Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 8589–8595

TETRAHEDRON

# Total synthesis of (±)-tangutorine and chiral HPLC separation of enantiomers

Tiina Putkonen,[a] Arto Tolvanen,[b] Reija Jokela,[a,*] Salvatore Caccamese[c] and Nunziatina Parrinello[c]

[a]*Laboratory of Organic Chemistry, Helsinki University of Technology, P.O. Box 6100, FIN-02015 HUT-Espoo, Finland*
[b]*Orion Corporation, Orion Pharma., P.O. Box 65, FIN-02101 Espoo, Finland*
[c]*Dipartimento di Scienze Chimiche, Università di Catania, viale A. Doria 6, 95125 Catania, Italy*

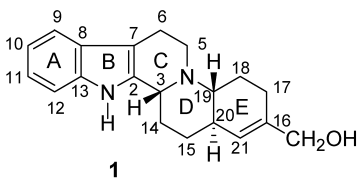
Received 8 July 2003; revised 8 August 2003; accepted 4 September 2003

**Abstract**—The first total synthesis of racemic tangutorine, a novel indole alkaloid, was performed in 7 steps. The key reactions, dithionite reduction and acidic cyclization provided easy access with good yields to the tangutorine skeleton. Comprehensive NMR spectroscopic data of new compounds are given. Chiral HPLC separation of enantiomers is reported.


## 1. Introduction

Tangutorine **1**, a biogenetically interesting indole alkaloid, was found in the leaves of *Nitraria tangutorum* in 1999.[1] It was isolated as a racemic mixture and contains three stereogenic centers. To date, this novel compound is the only known natural product containing the benz[*f*]-indolo[2,3-*a*]quinolizidine unit.

In the paper of Duan and colleagues, the structure of tangutorine was reported for the first time.[1,2] In contrast to their ring numbering system, we have proposed[3,4] a different numbering (Fig. 1) based on the biogenetic numbering[5] of the yohimbine skeleton (Fig. 2).




**1**

**Figure 1.**

Tangutorine can theoretically be related to yohimbine as follows: by disconnecting the C-15/C-16 bond in yohimbine skeleton and connecting C-16 to C-21, followed by disconnection of the C-21/N-4 bond and connection of C-19 to N-4, our suggestion to the biogenesis and thereby the biogenetic numbering of tangutorine is formed.

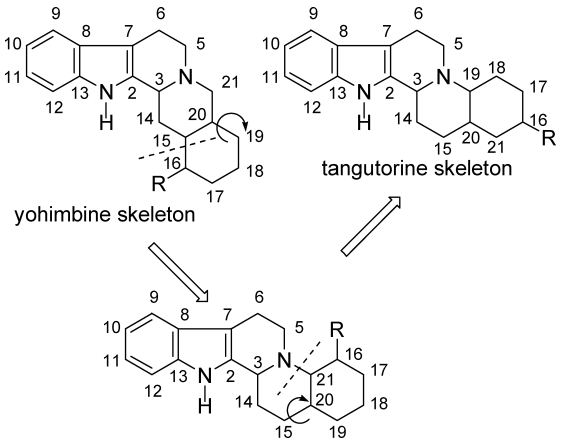



**Figure 2.** The possible biogenesis of tangutorine skeleton.

The basic ring system of tangutorine **1** was synthesized in our laboratory[3] and the first total synthesis was published in 2001.[4] We now report the total synthesis of tangutorine **1** in detail starting from 7,8-dihydroquinoline-5(6*H*)-one **3**. We also report the direct enantioseparation of tangutorine by chiral HPLC on two polysaccharide chiral stationary phases (CSP), and one network polymer. We report the different enantioselectivity on these CSP and the isolation of single enantiomers using Chiralcel OD. In addition, we measured the circular dichroism (CD) spectra and specific optical rotation of the isolated enantiomers.

*Keywords*: natural products; indole alkaloids; benz[*f*]indolo[2,3-α] quinolizidine.
* Corresponding author. Tel.: +358-9-4512531; fax: +358-9-4512538; e-mail: reija.jokela@hut.fi

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.09.010

## 2. Results and discussion

### 2.1. Synthesis

We have previously synthesized yohimbine alkaloids using tryptophyl bromide and a suitable isoquinoline derivative as starting material.[6] Here the required quinoline **4** was prepared via 3-aminocyclohex-2-enone **2** (cf. Section 4) and 7,8-dihydroquinoline-5(6*H*)-one **3** in 3 steps.

7,8-Dihydroquinoline-5(6*H*)-one **3** was prepared using a published method starting from 1,3-cyclohexanedione.[7] Reaction of **3** with dimethyl carbonate and NaH containing a catalytic amount of methanol for 3 h under reflux gave 5-oxo-5,6,7,8-tetrahydro-quinoline-6-carboxylic acid methyl ester **4** in 90% yield. It crystallized from hexane as an enol.

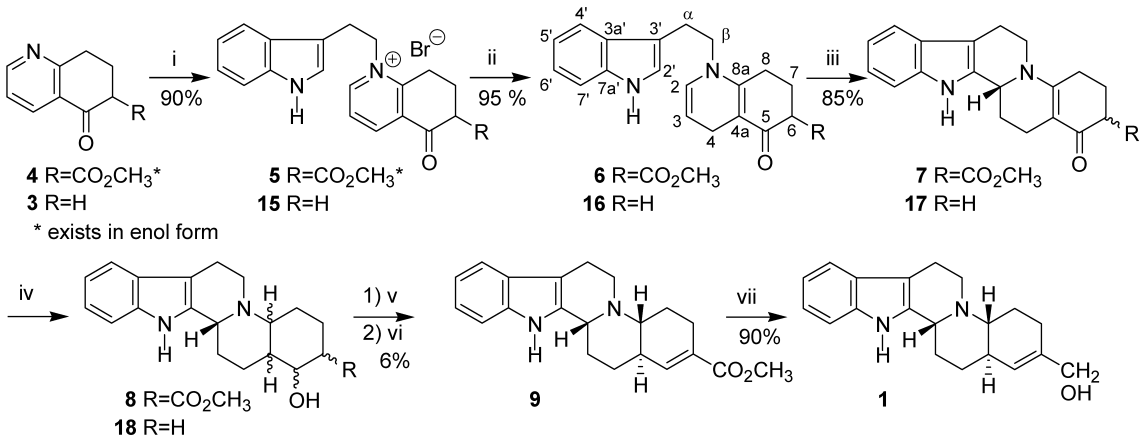
Alkylation of ester **4** with tryptophyl bromide afforded salt **5** as an enol in 90% yield. Treatment of this salt with sodium dithionite in water–methanol solution for 18 h at room temperature in the presence of sodium bicarbonate gave a 95% yield of compound **6** in keto form. Cyclization in HCl–MeOH for 3 days afforded the two diastereo isomers of compound **7** in 85% yield.

