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Total Synthesis of Deacetyl-caloporoside, A Novel Inhibitor of The $GABA_A$ Receptor Ion Channel

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Abstract : The total synthesis of deacetyl-caloporoside (**1**) which contains a β-D-mannopyranoside unit has been accomplished by coupling of the disaccharide-like segment derived from methyl α-D-mannopyranoside, with the hydroxyheptadecyl salicylic acid segment. The biological activity of **1** has also been evaluated.

Deacetyl-caloporoside (**1**) is a novel fungal inhibitor of the binding of ^{35}S-labelled *t*-butylbicyclophosphorothionate (^{35}S-TBPS) to the $GABA_A$/benzodiazepine chloride channel receptor complex *in vitro*.[1] On the other hand, caloporoside (**2**) has been reported to inhibit phospholipase C.[2] It would be therefore important to examine the possibility that deacetyl-caloporoside (**1**) also shows a similar enzyme inhibitory activity.

Herein, we report the first total synthesis of deacetyl-caloporoside (**1**) by coupling of a disaccharide-like segment (**8**) with a hydroxyheptadecyl salicylic acid segment (**18**) as part of a ongoing program to clarify the mode of action of enzyme inhibitors.[3-5]

The segment **8** was synthesized from methyl α-D-mannopyranoside through a common intermediate **4**. Methyl α-D-mannopyranoside was *O*-benzylated (BnBr, NaH, DMF, 17h) and subsequently hydrolyzed [aq 0.5M H_2SO_4-AcOH (1 : 4), 100°C, 1.5h] to give the protected mannose **3** (71%, syrup), which reacted with 2-naphthalenethiol (BF_3-Et_2O, CH_2Cl_2, 12h) to afford the 1-thio-mannoside **4**[6] (85%, syrup). On the other hand, $NaBH_4$ reduction (MeOH, 22h) of **3** followed by selective silylation (TBDPSCl, imidazole, DMF, 1.5h) gave the alcohol **5**[6]. In β-D-mannosylation of **5**, a large number of methods[7,8] including glycosyl donors [phenyl-1-thio and (pyridine-2-yl)-1-thio-mannosides *etc.*] and solvents used were assayed; the selective formation of β-mannopyranosides was in general difficult. The best result was realized by modification of the conditions of Fraser-Reid[9] using the bulky glycosyl donor **4** and acceptor **5** in EtOAc (NIS, 0.15M TfOH in CH_2Cl_2, -40°C, 1.5h). This process gave, after de-*O*-silylation (TBAF, THF, 13h), the desired β-mannoside **6**[6] as the major product [64%, syrup, $[\alpha]_D$ -22° (*c* 0.9, $CHCl_3$)] accompanied by the α-mannoside **7**[6] [24%, syrup, $[\alpha]_D$ +28° (*c* 1.0, $CHCl_3$)]. The stereochemistry (β or α) of the mannosides **6** and **7** was determined by NMR studies, especially based on the coupling constants[10] of $^1J(^{13}CH)$ (157 and 168 Hz, respectively) in ^{13}C NMR ($CDCl_3$). The structures of **6** and **7** were finally confirmed by the synthesis of **1**. Oxidation of **6** with oxalyl chloride-DMSO (Et_3N, CH_2Cl_2, -78° → 0°C, 0.5h) gave the aldehyde, which was then treated with sodium chlorite (H_2NSO_3H, aq dioxane, 1h) to afford the corresponding carboxylic acid **8**[6] [91%, syrup,

$[\alpha]_D$ -29° (*c* 1.0, $CHCl_3$), FAB-MS(m/z) 1077$(M-H)^-$]. The α-mannoside **7** was similarly converted into the carboxylic acid **9**[6][89%, syrup, $[\alpha]_D$ +8.7° (*c* 1.0, $CHCl_3$), FAB-MS(m/z) 1077$(M-H)^-$].

