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First Synthesis of Conagenin Diastereoisomers

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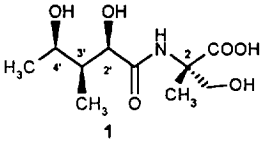
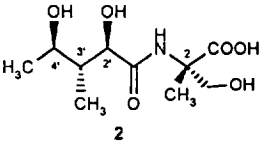
Abstract: The first synthesis of two conagenin analogs is described.

Conagenin (**1**), a low molecular weight immunomodulator, was discovered in fermentation broths of *Streptomyces roseosporus* MI696-AF3[1]. It is an immunomodulator of antitumor activity stimulating activated T cells and enhancing generation of antitumor cells. As conagenin itself does not show cytotoxicity to murine and human tumor cells and was found to be effective *in vivo* in improving antitumor activity of cyclophosphamide, mitomycin C and adriamycin against murine leukemias, it may be useful in cancer chemotherapy[2-5].

To our best knowledge there have been no synthetic efforts towards conagenin and its analogs yet. Herein, we wish to report the synthesis of the 3'-epimer of naturally occurring conagenin (3'-epiconagenin, **2**) and its 2*R*-diastereoisomer (**3**, Fig. 1).



1



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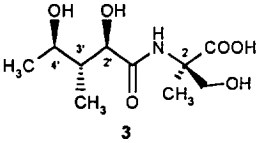

3

Fig. 1

5-Deoxy-1,2-O-isopropylidene-α-D-xylofuranose (**4**), which can be prepared from D-xylose in four steps[6], was chosen as starting material for synthesis of the dideoxy aldonic acid part of **2** and **3** (Fig. 2). Oxidation of the secondary OH-group with chromium trioxide-pyridine complex[7] resulted in the 3-ulose **5**, which was readily converted into the exomethylene compound **6**[8] *via* a Wittig reaction. Hydrogenolysis of

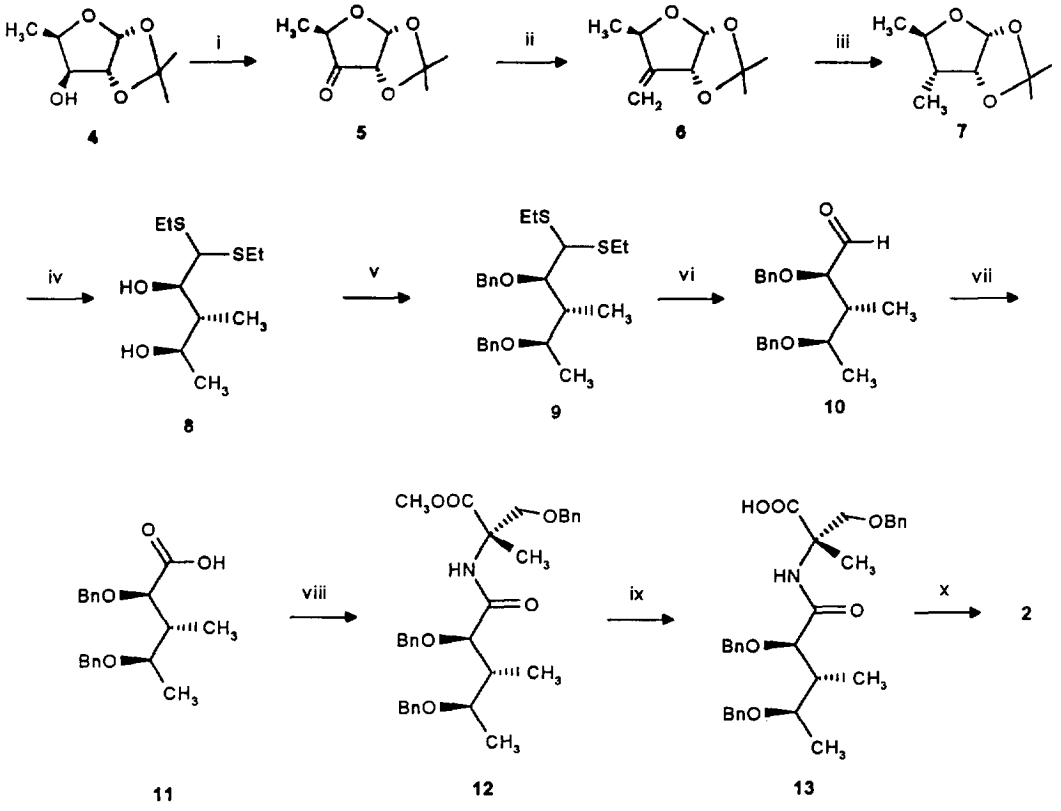

Fig. 2.

