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Communication

Synthesis of ACE tricyclic systems of daphnicyclidin A and dehydroxymacropodumine A

Qi Wang†, Chao Zhang†, Jun Yang*

Key Laboratory of the Ministry of Education for Medicinal Resources and Natural Pharmaceutical Chemistry, Key laboratory of Macromolecular Science of Shaanxi Province, School of Chemistry and Chemical Engineering, Shaanxi Normal University, Chang'an Campus, Xi'an 710119, China

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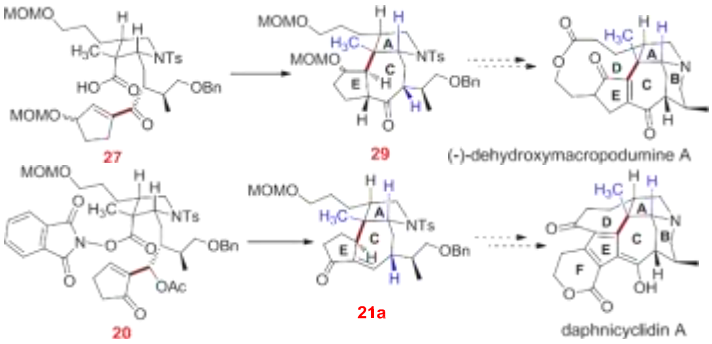

ABSTRACT

The synthesis of the ACE tricyclic system of daphnicyclidin A and dehydroxymacropodumine A are developed. The key reactions include an efficient aldol reaction to introduce chiral fragment **33** for further construction of piperidine ring B and seven-membered ring C, a nucleophilic addition of lithium pentene to aldehyde for installation of ring E, and a photocatalytic decarboxylation conjugate addition to construct ring C.

*Keywords:*Tricyclic System, Daphnicyclidin A ,Dehydroxymacropodumine A,Photocatalytic decarboxylation
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The *daphniphyllum* alkaloids are a unique group of azapolycyclic natural products (> 320 members) that are found in the genus *daphniphyllum*. Based on their different polycyclic skeletons, *daphniphyllum* alkaloids were classified into 20 types [1]. Calyciphylline A-type [2], daphnicyclidin-type [3] and macro-podumine-type [4] *daphniphyllum* alkaloids were biosynthesized from a common precursor proto-daphniphylline and possess a similar 5/5 AE bicyclic system [5]. The AE bicyclic can be considered as the core structure of these alkaloids because it fused with all of the rest rings and contain most of the chiral centers and quaternary carbons. The representative examples of those alkaloids are depicted in Fig. 1. Much attention has been attracted to the synthesis of them due to their complex polycyclic skeletons and wide range of biological activities, including anti-tumor, antiviral, and nerve growth factor-regulating properties [6]. To date, the total synthesis of several calyciphylline A-type alkaloids have been elegant accomplished by developing highly efficient synthesis strategies [7]. However, due to the construction of seven-membered ring C of daphnicyclidin-type is more a

* Corresponding author.
E-mail address: junyang@snnu.edu.cn
† These two authors contributed equally to this work.

challenge than the six-membered ring C in calyciphylline A-type, the total synthesis of daphnicyclidin-type was not reported so far, only a few reports on the synthesis of its partial ring system [8]. Herein, we disclose an efficient synthesis of the ACE tricyclic systems of daphnicyclidin A and dehydroxymacropodumine A *via* a decarboxylation radical conjugate addition reaction [9].

In our previous work, we have developed an efficient approach to access fast and stereoselective construction of 2,3,4-*cis* tri-substituted pyrrolidine **1** *via* tandem *N*-allylation/S_N2' reaction [8d]. Methylation of the *α*-position of lactone of **1**, followed by hydrolyzing the lactone, a carboxyl group at the 3-position could be delivered, which will produce a tertiary carbon radical under the catalysis of iridium or ruthenium complex. Consequently, it is reasonable that if the new generated free radical was captured by a cyclopentenone, the AE bicyclic system will be constructed.

