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ENANTIOSPECIFIC SYNTHESIS OF C_{20}-C_{28} SEGMENT OF CONCANAMYCIN A: APPLICATION OF DIETHYLISOPROPYLSILYL PROTECTING GROUP

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Summary: A complex C_{20}-C_{28} segment **5** of concanamycin A (**1**) has been first synthesized without side reactions by effective de-O-silylation of **2a**, which was constructed from the ethyl ketone **3** by glycosidation with the fluoride **4**.

The antibiotic concanamycin A (**1**) is a major component of concanamycins which were isolated in 1984 by Kinashi et al[1] and belongs to a new class of 18-membered macrolide with a long side chain which incorporates a six membered hemiketal ring having 2-deoxy-β-D-rhamnose moiety[1]. Concanamycin (**1**) was identified with the antifungal antibiotics, folimycin and A666-I and inhibits the proliferation of mouse splenic lymphocytes stimulated by concanavalin A[1]. The absolute configuration of **1** has been established by X-ray crystallographic analysis of its diacetate derivative[2]. In this article we would like to report the first enantiospecific synthesis of **5** which is a promising C_{20}-C_{28} segment of concanamycin A, and usefulness of diethylisopropylsilyl (DEIPS) group[3,4] as an effective O-protecting group, especially in deprotection of **2a**.

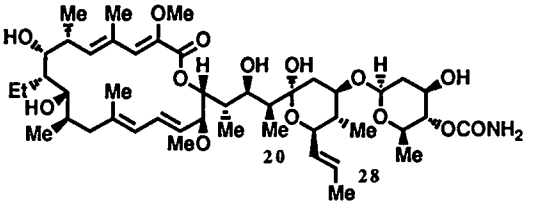
The construction of **2a** would be achieved by the glycosidation of the ethyl ketone segment **3** with the sugar segment **4**, both of which could be enantiospecifically synthesized from appropriate carbohydrate derivatives. The selective formation of β-glycosidic linkage of 2-deoxy-D-sugar would become formidable task[5] and the selection of the protecting groups, R^1 and R^2 should naturally become the key problem in the final stage of the conquest of **5** and **1**. Considering these points, we started the construction of **3**. The starting material **6**[6] was treated with acetone and catalytic amount of $BF_3 \cdot Et_2O$ (0.6 equiv)[3] at 26°C for 17h to afford **7**[7] ($[\alpha]_D$ +21° (c 1.26, $CHCl_3$)) in one step in 63% yield. Selective 5,6-de-O-isopropylidenation of **7** with 75% AcOH at 30°C for 2.5h gave diol **8**[7] ($[\alpha]_D$ +15° (c 0.62, $CHCl_3$)) in 72% yield. Periodate-oxidation ($NaIO_4$, acetone-H_2O, 26°C, 1h) of **8**, followed by the Wittig reaction of the generated aldehyde with 1.5 equiv. of methoxycarbonylmethylenetriphenylphosphorane at 25°C for 2h afforded desired trans product **9**[7] ($[\alpha]_D$ +52° (c 1.30, $CHCl_3$)) with high selectivity in 77% overall yield. The Wittig product **9** was treated with DIBAL in toluene under ice-cooling for 0.5h to give

the crude allylalcohol **10** which was converted (MsCl, LiBr, Et_3N, CH_2Cl_2, 25°C, 8h) into bromide **11**[7] ($[\alpha]_{546}$ +0.8° (c 1.20, $CHCl_3$)) in 81% overall yield from **9**. LAH-Reduction (ether, 26°C, 4h) of **11** proceeded cleanly to afford **12**[7] ($[\alpha]_D$ +11° (c 1.50, $CHCl_3$)) in 92% yield. Hydrolysis of **12** (50% AcOH-H_2O, 80°C, 0.5h) followed by LAH-reduction (THF, 70°C, 2.5h) afforded the triol, which was subjected to the selective protection of the 1,2-diol with carbonate (1.3equiv *N,N'*-carbonyldiimidazole, benzene, 26°C, 2h) and the resulted mono-alcohol **13**[7] (mp 62.5-63.5°C, $[\alpha]_D$ -45° (c 1.38, $CHCl_3$)) was silylated (DEIPSCl, imidazole, CH_2Cl_2, 25°C, 2h) to give **14**[7] (IR($CHCl_3$) ν_{max} $1800_{cm}{}^{-1}$, $[\alpha]_D$ -46° (c 0.98, $CHCl_3$)) in 75% overall yield from **12**. Hydrolysis (NaOH, MeOH, 0°C, 2.5h) of **14** followed by selective mono-tosylation (2.5 equiv TsCl, Py, 25°C, 4h) of the primary alcohol and epoxidation (NaOMe-MeOH, $CHCl_3$, 25°C, 1.5h) gave **15**[7] ($[\alpha]_D$ -10° (c 1.14, $CHCl_3$)) in 84% yield from **14**. Reaction of **15** with 2-ethyl-2-lithio-1,3-dithiane (5 equiv) (THF, -20°C, 1h) afforded the crude **16** whose dithioacetal group was cleaved (1:1 $HgCl_2$-HgO, 80% acetone-H_2O, 0°C, 0.5h) to give the pure ketone **3**[7] (IR($CHCl_3$) ν_{max} 1709 cm^{-1}, $[\alpha]_D$ +6.9°, (c 0.46, $CHCl_3$)) in 72% overall yield from **15**.

