Cobalt(I) Catalysis in the Diastereoselective Two-Step Synthesis of Tricyclic Systems

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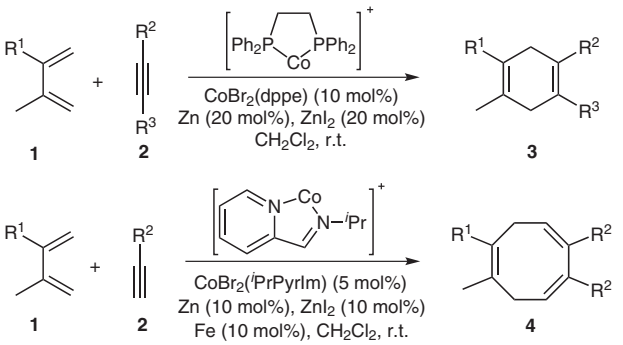
Received 27 January 2011

Abstract: The diastereoselective two-step synthesis of heterotricyclic systems is accomplished by regioselective cobalt-catalysed [4+2]- and [4+2+2]-cycloaddition reactions generating cyclohexa-1,4-diene and cycloocta-1,3,6-triene derivatives, and a hetero-Diels–Alder reaction. Thus, a set of selected cyclohexadienes and cyclooctatrienes were reacted with cyclic 1,3-diones and formaldehyde in a Knoevenagel–hetero-Diels–Alder multicomponent reaction to produce a variety of tricyclic products.

Key words: alkyne, catalysis, cobalt, cycloaddition, diene, multicomponent reaction, hetero-Diels–Alder reaction

Among the atom economic cobalt-catalysed carbon–carbon formation transformations,[1] the cobalt-catalysed [4+2] and [4+2+2] cycloadditions of 1,3-dienes with terminal and internal alkynes are convenient methods for the synthesis of six- and eight-membered carbocyclic compounds under mild reaction conditions.[2] The cobalt-catalysed neutral Diels–Alder reaction represents the more intensively investigated reaction of the two transformations and leads to the regioselective formation of cyclohexa-1,4-diene derivatives. Recently, these products served as substrates for the generation of 1,3-diketones[3] and polysubstituted arenes, which were utilised to synthesise functionalised terphenyls.[4] The cyclohexa-1,4-dienes can be produced by using a cobalt catalyst system consisting of a mixture of $CoBr_2$(dppe) {$CoBr_2$[1,2-bis(diphenylphosphino)ethane]}, ZnI_2, and zinc powder in dichloromethane applied at ambient temperature (Scheme 1). When unsymmetrical 1,3-dienes and alkynes are used, inversed regiocontrol can be accomplished by using a $CoBr_2$(pyridinylimine) catalyst precursor.[5] Furthermore, the chemoselectivity could be altered by using a catalyst system consisting of a mixture of $CoBr_2$(*i*-PrPyrIm) {$CoBr_2$[*N*-(pyridin-2-ylmethylene)propan-2-amine]}, ZnI_2, zinc, and iron powder in dichloromethane to predominantly generate cycloocta-1,3,6-trienes in an intermolecular and regioselective reaction.[2e] Accordingly, 1,3-dienes of type **1** could be reacted with terminal or internal (un)symmetrical alkynes **2** to give cyclohexa-1,4-dienes **3** or cycloocta-1,3,6-trienes **4** depending on the catalyst systems used (Scheme 1).[2c,d,5]

The results of the cobalt-catalysed cycloaddition reactions for the synthesis of selected cyclohexa-1,4-diene and cycloocta-1,3,6-triene derivatives are summarised in Table 1.



R^1 = H, Me; R^2 = alkyl, aryl, TMS, CO_2R; R^3 = alkyl, H, Me

Scheme 1 Cobalt-catalysed [4+2] and [4+2+2] cycloaddition using different active catalysts

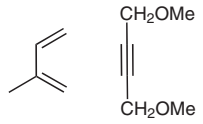
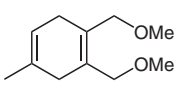
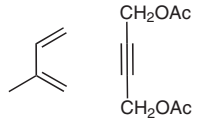
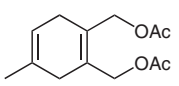
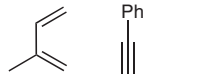
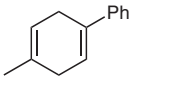
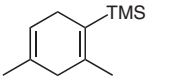
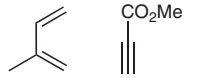
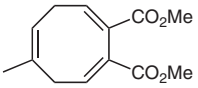
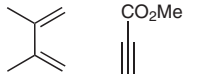
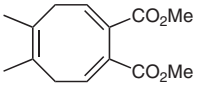
With an atom-economic and efficient route to products **3**/**4** thus available, a rapid and diastereoselective construction of complex structures, realised by a thermal hetero-Diels–Alder reaction, was envisaged. We were encouraged by reports from Koser and Hoffmann describing a Knoevenagel–hetero-Diels–Alder multicomponent reaction of cyclohexane-1,3-dione and formaldehyde with monoterpenes leading to tricyclic products in moderate yields.[6]

Following the original protocol, 1.0 equivalent of the cyclic 1,3-dione was reacted with 2.0 equivalents of paraformaldehyde and 2.3 equivalents of the dienophile in the presence of small amounts of hydroquinone and potassium acetate in glacial acetic acid at 70–90 °C. These conditions were necessary to obtain good yields of the hetero-Diels–Alder product of type **5** (Scheme 2) and to inhibit side reactions. An example for such an alternative reaction pathway could be the Michael addition, which could occur between the in situ generated hetero-1,3-diene and the cyclic 1,3-dione. Koser and Hoffmann inhibited this side reaction by applying molecular sieves and an excess of paraformaldehyde for the rapid generation of the hetero-1,3-diene, which is then exposed to an excess of the dienophile. In our studies, however, the use of molecular sieves had no significant influence on the isolated yields so that their use was abandoned. All other reaction parameters remained unchanged (Scheme 2).

