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Chiral Cyclopropenyl Ketones: Reactive and Selective Diels–Alder Dienophiles

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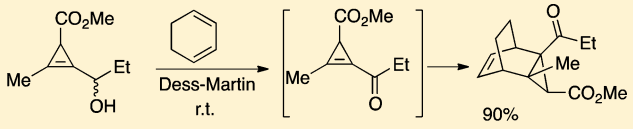
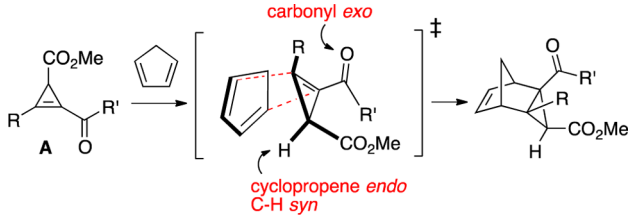
Supporting Information

ABSTRACT: The synthesis and Diels–Alder reactions of cyclopropenyl ketones are described. Cyclopropenyl ketones are highly reactive dienophiles that can engage a range of cyclic dienes and 2,3-dimethylbutadiene. The strategy of using cyclopropenyl ketones to facilitate Diels–Alder reactions is not limited to products that contain three-membered rings, as reductive opening by SmI_2 can be used to produce a product that lacks a cyclopropane but retains a quaternary stereogenic center.



The Diels–Alder reaction serves as a benchmark for efficiency and selectivity for the generation of molecular complexity.[1] Despite the impressive advances in the development of the Diels–Alder reaction, challenges still remain for engaging highly substituted dienophiles in selective cycloaddtions. For many years, cyclopropenes have been recognized as reactive dienophiles in the Diels–Alder reaction,[2] and high diastereoselectivity has been observed in the Diels–Alder reactions of cyclopropenes with C-3 hydrogens.[3] The high diastereoselectivity in such cyclopropene Diels–Alder reactions has been attributed to an attractive C–H π interaction between the allylic C–H and the diene via an *endo*, C–H *syn* transition state.,[3b,c] although the origin of stereocontrol is debated.[3d,e] Given this strong preference for *endo*-selectivity, we hypothesized that cyclopropenes should be able to dominate over other stereochemical directors that may be present in cycloaddition reactions. In particular, we hoped to develop chiral cyclopropenyl ketones (**A**) as tools for setting relative stereochemistry in cycloadditions (Scheme 1) in which the cyclopropene can override the carbonyl as a directing group and thereby control the stereochemical fate of Diels–Alder cycloadditions. As cyclopropanes can readily be cleaved, such strategies would not be limited to products that contain three-membered rings.

Scheme 1. Chiral Cyclopropenyl Ketones: Highly Reactive Dienophiles in Which the Cyclopropene Directs the Stereochemical Outcome



The Diels–Alder chemistry of cyclopropenes dates back to classic experiments by Wiberg in 1960.[2] Boger has elegantly described the reactions of cyclopropenone ketals with electron-deficient dienes, electron-rich dienes, and neutral dienes[4] and thereby established the ability of cyclopropenone ketals to cross the traditional boundaries of normal and inverse-electron-demand Diels–Alder reactivity.[5,6] However, there were relatively few studies of Diels–Alder reactions of chiral cyclopropenes, especially for derivatives that can be prepared in enantiomerically pure form.[7,8]

Among chiral cyclopropene derivatives, cycloprop-2-ene carboxylates are attractive synthetic building blocks that can be directly accessed via reactions of diazoesters with alkynes.[9] Through asymmetric catalysis or resolution, cycloprop-2-ene carboxylates can be prepared in enantiomerically enriched form with excellent substrate scope.[9] Although Diels–Alder reactions of cycloprop-2-ene carboxylic esters were first described in 1961,[8g] the scope of reactivity for such dienophiles had been limited.[8] One limitation had been the poor scope of reactivity for derivatives with 2,3-disubstitution. Cyclopentadiene had been shown to combine with methyl 2,3-diphenylcycloprop-2-ene carboxylate[8g] and methyl 2,3-dipropylcycloprop-2-ene carboxylate.[8j] Methyl 2,3-diphenylcycloprop-2-ene carboxylate also reacts with the cyclone from 1,3-diphenylacetone and acenaphthylene.[8h,j] However, the reactions of 2,3-dimethylbutadiene with either methyl 2,3-diphenylcycloprop-2-ene carboxylate or 2,3-diphenylcycloprop-2-ene carboxylic acid were reported to be sluggish, producing only low yields after prolonged reflux (eq 1).[8g,10]

A second limitation was that the vast majority of Diels–Alder reactions with derivatives of cycloprop-2-ene carboxylates involved combination with cyclopentadiene,[8] and few studies have engaged less reactive dienes. Corey and co-workers have demonstrated that the reaction of enantiomerically enriched ethyl 2-pentylcycloprop-2-enecarboxylate with 2,3-dimethylbu-

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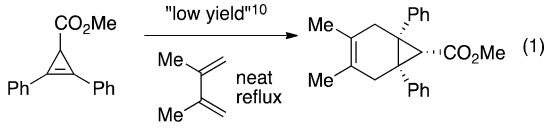
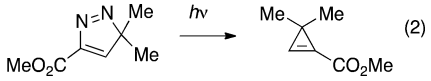


tadiene gives a single diastereomer in 89% yield.[8a] In 2008, our group described *endo*-selective Diels–Alder reactions in which 3-(cycloprop-2-en-1-oyl)-3*H*-benxooxazol-2-one combined with cyclopentadiene, 1,3-cyclohexadiene, and 1,3-octadiene in 64–95% yield.[8f]

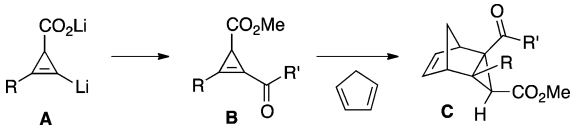
One approach to enhancing the reactivity of cyclopropenes in Diels–Alder reactions has been to activate the alkene through conjugation to an ester.[11,12] Most studied have been methyl 3,3-dimethylcycloprop-1-enecarboxylate and related derivatives, which can engage a range of cyclic and acyclic dienes.[12] This reactive dienophile can be produced by photochemical nitrogen extrusion of methyl 3,3-dimethyl-3*H*-pyrazole-5-carboxylate (eq 2), as first shown by Franck-



Neumann.[12a] Elegant studies by Rigby and co-workers have shown that the pyrazole precursor can also function in Diels–Alder reactions and that photochemical nitrogen extrusion yields the complementary stereoisomer relative to direct Diels–Alder reaction of 3,3-dimethylcycloprop-1-ene carboxylate.[12d,e] Together, these ester-conjugated cyclopropenes have enhanced Diels–Alder reactivity, but the dienophile scope has been restricted to a narrow set of achiral cyclopropenes with *gem*-dimethyl substition at C-3.

