A Platinum Open Access Journal for Organic Chemistry

Paper

Free to Authors and Readers

DOAJ Seal

Arkivoc **2025**, part __, 0-0

to be inserted by editorial office

Ring-closing metathesis studies in the context of the formal synthesis of the marine macrolide (–)-callyspongiolide

Aina Urbina, Arnau Calbó, Núria Llor, Joan Bosch, and Mercedes Amat*

Laboratory of Organic Chemistry, Faculty of Pharmacy and Food Sciences, and Institute of Biomedicine (IBUB), University of Barcelona, 08028 Barcelona, Spain

Email: amat@ub.edu

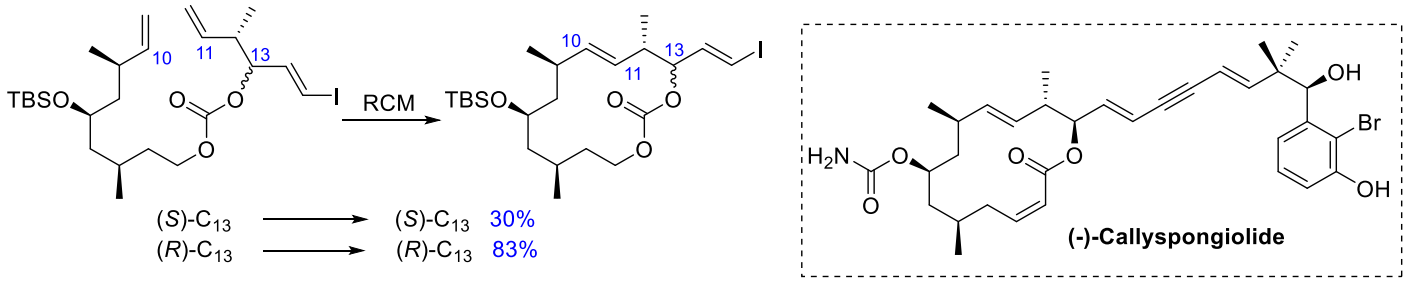
Special Issue "Women Chemists Worldwide"

Received mm-dd-yyyy **Accepted** mm-dd-yyyy **Published on line** mm-dd-yyyy

Dates to be inserted by editorial office

Abstract

Attempts to synthesize the natural product macrolide polyketide (–)-callyspongiolide have drawn great interest because of its potent cytotoxic activity. Its total synthesis has proven to be difficult, however, due to its challenging structure. The influence of the configuration of a homoallylic stereocenter on the closure of a 14-membered macrocyclic carbonate by ring-closing metathesis (RCM) from two epimeric dienes is described. The results offer some insights into the structural features which contribute to hampering the closure of the macrocyclic core of the macrolide polyketide. A formal synthesis of the marine macrolide (–)-callyspongiolide is also reported using a RCM approach (C_{10}-C_{11} bond formed) from analogous dienes bearing an α,β-unsaturated ester instead of a carbonate.



Keywords: Ring-closing olefin metathesis, macrocyclization, macrolactones, natural products, callyspongiolide.

Introduction

The macrolide polyketide (–)-callyspongiolide (**1**) was isolated in 2014[1] from the marine sponge *Callyspongia sp.* collected off the Indonesian coastline. Its potent cytotoxic activity[1-6] and unprecedented challenging structure soon attracted the attention of several synthetic-chemistry groups.[7] In 2016, Z. Xu and T. Ye[2], and, shortly thereafter, A. K. Ghosh[8], reported the first total synthesis of both enantiomers of callyspongiolide as well as of their C_{21} epimers, allowing the correct assignment of the absolute and relative configurations of this marine natural product. Two years later, the groups of P. G. Harran[3] and S. Ghosh[9] described their syntheses of (–)-callyspongiolide, and more recently, A. Fürstner[10] disclosed his endeavours on the total synthesis of the unnatural enantiomer of this natural product. Furthermore, the synthesis of the 14-membered macrocyclic core of callyspongiolide has been reported by S. Ghosh,[11] M. A. Brimble,[12] and our group.[13] The most challenging issues in the total synthesis of callyspongiolide are the control of the configuration of the six chiral centres and the four stereogenic double bonds, as well as the closure of the fourteen-membered macrolactone. In most approaches, this transformation involves the formation of bonds in the region of the α,β-unsaturated lactone moiety, either by intramolecular macrolactonization,[2,8] *Z*-selective Horner-Wadswoth-Emmons olefination,[11] palladium-catalysed carbonylative macrolactonization[3] or ring-closing alkyne metathesis (RCAM, C_2-C_3 bond).[10]

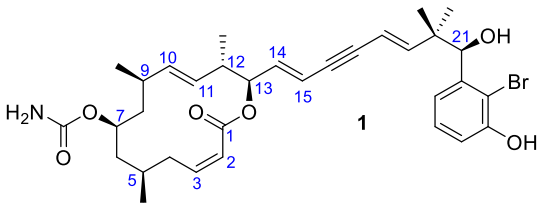
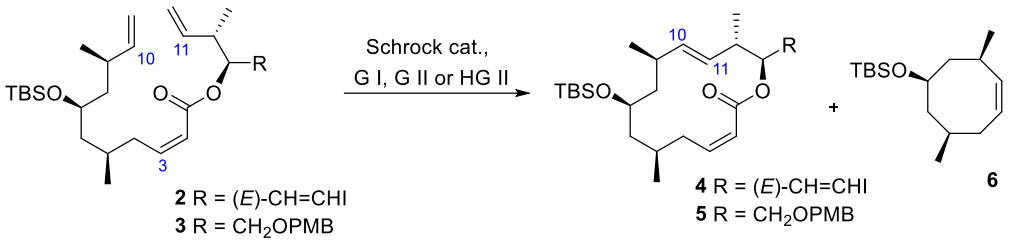


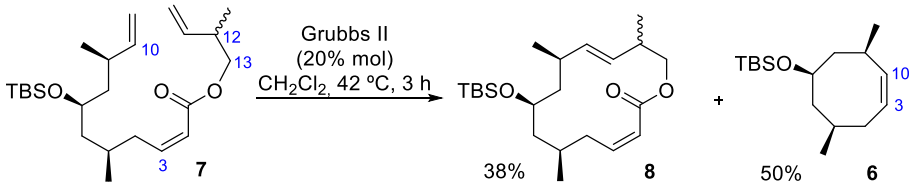
Figure 1. (–)-Callyspongiolide.

