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Diels–Alder Reactions of γ-Hydroxybutenolides: Approach to the Himbacine Tricyclic Core

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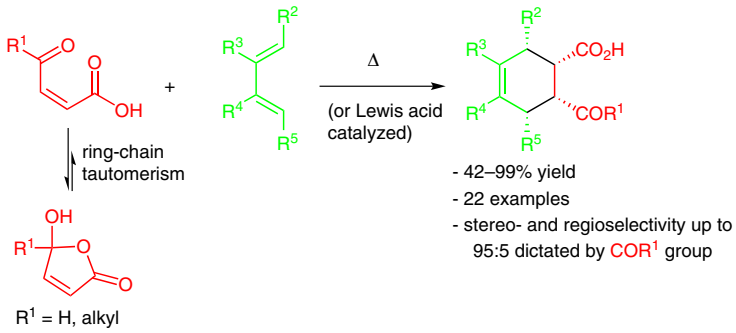

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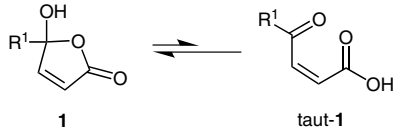
Abstract The Diels–Alder reaction of γ-hydroxybutenolides with dienes gave good yields of cycloadducts under thermal and Lewis acid catalyzed conditions. The application of this methodology to a more complex system was demonstrated by the synthesis of a model system for the tricyclic himbacine core. The stereo- and regioselective Diels–Alder reaction established three of the stereogenic centers, with the fourth stereogenic center secured by diastereoselective alkylation of the cycloadduct.

Key words γ-hydroxybutenolide, Diels–Alder reaction, himbacine, Lewis acid catalysis, isomerization

The Diels–Alder reaction is a powerful method for the stereoselective synthesis of cyclic compounds.[1] Alkenes possessing two electron-withdrawing groups are attractive dienophiles, but selectivity, both stereochemical and regiochemical, becomes an issue for many of these reactive alkenes.[2] In some cases, stereochemical selectivity for the reaction of these dienophiles is markedly improved with the use of Lewis acid catalysis.[2a,3]

At first inspection, γ-hydroxybutenolides **1** would not appear to be ideal dienophiles since they resemble substituted γ-lactones,[4] which usually require more forcing conditions for the Diels–Alder reaction compared to dienophiles with two electron-withdrawing groups (Scheme 1). The representation of the ring tautomer belies the reactivity of γ-hydroxybutenolides since there is interconversion to the chain tautomer (taut-**1**), which is also present in significant quantities at equilibrium.[5] In addition, several reactions of γ-hydroxybutenolides, including the Diels–Alder reaction, suggests that the rate of interconversion between the ring and chain tautomer is relatively fast on the laboratory timescale.[6] The reactive tautomer taut-**1** is a substituted acrylic acid, a functional group that possesses some challenges in its use as a dienophile, but several studies have shown that acrylic acids can be employed in stereoselective and regioselective Diels–Alder reactions.[2a,7]



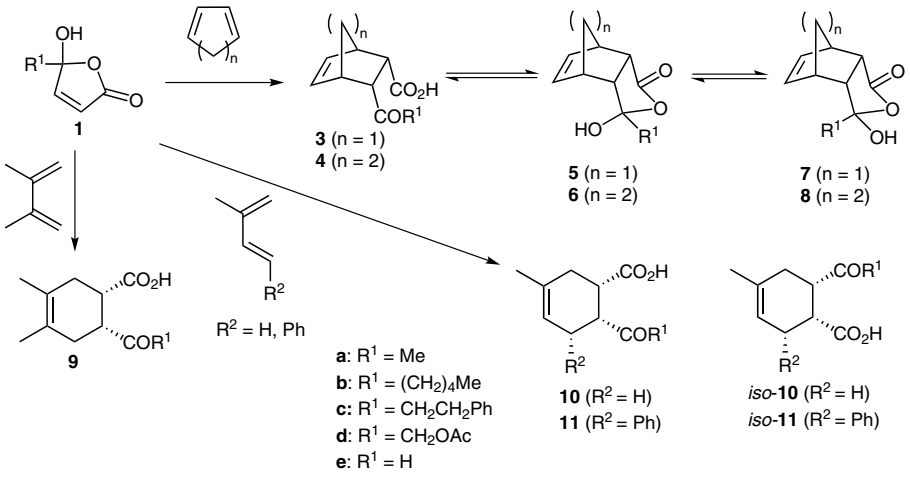
Scheme 1 Tautomerism of γ-hydroxybutenolides

The reaction of γ-hydroxybutenolides as dienophiles in the Diels–Alder reaction is limited to the reactions of the parent system **1e** (R^1 = H) with cyclopentadienes[8] and two other special cases.[9] Given the ready availability of γ-hydroxybutenolides **1** from several methods (photooxidation of substituted 2-silylfurans[10a,b] and 2-furaldehydes,[10c,d] and perchlorate oxidation of 2-substituted furans[10e]), we undertook a systematic study of their potential as dienophiles in the Diels–Alder reaction. In particular, we were interested in developing conditions that would lead to high regio- and stereoselectivity in the Diels–Alder reaction. Further, we were interested in investigating their potential in addressing the challenges of synthesizing the himbacine tricyclic core, a topic of continued interest.[11]

The thermal Diels–Alder reaction of several γ-hydroxybutenolides **1** with cyclopentadiene, 1,3-cyclohexadiene, 2,3-dimethyl-1,3-butadiene, isoprene, and (*E*)-3-methyl-1-phenyl-1,3-butadiene[12] (Scheme 2) are summarized in Table 1. γ-Hydroxybutenolides **1a–e** were readily prepared either by the photolysis of the corresponding trimethylsilylfuran, in the case of **1a–c**[10a,b] [acetone (1% H_2O); polymer-supported rose bengal; 200 W flood lamps; 0 °C], or the photolysis of the corresponding furaldehyde, in the case of **1d**[10d] and **1e**[10c] (MeOH; rose bengal; 200 W flood lamps; 0–25 °C; **1e** is also available by photolysis of 2-trimethylsilylfuran and is a commercial product) according to literature procedures. They were good dienophiles, reacting with cyclopentadiene to give Diels–Adler adducts in high yields and *endo*-selectivity at room temperature (Table 1, entries 1, 6, 11, 15, and 18). The less reactive 1,3-cyclohexadiene required more forcing conditions (entries 2, 7, 12, and 19), leading to some isomerization of γ-hydroxybutenolides **1b** and **1c** to the corresponding (*E*)-β-acylacrylic acids, which then reacted to give *trans*-products. 2,3-Dimethyl-1,3-butadiene reacted with **1a–e** (entries 3, 8, 13, 16, and 20) without isomerization and in good yields. The use of isoprene as a diene probed the issue of regiochemistry (entries 4, 9, and 14); there was little or no selectivity for the formation of **10**, in which the acyl group acted as a '*para*'-directing group relative to the methyl substituent of isoprene. The reaction of **1a**, **1b**, and **1d** with (*E*)-3-methyl-1-phenyl-1,3-butadiene gave diastereomer **11** with approximately 90–95% regio- and diastereoselectivity, the consequence of *endo*-selectivity and the acyl group acting as a strong '*ortho*/*para*'-directing group (entries 5, 10, and 17).

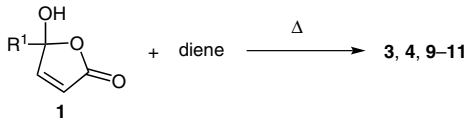
The identification of the Diels–Alder products by NMR spectroscopy was complicated by the tautomerization process of the cycloadducts. Unlike the Diels–Alder products of the reaction of (*E*)-β-acylacrylic acids with dienes in which there is a *trans*-relationship between the acyl group and carboxylic acid and no significant formation of the corresponding ring tautomer, the ring tautomer for the Diels–Alder products of γ-hydroxybutenolides **1** with dienes was evident, particularly in the case of bicyclic compounds and cycloadducts of **1e**. For bicyclic compounds **3** and **4**, the ring tautomers **5**/**7** and **6**/**8** were the major tautomeric species. For cycloadducts **9–11** derived from **1a–d**, however, there was very little evidence for significant amounts of the ring tautomer. In order to reduce the complexity of the NMR spectra, DABCO was added to catalyze the tautomerization process, leading to fast exchange and averaged spectra of the chain tautomer and the two diastereomeric ring tautomers. We have previously shown that the amine-catalyzed tautomerization of γ-hydroxybutenolides facilitates the identification of epimeric γ-hydroxybutenolides.[13,14] The assignment of the regiochemistry for the isoprene cycloadducts was determined by the isomerization (NaOH in MeOH) of **10a** to the known *trans*-isomer of **10a**;[2a,7a] the assignment of regiochemistry for **10b** and **10c** was based on the similarity of common features observed in the ^1H and ^{13}C NMR spectra for these compounds. The assignment of regiochemistry for cycloadducts **11** was based on a strong NOE enhancement observed for the *ortho*-protons of the phenyl ring when the alkenyl proton at δ = 5.4 was irradiated. The magnitudes for the coupling constants observed for **11** are best explained by a conformation in which the phenyl and carboxylic acid groups occupy a pseudo-equatorial position and the acyl group is pseudo-axial.

