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SYNTHESIS OF 2-SUBSTITUTED 1,3-CYCLOHEPTANEDIONE VIA A LEWIS ACID MEDIATED RING EXPANSION REACTION

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This paper is dedicated to Professor Victor Snieckus on the occasion of his 77th birthday.

Abstract – We have established a new route to provide 2-substituted 1,3-cycloheptanediones *via* a Lewis acid mediated ring expansion reaction of cyclobutanones as the key step. The ring expansion reactions were mediated by a series of Lewis acids. Among the used Lewis acids, ZnI_2 was the most practical mediator. This route has succeeded in providing the title compounds even on a multi-gram scale. During the research, the Baeyer-Villiger oxidation of the cyclobutanones to obtain the new bicyclic lactones was also examined. The regioselective oxidation was observed in the case of chlorinated cyclobutanones.

INTRODUCTION

We have recently established the chiral preparation of a Wieland-Miescher ketone analogue (**1b**) from 2-methyl-1,3-cycloheptanedione (**2b**).[1] The several chiral amines bearing a heterocyclic moiety, such as pyrrolidine, tetrazole, or piperazine, mediated the asymmetric intramolecular aldol reaction of the trione (**3**) in the presence of trifluoroacetic acid (TFA) to afford **1b** in an enantioselective fashion.[1c] Among the chiral amines, (*S*)-2-amino-1-phenyl-3-(pyrrolidin-1-yl)propane (**4**) was one of the most effective mediator to afford (*R*)-**1b** in high yield accompanied with over 80% ee. In connection with an ongoing synthetic project, we needed to prepare **2** bearing a variety of substituents (R^1). However, there have been few reports regarding the preparation of 2-substituted 1,3-cycloheptanediones (**2**) except for only limited substituents (R^1) such as methyl and ethyl groups (Figure 1).[2-4]

For example, Hirsch *et al*. reported that the direct *C*-ethylation of **2a** afforded **2c** in low yield along with 3-ethoxy-2-cycloheptenone as a major product.[4a] The limited direct alkylation of **2a** under basic conditions has also been reported by Swaminathan *et al*. They succeeded in preparation of **2b** and **2c** along with the recovery of the starting **2a**.[4b]

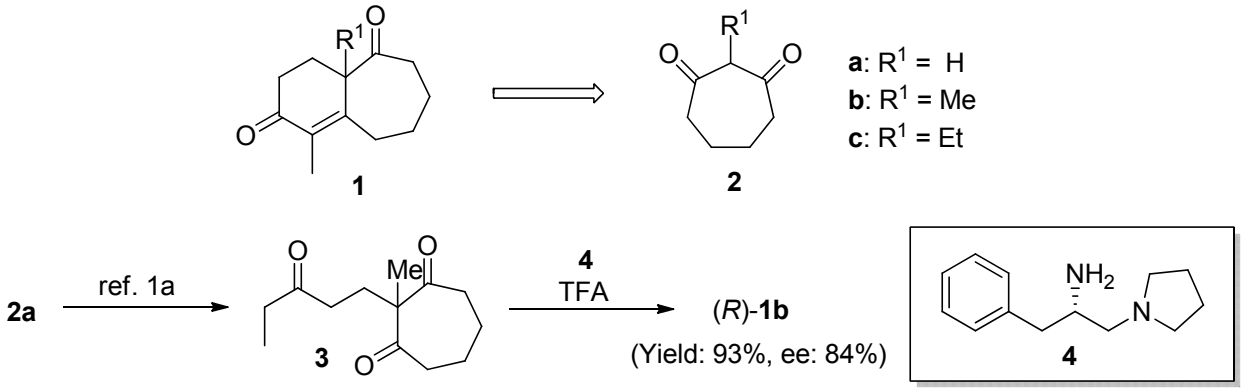
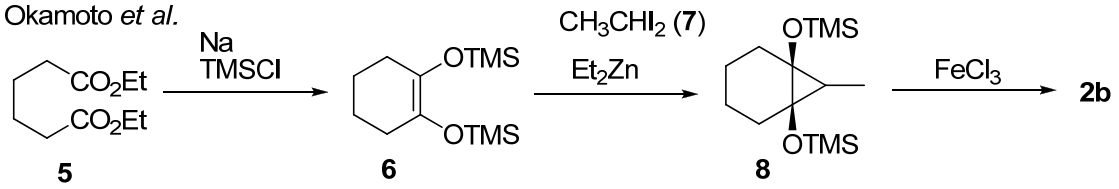
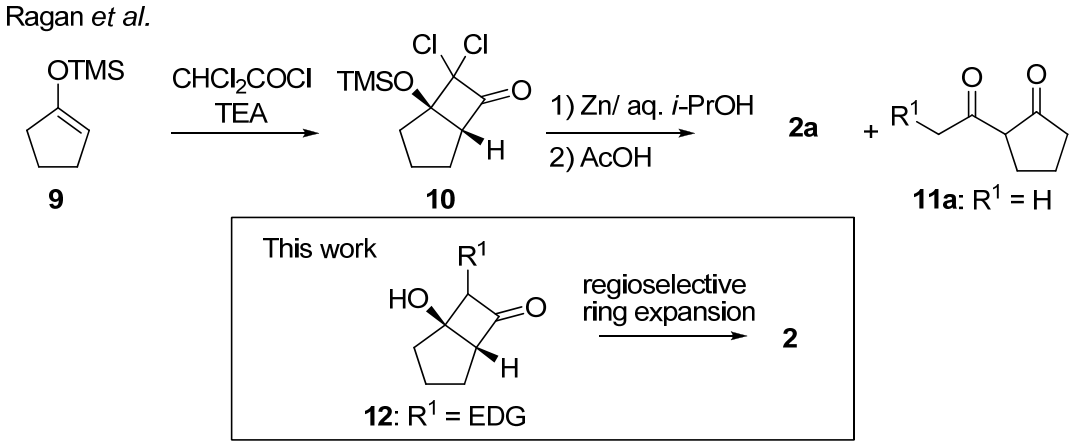


Figure 1. Preparation of Wieland-Miescher ketone analogue (**1**) bearing a 7-membered ring

Okamura and co-workers have reported the preparation of **2b** from diethyl adipate (**5**) *via* an acyloin condensation, Simmos-Smith cyclopropanation, and subsequent oxidative ring expansion mediated by $FeCl_3$ (Scheme 1).[3c] There have been some problems concerning the difficulties of the acyloin condensation on a large scale and of the effective preparation of 1,1-diiodoethane (**7**).[5] Therefore, practical methods to prepare 2-substituted 1,3-cycloheptanedione (**2**) are still required.