In 2020, our group,[13] and a few months later, M. A. Brimble,[12] reported the formal synthesis of callyspongiolide through an alternative synthetic approach in which the closure of the macrolactone involves a ring-closing metathesis (RCM, C_{10}-C_{11} bond). Surprisingly, in our lab, when dienes **2** or **3** were treated with the Schrock or the Grubbs first- (G I) or second-generation (G II) catalysts, under a variety of reaction conditions, cyclooctene **6**, resulting from a competitive RCM between C_{10} and C_3, was obtained as the only cyclized product (Scheme 1). Somewhat more satisfactorily, when treating compound **2** with the Hoveyda-Grubbs' second-generation catalyst (HG II), the desired trans stereoselective cyclization to give the macrolactone **4** took place, albeit in very low yield (<10%), with cyclooctene **6**, again, as the major product with partial recovery of the starting material. After several efforts to optimize the formation of **4**, the best reaction conditions were found to be the use of the HG II catalyst (30 mol%) in a 2.5 mM solution of **2** in toluene at 80 °C for 3 h. In this way, the desired macrolactone **4** was isolated in a modest 16% yield along with 25% of cyclooctene **6**. It is worth mentioning that longer reaction times provoked a decrease in the yield of **4**. In agreement with the above results, M. A. Brimble reported[12] that treatment of *ent*-**3** with the G II catalyst (20 mol% x 3) in a CH_2Cl_2 solution at room temperature for 5 days afforded a 9% yield of *ent*-**5** and a 42% yield of *ent*-**6**.



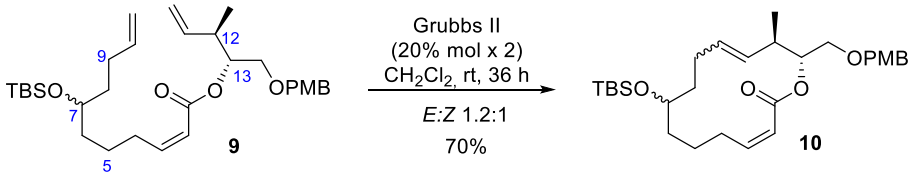
Scheme 1. Previous studies on the closure of the macrolactone ring of (–)-callyspongiolide by RCM.

To analyze whether there are structural factors that may influence the outcome of the cyclization of **2** and **3**, we subjected diene **7** (mixture of epimers at C_{12}), lacking the C_{13} bulky substituent, to RCM using the G II catalyst, and we observed an increase of up to 38% yield in the formation of the corresponding macrolactone **8**, also accompanied by cyclooctene **6** as the major product (Scheme 2).



Scheme 2. Model studies by our group on the closure of the macrolactone ring of (-)-callyspongiolide by RCM.

Moreover, M. A. Brimble[12] reported that the RCM of **9** (mixture of C_7 epimers), lacking the C_5 and C_9 methyl substituents present in callyspongiolide, rendered an *E*/*Z* mixture of lactone **10** exclusively as the only isolable product (70%, Scheme 3). Therefore, it is evident that the substituents near the diene moiety have a decisive influence on the outcome of the RCM step.

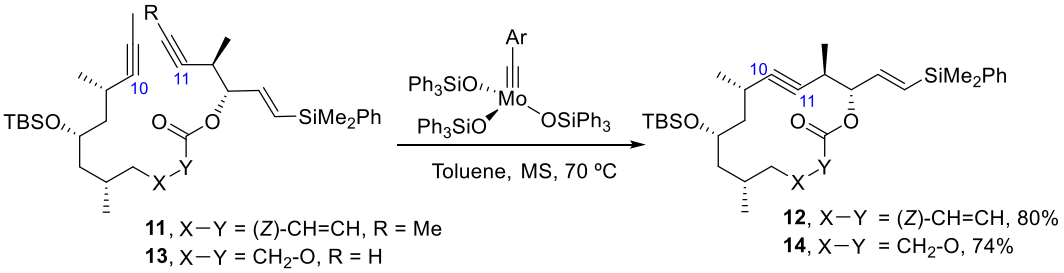


Scheme 3. Model studies by the Brimble group on the closure of the macrolactone ring of (–)-callyspongiolide by RCM.

To gain further insight into the factors that control the chemoselectivity in the formation of the 14-membered macrolactones **4**, **5** or **8** versus cyclooctene **6** by RCM, we decided to investigate the mechanism of this reaction through density functional theory (DFT) calculations.[14] These computational studies showed that the reaction occurs under thermodynamic control. To corroborate this theoretical conclusion, we treated a toluene solution of compound **4** with the HG II catalyst. After 30 min of heating at 80 ºC, a TLC control showed the formation of cyclooctene **6**, and, after 6 h, a GC-MS analysis of the crude mixture revealed a 35:65 ratio of compounds **4** and **6**, respectively. These results clearly show that the macrolactone **4** and cyclooctene **6** are in

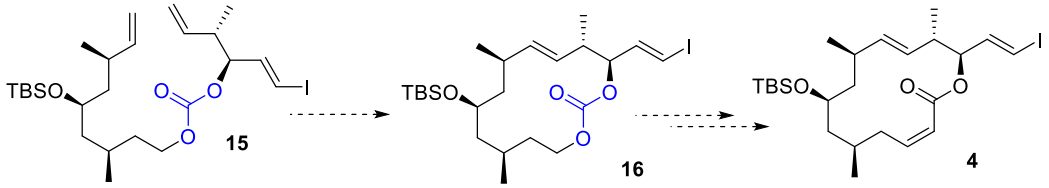
equilibrium under the RCM reaction conditions, and that this equilibrium is shifted towards cyclooctene **6**. This behavior is consistent with the observation that longer reaction times in the RCM reaction of **2** resulted in lower yields of the desired macrolactone **4**. Therefore, a modification of the reaction conditions or the catalyst is not expected to improve the conversion of **2** or **3** into macrolactones **4** or **5**, respectively.

At this point, we turned our attention to the results reported in 2019 by A. Fürstner[15] in the context of his studies on the synthesis of callyspongiolide by RCAM (C_{10}-C_{11} bond). Using his molybdenum-alkylidyne complex catalyst, the α,β-unsaturated ester **11** afforded the expected 14-membered macrolactone **12** in 80% yield, thus indicating that the two flanking methyl substituents had not negatively affected the cyclization (Scheme 4). Alternatively, when compound **13**, in which two key structural fragments for the synthesis of callyspongiolide are linked by a carbonate tether, was subjected to the RCAM conditions, the macrocycle **14** was isolated in 74% yield.



Scheme 4. RCAM studies by the Fürstner group on the synthesis of (+)-callyspongiolide.

