

Synthesis of (+)-Luzofuran and (–)-Ancistrofuran

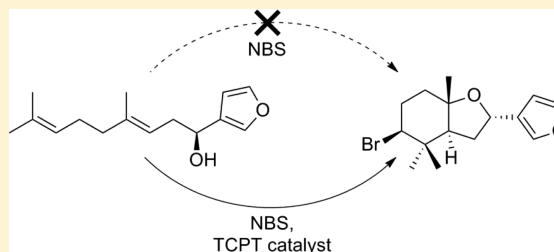
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S Supporting Information

ABSTRACT: The first synthesis of the furan-containing snyderane, (+)-luzofuran, is reported. The key step in this approach was an electrophilic brominative cyclization, which was accomplished using a nucleophilic *N*-heterocycle-flanked phosphoramidite catalyst in combination with the common laboratory reagent *N*-bromosuccinimide.



INTRODUCTION

More than 750 bromine-containing compounds have been isolated from *Laurencia* species of marine algae, making them the single largest source of brominated natural products yet known.¹ While there have been a vast number of innovative approaches to access the most abundant halogenated natural products, the C₁₅-acetogenins, other classes have served less often as synthetic targets. Take, for instance, the second largest family of halogenated sesquiterpenes isolated from *Laurencia*,¹ the snyderanes (Figure 1). Characterized by a bromocyclohexane ring with halogen incorporation at C10, this family of compounds includes members with acyclic side chains (1 and 2) as well as a variety of ring fusions, including 6,5-, 6,6- and 6,7-fused compounds (3–6). Their biogenesis likely involves an asymmetric brominative cyclization of nerolidol (7) followed by postcyclization modifications.²

Despite the synthetic attractiveness of such a simple approach, the enantioselective electrophilic bromination of unactivated alkenes remains a major challenge in organic chemistry.^{3–10} For instance, no catalytic methods exist for the enantioselective electrophilic brominative cyclization of polyenes.^{11–13} Several strategies have been employed to circumvent this limitation,^{14–18} and there is one report of a stoichiometric brominating reagent capable of delivering moderate levels of enantioselectivity.¹⁹ It is therefore unsurprising that only a handful of reports utilizing electrophilic brominative approaches to the snyderanes have been disclosed.

The parent α - and β -snyderols (1 and 2) have been synthesized in ca. 2% yield by an electrophilic bromination of nerolidol (7).^{20,21} A similar strategy was used to synthesize the 6,6-fused 8-bromo-*epi*-capirrapin oxide (4) in a more palatable 30% yield.²¹ An electrophilic brominative strategy to the 6,7-fused compound aplystatin (5)²² gave the desired compound in ca. 2% yield. Consequently, total syntheses of aplystatin (5)^{23,24} and palisadin (6)²⁵ using tin- and mercury-based methods, respectively, have been reported. To the best of our knowledge, there are no reports detailing the synthesis of 6,5-

fused snyderanes by electrophilic bromination or any other means. This paper details our first foray into the chemistry of snyderane natural products, the total synthesis of the 6,5-fused snyderane luzofuran (3).

Luzofuran (3) was isolated from an Okinawan collection of the red alga *Laurencia luzonensis* by Kuniyoshi and co-workers in 2005.²⁶ With only 3.8 mg being isolated from 1.1 kg of the predried alga, it is unsurprising that there are as yet no literature reports regarding any biological activities of the compound.

We elected to employ a biomimetically inspired brominative cyclization to access the 6,5-fused ring system. We anticipated that the electrophilic brominating reagent could be generated in situ from an unreactive but economical bromonium source and engage in a diastereoselective cyclization. Our approach was inspired by two considerations: (1) the seminal work of Ishihara and co-workers who developed a *stoichiometric* brominating reagent¹⁹ and (2) the highly conserved histidine and arginine-rich active site of the vanadium haloperoxidase class of enzymes that are responsible for in vivo brominative cyclizations.^{2,27–29} We sought to combine the attributes from both systems to give a catalytically active molecule that could function as a bromonium shuttle in the manner depicted in Figure 2.

Phosphoramidites chelate to metal centers exclusively via the tetrahedral phosphorus atom,³⁰ and they likewise protonate on phosphorus,³¹ so a BINOL-based phosphoramidite seemed the most appropriate molecule to function as a bromonium shuttle. The use of phosphorus(III) in this catalytic role has precedent in iodolactonizations.³² To this end, we recently reported the development of a library of *N*-heterocycle-substituted phosphoramidites.^{33,34} The required balance between oxidative stability versus catalytic activity led us to settle upon the 2,4,5-trichlorophenyltriazole (TCPT)-flanked catalyst 8 for this work (Figure 3).

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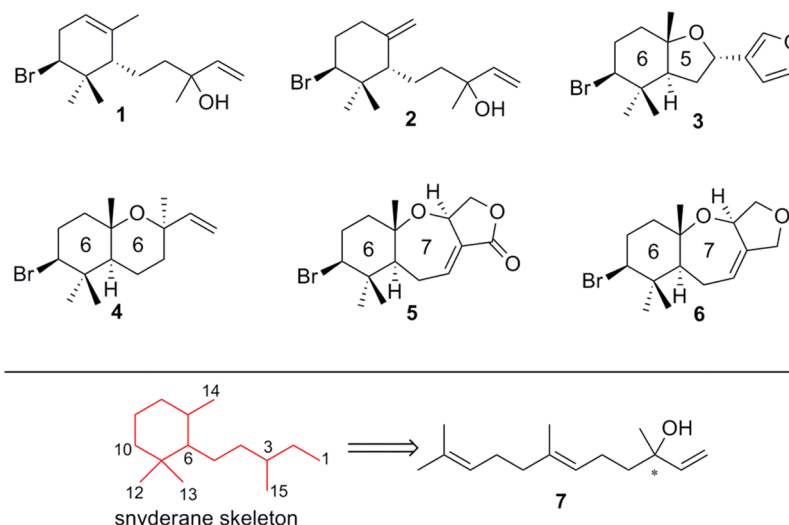


Figure 1. Examples of snyderane natural products.

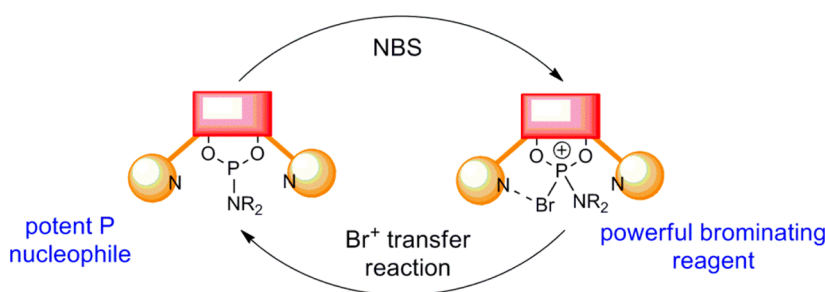


Figure 2. Proposed in situ activation of a bromonium source with a phosphoramidite.