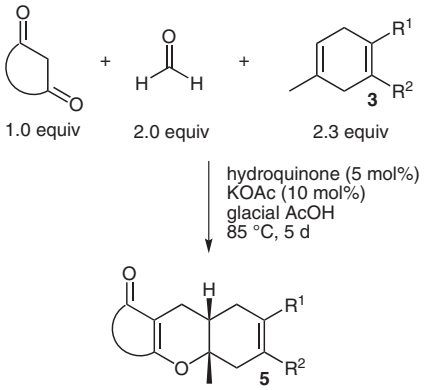
Cyclohexa-1,4-dienes were reacted with cyclohexa-1,3-dione, cyclopenta-1,3-dione, and 5,5-dimethylcyclohexa-

SYNTHESIS 2011, No. 6, pp 0972–0978
Advanced online publication: 10.02.2011
DOI: 10.1055/s-0030-1258433; Art ID: Z15411SS

Table 1 Selected Cyclohexa-1,4-dienes and Cycloocta-1,3,6-trienes Generated by Cobalt-Catalysed [4+2] and [4+2+2] Cycloadditions

Entry	1,3-Diene **1** Alkyne **2**	Product **3**, **4**	Yield (%)
1		 **3a**	98[a]
2		 **3b**	80[a]
3		 **3c**	99[a]
4		 **3d**	98[a]
5		 **4a**	78
6		 **4b**	88

[a] The product was isolated by filtration over a small plug of silica gel as pure compounds (>95%) and was used without further purification.



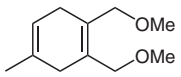
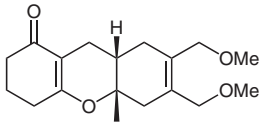
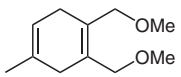
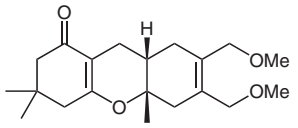
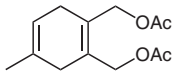
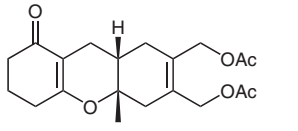
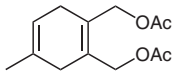
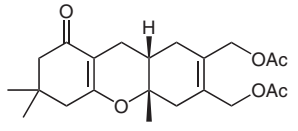
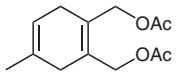
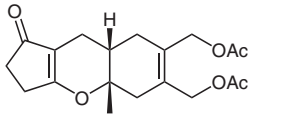
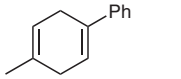
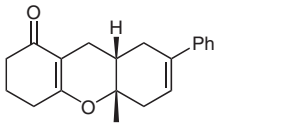
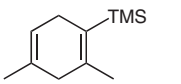
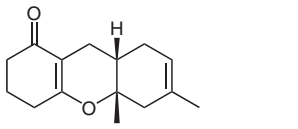
Scheme 2 Knoevenagel–hetero-Diels–Alder multicomponent reaction of cyclic 1,3-diones, formaldehyde, and cyclohexa-1,4-dienes towards the construction of tricyclic systems

1,3-dione (dimedone) to yield the corresponding tricyclic compounds in moderate yields. The results of these transformations are summarised in Table 2.

The yields for the presented conversions are as good as the yields for the cycloaddition of monoterpenes with the in situ formed hetero-1,3-diene as reported by Koser and Hoffmann.[6] Nevertheless, the transformations with the cyclohexa-1,4-diene derivatives are remarkable because the intermediates can be easily oxidised to the corresponding arene derivatives. Moreover, the double bonds could conceivably migrate under the acidic conditions applied to form the conjugated cyclohexa-1,3-diene derivatives, which would not undergo the conversion in the way presented here. Although the thermal cycloaddition could have given rise to regioisomers only products of type **5** were isolated. In the products, the methyl group is always found in 2-position with regard to the pyrane oxygen. The dienophile reacted preferably with the least sterically hindered and electron-richest double bond and only one of the two possible regioisomers was formed.

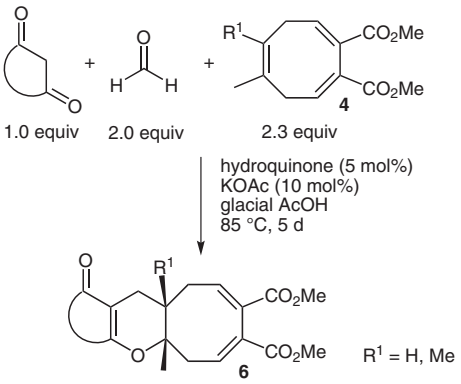
Conversions of ether- or ester-substituted cyclohexa-1,3-dienes **3a** and **3b** with cyclohexa-1,3-dione, dimedone, and cyclopenta-1,3-dione led to the corresponding tricy-

Table 2 Results of the Knoevenagel–Hetero-Diels–Alder Multicomponent Reaction of Cyclohexa-1,4-dienes, Formaldehyde, and Cyclic 1,3-Diones

Entry	1,4-Diene **3**	Product **5**[a]	Yield (%)
1	 **3a**	 **5a**	44
2	 **3a**	 **5b**	44
3	 **3b**	 **5c**	40
4	 **3b**	 **5d**	42
5	 **3b**	 **5e**	41
6	 **3c**	 **5f**	50
7	 **3d**	 **5g**	49

[a] Only one enantiomer is shown.

