Efficient Preparation of a Highly Strained Eleven-Membered Ring

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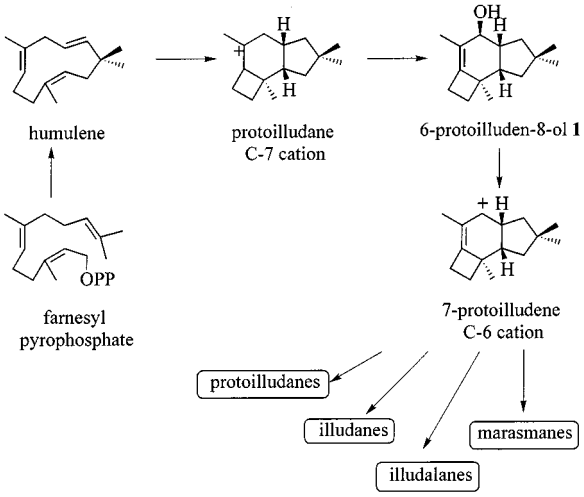
Two strategies have been explored to build the highly strained eleven-membered ring **2**, a potential precursor for the biosynthetic key intermediate of the protoilludane family: an intramolecular Horner–Wadsworth–Emmons olefination and an intramolecular Nozaki–Hiyama–Kishi type-ring closure.

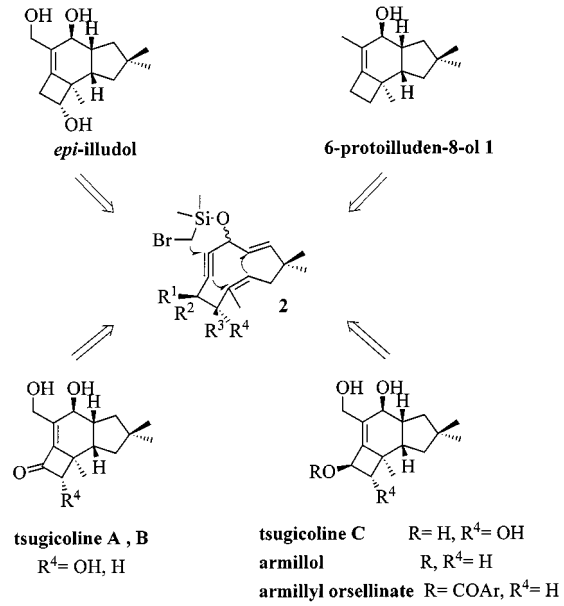
Introduction and Strategies

Natural protoilludanes, e.g. tsugicolines A, B, and C,[1] armillol,[2] and derivatives,[3] belong to a series of sesquiterpene metabolites produced by fungal basidiomycetes[4] and show interesting antibacterial activities. The key biosynthetic intermediate of this protoilludane family and of all the humulene-derived sesquiterpenes is the 7-protoilludene C-6 cation generated from 6-protoilluden-8-ol **1** (Scheme 1).[5]



Scheme 1. Biosynthesis of humulene-derived sesquiterpenes

A biomimetic approach to this particularly important biosynthetic precursor **1** was envisioned from the corresponding cycloundecadienynol **2** ($R^1 = R^2 = R^3 = R^4 = H$), based on a transannular radical cyclization strategy. This latter approach has already been successful for the diastereoselective total synthesis of (±)-*epi*-illudol, starting from the bromomethyldimethylsilyl (BMDMS) ether of a cycloundecadienynol derivative.[6] One of our goals in this approach was to develop an expedient entry to the particularly strained cycloundecadienynol precursor of **2** (Scheme 2).



Scheme 2. Transannular radical cyclization strategy to natural protoilludanes

Indeed, macrocyclization methodologies have witnessed a tremendous development during the past two decades, although surprisingly few are devoted to the efficient stereoselective construction of highly functionalized polyunsaturated eleven-membered rings. Despite the fact that access to humulene is well-known,[7] only a few examples of the synthesis of more strained skeletons have been described. Cycloundecatriene[8] and cycloundecadienyne[9][10] were prepared in an access to bertyadionol and jatrophone, respectively. Cycloundecenediynes[11][12] were also described and, finally, a cycloundecenyne was proposed in the synthesis of dolabellane.[13]

Toward this end, we envisaged two strategies to obtain the desired precursor **2**: the first one (route **A**) involves an intramolecular Horner−Wadsworth−Emmons approach[14] from aldehyde **3** while the second (route **B**) relies on an intramolecular Nozaki−Hiyama−Kishi type ring closure[15] between the iodoalkyne and enal moieties of **4**.

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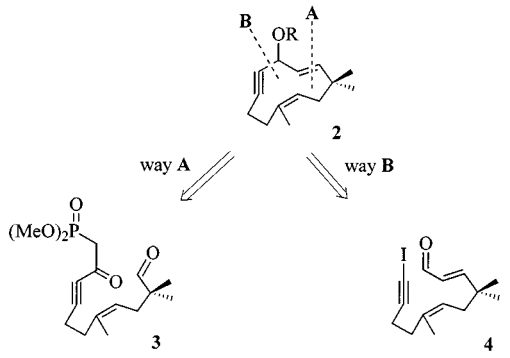
Herein, we describe our synthetic efforts aimed at this goal (Scheme 3).



Scheme 3. Retrosynthetic approach

Results and Discussion

Preparation of Precursors 3a−b

In the first strategy, the macrocycle could be obtained by an intramolecular Horner−Wardsworth−Emmons synthesis to create the disubstituted double bond (Scheme 3). The required enynal **3a** was prepared in 12 steps in 30% overall yield from the commercially available neryl acetate **5a**, which already possesses the trisubstituted double bond framework with a (*Z*) configuration (Scheme 4).

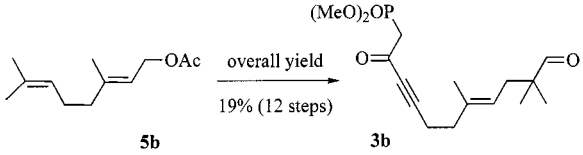
A dibromoolefin moiety, which is a direct precursor of the corresponding alkyne **6a**, was easily prepared in 54% overall yield using the Corey−Fuchs reaction[16] of the aldehyde resulting from the regioselective ozonolysis[17] of the neryl acetate **5a**. An acetate hydrolysis-elimination sequence provided, in 75% yield, the enynol **6a**, which was subsequently transformed into the corresponding allylic chloride. Treatment of the latter with lithium methyl isobutyrate enolate afforded the methyl nonenynoate **7a** in 83% overall yield starting from **6a**. Similar attempts at the nucleophilic substitution either from the corresponding allylic bromide or allylic mesylate, gave very low yields of the desired product. Reduction of **7a** with $LiAlH_4$, followed by DHP protection of the resulting alcohol and subsequent addition of the corresponding lithium acetylide to methyl chloroformate, led to the expected ynoate **8a** in 94% overall yield, starting from **7a**. Treatment of **8a** with lithium dimethoxyphosphonate afforded quantitatively the desired β-ketophosphonate. Finally, a THP ether cleavage-Swern oxidation[18] sequence produced quantitatively the aldehyde **3a**.

An identical sequence allowed the preparation of the (*E*)-isomer **3b** in 19% overall yield from geranyl acetate **5b** (Scheme 5).

Annelation of Precursors 3a−b

The intramolecular version of the Horner−Wadsworth−Emmons olefination is well documented for the construction of the 13-membered ring cembranolide skeletons. Indeed Marshall,[19] Tius[20] and Thomas[21] have reported successful preparations of polyfunctionalized structures, using the mild conditions described by Masamune[14] (LiCl/DBU or LiCl/Et_3N, high dilution).

