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First Enantioselective Total Synthesis of (−)-Tejedine

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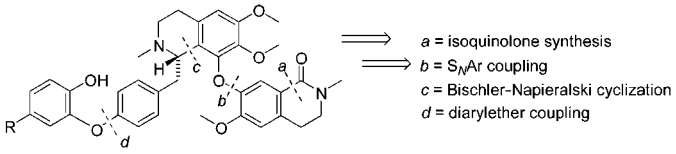
ABSTRACT

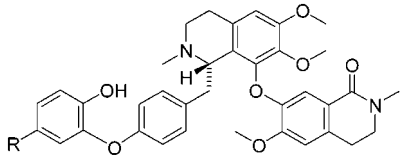


1: R = CO_2CH_3

The first enantioselective total synthesis of (−)-tejedine (1) is reported. Tejedine is a seco-bisbenzyltetrahydroisoquinoline isolated in 1998 as a minor component from *Berberis vulgaris*. The synthesis was achieved using a strategy employing four key steps, including a chiral auxiliary-assisted diastereoselective Bischler−Napieralski cyclization.

(−)-Tejedine (**1**), first reported in 1998 by the group of Suau et al.,[1] is a minor component of *Berberis vulgaris*. It is an example of a "Type VI" seco-bisbenzyltetrahydroisoquinoline,[2] a relatively rare group of compounds within the larger and diverse group of bisbenzylisoquinoline alkaloids.[3] Tejedine, whose biological properties have not been reported, is structurally very closely related to baluchistanamine (**2**), which was reported by Shamma et al.[4] in 1974.

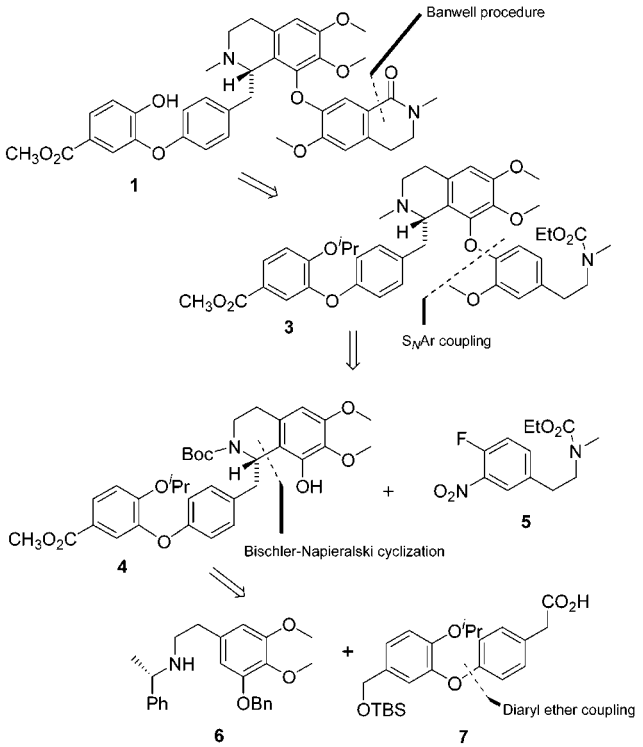
These two alkaloids possess only a single stereogenic center, but when the complexity of the substituents on the tetrahydroisoquinoline and dihydroisoquinolone subunits is also taken into consideration, they are synthetically relatively challenging. We herein report the first enantioselective total synthesis of (−)-tejedine.



1 Tejedine: R = CO_2CH_3
2 Baluchistanamine: R = CHO

The retrosynthetic plan in Scheme 1 outlines the synthetic approach taken. The first disconnection envisioned a ring closure to form the tetrahydroisoquinoline unit via a carbamate synthon, **3**. In turn, **3** can be constructed using a base-mediated S_NAr diaryl ether coupling of **4** with **5**. An

Scheme 1



(1) Suau, R.; Rico, R.; Lopez-Romfro, J. M.; Najera, F.; Cuevas, A. *Phytochemistry* **1998**, *49*, 2545−2549.

