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Stereocontrolled reduction of an oxazepinohexahydroindolo[2,3-*a*]quinolizine derivative: asymmetric total synthesis of (+)-tacamonine

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Abstract—Efficient, stereocontrolled total synthesis of the title compound is described, starting from enantiopure intermediates. A key step was the diastereoselective catalytic hydrogenation of a pentacyclic oxazepinohexahydroindolo[2,3-*a*]quinolizine derivative.

Tacamonine (**1**) is an indole alkaloid isolated[1] in 1984 from the constituents of *Tabernaemontana eglandulosa* Stapf, a plant which is widely distributed in Central Africa. The structural similarity between **1** and *Hunteria* alkaloids (e.g. (–)-eburnamonine (**2**)), which possess valuable vasodilator and hypotensive activities, promotes several efforts towards the synthesis of **1**.[2,3] The attachment of the ethyl group away from the D/E ring junction of the pentacyclic framework engenders an additional stereocenter, setting out three methine hydrogen atoms 3βH, 14βH and 20βH *cis* related as a point significant in pursuing a synthetic study of tacamonine (Fig. 1).

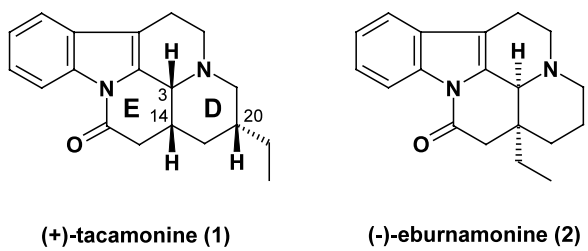
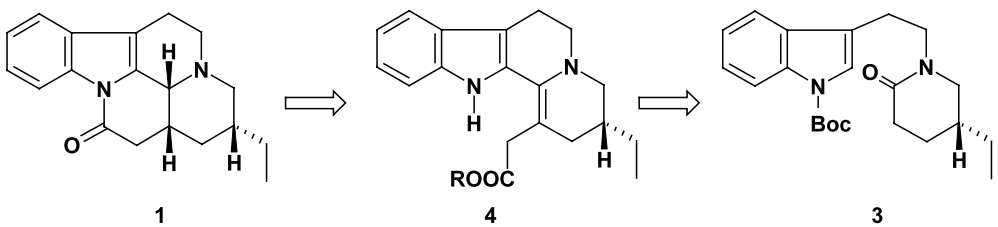


Figure 1.

Among the reported syntheses, an asymmetric approach[4] to **1** featured free radical cyclization to form the D ring, whereas another synthesis[5] relied on the development of the D ring component from a substituted pyridine. Just recently, an original route[6] was designed on the basis of symmetric considerations which emphasized the establishment of the relative *cis* configuration at C14 and C20 stereocenters. In a previous work,[7] we reported an efficient lipase-mediated preparation of the possible precursor **3** (Scheme 1), in an optically pure form, starting from asymmetrized 2-substituted propane-1,3-diols. Following this approach, we secured a formal enantioselective entry to tacamonine according to literature precedents,[8] which



Scheme 1.

Keywords: alkaloids; asymmetric synthesis; hydrogenation; diastereoselection.

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describe the conversion of racemic **3** into **1**, via **4**, using standard chemistry.

