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Asymmetric Total Synthesis of Botcinins C, D, and F

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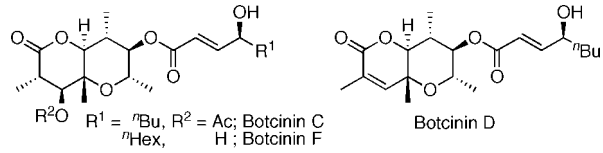
ABSTRACT



Stereoselective total synthesis of botcinins C, D, and F is effectively carried out through asymmetric aldol reactions, 6-*endo* ring closure, and SmI_2-mediated 3,4-*trans* or -*cis* stereoselective intramolecular Reformatsky reaction. Rapid esterification of the main skeleton of botcinins with the chiral side chain using MNBA and DMAP produced botcinin D, an antifungal chemical against a pathogen of rice blast disease.

Botcinins, metabolites isolated from *Botrytis cinerea*, have antifungal activities against *Magnaporthe grisea*, a pathogen of rice blast disease.[1] Botcinins have a peculiar structure consisting of a γ-hydroxy-α,β-unsaturated carboxylic acid part with an aliphatic alkyl long chain and a bicyclic moiety including a six-membered cyclic ether fused to a six-membered lactone in which all of the carbon atoms except the carbonyl carbon possess a chiral center. In this paper, we report an effective method for the synthesis of hexahydropyrano[3,2,*b*]pyran-2(3*H*)-one and the first stereoselective total synthesis of botcinins C, D, and F.

The retrosynthetic analysis of botcinins is described as shown in Scheme 1. It is assumed that the side chain **1a** and **1b** could be constructed by the enantioselective aldol reaction of **3** with **4**, followed by chain elongation according to our previous method.[2] The bicyclic part **2** should be prepared from **5** using an aldol-type cyclization. Cyclic ether[3] **5** could be constructed from **6** using the 6-*endo* ring closure according to Nicolaou's strategy.[4] The chiral linear compound **6** should be stereoselectively prepared from a lactic acid derivative **9** by four-carbon extension.

The synthetic route to the precursor of the fused-ring system corresponding to **5** is depicted in Scheme 2. First, the protection of (*S*)-**11** and the successive reduction of **12** afforded the chiral aldehyde **13**. The diastereoselective Mukaiyama aldol reaction of **13** with **10** gave the desired adduct **14** as a single stereoisomer. The reduction of **14** provided diol, which was then converted to the monoprotected alcohol **16** via **15**. Oxidation of **16**, olefination of the resulting aldehyde **17**, and successive reduction of the coupling product yielded allylic alcohol **18**. The asymmetric epoxidation of **18** produced the desired epoxy alcohol **19** as a single diastereomer. Alcohol **19** was oxidized to form the corresponding aldehyde, and the carbonyl group was masked by the Wittig reaction to give the vinyl epoxide **20**.[5] After deprotection of the TBS group in **20**, the six-membered cyclic ether **21** was obtained via the acid-promoted 6-*endo* ring closure in the presence of PPTS.[4] After combining **21** with

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(2) Shiina, I.; Takasuna, Y.; Suzuki, R.; Oshiumi, H.; Komiyama, Y.; Hitomi, S.; Fukui, H. *Org. Lett.* **2006**, *8*, 5279–5282.

(3) Another method for the synthesis of the similar cyclic system has been reported. See: (a) Chakraborty, T. K.; Goswami, R. K. *Tetrahedron Lett.* **2007**, *46*, 6463–6465.

(4) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330–5334.

(5) Fuwa, H.; Ebine, M.; Bourdelais, A. J.; Baden, D. G.; Sasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 16989–16999.

(6) Molander, G. A.; Etter, J. B.; Harring, L. S.; Thorel, P. J. *J. Am. Chem. Soc.* **1991**, *113*, 8036–8045.

