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EFFICIENT SYNTHESIS OF SEVEN-MEMBERED CYCLIC ETHERS USING Pd(II) CATALYST

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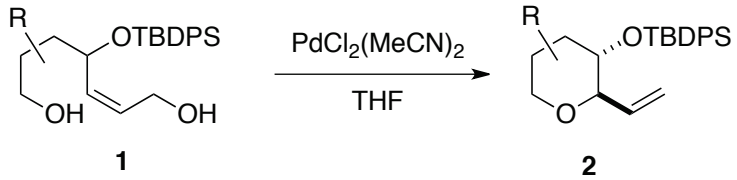
Abstract – We report a palladium(II)-catalyzed intramolecular cyclization of oct-2-ene-1,8-diol derivatives to afford seven-membered cyclic ethers without the need for high dilution and without dimer formation.

Marine polycyclic ethers have large ladder-like structures that have attracted considerable attention from synthetic organic chemists. Various methods have been employed for stereoselective construction of the ether ring systems,[1] but synthetic routes to seven- and eight-membered heterocyclic compounds via intramolecular alkylation are often slow and involve low yield.

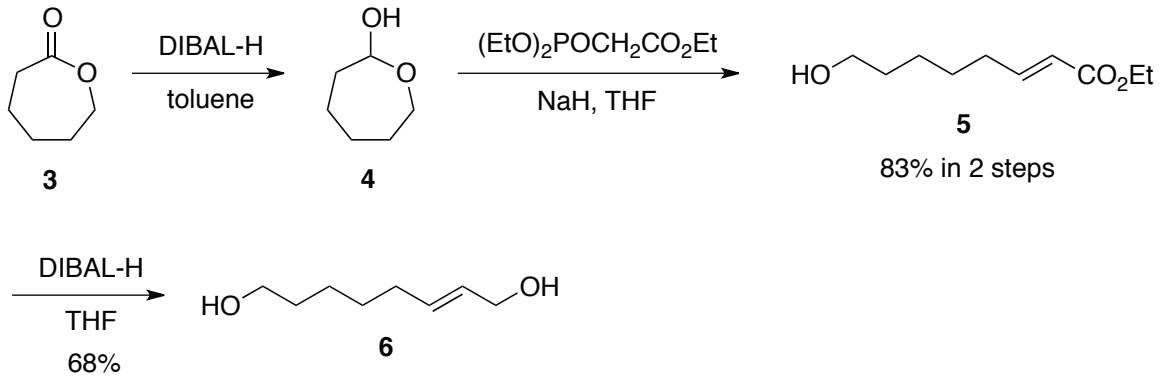
We have developed a stereoselective construction of cyclic ether via Pd(II)-catalyzed intramolecular *O*-alkylation of alcohol (Scheme 1), providing a powerful tool for construction of five- and six-membered heterocyclic ring systems.[2] Herein, we show that cyclic ethers containing seven-membered ring can be constructed using the same method.



1 **2**

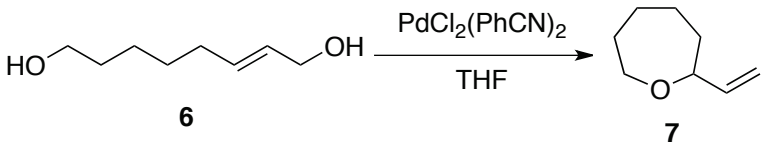
Scheme 1

We first investigated the cyclization reaction of oct-2-ene-1,8-diol (**6**)[3] in the presence of Pd(II)catalyst. The diol **6** was prepared from ε-caprolactone (**3**) as shown in Scheme 2. Reduction of ε-caprolactone with DIBAL-H in toluene gave the lactol **4**, which was converted to the α,β-unsaturated ester **5** in 83% yield over 2 steps. Reduction of **5** with DIBAL-H in THF gave the diol **6** in 68% yield.



Scheme 2

On the basis of our previous work,[4] cyclization was conducted with $PdCl_2(PhCN)_2$. Cyclization of **6** proceeded in the presence of 20 mol% of $PdCl_2(PhCN)_2$ in THF (10 mL/mmol) at room temperature to afford the 7-membered cyclic ether **7** in 63% yield without dimer formation. We next investigated the effect of concentration on the reaction. When the cyclization was conducted in more concentrated THF solution (0.5 M), the yield was little changed and again no dimer formation was observed (entry 2). Decreasing the amount of $PdCl_2(PhCN)_2$ to 5 mol% afforded the product **7** in 52% yield (entry 3).



