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ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 6463–6465

Studies directed towards the total synthesis of botcinic acid, the revised structure of botcinolide: synthesis of the highly substituted tetrahydropyran moiety☆

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Received 16 May 2007; revised 2 July 2007; accepted 11 July 2007
Available online 17 July 2007

Abstract—Synthesis of the highly substituted polyoxygenated tetrahydropyran ring of botcinic acid, the revised structure of botcinolide is achieved using, as key steps, a highly stereoselective aldol reaction of the titanium enolate from a lactate-derived chiral ketone and a stereoselective dihydroxylation.

Botcinolides belong to a family of novel phytotoxic metabolites, isolated from a strain of the plant pathogen *Botrytis cinerea*, a fungus responsible for both the so-called noble and gray rot in fruits.[1] The structure of botcinolide, which was originally reported as a nine-membered lactone,[1] was subsequently revised on the basis of spectroscopic data and chemical conversions.[2] The revised structure was found to have a highly substituted tetrahydropyran ring and, very surprisingly, a free carboxylic group. This prompted the investigators to rename the molecule botcinic acid (**1**). The pronounced biological activities of botcinolides as phytotoxins with relatively low acute toxicity[3] and their highly substituted structures make them attractive targets to synthetic organic chemists. While synthetic studies towards the earlier reported structure of epibotcinolides have been published,[4] no synthesis of the revised structure has yet been reported. As part of our studies directed towards the synthesis of various molecules of the botcinolide family, we describe herein the first synthesis of the polyhydroxylated tetrahydropyran ring **2** of botcinic acid **1** in suitably protected form for further synthetic work (Fig. 1).

Scheme 1 outlines the details of the synthesis of **2**. Aldol reaction of the titanium enolate derived from the chiral ketone **3**, prepared from (*S*)-lactic acid ethyl ester by a known procedure,[5] with methacrolein **4** gave the desired *syn*-isomer **5** as the major product in a 7:1 ratio.[6] The diastereomers were separated by column chromatography to afford pure *syn*-**5**. Protective group manipulations were required at this stage to silylate the hydroxyl groups appropriately for carrying out selective deprotection at a later stage. Thus, TIPS protection of the allylic alcohol of **5**, TBS deprotection of the secondary hydroxyl and finally TES-protection furnished inter-

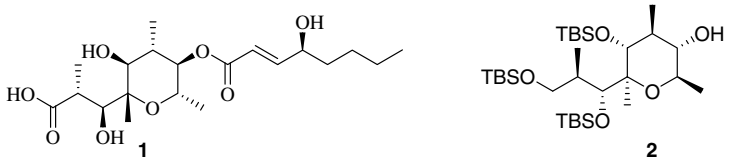

Figure 1. Revised structure of botcinic acid (**1**, Ref. 2) and our synthetic target **2**.

Keywords: Botcinolides; Botcinic acid; Dihydroxylation; Aldol reaction; Sharpless epoxidation.
☆ IICT Communication No. 070521.
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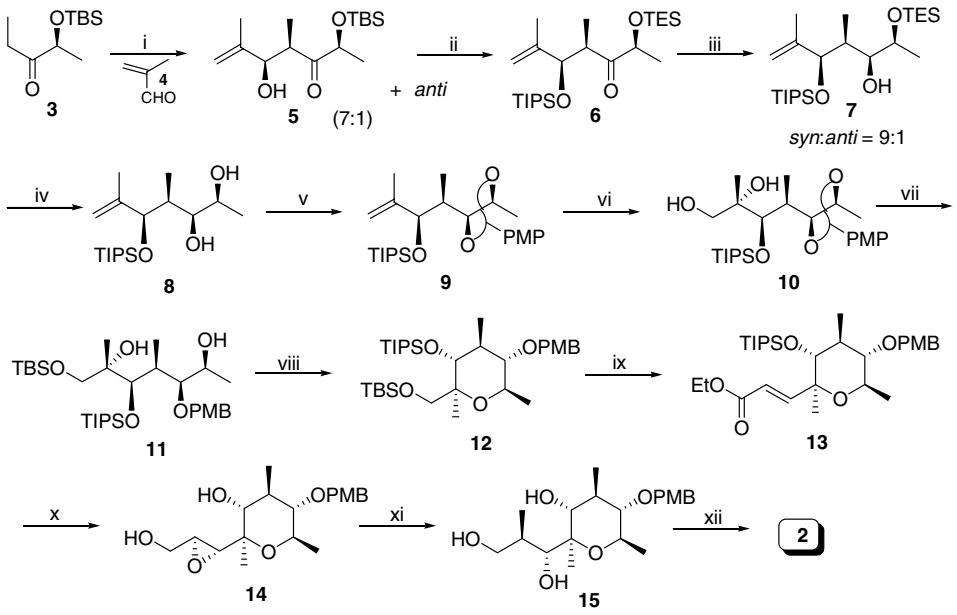
doi:10.1016/j.tetlet.2007.07.068



