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Tetrahedron Letters 47 (2006) 5847–5849
Tetrahedron Letters

Total synthesis of (+)-conagenin☆

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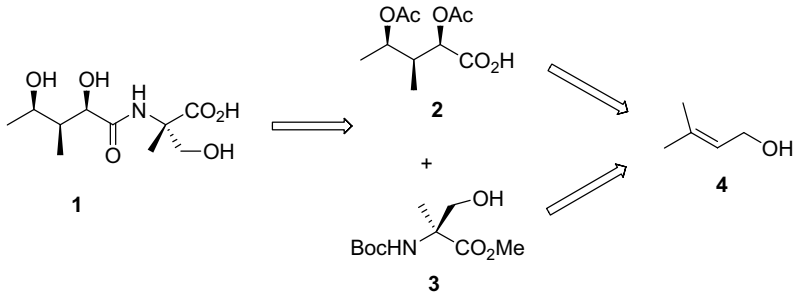
Received 10 May 2006; revised 6 June 2006; accepted 15 June 2006
Available online 3 July 2006

Abstract—The total synthesis of the immunomodulator, (+)-conagenin was achieved using, as a key step, a method developed by us for the synthesis of 2-methyl-1,3-diols via Ti(III)-mediated diastereo- and regioselective opening of trisubstituted 2,3-epoxy alcohols, to carry out the stereoselective construction of its pentanoic acid segment.

Conagenin (**1**) is a low molecular weight immunomodulator isolated from the fermentation broth of *Streptomyces roseosporus*.[1] This molecule exhibits wide-ranging biological activity. It stimulates activated T cells, which produce lymphokines and generate antitumor effector cells.[2] The antitumor efficacies of adriamycin and mitomycin C against murine leukemias are also enhanced by **1**, making it a potential candidate for cancer chemotherapy.[3] It has a densely functionalized structure consisting of a (2*R*,3*S*,4*R*)-2,4-dihydroxy-3-methylpentanoic acid moiety with three contiguous chiral centers, coupled to a (*S*)-α-methylserine possessing a quaternary chiral center. The pronounced biological activities of conagenin and its highly substituted structure make it an attractive target to synthetic organic chemists.[4]

We envisaged that the total synthesis of this molecule would not only provide access to larger quantities necessary for further biological studies, but also help to design and build more potent synthetic analogs. Retrosynthetic analysis of **1** reveals that it can be made easily from the two units **2** and **3**. In this letter, we describe the total synthesis of the conagenin (**1**) using 3-methyl-2-buten-1-ol (**4**) as a common starting material to build both the fragments, **2** and **3**.

The salient feature of our synthesis is the successful application, as a key step, of a very efficient method developed by us earlier for the synthesis of 2-methyl-1,3-diols via radical-mediated regioselective ring opening of trisubstituted 2,3-epoxy alcohols at the more substituted center using Cp_2TiCl.[5] The excellent diastereoselectivities observed in these reactions prompted us to employ it in our present study for the stereoselective construction of the propionate-derived acid component **2**.



Keywords: Conagenin; Epoxide opening; 2-Methyl-1,3-diol; Immunomodulator.
☆IICT Communication No. 060507.
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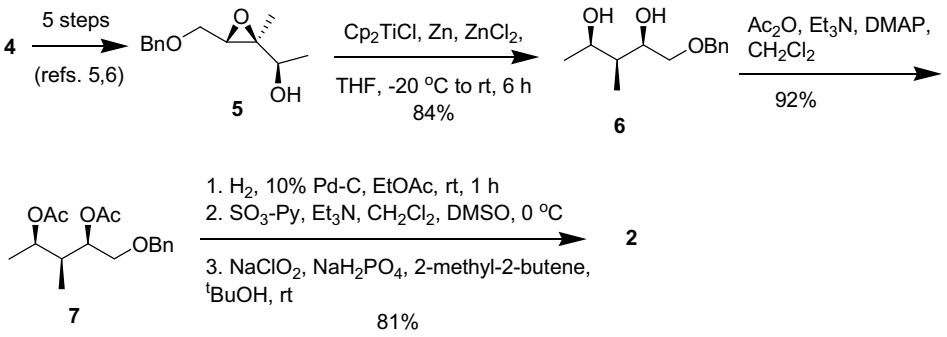
doi:10.1016/j.tetlet.2006.06.087



