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Total Synthesis of Sphingofungin E from D-Glucose

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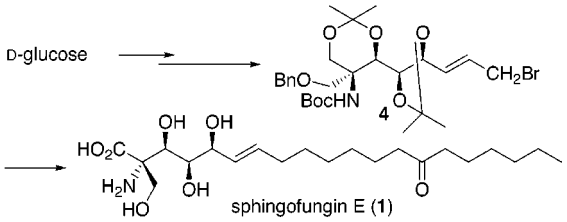
ABSTRACT



Total synthesis of sphingofungin E (1) is described. Overman rearrangement of an allylic trichloroacetimidate derived from diacetone-D-glucose generated tetra-substituted carbon with nitrogen, and subsequent Wittig olefination afforded the highly functionalized part in sphingofungin E (4) stereoselectively. Coupling reaction of 4 with the C_{12} hydrophobic part, followed by further manipulation, completed the total synthesis.

Sphingofungins are a new class of antifungal agents isolated from *Aspergillus* and *Paecilomyces* and are reported to be potent and specific inhibitors of serine palmitoyl transferase.[1,2] The structure elucidation study revealed that sphingofungins are novel polyhydroxy amino acid derivatives bearing a C_{20} straight carbon chain with *E*-olefin and four contiguous asymmetric centers.[3] While sphingofungins A, B, C, and D have one distal (*R*)-hydroxy group at C-14, sphingofungins E (**1**) and F (**2**) own a ketone carbonyl at C-14 instead and have another characteristic structural feature: they bear an extra carbon unit at C-2 possessing α,α-disubstituted α-amino acid structures. It was also shown that sphingofungin E is a 5-hydroxy derivative of myriocin **3**,[4] which has recently attracted renewed interest because of its potent immunosuppressive activity.[5] Such interesting structures and their potent biological properties have naturally received sizable attention of the synthetic community, and several reports on total synthesis of sphingofungins D, B, and F have been described.[6] Recently, total synthesis of

(1) van Middlesworth, F.; Giacobbe, R. A.; Lopez, M.; Garrity, G.; Bland, J. A.; Bartizal, K.; Fromtling, R. A.; Polishook, J.; Zweerink, M.; Edison, A. M.; Rozdilsky, W.; Wilson, K. E.; Monaghan, R. L. *J. Antibiot*. **1992**, *45*, 861.

(2) Horn, W. S.; Smith, J. L.; Bills, G. F.; Raghoobar, S. L.; Helms, G. L.; Kurtz, M. B.; Marrinan, J. A.; Frommer, B. R.; Thornton, R. A.; Mandala, S. M. *J. Antibiot*. **1992**, *45*, 1692.

(3) van Middlesworth, F.; Dufresne, C.; Wincott, F. E.; Mosley, R. T.; Wilson, K. E. *Tetrahedron Lett*. **1992**, *45*, 861.

(4) For total synthesis of myriocin, see: (a) Banfi, L.; Beretta, M. G.; Colombo, L.; Gennari, C.; Scolastico, C. *J. Chem. Soc., Chem. Commun*. **1982**, 488; *J. Chem. Soc., Perkin Trans. 1* **1983**, 1613. (b) Yoshikawa, M.; Yokokawa, Y.; Okuno, Y.; Murakami, N. *Chem. Pharm. Bull*. **1994**, *42*, 994; *Tetrahedron* **1995**, *51*, 6209. (c) Sano, S.; Kobayashi, Y.; Kondo, T.; Takebayashi, M.; Maruyama, S.; Fujita, T.; Nagao, Y. *Tetrahedron Lett*. **1995**, *36*, 2097. (d) Hatakeyama, S.; Yoshida, M.; Esumi, T.; Iwabuchi, Y.; Irie, H.; Kawamoto, T.; Yamada, H.; Nishizawa, M. *Tetrahderon Lett*. **1997**, *38*, 7887. (e) Oishi, T.; Ando, K.; Chida, N. *Chem. Commun*. **2001**, 1932.

(5) Miyake, Y.; Kozutsumi, Y.; Nakamura, S.; Fujita, T.; Kawasaki, T. *Biochem. Biophys. Res. Commun*. **1995**, *211*, 396.

