Efficient Transamination under Mild Conditions: Preparation of Primary Amine Derivatives from Carbonyl Compounds *via* Imine Isomerization with Catalytic Amounts of Potassium *tert*-Butoxide

Gianfranco Cainelli,* Daria Giacomini,* Alessandra Trerè, and Pietro Pilo Boyl

Dipartimento di Chimica "G. Ciamician", Università di Bologna, Via Selmi 2, I-40126 Bologna, Italy

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1,3-Prototropic rearrangement of *N*-diphenylmethanimines was successfully performed with a catalytic amount of potassium *tert*-butoxide. This procedure can also be used with aliphatic and aromatic aldimines and was extended to the isomerization of (1*R*)-camphorquinone monoimine and *N*-(4-methoxyphenyl)-4-phenyl-3-iminoazetidin-2-one. The isomerized imines were easily hydrolyzed and isolated as Cbz derivatives.

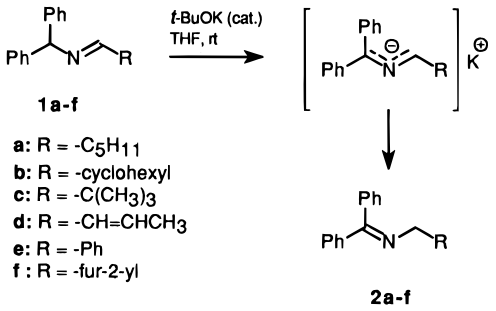
α,α′-Imine isomerization has been recognized as a prototype of the biochemical transamination reaction for many years. Several attempts have been made to mimic natural transaminases by converting amines into carbonyl compounds using prototropic rearrangement and equilibration of Schiff base intermediates.[1] The conversion of carbonyl compounds into amines by the same process has received less attention.[2]

The mechanism of base-catalyzed imine tautomerism was investigated by Cram and Guthrie,[3] who showed that it involves the formation of a delocalized 2-azaallyl anion. More recently, this intermediate has been generated through deprotonation of imines with a strong base,[4] tin−lithium exchange of 2-azaallyl stannanes,[5] desilylation of *N*-(silylmethyl) imines,[6] and conrotatory ring opening of *N*-metallo aziridines.[7] 2-Azaallylic anions have found useful synthetic applications as α-amino carbanion equivalents in alkylation reactions,[8] in Michael additions,[9] and as 4π components in cycloaddition reactions.[4a]

Continuing our studies on the reactivity of the azomethine group and the use of imines as a nitrogen source in the synthesis of natural products,[10] we report here our findings on the use of *N*-diphenylmethanimines **1** in the synthesis of primary amine derivatives *via* transamination using potassium *tert*-butoxide as a catalyst. We demonstrate the usefulness of this method through an application in β-lactam chemistry.

Results and Discussion

Our goal was to develop a simple and mild conversion of carbonyl compounds into amines *via* imine isomerization. The key step of this process is a 1,3-proton shift which allows the interconversion of the two isomeric imines. This transformation usually requires severe reaction conditions and the use of a strong base. Moreover, attempts to prepare 1-alkyl-3-phenyl-2-azaallyl anion with lithium dialkylamides have failed.[4a] Phase-transfer conditions have been successfully used in enantioselective alkylation of glycine imine derivatives.[11] We used *N*-diphenylmethanamine to form the starting imine **1** to provide a particularly acidic α-proton, which would then allow us to use milder basic conditions to effect deprotonation.



Treatment of **1a** with 10 mol % of *t*-BuOK gave **2a**. The starting imines **1a**−**f** were prepared from the corresponding aldehydes with diphenylmethanamine in CH_2Cl_2 in the presence of $MgSO_4$ as a dehydrating agent. Generally, the reaction with catalytic *t*-BuOK proceeds satisfactorily at room temperature with good yields for the isomerized products (Table 1). NMR analysis of the crude products showed almost pure compounds, while chromatography on silica gel showed a loss of material

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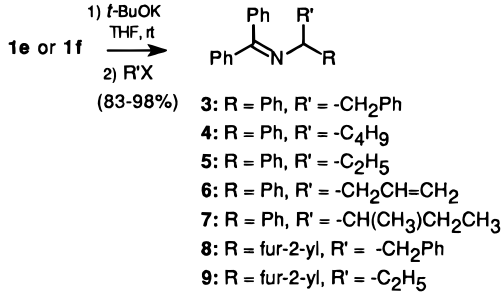
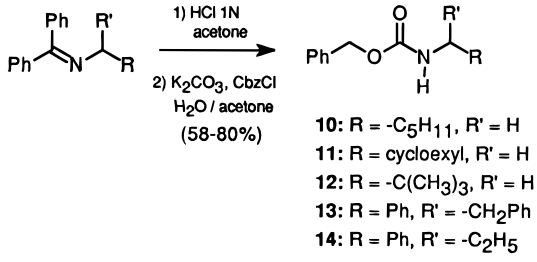
Table 1. Isomerization of Imines 1a−f

entry	imine	product	*t*-BuOK equiv	time	yield, %
1	**1a**	**2a**	1.2	20 min	97
2	**1a**	**2a**	0.1	20 min	91
3	**1b**	**2b**	0.1	1 h	87
4	**1c**	**2c**	0.1	2 h	95
5	**1d**	**2d**	0.1	50 min	94
6	**1e**	**2e**	1.2	1 h	60[a]
7	**1f**	**2f**	1.2	1 h	71[b]

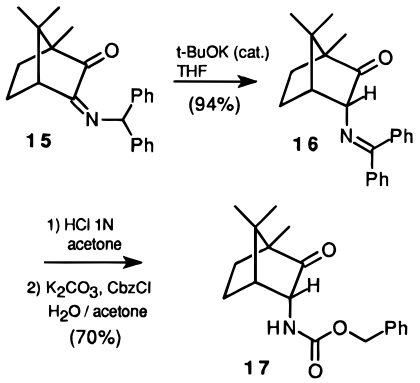
[a] The remaining 40% is starting material **1e**. [b] The remaining 29% is starting material **1f**.

