JOC*Note*

Synthesis of (+)-Cladospolide C

Chun-Yi Chou and Duen-Ren Hou*

Department of Chemistry, National Central University, Jung-Li City, Taoyuan, Taiwan 320

drhou@cc.ncu.edu.tw

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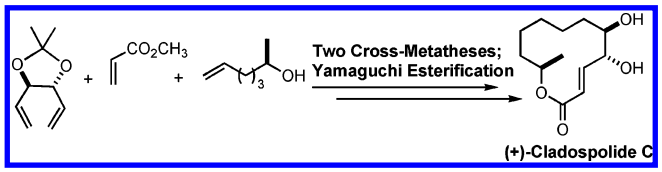
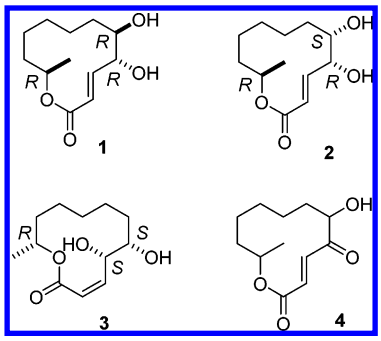


(+)-Cladospolide C was synthesized in eight steps with 5% total yield, using methyl acrylate, (3*R*,4*R*)-1,5-hexadiene-3,4-diol, and (6*R*)-6-hepten-2-ol as the starting materials. Two cross-metathesis reactions and Yamaguchi esterification were applied to assemble the three units into (+)-Cladospolide C. Unsuccessful routes using ring-closing metathesis are also discussed.

Cladospolide C (**1**) is a 12-membered macrolide isolated from the metabolites of the soil fungus *Cladosporium tenuissimum*.[1] Its diastereomers, Cladospolide A (**2**) and Cladospolide B (**3**), are prevalent in the metabolites of various *Cladosporium* species of fungi, and these macrolides **1**−**3** are plant growth regulators.[2−5] They all showed inhibitory effects to shoot elongation of rice seedlings.[1] Interestingly, Cladospolide A promotes root growth of lettuce seedlings, but Cladospolide B has opposite effects.[5b,c] Cladospolide D (**4**), a 4-oxo lactone, also shows antimicrobial activity against *Mucor racemosus* and *Pyricularia oryzae*, but its stereochemistry has not been determined.[6] Cladospolides A and B have attracted synthetic chemists' attention, and their total syntheses have been reported.[7,8] On the other hand, reports of the synthesis of Cladospolide C are limited. Banwell's group modified their synthesis of Cladospolide B to prepare (−)-Cladospolide C.[9] Although one of their chiral building blocks, *cis*-(1*S*,2*S*)-1,2-dihydro-3-chlorocatechol, was economically prepared from the enzymatic oxidation of chlorobenzene, the required (1*R*,2*R*)-counterpart for synthesizing the naturally occurring (+)-**1** is difficult to prepare in this way. Very recently, Sharma's group also reported their synthesis of Cladospolide C from 4-pentyn-1-ol utilizing asymmetric aldol and epoxidation reactions to form the stereocenters.[10] However, their assignment on the absolute configuration of natural Cladospolide C is opposite to previous work.[1,9,10]



Herein, we report the total synthesis of (+)-Cladospolide C (**1**) using methyl acrylate, (3*R*,4*R*)-1,5-hexadiene-3,4-diol (**5**), and (6*R*)-6-hepten-2-ol (**6**) as the starting materials. Olefin metathesis and the Yamaguchi esterification process were applied to assemble the three parts into **1** (Scheme 1).

We first attempted to form the macrolactone by ring-closing metathesis (RCM, Scheme 2). The C_2-symmetric (3*R*,4*R*)-1,5-hexadiene-3,4-diol (**5**) was prepared from D-mannitol according to Burke's procedure and protected as the ketal **7**.[11] Cross-metathesis of **7** with commercially available 5-hexenol catalyzed by second-generation Grubbs catalyst **8** gave the alcohol **9**. On the basis of ^{1}H NMR analysis, *E*-olefin **9** was dominant (>90%). Acrylation of **9** with acryloyl chloride provided triene **10**. Unfortunately, ring-closing metathesis of triene **10** failed. Various substrate concentrations (0.001−0.005 M) in refluxing CH_2Cl_2 or $ClCH_2CH_2Cl$ were examined; however, only unidentified mixtures were produced. Although it is reasonable to propose that RCM between the two terminal olefins is practical, the electron-deficient acrylate unit and the required rigid alignment for RCM may account for this disappointing result.

