


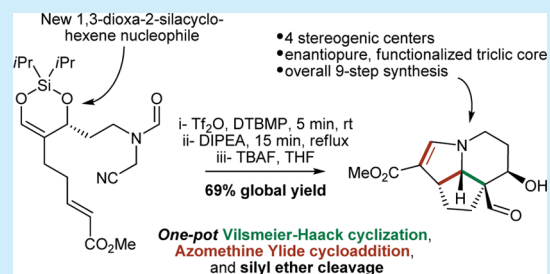
Short Approach toward the Nonracemic A,B,E Tricyclic Core of Calyciphylline B-Type Alkaloids

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 Supporting Information

ABSTRACT: A suitably functionalized tricyclic adduct containing the common A,B,E rings found in calyciphylline B-type alkaloids was obtained in nine linear steps. The key transformation features an efficient one-pot sequence of intramolecular Vilsmeier–Haack cyclization and azomethine ylide 1,3-dipolar cycloaddition in which three cycles, three new carbon–carbon bonds, and three stereocenters are formed, one being fully substituted. This work also demonstrates the first use of a chiral, nonracemic cyclic enol ether as an internal carbon nucleophile.



With over 300 structurally distinct structures identified to date, *Daphniphyllum* form one of the most diverse and unique family of polycyclic alkaloids. Their complex architectures along with their interesting biological activities have attracted attention for many years now, resulting in the development of several elegant and inventive synthetic approaches¹ triggered in great part by the pioneering work of Heathcock.² In 2003, Morita and Kobayashi isolated calyciphylline B from the leaves of *D. calycinum*, presenting a unique hexacyclic core (Figure 1).³

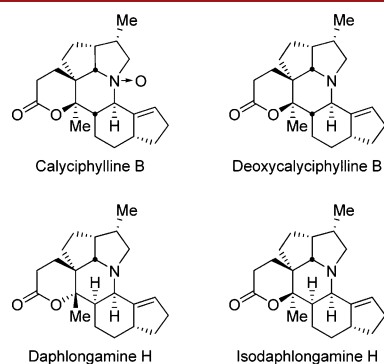
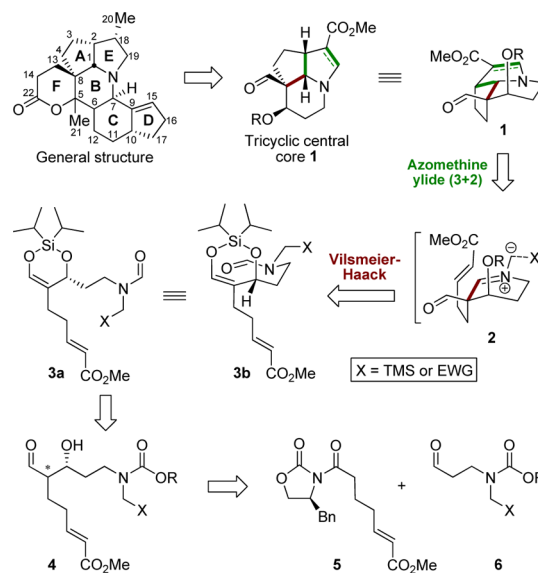


Figure 1. Representative calyciphylline B-type alkaloids.

Several other natural products possessing the same skeleton have since been identified. Surprisingly, synthetic efforts toward members of this family remained essentially nonexistent until recent work from the Hanessian group,⁴ ultimately leading to the synthesis of isodaphlongamine H.⁵

We envisaged preparing the tricyclic central core 1 of calyciphylline B-type alkaloids using a synthetic strategy developed by our group,⁶ namely, a sequence of intramolecular Vilsmeier–Haack reaction and azomethine ylide cycloaddition (Scheme 1).

