Title	Concise Construction of the ACDE Ring System of Calyciphylline A Type Alkaloids by a [5+2] Cycloaddition
Author(s)	Nakamura, Hugh; Kawakami, Manami; Tsukano, Chihiro; Takemoto, Yoshiji
Citation	Chemistry – A European Journal (2019), 25(37): 8701-8704
Issue Date	2019-07-02
URL	http://hdl.handle.net/2433/243179
Right	This is the peer reviewed version of the following article: H. Nakamura, M. Kawakami, C. Tsukano, Y. Takemoto, Chem. Eur. J. 2019, 25, 8701., which has been published in final form at https://doi.org/10.1002/chem.201901690. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions.; The full-text file will be made open to the public on 2 July 2020 in accordance with publisher's 'Terms and Conditions for Self-Archiving'.; This is not the published version. Please cite only the published version. この論文は出版社版でありません。引用の際には出版社版をご確認ご利用ください。
Type	Journal Article
Textversion	author

Concise construction of the ACDE ring system of calyciphylline A-type alkaloids via [5+2] cycloaddition

Hugh Nakamura, Manami Kawakami, Chihiro Tsukano,* and Yoshiji Takemoto*

Abstract: A concise route for construction of the ADE ring skeleton in calyciphylline A-type alkaloids was developed using an intramolecular [5+2] cycloaddition reaction of an oxidopyrylium species bearing a tetrasubstituted olefin. Key to the success of this reaction was the combination of acid and base, which accelerated the construction of this skeleton containing a spiro ring and vicinal quaternary carbon centers. The resultant tricyclic ADE ring compound was converted to an ACDE ring model through C–H oxidation and an aza-Wittig reaction.

The *Daphniphyllum* alkaloids are complex polycyclic alkaloids isolated from plants of the genus *Daphniphyllum*. [1] This class of alkaloids has received much attention owing to its complex three-dimensional structure and interesting biological activities. In particular, calyciphylline A-type alkaloids are *Daphniphyllum* alkaloids that contain a unique hexacyclic skeleton bearing two contiguous quaternary carbon centers and a spiro[4.5]decane skeleton (Figure 1).[2] Among them, and in addition to calyciphylline A, simple congeners including daphniyunnines and daphnipaxianines,[3] dimeric congener logeracemin A,[4a] and hybrid congeners hybridaphniphyllines[4b] have been elucidated. These natural products show various biological activities, including cytotoxicity and anti-HIV activity.[3,4]

Owing to their interesting structures, many research groups have engaged in synthetic studies toward calyciphylline A-type alkaloids.[5] At the end of 2017, asymmetric total syntheses of calyciphylline A-type alkaloids had accomplished by Li,[6] Zhai,[7] and Dixon and Paton.[8] Li and coworkers constructed a tetracyclic intermediate of daphniyunnine C (longeracinphyllin A) through a Ag-catalyzed alkyne cyclization and Luche radical cyclization, followed by a [3+2] cyclization to construct the sterically congested E ring bearing a quaternary carbon center. [6a] Based on this total synthesis, the authors also synthesized daphnipaxianine A, himalenine D, and hybridaphniphylline B. [6b,c] Zhai and coworkers also reported the total synthesis of (–)-daphnilongeranin B using an intermolecular [3+2] cycloaddition to construct the E ring bearing a quaternary carbon center and a late-stage aldol cyclization.[7] Dixon and Paton *et al.* achieved the total synthesis of (–)-himalensine A using an organocatalyzed enantioselective prototropic shift and intramolecular Diels–Alder reaction to construct the ACD ring skeleton.[8] Although several elegant total syntheses of calyciphylline A-type alkaloids have been reported, the construction of this complex ring system in short step remains challenging.

