Article

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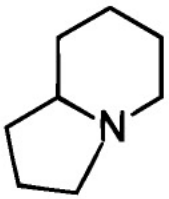
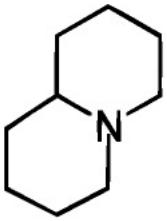
J. Comb. Chem., **2000**, 2 (4), 337-340• DOI: 10.1021/cc000006k • Publication Date (Web): 07 June 2000



Indolizidine



Quinolizidine

Solid-Phase Synthesis of Indolizidine and Quinolizidine Derivatives

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Received January 21, 2000

An efficient method for the construction of simple indolizidine and quinolizidine derivatives on solid support has been developed. An intramolecular tandem Michael reaction initiated by the nucleophilic attack of a suitably placed amino group on the tethered Wittig condensation products between 4- or 5-aminoaldehydes attached to a trityl chloride resin and 4-[(4-methylphenyl)sulfonyl]-1-(triphenylphosphoranylidene)-2-butanone is the key step.

The widespread occurrence of indolizidine and quinolizidine skeletons in a relatively large number of alkaloids and in human-made substances possessing biological activity has stimulated much research into their synthesis.[1,2]

The objective of this study was to develop a synthetic methodology whereby indolizidine and quinolizidine derivatives could be prepared by solid-phase chemistry (Figure 1).

Chemistry on solid support originally developed in peptide chemistry is now widely accepted as a powerful tool for accelerating a drug discovery program, offering the opportunity for rapidly synthesizing drug-like molecules without tedious and time-consuming purification. The need for developing new synthetic methodologies on solid support (especially carbon−carbon and carbon−heteroatom bond formation) has become urgent.

One of our interests is to investigate the methodology of multiple C−C or C−heteroatom bond formation in one-step solid-phase synthesis. Recently, we introduced 4-[(4-methylphenyl)sulfonyl]-1-(triphenylphosphoranylidene)-2-butanone **1** as a new four-carbon synthon for substituted divinyl ketones, the two double bonds adjacent to the central carbonyl group being generated by Wittig reaction of the ylide function with a suitable aldehyde and through a base-promoted β-elimination of the sulfone group, respectively. These compounds are able to participate in a domino reaction sequence initiated by a nitrogen- or carbon-centered nucleophile, allowing the construction of six-membered heterocyclic and carbocyclic rings (Scheme 1).[3]

As a part of our continuing efforts in the synthesis of nitrogen-containing systems, an intramolecular version of this scheme was envisaged as the basis of a novel cyclization strategy to the nitrogen-containing fused bicyclic system present in indolizidine and quinolizidine alkaloids. To this end, we envisioned the amino-containing tethered compounds **3a**,**b** as the logical precursors (Scheme 2).

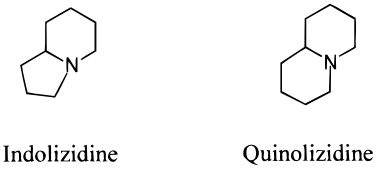
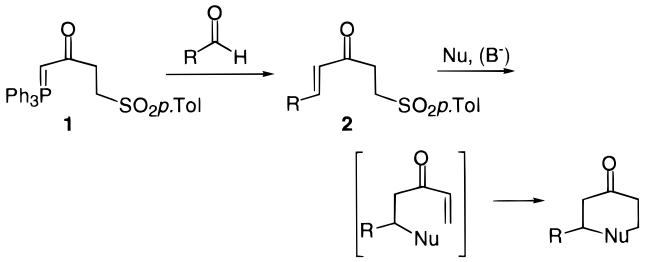
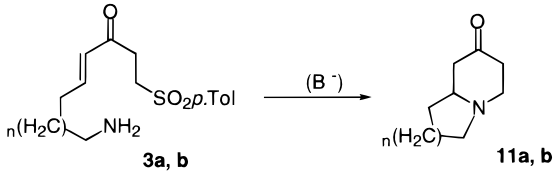


Figure 1.

