Facile Synthesis of 5-Hexyl-4-methyl-γ-butyrolactone *via Nef* Reaction as a Key Step

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A racemic *cis*/*trans* mixture of 5-hexyl-4-methyl-γ-butyrolactone was easily synthesized from 1-iodoheptane in four steps with inexpensive and readily available reagents. Our new synthesis method can be potentially employed for mass production of the 4-methyl-5-hexyl-γ-butyrolactone as well as other poly-alkyl substituted γ-butyrolactones.

Introduction. – 5-Hexyl-4-methyl-γ-butyrolactone (**1**, *Fig.*) exists in the volatile components of the juices of blood oranges as well as blond oranges [1]. It has been utilized as an active ingredient of oral bactericides in dentifrice [2]. The racemic *cis*-5-hexyl-4-methyl-γ-butyrolactone (racemic *cis*-**1**, *Fig.*) has been identified as an odoriferous component of the *Aerangis species* (native to Kenya and Tanzania) by *Kaiser* using a special trapping technique [3]. Racemic *cis*-**1** has also been used as an ingredient in perfumes due to its time-dependent and fascinating scent [3b].

Because of the usefulness and importance of 5-hexyl-4-methyl-γ-butyrolactone, great efforts have been made to synthesize it during the past decades. In 1979, the first synthesis of **1** was completed by *Shono et al.* [4] using the electroreduction of the methyl ester of 3-hydroxy-2-[1-(phenylsulfanyl)ethyl]nonanoic acid. In 1982, racemic *trans*-**1** (*Fig.*) was synthesized by *Thomas et al.* [5] by the reaction of tributyl[(2*E*)-1-(alkoxymethoxy)but-2-en-1-yl]stannane with heptanal as a key step. In 1989, racemic *cis*-**1** was first synthesized by *Larchevêque et al.* [6] by decarboxylation and cyclization of *syn*-MEM protected 5-(3-hydroxynonan-2-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione. In 1997, *Fukuzawa et al.* [7] reported the SmI_2 mediated asymmetric synthesis of both

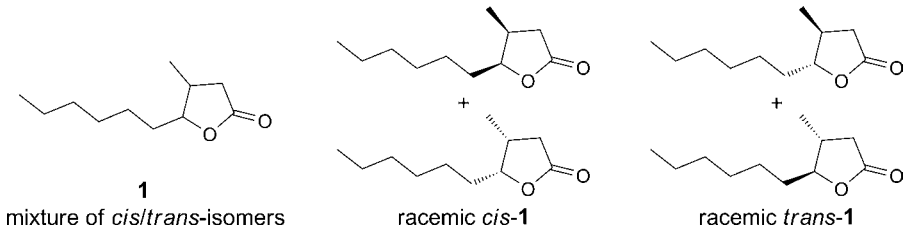


Figure. *Structure of 5-hexyl-4-methyl-γ-butyrolactone*

enantiomers of *cis*-**1** by the reaction of heptanal with *N*-methylephedrinyl acrylate and crotonate. Two years later, *Kitahara* and co-workers [8] reported another synthesis of both enantiomers of *cis*-**1** from enantiomers of 2-oxabicyclo[3.3.0]oct-6-en-3-one (= 3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*l*]furan-2-one as starting material in eight steps. In 2001, *Cassy et al.* [9] reported the synthesis of racemic *cis*-**1** by the reaction of α-(benzoyloxy)crotylstannane (=(2*E*)-1-stannanylbut-2-en-1-yl benzoate) with heptanal in liquid phase and on solid support. Almost at the same time, *Wu et al.* [10] reported another enantioselective synthesis of (+)-(*R,R*)-**1** using $TiCl_4$-mediated *Evans* asymmetric aldolization as the key step. This procedure included six steps. In 2012, *Ma* and co-workers reported the synthesis of (+)-(*R,R*)-**1** using stereoselective iodolactonization of 4-allenoic acid as a key step [11].

