Convenient Synthesis of *N*-Benzyl-1,4-dihydropyridines, Cyclohexenones, and Bicyclo[3.3.1]nonan-3-one Derivatives from 1-Aza-1,3-butadienes

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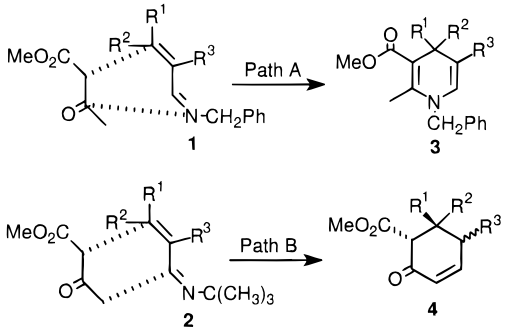
Readily available 1-aza-1,3-butadienes (enimines) react with methyl acetoacetate and acetylacetone in the presence of catalytic amounts of lithium iodide to form in high yields unsymmetrically substituted 1,4-dihydropyridines or cyclohexenones. The reaction pathway depends on the structure of the enimine used. This divergence was not observed when the enimines were reacted with dimethyl 1,3-acetonedicarboxylate to provide bicyclo[3.3.1]nonane-3-one derivatives in excellent yields in a remarkably stereoselective reaction.

Introduction

1-Aza-1,3-butadiene derivatives (enimines) are reported to be useful intermediates in various synthetic procedures[1−3] and natural product syntheses.[4−7] Their use as electrophiles in 1,2- and 1,4-additions has been investigated,[8−10] and their utility as dienes in hetero Diels−Alder reactions continues to be the subject of considerable interest.[11−13] Recently, reports have appeared on the structure[14,15] and application[16,17] of metal-coordinated 1-aza-1,3-diene complexes, and an improved procedure for the preparation of cyclic enimines has been described.[18] Our main interest regarding the 1-aza-1,3-butadienes has been to investigate whether enimines are suitable substrates in reactions that involve two consecutive steps, namely a Michael addition to the enimine with a subsequent ring-closure step.[19]

In this paper, we disclose results that demonstrate that the structure of the enimine determines whether it reacts to afford biologically important 1,4-dihydropyridines[20,21] or cyclohexenones, which have been identified as key intermediates in natural product synthesis.[22,23] The reaction of methyl acetoacetate with *N*-benzylenimines like **1** yielded 1,4-dihydropyridines (Scheme 1, path A), but if the benzyl group in **1** was replaced by a *tert*-butyl group, the reaction took a completely different course affording cyclohexenone derivatives, reportedly difficult to obtain by other methods[24,25] (Scheme 1, path B).

Scheme 1



Compound	R^1	R^2	R^3
a	Me	H	H
b	Et	H	H
c	Ph	H	H

Compound	R^1	R^2	R^3
d	Me	Me	H
e	Me	H	Me

In these reactions the 1,3-dicarbonyl compound contributes either two or three carbon atoms to the produced six-membered ring. On the basis of this observation the dicarbonyl compound has been depicted in Scheme 1 as a C_2-building block (path A) or as a C_3-building block (path B), respectively.

Results and Discussion

The 1-aza-1,3-butadienes **1** and **2** were conveniently prepared by stirring the dichloromethane solution of an α,β-unsaturated aldehyde and an amine over molecular sieves at ambient temperature for 24 h under nitrogen.

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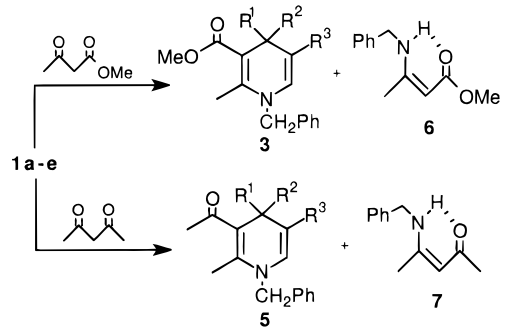
Scheme 2



This procedure afforded the air- and moisture-sensitive products as colorless or pale yellow oils in 50−80% yield after distillation. The molecular sieves could be replaced by potassium carbonate.[26] The protocol was in all cases advantageous compared with conventional condensation using a Dean−Stark trap. The *N*-*tert*-butylenimines were less sensitive toward air and moisture than their *N*-benzyl analogues and could be stored for months refrigerated under an inert atmosphere, as judged from their NMR spectra. It is noteworthy that neither acrolein nor α,β-unsaturated ketones produced the desired enimines.

