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Total synthesis of calonyctin A2, a macrolidic glycolipid with plant growth-promoting activity

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Abstract

Calonyctin A2, a tetrasaccharidic glycolipid having a 22-membered macrolidic structure, has been synthesized by the assembly of three 6-deoxygenated thioglycoside intermediates. The short-step synthesis was achieved by preparation of the most complicated b–c disaccharide unit from phenyl 2,2′:4,6:4′,6′-tri-*O*-benzylidene-1-thio-β-D-laminaribioside without any glycosidation reaction and by regioselective macrolactonization. © 2000 Elsevier Science Ltd. All rights reserved.

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Calonyctin extracted from the leaves of Yue-Guang-Hua (*Calonyction aculeatum* L. House) is a plant growth regulator, which promotes the tuber production of sweet potato and increases the crop yields of beans and wheat.[1] It is a mixture of homologous glycolipids consisting of a common deoxygenated tetrasaccharide residue and 11-hydroxy fatty acids,[2] which are named calonyctin A1 (**1**) and A2 (**2**), respectively (Fig. 1).[3] Furthermore, one of the sugar hydroxyl groups is acylated with (2*R*,3*R*)-3-hydroxy-2-methylbutyric acid. The most remarkable feature of their structure is that they have a 22-membered macloride ring. The absolute configuration of the aglycon moiety was determined as *S* by Schmidt's synthesis of **1** from a racemic fatty acid.[4] In this communication, we describe an expeditious synthesis of calonyctin A2 (**2**) using laminaribiose as the starting material. On the basis of our studies on the chemical modification of laminaribiose,[5] we envisioned that the readily accessible tri-*O*-benzylidene derivative **3** could be used as a synthon for the most complicated disaccharide unit (Qui-b and Qui-c) of **2**. Compound **3** was converted into a crucial disaccharide donor, phenyl 3′-*O*-allyl-2,2′-di-*O*-benzoyl-4,4′-di-*O*-benzyl-6,6′-dideoxy-1-thio-β-D-laminaribioside **8**, which had to be coupled with a monosaccharide intermediate **17** and a L-rhamnosyl donor **21**. Furthermore, an optically active 11(*S*)-hydroxymyristic acid derivative **14** could be prepared from the known (*S*)-γ-tosyloxymethyl-γ-butyrolactone in an enantioselective manner.

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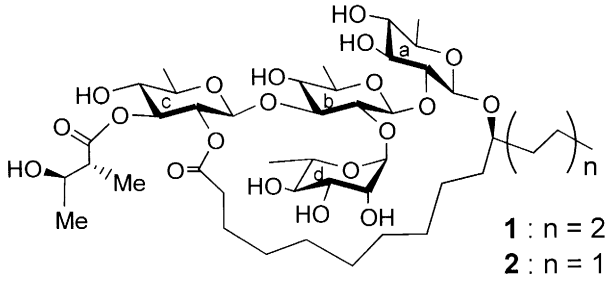
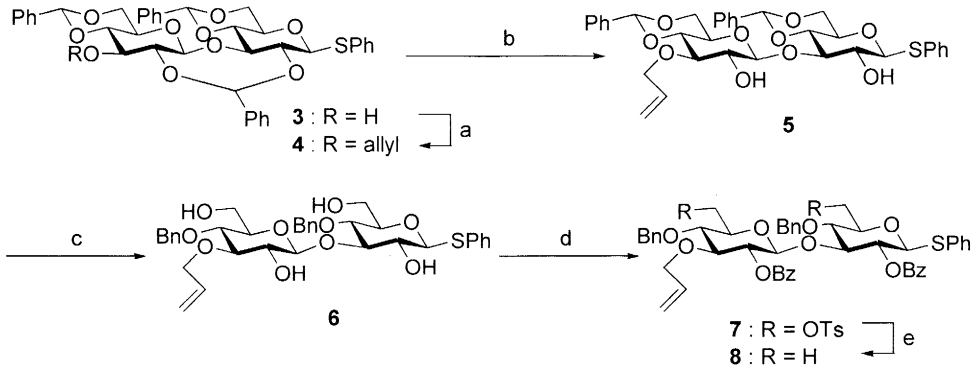


Fig. 1.

