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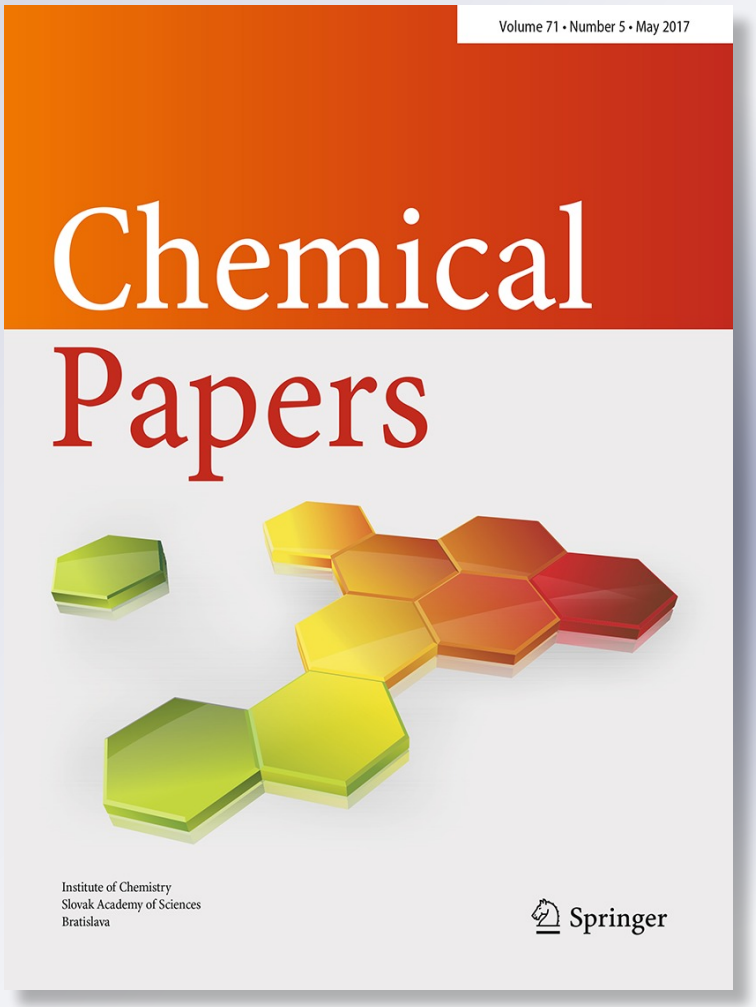

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ORIGINAL PAPER

Synthesis of tricyclic ring systems: [2+2] ketene addition reaction for preparation of tricyclic ketone, alcohol, and lactone derivatives

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Abstract The addition of dichloroketene to 1,4-cyclohexadiene was examined. Dichloroketene, which was easily prepared from trichloroacetyl chloride and Zn–Cu, reacted with 1,4-cyclohexadiene in the presence of $POCl_3$ to afford novel racemic products of single addition (**5**) and double addition (**6**). The adducts **6** and **7** were reacted separately with MCPBA (*meta*-chloroperbenzoic acid), H_2O_2, $LiAlH_4$, and *cis*-diol **10** was reacted with PCC (pyridinium chlorochromate) to afford lactone, alcohol, and ketone derivatives likely to exhibit biological activity. The structures of all the racemic molecules mentioned in the article were determined from ^1H NMR, ^{13}C NMR, MS, and IR data.

Keywords Ketene addition · Tricyclic molecules · Lactone · Ketone

Introduction

Bicyclic lactones used for the synthesis of tricyclic lactones with a variety of biological activities are important as nature's preferred building blocks (Fig. 1) (Makama 2012). Mono-, di-, and trisubstituted monocyclic lactone are described (Hofmann and Rabe 1985; Koch and Chamberlin 1995; Negishi and Kotora 1997; Bandichhor et al. 2005) in the literature, but there are few studies on the synthesis of bicyclic and tricyclic lactones. Bicyclic and tricyclic ring systems play an important role in biological profiles (Hall et al. 2001; Abel et al. 2002; Arya et al. 2002; Knepper et al. 2003; Seitz and Reiser 2005) because of their strong analgesic and anti-inflammatory (da Silva et al. 2005), antibacterial (Boudreaux et al. 2008), antifungal (Shain and Hillis 1971), leishmanicidal (Castano et al. 2009), antileukemic (Tandon and Rastogi 1976), anti-HIV (Schröder et al. 1990), antiplatelet (Yang et al. 2007), antiestrogenic (Martinez et al. 1998), anticonvulsant (Chen et al. 2007), and cytostatic properties (Janecki et al. 2005; Albrecht et al. 2008, 2010). The anticancer activity of halolactones against two cancer lines, Jurkat (human leukemia) and D17 (canine osteosarcoma), was studied (Gladkowski et al. 2013). In addition, some halolactones, which include atoms of chlorine or bromine in their structure, exhibit a variety of biological activities including antibacterial (Zhang et al. 2005; Vairappan et al. 2008), antiviral (Zhang et al. 2005), antimicrobial (Grabarczyk et al. 2014), and antifungal (Rodrigues et al. 2010). These important properties make bicyclic and tricyclic lactone systems significant for the synthesis of new drugs.

In this study, we aimed to synthesize several new tricyclic five-membered lactones, tricyclic alcohols, and tricyclic ketones with simple methods via ketene addition reactions reported in the literature (Santos-Martinez et al. 2014). Ketenes can react with alkenes to afford four-membered rings. Ketene [2+2] cycloaddition reactions proceed by a concerted mechanism and generally at room temperature (Snider 1988; Zengin et al. 1995; Sengül et al. 2000; Kishali et al. 2011; Heravi and Talaei 2014, 2015) (Fig. 2). Dichloroketene is typically generated in situ by

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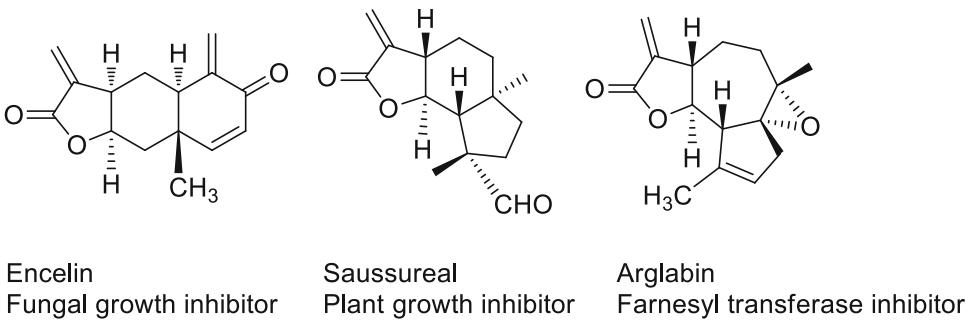


