Regioselective Spiroannulations of α-Acetyl Lactones

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Monocyclic spiroannulation precursors **3a–c** were obtained by Michael reactions of α-acetyl lactones **6a–c** with methyl vinyl ketone (**7**). The selective formation of either regioisomer of both β-oxo (**5a–c**) and δ-oxo (**4a–c**) lactones from **3a–c** was achieved by varying the reaction conditions. The δ-oxo lactones **4a–c** were obtained under basic (buffered) conditions in a pyrrolidine/AcOH system. Under acidic conditions, the annulation reaction afforded β-oxo lactones **5a–c**. Byproducts **8b**,**c** were identified to be the decomposition products of β-oxo lactones **5b** and **5c** by comparison with the spectra of the alcohols **10b**,**c** derived directly from δ-oxo lactones **4b** and **4c** by saponification/decarboxylation.

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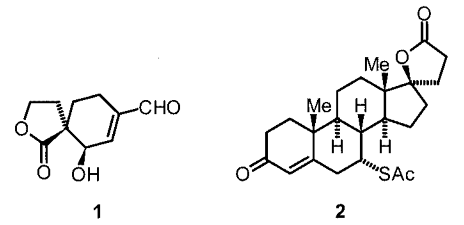
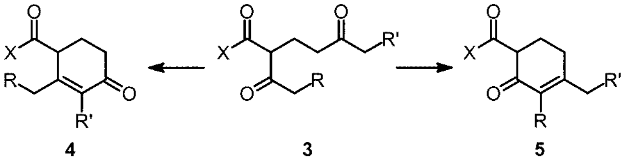
Introduction

The spirolactone skeleton is a common structural motif of several natural products[1] and other biologically active compounds. Examples range from terpenoid lactones, such as canangone (**1**),[2] which often exhibit remarkable antifeedant activities,[3] to pharmaceutically important steroids,[4] such as the well-known diuretic aldosterone antagonist, spironolactone (**2**) (Scheme 1).[5]



Scheme 1. Structures of spirolactones canangone (**1**) and spironolactone (**2**)

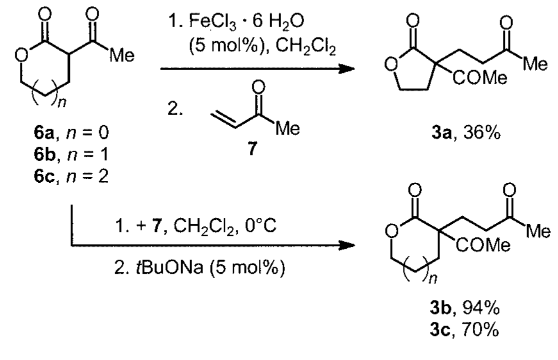
A synthetic strategy leading to spirocycles with at least one six-membered carbocycle is the sequence of a Michael reaction and an aldol condensation known as Robinson annulation.[6] A precondition, however, for successful spiroannulations of monocyclic 1,5-diketones **3** is the control of the regioselectivity of the closure of the cyclohexanone ring. As outlined in Scheme 2, annulation could lead to regioisomeric cyclohexenones **4** and **5**. Generally, the formation of the δ-dicarbonyl product **4** is observed in spiroannulations.[7] Herein, we report complementary reaction conditions that allow the selective formation of either regioisomer of both spirolactone annulation products, namely the more common δ-dicarbonyl (**4**) and the more rare β-dicarbonyl (**5**) structural motif.



Scheme 2. Formation of regioisomeric cyclohexenones **4** and **5** by the annulation reaction of 1,5-diketones **3**

Results and Discussion

The monocyclic spiroannulation precursors **3a−c** should be accessible by Michael reaction of α-acetyl lactones **6a−c**[8] with methyl vinyl ketone (**7**). Therefore, we treated donors **6a−c** with acceptor **7** utilizing $FeCl_3·6H_2O$ as the catalyst.[9] The butyrolactone derivative **3a**[10] was obtained in moderate yield (36%) and the valerolactone-derived addition product **3b** in low yield (17%), but the caprolactone derivative **3c** was not obtained when applying the protocol of iron catalysis (Scheme 3).



Scheme 3. Preparation of Michael addition products **3a−c**

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Moreover, a procedure using $Yb(OTf)_3$ as the catalyst, which has been reported for the successful synthesis of **3a** by Feringa et al.,[10] also failed for the preparation of **3c**. After a broad screening of procedures for this type of Michael reaction, which has to be limited to non-nucleophilic bases as catalysts and anhydrous reaction conditions in order to prevent side reactions and subsequent lactone ring opening, we finally identified sodium *tert*-butoxide as the catalyst and dichloromethane as the solvent for the successful preparation of **3b** and **3c**. It must be noted that the sequence of addition — addition of *t*BuONa to a mixture of **6** and **7** in CH_2Cl_2 — significantly influenced the yield. After a reaction time of 16 h in a temperature range between 0 and 23 °C, the new addition products **3b** and **3c** were isolated in 94 and 70% yield, respectively. All derivatives **3a−c** were obtained as colorless oils, but the monocyclic diketone **3c** crystallized after some days and its constitution was confirmed by X-ray crystallographic analysis[11] (Figure 1).

