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A Ring-Closing Metathesis Approach toward Formal Total Synthesis of (+)-Diplodialide A†

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Abstract: An asymmetric formal total synthesis of diplodialide A **1a** has been achieved starting from methyl acetoacetate **6** and (*R*)-3-buten-2-ol **7**. The macrocyclic ring core of (+)-diplodialide A **1a** was constructed, in an excellent yield, by using a ring-closing metathesis strategy.

The construction of the macrocyclic core of any natural product having a macrocyclic lactone unit is a challenging task in synthetic organic chemistry.[1] Over the past two decades, there has been an intense interest in the development of methodology for the formation of macrocyclic lactones.[2] Although there are several methods available for macrolactonization, the yield in the lactonization of ω-hydroxy acids by using most of these reported reagents is not always good.[3] Very recently, olefin metathesis has been proved to be a highly flexible method for the construction of macrocyclic rings.[4] Hundreds of naturally occurring macrocyclic lactones have been synthesized using ring closing metathesis (RCM) as a key step.[4] Herein, we wish to describe the details of our studies directed toward synthesis of (+)-diplodialide A **1a**, a 10-membered macrocyclic lactone, using a RCM based approach.

Diplodialides **1a**−**d** (Figure 1) are the family of 10-membered macrocyclic lactones isolated from the pathogenic fungus *Diplodia pinea* by Wada and co-workers.[5] Among the four **1a**−**d**, diplodialide A **1a** showed a significant inhibitory activity against progesterone 11α-hydroxylase in vegetable cell cultures of *Rhizopus stolonifer* at 125 ppm.[5] Subsequently, another 10-membered lactone of this family, (*R*)-phoracantholide **2**, was isolated from the metasternal gland secretion of *Phoracantha synonyma* by Moore et al.[6] Extensive studies have been carried out in the literature for the construction of the 10-membered lactone unit of diplodialide A **1a**,[7] which include macrolactonization using Corey's procedure,[8] sulfide ring contraction,[9] and intramolecular Reformatsky reaction.[10] It should be noted that in all the cases, yield of products in the cyclization step was less than 30%. Boeckman reported the first asymmetric synthesis of (+)-diplodialide A **1a** via intramolecular ring opening of dioxolenones by alcohol nucleophiles.[11] Although, in this particular case, the yield of cyclized product in the cyclization step was reasonably good (68%), it required very harsh conditions. These observations clearly showed that there was a need for a flexible method toward the construction of the 10-membered lactonic unit of (+)-diplodialide A **1a**. Since RCM is emerging as a powerful tool for the construction of macrocyclic molecules, we report here full details of our work toward synthesis of (+)-diplodialide A **1a** by using this methodology.

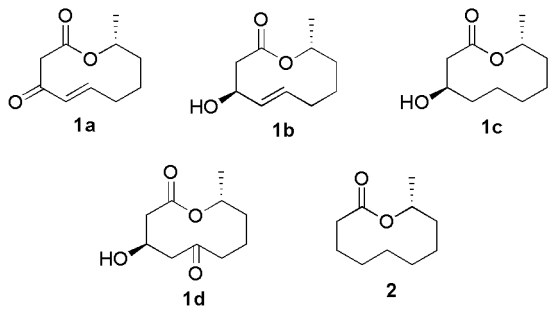

FIGURE 1.

A careful retrosynthetic analysis showed that both (+)-diplodialide A **1a** and (*R*)-phoracantholide[12] **2** could be obtained from a common intermediate **3** through simple steps (Scheme 1). The macrocyclic lactone **3** could be constructed from an acyclic diene ester **4** via RCM. The metathesis precursor **4** can be obtained starting from methyl acetoacetate **6**, homoallyl bromide **5** and (*R*)-3-buten-2-ol **7** through simple transformations.

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† Dedicated to Professor Sukh Dev on the occasion of his 80th birthday.

