Stereoselective Addition of Organoaluminium or Organomanganese Reagents to α-Formyl Amides or α-Methyl-Substituted β-Keto Amides

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Treatment of α-formyl amides with $RAlCl_2$ or $PhAlCl_2$ provided *threo*-α-alkyl-substituted β-hydroxy amides under high stereocontrol. The method was successfully applied to the selective addition of alkyl group to α-methyl-substituted β-keto amides or esters. Treatment of α-methyl-β-keto amides or α-methyl-β-keto esters with trialkylaluminium or alkylmanganese halide afforded the corresponding *erythro* (or *threo*) α-methyl-substituted β-hydroxy amides or α-methyl-substituted β-hydroxy esters with high stereoselectivity.

We have reported an effective procedure for the stereoselective $NaBH_4$ reduction of α-methyl-substituted β-keto amides or esters into *erythro* α-methyl-substituted β-hydroxy amides or esters in the presence of a catalytic amount of $MnCl_2$.[1] However, our attempts to obtain *threo* hydroxy amides or hydroxy esters selectively from keto amides or keto esters by the reduction with $NaBH_4$ in the presence of various metal chlorides other than $MnCl_2$ were not successful.[2] Thus, we started our research in the hope of developing an alternative method to obtain *threo*-α-methyl-substituted β-hydroxy amides or esters with high stereoselectivity. One promising solution to this problem is the stereoselective addition of organometallic reagent to 2-formylpropionamide (**1a**). Here we wish to report a procedure for the selective preparation of *threo* hydroxy amides by the use of organoaluminium reagents and also an extension of the method for the stereoselective addition of an organometallic reagent to β-keto amides or esters.[3]

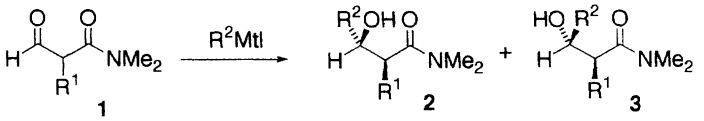
(1) Stereoselective Addition of Alkyl- or Phenylaluminium Dichloride to α-Formyl Amides Providing *threo* α-Alkyl-Substituted β-hydroxy Amides. α-Formylpropionamide (**1a**) was chosen as a substrate and the stereoselectivity in the addition of various organometallic reagents (Me-Mtl/Me stand for methyl, Mtl stand for metal) to **1a** was examined. Methyllithium or methylmagnesium iodide provided the complex mixture and the desired hydroxy amide was obtained in only <20% yield as a stereoisomeric mixture (**2a**:**3a**=40:60 or 43:57). Treatment of **1a** with $MeMnCl$[4] gave *threo*-3-hydroxy-2-methylbutanamide **2a** selectively (**2a**:**3a**=73:27) but the yield was poor (20%). Trimethylaluminium or $MeCeCl_2$,[5] which is a less basic reagent, afforded a mixture of **2a** and **3a** (59:41 or 34:66) in moderate yield (45 or 50%). The poor selectivity with these reagents might be attributed to the high reactivity of the formyl group compared to that of the keto group (vide infra). The addition of Me_3Al to formyl group could proceed without any formation of six-membered metal chelates with another organoaluminium reagent.

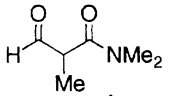
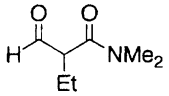
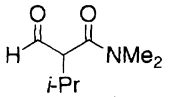
Methylaluminium dichloride, which is a weaker nucleophile but stronger Lewis acid than trimethylaluminium, proved to be effective for the addition and both the yield and the ratio of **2a** to **3a** were improved (**2a**:**3a**=97:3, Table 1, Entry 3). Ethylaluminium dichloride and phenylaluminium dichloride also gave the corresponding *threo* α-methyl-substituted β-hydroxy amides, **2b** and **2c**, with high selectivity. The *threo* selectivity increased as the size of the alkyl group of the starting amide increased. For instance, α-isopropyl-substituted amide **1c** afforded *threo* product **2g** with high stereoselectivity (**2g**:**3g**=99:1) upon treatment with $MeAlCl_2$. Two equivalents of aluminium dichloride were required to complete the reaction. The reaction did not take place with one equivalent of the reagent. Dichloromethane, hexane, and toluene were equally effective as solvents. The yield of the product decreased in diethyl ether and the reaction did not proceed in tetrahydrofuran. We assume the following reaction mechanism based on these facts. Coordination of the first aluminium reagent to α-formyl amide activates the carbonyl group and at the same time causes the formation of aluminate RAl^-Cl_3 from the second aluminium reagent,[6] which is a more effective nucleophile than aluminium dichloride, as shown in Scheme 1. The stereoselective attack of alkyl group of aluminate on formyl carbonyl carbon from the opposite side of 2-alkyl group of **1** in a six-membered metal chelate gives *threo* hydroxy amide **2** selectively.[7]

Meanwhile, organotitanium reagents[8] showed different behavior from organoaluminium dichloride. Treatment of **1a** with $MeTiCl_3$ afforded *erythro* hydroxy amide **3a** selectively. The replacing of chloride of $MeTiCl_3$ with isopropoxide did not improve the selectivity dramatically. The use of $PhTiCl_3$ provided *erythro* hydroxy amide **3c** with high stereoselectivity. High *erythro* selectivity was observed only for the reaction of **1a**, whereas the reaction of **1b** and **1c** proceeded with poor selectivity and gave *threo* isomers as major products (Entries 14 and 18). The reason for these variable selectivities was not clear.

