

AN EFFICIENT AND STEREOSELECTIVE CONVERSION OF LACTONES TO SUBSTITUTED CYCLIC ETHERS

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Abstract- A general route to substituted cyclic ethers has been described by using nucleophilic addition of Grignard reagents to lactones in the presence of CeCl_3 followed by the Lewis acid-induced deoxygenation of the corresponding hemiketals with Et_3SiH . Stereoselective reduction of the 5-membered adducts to the disubstituted tetrahydrofurans has been also investigated.

Structurally complex tetrahydrofuran and tetrahydropyran units are often found in many natural products¹ including pheromones,² polyether antibiotics,³ and polyene mycotoxins,⁴ and there has been increasing interest in the synthesis of such ring systems.⁵ Particularly, since tetrahydrofuran derivatives containing chiral 2,3-disubstituents serve as good templates for the convergent construction of antifungal metabolites,⁶ further exploitation of much more convenient stereodefined methods is strongly desired. Although one of the most effective ways to construct these types of compounds is electrophile-induced cyclization⁷ of γ , δ -unsaturated alcohols by use of iodine, *N*-bromosuccinimide, mercury(II) acetate, phenylselenenyl chloride, etc., highly stereoselective forms are not readily available.

On the other hand, direct conversion of lactones to cyclic ethers *via* Lewis acid-induced reduction of hemiketal intermediates with Et_3SiH has been studied especially in the carbohydrate area⁸ for the synthesis of C-glycosyl compounds, however, little has been known on simpler cyclic systems.⁹ The reduction of a hemiketal to a cyclic ether would introduce a new stereogenic center. Thus, in this report we wish to

disclose our results concerning the reactions of Grignard reagents with simple lactones in the presence of CeCl_3 followed by the Lewis acid-promoted deoxygenation. Stereoselective conversion of the three types of 5-membered lactones to the disubstituted tetrahydrofurans is also presented.

As shown in Table 1, we initially investigated the nucleophilic attack of butylmagnesium bromide to the lactone (**1**) in THF followed by the one-pot deoxygenation of the corresponding hemiketal intermediate (**2**) in CH_2Cl_2 with Et_3SiH in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ after evaporation of the solvent *in vacuo*. Whereas the reaction with Grignard reagent only resulted in the low and non-selective formation of the desired **3** (In this reaction accompanying formation of small amounts of **4** (7%) and **5** (5%) derived from the dialkylation of **1** was also observed.), the reaction in the presence of CeCl_3 (1.0 equiv.)¹¹ afforded **3** as a major product (entry 5). The use of other metal halides such as MgBr_2 , SmCl_3 , and MnCl_2 (entries 2-4) brought about unsatisfactory results. After detailed investigations the best result was observed under the conditions indicated in entry 6 in 76% isolated yield.

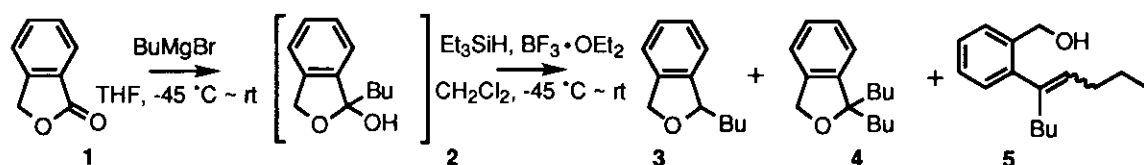


Table 1. Nucleophilic Addition of Grignard Reagents to **1** Followed by the One-pot Deoxygenation.

entry	BuMgBr (equiv.)	additive (equiv.)	Et_3SiH (equiv.)	$\text{BF}_3 \cdot \text{OEt}_2$ (equiv.)	products (%) ^{a)}		
					3	4	5
1	1.2	—	10	10	4	7	5
2	2.4	MgBr_2 (1.0)	10	10	— b)		
3	2.4	SmCl_3 (1.0)	10	10	— b)		
4	2.4	MnCl_2 (1.0)	10	10	5	trace	trace
5	2.4	CeCl_3 (1.0)	10	10	34	5	4
6	2.4	CeCl_3 (2.5)	10	10	76	trace	trace

a) Isolated yield based on the lactone (**1**). b) Grignard addition was not observed. c) Complex mixture.

