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[A0006]

Asymmetric Synthesis of Quaternary a-Amino Acids Using D-Ribonolactone Acetonide as a Chiral Auxiliary

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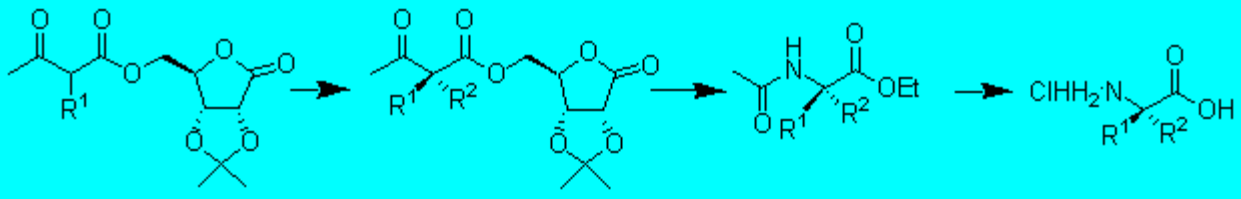
Abstract



$R^1 = CH_3$, $R^2 = PhCH_2$, 4-BrPhCH$_2$, 2-NaphtCH$_2$
$R^1 = Bu$, $R^2 = 4$-BrPhCH$_2$, 2-NaphtCH$_2$

Preparation of a,a -disubstituted glycines is a matter of current interest owing to their importance as enzyme inhibitors and peptide modifiers. Herein, we describe a new simple methodology to prepare enantiopure a,a -dialkylglycines based on the use of commercially available D-ribonolactone as chiral auxiliary. Enantiopure a -methyl and a -butyl series are prepared through diastereoselective alkylation and posterior Schmidt rearrangement of a,a -dialkylacetoacetates of D-ribonolactone acetonide. Absolute configuration was assigned through preparation of enantiopure 4,4-disubstituted 3-methyl-2-pyrazolin-5-ones.

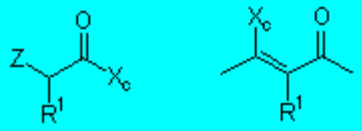
The high interest in the preparation of enantiomerically pure a,a -disubstituted glycines is based on their remarkable properties as enzyme inhibitors [1] and as conformational modifiers of peptides [2]. Especially a-methyl series have been extensively studied [3].

Due to the current interest in these compounds many synthetic methodologies have already been developed [4]. One synthetic approach is the use of cyclic derivatives such as Sch�llkopf's bis(lactim)ether, prepared generally from L-*tert*-leucine and including two amino ester separation in the process of isolation of desired products. Others cyclic substrates are Seebach's oxazolidinones, imidazolidinones and 2,5-dihydroimidazoles [5] their synthesis including classical resolution through diastereoisomeric salt formation or chromatographic separation on a chiral column. N�jera's oxazinones and tetrahydropyrazinones [6] have been also used with real success. Also remarkable are the results from Davies, who has used oxazolidinones derived from ferrocenecarbaldehyde and sodium (*S*)-alaninate [7] and the work of Sandri using chiral morpholine derivatives [8]. An alternative involves the palladium-

catalyzed asymmetric allylation of azlactones [9].

A different approach is based on the diastereoselective alkylation of activated methylene groups in open chain compounds. Remarkable diastereoselective alkylations have been achieved for 2-cyanoesters of enantiopure dicyclohexylsulfamoylisoborneol by Cativiela and coworkers [10] (**1**, Z=CN). After the appropriate rearrangement process the diastereomerically pure a, a-dialkylcyanoacetate can be elaborated to afford both enantiomers of the same amino acid. An alternative consists of the incorporation of the chiral auxiliary in the form of an enamine (**2**). Koga has reported [11] the alkylation of lithioenamines derived from a-alkyl-b-ketoesters and (*S*)-valine *tert*-butyl ester. The a,a-dialkyl- b-ketoesters obtained had been used by Georg and coworkers as intermediates to prepare a,a-disubstituted glycines [12]. Fukumoto et al. have worked on chiral derivatives of malonic acid. Precursors of amino acids are prepared through diastereoselective alkylation of 8-phenylmenthyl a-alkylmalonic monoesters (**1**, Z=COOH) followed by several transformations including a Curtius rearrangement [13].