Reaction of *N*-Benzyl-1-aza-1,3-butadienes with Acetoacetate and Acetylacetone. We have previously noted that basic reaction conditions in reactions between enimines and 1,3-dicarbonyl compounds did not yield any isolable products,[19] and this result was ascribed to the diminished reactivity of the enimine toward nucleophiles as compared to the corresponding unsaturated carbonyl compounds. In order to enhance the reactivity of the enimines the reaction was carried out with catalytic amounts of *p*-toluenesulfonic acid (TsOH) and produced in good yields **3a** from **1a** (Scheme 2) and **4a** from **2a** (Scheme 4). Unfortunately, the employment of TsOH as a catalyst was not extendable to the other enimines, and further efforts to promote the reaction by conventional Lewis acids ($AlCl_3$, $FeCl_3$, $TiCl_4$, $BF_3{\cdot}OEt_2$) did not furnish the products **3/4** in satisfactory yields. Recently, Scettri et al. reported on the use of lithium iodide as a preferable catalyst in the Michael reaction when performed under neutral reaction conditions.[27] A minor modification of their procedure was successful with our compounds. Stirring a dimethoxyethane (DME) solution of the reactants in the presence of 10 mol % of lithium iodide at ambient temperature for 24 h afforded the products **3** in good to excellent yields after chromatographic purification (Table 1).

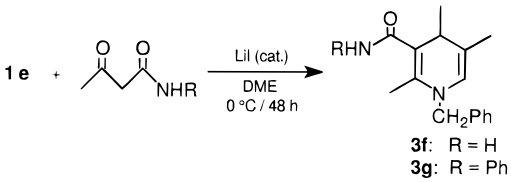
The reaction of **1a**−**e** with acetylacetone yielded the 1,4-DHP **5**, but only **5a,c,e** were obtained in satisfactory yields (see Table 1). The concomitant formation of the enamino ketone **7** was observed in 20−50% yields, and in the case of **1d** it was formed in 50% yield as the sole isolable product. An analogous product, the enamino ester **6**, was isolated in small amounts in the reaction of methyl acetoacetate with enimines **1c** and **1d** only. The formation **6** and **7** can be rationalized as an iminolysis of the dicarbonyl compound,[28,29] initiated by the attack of the imine nitrogen on the carbonyl group. The

Table 1. Preparation of Compounds 3, 4, 5, 8 and 10

compd	R^1	R^2	R^3	yield[a] (%)	bp (°C)/Torr [mp (°C)]
3a	Me	H	H	61	120−130/0.008
3b	Et	H	H	44	130−140/0.03
3c	Ph	H	H	55	180−200/0.03
3d	Me	Me	H	44	180−200/0.05
3e	Me	H	Me	72	140−150/0.008
3f		R = H		63	[173−174]
3g		R = Ph		27	[117−118]
4a	Me	H	H	66	95−100/0.04
4b	Et	H	H	60	70−80/0.008
4c	Ph	H	H	50	[90−92]
4d	Me	Me	H	20	30−40/0.05
5a	Me	H	H	50	110−120/0.005
5b	Et	H	H	20	110−120/0.008
5c	Ph	H	H	40	190−200/0.008
5e	Me	H	Me	45	130−140/0.06
8a	Me	H	H	38	55−65/0.04
8b	Et	H	H	56	80−90/0.008
8c	Ph	H	H	25	210−220/0.07
8e	Me	H	Me	30	80−90/0.008
10a	Me		H	44	50−60/0.008
10b	Et		H	80	40−50/0.008
10c	Ph		H	34	170−180/0.008
10e	Me		Me	62	70−80/0.06

[a] Satisfactory spectroscopic data were obtained for all compounds in the table.

Scheme 3



synthetic potential of this reaction sequence is exemplified by the transformation of **1e** into 1,4-dihydronicotinamide derivatives **3f,g** as depicted in Scheme 3.

Reaction of *N*-*tert*-Butyl-1-aza-1,3-butadienes with Acetoacetate and Acetylacetone. The reaction of enimines **2** with methyl acetoacetate furnished the cyclohexenones **4** in relatively high yields, as seen in Table 1. We did not succeed in isolating **4e** in pure form, yet the phenol **10e** was obtained in 62% yield in a one-pot procedure starting with the enimine **2e**.

A competitive reaction channel leading to products analogous to **6** and **7** was not detected in the case of enimines **2**, but the formation of different reaction products **9c,d** from **2c,d** was observed (Scheme 4). These highly conjugated reaction prodcuts are probably formed by an initial 1,2-addition of the dicarbonyl compound to the enimine with subsequent elimination of the amino functionality. It is noteworthy that the use of catalytic amounts of $Hg(OAc)_2$ seemed to generally facilitate such an 1,2-addition. Nevertheless, the isolated yields of **9** remained low (<25%).