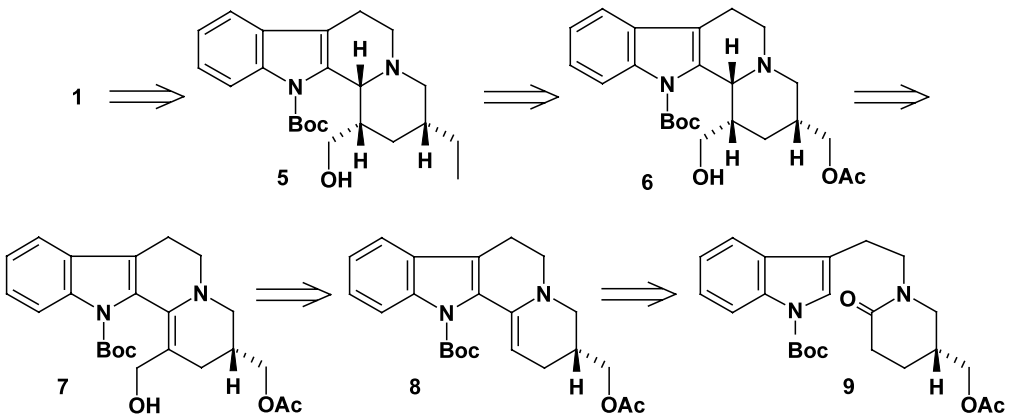
However, in that work, no attempt was made to control the relative configuration of the newly created stereogenic centers at C3 and C14. Moreover, to our knowledge, none of the above-mentioned stereoselective routes to **1** have been able to install efficiently the required *cis* D/E ring junction, avoiding in this way the final step of tedious diastereoisomeric separation. As a consequence, our studies were on going in order to furnish an efficient answer to this challenge. We report here an original approach that allowed us to reach a completely enantio- and diastereoselective synthesis of (+)-tacamonine **1**.

As shown retrosynthetically in Scheme 2, we envisaged the chiral, *all cis*-indoloquinolizidine **5** as a key advanced intermediate, whose conversion into tacamonine should be easily achievable.[9] Our strategy was based on the condition that an efficient stereocontrolled installation of C3 and C14 stereocenters could be accomplished via the catalytic hydrogenation of the chiral enamine **7** to give **6**. Access to **7** was envisioned through Bischler–Napieralsky and C14 hydroxymethylation reactions directly from the appropriate indolylethyl piperidinone **9**, easily preparable in optically pure form, as previously reported by us.[5]

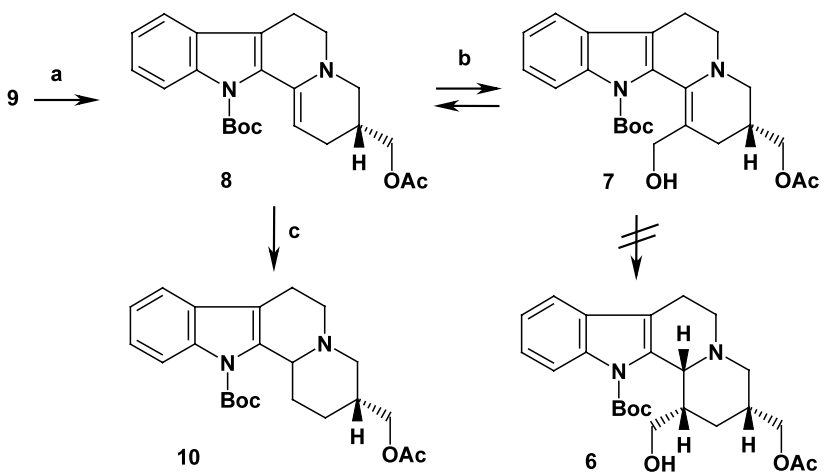
As will be seen, we assume that the stereofacial selectivity of hydrogen attack on enamine **7** would be influenced by the presence of the bulky acetoxymethyl substituent at C20. The required β-face diastereoselectivity would be favoured allowing the set-up of the correct absolute stereochemistry at the C3 and C14 carbon atoms.

With the hydroxymethyl derivative **6** at hand, we would be able to carry out the homologation of the C20 side chain and the construction of ring E, according to a standard reaction sequence, and thus to complete the totally stereoselective synthesis of tacamonine.

Enamine **8** was prepared by treatment of **9** with $POCl_3$ and then further reacted with paraformaldehyde in acetonitrile at room temperature (Scheme 3). The reaction gave cleanly the unstable enamine **7**, which was immediately hydrogenated over a Pt catalyst. Unfortunately, the only isolable product was the indoloquinolizidine **10**, whose formation can be explained by the kinetically favoured reduction of the less hindered



Scheme 2.



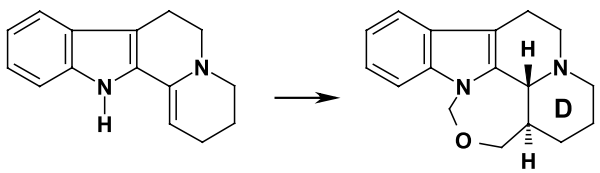
Scheme 3. (a) $POCl_3$, CH_2Cl_2, reflux, 78%; (b) $(CH_2O)_3$, THF, rt; (c) H_2/PtO_2, dioxane, 62%.

trisubstituted enamine double bond of **8**, formed transiently from **7**, by retroaldol condensation.