We hypothesized that Diels–Alder reactions of cyclopropenyl ketones **B** would be powerful tools for carbocyclic ring construction (Scheme 2). Because **B** is doubly activated

Scheme 2. Dianions of Cyclopropene Carboxylates as Precursors to Dienophiles

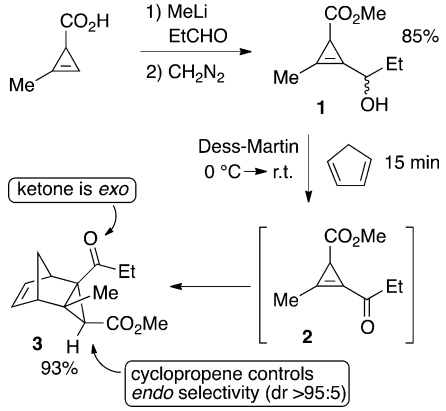


(by strain, and as an α,β-unsaturated ketone), it was expected to be a highly reactive dienophile. Diels–Alder reactions of **B** were also expected to be regioselective (controlled by the polarity of the enone) and stereoselective (controlled by the allylic hydrogen of the cyclopropene). We hypothesized that chiral dianions **A**[12] could be used to prepare cyclopropenyl ketones **B** (Scheme 2). 1-Lithiocyclopropenes have been used to stage intramolecular Diels–Alder reactions in elegant studies by Magnus[13] and Boger.[14]

In prior studies, it was shown that dianions **A** are much more stable than the monoanions of the corresponding esters.[15] It was also established that aldehydes react with lithio cyclopropenes of structure **A**.[16] We sought to learn if the resulting alcohols could be oxidized to create α,β-unsaturated cyclopropenyl ketones. It was unknown if the cyclopropene or the acyl group would direct the *endo*-selectivity of the reaction, or if a mixture of products would result.[16]

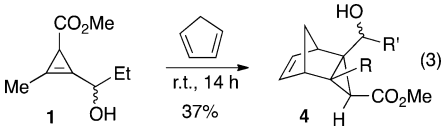
Studies were initiated by adding propanal to the dianion of 2-methylcycloprop-2-enecarboxylic acid (Scheme 3). After work-

Scheme 3. Dianion Approach to Cyclopropene Functionalization Followed by Oxidation and Cycloaddition with Cyclopentadiene



up, the crude hydroxyl acid was directly esterified with diazomethane to provide **1**. Compound **1** was then oxidized using Dess–Martin periodinane in a solution of freshly distilled cyclopentadiene and CH_2Cl_2 at 0 °C. The reaction proceeded with warming to rt, and within 15 min **1** was completely consumed and the product **3** was formed in 93% yield. The cyclopropene dominates the *endo*-selectivity[18] in the cycloaddition to give **3** as only one detectable diastereomer (>95:5 dr). While cyclopropenyl ketones can be generated and reacted in situ, they can also be isolated. Thus, compounds **6** and **8** (see Scheme 4) could be formed by Dess–Martin oxidation of the corresponding alcohols in 86% and 89% yield, respectively, and were found to be stable over a period of weeks when stored neat in the freezer.

The reactivity of tetrasubstituted alkene **2** toward cyclopentadiene is a striking contrast to the reactivity of precursor **1**. Without oxidation, alcohol **1** reacts only sluggishly with cyclopentadiene. After 14 h at rt in CH_2Cl_2, adduct **4** was formed in only 37% yield as a 4:1 mixture of diastereomers (eq 3). Both diastereomers were shown to be *endo* by oxidizing the



mixture with Dess–Martin periodinane to give **3** as the sole convergent product and by characterization of the 3,5-dinitrophenyl ester of the major diastereomer of **4** by X-ray diffraction.

The scope of the Diels–Alder reactions of cyclopropenyl ketones is further elaborated in Scheme 4. The reaction of **1** with 1,3-cyclohexadiene in the presence of Dess–Martin reagent produced a 90% yield of adduct **5** as a single diastereomer (>95:5 dr). The reaction of ketone **6** with 1-methoxy-1,3-cyclohexadiene was found to be sluggish at rt and in nonpolar solvents. The ideal conditions for this reaction, and several of the subsequent reactions, were to combine the purified enone in ethanol at 75 °C for 4 h. Under these conditions, the reaction proceeded to give **7** in 82% yield. The reaction of **8** with 2,3-dimethylbutadiene when subjected to identical reaction conditions produced **9** in 78% yield. The reaction of **8** with furan resulted in an 81% yield of **10** as a 2:1 mixture of diastereomers.[18] The low stereoselectivity with furan

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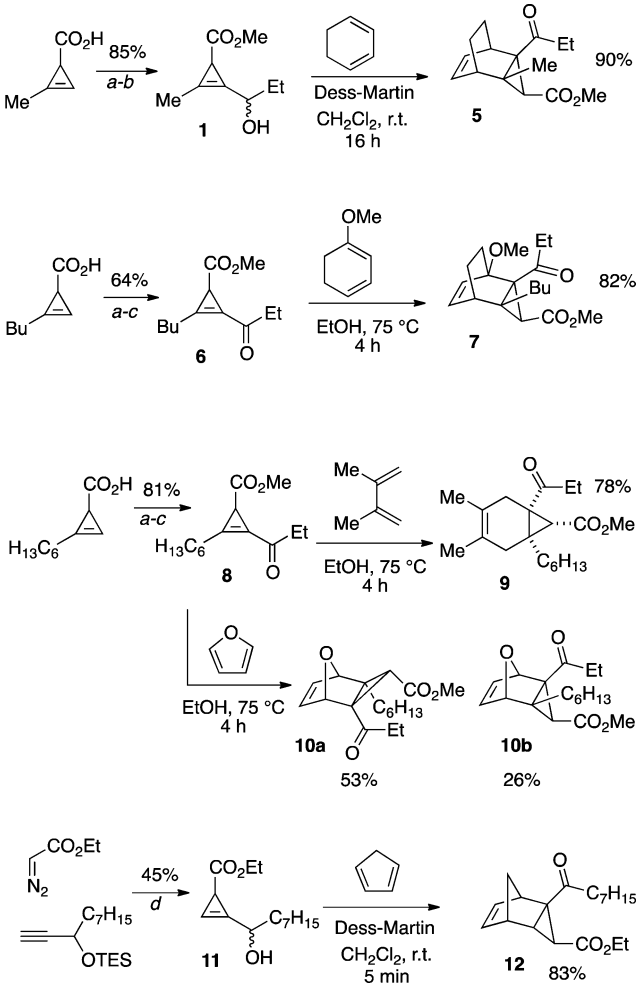
Scheme 4. Diels–Alder Reactions of Cyclopropenyl Ketones[a]

