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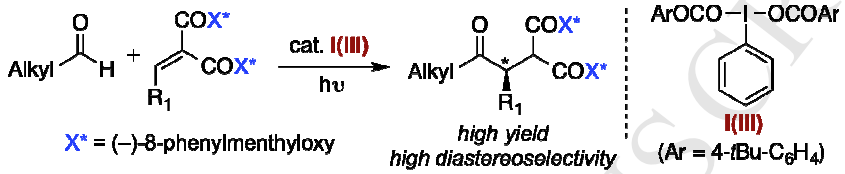

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Hypervalent Iodine(III) Catalyzed Radical Hydroacylation of Chiral Alkylidenemalonates with Aliphatic Aldehydes under Photolysis

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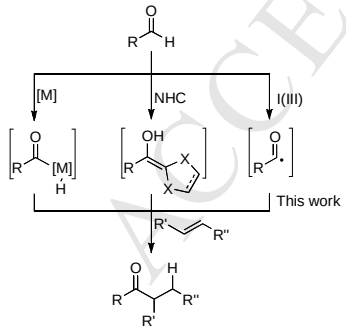
ABSTRACT

Hypervalent iodine(III) catalyzed diastereoselective radical hydroacylation of alkylidenemalonates bearing (–)-8-phenylmenthol as a chiral auxiliary with aliphatic aldehydes is realized under photolysis. This work represent the first example of diastereoselective addition of acyl radicals to olefins to afford chiral ketones in a highly stereoselective fashion. The reaction is initiated by the photolysis of hypervalent iodine(III) catalyst under mild and metal-free conditions. The synthetic potential of this methodology was demonstrated by the short formal sythesis of (–)-methyleneolactocin.

1. Introduction

Research in the last few decades has witnessed an incredible development of new methods for the C-C bond formation *via* radical chemistry.[1] Atom economical reaction between aldehyde and olefin namely hydroacylation represent one of the synthetically useful transformation for the construction of ketones has also received greater attention in recent years. Alternatively, radical hydroacylation[6] through generation of acyl radical from aldehydes also has the potential to become an attractive atom economical method for the synthesis of ketones (Scheme 1). However, this approach has been less investigated due to the instability of acyl radical derived from branched aldehydes under reaction condition. During the course of our ongoing projects on the effective use of hypervalent iodine(III) reagents under photolysis,[6g,7] we investigated the hydroacylation reaction of cyclohexanecarboxaldehyde **2a** with ethyl crotonate **3a** or diethyl ethylidenemalonate **3b** under the influence of various hypervalent iodine(III) reagents[8] as catalyst (Table 1). The *in situ* generation of acyl radicals from branched aldehydes and its subsequent trapping with electrophiles have not been previously developed to a synthetically useful level. To our delight, catalytic use of DIB **1a** under the irradiation of UV light (365 nm) gave the hydroacylation product **4a** or **4b** in 11% or 81% yield respectively with high selectivity for ketone formation (**4a**/**5a** = 5.8/1 and **4b**/**5b** = 22.5/1; entry 1). Only trace amounts of reaction products were detected in the absence of **1a** or black light under given conditions (entry 2 and 3). These results strongly indicate that the reaction undergoes a radical pathway, thereby generating desired acyl radicals[9] in the reaction mixture. We also investigated other iodine(III) catalysts **1b-e** (entries 4~7), and found that **1d** gave a satisfactory result (entry 6). Among the screened iodine(III) catalysts **1d** shows higher



Scheme 1. Hydroacylation of olefins with aldehydes

of ketones. Metal catalyzed hydroacylation[2] and *N*-heterocyclic carbenes (NHCs)[3] catalyzed Stetter reaction are most widely used approach for the addition of aldehydes to olefins (Scheme 1). In addition, the development of asymmetric metal catalyzed hydroacylation[4] and chiral *N*-heterocyclic carbenes (NHCs) ~~catalyzed~~ asymmetric Stetter reactions[5] to synthesize chiral