Reduction with sodium borohydride in glacial acetic acid overnight gave an inseparable mixture of diastereo isomers **8**. Dehydration[8] was carried out through the mesylate intermediate with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) to afford compound **9**. The overall yield for these 3 steps was 6%.

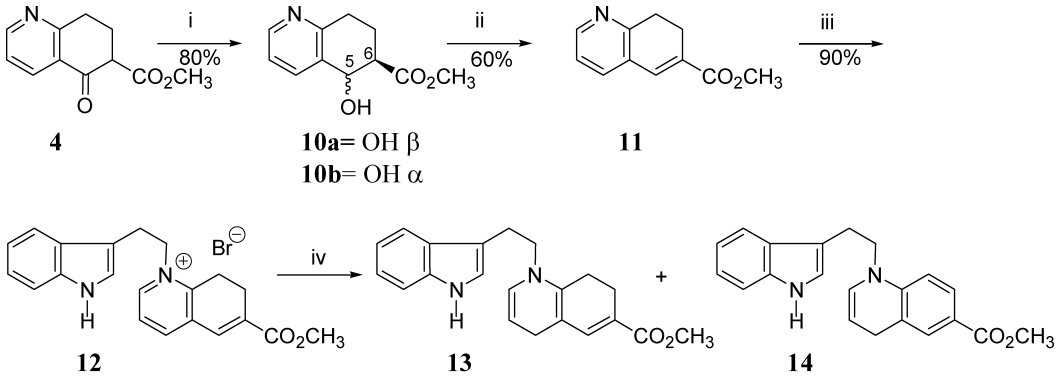
Finally, the ester group was reduced with lithium aluminum hydride in THF at room temperature for 4 h to give (±)-tangutorine **1** in 90% yield (Scheme 1).

To improve the total yield of our synthesis we modified it by changing the order of the reactions. By first building up the E-ring, we avoided the formation of a vinylogous amide, the presence of which lowers the yield of the $NaBH_4$ reduction and increases the number of stereoisomers produced.

Reduction of ester **4** afforded two diastereo isomers of alcohol **10** in 80% yield. The two small and one large coupling constants of C(6)H ($J$=3, 3.5, 11 Hz) in the major isomer confirmed that the hydroxy group was axial and the ester group equatorial. In the minor product both groups were equatorally oriented as revealed by coupling constants of C(6)H ($J$=3, 10, 12 Hz). The reaction of alcohols **10a** and **10b** with mesyl chloride in $CH_2Cl_2$ and triethylamine yielded the unsaturated ester **11** (60%). Triethylamine proved to be a base strong enough to remove the mesyl group, so that no DBU was needed. The alkylation of ester **11** with tryptophyl bromide gave salt **12**. However, the sodium dithionite reduction of salt **12** gave the desired compound **13** only as a side product, and we mainly obtained compound **14** with an aromatic E-ring (Scheme 2). The mass spectra of the product mixture showed $m/z$ 332




**Scheme 1.** (i) Tryptophyl bromide, 100°C; (ii) $Na_2S_2O_4$, $NaHCO_3$, MeOH, $H_2O$, rt, 18 h; (iii) HCl–MeOH, rt, 65 h; (iv) $NaBH_4$, $CH_3COOH$, rt, 16 h; (v) MsCl, $Et_3N$, $CH_2Cl_2$, 0°C, 1 h; (vi) DBU, 100°C, 2 h; (vii) $LiAlH_4$, THF, rt, 4 h.




**Scheme 2.** (i) $NaBH_4$, MeOH, −5°C, 15 min; (ii) MsCl, $Et_3N$, $CH_2Cl_2$, rt, 16 h; (iii) tryptophyl bromide, $Et_2O$, 100°C; (iv) $Na_2S_2O_4$, $NaHCO_3$, MeOH, $H_2O$, rt, 18 h.

corresponding to the molecular ion. The $^{13}C$ NMR spectrum also showed new signals at 110 and 140 ppm and corresponding aromatic signals were observed in the $^{1}H$ NMR spectrum. In spite of our efforts to modify the reduction conditions to avoid the aromatisation, the yield of compound **13** was not increased. Our attempts to purify product **13** failed because of its instability and tendency to aromatize into compound **14**.

We also modified the synthesis by adding the ester group after the sodium borohydride reduction and subsequent oxidation of **18**. The sequence of reactions (**3→15→16→17**) was carried out without difficulties (Scheme 1). However, the yield of the sodium borohydride reduction (**17→18**) and thus of the overall reaction was not improved.

### 2.2. HPLC separation of enantiomers

Table 1 shows the chromatographic results for the enantioseparation of tangutorine using as chiral stationary phases two polysaccharide-derived CSP (Chiralcel OD and Chiralpak AD) and a network polymer incorporating a bifunctional $C_2$-symmetric chiral selector (Kromasil CHI-DMB).

The addition of a small amount of diethylamine (DEA) to the mobile phase is crucial to obtain enantioseparation on the Chiralcel OD and Chiralpak AD columns, giving separation factor $\alpha$ of 1.85 and 2.28, respectively. This was observed in experiments performed on Chiralpak AD under the same conditions (polarity of the mobile phase and flow rate), as shown in lines 4 and 5 of Table 1 and other unreported experiments on Chiralcel OD. The beneficial effect of DEA in the mobile phase is due to the suppression of the partial ionization of the basic tertiary amine group in tangutorine leading to a better interaction on the CSP.

The use of Chiralcel OD affords a separation factor that remains unaffected by a variation in the flow rate of the mobile phase, as shown in lines 1 and 2 of Table 1. The value is lower than that obtained using Chiralpak AD under the same experimental conditions; however, the resolution factor $R_s$ is much better, as shown in lines 1 and 3 and in Figure 3(a) and (b). This is due to the presence of impurities in the sample that remain hidden under the enantiomeric peaks and that affect the baseline too, using Chiralpak AD. This is also shown by the ratio of the integrated areas of the enantiomeric peaks $A_1/A_2$ higher than 1, as reported in Table 1. Figure 3(a) shows among various impurities, an impurity in the descending edge of the first enantiomeric peak that was impossible to separate using the Chiralcel OD column. Figure 3(d) shows the dramatic inefficiency of the Chiralpak AD column when a mobile phase that undoped with DEA was used.