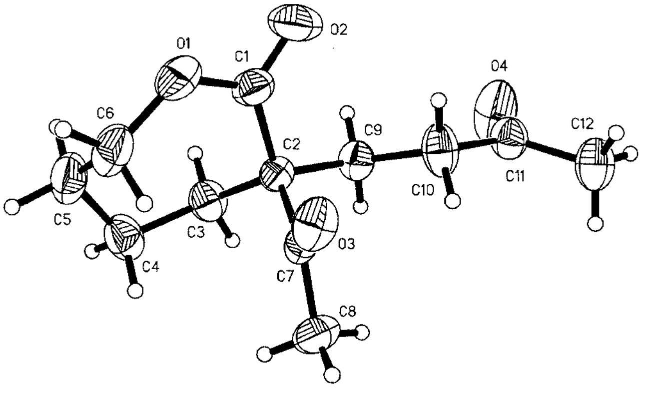
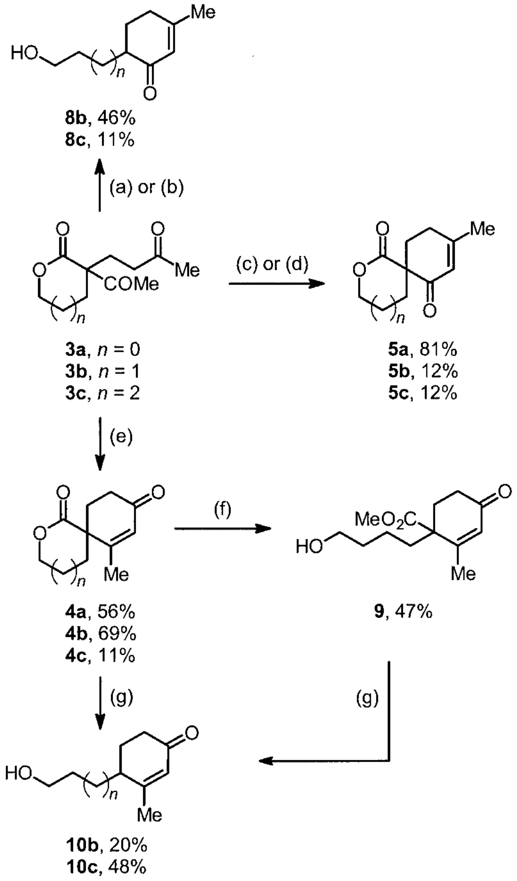


Figure 1. Molecular structure of lactone **3c**

Robinson annulation[6] of dioxo lactones **3a−c** can lead to regioisomeric spirocycles, either β-oxo lactones **5a−c** or δ-oxo lactones **4a−c**, as outlined in Scheme 4. By applying established reaction conditions[12] for the aldol condensation, the basic (buffered) pyrrolidine/AcOH system, the new δ-oxo lactones **4a−c** were formed. Compounds **4a** and **4b** were isolated as the only products in moderate yields (56 and 69%, respectively) from the reactions of starting materials **3a** and **3b**, respectively. In the case of **3c**, however, a nearly inseparable mixture of **4c** and alcohol **8c** was obtained. After repeated column chromatography on SiO_2 and subsequent recrystallization from petroleum ether/toluene, pure **4c** was isolated; the yield, however, was low (11%). The formation of alcohol **8c** as a byproduct is rationalized by saponification and decarboxylation of β-oxo lactone **5c**. Thus, **5c** is assumed to form during annulation of **3c** under the basic reaction conditions, although compound **5c** was never detected in these reaction mixtures, but its decomposition product **8c** was. Structure elucidation of compounds **4a−c** by NMR spectroscopy is based on the coupling pattern of the olefinic protons, which appear as a quadruplet with ^4J = 1.0 Hz. Moreover, the 1,5-dicarbonyl constitution of products **4a−c** was finally confirmed by single-crystal X-ray analysis.[11] ORTEP representations are given in Figure 2. The constitution of the byproduct **8c** was elucidated by NMR spectroscopy, in particular by the ^4J coupling pattern of the olefinic proton; a sextuplet is observed at δ = 5.84 ppm with ^4J = 1.2 Hz. Further evidence for its structure is given by comparison with spectra of the corresponding regioisomeric alcohol **10c**, the constitution of which is without doubt derived from δ-oxo lactone **4c** (vide infra).



Scheme 4. Annulation of dioxo lactones **3** to regioisomeric spirocycles **4** and **5**; reagents and conditions: (a) TFA, 60 °C (for **3b**); (b) *p*TsOH, CH_2Cl_2, 0 °C (for **3c**); (c) concd. H_2SO_4, 0 °C (for **3a**); (d) 1. TMSCl, $CHCl_3$, 0 °C, 2. HCl(g) (for **3b**,**c**); (e) pyrrolidine/AcOH, 0 °C; (f) H_2O/MeOH (1:1), K_2CO_3, 23 °C; (g) H_2O/THF (1:1), KOH, 80 °C

In our earlier work, strongly acidic reaction conditions led successfully to β-dicarbonyl annulation products[13] and, thus, we applied this protocol for the cyclization of **3a−c**. Indeed, lactone **3a** cyclized with concd. H_2SO_4 at 0 °C to give the known β-oxo lactone **5a**[14] in good yield (81%). When applied to homologous lactones **3b** and **3c**, however, only unspecific decomposition was observed. In the course of extensive studies on cyclization procedures, acidic reaction conditions were identified that transform **3b** and **3c** into alcohols **8b** and **8c** (TFA at 60 °C, 46% yield for **8b**; *p*TsOH at 0 °C, 11% yield for **8c**), which again indicate that hydrolysis and decarboxylation of β-oxo lactones **5b** and **5c** occur under the reaction conditions. The parent compounds **5b** and **5c** were, however, not detected in any case. By analogy to **8c**, the structure of **8b** was elucidated by

