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*Published in:* European Journal of Organic Chemistry

*DOI:* 10.1002/ejoc.201301903

Published: 01/01/2014

*Document Version*  
Peer reviewed version

*Please cite the original version:*  
Synthesis of (S)- and (R)-Harmicine from Proline: An Approach Toward Tetrahydro-β-carbolines

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Keywords: Asymmetric synthesis / Natural products / Chiral pool / Alkaloids / Amino acids

(S)- and (R)-Harmicine were synthesized from L- and D-proline, respectively. This chiral pool synthesis constitutes a new approach towards C1 substituted tetrahydro-β-carbolines. The developed route makes use of the 9-phenyl-9-fluorenyl protecting group strategy of amino acids to prevent racemization of the vulnerable α-amino carbonyl stereocenter. Enantiopure harmicine (> 99% ee) was obtained in nine steps from commercially available starting material. The synthesis was performed without the use of any silica gel flash chromatography.

Introduction

Tetrahydro-β-carbolines (THβC), a subgroup of the indole alkaloid family, consist of a large number of natural products with wide structural diversity, and many of these compounds have received a lot of attention within the synthetic community for decades. The large attention can partly be attributed to the interesting structural features associated with some of these compounds and partly to the fact that, in many cases, they possess highly interesting medical properties.[1] For example, compounds such as vincamine, ajmalicine, and yohimbine (not shown) have found some use in modern medicine, and reserpine is still being prescribed for the treatment of hypertension. Tadalafil, a non-natural THβC used for the treatment of erectile dysfunction, is currently one of the top grossing drugs on the market (Figure 1).

The synthesis of chiral C1 substituted THβCs has traditionally relied on a few classical approaches. Diastereoselective versions of the Pictet–Spengler reaction (PSR),[2,3] including substrate controlled reactions of tryptophan derivatives,[4] substrate controlled reactions of chiral aldehydes,[5] and the use of chiral N-auxiliaries,[6] have been developed extensively and utilized in the synthesis of a large number of these types of natural products. Asymmetric versions of the PSR have also been developed.[7] Furthermore, examples of asymmetric protocols using catalytic amounts of chiral Bronsted acids are emerging as powerful synthetic tools for the synthesis of THβC derivatives.[8] Another approach that has been widely employed is the use of the Bischler–Napieralski reaction followed by asymmetric reduction of the 3,4-dihydro-β-carbolines.[9–11] Other asymmetric strategies include addition of carbon nucleophiles to 3,4-dihydro-β-carbolines[12] chiral formamide carbanion chemistry,[13] and enzymatic PSR.[14]

Harmicine 1 was first isolated from the leaf extract of the Malaysian plant Kopsia griffithii.[15] The leaf extract possesses antileishmanial activity, and recently antinociceptive properties have been assigned to 1.[16] Structure elucidation revealed a new tetracyclic compound of the THβC class to be part of this extract. Harmicine itself has previously been synthesized on a number of occasions.[17–19]

We have been involved in natural product synthesis starting from compounds from the chiral pool, making use of the stereochemical information embedded within amino acids. In this context, we envisioned a strategy in which the side chain of amino acid 6 would end up in the C1 position of the THβC, thereby creating a new synthetic route to the THβC framework (Figure 2). Performing a lateral lithiation reaction between compound 4 and Weinreb amide 5 was...
expected to generate α-amino ketone 3. Further functionalization of the benzylic position followed by indolization and ring closure would lead to the basic structure 2, which is a C1 substituted THβC, in enantiopure form.

![Figure 2. Synthetic strategy towards the THβC framework; R = amino acid side chain, Pg = protecting group.](image)

It is known that α-amino ketones, and also to some extent α-amino amides, are prone to racemization under strongly basic conditions. To eliminate this as a possibility, we employed the 9-phenyl-9-fluorenyl (Pf) protecting group strategy for amino acids. This strategy has been successfully used in natural product synthesis and in the synthesis of medicinally interesting compounds on a number of occasions. To demonstrate the synthetic value of such a protocol we then embarked on the synthesis of harmicine.

### Results and Discussion

The synthesis started from proline 7, however, Pf-protection of 7 was not as trivial as first anticipated. In contrast to the Pf-protection of alanine, by using the standard literature procedure, partial racemization occurred at the labile α-stereogenic center giving rise to an ee of 89%.[23] This can most likely be attributed to the higher acidity of the cyclic α-proton in proline compared to that in alanine (Scheme 1).

