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Asymmetric Transfer Hydrogenation of α-Aminoalkyl α′-Chloromethyl Ketones with Chiral Rh Complexes

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Abstract: Asymmetric transfer hydrogenation of *N*-substituted (3*S*)-3-amino-1-chloro-4-phenyl-2-butanones in the presence of Cp*RhCl[(*R*,*R*)-Tsdpen] (S/C = 1000) with a mixture of formic acid/triethylamine gave *N*-substituted (2*R*,3*S*)-3-amino-1-chloro-2-hydroxy-4-phenylbutanes with up to 93% de in a quantitative yield, and reduction with the enantiomeric catalyst Cp*RhCl[(*S*,*S*)-Tsdpen] gave (2*S*,3*S*)-diastereomeric alcohol with up to 96% de.

Optically active *N*-(*tert*-butyloxycarbonyl)-(3*S*)-3-amino-1,2-epoxy-4-phenylbutanes (**1a**) are useful intermediates for the syntheses of pharmaceuticals such as inhibitors of HIV protease[1−3] and *β*-secretase in Alzheimer's disease.[4] As shown in Scheme 1, (2*S*,3*S*)-**1a** is used to produce saquinavir and amprenavir, while diastereomeric alcohol (2*R*,3*S*)-**1a** is similarly employed in the synthesis of atazanavir.[3] These diastereomers of **1a** are readily accessible using conventional procedures from *N*-(*tert*-butyloxycarbonyl)-(3*S*)-3-amino-1-chloro-2-hydroxy-4-phenylbutanes (**2**) obtained by means of chemical[5−7] or microbial reduction of the corresponding ketones (**3a**).[8] For example, the Meerwin−Pondorf−Verlay reduction of *N*-(*tert*-butyloxycarbonyl)-(3*S*)-3-amino-1-chloro-4-phenyl-2-butanone (**3a**) afforded (2*S*,3*S*)-**2a** in <98% de.[5] The reduction of **3a** with $NaBH_4$ at −10 °C gave a mixture of (2*S*,3*S*)-**2a** and (2*R*,3*S*)-**2a** in a ratio of 80:20, and a single crystallization increased the ratio to >98:2.[6] When LiAlH(O-*t*-Bu)$_3$ was used as a metal hydride agent, **3a** preferentially gave (2*R*,3*S*)-**2a** as a 87:13 mixture of (2*R*,3*S*)- and (2*S*,3*S*)-**2a**.[7] In these reductions, the carbonyl diastereofaces were differentiated by a proper combination of metal hydride species and the chirality of the adjacent nitrogen-substituted stereogenic center of **3**. To obtain the desired diastereomer, a matched combination of substrate and reducing reagent is crucial.

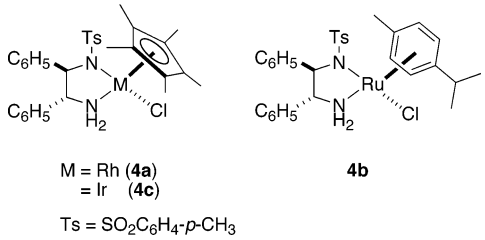

FIGURE 1. Chiral Rh, Ir, and Ru catalysts for asymmetric transfer hydrogenation.

Recently, we reported an industrial preparation of *N*-(*tert*-butyloxycarbonyl)-(3*S*)-3-amino-1-chloro-4-phenyl-2-butanone.[9] We have also developed a practical method for the asymmetric syntheses of optically active styrene oxides via 2-chloro-1-phenylethanols generated by the reductive transformation of ring-substituted 2-chloroacetophenones.[10] Optically active alcohols with up to 97% ee were obtainable from the asymmetric transfer hydrogenation of 2-chloroacetophenones with a substrate/catalyst (S/C) ratio of 1000−5000 in a formic acid/triethylamine mixture containing a chiral Rh complex, Cp*RhCl[(*R*,*R*)-Tsdpen] (**4a**), where Cp* = pentamethylcyclopentadienyl and TsDPEN = (1*R*,2*R*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine (Figure 1).[11] In this paper, we describe an effective means for preparing the desired diastereomers **2** with excellent to good selectivity by the asymmetric transfer hydrogenation of aliphatic ketones **3** with the catalyst **4a** (Scheme 2).