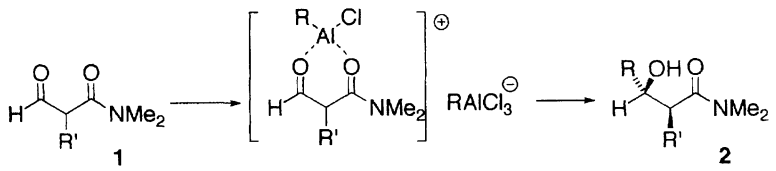
(2) Stereoselective Addition of Organoaluminium or Organomanganese Reagents to α-Methyl-Substituted β-Keto Amides or Esters. The aldol type reaction is a general preparative method for tertiary β-hydroxy carboxylic acid derivatives. However, it is difficult to control the stereochemistry of the

Table 1. Reaction of α-Formyl Amides with Organometallic Reagents[a)]

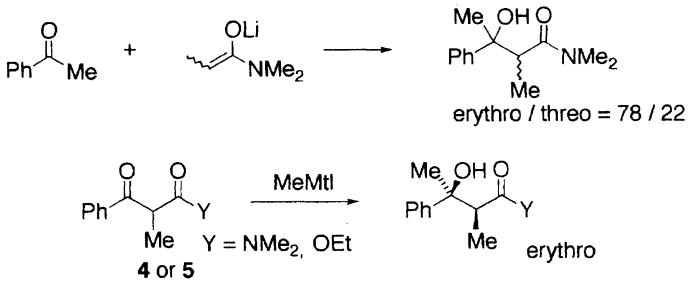


Entry	Substrate	R^2-Mtl	Yield/%	Ratio of **2** : **3**
1		Me_3Al	45	59 (**2a**) : 41 (**3a**)
2		Me_2AlCl	38	93 (**2a**) : 7 (**3a**)
3		$MeAlCl_2$	66	97 (**2a**) : 3 (**3a**)
4		$MeTiCl_3$	38	20 (**2a**) : 80 (**3a**)
5	**1a**	$MeTi(O\textit{i}Pr)Cl_2$	62	62 (**2a**) : 38 (**3a**)
6		$MeTi(O\textit{i}Pr)_2Cl$	66	86 (**2a**) : 14 (**3a**)
7		$MeTi(O\textit{i}Pr)_3$	44	76 (**2a**) : 24 (**3a**)
8		Et_3Al	60	35 (**2b**) : 65 (**3b**)
9		Et_2AlCl	84	90 (**2b**) : 10 (**3b**)
10		$EtAlCl_2$	63	96 (**2b**) : 4 (**3b**)
11		$PhAlCl_2$	53	93 (**2c**) : 7 (**3c**)
12		$PhTiCl_3$	43	4 (**2c**) : 96 (**3c**)
13		$MeAlCl_2$	56	97 (**2d**) : 3 (**3d**)
14		$MeTiCl_3$	74	53 (**2d**) : 47 (**3d**)
15		$EtAlCl_2$	40	99 (**2e**) : 1 (**3e**)
16	**1b**	$PhAlCl_2$	46	96 (**2f**) : 4 (**3f**)
17		$MeAlCl_2$	62	99 (**2g**) : 1 (**3g**)
18		$MeTiCl_3$	77	89 (**2g**) : 11 (**3g**)
19		$EtAlCl_2$	72	99 (**2h**) : 1 (**3h**)
20	**1c**	$PhAlCl_2$	55	99 (**2i**) : 1 (**3i**)

a) α-Formyl amide (1.0 mmol) and organometallic reagent (2.0 mmol) were employed. The reactions were performed at 0 °C.



Scheme 1.

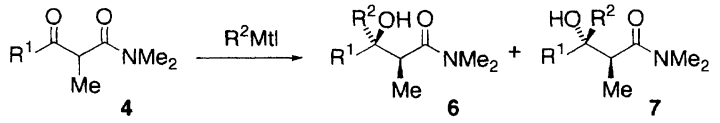


Scheme 2.

reaction between ketone and enolate anion. For example, acetophenone gave β-hydroxy amide as a stereoisomeric mixture (*erythro*: *threo*=78:22) upon treatment with enolate derived from propionamide. It then occurred to us that, if the reaction of α-alkyl-substituted β-keto amides or esters with alkyl carbanion instead of hydride should proceed through the same six-membered metal chelate as shown in the reduction of α-alkyl-substituted β-keto amides or esters with $MnCl_2$–$NaBH_4$ system, the addition of proper organometallics to α-alkyl-substituted β-keto amides or esters would provide a stereoselective preparative route to β-hydroxy amides or esters having tertiary hydroxy moiety (Scheme 2).

The methine proton of β-keto amides **4** or β-keto esters **5** is appreciably acidic. Thus, the amides **4** or esters **5** would yield highly stabilized enolate ions upon treat-

Table 2. Addition of Organometallic Reagents to α-Methyl β-Keto Amides[a)]