Scheme 1



Scheme 2



Throughout the paper: **a**, n = 1; **b**, n = 2

We first examined the preparation of the requisite starting materials through the Wittig reaction between the synthon **1** and the Fmoc- or Boc-*N*-acylated lactamols **6a**,**b** and **7a**,**b**, in turn easily prepared by sodium borohydride reduction[4] of the corresponding *N*-acyl lactams **4a**,**b** and **5a**,**b** under classical solution conditions (Scheme 3).

This operation proceeded in all cases with unexpectedly poor yields. Thus, the Fmoc-*N*-protected derivatives **6a**,**b** reacted with **1** to afford exclusively the Wittig condensation products **8a**,**b**, the Boc N-protected derivative **7a** reacted with **1** to give a mixture of the Wittig derivative **9a** beside the monocyclized products **10a**, while no reaction was observed

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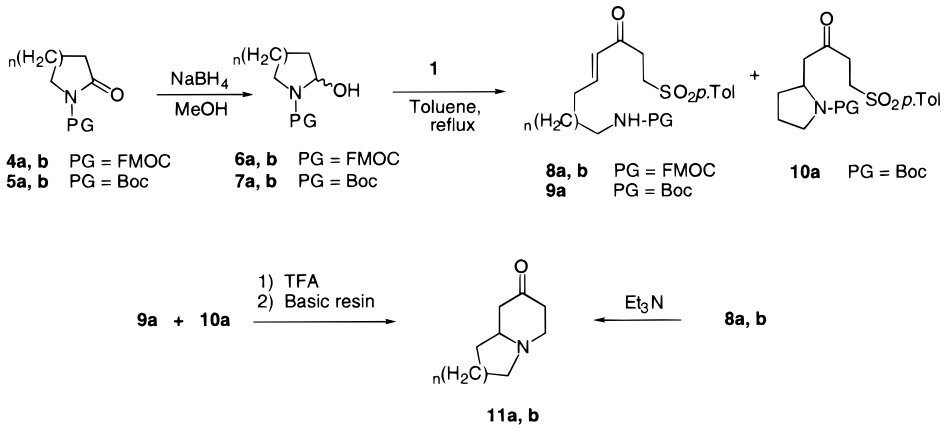
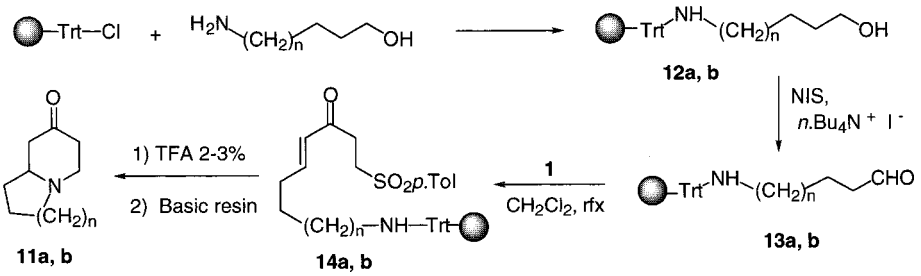
10.1021/cc000006k CCC: $19.00
Published on Web 06/07/2000

Scheme 3



Scheme 4



between **7b** and **1**. Compounds **8a**,**b** as well as **9a** and **10a** could be subsequently converted into the target compounds **11a**,**b** with low overall yields (see Experimental Section). Even using the ylide **1** anchored to a solid support[5] did not improve yields. We attributed these results both to the low reactivity of the lactamols toward **1** and to a possible base-promoted elimination of *p*-toluensulfinate, producing an easily polymerizable dienone.[3]

A more successful approach was subsequently employed entailing the polymer-supported aminoaldehydes **13a**,**b** which were prepared by attaching the corresponding commercially available amino alcohols to a trityl chloride resin, followed by oxidation of **12a**,**b** using *N*-iodo succinimide in the presence of tetrabutylammonium iodide (Scheme 4).[6,7] We found this protocol particularly suitable for the oxidation of nitrogen-containing compounds.