In order to increase the reaction rate and improve the regio- and stereoselectivity for the Diels–Alder reactions of **1**, we looked at a variety of Lewis acid catalyzed conditions, with some of the results summarized in Table 2. The two catalyst systems that worked best for the catalyzed Diels–Alder reaction of **1** were DIPEA/$SnCl_4$ and $Sc(OTf)_3$. In our previous studies of the Diels–Alder reactions of (*E*)-β-acylacrylic acids,[2a] we found that deprotonation of the acrylic



Scheme 2 Thermal Diels–Alder reaction of **1**

Table 1 Thermal Diels–Alder Reaction of γ-Hydroxybutenolides **1** with Dienes



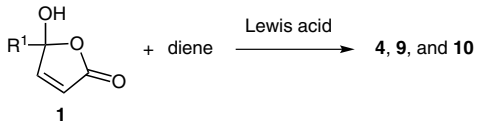
Entry	R^1	Diene	Solvent; temp; time	Product	Yield (%); dr[a]
1	Me (**1a**)	cyclopentadiene	CH_2Cl_2; 22 °C; 1 h	**3a**	99; >96:4
2	Me	1,3-cyclohexadiene	toluene; 110 °C; 20 h	**4a**	74; >96:4
3	Me	$(CH_2=CMe)_2$	CH_2Cl_2; 22 °C; 96 h	**9a**	94
4	Me	isoprene	toluene; 110 °C; 20 h	**10a**	93; 70:30 (15% *trans*-isomers)
5	Me	PhCH=CHCH(Me)=CH_2	CH_2Cl_2; 40 °C; 24 h	**11a**	51; 89:11[b]
6	$(CH_2)_4Me$ (**1b**)	cyclopentadiene	CH_2Cl_2; 22 °C; 1 h	**3b**	90; >96:4
7	$(CH_2)_4Me$	1,3-cyclohexadiene	toluene; 110 °C; 20 h	**4b**	79; 92:8 (5% *trans*-isomers)
8	$(CH_2)_4Me$	$(CH_2=CMe)_2$	CH_2Cl_2; 22 °C; 68 h	**9b**	74
9	$(CH_2)_4Me$	isoprene	toluene; 110 °C; 20 h	**10b**	93; 71:29 (20% *trans*-isomers)
10	$(CH_2)_4Me$	PhCH=CHCH(Me)=CH_2	CH_2Cl_2; 40 °C; 24 h	**11b**	65; 92:8[b]
11	$(CH_2)_2Ph$ (**1c**)	cyclopentadiene	CH_2Cl_2; 22 °C; 3 h	**3c**	83; >96:4
12	$(CH_2)_2Ph$	1,3-cyclohexadiene	toluene; 110 °C; 18 h	**4c**	78; 92:8[b] (5% *trans*-isomers)
13	$(CH_2)_2Ph$	$(CH_2=CMe)_2$	toluene; 110 °C; 16 h	**9c**	85
14	$(CH_2)_2Ph$	isoprene	toluene; 110 °C; 18 h	**10c**	87; 55:45 (20% *trans*-isomers)
15	CH_2OAc (**1d**)	cyclopentadiene	CH_2Cl_2; 22 °C; 3 h	**3d**	81; >96:4
16	CH_2OAc	$(CH_2=CMe)_2$	toluene; 80 °C; 18 h	**9d**	67
17	CH_2OAc	PhCH=CHCH(Me)=CH_2	CH_2Cl_2; 40 °C; 24 h	**11d**	55; 95:5[b]
18	H (**1e**)	cyclopentadiene	CH_2Cl_2; 22 °C; 2.5 h	**3e**	77; >96:4
19	H	1,3-cyclohexadiene	toluene; 110 °C; 20 h	**4e**	42; >96:4
20	H	$(CH_2=CMe)_2$	toluene; 110 °C; 18 h	**9e**	79

[a] Yields refer to cycloadducts purified by flash chromatography; diastereomeric ratio (dr) refers to the dr of crude reaction mixtures determined by ^{1}H NMR spectroscopy.
[b] Purification gave diastereomerically pure products.

acid moiety by DIPEA and addition of two equivalents of $SnCl_4$ led to an enhanced directing effect by the acyl group and a faster reaction. The use of the DIPEA/$SnCl_4$ protocol greatly enhanced the rate of reaction, which alleviated the isomerization issues that occurred in the thermal reactions of **1a–c** with 1,3-cyclohexadiene (Table 2, entries 1, 3, and 7). The use of the DIPEA/$SnCl_4$ protocol greatly enhanced reaction rate for the reaction of **1b** and **1c** with 2,3-dimethyl-1,3-butadiene without isomerization (entries 5 and 9). Unfortunately, there was no enhancement in the regioselectivity and lower yields in the Sn-catalyzed reaction of **1a–c** with isoprene (data not shown). $Sc(OTf)_3$ was an effective catalyst, with faster reaction rates for the reaction of **1b** with 1,3-cyclohexadiene and no evidence for isomerization (entry 4). We saw an enhancement of the regioselectivity for the reaction of isoprene with **1a–c** (entries 2, 6, and 10), although longer reaction times led to lower yields due to unidentified side reactions. The cycloadducts of **1c**, which have a phenyl group, decomposed to complex mixtures in the presence of $Sc(OTf)_3$ (entries 8 and 10), so its usefulness was severely limited for the reactions of **1c**. Low yields of cycloadducts **11** were obtained for the reaction of **1a–d** with (*E*)-3-methyl-1-phenyl-1,3-butadiene catalyzed by $Sc(OTf)_3$ or the DIPEA/$SnCl_4$ protocol, also presumably due to the side reactions caused by the presence of the phenyl ring.

In exploring the Lewis acid catalyzed Diels–Alder reaction of **1**, we uncovered the tendency for some of the cycloadducts, especially the bicyclic compounds **3** and **4**, to undergo isomerization to give the acyl group in the *exo*-position. Several studies have noted the tendency for *cis*-di-*endo* cycloadducts of cyclopentadiene to isomerize to the more stable *trans*-compounds.[15] When NaOH is added to methanolic solutions of **3a–c** and **4a–c**, there is epimerization at the α-carbon to the acyl group to give **12a–c** (57–88% yield) and **13a–c** (51–86% yield), respectively (Scheme 3). The epimerization of nonbicyclic compounds (e.g., **9b**) occurs more slowly (1 h vs 24 h) and in lower yields under

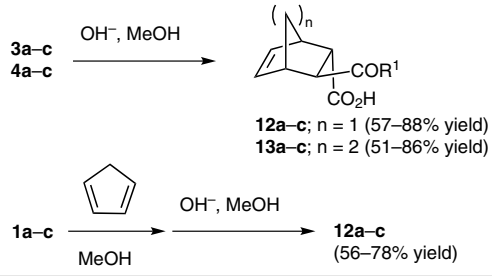
Table 2 Lewis Acid Catalyzed Diels–Alder Reaction of γ-Hydroxybutenolides **1** with Dienes[a]