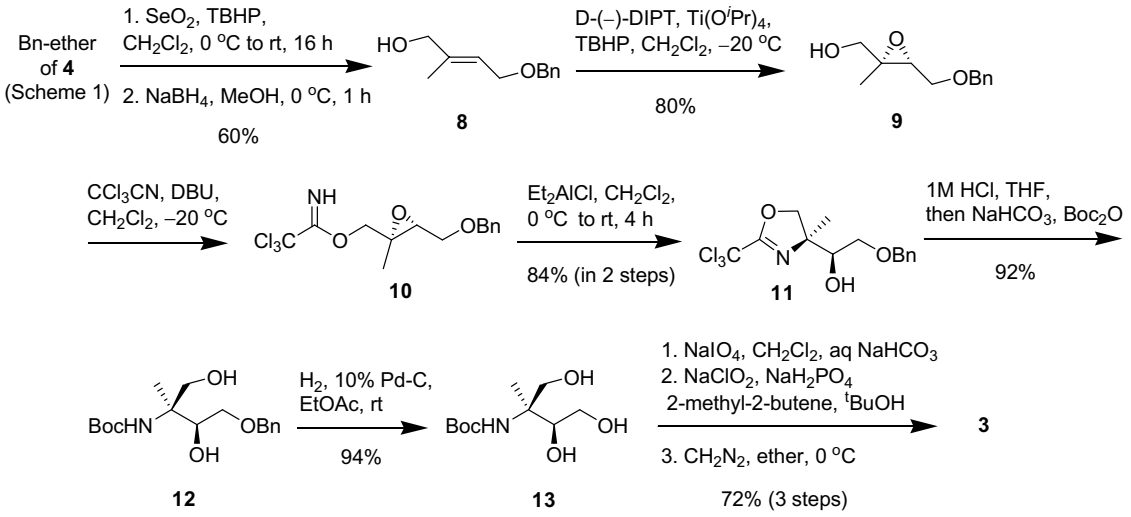
Scheme 1. Stereoselective synthesis of **2**.

Scheme 1 outlines the details of the synthesis of **2**. The *syn* epoxy alcohol **5** was prepared from **4** in five steps following the procedures reported earlier[5,6]—benzylation of the hydroxyl group, SeO_2-mediated allylic oxidation,[7] Grignard addition to the resulting aldehyde with MeMgI, Sharpless kinetic resolution[8] of the allylic alcohol and *m*CPBA epoxidation of the chiral allylic alcohol. Ring opening of **5** with $Cp_2Ti(III)Cl$, generated in situ from Cp_2TiCl_2 following the reported procedure,[5] gave the expected all *syn* product **6** almost exclusively as a single isomer. The trace amount of the *anti,anti* isomer could be easily removed by standard silica gel column chromatography. The ^{13}C NMR spectrum of the acetonide of **6** showed the chemical shifts of the methyl carbons of the acetonide function at 19.6 and 29.9 ppm and that of the ketal carbon at 98.8 ppm confirming it to be a '1,3-*syn*' acetonide.[9] Besides, the ^3J couplings of 2.4 Hz between 2H and 3H and 2.3 Hz between 3H and 4H in the acetonide support the *S*-configuration of the 3-Me substituent. Compound **6** was then transformed into its diacetate **7** in 92% yield. Debenzylation of **7** by catalytic hydrogenation was followed by a two-step oxidation of the resulting primary hydroxyl group to the acid **2** in 81% yield.