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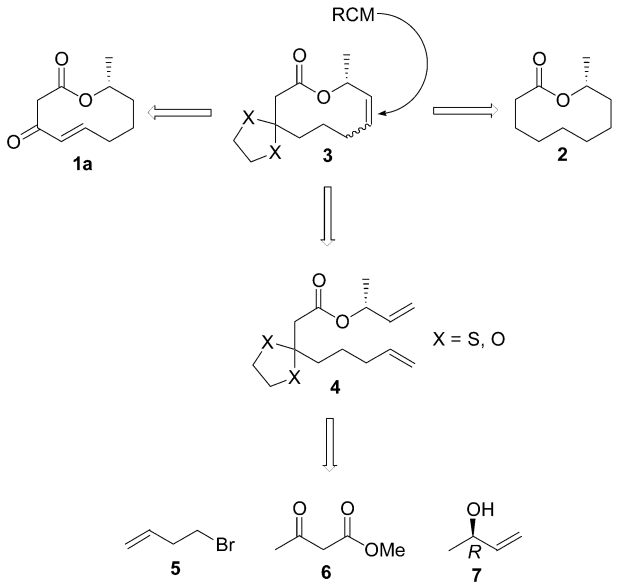
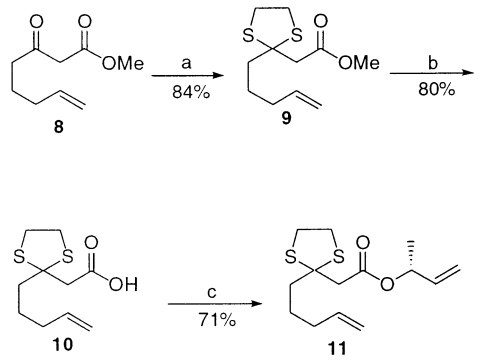
SCHEME 1



SCHEME 2[a]



[a] Reagents and conditions: (a) $HSCH_2CH_2SH$, $Cu(OTf)_2$, CH_2Cl_2, rt, 8 h; (b) 1 N LiOH, THF−H_2O (2:1), 0 °C to rt, 6 h; (c) (*R*)-3-buten-2-ol, DCC, DMAP, CH_2Cl_2, 0 °C to rt, 12 h.

The dianion of methyl acetoacetate **6** was treated with 4-bromo-1-butene **5** in THF at 0 °C for 4 h to afford the *β*-keto ester **8** in 77% yield. Next, we wanted to protect the ketone and then hydrolyze the ester. Thioketal was chosen as a protecting group because by using this it was possible to get both (+)-diplodialide **1a** and (*R*)-phoracantholide **2** from **3** by deprotection and reduction, respectively. Thus, treatment of **8** with ethanedithiol in the presence of 10 mol % of $Cu(OTf)_2$[13] gave the desired thioketal **9** in 84% yield. Ester hydrolysis of **9** was carried out by using 1 N aqueous LiOH solution in a THF/H_2O (2:1) mixture to provide **10** in 80% yield. The acid **10** was then condensed with (*R*)-3-buten-2-ol in the presence of DCC and DMAP to afford the diene ester **11**, a substrate for a metathesis reaction, in 71% yield (Scheme 2).

Ring-closing reaction of **11** was performed by using 20 mol % of Grubbs catalyst **I** in refluxing CH_2Cl_2. Unfortunately, in this case, no cyclized product was observed. It was probably due to the deactivation[14] of Ru catalyst by coordination of sulfur atom to form a stable chelate **12** (Figure 2). The use of second-generation catalysts, like

(13) For thioacetalization of carbonyl compounds using $Cu(OTf)_2$, see: Anand, R. V.; Saravanan, P.; Singh, V. K. *Synlett* **1999**, 415.