In an attempt to circumvent the problem, a more hindered base was tested. When switching from triethylamine (TEA), to disopropylethylamine (DIPEA), the ee could be improved to an acceptable level of 98%. However, when starting from a chiral pool substrate such as proline, every small loss in ee would constitute a disappointment. In that spirit, and because the use of strong bases such as TEA or DIPEA was not necessary, we opted for a weaker base. Using N-N,N-dimethylmorpholine (NMM; \( pK_{\text{aH}} \) 7.38, a difference of approximately 3.4 units to TEA, \( pK_{\text{aH}} \) 10.75), compound 8 was obtained in > 99%ee in 82% yield on a 100 mmol scale (Table 1). Acid 8 was isolated after an aqueous work up.

![Scheme 1. Phenyl fluorenylation of proline.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>ee [%][a]</th>
<th>Yield [%][b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TEA</td>
<td>89</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>DIPEA</td>
<td>98</td>
<td>n.d.</td>
</tr>
<tr>
<td>3</td>
<td>NMM</td>
<td>&gt; 99</td>
<td>82[c]</td>
</tr>
</tbody>
</table>

[a] Determined by HPLC analysis. [b] Isolated yield. [c] Scale up to 100 mmol, isolated yield.

Compound 8 was then subjected to an amide coupling reaction to obtain the corresponding Weinreb amide (Scheme 2). Initial attempts using 1,1-carbonyldiimidazole (CDI; Table 2, entries 2–4) proved unsuccessful, and even with the addition of 4-(dimethylamino)pyridine (DMAP), no conversion was observed. By using N,N-dicyclohexylcarbodiimide (DCC), in combination with DMAP, amide 9 was obtained in a modest yield (31%) after flash chromatography (Table 2, entry 1). However, one of the aims of the described synthesis was to keep the number of chromatographic purification steps to a minimum and due to the concerns associated with side-product formation originating from this particular coupling reaction (the removal of N,N-dicyclohexylurea often requires chromatographic purification procedures), DCC was not further explored as a viable option. Instead, propylphosphonic anhydride (T3P®), being slightly less expensive than 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), and also known to form water-soluble side products from the amide coupling reaction, was tested. By using a reported procedure for an α-amino acid (Table 2, entry 5), a moderate but encouraging yield of 9 of 60% was obtained.[24] Switching to a chiral pool substrate such as proline, every small loss in ee would constitute a disappointment. In that spirit, and because the use of strong bases such as TEA or DIPEA was not necessary, we opted for a weaker base. Using N-N,N-dimethylmorpholine (NMM; \( pK_{\text{aH}} \) 7.38, a difference of approximately 3.4 units to TEA, \( pK_{\text{aH}} \) 10.75), compound 8 was obtained in > 99%ee in 82% yield on a 100 mmol scale (Table 1). Acid 8 was isolated after an aqueous work up.

| Entry | Coupling Base Additive Solvent Time Yield [%][f] |
|-------|--------|---------|---------|------|
| 1     | DCC    | TEA     | DMAP[b] | CH2Cl2 26 31[e] |
| 2     | CDI    | TEA     | –       | THF 23 n.d.[d] |
| 3     | CDI    | TEA     | –       | CH2Cl2 26 n.d.[d] |
| 4     | CDI    | TEA     | DMAP[b] | THF 23 n.d.[d] |
| 5[e]  | T3P®   | pyridine | –       | EtOAc 18 60[d] |
| 6[e]  | T3P®   | TEA     | –       | EtOAc 18 60[e] |
| 7     | T3P®   | TEA     | DMAP[d] | EtOAc 26 81[o], 73[h] |

[a] Reactions were carried out on a 1 mmol scale with the exception of entry 1, which was carried out on a 2 mmol scale. [b] 5 mol-% used. [c] Isolated yield after flash chromatography. [d] No conversion was detected on TLC. [e] Carried out at 0 °C. [f] Isolated yield. [g] 20 mol-%. [h] Scale up to 56 mmol, isolated yield.
ing the base from pyridine to non-nucleophilic TEA, not surprisingly, diminished the yield substantially (Table 2, entry 6). By using an even more nucleophilic additive than pyridine, 20 mol-% DMAP, in combination with TEA (Table 2, entry 7), Weinreb amide 9 was obtained in good 81% yield. The product was obtained in satisfactory purity after simple aqueous work up.