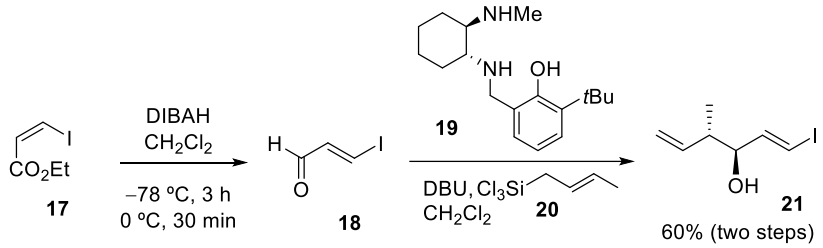
In the present work, to overcome the difficulties observed in the cyclization to the desired 14-membered macrolactone **4**, and inspired by the work of A. Fürstner,[15] we decided to study the ring-closing metathesis of diene **15**, which can be considered an analogue of **2** in which the unsaturated ester has been substituted by a carbonate tether (Scheme 5). Although compound **15** is expected to show a higher degree of conformational freedom than **2**, we were confident that the absence of the competing C_2-C_3 double bond would favor the RCM to the macrocyclic carbonate **16**, which would be converted into **4** in subsequent synthetic steps.



Scheme 5. Synthetic plan.

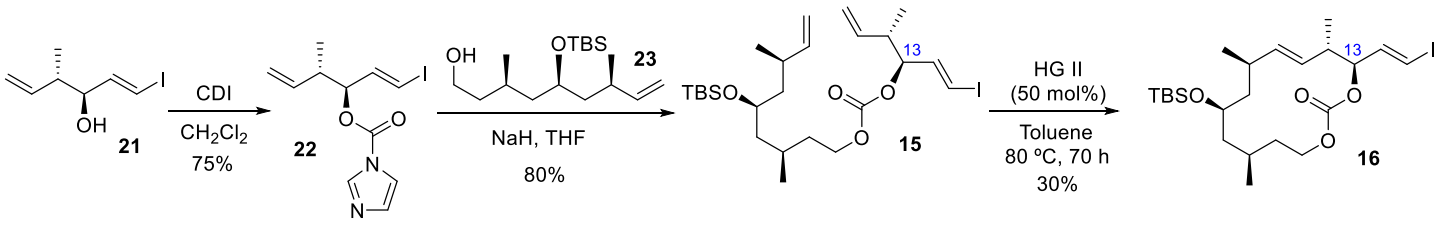
Results and Discussion

With this purpose in mind, we first synthesized the chiral alcohol **21** using a different procedure than that described in the literature[16] (Scheme 6). The reduction and isomerization of the commercial *cis*-iodoacrylate (**17**) using diisobutylaluminum hydride (DIBAH) yielded the unstable aldehyde **18**,[17] which was immediately subjected, without purification (only a ^{1}H NMR control), to an enantioselective Leighton crotylation using ligand **19**[18] and crotylchlorosilane **20**[19] to give **21** in 60% overall yield.



Scheme 6. Preparation of alcohol **21**.

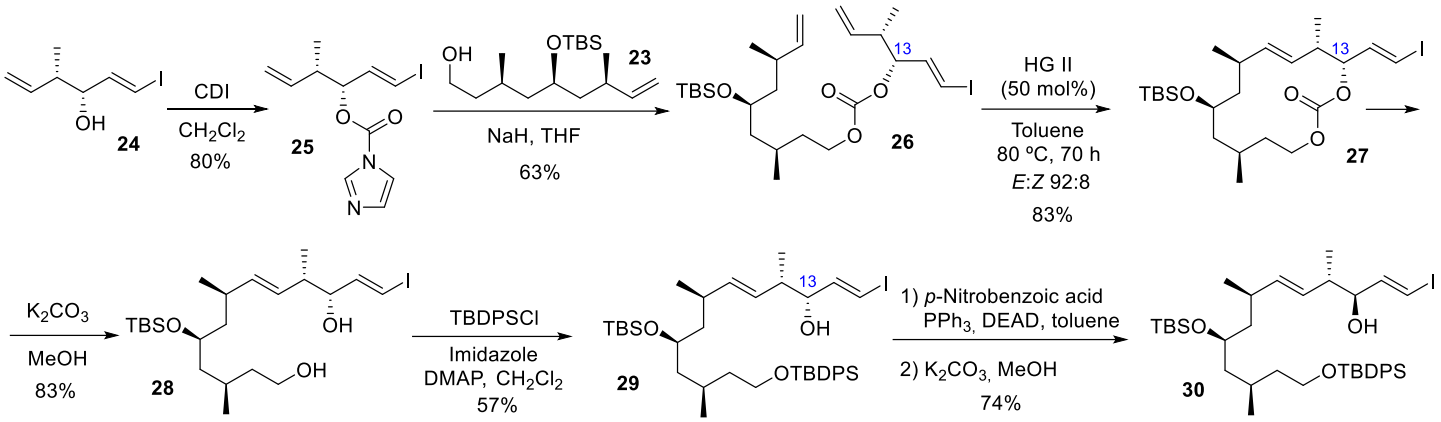
The required carbonate **15** was prepared from alcohol **21**, via carbamate **22**, and the monoprotected diol **23**, previously reported in the context of our studies on the synthesis of (–)-callyspongiolide[13] (Scheme 7). Disappointingly, when diene **15** was subjected to a variety of RCM conditions, in which the catalyst, solvent, concentration, temperature and reaction time were modified, only low yields of the macrocyclic carbonate **16** were observed, always accompanied by partial recovery of the starting material (Table S1, Supporting Information). The best results were obtained when using the HG II catalyst (50 mol%) in a 1 mM solution of **15** in toluene at 80 °C for 70 h. Under these conditions, the desired compound **16** was isolated in 30% yield.



Scheme 7. RCM of diene **15**.

In light of these modest results, we wondered if some specific structural features of the starting diene **15** might prevent the adoption of a favorable conformation for an efficient ring closure. While it was not readily evident what these features would be, we reasoned that, if the main goal of the work was the synthesis of (–)-callyspongiolide, the most affordable modification would be the inversion of the configuration of the C_{13} stereocenter. Using appropriate subsequent intermediates enroute to (–)-callyspongiolide, a Mitsunobu reaction would render the correct C_{13} stereochemistry.

The required carbonate **26** (the C_{13} epimer of **15**) was prepared from alcohols **23** and **24**[17] following the same procedure mentioned above for **15**. Gratifyingly, when diene **26** was subjected to RCM conditions using the HG II catalyst, the macrocyclic carbonate **27** was obtained stereoselectively in 83% yield. Only small amounts of the *Z* isomer (*E*:*Z* 92:8) were detected in the reaction mixture. This result is consistent with the above-mentioned RCM cyclization of diene **7** (Scheme 2), which lacks a bulky appendage at the C_{13}-position, to macrolactone **8**, and points out that the configuration of this stereocenter has a decisive influence in the evolution of compounds **2** and **3** under RCM conditions.



Scheme 8. RCM of diene **29**: synthesis of alcohol **30**, a synthetic precursor of (–)-callyspongiolide.

