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Cobalt-Catalyzed 1,4-Hydrovinylation of Allylsilane and Allylboronic Esters for the Synthesis of Hydroxy-Functionalized 1,4-Dienes

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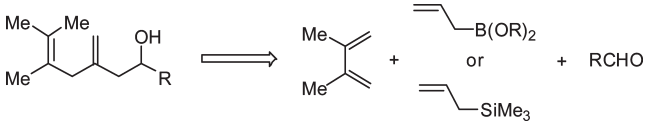
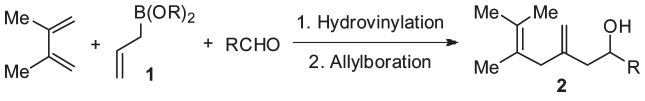


The cobalt(I)-catalyzed 1,4-hydrovinylation reaction of allyl trimethylsilane and allyl pinacol boronic ester with symmetrical and unsymmetrical 1,3-dienes generates building blocks for the in situ allylboration or the Lewis acid induced allylation reaction utilizing the corresponding allyl silane derivatives. The products of these three-component reactions are hydroxy-functionalized 1,4-dienes which can be used for the synthesis of pyranones. An alternate reaction sequence for the synthesis of the hydroxy-functionalized 1,4-dienes by performing the allylation first followed by the cobalt-catalyzed 1,4-hydrovinylation is also possible. Accordingly, polyfunctionalized complex structures can be generated by both approaches in a convergent fashion.

Introduction

New synthetic methods must fulfill various aspects to be of use to the scientific community. Besides fulfilling economic and ecologic demands the methods should also be very selective in terms of chemo-, regio-, and stereoselectivity. In addition, these methods should be highly tolerant toward other functional groups present in the starting material while avoiding side reactions and the need of protecting groups.[1] In this context the cobalt-catalyzed 1,4-hydrovinylation reaction of alkenes with 1,3-dienes has attracted considerable interest for the atom economic synthesis of 1,4-dienes.[2] This methodology allows the application of a broad range of tolerated functional groups permitting the rapid construction of very interesting functionalized building blocks. Of particular interest are building blocks with functionalities in vinylic or allylic position which can be directly used to perform additional carbon−carbon bond formation reactions. Toward this end we identified the cobalt-catalyzed 1,4-hydrovinylation of functionalized terminal alkenes in combination with an allylation reaction of aldehydes utilizing allylboron derivatives or allyl silanes as an appropriate tool to generate increasingly complex products in a short one-pot reaction sequence (Scheme 1).[3] These reactions exhibit a high level of selectivity and very little side reaction is generally observed.

SCHEME 1



(1) Key reference: Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010.

(2) (a) Hilt, G.; du Mesnil, F.-X.; Lüers, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 387. (b) Hilt, G.; Lüers, S. *Synthesis* **2002**, 609. (c) Hilt, G.; Lüers, S.; Schmidt, F. *Synthesis* **2003**, 634. (d) Hilt, G.; Danz, M.; Treutwein, J. *Org. Lett.* **2009**, *11*, 3322. (e) Hilt, G.; Treutwein, J. *Chem. Commun.* **2009**, 1395. For selected recent applications see: (f) Sharma, R. K.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2010**, *132*, 3295. (g) Saha, B.; Smith, C. R.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2008**, *130*, 9000. (h) Shirakura, M.; Suginome, M. *J. Am. Chem. Soc.* **2008**, *130*, 5410. (i) Saha, B.; RajanBabu, T. V. *J. Org. Chem.* **2007**, *72*, 2357. (j) Zhang, A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2006**, *128*, 54. (k) Zhang, A.; RajanBabu, T. V. *Org. Lett.* **2004**, *6*, 1515. (l) Zhang, A.; RajanBabu, T. V. *Org. Lett.* **2004**, *6*, 3159. (m) Kumareswaran, R.; Nandi, M.; RajanBabu, T. V. *Org. Lett.* **2003**, *5*, 4345. (n) Moreau, B.; Wu, J. Y.; Ritter, T. *Org. Lett.* **2009**, *11*, 337. (o) Grabulosa, A.; Muller, G.; Ordinas, J. I.; Mezzetti, A.; Maestro, M. A.; Font-Bardia, M.; Solans, X. *Organometallics* **2005**, *24*, 4961.

(3) For reviews on allylborations see: (a) Pietruszka, J.; Schone, N.; Frey, W.; Grundl, L. *Chem.—Eur. J.* **2008**, *14*, 5178. (b) Kennedy, J. W. J.; Hall, D. G. *J. Org. Chem.* **2004**, *69*, 4412. For recent applications of the Hosomi-Sakurai reaction see: (c) Reddy, U. C.; Bondalapati, S.; Saikia, K. A. *Eur. J. Org. Chem.* **2009**, 1625. (d) Sabot, C.; Guerard, K. C.; Canesi, S. *Chem. Commun.* **2009**, 2941. (e) Kumar, R. S. C.; Reddy, G. V.; Babu, K. S.; Rao, J. M. *Chem. Lett.* **2009**, *38*, 564. (f) Sabot, C.; Commare, B.; Duceppe, M.-A.; Nahi, S.; Guerard, K. C.; Canesi, S. *Synlett* **2008**, 3226. (g) Spangenberg, T.; Airiau, E.; Thuong, M. B. T.; Donnard, M.; Billet, M.; Mann, A. *Synlett* **2008**, 2859. (h) Xu, L.-W.; Yang, M.-S.; Qiu, H.-Y.; Lai, G.-Q.; Jiang, J.-X. *Synth. Commun.* **2008**, *38*, 1011. (i) Shizuka, M.; Snapper, M. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 5049.

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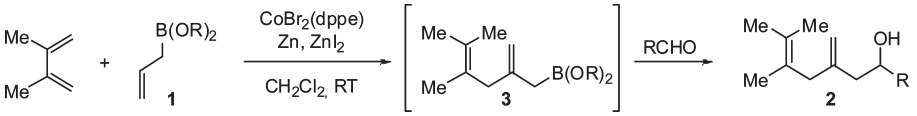
SCHEME 2



Furthermore, the generated products of type **2** are envisaged to serve as a platform for various follow-up chemical transformations. The access to pyranone derivatives upon ozonolysis and acid-induced cyclization of intermediately formed 5-hydroxy-1,3-dicarbonyl derivatives was envisaged as a promising example.[4] This three-component reaction starting from readily available educts inspired us to investigate the further scope of this reaction sequence.