Scheme 1



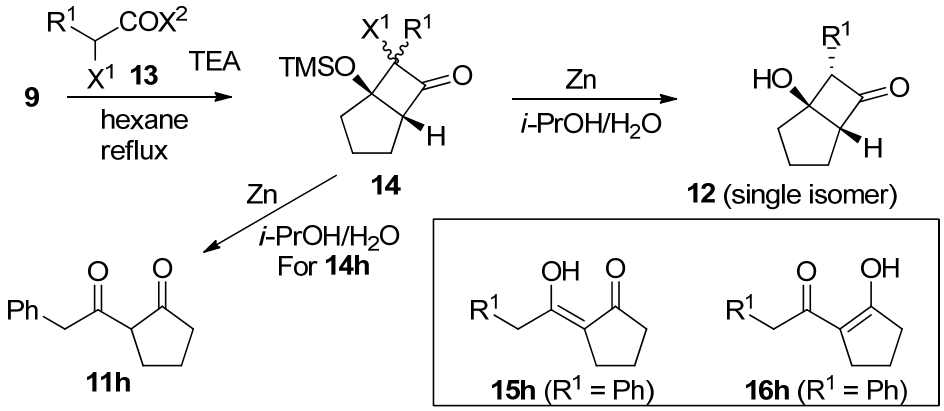
Scheme 2

We have been inspired by Ragan's synthesis of **2a** from **9** *via* the [2+2] cycloaddition and following zinc reduction of the chloride and the ring expansion of cyclobutanone.[2g] Although this process has been

effective, the undesired 2-acetylcyclopentanone (**11a**) sometimes has been predominantly obtained under slightly different reaction conditions, especially on a large scale.[2j] Also, it has been difficult to handle the compound (**10**) due to its instability during the purification process such as column chromatography or distillation. In Ragan's synthesis, we considered that the electron withdrawing dichloro substituents have promoted an undesired ring opening of the cyclobutanone in **10** and its instability against the purified process, and that the introduction of an electron donating group (EDG) on the cyclobutanone would be able to control the desired ring expansion to produce **2**. We now report the preparation of bicyclic cyclobutanones (**12**) bearing a series of substituents (R^1) and the regioselective ring expansion reaction of **12** mediated by Lewis acids to afford **2** (Scheme 2).

RESULTS AND DISCUSSION

First of all, we have started the [2+2] cycloaddition between **9**[2j,6] and ketenes, which were prepared from a variety of acid halides (**13**),[7-9] in the presence of triethylamine (TEA).[10,11] These results are summarized in Scheme 3 and Table 1. The chloroacetyl chloride (**13a**) and acetyl chloride (**13d**) hardly afforded **14a** or **14d**.[11] On the other hand, 2-chloropropionyl chloride (**13b**) afforded the desired **14b** as an inseparable mixture of two diastereomers regarding the methyl (R^1) and chloro (X^1) substituents. Based on these results, we considered that both the α-halo (X^1) and α-alkyl (R^1) substituents on **13** were needed to accelerate the effective [2+2] cycloaddition. The zinc reduction of **14b** without a further purification of diastereomers and following solvolysis of the trimethysilyl group in aqueous 2-propanol (*i*-PrOH) smoothly proceeded to afford **12b** as a single stereoisomer in 70% yield.



a: R^1 = H, X^1 = X^2 = Cl; **b**: R^1 = Me, X^1 = X^2 = Cl
c: R^1 = Et, X^1 = X^2 = Cl; **d**: R^1 = X^1 = H, X^2 = Cl
e: R^1 = Bn, X^1 = X^2 = Cl; **f**: R^1 = *i*-Pr, X^1 = Br, X^2 = Cl
g: R^1 = *i*-Bu, X^1 = X^2 = Cl; **h**: R^1 = Ph, X^1 = X^2 = Cl
i: R^1 = Me, X^1 = X^2 = Br

Scheme 3

We next examined versatile acid halides (**13**) bearing alkyl, branched alkyl and benzyl substituents (R^1) for these processes. Thus, the [2+2] cycloaddition using **13** and following zinc reduction afforded **12** as a single isomer (entries 3, 5-7). The α-bromo acid chloride (**13f**) and α-bromo acid bromide (**13i**) were also able to be used for the reaction. However, entry 9 showed that the zinc reduction of **14i** bearing an α-bromo substituent revealed a lower yield than that of the corresponding chloride compound (**14b**). When **13h** was used for the reaction, we could obtain **14h**, but the zinc reduction of **14h** afforded **11h** as a mixture of its tautomers (**15h** and/or **16h**) without the production of the desired **12h** (entry 8).[12] This result meant that an electron withdrawing substituent, such as a phenyl, at the α-position of the ketone (**14**) could not be used in this process. All of the compounds, (**12**) and (**14**), could be easily purified by silica gel column chromatography without any decomposition of the products. The reaction using 50 g of starting **9** also obtained almost the same results as entry 2 (entry 10).

Table 1. Preparation of the bicyclic butanones bearing the versatile substituents

Entry[a]	**13**	R^1	X^1	X^2	Yield[b] (**14**, %)	dr[c,d] (**14**)	Yield[b] (**12**, %)
1	**13a**	H	Cl	Cl	trace	ND[e]	NT[f]
2	**13b**	Me	Cl	Cl	62	63:37	70
3	**13c**	Et	Cl	Cl	56	85:15	54
4	**13d**	H	H	Cl	trace	ND[e]	NT[f]
5	**13e**	Bn	Cl	Cl	56	73:27	41
6	**13f**	*i*-Pr	Br	Cl	63	85:15	47
7	**13g**	*i*-Bu	Cl	Cl	95	83:17	61
8	**13h**	Ph	Cl	Cl	77	91:9	56[g]
9	**13i**	Me	Br	Br	39	27:73	26
10[h]	**13b**	Me	Cl	Cl	83	67:33	76

[a] 5 g of **9** was used in all reactions.

[b] Isolated yield.

[c] Diastereomeric ratio.

[d] Determined by ^{1}H-NMR of the crude products.

[e] Not determined.

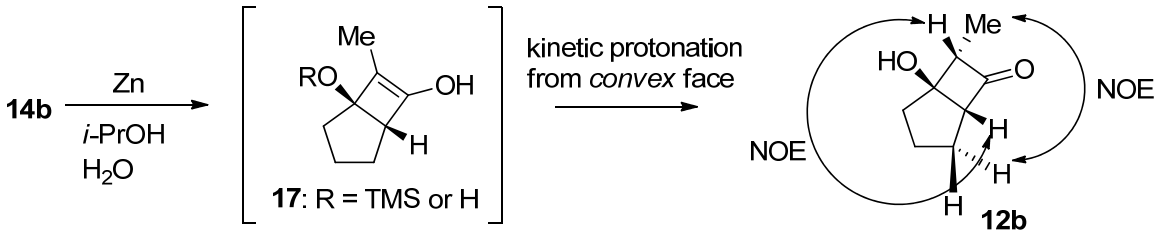
[f] Not treated.

