Asymmetric Syntheses of 3,4-Substituted Tetrahydroquinoline Derivatives by (–)-Sparteine-Mediated Dynamic Thermodynamic Resolution of 2-(α-Lithiobenzyl)-*N*-pivaloylaniline

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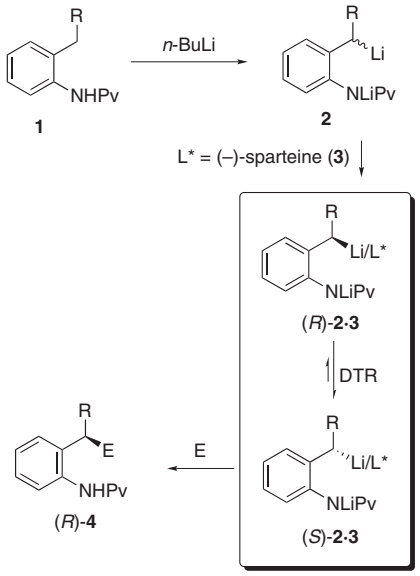
Abstract: (–)-Sparteine-mediated dynamic thermodynamic resolution of 2-(α-lithiobenzyl)-*N*-pivaloylaniline was investigated. A temperature- and concentration-controlled epimerization–substitution sequence provides a simple protocol for the preparation of a highly enantioenriched benzyl-substituted *N*-pivaloylaniline product (up to 98:2 er). Also, application of this simple methodology to asymmetric syntheses of 1,3,4- and 3,4-substituted tetrahydroquinoline derivatives is demonstrated.

Key words: asymmetric synthesis, enantiomeric resolution, alkylations, quinolines, stereoselective synthesis

Dynamic thermodynamic resolution (DTR) has been recognized recently as an effective synthetic method for obtaining highly enantioenriched products from racemic substrates.[1] The difference in the thermodynamic stabilities of two diastereomeric species under the influence of a chiral reagent is the primary source of asymmetric induction. Previous reports have demonstrated that management of experimental conditions can control the diastereomeric equilibrations and provide significantly improved stereoselectivities.[2]

For example, lateral lithiation reactions of 2-alkyl-*N*-pivaloylanilines **1** mediated by (–)-sparteine (**3**) can provide highly enantioenriched products **4** if diastereomeric organolithium intermediates (*R*)-**2**·**3** and (*S*)-**2**·**3** are allowed to reach thermodynamic equilibrium prior to electrophilic substitution (Scheme 1).[3] The successful application of DTR of dilithioaniline **2** in electrophilic substitution prompted us to apply this methodology to asymmetric syntheses of various *ortho*-substituted aniline derivatives. Herein we wish to report (–)-sparteine-mediated DTR of dilithioaniline **2**, in which an additional crystallization-induced dynamic resolution (CIDR) participates in reinforcing the asymmetric induction, as well as the application of this to asymmetric syntheses of tetrahydroquinoline derivatives.

For asymmetric syntheses of tetrahydroquinoline derivatives, *tert*-butyl bromoacetate was used as an electrophile in the substitution of 2-benzyl-*N*-pivaloylaniline (**5**). The experimental observations for the lithiation–substitution



Scheme 1 (–)-Sparteine-mediated dynamic thermodynamic resolution and electrophilic substitution of dilithioaniline **2**

of **5** to provide **6** in the presence of (–)-sparteine (**3**) are summarized in Table 1. As previously reported, the enantiomeric ratio (er) for the sequence is a function of temperature, as shown in entries 1–3. The enantiomeric ratio of 37:63 (*R*:*S*) obtained at –78 °C (Table 1, entry 1) was improved and inverted to 94:6 (*R*:*S*) when the lithiation of **5** in the presence of (–)-sparteine was carried out at –15 °C (entry 2) or at 0 °C (entry 3) for 1 h prior to cooling to –78 °C and addition of *tert*-butyl bromoacetate.[4] In addition, the reactions carried out at –15 °C and 0 °C provided **6** in better yields and comparable enantioselectivities (Table 1, entries 4 and 5).