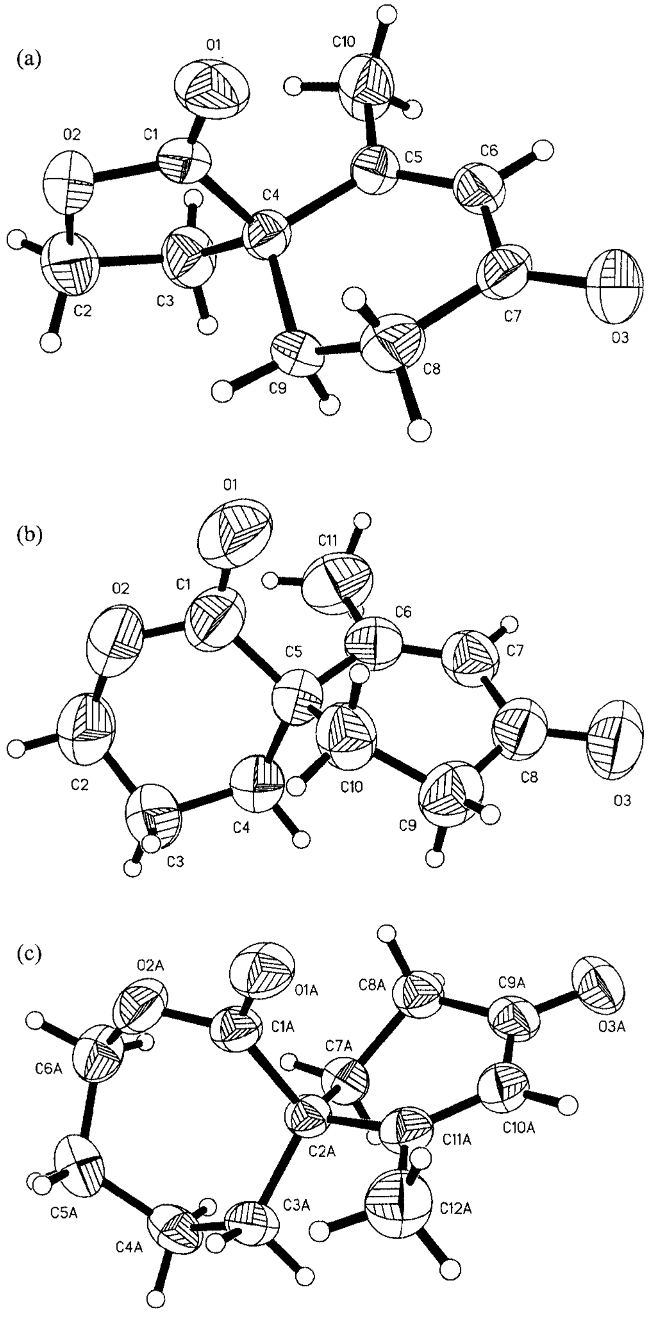


Figure 2. Molecular structures of spirocycles **4a** (a), **4b** (b), and **4c** (c)

comparison with regioisomer **10b** (derived from **4b**, Scheme 4).

Finally, an acid-catalyzed procedure, first reported by Kreiser et al.,[15] turned out to be suitable for the preparation of β-oxo lactones **5b** and **5c**; anhydrous HCl was passed through a chloroform solution of **3b** and **3c**, respectively, with equimolar amounts of TMSCl, giving both target compounds in 12% yield. Interestingly, as investigated for **3c**, the solvent ($CHCl_3$) seems to be essential for the success of this procedure, since other chlorinated hydrocarbons, such as CH_2Cl_2, again lead to decomposition product **8c**. As a mechanistic rationale to explain the regioselectivity of this method, a chelate-type coordination of the Me_3Si moiety to the 1,3-dicarbonyl groups in **3b**,**c** is assumed to fix the β-oxo constitution during product formation. The constitutions of the regioisomeric β-oxo lactones **5a−c** were also proved, as they were for compounds **4a−c**, by the coupling pattern of the olefinic proton (sextuplet, ^4J = 1.0 Hz) as well as by X-ray crystallographic analysis.[11] ORTEP views of the molecular structures of **5a** and **5c** are depicted in Figure 3.

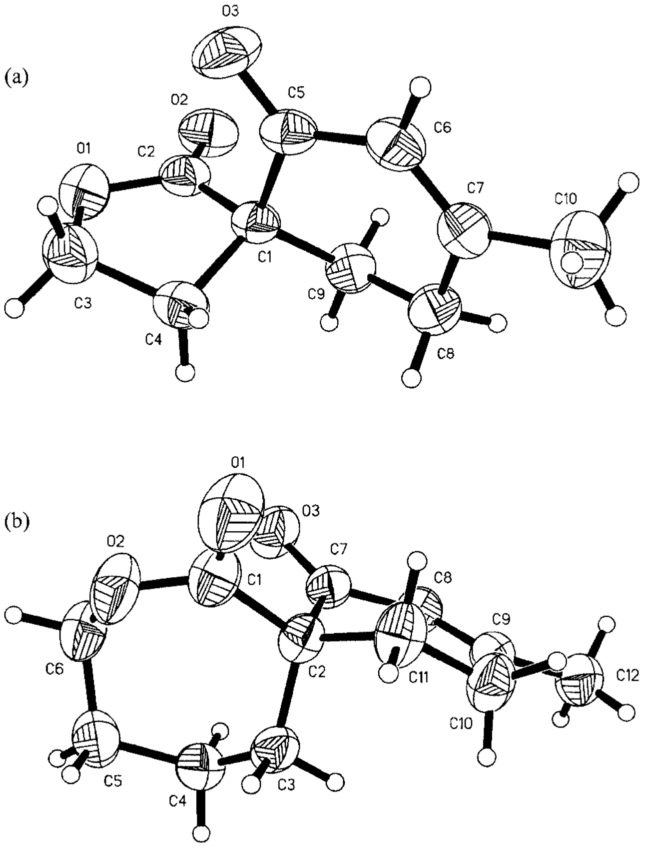


Figure 3. Molecular structures of spirocycles **5a** (a) and **5c** (b)

To establish the constitutions of decomposition products **8b** and **8c** unequivocally, the regioisomeric compounds **10b** and **10c** were prepared by saponification and decarboxylation of spirocycles **4b** and **4c**. Surprisingly, the conversion of **4c** with K_2CO_3 in MeOH/H_2O afforded the transesterification product **9**, and more drastic conditions (KOH in THF/H_2O at reflux) were needed to yield **10c** from **9**. Of course, the latter conditions were also applied directly to prepare alcohols **10b** and **10c** from the spirolactones **4b** and **4c** in low to moderate yields.

Conclusions

α-Acetyl lactones **6a−c** were converted into the monocyclic spiroannulation precursors **3a−c**. While **3a** was obtained by $FeCl_3{\cdot}6H_2O$-catalyzed Michael reaction, the new dioxo lactones **3b** and **3c** required basic conditions (*t*BuONa as the catalyst). A selective Robinson annulation of starting materials **3** to either of the regioisomeric 1,3- and 1,5-dicarbonyl-constituted spirocycles **5** and **4** became possible by varying the reaction conditions. δ-Oxo lactones **4a−c** were prepared in the basic (buffered) pyrrolidine/AcOH system. The cyclization of **3c**, however, gave not only spirocycle **4c**, but also alcohol **8c**. To obtain pure **4c**, an intensive purification was necessary, which diminished the isolated yield. The preparation of alcohol **10c** directly from **4c** indicates that alcohol **8c** must be the decomposition product of regioisomeric spirolactone **5c**, even though it was not detected in the reaction mixture. The 1,5-dicarbonyl constitution of compounds **4** was established by X-ray crystallographic analysis.