due to imine hydrolysis. In the imines **1a**−**d**, the proton was efficiently shuttled from the α to the α′ position by *t*-BuOK. Indeed, the difference in pK_a between the hydrogens in the two positions is the driving force of this reaction. The imines **1e,f**, which are derived from aromatic aldehydes, gave rise to an equilibrium between the starting materials and **2e,f**, which reflected the fact that the two positions had similar pK_a values. If the isomerization of **1e,f** is performed with 1.2 equiv of *t*-BuOK in the presence of an electrophile, a concomitant irreversible alkylation occurs with an almost quantitative conversion into the products. In an attempted tandem isomerization−alkylation reaction with the hexanal imine **1a**, the only product was the isomerized imine **2a**, even in presence of the electrophile. This suggests that, in the case of aliphatic aldimines, the intramolecular protonation of the intermediate 2-azaallyl anion was faster than its intermolecular alkylation. Various rearranged and alkylated imines were successfully hydrolyzed with 1 N HCl in acetone and isolated as carbobenzyloxy derivatives for complete characterization.





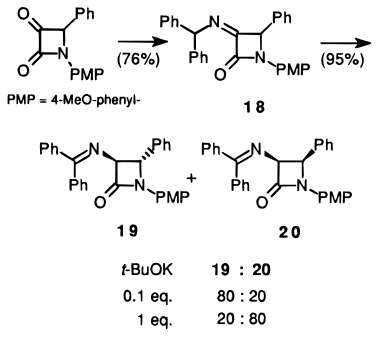
Attempts to isomerize imines of simple ketones such as 3-methylbutan-2-one with a catalytic amount of *t*-BuOK in THF failed. However, in the case of keto imines activated by a neighboring carbonyl group, such as the (1*R*)-camphorquinone monoimine **15**, prototropic rearrangement was successful and exclusively gave the rearranged product **16**. Imine **15** is the only product obtained by refluxing (1*R*)-(−)-camphorquinone and diphenylmethanamine in benzene in a Dean−Stark apparatus. Treatment with 10 mol % of *t*-BuOK gave the 3-aminobornan-2-one derivative **16** in good yield. Interestingly, **16** was obtained as the *endo* isomer, as confirmed



by a NOE DIFF experiment in $CDCl_3$ (the relevant correlations used to determine the relative stereochemistry are shown in the Experimental Section). This result demonstrated that *t*-BuOK attacked from the less-hindered *exo* position and shuttled the proton from the same side. Hydrolysis of **16** under acidic conditions and treatment with CbzCl gave the corresponding carbamate **17** in 70% yield after flash chromatography.

Following our interest in β-lactam chemistry and possessing *N*-(4-methoxyphenyl)-4-phenyl-3-oxoazetidin-2-one,[12] we tested this transamination on the corresponding highly functionalized imine. The product **18** was obtained as an *E*,*Z* mixture (40:60) from the 3-oxoazetidinone. In this isomerization, we observed that the amount of the base played an important role in the diastereofacial selectivity. In fact, exposure to 10% mol of *t*-BuOK in THF gave a 20:80 *cis*/*trans* mixture of the two β-lactams **19** and **20** in a quantitative yield. Interestingly, if a stoichiometric amount of potassium *tert*-butoxide was used, the ratio of the two isomers was reversed. The relative stereochemistry of the two isomers was assigned on the basis of the NMR signals of the annular protons. In the azetidinone **19**, the coupling constant was 1.8 Hz, which indicates a *trans* arrangement, while *cis* isomer **20** showed $J = 4.98$ Hz.

These results indicate that this method is useful for transforming carbonyl compounds to amines under very mild conditions. This method could be successfully used with "sensitive" compounds, such as β-lactams, and represents an improvement over Chiba's procedure[13] for obtaining 3-aminoazetidin-2-one *via* oxime reduction.



The mechanism of the transamination reaction in *t*-BuOK/*t*-BuOH has been studied thoroughly by Cram and Guthrie.[3c] They demonstrated that abstraction of the proton by the action of *t*-BuOK solvated by THF and

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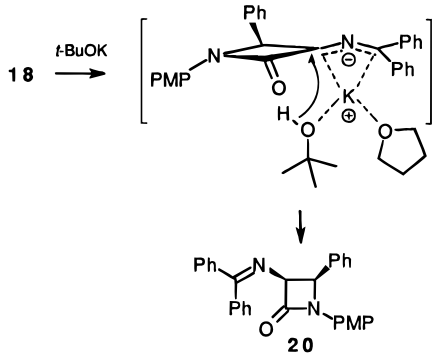
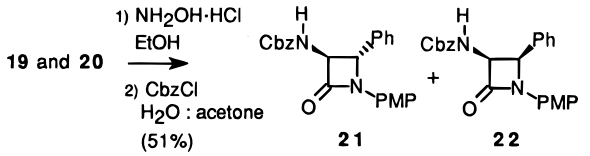
t-BuOH generates an ion pair[14] that is coordinated only by the potassium on the side from which the proton was abstracted. Collapse to the covalent state then occurs *via* a *syn* proton shift. In the case of imine **18**, the face opposite the 4-phenyl substituent could better accommodate the potassium with its ligands. Consistent with



a *syn* proton transfer, the *cis* diastereoisomer should be preferred. Indeed, this was observed with an equimolecular amount of the base, which leads to the quantitative formation of the azaallyl anion which undergoes rapid prototropic rearrangement. However, the catalytic protocol favors equilibration to give the thermodynamically more stable *trans* isomer. The existence of an equilibrium under these conditions was confirmed by treatment of the pure *cis* azetidinone imine **20** with 0.1 equiv of *t*-BuOK for 12 h to give a 20:80 mixture of *cis* and *trans* β-lactams **20:19** in quantitative yield. The same *cis:trans* ratio was obtained when we started from the pure *trans* azetidinone imine **19** with 0.1 equiv of *t*-BuOK for 12 h.

