Further studies on the reductive–alkylation of chiral *endo*-himimide derived from (*R*)-phenylglycinol

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Dedicated to Professor Chengye Yuan on the occasion of his 80th birthday
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Abstract
The scope of the reductive–alkylation of chiral *endo*-himimide derived from (*R*)-phenylglycinol was studied. Careful structural studies by means of both X-ray crystallographical analysis and ^{1}H NMR spectroscopy analysis on the intermediates and products obtained during these studies allowed us to assign the structures of all the products obtained, and then to conclude that both the Grignard reagents addition (to 1) and the reductive deoxygenation of **2**/**3** via *N*-acyliminium intermediates **A** occurred stereospecifically from the convex face of either **1** or **A**.

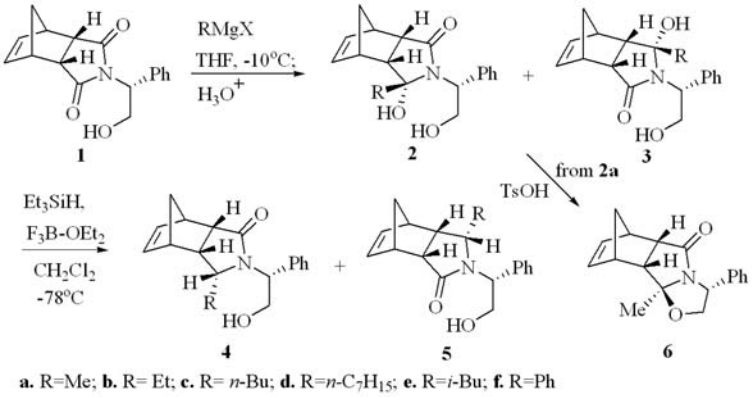
Keywords: (*R*)-Phenylglycinol, *N*-acyliminium, reductive alkylation, himimide asymmetric synthesis

Introduction

We have long been interested in the reductive-alkylation of imides[1]. In our most recent paper[2], the reduction-methylation of chiral *endo*-himimide (**1**) was disclosed (Scheme 1, R = Me).Among four possible products upon methyl magnesium iodide addition to **1**, we observed only two isomers. The structure of one isomer was partially determined in an indirect manner, namely by X-ray crystallographical analysis of its cyclized product (**6**). In continuation of this study, we now describe further structural studies on the products obtained during the reductive-methylation both by ^{1}H NMR technique and by X-ray single crystal analysis and the scope of the reductive-alkylation.

Results and Discussion

Since the structure of one of two isomers (**2a**) obtained during the methyl magnesium iodide addition to **1** (Scheme 1) has been partially determined in our previous study,[1] we focused our attention, firstly, to determine the structure of the other isomer (**3a**). Fortunately, we were able to obtain a single crystal of this isomer. X-ray crystallographical analysis showed that the structure of this isomer is **3a** (Figure 1).



Scheme 1. The reductive–alkylation of chiral *endo*-himimide.

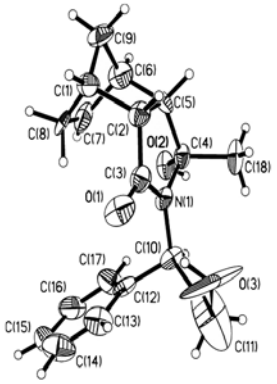


Figure 1. X-ray crystallographical structure of 3a.

Thus, the methyl magnesium iodide addition occurred from the less hindered convex face of the *endo*-himimide **1**. This allowed us to assume that the addition of Grignard reagent to another carbonyl would occur from the convex face as well, and 1ead to **2a**. *N*,*O*-acetal **2a** was then subjected to ionic hydrogenation conditions[3] (Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2,-78°C~rt) to give **4a** as the single diastereomer. Similar treatment of **3a** provided diastereoselectively **5a** as the only isomer.[4] The structure of both **4a** and **5a** were determined by mean of NOESY technology (Figure 2). Careful ^1H and ^{13}C-NMR analysis allowed us to fully assign the ^1H and ^{13}C-NMR peaks of **4a** and **5a** (Table 1).

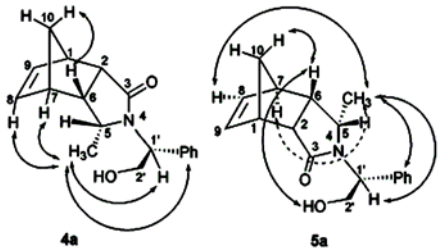


Figure 2. NOE correlations in NOESY spectrum of compound 4a and 5a.

