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Total Synthesis and Determination of Relative and Absolute Configuration of Multiplolide A

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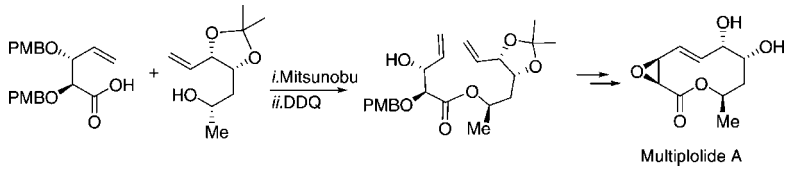

A flexible approach for total syntheses of possible multiplolide A diastereomers establishing the relative and absolute configuration is documented. The adopted strategy features ring-closing metathesis (RCM) as the key reaction and screening of a set of substrates for the feasibility of RCM in general and for the requisite *E*-configuration of ring olefin in particular. Selective protecting groups manipulation prior to the assembly of the central macrocyclic core was instrumental in installing the epoxide functionality on a fully deprotected nonenolide at the end of the synthesis.

Introduction

Though modern day analytical techniques have bestowed isolation chemists with deeper insights toward understanding the structures of isolated natural products, the opportunities for synthetic chemists to contribute in the area of natural product structure elucidation are not totally exhausted.[1] Nature sometimes tests and even teases the awesome influence of the analytical techniques by presenting simple looking structures out of its bag. Such was the case with the multiplolides A (**1**) and B (**2**), two new antifungal 10-membered lactones which were isolated in 2001 by Kittakoop and co-workers from the crude ethyl acetate extract of the culture broth of *Xylaria multiplex*.[2]

Multiplolides A (**1**) and B (**2**) exhibited antifungal activity against *Candida albicans* with IC_{50} values of 7 and 2 μg/mL, respectively. Chemical structures of **1** and **2** were elucidated on the basis of their spectral data (Figure 1). The relative stereochemistry of C-7, C-8, and C-10 was ascertained with the help of extensive 2D-NMR analysis. The absolute configuration at C-7 of **2** was determined as *S* by the application of the Mosher method,[3] which indirectly established the absolute configurations of both C-8 and C-10 centers as *R*,*R*. By taking into account the positive optical rotation shown by both **1** and **2**, similar absolute configurations of C-7, C-8, and C-10 were proposed for multiplolide A (**1**) (Figure 1).

The most striking features of multiplolides from a structural elucidation point of view are the epoxide functionality set in between lactone carbonyl and olefin and that the epoxide protons (H-C3, H-C4) are spatially isolated from the protons on other chiral centers resulting in partial structural elucidation, leaving the two possible diastereomeric structures (**3**, **4**) for the central core of multiplolides. Very recently, Tan et al. isolated 8-acetyl multiplolide A and concluded it was the derivative of multiplolide A by extensive 2D NMR analyses; however, this left the relative configuration of the oxirane ring in question.[4] The intriguing structure and its promising biological activity make these compounds attractive targets for total synthesis. This paper describes the first total synthesis of both the possible diastereomers of multiplolide A (**1**) and establishes the relative and absolute configurations.

The basic premise of our synthetic plan is to utilize a ring-closing metathesis (RCM) reaction[5,6] to construct the macro-

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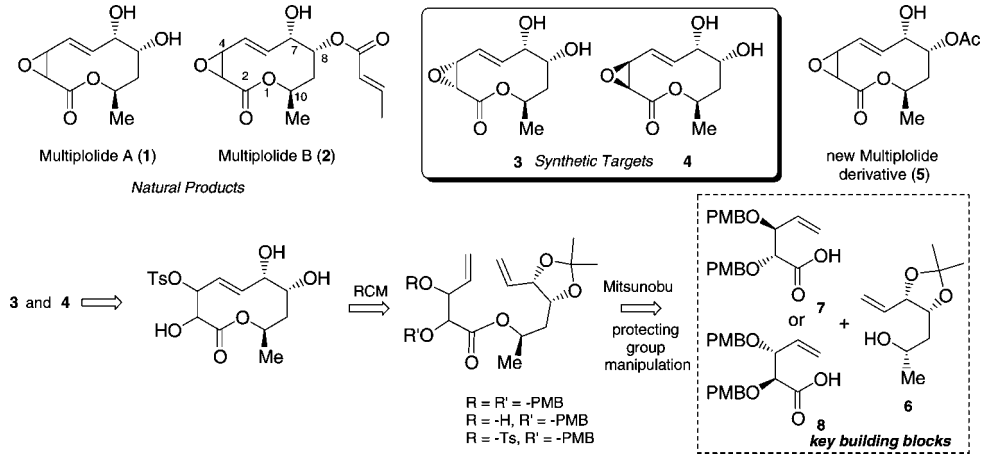
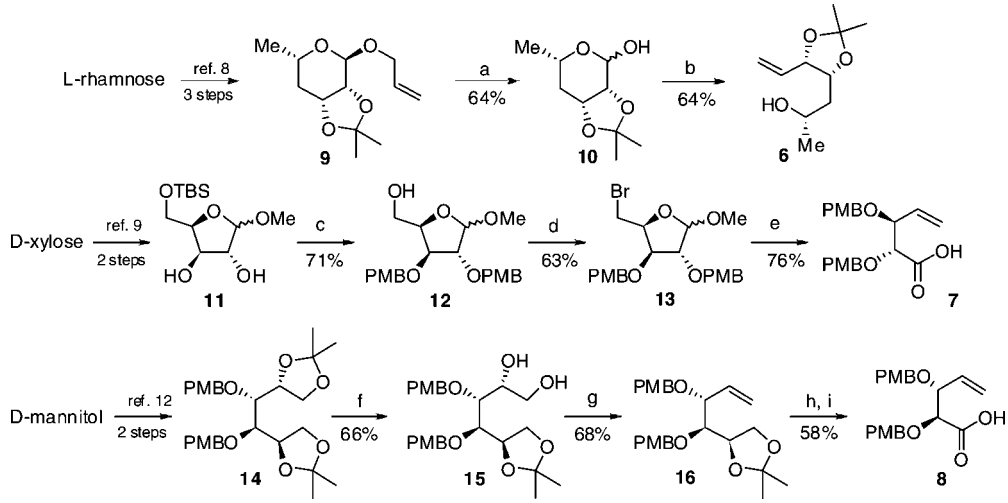


FIGURE 1. Chemical structures of multiplolide A and B and retrosynthetic analysis.

