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Evidence for a Stepwise Mechanism in Formal Hetero-Diels-Alder Reactions of N-Arylimines.

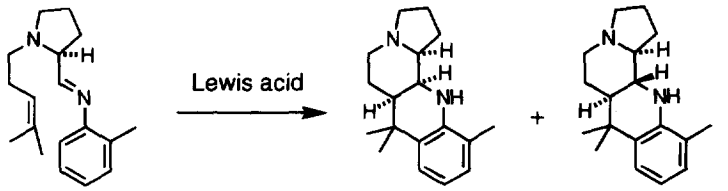
Frank Linkert, Sabine Laschat*, Sirpa Kotila and Thomas Fox

Organisch-Chemisches Institut der Universität Münster, Corrensstr. 40, D-48149 Münster, Germany

Abstract: In order to investigate the mechanism of Lewis acid-catalyzed cyclizations of ω-unsaturated N-arylimines, various prolinal-derived N-arylimines **17a-f** were synthesized and treated with Lewis acids. Whereas imine **17a** bearing a C-2 tether and imines **17d, f** with terminal alkene or alkyne moieties could not be cyclized under these conditions, imine **17b** with a C-3 tether gave three diastereomeric pyrrolo-[1',2':1,2]azepino[3,4-b]quinolines **18a-c** and imine **17c** gave two diastereomeric 7,7-diphenyl-indolizino-[3,4-b]quinolines **19a, b**. High *cis*/*trans*-ratios were observed in both cases. Imine **17e** bearing an internal alkyne underwent a cyclization/dehydrogenation to give the indolizino[3,4-b]quinoline **21**. From these results a stepwise mechanism was concluded. The configuration of **19a** was established by an X-ray crystal structure analysis.

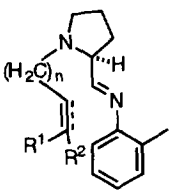
INTRODUCTION

Despite the synthetic utility of the hetero-Diels-Alder reaction for the preparation of a broad variety of heterocyclic systems,[1,2] there is still an open discussion, whether these reactions follow a concerted mechanism or not.[3] The mechanism seems to be highly dependent on the type of heteroatom and the presence of an acidic catalyst (i.e. Brønsted or Lewis acids). Whereas 1-oxabutadienes react in a concerted fashion, as was shown by semiempirical calculations by Tietze et al.,[4] the corresponding 2-aza-1,3-butadienes display an ambivalent behavior. For example, the thermally induced intramolecular cycloaddition of imines derived from 2-aminoisoxazole and an *o*-substituted salicylaldehyde reported by Tietze et al.[5] is explained by a concerted mechanism, although the authors stated that a stepwise protocol might be involved as well.[6] In contrast Mellor et al. described the acid-catalyzed intermolecular cycloaddition of imines derived from anilines and formaldehyde with electron-rich alkenes toward tetrahydroquinolines, where the intermediate carbenium ion could be trapped and isolated as the corresponding tertiary alcohols.[7,8] We recently reported the Lewis acid-catalyzed cyclization of prolinal-derived ω-unsaturated N-arylimine **1** to novel enantiomerically pure indolizino[3,4-b]quinolines **2a,b** (Scheme 1).[9] This imine displayed a remarkable Lewis acid-dependent reversal of the diastereoselectivity.



Scheme 1

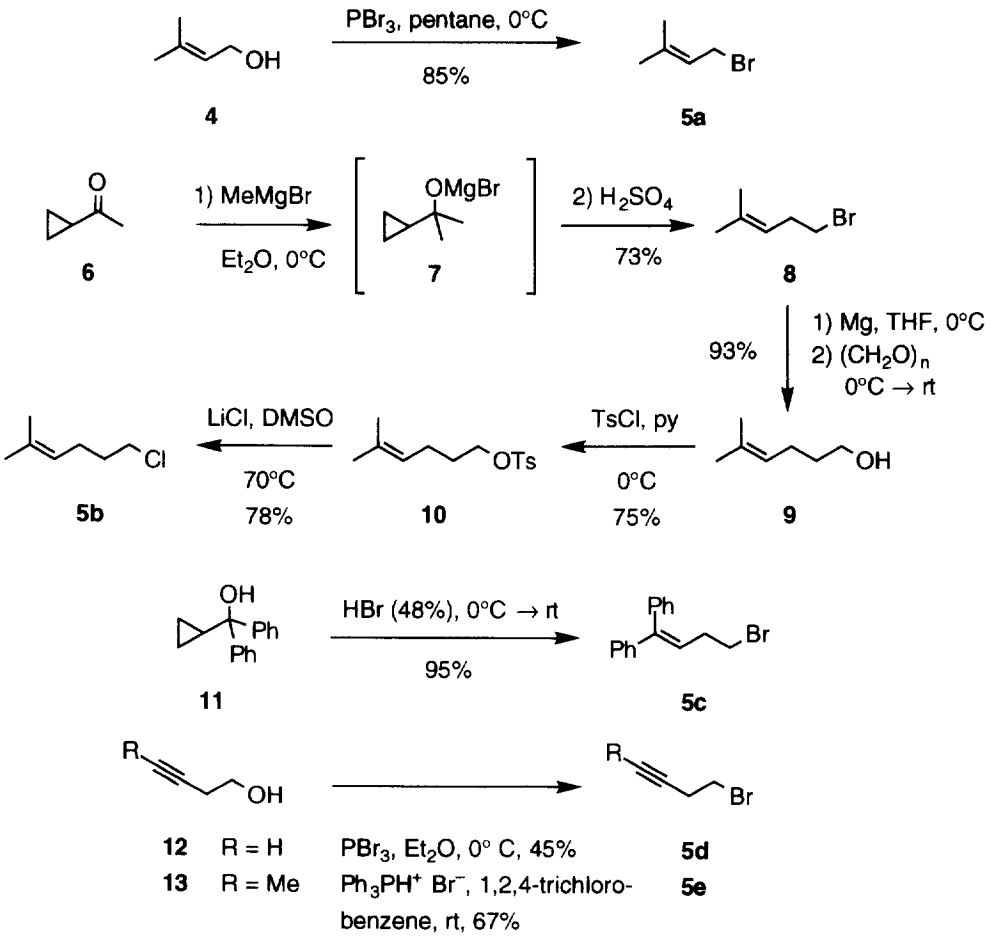
Force-field calculations suggested a stepwise iminium ion cyclization under thermodynamic control rather than a concerted pathway. Thus it was anticipated, that any variation of the dienophile and the length of the tether in the imine **3** should strongly influence both reactivity and diastereoselectivity and therefore further details of the mechanism should be obtained. In addition, the chelation controlled reversal of the product ratio should be highly sensitive towards changes of ring size and steric effects. The results concerning cyclizations of modified precursors **3** are described in this paper.



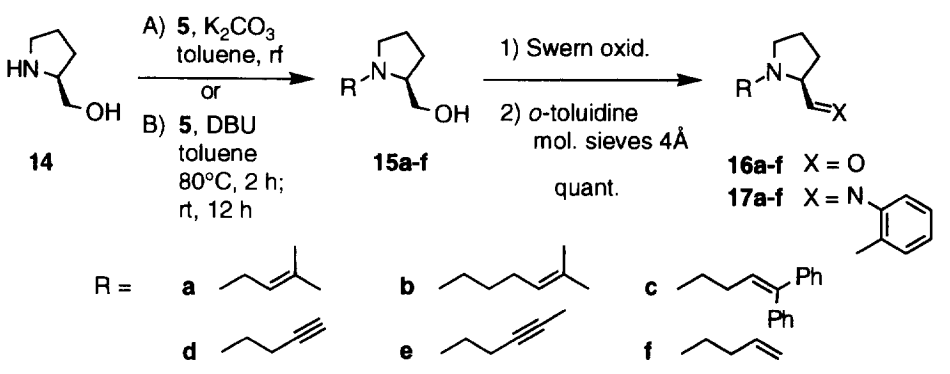
3

RESULTS AND DISCUSSION

Preparation of the cyclization precursors 17. As shown in Scheme 2, various alkenyl- and alkinyl halides **5a-e** were synthesized according to literature procedures. Thus treatment of 3-methyl-2-butenol **4** with phosphorus tribromide gave the corresponding bromide **5a** in 85% yield.[10] Reaction of acetylcyclopropane **6** with methyl magnesium bromide, followed by acid-catalyzed cyclopropane-rearrangement of the intermediate Grignard adduct **7** resulted in formation of bromide **8** in 73% yield.[11] Compound **8** was further used for one-carbon homologation by treatment of the corresponding Grignard reagent with paraformaldehyde, followed by tosylation and nucleophilic substitution with LiCl in DMSO to give the chloride **5b** in 54% overall yield (from **8**).[12] A similar cyclopropane rearrangement was used for the synthesis of 4-bromo-1,1-diphenyl-1-butene **5c** from cyclopropyldiphenylcarbinol **11** (95% yield).[13] 4-Bromo-butyne **5d** was obtained from the alcohol **12** in 45% yield by using the PBr_3 method.[14] 3-Pentyn-1-ol **13** was converted to the corresponding bromide **5e** by using triphenylphosphonium bromide.[15] N-Alkylation of (*S*)-prolinol **14** was either achieved by refluxing the halides **5b, d-f** in the presence of K_2CO_3 (method A)[16] or by using DBU as base (method B for halides **5a, c**)[17] (Scheme 3). Swern oxidation[18] of alcohols **15a-f** followed by reaction with *o*-toluidine in the presence of molecular sieves 4 Å gave the imines **17a-f**.