Fig. 1 Examples of tricyclic lactones

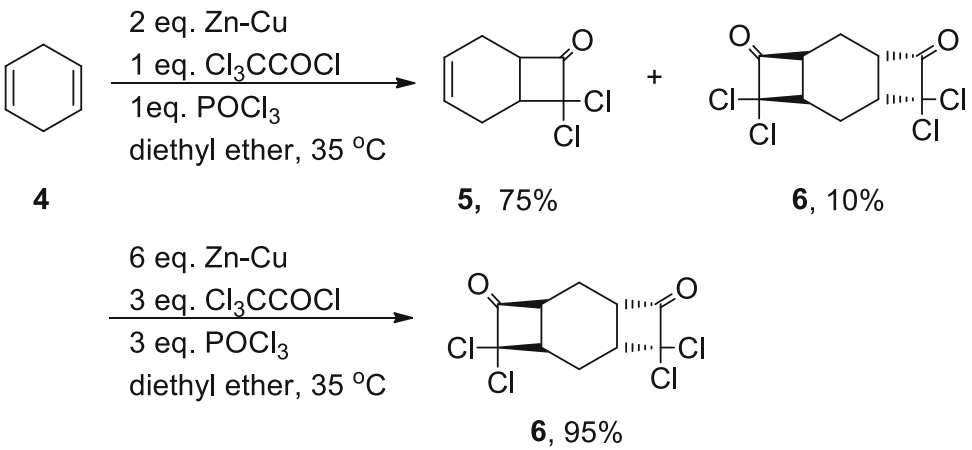


Fig. 2 Ketene addition to 1,4-cyclohexadiene (**4**)

dehalogenation with Zn–Cu couple (Zengin et al. 1995; Sengül et al. 2000).

The first step is to perform a ketene addition reaction to obtain a cyclobutanone ring, followed by a series of reactions such as reduction and oxidation to get tricyclic lactone, ketone, and alcohol derivatives, which are potentially useful for the synthesis of biologically active systems.

Experimental

Melting points were determined with a Mettler Toledo MP90 melting point system and were not corrected. Infrared spectra were recorded on a Perkin Elmer Win First® Satellite. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Ultrashield Plus Biospin GmbH 400 MHz spectrometer. Column chromatography was performed on silica gel (Kiesel 60, 230–400 mesh, Merck). TLC was carried out on Merck 0.2 mm silica gel 60 F_{254} analytical aluminum plates.

Activation of zinc

Zinc was activated according to the procedure described by Brady 1971. A stirred suspension of zinc dust (10 g, 0.15 mol) in 40 mL of water was degassed by bubbling through N_2 for 15 min. Then $CuSO_4$ (750 mg, 4.7 mmol) was added. The black suspension was stirred while N_2 was bubbled for 45 min. The Zn–Cu couple was collected on a sintered glass funnel under a stream of N_2 and washed with 100 mL of water and acetone. Then the Zn–Cu couple was dried under reduced pressure (0.2 mmHg) for 2 h.

Ketene addition reaction of 1,4-cyclohexadiene (4)

To a magnetically stirred solution of 1,4-cyclohexadien (**4**) (5 g, 62.5 mmol) in anhydrous diethyl ether (250 mL) at room temperature was added Zn–Cu (8.15 g, 125 mmol) in a 1 L three-necked flask equipped with a condenser, addition funnel, and nitrogen atmosphere. The suspension was stirred under N_2 and with a solution of trichloroacetyl chloride (11.35 g, 62.5 mmol) and phosphoryl trichloride (9.58 g, 62.5 mmol) in diethyl ether (50 mL). The mixture was stirred for 24 h at room temperature. After the mixture was filtered on Celite, the ethereal solution was washed with saturated $NaHCO_3$ and dried with $MgSO_4$. Chromatography of the residue on 50 g of silica gel eluting with ethyl acetate/hexane (1:9) afforded (±)-mono-addition product 5 (Kishali et al. 2011) (8.95 g, 75%) as a colorless liquid and (±)-di-addition product6 (1.89 g, 10%) as colorless crystals (Method I).

The same reaction was performed with 1,4-cyclohexadiene (4) (5 g, 62.5 mmol), Zn–Cu (24.45 g, 375 mmol), trichloroacetyl chloride (34.05 g, 187.5 mmol), and

phosphoryl trichloride (28.75 g, 187.5 mmol) and theonly product obtained was (±)-di-addition product 6 (18.31 g, 95%). The product of the reaction was chromatographed on silica gel (20 g) eluting with ethyl acetate/hexane (2:1) (Method II).

(±)-(1*R*,2*S*)-*rel*-8,8-Dichlorobicyclo[4.2.0]oct-3-en-7-one (5) (Kishali et al. 2011)

Yield: 75%, (as method I), colorless liquid. 1H ($CDCl_3$) d: 5.8 (m, 2H), 3.98 (ddd, J = 10.6, J = 6.8, J = 2.4 Hz,1H), 3.2 ppm (ddd, J = 8 Hz, J = 2 Hz, 1H), 2.6–2 (m, 4H). 13C (100 MHz, $CDCl_3$) d: 198.3, 127.3, 126.4,53.7, 45.2, 23.1, 21.3, FT-IR (neat) n = 2983, 1804, 1735, 1445, 1372, 1237, 1044 cm^{-1}.