Next, we examined the reactions with a variety of lactones under similar conditions in the presence of CeCl_3 . The results are summarized in Table 2. After nucleophilic addition of Grignard reagents to the

lactones (**6**), both reactions in Method A and Method B (entries 1,2) as well as the reactions with a 5-methyl substituent (entries 4,5) smoothly proceeded to give the substituted cyclic ethers (**8**) in moderate to good yields. In addition, it became apparent that the procedure described here was also applicable to the synthesis of 7-membered cyclic ether (**8e**) (entry 8).

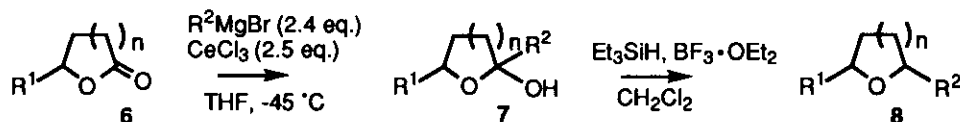


Table 2. Nucleophilic Addition of Grignard Reagents to **6** Followed by the Deoxygenation.

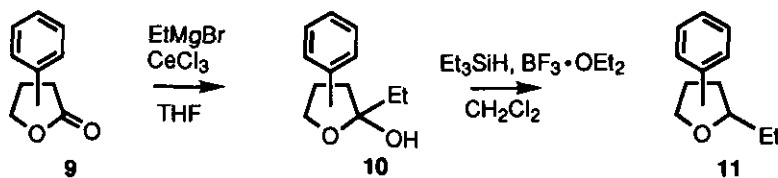
entry	n	lactone (6) R ¹	R ²	Et ₃ SiH (equiv.)	BF ₃ ·OEt ₂ (equiv.)	temp. (°C)	yield of 8 ^{c)} (%)
1 a)	1	H	Ph	4	4	-45 ~ rt	50 (8a)
2 b)	1	H	Ph	4	4	-45	48 (8a)
3 b)	1	H	C ₁₁ H ₂₃	4	4	-45 ~ rt	49 (8b)
4 a)	1	Me	Ph	10	10	-45 ~ rt	75 ^{d)} (8c)
5 b)	1	Me	Ph	4	4	-45	88 ^{d)} (8c)
6 a)	2	H	Ph	10	10	-45 ~ rt	23 (8d)
7 b)	2	H	Ph	4	4	-45	62 (8d)
8 b)	3	H	Ph	4	4	-45 ~ rt	39 (8e)

a) Method A; the deoxygenation was performed without extraction after evaporation of THF *in vacuo*.

b) Method B; the deoxygenation was performed after extraction with ether.

c) Isolated yield based on the lactone (**6**). d) The ratio of the stereoisomers was not determined.

With the above outcome in hand, we turned our attention to the investigations on the relative stereochemistry of the products derived from the reductive deoxygenation of the 5-membered ring lactones (**9**). As shown in Table 3, in the case of the reaction with 3-phenyllactone (**9a**) the Lewis acid-promoted deoxygenation with Et₃SiH proceeded with complete *trans* diastereoselectivity (100 : 0)¹² at low temperature (entry 2). In contrast, a change of the phenyl group to the 4-position on the lactone ring reversely led to the predominant *cis* selectivity (95 : 5) (entry 3 or 4). However, the reaction employing **9c** with 5-phenyl substituent did not indicate any diastereoselectivity.