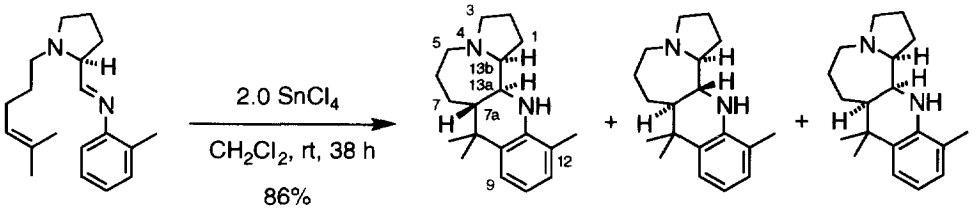


Scheme 2



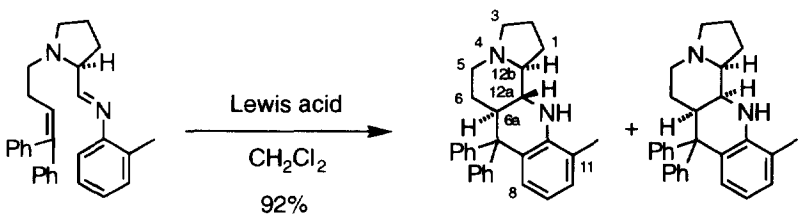
Scheme 3

Cyclization of N-arylimines 17a-f. When N-arylimines **17a, d, f** were treated with various Lewis or Brønsted acids (e.g. ≥ 2 equiv. of $EtAlCl_2$, BF_3OEt_2, $SnCl_4$, $TiCl_4$, HBF_4) in CH_2Cl_2 at room temperature, no traces of the desired cyclization products could be observed. Only starting material and hydrolysis products of the imines were obtained. However, imine **17b** bearing a C-3 tether cleanly cyclized in the presence of 2 equiv. of $SnCl_4$ to give a mixture of three diastereomeric pyrrolo[1',2':1,2]azepino[3,4-b]quinolines **18a-c** in a ratio of 75 : 23 : 2 (Scheme 4). Any attempts to use other Lewis acids for the cyclization of **17b** were completely unsuccessful. Unexpectedly, even $EtAlCl_2$ could not promote the reaction. When the diphenyl-substituted imine **17c** was subjected to Lewis acid catalysis, a mixture of two diastereomeric indolizino[3,4-b]quinolines **19a, b** was obtained (Scheme 5). Contrary to the previously described dimethyl-substituted imine **1**[9] no Lewis acid-induced reversal of the product ratio **19a / 19b** was observed.



17b → **18a** 75 + **18b** 23 + **18c** 2

Scheme 4



17c → **19a** + **19b**

	19a	**19b**
1.6 $EtAlCl_2$, rt, 16 h	98	2
1.6 $EtAlCl_2$, -78°C, 20 h	88	12
2.0 $SnCl_4$, rt, 14 h	99	1
2.0 $BF_3 \cdot OEt_2$, rt, 16 h	99	1

Scheme 5

The connectivity of the carbon skeleton of the cyclization products **18a-c** and **19a** was established by TOCSY together with HMQC and CH-correlation experiments. The relative configuration of **18a-c** was deduced from their vicinal coupling constants in the 1D-NMR spectra together with COSY spectra. The ^1H NMR spectrum of compound **18a** showed a doublet of doublets for 13a-H (J = 8.1/5.7 Hz), indicating a *trans* ring fusion. For isomer **18b** the corresponding signal for 13a-H was only incompletely visible, however the signals for 13b-H (ddd, $J_{13a,13b}$ = 8.7 Hz, $J_{1ax,13b}$ = 8.7 Hz, $J_{1eq,13b}$ = 6.0 Hz) and for 7a-H (ddd, $J_{7a,13a}$ = 10.1

Hz, $J_{7ax,7a}$ = 10.1 Hz, $J_{7eq,7a}$ = 2.1 Hz) confirmed the *all-trans* configuration. In addition irradiation of both 13a-H, 13b-H and 7a-H in **18b** produced no NOE-enhancements. In the third isomer **18c** 7a-H appeared as doublet of doublet of doublets ($J_{7a,7ax}$ = 12.3 Hz, $J_{7a,13a}$ = 3.9 Hz, $J_{7a,7eq}$ = 3.5 Hz). Although these NMR data did not unambigously establish the configuration, the chemical shifts of the ^{13}C-NMR spectra further confirmed these assignments. It was already observed in the parent indolizino[3,4-b]quinoline system **2a,b**, that the signal for C-12a of the *cis* isomer **2a** was shifted by about 10 ppm highfield as compared to the *trans* isomer **2b** ($\delta_{C\text{-}12a}$ 46.9 ppm for **2a**, 54.7 ppm for **2b**). The same shift difference concerning C-13a was found for **18c** as compared to **18a,b** ($\delta_{C\text{-}13a}$ 58.8 ppm for **18a**, 59.5 ppm for **18b**, 47.4 ppm for **18c**).[19] The *all-trans*-configuration of the diphenyl compound **19a** could be unambiguously established by an X-ray crystal structure analysis of the dichloromethane adduct **19aa**.[20] As can be seen in Figure 1 quaternization of the aliphatic nitrogen by the solvent CH_2Cl_2 occurred during the crystallization process, that means the aliphatic nitrogen N(4) was N-chloromethylated, while the second chlorine Cl(4) remains as the counterion. This shows the enhanced basicity of these tetracyclic diaza compounds.[21] In addition a second molecule of CH_2Cl_2, i.e. Cl(3)-C(15)-Cl(2), cocrystallized with the cyclization product.

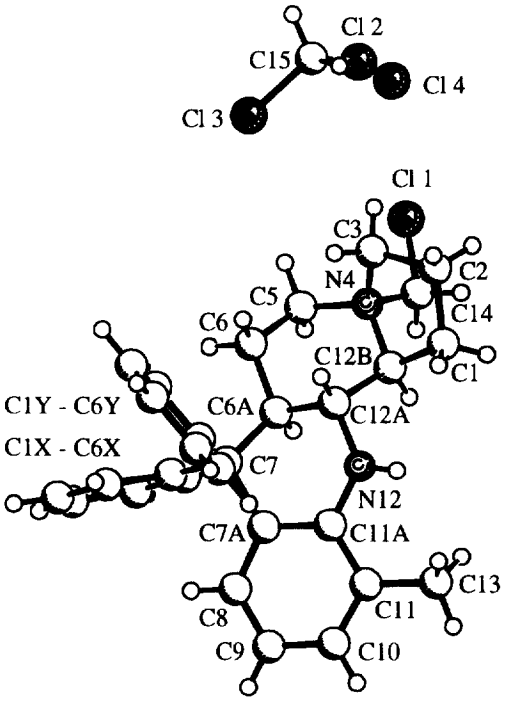
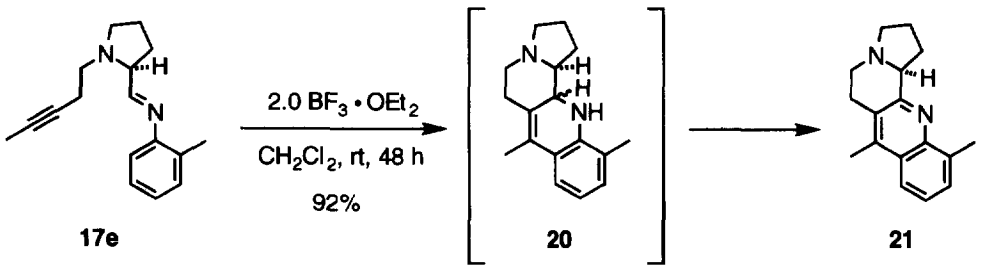


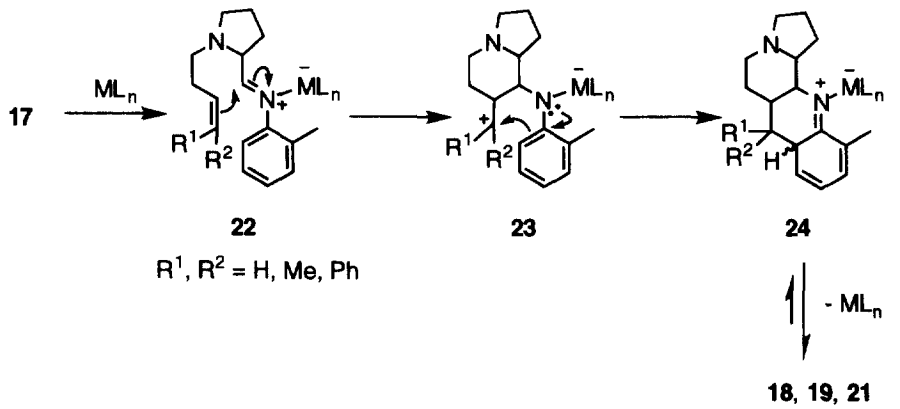
Figure 1 X-ray crystal structure of the N-chloromethylated analogue **19aa** of the 7,7-diphenyl-indolizino[3,4-b]quinoline **19a**.

Treatment of imine **17e** bearing an internal alkyne moiety with $BF_3 \cdot OEt_2$ resulted in the clean formation of the indolizino[3,4-b]quinoline **21** (Scheme 6). Obviously, the initially formed cyclization product **20** undergoes a rapid dehydrogenation to the aromatic compound **21**.