We rearranged our synthesis to circumvent the RCM involving the acrylate unit (Scheme 3). Thus, cross-metathesis (CM) between diene **7** and excess methyl acrylate (10 equiv) was

* Corresponding author. Phone: 88-63-422-7151 ext. 65981. Fax: 88-63-422-7664.

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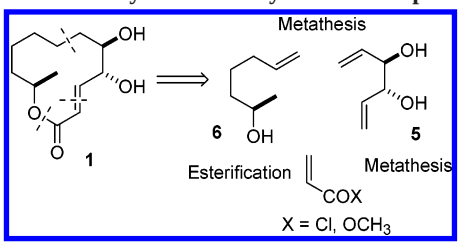
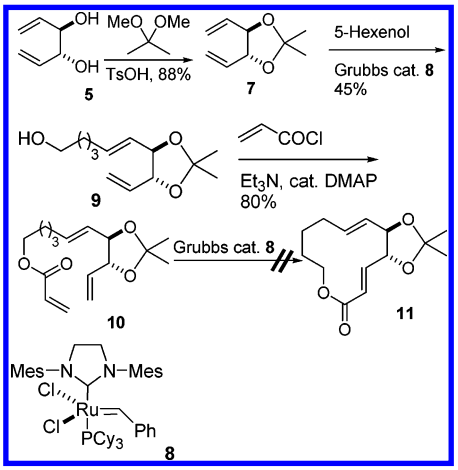
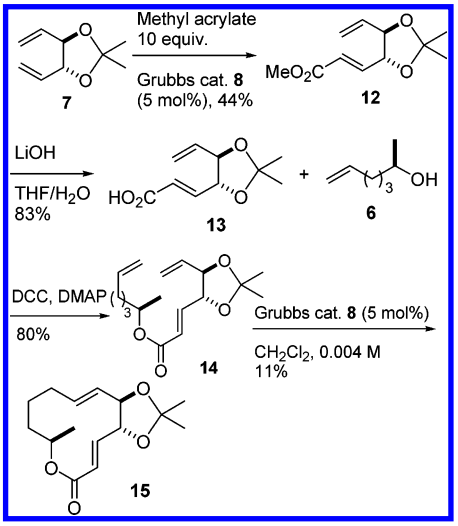
SCHEME 1. Retrosynthetic Analysis of Cladospolide C



SCHEME 2

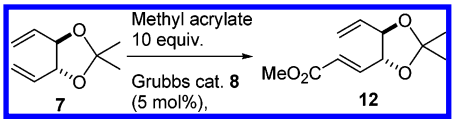


SCHEME 3



performed first.[12] However, this reaction proved to be elusive, and further adjustments in the reaction conditions were required. Some selective experimental results are summarized in Table 1. The desired product **12** was not formed when the reaction was performed in dichloromethane. Using excess methyl acrylate as the solvent and raising the reaction temperature to 80 °C gave only a trace of **12** (16%, entry 2). Performing the CM in refluxing toluene further improved the yield to 29%. Clearly, higher reaction temperatures were helpful in driving this metathesis reaction. We were glad to find that the yield can be further optimized to almost 50% by adding phenol or *p*-cresol (50 mol %) as reported by Forman et al. (entries 4−6).[13] Instead

TABLE 1. Cross-Metathesis between 7 and Methyl Acrylate



entry	solvent	*T* (°C)	time	yield[a] (%)
1	CH_2Cl_2	40	16	0
2	neat	80	16	16
3	toluene	120	3	29
4[b]	toluene	120	3	40
5[c]	toluene	120	3	44
6[c]	toluene	120	16	45

[a] Isolated yields. [b] Phenol (50 mol %) was added. [c] *p*-Cresol (50 mol %) was added.

