (t, J = 9.6Hz, 1H), 2.03 (s, 3H) and 1.04 (s, 3H).; ^{13}C NMR (CD_3OD) δ 16.73, 29.05, 29.78, 38.73, 70.40, 73.38, 81.55, 89.05, 129.08, 130.10, 132.36, 133.54, 134.35, 173.87, 208.61.