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Construction of medium-ring oxacycloalkenones. Extension towards benzo-fused cyclic ethers

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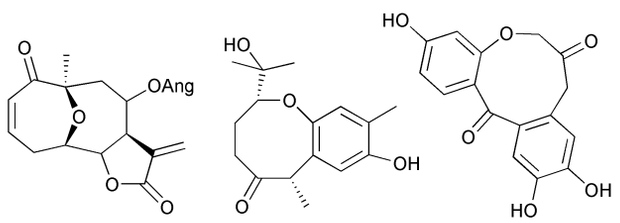
Application of the intramolecular Kulinkovich cyclopropanation of oxa-ω-alkenoic esters followed by Saegusa oxidation and dehydrohalogenation led to simple or benzo-fused oxacycloalkenones, basic structural elements in a wide range of naturally occurring compounds.

Introduction

The discovery of a large number of biologically active natural products containing medium-sized oxacycloalkenones in their structure has spurred efforts to enhance this challenge. Such skeletons are encountered, for example, in helivypolide B[1] **1** or (+)-heliannuol F[2] **2**, active allelopathic agents isolated from sunflower leaves. Another example is brazilone **3**, an anti-coagulant isolated from the leguminous plant *Caesalpinia sappan*[3] (Scheme 1).



1 **2** **3**

Scheme 1

Results and discussion

We report here a general method that provides easy access to oxacycloalkenones of different sizes, as an extension of methodology previously developed by Cha[4] in the synthesis of seven- and eight-membered carbocycles. The synthetic protocol consists of the intramolecular Kulinkovich cyclopropanation[5] on oxa-esters bearing a terminal double bond, followed by oxidative cleavage of the cyclopropanol moiety[6] and base-induced dehydrochlorination. We have applied this strategy to the synthesis of different medium-sized oxacycloalkenones such as oxepinone, tetrahydrooxocinone and oxoninone. Moreover, benzo-fused 7-, 8- and 9-membered cyclic ethers, challenging synthetic targets in the unusual structure of some bioactive natural products, have been achieved by our approach.

All starting esters were prepared using reported literature or adapted procedures. Thus, buten-3-ol was used as precursor for the synthesis of esters **4a**[7] and **4b**,[8] pent-4-enol for **4c**[8] while ether **4d** was obtained by basic condensation of ethyl bromoacetate on 2-vinylphenol acetate;[9] likewise, the esters **4e**,[10] **4f**[11] and **4g**[11] were prepared from the corresponding phenolic derivatives. It must be underlined that the allylic ethers were found unsuitable for such reactions.[12]

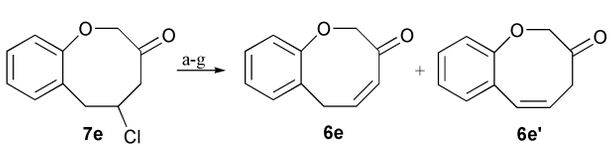
The cyclopropanations were performed using one or two equivalents of titanium tetraisopropoxide (in some cases, a significant improvement was observed using chlorotitanium triisopropoxide) and four equivalents of Grignard reagent.[13] Cyclohexylmagnesium chloride, normally a poor nucleophile towards esters,[14] appeared a very efficient reagent in such an intramolecular Kulinkovich reaction.[15]

The resulting *cis*-fused cyclopropanols **5a**–**g**, isolated with acceptable yields (see Table 1), were firstly treated with ferric(III) chloride, then underwent subsequent dehydrochlorination (sodium acetate, MeOH) to lead to the expected cycloalkenones **6a**–**g** of (*Z*) configuration. Formation of fused cyclopropanols **5a**–**g** and cycloalkenones **6a**–**g** is summarized in Table 1.

Excepting oxacycloalkenones **6a**[16] (recently obtained by ring closing metathesis) and **6d**[17] (prepared by oxidation of the corresponding oxacycloalkanone) for which, however, no spectral data were reported, the new cyclopropanols **5a**–**g** and enones **6b**, **c**, **e**, **e′**, **f and g** were characterized by their spectral data and their purities were checked by gas chromatography; starting compounds **4b**, **4c** and **4d** were also original.

The moderate yield observed in the formation of **5a** could be explained by the more strained structure of this compound. It must be underlined that in spite of efforts to improve the yields of cyclopropanol **5f**, only small amounts were obtained in order to perform the preparation of cycloalkenone **6f**; such difficulties with conjugated esters in the Kulinkovich cyclopropanation have been previously related in the literature.[18]

From the cyclopropanol **5e**, two products of dehydrochlorination were obtained. The isolation of the intermediate chloride showed the presence of only one regioisomer **7e** which led to the two benzo-fused oxacycloalkenones: the kinetic product **6e** and the thermodynamic product **6e′** (see evolution in entries b and c in Scheme 2). In fact, the selective formation of the products was highly dependent on the experimental procedure.



