



Title	Synthetic study of andrastins : stereoselective construction of the BCD-ring system
Author(s)	Yoshimura, Fumihiko; Abe, Taiki; Ishioka, Yuichi; Tanino, Keiji
Citation	The Journal of Antibiotics, 72, 384-388 https://doi.org/10.1038/s41429-018-0136-x
Issue Date	2019-01-16
Doc URL	http://hdl.handle.net/2115/74930
Type	article (author version)
Additional Information	There are other files related to this item in HUSCAP. Check the above URL.
File Information	J ANTIBIOT20190116.pdf



[Instructions for use](#)

1 **Synthetic study of andrastins: Stereoselective construction of the BCD-ring system**

2
3 Fumihiko Yoshimura,^{1,2*} Taiki Abe,³ Yuichi Ishioka³ and Keiji Tanino^{1*}

4
5 ¹Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060-0810, Japan

6 ²School of Pharmaceutical Sciences, University of Shizuoka, 52-1 Yada, Suruga-ku, Shizuoka
7 422-8526, Japan

8 ³Graduate School of Chemical Sciences and Engineering, Hokkaido University, Sapporo 060-0810,
9 Japan

10

11 Corresponding authors:

12 *E-mail: fumi@u-shizuoka-ken.ac.jp. (F.Y.)

13 *E-mail: ktanino@sci.hokudai.ac.jp. (K.T.)

14

15 **Dedication**

16 Dedicated with respect to Professor Samuel J. Danishefsky for his outstanding contributions to
17 natural products synthesis.

18

19 **Abstract**

20 Andrastins are meroterpenes isolated from *Penicillium* sp. FO-3929 that display highly potent
21 inhibitory activities toward protein farnesyltransferase. Structurally, they possess a unique steroidal
22 tetracyclic skeleton (the ABCD-ring) with three contiguous quaternary stereocenters on the C-ring.
23 Herein, we describe our nitrile cyclization-based approach to the stereoselective construction of the
24 BCD-ring system of andrastins, which contains three contiguous quaternary stereocenters on the
25 C-ring and the correct oxidation states of the D-ring.

26

27 **Keywords:** andrastins / antitumor antibiotics / carbocycles / cyclization / ene reaction / nitriles /
28 quaternary stereocenters

29

30 **Introduction**

31 Andrastins A–D (**1–4**) are fungal meroterpenes that were isolated from the cultured broth of
32 *Penicillium* sp. FO-3929 by Ōmura and co-workers in 1996.^{1–4} These compounds exhibit potent
33 inhibitory activities toward protein farnesyltransferase (IC₅₀, 13.3–47.1 μM).^{2,4} Because protein
34 farnesyltransferase is essential for maturation of the Ras oncogene protein, andrastins are
35 considered promising anti-cancer drug candidates.⁵ Structurally, andrastins A–D (**1–4**) share a
36 unique steroidal 6-6-6-5 tetracyclic skeleton (the ABCD-ring), differing only in the substituent at
37 the angular C10 position and the oxidation state at C3 of the A-ring (Scheme 1a). Their distinctive
38 biological and pharmacological properties, coupled with their complex chemical structures, have
39 made andrastins attractive targets for chemical synthesis. As a result, a number of research groups
40 have been involved in synthetic studies of andrastins.^{6–10} Recently, the first total synthesis of
41 (±)-andrastin D (**4**) was achieved by Newhouse, Maimone, and co-workers via a biomimetic
42 polyene cyclization and a diketene annulation as the key steps.⁶ Additionally, Toyota, Ihara, and
43 co-workers constructed the tetracyclic framework of andrastins that featured a stereoselective
44 intramolecular Diels–Alder reaction and a carbonyl ene reaction.^{7,8} Matsuya and co-workers
45 reported an alternative intramolecular Diels–Alder approach to the tetracyclic skeleton of
46 andrastins.^{9,10} In order to ultimately understand the detailed mode of action of andrastins at the
47 molecular level, we have engaged in synthetic studies of them. Herein, we report a novel nitrile
48 cyclization-based approach for the stereoselective construction of the BCD-ring system with three
49 contiguous quaternary asymmetric stereocenters, the common substructure in andrastins.