Results and Discussion

First we investigated the use of allyl pinacol boronic ester (**1**, $(OR)_2$ = pinacol) in the cobalt-catalyzed 1,4-hydrovinylation with a simple symmetrical 1,3-diene such as 2,3-dimethyl-1,3-butadiene (DMB) (Scheme 2). The reaction was performed in dichloromethane at room temperature utilizing the cobalt 1,2-bis-diphenylphosphinoethane dibromide complex as catalyst precursor.

Over the course of the investigation we realized that the isolation of the intermediate **3** is not advantageous mainly because of its instability upon column chromatography on silica gel. Therefore, the aldehydes were added at low temperatures to the reaction mixture after completion of the cobalt-catalyzed reaction without any purification of the intermediate **3**. For the isolation of the products of type **2** triethanolamine was added to cleave the boronates formed in situ (see the Experimental Section). The results of the reaction sequence utilizing various aldehydes are summarized in Table 1.

The results are consistently satisfying in the respect that all applied aldehydes were converted in the three-component one-pot reaction sequence. The steric demand of the aliphatic aldehydes could be increased up to a *tert*-butyl substituent, with virtually no loss of efficiency (entries 1−4), and aromatic aldehydes were also accepted in the reaction (entries 5−8). It should be noted that *p*-bromobenzaldehyde is converted to product **2g** in excellent yields without participation of the bromoaryl moiety in side reactions, e.g. a coupling reaction or a protodebromination via aryl zinc intermediates. Four products (**2e**−**h**) especially would lead to unsaturated products with extended π-systems upon elimination of water. Although zinc iodide is present in the reaction mixture that could act as a Lewis acid to facilitate the water elimination, such products were not encountered. When cinnamic aldehyde was used as the aldehyde in the allylation reaction such an elimination of water was detected to generate the even more extended π-system. However, the product consisted of several *E*/*Z*-isomers and could not be isolated in pure form. In view of the subsequently planned transformations of the products **2**, we were also delighted that further double bonds in the aldehyde component were tolerated (entries 9 and 11−13). These additional double bonds can be transformed into carbonyl groups by ozonolysis.

To access the application of unsymmetrical 1,3-dienes as starting material in the cobalt-catalyzed 1,4-hydrovinylation commercially available myrcene was used. In this case the 1,4-hydrovinylation can take place either at C1 or at C4 of the 1,3-diene subunit (Scheme 3). The regioselectivity is reasonably high when the cobalt 1,2-bis-diphenylphosphinoethane complex [$CoBr_2$(dppe)] is applied in the synthesis of intermediate **4** (C1:C4 = 18:82).

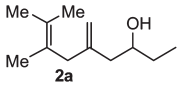
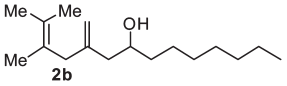
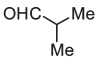
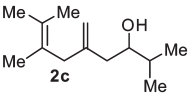
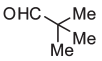
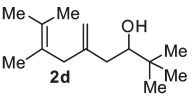
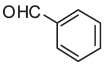
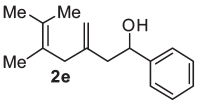
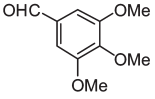
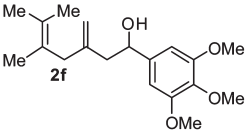
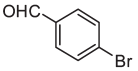
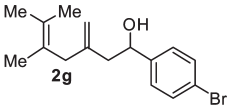
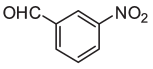
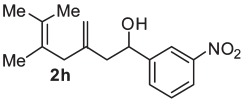
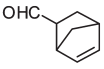
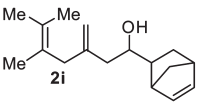
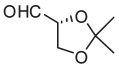
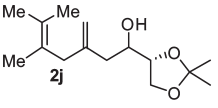
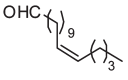
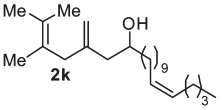
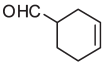
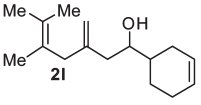
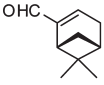
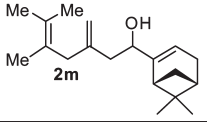
The desired product **5** was generated upon reaction with octanal in 42% yield over two steps. Accordingly, materials with various differently substituted double bonds can be envisaged to be generated in a short reaction sequence by this approach. In addition, it should be noted that commercially available myrcene consists of a mixture of double bond isomers of which 90% resemble the desired starting material. The cobalt catalyst very selectively converts the myrcene component of the mixture into the intermediate **4** while the other double bond isomers in the mixture remain untouched. In fact, products of type **5** are generated as single double bond isomers and the mild reaction conditions do not lead to double bond isomerization or elimination of the alcohol functionality to generate corresponding polyene structures.

A flexible route to products of type **2** can also be realized when the two reactions are exchanged. At the moment this aspect seems to be trivial but the applicability of the reaction sequence in both ways in the synthesis of a highly complex product, such as a natural product, is of additional value. The procedure was tested for the allylboration of norbornene carbaldehyde, applied as the commercially available mixture of *endo*/*exo* isomers (*endo*:*exo* = 1:0.31), to **6** followed by the cobalt-catalyzed 1,4-hydrovinylation reaction (Scheme 4).

Utilizing this methodology, the intermediate **6** was isolated in 83% as a mixture of diastereomers. From this intermediate the desired product was generated under cobalt-catalysis from 2,3-dimethyl-1,3-butadiene (DMB) with the [$CoBr_2$(dppe)] complex to afford **2i** in 72% yield. The application of octanal as the aldehyde in the allylboration reaction led to product **7** in 83% isolated yield. The cobalt-catalyzed transformation with myrcene as the 1,3-diene was performed with varying bidentate phosphine ligands. The product **5** was generated in 37% yield in a ratio of C1:C4 = 29:71 when dppe was applied as the ligand. The same reaction performed with dppp (1,3-bis-diphenylphosphinopropane) gave the desired product **5** in 59% and a C1:C4 ratio of 17:83. The best result was obtained when the dppp* ligand (2,2-dimethyl-1,3-bis-diphenylphosphinopropane) was utilized. In this case the desired product was obtained in 58% and a C1:C4 ratio of 8:92 was detected. This strategy gives similar good results as the previously described one-pot procedure using the cobalt-catalyzed reaction in the first transformation. Therefore, applications in the synthesis of more complex molecules by both strategies seem reasonable for the future.