The prepared cyclohexenones were easily converted to the aromatic compounds **10** by treatment with bromine in acetic acid.[22] Similar phenol derivatives have been used in natural product synthesis,[22,23,30] and related trifluoromethyl derivatives are reported to exhibit biological activity.[31] Attempts to develop this procedure into a one-pot protocol for the synthesis of phenols were

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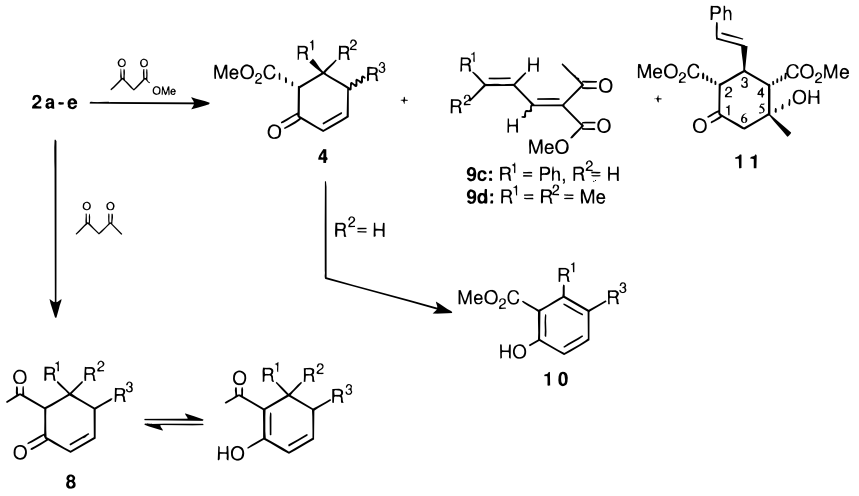
Scheme 4



unfruitful with regard to yields, apart from the previously mentioned **10e**.

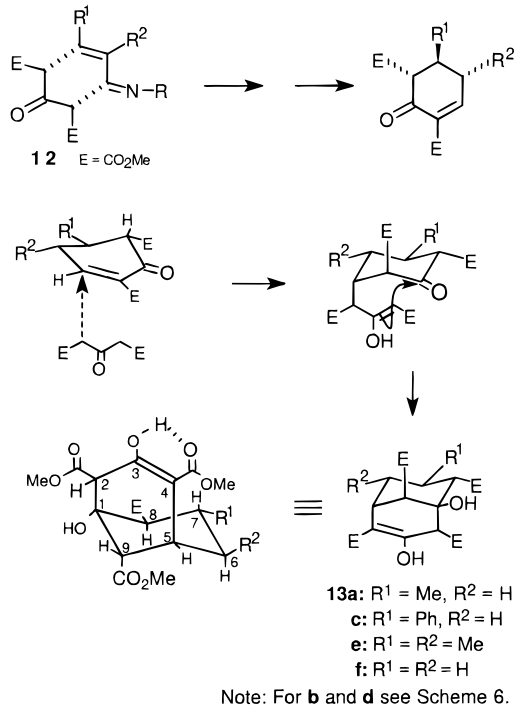
Analogously, enimines **2** and acetylacetone afforded cyclohexenones **8** in reasonable yields (see Table 1), except for enimine **2d**, which did not furnish detectable amounts of **8d**. All reactions produced to some extent the α,β-unsaturated aldehyde from which the enimine was originally prepared.

Spectroscopic Identification of the Products. The structures of all products were determined from their NMR spectral data by comparison with previously published data of known or similar compounds.

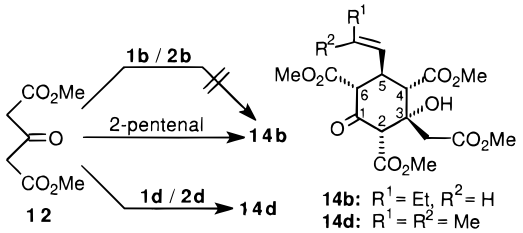
The ^{1}H NMR spectra of compounds **4** revealed for H-6, located α to both carbonyl groups, a doublet with a coupling constant between 11.4 and 12 Hz. The observation of this large $^3J_{(H\text{-}6,H\text{-}5)}$ led to the assignment of pseudoaxial dispositions for both pertinent nuclei, thereby reserving the pseudoequatorial positions for the larger groups (alkyl/phenyl at C-5 and carbomethoxy at C-6).[32] The high stereoselectivity achieved in these cases is concordant with the findings of other authors.[25]