Table 1. Assignment of ^{1}H and ^{13}C NMR peaks of 4a and 5a

Entry		**4a**			**5a**	
	^{1}H(ppm)	**J *(Hz)***	^{13}C (ppm)	^{1}H(ppm)	*J* (Hz)	^{13}C (ppm)
1	3.30	b	45.5	3.32	M	45.5
2	3.28	m	49.4	3.32	M	49.6
3			177.5			177.7
5	3.59	qd, *J* = 6.8, 7.2	54.3	3.78	qd, *J* = 6.8, 8.2	57.3
6	2.80	m	41.7	2.84	m	42.0
7	2.99	b	45.1	2.95	b	45.2
8	6.16	dd, *J* = 2.8, 5.6	134.8	6.05	dd, *J* = 2.9, 5.7	134.9
9	6.21	dd, *J* = 2.2, 5.6	135.1	6.29	dd, *J* = 2.3, 5.7	135.5
10	1.36	d, *J* = 8.4	51.6	1.38	d, *J* = 8.4	51.9
	1.58	d, *J* = 8.4		1.50	d, *J* = 8.4	
11	4.29	dd, *J* = 3.4, 8.1	61.2	4.49	dd, *J* = 3.9, 7.4	61.2
12	3.86	dd, *J* = 3.2, 12.1	64.1	4.01	ddd, *J* = 4.1, 5.1, 11.8	64.6
	4.21	dd, *J* = 8.1, 12.0		4.10	ddd, *J* = 7.4, 7.8, 11.8	
13			137.1			138.1
14	7.20	m	127.3	7.21	m	127.5
15	7.32	m	128.7	7.30	m	128.3
16	7.27	m	127.8	7.26	m	127.4
17	7.32	m	128.7	7.30	m	128.3
18	7.20	m	127.3	7.21	m	127.5
CH_3	1.10	d, *J* = 6.8	15.6	0.95	d, *J* = 6.8	16.9
OH				3.93	dd, *J* = 5.4, 7.8	

Next, we turned our attention to study the scope of this reductive-alkylation. As shown in Table 2, the reductive-alkylation of **1** with ethyl, *n*-butyl and *n*-heptyl magnesium reagents occurred in a similar way to methyl magnesium iodide (Table 2).

Table 2. Preparation of 4/5 via the reductive alkylation of *endo*-himimide 1

Entry	RMgX	Yield (%) (**2**+**3**)	Regiomeric ratio **4** : **5**	Yield (%) (**4**+**5**)
1	MeMgI	97	58 : 42 (**4a** : **5a**)	93
2	EtMgBr	93	70 : 30 (**4b** : **5b**)	90
3	*n*-BuMgBr	67	65 : 35 (**4c** : **5c**)	82
4	*n*-C_7H_{15}MgBr	72	71 : 29 (**4d** : **5d**)	89

However, when *i*-butyl magnesium bromide was used, its addition to **1** gave a more complex mixture of products in a combined yield of 71%. The subsequent deoxygenative reduction led to cyclized compound **7** (16%) and dehydrated compound **8** (58%, Figure 3) instead of the expected **4e** and **5e**. In addition, 20% of starting material **1** was recovered.

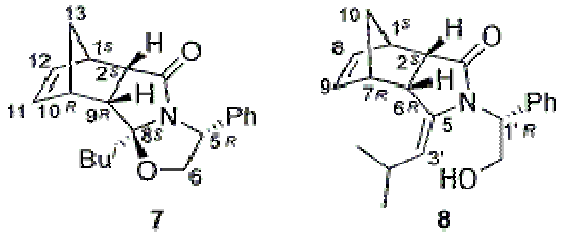


Figure 3. Products obtained from the reductive alkylation of 1 with *i*-butyl magnesium bromide.

Similarly, the attempted reductive-alkylation of **1** with phenyl magnesium bromide was unsuccessful: while the addition of phenyl magnesium bromide to **1** led to two isomers in a ratio of 68: 32 (determined by ^{1}H-NMR, combined yield 67%), the subsequent reductive deoxygenation led to, in addition to the desired **5f** (44%), **2f'** (16%) and an un-separable mixture of **9** and **10** in 57: 63 ratio (determined by ^{1}H NMR, combined yield 13%, Figure 4).

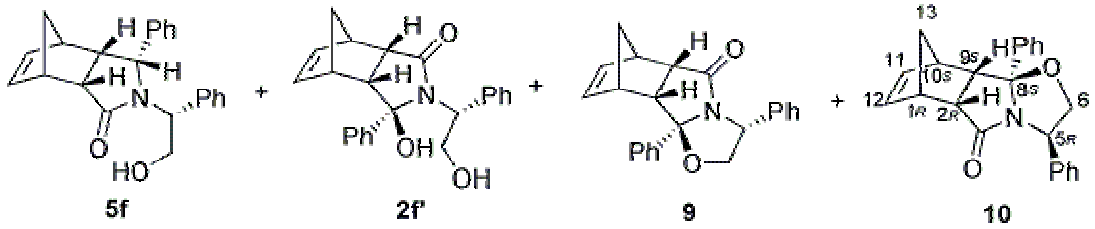
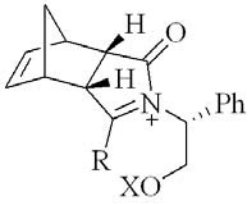


Figure 4. Products obtained from the reductive alkylation of 1 with phenyl magnesium bromide.

The different behavior of **2e**/**3e** and **2f**/**3f** compared with **2a**-**2d**/ **3a**-**3d** may due to steric hindrance of *i*-butyl and phenyl groups, which slowed down the intermolecular hydride addition to the *N*-acyliminium intermediate (**A,** Figure 5).[5] Thus the capture of the *N*-acyliminium intermediates (**A**) by intramolecular nucleophilic addition or water addition, or dehydration of **A** occurred, which led to **7** or **9**/**10** and **2f**, or **8** respectively.