(4) (a) Hilt, G.; Arndt, M.; Weske, D. F. *Synthesis* **2010**, 1321. For a review concerning the synthesis of 1,3-dicarbonyl compounds, see: (b) Hilt, G.; Weske, D. F. *Chem. Soc. Rev.* **2009**, *38*, 3082.

TABLE 1. Results for the Cobalt-Catalyzed Hydrovinylation−Allylboration Reaction Sequence

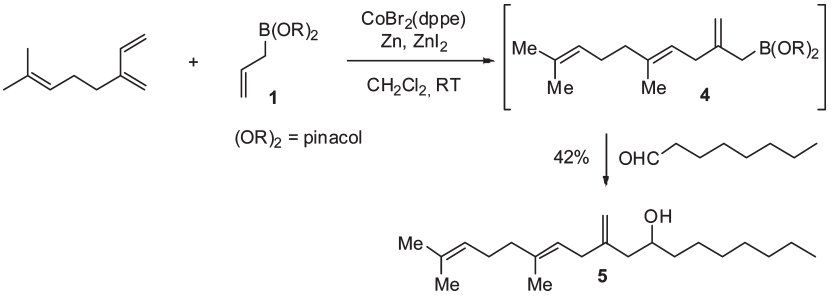
Entry	R	Product (2)[a]	Yield
1		 **2a**	99%
2		 **2b**	73%
3		 **2c**	66%
4		 **2d**	72%
5		 **2e**	83%
6		 **2f**	95%
7		 **2g**	94%
8		 **2h**	65%
9		 **2i**	67% (*endo*:*exo* = 1.0:0.68)
10		 **2j**	82% (*anti*:*syn* = 1.0:0.27)
11		 **2k**	84%
12		 **2l**	73%[b]
13		 **2m**	90%[c]

[a]The compounds **2a** and **2k** were described previously, see ref 4a. [b]Mixture of diastereomers in a ratio of 1.0:0.93. The assignment of the signals to one of the two diastereomers by two-dimensional NMR techniques was not successful. [c]Mixture of diastereomers in a ratio of 1.0:0.49. The assignment of the signals to one of the two diastereomers by two-dimensional NMR techniques was not successful.

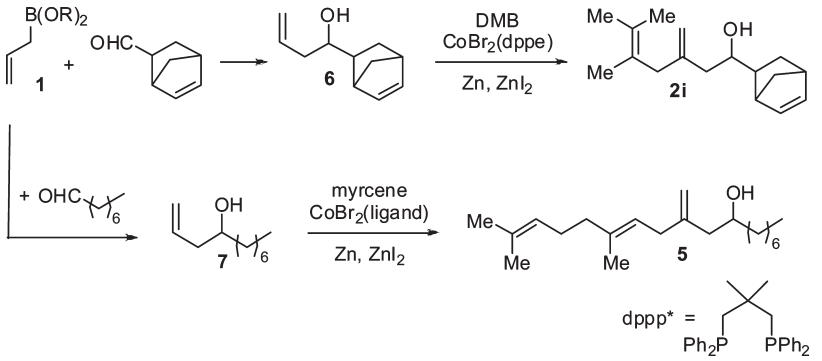
An application of the hydroxyl-functionalized 1,4-dienes of type **2** was realized in the ozonolysis/acid-initiated cyclization protocol leading to pyranone derivatives **8** in a one-pot procedure (Scheme 5).[5] The results of this one-pot procedure for various substituted derivatives of type **2** are summarized in Table 2.

The reaction sequence with the ethyl substituent led to **8a**, the natural product *hepialone*, in excellent yield,[6] and the

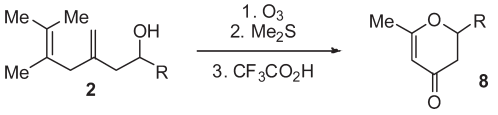
SCHEME 3



SCHEME 4



SCHEME 5



other aliphatic derivatives investigated gave similar good results for this two-step one-pot procedure. When additional double bonds are present in the starting material, ozonolysis leads to the cleavage of this additional double bond as well, leading to aldehyde **8e** in 40% yield. Continuing from there the synthesis of a lipid component isolated from *vanilla beans* can be realized as we were able to demonstrate beforehand.[7] Aryl substituents are also accepted as is shown for the phenyl-substituted derivative **8f** and the derivatives **8g** and **8h** with electron poor aromatic moieties. These compounds were isolated in moderate to good yields without degradation of the aryl substituent by ozonolysis. It should be noted that electron-rich aromatic moieties also react with ozone, leading to the degradation of these functional groups. Accordingly, when methoxy-functionalized aryl substituents were present in the starting material degradation was observed and no desired product could be isolated.

When viewed from the perspective of target-oriented multistep synthesis intermediates of type **3** and **4** generated by the cobalt-catalyzed hydrovinylation of allyl boronic esters do present a potentially serious drawback. These compounds present a pronounced lability toward silica gel column chromatography rendering the purification and isolation difficult, as we have observed. The use of allyl silanes as a much more stable alternative holds great promise. The conversion of allyl trimethylsilane (**9**) with DMB leads to intermediate **10**, which can then be converted under Lewis acid catalysis to the desired products of type **2i** and **2*l*** (Scheme 6).

Intermediate **10** was isolated in 99% yield and the conversion into the hydroxyl-functionalized 1,4-dienes **2i** in 88% yield and **2*l*** in 90% yield is even superior to the previously described approach utilizing allyl pinacol boronic ester **1**. Thereby, an alternative protocol for the generation of hydroxyl-functionalized 1,4-dienes has been established.