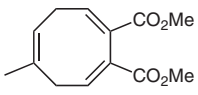
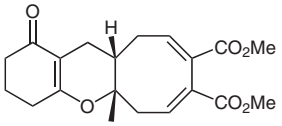
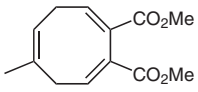
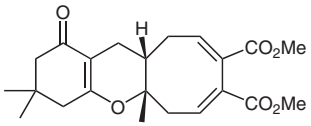
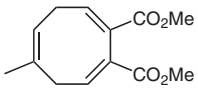
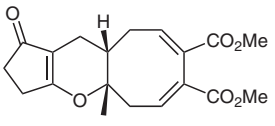
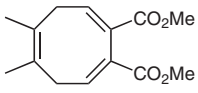
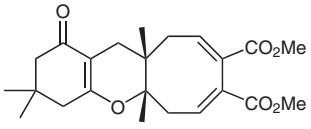
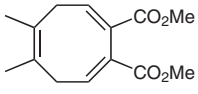
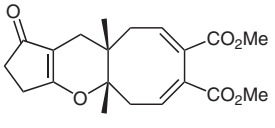
clic systems in comparable yields of 40–44% (Table 2, entries 1–5). The use of less polar cyclohexa-1,3-dienes such as **3c** and **3d** gave comparable yields of 50% and 49%, respectively (entries 6, 7). It should be mentioned that the vinylic trimethylsilyl group of **3d** was not stable under the reaction conditions and only the protodesilylated product could be isolated. Accordingly, the trimethylsilyl group in trimethylsilylpropyne utilised for the synthesis of **3d** by cobalt-catalysis served as a strong regiodirecting group in the cycloaddition process. Thereby, a synthon for propyne was realised, which regioselectively afforded the corresponding cyclohexa-1,4-diene derivative. Surprisingly, the formed tricyclic system **5g** did not react in a second hetero-Diels–Alder reaction to produce a corresponding pentacyclic by-product. Having explored the multicomponent reaction of cyclohexa-1,4-dienes thus far, the use of cobalt-generated cycloocta-1,3,6-trienes became of significant interest. Specifically, we were interested in determining if the reactivity of the [4+2+2] cycloadducts is lowered when the respecting double bond is not tri- but tetrasubstituted, as was observed by Koser and Hoffmann as they reacted cyclohexane-1,3-dione with 1,2,3,4,5,6,7,8-octahydronaphthalene.[6] The 1,3-diene subunits of the cycloocta-1,3,6-trienes are electron-deficient and therefore unreactive in the hetero-Diels–Alder multicomponent reaction under these conditions.



Scheme 3 Knoevenagel–hetero-Diels–Alder multicomponent reaction of cyclic 1,3-diones, formaldehyde, and cycloocta-1,3,6-trienes towards the construction of tricyclic systems

The cycloocta-1,3,6-trienes **4a** and **4b** were subjected to the same reaction conditions as the cyclohexa-1,4-dienes (Scheme 3). Again cyclohexane-1,3-dione, dimedone, and cyclopentane-1,3-dione were used as the hetero-1,3-diene components, and the results are summarised in Table 3.

Table 3 Results of the Knoevenagel–Hetero-Diels–Alder Multicomponent Reaction of Cycloocta-1,3,6-trienes, Formaldehyde, and Cyclic 1,3-Diones

Entry	1,4,7-Triene **4**	Product **6**[a]	Yield (%)
1	 **4a**	 **6a**	49
2	 **4a**	 **6b**	52
3	 **4a**	 **6c**	40
4	 **4b**	 **6d**	47
5	 **4b**	 **6e**	42

[a] Only one enantiomer is shown.

We were pleased to find that the cycloocta-1,3,6-trienes showed very similar reactivity. The yields were again in the range of 40–52%.

Moreover, the [4+2+2] cycloadduct **4b** with a tetrasubstituted double bond shows the same reactivity as the previously applied dienophiles with trisubstituted double bonds **3a**–**d** and **4a** (entries 4, 5). This can be explained through compensation of increased steric hindrance by increased electron density in the dienophile of type **4**. Again, all tricyclic products were formed as single diastereoisomers and represent the first examples of the cycloocta-1,3,6-triene derivatives **4a**,**b** applied.

In contrast to the tricyclic systems formed from cyclohexa-1,4-dienes, which were isolated as yellow oils, the tricyclic products obtained from the conversion of cycloocta-1,3,6-trienes were isolated as solid, white compounds.

The obtained crystallographic data of compounds **6a** (Figure 1) and **6d** (Figure 2) confirms the NMR spectroscopic assignments and verified the correct constitution and configuration of the tricylic systems. The *cis*-configuration of the product indicates that the reaction proceeded in a concerted manner and under frontier orbital control.