A

Figure 5. *N*-acyliminium intermediate.

To summarize, through careful structural studies, we were able to illustrate the stereochemical course of the reductive-alkylation of **1**, namely, both the Grignard reagents addition (to **1**) and the reductive deoxygenation of **2**/**3** via *N*-acyliminium intermediates **A** occurred stereospecifically from the convex face of either **1** or **A**. The reductive-alkylation is successful with un-branched alkyl magnesium reagent, but unsuccessful with *i*-butyl or phenyl analogues. Thus, the present study opens an easy access to various 4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-3-one derivatives, which may be useful for the syntheses of either 5-substituted 3-pyrrolin-2-ones (after a retro-Diels-Alder reaction),[4] chiral auxiliaries (after cleavage of the 2-hydroxy-1-phenylethyl group) or β-aminoalcohols (after carbonyl reduction).

Experimental Section

General Procedures. Melting points were determined on a Yanaco MP-500 micro melting point apparatus. Infrared spectra were measured with a Shimadza IR-408 spectrometer or a Nicolet Avatar 360 FT-IR spectrometer using film KBr pellet techniques. ^{1}H-NMR spectra were recorded in $CDCl_3$ on a Varian unity +500 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Mass spectra were recorded by Finnigan Mat-LCQ (ESI direct injection). Optical rotations were measured with Perkin-Elmer 341 automatic polarimeter. THF and diethyl ether used in the reactions were dried by distillation over metallic sodium and benzophenone; dichloromethane were distilled over P_2O_5. Silica gel (Zhifu, 300~400 mesh) was used for column chromatography, eluting (unless otherwise stated) with ethyl acetate/petroleum ether (PE) (60-90°C) mixtures.

(+)-(1*R*,2*R*,6*S*,7*S*)-4-[(1′*R*)-1′-phenyl-2′-hydroxy-ethyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3,5-dione (1). A mixture of *endo*-himic anhydride (644 mg, 3.93 mmol) and (*S*)-(+)-phenylglycinol (515 mg, 3.76 mmol) was stirred at 170 ^{o}C for 7 h.[6] The fused mixture was then cooled to rt, before CH_2Cl_2 was added. The resulting solution was dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Flash chromatography (EtOAc/PE = 1:2) afforded **1** (876 mg, 85% yield) as a white crystal. mp: 200-201 ^{o}C. $[\alpha]_D^{20}$ + 4.6 (*c* 0.91, $CHCl_3$); IR (KBr, Pellet) ν_{max}: 3464, 2992, 2968, 2945, 1754, 1686, 1393, 1368, 1174, 1055 cm^{-1}; ^{1}H NMR (500 MHz , $CDCl_3$) δ: 1.53 (d, J = 8.9 Hz, 1H, H-10), 1.71 (d, J = 8.9 Hz, 1H, H-10), 3.28 (m, 2H, H-2, H-6), 3.39 (m, 2H, H-1, H-7), 4.05 (dd, J = 4.9, 11.8 Hz, 1H, H-2′), 4.42 (dd, J = 8.6, 11.8 Hz, 1H, H-2′), 5.14 (dd, J = 4.9, 8.6 Hz, 1H, H-1′), 5.98 (m, 2H, H-8, H-9), 7.25 ~ 7.38 (m, 5H, C_6H_5) ppm; ^{13}C NMR (125 MHz , $CDCl_3$) δ: 44.93, 44.97, 45.26, 45.32, 51.86, 52.41, 61.15, 127.80, 127.95, 128.4, 136.28, 134.16, 134.34, 178.33, 178.44 ppm; MS (EI) (m/z): 284 (MH^+, 3), 253 (80), 199 (10), 186 (100), 158 (10), 120 (10), 106 (12), 92 (13).

General procedure for the preparation of by reductive alkylation of (*R*)-*endo*-himide derivative (1)

To an ice-bath cooled solution of **1** (1.0 mmol) in anhydrous THF (6 mL) was added dropwise a Grignard reagent (5 mmol) in Et_2O under N_2. After stirred at the same temperature for 2 h, the reaction was quenched with saturated aqueous NH_4Cl (6 mL) and extracted with CH_2Cl_2 (3×30 mL). The combined extracts were dried with anhydrous Na_2SO_4 and concentrated in vacuo. Filtration with a short pad of column eluting with EtOAc/PE = 1:2 yielded a mixture of two diastereomers **2** and **3**.

To a cooled (-78 ^{o}C) solution of diastereomer mixture of **2** and **3** (1.0 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise Et_3SiH (10 mmol) and $BF_3{\cdot}OEt_2$ (3.0 mmol) under N_2. After stirring at -78°C for 6 h, the mixture was allowed to warm to ambient temperature and stirred overnight. The reaction was quenched by saturated aqueous $NaHCO_3$ and extracted with dichloromethane (3×20 mL). The combined extracts were washed with brine and dried over anhydrous Na_2SO_4 then concentrated in vacuo. Flash chromatography (EtOAc/PE = 1:2) afforded the desired product **4** and a small amount of **5** (Table 2).