(±)-(1*R*,3*S*,6*S*,8*S*)-*rel*-5,5,9,9-Tetrachlorotricyclo[6.2.0.0^{3,6}]decane-4,10-dione (6)

Yield: 10%. (as method I), 95% (as method II), colorless crystals, compound slowly crystallised from a concentrated solution in chloroform at 25 °C. mp: 165–166 °C. 1H NMR ($CDCl_3$) d: 4.11–4.05 (dt, 2H, J =10.8, 7 Hz, 2 –CH), 3.24–3.18 (dt, 2H, J = 10.8, 7 Hz, 2 –CH), 2.18–2.13 (dt, 4H, J = 12.9, 7 Hz, 2 –CH2). 13C NMR (CDCl3) d: 194.5, 87.3, 50.85, 41.0, 22.9, 16.9. Found: C, 39.01; H, 2.98%. Calc. for $C_{10}H_8Cl_4O_2$: C,39.77; H, 2.67%. MS m/z: 301.9 (M^+), 267, 266, 265, 264, (M^+, –Cl), 162, 161, 159 (M^+, –3Cl), 104, 103, 102, 101, 100. IR, v = 1798 (CO).

Reduction of 5,5,9,9-tetrachlorotricyclo[6.2.0.0^{3,6}]decane-4,10-dione (6)

To a vigorously stirring suspension of Zn (12.98 g, 198.7 mmol) in 150 mL of glacial acetic acid at room temperature, was added dropwise a solution of (±)-di-addition product 6 (10 g, 33.1 mmol) in 50 mL of acetic acid. After addition was complete, the temperature was raised to at 100 °C and maintained for 20 h. The reaction mixture was cooled and treated with diethyl ether, and the zinc residue was filtered. The ethereal layer was washed with water and a saturated solution of sodium bicarbonate to remove acetic acid and then it was dried with MgSO4. The solvent was removed in an evaporator (Sengül et al. 2000). Chromatography of the residue on 50 g of silica gel eluting with diethyl ether/hexane (1:1) afforded bicyclic ketone 7 (5.16 g,95%) as a colorless liquid.

(±)-(1*R*,3*S*,6*S*,8*S*)-*rel*-Tricyclo[6.2.0.0^{3,6}]decane-4,10-dione (7)

Yield: 95% colorless liquid, 1H NMR ($CDCl_3$) d: 3.51–3.43 (m, 2H, 2–CH), 3.34-3.26 (B part of AB system, ddd, J = 17.8, 9.6, 2.8 Hz, 2H, –2–CH2), 2.79–2.73 (A part of AB system, dt, J = 17.8, 4, 2.8 Hz, 2H, 2–CH2),2.71–2.61 (m, 2H, 2–CH), 1.92–1.87 (m, 4H, 2–CH2). 13C NMR (100 MHz, $CDCl_3$) d: 211.3, 54.8, 50.8, 27.9,19.8, 17.6. Found: C, 72.86; H, 7.92%. Calc. for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37%. MS m/z: 164 (M^+), 136 (M^+, –CO), 122 (M^+, –CH_2), 80, 79, 78, 77, (M^+, –CO, –CH_2) 69, 68, 67, 66, 65. FT-IR (neat) = 2920, 2854, 1765, 1453, 1392, 1306, 1244, 1225, 1083, 1022, 957 cm^{-1}.

The reaction of (±)-tricyclo[6.2.0.0^{3,6}]decane-4,10-dione (7) with MCPBA

(±)-Tricyclo[6.2.0.03,6]decane-4,10-dione (**7**) (1 g, 6.1 mmol) was dissolved in 150 mL of chloroform, 1 eq. (1.5 g, 6.1 mmol) 70% MCPBA was added, and then the reaction was stirred at room temperature for 24 h. The reaction mixture was added to 15 mL of 50% NaHSO3 solution and the mixture was stirred for 15 min (Sengül et al. 2000). The organic layer was separated and then washed with saturated aqueous NaHCO3 (100 mL), dried with MgSO4 and concentrated to give two lactones, di-lactone 8 (0.27 g, 23%) and mono- lactone 9 (0.49 g, 45%) (Method III).

The same reaction was performed under 2 eq. (3 g, 12.2 mmol) 70% MCPBA conditions, and the only product (di-lactone **8**) was obtained in 95% yield (1.14 g) (Method IV).

(±)-(3a*R*,4a*S*,7a*S*,8a*R*)-*rel*-Hexahydrobenzo[1,2-*b*:5,4-*b*′]difuran-2,6(3*H*,7a*H*)-dione (8)

Yield: 23% (as method III), 95% (as method IV), colorless liquid. 1H NMR (CDCl3) d: 4.82-4.78 (dt, J = 7.28,5.55 Hz, 2H, –CH), 2.88–2.80 ppm (B part of AB system, dd, J = 18.2, 9.85 Hz, 2H, –CH2), 2.74–2.62 ppm (m,2H, –CH), 2.24–2.18 ppm (t, J = 5.49, 4H, –CH2 and A part of AB system of CH2), 1.62–1.58 ppm (t, J = 6.51Hz, 2H, –CH2). 13C NMR (100 MHz, $CDCl_3$) d: 176.2, 76.4, 34.9, 29.9, 29.8, 29.4. Found: C, 61.99; H:6.85%. Calcd. for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16%. MS m/z: 196 (M^+), 153, 152, 151, 150 (M^+, –COO), 137, 136, 135 (M^+, –O), 110, 109, 108, 107. FT-IR (neat) = 2942, 1754, 1461, 1417, 1349, 1298, 1167, 1020, 950 cm^{-1}.

(±)-(3a*R*,4a*S*,6a*S*,7a*R*)-*rel*-Hexahydrocyclobuta[*f*]isobenzofuran-2,6(3*H*,6a*H*)-dione (9)

Yield: 45% (as method III), colorless liquid. 1H NMR ($CDCl_3$) d: 4.86-4–82 ppm (m, 1H, –CH), 3.58–3.51 ppm (m, 1H, –CH), 3.42–3.35 ppm (B part of AB system, ddd, J = 17.6, 9.4 Hz, 2.4 1H, –CH2), 2.96–2.89 ppm (B part of

