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

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Dedication

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

Abstract

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

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

Introduction

Andrastins A–D (**1**–**4**) are fungal meroterpenes that were isolated from the cultured broth of *Penicillium* sp. FO-3929 by Ōmura and co-workers in 1996.[1–4] These compounds exhibit potent inhibitory activities toward protein farnesyltransferase (IC_{50}, 13.3–47.1 μM).[2,4] Because protein farnesyltransferase is essential for maturation of the Ras oncogene protein, andrastins are considered promising anti-cancer drug candidates.[5] Structurally, andrastins A–D (**1**–**4**) share a unique steroidal 6-6-6-5 tetracyclic skeleton (the ABCD-ring), differing only in the substituent at the angular C10 position and the oxidation state at C3 of the A-ring (Scheme 1a). Their distinctive biological and pharmacological properties, coupled with their complex chemical structures, have made andrastins attractive targets for chemical synthesis. As a result, a number of research groups have been involved in synthetic studies of andrastins.[6–10] Recently, the first total synthesis of (±)-andrastin D (**4**) was achieved by Newhouse, Maimone, and co-workers via a biomimetic polyene cyclization and a diketene annulation as the key steps.[6] Additionally, Toyota, Ihara, and co-workers constructed the tetracyclic framework of andrastins that featured a stereoselective intramolecular Diels–Alder reaction and a carbonyl ene reaction.[7,8] Matsuya and co-workers reported an alternative intramolecular Diels–Alder approach to the tetracyclic skeleton of andrastins.[9,10] In order to ultimately understand the detailed mode of action of andrastins at the molecular level, we have engaged in synthetic studies of them. Herein, we report a novel nitrile cyclization-based approach for the stereoselective construction of the BCD-ring system with three contiguous quaternary asymmetric stereocenters, the common substructure in andrastins.

[Please insert Scheme 1, single column size]

Results and discussion

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

Our synthesis commenced with the preparation of cyano alkene **6** (Scheme 2). Alkylation of ethyl isobutyrate (**11**) with 5-bromo-1-pentene followed by reduction with $LiAlH_4$ gave primary alcohol **12**, which underwent cobalt-catalyzed hydrocyanation[16] to furnish secondary nitrile **14** with complete regioselectivity. The product **14** was then converted to α,β-unsaturated ester **15** through a Swern oxidation and subsequent Horner–Wadsworth–Emmons olefination. Treatment of **15** with potassium bis(trimethylsilyl)amide (KHMDS) in THF–toluene at –78 °C induced an intramolecular conjugate addition[11] to give cyclization product **5** (the B-ring) with the quaternary stereocenter at the C8 position (96% yield) with high diastereoselectivity (dr = 95:5). The high stereoselectivity of

this cyclization can be explained through the chelated transition state model, wherein the keteniminate and α,β-unsaturated ester are both oriented equatorially in an antiparallel dipolar arrangement (Supplementary Information, Scheme S1). The stereochemistry of **5** was confirmed by NOESY experiments. Chemoselective reduction of the ester over the cyano group in **5** with diisobutylaluminum hydride (DIBAL-H) followed by Swern oxidation produced aldehyde **16**. This compound was converted to cyano alkene **6** as inseparable geometric isomers (68:32) in three steps, i.e., addition of methyl Grignard reagent, tetrapropylammonium perruthenate (TPAP) oxidation[17] of the resulting alcohol, and Wittig olefination of the resulting methyl ketone.

[Please insert Scheme 2, single column size]

With nitrile **6** in hand, we examined the key ene reaction for the C-ring formation (Scheme 3). Upon treatment of **6** with methanesulfonic acid (MsOH) (10 equiv.) in 1,2-dichloroethane at 80 °C, the intramolecular ene reaction of nitrile **6** and the subsequent isomerization of the olefin occurred smoothly. After the disappearance of **6**, which was monitored by TLC, the solvent was removed by evaporation, and the resulting mixture containing α,β-unsaturated iminium **19** and MsOH was hydrolyzed at 80 to 100 °C to afford enone **8** (86% yield). Thus, this intramolecular cyano ene reaction proved to be a powerful method for the formation of a cyclic enone because the C–C bond forming reaction proceeded at the sterically congested neopentyl position. At present, we assume that the MsOH-mediated cyclization of **6** proceeded via a cyano ene reaction, although an alternative reaction mechanism[18] involving a cationic cyclization of a nitrilium ion cannot be ruled out.

[Please insert Scheme 3, single column size]

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

[Please insert Scheme 4, double column size]

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

or basic conditions. To enhance the reactivity toward hydrolysis as well as to prevent unreactive enaminone formation, we designed the new cyclization precursor **30**, possessing an electron-withdrawing chlorine atom at the α-position of the cyano group. The requisite nitrile **30** was directly synthesized from **27** by a Swern oxidation using an excess amount of oxidant (3 equiv.).[19] As expected, the cyclization of **30** with BCl_3 gave α-chloro imine **31**, and the subsequent hydrolysis of **31** with aqueous MsOH afforded diketone **32** (50% yield, two steps). Finally, reductive dechlorination of **32** with Zn–AcOH followed by isomerization of the *exo* olefin yielded the tricyclic compound **10** (84% yield, two steps), thus completing the synthesis of the andrastin BCD-ring system.

