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Asymmetric total synthesis of (+)-carneic acid A and structure revision of its natural form

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ABSTRACT

This Letter describes the asymmetric total synthesis of (+)-carneic acid A via the stereoselective IMDA reaction of (*E*,*E*,*E*)-triene, which was prepared from the commercially available methyl (*S*)-3-hydroxy-2-methylpropionate. By this asymmetric total synthesis, we verified that the reported absolute structure of naturally occurring carneic acid A must be revised.

Carneic acid A was isolated as a major constituent of the stromata of *Hypoxylon carneum*, which showed a highly specific secondary metabolite profile in the study on xylariaceous ascomycetes using HPLC profiling.[1] Carneic acids showed weak antibacterial and moderate antifungal activities against selected microbial organisms in the serial dilution assay.[1] The relative stereochemistry of naturally occurring carneic acid A was determined based on the NMR data, and its absolute structure was elucidated by using the exciton chirality method.[1] The final absolute structure of naturally occurring carneic acid A was reported as that shown in Figure 1.

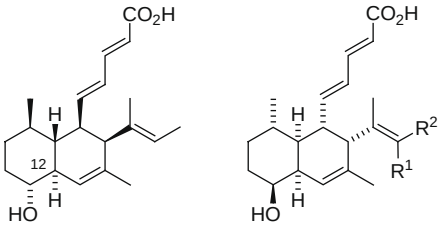
Although carneic acid A shows weak bioactivities, we were interested in its reported structure because it is closely related to that of phomopsidin (**2**) and MK8383 (**3**) (Fig. 1). The relative configuration of the reported structure of **1** is identical to that of **2**, except for the presence of the C12 stereogenic center; however, the reported structure of **1** is almost a mirror image of that of **2**.

In 2004[2] and 2009,[3] we reported the first total syntheses of **2** and **3**, respectively. Therefore, to explore the structure–activity relationships of these related compounds and to confirm the absolute structure of **1**, we carried out the asymmetric total synthesis of **1** and report herein the revised structure of the naturally occurring carneic acid A as well as the first asymmetric total synthesis of (+)-carneic acid A.

The total syntheses of **2** and **3** were successfully carried out via the transannular Diels–Alder (TADA) reaction of a 13-membered macrolide; this reaction effectively led to the formation of the *cis*-dehydrodecaline core that is incorporated in **2** and **3**. On the other hand, carneic acid A consists of a *trans*-dehydrodecaline core, which is speculated to be formed by the intramolecular Diels–Alder (IMDA) reaction of a substrate having a (*E*,*E*,*E*)-triene moiety.[4]

Consequently, the IMDA reaction of the linear precursor **6** (Scheme 1) was considered to yield the *trans*-fused compound **5**, which would be converted to **1** via the formation of alkyne **4**; this conversion was thought to be possible when it was carried out according to the method used in the total syntheses of **2** and **3**. The IMDA substrate **6** can be prepared from the aldehyde **7** by its Horner–Wadsworth–Emmons (HWE) reaction and then subjecting it to the reduction-oxidation sequence. The aldehyde **7** is expected to be prepared via the Suzuki–Miyaura coupling of the alkyne **8** with the iodoalkene **9**.

The alkyne **8** was prepared using methyl (*S*)-3-hydroxy-2-methylpropionate as the starting material by following the procedure reported[2] for the preparation of *ent*-**8** (Scheme 2). Then, the Suzuki–Miyaura coupling[5] of **8** with **9** was carried out. The alkyne **8** was first made to react with 9-BBN and then treated with benzaldehyde to convert the byproduct, a 1,1-bisboryl adduct, into the desired *trans*-alkenylborane;[6] finally, the *trans*-alkenylborane formed was reacted with **9** under the conditions shown in Scheme 2. The coupling reaction proceeded successfully; however, the product **10** was found to have structurally unknown impurities. Therefore, the crude product **10** was used in the next step without purification. The crude product **10** was treated with PPTS in ethanol, and to our delight, we obtained pure alcohol **11** by silica gel chromatography (76%, two steps). The oxidation of **11** with



carneic acid A (**1**) phomopsidin (**2**): R^1 = H, R^2 = Me
MK8383 (**3**): R^1 = Me, R^2 = H:

Figure 1. Structures of carneic acid A, phomopsidin, and MK8383.