Under acidic conditions, annulation led to β-oxo lactones **5a−c**. Derivative **3a** cyclized with concd. H_2SO_4 to give the known spirocycle **5a**. An extensive screening, however, of cyclization conditions was necessary to identify a modified acid-catalyzed procedure to be suitable for lactones **3b** and **3c**; both β-oxo lactones **5b** and **5c** were accessible by passing anhydrous HCl through a solution of **3b**,**c** and TMSCl in $CHCl_3$. Their 1,3-dicarbonyl constitutions were proved by X-ray crystallographic analysis. The constitution of decomposition products **8** was confirmed unambiguously by comparison with spectra of the regioisomeric alcohols **10** prepared from spirocycles **4b**,**c**.

Experimental Section

General: α-Acetyl lactones **6** were prepared according to a known procedure.[8] Melting points were determined with a Büchi 510 apparatus and are uncorrected. NMR spectra were recorded with Bruker ARX 500 (^{1}H NMR at 500 MHz, ^{13}C NMR at 125 MHz) and ARX 300 (^{1}H NMR at 300 MHz, ^{13}C NMR at 75 MHz) instruments at 23 °C using TMS as an internal standard. Multiplicities in ^{13}C NMR spectra were established by DEPT experiments. Mass spectra were obtained with a Varian MAT 711 instrument. IR spectra were recorded with Bruker IFS 28 and Perkin−Elmer 283 instruments. Column chromatography was accomplished using Merck SiO_2 60 (0.063−0.200 mm) with hexanes (petroleum ether, boiling range 40−60 °C; PE), EtOAc (EA), or *tert*-butyl methyl ether (MTBE) as eluents. All other starting materials were commercially available.

2-Acetyl-2-(3-oxobutyl)-4-butanolide (3a): $FeCl_3\cdot 6H_2O$ (63.0 mg, 0.233 mmol) was added to a solution of **6a** (600 mg, 4.68 mmol) in CH_2Cl_2 (1.0 mL) and then the reaction mixture was stirred at ambient temperature for 0.5 h. After addition of **7** (0.54 mL, 0.46 g, 6.5 mmol), the mixture was stirred overnight, filtered with MTBE through SiO_2 (2 cm), and then, after evaporation of the solvents, the crude product was chromatographed on SiO_2 with MTBE (R_f = 0.27) to give **3a** (330 mg, 1.66 mmol, 36%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.02 (dt, *J* = 13.0, 8.5 Hz, 1 H), 2.13−2.20 (m, 1 H), 2.16 (s, 3 H), 2.27−2.36 (m, 1 H), 2.33 (s, 3 H), 2.40−2.47 (m, 2 H), 2.82 (ddd, *J* = 3.8, 7.2, 11.0 Hz, 1 H), 4.18 (dt, *J* = 7.2, 8.7 Hz, 1 H), 4.33 (dt, *J* = 8.9, 3.8 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 50 MHz): δ = 25.77 (CH_3), 27.50 (CH_2), 29.90 (CH_2), 29.99 (CH_3), 38.42 (CH_2), 60.21 (C), 66.03 (CH_2), 175.33 (C), 202.55 (C), 206.26 (C) ppm. IR (ATR): ṽ = 1761 (vs), 1708 (vs), 1419 (m), 1358 (s), 1218 (m), 1160 (vs), 1077 (m), 1020 (s), 948 (m) cm^{-1}. HRMS (70 eV, CI): calcd. 199.0970 (for $C_{10}H_{15}O_4$), found 199.0973 [MH$^+$]. $C_{10}H_{14}O_4$ (198.22): calcd. C 60.58, H 7.12; found C 60.37, H 7.11.

General Procedure for the Preparation of Compounds 3b,c: *t*BuONa (5 mol %) was added to a solution of lactone **6** (1 equiv.) and methyl vinyl ketone (**7**) (4 equiv.) in CH_2Cl_2 (ca. 1.2 mmol/L) at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was warmed to room temperature and stirred for a further 16 h. All volatile materials were evaporated under high vacuum, and the crude product **3** was purified by chromatography on SiO_2.

2-Acetyl-2-(3-oxobutyl)-5-pentanolide (3b): From **6b** (600 mg, 4.22 mmol) and **7** (1.40 mL, 1.19 g, 16.9 mmol) in CH_2Cl_2 (8.0 mL), reaction with *t*BuONa (20.5 mg, 0.213 mmol), and chromatography with EA/PE (1:1) (R_f = 0.18), **3b** (840 mg, 3.96 mmol, 94%) was obtained as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.63 (ddd, *J* = 6.1, 8.1, 14.0 Hz, 1 H), 1.82−1.97 (m, 2 H), 2.11−2.23 (m, 2 H), 2.14 (s, 3 H), 2.27 (s, 3 H), 2.41 (dt, *J* = 14.0, 6.2 Hz, 1 H), 2.46−2.50 (m, 2 H), 4.23 (ddd, *J* = 4.6, 7.1, 11.7 Hz, 1 H), 4.35 (ddd, *J* = 5.0, 6.8, 11.7 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 50 MHz): δ = 20.53 (CH_2), 26.30 (CH_3), 27.06 (CH_2), 29.29 (CH_2), 29.99 (CH_3), 38.38 (CH_2), 59.58 (C), 69.28 (CH_2), 171.30 (C), 204.23 (C), 207.03 (C) ppm. IR (ATR): ṽ = 1705 (vs), 1356 (s), 1260 (s), 1156 (vs), 1105 (s), 1091 (s), 1069 (m), 952 (m) cm^{-1}. HRMS (70 eV, EI): calcd. 170.0943 (for $C_9H_{14}O_3$), found 170.0939 [M$^+$ − C_2H_2O]. $C_{11}H_{16}O_4$ (212.24): calcd. C 62.25, H 7.60; found C 62.16, H 7.73.