The difference in chiral recognition of cellulose and amylose derivatives is probably due to a different chiral environment around the carbamate residue and to the wider and more compact helix of the amylose derivative.[9]

**Table 1**. Enantioselective HPLC resolution of tangutorine on Chiralcel OD, Chiralpak AD and Kromasil CHI-DMB

| CSP | $A$ (%)[a] | $K_1'$[b] | $t_1$ | $t_2$ | $\alpha$ | $R_s$ | $A_1/A_2$[c] |
|---|---|---|---|---|---|---|---|
| OD | 20[d] | 2.43 | 11.8[e] | 19 | 1.85 | 2.0 | 1.39 |
| OD | 20[f] | 2.35 | 16.4[e] | 26.2 | 1.85 | 2.9 | 1.35 |
| AD | 20 | 2.13 | 10.3 | 19.4 | 2.28 | 1.3 | 1.36 |
| AD | 30 | 0.57 | 5.8 | 8.7 | 2.19 | 0.7 | 1.47 |
| AD | 30[g] | 1.90 | 9.6 | | NS[h] | | |
| Kromasil | 5[i] | 7.93 | 34.8 | 36.2 | 1.04 | <0.3 | 1.00 |
| Kromasil | 10[i] | 3.18 | 16.3 | | NS | | |

[a] Percentage of 2-propanol doped with 1% of DEA in *n*-hexane at a flow rate of 1 mL/min, unless otherwise specified, $t_0$=3.4 min (OD), 3.3 min (AD).
[b] Capacity factor of the first eluted enantiomer.
[c] Integrated areas ratio of the chromatographic peaks.
[d] Experimental conditions used for semipreparative isolation.
[e] Shoulder in the descending edge of the peak.
[f] Flow rate 0.7 mL/min, $t_0$=4.9 min.
[g] Undoped 2-propanol.
[h] Not separated.
[i] Percentage of 2-propanol doped with 0.2% AcOH and 1% DEA in *n*-hexane.

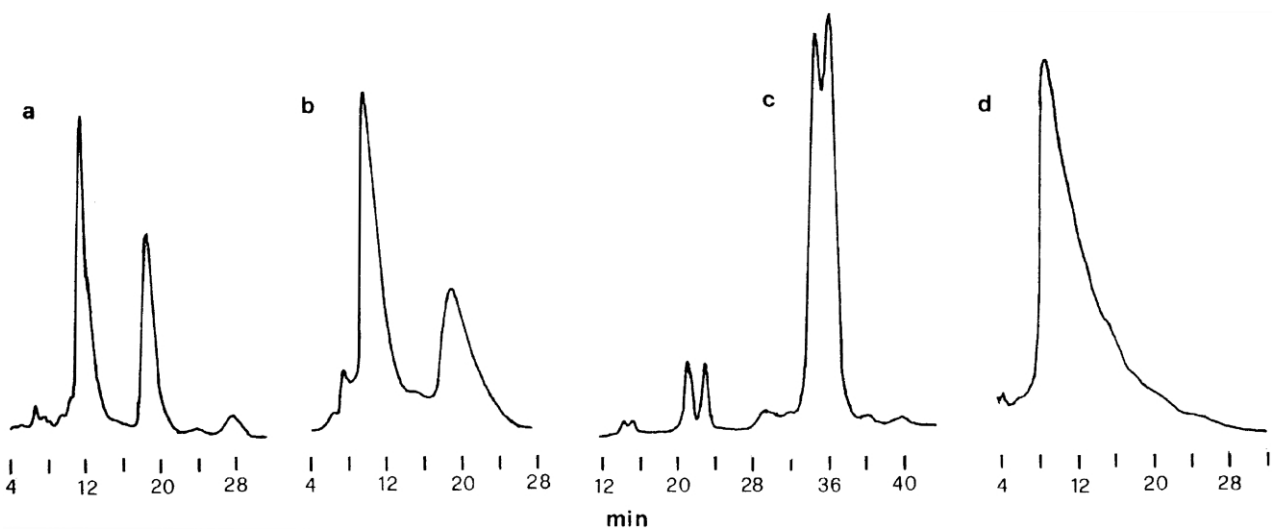



**Figure 3.** Typical HPLC separation of tangutorine, as a function of CSP and mobile phase composition. Conditions: Chiralcel OD (a), Chiralpak AD (b), mobile phase *n*-hexane/2-propanol doped with 1% of DEA, 80:20 at 1 mL/min in both cases. Kromasil CHI-DMB, mobile phase *n*-hexane–2-propanol doped with 0.2% AcOH and 1% DEA, 95:5 at 0.7 mL/min (c). Chiralpak AD, mobile phase *n*-hexane–2-propanol 70:30 at 1 mL/min (d).

Table 1 also shows that a very different CSP (Kromasil CHI-DMB), based on a $C_2$ tartardiamide-containing synthetic polymer,[10] gives poor enantioselectivity ($\alpha$=1.04) using very low polar mobile phase composition.

However, Figure 3(c) shows, besides two major peaks at 34.8 and 36.2 min with a very poor $R_s$, two other minor pairs of peaks in the 14–16 and 22–26 min regions of elution. These can be due to the enantiomeric pairs of other epimers obtained in the synthesis of tangutorine.

Based on the chromatographic results in Table 1, we resorted to the experimental conditions in line 1 to perform the isolation of the enantiomers of tangutorine. This was accomplished by repeated 50 μL injections (0.1–0.2 mg) of racemic tangutorine (15 mg) in ethanol and collection of the eluates corresponding to the two major chromatographic peaks to obtain 1.3 mg of each compound. However, some 'peak shaving' was necessary to avoid to collect the impurity present as a shoulder in the descending edge of the first peak, as shown in Figure 3(a). The CD spectra of both compounds were measured and they were the mirror image of each other, as shown in Figure 4, indicating their enantiomeric nature. Analytical HPLC reruns of the eluates indicated an enantiomeric excess (ee) of 100% for both peaks. However, the first enantiomer shows in the chiral HPLC trace 4.6% of other impurities eluting before the major compound. This can explain the slight difference in the molar ellipticity values of the CD spectra. Specific rotation $[\alpha]_D^{22}=-55.0$ ($c$ 0.1, EtOH) was measured for the first-eluted sample of tangutorine, while the second afforded an experimental $[\alpha]_D^{22}=+40.6$ ($c$ 0.1, EtOH).