[g] Yield of a mixture of **11h** and its tautomers (**15h** and/or **16h**). Compound (**12h**) was not observed.

[h] 50 g of **9** was used. The [2+2] cycloaddition with **13b** was carried out at room temperature.

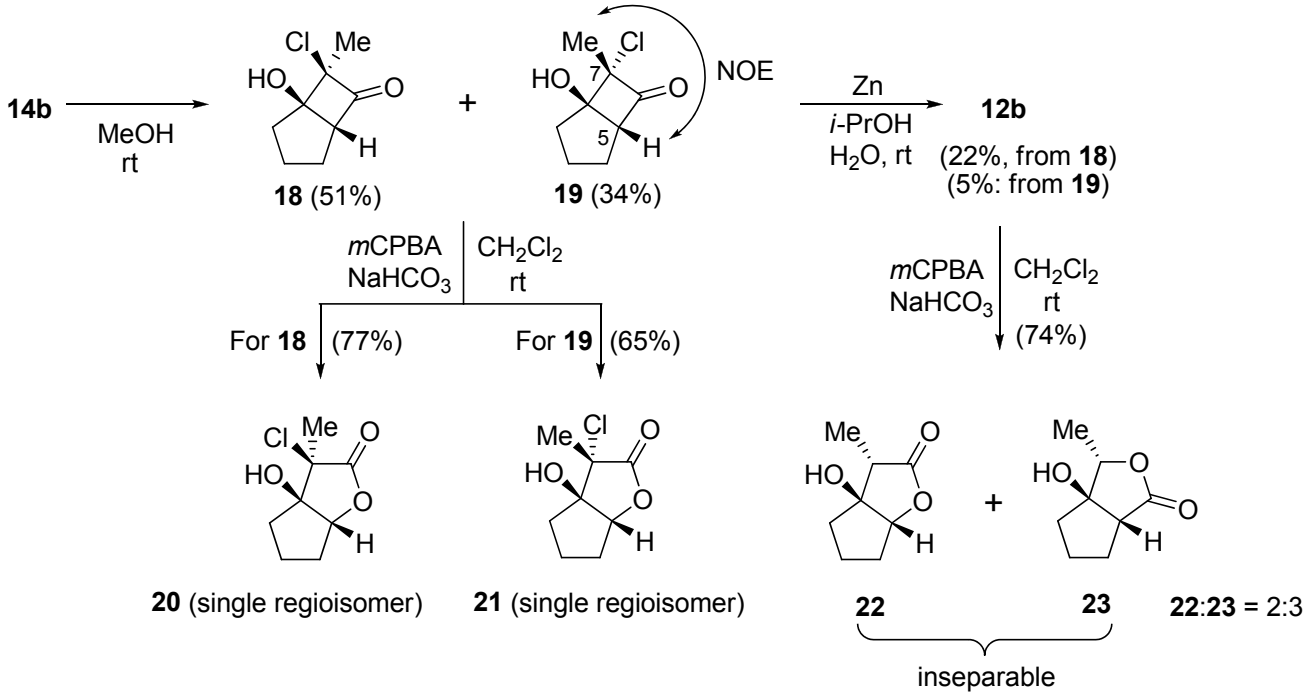
The relative configuration of **12b** was determined by NOE experiments as indicated in Scheme 4. From the NOE correlations, the stereochemistry between the methyl and hydroxyl substituents must be *trans*. The zinc reduction of the chloride in **14b** produced the enol (**17**), and the following kinetic protonation proceeded from a *convex* face of the bicyclo[3.2.0]heptane skeleton in **17** to afford **12b** as a single

stereoisomer (Scheme 4).



Scheme 4

As already described, **14b** was obtained as a mixture of diastereomers. As a mixture of the both diastereomers afforded **12b** as a single isomer, we next tried to separate them. Solvolysis of the TMS group in **14b** rapidly proceeded to afford **18** and **19**, which were readily separable by column chromatography. The NOE correlation between the methyl protons at C-7 and a methine proton at C-5 in **19** suggested the stereochemistry of **19** shown in Scheme 5. The zinc reduction of **18** and **19** respectively afforded **12b** and we could not observe any diastereomers of **12b** in both cases. These results support the kinetic protonation mechanism described above. However, the yields of **12b** in the both cases were very low, because of the decomposition of the starting **18** or **19** during the reactions (Scheme 5).

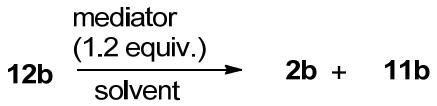


Scheme 5

At this stage, we examined the Baeyer-Villiger oxidation of the cyclobutanones to compare the electron

donating character at C-5 and C-7 between **12b** and **18** or **19**. Thus, the treatment of **18** or **19** with *m*-chloroperbenzoic acid (*m*CPBA) in the presence of sodium hydrogen carbonate respectively afforded the lactone **20** or **21** as a single regioisomer. On the other hand, **12b** afforded an inseparable mixture of **22** and **23** (**22**:**23** = 2:3) in 74% yield under the same reaction conditions (Scheme 5). These results showed us that C-7 in **18** or **19** was the electron withdrawing character due to the chloro substituent, and that both C-5 and C-7 in **12b** were almost the same electron donating character. Since the electron withdrawing chloro substituent in **18** or **19** would promote the undesired ring opening of the cyclobutanone moiety, **12b** was selected as a substrate for continued ring expansion reactions.

Table 2. Screening of the mediators for the ring expansion reaction of **12b**



Entry [a]	Mediator	Solvent	Temperature	Time (h)	Yield[b] (**2b**, %)	Yield[b,c] (**11b**, %)
1	AcOH	*i*-PrOH-H_2O	rt	-	NR[d]	-
2	*tert*-BuOK	THF	0 °C	2.5	13	50
3	*p*-TsOH	CH_2Cl_2	0 °C	47	46	19
4	$BF_3 \cdot OEt_2$	CH_2Cl_2	0 °C	0.5	52	8
5	$EtAlCl_2$	CH_2Cl_2	0 °C	1.5	37	10
6	Et_2AlCl	CH_2Cl_2	0 °C	21.5	9	11
7	$AlCl_3$	CH_2Cl_2	rt	109	56	2
8	$ZnCl_2$	CH_2Cl_2	rt	41.5	55	19
9	ZnI_2	CH_2Cl_2	rt	60	61	14
10	$ZrCl_4$	CH_2Cl_2	0 °C	0.1	46	23
11	$GaCl_3$	CH_2Cl_2	0 °C	0.2	50	14
12	$BiBr_3$	CH_2Cl_2	rt	1	41	25

[a] 100 mg of **12b** was used for the all reactions.