Figure 1

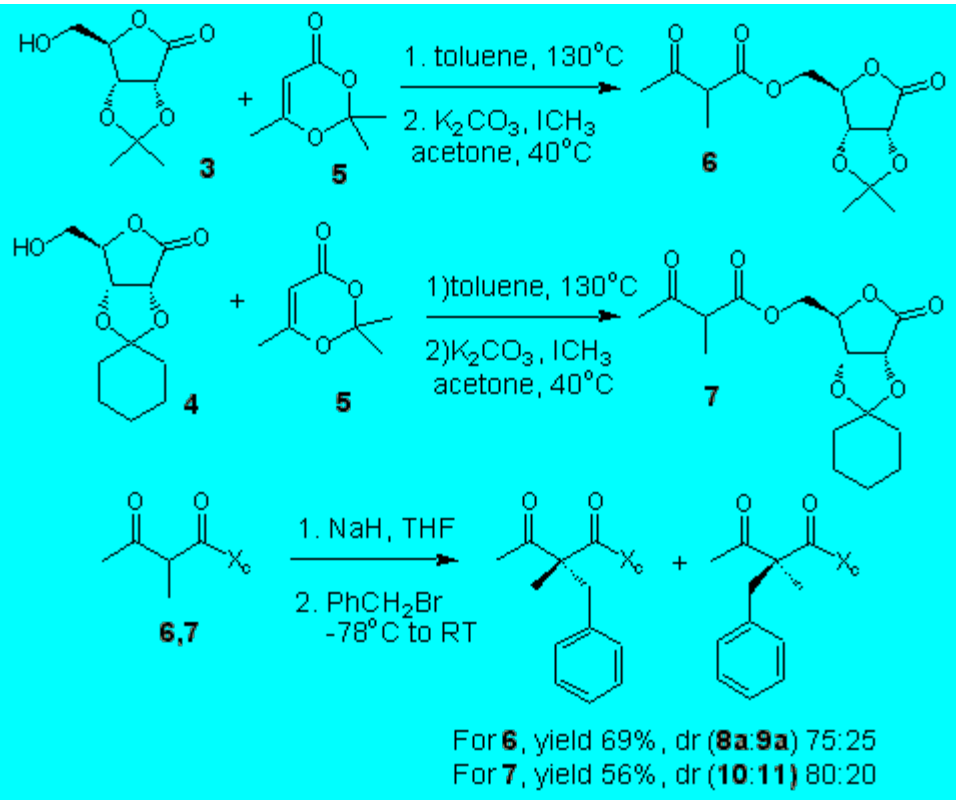


1 **2**

We have previously reported the preparation of enantiopure diphenylmethyl-, 9-fluorenyl and (1-adamantyl)glycines through cobalt mediated alkylation of (4*R*) and (4*S*)-3-acetoacetyl-4-benzyloxazolidin-2-ones (**1**, Z=acetyl, R^1=H) [14]. Several dialkylation attempts on the same substrate failed. However alkylation of (-)-8-phenylmenthyl 2-methylacetoacetate affords 8-phenylmenthyl 2-alkyl-2-methylacetoacetates in a maximal diastereomeric ratio of 85:15 [15]. Posterior elaboration to amino acids failed probably due to steric hindrance. This previous results made us to consider other alcohols as chiral auxiliaries. We chose D -ribonolactone for two main reasons: (a) It is a commercially available sugar derivative (b) Being a primary alcohol, its ester might be easily manipulated (this has failed in the case of (-)-8-phenylmenthol).

2,3-O-isopropyliden-[16] and 2,3-O-cyclohexyliden-g-D-ribonolactone [17] had been prepared by reactions previously described in the literature. These protected lactones react with 2,2,6-trimethyl-1,3-dioxen-4-one, **5**, in refluxing toluene to afford the corresponding methyl acetoacetates, **6** and **7** (74-82%) (Scheme 1). Methylation at C- a is carried out with potassium carbonate, methyl iodide in acetone at 40^{o}C (69-71%). We have first studied dialkylation process through generation of enolate with NaH at –78^{o}C and posterior addition of benzyl bromide, and we obtained a dr similar for the two chiral auxiliaries. In the case of cyclohexylidene protection we were unable to isolate the major diastereoisomer in pure form. Therefore, we chose 2,3-O-isopropyliden- g - D -ribonolactone as chiral auxiliary.