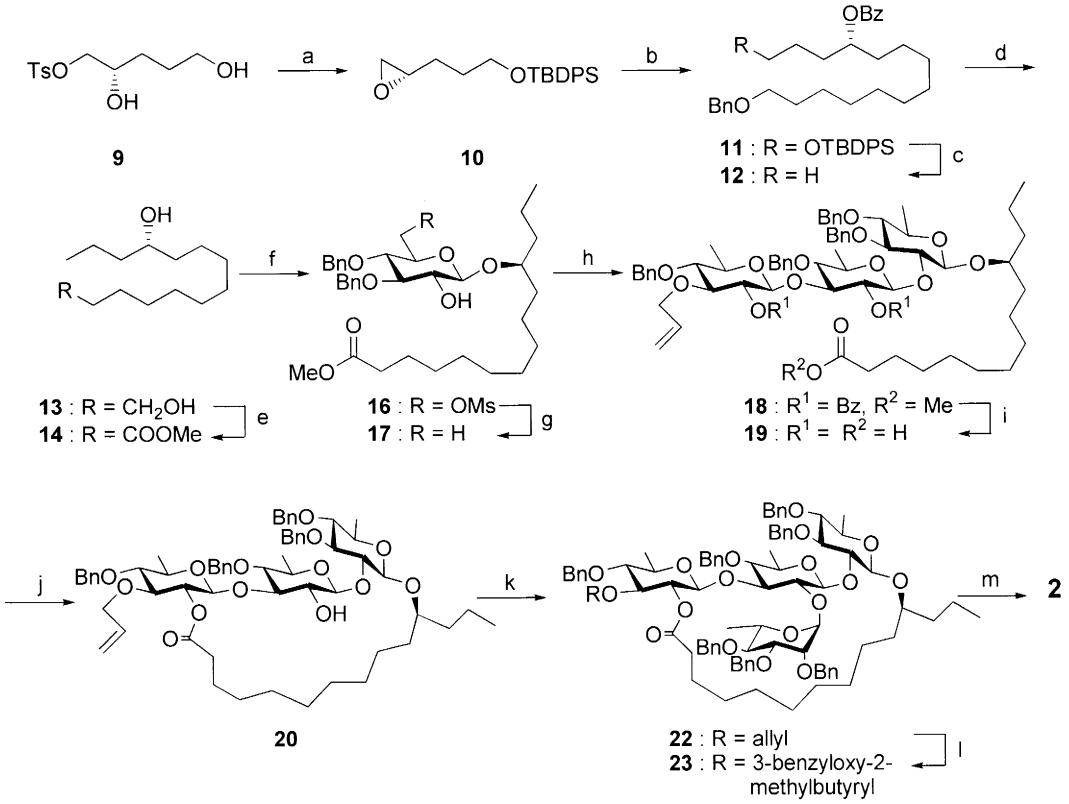
The synthetic route of the disaccharide donor **8** is illustrated in Scheme 1. Thus, **3** was allylated at the unprotected hydroxyl group to give the fully protected disaccharide[6] **4**. Upon treatment of **4** with PPTS in $CHCl_3$–MeOH at room temperature, the most labile *O*-benzylidene group with an eight-membered ring underwent selective cleavage, to give the 2,2′-diol[6] **5** in 79% yield based on consumed **4**. The following reductive cleavage of the benzylidene group in **5** was one of the most difficult steps in the present synthesis, and this was overcome by applying Kusumoto's reagent system.[7] Treatment of **5** with $BH_3 \cdot Me_2NH$–$BF_3 \cdot OEt_2$ in CH_2Cl_2 gave the desired 2,6,2′,6′-tetraol **6** in 77% yield without any affection on the other protecting groups.[8] The conventional reduction of **5**, or its 2,2′-di-*O*-acetyl derivative with $BH_3 \cdot Me_3N$–$AlCl_3$[9] or DAIBAL-H,[10] Super-Hydride®, failed due to poor regioselectivity and undesirable cleavage of the protecting group. Subsequently, **6** underwent selective esterification in a one-pot manner with TsCl and then with excess BzCl, giving the labile 2,2′-di-*O*-benzoyl-6,6′-di-*O*-tosyl derivative **7**. Without purification, **7** was reduced with $NaBH_4$ in DMF at 70°C into the dideoxy derivative[6] **8** in an overall yield of 47% from **6**.