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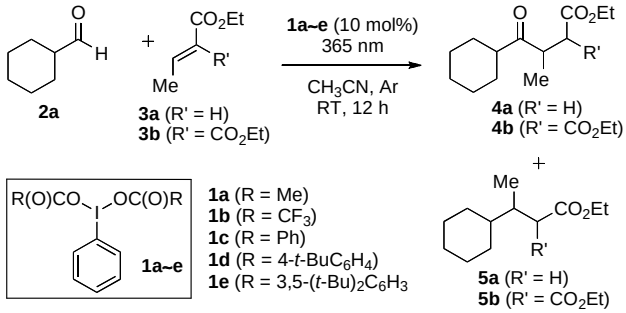
solubility in CH_3CN solvent. Evaluation of different solvents revealed CH_3CN as best solvent for this reaction. The concentration of the reaction mixture is also crucial for obtaining the high yield as well as selectivity, and indeed use of a more concentrated CH_3CN (1.0 M or 1.6 M) solution including catalyst **1d** significantly enhanced both the selectivity (6.4/1 and >25/1) and the yield (>99%) for **4a** and **4b** respectively (entries 8 and 9). Lowering the catalyst loading of **1d** decelerates the reaction progress, however high yield was obtained with prolonged reaction time (entry 10).

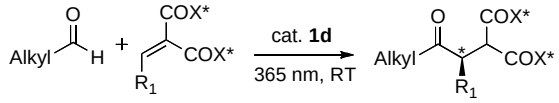
Table 1. Hydroacylation of cyclohexanecarboxaldehyde with ethyl crotonate or diethyl ethylidenemalonate by hypervalent iodine(III) catalysts[a]



Entry	Catalyst	Yield (%)[b]	**4a/5a**[c]	Yield (%)[b]	**4b/5b**[c]
1	**1a**	11	5.8/1	81	22.5/1
2	none	trace	n.d	trace	n.d
3[d]	**1a**	trace	n.d	trace	n.d
4	**1b**	trace	ND	31	12.6/1
5	**1c**	32	3.0/1	67	23.2/1
6	**1d**	24	4.8/1	83	25/1
7	**1e**	trace	ND	40	14/1
8[e]	**1d**	95	5.2/1	99(95)[h]	25/1
9[f]	**1d**	99(97)[h]	6.4/1	88	17.4/1
10[g]	**1d**	95[f]	6.6/1	99[e]	25/1

[a]Unless otherwise specified, reaction of **2a** (0.75 mmol) and **3a** (0.5 mmol) was conducted in the presence of **1** (10 mol%) in CH_3CN (0.5 M) with irradiation of UV light (λ = 365nm). [b]Determined by ^{1}H NMR analysis using 1,1',2,2'-tetrachloroethane as internal standard. [c]Determined by ^{1}H NMR analysis of crude mixture. [d]Reaction in the dark. [e]Reaction in 1.0 M CH_3CN. [f]Reaction in 1.6 M CH_3CN. [g]Reaction performed for 18 h using 5 mol% of **1d**. [h]Yield of isolated product.

To further demonstrate the synthetic potential of this approach, we have become interested in testing the possibility of adding acyl radical to chiral alkenes for the diastereoselective radical hydroacylation. Our approach also enables the use of various linear and branched aliphatic aldehydes, which have rarely been used with success in either metal catalyzed hydroacylation or NHC-catalyzed Stetter reaction.[10] Herein, we report the first diastereoselctive radical hydroacylation[11] of alkenes with aliphatic aldehydes for the stereoselective synthesis of chiral ketones (Scheme 2).

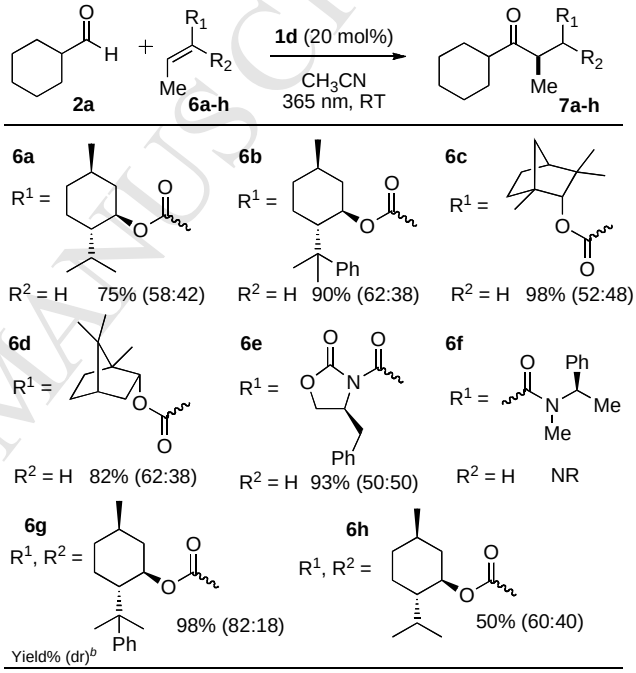


Scheme 2. Hypervalent iodine(III) catalyzed diastereoselective radical hydroacylation of chiral olefins with aldehydes.