In this work, we used a modified procedure in which lithiation of **5** was carried out in the presence of (–)-sparteine. The new procedure is operationally much simpler than the previously reported stepwise lithiation and addition of (–)-sparteine shown in Scheme 1. If the diastereomeric intermediates equilibrate rapidly under the reaction conditions, the stereochemical outcome should be independent of the method of diastereomeric complex formation. The results shown in entry 6 (Table 1) verify the reliability of the modified procedure.[5]

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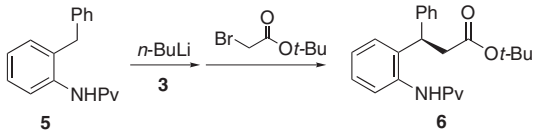
Table 1 Effects of Temperature and Concentration on the Lithiation and Substitution of Aniline Derivative **5**



5 **6**

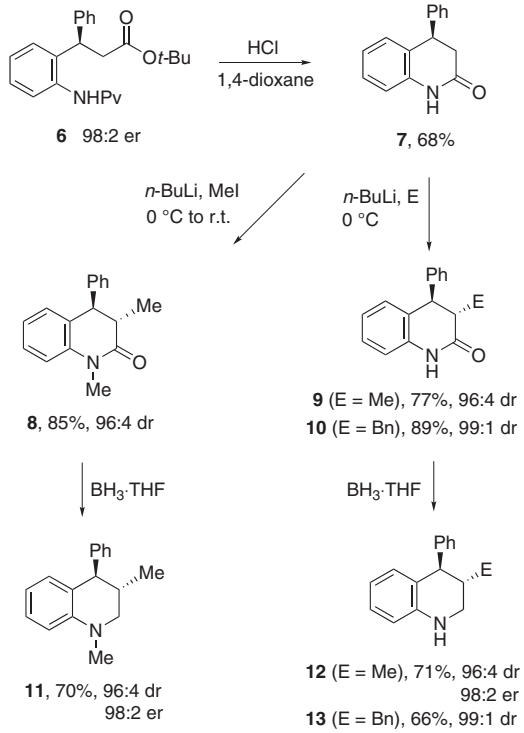
Entry[a]	Concentration of **5** (M)	Temp (°C)		Yield[b] (%)	er[c] (*R*:*S*)
		Step 1	Step 2		
1	0.05	–78	–78	42	37:63
2	0.05	–15	–78	87	94:6
3	0.05	0	–78	81	94:6
4	0.05	–15	–15	93	94:6
5	0.05	0	0	95	93:7
6[d]	0.05	–15	–15	87	94:6
7	0.20	–15	–15	85	98:2
8	0.20	0	0	81	93:7

[a] All reactions were carried out in MTBE.
[b] Isolated yields.
[c] The er values were determined by CSP-HPLC.
[d] Lithiation of **5** was carried out for 1 h at –15 °C prior to the addition of (–)-sparteine.

In an effort to improve the enantioselectivity, we carried out a series of reactions under selected experimental conditions. Interestingly, we found that the enantioselectivity was significantly improved at higher reactant concentration (0.20 M solution of **5** in MTBE). Addition of *n*-butyllithium to a solution of 2-benzylaniline **5** and (–)-sparteine (**3**) in methyl *tert*-butyl ether at –15 °C resulted in a precipitate being deposited. Subsequent stirring of the resulting suspension for one hour at –15 °C, followed by alkylation with *tert*-butyl bromoacetate provided the enantioenriched product **6** in 85% yield with 98:2 er (Table 1, entry 7). This indicates that selective crystallization in the resolution step can provide an additional opportunity to improve the asymmetric induction. The diastereomeric intermediates have different solubilities in methyl *tert*-butyl ether and the formation of solids results in the conversion of the more soluble diastereomer into the less soluble diastereomer.[6] In the reaction at 0 °C, however, precipitation does not occur and no improvement of enantioselectivity was obtained (Table 1, entry 8). This demonstrates the dual mechanisms of resolution by selective formation of soluble and insoluble diastereomers.