(+)-(1*R*,2*S*,5*R*,6*R*,7*S*)-5-Methyl-4-[(1′*R*)-1′-phenyl-2′-hydroxy-ethyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (4a); (-)-(1*S*,2*R*,5*S*,6*S*,7*R*)-5-methyl-4-[(1′*R*)-1′-phenyl-2′-hydroxy-ethyl]-4-azatricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (5a). Combined yield over two steps 90%. **4a** (faster eluting isomer): colorless oil. $[\alpha]_D^{20}$ +80.1 (*c* 0.76, $CHCl_3$); IR (film) ν_{max}: 3376, 3061, 2968, 2936, 2870, 1652, 1432, 1355, 1300, 1258, 1065 cm^{-1}; ^{1}H NMR (500 MHz , $CDCl_3$) δ: 1.09 (d, J = 6.7 Hz, 3H, CH_3), 1.36 (d, J = 8.3 Hz, 1H, H-10), 1.58 (d, J = 8.3 Hz, 1H, H-10), 2.79 (m, 1H, H-6), 2.99 (m, 1H, H-7), 3.28 (m, 1H, H-1), 3.30 (m, 1H, H-2), 3.59 (dq, J = 6.7, 8.3 Hz, 1H, H-5), 3.86 (dd, J = 3.7, 11.9 Hz, 1H, H-2′), 4.21 (dd, J = 8.2, 11.9 Hz, 1H, H-2′), 4.30 (dd, J = 3.7, 8.2 Hz, 1H, H-1′), 6.16 (dd, J = 2.8, 5.5 Hz, 1H, H-8), 6.20 (dd, J = 1.8, 5.5 Hz, 1H, H-9), 7.20~7.40 (m, 5H, C_6H_5) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ:15.60, 41.67, 45.00, 45.47, 49.36, 51.58, 54.26, 60.63, 63.90, 127.26, 127.69, 128.60, 136.99, 134.76, 135.05, 177.53 ppm; MS

(EI) (m/z) 284 (MH^+, 7), 252 (100), 199 (8), 187 (89), 117 (12), 106 (12), 99 (18); **5a** (slower eluting isomer): white crystal. mp: 100~101 ºC; $[\alpha]_D^{20}$ -51.4 (c 1.06, $CHCl_3$); IR (KBr, Pellet) ν_{max} 3392, 3058, 2974, 2924, 2870, 1654, 1445, 1368, 1053, 698 cm^{-1}; ^1H NMR (500 MHz , $CDCl_3$) δ: 0.95 (d, J = 6.6 Hz, 3H, CH_3), 1.38 (d, J = 8.3 Hz, 1H, H-10), 1.58 (d, J = 8.3 Hz, 1H, H-10), 2.84 (m, 1H, H-7), 2.95 (m, 1H, H-6), 3.32 (m, 1H, H-1), 3.34 (m, 1H, H-2), 3.60 (dq, J = 6.6, 7.2 Hz, 1H, H-5), 4.01 (dd, J = 4.0, 11.8 Hz, 1H, H-2′), 4.11 (dd, J = 7.3, 11.9 Hz, 1H, H-2′), 4.49 (dd, J = 4.0, 7.3 Hz, 1H, H-1′), 6.05 (dd, J = 2.9, 5.8 Hz, 1H, H-8), 6.28 (dd, J = 2.1, 5.8 Hz, 1H, H-9), 7.20~7.40 (m, 5H, C_6H_5) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.90 (1C, CH_3), 41.97, 45.10, 45.47, 49.52, 51.87, 57.29, 61.82, 64.55, 127.32, 127.49, 128.24, 138.02, 134.92, 135.42, 177.69 ppm; MS (EI) (m/z): 284 (MH^+, 2), 252 (49), 199 (3), 186 (100), 117 (7), 92 (7).