Scheme 3

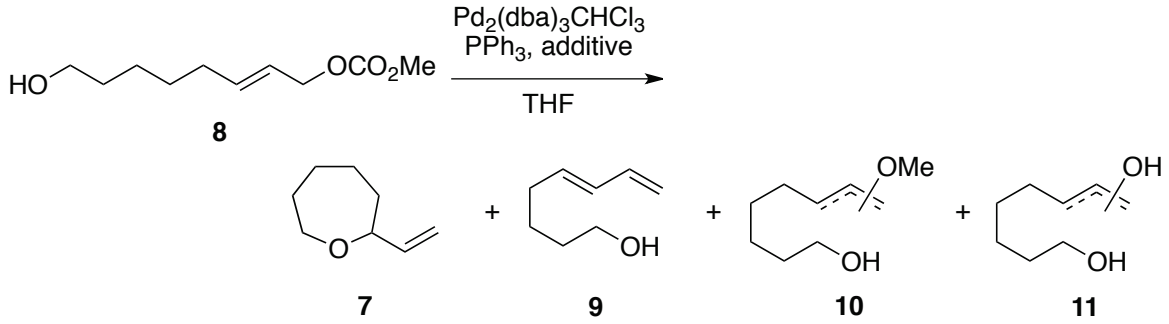
Table 1. Pd(II)-Catalyzed intramolecular cyclization of oct-7-ene-1,8-diol (**6**)[a]

Entry	Pd cat. (mol%)	Conc. [M]	Time (h)	Yield[b] (%)
1	20	0.1	6	63
2	20	0.5	2.5	58
3	5	0.5	5	52

[a] Reactions were carried out at room temperature in THF.
[b] Isolated yield.

We also compared the cyclization using Pd(0) catalyst and Pd(II) catalyst (Table 2). We prepared the allyl methyl carbonate **8** from the alcohol **5** in 3 steps. Treatment of the carbonate **8** with $Pd(PPh_3)_n$ in THF afforded the diene **9** and the allylic alcohol **11**, instead of the cyclized product **7** (entry 1).[5] When NaH was used to increase the nucleophilicity of the alcohol, the cyclized product was again not formed, although the allyl methyl ether **10** and the allylic alcohol **11** were formed (entry 2).

Next, we considered synthesis of the 6,7-fused cyclic ether (Table 3). The cyclization of the diol **12a** proceeded very smoothly in the presence of 10 mol% of $PdCl_2(PhCN)_2$ in THF at room temperature, affording the benzoxepin **13a** in 84% yield (entry 1).



Scheme 4

Table 2. The reaction of carbonate **8** using Pd(0) catalyst[a]

Entry	Additive	Time (h)	Yield[b] (%)	Ratio **7** : **9** : **10** : **11**
1	-	1.5	53	0 : 1.3 : 0 : 1
2	NaH	0.5	82	0 : 0 : 2.3 : 1