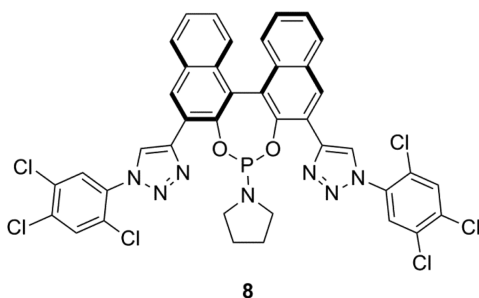


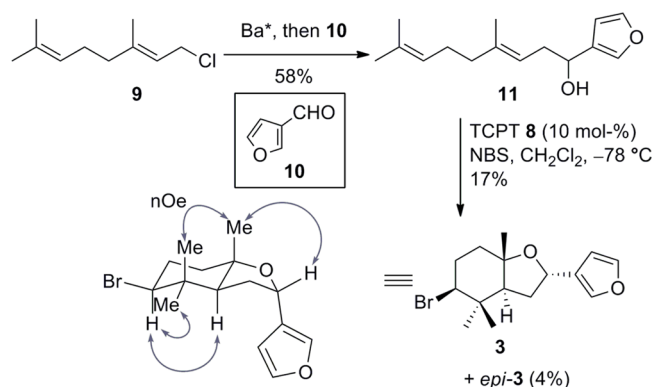
Figure 3. 2,4,5-Trichlorophenyltriazole-flanked catalyst 8 (TCPT).

RESULTS AND DISCUSSION

As shown in Scheme 1, our synthesis began with the organometallic union of the geranyl fragment **9** and the furan fragment **10**. Organobarium reagents are well-known to give extremely high levels of α -selectivity in reaction with aldehydes,^{35–37} and polyene-containing organobarium reagents can be made with complete retention of alkene geometry.³⁸ As such, reaction of geranyl chloride **9** with activated barium gave an organobarium reagent, which reacted with 3-furancarboxaldehyde **10** to give alcohol **11**. Treatment of **11** with 1 equiv of the cheap and readily available *N*-bromosuccinimide (NBS) and a catalytic amount of TCPT **8** furnished (\pm)-luzofuran (**3**) in 17% yield and (\pm)-4-*epi*-luzofuran (*epi*-**3**) in 4% yield.³⁹

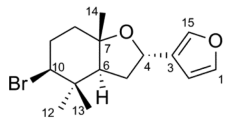
The relative stereochemistry of synthetic (\pm)-luzofuran (**3**) was assigned on the basis of the NOE enhancements between the hydrogens shown in Scheme 1 (see the Supporting

Scheme 1. Synthesis of (\pm)-Luzofuran (**3**)



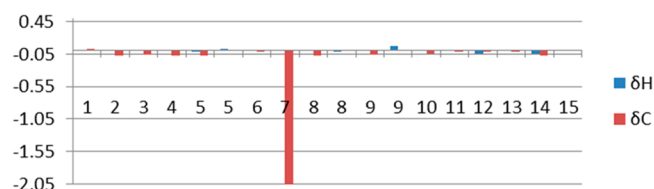
Information), which necessitates the relative configuration depicted. This is in excellent agreement with Kuniyoshi's assignment of the natural product stereochemistry.²⁶ However, a comparison of the ^1H and ^{13}C NMR shifts for naturally occurring luzofuran and our synthetic (\pm)-luzofuran revealed an anomaly (Table 1).

As depicted graphically in Figure 4, the ^1H NMR shifts were in almost perfect agreement, differing by no more than 0.08 ppm. Similarly, the ^{13}C NMR shifts differed by no more than 0.08 ppm with the exception of C7. At that center there was a marked difference between our observed chemical shift (80.15 ppm) and the reported value (78.1 ppm). We could not easily reconcile this unexpected outcome with the NOE data shown in Scheme 1.

Table 1. NMR Comparison of Synthetic and Isolated (\pm)-Luzofuran


(\pm)-3

carbon no.	reported ²⁶		synthetic		differences	
	δ H	δ C	δ H	δ C	Δ H	Δ C
1	7.39	143.5	7.38	143.47	0.01	0.03
2	6.32	108.4	6.32	108.47	0.00	-0.07
3		128.7		128.76		-0.06
4	5.10	70.4	5.08	70.47	0.02	-0.07
5	1.80	32.7	1.81	32.77	-0.01	-0.07
5	2.30		2.27		0.03	0.00
6	1.70	55.1	1.70	55.12	0.00	-0.02
7		78.1		80.15		-2.05
8	1.60	39.5	1.59	39.58	0.01	-0.08
8	1.90		1.91		-0.01	0.00
9	2.10	32.6	2.08	32.66	0.02	-0.06
9	2.35		2.27		0.08	0.00
10	3.95	65.5	3.95	65.55	0.00	-0.05
11		38.7		38.71		-0.01
12	1.01	30.3	1.05	30.32	-0.04	-0.02
13	0.99	17.0	0.98	17.01	0.01	-0.01
14	1.21	20.3	1.25	20.37	-0.04	-0.07
15	7.36	138.9	7.35	138.90	0.01	0.00

Figure 4. Chemical shift comparison between natural and synthetic (\pm)-luzofuran (3). δ H or δ C = [reported shift]–[observed shift] (ppm).