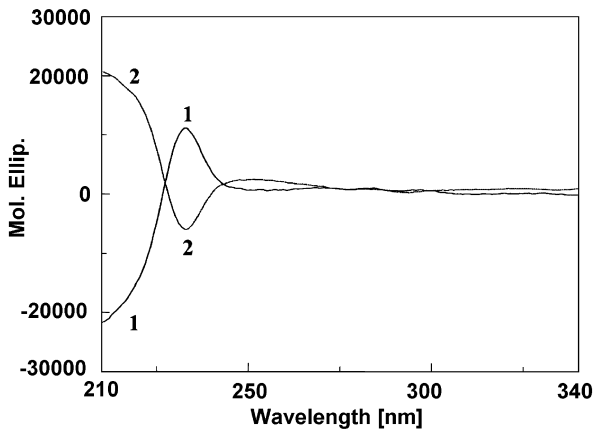



**Figure 4.** CD spectra (ethanol, 22°C) of the enantiomers of tangutorine obtained from the first (1) and the second (2) HPLC eluted peaks.

The similarity in the CD spectra of the enantiomers of tangutorine and vindeburnol[11] is interesting. This can be ascribed to the presence of the same indole chromophore in both compounds and the absence of other UV-absorbing conjugated groups.

## 3. Conclusion

The first total synthesis of racemic tangutorine was accomplished. Even though the yield of sodium borohydride reduction and dehydration was low due to the stability of the vinylogous amide and the number of isomers formed, the yields of all the other reaction steps were very high. The separation of the enantiomers of tangutorine was successfully performed. The CD spectra of both compounds were measured.

## 4. Experimental

### 4.1. HPLC measurements

The HPLC system consisted of a Varian 5060 liquid chromatograph with Valco sample loops, a Jasco Uvidec-III UV spectrophotometer operating at 280 nm, and a Varian Data Jet 4400 integrator or Houston Omniscribe recorder for fraction collecting. The polysaccharide derived columns (250 mm×4.6 mm) were Chiralcel OD (cellulose tris-3,5-dimethylphenylcarbamate) and Chiralpak AD (amylose tris-3,5-dimethylphenylcarbamate) both coated on 10 μ silica gel from Daicel (Tokyo, Japan). The network polymeric column (250 mm×4.6 mm) was Kromasil CHI-DMB (2*R*,3*R*-*N*,*N*′-diallyl-L-tartardiamide based) from EKA Nobel AB (Bohus, Sweden). Column void volume ($t_0$) was measured by injection of tri-*tert*-butylbenzene as a nonretained sample.[12] Resolution ($R_s$) was evaluated according to $R_s=2(t_2-t_1)/(w_1+w_2)$, i.e. the peak separation divided by the mean value of the baseline widths. Retention times ($t$) were mean values of two replicate determinations. Other HPLC chromatographic parameters were those typically employed.[13] Experiments were performed at ambient temperature. CD spectra were recorded on a Jasco 810 spectropolarimeter using a 1-mm cell and optical rotations were measured using a 10-cm microcell.

### 4.2. General methods

Infrared spectra were recorded on a Perkin–Elmer Spectrum One FT-IR. Melting points were determined with a Fisher–Johns melting point apparatus. NMR spectra were recorded on a Bruker AV-400 spectrometer. Chemical shifts ($\delta$) are reported in ppm relative to TMS ($^1$H NMR; $\delta_H$=0.00 ppm) and $CDCl_3$ ($^{13}$C NMR; $\delta_C$=77.000 ppm) if not otherwise stated. Signal assignments are based on standard APT, DEPT, HSQC, HMQC and $^1$H–$^1$H COSY experiments. Abbreviations s, d, t, m, def and br are used to designate singlet, doublet, triplet, multiplet, deformed and broad, respectively. Mass spectra (EI and HRMS, 70 eV, $m/z$) were obtained on a Jeol DX 303/DA 5000 instrument. Elementary analyses were carried out on a Perkin–Elmer 2400 CHN analyzer. Compounds were purified by column chromatography using Merck Kieselgel 60 (230–400 mesh).

**4.2.1. 3-Aminocyclohex-2-enone 2.** 1,3-Cyclohexanedione (5.61 g, 50 mmol) was added to a mixture of ammonium acetate (3.85 g, 50 mmol) in dry toluene (100 mL). The mixture was heated for 5 h under reflux using a Dean–Stark water separator. The red oily layer formed was separated and recrystallized with ethyl acetate to give the title compound (5.00 g, 90%) as yellow crystals, mp 133°C (ethyl acetate, lit.[7] 133–134°C). CHN-anal. calcd for $C_6H_9NO$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.60;

H, 8.13; N, 12.56; MS (EI): *m/z* 111 ($M^+$), 83 (100%), 55; IR, $\nu/cm^{-1}$: 3320 ($NH_2$), 1670 (C=O); NMR $\delta_H$ (400 MHz; DMSO-$d_6$): 6.70 (2H, br s, $NH_2$), 4.91 (1H, s, 2-H), 2.25 (2H, t, *J*=6 Hz, 6-H), 2.01 (2H, t, *J*=6 Hz, 4-H), 1.78 (2H, quintet, *J*=6 Hz, 5-H); NMR $\delta_C$ (100 MHz; DMSO-$d_6$): 194.3 (C=O), 167.0 (C-3), 97.5 (C-2), 35.9 (C-6), 27.9 (C-4), 21.5 (C-5).

**4.2.2. 7,8-Dihydroquinoline-5(6*H*)-one 3.** A solution of 1,1,3,3-tetraethoxylpropane (10 mL, 40 mmol), 3-amino-cyclohex-2-enone **2** (4.6 g, 40 mmol) and a catalytical amount of *p*-toluenesulfonic acid hydrate in DMF (17 mL) was heated under reflux for 18 h. The solvent was distilled in vacuo, the residue neutralized with $NaHCO_3$, extracted with $CH_2Cl_2$ and dried ($Na_2SO_4$). Column chromatography (silica gel, 2% MeOH in $CH_2Cl_2$) gave the title compound (2.06 g, 35%) as light yellow oil. HRMS calcd for $C_9H_9NO$: *m/z* 147.0684. Found: *m/z* 147.0610; MS (EI): *m/z* 147 ($M^+$), 119 (100%), 91; IR, $\nu/cm^{-1}$: 1690 (C=O); NMR $\delta_H$ (400 MHz): 8.68 (1H, dd, $J_{2,4}$=2 Hz, $J_{2,3}$=5 Hz, 2-H), 8.28 (1H, dd, $J_{4,2}$=2 Hz, $J_{4,3}$=8 Hz, 4-H), 7.29 (1H, dd, $J_{3,2}$=5 Hz, $J_{3,4}$=8 Hz, 3-H), 3.17 (2H, t, *J*=6.5 Hz, 6-H), 2.71 (2H, t, *J*=6.5 Hz, 8-H), 2.22 (1H, quintet, *J*=6.5 Hz, 7-H); NMR $\delta_C$ (100 MHz): 197.8 (C=O), 163.6 (C-8a), 153.5 (C-2), 134.9 (C-4), 128.1 (C-4a), 122.2 (C-3), 38.5 (C-6), 32.5 (C-8), 21.8 (C-7).