AB system, dd, J = 17.8, 10.6 Hz, 1H, –CH_2), 2.87–2.79 (m, 1H, –CH), 2.69-2.63 (A part of AB system, dt, J = 3.7 Hz, 1H, –CH2), 2.58-2.49 (m, 1H, –CH), 2.37–2.32 (A part of AB system, dd, J = 17.6, 2.4 Hz, 1H, –CH2), 2.16–2.09 (B part of AB system, ddd, J = 14.8 Hz, 8 Hz, 5.2 Hz, 1H, –CH_2), 2.01–1.94 (A part of AB system, ddd, J = 14.8, 8.4, 3.6 Hz, 1H, –CH2), 1.94–1.88 (B part of AB system, dt, J = 14.4, 4.8 Hz, 1H), 1.59–1.52 ppm (A part of AB system, ddd, J = 14.4, 10.2, 5.3, 1H, –CH2). 13C NMR (CDCl3) d: 210.0, 176.5, 76.5,53.3, 51.7, 34.8, 30.3, 29.5, 23.1, 18.8. Found: C, 67.09; H, 6.11%. Calcd. for $C_{10}H_{12}O_3$: C: 66.65, H:6.71%. MS *m/z:* 180 (M^+, –CO), 153, 152, (M^+, –CO), 123, 122, 121, 120, (M^+, –CO), 95, 94, 93, 92 (M^+, –O, –CH_2), 55, 54, 53 (M^+, –$2CH_2$), 42, 41, 40, 39. FT-IR (neat) = 2943, 1761, 1458, 1419, 1393, 1347, 1242, 1175, 1017, 946 cm^{-1}

Reduction of (±)-tricyclo[6.2.0.0^{3,6}]decane-4,10-dione (7)

A solution of diketone **7** (1 g, 6.1 mmol) in ether (50 mL) was added dropwise at 0 °C over 2 h to a magnetically stirred slurry of 2 eq. $LiAlH_4$ (0.46 g, 12.2 mmol) in 100 mL of ether. The mixture was stirred at room temperature for 5 h. Then the reaction mixture was cooled to 0 °C, cold water was added, and it was filtered through silica gel (20 g) (Gultekin et al. 2004). The organic layer was dried over $MgSO_4$ and the solvent was removed. The residue was chromatographed on a silica gel (30 g) column eluting with diethyl ether/hexane (3:1). The first fraction was identified as (±)-*trans*-diol **11** (0.38 g, 37%, colorless liquid) and the second fraction as (±)-*cis*-diol **10** (0.53 g, 52%, colorless crystals from methylene chloride/*n*-hexane) (method V).

The reduction was also performed with 1 eq. $LiAlH_4$ (0.23 g, 6.1 mmol) to afford (±)-*cis*-diol **10** (0.28 g, 27%) and (±)-*trans*-diol **11** (0.19 g, 19%) (method VI).

(±)-(1*S*,3*S*,4*S*,6*R*,8*S*,10*S*)-Tricyclo[6.2.0.0^{3,6}]decane-4,10-diol (10)

Yield: 52% (via method V), 27% (via method VI), colorless crystals, which slowly crystallized from a concentrated solution in chloroform at 25 °C. mp: 163–164 °C. ^{1}H NMR (CD_3OD) δ: 4.37–4.31 (q, J = 8.1 Hz, 2H, HO–CH), 2.79 (pd, J = 8.1, 3.01, 2H, CH), 2.47–2.39 (m, 2H, CH_2), 2.23–2.13 (m, 2H, CH), 1.83–1.76 (m, 4H, $2CH_2$), 1.53 (t, J = 6.2 Hz, 2H, CH_2). ^{13}C NMR (CD_3OD) δ: 66.5, 38.8, 37.7, 29.4, 23.5, 17.0. Found: C, 71.72; H, 9.12%. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59%. MS *m/z:* 135 (M^+, –2OH), 108, 107, 106, 105, 104, (M^+, –$2CH_2$) 80, 79, 78, 77 (M^+, –$2CH_2$), 67, 66, 65. FT-IR (neat) = 3325, 3245, 2964, 2936, 2915, 2899, 2853, 1456, 1360, 1339, 1315, 1277, 1190, 1151, 1119, 1102, 1052, 1011, 962 cm^{-1}.

(±)-(1*S*,3*S*,4*R*,6*R*,8*S*,10*S*)-Tricyclo[6.2.0.0^{3,6}]decane-4,10-diol (11)

Yield: 37% (via method V), 19% (via method VI), colorless crystals, which slowly crystallized from a concentrated solution in chloroform at 25 °C. mp: 114.5–115 °C. ^{1}H NMR ($CDCl_3$) δ: 4.35–4.30 (qd, J = 7.6, 0.8 Hz, 2H, 2HO–CH), 2.72–2.64 (p, J = 7.6 Hz, 2H, CH), 2.50–2.46 (td, J = 8.0, 2.4, Hz, 1H, CH), 2.47–2.42 (td, J = 8.0, 2.4 Hz, 1H, CH), 2.34–2.25 (h, J = 7.6, 2H, CH), 1.87–1.80 (m, 2H, CH_2), 1.74 (bs, 1H, OH), 1.65–159 (m, 2H, CH_2). ^{13}C NMR ($CDCl_3$) δ: 67.3, 36.9, 36.5, 23.9, 22.0. Found: C, 71.87; H, 8.95%. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59%. FT-IR (neat) ν = 3251, 2918, 2854, 1438, 1332, 1315, 1235, 1163, 1149, 1091, 1077, 1042, 1027, 937 cm^{-1}.

Oxidation of (±)-tricyclo[6.2.0.0^{3,6}]decane-4,10-diol (10) with PCC

PCC (0.65 g, 3.01 mmol) was added to a solution of (±)-*cis*-diol **10** (0.5 g, 3.01 mmol) in dry dichloromethane (30 mL). The mixture was stirred for 2 h and then filtered through a Celite and silica mixture. The removal of solvent left a dark brown crude product that after chromatography with diethyl ether afforded (±)-diketone **7** and (±)-hydroxyketone **12** (0.21 g, 43%).