The Reaction of 1-Aza-1,3-butadienes with Dimethyl 1,3-Acetonedicarboxylate. In continuing our studies on the synthetic utility of enimines derived from relatively simple open-chain α,β-unsaturated aldehydes, we wished to diversify the products and at the same time obtain compounds that could serve as intermediates for further transformations. For that purpose, enimines **1** and **2** were reacted with dimethyl 1,3-acetonedicarboxylate (dimethyl 3-oxopentanedioate) **12**, in the hope of realizing similar control of the reaction pathway as outlined in Scheme 1. When the keto diester **12** was treated with either **1a** or **2a**, the only isolable product was a crystalline compound, whose ^{1}H and ^{13}C NMR spectra revealed four methoxycarbonyl groups. This result suggested the participation of two molecules of the keto diester in the reaction, and so the reaction was repeated with a diester/enimine ratio of 2:1, affording the same crystalline product **13a** in 80% yield after recrystallization. Similarly, enimines **1c/2c** and **1e/2e** produced the bicyclo derivatives **13c** and **13e** as the sole products in 82% and 73% yields, respectively. A probable pathway for the formation of the bicyclo[3.3.1]nonan-3-one derivatives **13a,c,e** is outlined in Scheme 5, proposing the intermediate formation of a cyclohexenone derivative

Scheme 5



Scheme 6



that undergoes a second Michael addition with **12** with an ensuing ring closure. All attempts to isolate or to identify the cyclohexenone intermediate were to no avail, and in Scheme 5 the stereochemistry of this intermediate has been tentatively drawn with reference to **4**. Unexpectedly, enimines **1b/2b** did not afford any isolable products. The reaction of **12** with enimines **1d/2d** provided the cyclohexanone derivative **14d** in 96% yield, after recrystallization (Scheme 6). The formation of **14d** can easily be explained as an initial 1,2-addition of the

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keto diester to the enimine to afford a product analogous to **9**. A second molecule of the keto diester then undergoes a Michael addition (1,4-addition) to this intermediate with a subsequent cyclization. With this in mind, we returned to the reaction of methyl acetoacetate with enimines **1c,d/2c,d**, which produced **9c,d**. A closer look at these reactions revealed that only the reaction for **1c/2c**, when performed in the presence of catalytic amounts of $Hg(OAc)_2$, rendered small amounts of a compound **11** comparable to **14d** (Scheme 4). The yields of **11** were increased to 33% if the ratio of acetoacetate/enimine was raised from 1:1 to 2:1. An analogous cyclohexanone derivative has been reported as a side product in a Hantzsch-related synthesis of N-substituted dihydropyridines.[33] The stereochemistry proposed for **11** and displayed in Scheme 4 is based on the observation that the signals assigned to H-2 and H-4 appeared as doublets with $J = 11.9$ Hz. A third signal at δ 3.87 was assigned to H-3 and exhibited a dt with $J = 9.7$ and 11.9 Hz. This led to the assignment of axial dispositions for all three protons. The proposed relative configuration at C-5 is supported by the observation of a long-range coupling between the hydroxyl proton of the C-5 hydroxyl and a proton at C-6, indicating that both the hydroxyl group and the H-6 are in axial dispositions. The hydroxyl group is probably hydrogen bonded to the ester carbonyl at C-4, which might provide the conformational homogeneity to allow detectable long-range coupling. An analogous argument was used to define the stereochemistry of **14b,d**. A long range coupling between the hydroxyl proton of the C-3 hydroxyl and H-4 was observed in both cases.

Interestingly, the base-catalyzed Michael reaction between the keto diester **12** and the corresponding α,β-unsaturated aldehyde furnished in excellent yield compounds **13a,c,e** and **14b,d**. As previously noted, enimines **1b/2b** did not afford any identifiable products in the reaction with the keto diester, but the corresponding aldehyde, 2-pentenal, reacted to produce a cyclohexanone derivative **14b** in 68% yield (Scheme 6). Acrolein, which defied transformation to an enimine, reacted to form a bicyclo[3.3.1]nonan-3-one derivative **13f** in 67% yield. The transformation of the α,β-unsaturated aldehyde to the less reactive 1-aza-1,3-butadiene derivative obviously offers no advantages in these cases. Compounds **13** are thus accessible by a remarkably simple procedure from readily available starting materials.