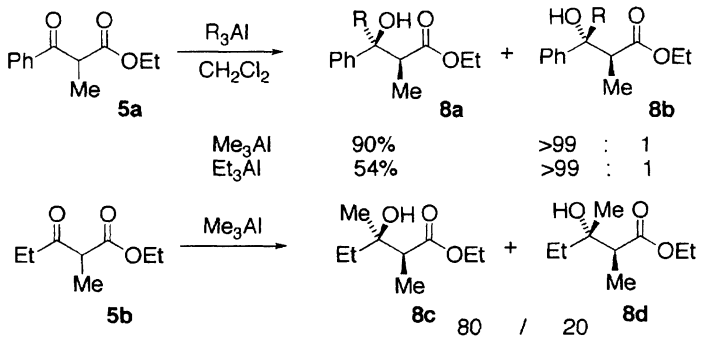


Entry	Keto Amide	R^2-Mtl	Solvent	Yield/%	Ratio of **6** : **7**
1		MeMnCl	THF	93	>99 (**6a**) : <1 (**7a**)
2		Me_3Al	CH_2Cl_2	90	>99 (**6a**) : <1 (**7a**)
3		$MeTiCl_3$	Ether	80	>99 (**6a**) : <1 (**7a**)
4	Ph, NMe₂, Me (**4a**)	Et_2AlCl	CH_2Cl_2	88	>99 (**6b**) : <1 (**7b**)
5		*n*-BuMnCl	THF	98	>99 (**6c**) : <1 (**7c**)
6		$(n\text{-BuC}\equiv\text{C})_3Al$[b)]	Ether	84	>99 (**6d**) : <1 (**7d**)
7		CH_2=CHMnI	Ether	83	>99 (**6e**) : <1 (**7e**)
8		Et_3Al	CH_2Cl_2	18	>99 (**6f**) : <1 (**7f**)
9		Et_2AlCl	CH_2Cl_2	76	>99 (**6f**) : <1 (**7f**)
10	Me, NMe₂, Me (**4b**)	*n*-BuMnCl	THF	74	83 (**6g**) : 17 (**7g**)
11		PhMnCl	THF	83	>99 (**7a**) : <1 (**6a**)
12		CH_2=CHMnI	Ether	66	90 (**6h**) : 10 (**7h**)
13		Me_3Al	CH_2Cl_2	81	>99 (**7f**) : <1 (**6f**)
14	Et, NMe₂, Me (**4c**)	MeMnCl[c)]	THF	25	d)
15		MeMnCl	Ether	91	83 (**7f**) : 17 (**6f**)
16		PhMnI	Ether	52	93 (**7b**) : 7 (**6b**)
17		MeMnCl	THF	<10	d)
18	*t*-Bu, NMe₂, Me (**4d**)	Me_3Al	CH_2Cl_2	87	>99 (**6i**) : <1 (**7i**)
19		$MeTiCl_3$	Ether	58	>99 (**6i**) : <1 (**7i**)

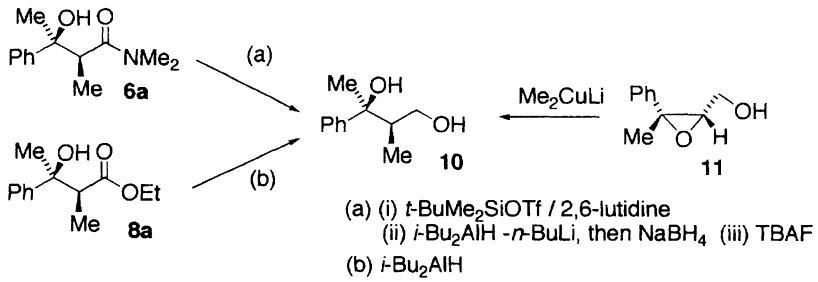
a) β-Keto amide (1.0 mmol) and organometallic reagent (2.0 mmol) were employed. The reactions were performed at 0 °C. b) Prepared from $AlCl_3$ and three equivalents of lithium acetylide. c) Methylmanganese chloride (4.0 mmol) were employed. d) Not determined.

ment with a base. In fact, methyllithium mainly attacked the methine proton of **4a** to generate the lithium enolate, which gave the starting β-keto amide **4a** (51%) upon workup, and the desired β-hydroxy amide was obtained as a stereoisomeric mixture (**6a**:**7a**=22:78) in only 37% combined yield. The use of methylmagnesium iodide resulted in a selective formation of **6a** (**6a**:**7a**=99:1) in moderate yield (51%).[9] We expected that an addition of a less basic organomanganese reagent such as MeMnCl or *n*-BuMnCl to **4a** would provide the corresponding *erythro*-3-methyl (or 3-butyl)-3-hydroxy-2-methyl alkanamide **6a** (or **6c**) stereoselectively in good yield. This was indeed the case and treatment of **4a** with MeMnCl (or *n*-BuMnCl) gave *erythro*-3-phenyl-3-hydroxy-2-methylbutanamide **6a** (or *erythro*-3-phenyl-3-hydroxy-2-methylheptanamide **6c**) exclusively.[10] The selective formation of erythro product **6a** or **6c** can be attributed to the selective attack of methyl group or butyl group from the opposite side of the 2-methyl group of **4a** in a six-membered metal chelate. Meantime, the reaction of **4b** with PhMnCl provided the opposite stereoisomer, *threo*-3-phenyl-3-hydroxy-2-methylbutanamide **7a** stereoselectively (Table 2, Entry 11). Thus, both stereoisomers **6a** and **7a** could be obtained with high stereoselectivity by exchanging the R^1 group of the substrate for the R^2 group of the organometallic reagent.

As shown in Table 2, the stereoselectivities are high for all of the substrates **4a**—**4d** with the exception of the reaction of **4b** with *n*-BuMnCl. An addition of an equimolar amount of MeMnCl to **4a** resulted in the formation of **6a** in <50% yield along with the recovered starting material.[11] Two equivalents of organomanganese reagent were necessary for the completion of the reaction.[12] The reaction may involve the coordination of the β-keto amide **4a** to the first organomanganese reagent, forming a six-membered metal chelate. The stereoselectivity of alkylation is thus interpreted by the attack of the second organomanganese reagent on the carbonyl carbon from the opposite side of the methyl group of **4a**.[13] Organoaluminium reagents proved to be as effective as organomanganese reagents for the stereoselective formation of α-methyl-substituted β-hydroxy amides. Not only alkyl groups but also alkynyl groups could be introduced stereoselectively. Organotitanium reagent ($MeTiCl_3$) gave the same stereoisomeric products as trimethylaluminium, in contrast to the alkylation of α-formyl amide discussed in Section (1), in which organotitanium reagent afforded different stereochemical outcomes from aluminium reagent.



Scheme 3.



Scheme 4.

Additions of organometallic reagents to β-keto ester **5a** or **5b** instead of β-keto amides **4** was examined (Scheme 3). In such cases, organoaluminium reagents proved to be superior to the corresponding organomanganese reagents. For instance, treatment of **5a** with trimethylaluminium gave the desired β-hydroxy ester **8a**[14] selectively in 90% yield. On the other hand, the addition of *n*-BuMnCl to **5a** gave a complex mixture and no trace of **8a** was observed in the reaction mixture.[15] The reaction of **5a** with triethylaluminium provided the corresponding β-hydroxy ester in moderate yield (54%), along with a reduced product (PhCH(OH)CHMeCOOEt) in 33% yield (*erythro*/*threo*=57/43).