Compounds **13a**,**b** underwent Wittig reaction with the reagent **1** in refluxing methylene chloride to produce **14a**,**b** in excellent yield (89% calculated on the basis of the isolated triphenylphosphine oxide). The known indolizidine[8] and quinolizidine[9] derivatives **11a**,**b** were obtained after detachment from the solid support by treatment with 3% trifluoroacetic acid and exposure to Amberlyst A-21 resin to promote the cyclization of the intermediate Wittig condensation products. Column chromatographic purification on deactivated (gaseous ammonia) silica gel furnished **11a**,**b** in 46 and 40% overall yield, respectively. The moderate overall yields of the sequence may be attributed to the required purification on acid support since the Wittig reaction proceeded very satisfactorily. In scaling-up the sequence, the purification of **11a**,**b** might be done simply by distillation,[8,9] thus improving the overall yield.

In conclusion, these preliminary results demonstrate that the reagent **1** provides the basis of a useful and versatile protocol for the preparation of indolizidine and quinolizidine derivatives in solid-phase chemistry through a suitable choice of a solid support—the trityl resin acting as an efficient nitrogen protecting group, which works much better than the conventional urethanic ones (Fmoc or Boc). The synthesis of these simple indolizidine and quinolizidine structures provides a foundation for the extension of the methodology to more functionalized systems. The biological and medicinal properties of these general types of structures provide added incentive for the development of this strategy for their preparation, which is currently underway in our laboratories.

Experimental Section

General Remarks. Melting points were determined on a Reichert-Kofler apparatus and are uncorrected. Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were recorded on a Bruker AC-200 spectrometer for solutions in $CDCl_3$ unless otherwise noted, and chemical shifts are given in parts per million (δ) downfield from tetramethylsilane as an internal standard. Coupling constants are given in hertz. Infrared (IR) spectra were taken on a FT-IR Paragon 500 spectrometer; characteristic bands are reported in cm^{-1}. Organic solutions were dried over anhydrous magnesium sulfate and evaporated with a rotary evaporator. Petroleum ether refers to the fractions boiling in the range 40−60 °C. Thin-layer chromatography was done with precoated plates of silica gel (Merk F-254) using the indicated solvent system. All chemicals were purchased from Fluka AG. The copoly-styrene trityl chloride resin (0.95 equiv/g, 1% cross-linking, 200−400 mesh, batch no. A21292) was from Novabiochem.

General Procedure for the Syntheses of *N*-Fmoc Lactams 4a,b. To a solution of the commercialy available lactam (10 mmol) in CH_2Cl_2 (20 mL) was added Fmoc-OSu (10 mmol) under magnetical stirring. After 6 h the mixture was

washed as follows: water (2 × 10 mL), 5% $NaHCO_3$ (2 × 10 mL), water (2 × 10 mL), 0.1 N HCl (2 × 10 mL), and water (2 × 10 mL). The organic solution was dried and the solvent evaporated to give **4a**,**b**.

2-Oxo-pyrrolidine-1-carboxylic Acid *9*H-Fluoren-9-ylmethyl Ester (4a).[10] Yield: solid (96%). Mp: 80−2 °C. IR (KBr): 2945, 1715, 1690, 1451, 1265. ^{1}H NMR: 1.79−2.09 (m, 2 H); 2.45 (t, 2 H, J = 7.5 Hz); 3.50 (t, 2 H J = 7.6 Hz).

2-Oxo-piperidine-1-carboxylic Acid 9*H*-Fluoren-9-ylmethyl Ester (4b). Yield: solid (92%). Mp: 75−77 °C. IR (KBr): 2951, 1713, 1686, 1445, 1199. ^{1}H NMR: 1.60−1.89 (m, 4 H); 2.40 (t, 2 H, J = 7.4 Hz); 3.95 (t, 2 H, J = 7.7 Hz). C_{20} $H_{19}NO_3$ (321.37): calcd C 74.75, H 5.96, N 4.36; found C 74.99, H 5.65, N 4.15.