SCHEME 1. Synthesis of Coupling Partners 6−8[a]



[a] Reagents and conditions: (a) (i) KO^{t}Bu, DMSO, 100 °C, 1 h, (ii) HgO, $HgCl_2$, rt, 8 h; (b) $Ph_3P{=}CH_2$, THF, DMSO, rt, 24 h; (c) (i) NaH, PMBBr, DMF, 0 °C → rt, 16 h, (ii) TBAF, THF, rt, 16 h; (d) PPh_3, CBr_4, Et_3N, CH_2Cl_2, rt, 40 h; (e) (i) Zn, EtOH, reflux, 0.5 h, (ii) NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene, *t*-BuOH/H_2O (3:1), rt, 1 h; (f) PPTS, MeOH, 0 °C → rt, 12 h; (g) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C → rt, 1 h, (ii) NaI, 2-butanone, 80 °C, 10 h; (h) PPTS, MeOH, rt, 36 h; (i) (i) $NaIO_4$, CH_2Cl_2, rt, 1 h, (ii) NaH_2PO_4, $NaClO_2$, *t*-BuOH/H_2O (3:1), 2-methyl-2-butene, rt, 1 h.

cyclic framework. A vicinal diol unit was designated as the surrogate for the epoxide. We opted PMB protection for both the hydroxyl groups of the vicinal diol anticipating selective mono PMB deprotection at an advanced stage.[7] Taking into account the difficulty in the prediction of the stereochemical outcome of the RCM reaction, the path was chosen so as to offer enough flexibility with the substrates for RCM by means of changing R and R′ to attain the required *E* configuration at the olefin under construction (Figure 1).

Results and Discussion

The syntheses of the alcohol **6** and the enantiomeric acids **7** and **8** were achieved through functional group manipulations on corresponding sugar building blocks, keeping the requisite stereochemical information intact. The synthesis of the alcohol **6** started with the known allyl 4-deoxy-2,3-*O*-isopropylidene-L-rhamnopyranoside (**9**) (Scheme 1).[8] The removal of the allyl group at the anomeric oxygen was effected first by isomerization of the double bond with potassium *tert*-butoxide−DMSO followed by treatment with Hg^{2+} salts to give **10**.[8] One-carbon homologation of **10** with $Ph_3P{=}CH_2$ completed the synthesis of the alcohol **6**.

D-Xylose was converted into the known derivative **11**.[9] Protection of the secondary hydroxyl functions in **11** as their PMB ethers and the removal of TBS protection of the resulting compound afforded the primary alcohol **12**. Conversion of alcohol **12** to the corresponding bromo derivative **13**, subsequent Bernet–Vasella fragmentation,[10] and oxidation of the intermediate aldehyde using sodium chlorite[11] gave acid **7** (Scheme 1).

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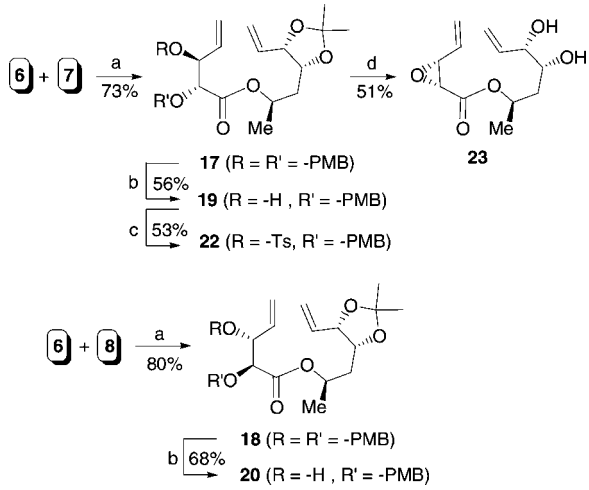
SCHEME 2. Synthesis of RCM Substrates[a]



[a] Reagents and conditions: (a) PPh_3, DEAD, THF, 0 °C → rt, 3 h; (b) DDQ, CH_2Cl_2, buffer, 0 °C → rt, 4 h; (c) TsCl, *i*-Pr_2NEt, DMAP, CH_2Cl_2, rt, 36 h; (d) TFA, CH_2Cl_2, rt, 35 h then *i*-Pr_2NEt, 0.5 h, rt.

Synthesis of another key intermediate **8** (Scheme 1) was initiated from the known di-*O*-isopropylidene-D-mannitol derivative (**14**).[12] The controlled hydrolysis of C_2-symmetric diacetonide **14** was efficiently dealt with by employing PPTS in methanol. In order to derive the olefin from the resulting diol **15**, it was first mesylated and then the resulting dimesylate was treated with NaI in refluxing 2-butanone to yield the olefin **16**.[13] The acid-catalyzed hydrolysis of **16** with PPTS in methanol followed by sodium periodate cleavage and oxidation of the resulting aldehyde with sodium chlorite afforded **8**.

Alcohol **6** was coupled with acids **7** and **8** under Mitsunobu conditions[14] to afford the diene esters **17** and **18**, respectively. The inversion of configuration was confirmed in each case by the hydrolysis of the resulting esters **17**/**18** and comparing the analytical data of so as obtained *epi*-**6** with **6**. The first set of substrates (**17** and **18**) for RCM was examined under various reaction conditions anticipating all the possible geometrical outcomes of the cylization, but to a little surprise RCM of both the substrates resulted in complex mixtures under any of the conditions attempted. Attributing this failure to the crowding around the reaction centers because of protecting groups, the attempted deprotection of **17** and **18** with DDQ resulted into exclusive allylic –OPMB removal to afford the second set of substrates **19** and **20**, respectively, for the RCM. After various conditions with **19** and **20** were explored, though unsuccessful with diene **19**, the RCM of substrate **20** was successful with Grubbs' second-generation catalyst in refluxing dichloromethane (36 h) and/or benzene (6 h) and resulted in the formation of compound **21** with exclusive *E*-configuration at the newly formed olefin in each case. The difference in the outcome of the RCM reaction with respect to reversal of stereochemistry on the one side of the diene (**19** and **20**) is particularly striking and nicely exemplifies the substrate specific nature of the reaction.[15]