[b] Isolated yield.

[c] Yield of a mixture of **11b** and its tautomers (**15b** and/or **16b**).

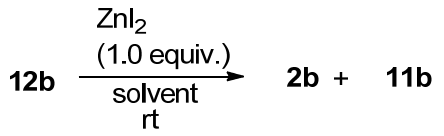
[d] No reaction.

Next, we examined the ring expansion reaction of **12b** mediated by Lewis acidic or basic conditions.[13,14] The results are summarized in Table 2. All the reactions were performed in the presence of 1.2 equivalents of the Lewis acidic or Lewis basic mediators to afford **2b** accompanied by **11b**, which were easily separable by silica gel column chromatography. The ^{1}H-NMR of **11b** in $CDCl_3$ suggested that **11b** was obtained as an inseparable 1:1 mixture of **11b** and its tautomers (**15b** and/or **16b**).[15] First of all, according to Ragan's method,[2g] **12b** was exposed to acetic acid in aqueous 2-propanol. However, no reaction was observed. Basic

conditions using potassium *tert*-butoxide (*t*-BuOK) in THF predominantly afforded the undesired **11b**. Although most of the Lewis acidic conditions predominantly afforded **2b**, the yields of **2b** varied. When $AlCl_3$ was used, the most selective reaction was observed. However, the yield of **2b** slightly decreased and a longer reaction time was required. The stronger Lewis acid, such as $ZrCl_4$ and $GaCl_3$, also rapidly promoted the reaction, however, both the regioselectivity and yield of the desired **2b** decreased. Since ZnI_2 exhibited the highest yield of **2b** among a variety of tested Lewis acids, we selected it as a mediator to develop further experiments.

We next examined the solvent effects of the ring expansion reaction of **12b** mediated by a stoichiometric amount of ZnI_2. The results are summarized in Table 3. Using nonprotic polar solvents, such as acetonitrile and THF, and a prolonged reaction time afforded the desired **2b** in a lower yield than those in dichloromethane or 1,2-dichloroethane. Less polar solvents, such as toluene and hexane, decreased the yield of **2b**. A catalytic reaction was also examined (entry 7). Thus, the reaction using 0.1 equivalent of ZnI_2 prolonged the reaction time to completion and afforded **2b** in a lower yield than the stoichiometric conditions. Therefore, we selected the stoichiometric ZnI_2 in dichloromethane for further experiments.

Table 3. Solvent effects for the ring expansion reaction of **12b**



Entry[a]	Solvent	Time (h)	Yield[b] (**2b**, %)	Yield[b,c] (**11b**, %)
1	CH_2Cl_2	60	61	14
2	THF	261	4	13
3	MeCN	261	13	26
4	DCE[d]	61.5	57	19
5	toluene	61.5	44	5
6	hexane	63	45	25
7[e]	CH_2Cl_2	166	50	8

[a] 100 mg of **12b** was used for the all reactions.

[b] Isolated yield.

[c] Yield of a mixture of **11b** and its tautomer (**15b** or **16b**).

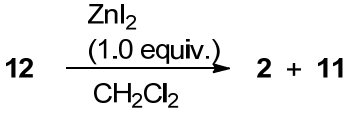
[d] 1,2-Dichloroethane

[e] 0.1 equiv. of ZnI_2 was used.

Finally, the optimized conditions for the ring expansion reaction were used with **12** bearing versatile substituents (Table 4). Most of the substrates (**12**) predominantly afforded known or unknown cycloheptanediones (**2**) accompanied by a tautomeric mixture of **11**, **15** and/or **16**. The reaction using 27 g

of **12b** was also examined to observe the shorter reaction time and the slightly lower yield of **2** than the case on a small scale (entry 6). We have succeeded in preparing a 2-substituted 1,3-cycloheptanedione bearing an alkyl, branched alkyl and benzyl groups.

Table 4. Ring expansion reactions of **12** mediated by ZnI_2



Entry	Substrate[a] (**12**)	R^1	Time (h)	Yield[b] (**2**, %)	Yield[b, c] (**11**, %)
1	**12b**	Me	60	61	14
2	**12c**	Et	44	62	21
3	**12e**	Bn	66	48	36
4	**12f**	*i*-Pr	38	69	19
5	**12g**	*i*-Bu	43	52	34
6	**12b**[d]	Me	20	53	29

[a] 0.1-1.5 g of **12** was used for all reactions.

[b] Isolated yield.

[c] Yield of a mixture of **11** and its tautomers (**15** and/or **16**).

[d] 27 g of **12b** was used.

In conclusion, we have established a new route to provide 2-substituted 1,3-cycloheptanediones (**2**) *via* a Lewis acid mediated ring expansion reaction of cyclobutanones (**12**) as the key step. The ring expansion reactions were mediated by a series of Lewis acids. Among the used Lewis acids, ZnI_2 was the most practical mediator. This route succeeded in providing the title compounds even on a multi-gram scale. During the research, the Baeyer-Villiger oxidation of the cyclobutanones to obtain the new bicyclic lactones was also examined. The regioselective oxidation was observed in the case of chlorinated cyclobutanones. The use of **2** to achieve the preparation of a new Wieland-Miescher ketone analogue (**1**) is currently in progress.

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a JEOL-AX-400 (^{1}H 400 MHz, ^{13}C 100 MHz) spectrometer and calibrated using trimethysilane as the internal standard. The mass spectra were recorded on a JEOL-DX-303 or JEOL JMS-MS700 spectrometer.

Typical procedure for [2+2] cycloaddition of 9 with 13 and subsequent zinc reduction of 14.

To a stirred solution of **9** (5 g, 32.1 mmol) and triethylamine (TEA, 8.0 mL, 57.7 mmol) in hexane (80 mL) was added 2-chlorobutyryl chloride (**13c**) (7.23 g, 51.3 mmol) in hexane (10 mL) in one portion at 0 ^{o}C.