Scheme 1. Retrosynthetic Analysis toward the Tricyclic Core of Calyciphylline B-Type Alkaloids



This key step would allow the formation of three of the six rings of calyciphylline B-type general structure in a single transformation. To achieve this sequence in a stereocontrolled fashion, our strategy relies on the use of a chiral cyclic silyl enol ether, namely, a 1,3-dioxo-2-silacyclohexene. The latter would act as the nucleophile in the Vilsmeier–Haack cyclization. The single stereocenter would force the adoption of the only possible reactive chair conformation 3b, locking the dipolarophile chain in the axial position. This specific arrangement would lead to a single diastereomer at C1, C2, and C8 during the formation of

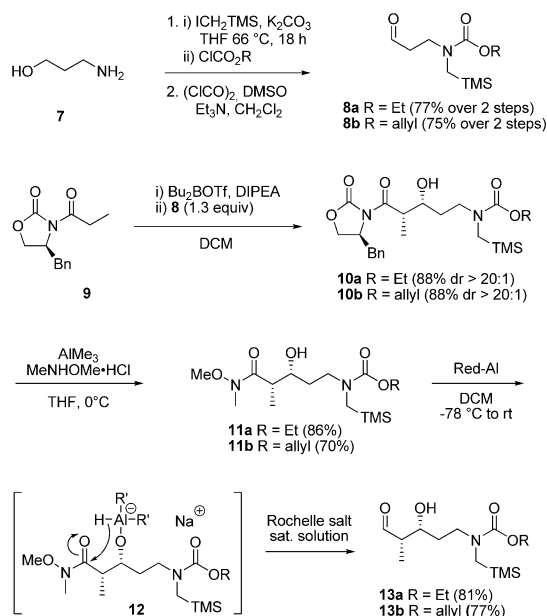
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the A, B, and E rings. Azomethine ylide **2** would be generated by desilylation ($X = \text{TMS}$) or deprotonation ($X = \text{electron-withdrawing group, EWG}$) of the corresponding iminium ion, itself obtained from the Vilsmeier–Haack cyclization initiated by activation of formamide **3**. The cyclic silyl enol ether should be obtained from β -hydroxyaldehyde **4**. However, special attention will be needed when setting reaction conditions to prevent any potential elimination of the hydroxyl group or retro-aldol reaction. Aldehyde **4** would be derived from an Evans aldol reaction between oxazolidinone **5** and aldehyde **6**.

The synthesis of 1,3-dioxo-2-silacyclohexene is poorly documented,⁷ and its use as a carbon-based nucleophile has not been investigated to date. To validate such a nucleophile in the Vilsmeier–Haack cyclization, we synthesized a model substrate lacking the dipolarophile chain that was replaced with a simple methyl group. The synthesis of model substrate **13a** started with alkylation of 3-aminopropanol (**7**) with iodomethyltrimethylsilane and then protection as a carbamate using ethyl chloroformate (Scheme 2).

Scheme 2. Synthesis of Model Substrate **13**



The resulting alcohol was oxidized under Swern conditions to give aldehyde **8a**. Evans aldol reaction with oxazolidinone **9** afforded alcohol **10a** with good diastereoselectivity.⁸ Transamidation toward Weinreb amide **11a** was performed smoothly without affecting the carbamate group.⁹ Standard reduction conditions using DIBAL-H failed to afford aldehyde **13a**.¹⁰ We believe that, after a rapid deprotonation of the free alcohol, the resulting $\text{O-Al}^i\text{Bu}_2$ complex hinders the amide to a point where reduction with an additional equiv of DIBAL-H can no longer occur. Switching to a reducing agent containing several hydrides was appealing: after the initial deprotonation, an aluminate complex such as **12** could deliver another hydride intramolecularly to the amide. The proximity of the hydride source to the amide group may become very important on more functionalized substrates bearing the dipolarophile branch to ensure a chemoselective reduction. Unfortunately, LiAlH_4 led to poor yields, mainly because of over reduction of the resulting aldehyde.¹¹ After a quick survey of reducing agents bearing only the two needed hydrides for initial deprotonation and intra-

molecular reduction, we turned our attention toward Red-Al. Gratifyingly, aldehyde **13a** was obtained in high yield.¹²