With the hope that the RCM would click at some stage, compound **19** was processed further to prepare the proposed tosylate **22** and consequently the penultimate epoxide diene **23**, as the attempted RCM of **22** was a failure. Eventually, the RCM of **23** was successful with Grubbs' second-generation catalyst in refluxing dichloromethane, however, resulted in **24** with exclusive Z-configuration. The success of RCM of compound **23** containing an activated oxirane ring and two potential nucleophiles in the form of free –OH groups highlights the high functional group tolerance of Grubbs' catalyst.[16]

Although, the synthesis of the diastereomer **3** was narrowly missed due to the undesired stereochemical outcome of the RCM reaction in the very last step, we proceeded further for the synthesis of diastereomer **4** with the available *E*-configured lactone **21**. The synthesis of (3*S*,4*S*)-multiplolide A (**4**) was completed in three steps (Scheme 4) from **21**. The analytical and spectral data for **4** were found to be in excellent agreement with those for natural product, barring the deviation in the magnitude of specific rotation: $[\alpha]^{\text{synthetic}}_D$ +22.6 (*c* 0.3, $CHCl_3$) [lit.[2] $[\alpha]^{\text{lit.}}_D$ +6.7 (*c* 0.18, $CHCl_3$)].

In the context of the discrepancy in the magnitudes of the specific rotations, total synthesis of the other possible diastereomer **3** was thought even more important to establish the relative and absolute configuration of multiplolide A beyond any ambiguity. Having met the failure in our attempt to tune the RCM reaction for the synthesis of **3**, we now focused our attention to tune the position of leaving group starting from the compound **21** in our hands. As outlined in Scheme 5, by exchanging the positions of the leaving group and nucleophile, subsequent epoxide formation and acetonide deprotection afforded **3**.

Interestingly, compound **3** was found to exist as an equilibrating mixture of conformational isomers (3:1, at 25 °C) in solution. The major:minor ratio was observed to be temperature dependent to some extent. Maximum separation in the signals due to each isomers was observed when the ^1H NMR was recorded at 0 °C in $CDCl_3$. Whereas a substantial increment in the ratio of major isomer was noticed when the NMR was recorded at high temperatures in DMSO-d_6.When the NMR was recorded at 80 °C the peaks due to major and minor isomer merged into each other at the expense of the multiplicity of the peaks. From the comparison of the data from natural product and **4** with the $\mathbf{3}_{\text{major}}$ and $\mathbf{3}_{\text{minor}}$ it is evident that both the components represent the same constitution and configuration and presumably are conformational isomers. The fact that the natural product did not exist as the mixture of conformational isomers and no correlation of the data of any of the conformers of **3** with natural multiplolide A unequivocally designated **4** as the natural product and established the absolute stereochemistry of multiplolide A as 3*S*,4*S*,7*S*,8*R*,10*R*.

To conclude, the objective of establishing relative and absolute stereochemistry of multiplolide A has been accomplished by total synthesis of the possible diastereomers. The

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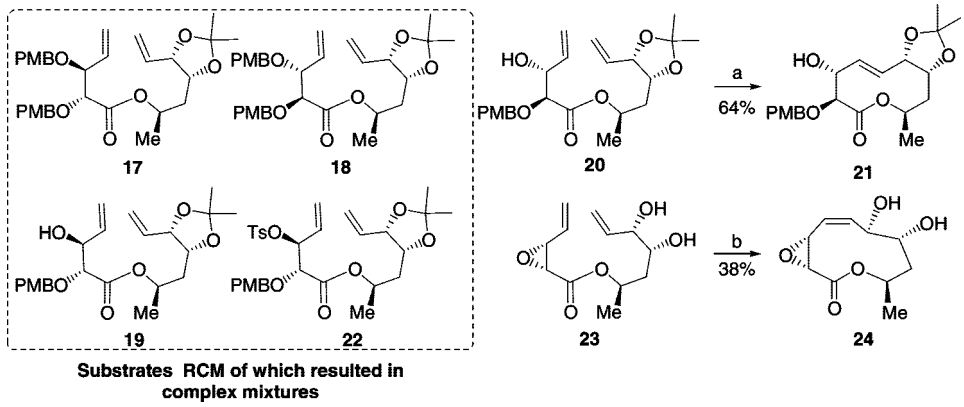
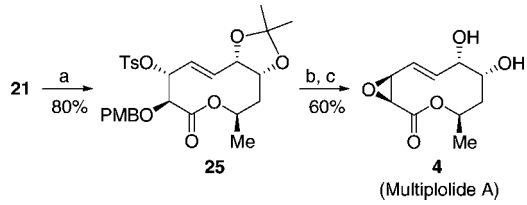
SCHEME 3. Summary of RCM Reactions Carried out on Various Dienes[a]



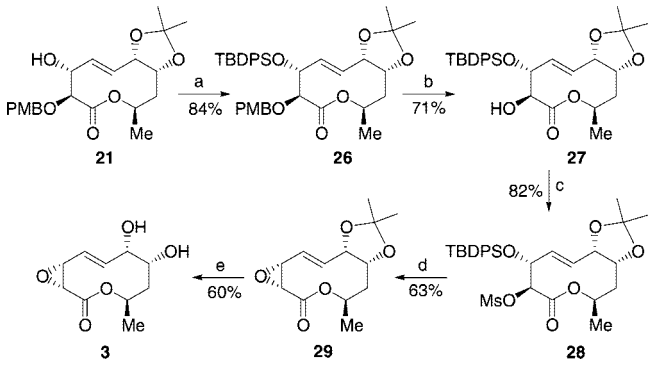
[a] Reagents and conditions: (a) Grubbs' second-generation catalyst, benzene, reflux, 6 h; (b) Grubbs' second-generation catalyst, CH_2Cl_2, reflux, 1 h.

