Published in final edited form as:

Tetrahedron Lett. 2015 June 3; 56(23): 3503–3506. doi:10.1016/j.tetlet.2015.01.121.

Toward the ABCD Core of the Calyciphylline A-Type Daphniphyllum Alkaloids: Solvent non-Innocence in Neutral Aminyl Radical Cyclizations

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Abstract

The *Daphniphyllum* alkaloids remain an attractive target in the synthetic community because of their unique framework and promising biological activities. We have shown that the ABC core of the calyciphylline A-type alkaloids can be rapidly accessed via the tandem cyclization of a neutral aminyl radical with a polarized cyclic olefin. Deuterium labeling experiments and reactions omitting a tin hydride reagent suggest that the solvent is the major source of the terminating hydrogen atom in the cyclization cascade. Incorporation of an internal alkyne in the radical pathway was tolerated in the reaction, and it provided the necessary atoms to enable completion of the D ring of the calyciphylline A-type alkaloids.

The *Daphniphyllum* alkaloids are a structurally diverse family of natural products native to evergreen trees and shrubs in Japan and China.¹ Yagi and coworkers first reported these molecules in 1909,² but their structures were not elucidated until decades later.³ Members of this family of alkaloids exhibit biological activities ranging from cytotoxicity to enhanced expression of nerve growth factor.¹ Meanwhile, these compounds boast a unique framework of densely functionalized bridged and fused ring systems (Figure 1). The structural complexity and observed bioactivities of the *Daphniphyllum* alkaloids have inspired numerous efforts toward their synthesis.^{4,5,6}

We recently reported an efficient approach to the ABC core of the calyciphylline A and daphniphyllidin A-type alkaloids featuring a tandem radical cyclization initiated at nitrogen in only 4 steps and 61% overall yield from known lactone **1**, which is accessible in 3 steps from (+)-carvone (Scheme 1).⁴ This strategy utilized a neutral dialkyl aminyl radical⁷ derived from chloroamine **2** to access tricyclic core **3**.⁸ This cyclization was the first to employ a neutral aminyl radical in a cyclization with an enone, and represented one of two reported 6-*exo* cyclizations of aminyl radicals.^{7b,c} Based on these results, we postulated that

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Supplementary materials

Experimental procedures and spectroscopic data (¹H-NMR, ¹³C-NMR, IR, HRMS, and optical rotation) are provided for all new compounds. This material is available free of charge on the Internet.

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the olefin undergoing cyclization should be polarized to enable efficient reactions with neutral aminyl radicals.

During the course of our optimization of the cyclization of chloroamine **2**, we noticed a significant decrease in the efficacy of cyclizations in benzene vs. toluene.⁴ Before investigating internally substituted alkynes, which might more readily facilitate construction of the D ring, we sought a better understanding of the role of the solvent in the cyclization. At lower temperatures, chlorine atom-transfer side products are observed, and the isolated yield of **3** is lower.⁴ Meanwhile, in benzene, increased amounts of reduction products are observed. We also observed products of addition to benzene itself. The potential for alkyl radicals to participate in chain-terminating addition reactions with arenes is well established.^{7b,9} The observed chain termination is due to the inability of cyclohexadienyl radicals to efficiently abstract a hydrogen atom from Bu₃SnH,⁹ and it can be ameliorated by the addition of PhSeH or PhSeSePh.¹⁰ While this mode of reactivity is expected to be more problematic for benzene than toluene,⁹ we also considered that toluene might serve as an H-atom donor in the reaction, given its ability to generate a resonance-stabilized benzylic radical (PhCH₂•). This species would participate mainly in chain-terminating pathways, such as dimerization.⁹ The fact that our reaction performed best in the presence of 0.5 equiv AIBN was supportive of this possibility. High loadings of initiator generally indicate that the radical chain mechanism is either very short or is not propagated.⁹

Thus, we generated a working hypothesis for the cyclization mechanism to guide our further studies (Scheme 2). Upon thermolysis of AIBN and reaction with tributyltin hydride, the resultant stannyl radical would abstract a chlorine atom from the substrate (**2**, BDE_{N-Cl} ≈ 67 kcal/mol) generating neutral dialkyl aminyl radical **4** and Bu₃SnCl (BDE_{Sn-Cl} ≈ 97 kcal/mol).¹¹ Subsequent 6-*exo*-trig cyclization occurs with no observed [1,5]-H• transfer side reactions, generating tertiary radical **5**. Upon 5-*exo*-dig cyclization with the pendant alkyne, a highly reactive vinylic radical (**6**) is generated.¹² Finally, H• abstraction from either toluene (BDE_{C-H} ≈ 88 kcal/mol)¹³ or Bu₃SnH (BDE_{Sn-H} ≈ 78 kcal/mol)¹¹ affords the product (**3**). The resulting stannyl radical can propagate the radical chain whereas abstraction from the solvent would largely result in chain termination, as described above.