Highly enantioenriched product **6** (98:2 er), obtained by the developed DTR method, was used for the preparation of highly enantioenriched 3,4- and 1,3,4-substituted tetrahydroquinoline derivatives **11**–**13** (Scheme 2). Hydrolysis of **6** provided cyclized product **7** in 68% yield. Further conversion of **7** into 1,3,4-substituted **8** was accomplished by a highly stereoselective lithiation–methylation sequence at 0 °C, in which the reaction mixture was allowed to warm to room temperature before quenching. Subsequent reduction with the borane–tetrahydrofuran complex completed the synthetic sequence to provide the 1,3,4-substituted tetrahydroquinoline *trans*-**11**.[7] However, if the alkylation reaction mixture was quenched at 0 °C, 3,4-substituted product **9** was obtained as the major product instead. No epimerization at the 4-position during the alkylation sequence was confirmed by chiral-stationary-phase high-performance liquid chromatography (CSP-HPLC) analyses of **11** and **12**. In addition, the lithiation–benzylation of **7** at 0 °C and subsequent reduction provided 3,4-substituted tetrahydroquinoline **13** in high diastereoselectivity (99:1 dr). The relative configuration of **13** was provisionally assigned by analogy to the formation of *trans*-**11**.

In summary, we have shown that dynamic thermodynamic resolution of dilithioaniline can be successfully applied to the preparation of highly enantioenriched tetrahydroquinoline derivatives. Significantly improved enantioselectivity is obtained with concentration-controlled thermodynamic resolution coupled with selective crystallization. The methodology of the present work could also be applicable to stereoselective syntheses and mechanistic analyses of a number of related systems.



Scheme 2 Asymmetric syntheses of tetrahydroquinoline derivatives

Commercially available (–)-sparteine was distilled from CaH_2 under nitrogen. All other commercial reagents were used without further purification. Analytical chiral-stationary-phase HPLC was performed on a pump system coupled to an absorbance detector (215 nm). A ChiralPak AD-H column (25 cm × 4.6 mm i.d.) with

isopropanol/hexane as mobile phase was used to determine enantiomeric ratios. ^{1}H NMR and ^{13}C NMR spectra were acquired on either U400 (400 MHz ^{1}H, 100.6 MHz ^{13}C) or U500 (500 MHz ^{1}H, 125.7 MHz ^{13}C) spectrometers. Mass spectrometric data were acquired at University of Illinois Mass Spectrometry Laboratory by electrospray ionization (ESI) technique.

tert-Butyl 3-{2-[(2,2-Dimethylpropanoyl)amino]phenyl}-3-phenylpropanoate (6)

To a 0.20 M soln of aniline derivative **5** (266 mg, 1.0 mmol) and (–)-sparteine (**3**; 702 mg, 3.0 equiv) in MTBE (5 mL) at –15 °C was added 1.6 M *n*-BuLi in hexane (1.4 mL, 2.2 equiv). After the mixture had stirred at –15 °C for 1 h, *tert*-butyl bromoacetate (488 mg, 2.5 equiv) was added. The mixture was stirred for 10 min at –15 °C and then quenched with excess MeOH. The resulting mixture was extracted with EtOAc (3 × 5 mL) and the combined extracts were washed with sat. NH_4Cl (5 mL), dried ($MgSO_4$), and concentrated in vacuo. Chromatographic separation (silica gel, hexane–EtOAc, 5:1) afforded **6** as a colorless oil.

Yield: 354 mg (93%); $[\alpha]_D^{20}$ +49.4 (*c* 0.36, $CHCl_3$).

CSP-HPLC: 98:2 er (*R*:*S*), t_R (*R*) = 10.0 min, t_R (*S*) = 13.9 min (Chiralpak AD-H column; *i*-PrOH–hexane, 10:90; 0.5 mL/min).