Conditions: i) CrO_3·2pyr, Ac_2O, CH_2Cl_2; ii) Ph_3PCH_3Br, nBuLi, THF, 60% from **4**; iii) 10% Pd/C, H_2, EtOAc, 87%; iv) EtSH, cc.HCl, THF, 0°C, 84%; v) BnBr, NaH, Bu_4NI, THF, 97%; vi) $HgCl_2$, $CdCO_3$, acetone/water; vii) PDC, DMF, 55% from **9**; viii) HOBT, DCC, (*S*)-O-benzyl-2-methylserine methyl ester[11], CH_2Cl_2, 83%; ix) 1M KOH, dioxane, 82%; x) 10% Pd/C, H_2, MeOH, 66%

6 with 10% Pd on charcoal catalyst gave the 3-deoxy-3-C-methyl derivative **7** as a single diastereomer, which was identical (by ^{1}H-NMR and specific rotation) with the compound synthesized by Tronchet et al. *via* a different route[9]. Direct mercaptalization of **7** gave the D-*ribo*-derivative **8**, which was efficiently benzylated *via* conventional methodology. Mercury salt promoted demercaptalization of **9** afforded unstable aldehyde **10**, which was oxidized without purification. For this purpose the Corey method[10] proved to be the most effective.

The syrupy ribonic acid derivative **11** was coupled with (*S*)-O-benzyl-2-methylserine methyl ester[11] by the use of HOBT and DCC giving rise to the fully protected conagenin diastereomer **12**. The ester group was hydrolized with 1M KOH solution in dioxane. Subsequent catalytic hydrogenation of compound **13** led to 3'-epiconagenin (**2**).

Using (*R*)-O-benzyl-2-methylserine methyl ester[12] the same procedures were followed to obtain **3** (Fig. 3).

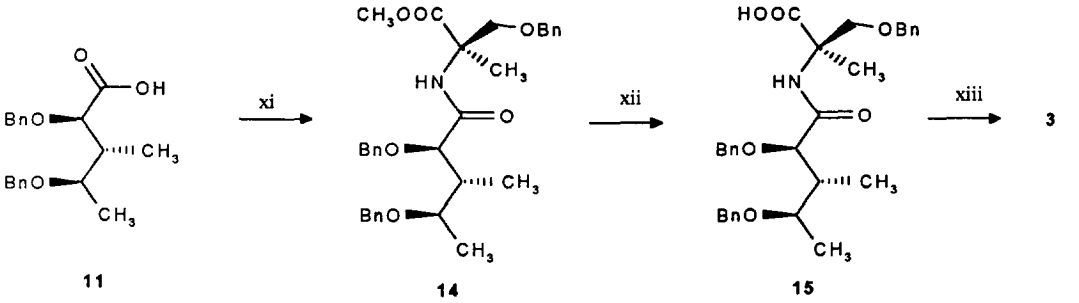

Fig. 3

Conditions: xi) HOBT, DCC, (*R*)-O-benzyl-2-methylserine methyl ester[12], CH_2Cl_2, 77%; xii) 1M KOH, dioxane, 82%; xiii) 10% Pd/C, H_2, MeOH, 95%

The synthesis of conagenin and its other analogs is in progress in our laboratory. The biological activity of **2**, **3** and further analogs compared with **1** will be published later.