7e **6e** **6e'**

Conditions	Time	y%		Ratio
a: NaOAc, MeOH, reflux	3h	72	0	100
b: NaOAc, MeOH, rt	24h	70	0	100
c: NaOAc, MeOH, -5°C	4d	65	64	36
d: NaOAc, MeOH, -25°C	24h	0		
e: NEt_3, Et_2O, rt	3d	70	0	100
f: DBU, Et_2O, -10°C	6h	85	0	100
g: H_2SO_4, THF, H_2O	24h	0		

Scheme 2

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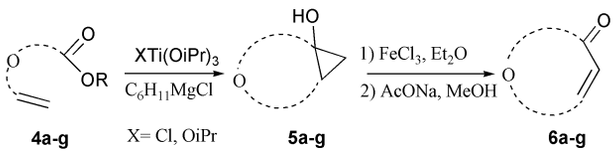
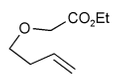
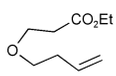
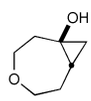
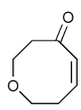
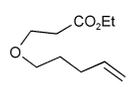
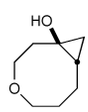
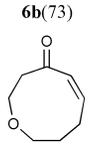
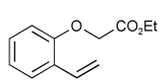
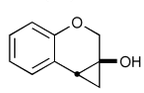
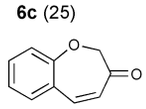
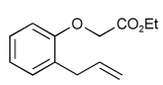
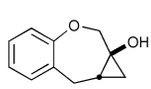
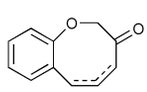
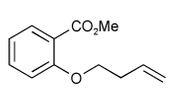
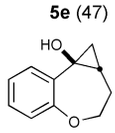
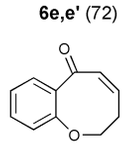
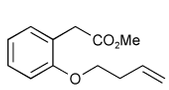
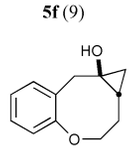
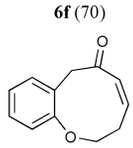
Table 1 Cyclopropanation and oxidation–dehydrochlorination of oxa-ω-alkenoic esters **4a**–**g**



4a-g **5a-g** **6a-g**

Entry	Oxa-esters	Cyclopropanols (%)	Oxacycloalkenones (%)
1	 **4a**	 **5a** (35)	 **6a** (70)
2	 **4b**	 **5b** (62)	 **6b**(73)
3	 **4c**	 **5c** (49)	 **6c** (25)
4	 **4d**	 **5d** (46)	 **6d** (76)
5	 **4e**	 **5e** (47)	 **6e,e'** (72)
6	 **4f**	 **5f** (9)	 **6f** (70)
7	 **4g**	 **5g** (52)	 **6g** (55)

Thus, dehydrochlorination effected in standard conditions (sodium acetate in methanol or treatment with triethylamine or DBU in ether) yielded only alkenone **6e′** while the reaction promoted with sodium acetate in methanol at low temperature, furnished a mixture of the alkenones **6e** and **6e′**. Aqueous sulfuric acid in THF [19] gave no reaction (Scheme 2).

This result was in agreement with calculated energies of respectively −2547.38 and −2545.90 kcal mol^{-1} [20] for products **6e** and **6e′**; the difference of 1.48 kcal mol^{-1} appears to be sufficiently important to explain the favoured formation of the benzo-conjugated product **6e′**.

Conclusion

We have developed an interesting pathway to the synthesis of varying medium-sized cyclic ethers. This synthetic study should allow the synthesis of bioactive benzo-fused cyclic ethers, while further applications of this methodology are under current investigation.

Experimental

General

Preparative column chromatography was performed on SDS normal silica gel (70–230 mesh), on SDS flash silica gel (35–70 mesh) or on Fluka neutral alumina 507c (100–200 mesh). Melting points (uncorrected) were determined with a Mettler FP51 apparatus. ^{1}H (200, 250 and 360 MHz) and ^{13}C (50 and 63 MHz) NMR spectra were recorded in $CDCl_3$ or C_6D_6 on Bruker AM360, AM250, AC250 and AM200 spectrometers and the data are reported in δ (ppm) from $CDCl_3$ (^{1}H = 7.27 and ^{13}C = 77) and C_6D_6 (^{1}H = 7.17). Coupling constant (J) values are given in Hz. Infrared (IR) spectra were recorded as thin films on an FT-IR Perkin Elmer Spectrum One spectrometer. Electron impact (EI) mass spectra were obtained using a Nermag R-10 apparatus coupled with an OKI DP 125 gas chromatograph. Relative percentages are shown in brackets; high-resolution mass spectra were recorded with a Finnigan MAT 95S.