The other segment **18** was synthesized from the phosphonium salt **10**, which was prepared from (*R*)-1,3-butanediol in our laboratories.[11] The Wittig reaction (DMSO-NaH, *n*-BuLi, THF, 1h)[11] of **10** with the aldehyde **11**[12] gave the bromo-olefin **12**, which was treated with PPh_3 (MeCN, 80°C, 25h) to give the new phosphonium salt **13**[6] (90%, syrup). The second Wittig reaction (DMSO-NaH, 1.5h) of **13** with the hemiacetal **14**[13] afforded a mixture of olefins, which was submitted to catalytic reduction (H_2, Pd-C, EtOH) to yield the saturated alcohol **15**[6] [64%, mp 80~81°C(toluene), $[\alpha]_D$ -4.2° (*c* 1.1, $CHCl_3$), FAB-MS(m/z) 405$(M-H)^-$]. De-*O*-methylation[14] with LiCl (DMF, 150°C, 3h) provided a salicylic acid derivative **16**[6] [87%, mp 77~79°C(toluene), $[\alpha]_D$ -3.8° (*c* 1.1, MeOH)], the physico-chemical data being identical with those for the naturally derived sample.[1]

Esterification of **16** (EtOAc-MeOH, 2h) with benzophenone hydrazone and HgO[15] (Petr. ether, 3h) gave the benzhydryl ester **17**[6], which was selectively benzylated (BnBr, K_2CO_3, Me_2CO, 15h) to the alcohol **18**[6] [85%, syrup, $[\alpha]_D$ -2.7° (*c* 1.1, $CHCl_3$), FAB-MS(m/z) 671$(M+Na)^+$].

The final stage, coupling of the carboxylic acid **8** with the alcohol **18**, was accomplished by using the modified conditions of Yamaguchi.[16] After treatment of **8** with 1-naphthoyl chloride (Et_3N, THF, 1h), the solution was filtered and the filtrates were added to the alcohol **18** (DMAP, PhMe, 1h) to give the ester **19**[6] [74%, syrup, $[\alpha]_D$ -22° (*c* 0.7, $CHCl_3$), FAB-MS(m/z) 1732$(M+H+Na)^+$]. Hydrogenolysis of **19** (H_2, Pd-C, dioxane-aq AcOH) furnished the desired product **1**[6] [72%, syrup, $[\alpha]_D$ -19° (*c* 1.0, MeOH), FAB-MS(m/z) 731$(M-H)^-$], which was identical with natural deacetyl-caloporoside in all respects.[1] Similarly **9** was transformed into the α-mannoside analog **21**[6] [58% total yield, syrup, $[\alpha]_D$ +18° (*c* 1.0, MeOH), FAB-MS(m/z) 731$(M-H)^-$] through **20**[6][syrup, $[\alpha]_D$ +8.0° (*c* 1.3, $CHCl_3$), FAB-MS(m/z) 1732$(M+H+Na)^+$]. Coupling of the acid **8** with the alcohol **17**, without protection of the phenolic hydroxyl group, gave the product **1** albeit in lower yield (20%) after hydrogenolysis.

On preliminary biological assays, both products **1** and **21** were found to exhibit a similar inhibitory activity against the binding of a ligand to the $GABA_A$/benzodiazepine chloride channel receptor complex *in vitro* (IC_{50} 60 - 40 μM), and also against phospholipase C isolated from rat brain (IC_{50} 12 μM). Further biological evaluation is underway and will be reported in due course.

Acknowledgment: We are grateful to Meiji Seika Kaisha, Ltd., Shikoku Chemicals Co., Yamanouchi Pharmaceutical Co., Ltd. and the Institute of Microbial Chemistry for the generous support of our program.