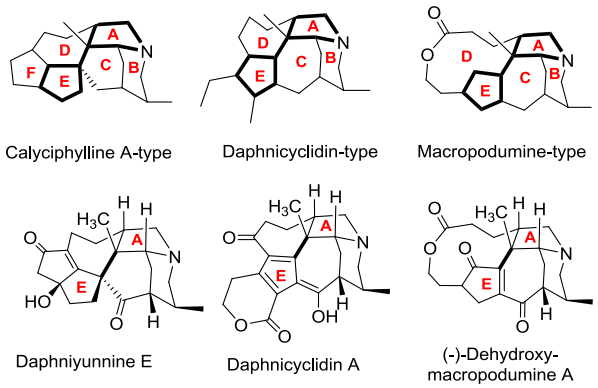
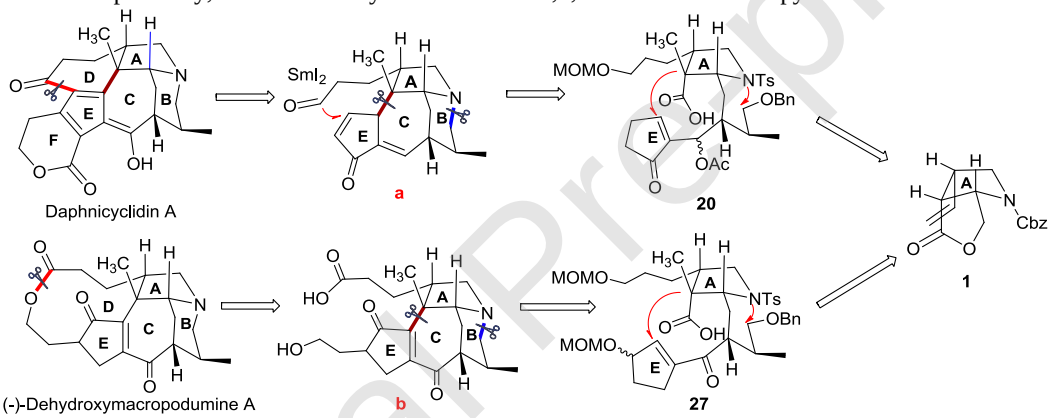


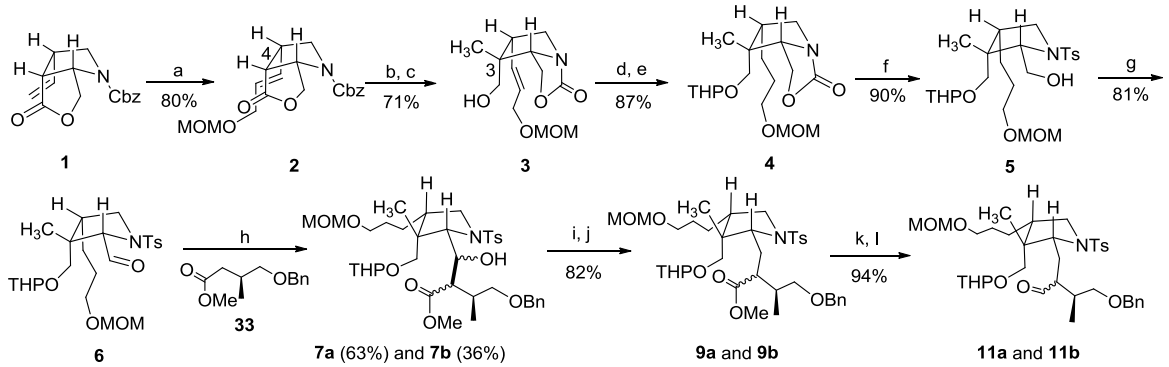
Fig. 1. Representative structures of calyciphylline A-type, daphnicyc-lidin-type and macropodumine-type alkaloids.

Our retrosynthesis is described in Scheme 1, ring D of daphnicyclidin A could be constructed by a SmI_2-mediated radical Michael addition [10] from intermediate **a**, and the 11-membered macrolide ring of dehydroxymacropodumine A could be assembled by macrolactonization [11] from intermediate **b**. The ring B of those two alkaloids can be formed by the formation of lactam. Finally, Seven-membered ring C and C-5 quaternary carbon center can be constructed *via* a photocatalyzed decarboxylation radical conjugate addition from **20** and **27** respectively, which can be synthesized from 2,3,4-*cis* tri-substituted pyrrolidine **1**.