Cleavage of the carbonate tether of **27**, followed by chemoselective protection of the primary hydroxy group of the resulting diol **28** as a silyl ether, afforded compound **29**. Inversion of the configuration of the C_{13} stereocenter of **29** using the Mitsunobu protocol afforded alcohol **30** (15% overall yield from **24**), whose spectroscopic data and specific rotation were coincident with those reported by S. Ghosh[9] for the same compound. The synthesis of alcohol **30** constitutes an enantioselective formal synthesis of the marine macrolide callyspongiolide.

Conclusions

In our previous work we reported that the synthesis of the 14-membered macrolactones **4** and **5**, as precursors of the marine natural product (–)-callyspongiolide, by RCM is limited by the competitive formation of cyclooctene **6** as the major product. Theoretical and experimental studies showed that compounds **4** and **6** are in equilibrium under the RCM reaction conditions, and that this equilibrium is shifted towards cyclooctene **6**. In the present work we have demonstrated that the configuration of the C_{13} stereocenter of diene epimers **15** and **26** has a significant influence on the overall reaction efficiency of the RCM reaction leading to the 14-membered macrocyclic carbonates **16** and **27**. Considering the structural analogies of these carbonates with the unsaturated ester **2** and macrolactone **4**, these results may shed some light on the structural factors influencing the outcome of the RCM reaction as a key step in the generation of macrolactones enroute to the marine macrolide callyspongiolide. The macrocyclic carbonate **27** was converted into alcohol **30**, which has been previously transformed into (–)-callyspongiolide.

Experimental Section

General. All air-sensitive reactions were performed under a dry argon or nitrogen atmosphere with dry, freshly distilled solvents using standard procedures. Evaporation of solvent was accomplished with a rotatory evaporator. Drying of organic extracts during the work-up of reactions was performed over anhydrous Na_2SO_4 or $MgSO_4$. Thin-layer chromatography was done on SiO_2 (silica gel 60 F_{254}), and the spots were located by UV light and a 1% $KMnO_4$ solution. Chromatography refers to flash column chromatography and was carried out on SiO_2 (silica gel 60, 230-400 mesh). Diastereomeric ratios were calculated by ^1H NMR from the crude reaction

mixtures. NMR spectra were recorded on a Varian VNMRS-400 or Mercury 400 spectrometer [400 MHz (^{1}H) and 100.6 MHz (^{13}C)], and chemical shifts are reported in δ values, in parts per million (ppm) relative to Me_4Si (0 ppm) or relative to residual chloroform (7.26 ppm, 77.0 ppm) as an internal standard. Data are reported in the following manner: chemical shift, multiplicity, coupling constant (*J*) in hertz (Hz), integrated intensity, and assignment. Assignments and stereochemical determinations are given only when they are derived from definitive two-dimensional NMR experiments (g-HSQC-COSY). IR spectra were performed in a spectrophotometer Nicolet Avatar 320 FT-IR and only noteworthy IR absorptions (cm^{-1}) are listed. Optical rotations were measured on a Perlin-Elmer 241 polarimeter; $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. High resolution mass spectra (HMRS) were performed by Centres Científics i Tecnològics de la Universitat de Barcelona.

(3*S*,4*S*,1*E*)-1-Iodo-4-methyl-1,5-hexadien-3-ol (21). DBU (1.93 mL, 12.9 mmol) was added to a cooled solution (0 °C) of diamine **19**[18] (1.25 g, 4.3 mmol) in anhydrous CH_2Cl_2 (10 mL). Then, a solution of (*E*)-crotyltrichlorosilane (**20**)[19] (894 mg, 4.69 mmol) in anhydrous CH_2Cl_2 (1 mL) was added, the ice-water bath was removed, and the mixture was stirred at room temperature for 1 h. The mixture was recooled to 0 °C, a solution of crude (*E*)-iodoacrolein (**18**) freshly prepared from (*Z*)-β-iodoacrylate (**17**),[17] in anhydrous CH_2Cl_2 (4 mL) was added, and the solution was allowed to warm to room temperature for 15 h. The mixture was re-cooled to 0 °C, treated with *n*-Bu_4NF (3.9 mL of a 1.0 M solution in THF, 3.9 mmol), and stirred at room temperature for 30 min. The mixture was concentrated, and the resulting residue was chromatographed (9:1 hexane–EtOAc) to afford alcohol **21**[16] (554 mg, 60% from **17**). $[\alpha]^{22}_D$ –14.9 (*c* 4.27, $CHCl_3$), reported[20] for a 45/1 *anti/syn* mixture of **21** of 94% ee [α] = - 17.1 (*c* 4.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, *g*-HSQC) δ 1.03 (d, *J* = 6.8 Hz, 3H, CH_3), 2.26–2.31 (m, 1H, H-4), 3.87 (t, *J* = 6.8 Hz, 1H, H-3), 5.13–5.18 (m, 2H, H-6), 5.73 (ddd, *J* = 8.0, 10.8, 18.6 Hz, 1H, H-5), 6.37 (dd, *J* = 1.2, 14.4 Hz, 1H, H-1), 6.56 (dd, *J* = 6.8, 14.4 Hz, 1H, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.6 (CH_3), 43.9 (C-4), 77.6 (C-3), 78.2 (C-1), 117.2 (C-6), 139.2 (C-5), 146.3 (C-2).
(3*S*,4*S*,*E*)-3-[(1-Imidazolylcarbonyl)oxy]-1-iodo-4-methyl-1,5-hexadiene (22). 1,1'-Carbonyldiimidazole (1.22 g, 6.98 mmol) was added to a solution of alcohol **21** (554 mg, 2.33 mmol) in anhydrous CH_2Cl_2 (9 mL), and the solution was stirred at room temperature for 15 h. The solution was concentrated, and the resulting residue was chromatographed (9:1 to 8:2 hexane-EtOAc) to afford carbamate **22** (589 mg, 75%). $[\alpha]^{22}_D$ −25.1 (*c* 1.0, $CHCl_3$). IR (film) 3131, 2974, 1766, 1392 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.10 (d, *J* = 6.8 Hz, 3H, CH_3), 2.55–2.63 (m, 1H, H-4), 5.12–5.17 (m, 2H, H-6), 5.22 (t, *J* = 7.5 Hz, 1H, H-3), 5.71 (ddd, *J* = 7.8, 10.2, 17.2 Hz, 1H, H-5), 6.56 (dd, *J* = 7.5, 14.8 Hz, 1H, H-2), 6.66 (d, *J* = 14.8 Hz, 1H, H-1), 7.07 (t, *J* = 0.8 Hz, 1H, H-4'), 7.39 (t, *J* = 1.4 Hz, 1H, H-5'), 8.10 (s, 1H, H-2').^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.7 (CH_3), 41.5 (C-4), 82.9 (C-3), 83.4 (C-1), 116.9 (C-5'), 117.4 (C-6), 130.8 (C-4'), 136.9 (C-2'), 137.5 (C-5), 140.3 (C-2), 147.8 (NCO). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd. for $C_{11}H_{14}IN_2O_2$ 333.0022; found 333.0018.