Successful hydrolysis was effected by treating the isomerized imines **19** and **20** in CH_2Cl_2 with a 0.5 M solution of $NH_2OH{\cdot}HCl$ in EtOH at 40 °C for 5 min to give, after treatment with CbzCl, the derivatives **21** and **22**.



In summary, *N*-diphenylmethanimines derived from alkyl and aryl aldehydes undergo rapid prototropic rearrangement with a catalytic amount of *t*-BuOK. Furthermore, we have shown that this mild protocol for transamination can be applied to highly functionalized compounds. In fact, (1*R*)-camphorquinone monoimine and 3-oxoazetidinone imine each gave good yields of the corresponding Cbz derivatives.

Experimental Section

Commercially available compounds were used without further purification, unless otherwise indicated. All reactions were performed under a positive pressure of argon. CH_2Cl_2 was distilled from P_2O_5 immediately prior to use. THF was distilled from $Na/Ph_2C{=}O$ under argon and diethyl ether, and benzene was distilled from Na. Final solutions were dried over Na_2SO_4 before rotatory evaporation. Melting points are uncorrected. NMR spectra were obtained on 300- and 200-MHz instruments with TMS as an internal standard. A differential NOE experiment was performed using NOE DIFF sequences in NMR tubes degassed using the freeze−pump−thaw technique. Mass spectra were recorded at an ionization energy of 70 eV.

Imines 1a−f. General Procedure. To a stirred solution of diphenylmethanamine (10 mmol) in dry CH_2Cl_2 (25 mL) under an inert atmosphere at rt were successively added $MgSO_4$ (2.6 g, 22 mmol) and the aldehyde (10 mmol). The resulting mixture was stirred at room temperature until the starting aldehyde was consumed (GC-monitoring). The filtered solution was evaporated to give the crude imine.

***N*-Hexylidene-1,1-diphenylmethylamine (1a)** was obtained by the general procedure as a colorless oil (2.597 g, Y = 98%): *m*/*z* 265 (M^+, 0.2), 209 (28), 167 (100), 91 (3), 77 (4); IR (film) 1667 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.9 (t, J = 7.2 Hz, 3 H), 1.30−1.65 (m, 6H), 2.38 (dt, J = 8.1 and 4.8 Hz, 2 H), 5.38 (s, 1H), 7.2−7.4 (m, 10 H), 7.77 (t, J = 4.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 13.9, 22.4, 25.6, 31.4, 35.8, 78.1, 126.8, 127.4, 127.5, 128.3, 143.7, 165.6.

***N*-(Cyclohexylmethylidene)-1,1-diphenylmethylamine (1b)** was obtained by the general procedure as a white solid (2.216 g, Y = 80%) crystallized from pentane/CH_2Cl_2: mp 48−49 °C; *m*/*z* 277 (M^+, 1.2), 209 (25), 167 (100), 91 (4.3), 77 (3.0); IR (Nujol) 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.1−1.9 (m, 10 H), 2.2 (bs, 1 H), 5.33 (s, 1 H), 7.15−7.60 (m, 10 H), 7.70 (d, J = 5.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 25.4, 26.0, 29.7, 43.5, 77.9, 126.7, 127.5, 128.3, 143.9, 169.0. Anal. Calcd for $C_{20}H_{23}N$: C, 86.59; H, 8.36; N, 5.05. Found: C, 86.63; H, 8.40; N, 5.11.

***N*-(2,2-Dimethylpropylidene)-1,1-diphenylmethylamine (1c)** was obtained by the general procedure as a pure solid compound and used without further purification (2.134 g,Y = 85%): mp 44−46 °C; *m*/*z* 251 (M^+, 1), 236 (0.5), 194 (0.4), 167 (100), 91 (3.0), 77 (2.9); IR (Nujol) 1667 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.12 (s, 9 H), 5.35 (s, 1 H), 7.20−7.35 (m, 10 H), 7.8 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.9, 36.4, 77.4, 126.7, 126.9, 127.5, 128.3, 144.2, 171.6. Anal. Calcd for $C_{18}H_{21}N$: C, 86.01; H, 8.42; N, 5.57. Found: C, 85.95; H, 8.36; N, 5.61.

***N*-(2-Butenylidene)-1,1-diphenylmethylamine (1d)** was obtained by the general procedure as a yellow oil (2.279 g), *cis*/*trans* = 10:90, Y = 97%: *m*/*z* 235 (M^+, 10), 220 (3), 167 (100), 91 (3), 77 (3.6); IR (film) 1657, 1619 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.18 (d, J = 6.3 Hz, 3 H *cis*), 1.9 (d, J = 6.4 Hz, 3 H *trans*), 5.42 (s, 1H), 6.20−6.44 (m, 2 H), 7.20−7.45 (m, 10 H) 8.03 (d, J = 8.0 Hz, 1 H *trans*), 8.51 (d, J = 8.5 Hz 1 H *cis*); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 18.3 (*trans*), 20.9 (*cis*), 77.8 (*trans*), 78.0 (*cis*), 126.7, 127.0, 127.3, 127.5, 128.3, 132.0, 141.2, 143.6, 162.7 (*trans*), 163.8 (*cis*).

