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# An organocatalytic enantioselective synthesis of (+)-duryne

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ABSTRACT

An efficient enantioselective synthesis of the potent anticancer agent (+)-duryne was achieved by the use of a one-pot organocatalyzed hydroxylation/Ohira–Bestmann and Grubbs cross-metathesis/selective *cis*-Wittig reaction. This new approach is envisioned to facilitate the synthesis of every representative member of the family.



## 1. Introduction

Enantioenriched propargylic alcohols are key structural units of many natural products isolated from various marine sponges such as *Cribrochalina dura*, *Diplastrella*, *Petrosia*, and *Haliclona*.[1] Molecules derived from these marine sponges were reported to be endowed with potent cytotoxicity toward tumor cell lines.[2] The exceedingly cytotoxic property was attributed to the occurrence of the enantioenriched propargylic alcohol motif. Among the first one reported was the highly cytotoxic duryne molecule **1a**, isolated from *Cribrochalina dura*, which inhibits several human tumor cell lines, in particular against p388 murine leukemia with an $IC_{50}$ of 0.07 μg/mL.[3]

The (+)-duryne molecule possesses $C_2$ symmetry, encompassing a terminal propargylic alcohol linked by a *trans* double bond with a pendant $C_9$ long chain carbon unit and the same fragment connected to each side of a *cis* double bond. The structurally related petrosynol **1b** has been isolated from the Red Sea sponge *Petrocia* sp. and was synthesized due to its inhibitory activity of the reverse transcriptase of the human immunodeficiency virus (HIV).[4] Novel brominated polyacetylenic diols diplynes C **1c** has been isolated along with several related family members via an inhibitory activity guided screening and their absolute configurations established.[1d,5] A C-17 polyacetylenic diol falcarindiol **1d** has also been isolated as an algicidal principle against the harmful red tide dinoflagellate[6] (Fig. 1).

## 2. Results and discussion

Due to the interesting biological activities of **1a**, many synthetic approaches have been recorded.[7] Recently, Gung et al.[8] achieved the unambiguous total synthesis of natural polyacetylenic alcohol (+)-duryne **1a** and established the central olefin geometry as well as the absolute configuration of stereogenic centers to be (15*Z*,3*S*,28*S*) (Fig. 1). In all of the previous syntheses of (+)-duryne, the stereogenic centers were determined by enzymatic kinetic resolution of the respective racemic substrates. In view of the exceptional pharmacological profile coupled with low natural abundance, we herein report an alternative strategy for the synthesis of **1a**.

With our continued interest in developing catalytic routes to bioactive small molecules,[9] we recently developed a flexible organocatalytic enantioselective synthesis of heptadeca-1-ene-4,6-diyne-(3*S*,8*R*,9*S*,10*S*)-tetrol and its congeners using the proline-catalyzed aminoxylation as the key step.[10] As a logical extension, we herein report the enantioselective synthesis of the natural product (+)-duryne, which relies on two catalytic steps; (a) a one-pot organocatalyzed hydroxylation/Ohira–Bestmann reaction[11] and (b) a Grubbs cross-metathesis. Our retrosynthetic approach is shown in Scheme 1. We envisioned that **1a** could be obtained by a *cis*-Wittig reaction between fragments (*S*)-**2** and (*S*)-**3**, which in turn could be derived from a common advanced intermediate (*S*)-**2**. The crucial synthone (*S*)-**2** could be generated via a cross metathesis between MOM-protected allyl substrate (*S*)-**4** and a terminal olefin $C_{12}$ carbinol **5**. The MOM-protected allyl substrate (*S*)-**4** could be obtained from the substituted propargyl alcohol (*S*)-**6**, which in turn could be synthesized by a one-pot organocatalyzed hydroxylation/Ohira–Bestmann reaction.

Our initial interest was focused on the synthesis of crucial synthon (*S*)-**6** and terminal olefin $C_{12}$ carbinol **5**. The synthesis of **5** began with diol **7**. The monobromination of **7** yielded **8**, and was followed by protection of the primary alcohol to its TBS ether to yield **9**. Base induced dehydrobromination of **9** and subsequent cleavage of the silyl group gave **5** in 60% overall yield (Scheme 2).

We envisaged that a one-pot reaction could be used to install a hydroxyl stereogenic center as well as the propargyl functionality to give (*S*)-**6**. Initially, a proline-catalyzed α-aminoxylation strategy[12] was adopted for **11** to give labile α-aminoxy aldehyde