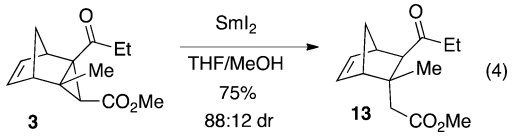


[a]Key: (a) MeLi, propanal; (b) CH_2N_2; (c) Dess–Martin periodinane; (d) $Rh_2(OAc)_4$ (0.5 mol %), then TBAF.

is precedented by the Diels–Alder reaction between furan and cyclopropene.[17]

While 2,3-disubstituted cyclopropene carboxylates were constructed using dianion chemistry, cyclopropene **11** could be prepared in one pot from 3-triethylsiloxy-1-decyne. Diels–Alder reaction with in situ oxidation by Dess–Martin periodinane gave an 83% yield of adduct **12** (Scheme 4, bottom). Unfortunately, our attempts to use 1,3-octadiene and 1,3-cycloheptadiene were unsuccessful and led only to decomposition products under forcing conditions. Danishefsky's diene does react with the enone **2**, but the isolated product is not a simple 4 + 2 adduct. Exploration of the reactivity of silyloxy dienes with cyclopropenyl ketones is ongoing.

As the Diels–Alder adducts in Schemes 3 and 4 are 1,2-diacylcyclopropanes, it was anticipated that the cyclopropane rings could be opened under reductive conditions and thereby translate the chirality of cyclopropene carboxylates to compounds that lack 3-membered rings. Indeed, compound **3** readily opens upon treatment with SmI_2 to provide **13** in 75% yield as an 88:12 mixture of diastereomers (eq 4). The major diastereomer was assigned through an NOE experiment.



(4)

In summary, the synthesis and Diels–Alder reactivity of cyclopropenyl ketones are described. These dienophiles can readily be prepared via additions of aldehydes with dianions of chiral cycloprop-2-ene carboxylic acids. Cyclopropenyl ketones are significantly more reactive than their allylic alcohol precursors, and can engage a range of cyclic dienes and 2,3-dimethylbutadiene. This strategy of using cyclopropenyl ketones to facilitate Diels–Alder reactions is not limited to the synthesis of products that contain 3-membered rings. Reductive opening by SmI_2 provides a method for synthesizing products that lack a cyclopropane ring but still retain a quaternary stereogenic center.

EXPERIMENTAL SECTION

Diastereomers of Methyl 2-(1-Hydroxypropyl)-3-methylcycloprop-2-enecarboxylate (1). To a dried 25 mL flask was added 2-methylcycloprop-2-enecarboxylic acid[19] (120 mg, 1.23 mmol). THF (7.7 mL) was added via syringe, and the solution was cooled (−78 °C). MeLi (1.70 mL of a 1.6 M solution in Et_2O, 2.70 mmol) was added via syringe. After 10 min, the cold bath was removed and stirring continued until an internal temperature of ∼0–5 °C was reached. To the yellow solution was added propionaldehyde (185 mg, 232 μL, 3.19 mmol) via syringe. After being stirred at rt for 10 min, the reaction was quenched with 15 mL of water, and aq. 3 M HCl was added to render the solution acidic (pH 1–2). NaCl was added to saturate the aqueous layer. The aqueous phase was extracted eight times with ethyl acetate. The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was then taken up in 75 mL of diethyl ether and transferred to a 125 mL Erlenmeyer flask. Diazald (789 mg, 3.68 mmol) was taken up in 75 mL of absolute ethanol in a Lombardi flask.[15] Behind a blast shield, NaOH (1.13 g, 28.2 mmol) in 2.8 mL of water was added dropwise, and the resulting diazomethane was bubbled into the flask containing the cyclopropene using a stream of nitrogen. After the diazomethane solution had changed from yellow to colorless, nitrogen was bubbled for an additional 15 min. The solution was concentrated and the residue chromatographed (5–30% ethyl acetate in hexanes) to provide 175 mg (84%) of a 53:47 (NMR) mixture of diastereomers as a clear oil. An 85% yield was obtained in a repetition on 289 mg scale: ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 4.45–4.68 (m, 1H), 3.69 (s, 3H), 2.22 (s, 1H), 2.13 (s, 3H), 1.70–1.80 (m, 2H), 1.01 (t, J = 7.5 Hz, 3H, minor diastereomer), 0.96 (t, J = 7.54 Hz, 3H, major diastereomer); ^{13}C NMR ($CDCl_3$, 90 MHz, δ) 177.12 (C), 177.06 (C), 107.4 (C), 107.2 (C), 105.0 (C), 104.9 (C), 68.2 (CH), 67.6 (CH), 51.6 (CH_3, two overlapping peaks), 28.9 (CH_2), 28.3 (CH_2), 22.8 (CH_3), 22.7 (CH_3), 9.93 (CH_3), 9.92 (CH_3), 9.48 (CH_3), 9.45 (CH_3); IR (neat, cm^{-1}): 3440, 2964, 2879, 1727, 1437, 1249, 1198, 974; HRMS-ESI m/z [M + Na] calcd for $C_9H_{14}O_3Na$ 193.0841, found 193.0837.

(*rel*-1*S*,2*S*,4*S*,5*R*)-Methyl 2-Methyl-4-propionyltricyclo-[3.2.1.0^{2,4}]oct-6-ene-3-carboxylate (3). A 4-dram vial equipped with a stirbar was charged with **1** (35 mg, 0.20 mmol). CH_2Cl_2 (0.4 mL) was added followed by cyclopentadiene (135 mg, 168 μL, 2.04 mmol) and Dess–Martin periodinane (DMP, 130 mg, 0.307 mmol). After 5 min, the solution was filtered through Celite using diethyl ether. Chromatography (5 – 10% ethyl acetate in hexanes) gave 43 mg (90%) of the title compound. The yield was 95% for a repetition on 175 mg scale. For larger scale preparations, it was necessary to cool the reaction mixture during the addition of DMP: inseparable diastereomers were obtained if this precaution was not taken (plausibly due to the exothermicity of DMP solvation). Thus, a 25 mL flask was charged with **1** (831 mg, 4.89 mmol). CH_2Cl_2 was added (9.8 mL) followed by cyclopentadiene (3.2 g, 4.0 mL, 49 mmol). The