To probe the last step of this mechanism, we subjected terminal alkyne **2** to *d*₈-toluene and/or varying amounts of Bu₃SnD (Table 1).¹⁴ In the absence of a D• source, a relative isotope distribution of ~100:15:1 is observed for **3** (entries 1 and 2), consistent with the calculated natural isotope abundance of the non-labeled substrate (100:14.7:1.2). When tributyltin deuteride is employed in the presence of toluene, the intensity of the 207 m/z and 208 m/z peaks increase, indicating a small amount of deuterium incorporation (entry 3). A larger amount of D is incorporated in the reaction employing Bu₃SnH and *d*₈-toluene (entry 4). As a control, both Bu₃SnD and *d*₈-toluene were employed. This adjustment resulted in a shift of the main isotope, as expected, but significantly lowered the yield (entry 5). Observation of a peak at 206 m/z was unexpected in this case, but it may arise from adventitious H-atom donors such as the C–H bond α to nitrogen in the substrate or product,¹⁵ the C–H bond α to Sn in Bu₃SnD, or partially labeled solvent. Taken together, these results support a mechanism where the final H• transfer occurs more often through reaction of radical **6** with toluene than with Bu₃SnH.

We expected that this competition could be adjusted by controlling the concentration of Bu₃SnH in solution. We tested this hypothesis by conducting the reaction in the presence of Bu₃SnD, without slow addition (entry 6). The yield decreases in this case, but the amount of D incorporation increases as compared with entry 3. Additionally, a slow addition of 4.0 equiv Bu₃SnD, rather than 2.0 equiv, led to a similar result (entry 7). The increased D incorporation observed for these reactions was consistent with our expectations that increased solution concentrations of Bu₃SnD would result in more D-atom transfer.

We were interested in probing the role of the solvent as a terminal H• donor further, so we considered the reaction of the substrate in the absence of any tin hydride. In this case, the isobutyronitrile radical (•CMe₂CN) could either directly abstract a chlorine atom from **2**, or it could abstract H• from solvent (H–CMe₂CN BDE_{C–H} ≈ 91 kcal/mol),¹¹ likely leading to either Cl-atom abstraction¹⁶ or termination of the radical chain. This modification drastically alters the efficacy of the cyclization, resulting in only 9% isolated yield of the desired product and substantial amounts of unidentified by-products (Table 2, entry 1). Using *o*-xylene, which has a slightly lower BDE_{C–H} (~87 kcal/mol),¹¹ improves the yield to 30% (entry 2). In the case of ethylbenzene (BDE_{C–H} ≈ 85 kcal/mol),¹¹ the desired product is isolated in 42% yield (entry 3). Finally, when cumene (isopropylbenzene, BDE_{C–H} ≈ 83–84 kcal/mol)¹¹ is employed as the solvent, tricycle **3** is isolated in 49% yield (entry 4). These results serve as compelling evidence for the hypothesis that the solvent serves as an important H-atom donor in our cyclization reactions. Additionally, the extent to which the solvent participates in the reaction can be adjusted by tuning the BDE. In the case of entries 2–4, N–Cl reduction (i.e. abstraction of H• by radical **4**) is observed via GCMS during the reaction.¹⁷ The presence of this species increases (qualitatively) as the BDE decreases. This relationship is consistent with an N–H BDE near 88 kcal/mol.¹¹ A larger energy gap between the N–H bond and the benzylic C–H bond correlates with increased formation of reduction products. No desired product (**3**) was isolated when the reaction was conducted in either benzene (80 °C) or trifluoromethylbenzene. In benzene, some chlorine atom transfer product was observed by LCMS.

H-atom donation from toluene and other solvents has been observed previously. The Curran group has proposed H-atom abstraction from cyclohexane.¹⁸ Sevéant and co-workers report H-atom transfer from acetonitrile and DMSO to a variety of aryl radical species with rate constants of ~10⁸ – 10⁹ M•s^{–1} and *k_H*/*k_D* values of 6–14.¹⁹ This large kinetic isotope effect is qualitatively consistent with our observations in Table 1. Slower D• transfer results in more side reactions of intermediate radical species, ultimately lowering the isolated yield of tricycle **3**. The estimated rate constant for the reaction of Ph• with H–CH₂Ph is 3 × 10⁶ M•s^{–1}.²⁰ Taking Ph• as a model for the vinylic radical **6** provides a rough estimate of the rate of the final H• abstraction. Given the slow cyclization rates estimated by Newcomb and co-workers for neutral aminyl radicals (*k_c* = 4 × 10⁴ s^{–1} at 50 °C), as well as high relative rates for trapping with Bu₃SnH vs. cyclization (*k_T*/*k_c* = 23 ± 2 at 50 °C),²¹ the competitive formation of reduction products in the tin-free reactions in Table 2 is unsurprising.

