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Intramolecular Interception of Reactive Intermediates in the Raney Nickel "Generated in *Situ*" Reduction of Oximes. Synthetic and Mechanistic Implications.

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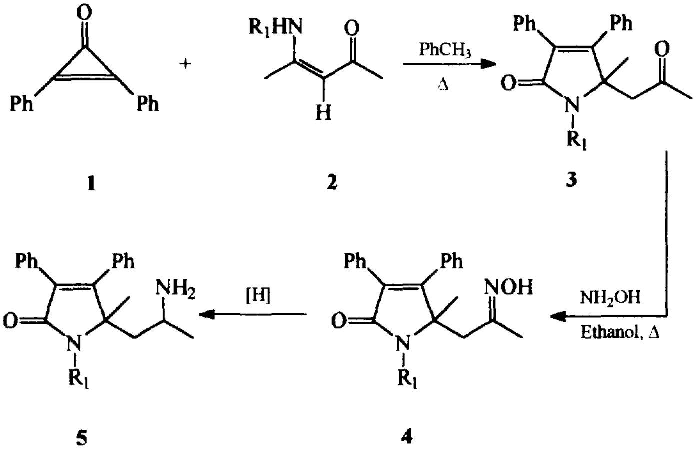
Abstracts : Reduction of oximes **4**, obtained from 1.5 di-hydro-*2H*-pyrrol-2-ones **3**, with Raney nickel "generated *in situ*" afforded pyrrolo [3,2b] pyrrolone derivatives **6** and **7** and, in some cases, amines **5**. The reduction of **4** with W7 Raney nickel afforded only amines **5** . Mechanistic aspects of these reductions were investigated The formation of **6** and **7** is attributed to the deactivation of the catalyst by sodium hydroxide Copyright © 1996 Elsevier Science Ltd

We have reported that the reaction of diphenylcyclopropenone **1** with primary and secondary acyclic enaminones, e.g. **2**, provides a convenient route to 5-functionalized 1,5 di-hydro-*2H*-pyrrol-2-ones **3**.[1]



SCHEME 1

As part of our interest in the development of new synthetic routes to heterocyclic compounds, we envisioned the use of **3** as intermediates in the preparation of more complex systems. In this context, we have been investigating transformations of the ketone fragment of **3** to other versatile functional groups, such as the

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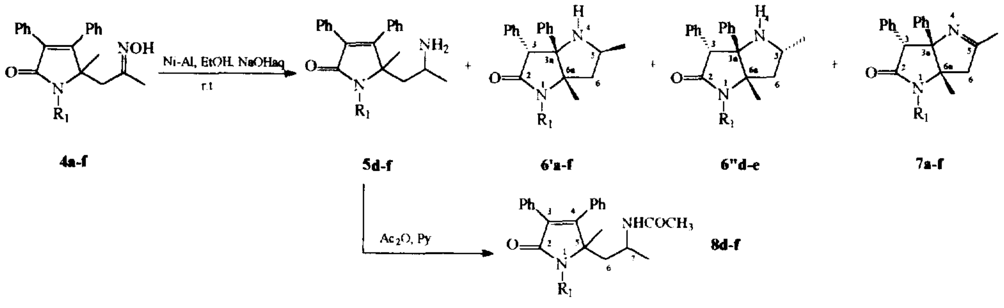
[+] Present address: Departamento de Química, UFAL, Maceió, Al-Brasil 57072-970 primary amine of **5**. To achieve this goal, we chose the sequence shown in Scheme 1, which included the reductions of the corresponding oximes **4**. A well established procedure here involves submitting the oxime to Raney nickel "generated *in situ*" conditions.[2]

Surprisingly, the reductions of oximes **4a-c** with Raney nickel "generated *in situ*" gave only bicyclic compounds **6'a-c** and **7a-c** (Table 1), obtained as single diastereomers, while hydrogenation using W7 Raney nickel produced only amines **5** (as 1:1 mixtures of diastereomers).

Table 1. Products of reduction of 4 with Raney nickel "generated *in situ*" [*]



entry	4	R_1	% yield **6** (**6'** : **6"**)	% yield **7**	% yield **8**[†]	relative ratio **6** : **7**
1	**a**[‡]	*tert*-butyl	16 (1 : 0)	42	-	1 : 2.6
2	**b**	*iso*-propyl	36 (1 : 0)	47	-	1 : 1.3
3	**c**	benzyl	41 (1 : 0)	48	-	1 : 1.2
4	**d**	ethyl	27 (6.3 : 1)	26	28.5	1 : 1
5	**e**	methyl	28 (5 : 1)	26	28	1.1 : 1
6	**f**	H	13 (1 : 0)	4	37	3.3 : 1

[*]all relative ratios were calculated based on ^{1}H NMR spectra./[‡] this reaction also affords **3a** (9%)./ [†]obtained as a 1 : 1 mixture of C7 epimers.

A NOE difference experiment performed on **6'c** (figure 1) afforded the relative configuration of **6'a-c**. The key correlations here are those of the C3a-Ph (ortho hydrogens which appear at lower field, separated from the aromatic envelope) with C3-H, C5-Me, and C6a-Me.