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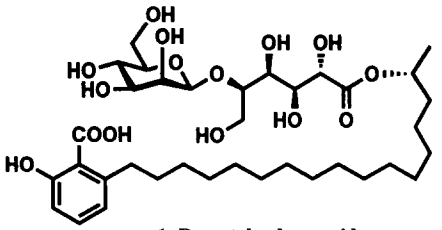
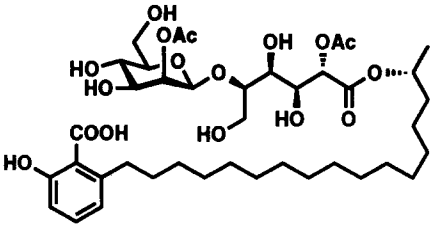
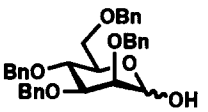
6. All compounds were purified by silica-gel column chromatography and/or recrystallization, and were fully characterized by spectroscopic means. Optical rotations were measured using a 0.5 dm tube at 22°C.



1: Deacetyl-caloporoside



2: Caloporoside



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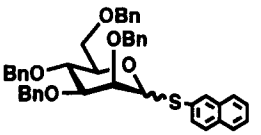

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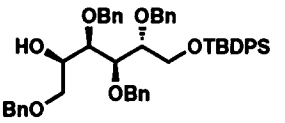

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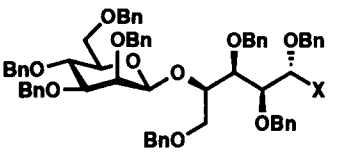
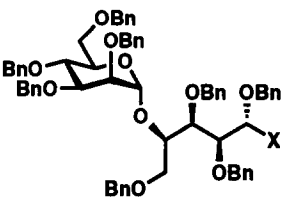
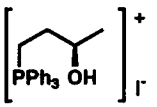


6: X= CH_2OH
8: X= COOH



7: X= CH_2OH
9: X= COOH



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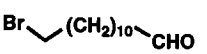

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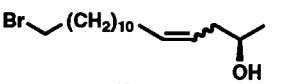

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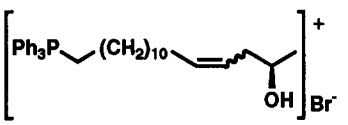

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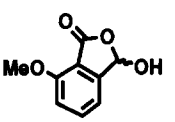

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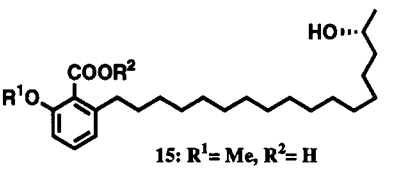
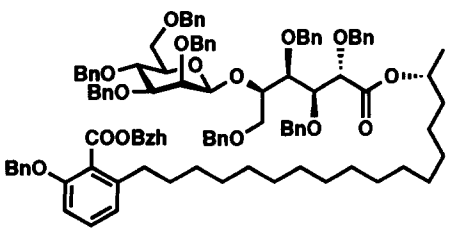


15: R^1= Me, R^2= H
16: R^1= R^2= H
17: R^1= H, R^2= Bzh
18: R^1= Bn, R^2= Bzh



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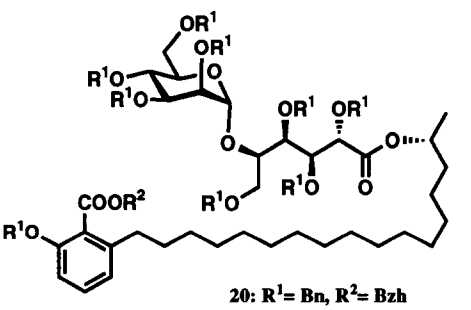

20: R^1= Bn, R^2= Bzh
21: R^1= R^2= H

Significant ^{1}H-NMR spectral data (270 , 400 and 500 MHz, $CDCl_3$, δ; TMS=0, unless otherwise noted) are the following.

1 (500MHz, CD_3OD): δ 1.24(3H, d, *J*=6Hz), 2.95(2H, br t, *J*=7Hz), 3.23(1H, ddd, *J*=10, 8 &2Hz), 3.44(1H, dd, *J*=10 &3Hz), 3.49(1H, t, *J*=10Hz), 3.82(1H, br d, *J*=9Hz), 3.87(1H, ddd, *J*=9, 6&3Hz), 3.97(1H, d, *J*=3Hz), 4.14(1H, d, *J*=9Hz), 4.72(1H, s, anomeric), 4.96(1H, tq, *J*=6 &6Hz, H-23).