Reduction of *N*-(*tert*-butyloxycarbonyl)-(3*S*)-3-amino-1-chloro-4-phenyl-2-butanone, **3a**, with the use of the chiral Rh complex (**4a**) in a 5:2 formic acid/triethylamine azeotropic mixture (S/C = 1000, S/HCOOH = 1/1) in 0.8 M ethyl acetate at 25 °C afforded (2*R*,3*S*)-**2a** with 80% de in a quantitative yield. When the reduction was conducted with the enantiomeric catalyst (*S*,*S*-**4a**), the corresponding diastereomer (2*S*,3*S*)-**1a** with 80% de was obtained quantitatively. Thus, the diastereoselectivity of the reduction was controlled by the chirality of the ligand, while the chirality of the adjacent stereogenic center did

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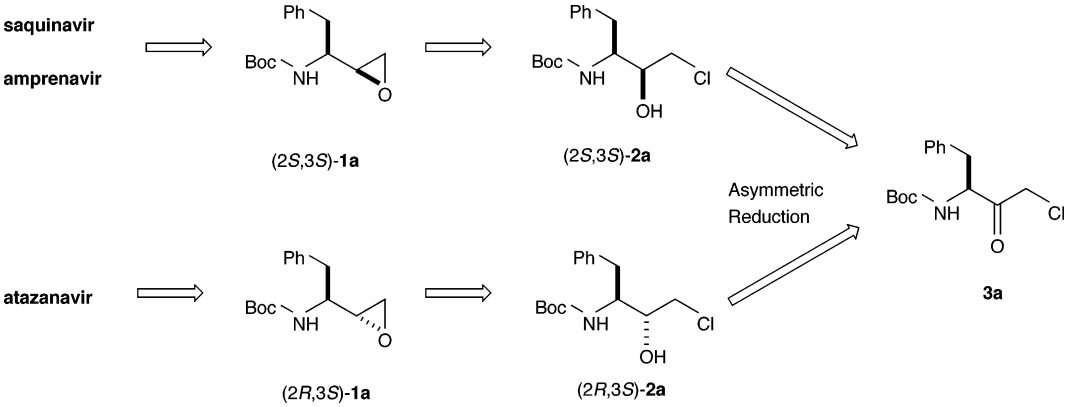
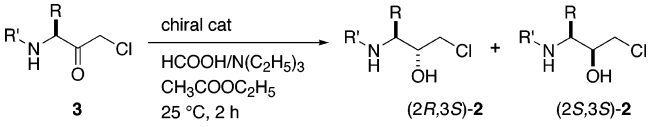
SCHEME 1



SCHEME 2



3a: R = $C_6H_5CH_2$, R' = Boc
3b: R = $C_6H_5CH_2$, R' = Cbz
3c: R = $C_6H_5CH_2$, R' = Bz
3d: R = $C_6H_5CH_2$, R' = Ts
3e: R = $(CH_3)_2CHCH_2$, R' = Cbz
3f: R = *p*-F-$C_6H_4CH_2$, R' = Cbz
3g: R = 2-naphCH_2, R' = Cbz

TABLE 1. Asymmetric Transfer Hydrogenation of *N*-(*tert*-Butyloxycarbonyl)-(3*S*)-3-amino-1-chloro-4-phenyl-2-butanone (3a) Catalyzed by Chiral Catalysts 4a with a HCOOH/N(C_2H_5)$_3$ Mixture in Various Solvents[a]

solvent	Rh(*R*,*R*)-Tsdpen (*R*,*S*)-**2a**/(*S*,*S*)-**2a**	Rh(*S*,*S*)-Tsdpen (*R*,*S*)-**2a**/(*S*,*S*)-**2a**
ethyl acetate	90:10	10:90
toluene	89:11	11:89
dichloromethane	87:13	10:90
2-propanol	90:10	11:89