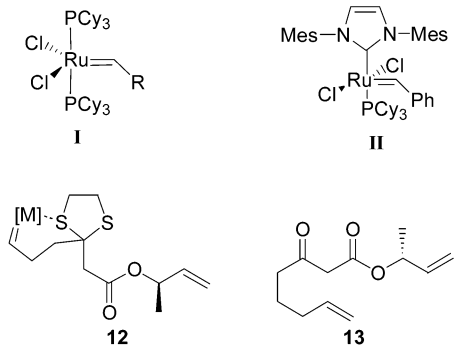


FIGURE 2.

II, also did not help.[15] In fact, an inseparable complex mixture of products was obtained when we tried to cyclize the diene **11** in the presence of 10 mol % of **II** in refluxing CH_2Cl_2. Then we planned to decrease the coordination ability of the sulfur atoms by adding a catalytic amount of $BF_3{\cdot}OEt_2$.[16] The logic behind this was that $BF_3{\cdot}OEt_2$ would coordinate to the sulfur atoms prior to Ru catalyst and thereby reduce the coordination ability of sulfur toward Ru center. Surprisingly, exposure of **11** to 10 mol % of Grubbs catalyst **I** in the presence of 50 mol % of $BF_3{\cdot}OEt_2$ gave only the hydrolyzed product **10** in 15% yield along with unreacted starting material.[17] Since the thioacetal group gave problem in the ring-closing step, we decided to deprotect it and then carry out the metathesis reaction. Among the various reagents tried, (diacetoxy)iodobenzene was found to be the best for the deprotection of thioacetal group of **11**. Thus, treatment of **11** with 1.5 equiv of (diacetoxy)iodobenzene[18] in MeOH−H_2O mixture at room temperature gave the desired *β*-ketoester **13** in 35% yield. The cyclization of **13** in the presence of 10 mol % of **I** in refluxing CH_2Cl_2 again gave a complex mixture of products. The addition of $Ti(^iPrO)_4$[19] also did not help to get clean reaction products.

Due to the failure of the ring-closing of either **11** or **13**, we decided to choose a simple acetal group as a protective group. Thus, treatment of **8** with ethylene glycol in the presence of a catalytic amount of *p*-TsOH gave a desired ketal **14** in 83% yield. The methyl ester **14** was hydrolyzed using 1 N aqueous LiOH solution in a THF−H_2O mixture to provide **15** in 94% yield. The acid

(14) Similar problems with RCM reactions of dienes containing thioether functions have been reported in the literature. For references, see: (a) Fürstner, A.; Seidel, G.; Kindler, N. *Tetrahedron* **1999**, *55*, 8215. (b) Shon, Y.-S.; Lee, T. R. *Tetrahedron Lett*. **1997**, *38*, 1283. (c) Armstrong, S. K.; Christie, B. A. *Tetrahedron Lett*. **1996**, *37*, 9373. (d) Mascarenas, J. L.; Rumbo, A.; Castedo, L. *J. Org. Chem*. **1997**, *62*, 8620.

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(16) Initially, we planned to use Hg salts in the cyclization of the diene **11**. Since, Hg salts are known to cleave thioacetal groups, we used $BF_3{\cdot}OEt_2$.

(17) For cleavage of methyl esters with $BF_3{\cdot}OEt_2$, see: Pearlman, B. A.; McNamara, J. M.; Hasan, I.; Hatakeyama, S.; Sekizaki, H.; Kishi, Y. *J. Am. Chem. Soc*. **1981**, *103*, 4248.

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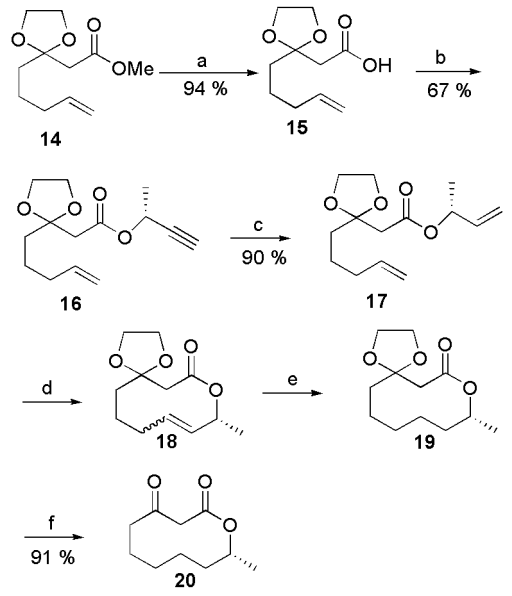
SCHEME 3[a]