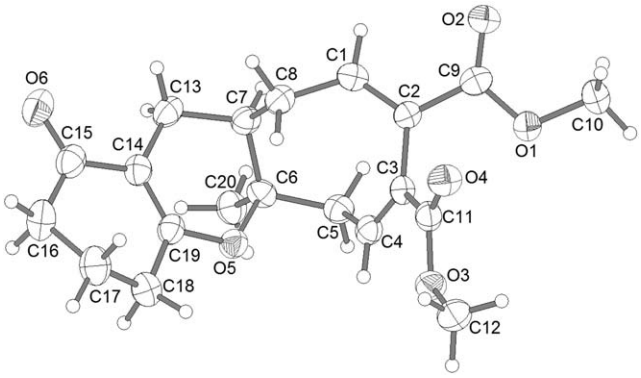


Figure 1 Crystal structure of compound **6a**[7]

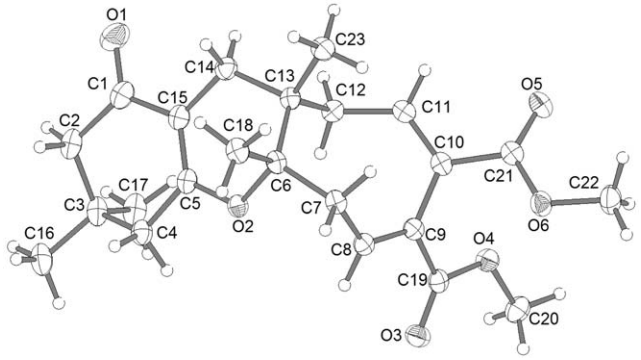


Figure 2 Crystal structure of compound **6d**[7]

In conclusion, four different types of tricyclic ring systems were produced in a short two-step reaction sequence. The cobalt-catalysed reactions as well as the multicomponent Knoevenagel-hetero-Diels–Alder proceeded with excellent regio- and diastereoselectivity and good overall yields for the construction of tricyclic products were obtained. Furthermore, the correct constitution of the tricyclic products was confirmed by X-ray crystal structure analysis.

Column chromatography was performed using silica gel (Macherey-Nagel, 230–400 mesh size) and TLC was carried out using silica gel (Merck) plates. IR spectra were obtained using a Bruker Physics IFS 200 Interferometer or a Nicolet Magna IR 750 spectrometer. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded using a Bruker Physics Avance-300 instrument with $CDCl_3$ as the solvent. Low-resolution mass spectra were recorded using a Varian MAT CH 7A, or a Micromass VG 7070 spectrometer for EI measurements, or a Micromass VG Autospec spectrometer for ESI measurements. HRMS were obtained using a Finnigan MAT 95S instrument for EI measurements or a Micromass VG Autospec spectrometer for ESI measurements

Preparative Cobalt-Catalysed [4+2] Cycloaddition; General Procedure

A Schlenk flask was charged with $CoBr_2$(dppe) (309 mg, 0.5 mmol, 10 mol%), anhyd ZnI_2 (319 mg, 1.0 mmol, 20 mol%), and Zn powder (65 mg, 1.0 mmol, 20 mol%) under argon atmosphere. After the addition of anhyd CH_2Cl_2 (5.0 mL), the 1,3-diene **1** (6.0 mmol) and the alkyne **2** (5.0 mmol) were added. The mixture was stirred at r.t. and the conversion was monitored by GC/MS. After the conversion was complete, the mixture was diluted with pentane to precipitate the metal salts and filtered through a small plug of silica gel using Et_2O–pentane or pure pentane as eluent. Further purification by column chromatography was not necessary.

(4-Methylcyclohexa-1,4-diene-1,2-diyl)bis(methylene) Diacetate (3b)

Eluent: pentane–Et_2O (5:1); yield: 0.95 g (3.99 mmol, 80%); pale yellow oil; R_f = 0.80 (pentane–Et_2O, 10:1).

IR (KBr): 3420, 2966, 2931, 2820, 1738, 1619, 1507, 1440, 1378, 1226, 1026, 963, 822, 607 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.39–5.38 (m, 1 H), 4.67–4.66 (m, 4 H), 2.78–2.75 (m, 2 H), 2.69–2.64 (m, 2 H), 2.06 (s, 3 H), 2.04 (s, 3 H), 1.68 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.9, 130.5, 129.4, 129.3, 117.7, 63.3, 63.2, 34.0, 30.3, 22.7, 20.9.

MS (EI, 70 eV): *m*/*z* (%) = 178 (4), 133 (1), 118 (100), 105 (24), 91 (14), 77 (6), 65 (2), 51 (1).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{21}H_{27}NO_2$: 238.1205; found: 238.1206.

(2,4-Dimethylcyclohexa-1,4-dienyl)trimethylsilane (3d)

Eluent: pentane; yield: 1.76 g (9.78 mmol, 98%); colourless oil; R_f = 0.86 (pentane).

IR (KBr): 2961, 2911, 2862, 2809, 1698, 1627, 1447, 1384, 1303, 1250, 1205, 1158, 1000, 976, 943, 902, 837, 785, 753, 687, 640 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.47–5.43 (m, 1 H), 2.75–2.69 (m, 2 H), 2.54–2.48 (m, 2 H), 1.80–1.78 (m, 3 H), 1.67–1.65 (m, 3 H), 0.14 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.4, 130.8, 126.1, 119.1, 38.2, 31.6, 23.3, 22.9, 0.0.

MS (EI, 70 eV): *m*/*z* (%) = 180 (4, [M]$^+$), 165 (4), 149 (2), 135 (3), 121 (2), 106 (91), 97 (4), 91 (41), 79 (6), 73 (100), 65 (5), 59 (35), 53 (4).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{11}H_{20}Si$: 180.1334; found: 180.1332.

Preparative Cobalt-Catalysed [4+2+2] Cycloaddition; General Procedure

A Schlenk flask was charged with $CoBr_2$(*i*-PrPyrIm) (185 mg, 0.5 mmol, 5 mol%), anhyd ZnI_2 (319 mg, 1.0 mmol, 10 mol%), Zn powder (65 mg, 1.0 mmol, 10 mol%), and Fe powder (55 mg, 1.0 mmol, 10 mol%) under argon atmosphere. After the addition of anhyd CH_2Cl_2 (5.0 mL), the 1,3-diene **1** (10.0 mmol) and the alkyne **2** (10.0 mmol) were added. The mixture was stirred at r.t. and the conversion was monitored by GC/MS. After the conversion was complete, the mixture was diluted with pentane to precipitate the metal salts and filtered through a small plug of silica gel using Et_2O–pentane as eluent. After evaporation of the solvent, the residue was purified by flash chromatography on silica gel.