Entry	R^1	Diene	Catalyst	Product	Yield (%); dr[b]
1	Me (**1a**)	1,3-cyclohexadiene	DIPEA/$SnCl_4$	**4a**	78; >96:4
2	Me	isoprene	$Sc(OTf)_3$	**10a**	23; 88:12 (~5% *trans*)
3	$(CH_2)_4Me$ (**1b**)	1,3-cyclohexadiene	DIPEA/$SnCl_4$	**4b**	78; >96:4
4	$(CH_2)_4Me$	1,3-cyclohexadiene	$Sc(OTf)_3$	**4b**	67; >96:4
5	$(CH_2)_4Me$	$(CH_2{=}CMe_2)_2$	DIPEA/$SnCl_4$	**9b**	80
6	$(CH_2)_4Me$	isoprene	$Sc(OTf)_3$	**10b**	57; 86:14 (~5% *trans*)
7	$(CH_2)_2Ph$ (**1c**)	1,3-cyclohexadiene	DIPEA/$SnCl_4$	**4c**	70; >96:4
8	$(CH_2)_2Ph$	1,3-cyclohexadiene	$Sc(OTf)_3$	**4c**	9; >96:4 (20% *trans*)
9	$(CH_2)_2Ph$	$(CH_2{=}CMe_2)_2$	DIPEA/$SnCl_4$	**9c**	83
10	$(CH_2)_2Ph$	isoprene	$Sc(OTf)_3$	**10c**	21; 80:20 (~5% *trans*)

[a] All reactions were performed in CH_2Cl_2 for 1 h; DIPEA/$SnCl_4$ reactions were performed at 0 °C and $Sc(OTf)_3$ reactions at 22 °C.
[b] Yields refer to cycloadducts purified by flash chromatography; diastereomeric ratio (dr) refers to the dr of crude reaction mixtures determined by ^1H NMR spectroscopy.

similar reaction conditions. A simple one-pot procedure was developed, in which the Diels–Alder reaction was run in methanol and the base is added directly to the crude cycloadduct, for the synthesis of **12a–c** from **1a–c** (78–81% yield).[16–20] Amine bases such as DIPEA and triethylamine also gave isomerization but at slower rates. With the Diels–Alder reaction of γ-hydroxybutenolides and β-acylacrylic acids, and this isomerization reaction, three of the possible four diastereomers of these bicyclic compounds are readily prepared.



Scheme 3 Isomerization of **3** and **4**

In considering the application of the Diels–Alder reaction of γ-hydroxybutenolides to the synthesis of biologically important molecules, we immediately recognized compounds such as himbacine and related pharmaceuticals (e.g., vorapaxar) as potential targets (Figure 1).[21–28] Himbacine, a powerful muscarinic receptor antagonist that was proposed as a potential candidate for treating Alzheimer's disease, and vorapaxar,[22] a thrombin receptor antagonist recently approved by the FDA for reducing the risk of cardiovascular events, have a tricyclic core attainable using the methodology described herein. We envisioned a regio- and diastereoselective Diels–Alder reaction establishing the stereogenic centers of the A/B ring and C-4, with the stereogenic center at C-3 established by the reduction or alkylation of the Diels–Alder products. Employing the Diels–Alder reaction in the synthesis of himbacine and their derivatives has been a common and highly successful strategy, with most approaches using an intramolecular Diels–Alder reaction to prepare the tricyclic core,[23–26] although there are reports using an intermolecular Diels–Alder reaction.[27,28]

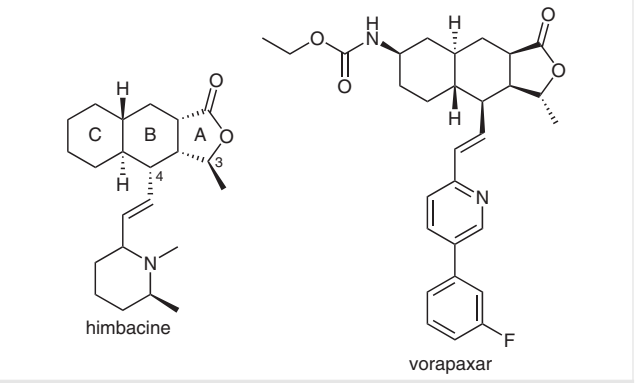
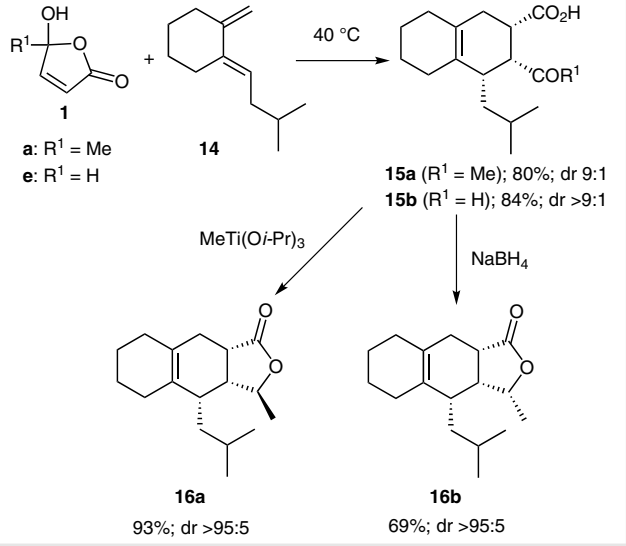


Figure 1 Structures of himbacine and vorapaxar

For our model studies, we prepared diene **14** in three steps from cyclohexanone (see Supporting Information), which incorporated a simple isobutyl group that was a stand-in for the more complicated substituents normally

found at C-4 in himbacine-related compounds. The Diels–Alder reaction of **1a** and **1e** with diene **14** gave Diels–Alder products **15a** and **15b**, respectively, in good yields (Scheme 4). In both cases, the dr of the crude products was >90:10, which upon purification gave cycloadducts **15a** and **15b** free of diastereomeric impurities. The selective formation of **15a** and **15b** reflects an *endo* transition state as well as the formyl or acyl group acting as a strong '*ortho*'-directing group.



Scheme 4 Synthesis of **16a** and **16b**

With access to both **15a** and **15b**, the stage was set for the establishment of the C-3 stereogenic center of the lactone ring. The reduction of cyclic γ-keto acids developed by Rovis[29] and others[30] for the formation of the C-3 stereogenic center was clearly relevant and served as a guide for our studies. The γ-keto acids of these studies, most lacking a substituent at the stereogenic center of 'C-4', gave *anti*-products (corresponding to compound **16a**) with Ph_2MeSiH/CF_3CO_2H, and *syn*-products (corresponding to compound **16b**) with hydride reagents. Our studies with the additional stereogenic center at 'C-4' gave the opposite stereochemical results. Reduction of **15a** with typical hydride reagents [$NaBH_4$, DIBAL, $Zn(BH_4)_2$] gave good yields and high diastereoselectivity (>95:5) of **16b** (Scheme 4). Employing Rovis' protocol using silanes (Et_3SiH, Ph_2MeSiH) with CF_3CO_2H, **16a** was obtained with modest stereoselectivity but in low yields. Our results clearly show the importance of the 'C-4' stereogenic center in determining the stereochemical outcome for the reduction of cyclic γ-keto acids.[29] The alkylation of **15b** was then explored as an alternative approach to the desired lactone **16a**. The addition of MeLi in Et_2O gave a 78% yield of the lactone products but with poor diastereoselectivity (77:23 dr; **16a**:**16b**). Excellent diastereoselectivity (>95:5) for the desired lactone was achieved using MeMgBr, Me_2CuLi, and $MeTi(O\text{-}iPr)_3$, with the highest yields achieved using the in situ-generated titanium reagent (93% yield). Recrystallization of **16a** from hexanes gave crystals suitable for X-ray diffraction studies, which conclusively established the stereochemical assignment of **16a** and **16b** (Figure 2).

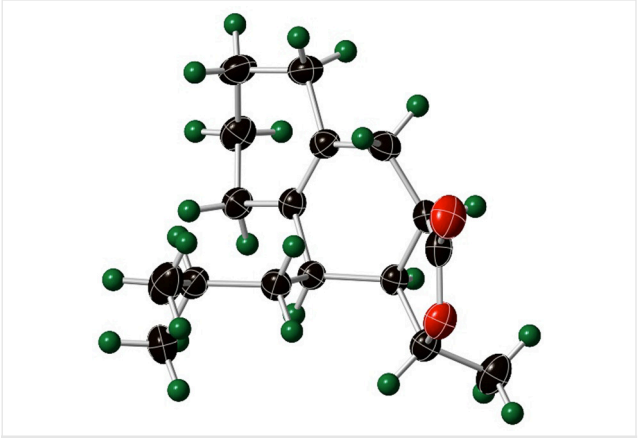


Figure 2 X-ray crystal structure of **16a**

This study establishes γ-hydroxybutenolides as excellent dienophiles in the Diels–Alder reaction. Reactive dienes gave good yields of cycloadducts under thermal conditions, although isomerization of the γ-hydroxybutenolides was evident with less reactive dienes such as 1,3-cyclohexadiene and isoprene. In some cases, this issue was overcome by employing Lewis acids, which also lead to enhanced stereo- and regioselectivity. The tendency for γ-hydroxybutenolides to isomerize to the more stable (*E*)-acylacrylic acids is a problem that still needs to be addressed in the case for less reactive dienes. These cycloadducts have the potential for transformation to stereochemically defined γ-lactones as evidenced by the stereoselective reduction of **15a** and the alkylation of **15b**. Even though the completion of the synthesis of the tricyclic core of himbacine awaits the development of a stereoselective *trans*-reduction of the alkenyl moiety, the potential for the synthesis of himbacine derivatives has been demonstrated. The development of an enantioselective version to give scalemic cycloadducts will be the next challenge. In conclusion, this study demonstrates some of the potential of γ-hydroxybutenolides as dienophiles in the Diels–Alder reaction, which promises to be an important contributor to the synthesis of γ-lactones and related compounds.