2-Acetyl-2-(3-oxobutyl)-6-hexanolide (3c): From **6c** (1.00 g, 6.40 mmol), **7** (2.50 mL, 2.12 g, 30.3 mmol) in CH_2Cl_2 (5.0 mL), reaction with *t*BuONa (44.0 mg, 0.458 mmol), and chromatography with EA/PE (gradient from 1:2 to 1:1) [R_f (EA/PE, 1:1) = 0.81], **3c** (1.02 g, 4.51 mmol, 70%) was obtained as a colorless oil, that crystallized after some days, m.p. 49−51 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.60−1.68 (m, 1 H), 1.72−1.90 (m, 4 H), 2.08−2.20 (m, 3 H), 2.14 (s, 3 H), 2.24 (s, 3 H), 2.48 (ddd, *J* = 5.4, 9.2, 18.2 Hz, 1 H), 2.60 (ddd, *J* = 5.9, 9.3, 18.3 Hz, 1 H), 3.93−3.98 (m, 1 H), 4.25−4.29 (m, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 24.12 (CH_2), 26.59 (CH_3), 28.21 (CH_2), 30.07 (CH_3), 31.00 (CH_2), 31.41 (CH_2), 38.64 (CH_2), 64.10 (C), 68.41 (CH_2), 173.47 (C), 205.98 (C), 207.51 (C) ppm. IR (film): ṽ = 2936 (vs), 1726 (vs, br.), 1477 (m), 1432 (m), 1358 (vs), 1288 (s), 1206 (vs), 1164 (vs), 1078 (s), 733 (m) cm^{-1}. HRMS (CI): calcd. 227.1283 (for $C_{12}H_{19}O_4$), found 227.1280 [MH$^+$]. $C_{12}H_{18}O_4$ (226.27): calcd. C 63.70, H 8.02; found C 63.46, H 7.95.

3-Methyl-6-(3-hydroxypropyl)cyclohex-2-en-1-one (8b): A solution of **3b** (174 mg, 0.820 mmol) in TFA (1.5 mL) was stirred at 60 °C overnight, and then diluted with CH_2Cl_2 (5.0 mL). After evaporation of all volatile materials under high vacuum, the residue was chromatographed on SiO_2 [gradient from PE/EA (1:1) to EA] [R_f (PE/EA, 1:1) = 0.13] to yield **8b** (64.0 mg, 0.380 mmol, 46%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.44−1.50 (m, 1 H), 1.54−1.69 (m, 2 H), 1.72−1.80 (m, 1 H), 1.82−1.89 (m, 1 H), 1.95 (s, 3 H), 2.09 (dq, *J* = 13.3, 4.9 Hz, 1 H), 2.20−2.26 (m, 1 H), 2.33 (t, br., *J* = 6.0 Hz, 2 H), 2.90 (s, br., OH), 3.62 (t, *J* = 6.4 Hz, 2 H), 5.84 (sext, *J* = 1.2 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 24.02 (CH_3), 25.22 (CH_2), 27.67 (CH_2), 29.87 (CH_2), 30.10 (CH_2), 44.88 (CH), 62.17 (CH_2), 125.96 (CH), 161.95 (C), 202.02 (C) ppm. IR (ATR): ṽ = 3386 (s, br.), 2923 (s), 2863 (s), 1649 (vs), 1432 (s), 1380 (s), 1212 (s), 1056 (vs), 873 (m) cm^{-1}. HRMS (70 eV, EI): calcd. 150.1045 (for $C_{10}H_{14}O$), found 150.1045 [M$^+$ − H_2O].

3-Methyl-6-(4-hydroxybutyl)cyclohex-2-en-1-one (8c): PTSA (2 mg, 0.01 mmol) was added to a solution of **3c** (54 mg, 0.239 mmol) in

CH_2Cl_2 (1.0 mL) at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was warmed to room temperature and stirred for a further 16 h. The solvent was evaporated, and the residue was chromatographed on SiO_2 with EA/PE (2:1). Starting material **3c** was recovered in a first fraction (41.0 mg, 0.181 mmol, 76%, R_f = 0.32), followed in a second fraction by the title compound **8c** (5.0 mg, 0.027 mmol, 11%, R_f = 0.22) as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.37−1.47 (m, 3 H), 1.56−1.62 (m, 3 H), 1.71−1.78 (m, 1 H), 1.81−1.86 (m, 1 H), 1.94 (s, 3 H), 2.08 (ddd, *J* = 4.9, 9.7, 13.3 Hz, 1 H), 2.18−2.23 (m, 1 H), 2.31 (t, br., 2 H), 3.66 (t, *J* = 6.5 Hz, 2 H), 5.84 (sext, *J* = 1.2 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 23.15 (CH_2), 24.19 (CH_3), 27.68 (CH_2), 28.81 (CH_2), 30.26 (CH_2), 32.67 (CH_2), 45.39 (CH), 62.72 (CH_2), 126.33 (CH), 161.47 (C), 201.81 (C) ppm. IR (film): $\tilde{\nu}$ = 3431 (vs, br.), 2934 (vs), 2862 (s), 1712 (s), 1665 (vs), 1434 (s), 1380 (s), 1213 (s), 1058 (s), 1033 (s), 874 (m) cm^{-1}. HRMS (70 eV, EI): calcd. 182.1307 (for $C_{11}H_{18}O_2$), found 182.1307 [M^+].

8-Methyl-2-oxaspiro[4.5]dec-7-ene-1,6-dione (5a): Ice-cold concd. H_2SO_4 (1 mL) was added at 0 °C to **3a** (235 mg, 1.19 mmol), and the reaction mixture was stirred for 1 h at 0 °C and then warmed to room temperature. The reaction mixture was added dropwise to saturated aqueous $NaHCO_3$ (200 mL) and extracted with EA (2 × 50 mL) and PE (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), concentrated, and the residue was chromatographed on SiO_2 with PE/EA (1:2) [R_f (MTBE) = 0.29] to give **5a** (174 mg, 0.966 mmol, 81%) as a colorless solid, m.p. 66 °C. All data are in accordance with those reported in the literature.[14]

General Procedure for the Preparation of 5b,c: TMSCl (2 equiv.) was added to a solution of **3b** or **3c** (1 equiv.) in $CHCl_3$ (7.0 mL; ca. 0.4 mmol/L) in the presence of molecular sieves (4 Å). Hydrogen chloride was then passed through the reaction mixture at 0 °C for 15−20 min. After being warmed to room temperature, the reaction mixture was stirred for a further 16 h, filtered, the solids were washed with CH_2Cl_2, and the combined solutions concentrated. The residue was chromatographed on SiO_2 to yield products **5**.