It is worthy of note that the prepared compounds **13** exhibited considerable antitumor activity.[34] Moreover, these compounds deserve attention in view of the fact that bicyclo[3.3.1]nonan-3-one derivatives have been used as key precursors in a synthetic strategy toward the taxane skeleton.[35−37]

The structures of **13** were elucidated on the basis of their spectral data, representatively illustrated for compound **13a** (see Scheme 5, R = Me, R′ = H). It has been argued[38,39] for bicyclo[3.3.1]nonane derivatives that an equatorial substituent on C-7 excludes the boat form for the cyclohexane ring defined by C-9, C-5, C-6, C-7, C-8, and C-1, due to a repulsive interaction with hydrogen or a substituent on C-9. The stereochemical assignments at C-7, C-8, and C-9 of **13a** were determined for the following data. In the ^{1}H NMR spectrum, a doublet at δ 2.70 ppm was assigned to the proton at C-8. The large coupling constant, $^3J = 12.05$ Hz, was interpreted as being due to axial−axial interaction, positioning both the proton at C-7 and the proton at C-8 in the axial configurations. A signal observed at δ 1.59 ppm (dtd) was assigned to the equatorial proton at C-6. This signal displayed a long-range coupling constant, $^4J = 1.0$ Hz, suggesting that the proton at C-9 possessed an equatorial orientation. A broad singlet at δ 11.96 ppm was indicative of the fully enolized structure; treatment of **13a** with acetic anhydride in the presence of 4-(dimethylamino)-pyridine led to the acetylation of the enolic hydroxy group.

In light of previous results illustrated in Scheme 1, it is noteworthy that dimethyl 1,3-acetonedicarboxylate reacted with **1** and **2** merely as a C_3-building block, irrespective of which group, benzyl or *tert*-butyl, was attached to the nitrogen atom.

In spite of the absence of rigorous data, the formation of the products **3**, **4**, **5**, **8**, and **13** can be rationalized as a two-step reaction, the second step being the cyclization of the Michael adduct **15**, depicted in Scheme 7 for enimines **1a/2a**. Examination of models with R′ = H suggests that when R = *tert*-butyl, steric crowding in the intermediate **16** is responsible for the alternate reaction along pathway B. By presuming that the intermediate **15** cyclizes to form **4** through its enol tautomer **17**, it can be tentatively inferred that the low concentration of **17** makes this reaction channel only feasible when pathway A is hindered. With R′ = methoxycarbonyl, the situation is arguably different, i.e., the keto−enol tautomerism favors tautomer **18** as compared to **17**, and cyclohexenone formation is apparently faster than a competitive reaction along pathway A, irrespective of which group is attached to the enimine nitrogen.

In summary, we have disclosed how 1-aza-1,3-butadienes, derived from simple open-chain α,β-unsaturated aldehydes, give access to unsymmetrically substituted 1,4-DHP or cyclohexenones, depending on the structure of the 1-aza-1,3-butadiene. For the formation of the cyclohexenone derivatives **4** and **8** it is clearly advantageous to convert the α,β-unsaturated aldehydes to the less reactive enimines before conducting the Michael reaction. Contrary to this result, for the formation of the bicyclo[3.3.1]nonan-3-one derivatives **13** it is more expedient to apply to enals directly. We did not succeed in preparing enimines from α,β-unsaturated ketones, and that limits the scope of the reaction.

Experimental Section

The ^{1}H and ^{13}C NMR spectra were recorded on a 250 MHz spectrometer. Chemical shifts are reported in ppm with respect to residual $CHCl_3$ at 7.26 downfield from Me_4Si. Multiplicities in the ^{13}C NMR spectra were determined using DEPT pulse sequences. 2D COSY (H/H and C/H) experiments were performed with compounds **13a,e** and **14b**. IR spectra were recorded as thin films or KBr pellets. Elemental analyses were carried out at the University of Iceland. Melting points were determined in open capillaries and are uncorrected.