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solution was cooled in an ice bath for 5 min, and DMP (3.1 g, 7.3 mmol) was added. The solution was allowed to stir for an additional 5 min before removing the ice bath and allowing it to warm to rt with stirring for 20 min. Purification gave 1.05 g (91%) of the title compound as a clear oil. ^{1}H NMR ($CDCl_3$, 400 MHz, δ) 6.06−6.09 (m, 1H), 6.01−6.04 (m, 1H), 3.67 (s, 3H), 3.27−3.33 (m, 1H), 2.76−2.79 (m, 1H), 2.53−2.71 (m, 2H), 2.08 (s, 1H), 1.97−2.01 (m, 1H), 1.75−1.80 (m, 1H), 1.50 (s, 1H), 1.07 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz, δ) 207.6 (C), 169.8 (C), 134.5 (CH), 133.4 (CH), 60.6 (C), 51.6 (CH_3), 51.5 (CH), 47.8 (CH), 43.1 (CH_2), 41.6 (CH), 38.2 (C), 34.1 (CH_2), 13.3 (CH_3), 7.7 (CH_3); IR (neat, cm^{-1}) 2974, 2874, 1729, 1680, 1436, 1219, 1042, 753; HRMS-ESI m/z [M + Na] calcd for $C_{14}H_{18}O_3Na$ 257.1154, found 257.1161.

***rel*-(1*S*,2*S*,4*S*,5*S*)-Methyl 2-Methyl-4-propionyltricyclo-[3.2.2.0^{2,4}]non-6-ene-3-carboxylate (5).** Compound **1** (37 mg, 0.22 mmol) was added to a 4-dram vial equipped with a stirbar. CH_2Cl_2 (0.5 mL) was added followed by 1,3-cyclohexadiene (52 mg, 62 μL, 0.65 mmol) and Dess−Martin periodinane (138 mg, 0.326 mmol). After 16 h at rt, the solution was filtered through Celite using diethyl ether. Chromatography (5 − 10% ethyl acetate in hexanes) gave 47 mg (87%) of the title compound as a clear oil. The yield was 93% for a repetition on 44 mg scale: ^{1}H NMR ($CDCl_3$, 400 MHz, δ) 5.98−6.05 (m, 1H), 5.91−5.98 (m, 1H), 3.61 (s, 3H), 2.84−2.94 (m, 1H), 2.38−2.65 (m, 3H), 1.86−1.95 (m, 1H), 1.77 (s, 1H), 1.60−1.68 (m, 1H), 1.36 (s, 3H), 1.05−1.16 (m, 5H); ^{13}C NMR ($CDCl_3$, 90 MHz, δ) 208.2 (C), 171.8 (C), 131.7 (CH), 129.1 (CH), 51.7 (CH_3), 40.1 (C), 38.4 (CH), 34.5 (CH_2), 34.0 (CH), 28.1 (C), 27.3 (CH), 21.8 (CH_2), 21.1 (CH_2), 11.4 (CH_3), 7.9 (CH_3); IR (neat, cm^{-1}) 2947, 2875, 1726, 1437, 1325, 1201, 1148, 863; HRMS-ESI m/z [M + Na] calcd for $C_{15}H_{20}O_3Na$ 271.1310, found 271.1317.

Diastereomers of Methyl 2-Butyl-3-(1-hydroxypropyl)-cycloprop-2-enecarboxylate. The procedure was identical to that used to prepare **1** using 2-butylcycloprop-2-enecarboxylic acid[20] (427 mg, 3.05 mmol), THF (19 mL), MeLi (4.19 mL of a 1.6 M solution in Et_2O, 6.7 mmol), and propionaldehyde (460 mg, 576 μL, 7.93 mmol) for the first step and Diazald (1.96 g, 9.15 mmol), ethanol (175 mL), NaOH (2.81 g, 70.2 mmol), and water (7 mL) in the second step. The procedure gave 471 mg (73%) of a 56:44 (NMR) mixture of diastereomers as a clear oil. When repeated on 223 mg scale, the yield was 72%: ^{1}H NMR ($CDCl_3$, 400 MHz, δ) 4.57−4.66 (m, 1H, major diastereomer), 4.47−4.57 (m, 1H, minor diastereomer), 3.67 (s, 3H), 2.46 (t, J = 7.57 Hz, 2H), 2.22 (s, 1H), 2.04−2.16 (m, 1H), 1.66−1.81 (m, 2H), 1.50−1.60 (m, 2H), 1.32−1.43 (m, 2H), 0.89−1.02 (m, 6H); ^{13}C NMR ($CDCl_3$, 90 MHz, δ) 177.2 (C, 2 overlapping peaks), 109.2 (C), 108.9 (C), 106.7 (C), 106.4 (C), 68.3 (CH), 67.7 (CH), 51.63 (CH_3), 51.59 (CH_3), 29.03 (CH_2), 29.01 (CH_2), 28.97 (CH_2), 28.3 (CH_2), 24.29 (CH_2), 24.28 (CH_2), 22.4 (CH_2, 2 overlapping peaks), 21.8 (CH, 2 overlapping peaks), 13.8 (CH_3, 2 overlapping peaks), 9.51 (CH_3), 9.49 (CH_3); IR (neat, cm^{-1}) 3439, 2960, 2875, 1726, 1705, 1436, 1201, 992; HRMS-ESI m/z [M − OH] calcd for $C_{12}H_{19}O_2$ 195.1385, found 195.1382.

Methyl 2-Butyl-3-propionylcycloprop-2-enecarboxylate (6). A 10 mL flask was charged with methyl 2-butyl-3-(1-hydroxypropyl)-cycloprop-2-enecarboxylate (187 mg, 0.880 mmol) and CH_2Cl_2 (1 mL). Dess−Martin periodinane (DMP, 560 mg, 1.32 mmol) was added, and the solution was stirred at rt for 15 min. Excess DMP was filtered on Celite. Solvent removal and chromatography (5% ethyl acetate in hexanes) gave 163 mg (88%) of the title compound as a yellow oil. When repeated on 603 mg scale, the yield was 83%: ^{1}H NMR ($CDCl_3$, 400 MHz, δ) 3.68 (s, 3H), 2.64−2.84 (m, 4H), 2.47 (s, 1H), 1.62−1.72 (m, 2H), 1.35−1.47 (m, 2H), 1.16 (t, J = 7.4 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz, δ) 191.7 (C), 174.0 (C), 124.9 (C), 104.3 (C), 51.8 (CH_3), 36.7 (CH_2), 28.6 (CH_2), 26.0 (CH_2), 23.5 (CH), 22.4 (CH_2), 13.7 (CH_3), 7.8 (CH_3); IR (neat, cm^{-1}) 2958, 2875, 1853, 1729, 1685, 1436, 1343, 1256, 1176, 1027, 802; HRMS-ESI m/z [M + H], calcd for $C_{12}H_{19}O_3$ 211.1334, found 211.1330.