2. Results and discussion

At the outset, we first investigated the effect of chiral auxiliary for the diastereoselctive radical hydroacylation between cyclohexanecarboxaldehyde **2a** with various chiral alkenes **6a-h**. Chiral crotyl esters derived from alcohols such as (–)-menthol, (–)-8-phenylmenthol, (–)-borneol, (+)-fenchol afforded hydroacylated product **7a-h** in good yield with poor diastereoslectivity. Crotyl imides **6e** derived from (*S*)-4-benzyl-2-oxazolidinone also gave hydroacylated product in 1:1 diastereoselectivity. Interestingly, crotyl amide **6f** derived from (*R*)-(–)-1-phenylethylamine was found to remain unreactive under standard condition (Table 2).

Table 2. Diasteroselective Hydroacylation of chiral crotonates and alkylidenemalonates[a]

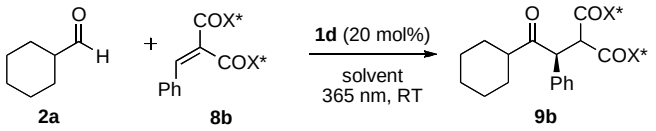


[a]The reaction of **2a** (0.225 mmol) and **6** (0.15 mmol) was conducted in the presence of **1d** (20 mol%) in CH_3CN (2.4 M) with irradiation by UV light (λ = 365nm). [b]Yield of isolated product and diastereoselectivity was determined by ^{1}H NMR analysis of crude reaction mixture.

Then we turned our attention to use chiral alkylidenemalonates as substrate. Since the crotyl ester derived from (–)-8-phenylmenthol **6b** shows higher reactivity and better selectivity among other chiral auxiliaries, the corresponding alkylidenemalonate[12] was synthesized and subjected to standard reaction condition. To our surprise, diastereoselectivity of the reaction increased significantly to 82:18 d.r. and afforded the

corresponding ketone **7g** in high yield. It is worth mentioning here that with analogous (–)-menthol derived alkylidenemalonate **6h** diastereoselectivity of the hydroacylated product dropped drastically to 60:40 and afforded the corresponding ketone **7h** in moderate yield. Having identified the best chiral auxiliary for this reaction, we turned our attention to optimize other reaction parameter. A series of solvents was screened for the diastereoselective radical hydroacylation between cyclohexanecarboxaldehyde **2a** and (–)-8-phenylmenthol derived benzylidenemalonate **8b** (Table 3).

Table 3. Optimization of reaction condition[a]



2a **8b** **9b**

X* = (–)-8-phenylmenthyloxy

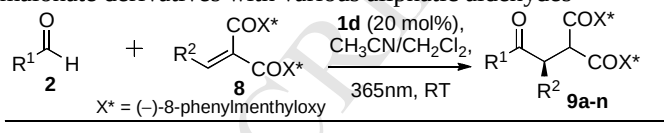
Entry	Solvent	Time (h)	Yield (%)[b]	d.r.[c]
1	CH_3CN	12	98	82:18
2	CH_2Cl_2	12	80	87:13
3	None	16	98	87:13
4	Benzene	12	98	91:9
5	Toluene	18	98	90:10
6	*o*-Xylene	18	98	90:10
7	C_6F_6	12	96	90:10
8	$CF_3C_6H_5$	12	92	90:10
9	CH_3CN/CH_2Cl_2	12	91	92:8
10[d]	CH_3CN/CH_2Cl_2	12	65	87:13

[a]The reaction of **2a** (0.225 mmol) and **8b** (0.15 mmol) was conducted in the presence of **1d** (20 mol%) in solvent (2.4 M) with irradiation of UV light (λ = 365nm). [b]Determined by ^{1}H NMR analysis using 1,1',2,2'-tetrachloroethane as internal standard. [c]Determined by ^{1}H NMR analysis of crude mixture. [d]Reaction performed with irradiation of visible light (λ = 400nm).