An alternative route to the Weinreb amide 9 was also developed. The commercially available proline methyl ester HCl salt 10 was Pf-protected under conditions developed for aspartic acid, in 82% yield (Scheme 3).[23] Amidation formation using iPrMgCl as the base gave the corresponding Weinreb amide in 92% yield. The sequence was high yielding but required at least one flash chromatographic step. Furthermore, partial racemization of the α-stereocenter, most likely in the Pf-protection step, once again proved to be an issue. The ee of 9 obtained from this route was 97%.

Scheme 3. Alternative route to Weinreb amide 9.

Boc-toluidine[25], prepared from o-toluidine, was then coupled with Weinreb amide 9, by using two equivalents of sBuLi, giving ketone 11 in good yield (85%; Scheme 4). The best results were obtained by using an excess (200 mol-%) of 4 (Table 3). The use of lower amounts led to poorer yields due to incomplete reactions, as shown by the presence of unreacted starting material. The product could be purified by triturating the crude material with Et_2O, giving 11 as a white solid after filtration. The reaction was scaled up to 38 mmol.

Table 3. Coupling of Boc-toludine 4 and Weinreb amide 9.

<table>
<thead>
<tr>
<th>Entry</th>
<th>9 [mol-%]</th>
<th>4 [mol-%]</th>
<th>sBuLi [mol-%]</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>120</td>
<td>277</td>
<td>60[a]</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>150</td>
<td>300</td>
<td>70[a]</td>
</tr>
<tr>
<td>3</td>
<td>100</td>
<td>200</td>
<td>400</td>
<td>87[b, 85[c]</td>
</tr>
</tbody>
</table>

[a] Isolated yield after flash chromatography. [b] Isolated yield after trituration in Et_2O. [c] Scale up to 38 mmol, isolated yield.

Ketone 11 was then enolized by using 100 mol-% KHMDs in combination with hexamethylphosphoramide (HMHA; needed to facili tate the formation of the enolate), and subsequently quenched with an acetate electrophile to give intermediate 12 (Scheme 5). Ethyl iodoacetate proved to work very well in the reaction. However, because we were unable to isolate 12, the crude material was treated directly with sulfuric acid in EtOH, using CH_2Cl_2 as a cosolvent to cleave the Boc group. Upon Boc cleavage aniline nitrogen condensed with the ketone to give indole 13 in 69% over two steps. Compound 13 was purified by trituration from an EtOAc/hexane mixture, giving an amorphous solid after filtration.

Having installed the carbon framework, all that remained was the removal of the Pf-group followed by lactam formation and reduction to give harmicine. The Pf-deprotection under hydrogenolysis of 13, however, required some optimization of the reaction conditions (Table 4). Conventional hydrogenation using Pd/C under 1 atm H_2 (g) gave essentially no conversion. Using Pearlman’s catalyst under conditions developed for a Pf-protected pyrroleproline also proved unsuccessful (Table 4, entry 4).[26] Preparing the Pd/C in situ from Pd(OAc)_2 and activated charcoal did not improve the reaction outcome (Table 4, entry 5).[27] By using Pd/C, 1 atm H_2 (g), and HCl in EtOH heated to re-

Scheme 4. Lateral lithiation of 4.

Scheme 5. Transformation of ketone 11 into harmicine 1.
The synthesis of harmicine was then completed by reducing the lactam with lithium aluminum hydride (LAH) in tetrahydrofuran (THF) at room temp. Harmicine was isolated from the crude mixture after aqueous work up in 78% yield. Both (S)-harmicine and (R)-harmicine (from D-proline) and (R)-harmicine (from L-proline) were synthesized and chiral HPLC analysis confirmed the ee to be >99%. The nine-step sequence from commercially available starting material was performed without the use of any flash chromatographic purification and the synthesis was scaled up to give 1.16 g of (S)-harmicine in one batch.

Conclusions

The synthesis of (S)-harmicine and (R)-harmicine was completed from L-proline and D-proline, respectively, by using the Pf-group as an amine protecting group strategy. The synthesis was optimized to the point where no silica gel flash chromatography was required and gave the title compound in a total yield of 19% over nine steps with an ee of >99%. During the course of the synthesis, some problems concerning the use of Pf as a protecting group were encountered; however, these problems were subsequently solved. Racemization of proline in the Pf-protection step was circumvented by the use of a weaker base. We also report, to the best of our knowledge, the first Pf-deprotection under transfer hydrogenation conditions. As a final conclusion, this study constitutes a new approach to the synthesis of chiral tetrahydro-β-carbolines and further work involving the synthesis of other natural products from the tetrahydro-β-carboline class by using different amino acids will be reported in due time.