Scheme 1. Reagents and conditions: (a) AllylBr, NaH, DMF; (b) PPTS, MeOH/$CHCl_3$; (c) $BF_3 \cdot OEt_2$, $Me_2NH \cdot BH_3$, CH_2Cl_2, under N_2; (d) TsCl, pyridine, then BzCl; (e) $NaBH_4$, DMF, 70°C

For the synthesis of the aglycon moiety of **2**, the optically active pentanetriol[11] **9** derived from L-glutamic acid was subjected to selective silylation and subsequent basic treatment with *tert*-BuOK in THF to give the epoxide **10** (Scheme 2). Treatment of **10** in THF with 9-(benzyloxy)nonyl magnesium bromide in the presence of CuI and subsequent benzoylation gave **11**[6] in an overall yield of 72%. A three-step reaction involving de-*O*-silylation with Bu_4NF, bromination with CBr_4–PPh_3,[12] and reduction with Bu_3SnH–AIBN was carried out to give **12**.[6] Treatment of **12** with methanolic sodium methoxide followed by Birch reduction gave the tetradecan-1,11-diol[6] **13**. Finally, a primary hydroxyl group of **13** was subjected to two-step oxidation[13] with TEMPO and subsequently with sodium chlorite to give 11(*S*)-hydroxymyristic acid, which was isolated and characterized as the methyl ester **14**.[6] In order

to construct the target compound **2**, two other intermediates, phenyl 2-*O*-acetyl-3,4-di-*O*-benzyl-6-*O*-mesyl-1-thio-β-D-glucopyranoside[14] **15** and phenyl 2,3,4-tri-*O*-benzyl-1-thio-α-L-rhamnopyranoside[15] **21**, were prepared.



Scheme 2. Reagents and conditions: (a) TBDPSCl, pyridine/CH_2Cl_2, then *tert*-BuOK, THF; (b) 9-(benzyloxy)nonyl magnesium bromide, CuI, THF, 0°C: BzCl, pyridine; (c) *n*-Bu_4NF, THF: CBr_4, Ph_3P, DMF, then Bu_3SnH, AIBN, toluene, 80°C; (d) NaOMe, MeOH, 70°C, then liq. NH_3, Na, −80°C; (e) TEMPO, TBACl, NCS, CH_2Cl_2/H_2O, pH 8.6: $NaClO_2$, NaH_2PO_4, *tert*-BuOH, 2-methyl-2-butene/H_2O, then CH_2N_2, Et_2O; (f) thioglycoside[14] **15**, NIS–TfOH, CH_2Cl_2, MS 4 Å, −20°C, then NaOMe, MeOH; (g) $NaBH_4$, DMF, 70°C; (h) **8**, NIS–TfOH, CH_2Cl_2, MS 4 Å, −20°C; (i) 2 M KOH, MeOH, 40°C; (j) $Cl_3C_6H_2COCl$, Et_3N, DMAP, toluene; (k) thioglycoside[15] **21**, NIS–TfOH, CH_2Cl_2, MS 4 Å, −20°C; (l) $RhCl(PPh)_3$, diazabicyclo[2,2,2]octane, EtOH, reflux: 2 M HCl, 45°C, then (2*R*,3*R*)-3-benzyloxy-2-methylbutyric acid, DMAP, WSC, CH_2Cl_2; (m) Pd/C, H_2, MeOH