50

51 [Please insert Scheme 1, single column size]

52

53 **Results and discussion**

54 From a synthetic perspective, the major challenges posed by andrastins **1–4** are (1) construction of
55 the stereochemically dense C-ring, which has three contiguous quaternary stereocenters at the C8,
56 C13, and C14 positions, and (2) construction of the five-membered D-ring, which has a sensitive
57 1,3-diketone moiety. To overcome these challenges, we designed a synthetic strategy based on
58 nitrile cyclizations (Scheme 1b). To confirm our strategy, tricyclic model compound **10** was chosen
59 as the initial target. We planned to synthesize **10** from cyclic nitrile **5** (the B-ring model),
60 whereupon a quaternary stereocenter at the C8 position would be constructed by the intramolecular
61 conjugate addition of α,β -unsaturated esters bearing an alkanenitrile side chain.¹¹ An intramolecular
62 ene reaction of nitrile **6** would construct the C-ring structure **8** after isomerization of the olefin in
63 the ene product **7** and the subsequent hydrolysis of the resulting imine moiety. In contrast to
64 carbonyl ene reactions that have been widely used in organic synthesis,¹² cyano ene reactions have
65 been less frequently explored due to the poor reactivity of the cyano group as an enophile.^{13–15}
66 However, we anticipated that the cyano ene reaction of the simple non-activated alkanenitrile **6**
67 would proceed upon activation by a Brønsted or Lewis acid because of an entropically favored
68 intramolecular process. Lastly, formation of the D-ring with the desired oxidation states would be
69 achieved through a similar intramolecular cyano ene reaction of β -ketonitrile **9** to afford tricyclic
70 compound **10**.

71 Our synthesis commenced with the preparation of cyano alkene **6** (Scheme 2). Alkylation of
72 ethyl isobutyrate (**11**) with 5-bromo-1-pentene followed by reduction with LiAlH_4 gave primary
73 alcohol **12**, which underwent cobalt-catalyzed hydrocyanation¹⁶ to furnish secondary nitrile **14** with
74 complete regioselectivity. The product **14** was then converted to α,β -unsaturated ester **15** through a
75 Swern oxidation and subsequent Horner–Wadsworth–Emmons olefination. Treatment of **15** with
76 potassium bis(trimethylsilyl)amide (KHMDs) in THF–toluene at $-78\text{ }^\circ\text{C}$ induced an intramolecular
77 conjugate addition¹¹ to give cyclization product **5** (the B-ring) with the quaternary stereocenter at
78 the C8 position (96% yield) with high diastereoselectivity (dr = 95:5). The high stereoselectivity of

79 this cyclization can be explained through the chelated transition state model, wherein the
80 keteniminate and α,β -unsaturated ester are both oriented equatorially in an antiparallel dipolar
81 arrangement (Supplementary Information, Scheme S1). The stereochemistry of **5** was confirmed by
82 NOESY experiments. Chemoselective reduction of the ester over the cyano group in **5** with
83 diisobutylaluminum hydride (DIBAL-H) followed by Swern oxidation produced aldehyde **16**. This
84 compound was converted to cyano alkene **6** as inseparable geometric isomers (68:32) in three steps,
85 i.e., addition of methyl Grignard reagent, tetrapropylammonium perruthenate (TPAP) oxidation¹⁷ of
86 the resulting alcohol, and Wittig olefination of the resulting methyl ketone.

87

88 [Please insert Scheme 2, single column size]

89

90 With nitrile **6** in hand, we examined the key ene reaction for the C-ring formation (Scheme 3).
91 Upon treatment of **6** with methanesulfonic acid (MsOH) (10 equiv.) in 1,2-dichloroethane at 80 °C,
92 the intramolecular ene reaction of nitrile **6** and the subsequent isomerization of the olefin occurred
93 smoothly. After the disappearance of **6**, which was monitored by TLC, the solvent was removed by
94 evaporation, and the resulting mixture containing α,β -unsaturated iminium **19** and MsOH was
95 hydrolyzed at 80 to 100 °C to afford enone **8** (86% yield). Thus, this intramolecular cyano ene
96 reaction proved to be a powerful method for the formation of a cyclic enone because the C–C bond
97 forming reaction proceeded at the sterically congested neopentyl position. At present, we assume
98 that the MsOH-mediated cyclization of **6** proceeded via a cyano ene reaction, although an
99 alternative reaction mechanism¹⁸ involving a cationic cyclization of a nitrilium ion cannot be ruled
100 out.