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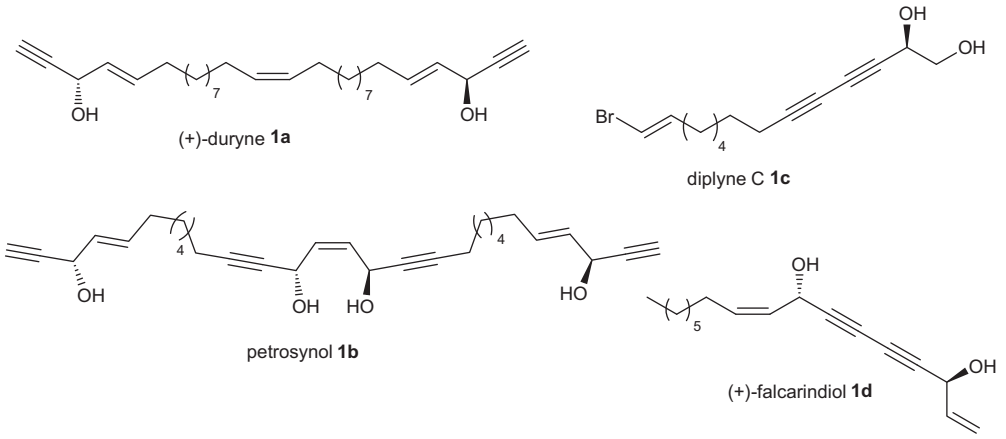
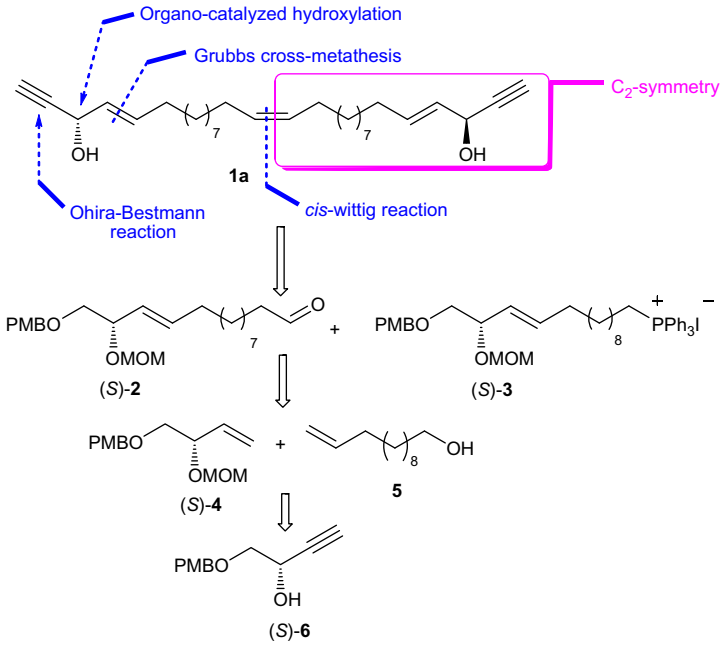


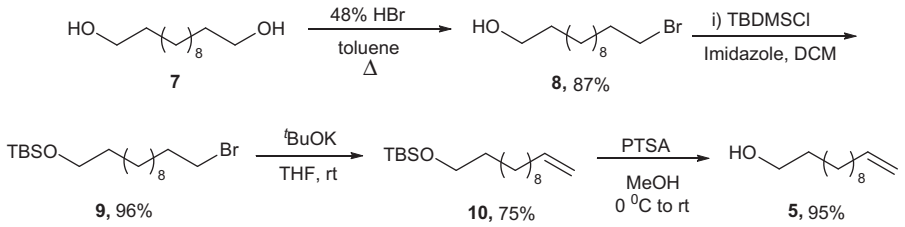

**Figure 1.** Natural polyacetylenic alcohols **1a–d**.




**Scheme 1.** Retrosynthetic analysis of (+)-duryne.

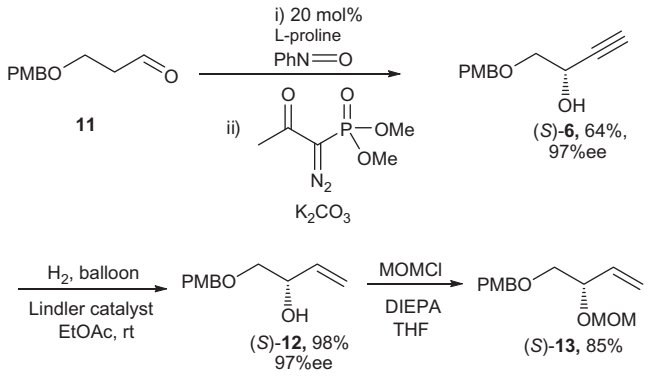
and attempted to capture the labile aminoxylated aldehyde by a Wittig reaction under various conditions. Unfortunately, we could not succeed to generate the anticipated compound (*S*)-**12**. The labile α-aminoxy aldehyde was also subjected to the Ohira–Bestmann reaction in situ in order to convert the aldehyde to a terminal acetylene using different reaction conditions, such as DMSO[12a] or $CHCl_3$,[12b] however no trace of the desired compound (*S*)-**6** was observed.

The desired transformation was eventually achieved by evaporation of the original acetonitrile solvent and the resulting residue was dissolved in MeOH followed by the addition of an Ohira–Bestmann reagent/base and stirring for 24 h at ambient temperature. The desired compound (*S*)-**6**[13] was obtained in 64% yield with 97% enantiomeric purity, while avoiding an O–N cleavage step. With (*S*)-**6** in hand, we next determined the enantiomeric purity and the absolute configuration of the new stereogenic center in




**Scheme 2.** Synthesis of terminal olefin $C_{12}$ carbinol **5**.

(*S*)-**6**. Hence, the terminal acetylene in (*S*)-**6** was reduced to an olefin under Lindlar conditions to provide (*S*)-**12** in 98% yield and 97% ee. The enantiomeric purity and absolute configuration of the new stereogenic center in (*S*)-**12** were determined by comparing the specific rotation data reported in the literature.[10] Protection of the secondary alcohol with MOM-Cl under basic conditions furnished (*S*)-**13** in 85% yield (Scheme 3). At first, we attempted to carry out a cross metathesis between (*S*)-**12** and olefin **10** using a second-generation Grubbs catalyst. However, when this reaction was carried out, no trace of the required product (*S*)-**14a** was observed (Table 1, entry 1). The MOM ether (*S*)-**13** and **10** were subjected to a cross-metathesis reaction under otherwise similar conditions. However, this reaction also failed to give the anticipated product (*S*)-**14b** (Table 1, entry 2). Eventually the cross metathesis reaction between (*S*)-**13** and tethered alcohol olefin **5** was carried out by using 10 mol % of second-generation Grubbs catalyst to give (*S*)-**14c** in moderate yield (Table 1, entry 3). After substantial experimentation, by varying the stoichiometry of the coupling partners of (*S*)-**13** and **5** (Table 1, entries 4 and 5), we found that using 8 mol % of second-generation Grubbs catalyst resulted in the formation of (*S*)-**14c** (76%) with an *E*/*Z* ratio of 9:1 ($^1$H NMR) (Table 1, entry 6).[14]