Carbonate 15. A solution of alcohol **23**[13] (155 mg, 0.52 mmol) in anhydrous THF (1.5 mL) was slowly added to a suspension of NaH (15.7 mg, 0.63 mmol) in anhydrous THF (5 mL) at 0 °C, and the mixture was stirred at room temperature for 30 min. Carbamate **22** (200 mg, 0.60 mmol) was added, and the solution was stirred at room temperature for 17 h. The reaction was quenched with H_2O, and the mixture was extracted once with CH_2Cl_2 and twice with EtOAc. The combined organic extracts were washed with brine, dried, filtered, and concentrated. Flash chromatography (9:1 to 8:2 hexane-CH_2Cl_2) of the residue afforded carbonate **15** (234 mg, 80%) as a colorless oil. $[\alpha]^{22}_D$ −29.1 (*c* 1.01, $CHCl_3$). IR (film) 2957, 2928, 1746, 1257 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.04 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.88 [s, 9H, $C(CH_3)_3$], 0.90 (d, *J* = 6.4 Hz, 3H, CH_3-H3), 0.99 (d, *J* = 6.8 Hz, 3H, CH_3-H7), 1.04 (d, *J* = 7.2 Hz, 3H, CH_3-H4'), 1.27–1.36 (m, 2H, H-4 and H-6), 1.37–1.47 (m, 3H, H-2,

H-4 and H-6), 1.61–1.66 (m, 1H, H-3), 1.68–1.76 (m, 1H, H-2), 2.24–2.36 (m, 1H, H-7), 2.45–2,51 (m, 1H, H-4'), 3.70–3.76 (m, 1H, H-5), 4.10–4.21 (m, 2H, H-1), 4.91–4.99 (m, 3H, H-3' and H-9), 5.08–5.13 (m, 2H, H-6'), 5.63–5.76 (m, 2H, H-3 and H-8), 6.47–6.49 (m, 2H, H-1' and H-2'). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −4.1 ($SiCH_3$), −3.9 ($SiCH_3$), 15.3 (CH_3-C-4'), 18.1 [*C*(CH_3)$_3$], 19.8 (CH_3-C3), 21.2 (CH_3-C7), 25.9 [C(*C*H_3)$_3$], 26.4 (C-3), 34.1 (C-7), 35.8 (C-2), 41.4 (C-4'), 44.3 (C-4 or C-6), 44.4 (C-4 or C-6), 66.5 (C-1), 68.6 (C-5), 81.2 (C-1'), 82.2 (C-3'), 112.8 (C-9), 116.6 (C-6'), 138.2 (C-5'), 141.5 (C-2'), 144.5 (C-8), 154.5 (CO). HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ Calcd for $C_{25}H_{45}INaO_4Si$ 587.2019; found 587.2024.

Macrocyclic carbonate 16. Second-generation Hoveyda-Grubbs catalyst (8.3 mg, 13 µmol) in CH_2Cl_2 (10 mL) was added at 2 mL/h (syringe pump) to a stirred solution of carbonate **15** (25 mg, 44 µmol) in anhydrous toluene (40 mL) at 80 °C. After 12 h, additional 2nd generation Hoveyda-Grubbs catalyst (3 mg, 4.3 µmol) in CH_2Cl_2 (5 mL, 2 mL/h) was added, the mixture was stirred for 10 h, and additional 2nd generation Hoveyda-Grubbs catalyst (3 mg, 4.3 µmol) in CH_2Cl_2 (5 mL, 2 mL/h) was added. After 17 h of stirring, the solvent was evaporated, and the residue was chromatographed (hexane to 8:2 hexane–CH_2Cl_2) to afford macrocycle **16** (7 mg, 30%) and carbonate **15** (5 mg). $[\alpha]^{22}_D$ −73.2 (*c* 1.04, $CHCl_3$). IR (film) 2955, 2929, 1742, 1264 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.05 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.87 [s, 9H, C(CH_3)$_3$], 0.93 (d, *J* = 6.8 Hz, 3H, CH_3), 0.95 (d, *J* = 7.2 Hz, 3H, CH_3), 0.96 (d, *J* = 6.8 Hz, 3H, CH_3), 1.25–1.35 (m, 2H, H-4 and H-6), 1.38–1.45 (m, 2H, H-4 and H-6), 1.48–1.53 (m, 1H, H-2), 1.88–1.96 (m, 2H, H-2 and H-3), 2.14–2.21 (m, 1H, H-7), 2.23–2,32 (m, 1H, H-10), 3.51–3.57 (m, 1H, H-5), 4.02 (ddd, *J* = 11.6, 10.0, 1.6 Hz, 1H, H-1), 4.47 (ddd, *J* = 11.6, 6.0, 2.0 Hz, 1H, H-1), 4.71 (dd, *J* = 10.8, 7.6 Hz, 1H, H-11), 5.07 (dd, *J* = 15.2, 9.2 Hz, 1H, H-9), 5.18 (dd, *J* = 15.2, 9.2 Hz, 1H, H-8), 6.47 (dd, *J* = 14.4, 7.6 Hz, 1H, H-12), 6.55 (d, *J* = 14.4 Hz, 1H, H-13). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −3.8 ($SiCH_3$), −3.7 ($SiCH_3$), 16.8 (CH_3), 18.3 [*C*(CH_3)$_3$], 20.5 (CH_3), 22.3 (CH_3), 26.0 [C(*C*H_3)$_3$], 26.6 (C-3), 32.4 (C-2), 35.2 (C-7), 42.0 (C-10), 44.9 (C-4 or C-6), 47.4 (C-4 or C-6), 82.0 (C-11 or C-13), 82.2 (C-11 or C-13), 129.1 (C-8 or C-9), 140.4 (C-8 or C-9), 142.5 (C-12), 154.5 (CO). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{23}H_{42}IO_4Si$ 537.1892; found 537.1896.