(1*E*,2*E*,5*Z*)-Dimethyl 5-Methylcycloocta-2,5,8-triene-1,2-dicarboxylate (4a)

Eluent: pentane–Et_2O (3:1); yield: 0.98 g (3.89 mmol, 78%); colourless oil; R_f = 0.38 (pentane–Et_2O, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.78–6.72 (m, 2 H), 5.33–5.28 (m, 1 H), 3.66 (s, 6 H), 2.68–2.63 (m, 4 H), 1.70 (br s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 138.2, 137.6, 133.2, 131.3, 130.9, 118.0, 51.7, 33.0, 27.4, 27.0.

MS (EI, 70 eV): *m*/*z* (%) = 236 (4) [M]$^+$, 221 (1), 205 (7), 177 (100), 175 (26), 119 (12), 117 (24), 105 (7).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{13}H_{16}O_4$: 236.1049; found: 236.1044.

(1*E*,2*E*,5*Z*)-Dimethyl 5,6-Dimethylcycloocta-2,5,8-triene-1,2-dicarboxylate (4b)

Eluent: pentane–Et_2O (3:1); yield: 1.10 g (4.38 mmol, 88%); colourless oil; R_f = 0.41 (pentane–Et_2O, 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.80 (t, *J* = 8.1 Hz, 2 H), 3.72 (s, 6 H), 2.24 (d, *J* = 8.1 Hz, 4 H), 1.74 (br s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6, 138.7, 131.1, 124.6, 52.0, 35.7, 23.6.

MS (EI, 70 eV): *m*/*z* (%) = 250 (6) [M]$^+$, 235 (1), 218 (8), 203 (2), 190 (100), 175 (10), 159 (16), 147 (4), 132 (60).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{14}H_{18}O_4$: 250.1205; found: 250.1192.

Preparative Knoevenagel-Hetero-Diels–Alder Multicomponent Reaction of Cyclohexa-1,4-dienes with Cyclic 1,3-Diones and Formaldehyde; General Procedure

A thick walled Schlenk tube was charged with hydroquinone (5 mg, 0.043 mmol, 5 mol%), KOAc (9 mg, 0.086 mmol, 10 mol%), the appropriate cyclic 1,3-dione (0.86 mmol, 1.0 equiv), paraformaldehyde (52 mg, 1.72 mmol, 2.0 equiv), the appropriate cyclohexa-1,4-diene **3** (1.98 mmol, 2.3 equiv), and glacial AcOH (1.0 mL). The mixture was heated to 85 °C and stirred for 5 d, until GC/MS-monitoring indicated no further conversion of the cyclohexa-1,4-diene **3**. The mixture was partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and the solvent was evaporated. The residue was purified by flash chromatography on silica gel.

6,7-Bis(methoxymethyl)-10a-methyl-2,3,4,5,8,8a,9,10a-octahydro-1*H*-xanthen-1-one (5a)

Eluent: Et_2O–EtOAc (10:1); yield: 117 mg (0.38 mmol, 44%); yellow oil; R_f = 0.25 (Et_2O–EtOAc, 10:1).

IR (KBr): 3473, 2928, 2821, 1732, 1702, 1618, 1440, 1386, 1292, 1236, 1186, 1150, 1087, 921, 731 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.97–3.83 (m, 4 H), 3.26 (s, 3 H), 3.25 (s, 3 H), 2.36–2.30 (m, 7 H), 2.06–1.90 (m, 6 H), 1.31 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.3, 169.7, 130.1, 128.5, 109.4, 77.7, 71.0, 57.8, 37.2, 36.7, 33.3, 31.9, 28.8, 24.7, 21.5, 21.0.

MS (EI, 70 eV): *m*/*z* (%) = 306 (1, [M]$^+$), 291 (2), 274 (52), 259 (16), 242 (57), 227 (9), 213 (4), 199 (6), 186 (8), 171 (8), 163 (62), 149 (61), 132 (63), 119 (70), 105 (100), 91 (45), 75 (28), 55 (25).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{18}H_{26}O_4$: 306.1831; found: 306.1836.

6,7-Bis(methoxymethyl)-3,3,10a-trimethyl-2,3,4,5,8,8a,9,10a-octahydro-1*H*-xanthen-1-one (5b)

Eluent: Et_2O–EtOAc (10:1); yield: 127 mg (0.38 mmol, 44%); yellow oil; R_f = 0.33 (Et_2O–EtOAc, 10:1).

IR (KBr): 3457, 2925, 2819, 1735, 1622, 1457, 1387, 1293, 1230, 1195, 1153, 1092, 960, 888, 652 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.97–3.83 (m, 4 H), 3.26–3.24 (m, 6 H), 2.45–2.29 (m, 3 H), 2.23–2.17 (m, 5 H), 2.07–1.92 (m, 3 H), 1.30 (s, 3 H), 1.03–1.02 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.0, 168.0, 130.3, 128.5, 108.0, 77.7, 71.0, 57.7, 50.6, 42.6, 37.4, 33.1, 32.2, 31.8, 28.5, 28.3, 24.7, 21.3.

MS (EI, 70 eV): *m*/*z* (%) = 334 (1, [M]$^+$), 319 (2), 303 (29), 287 (16), 270 (90), 255 (11), 237 (3), 227 (3), 191 (45), 171 (9), 162 (33), 149 (58), 132 (93), 118 (81), 105 (100), 91 (52), 75 (30), 55 (35).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{20}H_{30}O_4$: 334.2144; found: 334.2143.

