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Studies directed towards the synthesis of botcinolides: synthesis of the nonalactone ring of 2-epibotcinolide☆

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Abstract—Synthesis of the polyoxygenated nonalactone ring of 2-epibotcinolide was achieved using a highly stereoselective aldol reaction of the titanium enolate from a lactate-derived chiral ketone, a stereoselective dihydroxylation and a Yamaguchi macrolactonization reaction.

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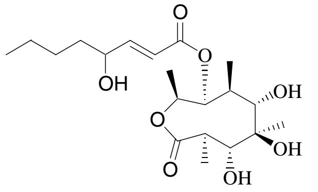
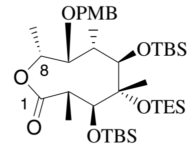
Botcinolides belong to a family of novel phytotoxic metabolites isolated from a strain of the plant pathogen *Botrytis cinerea*, a fungus that is responsible for both the so-called noble and grey rot in fruits.[1] The pronounced biological activities of botcinolides as phytotoxins with relatively low acute toxicity[2] and their structures with a polyhydroxylated nonalactone ring acylated with a fatty acid side chain, make them attractive targets to synthetic organic chemists. While the biosynthesis of the botcinolide skeleton has been investigated in detail, no synthesis of any member of this family has yet been achieved.[3] The relative configurations of these molecules have been deduced by extensive spectroscopic methods.[1c] However, their absolute stereochemistries are yet to be determined. We envisaged that the total synthesis of these molecules would not only provide access to larger quantities necessary for further biological studies, but also help to establish their absolute stereochemistries. As part of our studies directed towards the synthesis of 2-epibotcinolide **1**, we describe herein the first synthesis of the polyhydroxylated nonalactone ring of the molecule **2** in suitably protected form for further synthetic work.



1



2

Scheme 1 outlines the details of the synthesis of **2**. Benzylation of commercially available methyl (*S*)-3-hydroxy-2-methylpropionate **3** with *O*-benzyl trichloroacetimidate under acidic conditions[4] was followed by reduction of the ester with lithium aluminium hydride (LAH) to provide the chiral alcohol **4**. Oxidation of **4** gave an aldehyde, which was subjected to olefination using the stabilized ylide $Ph_3P{=}C(CH_3)CO_2Et$ to furnish, exclusively, the *E*-olefin **5**. Compound **5** was next transformed into the aldehyde **6** in two steps—reduction with LAH to an alcohol followed by oxidation to the aldehyde. Aldol reaction of **6** with the titanium enolate derived from the chiral ketone **7**[5] gave the desired *syn* isomer **8** as the major product in a 6:1 ratio.[6] The product was purified and silylation of the allylic hydroxyl was carried out followed by protective group manipulations, necessitated in order to achieve selective deprotection at a later stage, to furnish the intermediate **9**. Diastereoselective 1,3-*syn* hydride reduction of the β-alkoxy ketone **9** with DIBAL-H gave the all *syn* product **10** as the major isomer.[7] The minor *anti*-isomer could be easily separated by standard silica gel column chromatography. The stereochemistry of the major product **10** was determined after three more steps.

Keywords: Botcinolides; 2-Epibotcinolide; Dihydroxylation; Aldol reaction; Yamaguchi reaction.