101

102 [Please insert Scheme 3, single column size]

103

104 Our next objective was the synthesis of the D-ring cyclization precursor **27** (Scheme 4).
105 Treatment of enone **8** with trimethylsilyl cyanide (TMSCN) in the presence of a trimethylsilyl
106 trifluoromethanesulfonate (TMSOTf) catalyst afforded a diastereomeric mixture of cyanohydrins
107 and their trimethylsilyl (TMS) ethers **20**. Dehydration of the crude products **20** with MsOH yielded
108 the desired unsaturated nitrile **21** along with enone **8** and β -cyano ketone **22**. Construction of the
109 quaternary stereocenter at the C14 position was accomplished by deconjugative alkylation of **21**.
110 Upon treatment of **21** with lithium diisopropylamide (LDA) in THF at $-78\text{ }^\circ\text{C}$ followed by addition
111 of benzyloxymethyl chloride (BOMCl), deconjugative alkylation proceeded at the less hindered
112 face of the six-membered ring, i.e., the opposite side of the C8 methyl group, to provide target
113 compound **23** in 82% yield (dr = 92:8) accompanied by γ -alkylation product **24** (14% yield). The
114 stereochemistry of **23** was determined by an NOE experiment of alcohol **25** after removal of the
115 benzyl group in **23**. Alcohol **25** was successfully converted to nitrile **27** as an inseparable mixture of
116 four isomers (dr = 55:26:12:7) by a three-step sequence: (1) partial hydrogenation of the diene in **25**
117 using Pd/C (5%) with concomitant isomerization to afford tetrasubstituted olefin **26**, wherein a
118 minor diastereomer derived from **23** was separated, (2) Swern oxidation of the primary alcohol, and
119 (3) addition of the deprotonated propionitrile to the resulting aldehyde.

120

121 [Please insert Scheme 4, double column size]

122

123 The final task in the synthesis was the challenging cyano ene reaction for the formation of the
124 D-ring with construction of the quaternary stereocenter at the C13 position (Scheme 5). To this end,
125 alcohol **27** was oxidized with pyridinium chlorochromate (PCC) to β -ketonitrile **9**. The
126 intramolecular cyano ene reaction of **9** proceeded smoothly when treated with BCl_3 (6 equiv.) at
127 room temperature, affording the stable enaminone **28** as a single diastereomer (93% yield). NOESY
128 experiments revealed that **28** possessed the 6,5-*cis*-fused ring system (the CD-ring) with the correct
129 stereostructure. However, enaminone **28** resisted hydrolysis to 1,3-diketone **29** under either acidic

130 or basic conditions. To enhance the reactivity toward hydrolysis as well as to prevent unreactive
131 enaminone formation, we designed the new cyclization precursor **30**, possessing an
132 electron-withdrawing chlorine atom at the α -position of the cyano group. The requisite nitrile **30**
133 was directly synthesized from **27** by a Swern oxidation using an excess amount of oxidant (3
134 equiv.).¹⁹ As expected, the cyclization of **30** with BCl₃ gave α -chloro imine **31**, and the subsequent
135 hydrolysis of **31** with aqueous MsOH afforded diketone **32** (50% yield, two steps). Finally,
136 reductive dechlorination of **32** with Zn–AcOH followed by isomerization of the *exo* olefin yielded
137 the tricyclic compound **10** (84% yield, two steps), thus completing the synthesis of the andrastin
138 BCD-ring system.

139

140 [Please insert Scheme 5, double column size]

141

142 **Conclusion**

143 In conclusion, we have developed a stereoselective synthetic route to the BCD-ring system of novel
144 protein farnesyltransferase inhibitors, andrastins. The synthesis features (1) construction of the
145 B-ring through a stereoselective conjugate addition of an α -cyano carbanion to an α,β -unsaturated
146 ester, and (2) intramolecular cyano ene reactions for the formation of the C and D-rings. The
147 successful synthesis of the highly sterically congested BCD-ring component having three
148 contiguous stereocenters on the C-ring demonstrates the synthetic utility of nitrile cyclizations (i.e.,
149 an intramolecular conjugate addition and a cyano ene reaction). Further efforts on the total
150 syntheses of andrastins are currently underway.

151

152 **Conflict of interest**

153 The authors declare no conflict of interest.

154

155 **Acknowledgements**

156 We acknowledge Dr. Eri Fukushi and Mr. Yusuke Takata (GC-MS & NMR Laboratory, Faculty of
157 Agriculture, Hokkaido University) for their mass spectral measurements. T.A. is a Research Fellow
158 of the Japan Society for the Promotion of Science (JSPS). This work was supported by JSPS
159 KAKENHI Grant Numbers JP15K01795, JP18K05339, JP18H01970, and JP15H05842 in Middle
160 Molecular Strategy.