(6) For total synthesis of sphingofungin D, see: (a) Chida, N.; Ikemoto, H.; Noguchi, A.; Amano, S.; Ogawa, S. *Nat. Prod. Lett*. **1995**, *6*, 295. (b) Mori, K.; Otaka, K. *Tetrahedron Lett*. **1994**, *35*, 9207. (c) Otaka, K.; Mori, K. *Eur. J. Org. Chem*. **1999**, 1795. For total synthesis of sphingofungin B, see: (d) Kobayashi, S.; Hayashi, T.; Iwamoto, S.; Furuta, T.; Mataumura, M. *Synlett* **1996**, 672. For total synthesis of sphingofungins B and F, see: (e) Kobayashi, S.; Matsumura, M.; Furuta, T.; Hayashi, T.; Iwamoto, S. *Synlett* **1997**, 301. (f) Kobayashi, S.; Furuta, T.; Hayashi, T.; Nishijima, M.; Hanada, K. *J. Am. Chem. Soc*. **1998**, *120*, 908. (g) Kobayashi, S.; Furuta, T. *Tetrahedron* **1998**, *54*, 10275. For total synthesis of sphingofungin F, see: (h) Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc*. **1998**, *120*, 6818. (i) Liu, D.-G.; Wang, B.; Lin, G.-Q. *J. Org. Chem*. **2000**, *65*, 9114.

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sphingofungin E has been reported from three laboratories, which successfully assigned the absolute structure of the natural product.[7] For construction of the tetra-substituted carbon in sphingofungins E and F, previous successful syntheses adopted Schöllkopf's bislactim method,[6e−g] Pd-catalyzed asymmetric alkylation of azlactone,[6h,7c] Lewis acid catalyzed cyclization of an epoxytrichloroacetimidate,[6i,7a] and the Darzen reaction.[7b] In this communication, we report the alternative and efficient total synthesis of sphingofungin E starting from D-glucose.

Our previous success in total synthesis of lactacystin from D-glucose[8] and myriocin from D-mannose[4e] suggested that the Overman rearrangement[9] on furanose scaffolds, followed by further transformation utilizing the functional groups in the carbohydrate residue, would provide the highly functionalized intermediate of sphingofungin E in a stereoselective manner and short reaction steps. This idea involves disconnection of the carbon framework of **1** into allyl bromide **4** and the hydrophobic C_{12} counterpart, sulfone **5** (Figure 1). The sulfone−allyl bromide coupling reaction,

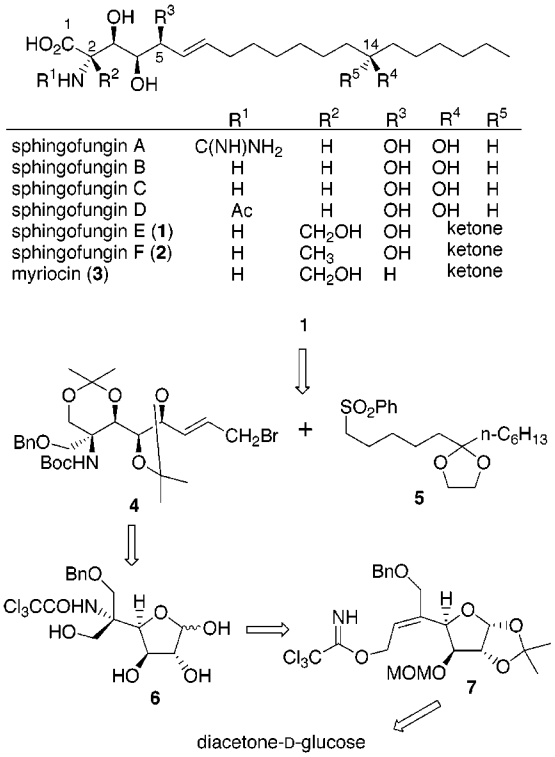
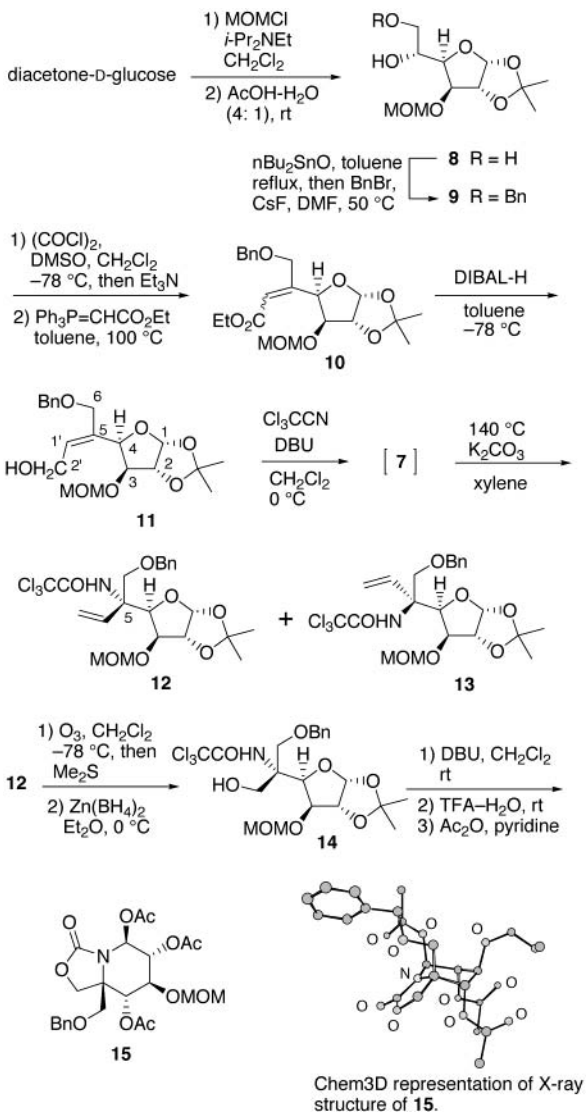