Summary

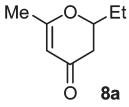
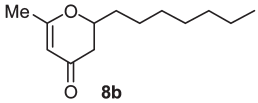
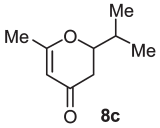
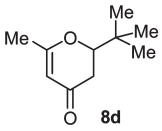
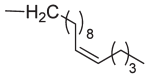
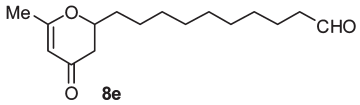
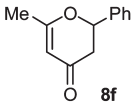
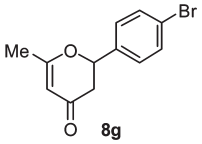
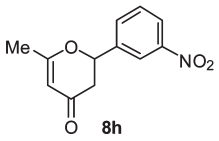
The combination of a cobalt-catalyzed 1,4-hydrovinylation of allyl boron reagents as well as allyl silanes and a subsequent allylation reaction of aldehydes can be used for the fast assembly of hydroxyl-functionalized 1,4-dienes of type **2**. These materials can be used as a platform for the synthesis of pyranone derivatives of type **8** by an ozonolysis/acid-induced cyclization reaction. As we could demonstrate, the sequence is flexible enough to permit the allylation reaction to be performed first leading to homoallylic alcohols of type **6**/**7**. These can then be used to afford the hydroxyl-functionalized 1,4-dienes of type **2** with similar good results. Therefore, the method presented herein shows strong promise of being applicable toward the synthesis of more complex compounds in the future.

(5) For selected examples regarding the use of 1,3-diketone dianions see: (a) Karapetyan, V.; Mkrtchyan, S.; Ghazaryan, G.; Villinger, A.; Fischer, C.; Langer, P. *Tetrahedron* **2009**, *65*, 9271. (b) Ahmad, R.; Khera, R. A.; Villinger, A.; Langer, P. *Tetrahedron Lett.* **2009**, *50*, 3020.

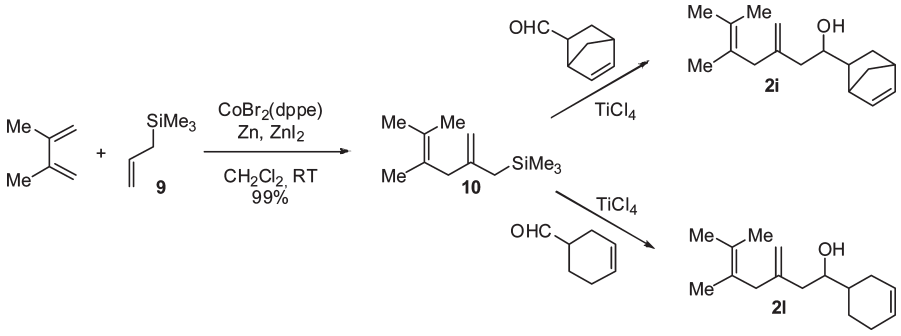
(6) (a) Rao, B. V.; Rao, A. S. *Synth. Commun.* **1995**, *25*, 1531. (b) Kubo, I.; Matsumoto, T.; Wagner, D. L.; Shoolery, J. N. *Tetrahedron Lett.* **1985**, *26*, 563.

(7) See ref 4. Ramaroson-Raonizafinimanana, B.; Gaydou, E. M.; Bombarda, I. *J. Agric. Food Chem.* **1999**, *47*, 3202.

TABLE 2. Results for the Ozonolysis/Acid-Initiated Cyclization Protocol

Entry	R	Product (8)	Yield
1	Ethyl	 **8a**	96%
2	*n*-Heptyl	 **8b**	90%
3	*iso*-Propyl	 **8c**	74%
4	*t*Butyl	 **8d**	73%
5		 **8e**	40%
6	Phenyl	 **8f**	61%
7	4-Bromophenyl	 **8g**	60%
8	3-Nitrophenyl	 **8h**	31%

SCHEME 6



Experimental Section

General Methods. All reactions were carried out under an argon atmosphere in heat gun-dried glassware. Dichloromethane was distilled under nitrogen from P_4O_{10} and ZnI_2 was dried in vacuo at 150 °C prior to use. Commercially available materials were used without further purification.

General Procedure for the Cobalt-Catalyzed 1,4-Hydrovinylation−Allylboration Reaction Sequence. Anhydrous zinc iodide (10 mol %), zinc powder (10 mol %), and cobalt (1,2-bis-diphenylphosphinoethane) dibromide (5 mol %) were suspended under an argon atmosphere in 1.0 mL of dichloromethane. Then 2,3-dimethyl-1,3-butadiene (1.2 mmol) and 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1**) (1.0 mmol) were added and the mixture was stirred at room temperature until complete conversion of the starting materials was observed as monitored by GC/MS. The reaction mixture was cooled to −78 °C and the aldehyde (1.0 mmol) was added. The mixture was stirred for 1 h at −78 °C and then allowed to warm to room temperature. Triethanolamine (1.2 mmol) was added and the

reaction mixture was stirred for another hour. Then the mixture was filtered over a short pad of silica gel (eluent: diethyl ether) and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel to obtain the products of type **2**.

7,8-Dimethyl-5-methylenenon-7-en-3-ol (2a): colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.85−4.80 (m, 2H), 3.65−3.56 (m, 1H), 2.79 (d, 1H, J = 15.5 Hz), 2.68 (d, 1H, J = 15.4 Hz), 2.16 (dd, 1H, J = 13.7, 3.4 Hz), 1.98 (dd, 1H, J = 13.7, 9.4 Hz), 1.89 (s, 1H), 1.66 (s, 3H), 1.62 (s, 3H), 1.57 (s, 3H), 1.53−1.43 (m, 2H), 0.94 (t, 3H, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 126.3, 124.7, 112.7, 70.2, 43.9, 41.1, 29.8, 20.5, 20.4, 18.2, 9.9; MS (EI) m/z (%) 182 (M^+), 149, 135, 121, 109, 93; HRMS (m/z) calcd for $C_{12}H_{22}O$ 182.1671, found 182.1678; IR (Nujol) 3434, 3075, 2962, 2920, 1641, 1440, 1373, 1113, 1020, 972, 894.