(+)-(1*R*,2*S*,5*R*,6*R*,7*S*)-5-ethyl-4-[(1′*R*)-1′-phenyl-2′-hydroxy-ethyl]-4 azatricyclo[5.2.1.$0^{2,6}$] dec-8-en-3-one (4b); (-)-(1*S*,2*R*,5*S*,6*S*,7*R*)-5-Ethyl-4-[(1′*R*)-1′-phenyl-2′-hydroxy-ethyl]-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-3-one (5b). Combined yield over two steps 84%. **4b** (faster eluting isomer): white crystal, mp: 112~113ºC; $[\alpha]_D^{20}$ +129.3 (*c* 1.37, $CHCl_3$); IR (KBr Pellet)ν_{max} 3298, 3061, 2983, 2970, 2876, 1637, 1438, 1358, 1291, 1240, 1066, 695cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.92 (t, J = 7.3 Hz, 3H, CH_3), 1.26 (m, 1H, $CHCH_3$), 1.37 (d, J = 8.6 Hz, 1H, H-10), 1.57 (d, J = 8.6 Hz, 1H, H-10), 1.66 (m, 1H, $CHCH_3$), 2.81 (m, 1H, H-6), 3.08 (m, 1H, H-7), 3.28 (m, 1H, H-1), 3.30 (m, 1H, H-2), 3.36 (ddd, J = 3.7, 7.9, 15.0 Hz, 1H, H-5), 3.89 (dd, J = 3.7, 12.2 Hz, 1H, H-2′), 4.19 (dd, J = 7.9, 12.2 Hz, 1H, H-2′), 4.41 (dd, J = 3.7, 7.9 Hz, 1H, H-1′), 6.15 (dd, J = 2.8, 5.5 Hz, 1H, H-8), 6.20 (dd, J = 2.8, 5.5 Hz, 1H, H-9), 7.20~7.40 (m, 5H, C_6H_5) ppm; MS (EI) (m/z): 298 (MH^+, 5), 266 (52), 200 (100), 173 (16), 112 (25), 106 (5), 91 (13); **5b** (slower eluting isomer): colorless oil. $[\alpha]_D^{20}$ +7.1 (*c* 0.58, $CHCl_3$); IR (film) ν_{max} 3367, 3058, 2964, 2926, 2853, 1654, 1445, 1363, 1260, 1093, 1022, 800, 699cm^{-1}; ^1H NMR (500 MHz , $CDCl_3$), δ 0.89 (t, J = 7.4 Hz, 3H, CH_3), 1.09 (m, 1H, $CHCH_3$), 1.40 (d, J = 8.2 Hz, 1H, H-10), 1.59 (d, J = 8.2 Hz, 1H, H-10), 1.69 (m, 1H, $CHCH_3$), 2.89 (m, 1H, H-6), 3.05 (m, 1H, H-7), 3.30 (m, 1H, H-1), 3.35 (m, 1H, H-2), 3.54 (m, 1H, H-5), 4.00 (dd, J = 2.9, 11.0 Hz, 1H, H-2′), 4.11 (dd, J = 7.3, 11.0 Hz, 1H, H-2′), 4.41 (m, 1H, H-1′), 6.06 (dd, J = 2.5, 5.4 Hz, 1H, H-8), 6.20 (dd, J = 2.5, 5.4 Hz, 1H, H-9), 7.20~7.40 (m, 5H, C_6H_5) ppm; MS (EI) (m/z) 298 (MH^+, 4), 266 (61), 200 (100), 173 (10), 112 (12), 106 (3), 92 (10).

(+)-(1*R*,2*S*,5*R*,6*R*,7*S*)-5-*n*-Butyl-4-[(1′*R*)-1′-phenyl-2′-hydroxy-ethyl]-4-azatricycl[5.2.1.$0^{2,6}$] dec-8-en-3-one (4c); (-)-(1*S*,2*R*,5*S*,6*S*,7*R*)-5-*n*-Butyl-4-[(1′*R*)-1′-phenyl-2′-hydroxy-ethyl]-4-azatricyclo [5.2.1.$0^{2,6}$]dec-8-en-3-one (5c). Combined yield over two steps 90%. **4c** (faster eluting isomer): white crystal, mp: 76~77ºC; $[\alpha]_D^{20}$ +105.9 (*c* 1.1, $CHCl_3$); IR (KBr Pellet)ν_{max} 3384, 3063, 2959, 2932, 2863, 1638, 1440, 1068, 696cm^{-1}; ^1H NMR (500 MHz , $CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3H, CH_3), 1.14, 1.26, 1.42, 1.60 (4m, 6H, 3C$\underline{H}_2$), 1.38 (d, J = 8.3 Hz, 1H, H-10), 1.58 (d, J = 8.3 Hz, 1H, H-10), 2.81 (m, 1H, H-6), 3.06 (m, 1H, H-7), 3.28 (m, 1H, H-1), 3.31 (m, 1H, H-2), 3.42 (m, 1H, H-5), 3.88 (m, 1H, H-2′), 4.22 (m, 1H, H-2′), 4.39 (m, 1H, H-1′), 6.16 (dd, J = 3.0, 5.2 Hz, 1H, H-8), 6.20 (dd, J = 1.4, 5.2 Hz, 1H, H-9), 7.20~7.40 (m, 5H, C_6H_5) ppm; MS (EI) (m/z): 326 (MH^+, 1), 294 (64), 228 (100), 206 (15), 173 (12), 140 (33), 92 (14); **5c** (slower eluting isomer): colorless oil. $[\alpha]_D^{20}$ -6.1 (*c* 0.59, $CHCl_3$); IR (film)ν_{max}: 3367, 3062,

2957, 2931, 2869, 1656, 1446, 1370, 1060, 699 cm^{-1}; ^1H NMR (500 MHz , $CDCl_3$) δ: 0.81 (t, J = 7.0 Hz, 3H, CH_3), 1.09 ~ 1.28 (m, 6H, $3CH_2$), 1.39 (d, J = 8.3 Hz, 1H, H-10), 1.59 (d, J = 8.3 Hz, 1H, H-10), 2.87 (m, 1H, H-6), 3.02 (m, 1H, H-7), 3.32 (m, 1H, H-1), 3.35 (m, 1H, H-2), 3.60 (m, 1H, H-5), 4.01 (dd, J = 3.5, 11.9 Hz, 1H, H-2′), 4.12 (dd, J = 7.3, 11.9 Hz, 1H, H-2′), 4.46 (dd, J = 3.5, 7.3 Hz, 1H, H-1′), 6.06 (dd, J = 2.8, 5.4 Hz, 1H, H-8), 6.20 (dd, J = 2.5, 5.4 Hz, 1H, H-9), 7.20~7.40 (m, 5H, C_6H_5) ppm; MS (EI) (m/z): 325 (MH^+, 4), 294 (85), 228 (100), 173 (8), 140 (11), 92 (14).