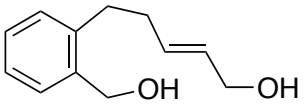
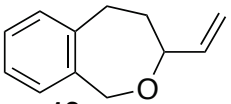
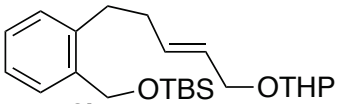
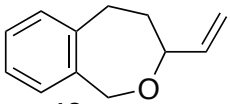
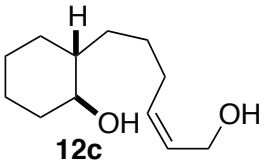
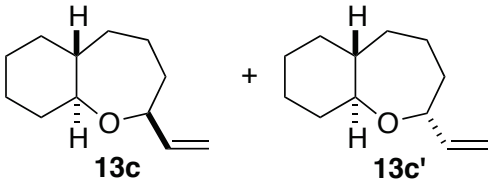
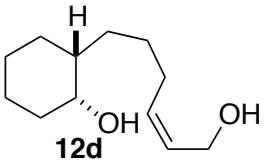
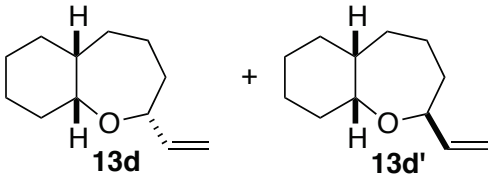
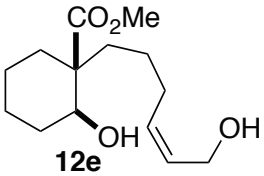
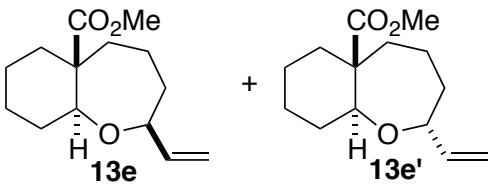
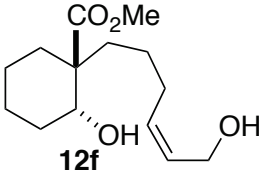
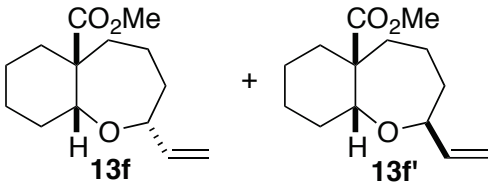
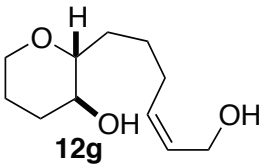
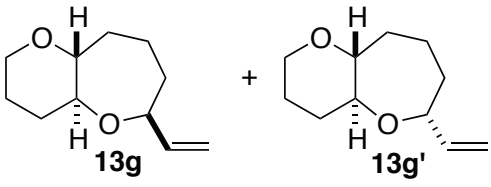
[a] Reactions were carried out at room temperature in THF with carbonate **8**, $Pd_2(dba)_3CHCl_3$ (5 mol%), and PPh_3 (20 mol%).
[b] Total yield of **9**, **10**, and **11**.

The cyclization of the TBS and THP protected substrate **12b** proceeded more slowly than that of **12a** and the isolated yield of **13a** was decreased to 27% (entry 2). In this case, the substrate **12b** was led to the diol **12a** by using 2-propanol and Pd(II) catalyst as a Lewis acid, and then cyclization proceeded. Cyclization of **12c** and **12d** gave the *trans*-fused and *cis*-fused oxepins **13c**, **13c'** and **13d**, **13d'**, respectively, in moderate yield (entries 3 and 4). The stereoselectivity of 1,3-*trans* : 1,3-*cis* was almost constant at 60 : 40 to 65 : 35. The epimers were easily separated by silica gel column chromatography. The methoxycarbonyl substrates **12e** and **12f** afforded almost the same yield and stereoselectivity of the oxepin (entries 5 and 6). Finally, substrate **12g** afforded the oxepin as a 30 : 70 mixture of **13g** : **13g'** in 63% yield (entry 7).

The relative stereochemistry of **13** was established by NOE experiments. For example, as shown in Figure 1, NOE correlation of **13c** was observed between the C-9a hydrogen and the C-2 α-hydrogen, whereas no NOE correlation was observed between C-9a hydrogen and C-2 β-hydrogen of **13'**.

In summary, we have found that oct-2-ene-1,8-diol derivatives undergo facile palladium(II)-catalyzed intramolecular cyclization to provide perhydrooxepins. The cyclization does not require high dilution, and the dimer was not formed.

Table 3. Pd(II)-Catalyzed intramolecular cyclization to affod 7-membered cyclic ether fused to a 6-membered ring[a]

Entry	Substrate	Time (h)	Product	Yield (%)[b]	Ratio
1[c]	 **12a**	1.5	 **13a**	84	-
2[d]	 **12b**	6	 **13a**	27	-
3	 **12c**	23	 **13c** + **13c'**	54	60 : 40
4	 **12d**	16.5	 **13d** + **13d'**	51	65 : 35
5	 **12e**	23	 **13e** + **13e'**	58	55 : 45
6	 **12f**	23	 **13f** + **13f'**	56	70 : 30
7	 **12g**	23	 **13g** + **13g'**	63	30 : 70

[a] Reactions were carried out at room temperature in THF (20 mL/mmol) with $PdCl_2(PhCN)_2$ (20 mol%).
[b] Isolated yield.
[c] $PdCl_2(PhCN)_2$ (10 mol%) was used.
[d] $PdCl_2(PhCN)_2$ (30 mol%) and 2-propanol (10 equiv.) were used.