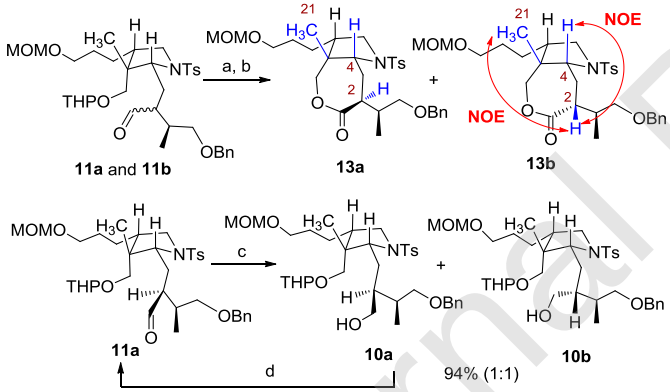
Scheme 1. Retrosynthesis of daphnicyclidin A and dihydroxy-macropodumine A.

We first modified the substituents at the 2,3,4-position of **1**. As showed in Scheme 2, under the catalysis of Grubbs(II) catalyst, the 4-vinyl group of **1** react with MOM protected allyl alcohol give **2** in 80% yield. Treatment of **2** with LiHMDS and MeI in THF at -78 to -45 °C, the product of C-3 methylation was delivered with no formation of undesired isomer. Hydrolyzing the lactone of **2a** with sodium hydroxide in MeOH/H_2O results in the formation of oxazolinone carboxylic acid sodium salt. After removing MeOH/H_2O, the residue was added THF followed by ethyl chloroformate, a mixed-anhydride was produced which was reduced by $NaBH_4$ to give alcohol **3** in 71% yield. Protecting the alcohol with THP and reduce the double bond with 10% Pd/C under 1 atm of hydrogen afford **4** in 87% yield. The following hydrolysis of the oxazolinone with *t*-BuOK in aqueous *t*-BuOH at 100 °C deliver a 2-hydroxymethyl pyrrolidine intermediate, which react with *p*-TsCl by adjusting pH of the reaction solution to 8-9 give **5** in 90% yield. Subsequently oxidation of the primary alcohol with Dess-Martin reagent produces aldehyde **6** for further aldol reaction. Treatment of ester **33** with LiHMDS in THF at -78 °C followed by addition of aldehyde **6** smoothly deliver secondary alcohol **7a** and **7b** in 63% and 36% yield, respectively. The hydroxyl of **7a** and **7b** was removed by Barton deoxygenation [12] give **9a** and **9b** in 82% yield. Convention of the ester group of **9a** and **9b** into alcohol with $LiAlH_4$ in THF at -20 °C then oxidize the resulting alcohol with NMO/TPAP give aldehyde **11a** and **11b** as a pair of diastereomers.



Scheme 2. Synthesis of aldehyde **11a** and **11b**. Reagents and conditions: (a) $MOMOCH_2CH=CH_2$, Grubbs(II) (3.0%), CH_2ClCH_2Cl, 70 °C, 48 h; (b) LiHMDS, CH_3I, THF, -78 °C to -45 °C; (c) NaOH (2.0 eq.), MeOH:H_2O = 4:1, 25 °C, then THF, 0 °C, ClCOOEt, then $NaBH_4$; (d) PPTs, DHP, DCM, 25 °C, 8 h; (e) Pd/C (10.0 %), H_2, 1 atm, MeOH, 25 °C, 2 h; (f) *t*-BuOK, *t*-BuOH:H_2O = 10:1, 100 °C, then HCl (1 mol/L) (pH 8-9), then TsCl, 25 °C, 5 h; (g) NMO, TPAP, DCM, 35 °C, 10 min; (h) LiHMDS, THF, -78 °C, **33**; (i) CS_2, NaH, THF, 0 °C to 25 °C, 8 h, then MeI, 25 °C, 2 h; (j) *n*-Bu_3SnH, AIBN, PhMe, 105 °C, 5 h; (k) $LiAlH_4$, THF, -20 °C, 2 h; (l) NMO, TPAP, DCM, 35 °C, 10 min.