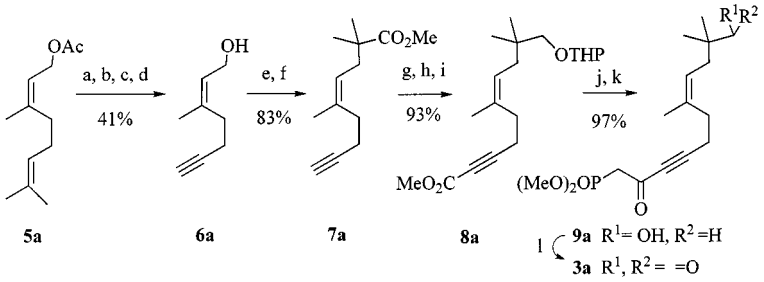
We focused on different experimental procedures and our results starting from (*Z*)-precursor **3a** (Scheme 6) are presented in Table 1. Slow addition (0.067 mmol·h^{-1}) of the substrate to a lithium chloride/DBU solution in acetonitrile[19] did not lead to any traces of the expected macrocycle **10a** (entry 1). In contrast, slow addition of DBU (0.019 mmol·h^{-1}) to a substrate/lithium chloride solution in acetonitrile,[21] afforded 14% of the desired product **10a** (entry 2). An optimization study was conducted that involved lowering the addition rate and the amount of base. The best result, 27% yield, was obtained using a 0.0095 mmol·h^{-1} addition of 1.3 equiv. of a DBU solution to a mixture of aldehyde **3a** and LiCl in MeCN (entry 3).



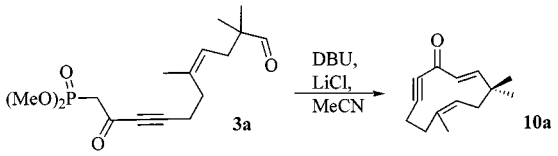
Scheme 5. Synthesis of the (*E*)-precursor **3b**

Both procedures were unsuccessful in the case of the (*E*)-precursor **3b**.

Although **10a** was obtained in fairly low yield, the fact that it formed was encouraging. Assuming that the linear



Scheme 4. (a) (*i*) O_3, CH_2Cl_2, −78°C; (*ii*) Me_2S, 59%; (b) CBr_4 (2 equiv), PPh_3 (4 equiv), CH_2Cl_2, 91%; (c) K_2CO_3 (cat.), MeOH, room temp., 97%; (d) *n*BuLi (3 equiv), THF, −78°C to 20°C, 78%; (e) PPh_3, CCl_4, 90%; (f) *i*$PrCO_2Me$, *n*BuLi, THF, 92%; (g) LAH, Et_2O, 0°C, quant.; (h) DHP, PPTS, CH_2Cl_2, room temp., 95%; (i) BuLi, $ClCO_2Me$, THF, 98%; (j) $CH_3P(O)(OMe)_2$, *n*BuLi, THF, 99%; (k) PPTS, MeOH, reflux, 98%; (l) Swern oxidation, 98%



Scheme 6. Macrocyclization of keto phosphonate **3a**

Table 1. Macrocyclization of ketophosphonate **3a** to macrocyclic ketone **10a**

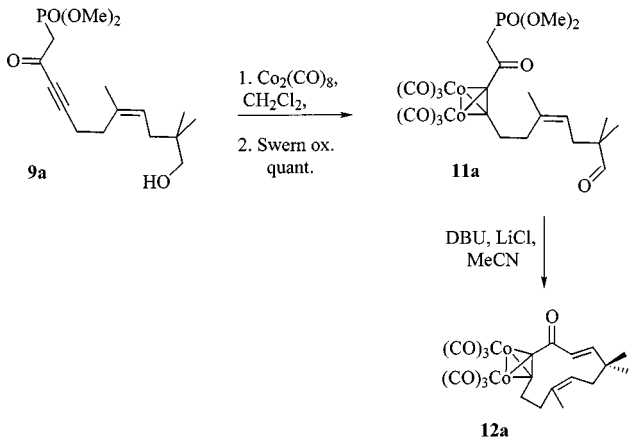
Entry	**3a** conc. [mol/L]	LiCl/DBU equiv	Method[a]	Addition rate [mol/L]	*T* [°C]	**10a** yield [%]
1	0.0085	10/5	A	0.000067	20	0
2	0.002	10/2	B	0.000019	50	14
3	0.002	10/1.3	B	0.0000095	50	27

[a] Method A: A solution of **3a** on a mixture of LiCl and DBU in MeCN; method B: A solution of DBU on a mixture of **3a** and LiCl in MeCN.

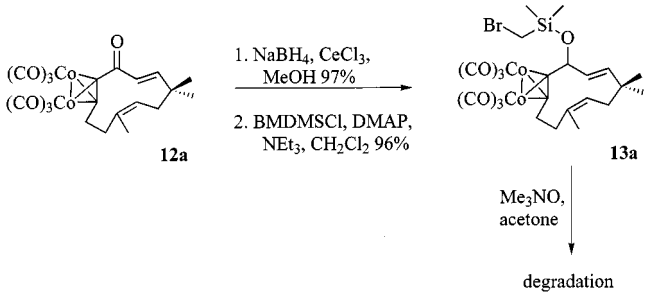
arrangement of the triple bond prevents, to a certain extent, an efficient closure, we anticipated that a possible solution to this problem could be associated with the geometrical transformation resulting from the protection of the triple bond as a cobalt cluster complex. Thus, we explored the behavior of the corresponding dicobalt hexacarbonyl complex **11a** (Scheme 7).[22] Starting from the alcohol **9a**, a complexaion−Swern oxidation sequence gave quantitatively the hexacarbonyldicobalt complex **11a** (Table 2). This latter complex, when submitted to the previously determined cyclization conditions, underwent complete degradation. Faster addition (48 h), (entry 1, Table 2), led to the decomplexed compound **10a** in 18% isolated yield. When the reaction was carried out at room temperature, a 1:1 mixture of the decomplexed product **10a** and the desired compound **12a** was obtained in 30% yield (entry 2). Eventually, this latter compound could be isolated in 34% yield by using 1.1 equiv. of DBU (entry 3).

We continued by attempting the last steps to obtain the desired precursor **2**. Luche reduction[23] followed by classical silylation afforded almost quantitatively the BMDMS ether **13a** (Scheme 8).

An initial study on an acyclic model 3-bromomethyldimethylsilyloxy-2-methylenenon-4-yne showed that among the three usual decomplexation methods, i.e. CAN,[24] Fe^{3+},[25] and Me_3NO,[26] only the last one quantitatively gave a 2:1 mixture of the expected decomplexed products, the BMDMS ether and the corresponding alcohol. However, when these neutral mild conditions were applied to **13a**, only intractable materials were obtained.



Scheme 7. Preparation and macrocyclization of the hexacarbonyl dicobalt complex **11a**



Scheme 8. Reduction-silylation-decomplexation sequence on macrocycle **12a**

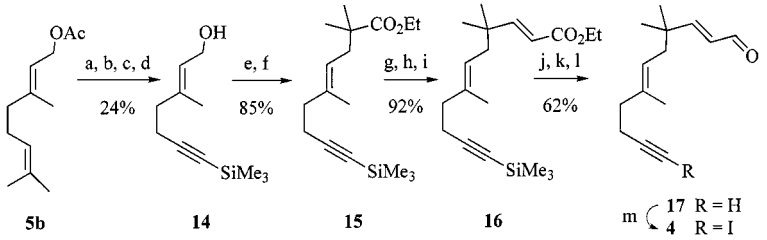
Next, we turned our attention to the second strategy, which relies on an intramolecular Nozaki−Hiyama−Kishi ring closure involving an iodoalkyne and an enal. In this case, a hydroxyl macrocycle should be formed instead of the previously expected macrocyclic ketone **10a**. The introduction of an sp^3 carbon instead of an sp^2 carbon should release some strain and render the formation of macrocyclic derivatives easier.