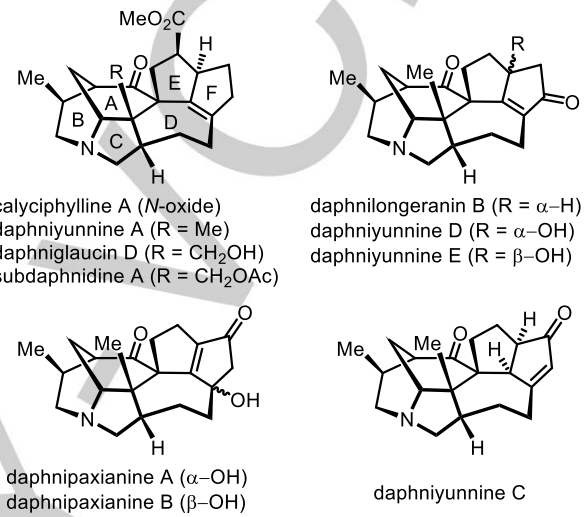
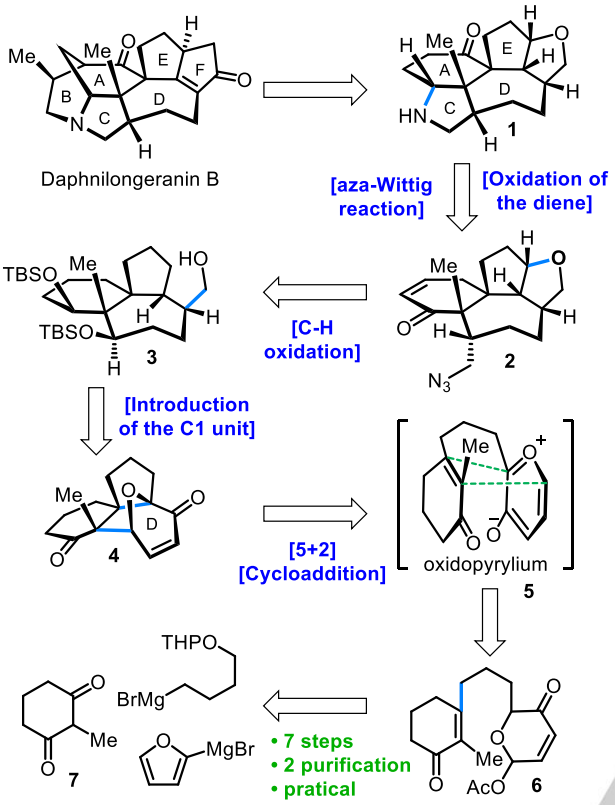


Figure 1. Representative calyciphylline A-type alkaloid.

Key to the synthesis of calyciphylline A-type alkaloids is construction of the ADE ring skeleton containing a spiro ring (E ring) and vicinal quaternary carbon centers. In previous synthetic studies, stepwise sequences were used to obtain this structure. We envisaged constructing the ADE ring skeleton in one step using a [5+2] cycloaddition reaction, which has successfully been employed in the synthesis of other complex natural products.[9] However, it was not clear whether an intramolecular [5+2] cycloaddition reaction could be applied to oxidopyrylium species bearing a tetrasubstituted olefin, with no examples reported. To investigate this possibility, ACDE ring core **1** was selected as a model compound. The C ring would be constructed through an aza-Wittig reaction of compound **2**, followed by oxidation of the A ring to install an oxygen functionality. Compound **2** would be synthesized from compound **4** by introducing a C1 unit onto the seven-membered D ring followed by C–H oxidation of compound **3**. Compound **4** would be constructed from the [5+2] cycloaddition of oxidopyrylium species **5**, which would be generated from acetoxylpyranone **6**. Two quaternary carbon centers are constructed in this intramolecular [5+2] cycloaddition. Herein, we report the synthesis of the ACDE ring model compound, in which an intramolecular [5+2] cycloaddition was used to construct the congested skeleton.