**Scheme 3.** Organo-catalyzed synthesis of **13**.

Having obtained compound (*S*)-**14c** in substantial amounts, we generated the two crucial intermediates **2** and **3** from the same synthon. Accordingly, the primary alcohol of (*S*)-**14c** was converted into iodo (*S*)-**15** in the presence of iodine, triphenylphosphine, and imidazole. Refluxing the corresponding iodo compound (*S*)-**15** with triphenylphosphine in acetonitrile resulted in Wittig salt (*S*)-**3** and the crude salt was subjected to further reaction. The IBX oxidation of (*S*)-**14c** also furnished aldehyde (*S*)-**2** in 90% isolated yield (Scheme 4). Primarily, we adopted an auto oxidation process under salt free conditions[15] using phosphonium salt (*S*)-**3**. However, only trace amounts of the required product (*S*,*S*)-**16** were isolated. Next we screened conditions for the Wittig reaction to access the symmetrical Z-olefination. Thus, the reaction of (*S*)-**2** and (*S*)-**3** in the presence of the Rochow base (NaHMDS) in THF at 0 °C gave (*S*,*S*)-**16** as a detectable isomer in 60% yield with >99% diastereoselectivity (assessed by $^1$H NMR).[16] Oxidative deprotection of PMB resulted in diol (*S*,*S*)-**17**. The terminal acetylenic functionality was installed by a two step sequence. Diol (*S*,*S*)-**17** was subjected to oxidation using DMP in DCM and the resulting crude aldehyde was then reduced with an Ohira–Bestmann reagent under basic conditions in MeOH to give MOM protected $C_2$ symmetric (+)-duryne (*S*,*S*)-**18**.[17]

The deprotection of the MOM group in (*S*,*S*)-**18** using acidic reagents gave us cause for concern. None of the mineral acids (1 M HCl in THF or MeOH or MeCN) were able to give us the required deprotection. Eventually, the (*S*,*S*)-**18** to **1a** transformation was achieved by using PTSA in MeOH at ambient temperature to give **1a** in 72% yield (Scheme 5). The optical and spectroscopic data of **1a** {$[\alpha]_D^{23} = +24.8$ (*c* 1.8, $CHCl_3$), lit.[8] $[\alpha]_D^{23} = +25$ (*c* 1.4, $CHCl_3$)} were in full accordance with those reported in the literature.[8]

## 3. Conclusion

In conclusion, we have developed a concise enantioselective route for the synthesis of natural product (+)-duryne. The salient features of this concise synthesis are; (i) the genesis of chirality through an organocatalytic reaction; (ii) the two critical intermediates are generated from the same synthon, which in turn can be obtained by two catalytic reactions. The advanced intermediates generated in this protocol by a one-pot organocatalyzed hydroxylation/Ohira–Bestmann reaction circumvent the need for an O–N cleavage step. This advanced intermediate can facilitate the synthesis of each representative member of the *Haplosclerid* and *Spira-strellid* sponges.

## 4. Experimental

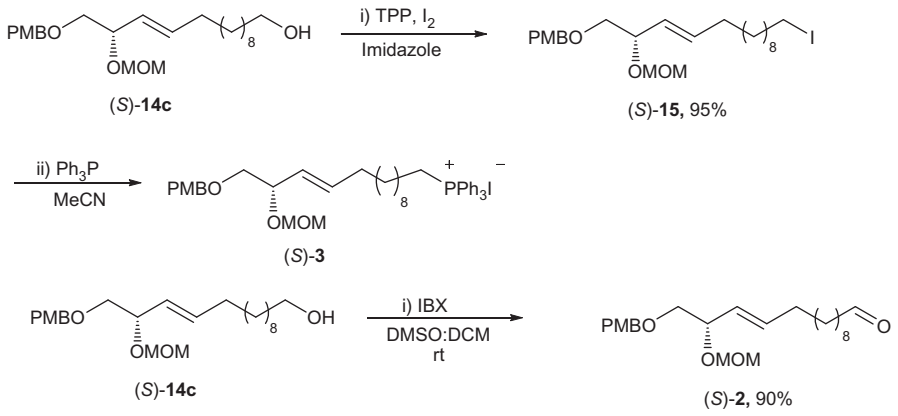
### 4.1. General

All reactions were conducted under an atmosphere of nitrogen (IOLAR, Grade I). The apparatus used for the reactions were oven dried and THF was distilled over sodium benzophenone ketyl before use. All other chemicals used were commercially available. The progress of the reactions was monitored by TLC on Silica Gel 60 F-254 pre-coated. Evaporation of the solvents was performed at reduced pressure on a rotary evaporator. Column chromatography was carried out with silica gel grade 60–120, 100–200 mesh. $^1$H NMR spectra were recorded at 300 and 500 MHz and $^{13}$C NMR at 75 MHz in $CDCl_3$. *J* values were recorded in Hertz and