Preparation of Precursor 4

The required dienynal **4** was synthetized in 13 steps and 7% overall yield from the commercially available neryl acetate **5b** (Scheme 9). Silylated enyne **14** was easily prepared following the four-step sequence previously described (vide

Table 2. Macrocyclization of ketophosphonate **11a** to macrocyclic ketone **12a**; method: DBU solution on a mixture of **11a** and LiCl in MeCN

Entry Entry	**11a** conc. [mol/L]	LiCl/DBU equiv	Addition rate [mol/L]	*T* [°C]	Isolated products	Yield [%]
1	0.002	10/1.5	0.000017	50	**10a**	18
2	0.002	10/1.5	0.000017	20	**10a/12a** (50:50)	30
3	0.002	10/1.1	0.000013	20	**12a**	34

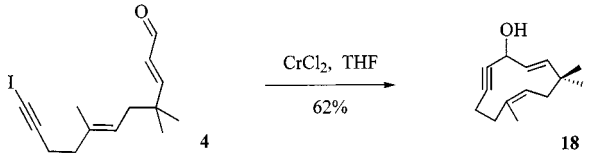


Scheme 9. (a) (*i*) O_3, CH_2Cl_2, −78°C; (*ii*) Me_2S, 50%; (b) CBr_4 (2 equiv), PPh_3 (4 equiv), CH_2Cl_2, 76%; (c) K_2CO_3 (cat.), MeOH, room temp., 97%; (d) (*i*) *n*BuLi (3 equiv), THF, −78°C, (*ii*) TMSCl, −78°C, 66%; (e) LiCl, 2,6-lutidine, MsCl; (f) *i*$PrCO_2Me$, *n*BuLi, THF, 85% (2 steps); (g) LAH, Et_2O, 0°C, quant.; (h) Swern oxidation, quant.; (i) $EtO_2CCH_2P(O)(OEt)_2$, LiCl, NEt_3, 92%; (j) DIBAL-H, 65%; (k) Swern oxidation, 98%; (l) KF, DMSO, MeOH, 98%; (m) NIS, $AgNO_3$, acetone, 62%

infra) from **5a**, but using a final TMSCl quenching to generate, after acidic hydrolysis, the *C*-silylated alcohol **14** in 24% overall yield. Chlorination under Collington−Meyers conditions[27] followed by nucleophilic alkylation, produced the desired ester **15** in 85% yield from **14**. LAH reduction, followed by Swern oxidation and olefination under the mild conditions of Masamune and Roush, provided stereoselectively and almost quantitatively the *E*-unsaturated ester **16**. Reduction of the latter with DIBAL-H, followed by Swern oxidation of the resulting alcohol and then desilylation, gave the enal **17** in 64% yield from **16**. Finally, mild iodination conditions[28] furnished the expected precursor **4** in 62% yield.

Annelation of Precursor 4

The slow addition (12 h) of the iodoalkyne **4** (2.3 mmol, 0.015 M in THF) to a suspension of chromium(II) chloride (0.16 M in THF) produced the desired macrocycle **18** in 62% yield (Scheme 10).

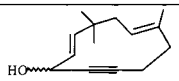
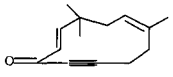
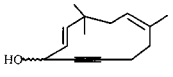
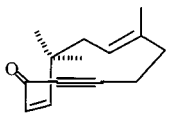
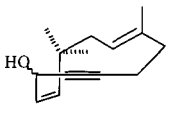
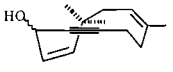


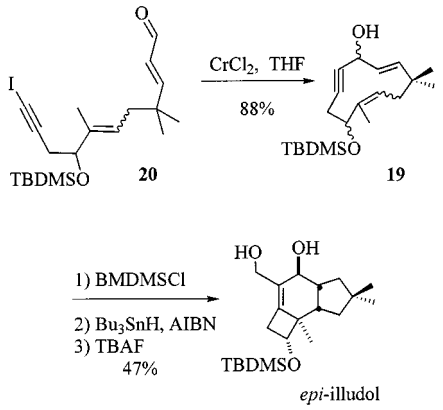
Scheme 10. Macrocyclization of the iodoalkyne **4**

The highly strained eleven-membered ring **18** was synthesized, for the first time, by the efficient Nozaki−Hiyama−Kishi method from the (*E*)-precursor **5a**. Compared to our previously described best result leading to the *epi*-illudol precursor[6] (88% yield for the macrocyclization), one can speculate on the role of the OTBDMS substituent.

In order to gain further insight into these experimental data, we performed AM1 calculations of the relative stabilities of the eleven-membered rings **10a** and **18**, as well

Table 3. AM1 calculations on relative stabilities of eleven-membered rings **10a** and **18**

$\Delta_fH°$ [kcal/ mol]	**10a**	Stereochemistry	**18**	$\Delta_fH°$ [kcal/ mol]	$\Delta_fH°$ [kcal/mol]
28.17		*E,E*		5.76 α-OH 6.71 β-OH	-22.41 -21.45
25.99		*E,Z*		3.95 α-OH 4.94 β-OH	-22.04 -21.05
29.86		*Z,E*		8.58 α-OH 11.92 β-OH	-21.28 -17.94
33.84		*Z,Z*		12.36 α-OH 15.94 β-OH	-21.48 -17.90
-63.31	cyclohexanone		cyclohexanol	-75.34 OH eq. -73.65 OH ax.	-12.03 -10.34

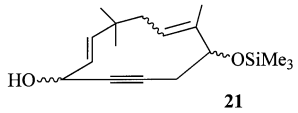


Scheme 11. *epi*-Illudol synthesis

as of the "unstrained" cyclohexanone/cyclohexanol system (Table 3).[29] It is worthy of note that these AM1 calculations confirm the more strained character (ca.20 kcal/mol) of the macrocyclic ketone **10a** compared to the corresponding hydroxyl derivative **18**. This could explain the better result obtained in the second strategy.

Moreover, the (*E*,*Z*)-alcohol appears as the most stable (3.95 kcal/mol for α-OH and 4.94 kcal/mol for β-OH), but our choice to synthesize the (*E*,*E*)-isomer **4** (5.76 kcal/mol for α-OH and 6.71 kcal/mol for β-OH) was directed by the stereochemical outcome we observed during the total synthesis of *epi*-illudol,[6] where the (*E*,*E*)-major substrate **19** involved in the radical cascade provided the expected natural product relative stereochemistry (Scheme 11).

Indeed, during the macrocyclization step from **20** to **19**, a mixture of diastereomers was isolated and directly engaged in the cascade. We can assume that the major isomer of **19** was the *E*,*E-anti* diastereomer, leading to the natural *epi*-illudol, as suggested by AM1 calculations on a simplified compound **21** ($SiMe_3$ instead of TBDMS, Scheme 12) where the *E*,*E-anti* diastereomer was indeed the most stable ($\Delta_fH°$ = −88.87 kcal/mol) (Table 4).



Scheme 12. Macrocycle **21**

Table 4. AM1 calculations of $\Delta_fH°$ of the various diastereomers of the eleven-membered ring **21**

OH/$OSiMe_3$	*anti*	*syn*	*anti*	*syn*
Stereochemistry	*E,E*	*E,E*	*E,Z*	*E,Z*
$\Delta_fH°$ [kcal/mol]	−88.87	−87.87	−86.03	−85.07

Conclusion

In summary, two approaches to the eleven-membered ring have been studied. The Horner−Wadsworth−Emmons strategy leads to a highly strained macrocyclic ketone **10a** in low yields. The geometrical transformation originating from the use of the corresponding cobalt cluster complex did not release enough strain to improve the macrocyclization step. However, a Nozaki−Hiyama−Kishi ring closure of precusor **4** appears particularly efficient. Moreover, AM1 calculations a posteriori are consistent with the hypothesis that the macrocyclic alcohol **18** formed in this last case is less strained than the corresponding ketone **10a**. Thus, this study provides efficient and general macrocyclization conditions, which open a general route to the preparation of the requisite macrocyclic precursors in the proposed strategy for the one-step access to the protoilludane family. This route is under active investigation in our laboratory.

Experimental Section

General: Unless otherwise specified, materials were used without purification. THF was distilled from the Na benzophenone ketyl. EtO_2 and CH_2Cl_2 were distilled from calcium hydride.

^1H NMR and ^{13}C NMR spectra were recorded on 200 MHz Bruker AC 200, 300 MHz Bruker AM 300 and 400 MHz Bruker ARX 400 spectrometers. Chemical shifts are reported in ppm referenced to the residual proton resonances of the solvents. − Infrared (IR) spectra were recorded on a Perkin−Elmer 1420 spectrometer. − Mass spectra (MS) were obtained on a GC-MS Hewlett-Packard HP 5971 apparatus. − Elemental analyses were performed at the Service Régional de Microanalyse de l'Université P. et M. Curie. − Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F 254. Silica gel Merck Geduran SI (40−63 μm) was used for flash column chromatography. Eluent PE (petroleum ether) was distilled before use. Eluent EE (diethyl ether) was used as received.