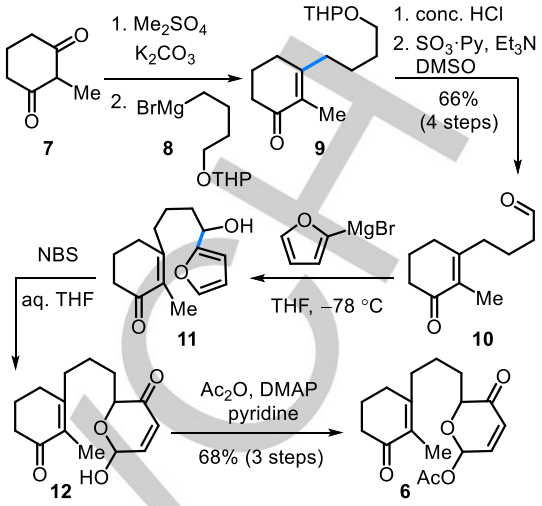
Dr. H. Nakamura, M. Kawakami, Dr. C. Tsukano, Prof. Dr. Yoshiji Takemoto
Graduate School of Pharmaceutical Sciences
Kyoto University
Yoshida, Sakyo-ku, Kyoto, 606-8501 (Japan)
E-mail: tsukano@pharm.kyoto-u.ac.jp
E-mail: takemoto@pharm.kyoto-u.ac.jp

Supporting information for this article is given via a link at the end of the document.



Scheme 1. Retrosynthetic analysis of ACDE model compound **1**.

Cyclization precursor **6** was synthesized from commercially available 2-methylcyclohexane-1,3-dione **7** (Scheme 2). The formation of a vinylogous methyl ester was followed by the nucleophilic addition of Grignard reagent **8**[10] and acidic workup to give α,β-unsaturated ketone **9**. After removing the tetrahydropyranyl (THP) group, the resultant primary alcohol was oxidized to aldehyde **10**, which was then coupled with 2-furanylmagnesium bromide to give alcohol **11**. An Achmatowicz rearrangement[11] of compound **11** by treating with *N*-bromosuccinimide (NBS) was followed by the acetylation of hemiacetal **12** to give cyclization precursor **6** in 68% yield from aldehyde **10**.

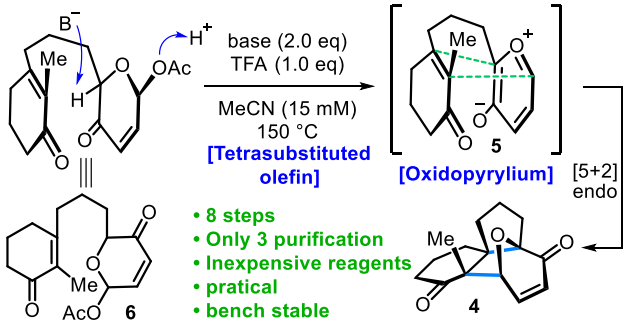


Scheme 2. Synthesis of cyclization precursor **6**.

With cyclization precursor **6** in hand, we examined the [5+2] cycloaddition of oxidopyrylium species **5** (Table 1). Initially, we attempted the cyclization of **6** at 150 °C using no additive. As expected, the reaction afforded no desired product, presumably due to the low reactivity of the tetrasubstituted olefin (entry 1). When trifluoroacetic acid (TFA) was added, the starting material was consumed within 1 h, but the reaction gave desired product **4** in a low yield along with byproduct **13** (entry 2). In contrast, the reaction with iPr_2NH gave **4** in 66% yield, but required a long reaction time (entry 3). Interestingly, combining iPr_2NH and TFA accelerated the reaction to completion within 24 h while maintaining the good yield (entry 4). This tendency was also observed in the reaction using 2,2,6,6-tetramethylpiperidine (TMP) and acetic acid (entries 5 and 6). Therefore, we next investigated combinations of a base (2.0 equiv.) and acid (1.0 equiv.). When piperidine was employed as base, the reaction gave only byproduct **14** containing furan in 40% yield, while congested secondary amines, such as TMP, were effective (entries 5 and 7). When 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used as base,[12] the starting material was decomposed, presumably due to the strong basicity (entry 8). 4-Dimethylaminopyridine (DMAP) was effective, although the reaction time had to be prolonged to 7 h (entry 9). Several tertiary amines, including triethylamine, quinuclidine, and 1,4-diazabicyclo[2.2.2]octane (DABCO) were also examined (entries 10–12). Although the cyclization with triethylamine gave the desired product in 35% yield along with a significant amount of byproduct **13**, quinuclidine and DABCO were effective. Considering the yield and reaction time, DABCO was employed as base for further investigations. Combining DABCO with acetic acid instead of TFA resulted in a lower yield (entry 13). Further investigations regarding temperature resulted in an improved yield of 70% at 180 °C (entries 14 and 15). These results indicated that the bulkiness and basicity of the amine were important for this [5+2]