(±)-(1*S*,3*S*,6*S*,8*R*,10*S*)-*rel*-10-Hydroxytricyclo[6.2.0.0^{3,6}]decan-4-one (12)

Yield: 43%, colorless liquid. ^{1}H NMR ($CDCl_3$) δ: 4.42–4.37 (q, J = 7.6 Hz, 1H, CH), 3.51–3.44 (m, 1H, CH), 3.14–3.06 (B part of AB system, ddd, J = 18.0, 8.2, 4.4 Hz, 1H), 2.81–2.79 (dd, J = 6.2, 3.2 Hz, 1H, CH), 2.77–2.67 (A part of AB system, m, 2H, CH_2), 2.66–2.58 (B part of AB system, ddd, J = 20, 7.6, 3.2 Hz, 1H, CH_2), 2.56–2.49 (m, 1H, CH), 2.41 (bs, 1H, OH), 2.31–2.21 (h, J = 8.2 Hz, 1H, CH), 1.99–1.91 (B part of AB system, ddd, J = 14.0, 10.8, 6.2 Hz, 1H, CH_2), 1.89–1.82 (A part of two AB system, m, 2H, $2CH_2$), 1.79–1.69 (A part of two AB system, m, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 214.9, 66.0, 56.2, 50.1, 37.9, 36.9, 28.0, 21.6, 17.7. Found: C, 72.72; H, 9.07%. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49%. MS *m/z:* 164 (M^+), 138, (M^+, –CO), 121, 122, 123, (M^+, –OH), 95, 94, 93,

92, 91, (M^+, $-CH_2$), 81, 80, 79, 78 (M^+, $-CH_2$), 66, 65, 64, 63. FT-IR (neat) = 3391, 2925, 1760, 1338, 1255, 1176, 1136, 1098 cm^{-1}.

Reaction of (±)-6-hydroxyoctahydrocyclobuta[*f*]benzofuran-2(3*H*)-one (12) with MCPBA

The reaction was carried out as described above by using (±)-hydroxyketone **12** (100 mg, 0.6 mmol) and MCPBA (70%) (148 mg, 0.85 mmol). The residue was chromatographed on a silica gel (5 g) column eluting with diethyl ether to afford a single product, (±)-lactone **13** (104 mg, 0.57 mmol).

(±)-(3a*S*,4a*R*,6*S*,6a*S*,7a*S*)-rel-6-Hydroxyoctahydrocyclobuta[*f*]benzofuran-2(3*H*)-one (13)

Yield: 95% colorless liquid. ^{1}H NMR ($CDCl_3$) δ: 5.05–5.01 (dt, $J = 8.8$, 4.2 Hz, 1H, –CH–O–), 4.50–4.44 (q, $J = 6.8$ Hz, 1H, –CH–OH), 2.92–2.83 (m, 1H, CH), 2.73–2.66 (B part of AB system, dd, $J = 18.3$, 10.6 Hz, 1H, CH_2), 2.65–2.57 (m, 2H, CH and one proton of CH_2), 2.35–2.26 (A part of AB system, dd, $J = 18.3$, 6.8 Hz, 1H, CH_2), 2.23–2.16 (h, $J = 8.8$ Hz, 1H, CH), 2.11–2.04 (B part of AB system, ddd, $J = 14.4$, 10.6, 4.2 Hz, 1H, CH_2), 1.92–1.86 (A part of AB system, ddd, $J = 14.4$, 6.8, 4.2 Hz, 1H, CH_2), 1.81–1.70 (m, 2H, one proton of the two different CH_2), 1.64–1.57 (ddd, $J = 8.8$, 4.2 Hz, 1H, one proton of CH_2). ^{13}C NMR ($CDCl_3$) δ: 177.5, 78.5, 66.0, 37.2, 34.0, 33.8, 30.4, 28.8, 22.8, 21.7. Found: C, 66.62; H, 8.12%. Calcd. for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74%. MS *m*/*z*: 164, (M^+, –OH), 139.1, 138, 136 (M^+, $-2CH_2$), 122, 121, 120 (M^+, –O), 108, 107, 106 (M^+, –O), 95, 94, 93 (M^+, $-CH_2$), 81, 80, 79, 78, 77 (M^+, $-CH_2$), 67, 66, 65. FT-IR (neat) = 3401, 2933, 1748, 1369, 1188, 1095, 1014 cm^{-1}.

Reaction of (±)-5,5,9,9-tetrachlorotricyclo[6.2.0.0^{3,6}]decane-4,10-dione (6) with H_2O_2

A solution of H_2O_2 (0.1 g, 30%) in acetic acid (0.5 mL) was added to a solution of (±)-5,5,9,9-tetrachlorotricyclo[6.2.0.0^{3,6}] decane-4,10-dione (**6**) (0.3 g, 1.0 mmol) in CH_2Cl_2 (5 mL) and the resulting mixture was stirred for 20 h at room temperature. After completion of the reaction, the mixture was washed with water and saturated $NaHCO_3$. The organic phase was dried over $MgSO_4$. The residue was chromatographed on a silica gel (5 g) column eluting with ethyl acetate/hexane (1:1) to afford a single product, dichlorodilactone **14** (0.32 g, 0.94 mmol).

(±)-(3a*R*,4a*R*,7a*R*,8a*S*)-*rel*-3,3,5,5-Tetrachlorohexahydrobenzo[1,2-*b*:5,4-*b*′]difuran-2,6(3*H*,7a*H*)-dione (14)

Yield: 95% mp: 183–183.5 °C, colorless crystals, which slowly crystallized from a concentrated solution in chloroform at 25 °C. ^{1}H NMR ($CDCl_3$) δ: 0.01–5.02 (q, $J = 5.51$ Hz, 2H, CH), 3.01–2.96 (q, $J = 6.82$ Hz, 2H, CH), 2.48–2.45 (t, $J = 5.51$ Hz, 2H, CH_2), 2.09–2.06 (t, $J = 6.82$ Hz, 2H, CH_2). ^{13}C NMR ($CDCl_3$): δ 166.6, 80.7, 73.7, 47.5, 28.9, 23.5. Found: C, 35.76; H, 2.52%. Calcd for: C, 35.96; H, 2.41%. MS *m*/*z*: 297.8, (M^+, –Cl), 227, 226 (M^+, –2Cl), 212, 211, 210 (M^+, –O), 177, 176, 175, 174 (M^+, –Cl), 161, 160, 159 (M^+, –O), 135, 134, 133, 132 (M^+, –O, $-CH_2$), 73, 72, 71, 70, 69. FT-IR (neat) = 2959, 1787, 1461, 1371, 1347, 1313, 1266, 1194, 1167, 1026, 970.

Reduction of (±)-5,5,9,9-tetrachlorotricyclo[6.2.0.0^{3,6}]decane-4,10-dione (6) with $LiAlH_4$

The reaction was carried out as described above by using adduct **6** (0.3 g, 1 mmol) and $LiAlH_4$ (0.08 g, 2 mmol). The residue was chromatographed on a silica gel (20 g) column eluting with diethyl ether/hexane (3:2) to afford *cis*-diol **15** (0.198 g, 0.65 mmol) and *trans*-diol **16** (0.097 g, 0.32 mmol).