Scheme 6

From the above results, together with our earlier investigations[9] several conclusions can be drawn concerning the mechanism. The absence of any cyclization product in the case of imines **17d**, **f** with terminal alkene or alkyne moieties can be taken as evidence that the cyclization proceeds indeed by a stepwise mechanism, i.e. iminium ion cyclization of **22** to give the tertiary carbenium ion **23**, which undergoes a Friedel-Crafts-type alkylation to **24**, followed by tautomerization (Scheme 7). Thus the presence of at least one cation stabilizing group (e.g. R^1, R^2 = Me, Ph) is required for this particular cyclization. Alternatively, if one considers a Diels-Alder mechanism, the bond forming and bond breaking steps are probably asynchronous due to the polarization by the imino nitrogen and therefore similar cation stabilizing effects might be operative. However, under thermal conditions without any Lewis acid no cyclization of the N-arylimines was observed. This further confirms the stepwise mechanism. The failure of imine **17a** to undergo formation of the expected tetracyclic system with a central five-membered ring might be due to the steric constraints during the Friedel-Crafts-type alkylation. This result is in good agreement with the clean cyclization of imine **17b** with an extended carbon tether, which gives products **18a-c** bearing a seven-membered ring. In addition, the



Scheme 7

diastereomeric ratios of **18a-c** and **19a,b** show, that a Lewis acid-induced chelation control, as it was observed with imine **1**, can be overruled by steric factors. The presence of two bulky phenyl groups in **17c** makes the transition state **A** leading to the *cis*-product **19b** unfavorable as compared to the corresponding non-chelated transition state with the imino moiety beeing equatorially oriented (leading to the *trans*-product **19a**). Imine **17b** contains a much more flexible tether, so that the *quasi-chair*-conformation in **B** with N-N distances being too large for chelation by the Lewis acid should be energetically favored over other possible conformations.

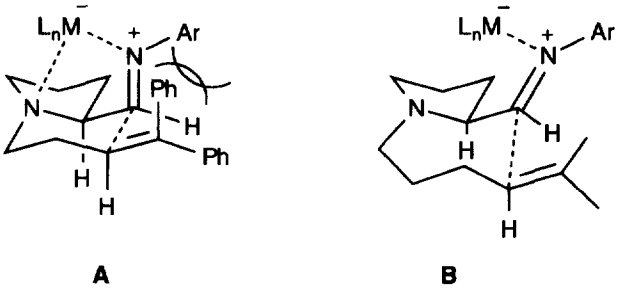


Figure 2 Possible transisition state geometries for the cyclization of imines **17c** (TS **A**) and **17b** (TS **B**).

EXPERIMENTAL

General experimental conditions are described elsewhere.[9] 600 MHz ^{1}H NMR spectra (and 150 MHz ^{13}C NMR spectra) were recorded on a Varian Unity-plus. Swern oxidation and preparation of the imines **17a-f** was carried out according to ref.[9]. Preparative HPLC was done on a Knauer Compact HPLC with a Knauer variable wavelength detector at 285 nm. The following conditions were used for HPLC: Jasco Sepsil Si 100 10µm column, 250 x 25 mm, flow 15 $cm^3\ min^{-1}$, eluent: n-heptane / chloroform / NEt_3 = 100 : 1 : 2.

General procedure for the N-alkylation of (S)-prolinol by the K_2CO_3 method (method A). To an ice-cooled suspension of K_2CO_3 (13.7 g, 0.10 mol) and (*S*)-prolinol **14** (10.0 g, 0.099 mol) in abs. toluene (50 ml) was added dropwise halide **5b, d-f** (0.119 mmol) and the remaining mixture was refluxed for 72 h. Then the mixture was extracted with 2 N HCl (4 x 70 ml). The aqueous layer was washed with Et_2O (2 x 50 ml), adjusted to pH 8-9 by careful addition of conc. NH_3 and then extracted with CH_2Cl_2 (4 x 70 ml). After drying of the combined CH_2Cl_2 layers and evaporation of the solvent, the remaining oils were used without further purification.

General procedure for the N-alkylation of (S)-prolinol by the DBU method (method B). To an ice-cooled solution of (*S*)-prolinol **14** (0.82 g, 8.72 mmol) and DBU (1.33 g, 8.72 mmol) in abs. toluene (15 ml) was added dropwise over 30 min alkyl halide **5a, c** (8.98 mmol) and the remaining mixture was heated at 80°C for 2 h and then stirred at room temperature for 12 h. The colorless precipitate was removed by filtration. The filtrate was extracted with 2 N HCl (2 x 50 ml) and the aqueous layer was washed with Et_2O (50 ml), neutralized with conc. NH_3 and then extracted with CH_2Cl_2 (3 x 50 ml). After drying the combined CH_2Cl_2

layers over $MgSO_4$ and evaporation of the solvent, the resulting crude products were used for the Swern oxidation without further purification.

(S)-N-(3-Methyl-2-butenyl)-prolinol **(15a).** 1.36 g (92%) of a pale yellow oil; $[\alpha]_D^{20}$ = - 39.2° (c = 1.00; CH_2Cl_2); IR (Film) $\tilde{\nu}$ 3368, 3046, 3023, 2966, 2915, 2873, 2809, 1448, 1378, 1266, 1082, 1046, 909 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.18 - 5.11 (m, 1 H, 2'-H), 3.69 (br. s, 1 H, OH), 3.46 (dd, 1 H, *J* = 11.0/4.3 Hz, 1"-H), 3.31 (dd, 1 H, *J* = 11.0/3.3 Hz, 1"-H), 3.21 (dd, 1 H, *J* = 13.5/6.3 Hz, 1'-H), 3.00 - 2.93 (m, 1 H, 2-H), 2.83 (dd, 1 H, *J* = 13.5/7.6 Hz, 1'-H), 2.52 - 2.44 (m, 1 H, 5-H), 2.21 - 2.12 (m, 1 H, 5-H), 1.82 - 1.50 (m, 4 H, 3-H, 4-H), 1.58 (s, 3 H, 5'-H), 1.51 (s, 3 H, 4'-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 134.1 (C-3'), 120.9 (C-2'), 64.0 (C-2), 62.1 (C-1"), 53.8 (C-5), 51.2 (C-1'), 27.3 (C-3), 25.3 (C-5'), 22.8 (C-4), 17.4 (C-4'); GC-MS (EI) *m/z* (%): 169 (M, 1), 154 (4), 138 (48), 122 (2), 108 (1), 84 (4), 70 (100), 55 (4), 41 (25); HRMS (EI) calcd. for $C_{10}H_{19}NO$ 169.1467, found 169.1470. Anal. calcd. for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.27. Found: C, 70.78; H, 11.40; N, 8.28.

(S)-N-(5-Methyl-4-hexenyl)prolinol **(15b).** 13.27 g (67.3 mmol, 68%) of a pale yellow oil; $[\alpha]_D^{20}$ = - 48.2° (c = 1.00; CH_2Cl_2); IR (film) 3360, 2964, 2931, 2874, 2800, 1449, 1376, 1081, 1044, 909 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.03 ("t", 1 H, *J* = 7.0 Hz, 4'-H), 3.53 (dd, 1 H, *J* = 11.0/3.8 Hz, 1"-H), 3.34 (dd, 1 H, *J* = 11.0/2.9 Hz, 1"-H), 3.16 - 3.09 (m, 1 H, 2-H), 2.73 - 2.63 (m, 1 H, 1'-H_a), 2.58 - 2.50 (m, 1 H, 5-H), 2.27 - 2.16 (m, 1 H, 1'-H), 2.01 - 1.43 (m, 9 H, 3-H, 4-H, 5-H, 2'-H, 3'-H), 1.61 (s, 3 H, 7'-H), 1.53 (s, 3 H, 6'-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 131.7 (C-5'), 123.9 (C-4'), 65.2 (C-2), 61.8 (C-1"), 54.3 (C-5), 54.1 (C-1'), 28.7 (C-3'), 27.5 (C-3), 25.7 (C-2'), 25.5 (C-7'), 23.4 (C-4), 17.5 (C-6'); GC-MS (EI) *m/z* (%) 197 (M^+, 4), 166 (76), 140 (4), 96 (14), 84 (100), 70 (32), 55 (40), 41 (48); HRMS (EI) calcd. for $C_{12}H_{23}NO$ 197.1780, found 197.1775. Anal. calcd. for $C_{12}H_{23}NO$: C, 73.04; H, 11.75; N, 7.10. Found: C, 72.98; H, ;11.76 N, 7.15.