All reactions were carried out under argon. All glassware was dried in the oven (110 °C) before use. Yields refer to isolated compounds that are greater than >95% pure as determined by ^1H and ^{13}C NMR spectroscopy. IR spectra were obtained on an FT-IR spectrophotometer. The ^1H and ^{13}C NMR were recorded at 400 MHz and 100 MHz, respectively. All chemical shifts in the ^1H NMR are reported in ppm relative

to TMS (δ = 0.00) or $CHCl_3$ (δ = 7.26) and in the ^{13}C NMR are reported in ppm relative to $CDCl_3$ (δ = 77.16). Flash chromatography was performed on 60 Å silica gel (40–75 μm). CH_2Cl_2 and toluene were dried over molecular sieves. Single crystals of **16a** were prepared by recrystallization from hexanes. X-ray data were acquired at 173 K on a Bruker Smart Apex CCD diffractometer employing graphite monochromated MoKα radiation (δ = 0.71073 Å). The Bruker Apex2 suite of program[31] was used to process the data and the Bruker SAINT software package[32] was used to integrate the frames with a narrow-frame algorithm. The multi-scan method (SADABS)[33] was used to correct the data for absorption effects. The Bruker SHELXTL software package[34] was used to perform structure solution by direct methods, and refinement by full-matrix least-squares on F2. All non-hydrogen atoms were refined anisotropically with suggested weighting factors and the hydrogens were calculated on a riding model. All cif files were validated with the checkCIF/Platon facility of IUCr that was accessed with the software program enCIFer. High-resolution mass spectra were obtained using a direct analysis in real time – time-of-flight (DART-TOF) mass spectrometer.

Thermal Diels–Alder Reaction of 1 with Dienes; General Procedure (Table 1)

A solution of **1** (1.0–1.3 mmol) and respective diene (3–5 equiv) in CH_2Cl_2 (5 mL) or toluene (5 mL) was stirred for the time and temperature specified in Table 1. The reactions employing toluene at 110 °C were done in a sealed tube. The volatiles were removed on the rotary evaporator and the crude product was purified by flash chromatography (silica gel; hexanes → 50% EtOAc in hexanes) to give **3**, **4**, **9**, **10**, or **11**. For convenience, the Diels–Alder products are listed as the chain tautomer even when the ring tautomers are the major species. NOE experiments established the major ring tautomers of **3a** and **4a** as **7a** and **8a**, respectively; the assignment of the ring tautomers of **3b**–**d**, **4b**, and **4c** was based on chemical shift arguments of the alkenyl protons of these compounds compared to the alkenyl protons of **3a** and **4a**.

(1*R**,2*S**,3*R**,4*S**)-3-Acetylbicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (3a)[16]

White solid; yield: 0.205 g [99% based on 0.131 g (1.15 mmol) of **1a**]; >96:4 dr; **3a**:**5a**:**7a** = 40:15:45; mp 76–77.5 °C.

^1H NMR (400 MHz, $CDCl_3$; 8% DABCO): δ = 6.99 (br s, 1 H), 6.23 (dd, *J* = 2.9, 5.5 Hz, 1 H), 6.20 (dd, *J* = 2.9, 5.5 Hz, 1 H), 3.39 (dd, *J* = 4.0, 9.2 Hz, 1 H), 3.22 (br s, 1 H), 3.17 (dd, *J* = 3.6, 9.2 Hz, 1 H), 3.12 (br s, 1 H), 1.83 (s, 3 H), 1.54 (br d, *J* = 8.4 Hz, 1 H), 1.39 (br d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$; 8% DABCO): δ = 177.3, 135.7, 134.4, 54.0, 50.7, 49.2, 46.1, 45.6, 44.4, 28.4.

(1*R**,2*S**,3*R**,4*S**)-3-Acetylbicyclo[2.2.2]oct-5-ene-2-carboxylic Acid (4a)

Off-white solid; yield: 0.186 g [74% based on 0.147 g (1.29 mmol) of **1a**]; >96:4 dr; **6a**:**8a** = 30:70; mp 126–127.5 °C.

IR (CH_2Cl_2): 3567, 1771 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.38 (m, 0.3 H), 6.31 (m, 0.3 H), 6.25–6.20 (m, 1.4 H) 3.75 (br s, 0.7 H), 3.24 (br s, 0.3 H), 3.18–3.08 (m, 1.7 H), 3.02 (dd, *J* = 3.7, 9.9 Hz, 0.3 H), 2.92 (m, 0.3 H), 2.79 (m, 0.7 H), 2.56 (dd, *J* = 2.6, 9.9 Hz, 0.3 H), 2.51 (dd, *J* = 2.4, 8.6 Hz, 0.7 H), 1.592 (s, 2.1 H), 1.585 (s, 0.9 H), 1.56–1.49 (m, 12 H), 1.33–1.24 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$; 30% DABCO): δ = 177.9, 133.3, 132.5, 114.6 (br), 49.6, 47.5, 32.0, 30.7, 26.5, 25.0, 22.7.

HRMS (DART-TOF): *m*/*z* [M + 1]$^+$ calcd for $C_{11}H_{15}O_3$: 195.1021; found: 195.1023.

(1*S**,6*R**)-6-Acetyl-3,4-dimethylcyclohex-3-enecarboxylic Acid (9a)

White solid; yield: 0.570 g [94% based on 0.352 g (3.08 mmol) of **1a** in 15 mL of CH_2Cl_2]; mp 110.5–113 °C.

IR (CH_2Cl_2): 3300–2700, 1746, 1709 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.04 (dt, *J* = 3.6, 6.2 Hz, 1 H), 2.84 (dt, *J* = 3.6, 6.8 Hz, 1 H), 2.51–2.22 (m, 4 H), 2.19 (s, 3 H), 1.64 (s, 3 H), 1.62 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.3, 179.0, 123.7, 122.5, 46.9, 39.1, 31.1, 30.7, 26.8, 18.2, 18.0.

HRMS (DART-TOF): *m*/*z* [M + 1]$^+$ calcd for $C_{11}H_{17}O_3$: 197.1178; found: 197.1179.

(1*S**,6*R**)-6-Acetyl-3-methylcyclohex-3-enecarboxylic Acid (10a)

Pale yellow oil; yield: 0.214 g [93% based on 0.144 g (1.26 mmol) of **1a**]; **10a**:*iso*-**10a** (15% *trans*-isomers) = 70:30.

IR (CH_2Cl_2): 3400–2800, 1746, 1709 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.95 (br s, 1 H), 5.39 (br s, 1 H), 3.04 (m, 1 H), 2.85 (m, 1 H), 2.54–2.20 (m, 4 H), 2.17 (s, 3 H), 1.65 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.3, 179.9, 133.3, 118.6, 47.0, 39.9, 30.6, 27.8, 25.8, 23.4.

HRMS (DART-TOF): *m*/*z* [M + 1]$^+$ calcd for $C_{10}H_{15}O_3$: 183.1021; found: 183.1023.

(1*R**,2*R**,3*S**)-2-Acetyl-5-methyl-3-phenylcyclohex-4-ene-1-carboxylic Acid (11a)

White solid; yield: 0.139 g [51% based on 0.120 g (1.05 mmol) of **1a**]; **11a**:*iso*-**11a** = 89:11 (crude); mp 140 °C (dec.).