[a] Reaction of **3** in a 1.0 M solution containing the catalyst (**4a**) was conducted with a mixture of HCOOH and N(C_2H_5)$_3$ at 25 °C. The product ratio was determined by HPLC analysis using an Inertsil ODS-2 column.

not play significant role. The effect of the solvent was also examined. Table 1 shows that ethyl acetate gave the highest turnover number in the asymmetric reduction of **3a**, as observed in the asymmetric transfer hydrogenation of 2-chloroacetophenones with the same catalyst.[10] The diastereoselectivity of **2a** was solvent-dependent; for instance, the most suitable solvent for the preparation of (2*R*,3*S*)-**2a** was 2-propanol, while for (2*S*,3*S*)-**2a** it was ethyl acetate.

Various chloro ketones can be reduced with chiral Rh catalysts **4a**, leading to chiral alcohols in excellent yields. Table 2 shows the results of the reduction of a series of chloromethyl ketones (**3a**−**g**) derived from L-amino acids. The outcome of the reaction in terms of product yield and diastereoselectivity is influenced by the catalyst used and the structures of the substrates, including *N*-protecting groups. The de values of the reduction products obtained with the (*S*,*S*)-TsDPEN catalyst are somewhat higher than those obtained with the (*R*,*R*) enantiomeric catalyst, regardless of the structures of the R substituents and *N*-protecting groups, except for the reaction of **3c** bearing

TABLE 2. Asymmetric Transfer Hydrogenation of Aminoalkyl Chloromethyl Ketones, 3, Catalyzed by Chiral Catalysts 4a with a HCOOH/N(C_2H_5)$_3$ Mixture[a]

ketone	R	R′	Rh(*R*,*R*)-Tsdpen (*R*,*S*)-**2**/(*S*,*S*)-**2**	Rh(*S*,*S*)-Tsdpen (*R*,*S*)-**2**/(*S*,*S*)-**2**
3a	$C_6H_5CH_2$	Boc	90:10	10:90
3b	$C_6H_5CH_2$	Cbz	90:10	9:91
3c	$C_6H_5CH_2$	Bz	97:3	4:96
3d	$C_6H_5CH_2$	Ts	91:9	2:98
3e	$(CH_3)_2CHCH_2$	Cbz	83:17	11:89
3f	*p*-F−$C_6H_4CH_2$	Cbz	87:13	5:95
3g	2-NaphCH_2	Cbz	91:9	8:92

[a] Reaction of **3** in a 1.0 M solution containing the catalyst (**4a**) was conducted with a mixture of HCOOH and N(C_2H_5)$_3$ at 25 °C. The product ratio was determined by HPLC analysis using an Inertsil ODS-2 column.

a benzoyl protecting group. The reduction of **3d** bearing a tosyl protecting group with (*S*,*S*)-**4a** gave the product (2*S*,3*S*)-**2d** with the highest de value (up to 96%). It should be noted that the reduction of the nonaromatic substrates **3e** derived from L-leucine with the chiral Rh complex gave the product with a moderate de. While aryl and α,β-unsaturated groups at the α-position in carbonyl compounds were the crucial structural factors leading to excellent enantioselectivity for asymmetric transfer hydrogenation using RuCl[(*R*,*R*)-Tsdpen](*p*-cymene)[12,13] or a Rh-diamine complex.[11] However, this reaction provides one of the successful examples of asymmetric transfer hydrogenation of acyclic dialkyl ketones.[14]

The asymmetric transfer hydrogenation of **3a** with the chiral Ru complex, RuCl[(*R*,*R*)-Tsdpen]](*p*-cymene) (**4b**), resulted in a low conversion, while that with an Ir complex, Cp*IrCl[(*R*,*R*)-Tsdpen] (**4c**), provided the de-

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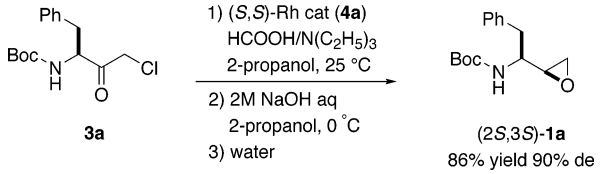
SCHEME 3



sired product in quantitative yield, albeit with low de. Formic acid was the best hydrogen source. The simple mixture of formic acid and triethylamine could be used instead of a 5:2 formic acid/triethylamine azeotropic mixture. Attempted reactions using a 2-propanol solution of **3a** containing (*S*,*S*)-**4a** and KO-*t*-Bu hardly proceeded (S/C = 100, <1% yield, after 24 h at 25 °C).