(4a-Methyl-8-oxo-4,4a,5,6,7,8,9,9a-octahydro-1*H*-xanthene-2,3-diyl)bis(methylene) Diacetate (5c)

Eluent: Et_2O–EtOAc (10:1); yield: 124 mg (0.34 mmol, 40%); yellow oil; R_f = 0.30 (Et_2O–EtOAc, 10:1).

IR (KBr): 3463, 2936, 1739, 1650, 1621, 1432, 1389, 1298, 1231, 1189, 1159, 1117, 1073, 1025, 961, 926, 732 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.65–4.54 (m, 4 H), 2.45–2.14 (m, 8 H), 2.05–2.04 (m, 7 H), 1.98–1.92 (m, 4 H), 1.31 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.3, 170.8, 169.5, 129.7, 127.8, 109.4, 77.2, 63.1, 62.9, 37.3, 36.7, 33.1, 31.8, 28.8, 24.6, 21.4, 21.0, 20.8.

MS (EI, 70 eV): *m*/*z* (%) = 362 (1, [M]$^+$), 319 (1), 302 (4), 278 (1), 260 (3), 242 (100), 227 (6), 213 (2), 201 (3), 190 (7), 177 (2), 163 (13), 148 (9), 135 (14), 118 (60), 105 (23), 91 (23), 79 (10), 65 (3), 55 (11).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{20}H_{26}O_6$: 362.1729; found: 362.1744.

(4a,6,6-Trimethyl-8-oxo-4,4a,5,6,7,8,9,9a-octahydro-1*H*-xanthene-2,3-diyl)bis(methylene) Diacetate (5d)

Eluent: Et_2O–EtOAc (10:1); yield: 129 mg (0.33 mmol, 42%); yellow oil; R_f = 0.45 (Et_2O–EtOAc, 10:1).

IR (KBr): 3463, 2957, 2932, 1740, 1652, 1623, 1432, 1386, 1293, 1230, 1162, 1119, 1061, 1025, 964, 932, 733 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.67–4.53 (m, 4 H), 2.44–2.17 (m, 8 H), 2.09–1.93 (m, 9 H), 1.30 (s, 3 H), 1.05–1.04 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.0, 170.7, 167.9, 129.8, 127.8, 107.9, 77.2, 63.1, 63.0, 50.6, 42.6, 37.7, 33.0, 32.2, 31.7, 28.6, 28.1, 24.6, 21.2, 20.8.

MS (EI, 70 eV): *m*/*z* (%) = 390 (1, [M]$^+$), 331 (2), 288 (2), 270 (100), 255 (6), 237 (3), 225 (1), 191 (10), 171 (5), 159 (2), 148 (7), 135 (11), 118 (47), 105 (12), 91 (12), 69 (7), 55 (8).

HRMS: *m*/*z* [M]$^+$ calcd for $C_{22}H_{30}O_6$: 390.2042; found: 390.2053.

(4a-Methyl-1-oxo-1,2,3,4a,5,8,8a,9-octahydrocyclopenta[*b*]chromene-6,7-diyl)bis(methylene) Diacetate (5e)
Eluent: Et_2O–EtOAc (1:1); yield: 123 mg (0.35 mmol, 41%); yellow oil; R_f = 0.28 (Et_2O–EtOAc, 1:1).

IR (KBr): 3461, 2926, 1739, 1693, 1630, 1441, 1401, 1380, 1297, 1234, 1159, 1114, 1079, 1052, 1026, 985, 962, 881, 830 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.63–4.51 (m, 4 H), 2.51–2.49 (m, 2 H), 2.43–2.38 (m, 3 H), 2.30–2.24 (m, 3 H), 2.04 (s, 3 H), 2.01 (s, 3 H), 2.00–1.93 (m, 3 H), 1.33 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 204.1, 182.6, 170.7, 129.7, 127.6, 112.5, 80.3, 63.0, 62.8, 37.7, 33.2, 32.7, 31.5, 26.6, 20.8, 20.3.

MS (EI, 70 eV): *m*/*z* (%) = 348 (1, $[M]^+$), 288 (11), 246 (3), 228 (100), 213 (8), 199 (5), 185 (7), 171 (5), 158 (4), 149 (10), 135 (28), 118 (78), 105 (32), 91 (33), 77 (14), 65 (7), 55 (13).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{19}H_{24}O_6$: 348.1573; found: 348.1564.

10a-Methyl-7-phenyl-2,3,4,5,8,8a,9,10a-octahydro-1*H*-xanthen-1-one (5f)
Eluent: Et_2O; yield: 255 mg (0.87 mmol, 50%); yellow oil; R_f = 0.48 (Et_2O).

IR (KBr): 3027, 2917, 1739, 1654, 1624, 1493, 1446, 1386, 1325, 1291, 1250, 1223, 1184, 1134, 1087, 1070, 998, 920, 851, 759, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.15 (m, 5 H), 5.25 (s, 1 H), 2.48–2.44 (m, 2 H), 2.41–2.40 (m, 2 H), 2.35–2.31 (m, 1 H), 2.29–2.24 (m, 2 H), 2.04–1.99 (m, 2 H), 1.96–1.87 (m, 4 H), 1.62 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.4, 169.9, 144.5, 132.9, 128.5, 127.3, 125.3, 124.7, 117.0, 110.5, 81.0, 36.8, 36.7, 32.8, 28.7, 23.2, 22.0, 21.0.

