ORGANIC LETTERS

2009
Vol. 11, No. 8
1833−1836

Synthetic Studies on Daphnicyclidin A: Enantiocontrolled Construction of the BCD Ring System

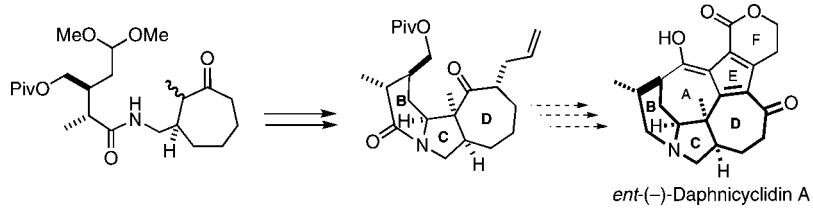
Shuhei Ikeda, Masatoshi Shibuya, Naoki Kanoh, and Yoshiharu Iwabuchi*

Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University, Aoba, Sendai 980-8578, Japan

iwabuchi@mail.pharm.tohoku.ac.jp

Received February 16, 2009

ABSTRACT



ent-(−)-Daphnicyclidin A

An enantiocontrolled entry to the tricyclic core of daphnicyclidin A with five chiral centers including an all-carbon quaternary center is reported. The synthesis features a highly diastereoselective conjugate addition of nitromethane, an Ireland−Claisen rearrangement, and a tandem acyliminium/Mannich-type reaction.

In 2001, Kobayashi and co-workers reported the isolation of a novel class of *Daphniphyllum* alkaloids, daphnicyclidins A−H, from the stems of *D. humile* and *D. Teijsmanni*.[1] Extensive spectroscopic analyses including X-ray crystallography and CD analysis unambiguously revealed their unprecedented fused penta- or hexacyclic skeletons including their absolute stereochemistries. As a unique common structure, members of this class of *Daphniphyllum* alkaloids possess the reactive fulvene moiety. These alkaloids are cytotoxic against murine lymphoma L1210 and human epidermoid carcinoma KB cells with IC_{50} values ranging from 0.1 to 10 μg/mL. Owing to the interesting biological activities coupled with highly complex structural features, daphnicyclidins have attracted our attention as targets for total synthesis. In this paper, we describe an enantiocontrolled entry to the tricyclic intermediate corresponding to the BCD portion (6-5-7) of daphnicyclidin A (**1**), which represents the first publication on the synthesis of these natural products.[2]

Our retrosynthetic analysis of daphnicyclidin A (**1**) is depicted in Scheme 1. We ranked **2** as an important synthetic platform in this research, because tricyclic intermediate **2** sets all of the chiral centers of **1**. In particular, the structural feature of **2** having three contiguous chiral centers (C4-5-6), one of which is an all-carbon quaternary center, poses significant challenges for stereoselective construction. For efficient synthesis of the BCD ring system, we envisioned a tandem acyliminium/Mannich-type reaction of chiral amide **3**. Demonstration of this strategy was also expected to be of value for broadening the scope of the Mannich reaction, since to the best of our knowledge there are no examples[3] in which such a tactic has been applied to the construction of an all-carbon quaternary center using a seven-membered ketone as a nucleophile. Chiral amide **3** was dissected into two fragments, **4** and **5**. Chiral amine **4** could potentially be prepared from enoate **6** with an appropriate chiral auxiliary