Non-polar solvents afforded hydroacylated product in high diastereoselectivity and yield than polar solvents such as CH_3CN (Table 3, entries 4-7 vs. entry 1). Interestingly, mixed solvent system CH_3CN/CH_2Cl_2 gave the corresponding product in higher diastereoselectivity (Table 3, entry 9). Slightly lowered yield and diastereoselectivity was observed, when the reaction performed under visible light (λ = 400nm) irradiation (Table 3, entry 10).

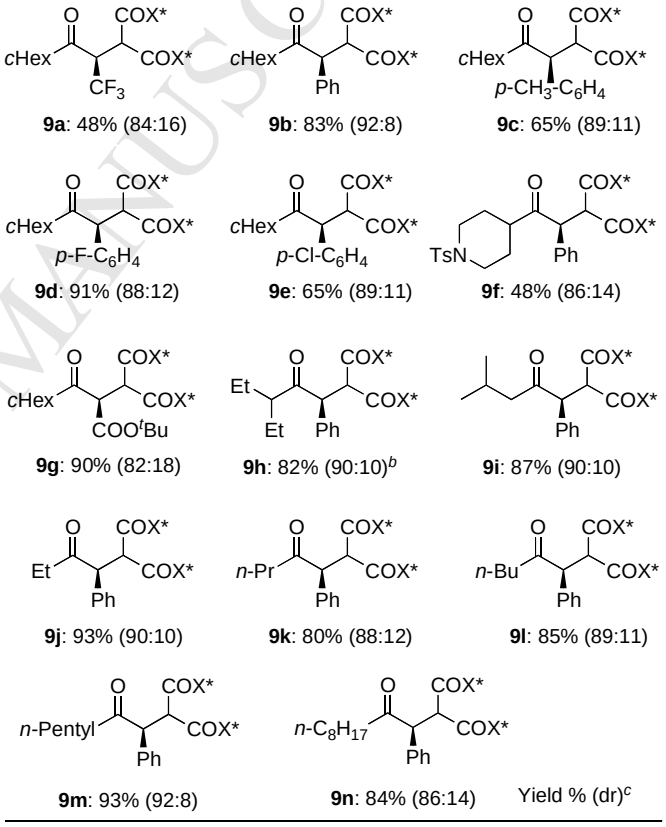
To demonstrate the scope of the reaction, a series of aldehydes were hydroacylated with alkenes **8**, providing the corresponding ketones **9** in uniformly good yield and high diastereoselectivity (Table 4). When employing β-trifluoromethyl alkylidene-malonates **8a** as substrate, α-trifluoromethylated chiral ketone **9a** was obtained in moderate yield with 84:16 d.r. In the case on benzylidenemalonates, introduction of electron-withdrawing and electron-donating susbtituents on the aryl ring of **8b** did not affect the yield and diastereoselectivities (Table 4, **9c-e**). Introduction of heteroatom into the cyclohexane ring of aldehyde altered the reactivity and stereochemical outcome of the reaction (Table 2, **9b** vs **9f**). The reaction of ethene tricarboxylates **8g** with cyclohexanecarboxaldehyde **2a** proceeded efficiently to afford the corresponding ketones **9g** in good yield and diastereoselectivity (Table 2). In addition to α-branched and β branched aldehydes, various linear aldehydes **2l-o** were reacted efficiently with benzylidene malanote **8b** to give the corresponding ketones **9j-n**[13] with excellent yields and diastereoselectivities.

Table 4. Diasteroselective Hydroacylation of alkylidene-malonate derivatives with various aliphatic aldehydes[a]



2 **8** **9a-n**

X* = (–)-8-phenylmenthyloxy



9a: 48% (84:16) **9b**: 83% (92:8) **9c**: 65% (89:11)

9d: 91% (88:12) **9e**: 65% (89:11) **9f**: 48% (86:14)

9g: 90% (82:18) **9h**: 82% (90:10)[b] **9i**: 87% (90:10)

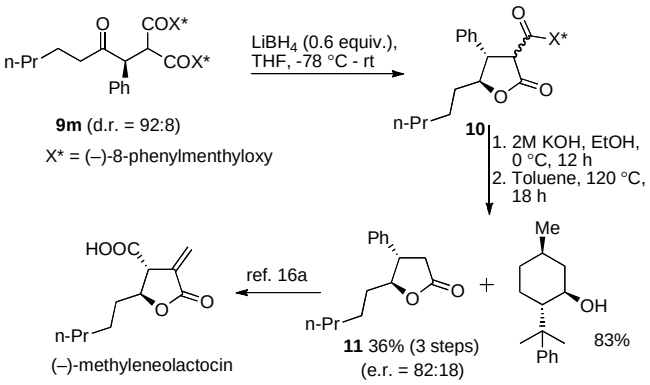
9j: 93% (90:10) **9k**: 80% (88:12) **9l**: 85% (89:11)