Interestingly, **7** were recovered unchanged when submitted to the Raney nickel "generated *in situ*" reaction conditions, thus demonstrating that they are not intermediates in the formation of **6'**. On the other hand, the imine fragment of **7a-b** was easily reduced under other hydrogenation conditions (PtO_2 or W7 Raney nickel as catalysts). Under these conditions, a single reduction product was obtained in each case which was

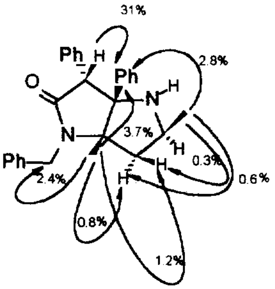
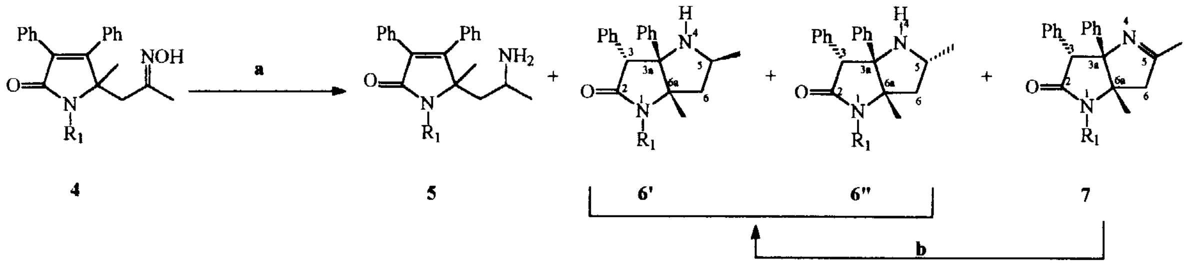


FIGURE 1. NOE experiment for 6'c

different from **6'**, yet clearly a diastereomer of the latter as revealed by analysis of the ^{1}H NMR spectra (Table 2). Evidence for the configuration of this diastereomer and that of **7** was found in the reduction of **4d-e** with Raney nickel "generated *in situ*" (see Table 1). In this case, two diastereomer of **6** were obtained one of which, from analysis of Table 2, is clearly analogous to **6'a-c** while the other is analogous to the diastereomer produced in the catalytic reduction (i.e. PtO_2) of **7a-b**. Here also, **7d-e** were produced as single diastereomers, along with amines **5d-e** (obtained as 1:1 diastereomeric mixtures), which were characterized as the acetamide derivatives **8d-e**. It should be mentioned that amines **5d-e** were recovered unchanged when submitted to the reaction conditions, thus demonstrating that they are not intermediates in the formation of **6**. In as much as neither **6** nor **7** suffered epimerization under the reaction conditions, it is clear that the isomers of **6** correspond to C5 epimers. Since the configuration of **6'** has been determined by the NOE experiment, the configurations of **6"** and **7** must be as shown (Table 1). Examination of molecular models indicates less steric hindrance to approach at the *Si* face of the imine fragment of 7, thus favoring hydrogenation to **6"**. Heterocycles **6** and **7** are pyrrolo [3,2b] pyrrole derivatives. Several examples of systems containing this nucleus have been cited[3], but few oxo derivatives has been documented.[4]

It is apparent from the above results that **4** serve as efficient probes for structural and reaction condition requirements necessary to the process of intramolecular interception of reactive intermediates in the reduction of oximes. To the best of our knowledge, this cyclization process has not been previously observed. Examination of data in Table 1 provides an explanation for the unique behavior of **4** in the present study. As may been seen, the tendency toward cyclization is a direct function of increased steric bulk of the substituent on nitrogen. This situation favors a greater proximity of the C5 oxime fragment and the C4 receptor carbon. Of course, all of this occurs on a catalyst surface, which we represent in Scheme 2. The high diasteroselectivity observed in the transformation of **4** to **6** may be understood in terms of participation of intermediate **9** in a one-step process. Formation of the new C4-N8 bond requires approach of N8 from below the heterocycle plane, thus favoring transfer of hydrogen from the catalyst surface to the imine fragment via the *Re* face. For those **4** containing smaller substituents on nitrogen, competing reduction to **10** and, eventually to **5**, occurs without selectivity.

Table 2. C3-H and C6H ^{1}H NMR Chemical Shifts† of 6' and 6" and their Relative Ratios



