Unusual Regioselective Intramolecular Diels−Alder Reaction Forming Tricyclo[4.3.1.0^{3,7}]decane System

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The intramoleculae Diels−Alder reaction of cyclohexenone having an unsaturated ester side chain afforded tricyclo[4.3.1.0^{3,7}]decanone in both a regio- and stereoselective manner under TMSCl−NEt_3−$ZnBr_2$ conditions. Unexpectedly, the regiochemical control was against the conventional orbital requirement.

Intramolecular Diels−Alder (IMDA) reactions have been widely utilized as one of the most powerful tools in organic synthesis.[1] The reaction generates two new carbon−carbon bonds to produce a polycyclic compound from a substrate having two separate functional groups, diene and dienophile. The question of regiocontrol in the IMDA reaction is of great interest. The two alternatives lead to either fused or bridged products (Figure 1). The selectivity would be generally governed by the steric and/or orbital requirements. The orbital effect can be expected by considering the atomic coefficients on the basis of frontier molecular orbital (FMO) theory.[2] For example, the Diels−Alder reaction of a 2-siloxydiene with an α,β-unsaturated ester furnishes only the 4-substituted cyclohexanone skeleton (polarized Diels−Alder reaction[3]).

On the other hand, we have developed an intramolecular double Michael (IDM) reaction[4−6] to construct polycyclic systems. Namely, the reaction of a substrate possessing two α,β-unsaturated carbonyl moieties produces a 4-substituted cyclohexanone ring. The regiochemical mode of the annulation in the IDM reaction can be predicted with ease by the sequence of Michael additions and is always consistent with that of the polarized Diels−Alder reaction.[7] For instance, cyclopentenone **1** possessing an α,β-ester side chain afforded tricyclo[6.3.0.0^{3,9}]decanone **2** under IDM conditions (Figure 2).[5e]

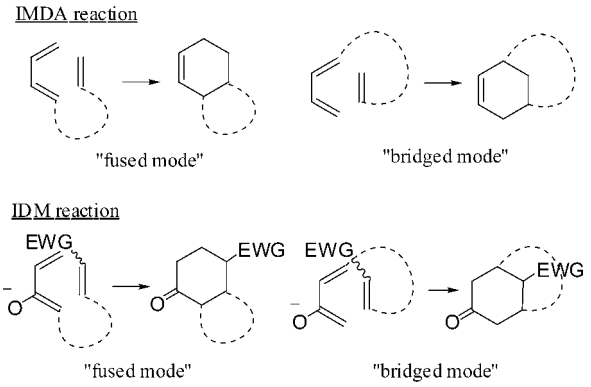

Figure 1. Regiochemical modes in IMDA and IDM reactions.

Figure 2. IDM reaction of cyclopentenone **1**.

To further investigate the IDM reaction, we planned to synthesize a twistane derivative, tricyclo[4.4.0.0^{3,8}]-decanone **4**, from cyclohexenone **3** (Figure 3). During the course of the investigation, we observed an unexpected regiochemical outcome in the reaction of **3**. We here report the regioselective formation of tricyclo[4.3.1.0^{3,7}]-decanone by means of an intramolecular Diels−Alder reaction against the general frontier orbital requirement.

The substrate **3** was prepared as described in Scheme 1. After the oxidation of alcohol **5**[8] with SO_3−pyridine complex[9] to the corresponding aldehyde, Wittig olefina-

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(2) (a) Fukui, K. *Acc. Chem. Res.* **1971**, *4*, 57−64. (b) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976.

(3) Kahn, S. D.; Pau, C. F.; Overman, L. E.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7381−7396.

(4) For a review: see, Ihara, M.; Fukumoto, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1010−1022.

(5) For recent examples: see: (a) Ihara, M.; Makita, K.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1994**, *59*, 6008−6013. (b) Ihara, M.; Makita, K.; Fujiwara, Y.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1996**, *61*, 6416−6421. (c) Ihara, M.; Makita, K.; Takasu, K. *J. Org. Chem.* **1999**, *64*, 1259−1264. (d) Suzuki, M.; Ihara, M. *Heterocycles* **2000**, *52*, 1083−1085. (e) Takasu, K.; Mizutani, S.; Noguchi, M.; Makita, K.; Ihara, M. *J. Org. Chem.* **2000**, *65*, 4112−4119. (f) Kuwahara, S.; Hamade, S.; Leal, W. S.; Ishikawa, J.; Kodama, O. *Tetrahedron* **2000**, *56*, 8111−8117.

(6) For recent efforts of the intermolecular version see: (a) Gutke, H. J.; Oesterreich, K.; Spitzner, D.; Braun, N. A. *Tetrahedron* **2001**, *57*, 997−1003. (b) Giardini, A.; Lesma, G.; Passarella, D.; Perez, M.; Silvani, A. *Synlett* **2001**, 132−134. (c) Hagiwara, H.; Sakai, H.; Kirita, M.; Hoshi, T.; Suzuki, T.; Ando, M. *Tetrahedron* **2000**, *56*, 1445−1449. (d) Tokuzaki, K.; Kanemitu, Y.; Yoshimitsu, T.; Nagaoka, H. *Tetrahedron Lett.* **2000**, *41*, 5923−5926.

(7) Although it is sometimes difficult to distinguish the reaction mechanisms between a double Michael reaction and the polarized Diels−Alder reaction, many results support a stepwise mechanism.[5a]

(8) Leyendecker, F.; Mandville, G.; Conia, J.-M. *Bull. Soc. Chim. Fr.* **1970**, 556−562.

(9) Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.

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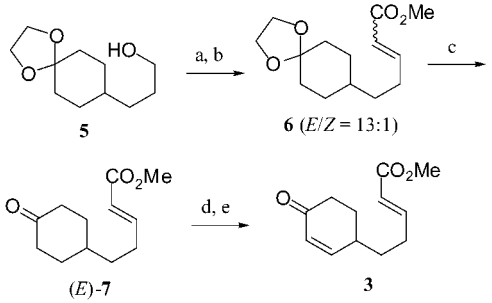
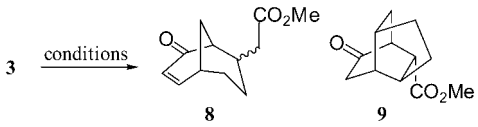
Figure 3. IDM reaction of 4-substituted cyclohexenone **3**.

Scheme 1[a]



[a] Legend: (a) SO_3−pyridine, DMSO, NEt_3; (b) $Ph_3PCH{=}CO_2Me$, CH_3CN (>99% for two steps); (c) 10% $HClO_4$ (89%); (d) NEt_3, TMSOTf, CH_2Cl_2, −78 °C; (e) $Pd(OAc)_2$, CH_3CN (91% for two steps).

Table 1. Reaction of 3 under Representative IDM Conditions



run	conditions	yield of **8** (%)	yield of **9** (%)
1	LHMDS, −78 °C to room temp	18[a]	0
2	TBDMSO Tf, NEt_3, room temp	7[a]	0
3	TMSI, HMDS, room temp	0	0
4	TMSCl, NEt_3, $ZnBr_2$, 180 °C	0	62

[a] 1.4:1 diastereomeric mixture.

tion of the resulting aldehyde with $Ph_3P{=}CHCO_2Me$ mainly afforded the (*E*)-enoate **6** along with its *Z* isomer in quantitative overall yield. Deketalization of a stereoisomeric mixture of **6** furnished ketone **7**, whose *E*/*Z* isomers could be easily separated by column chromatography on silica gel. The treatment of (*E*)-**7** with TMSOTf in the presence of NEt_3 at −78 °C, followed by the Pd(II)-promoted oxidation,[10] produced enone **3** in 91% overall yield.

The results of the reaction of **3** under several representative IDM conditions, which have been reported in our previous studies,[5] are summarized in Table 1. The reaction of **3** with lithium hexamethyldisilazide (LHMDS) at −78 °C to ambient temperature in THF gave bicyclo[3.3.1]nonenone **8** as an inseparable diastereomeric mixture (1.4:1) in 18% yield. The rest of **3** was consumed in the side reactions only to give complex polar compounds (run 1). The employment of **3** with NEt_3 and *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) resulted in the low production of **8** (7% yield) with the same diastereomeric ratio (run 2). The formation of **8** was caused from mono Michael addition, but no double Michael adduct **4** was observed under the both conditions. The reaction of **3** with trimethylsilyl iodide (TMSI)−

(10) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011−1013.

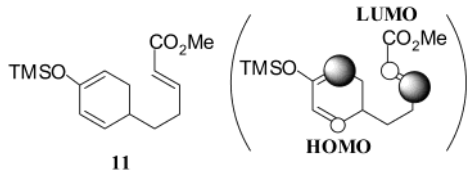
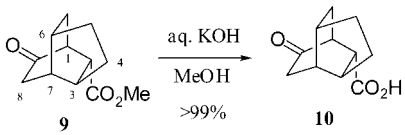


Figure 4. Reaction intermediate **11** and its orbital coefficients.

Scheme 2



hexamethyldisilazane (HMDS) coreagents gave neither **4** nor **8** (run 3). Upon treatment of **3** with trimethylsilyl chloride (TMSCl), NEt_3, and $ZnBr_2$ in toluene in a sealed tube at 180 °C for 20 h, tricyclic **9** was obtained in 62% yield as the sole diastereomer (run 4). The relative configuration of **9** was determined by X-ray analysis after the transformation into acid **10** (Scheme 2). The crystallographic structure of **10**, whose single crystals (colorless prisms) were prepared by the slow recrystallization from $^iPr_2O$, revealed that the adduct **9** has a isotwistane, tricyclo[4.3.1.$0^{3,7}$]decane, skeleton.

The tricyclodecanone **9** was produced from the reaction proceeding through the IMDA pathway in the fused mode. It is noteworthy that the regiochemical relationship resulted in the reverse of that obtained in the general orbital controlled reaction.[11] To best of our knowledge, this is the first time that the opposite regioselectivity is observed under TMSCl−NEt_3−ZnX_2 conditions, although the conditions are one of the representative IDM circumstances. The reactive intermediate should be, no doubt, concluded in 2-siloxydiene **11**. This result indicated that the intramolecular steric effect would dominate the frontier orbital demand in the transition state (Figure 4). Consequently, the fused annulation of **11** proceeded rather than the bridged annulation[12] to furnish tricyclo[4.3.1.$0^{3,7}$]decanone **9**. It should also be noted that IMDA reaction of **11** occurred via the endo transition state.

In summary, an unexpected regioselective intramolecular Diels−Alder reaction against the conventional orbital requirement was observed. The reaction of 4-substituted cyclohexenone **3** afforded tricyclo[4.3.1.$0^{3,7}$]-decanone **9** in both a regio- and stereoselective manner under TMSCl−NEt_3−$ZnBr_2$ conditions. We are now planning that this methodology will be utilized for the total synthesis of pupukeanones.[13]

Experimental Section

General Procedure. All reactions were carried out under a positive atmosphere of Ar unless otherwise indicated. Anhydrous THF, Et_2O, and CH_2Cl_2 were purchased from the

(11) To best of our knowledge, one example was reported for the reverse regiochemical outcome in the Diels−Alder reaction of 2-siloxydiene with an α,β-unsaturated ester: Kraus, G. A.; Liras, S. *Tetrahedron Lett.* **1989**, *30*, 1907−1908.

(12) For examples of an IMDA reaction with a bridged mode, see: (a) Snider, B. B.; Duncia, J. V. *J. Org. Chem.* **1980**, *45*, 3461−3464. (b) Greuter, H.; Schmid, H.; Fráter, G. *Helv. Chim. Acta* **1977**, *60*, 1701−1729. (c) Corey, E. J.; Petrzilka, M. *Tetrahedron Lett.* **1975**, 2537−2540.

Kanto Chemical Co., Inc. Toluene, $ClCH_2CH_2Cl$, and NEt_3 were distilled from CaH_2. HMDS and DMSO were distilled from CaH_2 under reduced pressure. Unless otherwise described, the materials were obtained from commercial suppliers and used without further purification. Organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure using an evaporator. The ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, and were reported in ppm downfield from TMS (δ 0) for the ^1H NMR and relative to the central $CDCl_3$ resonance (δ 77.00) for the ^{13}C NMR.

8-[(3*E* and 3*Z*)-4-(Methoxycarbonyl)-3-butenyl]-1,4-dioxaspiro[4.5]decane (6). To a solution of alcohol **5**[8] (614 mg, 3.06 mmol) in DMSO (20 mL) was added NEt_3 (4.27 mL, 30.6 mmol), and the mixture was stirred at ambient temperature for 15 min. To the resulting mixture was added SO_3−pyridine complex (1.46 g, 9.19 mmol), and the mixture was stirred for 1.5 h at the same temperature. The mixture was diluted with saturated $NaHCO_3$, extracted with Et_2O, and washed with brine. The removal of the solvent afforded the corresponding crude aldehyde, which was used in the next reaction without further purification. To a solution of the above aldehyde in CH_3CN (20 mL) was added methyl (triphenylphosphoranylidene)acetate (2.05 g, 6.13 mmol), and the mixture was stirred for 23 h at ambient temperature. After the concentration of the mixture, the resulting residue was purified by column chromatography on silica gel (1:4 v/v AcOEt/hexane) to give a 13:1 mixture of (*E*)- and (*Z*)-**6** (782 mg, >99% for two steps) as a colorless oil: ^1H NMR ($CDCl_3$) δ 6.97 (0.93H, dt, J = 15.7, 6.9 Hz), 6.23 (0.07H, dt, J = 11.5, 7.7 Hz), 5.82 (0.93H, dt, J = 15.7, 1.4 Hz), 5.76 (0.07H, dt, J = 11.5, 1.6 Hz), 3.94 (4H, s), 3.73 (2.79H, s), 3.71 (0.21H, s), 2.67 (0.14H, tt, J = 7.7, 1.6 Hz), 2.22 (1.86H, tt, J = 6.9, 1.4 Hz), 1.79−1.66 (4H, m), 1.58−1.15 (7H, m); IR (neat) 1715, 1659 cm^{-1}; LRMS m/z 254 (M^+). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.10; H, 8.79.

4-[(3*E*)-4-(Methoxycarbonyl)-3-butenyl]-1-cyclohexanone ((*E*)-7). To a solution of **6** (164 mg, 0.645 mmol) in THF (2.2 mL) was added a 10% aqueous solution of $HClO_4$ (4.4 mL) at ambient temperature, and the resulting mixture was stirred for 15 h at the same temperature. After dilution with Et_2O, the mixture was neutralized with $NaHCO_3$ and then extracted with Et_2O. The organic layer was washed with brine. The organic layer was dried and concentrated. Column chromatography on silica gel (1:4 v/v AcOEt/hexane) afforded (*E*)-**7** (121 mg, 89%) as a colorless oil and the *Z* isomer (8.7 mg, 6%) as a colorless oil. **(*E*)-7**: ^1H NMR ($CDCl_3$) δ 6.98 (1H, dt, J = 15.7, 6.9 Hz), 5.86 (1H, dt, J = 15.7, 1.6 Hz), 3.74 (3H, s), 2.44−2.23 (6H, m), 2.11−2.00 (2H, m), 1.83−1.67 (1H, m), 1.54−1.33 (4H, m); ^{13}C NMR ($CDCl_3$) δ 211.8, 166.9, 148.9, 121.1, 51.2, 40.4, 35.1, 33.5, 32.2, 29.5; IR 1710, 1650 cm^{-1}; LRMS m/z 210 (M^+). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.65; H, 8.85.

4-[(3*Z*)-4-(Methoxycarbonyl)-3-butenyl]-1-cyclohexanone ((*Z*)-7): ^1H NMR ($CDCl_3$) δ 6.25 (1H, dt, J = 11.5, 7.4 Hz), 5.81 (1H, dt, J = 11.5, 1.6 Hz), 3.72 (3H, s), 2.74 (2H, tt, J = 7.4, 1.6 Hz), 2.44−2.25 (4H, m), 2.16−2.04 (2H, m), 1.84−1.68 (1H, m), 1.52−1.34 (4H, m); ^{13}C NMR ($CDCl_3$) δ 212.0, 166.6, 150.1, 119.4, 50.7, 40.4, 35.4, 34.3, 32.2, 26.4; LRMS m/z 210 (M^+); HRMS calcd for $C_{12}H_{18}O_3$ (M^+) 210.1256, found 210.1239.