**4.2.3. 5-Oxo-5,6,7,8-tetrahydroquinoline-6-carboxylic acid methyl ester 4.** 7,8-Dihydroquinoline-5(6*H*)-one **3** (1.76 g, 12 mmol) was added to a stirred suspension of sodium hydride (1.4 equiv. washed with hexane) in dimethyl carbonate (10 mL). A few drops of dry methanol were added to initiate the reaction. The reaction mixture turned lilac and was refluxed for 5 h. It was allowed to cool to room temperature and neutralized with 2N HCl. The mixture was extracted with $CH_2Cl_2$, dried ($Na_2SO_4$) and crystallized to yield a pale yellow crystalline solid (2.21 g, 90%), mp 67°C (hexane, enol). CHN-anal. calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.41; H, 5.32; N, 6.76; MS (EI): *m/z* 205 ($M^+$), 190, 173, 146, 145, 117 (100%), 91; IR, $\nu/cm^{-1}$: 3280 (OH, enol), 1740 ($CO_2CH_3$, keto), 1650 ($CO_2CH_3$, enol), 1620 (C=O, keto); NMR $\delta_H$ (400 MHz): 12.30 (1H, s, OH, enol), 8.71 (1H, dd, $J_{2,4}$=2 Hz, $J_{2,3}$=5 Hz, 2-H, keto), 8.49 (1H, dd, $J_{2,4}$=2 Hz, $J_{2,3}$=5 Hz, 2-H, enol), 8.30 (1H, dd, $J_{4,2}$=2 Hz, $J_{4,3}$=8 Hz, 4-H, keto), 8.03 (1H, dd, $J_{4,2}$=2 Hz, $J_{4,3}$=7.5 Hz, 4-H, enol), 7.32 (1H, dd, $J_{3,2}$=5 Hz, $J_{3,4}$=8 Hz, 3-H, keto), 7.23 (1H, dd, $J_{3,2}$=5 Hz, $J_{3,4}$=7.5 Hz, 3-H, enol), 3.85 (3H, s, $-OCH_3$, enol), 3.79 (3H, s, $-OCH_3$, keto), 3.67 (1H, dd, $J_{6ax,7eq}$=5 Hz, $J_{6ax,7ax}$=10 Hz, $6_{ax}$-H, keto), 3.28 (1H, ddd $J_{8eq,7ax}$=5 Hz, $J_{8eq,7eq}$=6 Hz, $J_{8eq,8ax}$=18 Hz, $8_{eq}$-H, keto), 3.17 (1H, ddd, $J_{8ax,7eq}$=5 Hz, $J_{8ax,7ax}$=9 Hz, $J_{8ax,8eq}$=18 Hz, $8_{ax}$-H, keto), 3.03 (2H, t, *J*=8 Hz, 8-H, enol), 2.69 (2H, t, *J*=8 Hz, 7-H, enol) 2.57 (1H, dddd, $J_{7ax,8eq}$=5 Hz, $J_{7ax,8ax}$=9 Hz, $J_{7ax,6ax}$=10 Hz, $J_{7ax,7eq}$=14 Hz, $7_{ax}$-H, keto), 2.43 (1H, dddd, $J_{7eq-6ax}$=5 Hz, $J_{7eq-8ax}$=5 Hz, $J_{7eq-8eq}$=6 Hz, $J_{7eq-7ax}$=14 Hz, $7_{eq}$-H, keto); NMR $\delta_C$ (100 MHz): 192.8 (C=O, keto), 172.7 ($-CO_2CH_3$, enol), 170.0 ($-CO_2CH_3$, keto), 163.3 (C-8b, enol), 162.8 (C-8b, keto), 159.4 (C-5, enol), 154.0 (C-2, keto), 150.4 (C-2, enol), 135.6 (C-6, enol), 135.6 (C-4, keto), 131.5 (C-4, enol), 122.4 (C-3, keto), 121.8 (C-3, enol), 97.5 (C-4b), 53.8 (C-6, keto), 52.5 ($-CO_2CH_3$, keto), 51.8 ($-CO_2CH_3$, enol), 30.5 (C-8, keto), 30.4 (C-8, enol), 25.0 (C-7, keto), 19.9 (C-7, enol).

**4.2.4. 1′-[2′-(3′-Indolyl)-ethyl]-6-methoxycarbonyl-5-oxo-5,6,7,8-tetrahydroquinolinium bromide 5.** Ester **4** (820 mg, 4 mmol) was alkylated with tryptophyl bromide (895 mg, 4 mmol) at 100°C for 2 h. The crude product was washed several times with $CH_2Cl_2$ to give salt **5** (1.54 g, 90%) as yellow powder (enol). IR, $\nu/cm^{-1}$: 3170 (NH), 1660 ($CO_2CH_3$); NMR $\delta_H$ (400 MHz; $CD_3OD$): 8.60 (1H, d, $J_{4,3}$=8 Hz, 4-H), 8.58 (1H, d, $J_{2,3}$=6.5 Hz, 2-H), 7.82 (1H, dd, $J_{3,2}$=6.5 Hz, $J_{3,4}$=8 Hz, 3-H), 7.35 (1H, d, *J*=8 Hz, 7′-H), 7.26 (1H, d, *J*=8 Hz, 4′-H), 7.10 (1H, t, *J*=8 Hz, 6′-H), 6.98 (1H, s, 2′-H), 6.96 (1H, t, *J*=8 Hz, 5′-H), 4.95 (2H, t, *J*=6 Hz, β-H), 3.84 (3H, s, $-OCH_3$), 3.46 (2H, t, *J*=6 Hz, α-H), 3.08 (2H, t, $J_{8,7}$=8 Hz, 8-H), 2.29 (2H, t, *J*=8 Hz, 7-H); NMR $\delta_C$ (100 MHz; $CD_3OD$): 172.6 ($-CO_2CH_3$), 158.9 (C-8a), 157.9 (C-5), 146.8 (C-2), 139.8 (C-4), 138.1 (C-6), 132.2 (C-7a′), 128.2 (C-3a′), 126.6 (C-3), 125.2 (C-2′), 123.1 (C-6′), 120.6 (C-5′), 118.2 (C-4′), 112.8 (C-7′), 109.4 (C-3′), 101.2 (C-4a), 60.2 (C-β), 53.0 ($-CO_2CH_3$), 27.3 (C-α), 25.9 (C-8), 19.3 (C-7).