Figure 1. Structures of sphingofungins and myriocin and retrosynthetic route to sphingofungin E.

which had been employed in our previous total synthesis of sphingofungin D[6a] and myriocin,[4e] was expected to construct the carbon backbone possessing *E*-olefin in **1** stereoselectively. On the basis of these considerations, the functionalized part, allyl bromide **4**, was to be prepared from a furanose derivative with a tetra-substituted carbon (**6**). The furanose **6** would derive from Overman rearrangement of an allylic trichloroacetimidate **7**, which was envisioned as arising from diacetone-D-glucose.

Synthesis of the functionalized part **4** commenced with 1,2-*O*-isopropylidene-3-*O*-methoxymethyl-α-D-glucofuranose **8**[10] prepared from diacetone-D-glucose in two steps in 90% yield (Scheme 1). The primary hydroxy group in **8** was

Scheme 1



selectively benzylated[11] to afford **9**[12] in 95% yield. Swern oxidation of **9** generated ketone, which was submitted to Wittig reaction to provide an inseparable mixture of alkenes

(7) For total synthesis of sphingofungin E, see: (a) Wang, B.; Yu, X.-M.; Lin, G.-Q. *Synlett* **2001**, 904. (b) Nakamura, T.; Shiozaki, M. *Tetrahedron Lett*. **2001**, *42*, 2701. (c) Lee, C. B. Ph.D. Dissertation, Stanford University, Stanford, CA, 1999.

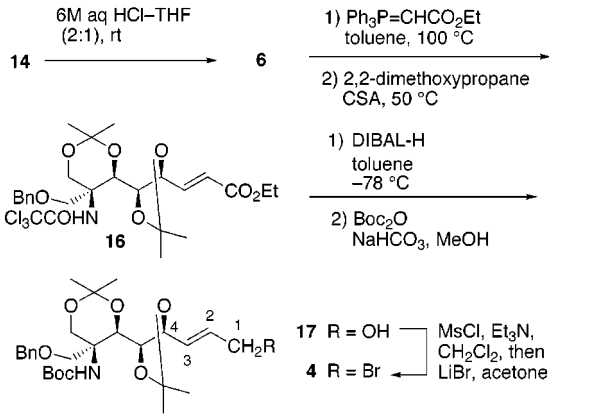
(8) (a) Chida, N.; Takeoka, J.; Tstutsumi, N.; Ogawa, S. *J. Chem. Soc., Chem. Commun.* **1995**, 793. (b) Chida, N.; Takeoka, J.; Ando, K.; Tsutstumi, N.; Ogawa, S. *Tetrahedron* **1997**, *53*, 16287.