(S)-N-(4,4-Diphenyl-3-butenyl)prolinol **(15c).** 8.81 g (28.7 mmol, 58%) of a yellow oil; $[\alpha]_D^{20}$ = - 39.8° (c = 1.00; CH_2Cl_2); IR (film) 3400, 3101, 3079, 3055, 3023, 2962, 2955, 2872, 2799, 1621, 1598, 1495, 1457, 1443, 1405, 1378, 1359, 1325, 1306, 1283, 1266, 1198, 1179, 1155, 1132, 1106, 1074, 1046, 1030, 762, 731, 702, cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.48 - 7.22 (m, 10 H, 2 x Ph), 6.18 ("t", 1 H, *J* = 7.2 Hz, 3'-H), 3.68 (dd, 1 H, *J* = 10.6/3.7 Hz, 1"-H), 3.45 (dd, 1 H, *J* = 10.6/2.4 Hz, 1"-H), 3.12 - 3.05 (m, 1 H, 2-H), 2.97 - 2.85 (m, 1 H, 1'-H), 2.95 (br. s, 1 H, OH), 2.67 - 2.58 (m, 1 H, 5-H), 2.49 - 2.35 (m, 3 H, 1'-H, 2'-H), 2.27 - 2.18 (m, 1 H, 5-H), 1.98 - 1.69 (m, 4 H, 3-H, 4-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.4 (C-i), 140.0 (C-4'), 129.7, 128.0, 127.1, 126.8, 128.9 (C-3'), 64.4 (C-2), 61.8 (C-1"), 54.0 (C-5), 53.8 (C-1'), 29.3 (C-2'), 27.6 (C-3), 23.4 (C-4); GC-MS (EI) *m/z* (%) 306 (M^+-1, 2), 276 (34), 206 (6), 191 (14), 178 (16), 160 (16),151 (6), 138 (10), 129 (76), 115 (100), 91 (90), 82 (26), 70 (28), 55 (34), 44 (100); HRMS (CI) calcd. for $C_{21}H_{25}NO + H^+$ 308.2014, found 308.1995. Anal. calcd. for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 82.07 H, 8.18; N, 4.39.

(S)-N-(3-Butynyl)prolinol **(15d).** 1.20 g (7.83 mmol, 72%) of a pale yellow oil; $[\alpha]_D^{20}$ = - 38.4 (c = 1.00; CH_2Cl_2); IR (film) 3388, 3297, 2953, 2919, 2874, 2811, 2117, 1459, 1430, 1404, 1382, 1358, 1330, 1297, 1225, 1201, 1153, 1127, 1080, 1043 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.52 (dd, 1 H, *J* = 10.7/3.8 Hz, 1"-H), 3.30 (dd, 1 H, *J* = 10.7/3.0 Hz, 1"-H), 3.16 - 3.04 (m, 1 H, 2-H), 3.05 (br. s, 1 H, OH), 2.84 (ddd, 1 H, *J* = 12.1/7.8/7.8 Hz, 1'-H), 2.61 - 2.54 (m, 1 H, 5-H) 2.43 (ddd, 1 H, *J* = 12.1/6.7/5.6 Hz, 1'-H), 2.31 - 2.18 (m,

3 H, 5-H, 2'-H), 1.91 (t, 1 H, J = 2.6 Hz, 4'-H), 1.85 - 1.60 (m, 4 H, 3-H, 4-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 82.6 (C-3'), 69.0 (C-4'), 64.4 (C-2), 62.1 (C-1"), 53.9 (C-5), 52.8 (C-1'), 27.4 (C-3), 23.5 (C-4), 18.8 (C-2'); GC-MS (EI) *m/z* (%) 136 (M^+-OH, 3), 122 (100), 107 (5), 94 (39), 80 (8), 73 (13), 67 (5), 55 (8), 44 (12); HRMS (EI) calcd. for $C_9H_{15}NO$ 153.1154, found 153.1157. Anal. calcd. for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.45; H, 9.84; N, 9.20.

***(S)-N-(3-Pentynyl)prolinol* (15e).** 1.35 g (8.05 mmol, 83%) of a pale yellow oil; $[\alpha]_D^{20}$ = - 49.1° (c = 1.00; CH_2Cl_2); IR (film) 3425, 2952, 2918, 2872, 2809, 2231, 1456, 1405, 1381, 1357, 1290, 1201, 1126, 1081, 1043 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.55 (dd, 1 H, J = 10.8/3.7 Hz, 1"-H), 3.31 (dd, 1 H, J = 10.8/2.7 Hz, 1"-H), 3.16 - 3.09 (m, 1 H, 2-H), 2.93 (br. s, 1 H, OH), 2.80 (ddd, 1 H, J= 12.1/7.8/7.8 Hz, 1'-H), 2.62 - 2.55 (m, 1 H, 5-H), 2.43 (ddd, 1 H, J = 12.1/6.7/5.6 Hz, 1'-H), 2.28 - 2.19 (m, 3 H, 5-H, 2'-H), 1.85 - 1.62 (m, 4 H, 3-H, 4-H), 1.72 (t, 3 H, J = 2.6 Hz, 5'-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 77.4 (C-3'), 76.3 (C-4'), 64.3 (C-2), 62.1 (C-1"), 53.9 (C-5), 53.5 (C-1'), 27.6 (C-3), 23.6 (C-4), 19.3 (C-2'), 3.3 (C-5'); GC-MS (EI)*m/z* (%): 167 (M^+, 1), 136 (78), 121 (26), 114 (100), 108 (10), 82 (5), 70 (16), 67 (10), 55 (7), 44 (16); HRMS (CI) calcd. for $C_{10}H_{17}NO + H^+$ 168.1388, found 168.1365. Anal. calcd. for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.37. Found: C, 71.80; H, 10.37; N, 8.41.

***(S)-N-(3-Butenyl)prolinol* (15f).** 2.61 g (16.8 mmol, 85%) of pale yellow oil; $[\alpha]_D^{20}$ = - 53.8° (c = 1.00; CH_2Cl_2); IR (film) 3400, 3076, 2967, 2946, 2874, 2802, 1641, 1458, 1440, 1415, 1405, 1382, 1357, 1201, 1142, 1084, 1046, 911 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.64 (dddd, 1 H, J=17.0/10.3/6.7/6.7 Hz, 3'-H), 4.89 (dd, 1 H, J = 17.0/1.2 Hz, 4a'-H), 4.84 (dd, 1 H, J = 10.3/1.2 Hz, 4b'-H), 3.42 (dd, 1 H, J = 10.7/4.3 Hz, 1"-H), 3.26 (br. s, 1 H, OH), 3.25 (dd, 1 H, J= 10.7/3.1 Hz, 1"-H), 3.04 - 2.96 (m, 1 H, 2-H), 2.66 (ddd, 1 H, J= 11.7/8.1/7.6 Hz, 1'-H), 2.45 - 2.38 (m, 1 H, 5-H), 2.24 - 2.13 (m, 1 H, 1'-H), 2.12 - 2.04 (m, 3 H, 5-H, 2'-H), 1.78 - 1.50 (m, 4 H, 3-H, 4-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.0 (C-3'), 115.1 (C-4'), 64.5 (C-2), 61.8 (C-1"), 53.6 (C-5), 53.6 (C-1'), 32.8 (C-2'), 27.1 (C-3), 22.9 (C-4); GC-MS (EI)*m/z* (%) 155 (M^+, 1), 138 (4), 124 (100), 108 (1), 96 (13), 84 (4), 70 (13), 55 (18), 44 (17); HRMS (CI) calcd. for $C_9H_{17}NO + H^+$ 156.1388, found 156.1428. Anal. calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.58; H, 11.06; N, 9.19.

***(S)-N-(3-Methyl-2-butenyl)pyrrolidine carboxaldehyde* (16a).** 1.164 g (6.96 mmol, 98%) of a yellow oil; $[\alpha]_D^{20}$ = - 43.0° (c = 1.00; CH_2Cl_2); IR (film) ν̃ 2970, 2917, 2874, 2815, 1728, 1676, 1446, 1378, 1317, 1299, 1263, 1208, 1143, 1134, 1090, 1064, 1035, 1017 cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz) δ 9.39 (d, 1 H, J = 4.0 Hz, CHO), 5.29 - 5.22 (m, 1 H, 2'-H), 2.97 (d, br, 1 H, J = 7.2 Hz, 1'-H), 2.92 - 2.86 (m, 1 H, 2-H), 2.67 - 2.60 (m, 1 H, 5-H), 2.05 - 1.93 (m, 2 H, 1'-H, 5-H), 1.61 - 1.29 (m, 4 H, 3-H, 4-H), 1.57 (s, 3 H, 5'-H), 1.47 (s, 3 H, 4'-H); ^{13}C NMR (C_6D_6, 75 MHz) δ 201.6 (CHO), 135.4 (C-3'), 122.1 (C-2'), 71.6 (C-2), 54.3 (C-1'), 52.4 (C-5), 26.6 (C-3), 25.7 (C-5'), 24.0 (C-4), 18.0 (C-4'); GC-MS (EI) *m/z* (%) 168 (M^++1, 3), 138 (32), 122 (1), 100 (2), 84 (3), 70 (100), 55 (4), 41 (58); HRMS (EI) calcd. for $C_{10}H_{17}NO$ 167.1310, found 167.1313.

***(S)-N-(5-Methyl-4-hexenyl)pyrrolidine carboxaldehyde* (16b).** 3.89 g (19.9 mmol, 98%) of a yellow oil; $[\alpha]_D^{20}$ = - 133.4° (c = 1.00; CH_2Cl_2); IR (film) 2967, 2932, 2861, 2802, 1730, 1447, 1376, 1295, 1205, 1172, 1146, 1111, 1072, 1037; ^{1}H NMR (C_6D_6, 300 MHz) δ 9.38 (d, 1 H, J = 3.9 Hz, CHO), 5.10 ("t", 1 H,

J = 7.2 Hz, 4'-H), 2.94 - 2.86 (m, 1 H, 2-H), 2.63 - 2.55 (m, 1 H, 5-H), 2.49 - 2.39 (m, 1 H, 1'-H), 2.28 - 2.19 (m, 1 H, 1'-H), 2.02 - 1.89 (m, 3 H, 5-H, 3'-H), 1.61 (s, 3 H, 7'-H), 1.59 - 1.30 (m, 6 H, 3-H, 4-H, 2'-H), 1.51 (s, 3 H, 6'-H); ^{13}C NMR (C_6D_6, 75 MHz) δ 202.0 (CHO), 131.5 (C-5'), 124.7 (C-4'), 72.3 (C-2), 55.3 (C-1'), 54.1 (C-5), 29.6 (C-3'), 26.5 (C-3), 26.4 (C-2'), 26.0 (C-7'), 24.2 (C-4), 17.7 (C-6'); GC-MS (EI)*m/z* (%): 196 (M^++1, 5), 166 (30), 136 (1), 122 (1), 110 (1), 96 (3), 84 (100), 70 (3), 69 (3), 55 (5), 41 (13); HRMS (EI) calcd. for $C_{12}H_{21}N_2$ 195.1623, found 195.1619.