2,3-Dimethyl-5-methylenetetradec-2-en-7-ol (2b): colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.87−4.81 (m, 2H), 3.74−3.63 (m, 1H), 2.81 (d, 1H, J = 15.5 Hz), 2.70 (d, 1H, J = 15.5 Hz), 2.18 (dd, 1H, J = 13.7, 3.2 Hz), 2.01 (dd, 1H, J = 13.7, 9.5 Hz), 1.77 (d, 1H, J = 2.0 Hz), 1.69 (s, 3H), 1.64 (s, 3H), 1.59 (s, 3H), 1.50−1.22 (m, 12H), 0.88 (t, 3H, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 126.5, 124.7, 112.9, 68.8, 44.5, 41.1, 37.1, 31.8, 29.6, 29.3, 25.7, 22.7, 20.6, 20.5, 18.3, 14.1; MS (EI) m/z (%) 252 (M^+), 209, 182, 135, 124, 109, 93, 69, 55; HRMS (m/z) calcd for $C_{17}H_{32}O$ 252.2453, found 252.2439; IR (Nujol) 3387, 2955, 2927, 2857, 1642, 1457, 1374, 1125, 1054, 966, 895.

2,7,8-Trimethyl-5-methylenenon-7-en-3-ol (2c): colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.88−4.83 (m, 2H), 3.49−3.40 (m, 1H), 2.83 (d, 1H, J = 15.4 Hz), 2.69 (d, 1H, J = 15.4 Hz), 2.20 (dd, 1H, J = 13.6, 2.4 Hz), 1.97 (dd, 1H, J = 13.6, 10.3 Hz), 1.75 (s, 1H), 1.73−1.62 (m, 1H), 1.69 (s, 3H), 1.66 (s, 3H), 1.60 (s, 3H), 0.95 (d, 3H, J = 6.8 Hz), 0.92 (d, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.2, 126.5, 124.7, 113.0, 73.2, 41.1, 40.9, 33.4, 20.6, 20.5, 18.6, 18.3, 17.8; MS (EI) m/z (%) 196 (M^+), 163, 135, 126, 109, 93, 67, 55; HRMS (m/z) calcd for $C_{13}H_{24}O$ 196.1827, found 196.1824; IR (KBr) 3468, 3074, 2959, 2914, 2873, 1641, 1467, 1446, 1372, 1262, 1045, 1002, 896.

2,2,7,8-Tetramethyl-5-methylenenon-7-en-3-ol (2d): colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.87−4.84 (m, 2H), 3.31 (dd, 1H, J = 10.9, 1.9 Hz), 2.85 (d, 1H, J = 15.4 Hz), 2.69 (d, 1H, J = 15.4 Hz), 2.21 (d, 1H, J = 13.5 Hz), 1.93 (dd, 1H, J = 13.5, 11.0 Hz), 1.75 (s, 1H), 1.69 (s, 3H), 1.65 (s, 3H), 1.60 (s, 3H), 0.92 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.7, 126.5, 124.7, 113.2, 75.7, 40.7, 38.7, 34.4, 28.8, 20.6, 20.6, 18.3; MS (EI) m/z (%) 210 (M^+), 177, 149, 135, 124, 109, 93, 69, 57; HRMS (m/z) calcd for $C_{14}H_{26}O$ 210.1984, found 210.1971; IR (KBr) 3568, 3072, 2955, 2867, 1639, 1479, 1363, 1072, 1009, 899.

5,6-Dimethyl-3-methylene-1-phenylhept-5-en-1-ol (2e): colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.24 (m, 5H), 4.95−4.92 (m, 1H), 4.91 (dd, 1H, J = 3.1, 1.5 Hz), 4.80 (ddd, 1H, J = 8.7, 4.7, 2.2 Hz), 2.88 (d, 1H, J = 15.4 Hz), 2.75 (d, 1H, J = 15.4 Hz), 2.45−2.30 (m, 2H), 2.21 (d, 1H, J = 2.2 Hz), 1.70 (s, 3H), 1.69 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 144.1, 128.4, 127.4, 126.6, 125.7, 124.6, 113.7, 71.6, 46.6, 41.1, 20.6, 20.5, 18.3; MS (EI) m/z (%) 212, 197, 160, 145, 107, 91, 79; HRMS (m/z) calcd for $C_{16}H_{22}O$ 230.1671, found 230.1671; IR (KBr) 3404, 3029, 2986, 2914, 2859, 1642, 1493, 1453, 1373, 1049, 896, 757, 700.

5,6-Dimethyl-3-methylene-1-(3,4,5-trimethoxyphenyl)hept-5-en-1-ol (2f): light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.59 (s, 2H), 4.96−4.92 (m, 1H), 4.92−4.89 (m, 1H), 4.76−4.68 (m, 1H), 3.87 (s, 6H), 3.83 (s, 3H), 2.87 (d, 1H, J = 15.5 Hz), 2.74 (d, 1H, J = 15.4 Hz), 2.43−2.28 (m, 2H), 2.24−2.19 (m, 1H), 1.70 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 144.3, 139.9, 137.2, 126.6, 124.7, 113.6, 102.7, 71.8, 60.8, 56.1, 46.6, 41.1, 20.6, 20.5, 18.3; MS (EI) m/z (%) 320 (M^+), 302, 287, 259, 233, 197, 181, 169, 138, 109, 91, 77; HRMS (m/z) calcd for $C_{19}H_{28}O_4$ 320.1988, found 320.1987; IR (Nujol) 3475, 3074, 2995, 2936, 1593, 1508, 1462, 1421, 1327, 1234, 1129, 1009, 756.

1-(4-Bromophenyl)-5,6-dimethyl-3-methylenehept-5-en-1-ol (2g): light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, 2H, J = 8.4 Hz), 7.24 (d, 2H, J = 8.4 Hz), 4.91 (s, 2H), 4.79−4.71 (m, 1H), 2.86 (d, 1H, J = 15.4 Hz), 2.74 (d, 1H, J = 15.4 Hz), 2.41−2.23 (m, 2H), 2.23−2.19 (m, 1H), 1.70 (s, 3H), 1.67 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 143.1, 131.4, 127.5, 126.7, 124.5, 121.1, 114.0, 71.0, 46.6, 41.1, 20.6, 20.5, 18.3; MS (EI) m/z (%) 292, 277, 238, 196, 185, 169, 159, 121, 109, 93, 77; HRMS (m/z) calcd for $C_{16}H_{21}BrO$ 308.0776, found 308.0754; IR (Nujol) 3412, 3075, 2987, 2915, 2864, 1642, 1590, 1485, 1440, 1398, 1064, 1011, 894, 820.