**4.2.5. 1′-[2′-(3′-Indolyl)-ethyl]5-oxo-1,4,5,6,7,8-hexahydroquinoline-6-carboxylic acid methyl ester 6.** Sodium dithionite (750 mg, 4.3 mmol, 6.2 equiv.) was added in small portions during 20 minutes to the solution of bromide salt **5** (300 mg, 0.7 mmol) and $NaHCO_3$ (940 mg, 11.2 mmol, 16 equiv.) in 50 mL aqueous MeOH (1:2; $H_2O$–MeOH). The mixture was stirred for 18 h at room temperature and evaporated under vacuum. The residue was extracted several times with $CH_2Cl_2$, dried over $Na_2SO_4$ and evaporated under vacuum to give nearly pure product **6** (235 mg, 95%) as yellow amorphous solid. To avoid dissociation, the product was not purified. HRMS calcd for $C_{21}H_{22}N_2O_3$: *m/z* 350.1630. Found: *m/z* 350.1600; MS (EI): *m/z* 350 ($M^+$), 319, 291, 220, 144, 130 (100%); IR, $\nu/cm^{-1}$: 3270 (NH), 1735 ($CO_2CH_3$), 1610 (C=O); NMR $\delta_H$ (400 MHz): 8.31 (1H, s, NH), 7.57 (1H, d, *J*=8 Hz, 4′-H), 7.37 (1H, d, *J*=8 Hz, 7′-H), 7.20 (1H, t, *J*=8 Hz, 6′-H), 7.13 (1H, t, *J*=8 Hz, 5′-H), 7.03 (1H, d, *J*=2.5 Hz, 2′-H), 5.78 (1H, br d, $J_{2,3}$=8 Hz, 2-H), 5.02 (1H, ddd, $J_{3,4}$=4, 4 Hz, $J_{3,2}$=8 Hz, 3-H), 3.70 (3H, s, $-OCH_3$), 3.53 (2H, t, *J*=7 Hz, β-H), 3.19 (1H, dd, $J_{6ax,7eq}$=5 Hz, $J_{6ax,7ax}$=8.5 Hz, $6_{ax}$-H), 3.08 (2H, def d, 4-H), 3.02 (2H, t, *J*=7 Hz, α-H), 2.2–2.3 (1H, m, $8_{eq}$-H), 1.9–2.1 (2H, m, $7_{ax}$-H, $8_{ax}$-H), 1.75–1.85 (1H, m, $7_{eq}$-H); NMR $\delta_C$ (100 MHz): 189.7 (C=O), 171.5 ($-CO_2CH_3$), 155.6 (C-8a), 136.3 (C-7a′), 128.9 (C-2), 127.0 (C-3a′), 122.6 (C-2′), 122.3 (C-6′), 119.7 (C-5′), 118.1 (C-4′), 111.6 (C-3′), 111.4 (C-7′), 107.8 (C-3), 104.7 (C-4a), 52.0 ($-CO_2CH_3$), 51.2 (C-6), 50.2 (C-β), 25.7 (C-α), 23.7 (C-7), 23.6 (C-8), 21.5 (C-4).

**4.2.6. Compound 7.** Ester **6** (690 mg, 2.0 mmol) was dissolved in HCl/MeOH (240 mL) and stirred for 65 h. The solvent was evaporated and the residue was neutralized with aq. $NaHCO_3$ and extracted with $CH_2Cl_2$. Purification (silica gel, 5% MeOH–$CH_2Cl_2$) gave two isomers (585 mg, 85%) of the title product as amorphous yellow solid. The overall yield of two reactions (**5→7**) was 80%. HRMS calcd for $C_{21}H_{22}N_2O_3$: *m/z* 350.1630. Found: *m/z* 350.1669; MS (EI): *m/z* 350 (M+, 100%), 291, 169, 156; IR, $\nu/cm^{-1}$: 3260

(NH), 1735 ($CO_2CH_3$, *trans*), 1730 ($CO_2CH_3$, *cis*), 1600 (C=O); NMR $\delta_H$ (400 MHz): 8.84 (1H, s, NH, *trans*), 8.83 (1H, s, NH, *cis*), 7.47 (1H, d, $J$=7.5 Hz, 9-H), 7.36 (1H, d, $J$=7.5 Hz, 12-H), 7.16 (1H, t, $J$=7.5 Hz, 11-H), 7.10 (1H, t, $J$=7.5 Hz, 10-H), 4.59 (1H, br d, $J$=10 Hz, 3-H, *trans*), 4.54 (1H, br d, $J$=10 Hz, 3-H, *cis*), 4.19 (1H, ddd, $J_{5ax,6eq}$=4 Hz, $J_{5ax,6ax}$=12 Hz, $J_{5ax,5eq}$=13 Hz, $5_{ax}$-H), 3.69 (3H, s, $-OCH_3$), 3.36 (1H, dd, $J_{16ax,17eq}$=4.5 Hz, $J_{16ax,17ax}$=11 Hz, $16_{ax}$-H *cis*), 3.36 (1H, dd, $J_{16eq,17eq}$=5 Hz, $J_{16eq,17ax}$=6 Hz, $16_{eq}$-H, *trans*), 3.2–3.3 (1H, m, $5_{eq}$-H), 2.85–2.95 (2H, m, $6_{ax}$-H, $6_{eq}$-H), 2.75–2.85 (1H, m, 18-H), 2.65–2.75 (1H, m, 15-H), 2.5–2.8 (1H, m, 18-H), 2.45–2.50 (1H, m, 14-H), 2.35–2.45 (1H, m, 17-H), 2.25–2.35 (1H, m, 15-H), 2.15–2.25 (1H, m, 17-H), 1.7–1.8 (1H, m, 14-H); NMR $\delta_C$ (100 MHz): 188.5 (C=O, *cis*), 187.8 (C=O, *trans*), 172.2 ($-CO_2CH_3$, *cis*), 171.8 ($-CO_2CH_3$, *trans*), 159.8 (C-19, *trans*), 159.3 (C-19, *cis*), 136.3 (C-13), 133.7 (C-2, *cis*), 133.6 (C-2, *trans*), 126.6 (C-8), 121.9 (C-11), 119.6 (C-10), 118.0 (C-9, *cis*), 117.9 (C-9, *trans*), 111.3 (C-12), 108.1 (C-7, *cis*), 108.0 (C-7, *trans*), 106.6 (C-20, *trans*), 106.4 (C-20, *cis*), 54.6 (C-3), 52.2 ($-CO_2CH_3$, *trans*), 52.1 ($-CO_2CH_3$, *cis*), 51.4 (C-16, *cis*), 50.2 (C-16, *trans*), 45.3 (C-5, *trans*), 45.0 (C-5, *cis*), 27.6 (C-14, *cis*), 27.5 (C-14, *trans*), 25.9 (C-17, *cis*), 24.8 (C-18, *cis*), 24.7 (C-18, *trans*), 24.5 (C-17, *trans*), 22.2 (C-6), 19.0 (C-15, *cis*), 18.8 (C-15, *trans*).