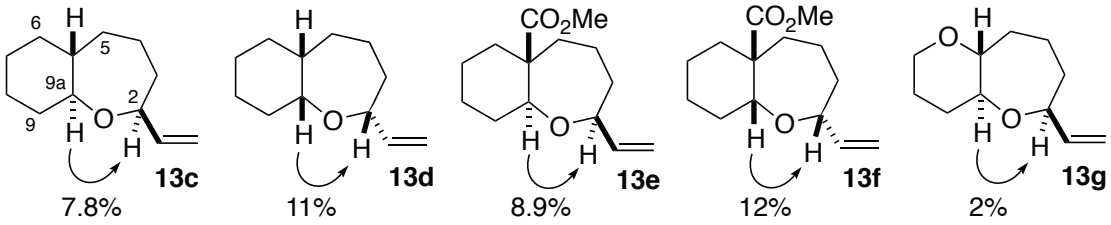


Figure 1. NOE correlations in the 6,7-fused perhydrooxepins **13c**-**13g**

EXPERIMENTAL

General Remarks: All moisture sensitive reactions were carried out under an argon atmosphere. Anhydrous solvents were obtained as follows: tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were purchased from Kanto Chemical Co., Ltd.; toluene was distilled from Na. Column chromatography was performed with Silica gel 60N and Fuji BW-820. Analytical thin layer chromatography (TLC) was conducted on precoated TLC plates (silica gel $60F_{254}$, Merck) visualized under UV light and stained with either phosphomolybdic acid or *p*-anisaldehyde. IR spectra were measured with a JASCO Model FT/IR-6100 spectrometer. High resolution mass spectra (HRMS) were recorded at a JEOL JMS-700 spectrometer or a SHIMADZU LCMS-IT-TOF. ^{1}H NMR spectra were recorded at 600 MHz with a JEOL JNM-ECP 600 using tetramethylsilane (TMS) as the internal standard (0.00 ppm). Chemical shifts were reported in ppm (δ) downfield from TMS. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet. ^{13}C NMR spectra were recorded at 75 MHz with a JEOL JNM-ECX 300 spectrometer with chemical shifts reported in ppm (δ).

Ethyl (*E*)-8-Hydroxyoct-2-enoate (5). To a solution of ε-caprolactone (2.29 g, 20 mmol) in toluene (150 mL) was added slowly dropwise diisobutylaluminum hydride (DIBAL-H) (20 mL, 20 mmol) at -78 ºC under an Ar atmosphere, and the mixture was stirred for 10 min. The reaction mixture was quenched with 10% HCl aqueous solution. The aqueous phase was extracted with AcOEt (3 times). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo to give the crude lactol.

To a suspension of NaH (729 mg, 16.7 mmol) in THF (90 mL) was added diethyl phosphonoacetic acid ethyl ester (3.6 mL, 18.2 mmol) at 0 ºC under an Ar atmosphere and the mixture was stirred for 30 min. The reaction mixture was cooled to -78 ºC. To the reaction mixture was added the crude lactol (1.76 g, 15.2 mmol) at -78 ºC, and the mixture was stirred for 10 min. The reaction mixture was quenched with saturated aqueous NH_4Cl and the resulting mixture was extracted with AcOEt (3 times).

The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/ AcOEt, 85 : 15) to afford the ester (2.35 g, 83% in 3 steps) as a colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 6.92 (dt, J = 15.8, 7.0 Hz, 1H),

5.78 (dt, *J* = 15.8, 1.5 Hz, 1H), 4.15 (q, *J* = 7.3 Hz, 2H), 3.60 (t, *J* = 6.6 Hz, 2H), 2.18 (ddt, *J* = 7.3, 7.0, 1.5 Hz, 2H), 1.54 (tt, *J* = 7.3, 6.6 Hz, 2H), 1.46 (tt, *J* = 7.7, 7.3 Hz, 2H), 1.39-1.35 (m, 2H), 1.25 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 166.7, 149.1, 121.4, 62.6, 60.1, 32.4, 32.0, 27.7, 25.2, 14.2; IR (neat) cm^{-1} 3421, 2934, 2861, 1719, 1654.