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Scheme 1. Structure of Botcinins and Retrosynthetic Analysis

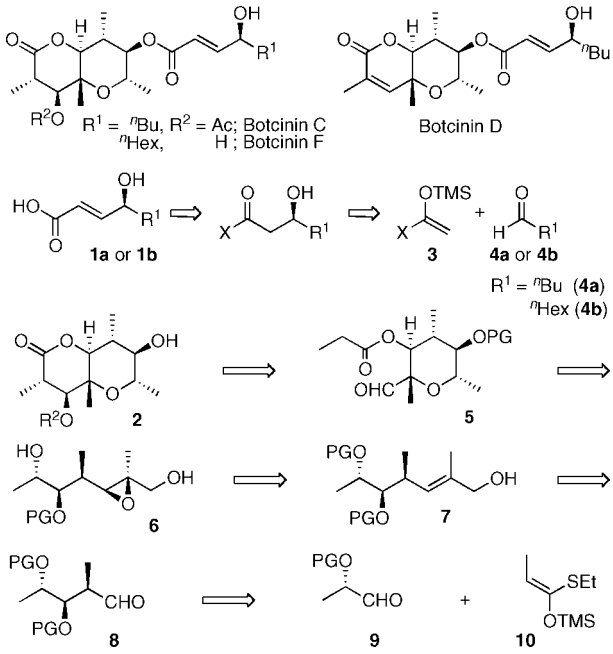
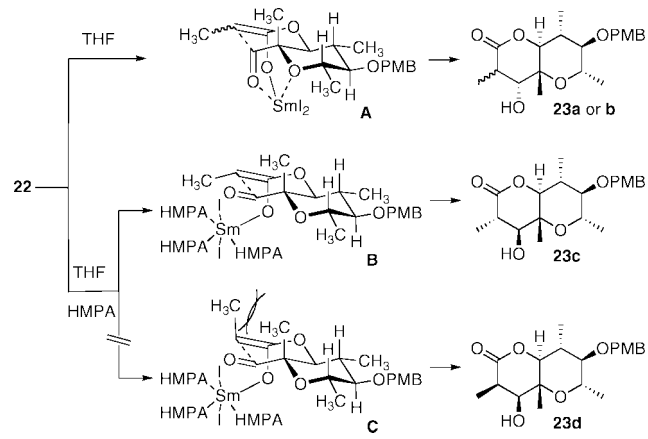


Table 1. Diastereoselectivity of the Reformatsky Reaction

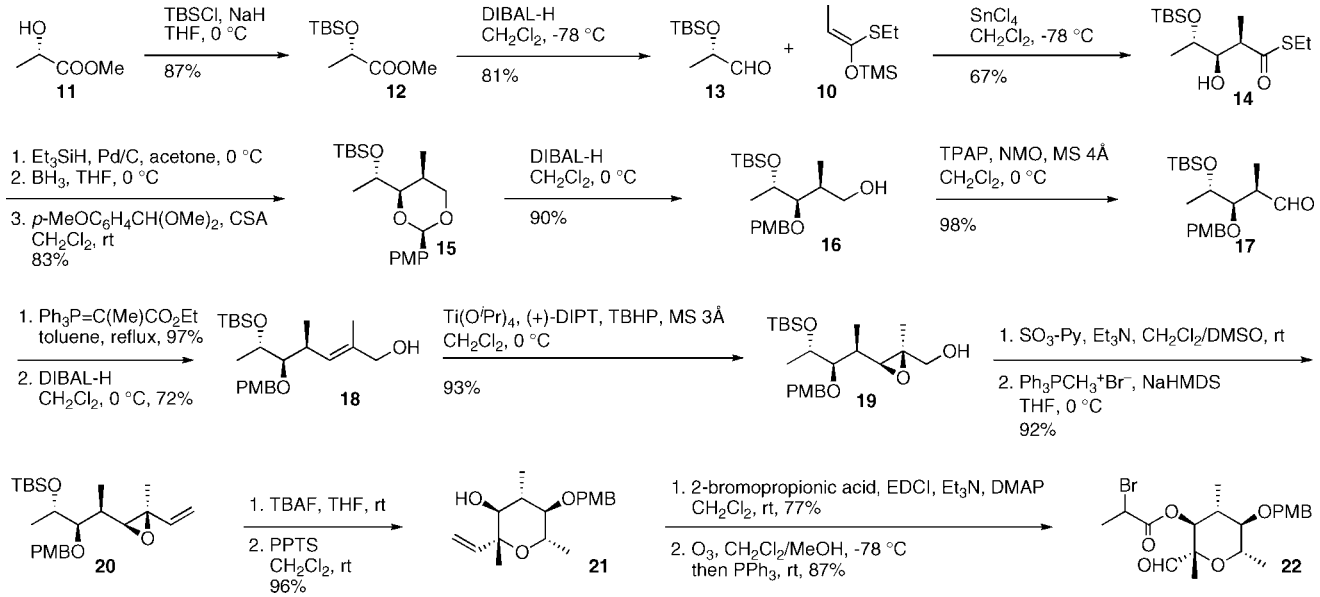


			yield (%)			
entry	solvent	temp (°C)	**23a**	**23b**	**23c**	total
1	THF	−18	46	30	0	76
2	THF/HMPA 8:1	0	13	19	30	62
3	THF/HMPA 8:1	−18	13	15	40	68
4	THF/HMPA 8:1	−43	20	23	37	80
5	THF/HMPA 1:1	0	13	21	30	64
6	THF/HMPA 1:1	−18	14	14	36	64

2-bromopropionic acid using EDCI, the key intermediate aldehyde **22** was furnished by ozonolysis of the double bond.