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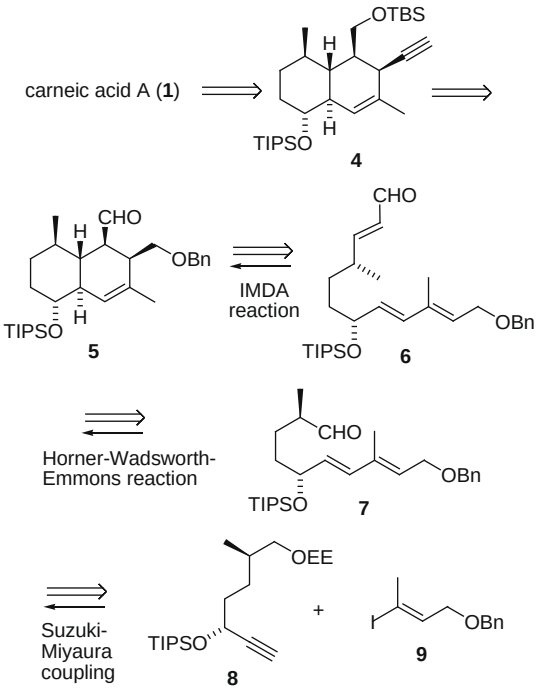
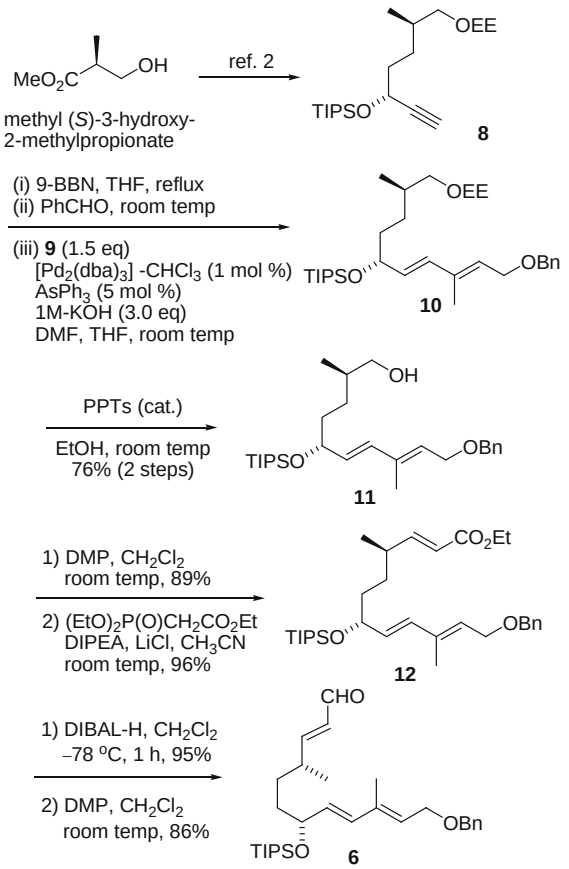
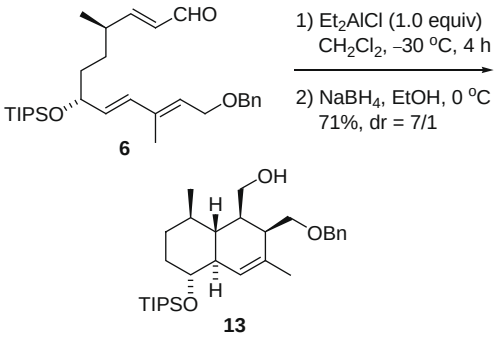


Scheme 1.

Dess–Martin periodinane (89%) and subsequent HWE reaction afforded an α,β-unsaturated ester **12** (96%); the DIBAL reduction of **12** (95%) followed by Dess–Martin oxidation (86%) yielded the aldehyde **6**, which serves as the substrate for the IMDA reaction.



Scheme 2.



Scheme 3.

As the IMDA reaction of **6** proceeded sluggishly at elevated temperature, we examined the Lewis acid-catalyzed IMDA reaction. Among the various Lewis acids examined, $EtAlCl_2$ effectively accelerated the IMDA reaction of **6** at −30 °C to afford the desired product **5**, which was reduced with $NaBH_4$ to afford **13** in 71% yield (two steps) with a diastereomeric ratio of 7/1 (Scheme 3). The crystalline triol **13a** (Fig. 2), which was derived from the major product **13**, was suitable for X-ray crystallographic analysis to confirm its absolute structure,[7] because it was synthesized from a structurally known starting compound, that is, methyl (*S*)-3-hydroxy-2-methylpropionate. Although the minor product was not a crystalline derivative, analysis of the NOESY spectrum of its dinitrobenzoate derivative indicated that the minor compound has a *cis*-fused core. However, the whole structure has not been determined.

The cycloadduct **13** was converted to the TBS ether (92%) (Scheme 4), and then, the benzyl group was removed by lithium naphthalenide to give **14** (93%). The Dess–Martin oxidation of **14** (88%) followed by the Corey–Fuchs protocol[8] gave the alkyne **4**. Negishi's carbometalation–iodination protocol[9] was carried out under Wipf's conditions[10] to afford **15** in a yield of 86%. The Pd(0)-catalyzed coupling reaction[11] of **15** with dimethylzinc proceeded smoothly and was followed by the selective removal of the TBS group and Dess–Martin oxidation to produce the aldehyde **16**.