At this point, we were ready to install the 1,3-dioxo-2-silacyclohexene as the chiral nucleophile needed in the first step of the key reaction sequence, namely, the Vilsmeier–Haack cyclization. We chose dialkylsilyl bis(trifluoromethanesulfonate) reagents as they are commercially available and possess a good Lewis acidity. Indeed, after silylation of the free alcohol **13a**, we expected the resulting silicon monotriflate to act as an internal Lewis acid to promote enolization of the aldehyde in the desired geometry. Although di-*tert*-butylsilyl ditriflate led to no conversion (Table 1, entry 1), the less bulky diisopropyl

Table 1. Preparation of the 1,3-Dioxo-2-silacyclohexene

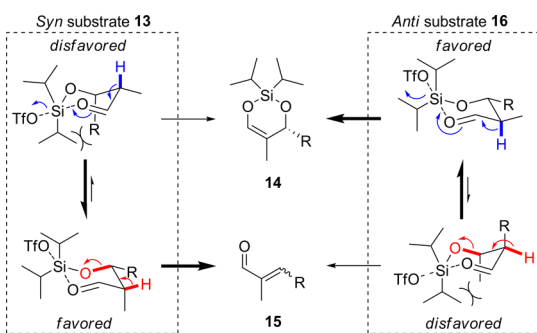
entry	R ¹	R ²	base	temp (°C)	yield (%)
1	Et	<i>t</i> -Bu	DIPEA	rt	0
2	Et	<i>i</i> -Pr	DIPEA	rt	17
3	Et	<i>i</i> -Pr	DIPEA	-40	51
4	Et	<i>i</i> -Pr	DIPEA	-78	25
5	Et	<i>i</i> -Pr	none	-40	0
6	Et	<i>i</i> -Pr	LDA	-40	0
7	Et	<i>i</i> -Pr	Et_3N	-40	32
8	Et	<i>i</i> -Pr	2,6-lutidine	-40	22
9	Et	<i>i</i> -Pr	DIPEA, DMAP	-40	27
10	all	<i>i</i> -Pr	DIPEA	-40	47
11 ^a	all	<i>i</i> -Pr	DIPEA	-40	72

^aFrom *anti* substrate **16** (cf. **13b**, β -Me).

equivalent furnished the expected silyl enol ether **14a**, albeit in poor yield (entry 2). Significant improvement was obtained when the reaction was run at -40 °C (entry 3). Lower temperature resulted in a slower reaction without any significant yield improvement (entry 4). Further investigation revealed that the base was required (entry 5). However, a strong base appeared to be too reactive (entry 6) and led to decomposition. DIPEA was the most suitable base (entry 4) as it led to yields higher than those of triethylamine or 2,6-lutidine (entries 7 and 8, respectively). The use of a pyridine catalyst (DMAP, entry 9) had no significant effect on the outcome of the reaction.

From the perspective of using the synthetic route described in Scheme 2 to access a substrate bearing the dipolarophile branch, we foresaw compatibility issues for the eventual ethyl carbamate cleavage. For this reason, we also tested the allyl carbamate as the nitrogen protecting group.^{13,14} The synthesis of allyl carbamate **13b** uneventfully followed the sequence described in Scheme 2. The corresponding 1,3-dioxo-2-silacyclohexene **14b** was obtained in approximately the same yield as that for product **13a** (Table 1, entries 3 and 10). A side product observed in all these silylation conditions was the corresponding unsaturated aldehyde **15**, arising from the elimination of the alcohol on substrate **13** (Scheme 3). A conformational analysis brought some insight on this side reaction. Indeed, when the *syn* substrate **13** is subjected to silylation, the O-silylated alcohol is presumed to intramolecularly activate the aldehyde as a six-membered ring complex. Two chairlike conformations are then possible: the top conformation exposes a severe steric interaction between the carbamate side chain (R) and one of the isopropyl on silicon,