After stirring the mixture at rt for 10 min, the mixture was heated to reflux for 17 h. After cooling, the mixture was filtered to remove the TEA hydrochloride and the filtrate was washed with saturated aqueous $NaHCO_3$ and brine. After drying (Na_2SO_4), the solvent was removed under reduced pressure. The residue was chromatographed (1% Et_2O-hexane to 2% Et_2O-hexane) to afford **14c** (4.76 g, 56%) as a 85:15 diastereomeric mixture and a pale yellow oil. The compound (**14c**) was used for the next reaction without further purification. To a stirred solution of **14c** (2.0 g, 7.68 mmol) in 2-propanol (20 mL) and H_2O (10 mL) was added zinc powder (2.51 g, 38.4 mmol) in one portion at rt. The mixture was stirred at the same temperature for 51 h. The mixture was filtered through a Celite pad and the filtrate was evaporated under reduced pressure. The residue was dissolved in AcOEt and the mixture was washed with saturated aqueous $NaHCO_3$ and brine. After drying (Na_2SO_4), the solvent was removed under reduced pressure. The residue was chromatographed (15% AcOEt-hexane) to afford **12c** (643 mg, 54%) as a single stereoisomer and a colorless oil.

(1*S, 5*R**, 7*S**)-7-Ethyl-1-hydroxybicyclo[3.2.0]heptan-6-one (12c)**

^{1}H-NMR ($CDCl_3$) δ 1.03 (t, *J* = 7.2 Hz, 3H), 1.33-1.49 (m, 2H), 1.58-1.83 (m, 3H), 1.85-1.98 (m, 2H), 2.08-2.14 (brs, 1H, D_2O exchangeable), 2.22 (dd, *J* = 6.8 Hz, 13.2 Hz, 1H), 3.26-3.34 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 12.1, 16.7, 26.6, 27.8, 35.1, 68.5, 70.2, 79.8, 215.6; EIMS (*m*/*z*) 154 (M^+), 126, 97 (100%), 84, 55; HRMS calcd for $C_9H_{14}O_2$ 154.0994. Found. 154.0995.

(1*S, 5*R**, 7*S**)-1-Hydroxy-7-methylbicyclo[3.2.0]heptan-6-one (12b)**

Yiled: 70% (colorless oil); ^{1}H-NMR ($CDCl_3$) δ 1.06 (d, *J* = 7.2 Hz, 3H), 1.30-1.45 (m, 1H), 1.65-1.83 (m, 2H), 1.88 (dd, *J* = 5.8 Hz, 12.6 Hz, 1H), 1.95 (dd, *J* = 6.3 Hz, 12.6 Hz, 1H), 2.10-2.16 (brs, 1H, D_2O exchangeable), 2.21 (dd, *J* = 6.3 Hz, 13.0 Hz, 1H), 3.35 (dd, *J* = 4.8 Hz, 8.2 Hz, 1H), 3.46-3.54 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ 6.87, 26.3, 28.0, 34.8, 63.3, 68.6, 79.7, 216.4; EIMS (*m*/*z*) 140 (M^+), 122, 112, 84 (100%), 83; HRMS calcd for $C_8H_{12}O_2$ 140.0837. Found. 140.0831.

(1*R, 5*R**, 7*S**)-7-Benzyl-1-hydroxybicyclo[3.2.0]heptan-6-one (12e)**

Yiled: 41% (colorless oil); ^{1}H-NMR ($CDCl_3$) δ 1.43-1.60 (m, 1H), 1.68-1.86 (m, 2H), 1.88-2.03 (m, 2H), 2.03-2.14 (brs, 1H, D_2O exchangeable), 2.28 (dd, *J* = 5.3 Hz, 13.5 Hz, 1H), 2.73 (dd, *J* = 9.2 Hz, 15.5 Hz, 1H), 3.02 (dd, *J* = 5.8 Hz, 15.5 Hz, 1H), 3.39 (dd, *J* = 4.3 Hz, 8.2 Hz, 1H), 3.81 (quint, *J* = 4.8 Hz, 1H), 7.19-7.24 (m, 1H), 7.25-7.34 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ 26.8, 28.0, 29.3, 35.7, 68.80, 68.84, 80.2, 126.3, 128.4, 128.6, 128.9, 138.8, 213.5; EIMS (*m*/*z*) 216 (M^+), 188, 97 (100%), 91, 84; HRMS calcd for $C_{14}H_{16}O_2$ 216.1150. Found. 216.1152.

(1*R, 5*R**, 7*S**)-1-Hydroxy-7-isopropylbicyclo[3.2.0]heptan-6-one (12f)**

Yield: 47% (pale yellow oil); ^{1}H-NMR ($CDCl_3$) δ 0.97 (d, *J* = 6.8 Hz, 3H), 1.12 (d, *J* = 6.3 Hz, 3H), 1.37-1.51 (m, 1H), 1.70-1.96 (m, 5H), 2.00 (brs, 1H, D_2O exchangeable), 2.27 (dd, *J* = 7.2 Hz, 12.6 Hz, 1H),

3.03 (dd, *J* = 4.3 Hz, 11.1 Hz, 1H), 3.25 (dd, *J* = 4.3 Hz, 7.7 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 20.8, 20.9, 24.9, 26.8, 27.6, 35.7, 68.3, 75.1, 80.0, 214.0; EIMS (*m*/*z*) 168 (M^+), 140, 97 (100%), 84; HRMS calcd for $C_{10}H_{16}O_2$ 168.1150. Found. 168.1149.

(1*R, 5*R**, 7*S**)-1-Hydroxy-7-isobutylbicyclo[3.2.0]heptan-6-one (12g)**

Yield: 61% (pale yellow oil); ^{1}H-NMR ($CDCl_3$) δ 0.93 (d, *J* = 7.2 Hz, 6H), 1.25-1.53 (m, 3H), 1.66-1.82 (m, 3H), 1.84-1.97 (m, 2H), 2.05 (brs, 1H, D_2O exchangeable), 2.21 (dd, *J* = 6.8 Hz, 13.5 Hz, 1H), 3.31 (dd, *J* = 4.3 Hz, 8.2 Hz, 1H), 3.45 (dd, *J* = 5.8 Hz, 14.0 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 22.3, 22.5, 26.4, 26.5, 27.9, 32.2, 35.5, 67.1, 68.6, 80.1, 215.5; EIMS (*m*/*z*) 182 (M^+), 154, 111, 84 (100%), 55; HRMS calcd for $C_{11}H_{18}O_2$ 182.1307. Found. 182.1301.