Table 3. Stereoselective Deoxygenation of the Substituted 5-Membered Lactones (**9**).

entry	lactone 9 a)	temp. (°C)	yield of 11 b) (%)	<i>cis</i> : <i>trans</i> c)
1	9a	-78 ~ rt	25 (11a)	11 : 89
2	9a	-78 ~ -60	23 (11a)	0 : 100
3	9b	-78 ~ rt	38 (11b)	95 : 5
4	9b	-78	44 (11b)	95 : 5
5	9c	-78 ~ rt	53 (11c)	57 : 43
6	9c	-78	53 (11c)	60 : 40

a) **9a**: 3-phenyl-, **9b**: 4-phenyl-, **9c**: 5-phenyllactone.¹³

b) Isolated yield based on the lactone **9** and not optimized. c) Determined by GC analysis.

Recently Schmitt *et al.* reported the replacement of the hydroxyl group of γ -lactols by the alkyl group of organometallic reagents, where 1,2- and 1,3-induction by a single phenyl substituent leads to *trans* selectivities in the formation of tetrahydrofuran derivatives.¹² They rationalize the observed stereochemical outcome based on the reactivity and stability of the oxocarbenium ion intermediate. In our case, the Felkin-Anh model A derived from the 3-phenyl-substituted lactone (**9a**) is also the thermodynamically preferred conformation rather than B (Figure 1). Since phenyl and ethyl groups on the ring occupy the remotest positions each other owing to the steric repulsion, the attack of Et_3SiH could occur preferentially from the less hindered left-site due to the shielding effect of the ethyl function, leading to the *trans*-selective formation of the product. On the other hand, for the 4-phenyl-substituted lactone (**9b**) the phenyl group strongly hinders the attack from the right-site in the thermodynamically less stable model D. Consequently the reaction also could proceed through the attack to the oxocarbenium ion from the left-site of the more stable model C to give the *cis*-selective product predominantly. In the case of the 5-substituted lactone (**9c**), the phenyl substituent is situated in a rather remote position from the reaction center, expecting no selectivity for the formation of the product.

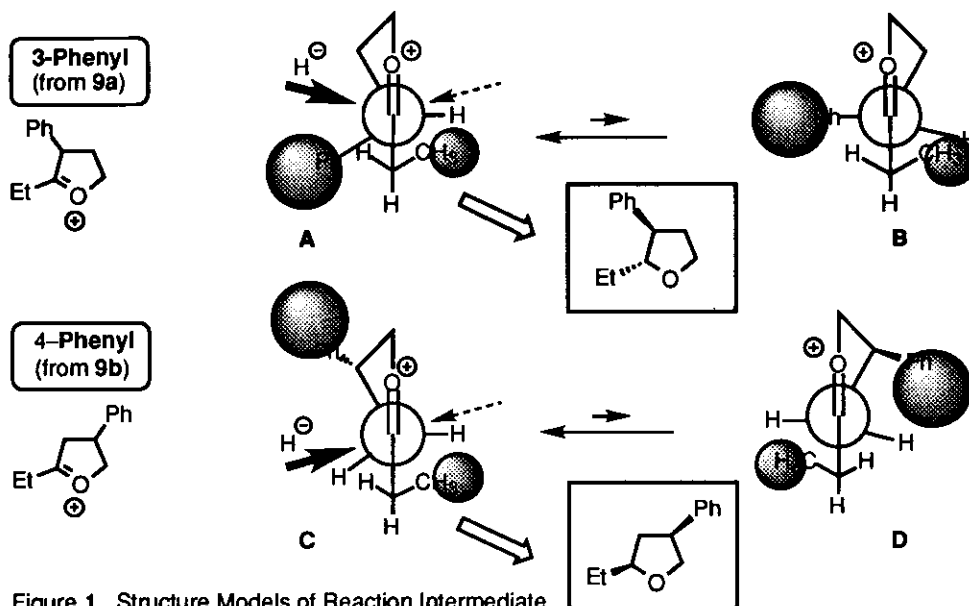


Figure 1. Structure Models of Reaction Intermediate.