General Procedure for the Syntheses of *N*-Boc Lactams 5a,b. In a three-necked flask equipped with a magnetical stirrer and an argon inlet, Et_3N (10 mmol), DMAP (1 mmol), and Boc_2O (15 mmol) were added, in order, to a solution of the commercialy available lactam (10 mmol) in CH_2Cl_2 (20 mL). After 4 h the solvent was evaporated, and the orange mixture was separated with column chromatography to give **5a**,**b**.

2-Oxo-pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (5a).[11] Eluant: EtOAc/Et_2O 1/1. Yield: oil (99%). IR (neat): 2980, 1782, 1752, 1712, 1368, 1312, 1153, 1019. ^{1}H NMR: 1.49 (s, 9 H); 1.81−2.12 (m, 2 H); 2.52 (t, 2H, J = 7.3 Hz); 3.55 (t, 2H J = 7.5 Hz).

2-Oxo-piperidine-1-carboxylic Acid *tert*-Butyl Ester (5b).[11] Eluant: EtOAc/Et_2O 1/1. Yield: oil (94%). IR (neat): 2979, 1771, 1745, 1714, 1368, 1298, 1143. ^{1}H NMR: 1.51 (s, 9 H); 1.77−1.91 (m, 4 H); 2.48 (t, 2 H, J = 7.6 Hz); 3.71 (t, 2 H, J = 7.7 Hz).

General Procedure for Reduction of N-Protected Lactams. Syntheses of N-Protected Lactamols 6a,b and 7a,b. Sodium borohydride (10 mmol) was added to a solution of the N-protected lactam (5 mmol) in methanol (15 mL) at −4 °C. The solution was stirred at −4 °C for 2 h, the solvent evaporated, and the crude mixture separated by column chromatography on silica gel with the appropriate eluant to give **6a,b** and **7a,b.**

2-Hydroxy-pyrrolidine-1-carboxylic Acid 9*H*-Fluoren-9-ylmethyl Ester (6a). Eluant: Et_2O/petroleum ether 1/2. Yield: colorless solid (79%). Mp: 99−100 °C. IR: 3399, 1683. ^{1}H NMR: 1.76−2.02 (m, 4 H); 3.18−3.25 (m, 2 H); 3.78 (dd, 1 H); 4.25 (t, 1 H); 4.51 (d, 2 H); 5.45 (br s, 1 H); 7.19−7.85 (m, 8 H). ^{13}C NMR: 22.7, 32.7, 45.9, 47.9, 69.7, 81.5, 121.1, 123.8, 127.5, 130.1, 144.0, 148.6, 159.2. $C_{19}H_{19}NO_3$ (309.36): calcd C 73.77, H 6.19, N 4.53; found C 73.67, H 6.09, N 4.49.

2-Hydroxy-piperidine-1-carboxylic Acid 9*H*-Fluoren-9-ylmethyl Ester (6b). Eluant: Et_2O/petroleum ether 1/2. Yield: colorless solid (81%). Mp: 90−93 °C. IR: 3395, 1686. ^{1}H NMR: 1.37−1.87 (m, 6 H); 3.10−3.18 (m, 2 H); 3.80 (dd, 1 H); 4.21 (t, 1 H); 4.43 (d, 2 H); 5.68 (br s, 1 H); 7.24−7.70 (m, 8 H). ^{13}C NMR: 17.6, 24.7, 30.4, 39.2, 47.2, 67.1, 74.7, 120.0, 124.9, 127.0, 127.7, 141.3, 143.9, 156.0. $C_{20}H_{21}NO_3$ (323.39): calcd C 74.28, H 6.55, N 4.33; found C 74.27, H 6.59, N 4.33.