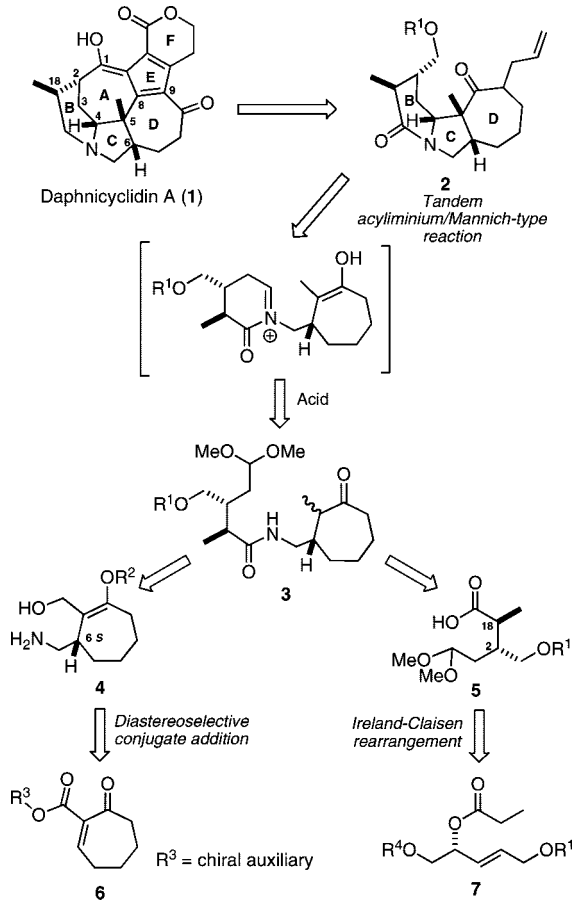
(1) Kobayashi, J.; Inaba, Y.; Shiro, M.; Yoshida, N.; Morita, H. *J. Am. Chem. Soc.* **2001**, *123*, 11402.

(2) In the structural analogy to **1**, racemic synthesis of the tricyclic core of calyciphylline A, one of the *Daphniphyllum* alkaloids, was reported: Solé, D.; Urbaneja, X.; Bonjoch, J. *Org. Lett.* **2005**, *7*, 5461.

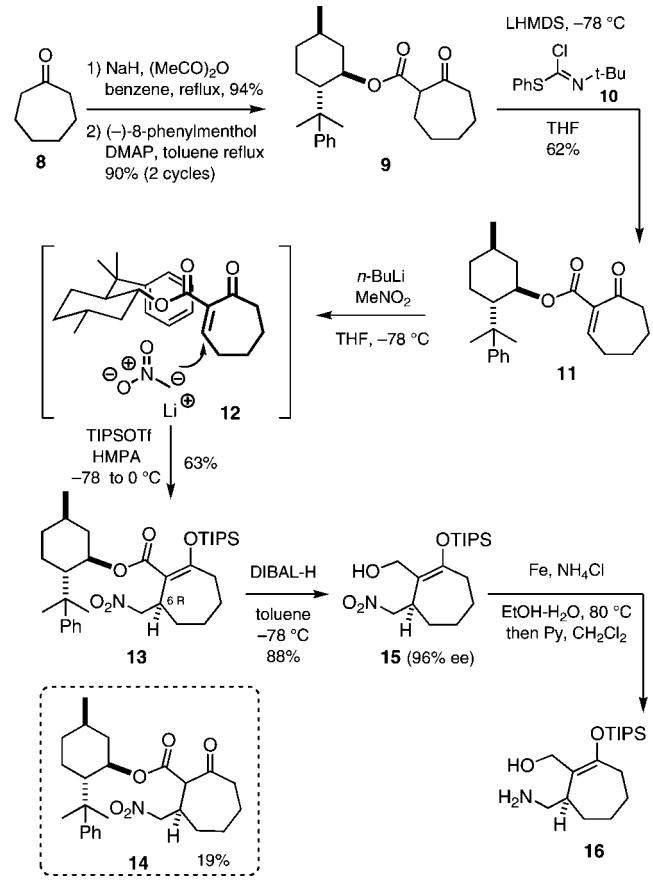
(3) (a) Earley, W. G.; Oh, T.; Overman, L. E. *Tetrahedron Lett.* **1988**, *29*, 3785. (b) Uchida, K.; Yokoshima, S.; Kan, T.; Fukuyama, T. *Org. Lett.* **2006**, *8*, 5311. (c) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. (d) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (e) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431.