IR (CH_2Cl_2): 3300–2700, 1744, 1711, 1603 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.32 (br t, *J* = 7.1 Hz, 2 H), 7.24 (m, 1 H), 7.17 (d, *J* = 7.0 Hz, 2 H), 5.42 (br s, 1 H), 3.85 (br s, 1 H), 3.60 (dd, *J* = 3.7, 6.6 Hz, 1 H), 3.01 (m, 1 H), 2.86 (m, 1 H), 2.33 (dd, *J* = 6.2, 17.2 Hz, 1 H), 1.84 (s, 3 H), 1.39 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.9, 180.3, 142.0, 135.6, 128.8, 128.4, 127.2, 120.7, 49.9, 44.5, 43.2, 33.7, 29.8, 23.6.

HRMS (DART-TOF): *m*/*z* [M + 1]$^+$ calcd for $C_{16}H_{19}O_3$: 259.1334; found: 259.1337.

(1*R**,2*S**,3*R**,4*S**)-3-Hexanoylbicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (3b)

White solid; yield: 0.263 g [90% based on 0.211 g (1.24 mmol) of **1b**]; >96:4 dr; **3b**:**5b**:**7b** = 61:18:21; mp 69–71 °C.[17]

IR (CH_2Cl_2): 3536, 1765, 1712 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$; 8 mol% DABCO): δ = 7.44 (br s, 1 H), 6.26 (dd, *J* = 2.9, 5.5 Hz, 1 H), 6.18 (dd, *J* = 2.9, 5.5 Hz, 1 H), 3.32 (dd, *J* = 3.6, 9.2 Hz, 1 H), 3.26 (br d, *J* = 8.8 Hz, 1 H), 3.20 (br s, 1 H), 3.12 (br s, 1 H), 2.16 (br s, 2 H), 1.55–1.23 (m, 8 H), 0.89 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$; 30 mol% DABCO): δ = 177.0, 135.3, 134.6, 54.1, 49.8, 49.7, 46.4, 46.2, 42.8, 31.7, 23.5, 22.7, 14.1.

HRMS (DART-TOF): *m*/*z* [M + 1]$^+$ calcd for $C_{14}H_{21}O_3$: 237.1491; found: 237.1495.

(1*R,2*S**,3*R**,4*S**)-3-Hexanoylbicyclo[2.2.2]oct-5-ene-2-carboxylic Acid (4b)**

White solid; yield: 0.245 g [79% based on 0.211 g (1.24 mmol) of **1b**]; 92:8 dr; **6b**:**8b** (~5% *trans*-isomers) = 59:41; mp 105–107 °C.

IR (CH_2Cl_2): 3570, 1768 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$; 12 mol% DABCO): δ = 6.32–6.24 (m, 2 H), 4.12 (br s, 1 H), 3.11 (br s, 1 H), 3.01 (dd, *J* = 3.7, 9.5 Hz, 1 H), 2.81 (br s, 1 H), 2.55 (br d, *J* = 9.5 Hz, 1 H), 1.84–1.74 (m, 2 H), 1.55–1.24 (m, 10 H), 0.90 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$; 12 mol% DABCO): δ = 177.4, 133.5, 132.9, 116.0, 48.7, 47.8, 40.4, 32.0, 31.9, 30.4, 24.9, 22.9, 22.8, 22.7, 14.1.

HRMS (DART-TOF): *m*/*z* [M + 1]$^+$ calcd for $C_{15}H_{23}O_3$: 251.1647; found: 251.1651.

(1*S,6*R**)-6-Hexanoyl-3,4-dimethylcyclohex-3-enecarboxylic Acid (9b)**

White solid; yield: 0.231 g [74% based on 0.211 g (1.24 mmol) of **1b**]; mp 75–77 °C.

IR (CH_2Cl_2): 3300–2700, 1746, 1706 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.99 (dt, *J* = 3.5, 6.6 Hz, 1 H), 2.87 (dt, *J* = 3.7, 6.6 Hz, 1 H), 2.54–2.21 (m, 4 H), 2.46 (t, *J* = 7.3 Hz, 2 H), 1.64 (s, 3 H), 1.62 (s, 3 H), 1.56 (pent, *J* = 7.4 Hz, 2 H), 1.34–1.20 (m, 4 H), 0.88 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.5, 179.9, 124.9, 123.5, 47.4, 40.1, 40.0, 32.1, 31.8, 31.5, 23.4, 22.6, 19.2, 19.0, 14.1.

HRMS (DART-TOF): *m*/*z* [M + 1]$^+$ calcd for $C_{15}H_{25}O_3$: 253.1804; found: 253.1809.

(1*S,6*R**)-6-Hexanoyl-3-methylcyclohex-3-enecarboxylic Acid (10b)**

Oil; yield: 0.273 g [93% based on 0.211 g (1.24 mmol) of **1b**]; **10b**:*iso*-**10b** (20% *trans*-isomers) = 71:29.

IR (CH_2Cl_2): 1746, 1707 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.37 (m, 1 H), 3.00 (m, 1 H), 2.91 (m, 1 H), 2.60–2.20 (m, 5 H), 1.67 (s, 3 H), 1.61–1.52 (m, 3 H), 1.35–1.20 (m, 5 H), 0.88 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.4, 179.9, 133.4, 119.08, 46.4, 39.9, 31.4, 30.5, 25.8, 23.41, 23.38, 22.6, 14.0.

HRMS (DART-TOF): *m*/*z* [M + 1]$^+$ calcd for $C_{14}H_{23}O_3$: 239.1647; found: 239.1696.

(1*R,2*R**,3*S**)-2-Hexanoyl-5-methyl-3-phenylcyclohex-4-ene-1-carboxylic Acid (11b)**

White solid; yield: 0.183 g [65% based on 0.153 g (0.90 mmol) of **1b**]; >96:4 dr; mp 160 °C (dec).

IR (CH_2Cl_2): 3300–2700, 1745, 1711 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.29 (br t, *J* = 7.1 Hz, 2 H), 7.23 (m, 1 H), 7.14 (m, 2 H), 5.41 (br s, 1 H), 3.82 (br s, 1 H), 3.52 (dd, *J* = 3.6, 7.0 Hz, 1 H), 3.01 (m, 1 H), 2.87 (m, 1 H), 2.33 (dd, *J* = 5.9, 17.2 Hz, 1 H), 2.06 (m, 1 H), 1.83 (s, 3 H), 1.25–0.78 (m, 7 H), 0.74 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.4, 180.3, 142.1, 135.6, 128.7, 128.4, 127.1, 120.8, 49.6, 46.3, 44.7, 43.2, 31.0, 30.0, 23.6, 22.4, 22.2, 14.0.

HRMS (DART-TOF): *m*/*z* [M + 1]$^+$ calcd for $C_{20}H_{27}O_3$: 315.1960; found: 315.1975.

(1*R,2*S**,3*R**,4*S**)-3-(3-Phenylpropanoyl)[2.2.1]hept-5-ene-2-carboxylic Acid (3c)**

White solid; yield: 0.257 g [83% based on 0.234 g (1.15 mmol) of **1c**]; >96:4 dr; **3c**:**5c**:**7c** = 62:18:20; mp 84–86 °C.

IR (CH_2Cl_2): 3565, 1768, 1714 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$; 20 mol% DABCO): δ = 7.92 (br s, 1 H), 7.27 (m, 2 H), 7.21–7.16 (m, 3 H), 6.23 (dd, *J* = 2.8, 5.3 Hz, 1 H), 6.13 (dd, *J* = 2.9, 5.5 Hz, 1 H), 3.34 (dd, *J* = 3.7, 9.5 Hz, 1 H), 3.24 (dd, *J* = 3.3, 9.5 Hz, 1 H), 3.18 (br s, 1 H), 3.07 (br s, 1 H), 2.93–2.76 (m, 2 H), 2.62–2.47 (m, 2 H), 1.47 (d, *J* = 8.4 Hz, 1 H), 1.33 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$; 20 mol% DABCO): δ = 177.3, 141.4, 135.3, 134.6, 128.6, 128.4, 126.1, 54.3, 49.8, 49.4, 46.4, 46.1, 44.2, 29.9.

HRMS (DART-TOF): *m*/*z* [M + 1]$^+$ calcd for $C_{17}H_{19}O_3$: 271.1334; found: 271.1343.