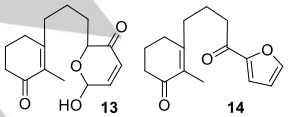
cycloaddition. Notably, this established sequence including a [5+2] cycloaddition readily furnished the ADE ring core bearing the spiro structure and vicinal quaternary carbon centers from commercially available material through eight steps and three purifications using silica gel chromatography.

Table 1. Investigation into [5+2] cycloaddition of tetrasubstituted olefin.



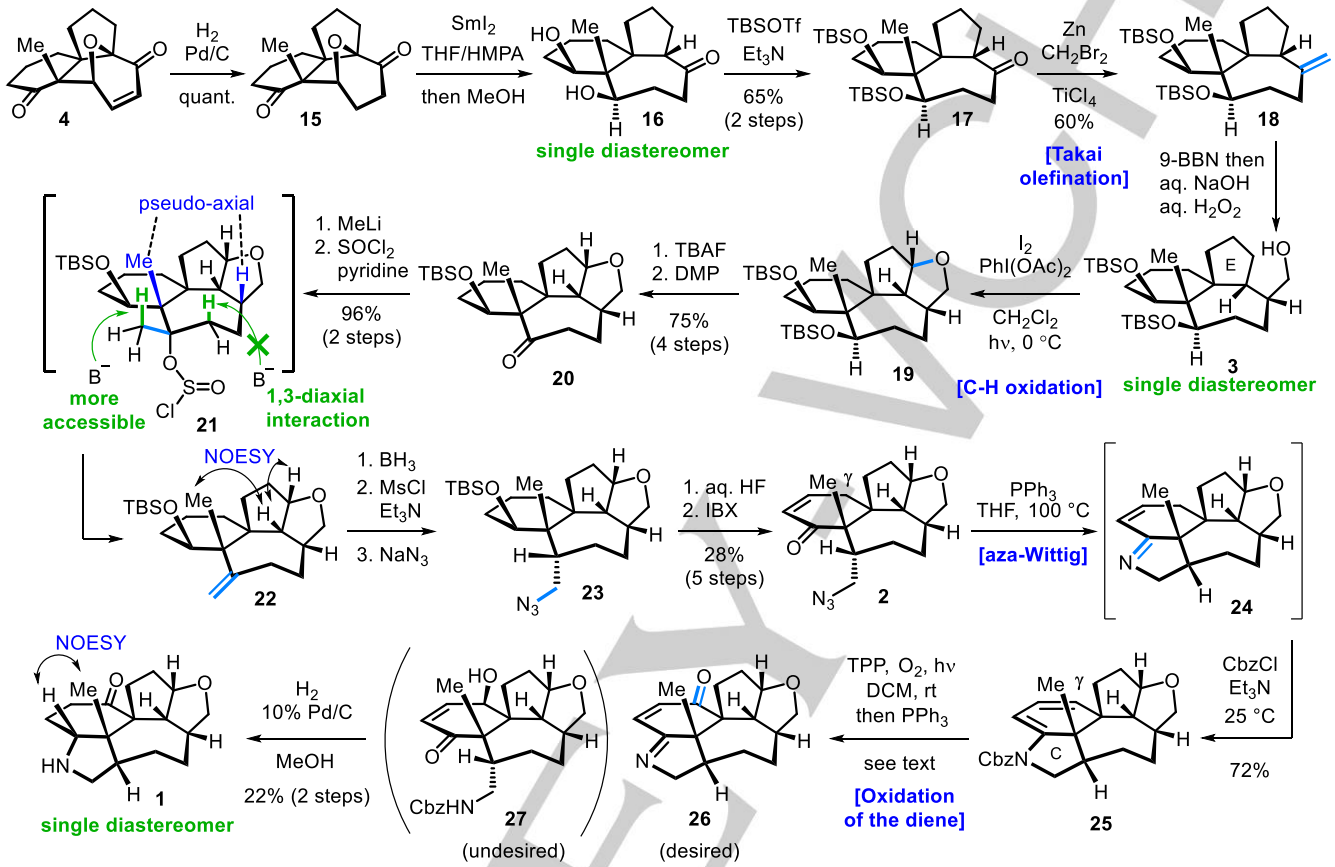
entry	reagents[a]	temp (°C)	time	yield[b]	byproduct[b]
1	none	150	24 h	0%[c]	
2	TFA	150	1 h	11%	**13** (26%)
3	*i*PrNH$_2$	150	69 h	64%	
4	*i*PrNH$_2$, TFA[d]	150	24 h	66%	
5	TMP	150	24 h	61%	
6	TMP, AcOH[d]	150	5 h	56%	
7	 , TFA	150	23 h	0%	**14** (40%)
8	DBU, TFA	150	1 h	0% [e]	-
9	DMAP, TFA	150	7 h	68%	-
10	Et$_3$N, TFA	150	1.5 h	35%	**13** (35%)
11	 , TFA	150	1 h	49%	-
12	DABCO, TFA	150	2 h	61%	-
13	DABCO, AcOH	150	2 h	42%	-
14	DABCO, TFA	100	5.5 h	37%	-
15	DABCO, TFA	180	0.5 h	70%	-