(9) (a) Overman, L. E. *J. Am. Chem. Soc*. **1978**, *98*, 2901. (b) Overman, L. E. *Angew. Chem., Int. Ed. Engl*. **1984**, *23*, 579.

10 (*E*:*Z* = 1:4) in 95% yield from **9**. Reduction of **10** with DIBAL-H and subsequent chromatographic separation gave geometrically pure *Z*-allyl alcohol **11** in 71% isolated yield along with its *E*-isomer (13%). The observed NOEs of **11** (between H-6 and H-1′, and H-4 and H-2′) clearly assigned its *Z*-geometry. Treatment of **11** with trichloroacetonitrile and DBU afforded trichloroacetimidate **7**, which without isolation was heated in xylene in the presence of K_2CO_3[13] in a sealed tube at 140 °C for 140 h to give products of the Overman rearrangement, **12** and its C-5 epimer **13**, in 60% and 14% isolated yields from **11**, respectively.[14] Ozonolysis of **12** (Me_2S workup) followed by reduction with $ZnBH_4$ afforded **14**[15] in 93% yield. The newly formed stereochemistry in **12** was assigned by transformation of **14** into bicyclic compound **15**. Thus, treatment of **14** with DBU smoothly induced the carbamate formation, and subsequent treatment with aqueous acid, followed by conventional acetylation, afforded crystalline **15** in 26% overall yield from **14**, whose single crystal X-ray analysis unambiguously revealed that the major isomer in Overman rearrangement **12** possessed 5*R* configuration.[16]

Having established the structure of the rearranged product, transformation of **14** into allyl bromide **4** was then explored. Treatment of **14** with aqueous HCl gave furanose derivative **6** in 91% yield (Scheme 2). Reaction of **6** with $Ph_3P{=}CHCO_2$-

Scheme 2



Et afforded only *E*-alkene, which was treated with 2,2-dimethoxypropane in the presence of CSA to afford diacetonide **16** in 53% yield from **6**. Reaction of **16** with DIBAL-H at −78 °C reduced the ester function as well as the *N*-trichloroacetamide moiety to afford amine, which was isolated as its *N*-Boc derivative **17** in 90% yield. The primary hydroxy group in **17** was converted into the corresponding bromide to furnish the highly functionalized part (**4**) of sphingofungin E in 85% yield.

The hydrophobic counterpart, sulfone **5**, was synthesized from cyclohexanone by the same procedure employed for the total synthesis of myriocin.[4e] The sulfone **5** was lithiated by treatment with *n*-BuLi and then reacted with the allyl bromide **4** to provide the coupling product **19** in 86% yield as a mixture of diastereomers (Scheme 3). Treatment of **19** with Li and naphthalene[17,18] in THF successfully removed both sulfonyl and *O*-benzyl groups to give primary alcohol **20** in 55% yield. Swern oxidation of **20** and subsequent treatment with $NaClO_2$ provided carboxylic acid **21**, whose acidic hydrolysis, followed by conventional acetylation, afforded γ-lactone **22** in 68% yield from **20**. Finally, saponification of **22** followed by neutralization with acidic resin (Amberlite IRC-76) furnished sphingofungin E (**1**) in 88% yield. The physical properties as well as spectroscopic data[19] showed good accordance with those reported for the authentic sample.

In summary, total synthesis of sphingofungin E (**1**) starting from D-glucose was accomplished. This work established the novel synthetic pathway to sphingofungins and their analogues. This synthesis and previous successes in total

(10) Mulzer, J.; Angermann, A.; Münch, W.; Schlichthörl, G.; Hentzschel, A. *Liebigs Ann. Chem.* **1987**, 7.

(11) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643.

(12) All new compounds described in this letter were characterized by 300 MHz ^{1}H NMR, 75 MHz ^{13}C NMR, IR, and mass spectrometric and/or elemental analyses.

(13) Nishikawa, T.; Asai, M.; Ohyabu, N.; Isobe, M. *J. Org. Chem.* **1998**, *63*, 188.

(14) Overman rearrangement of the *E*-isomer of **11** afforded **12** and **13** in 11% and 41% isolated yields, respectively.