(S)-N-(4,4-Diphenyl-3-butenyl)pyrrolidine carboxaldehyde **(16c).** 2.46 g (8.05 mmol, 99%) of a yellow oil; $[\alpha]_D^{20}$ = - 69.0° (c = 1.00; CH_2Cl_2); IR (film) 3079, 3055, 3022, 2969, 2934, 2873, 2799, 1728, 1598, 1495, 1444, 1380, 1292, 1202, 1154, 1137, 1113, 1073, 1030, 762, 732, 702 cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz) δ 9.48 (d, 1 H, *J* = 3.8 Hz, CHO), 7.45 - 7.18 (m, 10 H, 2 x Ph), 6.18 ("t", 1 H, *J* = 7.2 Hz, 3'-H), 2.94 - 2.87 (m, 1 H, 2-H), 2.75 - 2.66 (m, 2 H, 5-H, 1'-H), 2.46 - 2.30 (m, 3 H, 1'-H, 2'-H), 2.01 - 1.88 (m, 1 H, 5-H), 1.69 - 1.33 (m, 4 H, 3-H, 4-H); ^{13}C NMR (C_6D_6, 75 MHz) δ 201.0 (CHO), 142.4 (C-i), 139.8 (C-4'), 129.4, 127.7, 127.6, 126.6, 126.5 (C-3'), 71.2 (C-2), 54.5 (C-5), 52.8 (C-1'), 29.0 (C-2'), 25.4 (C-3), 23.2 (C-4); GC-MS (EI) *m/z* (%) 305 (M^+, 0.2), 276 (M^+-CHO, 20), 206 (4), 191 (5), 178 (7), 165 (6), 129 (40), 112 (100), 91 (14), 84 (56), 77 (4), 65 (3), 55 (12), 42 (11); HRMS (EI) calcd. for $C_{21}H_{23}NO$ 305.1780, found 305.1770.

(S)-N-(3-Butinyl)pyrrolidine carboxaldehyde **(16d).** 1.16 g (7.67 mmol, 98%) of a yellow oil; $[\alpha]_D^{20}$ = - 42.6° (c = 1.00; CH_2Cl_2); IR (film) 3291, 2969, 2947, 2919, 2873, 2811, 2129, 1727, 1457, 1432, 1376, 1298, 1225, 1204, 1130, 1204, 1130, 1113, 1076, 1035 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.44 (d, 1 H, *J* = 3.7 Hz, CHO), 3.24 - 3.16 (m, 1 H, 2-H), 2.94 - 2.88 (m, 1 H, 5-H), 2.80 (ddd, 1 H, *J* = 12.4/7.6/7.4 Hz, 1'-H), 2.67 (ddd, 1 H, *J* = 12.4/7.1/6.9 Hz, 1'-H), 2.42 - 2.29 (m, 3 H, 5-H, 2'-H), 2.03 - 1.76 (m, 4 H, 3-H, 4-H), 1.93 (t, 1 H, *J* = 2.6 Hz, 4'-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.0 (CHO), 83.2 (C-3'), 71.7 (C-2), 69.2 (C-4'), 54.0 (C-5), 45.9 (C-1'), 26.6 (C-3), 24.1 (C-4), 18.9 (C-2'); GC-MS (EI) *m/z* (%) 152 (M^++1, 20), 122 (100), 107 (7), 94 (30), 84 (20), 77 (5), 67 (4), 55 (7), 53 (8), 42 (11), 39 (15); HRMS (GC-MS/CI) calcd. for $C_9H_{13}NO + H^+$ 152.1075, found 152.1028.

(S)-N-(3-Pentynyl)pyrrolidine carboxaldehyde **(16e).** 0.901 g (5.45 mmol, 96%) of a yellow oil; $[\alpha]_D^{20}$ = - 107.9° (c = 1.00; CH_2Cl_2); IR (film) 2946, 2918, 2807, 2233, 1725, 1447, 1376, 1355, 1339, 1294, 1204, 1113, 1075, 1030 cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz) δ 9.37 (d, 1 H, *J* = 3.8 Hz, CHO), 2.87 - 2.80 (m, 1 H, 2-H), 2.66 - 2.57 (m, 2 H, 5-H, 1'-H), 2.47 - 2.38 (m, 1 H, 1'-H), 2.21 - 2.19 (m, 2 H, 2'-H), 1.98 - 1.89 (m, 1 H, 5-H), 1.56 - 1.23 (m, 4 H, 3-H, 4-H), 1.51 (t, 3 H, *J* = 2.6 Hz, 5'-H); ^{13}C NMR (C_6D_6, 75 MHz) δ 202.0 (CHO), 77.5 (C-3'), 76.6 (C-4'), 71.8 (C-2), 54.8 (C-5), 53.9 (C-1'), 26.6 (C-3), 24.3 (C-4), 19.7 (C-2'), 3.3 (C-5'); GC-MS (EI) *m/z* (%) 165 (M^+, 3), 148 (3), 136 (100), 121 (30), 120 (30), 110 (16), 108 (18), 91 (16), 84 (16), 70 (16), 67 (16), 55 (22), 41 (52); HRMS (CI) calcd. for $C_{10}H_{15}NO + H^+$ 166.1232, found 166.1249 .

(S)-N-(3-Butenyl)pyrrolidine carboxaldehyde **(16f).** 1.465 g (9.56 mmol, 97%) of a yellow oil; $[\alpha]_D^{20}$ = - 56.0° (c = 1.00; CH_2Cl_2); IR (film) 3077, 2973, 2940, 2874, 2800, 1728, 1641, 1459, 1441, 1375, 1205, 1147, 1094, 1076 cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz) δ 9.36 (d, 1 H, *J* = 4.0 Hz, CHO), 5.68 (dddd, 1 H, *J* = 17.0/10.2/6.7/6.7 Hz, 4a'-H), 4.98 (dd, 1 H, *J* = 17.0/1.4 Hz, 4b'-H), 4.94 (dd, 1 H, *J* = 10.2/1.4 Hz, 3'-H),

2.88 - 2.81 (m, 1 H, 2-H), 2.62 - 2.55 (m, 1 H, 5-H), 2.52 - 2.43 (m, 1 H, 1'-H), 2.29 - 2.20 (m, 1 H, 1'-H) 2.10 - 2.02 (m, 2 H, 2'-H), 1.92 - 1.83 (m, 1 H, 5-H), 1.55 - 1.27 (m, 4 H, 3-H, 4-H); ^{13}C NMR (C_6D_6, 75 MHz) δ 201.9 (CHO), 136.7 (C-3'), 115.6 (C-4'), 72.1 (C-2), 55.0 (C-5), 53.9 (C-1'), 33.8 (C-2'), 26.5 (C-3), 24.2 (C-4); GC-MS (EI)*m/z* (%) 154 (M^+, 4), 124 (100), 112 (3), 96 (17), 84 (42), 70 (30), 55 (42), 39 (32); HRMS (CI) calcd. for $C_9H_{15}NO + H^+$ 154.1232, found 154.1228.

(S)-N-[N'-(3-Methyl-2-butenyl)pyrrolidine-2-methylidene]-o-toluidine **(17a).** 1.117 g (4.27 mmol, 98%) of a yellow oil; $[\alpha]_D^{20}$ = - 115.2° (c = 1.00; CH_2Cl_2); IR (film) 3055, 3018, 2968, 2913, 2869, 2815, 1656, 1606, 1597, 751, 720 cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz) δ 7.58 (d, 1 H, *J* = 6.4 Hz, HC=N), 7.07 - 6.92 (m, 3 H, 3"-H, 4"-H, 5"-H), 6.76 - 6.73 (m, 1 H, 2"-H), 5.28 - 5.22 (m, 1 H, 2'-H), 3.42 - 3.35 (m, 1 H, 1'-H), 3.21 - 3.13 (m, 1 H, 2-H), 3.08 - 2.98 (m, 1 H, 5-H), 2.31 (s, 3 H, 7"-H), 2.15 - 2.08 (m, 1 H, 1'-H), 2.07 - 1.94 (m, 1 H, 5-H), 1.84 - 1.45 (m, 4 H, 3-H, 4-H), 1.63 (s, 3 H, 5'-H), 1.52 (s, 3 H, 4'-H); ^{13}C NMR (C_6D_6, 75 MHz) δ 166.2 (HC=N), 150.7 (C-1"), 133.0 (C-3'), 130.1 (C-6'), 129.4, 126.0, 124.5, 177.5 (C-2", C-3", C-4", C-5"), 121.8 (C-2'), 67.3 (C-2), 53.2 (C-1'), 51.1 (C-5), 28.4 (C-3), 24.9 (C-5'), 22.6 (C-4), 17.0 (C-4'), 16.6 (C-7"); GC-MS (EI)*m/z* (%) 257 (M^++1, 78), 256 (23), 199 (2), 187 (13), 173 (11), 160 (4), 150 (67), 138 (100), 118 (11), 108 (3), 97 (10), 91 (17), 82 (16), 70 (100), 41 (55); HRMS (EI) calcd. for $C_{17}H_{24}N_2$ 256.1940, found 256.1945.