***N*-Benzylidene-1,1-diphenylmethylamine (1e)** was obtained by the general procedure as pale yellow solid (crystallized from pentane), 2.303 g, 85% yield: mp 98−100 °C; *m*/*z* 271 (M^+, 10), 270 (4), 194 (3), 167 (100), 90 (4), 77 (7); IR ($CHCl_3$) 1637 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.63 (s, 1 H), 7.2−7.9 (m, 15 H), 8.45 (s, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 77.9, 127.0, 127.7, 128.4, 130.7, 136.3, 143.9, 160.8. Anal. Calcd for $C_{20}H_{17}N$: C, 88.52; H, 6.31; N, 5.16. Found: C, 88.47; H, 6.23; N, 5.24.

***N*-(Furan-2-ylmethylidene)-1,1-diphenylmethylamine (1f)** was obtained by the general procedure as white solid (crystallized from hexane, 2.088 g, 80% yield): mp 96−98 °C; *m*/*z* 261 (M^+, 33), 260 (8), 232 (1), 184 (4), 167 (100); IR (Nujol) 1645 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 5.60 (s, 1 H), 6.50 (dd, J = 1.8 and J = 3.5 Hz, 1 H), 6.82 (d, J = 3.5 Hz, 1 H), 7.2−7.4 (m, 10 H), 7.56 (d, J = 1.8 Hz, 1 H), 8.22 (s, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 77.9, 111.6, 114.5, 127.0, 127.7, 128.4, 143.2, 144.8, 149.6, 151.6. Anal. Calcd for $C_{18}H_{15}NO$: C, 82.73; H, 5.79; N, 5.36. Found: C, 82.80; H, 5.83; N, 5.34.

Isomerization Reaction. General Procedure. In a 25 mL flask under an inert atmosphere was placed 1 mmol of the starting imine in THF (10 mL), and 0.1 mL of a 1 M THF solution of *t*-BuOK was added, giving a pale rose reaction mixture. After the starting material disappeared (GC-

(14) For X-ray structure of the 1,3-diphenyl-2-azaallyl anion−potassium pair, see: Veya, P.; Floriani, C.; Chiesi-Villa, A.; Guastini, C. *J. Chem. Soc., Chem. Commun.* **1991**, 991.

monitoring), the reaction mixture was quenched with ice and extracted with CH_2Cl_2, dried, and evaporated, obtaining the crude oily isomerized imines which were found to be pure by ^1H NMR and GC analysis.

***N*-(Diphenylmethylidene)hexylamine (2a)** (0.240 g, 91% yield) was obtained by the general procedure starting from 0.265 g (1 mmol) of **1a**: *m/z* 265 (M^+, 24), 264 (59), 250 (14), 236 (29), 222 (12), 208 (95), 194 (100), 180 (23), 165 (30), 91 (89), 77 (25); IR (film) 1625 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.85 (t, J = 7.3 Hz, 3 H), 1.2−1.4 (m, 6H), 1.67 (m, 2 H), 3.36 (t, J = 7.1 Hz, 2 H), 7.10−7.65 (m, 10 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz,) δ 14.0, 22.5, 27.1, 31.1, 31.6, 53.9, 126.8, 127.7, 127.9, 128.2, 129.6, 137.0, 140.0, 167.5.

***N*-(Diphenylmethylidene)-1-cyclohexylmethylamine (2b).** Starting from 0.277 g (1 mmol) of **1b** by the general procedure **2b** was obtained, 0.240 g 87% yield: *m/z* 277 (M^+, 10), 276 (17.2), 194 (77.4), 180 (9.1), 165 (18.6), 91 (100), 77 (12.9); IR (film) 1620 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.8−1.9 (m, 11 H), 3.22 (d, J = 6.0 Hz, 2 H), 7.1−7.7 (m, 10 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 26.1, 26.6, 31.4, 39.7, 60.5, 127.9, 128.0, 128.3, 129.6, 137.1, 140.1, 167.4.

***N*-(Diphenylmethylidene)-2,2-dimethylpropylamine (2c)** was obtained by the general procedure starting from **1c**, 2.238 g, 95% yield: *m/z* 251 (M^+, 3), 250 (2), 236 (4), 194 (52), 180 (3), 165 (23), 91 (100), 77 (10); IR (film) 1627 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.9 (s, 9 H), 3.15 (s, 2 H), 7.12−7.70 (m, 10 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 28.0, 32.8, 65.4, 127.9, 128.0, 128.2, 128.3, 129.6, 137.1, 140.2, 167.2.

***N*-(Diphenylmethylidene)-1-butenylamine (2d)** was obtained by the general procedure starting from **1d**, 0.221 g, 94% yield: *m/z* 235 (M^+, 51), 234 (46), 220 (39), 206 (16), 193 (18), 180 (9), 165 (100), 91 (10), 77 (24); IR (film) 1624, 1599 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ *cis isomer* 1.11 (t, J = 7.5 Hz, 3 H), 2.69 (quintet, J = 7.5 Hz, 2 H), 5.37 (dt, J = 7.5 and J = 7.6 Hz, 1 H), 6.64 (dt, J = 7.6 and J = 12.9 Hz, 1 H), 7.1−7.8 (m, 10 H); *trans* isomer 1.02 (t, J = 7.43 Hz, 3 H), 2.12 (quintet, J = 7.36 Hz, 2 H), 6.25 (dt, J = 7.16 and J = 12.98 Hz, 1 H), 6.77 (t, J = 12.98 Hz, 1 H), 7.1−7.8 (m, 10 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ *cis* isomer 14.2, 19.9, 127.2, 128.0, 128.3, 128.4, 128.6, 129.9, 136.4, 139.7, 139.7, 164.6; *trans* isomer 13.9, 23.8, 126.7, 127.2, 128.0, 128.3, 128.4, 128.6, 129.9, 136.4, 139.7, 164.6.