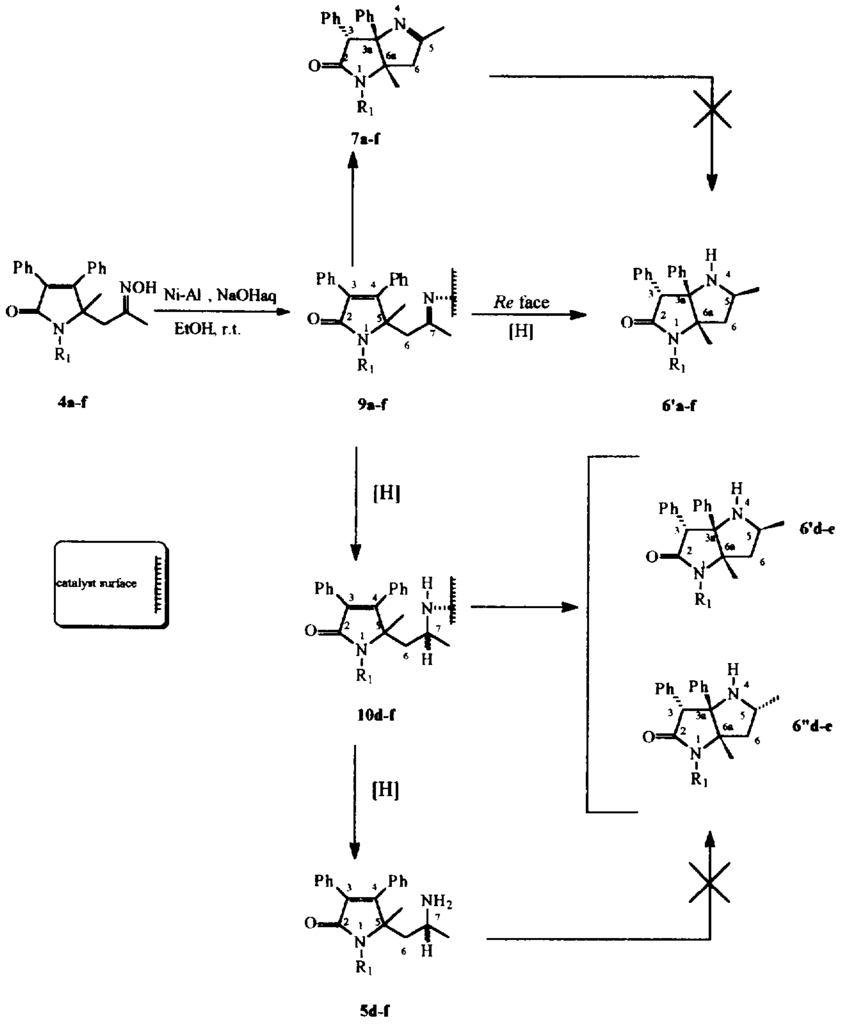
4 5 6' 6" 7

a) Ni-Al, EtOH, NaOH$_{aq}$, r. t.; b) EtOH, H$_2$, 1atm, PtO$_2$, r. t.

entry	reaction condition	substrate	C3-H of 6 (major or exclusive epimer) δ (ppm) J=Hz	C3-H of 6 (minor epimer) δ (ppm) J=Hz	C6-H of 6 (major or exclusive epimer) δ (ppm) J=Hz	C6H of 6 (minor epimer) δ (ppm) J=Hz	^{1}H NMR pattern*	relative configuration *·◆	relative ratio ^{1}H NMR *pattern A* epimer 6' : ^{1}H NMR *pattern B* epimer 6"
1	a	**4a**	4.6O,s	—	1.35 (1H, d, J=12) 2.43 (1H,dd, J=12, J=5)	—	*A*	**6'**	1 : 0
2	a	**4b**	4,45,s	—	1.28 (part of doublet) 1.,87 (1H, dd, J=12, J=5)	—	*A*	**6'**	1 : 0
3	a	**4c**	4.78, s	—	1.20 (1H, d, J=12) 1.95(1H, dd, J=12, J=6)	—	*A*	**6'**	1 : 0
4	a	**4d**	4.53, s		one proton covered 1.93 (1H, dd, J=14, J=4)		*A*	**6'**	6.3 : 1
5	a	**4e**	4.70, s		1.30 (1H, d, J=12) 2.00 (1H, dd, J=12, J=6)		*A*	**6'**	5 : 1
6	a	**4f**	4.80, s	—	1.40 (1H, d, J=12) 1.85 (1H, dd, J=12, J=4)	—	*A*	**6'**	1 : 0
7	b	**7a**				—		**6"**	0 : 1
8	b	**7b**				—		**6"**	0 : 1
9	b	**7d**		4.53, s		one proton covered 1.93 (1H, dd, J=14, J=4)		**6"**	1 : 10
10	b	**7e**	4.70, s		1.30 (1H, d, J=12) 2.00 (1H, dd, J=12, J=6)			**6"**	2 : 1

† CDCl$_3$: **6'a, 6'c, 6'e-f, 6"e**; CCl$_4$: **6'b, 6'd, 6"a-b, 6"d** / *relative to 6 obtained: exclusively from **4a-c** , **4f** and **7a-b** (entries 1-3, 6, 7-8), as major epimers from **4d-e** and **7d** (entries 4-5 and 9) and as minor epimer from **7e** (entry 10) / ◆ infered from the NOE experiment of **6'c.**

As mentioned above, utilization of hydrogenation conditions employing W7 Raney catalyst produced amines **5** exclusively in the reductions of **4a-f**. However, the addition of an aqueous NaOH solution (the same as that used in the " *in situ*" preparation) to the W7 Raney nickel prior to hydrogenation resulted in the same product distribution observed for the "*in situ*" condition. We suggest that NaOH deactivates the catalyst surface thus diminishing the velocities of steps **9**→ **10**→ **5** (Scheme 2) and, consequently, permits interception of reactive intermediates **9**. The study herein reported represents a new approach to C-N bond formation which may find utility in the synthesis of other nitrogen containing heterocycles.



Scheme 2

Experimental Section

The melting points are uncorrected. The IR spectra (KBr disks unless otherwise indicated) were measured with a Perkin Elmer 399 B spectrophotometer, ^{1}H NMR spectra (in $CDCl_3$, unless otherwise stated) with a Brucker AW-80 instrument with a Me_4Si as an internal standard, the NOE experiment was performed with a Varian Gemini 300, ^{13}C NMR spectra (in CCl_4) with a Varian XL-100 instrument and mass spectra with a Varian MAT 311 A spectrometer.

The enaminones[5] and diphenylcyclopropenone[6] were prepared according to known procedures.

Reaction of diphenylcyclopropenone 1 with enaminones 2 (derivatives **a**, **e** and **f** were already prepared[1,7]). In a typical reaction, a solution of **1** (2 mmol) and **2** (2 mmol) in toluene (10 mL) was heated under reflux for 6 days after which time the solvent was removed by rotatory evaporation. The following new **3** were obtained with trituration with ethyl ether :

3b (507 mg, 73% yield) m.p. 115.0-117.0 °C ^{1}H NMR δ 1.45 (s, 3H), 1.47 (d, 3H, J=6), 1.58 (d, 3H, J=6), 2.03 (s, 3H), 2.73 (AB, 2H, J=18), 3.4-3.7 (m, 1H), 7.0-7.5 (m, 10H); IR 1710, 1670 cm^{-1}. Anal. Calcd for $C_{23}H_{25}NO_2$: C, 79.51; H, 7.25; N, 4.03. Found: C, 79.38; H, 7.18; N, 3.91