of using catalysts with bidentate, oxygenated carbenes, such as the Hoveyda−Grubbs catalyst,[14] adding these beneficial additives could be an inexpensive alternative for cross-metathesis.[15] Furthermore, extending the reaction time to 16 h did not increase the yield of product significantly. Only the *E*-diastereomer of **12** was observed in the ^{1}H NMR spectrum. The ester **12** was hydrolyzed to acid **13** and coupled with chiral alcohol **6**[16] to form triene **14** in good yield. Ring-closing metathesis of **14** provided the cyclized lactone **15** but in dismal yield (11%), even after numerous trials.[17]

The failure or low yield of RCM in the previous two routes hampered further synthetic exploration. On the other hand, the success of both CM reactions for preparing compounds **12** and **9** prompted us to adopt a new approach with two consecutive cross-metatheses and then cyclization (Scheme 4). Diene **16** was efficiently prepared from compounds **12** and **6** in 60% yield. Because Cladospolide C is an α,β-unsaturated ester, selective hydrogenation of diene **16** to preserve the conjugated olefin moiety was desired. After several attempts, we were unable to effect the desired selective hydrogenation. This is consistent with the observations by Trost et al. in their efforts to hydrogenate a related substrate.[18] Consequently, diene **16** was completely reduced to the saturated ester **17**, the hydrolysis of which afforded the acid **18**. Cyclization of **18** to lactone **19** was achieved by Yamaguchi esterification.[19]

The α,β-unsaturated ester **20** was regenerated by selenylation/deselenylation.[20] Here, we found that fresh phenylselenenyl bromide, prepared in situ from diphenyl diselenide and bromine, gave a better yield (57%, two steps) than using commercial phenylselenenyl bromide.[21]

(+)-Cladospolide C was produced after the acetonide moiety of **20** was removed under an acidic condition.[8a] The ^{1}H and ^{13}C NMR spectra from our synthetic **1** are consistent with those

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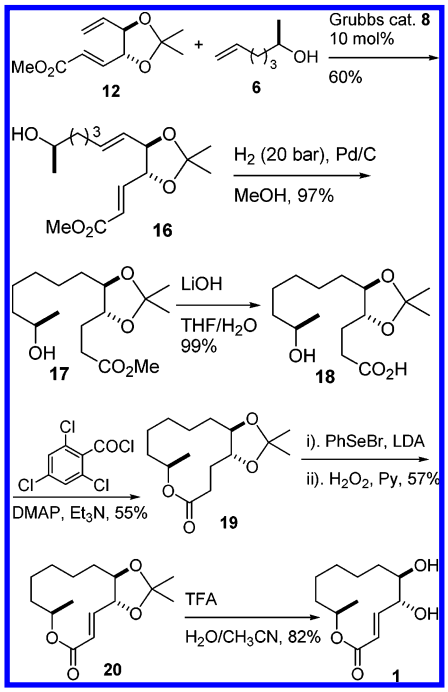
SCHEME 4. Approach with Two Consecutive Cross-Metatheses



reported for natural Cladospolide C and Banwell's work.[1,9] The specific rotation of our product **1** is +58.2 (*c* 0.5, MeOH), also close to the reported value (+59.7, *c* 0.4, MeOH) for natural Cladospolide C,[1] and has the opposite rotation as compared to that of Banwell's enantiomer.[9] Therefore, our results support the original stereochemical assignment for Cladospolide C.

In summary, (+)-Cladospolide C was synthesized in eight steps with 5% overall yield, starting with mannitol-derived diene **5**. An approach involving two CM reactions and ring closure by Yamaguchi esterification proved to be effective in this case, in preference to routes using RCM. With Grubbs' catalyst **8**, unfavorable factors, such as the rigid/strained structure and product liability, for effecting RCM with compounds **10** and **14** were difficult to overcome; however, the CM successfully provided an alternative solution for the synthesis of (+)-Cladospolide C (**1**).