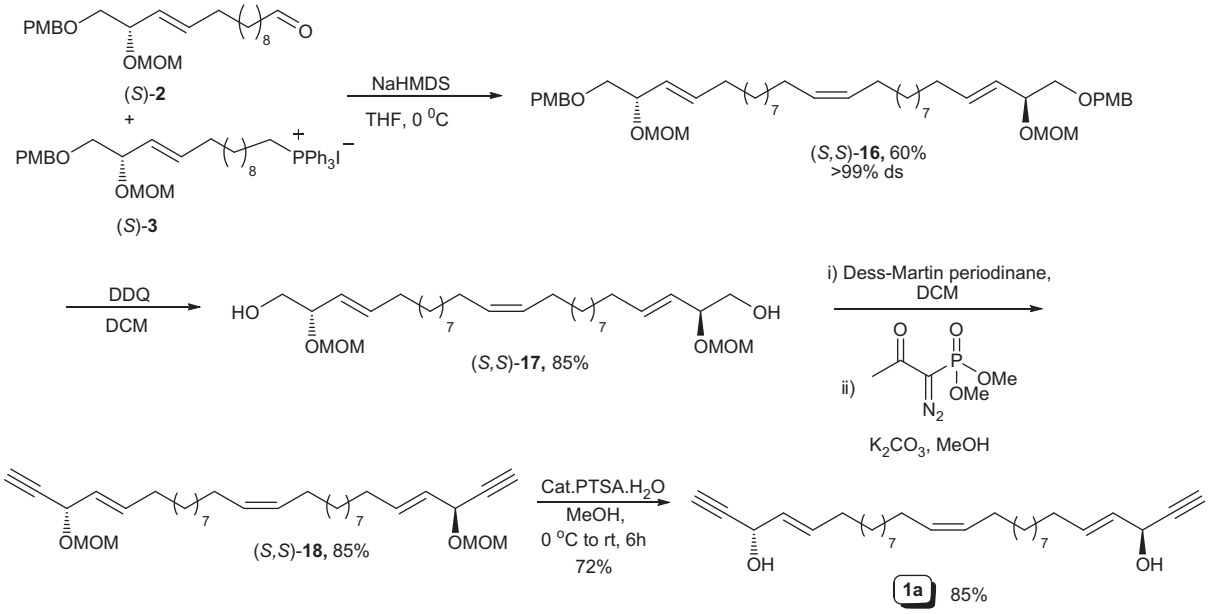
**Table 1**
Stoichiometry variation in the Grubbs cross metathesis reaction

| Entry | PMBO, OR | OR' | Catalyst mol % | PMBO, OR, OR' (*S*)-**14a-c**[b] | Yield %[a] |
|---|---|---|---|---|---|
| 1 | (*S*)-**12**, R = H (1 equiv) | **10**, R′ = TBDMS (1.5 equiv) | 10 | (*S*)-**14a**, R = H, R′ = TBDMS | NR |
| 2 | (*S*)-**13**, R = MOM (1 equiv) | **10**, R′ = TBDMS (1.5 equiv) | 10 | (*S*)-**14b**, R = MOM, R′ = TBDMS | NR |
| 3 | (*S*)-**13**, R = MOM (1 equiv) | **5**, R′ = H (1.5 equiv) | 10 | (*S*)-**14c**, R = MOM, R′ = H | 60 |
| 4 | (*S*)-**13**, R = MOM (1 equiv) | **5**, R′ = H (1 equiv) | 10 | (*S*)-**14c**, R = MOM, R′ = H | 65 |
| 5 | (*S*)-**13**, R = MOM (1.5 equiv) | **5**, R′ = H (1 equiv) | 10 | (*S*)-**14c**, R = MOM, R′ = H | 76 |
| 6 | (*S*)-**13**, R = MOM (1.5 equiv) | **5**, R′ = H (1 equiv) | 8 (5+3)[c] | (*S*)-**14c**, R = MOM, R′ = H | 76 |

[b] Major *E*-isomer and *E*/*Z* (9:1) ratio established by $^1$H NMR.
[a] Isolated yield of the purified material.
[c] Catalyst was added in two portions.




**Scheme 4.** Synthesis of aldehyde (*S*)-**2** and Wittig salt (*S*)-**3**.




**Scheme 5.** Synthesis of natural molecule (+)-duryne **1a**.

the abbreviations used are s-singlet, d-doublet, t-triplet, q-quartet, m-multiplet, and br-broad. Chemical shifts ($\delta$) are reported relative to TMS ($\delta$ = 0.0) as the internal standard. IR spectra were recorded on FT/IR-5700. Mass spectral data were compiled using MS (ESI) and HRMS mass spectrometers. Optical rotations were recorded on high sensitive polarimeter with a 10 mm cell.

#### 4.1.1. 12-Bromododecan-1-ol 8

To a solution of diol **7** (28 g, 0.14 mol) in toluene (600 mL) was added concentrated HBr [27.5 mL of a 48% (9 M) aqueous solution, 0.162 mol]. The heterogeneous mixture was heated at reflux for 36 h, after which TLC analysis showed that 20% of the diol still remained. Thus, a further quantity of HBr (10 mL, 0.09 mol) was added, and the mixture was heated at reflux for a further 12 h, after which TLC analysis showed no diol remaining. The reaction mixture was allowed to return to room temperature, and the phases were separated. The organic layer was diluted with ether (200 mL) and washed with 1 M NaOH solution (200 mL) and brine solution (300 mL). Drying over anhydrous $Na_2SO_4$, filtration and concentration of the organic layer gave a yellow oil, which was purified by column chromatography using hexane/ether as eluent (7:3) to provide **8** as a pale yellow oil (32.0 g, 87%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 3.64 (t, $J$ = 6.6 Hz, 2H), 3.40 (t, $J$ = 7.0 Hz, 2H), 1.89–1.80 (m, 2H), 1.61–1.51 (m, 2H), 1.44–1.27 (m, 16H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 62.8, 33.9, 32.7, 32.6, 29.5, 29.4, 29.3, 28.7, 28.1, 25.6; IR (neat): 3358, 2923, 2362,1740,1515, 1052 cm$^{-1}$; ESI-MS: $m/z$ 365 (M+H)$^+$.

#### 4.1.2. (12-Bromododecyloxy)(*tert*-butyl)dimethylsilane 9

To a solution of bromo alcohol **8** (2.0 g, 7.55 mmol) in dichloromethane (25 mL), imidazole (0.62 g 9.06 mmol), followed by TBSCl (1.25 g, 8.30 mmol) were added at 0 °C. This reaction mixture was allowed to stir at room temperature for 2 h. The reaction mixture was quenched with cold water (25 mL), and the phases were separated. The organic layer was washed with brine (25 mL), dried over anhydrous $Na_2SO_4$ and concentration of the organic layer gave a yellow oil, which was purified by column chromatography using hexane as eluent to provide title compound **9** as a colorless oil (2.74 g, 96%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 3.57 (t, $J$ = 6.4 Hz, 2H), 3.37 (t, $J$ = 6.8 Hz, 2H), 1.90–1.80 (m, 2H), 1.51–1.41 (m, 4H), 1.34–1.24 (m, 14H), 0.03 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 63.3, 33.9, 32.9, 32.8, 29.6, 29.5, 29.4, 28.8, 28.2, 26.0, 25.8, 18.4,

-5.3; IR (neat): 2927, 2333, 1516, 1099, 837 $cm^{-1}$; ESI-MS: *m*/*z* 379 $(M+H)^+$; ESI-HRMS: calcd for $C_{18}H_{40}OSiBr$ 379.2031, found 379.2015.