[a] 2 equiv. of base and/or 1 equiv. of acid were employed. [b] Isolated yield. [c] No reaction. [d] 2 equiv. of acid was employed. [e] Decomposition. TFA = trifluoroacetic acid, TMP = 2,2,6,6-tetramethylpiperidine, DABCO = 1,4-diazabicyclo[2.2.2]octane.



Having established a concise route to cyclized compound **4**, it was then converted to tricyclic compound **16** through hydrogenation and reductive ring-opening using SmI_2[13] (Scheme 3). After silylation of the resulting secondary alcohol **16**, the Takai reaction was used to introduce an *exo*-methylene moity,[14] affording compound **18**, whereas the Wittig reaction using $Ph_3P{=}CH_2$ did not proceed. The hydroboration of **18** with 9-borabicyclo[3.3.1]nonane (9-BBN) proceeded stereoselectively to give alcohol **3**. After an extensive investigation into functionalization of the E ring, C–H oxidation using I_2 and $PhI(OAc)_2$ under light irradiation[15] afforded tetracyclic compound **19**. Functionalizing this complex molecule in a high yield with excellent regioselectivity was beneficial to this strategy. Removal of the TBS group followed by Dess–Martin oxidation[16] gave ketone **20** in 75% overall yield from *exo*-methylene compound **18**. Our attention then turned to the stereoselective introduction of another one-carbon unit on the D ring. After treating ketone **20** with MeLi, the resulting tertiary alcohol was dehydrated under using $SOCl_2$ and pyridine to give *exo*-methylene compound **22** in excellent yield. This site-selectivity was attributed to the less hindered proton of the methyl group in **21** being selectively deprotonated instead of a methylene proton. *Exo*-methylene compound **22** was derivatized to azide **23** through hydroboration, mesylation, and S_N2 azide displacement. After removing the TBS group using aqueous HF, the resulting secondary alcohol was directly oxidized to enone **2** using 2-iodoxybenzoic acid (IBX).[17]