9-Methyl-2-oxaspiro[5.5]undec-8-ene-1,7-dione (5b): From **3b** (681 mg, 3.21 mmol) and TMSCl (0.86 mL, 740 mg, 6.8 mmol), chromatography with EA/PE (1:1) (R_f = 0.23), and recrystallization from PE/EA, **5b** (76.0 mg, 0.391 mmol, 12%) was obtained as a colorless solid, m.p. 82 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.76−1.88 (m, 2 H), 1.94−1.97 (m, 1 H), 1.99 (s, 3 H), 2.01−2.08 (m, 1 H), 2.30−2.38 (m, 2 H), 2.45 (dt, *J* = 19.0, 5.0 Hz, 1 H), 2.74 (ddd, *J* = 5.6, 9.5, 14.3 Hz, 1 H), 4.32 (ddd, *J* = 4.3, 8.4, 12.5 Hz, 1 H), 4.50 (dddd, *J* = 1.3, 4.8, 5.8, 11.0 Hz, 1 H), 5.86 (sext, *J* = 0.9 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 19.54 (CH_2), 24.02 (CH_3), 27.16 (CH_2), 28.19 (CH_2), 32.18 (CH_2), 52.74 (C), 69.81 (CH_2), 123.84 (CH), 162.26 (C), 170.76 (C), 196.50 (C) ppm. IR (ATR): $\tilde{\nu}$ = 1720 (vs), 1651 (vs), 1627 (m), 1344 (m), 1270 (s), 1258 (s), 1212 (s), 1169 (vs), 1154 (vs), 1115 (s), 1097 (vs), 1065 (s), 974 (s) cm^{-1}. MS (70 eV, EI): *m/z* (%) = 194 (11) [M^+], 176 (28), 166 (5), 150 (5), 134 (12), 121 (10), 82 (100), 54 (8). $C_{11}H_{14}O_3$ (194.23): calcd. C 68.02, H 7.26; found C 67.77, H 7.24.

3-Methyl-8-oxaspiro[5.6]dodec-2-ene-1,7-dione (5c): From **3c** (684 mg, 3.02 mmol) and TMSCl (0.860 mL, 740 mg, 6.81 mmol), and chromatography with EA/PE (1:1) (R_f = 0.19), **5c** (75.0 mg, 0.360 mmol, 12%) was obtained as a colorless solid, m.p. 79−80 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.56−2.02 (m, 6 H), 1.96 (s, 3 H), 2.18−2.27 (m, 1 H), 2.33−2.50 (m, 2 H), 2.70 (ddd, *J* = 5.7, 7.6, 13.9 Hz, 1 H), 4.24−4.31 (m, 1 H), 4.63−4.71 (m, 1 H), 5.86−5.87 (m, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 23.59 (CH_2), 23.71 (CH_3), 28.52 (CH_2), 28.72 (CH_2), 30.04 (CH_2), 31.57 (CH_2), 57.99 (C), 68.70 (CH_2), 124.98 (CH), 160.96 (C), 174.16 (C), 197.15 (C) ppm. IR (ATR): $\tilde{\nu}$ = 1697 (vs), 1648 (vs), 1626 (s), 1434 (m), 1400 (m), 1357 (m), 1218 (vs), 1172 (vs), 1054 (s), 1026 (s), 978 (s), 890 (s) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 208 (24) [M^+], 190 (16), 180 (8), 136 (7), 121 (10), 82 (100), 54 (7). $C_{12}H_{16}O_3$ (208.26): calcd. C 69.21, H 7.74; found C 69.02, H 7.72.

General Procedure for the Cyclization with Pyrrolidine/AcOH: Pyrrolidine (1 equiv.) and then glacial AcOH (1 equiv.) were added to a solution of **3** (1 equiv.) in MTBE (ca. 0.12 mmol/L) at ambient temperature (**3a**) or at 0 °C (**3b**,**c**). After stirring at ambient temperature for 16 h, all volatile materials were evaporated under high vacuum, and the residue was chromatographed on SiO_2 to give products **4**.

6-Methyl-2-oxaspiro[4.5]dec-6-ene-1,8-dione (4a): From **3a** (103 mg, 0.520 mmol) in MTBE (4.0 mL), pyrrolidine (0.04 mL, 0.034 g, 0.5 mmol) and AcOH (0.03 mL, 0.031 g, 0.5 mmol), and chromatography with MTBE (R_f = 0.12), **4a** (52.0 mg, 0.289 mmol, 56%) was obtained as a colorless solid, m.p. 88 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.98 (d, *J* = 0.9 Hz, 3 H), 2.10−2.17 (m, 1 H), 2.33−2.53 (m, 4 H), 2.57−2.65 (m, 1 H), 4.38 (ddd, *J* = 7.9, 9.2, 16.5 Hz, 1 H), 4.48 (ddd, *J* = 3.6, 8.9, 12.5 Hz, 1 H), 6.01 (q, *J* = 1.0 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 50 MHz): δ = 20.23 (CH_3), 30.37 (CH_2), 31.47 (CH_2), 33.08 (CH_2), 48.15 (C), 65.64 (CH_2), 129.77 (CH), 157.67 (C), 177.52 (C), 196.73 (C) ppm. IR (ATR): $\tilde{\nu}$ = 1757 (vs), 1669 (vs), 1626 (s), 1374 (s), 1202 (s), 1161 (vs), 1017 (vs), 975 (s), 863 (s) cm^{-1}. HRMS (70 eV, EI): calcd. 180.0786 (for $C_{10}H_{12}O_3$), found 180.0785 [M^+]. $C_{10}H_{12}O_3$ (180.20): calcd. C 66.65, H 6.71; found C 66.50, H 6.46.