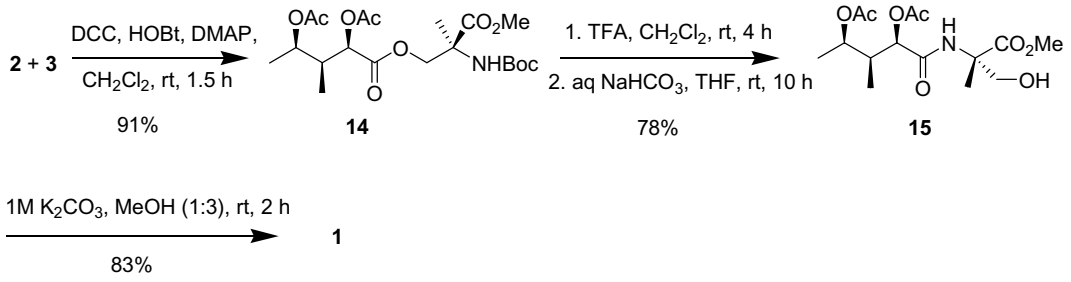
The synthesis of fragment **3** is described in Scheme 2. The aldehyde obtained by the SeO_2 oxidation of benzylated **4** from Scheme 1 was reduced with $NaBH_4$ to furnish the allylic alcohol **8** in 60% yield in two steps. Katsuki–Sharpless catalytic asymmetric epoxidation[10] of **8** using D-(−)-tartrate gave the requisite chiral epoxy alcohol **9** in 80% yield (>95% ee). The trichloroacetimidate **10** of this epoxy alcohol underwent facile intramolecular S_N2 opening of the epoxide ring under acidic conditions[4a,11] to furnish the oxazole **11** in 84% yield. Acid hydrolysis of the oxazole ring gave an amino diol which was protected in situ using Boc_2O to furnish **12** in 92% yield. Debenzylation of **12** by catalytic hydrogenation gave a triol intermediate whose 1,2-diol moiety was oxidatively cleaved using $NaIO_4$. The resulting aldehyde was next oxidized to an acid and esterified using CH_2N_2 to give Boc-(*S*)-α-methylserine methyl ester **3** in 72% yield in three steps from **13**.

The coupling of the fragments **2** and **3** and the final stages of the synthesis are shown in Scheme 3. Acid **2** was esterified with the alcohol **3** using DCC, HOBt, and DMAP to furnish the ester **14** in 91% yield.[4d]

Deprotection of the Boc-group freed the amine, which underwent a smooth ester to amide rearrangement on treatment with aqueous $NaHCO_3$[4c,d] to give **15** in 78% yield. Finally saponification of **15** furnished the target molecule **1** in 83% yield. The spectroscopic data,



Scheme 2. Stereoselective synthesis of **3**.



Scheme 3. Synthesis of (+)-conagenin **1**.

namely, IR, NMR, mass spectra as well as the rotation of our synthetic products, **15** and **1**,[12] were in conformity with those reported earlier.[1,4]

Acknowledgments

The authors wish to thank CSIR, New Delhi, for a research fellowship (G.S.).

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12. Data for diacetylconagenin methyl ester **15**: $R_f = 0.4$ (silica gel 70% EtOAc in petroleum ether); $[\alpha]_D^{29}$ +33.0 (*c* 0.51, $CHCl_3$); IR (neat) ν_{max} 3400, 3020, 1737, 1682 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.15 (s, 1H, NH), 5.09–5.89 (m, 2H), 4.15 (dd, $J = 10.9$, 3.1 Hz, 1H), 3.83 (dd, $J = 10.9$, 5.4 Hz, 1H), 3.80 (s, 3H, CO_2Me), 2.29 (qt, $J = 7$, 5.4 Hz, 1H), 2.19 (s, 3H, CH_3CO–), 2.07 (s, 3H, CH_3CO), 1.55 (s, 3H), 1.26 (d, $J = 6.2$ Hz, 3H) 1.02 (d, $J = 7$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.4, 170.8, 170.2, 168.8, 75.1, 71.0, 65.4, 62.4, 53.0, 39.7, 21.1, 20.6, 19.6, 18.0, 9.6; MS (LSIMS): *m*/*z* (%) 348 (5) $[M+H]^+$, 370 (72) $[M+Na]^+$.
Data for (+)-conagenin (**1**): $[\alpha]_D^{31}$ +50.2 (*c* 0.38, MeOH); ^1H NMR (CD_3OD, 500 MHz): δ 4.16 (d, $J = 2.4$ Hz, 1H), 4.10 (d, $J = 11$ Hz, 1H), 3.93–3.82 (m, 2H), 1.93 (m, 1H), 1.50 (s, 3H), 1.23 (d, $J = 6.1$ Hz, 3H), 0.94 (d, $J = 7.3$ Hz, 3H); MS (LSIMS): *m*/*z* (%) 272 (18) $[M+Na]^+$.