The purification of the product (2*S*,3*S*)-**2a** having 93% de after reduction was performed by crystallization from a mixture of toluene−EtOH−water to give the product in >98% de in 80% yield. The reaction of **3a** with Cp*RhCl[(*R*,*R*)-Tsdpen] (**4a**) was followed by the precipitation of minor product (2*S*,3*S*)-**2a** to give (2*R*,3*S*)-**2a** with >96% de in 80% yield after crystallization from 2-propanol-water.[15] These diastereomers **2** can be converted to epoxides **1** in good yields without a decrease in de value under basic conditions. This reductive transformation of **2a** to the optically active epoxides **1a** is more appealing as a one-pot synthetic procedure as shown in Scheme 3. A sequential asymmetric reduction of **3a** with a mixture of formic acid and triethylamine in 2-propanol containing the catalyst Cp*RhCl[(*S*,*S*)-Tsdpen] or Cp*-RhCl[(*R*,*R*)-Tsdpen] and treatment of its reaction mixture with 1 M NaOH aqueous solution at 0 °C gave (2*S*,3*S*)-**1a** in 86% yield with 90% de or (2*R*,3*S*)-**1a** in 83% yield with 80% de as crystals after the addition of water. These diastereomers (2*S*,3*S*)- and (2*R*,3*S*)-**1a** were separable as reported in the literature.[16]

In summary, we have demonstrated that the asymmetric transfer hydrogenation of aliphatic ketones **3** with catalyst **4a** gives the desired corresponding diastereomers **2** in excellent yields with high de with a simple change in the ligand chirality. The diastereoselectivity of the reaction is markedly influenced by both the *N*-protecting group of **3** and the solvent used. This reductive transformation of chloro ketones to optically active alcohols is characterized by high reactivity and practicality. A simple 1:1 mixture of 98% formic acid and triethylamine can also be used instead of its azeotrope. Commercially available reagents and solvents could be used in this reaction without special purification. One-pot synthesis of chiral epoxide **1** from the corresponding chloro ketones **3** can be readily performed at room temperature.

Experimental Section

The NMR spectra (400 MHz) were recorded in $CDCl_3$ with TMS (δ 0.00) as internal standard. Infrared (IR) spectra were obtained by placing neat samples directly in situ IR instrument. Diastereomer excess of samples were determined by HPLC. Yields are for isolated product, and no impurities were detectable by NMR and HPLC.

Typical Experimental Procedure for Preparation of 1-Chloro-2-hydroxy-3-(*N*-substituted amino)-4-phenylbutane (2). Formic acid (46 μL, 1.05 mmol) was added to an ethyl acetate solution (1.25 mL) of 1-chloro-3-(*N*-substituted)-4-phenylbutanone **3** (1.0 mmol), catalyst (1.0 μmol), and triethylamine (0.14 mL, 1.05 mmol). The mixture was stirred at 25 °C for 2 h and diluted with methanol to dissolve completely in order to determine the yield and de value by HPLC analysis. Crystallization of crude product gave 1-chloro-2-hydroxy-3-(*N*-substituted)amino-4-phenylbutane **2**.

Spectral Data. These compounds **2a**,[17] **2b**,[18] and **2e**[17] were identified by the spectral data described in the literature.