SCHEME 4. Total Synthesis of Multiplolide A (4)[a]



[a] Reagents and conditions: (a) *p*-TsCl, *i*-Pr_2NEt, DMAP, CH_2Cl_2, rt, 20 h; (b) TFA, CH_2Cl_2, rt, 48 h; (c) NaH, THF; 0 °C, 1 h.

SCHEME 5. Total Synthesis of Diastereomer 3[a]



[a] Reagents and conditions: (a) TBDPS-Cl, Imidazole, CH_2Cl_2, reflux, 10 h; (b) DDQ, CH_2Cl_2−H_2O (18:1), rt, 3 h; (c) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C → rt, 2 h; (d) TBAF (1 M solution in THF), THF, 0 °C → rt, 8 h; (e) TFA, CH_2Cl_2, 0 °C → rt, 4 h.

summary of the results of RCM reactions of closely related substrates indicates the influence of conformation control on the outcome of the transformation. Further studies to understand this in details are in progress.

Experimental Section

Coupling of 6 and 7. To a solution of **6** (200 mg, 1.07 mmol), **7** (500 mg, 1.34 mmol), and PPh_3 (563 mg, 2.15 mmol) in THF (8 mL) at 0 °C was added DEAD (0.34 mL, 2.16 mmol). Stirring was continued at 0 °C for 1 h and then at rt for 2 h, at which time the solution was concentrated and the crude residue was purified on silica gel by eluting with ethyl acetate−light petroleum (1:9) to afford **17** (423 mg, 73%). $[\alpha]^{25}_D$ = +47.7 (*c* 1.4, $CHCl_3$). IR ($CHCl_3$): 2936, 1736, 1613, 1586, 1248, 1037 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.25 (d, *J* = 6.3 Hz, 3H), 1.31 (s, 3H), 1.47 (s, 3H), 1.53 (ddd, *J* = 5.3, 7.6, 14.0 Hz, 1H), 1.86 (ddd, *J* = 6.6, 8.7, 14.0 Hz, 1H), 3.79 (s, 3H), 3.80 (s, 3H), 3.93 (d, *J* = 4.8 Hz, 1H), 4.11 (dd, *J* = 4.8, 7.7 Hz, 1H), 4.13–4.23 (m, 1H), 4.33, 4.42, 4.54, 4.70 (4d, *J* = 11.6 Hz, 4H), 4.44 (dd, *J* = 5.3, 13.7 Hz, 1H), 5.01–5.17 (m, 1H), 5.20–5.35 (m, 4H), 5.65–5.96 (m, 2H), 6.82, 6.83, 7.19, 7.24 (4d, *J* = 8.8 Hz, 8H). ^{13}C NMR ($CDCl_3$, 50 MHz): 19.6 (q), 25.6 (q), 28.1 (q), 36.3 (t), 55.0 (q), 69.4 (d), 70.3 (t), 72.4 (t), 74.5 (d), 79.4 (d), 80.5 (d), 80.6 (d), 108.3 (s), 113.45 (d), 113.50 (d), 118.5 (t), 119.3 (t), 129.1 (d), 129.2 (s), 129.6 (d), 129.9 (s), 133.9 (d), 134.3 (d), 158.9 (s), 159.9 (s), 169.6 (s) ppm. ESI-MS *m/z*: 563 $[M + Na]^+$. Anal. Calcd for $C_{31}H_{40}O_8$: C, 68.89; H, 7.41. Found: C, 69.14; H, 7.67.

Coupling of 6 and 8. To a solution of **6** (200 mg, 1.07 mmol), **8** (500 mg, 1.34 mmol), and PPh_3 (563 mg, 2.15 mmol) in THF (8 mL) at 0 °C was added DEAD (0.34 mL, 2.16 mmol). Stirring was continued at 0 °C for 1 h and then at rt for the next 2 h, at which time it was concentrated and the crude residue was purified on silica gel by eluting with ethyl acetate-light petroleum (1:9) to afford **18** (467 mg, 80%). $[\alpha]^{25}_D$ = –38.9 (*c* 1, $CHCl_3$); IR ($CHCl_3$): 2934, 1736, 1612, 1513, 1464, 1381, 1249, 1173, 1037, 667 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.20 (d, *J* = 6.3 Hz, 3H), 1.32 (s, 3H), 1.47 (s, 3H), 1.54 (ddd, *J* = 4.9, 6.6, 14.0 Hz, 1H), 1.86 (ddd, *J* = 6.6, 9.1, 14.0 Hz, 1H), 3.77 (s, 3H), 3.78 (s, 3H), 3.92 (d, *J* = 4.7 Hz, 1H), 4.09 (br dd, *J* = 4.7, 7.9 Hz, 1H), 4.17 (ddd, *J* = 5.0, 6.0, 9.1 Hz, 1H), 4.31, 4.40, 4.54, 4.69 (4d, *J* = 11.7 Hz, 4H), 4.48 (br.dd, *J* = 6.3, 7.7 Hz, 1H), 5.10 (q, *J* = 6.5 Hz, 1H), 5.20–5.36 (m, 4H), 5.66–5.96 (m, 2H), 6.81, 6.83, 7.19, 7.24 (4d, *J* = 8.7 Hz, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz): 19.7 (q), 25.7 (q), 28.3 (q), 36.5 (t), 55.2 (q), 69.5 (d), 70.4 (t), 72.6 (t), 74.9 (d), 79.6 (d), 80.5 (d), 80.8 (d), 108.5 (s), 113.6 (d), 113.7 (d), 118.7 (t), 119.4 (t), 129.4 (d), 129.5 (s), 129.7 (d), 130.1 (s), 134.0 (d), 134.6 (d), 159.1 (s), 159.4 (s), 169.6 (s) ppm. ESI-MS *m/z*: 563 $(M + Na)^+$. Anal. Calcd for $C_{31}H_{40}O_8$: C, 68.89; H, 7.41. Found: C, 69.22; H, 7.54.