161

162 **Supplementary Information**

163 Experimental procedures, characterization data, and NMR and MS spectra for the key reactions can
164 be found in the Supplementary Information. eSupplementary information is available at the Journal
165 of Antibiotics website.

166

167 **References**

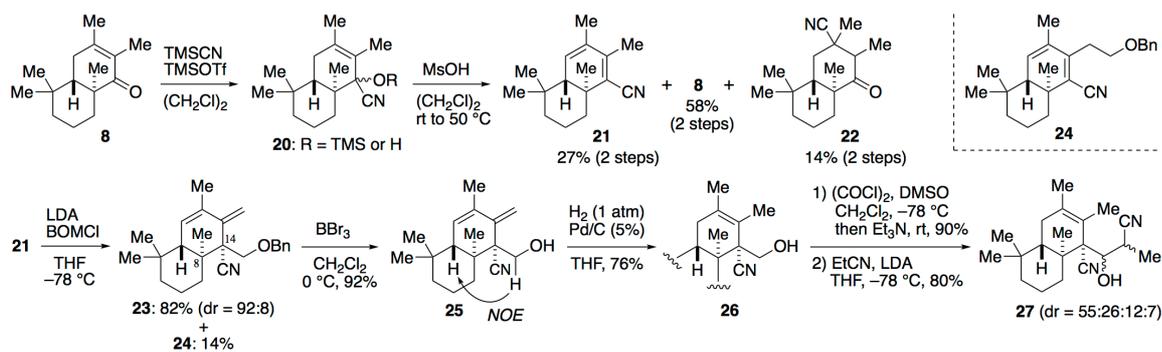
- 168 1 Shiomi K et al. Andrastins A~C, New Protein Farnesyltransferase Inhibitors, Produced by
169 *Penicillium* sp. FO-3929. *Tetrahedron Lett.* 1996;37:1265–8.
- 170 2 Ōmura S et al. Andrastins A-C, New Protein Farnesyltransferase Inhibitors Produced by
171 *Penicillium* sp. FO-3929 I. Producing Strain, Fermentation, Isolation, and Biological Activities.
172 *J Antibiot.* 1996;49:414–7.
- 173 3 Uchida R et al. Andrastin A-C, New Protein Farnesyltransferase Inhibitors Produced by
174 *Penicillium* sp. FO-3929 II. Structure Elucidation and Biosynthesis. *J Antibiot.* 1996;49:418–
175 24.
- 176 4 Uchida R et al. Andrastin D, Novel Protein Farnesyltransferase Inhibitor Produced by
177 *Penicillium* sp. FO-3929. *J Antibiot.* 1996;49:1278–80.
- 178 5 Hinterding K, Alonso-Díaz, D, Waldmann H. Organic Synthesis and Biological Signal
179 Transduction. *Angew Chem, Int Ed.* 1998;37:688–749.
- 180 6 Xu G, Elkin M, Tantillo DJ, Newhouse TR, Maimone TJ. Traversing Biosynthetic Carbocation
181 Landscapes in the Total Synthesis of Andrastin and Terretonin Meroterpenes. *Angew Chem, Int*