In summary, our results demonstrate that the conversion of lactones to cyclic ethers on simpler systems can be achieved in good yield through the nucleophilic addition of Grignard reagents in the presence of CeCl_3 followed by the Lewis acid-induced deoxygenation and furthermore an efficient method to control the stereochemistry of the 1,2- and 1,3-positions in the furan rings has been developed. This strategy provides a new synthetic opportunity for the synthesis of biologically active natural products.

EXPERIMENTAL

IR spectra were recorded on a JASCO Model A-3 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL Model EX-90 spectrometer (operated at 90 and 22.4 MHz, respectively) in CDCl_3 referenced to internal tetramethylsilane (TMS) at 0.0 ppm. MS spectra were recorded on a GCMS-QP5050 Shimadzu, Japan. Reactions were monitored by TLC using 0.25 mm Merck silica gel 60-F254 precoated silica gel plates. Column chromatography was performed on Merck silica gel Kieselgel 60 eluting with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^1H - and ^{13}C -NMR) homogeneous materials. All compounds obtained here are well known and fully characterized.

A TYPICAL PROCEDURE OF METHOD A

2-Phenyltetrahydrofuran (8a): Cerium chloride ($\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$) (0.716 g, 2.90 mmol) was quickly and finely ground to a powder and placed in a flask, which was immersed in an oil bath and heated gradually to 135–140 °C with evacuation (*ca.* 1.0 Torr). After maintenance of the cerium chloride for 1 h, a solution of lactone (**6**) (0.1 g, 1.16 mmol) in THF (6 mL) was added and stirred for 1 h under nitrogen at rt. Then, the reaction mixture was cooled to -45 °C and phenylmagnesium bromide (1.2 M in THF, 2.4 mL, 2.88 mmol) was added. After the solution was stirred for 1 h at the same temperature, it was concentrated *in vacuo*. The residue was dissolved in 6 mL of CH_2Cl_2 and quickly cooled to -45 °C again.

To this solution was added Et_3SiH (1.316 g, 11.32 mmol) and after the mixture was stirred for 5 min, $\text{BF}_3 \cdot \text{OEt}_2$ (1.689 g, 11.89 mmol) was slowly added. Then, the reaction flask was gradually warmed to rt for 2 h. It was quenched by the addition of saturated aqueous NaHCO_3 (3 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by using silica gel column chromatography (20:1 hexane-ethyl acetate) to afford 0.085 g (0.574 mmol, 50%) of the furan (**8a**) as a colorless oil: IR(neat) cm^{-1} 2980, 2870, 1070, 760, 700; $^1\text{H-NMR}$ δ 7.70-7.10 (m, 5H, Ph), 4.88 (t, $J = 7.2$ Hz, 1H, $\text{CH}_2\text{CH}(\text{Ph})\text{O}$), 4.28-3.75 (m, 2H, OCH_2CH_2), 2.48-1.62 (m, 4H, $\text{OCH}_2\text{CH}_2\text{CH}_2\text{CH}(\text{Ph})$); $^{13}\text{C-NMR}$ δ 143.5, 128.3, 127.1, 125.6, 80.6, 68.6, 34.6 26.0; GC-MS m/z 148 (64%, M^+), 147 (78), 105 (100), 77 (48) 42 (51). *Anal.* Calcd for $\text{C}_{10}\text{H}_{12}\text{O}$: C, 81.04; H, 8.16. Found: C, 81.32; H, 8.12.