(3*R*,4*S*,*E*)-3-[(1-Imidazolylcarbonyl)oxy]-1-iodo-4-methyl-1,5-hexadiene (25). 1,1'-Carbonyldiimidazole (549 g, 3.15 mmol) was added to a solution of alcohol **24**[17] (248 mg, 1.03 mmol) in anhydrous CH_2Cl_2 (4 mL), and the solution was stirred at room temperature for 15 h. The solution was concentrated, and the resulting residue was chromatographed (from 9:1 to 8:2 hexane–EtOAc) to afford carbamate **25** (275 mg, 80%) as a yellowish oil. $[\alpha]^{22}_D$ +27.7 (*c* 1.04, $CHCl_3$). IR (film) 999.5, 1392.4, 1759.5, 2974.8, 3131.6 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 1.12 (d, *J* = 6.8 Hz, 3H, CH_3), 2.60–2.69 (m, 1H, H-4), 5.15 (dt, *J* = 1.2, 12.0 Hz, 1H, H-6), 5.18 (dt, *J* = 1.2, 5.2 Hz, 1H, H-6), 5.26 (dd, *J* = 6.0, 7.6 Hz, 1H, H-3), 5.76 (ddd, *J* = 7.4, 10.6, 17.2 Hz, 1H, H-5), 6.56 (dd, *J* = 7.4, 14.4 Hz, 1H, H-2, 6.64 (d, *J* = 14.4 Hz, 1H, H-1), 7.09 (dd, *J* = 1.0, 1.8 Hz, 1H, H-3'), 7.41 (t, *J* = 1.6 Hz, 1H, H-4'), 8.14 (t, *J* = 1.0, 1H, H-2'). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.1 (CH_3), 40.8 (C-4), 82.9 (C-3), 83.3 (C-1), 117.0 (C-4'), 117.4 (C-6), 130.6 (C-3'), 136.9 (C-2'), 137.1 (C-5), 140.0 (C-2), 147.7 (C-1'). HRMS (ESI-TOF) m/z: [M + H]+ Calcd. for $C_{11}H_{14}IN_2O_2$ 333.0022; found 333.0020.

Carbonate 26. A solution of alcohol **23**[13] (487 mg, 1.62 mmol) in THF (4.5 mL) was slowly added to a suspension of NaH (50 mg, 1.88 mmol) in anhydrous THF (10 mL) at 0 °C. After stirring for 30 min at room temperature, a solution of carbamate **25** (584 mg, 1.76 mmol) in THF (4 mL) was added, and the mixture was stirred at room temperature for 17 h. The reaction was quenched with H_2O and EtOAc, and the organic phase was washed with H_2O and brine, dried, and concentrated. Flash chromatography (from 95:5 hexane–CH_2Cl_2 to CH_2Cl_2) gave carbonate **26** (579 mg, 63%) as a colorless oil. $[\alpha]^{22}_D$ +18.3 (*c* 1.0, $CHCl_3$). IR (film) 2957, 2928, 1746, 1257 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.04 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.88 [s, 9H, C(CH_3)$_3$], 0.90 (d,

J = 6.8 Hz, 3H, CH_3), 0.99 (d, *J* = 7.2 Hz, 3H, CH_3), 1.05 (d, *J* = 6.8 Hz, 3H, CH_3), 1.27–1.45 (m, 4H, H-4 and H-6), 1.40–1.50 (m, 1H, H-2), 1.59–1.66 (m, 1H, H-3), 1.69–1.76 (m, 1H, H-2), 2.26–2.37 (m, 1H, H-7), 2.46–2.55 (m, 1H, H-4'), 3.71–3.77 (m, 1H, H-5), 4.10–4.22 (m, 2H, H-1 and H-2), 4.90–5.00 (m, 3H, H-3' and H-9), 5.07–5.10 (dt, *J* = 1.2, 10.0 Hz, 1H, H-6'), 5.11–5.13 (m, 1H, H-6'), 5.63–5.78 (m, 2H, H-8 and H-5'), 6.44–6.54 (m, 2H, H-1' and H-2'). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −4.1 ($SiCH_3$), −3.9 ($SiCH_3$), 15.1 (CH_3), 18.1 [*C*(CH_3)$_3$], 19.8 (CH_3), 21.2 (CH_3), 25.9 [C(*C*H_3)$_3$], 26.4 (C-3), 34.1 (C-7), 35.9 (C-2), 40.9 (C-4'), 44.4 (C-4 or C-6), 45.4 (C-4 or C-6), 66.5 (C-1), 68.7 (C-5), 81.1 (C-1'), 82.3 (C-3'), 112.8 (C-9), 116.5 (C-6'), 137.9 (C-5'), 141.6 (C-2'), 144.5 (C-8), 154.5 (CO). HRMS (ESI-TOF) *m/z*: $[M + NH_4]^+$ Calcd for $C_{25}H_{49}INO_4Si$ 582.2470; found 582.2468.

Macrocyclic carbonate 27. A solution of 2nd generation Hoveyda-Grubbs catalyst (84.7 mg, 0.13 mmol) in CH_2Cl_2 (10 mL) was added at 2 mL/h (syringe pump) to a stirred solution of carbonate **26** (246 mg, 0.44 mmol) in anhydrous toluene (450 mL) at 80 °C. After 20 h, a solution of 2nd generation Hoveyda-Grubbs catalyst (56.3 mg, 87 µmol) in CH_2Cl_2 (5 mL) was added at 2 mL/h (syringe pump). After 15 h, the solvent was evaporated, and the crude residue was purified by flash chromatography (9:1 to 7:3 hexane–CH_2Cl_2) to afford macrocycle **27** (195 mg, 83%). $[\alpha]^{22}_D$ +34.3 (*c* 0.99, $CHCl_3$). IR (film) 2956, 2928, 1746, 1250 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.08 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.89 [s, 9H, C(CH_3)$_3$], 0.93 (d, *J* = 6.8 Hz, 3H, CH_3), 0.95 (d, *J* = 6.8 Hz, 3H, CH_3), 1.00 (d, *J* = 7.2 Hz, 3H, CH_3), 1.16–1.29 (m, 2H, H-4 and H-6), 1.42–1.52 (m, 2H, H-2 and H-4), 1.56–1.63 (m, 2H, H-2 and H-6), 1.71-1.78 (m, 1H, H-3), 2.23–2.29 (m, 1H, H-7), 2.69–2.76 (m, 1H, H-10), 3.56–3.62 (m, 1H, H-5), 3.89 (ddd, *J* = 5.0, 8.2, 11.2 Hz, 1H, H-1), 4.38–4.44 (m, 1H, H-1), 5.12 (ddd, *J* = 1.2, 4.0, 6.4 Hz, 1H, H-11), 5.24 (dd, *J* = 8.0, 15.4 Hz, 1H, H-8 or H-9), 5.31 (dd, *J* = 6.8, 15.4 Hz, 1H, H-8 or H-9), 6.47 (dd, *J* = 0.8, 14.4 Hz, 1H, H-13), 6.57 (dd, *J* = 6.0, 14.4 Hz, 1H, H-12). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −3.9 ($SiCH_3$), −3.6 ($SiCH_3$), 15.8 (CH_3), 18.1 [*C*(CH_3)$_3$], 21.8 (CH_3), 21.9 (CH_3), 25.9 [C(*C*H_3)$_3$], 28.4 (C-3), 34.6 (C-7), 35.2 (C-2), 39.1 (C-10), 45.9 (C-4), 48.1 (C-6), 66.2 (C-1), 71.5 (C-5), 80.1 (C-13), 81.6 (C-11), 128.7 (C-8 or C-9), 138.3 (C-8 or C-9), 140.6 (C-12), 153.7 (CO). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{42}IO_4Si$ 537.1892; found 537.1896.