(1*R,2*S**,3*R**,4*S**)-3-(3-Phenylpropanoyl)[2.2.2]oct-5-ene-2-carboxylic Acid (4c)**

White solid; yield: 0.244 g [78% based on 0.224 g (1.10 mmol) of **1c**]; 92:8 dr; **6c**:**8c** (~5% *trans*-isomers) = 59:41; mp 115.5–118 °C.

IR (CH_2Cl_2): 3564, 1769 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$; 30 mol% DABCO): δ = 7.32–7.17 (m, 5 H), 6.31–6.25 (m, 2 H). 4.14 (br s, 1 H), 3.11 (m, 1 H), 3.05 (dd, *J* = 3.7, 9.5 Hz, 1 H), 2.84–2.78 (m, 3 H), 2.59 (dd, *J* = 2.2, 9.5 Hz, 1 H), 2.23–2.10 (m, 2 H), 1.57–1.45 (m, 2 H), 1.36 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$; 30 mol% DABCO): δ = 177.4, 141.2, 133.6, 132.8, 128.7, 128.5, 126.3, 120.9, 49.5, 48.0, 42.2, 32.2, 30.5, 29.6, 24.9, 23.0.

HRMS (DART-TOF): *m*/*z* [M + 1]$^+$ calcd for $C_{18}H_{21}O_3$: 285.1491; found: 285.1497.

(1*S,6*R**)-3,4-Dimethyl-6-(3-phenylpropanoyl)cyclohex-3-enecarboxylic Acid (9c)**

White solid; yield: 0.286 g [85% based on 0.241 g (1.18 mmol) of **1c**]; mp 102–104 °C.

IR (CH_2Cl_2): 3300–2700, 1746, 1708 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.27 (m, 2 H), 7.21–7.16 (m, 3 H), 3.01 (m, 1 H), 2.93–2.78 (m, 5 H), 2.50 (dd, *J* = 5.2, 17.5 Hz, 1 H), 2.42–2.12 (m, 3 H), 1.61 (br s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.2, 179.8, 141.4, 128.6, 128.5, 126.2, 124.9, 123.4, 47.6, 41.8, 40.1, 32.1, 31.7, 29.7, 19.2, 19.0.

HRMS (DART-TOF): *m*/*z* [M + 1]$^+$ calcd for $C_{18}H_{23}O_3$: 287.1647; found: 287.1658.

(1*S,6*R**)-3-Methyl-6-(3-phenylpropanoyl)cyclohex-3-enecarboxylic Acid (10c)**

White solid; yield: 0.260 g [87% based on 0.225 g (1.10 mmol) of **1c**]; **10c**:*iso*-**10c** (20% *trans*-isomers) = 55:45; mp 64–72 °C.

IR (CH_2Cl_2): 1745, 1708 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.16 (m, 5 H), 5.33 (br s, 1 H), 3.08–2.78 (m, 6 H), 2.50–2.20 (m, 4 H), 1.66 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.2, 179.8, 141.3, 133.4, 128.5, 128.4, 126.1, 118.5, 46.5, 41.7, 39.9, 30.5, 29.7, 25.6, 23.5.

HRMS (DART-TOF): *m*/*z* [M + 1]$^+$ calcd for $C_{17}H_{21}O_3$: 273.1491; found: 273.1491.

(1*R,2*S**,3*R**,4*S**)-3-(2-Acetoxyacetyl)bicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (3d)**

Off-white solid; yield: 0.233 g [81% based on 0.206 (1.21 mmol) of **1d**]; **3d**:**5d**:**7d** = 4:53:43; mp 66–70 °C.

IR (CH_2Cl_2): 3552, 1775, 1751 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.37 (dd, *J* = 2.9, 5.5 Hz, 0.55 H), 6.28 (dd, *J* = 3.3, 5.9 Hz, 0.45 H), 6.22 (dd, *J* = 2.9, 5.5 Hz, 0.55 H), 6.15 (dd, *J* = 2.8, 5.6 Hz, 0.45 H), 4.28 (d, *J* = 12.1 Hz, 0.45 H), 4.25 (d, *J* = 12.1 Hz, 0.55 H), 4.13 (d, *J* = 11.7 Hz, 0.45 H), 4.04 (d, *J* = 11.7 Hz, 0.55 H), 3.88 (br s, 0.45 H), 3.63 (br s, 0.55 H), 3.55 (dd, *J* = 5.0, 8.6 Hz, 0.45 H), 3.43 (dd, *J* = 5.0, 8.9 Hz, 0.55 H), 3.32 (m, 1 H), 3.18 (m, 1 H), 3.03 (m, 1 H), 2.16 (s, 1.35 H), 2.12 (s, 1.65 H), 1.71–1.61 (m, 1 H), 1.49-1.43 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.0, 175.6, 170.82, 170.76, 136.9, 136.7, 134.1, 133.7, 104.4, 103.8, 69.0, 65.8, 53.2, 52.0, 50.6, 49.9, 47.9, 47.6, 45.8, 45.0, 44.8, 43.9, 20.83, 20.76.

HRMS (DART-TOF): *m*/*z* [M + 1]$^+$ calcd for $C_{12}H_{15}O_5$: 239.0919; found: 239.0921.

(1*S,6*R**)-6-(2-Acetoxyacetyl)-3,4-dimethylcyclohex-3-enecarboxylic Acid (9d)**

Tan solid; yield: 0.211 g [67% based on 0.206 g (1.24 mmol) of **1d**]; **9d**:**9d**-ring tautomers = 93:7; mp 102–103.5 °C.

IR (CH_2Cl_2): 1783, 1750, 1707 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 11.05 (br s, 1 H), 4.82 (s, 2 H), 3.06 (m, 1 H), 2.98 (m, 1 H), 2.51 (dd, *J* = 5.0, 17.4 Hz, 1 H), 2.36–2.27 (m, 3 H), 2.15 (s, 3 H), 1.64 (br s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.7, 179.5, 170.5, 125.0, 122.9, 66.9, 44.3, 40.1, 31.8, 30.7, 20.5, 19.0, 18.9.

HRMS (DART-TOF): *m*/*z* [M + 1]$^+$ calcd for $C_{13}H_{19}O_5$: 255.1232; found: 255.1239.

(1*R,2*R**,3*S**)-2-(2-Acetoxyacetyl)-5-methyl-3-phenylcyclohex-4-ene-1-carboxylic Acid (11d)**

White solid; yield: 0.174 g [55% based on 0.172 g (1.01 mmol) of **1d**]; 95:5 dr; mp 144–148 °C.

IR (CH_2Cl_2): 1745, 1727, 1702 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.33 (t, *J* = 7.3 Hz, 2 H), 7.26 (m, 1 H), 7.14 (d, *J* = 7.7 Hz, 2 H), 5.43 (br s, 1 H), 4.46 (d, *J* = 17.2 Hz, 1 H), 3.85 (br s, 1 H), 3.50 (m, 1 H), 3.16 (d, *J* = 16.8 Hz, 1 H), 3.10 (m, 1 H), 2.81 (m, 1 H), 2.39 (dd, *J* = 6.2, 17.6 Hz, 1 H), 1.99 (s, 3 H), 1.84 (br s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.5, 179.0, 169.9, 141.3, 136.0, 129.0, 128.8, 128.2, 127.5, 127.1, 120.5, 69.9, 46.3, 44.5, 43.1, 30.0, 23.5, 20.5.

HRMS (DART-TOF): *m*/*z* [M + 1]$^+$ calcd for $C_{18}H_{21}O_5$: 317.1389; found: 317.1394.

(1*R,2*S**,3*R**,4*S**)-3-Formylbicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (3e)**[8]

White solid; yield: 0.154 g [77% based on 0.120 g (1.00 mmol) of **1e**]; >96:4 dr; **7e**:**5e** = >98:2; mp 99–100 C (hexanes).

^1H and ^{13}C NMR spectra match with those described in the literature.[8]

(1*R,2*S**,3*R**,4*S**)-3-Formylbicyclo[2.2.2]oct-5-ene-2-carboxylic Acid (4e)**

White solid; yield: 0.076 g [42% based on 1.00 g (1.00 mmol) of **1e**]; >96:4 dr; **8e**:**6e** = 95:5; mp 147–149 °C.

IR (CH_2Cl_2): 3578, 1773 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.29 (m, 1 H), 6.24 (m, 1 H), 5.34 (dd, *J* = 1.8, 4.0 Hz, 1 H), 3.61 (d, *J* = 4.4 Hz, 1 H), 3.08 (m, 1 H), 2.95 (dd, *J* = 3.7, 9.5 Hz, 1 H), 2.86 (m, 1 H), 2.50 (dt, *J* = 9.5, 2.4 Hz, 1 H), 1.58–1.50 (m, 2 H), 1.36–1.25 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.0, 134.1, 132.7, 102.7, 47.2, 45.9, 31.9, 31.8, 23.6, 23.3.