- 182 *Ed.* 2017;56:12498–502.
- 183 7 Okamoto R, Takeda K, Tokuyama H, Ihara M, Toyota M. Toward the Total Synthesis of
184 (\pm)-Andrastin C. *J Org Chem.* 2013;78:93–103.
- 185 8 Toyota M, Okamoto R, Ogata T, Ihara, M. Ti(III)-induced radical cyclization. A stereoselective
186 entry to the perhydrobenzo[*e*]indene unit of new protein farnesyltransferase inhibitors,
187 andrastins A–D. *Tetrahedron Lett.* 2004;45:9203–5.
- 188 9 Yin S, Sugimoto K, Nemoto H, Matsuya Y. Synthetic Study towards Construction of Potential
189 Scaffold of Antitumor Agents Andrastins. *Heterocycles.* 2017;95:187–99.
- 190 10 Yin S et al. Construction of *cis*-Fused Hydrindane Skeleton with a Lactone Tether Utilizing
191 Intramolecular Diels–Alder Reaction. *Heterocycles.* 2016;93:783–91.
- 192 11 Yoshimura F, Torizuka M, Mori G, Tanino K. Intramolecular Conjugate Addition of
193 α,β -Unsaturated Lactones Having an Alkanenitrile Side Chain: Stereocontrolled Construction
194 of Carbocycles with Quaternary Carbon Atoms. *Synlett.* 2012;2:251–4.
- 195 12 Clarke ML, France MB. The carbonyl ene reaction. *Tetrahedron* 2008;64:9003–31.
- 196 13 Hamana H, Sugasawa T. THE ENE REACTION OF TRISUBSTITUTED ALKENES WITH
197 ELECTRON-DEFICIENT NITRILES IN THE PRESENCE OF BORON TRICHLORIDE.
198 *Chem Lett.* 1985;14:575–8.
- 199 14 Shimizu H, Murakami M. Reaction of 2-Alkynylbenzoyl Cyanides with Carboxylic Acids
200 Producing Functionalized Indenones. *Synlett.* 2008;1817–20.
- 201 15 Sakai T, Danheiser RL. Cyano Diels–Alder and Cyano Ene Reactions. Applications in a
202 Formal [2+2+2] Cycloaddition Strategy for the Synthesis of Pyridines. *J Am Chem Soc.*
203 2010;132:13203–5.
- 204 16 Gasper B, Carreira EM. Mild Cobalt-Catalyzed Hydrocyanation of Olefins with Tosyl Cyanide.
205 *Angew Chem, Int Ed.* 2007;46:4519–22.
- 206 17 Ley SV, Norman J, Griffith WP, Marsden SP. Tetrapropylammonium Perruthenate,
207 $\text{Pr}_4\text{N}^+\text{RuO}_4^-$, TPAP: A Catalytic Oxidant for Organic Synthesis. *Synthesis.* 1994;639–66.

208 18 Hill RK, Conley RT. Abnormal Beckmann Rearrangement of Spiroketoximes in
209 Polyphosphoric Acid. *J Am Chem Soc.* 1960;82:645–52.

210 19 Smith AB III, Leenay TL, Liu H-J, Nelson LAK, Ball, RG. A Caveat on the Swern Oxidation.
211 *Tetrahedron Lett.* 1988;29:49–52.

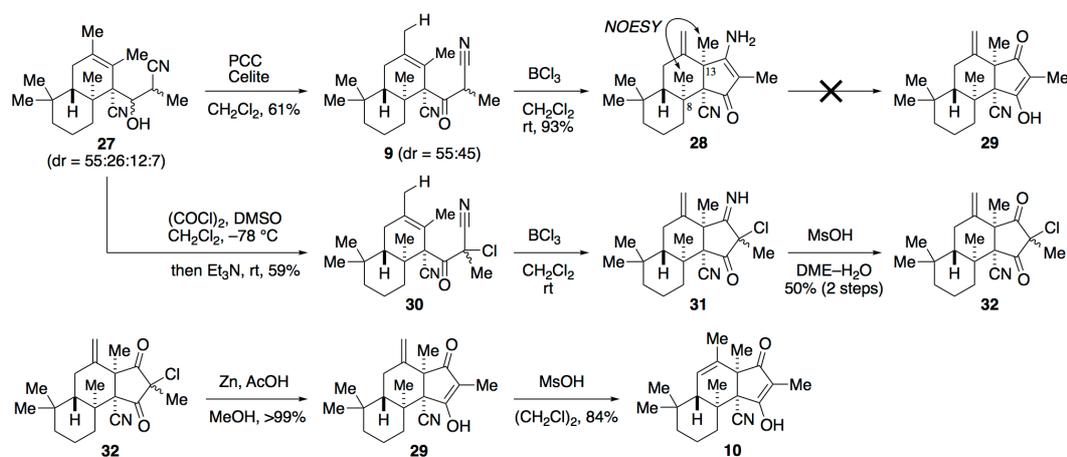
212



221

222 **Scheme 4**

223



224

225 **Scheme 5**

226

227

228 **Figure legends**

229 **Scheme 1** (a) Structures of andrastins A–D (1–4). (b) Strategy for the synthesis of the tricyclic
 230 model compound 10.

231 **Scheme 2** Synthesis of nitrile 6.232 **Scheme 3** Cyclization of nitrile 6.233 **Scheme 4** Synthesis of nitrile 27.234 **Scheme 5** Synthesis of the tricyclic model compound 10.