Experimental Procedures

Preparation of Compound 12 with Cross Metathesis. A 10 mL round-bottomed flask equipped with a condenser and a stir bar was flame-dried under vacuum and filled with nitrogen after cooling. Compound **7**[11] (500 mg, 3.24 mmol), methyl acrylate (2.79 g, 32.4 mmol), *p*-cresol (170 mg, 1.62 mmol), and toluene (1 mL) were added to the flask by syringe. Grubbs' catalyst **8** (13.7 mg, 0.016 mmol) in toluene (1 mL) was also added to the mixture. The reaction was refluxed for 3 h. After being cooled to room temperature, the solvent was removed under reduced pressure. The crude product was purified by column chromatography (SiO_2/ethyl acetate/hexanes, 1:5; R_f 0.50) to give pure compound **12** (309 mg, 1.45 mmol, 45%) as a light-yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.43 (s, 3H), 1.45 (s, 3H), 3.73 (s, 3H), 4.11 (dd, J = 8.3 and 7.1 Hz, 1H), 4.22 (ddd, J = 8.3, 5.3, and 1.4 Hz, 1H), 5.29 (dd, J = 10.4 and 1 Hz, 1H), 5.38 (dd, J = 17.3 and 1 Hz, 1H), 5.81 (ddd, J = 17.3, 10.4, and 7.1 Hz, 1H), 6.1 (dd, J = 15.7 and 1.4 Hz, 1H), 6.85 (dd, J = 15.7 and 5.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.7, 26.9, 51.7, 79.8, 82.1, 110.0, 119.9, 122.3, 133.5, 143.1, 166.4; $[\alpha]^{20}_D$ −11.0 (*c* 1.7, $CHCl_3$); IR (neat) 3025, 2984, 2942, 2864, 1726, 1659, 1450, 1345, 1255, 1204, 1157, 1001, 950 cm^{-1}; HRMS (FAB) calcd for $[M + H]^+$ ($C_{11}H_{17}O_4$) 213.1127, found 213.1122.

(*E*)-Methyl 3-((4*R*,5*R*)-5-((*R*,*E*)-6-Hydroxyhept-1-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl) Acrylate (16). Compound **12** (150 mg, 0.71 mmol), alcohol **6** (121 mg, 1.06 mmol), *p*-cresol (38 mg, 0.35 mmol), and Grubbs' catalyst **8** (30 mg, 0.035 mmol) in dichloromethane (2 mL) were refluxed for 16 h under nitrogen. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (SiO_2/ethyl acetate/hexanes, 1:1; R_f 0.50) to give compound **16** (110 mg, 0.37 mmol, 60%) as a brown oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.15 (d, 3H, J = 6.2 Hz), 1.3−1.49 (m, 4H), 1.37 (s, 3H), 1.38 (s, 3H), 1.59 (brs, 1H), 1.89−2.18 (m, 2H), 3.71 (s, 3H), 3.71−3.81 (m, 1H), 4.05 (dd, J = 8.2 and 8.2 Hz 1H), 4.18 (ddd, J = 8.2, 5.2, and 1.5 Hz, 1H), 5.42 (dd, J = 15.4 and 7.9 Hz, 1H), 5.73−5.83 (m, 1H), 6.07 (d, J = 15.6 Hz, 1H), 6.82 (dd, J = 15.6 and 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.5, 24.9, 26.7, 27.1, 32.1, 38.7, 51.7, 67.8, 79.9, 82.0, 109.7, 122.1, 125.4, 137.4, 143.5, 166.4; $[\alpha]^{20}_D$ +12.9 (*c* 0.11, $CHCl_3$); IR (neat) 3400, 2976, 2915, 2851, 1724, 1659, 1425, 1360, 1301, 1240, 1150, 981, 895 cm^{-1}; HRMS (FAB) calcd for $[M + H]^+$ ($C_{16}H_{27}O_5$) 299.1858, found 299.1852.