(3*R*,5*R*,7*R*,8*E*,10*S*,11*R*,12*E*)-5-[(*tert*-Butyldimethylsilyl)oxy]-13-iodo-3,7,10-trimethyl-8,12-tridecadiene-1,11-diol (28). A mixture of carbonate **27** (51 mg, 95 µmol) and K_2CO_3 (39 mg, 0.28 mmol) in MeOH (1.2 mL) was stirred at room temperature for 24 h. Saturated aqueous NH_4Cl solution was added, and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried, filtered, and evaporated. Flash chromatography (9:1 to 8:2 hexane–EtOAc) of the residue afforded diol **28** (40 mg, 83%) as a colourless oil. $[\alpha]^{22}_D$ –5.1 (*c* 1.11, $CHCl_3$). IR (film) 3356, 2928, 1254 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.06 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.89 [s, 9H, C(CH_3)$_3$], 0.90 (d, *J* = 7.6 Hz, 3H, CH_3), 0.97 (d, *J* = 6.8 Hz, 3H, CH_3), 1.00 (d, *J* = 7.2 Hz, 3H, CH_3), 1.25–1.34 (m, 2H, H-8 and H-10), 1.36–1.43 (m, 2H, H-8 and H-10), 1.45–1.48 (m, 1H, H-12), 1.56–1.64 (m, 2H, H-11 and H-12), 2.29–2.35 (m, 2H, H-4 and H-7), 3.63–3.72 (m, 2H, H-13), 3.73–3.79 (m, 1H, H-9), 3.96–3.99 (m, 1H, H-3), 5.27 (dd, *J* = 7.8, 15.4 Hz, 1H, H-5), 5.40 (dd, *J* = 7.8, 15.4 Hz, 1H, H-6), 6.31 (ddd, *J* = 1.0, 1.4, 14.4 Hz, 1H, H-1), 6.56 (ddd, *J* = 0.8, 6.0, 14.4 Hz, 1H, H-2). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ −4.0 ($SiCH_3$), −3.8 ($SiCH_3$), 15.5 (CH_3), 18.2 [*C*(CH_3)$_3$], 20.2 (CH_3), 22.0 (CH_3), 25.9 [C(*C*H_3)$_3$], 26.3 (C-11), 33.3 (C-4 or C-7), 40.3 (C-12), 42.4 (C-4 or C-7), 44.5 (C-8 or C-10), 45.3 (C-8 or C-10), 60.9 (C-13), 69.2 (C-9), 77.5 (C-1), 77.6 (C-3), 128.8 (C-5), 139.2 (C-6), 146.2 (C-2). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{43}INaO_3Si$ 533.1918; found 533.1919.

(1*E*,3*R*,4*S*,5*E*,7*R*,9*R*,11*R*)-9-[(*tert*-Butyldimethylsilyl)oxy]-13-[(*tert*-butyldiphenylsilyl)oxy]-1-iodo-4,7,11-trimethyl-1,5-tridecadien-3-ol (29). Imidazole (4.3 mg, 63 µmol) and DMAP (0.4 mg, 33 µmol) were added to a solution of diol **28** (27.4 mg, 48 µmol) in anhydrous CH_2Cl_2 (1 mL) at 0 °C. TBDPSCl (14 µL, 53 µmol) was added dropwise, and the mixture was stirred at 0 °C for 1 h and at room temperature overnight. Saturated aqueous

NH_4Cl solution was added, and the aqueous layer was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash chromatography (95:5 to 9:1 hexane–CH_2Cl_2) to afford compound **29** (23 mg, 57%) as a colourless oil. $[\alpha]^{22}_D$ –7.2 (*c* 0.63, $CHCl_3$). IR (film) 3455 (OH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.04 and 0.05 [s, 6H, CH_3(TBS)], 0.82 (d, *J* = 6.4 Hz, 3H, CH_3C-11), 0.88 [s, 9H, $(CH_3)_3$(TBS)], 0.96 (d, *J* = 6.8 Hz, 3H, CH_3C-4/7), 1.00 (d, *J* = 6.8 Hz, 3H, CH_3C-4/7), 1.05 [s, 9H, $(CH_3)_3$(TBDPS)], 1.20–1.29 (m ,1H, H-8), 1.32–1.48 (m, 4H, H-8, H-10, and H-12), 1.55–1.68 (m, 2H, H-11 and H-12), 2.27–2.37 (m, 2H, H-4 and H-7), 3.64–3.75 (m, 3H, H-9 and H-13), 3.94–3.99 (m, 1H, H-3), 5.26 (dd, *J* = 15.6, 6.8 Hz, 1H, H-5), 5.40 (dd, *J* = 15.6, 8.0 Hz, 1H, H-6), 6.30 (dd, *J* = 14.4, 1.2 Hz, 1H, H-1), 6.55 (dd, *J* = 14.4, 5.6 Hz, 1H, H-2), 7.35–7.44 (6H, ArH), 7.65–7.69 (4H, ArH). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ –4.1 and –3.9 [(CH_3)TBS], 15.5 (CH_3), 18.1 and 19.2 (C_q), 20.0 (CH_3C-11), 22.1 (CH_3), 26.0 [$(CH_3)_3$(TBS)], 26.2 (C-11), 26.9 [$(CH_3)_3$(TBDPS)], 33.1 (C-7), 40.4 (C-12), 42.4 (C-4), 44.2 (C-10), 45.2 (C-8), 61.9 (C-13), 69.2 (C-9), 77.1 (C-1), 77.5 (C-3), 127.6 (CH-Ar), 128.6 (C-5), 129.5 (CH-Ar), 134.0 (CH-Ar), 135.5 (CH-Ar), 139.3 (C-6), 146.2 (C-2). HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{38}H_{61}INaO_3Si_2$ 771.3096; found 771.3089.