3c (538 mg, 68% yield) m.p. 158.0-160.0 °C ^{1}H NMR δ 1.40 (s, 3H), 1.50 (s, 3H) , 2.62 (AB, 2H, J=17), 4.73 (AB, 2H, J=16) 7.0-7.6 (m, 15H); IR 1710, 1660 cm^{-1}. Anal. Calcd for $C_{27}H_{25}NO_2$: C, 82.00; H, 6.37; N, 3.54. Found: C, 82.21; H, 6.50; N, 3.40

3d (466 mg, 70% yield) m.p. 103.0-104.0 °C ^{1}H NMR δ(CCl_4) 1.20 (t, 3H, J=18), 1.38 (s, 3H), 1.90 (s, 3H), 2.68 (AB, 2H, J=16), 3.0-3.7 (m, 2H), 7.0-7.2 (m, 10H); IR 1710, 1670 cm^{-1}. Anal. Calcd for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20. Found: C, 79.48; H, 6.81; N, 4.12

Reaction of 3 with hydroxylamine. In a typical reaction, a mixture of **3** (500 mg), ethanol (20 mL) , hydroxylamine hydrochloride (500 mg) and pyridine (0.50 mL) was heated under reflux for 3 h after which time the solvent was evaporated and 25 mL of water was added. The mixture was extracted with methylene chloride (5 X 30 mL) and the combined extracts were washed with water (4 X 20 mL), dried ($MgSO_4$) and the solvent was removed by rotatory evaporation. The following **4** were obtained:

4a Recrystallization of the residue of the reaction of **3a** (500 mg, 1.38 mmol). with methylene chloride-hexane provided **4a** as a yellowish solid (480 mg, 92%) : mp 186.0-189.0 °C; ^{1}H NMR δ 1.60 (s, 12H), 1.83 (s, 3H); 2.83 (s, 2H); 7.0-7.4 (m, 10H); IR 3340,1660,1370 cm^{-1}. Anal. Calcd for $C_{24}H_{28}N_2O_2$: C, 76.56; H, 7.50; N, 7.44. Found: C, 76.27; H, 7.41; N, 7.33.

4b. Recrystallization of the residue of the reaction of **3b** (500 mg, 1.44 mmol). with methylene chloride-hexane provided **4b** as a yellowish solid (485 mg, 93%): mp 174.0-176.0 °C; ^{1}H NMR δ 1.45 (s, 3H), 1.48 (d, 3H, J=7),1.56 (d, 3H, J=7),1.80 (s, 3H); 2.65 (s, 2H); 3.4-3.9 (m, 1H), 7.0-7.5 (m, 10H); IR 3340,1660,1430 cm^{-1}. Anal. Calcd for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 76.42; H, 7.12; N, 7.62.

4c. Recrystallization of the residue of the reaction of **3c** (500 mg, 1.26 mmol) with methylene chloride-hexane provided **4c** as a yellowish solid (466 mg, 90%): mp 178.0-183.0 °C; ^{1}H NMR δ 1.19 (s, 3H), 1.66 (s, 3H); 2.63 (s, 2H); 4.70 (AB, 2H, J=17), 7.0-7.6 (m, 15H); IR 3360,1680,1420 cm^{-1}; mass spectrum, m/e (relative intensity) 410(29), 338 (100), 248 (8). Anal. Calcd for $C_{27}H_{26}N_2O_2$: C, 79.00; H, 6.38; N, 6.82. Found: C, 79.23; H, 6.50; N, 7.00

4d. Recrystallization of the residue of the reaction of **3d** (500 mg, 1.50 mmol) with methylene chloride-hexane provided **4d** as a yellowish solid (470 mg, 90%): mp 175.0-180.0 °C (dec.); ^{1}H NMR δ 1.25 (t, 3H, J=6), 1.40 (s, 3H);1.75 (s, 3H), 2.65 (s, 2H); 3.2-3.9 (m ,2H), 7.0-7.4 (m, 10H); IR 3270,1670,1420 cm^{-1} · Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04 Found: C, 75.60; H, 6.81; N, 8.15.

4e. Recrystallization of the residue of the reaction of **3e** (500 mg, 1.57 mmol) with methylene chloride-hexane provided **4e** as a yellowish solid (504 mg, 96%): mp 178.0-187.0 °C (dec.); ^{1}H NMR δ 1.40 (s, 3H), 1.75 (s, 3H); 2.73 (s, 2H); 3.05 (m ,3H), 7.0-7.4 (m, 10H); IR 3220,1660,1430 cm^{-1}; mass spectrum, m/e (relative intensity) 334(13), 262 (100), 178 (8). Anal. Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.30; H, 6.58; N, 8.31.

4f. Recrystallization of the residue of the reaction of **3f** (500 mg, 1.64 mmol) with methylene chloride-hexane provided **4f** as a colorless solid (435 mg, 83%): mp 165.0-170.0 °C; ^{1}H NMR δ 1.50 (s, 3H), 1.90 (s, 3H); 2.60 (s, 2H); 7.0-7.4 (m, 10H) 7.6 (brs, 1H); IR 3280,1660,1370 cm^{-1}; mass spectrum, m/e (relative intensity) 320 (20), 248 (100), 178 (13). Anal. Calcd for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74. Found: C, 74.80; H, 6.40; N, 8.65.