Methyl 3-((4*R*,5*R*)-5-((*R*)-6-Hydroxyheptyl)-2,2-dimethyl-1,3-dioxolan-4-yl) Propanoate (17). A suspension of compound **16** (220 mg, 0.073 mmol), Pd/C (5%, 30 mg), and methanol (5 mL) was placed in a bomb and filled with hydrogen (20 bar) at room temperature. The pressure was released after 2 h, and the reaction mixture was filtered with a plug of silica gel and concentrated to give **17** (215 mg, 0.71 mmol, 97%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.13 (d, 3H, J = 6.2 Hz), 1.25−1.51 (m, 16H), 1.59−1.95 (m, 3H), 2.29−2.59 (m, 2H), 3.47−3.58 (m, 2H), 3.63 (s, 3H), 3.67−3.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.4, 25.5, 25.9, 27.2, 27.3, 27.9, 29.6, 30.4, 32.7, 39.2, 51.6, 67.9, 79.8, 80.6, 108.1, 173.7; $[\alpha]^{20}_D$ +16.0 (*c* 0.16, $CHCl_3$); IR (neat) 3415, 2933, 2859, 1713, 1377, 1216, 1064, 934 cm^{-1}; HRMS (FAB) calcd for $[M + H]^+$ ($C_{16}H_{31}O_5$) 303.2171, found 303.2178.

3-((4*R*,5*R*)-5-((*R*)-6-Hydroxyheptyl)-2,2-dimethyl-1,3-dioxolan-4-yl) Propanoic Acid (18). Aqueous lithium hydroxide (43 mg, 1.04 mmol, in 2.5 mL of water) was added to the solution of ester **17** (210 mg, 0.69 mmol) in THF (2.5 mL). After stirring at room temperature for 16 h, the reaction mixture was acidified to pH 4 with diluted $HCl_{(aq)}$ (1 N) and extracted with ethyl acetate (20 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered, and concentrated to give the acid **18** (200 mg, 0.69 mmol, 99%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.15 (d, 3H, J = 6.2 Hz), 1.22−1.55 (m, 16H), 1.63−1.97 (m, 2H), 2.32−2.62 (m, 2H), 3.48−3.67 (m, 2H), 3.67−3.91 (m, 1H), 4.71−4.94 (br, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 23.3, 25.4, 25.7, 27.1, 27.3, 27.6, 29.4, 30.4, 32.5, 38.9, 68.2, 79.8, 80.5, 108.2, 177.9; $[\alpha]^{20}_D$ +14.9 (*c* 1.0, $CHCl_3$); IR (neat) 3415, 2933, 2859, 1713, 1377, 1241, 1216, 1064, 934 cm^{-1}; HRMS (FAB) calcd for $[M + H]^+$ ($C_{15}H_{29}O_5$) 289.2015, found 289.2017.

(+)-Dihydro Cladospolide C Ethylene Acetal 19. 2,4,6-Trichlorobenzoyl chloride (90 mg, 0.37 mmol) was added to a solution of compound **18**, triethylamine (41 mg, 0.40 mmol), and THF (3 mL) in an ice/water bath. The reaction was stirred for 1 h at 0 °C, diluted with toluene (27 mL), and transferred into a solution of DMAP (205 mg, 0.168 mmol) and toluene (27 mL). The resulting mixture was refluxed for 1 h and quenched with sat. $NaHCO_{3(aq)}$ (10 mL) after being cooled to room temperature. The aqueous layer was separated and extracted with ethyl acetate (10 mL × 3). The combined organic layer was washed with sat. $CuSO_{4(aq)}$ (10 mL), water (10 mL), and sat. $NaCl_{(aq)}$ (10 mL); dried over Na_2SO_4; filtered; and concentrated. The crude product was further purified by column chromatography (SiO_2/ethyl acetate/hexanes, 1:5; R_f 0.50) to give lactone **19** (45 mg, 0.17 mmol, 55%) as a light-yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.19 (d, 3H, J = 6.4 Hz), 1.27−1.52 (m, 14H), 1.53−1.74 (m, 2H), 2.47 (t, 2H, J = 5.9 Hz), 3.61−

85 (m, 2H), 4.91−5.16 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.4, 19.9, 20.6, 26.8, 27.1, 27.1 27.6, 28.1, 31.5, 32.3, 70.9, 77.1, 79.2, 107.4, 172.4; $[\alpha]^{20}_D$ +4.2 (*c* 0.9, $CHCl_3$,); IR (neat) 3444, 2982, 2933, 2858, 1730, 1456, 1369, 1253, 1065 cm^{-1}; HRMS (FAB) calcd for $[M + H]^+$ ($C_{15}H_{27}O_4$) 271.1909, found 271.1897.