We therefore performed a *J*-value comparison using the reported data,²⁶ our observed values, and those predicted for the low energy conformations of all diastereomers about the luzofuran core (see the Supporting Information).⁴⁰ We anticipated that any alteration in the chemical environment of

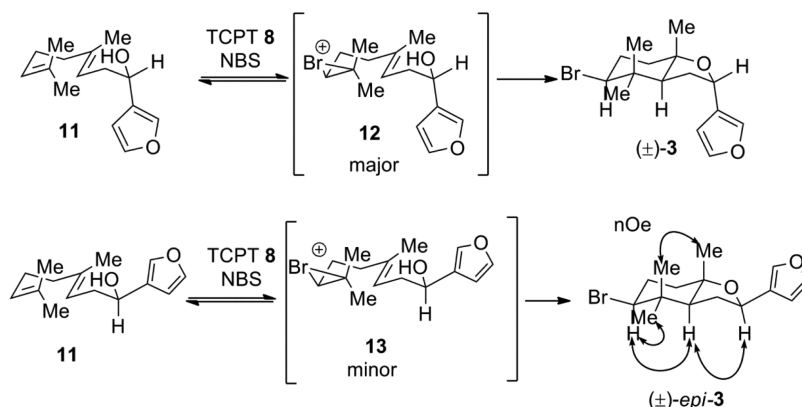
C7 would affect the ring conformation such that the coupling constants around the bicyclic structure would be perturbed. The diagnostic signal for the hydrogen appended to C4 was most useful for monitoring this process. Of the available possibilities (see the Supporting Information), the only diastereomer that had matching (predicted) coupling constants and that could possess the observed NOE interactions was the (4*S**,6*S**,7*S**,10*S**) isomer. This supported our assignment of the relative stereochemistry of (\pm)-luzofuran 3.⁴¹ Unambiguous confirmation of the relative stereochemistry was secured by conversion of 3 (and *epi*-3) into known compounds (vide infra).

The structure of the minor product, (\pm)-*epi*-luzofuran (*epi*-3) differs from the natural product at C4 only (Scheme 2). The 4:1 diastereomeric ratio of the products may reflect a Stork–Eschenmoser scenario in which cyclization occurs more readily when the acyclic precursor is in the appropriate conformation.^{42,43} Concerted cyclizations of this fashion have been proposed for other snyderanes.^{44,45} Although a single enantiomer of TCPT 8 was employed in the cyclization, the production of a racemate convinced us that the level of diastereoselection was substrate rather than catalyst-controlled, and that the ratio of products reflected the thermodynamic preference for the furyl unit to be pseudoaxial, as in 12, rather than pseudoequatorial as in 13. The most direct way to probe this hypothesis was to generate the cyclization precursor as a single enantiomer and measure the diastereomeric ratio of the ensuing product mixture.

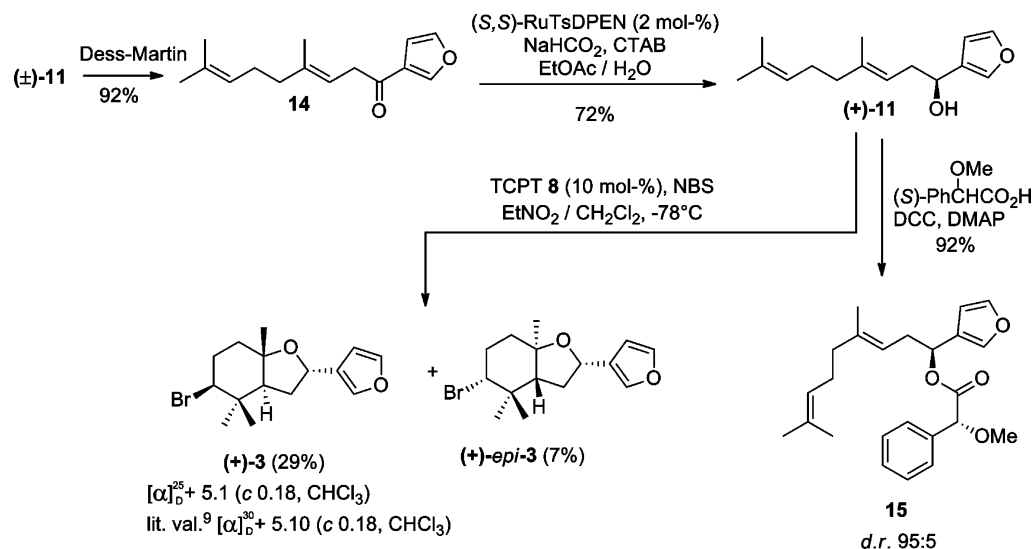
The enantioselective synthesis of (+)-luzofuran (+)-3 required the corresponding (*S*)-configured alcohol (+)-11. We anticipated that this could be generated by an enantioselective reduction of the corresponding ketone 14 (Scheme 3). As such, the racemic alcohol 11 was oxidized with the Dess–Martin periodinane to give 14.^{46,47} Enantioselective transfer hydrogenation with Noyori's (*S,S*)-RuTsDPEN catalyst proceeded in excellent yield.⁴⁸ The enantiomeric ratio was determined by ¹H NMR analysis of the corresponding *O*-methyl mandalate 15 to be 95:5.

Compound (+)-11 was treated with 1 equiv of NBS and a catalytic amount of TCPT 8 to furnish (+)-luzofuran (+)-3 in 29% yield and (4*S*,6*R*,7*R*,10*R*)-*epi*-luzofuran (+)-(*epi*-3) in 7% yield. Comparison of product ratio of luzofuran and 4-*epi*-luzofuran revealed that the cyclization was indeed immune to the absolute stereochemistry of the C4 center, ruling out a matched, mis-matched catalyst–substrate explanation for the observed 4:1 product ratio. Rather, that unaltered product ratio

Scheme 2. Stork–Eschenmoser-Type Cyclization



Scheme 3. Synthesis of (+)-Luzofuran (+)-3.



lends weight to the hypothesized Stork–Eschenmoser cyclization depicted in Scheme 2.

The value of optical rotation for this synthetic sample of luzofuran was identical in both magnitude and direction to that reported for the natural product. This necessitates the absolute stereochemistry of naturally occurring luzofuran to be (4*S*,6*S*,7*S*,10*S*). Final confirmation of the relative and absolute stereochemistry of the products was attained by conversion into the known compounds (±)-*epi*-ancistrofuran **16** and (–)-ancistrofuran **17**.