First Strategy − Preparation of Enynol 6a

(4*Z*)-6-Acetoxy-4-methylhex-4-enal: A solution of neryl acetate **5a** (21.6 mL, 110 mmol) in 470 mL of CH_2Cl_2, at −78 °C, was treated with a stream of ozone. The reaction was monitored by TLC and, after completion, dimethylsulfide (40 mL, 550 mmol) was added to the yellow solution. After stirring for 12 h, the solvent was removed in vacuo and the crude product was purified by flash chromatography (EE/PE: 50:50) to give 11 g of the expected mono-aldehyde (59%). − ^1H NMR (300 MHz, $CDCl_3$) δ = 9.78 (t, *J* = 1.0 Hz, 1 H), 5.41 (td, *J* = 7.1, 1.2 Hz, 1 H), 4.58 (d, *J* = 7.1 Hz, 2 H), 2.57−2.44 (m, 4 H), 1.76 (d, *J* = 0.9 Hz, 3 H). − IR (neat): $\tilde{\nu}$ = 2970, 2640, 1740, 1670, 1230, 1030 cm^{-1}.

(2*Z*)-1-Acetoxy-7,7-dibromo-3-methylhepta-2,6-diene: To a solution of triphenylphosphane (6.56 g, 25 mmol) in 40 mL of CH_2Cl_2 at 0 °C, was added dropwise a CH_2Cl_2 (10 mL) solution of CBr_4 (3.97 g, 12 mmol). To the resulting mixture was added the previous aldehyde (1 g, 5.9 mmol) in CH_2Cl_2 (10 mL), and the solution was warmed to room temperature. After stirring for 1 h, phosphonium salts were precipitated with pentane (40 mL) and filtered off through celite. Solvents were removed in vacuo and the residue was purified by flash chromatography (EE/PE: 40:60) to give 1.73 g of the expected dibromoolefin (91%). − ^1H NMR (300 MHz, $CDCl_3$): δ = 6.40−6.35 (m, 1 H), 5.43 (td, *J* = 7.4, 1.3 Hz, 1 H), 4.56 (d, *J* = 7.4 Hz, 2 H), 2.27−2.17 (m, 4 H), 2.06 (s, 3 H), 1.78 (d, *J* = 1.0 Hz, 3 H). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 170.9, 140.8, 120.5, 89.5, 60.7, 31.3, 29.8, 23.2, 21.1. − IR (neat): $\tilde{\nu}$ = 3020, 2980, 1740, 1670, 1620, 1450, 1390, 1235, 1025 cm^{-1}. − MS (EI); *m*/*z* (relative intensity): 201 [M^+] (1), 43 (100).

(2*Z*)-7,7-Dibromo-3-methylhepta-2,6-dien-1-ol: To a MeOH (50 mL) solution of the previous acetate (22.4 g, 68.7 mmol) was added potassium carbonate (5 g, 36.2 mmol) at room temperature. After stirring for 30 min, the potassium carbonate was filtered off and the methanol was evaporated. The residue was extracted with ether, washed with NH_4Cl and brine, dried with $MgSO_4$, filtered, concentrated and used in the next step without further purification (yield 97%). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.38−6.35 (m, 1 H), 5.45 (td, *J* = 7.0, 1.4 Hz, 1 H), 4.11 (dd, *J* = 7.0, 1.0 Hz, 2 H), 2.24−2.18 (m, 4 H), 1.76 (d, *J* = 1.1 Hz, 3 H). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 137.7, 137.6, 125.6, 89.4, 58.7, 31.4, 28.8. − IR (neat): $\tilde{\nu}$ = 3350, 2980, 1670, 1585, 1450, 1380, 1000, 810, 760 cm^{-1}. − MS (EI); *m*/*z* (relative intensity): 269 [M^+] (1), 97 (13.7), 41 (100), 29 (76.1).

(2*Z*)-3-Methylhept-2-en-6-yn-1-ol (6a): To a solution of the previous dihalogenated compound (8.8 g, 31 mmol) in THF was added a solution of *n*BuLi (1.45 M in hexane, 66.4 mL, 96 mmol) at −78°C. After 0.5 h, the mixture was allowed to reach room temperature during 0.5 h, and then quenched with an aqueous HCl solution (4%, 45 mL) and extracted with ether (250 mL). The organic layer was washed twice with brine, dried with $MgSO_4$ and the solvent was removed under reduced pressure. The residue was chromatographed with a 40:60 mixture of EE/PE to give 78% yield of alcohol **6a** (liquid). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.56 (td, *J* = 7.3, 0.7 Hz, 1 H), 4.12 (dd, *J* = 7.3, 0.7 Hz, 2 H), 2.32 (m, 4 H), 1.98 (t, *J* = 2.4 Hz, 1 H), 1.76 (s, 3 H). − IR (neat): $\tilde{\nu}$ = 3350, 3290, 3030, 2920, 2110, 1665, 1440, 1000 cm^{-1}.

Preparation of Enynoate 7a

(2*Z*)-1-Chloro-3-methylhept-2-en-6-yne: To a solution of **6a** (0.30 g, 2.4 mmol) in CCl_4 was added PPh_3 (1.21 g, 4.9 mmol). The reaction mixture was heated at reflux until the solution became brown. The temperature was then lowered to 0°C and pentane (15 mL) was added to precipitate the phosphonium salts. After filtration and evaporation, the crude product was washed again with pentane (5 mL) and stored for one day at −18°C. This precipitation operation could be repeated if necessary. The crude product (89%) was then directly used in the next step. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.54 (bt, *J* = 8.2 Hz, 1 H), 4.11 (d, *J* = 8.2 Hz, 2 H), 2.34 (bd, 4 H), 1.96 (bs, 1 H), 1.79 (d, *J* = 0.7 Hz, 3 H). − IR (neat): $\tilde{\nu}$ = 3300, 3040, 2960, 2120, 1660, 700, 680 cm^{-1}.

(4*Z*)-Methyl-2,2,5-trimethylnon-4-en-8-ynoate (7a): To a solution of diisopropylamine (1.93 mL, 13.7 mmol) in THF (31 mL) was added dropwise *n*BuLi (1.57 M in hexanes, 8.5 mL, 13.2 mmol) at 0°C. After stirring for 10 min, the reaction mixture was cooled to −78°C and a solution of methyl isobutyrate (1.58 mL, 13.7 mmol) in THF (10 mL) was slowly added during 3 h. The temperature was then allowed to reach 0°C during 15 min and then decreased again to −78°C. A THF (5 mL) solution of the crude chloride (1.51 g, 10.5 mmol) was added and the solution was allowed to warm to room temperature. After stirring for 1 h, the resulting solution was diluted with ether and washed with an aqeuous saturated solution of NH_4Cl and then brine. The organic layer was dried ($MgSO_4$) and concentrated under vacuum. The crude product was used without further purification. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.14 (bt, *J* = 7.4 Hz, 1 H), 3.66 (s, 3 H), 2.31−2.21 (m, 6 H), 1.95 (t, *J* = 2.2 Hz, 1 H), 1.71 (d, *J* = 0.8 Hz, 3 H), 1.17 (s, 6 H). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 178.2, 135.9, 122.0, 84.2, 68.4, 51.7, 42.6, 38.6, 30.8, 24.9, 23.3, 17.2. − IR (neat): $\tilde{\nu}$ = 3300, 2960, 2120, 1730, 1380, 1190 cm^{-1}. − MS (EI): *m*/*z* (relative intensity): 208 [M^+] (1), 148 (16.4), 91 (67), 41 (100).