(+)-Cladospolide C Ethylene Acetal 20. Lithium diisopropyl amide (LDA), freshly prepared from *n*-BuLi (1.6 M, 0.35 mL, 0.57 mmol) and disopropyl amine in THF (0.4 mL), was added to a solution of compound **19** (64 mg, 0.24 mmol) and THF (0.4 mL) at −78 °C. After stirring at −78 °C for 1 h, the solution of enolate was added to a solution of phenylselenenyl bromide (40 mg, 0.17 mmol) and THF (0.4 mL) and stirred for another 1 h at −78 °C. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (4 mL), diluted with water (2 mL), and extracted with ether (5 mL × 3). The combined organic layer was washed with water (1 mL), dried over Na_2SO_4, filtered, and concentrated to give a yellow crude oil (128 mg). Dichloromethane (3 mL), pyridine (48 mg, 0.60 mmol), and hydrogen peroxide (35% in water, 102 mg, 3.0 mmol) were added to the crude selenenylated compound at 0 °C, stirred, and warmed up to room temperature in 15 h. The reaction mixture was washed with water (2 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was further purified by column chromatography (SiO_2/ethyl acetate/hexanes, 1:5; R_f 0.41) to give lactone **20** (36.5 mg, 0.14 mmol, 57%) as a light-yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.15−1.26 (m, 3H), 1.29 (d, 3H, J = 6.4 Hz), 1.35−1.49 (m, 8H), 1.52−1.62 (m, 3H), 1.64−1.72 (m, 1H), 1.9−2.01(m, 1H), 3.81−3.93 (m, 1H), 4.02 (dd, J = 9 Hz, J = 9 Hz, 1H), 4.95−4.98 (m, 1H), 6.20 (d, 1H, J = 15.8 Hz), 6.77 (dd, J = 9.5 and 15.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.6, 24.9, 25.1, 26.8, 27.2, 27.8, 29.5, 35.4, 75.4, 80.1, 80.4, 109.3, 125.9, 143.9, 166.6; $[\alpha]^{20}_D$ +12.0 (*c* 0.22, $CHCl_3$); IR (neat) 2982, 2934, 2864, 1719, 1648, 1462, 1370, 1252, 1051, 857 cm^{-1}; HRMS (FAB) calcd for $[M + H]^+$ ($C_{15}H_{25}O_4$) 269.1753, found 269.1758.

(+)-Cladospolide C (1)[1]. Trifluoroacetic acid (0.45 mL) was added to a solution of lactone **20** (15.8 mg, 0.060 mmol) and acetonitrile/water (2:1, v/v, 0.9 mL) at 0 °C. The ice/water bath was removed, and the reaction was stirred at room temperature for another 1 h, diluted with dichloromethane (40 mL), washed with sat. $NaHCO_{3(aq)}$ (20 mL), dried over Na_2SO_4, filtered, and concentrated to give compound **1** (11 mg, 0.047 mmol, 82%) as a colorless solid. Mp 90−91 °C; $[\alpha]^{20}_D$ +58.2 (*c* 0.5, MeOH); IR (neat) 3402, 2933, 2860, 1715, 1646, 1461, 1260, 1036 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.05−1.79 (m, 10H), 1.28 (d, 3H, J = 6.3 Hz), 2.35−2.69 (brs, 2H), 3.49−3.61 (m, 1H), 3.96 (dd, J = 7.9 and 9.1 Hz, 1H), 4.85−5.06 (m, 1H), 6.03 (d, 1H, J = 15.8 Hz), 6.79 (dd, J = 9.1 and 15.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.8, 24.0, 24.5, 27.3, 32.1, 33.9, 74.3, 76.5, 77.5, 124.5, 145.3, 166.7.

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Supporting Information Available: Experimental details for the preparation of compounds **7**, **9, 10**, and **13**−**15** and detailed spectroscopic data of all new compounds **7**, **9**, **10**, **12**−**20**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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