[a] Reagents and conditions: (a) 1 N LiOH in THF−H_2O (2:1), 0 °C to rt, 8 h; (b) (*S*)-3-butyn-2-ol, DIAD, PPh_3, Et_2O, 0 °C to rt, 12 h; (c) Pd/$CaCO_3$, quinoline, hexane−EtOH (1:1), H_2 (1 atm), 1 h; (d) 10 mol% of Ruthenium carbene **II**; C_6H_6, reflux, 8 h; (e) Pd/C, H_2 (30 psi), EtOH, 8 h; 88% for two steps; (f) *p*-TsOH (cat.), wet acetone, rt, 6 h.

15, on Mitsunobu reaction with (*S*)-3-butyn-2-ol[20] in the presence of DIAD and PPh_3, provided an alkyne ester **16**, which on Lindlar reduction with Pd/$CaCO_3$ in the presence of catalytic amount of quinoline under H_2 atmosphere gave the metathesis precursor **17** in 90% yield (Scheme 3). We, then, carried out cyclization of the diene ester **17** in the presence of 20 mol % of Grubbs catalyst **I** in refluxing benzene under high dilution conditions. Unfortunately, a complex mixture of products was again obtained. However, the use of 10 mol % of the second-generation Grubbs catalyst **II** gave the desired cyclized product **18** as a mixture of cis and trans isomers (2:1 ratio), which was directly reduced with Pd/C under H_2 atmosphere (30 psi) to provide the saturated lactone **19** in an overall yield of 88%. Deprotection of the ketal moiety in **19** using a catalytic amount of *p*-TsOH in wet acetone gave the β-keto lactone **20** in 91% yield. Since, the conversion of **20** to (+)-diplodialide A **1a** is known in the literature,[7,8] we stopped our synthesis at this stage.

In conclusion, we have achieved a formal synthesis of (+)-diplodialide A **1a** using ring closing metathesis as a key step. The overall yield of the β-keto lactone **20** by our method is 29%, which is very high in comparison with other literature known methods.[7,8]

Experimental Section

^{1}H NMR spectra were recorded on a 400 MHz NMR spectrophotometer using TMS as internal standard. Chemical shifts are reported in ppm, and coupling constants are reported in Hz. Routine monitoring of reactions was performed using silica gel-G obtained from Acme. Column chromatographic separations were done by using silica gel (Acme's 60−120 mesh). Petroleum ether used was of boiling range 60−80 °C. Reactions that needed anhydrous conditions were run under an atmosphere of nitrogen or argon using flame-dried glasswares. The organic extracts were dried over anhydrous sodium sulfate. Evaporation of solvents was performed at reduced pressure. Tetrahydrofuran(THF) was distilled from sodium benzophenone ketyl under nitrogen. Benzene, toluene, and CH_2Cl_2 were distilled from CaH_2. (*R*)-3-Buten-2-ol and (*S*)-3-butyn-2-ol were obtained from Fluka and Lancaster, respectively. Benzylidine [1,3-bis(2,4,6-trimethylphenyl)-2-imidazolinylidine]dichloro(tricyclohexyl phosphine)ruthenium was obtained from Fluka.