4b: Ethyl 3-(3-buten-1-yloxy)propanoate. To a solution of 3-(3-buten-1-yloxy)propanoic acid (5.855 g, 40.6 mmol) in 30 ml of absolute ethanol was added thionyl chloride (5 ml, 0.068 mmol). After stirring and refluxing for 60 h, the solution was evaporated and diluted with 150 ml of pentane. The organic phase was washed with water (3 × 40 ml), dried over magnesium sulfate and concentrated to give the pure ester **4b** (5.3 g, 30.4 mmol).

Colourless liquid; yield 75%; HRMS calcd. for $C_9H_{16}O_3$: 172.1099. Found: 172.1102; ν_{max}/cm^{-1} (neat) 2981, 1738, 1642; δ_H (250 MHz, $CDCl_3$) 5.91–5.71 (1 H, m), 5.08 (1 H, d, J 17.1),

5.03 (1 H, d, *J* 10.5), 4.16 (2 H, q, *J* 7.1), 3.72 (2 H, t, *J* 6.6), 3.51 (2 H, t, *J* 6.8), 2.57 (2 H, t, *J* 6.6), 2.33 (2 H, qt, *J* 6.8, 1.5), 1.26 (3 H, t, *J* 7.1); δ_C (63 MHz, $CDCl_3$) 171.4, 134.9, 116.1, 70.1, 65.9, 60.2, 34.9, 33.8, 14.0; *m*/*z* (EI) 172 (0.1, M^+), 131 (100), 101 (37), 73 (65), 59 (92), 55 (41).

4c: Ethyl 3-(4-penten-1-yloxy)propanoate. To a solution of 3-(4-penten-1-yloxy)propanoic acid[8] (6.5 g, 41.1 mmol) in 75 ml of ethanol was added thionyl chloride (3 ml, 0.041 mmol). After refluxing and stirring for 60 h, the solution was evaporated and purified by column chromatography to furnish the expected ester **4c** (4.59 g, 24.7 mmol).

Eluent for column chromatography: pentane–Et_2O 9 : 1; colourless liquid; yield 60%; HRMS calcd. for $C_{10}H_{18}O_3$: 186.1255. Found: 186.1245; ν_{max}/cm^{-1} (neat) 2938, 1739, 1641; δ_H (250 MHz, $CDCl_3$) 5.92–5.71 (1 H, m), 5.01 (1 H, d, *J* 17.1), 4.96 (1 H, d, *J* 11.5), 4.16 (2H, q, *J* 7.2), 3.69 (2H, t, *J* 6.3), 3.45 (2H, t, *J* 7.1), 2.57 (2H, t, *J* 6.3), 2.10 (2H, q, *J* 7.1), 1.66 (2H, q, *J* 7.1), 1.27 (3H, t, *J* 7.2); δ_C (63 MHz, $CDCl_3$) 171.4, 137.9, 114.5, 70.1, 65.9, 60.2, 35.0, 30.0, 28.5, 14.0; *m*/*z* (EI) 186 (0.6, M^+), 131 (93), 119 (30), 101 (40), 73 (65), 69 (62), 68 (40), 59 (100).

4d: Ethyl (2-vinylphenoxy)acetate. To a solution of 2-vinylphenol acetate[9] (6 g, 37 mmol) and ethyl bromoacetate (6.15 ml, 55.5 mmol) in 120 ml of ethanol was added under argon at room temperature a solution of freshly prepared sodium ethylate (5.1 g, 74 mmol) in 115 ml of ethanol. After refluxing for 2 h, the mixture was concentrated under reduced pressure and to the residue, ether (200 ml) and water (50 ml) were added. The aqueous phase was extracted with ether (50 ml) and the combined organic layers were dried on magnesium sulfate, evaporated and chromatographed on silica gel to obtain the ester **4d** (6.33 g, 30 mmol).

Eluent for flash chromatography: pentane–CH_2Cl_2 6 : 4 then 3 : 7; yellow oil; yield 83%; HRMS calcd. for $C_{12}H_{14}O_3$: 206.0942. Found: 206.0943; ν_{max}/cm^{-1} (neat) 1759, 1733, 1599; δ_H (250 MHz, $CDCl_3$) 7.50 (1 H, d, *J* 7.7), 7.21 (1 H, dd, *J* 7.7, 7.6), 7.13 (1 H, dd, *J* 17.4, 10.9), 6.99 (1 H, dd, *J* 7.7, 7.6), 6.77 (1 H, d, *J* 7.7), 5.81 (1 H, d, *J* 17.4), 5.31 (1 H, d, *J* 10.9), 4.66 (2 H, s), 4.28 (2 H, q, *J* 7.2), 1.31 (3 H, t, *J* 7.2); δ_C (63 MHz, $CDCl_3$) 168.7, 155.0, 135.5, 131.3, 127.3, 126.7, 121.7, 114.9, 112.2, 65.9, 61.2, 14.0; *m*/*z* (EI) 206 (100, M^+), 133 (89), 119 (31), 105 (92), 91 (40), 77 (32).