A TYPICAL PROCEDURE OF METHOD B

2-Phenyltetrahydrofuran (8a): To a suspension of cerium chloride (0.715 g, 2.90 mmol) prepared by the procedure described above in 4 mL of THF was added a solution of lactone (**6**) (0.101 g, 1.17 mmol) in THF (2 mL) and stirred for 1 h under nitrogen at rt. Then, the reaction mixture was cooled to -45°C and phenylmagnesium bromide (1.2 M in THF, 2.4 mL, 2.88 mmol) was added. After the solution was stirred for 1 h at the same temperature, it was quenched by the addition of water (3 mL) and filtered through a pad of Celite followed by the extraction with ether (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give an oil of the crude hemiketal. A solution of the above hemiketal in CH_2Cl_2 (1 mL) was cooled to -45°C and Et_3SiH (0.541 g, 4.65 mmol) was added. After the mixture was stirred for 5 min, $\text{BF}_3 \cdot \text{OEt}_2$ (0.66 g, 4.65 mmol) was slowly added. The solution was further stirred for 2 h at the same temperature and quenched by the addition of saturated aqueous NaHCO_3 (3 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic extracts were dried (Na_2SO_4) followed by the concentration *in vacuo*. The residue was chromatographed (20:1 hexane-ethyl acetate) to give 0.083 g (0.56 mmol, 48%) of the furan (**8a**) as a colorless oil.

2-Butylphthalan (3): colorless oil; IR(neat) cm^{-1} 2960, 2940, 2870, 1460, 1050, 1030, 760; $^1\text{H-NMR}$ δ 7.48-7.05 (m, 4H, Ph), 5.36-5.15 (m, 1H, $\text{PhCH}(\text{Bu})\text{O}$), 5.11 (s, 1H, PhCH_2O), 5.09 (s, 1H, PhCH_2O), 2.08-1.70 (m, 2H, $\text{CHCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.70-1.16 (m, 4H, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.95 (t, $J = 6.3$ Hz, 3H, CH_2CH_3); $^{13}\text{C-NMR}$ δ 142.4, 139.5, 127.3, 127.2, 121.1, 120.9, 84.0, 72.4, 36.1, 27.4, 22.8 14.1; GC-MS m/z 176 (3%, M^+), 119 (100), 91 (39), 65 (14). *Anal.* Calcd for $\text{C}_{12}\text{H}_{16}\text{O}$: C, 81.77; H, 9.15. Found: C, 81.68; H, 9.29.

2,2-Dibutylphthalan (4): colorless oil; IR(neat) cm^{-1} 2900, 2850, 1270, 1130, 1050, 720; $^1\text{H-NMR}$ δ 7.43-6.93 (m, 4H, Ph), 5.07 (s, 2H, PhCH_2O), 2.08-1.03 (m, 12H, $\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.83 (t, $J = 6.0$ Hz, 6H, CH_2CH_3). *Anal.* Calcd for $\text{C}_{16}\text{H}_{24}\text{O}$: C, 82.70; H, 10.41. Found: C, 82.81; H, 10.35.

5-(2'-Hydroxymethylphenyl)-4-nonene (5): colorless oil; IR(neat) cm^{-1} 3600-3000, 2900, 1450, 1020, 730; $^1\text{H-NMR}$ δ 7.73-6.90 (m, 4H, Ph), 5.44, 5.33 (2t, $J = 7.0, 7.0$ Hz, 1H, CCHCH_2), 4.68, 4.62 (2s, 2H, PhCH_2OH), 2.62-1.98 (m, 5H, $\text{CCHCH}_2\text{CH}_2$, $\text{PhCCH}_2\text{CH}_2$, CH_2OH), 1.98-0.47 (m, 12H, $\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$). *Anal.* Calcd for $\text{C}_{16}\text{H}_{24}\text{O}$: C, 82.70; H, 10.41. Found: C, 82.59; H, 10.58.

2-Undecyltetrahydrofuran (8b): colorless oil; IR(neat) cm^{-1} 2930, 2850, 1460, 1080; $^1\text{H-NMR}$ δ

4.11-3.54 (m, 3H, OCH₂CH₂, CH₂CH(C₁₁H₂₃)O), 2.10-1.01 (m, 24H, OCH₂CH₂CH₂CH-(C₁₁H₂₃), CH(CH₂)₁₀CH₃), 0.88 (t, *J* = 5.4 Hz, 3H, (CH₂)₁₀CH₃); ¹³C-NMR δ 79.5, 67.6, 35.8, 32.0, 31.5, 29.9, 29.7, 29.4, 26.5, 25.8, 22.8 14.1; GC-MS *m/z* 226 (0.02%, M⁺), 225 (0.08), 71 (100), 55 (8.9), 43 (30). *Anal.* Calcd for C₁₅H₃₀O: C, 79.58; H, 13.36. Found: C, 79.29; H, 13.51.