***N*-(Diphenylmethylidene)-1-phenylmethylamine (2e)** was obtained by the general procedure starting from **1e**, 0.163 g, 60% yield: *m/z* 271 (M^+, 66), 270 (100), 193 (28), 180 (14), 165 (48), 91 (90), 77 (31); IR (film) 1623 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.67 (s, 2 H); 7.2−7.9 (m, 15 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 57.3, 126.4, 128.0, 128.2, 128.3, 130.0, 136.6, 149.7, 168.6.

***N*-(Diphenylmethylidene)-1-furylmethylamine (2f)** was obtained by the general procedure starting from **1f**, 0.185 g, 71% yield: *m/z* 261 (M^+, 100), 260 (61), 232 (14), 180 (11), 165 (24), 81 (92.0); IR (film) 1625, 1640, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.57 (s, 2 H), 6.24 (dd, J = 3.14 and J = 1.1 Hz, 1 H), 6.35 (dd, J = 3.14 and J = 1.84 Hz, 1 H), 7.2−7.7 (m, 10 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 50.9, 106.2, 110.1, 127.8, 128.1, 128.4, 129.8, 136.1, 139.4, 141.4, 153.6, 169.7.

***N*-(Diphenylmethylidene)-1,2-diphenylethylamine (3).** In a 25 mL flask were placed 10 mL of THF and 0.271 g (1 mmol) of **1e**. At room temperature were added *t*-BuOK (1.2 mL, 1 M solution in THF, 1.2 mmol) and 0.15 mL (1.2 mmol.) of benzyl bromide. After 45 min, the reaction was quenched with cold water and the solution was extracted with CH_2Cl_2 (3 × 20 mL). The crude product (0.249 g, 92%) results as a pure oil by ^1H NMR and GC: *m/z* 360 (0.1), 270 (100), 165 (30), 91 (5), 77 (3); IR (film) 1626 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.07 (dd, J = 4.1 and J = 13.0 Hz, 1 H), 3.26 (dd, J = 9.0 and J = 13.0, 1 H), 4.54 (dd, J = 4.1 and J = 9.0 Hz, 1 H), 6.5−7.7 (m, 20 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 31.2, 68.8, 125.2−128.6, 139.4, 166.4 Anal. Calcd for $C_{27}H_{23}N$: C, 89.71; H, 6.41; N, 3.87. Found: C, 89.80; H, 6.48; N, 3.93.

***N*-(Diphenylmethylidene)-1-phenylpentylamine (4)** was obtained as for **3**, with *n*-butyl bromide (1.2 mmol, 0.108 mL), 98% yield (0.320 g): *m/z* 327 (M^+, 24), 326 (12), 270 (100), 193 (11), 180 (19), 165 (80), 91 (72), 77 (26); IR (film) 1620 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.9 (t, J = 6.8 Hz, 3 H), 1.1−2.0 (m, 6 H), 4.43 (dd, J = 8.7 and J = 11.7 Hz, 1 H), 7.1−7.8 (m, 15 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 13.9, 22.5, 28.6, 39.3, 66.6, 126.4, 126.8, 127.5, 127.7, 128.1, 128.3, 129.7, 137.1, 140.0, 145.3, 166.1. Anal. Calcd for $C_{24}H_{25}N$: C, 88.03; H, 7.69; N, 4.28. Found: C, 88.11; H, 7.73; N, 4.24.

***N*-(Diphenylmethylidene)-1-phenylpropylamine (5)** was obtained as for **3**, with ethyl bromide, 89% yield (0.268 g): *m/z* 299 (M^+, 10), 270 (100), 165 (44), 91 (59), 77 (20); IR (film) 1629 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.9 (t, J = 5.0 Hz, 3 H), 2.0 (m, 2 H), 4.37 (dd, J = 5.6 and J = 7.5 Hz, 1 H), 7.10−7.75 (m, 15 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 11.1, 32.4, 68.07, 126.5−128.5, 137.2, 140.0, 145.1, 166.4. Anal. Calcd for $C_{22}H_{21}N$: C, 88.25; H, 7.07; N, 4.68. Found: C, 88.20; H, 6.98; N, 4.71.

***N*-(Diphenylmethylidene)-1-phenyl-3-butenylamine (6)** was obtained as for **3**, with allyl bromide, 84% yield (0.261 g): *m/z* 311 (M^+, 2), 310 (1), 270 (100), 193 (2), 180 (2), 165 (51), 91 (10), 77 (11); IR (film) 1620, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.7 (m, 2 H), 4.5 (dd, J = 8.6 Hz and J = 11.3 Hz, 1 H), 5.05 (m, 2 H), 5.75 (m, 1 H), 7.05−7.90 (m 15 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 43.9, 66.5, 116.6, 126.5, 126.6, 127.1, 127.8, 128.2, 128.5, 129.8, 134.4, 135.7, 140.0, 146.3, 166.6. Anal. Calcd for $C_{23}H_{21}N$: C, 88.71; H, 6.80; N, 4.50. Found: C, 88.80; H, 6.78; N, 4.61.

***N*-(Diphenylmethylidene)-1-phenyl-2-methylbutylamine (7)** was obtained as for **3**, with *sec*-butyl bromide, 83% yield (0.271 g) of a 1/1 mixture of *syn:anti* isomers: *m/z* 327 (M^+, 6), 326 (1), 270 (100), 165 (27), 91 (4), 77 (2); IR (film) 1623 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.7−1.0 (m, 6 H), 1.1−2.1 (m, 3 H), 4.08 (d, J = 5.0 Hz, 1 H, 1° isomer), 4.18 (d, J = 4.0 Hz, 1 H, 2° isomer), 7.0−7.9 (m, 15 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 11.5, 11.7, 15.3, 15.6, 25.7, 26.2, 42.5, 42.8, 71.0, 72.0, 126.3, 126.4, 126.9, 127.6, 127.9, 128.2, 128.3, 128.7, 129.9, 130.6, 137.1, 137.2, 140.1, 140.1, 143.8, 144.8, 144.1, 144.0, 166.0, 166.1. Anal. Calcd for $C_{24}H_{25}N$: C, 88.03; H, 7.69; N, 4.28. Found: C, 88.00; H, 7.75; N, 4.23.