4e: Ethyl (2-allylphenoxy)acetate. To a solution of 2-allylphenol (9.14 g, 68 mmol), anhydrous potassium carbonate (20 g, 145 mmol), and ethyl bromoacetate (12.1 g, 72.5 mmol) in 130 ml of acetone was added potassium iodide (140 mg, 0.86 mmol). The mixture was refluxed for 16 h, then cooled to room temperature, filtered off and the resulting cake was washed with acetone. The filtrate was evaporated and isolated by column chromatography to give the expected product **4e** (14.8 g, 67.5 mmol).

Eluent for column chromatography: pentane–Et_2O 9 : 1; colourless oil; yield 99%; HRMS calcd. for $[C_{13}H_{16}O_3 + Na]^+$: 243.09971. Found: 243.09959; ν_{max}/cm^{-1} (neat) 1736, 1760, 1638; δ_H (250 MHz, $CDCl_3$) 7.17 (2 H, dd, *J* 7.0, 6.9), 6.95 (1 H, dd, *J* 7, 6.9), 6.74 (1 H, d, *J* 6.9), 6.14–5.92 (1 H, m), 5.16–4.95 (2 H, m), 4.64 (2 H, s), 4.27 (2 H, q, *J* 7.1), 3.48 (2 H, d, *J* 6.8), 1.30 (3 H, t, *J* 7.1); δ_C (63 MHz, $CDCl_3$) 168.7, 155.3, 136.6, 129.9, 129.0, 127.0, 121.3, 111.1, 115.2, 65.3, 60.9, 34.1, 13.9; *m*/*z* (EI) 220 (100, M^+), 133 (89), 131 (52), 115 (50), 105 (42), 91 (66), 77 (25).

General procedure for the synthesis of the cyclopropanols 5a–g

To a solution of oxa-ω-alkenoic esters **4a**–**g** (1.6 mmol) and titanium tetraisopropoxide (0.48 ml, 1.6 mmol for **4a**, **4b**, **4d** and 0.96 ml, 3.2 mmol for **4c**) or chlorotitanium triisopropoxide (0.42 g, 1.6 mmol for **4e**, **4f and 4g**) in anhydrous THF (40 ml) was added over four hours at room temperature under argon 4 ml (6.4 mmol) of a solution of cyclohexylmagnesium chloride (1.6 M in diethyl ether). After stirring one additional hour at room temperature, the black solution was cooled at 0 °C and 40 ml of diethyl ether was added. The mixture was quenched by addition of 10 ml of a saturated ammonium chloride solution and the white precipitate was filtered off through a plug of Celite, washed with 50 ml of ether and the filtrate was dried over magnesium sulfate. After evaporation, the pure products were isolated by column chromatography.

5a: 3-Oxabicyclo[4.1.0]heptan-1-ol. Eluent for flash chromatography: pentane–EtOAc 2.5 : 7.5; colourless oil; yield 35%; HRMS calcd. for $C_6H_{10}O_2$: 114.0680. Found: 114.0676; ν_{max}/cm^{-1} (neat) 3385, 2931, 1450; δ_H (360 MHz, $CDCl_3$) 4.05 (1 H, d, *J* 10.7), 3.73 (1 H, d, *J* 10.7), 3.61 (1 H, ddd, *J* 11.3, 6.5, 2.6), 3.33 (1 H, ddd, *J* 11.3, 11.2, 4.9), 2.30 (1 H, s), 2.00–1.91 (1 H, m), 1.69–1.60 (1 H, m), 1.33–1.26 (1 H, m), 0.99 (1 H, dd, *J* 10.4, 5.2), 0.63 (1H, dd, *J* 5.8, 5.7; δ_C (63 MHz, $CDCl_3$) 69.7, 64.8, 51.4, 24.3, 18.4, 16.4; *m*/*z* (EI) 114 (25, M^+), 95 (20), 84 (69), 83 (100), 71 (26), 70 (28), 69 (43), 60 (17), 58 (57), 57 (23), 55 (86), 43 (40), 41 (52).