Preparation of Nonenyne 8a

(4*Z*)-2,2,5-Trimethylnon-4-en-8-yn-1-ol: To a solution of lithium aluminium hydride (0.4 g, 10.5 mmol) in anhydrous ether (55 mL) was cannulated a solution of the crude ester **7a** in ether (20 mL) at 0°C and the mixture was stirred for 1 h. After this time no starting ester remained (TLC control). The reaction mixture was quenched by slow addition of water at 0°C, and extractive workup with ether afforded a yellow oil, which was purified by silica gel chromatography (EE/PE: 40:60) to give 83% of the alcohol (2 steps). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.25 (t, *J* = 7.4 Hz, 1 H), 3.27 (s, 2 H), 2.28−2.20 (m, 4 H), 1.97−1.92 (m, 3 H), 1.70 (d, *J* = 1.2 Hz, 3 H), 0.84 (s, 6 H). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 178.2, 135.9, 122.0, 84.2, 68.4, 51.7, 42.6, 38.6, 30.8, 24.9, 23.3, 17.2. − IR (neat): $\tilde{\nu}$ = 3350, 3310, 3040, 2960, 2120, 1040 cm^{-1}.

(4*Z*)-2,2,5-Trimethyl-1-tetrahydropyranyloxynon-4-en-8-yne: This compound was prepared according to the literature[30] in 95% yield. Purified with EE/PE (5:95). Directly used in the next step.

Methyl (6*Z*)-6,9,9-Trimethyl-10-(tetrahydropyranyloxy)dec-6-en-2-ynoate (8a): *n*BuLi (1.56 M in hexane, 0.4 mL, 0.63 mmol) was added dropwise to a solution of the previous THP ether (0.16 g, 0.6 mmol) in THF (5 mL) at −78°C. The temperature was allowed to reach 20°C in 1 h and then decreased to −78°C. Methyl chloroformate (0.056 mL, 7.3 mmol) was added and the temperature was raised to room temperature. After dilution, the solution was washed with NH_4Cl and brine, dried with $MgSO_4$, concentrated and purified by silica gel chromatography (EE/PE: 10:90) to give 98% of the ester **8a**. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.29 (t, *J* = 7.7 Hz, 1 H), 4.53 (m, 1 H), 3.87−3.81 (m, 1 H), 3.75 (s, 3 H), 3.74−3.48 (m, 1 H), 3.43 (d, *J* = 9.1 Hz, 1 H), 2.97 (d, *J* = 9.1 Hz, 1 H), 2.42−2.31 (m, 4 H), 1.99 (t, *J* = 7.7 Hz, 2 H), 1.72 (d, *J* = 1.1 Hz, 3 H), 1.84−1.50 (m, 6 H), 1.56 (s, 3 H), 0.90 (s, 3 H), 0.88 (s, 3 H). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 154.2, 133.9, 123.8, 99.0, 89.5, 75.9, 72.9, 61.8, 52.5, 36.9, 35.0, 30.7, 29.8, 25.6, 24.6, 24.4, 23.3, 19.4, 17.5. − IR (neat): $\tilde{\nu}$ = 2950, 2220, 1715, 1205, 1070, 1030 cm^{-1}. − MS (EI): *m*/*z* (relative intensity): 239 [M^+] (2), 161 (10), 105 (11), 85 (100), 41 (43).

Preparation of Enynone 9a

(7*Z*)-1-Dimethoxyphosphiryl-7,10,10-trimethyl-11-(tetrahydropyranyloxy)undec-7-en-3-yn-2-one: To a THF (3 mL) solution of dimethyl methylphosphonate (0.091 mL, 0.85 mmol) at −78°C was added *n*BuLi (1.56 M in hexanes, 0.54 mL, 0.82 mmol). The temperature was raised to 0°C during 15 min, decreased again to −78°C and a THF (2 mL) solution of ester **8a** (0.124 g, 0.38 mmol) was added dropwise. The reaction mixture was allowed to warm to 20°C. After completion of the reaction the solution was diluted with ether, washed with NH_4Cl and brine, then dried with $MgSO_4$, concentrated, and purified by silica gel chromatography (MeOH/CH_2Cl_2: 10:90) to give 99% of the ketophosphonate. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.30 (t, *J* = 7.5 Hz, 1 H), 4.55−4.53 (m, 1 H), 3.87−3.80 (m, 1 H), 3.83 (s, 3 H), 3.79 (s, 3 H), 3.53−3.49 (m, 1 H), 3.45 (d, *J* = 9.1 Hz, 1 H), 3.30 (s, 1 H), 2.98 (d, *J* = 9.1 Hz, 1 H), 2.49−2.43 (m, 2 H), 2.36−2.30 (m, 2 H), 2.23 (s, 1 H), 1.99 (d, *J* = 7.5 Hz, 2 H), 1.87−1.50 (m, 6 H), 1.74 (s, 3 H), 0.90 (s, 3 H), 0.89 (s, 3 H). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 175.5 (d, *J* = 7.0 Hz), 133.8, 123.9, 99.1, 96.5, 81.2, 75.9, 62.0, 53.3, 53.2, 43.5 (d, *J* = 130.0 Hz), 37.0, 35.1, 30.7, 29.8, 25.6, 24.7, 24.5, 23.3, 19.5, 18.1. − IR (neat): $\tilde{\nu}$ = 3070, 2205, 1675, 1260, 1030 cm^{-1}.

(7*Z*)-11-Hydroxy-1-dimethoxyphosphiryl-7,10,10-trimethylundec-7-en-3-yn-2-one (9a): A solution of the THP ether (0.217 g, 0.52 mmol) and a catalytic amount of PPTS in methanol (4 mL)

was refluxed for 3 h. The solution was diluted with ether (30 mL), washed with brine, dried with $MgSO_4$, concentrated, and purified by silica gel chromatography (MeOH/CH_2Cl_2: 10:90) to give 98% of the alcohol **9a**. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.32 (t, *J* = 7.7 Hz, 1 H), 3.83 (s, 3 H), 3.79 (s, 3 H), 3.30 (s, 2 H), 3.23 (s, 1 H), 2.51−2.46 (m, 2 H), 2.38−2.33 (m, 2 H), 2.01 (d, *J* = 7.7 Hz, 2 H), 1.74 (s, 3 H), 0.88 (s, 6 H). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 177.5 (d, *J* = 6.9 Hz), 139.9, 123.9, 96.7, 81.2, 71.4, 53.3, 53.2, 43.5 (d, *J* = 129.9 Hz), 36.5, 35.9, 29.5, 24.1, 23.8, 23.2, 17.8. − IR (neat): ν̃ = 3300, 2960, 2205, 1675, 1255, 1110, 1045 cm^{-1}.

(4*Z*)-10-Oxo-11-dimethoxyphosphiryl-2,2,5-trimethylundec-4-en-8-ynal (3a): A solution of $(COCl)_2$ (0.064 mL, 0.72 mmol) in anhydrous CH_2Cl_2 (2 mL) was cooled to −78°C and treated with a solution of DMSO (0.095 mL, 1.44 mmol) in CH_2Cl_2. After 10 min, a solution of alcohol **9a** (0.17 g, 0.51 mmol) in CH_2Cl_2 (2 mL) was added. After 10 min, triethylamine (0.36 mL, 2.57 mmol) was introduced, and the mixture was stirred at −78°C until completion as monitored by TLC (2−3 h). The reaction was then quenched with a saturated aqueous NH_4Cl solution and extracted with ether. The combined organic phases were washed with brine (× 3), dried, and concentrated. Chromatography of the residue (elution with 15% methanol in dichloromethane) afforded 21.9 g (98%) of the aldehyde **3a**. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.47 (s, 1 H), 5.17 (t, *J* = 7.4 Hz, 1 H), 3.88 (s, 3 H), 3.74 (s, 3 H), 3.26 (d, *J* = 22.2 Hz, 2 H), 2.24−2.35 (m, 4 H), 2.20 (d, *J* = 7.4 Hz, 2 H), 1.72 (d, *J* = 1.2 Hz, 3 H), 1.06 (s, 6 H). − IR (neat): ν̃ = 2980, 2700, 2210, 1720, 1670, 1260, 1030 cm^{-1}.

Exactly the same procedures were followed to obtain the (*E*)-precursor **3b** from the commercial (*E*)-acetate **5b**.

(4*E*)-10-Oxo-11-dimethoxyphosphiryl-2,2,5-trimethylundec-4-en-8-ynal (3b): ^{1}H NMR (300 MHz, C_6D_6): δ = 9.32 (s, 1 H), 5.04 (t, *J* = 7.0 Hz, 1 H), 3.46 (s, 3 H), 3.43 (s, 3 H), 3.13 (d, *J* = 22.0 Hz, 2 H), 2.01−1.90 (m, 4 H), 1.86 (m, 2 H), 1.31 (s, 3 H), 0.87 (s, 6 H). − IR (neat): ν̃ = 2960, 2920, 2850, 2700, 2210, 1730, 1690, 1280, 1200, 1040 cm^{-1}.