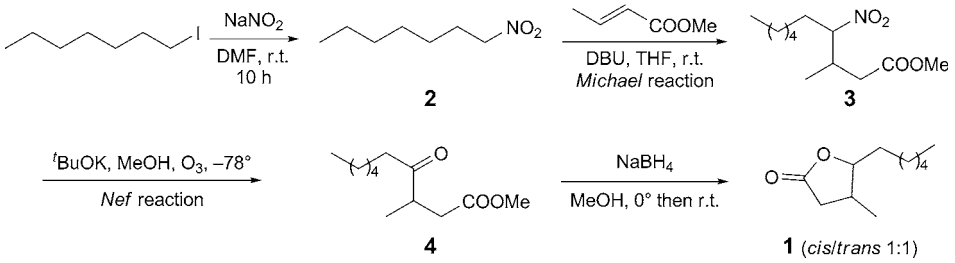
Results and Discussion. – As described above, many protocols have been reported concerning the synthesis (or enantioselective synthesis) of the 5-hexyl-4-methyl-γ-butyrolactone (**1**). However, these reported methods encountered some drawbacks arising from long synthesis route (more than four steps), expensive reagents or difficultly prepared starting materials.

It is still a challenge to synthesize the 5-hexyl-4-methyl-γ-butyrolactone (**1**) in a short route (within four steps) with inexpensive commercially available reagents or starting materials. In this study, we tried to explore a facile synthesis route to the 5-hexyl-4-methyl-γ-butyrolactone (**1**) with inexpensive commercially available reagents.

As shown in *Scheme 1*, 5-hexyl-4-methyl-γ-butyrolactone (**1**) could be synthesized from the commercially available 1-iodoheptane in four steps by our approach. For mass production, the reagents employed in our synthesis should be inexpensive, commercially available or conveniently generated by industrial processes. It is worth to note that the *Nef* reaction (for a recent review of the *Nef* reaction, see [12]) has been proven to be an efficient method for transforming $-NO_2$ groups into C=O groups. However, the feasibility and the optimum conditions remained unknown in our synthesis route due to the possibility of hydrolysis or decomposition of the methyl 3-methyl-4-nitrodecanoate (**3**) under the typical *Nef* reaction conditions (basic and oxidative conditions).

We initiated our research by the synthesis of 1-nitroheptane (**2**) from 1-iodoheptane and $NaNO_2$ [13]. The reaction proceeded quite smoothly in DMF at room temperature. Compound **2** was obtained in 65% yield. With 1-nitroheptane (**2**) in hand, we tried

Scheme 1. *Synthesis of 5-Hexyl-4-methyl-γ-butyrolactone* (**1**)



to synthesize **3** *via Michael* reaction (for some examples of the *Michael* reaction of alkyl-nitro-compounds with methyl crotonate, see [14]). In the presence of DBU at room temperature in THF, **3** was obtained in 82% yield as a 1:1 mixture of diastereoisomers.

Subsequently, we tried to transform **3** into **4** by *Nef* reaction. Many oxidants for the *Nef* reaction were screened in order to obtain **4** in high yield (*Table*).

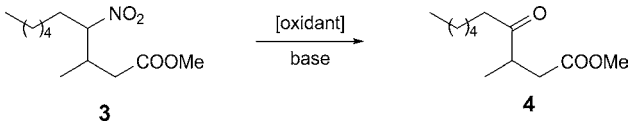
As shown in the *Table*, **3** decomposed substantially when $KMnO_4$ [15] (*Entries 1–3*) or H_2O_2 [16] (*Entries 4* and *5*) were used as oxidants. This may result from the strong oxidative ability of $KMnO_4$ and H_2O_2. When **3** was subjected to $Ce(NH_4)_2(NO_3)_6$ [17]/NaOH/MeOH system, **4** was obtained in modest yield (*Entry 6*). This indicated that **3** can be transformed into **4** under milder oxidative conditions. Next, **3** was subjected to MnO_2/NaOH/MeOH (*Entries 7* and *8*), but **3** remained intact. When air (*Entries 9–11*) was used as an oxidant [18], **3** also remained intact (*Entries 9* and *10*) when the reactions were carried out at room temperature. However, **3** decomposed (*Entry 11*) after reflux in H_2O as a result of hydrolysis in the presence of NaOH and H_2O.

After many trials, it was indicated that the oxidant should not be too strong in order to suppress the decomposition of **3**. On the other hand, the oxidant should not be too weak for transforming **3** into **4** efficiently. O_3, which can be conveniently generated by an ozone generator [19], was then tested due to its appropriate oxidative ability and the easy removal from the reaction system. Thus, **4** was obtained in 85% yield when O_3 was used as oxidant in the presence of ^{t}BuOK at $-78°$ in MeOH.

Finally, **4** was reduced with $NaBH_4$ and cyclized into 5-hexyl-4-methyl-γ-butyrolactone (**1**) in 80% yield as a 1:1 mixture of diastereoisomers (*Scheme 2*).