IR (neat): 3338, 2975, 1732, 1683, 1507, 1449, 1367, 1149 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.03 (s, 1 H), 7.72 (d, *J* = 8.0 Hz, 1 H), 7.29–7.08 (m, 8 H), 4.66 (dd, *J* = 6.0, 9.5 Hz, 1 H), 3.01 (m, 2 H), 1.32 (s, 9 H), 1.29 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.4, 172.5, 143.1, 136.2, 135.8, 129.2, 128.3, 128.1, 127.4, 127.3, 125.9, 125.8, 81.6, 42.1, 41.1, 39.9, 28.3, 28.0.

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{32}NO_3$: 382.2382; found: 382.2382.

4-Phenyl-3,4-dihydroquinolin-2(1*H*)-one (7)

To a soln of **6** (303 mg, 0.79 mmol) in 1,4-dioxane (3 mL) was added H_2O (3 mL) and concd HCl (3 mL). The soln was refluxed for 36 h. Upon cooling of the soln to r.t., the solvent was removed in vacuo. Chromatographic separation (silica gel, hexane–EtOAc, 5:1) afforded **7** as a white solid.

Yield: 120 mg (68%); mp 168–169 °C; $[\alpha]_D^{20}$ –53.4 (*c* 0.12, $CHCl_3$).

IR (KBr): 3211, 3065, 2908, 1681, 1592, 1487, 1374 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.57 (s, 1 H), 7.36–6.91 (m, 9 H), 4.66 (t, *J* = 7.5 Hz, 1 H), 2.95 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 141.9, 137.5, 129.3, 128.8, 128.4, 128.2, 127.6, 127.1, 123.8, 116.2, 42.4, 38.8.

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{14}NO$: 224.1075; found: 224.1072.

1,3-Dimethyl-4-phenyl-3,4-dihydroquinolin-2(1*H*)-one (8)

To a soln of **7** (80 mg, 0.36 mmol) in THF (4 mL) was added 1.6 M *n*-BuLi in hexanes (2.2 equiv) at 0 °C. The brown soln was stirred at 0 °C for 0.5 h. After MeI (3.0 equiv) had been added at 0 °C, the soln was stirred at r.t. for 30 min. The reaction was quenched with excess MeOH and dissolved in EtOAc (5 mL). The resulting mixture was washed with sat. NH_4Cl (5 mL), dried ($MgSO_4$), and concentrated in vacuo. Chromatographic separation (silica gel, hexane–EtOAc, 4:1) afforded **8** as a mixture of two diastereomers.

Colorless oil; yield: 78 mg (85%); 96:4 dr; $[\alpha]_D^{20}$ –63.1 (*c* 0.15, $CHCl_3$).

IR (neat): 3029, 2971, 2931, 1672, 1599, 1456, 1361 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): major diastereomer: δ = 7.35–6.84 (m, 9 H), 3.87 (d, *J* = 8.5 Hz, 1 H), 3.41 (s, 3 H), 2.94 (m, 1 H), 1.16 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): major diastereomer: δ = 172.7, 141.5, 140.3, 129.2, 129.1, 128.9, 128.7, 128.2, 127.5, 123.3, 114.9, 49.4, 42.5, 30.3, 15.9.

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}NO$: 252.1388; found: 252.1379.

3-Methyl-4-phenyl-3,4-dihydroquinolin-2(1*H*)-one (9)

To a soln of **7** (110 mg, 0.49 mmol) in THF (5 mL) was added 1.6 M *n*-BuLi in hexanes (2.2 equiv) at 0 °C. The brown soln was stirred at 0 °C for 0.5 h. After MeI (2.0 equiv) had been added at 0 °C, the reaction was quenched in less than 1 min with excess MeOH. The resulting mixture was dissolved in EtOAc (5 mL), washed with sat. NH_4Cl (5 mL), dried ($MgSO_4$), and concentrated in vacuo. Chromatographic separation (silica gel, hexane–EtOAc, 4:1) afforded **9** as a mixture of two diastereomers.