2-Methyl-5-phenyltetrahydrofuran (8c): colorless oil; IR(neat)cm⁻¹ 2980, 1450, 1080, 1030, 760, 700; ¹H-NMR δ 7.53-7.09 (m, 5H, Ph), 5.14-4.70 (m, 1H, CH₂CH(Ph)O), 4.52-3.93 (m, 1H, OCH(Me)CH₂), 2.51-1.43 (m, 4H, CH(Me)CH₂CH₂CH(Ph)), 1.34, 1.28 (2d, *J* = 6.2, 6.2 Hz, 3H, CHCH₃); ¹³C-NMR δ 128.3, 127.1, 127.0, 125.8, 125.5, 81.0, 80.2, 75.9, 35.6, 34.6, 34.2, 33.1, 21.6, 21.3; GC-MS *m/z* 162 (75%, M⁺), 105 (99), 77 (56), 56 (100), 41 (65). *Anal.* Calcd for C₁₁H₁₄O: C, 81.44; H, 8.70. Found: C, 81.66; H, 8.58.

2-Phenyltetrahydropyran (8d): colorless oil; IR(neat)cm⁻¹ 2950, 2850, 1100, 1060, 1050, 760, 700; ¹H-NMR δ 7.68-7.10 (m, 5H, Ph), 4.48-3.96 (m, 2H, OCH₂CH₂), 3.80-3.36 (m, 1H, CH₂CH(Ph)O), 2.10-1.27 (m, 6H, OCH₂CH₂CH₂CH₂CH(Ph)); ¹³C-NMR δ 143.4, 128.2, 127.2, 125.8, 80.1, 68.9, 34.1, 25.9, 24.0; GC-MS *m/z* 162 (60%, M⁺), 161 (54), 105 (100), 77 (53), 41 (51). *Anal.* Calcd for C₁₁H₁₄O: C, 81.44; H, 8.70. Found: C, 81.23; H, 8.81.

2-Phenyloxepane (8e): colorless oil; IR(neat)cm⁻¹ 2930, 2850, 1450, 1130, 1040, 750, 700; ¹H-NMR δ 7.49-7.15 (m, 5H, Ph), 4.57 (dd, *J* = 8.4, 4.1 Hz, 1H, CH₂CH(Ph)O), 4.20-3.52 (m, 2H, OCH₂CH₂), 2.28-1.36 (m, 8H, OCH₂CH₂CH₂CH₂CH₂CH(Ph)); ¹³C-NMR δ 144.7, 128.2, 126.8, 125.7, 81.4, 68.7, 37.9, 31.1, 26.8, 25.9; GC-MS *m/z* 176 (39%, M⁺), 107 (53), 105 (100), 79 (44), 42 (65). *Anal.* Calcd for C₁₂H₁₆O: C, 81.77; H, 9.15. Found: C, 81.92; H, 9.03.