Experimental Section

General Information: Dry solvents (THF, MeCN, CH2Cl2 and toluene) were obtained from a solvent drying system (MB SPS-800, using neutral alumina as dessicant). Other solvents used were of P.A. quality, with the exception of HPLC grade hexane for the intended use of HPLC analysis, and used as such directly from the bottles. HMPA and NMM were distilled from CaH2 and stored over 4 Å molecular sieves. TMSCl was distilled from CaH2. Pb(NO3)2 and K3PO4 were dried in an oven prior to use. Reagents were obtained from Sigma–Aldrich, TCI Europe, or Johnson Matthey Chemicals Limited. Celleit used for filtration was Celite 535, purchased from Sigma–Aldrich. TLC monitoring was performed on silica gel 60 F254 on aluminum support obtained from Merck. Visualization of TLC plates was done using UV light (λ = 254 nm) and/or staining the plates with ninhydrin solution (1 g of ninhydrin dissolved in 100 mL of EtOH and 0.2 mL glacial AcOH) or vanillin solution (2.4 g of vanillin dissolved in 100 mL of EtOH, 2 mL of conc. H2SO4 and 1.2 mL glacial AcOH). NMR spectra were recorded on a Bruker Avance 400 spectrometer at ambient temperature and the peaks were calibrated to TMS (ΔH = 0.00 ppm), or residual solvent 13C in CDCl3 (13C: δ = 77.0 ppm) or D2O/DMSO (1H: δ = 3.5 ppm). Optical rotations were measured with a Perkin–Elmer 343 Polarimeter equipped with a sodium lamp and a
1.63 (m, 1 H) ppm. 13C NMR (CDCl 3): δ = 7.79 (br. d, J = 7.8 Hz, 1 H), 7.19 (t, J = 7.8 Hz, 1 H), 7.14 (d, J = 7.4 Hz, 1 H), 6.99 (t, J = 7.4 Hz, 1 H), 2.25 (s, 3 H), 1.52 (s, 9 H) ppm. 13C NMR (CDCl 3): δ = 153.0, 130.2, 127.2, 126.7, 126.3, 120.9, 80.3, 28.3, 17.6 ppm. C2H2NO2 (207.27): calc. C 69.54, H 8.27, N 6.74.

(S)-1-(9-Phenyl-9H-fluoren-9-yl)pyrrolidine-2-carboxylic Acid (8): To a suspension of l-proline (11.5 g, 100 mmol, 100 mol-%) in anhydrous CH2Cl2 (400 mL) and anhydrous MeCN (50 mL) in a flame-doused Morton flask under argon was added TMSCl (12.7 mL, 100 mmol, 100 mol-%). The resulting solution was heated to reflux for 1 h, after which it was cooled to room temp. Evaporation of the orange oil, which was crystallized from hexane (20 mL) to form white translucent needles, yield 33 g (85%); Rf = 0.36 (Hex/EtOAc, 9:1).

IR (film): ν = 3271, 2983, 2967, 1701, 1678, 1585, 1521, 1456, 1390, 1363, 1292, 1245, 1198, 1153, 1050, 1024, 988, 948, 910, 860, 843, 777, 744, 733, 710, 635 cm⁻¹. 1H NMR (400 MHz, CDCl 3): δ = 7.50 (m, 1 H), 7.39 (m, 1 H), 7.30 (m, 1 H), 7.27–7.14 (m, 5 H), 3.71 (br., 1 H), 3.40 (m, 1 H), 3.35 (s, 2 H), 3.13 (m, 1 H), 2.25 (s, 3 H), 1.76 (m, 2 H), 1.61 (m, 2 H), 1.54 (s, 9 H) ppm. 13C NMR (CDCl 3): δ = 141.4, 140.6, 139.3, 129.0, 128.6, 128.0, 127.8, 127.7, 126.8, 126.0, 125.8, 120.3, 120.0, 76.9, 62.5, 50.7, 30.9, 24.7 ppm. HRMS: calc. for C24H22N2O2 [M + H⁺] 399.1703; found 399.1701.