2-Hydroxy-pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (7a).[12] Eluant: Et_2O/petroleum 2/1. Mp: oil (78%). IR: 3440, 2935, 1700, 1669, 1410. ^{1}H NMR: 1.48 (s, 9 H); 1.76−2.03 (m, 4 H); 3.10−3.28 (m, 1 H); 3.41−3.65 (m, 1 H); 5.31−5.55 (m, 1 H). ^{13}C NMR 22.1, 28.5, 32.7, 45.9, 80.0, 81.7, 156.

2-Hydroxy-piperidine-1-carboxylic Acid *tert*-Butyl Ester (7b).[12] Eluant: Et_2O/petroleum 2/1. Yield: oil (78%). IR: 3435, 2941, 1698, 1678, 1417, 1366, 1254, 1163, 993. ^{1}H NMR: 1.43 (s, 9 H); 1.47−1.90 (m, 7 H); 3.07 (dt, 1 H, J = 2.8 and 12 Hz); 3.78 (br d, 1 H, J = 12 Hz); 5.70 (br dd, 1 H, J = 2.8 Hz). ^{13}C NMR: 17.8, 24.8, 28.3, 30.6, 39.2, 74.6, 80.1, 154.8.

1-[(4-Methylphenyl)sulfonyl]-8-[(9*H*-fluoren-9-yl)methoxycarbonylamino]oct-4-en-3-one (8a). To a solution of lactamol **6a** (309 mg, 1 mmol) in toluene (10 mL) was added 4[(4-methylphenyl)sulfonyl]-1-triphenylphosphoralidene-2-butanone **1** (486 mg, 1 mmol), and the mixture was refluxed for 5 h. The crude oil resulting after evaporation was chromatographed (c-hexane/EtOAc 2/1) to give **8a** as a solid (212 mg, 41%): mp 75−77 °C. The balance was partly (29%) given by the recovered **6a**. IR (KBr): 1690 (br), 1321, 1120. ^{1}H NMR: 1.62−1.69 (m, 2 H); 2.24−2.27 (m, 2 H); 2.46 (s, 3 H); 3.03−3.15 (m, 4 H); 3.36−3.43 (m, 2 H); 4.25 (t, 1 H); 4.42 (d, 2 H); 4.65 (br, 1 H); 6.08 (d, 1 H, J = 16 Hz); 6.80−6.95 (m, 1 H); 7.30−7.85 (m, 8 H). $C_{30}H_{31}NO_5S$ (517.64): calcd C 69.61, H 6.04, N 2.71, S 6.19; found C 69.51, H 5.99, N 2.69, S 6.24.

1-[(4-Methylphenyl)sulfonyl]-9-[(9*H*-fluoren-9-yl)methoxycarbonylamino]non-4-en-3-one (8b). It was obtained from **6b** (307 mg, 1 mmol) as described above for **8a** (133 mg, 25%): mp 67−8 °C. The balance was partly (51%) given by the recovered **5b**. IR (KBr): 1681 (br), 1315, 1115. ^{1}H NMR: 1.48−1.52 (m, 4 H); 2.22−2.27 (m, 2 H); 2.44 (s, 3 H); 3.04 (t, 2 H); 3.19−3.22 (m, 2 H); 3.40 (t, 2 H); 4.22 (t, 1 H); 4.41 (d, 2 H); 4.78 (t, 1 H); 6.07 (d, 1 H, J = 16 Hz); 6.60−6.70 (m, 1 H); 7.26−7.81 (m, 8 H). $C_{31}H_{33}NO_5S$ (531.66): calcd C 70.03, H 6.26, N 2.63, S 6.03; found C 69.91, H 6.16, N 2.59, S 6.10.

Hexahydro-indolizin-7-one (11a)[8] from 8a. To a solution of **8a** (200 mg, 0.39 mmol) in CH_2Cl_2 (10 mL) was added Et_3N (0.5 mL) under magnetical stirring. After 10 h the reaction mixture was evaporated to give an oil that was separated by column chomatography on deactivated (gaseous ammonia) silica gel (EtOAc/c-hexane 2/1) to give **11a** as an oil (29 mg, 52%). The IR and NMR data were identical to those of the sample obtained in solid-phase synthesis.

Octahydro-quinolizin-2-one (11b)[9] from 8b. Compound **11b** was obtained from **8b** (100 mg, 0.19 mmol) as described above for **11a**. Yield: 18 mg, 61%. The IR and NMR data were identical to those of the sample obtained in solid-phase synthesis.

1-[(4-Methylphenyl)sulfonyl]-8-(*tert*-butoxycarbonylamino)oct-4-en-3-one (9a) and 1-[(4-Methylphenyl)sulfonyl]-4-[(1-carboxylic Acid *tert*-Butyl Ester)pyrrolidine-2-yl]butan-3-one (10a). To a solution of lactamol **7a** (187 mg, 1 mmol) in toluene (10 mL) was added 4[(4-methylphenyl)sulfonyl]-1-triphenylphosphoralidene-2-butanone **1** (486 mg, 1 mmol). The mixture was refluxed for 7 h, and then

triphenyphosphine oxide was filtered off. The supernatant after concentration was separated by column chromatography (Et_2O/petroleum ether 6/1) to give **9a** (71 mg, 18%) and **10a** (59 mg, 15%) as oils.

For **9a**: ^{1}H NMR: 1.44 (s, 9 H); 1.62−1.70 (m, 2 H); 2.21−2.30 (m, 2 H), 2.46 (s, 3 H); 3.00−3.16 (m, 4 H); 3.36−3.44 (m, 2 H); 4.58 (br t, 1 H); 6.09 (d, 1 H, J = 16 Hz); 6.89 (dt, 1H, J = 16 and 7.8 Hz); 7.37 (d, 2 H, J = 8 Hz); 7.79 (d, 2 H, J = 8 Hz). $C_{20}H_{29}NO_5S$ (395.51): calcd C 60.73, H 7.39 N 3.54, S 8.11; found C 60.85, H 7.51, N 3.59, S 8.19.

For **10a**: ^{1}H NMR: 1.51 (s, 9 H); 1.59−1.69 (m, 1 H); 1.90−2.21 (m, 3 H); 2.82−2.99 (m, 3 H); 3.16−3.45 (m, 5 H); 3.80 (m, 1 H); 7.51 (d, 2 H, J = 8 Hz); 7.76 (d, 2 H, J = 8 Hz). $C_{20}H_{29}NO_5S$ (395.51): calcd C 60.73, H 7.39 N 3.54, S 8.11; found C 60.60, H 7.11, N 3.48, S 8.22.

Hexahydro-indolizin-7-one (11a)[8] from 9a and 10a. To a solution of a mixture of **9a** (71 mg, 0.18 mmol) and **10a** (59 mg, 0.15 mmol) in CH_2Cl_2 (10 mL) was added TFA (0.5 mL) under magnetical stirring. After 1 h the reaction mixture was evaporated, the residue dissolved in EtOH (10 mL), and an anion exchanger resin (Fluka, Amberlist A-21, 250 mg) was added. After 6 h of stirring the resin was filtered off and the solvent evaporated to give an oil that was separated by column chomatography on deactivated (gaseous ammonia) silica gel (EtOAc/c-hexane 2/1) to give **11a** as an oil (19 mg, 41%). The IR and NMR data were identical to those of the sample obtained in solid-phase synthesis.

General Procedure for Coupling Amino Alcohols to Trityl Chloride Resin. Syntheses of 12a,b. Trityl chloride resin (2 g, 1.9 mmol) was swollen in dry CH_2Cl_2 (20 mL) for 20 min, and then a solution of 4-aminobutanol (890 mg, 10 mmol) in dry CH_2Cl_2 (10 mL) was added. The suspension was shaken for 24 h at room temperature. The trityl resins **12** were washed two times with CH_2Cl_2, MeOH, CH_2Cl_2, and Et_2O and dried under high vacuum.