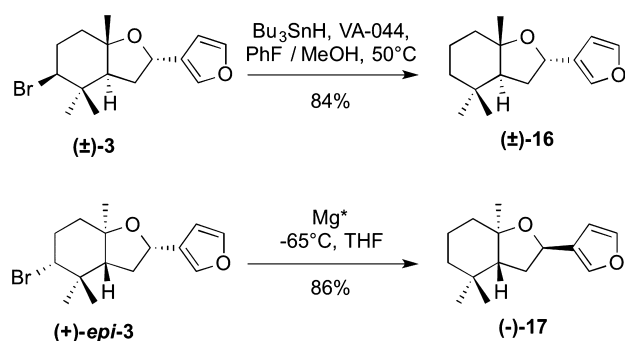
Ancistrofuran was isolated from the defensive secretions of the West African termite *Ancistrotermes cavithorax* by Baker, Evans and co-workers.⁴⁹ A combination of spectroscopic techniques and chemical derivatization was employed to elucidate the gross structure of ancistrofuran. Several total syntheses have subsequently confirmed the relative stereochemistry of the natural product, and although the absolute stereochemistry remains undetermined both enantiomers of ancistrofuran have been synthesized.^{50–53}

As depicted in Scheme 4, radical-mediated debromination of (±)-luzofuran (±)-**3** gave (±)-*epi*-ancistrofuran (±)-**16**. Employing the same protocol on (4*S*,6*R*,7*R*,10*R*)-*epi*-luzofuran (*epi*-**3**) gave (–)-ancistrofuran, but the sample was contaminated with traces of an inseparable byproduct. We were pleased to find that debromination of (4*S*,6*R*,7*R*,10*R*)-*epi*-luzofuran (*epi*-**3**) with activated magnesium smoothly gave (–)-ancistrofuran (**17**) in good yield.^{49,50}

As shown in Table 2 and Table 3, comparison of the NMR chemical shifts of **16** and **17** with

Table 2. NMR Comparison of (–)-Ancistrofuran

carbon no.	reported ⁵⁴		synthetic		differences	
	δH	δC	δH	δC	ΔH	ΔC
1	7.36	143.1	7.37	143.1	–0.01	0.0
2	6.37	109.1	6.38	109.1	–0.01	0.0
3		129.3		129.3		0.0
4	4.91	71.6	4.91	71.6	0.00	0.0
5	2.19	32.9	2.20	32.9	–0.01	0.0
5	1.97–1.32	32.9	1.80	32.9		0.0
6	1.97–1.32	57.4	1.63	57.4		0.0
7		81.0		81.0		0.0
8	1.24–1.16	40.8	1.26–1.94	40.9		–0.1
8	1.97–1.32	40.8	1.26–1.94	40.9		–0.1
9	1.97–1.32	33.2	1.26–1.94	33.2		0.0
9	1.97–1.32	33.2	1.26–1.94	33.2		0.0
10	1.97–1.32	39.1	1.26–1.94	39.2		–0.1
10	1.97–1.32	39.1	1.26–1.94	39.2		–0.1
11		31.4		31.5		–0.1
12	0.98	23.4	0.99	23.4	–0.01	0.0
13	0.86	21.3	0.87	21.4	–0.01	–0.1
14	1.13	20.4	1.14	20.5	–0.01	–0.1
15	7.36	138.8	7.37	138.8	–0.01	0.0

Scheme 4. Synthesis of (±)-*epi*-Ancistrofuran (**16**) and (–)-Ancistrofuran (**17**)

the literature values showed excellent agreement. The successful synthesis of (±)-*epi*-ancistrofuran (±)-**16** and (–)-ancistrofuran (**17**) confirms the relative stereochemistry of *epi*-luzofuran (*epi*-**3**) and luzofuran (**3**).

Our attention then turned to gaining a mechanistic understanding of how the TCPT catalyst (**8**) affects the brominative cyclization. The importance of the catalyst structure was illustrated by the observations that are summarized in Scheme 5. First, the cyclization of substrate **11** did not proceed in the absence of TCPT (**8**). Second, attempted cyclization using a phosphine catalyst was unsuccessful. Third, cyclization with a catalytic loading of a BINOL–phosphoramidite lacking only the pendant *N*-heterocycles (MorPhos) was completely ineffective. Even when a

Table 3. NMR Comparison of (\pm)-*epi*-Ancistrofuran

carbon no.	reported ⁵¹	synthetic	differences
	δ H	δ H	Δ H
1	7.38	7.35–7.37	–0.02
2	6.36	6.34	–0.02
4	5.06	5.03	–0.03
5	1.4–2.3	2.16	
5	1.4–2.3	1.3–1.95	
6	1.4–2.3	1.3–1.95	
8–10	1.4–2.3	1.3–1.95	
8–10	1.4–2.3	1.3–1.95	
8–10	1.4–2.3	1.3–1.95	
8–10	1.4–2.3	1.3–1.95	
8–10	1.4–2.3	1.3–1.95	
12	0.94	0.93	–0.01
13–14	0.88	0.89	0.01
13–14	1.20	1.16	–0.04
15	7.38	7.35–7.37	–0.02

stoichiometric quantity of MorfPhos was employed for extended reaction times (3 h), the reaction was extremely low yielding (<5%). And finally, in line with Snyder's observations, the unprotected alcohol of compound **11** rendered it incompatible with the potentially electrophilic reagent BDSB.^{11,12}

Quantum mechanical calculations at the M06-2X/6-311+G-(3df,2p)//M05-2X/6-31G(d) level of theory with the inclusion of solvation effects using the SMD continuum model (see the Supporting Information) show that the bromine atom is indeed transferred from NBS onto the phosphorus atom of the TCPT catalyst (Figure 5). Subsequent transfer of the catalyst-bound bromine onto the alkene is accompanied by succinimide deprotonation of the alcohol which assists cyclization. The involvement of the bromonium shuttle in the delivery of the bromine atom to the alkene renders the process substantially more energetically favorable than the uncatalyzed process. Instructively, no carbocation intermediates were detected during these computational studies.

CONCLUSION

We report the first synthesis of the 6,5-fused snyderane, luzofuran (**3**), in both racemic and enantioenriched form. Excision of the halogen from *epi*-**3** gave the insect-derived natural product (–)-ancistrofuran (**17**), while debromination of (\pm)-luzofuran (**3**) gave the known compound (\pm)-*epi*-ancistrofuran (\pm)-**16**. The heightened nucleophilicity of the

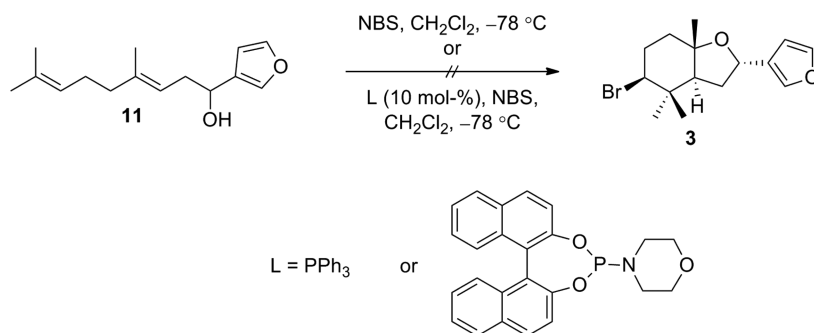
N-heterocycle-flanked phosphoramidite **8** enabled us to perform a diastereoselective brominative cyclization using the common laboratory reagent NBS. We anticipate that this strategy will provide general access to the snyderane class of natural products.