Assembly of the four intermediates (**8**, **14**, **15** and **21**) were performed by iodonium activation of the thioglycosides. At first, **14** and the glucosyl donor **15** were treated with NIS–TfOH[16] in CH_2Cl_2 at −20°C, and the β-glucoside **16** was isolated after de-*O*-acetylation. Reduction of the mesyloxy group in **16** with $NaBH_4$ in DMF gave the glycosyl acceptor[6] **17**, which was coupled with **8** in a similar way to afford the trisaccharide[6] **18** in 71% yield. After saponification with aqueous NaOH, the resulting carboxylic acid **19** was subjected to macrolactonization by a mixed anhydride procedure[17] under high-dilution conditions in toluene (1.71×10^{-4} M). Although two possible hydroxyl groups are present at the 2b- and 2c-positions, the desired 22-membered macrolide[6] **20** was obtained as a single product in 60% yield together with recovered starting material **19**. The structure of **20** was unambiguously corroborated by two-dimensional COSY and NOESY NMR spectroscopy. Similar glycosylation of **20** with the L-rhamnosyl donor **21** gave the tetrasaccharide[6] **22** in 15% yield, which was not improved by use of another thiophilic reagent, MeOTf. The low yield was probably due to steric hindrance of the hydroxyl

group at the 2a-position. To synthesize the target compound, the allyl group in **22** was isomerized with Wilkinson's catalyst and the propenyl group was removed by acid hydrolysis. The resulting alcohol was esterified with (2*R*,3*R*)-3-benzyloxy-2-methylbutyric acid[4] in the presence of water-soluble carbodiimide in CH_2Cl_2, giving the fully protected derivative **23** in 62% yield. Finally, removal of all benzyl groups in **23** by catalytic hydrogenolysis gave calonyctin A2 (**2**), of which the NMR spectra in pyridine-d_5 were consistent with those already reported.[2]