HRMS (DART-TOF): *m*/*z* [M + 1]$^+$ calcd for $C_{10}H_{13}O_3$: 181.0865; found: 181.0861.

(1*S*,6*R*)-6-Formyl-3,4-dimethylcyclohex-3-enecarboxylic Acid (9e)[35]

Colorless oil; yield: 0.146 g [79% based on 0.102 g (1.02 mmol) of **1e**]; >96% ring tautomer.

IR (CH_2Cl_2): 3577, 1778 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$; 4 mol% DABCO): δ = 6.34 (br s, 1 H), 4.15 (br s, 1 H), 3.06 (dt, *J* = 7.5, 3.9 Hz, 1 H), 2.63 (q, *J* = 7.2 Hz, 1 H), 2.39 (m, 1 H), 2.29–2.15 (m, 2 H), 1.96 (dd, *J* = 16.9, 6.6 Hz, 1 H), 1.65 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$; 4 mol% DABCO): δ = 178.9, 125.0, 123.9, 44.6, 41.1, 37.7, 30.1, 29.2, 19.4, 19.1 (hemi-acetal carbon was not observed).

HRMS (DART-TOF): *m*/*z* [M + 1]$^+$ calcd for $C_{10}H_{15}O_3$: 183.1021; found: 183.1023.

$SnCl_4$-Promoted Diels–Alder Reaction of 1 with Dienes; General Procedure (Table 2)

A solution of **1a**, **1b**, or **1c** (1.20 mmol) with the respective diene [3–5 equiv; 1.3 equiv in the case of (*E*)-3-methyl-1-phenyl-1,3-butadiene] in CH_2Cl_2 (5 mL) was cooled to 0 °C. DIPEA (0.22 mL, 1.26 mmol) and $SnCl_4$ (0.29 mL, 2.5 mmol) were added dropwise and the reaction mixture was stirred for the 1 h at 0 °C. The mixture was quenched with H_2O (10 mL), the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic extracts were washed with H_2O (50 mL) and brine (50 mL), and dried over Na_2SO_4. The volatiles were removed on the rotary evaporator and the crude product was purified by flash chromatography (silica gel; hexanes → 50% EtOAc in hexanes). The yields and dr are summarized in Table 2.

$Sc(OTf)_3$-Catalyzed Diels–Alder Reaction of 1 with Dienes; General Procedure (Table 2)

To a solution of **1** (1.2 mmol) and the respective diene (3–5 equiv) in CH_2Cl_2 (5 mL) was added $Sc(OTf)_3$ (0.12 g, 0.24 mmol) and the reaction mixture was stirred for the time and temperature specified in Table 2. The mixture was washed with H_2O (2 × 20 mL), the volatiles were removed on the rotary evaporator, and the crude product was purified by flash chromatography (silica gel; hexanes → 50% EtOAc in hexanes). The yields and dr are summarized in Table 2.

Isomerization of Diels–Alder Products 3a–c and 4a–c; General Procedure

To a solution of **3a**–**c** or **4a**–**c** (0.5–1.1 mmol) in MeOH (1 mL) was added NaOH (4–6 equiv) in MeOH (1.0 M). The reaction mixture was stirred for 2 h and then quenched with 1.0 M aq HCl (4–6 mL). Brine (10 mL) and EtOAc (10 mL) were added and the organic phase was separated. The aqueous phase was extracted with EtOAc (2 × 10 mL), the combined organic phases were washed with brine (10 mL), and

dried over Na_2SO_4. The crude product was purified by flash chromatography (silica gel; hexanes → 50% EtOAc in hexanes) to give **12a–c** and **13a–c**.

(1*R,2*S**,3*S**,4*S**)-3-Acetylbicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (12a)**[2a]

White solid; yield: 0.085 g [57% based on 0.149 g (0.083 mmol) of **3a**]; mp 103–105 °C.

^{1}H and ^{13}C NMR spectra match with those described in the literature.[2a]

(1*R,2*S**,3*S**,4*S**)-3-Hexanoylbicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (12b)**

White solid; yield: 0.221 g [88% based on 0.250 (1.06 mmol) of **3b**]; mp 92–94 °C.

IR (CH_2Cl_2): 3300–2750, 1744, 1703 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.31 (dd, *J* = 2.9, 5.5 Hz, 1 H), 6.17 (dd, *J* = 2.7, 5.7 Hz, 1 H), 3.46 (t, *J* = 4.2 Hz, 1 H), 3.27 (br s, 1 H), 3.01 (br s, 1 H), 2.77 (m, 1 H), 2.64–2.48 (m, 2 H), 1.64–1.25 (m, 8 H), 0.89 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.8, 179.9, 137.8, 135.9, 54.6, 47.0, 46.7, 46.6, 45.4, 42.6, 31.5, 23.7, 22.6, 14.0.

HRMS (DART-TOF): *m*/*z* [M + 1]$^+$ calcd for $C_{14}H_{21}O_3$: 237.1491; found: 237.1497.

(1*R,2*S**,3*S**,4*S**)-3-(3-Phenylpropanoyl)[2.2.1]hept-5-ene-2-carboxylic Acid (12c)**

Off-white solid; yield: 0.202 g [74% based on 0.271 g (1.00 mmol) of **3c**]; mp 60.5–62 °C.

IR (CH_2Cl_2): 3300–2700, 1744, 1706 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (m, 2 H), 7.19 (m, 3 H), 6.26 (dd, *J* = 3.3, 5.5 Hz, 1 H), 6.15 (dd, *J* = 2.9, 5.5 Hz, 1 H), 3.42 (t, *J* = 4.0 Hz, 1 H), 3.25 (br s, 1 H), 2.97–2.82 (m, 5 H), 2.75 (dd, *J* = 1.1, 4.4 Hz, 1 H), 1.47 (br d, *J* = 8.8 Hz, 1 H), 1.36 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.6, 179.4, 141.1, 137.8, 135.9, 128.6, 128.5, 126.3, 54.8, 46.8 (2 C), 46.5, 45.4, 44.2, 30.1.

HRMS (DART-TOF): *m*/*z* [M + 1]$^+$ calcd for $C_{17}H_{19}O_3$: 271.1334; found: 271.1343.

(1*R,2*S**,3*S**,4*S**)-3-Acetylbicyclo[2.2.2]oct-5-ene-2-carboxylic Acid (13a)**[2a]

White solid; yield: 0.089 g [86% based on 0.104 g (0.53 mmol) of **4a**]; mp 104–106 °C.

^{1}H and ^{13}C NMR spectra match with those described in the literature.[2a]

(1*R,2*S**,3*S**,4*S**)-3-Hexanoylbicyclo[2.2.2]oct-5-ene-2-carboxylic Acid (13b)**

Pale yellow oil; yield: 0.0137 g [81% based on 0.169 g (0.67 mmol) of **4b**].

IR (CH_2Cl_2): 3400–2700, 1741, 1707 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.39 (t, *J* = 7.1 Hz, 1 H), 6.25 (br t, *J* = 7.1 Hz, 1 H), 3.30 (dd, *J* = 2.1, 5.5 Hz, 1 H), 3.06 (m, 1 H), 2.93–2.87 (m, 2 H), 2.58–2.42 (m, 2 H), 1.64–1.56 (m, 3 H), 1.37–1.22 (m, 6 H), 1.07 (m, 1 H), 0.87 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.4, 180.7, 134.6, 133.2, 53.7, 43.4, 41.4, 32.4, 32.2, 31.5, 24.3, 23.7, 22.6, 20.1, 14.1.

HRMS (DART-TOF): *m*/*z* [M + 1]$^+$ calcd for $C_{15}H_{23}O_3$: 251.1647; found: 251.1655.

(1*R,2*S**,3*S**,4*S**)-3-(3-Phenylpropanoyl)[2.2.2]oct-5-ene-2-carboxylic Acid (13c)**

White solid; yield: 0.147 g [51% based on 0286 g (1.00 mmol) of **4c**]; mp 113.5–115 °C.