With these observations in hand, we focused our efforts toward the synthesis of daphniyunnine C (**7**),²² a calyciphylline A-type alkaloid (Scheme 3). We envisioned that an elaborated core structure containing the carbons needed to construct the D ring could be

accessed using our cyclization reaction. Disconnection of the E and F rings of **7** revealed tetracyclic core **8**, which could potentially be accessed through a variety of transformations employing pendant ketone **9**. A potential masking group for this ketone is a 1,1-disubstituted olefin. Tricycle **10** could therefore serve as a viable intermediate in the synthesis of daphniyunnine C. Tricycle **10** would arise from a tandem intramolecular cyclization of a neutral aminyl radical generated from homolysis of the N–Cl bond in carvone derivative **11**.

At this point, we turned our attention to the synthesis of alkynyl retron **11**. We envisioned assembling chloroamine **11** as with propargyl substrate **2**.⁴ Thus, we needed to generate propargyl amine derivative **15** (Scheme 4). *N*-Propargylphthalimide (**12**) and 1-chloro-2-methyl-propene (**13**) were joined via copper-mediated cross coupling, providing eneyne **14** in 96% yield.²³ Subsequent phthalimide cleavage provided free amine **15** in 76% yield.

Reductive amination of lactol **1** with amine **15** provided secondary amine **16** in 54% yield (Scheme 5). Chlorination and oxidation were performed in a single reaction vessel to afford *N*-chloroenone **11** in up to 96% yield, depending on the reaction scale.²⁴ Tandem radical cyclization under our previously optimized conditions afforded tricyclic amine **10** in 58% yield.²⁵ In the absence of Bu₃SnH, the product is isolated in 12% yield. The product is a 1:1 mixture of olefin isomers, as was expected owing to the rapid rate of inversion of vinylic radicals at high temperatures.²⁶

In summary, we have established that the solvent plays a major role in the outcome of our tandem cyclization of a neutral dialkylaminyl radical with a cyclic enone. In reactions where tributyltin hydride is present, both the stannane and the solvent serve as terminal H-atom donors for the cyclization cascade. However, because we observed greater incorporation of D in the presence of *d*₈-toluene with Bu₃SnH, it is likely that the solvent is the primary H-atom donor in our cyclizations. This conclusion is further corroborated by the ability to execute the reaction in the absence of any tin hydride source with yields inversely proportional to the benzylic C–H BDE. We have also established that internal alkynes are effective in the cyclization, and rapid inversion of the vinylic radical leads to a 1:1 ratio of olefin isomers. Efforts to elaborate this advanced intermediate to daphniyunnine C are ongoing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors would like to thank the National Institutes of Health (R00-GM097095, R00-GM097095-S1) and Wayne State University for generous financial support. We also gratefully acknowledge the staff of the WSU Lumigen Instrument Center for spectroscopic support.

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Figure 1.
Representative *Daphniphyllum* alkaloids.

Scheme 1.

Cyclization of a neutral dialkyl aminyl radical to access the ABC core.

Scheme 2.

Working hypothesis for the major mechanistic pathway for the cyclization (BDEs from Refs 11 and 13).

Scheme 3.
Strategies to access an elaborated ABC-core of the calyciphylline A-type *Daphniphyllum* alkaloids.

Scheme 4.

Synthesis of a propargylamine derivative incorporating a masked ketone moiety.

Scheme 5.

Assembly of the ABC ring system bearing all carbon atoms needed for the D ring.

Deuterium incorporation studies supporting the hypothesis that toluene donates an H-atom during the cyclization.

Table 1

entry	solvent	stannane	(equiv)	isolated yield (%)	observed MS intensities (m/z) ^c		
					206	207	208
1	PhMe	–	–	9	100	15	1
2	PhMe	Bu ₃ Sn–H	2.0	74	100	15	1
3	PhMe	Bu ₃ Sn–D	2.0	66	100	32	5
4	<i>d</i> ₈ –PhMe	Bu ₃ Sn–H	2.0	46	100	93	15
5	<i>d</i> ₈ –PhMe	Bu ₃ Sn–D	2.0	26	17	100	17
6 ^b	PhMe	Bu ₃ Sn–D	2.0	54	100	51	7
7	PhMe	Bu ₃ Sn–D	4.0	39	100	54	8

^a A solution of AIBN and stannane (as relevant) was added dropwise to a heated solution of the substrate in solvent over 1 h, followed by stirring until 2 is fully consumed.

^b The reagents were added all at once at the beginning of the reaction.

^c Calculated m/z for C₁₃H₁₉NO: 205 (100.0%), 206(14.7%), 207(1.2%), for C₁₃H₁₈DNO: 206 (100.0%), 207 (14.7%), 208 (1.2%).

Table 2

Solvents with appropriate benzylic BDEs can serve as H-atom donors in the cyclization with no added stannane.

entry	solvent	BDE (kcal/mol)	isolated yield (%)
1	Ph-Me	88	9
2	<i>o</i> -xylene	87	30
3	Ph-Et	85	42
4	Ph-(<i>i</i> -Pr)	83	49

^a AIBN was added at the start of the reaction, then the reaction was heated for 5 h.