With enone **2** in hand, the introduction of an oxygen functionality on the A ring was investigated extensively. However, we realized that oxidation of the γ-position in enone **2** via a silyl enol ether was difficult. For example, treating **2** with a base (lithium diisopropylamide, KO*t*Bu, or Et_3N) and TMSCl (or TMSOTf) gave no reaction. Therefore, we focused on an intramolecular aza-Wittig reaction of enone **2** and oxidation (Scheme 3). Reduction of the azide group using PPh_3 in THF at 100 °C smoothly produced an amine. Intramolecular nucleophilic attack of the amine was used to form unstable enaminone **24**, which was then trapped using CbzCl as dienamide **25** in 72% yield. Various oxidation conditions, including H_2O_2/HCO_2H,[18] MoO_5·pyridine complex,[19] and PhNO,[20] were tested, but compound **25** did not react at all under these conditions. Furthermore, using 3-chloroperoxybenzoic acid (*m*CPBA)[21] or NBS[22] resulted in the decomposition of starting material **25**. Interestingly, a facile [4+2] cycloaddition of **25** with O_2 in the presence of a catalytic amount of tetraphenylporphyrin under light irradiation[23] proceeded to give a peroxide that was too unstable to isolate. While treating the peroxide with Me_2S gave a mixture of desired product **26** and ring-opening product **27**, using PPh_3 suppressed formation of the ring-opening product **27**. As separating the desired product from $Ph_3P{=}O$ was difficult, it was directly subjected to hydrogenation conditions using Pd/C to afford pentacyclic model **1** as a single diastereomer. The newly generated stereochemistry was determined using a NOESY experiment.



Scheme 3. Construction of ACDE ring model compound **1**.

In summary, we have established a concise route for the synthesis of a tricyclic compound containing a spiro structure and vicinal quaternary carbon centers using an intramolecular [5+2] cycloaddition. In this reaction, a combination of acid and base accelerates the [5+2] cycloaddition of compound **6** containing a tetrasubstituted olefin. To our knowledge, this is the first example of a [5+2] cycloaddition reaction of oxidopyrylium species bearing a tetrasubstituted olefin. The resultant tricyclic compound **4** was converted to ACDE ring model **1**, found in calyciphylline A-type alkaloids, via C–H oxidation and an aza-Wittig reaction. Based on this strategy, we are now investigating the synthesis of calyciphylline A-type alkaloids.

Acknowledgments

This work was supported by a Grant-in-Aid for Scientific Research (S) (JSPS KAKENHI no. 16H06384, Y.T.), a Grant-in-Aid for JSPS fellows (H.N.) and the JSPS KAKENHI (Grant No. JP17H05051, C.T.), and JSPS KAKENHI (Grant No. JP18H04407, C.T.) in the Middle Molecular Strategy.

Keywords: Daphniphyllum alkaloids • [5+2] cycloaddition • synthetic strategy • calyciphylline A • daphniyunnine

References

[1] J. Kobayashi, T. Kubota, *Nat. Prod. Rep.* **2009**, *26*, 936.
[2] H. Morita, J. Kobayashi, *Org. Lett.* **2003**, *5*, 2895.
[3] a) H. Takatsu, H. Morita, Y. C. Shen, J. Kobayashi, *Tetrahedron*, **2004**, *60*, 6279; b) X. Chen, Z. J. Zhan, J. M. Yue, *Helv. Chim. Acta*, **2005**, *88*, 854; c) S. P. Yang, H. Zhang, C. R. Zhang, H. D. Chang, J. M. Yue, *J. Nat. Prod.* **2006**, *69*, 79; d) H. Zhang, S.-P. Yang, C. Q. Fan, J. Ding, J. M. Yue *J. Nat. Prod.* **2006**, *69*, 553; e) Y. T. Di, H. P. He, Y. L. Ping, Y. L. Li, L. Wu, X. J. Hao, *J. Nat. Prod.* **2006**, *69*, 1074; f) S. Z. Mu, C. S. Li, H. P. He, Y. T. Di, Y. Wang, Y. H. Wang, Z. Zhang, Y. Lu, L. Zhang, X. J. Hao, *J. Nat. Prod.* **2007**, *70*, 1628.