(S)-N-[N'-(5-Methyl-4-hexenyl)pyrrolidine-2-methylidene]-o-toluidine **(17b).** 5.14 g (18.1 mmol, 98%) of a yellow oil; $[\alpha]_D^{20}$ = - 54.4° (c = 1.00 in CH_2Cl_2); IR (film) 3017, 2966, 2928, 2858, 2798, 1657, 1605, 1597, 1583, 1503, 1487, 1448, 751, 720 cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz) δ 7.53 (d, 1 H, *J* = 6.4 Hz, HC=N), 7.07 - 6.92 (m, 3 H, 3"-H, 4"-H, 5"-H), 6.77 - 6.74 (m, 1 H, 2"-H), 5.16 ("t", 1 H, *J* = 7.2 Hz, 4'-H), 3.18 - 3.11 (m, 1 H, 2-H), 3.07 - 3.00 (m, 1 H, 5-H), 2.80 (ddd, 1 H, *J* = 12.0/8.0/8.0 Hz, 1'-H), 2.34 - 2.25 (m, 1 H, 1'-H, 2.33 (s, 3 H, 7"-H), 2.10 - 1.99 (m, 3 H, 5-H, 3'-H), 1.89 - 1.45 (m, 6 H, 3-H, 4-H, 2'-H), 1.62 (s, 3 H, 7'-H), 1.51 (s, 3 H, 6'-H); ^{13}C NMR (C_6D_6, 75 MHz) δ 166.3 (HC=N), 150.8 (C-1"), 130.4 (C-5'), 130.0 (C-6"), 129.4, 126.0, 124.5, 117.5 (C-2", C-3", C-4", C-5"), 124.0 (C-4'), 68.0 (C-2), 53.5 (C-1'), 53.0 (C-5), 28.3 (C-3'), 25.1 (C-3, C-2'), 24.8 (C-7'), 22.8 (C-4), 17.0 (C-6'), 16.8 (C-7"); GC-MS (EI)*m/z* (%) 284 (M^+, 2), 241 (1), 215 (1), 201 (5), 178 (13), 144 (2), 130 (2), 118 (5), 91 (12), 84 (100), 70 (7), 69 (7), 65 (9), 55 (10), 41 (21); HRMS (EI) calcd. for $C_{19}H_{28}N_2$ 284.2252, found 284.2244.

(S)-N-[N'-(4,4-Diphenyl-3-butenyl)pyrrolidine-2-methylidene]-o-toluidine **(17c).** 1.37 g (4.81 mmol, 99%) of a yellow oil; $[\alpha]_D^{20}$ = - 47.1° (c = 1.00; CH_2Cl_2); IR (film) 3078, 3055, 3020, 2965, 2925, 2869, 2857, 2798, 1653, 1597, 1583, 1576, 1495, 1487, 1444, 1377, 1362, 1302, 1288, 1251, 1217, 1155, 1140, 1112, 1073, 1031, 753, 720, 701 cm^{-1}; ^{1}H NMR (C_6D_6, 300 MHz) δ 7.48 (d, 1 H, *J* = 6.4 Hz, HC=N), 7.27 - 7.23 (m, 2 H), 7.18 - 6.96 (m, 11 H), 6.75 - 6.71 (m, 1 H), 6.13 ("t", 1 H, *J* = 7.4 Hz, 3'-H), 3.17 - 3.09 (m, 1 H, 2-H), 2.95 - 2.84 (m, 2 H, 5-H, 1'-H), 2.42 - 2.27 (m, 3 H, 1'-H, 2'-H), 2.30 (s, 3 H, 7"-H), 2.00 - 1.89 (m, 1 H, 5-H), 1.84 - 1.36 (m, 4 H, 3-H, 4-H); ^{13}C NMR (C_6D_6, 75 MHz) δ 166.2 (HC=N), 150.9 (C-1"), 142.3 (C-i), 140.0 (C-4'), 131.4 (C-6"), 129.7, 126.5, 124.9, 117.8 (C-2", C-3", C-4", C-5"), 129.5, 127.8, 127.6, 126.5, 126.5 (C-3'), 67.8 (C-2), 54.1 (C-5), 53.1 (C-1'), 29.3 (C-2'), 28.5 (C-3), 22.0 (C-4), 17.4 (C-7"); GC-MS (EI) *m/z* (%) 395 (M^++1, 5), 365 (1), 276 (18), 227 (1), 201 (100), 173 (5), 129 (11), 115 (9), 91 (18), 84 (46), 65 (6), 55 (4), 42 (7); HRMS (EI) calcd. for $C_{28}H_{30}N_2$ 394.2409, found 394.2417.

(S)-N-[N'-(3-Butynyl)pyrrolidine-2-methylidene]-o-toluidine **(17d).** 1.75 g (7.21 mmol, 99%) of a yellow oil; $[\alpha]_D^{20}$ = - 75.7° (c = 1.00; CH_2Cl_2); IR (film) 3298, 3064, 3018, 2968, 2946, 2916, 2869, 2810, 2132, 1656, 1606, 1597, 1581, 1511, 1487, 1458, 1433, 1377, 1363, 1289, 1251, 1217, 1188, 1158, 1137, 1112, 1045, 770, 753, 721, 635 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ = 7.48 (d, 1 H, *J* = 6.4 Hz, HC=N), 7.09 - 6.90 (m, 3 H, 3"-H, 4"-H, 5"-H), 6.70 - 6.66 (m, 1 H, 2"-H), 3.20 - 3.10 (m, 2 H, 2-H, 5-H), 2.90 (ddd, 1 H, *J* = 12.2/7.7/7.7 Hz, 1'-H), 2.56 (ddd, 1 H, *J* = 12.2/7.6/6.5 Hz, 1'-H), 2.35 - 2.28 (m, 3 H, 5-H, 2'-H), 2.18 (s, 3 H, 7"-H), 2.06 - 1.98, 1.88 - 1.74 (m, 4 H, 3-H, 4-H), 1.87 (t, 1 H, *J* = 2.6 Hz, 4'-H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.8 (HC=N), 150.6 (C-1"), 130.2 (C-6"), 129.8, 126.4, 125.1, 118.0 (C-2", C-3", C-4", C-5"), 82.5 (C-3'), 68.8 (C-4'), 68.2 (C-2), 53.7 (C-1'), 53.1 (C-5), 28.9 (C-3), 23.1 (C-4), 18.5 (C-2'), 17.5 (C-7"); GC-MS (EI) *m/z* (%) 241 (M^++1, 38), 225 (3), 211 (2), 201 (5), 184 (3), 170 (3), 158 (1), 144 (2), 134 (20), 122 (100), 107 (8), 94 (35), 91 (20), 84 (12), 77 (7), 65 (12), 55 (8), 39 (12); HRMS (EI) calcd. for $C_{16}H_{20}N_2$ 240.1626, found 240.1630.

(S)-N-[N'-(3-Pentynyl)pyrrolidine-2-methylidene]-o-toluidine **(17e).** 0.915 g (3.59 mmol, 99%) of a yellow oil; $[\alpha]_D^{20}$ = - 90.1° (c = 1.00; CH_2Cl_2); IR (film) 3017, 2966, 2945, 2916, 2856, 2806, 2235, 1656, 1604, 1597, 1582, 1501, 1486, 1456, 1447, 1377, 1362, 1291, 1217, 1188, 1157, 1135, 1112, 1045, 769, 752, 721 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 7.52 (d, 1 H, *J* = 6.4 Hz, HC=N), 7.07 - 6.94 (m, 3 H, 3"-H, 4"-H, 5"-H), 6.77 - 6.73 (m, 1 H, 2"-H), 3.19 - 3.11 (m, 1 H, 2-H), 3.03 - 2.93 (m, 2 H, 5-H, 1'-H), 2.53 (ddd, 1 H, *J* = 11.9/7.2/7.2 Hz, 1'-H), 2.37 - 2.29 (m, 2 H, 2'-H), 2.32 (s, 3 H, 7"-H), 2.07 - 1.98 (m, 1 H, 5-H), 1.84 - 1.36 (m, 4 H, 3-H, 4-H), 1.53 (t, 3 H, *J* = 2.5 Hz, 5'-H); ^{13}C NMR (C_6D_6, 75 MHz) δ 165.9 (HC=N), 150.7 (C-1"), 130.1 (C-6"), 129.4, 126.0, 124.5, 117.4 (C-2", C-3", C-4", C-5"), 76.9 (C-3'), 75.3 (C-4'), 67.4 (C-2), 53.3 (C-5), 52.9 (C-1'), 28.3 (C-3), 22.8 (C-4), 18.7 (C-2'), 17.0 (C-7"), 2.4 (C-5'); GC-MS (EI)*m/z* (%) 254 (M^+, 3), 201 (14), 184 (3), 148 (16), 136 (100), 121 (24), 120 (16), 91 (10), 84 (18), 65 (8), 41 (9); HRMS (CI) calcd. for $C_{17}H_{22}N_2 + H^+$ 255.1861, found 255.1876.