The stereochemistry of the products **6** or **8** was assigned as follows. Reduction of *erythro*-amide **6a** with *n*-BuLi-*i*-Bu_2AlH followed by $NaBH_4$[16] gave *erythro* diol **10**, which was identical with a sample derived from epoxy alcohol **11** upon treatment with Me_2CuLi.[17] Reduction of β-hydroxy ester **8a** with *i*-Bu_2AlH afforded the same diol **10** (Scheme 4). Treatment of an epoxy alcohol derived from (*E*)-3-phenyl-2-buten-1-ol with Me_2CuLi afforded *threo* diol **12** (PhC(OH)MeCH(Me)-CH_2OH), which was identical with a sample derived from **7a**.

In conclusion, (1) addition of alkylaluminium dichloride or phenylaluminium dichloride to α-formyl amides provided *threo*-α-alkyl β-hydroxy amide with high stereoselectivity; this new method complements the selective preparation of *erythro*-α-alkyl β-hydroxy amide by the reduction of α-alkyl β-keto amides with $NaBH_4$ in the presence of a catalytic amount of $MnCl_2$. And (2), treatment of α-methyl β-keto amides (or esters) with trialkylaluminium or alkylmanganese halide provided both *erythro*-α-methyl β-hydroxy amides (or esters) and *threo* isomers with high stereoselectivity.

Experimental

Distillation of the products was performed by the use of Kugelrohr (Büchi), and boiling points are indicated by air-bath temperature values without correction. Melting points were obtained on a Yanako MP-50929 melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were taken on a Varian GEMINI 300 spectrometer, $CDCl_3$ was used as solvent, and chemical shifts are given in δ with tetramethylsilane as an internal standard. IR spectra were determined on a JASCO IR-810 spectrometer. The analyses were carried out at the Elemental Analysis Center of Kyoto University.

Preparation of α-Formyl Amides. α-Formyl Amides **1a**,[18] **1b**, and **1c** were prepared by Claisen condensation of ethyl formate with lithium enolate derived from *N*,*N*-dimethylpropionamide, *N*,*N*-dimethylbutanamide, and *N*,*N*,3-trimethylbutanamide, respectively (70—80% yields).

2-Formyl-*N*,*N*-dimethylbutanamide (1b): Bp 59—60 °C (6 Torr, 1 Torr=133.322 Pa); IR (neat) 3428, 2964, 2934, 2876, 1725, 1639, 1500, 1460, 1401, 1264, 1154 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.97 (t, *J*=7.5 Hz, 3H), 1.89—2.04 (m, 2H), 3.00 (s, 3H), 3.06 (s, 3H), 3.42 (td, *J*=7.0, 3.3 Hz, 1H), 9.61 (d, *J*=3.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ=11.61, 21.19, 35.59, 37.31, 57.12, 168.7, 199.6. Found: C, 58.46; H, 9.38%. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15%.

2-Formyl-3,*N*,*N*-trimethylbutanamide (1c): Bp 51—53 °C (0.7 Torr); IR (neat) 3420, 2960, 2872, 1724, 1636, 1498, 1470, 1399, 1155 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ= 0.99 (d, *J*=6.8 Hz, 6H), 2.51—2.63 (m, 1H), 3.00 (s, 3H), 3.06 (s, 3H), 3.20 (dd, *J*=9.5, 4.7 Hz, 1H), 9.60 (d, *J*=4.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ=19.99, 20.66, 28.79, 35.65,

37.46, 63.22, 168.3, 200.9. Found: C, 60.94; H, 9.8%. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62%.

Preparation of β-Keto Amides and β-Keto Esters. These compounds were prepared according to the reported procedure.[1b)]

General Procedure for the Reaction of α-Formyl Amides with Organometallic Reagents. The reaction of **1c** with $MeAlCl_2$ was representative. Methylaluminium dichloride (1.0 M hexane solution, 1 M=1 mol dm^{-3}, 2.0 ml, 2.0 mmol) was added to a solution of 2-formyl-3-methylbutanamide **1c** (158 mg, 1.0 mmol) in dichloromethane (5.0 ml) at 0 °C under argon atmosphere and the reaction mixture was stirred for 2 h at 25 °C. The resulting mixture was poured into 1 M HCl and extracted with $CHCl_3$–EtOH (3:1, 20 ml×2). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by silica-gel column chromatography gave a stereoisomeric mixture of **2g** and **3g** (106 mg, 62% yield), whose isomeric ratio was determined by capillary gas chromatography (Silicone OV-17, 0.32 mm i.d., 50 m, 150° C, **2g**:**3g**=99:1).

***threo*-3-Hydroxy-2-isopropyl-*N*,*N*-dimethylbutanamide (2g):** Bp 55—56 °C (6 Torr); IR (neat) 3398, 2960, 2870, 1612, 1459, 1400, 1163, 1124, 1029 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.90 (d, J=6.5 Hz, 3H), 1.06 (d, J=6.3 Hz, 3H), 1.14 (d, J=6.5 Hz, 3H), 2.20—2.32 (m, 1H), 2.35 (dd, J=10.0, 2.9 Hz, 1H), 3.02 (s, 3H), 3.08 (s, 3H), 3.95—4.07 (m, 1H), 4.47 (d, J=9.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ= 20.38, 21.20, 22.63, 28.50, 35.23, 38.10, 52.73, 66.03, 176.4. Found: C, 62.12; H, 11.28%. Calcd for $C_9H_{19}NO_2$: C, 62.39; H, 11.05%.