(+)-(1*R*,2*S*,5*R*,6*R*,7*S*)-5-*n*- Heptyl-4-[(1′*R*)-1′-phenyl-2′- hydroxy-ethyl]-4- azatricyclo [5.2.1.$0^{2,6}$] dec-8-en-3-one (4d); (-)-(1*S*,2*R*,5*S*,6*S*,7*R*)-5-*n*-Heptyl-4-[(1′*R*)-1′-phenyl-2′-hydroxy-ethyl]-4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-3-one (5d). Combined yield over two steps 64%. **4d** (faster eluting isomer): colorless oil. $[\alpha]_D^{20}$ +88.1 (*c* 0.74, $CHCl_3$); IR (film)ν_{max}: 3367, 3061, 2955, 2961, 2856, 1654, 1431, 1065 cm^{-1}; ^1H NMR (500 MHz , $CDCl_3$) δ: 0.87 (t, J = 7.2 Hz, 3H, CH_3, H), 1.15 ~ 1.23 (m, 13H, C_6H_{13}), 1.37 (d, J = 8.3 Hz, 1H, H-10), 1.56 (d, J = 8.3 Hz, 1H, H-10), 2.80 (ddd, J = 8.3, 8.3, 3.6 Hz, 1H, H-6), 3.05 (m, 1H, H-7), 3.27 (m, 2H, H-2), 3.30 (b, 1H, H-1), 3.41 (ddd, J = 11.1, 8.1, 3.6 Hz, 1H, H-5), 3.87 (dd, J = 3.5, 12.0 Hz, 1H, H-2′, H), 4.22 (dd, J = 8.3, 12.0 Hz, 1H, H-2′), 4.38 (dd, J = 3.5, 8.1 Hz, 1H, H-1′), 6.15 (dd, J = 2.6, 5.5 Hz, 1H, H-8), 6.20 (dd, J = 2.6, 5.5 Hz, 1H, H-9), 7.20 ~ 7.40 (m, 5H, C_6H_5, H) ppm; HRMS (M+H): calcd 368.2584, found 368.2588. **5d** (slower eluting isomer): colorless oil. $[\alpha]_D^{20}$ +1.9 (*c* 0.63, $CHCl_3$); IR (film) ν_{max}: 3366, 3062, 2926, 2855, 1654, 1446, 1372, 1061, 699 cm^{-1}; ^1H NMR (500 MHz , $CDCl_3$) δ: 0.86 (t, J = 7.2 Hz, 3H, CH_3), 1.24 ~ 1.30 (m, 13H, C_6H_{13}), 1.36 (d, J = 8.3 Hz, 1H, H-10), 1.57 (d, J = 8.3 Hz, 1H, H-10), 2.86 (m, 1H, H-6), 3.01 (b, 1H, H-7), 3.31 (m, 2H, H-1, H-2), 3.59 (m, 1H, H-5), 4.00 (dd, J = 3.7, 11.8 Hz, 1H, H-2′), 4.11 (dd, J = 7.4, 11.8 Hz, 1H, H-2′), 4.46 (dd, J = 3.7, 7.4 Hz, 1H, H-1′), 6.05 (dd, J = 2.8, 5.5 Hz, 1H, H-8), 6.29 (dd, J = 2.2, 5.5 Hz, 1H, H-9), 7.20 ~ 7.40 (m, 5H, C_6H_5) ppm; HRMS (M+H): calcd 368.2584, found 368.2586.

(+)-(1*S*,2*S*,5*R*,8*S*,9*R*,10*R*)-8-*i*-Butyl-4-aza-5-phenyl-7-oxotetracyclo[8.2.1.$0^{2,9}$.$0^{4,8}$]tridec-11-en-3-one (7);(+)-(1*R*,2*R*,6*S*,7*S*)-5-*i*-Butylidene-4-[(1′*R*)-1′-phenyl-2′-hydroxy-ethyl]-4-azatricyclo [5.2.1.$0^{2,6}$]dec-8-en-3-one (8). Following the general reductive alkylation procedure, **7** (16%), **8** (58%) and recovered starting material (**1**, 20%) were obtained. The yield of the *iso*-butyl magnesium addition was 91% based on the recovered starting material (**1**, 20%). Compound **7**: colorless oil. $[\alpha]_D^{20}$: -129.5 (*c* 1.1, $CHCl_3$); IR (film) ν_{max}: 3058, 3027, 2955, 2871, 1676, 1603, 1451, 1365, 1156, 1021, 840, 702 m^{-1}; ^1H NMR (500 MHz , $CDCl_3$) δ: 0.93 (t, J = 7.0 Hz, 3H, CH_3), 0.88 (t, J = 6.5 Hz, 3H, CH_3), 1.59 (d, J = 8.3 Hz, 1H, H-13), 1.68 (d, J = 8.3 Hz, 1H, H-13), 1.31 (dd, J = 3.8, 14.9 Hz, 1H, $CHCH_2$), 1.9 (m, 1H, $CHCH_2$), 3.18 (dd, J = 3.7, 9.0 Hz, 1H, H-9), 3.24 (dd, J = 2.5, 2.9 Hz, 1H, H-1, H-10), 3.31 (dd, J = 5.1, 9.0 Hz, 1H, H-2), 3.78 (dd, J = 6.7, 8.5 Hz, 1H, H-6), 4.52 (dd, J = 8.6, 8.6 Hz, 1H, H-6), 5.14 (dd, J = 7.2, 8.2 Hz, 1H, H-5), 6.33 (dd, J = 2.9, 5.7 Hz, 1H, H-11), 6.43 (dd, J = 2.4, 5.0 Hz, 1H, H-12), 7.20 ~7.38 (m, 5H, C_6H_5) ppm; HRMS (M+H): calcd 324.1958, found 324.1963; Compound **8**: colorless oil. $[\alpha]_D^{20}$ +22.0 (*c* 0.76, $CHCl_3$); IR (film)ν_{max} 3389, 3062, 2957, 2867, 1700, 1657, 1409, 1340, 1229, 1055, 699 cm^{-1}; ^1H NMR (500 MHz , $CDCl_3$) δ 0.88 (d, J = 6.6 Hz, 3H, CH_3), 0.97 (d, J = 6.6