In summary, a 1:1 mixture of diastereoisomers of 5-hexyl-4-methyl-γ-butyrolactone (**1**) was easily synthesized from 1-iodoheptane in four steps with inexpensive

Table. *Nef Reaction of* **3**

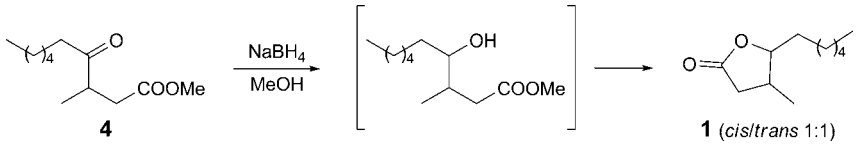


3 **4**

Entry	Base/Equiv.	Oxidant/Equiv.	Solvent	Temperature [°]	Yield[a]) of **4** [%]
1	NaOH/1.0	$KMnO_4$/1.0	MeOH	r.t.	0[b])
2	NaOH/1.0	$KMnO_4$/1.0	MeOH	0	0[b])
3	NaOH/1.0	$KMnO_4$/0.5	MeOH	0	15
4	NaOH/1.0	H_2O_2/1.0	H_2O	r.t.	0[b])
5	NaOH/1.0	H_2O_2/1.0	H_2O	0	0[b])
6	NaOH/1.0	CAN /0.5	MeOH	0	53
7	NaOH/1.0	MnO_2/1.0	MeOH	r.t.	0[c])
8	NaOH/1.0	MnO_2/1.0	MeOH	reflux	0[c])
9	NaOH/1.0	Air	MeOH	r.t.	0[c])
10	NaOH/1.0	Air	H_2O	r.t.	0[c])
11	NaOH/1.0	Air	H_2O	reflux	0[b])
12	^{t}BuOK/1.0	O_3	MeOH	−78	85

[a]) Yield of isolated **4**. [b]) Decomposition of starting material. [c]) Recovery of starting material.

Scheme 2



4 **1** (*cis*/*trans* 1:1)

and readily available reagents. O_3, which can be conveniently generated by an ozone generator, has been proven to be an appropriate and efficient oxidant for transforming **3** into **4** in the key *Nef* reaction. Our new synthesis can be potentially employed for the preparation of other poly-alkyl substituted γ-butyrolactones. This work is under research in our lab and further results will be reported in due course.

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Experimental Part

General. All commercially available reagents were used without further purification unless otherwise stated. All dry solvents were freshly distilled under N_2 from appropriate drying agents: THF was distilled from Na/benzophenone; DMF was distilled from $MgSO_4$. Column chromatography (CC): silica gel (SiO_2, 200–300 mesh). IR Spectra: *Thermo Fisher Nicolet iS10* FT-IR spectrometer; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker* NMR spectrometer; at 400 and 100 MHz, resp.; δ in ppm rel. to Me_4Si as internal standard, J in Hz.

Synthesis of 1-Nitroheptane (**2**) [13]. A mixture of 1-iodoheptane (15.0 g, 0.066 mol) and $NaNO_2$ (14.37 g, 0.099 mol) in DMF (130 ml) was stirred at r.t. under N_2 for 10 h. The mixture was poured into ice water (200 ml) and extracted with Et_2O (3 × 80 ml). The combined org. layers were washed with sat. NH_4Cl, dried ($MgSO_4$), filtered, concentrated, and the residue was distilled in vacuum to give the product as a colorless liquid (6.26 g, 65%). ^1H-NMR ($CDCl_3$): 4.38 (*t*, *J* = 6.9, 2 H); 2.08–1.95 (*m*, 2 H); 1.46–1.22 (*m*, 8 H); 0.88 (*t*, *J* = 6.9, 3 H). The data are identical with those reported in [13b].