Reduction of 4 with Raney nickel generated *in situ.** In a typical procedure, to a solution of **4** (500 mg) in ethanol (10 mL) and aqueous NaOH 2N (10 mL) was added Ni-Al (Carlo Erba) (0.75g). The reaction mixture was vigorous and mechanically stirred at rt for 15 h. The mixture was filtered. The filter residue was washed with methylene chloride (150 mL). The filtrate was concentrated by rotatory evaporation and extracted with methylene chloride (5 X 40 mL). The combined organic extracts were washed with water (2 X 20 mL), dried ($MgSO_4$) and the solvent was removed by rotatory evaporation. The residue was treated as follows.

Reduction of 4a. Chromatography of the residue of reaction of **4a** (500 mg, 1.33 mmol) on silica gel afforded **6'a** (77 mg, 16% yield) as a colorless solid (20% ethyl ether-hexane as eluant), which was recrystallized with methylene chloride-hexane: mp 155.4-157.0 °C; ^{1}H NMR δ 1.08 (s, 3H), 1.18(d, 3H, J=6), 1.35 (d, 1H, J=12), 1.63 (s, 9H), 2.43(dd, 1H, J=12, J=5) 3.2-3.7(m, 1H), 4.60(s, 1H); 6.9-7.3 (m, 8H), 7.6-7.8 (m, 2H); ^{13}C NMR δ 20.5, 25.0, 29.1, 44.1, 49.1, 55.4, 56.1 73.0, 73.9, 125.9, 126.0, 126.3, 126.7, 127.1, 127.5, 127.8, 128.6, 128.9, 129.4, 134.6, 143.1, 171.8 ; IR 3400,1675,1450 cm^{-1}; mass spectrum, m/e (relative intensity) 362(100), 173 (53), 158 (23). Anal. Calcd for $C_{24}H_{30}N_2O$: C,79.52; H, 8.34; N, 7.73. Found: C, 79.73; H, 8.21; N, 7.65.

Elution with 50% ethyl ether-hexane afforded **3a** (43 mg, 9% yield). mp 100-102 °C (lit.[8] mp 101-102 °C). ^{1}H NMR δ 1.60 (s, 12H), 2.00 (s, 3H), 2.83 (AB, 2H, J=16), 6.9-7.4 (m, 10H); IR 1725, 1660 cm^{-1}

Elution with 70% ethyl ether-hexane afforded **7a** as a colorless solid (200 mg, 42% yield) which was recrystallized with methylene chloride-hexane: mp 141.0-145.0 °C; ^{1}H NMR δ 1.10 (s, 3H), 1.58 (s, 9H), 2.00 (s, 3H) 2.80 (AB, 2H, J=18); 4.43(s, 1H), 7.1(s, 5H), 7.3 (s, 5H); IR 1675 ,1650, 1360 cm^{-1}; mass spectrum, m/e (relative intensity) 360 (57), 166 (95), 110 (100). Anal. Calcd for $C_{24}H_{28}N_2O$: C, 80.41; H, 7.31; N, 7.81. Found: C, 80.12; H, 7.16; N, 8.00.

Reduction of 4b. Chromatography of the residue of reaction of **4b** (500 mg, 1.38 mmol) on silica gel afforded **6'b** (173 mg, 36% yield) as a colorless solid (30% ethyl ether-hexane as eluant), which was recrystallized with methylene chloride-hexane: mp 140.6-142.0 °C; ^{1}H NMR (CCl_4) δ 0.85 (s, 3H), 1.08 (d, 3H, J=6), 1.28 (part of a doublet), 1.45 (d, 3H, J=6), 1.50 (d, 3H, J=6), 1.87 (dd, 1H, J=12, J=5), 3.0-3.6 (m, 2H), 4.45 (s, 1H), 6.9-7.5 (m, 8H), 7.7-7.9 (m, 2H); ^{13}C NMR δ 19.6, 20.3, 22.4, 42.5, 45.3, 48.7, 56.0 71.6, 72.5, 125.8, 126.1, 126.8, 127.3, 128.8, 134.3, 143.4, 169.9 ; IR, 3400, 1680, 1500 cm^{-1}. Anal. Calcd for $C_{23}H_{28}N_2O$: C,79.27; H, 8.10; N, 8.04 Found: C, 79.09; H, 8.02; N, 8.15.

Elution with 70% ethyl ether-hexane afforded **7b** as a colorless solid (225 mg, 47% yield) which was recrystallized with methylene chloride-hexane: mp 145.0-147.0 °C; ^{1}H NMR δ 0.95 (s, 3H), 1.40 (d, 3H, J=7),1.43 (d, 3H, J=7), 2.05 (s, 3H), 2.45 (AB, 2H, J=18); 3.1-3.5(m, 1H), 4.35 (s, 1H), 7.1 (s, 5H) 7.3 (s, 5H); IR 1680 ,1640, 1430 cm^{-1}. Anal. Calcd for $C_{23}H_{26}N_2O$: C, 79.73; H, 7.56; N, 7.81. Found: C, 79.51; H, 7.40; N, 8.00.

Reduction of 4c. Chromatography of the residue of reaction of **4c** (500 mg, 1.22 mmol) on silica gel afforded **6'c** (198 mg, 41% yield) as a colorless solid (35% ethyl ether-hexane as eluant), which was recrystallized with methylene chloride-hexane: mp 161.0-162.0 °C; ^{1}H NMR δ 0.78 (s, 3H), 0.95 (d, 3H, J=6), 1.20 (d, 1H, J=12), 1.55 (s, 1H, D_2O exchangeable, NH), 1.95 (dd, 1H, J=12, J=6), 2.9-3.4 (m, 1H), 4.58 (s, 2H), 4.78 (s, 1H), 6.9-7.5 (m, 13H), 7.7-7.9 (m, 2H); IR, 3340, 1680, 1490, 1430 cm^{-1}; mass spectrum, m/e (relative intensity) 396 (39), 173 (100), 158 (22), 91(10.7%). Anal. Calcd for $C_{27}H_{28}N_2O$: C, 81.78; H, 7.12; N, 7.06 Found: C, 81.61; H, 7.14; N,7.12.