2-(2-Phenylacetyl)cyclopentanone (11h)

Yield: 56% (pale yellow oil) as an equilibrium mixture of **11h** and its tautomers (**15h** and/or **16h**); ^{1}H-NMR ($CDCl_3$) δ 1.75-2.09 (m, 2H), 2.18-2.32 (m, 1H), 2.41 (t, *J* = 7.7 Hz, 2H), 2.58 (t, *J* = 7.2 Hz, 1H), 3.48 (t, *J* = 8.2 Hz, 0.5H), 3.56 (s, 1H), 3.95 (d, *J* = 15.9 Hz, 0.5H), 4.01 (d, *J* = 15.5 Hz, 0.5H), 7.20-7.36 (m, 5H), 13.4-13.7 (brs, 0.5H, D_2O exchangeable); ^{13}C-NMR ($CDCl_3$) δ 20.2, 20.5, 25.2, 25.6, 36.7, 38.8, 41.0, 49.7, 60.5, 190.7, 126.8, 127.0, 128.5, 128.6, 128.9, 129.6, 133.6, 135.2, 176.3, 202.0, 205.4, 212.8; EIMS (*m*/*z*) 202 (M^+), 111 (100%), 91, 83; HRMS calcd for $C_{13}H_{14}O_2$ 202.0994. Found. 202.0991.

Solvolysis of 14b

A solution of **14b** (1.16 g, 4.71 mmol) in MeOH (10 mL) was a stirred at rt for 1 h. The solvent was removed under reduced pressure and the residue was chromatographed (silica gel: spherical, 10% to 15% AcOEt-hexane) to afford **18** (414 mg, 51%) and **19** (276 mg, 34%).

(1*R, 5*R**, 7*R**)-7-Chloro-1-hydroxy-7-methylbicyclo[3.2.0]heptan-6-one (18)**

Colorless oil; ^{1}H-NMR ($CDCl_3$) δ 1.34-1.48 (m, 1H), 1.57 (s, 3H), 1.82-2.00 (m, 2H), 2.01- 2.11 (m, 2H), 2.17 (dd, *J* = 6.8 Hz, 13.5 Hz, 1H), 3.08 (s, 1H, D_2O exchangeable), 3.63 (d, *J* = 7.7 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 16.9, 25.9, 28.3, 34.8, 69.2, 81.3, 83.0, 208.8; EIMS (*m*/*z*) 176 (M^++2), 174 (M^+), 138, 111 (100%), 84; HRMS calcd for $C_8H_{11}{}^{35}ClO_2$ 174.0448. Found. 174.0453; HRMS calcd for $C_8H_{11}{}^{37}ClO_2$ 176.0418. Found. 176.0417.

(1*R, 5*R**, 7*S**)-7-Chloro-1-hydroxy-7-methylbicyclo[3.2.0]heptan-6-one (19)**

Colorless oil; ^{1}H-NMR ($CDCl_3$) δ 1.56-1.68 (m, 1H), 1.75 (s, 3H), 1.79-1.97 (m, 3H), 2.07 (dd, *J* = 6.3 Hz, 11.1 Hz, 1H), 2.16 (s, 1H, D_2O exchangeable), 2.59 (dd, *J* = 6.8 Hz, 12.6 Hz, 1H), 3.47 (d, *J* = 8.7 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 21.0, 26.2, 29.5, 38.6, 66.0, 78.4, 83.9, 209.2; EIMS (*m*/*z*) 176 (M^++2), 174 (M^+), 138, 111 (100%), 84; HRMS calcd for $C_8H_{11}{}^{35}ClO_2$ 174.0448. Found. 174.0413; HRMS calcd for $C_8H_{11}{}^{37}ClO_2$ 176.0418. Found. 176.0413.

Typical procedure for zinc reduction of 18 and 19

To a stirred solution of **18** (100 mg, 0.575 mmol) in a mixture of 2-propanol (3 mL) and H_2O (3 mL) was added zinc powder (188 mg, 2.87 mmol) in one portion at rt. The mixture was stirred at rt for 49 h. The mixture was then filtered through a Celite pad and the filtrate was evaporated under reduced pressure. The residue was dissolved in AcOEt and was washed with saturated aqueous $NaHCO_3$ and brine. After drying (Na_2SO_4), the solvent was removed under reduced pressure. The residue was chromatographed (15% AcOEt-hexane) to afford **12b** (18 mg, 22%) as a single stereoisomer and colorless oil. All of the spectroscopic data were identical to **12b** as already described.

Typical procedure for the Baeyer-Villiger oxidation of the cyclobutanones.

To a stirred suspension of **18** (100 mg, 0.575 mmol) and $NaHCO_3$ (241 mg, 2.87 mmol) in CH_2Cl_2 (2 mL) was added *m*CPBA (149 mg, 0.862 mmol) in an ice bath. After stirring at the same temperature for 10 min, the mixture was further stirred at rt for 1.5 h. The mixture was filtered through a Celite pad and the filtrate was washed with 10 (w/v) % aqueous Na_2SO_3, saturated aqueous $NaHCO_3$ and brine. After drying (Na_2SO_4), the solvent was removed under reduced pressure. The residue was chromatographed (20% AcOEt-hexane) to afford **20** (84 mg, 77%) as a single regioisomer and a colorless oil.

(3*R,3a*R**,6a*R**)-3-Chloro-3a-hydroxy-3-methylhexahydro-2*H*-cyclopenta[*b*]furan-2-one** (**20**)

^{1}H-NMR ($CDCl_3$) δ 1.66-1.74 (m, 1H), 1.73 (s, 3H), 1.87-1.96 (m, 2H), 1.97-2.14 (m, 2H), 2.17-2.28 (m, 1H), 2.57 (s, 1H, D_2O exchangeable), 4.59 (d, J = 5.3 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 19.5, 23.8, 28.8, 33.0, 69.8, 87.5, 88.2, 172.0; EIMS (*m*/*z*) 192 (M^++2), 190 (M^+), 155, 111 (100%), 90, 83; HRMS calcd for $C_8H_{11}{}^{35}ClO_3$ 190.0396. Found. 190.0388; HRMS calcd for $C_8H_{11}{}^{37}ClO_3$ 192.0367. Found. 192.0358.

(3*S,3a*R**,6a*R**)-3-Chloro-3a-hydroxy-3-methylhexahydro-2*H*-cyclopenta[*b*]furan-2-one** (**21**)

Yield: 65% (colorless needles); mp 83-84 °C (from Et_2O-hexane); ^{1}H-NMR ($CDCl_3$) δ 1.56-1.72 (brs, 1H, D_2O exchangeable), 1.80 (s, 3H), 1.82-2.11 (m, 4H), 2.16-2.36 (m, 2H), 4.56 (d, J = 5.3 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 23.1, 23.8, 30.9, 37.8, 71.0, 86.8, 88.9, 174.1; EIMS (*m*/*z*) 192 (M^++2), 190 (M^+), 155, 111 (100%), 90, 83; HRMS calcd for $C_8H_{11}{}^{35}ClO_3$ 190.0396. Found. 190.0403; HRMS calcd for $C_8H_{11}{}^{37}ClO_3$ 192.0367. Found. 192.0370.