(±)-(1*S*,3*S*,4*R*,6*R*,8*R*,10*S*)-5,5,9,9-Tetrachlorotricyclo[6.2.0.0^{3,6}]decane-4,10-diol (15)

Yield: 65% colorless crystals, which slowly crystallized from a concentrated solution in chloroform at 25 °C. mp: 142.5–143 °C. ^{1}H NMR (CD_3OD) δ: 4.19–4.16 (dd, $J = 8.12$, 1.19, 2H, HO–CH), 2.97–2.91 (qd, $J = 7.26$, 1.19 Hz, 2H, CH), 2.63–2.55 (m, 2H, CH), 2.06–2.02 (t, $J = 7.26$ Hz, 2H, CH_2), 1.93–1.89 (t, $J = 7.26$ Hz, 2H, CH_2). ^{13}C NMR (CD_3OD) δ: 91.5, 83.4, 44.8, 37.2, 24.8, 24.1. Found: C, 39.42; H, 3.77%. Calcd. for $C_{10}H_{12}Cl_4O_2$: C, 39.25; H, 3.95%. MS *m*/*z*: 232.9 (M^+, –2Cl), 216, 215, 214 (M^+, –OH), 149, 148, 147 (M^+, –2Cl), 122, 121, 120, 119, 118 (M^+, $-2CH_2$), 105, 104, 103 (M^+, –OH), 80, 79, 78, 77 (M^+, $-2CH_2$), 57, 55, 54, 53. FT-IR (neat) = 3323, 2935, 2857, 1439, 1277, 1206, 1153, 1131, 1067, 1029, 956 cm^{-1}.

(±)-(1*S*,3*S*,4*R*,6*R*,8*R*,10*R*)-5,5,9,9-Tetrachlorotricyclo[6.2.0.0^{3,6}]decane-4,10-diol (16)

Yield: 32%, colorless liquid. ^{1}H NMR (CD_3OD) δ: 4.67–4.65 (dd, $J = 8.51$, 1.63 Hz, 2H, HO–CH–), 3.29–3.23 (dtd, $J = 8.51$, 6.76, 1.58 Hz, 2H, CH), 3.07–2.99 (p, $J = 8.52$ Hz, 2H, CH), 2.14–2.11 (t,

$J = 6.76$ Hz, 2H, CH_2), 1.77–1.73 (t, $J = 8.51$ Hz, 2H, CH_2). ^{13}C (CD_3OD): δ 94.8, 80.6, 46.62, 33.1, 20.1, 14.8. Found: C, 39.52; H, 3.72%. Calcd. for $C_{10}H_{12}Cl_4O_2$: C, 39.25; H, 3.95%. MS *m/z*: 200, 199, 198, 197 (M^+, –2OH, –2Cl), 133, 132, 131, 130, 129, 128 (M^+, –2Cl), 106, 105, 104, 103, 102 (M^+, $-2CH_2$), 66, 65, 64, 63, 62. FT-IR (neat) = 3382, 2929, 2854, 1436, 1407, 1337, 1155, 1122, 1068, 1044, 993 cm^{-1}.

Crystallography

Single crystals of molecule **6** were obtained by slow evaporation of the compounds in acetonitrile at room temperature. A selected single crystal of compound **6** was used for data collection on a Bruker SMART BREEZE CCD diffractometer. The graphite-monochromatized MoK_α radiation ($\lambda = 0.71073$ Å) and oscillation scans technique with $\Delta\omega = 5°$ for one image were used for data collection. The lattice parameters were determined by the least-squares methods on the basis of all reflections with $F^2 > 2\sigma(F^2)$. Integration of the intensities, correction for Lorentz and polarization effects, and cell refinement were performed using Bruker SAINT (Bruker AXS Inc, 2012) software. The structures were solved by direct methods using SHELXS-97 (Bruker 2012) and refined by a full-matrix least-squares procedure using the same software (Sheldrick 1997). H atoms were positioned geometrically and refined using a riding model. The final difference Fourier maps showed no peaks of chemical significance. Crystal data for **6**: $C_{10}H_{8}Cl_4O_2$, crystal system, space group: monoclinic, $P2_1/c$ (no. 14); unit cell dimensions: $a = 6.3593(3)$, $b = 9.4053(3)$, $c = 20.2212(9)$ Å, $\alpha = 90$, $\beta = 90.658(5)$, $\gamma = 90°$; volume: 1209.37(1) $Å^3$; $Z = 4$; calculated density: 1.66 g/cm^3; absorption coefficient: 0.958 mm^{-1}; $F(000)$: 608; θ range for data collection 2.0–26.4°; refinement method: full matrix least-square on F^2; data/parameters: 2460/146; goodness-of-fit on F^2: 1.031; final R indices [$I > 2\sigma(I)$]: $R_1 = 0.038$, $wR_2 = 0.084$; largest diff. peak and hole: 0.513 and -0.418 e $Å^{-3}$.

CCDC-1033272 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Results and discussion

We attempted to obtain both racemic single addition product **5** (Kishali et al. 2011) and double addition product **6** (not in the literature) using different amounts of Zn–Cu. We treated 1,4-cyclohexadiene (**4**) with 2 eq. Zn–Cu, 1 eq. Cl_3CCOCl, and 1 eq. $POCl_3$ and obtained 75% yield of **5** and 10% yield of **6** (Fig. 2). When we increased the amount of Zn–Cu to 6 eq. and the amount of $POCl_3$ to 3 eq., we obtained only adduct **6** in essentially quantitative yield (Fig. 2).

The structures of the addition products **5** (Kishali et al. 2011) and **6** were solved with ^1H and ^{13}C NMR spectroscopy. There are four signals in the ^1H NMR spectroscopy of product **6** with two different methylene signals verifying the structure. The structure of product **6** was also fully elucidated by X-ray analysis (Fig. 3).