***N*-(Diphenylmethylidene)-1-furyl-2-phenylethylamine (8)** was obtained from **1f** following the same protocol for **3**, with benzyl bromide, 90% yield (0.316 g): *m/z* 260 (M^+ − 91,100), 180 (2), 165 (16), 91 (12), 77 (8); IR (film) 1624 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.3 (d, J = 7.3 Hz, 2 H), 4.68 (t, J = 7.3 Hz, 1 H) 6.21 (d, J = 3.3 Hz, 1 H), 6.35 (dd, J = 3.4 and J = 2.2 Hz, 1 H) 7.0−7.5 (m, 1H), 6.6−7.7 (m, 15 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 41.5, 62.2, 105.5, 110.1, 126.1, 127.6, 127.9, 128.0, 128.2, 128.4, 128.7, 129.9, 130.0, 132.4, 138.6, 141.5, 156.1, 168.9. Anal. Calcd. for $C_{25}H_{21}NO$: C, 85.44; H, 6.02; N, 3.99. Found: C, 85.49; H, 6.11; N, 4.06.

***N*-(Diphenylmethylidene)-1-furylpropylamine (9)** was obtained as for **8**, with ethyl bromide, 86% yield (0.248 g): *m/z* 289 (M^+, 74), 260 (100), 165 (35), 157 (13), 128 (12), 109 (31), 81 (12); IR (film) 1620 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.85 (t, J = 8.0 Hz, 3 H), 1.98 (m, 2 H), 4.41 (t, J = 6.4 Hz, 1 H), 6.17 (m, 1 H), 6.31 (m, 1 H), 7.2−7.7 (m, 11 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 10.7, 28.3, 61.8, 105.3, 109.9, 128.0, 128.3, 128.7, 130.0, 136.9, 139.9, 141.3, 156.8, 168.4. Anal. Calcd for $C_{20}H_{19}NO$: C, 83.01; H, 6.62; N, 4.84. Found: C, 82.94; H, 6.68; N, 4.76.

Imine Hydrolysis. General Procedure. The isomerized imine (1 mmol) was diluted in acetone (7 mL), and 1 N HCl (3 mL) was added. After the starting material disappeared (TLC-monitoring), H_2O (4 mL) was added, the pH was adjusted to 7−8 with solid K_2CO_3, and CbzCl (0.16 mL, 1.1 mmol) was added. The resulting mixture was stirred at rt overnight. Then after evaporation at low pressure of the acetone, the water phase was extracted with CH_2Cl_2 (3 × 20 mL). Evaporation gave a crude product that was purified by flash chromatography (eluent cyclohexane/ethyl acetate = 95:5).

***N*-(Carbobenzyloxy)hexylamine (10)** was obtained by the general hydrolysis procedure as low-melting solid starting from **2a** with 80% yield (0.188 g): *m/z* 235 (M^+, 0.4), 120 (1), 108 (58), 91 (100), 77 (5); IR (Nujol) 3315, 1684 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.9 (t, J = 6.8 Hz, 3 H), 1.2−1.4 (m, 6 H), 1.5 (m, 2 H), 3.2 (dt, J = 6.81 and 6.6 Hz, 2 H), 4.8 (bs, 1 H), 5.1 (s, 2 H), 7.2−7.5 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 13.9, 22.5, 26.3, 29.8, 31.4, 41.0, 66.4, 127.2, 127.8, 128.0, 128.2,

128.5, 136.6, 156.3. Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.40; H, 9.04; N, 5.91.

***N*-(Carbobenzyloxy)-1-cyclohexylmethylamine (11)** was obtained by the general procedure starting from **2b** as white pure solid compound used without further purification (81% yield, 0.200 g), mp 89 °C: *m*/*z* 247 (M^+, 1), 226 (15), 108 (60), 91 (100); IR (Nujol) 3345, 1692 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz,) δ 0.8−1.8 (m, 11 H), 3.02 (t, J = 6.9 Hz, 2 H), 5.1 (s, 2 H), 6.0 (d, J = 6.9 Hz, 1 H), 7.2−7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 25.7, 26.3, 30.5, 38.1, 66.5, 66.9, 127.1, 127.6, 128.0, 128.5, 141.5, 155.5. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.89; H, 8.61; N, 5.61.

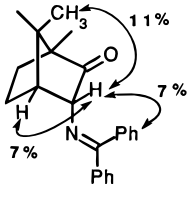
***N*-(Carbobenzyloxy)-2,2-dimethylpropylamine (12)** was obtained as an oil by the general procedure starting from **2c**, 76% yield (0.168 g): *m*/*z* 221 (M^+, 0.7), 108 (21), 91 (100), 77 (7); IR (Nujol) 3353, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.91 (s, 9 H), 3.10 (d, J = 6.5 Hz, 2 H), 4.84 (bs, 1 H), 5.12 (s, 2 H), 7.35−7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 26.9, 31.9, 52.4, 66.6, 127.8, 128.0, 128.1, 128.4, 128.6, 136.6, 156.7. Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.50; H, 8.71; N, 6.28.