Elution with 70% ethyl ether-hexane afforded 7c as a colorless solid (232 mg, 48% yield) which was recrystallized with methylene chloride-hexane: mp 221.0-225.0 °C; ^{1}H NMR δ 1.00 (s, 3H), 1.78 (s, 3H), 2.28 (AB, 2H, J=18);), 4.50 (AB, 2H, J=18); 4.70 (s, 1H), 7.15 (s, 5H), 7.30 (s, 5H) 7.35 (s, 5H) ; IR 1685,1645, 1495, 1405 cm^{-1}, mass spectrum, m/e (relative intensity) 394 (28), 220 (17), 200 (100), 178(17.5%), 91(70%). Anal. Calcd for $C_{27}H_{26}N_2O$: C, 82.20; H, 6.64; N, 7.10 Found: C, 82.49; H, 6.50; N, 6.93.

Reduction of 4d. Chromatography of the residue of reaction of **4d** (500 mg, 1.43 mmol) on silica gel afforded **6'd** and **6"d** (6.3 : 1) (130 mg, 27% yield) as a colorless solid (30% ethyl ether-hexane as eluant), which was recrystallized with methylene chloride-hexane: After successive recristallizations with methylene chloride-hexane **6'd** was separated from the mixture: mp 122.5-123.5°C; ^{1}H NMR (CCl_4) δ 0.85(s, 3H), 1.08 (d, 3H, J=7), 1.25 (t, 3H, J=6), 1.93 (dd, 1H, J=14, J=4), 3.1-3.6 (m, 1H), 3.0-3.5 (m, 2H), 4.53 (s, 1H), 6.8-7.5 (m, 8H), 7.7-7.9 (m, 2H); IR, 3390, 1680, 1450 cm^{-1}; Anal. Calcd for $C_{22}H_{26}N_2O$: C, 79.01; H, 7.84; N, 8.38. Found: C, 78.83; H, 7.96; N, 8.29.

Elution with 90% ethyl ether-hexane afforded **7d** (124 mg, 26% yield). which was recrystallized with methylene chloride-hexane: mp 182.0-184.0 °C; ^{1}H NMR δ 0.95 (s, 3H), 1.20 (t, 3H, J=6), 2.00 (s, 3H), 2.50 (AB, 2H, J=18), 3.1-3.5 (m, 2H), 4.40 (s, 1H), 7.0-7.2 (m, 5H), 7.3 (s, 5H); IR 1685,1640, 1500, 1395. Anal. Calcd for $C_{22}H_{24}N_2O$: C, 79.48; H, 7.28; N, 8.43 Found: C, 79.69; H, 7.41; N, 8.21.

Elution with 10 % methanol-ethyl ether afforded **5d**. To this material was added acetic anhydride (0.5 mL) and pyridine (0.5 mL) and the solution was left at rt for 24 h after which time water (30 mL) was added. The mixture was extracted with methylene chloride (4 X 10 mL) and the combined extracts were washed with water (3 X 10 mL), dried ($MgSO_4$) and the solvent was removed by rotatory evaporation resulting in an oil corresponding to a 1 : 1 mixture of **8d** (153 mg, 28.5% yield). ^{1}H NMR (a mixture of diastereomers) δ 1.15 (d, 3H, J=8), 1.20 (d, 3H, J=8), 1.25 (t, 3H, J=6), 1.2-2.2 (m, 4H) 1.35 (s, 3H and t, 3H, J=6), 1.40 (s, 3H) ,1.75 (s, 3H),1.83 (s, 3H), 3.0-4.0 (m, 6H), 5.3 (1H, NH), 5.9 (1H, ,NH), 6.9-7.4 (m, 20H); IR (film), 3320, 1670(br), 1550 cm^{-1}; Anal. Calcd for $C_{24}H_{28}N_2O_2$: C, 76.56; H, 7.50; N, 7.44 Found: C, 76.28; H, 7.41; N, 7.32.

Reduction of 4e. Chromatography of the residue of reaction of **4e** (500 mg, 1.50 mmol) on silica gel afforded **6'e** and **6"e** (5 : 1) (134 mg, 28% yield) as a colorless solid (40% ethyl ether-hexane as eluant), which was recrystallized with methylene chloride. After successive recristallizations with methylene chloride-hexane **6'e** was separated from the mixture: mp 150.0-151.0 °C; ^{1}H NMR δ 0.90 (s, 3H), 1.10 (d, 3H, J=6), 1.30 (d, 1H, J=12), 2.00 (dd, 1H, J=12, J=6), 2.90 (s, 3H) 3.1-3.5 (m, 1H), 4.70 (s, 1H), 6.8-7.5 (m, 8H), 7.6-7.8 (m, 2H); IR, 3390, 1680, 1450 cm^{-1}; mass spectrum, m/e (relative intensity) 320(86), 173 (100), 158(44). Anal. Calcd for $C_{21}H_{24}N_2O$: C, 78.72; H, 7.55; N, 8.74. Found: C,78.51; H, 7.41; N, 8.68.

Elution with 90% ethyl ether-hexane afforded **7e** as a colorless solid (124 mg ,26%). which was recrystallized with methylene chloride-hexane: mp 195.0-197.4 °C; ^{1}H NMR δ 0.98 (s, 3H), 2.08 (s, 3H), 2.58 (AB, 2H, J=18); 2.85 (s, 3H), 4.60 (s, 1H) 7.1-7.2 (brs, 5H), 7.3 (s, 5H); IR 1675,1640, 1395 cm^{-1}; mass spectrum, m/e (relative intensity) 318 (18.5), 124 (100), 220 (18.5). Anal. Calcd for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.96; N, 8.80. Found: C, 79.00; H, 6.89; N, 8.91.