Then the subsequent reductive elimination of the chlorine in adduct **6** was accomplished by using Zn in acetic acid at 100 °C to yield bicyclic diketone **7** in 95% yield. The structure of (±)-bicyclic diketone **7** was solved with ^1H, ^{13}C, APT, and HETCOR NMR techniques. Then (±)-bicyclic diketone **7** was reacted with 70% MCPBA to afford (±)-dilactone **8**, (±)-monolactone **9**, and unreacted (±)-bicyclic diketone **7** (Fig. 4). The two products were successfully separated via column chromatography with diethyl ether. (±)-Dilactone **8** was formed in quantitative yield by using two times the amount of MCPBA (Sengül et al. 2000). The structures of **8** and **9** were assigned on the basis of ^1H, APT, HETCOR, and COSY NMR spectra. The six-line ^{13}C NMR spectrum of **8** clearly indicates that the molecule is symmetrical. Three AB systems are present in the structure of **8**; two AB systems ($-CH_2-C{=}O$) overlapped at $\delta = 2.24$ (B part of AB system) and $\delta = 2.18$ ppm (A part of AB system). Four AB systems are consistent with the structure of (±)-monolactone **9**. The location of each system was determined by HETCOR and COSY methods. The absorption bands at 1754 cm^{-1} (**8**) and 1761 cm^{-1} (**9**) in the FT-IR spectra confirmed the lactone ring in the structure.

Reduction of bicyclic ketone **7** with $LiAlH_4$ afforded (±)-*cis*-diol **10**, (±)-*trans*-diol **11** and unreacted (±)-

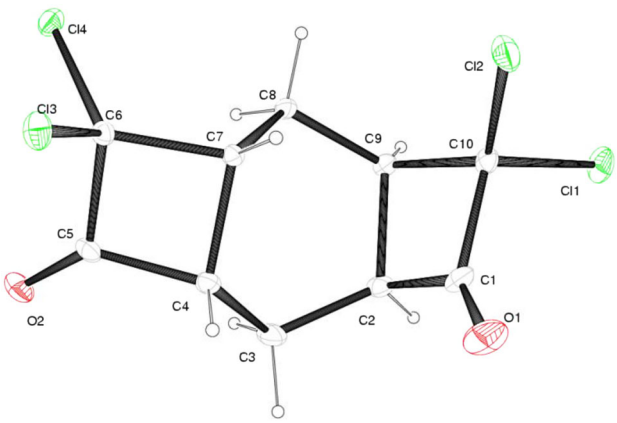


Fig. 3 X-ray structure of product **6**

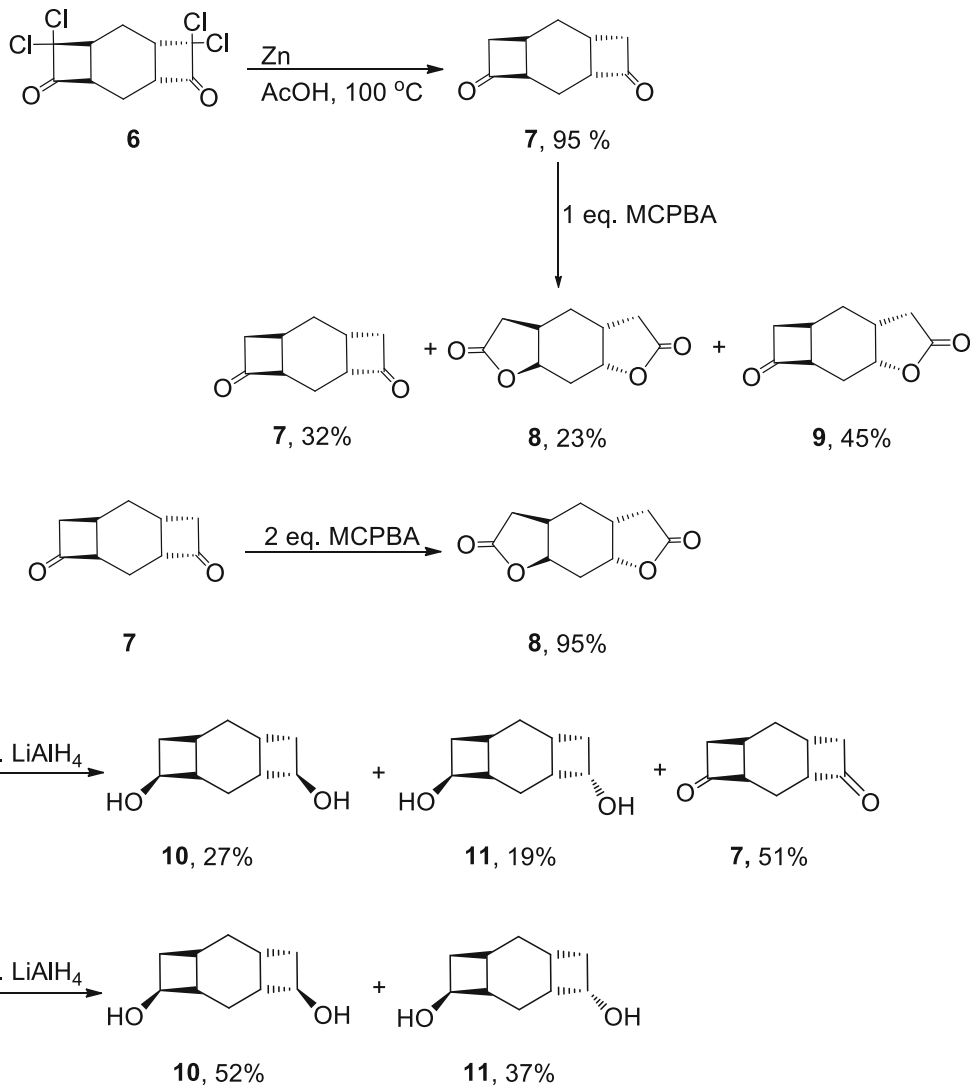


Fig. 4 Reduction reaction of adduct **6** and the synthesis of (±)-dilactone **8** and (±)-monolactone **9**

Fig. 5 Synthesis of (±)-*cis*-diol **10** and (±)-*trans*-diol **11** from diketone **7**

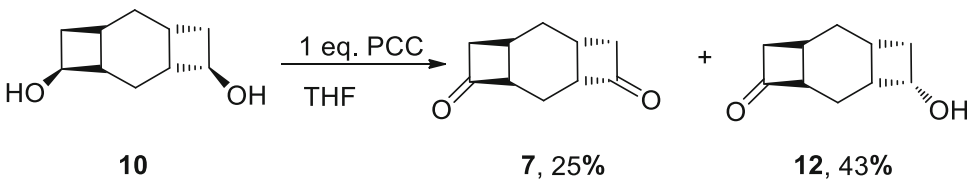


Fig. 6 Synthesis of (±)-hydroxyketone **12**

bicyclic ketone **7** (Fig. 5). When 1 eq. $LiAlH_4$ was used, both carbonyl groups were reduced and bicyclic diketone **7** remained in the reaction medium. Consequently, the (±)-hydroxyketone **12** we intended to synthesize was not obtained. Two products, (±)-*cis*-diol **10** (52%) and (±)-*trans*-diol **11** (37%), were obtained with two equivalents of $LiAlH_4$. The structures of the synthesized molecules were determined by NMR spectroscopy. The ^{1}H NMR spectra of (±)-*trans*-diol **11** and (±)-*cis*-diol **10** were highly symmetrical owing to the symmetry in the molecule.