**4.2.7. Compound 9.** The isomeric mixture of product **7** (780 mg, 2.2 mmol) was dissolved in glacial acetic acid (160 mL) and $NaBH_4$ (7.6 g, 0.2 mol, 90 equiv.) was added in small portions (0°C). The mixture was stirred for 16 h at room temperature. After neutralization with $NaHCO_3$, the solution was extracted with $CH_2Cl_2$. The $CH_2Cl_2$ extracts were dried ($Na_2SO_4$) and evaporated.

To the solution of the crude reduction product **8** (890 mg) in $CH_2Cl_2$ (35 mL) at 0°C, $Et_3N$ (12 mL) and MsCl (1.7 mL, 21 mmol, 10 equiv.) were added. After stirring for 1 h at 0°C, DBU (6.5 mL, 43 mmol, 20 equiv.) was added. The solution was heated at 100°C for 2 h, diluted with saturated $NaHCO_3$ solution and extracted with $CH_2Cl_2$. The $CH_2Cl_2$ extracts were dried ($Na_2SO_4$) and evaporated. Purification (silica gel, 7% MeOH in $CH_2Cl_2$) gave 45 mg (total yield 6%) of compound **9** as amorphous yellow solid. HRMS calcd for $C_{21}H_{24}N_2O_2$: $m/z$ 336.1838. Found: $m/z$ 336.1793; MS (EI): $m/z$ 336 ($M^+$, 100%), 277, 170, 169, 156; IR, $\nu$/cm$^{-1}$: 3270 (NH), 1710 ($CO_2CH_3$); NMR $\delta_H$ (400 MHz): 7.73 (1H, br s, NH), 7.47 (1H, d, $J$=7.5 Hz, 9-H), 7.31 (1H, d, $J$=7.5 Hz, 12-H), 7.13 (1H, t, $J$=7.5 Hz, 11-H), 7.08 (1H, t, $J$=7.5 Hz, 10-H), 6.68 (1H, br s, 21-H), 3.75 (3H, s, $-OCH_3$), 3.6–3.65 (1H, m, $5_{ax}$-H), 3.50 (1H, br d, $J$=10 Hz, 3-H), 2.85–3.0 (2H, m, $6_{eq}$-H, $6_{ax}$-H), 2.75–2.85 (1H, br d, $J$=15 Hz, $17_{eq}$-H), 2.6–2.65 (1H, br d, $J$=15 Hz, $5_{eq}$-H), 2.4–2.5 (1H, m, 18-H), 2.25–2.45 (1H, m, 20-H), 2.2–2.3 (1H, m, $14_{ax}$-H), 2.15–2.25 (1H, m, 19-H), 2.1–2.2 (1H, m, $17_{ax}$-H), 1.80 (1H, dddd, $J_{15ax,14eq}$=3.5 Hz, $J_{15ax,14ax}$=10 Hz, $J_{15ax,20}$=12 Hz, $J_{15ax,15eq}$=13 Hz, $15_{ax}$-H), 1.6–1.76 (1H, m, $14_{eq}$-H), 1.55–1.6 (1H, m, 18-H), 1.4–1.5 (1H, br d, $J_{15eq,15ax}$=13 Hz, $15_{eq}$-H); NMR $\delta_C$ (100 MHz): 167.4 ($-CO_2CH_3$), 141.4 (C-21), 136.2 (C-13), 133.4 (C-2), 129.2 (C-16), 126.9 (C-8), 121.5 (C-11), 119.3 (C-10), 118.1 (C-9), 111.0 (C-12), 108.1 (C-7), 64.0 (C-19), 60.3 (C-3), 51.7 ($-CO_2CH_3$), 45.0 (C-5), 49.4 (C-20), 29.8 (C-15), 29.6 (C-14), 25.4 (C-18), 24.8 (C-17), 22.1 (C-6).

**4.2.8. (±)-Tangutorine 1.** The dehydration product **9** (45 mg, 0.13 mmol) in THF (6 mL) was added to a solution of $LiAlH_4$ (15 mg, 0.4 mmol, 3 equiv.) in THF (3 mL) at 0°C. The mixture was stirred for 4 h at room temperature. After addition of water, the residue was extracted with $CH_2Cl_2$. The $CH_2Cl_2$ extracts were dried and evaporated. Purification (silica gel, 5% MeOH in $CH_2Cl_2$) gave (±) tangutorine **1** in 90% yield. The spectral data (IR, MS, HRMS, $^1$H and $^{13}$C NMR) of tangutorine **1** obtained correspond to those in the original paper of Duan et al.[1]

**4.2.9. 5-Hydroxy-5,6,7,8-tetrahydroquinoline-6-carboxylic acid methyl ester 10.** To the solution of ester **4** (200 mg, 0.98 mmol) in methanol (6.5 mL), sodium borohydride (37 mg, 1 equiv.) was added in two portions (−5°C). The mixture was stirred for 15 min, water (5 mL) was added, methanol evaporated and the residue extracted with $CH_2Cl_2$. The $CH_2Cl_2$ extracts were dried and evaporated. Purification (silica gel, 3% MeOH in $CH_2Cl_2$) gave 163 mg (80%) of compound **10** as white crystals, mp 146–147°C (hexane–chloroform). CHN-anal. calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.25; H, 6.23; N, 6.67; MS (EI): $m/z$ 207 ($M^+$), 189, 130 (100%), 93.