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6. All new compounds had satisfactory elemental analysis data or high-resolution mass spectra. Optical rotations were measured in $CHCl_3$ at 25°C unless otherwise noted. Selected data for **4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.72, 5.59, 5.56 (each s, Ph*CH*); $[\alpha]_D$ −59.2 (*c* 2.0). Compound **5**: δ_H 5.58, 5.53 (each s, Ph*CH*), 4.68 (d, *J*=9.6, H-1), 4.65 (d, *J*=7.0, H-1′); $[\alpha]_D$ −43.4 (*c* 0.47 in $CHCl_3$); HRMS (FAB+) *m/z* for $C_{35}H_{39}O_{10}S$ $(M+H)^+$, calcd: 651.2263; found: 651.2236. Compound **6**: δ_H 5.72, 5.59, 5.56 (each s, Ph*CH*); $[\alpha]_D$ −3.8 (*c* 5.74). Compound **8**: δ_H 4.75 (d, *J*=8.0, H-1′), 4.70 (d, *J*=10.1, H-1). Compound **9**: δ_H 3.85 (m, CH), 3.65 (t, *J*=5.6, CH_2). Compound **11**: δ_H 3.69 (t, *J*=6.0, 14-CH_2), 3.46 (t, *J*=6.7, 1-CH_2), 2.00 (bs, OH); $[\alpha]_D$ +2.1 (*c* 0.40 in $CHCl_3$); HRMS (FAB+) *m/z* for $C_{44}H_{59}O_4Si$ $(M+H)^+$, calcd: 679.4155; found: 679.4183. Compound **12**: δ_H 0.93 (t, *J*=7.3, 14-CH_3), 4.49 (s, Ph*CH*$_2$), 5.15 (m, 11-CH); $[\alpha]_D$ +3.7 (*c* 0.29); HRMS (FAB+) *m/z* for $C_{28}H_{41}O_3$ $(M+H)^+$, calcd: 425.3056; found: 425.3060. Compound **13**: δ_D 3.64 (t, *J*=6.6, 1-CH_2), 3.61 (m, 11-CH); $[\alpha]_D$ +1.8 (*c* 0.80). Compound **14**: m.p. 41.4–42°C; δ_D 3.67 (s, CH_3O), 3.60 (m, 11-CH); $[\alpha]_D$ 0.7 (*c* 0.25). Compound **17**: δ_D 4.25 (d, *J*=7.3, H-1), 3.66 (s, COO*CH*$_3$), 0.90 (t, *J*=7.1, CH_3); $[\alpha]_D$ −17.5 (*c* 5.44). Compound **18**: δ_D 4.99 (d, *J*=7.5, H-1b), 4.73 (d, *J*=7.7, H-1c), 4.22 (d, *J*=7.5, H-1a); $[\alpha]_D$ +10.1 (*c* 0.43). Compound **20**: δ_D 4.99 (d, *J*=7.5, H-1b), 4.73 (d, *J*=7.7, H-1c), 4.22 (d, *J*=7.5, H-1a); $[\alpha]_D$ −18.7 (*c* 0.69); HRMS (FAB+) *m/z* for $C_{63}H_{84}O_{14}Na$ $(M+Na)^+$, calcd: 1087.5759; found: 1087.5740. Compound **22**: δ_H ($(CD_3)_2CO$): 5.44 (d, *J*=0.9, H-1d), 4.32 (d, *J*=7.6, H-1a), 4.27 (bs, 1H, H-2d); $[\alpha]_D$ −6.3 (*c* 0.20); HRMS (FAB+) *m/z* for $C_{90}H_{112}O_{18}Na$ $(M+Na)^+$, calcd: 1503.7746; found: 1503.7730. Compound **23**: δ_H ($(CD_3)_2CO$): 5.51 (t, *J*=9.4, H-3c), 5.41 (s, H-1d), 5.15 (d, *J*=7.9, H-1c), 5.08 (t, *J*=8.8, H-2c), 4.85 (d, *J*=8.8, H-1b), 4.38 (bs, H-2d), 4.31 (d, *J*=7.6, H-1a), 4.12 (bd, *J*=9.3, H-3d), 4.01 (t, *J*=9.4, H-3b), 3.61 (t, *J*=8.6, H-2a), 3.45 (t, *J*=8.4, H-4c), 3.37–3.27 (m, H-5a), 3.18 (t, *J*=8.8, H-4a), 3.21–3.11 (m, H-5a), 2.92 (t, *J*=9.1, H-4b), 2.33–2.22 (m, *CH*$_2$COO), 0.86 (t, *J*=7.0, CH_3); δ_C ($(CD_3)_2CO$): 174.0, 172.8, 139.9, 139.4, 139.3, 139.2, 129.2, 128.7, 128.6, 128.5, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 103.0, 100.7, 99.6, 86.3, 84.4, 82.0, 81.9, 81.4, 78.8, 77.5, 75.8, 75.4, 74.9, 74.8, 74.7, 73.9, 72.8, 71.9, 71.6, 71.1, 45.3, 38.7, 35.6, 33.7, 31.0, 30.5, 30.3, 30.1, 29.8, 29.6, 29.3, 29.1, 28.8, 28.6, 25.9, 25.8, 25.4, 25.2, 22.8, 18.5, 18.2, 18.0, 17.9, 17.8, 15.9, 14.1, 13.9, 12.9, 12.1; $[\alpha]_D$ −8.9 (*c* 0.23); HRMS (FAB+) *m/z* for $C_{99}H_{123}O_{20}Na$ $(M+H+Na)^+$, calcd: 1654.8505; found: 1654.8634. Compound **2**: $[\alpha]_D$ −51.7 (*c* 0.12, EtOH); HRMS (FAB+) *m/z* for $C_{43}H_{74}O_{20}Na$ $(M+Na)^+$, calcd: 933.4671; found: 933.4670.
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15. New compound **21** [^{1}H NMR: 5.49 (bs, H-1); $[\alpha]_D$ +0.65 (*c* 0.70)] was prepared by the Lewis acid-promoted thioglycosidation of the fully acetylated rhamnose, followed by de-*O*-acetylation and *O*-benzylation.
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