Elution with 10 % methanol-ethyl ether afforded **5e**. To this material was added acetic anhydride (0.5 mL) and pyridine (0.5 mL) and the solution was left at rt for 24 h after which time water (30 mL) was added. The mixture was extracted with methylene chloride (4 X 10 mL) and the combined extracts were washed with water (3 X 10 mL), dried ($MgSO_4$) and the solvent was removed by rotatory evaporation resulting in an oil corresponding to a 1 : 1 mixture of **8e** (145 mg, 28% yield).m.p. 154,0-163,0 °C; ^{1}H NMR (a mixture of diastereomer) δ 1.05 (d, 6H, J=6), 1.8-2.3 (m, 4H), 1.35 (s, 3H), 1.40 (s, 3H), 1.80 (s, 3H) , 1.88 (s, 3H) 2.95

(s, 3H), 3.08 (s, 3H), 3.7-4.1 (m, 2H), 4.9-5.6 (2H, br, NH), 7.0-7.4 (m, 20H); IR 3340, 1680 (br), 1540, 1400 cm^{-1}. Anal. Calcd for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23; N, 7.73. Found: C, 75.94; H, 7.34; N,7.65

Reduction of 4f. Chromatography of the residue of reaction of **4f** (500 mg, 1.56 mmol) on silica gel afforded **6'f** (62 mg, 13% yield) as a colorless solid (60% ethyl ether-hexane as eluant), which was recrystallized with methylene chloride-hexane: mp 191.0-192.5°C; ^1H NMR δ 0.95 (s, 3H), 1.13 (d, 3H, J=8), 1.40 (d, 1H, J=12), 1.85 (dd, 1H, J=12, J=4), 3.3-3.8 (m, 1H), 4.80 (s, 1H), 7.0-7.5 (m, 8H), 7.7-7.9 (m, 2H), 7.0-8.0 (1H, D_2O exchangeable, NH); IR, 3300, 1700, 1380 cm^{-1}. mass spectrum, m/e (relative intensity) 306 (39), 173 (100), 158 (11). Anal. Calcd for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.66; H, 7.09; N, 9.33.

Elution with 90% ethyl ether-hexane afforded **7f** as a yellowish oil (19 mg ,4% yield); ^1H NMR δ 1.00 (s, 3H), 2.15 (s, 3H), 2.60 (AB, 2H, J=18), 4.60 (s, 1H); 7.0-7.3 (1H, D_2O exchangeable, NH), 7.15 (s, 5H), 7.30(s, 5H); IR (film) 3400-3200,1680, 1645, 1500 cm^{-1}. Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.63; H, 6.41; N, 9.09.

Elution with 10% methanol-ethyl ether afforded **5f**. To this material was added acetic anhydride (0.5 mL) and pyridine (0.5 mL) and the solution was left at rt for 24 h after which time water (30 mL) was added. The mixture was extracted with methylene chloride (4 X 10 mL) and the combined extracts were washed with water (3 X 10 mL), dried ($MgSO_4$) and the solvent was removed by rotatory evaporation resulting in an oil corresponding to a 1 : 1 diastereomeric mixture of **8f** (201 mg, 37% yield). ^1H NMR (a mixture of diastereomers) δ 1.05 (d, 6H, J=8), 1.2-2.3 (m, 4H), 1.30 (s, 3H), 1.35 (s, 3H), 1.80 (s, 3H), 1.83 (s, 3H) ,3.9-4.3 (m, 2H), 5.3-5.8 (m, 2H), 7.0-7.5 (m, 22H), IR (film) , 3200-3400, 1670, 1550 cm^{-1}; m/e (relative intensity) 348 (25), 249 (50), 248 (100). Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 76.02; H, 7.15; N, 8.23.

Catalytic Hydrogenation of 7. In a typical reaction , to a solution of 7 (100 mg) in ethanol (10 mL) was added a catalytic amount of PtO_2. The system was purged several times with hydrogen. The mixture was stirred at rt under hydrogen atmosphere (1 atm) for 30h. The catalyst was removed by filtration and washed with ethanol. The solvent was removed by rotatory evaporation.

7a. Reaction of **7a** (100 mg, 0.28 mmol) afforded a *quantitative* residue that was pure based on ^1H NMR. Recristallization from petroleum ether gave **6"a** as a colorless solid: m.p. 132.2-132.8°C. ^1H NMR (CCl_4) δ 1.05 (d, 3H, J=6), 1.10 (s, 3H), 1.20 (1H, D_2O exchangeable, NH), 1.60 (s, 9H), 1.95 (m, 2H), 3.3-3.6 (m, 1H), 4.12 (s, 1H); 6.9-7.5 (m, 10H), ^{13}C NMR δ 21.8, 26.5, 28.9, 47.8, 51.2, 55.8, 58.5, 74.3, 74.4, 125.8, 126.6, 126.8, 126.9, 129.4, 135.1, 143.8, 171.9; IR 3400,1680,1460 cm^{-1} Anal. Calcd for $C_{24}H_{30}N_2O$: C,79.52; H, 8.34; N, 7.73. Found: C, 79.64; H, 8.42; N, 7.91.