(S)-N-Methoxy-N-methyl-1-(9-phenyl-9H-fluoren-9-yl)pyrrolidine-2-carboxamide (9): To a suspension of 8 (19.9 g, 56 mmol, 100 mol-%) and HClHN(O)Me (8.19 g, 84mmol, 150 mol-%) in EtOAc (230 mL) were added Et3N (35.1 mL, 252 mmol, 450 mol-%) and DMAP (1.37 g, 11.2 mmol, 20 mol-%). T3P (50 mL, 84 mmol, 150 mol-%, 50 wt.-% solution in EtOAc) was then added by using an addition funnel at room temp. The suspension was stirred for 2 h, then the reaction was quenched with 0.5 m aqueous HCl (400 mL). The organic phase was separated and washed with 0.5 m aqueous HCl (2 × 300 mL), then the combined aqueous phases were back-extracted once with EtOAc (300 mL). The combined organic phases were washed with 10 wt.-% K2CO3 (300 mL), brine (300 mL), dried with Na2SO4, filtered and finally evaporated to dryness to give a thick red oil. Upon addition of Et2O (50 mL) followed by evaporation, the oil solidified into a red-orange solid (16.3 g, 73%), which was subjected to chiral HPLC analysis (Chiralpak IA; Hex/EtOH, 98:2; 1 mL/min): Rf = 9.8 (S), 10.6 (R) min; > 99% ee for both (S) and (R) enantiomers; Rf = 0.45 (Hex/EtOAc, 1:1); [α]D^20 +49.8 (S) (c = 0.8, CH2Cl2); [α]D^20 –49.1 (R) (c = 0.78, CH2Cl2).

IR (film): ν = 3059, 2964, 2868, 1716, 1659, 1599, 1449, 1386, 1352, 1314, 1281, 1175, 1114, 1087, 1031, 1000, 909, 763, 734, 704, 618, 641 cm⁻¹. 1H NMR (400 MHz, CDCl 3): δ = 7.20 (d, J = 7.5 Hz, 1 H), 7.63–7.59 (m, 4 H), 7.45 (d, J = 7.7 Hz, 1 H), 7.39 (m, 1 H), 7.30–7.14 (m, 5 H), 3.71 (br. 1 H), 2.91 (br. m, 7 H), 1.93 (m, 1 H), 1.84 (m, 1 H), 1.61 (m, 2 H) ppm. 13C NMR (CDCl 3): δ = 177.1, 148.7, 147.9, 144.1, 140.9, 139.7, 128.1, 128.0, 127.8, 127.5, 127.4, 127.3, 126.9, 126.8, 126.4, 119.4, 112.9, 77.0, 60.2, 57.6, 50.1, 32.0, 32.0, 24.8 ppm. HRMS: calc. for C26H22N2O2 [M + H⁺] 399,2073; found 399,2062.
(S)-Ethyl 2-[2-[1-(9-Phenyl-9H-fluoren-9-yl)pyrrolidin-2-yl]-1H-indol-3-yl]acetate (13): To a flame-dried flask equipped with a condenser was charged with 13 (5.13 g, 10 mmol, 100 mol-%), NH4H2PO2 (4.98 g, 60 mmol, 600 mol-%) and EtOH (100 mL). The suspension was degassed and 10 wt.-% Pd/C (0.53 g, 0.5 mmol, 5 mol-%) was added. The reaction mixture was heated to reflux for 3 h, then cooled to room temp. The thick suspension was filtered through Celite and eluted with EtOH (100 mL). The EtOH was evaporated and the resulting solid was partitioned between CH2Cl2 (300 mL) and 10 wt.-% K2CO3 (200 mL). The aqueous phase was extracted with CH2Cl2 (200 mL) and the combined organic phase was washed with brine (200 mL), dried with Na2SO4, filtered, and evaporated to give a yellow solid. The crude product was suspended together with Na2CO3 (10.6 g, 100 mmol, 1000 mol-%) in EtOH (200 mL) and stirred at room temp. for 2 h. The reaction solvent was evaporated and the solid was partitioned between CH2Cl2 (300 mL) and H2O (200 mL). The aqueous phase was extracted with CH2Cl2 (2 × 200 mL) and the combined organic phases where washed with brine (400 mL), dried with Na2SO4, filtered, and evaporated to give a yellow solid. The solid was suspended in toluene (5 mL) and filtered. The filter cake was washed with toluene (3 × 3 mL) and hexane (5 mL) to give 14 (1.83 g, 81%) as a pale-yellow powder. Rf = 0.28 (CH2Cl2/MeOH, 95:5); [δH]D6–DMSO = −107.1 (s = 0.4, DMSO); [δD]D6 +108.2 (R) (s = 0.4, DMSO).