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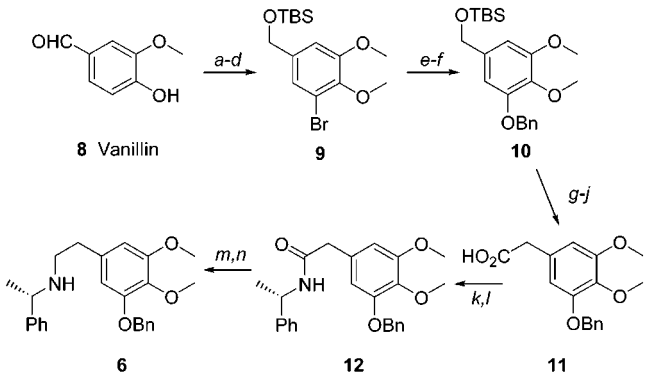
enantioselective Bischler−Napieralski[5] disconnection suggested that **4** could be constructed via the reaction of synthons **6** with **7**. Synthon **7** itself requires a diaryl ether coupling disconnection. Vanillin (**8**) was chosen as the starting compound for **6** (Scheme 2): bromination, followed

Scheme 2[a]



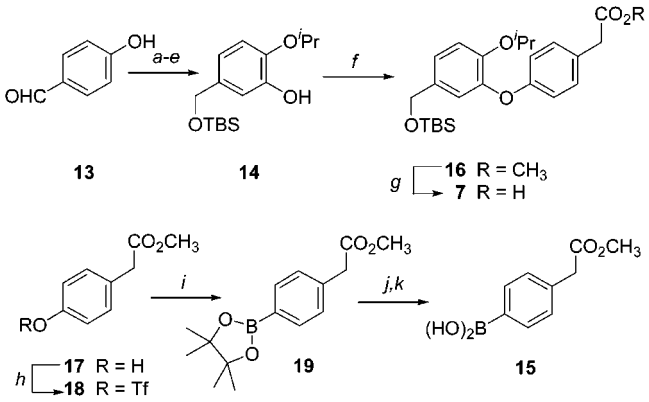
[a] Reagents and conditions: (a) Br_2, AcOH, rt, 1 h (94%); (b) $(CH_3)_2SO_4$, NaOH, Adogen 464^R, CH_2Cl_2, rt, 15 h (89%); (c) $NaBH_4$, THF/MeOH, 2 h; (d) TBSCl, imidazole, DMF, rt, 12 h (92%); (e) *n*-BuLi, −78 °C 1 h; $B(OCH_3)_3$, 12 h, −78 °C→rt; H_2O_2, rt, 12 h (78%); (f) BnBr, K_2CO_3, acetone, reflux, 12 h (75%); (g) Bu_4NF, THF, 0 °C, 2 h (quant); (h) $SOCl_2$, benzene, rt, 12 h (88%); (i) NaCN, DMSO/benzene, rt, (89%); (j) NaOH (4 M), EtOH, reflux, 20 h (98%); (k) $(COCl)_2$, benzene, rt, 2 h; (l) (*S*)-α-methylbenzylamine, aq 5% NaOH/CH_2Cl_2 (1.5:1), rt, 1 h (90%); (m) B_2H_6·THF/BF_3·Et_2O, THF, reflux; (n) aq 20% HCl (98%).

by methylation, $NaBH_4$ reduction, and protection of the resulting primary alcohol as the TBS ether afforded **9** (92%). Lithiation of **9** was followed by transmetalation to form the arylboronate, which was quenched with hydrogen peroxide to form the corresponding phenol.

Protection of the phenolic group as the benzyl ether **10** was followed by homologation to the trisubstituted phenylacetic acid **11**. The readily available (*S*)-α-methylbenzylamine[6] was found to be the most efficient chiral auxiliary to effect a diastereoselective Bischler−Napieralski cyclization at a subsequent stage. Reaction of **11** with (*S*)-α-methylbenzylamine using Schotten−Baumann conditions resulted in the amide **12** (90%), which was converted to synthon **6**.

Synthesis of the diaryl ether **7** was achieved in 40% overall yield, using the reactions shown in Scheme 3: 4-hydroxybenzaldehyde (**13**) was converted to **14** via a five-step

Scheme 3[a]



[a] Reagents and conditions: (a) $Br_2/CHCl_3$, rt 12 h (55%); (b) *i*-PrBr, DMSO, K_2CO_3, 55 °C, 12 h (94%); (c) $NaBH_4$, THF/MeOH, rt, 2 h (98%); (d) TBSCl, imidazole, DMF, rt, 12 h (95%); (e) *n*-BuLi/THF, −78 °C→rt, 12 h; H_2O_2, rt, 24 h (**14**, 82%); (f) **14** + **15**, $Cu(OAc)_2$, py, CH_2Cl_2, 4 Å mol sieves, rt, 48 h (**16**, 57%); (g) **16**, LiOH, 1:3:1 MeOH/THF/H_2O, rt, 2 h (quant); (h) