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Concise Approach to the Carbocyclic Core of the Naturally Occurring Sphingomyelinase Inhibitor Scyphostatin

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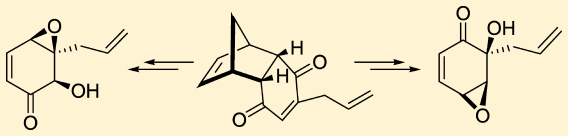
Supporting Information

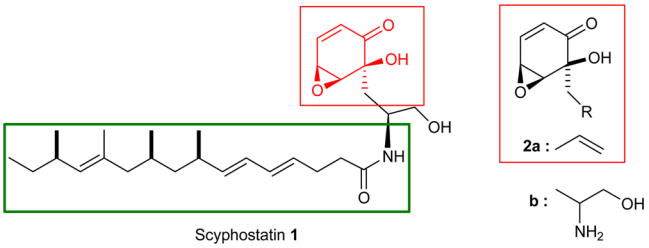
ABSTRACT: A flexible strategy toward the carbocyclic core of the naturally occurring sphingomyelinase inhibitor scyphostatin, from the readily available Diels–Alder adducts of cyclopentadiene and 2-allyl-*p*-benzoquinone, has been devised. This approach leverages the stereochemical predisposition of the norbornyl-fused scaffolds to generate the desired stereochemical pattern and leads to a concise synthesis of the epoxycyclohexenoid core of scyphostatin with a manipulable allyl side arm.



Sphingomyelinase (SMase) phosphodiesterases are hydrolase enzymes involved in the degradation of sphingomyelin (SM), an integral constituent of bacterial and eukaryotic cell membranes, particularly of the membranous myelin sheath that surrounds some neuronal axons.[1] These sphingomyelinase (SMase) phosphatases break down SM, one of the more abundant cellular sphingolipids, to phosphocholine and ceramide.[2] SM-derived ceramide has been recognized as a second messenger in cell membranes and plays a significant role in diverse biological events that include regulation of cell proliferation, differentiation, and apoptosis.[3,4] SMase inhibitors therefore constitute an important class of chemical entities for understanding the biological function of these enzymes and modulating the release of the second messenger ceramide.[4] Release of the secondary messenger ceramide has implications in apoptosis that accompanies serious events like ischemia and myocardial infarction, the cell cycle of inflammatory processes,[5] neurological disorders, and autoimmune diseases.[6]

In 1997, Ogita and co-workers from Sankyo disclosed the isolation and structure determination of scyphostatin (**1**) from the mycelial extract of *Dasyscyphusmollissimus* SANK-13892,[7] embodying a putative amphiphilic architecture with a polar epoxycyclohexenone headgroup and a long hydrophobic tail. These authors also made a significant observation that **1** is a specific and potent inhibitor of mammalian, magnesium-dependent, neutral sphingomyelinase (N-SMase) with an IC_{50} value of 1.0 μM.[7] To date, **1** remains the most efficacious reversible inhibitor of N-SMases. This specific activity of scyphostatin **1** against N-SMases is particularly noteworthy as sphingomyelinase activity is known to be pH dependent, i.e., acidic, neutral, or basic. Indeed, **1** was found to be inactive against acidic S-Mases, and this specificity toward N-SMases confers a special attribute to the natural product, worthy of further therapeutic assessment.

Owing to its impressive bioactivity and a novel bipolar lipid-like construct, scyphostatin (**1**) has evoked sustained interest from both synthetic and medicinal chemistry communities.[8−10] Several total syntheses[8] and model studies,[9] targeting its polar cyclohexenoid core and structural analogues,[10] have been reported during the past decade. In the context of evaluating the therapeutic space around the natural product for SAR studies and diversity generation, it was further recognized that it is mainly the long hydrophobic chain in **1** (green box), readily installed through *N*-acylation of the side arm on the hydrophilic segment, that offers considerable latitude. Therefore, gaining access to the polar oxygenated epoxycyclohexenoid core **2** (red box) of **1** with a suitably embellished side arm (R) has been central to the efforts in this arena, and several strategies[9] have been explored toward this end. In view of the continuing interest in the synthesis of **1** and **2** and their analogues, we were drawn to the challenge of devising a new, concise, and flexible approach to **2** via **1**.



Evolution of the present approach to **2** had its origin in our versatile synthetic strategy toward oxygenated epoxycyclohexanoid natural products from the readily available Diels–Alder adduct of cyclopentadiene and an appropriately substituted *p*-benzoquinone.[11] The resulting *endo*-tricyclic D–A adducts, incorporating a tricyclo[6.2.1.$0^{2,7}$]undecane framework, displays predictable stereo- and regioselective preferences associated with fused norbornyl systems.[11] This strategy appeared suitable for accessing an advanced derivative **2a**,[9a,d,k] as its allyl side arm was well poised for the introduction of the requisite functionalities through aminohydroxylation[12] (see **2b**) or the installation of diversified hydrophobic chains through cross-

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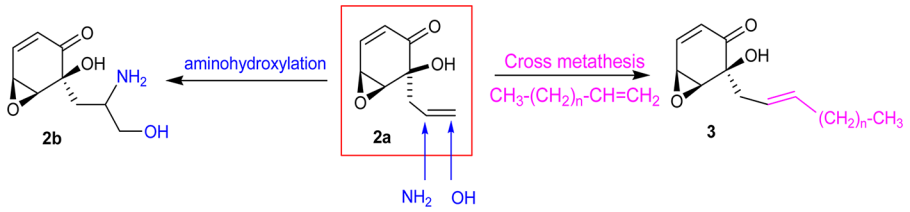
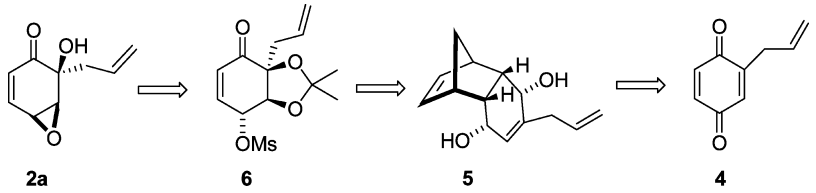
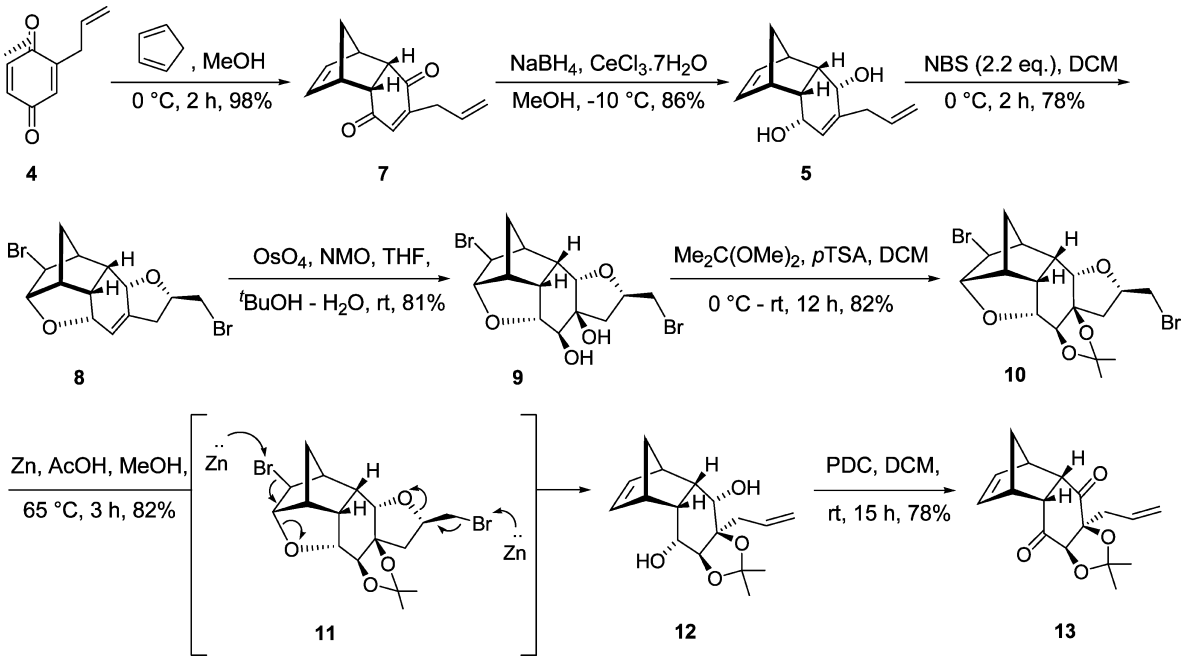
Scheme 1



Scheme 2. Retrosynthetic Plan for the Scyphostatin Carbocyclic Core



Scheme 3. Synthesis of the Advanced Intermediate 13



metathesis[9k] protocols (see **3**) (Scheme 1). Indeed, given its potential for diversity generation, **2a** has been a preferred subtarget in earlier studies aimed at the total synthesis of scyphostatin.

A retrosynthetic analysis, leading to **2a** from the readily available[11g] D–A adduct of cyclopentadiene and 2-allyl-*p*-benzoquinone **4** via the tricyclic *cis*-diol **5** and involving the intermediacy of the stereochemically secured cyclohexanoidtriol **6**, is displayed in (Scheme 2). Implementation of this conceptualization commenced from the Diels–Alder reaction between the quinone **4** and cyclopentadiene to furnish the *endo*-tricyclic adduct **7**. Luche reduction[13] on **7** was stereoselective, with hydride addition from the topologically favored convex surface, leading to the *cis*-diol **5** as a single diastereomer. The two *endo*-hydroxyl groups as well as the norbornene and allyl double bonds in **5** needed to be protected in order to oxyfunctionalize the remaining cyclohexene double bond in a regio- and stereoselective manner. This was accomplished by employing an intramolecular double bromo-etherification stratagem.[14] Exposure of **5** to NBS (2.2 equiv) indeed led to the pentacyclicdibromide **8** in which all four aforementioned functionalities were internally protected in a one-pot operation. The remaining cyclohexene double bond was now freely available for implementing an oxyfunctionalization protocol (Scheme 3). OsO_4-mediated catalytic dihydroxylation[15] in **8** was expectedly *exo*-selective and furnished a pentacyclic *cis*-diol **9**, which was further protected as an acetonide **10**. At this stage, the four protected functionalities in **10** were disengaged (as depicted in **11**) by exposing it to Zn in MeOH–AcOH milieu[16] to yield a protected tetrol **12** (Scheme 3). Chemodifferentiation between the two hydroxyl groups of the *cis*-1,4-diol moiety in **12** was now mandated. However, a direct hydroxyl derivatization on **12**, like monomesylate or monoacetate formation, was unproductive so that recourse to a more circuitous route became necessary. Consequently, **12** was oxidized with excess of PDC to furnish a diketone **13** which was now amenable to a regioselective maneuver.

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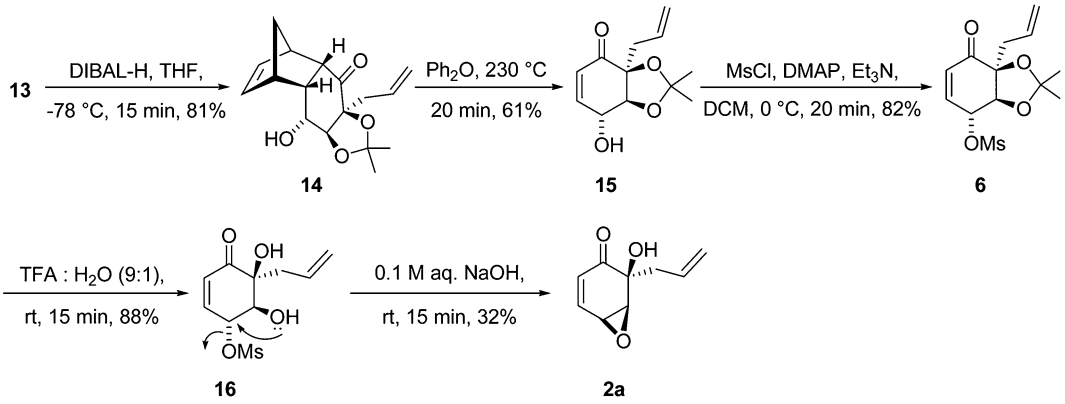
Scheme 4. Synthesis of the Scyphostatin Carbocyclic Core 2a



Controlled DIBAL reduction in **13**, possibly steered by chelation control[11g] involving the less encumbered oxygen of the acetonide moiety, led to the formation of hydroxyketone **14** in a regio- and stereoselective manner (Scheme 4). It was necessary to secure the stereostructure of **14** at this stage and was accomplished using single-crystal X-ray structure determination (Figure 1). Having secured the requisite stereochemistry

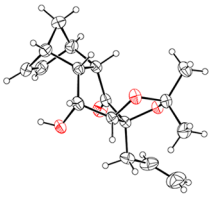


Figure 1. ORTEP diagram of **14**.

in **14**, it was now time to jettison its cyclopentadiene appendage. Retro-D–A reaction in **14** was smoothly carried out, albeit in modest yield, to deliver the hydroxycyclohexenone **15**. The stage was now set for the epoxide generating[9d,g] end game en route **2a** utilizing the strategically positioned functionalities.

Toward this end, the free hydroxyl group in **15** was converted into the mesylate **6** as per the retrosynthetic delineation (Scheme 2); further acetonide deprotection in **6** delivered **16**[9d] (Scheme 4). The dihydroxymesylate **16** was now well poised for an intramolecular S_N2-type displacement (see arrows in **16**) to deliver the epoxide ring. Exposure of **16** to base readily delivered the targeted **2a** and its characterization followed from its spectral data and comparison with the values reported in the literature.[9a,d]

Having accessed the targeted structure **2a**, it was of interest to scope the diversity space around its core from the intermediates already in hand. A variation that appealed in this context was to reposition the allyl arm on the cyclohexanoid framework through an exercise in diverted organic synthesis (DOS), formally amounting to a 1,2-allyl shift. For this purpose, the tricyclic *cis*-diol **12** was subjected to a controlled, regioselective oxidation to eventuate in the hydroxyketone **17** in which the hydroxyl and the carbonyl groups were "swapped" as compared to **14**, deployed earlier for the synthesis of **2a**. Structure of **17** was secured through a single-crystal X-ray structure determination (Figure 2). Retro-D–A reaction in **17** was uneventful and resulted in the disengagement of the cyclopentadiene moiety to deliver the

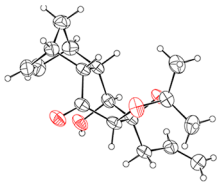


Figure 2. ORTEP diagram of **17**.

cyclohexenone **18**. Mesylation of the free hydroxyl group in **18** led to **19** and further acetonide deprotection to **20** set the stage for the epoxide generation step. Exposure of **19** to base led to mesylate displacement by the tactically positioned neighboring hydroxyl group and resulted in the epoxy-cyclohexenone **21** whose structure was secured through incisive analysis of its spectral data (Scheme 5). The polar epoxycyclohexenone **21** represents a "confused" core[17] of the scyphostatin natural product and can be further elaborated to access "un-natural" analogues.

Synthesis of an allyl group bearing an epoxycyclohexenoid core, representing the polar headgroup of scyphostatin, has been accomplished from the readily available Diels–Alder adduct of cyclopentadiene and 2-allyl-*p*-benzoquinone through a series of regio- and stereocontrolled steps among which internal protection of four functionalities via double bromoetherfication was a key step. In a diversionary tactic, a "confused" un-natural analogue of the epoxy cyclohexanoid core has also been prepared.

EXPERIMENTAL SECTION

General Experimental Methods. All moisture- and air-sensitive reactions were performed using standard syringe–septum technique in an atmosphere of nitrogen with dry, freshly distilled solvents. Low temperatures were maintained using liquid nitrogen in combination with appropriate solvent. Hexanes refer to the petroleum ether fraction boiling between 60 and 80 °C. Dry THF and ether were prepared by distilling them from sodium benzophenoneketyl. DCM and TEA were distilled over calcium hydride just before use. Methanol was distilled from its alkoxide (formed by the reaction with activated magnesium) and stored over 4 Å molecular sieves. Reactions were monitored by thin-layer chromatography (TLC). Visualization of the spots on TLC plates was achieved by exposure to iodine vapor, under UV light, or by spraying with either ethanolic vanillin or 30% H_2SO_4–methanol solution and heating the plates at ~120 °C. Commercial silica gel (100–200 mesh particle size) was used for column chromatography. ^1H and ^{13}C NMR samples were generally made in $CDCl_3$ and chemical shifts are expressed in parts per million (δ) scale using tetramethylsilane (Me_4Si) as the internal standard. The standard

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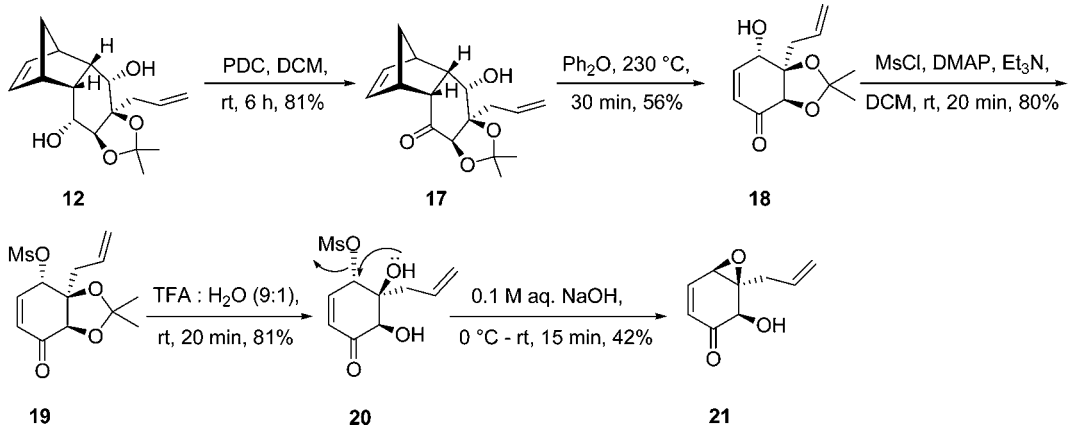
Scheme 5. Synthesis of the Epoxycyclohexenone Moiety 21



abbreviations s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet respectively. Coupling constants (*J*), whenever discernible, have been reported in Hz. High-resolution mass spectra (HRMS) were recorded on Q-TOF Micro mass spectrometer.

***rel*-(1*S*,4*R*,4a*S*,5*S*,8*R*,8a*R*)-6-Allyl-1,4,4a,5,8,8a-hexahydro-1,4-methanonaphthalene-5,8-diol (5).** To a stirred solution of the enedione **7** (720 mg, 3.36 mmol) in MeOH (10 mL), cooled to −10 °C, was added $CeCl_3·7H_2O$ (2.62 g, 7.06 mmol), followed by portionwise addition of $NaBH_4$ (261 mg, 7.06 mmol). After 15 min, the reaction was quenched with saturated aqueous ammonium chloride solution. The organic layer was separated and the aqueous layer extracted with EtOAc (50 × 3 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered, and the solvent was evaporated under reduced pressure to afford the crude product. The crude residue was purified by silica gel column chromatography (eluent: 25% EtOAc in hexane) to afford the diol **5** (630 mg, 86%) as a colorless microcrystalline solid: mp 92−94 °C; IR (thin film) $\bar{\nu}$ = 3302, 3057, 2978, 2912, 1641, 1315, 1053, 742 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$) δ 6.12−6.11 (m, 2H), 5.87−5.76 (m, 2H), 5.13−5.07 (m, 2H), 4.36 (d, *J* = 5 Hz, 1H), 4.19 (t, *J* = 5 Hz, 1H), 2.91−2.88 (m, 4H), 2.56−2.51 (m, 2H), 2.26 (d, *J* = 7 Hz, 1H), 2.08 (d, *J* = 6 Hz, 1H), 1.49−1.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 135.8, 134.4, 134.0, 128.9, 116.8, 68.8, 66.0, 52.4, 45.4, 45.3, 45.2, 45.1, 39.1; HRMS (ES) *m*/*z* calcd for $C_{14}H_{18}NaO_2$ $(M + Na)^+$ 241.1204, found 241.1205.

Formation of Pentacyclicdibromide (8). *N*-Bromosuccinimide (1.07 g, 6.05 mmol) was added to a stirred solution of the diol **5** (600 mg, 2.75 mmol) in dry DCM (8 mL) at 0 °C, and the resulting reaction mixture was stirred for 1 h at room temperature. After completion of the reaction, the reaction mixture was diluted with DCM. The organic layer was washed successively with 20% aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and brine and then dried over Na_2SO_4. Concentration of the solvent afforded a residue, which was purified by column chromatography (eluent: 6% EtOAc in hexane) to obtain **8** (810 mg, 78%) as a colorless oil. IR (neat) $\bar{\nu}$ = 2961, 2903, 1658, 1433, 1045, 736, 659 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.67 (s, 1H), 4.56−4.52 (m, 2H), 4.44 (brs, 1H), 4.32−4.26 (m, 1H), 3.99 (s, 1H), 3.73 (t, *J* = 6.1 Hz, 1H), 3.54−3.45 (m, 2H), 2.90 (s, 1H), 2.75 (dd, *J* = 15.2 and 6.7 Hz, 1H), 2.63−2.50 (m, 2H), 2.49 (m, 1H), 2.13 (d, *J* = 11.2 Hz, 1H), 1.52 (d, *J* = 10.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 120.5, 90.8, 76.0, 74.4, 74.3, 53.7, 50.8, 45.5, 40.4, 36.3, 35.4, 35.2, 34.4; HRMS (ES) *m*/*z* calcd for $C_{14}H_{16}NaBr_2O_2$ $(M + Na)^+$ 396.9415, found 396.9416.

Formation of Pentacyclicdiol (9). To a solution of **8** (500 mg, 1.32 mmol) in THF (6 mL) were added successively at room temperature *N*-methylmorpholine *N*-oxide (187 mg, 1.59 mmol), *tert*-butyl alcohol (3 mL), water (0.5 mL), and OsO_4 (1.6 mL, 0.066 mmol, 0.05 M in *tert*-butyl alcohol) at room temperature. The reaction mixture was stirred for 5 h, quenched with solid Na_2SO_3 (500 mg), and stirred at room temperature for 15 min. Florisil (550 mg) was added. The mixture was stirred for 15 min and then filtered through Celite. Concentration and column chromatography (eluent: 50% EtOAc in hexane) gave diol **9** as a white solid (440 mg, 81%): mp 120−122 °C; IR (thin film) $\bar{\nu}$ = 3398, 2970, 2918, 1655, 1456, 1116, 1043, 702, 675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.53 (d, *J* = 8 Hz, 1H), 4.38 (d, *J* = 12 Hz, 1H), 4.32−4.27 (m, 1H), 4.15−4.11 (m, 3H), 3.79 (s, 1H), 3.56−3.51(m, 2H), 2.87 (brs, 1H), 2.62−2.51 (m, 3H), 2.18 (d, *J* = 12 Hz, 1H), 2.05 (s, 1H), 1.90 (dd, *J* = 13, 7 Hz, 1H), 1.62 (brs, 1H), 1.59 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 88.8, 83.4, 79.6, 78.7, 77.2, 73.1, 56.0, 48.7, 45.3, 41.3, 38.7, 36.3, 36.1, 35.7; HRMS (ES) *m*/*z* calcd for $C_{14}H_{18}NaBr_2O_4$ $(M + Na)^+$ 430.9470, found 430.9472.

Formation of Hexacyclicacetonide (10). To a stirred solution of **9** (400 mg, 0.97 mmol) and 2,2-dimethoxypropane (4 mL, 19.5 mmol) in DCM (1 mL) was added *p*TSA (68 mg, 0.39 mmol), and the reaction mixture was stirred for 12 h at rt. The reaction was quenched by addition of water (5 mL). The layers were separated, and the aqueous layer was extracted with DCM (3 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified through a silica gel column chromatography (eluent: 4% EtOAc in hexane) to give acetonide **10** (360 mg, 82%) as a colorless oil: IR (neat) $\bar{\nu}$ = 2982, 2856, 1221, 1101, 1059, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.50−4.49 (m, 1H), 4.43 (dd, *J* = 11, 3 Hz, 1H), 4.36−4.35 (m, 1H), 4.28 (brs, 1H), 4.22−4.21 (m, 1H), 4.05 (brs, 1H), 3.51−3.50 (m, 2H), 2.97 (brs, 1H), 2.72−2.64 (m, 2H), 2.43−2.36 (m, 2H), 2.25−2.19 (m, 2H), 1.64 (d, *J* = 11 Hz, 1H),1.38 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.6, 87.7, 85.5, 80.7, 77.6, 76.4, 73.5, 57.1, 48.4, 44.9, 42.1, 38.8, 35.4, 35.0, 34.5, 27.7, 26.3; HRMS (ES) *m*/*z* calcd for $C_{17}H_{23}Br_2O_4$ $(M + H)^+$ 450.9943, found 450.9949.

***rel*-(3a*R*,4*S*,4a*S*,5*R*,8*S*,8a*R*,9*R*,9a*S*)-3a-Allyl-2,2-dimethyl-3a,4,4a,5,8,8a,9,9a-octahydro-5,8-methanonaphtho[2,3-*d*]-[1,3]dioxole-4,9-diol (12).** Freshly activated zinc powder (2.39 g, 36.66 mmol) and acetic acid (1 mL) were successively added to a stirred solution of **10** (330 mg, 0.73 mmol) in methanol (20 mL) at room temperature. The mixture was gradually warmed to 65 °C and stirred for 3 h at same temperature. After being cooled , the mixture was diluted with ether (30 mL) and filtered through Celite. The filtrate was washed with saturated aqueous $NaHCO_3$ and brine and then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue that was purified by column chromatography (eluent: 30% EtOAc in hexane) to give **12** (175 mg, 82%) as a white solid: mp 96−98 °C; IR (thin film) $\bar{\nu}$ = 3302, 3074, 2961, 2930, 1641, 1454, 1178, 1045 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.20−6.18 (m, 2H), 6.04−5.99 (m, 1H), 5.20−5.16 (m, 2H), 4.18 (brs, 1H), 4.01 (s, 1H), 3.94 (d, *J* = 7 Hz, 1H), 2.92 (brs, 1H), 2.90 (brs, 1H), 2.83 (d, *J* = 8 Hz, 1H), 2.75−2.65 (m, 3H), 2.55 (d, *J* = 7 Hz, 1H), 2.47 (dd, *J* = 14, 6 Hz 1H), 1.44 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.4, 134.4, 133.9, 118.3, 108.7, 84.6, 83.6, 70.3, 69.9, 53.0, 45.8, 45.3, 44.0, 39.9, 39.8, 27.6, 27.3; HRMS (ES) *m*/*z* calcd for $C_{17}H_{24}NaO_4$ $(M + Na)^+$ 315.1572, found 315.1572.

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***rel*-(3a*S*,4a*S*,5*R*,8*S*,8a*R*,9a*R*)-3a-Allyl-2,2-dimethyl-4a,5,8,8a-tetrahydro-5,8-methanonaphtho[2,3-*d*][1,3]dioxole-4,9-(3a*H*,9a*H*)-dione (13).** To a DCM (20 mL) solution of the diol **12** (150 mg, 0.51 mmol) was added PDC (3.9 g, 10.27 mmol). The reaction mixture was stirred for 15 h at rt. After completion of the reaction, the reaction mixture was directly loaded on a silica gel column and eluted with 5% EtOAc in hexane to afford **13** (115 mg, 78%) as a colorless liquid: IR (neat) $\bar{\nu}$ = 2926, 2854, 1720, 1645, 1456, 1167, 1059 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$) δ 6.14−6.12 (m, 1H), 5.99−5.97 (m, 1H), 5.48−5.42 (m, 1H), 5.11 (s, 1H), 5.07 (d, *J* = 5 Hz, 1H), 4.20 (s, 1H), 3.78 (m, 2H), 3.39 (s, 1H), 3.27 (s, 1H), 2.43−2.41 (m, 2H),1.65 (s, 1H), 1.56 (s, 3H), 1.49 (d, *J* = 8 Hz, 1H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.3, 205.5, 136.6, 136.4, 130.3, 120.6, 112.3, 86.2, 83.2, 51.4, 50.9, 47.3, 45.0, 43.1, 36.5, 27.3, 26.1; HRMS (ES) *m*/*z* calcd for $C_{17}H_{20}NaO_4$ $(M + Na)^+$ 311.1259, found 311.1260.

***rel*-(3a*S*,4a*S*,5*R*,8*S*,8a*R*,9*R*,9a*S*)-3a-Allyl-9-hydroxy-2,2-dimethyl-4a,5,8,8a,9,9a-hexahydro-5,8-methanonaphtho[2,3-*d*][1,3]dioxol-4(3a*H*)-one (14).** DIBAL-H (0.20 mL, 0.305 mmol, 1 M solution in toluene) was added dropwise to a stirred solution of **13** (80 mg, 0.277 mmol) in dry THF (2 mL) at −78 °C. The resulting mixture was stirred at −78 °C for 15 min and then quenched with aqueous sodium potassium tartarate solution. After separation of the layers, the aqueous phase was extracted further with EtOAc (25 × 2 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo to obtain a residue, which on silica gel column chromatography (eluent: 20% EtOAc in hexane) afforded **14** (65 mg, 81%) as a white crystalline solid: mp 70−72 °C; IR (thin film) $\bar{\nu}$ = 3543, 3076, 2964, 1720, 1639, 1435, 1170, 1057 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49−6.47 (m, 1H), 6.22−6.20 (m,1H), 5.94−5.87 (m, 1H), 5.16 (s, 1H), 5.13 (d,*J* = 8 Hz, 1H), 4.03 (s, 1H), 3.84 (s, 1H), 3.63 (dd, *J* = 11.8 and 3.1 Hz, 1H), 3.29−3.24 (m, 1H), 3.08 (brs, 1H), 2.97 (brs, 1H), 2.79 (dd, *J* = 16.0 and 8.1 Hz, 1H), 2.41 (dd, *J* = 15.9 and 8.0 Hz, 1H), 2.01 (s, 1H), 1.56 (s, 3H), 1.53 (d, *J* = 8.1 Hz, 1H), 1.47 (s, 3H), 1.38 (d,*J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.8, 139.1, 133.7, 132.9, 118.8, 113.0, 90.0, 85.5, 69.2, 51.7, 46.0, 45.8, 43.2, 42.5, 41.9, 28.1, 27.7; HRMS (ES) *m*/*z* calcd for $C_{17}H_{22}NaO_4$ $(M + Na)^+$ 313.1416, found 313.1416.

***rel*-(3a*S*,7*R*,7a*S*)-3a-Allyl-7-hydroxy-2,2-dimethyl-7,7a-dihydrobenzo[*d*][1,3]dioxol-4(3a*H*)-one (15).** A solution of **14** (60 mg, 0.206 mmol) in diphenyl ether (2 mL) was heated at 230 °C for 20 min with stirring. The reaction mixture, after cooling to rt, was directly loaded on a silica gel column. After removal of diphenyl ether, elution with 45% EtOAc in hexane provided the retro-Diels−alder product **15** (28 mg, 61%) as a colorless viscous oil: IR (neat) $\bar{\nu}$ = 3447, 2984, 2854, 1682, 1456, 1116, 1057 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87−6.84 (m, 1H), 6.12 (dd,*J* = 10.1 and 2.4 Hz, 1H), 5.88−5.79 (m, 1H), 5.23−5.14 (m, 2H), 4.66 (s, 1H), 4.32 (brs, 1H), 2.64−2.58 (m, 2H), 1.68 (brs, 1H), 1.39 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 144.4, 132.0, 128.5, 120.1, 108.7, 81.6, 80.3, 64.7, 38.4, 27.4, 26.5; HRMS (ES) *m*/*z* calcd for $C_{12}H_{16}NaO_4$ $(M + Na)^+$ 247.0946, found 247.0947.

***rel*-(3a*S*,4*R*,7a*S*)-7a-Allyl-2,2-dimethyl-7-oxo-3a,4,7,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-yl Methanesulfonate (6).** Methanesulfonyl chloride (0.07 mL, 0.891 mmol) was added at 0 °C to a stirred solution of **15** (20 mg, 0.089 mmol) in dichloromethane (3 mL), containing triethylamine (0.18 mL, 1.27 mmol) and DMAP (10.89 mg, 0.089 mmol). The resulting reaction mixture was stirred for 20 min at room temperature. The reaction was quenched with saturated sodium hydrogen carbonate solution (3 mL) at 0 °C, and the mixture was diluted with ether. The organic layer was washed successively with 3% aqueous HCl, saturated aqueous $NaHCO_3$, and brine and then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified by column chromatography (eluent: 6% EtOAc in hexane) to give **6** (22 mg, 82%) as a colorless oil: IR (neat) $\bar{\nu}$ = 3072, 2964, 2872, 1728, 1620, 1427, 1126, 1049 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96−6.90 (m, 1H), 6.20 (dd,*J* = 10.0 and 2.3 Hz, 1H), 5.78−5.69 (m, 1H), 5.61 (s, 1H), 5.20−5.14 (m, 2H), 4.29 (s, 1H), 3.23 (s, 3H), 2.74−2.37 (m, 2H), 1.60 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3, 147.9, 131.1, 129.3, 115.3, 111.5, 85.7, 80.9, 77.9, 41.7, 39.0, 27.3, 26.6; HRMS (ES) *m*/*z* calcd for $C_{13}H_{18}NaO_6S$ $(M + Na)^+$ 325.0722, found 325.0724.