(*E*)-Oct-2-ene-1,8-diol (6). To a solution of the unsaturated ester (88 mg, 0.47 mmol) in THF (5 mL) was added slowly dropwise diisobutylaluminum hydride (1.2 mL, 1.2 mmol) at –78 ºC under an Ar atmosphere and the mixture was stirred for 30 min. The reaction mixture was quenched with 10 % HCl aqueous solution. The aqueous phase was extracted with AcOEt (3 times). The combined organic layers were washed with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane / AcOEt 70 : 30) to afford the diol **6** (46.3 mg, 68%) as a colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.65 (dt, *J* = 15.4, 6.2 Hz, 1H), 5.60 (dt, *J* = 15.4, 5.9 Hz, 1H), 4.04 (d, *J* = 5.9 Hz, 2H), 3.59 (t, *J* = 6.6 Hz, 2H), 2.04 (dt, *J* = 7.0, 6.6 Hz, 2H), 1.54 (tt, *J* = 7.0, 6.6 Hz, 2H), 1.42-1.32 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 133.0, 129.1, 63.6, 62.7, 32.4, 32.0, 28.8, 25.1; IR (neat) cm^{-1} 3318, 2931, 2857, 1459.

2-Vinyloxepane (7). To a solution of the allyl alcohol (15 mg, 0.10 mmol) in THF (1 mL) was added bis(benzonitrile)palladium (II) dichloride (8.0 mg, 0.020 mmol) at room temperature under an Ar atmosphere, and the mixture was stirred for 6 h. The reaction mixture was diluted with Et_2O. The organic layer was filtered through a pad of silica gel and followed by a pad of florisil sequentially with Et_2O. The organic layers were concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt, 99 : 1) to afford the cyclic ether **7** (8.2 mg, 63%) as a colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.87 (ddd, *J* = 17.2, 10.6, 5.1 Hz, 1H), 5.20 (ddd, *J* = 17.2, 1.8, 1.8 Hz, 1H), 5.05 (ddd, *J* = 10.6, 1.8, 1.8 Hz, 1H), 4.04 (ddddd, *J* = 9.2, 5.2, 4.0, 1.8, 1.8 Hz, 1H), 3.84 (ddd, *J* = 12.5, 6.6, 4.0 Hz, 1H), 3.62 (ddd, *J* = 12.5, 7.3, 4.0 Hz, 1H), 1.89-1.84 (m, 2H), 1.79-1.72 (m, 2H), 1.69-1.64 (m, 2H), 1.61-1.52 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 140.5, 113.9, 79.6, 68.1, 35.9, 31.5, 27.5, 25.7; IR (neat) cm^{-1} 1734, 1216; HRMS (IT-TOF) calcd. for $C_8H_{15}O$ ($[M+H]^+$) 127.1124, found 127.1077.

General procedure for synthesis of 6,7-fused cyclic ethers 13 and 13'. To a solution of the allyl alcohol **12** (0.10 mmol) in THF (2 mL) was added bis(benzonitrile)palladium(II) dichloride (7.7 mg, 0.02 mmol) at room temperature under an Ar atmosphere, and the mixture was stirred for 23 h. The reaction mixture was diluted with Et_2O. The organic layer was filtered through a pad of silica gel and followed by a pad of florisil sequentially with Et_2O. The filtrate was concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/AcOEt) to afford the cyclic ethers **13** and **13'**.

1,3,4,5-Tetrahydro-3-vinyl-2-benzoxepin (13a): a colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.22-7.13 (m, 4H), 5.90 (ddd, *J* = 17.3, 10.7, 5.6 Hz, 1H), 5.26 (ddd, *J* = 17.3, 1.7, 1.5 Hz, 1H), 5.11 (ddd, *J* = 10.7, 1.5, 1.5 Hz, 1H), 4.74 (d, *J* = 13.7 Hz, 1H), 4.73 (d, *J* = 13.9 Hz, 1H), 4.28-4.24 (m, 1H), 3.13

(ddd, *J* = 14.9, 12.2, 2.0 Hz, 1H), 2.92 (ddd, *J* = 14.9, 6.8, 1.7 Hz, 1H), 1.99 (dddd, *J* = 14.2, 6.8, 2.2, 2.0 Hz, 1H), 1.67 (dddd, *J* = 14.2, 12.2, 10.5, 1.7 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 142.0, 139.8, 139.5, 129.1, 128.4, 127.9, 126.2, 114.6, 85.1, 73.3, 34.8; 34.0; IR (neat) cm^{-1} 3066, 3019, 2933, 2843, 1646, 1494, 1454, 1374, 1300, 991, 923, 758, 722; HRMS (FAB) calcd. for $C_{12}H_{14}ONa$ ([M+Na]$^+$) 197.0943, found 197.0921.