For the preparation of the desired bicyclic compounds **23a**−**d**, the SmI_2-promoted Reformatsky reaction was examined according to Molander's studies[6] as shown in Table 1. When the reaction was accelerated by SmI_2 in the absence of HMPA (entry 1), the *β*-oriented alcohols **23a** and **23b** were predominantly obtained. It was anticipated that the 3,4-*trans* diastereomers **23a** and **23b** could be produced via the chelation control as depicted in transition state **A**. On the other hand, the 3,4-*cis* diastereomer **23c** was preferentially produced by the addition of HMPA to the reaction mixture (entries 2−6) because the addition of HMPA might reduce the chelation effect of the substrate to the Sm metal so that the alternative transition state **B** might be preferred. Another transition state **C** leading to the product **23d** might have much higher energy due to 1,3-diaxial repulsion between two methyl groups. The total yields of **23a**−**c** increased up to

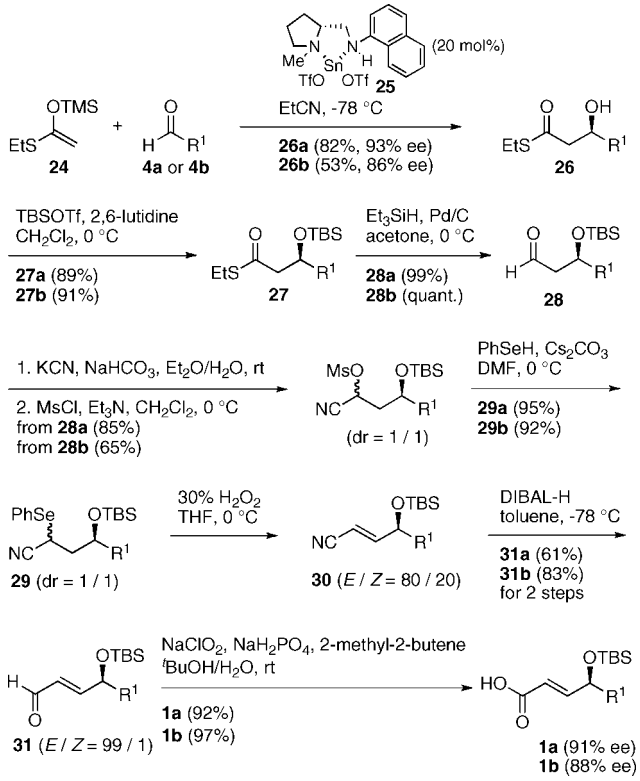
Scheme 2. Synthesis of the Six-Membered Cyclic Ether



80% under the suitable reaction conditions at a low temperature (entry 4), and there is no advantage using other additives such as water or alcohols to improve the stereoselectivities and yields for the cyclization.

The chiral side chains **1a** and **1b** were prepared according to our previous study as shown in Scheme 3.[2] First, the