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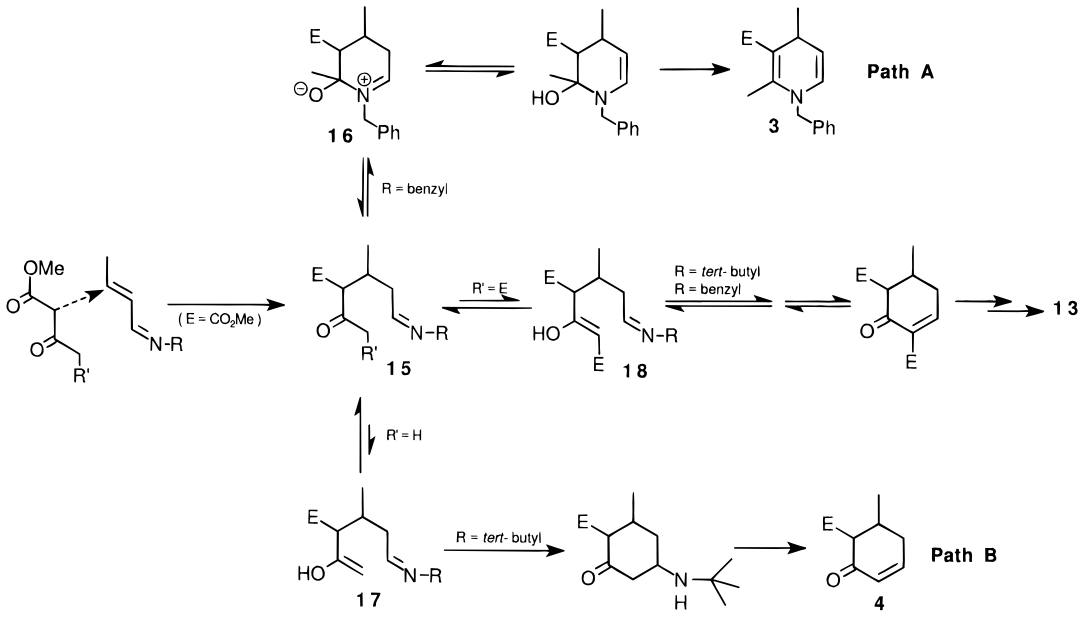
Scheme 7



Distillation of small amounts was effected with a bulb-to-bulb distillation in a Kugelrohr oven. Analytical TLC was performed by using 0.25 mm coated silica gel plates with F-254 indicator. Visualization was accomplished by UV light.

General Procedure. The reactions were carried out under nitrogen in thoroughly dried glassware, and the procedure was essentially the same in all cases. A solution of the dicarbonyl compound (0.01 mol) and lithium iodide (0.001 mol) in 2−3 mL of dry DME was added dropwise to a stirred solution of the enimine (0.01 mol) in 5−10 mL of dry DME. The resulting mixture was stirred at ambient temperature for 24 h (for the preparation of **3f,g**, molecular sieves (4A) were added and the mixture was stirred at 0 °C for 48 h). After removal of the solvent under reduced pressure, oily residues were purified by short column chromatography (silica gel, eluted with dichloromethane/ethyl acetate) and Kugelrohr distillation. Crystals were recrystallized from dichloromethane (**3f**), 1-butanol (**3g**), hexane (**4c**, **11**), and methanol (**13**, **14**).

Compounds **3**, **4**, **5**, **8**, and **10** are either known or similar to known compounds. The analytical and spectra data for **11**, **13**, and **14** are as follows.

5-Hydroxy-2,4-Bis(methoxycarbonyl)-5-methyl-3-(2-phenylethenyl)cyclohexanone (11): mp 182−183 °C (hexane); IR (KBr) 1710, 1725, 1740, 3410 cm^{-1}; ^1H NMR (C_6D_6) δ 0.93 (3 H, s), 1.67 (1 H, dd, J = 2.7, 14.3 Hz), 2.26 (1 H, d, J = 11.9 Hz), 2.53 (1 H, d, J = 14.3 Hz), 3.06 (3 H, s), 3.07 (1 H, d, J = 11.9 Hz), 3.37 (3 H, s), 3.59 (1 H, d, J = 2.7 Hz (D_2O-exchangeable)), 3.87 (1 H, dt, J = 9.7, 11.9 Hz), 5.83 (1 H, dd, J = 9.7, 15.6 Hz), 6.50 (1 H, d, J = 15.6 Hz), 7.05−7.19 (5 H, m); ^{13}C NMR ($CDCl_3$) δ 28.7 (q), 43.6 (d), 52.2 (d), 52.3 (q), 52.4 (t), 55.6 (d), 61.5 (d), 72.9 (s), 126.5 (d, 3 C), 128.0 (d), 128.6 (d, 2 C), 133.8 (d), 136.3 (s), 168.3 (s), 174.4 (s), 200.8 (s). A resolution of the signal at 126.5 ppm was achieved in acetone-d_6; LD-FTMS m/z 385 ($M + K^+$), 329. Anal. Calcd for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40; O, 27.71. Found: C, 65.54; H, 6.47.