The HWE reaction of aldehyde **16** with phosphonate, with which it would react to give the TIPS-protected carneic acid A, gave no products under the same conditions as those used in the total synthesis of phomopsidin (**2**). However, the HWE reaction of **16** with triethyl phosphonoacetate under Masamune's conditions[12] proceeded slowly to afford the α,β-unsaturatedester **17** (96%). The NMR studies of **16** suggested that the epimerization of the C6 stereogenic center occurred during the HWE reaction.[13] To confirm the occurrence of this epimerization, **17** was converted to the corresponding enal by subjecting it to the reduction (90%)-oxida-

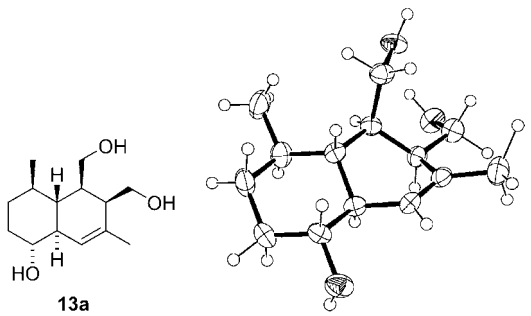
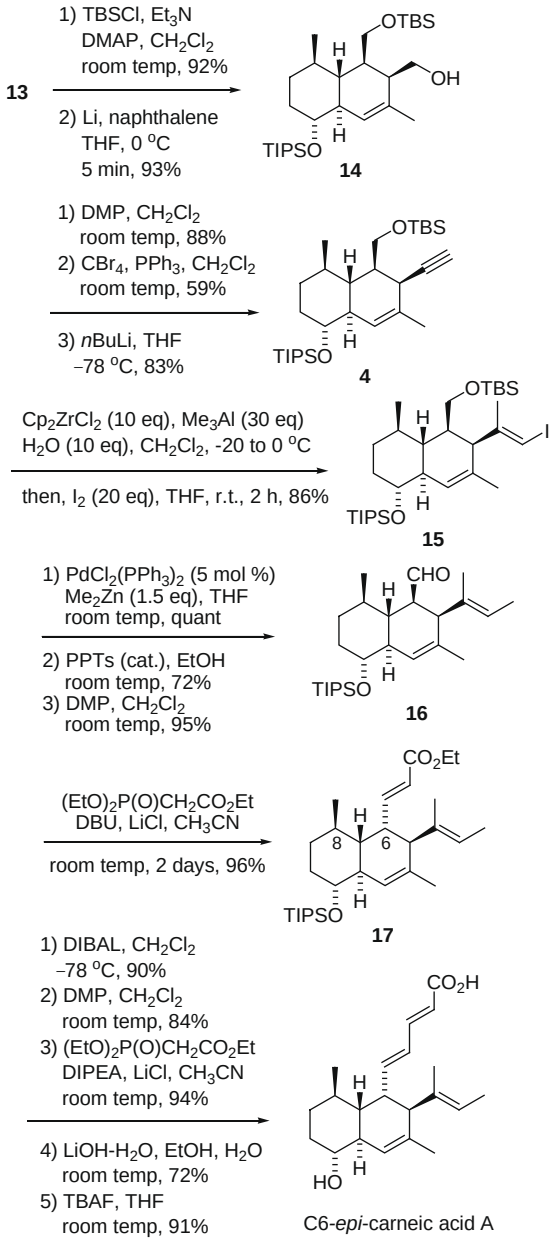
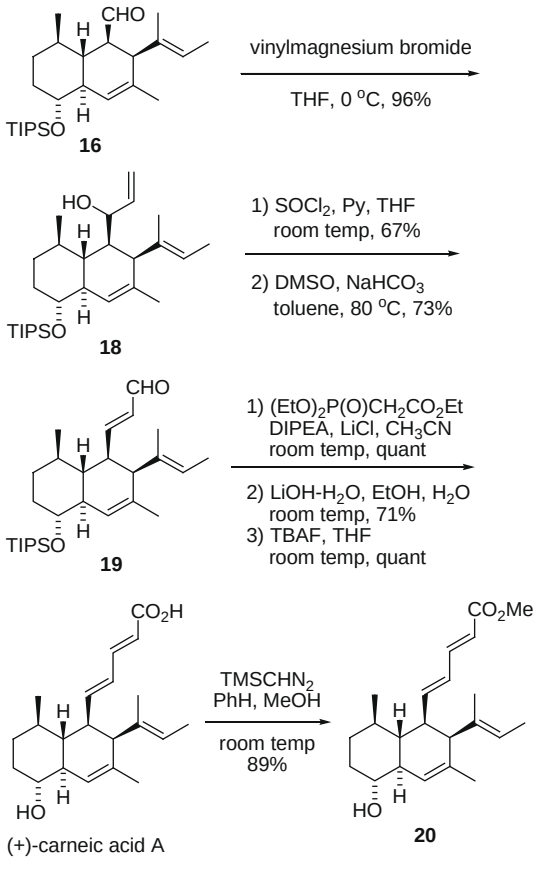


Figure 2. X-ray crystallographic structure of **13a**.