***rel*-(2*R*,5a*S*,9a*R*)-Decahydro-2-vinyl-1-benzoxepin (13c):** a colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.88 (ddd, *J* = 17.3, 10.7, 4.7 Hz, 1H), 5.20 (ddd, *J* = 17.2, 1.8, 1.8 Hz, 1H), 5.03 (ddd, *J* = 10.6, 1.8, 1.8 Hz, 1H), 4.13-4.10 (m, 1H), 2.99 (ddd, *J* = 10.8, 9.7, 4.8 Hz, 1H), 1.98-1.94 (m, 1H), 1.82-1.12 (m, 12H), 1.03-0.96 (m, 1H), 0.89-0.86 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 140.6, 113.3, 84.6, 79.6, 35.3, 34.8, 34.3, 33.4, 29.7, 25.7, 25.4, 22.8; IR (neat) cm^{-1} 2925, 2856, 1450, 1093, 1074, 917; HRMS (IT-TOF) calcd. for $C_{12}H_{21}O$ ([M+H]$^+$) 181.1593, found 181.1597.

***rel*-(2*R*,5a*R*,9a*S*)-Decahydro-2-vinyl-1-benzoxepin (13c'):** a colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.91 (ddd, *J* = 17.3, 10.7, 4.7 Hz, 1H), 5.20 (ddd, *J* = 17.4, 1.8, 1.8 Hz, 1H), 5.08 (ddd, *J* = 10.8, 1.7, 1.7 Hz, 1H), 4.21 (ddd, *J* = 11.1, 5.4, 5.4 Hz, 1H), 3.18 (ddd, *J* = 10.4, 10.2, 4.6 Hz, 1H), 1.96-1.92 (m, 1H), 1.90-1.88 (m, 1H), 1.80-1.76 (m, 1H), 1.74-1.70 (m, 3H), 1.64-1.57 (m, 3H), 1.52-1.46 (m, 1H), 1.35-1.24 (m, 1H), 1.22-1.10 (m, 2H), 1.08-1.02 (m, 1H), 0.96-0.89 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 140.5, 113.2, 84.6, 79.5, 47.5, 35.2, 34.8, 34.3, 33.3, 25.7, 25.4, 22.8; IR (neat) cm^{-1} 2926, 2856, 1450, 1150, 1084; HRMS (IT-TOF) calcd. for $C_{12}H_{21}O$ ([M+H]$^+$) 181.1593, found 181.1542.

***rel*-(2*R*,5a*R*,9a*R*)-Decahydro-2-vinyl-1-benzoxepin (13d):** a colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.86 (ddd, *J* = 17.1, 10.5, 5.1 Hz, 1H), 5.23 (ddd, *J* = 17.4, 1.8, 1.8 Hz, 1H), 5.03 (ddd, *J* = 10.2, 1.8, 1.8 Hz, 1H), 4.06-4.03 (m, 1H), 3.73 (ddd, *J* = 6.0, 3.5, 3.5 Hz, 1H), 1.83-1.76 (m, 2H), 1.73-1.68 (m, 2H), 1.66-1.57 (m, 3H), 1.55-1.42 (m, 5H), 1.39-1.32 (m, 2H), 1.31-1,24 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 141.3, 113.5, 78.5, 77.1, 40.5, 37.5, 32.9, 32.4, 30.4, 25.0, 23.6, 22.5; IR (neat) cm^{-1} 2928, 2855, 1644, 1448; HRMS (FAB) calcd. for $C_{12}H_{20}ONa$ ([M+Na]$^+$) 203.1412, found 203.1408.

***rel*-(2*S*,5a*R*,9a*R*)-Decahydro-2-vinyl-1-benzoxepin (13d'):** a colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.92 (ddd, *J* = 17.2, 10.7, 4.4 Hz, 1H), 5.20 (ddd, *J* = 17.4, 1.8, 1.8 Hz, 1H), 5.08 (ddd, *J* = 10.2, 1.7, 1.7 Hz, 1H), 4.25-4.21 (m, 1H), 3.82 (br, 1H), 1.96-1.91 (m, 1H), 1.84-1.77 (m, 2H), 1.76-1.68 (m, 2H), 1.67-1.57 (m, 4H), 1.55-1.46 (m, 4H), 1.44-1.33 (m, 1H), 1.16-1.14 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 140.5, 114.2, 76.8, 69.5, 41.0, 37.0, 35.2, 33.8, 27.6, 26.7, 21.4, 20.9; IR (neat) cm^{-1} 2927, 2856, 1643, 1445; HRMS (FAB) calcd. for $C_{12}H_{20}ONa$ ([M+Na]$^+$) 203.1412, found 203.1401.