10.1021/ol9003405 CCC: $40.75
Published on Web 03/25/2009

Scheme 1. Retrosynthetic Analysis



Scheme 2. Synthesis of Chiral Amine Fragment **16**



by means of a diastereoselective conjugate addition of nitromethane. On the other hand, chiral acid **5**, bearing two contiguous chiral centers (C2−C18), could be obtained via an Ireland−Claisen rearrangement of chiral allyl ester **7**.

In launching this strategy, we selected (−)-8-phenylmenthol as the chiral auxiliary for the crucial conjugate addition to enoate **6** because of its reliable utility and availability.[4] According to the empirical rule developed by Oppolzer and co-workers,[5] the configuration at the C6 chiral center installed by the reaction was expected to be *R*, which is opposite to that of the natural product, (+)-daphnicyclidin A (**1**). In this context, we decided to synthesize the acid fragment from an antipode of **7** to tentatively establish the enantiocontrolled synthetic route for **1**.[6]

As shown in Scheme 2, the synthesis of the amine fragment commenced from commercially available cycloheptanone (**8**). Installation of the methoxycarbonyl group to **8** followed by transesterification[7] with (−)-8-phenylmenthol gave *β*-ketoester **9**. Regioselective one-pot dehydrogenation of **9** using Mukaiyama−Matsuo reagent **10**[8] furnished enoate **11**. Upon treatment of **11** with the lithium salt of nitromethane in THF at −78 °C, the expected conjugate addition reaction took place presumably through the *s-trans* (C=C/C=O) conformation **12** to give a transient enolate, which was trapped by TIPSOTf to afford silyl enol ether **13** and *β*-ketoester **14**. Reduction of **13** with DIBAL-H gave nitro alcohol **15** along with recovered (−)-8-phenylmenthol (90%). At this stage, the optical purity was determined to be 96% ee by chiral HPLC analysis.[9] Finally, reduction of nitro alcohol **15** using Fe-NH_4Cl furnished chiral amine **16**.[10]

(4) (−)-8-Phenylmenthol is now commercially available: (a) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908. (b) Ort, O. *Organic Synthesis*; Wiley: New York, 1993; *Collect. Vol. VIII*, p 522.

(5) (a) Oppolzer, W.; Löher, H. *Helv. Chim. Acta* **1981**, *64*, 2808. (b) Oppolzer, W.; Moretti, R.; Godel, T.; Meunier, A.; Löher, H. *Tetrahedron Lett.* **1983**, *24*, 4971.

(6) To obtain the *S* configuration at C6, we can choose (−)-camphor derived alcohol as a chiral auxiliary, which is prepared from (−)-camphor over 6 steps. See: (a) Oppolzer, W.; Chapuis, C.; Dupuis, D.; Guo, M. *Helv. Chim. Acta* **1985**, *68*, 2100. (b) Fabris, F.; Zambrini, L.; Rosso, E.; De Lucchi, O. *Eur. J. Org. Chem.* **2004**, 3313.

(7) Taber, D. F.; Amedio, J. C., Jr.; Patel, Y. K. *J. Org. Chem.* **1985**, *50*, 3618.

(8) Matsuo, J.; Aizawa, Y. *Tetrahedron Lett.* **2005**, *46*, 407.