IR (CH_2Cl_2): 3400–2800, 1742, 1705 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (m, 2 H), 7.21–7.17 (m, 3 H), 6.36 (br t, *J* = 7.1 Hz, 1 H), 6.25 (br t, *J* = 7.0 Hz, 1 H), 3.30 (dd, *J* = 2.0, 5.6 Hz, 1 H), 3.05 (m, 1 H), 2.96–2.74 (m, 6 H), 1.59 (m, 1 H), 1.29–1.21 (m, 2 H), 1.01 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.1, 180.5, 141.1, 134.6, 133.2, 128.6, 128.5, 126.3, 53.4, 43.4, 43.1, 32.3, 32.2, 30.0, 24.3, 20.0.

HRMS (DART-TOF): *m*/*z* [M + 1]$^+$ calcd for $C_{18}H_{21}O_3$: 285.1491; found: 285.1494.

One-Pot Procedure for the Synthesis of 12a–c from 1a–c; General Procedure

To a solution of **1a**, **1b**, or **1c** (1.0 mmol) in MeOH (5 mL) was added 1,3-cyclopentadiene (0.50 mL, 6.0 mmol) and the reaction mixture was stirred for 4 h at 22 °C. Aq 2 M NaOH (5.0 mL, 10 mmol) was added and the mixture was stirred 0.5 h at 22 °C. The mixture was quenched with aq 1 M HCl (15 mL). The aqueous phase was extracted with EtOAc (2 × 25 mL), the combined organic phases were gently washed with brine (50 mL), and dried over Na_2SO_4. The solvent was removed on the rotary evaporator, and the crude product was purified by flash chromatography (silica gel; hexanes → 50% EtOAc in hexanes) to give **12a** (78%), **12b** (56%) or **12c** (78%).

(2*S,3*R**,4*S**)-3-Acetyl-4-isobutyl-1,2,3,4,5,6,7,8-octahydronaphthalene-2-carboxylic Acid (15a)**

A solution of (*E*)-1-(3-methylbutylidene)-2-methylidenecyclohexane (**14**; 1.026 g, 6.25 mmol; see Supporting Information) and **1a** (0.530 g, 4.65 mmol) in CH_2Cl_2 (15 mL) was stirred at 40 °C for 20 h. After removing the volatiles on the rotary evaporator, the crude product (90:10 dr) was purified by flash chromatography (silica gel; 10 → 50% EtOAc in hexanes) to give **15a** as the chain tautomer; white solid; yield: 1.04 g (80%); mp 104–107 °C.

IR (CH_2Cl_2): 3300–2500, 1752, 1708 1681 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.38 (br s, 1 H) 2.90 (m, 1 H), 2.50–2.37 (m, 2 H) 2.24 (s, 3 H), 1.18–2.15 (m, 12 H), 0.88 (d, *J* = 6.2, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.8, 178.8, 128.8, 127.5, 51.2, 41.6, 40.2, 38.2, 32.0, 30.7 (2 C), 28.2, 26.1, 23.8, 23.5, 22.7, 21.7.

HRMS (DART-TOF): *m*/*z* [M + 1]$^+$ calcd for $C_{17}H_{27}O_3$: 279.1960; found: 279.1964.

(2*S,3*R**,4*S**)-3-Formyl-4-isobutyl-1,2,3,4,5,6,7,8-octahydronaphthalene-2-carboxylic Acid (15b)**

A solution of **14** (2.50 g, 15.2 mmol) and **1e** (1.00 g, 10.0 mmol) in CH_2Cl_2 (30 mL) was heated to 40 °C for 18 h. After removing the volatiles on the rotary evaporator, the crude product was purified by flash chromatography (silica gel; hexanes → 50% EtOAc in hexanes) to give **15b** as the ring tautomer; white solid; yield: 2.22 g (84%); mp 108–111 °C.

IR (CH_2Cl_2): 3570, 1775 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.40 (br s, 1 H), 3.80 (br s, 1 H), 3.11 (m, 1 H), 2.66 (m, 1 H), 2.34–2.13 (m, 3 H), 1.97 (br s, 4 H), 1.70 (m, 1 H), 1.61–1.50 (m, 4 H), 1.42–1.23 (m, 2 H), 0.93 (d, *J* = 6.6 Hz, 3 H), 0.89 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.8, 133.0, 130.8, 100.9, 46.3, 39.4, 37.0, 36.0, 30.7, 29.3, 27.7, 25.5, 23.4 (2C), 22.8, 22.5.

HRMS (DART-TOF): *m*/*z* [M + 1]$^+$ calcd for $C_{16}H_{25}O_3$: 265.1804; found: 265.1807.

(3*S,3a*R**,4*S**,9a*S**)-4-Isobutyl-3-methyl-3a,4,5,6,7,8,9,9a-octahydronaphtho[2,3-*c*]furan-1(3*H*)-one (16a)**

To a solution of ClTi(O-*i*Pr)$_3$ (0.81 mL 3.50 mmol) in anhyd THF (6 mL) at 0 °C was added MeLi (2.0 mL, 1.6 M in hexanes, 3.2 mmol) and the reaction mixture was stirred for 1 h. After the mixture was warmed to 22 °C, **15b** (0.260 g, 0.985 mmol) was added and the mixture was stirred at 22 °C for 19 h. The mixture was quenched with aq 1 M HCl (40 mL), stirred vigorously for 15 min, and extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (50 mL) and dried over Na_2SO_4. The volatiles were removed on the rotary evaporator and the crude product was purified by flash chromatography (5% EtOAc in hexanes → 50% EtOAc in hexanes) to give **16a**; white solid; yield: 0.241 g (93%); mp 81–84 °C.

IR (CH_2Cl_2): 1763 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.18 (dq, *J* = 4.2, 6.4 Hz, 1 H) 3.00 (qd, *J* = 2.9, 8.2, 10.5 Hz, 1 H), 2.44 (dt, *J* = 4.5, 10.5 Hz, 1 H), 2.33 (dd, *J* = 2.8, 15.6 Hz, 1 H), 2.24–2.13 (m, 2 H), 1.99 (br s, 3 H) 1.67–1.49 (m, 6 H), 1.36 (m, 1 H), 1.35 (d, *J* = 6.2 Hz, 3 H), 1.19 (m, 1 H), 0.93 (d, *J* = 6.6 Hz, 3 H), 0.89 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.6, 133.0, 130.7, 77.3, 45.3, 39.4, 37.3, 37.0, 30.6, 29.3, 28.3, 25.6, 23.4, 23.2, 22.9, 22.7.

HRMS (DART-TOF): *m*/*z* [M + 1]$^+$ calcd for $C_{17}H_{27}O_2$: 263.2011; found: 263.2017.

(3*R,3a*R**,4*S**,9a*S**)-4-Isobutyl-3-methyl-3a,4,5,6,7,8,9,9a-octahydronaphtho[2,3-*c*]furan-1(3*H*)-one (16b)**

To a solution **15a** (0.094 g, 0.38 mmol) in EtOH (2 mL) was added $NaBH_4$ (0.075 g, 0.19 mmol) and the reaction mixture was stirred for 1 h at 22 °C. H_2O (10 mL) and aq 1 M HCl (10 mL) were added and the mixture was stirred vigorously for 1 h. The mixture was extracted with Et_2O (3 × 30 mL), the combined organic extracts were washed with brine (30 mL), dried over $NaSO_4$, and concentrated on the rotary evaporator. The crude product (**16a**:**16b** = 6:94) was purified by flash chromatography (silica gel; 10 → 25% EtOAc in hexanes) to give **16b**; white solid; yield: 0.061 g (69%); mp 125–127 °C.

IR (CH_2Cl_2): 1765 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.67 (dq *J* = 5.0, 6.8 Hz, 1 H) 2.88 (ddd, *J* = 5.0, 8.4, 11.2 Hz, 1 H), 2.48 (m, 1 H), 2.38 (m, 1 H), 2.25–1.88 (m, 6 H) 1.70–1.40 (m, 5 H), 1.50 (d, *J* = 6.6 Hz, 3 H), 1.25–1.12 (m, 2 H), 0.91 (d, *J* = 6.6 Hz, 3 H), 0.77 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.2, 134.6, 127.7, 79.0, 44.0, 39.6, 38.7, 37.0, 32,1, 30.6, 27.3, 26.3, 24.8, 23.4, 23.2, 21.3, 14.9.

HRMS (DART-TOF): *m*/*z* [M + 1]$^+$ calcd for $C_{17}H_{27}O_2$: 263.2011; found: 263.2019.

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Supporting Information

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