2-Deoxy-D-glucose was selected as the starting material for the construction of **4**. Benzyl glycosidation (BzlOH, $BF_3 \bullet Et_2O$, 80°C, 3h) of 2-deoxy-D-glucose, followed by selective iodonation (1.4 equiv I_2, 1.5 equiv PPh_3, 3.0 equiv imidazole, 70°C, 2h) afforded **17**[7] which was subjected to Bu_3SnH-reduction (AIBN, 80°C, 3h) to give **18**[7] in 71% overall yield from 2-deoxy-D-glucose. Mono silylation (1.2 equiv DEIPSCl, 1.3 equiv imidazole, CH_2Cl_2, 25°C, 3h) proceeded cleanly with high selectivity to afford **19**[7] whose free alcohol was carbamoylated (1. Chloroacetyl isocyanate, CH_2Cl_2, 0°C, 1h; 2. Zn, MeOH, 25°C, 5h)[8] to afford **20**[7] in 88% overall yield from **18**. **20** was hydrogenerated by H_2 in the presence of $Pd(OH)_2$ in dioxane at 25°C for 4h to give **21**[7] in 97% yield. Conversion of the free sugar **21** into the fluoride was accomplished by using 1.2 equiv. of DAST[9] in THF-ether (2:1) (-30 → +25°C, 20 min) to afford **4**[7] (mp 103.5-104.5°C, $[\alpha]_D$ +21°, (c 1.10, $CHCl_3$)) in 86% yield (α/β=14/1).

The glycosidation of **4** to the hydroxy group of **3** was best effected by carefully modified Mukaiyama method[10] (1 equiv **3**, 1 equiv **4**, 1 equiv $SnCl_2$, MS 4A, CH_2Cl_2, -50°C, 3h then -40°C, 5h) to give the desired β-glycoside **2a**[7] (mp 141-142°C, $[\alpha]_D$ -15°, (c 1.00, $CHCl_3$)) with moderate selectivity in 30 % yield. By the procedure described in the synthesis of **2a**, the another segment **2b**[7] (mp 150-151°C, $[\alpha]_D$ -11°, (C 0.82, $CHCl_3$)) was also prepared by using only TBDMS-Cl as the silylating agent. In the deprotection of **2a** and **2b**, mild acidic condition was used without side reactions instead of tetrabutylammonium fluoride as the deprotection reagent because of, their labile β-ketol type structure[3,11]. Treatment of **2b** with AcOH:1%$KF \bullet HF_{(aq)}$:THF (3:1:3) did not give the desired **5** even at 30°C for 46 h but gave **22**[7] in 94% yield. In contrast to this fact, the desilylation of **2a** by AcOH:1%$KF \bullet HF_{(aq)}$:THF (3:1:3) (30°C, 46h) proceeded smoothly to afford **5**[7] (mp 170-171°C, [a]$_D$ -29°, (c 0.72, MeOH)) in 83% yield.

Thus C_{20}-C_{28} segment **5** of concanamycin A which is a promising key intermediate for the synthesis of **1** has been first synthesized by effective use of DEIPS group which was recently developed[3] and characterized[4] in our laboratories. Improvement of the glycosidation of **4** with **3** is now under study.



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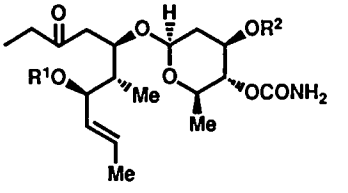
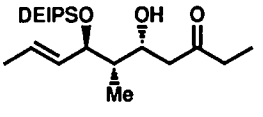


2a:R^1=R^2=DEIPS
2b:R^1=DEIPS, R^2=TBDMS



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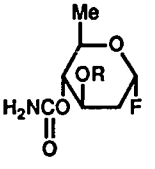
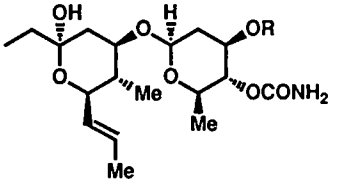
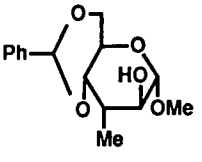