#### 4.1.3. *tert*-Butyl(dodec-11-enyloxy)dimethylsilane 10

To a solution of alkyl bromide **9** (4.36 g, 11.5 mmol) in THF (60 mL), *t*-BuOK (3.86 g, 34.4 mmol) was added in one portion at 0 °C under nitrogen atmosphere. The reaction mixture was then allowed to stir at room temperature. After completion of the reaction (monitored by TLC 1 h), ice cubes were added and extracted with ether (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude residue was subjected to column chromatography using hexane as the eluent to afford olefin **10** as a colorless oil (2.57 g, 75%). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 5.83–5.70 (m, 1H), 4.99–4.88 (m, 2H), 3.58 (t, *J* = 6.4 Hz, 2H), 2.03 (q, *J* = 7.0 Hz, 2H), 1.49 (t, *J* = 6.2 Hz, 2H), 1.32–1.23 (m, 14H), 0.03 (s, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 139.2, 114.1, 63.32, 33.8, 32.9, 29.6, 29.5, 29.4, 29.1, 28.9, 26.0, 25.8, 18.4, -5.3; IR (neat): 2926, 2362, 11646, 1099, 774 $cm^{-1}$; ESI-MS: *m*/*z* 299 $(M+H)^+$.

#### 4.1.4. Dodec-11-en-1-ol 5

At first, PTSA (0.464 g, 2.44 mmol), was added to a solution of TBS–ether **10** (7.3 g, 24.4 mmol) in methanol (75 mL) at 0 °C. The reaction mixture was allowed to stir at 0 °C to room temperature for 1 h. The solvent was then removed under reduced pressure. The resultant residue was dissolved in ether (100 mL), and satd $NaHCO_3$ (50 mL) and brine (50 mL) washes were applied, after which the residue was dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The crude residue was subjected to column chromatography using hexane/ethyl acetate (9:1) as eluent to afford alcohol **5** as a colorless oil (4.27 g, 95%). $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 5.85–5.77 (m, 1H), 5.00–4.91 (m, 2H), 3.63 (t, *J* = 6.9 Hz, 2H), 2.03 (q, *J* = 6.9 Hz, 2H), 1.59–1.53 (m, 2H), 1.38–1.22 (m, 14H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 139.2, 114.0, 62.9, 33.8, 32.7, 29.5, 29.4, 29.1, 28.9, 25.7; IR (neat): 3334, 2924, 2362, 1645, 1462, 909 $cm^{-1}$; ESI-MS: *m*/*z* 185 $(M+H)^+$.

#### 4.1.5. (*S*)-1-(4-Methoxybenzyloxy)but-3-yn-2-ol (*S*)-6

Compound **11** (160 mg, 0.82 mmol) was dissolved in acetonitrile (5 mL) and cooled to −20 °C. To this, L-proline (19 mg, 0.16 mmol) was added followed by nitroso benzene (88 mg, 0.82 mmol). The resultant reaction mixture was stirred for 24 h during which time, the acetonitrile solvent evaporated and the residue was redissolved in methanol (8 mL). Next, the Ohira–Bestmann reagent (236 mg, 1.23 mmol) in methanol (8 mL) and $K_2CO_3$ (226 mg, 1.64 mmol) were added sequentially. The reaction mixture was allowed to stir for 8 h at 0 °C. The reaction mixture was quenched by satd $NH_4Cl$ (10 mL) and the combined contents were stirred for an additional 24 h at ambient temperature. The organic solvent was removed under reduced pressure and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography using hexane/ethyl acetate (7:1) as eluent to give title compound (*S*)-**6** as a pale yellow oil (108 mg, 64% for three conversions). $[\alpha]_D^{24} = +4.8$ (*c* 1.9, $CHCl_3$) 97% ee; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.28–7.25 (m, 2H), 6.90–6.87 (m, 2H), 4.54 (d, *J* = 3.02 Hz, 2H), 3.80 (s, 3H), 3.64–3.52 (m, 2H), 2.46 (d, *J* = 2.26 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 159.2, 129.5, 128.6, 114.0, 73.6, 73.1, 73.0, 65.0, 61.4, 55.3; IR (neat): 3402, 3280, 2118, 1615, 1514, 1466, 1363, 1303, 1246, 1177, 1101, 1088, 1029, 925, 816 $cm^{-1}$; ESI-MS (*m*/*z*): 229 $(M+Na)^+$; HRMS calcd for $C_{12}H_{14}O_3Na$ 229.0835, found 229.0828.