1-Hydroxy-2,4,8,9-tetrakis(methoxycarbonyl)-7-methylbicyclo[3.3.1]nonan-3-one (13a): yield 80%; mp 163−165 °C (methanol); IR (KBr) 1710, 1735, 1760, 3490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (3 H, d, J = 6.4 Hz), 1.15 (1 H, ddd, J = 3.2, 11.8, 14.1 Hz), 1.59 (1 H, dtd, J = 1.0, 3.2, 14.1 Hz), 1.87 (1 H, m), 2.70 (1 H, d, J = 12.0 Hz), 3.50 (1 H, q, J = 3.2 Hz), 3.53 (1 H, dd, J = 1.0, 3.2 Hz), 3.71 (3 H, s), 3.73 (3 H, s), 3.78 (3 H, s), 3.79 (3 H, s), 4.45 (1 H, s) 4.52 (1 H, s), 11.96 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 19.3 (q), 28.0 (d), 31.8 (d), 34.1 (t), 46.4 (d), 51.8 (q), 51.88 (d), 51.92 (q), 52.3 (q), 52.4 (q), 57.9 (d), 71.9 (s), 101.9 (s), 167.6 (s), 170.2 (s), 170.8 (s), 173.0 (s), 173.5 (s); LD-FTMS m/z 439 ($M + K^+$), 351, 319. Anal. Calcd for $C_{18}H_{24}O_{10}$: C, 54.00; H, 6.04; O, 39.96. Found: C, 54.34; H, 5.96.

1-Hydroxy-2,4,8,9-tetrakis(methoxycarbonyl)-7-phenylbicyclo[3.3.1]nonan-3-one (13c): yield 82%; mp 176−177 °C (methanol); IR (KBr) 1730, 1755, 3500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.64 (1 H, ddd, J = 3.1, 12.3, 14.0 Hz), 1.69 (1 H, ddd, J = 3.1, 5.6, 14.0 Hz), 2.98 (1 H, dt, J = 5.6, 12.3 Hz), 3.42 (1 H, d, J = 12.3 Hz), 3.42 (3 H, s), 3.60 (1 H, q, J = 3.1 Hz), 3.65 (1 H, d, J = 3.1 Hz), 3.74 (3 H, s), 3.78 (3 H, s), 3.85 (3 H, s), 4.49 (1 H, s), 4.50 (1 H, s), 7.11−7.28 (5 H, m), 12.07 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 32.0 (d), 33.7 (t), 39.6 (d), 46.4 (d), 51.7 (q), 51.9 (q), 52.2 (d), 52.4 (q), 52.5 (q), 56.3 (d), 72.0 (s), 101.8 (s), 127.0 (d), 127.5 (d, 2 C), 128.4 (d, 2 C), 141.2 (s), 167,7 (s), 170.0 (s), 170.8 (s), 172.1 (s), 173.4 (s). Anal. Calcd for $C_{23}H_{26}O_{10}$: C, 59.74; H, 5.67; O, 34.58. Found: C, 59.85, H, 5.53.

1-Hydroxy-2,4,8,9-tetrakis(methoxycarbonyl)-6,7-dimethylbicyclo[3.3.1]nonan-3-one (13e): yield 73%; mp 127−128 °C (methanol); IR (KBr) 1735, 1750, 3500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.78 (3 H, d, J = 5.4 Hz), 0.81 (3 H, d, J = 5.8 Hz), 1.24 (1 H, ddq, J = 3.0, 12.0, 5.8 Hz), 1.48 (1 H, tq, J = 12.0, 5.4 Hz), 2.78 (1 H, d, J = 12.0 Hz), 3.47 (1 H, t, J = 3.0 Hz), 3.53 (1 H, d, J = 3.0 Hz), 3.70 (3 H, s), 3.73 (3 H, s), 3.77 (3 H, s), 3.78 (3 H, s), 4.50 (2 H, s), 12.24 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 16.4 (q), 16.9 (q), 33.2 (d), 37.1 (d), 38.7 (d), 47.8 (d), 51.6 (q), 51.8 (d), 51.9 (q), 52.3 (q), 52.4 (q), 57.8 (d), 71.8 (s), 99.6 (s), 168.4 (s), 170.2 (s), 171.6 (s), 173.2 (s), 173.6 (s); LD-FTMS m/z 437 ($M + Na^+$), 405, 365. Anal. Calcd for $C_{19}H_{26}O_{10}$: C, 55.07, H, 6.32; O, 38.61. Found: C, 54.96; H, 6.18.