***rel*-(2*R*,5a*R*,9a*R*)-Decahydro-5a-methoxycarbonyl-2-vinyl-1-benzoxepin (13e):** a colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.84 (ddd, *J* = 17.1, 10.5, 6.0 Hz, 1H), 5.19 (ddd, *J* = 17.4, 1.5, 1.5 Hz, 1H), 5.02 (ddd, *J* = 10.8, 1.4, 1.4 Hz, 1H), 4.16 (ddd, *J* = 6.0, 5.6, 5.6 Hz, 1H), 3.70 (s, 3H), 3.26 (dd, *J* = 12.3,

4.5 Hz, 1H), 2.19 (ddd, *J* = 14.1, 6.3, 2.4 Hz, 1H), 2.13 (dd, *J* = 11.7, 3.9 Hz, 1H), 1.99 (dd, *J* = 13.2, 1.8 Hz, 1H), 1.88-1.58 (m, 6H), 1.47-1.45 (m, 1H), 1.31 (ddd, *J* = 14.1, 11.1, 3.0 Hz, 1H), 1.27-1.15 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 174.1, 140.5, 113.1, 81.1, 77.6, 52.3, 50.9, 40.0, 36.5, 33.7, 29.8, 24.4, 21.7, 19.6; IR (neat) cm^{-1} 2932, 2860, 1715, 1448, 1220, 1192, 1174, 1132, 1111, 1095; HRMS (IT-TOF) calcd. for $C_{14}H_{23}O_3$ ([M+H]$^+$) 239.1648, found 239.1591.

***rel*-(2*S*,5a*R*,9a*R*)-Decahydro-5a-methoxycarbonyl-2-vinyl-1-benzoxepin (13e'):** a colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.93 (ddd, *J* = 17.3, 10.7, 5.0 Hz, 1H), 5.20 (ddd, *J* = 17.4, 1.5, 1.5 Hz, 1H), 5.10 (ddd, *J* = 10.2, 1.5, 1.5 Hz, 1H), 4.22 (ddd, *J* = 11.8, 5.7, 5.7 Hz, 1H), 3.71 (s, 3H), 3.35 (dd, *J* = 11.7, 5.1 Hz, 1H), 2.42 (ddd, *J* = 13.8, 3.0, 3.0 Hz, 1H), 2.19 (dddd, *J* = 12.7, 12.7, 12.5, 4.4 Hz, 1H), 2.00-1.93 (m, 2H), 1.74-1.67 (m, 3H), 1.65-1.57 (m, 1H), 1.43-1.40 (m, 1H), 1.37-1.29 (m, 1H), 1.22-1.12 (m, 1H), 1.06-1.00 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 175.2, 139.7, 114.8, 74.7, 52.2, 51.3, 43.4, 37.7, 34.0, 30.9, 29.7, 25.0, 22.5, 21.7; IR (neat) cm^{-1} 2928, 2856, 1729, 1456, 1223, 1191, 1176, 1147, 1120, 1073; HRMS (IT-TOF) calcd. for $C_{14}H_{23}O_3$ ([M+H]$^+$) 239.1648, found 239.1603.

***rel*-(2*R*,5a*S*,9a*R*)-Decahydro-5a-methoxycarbonyl-2-vinyl-1-benzoxepin (13f):** a colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.88 (ddd, *J* = 17.4, 10.8, 4.8 Hz, 1H), 5.24 (ddd, *J* = 17.4, 1.8, 1.8 Hz, 1H), 5.05 (ddd, *J* = 10.8, 2.0, 2.0 Hz, 1H), 4.15 (br s, 1H), 4.01 (ddd, *J* = 9.8, 4.4, 4.4 Hz, 1H), 3.69 (s, 3H), 1.96 (br d, *J* = 13.8 Hz, 1H), 1.91-1.85 (m, 2H), 1.83-1.81 (m, 1H), 1.75-1.68 (m, 1H), 1.66-1.53 (m, 5H), 1.50-1.37 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 177.4, 140.6, 113.8, 82.8, 77.9, 52.0, 51.0, 40.7, 38.5, 32.5, 31.0, 23.9, 21.1, 20.4; IR (neat) cm^{-1} 2935, 2862, 1725, 1452, 1241, 1204, 1154, 1061, 1011; HRMS (IT-TOF) calcd. for $C_{14}H_{23}O_3$ ([M+H]$^+$) 239.1648, found 239.1582.