4 (270MHz): δ 3.58(1H, ddd, *J*=10, 7 &2Hz), 3.66(1H, dd, *J*=10 &3Hz), 4.10(1H, t, *J*=10Hz), 4.20(1H, d, *J*=3Hz), 4.33(1H, ddd, *J*=10, 5 &2Hz), 5.73(1H, d, *J*=2Hz, anomeric).

5 (400MHz): δ 1.06(9H, s), 2.67(1H, d, *J*=7Hz), 3.59(1H, dd, *J*=10 &5Hz), 3.95(1H, dd, *J*=12 &5Hz), 4.02(1H, m), 4.10(1H, dd, *J*=7 &3Hz).

6 (500MHz): δ 3.37(1H, ddd, *J*=10, 5 &2Hz), 3.42(1H, dd, *J*=10 &3Hz), 3.80(1H, t, *J*=10Hz), 3.92(1H, d, *J*=3Hz), 4.16(1H, ddd, *J*=7, 5 &3Hz), 4.60(1H, s, anomeric).

7 (500MHz): δ 3.90(1H, dd, *J*=10 &3Hz), 3.97(1H, t, *J*=10Hz), 4.03(1H, ddd, *J*=10, 5 &1Hz), 4.09(1H, m), 5.04(1H, d, *J*=2Hz, anomeric).

8 (400MHz): δ 3.36(1H, ddd, *J*=10, 7 &1Hz), 3.44(1H, dd, *J*=10 &3Hz), 3.92(1H, d, *J*=3Hz), 4.33(1H, d, *J*=2Hz), 4.57(1H, s, anomeric).

9 (400MHz): δ 3.94(1H, t, *J*=10Hz), 3.97(1H, m), 4.00(1H, dd, *J*=6 &3Hz), 4.06(1H, d, *J*=3Hz), 4.10(1H, m), 5.09(1H, d, *J*=2Hz, anomeric).

15 (270MHz): δ 1.20(3H, d, *J*=6Hz), 2.73(2H, m), 3.82(1H, m), 3.90(3H, s).

16 (270MHz, CD_3OD): δ 1.14(3H, d, *J*=6Hz), 2.88(2H, m), 3.70(1H, m).

17 (400MHz): δ 1.19(3H, d, *J*=6Hz), 2.91(2H, m), 3.78(1H, m), 7.20(1H, s), 11.05(1H, s).

18 (270MHz): δ 1.18(3H, d, *J*=6Hz), 2.41(2H, m), 3.78(1H, m).

19 (400MHz): δ 1.07(3H, d, *J*=7Hz), 2.39(2H, m), 3.30(1H, ddd, *J*=10, 5 &2Hz), 3.93(1H, d, *J*=3Hz), 4.22(1H, m), 4.27(1H, d, *J*=7Hz), 4.57(1H, s, anomeric), 4.94(1H, m, H-23).

20 (400MHz): δ 1.11(3H, d, *J*=7Hz), 2.39(2H, m), 4.02(1H, m), 4.15(1H, m), 4.20(1H, d, *J*=6Hz), 4.98(1H, m, H-23), 5.10(1H, d, *J*=1Hz, anomeric).

21 (500MHz, CD_3OD): δ 1.26(3H, d, *J*=6Hz), 2.92(2H, br t, *J*=7Hz), 3.60(1H, t, *J*=10Hz), 3.70(1H, m), 3.74(1H, dd, *J*=10 &3Hz), 3.80(1H, m), 3.87(1H, dd, *J*=8 &1Hz),3.88(1H, dd, *J*=3 &2Hz), 4.21(1H, d, *J*=8Hz), 4.95(1H, d, *J*=2Hz, anomeric), 4.98(1H, tq, *J*=6 &6Hz, H-23).

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