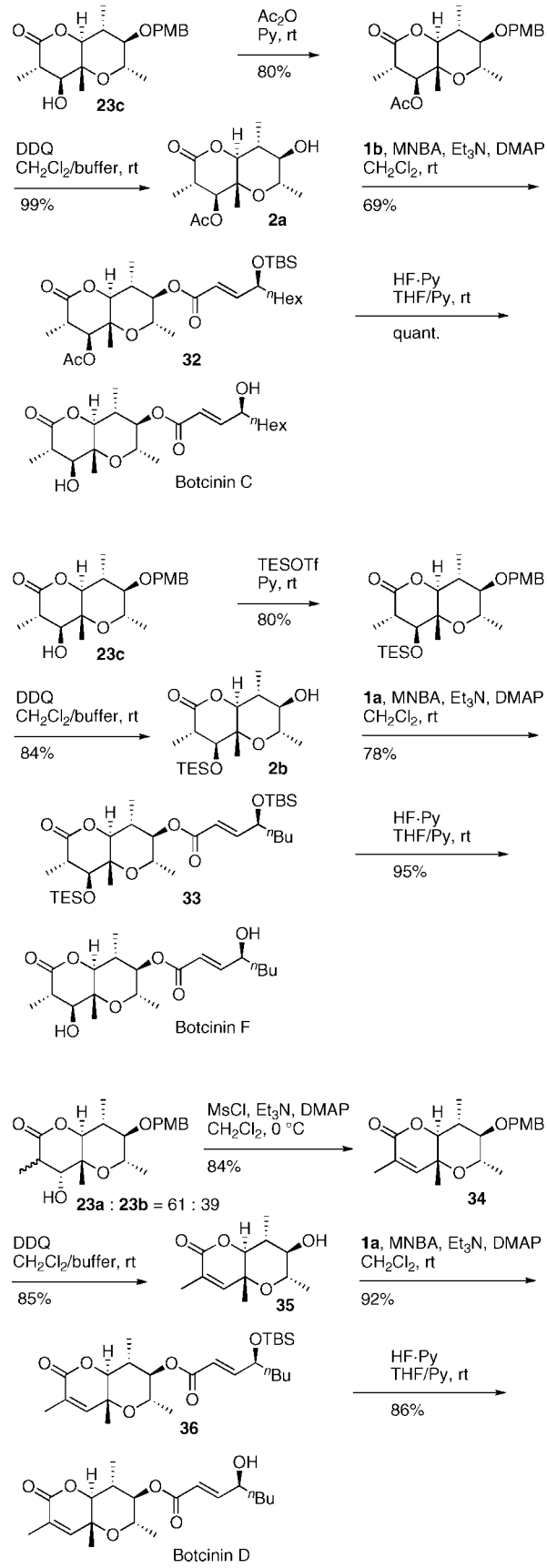
Scheme 3. Synthesis of the Side Chain Moiety



asymmetric aldol reaction of aldehydes **4a**/**b** with enol silyl ether **24** was carried out in the presence of a catalytic amount of the chiral diamine−Sn(II) complex **25**, and the desired β-hydroxy thioesters **26a**/**b** were obtained in good yields with high enantioselectivities (93% ee for **26a** and 86% ee for **26b**). After transforming the aldol adducts into the corresponding TBS ethers **27a**/**b**, siloxy aldehydes **28a**/**b** were prepared in satisfactory yields.[7] The formation of cyanohydrins, mesylation of the hydroxyl groups, and successive substitution with phenylselenol afforded a mixture of the diastereomeric isomers **29a**/**b**. The oxidative elimination of the phenylseleno groups in **29a**/**b**, followed by reduction with DIBAL-H and oxidation[8] of the resulting aldehydes **31a**/**b** yielded the optically active α,β-unsaturated carboxylic acids **1a**/**b**.

Installation of the side chain to the main skeleton to form botcinins C, D, and F was carried out as depicted in Scheme 4. For the preparation of botcinins C and F, **23c** was converted to either the monohydroxy acetate **2a** or TES ether **2b**. The coupling of **2a** with side chain **1b** was carried out in the presence of 2-methyl-6-nitrobenzoic anhydride (MNBA) and DMAP to produce the corresponding ester **32** in a good

Scheme 4. Synthesis of Botcinins C, D, and F



yield,[9] whereas the combining **2b** with **1a** also provided **33** in a high yield. Finally, the total synthesis of botcinins C and F was successfully accomplished by cleaving the protective groups in their precursors. Next, the α,β-unsaturated lactone **34** was prepared from the mixture of **23a** and **23b** by elimination and was then transformed into the corresponding alcohol **35** through deprotection of the PMB group. The MNBA-promoted acylation of **35** with **1a**[10] followed by cleavage of the TBS group also afforded botcinin D in a high yield.

In summary, we achieved the first enantioselective total synthesis of botcinins C, D, and F. Stereoselective aldol reactions, 6-*endo* ring closure, and SmI_2-mediated 3,4-*trans* or -*cis* stereoselective intramolecular Reformatsky reaction were employed for the construction of the main skeletons and the side chains. Effective acylation of the sterically hindered alcohol with the side chain was attained by a very rapid coupling using MNBA and DMAP giving botcinin D, an antifungal chemical against a pathogen of rice blast disease.

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Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) For the coupling reaction of **35** and **1a**, EDCI was not effective and the corresponding ester **36** was obtained in only 9% yield.