***rel*-(1*S*,2*S*,4*S*,5*S*)-Methyl 4-Butyl-1-methoxy-2-propionyltricyclo[3.2.2.0^{2,4}]non-6-ene-3-carboxylate (7).** To a 4-dram vial equipped with a stirbar were added **6** (50.4 mg, 0.240 mmol), 1-methoxy-1,3-cyclohexadiene (technical grade, 65% pure, 107 mg, 115 μL, 0.720 mmol), and ethanol (0.5 mL). The cap was replaced, and the vial was heated in a 75 °C oil bath for 4 h. The solvent was stripped, and the residue chromatographed on silica (5−15% ether in hexanes) to provide 61 mg (80%) of the title compound as a clear oil. When repeated on 185 mg scale the yield was 81%: ^{1}H NMR ($CDCl_3$, 400 MHz, δ) 6.14 (d, J = 8.5, 1H), 5.93 (dd, J = 8.5, 6.8 Hz, 1H), 3.62 (s, 3H), 3.34 (s, 3H), 2.66−2.73 (m, 1H), 2.38−2.58 (m, 2H), 2.02−2.12 (m, 1H), 1.86−1.93 (m, 1H), 1.75−1.85 (m, 2H), 1.61−1.70 (m, 1H) 1.17−1.46 (m, 5H), 1.03 (t, J = 7.3 Hz, 3H), 0.90−0.80 (m, 1H), 0.83 (t, J = 7.3 Hz, H); ^{13}C NMR ($CDCl_3$, 90 MHz, δ) 207.2 (C), 171.9 (C), 129.9 (CH), 129.0 (CH), 82.2 (C), 52.3 (CH_3), 51.7 (CH_3), 44.2 (C), 37.5 (CH_2), 34.1 (CH), 33.1 (C), 29.6 (CH_2), 25.6 (CH_2), 25.3 (CH), 24.0 (CH_2), 23.6 (CH_2), 22.8 (CH_2), 14.1 (CH_3), 8.0 (CH_3); IR (neat, cm^{-1}) 3054, 2932, 2833, 1731, 1617, 1437, 1344, 1193, 932, 705; HRMS-ESI m/z [M + H] calcd for $C_{19}H_{29}O_4$ 321.2066, found 321.2057.

Diastereomers of Methyl 2-Hexyl-3-(1-hydroxypropyl)-cycloprop-2-enecarboxylate. The procedure was identical to that used to prepare **1** using 2-hexylcycloprop-2-enecarboxylic acid[19] (1.32 g, 7.86 mmol), THF (49 mL), MeLi (10.8 mL of a 1.6 M solution in Et_2O, 17.3 mmol), and propionaldehyde (1.19 g, 1.49 mL, 20.4 mmol) for the first step and Diazald (5.05 g, 23.6 mmol), ethanol (150 mL), NaOH (7.23 g, 181 mmol), and water (18 mL) in the second step. The procedure gave 1.73 g (91%) of a 65:35 (NMR) mixture of diastereomers as a clear oil. The yield was 90% for a repetition on 611 mg scale: ^{1}H NMR ($CDCl_3$, 400 MHz, δ) 4.55−4.64 (m, 1H, major diastereomer), 4.46−4.55 (m, 1H, minor diastereomer), 3.66 (s, 3H), 2.44 (t, J = 7.3 Hz, 2H), 2.26−2.34 (bs, 1H), 2.20 (app s, 1H), 1.65−1.78 (m, 2H), 1.51−1.59 (m, 2H), 1.25−1.35 (m, 6H), 0.98 (t, J = 7.2 Hz, 3H minor diastereomer), 0.93 (t, J = 7.2 Hz, 3H, major diastereomer), 0.87 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz, δ) 177.2 (C, two overlapping peaks), 109.1 (C), 108.9 (C), 106.7 (C), 106.4 (C), 68.3 (CH), 67.6 (CH), 51.6 (CH_3), 51.6 (CH_3), 31.5 (CH_2, 2 overlapping peaks), 29.0 (CH_2), 28.9 (CH_2), 28.3 (CH_2, 2 overlapping peaks), 26.89 (CH_2), 26.86 (CH_2), 24.6 (CH_2), 24.5 (CH_2), 22.6 (CH_2, 2 overlapping peaks), 22.4 (CH), 21.8 (CH), 14.1 (CH_3, 2 overlapping peaks), 9.6 (CH_3), 9.5 (CH_3); IR (neat, cm^{-1}) 3432, 2926, 1897, 1723, 1436, 1344, 1202, 976, 734; HRMS-ESI m/z [M + Na] calcd for $C_{14}H_{24}O_3Na$ 263.1623, found 263.1622.

Methyl 3-Hexyl-2-propionylcycloprop-2-enecarboxylate (8). To a 25 mL flask was added methyl 2-hexyl-3-(1-hydroxypropyl)-cycloprop-2-ene carboxylate (1.57 g, 6.55 mmol), which was then dissolved in CH_2Cl_2 (8 mL). Dess−Martin periodinane (DMP, 4.17 g, 9.83 mmol) was added, and the solution was stirred at rt for 15 min. Excess DMP was filtered on Celite. Solvent removal and chromatography (5% ethyl acetate in hexanes) gave 1.43 g (92%) of the title compound as a yellow oil. The yield was 85% for a repetition on 339 mg scale: ^{1}H NMR ($CDCl_3$, 400 MHz, δ) 3.66 (s, 3H), 2.60−2.81 (m, 4H), 2.45 (s, 1H), 1.59−1.71 (m, 2H), 1.24−1.41 (m, 6H), 1.13 (t, J = 7.3 Hz, 3H), 0.86 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz, δ) 191.6 (C), 174.0 (C), 124.9 (C), 104.2 (C), 51.8 (CH_3), 36.7 (CH_2), 31.3 (CH_2), 28.9 (CH_2), 26.5 (CH_2), 26.2 (CH_2), 23.4 (CH), 22.5 (CH_2), 14.0 (CH_3), 7.7 (CH_3); IR (neat, cm^{-1}) 3449, 2934, 2860, 1853, 1731, 1685, 1436, 1343, 1176, 1028, 802; HRMS-ESI m/z [M + H] calcd for $C_{14}H_{23}O_3$ 239.1647, found 239.1638.