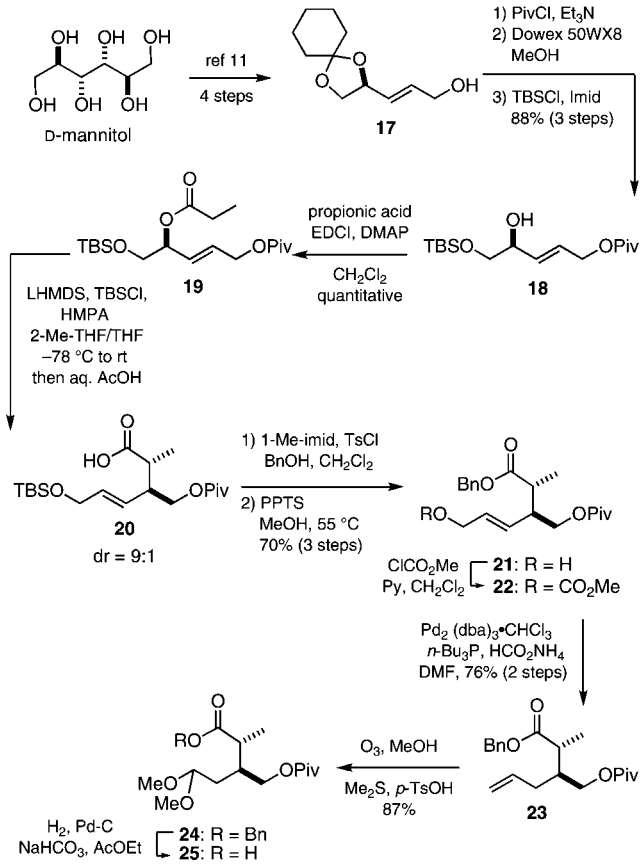
(9) The absolute stereochemistry at C6 was confirmed at a later stage (Scheme 4). As far as we know, since the conjugate addition of nucleophiles to chiral enoates has been reported exclusively for acyclic systems, our result is expected to provide an attractive methodology for the asymmetric functionalization of cyclic compounds: (a) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771. (b) Whitesell, J. K. *Chem. Rev.* **1992**, *92*, 953.

(10) **16** was used in the next step without further purification as a CH_2Cl_2 solution including pyridine because of the instability to acid and concentration.

(11) Banerjee, S.; Ghosh, S.; Sinha, S.; Ghosh, S. *J. Org. Chem.* **2005**, *70*, 4199.

(12) Soldermann, N.; Velker, J.; Neels, A.; Stoeckli-Evans, H.; Neier, R. *Synthesis* **2007**, 2379.

Scheme 3. Synthesis of Chiral Acid Fragment **25**



Scheme 3 shows the synthesis of the acid fragment from the known chiral allyl alcohol **17** prepared from D-mannitol.[11] Allyl alcohol **17** was converted to allyl ester **19** via a four-step sequence. With the requisite allyl ester **19** in hand, our attention was then focused on the Ireland−Claisen rearrangement. After several attempts, we found that treatment of allyl ester **19** with LHMDS (THF solution) in the presence of TBSCl and HMPA in 2-Me-THF[12] gave carboxylic acid **20** in good yield. The diastereoselectivity in this reaction was estimated to be 9:1 based on the ^{1}H NMR analysis of allyl carbonate **22**.[13] Upon sequential protection of the carboxyl group as a benzyl ester,[14] deprotection of the TBS group, and carbonate formation with $ClCO_2Me$ in pyridine, **20** afforded **22**. The successful palladium-catalyzed formate reduction[15] of **22** furnished terminal alkene **23**. Finally, the desired acid **25** was obtained by ozonolysis, dimethyl acetal formation, and hydrogenolysis of benzyl ester **24**.

As illustrated in Scheme 4, condensation of **16** and **25** in the presence of EDCI-DMAP proceeded smoothly to give amide **26**. After conversion of **26** to tosylate by Tanabe's protocol,[16] removal of the TIPS group by TBAF in a one-pot process led to the successive elimination of tosylate to provide enone **27**. Hydrogenation of the *exo* olefin in the presence of Pd−C/$NaHCO_3$ furnished chiral amide **28**.