5b: 4-Oxabicyclo[5.1.0]octan-1-ol. Eluent for flash chromatography: pentane–EtOAc 2.5 : 7.5; colourless oil; yield 62%; HRMS calcd. for $C_7H_{12}O_2$: 128.0837. Found: 128.0834; ν_{max}/cm^{-1} (neat) 3391, 2943, 1465; δ_H (360 MHz, $CDCl_3$) 3.85 (1 H, ddd, *J* 12.5, 8.5, 1.5), 3.73–3.60 (3 H, m), 2.39 (1 H, dd, *J* 15.4, 6.6), 2.28–2.21 (1 H, m), 2.00 (1 H, s), 1.86 (1 H, dd, *J* 15.4, 8.5), 1.37–1.20 (2 H, m), 0.99 (1 H, dd, *J* 9.8, 5.5), 0.66 (1 H, dd, *J* 5.8, 5.5); δ_C (63 MHz, $CDCl_3$) 71.0, 68.7, 58.0, 40.4, 32.8, 23.6, 20.5; *m*/*z* (EI) 128 (17, M^+), 100 (53), 83 (77), 70 (89), 56 (47), 55 (100), 43 (90), 41 (99).

5c: 4-Oxabicyclo[6.1.0]nonan-1-ol. Eluent for flash chromatography: pentane–EtOAc 2.5 : 7.5; colourless oil; yield 49%; HRMS calcd. for $C_8H_{14}O_2$: 142.0993. Found: 142.0990; ν_{max}/cm^{-1} (neat) 3390, 2924, 1472; δ_H (250 MHz, $CDCl_3$) 3.92–3.61 (4 H, m), 2.18–1.94 (2 H, m), 1.80–1.45 (4 H, m), 1.02–0.80 (3 H, m), 0.23–0.12 (1 H, m); δ_C (63 MHz, $CDCl_3$) 70.5, 66.9, 55.1, 35.9, 29.1, 27.4, 24.0, 19.0; *m*/*z* (EI) 142 (6, M^+), 114 (13), 84 (13), 83 (25), 71 (100), 70 (33), 69 (13), 55 (32), 43 (27), 41 (40).

5d: 1,7b-Dihydrocyclopropa[*c*]chromen-1a(2*H*)-ol. Eluent for flash chromatography: CH_2Cl_2–Et_2O 9 : 1; colourless oil; yield 46%; HRMS calcd. for $C_{10}H_{10}O_2$: 162.0680. Found: 162.0673; ν_{max}/cm^{-1} (neat) 3550, 3029, 1491; δ_H (360 MHz, $CDCl_3$) 7.20 (1 H, d, *J* 7.7), 7.07 (1 H, ddd, *J* 7.7, 7.6, 1.5), 6.91 (1 H, ddd, *J* 7.7, 7.6, 1.5), 6.83 (1 H, d, *J* 7.7), 4.40 (1 H, d, *J* 10.1), 3.89 (1 H, d, *J* 10.1), 2.39 (1 H, br s), 2.18 (1 H, dd, *J* 9.8, 5.3), 1.41 (1 H, dd, *J* 9.8, 5.5), 1.34 (1H, dd, *J* 5.5, 5.3); δ_C (63 MHz, $CDCl_3$) 151.7, 128.0, 126.4, 121.9, 117.0, 121.3, 64.6, 59.4, 21.6, 18.8; *m*/*z* (EI) 162 (33, M^+), 147 (29), 131 (23), 120 (100), 103 (20), 91 (31), 77 (15).

5e: 8,8a-Dihydro-1*H*-benzo[*b*]cyclopropa[*c*]oxepin-1a(2*H*)-ol. Eluent for flash chromatography: pentane–EtOAc 7.5 : 2.5; white solid; yield 47%; mp 55–57 °C; HRMS calcd. for $C_{11}H_{12}O_2$: 176.0837. Found: 176.0829; ν_{max}/cm^{-1} (neat) 3368, 3017, 1487; δ_H (360 MHz, $CDCl_3$) 7.12 (1 H, dd, *J* 7.7, 7.6), 6.97 (1 H, d, *J* 7.6), 6.87 (1 H, d, *J* 7.6), 6.83 (1 H, dd, *J* 7.7, 7.6), 4.57 (1 H, d, *J* 13.4), 4.46 (1 H, d, *J* 13.4), 3.00 (1 H, dd, *J* 16.2, 8.6), 2.83 (1 H, dd, *J* 16.2, 8.6), 2.74 (1 H, s), 1.75–1.66 (1H, m), 1.16 (1 H, dd, *J* 9.0, 5.8), 0.73 (1H, dd, *J* 5.8, 5.6); δ_C (63 MHz, $CDCl_3$) 157.0, 131.3, 127.8, 126.2, 120.9, 119.6, 74.5, 57.1, 36.5, 24.4, 20.8; *m*/*z* (EI) 176 (25, M^+), 134 (25), 133 (22), 119 (51), 118 (100), 115 (21), 107 (72), 91 (69), 77 (20), 51 (10).