***erythro*-3-Hydroxy-2-isopropyl-*N*,*N*-dimethylbutanamide (3g):** Bp 65—66 °C (6 Torr); IR (neat) 3386, 2960, 2872, 1620, 1500, 1459, 1401, 1166, 1112, 1080 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.96 (d, J=6.8 Hz, 3H), 1.03 (d, J=6.9 Hz, 3H), 1.26 (d, J=6.4 Hz, 3H), 2.15—2.27 (m, 1H), 2.65 (dd, J=6.9, 5.1 Hz, 1H), 2.83 (bs, 1H), 2.98 (s, 3H), 3.10 (s, 3H), 4.11 (qd, J=6.5, 5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ= 20.60, 20.70, 21.89, 27.31, 35.39, 38.21, 52.25, 68.29, 174.7. Found: C, 62.17; H, 11.05%. Calcd for $C_9H_{19}NO_2$: C, 62.39; H, 11.05%.

Physical data of **2a**,[1b)] **3a**,[1b)] **2b**,[1b)] **3b**,[1b)] **2c**,[1b)] **3c**,[1b)] **2f**,[19)] and **3f**,[19)] are available in the literature and those of **2d**, **3d**, **2e**, **3e**, **2h**, **3h**, and **2i** are shown below.

***threo*-3-Hydroxy-2-ethyl-*N*,*N*-dimethylbutanamide (2d):** Bp 60—61 °C (6 Torr); IR (neat) 3380, 2962, 2930, 2874, 1618, 1500, 1459, 1415, 1401, 1264, 1161, 1116 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.96 (t, J=7.5 Hz, 3H), 1.20 (d, J=6.4 Hz, 3H), 1.70—1.85 (m, 2H), 2.60 (td, J=7.1, 4.2 Hz, 1H), 3.00 (s, 3H), 3.08 (s, 3H), 3.85—3.98 (m, 1H), 4.15 (d, J=8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ=11.79, 22.12, 23.35, 35.31, 37.73, 48.09, 68.12, 176.1. Found: C, 60.14; H, 10.98%. Calcd for $C_8H_{17}NO_2$: C, 60.35; H, 10.76%.

***erythro*-3-Hydroxy-2-ethyl-*N*,*N*-dimethylbutanamide (3d):** Bp 60—62 °C (5 Torr); IR (neat) 3376, 2962, 2930, 2872, 1617, 1505, 1463, 1403, 1162, 1081 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.92 (t, J=7.5 Hz, 3H), 1.20 (d, J=6.6 Hz, 3H), 1.66—1.88 (m, 2H), 2.63 (ddd, J=9.2, 5.1, 3.0 Hz, 1H), 3.00 (s, 3H), 3.09 (s, 3H), 3.95—4.05 (m, 2H); ^{13}C NMR ($CDCl_3$) δ=12.11, 19.32, 20.39, 35.42, 37.76, 47.45, 67.83, 176.6. Found: C, 60.10; H, 10.88; N, 8.64%. Calcd for $C_8H_{17}NO_2$: C, 60.35; H, 10.76; N, 8.80%.

***threo*-3-Hydroxy-2-ethyl-*N*,*N*-dimethylpentanamide (2e):** Bp 55—56 °C (3 Torr); IR (neat) 3386, 2960, 2932, 2874, 1618, 1500, 1463, 1416, 1400, 1161, 1126 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.96 (t, J=7.5 Hz, 3H), 0.97 (t, J=7.4 Hz, 3H), 1.33—1.55 (m, 2H), 1.71—1.83 (m, 2H), 2.66 (td, J=7.2, 3.5 Hz, 1H), 2.99 (s, 3H), 3.08 (s, 3H), 3.57 (m, 1H), 4.24 (d, J=9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ=10.61, 11.91, 23.48, 29.25, 35.28, 37.70, 45.93, 73.75, 176.5. Found: C, 62.14; H, 11.02; N, 8.05%. Calcd for $C_9H_{19}NO_2$: C, 62.39; H, 11.05; N, 8.08%.

***erythro*-3-Hydroxy-2-ethyl-*N*,*N*-dimethylpentanamide (3e):** Bp 60—61 °C (3 Torr); IR (neat) 3402, 2960, 2932, 2872, 1623, 1501, 1460, 1402, 1156, 979 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.91 (t, J=7.5 Hz, 3H), 0.97 (t, J=7.4 Hz, 3H), 1.36—1.88 (m, 4H), 2.70 (ddd, J=9.7, 4.4, 2.9 Hz, 1H), 3.00 (s, 3H), 3.09 (s, 3H), 3.67 (ddd, J=7.9, 5.2, 2.9 Hz, 1H), 4.08 (s, 1H); ^{13}C NMR ($CDCl_3$) δ=10.50, 12.17, 19.20, 27.15, 35.76, 37.74, 45.65, 73.42, 176.7. Found: C, 62.46; H, 11.13; N, 7.93%. Calcd for $C_9H_{19}NO_2$: C, 62.39; H, 11.05; N, 8.08%.

***threo*-3-Hydroxy-2-isopropyl-*N*,*N*-dimethylpentanamide (2h):** Bp 54—55 °C (2.5 Torr); IR (neat) 3394, 2958, 2930, 2872, 1616, 1465, 1399, 1164, 1126 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.90 (d, J=6.5 Hz, 3H), 0.98 (t, J=7.3 Hz, 3H), 1.06 (d, J=6.4 Hz, 3H), 1.22—1.48 (m, 2H), 2.24—2.36 (m, 1H), 2.40 (dd, J=10.1, 2.6 Hz, 1H), 3.00 (s, 3H), 3.08 (s, 3H), 3.61—3.70 (m, 1H), 4.42 (d, J=10.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ=10.80, 20.42, 21.18, 28.47, 29.78, 25.17, 38.01, 51.16, 71.90, 176.6. Found: C, 64.15; H, 11.28; N, 7.45%. Calcd for $C_{10}H_{21}NO_2$: C, 64.13; H, 11.30; N, 7.48%.