Selective Mono-PMB Deprotection of 17. To a solution of **17** (350 mg, 0.65 mmol) in CH_2Cl_2 (30 mL) at 0 °C were added aqueous NaH_2PO_4/Na_2HPO_4 (pH 7) buffer (12 mL) and DDQ (700 mg, 3.08 mmol). The reaction was allowed to warm to rt. After 4 h at rt, the reaction mixture was filtered through a Celite pad, and layers were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layer was dried over sodium sulfate and concentrated. The residue was purified on silica gel by eluting with ethyl acetate−light petroleum (1:6) to afford **19** (104 mg, 56%, on the basis of recovered starting material 110 mg). $[\alpha]^{25}_D$ = +37.7 (*c* 0.9, $CHCl_3$). IR ($CHCl_3$): 3565, 3464, 2988, 1741, 1613, 1586, 1250, 1100, 1038 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.29 (d, *J* = 6.3 Hz, 3H), 1.34 (s, 3H), 1.48 (s, 3H), 1.57–1.62 (m, 1H), 1.86 (ddd, *J* = 8.0, 9.0, 14.6 Hz, 1H), 2.85 (br. d, *J* = 7.3 Hz, 1H), 3.80 (s, 3H), 3.88 (d, *J* = 4.5 Hz, 1H), 4.22 (ddd, *J* = 4.5, 6.0, 9.3 Hz, 1H), 4.36–4.40 (br. m, 1H), 4.43, 4.72 (2d, *J* = 11.4 Hz, 2H), 4.51 (dd, *J* = 6.8, 7.3 Hz, 1H), 5.10–5.18 (m, 1H), 5.20–5.37 (m, 4H), 5.76 (ddd, *J* = 7.8, 10.3, 17.1 Hz, 1H), 5.87 (ddd, *J* = 5.8,

10.6, 17.1 Hz, 1H), 6.86, 7.25 (2d, J = 8.6 Hz, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): 20.2 (q), 25.5 (q), 28.0 (q), 36.6 (t), 55.1 (q), 70.1 (d), 72.3 (t), 73.2 (d), 75.3 (d), 79.6 (d), 80.4 (d), 108.6 (s), 113.7 (d), 116.9 (t), 118.7 (t), 129.0 (s), 129.8 (d), 134.0 (d), 136.2 (d), 159.5 (s), 169.8 (s) ppm. ESI-MS m/z: 443 $[M + Na]^+$. Anal. Calcd for $C_{23}H_{32}O_7$: C, 65.71; H, 7.62. Found: C, 65.48; H, 7.50.

Selective Mono-PMB Deprotection of 18. To a solution of **18** (400 mg, 0.74 mmol) in CH_2Cl_2 (35 mL) at 0 °C were added aqueous NaH_2PO_4/Na_2HPO_4 (pH 7) buffer (15 mL) and DDQ (800 mg, 3.52 mmol). The reaction was allowed to warm to room temperature. After 4 h at rt, it was filtered through Celite, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layer was dried over sodium sulfate and concentrated. The residue was purified on silica gel by eluting with ethyl acetate−light petroleum (1:6) to afford unreacted **18** (94 mg) and **20** (162 mg, 68%). $[\alpha]^{25}_D$ = +4.3 (c 1.2, $CHCl_3$). IR ($CHCl_3$): 3436, 2925, 2854, 1744, 1615, 1518, 1459, 1379, 1250, 1171, 1097, 1037 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.24 (s, 3H), 1.29 (d, J = 6.3 Hz, 3H), 1.34 (s, 3H), 1.49 (s, 3H), 1.60 (ddd, J = 4.6, 5.8, 14.2 Hz, 1H), 1.89 (ddd, J = 7.2, 8.9, 14.2 Hz, 1H), 2.70 (s, 1H), 3.81 (s, 3H), 3.88 (d, J = 4.8 Hz, 1H), 4.23 (ddd, J = 4.6, 6.0, 9.0 Hz, 1H), 4.41 (br. d, J = 11.2 Hz, 1H), 4.52 (t, J = 7.0 Hz, 1H), 4.50 (br. dd, J = 6.2, 7.6 Hz, 1H), 4.70 (d, J = 11.2 Hz, 1H), 5.14–5.40 (m, 5H), 5.70–5.95 (m, 2H), 6.88, 7.27 (2d, J = 8.7 Hz, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): 20.0 (q), 25.6 (q), 28.2 (q), 36.6 (t), 55.2 (q), 70.0 (d), 72.5 (t), 73.4 (d), 75.1 (d), 79.7 (d), 80.7 (d), 108.6 (s), 113.9 (d), 117.2 (t), 118.7 (t), 128.9 (s), 129.9 (d), 134.0 (d), 136.0 (d), 159.6 (s), 169.9 (s) ppm. ESI-MS m/z: 443 $(M + Na)^+$. Anal. Calcd for $C_{23}H_{32}O_7$: C, 65.71; H, 7.62. Found: C, 65.95; H, 7.80.

RCM Reaction of 20. A degassed solution of **20** (124 mg, 0.3 mmol) and Grubbs' second-generation catalyst (7 mg, 8 μmol) in dry benzene (150 mL) was heated under reflux under argon for 6 h and then concentrated. The residue was purified on silica gel by eluting with ethyl acetate−light petroleum (1:4) to furnish compound **21** (74 mg, 64%). $[\alpha]^{25}_D$ = +36.4 (c 1.1, $CHCl_3$). IR ($CHCl_3$): 3448, 2983, 2934, 1719, 1607, 1514, 1458, 1381, 1253, 1170, 1103 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.34 (s, 3H), 1.39 (d, J = 6.8 Hz, 3H), 1.42 (s, 3H), 1.48–1.50 (m, 1H), 2.31 (br. s, 1H), 2.52 (ddd, J = 4.3, 9.8, 15.8 Hz, 1H), 3.79 (s, 3H), 4.08 (d, J = 3.9 Hz, 1H), 4.32 (d, J = 11.2 Hz, 1H), 4.42 (dd, J = 6.4, 9.8 Hz, 1H), 4.51 (d, J = 11.2 Hz, 1H), 4.48–4.52 (m, 1H), 4.78 (dd, J = 6.6, 8.1 Hz, 1H), 5.05–5.19 (m, 1H), 5.71 (ddd, J = 1.2, 8.0, 16.5 Hz, 1H), 5.97 (dd, J = 3.0, 16.5 Hz, 1H), 6.85, 7.21 (2d, J = 8.7 Hz, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): 18.2 (q), 25.2 (q), 28.0 (q), 35.2 (t), 55.2 (q), 69.3 (d), 70.0 (d), 72.4 (t), 75.3 (d), 78.5 (d), 83.2 (d), 108.5 (s), 114.0 (d), 126.1 (d), 128.8 (s), 129.8 (d), 133.3 (d), 159.7 (s), 170.7 (s) ppm. ESI-MS m/z: 415 $(M + Na)^+$. Anal. Calcd for $C_{21}H_{28}O_7$: C, 64.29; H, 7.14. Found: C, 64.64; H, 7.07.