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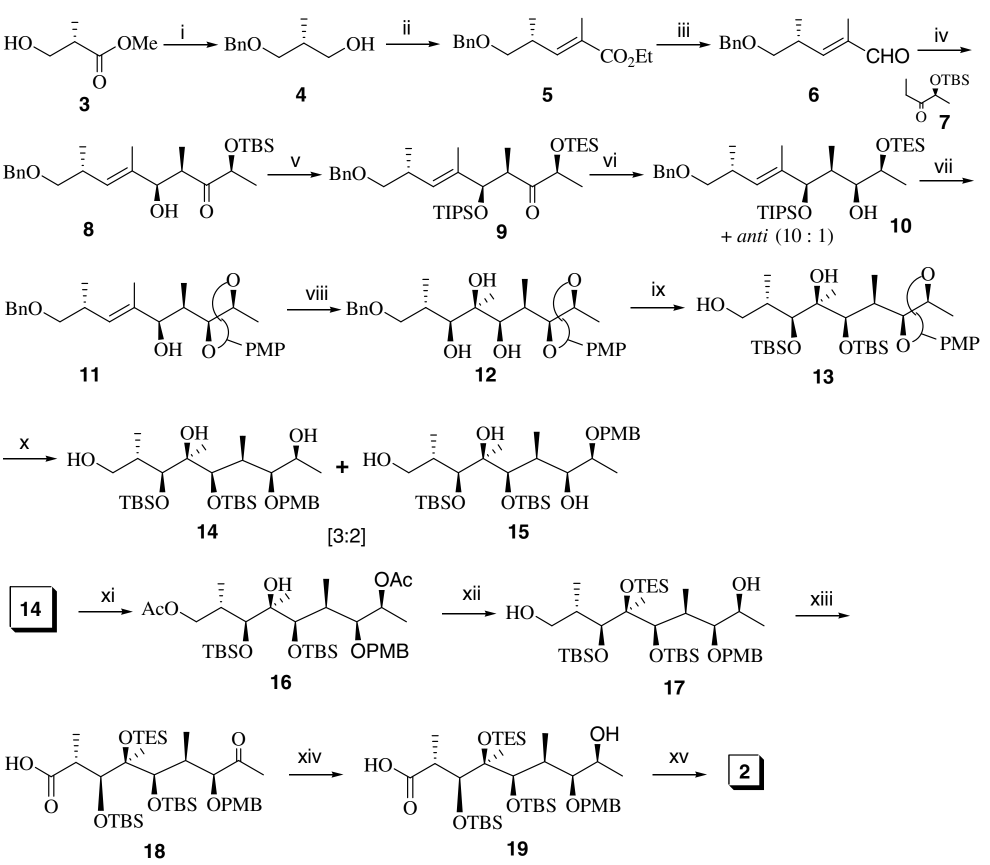

Scheme 1. Reagents and conditions: (i) (a) $CCl_3C(OBn){=}NH$, TfOH, cyclohexane/CH_2Cl_2 (2:1), 0 °C, 5 h; (b) LAH, dry ether, 0 °C, 5 min, 85% yield after two steps; (ii) (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (b) $Ph_3P{=}C(CH_3)CO_2Et$, CH_2Cl_2, rt, 3 h, 84% yield after two steps; (iii) (a) LAH, dry ether, 0 °C, 10 min; (b) SO_3–Py, Et_3N, DMSO/CH_2Cl_2 (2:1.6), 0 °C, 30 min, 87% yield after two steps; (iv) **7**, $TiCl_4$, $^i Pr_2NEt$, CH_2Cl_2, −78 °C, 3 h, 85%; (v) (a) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, rt, 1 h; (b) CSA, CH_2Cl_2/MeOH, 0 °C, 8 h; (c) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 5 min, 67% after three steps; (vi) DIBAL-H, CH_2Cl_2, −78 °C, 15 min, quantitative yield; (vii) (a) CSA, CH_2Cl_2/MeOH (4:1), 0 °C, 15 min; (b) PMP–$C(OMe)_2$, CSA, CH_2Cl_2, 0 °C, rt, 1 h; (c) TBAF, THF, 0 °C, rt, 6 h, 80% after three steps; (viii) OsO_4, acetone/H_2O (20:1), 0 °C, rt, 12 h, 84% yield; (ix) (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, rt, 2 h; (b) H_2, Pd/C, dry EtOAc, 5 h, 74% after two steps; (x) $NaCNBH_3$, TMSCl, CH_3CN, 4 Å MS, 0 °C, 10 min, 54% of **14**; (xi) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C, 30 min, quantitative yield; (xii) (a) TESOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, rt, 36 h; (b) DIBAL-H, CH_2Cl_2, −78 °C, 10 min, 75% after two steps; (xiii) (a) TPAP, 4 Å MS, NMO, CH_2Cl_2, 10 min; (b) $NaClO_2$, $NaH_2PO_4{\cdot}H_2O$, 2-methyl-2-butene: $^t BuOH$ (1:2), rt, 30 min, 86% after two steps; (xiv) DIBAL-H, CH_2Cl_2, −78 °C, 10 min, 85%; (xv) 2,4,6-trichlorobenzoyl chloride, Et_3N, dry THF, rt, 4 h; the mixed anhydride was then slowly added to DMAP in dry toluene, 10^{-3} M, 100 °C, 2 h, 62%.