1-Hydroxy-2,4,8,9-tetrakis(methoxycarbonyl)bicyclo-[3.3.1]nonan-3-one (13f): yield 67%; mp 116−117 °C (methanol); IR (KBr) 1725, 1760, 3510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.57 (3 H, m), 1.81 (1 H, m), 3.33 (1 H, dd, J = 4.5, 12.6 Hz), 3.45 (1 H, q, J = 2.9 Hz), 3.50 (1 H, d, J = 2.9 Hz), 3.74 (3 H, s), 3.75 (3 H, s), 3.76 (3 H, s), 3.78 (3 H, s), 4.18 (1 H, s), 4.67 (1 H, s), 12.00 (1 H, s); ^1H NMR (C_6D_6) δ 1.22−1.30 (1 H, m), 1.38−1.70 (3 H, m), 3.14 (3 H, s), 3.16 (3 H, s), 3.25 (3 H, s), 3.40 (3 H, s), 3.42 (1 H, q, J = 3.2 Hz), 3.49 (1 H, dd, J = 4.8, 12.5 Hz), 3.95 (1 H, dd, J = 0.8, 3.2 Hz), 4.72 (1 H, s), 5.10 (1 H, s), 12.66 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 21.4 (t), 24.7 (t), 32.0 (d), 46.6 (d), 48.7 (d), 51.9 (q), 52.11 (q), 52.14 (q), 52.6 (q), 53.0 (d), 71.3 (s), 101.4 (s), 167.4 (s), 169.8 (s), 170.9 (s), 173.1 (s), 173.9 (s); LD-FTMS m/z 409 ($M + Na^+$), 355, 337. Anal. Calcd for $C_{17}H_{22}O_{10}$: C, 52.85; H, 5.74; O, 41.41. Found: C, 53.00; H, 5.74.

5-(1-Butenyl)-3-hydroxy-2,4,6-tris(methoxycarbonyl)-3-[(methoxycarbonyl)methyl]cyclohexanone (14b): yield 68%; mp 140−141 °C (methanol); IR (KBr) 1730, 1750, 3530

cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (3 H, t, J = 7.5 Hz), 1.92 (2 H, ddq, J = 1.2, 6.5, 7.5 Hz), 2.71 (AB system 2 H, ν_A = 2.64 ppm, ν_B = 2.79 ppm, J_{AB} = 17.6 Hz), 3.17 (1 H, dd, J = 1.8, 12.0 Hz), 3.34 (1 H, dd, J = 0.6, 12.0 Hz), 3.59 (1 H, dt, J = 8.7, 12.0 Hz), 3.67 (3 H, s), 3.699 (3 H, s), 3.701 (3 H, s), 3.78 (3 H, s), 4.33 (1 H, d, J = 0.6 Hz), 4.47 (1 H, d, J = 1.8 Hz (D_2O-exchangeable)), 5.16 (1 H, ddt, J = 15.3, 8.7, 1.2 Hz), 5.67 (1 H, dt, J = 15.3, 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 13.6 (q), 25.4 (t), 41.2 (d), 42.4 (t), 51.8 (q), 51.9 (q), 52.1 (q), 52.6 (q), 52.9 (d), 61.5 (d), 61.8 (d), 74.7 (s), 126.1 (d), 137.6 (d), 167.6 (s), 169.8 (s), 170.5 (s), 170.5 (s, 2 C), 197.7 (s). Anal. Calcd for $C_{19}H_{26}O_{10}$: C, 55.07; H, 6.32; O, 38.61. Found: C, 55.10; H, 6.35.

3-Hydroxy-2,4,6-tris(methoxycarbonyl)-3-[(methoxycarbonyl)methyl]-5-(2-methyl-1-propenyl)cyclohexanone (14d): yield 96%; mp 148−149 °C (methanol); IR (KBr) 1730, 1750, 3490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63 (3 H, d, J = 1.3 Hz), 1.66 (3 H, d, J = 1.3 Hz), 2.70 (AB system 2H, ν_A = 2.63 ppm, ν_B = 2.78 ppm, J_{AB} = 17.6 Hz), 3.11 (1 H, dd, J = 1.8, 11.8 Hz), 3.28 (1 H, dd, J = 0.6, 11.9 Hz), 3.65 (3 H, s), 3.69 (3 H, s), 3.70 (3 H, s), 3.78 (3 H, s), 3.94 (1 H, ddd, J = 10.3, 11.8, 11.9 Hz), 4.36 (1 H, d, J = 0.6 Hz), 4.53 (1 H, d, J = 1.8 Hz (D_2O-exchangeable)), 4.82 (1 H, dm, J = 10.3 Hz); ^{13}C NMR ($CDCl_3$) δ 18.1 (q), 25.8 (q), 37.5 (d), 42.4 (t), 51.8 (q), 51.9 (q), 52.1 (q), 52.7 (q), 53.1 (d), 61.6 (d), 61.8 (d), 74.8 (s) 122.0 (d), 138.1 (s), 167.7 (s), 170.0 (s), 170.5 (s), 170.6 (s), 197.9 (s); LD-FTMS m/z 453 ($M + K^+$), 405, 365. Anal. Calcd for $C_{19}H_{26}O_{10}$: C, 55.07; H, 6.32; O, 38.61. Found: C, 54.92; H, 6.18.

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