(1*E*,3*S*,4*S*,5*E*,7*R*,9*R*,11*R*)-9-[(*tert*-Butyldimethylsilyl)oxy]-13-[(*tert*-butyldiphenylsilyl)oxy]-1-iodo-4,7,11-trimethyl-1,5-tridecadien-3-ol (30). *First step:* A mixture of **29** (30.6 mg, 41 µmol), 4-nitrobenzoic acid (30.6 mg, 0.18 mmol), and PPh_3 (56.4 mg, 0.20 mmol) in anhydrous toluene (0.6 mL) was stirred at room temperature for 5 min. DEAD (41 µL, 0.20 mmol) was added dropwise, and the resulting yellow mixture was stirred for another 16 h. The solvent was evaporated, and the residue was purified by column chromatography (from 9:1 to 1:1 hexane-CH_2Cl_2) to give the *p*-nitrobenzoate derived from **29** as a light-yellow oil. *Second step:* This *p*-nitrobenzoate was dissolved in MeOH (0.5 mL), and K_2CO_3 (8 mg, 56 µmmol) was added. The mixture was stirred at room temperature for 20 h and extracted with EtOAc. The combined organic extracts were dried, filtered, and concentrated. Flash column chromatography (95:5 hexane-CH_2Cl_2) gave **30**[9] (22.4 mg, 74%) as a colourless oil. $[\alpha]^{22}_D$ –20.6 (*c* 0.71, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, COSY, *g*-HSQC) δ 0.00–0.10 (m, 6H, $[(CH_3)_2$TBS], 0.82 (d, *J* = 6.8 Hz, 3H, CH_3), 0.88 [s, 9H, $(CH_3)_3$], 0.95–1.01 (m, 6H), 1.05 [s, 9H, $(CH_3)_3$], 1.22–1.31 (m, 1H), 1.35–1.46 (m, 4H), 1.54–1.62 (m, 2H), 1.71 (brs, 1H, OH), 2.18 (sex, *J* = 7.2 Hz, 1H), 2.28–2.39 (m, 1H), 3.63–3.79 (m, 4H), 5.23 (dd, *J* = 15.2, 8.0 Hz, 1H), 5.44 (dd, *J* = 15.2, 7.6, 1H), 6.32–6.38 (m, 1H), 6.54 (dd, *J* = 14.4, 6.4 Hz, 1H), 7.34–7.45 (m, 6H), 7.63–7.70 (m, 4H).

Acknowledgements

Financial support from the MINECO/FEDER (Project RTI2018-093974-B-I00) is gratefully acknowledged. We also acknowledge networking contribution by the COST Action CM1407. Thanks are also due to the MICIU, Spain, for fellowships to A.C. (grant FPU19/04160) and A.U. (grant BES-2016-076479).

Supplementary Material

Copies of ^1H and ^{13}C NMR spectra of compounds **15**, **16**, **21**, **22**, **25-29** and ^1H NMR spectrum of **30** are available in the Supplementary Material file associated with this paper.

References

1. Pham, C-D.; Hartmann, R.; Bölher, P.; Stork, B.; Wesselborg, S.; Lin, W.; Daowan, L.; Proksch, P. *Org. Lett.* **2014**, *16*, 266. https://doi.org/10.1021/ol403241v
2. Zhou, J.; Gao, B.; Xu, Z.; Ye, T. *J. Am. Chem. Soc*. **2016**, *138*, 6948. https://doi.org/10.1021/jacs.6b03533
3. Manoni, F.; Rumo, C.; Li, L.; Harran, P. G. *J. Am. Chem. Soc.* **2018**, *140*, 1280. https://doi.org/10.1021/jacs.7b13591
4. Fogarty, S.; Ouyang, Y.; Li, L.; Chen, Y.; Rane, H.; Manoni, F.; Parra, K. J.; Rutter, J.; Harran P. G. *J. Nat. Prod.* **2020**, *83*, 3381. https://doi.org/10.1021/acs.jnatprod.0c00813
5. Lee, S.; Jeong, Y.; Roe, J-S.; Huh, H.; Paik, S. H.; Song, J. *BMB Rep*. **2021**, *54*, 227. https://doi.org/10.5483/BMBRep.2021.54.4.037
6. Ha, J.; Park, S. B. *Commun. Biol*. **2021**, *4*, 1123. https://doi.org/10.1038/s42003-021-02643-8
7. For a review, see: Ko, K.-Y.; Wilson, Z. E.; Brimble, M. A. *Chem. Eur. J.* **2021**, *27*, 2589. https://doi.org/10.1002/chem.202003898
8. Ghosh, A. K.; Kassekert, L. A.; Bungard, J. D. *Org. Biomol. Chem.* **2016**, *14*, 11357. https://doi-org.sire.ub.edu/10.1039/C6OB02051H
9. Sharma, A.; Athe, S.; Ghosh, S. *ACS Omega* **2018**, *3*, 16563. https://doi.org/10.1021/acsomega.8b02156
10. Wölfl, B.; Mata, G.; Fürstner, A. *Chem. Eur. J.* **2019**, *25*, 255. https://doi.org/10.1002/chem.201804988
11. Athe, S.; Sharma, A.; Marumudi, K.; Ghosh, S. *Org. Biomol. Chem*. **2016**, *14*, 6769. https://doi.org/10.1039/C6OB01007E
12. Ko, K.-Y.; Wilson, Z. E.; Furket, D. P.; Brimble, M. A. *ChemCatChem*. **2020**, *12*, 5759. https://doi.org/10.1002/cctc.202001139
13. Urbina, A.; Llor, N.; Barbieri, M. V.; Bosch, J.; Amat, M. *Chem. Commun.* **2020**, *56*, 5536. https://doi-org.sire.ub.edu/10.1039/D0CC01978J
14. Díaz-Ruiz, M.; Urbina, A; Llor, N.; Bosch, J.; Amat, M. Maseras, F. *Tetrahedron*, **2022**, *124*, 133016. https://doi.org/10.1016/j.tet.2022.133016
15. Mata, G.; Wölfl, B.; Fürstner, A. *Chem. Eur. J.* **2019**, *25*, 246. https://doi.org/10.1002/chem.201804987
16. Matoušová, E.; Koukal, P.; Formánek, B.; Kotora, M. *Org. Lett.* **2016**, *18*, 5656. https://doi.org/10.1021/acs.orglett.6b02897
17. Fuwa, H.; Suzuki, T.; Kubo, H.; T. Yamori, T.; Sasaki, M. *Chem. Eur. J.* **2011**, *17*, 2678. https://doi.org/10.1002/chem.201003135
18. Suen, L. M.; Steigerwald, M. L.; Leighton, J. L. *Chem. Sci*. **2013**, *4*, 2413. https://doi.org/10.1039/C3SC50714A
19. O'Hora, P. S.; Incerti-Pradillos, C. A.; Kabeshov, M. A.; Shipilovskikh, S. A.; Rubtsou, A. E.; Elsegood, M. R. J.; Malkov, A. V. *Chem. Eur. J.* **2015**, *21*, 4551. https://doi.org/10.1002/chem.201500176
20. Koukal, P.; Ulč, J.; Nečas, D.; Kotora, M. *Eur. J. Org. Chem.* **2016**, 2110. https://doi.org/10.1002/ejoc.201600286