***rel*-(1*R*,5*S*,6*S*)-5-Allyl-5,6-dihydroxy-4-oxocyclohex-2-enyl Methanesulfonate (16).** A solution of **6** (15 mg, 0.049 mmol) in trifluoroacetic acid (1.8 mL) and water (0.2 mL) was stirred at room temperature for 15 min. The mixture was concentrated in vacuo to afford a residue, which was purified by column chromatography (eluent: 45% EtOAc in hexane) to give **16** (11.5 mg, 88%) as a colorless viscous oil: IR (neat) $\bar{\nu}$ = 3429, 3055, 2961, 2856, 1722, 1680, 1435, 1215, 1045 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95−6.82 (m, 1H), 6.36 (d,*J* = 10.0 Hz, 1H), 6.05−5.98 (m, 1H), 5.34 (s, 1H), 5.31−5.26 (m,2H), 4.37 (s, 1H), 3.30 (d,*J* = 7.2 Hz, 1H),3.15 (s, 3H),2.90 (brs, 1H), 2.77−2.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 140.9, 130.7, 129.9, 115.2, 76.1, 75.1, 74.7, 40.3, 39.7; HRMS (ES) *m*/*z* calcd for $C_{10}H_{14}NaO_6S$ $(M + Na)^+$ 285.0408, found 285.0408.

***rel*-(1*S*,2*S*,6*S*)-2-Allyl-2-hydroxy-7-oxabicyclo[4.1.0]hept-4-en-3-one (2a).** A solution of NaOH (1.5 mL, 0.15 mmol, 0.1 M in water) was added dropwise to a stirred solution of **16** (40 mg, 0.240 mmol) in dichloromethane (4 mL) at 0 °C. After the addition was complete, the cooling bath was removed, and the reaction mixture was allowed to warm to room temperature. After 15 min of stirring at rt, the product was diluted with water (15 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic layer was dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue, which was purified through column chromatography (eluent: 30% EtOAc in hexane) to give **2a** (8 mg, 32%) as a yellow oil: IR (neat) $\bar{\nu}$ = 3520, 3078, 2950, 2861, 1718, 1630, 1385, 1212, 1066 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (dd, 1H, *J* = 10.0 and 4.0 Hz, 1H), 6.12 (dd, *J* = 10.0 and 1.2 Hz, 1H), 5.84−5.76 (m, 1H), 5.18−5.12 (m, 2H), 3.97 (d, *J* = 5 Hz, 1H), 3.73 (br s, 1H), 3.67 (m, 1H), 2.81−2.75 (m, 1H), 2.39−2.33 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0, 146.8, 132.7, 129.8, 116.1, 75.4, 58.6, 47.7, 40.0; HRMS (ES) *m*/*z* calcd for $C_9H_{10}NaO_3$ $(M + Na)^+$ 189.0528, found 189.0528.

***rel*-(3a*R*,4a*R*,5*S*,8*R*,8a*S*,9*S*,9a*R*)-9a-Allyl-9-hydroxy-2,2-dimethyl-4a,5,8,8a,9,9a-hexahydro-5,8-methanonaphtho[2,3-*d*][1,3]dioxol-4(3a*H*)-one (17).** To a DCM (20 mL) solution of the diol **12** (200 mg, 0.68 mmol) was added PDC (2.6 g, 6.84 mmol). The reaction mixture was stirred for 6 h at rt. After completion of the reaction, the reaction mixture was directly loaded on a silica gel column and eluted with 15% EtOAc in hexane to afford **17** (161 mg, 81%) as a white crystalline solid: mp 64−66 °C; IR (thin film) $\bar{\nu}$ = 3523, 3095, 2980, 1720, 1627, 1457, 1156, 1057 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.48−6.46 (m, 1H), 6.18−6.17 (m, 1H), 5.89−5.87 (m, 1H), 5.10−5.05 (m, 2H), 4.35−4.30 (m, 2H), 3.53−3.49 (m, 1H), 3.25−3.21 (m,1H), 3.14 (brs, 1H), 2.98 (brs, 1H), 2.72−2.66 (m, 1H), 2.44−2.39 (m, 1H), 1.75 (d, *J* = 4.0 Hz, 1H), 1.56 (s, 3H), 1.53 (d, *J* = 8.1 Hz, 1H), 1.44 (s, 3H), 1.39 (d,*J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.7, 139.4, 134.1, 133.1, 118.0, 111.8, 83.8, 83.3, 68.3, 51.2, 46.5, 45.5, 43.6, 43.0, 40.1, 27.4, 26.9; HRMS (ES) *m*/*z* calcd for $C_{17}H_{22}NaO_4$ $(M + Na)^+$ 313.1416, found 313.1419.

***rel*-(3a*R*,7*S*,7a*R*)-7a-Allyl-7-hydroxy-2,2-dimethyl-7,7a-dihydrobenzo[*d*][1,3]dioxol-4(3a*H*)-one (18).** A solution of **17** (150 mg, 0.51 mmol) in diphenyl ether (3 mL) was heated at 230 °C for 30 min with stirring. The reaction mixture, after cooling to rt, was directly loaded on a silica gel column. After removal of diphenyl ether, elution with 40% EtOAc in hexane provided the retro-Diels−Alder product **18** (65 mg, 56%) as a colorless viscous oil: IR (neat) $\bar{\nu}$ = 3441, 3094, 2928, 2861, 1733, 1635, 1453, 1158, 1060 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (dd, *J* = 10.0 and 2.0 Hz, 1H), 6.13 (dd, *J* = 10.1 and 2.4 Hz, 1H), 5.88−5.80 (m, 1H), 5.18−5.09 (m, 2H), 4.75 (s, 1H), 4.25 (s, 1H), 2.80−2.75 (m, 1H), 2.39−2.33 (m, 1H), 1.67 (s, 1H), 1.50 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.3, 151.8, 132.5, 128.1, 119.6, 110.7, 86.8, 77.9, 71.7, 34.6, 27.9, 26.9; HRMS (ES) *m*/*z* calcd for $C_{12}H_{16}NaO_4$ $(M + Na)^+$ 247.0946, found 247.0947.