Scheme 1

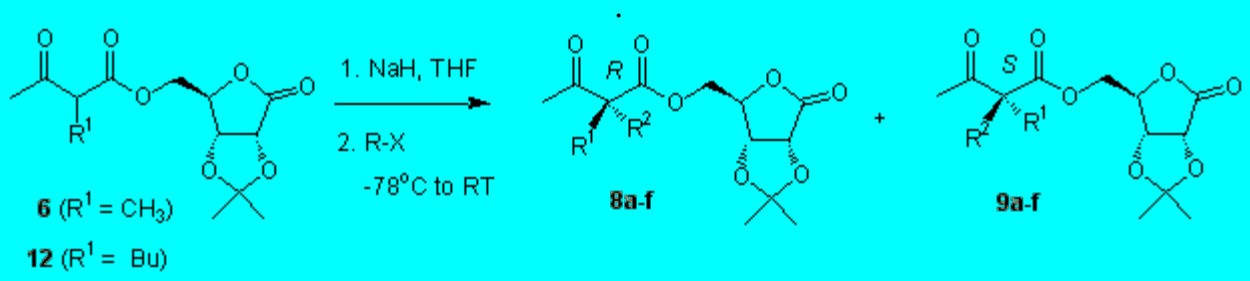


Some attempts have been made to optimize the process: (a) Other bases such as LDA, phosphazene P_4-*t*-Bu in *n*-hexane ($C_{22}H_{63}N_{13}P_4$) and sodium bis(trimethylsilyl)amide gave similar or worse dr; (b) Addition of *N*,*N*'-dimethylpropyleneurea (DMPU) or change of THF to DMPU, when using NaH, did not give better results.

Alkylation of **6** with a series of alkyl halides furnished compounds **8a-d** and **9a-d** in reasonable diastereomeric excesses (Table 1) [18]. The major diastereoisomers were isolated in pure form in all cases except for R^2 = $PhCH{=}CHCH_2$.

We were also interested in disubstituted glycines with one group different from methyl. Compound **12** was easily prepared from 2,3-O-isopropyliden- g - D -ribonolactone acetoacetate with NaH in refluxing THF and *n*-butyl iodide in 71% yield. Even with the bulkier *n*-butyl substituent high yields are obtained in the dialkylation process (Table 1).

Table 1 . Results of diastereoselective dialkylation of **6** and **12** with a series of alkyl halides



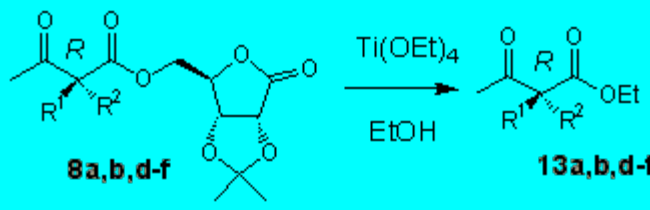
R^1	R^2	products[a][19]	yield (%)	dr
CH_3	$PhCH_2$	**8a**+**9a**	69	75:25
CH_3	4-$BrPhCH_2$	**8b**+**9b**	64	78:22

CH_3	$PhCH=CHCH_2$	**8c+9c**	71	80:20
CH_3	2-NaphtCH_2	**8d+9d**	74	80:20
Bu	4-Br$PhCH_2$	**8e+9e**	75	80:20
Bu	2-NaphtCH_2	**8f+9f**	69	80:20

a All pure diastereoisomers **8a,b,d-f** and **9a,b,d-f** and the mixture **8c+9c** gave correct elemental analysis (C, H).

Table 2 summarizes the results for transesterification of pure diastereoisomers **8a,b,d-f** [20]. By using an excess of titanium(IV) tetraethoxidein refluxing ethanol the corresponding enantiopure ethyl a,a -dialkyl acetoacetates are obtained in excellent yields when $R^1 = CH_3$. Experiments with sodium ethoxide gave worse results. For butyl substituent as in compounds **8e,f,** less efficient reactivity is found, as expected.

Table 2. Results of transesterification reaction.



8a,b,d-f **13a,b,d-f**

R^1	R^2	products[a]	bp (mmHg)	yield (%)
CH_3	$PhCH_2$	**13a**[11][21]	125 °C. (0.07)	92
CH_3	4-Br$PhCH_2$	**13b**	150 °C. (0.07)	90
CH_3	2-NaphtCH_2	**13d**	175 °C. (0.07)	93
Bu	4-Br$PhCH_2$	**13e**	150 °C. (0.07)	37
Bu	2-NaphtCH_2	**13f**	-	49

a All products **13** gave correct elemental analysis (C, H).

Schmidt rearrangement on **13** with sodium azide and methanesulfonic acid in dimethoxyethane afforded acetamides **14** [22]. We have previously recommended the use of DME as an alternative to the unsafe chlorinated solvents normally used in Schmidt rearrangement [23]. Acetamides **14** were hydrolyzed in refluxing 6M HCl to give the amino acids hydrochlorides **15** in excellent yields.