#### 4.1.6. (*S*)-1-(4-Methoxybenzyloxy)but-3-en-2-ol (*S*)-12

To a stirred solution of (*S*)-**6** (70 mg, 0.109 mmol) in ethyl acetate (3 mL) were added sequentially quinoline (17 mL, 0.131 mmol) and Lindlar's catalyst (15 mg). The solution was placed under an atmosphere of $H_2$ and allowed to stir for 6 h at room temperature. The solution was filtered through a small plug of Celite and further washed with EtOAc. The filtrate was concentrated under reduced pressure and the crude residue was purified by column chromatography using hexane/ethyl acetate (7:1) as eluent to give (*S*)-**12** (0.068 g, 98%) as a colorless oil. $[\alpha]_D^{24} = -2.0$ (*c* 2.0, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 7.26 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 5.83 (ddd, *J* = 16.4, 10.4, 5.5 Hz, 1H), 5.35 (d, *J* = 17.4 Hz, 1H), 5.19 (d, *J* = 10.6 Hz, 1H), 4.50 (s, 2H), 4.33 (br s, 1H), 3.81 (s, 3H) 3.52 (dd, *J* = 9.6, 3.4 Hz, 1H), 3.44 (dd, *J* = 9.4, 7.9 Hz, 1H), 2.45 (br s, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 159.1, 136.5, 129.7, 129.3, 116.2, 113.7, 73.6, 72.8, 55.1, 25.5; IR (neat) 3448, 2860, 2362, 1613, 1462, 1096, 820 $cm^{-1}$; ESIMS (*m*/*z*): 231 $(M+Na)^+$; HRMS calcd for $C_{12}H_{16}O_3Na$ 231.0997, found 231.1000.

#### 4.1.7. (*S*)-1-Methoxy-4-((2-(methoxymethoxy) but-3-enyloxy) methyl) benzene (*S*)-13

At first, MOM-Cl (2.71 mL, 35.68 mmol) was added to a solution of alcohol (*S*)-**12** (2.47 g, 11.9 mmol) and diisopropyl ethylamine (26.8 mL) in dichloromethane (30 mL) at 0 °C. This resultant reaction mixture was stirred at 0 °C to room temperature for 2 h. Then the reaction was quenched with water (20 mL). The organic layer was separated and the aqueous layer extracted with dichloromethane (2 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The resultant residue was purified by silica gel column chromatography using hexane/ethyl acetate (7:1) as eluent to give title compound (*S*)-**13** as a pale yellow oil (2.85 g, 85%). $[\alpha]_D^{24} = +12.4$ (*c* 1.9, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.26 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz), 5.80 (ddd, *J* = 7.0 Hz, *J* = 10.4 Hz, *J* = 17.4 Hz, 1H), 5.32 (d, $J_1$ = 17.9 Hz, 1H), 5.25 (d, *J* = 10.4 Hz, 1H), 4.68 (dd, *J* = 6.6 Hz, *J* = 22.5 Hz, 2H), 4.51 (s, 3H), 4.26 (dd, *J* = 6.0 Hz, *J* = 11.7 Hz, 1H), 3.80 (s, 3H), 3.54–3.48 (m, 2H), 3.38 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 158.9, 135.1, 129.3, 129.0, 117.9, 113.7, 113.5, 94.0, 75.8, 72.7, 72.4, 55.1, 55.0; IR (neat): 2925, 2333, 1612, 1513, 1248, 1099, 821 $cm^{-1}$; ESI-MS: *m*/*z* 270 $(M+NH_4)^+$; ESI-HRMS: calcd for $C_{14}H_{20}O_4Na$ 275.1259, found 275.1251.

#### 4.1.8. (*S*,*E*)-14-(4-Methoxybenzyloxy)-13-(methoxymethoxy) tetradec-11-en-1-ol (*S*)-14c

To a solution of the cross metathesis partners [dodecenol **5**, 1.33 g, 7.23 mmol; olefin (*S*)-**13**, 2.19 g, 8.67 mmol] in dichloromethane (25 mL) was added Grubbs 2nd generation catalyst (600 mg, 0.71 mmol) at room temperature. Then, the reaction was heated at reflux for 6 h. The TLC analysis indicated that ~20% of starting materials still remained. Thus, a further quantity of (146 mg, 0.17 mmol) Grubbs 2nd generation catalyst was added, and the reaction mixture was heated at reflux for a further 4 h. The solvent was then removed under reduced pressure, and the residue was purified by column chromatography using hexane/ethyl acetate (6:1) as eluent to afford title compound (*S*)-**14c** as a brown oil (2.24 g, 76%, 9:1 *E*/*Z*) $[\alpha]_D^{24} = +29.6$ (*c* 1.4, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.20 (t, *J* = 8.4 Hz, 2H), 6.83–6.80 (m, 2H), 5.72–5.64 (m, 1H), 5.45–5.28 (m, 1H), 4.70–4.55 (m, 2H), 4.48–4.44 (m, 2H), 4.23–4.09 (m, 1H), 3.80 (s, 3H), 3.60 (t, *J* = 7.3 Hz, 2H), 3.48–3.39 (m, 2H), 3.34 (s, 3H), 2.06–2.02 (m, 2H), 1.57–1.52 (m, 2H),1.43–1.25 (m, 14H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 159.1, 130.8, 130.2, 129.1, 126.4, 113.6, 94.2, 94.1, 74.9, 74.9, 72.8, 72.5, 55.3, 55.2, 32.7, 32.2, 29.6, 29.5, 29.4, 29.3, 29.0, 28.9, 25.7; IR (neat): 3565, 2852, 2362, 1513, 1246, 1099, 1101 $cm^{-1}$; ESI-MS:

*m*/*z* 431 $(M+Na)^+$ ESI-HRMS: calcd for $C_{24}H_{40}O_5Na$ 431.2773, found 431.2783.