***rel*-(1*R*,6*R*)-Methyl 1-Hexyl-2,5-dimethyl-6-propionylbicyclo[4.1.0]hept-3-ene-7-carboxylate (9).** To a 4-dram vial equipped with a stirbar were added **8** (20 mg, 0.84 mmol), 2,3-dimethylbutadiene (20.7 mg, 29.0 μL, 0.252 mmol), and ethanol (0.25 mL). The cap was replaced, and the vial was heated in a 75 °C oil bath for 3 h. The solvent was stripped and the residue chromatographed (0−10% ether in hexanes) to produce 22 mg (81%) of the title compound as a clear oil. The yield was 76% for a repetition on 34 mg scale: ^{1}H NMR ($CDCl_3$, 400 MHz, δ) 3.63 (s, 3H), 2.43−2.58 (m, 2H), 2.18−2.38 (m, 4H), 1.92 (s, 1H), 1.67−1.82 (m, 2H), 1.58 (s, 6H), 1.12−1.35−1.51 (m, 1H), 1.19−1.28 (m, 6H), 1.00−1.10 (m, 1H), 1.05 (t, J = 7.0 Hz, 3H), 0.85 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz, δ) 208.2 (C), 171.7 (C), 122.7 (CH), 120.8 (CH), 51.5 (CH_3), 44.4 (C), 36.5 (CH_2), 34.9 (C), 34.7 (CH_2), 33.9 (CH_2),

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31.8 (CH_2), 30.2 (CH_2), 29.7 (C), 29.6 (CH), 26.8 (CH_2), 22.6 (CH_2), 19.0 (CH_3), 18.8 (CH_3), 14.0 (CH_3), 8.0 (CH_3); IR (neat, cm^{-1}) 3430, 2928, 1725, 1437, 1178, 988; HRMS-ESI m/z [M + Na] calcd for $C_{20}H_{32}O_3Na$ 343.2249, found 343.2246.

***rel*-(1*R*,2*R*,3*R*,4*R*,5*S*)-Methyl 2-Hexyl-4-propionyl-8-oxatricyclo[3.2.1.0^{2,4}]oct-6-ene-3-carboxylate (10a) and *rel*-(1*S*,2*R*,3*R*,4*R*,5*R*)-Methyl 2-Hexyl-2-propionyl-8-oxatricyclo-[3.2.1.0^{2,4}]oct-6-ene-3-carboxylate (10b).** To a 4-dram vial equipped with a stirbar were added **8** (40.0 mg, 0.168 mmol), furan (34.3 mg, 37.0 μL, 0.504 mmol), and ethanol (0.5 mL). The cap was replaced, and the vial was heated in a 75 °C oil bath for 4 h. The solvent was stripped, and the residue was chromatographed on silica (5−15% ether in hexanes) to produce 27 mg (53%) of the major diastereomer and 14 mg (26%) of the minor diastereomer of the title compound as clear oils. A repetition on 32 mg scale gave 60% and 21% of the two diastereomers: ^{1}H NMR ($CDCl_3$, 400 MHz, δ) major diastereomer (**10a**) 6.74 (dd, J = 1.6, 4.1 Hz, 1H), 6.63 (dd, J = 1.6, 4.1, 1H), 4.96 (d, J = 1.5 Hz, 1H), 4.79 (d, J = 1.5 Hz, 1H), 3.68 (s, 3H), 3.02 (s, 1H), 2.29−2.55 (m, 2H), 1.94−2.06 (m, 1H), 1.24−1.50 (m, 9H), 1.03 (t, J = 7.1 Hz, 3H), 0.88 (t, J = 6.7 Hz, 3H); minor diastereomer 6.35 (dd, J = 1.7, 4.0 Hz, 1H), 6.26 (dd, J = 1.7, 4.0 Hz, 1H), 5.35 (app t, J = 1.7 Hz), 4.90 (app t, J = 1.7 Hz, 1H), 3.69 (s, 3H), 2.65−2.86 (m, 2H), 2.24 (s, 1H), 1.90−2.07 (m, 1H), 1.70−1.84 (m, 1H), 1.24−1.60 (m, 8H), 1.08 (t, J = 7.2 Hz, 3H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz, δ) major diastereomer 205.8 (C), 169.3 (C), 138.8 (CH), 137.8 (CH), 80.5 (CH), 79.4 (CH), 51.8 (CH_3), 49.0 (C), 47.3 (C), 36.29 (CH_2), 36.27 (CH), 31.7 (CH_2), 29.5 (CH_2), 28.4 (CH_2), 24.1 (CH_2), 22.6 (CH_2), 14.1 (CH_3), 7.4 (CH_3); minor diastereomer (**10b**) 206.1 (C), 167.9 (C), 133.4 (CH), 133.1 (CH), 83.7 (CH), 81.8 (CH), 51.8 (CH_3), 45.6 (CH), 45.5 (C), 44.7 (C), 33.4 (CH_2), 31.7 (CH_2), 29.6 (CH_2), 28.1 (CH_2), 25.6 (CH_2), 22.6 (CH_2), 14.1 (CH_3), 7.6 (CH_3); IR (neat, cm^{-1}) major diastereomer 2929, 2858, 1729, 1438, 1171, 908; minor diastereomer 2930, 2857, 1742, 1689, 1437, 1176, 864; HRMS-ESI m/z [M + Na] calcd for $C_{18}H_{26}O_4Na$, 329.1729, found 329.1743.

3-Triethylsiloxydecyne. A flask was charged with dec-1-yn-3-ol[21] and THF (54 mL) and cooled to 0 °C in an ice bath. After the solution was stirred for 10 min, DBU (1.97 g, 1.94 mL, 13.0 mmol) and TESCl (1.63 g, 1.81 mL, 10.8 mmol) were added, and the solution was stirred overnight while warming to rt. The solution was diluted with 50 mL of diethyl ether and washed twice with equal amounts of water and once with brine. The combined organics were dried (Na_2SO_4), filtered, and concentrated. The residue was chromatographed (0−5% ether in hexanes) to provide 2.31 g (80%) of the title compound as a clear oil. A repetition on 765 mg scale gave 90%: ^{1}H NMR ($CDCl_3$, 400 MHz, δ) 4.33 (td, J = 4.5, 2.1, 1H), 2.36 (d, J = 2.1 Hz, 1H), 1.61−1.72 (m, 2H), 1.36−1.49 (m, 2H), 1.22−1.34 (m, 8H), 0.97 (t, J = 8.0 Hz, 9H), 0.88 (t, J = 6.9 Hz, 3H), 0.59−0.71 (m, 6H); ^{13}C NMR ($CDCl_3$, 90 MHz, δ) 85.6 (C), 71.8 (CH), 62.5 (CH), 38.7 (CH_2), 31.8 (CH_2), 29.3 (CH_2, 2 overlapping peaks), 25.1 (CH_2), 22.7 (CH_2), 14.1 (CH_3), 6.8 (CH_3), 4.7 (CH_2); IR (neat, cm^{-1}) 3312, 2877, 1460, 1240, 1095, 1006, 745; HRMS-ESI m/z [M-C_2H_5], calcd for $C_{14}H_{27}OSi$ 239.1831, found 239.1827.