MS (EI, 70 eV): *m*/*z* (%) = 294 (4, $[M]^+$), 226 (5), 182 (5), 170 (51), 155 (65), 141 (13), 126 (100), 115 (20), 102 (5), 91 (35), 77 (21), 65 (8), 55 (15).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{20}H_{22}O_2$: 294.1620; found: 294.1611.

6,10a-Dimethyl-2,3,4,5,8,8a,9,10a-octahydro-1*H*-xanthen-1-one (5g)
Eluent: pentane–Et_2O (1:2); yield: 196 mg (0.84 mmol, 49%); yellow oil; R_f = 0.50 (pentane–Et_2O, 1:2).

IR (KBr): 3456, 2911, 1739, 1652, 1622, 1436, 1390, 1284, 1231, 1190, 1167, 1134, 1096, 1078, 1025, 994, 935, 855, 822, 796, 637 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.24 (s, 1 H), 2.37–2.24 (m, 6 H), 2.07–2.01 (m, 2 H), 1.96–1.83 (m, 5 H), 1.61 (s, 3 H), 1.30 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.6, 169.9, 129.7, 118.2, 109.9, 78.6, 39.0, 36.6, 33.1, 29.3, 28.9, 24.9, 23.1, 21.5, 21.0.

MS (EI, 70 eV): *m*/*z* (%) = 232 (25, $[M]^+$), 214 (38), 199 (7), 189 (5), 176 (3), 163 (14), 155 (2), 143 (5), 127 (7), 120 (60), 113 (87), 105 (39), 93 (100), 77 (32), 65 (13), 55 (16).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{15}H_{20}O_2$: 232.1463; found: 232.1460.

Preparative Knoevenagel-Hetero-Diels–Alder Multicomponent Reaction of Cycloocta-1,3,6-trienes with Cyclic 1,3-Diones and Formaldehyde; General Procedure
A Schlenk tube was charged with hydroquinone (5 mg, 0.043 mmol, 5 mol%), KOAc (9 mg, 0.086 mmol, 10 mol%), the appropriate cyclic 1,3-dione (0.86 mmol, 1.0 equiv), paraformaldehyde (52 mg, 1.72 mmol, 2.0 equiv), the appropriate cycloocta-1,3,6-triene **4** (1.98 mmol, 2.3 equiv) and glacial AcOH (1.0 mL). The mixture was heated to 85 °C and stirred for 5 d until GC/MS-monitoring indicated no further conversion of the cycloocta-1,3,6-triene **4**. The mixture was partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic phases were dried ($MgSO_4$). After filtration and evaporation of the solvent, the residue was purified by flash chromatography on silica gel.

Dimethyl (7*E*,9*E*)-5a-Methyl-1-oxo-2,3,4,5a,6,11,11a,12-octahydro-1*H*-cycloocta[*b*]chromene-8,9-dicarboxylate (6a)
Eluent: Et_2O–EtOAc (10:1); yield: 115 mg (0.32 mmol, 49%); white solid; mp 93–95 °C; R_f = 0.29 (Et_2O–EtOAc, 10:1).

IR (KBr): 3425, 2949, 1724, 1648, 1623, 1437, 1391, 1352, 1266, 1188, 1134, 1098, 1062, 1043, 1015, 1001, 924, 839, 805, 771, 752 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.22–7.16 (m, 1 H), 7.09–7.04 (m, 1 H), 3.73 (s, 6 H), 2.82–2.32 (m, 7 H), 2.25–1.86 (m, 6 H), 1.30 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.1, 168.8, 166.4, 144.4, 140.5, 130.4, 129.3, 107.7, 124.7, 76.1, 52.2, 52.0, 40.4, 36.7, 34.7, 31.6, 28.7, 28.5, 28.1, 25.7, 20.9, 20.8.

MS (EI, 70 eV): *m*/*z* (%) = 360 (8, $[M]^+$), 345 (1), 328 (65), 313 (9), 300 (16), 287 (23), 268 (28), 253 (6), 241 (29), 225 (9), 213 (8), 203 (17), 189 (32), 177 (59), 163 (100), 145 (33), 128 (18), 117 (60), 105 (27), 91 (48), 77 (38), 59 (42).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{20}H_{24}O_6$: 360.1573; found: 360.1578.

Dimethyl (7*E*,9*E*)-3,3,5a-Trimethyl-1-oxo-2,3,4,5a,6,11,11a,12-octahydro-1*H*-cycloocta[*b*]chromene-8,9-dicarboxylate (6b)
Eluent: Et_2O–EtOAc (10:1); yield: 156 mg (0.40 mmol, 52%); white solid; mp 77 °C; R_f = 0.40 (Et_2O–EtOAc, 10:1).

IR (KBr): 3417, 2954, 1724, 1628, 1437, 1393, 1347, 1264, 1135, 1099, 1061, 1044, 1010, 970, 936, 886, 851, 806, 772, 751 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.22–7.16 (m, 1 H), 7.08–7.02 (m, 1 H), 3.74–3.71 (m, 6 H), 2.89–2.40 (m, 4 H), 2.22–2.20 (m, 4 H), 2.02–1.57 (m, 3 H), 1.30 (s, 3 H), 1.04–0.98 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.8, 167.2, 166.4, 144.3, 140.4, 130.3, 129.3, 106.4, 124.7, 76.2, 52.1, 52.0, 50.6, 42.3, 40.4, 34.6, 32.2, 31.6, 28.9, 28.1, 27.7, 25.5.

MS (EI, 70 eV): *m*/*z* (%) = 388 (15, $[M]^+$), 373 (3), 356 (64), 341 (31), 324 (33), 313 (21), 296 (42), 281 (16), 269 (41), 253 (13), 241 (8), 229 (12), 218 (11), 204 (34), 192 (98), 177 (100), 163 (41), 145 (46), 128 (25), 117 (80), 105 (36), 83 (63), 59 (52).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{22}H_{28}O_6$: 388.1886; found: 388.1885.