***N*-(Carbobenzyloxy)-1,2-diphenylethylamine (13)** was obtained as an oil by the general procedure starting from **3**, 66% yield (0.218 g): *m*/*z* 223 (M^+ − 107, 1), 178 (1.5), 152 (1), 132 (100), 91 (18.1), 77; IR (Nujol) 3341, 1683 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.1 (d, J = 4.0 Hz, 2 H), 5.05 (m, 4 H), 7.0−7.5 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 42.9, 56.3, 66.5, 126.3, 126.4, 127.2, 127.4, 127.9, 128.2, 128.3, 128.7, 129.2, 136.3, 137.1, 141.7, 155.5. Anal. Calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.79; H, 6.30; N, 4.27.

***N*-(Carbobenzyloxy)-1-phenylpropylamine (14)** was obtained as oil by the general procedure starting from **5**, 58% yield (0.156 g): *m*/*z* 240 (M^+ − 29, 31), 196 (15), 178 (6.8), 134 (4), 91 (100), 77; IR (film) 3338, 1656 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.9 (t, J = 7.9 Hz, 3 H), 1.8 (m, 2 H), 4.6 (m, 1 H), 5.1 (m, 3 H), 7.2−7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 10.6, 29.5, 56.8, 66.6, 126.3, 127.2, 127.4, 127.7, 128.0, 128.4, 136.4, 155.8. Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.78; H, 7.19; N, 5.17.

***N*-(Diphenylmethyl)-3-imino-2,3-bornanedione (15).** In a Dean−Stark apparatus were placed dry benzene (27 mL), diphenylmethanamine (1.33 mL, 7.4 mmol), and camphorquinone (0.664 g, 4 mmol). After 7 h at reflux, the solvent was evaporated and the crude product was treated with petroleum ether (40−60 °C), affording **15** as a solid (1.18 g, 3.56 mmol, 89%): mp 102−103 °C; $[\alpha]^{20}_D$ = +80.3 (*C* = 3.075, $CHCl_3$); IR (Nujol) 1754, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.75 (s, 3 H), 1.00 (s, 3 H), 1.08 (s, 3 H), 1.20−2.15 (m, 4 H), 3.08 (d, J = 4.5 Hz, 1 H), 5.70 (s, 1 H), 7.20−7.46 (m, 10 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 9.0, 17.6, 20.6, 23.2, 30.2, 44.2, 49.3, 57.9, 70.3, 126.9, 127.1, 127.4, 127.8, 128.46, 143.0, 143.2, 171.3, 205.1. Anal. Calcd for $C_{23}H_{25}NO$: C, 83.34; H, 7.60; N, 4.23. Found: C, 83.40; H, 7.69; N, 4.30.

***N*-(Diphenylmethylidene)-3-aminobornan-2-one (16)** was obtained after 12 h by the general isomerization procedure as an oil (0.330 g, 94%) starting from 0.331 g (1 mmol) of **15**: *m*/*z* 331 (M^+, 11), 303 (29), 220 (100), 193 (21), 165 (55), 91 (25), 77 (13); IR (film) 1754, 1625 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.69 (s, 3 H), 0.96 (s, 3 H), 1.01 (s, 3 H), 1.60−2.1 (m, 4 H), 2.61 (dt, J = 7.9 and J = 7.9 Hz, 1 H), 4.11 (d, J = 4.65 Hz, 1 H), 7.25−7.70 (m, 10 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 9.6, 19.0, 19.6, 19.9, 31.5, 44.3, 50.4, 58.3, 69.0, 127.3, 127.8, 128.3, 128.4, 128.5, 128.7, 129.9, 132.4, 136.4, 139.6, 170.7, 216.1. NOE effect in compound **16**:



***N*-(Carbobenzyloxy)-3-aminobornan-2-one (17)** was obtained by the general hydrolysis procedure starting from 0.330 g (0.99 mmol) of **16**. After silica gel chromatography (cyclohexane/ethyl acetate = 9:1) we obtain 0.200 g (0.7 mmol) of **17** in 70% yield: $[\alpha]^{20}_D$ = +26.3 (*c* = 9.405, $CHCl_3$); *m*/*z* 301 (M^+, 1), 273 (3), 190 (25), 146 (20), 91 (100); IR (film) 3320, 1752, 1719 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.95 (s, 3 H), 0.97 (s, 3 H), 1.02 (s, 3 H), 1.2−1.8 (m, 4 H), 2.48 (bs, 1 H), 4.3 (t, J = 5.1 Hz, 1 H), 5.1 (bs, 3 H), 7.3−7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 9.2, 18.9, 19.2, 19.6, 32.2, 44.0, 47.9, 58.6, 59.34 66.9, 128.0, 128.3, 136.1, 156.3, 217.0. Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.68; H, 7.74; N, 4.60.

***N*-(4-Methoxyphenyl)-3-((diphenylmethyl)imino)-4-phenylazetidin-2-one (18).** Under an inert atmosphere in a 50 mL flask were placed the *N*-(4-methoxyphenyl)-3-oxo-4-phenylazetidinone[12] (1.340 g, 5 mmol.), 1,1-diphenylmethanamine (0.86 mL, 5 mmol), and $MgSO_4$ (1.200 g) in 20 mL of dry CH_2Cl_2. The mixture was refluxed for 3 h. The filtered solution was evaporated, and the crude product was triturated with pentane and filtered, affording a white solid as a 60:40 mixture of the *E*:*Z* imine (1.65 g, 76%): mp 214−215 °C; IR (Nujol) 1742, 1726 cm^{-1}; *m*/*z* 211 (78), 196 (100), 167 (26), 141 (11), 115 (12), 77 (17); ^1H NMR ($CDCl_3$, 200 MHz) δ 3.74 (s, 3 H), 3.77 (s, 3 H), 5.51 (s, 2 H), 5.52 (s, 1 H), 5.56 (s, 1 H), 6.7−7.5 (m, 14 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 55.4, 67.8, 68.3, 69.2, 69.7, 114.6, 114.6, 119.0, 119.1, 126.9, 127.2, 127.3, 128.0, 128.3, 128.52, 128.9, 129.0, 129.5, 130.5, 134.5, 134.7, 141.7, 142.6, 143.0, 143.1, 157.0, 157.2, 157.2, 160.4, 163.9. Anal. Calcd for $C_{29}H_{24}N_2O_2$: C, 80.53; H, 5.59; N, 6.48. Found: C, 80.29; H, 5.86; N, 6.43.