4-[(3*E*)-4-(Methoxycarbonyl)-3-butenyl]-2-cyclohexen-1-one (3). To a solution of (*E*)-**7** (1.49 g, 7.10 mmol) and NEt_3 (4.95 mL, 35.5 mmol) in CH_2Cl_2 (35 mL) was added TMSOTf (3.85 mL, 21.3 mmol) at −78 °C, and the mixture was stirred for 3 h. After dilution with saturated $NaHCO_3$, the mixture was extracted with Et_2O. The organic layer was dried and concentrated to give the corresponding crude silyl enol ether, which was used in the next reaction without further purification. To a suspension of $Pd(OAc)_2$ (1.91 g, 8.52 mmol) in CH_3CN (30 mL) was added a solution of the above silyl enol ether in CH_3CN (10 mL) at ambient temperature and the stirring continued for 4.5 h. After dilution with Et_2O, the reaction mixture was filtered through Celite. Evaporation of the filtrate gave a residue, which was purified by column chromatography on silica gel (29:78:3 v/v/v AcOEt/hexane/NEt_3) to give **3** (1.35 g, 91% for two steps) as a colorless oil: ^1H NMR ($CDCl_3$) δ 6.98 (1H, dt, J = 15.7, 6.9 Hz), 6.83 (1H, ddd, J = 10.2, 2.7, 1.4 Hz), 6.01 (1H, dd, J = 10.2, 2.5 Hz), 5.88 (1H, dt, J = 15.7, 1.6 Hz), 3.74 (3H, s), 2.57−2.28 (5H, m), 2.19−2.08 (1H, m), 1.79−1.53 (3H, m); ^{13}C NMR ($CDCl_3$) δ 199.3, 166.6, 153.8, 147.9, 129.1, 121.5, 51.1, 36.4, 35.0, 32.4, 29.0, 28.0; LRMS m/z 208 (M^+). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.08; H, 7.76.

(1*R,2*R**,5*S**)- and (1*R**,2*S**,5*S**)-2-((Methoxycarbonyl)-methyl)bicyclo[3.3.1]non-6-en-8-one (8). Run 1 in Table 1.** To a solution of HMDS (55 mL, 0.26 mmol) in Et_2O (1.5 mL) at 0 °C was added BuLi (1.52 M in hexane, 128 mL. 0.20 mmol). The solution was stirred at 0 °C for 2 h and then cooled to −78 °C. To this was added a solution of **3** (27.1 mg, 0.13 mmol) in Et_2O (1.5 mL) dropwise at −78 °C. The resulting mixture was stirred for 2 h at −78 °C and for a further 2 h at ambient temperature. After dilution with Et_2O, the mixture was washed with 10% HCl and brine. The organic layer was dried and concentrated. Column chromatography on silica gel (3:7 v/v AcOEt/hexane) afforded **8** (5.0 mg, 18%) as a colorless oil (1.4:1 diastereomeric mixture): ^1H NMR ($CDCl_3$) δ 6.99−6.91 (1H, m), 6.17 (1H, d, J = 9.9 Hz), 3.68 (1.75 H, s), 3.67 (1.25 H, s), 2.68−1.17 (11H, m); IR (neat) 1730, 1665 cm^{-1}; LRMS m/z 208 (M^+); HRMS calcd for $C_{12}H_{16}O_3$ (M^+) 208.1100, found 208.1105.

Run 2 in Table 1. To a solution of **3** (31 mg, 0.15 mmol) and NEt_3 (0.20 mL, 1.5 mmol) in $ClCH_2CH_2Cl$ (3 mL) was added dropwise TBDMSOTf (57 mL, 0.40 mmol) at 0 °C. Stirring of the mixture for 1 h at the same temperature, followed by a workup and purification procedure similar to that above, yielded a 1.4:1 diastereomeric mixture of **8** (2.0 mg, 7%) as a colorless oil, which was identical with the above product in all respects.