(15) Selected data for **14**: $[\alpha]^{24}_D$ +8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.32 and 1.49 (2s, each 3 H), 3.28 (s, 3 H), 3.90 (s, 2 H), 3.92 and 4.25 (2d, each 1 H, *J* = 12.5 Hz), 4.29 (m, 2 H), 4.40−4.62 (m, 5 H), 5.89 (d, 1 H, *J* = 3.7 Hz), 7.26−7.35 (m, 5 H), 8.66 (bs, 1 H); HRMS (EI) *m*/*z* 527.0882, calcd for $C_{21}H_{28}NO_8{}^{35}Cl_3$ (M + H)$^+$ 527.0880. For **4**: $[\alpha]^{24}_D$ +6 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.40−1.44 (bs, 21 H), 1.62 (bs, 1 H), 3.74 and 3.83 (2d, each 1 H, *J* = 9.8 Hz), 3.86−3.90 (m, 3 H), 3.94 (bs, 1 H, J ∼ 0 Hz), 3.98 (bd, 1 H, *J* = 8.5 and ∼0 Hz), 4.33, 4.42 and 4.51 (3d, each 1 H, *J* = 11.9 Hz), 4.45 (dd, 1 H, *J* = 7.6 and 8.5 Hz), 5.56 (dd, 1 H, *J* = 7.6 and 15.1 Hz), 5.97 (dt, 1 H, *J* = 15.1 and 7.3 Hz), 6.16 (bs, 1 H), 7.24−7.39 (m, 5 H); HRMS (FAB) *m*/*z* 572.2059, calcd for $C_{27}H_{41}{}^{81}BrNO_7$ (M + H)$^+$ 572.2046. For **20**: $[\alpha]^{24}_D$ +3 (*c* 0.45, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 3 H, *J* = 6.7 Hz), 1.23−1.37 (m, 16 H), 1.40 and 1.44 (2s, each 6 H), 1.45 (s, 9 H), 1.53−1.63 (m, 4 H), 2.06 (dt, 2 H, *J* = 6.8 and 6.8 Hz), 3.54−3.61 (m, 2 H), 3.71 (d, 1 H, *J* = 8.3 Hz), 3.77 and 4.22 (2d, each 1 H, *J* = 12.5 Hz), 3.87−3.94 (m, 1 H), 3.92 (s, 4 H), 4.37 (dd, 1 H, *J* = 8.3 and 8.3 Hz), 4.43 (dd, 1 H, *J* = 3.4 and 9.0 Hz), 5.40 (dd, 1 H, *J* = 8.3 and 15.3 Hz), 5.76 (dt, 1 H, *J* = 15.3 and 6.8 Hz), 6.07 (bs, 1 H); HRMS (FAB) *m*/*z* 628.4424, calcd for $C_{34}H_{62}NO_9$ (M + H)$^+$ 628.4424. For **22**: $[\alpha]^{24}_D$ +49 (*c* 0.27, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 3 H, *J* = 6.7 Hz), 1.18−1.36 (m, 12 H), 1.46−1.61 (m, 4 H), 1.96−2.05 (m, 2 H), 2.02 (s, 6 H), 2.09 and 2.12 (2s, each 3 H), 2.38 (t, 2 H, *J* = 7.4 Hz), 4.49 and 4.56 (2d, each 1 H, *J* = 11.4 Hz), 4.76 (dd, 1 H, *J* = 4.9 and 7.8 Hz), 5.33 (dd, 1 H, *J* = 7.8 and 15.3 Hz), 5.53 (dd, 1 H, *J* = 7.8 and 7.8 Hz), 5.80 (d, 1 H, *J* = 4.9 Hz), 5.86 (dt, 1 H, *J* = 15.3 and 7.2 Hz), 5.97 (bs, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 20.5, 20.6, 21.1, 22.5, 22.7, 23.7, 23.8, 28.2, 28.9, 29.0, 31.6, 32.3, 42.7, 42.8, 62.4, 62.9, 70.4, 71.6, 77.2, 80.6, 122.0, 139.5, 168.1, 169.2, 169.6, 170.2, 171.7, 211.6; HRMS (EI) *m*/*z* 567.3046, calcd for $C_{29}H_{45}NO_{10}$ (M$^+$) 567.3044.