5,6-Dimethyl-3-methylene-1-(3-nitrophenyl)hept-5-en-1-ol (2h): yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (t, 1H, J = 1.9 Hz), 8.13 (ddd, 1H, J = 8.1, 2.3, 1.0 Hz), 7.70 (d, 1H, J = 7.7 Hz), 7.52 (t, 1H, J = 7.9 Hz), 4.97−4.93 (m, 2H), 4.89 (ddd, 1H, J = 9.6, 3.7, 2.2 Hz), 2.88 (d, 1H, J = 15.5 Hz), 2.77 (d, 1H, J = 15.4 Hz), 2.43 (dd, 1H, J = 13.8, 3.8 Hz), 2.39−2.36 (m, 1H), 2.31 (dd, 1H, J = 13.8, 9.6 Hz), 1.71 (s, 3H), 1.70−1.67 (m, 3H), 1.63−1.59 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 146.2, 143.5, 131.8, 129.3, 127.0, 124.3, 122.4, 120.8, 114.6, 70.5, 46.7, 41.0, 20.6, 20.6, 18.3; MS (EI) m/z (%) 257, 242, 205, 188, 152, 123, 109, 93, 77; HRMS (m/z) calcd for $C_{16}H_{21}NO_3$ 275.1521, found 275.1521; IR (Nujol) 3448, 3080, 2988, 2916, 2865, 1530, 1440, 1350, 1057, 900, 738.

1-(Bicyclo[2.2.1]hept-5-en-2-yl)-5,6-dimethyl-3-methylenehept-5-en-1-ol (2i). Main isomer: colorless liquid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.13 (dd, 1H, J = 5.5, 3.1 Hz), 6.04 (dd, 1H, J = 5.6, 2.9 Hz), 4.85−4.83 (m, 2H), 3.08−3.06 (m, 1H), 3.00 (tt, 1H, J = 15.3, 2.2 Hz), 2.84−2.77 (m, 2H), 2.65 (d, 1H, J = 15.4 Hz), 2.20 (d, 1H, J = 13.7 Hz), 2.03−1.97 (m, 1H), 1.90 (dd, 1H, J = 13.9, 10.3 Hz), 1.79−1.77 (m, 1H), 1.77−1.73 (m, 1H), 1.66 (s, 3H), 1.61 (s, 3H), 1.56 (s, 3H), 1.44−1.39 (m, 1H), 1.23 (d, 1H, J = 8.2 Hz), 0.50 (ddd, 1H, J = 11.5, 4.4, 2.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0, 137.2, 132.9, 126.4, 124.7, 113.3, 72.3, 49.2, 45.8, 44.2, 43.3, 42.2, 41.0, 29.2, 20.6, 20.5, 18.1.

Resolved signals for the minor component: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.18 (dd, 1H, J = 5.6, 3.1 Hz), 5.86 (dd, 1H, J = 5.7, 2.7 Hz), 4.86−4.83 (m, 2H), 2.34 (d, 1H, J = 13.5 Hz), 2.05 (ddd, 1H, J = 13.1, 8.9, 3.9 Hz), 1.69 (s, 3H), 1.65 (s, 3H), 1.59 (s, 3H), 1.27 (d, 1H, J = 8.1 Hz), 1.03 (ddd, 1H, J = 11.8, 4.3, 2.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 138.1, 131.6, 126.5, 124.7, 113.2, 73.0, 49.7, 46.3, 44.4, 43.5, 42.4, 40.9, 30.0, 20.5, 18.2; MS (EI) m/z (%) 213, 203, 176, 147, 124, 109, 91, 77, 67; HRMS (m/z) calcd for $C_{17}H_{26}O$ 246.1984, found 246.1971; IR (KBr) 3459, 3059, 2969, 2936, 2865, 1640, 1446, 1338, 1070, 1024, 897, 721.

1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-5,6-dimethyl-3-methylenehept-5-en-1-ol (2j): colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.89−4.84 (m, 2H), 4.07−3.92 (m, 3H), 3.84−3.76 (m, 1H), 2.82 (d, 1H, J = 15.5 Hz), 2.73 (d, 1H, J = 15.4 Hz), 2.28 (dd, 1H, J = 14.0, 3.8 Hz), 2.09−1.98 (m, 2H), 1.68 (s, 3H), 1.65 (s, 3H), 1.59 (s, 3H), 1.42 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 126.7, 124.5, 113.2, 109.1, 78.5, 69.2, 65.6, 41.0, 40.0, 26.5, 25.2, 20.6, 20.5, 18.3; MS (EI) m/z (%) 254 (M^+), 239, 211, 163, 153, 145, 131, 123, 109, 101, 93, 81; HRMS (m/z) calcd for $C_{15}H_{26}O_3$ 254.1882, found 254.1895; IR (KBr) 3480, 3075, 2987, 2915, 1643, 1455, 1439, 1372, 1252, 1215, 1156, 1066, 857.

2,3-Dimethyl-5-methylenedocosa-2,17-dien-7-ol (2k): colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.36−5.32 (m, 2H), 4.86−4.83 (m, 2H), 3.73−3.65 (m, 1H), 2.81 (d, 1H, J = 15.4 Hz), 2.70 (d, 1H, J = 15.4 Hz), 2.18 (dd, 1H, J = 13.7, 3.2 Hz), 2.04−1.97 (m, 5H), 1.77 (d, 1H, J = 2.2 Hz), 1.69 (s, 3H), 1.64 (s, 3H), 1.60 (s, 3H), 1.51−1.24 (m, 20H), 0.93−0.86 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 129.9, 129.8, 126.5, 124.7, 112.9,

68.8, 44.5, 41.1, 37.1, 32.0, 29.8, 29.7, 29.6, 29.6, 29.5, 29.3, 27.2, 26.9, 25.7, 22.3, 20.6, 20.5, 18.3, 14.0; MS (EI) *m*/*z* (%) 362 (M^+), 344, 319, 301, 277, 237, 220, 193, 179, 163, 149, 135, 124, 109, 95; HRMS (*m*/*z*) calcd for $C_{25}H_{46}O$ 362.3549, found 362.3558; IR (Nujol) 3376, 2925, 2855, 1641, 1463, 894, 721.