2-Ethyl-3-phenyltetrahydrofuran (11a)¹²: colorless oil; IR(neat)cm⁻¹ 2840, 1450, 1090, 1060, 1030, 750, 700; ¹H-NMR (*trans*-11a) δ 7.52-7.01 (m, 5H, Ph), 4.01 (t, *J* = 7.1 Hz, 2H, CH₂CH₂O), 3.73 (td, *J* = 6.1, 7.6 Hz, 1H, OCH(Et)CH(Ph)), 2.90 (q, *J* = 8.4 Hz, 1H, CH(Et)CH(Ph)CH₂), 2.36 (dddd, *J* = 12.5, 8.5, 7.0, 5.0 Hz, 1H, CH(Ph)CH₂CH₂), 2.11 (dddd, *J* = 12.5, 9.0, 8.5, 7.5 Hz, 1H, CH(Ph)CH₂CH₂), 1.78-1.36 (m, 2H, CHCH₂CH₃), 0.91 (t, *J* = 7.2 Hz, 3H, CH₂CH₃); ¹³C-NMR (*trans*-11a) δ 142.4, 128.6, 127.7, 126.5, 87.5, 67.5, 50.9, 35.8, 26.9, 10.6; ¹³C-NMR (*cis*-11a) δ 142.4, 128.6, 128.1, 126.2, 84.5, 66.8, 47.7, 33.5, 24.3, 10.9; GC-MS (*trans*-11a) *m/z* 176 (16%, M⁺), 118 (100), 117 (95), 91 (33); GC-MS (*cis*-11a) *m/z* 176 (10%, M⁺), 118 (100), 117 (76), 57 (22).

2-Ethyl-4-phenyltetrahydrofuran (11b)¹²: colorless oil; IR(neat)cm⁻¹ 2850, 1460, 1080, 1050, 1020, 750, 700; ¹H-NMR (*cis*-11b) δ 7.52-7.13 (m, 5H, Ph), 4.34-3.24 (m, 3H, OCH(Et)CH(Ph), CH(Ph)CH₂O), 2.62-2.20 (m, 1H, CH₂CH(Ph)CH₂), 1.90-1.33 (m, 4H, CH(Et)CH₂CH(Ph), CHCH₂CH₃), 0.98 (t, *J* = 7.2 Hz, 3H, CH₂CH₃); ¹³C-NMR (*trans*-11b) δ 142.8, 128.6, 127.2, 126.5, 80.9, 74.6, 44.7, 39.4, 29.0, 10.4; ¹³C-NMR (*cis*-11b) δ 142.8, 128.6, 127.2, 126.5, 81.8, 74.2, 45.6, 40.7, 28.6, 10.4; GC-MS (*trans*-11b) *m/z* 176 (12%, M⁺), 147 (52), 117 (80), 104 (65), 91 (100); GC-MS (*cis*-11b) *m/z* 176 (15%, M⁺), 147 (74), 117 (98), 104 (59), 91 (100).

2-Ethyl-5-phenyltetrahydrofuran (11c)¹²: colorless oil; IR(neat)cm⁻¹ 2850, 1450, 1080, 1060, 1030, 750, 700; ¹H-NMR (*trans*-11c) δ 7.59-7.12 (m, 5H, Ph), 4.97 (t, *J* = 7.0 Hz, 1H, CH₂CH(Ph)O), 4.29-3.73 (m, 1H, OCH(Et)CH₂), 2.52-1.20 (m, 6H, CH(Et)CH₂CH₂CH(Ph), CHCH₂CH₃), 0.96 (t, *J* = 7.3 Hz, 3H, CH₂CH₃); ¹H-NMR (*cis*-11c) δ 7.59-7.12 (m, 5H, Ph), 4.86 (t, *J* = 6.7 Hz,

1H, CH₂CH(Ph)O), 4.29-3.73 (m, 1H, OCH(Et)CH₂), 2.52-1.20 (m, 6H, CH(Et)CH₂CH₂CH(Ph), CHCH₂CH₃), 0.99 (t, *J* = 7.1 Hz, 3H, CH₂CH₃); ¹³C-NMR (*trans*-11c) δ 144.0, 128.2, 127.1, 125.8, 81.4, 80.2, 35.4, 31.9, 28.9, 10.4; ¹³C-NMR (*cis*-11c) δ 143.6, 128.2, 127.0, 125.6, 81.3, 80.8, 34.5, 30.9, 28.9, 10.3; GC-MS (*trans*-11c) *m/z* 176 (51%, M⁺), 147 (100), 129 (50), 105 (59), 91 (91); GC-MS (*cis*-11c) *m/z* 176 (49%, M⁺), 147 (100), 117 (47), 105 (63), 91 (81).

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