Colorless oil; yield: 90 mg (77%); 96:4 dr; $[\alpha]_D^{20}$ –85.7 (*c* 0.10, $CHCl_3$).

IR (neat): 3222, 3069, 2976, 2928, 1681, 1594, 1488, 1376 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): major diastereomer: δ = 8.75 (s, 1 H), 7.35–6.80 (m, 9 H), 3.92 (d, *J* = 9.0 Hz, 1 H), 2.91 (m, 1 H), 1.20 (d, *J* = 4.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): major diastereomer: δ = 174.3, 141.8, 137.1, 129.4, 129.3, 128.8, 128.3, 127.6, 126.8, 123.6, 115.7, 50.0, 42.3, 15.5.

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{16}NO$: 238.1232; found: 238.1225.

3-Benzyl-4-phenyl-3,4-dihydroquinolin-2(1*H*)-one (10)

To a soln of **7** (120 mg, 0.54 mmol) in THF (3 mL) was added 1.6 M *n*-BuLi in hexanes (2.2 equiv) at 0 °C. The brown soln was stirred at 0 °C for 0.5 h. After BnBr (2.0 equiv) had been added at 0 °C, the reaction was quenched in less than 1 min with excess MeOH. The resulting mixture was dissolved in EtOAc (5 mL), washed with sat. NH_4Cl (5 mL), dried ($MgSO_4$), and concentrated in vacuo. Chromatographic separation (silica gel, hexane–EtOAc, 4:1) afforded **10** as a mixture of two diastereomers.

Colorless oil; yield: 150 mg (89%); 99:1 dr; $[\alpha]_D^{20}$ –67.5 (*c* 0.27, $CHCl_3$).

IR (neat): 3206, 3057, 2928, 1671, 1594, 1489, 1378 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): major diastereomer: δ = 10.00 (s, 1 H), 7.41–6.94 (m, 14 H), 3.92 (d, *J* = 2.8 Hz, 1 H), 3.22 (m, 2 H), 2.77 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): major diastereomer: δ = 172.7, 142.6, 138.7, 136.9, 130.4, 129.6, 129.1, 129.0, 128.6, 127.8, 127.3, 127.1, 124.7, 124.2, 115.8, 50.7, 45.4, 36.6.

ESI-HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{20}NO$: 314.1545; found: 314.1551.

1,3-Dimethyl-4-phenyl-1,2,3,4-tetrahydroquinoline (11)

To a soln of **8** (58 mg, 0.23 mmol) in THF (3 mL) was added 1.0 M BH_3·THF (5.0 equiv), and the mixture was refluxed for 12 h. The reaction was quenched by addition of MeOH (0.5 mL) under ice-water cooling, and the solvents were evaporated. A 5% aq soln of HCl (2 mL) was added to the residue, and the mixture was refluxed for 1 h. The mixture was made basic with K_2CO_3, saturated with NaCl, and extracted with $CHCl_3$ (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatographic separation (silica gel, hexane–EtOAc, 4:1) afforded **11** as a mixture of two diastereomers.

Colorless oil; yield: 38 mg (70%); 96:4 dr; $[\alpha]_D^{20}$ –55.3 (*c* 0.10, $CHCl_3$).

CSP-HPLC: 98:2 er (3*S*,4*R*:3*R*,4*S*), t_R (3*R*,4*S*) = 8.5 min, t_R (3*S*,4*R*) = 8.9 min (Chiralpak AD-H column; *i*-PrOH–hexane, 2:98; 0.5 mL/min).

IR (neat): 3024, 2924, 2815, 1599, 1506, 1456, 1339 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): major diastereomer: δ = 7.30–6.41 (m, 9 H) 3.62 (d, *J* = 8.4 Hz, 1 H), 3.15 (dd, *J* = 3.6, 11.2 Hz, 1 H), 2.91 (m, 1 H), 2.86 (s, 3 H), 2.11 (m, 1 H), 0.81 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): major diastereomer: δ = 147.0, 146.2, 130.7, 129.6, 128.7, 127.6, 126.6, 125.6, 116.8, 111.2, 57.2, 52.2, 39.8, 35.4, 18.6.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{20}N$: 238.1596; found: 238.1590.