***erythro*-3-Hydroxy-2-isopropyl-*N*,*N*-dimethylpentanamide (3h):** Mp 98.5—99.0 °C; IR (Nujol) 3348, 2920, 2852, 1614, 1459, 1421, 1378, 1367, 1099, 1082, 975 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.97 (d, J=6.8 Hz, 3H), 0.97 (t, J=7.4 Hz, 3H), 1.02 (d, J=7.0 Hz, 3H), 1.55 (qd, J=7.5, 7.0 Hz, 2H), 2.19—2.30 (m, 1H), 2.68 (dd, J=6.4, 5.0 Hz, 1H), 2.98 (s, 3H), 3.07 (d, J=3.3 Hz, 1H), 3.09 (s, 3H), 3.75—3.83 (m, 1H); ^{13}C NMR ($CDCl_3$) δ=10.68, 20.42, 22.01, 27.10, 27.36, 35.35, 38.15, 50.85, 73.84, 174.9. Found: C, 63.86; H, 11.18%. Calcd for $C_{10}H_{21}NO_2$: C, 64.13; H, 11.30%.

***threo*-2-(α-Hydroxybenzyl)-*N*,*N*,3-trimethylbutanamide (2i):** Bp 63—64 °C (0.6 Torr); IR (neat) 3344, 2958, 2870, 1611, 1453, 1415, 1400, 1156, 1057, 701 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.91 (d, J=6.6 Hz, 3H), 1.21 (d, J=6.6 Hz, 3H), 2.33—2.46 (m, 1H), 2.42 (s, 3H), 2.60 (dd, J=10.3, 2.7 Hz, 1H), 2.73, (s, 3H), 5.00 (dd, J=9.5, 2.7 Hz, 1H), 5.48 (d, J=9.5 Hz, 1H), 7.20—7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ=20.30, 21.29, 28.42, 34.96, 37.24, 54.75, 72.05, 125.0, 127.0, 128.0, 144.0, 175.1. Found: C, 71.35; H, 8.99%. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99%.

General Procedure for Addition of Organometallic Reagents to α-Methyl-β-Keto Amides. A typical experimental procedure is as follows. A THF solution of β-keto amide **4a**(0.21 g, 1.0 mmol) was added to a solution of MeMnCl (2.0 mmol) prepared from $MnCl_2$and MeLi in THF at 0 °C under argon atmosphere. After being stirred for 1 h at 0 °C, the resulting mixture was poured into water and extracted with ethyl acetate (20 ml×3). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification by silica-gel column chromatography gave *erythro*-α-methyl β-hydroxy amide **6a** (0.21 g) in 93% yield: Mp 130—131 °C; IR (nujol) 3252, 2920, 2852, 1611, 1499, 1459,

1421, 1377, 1309, 1255, 1202, 1146, 1120, 1066, 705, 682, 649 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.88 (d, J=7.0 Hz, 3H), 1.52 (s, 3H), 3.01 (q, J=6.9 Hz, 1H), 3.04 (s, 3H), 3.15 (s, 3H), 5.91 (s, 1H), 7.2—7.6 (m, 5H); ^{13}C NMR ($CDCl_3$) δ=12.58, 29.97, 35.53, 37.67, 43.81, 74.69, 124.9, 126.4, 128.0, 146.0, 177.7. Found: C, 70.49; H, 8.85%. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65%.

***threo*-3-Phenyl-3-hydroxy-*N*,*N*,2-trimethylbutanamide (7a):** Mp 72.0—73.0 °C; IR (Nujol) 3356, 2926, 2852, 1615, 1459, 1378, 1365, 1316, 1258, 1231, 1138, 1087, 1064, 935, 770, 711, 657, 627 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.35 (d, J=7.0 Hz, 3H), 1.47 (s, 3H), 2.65 (s, 3H), 2.80 (s, 3H), 3.19 (q, J=7.0 Hz, 1H), 6.05 (s, 1H), 7.2—7.6 (m, 5H); ^{13}C NMR ($CDCl_3$) δ=12.14, 27.11, 35.01, 37.15, 43.16, 72.65, 124.4, 127.9, 148.7, 177.0. Found: C, 70.58; H, 8.84%. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65%.

***erythro*-3-Phenyl-3-hydroxy-*N*,*N*,2-trimethylpentanamide (6b):** Mp 95.0—95.5 °C; IR (Nujol) 3204, 2850, 1617, 1456, 1376, 1132, 968, 766, 711 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.65 (t, J=7.3 Hz, 3H), 0.87 (d, J=7.0 Hz, 3H), 1.69 (m, 2H), 3.02 (q, J=7.1 Hz, 1H), 3.04 (s, 3H), 3.16 (s, 3H), 5.61 (s, 1H), 7.20—7.45 (m, 5H); ^{13}C NMR ($CDCl_3$) δ=7.816, 12.56, 34.14, 35.51, 37.68, 43.60, 77.74, 125.6, 126.2, 127.9, 143.5, 177.9. Found: C, 71.34; H, 8.88%. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99%.

***threo*-3-Phenyl-3-hydroxy-*N*,*N*,2-trimethylpentanamide (7b):** Mp 103.0—103.5 °C; IR (Nujol) 3334, 2924, 2852, 1608, 1458, 1402, 1377, 1308, 1164, 1060, 703 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.65 (t, J=7.4 Hz, 3H), 1.28 (d, J=6.9 Hz, 3H), 1.64 (dq, J=13.5, 7.4 Hz, 1H), 2.00 (dq, J=13.5, 7.4 Hz, 1H), 2.63 (s, 3H), 2.84 (s, 3H), 3.20 (q, J=7.0 Hz, 1H), 6.00 (s, 1H) 7.15—7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ=7.484, 11.88, 31.57, 35.01, 37.23, 42.81, 77.21, 125.3, 126.2, 127.8, 146.3, 177.2. Found: C, 71.39; H, 9.29%. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99%.