7-Methyl-2-oxaspiro[5.5]undec-7-ene-1,9-dione (4b): From **3b** (184 mg, 0.867 mmol) in CH_2Cl_2 (4.0 mL), pyrrolidine (0.08 mL, 70 mg, 1 mmol) and AcOH (0.04 mL, 42 mg, 0.7 mmol), filtration through SiO_2 with EA (200 mL), concentration, and chromatography with EA (R_f = 0.30), **4b** (117 mg, 0.602 mmol, 69%) was obtained as a colorless solid, m.p. 96 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.91−1.97 (m, 1 H), 1.99 (d, *J* = 1.0 Hz, 3 H), 2.06−2.14 (m, 2 H), 2.24 (dt, *J* = 4.1, 12.7 Hz, 1 H), 2.39−2.54 (m, 4 H), 4.37−4.43 (m, 1 H), 4.50−4.54 (m, 1 H), 5.95 (s, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 20.47 (CH_2), 20.90 (CH_3), 28.42 (CH_2), 31.98 (CH_2), 32.20 (CH_2), 48.42 (C), 70.48 (CH_2), 128.79 (CH), 160.61 (C), 172.61 (C), 196.83 (C) ppm. IR (ATR): $\tilde{\nu}$ = 1711 (vs), 1663 (vs), 1462 (m), 1380 (m), 1343 (m), 1256 (vs), 1193 (m), 1157 (vs), 1107 (s), 1082 (vs), 1055 (m), 991 (m), 959 (s), 944 (vs) cm^{-1}. HRMS (70 eV, EI): calcd. 194.0943 (for $C_{11}H_{14}O_3$), found 194.0946 [M^+]. $C_{11}H_{14}O_3$ (194.23): calcd. C 68.02, H 7.26; found C 68.01, H 7.27.

1-Methyl-8-oxaspiro[5.6]dodec-1-ene-3,7-dione (4c): From **3c** (362 mg, 1.60 mmol) in CH_2Cl_2 (7.0 mL), pyrrolidine (0.13 mL, 112 mg, 1.57 mmol) and AcOH (0.07 mL, 73.5 mg, 1.23 mmol). After chromatography with EA/PE (gradient from 1:1 to 2:1), starting material **3c** (160 mg, 0.707 mmol, 44%) [R_f (EE/PE, 1:1) = 0.81] was recovered in a first fraction. In a second fraction, a mixture of **8c** and **4c** (95 mg) [R_f (EA/PE, 2:1) = 0.23] was obtained. To isolate pure **4c**, a second chromatography with EA/PE (2:1) and subsequent recrystallization from PE/toluene (1:5) were necessary to give **4c** (38.0 mg, 0.182 mmol, 11%) as a colorless solid, m.p. 96 °C. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.67−1.74 (m, 1 H), 1.86−1.99 (m, 4 H), 2.02 (d, *J* = 1.5 Hz, 3 H), 2.04−2.23 (m, 2 H), 2.40−2.45 (m, 2 H), 2.64 (dt, *J* = 13.9, 5.1 Hz, 1 H), 4.37−4.42 (m, 2 H), 5.91 (q, *J* = 1.1 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ =

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21.17 (CH_3), 22.82 (CH_2), 28.98 (CH_2), 29.74 (CH_2), 32.66 (CH_2), 33.51 (CH_2), 52.60 (C), 69.59 (CH_2), 127.78 (CH), 162.19 (C), 173.88 (C), 197.28 (C) ppm. IR (KBr): $\tilde{\nu}$ = 2940 (s), 2920 (vs), 1726 (vs, br.), 1690 (vs), 1680 (vs), 1652 (vs), 1461 (s), 1281 (s), 1201 (vs), 1159 (vs), 1129 (vs), 875 (s) cm^{-1}. HRMS (70 eV, EI): calcd. 208.1099 (for $C_{12}H_{16}O_3$), found 208.1099 [M^+]. $C_{12}H_{16}O_3$ (208.26): calcd. C 69.21, H 7.74; found C 69.23, H 7.77.

Methyl 1-(4-Hydroxybutyl)-2-methyl-4-oxocyclohex-2-ene-1-carboxylate (9): A solution of **4c** (100 mg, 0.480 mmol) in MeOH (3.0 mL) was added to a solution of K_2CO_3 (171 mg, 1.24 mmol) in H_2O (3.0 mL) at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was warmed to room temperature, stirred for a further 16 h, and then added dropwise to aqueous citric acid (20%, 30 mL) and extracted with EA (3 × 15 mL). The combined organic layers were washed with H_2O (30 mL), dried ($MgSO_4$), and concentrated. The residue was chromatographed on SiO_2 with EA/PE (2:1) (R_f = 0.31) to yield **9** (54.0 mg, 0.224 mmol, 47%) as a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.31−1.50 (m, 2 H), 1.56−1.65 (m, 2 H), 1.72 (ddd, J = 5.0, 11.7, 13.7 Hz, 1 H), 1.97−2.09 (m, 2 H), 2.00 (d, J = 0.9 Hz, 3 H), 2.13 (s, 1 H), 2.34−2.44 (m, 2 H), 2.48−2.61 (m, 1 H), 3.66 (t, J = 6.3 Hz, 2 H), 3.74 (s, 3 H), 5.93 (q, J = 0.7 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 20.99 (CH_2), 21.35 (CH_3), 29.93 (CH_2), 32.82 (CH_2), 34.36 (CH_2), 35.23 (CH_2), 50.80 (C), 52.48 (CH_3), 62.15 (CH_2), 129.19 (CH), 161.03 (C), 173.85 (C), 198.59 (C) ppm. IR (film): $\tilde{\nu}$ = 3437 (s, br.), 2952 (vs), 2871 (s), 1728 (vs), 1669 (vs), 1435 (s), 1379 (s), 1339 (s), 1251 (vs), 1195 (s), 1169 (vs), 1069 (s), 982 (m), 915 (s), 734 (vs) cm^{-1}. HRMS (70 eV, EI): calcd. 240.1362 (for $C_{13}H_{20}O_4$), found 240.1363 [M^+].