Scheme 4.



Scheme 5.

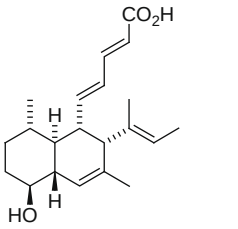


Figure 3. Revised absolute structure of naturally occurring carneic acid A.

tion (84%) sequence followed by the HWE reaction (94%), hydrolysis of the ester (72%), and removal of the TIPS ether (91%) to afford the final product. This compound was not identical to the naturally occurring carneic acid A. Thus, it was confirmed that the α,β-unsaturated ester **17** has a C6 configuration dissimilar to that of carneic acid A, and the final product was thought to be the C6-epimer of carneic acid A.

The reaction of **16** with a bulky nucleophile was slow, while its reactions with small nucleophiles afforded the products. Therefore, **16** was made to react with a vinylmagnesium bromide to afford the allylic alcohol **18** (96%), which was converted to primary allylic chloride using thionyl chloride (67%) (Scheme 5). The resulting chloride was treated with DMSO[14] in the presence of sodium bicarbonate to afford the aldehyde **19** (73%); **19** underwent the HWE reaction with triethyl phosphonoacetate (quant) followed by hydrolysis of the ester (71%) and removal of the TIPS ether with TBAF (quant) to afford the final product.

Although all spectroscopic data of the synthesized carneic acid A methyl ester **20** were nearly identical to the reported data,[15] the specific rotation of the synthesized carneic acid A was found to be $[\alpha]_D^{28}$ +1.30 (*c* 0.4, $CHCl_3$); this value was different from that of naturally occurring carneic acid A, that is, $[\alpha]_D^{20}$ −4.0 (*c* 0.5, $CHCl_3$).[1,12] Moreover, the CD spectrum of the *p*-nitrobenzoate derivate of **20** showed negative (283 nm) and positive (243 nm) Cotton effects, which are reverse of those described in the literature.[1]

With the difference in sign (+ and −) in both their specific rotation and their CD spectrum, we speculate that the absolute structure of the naturally occurring carneic acid, (−)-carneic acid A, corresponds to that shown in Figure 3, and that the compound synthesized in our study must be its antipode, that is, (+)-carneic acid A because the total synthesis was carried out using a known starting compound having a definite absolute configuration.[16]

In conclusion, we successfully carried out the asymmetric total synthesis of (+)-carneic acid A via the stereoselective IMDA reaction of (*E*,*E*,*E*)-triene, which was prepared from the commercially

available methyl (*S*)-3-hydroxy-2-methylpropionate. By this asymmetric total synthesis, we verified that the reported absolute structure of naturally occurring carneic acid A must be revised as that shown in Figure 3. The bioactivity of (+)-carneic acid A and its C6-epimer is currently being investigated.

Acknowledgments

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Supplementary data

Supplementary data (all spectroscopic data of (+)-carneic acid A and its methyl ester, and comparison of the NMR data for natural and synthetic carneic acid A) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.024.

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7. Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data center as supplementary publication number CCDC 736405. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 IEZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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13. Although the C6-epimer of **16** possesses two pseudoaxial substituents, a formyl group and (*E*)-1-methyl-1-propenyl group, the C6-epimer of **16** would be energetically more favorable than **16** because the steric strain between C8 methyl and C6 substituent in **16** is large.
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15. The synthesized carneic acid A showed slightly different spectroscopic data in part (see Supplementary data). We speculate that the difference in the chemical shift values of the NMR spectra and the difference in the $[\alpha]_D$ values between the naturally occurring and the synthesized carneic acid A could be attributed to the different forms of the carboxylic acid. In other words, the naturally occurring carneic acid A used for the measurement of NMR spectra and specific rotation might be in the form of salt, which results in a different value; this speculation is based on a similar past experience during the total synthesis of phomopsidin. However, according to Dr. Marc Stadler, a corresponding author of the paper on structure elucidation of carneic acid A, there are no naturally occurring carneic acid A currently available; hence, we cannot verify our speculation.
16. The reversal of the Cotton effects indicates that the authors of Ref. 1 made a mistake in the assignment of the CD spectrum.