Hz, 3H, CH_3), 1.52 (d, J = 7.3 Hz, 1H, H-10), 1.58 (d, J = 7.0 Hz, 1H, H-10), 2.66 (m, 1H, CHCH=), 3.22 (dd, J = 4.3, 8.6Hz, 1H, H-6), 3.29 (m, 2H, H-1, H-7), 3.46 (m, 1H, H-2), 3.74 (b, 1H, OH), 4.10 (m, 2H, H-1′, H-2′), 4.32 (d, J = 10.0 Hz, 1H, CHCH=), 4.88 (b, 1H, H-2′), 6.16 (dd, J = 2.8, 5.5 Hz, 1H, H-8), 6.20 (dd, J = 1.8, 5.7 Hz, 1H, H-9), 7.20~7.40 (m, 5H, C_6H_5) ppm; HRMS (M+H): calcd 324.1958, found 324.1959.

(1*R*,2*S*,5*R*,8*R*,9*R*,10*S*)-4-Aza-5-phenyl-8-phenyl-7-oxotetracyclo[8.2.1.$0^{2,9}$.$0^{4,8}$]tridec-11-en-3-one (9); (1*S*,2*R*,5*R*,8*R*,9*S*,10*R*)-4-aza-5-phenyl-8-phenyl-7-oxotetracyclo [8.2.1.$0^{2,9}$.$0^{4,8}$] tridec-11-en-3-one (10); (+)-(1*R*,2*S*,5*R*,6*R*,7*S*)-4-[(1′*R*)-1′-phenyl-2′-hydroxy-ethyl]-5phenyl-5-hydroxy-4-azatricyclo [5,2,1,$0^{2,6}$]dec-8-en-3-one (2f′); (+)-(1*S*,2*R*,5*R*,6*S*,7*R*)-4-[(1′*R*)-1′-phenyl-2′-hydroxy-ethyl]-5-phenyl-4-azatricyclo [5.2.1.$0^{2,6}$] dec-8-en-3-one (5f). Following the general reductive alkylation procedure, **5f** (44%), **2f'** (16%) and an un-separable mixture of **9** and **10** in 57: 63 ratio (determined by ^{1}H NMR of the crude, combined yield 13%) were obtained. The yield of the phenyl magnesium addition was 91%. Compound **9**: ^{1}H NMR (500 MHz , $CDCl_3$) δ 1.31 (d, J = 8.4 Hz, 1H, H-13), 1.56 (d, J = 8.4 Hz, 1H, H-13), 2.88 (dd, J = 4.9, 8.4 Hz, 1H, H-2), 3.24 (m, 1H, H-1), 3.31 (m, 1H, H-10), 3.68 (dd, J = 5.2, 8.4 Hz, 1H, H-9), 3.84 (dd, J = 8.7, 8.7 Hz, 1H, H-6), 4.60 (dd, J = 8.3, 8.4 Hz, 1H, H-5), 4.90 (dd, J = 8.3, 8.3 Hz, 1H, H-6), 6.15 (dd, J = 3.0, 5.4 Hz, 1H, H-11), 6.31 (dd, J = 3.2, 5.4 Hz, 1H, H-12), 7.05~7.38 (m, 10H, C_6H_5) ppm; Compound **10**: ^{1}H NMR (500 MHz , $CDCl_3$) δ 1.44 (d, J = 7.4 Hz, 1H, H-13), 1.56 (d, J = 7.4 Hz, 1H, H-13), 2.60 (m, 1H, H-10), 3.30 (m, 1H, H-1), 3.46 (dd, J = 4.5, 9.2 Hz, 1H, H-2), 3.50 (dd, J = 3.9, 9.2 Hz, 1H, H-9), 3.56 (dd, J = 8.3, 8.3 Hz, 1H, H-6), 4.38 (dd, J = 8.3, 8.3 Hz, 1H, H-5), 5.16 (dd, J = 8.3, 8.3 Hz, 1H, H-6), 5.34 (dd, J = 2.7, 5.5 Hz, 1H, H-11), 6.20 (dd, J = 3.0, 5.6 Hz, 1H, H-12), 7.20~7.38 (m, 10H, C_6H_5) ppm; **2f′**: colorless oil; $[\alpha]_D^{20}$ +6.4 (*c* 1.1, $CHCl_3$); IR (film) ν_{max}: 3370, 3032, 2957, 2929, 1701, 1393, 1409, 1357, 1279, 1035, 699 cm^{-1}; ^{1}H NMR (500 MHz , $CDCl_3$) δ 1.27 (d, J = 8.6 Hz, 1H, H-10), 1.58 (d, J = 8.6 Hz, 1H, H-10), 2.76 (dd, J = 3.9, 8.4 Hz, 1H, H-2), 3.26 (m, 1H, H-7), 3.32 (m, 1H, H-1), 3.46 (dd, J = 4.8, 8.4 Hz, 1H, H-6), 4.12 (dd, J = 5.4, 8.4 Hz, 1H, H-12), 4.19 (dd, J = 8.4, 8.4 Hz, 1H, H-12), 4.28 (dd, J = 5.4, 8.3 Hz, 1H, H-11), 6.17 (dd, J = 3.0, 5.4 Hz, 1H, H-8), 6.52 (dd, J = 2.8, 5.3 Hz, 1H, H-9), 7.20~7.38 (m, 10H, C_6H_5) ppm; HRMS (M^+-H_2O): calcd 344.1651, found 3344.1654; **5f**: yield 44%, colorless oil; $[\alpha]_D^{20}$ +10.8 (*c* 1.04, $CHCl_3$); IR (film)ν_{max} 3358, 3058, 2970, 2935, 2867, 1661, 1455, 1428, 1353, 1285, 1051, 702 cm^{-1}; ^{1}H NMR (500 MHz , $CDCl_3$) δ: 1.32 (d, J = 8.4 Hz, 1H, H-10), 1.44 (d, J = 8.4 Hz, 1H, H-10), 2.44 (m, 1H, H-7), 3.20 (ddd, J = 3.6, 9.5, 9.8 Hz, 1H, H-6), 3.28 (m, 1H, H-1), 3.45 (dd, J = 4.8, 9.8 Hz, 1H, H-2), 3.96 (m, 1H, H-12), 4.30 (dd, J = 3.8, 8.4 Hz, 1H, H-11), 4.38 (m, 1H, H-12), 4.56 (dd, J = 6.9, 7.1 Hz, 1H, OH), 4.62 (d, J = 9.5 Hz, 1H, H-5), 5.66 (dd, J = 2.7, 5.5 Hz, 1H, H-8), 6.22 (dd, J = 3.0, 5.5 Hz, 1H, H-9), 7.08~7.38 (m, 10H, C_6H_5) ppm; HRMS (M+H): calcd 346.1802, found 346.1794.