Looking for the possibility of making compound **7** more stable, discouraging in this way the observed reaction pathway, we attempted to protect the C14-hydroxymethyl group. A variety of classical methods (Ac_2O/Py; MOMCl, Et_3N; TBDMSCl, DIPEA) proved to be unsuccessful.

On the basis of our earlier experience on the chemistry of eburnamine-vincamine indole alkaloids, we were aware that enamines such as **11** (Scheme 4) react with formaldehyde and then sodium borohydride to give pentacyclic compounds (**12**) embodying an oxazepinoindoloquinolizine skeleton,[10,11] which possesses a seven-membered heterocyclic ring joined by a *trans*-junction with ring D.

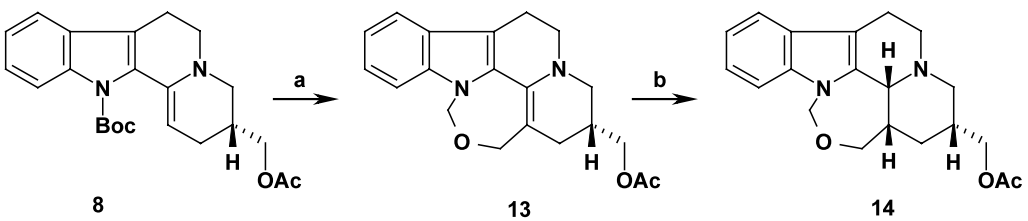
We felt that if we were able to convert **8** into the pentacycle **13**, still containing the C3–C14 double bond, we would obtain an ideal substrate for achieving diastereoselection in the addition of hydrogen to the enamine double bond. Following these ideas, we allowed the *N*-Boc-protected enamine **8** to react with excess aqueous formaldehyde and catalytic formic acid in refluxing acetonitrile. After 1 h, we could isolate the expected compound **13**[12] (Scheme 5) as the unique product. Molecular mechanics calculations suggested a rigid framework for **13**, with a minimum energy conformation in which approach from the concave α-face of the molecule would be severely hindered by the *pseudo*-axial oriented acetoxymethyl group at C20.



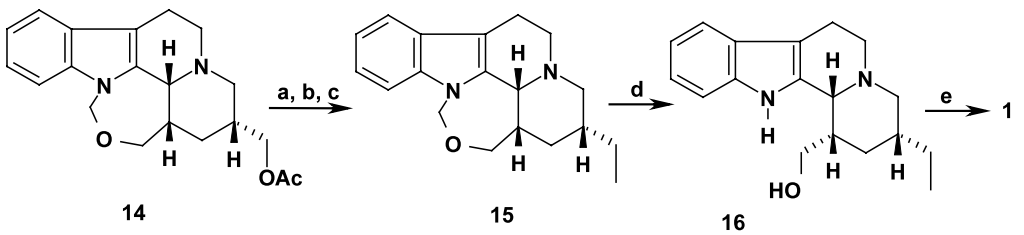
Scheme 4.

Indeed, Pt-catalyzed hydrogenation of **13** afforded **14**[13] in 75% yield and 95% d.e., in which the 3βH, 14βH configuration was set. The assignment of the stereochemistry was performed by comparison of the CD spectrum of **14** with those of pentacyclic tacamane alkaloids.[14] Analysis of NMR spectra (^1H and ^{13}C) allowed the establishment of the diastereoisomeric ratio and confirmed the stereochemistry, by observation of diagnostic NOE contacts between 3βH (δ 4.57) and 14βH (δ 2.25) and between 14βH and 20βH (δ 2.05). Having attained the complete control of absolute configuration at all three stereogenic centers of tacamonine framework, we proceeded to complete our synthetic plan. The homologation of the C20 acetoxymethyl side chain was attained by a three-step sequence involving hydrolysis of acetate, tosylation and displacement of the tosylate with lithium dimethylcuprate (Scheme 6).