Having succeeded in the synthesis of chiral amide **28**, then we extensively investigated the key tandem acyliminium/Mannich-type reaction, which has the potential for the one-step construction of the B-C ring system bearing a quaternary methyl carbon. After considerable experimentation, the intended tandem cyclizations were accomplished by exposure of **28** to refluxing isopropanol with the evolution of hydrogen chloride in situ. It was found that the undesired tricycle **30** (56%)[17] predominated over the desired tricycle **31** (31%). The stereochemistries of **30** and **31** were verified by X-ray crystallographic analysis and NOESY correlations, respectively. These assignments unambiguously confirmed the configuration of the three preformed chiral centers (C4-5-6) as expected, one of which was installed by the diastereoselective conjugate addition of nitromethane, whereas the others were introduced by the Ireland−Claisen rearrangement. Considering the fact that the products do not interconvert under the reaction conditions, the stereochemical outcome may be rationalized by transition state models *exo*-**A** and *endo*-**B**, where the steric hindrance of *endo*-**B** (pivaloyloxymethyl vs six-membered ring) overrides that of *exo*-**A** (methyl vs six-membered ring). Two additional experiments with alternative substrates **29** and **33**,[18] which offer the reduction of steric factors, afforded the enhanced preferences in *endo*-selectivity (36:32 for **29**; 61:22 for **33**), supporting the validity of the working model to allow further improvement.

Finally, we have focused on the functionalization at C9, which will serve for construction of the remaining AEF ring system. Upon treatment of **31** with KHMDS at −50 °C followed by the addition of allyl iodide, the allylation at α-position was realized in 60% yield. The stereochemistry of **32** was assigned from NOESY correlations.

In conclusion, we have developed an enantiocontrolled route to the BCD ring system having all the chiral centers

(13) Ultimately, a small amount of minor diastereomeric compound originating from the rearrangement was separated during the conversion of **28** to **30** and **31** (Scheme 4); see ref 17.

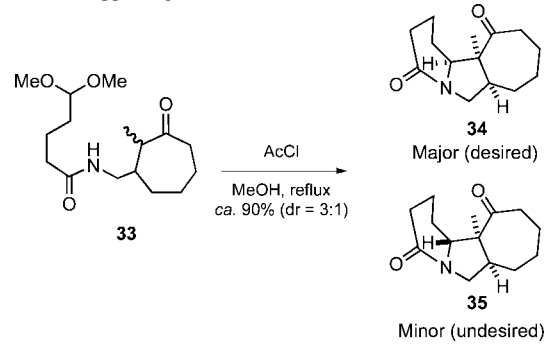
(14) Wakasugi, K.; Iida, A.; Misaki, T.; Nishii, Y.; Tanabe, Y. *Adv. Synth. Catal.* **2003**, *345*, 1209.

(15) Tsuji, J.; Yamakawa, T. *Tetrahedron Lett.* **1979**, 613.