(2*R*,3*S*)-1-Chloro-2-hydroxy-3-(*N*-benzylamino)-4-phenylbutane (2c): mp 161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.01−3.17 (m, 2H), 3.54 (d, 2H, J = 12.2 Hz), 3.87 (dd, 1H, J = 8.6, 3.6 Hz), 4.38 (dd, 1H, J = 8.6, 3.6 Hz), 7.23- -7.70 (m, 10H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 168.46, 138.07, 134.33, 132.26, 129.71, 129.12, 129.07, 127.38, 127.20, 71.89, 54.08, 48.06, 38.36; IR (neat, cm^{-1}) 3327, 1627, 1538, 1181, 1046, 700.4; $[\alpha]^{25}_{Na}$ −75.2 (c 1.0, $CHCl_3$); MS(FAB) *m*/*z* 304 [M$^+$ + H]. Anal. Calcd for $C_{17}H_{18}ClNO_2$: C, 67.21; H, 5.97; N, 4.61. Found; C, 66.96; H, 5.89; N, 4.53.

(2*S*,3*S*)-1-Chloro-2-hydroxy-3-(*N*-benzylamino)-4-phenylbutane (2c): mp 200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.01−3.17 (m, 2H), 3.54 (d, 2H, J = 10.3 Hz), 3.87 (m, 1H, J = 8.4, 4.6 Hz), 4.38 (dd, 1H, J = 8.4, 10.3 Hz), 7.23−7.70 (m, 10H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 168.45, 138.06, 132.26, 129.70, 129.12, 129.07, 127.37, 127.21, 71.91, 54.08, 48.08, 38.37; IR (neat, cm^{-1}) 3392, 1640, 1532, 1333, 1054, 696.6; $[\alpha]^{25}_{Na}$ −38.3 (*c* 1.0, $CHCl_3$); MS(FAB) *m*/*z* 304 [M$^+$ + H]. Anal. Calcd for $C_{17}H_{18}ClNO_2$: C, 67.21; H, 5.97; N, 4.61. Found; C, 67.22; H, 5.84; N, 4.50.

(2*R*,3*S*)-1-Chloro-2-hydroxy-3-(*N*-tosylamino)-4-phenylbutane (2d): mp 91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2,40 (s, 3H), 2.56−2.61 (m, 1H), 2.83−2.90 (m, 2H), 3.43−3.67 (m, 2H), 6.95−7.70 (m, 9H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 143.93, 138.09, 137.26, 130.21, 130.13, 129.89, 129.59, 129.10, 127.45, 127.31, 127.15, 71.20, 57.16, 47.85, 39.11, 21.94, 14.59; IR (neat, cm^{-1}) 3496, 3274, 1455, 1322, 1152, 1092, 1059, 700.4; $[\alpha]^{25}_{Na}$ −72.7 (c 1.0, $CHCl_3$); MS(FAB) *m*/*z* 352[M$^+$ + H]. Anal. Calcd for $C_{17}H_{20}ClNO_3S$: C, 57.70; H, 5.70; N, 3.96. Found; C, 57.54; H, 5.57; N, 3.72.

(2*S*,3*S*)-1-Chloro-2-hydroxy-3-(*N*-tosylamino)-4-phenylbutane (2d): syrup; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2,40 (s, 3H), 2.66−2.79 (m, 2H), 3.18 (d, 1H, J = 3.5 Hz), 3.56−3.69 (m, 2H), 3.88−3.91 (m, 1H), 6.92−7.80 (m, 9H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 143.80, 137.04, 136.46, 130.09, 129.87, 129.65, 129.04, 127.43, 127.32, 127.07, 73.03, 57.33, 46.96, 35.46, 21.92, 14.59; IR (neat, cm^{-1}) 3471, 3255, 1428, 1318, 1150, 1086, 700.4; $[\alpha]^{25}_{Na}$ −35.0 (*c* 1.0, $CHCl_3$); MS(FAB), *m*/*z* 352 [M$^+$ + H]. Anal. Calcd for $C_{17}H_{20}ClNO_3S$: C, 57.70; H, 5.70; N, 3.96. Found; C, 57.68; H, 5.58; N, 3.83.