Dimethyl (6*E*,8*E*)-4a-Methyl-1-oxo-1,2,3,4a,5,10,10a,11-octahydrocycloocta[*e*]cyclopenta[*b*]pyran-7,8-dicarboxylate (6c)
Eluent: Et_2O–EtOAc (2:1); yield: 117 mg (0.34 mmol, 40%); white solid; mp 96–98 °C; R_f = 0.19 (Et_2O–EtOAc, 2:1).

IR (KBr): 3435, 2951, 1723, 1635, 1440, 1403, 1339, 1266, 1244, 1141, 1095, 1075, 1059, 1038, 985, 938, 842, 806, 782, 772 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.22–7.16 (m, 1 H), 7.11–7.05 (m, 1 H), 3.74–3.71 (m, 6 H), 2.88–2.81 (m, 1 H), 2.56–2.49 (m, 3 H), 2.42–2.37 (m, 2 H), 2.27–2.19 (m, 1 H), 2.18–1.99 (m, 2 H), 1.91–1.85 (m, 1 H), 1.66–1.91 (m, 1 H), 1.34 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.9, 181.8, 166.4, 143.9, 140.1, 130.6, 129.5, 112.0, 111.2, 79.4, 52.1, 52.0, 40.1, 34.6, 33.3, 31.6, 28.1, 26.4, 25.0.

MS (EI, 70 eV): *m*/*z* (%) = 346 (9, $[M]^+$), 314 (100), 299 (17), 286 (20), 273 (44), 254 (53), 239 (8), 227 (48), 213 (9), 203 (37), 189 (28), 177 (86), 163 (33), 150 (44), 141 (13), 128 (23), 117 (71), 105 (26), 91 (52), 77 (38), 59 (37).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{19}H_{22}O_6$: 346.1416; found: 346.1427.

Dimethyl (7*E*,9*E*)-3,3,5a,11a-Tetramethyl-1-oxo-2,3,4,5a,6,11,11a,12-octahydro-1*H*-cycloocta[*b*]chromene-8,9-dicarboxylate (6d)

Eluent: Et_2O–EtOAc (15:1); white solid; yield: 107 mg (0.27 mmol, 47%); mp 113 °C; R_f = 0.47 (Et_2O–EtOAc, 15:1).

IR (KBr): 3414, 2955, 1724, 1634, 1437, 1393, 1263, 1230, 1195, 1142, 1121, 1075, 1048, 1028, 931, 807, 773 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.17–7.05 (m, 2 H), 3.73–3.72 (m, 6 H), 2.57–2.25 (m, 4 H), 2.22–2.17 (m, 4 H), 2.15–2.07 (m, 1 H), 1.87–1.81 (m, 1 H), 1.34–1.25 (m, 3 H), 1.05–1.02 (m, 6 H), 0.98–0.90 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.5, 166.7, 166.5, 143.8, 141.7, 130.3, 129.8, 107.3, 106.5, 81.4, 52.1, 52.0, 50.4, 42.0, 36.0, 35.7, 34.6, 33.5, 32.3, 28.8, 27.8, 25.0, 22.4.

MS (EI, 70 eV): *m*/*z* (%) = 402 (4, $[M]^+$), 370 (31), 355 (19), 338 (5), 327 (5), 315 (24), 295 (9), 283 (10), 267 (5), 243 (4), 231 (5), 218 (12), 206 (100), 191 (37), 179 (24), 159 (17), 143 (7), 131 (35), 115 (21), 97 (8), 83 (37), 59 (27).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{23}H_{30}O_6$: 402.2042; found: 402.2060.

Dimethyl (6*E*,8*E*)-4a,10a-Dimethyl-1-oxo-1,2,3,4a,5,10,10a,11-octahydrocycloocta[*e*]cyclopenta[*b*]pyran-7,8-dicarboxylate (6e)

Eluent: Et_2O–EtOAc (1:1); yield: 130 mg (0.36 mmol, 42%); white solid; mp 94–96 °C; R_f = 0.24 (Et_2O–EtOAc, 1:1).

IR (KBr): 3433, 2951, 1723, 1640, 1439, 1401, 1261, 1234, 1192, 1153, 1116, 1093, 1070, 1046, 1014, 958, 931, 901, 852, 821, 773 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.17–7.06 (m, 2 H), 3.73–3.71 (m, 6 H), 2.64–2.57 (m, 1 H), 2.53–2.47 (m, 2 H), 2.44–2.36 (m, 3 H), 2.23–2.02 (m, 3 H), 1.86–1.79 (m, 1 H), 1.41–1.08 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 203.3, 181.2, 166.5, 166.3, 143.3, 141.3, 130.5, 130.1, 112.2, 84.4, 52.2, 52.0, 35.9, 35.7, 34.7, 33.4, 33.2, 26.2, 24.9, 22.6.

MS (EI, 70 eV): *m*/*z* (%) = 360 (6, $[M]^+$), 328 (46), 318 (6), 300 (12), 286 (7), 273 (33), 253 (8), 241 (18), 227 (5), 217 (33), 203 (22), 190 (42), 177 (36), 164 (100), 149 (28), 131 (51), 115 (36), 105 (22), 91 (47), 77 (33), 59 (33).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{20}H_{24}O_6$: 360.2573; found: 360.1569.

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(7) The X-ray data have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition numbers CCDC 809255 (**6a**) and CCDC 809256 (**6d**). These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223)336033, E-mail: deposit@ccdc.cam.ac.uk].