Macrocyclization of Aldehyde 3a

(6*Z*,10*E*)-6,9,9-Trimethylcycloundeca-6,10-dien-2-yn-1-one (10a): To a solution of aldehyde **3a** (0.098 g, 0.298 mmol) and LiCl (0.126 g, 2.98 mmol) in acetonitrile (150 mL) at 55°C, was slowly added, over 41 h by syringe-pump, a DBU solution (0.058 mL, 0.388 mmol) in acetonitrile (29 mL). After 3 h of additional stirring at 55°C followed by concentration, the crude product was quenched with water (5 mL) and extracted with ether (× 4). The combined organic phases were washed with brine (× 3), dried, and concentrated. Column chromatography of the residue (elution with 20% ether in petroleum ether) afforded the expected macrocycle **10a** in 27% yield. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 15.9 Hz, 1 H), 5.92 (d, *J* = 15.9 Hz, 1 H), 5.38 (dd, *J* = 12.5, 5.3 Hz, 1 H), 2.93−2.56 (m, 3 H), 2.30 (dd, *J* = 12.7, 12.5 Hz, 1 H), 2.08 (d, *J* = 12.9 Hz, 1 H), 1.89 (dd, *J* = 12.7, 5.3 Hz, 1 H), 1.75 (s, 3 H), 1.14 (s, 3 H), 1.11 (s, 3 H). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 182.2, 166.2, 135.4, 128.8, 123.8, 106.9, 84.5, 41.7, 37.8, 30.0, 27.6, 23.0, 22.7, 17.6. − IR (neat): ν̃ = 2280, 2190, 1655, 1450, 1220 cm^{-1}. − MS (EI); *m/z* (relative intensity): 202 (1), 159 (20), 91 (100), 41 (83), 39 (82).

Preparation of Cobalt Carbonyl Complex (11a): A solution of alcohol **9a** (0.175 g, 0.529 mmol) in CH_2Cl_2 (1 mL) was added dropwise at room temperature to a solution of $Co_2(CO)_8$ (0.199 g, 0.582 mmol) in dry CH_2Cl_2 (10 mL) with stirring under argon. Evolution of CO occurred and the reaction mixture was stirred for 2.5 h. The final mixture was filtered through a short column of silica gel and washed with CH_2Cl_2 to eliminate the undesired cobalt derivatives, and then with 5% methanol in dichloromethane to provide 0.324 g of the expected dark-red complex (99%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.34 (t, *J* = 7.15 Hz, 1 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 3.45 (d, *J* = 22 Hz, 2 H), 3.33 (s, 2 H), 2.99 (m, 2 H), 2.44 (m, 2 H), 2.04 (d, *J* = 7.7 Hz, 2 H), 1.85 (s, 3 H), 0.91 (s, 6 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.5, 194.2, 183.0, 135.5, 123.1, 101.4, 86.9, 71.7, 53.5, 53.4, 41.7 (d, J_{C-P} = 132 Hz, 1C), 36.7, 36.3, 34.6, 32.8, 24.1 (2C). − IR (neat): ν̃ = 3400, 2950, 2860, 2090, 2030, 1660, 1580, 1250, 1030 cm^{-1}. − MS (CI/NH_3); *m/z* (relative intensity): 634 [M + 18] (7), 617 [M + 1] (19), 167 (16), 142 (27), 125 (30), 96 (100), 79 (57). − $C_{22}H_{27}Co_2O_{11}P$: Calcd. C 42.87, H 4.41; found C 42.01, H 4.47.

This alcohol was then submitted to the classical Swern procedure as described for **3a** to afford quantitatively aldehyde **11a**. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.41 (s, 1 H), 5.23 (m, 1 H), 3.75 (m, 6 H), 3.34 (d, *J* = 22 Hz, 2 H), 2.83 (m, 2 H), 2.31 (m, 2 H), 2.13 (m, 2 H), 1.94 (s, 3 H), 1.18 (s, 6 H). − IR (neat): ν̃ = 2960, 2850, 2700, 2100, 2020, 1725, 1665, 1580, 1470, 1260, 1030 cm^{-1}.

Macrocyclization of 11a: A solution of DBU (79 μL, 0.53 mmol) in anhydrous acetonitrile (30 mL) was added over 42 h by syringe pump (1.26·10^{-5} mol/h), under argon, to a solution of aldehyde **11a** (296 mg, 0.48 mmol) and anhydrous LiCl (203 mg, 4.80 mmol) in acetonitrile (230 mL) at room temperature. The reaction mixture was concentrated, diluted with CH_2Cl_2, and then filtered through a short pad of silica gel. The pad was washed with methanol, the filtrate was concentrated and purified by flash chromatography using CH_2Cl_2 as eluent to afford 80 mg of macrocycle **12a** (34%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 (d, *J* = 16.5 Hz, 1 H), 6.23 (d, *J* = 16.5 Hz, 1 H), 5.44 (m, 1 H), 2.93−1.79 (m, 6 H), 1.90 (s, 3 H), 1.16 (s, 6 H). − IR (neat): ν̃ = 2960, 2920, 2850, 2090, 2050, 2020, 1640, 1590, 1210 cm^{-1}.

Reduction of Ketone 12a: To a solution of ketone **12a** (65 mg, 0.13 mmol) in anhydrous methanol (20 mL), at 10°C, was added $CeCl_3$ (33 mg, 0.13 mmol) followed by $NaBH_4$ (5 mg, 0.133 mmol). After 1 h of stirring, a second equivalent of both $CeCl_3$ and $NaBH_4$ was added. The reaction mixture was quenched with water and extracted with ether. The combined organic layers were washed twice with brine and dried with $MgSO_4$. The crude product was directly silylated as described below. − ^{1}H NMR (400 MHz, $CDCl_3$): characteristic signals δ = 5.69 (d, *J* = 15.4 Hz, 1 H), 5.40 (m, 1 H), 5.20 (m, 2 H). − IR (neat): ν̃ = 3420, 2910, 2090, 2020, 2000 cm^{-1}.

Silylation of the Corresponding Alcohol: To a solution of the crude alcohol (58.5 mg, 0.119 mmol) in 10 mL of CH_2Cl_2, at 0°C, was added DMAP (0.1 equiv) followed by triethylamine (0.018 mL, 0.13 mmol) and BMDMSCl (0.98 equiv, 0.016 mL, 0.116 mmol). The resulting solution was allowed to reach room temperature and stirred until completion as indicated by TLC (15−30 min). The reaction mixture was then quenched with saturated NH_4Cl solution and extracted with ether. The combined organic layers were washed with brine, dried with $MgSO_4$, and the solvent was removed under vacuum. The residue was chromatographed, eluting with a mixture of 20% ether in petroleum ether, to afford quantitatively the silyl ether **13a**. − ^{1}H NMR (400 MHz, $CDCl_3$): characteristic signals δ = 5.39 (m, 1 H), 5.20−4.85 (m, 3 H), 2.19 (s, CH_2Br), 0.00 (s, 6 H). − IR (neat): ν̃ = 2950, 2910, 2840, 2080, 2040, 2010, 1460, 1280, 1250, 1070 cm^{-1}.

Second Strategy − Preparation of Enynol 14

(4*E*)-6-Acetoxy-4-methylhex-4-enal: The same ozonolysis procedure as described for (4*Z*)-6-acetoxy-4-methylhex-4-enal was used with

geranyl acetate (8.75 mL, 40 mmol) to give 3.4 g of mono-aldehyde (50%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.72 (t, *J* = 1.8 Hz, 1 H), 5.31 (tt, *J* = 6.6, 1.8 Hz, 1 H), 4.52 (d, *J* = 6.6 Hz, 2 H), 9.72 (td, *J* = 7.6, 1.8 Hz, 2 H), 2.32 (t, *J* = 7.6 Hz, 2 H), 2.00 (s, 3 H), 1.67 (s, 3 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 201.6, 170.8, 139.9, 119.1, 60.9, 41.5, 31.3, 20.8, 16.4. − IR (neat): ṽ = 2960, 2740, 1730, 1360, 1240, 1030 cm^{-1}. − $C_9H_{14}O_3$: Calcd. C 63.51, H 8.29; found C 63.28, H 8.25.