Synthesis of Methyl 3-Methyl-4-nitrodecanoate (**3**, mixture of diastereoisomers). To a stirred soln. of **2** (6.0 g, 0.041 mol) and methyl but-2-enoate (8.27 g, 0.083 mol) in THF (100 ml) under N_2 was added DBU (= 1,8-diazabicyclo[5.4.0]undec-7-ene; 1.86 ml, 0.041 mol). After stirring at r.t. overnight, the mixture was poured into sat. NH_4Cl, extracted by AcOEt (3 × 30 ml), dried ($MgSO_4$), filtered, concentrated, and the residue purified by flash chromatography (PE/AcOEt 8 : 1) to give the product as a colorless liquid (8.61 g, 82%, dr 1 : 1). IR (neat): 2956, 2930, 2859, 1740, 1549, 1458, 1436, 1367, 1197, 1007. ^1H-NMR ($CDCl_3$): 4.52–4.40 (*m*, 1 H); 3.68 (*s*, 1.5 H); 3.67 (*s*, 1.5 H); 2.51–2.41 (*m*, 2 H); 2.29–2.16 (*m*, 1 H); 2.04–1.93 (*m*, 1 H); 1.68–1.65 (*m*, 1 H); 1.27–1.25 (*m*, 8 H); 1.04–0.99 (*m*, 3 H); 0.85 (*t*, *J* = 6.8, 3 H). ^{13}C-NMR ($CDCl_3$): 172.2; 92.7; 92.1; 51.9; 37.6; 37.1; 33.9; 33.8; 31.6; 30.9; 30.8; 28.8; 26.1; 26.0; 22.6; 16.4; 15.6; 14.1. HR-EI-MS: 199.1690 ($[C_{12}H_{23}NO_4–NO_2]^+$; calc. 199.1693).

Synthesis of Methyl 3-Methyl-4-oxodecanoate (**4**, mixture of diastereoisomers). To a soln. of **3** (4.0 g, 0.016 mol) in MeOH (40 ml) was added ^{t}BuOK (1.83 g, 0.016 mol) under N_2. After stirring at r.t. for 15 min, the mixture was cooled to $-78°$, and a stream of O_3 was passed through for 40 min. The mixture was purged with O_2 until the blue color disappeared plus another 5 min. After slowly warming to r.t., the mixture was filtered through *Celite*, and washed with AcOEt. The filtrate was concentrated, purified by flash chromatography (PE/AcOEt 5 : 1) to give the product as a colorless liquid (3.50 g, 85%). IR (neat): 2955, 2931, 2858, 1740, 1715, 1458, 1437, 1357, 1198, 1005. ^1H-NMR ($CDCl_3$): 3.61 (*s*, 3 H); 3.01–2.92 (*m*, 1 H); 2.74 (*dd*, *J* = 8.8, 16.4, 1 H); 2.55–2.42 (*m*, 2 H); 2.25 (*dd*, *J* = 5.2, 16.8, 1 H); 1.56–1.51 (*m*, 2 H); 1.29–1.22 (*m*, 6 H); 1.09 (*d*, *J* = 7.6, 3 H); 0.84 (*t*, *J* = 6.8, 3 H). ^{13}C-NMR ($CDCl_3$): 213.1; 172.9; 51.8; 42.1; 41.3; 36.8; 31.8; 29.0; 23.7; 22.6; 16.9; 14.2. HR-EI-MS: 214.1573 ($C_{12}H_{22}O_3^+$; calc. 214.1569).

Synthesis of 5-Hexyl-4-methyl-γ-butyrolactone (= *5-Hexyldihydro-4-methylfuran-2(3*H*)-one*; **1** (*cis*/*trans* mixture)). To a stirred soln. of **4** (3.0 g, 0.014 mol) in MeOH at 0° was added $NaBH_4$ (1.06 g, 0.028 mol). After stirring for 2 h, the mixture was slowly warmed to r.t. The mixture was poured into ice-water, extracted with AcOEt (3 × 20 ml), dried ($MgSO_4$), filtered, concentrated, and the residue purified by flash chromatography (PE/AcOEt 5 :1) to give the product as a colorless liquid (2.06 g, 80%, dr 1 :1). IR (neat): 2931, 2858, 1781, 1458, 1210, 1166, 1078. ^{1}H-NMR ($CDCl_3$): 4.41 – 4.36 (*m*, 0.5 H); 3.98 – 3.93 (*m*, 0.5 H); 2.67 – 2.50 (*m*, 1.5 H); 2.21 – 2.10 (*m*, 1.5 H); 1.65 – 1.53 (*m*, 1.5 H); 1.47 – 1.45 (*m*, 1.5 H); 1.30 – 1.24 (*m*, 7 H); 1.09 (*d*, *J* = 6.4, 1.5 H); 0.96 (*d*, *J* = 6.4, 1.5 H); 0.84 (*t*, *J* = 6.4, 3 H). ^{13}C-NMR ($CDCl_3$): 177.0; 176.6; 87.5; 83.7; 37.6; 37.2; 36.1; 34.1; 33.1; 31.7; 30.0; 29.2; 29.1; 25.9; 25.8; 22.6; 17.5; 14.1; 13.9. HR-EI-MS: 184.1459 ($C_{11}H_{20}O_2^+$; calc. 184.1463)

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