Table 3. Schmidt reaction of a,a -disubstituted acetoacetates 13 and posterior hydrolysis of acetamides 14.

13a,b,d-f **14a,b,d-f** **15a,b,d-f**

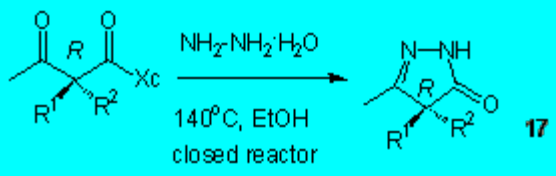
R^1	R^2	**14** (%)[a]	**15**(%)[b]	**15**, [a]

				D
CH_3	$PhCH_2$	**14a**[13b](82)	**15a** (81)	-7 (c 1.22, H_2O)
CH_3	4-$BrPhCH_2$	**14b** (63)	**15b** (81)	-8 (c 1.05, H_2O)
CH_3	2-$NaphtCH_2$	**14d** (82)	**15d** (76)	5 (c 1.14, EtOH)
Bu	4-$BrPhCH_2$	**14e** (43)	**15e** (73)	7 (c 1.06, EtOH)
Bu	2-$NaphtCH_2$	**14f** (41)	**15f** (65)	-3 (c 0.90,EtOH)

a Compounds **14**[24]gave correct elemental analysis. [b] Compounds **15a**,**b**,**d**,**e**[25]gave good elemental analysis. Compound **15f** [25] gave correct elemental analysis for C and N.

We have previously described a method for the preparation of enantiomerically pure (4*R*)-4,4-disubstituted 2-pyrazolin-5-ones from (-)-8-phenylmenthyl (2*R*)-2-alkyl-2-methylacetoacetates, **16**[26]. Reaction of **16** with hydrazine hydrate afforded (4*R*)-4-alkyl-3,4-dimethyl-2-pyrazolin-5-ones, **17** (Table 4). X-Ray difracction studies on **16a** and **16b** showed *R* configuration at C-a. Accordingly, the new stereogenic center of **17a** and **17g** was also *R*. Compounds **8a,b,d-f** were converted into **17a,b,d-f** in excellent yields. Compound **17a** obtained from **8a** has the same $[a]_D$ as the one obtained from **16a**. Configuration to **17b,d-f** was assigned by comparison of the circular dichroism with those of **17a** and **17g**. All of them present a strong negative Cotton effect. Therefore the major diastereoisomers obtained in the dialkylation process using D -ribonolactone acetonide as chiral auxiliary have *R* absolute configuration at C-a, and consequently enantiopure hydrochlorides of (*S*)-a-alkyl alanines, **15a**,**b**,**d**, and (*S*)- a -alkyl- a -butylglycines glycines, **15e**,**f**, had been prepared.

Table 4. Preparation of enantiomerically pure 4,4-disubstituted 2-pyrazolin-5-ones, **17**.



16 (X_cH = (-)-8-phenylmenthol)
8 (X_cH = D-ribonolactone acetonide)

	R^1	R^2	products[a]	yield (%)	$[a]_D$[b]
16a	CH_3	$PhCH_2$	**17a**[26]	95	-186 (c 1.24)
16b	CH_3	4-$ClPhCH_2$	**17g**[26]	88	-87 (c 0.12)
8a	CH_3	$PhCH_2$	**17a**	92	-180 (c 1.20)
8b	CH_3	4-$BrPhCH_2$	**17b**	86	-144 (c 1.01)
8d	CH_3	2-$NaphtCH_2$	**17d**	75	-211 (c 0.88)
8e	Bu	4-$BrPhCH_2$	**17e**	74	-88 (c 1.04)
8f	Bu	2-$NaphtCH_2$	**17f**	70	-127 (c 1.01)

a Compounds **17b**,**d**,**e**[27] gave correct elemental analysis. Compound **17f** gave good HRMS.

[b] All determined in $CHCl_3$.

In conclusion, we have developed a new simple method for the synthesis of enantiopure (*S*)- a,a -disubstituted glycines using D -ribonolactone acetonide as a chiral auxiliary. The advantages of this approach are: (a) The facility to obtain the chiral auxiliary (only protection of available material is needed); (b) The fact that only one diastereomeric separation is needed (classical column chromatography); (c) The method allows the introduction of substituents bulkier than methyl.