RCM of Vinyl Epoxide 23. To a thoroughly degassed solution of **23** (12 mg, 49.59 μmol) in anhydrous CH_2Cl_2 (15 mL) was added Grubbs' second-generation catalyst (3 mg, 3.42 μmol) under argon atmosphere, and the resulting solution was heated to reflux under argon for 1 h. Volatiles were removed under reduced pressure, and the residue was purified on silica gel by eluting with ethyl acetate−light petroleum (2:1) to furnish **24** (4 mg, 38%). $[\alpha]^{25}_D$ = −13.5 (c 0.15, $CHCl_3$). IR ($CHCl_3$): 3426, 1755, 1057, 1029 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.39 (d, J = 6.9 Hz, 3H), 1.62 (dt, J = 2.3, 15.2 Hz, 1H), 2.15 (ddd, J = 4.6, 11.9, 15.2 Hz, 1H), 3.79 (d, J = 4.6 Hz, 1H), 3.82 (d, J = 4.6 Hz, 1H), 4.22 (ddd, J = 2.8, 3.2, 11.9 Hz, 1H), 4.62–4.68 (m, 1H), 5.15–5.21 (m, 1H), 5.84–5.87 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): 17.7 (q), 35.8 (t), 51.6 (d), 54.9 (d), 68.8 (d), 69.2 (d), 70.6 (d), 126.2 (d), 131.3 (d), 166.5 (s) ppm. ESI-MS m/z: 237 $[M + Na]^+$. Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.54. Found: C, 55.85; H, 6.71.

Tosylation of 21. A solution of **21** (71 mg, 0.18 mmol), diisopropylethylamine (100 μL, 0.58 mmol), p-toluenesulfonyl chloride (69 mg, 0.36 mmol), and DMAP (27 mg, 0.22 mmol) in dry CH_2Cl_2 (5 mL) was stirred at rt for 20 h and concentrated. The residue was purified on silica gel by eluting with ethyl acetate−light petroleum (1:4) to afford **25** (79 mg, 81%). $[\alpha]^{25}_D$ = +16.2 (c 0.6, $CHCl_3$). IR ($CHCl_3$): 2923, 1733, 1613, 1459, 1374, 1174, 1112, 1070 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.32 (s, 3H), 1.35 (d, J = 7.0 Hz, 3H), 1.40 (s, 3H), 1.45–1.53 (m, 1H), 2.36–2.41 (m, 1H), 2.44 (s, 3H), 3.81 (s, 3H), 4.20 (d, J = 3.5 Hz, 1H), 4.31 (d, J = 11.0 Hz, 1H), 4.42 (br. dd, J = 6.7, 9.5 Hz, 1H), 4.44 (d, J = 11.0 Hz, 1H), 4.66 (dd, J = 6.7, 7.7 Hz, 1H), 5.10 (dd, J = 3.0, 3.5 Hz, 1H), 5.13–5.18 (m, 1H), 5.71 (dd, J = 7.8, 16.3 Hz, 1H), 5.80 (dd, J = 3.0, 16.3 Hz, 1H), 6.85, 7.16 (2d, J = 8.5 Hz, 4H), 7.29, 7.77 (2d, J = 8.2 Hz, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): 18.2 (q), 21.7 (q), 25.2 (q), 27.9 (q), 35.2 (t), 55.2 (q), 68.6 (d), 72.5 (t), 75.3 (d), 75.4 (d), 78.3 (d), 81.5 (d), 108.6 (s), 114.0 (d), 127.1 (d), 128.0 (d), 129.4 (s), 129.5 (d), 129.8 (d), 129.9 (d), 133.4 (s), 144.9 (s), 159.7 (s), 167.6 (s) ppm. ESI-MS m/z: 569 $(M + Na)^+$. Anal. Calcd for $C_{28}H_{34}O_9S$: C, 61.54; H, 6.23. Found: C, 61.77; H, 6.41.

Synthesis of Multiplolide A (4). A solution of **25** (47 mg, 86.1 μmol) and trifluroacetic acid (0.05 mL) in CH_2Cl_2 (10 mL) was stirred at rt for 48 h. Diisopropylethylamine (0.5 mL) was introduced and concentrated. The crude product (23 mg, 59.6 μmol) was dissolved in THF (4 mL) and cooled to 0 °C, and then sodium hydride (60% dispersion in mineral oil, 25 mg, 0.62 mmol) was added. After 1 h, the reaction mixture was diluted with ice–water and extracted with ethyl acetate. The combined organic extract was dried over sodium sulfate and concentrated. The residue was purified on silica gel by eluting with ethyl acetate−light petroleum (1:1) to afford **4** (11 mg, 60%). $[\alpha]^{25}_D$ = +22.6 (c 0.3, $CHCl_3$). IR ($CHCl_3$): 3430, 1716, 1280, 1217, 1060 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.28 (dd, J = 4.0, 16.0 Hz, 1H), 1.36 (d, J = 6.7 Hz, 3H), 2.24 (ddd, J = 3.4, 8.5, 16.0 Hz, 1H), 2.24 (br.s, overlapped, 1H), 3.65 (d, J = 4.6 Hz, 1H), 3.79–3.81 (m, 1H), 4.05 (dd, J = 3.0, 8.4 Hz, 1H), 4.53–4.57 (m, 1H), 5.27–5.34 (m, 1H), 5.76 (ddd, J = 1.4, 2.1, 15.6 Hz, 1H), 5.93 (ddd, J = 1.1, 2.5, 15.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): 17.8 (q), 35.4 (t), 54.5 (d), 55.1 (d), 67.9 (d), 68.3 (d), 72.4 (d), 117.7 (d), 133.3 (d), 167.2 (s) ppm. ESI-MS m/z: 254 $(M + H + K)^+$. Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.54. Found: C, 55.83; H, 6.68.