3-Oxooct-7-enoic Acid Methyl Ester (8). Methyl acetoacetate **6** (4.8 mL, 44.4 mmol) was added dropwise to a stirred suspension of NaH (60% suspension in mineral oil) (2.13 g, 53.3 mmol) in a mixture of anhydrous THF (90 mL) and HMPA (10 mL) at 0 °C. After the mixture was stirred for 10 min, *n*-BuLi (15% w/v solution in hexane, 21 mL, 48.9 mmol) was added dropwise at 0 °C and the resulting yellow solution was stirred for further 10 min. A solution of 4-bromo-1-butene **5** (2.3 mL, 22.2 mmol) in anhydrous THF was then added dropwise, and the resulting heterogeneous mixture was stirred at 0 °C for further 4 h. It was warmed to rt and quenched with saturated aqueous NH_4Cl solution. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layer was washed with saturated brine solution and dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuo gave the crude product, which on purification over silica gel column using 2% EtOAc in petroleum ether gave pure compound **8** as a colorless oil: yield 2.9 g (77%); R_f 0.65 (20% EtOAc in petroleum ether); FT IR (neat) 1750, 1644 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.70 (quintet, J = 7.6 Hz, 2H), 2.07 (q, J = 7.3 Hz, 2H), 2.55 (t, J = 7.3 Hz, 2H), 3.45 (s, 2H), 3.74 (s, 3H), 4.97−5.06 (m, 2H), 5.71−5.82 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.4, 32.8, 42.1, 49.0, 52.3, 115.4, 137.7, 167.6, 202.5; MS (ES) 171 (M^+ + 1). Anal. Calcd for $C_9H_{14}O_3$: C, 63.53; H, 8.23. Found: C, 63.42; H, 8.08.

(2-Pent-4-enyl[1,3]dithiolan-2-yl)acetic Acid Methyl Ester (9). $Cu(OTf)_2$ (106 mg, 0.29 mmol) was added to a solution of ketoester **8** (500 mg, 2.9 mmol) and 1,2-ethanedithiol (296 μL, 3.5 mmol) in anhydrous CH_2Cl_2 at rt and stirred at ambient temperature for a further 8 h. The reaction mixture was then diluted with CH_2Cl_2, washed with 15% NaOH solution followed by saturated brine solution, and dried over anhydrous Na_2SO_4. Evaporation of solvent gave a crude compound which on purification over silica gel column using 5% EtOAc in petroleum ether provided the pure thioketal **9** as a colorless oil: yield 608 mg (84%); R_f 0.50 (10% EtOAc in petroleum ether); FT IR (neat) 1739 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.60−1.63 (m, 2H), 2.06−2.14 (m, 4H), 3.05 (s, 2H), 3.30 (s, 4H), 3.70 (s, 3H), 4.95−5.05 (m, 2H), 5.75−5.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.4, 33.6, 39.7, 42.0, 48.0, 51.7, 67.0, 114.8, 138.3, 170.5; MS (ES) 247 (M^+ + 1). Anal. Calcd for $C_{11}H_{18}O_2S_2$: C, 53.65; H, 7.32. Found: C, 53.60; H, 7.29.

(2-Pent-4-enyl[1,3]dithiolan-2-yl)acetic Acid (10). A solution of 1 N aqueous LiOH (20 mL, 20.0 mmol) was added dropwise to a solution of methyl ester **9** (500 mg, 2.0 mmol) in THF (40 mL) and water (20 mL) mixture at 0 °C. The reaction mixture was then slowly warmed to rt and stirred for additional 6 h. It was again cooled to 0 °C, neutralized with 2 N HCl, and extracted with ethyl acetate. The combined organic layer was washed with saturated brine solution and dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuo followed by purification over silica gel column using 30% EtOAc in petroleum ether gave the pure acid **10** as a pale yellow solid: yield 370 mg (80%); mp 79−81 °C; R_f 0.50 (50% EtOAc in petroleum ether); FT IR (KBr) 3066−2741 (br), 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.52−1.59 (m, 2H), 1.99−2.08 (m, 4H), 3.04 (s, 2H), 3.25 (s, 4H), 4.90 (td, J = 10.2, 1.2 Hz, 1H), 4.96 (qd, J = 17.1, 1.5 Hz, 1H), 5.69−5.77 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.3, 33.5, 39.7, 42.0, 48.0, 66.6, 114.9, 138.2,175.6; MS (ES) 233 (M^+ + 1). Anal. Calcd for $C_{10}H_{16}O_2S_2$: C, 51.72; H, 6.90. Found: C, 51.74; H, 6.84.