(3*S,3a*S**,6a*R**)-3a-hydroxy-3-methylhexahydro-2*H*-cyclopenta[*b*]furan-2-one (22) and (3*S**,3a*R**, 6a*R**)-3a-hydroxy-3-methylhexahydro-1*H*-cyclopenta[*c*]furan-1-one (23)**

Yield: 74% (colorless oil) as an inseparable mixture of **22** and **23**; ^{1}H-NMR ($CDCl_3$) δ 1.26 (d, J = 7.2 Hz, 1.2H), 1.40 (d, J = 6.3 Hz, 1.8H), 1.50-2.80 (m, 6H, 1H: D_2O exchangeable), 2.87 (q, J = 7.2 Hz, 0.4H), 2.93 (ddd, J = 1.6 Hz, 3.9 Hz, 7.7 Hz, 0.6H), 4.52 (q, J = 6.3 Hz, 0.6H), 4.54 (d, J = 6.3 Hz, 0.4H); ^{13}C-NMR ($CDCl_3$) δ 9.2, 14.2, 23.5, 25.0, 27.6, 30.8, 33.9, 34.3, 45.6, 53.1, 81.8, 86.8, 86.9, 88.9, 178.0, 179.0; EIMS (*m*/*z*) 156 (M^+), 128, 100, 84 (100%), 72; HRMS calcd for $C_8H_{12}O_3$ 156.0786. Found 156.0780.

Typical procedure for a ring expansion reaction of 12.

To a stirred solution of **12b** (100 mg, 0.714 mmol) in CH_2Cl_2 (3 mL) was added ZnI_2 (274 mg, 0.857 mmol) at 0 °C. After stirring the mixture for 30 min, the mixture was further stirred at rt for 60 h. After adding saturated aqueous $NaHCO_3$ at 0 °C, the mixture was filtered through a Celite pad. The filtrate was extracted with CH_2Cl_2. The combined organic layer was washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure. The residue was chromatographed (10% Et_2O-hexane to 15% Et_2O-hexane) to afford **11b** (14 mg, 14%) as a colorless oil and **2b** (61 mg, 61%) as a colorless oil. The ^{1}H-NMR spectrum of **11b** in $CDCl_3$ was observed as a 1:1 mixture of **11b** and its tautomers (**15b** and/or **16b**).

2-Methyl-1,3-cycloheptanedione (2b)[3]

^{1}H-NMR ($CDCl_3$) δ 1.23 (d, J = 6.8 Hz, 3H), 1.78-1.97 (m, 2H), 1.98-2.13 (m, 2H), 2.46-2.65 (m, 4H), 3.75 (q, J = 6.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 11.1, 25.7, 43.3, 60.8, 208.0; EIMS (*m*/*z*) 140 (M^+), 112, 97 (100%); HRMS calcd for $C_8H_{12}O_2$ 140.0837. Found. 140.0832.

2-Propanoylcyclopentanone (11b)[15,16]

^{1}H-NMR ($CDCl_3$) δ 1.06 (t, J = 7.2 Hz, 1.5H), 1.15 (t, J = 7.7 Hz, 1.5H), 1.79-1.96 (m, 1.5H), 2.01-2.13 (m, 1H), 2.27 (q, J = 7.7 Hz, 2H), 2.38-2.58 (m, 3H), 2.82-2.94 (m, 0.5H), 3.38 (t, J = 7.7 Hz, 0.5H), 13.4-13.8 (brs, 0.5H, D_2O exchangeable); ^{13}C-NMR ($CDCl_3$) δ 7.2, 9.3, 20.2, 20.7, 25.3, 25.5, 27.9, 36.3, 36.5, 38.7, 61.6, 108.8, 181.4, 203.4, 205.1, 213.2; EIMS (*m*/*z*) 140 (M^+), 111 (100%), 84; HRMS calcd for $C_8H_{12}O_2$ 140.0837. Found. 140.0839.

2-Ethyl-1,3-cycloheptanedione (2c)[4]

Yield: 62% (pale yellow oil); ^{1}H-NMR ($CDCl_3$) δ 0.87 (t, J = 7.2 Hz, 3H), 1.80-1.94 (m, 4H), 1.99-2.11 (m, 2H), 2.45-2.60 (m, 4H), 3.57 (t, J = 7.2 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 11.5, 19.6, 25.7, 43.7, 68.3, 207.4; EIMS (*m*/*z*) 154 (M^+), 126, 97 (100%), 55; HRMS calcd for $C_9H_{14}O_2$ 154.0994. Found. 154.0999.

2-*n*-Butyrylcyclopentanone (11c)[17]

Yield: 21% (pale pink oil) as an equilibrium mixture of **11c** and its tautomers (**15c** and/or **16c**); ^{1}H-NMR ($CDCl_3$) δ 0.92 (t, J = 7.2 Hz, 1.5H), 0.97 (t, J = 7.7 Hz, 1.5H), 1.54-1.71 (m, 2H), 1.80-1.96 (m, 1.5H), 2.01-2.12 (m, 1H), 2.18-2.30 (m, 1.5H), 2.38 (m, 3.5H), 2.38-2.58 (m, 3.5H), 2.80 (td, J = 7.7 Hz, 17.4 Hz, 0.5H), 3.37 (t, J = 7.7 Hz, 0.5H), 13.5-13.8 (brs, 0.5H, D_2O exchangeable); ^{13}C-NMR ($CDCl_3$) δ 13.5, 13.7, 16.6, 18.9, 20.2, 20.7, 25.2, 25.5, 36.2, 36.8, 38.6, 44.9, 61.7, 109.4, 178.9, 204.6, 205.1, 213.0; EIMS (*m*/*z*) 154 (M^+), 126, 111 (100%), 84; HRMS calcd for $C_9H_{14}O_2$ 154.0994. Found. 154.0994.

2-Benzyl-1,3-cycloheptanedione (2e)[18]

Yield: 48% (colorless oil); ^{1}H-NMR ($CDCl_3$) δ 1.78-1.90 (m, 2H), 2.03-2.15 (m, 2H), 2.47 (ddd, J = 3.9 Hz, 8.7 Hz, 14.5 Hz, 2H), 2.55 (ddd, J = 4.3 Hz, 8.7 Hz, 14.5 Hz, 2H), 3.15 (d, J = 6.8 Hz, 2H), 4.22 (t, J = 6.8 Hz, 1H), 7.12-7.20 (m, 3H), 7.21-7.28 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 25.0, 31.8, 44.3, 68.3, 126.3, 128.4,

128.9, 139.1, 205.4; EIMS (*m*/*z*) 216 (M^+, 100%), 188, 159, 131, 91; HRMS calcd for $C_{14}H_{16}O_2$ 216.1150. Found. 216.1149.