(2*R*,3*S*)-1-Chloro-2-hydroxy-3-(*N*-benzyloxycarbonylamino)-4-(*p*-fluorophenyl)butane (2f): mp 114 °C; ^{1}H NMR (400

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MHz, $CDCl_3$) δ 2.87−2.98 (m, 2H), 3.52 (d, 2H, J = 10.0 Hz), 3.87 (m, 1H), 3.92 (dd, 1H, J = 10.0 Hz, 5.0 Hz), 5.11 (s, 2H), 6.94−7.38 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.55, 156.60, 136.20, 133.16, 130.77, 130.69, 128.28, 128.05, 115.57, 115.36, 71.28, 67.04, 54.36, 47.77, 37.77; IR (neat, cm^{-1}) 3330, 1694, 1677, 1542, 1509, 1262, 1219, 1027, 750.6, 698.5; $[\alpha]^{25}_{Na}$ −36.8 (*c* 1.0, $CHCl_3$); MS(FAB) *m*/*z* 350 [M^+ + H]. Anal. Calcd for $C_{18}H_{19}ClFNO_3$: C, 61.45; H, 5.44; N, 3.98. Found; C, 61.52; H, 5.22; N, 3.90.

(2*S*,3*S*)-1-Chloro-2-hydroxy-3-(*N*-benzyloxycarbonylamino)-4-(*p*-fluorophenyl)butane (2f): mp 176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.88−2.97 (m, 2H), 3.62 (dd, 2H, J = 4.6, 18.8 Hz), 3.84 (m, 1H), 3.95 (m, 1H), 5.03 (s, 2H), 6.93−7.35 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.02, 156.20, 136.83, 135.48, 132.73, 130.83, 128.57, 128.30, 128.05, 115.57, 115.36, 73.23, 67.00, 54.70, 46.70, 34.88; IR (neat, cm^{-1}) 3311, 1692, 1546, 1509, 1264, 1219, 1027, 748.7, 698.5; $[\alpha]^{25}_{Na}$ −5.6 (*c* 1.0, $CHCl_3$); MS(FAB) *m*/*z* 350 [M^+ + H]. Anal. Calcd for $C_{18}H_{19}ClFNO_3$: C, 61.45; H, 5.44; N, 3.98. Found: C, 61.65; H, 5.29; N, 3.88.

(2*R*,3S)-1-Chloro-2-hydroxy-3-(*N*-benzyloxycarbonylamino)-4-(2-naphthyl)butane (2g): mp 118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.05−3.17 (m, 2H), 3.52 (d, 2H, J = 4.1 Hz), 3.87 (m, 1H), 4.04 (dd, 1H, J = 8.6 Hz, 3.6 Hz), 5.06(s, 1H), 7.19−7.81 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.97, 136.61, 135.42, 133.93, 132.74, 128.77, 128.66, 128.39, 128.30, 128.08, 127.96, 127.83, 126.56, 71.61, 67.41, 54.73, 48.20, 39.11; IR (neat, cm^{-1}) 3330, 1690, 1536, 1268, 1237, 1042, 752.5, 696.6; $[\alpha]^{25}_{Na}$ −39.5 (*c* 1.0, MeOH); MS(FAB) *m*/*z* 384 [M^+ + H]. Anal. Calcd for $C_{22}H_{22}ClNO_3$: C, 68.84; H, 5.78; N, 3.65. Found: C, 68.68; H, 5.65; N, 3.55.

(2*S*,3*S*)-1-Chloro-2-hydroxy-3-(*N*-benzyloxycarbonylamino)-4-(2-naphthyl)butane (2g): mp 171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.99−3.19 (m, 2H), 3.64 (m, 2H), 3.90 (m, 1H, J = 8.6 Hz), 4.09 (m, 1H), 5.00 (s, 2H), 7.20−7.82 (m, 12H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.31, 145.83, 136.15, 134.63, 133.50, 132.36, 128.51, 128.36, 128.17, 128.05, 127.93, 127.68, 127.58, 126.18, 125.68, 73.35, 66.95, 54.74, 47.62, 35.88; IR (neat, cm^{-1}) 3313, 1688, 1540, 1268, 1032, 742.9, 698.5; $[\alpha]^{25}_{Na}$ −2.7 (*c* 1.0, MeOH); MS(FAB) *m*/*z* 384 [M^+ + H]. Anal. Calcd for $C_{22}H_{22}ClNO_3$: C, 68.84; H, 5.78; N, 3.65. Found: C, 68.86; H, 5.65; N, 3.56.

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