***rel*-(2*R*,5a*R*,9a*S*)-Decahydro-5a-methoxycarbonyl-2-vinyl-1-benzoxepin (13f'):** a colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.96 (ddd, *J* = 17.4, 10.8, 4.8 Hz, 1H), 5.21 (ddd, *J* = 16.8 , 1.5, 1.5 Hz, 1H), 5.16 (ddd, *J* = 10.8, 1.7, 1.7 Hz, 1H), 4.29-4.26 (m, 1H), 4.16 (br s, 1H), 3.67 (s, 3H), 1.97-1.92 (m, 1H), 1.86 (ddd, *J* = 12.9, 12.9, 4.2 H, 1H), 1.70-1.58 (m, 10 H), 1.46-1.40 (m, 1H), 1.37-1.26 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 177.3, 139.4, 115.2, 76.5, 69.1, 51.6, 51.1, 41.5, 33.9, 30.8, 28.8, 23.0, 20.6, 19.4; IR (neat) cm^{-1} 2934, 2861, 1728, 1446, 1241, 1205, 1148, 1090, 1062; HRMS HRMS (IT-TOF) calcd. for $C_{14}H_{23}O_3$ ([M+H]$^+$) 239.1648, found 239.1589.

***rel*-(4a*R*,6*R*,9a*S*)-Octahydro-6-vinyl-2*H*-pyrano[3,2-*b*]oxepin (13g):** a colorless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 5.84 (ddd, *J* = 17.2, 10.6, 5.5 Hz, 1H), 5.22 (ddd, *J* = 17.2, 1.5, 1.5 Hz, 1H), 5.06 (ddd, *J* = 10.6, 1.5, 1.5 Hz, 1H), 4.17 (ddddd, *J* = 5.5, 5.5, 1.5, 1.5, 1.5 Hz, 1H), 3.87 (dddd, *J* = 11.4, 4.4, 1.8, 1.8 Hz, 1H), 3.32 (ddd, *J* = 11.4, 3.7, 3.7 Hz, 1H), 3.17 (ddd, *J* = 11.0, 9.2, 4.8 Hz, 1H), 3.06 (ddd, *J* = 9.2, 5.1, 5.1 Hz, 1H), 2.11-2.07 (m, 1H), 2.05-2.01 (m, 1H), 1.87-1.81 (m, 1H), 1.73-1.59 (m, 5H), 1.52-1.43 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 140.5, 114.0, 81.5, 70.3, 66.8, 60.5, 36.2, 33.3, 31.6, 25.4, 20.2;

IR (neat) cm^{-1} 2926, 2856, 1642, 1447; HRMS (FAB) calcd. for $C_{11}H_{18}O_2Na$ ($[M+Na]^+$) 205.1205, found 205.1223.

***rel*-(4a*S*,6*R*,9a*R*)-Octahydro-6-vinyl-2*H*-pyrano[3,2-*b*]oxepin (13g'):** a colorless oil; ^1H NMR (600 MHz, $CDCl_3$) δ: 5.89 (ddd, *J* = 17.2, 10.6, 4.4 Hz, 1H), 5.21 (ddd, *J* = 17.2, 1.5, 1.5 Hz, 1H), 5.12 (ddd, *J* = 10.6, 1.5, 1.5 Hz, 1H), 4.19 (ddddd, *J* = 11.4, 6.2, 4.4, 1.5, 1.5 Hz, 1H), 3.84 (ddd, *J* = 11.4, 4.0, 1.8, 1.8 Hz, 1H), 3.30 (ddd, *J* = 11.4, 3.3, 3.3 Hz, 1H), 3.25 (ddd, *J* = 11.0, 9.2, 5.1 Hz, 1H), 3.08 (ddd, *J* = 10.3, 9.2, 5.5 Hz, 1H), 2.15-2.11 (m, 1H), 2.05-2.01 (m, 1H), 1.99-1.94 (m, 1H), 1.76-1.71 (m, 1H), 1.66-1.50 (m, 4H), 1.46-1.39 (m, 1H), 1.30-1.23 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 139.4, 114.3, 81.7, 70.2, 70.1, 67.2, 36.6, 33.7, 31.9, 25.6, 20.3; IR (neat) cm^{-1} 2927, 2855, 1640, 1449; HRMS (FAB) calcd. for $C_{11}H_{18}O_2Na$ ($[M+Na]^+$) 205.1205, found 205.1219.

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