Deprotection of **15**[15] with $BF_3{\cdot}Et_2O$, according to *Sundberg* protocol,[16] gave **16**[17] in good yield. At this point, completion of the total enantiosynthesis of **1** was performed according to literature precedents.[9] The hydroxy group of **16** was converted into the corresponding tosylate and then homologated with KCN. Eventually, base treatment with MeONa in MeOH at reflux, followed by acid hydrolysis allowed the closure of the fifth ring to give enantiopure (+)-tacamonine **1**, which was recrystallized from acetone to provide colorless needles {$[\alpha]_D = 122$ ($c = 0.2$, $CHCl_3$), mp 180°C (lit.[1] 180–181°C)}, whose UV, CD, ^1H NMR and MS spectral data were identical in all respects to the reported ones.[1,8]



Scheme 5. (a) $(CH_2O)_3$, HCO_2H, THF, reflux, 90%; (b) H_2/PtO_2, dioxane, 75%.



Scheme 6. (a) NaOH, THF/H_2O, 98%; (b) TsCl, Et_3N, CH_2Cl_2, 76%; (c) Me_2CuLi, Et_2O, −10°C, 72%; (d) Ac_2O, $BF_3{\cdot}Et_2O$, LiBr, rt, 61%; (e) see Ref. 9, 48%.