(2-Pent-4-enyl[1,3]dithiolan-2-yl)acetic Acid (1′*R*)-Methylallyl Ester (11). A solution of DCC (290 mg, 1.4 mmol) in

(20) Since Fluka Chemical Co. stopped producing (*R*)-3-buten-2-ol, we used (*S*)-3-butyn-2-ol, which was obtained from Lancaster.

anhydrous CH_2Cl_2 (1 mL) was added dropwise to a stirred solution of the acid **10** (295 mg, 1.27 mmol), (*R*)-3-buten-2-ol **7** (132 μL, 1.53 mmol), and 4-DMAP (117 mg, 0.95 mmol) in anhydrous CH_2Cl_2 (4 mL) at 0 °C. After being stirred for an additional 12 h at rt, the reaction mixture was filtered through a pad of Celite, and the filtrate was washed with water and saturated brine solution and dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure to give crude material, which on purification over silica gel column using 2% EtOAc in petroleum ether gave pure ester **11** as colorless oil: yield 258 mg (71%); R_f 0.60 (10% EtOAc in petroleum ether); $[\alpha]^{25}_D$ +6.50 (*c* 1.75, $CHCl_3$); FT IR (neat) 1733 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.33 (d, J = 6.4 Hz, 3H), 1.59−1.64 (m, 2H), 2.05−2.14 (m, 4H), 3.05 (s, 2H), 3.29 (s, 4H), 4.96 (td, J = 10.2, 1.0 Hz, 1H), 5.02 (qd, J = 17.0, 1.7 Hz, 1H), 5.15 (td, J = 10.8, 1.2 Hz, 1H), 5.27 (td, J = 17.1, 1.2 Hz, 1H), 5.35−5.41 (m, 1H), 5.75−5.89 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.9, 26.3, 33.6, 39.6, 42.2, 48.3, 67.0, 71.41, 100.5, 114.8, 116.1, 137.4, 138.3, 169.2; MS (ES) 287 (M^+ + 1). Anal. Calcd for $C_{14}H_{22}O_2S_2$: C, 58.74; H, 7.69. Found: C, 58.70; H, 7.68.

(2-Pent-4-enyl[1,3]dioxolan-2-yl)acetic Acid Methyl Ester (14). A solution of ketoester **8** (400 mg, 2.4 mmol), ethylene glycol (395 μL, 7.1 mmol), and *p*-TsOH·H_2O (45 mg, 0.24 mmol) in anhydrous benzene was refluxed at 90 °C for 8 h. During the reaction, the benzene−water azeotrope was removed using Dean−Stark apparatus. The reaction mixture was then washed with saturated aqueous $NaHCO_3$ solution followed by saturated brine solution and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by purification over silica gel column using 5% EtOAc in petroleum ether gave pure ketal **14** as colorless oil: yield 417 mg, (83%); R_f 0.35 (10% EtOAc in petroleum ether); FT IR (neat) 1739 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.47−1.54 (m, 2H), 1.79−1.84 (m, 2H), 2.07 (q, J = 6.8 Hz, 2H), 2.66 (d, J = 1.9 Hz, 2H), 3.69 (d, J = 1.9 Hz, 3H), 3.94−4.00 (m, 4H), 4.95 (td, J = 10.3, 1.0 Hz, 1H), 5.01 (td, J = 17.1, 1.4 Hz, 1H), 5.74−5.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.7, 33.6, 37.0, 42.4, 51.7, 65.1, 109.2, 114.6, 138.4, 169.9; MS (ES): 215 (M^+ + 1). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.68; H, 8.41. Found: C, 61.42; H, 8.53.