9m: 93% (92:8) **9n**: 84% (86:14) Yield % (dr)[c]

[a]The reaction of **2** (0.225 mmol) and **8** (0.15 mmol) was conducted in the presence of **1** (20 mol%) in 1:1 CH_3CN/CH_2Cl_2 (2.4 M) with irradiation by UV light (λ = 365nm). [b]4 equivalents of **2h** were used without solvent for 48 h. [c]Yield of isolated product and diastereoselectivity was determined by ^{1}H NMR analysis of crude mixture.

The further synthetic utility of the present diastereselective radical hydroacylation was successfully demonstrated in the short formal synthesis of (–)-methyleneolactocin (Scheme 3),[14-16] which exhibits potent antibacterial and antitumor activities. Exposure of ketone **9m** with 0.6 equivalent of $LiBH_4$ leads to the formation of γ-butyrolactone **10** which upon subsequent base hydrolysis with KOH followed by decarboxylation upon refluxing in toluene afforded γ-butyrolactone **11** in 36% overall yield. The lactone **11** can be converted to (–)-methyleneolactocin in two steps using literature known method.[16a] Though the

stereoselectivity of the product was slightly decreased, γ-butyrolactone **11** was obtained in only three steps from ketone **9m**. It is worth mentioning here that during this transformation, (–)-8-phenylmenthol was successfully recovered in 83% yield.



Scheme 3. Formal total synthesis of (–)-methyleneolactocin.

Based on the observed stereochemistry, transition state models can be proposed as shown in Figure 1. During the radical addition step, the in situ generated acyl radical will prefer sterically less congested face of alkenes. However, *Re* face of the alkene is effectively shielded by the phenyl group of one of the chiral auxiliary, which would explain the low diastereoselectivity achieved when using **6h**. As a result, *Si* face addition of radical occurs to provide *S* isomer predominantly.

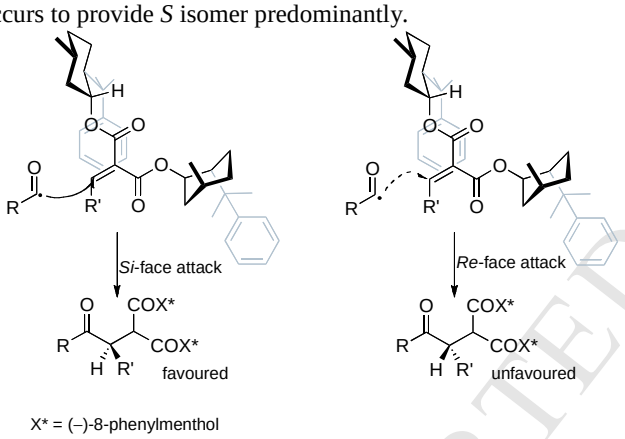


Figure 1. Proposed transition state model for stereochemical outcome.

3. Conclusions

In summary, we have developed a mild and efficient method for the synthesis of chiral ketones via diastereoselective radical hydroacylation of (–)-8-phenylmenthol derived chiral alkylidenemalonates with aldehydes in highly stereoselective fashion. The reaction proceeds with low catalyst loading of hypervalent iodine(III) reagent under UV-light irradiation. Furthermore, the synthetic utility of this transformation has been demonstrated in the concise formal synthesis of (–)-methyleneolactocin.

4. Experimental section

4.1. General

Infrared (IR) spectra were recorded on a Thermo Scientific Nicolet iS5 spectrometer. ^{1}H NMR spectra were measured on JEOL JNM-ECA500 (500 MHZ) spectrometer. Chemical shits were reported in ppm from tetramethylsilane (in the case of $CDCl_3$) as an internal standard. Data were reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, and app = apparent), and coupling constants (Hz). ^{13}C NMR spectra were recorded on JEOL JNM-ECA500 (125 MHZ) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. Photochemical reactions (365 nm) were carried out using VBL-F30 LED lamp (VBL-F30L-U (365)-3W-H28). High performance liquid chromatography (HPLC) was performed on Shimadzu 20A instruments using chiral columns. The high-resolution mass spectra (HRMS) were performed on Bruker microTOF. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. The products were purified by flash column chromatography on neutral silica gel 60N (Kanto Chemical Co. Inc., 40-50mm). Other simple chemicals were purchased and used as such.