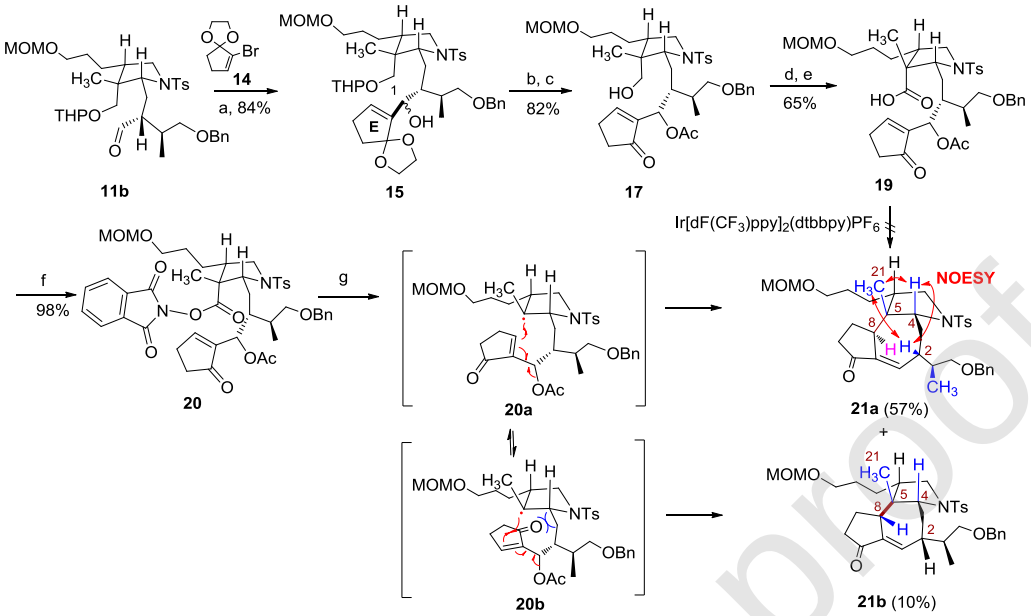
The determination of the stereochemistry of **11a** and **11b** was conducted by conversion of **11a-b** into 6-hexanolactone **13a-b** by deprotecting the THP group then oxidation of the resulting hemiacetal to lactone. The ^1H and ^{13}C NMR signal of **13a-b** were assigned by detailed analyses of 1D and 2D NMR spectra (Tables S1 and S2 in Supporting information). In the NOESY spectra of **13a**, cross-peak of H-2 (δ_H 2.46) to H-4 (δ_H 2.77) and H-2 to H-21 (δ_H 0.94) was not observed, indicated that the relative configuration of **13a** is 2,4-*trans*-4,5-*cis* (Fig. S1 in Supporting information). Likewise, the ^1H and ^{13}C NMR signal of **13b** were assigned, the cross-peak H-2 (δ_H 2.42) to H-4 (δ_H 3.53) and H-21 (δ_H 0.75) were observed in NOESY revealed that the relative configuration of **13b** is 2,4,5-*cis* (Fig. S2 in Supporting information), which is consistent with that of daphnicyclidin A and dihydroxy-macropodumine A. Subsequently, we attempted to change the configuration of the α-position of aldehyde **11a** under basic conditions. Treatment of **11a** with DBU in CH_3CN at 75 °C, a mixture of **11a** and **11b** was obtained in a 1:1 ratio. Aldehyde **11a** and **11b** cannot be separated by column chromatography. Fortunately, alcohols **10a** and **10b** obtained by reduction of the aldehyde group can be separated by column chromatography. Consequently, oxidation of **10b** could give **11b**, while **10a** can be oxidized to **11a**, and then repeated the configuration inversion process.



Scheme 3. Determination of the stereochemistry of **11a**, **11b** and transformation of **11a** to **10b**. Reagents and conditions: (a) *p*-TSA, acetone:H_2O = 4:1, 25 °C, 24 h; (b) Jones' reagent, acetone, 0 °C, 10 min; (c) DBU, CH_3CN, 75 °C, 12 h, then $NaBH_4$, H_2O, 25 °C, 15 min; (d) NMO/TPAP, DCM.