5f: 1,1a,2,3-Tetrahydro-8b*H*-benzo[*b*]cyclopropa[*d*]oxepin-8b-ol. Eluent for flash chromatography: pentane–EtOAc 7.5 :

2.5; colourless oil; yield 9%; HRMS calcd. for $C_{11}H_{12}O_2$: 176.0837. Found: 176.0834; ν_{max}/cm^{-1} (neat) 3392, 3074, 1603; δ_H (200 MHz, $CDCl_3$) 7.58 (1 H, d, *J* 7.4), 7.32–7.12 (2 H, m), 7.01 (1 H, d, *J* 7.4), 4.29 (1 H, ddd, *J* 12.1, 11.0, 4.1), 3.94 (1 H, ddd, *J* 11.0, 5.8, 2.0), 2.5 (1 H, br s), 2.17 (1 H, dddd, *J* 15.3, 4.5, 4.1, 2.0), 1.52–1.26 (2 H, m), 1.01–0.83 (1 H, m), 0.56 (1H, dd, *J* 5.2, 4.8); δ_C (63 MHz, $CDCl_3$) 153.2, 134.9, 131.1, 129.3, 124.7, 122.0, 70.4, 55.5, 29.2, 20.5, 19.0; *m*/*z* (EI) 176 (45, M$^+$), 147 (100), 145 (56), 132 (83), 131 (46), 121 (91), 120 (49), 77 (22).

5g: 1,1a,2,3-Tetrahydrobenzo[*b*]cyclopropa[*e*]oxocin-9a(9*H*)-ol. Eluent for flash chromatography: pentane–EtOAc 7.5 : 2.5; white solid; yield 52%; mp 68–70 °C; HRMS calcd. for $C_{12}H_{14}O_2$: 190.0993. Found: 190.0990; ν_{max}/cm^{-1} (neat) 3409, 2931, 1490; δ_H (250 MHz, $CDCl_3$) 7.30–7.24 (2 H, m), 7.14–7.07 (2 H, m), 4.52 (1 H, dd, *J* 11.6, 3.2), 3.68 (1 H, dd, *J* 11.6, 11.4), 3.09 (1 H, d, *J* 13.3), 2.89 (1 H, d, *J* 13.3), 2.28 (1 H, ddd, *J* 15.9, 5.3, 5.2), 1.94 (1 H, s), 1.61–1.43 (1 H, m), 1.18 (1 H, dd, *J* 9.7, 5.6), 0.97–0.85 (1 H, m), 0.53 (1 H, dd, *J* 5.7, 5.6); δ_C (63 MHz, $CDCl_3$) 162.8, 133.4, 131.3, 128.3, 123.9, 123.0, 77.0, 60.4, 37.1, 34.7, 24.0, 21.7; *m*/*z* (EI) 190 (47, M$^+$), 147 (32), 134 (62), 133 (62), 131 (29), 107 (100), 91 (40), 78 (29), 77 (31), 55(24).

General procedure for the synthesis of the β-chloroketone 7e and oxacycloalkenones 6a–g

To a solution of ferric(III) chloride (428 mg, 2.67 mmol) and pyridine (0.1 ml, 1.2 mmol) in 2 ml of anhydrous diethyl ether cooled at 0° under argon was added dropwise cyclopropanols **5a–g** (1.2 mmol) in 1 ml of anhydrous diethyl ether. After stirring for three hours at the same temperature, the reaction mixture was quenched by addition of water (2 ml). The aqueous phase was extracted with ether (3 × 5 ml) and the combined organic layers were dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The crude residue was then purified by column chromatography for the chloride **7e** or used directly for the next step.

To the crude product in 2 ml of anhydrous methanol was added at room temperature in one portion anhydrous sodium acetate (502 mg, 6.1 mmol) and the mixture was stirred overnight. After monitoring by gas chromatography, the resulting mixture was diluted with water (1 ml) and extracted with dichloromethane (3 × 5 ml). The organic layers were then dried over anhydrous magnesium sulfate, evaporated and purified by column chromatography.

7e: 5-Chloro-5,6-dihydro-2*H*-1-benzoxocin-3(4*H*)-one. Eluent for column chromatography: pentane–Et_2O 9.2 : 0.8 then 8 : 2; white solid; yield 84%; mp 48–50 °C; HRMS calcd. for $C_{11}H_{11}ClO_2$: 210.0447. Found: 210.0439; ν_{max}/cm^{-1} (neat) 1721, 1492; δ_H (250 MHz, $CDCl_3$) 7.38–7.32 (1 H, m), 7.26–7.04 (3 H, m), 4.60 (1 H, d, *J* 13.1), 4.39 (1 H, d, *J* 13.1), 4.39–4.31 (1 H, m), 3.56–3.34 (3 H, m), 3.19 (1 H, dd, *J* 11.2, 2.9); δ_C (63 MHz, $CDCl_3$) 207.1, 157.8, 132.4, 129.7, 129.6, 125.3, 121.8, 81.8, 56.4, 50.5, 41.8; *m*/*z* (EI) 212 (32, M$^+$), 210 (100, M$^+$), 175 (43), 131 (33), 121 (79), 115 (35), 91 (56).