Compound **10** was next treated with CSA to deprotect selectively the TES-group and the resulting 1,2-diol was protected as its *p*-methoxybenzylidene acetal. The ^1H NMR spectrum at this stage showed a ^3J coupling of 5.3 Hz between C7-H and C8-H supporting the structure assigned to the major product during the hydride reduction.[8] Finally, TIPS-deprotection with TBAF furnished **11**.

cis-Hydroxylation of **11** with a catalytic amount of OsO_4 gave the all *syn* triol **12**.[9,10] Selective silylation of the two secondary hydroxyl groups of **12** was followed by debenzylation to furnish **13**. Reductive ring opening of the *p*-methoxybenzylidene acetal of **13** gave a mixture of products **14** and **15**, in a 3:2 ratio, which could be separated by standard silica gel column chromatography.[11] The requisite intermediate **14** was diacylated to give **16**. The *tert*-hydroxyl group of **16** was next protected as its TES-ether and hydride reduction was carried out to deprotect the acetates to furnish **17**. A two-step oxidation protocol then followed to give the keto acid **18**. Diastereoselective reduction of the keto group of **18** using DIBAL-H furnished the *syn* product **19**. Although the stereochemistry of the newly generated C8-OH was to be determined, based on earlier work on the reduction of α-alkoxy ketones, it was assumed to have the desired *S* stereochemistry.[12]

With the requisite intermediate **19** in hand, the stage was now set to carry out the crucial Yamaguchi macrolactonization reaction.[13] Following a reverse-addition protocol, the mixed anhydride from **19** dissolved in toluene, after evaporation of THF under reduced pressure, was slowly added using a syringe pump over ca. 5 h to a solution of DMAP in toluene (final concentration 10^{-3} M) at 100 °C to furnish the desired nonalactone **2** in 62% yield.[14]

Work is now in progress to attach the side chain at the C7-OH to complete the total synthesis of the target molecule and assign its absolute stereochemistry.

Acknowledgement

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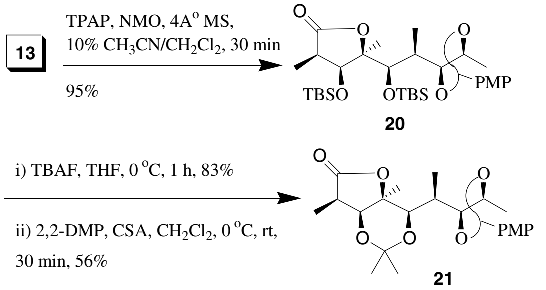
References and notes

1. (a) Collado, I. G.; Aleu, J.; Hernández-Galán, R.; Durán-Patrón, R. *Curr. Org. Chem.* **2000**, *4*, 1261–1286; (b) Cutler, H. G.; Parker, S. R.; Ross, S. A.; Crumley, F. G.; Schreiner, P. R. *Biosci. Biotechnol. Biochem.* **1996**, *60*, 656–658; (c) Collado, I. G.; Aleu, J.; Hernández-Galán, R.; Hanson, J. R. *Phytochemistry* **1996**, *42*, 1621–1624; (d) Jacyno, J. M.; Harwood, J. S.; Cutler, H. G.; Dublik, D. M. *Tetrahedron* **1994**, *50*, 11585–11592; (e) Cutler, H. G.; Jacyno, J. M.; Harwood, J. S.; Dulik, D.; Goodrich, P. D.; Roberts, R. G. *Biosci. Biotechnol. Biochem.* **1993**, *57*, 1980–1982.
2. (a) Siewers, V.; Viaud, M.; Jimenez-Teja, D.; Collado, I. G.; Gronover, C. S.; Pradier, J. M.; Tudzynski, B.; Tudzynski, P. *Mol. Plant-Microbe Interact.* **2005**, *18*, 602–612; (b) Reino, J. L.; Hernández-Galán, R.; Durán-Patrón, R.; Collado, I. G. *J. Phytopathol.* **2004**, *152*, 563–566; (c) Collado, I. G.; Aleu, J.; Hernández-Galán, R. Derivados con esqueleto de botcinolida como herbicidas de contacto, naturales y biodegradables. Spanish Pat. P 200301467, 2003.; (d) Cutler, H. G.; Parker, S. R. Botcinol: a natural Product Herbicide. U.S. Pat. US 5679341A; *CAN* **1997**, *127*, 342923; (e) Cutler, H. G.; Jacyno, J. M. Botcinolide: a natural herbicide, which is a hydroxylated nanolactone. U.S. Pat. US 5455221 A; *CAN* **1995**, *124*, 138653.
3. Reino, J. L.; Durán-Patrón, R. M.; Daoubi, M.; Collado, I. G.; Hernández-Galán, R. *J. Org. Chem.* **2006**, *71*, 562–565, and references cited therein.
4. (a) Wessel, H.-P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247–2250; (b) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139–4142.
5. Paterson, I.; Wallace, D. J.; Cowden, C. J. *Synthesis* **1998**, 639–652.
6. Solsona, J. G.; Romea, P.; Urpí, F.; Vilarrasa, J. *Org. Lett.* **2003**, *5*, 519–522.
7. (a) Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, 8537–8540; (b) Evans, D. A.; Dart, M. J.; Duffy, J. L. *Tetrahedron Lett.* **1994**, *35*, 8541–8544.
8. Chakraborty, T. K.; Das, S.; Raju, T. V. *J. Org. Chem.* **2001**, *66*, 4091–4093, and references cited therein.
9. To prove the stereochemistry of the hydroxylated product **12**, compound **13** was oxidized to a γ-lactone **20**, which was desilylated and the resulting 1,3-diol was protected as an acetonide **21**.