***erythro*-3-Phenyl-3-hydroxy-*N*,*N*,2-trimethylheptanamide (6c):** Bp 63—64 °C (0.4 Torr); IR (Nujol) 3326, 2932, 2866, 1618, 1451, 1417, 1401, 1175, 1133, 702, 632 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.76 (t, J=7.5 Hz, 3H), 0.85 (d, J=7.1 Hz, 3H), 1.05—1.46 (m, 4H), 1.69—1.79 (m, 2H), 2.99 (q, J=7.1 Hz, 1H), 3.04 (s, 3H), 3.16 (s, 3H), 5.70 (s, 1H), 7.20—7.45 (m, 5H); ^{13}C NMR ($CDCl_3$) δ=12.50, 14.04, 23.05, 25.71, 35.56, 37.71, 41.41, 43.80, 125.5, 126.2, 127.9, 144.0, 178.0. Found: C, 72.90; H, 9.77%. Calcd for $C_{16}H_{25}NO_2$: C, 72.97; H, 9.57%.

***threo*-3-Phenyl-3-hydroxy-*N*,*N*,2-trimethylheptanamide (7c):** Bp 63—65 °C (0.4 Torr); IR (neat) 3324, 2952, 1618, 1459, 1447, 1414, 1397, 1163, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.78 (t, J=7.2 Hz, 3H), 1.10—1.40 (m, 4H), 1.33 (d, J=6.9 Hz, 3H), 1.57—1.67 (m, 1H), 1.88—1.97 (m, 1H), 2.62 (s, 3H), 2.83 (s, 3H), 3.18 (q, J=7.0 Hz, 1H), 6.01 (d, J=1.5 Hz, 1H), 7.15—7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ=11.94, 13.96, 23.12, 25.22, 35.04, 37.24, 38.81, 43.13, 125.2, 126.2, 127.8, 146.7, 177.2. Found: C, 72.75; H, 9.76%. Calcd for $C_{16}H_{25}NO_2$: C, 72.97; H, 9.57%.

***threo*-3-Phenyl-3-hydroxy-*N*,*N*,2-trimethyl-4-nonynamide (6d):** Bp 76—78 °C (0.45 Torr); IR (neat) 3294, 2954, 2928, 2870, 1623, 1452, 1415, 1399, 1171, 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.87 (d, J=7.0 Hz, 3H), 0.19 (t, J=7.1 Hz, 3H), 1.34—1.52 (m, 4H), 2.20 (t, J=5.3 Hz, 2H), 3.06 (s, 3H), 3.11 (q, J=7.1 Hz, 1H), 3.15 (s, 3H), 6.44 (s, 1H), 7.22—7.40 (m, 3H), 7.60—7.63 (m, 2H); ^{13}C NMR ($CDCl_3$) δ=11.24, 13.60, 18.32, 21.74, 30.68, 35.55, 37.71, 46.02, 72.27, 83.88, 83.96, 125.9, 127.2, 127.8, 142.3, 177.2. Found: C, 75.03; H, 8.95%. Calcd for $C_{18}H_{25}NO_2$: C, 75.23; H, 8.76%.

***threo*-3-Hydroxy-*N*,*N*,2,3-tetramethylpentanamide (6f):** Bp 105 °C (8 Torr); IR (neat) 3380, 2968, 2936, 1619, 1459, 1398, 1138, 980, 915 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.86 (t, J=7.6 Hz, 3H), 1.14 (s, 3H), 1.15 (d, J=7.0 Hz, 3H), 1.38—1.69 (m, 2H), 2.69 (q, J=7.0 Hz, 1H), 2.99 (s, 3H), 3.09 (s, 3H), 5.26 (s, 1H); ^{13}C NMR ($CDCl_3$) δ=7.967, 11.49, 25.45, 31.24, 35.30, 37.56, 40.23, 72.70, 177.9. Found: C, 62.09; H, 11.27%. Calcd for $C_9H_{19}NO_2$: C, 62.39; H, 11.05%.

***erythro*-3-Hydroxy-*N*,*N*,2,3-tetramethylpentanamide (7f):** Bp 105 °C (8 Torr); IR (neat) 3380, 2968, 2932, 1619, 1459, 1418, 1400, 1134, 917 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.89 (t, J=7.5 Hz, 3H), 1.10 (s, 3H), 1.20 (d, J=7.1 Hz, 3H), 1.41 (dq, J=14.0, 7.0 Hz, 1H), 1.55 (dq, J=13.8, 7.3 Hz, 1H), 2.68 (q, J=7.1 Hz, 1H), 2.98 (s, 3H), 3.08 (s, 3H), 5.03 (s, 1H); ^{13}C NMR ($CDCl_3$) δ=8.582, 12.81, 22.52, 34.50, 35.31, 37.46, 40.95, 73.11, 178.7. Found: C, 62.09; H, 11.27%. Calcd for $C_9H_{19}NO_2$: C, 62.39; H, 11.05%.

***threo*-3-Hydroxy-*N*,*N*,2,3-tetramethylheptanamide (6g):** Bp 67—68 °C (6 Torr); IR (neat) 3378, 2952, 2932, 2868, 1619, 1459, 1416, 1400, 1136 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.88 (t, J=7.1 Hz, 3H), 1.11 (s, 3H), 1.20 (d, J=7.1 Hz, 3H), 1.10—1.53 (m, 6H), 2.66 (q, J=7.2 Hz, 1H), 2.98 (s, 3H), 3.08 (s, 3H), 5.07 (s, 1H); ^{13}C NMR ($CDCl_3$) δ=12.05, 14.10, 23.27, 26.54, 35.33, 37.49, 38.69, 41.23, 41.91, 72.87, 178.0. Found: C, 65.60; H, 11.79%. Calcd for $C_{11}H_{23}NO_2$: C, 65.63; H, 11.52%.