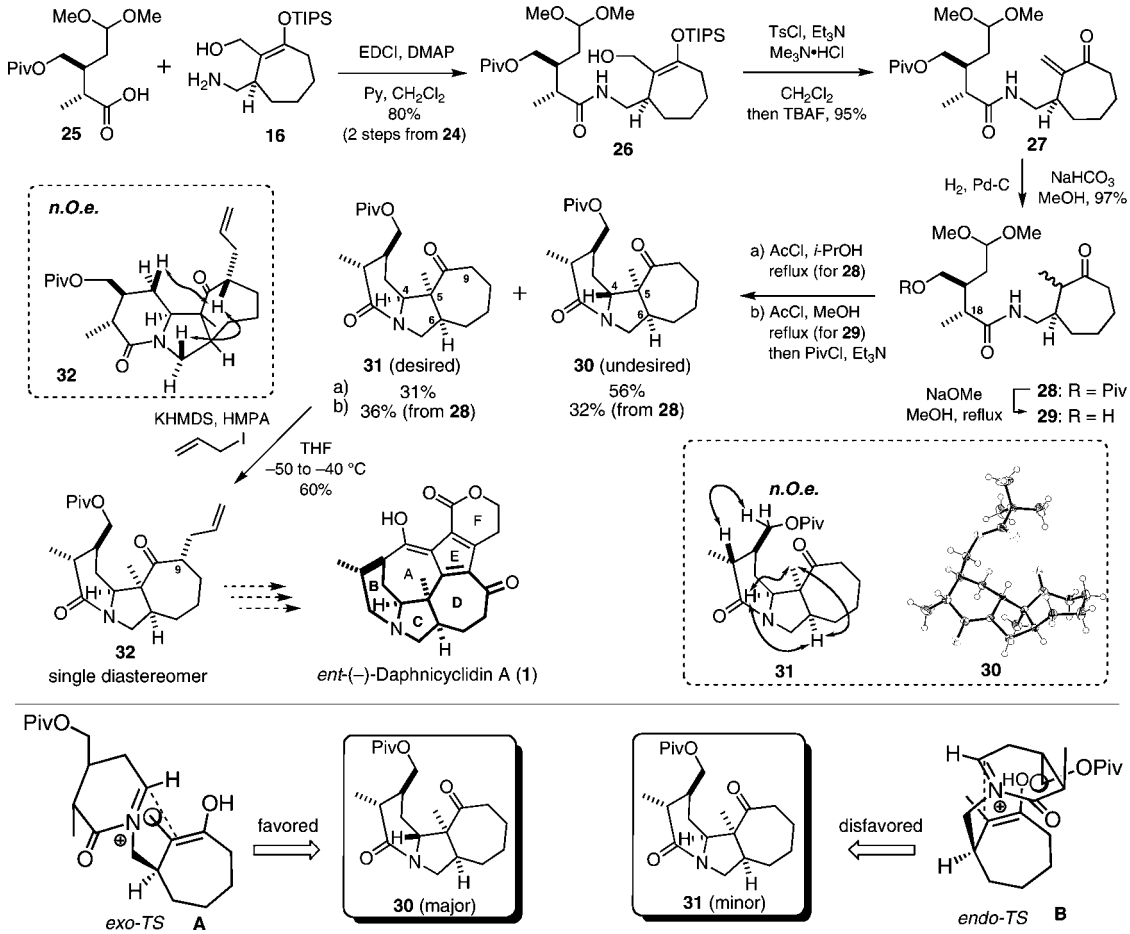
(16) Yoshida, Y.; Sakakura, Y.; Aso, N.; Okada, S.; Tanabe, Y. *Tetrahedron* **1999**, *55*, 2183.

(17) The *exo*-tricycle **30** was accompanied by another minor diastereomer (10:1) after silica gel column chromatography. Thus, the yield of **30** was determined from the ^{1}H NMR spectrum. The minor tricycle may arise from a small amount of the C18 epimer of **28** originating from the Ireland−Claisen rearrangement.

(18) In our model studies of the tandem cyclization, treatment of racemic amide **33** with methanolic hydrogen chloride provided the desired *endo*-tricycle **34** predominantly. Details and further consideration of this reaction are shown in Supporting Information.



Scheme 4. Construction of the BCD Ring System of Daphnicyclidin A (**1**)



of daphnicyclidin A (**1**). The synthesis features (1) the highly diastereoseletive conjugate addition of nitromethane to chiral enoate **11**, (2) the Ireland−Claisen rearrangement of chiral allyl ester **19**, and (3) the tandem acyliminium/Mannich-type reaction of chiral amide **28**. In addition, we have succeeded in functionalizing the D-ring of the desired **31** for construction of the remaining AEF ring framework. Synthetic efforts toward *ent*-(−)-daphnicyclidin A (**1**) including improvement of the stereoselectivity of the tandem cyclization are now underway.

Acknowledgment. This work was financially supported, in part, by Grobal COE program for International Center of Research & Education for Molecular Complex Chemistry, Tohoku University.

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

OL9003405