FT-IR of **12a**: 3458, 3297, 1055.

FT-IR of **12b**: 3495, 3312, 1053.

General Procedure for Oxidation of Amino Alcohol Resins 12. Syntheses of 13a,b. Resins **12a**,**b** (2 g, respectively 1.81 and 1.79 mmol) were swollen in dry CH_2Cl_2 (5 mL) for 20 min, and then *N*-iodosuccinimide (2.137 g, 9.5 mmol) and tetrabutylammonium iodide (760 mg, 2.1 mmol) were added. The suspensions were shaken for 7 h at room temperature. The resins **13a**,**b** were washed two times with CH_2Cl_2, MeOH, CH_2Cl_2, and Et_2O and dried under high vacuum.

FT-IR of **13a**: 3521, 1724.

FT-IR of **13b**: 3553, 1728.

General Procedure for Wittig Reaction of Aldehyde Resins 13a,b with Stabilized Ylide 1. Syntheses of 14a,b. Resins **13a**,**b** (2 g, respectively 1.8 and 1.78 mmol) were swollen in dry CH_2Cl_2 (5 mL) for 20 min and then 4[(4-methylphenyl)sulfonyl]-1-(triphenylphosphoralidene)-2-butanone 1 (1.847 g, 3.8 mmol) was added. The suspensions were refluxed for 4 h. The resins **14a**,**b** were washed two times with CH_2Cl_2, MeOH, CH_2Cl_2, and Et_2O and dried under high vacuum. In the synthesis of **14a**, the collected organic washes were concentrated and the resulting oil was chromatographed (c-hexane/EtOAc 1/1) to isolate triphenylphosphine oxide (449 mg, 89%).

FT-IR of **14a**: 3555, 1682, 1321, 1111.

FT-IR of **14b**: 3568, 1682, 1325, 1123.

General Procedure for Cyclization and Cleavage of Trityl Resins 14. Syntheses of Hexahydro-indolizin-7-one (11a)[8] and Octahydro-quinolizin-2-one (11b).[9] Resins **14a**,**b** (0.5 g, respectively 0.37 and 0.38 mmol) were swollen in dry CH_2Cl_2 (10 mL) for 20 min and cooled at 0 °C, and then TFA (200 mg, 1.7 mmol) was added. The orange suspensions were shaken for 15 min and washed three times with methanol. The collected washes were concentrated to 10 mL, and an anion exchanger resin (Fluka Amberlyst A-21, 500 mg) was added. The suspensions were shaken for 10 h at room temperature and then washed three times with methanol. The combined methanol washes were concentrated under high vacuum to give a crude mixture that was separated by column chomatography on deactivated (gaseous ammonia) silica gel (EtOAc/c-hexane 2/1) to give **11a**,**b** as oils.

For **11a**: Yield: oil (24 mg, 46%). ^{1}H NMR: 1.5−1.95 (m, 4H); 2.20−2.40 (m, 5H); 2.45−2.60 (m, 2H), 3.1−3.3 (m; 2H). IR (neat): 2895, 1720. $C_8H_{13}NO$ (139.20): calcd C 69.03, H 9.41, N 10.06; found C 69.61, H 9.57, N 10.28.

For **11b**: Yield: oil (22 mg, 40%). ^{1}H NMR: 1.11−1.58 (m, 4H); 1.65−1.77 (m, 2H), 1.89−2.43 (m, 4H); 2.55−3.01 (m, 4H); 3.20 (m, 1H). IR (neat): 2950, 1725, 1295, 1110. $C_9H_{15}NO$ (153.23): calcd C 70.55, H 9.87, N 9.14; found C 70.84, H 10.01, N 9.15.

Acknowledgment. This work was financially supported by the Consiglio Nazionale delle Ricerche (CNR) and Ministero dell'Università e della Ricerca Scientifica e Tecnologica (Cofin 1998).

References and Notes

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