***rel*-(3a*S*,4*S*,7a*R*)-3a-Allyl-2,2-dimethyl-7-oxo-3a,4,7,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-yl Methanesulfonate (19).** Metha-

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nesulfonyl chloride (0.11 mL, 1.33 mmol) was added at 0 °C to a stirred solution of **18** (30 mg, 0.13 mmol) in dichloromethane (4 mL) containing triethylamine (0.27 mL, 1.91 mmol) and DMAP (16.34 mg, 0.13 mmol). The resulting reaction mixture was stirred for 20 min at room temperature. The reaction was quenched with saturated sodium hydrogen carbonate solution (2 mL) at 0 °C, and the mixture was diluted with ether. The organic layer was washed successively with 3% aqueous HCl, saturated aqueous $NaHCO_3$, and brine and then dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue that was purified by column chromatography (eluent: 5% EtOAc in hexane) to give **19** (32 mg, 80%) as a colorless oil: IR (neat) $\bar{\nu}$ = 3050, 2959, 2851, 1738, 1459, 1169, 1019 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.93−6.88 (m, 1H), 6.25−6.22 (m, 1H), 5.88−5.77 (m, 1H), 5.38 (s, 1H), 5.20−5.15 (m, 2H), 4.31 (s, 1H), 3.29 (s, 3H), 2.86−2.81 (m, 1H), 2.65−2.50 (m, 1H), 1.57 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 148.2, 132.0, 129.7, 115.3, 111.3, 85.6, 78.3, 72.7, 41.9, 38.9, 27.5, 26.9; HRMS (ES) m/z calcd for $C_{13}H_{18}NaO_6S$ $(M + Na)^+$ 325.0722, found 325.0723.

***rel*-(1*S*,5*R*,6*S*)-6-Allyl-5,6-dihydroxy-4-oxocyclohex-2-enyl Methanesulfonate (20).** A solution of **19** (20 mg, 0.06 mmol) in trifluoroacetic acid (1.8 mL) and water (0.2 mL) was stirred at room temperature for 20 min. The mixture was concentrated in vacuo to afford a residue that was purified by column chromatography (eluent: 40% EtOAc in hexane) to give **20** (14 mg, 81%) as a colorless oil: IR (neat) $\bar{\nu}$ = 3437, 3076, 2924, 2854, 1720, 1641, 1462, 1244, 1059 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.94−6.83 (m, 1H), 6.53 (dd, J = 9.6 and 2.8 Hz, 1H), 5.98−5.87 (m, 1H), 5.38 (s, 1H), 5.19−5.14 (m, 2H), 4.44 (s, 1H), 3.31 (d, J = 2.8 Hz, 1H), 3.11(s, 3H), 3.00 (s, 1H), 2.84−2.78 (m, 1H), 2.45−2.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3, 141.9, 132.5, 129.6, 115.3, 86.8, 77.9, 71.7, 40.5, 39.9; HRMS (ES) m/z calcd for $C_{10}H_{14}NaO_6S$ $(M + Na)^+$ 285.0408, found 285.0408.

***rel*-(1*S*,2*R*,6*R*)-1-Allyl-2-hydroxy-7-oxabicyclo[4.1.0]hept-4-en-3-one (21).** To a stirred solution of **20** (13 mg, 0.04 mmol) in DCM (2 mL) at 0 °C was added dropwise 0.1 M NaOH solution (1.4 mL, 0.14 mmol). After 15 min, the mixture was extracted with DCM (2 × 25 mL). The combined extracts were washed with brine and dried over Na_2SO_4. Concentration of the solvent in vacuo afforded a residue that was purified by column chromatography (eluent: 25% EtOAc in hexane) to give **21** (3.5 mg, 42%) as a colorless oil: IR (neat) $\bar{\nu}$ = 3523, 3073, 2958, 2865, 1720, 1632, 1380, 1210, 1068 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.92−6.89 (m, 1H), 6.24 (dd, J = 10.4 and 2.4 Hz, 1H), 5.85−5.77 (m, 1H), 5.20−5.14 (m, 2H), 4.06 (d, J = 6.4 Hz, 1H), 3.67 (s, 1H), 3.57 (d, J = 5.2 Hz, 1H), 2.86−2.80 (m, 1H), 2.60−2.54 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 145.5, 133.4, 128.7, 116.5, 73.6, 59.7, 48.6, 40.4; HRMS (ES) m/z calcd for $C_9H_{10}NaO_3$ $(M + Na)^+$ 189.0528, found 189.0528.

Crystal Data of Compound 14. Single-crystal X-ray diffraction data were collected for **14** at 291 K (Mo Kα; λ = 0.71073 Å), and the crystal structure was solved by direct methods using SIR92 and refined by full-matrix least-squares methods on F^2 using SHELXL97. Crystal data for **14**: $C_{17}H_{22}O_4$, M = 290.35, orthorhombic, $P2_12_12_1$, a = 8.2706(4) Å, b = 11.4435(5) Å, c = 16.3880(9) Å, V = 1551.04(13) $Å^3$, Z = 4, ρ_{calcd} = 1.243 g/cm^3, 5335 reflections measured, 1662 unique (R_{int} = 0.024), R1 = 0.0339 and wR2 = 0.0762 for 1478 observed reflections. CCDC 899201 contains the supplementary crystallographic data for this paper.

Crystal Data of Compound 17. Single-crystal X-ray diffraction data were collected for **17** at 291 K (Mo Kα; λ = 0.71073 Å), and the crystal structure was solved by direct methods using SHELXS97 and refined by full-matrix least-squares method on F^2 using SHELXL97.-Crystal data for **17**: $C_{17}H_{22}O_4$, M = 290.35, monoclinic,$C2/c$, a = 28.465(14) Å, b = 16.248(3) Å, c = 23.16(3) Å, V = 9063(14) $Å^3$, Z = 24, ρ_{calcd} = 1.277 g/cm^3, 16988 reflections measured, 7671 unique (R_{int} = 0.0993), R1 = 0.0948 and wR2 = 0.2048 for 3101 observed reflections. CCDC 902878 contains the supplementary crystallographic data for this paper.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H NMR and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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