EXPERIMENTAL SECTION

(\pm)-9-Hydroxydendrolasin (11**).⁵⁵ To a suspension of anhydrous barium iodide (3.12 g, 7.97 mmol, 4.5 equiv) in THF (30 mL) was added a solution of lithium biphenylide, prepared by stirring (2 h) freshly cut lithium pieces (110 mg, 15.9 mmol, 9.0 equiv) and biphenyl (2.44 g, 15.8 mmol, 9.0 equiv) in THF (30 mL). This mixture was stirred (1 h) and then cooled to –78 °C, and a solution of (*E*)-geranyl chloride (**9**) (620 mg, 3.59 mmol, 1.0 equiv) in THF (20 mL) was added over 1.5 h. The resulting mixture was stirred (1 h) at –78 °C, and then a solution of 3-furancarboxaldehyde (310 μ L, 3.58 mmol, 1.0 equiv) in THF (10 mL) added over 10 min. The mixture was stirred (0.5 h) at –78 °C and then quenched via the addition of hydrochloric acid (0.2 M, 100 mL). The aqueous phase was extracted with Et₂O (2 \times 50 mL), and the organic extracts were combined with the organic partition of the reaction mixture, washed with water (2 \times 200 mL) and brine (100 mL), dried over sodium sulfate, and concentrated. Column chromatography (ethyl acetate/light petroleum 5/95) gave **11** (494 mg, 2.11 mmol, 58%) as a colorless oil: *R*_f 0.50 (ethyl acetate/hexanes 1/9); IR (cm^{–1}) 3383, 2917, 1108, 1024, 787; ¹H NMR (300 MHz; CDCl₃) 7.39 (2 H, m), 6.41 (1 H, m), 5.16 (1 H, ddd, *J* 7.9, 6.8, 0.9), 5.06 (1 H, m), 4.66 (1 H, ddd, *J* 7.2, 5.8, 3.9), 2.45–2.49 (2 H, m), 2.03–2.10 (4 H, m), 1.91 (1 H, d, *J* 4.0), 1.68 (3 H, s), 1.64 (3 H, s), 1.60 (3 H, s); ¹³C NMR (75 MHz; CDCl₃) 143.3 (CH), 139.7 (CH), 139.2 (C), 131.9 (C), 128.8 (C), 124.2 (CH), 119.5 (CH), 108.8 (CH), 68.9 (CH), 40.0 (CH₂), 36.9 (CH₂), 26.6 (CH₂), 25.8 (CH₃), 17.8 (CH₃), 16.5 (CH₃); MS (EI) *m/e* (relative intensity) 216 (25), 201 (16), 147 (100), 129 (70), 95 (81), 91 (64); HRMS (ESI) *m/e* [*M* + Na] calcd for C₁₅H₂₂O₂Na 257.15120, obsd 257.15130.**

(*E*)-9-Oxodendrolasin (14**).⁵⁶ Sodium hydrogen carbonate (200 mg, 2.38 mmol, 3.46 equiv) was added to a solution of the Dess–Martin periodinane (335 mg, 789 μ mol, 1.15 equiv) in CH₂Cl₂ (5 mL) and the mixture stirred (5 min) with cooling to 0 °C. A solution of **11** (150 mg, 687 μ mol, 1.00 equiv) in CH₂Cl₂ (5 mL) was added slowly, and the mixture was stirred and allowed to warm to 15 °C. Stirring was continued (1 h), a solution of sodium sulfite (5% in water, 20 mL) was added, the aqueous phase was extracted with CH₂Cl₂ (2 \times 5 mL), and the organic extracts combined with the organic partition of the reaction mixture and washed with water (2 \times 50 mL), brine (50 mL), dried over sodium sulfate, and concentrated. Column chromatography (ether/light petroleum 5/95) gave **14** (137 mg, 92%) as a slightly yellow oil: *R*_f 0.48 (ether/hexanes 1/9); IR (cm^{–1}) 2947, 1678, 1154, 873, 743; ¹H NMR (300 MHz; CDCl₃) 8.02 (1 H, m), 7.41 (1 H, m), 6.75 (1 H, m), 5.40 (1 H, app t *J* 7.0), 5.04 (1 H, m), 3.44 (2 H, d *J* 7.0), 1.96–2.11 (4 H, m), 1.67 (3 H, s), 1.64 (3 H, s), 1.57 (3 H, s); ¹³C NMR (75 MHz; CDCl₃) 193.4 (C), 147.3 (CH), 144.1 (CH), 139.2 (C), 131.7 (C), 127.5 (C), 124.0 (CH), 116.2 (CH), 108.9 (CH), 40.5 (CH₂), 39.7 (CH₂), 26.5 (CH₂), 25.7 (CH₃), 17.7 (CH₃),**