(S)-Harmicine (1): In a flame-dried flask under argon, 14 (1.58 g, 7 mmol, 100 mol-%) was suspended in anhydrous THF (70 mL). LAH (1.59 g, 42 mmol, 600 mol-%) was added to the reaction in two equally sized portions. The reaction mixture was stirred at room temp. for 5 h, then cooled to 0°C and water (1.6 mL) was carefully added dropwise. The reaction mixture was filtered off, and the filtrate was evaporated to give harmicine as a yellow solid (1.16 g, 78%). The solid was subjected to chiral HPLC analysis (Chiralpak IB; Hex/ Ethanol, 95:5; 1 mL/min): Rf = 0.80 (R), 9.5 (S) min; > 99% ee for both (S) and (R) enantiomers. Rf = 0.27 (toluene/isopropanol, 98:2); 0.55 (Hex/EtOAc, 75:25); 0.60–0.70 (S = 0.79, CH2Cl2); 0.65–0.85 (R (s = 0.83, CH2Cl2). IR (film): ν = 3398, 3058, 2974, 2868, 1718, 1600, 1487, 1446, 1385, 1348, 1329, 1269, 1239, 1154, 1131, 1065, 1031, 905, 725, 700, 638, 618 cm–1. 1H NMR (400 MHz, [D6]DMSO): δ = 7.76 (s, 1 H), 7.76 (d, J = 7.5 Hz, 1 H), 7.58 (d, J = 7.5 Hz, 1 H), 7.49–7.45 (m, 4 H), 7.37–7.31 (m, 3 H), 7.24–7.16 (m, 3 H), 7.10 (m, 1 H), 7.01 (m, 1 H), 6.84 (dt, J = 7.5, 1.0 Hz, 1 H), 6.67 (d, J = 7.7 Hz, 1 H), 6.20 (dt, J = 7.5, 1.0 Hz, 1 H), 3.93 (q, J = 7.1 Hz, 2 H), 2.73 (m, 1 H), 2.47 (m, 1 H), 2.30 (m, 1 H), 3.20 (m, 1 H), 3.11 (d, J = 15.2 Hz, 1 H), 2.77 (d, J = 15.0 Hz, 1 H), 1.93 (m, 2 H), 1.68 (m, 2 H), 1.09 (t, J = 7.3 Hz, 3 H) ppm. 13C NMR (CDCl3): δ = 171.9, 148.3, 146.3, 143.5, 142.4, 141.4, 138.0, 134.5, 128.9, 128.7, 128.2, 127.5, 127.4, 127.1, 126.7, 126.6, 125.0, 120.8, 119.7, 118.9, 118.0, 110.4, 102.9, 77.0, 60.3, 54.2, 51.1, 35.2, 30.0, 25.2, 14.1 ppm. HRMS: calcd. for C36H35N2O4 [M + H]+ 513.2542; found 513.2551.

(S)-2,3,3,11b-Tetrahydro-1H-indolizino[8,7-b]flavon-5(6H)-one (14): A one-necked flask equipped with a condenser was charged with 13 (5.13 g, 10 mmol, 100 mol-%), NH4H2PO2 (4.98 g, 60 mmol, 600 mol-%) and EtOH (100 mL). The suspension was degassed and 10 wt.-% Pd/C (0.53 g, 0.5 mmol, 5 mol-%) was added. The reaction mixture was heated to reflux for 3 h, then cooled to room temp. The thick suspension was filtered through Celite and eluted with

Supporting Information (see footnote on the first page of this article): Alternative synthesis of 9 via 15. HPLC chromatograms for
enantiopurity determination of compounds 9, 10, 13, 1. Copies of the 1H and 13C NMR spectra of compounds 4, 8, 15, 9, 11, 13, 14, 1.

Acknowledgments

The National Graduate School of Organic Chemistry and Chemical Biology and Aalto University are gratefully acknowledged for providing funding for this project.


Received: December 22, 2013
Published Online: February 12, 2014