(S)-N-[N'-(3-Butenyl)pyrrolidine-2-methylidene]-o-toluidine **(17f).** 0.658 g (2.71 mmol, 99%) of a yellow oil; $[\alpha]_D^{20}$ = - 65.0° (c = 1.00; CH_2Cl_2); IR (film) 3072, 3018, 2969, 2942, 2870, 2800, 1657, 1642, 911, 771, 752, 721 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 7.51 (d, 1 H, *J* = 6.4 Hz, HC=N), 7.07 - 6.94 (m, 3 H, 3"-H, 4"-H, 5"-H), 6.76 - 6.71 (m, 1 H, 2"-H), 5.79 (dddd, 1 H, *J* = 17.2/10.3/6.7/6.7 Hz, 4a'-H), 5.02 (dd, 1 H, *J* = 17.2/1.4 Hz, 4b'-H), 4.96 (dd, 1 H, *J* = 10.3/1.4 Hz, 3'-H), 3.18 - 3.10 (m, 1 H, 2-H), 3.03 - 2.96 (m, 1 H, 5-H), 2.88 - 2.78 (m, 1 H, 1'-H), 2.40 - 2.31 (m, 1 H, 1'-H), 2.31 (s, 3 H, 7"-H), 2.28 - 2.13 (m, 2 H, 2'-H), 2.06 - 1.97 (m, 1 H, 5-H), 1.85 - 1.40 (m, 4 H, 3-H, 4-H); ^{13}C NMR (C_6D_6, 75 MHz) δ 166.0 (HC=N), 150.7 (C-1"), 136.2 (C-3'), 130.0 (C-6"), 129.4, 126.0, 124.5, 117.5 (C-2", C-3", C-4", C-5"), 114.4 (C-4'), 67.7 (C-2), 53.5 (C-5), 52.9 (C-1'), 32.8 (C-2'), 28.3 (C-3), 22.7 (C-4), 17.0 (C-7"); GC-MS (EI) *m/z* (%): 243 (M^++1, 2), 201 (8), 184 (5), 147 (4), 136 (12), 124 (100), 91 (21), 84 (17), 70 (15), 65 (15), 55 (23), 39 (19); HRMS (CI) calcd. for $C_{16}H_{22}N_2 + H^+$ 243.1861, found 243.1873.

1,2,3,5,6,7,7a,8,13,13a,13b-Undecahydro-8,8,12-trimethyl-pyrrolo[1',2':1,2]azepino[3,4-b]quinoline **(18).** To a solution of imine **17b** (1.50 g, 5.27 mmol) in CH_2Cl_2 (40 ml) was added dropwise over 30 min at -78°C $SnCl_4$ (10.6 ml, 10.6 mmol, 1 M solution in CH_2Cl_2). After addition has been finished, the cooling bath was removed and the mixture was stirred at room temperature for 36 h. Hydrolysis and work-up were carried

out as described for **19a**. The crude product was purified by flash chromatography on SiO_2 (hexanes / ethyl acetate / NEt_3, 100 : 1 : 5) to give 1.29 g (86%) of a yellow oil as a mixture of diastereomers (**18a** : **18b** : **18c** = 75 : 23 : 2, determined by GC). The diastereomers were separated by preparative HPLC.

***(7aR,13aS,13bS)-Isomer* (18a).** $[\alpha]_D^{20}$ = - 117.2° (c = 1.00; CH_2Cl_2); IR (film) 3438, 3049, 2928, 2865, 2795, 2748, 2698, 1598, 1474, 1372, 1293, 1266, 1192, 1134, 1075, 740 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 6.98 (d, 1 H, *J* = 7.2 Hz, 9-H), 6.88 (d, 1 H, *J* = 7.3 Hz, 11-H), 6.53 (dd, 1 H, *J* = 7.3/7.2 Hz, 10-H), 3.59 (dd, 1 H, *J* = 8.1/5.7 Hz, 13a-H), 3.43 (s, br., 1 H, NH), 3.14 (dd, 1 H, *J* = 12.2/5.2 Hz, 3-H_{eq}), 3.11 - 3.07 (m, 1 H, 5-H_{eq}), 2.44 - 2.38 (m, 1 H, 13b-H), 2.33 - 2.29 (m, 1 H, 5-H_{ax}), 2.26 - 2.18 (m, 2 H, 1-H_{eq}, 3-H_{ax}), 2.09 (s, 3 H, 14-H), 1.88 - 1.76 (m, 4 H, 1-H_{ax}, 2-H, 7a-H), 1.72 - 1.67 (m, 1 H, 6-H_{eq}), 1.66 - 1.57 (m, 1 H, 6-H_{ax}), 1.38 (s, 3 H, 16-H), 1.38 - 1.34 (m, 1 H, 7-H_{eq}), 1.21 (s, 3 H, 15-H), 1.06 - 0.98 (m, 1 H, 7-H_{ax}); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 140.6 (C-12a), 127.8 (C-9), 127.5 (C-8a), 122.9 (C-11), 118.4 (C-12), 115.2 (C-10), 70.9 (C-13b), 58.8 (C-13a), 58.3 (C-3), 57.8 (C-5), 46.4 (C-7a), 35.9 (C-8), 31.5 (C-1), 31.4 (C-6), 30.8 (C-15), 25.8 (C-16), 23.9 (C-2), 22.2 (C-7), 17.2 (C-14); GC-MS (EI) *m/z* (%) 284 (M^+, 22), 269 (88), 200 (7), 184 (4), 172 (100), 158 (15), 144 (10), 130 (5), 110 (10), 98 (20), 83 (32), 68 (8), 55 (16), 41 (14); HRMS (EI) calcd. for $C_{19}H_{28}N_2$ 284.2252, found 284.2247. Anal. calcd. for $C_{19}H_{28}N_2$: C, 80.23; H, 9.92; N, 9.85. Found: C, 80.21; H, 9.88; N, 9.91.

***(7aS,13aR,13bS)-Isomer* (18b).** $[\alpha]_D^{20}$ = - 103.9° (c = 1.00; CH_2Cl_2); IR (film) 3437, 3047, 2928, 2866, 2797, 2749, 1597, 1473, 1372, 1294, 1265, 1192, 1136, 1075, 741 cm^{-1}; ^1H NMR (C_6D_6, 600 MHz) δ 7.21 (d, 1 H, *J* = 7.8 Hz, 9-H), 6.94 (d, 1 H, *J* = 7.2 Hz, 11-H), 6.79 (dd, 1 H, *J* = 7.8/7.2 Hz, 10-H), 3.48 (s, br, 1 H, NH), 2.95 (ddd, 1 H, *J* = 9.0/6.6/2.8 Hz, 3-H_{eq}), 2.91 - 2.86 (m, 2 H, 5-H_{eq}, 13a-H), 2.40 (ddd, 1 H, *J* = 8.7/8.7/6.0 Hz, 13b-H), 2.32 (ddd, 1 H, *J* = 11.8/7.6/4.6 Hz, 5-H_{ax}), 2.26 (ddd, 1 H, *J* = 9.1/9.1/6.7 Hz, 3-H_{ax}), 1.98 (s, 3 H, 14-H), 1.89 - 1.80 (m, 2 H, 1-H_{eq}, 6-H_{eq}), 1.77 - 1.70 (m, 1 H, 7-H_{eq}), 1.66 - 1.60 (m, 2 H, 2-H_{eq}, 7-H_{ax}), 1.59 - 1.53 (m, 1 H, 1-H_{ax}), 1.45 - 1.39 (m, 1 H, 2-H_{ax}), 1.40 (ddd, 1 H, *J* = 10.1/10.1/2.1 Hz, 7a-H), 1.37 - 1.32 (m, 1 H, 6-H_{ax}), 1.31 (s, 3 H, 16-H), 1.18 (s, 3 H, 15-H); ^{13}C NMR (C_6D_6, 150 MHz) δ 141.9 (C-12a), 131.2 (C-8a), 127.7 (C-11), 125.3 (C-9), 120.6 (C-12), 117.2 (C-10), 68.2 (C-13b), 59.5 (C-13a), 57.5 (C-3), 53.7 (C-5), 50.8 (C-7a), 37.0 (C-8), 31.0 (C-1), 27.9 (C-15), 27.7 (C-6), 26.7 (C-16), 23.4 (C-2), 23.3 (C-7), 17.4 (C-14); GC-MS (EI) *m/z* (%) 284 (M^+, 18), 269 (78), 200 (7), 184 (4), 172 (100), 158 (15), 144 (10), 130 (5), 110 (10), 98 (20), 83 (32), 68 (8), 55 (16), 41 (14); HRMS (EI) calcd. for $C_{19}H_{28}N_2$ 284.2252, found 284.2247. Anal. calcd. for $C_{19}H_{28}N_2$: C, 80.23; H, 9.92; N, 9.85. Found: C, 80.20; H, 9.94; N, 9.86.