Diastereomers of Ethyl 2-(1-Hydroxyoctyl)cycloprop-2-ene-carboxylate (11). To a dried 10 mL flask were added 3-triethylsiloxydec-1-yne (0.520 g, 1.94 mmol), $Rh_2(OAc)_4$ (1.4 mg, 0.0032 mmol), and 0.25 mL of CH_2Cl_2. Ethyl diazoacetate (84.7 mg, 77.0 μL, 0.646 mmol) in 0.25 mL of $CH_2Cl_2$was added at a rate of 1 mL/h. After the addition was complete, the mixture was stirred for 5 min before being concentrated. TBAF (0.74 mL of a 1.0 M solution in THF) was added and the mixture stirred for 5 min. The solvents were stripped, and the residue was chromatographed (5−15% ether in hexanes) to produce 74.8 mg (48%) of the title compounds as a clear oil. The yield was 41% for a repetition on 177 mg scale. Small peaks attributed to impurities were observed at 2.4 ppm in the ^{1}H NMR spectrum and at 68, 53, and 28 and 20.8 ppm in the ^{13}C NMR. Compound **11** is only moderately stable and was immediately carried forward in the subsequent oxidation/Diels−Alder reaction: ^{1}H NMR ($CDCl_3$, 400 MHz, δ) 6.51 (s, 1H), 4.57−4.67 (m, 1H), 4.05−4.15 (m, 2H), 3.37 (bs, 1H), 2.25 (app s, 1H), 1.59−1.76 (m, 2H), 1.19−1.42 (m, 13H), 0.81−0.86 (t, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz, δ) 176.48 (C), 176.46 (C), 117.0 (C), 116.8 (C), 96.1 (CH), 96.0 (CH), 66.9 (CH), 66.8 (CH), 60.6 (CH_2, 2 overlapping peaks), 35.2 (CH_2), 35.0 (CH_2), 31.8 (CH_2, 2 overlapping peaks), 29.38 (CH_2), 29.35 (CH_2), 29.2 (CH_2, 2 overlapping peaks), 25.10 (CH_2), 25.05 (CH_2), 22.6 (CH_2, 2 overlapping peaks), 21.0 (CH_2), 20.2 (CH), 14.3 (CH_3), 14.1 (CH_3); IR (neat, cm^{-1}) 3428, 2927, 2856, 1726, 1465, 1185, 724.

***rel*-(1*S*,2*R*,3*S*,5*R*)-Ethyl 2-Octanoyltricyclo[3.2.1.0^{2,4}]oct-6-ene-3-carboxylate (12).** A 4-dram vial was charged with a small stirbar, **11** (66 mg, 0.28 mmol), CH_2Cl_2 (1.1 mL), and freshly distilled cyclopentadiene (183 mg, 233 μL, 2.77 mmol). To this stirred solution was added Dess−Martin periodinane (176 mg, 0.416 mmol). After 5 min, the solution was filtered through Celite using diethyl ether. Chromatography (5−10% ethyl ether in hexanes) gave 72 mg (85%) of the title compound. The yield was 81% for a repetition on 75 mg scale. Small peaks attributed to impurities were observed at 8.03, 7.97, 7.42, 7.19, and 1.42 ppm in the ^{1}H NMR spectrum: ^{1}H NMR ($CDCl_3$, 400 MHz, δ) 5.98−6.09 (m, 1H), 5.89−5.98 (m, 1H), 4.01−4.19 (m, 2H), 3.27 (m, 1H), 3.06 (m, 1H), 2.54−2.68 (m, 3H), 1.88−2.02 (m, 2H), 1.75 (m, 1H), 1.52−1.62 (m, 2H), 1.20−1.30 (m, 11H), 0.86 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 90 MHz, δ) 208.1 (C), 169.6 (C), 134.0 (CH), 132.7 (CH), 63.0 (CH_2), 60.9 (CH_2), 46.9 (CH), 43.3 (CH), 42.3 (C), 41.1 (CH_2), 40.0 (CH), 31.7 (CH_2), 30.9 (CH), 29.18 (CH_2), 29.16 (CH_2), 23.7 (CH_2), 22.6 (CH_2), 14.14 (CH_3), 14.11 (CH_3); IR (neat, cm^{-1}) 2930, 2857, 1729, 1690, 1384, 1184, 1046, 745; HRMS-ESI m/z [M + Na] calcd for $C_{19}H_{28}O_3Na$ 327.1936, found 327.1932.

Methyl 2-((*rel*-1*R*,2*R*,3*R*,4*R*)-2-Methyl-3-propionylbicyclo-[2.2.1]hept-5-en-2-yl)acetate (13). Into a 250 mL flask was placed **3** (643 mg, 2.75 mmol). The flask was evacuated and backfilled with nitrogen. To this were added THF (63.7 mL) and methanol (18.2 mL). A 0.1 M solution of samarium iodide in THF (7−10 equiv) was added dropwise until the reaction was judged complete (TLC). The reaction was quenched (3 M HCl) and diluted with 100 mL of ethyl acetate. The organic layer was separated and sequentially washed with aqueous sodium thiosulfate and brine. The organics were dried (Na_2SO_4), concentrated, and chromatographed on silica (5−7.5% ethyl acetate in hexanes) to give 489 mg (75%) of the title compound as a clear oil as an 88:12 (NMR) mixture of diastereomers. The yield was 74% for a repetition on 152 mg scale: ^{1}H NMR of ($CDCl_3$, 400 MHz, δ) 6.16−6.27 (m, 2H), 3.66 (s, 3H, major diastereomer), 3.58 (s, 3H, minor diastereomer), 2.91 (m, 1H, minor diastereomer), 2.77 (m, 1H, major diastereomer), 2.58 (m, 1H), 2.35−2.55 (m, 2H), 2.10−2.34 (m, 3H), 2.05 (d, J = 9.4 Hz, 1H), 1.58−1.65 (m, 1H, minor diastereomer), 1.43−1.48 (m, 1H, major diastereomer), 1.41 (s, 3H, minor diastereomer), 1.08 (s, 3H, major diastereomer), 1.02 (t, J = 7.2 Hz, 3H, major diastereomer), 0.98 (t, J = 7.2 Hz, 3H, minor diastereomer); ^{13}C NMR ($CDCl_3$, 90 MHz, δ) 213.8 (C), 172.5 (C), 138.1 (CH), 137.1 (CH), 58.2 (CH_3), 53.1 (CH), 51.4 (CH), 47.5 (CH), 46.8 (C), 46.4 (CH_2), 46.2 (CH_2), 38.6 (CH_2), 23.0 (CH_3), 7.6 (CH_3); resonances attributed to the minor diastereomer were observed at: 135.7 (CH), 135.4 (CH), 61.2 (CH_3), 53.5 (CH), 51.1 (CH), 46.5 (CH), 45.2 (C), 41.1 (CH_2), 28.2 (CH_3); IR (neat, cm^{-1}) 2954, 1734, 1459, 1353, 1171, 1013, 714; HRMS-ESI m/z [M + Na] calcd for $C_{14}H_{20}O_3Na$ 259.1310, found 259.1308.