#### 4.1.9. (*S*,*E*)-1-((14-Iodo-2-(methoxymethoxy) tetradec-3-enyloxy) methyl)-4methoxybenzene (*S*)-15

To a solution of alcohol (*S*)-**14c** (1 g, 2.45 mmol) in dichloromethane (30 mL), triphenyl phosphine (707 mg, 2.7 mmol) followed by imidazole (333 mg, 4.9 mmol) were added at room temperature, then the reaction temperature was decreased to 0 °C and $I_2$ (686 mg, 2.7 mmol) was added. This reaction mixture was allowed to stir at 0 °C to room temperature for 1 h. The reaction was diluted with dichloromethane (20 mL), then washed with satd $NaHCO_3$ (30 mL), sodium thiosulfate (30 mL), and brine (30 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography using hexane/ethyl acetate (11:1) as eluent to give iodide (*S*)-**15** as a pale yellow oil (1.2 g, 95%). $[\alpha]_D^{24} = +11.6$ (*c* 0.3, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.26 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.77–5.67 (m, 1H), 5.37–5.30 (m, 1H), 4.73 (d, *J* = 6.6 Hz, 1H), 4.60 (d, *J* = 6.6 Hz, 1H), 4.51 (s, 2H), 4.24 4.18 (m, 1H), 3.80 (s, 3H), 3.52–3.44 (m, 2H), 3.37 (s, 3H), 3.18 (t, *J* = 7.0 Hz, 2H), 2.03 (q, *J* = 7.0 Hz, 2H),1.86–1.76 (m, 2H), 1.42–1.26 (m, 14H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 159.0, 135.8, 130.4, 129.1, 126.4, 113.6, 93.6, 75.5, 72.9, 72.8, 55.2, 33.5, 32.3, 30.4, 29.6, 29.4, 29.1, 29.0, 28.5; IR (neat): 2925,2853, 2362, 1647, 1515, 1248, 1034 $cm^{-1}$; ESI-MS: *m*/*z* 536 $(M+NH_4)^+$; ESI-HRMS: calcd for $C_{24}H_{39}O_4NaI$ 541.1790, found 541.1771.

#### 4.1.10. (*S*,*E*)-14-(4-Methoxybenzyloxy)-13-(methoxymethoxy) tetradec-11-enal (*S*)-2

Dichloromethane (20 mL) was added to a mixture of alcohol (*S*)-**14c** (1.1 g, 2.7 mmol), IBX (1.51 g, 5.4 mmol), and DMSO (2 mL) under nitrogen atmosphere. The reaction mixture was stirred for 6 h at room temperature, and then the solvent was removed, adsorbed on silica gel and purified by column chromatography using hexane/ethyl acetate (9:1) as eluent to give aldehyde (*S*)-**2** as a colorless oil (0.99 g, 90%). $[\alpha]_D^{24} = +40.6$ (*c* 0.75, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 9.75 (s, 1H), 7.25 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.3 Hz, 2H), 5.76–5.66 (m, 1H), 5.37–5.29(m, 1H), 4.72 (d, *J* = 6.8 Hz, 1H), 4.59 (d, *J* = 6.8 Hz, 1H),4.50 (s, 2H), 4.23–4.17 (m, 1H), 3.80 (s, 3H), 3.58–3.44 (m, 2H), 3.36 (s, 3H), 2.41 (t, *J* = 6.8 Hz, 2H), 2.06–1.99 (m, 2H), 1.70–1.57 (m, 2H), 1.43–1.15 (m, 14H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 202.9, 159.0, 135.8, 130.4, 129.1, 126.5, 113.6, 93.6, 75.5, 72.9, 72.8, 55.2, 43.8, 32.3, 29.3, 29.1, 29.0, 22.0; IR (neat): 2925, 2362,1724, 1514, 1247, 1096. $cm^{-1}$; ESI-MS: *m*/*z* 429 $(M+Na)^+$.

#### 4.1.11. (6*E*,17*E*,28*E*)-5,30-Bis((4-methoxybenzyloxy)methyl)-2,4,31,33-tetraoxatetratriaconta-6,17,28-triene (*S*,*S*)-16

To a solution of iodide (*S*)-**15** (302 mg, 0.58 mmol) in dry acetonitrile (15 mL) triphenylphosphine (229 mg, 0.87 mmol) was added at room temperature and the contents were refluxed for 12 h. The solvent was removed under reduced pressure, and the resultant material (*S*)-**3** was washed with hexane (2 × 5 mL) and dried under vacuum. The crude salt (*S*)-**3** was dissolved in dry THF (5 mL) and to this, a 1 M solution of NaHMDS in THF (0.55 mL) was added at 0 °C. The resulting red brown reaction mixture was allowed to stir at room temperature for 45 min, thereafter, after which the temperature was shifted to 0 °C. Next, aldehyde (*S*)-**2** (214 mg, 0.53 mmol) in THF (2 mL) was added slowly. After the addition, the reaction contents were allowed to stir from 0 °C to room temperature over a period of 45 min. The reaction mixture was quenched with water, and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified over silica gel column chromatography using hexane/ethyl acetate (7:1) to give (*S*,*S*)-**16** as a pale yellow oil (250 mg, 60%, >99% diastereoselectivity). $[\alpha]_D^{24} = +21.3$ (*c* 3.8, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.21 (d, *J* = 8.3 Hz, 4H), 6.81 (d, *J* = 9.1 Hz, 4H), 5.74–5.64 (m, 2H), 5.34–5.26 (m, 4H), 4.67 (d, *J* = 6.0 Hz, 2H), 4.54 (d, *J* = 6.8 Hz, 2H), 4.48 (s, 4H), 4.19–4.13 (m, 2H), 3.79 (s, 6H), 3.49–3.38 (m, 4H), 3.34 (s, 6H), 2.07–1.96 (m, 8H), 1.39–1.26 (m, 28H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 159.1, 135.9, 130.4, 129.8, 129.1, 126.4, 113.7, 93.5, 75.6, 72.9, 72.8, 55.2, 32.3, 29.8, 29.7, 29.6, 29.4, 29.3, 29.1, 29.0, 27.2; IR (neat): 2923, 2852, 2362, 1709,1513, 1248, 1030, 821 $cm^{-1}$; ESI-MS: *m*/*z* 799 $(M+NH_4)^+$; ESI-HRMS: calcd for $C_{48}H_{76}O_8Na$ 803.5437, found 803.5462.