[4] a) J. B. Xu, H. Zhang, L. S. Gan, Y. S. Han, M. A. Wainberg, J. M. Yue, *J. Am. Chem. Soc.* **2014**, *136*, 7631; b) F. Wang, M. F. Mao, G. Z. Wei, Y. Gao, F. C. Ren. J. K. Liu, *Phytochem*. **2013**, *95*, 428; c) Y. T. Di, C. S. Wee, C. S. Li, N. C. Kong, J. S. Wang, X. Fang, H. J. Zhu, Y. D. Wu, X. J. Hao, *Tetrahedron* **2014**, *70*, 4017.

[5] For selected examples of synthetic studies on calyciphylline A-type alkaloids, see: a) R. Yamada, T. Fukuyama, S. Yokoshima, *Org. Lett.* **2018**, *20*, 4504; b) Y. Sasano, J. Koyama, K. Yoshikawa, N. Kanoh, E. Kwon, Y. Iwabuchi, *Org. Lett.* **2018**, *20*, 3053; c) A. M. Lopez, A. A. Ibrahim, G. J. Rosenhauer, H. S. Sirinimal, J. L. Stockdill, *Org. Lett.* **2018**, *20*, 2216; d) X.-F. Mo, Y.-F. Li, M.-H. Sun, Q.-Y. Dong, Q.-X. Xie, P. Tang, F. Xue, Y. Qin, *Tetrahedron Lett.* **2018**, *59*, 1999; e) Y. Kitabayashi, T. Fukuyama, S. Yokoshima, *Org. Biomol. Chem.* **2018**, *16*, 3556; f) I. Hayakawa, K. Niida, H. Kigoshi, *Chem. Commun.* **2015**, *51*, 11568; f) A. A. Ibrahim, A. N. Golonka, A. M. Lopez, J. L. Stockdill, *Org. Lett.* **2014**, *16*, 1072; h) M. Yang, L. Wang, Z.-H. He, S.-H. Wang, S.-Y. Zhang, Y.-Q. Tu, F.-M. Zhang, *Org. Lett*. **2012**, *14*, 5114; i) Y. Yao, G. Liang, *Org. Lett*. **2012**, *14*, 5499; j) C. Xu, Z. Liu, H. Wang, B. Zhang, Z. Xiang, X. Hao, D. Z. Wang, *Org. Lett.* **2011**, *13*, 1812; k) D. Solé, X. Urbaneja, J. Bonjoch, *Org. Lett.* **2005**, *7*, 5461.

[6] a) J. Li, W. Zhang, Y. Chen, A. Li, *J. Am. Chem. Soc.* **2017**, *139*, 14893; b) Y. Chen, W. Zhang, R. Lu, J. Li, A. Li, *Angew. Chem. Int. Ed.* **2018**, *57*, 952; c) W. Zhang, M. Ding, J. Li, Z. Guo, M. Lu, Y. Chen, L. Liu, Y.-H. Shen, A. Li, *J. Am. Chem. Soc.* **2018**, *140*, 4227.

[7] Z. Chen, H.-J. Zhang, X. Yang, H. Lv, X. Shao, C. Tao, H. Wang, B. Cheng, Y. Li, J. Guo, J. Zhang, H. Zhai, *Angew. Chem. Int. Ed.* **2018**, *57*, 947.