1-(Cyclohex-3-enyl)-5,6-dimethyl-3-methylenehept-5-en-1-ol (2*l*): colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75−5.61 (m, 2H), 4.90−4.84 (m, 2H), 3.63−3.42 (m, 1H), 2.84 (d, 1H, J = 15.4 Hz), 2.70 (d, 1H, J = 15.4 Hz), 2.26 (d, 1H, J = 13.6 Hz), 2.19−1.87 (m, 5H), 1.83 (d, 1H, J = 2.5 Hz), 1.76 (d, 1H, J = 2.3 Hz), 1.69 (s, 3H), 1.65 (s, 3H), 1.60 (s, 3H), 1.46−1.21 (m, 1H).

Main isomer: ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 127.3, 126.5, 126.5, 124.7, 113.2, 72.0, 41.4, 40.9, 39.6, 26.8, 25.3, 24.5, 20.6, 20.5, 18.3.

Resolved signals for the minor component: ^{13}C NMR (75 MHz, $CDCl_3$) δ 126.8, 126.0, 124.6, 113.3, 71.9, 41.3, 40.9, 39.4, 27.9, 25.3, 20.5; ratio of the diastereomers determined by ^{13}C NMR 1:0.93; MS (EI) *m*/*z* (%) 234 (M^+), 191, 135, 124, 109, 81; HRMS (*m*/*z*) calcd for $C_{16}H_{26}O$ 234.1984, found 234.1980; IR (Nujol) 3308, 3072, 3020, 2968, 2858, 1640, 1445, 1070, 897, 662.

1-((1*R*,5*S*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)-5,6-dimethyl-3-methylenehept-5-en-1-ol (2m): colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.51−5.46 (m, 1H), 4.90−4.79 (m, 2H), 4.16−4.08 (m, 1H), 2.89−2.67 (m, 2H), 2.46−1.98 (m, 7H), 1.68 (s, 3H), 1.65 (s, 3H), 1.60 (s, 3H), 1.29 (s, 3H), 1.18 (t, 1H, J = 8.3 Hz), 0.83 (d, 3H, J = 8.7 Hz).

Main isomer: ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.4, 144.4, 126.4, 124.8, 117.4, 112.9, 71.8, 42.3, 42.2, 41.0, 40.9, 37.8, 31.7, 31.1, 26.2, 21.4, 20.6, 20.5, 18.3.

Resolved signals for the minor component: ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8, 126.4, 124.7, 117.6, 113.0, 71.7, 42.2, 42.1, 41.0, 37.7, 26.2; ratio of the diastereomers determined by ^{13}C NMR 1:0.54; MS (EI) *m*/*z* (%) 274 (M^+), 256, 231, 191, 133, 117, 109, 91; HRMS (*m*/*z*) calcd for $C_{19}H_{30}ONa$ 297.2194, found 297.2193; IR (Nujol) 3460, 3075, 2985, 2914, 2832, 2724, 1681, 1643, 1620, 1433, 1382, 1366, 1041, 888, 804.

(*E*)-13,17-Dimethyl-10-methyleneoctadeca-12,16-dien-8-ol (5): colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.17 (tq, 1H, J = 7.3, 1.2 Hz), 5.13−5.05 (m, 1H), 4.92−4.89 (m, 1H), 4.85−4.81 (m, 1H), 3.77−3.65 (m, 1H), 2.73 (d, 2H, J = 7.5 Hz), 2.25 (dd, 1H, J = 13.6, 3,1 Hz), 2.15−1.92 (m, 5H), 1.72 (d, 1H, J = 2.8 Hz), 1.68 (s, 3H), 1.60 (s, 6H), 1.54−1.20 (m, 12H), 0.88 (t, 3H, J = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.1, 137.1, 131.5, 124.2, 121.4, 112.5, 68.8, 44.7, 39.7, 37.2, 34.7, 31.8, 29.6, 29.3, 26.6, 25.7, 25.7, 22.6, 17.7, 15.9, 14.1; MS (EI) *m*/*z* (%) 306 (M^+), 288, 273, 245, 219, 178, 163, 123, 109, 95, 81; HRMS (*m*/*z*) calcd for $C_{21}H_{38}O$ 306.2923, found 306.2919; IR (Nujol) 3439, 3074, 2957, 2926, 2855, 1643, 1440, 1383, 1054, 894.

General Procedure for the Cobalt-Catalyzed 1,4-Hydrovinylation/Allylation Reaction Sequence with Allyl Trimethylsilane. When allyl silane **9** was used the hydrovinylation products were isolated as described before. The allylation was then performed following a protocol by Hosomi.[8] The aldehyde (1.0 mmol) was dissolved under an argon atmosphere in 0.5 mL of dichloromethane. A solution of $TiCl_4$ (0.5 mmol, c = 1 mol/L) in dichloromethane was added dropwise at −78 °C. The mixture was stirred for 5 min and the silyl-functionalized hydrovinylation product **10** (1.0 mmol) was subsequently added. The reaction mixture was stirred at −78 °C until complete conversion was detected by TLC or GC/MS analysis. The reaction was quenched with water then extracted with dichloromethane and the combined organic phases were dried over $MgSO_4$. The solvent was removed and the residue was purified by flash column chromatography on silica gel.

(8) Hosomi, A.; Miura, K. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 835.

General Procedure for the Ozonolysis/Acid-Induced Cyclization Reaction Sequence. A Schlenk tube, fitted with a glass tube to admit ozone, was charged with the hydroxyl-functionalized 1,4-diene **2** (1.0 mmol) and 10 mL of dichloromethane. The flask was cooled to −78 °C and ozone in a stream of oxygen was bubbled through the solution with stirring. When the solution turned blue, ozone addition was stopped, the excess of ozone was removed by a stream of oxygen, and dimethyl sulfide (2.0 mmol) and 2,2,2-trifluoroacetic acid (1.0 mmol) were added successively. The solution was allowed to warm to room temperature. After being stirred for 1 h, saturated sodium bicarbonate solution (5.0 mL) was added. The organic layer was separated and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel to obtain the products of type **8**.