The ^{13}C NMR spectrum of **21** showed the chemical shifts of the methyl carbons of the acetonide function at 21.4 and 31.8 ppm and that of ketal carbon at 96.2 ppm confirming it to be a 1,3-*syn* acetonide (Ref. 10).

10. (a) Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res.* **1998**, *31*, 9–17; (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099–7102.
11. Johansson, R.; Samuelsson, B. *J. Chem. Soc., Chem. Commun.* **1984**, 201–202.
12. Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556–569.
13. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.
14. Data of the cyclized product **2**. $R_f = 0.4$ (silica, 10% diethyl ether in *n*-hexane eluant); $[\alpha]_D^{32}$ −10.0 (*c* 2.6 in CHCl$_3$); IR (KBr): ν_{max} 2930, 2881, 2857, 1734, 1613, 1513, 1463, 1249 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.24 (d, $J = 8.6$ Hz, 2H, Ar–H), 6.78 (d, $J = 8.6$ Hz, 2H, Ar–H), 5.27 (dq, $J = 4.9$, 6.7 Hz, 1H, H-8), 4.78 (d, $J = 2.1$ Hz, 1H, H-5), 4.55 (ABq, 2H, –O–CH_2–Ar), 3.8 (s, 3H, Ar–O–CH_3), 3.64 (d, $J = 1.8$ Hz, 1H, H-3), 3.48 (dd, $J = 4.9$, 1.0 Hz, 1H, H-7), 2.55 (dq, $J = 1.8$, 7.3 Hz, 1H, H-2), 2.29 (ddq, $J = 1$, 2.1, 7.3 Hz 1H, H-6), 1.35 (s, 3H, C$_4$–Me), 1.31 (d, $J = 6.7$ Hz, 3H, C$_8$–Me), 1.24 (d, $J = 7.3$ Hz, 3H, C$_2$–Me), 0.98–0.93 (m, 21H, ^{t}Bu–Si, Si–CH$_2$–CH_3, C$_6$–Me), 0.83 (s, 9H, ^{t}Bu–Si), 0.66 (q, $J = 8.0$ Hz, 6H, Si–CH_2–CH$_3$), 0.11, 0.08, −0.06 and −0.07 (four s, 12H, –Si–Me); ^{13}C NMR (100 MHz, CDCl$_3$): δ 174.4, 158.8, 130.7, 129.2, 113.3, 85.3, 85.0, 84.9, 75.1, 71.9, 71.6, 55.2, 45.5, 37.1, 30.5, 26.7, 26.1, 19.2, 18.2, 17.1, 17.0, 16.4, 7.5, 7.4, −3.2, −3.4, −3.9, −5.1; MS (ESI): *m*/*z* (%) 748 (5) [M+Na]$^+$.