(2-Pent-4-enyl[1,3]dioxolan-2-yl)acetic Acid (15). A solution of 1 N aqueous LiOH (13 mL, 13.0 mmol) was added dropwise to a solution of methyl ester **14** (280 mg, 1.3 mmol) in THF (30 mL) and water (15 mL) mixture at 0 °C. The reaction mixture was then slowly warmed to room temperature and stirred for an additional 8 h. It was again cooled to 0 °C, neutralized with 2 N HCl, and extracted with EtOAc. The combined organic layer was washed with saturated brine solution and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by purification over silica gel column using 30% EtOAc in petroleum ether gave the pure acid **15** as colorless oil: yield 245 mg (94%); R_f 0.50 (neat EtOAc); FT IR (neat) 3065−2894 (br), 1716 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.47−1.55 (m, 2H), 1.79−1.84 (m, 2H), 2.07 (bq, J = 7.3 Hz, 2H), 2.71 (s, 2H), 3.98−4.06 (m, 4H), 4.96 (dd, J = 10.2, 1.2 Hz, 1H), 5.01 (dd, J = 17.1, 1.5 Hz, 1H), 5.74−5.84 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.7, 33.5, 36.9, 42.3, 65.1, 109.2, 114.9, 138.3, 173.5; MS (ES) 201 (M^+ + 1). Anal. Calcd for $C_{10}H_{16}O_4$: C, 60.0, H, 8.0. Found: C, 59.83; H, 8.12.

(2-Pent-4-enyl[1,3]dioxolan-2-yl)acetic Acid (1′*R*)-Methylprop-2-ynyl Ester (16). A solution of (*S*)-3-butyn-2-ol (240 μL, 3.0 mmol) and PPh_3 (656 mg, 2.5 mmol) in anhydrous ether (3 mL) was added dropwise to a solution of the acid **15** (500 mg, 2.5 mmol) and diisopropyl azadicarboxylate (DIAD) (485 μL, 2.5 mmol) in anhydrous ether (3 mL) at 0 °C. After being stirred for 12 h at rt, the reaction mixture was filtered through a pad of Celite to remove O=PPh_3, and the filtrate was concentrated under vacuum to give crude material, which on purification over silica gel column using 5% EtOAc in petroleum ether gave pure ester **16** as a colorless oil: yield 420 mg (67%); R_f 0.50 (10% EtOAc in petroleum ether); $[\alpha]^{25}_D$ −44.5 (*c* 1.15, $CHCl_3$); FT IR (neat) 3301, 2123, 1739 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.47−1.55 (m, 2H), 1.51 (d, J = 6.8 Hz, 3H), 1.79−1.84 (m, 2H), 2.07 (bq, J = 7.1 Hz, 2H), 2.45 (d, J = 2.2 Hz, 1H), 2.68 (s, 2H), 3.94−4.04 (m, 4H), 4.95 (dd, J = 10.2, 1 Hz, 1H), 5.01 (dd, J = 17.1, 1.4 Hz, 1H), 5.47 (dq, J = 6.6, 1.9 Hz, 1H), 5.75−5.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1, 22.7, 33.6, 37.3, 42.5, 60.0, 65.1, 72.9, 81.9, 109.3, 114.7, 138.5, 168.3. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.67; H, 7.94. Found: C, 66.73; H, 7.88.