6a: 6,7b-Dihydro-3(2*H*)-oxepinone. Eluent for flash chromatography: pentane–Et_2O 9 : 1; colourless oil; yield 70%; HRMS calcd. for $C_6H_8O_2$: 112.0524. Found: 112.0524; ν_{max}/cm^{-1} (neat) 2932, 1655; δ_H (250 MHz, $CDCl_3$) 6.59 (1 H, td, *J* 12.4, 4.4), 6.07 (1 H, td, *J* 12.4, 1.8), 4.33 (2 H, s), 3.96 (2 H, t, *J* 5.4), 2.71 (2 H, dq, *J* 5.4, 1.8); δ_C (63 MHz, $CDCl_3$) 204.4, 145.2, 130.3, 78.9, 69.6, 35.2; *m*/*z* (EI) 112 (43, M$^+$), 84 (83), 83 (43), 81 (54), 55 (20), 54 (100), 53 (41).

6b: 2,3,7,8-Tetrahydro-4*H*-oxocin-4-one. Eluent for flash chromatography: pentane–EtOAc 1 : 1; colourless oil; yield 73%; HRMS calcd. for $C_7H_{10}O_2$: 126.0680. Found: 126.0681; ν_{max}/cm^{-1} (neat) 2950, 1659; δ_H (250 MHz, $CDCl_3$) 6.49 (1 H, td, *J* 12.1, 8.0), 6.23 (1 H, d, *J* 12.1), 3.91 (2 H, t, *J* 6.8), 3.69 (2 H, t, *J* 6.6), 2.90 (2 H, t, *J* 6.8), 2.76 (2H, q, *J* 6.6); δ_C (63 MHz, $CDCl_3$) 201.0, 139.0, 136.0, 65.03, 64.98, 44.2, 29.4; *m*/*z* (EI) 126 (21, M$^+$), 99 (29), 96 (14), 81 (11), 68 (100), 54 (50).

6c: 2,3,8,9-Tetrahydro-4(7*H*)-oxoninone. Eluent for flash chromatography (alumina): CH_2Cl_2–Et_2O 8.5 : 1.5; colourless oil; yield 25%; HRMS calcd. for $C_8H_{12}O_2$: 140.0837. Found: 140.0835; ν_{max}/cm^{-1} (neat) 2924, 1652; δ_H (250 MHz, $CDCl_3$) 6.34 (1 H, ddd, *J* 12.5, 9.2, 9.0), 6.11 (1 H, d, *J* 12.5), 3.93–3.88 (2 H, m), 3.64–3.54 (2 H, m), 2.88–2.83 (2 H, m), 2.78–2.74 (2H, m), 1.72–1.64 (2 H, m); δ_C (63 MHz, $CDCl_3$) 204.3, 141.9, 133.9, 69.9, 68.5, 45.4, 29.4, 24.6; *m*/*z* (EI) 140 (65, M$^+$), 139 (49), 113 (45), 111 (34), 99 (45), 95 (32), 82 (34), 81 (61), 71 (100), 67 (34), 54 (41), 53 (33), 41 (39).

6d: 1-Benzoxepin-3(2*H*)-one. Eluent for flash chromatography: pentane–EtOAc 9.2 : 0.8 then 8.7 : 1.3; colourless oil; yield 76%; HRMS calcd. for $C_{10}H_8O_2$: 160.0524. Found: 160.0520; ν_{max}/cm^{-1} (neat) 1667, 1612, 1565; δ_H (250 MHz, $CDCl_3$) 7.49–7.43 (2 H, m), 7.33 (1 H, d, *J* 8.6), 7.29 (1 H, d, *J* 12.2), 7.17 (1 H, dd, *J* 8.6, 7.9), 6.45 (1 H, d, *J* 12.2), 4.64 (2 H, s); δ_C (63 MHz, $CDCl_3$) 196.6, 158.7, 142.1, 133.3, 132.1, 128.9, 127.2, 124.1, 120.5, 77.5; *m*/*z* (EI) 160 (95, M$^+$), 132 (84), 131 (100), 119 (23), 103 (41), 102 (51), 91 (26), 76 (28), 63 (20), 51 (38).

6e: 2*H*-1-Benzoxocin-3(6*H*)-one. Eluent for column chromatography: pentane–CH_2Cl_2 9.9 : 0.1; white solid; yield from **7e** (NaOAc, MeOH, −5 °C) 42%; mp 40–42 °C; HRMS calcd. for $C_{11}H_{10}O_2$: 174.0680. Found: 174.0675; ν_{max}/cm^{-1} (neat) 3035, 1686; δ_H (360 MHz, $CDCl_3$) 7.28–7.24 (1 H, m), 7.16–7.03 (3 H, m), 6.59 (1 H, td, *J* 13.3, 7.1), 6.05 (1 H, d, *J* 13.3), 4.74 (2 H, s), 3.67 (2 H, d, *J* 7.1); δ_C (50 MHz, $CDCl_3$) 203.0, 158.4, 140.1, 130.8, 129.9, 128.9, 128.6, 124.1, 121.2, 79.7, 33.4, 25.9; *m*/*z* (EI) 174 (66, M$^+$), 159 (24), 145 (36), 131 (86), 119 (80), 118 (100), 115 (73), 91 (67), 68 (46).