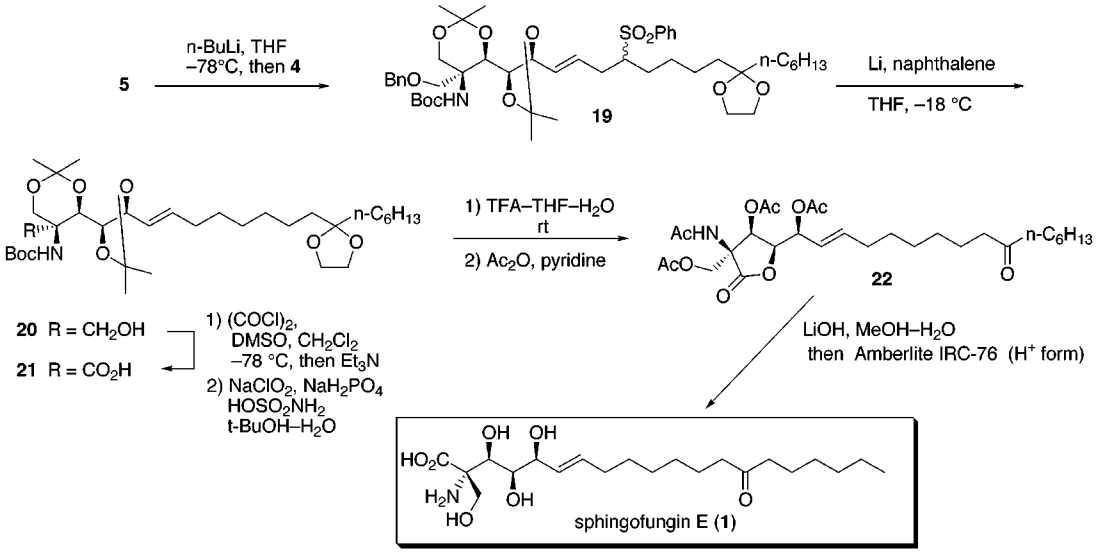
(16) Kani, Y.; Ohba, S.; Oishi, T.; Ando, K.; Inomiya, K.; Chida, N. *Acta Crystallogr., Sect. C* **2000**, *C56*, e223.

(17) (a) Liu, H.-J.; Yip, J. *Tetrahedron Lett.* **1997**, *38*, 2253. (b) Shimshock, S. T.; Waltermire, R. E.; DeShong, P. *J. Am. Chem. Soc.* **1991**, *113*, 8791.

(18) Birch reduction (Li or Ca in liquid NH_3−THF, −78 °C) of **19** gave less satisfactory and reproducible results; compound **20** was obtained in only 0−15% yields.

(19) Mp 144−146 °C; $[\alpha]^{25}_D$ −5.6 (*c* 0.14, MeOH); lit.[7b] mp 145−147 °C, $[\alpha]^{25}_D$ −5.43 (*c* 0.48, MeOH); ^{1}H NMR (300 MHz, MeOH-d_4) δ 0.94 (t, 3 H, *J* = 6.7 Hz), 1.21−1.45 (m, 12 H), 1.48−1.60 (m, 4 H), 2.04 (dt, 2 H, *J* = 6.3 and 6.3 Hz), 2.43 (t, 4 H, *J* = 7.4 Hz), 3.63 (d, 1 H, *J* = 7.3 Hz), 3.84 (d, 1 H, *J* = 11.0 Hz), 3.94 (bs, 1 H), 3.97 (d, 1 H, *J* = 11.0 Hz), 4.10 (dd, 1 H, *J* = 7.6 and 7.6 Hz), 5.44 (dd, 1 H, *J* = 7.6 and 15.4 Hz), 5.77 (dt, 1 H, *J* = 15.4 and 6.3 Hz); ^{13}C NMR (75 MHz, MeOH-d_4) δ 14.4, 23.6, 24.9, 30.02, 30.03, 30.15, 30.18, 32.8, 33.4, 43.47, 43.51, 64.9, 70.0, 71.2, 75.6, 76.3, 130.2, 135.7, 173.2, 214.4; HRMS (FAB) *m*/*z* 418.2805, calcd for $C_{21}H_{40}NO_7$ (M + H)$^+$ 418.2805.

Scheme 3



syntheses of lactacystin[8] and myriocin[4e] also revealed that the methodology involving Overman rearrangement on furanose scaffolds, followed by further manipulation by use of the residual functional groups in carbohydrates, is quite effective for the chiral synthesis of natural products possessing complex α,α-disubstituted α-amino acid structures.

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