Scheme 5. Attempted Catalyst-Free Cyclizations



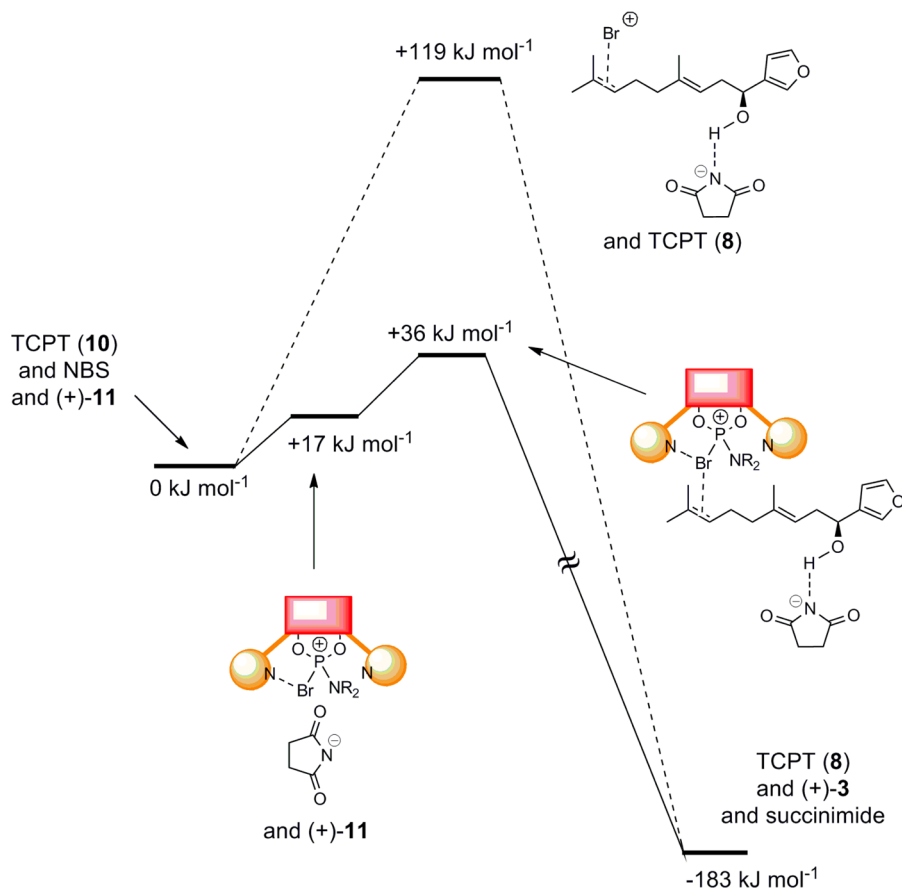


Figure 5. Calculated schematic energy profiles for the catalyzed brominative cyclization of (+)-11.

16.6 (CH₃); MS (ESI) *m/e* (relative intensity) 271 (100, MK⁺); HRMS (ESI) *m/e* [M + Na] calcd for C₁₅H₂₀O₂Na 255.13555, obsd 255.13551.

(S)-9-Hydroxydendrolasin ((S)-11). Dichloro(*p*-cymene)-ruthenium(II) dimer (36 mg, 59 μmol, 0.051 equiv) and (*S,S*)-TsDPEN (51 mg, 0.14 mmol, 0.12 equiv) were heated to reflux (1 h) in degassed CH₂Cl₂ (20 mL). The solvent was removed under a stream of argon, and a solution of sodium formate (800 mg, 11.8 mmol, 10 equiv) in degassed, deionized water (15 mL) and then a solution of cetyltrimethylammonium bromide (16 mg, 44 μmol, 0.04 equiv) and **14** (250 mg, 1.16 mmol, 1.0 equiv) in degassed ethyl acetate (8 mL) were added. The mixture was stirred at room temperature (16 h) and then poured onto water (100 mL), and saturated aqueous ammonium chloride (100 mL) was added. The mixture was extracted with ether/hexanes 1/1 (3 × 50 mL), the combined organic extracts were passed through a plug of Celite, washing with ether/hexanes:1/1 (100 mL), and the filtrate was concentrated. Column chromatography (ethyl acetate/light petroleum: 5/95) gave (*S*)-**11** (199 mg, 79%) as a colorless oil: [α]_D²⁰ −6.2 (c 2.1, THF).

(S)-((S,E)-1-(Furan-3-yl)-4,8-dimethylnona-3,7-dien-1-yl) 2-methoxy-2-phenyl Acetate (15). To a solution of (*S*)-**11** (20 mg, 85 μmol, 1.0 equiv) in CH₂Cl₂ (5 mL) were added DCC (18 mg, 87 μmol, 1.0 equiv), then (*S*)-(+)-α-methoxyphenylacetic acid (14.5 mg, 8.73 μmol, 1.0 equiv), and then 4-dimethylaminopyridine (1.0 mg, 8.2 μmol, 0.10 equiv). The mixture was stirred (8 h) and then filtered, washing with CH₂Cl₂ (5 mL), and the filtrate concentrated. Column chromatography (ether/light petroleum 7/93) gave **15** (30 mg, 92%): [α]_D²⁰ + 2.2 (c 0.054, CHCl₃); *R*_f 0.35 (ether/hexanes 1/9); IR (cm^{−1}) 2924, 1747, 1171, 1106, 1023, 874; ¹H NMR (500 MHz; CDCl₃) 7.42–7.44 (2 H, m), 7.32–7.37 (5 H, m), 6.36 (1 H, m), 5.79 (1 H, app t *J* 6.8), 5.00 (1 H, app tt, *J* 10.4, 1.4), 4.81 (1 H, dddd *J* 7.2, 7.0, 1.3, 1.2), 4.73 (1 H, s), 3.39 (3 H, s), 2.47 (1 H, ddd, *J* 14.5, 7.2, 6.8), 2.40 (1 H, ddd, *J* 14.5, 6.8, 6.4), 1.90–1.96 (2 H, m), 1.82 (2 H, app t,

J 7.66), 1.67 (3 H, s), 1.57 (3 H, s), 1.46 (3 H, s); ¹³C NMR (75 MHz; CDCl₃) 170.3 (C), 143.2 (CH), 140.5 (CH), 138.6 (C), 136.5 (C), 131.6 (C), 128.8 (CH), 128.7 (CH), 128.7 (CH), 127.4 (CH), 127.4 (CH), 124.6 (C), 124.2 (CH), 118.3 (CH), 109.2 (CH), 82.8 (CH), 69.6 (CH), 57.5 (CH), 39.7 (CH₂), 33.3 (CH₂), 26.6 (CH₂), 25.8 (CH₃), 17.8 (CH₃), 16.3 (CH₃); MS (ESI) *m/e* (relative intensity) 787 (100), 405 (MNa⁺, 30); HRMS (ESI) *m/e* [M + Na] Calcd for C₂₄H₃₀O₄Na 405.20363, obsd 405.20367. A diastomeric mixture was synthesized according to the above procedure, using (±)-**11**. (*S*)-((*R,E*)-1-(furan-3-yl)-4,8-dimethylnona-3,7-dien-1-yl) 2-methoxy-2-phenyl acetate (*epi*-**15**) showed key signals: IR (cm^{−1}) 2915, 1732, 1197, 1108, 1023, 874, 791, 726; ¹H NMR (500 MHz; CDCl₃) 7.09 (1 H, m), 6.11 (1 H, m), 5.79 (1 H, app t, *J* 6.8), 4.76 (1 H, s), 3.40 (3 H, s); ¹³C NMR (125 MHz; CDCl₃) 170.1 (C), 143.0 (CH), 140.0 (CH), 138.6 (C), 136.3 (C), 131.5 (C), 128.8 (CH), 128.7 (2 C, CH), 127.4 (2 C, CH), 124.5 (C), 124.2 (CH), 118.5 (CH), 108.8 (CH), 82.8 (CH), 69.7 (CH), 57.4 (CH), 39.8 (CH₂), 33.7 (CH₂), 26.6 (CH₂), 25.8 (CH₃), 17.8 (CH₃), 16.4 (CH₃). Integration of the peaks of the major and minor diastereomers in the ¹H NMR spectrum of **15** indicated a 95:5 diastomeric ratio of esters.