3-Methyl-4-phenyl-1,2,3,4-tetrahydroquinoline (12)

To a soln of **9** (55 mg, 0.23 mmol) in THF (2 mL) was added 1.0 M BH_3·THF (5.0 equiv), and the mixture was refluxed for 12 h. The reaction was quenched by addition of MeOH (0.5 mL) under ice-water cooling, and the solvents were evaporated. A 5% aq soln of HCl (2 mL) was added to the residue, and the mixture was refluxed for 1 h. The reaction mixture was made basic with K_2CO_3, saturated with NaCl, and extracted with $CHCl_3$ (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatographic separation (silica gel, hexane–EtOAc, 5:1) afforded **12** as a mixture of two diastereomers.

Pale yellow oil; yield: 36 mg (71%); 96:4 dr; $[\alpha]_D^{20}$ –39.3 (*c* 0.11, $CHCl_3$).

CSP-HPLC: 98:2 er (3*S*,4*R*:3*R*,4*S*), t_R (3*S*,4*R*) = 14.2 min, t_R (3*R*,4*S*) = 17.7 min (Chiralpak AD-H column; *i*-PrOH–hexane, 5:95; 0.5 mL/min).

IR (neat): 3410, 3022, 2924, 1506, 1457 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): major diastereomer: δ = 7.32–6.54 (m, 9 H), 3.94 (br s, 1 H), 3.65 (d, *J* = 8.4 Hz, 1 H), 3.31 (dd, *J* = 3.2, 11.2 Hz, 1 H), 3.04 (dd, *J* = 11.2, 8.8 Hz, 1 H), 2.18 (m, 1 H), 0.93 (d, *J* = 6.4 H, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): major diastereomer: δ = 146.2, 145.0, 131.1, 129.6, 128.7, 127.4, 126.6, 124.4, 117.6, 114.3, 51.7, 47.5, 35.3, 18.4.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{17}N$: 224.1439; found: 224.1446.

3-Benzyl-4-phenyl-1,2,3,4-tetrahydroquinoline (13)

To a soln of **10** (100 mg, 0.32 mmol) in THF (2 mL) was added 1.0 M BH_3·THF (5.0 equiv), and the mixture was refluxed for 12 h. The reaction was quenched by addition of MeOH (0.5 mL) under ice-water cooling, and the solvents were evaporated. A 5% aq soln of HCl (2 mL) was added to the residue, and the mixture was refluxed for 1 h. The reaction mixture was made basic with K_2CO_3, saturated with NaCl, and extracted with $CHCl_3$ (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Chromatographic separation (silica gel, hexane–EtOAc, 5:1) afforded **13** as a mixture of two diastereomers.

Pale yellow oil; yield: 63 mg (66%); 99:1 dr; $[\alpha]_D^{20}$ –45.8 (*c* 0.30, $CHCl_3$).

IR (neat): 3416, 3023, 2913, 2852, 1605, 1493, 1316 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): major diastereomer: δ = 7.35–6.61 (m, 14 H), 3.97 (br, 1 H), 3.92 (d, *J* = 8.4 Hz, 1 H), 3.21 (dd, *J* = 3.6, 12.0 Hz, 1 H), 2.97 (dd, *J* = 6.0, 11.6 Hz, 1 H), 2.82 (dd, *J* = 5.6, 13.6 Hz, 1 H), 2.55 (dd, *J* = 9.2, 13.6 Hz, 1 H), 2.33 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): major diastereomer: δ = 147.0, 145.0, 141.0, 131.8, 129.6, 129.4, 128.8, 128.7, 127.7, 126.6, 126.5, 122.6, 117.7, 114.4, 48.8, 42.7, 42.2, 39.1.

ESI-HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{22}N$: 300.1752; found: 300.1743.

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