3,4-*trans*-*N*-(4-Methoxyphenyl)-3-(*N*′-((diphenylmethylidene)amino)-4-phenylazetidin-2-one (19) and 3,4-*cis*-*N*-(4-Methoxyphenyl)-3-(*N*′-(diphenylmethylidene)amino)-4-phenylazetidin-2-one (20) were obtained starting from **18** 0.434 g, 1 mmol) in THF (5 mL). The general isomerization procedure using a catalytic amount of *t*-BuOK resulted in a **19:20** = 80:20 mixture in 98% yield (0.336 g). After crystallization of the mixture with pentane, the pure *trans* isomer **19** was isolated (0.210 g, 48% yield). Starting from **18** (1 mmol) with a stoichiometric amount of *t*-BuOK (1 mmol, 1 mL, 1M THF solution), after 3 h at room temperature we obtained a **19:20** = 20:80 mixture of the two azetidinones in 95% yield. After crystallization of the latter mixture with pentane, the pure *cis* isomer was recovered in a 71% yield (0.308 g). **19**: white solid; mp 198−200 °C; IR (Nujol) 1750, 1612 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.75 (s, 3 H), 4.66 (d, J = 1.8 Hz, 1 H), 5.31 (d, J = 1.8 Hz, 1 H), 6.7−7.7 (m, 19 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 55.3, 62.4, 78.5, 114.2, 118.7, 126.4, 128.1, 128.2, 128.9, 129.0, 130.6, 131.0, 135.1, 136.5, 139.4, 156.1, 163.6, 172.7. Anal. Calcd for $C_{29}H_{24}N_2O_2$: C, 80.53; H, 5.59; N, 6.48. Found: C, 80.40; H, 5.89; N, 6.44. **20:** white solid; mp 134−135 °C; IR (Nujol), 1757, 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.78 (s, 3 H), 5.17 (d, J = 4.98 Hz, 1 H), 5.23 (d, J = 4.98 Hz, 1 H), 6.83−7.65 (m, 19 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 55.4, 62.4, 71.6, 114.3, 118.6, 127.8, 131.2, 134.6, 135.4, 139.3, 156.1, 163.9, 171.8. Anal. Calcd for $C_{29}H_{24}N_2O_2$: C, 80.53; H, 5.59; N, 6.48. Found: C, 80.42; H, 5.77; N, 6.42.

3,4-*trans*-*N*-(Carbobenzyloxy)-3-amino-4-phenylazetidin-2-one (21). In a 50 mL flask was placed 0.434 g (1mmol) of **19** dissolved in 1 mL of CH_2Cl_2 and 10 mL of 80% NH_2OH·HCl in EtOH. The mixture was refluxed for 5 min. The solvent was removed *in vacuo*, and the mixture was diluted in acetone (10 mL). Then H_2O (10 mL) was added and the pH was adjusted to 8 with solid Na_2CO_3; finally CBzCl (0.18 mL, 1.2 mmol) was added. The resulting mixture was stirred at room temperature overnight. After evaporation of the organic solvent at low pressure, the water phase was extracted with CH_2Cl_2, dried, and evaporated, affording the crude product which was purified by flash chromatography (eluent: cyclohexane/ethyl acetate = 9:1), obtaining 0.205 g(0.509 mmol, 51%) of a white solid: mp 130−131 °C; *m*/*z* 402 (M^+, 7), 294 (2), 253 (4), 212 (35), 196 (11), 149 (22), 91 (100), 77 (8); IR (Nujol) 3278, 1758, 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.75 (s, 3 H), 4.51 (m, 1 H), 5.15 (s, 2 H), 5.54 (m, 1 H), 6.8−7.4 (m, 14 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 55.3, 63.6, 66.9, 67.3, 114.2, 118.8, 126.0, 128.1, 128.5, 128.7,

129.1, 130.5, 135.8, 136.2, 155.4, 156.2, 163.3. Anal. Calcd for $C_{24}H_{22}N_2O_4$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.58; H, 5.54; N, 6.92.

3,4-*cis*-*N*-(Carbobenzyloxy)-3-amino-4-phenylazetidin-2-one (22) was obtained by the same protocol used for **21**, starting from **20** (0.434 g, 1 mmol). The product was a white solid (0.203 g, 0.504 mmol, 51% yield): mp 134−135 °C; *m*/*z* 402 (M^+, 6), 251 (7), 212 (67), 196 (16), 149 (11), 91 (100), 77 (8); IR (Nujol) 3350, 1757, 1706 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.76 (s, 3 H), 4.92 (d, J = 9.0 Hz, 1 H), 4.98 (s, 2 H), 5.35 (d, J = 6.0 Hz, 1 H), 5.49 (dd, J = 6.0 and J = 9.0 Hz, 1 H), 6.75−7.45 (m, 14 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 55.4, 61.3, 67.0, 67.3, 114.3, 118.6, 126.8, 127.7, 128.1, 128.4, 129.0, 129.1, 130.5, 133.4, 136.8, 155.4, 156.4, 163.02. Anal. Calcd for $C_{24}H_{22}N_2O_4$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.70; H, 5.48; N, 6.99.

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Supporting Information Available: ^1H NMR spectra of the synthetic intermediates **1d**, **2a**, **2b**, **3c**, **2d**, **2e**, **2f**, and **16** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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