(±)-Luzofuran (3).²⁶ A solution of (±)-**11** (120 mg, 512 μmol, 1.00 equiv) and (*S*)-TCPT catalyst **8** (90 mg, 0.10 mmol, 0.200 equiv) in CH₂Cl₂ (10 mL) was stirred (7 h) over activated 4 Å molecular sieves (0.5 g). The mixture was cooled to −78 °C, and a solution of *N*-bromosuccinimide (92 mg, 517 μmol, 1.01 equiv) in CH₂Cl₂ (7 mL) was added over 5 min. The solution was stirred (10 min) at −78 °C then quenched via the addition of a solution of sodium sulfite (5% in water, 20 mL) and allowed to warm to room temperature. The aqueous phase was extracted with CH₂Cl₂ (2 × 5 mL), and the organic extracts were combined with the organic partition of the reaction mixture, washed with water (50 mL) and brine (50 mL), dried over sodium sulfate, and concentrated. Column chromatography (ether/light petroleum 7/93) gave (±)-luzofuran (**3**) as a colorless oil (27

mg, 17%) and (4S*,6R*,7R*,10R*)-2-(furan-3-yl)-7,11,11-trimethyloctahydrobenzofuran (4-*epi*-3) as a colorless solid (8.0 mg, 4%).

(S)-(+)-Luzofuran (3).²⁶ A solution of (S)-11 (200 mg, 853 μ mol, 1.00 equiv) and (S)-TCPT catalyst **8** (161 mg, 183 μ mol, 0.200 equiv) in CH_2Cl_2 (14 mL) was stirred (7 h) over activated 4 Å molecular sieves (0.5 g). The mixture was cooled to -78°C , and a solution of *N*-bromosuccinimide (165 mg, 927 μ mol, 1.01 equiv) in CH_2Cl_2 (10 mL) was added over 5 min. The solution was stirred (10 min) at -78°C , quenched via the addition of a solution of sodium sulfite (5% in water, 20 mL), and allowed to warm to room temperature. The aqueous phase was extracted with CH_2Cl_2 (2×5 mL), and the organic extracts were combined with the organic partition of the reaction mixture, washed with water (50 mL) and brine (50 mL), dried over sodium sulfate, and concentrated. Column chromatography (ether/light petroleum 7/93) gave (+)-luzofuran (**3**) as a colorless oil (44 mg, 15%): $[\alpha]_D^{20} + 5.1$ (*c* 0.18, CHCl_3); R_f 0.53 (ethyl acetate/hexanes 1/9); IR (neat) $\nu_{\text{max}}/\text{cm}^{-1}$ 2955, 1458, 1157, 1023, 896, 599; ^1H NMR (500 MHz; CDCl_3) 7.38 (1 H, m), 7.35 (1 H, m), 6.32 (1 H, m), 5.08 (1 H, dd *J* 9.2, 2.4), 3.94 (1 H, dd *J* 12.5, 4.6), 2.21–2.33 (2 H, m), 2.08 (1 H, dddd *J* 14.4, 13.6, 12.5, 4.0), 1.91 (1 H, ddd *J* 12.4, 4.0, 3.1), 1.81 (1 H, ddd *J* 9.8, 7.0, 2.6), 1.70 (1 H, dd *J* 13.2, 7.0), 1.60 (1 H, dddd *J* 13.5, 12.5, 4.4, 0.9), 1.25 (3 H, d *J* 0.9), 1.05 (3 H, s), 0.98 (3 H, s); ^{13}C NMR (125 MHz; CDCl_3) 143.5 (CH), 138.9 (CH), 128.8 (C), 108.5 (CH), 80.2 (C), 70.5 (CH), 65.6 (CH), 55.1 (CH), 39.6 (CH₂), 38.7 (CH₂), 32.8 (C), 32.7 (CH₂), 30.3 (CH₃), 20.4 (CH₃), 17.0 (CH₃); MS (EI) *m/e* (relative intensity) 299 (6), 297 (6), 219 (12), 217 (12), 137 (64), 121 (57), 95 (48), 81 (100); HRMS (ESI) *m/e* [*M* + *Na*] calcd for $\text{C}_{15}\text{H}_{21}^{79}\text{BrO}_2\text{Na}$ 335.06171, obsd 335.06174, calcd for $\text{C}_{15}\text{H}_{21}^{81}\text{BrO}_2\text{Na}$ 337.05967, obsd 337.05968. (4S,6R,7R,10R)-2-(Furan-3-yl)-7,11,11-trimethyloctahydrobenzofuran (4-*epi*-3) was also obtained as a colorless solid (11 mg, 4%): $\Delta\epsilon_{261}^{20} -4.38$ (THF); mp 40–44 $^\circ\text{C}$; R_f 0.45 (ethyl acetate/hexanes 1/9); IR (neat) $\nu_{\text{max}}/\text{cm}^{-1}$ 2922, 1488, 1185, 1161, 956, 752, 687; ^1H NMR (300 MHz; CDCl_3) 7.36–7.39 (2 H, m), 6.37 (1 H, m), 4.99 (1 H, ddd, *J* 9.2, 6.8, 0.95), 3.94 (1 H, dd, *J* 12.5, 4.8), 2.21–2.32 (2 H, m), 2.07 (1 H, dddd, *J* 14.3, 13.5, 12.5, 4.1), 1.76 (1 H, dd, *J* 13.4, 5.2), 1.58 (1 H, dddd *J* 13.5, 12.5, 4.3, 0.95), 1.20 (3 H, d *J* 0.95), 1.12 (3 H, s), 0.98 (3 H, s); ^{13}C NMR (75 MHz; CDCl_3) 143.4 (CH), 139.0 (CH), 128.9 (C), 109.0 (CH), 80.1 (C), 72.8 (CH), 65.6 (CH), 57.0 (CH), 40.2 (CH₂), 39.0 (C), 33.2 (CH₂), 32.7 (CH₂), 30.6 (CH₃), 23.6 (CH₃), 17.7 (CH₃); MS (EI) *m/e* (relative intensity) 299 (32), 297 (29), 219 (16), 217 (16), 137 (62), 121 (74), 95 (53), 81 (100); MS (ESI; MeOH/LiCl) *m/e* (relative intensity) 241 (100), 257 (48), 319 (20), 321 (21); HRMS (ESI) *m/e* [*M* + *Li*] calcd for $\text{C}_{15}\text{H}_{21}^{79}\text{BrO}_2^7\text{Li}$ 319.08795, obsd 319.08811, calcd for $\text{C}_{15}\text{H}_{21}^{81}\text{BrO}_2^7\text{Li}$ 321.08590, obsd 321.08603. Elution with ethyl acetate allowed recovery of the catalyst as the phosphoramidate (160 mg, 98% recovery). When the catalyst/substrate system is prepared by addition of a solution of the (S)-TCPT catalyst **8** in CH_2Cl_2 (2 mL) to a solution of the substrate in nitroethane (20 mL), followed by drying over activated 4 Å molecular sieves and proceeding as above the reaction gives luzofuran (**3**) (84 mg, 29%) and 4-*epi*-3 (21 mg, 7%) with recovery of the unreacted substrate (65 mg, 33%).