4.2. General procedure for the radical hydroacylation

*4.2.1.Bis(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl)2-((S)-2-Cyclohexyl-2-oxo-1-phenylethyl)malonate (**9b**)*

In a reaction tube containing alkylidene malonate **8b** (0.15 mmol), hypervalent iodine (III) catalyst **1d** (0.03 mmol) and cyclohexanecarboxaldehyde (0.225 mmol) were mixed in CH_3CN:CH_2Cl_2 (1:1) (2.4 M) under argon atmosphere. The mixture was irradiated by UV light (365 nm) with stirring for 12 h. After completion of reaction, solvent was removed under reduced pressure. The diastereoselectivity of hydroacylated products were calculated from 1H NMR spectra of crude products. Purification by flash column chromatography (eluting with hexane/ethyl acetate = 20:1 to 4:1) gave the corresponding hydroacylated product **9b** (91.1 mg, 0.124 mmol, 83% yield). *dr* = 92:08; $[a]^{23}_D$ = 137.97 (*c* 1.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) d 7.32-7.07 (15H, m), 4.80 (1H, dt, *J* = 11.0, 4.5 Hz), 4.72 (0.08H, m), 4.55 (1H, dt, *J* = 11.0, 4.5 Hz), 4.47 (0.92H, d, *J* = 11.5 Hz), 3.95 (1H, m), 2.43 (1H, m), 2.12 (1H, m), 1.94 (1H, m), 1.78 (2H, m), 1.64-1.45 (6H, m), 1.42-1.05 (24H, m), 0.97-0.86 (2H, m), 0.82 (3H, d, *J* = 6.5 Hz), 0.67 (1H, m), 0.60 (3H, d, *J* = 6.5 Hz), 0.52-0.43 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) (data given for major isomer) d 210.4, 168.4, 167.6, 150.6, 150.4, 134.1, 129.8, 128.9, 128.1, 126.1, 126.0, 125.5, 125.3, 76.6, 76.2, 56.3, 55.4, 50.8, 50.3, 49.9, 41.1, 40.6, 40.3, 34.6, 34.2, 31.5, 31.3, 31.0, 29.5, 28.8, 28.6, 27.2, 27.1, 26.0, 25.8, 25.4, 25.1, 23.1, 21.8, 21.5; IR (neat) 2929, 1739, 1707, 1594, 1264 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{49}H_{64}NaO_5$: 755.4646 ([M + Na]$^+$), Found: 755.4653 ([M + Na]$^+$).

*4.2.2. Synthesis of (4S, 5S)-5-Pentyl-4-phenyldihydrofuran-2(3H)-one (**11**)*

To a solution of ketone **9m** (0.228 mmol) in dry THF (2 mL) was added a 3.0 M THF solution of $LiBH_4$ (0.1368 mmol, 45.5 mL) at –78 °C. The reaction mixture was gradually warmed to room temperature within 3 h and continued to stir overnight. The reaction mixture was carefully quenched with saturated aq NH_4Cl solution and extracted with ethyl acetate (3x10 mL). The combined organic extracts were washed with brine (20 mL), then dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude compound was purified by flash column chromatography on silica gel (eluting with hexane/AcOEt = 5/1) to give diastereomeric mixture of γ-butyrolactone **10** and 8-phenyl menthol, which was subjected to next step without further purification. To a solution of **10** (0.164 mmol) in EtOH (2 mL) was added a 3M aqueous solution of KOH (500 mL) at 0 °C. The reaction mixture was allowed to stir at same temperature for 12 h.

It was then poured into mixture of 2N HCl and brine solution. Aqueous layer was then extracted with ethyl acetate (3x10 mL). The combined organic extracts were washed with brine (20 mL), then dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude product was then dissolved in toluene (3 mL) and heated to reflux for 3 h. The reaction mixture was cooled to room temperature and concentrated in *vacuo*. The crude compound was purified by flash column chromatography on silica gel (eluting with hexane/AcOEt = 5/1) to give γ-butyrolactone **11** (18.2 mg, 0.082 mmol, 36% yield).

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