Scheme 1. Reagents and conditions: (i) **4**, $TiCl_4$, $^iPr_2NEt$, CH_2Cl_2, −78 °C, 2 h, 76%; (ii) (a) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 30 min; (b) CSA, CH_2Cl_2/MeOH (1:1), 0 °C, 9 h; (c) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 5 min, 70% in three steps; (iii) DIBAL-H, CH_2Cl_2, −78 °C, 10 min, quantitative yield; (iv) CSA, CH_2Cl_2/MeOH (4:1), 0 °C, 5 min, 68% with respect to *syn*-product **8**; (v) $PMB(OMe)_2$, CH_2Cl_2, 0 °C to rt, 30 min, 90%; (vi) OsO_4, NMO, acetone/H_2O (20:1), rt, 3 d, 91%; (vii) (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 5 min; (b) DIBAL-H, CH_2Cl_2, −78 °C, 20 min, 58% in two steps; (viii) (a) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 15 min; (b) K_2CO_3, MeOH, rt, 18 h, 52% in two steps; (ix) (a) CSA, CH_2Cl_2/MeOH (1:1), 0 °C, 6 h; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 2 h; (c) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, rt, 3 d, 78% in three steps; (x) (a) DIBAL-H, CH_2Cl_2, −78 °C, 15 min; (b) TBAF, THF, 0 °C to rt, 6 h; (c) $Ti(O^iPr)_4$, (+)-DIPT, TBHP, 4 Å MS, CH_2Cl_2, −20 °C, 8 h, 43% in three steps; (xi) (a) Me_2CuLi, Et_2O, −20 °C to rt, overnight; (b) $NaIO_4$, THF/H_2O (1:1), 0 °C to rt, 3 h, 55% in two steps; (xii) (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 2 d; (b) DDQ, CH_2Cl_2/phosphate buffer (pH 7) (20:1), 1.5 h, 55% in two steps.

mediate **6**. Diastereoselective 1,3-*syn* hydride reduction of β-silyloxy ketone **6** with DIBAL-H gave the all *syn*-product **7** as the major diastereomer.[7] The minor *anti*-isomer could be easily separated by standard silica gel column chromatography. The stereochemistry of the major product **7** was confirmed after two further transformations.

Compound **7** was treated with CSA to selectively deprotect the TES-group and the resulting 1,2-diol **8** was protected as *p*-methoxybenzylidene acetal **9**. The ^1H NMR spectrum of **9** showed a ^3J coupling of 5.9 Hz between C2–H and C3–H supporting the structure assigned to the major product of the hydride reduction.[8] Diastereoselective cis-hydroxylation of **9** with a catalytic amount of OsO_4 gave the desired diol **10**.[9] Selective silylation of the primary hydroxyl group of **10** was followed by reductive ring opening of the *p*-methoxybenzylidene acetal to give diol **11**.[10] Mesylation of the methyl carbinol of **11** was followed by treatment with anhydrous K_2CO_3 in dry methanol to enable a facile ring closing reaction involving an intramolecular 6-*exo* S_N2 type substitution of the –OMs group to furnish the cyclized tetrahydropyran ring **12**.

Selective deprotection of the primary *O*-silyl group of **12** gave an alcohol, which was oxidized to an aldehyde and reacted with the stabilized ylide, (carboethoxymethylene)triphenylphosphorane, to furnish α,β-unsaturated ester **13**. The ^3J coupling of 15.7 Hz between the olefinic protons confirmed the trans geometry of the double bond in **13**. Reduction of the ester group of **13** gave an allylic alcohol, which, after TIPS-deprotection, was subjected to Katsuki–Sharpless epoxidation[11] to furnish the epoxy alcohol **14**. Opening of the epoxide ring of **14** with Me_2CuLi furnished '2-methyl-1,3-diol' **15** as the major product, which was subjected to oxidative cleavage with $NaIO_4$ to remove the minor 1,2-diol. The purified triol **15** was persilylated followed by deprotection of the PMB–ether to furnish the desired intermediate **2**.[12]

In conclusion, we have described here the first synthesis of the highly substituted tetrahydropyran moiety **2** of the revised structure of botcinic acid **1** in suitably protected form for further synthetic work, currently in progress.

Acknowledgement

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

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12. Data of cyclized product **2**. Gummy liquid; $R_f = 0.50$ (SiO_2, 10% EtOAc in petroleum ether); $[\alpha]_D^{34}$ −20.0 (*c* 0.15, $CHCl_3$); IR (neat): ν_{max} 3446, 2925, 2854, 1627 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.17–4.01 (m, 2H), 3.85 (d, $J = 9.8$ Hz, 1H), 3.71 (s, 1H, H-1′), 3.41 (dd, $J = 10.6$, 9.8 Hz, 1H), 3.23 (br d, $J = 7.6$ Hz, 1H), 2.38–2.24 (m, 2H), 1.25 (s, 3H, methyl), 1.17–1.03 (three d, 9H, three methyls), 0.93 (s, 9H, ^{t}Bu), 0.89–0.87 (two s, 18H, two ^{t}Bu), 0.17–0.03 (six s, 18H, six Si–CH_3); HRMS (ESI): $[M+Na]^+$ calcd for $C_{30}H_{66}O_5NaSi_3$, 613.4115; found, 613.4103.