epi-Ancistrofuran ((±)-16).⁵⁷ To a solution of (±)-3 (7.0 mg, 22 μ mol, 1.0 equiv) in fluorobenzene (1 mL) was added tributyltin hydride (13 μ L, 48 μ mol, 2.1 equiv) and the mixture heated to 50°C . A solution of VA-044 (7.1 mg, 22 μ mol, 1.0 equiv) in methanol (1 mL) was added over 10 h. After the solution was stirred at 50°C (6 h) TLC analysis showed incomplete conversion. Tributyltin hydride (5.0 μ L, 19 μ mol, 2 equiv) and VA-044 (2.0 mg, 6.2 μ mol, 0.28 equiv) in methanol (0.5 mL) were added, and stirring was continued at 50°C (8 h). The solution was cooled to room temperature and partitioned between ether (10 mL) and a solution of potassium fluoride (5% in water, 10 mL), and then the aqueous partition was extracted with ether (10 mL). The combined organic extracts were washed with water (50 mL), a solution of potassium fluoride (5% in water, 10 mL), and a saturated solution of ammonium chloride (10 mL), dried over sodium sulfate, and concentrated. Column chromatography with 10% potassium carbonate on silica (ethyl acetate/light petroleum 1/19) gave (±)-16 (4.1 mg, 84%) as a colorless oil: R_f 0.25 (ether/hexanes

1/19); IR (neat) $\nu_{\text{max}}/\text{cm}^{-1}$ 2931, 1461, 1261, 1158, 1025, 874; ^1H NMR (300 MHz; CDCl_3) 7.35–7.37 (2 H, m), 6.34 (1 H, m), 5.03 (1 H, ddd, *J* 9.2, 2.5, 0.4), 2.16 (1 H, ddd, *J* 13.6, 11.6, 9.3) 1.88–1.95 (1 H, m), 1.75 (1 H, dddd, *J* 11.6, 7.0, 2.7, 0.5), 1.3–1.65 (6 H, m), 1.16 (3 H, d, *J* 0.6), 0.93 (3 H, s), 0.89 (3 H, s); ^{13}C NMR (75 MHz; CDCl_3) 143.4 (CH), 139.1 (CH), 129.5 (C), 108.8 (CH), 81.4 (C), 69.5 (CH), 55.6 (CH), 41.2 (CH₂), 39.0 (CH₂), 33.3 (C), 32.9 (CH₃), 31.7 (CH₂), 21.3 (CH₂), 20.5 (CH₃), 20.1 (CH₃); MS (ESI; MeOH/LiCl) *m/e* (relative intensity) 241 (100); HRMS (ESI) *m/e* [*M* + *Li*] calcd for $\text{C}_{15}\text{H}_{22}\text{O}_2^7\text{Li}$ 241.17744, obsd 241.17763, calcd for $\text{C}_{30}\text{H}_{44}\text{O}_4^7\text{Li}$ 475.33942, obsd 475.33942.

(-)-Ancistrofuran ((-)-17).⁵⁰ Lithium (5.0 mg, 0.72 mmol, 23 equiv), anhydrous magnesium chloride (30 mg, 0.32 mmol, 10 equiv), and naphthalene (13 mg, 0.10 mmol, 3.3 equiv) were taken up in THF (1.5 mL) and stirred vigorously (3 h). The resulting black suspension of active magnesium was cooled to -78°C , and a solution of (S)-4-*epi*-3 (10 mg, 3.1 μ mol, 1.0 equiv) in THF (1.0 mL) added over 0.5 h. The solution was stirred, allowing to warm to -65°C (16 h). A solution of *tert*-butyl alcohol (10% in THF, 3.0 mL) was added slowly and the solution stirred at -65°C (0.5 h). Isopropyl alcohol (5 mL) was added, the reaction partitioned between ether (10 mL) and water (50 mL), and the aqueous partition extracted with ether (10 mL). The combined organic extracts were washed with water (3×50 mL), dried over sodium sulfate, and concentrated. Column chromatography (ether/light petroleum 7/93) gave (S)-(-)-17 (6.4 mg, 86%) as a colorless oil: R_f 0.35 (ether/hexanes 1/19); $[\alpha]_D^{20} -2.6$ (*c* 0.20, CHCl_3); IR (neat) $\nu_{\text{max}}/\text{cm}^{-1}$ 2865, 1458, 1374, 1259, 1156, 1049, 1024; ^1H NMR (300 MHz; CDCl_3) 7.37 (2 H, m), 6.38 (1 H, m), 4.91 (1 H, dd, *J* 9.1, 6.8), 2.20 (1 H, dddd, *J* 11.6, 6.4, 4.8, 0.7) 1.87–1.94 (1 H, m), 1.80 (1 H, ddd, *J* 13.7, 11.2, 9.1), 1.63 (1 H, dd, *J* 13.7, 5.2), 1.26–1.74 (6 H, m), 1.14 (3 H, d, *J* 0.7), 0.99 (3 H, s), 0.87 (3 H, s); ^{13}C NMR (75 MHz; CDCl_3) 143.1 (CH), 138.8 (CH), 129.3 (C), 109.1 (CH), 81.0 (C), 71.6 (CH), 57.4 (CH), 40.9 (CH₂), 39.2 (CH₂), 33.2 (C), 32.9 (CH₃), 31.5 (CH₂), 23.4 (CH₃), 21.4 (CH₂), 20.5 (CH₃); MS (ESI; MeOH/LiCl) *m/e* (relative intensity) 241 (100); HRMS (ESI) *m/e* [*M* + *Li*] Calcd for $\text{C}_{15}\text{H}_{22}\text{O}_2^7\text{Li}$ 241.17744, obsd 241.17764, calcd for $\text{C}_{30}\text{H}_{44}\text{O}_4^7\text{Li}$ 475.33942, obsd 475.33948.

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra, coupling constant analysis, and computational details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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■ NOTE ADDED AFTER ASAP PUBLICATION

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