2-(3-Phenylpropanoyl)cyclopentanone (11e)[19]

Yield: 36% (pale yellow oil) as an equilibrium mixture of **11e** and its tautomers (**15e** and/or **16e**); ^{1}H-NMR ($CDCl_3$) δ 1.79-1.91 (m, 2H), 1.99-2.10 (m, 1H), 2.15-2.30 (m, 1H), 2.34-2.46 (m, 2.5H), 2.24 (t, *J* = 3.0 Hz, 1H), 2.75-2.95 (m, 2H), 3.20 (ddd, *J* = 4.8 Hz, 7.7 Hz, 16.4 Hz, 0.5H), 3.34 (t, *J* = 7.7 Hz, 0.5H), 7.14-7.32 (m, 5H), 13.30-13.80 (brs, 0.5H, D_2O exchangeable); ^{13}C-NMR ($CDCl_3$) δ 20.2, 20.7, 25.2, 25.5, 29.3, 31.5, 36.4, 36.8, 38.7, 44.4, 62.0, 109.9, 126.0, 126.2, 128.3, 128.4, 140.7, 140.8, 177.8, 203.6, 204.8, 212.9; EIMS (*m*/*z*) 216 (M^+), 198, 111, 91 (100%); HRMS calcd for $C_{14}H_{16}O_2$ 216.1150. Found. 216.1145.

2-Isopropyl-1,3-cycloheptanedione (2f)

Yield: 69% (colorless needles); mp 47.5-48 °C (from hexane); ^{1}H-NMR ($CDCl_3$) δ 0.92 (d, *J* = 6.8 Hz, 6H), 1.82-1.93 (m, 2H), 1.99-2.10 (m, 2H), 2.42-2.57 (m, 5H), 3.53 (d, *J* = 7.7 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 20.1, 25.6, 26.3, 44.4, 73.4, 207.2; EIMS (*m*/*z*) 168 (M^+), 150, 125, 97 (100%), 84, 69; HRMS calcd for $C_{10}H_{16}O_2$ 168.1150. Found. 168.1156.

2-(3-Methyl-*n*-butanoyl)cyclopentanone (11f)

Yield: 19% (colorless oil) as an equilibrium mixture of **11f** and its tautomers (**15f** and/or **16f**); ^{1}H-NMR ($CDCl_3$) δ 0.88-0.99 (m, 6H), 1.86-1.96 (m, 1.75H), 2.00-2.30 (m, 2.25H), 2.55 (t, *J* = 7.2 Hz, 1H), 2.61-2.69 (m, 0.25H), 3.36 (t, *J* = 7.7 Hz, 0.25H), 13.56-13.76 (brs, 0.75H, D_2O exchangeable); ^{13}C-NMR ($CDCl_3$) δ 20.2, 20.6, 22.1, 22.2, 22.4, 23.1, 23.6, 23.8, 25.2, 26.2, 30.5, 34.3, 35.7, 36.8, 37.0, 38.6, 42.8, 42.9, 46.2, 46.5, 51.8, 61.9, 85.7. 110.0, 117.2, 204.3, 206.4, 213.0, 215.0; EIMS (*m*/*z*) 168 (M^+), 153, 126, 111 (100%), 85, 57; HRMS calcd for $C_{10}H_{16}O_2$ 168.1150. Found. 168.1144.

2-Isobutyl-1,3-cycloheptanedione (2g)

Yield: 52% (colorless oil); ^{1}H-NMR ($CDCl_3$) δ 0.87 (d, *J* = 6.8 Hz, 6H), 1.49 (sept, *J* = 6.8 Hz, 1H), 1.72 (t, *J* = 7.2 Hz, 2H), 1.82-1.93 (m, 2H), 2.01-2.11 (m, 2H), 2.46-2.61 (m, 4H), 3.74 (t, *J* = 7.2 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 22.4, 25.7, 25.9, 35.0, 43.6, 65.0, 207.7; EIMS (*m*/*z*) 182 (M^+), 127 (100%), 111, 55; HRMS calcd for $C_{11}H_{18}O_2$182.1307. Found. 182.1300.

2-(4-Methyl-*n*-pentanoyl)cyclopentanone (11g)

Yield: 34% (colorless oil) as an equilibrium mixture of **11g** and its tautomers (**15g** and/or **16g**); ^{1}H-NMR ($CDCl_3$) δ 0.89, 0.91 (pair of d, *J* = 6.3 Hz, 6.3 Hz, 6H), 1.43-1.65 (m, 3H), 1.81-1.96 (m, 1.5H), 2.00-2.12 (m, 1H), 2.19-2.30 (m, 2H), 2.38-2.58 (m, 3H), 2.77-2.87 (m, 0.5H), 3.39 (t, *J* = 8.2 Hz, 0.5H), 13.50-13.80 (brs, 0.5H, D_2O exchangeable); ^{13}C-NMR ($CDCl_3$) δ 20.3, 20.7, 22.2, 22.3, 22.4, 25.4, 25.6, 27.5, 27.8, 31.9, 32.4, 34.3, 36.8, 38.7, 41.1, 61.8, 109.2, 179.8, 204.83, 204.86, 213.2; EIMS (*m*/*z*) 182 (M^+), 139, 126, 111 (100%); HRMS calcd for $C_{11}H_{18}O_2$182.1307. Found. 182.1304.

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12. Compound **11h** was isolated as a single spot by thin layer chromatography (TLC). However, the ^{13}C-NMR spectra of **11h** in $CDCl_3$ indicated that there were three carbonyl carbon signals at δ 202.0, 205.4, and 212.8 and two olefinic carbon signals at δ 109.7 and 176.3 due to the α,β-unsaturated carbon. Also, we observed a broad singlet proton at δ 13.4-13.7, which was suggested as a hydrogen-bonded enol proton in the ^{1}H-NMR spectrum of **11h**. These results showed that **11h** was obtained along with its tautomers **15h** and/or **16h**. Since the two enolic forms **15h** and **16h** are in a rapid dynamic equilibrium, the peaks in the NMR spectrum for **15h** and **16h** cannot be distinguished. The same tendency was observed for all of the compounds **11** which were obtained by a ring expansion reaction. See also refs. 15 and 20.
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