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References

1. For relative reductive alkylation of imides, see: (a) Burgess, L. E.; Meyers, A. I. *J. Org. Chem*. **1992**, *57*, 1656. (b) Yoda, H.; Kitayama, H.; Yamada, W.; Katagiri, T.; Takabe, K. *Tetrahedron: Asymmetry* **1993**, *4,* 1451. (c) Huang, P.-Q.; Wang, S. L.; Zheng, H.; Fei, X. S. *Tetrahedron Lett*. **1997**, *38*, 271. (d) Huang, P.-Q.; Wang, S. L.; Ye, J. L.; Ruan, Y. P.; Huang, Y. Q.; Zheng, H.; Gao, J. X. *Tetrahedron* **1998**, *54*, 12547. (e) Huang, P.-Q; Chen, Q. F.; Chen, C.-L.; Zhang, H.-K. *Tetrahedron: Asymmetry* **1999**, *10*, 3827. (f) Chen, M. D.; He, M. Z.; Huang, L. Q.; Ruan, Y. P.; Huang, P.-Q. *Chin. J. Chem*. **2002**, *20*, 1149. (g) Huang, P.-Q.; Zheng, X. *ARKIVOC* **2003**, *(ii)*, 7. (h) Chen, M. D.; Zhou, X.; He, M. Z.; Ruan, Y. P.; Huang, P.-Q. *Tetrahedron* **2004**, *60*, 1651.
2. Ye, J. L.; Wei, Z. B., Chen, Z; Huang, P. Q. *Chin. J. Struct. Chem.* **2003**, *22,* 228.
3. Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633.
4. For other approaches to 5-substituted 4-azatricyclo[5.2.1.$0^{2,6}$]dec-8-en-3-ones, see: (a) Arai, Y.; Kontani, T.; Koizumi, T. *Chem. Lett.* **1991**, 2135. (b) Arai,Y.; Fujii, A.; Ohno, T.; Koizumi, T. *Chem. & Pharm. Bull*. **1992**, *40*, 1670. (c) Arai, Y.; Kontani, T.; Koizumi, T. *Tetrahedron: Asymmetry* **1992**, *3*, 535. (d) Arai, Y.; Kontani, T.; Koizumi, T. *J. Chem. Soc., Perk. Trans. 1* **1994**, 15.
5. For recent reviews on the N-acyliminium chemistry, see: (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (b) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104,* 1431.
6. Wijnberg, B. P.; Speckamp, W. N.; Oostveen, A. R. C. *Tetrahedron* **1982,** *38,* 209.