[Please insert Scheme 5, double column size]

Conclusion

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

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

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Supplementary Information

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

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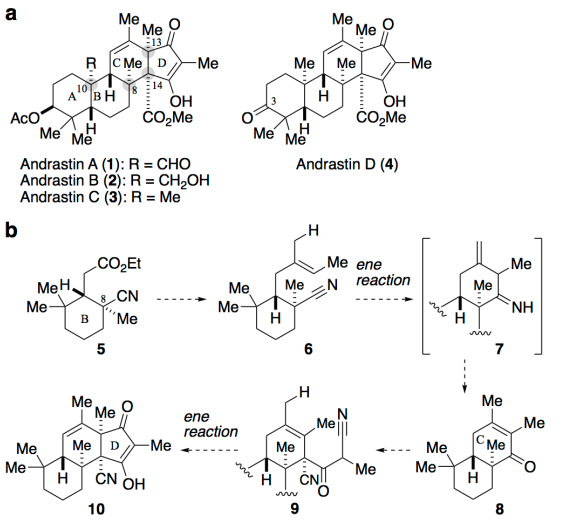

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214 **Scheme 1**

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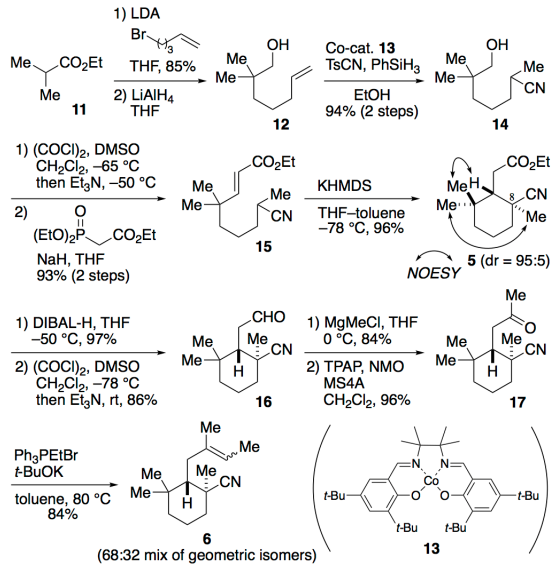

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217 **Scheme 2**

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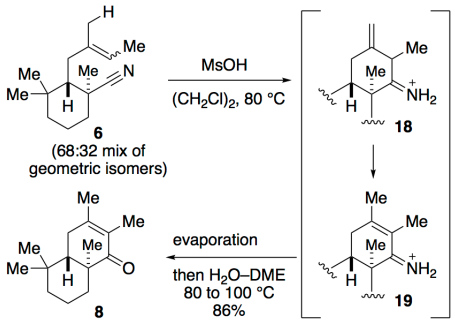

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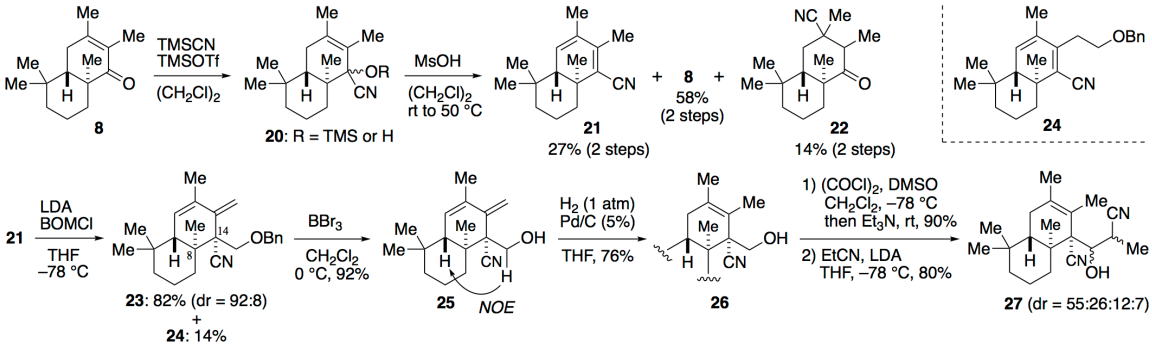

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222 **Scheme 4**

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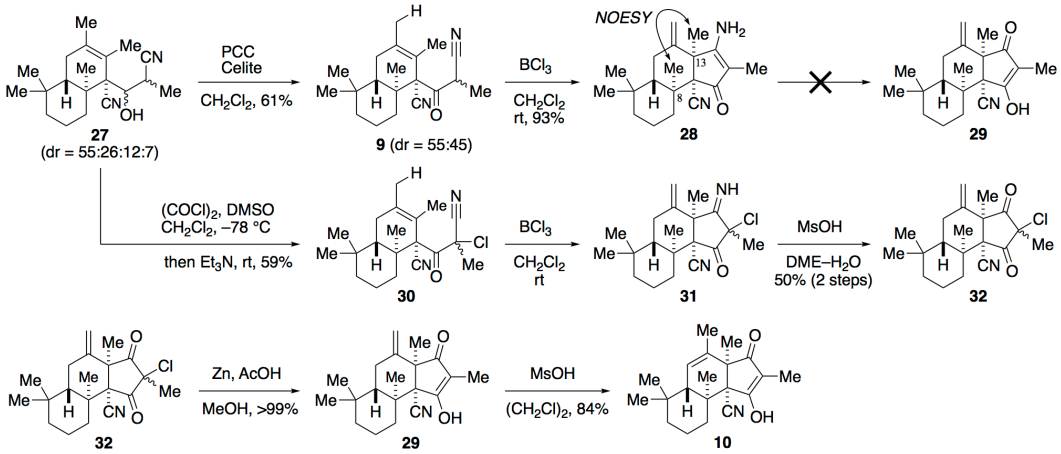

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225 **Scheme 5**

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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**.