***(7aS,13aS,13bS)-Isomer* (18c).** IR (film) 3438, 3049, 2928, 2865, 2795, 2748, 2698, 1598, 1474, 1372, 1293, 1266, 1192, 1134, 1075, 740 cm^{-1}; ^1H NMR (C_6D_6, 600 MHz) δ 7.18 (d, 1 H, *J* = 8.0 Hz, 9-H), 6.98 (d, 1 H, *J* = 7.3 Hz, 11-H), 6.82 (dd, 1 H, *J* = 8.0 / 7.3 Hz, 10-H), 3.62 (s, br., 1 H, NH), 3.61 - 3.59 (m, 1 H, 13a-H), 2.89 (ddd, 1 H, *J* = 8.4/8.4/1.4 Hz, 3-H_{eq}), 2.82 (ddd, 1 H, *J* = 10.7/4.4/2.4 Hz, 5-H_{eq}), 2.08 (s, 3 H, 14-H), 1.89 - 1.81 (m, 2-H, 3-H_{ax}, 13a-H), 1.71 (ddd, 1 H, *J* = 11.5/11.5/3.2 Hz, 5-H_{ax}), 1.68 - 1.61 (m, 1 H, 2-H_{eq}), 1.58 - 1.53 (m, 1 H, 1-H_{eq}), 1.52 - 1.45 (m, 1 H, 2-H_{ax}), 1.31 - 1.18 (m, 5 H, 1-H_{ax}, 6-H, 7-H), 1.25 (s, 3 H, 6-H), 1.23 (s, 3 H, 15-H), 1.03 (ddd, 1 H, *J* = 12.3/3.9/3.5 Hz, 7a-H); ^{13}C NMR (C_6D_6, 150 MHz) δ 141.1 (C-12a), 127.4 (C-8a), 127.2 (C-11), 124.4 (C-9), 122.8 (C-12), 117.6 (C-10), 67.2 (C-13b), 54.3 (C-3), 52.5 (C-5), 47.4 (C-13a), 44.5 (C-7a), 35.8 (C-8), 33.4 (C-1), 27.1 (C-6), 26.7 (C-15), 25.4 (C-16), 23.3 (C-2), 21.7 (C-7), 17.7 (C-14); GC-MS (EI) *m/z* (%) 284 (M^+, 20), 269 (82), 200 (5), 184 (6), 172 (100), 158 (12), 144 (11), 130 (5), 110 (12), 98 (20), 83 (32), 68 (8), 55 (15), 41 (18); HRMS (EI) calcd. for $C_{19}H_{28}N_2$ 284.2252, found 284.2247.

(6aS,12aR,12bS)-1,2,3,5,6,6a,7,12,12a,12b-Decahydro-11-methyl-7,7-diphenyl-indolizino-[3,4-b]quinoline **(19a).** To a solution of imine **17c** (2.00g, 5.07 mmol) in CH_2Cl_2 (40 ml) was added dropwise over 30 min at -78°C $BF_3 \cdot OEt_2$ (1.44 g, 10.1 mmol). After addition was finished, the cooling bath was removed and the mixture was stirred for 24 h at room temperature. Then the mixture was poured into ice-cooled 2 N NaOH (100 ml), the layers were separated and the aqeous layer was extracted with CH_2Cl_2 (3 x 50 ml). The combined organic layers were washed with brine (100 ml), dried over Na_2SO_4 and evaporated. Further purification by flash chromatography on SiO_2 ($CHCl_3$ / NEt_3, 100 : 3) yielded 1.84 g (92 %) of a yellow solid; $[\alpha]_D^{20}$ = - 54.8° (c = 1.00; CH_2Cl_2); IR (KBr) 3426, 3081, 3053, 3028, 2960, 2944, 2933, 2897, 2863, 2783, 2745, 1598, 1494, 1475, 1442, 1423, 1379, 1362, 1319, 1284, 1135, 1081, 1036, 922, 783, 783, 772, 721, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.32 (d, 2 H, *J* = 8.2 Hz, 2'-H, 6'-H), 7.30 (dd, 2 H, *J* = 8.2/7.1 Hz, 3'-H, 5'-H), 7.23 (d, 1H, *J* = 7.1 Hz, 4'-H), 7.20 (dd, 2 H, *J* = 7.3/7.1 Hz, 3"-H, 5"-H), 7.16 (d, 1 H, *J* = 7.1 Hz, 4"-H), 6.93 (d, 2 H, *J* = 7.3 Hz, 2"-H, 6"-H), 6.92 (d, 1 H, *J* = 7.6 Hz, 10-H), 6.36 (dd, 1 H, *J* = 7.6 / 7.5 Hz, 9-H), 6.20 (d, 1 H, *J* = 7.5 Hz, 8-H), 3.74 (s, br., 1 H, NH), 3.06 (ddd, 1 H, *J* = 10.7/3.0/3.0 Hz, 5-H_{eq}), 3.01 (ddd, 1 H, *J* = 8.4/8.0/1.5 Hz, 3-H_{eq}), 2.60 (ddd, 1 H, $J_{6a/12a}$ = 10.5 Hz, $J_{6a/6ax}$ = 10.5 Hz, $J_{6a/6eq}$ = 2.9 Hz, 6a-H), 2.57 (dd, 1 H, $J_{12a/6a}$ = 10.5 Hz, $J_{12a/12b}$ = 7.8 Hz, 12a-H), 2.17 - 2.10 (m, 2 H, 3-H_{ax}, 5-H_{ax}), 2.15 (s, 3 H, 13-H), 2.09 - 2.03 (m, 1 H, 1-H_{eq}), 1.96 (ddd, 1 H, $J_{12b/12a}$ = 7.8 Hz, $J_{12b/1ax}$ = 7.8 Hz, $J_{12b/1eq}$ = 7.8 Hz, 12b-H), 1.93 - 1.89 (m, 1 H, 6-H_{eq}), 1.87 - 1.79 (m, 1 H, 2-H_{eq}), 1.78 - 1.71 (m, 1 H, 2-H_{ax}), 1.67 - 1.60 (m, 1 H, 6-H_{ax}), 1.52 - 1.45 (m, 1 H, 1-H_{ax}); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 145.2 (C-1'), 142.6 (C-1"), 141.4 (C-11a), 131.4 (C-2", C-6"), 130.0 (C-2', C-6'), 128.6 (C-10), 128.2 (C-8), 127.8 (C-3', C-5'), 127.6 (C-7a), 127.1 (C-3", C-5"), 126.2 (C-4', C-4"), 119.5 (C-11), 115.8 (C-9), 70.6 (C-12b), 55.2 (C-12a), 55.0 (C-7), 53.6 (C-3), 52.3 (C-5), 44.9 (C-6a), 27.9 (C-1), 26.1 (C-6), 21.4 (C-2), 17.4 (C-12); GC-MS (EI)*m/z* (%) 394 (M^+, 13), 325 (6), 310 (10), 284 (12), 220 (15), 206 (6), 196 (6), 165 (5), 158 (5), 122 (13), 111 (24), 84 (100), 55 (5); HRMS (EI) calcd. for $C_{28}H_{30}N_2$ 394.2409, found 394.2417. Anal. calcd. for $C_{28}H_{30}N_2$: C, 85.24; H, 7.66; N, 7.10. Found: C, 85.23; H, 7.67; N, 7.10.

(12bS)-1,2,3,5,6,12b-Hexahydro-7,11-dimethyl-indolizino[3,4-b]quinoline **(21).** To a solution of imine **17e** (1.29 g, 5.07 mmol) in CH_2Cl_2 (30 ml) was added dropwise over 30 min at - 78°C $BF_3 \cdot OEt_2$ (1.44 g, 10.14 mmol). After addition has been finished, the cooling bath was removed and the mixture was stirred at room temperature for 48 h. Hydrolysis and work-up were carried out as described for **19a**. The crude product was purified by flash-chromatography on neutral Al_2O_3 (hexanes / ethyl acetate 10 : 1) followed by bulb to bulb-distillation (0.5 mbar, bp. 152°C) to give 793 mg (92 %) of a pale brown oil; $[\alpha]_D^{20}$ = - 189.0° (c = 1.00; CH_2Cl_2); IR (film) 3070, 3014, 2956, 2876, 2787, 2723, 2679, 2633, 1590, 1495, 1456, 1383, 1323, 1271, 1214, 1165, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.80 (d, 1 H, *J* = 8.0 Hz, 8-H), 6.98 (d, 1 H, *J* = 7.3 Hz, 10-H), 6.68 (dd, 1 H, *J* = 8.0/7.3 Hz, 9-H), 3.68 (dd, 1 H, *J* = 8.0/8.0 Hz, 12b-H), 3.42 - 1.67 (m, 10 H, 1-H, 2-H, 3-H, 5-H, 6-H), 2.74 (s, 3 H, 14-H), 2.53 (s, 3 H, 13-H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 157.4 (C-12a), 145.0 (C-11a), 140.5 (C-7), 137.2 (C-11), 128.0 (C-10), 126.5 (C-6a), 125.3 (C-7a), 124.9 (C-8), 121.0 (C-9), 67.2 (C-12b), 53.6 (C-5), 48.4 (C-3), 29.2 (C-6), 26.6 (C-1), 22.1 (C-2), 17.8 (C-13), 13.6 (C-14); GC-MS (EI) *m/z* (%) 252 (M^+, 25), 251 (100), 237 (3), 224 (12), 208 (3), 196 (10), 180 (3), 168 (2), 154 (5), 141 (2), 127 (2), 115 (2), 103(2), 77 (2), 63 (2), 39 (6). HRMS (EI) calcd. for $C_{17}H_{20}N_2$ 252.1626, found 252.1620. Anal. calcd. for $C_{17}H_{20}N_2$: C, 80.91; H, 7.99; N, 11.10. Found: C, 80.79; H, 8.03; N, 11.14.

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19. The chemical shift for C-12a (δ 55.2 ppm) of the *all-trans* compound **19a** is in good agreement with the above mentioned data.
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