4:R=DEIPS



5:R=H
22:R=TBDMS



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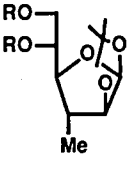
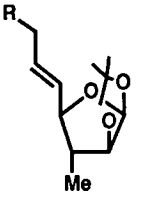
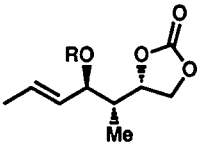


7:R=acetonide
8:R=H

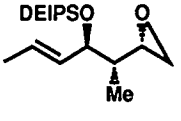
9



10:R=OH
11:R=Br
12:R=H



13:R=H
14:R=DEIPS



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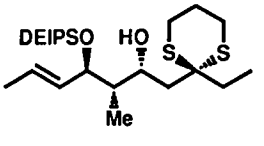
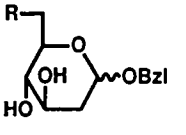
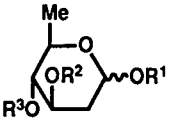


16



17:R=I
18:R=H



19:R^1=Bzl, R^2=DEIPS, R^3=H
20:R^1=Bzl, R^2=DEIPS, R^3=$CONH_2$
21:R^1=H, R^2=DEIPS, R^3=$CONH_2$

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7). All compounds were purified by silica gel column chromatography and were fully characterized by spectroscopic means and elemental analyses. Optical rotations were mesured using a 0.2dm or 0.5dm tube at 25°C. Melting points were uncorrected. Significant ^{1}H-NMR spectra [δ (TMS), J(Hz)] are the following. **3**: (270MHz, $CDCl_3$) 0.55-0.7 (4H, m), 0.94 (3H, d, J=7.8), 0.95-1.05 (13H, m), 1.06 (3H, t, J=7.6), 1.51 (1H, ddt, J=7.8, 4.4, 2.0), 1.71 (3H, d, J=4.8), 2.32 (1H, dd, J=15.6, 4.0), 2.49 (2H, dq, J=7.6, 2.0), 2.69 (1H, dd, J=15.6, 7.2), 3.52 (1H, br s, OH), 4.12(1H, ddd, J=4.4, 4.4, 1.2), 4.51 (1H, ddd, J=7.2, 4.0, 2.0), 5.45-5.7 (2H, m). **4**: (270MHz, $CDCl_3$) 0.55-0.7 (4H, m), 0.9-1.05 (13H, m), 1.25 (3H, d, J=6.4), 1.81 (1H, dddd, J=40.4, 13.8, 11.0, 2.4), 2.28 (1H, dddd, J=13.8, 9.8, 6.0, 1.6), 3.91 (1H, dq, J=10.0, 6.4), 4.07 (1H, ddd, J=11.0, 10.0, 6.0), 4.54 (1H, dd, J=10.0, 10.0), 4.65- 4.8 (2H, m), 5.63 (1H, ddd, J=51.8, 2.4, 1.6). **2a**: (270MHz, $CDCl_3$) 0.5-0.7 (8H, m), 0.78 (3H, d, J=6.8), 0.9-1.05 (14H, m,), 1.04 (3H, t, J=7.2), 1.15-1.3 (1H, m), 1.21 (3H, d, J=6.2), 1.5-1.65 (1H, m), 1.68 (3H, dd, J=6.2, 1.6), 1.95 (1H, ddd, J=12.8, 5.4, 1.8), 2.35-2.55 (3H, m), 2.77 (1H, dd, J=15.8, 8.4), 3.26 (1H, dq, J=9.6, 6.2), 3.71 (1H, ddd, J=9.8, 8.6, 5.4), 4.13 (1H, dd, J=8.2, 8.2), 4.39 (1H, dd, J=9.8, 9.8), 4.45-4.55 (1H, m), 4.52 (1H, dd, J=10.0, 10.0), 4.64 (2H, br s), 5.35 (1H, ddq, J=15.6, 8.2, 1.6), 5.55 (1H, dq, J=15.6, 6.2). **5**: (250MHz, pyridine-d_5) 1.13 (3H, t, J=7.8), 1.17 (3H, d, J=6.3), 1.42 (3H, d, J=6.0), 1.5-1.7 (2H, m), 1.62 (3H, d, J=4.8), 1.94 (2H, q, J=7.8), 2.05-2.25 (1H, m), 2.45-2.6 (2H, m), 3.50 (1H, dq, J=10.0, 6.0), 4.05-4.2 (1H, m), 4.25-4.4 (2H, m), 4.7-4.85 (2H, m), 4.89 (1H, dd, J=9.8, 1.3), 5.01 (1H, dd, J=9.5, 9.5), 5.5-5.75 (2H, m).

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