(*rel*-(1*R*,2*S*,4*S*,5*S*)-Methyl 2-(1-Hydroxypropyl)-4-methyl-tricyclo[3.2.1.0^{2,4}]oct-6-ene-3-carboxylate. A dry 1 dram vial was charged with **1** (0.29 mmol, 50 mg) in dichloromethane (0.58 mL). Cyclopentadiene (2.9 mmol, 194 mg) was then added and the mixture allowed to stir at rt for 14 h. Chromatography (hexanes to 50% diethyl ether in hexanes) furnished 26 mg (0.11 mmol, 37%) of the title compound, a clear oil, as a 4:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.04−6.03 (m, 1H), 5.98−5.96 (m, 1H), 4.35−4.33 (dd, J = 8.9, 4.4 Hz, 1H, minor diastereomer) 4.00−3.97 (dd, J = 10.5, 2.8 Hz, 1H, major diastereomer), 3.67 (s, 3H, major diastereomer), 3.60 (s, 3H, minor diastereomer), 3.05 (s, 1H), 2.66 (s, 1H, minor diastereomer), 2.64 (s, 1H, major diastereomer), 2.08−2.07 (m, 1H, minor diastereomer), 1.86−1.84 (m, 1H, major diastereomer), 1.69−1.66 (m, 2H), 1.57−1.50 (m, 3H), 1.53 (s, 3H), 1.09−

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1.07 (t, J = 7.4 Hz, 3H, major diastereomer), 0.96−0.94 (t, J = 7.5 Hz, 3H, minor diastereomer); δ major diastereomer 171.9 (C), 134.3 (CH), 133.5 (CH), 71.1 (CH), 59.6 (CH_2), 51.7 (CH_3), 51.3 (CH), 46.7 (CH), 37.1 (C), 36.9 (CH), 31.3 (C), 27.2 (CH_2), 13.0 (CH_3), 11.37 (CH_3); minor diastereomer: 171.9 (C), 134.4 (CH), 133.3 (CH), 68.4 (CH), 60.8 (CH_2), 51.6 (CH_3), 51.3 (CH), 46.0 (CH), 37.1 (C), 36.5 (CH), 31.3 (C), 29.4 (CH_2), 12.2 (CH_3), 10.5 (CH_3); IR (neat, cm^{-1}) 3446, 2966, 2875, 1727, 1456, 1436, 1329, 1199, 1173; HRMS-EI (M − H_2O) m/z calcd for $C_{14}H_{18}O_2$ 218.1307, found 218.1307.

(*rel*-1*R*,2*S*,4*S*,5*S*)-Methyl 2-(1-((3,5-Dinitrobenzoyl)oxy)-propyl)-4-methyltricyclo[3.2.1.0^{2,4}]oct-6-ene-3-carboxylate. A 10 mL round-bottom flask was charged with (*rel*-(1*R*,2*S*,4*S*,5*S*)-methyl 2-(1-hydroxypropyl)-4-methyltricyclo[3.2.1.0^{2,4}]oct-6-ene-3-carboxylate (50 mg, 0.21 mmol) and 4-dimethylaminopyridine (32 mg, 0.26 mmol) in 2.2 mL of dichloromethane and cooled to 0 °C. To this solution was added 3,5-dinitrobenzoyl chloride (54 mg, 0.23 mmol). The reaction was allowed to warm to rt and stir overnight. The reaction was quenched with aq HCl (1 M). The mixture was extracted with dichloromethane (20 mL × 3), and the combined organics were then dried over magnesium sulfate, filtered, and concentrated onto silica gel. Chromatography (hexanes to 30% diethyl ether in hexanes) yielded 45 mg (0.10 mmol, 48%) of the title compound as a solid as a 3:1 mixture of diastereomers. The major diastereomer crystallized from ethyl acetate/hexane and was analyzed by X-ray crystallography: ^{1}H NMR ($CDCl_3$, 400 MHz) δ major diastereomer 9.26−9.24 (m, 1H), 9.15 (d, J = 2.1 Hz, 2H), 6.15−5.96 (m, 2H), 5.81−5.77 (dd, J = 11.0, 2.9 Hz, 1H), 3.65 (s, 3H), 3.31−3.28 (m, 1H), 2.70 (s, 1H), 2.15−2.05 (m, 2H), 1.79−1.65 (m, 3H), 1.63 (s, 3H), 1.05 (t, J = 7.4 Hz, 3H); minor diastereomer 9.26−9.24 (m, 1H), 9.19 (d, J = 2.1 Hz, 2H), 6.15−5.96 (m, 3H), 3.68 (s, 3H), 3.33−3.30 (m, 1H), 2.65 (s, 1H), 2.15−2.05 (m, 2H), 1.79−1.65 (m, 3H), 1.46 (s, 3H), 0.95−0.92 (t, J = 7.4, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) major diastereomer 169.9 (C), 161.75 (C), 148.6 (C), 134.7 (CH), 134.4 (C), 133.2 (CH), 129.4 (CH), 122.2 (CH), 77.2 (CH), 59.8 (CH_2), 51.8 (CH_3), 51.5 (CH), 47.0 (CH), 36.8 (CH), 36.4 (C), 31.9 (C), 26.1 (CH_2), 13.0 (CH_3), 11.0 (CH_3); minor diastereomer 170.0 (C), 161.4 (C), 148.7 (C), 134.8 (CH), 134.3 (C), 132.8 (CH), 129.4 (CH), 122.3 (CH), 74.8 (CH), 60.4 (CH_2), 51.6 (CH_3), 51.2 (CH), 46.6 (CH), 37.5 (CH), 35.8 (C), 29.7 (C), 27.4 (CH_2), 12.0 (CH_3), 10.2 (CH_3); IR (neat, cm^{-1}) 2926, 1733, 1545, 1344, 1275, 1171, 730, 721; HRMS-EI (M^+) m/z calcd for $C_{21}H_{22}N_2O_8$ 430.1376, found 430.1371.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra. 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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