General Procedure for the Preparation of Alcohols 10: KOH (4 equiv.) and H_2O were added to a solution of **4** (1 equiv.) in THF [THF/H_2O (1:1 or 5:2)]. After stirring at 80 °C for 16 h, the reaction mixture was diluted with H_2O (2.0 mL) and extracted with MTBE (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), concentrated, and the residue was chromatographed on SiO_2 to yield the alcohol **10**.

3-Methyl-4-(3-hydroxypropyl)cyclohex-2-en-1-one (10b): From **4b** (35 mg, 0.18 mmol) in THF (1.0 mL), KOH (50 mg, 0.89 mmol) and H_2O (1.0 mL), and chromatography with EA (R_f = 0.24), **10b** (6.00 mg, 0.036 mmol, 20%) was obtained as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.48−1.55 (m, 2 H), 1.56−1.63 (m, 1 H), 1.71−1.78 (m, 2 H), 1.87−1.93 (m, 1 H), 1.98 (s, 3 H), 2.05−2.11 (m, 1 H), 2.25−2.33 (m, 2 H), 2.44 (ddd, J = 4.8, 10.8, 17.1 Hz, 1 H), 3.71 (t, J = 6.1 Hz, 2 H), 5.84 (s, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75 MHz): δ = 22.97 (CH_3), 26.17 (CH_2), 27.07 (CH_2), 30.72 (CH_2), 33.79 (CH_2), 39.23 (CH), 62.61 (CH_2), 126.76 (CH), 165.88 (C), 199.46 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3403 (s, br.), 2924 (s), 2866 (s), 1654 (vs), 1437 (m), 1380 (s), 1256 (s), 1201 (m), 1055 (vs), 1023 (m) cm^{-1}. HRMS (70 eV, EI): calcd. 168.1150 (for $C_{10}H_{16}O_2$), found 168.1149 [M^+].

3-Methyl-4-(4-hydroxybutyl)cyclohex-2-en-1-one (10c): From **4c** (136 mg, 0.653 mmol) in THF (5.0 mL), KOH (100 mg, 1.78 mmol) and H_2O (2.0 mL), and chromatography with EA (R_f = 0.29), **10c** (57.0 mg, 0.313 mmol, 48%) was obtained as a colorless oil. ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.34−1.51 (m, 3 H), 1.52−1.67 (m, 3 H), 1.88−1.94 (m, 1 H), 1.97 (s, 3 H), 2.03−2.10 (m, 1 H), 2.24−2.32 (m, 3 H), 2.43 (ddd, J = 4.9, 11.1, 16.9 Hz, 1 H), 3.69 (t, J = 6.2 Hz, 2 H), 5.83 (s, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 23.03 (CH_3), 24.09 (CH_2), 26.08 (CH_2), 30.63 (CH_2), 32.71 (CH_2), 33.76 (CH_2), 39.45 (CH), 62.67 (CH_2), 126.68 (CH), 166.05 (C), 199.51 (C) ppm. IR (film): $\tilde{\nu}$ = 3394 (s, br.), 2930 (vs), 2861 (s), 1655 (vs), 1437 (s), 1379 (s), 1253 (s), 1058 (s), 863 (m) cm^{-1}. HRMS (70 eV, EI): calcd. 182.1307 (for $C_{11}H_{18}O_2$), found 182.1307 [M^+].

X-ray Single-Crystal Analysis: Single-crystal X-ray diffraction data were collected for lactones **3c**, **4a−c**, **5a** and **5c**. For each structure, the data were collected either with a Nicolet P3 diffractometer by using a graphite monochromator with Mo-K_α radiation (λ = 0.71073 Å) (**4a**, **5a**) or with a Siemens P4 diffractometer by using Cu-K_α radiation (λ = 1.54178 Å). The structures were solved by direct methods and refined[16] against F^2.

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Table 1. X-ray single-crystal analysis data for compounds **3c**, **4a−c**, **5a**,**c**

	3c	**4a**	**4b**	**4c**	**5a**	**5c**
Empirical formula	$C_{12}H_{18}O_4$	$C_{10}H_{12}O_3$	$C_{11}H_{14}O_3$	$C_{12}H_{16}O_3$	$C_{10}H_{12}O_3$	$C_{12}H_{16}O_3$
Formula mass [g mol^{-1}]	226.27	180.20	194.22	208.25	180.20	208.25
Crystal system	monoclinic	orthorhombic	orthorhombic	triclinic	triclinic	monoclinic
Space group	$P2_1/n$	$Pbca$	$Pbca$	$P\bar{1}$	$P\bar{1}$	$P2_1/n$
a [Å]	7.7253(3)	7.8917(16)	12.3415(6)	6.9016(3)	5.7249(4)	6.1347(5)
b [Å]	8.4409(4)	11.686(3)	6.7521(4)	10.2784(5)	7.3419(5)	15.6825(10)
c [Å]	18.4399(9)	19.671(4)	23.9264(14)	15.6342(9)	11.1880(8)	11.7704(6)
α [°]	90	90	90	84.837(5)	97.168(6)	90
β [°]	92.153(5)	90	90	83.213(5)	97.513(6)	104.199(4)
γ [°]	90	90	90	86.713(6)	100.346(6)	90
Z	4	8	8	4	2	4
V [$Å^3$]	1201.59(9)	1814.0(7)	1993.81(19)	1095.59(10)	453.30(5)	1097.80(13)
$\delta_{calcd.}$ [g cm^{-3}]	1.251	1.320	1.294	1.263	1.320	1.260
T [K]	293	293	293	293	293	293
λ [Å]	1.54178	0.71073	1.54178	1.54178	0.71073	1.54178
μ [mm^{-1}]	0.768	0.097	0.766	0.731	0.097	0.729
R_w (F^2)	0.1606	0.1628	0.2270	0.2135	0.1414	0.1692
$R(F)$ [$I > 2\sigma(I)$]	0.0549	0.0867	0.0653	0.0617	0.0565	0.0561
Goodness-of-fit on F^2	1.083	1.066	1.062	1.103	1.083	1.075

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[11] CCDC-200949 (**4c**), -200950 (**3c**), -200951 (**4b**), -200952 (**5a**), -200953 (**4a**), and -200954 (**5c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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