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8. All of the compounds gave satisfactory microanalytical and/or spectroscopic evidence. Selected spectroscopic and physical data are the following. Compounds without mp are syrupy substances. Specific rotations were measured at room temperature. Compound **6**: $[\alpha]_D$= +127.1 (c 0.63 $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 5.08 (1H, d) and 5.33 (1H, d, C=CH_2, *J*= 2 Hz). Compound **7**: $[\alpha]_D$= +33.3 (c 0.98, $CHCl_3$); lit.[8] +36.1 (c 1.2, $CHCl_3$). Compound **8**: $[\alpha]_D$= −49.2 (c 2.25 $CHCl_3$); FAB-MS m/z 238 (M^+). Compound **9**: $[\alpha]_D$= +15.1 (c 1.07, $CHCl_3$); EI-MS m/z 357 $(M+H-SEt)^+$. Compound **10**: FTIR (KBr) $\nu_{C=O}$= 1732 cm^{-1}; EI-MS m/z 283 $(M-CHO)^+$. Compound **11**: $[\alpha]_D$= +3.4 (c 0.71, $CHCl_3$); FTIR (KBr) $\nu_{C=O}$= 1714 cm^{-1}; EI-MS m/z 329 $(M+H)^+$. Compound **12**: $[\alpha]_D$= +20.0 (c 0.69, $CHCl_3$); FAB-MS m/z 534 (M^+). Compound **13**: mp 152-153 °C (CH_2Cl_2-hexane); $[\alpha]_D$= +4.0 (c 0.62, $CHCl_3$); CI-MS m/z 520 (M^+). Compound **2**: (2*S*)N-[(2'*R*,3'*R*,4'*R*)2',4'-dihydroxy-3'-methylpentanoyl]-2-methylserine, mp 105-106 °C (MeOH, dec.); $[\alpha]_D$= +25.8 (c 1.25, MeOH); MS (thermospray) m/z 250 $(M+H)^+$; ^1H NMR (400 MHz, MeOD): δ 0.94 (3H, d, $J_{3',3'\text{-methyl}}$= 7.1 Hz, 3'-CH_3), 1.16 (3H, d, $J_{4',5'}$= 6.4 Hz, 5'-H), 1.43 (3H, s, 2-CH_3), 1.95 (1H, m, 3'-H), 3.82 (1H, dq, $J_{3',4'}$= 7.1 Hz, 4'-H), 3.83 and 4.04 (2H, ABq, *J*= 10.9 Hz, CH_2OH), 4.08 (1H, d, $J_{2',3'}$= 4.0 Hz, 2'-H); ^{13}C NMR (90 Hz, MeOD): δ 180.5 and 175.9 (carbonyl and amide), 75.0 (2'-C), 69.8 (4'-C), 66.7 (CH_2OH), 63.1 (2-C), 45.8 (3'-C), 21.4 (5'-C), 20.5 (2-CH_3), 13.1 (3'-CH_3). Compound **14**: $[\alpha]_D$= +22.7 (c 0.93, $CHCl_3$); EI-MS m/z 535 $(M+H)^+$. Compound **15**: mp 137-138 °C (CH_2Cl_2-hexane); $[\alpha]_D$= +22.0 (c 0.75, $CHCl_3$); EI-MS m/z 428 $(M-Bn)^+$. Compound **3**: (2*R*)N-[(2'*R*,3'*R*,4'*R*)2',4'-dihydroxy-3'-methylpentanoyl]-2-methylserine, mp 168-170 °C (MeOH, subl.); $[\alpha]_D$= +6.0 (c 1.06, MeOH); FAB-MS m/z 250 $(M+H)^+$; ^1H NMR (200 MHz, D_2O): δ 0.92 (3H, d, $J_{3',3'\text{-methyl}}$= 7.1 Hz, 3'-CH_3), 1.17 (3H, d, $J_{4',5'}$= 6.4 Hz, 5'-H), 1.42 (3H, s, 2-CH_3), 2.01 (1H, m, 3'-H), 3.83 and 3.94 (2H, ABq, *J*= 11.3 Hz, CH_2OH), 3.91 (1H, dq, $J_{3',4'}$= 7.1 Hz, 4'-H), 4.10 (1H, d, $J_{2',3'}$= 4.8 Hz, 2'-H); ^{13}C NMR (90 MHz, D_2O): 180.2 and 175.4 (carbonyl and amide), 74.9 (2'-C), 69.2 (4'-C), 65.9 (CH_2OH), 63.2 (2-C), 44.4 (3'-C), 20.3 (5'-C), 20.2 (2-CH_3), 12.3 (3'-CH_3).
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