[8] a) H. Shi, I. N. Michaelides, B. Darses, P. Jakubec, Q. N. N. Nguyen, R. S. Paton, D. J. Dixon, *J. Am. Chem. Soc.* **2017**, *139*, 17755.

[9] For reviews of [5+2] cycloadditions, see: a) V. Singh, U. M. Krishna, Vikrant, G. K. Trivedi, *Tetrahedron* **2008**, *64*, 3405; b) H. Pellissier, *Adv. Synth. Catal*. **2011**, *353*, 189; c) K. E. O. Ylijoki, J. M. Stryker, *Chem. Rev.* **2013**, *113*, 2244; d) J. M. Kuthanapillil, A. Nijamudheen, N. Joseph, P. Prakash, E. Suresh, A. Datta, K. V. Radhakrishnan, *Tetrahedron* **2013**, *69*, 9751.

[10] D. Michelot, *Synthesis*, **1983**, 130.

[11] O. Achmatowicz, P. Bukowski, B. Szechner, Z. Zwierzchowska, A. Zamojski, *Tetrahedron*, **1971**, *27*, 1973.

[12] P. A. Wender, C. D. Jesudason, H. Nakahira, N. Tamura, A. L. Tebbe, Y. Ueno, *J. Am. Chem. Soc.* **1997**, *119*, 12976.

[13] B. Chen, R. Y. Y. Ko, M. S. M. Yuen, K. F. Cheng, P. Chiu, *J. Org. Chem.* **2003**, *68*, 4195.

[14] K. Takai, T. Kakiuchi, Y. Kataoka, K. Uchimoto, *J. Org. Chem.* **1994**, *59*, 2668.

[15] R. Hernandez, S. M. Velazquez, E. Suarez, M. S. Rodriguez, *J. Org. Chem.* **1994**, *59*, 6395.

[16] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155.

[17] K. C. Nicolaou, Y. L. Zhong, P. S. Baran, *J. Am. Chem. Soc.* **2000**, *122*, 7596.

[18] S. Hosztafit, C. Simon, S. Makleit, *Syn. Commun*. **1992**, *22*, 2527.

[19] C. Yuan, Y. Jin, N. C. Wilde, P. S. Baran, *Angew. Chem. Int. Ed.* **2016**, *55*, 8280.

[20] K. S. Feldman, B. R. Selfridge, *J. Org. Chem.* **2013**, *78*, 4499.

[21] H. A. J. Carless, O. Z. Oak, *J. Chem. Soc. Chem. Commun.* **1991**, *2*, 61.

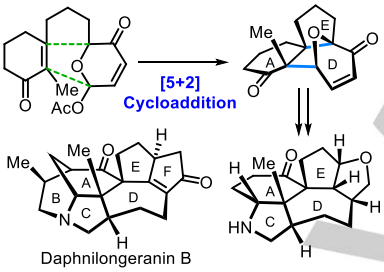
[22] K. Mizuki, K. Iwahashi, N. Murata, M. Ikeda, Y. Nakai, H. Yoneyama, S. Harusawa, Y. Usami, *Org. Lett.* **2014**, *16*, 3760.

[23] Y. Sütbeyaz, H. Seçen, M. Balci, *J. Chem. Soc. Chem. Commun.* **1988**, *19*, 1330.

Entry for the Table of Contents

Communication

A concise route to the ADE ring skeleton of calyciphylline A-type alkaloids was developed using the intramolecular [5+2] cycloaddition of an oxidopyrylium species bearing a tetrasubstituted olefin. This ring system containing a spiro ring and vicinal quaternary carbon centers was successfully constructed using a combination of acid and base to accelerate the reaction. The tricyclic ADE ring system was converted to the ACDE ring model through C–H oxidation and an aza-Wittig reaction.



H. Nakamura, M Kawakami, C. Tsukano, Y. Takemoto**

Page No. – Page No.

Concise construction of the ACDE ring system of calyciphylline A-type alkaloids via [5+2] cycloaddition