(2*E*)-1-Acetoxy-7,7-dibromo-3-methylhepta-2,6-diene: The same procedure as described for (2*Z*)-1-acetoxy-7,7-dibromo-3-methylhepta-2,6-diene was used with the above **(***E***)**-aldehyde (8.75 mL, 40 mmol) to give 12.4 g of dibromoolefin (76%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.25 (t, *J* = 7.1 Hz, 1 H), 5.26 (t, *J* = 6.6 Hz, 1 H), 4.48 (d, *J* = 6.6 Hz, 2 H), 2.12 (t, *J* = 7.8 Hz, 2 H), 2.04 (m, 2 H), 1.96 (s, 3 H), 1.61 (m, 3 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.1, 140.5, 137.7, 119.7, 89.3, 61.2, 37.3, 31.1, 21.2, 16.4. − IR (neat): ṽ = 2920, 1730, 1440, 1360, 1230, 1020 cm^{-1}.

(2*E*)-7,7-Dibromo-3-methylhepta-2,6-dien-1-ol: The same procedure as described for (2*Z*)-7,7-dibromo-3-methylhepta-2,6-dien-1-ol was used with the above (*E*)-acetate (12.4 g, 38 mmol) to give the corresponding alcohol, which was used in the next step without further purification. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.36 (m, 1 H), 5.45 (td, *J* = 7.0 Hz, 1 H), 4.12 (d, *J* = 7.0 Hz, 2 H), 2.24−2.18 (m, 4 H), 1.76 (s, 3 H). − ^{13}C NMR (50 MHz, $CDCl_3$): δ = 137.7, 137.6, 125.6, 89.4, 58.7, 31.4, 28.8, 23.5. − IR (neat): ṽ = 3350, 2920, 1670, 1585, 1450, 1380, 1000 cm^{-1}.

(2*E*)-7-Trimethylsilyl-3-methylhept-2-en-6-yn-1-ol (14): To a solution of crude alcohol in THF (50 mL), at −78°C, was added dropwise *n*BuLi (2.5 M in hexanes, 113.15 mmol, 45.3 mL) followed by, after stirring for 15 min, TMSCl (36.3 mmol, 4.6 mL). After completion of the reaction the mixture was quenched with a saturated solution of NH_4Cl, diluted with ether, and washed with brine. The organic layer was dried ($MgSO_4$) and concentrated under vacuum. Flash column chromatography (silica gel, EE/PE: 50:50) gave 4.9 g of alcohol **14** (66%). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.43 (t, *J* = 6.6 Hz, 1 H), 4.12 (d, *J* = 6.6 Hz, 2 H), 2.34 (t, *J* = 6.8 Hz, 2 H), 2.22 (t, *J* = 6.8 Hz, 2 H), 1.67 (s, 3 H), 0.12 (s, 9 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.6, 124.5, 106.6, 84.9, 59.0, 38.2, 18.8, 16.0, 0.00 (3C). − IR (neat): ṽ = 3340, 2940, 2160, 1245, 1030, 1000 cm^{-1}. − $C_{11}H_{20}OSi$: Calcd. C 67.28, H 10.26; found C 67.42, H 10.29.

Preparation of Enyne 15

(2*E*)-7-Trimethylsilyl-1-chloro-3-methylhept-2-en-6-yne: To a solution of alcohol **14** (4.6 g, 23.5 mmol) in DMF (30 mL) were added anhydrous lithium chloride (1 g, 23.5 mmol) and 2,6-lutidine (3 mL, 25.8 mmol) at room temperature. After stirring for 10 min, mesyl chloride was added (2 mL, 25.8 mmol). After 1 h of stirring, the reaction mixture was diluted with ether and washed with saturated NH_4Cl and brine. The organic layer was dried ($MgSO_4$) and concentrated under vacuum. The crude product was used in the following step without further purification. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.49 (t, *J* = 7.6 Hz, 1 H), 4.08 (d, *J* = 7.6 Hz, 2 H), 2.34 (t, *J* = 7.1 Hz, 2 H), 2.25 (t, *J* = 7.1 Hz, 2 H), 1.73 (s, 3 H), 0.13 (s, 9 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.6, 121.4, 106.2, 85.1, 40.6, 38.1, 18.5, 15.8, 0.00 (3C). − IR (neat): ṽ = 2940, 2910, 2860, 2160, 1245, cm^{-1}.

(4*E*)-Ethyl 2,2,5-trimethyl-9-trimethylsilylnon-4-en-8-ynoate (15): The same procedure as described for ester **7a** was used with a solution of the corresponding crude chloride. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.03 (t, *J* = 7.6 Hz, 1 H), 3.98 (q, *J* = 7.4 Hz, 2 H), 2.20−2.05 (m, 4 H), 1.48 (s, 3 H), 1.11 (t, *J* = 7.4 Hz, 3 H), 1.02 (s, 6 H), 0.00 (s, 9 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.5, 135.9, 121.1, 106.9, 84.4, 60.0, 42.5, 38.7, 38.1, 24.6 (2C), 19.0, 15.9, 14.1, 0.00 (3C). − IR (neat): ṽ = 2960, 2160, 1720, 1245 cm^{-1}.

Preparation of Dienyne 16

(4*E*)-2,2,5-Trimethyl-9-trimethylsilylnon-4-en-8-yn-1-ol: The same procedure as described for (4*Z*)-2,2,5-trimethylnon-4-en-8-yn-1-ol was used with the crude ester described above. The yield was 85% over the three steps (4.43 g). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.15 (t, *J* = 7.6 Hz, 1 H), 3.18 (s, 2 H), 2.20 (t, *J* = 7.1 Hz, 2 H), 2.08 (t, *J* = 7.1 Hz, 2 H), 1.83 (d, *J* = 7.6 Hz, 2 H), 1.48 (s, 3 H), 0.75 (s, 6 H), 0.00 (s, 9 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.1, 121.8, 107.0, 84.5, 71.7, 38.6, 36.6, 36.1, 23.7 (2C), 18.9, 15.8, 0.0 (3C). − IR (neat): ṽ = 3360, 2940, 2920, 2860, 2160, 1460, 1245, 1040 cm^{-1}. − $C_{15}H_{28}OSi$: Calcd. C 71.37, H 11.17; found C 71.21, H 11.26.

(4*E*)-2,2,5-Trimethyl-9-trimethylsilylnon-4-en-8-ynal: The same procedure as described for aldehyde **3a** was used with the above alcohol (20 mmol). The crude product was used in the following step without further purification. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.35 (s, 1 H), 5.03 (t, *J* = 7.6 Hz, 1 H), 2.19 (t, *J* = 6.9 Hz, 2 H), 2.09−2.03 (m, 4 H), 1.48 (s, 3 H), 0.93 (s, 6 H), 0.00 (s, 9 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.0, 136.5, 119.8, 106.7, 84.4, 46.3, 38.0, 35.0, 21.0 (2C), 18.8, 15.7, 0.00 (3C). − IR (neat): ṽ = 2940, 2690, 2160, 1720, 1460, 1245, 1040 cm^{-1}. − $C_{15}H_{26}OSi$: Calcd. C 71.94, H 10.46; found C 71.90, H 11.45.