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[18] **General Procedure for Diastereoselective Alkylation of Compounds 6 and 12.** Compound **6** (4.65 g, 16.2 mmol) in anhydrous THF (12 mL) was added to magnetically stirred NaH (60% suspension in mineral oil, 0.84 g (21.1 mmol)) in anhydrous THF (10 mL) at room temperature and under nitrogen atmosphere. Thereaction mixture was stirred for 15 minutes, cool down to –78^{o}C and then a solution of benzyl bromide (4.17 g, 24.2 mmol) in anhydrous THF (10 mL) was added. The reaction was allowed to warm to room temperature and was stirred for 12 h. THF was evaporated, and the residue partitioned between CH_2Cl_2:H_2O. The aqueous layer was washed with CH_2Cl_2 (3x20 mL). The combined dichloromethane extracts were dried with anhydrous sodium sulfate and the solvent was evaporated to give a crude which was a mixture of **8a** and **9a** in a ratio ca. 75:25 determined by integration of the ^{1}H NMR signal of the C$\underline{H}_3$CO protons at d 2.10 and 2.19. The crude was chromatographed on silica gel under pressure, eluting with hexane: diethyl ether mixtures of increasing polarity to afford 2.81 g (46%) of **8a** and 1.04 g (17%) of **9a**. **8a**: white solid; mp 101-103^{o}C.; [a]$_D$ = 16 (c = 1.09, $CHCl_3$); IR (KBr) 1785 (s), 1729 (s), 1715 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) d 1.23 (s, 3H), 1.29 (s, 3H), 1.37 (s, 3H), 2.11 (s, 3H), 2.90 (d, *J* = 13.1 Hz, 1H), 3.17 (d, *J* = 13.1 Hz, 1H), 4.20-4.36 (m, 4H), 4.70 (t, *J* = 2.2 Hz, 1H), 7.06-7.27 (m, 5H). ^{13}C NMR (62.5 MHz, $CDCl_3$) d 19.9, 25.5, 26.6, 26.7, 41.0, 61.1, 64.2, 74.9, 77.5, 79.1, 113.6, 127.0, 128.3 (2C), 130.1 (2C), 136.2, 171.3, 173.1, 204.9. Anal. Calcd for $C_{20}H_{24}O_7$: C 63.82, H 6.43. Found: C 63.70, H 6.48. **9a**: white solid; mp 67-68^{o}C.; [a]$_D$ = -39 (c = 1.03, $CHCl_3$); IR (KBr) 1792 (s), 1750 (s), 1715 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) d 1.37 (s , 3H), 1.38 (s, 3H), 1.44 (s, 3H), 2.10 (s, 3H), 2.94 (d, *J* = 13.1 Hz, 1H), 3.31 (d, *J* = 13.1 Hz, 1H), 4.07 (dd, *J* = 12.4 and 2.7 Hz, 1H), 4.16 (d, *J* = 5.8 Hz, 1H), 4.36 (dd, *J* = 12.4 and 2.7 Hz, 1H), 4.44 (d, *J* = 5.8 Hz, 1H), 4.67 (t, *J* = 2.7 Hz, 1H), 7.12-7.22 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) d 18.5, 25.4, 26.3, 26.5, 40.8, 61.0, 64.2, 74.9, 77.5, 79.2, 113.7, 127.1, 128.4 (2C), 130.0 (2C), 135.8, 171.3, 173.1, 204.7; Anal. Calcd for $C_{20}H_{24}O_7$: C 63.82, H 6.43. Found: C 63.86, H 6.55.

[19] **8a**: mp 101-103^{o}C.; **9a**: mp 67-68^{o}C.; **8b**: mp 94-95^{o}C.; **9b**: mp 95-96^{o}C.; **8d**: mp 108-109^{o}C.; **9d**: mp 105-107^{o}C.; **8e**: mp 64-65^{o}C.; **9e**: mp 72-74^{o}C.; **8f**: mp 38-40^{o}C.; **9f**: mp 112-114^{o}C.