2-Ethyl-6-methyl-2*H*-pyran-4(3*H*)-one, hepialone (8a):[6] light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.31 (s, 1H), 4.34−4.24 (m, 1H), 3.73−3.65 (m, 1H), 2.41−2.37 (m, 2H), 2.00 (s, 3H), 1.90−1.72 (m, 2H), 1.01 (t, 3H, J = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.8, 174.2, 104.7, 80.4, 40.3, 27.5, 21.0, 9.2.

2-Heptyl-6-methyl-2*H*-pyran-4(3*H*)-one (8b): light yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.30 (s, 1H), 4.40−4.28 (m, 1H), 2.42−2.32 (m, 2H), 1.99 (s, 3H), 1.87−1.72 (m, 1H), 1.71−1.57 (m, 1H), 1.53−1.19 (m, 10H), 0.88 (t, 3H, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.0, 174.3, 104.7, 79.3, 40.8, 34.5, 31.7, 29.3, 29.1, 24.8, 22.6, 21.0, 14.0; MS (EI) *m*/*z* (%) 210 (M^+), 195, 167, 152, 111, 85, 69; HRMS (*m*/*z*) calcd for $C_{13}H_{22}O_2$ 210.1620, found 210.1626; IR (KBr) 3470, 2955, 2927, 2857, 1671, 1613, 1399, 1336, 1240, 1033.

2-Isopropyl-6-methyl-2*H*-pyran-4(3*H*)-one (8c):[9] light yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.29 (s, 1H), 4.09 (ddd, 1H, J = 13.8, 5.9, 3.9 Hz), 2.41 (dd, 1H, J = 16.6, 13.8 Hz), 2.30 (ddd, 1H, J = 16.7, 3.9, 0.7 Hz), 1.99 (s, 3H), 2.04−1.90 (m, 1H), 1.00 (d, 3H, J = 6.8 Hz), 0.97 (d, 3H, J = 6.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.4, 174.7, 104.6, 83.8, 37.8, 31.7, 20.9, 17.8, 17.7.

2-*tert*-Butyl-6-methyl-2*H*-pyran-4(3*H*)-one (8d):[10] light yellow liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.30 (s, 1H), 3.97 (dd, 1H, J = 14.4, 3.8 Hz), 2.42 (dd, 1H, J = 16.5, 14.4 Hz), 2.31 (ddd, 1H, J = 16.6, 3.9, 0.7 Hz), 2.00 (s, 3H), 0.98 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.7, 174.8, 104.5, 86.6, 36.2, 33.7, 25.4, 20.9.

10-(6-Methyl-4-oxo-3,4-dihydro-2*H*-pyran-2-yl)decanal (8e): colorless liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (t, 1H, J = 1.8 Hz), 5.31 (s, 1H), 4.33 (tdd, 1H, J = 11.4, 7.2, 5.6 Hz), 2.46−2.35 (m, 4H), 1.99 (s, 3H), 1.88−1.27 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.7, 193.0, 174.3, 104.7, 79.3, 43.9, 40.8, 34.4, 29.4, 29.3, 29.3, 29.1, 24.8, 22.0, 21.0; MS (EI) *m*/*z* (%) 265 ($M^+ - 1$), 237, 223, 180, 139, 125, 111, 85; HRMS (*m*/*z*) calcd for $C_{16}H_{26}O_3 + Na^+$ 289.1780, found 289.1774; IR (Nujol) 3463, 2926, 1703, 1666, 1618, 1454, 1397, 1337, 996, 835, 693.

6-Methyl-2-phenyl-2*H*-pyran-4(3*H*)-one (8f):[11] yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46−7.34 (m, 5H), 5.44 (s, 1H), 5.39 (dd, 1H, J = 14.2, 3.6 Hz), 2.81 (dd, 1H, J = 16.8, 14.2 Hz), 2.59 (ddd, 1H, J = 16.8, 3.6, 0.8 Hz), 2.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.3, 174.3, 138.2, 128.8, 126.1, 105.2, 80.8, 42.3, 21.1.

2-(4-Bromophenyl)-6-methyl-2*H*-pyran-4(3*H*)-one (8g):[9] yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58−7.52 (m, 2H),

(9) The analytical data are consistent with the literature: Yang, W.; Shang, D.; Liu, Y.; Du, Y.; Feng, X. *J. Org. Chem.* **2005**, *70*, 8533.

(10) The analytical data are consistent with the literature: Organ, M. G.; Froese, R. D. J.; Goddard, J. D.; Taylor, N. J.; Lange, G. L. *J. Am. Chem. Soc.* **1994**, *116*, 3312.

(11) The analytical data are consistent with the literature: Reiter, M.; Ropp, S.; Gouverneur, V. *Org. Lett.* **2004**, *6*, 91.

7.31−7.26 (m, 2H), 5.43 (s, 1H), 5.35 (dd, 1H, J = 13.9, 3.7 Hz), 2.75 (dd, 1H, J = 16.8, 14.0 Hz), 2.57 (ddd, 1H, J = 16.8, 3.7, 1.0 Hz), 2.07 (d, 3H, J = 0.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.7, 174.0, 137.3, 132.0, 127.8, 122.8, 105.4, 80.1, 42.3, 21.0.

6-Methyl-2-(3-nitrophenyl)-2*H*-pyran-4(3*H*)-one (8h): yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35−8.31 (m, 1H), 8.25 (ddd, 1H, J = 8.1, 2.2, 1.1 Hz), 7.75−7.69 (m, 1H), 7.62 (t, 1H, J = 7.9 Hz), 5.50 (dd, 1H, J = 13.4, 4.1 Hz), 5.49−5.47 (m, 1H), 2.78 (dd, 1H, J = 16.7, 13.7 Hz), 2.66 (ddd, 1H, J = 16.7, 4.0, 0.9 Hz), 2.12 (d, 3H, J = 0.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.9, 173.7, 140.4, 131.9, 129.9, 123.6, 122.5, 121.2, 105.7, 79.4, 42.3, 21.0; MS (EI) m/z (%) 233 (M^+), 203, 185, 161, 149, 119, 111, 103, 91, 85, 77; HRMS (m/z) calcd for $C_{12}H_{11}NO_4$ 233.0688, found 233.0678; IR (KBr) 3081, 2886, 1655, 1605, 1528, 1400, 1347, 1330, 1237, 1029, 1009, 825, 737.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.