#### 4.1.12. (2*S*,3*E*,14*Z*,25*E*,27*S*)-2,27-Bis(methoxymethoxy)octacosa-3,14,25-triene-1, 28-diol (*S*,*S*)-17

To a stirred solution of (*S*,*S*)-**16** (320 mg, 0.41 mmol) in dichloromethane/water (19:1, 10 mL), DDQ (140 mg, 0.62 mmol) was added at 0 °C. The reaction mixture was stirred at 0 °C to room temperature for 1 h, and then the reaction was diluted with dichloromethane (10 mL) and quenched with satd $NaHCO_3$ solution (10 mL). The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by silica gel column chromatography using hexane/ethyl acetate (3:1) to give title compound (*S*,*S*)-**17** as a pale yellow oil (188 mg, 85%). $[\alpha]_D^{24} = +34.6$ (*c* 0.8, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 5.79–5.73 (m, 2H), 5.37–5.29 (m, 4H), 4.74 (d, *J* = 7.0 Hz, 2H), 4.61 (d, *J* = 6.0 Hz, 2H), 4.11–4.07 (m, 2H), 3.61–3.54 (m, 4H), 3.40 (s, 6H), 2.08–1.96 (m, 8H), 1.38–1.2 (m, 28H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 136.5, 129.8, 125.8, 94.1, 78.8, 65.7, 55.4, 35.0, 29.7, 29.5, 29.4, 29.3, 29.1, 29.0, 27.2; IR (neat): 3449, 2925, 2854, 2362, 1709, 1693, 1516, 1034 $cm^{-1}$; ESI-MS: *m*/*z* 563 $(M+Na)^+$; ESI-HRMS: calcd for $C_{32}H_{60}O_6Na$ 563.4287, found 563.4306.

#### 4.1.13. (6*E*,17*Z*,28*E*)-5,30-Diethynyl-2,4,31,33-tetraoxatetratriaconta-6,17,28-triene (*S*,*S*)-18

To a solution of diol (*S*,*S*)-**17** (167 mg, 0.31 mmol) in dichloromethane (8 mL) was added DMP (394 mg, 0.93 mmol) at 0 °C. The resulting reaction mixture was stirred at room temperature for 1 h, and then the reaction mixture was further diluted with dichloromethane (10 mL) and washed with satd $NaHCO_3$ (4 mL), sodium thiosulfate (4 mL), and brine (4 mL) and dried over anhydrous $Na_2SO_4$. The contents were filtered and concentrated under reduced pressure. The resultant crude residue was passed through a small plug of silica gel using ether as eluent. Removal of the ether solvent under reduced pressure afforded the aldehyde, which was immediately dissolved in anhydrous MeOH (6 mL). To this reaction mixture, Ohira–Bestmann reagent (178 mg, 0.93 mmol) and $K_2CO_3$ (171 mg, 1.24 mmol) were sequentially added at 0 °C. After 4 h of stirring, the solvent was evaporated under reduced pressure. To the resulting residue, satd $NH_4Cl$ solution (5 mL) was added and the aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous $Na_2SO_4$, filtered, and concentrated under reduced pressure. The resultant crude residue was purified over silica gel column chromatography eluting with hexane/ethyl acetate (11:1) to give (*S*,*S*)-**18** as a pale yellow oil (139 mg, 85%). $[\alpha]_D^{24} = -14.0$ (*c* 0.8, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 5.97–5.87 (m, 2H), 5.57–5.49 (m, 2H), 5.34 (t, *J* = 4.7 Hz, 2H), 4.86 (d, *J* = 6.8 Hz, 2H), 4.79 (d, *J* = 6.6 Hz, 2H), 4.65 (d, *J* = 7.0 Hz, 2H), 3.39 (s. 6H), 2.53 (d, *J* = 2.3 Hz, 2H), 2.11–1.98 (m, 8H), 1.42–1.22 (m, 28H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 135.9, 129.8, 126.0, 93.5, 81.3, 74.4, 65.7, 55.6, 32.0, 29.8, 29.6, 29.5, 29.3, 29.2, 28.8, 27.2; IR (neat): 2926,

2854, 2362, 1741, 1693, 1516, 1029, 671 $cm^{-1}$; ESI-MS: *m*/*z* 551 $(M+Na)^+$; ESI-HRMS: calcd for $C_{34}H_{56}O_4Na$ 551.4076, found 551.4066.

### 4.1.14. (+)-Duryne 1a

To a methanolic (2 mL) solution of MOM protected (*S,S*)-**18** (31 mg, 0.059 mmol) was added PTSA·$H_2O$ (2.3 mg, 0.012 mmol) at 0 °C. The resulting reaction mixture was warmed to ambient temperature (6 h), and then solid $NaHCO_3$ (excess) was added, followed by silica adsorption and purified by silica gel column chromatography using hexane/ethyl acetate (7:3) as eluent to give (+)-duryne, **1a** as a low melting white solid (18 mg, 72%). $[\alpha]_D^{24} = +24.8$ (*c* 1.8, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 5.87 (dt, *J* = 15.1, 6.8 Hz, 2H), 5.56 (dd, *J* = 15.5, 6.8 Hz, 2H), 5.30 (t, *J* = 4.5 Hz, 2H), 4.77 (d, *J* = 5.8, 2H), 2.48 (d, *J* = 1.9 Hz, 2H), 2.10–1.96 (m, 8H), 1.72–1.20 (m, 28H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 134.6, 129.9, 128.3, 83.3, 73.9, 62.8, 32.6, 31.9, 29.74, 29.68, 29.5, 29.4, 29.3, 29.2, 28.8, 27.2; IR (neat): 3357, 2922, 2859, 2367, 1740, 1696, 1316, 1021 $cm^{-1}$; ESI-MS: *m*/*z* 463 $(M+Na)^+$; ESI-HRMS: calcd for $C_{30}H_{48}O_2Na$ 463.3552, found 463.3568.

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17. In addition to **18**, we also isolated a minor compound which was tentatively found to be a minor geometrical isomer derived from the Grubbs cross metathesis reaction. At this juncture, we may not rule out the product arising from the Wittig olefination. The isolated compound was not sufficient for further characterization.