Compound **10a** (major; $5_{eq}$-H/$6_{ax}$-H): IR, $\nu$/cm$^{-1}$: 3350 (OH), 1735 ($CO_2CH_3$); NMR $\delta_H$ (400 MHz): 8.45 (1H, d, $J$=5 Hz, 2-H), 7.74 (1H, d, $J$=7.5 Hz, 4-H), 7.16 (1H, dd, $J_{3,2}$=5 Hz, $J_{3,4}$=7.5 Hz, 3-H), 5.04 (1H, d, $J_{5,6}$=3 Hz, 5-H), 3.78 (3H, s, $-OCH_3$), 3.07 (1H, ddd, $J$=4.5, 5.5 Hz, $J_{8eq,8ax}$=17.5 Hz, $8_{eq}$-H), 2.9–3.0 (1H, m, $8_{ax}$-H), 2.88 (1H, ddd, $J_{6,5}$=3 Hz, $J_{6,7eq}$=3.5 Hz, $J_{6,7ax}$=11 Hz, 6-H), 2.3–2.4 (1H, m, $7_{ax}$-H), 2.15–2.2 (1H, m, $7_{eq}$-H); NMR $\delta_C$ (100 MHz): 174.5 ($-CO_2CH_3$), 156.2 (C-8a), 149.1 (C-2), 137.5 (C-4), 132.2 (C-4a), 121.6 (C-3), 67.5 (C-5), 52.1 ($-CO_2CH_3$), 44.8 (C-6), 31.1 (C-8), 20.1 (C-7).

Compound **10b** (minor; $5_{ax}$-H/$6_{ax}$-H): IR, $\nu$/cm$^{-1}$: 3350 (OH), 1735 ($CO_2CH_3$); NMR $\delta_H$ (400 MHz): 8.41 (1H, d, $J$=5 Hz, 2-H), 7.93 (1H, d, $J$=7.5 Hz, 4-H), 7.16 (1H, dd, $J_{3,2}$=5 Hz, $J_{3,4}$=7.5 Hz, 3-H), 5.06 (1H, d, $J_{5,6}$=12 Hz, 5-H), 3.79 (3H, s, $-OCH_3$), 3.04 (1H, ddd, $J$=4.5, 5.5 Hz, $J_{8eq,8ax}$=17.5 Hz, $8_{eq}$-H), 2.9–3.0 (1H, m, $8_{ax}$-H), 2.73 (1H, ddd, $J_{6,7eq}$=3 Hz, $J_{6,7ax}$=9.5 Hz, $J_{6,5}$=12 Hz, 6-H), 2.15–2.2 (1H, m, $7_{ax}$-H), 1.95–2.0 (1H, m, $7_{eq}$-H); NMR $\delta_C$ (100 MHz): 174.8 ($-CO_2CH_3$), 156.2 (C-8a), 148.3 (C-2), 135.3 (C-4), 132.2 (C-4a), 121.6 (C-3), 69.0 (C-5), 52.1 ($-CO_2CH_3$), 48.0 (C-6), 31.3 (C-8), 23.5 (C-7).

**4.2.10. 7,8-Dihydroquinoline-6-carboxylic acid methyl ester 11.** Alcohol **10** (245 mg, 1.2 mmol) was dissolved in $CH_2Cl_2$ (20 mL) and triethylamine (6 mL) and mesyl chloride (0.9 mL, 12 mmol, 10 equiv.) was added on ice bath. The mixture was stirred for 16 h at room temperature, diluted with saturated $NaHCO_3$ solution, extracted with $CH_2Cl_2$ and washed twice with brine. Purification (silica gel, 2% MeOH in $CH_2Cl_2$) gave 130 mg (60%) of amorphic compound **11**. HRMS calcd for $C_{11}H_{11}NO_2$: $m/z$ 189.0790. Found: $m/z$ 189.0781; MS (EI): $m/z$ 189 ($M^+$), 130 (100%); IR, $\nu$/cm$^{-1}$: 1710 ($CO_2CH_3$); NMR $\delta_H$ (400 MHz): 8.40

(1H, d, $J$=5 Hz, 2-H), 7.46 (1H, s, 5-H), 7.44 (1H, d, $J$=7.5 Hz, 4-H), 7.13 (1H, dd, $J_{3,2}$=5 Hz, $J_{3,4}$=7.5 Hz, 3-H), 3.82 (3H, s, $-OCH_3$), 3.06 (2H, t-like, $J$=8.5 Hz, 8-H), 2.76 (2H, t-like, $J$=8.5 Hz, 7-H); NMR $\delta_C$ (100 MHz): 167.2 ($-CO_2CH_3$), 157.8 (C-8a), 149.3 (C-2), 134.7 (C-4, C-5), 130.4 (C-6), 127.7 (C-4a), 52.0 ($-CO_2CH_3$), 30.2 (C-8), 22.4 (C-7).

## Acknowledgements

S. Caccamese thanks the MIUR, Rome (Ministero Istruzione Università e Ricerca) for financial support (PRIN 2001-2002).

## References

1. Duan, J.-A.; Williams, I. D.; Che, C.-T.; Zhou, R.-H.; Zhao, S.-X. *Tetrahedron Lett.* **1999**, *40*, 2593–2596.
2. The originally reported H-3α stereochemistry[1] should be H-3β, as demonstrated in Refs. 3,4.
3. Berner, M.; Tolvanen, A.; Jokela, R. *Tetrahedron Lett.* **1999**, *40*, 7119–7122.
4. Putkonen, T.; Tolvanen, A.; Jokela, R. *Tetrahedron Lett.* **2001**, *42*, 6593–6594.
5. Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508–510.
6. Päiviö, E.; Berner, M.; Tolvanen, A.; Jokela, R. *Heterocycles* **2000**, *53*, 2241–2246. Lounasmaa, M.; Jokela, R. *Tetrahedron* **1990**, *46*, 615–622.
7. Huang, Y.; Hartmann, R. W. *Synth. Commun.* **1998**, *28*, 1197–1200.
8. Christie, B. D.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1239–1246.
9. Okamoto, Y.; Yashima, E. *Angew. Chem. Int. Ed.* **1998**, *37*, 1020–1043.
10. Allenmark, S. G.; Andersson, S.; Möller, P.; Sanchez, D. *Chirality* **1995**, *7*, 248–256.
11. Caccamese, S.; Principato, G.; Jokela, R.; Tolvanen, A.; Din Belle, D. *Chirality* **2001**, *13*, 691–693.
12. Koller, H.; Rimböck, K.-E.; Mannschreck, A. *J. Chromatogr.* **1983**, *282*, 89–94.
13. Allenmark, S. *Chromatographic Enantioseparation: Methods and Applications*; 2nd ed. Ellis Horwood: Chichester, 1991; p 82.