Acknowledgements

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12. Selected data for **13**: $[\alpha]_D = -7.20$ ($c = 1$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.45 (d, 1H, $J = 8.1$ Hz), 7.20–7.05 (m, 3H), 5.75 and 5.52 (AB system, 2H, $J = 10.0$ Hz), 4.48 (m, 2H), 4.14 (dd, 1H, $J = 11.5$, 5.5 Hz), 4.05 (dd, 1H, $J = 11.5$, 6.2 Hz), 3.22 (br t, 1H, $J = 10.2$), 3.17 (dd, 1H, $J = 10.9$, 5.6 Hz), 3.08 (ddd, 1H, $J = 10.9$, 7.2, 5.0 Hz), 2.94 (m, 2H), 2.82 (dd, 1H, $J = 10.9$, 9.2 Hz), 2.39 (m, 1H), 2.10 (m, 1H), 2.08 (s, 3H), 1.93 (dd, 1H, $J = 16.0$, 9.1 Hz); FAB$^+$MS m/z: 339 [MH$^+$]; EI-HRMS for $C_{20}H_{22}N_2O_3$: calcd 338.1630; found 338.1622.
13. Selected data for **14**: $[\alpha]_D = -5.38$ ($c = 1$, $CHCl_3$); CD (MeOH): λ ($\Delta\varepsilon$) 236 (−5.2), 248 (−1.4), 268 (−2.6); ^1H NMR (300 MHz, $CDCl_3$): δ 7.48 (d, 1H, $J = 8.0$ Hz), 7.27 (d, 1H, $J = 8.0$ Hz), 7.19 (t, 1H, $J = 8.0$ Hz), 7.10 (t, 1H, $J = 8.0$ Hz), 5.93 and 5.01 (AB system, 2H, $J = 10.8$ Hz), 4.57 (br s, 1H), 4.29 (br dd, 1H, $J = 12.9$, 2.9 Hz), 3.93 (br d, 1H, $J = 12.9$ Hz), 3.91 (dd, 1H, $J = 11.0$, 5.8 Hz), 3.74 (dd, 1H, $J = 11.0$, 7.5 Hz), 3.34 (br dd, 1H, $J = 12.8$, 6.6 Hz), 3.23 (ddd, 1H, $J = 12.8$, 11.2, 5.0 Hz), 3.05 (m, 1H), 2.78 (dd, 1H, $J = 11.5$, 3.5 Hz), 2.59 (dd, 1H, $J = 15.8$, 4.5 Hz), 2.45 (t, 1H, $J = 11.5$ Hz), 2.25 (m, 1H), 2.05 (m, 1H), 2.00 (s, 3H), 1.61 (m, 1H), 1.24 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 170.7, 135.1, 133.7, 126.9, 121.7, 119.3, 118.1, 109.9, 108.9, 79.0, 77.9, 66.8, 58.7, 51.2, 47.9, 42.5, 36.4, 27.0, 20.7, 16.4; FAB$^+$MS m/z: 341 [MH$^+$]; EI-HRMS for $C_{20}H_{24}N_2O_3$: calcd 340.1787; found 340.1789. Selected data for 3-*epi*,14-*epi* **14**: CD (MeOH): λ ($\Delta\varepsilon$) 236 (+4.2), 252 (+1.2), 263 (+1.8), 271 (+1.4); ^1H NMR (300 MHz, $CDCl_3$): δ 7.46 (d, 1H, $J = 8.0$ Hz), 7.26 (d, 1H, $J = 8.0$ Hz), 7.18 (t, 1H, $J = 8.0$ Hz), 7.10 (t, 1H, $J = 8.0$ Hz), 5.92 and 5.01 (AB system, 2H, $J = 11.0$ Hz), 4.49 (br s, 1H), 4.37 (dd, 1H, $J = 14.5$, 7.5 Hz), 4.33 (dd, 1H, $J = 14.5$, 7.0 Hz), 4.20 (dd, 1H, $J = 12.8$, 4.0 Hz), 3.90 (dd, 1H, $J = 12.8$, 2.0 Hz), 3.21 (m, 2H), 3.03 (m, 1H), 2.88 (dd, 1H, $J = 12.0$, 4.2 Hz), 2.58 (br d, 1H, $J = 12.0$ Hz), 2.53 (m, 1H), 2.33 (m, 1H), 2.05 (s, 3H), 2.03 (m, 1H), 1.71 (dt, 1H, $J = 5.0$, 13.8 Hz), 1.51 (br d, 1H, $J = 13.8$ Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 171.0, 135.0, 133.8, 127.0, 121.6, 119.4, 119.0, 110.1, 109.0, 79.0, 78.1, 65.2, 59.1, 51.5, 45.3, 37.3, 32.6, 24.8, 20.9, 16.5; FAB$^+$MS m/z: 341 [MH$^+$].
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15. Selected data for **15**: $[\alpha]_D = -9.12$ ($c = 0.8$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.45 (d, 1H, $J = 8.0$ Hz), 7.25–7.05 (m, 3H), 5.91 and 5.00 (AB system, 2H, $J = 10.8$ Hz), 4.55 (br s, 1H), 4.29 (dd, 1H, $J = 12.0$, 3.6 Hz), 3.93 (br d, 1H, $J = 12.0$ Hz), 3.36 (m, 2H), 3.05 (m, 1H), 2.82 (dd, 1H, $J = 11.5$, 3.5 Hz), 2.56 (dd, 1H, $J = 16.5$, 4.7 Hz), 2.43 (t, 1H, $J = 11.5$ Hz), 2.22 (m, 1H), 2.00 (m, 1H), 1.51 (br d, 1H, $J = 13.5$ Hz), 1.15 (m, 3H), 0.88 (t, 3H, $J = 7.5$ Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 133.5, 122.8, 121.8, 119.4, 109.9, 109.4, 79.0, 77.5, 65.9, 59.9, 51.1, 42.3, 39.4, 29.6, 26.9, 26.6, 16.5, 11.4; FAB$^+$MS m/z: 297 [MH$^+$]; EI-HRMS for $C_{19}H_{24}N_2O$: calcd 296.1889; found 296.1892.
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17. Selected data for **16**: Amorphous solid; ^1H NMR (300 MHz, $CDCl_3$): δ 10.22 (br s, 1H), 7.50–7.05 (m, 4H), 4.78 (t, 1H, $J = 1.9$ Hz), 4.05 (d, 2H, $J = 5.0$ Hz), 3.18–2.88 (m, 3H), 2.85–2.45 (m, 4H), 1.15 (m, 2H), 0.85 (t, 3H, $J = 7.5$ Hz); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 135.5, 130.0, 127.0, 121.3, 119.2, 118.0, 111.1, 106.9, 65.1, 59.6, 51.5, 41.3, 37.4, 28.6, 27.0, 16.5, 11.4; FAB$^+$MS m/z: 285 [MH$^+$]; EI-HRMS for $C_{18}H_{24}N_2O$: calcd 284.1889; found 284.1880.