***erythro*-3-Hydroxy-*N*,*N*,2,3-tetramethylheptanamide (7g):** Bp 67—68 °C (6 Torr); IR (neat) 3380, 2954, 2934, 2866, 1620, 1460, 1398, 1371, 1139 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.93 (t, J=7.0 Hz, 3H), 1.15 (s, 3H), 1.15 (d, J=7.0 Hz, 3H), 1.15—1.56 (m, 6H), 2.68 (q, J=7.0 Hz, 1H), 2.99 (s, 3H), 3.08 (s, 3H), 5.27 (s, 1H); ^{13}C NMR ($CDCl_3$) δ=11.62, 14.04, 23.26, 25.84, 26.19, 35.33, 37.61, 38.64, 40.68, 72.41, 177.9. Found: C, 65.48; H, 11.64%. Calcd for $C_{11}H_{23}NO_2$: C, 65.63; H, 11.52%.

***threo*-3-Hydroxy-*N*,*N*,2,3-tetramethyl-4-pentenamide (6h):** Bp 65—67 °C (15 Torr); IR (neat) 3358, 2976, 2934, 1618, 1416, 1400, 1140, 924, 634 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.22 (s, 3H), 1.23 (d, J=7.0 Hz, 3H), 2.75 (q, J=7.0 Hz, 1H), 2.93 (s, 3H), 3.05 (s, 3H), 5.00 (dd, J=10.6, 1.3 Hz, 1H), 5.24 (dd, J=17.2, 1.3 Hz, 1H), 5.44 (s, 1H), 5.88 (dd, J=17.2, 10.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ=11.56, 24.87, 35.22, 37.48, 41.69, 73.27, 112.2, 145.0, 177.2. Found: C, 63.08; H, 9.91%. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01%.

***erythro*-3-Hydroxy-*N*,*N*,2,3-tetramethyl-4-pentenamide (7h):** Bp 65—67 °C (15 Torr); IR (neat) 3366, 2972, 2932, 1619, 1465, 1420, 1402, 1125, 997, 931 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.13 (d, J=7.1 Hz, 3H), 1.26 (s, 3H), 2.67 (q, J=7.1 Hz, 1H), 3.00 (s, 3H), 3.09 (s, 3H), 5.13 (dd, J=10.7, 1.8 Hz, 1H), 5.36 (dd, J=17.2, 1.8 Hz, 1H), 5.38 (d, J=1.1 Hz, 1H), 5.70 (ddd, J=17.2, 10.7, 1.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ=12.48, 28.10, 35.34, 37.57, 41.85, 73.45, 113.3, 142.3, 177.4. Found: C, 63.08; H, 9.84%. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01%.

***erythro*-3-Hydroxy-*N*,*N*,2,3,4,4-hexamethylpentan-**

amide (6i): Bp 76—77 °C (14 Torr); IR (neat) 3374, 2956, 2874, 1622, 1473, 1397, 1171, 1099, 911 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.02 (s, 9H), 1.13 (s, 3H), 1.24 (d, J=6.9 Hz, 3H), 2.97 (s, 3H), 3.01 (q, J=6.9 Hz, 1H), 3.09 (s, 3H), 4.65 (s, 1H); ^{13}C NMR ($CDCl_3$) δ=14.85, 23.67, 26.98, 35.50, 37.77, 38.46, 39.99, 76.13, 178.6. Found: C, 65.40; H, 11.37%. Calcd for $C_{11}H_{23}NO_2$: C, 65.63; H, 11.51%.

Ethyl 3-Hydroxy-2,3-dimethylpentanoate (8c/8d=80/20): Bp 53—54 °C (8 Torr); IR (neat) 3444, 2974, 2938, 1731, 1713, 1460, 1376, 1340, 1194 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.89 (t, J=7.6 Hz, 2.4H), 0.93 (t, J=7.5 Hz, 0.6H), 1.12 (s, 0.6H), 1.18 (s, 2.4H), 1.18—1.21 (two d, 3H, including δ=1.19, J=7.2 Hz, 2.4H for **8c**), 1.29 (t, J=7.1 Hz, 3H), 1.48—1.56 (two dq, 2H, including δ=1.52, J=7.7, 2.0 Hz, 1.6H for **8c**), 2.51 (q, J=7.2 Hz, 0.8H), 2.55 (q, J=7.4 Hz, 0.2H), 3.23 (s, 0.2H), 3.25 (s, 0.8H), 4.14—4.22 (two qd, 2H, including δ=4.18, J=7.2, 1.0 Hz, 1.6H for **8c**); ^{13}C NMR ($CDCl_3$) δ=7.940, 8.107, 11.93, 12.34, 14.16, 22.47, 25.14, 30.90, 34.01, 46.76, 46.96, 60.57, 72.77, 73.05, 176.9. Found: C, 61.80; H, 10.23%. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41%.

***cis*-3-Phenyl-2,3-epoxy-1-butanol (11):** Bp 69—70 °C (9 Torr); IR (neat) 3366, 2972, 2926, 1725, 1498, 1445, 1379, 1053, 1028, 1007, 863, 763, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.45 (bs, 1H), 1.68 (s, 3H), 3.24—3.33 (m, 2H), 3.42—3.47 (m, 1H), 7.26—7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ=24.64, 61.83, 62.84, 64.40, 126.1, 127.5, 128.3, 138.9. Found: C, 72.87; H, 7.49%. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37%.

***erythro*-2-Methyl-3-phenyl-1,3-butanediol (10):** Bp 90—93 °C (0.3 Torr); IR (neat) 3324, 2926, 2884, 1495, 1447, 1375, 1140, 1105, 1069, 1057, 1026, 927, 763, 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.81 (d, J=7.1 Hz, 3H), 1.66 (s, 3H), 1.98—2.15 (m, 1H), 2.98 (bs, 2H), 3.55 (dd, J=11.0, 6.0 Hz, 1H), 3.84 (dd, J=11.0, 3.5 Hz, 1H), 7.2—7.6 (m, 5H); ^{13}C NMR ($CDCl_3$) δ=12.70, 29.21, 44.22, 65.70, 78.13, 125.3, 126.6, 127.9, 146.0. Found: C, 73.13; H, 9.00%. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95%.

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