TBDPS Protection of 21. To a solution of **21** (150 mg, 0.38 mmol) and imidazole (39 mg, 0.57 mmol) in dry CH_2Cl_2 (10 mL) was added *tert*-butyldiphenylchlorosilane (126 μL, 0.49 mmol), and the reaction mixture was refluxed for 10 h and then concentrated. The residue was purified on silica gel column by eluting with ethyl acetate−light petroleum (1:9) to afford **26** (203 mg, 84%). $[\alpha]^{25}_D$ = +2.9 (c 3.3, $CHCl_3$). IR ($CHCl_3$): 3018, 2929, 2856, 2742, 1725, 1701, 1685, 1601, 1578, 1501 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.11 (s, 9H), 1.34 (d, J = 6.9 Hz, 3H), 1.39 (s, 3H), 1.47 (s, 3H), 1.44–1.52 (m, overlapped, 1H), 2.50 (ddd, J = 3.9, 9.9, 15.2 Hz, 1H), 3.66 (d, J = 3.8 Hz, 1H), 3.78 (s, 3H), 3.93, 4.11 (2d, J = 11.1 Hz, 2H), 4.44– 4.51 (m, 2H), 4.83 (dd, J = 6.5, 7.4 Hz, 1H), 5.13–5.21 (m, 1H), 5.93 (dd, J = 2.4, 16.0 Hz, 1H), 6.06 (dd, J = 7.0, 16.0 Hz, 1H), 6.76, 6.96 (2d, J = 8.6 Hz, 4H), 7.32–7.44 (m, 6H), 7.57–7.61 (m, 2H), 7.76–7.81 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.2 (q), 19.3 (s), 25.3 (q), 26.9 (q), 28.0 (q), 35.3 (t), 55.2 (q), 67.8 (d), 71.1 (d), 72.1 (t), 75.5 (d), 78.9 (d), 83.6 (d), 108.3 (s), 113.7 (d), 127.1 (d), 127.68 (d), 127.73 (d), 129.0 (d), 129.6 (d), 129.8 (d), 129.9 (s), 132.9 (s), 133.3 (d), 133.6 (d), 134.8 (d), 135.7 (d), 136.1 (d), 159.4 (s), 168.7 (s) ppm. ESI-MS m/z: 653 $[M + Na]^+$. Anal. Calcd for $C_{37}H_{46}O_7Si$: C, 70.48; H, 7.30. Found: C, 70.73; H, 7.17.

PMB Deprotection of 26. At rt, a solution of **26** (190 mg, 0.30 mmol) and DDQ (170 mg, 0.75 mmol) in CH_2Cl_2−water (6 mL, 18:1) was stirred for 3 h. To this was added aqueous sodium bicarbonate solution, and the contents were partitioned between water and DCM. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layer was dried over sodium sulfate and concentrated. The residue was purified on silica gel column by eluting with ethyl acetate−light petroleum (1:6) to give **27** (110

mg, 71%) as a colorless oil. $[\alpha]^{25}_D = +1.43$ (*c* 2.6, $CHCl_3$); IR ($CHCl_3$): 3448, 3072, 3015, 2984, 2931, 2858, 1735, 1680, 1599, 1578, 1511 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.12 (s, 9H), 1.35 (d, $J = 6.9$ Hz, 3H), 1.39 (s, 3H), 1.48 (s, 3H), 1.57 (br. dd, $J = 5.2$, 7.1 2H), 2.56 (ddd, $J = 4.2$, 9.9, 15.8 Hz, 1H), 3.97 (t, $J = 4.8$ Hz, 1H), 4.37–4.45 (m, 2H), 4.80 (dd, $J = 6.4$, 8.1 Hz, 1H), 5.12–5.26 (m, 1H), 5.95 (dd, $J = 3.0$, 16.1 Hz, 1H), 6.14 (ddd, $J = 1.0$, 8.1, 16.1 Hz), 7.37–7.43 (m, 6H), 7.60–7.65 (m, 2H), 7.79–7.84 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): 18.2 (q), 19.3 (s), 25.3 (q), 26.9 (q), 28.0 (q), 35.2 (t), 68.7 (d), 71.8 (d), 75.4 (d), 76.9 (d), 78.8 (d), 108.5 (s), 127.7 (d), 127.8 (d), 128.8 (d), 129.8 (d), 130.0 (d), 132.0 (d), 132.8 (s), 133.4 (s), 135.7 (d), 136.0 (d), 167.7 (s) ppm. ESI-MS *m/z*: 533 $[M + Na]^+$. Anal. Calcd for $C_{29}H_{38}O_6Si$: C, 68.23; H, 7.45. Found: C, 68.38; H,7.67.

Methanesulfonylation of 27. At 0 °C, a solution of **27** (100 mg, 0.19 mmol), triethylamine (66 μL, 0.475 mmol), and DMAP (catalytic) in CH_2Cl_2 was treated with methanesulfonyl chloride (34 μL, 0.437 mmol), and the reaction mixture was warmed to rt and stirred for 2 h. The reaction was portioned between water and CH_2Cl_2, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was dried over sodium sulfate and concentrated. Purification of the resulting crude product by column chromatography (1:6 ethyl acetate− light petroleum) afforded **28** (95 mg, 82%) as a sticky white solid. $[\alpha]^{25}_D = +2$ (*c* 1.4, $CHCl_3$). IR ($CHCl_3$): 3018, 2986, 2932, 2859, 1741, 1589 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.14 (s, 9H), 1.35 (d, $J = 6.8$ Hz, 3H), 1.40 (s, 3H), 1.49 (s, 3H), 1.53 (br. m, 1H), 2.49–2.56 (m, 1H), 2.51 (s, 3H), 4.37 (d, $J = 3.8$ Hz, 1H), 4.47 (dd, $J = 6.5$, 9.5 Hz, 1H), 4.55 (dt, $J = 1.3$, 3.7 Hz, 1H), 4.84 (dd, $J = 7.0$, 8.0 Hz, 1H), 5.20–5.23 (m, 1H), 5.88 (dd, $J = 3.0$, 16.1 Hz, 1H), 6.16 (ddd, $J = 1.0$, 8.5, 16.1 Hz, 1H), 7.38–7.48 (m, 6H), 7.60–7.62 (m, 2H), 7.83–7.85 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): 17.9 (q), 19.3 (s), 25.3 (q), 26.8 (q), 27.9 (q), 35.2 (t), 37.4 (q), 69.2 (d), 70.1 (d), 75.4 (d), 78.6 (d), 80.2 (d), 108.6 (s), 127.9 (d), 128.1 (d), 129.4 (d), 130.1 (d), 130.4 (d), 130.8 (d), 132.1 (s), 133.0 (s), 135.7 (d), 136.1 (d), 164.5 (s) ppm. ESI-MS *m/z*: 611 $[M + Na]^+$. Anal. Calcd for $C_{30}H_{40}O_8SSi$: C, 61.22; H, 6.80. Found: C, 61.48; H, 6.73.