[20] **General Procedure for Transesterification Reaction.** A solution of **8a** (1.00 g, 2.6 mmol) and $Ti(OEt)_4$ (1.21 g, 5.3 mmol) in ethanol (40 mL) was refluxed for five hours. The solution was evaporated and the crude solid was purified by column chromatography on silica gel under pressure, eluting with a mixture of hexanes: ethyl acetate. Product **13a** was obtained as a colorless oil (0.57 g , 92%): bp 125^{o}C. (0.07 mmHg); [a]$_D$ = 66 (c = 0.64, $CHCl_3$) ([a]$_D$= 62.5 (c = 0.42, $CHCl_3$)[11,21]); IR (film) 2994, 1743 (s), 1715 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) d 1.25 (t, *J* = 6.6 Hz, 3H), 1.29 (s, 3H), 2.17 (s, 3H), 3.05 (d, *J* = 13.9, 1Hz), 3.27 (d, *J* = 13.9 Hz, 1H), 4.18 (m, 2H), 7.06-7.27 (m, 5H); ^{13}C NMR (62.5 Hz, $CDCl_3$) d 13.9, 18.9, 26.4, 40.3, 60.7, 61.3, 126.8, 128.2 (2C), 130.1 (2C), 136.4, 172.3, 205.3; Anal. Calcd for $C_{14}H_{18}O_3$: C 71.77, H 7.74. Found: C 71.89, H 7.95.

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[22] **General Procedure for Schmidt Rearrangement**. Methanesulfonic acid (5.8 mL) was dropwise added to a stirred mixture of ketoester **13d** (1.30 g, 4.6 mmol) and DME (5 mL) cooled at –30^{o}C. Sodium azide (0.89 g, 13.7 mmol) was then added portionwise. When the evolution of nitrogen ceased the mixture was left at room temperature 24h. More DME (10 mL) and 30% aqueous ammonia were added till pH ca. 9. The mixture was partitioned between dichlorometane and water. The organic layer was dried and evaporated. The residue was purified through silica-gel eluting with hexanes: ethyl acetate mixtures of increasing polarity to afford **14d** (1.13 g, 82%) as an oil: bp 200^{o}C (0.07 mmHg); [a]$_D$ = 51(c = 0.97, $CHCl_3$); IR (film) 3290 , 1736, 1652 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) d 1.24 (t, *J* = 7.3 Hz, 3H), 1.60 (s, 3H), 1.86 (s, 3H), 3.28 (d, *J* = 13.8 Hz, 1H), 3.56 (d, *J* = 13.8 Hz, 1H), 4.15

(q, *J* = 7.3 Hz, 2H), 6.10 (broad s, 1H), 7.07-7.11(m, 1H), 7.33-7.39 (m, 2H), 7.43 (s, 1H), 7.62-7.72 (m, 3H); ^{13}C NMR (62.5 Hz, $CDCl_3$) d 14.1, 23.4, 23.9, 40.9, 61.1, 61.8, 125.6, 125.9, 127.5 (2C), 128.0, 128.6, 132.3, 133.3, 134.1, 169.6, 173.9; Anal. Calcd for $C_{18}H_{21}NO_3$: C 72.22, H 7.07, N 4.68. Found: C 71.81, H 7.34, N 4.33.

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[24] **14a**: bp 175^{o}C./0.07 mmHg; **14b**: mp 69-71^{o}C.; **14d**: bp 200^{o}C./0.07 mmHg; **14e**: mp 88-90^{o}C.; **14f**: mp 72-74^{o}C.

[25] **15a**: white solid; mp 160-164^{o}C. (d); Anal. Calcd for $C_{10}H_{14}NO_2Cl$: C 55.69, H 6.54, N 6.49. Found: C 55.52, H 6.62, N 6.07. **15b**: white solid; 161-163^{o}C. (d); Anal. Calcd for $C_{10}H_{13}BrNO_2Cl$: C 40.77, H 4.45, N 4.75. Found: C 40.60, H 4.38, N 4.52. **15d**: white solid; mp 170-174^{o}C. (d); Anal. Calcd for $C_{14}H_{16}NO_2Cl.H_2O$.: C 59.26, H 6.39, N 4.94. Found: C 59.12, H 6.41, N 4.83. **15e**: white solid; mp 169-173^{o}C (d); Anal. Calcd for $C_{13}H_{19}BrClNO_2.1/2H_2O$: C 45.16, H 5.79, N 4.05. Found: C 44.88, H 5.80, N 3.94; **15f**: white solid; 110-112^{o}C. (d); Anal. Calcd for $C_{17}H_{22}NO_2Cl{\cdot}H_2O$: C 62.66, N 4.30. Found: C 62.88, N 4.59.

[26] Moreno-Ma&#65533;as, M.; Sebasti&#65533;n, R. M.; Vallribera, A. Molins, E.; Espinosa, E. *Tetrahedron: Asymmetry* **1997**, *8*, 1525-1527.

[27] Mp's (^{o}C): **17b**: 52-54; **17d**: 131-133; **17e**: 133-135; **17f**: 87-88.