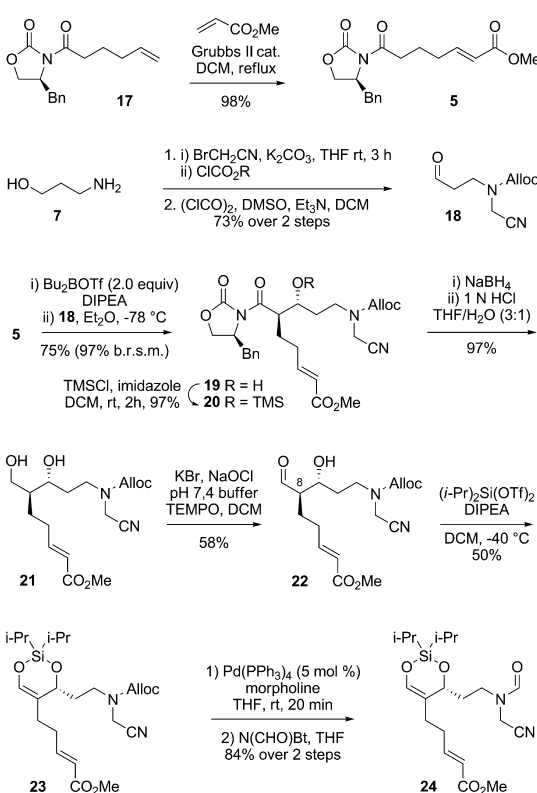
Scheme 3. Effect of Relative Configuration on the Formation of 1,3-Dioxa-2-silacyclohexene 14



thus favoring the bottom conformation. The latter has no proper alignment to allow enolization of the aldehyde, leading mainly to elimination product **15**. When the same rationale was applied to a substrate **16** presenting an *anti* relationship between the carbamate side chain (R) and the methyl in the six-membered ring complex, the top conformation should be favored. The latter is perfectly suited for enolization of the aldehyde, and the desired 1,3-dioxa-2-silacyclohexene **14** should now be favored. This was confirmed by preparing *anti* substrate **16**,^{15,16} and as expected, a remarkable yield increase was observed (Table 1, entry 11).

Having developed the chemoselective Weinreb amide reduction and the successful preparation of the sensitive 1,3-dioxa-2-silacyclohexene moiety, we were ready to synthesize the key cyclization precursor **25** (Scheme 4). A cross-metathesis performed on compound **17**¹⁷ with methyl acrylate led to the unsaturated ester **5**.¹⁸ The latter was then submitted to Heathcock aldol conditions with aldehyde **18** to afford the *anti* product **19** in 75% yield (97% based on recovered starting

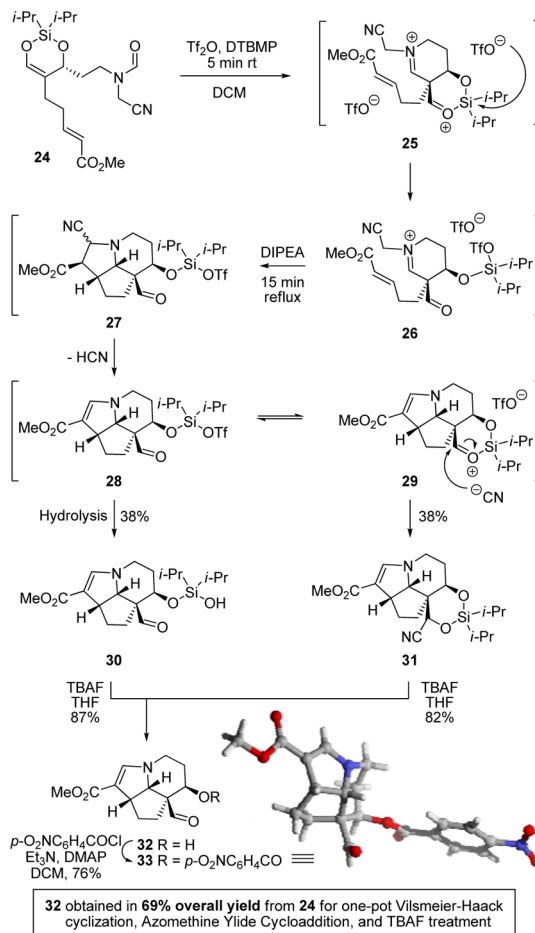
Scheme 4. Synthesis of Key Step Precursor 24