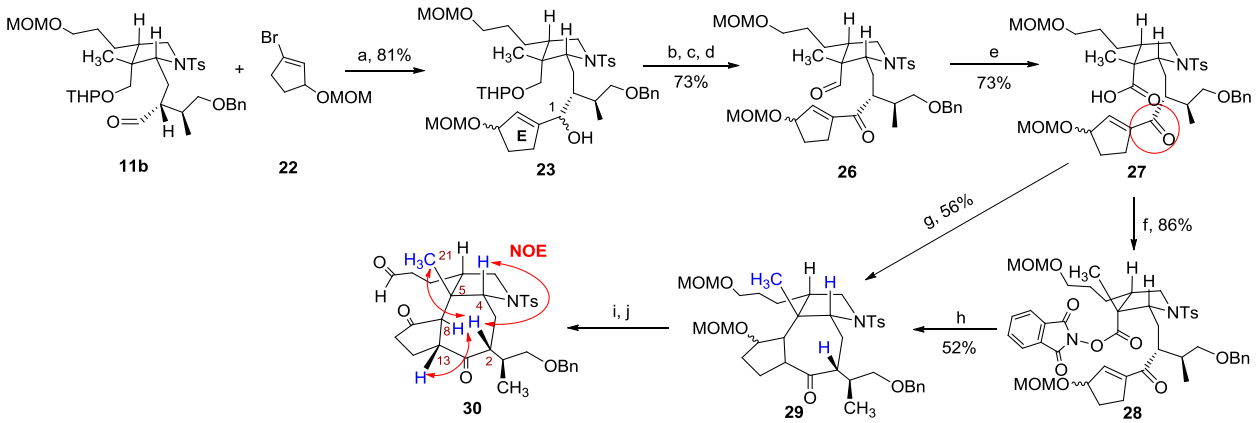
With **11b** in hand, we first attempted to attach the cy-clopentenone to the aldehyde **11b** by MBH reaction [13], but it was unsuccessful. Therefore, we converted cyclopentenone to alkenyl bromide **14**, as showed in Scheme 4, treatment of **14** with *t*-BuLi in THF at -78 °C, followed by addition of **11b**, the product **15** was delivered in 85% yield. Protection of the new formed secondary alcohol with acetyl group and removed the ethylene glycol and THP protecting group to give a primary alcohol **17** in 82% yield. Conversion of the hydroxyl group to aldehyde with NMO/TPAP then oxidation of the resulting aldehyde with NaH_2PO_4/$NaClO_2$ give the carboxylic acid **19**, which was subjected to the decarboxylation radical conjugate addition using MacMillan's condition [9a]. However, this reaction is complicated, and the conjugate addition products were not isolated. We next converted the carboxyl group to *N*-hydroxyphthalimide ester to give **20** and try Overman's condition [9b,9c]. Using $[Ru(bpy)_3](BF_4)_2$ as catalyst, diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate as photoelectron transfer agent, DIPEA as a base and deoxygenated DCM as solvent, under the irradiation of blue light, the product **21a-b** was obtained in a 67% yield. Compounds **21a-b** are a pair of inseparable diastereoisomers in a 5.7:1 ratio. In the ^1H NMR of **21a-b**, the proton signal of double bond at δ = 6.54 (major) and 6.57 (minor) ppm were observed and the proton signal of acetyl group were absent, indicated that the acetyl group was kicked off after the conjugate addition. The molecular formula of **21a-b** was established as $C_{35}H_{47}NO_6S$ by HRMS at *m/z* 632.3011 $[M+Na]^+$(calcd. 632.3016), further confirming the absence

of acetoxyl group. The ^{1}H and ^{13}C NMR signal of the major product **21a** were assigned by detailed analyses of 1D and 2D NMR spectra. (Table S3 in Supporting information). In the NOESY spectra of **21a**, the cross-peak of H-8 (δ_H 3.36) to H-2 (δ_H 3.27), H-4 (δ_H 3.49) or H-21 (δ_H 0.86) were not observed, indicated that the relative configuration of **21a** is 2,4,5-*cis*-5,8-*trans* (Fig. S3 in Supporting information). It is believed that the diastereoselectivity shown in this reaction is due to the steric hindrance of transition state **20a** is less than **20b**. The ^{1}H and ^{13}C signals of **20b** are fail to be assigned because most of its NMR signals are overlap with **21a**.