(2-Pent-4-enyl[1,3]dioxolan-2-yl)acetic Acid (1′*R*)-Methylallyl Ester (17). Quinoline [1 mL of a stock solution (40 μL quinoline in 20 mL of hexane)] and the alkyne **16** (770 mg, 3.05 mmol) were dissolved in a hexane (5 mL) and ethanol (5 mL) mixture. Commercially available Lindlar catalyst [Pd/$CaCO_3$] (100 mg) was added to the mixture, and the resulting suspension was stirred for 1 h under an atmosphere of H_2 (1 atm). The catalyst was filtered off through a pad of Celite, solvent was evaporated, and the residue was purified over silica gel column using 5% EtOAc in petroleum ether to give pure diene **17** as a colorless oil: yield 700 mg (90%); R_f 0.30 (10% EtOAc in petroleum ether); $[\alpha]^{25}_D$ −14.70 (*c* 1.05, $CHCl_3$); FT IR (neat) 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.32 (d, J = 6.3 Hz, 3H), 1.47−1.55 (m, 2H), 1.79−1.84 (m, 2H), 2.07 (bq, J = 7.3 Hz, 2H), 2.65 (s, 2H), 3.94−4.02 (m, 4H), 4.95 (qd, J = 10.3, 1.2 Hz, 1H), 5.01 (qd, J = 17.3, 1.7 Hz, 1H), 5.14 (td, J = 10.5, 1.2 Hz, 1H), 5.27 (td, J = 17.3, 1.5 Hz, 1H), 5.34−5.41 (m, 1H), 5.75−5.89 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.8, 22.7, 33.6, 37.2, 42.8, 65.1, 71.1, 109.4, 114.7, 115.9, 137.5, 138.5, 168.7; MS (ES) 255 (M^+ + 1). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.14; H, 8.66. Found: C, 66.39; H, 8.65.

(9*R*)-Methyl-1,4,8-trioxaspiro[4.9]tetradecan-7-one (19). A solution of ruthenium carbene **II** (167 mg, 0.197 mmol) in anhydrous benzene (100 mL) was added dropwise to a solution of diene **17** (500 mg, 1.97 mmol) in anhydrous benzene (100 mL) at 80 °C over a period of 4 h. After being stirred for an additional 6 h at reflux temperature, the solvent was evaporated and the crude material was filtered through a pad of silica gel. The solvent was removed under reduced pressure, and the residue (435 mg) was redissolved in EtOH (30 mL) and taken in a hydrogenation flask. Pd/C (80 mg) was added to it. The reaction flask was then fixed in a hydrogenation apparatus and hydrogenated under H_2 pressure (30 psi) for 8 h. It was filtered and washed with EtOH. The solvent was removed under reduced pressure and the crude residue on purification over silica gel column using 25% EtOAc in petroleum ether gave pure macrolactone **19** as viscous liquid: yield 395 mg (88%); R_f 0.65 (40% EtOAc in petroleum ether); $[\alpha]^{25}_D$ +4.29 (*c* 0.70, $CHCl_3$); FT IR (neat) 1730 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.21 (d, J = 6.1 Hz, 3H), 1.24−1.59 (m, 8H), 1.71−1.80 (m, 2H), 2.56−2.66 (m, 2H), 3.95−3.99 (m, 4H), 4.95−4.98 (m, 1H); MS (FAB) 229 (M^+ + 1). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.16; H, 8.77. Found: C, 63.11; H, 8.49.

(9*R*)-3-Oxodecan-9-olide (20).[8] *p*-TsOH·H_2O (20 mg, 0.11 mmol) was added to a solution of the acetal **19** (120 mg, 0.52 mmol) in wet acetone (3 mL) at rt. After being stirred for 6 h at rt, the solvent was evaporated and the residue was directly loaded on a silica gel column and chromatographed using 20% EtOAc in petroleum ether to give β-ketolactone **20** as low melting solid: yield 88 mg (91%); R_f 0.65 (40% EtOAc in petroleum ether); $[\alpha]^{25}_D$ +34.0 (*c* 1, $CHCl_3$); FT IR (KBr) 1734, 1644 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.23 (d, J = 6.4 Hz, 3H), 1.26−1.33 (m, 4H), 1.50−1.69 (m, 4H), 2.45−2.63 (m, 2H), 3.41 (s, 2H), 4.93−5.01 (m, 1H); MS (FAB) 185 (M^+ + 1). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.22; H, 8.70. Found: C, 65.46; H, 8.62.

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