6e′: 2*H*-1-Benzoxocin-3(4*H*)-one. Eluent for column chromatography: pentane–CH_2Cl_2 9.9 : 0.1; colourless oil; yield from **7e** (DBU, Et_2O, −10 °C) 85%; HRMS calcd. for $C_{11}H_{10}O_2$: 174.0680. Found: 174.0681; ν_{max}/cm^{-1} (neat) 3026, 1726, 1601; δ_H (250 MHz, $CDCl_3$) 7.30–7.17 (2 H, m), 7.13–7.07 (2 H, m), 6.49 (1 H, d, *J* 13.7), 5.71 (1 H, td, *J* 13.7, 7.8), 4.58 (2 H, s), 3.57 (2 H, d, *J* 7.8); δ_C (50 MHz, $CDCl_3$) 206.4, 156.4, 133.3, 131.5, 129.7, 125.9, 123.8, 122.0, 121.9, 75.5, 41.4; *m*/*z* (EI) 174 (82, M$^+$), 145 (45), 131 (100), 118 (22), 115 (54).

6f: 2,3-Dihydro-6*H*-1-benzoxocin-6-one. Eluent for column chromatography: CH_2Cl_2–Et_2O 9.5 : 0.5; colourless oil; yield 70%; HRMS calcd. for $C_{11}H_{10}O_2$: 174.0680. Found: 174.0680; ν_{max}/cm^{-1} (neat) 2875, 1634, 1448; δ_H (250 MHz, $CDCl_3$) 7.78 (1 H, d, *J* 7.2), 7.54 (1 H, dd, *J* 7.2, 7.1), 7.27 (1 H, dd, *J* 7.2, 7.1), 7.15 (1 H, d, *J* 7.2), 6.61–6.47 (2 H, m), 4.16 (2 H, t, *J* 7.1), 2.37 (2 H, q, *J* 7.1); δ_H (250 MHz, C_6D_6) 7.95 (1 H, d, *J* 7.8), 7.02 (1 H, dd, *J* 7.8, 7.2), 6.83 (1 H, dd, *J* 7.8, 7.2), 6.75 (1 H, d, *J* 7.2), 6.60 (1 H, d, *J* 11.8), 5.77 (1 H, td, *J* 11.8, 8.5), 3.48 (2 H, t, *J* 5.8), 1.65–1.52 (2 H, m); δ_C (63 MHz, $CDCl_3$) 191.7, 156.0, 138.2, 136.9, 135.6, 134.0, 130.5, 125.0, 123.2, 73.2, 25.9; *m*/*z* (EI) 174 (100, M$^+$), 144 (17), 131 (20), 120 (46), 115 (19), 92 (20), 81 (17).

6g: 2,3-Dihydro-1-benzoxonin-6(7*H*)-one. Eluent for flash chromatography: CH_2Cl_2–EtOAc 9.5 : 0.5; colourless oil; yield 55%; HRMS calcd. for $C_{12}H_{12}O_2$: 188.0837. Found: 188.0843; ν_{max}/cm^{-1} (neat) 3021, 1695, 1636; δ_H (250 MHz, $CDCl_3$) 7.21–6.94 (4 H, m), 6.01 (1 H, d, *J* 12.1), 5.90 (1 H, ddd, *J* 12.1, 7.9, 7.6), 4.24 (2 H, m), 3.71 (2 H, s), 2.51–2.43 (2 H, ddd, *J* 10.4, 7.6, 5.3); δ_H (250 MHz, C_6D_6) 7.01–6.92 (1 H, m), 6.77–6.72 (2 H, m), 6.62 (1 H, d, *J* 8.3), 5.63 (1 H, d, *J* 12.0), 5.24 (1 H, td, *J* 12.0, 8.2), 3.64 (2 H, dd, *J* 5.4, 5.3), 3.45 (2 H, s), 2.03–1.95 (2

H, m); δ_C (63 MHz, $CDCl_3$) 205.5, 159.2, 135.0, 130.8, 130.4, 128.9, 128.7, 122.8, 119.2, 72.5, 46.7, 27.9; *m/z* (EI) 188 (43, M^+), 145 (24), 132 (32), 131 (28), 129 (52), 119 (25), 116 (100), 91 (43), 81(99), 78 (38).

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