Scheme 4. Construction of ACE tricyclic of daphnicyclidin A by decarboxylation conjugate addition. Reagents and conditions: (a) **14**, *t*-BuLi, THF, -78 °C; (b) Ac_2O, Et_3N, DMAP, DCM, 25 °C, 2 h; (c) *p*-TSA, acetone:H_2O = 4:1, 35 °C, 12 h; (d) NMO, TPAP, DCM, 35 °C; (e) NaH_2PO_4, $NaClO_2$, *t*-BuOH/CH_3CN/H_2O = 2:2:1, 0 °C to 25 °C; (f) N-hydroxy-phthalimide, DCC, THF, 25 °C, 24 h; (g) Diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate, CH_2Cl_2, DIPEA, blue light, $[Ru(bpy)_3](BF_4)_2$, 25 °C, 2 h.

After successfully construction of the ACE tricyclic system of daphnicyclidin A, using the same strategy, we studied the synthesis of the ACE tricyclic system of dehydroxymacro-podumine A. As showed in Scheme **5**, treatment of **22** with *t*-BuLi in THF at -78 °C followed by addition of **11b**, a cyclopentene was attached to afford secondary alcohol **23** in 81% yield. Oxidation of the alcohol with Dess-Martin reagent, deprotection of the THP group and oxidation of the resulting primary alcohol give aldehyde **26** in 73% yield. Further oxidation of the aldehyde group to carboxylic acid gave **27**, which was subjected to MacMillan's photocatalyst condition. To our delight, using 1 mol% $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ as catalyst in deoxygenated DMF, a household 26 W fluorescent light bulb irradiation about 16 h, the conjugate addition product **29** was delivered in 56% yield. We also examined Overman's condition by conversion of carboxylic acid **27** to *N*-hydroxyphthalimide ester **28**. Using the same reaction condition with that of **20** to **21a**, compound **29** was also delivered in 52% yield. The molecular formula of **29** was established as $C_{37}H_{47}NO_6S$ by HRMS at *m/z* 672.3565 $[M+H]^+$(calcd. 672.3569), consistent with its structure. The NMR spectra of **29** were complicated because it is a mixture of several diastereoisomers. To further identify the structure of **29**, the MOM group was removed and the resulting hydroxyl groups were converted to carbonyl group afforded **30**. The molecular formula of **30** was established as $C_{33}H_{41}NO_6S$ by HRMS at *m/z* 602.2554 $[M+Na]^+$(calcd. 602.2547). The NMR of **30** indicated that it is mainly a single compound and its ^{1}H and ^{13}C NMR signal were assigned by detailed analyses of 1D and 2D NMR spectra (Table S4 in Supporting inforamtion). The NOESY cross-peaks of H-2 (δ_H 3.68) to H-4 (δ_H 3.46), H-4 to H-21 (δ_H 0.67) and H-2 to H-13 (δ_H 3.29) showed that H-2, H-4, H-13 were at the convex side and the H-8 (δ_H 3.18) on the concave side (Fig. S4 in Supporting information). The configuration of C-8 is identical to the configuration of C-8 in compound **21a**.



Scheme 5. Construction of ACE tricyclic of dehydroxymacro-podumine A by decarboxylation conjugate addition. Reagents and conditions: (a) **22**, *t*-BuLi, THF, -78 °C; (b) DMP, DCM, 25 °C; (c) 1 mol/L HCl, MeOH, 25 °C, 24 h; (d) DMP, DCM, 25 °C; (e) NaH_2PO_4, $NaClO_2$, *t*-BuOH/CH_3CN/H_2O = 2:2:1, 0 °C to 25 °C; (f) *N*-hydroxy-phthalimide, DIC, THF, 25 °C, 24 h; (g) 1 mol% $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$, K_2HPO_4, DMF, 25 °C, 26 W GFL, 16 h; (h) diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridine-dicarboxylate, CH_2Cl_2, DIPEA, blue light, $[Ru(bpy)_3](BF_4)_2$, 25 °C, 2 h; (i) 3 mol/L HCl, MeOH, 12 h; (j) DMP, DCM, 25 °C.

In summary, we have developed a novel synthesis toward the ACE tricyclic cores of daphnicyclidin A and dehydroxy-macropodumine A. The chiral fragment **33** was introduced by aldol reaction for further construction of piperidine ring B and seven-membered ring C, the E ring was introduced by nucleophilic addition of lithium pentene to aldehyde and the two ACE tricyclic systems were finally constructed by photocatalytic decarboxylation conjugate addition. The total synthesis of dehydroxymacropodumine A is underway in our laboratory and will be disclosed in due course.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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