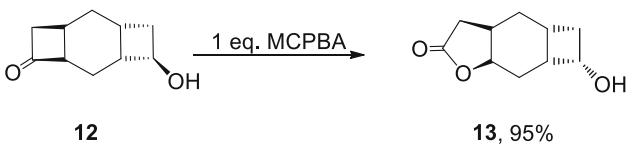
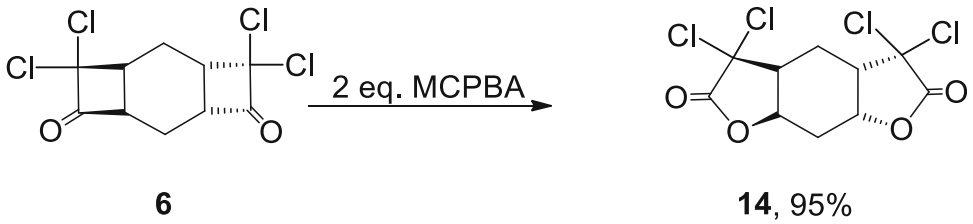


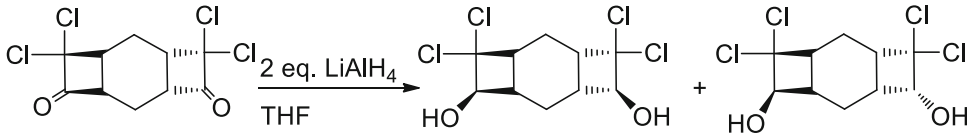
Fig. 7 Synthesis of (±)-hydroxylactone **13**

Absorption bands of the hydroxyl group occurred at 3251 cm^{-1} ((±)-*trans*-diol **11**) and 3325 and 3245 cm^{-1} ((±)-*cis*-diol **10**), and the characteristic signal of –OH was



6 **14**, 95%

Fig. 8 Synthesis of (±)-halolactone **14**



6 **15**, 65% **16**, 32%

Fig. 9 Synthesis of (±)-diols **15** and **16**

observed as a broad singlet at 1.74 ppm in the NMR spectrum of compound **11**. The NOESY results confirmed the relative *cis* configuration of the hydroxyl groups in **10**. While the –CH(OH) proton of one cyclobutane ring interacted with methylene protons of the cyclohexane –CH(OH), the corresponding proton of the other cyclobutane ring did not and thus the interaction was weak. According to the NOESY NMR results of **11**, the –CH(OH) protons of both cyclobutane rings do not interact with the methylene protons of the cyclohexane. The interaction was weak relative to the other signals as there were interactions in just one ring. This indicates a *trans* structure.

After the diols were obtained, we aimed to synthesize (±)-hydroxyketone **12**. For this, (±)-*cis*-diol **10** was reacted with 1 eq. PCC in THF at room temperature. The products of the reaction were (±)-hydroxyketone **12** as the main product in 43% yield and (±)-bicyclic diketone **7** as a by-product in 25% yield (Fig. 6). (±)-Hydroxyketone **12** was identified by spectroscopic methods. The hydroxyl group was observed as a broad singlet at $\delta = 2.41$ ppm, an A part of an AB system for $–CH_2–CH–OH$ and $–CH–CH_2–CH–$, and another AB system for $–CH–CH_2–CH–$ overlapped at $\delta = 1.89–1.69$ ppm in the NMR spectrum.

(±)-Hydroxyketone **12** reacted with MCPBA in methylene chloride at room temperature to afford (±)-hydroxylactone **13** as the only product in nearly quantitative yield (Fig. 7).

Adduct **6** reacted with 2 eq. 70% MCPBA to afford (±)-dichlorodilactone **14** as the only product in 95% yield (Fig. 8). Structural assignments were obtained from various NMR spectra (^1H, ^{13}C, APT, HETCOR, COSY). The six-line ^{13}C NMR spectrum of (±)-dichlorodilactone **14** clearly indicates the symmetry of the structure.

We also planned to obtain (±)-chlorohydroxy derivatives **15** and **16**. The carbonyl groups of adduct **6** were reduced to with $LiAlH_4$ to afford (±)-*cis*-diol **15** and (±)-*trans*-diol **16** (Fig. 9). The spectroscopic data confirmed the structure of the molecules. Absorption bands at 3323 cm^{-1} (in **15**) and 3382 cm^{-1} (in **16**) indicate the presence of an hydroxy group, and characteristic signals for –CH–OH in the range 4.65–4.67 ppm (in **15**) and 4.17–4.19 ppm (in **16**) in the were observed ^1H NMR spectrum.

The NOESY NMR results of structure **15** shows that hydroxyl groups are in the *cis* position. While the –CH(OH) proton of one cyclobutane ring interacts with the methylene protons of the cyclohexane [–CH(OH)], the corresponding proton of the other cyclobutane ring does not. The NOESY NMR results of **16** show that –CH(OH) protons of both cyclobutane rings interact with the hydrogen atoms of the cyclobutane but they do not interact with the methylene protons of the cyclohexane, thereby indicating a *trans* structure.

Conclusion

Tricyclic lactone (**8**, **9**, **13**, **14**), tricyclic alcohol (**10**, **11**, **12**, **15**, **16**), and tricyclic ketone (**6**, **7**) derivatives, which are useful multifunctional building blocks, were synthesized successfully via a simple ketene addition reaction in excellent yields. Most importantly, a novel, practical, and efficient method was developed for the synthesis of tricyclic molecules.

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