(1*R,2*S**,3*R**,6*R**,7*S**)-2-(Methoxycarbonyl)tricyclo-[4.3.1.0^{3,7}]decan-9-one (9). Run 4 in Table 1.** A mixture of **3** (30 mg, 0.15 mmol), $ZnBr_2$ (0.33 g, 1.5 mmol), NEt_3 (1.49 mL, 11 mmol), and TMSCl (0.90 mL, 7.1 mmol) in toluene (3 mL) was heated for 20 h at 180 °C in a sealed tube. After dilution with AcOEt, the mixture was washed with 10% HCl and brine. The organic layer was dried and concentrated. Column chromatography on silica gel (3:7 v/v AcOEt/hexane) afforded **9** (18.8 mg, 62%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 3.67 (3H, s), 2.58−2.47 (3H, m), 2.44−2.33 (2H, m), 2.25−1.92 (5H, m), 1.72−1.44 (3H, m); ^{13}C NMR ($CDCl_3$) δ 213.7, 174.9, 51.9, 51.5, 43.5, 39.1, 37.8, 36.2, 33.9, 33.0, 32.6; IR (neat) 1730, 1695 cm^{-1}; LRMS m/z 208 (M^+); HRMS calcd for $C_{12}H_{16}O_3$ (M^+) 208.1100, found 208.1138.

(1*R,2*S**,3*R**,6*R**,7*S**)-9-Oxotricyclo[4.3.1.0^{3,7}]decane-2-carboxylic Acid (10).** To a solution of **9** (157 mg, 0.75 mmol) in MeOH (4 mL) was added 63% aqueous KOH at ambient temperature. After it was left for 2 min, the mixture was concentrated to remove MeOH and then diluted with H_2O. The aqueous layer was washed with Et_2O and acidified with 10% HCl. After extraction with $CHCl_3$, the extract was dried and concentrated. The residue was purified by recrystallization from $^iPr_2O$ to give **10** (147 mg, >99%) as colorless prisms: mp 123−124 °C; ^1H NMR ($CDCl_3$) δ 8.72 (1H, br s), 2.59−1.91 (10H, m), 1.68−1.42 (3H, m); ^{13}C NMR ($CDCl_3$) δ 214.6, 179.8, 51.4, 43.2, 39.2, 38.0, 36.2, 34.0, 33.0, 32.9, 32.7; IR ($CHCl_3$) 1715, 1705 cm^{-1}; LRMS m/z 194 (M^+). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 68.05; H, 7.19.

X-ray Crystallography. Crystallographic data were collected at 20.0 °C on a Rigaku AFC5R diffractometer with graphite-monochromated Mo Kα (λ = 0.71 Å) radiation and a rotating anode generator. The structure was solved using the programs in teXsan. Prismatic crystals of **10** (0.20 × 0.20 × 0.30 mm) suitable for X-ray crystallography were grown by slow crystallization from *i*-Pr_2O. The compound **10** belongs to the monoclinic space group $P2_1/c$ with a = 12.023(2) Å, b =

(13) (a) Johannes, R. E. *Veliger* **1963**, *5*, 104−105. (b) Burreson, B. J.; Scheuer, P. J.; Finer, J.; Clardy, J. *J. Am. Chem. Soc.* **1975**, *97*, 4763−4764. (c) Hagadone, M. R.; Burreson, B. J.; Scheuer, P. J.; Finer, J. S.; Clardy, J. *Helv. Chim. Acta* **1979**, *62*, 2484−2494.

7.2518(9) Å, $c = 12.319(2)$ Å, $\beta = 116.457(9)°$, $V = 961.6(2)$ Å^3, $Z = 4$, and $D = 1.342$ g/cm^3. $R = 0.066$ and $R_w = 0.072$ for 2230 unique reflections. GOF = 2.45.

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Supporting Information Available: X-ray crystallographic data for compound **10** and copies of NMR spectra for compounds (*Z*)-**7**, **8**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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