(2*E*,6*E*)-Ethyl 4,4,7-trimethyl-11-trimethylsilylundeca-2,6-dien-10-ynoate (16): To a solution of anhydrous lithium chloride (1.01 g, 24.0 mmol) and triethylphosphonoacetate (4.25 mL, 21.4 mmol) in CH_3CN (10 mL), was added a solution of Et_3N (3.15 mL, 22.4 mmol) in CH_3CN (10 mL). After stirring at room temperature for 10 min, a solution of the aldehyde (20.4 mmol) in CH_3CN (5 mL) was added dropwise and the reaction mixture was stirred overnight. After being quenched with 10% dilute aqueous HCl, the reaction mixture was extracted with ether (× 3). The organic extracts were combined, dried with $MgSO_4$, and concentrated under vacuum to give a residue that was purified by chromatography (silica gel, EE/EP: 30:70) to afford the unsaturated ester (5.9 g, 92% for two steps). − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.93 (d, *J* = 15.8 Hz, 1 H), 5.71 (d, *J* = 15.8 Hz, 1 H), 5.17 (t, *J* = 7.6 Hz, 1 H), 4.18 (q, *J* = 6.9 Hz, 2 H), 2.31 (t, *J* = 7.1 Hz, 2 H), 2.21 (t, *J* = 7.1 Hz, 2 H), 2.05 (d, *J* = 7.6 Hz, 2 H), 1.58 (s, 3 H), 1.29 (t, *J* = 6.9 Hz, 3 H), 1.04 (s, 6 H), 0.12 (s, 9 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 157.7, 135.9, 121.0, 117.5, 106.9, 84.3, 59.9, 39.8, 38.7, 37.4, 26.0 (2C), 19.0, 15.8, 14.1, 0.00 (3C). − IR (neat): ṽ = 2960, 2160, 1720, 1640, 1360, 1300, 1250, 1170, 1170, 1040 cm^{-1}. − $C_{19}H_{32}O_2Si$: Calcd. C 71.20, H 9.90; found C 71.15, H 10.08.

Preparation of Dienynal 17

(2*E*,6*E*)-4,4,7-Trimethyl-11-trimethylsilylundeca-2,6-dien-10-yn-1-ol: To a stirred solution of ester **16** (6 g, 18.7 mmol) in CH_2Cl_2 (20 mL) at −78°C, was added dropwise diisobutylaluminium hydride (37.4 mL, 37.4 mmol, 1 M in dichloromethane) over a 15 min period. After this time the mixture was allowed to warm up to room temperature. Once the reaction was found to be complete by TLC analysis, the reaction mixture was poured into a cold ice/acetone mixture and stirring was maintained for 30 min. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic phases were washed with brine, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (eluting with EE/PE: 1:1) to yield 3.4 g (65%) of unsaturated alcohol. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.70 (d, *J* = 15.8 Hz,

1 H), 5.53 (dt, J = 6.1 and 15.8 Hz, 1 H), 5.21 (t, J = 7.1 Hz, 1 H), 4.12 (d, J = 6.1 Hz, 2 H), 2.32 (t, J = 6.6 Hz, 2 H), 2.21 (t, J = 6.6 Hz, 2 H), 1.98 (d, J = 7.1 Hz, 2 H), 1.59 (s, 3 H), 1.00 (s, 6 H), 0.14 (s, 9 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.7, 135.0, 124.4, 122.0, 107.2, 84.4, 63.7, 10.4, 38.7, 36.4, 26.6, 19.1, 15.9, 0.00. − IR (neat): ṽ = 3360, 2940, 2160, 1245, 1090 cm^{-1}.

(2*E*,6*E*)-4,4,7-Trimethyl-11-trimethylsilylundeca-2,6-dien-10-yn-1-al: The same procedure as described for aldehyde **3a** was used with the above alcohol (2.7 g, 9.7 mmol). The crude product was used in the following step without further purification. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.50 (d, J = 7.6 Hz, 1 H), 6.79 (d, J = 15.8 Hz, 1 H), 6.03 (dd, J = 7.6, 15.8 Hz, 1 H), 5.18 (t, J = 7.6 Hz, 1 H), 2.31−2.19 (m, 4 H), 2.13 (d, J = 7.6 Hz, 2 H), 1.60 (s, 3 H), 1.10 (s, 6 H), 0.15 (s, 9 H). − IR (neat): ṽ = 2940, 1680, 1620, 1460, 1430, 1210, 1130, 1100, 1010 cm^{-1}. − $C_{17}H_{28}OSi$: C 73.85, H 10.20; found C 73.70, H 10.14.

(2*E*,6*E*)-4,4,7-Trimethylundeca-2,6-dien-10-yn-1-al (17): To a solution of the above aldehyde in DMSO (15 mL) was added KF (2.81 g, 48.5 mmol) and water (20 equiv). After completion, the reaction mixture was diluted with ether and washed with a saturated solution of NH_4Cl and brine. The organic layer was dried with $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (eluting with EE/PE: 20:80) to yield 1.94 g (98%) of alkyne **17**. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.50 (d, J = 7.6 Hz, 1 H), 6.79 (d, J = 15.7 Hz, 1 H), 6.03 (dd, J = 7.6, 15.7 Hz, 1 H), 5.18 (t, J = 7.6 Hz, 1 H), 2.31−2.19 (m, 4 H), 2.13 (d, J = 7.6 Hz, 2 H), 1.94 (t, J = 2.5 Hz, 1 H), 1.60 (s, 3 H), 1.10 (s, 6 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.6, 168.0, 136.1, 129.5, 121.1, 84.2, 68.8, 40.1, 38.6, 38.4, 26.1 (2C), 17.5, 16.0. − IR (neat): ṽ = 3280, 2940, 1680, 1460, 1430, 1210, 1130, 1100, 1010 cm^{-1}.

(2*E*,6*E*)-4,4,7-Trimethyl-11-iodoundeca-2,6-dien-10-yn-1-al (4): A solution of alkyne **17** (9.7 mmol) in acetone (500 mL) was treated at room temperature with *N*-iodosuccinimide (2.61 g, 11.64 mmol) and 200 mg of silver nitrate. After 15 min the reaction mixture was poured with stirring into ice/water and the resulting precipitate was filtered off and dissolved in ether. The resulting solution was washed with water, dried, evaporated to dryness in vacuo and the final product was purified by chromatography, eluting with 20% EE in PE. Purification yielded 2 g (62%) of the expected iodoalkyne. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.57 (d, J = 7.6 and 4.0 Hz, 1 H), 6.93 (dd, J = 15.7 and 4.0 Hz, 1 H), 6.09 (dd, J = 15.7 and 7.6 Hz, 1 H), 5.27 (t, J = 7.1 Hz, 1 H), 2.52 (t, J = 7.1 Hz, 2 H), 2.26 (t, J = 7.1 Hz, 2 H), 2.19 (d, J = 7.1 Hz, 2 H), 1.67 (s, 3 H), 1.19 (s, 6 H). − ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.0, 166.5, 134.5, 128.0, 120.1, 38.8, 37.2, 37.0, 24.8 (2C), 18.6, 14.7. − IR (neat): ṽ = 2940, 2920, 1680, 1620, 1460, 1360, 1130, 1100, 1010 cm^{-1}.

Macrocyclization of Dienynal 4

(2*E*,6*E*)-4,4,7-Trimethylcycloundeca-2,6-dien-10-yn-1-ol (18): To a suspension of $CrCl_2$ (1.95 g, 15.9 mmol) in 150 mL of anhydrous and degassed THF, was added a solution of the iodo alkyne **4** (0.75 g 2.27 mmol) in THF (20 mL) by syringe-pump (15 mL/h). After 24 h the reaction was quenched with a saturated NH_4Cl solution and extracted with ether. The organic layer was diluted with ether and washed with brine, dried with $MgSO_4$, and finally concentrated under vacuum to give an oil, which was chromatographed (EE/PE: 40:60). Purification yielded 287 mg (62%) of the macrocycle **18**. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.60 (dd, J = 6.1, 15.8 Hz, 1 H), 5.44 (d, J = 15.8 Hz, 1 H), 5.18 (dd, J = 5.1, 9.7 Hz, 1 H), 4.94 (m, 1 H), 2.40−2.35 (m, 2 H), 2.32−2.23 (m, 2 H), 2.17 (dd, J = 10.2 Hz, 1 H), 1.97 (dd, J = 5.1 Hz, 1 H), 1.58 (s, 3 H), 1.21 (s, 3 H), 1.18 (s, 3 H). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 139.2, 134.5, 131.2, 125.6, 88.1, 87.9, 63.5, 42.3, 39.5, 38.0, 29.2, 24.8, 17.4, 14.7. − IR (neat): ṽ = 3360, 2940, 1440, 1380, 1355, 1295, 1120, 1060 cm^{-1}. − $C_{14}H_{20}O$: Calcd. C 82.3, H 9.86; found C 81.8, H 9.81.

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