7b. Reaction of **7b** (100 mg, 0.29 mmol) afforded a *quantitative* residue that was pure based on ^1H NMR. Recrystallization from petroleum ether gave **6"b** as a colorless solid: m.p. 126.6-127.3°C. ^1H NMR (CCl_4) δ 1.00 (s, 3H), 1.13 (d, 3H, J=6), 1.45(d, 3H, J=6) 1.60 (d, 3H, J=6), 1.75 (m, 2H), 3.0-3.8 (m, 2H), 4.20 (s, 1H), 6.9-7.6 (m, 10H); ^{13}C NMR δ 19.8, 23.3, 23.6, 43.8, 45.2, 50.6, 57.3, 72.8, 73.8, 125.9, 126.6, 127.1, 127.3, 127.5, 129.5, 131.6, 134.2, 146.5, 169.8; IR, 3400, 1675, 1510 cm^{-1}. Anal. Calcd for $C_{23}H_{28}N_2O$: C,79.27; H, 8.10; N, 8.04 Found: C, 79.14; H, 8.33; N, 8.11.

7d. Reaction of **7d** (100 mg, 0.30 mmol) afforded a *quantitative* residue corresponding to a 10 : 1 mixture of **6"d** and **6'd** by ^{1}H NMR analysis of the residue. This material was dissolved in hot petroleum ether. Cooling furnished colorless crystals of **6"d**. m.p. 134.2-138.0°C; ^{1}H NMR (CCl_4) δ 0.95(s, 3H), 1.05 (d, 3H, J=6), 1.25 (t, 3H, J=7), 1.70 (m, 2H), 3.0-3.8 (m, 3H), 4.30 (s, 1H), 6.9-7.5 (m, 10H); IR, 3400, 1670, 1440 cm^{-1}. Anal. Calcd for $C_{22}H_{26}N_2O$: C, 79.01; H, 7.84; N, 8.38. Found: C, 79.26; H, 8.00; N, 8.51.

7e. Reaction of **7e** (100 mg, 0.30 mmol) afforded a *quantitative* residue corresponding to a 2 : 1 mixture of **6'e** and **6"e** by ^{1}H NMR analysis of the residue. Successive recristallizations with methylene chloride-hexane affords a 4 : 1 mixture of **6"e** and **6'e** m.p.: 213.1-218.7 °C. (**6"e** component) :^{1}H NMR δ 0.93 (s, 3H), 1.10 (d, 3H, J=6), 1.60 (1H, br, NH), 1.85 (m, 2H), 2.90 (s, 3H), 3.5-4.0 (m, 1H), 4.55 (s, 1H), 6.9-7.5 (m, 10H); IR, 3390, 1685, 1440 cm^{-1}.

Reduction of 4 with Raney nickel W7[8]. In a typical reaction, to a solution of **4** (100 mg) in absolute ethanol (10 mL) was added a catalytic amount of Raney nickel W7. The system was purged several times with hydrogen. The mixture was stirred at rt under a hydrogen atmosphere (1 atm) for 30h. The catalyst was removed by filtration and washed with ethanol. The solvent was removed by rotatory evaporation. To this material was added acetic anhydride (0.15 mL) and pyridine (0.15 mL) and the solution was left at rt for 24 h after which time the solvent 10 mL of water was added. The mixture was extracted with methylene chloride (5 X 10 mL) and the combined extracts were washed with water (3 X 10 mL), dried ($MgSO_4$) and the solvent was removed by rotatory evaporation.

reduction of 4a: Trituration of the residue of the reaction of **4a** (100 mg, 0.26 mmol) with petroleum ether afforded a 1 :1 mixture of C7 epimers of **8a** (72 mg, 67% yield) as a colorless oil. ^{1}H NMR (a mixture of diastereomers) δ 1.15 (d, 3H, J=7), 1.20 (d, 3H, J=7), 1.35 (s, 3H),1.40 (s, 3H), 1.4-2.1 (m, 4H), 1.35 (s, 3H),1.40 (s, 3H), 1.65 (s, 9H), 1.70 (s, 9H), 1.80 (s, 3H), 1.83 (s, 3H), 3.9-4.2 (m, 2H), 5.4-5.6 (m, 2H), 7.0-7.4 (m, 20H), IR (film) , 3380, 1640(br), 1570 cm^{-1}; m/e (relative intensity) 404 (4), 248 (100), 262 (30). Anal. Calcd for $C_{26}H_{32}N_2O_2$: C, 77.19; H, 7.97; N, 6.92. Found: C, 76.92; H, 8.09; N, 6.85.

reduction of 4e: Recristallization of the residue of the reaction of **4e** (100 mg, 0.30 mmol) with methylene chloride-hexane afforded a 1 :1 mixture of C7 epimers of **8e** (76 mg, 70% yield) as a pale yellow solid: m.p. 155.0-164.0 °C .

Reduction of 4c with Raney nickel W7 and NaOH. To a solution of **4c** (100 mg, 0.24 mmol) in ethanol (10 mL) was added a catalytic amount of Raney nickel W7 and 2 mL NaOH aqueous solution. The system was purged several times with hydrogen. The mixture was stirred at rt under a hydrogen atmosphere (1 atm) for 30h. The catalyst was removed by filtration and washed with ethanol. The solvent was removed by rotatory evaporation resulting a colorless solid. ^{1}H NMR of the crude material was identical to the ^{1}H NMR of the crude material of the reduction of **4c** with Raney nickel-generated *in situ.*).

Reduction of 7a with Raney nickel W7 To a solution of **7a** (100 mg, 0.28 mmol) in ethanol (10 mL) was added a catalytic amount of Raney nickel. The system was purged several times with hydrogen. The mixture was stirred at rt under a hydrogen atmosphere (1 atm) for 30h. The catalyst was removed by filtration and washed with ethanol. The solvent was removed by rotatory evaporation. Recristallization from petroleum ether gave **6"a** (46 mg, 45% yield) as a colorless solid : m.p. 132.2-133.0°C.

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