material.¹⁶ We chose here to use a cyano group instead of the TMS to later generate the azomethine ylide by deprotonation rather than by desilylation as it usually requires milder conditions.^{6a,19} The direct reduction of **20** proved to be more difficult than with model compound **13a**,²⁰ so we chose to protect the free alcohol with a TMS group, which was removed in the acidic quench of the subsequent reduction reaction, affording the diol **21** in essentially quantitative yields for these two steps. A chemoselective oxidation of the primary alcohol was then performed using catalytic TEMPO and sodium hypochlorite as co-oxidant.²¹ During this step, we observed an erosion of the diastereomeric ratio probably due to epimerization at the C8 position. However, this was inconsequential because the next step was the enolization to the cyclic silyl enol ether. Formation of the latter was performed using the conditions previously developed (see Scheme 2), albeit in lower yield for reasons that remain unknown. Deallyloxyacylation¹⁴ of **23** followed by immediate formylation using Katritzky reagent²² satisfyingly afforded key polycyclization precursor **24**.

Once submitted to amide activation conditions (1.1 equiv of Tf₂O and 1.1 equiv of DTBMP), the Vilsmeier–Haack cyclization proceeded cleanly and almost instantaneously to form iminium ion **25** (Scheme 5). When the reaction solution was transferred to a flask containing a refluxing solution of DIPEA (5.0 equiv) in dichloromethane, the cycloaddition reaction also occurred very rapidly.²³ To our delight, the excess of DIPEA employed in the azomethine ylide generation was sufficient to promote elimination of the cyanide. Two different

Scheme 5. Possible Reaction Pathways to 30 and 31²⁵



cycloadducts were obtained: the expected tricyclic aldehyde **30** and the tetracyclic silylated cyanohydrin **31**, in a 1:1 ratio. To explain the formation of these two products, we suspect a partial conversion of silyl triflate **28** to cyclic oxocarbenium ion **29**. The latter can be trapped by the cyanide generated during the elimination, leading to cyanohydrin **31**. Hydrolysis of the remaining silyl triflate **28** in the aqueous reaction quench would lead to aldehyde **30**. Gratifyingly, both **30** and **31** can independently be desilylated using TBAF to generate the tricyclic targeted product **32** in good yields. When the key Vilsmeier–Haack/cycloaddition sequence followed by TBAF treatment was run as a one-pot procedure, an excellent 69% overall yield of product **32** was obtained from substrate **24**. Relative configuration was secured by X-ray analysis of crystalline *p*-nitrobenzoyl derivative **33**²⁴ and was consistent with stereochemical analysis presented in Scheme 1 (see 3 to 1).

In conclusion, we described the preparation and the unprecedented cyclization of a chiral cyclic enol ether onto an activated formamide. The following one-pot intramolecular azomethine ylide generation and 1,3-dipolar cycloaddition generated a functionalized enantiopure tricyclic core obtained in as few as nine linear synthetic steps. This core will be used as a common intermediate toward the synthesis of various members of the calyciphylline B-type alkaloids family. Methods to implement the remaining C, D, and F rings are currently under investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.7b01566](https://doi.org/10.1021/acs.orglett.7b01566).

Experimental procedures, characterization data, and copies of the ¹H and ¹³C NMR spectra for all new compounds (PDF)

Single-crystal X-ray data for **33** (CIF)

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Notes

The authors declare no competing financial interest.

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(23) Longer reaction times for that step provided the same products **30** and **31** albeit in a lower combined yield (50%).

(24) An ORTEP representation of **33** is found in the Supporting Information. Crystallographic data for this compound have been deposited with the Cambridge Crystallographic Data Centre (CCDC no. 1548926). Coordinates can be obtained at <http://www.ccdc.cam.ac.uk/deposit>.

(25) For representation of X-ray structure, see: *CYLview*, 1.0b; Legault, C. Y., Université de Sherbrooke, 2009 (<http://www.cylview.org>).