Preparation of 29. To a solution of **28** (90 mg, 0.15 mmol) in dry THF (2 mL) was added a 1 M solution of TBAF in THF (0.36 mL, 0.36 mmol) at 0 °C, and the contents were stirred at rt for 8 h. To this was added saturated ammonium chloride, the aqueous layer was extracted with ethyl acetate, and the combined organic layer was dried with sodium sulfate and concentrated. The residue was purified on silica gel column by eluting with ethyl acetate−light petroleum (1: 9) to afford **29** (24 mg, 63%) as colorless oil. $[\alpha]^{25}_D = +3.6$ (*c* 1.7, $CHCl_3$); IR ($CHCl_3$): 2986, 2927, 2855, 1737, 1456, 1371, 1221, 1167, 1080 cm^{-1}. ^1H NMR (acetone-d_6, 400 MHz): δ 1.31 (s, 3H), 1.40 (d, $J = 6.9$ Hz, 3H), 1.40 (s, 3H), 1.65–1.71 (m, 1H), 2.25 (ddd, $J = 1.7$, 9.8, 15.9 Hz, 1H), 3.75 (ddd, $J = 0.7$, 2.2, 3.9 Hz, 1H), 3.78 (d, $J = 4.1$ Hz, 1H), 4.39 (dd, $J = 6.2$, 9.6 Hz, 1H), 4.73 (dd, $J = 7.1$, 8.3 Hz, 1H), 4.93–4.99 (m, 1H), 5.58 (dd, $J = 9.0$, 16.2 Hz, 1H), 5.95 (d, $J = 16.2$ Hz, 1H). ^{13}C NMR (acetone-d_6, 100 MHz): 24.6 (q), 27.4 (q), 29.4 (t), 52.7 (d), 57.3 (d), 69.8 (d), 75.4 (d), 77.9 (d), 107.9 (s), 127.4 (d), 128.0 (d), 166.3 (s) ppm. ESI-MS *m/z*: 277 $[M + Na]^+$. Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.42; H, 7.09. Found: C, 61.63; H, 7.26.

Synthesis of Multiplolide A Diastereomer 3. At 0 °C, a solution of **29** (20 mg, 78.7 μmol) in dry CH_2Cl_2 (1 mL) was treated with TFA (10 μL) and stirred for 4 h at rt. The reaction mixture was concentrated under reduced pressure, and the resulting residue was purified on silica gel column by eluting with ethyl acetate− light petroleum (1: 1) to furnish **3** (10 mg, 60%). $[\alpha]^{25}_D = -11.8$ (*c* 0.5, $CHCl_3$). IR ($CHCl_3$): 3401, 2926, 2854, 1731, 1648, 1460, 1369, 1221, 1103, 1065 cm^{-1}. ESI-MS *m/z*: 237 $[M + Na]^+$, 254 $[M + H + K]^+$. Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.54. Found: C, 55.79; H, 6.27.

Spectral Data of Major Conformer. ^1H NMR ($CDCl_3$, 400 MHz, 25 °C): δ 1.38 (d, $J = 6.7$ Hz, 3H), 1.53 (dd, $J = 6.3$, 16.1 Hz, 1H), 2.28 (ddd, $J = 2.3$, 7.7, 16.1 Hz, 1H), 3.68–3.73 (m, 2H), 3.90 (dd, $J = 3.1$, 7.4 Hz, 1H), 4.19 (dd, $J = 3.1$, 8.3 Hz, 1H), 5.18–5.25 (m, 1H), 5.64 (dd, $J = 8.3$, 16.1 Hz, 1H), 5.80 (dd, $J = 1.8$, 16.1 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): 19.7 (q), 35.7 (t), 53.0 (d), 58.0 (d), 69.7 (d), 72.1 (d), 75.6 (d), 125.9 (d), 129.3 (d), 166.7 (s) ppm.

Spectral Data of Minor Conformer. ^1H NMR ($CDCl_3$, 400 MHz, 0 °C): δ 1.37–1.42 (m, 1H, merged with methyl peaks), 1.41 (d, $J = 6.9$ Hz, 3H), 2.51 (ddd, $J = 2.3$, 7.8, 16.1 Hz, 1H), 3.25 (br. s, 2H), 3.79 (d, $J = 4.5$ Hz, 1H), 3.93–3.95 (m, 1H) 3.98 (dd, $J = 2.9$, 8.2 Hz, 1H), 4.49–4.51 (m, 1H), 5.18–5.25 (m, 1H, merged with major conformer peak), 5.71 (dt, $J = 2.0$, 16.8 Hz, 1H), 5.80–5.84 (^1H, merged with the major conformer peak). ^{13}C NMR ($CDCl_3$, 125 MHz): 17.9 (q), 34.9 (t), 53.03 (d), 55.2 (d), 68.9 (d), 70.3 (d), 72.5 (d), 121.3 (d), 137.4 (d), 167.6 (s) ppm.

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Supporting Information Available: Experimental details, spectral and analytical data of all new compounds, ^1H, ^{13}C, and DEPT spectra for compounds **6–8**, **21**, **3**, and **4**, and 2D NMR of **21** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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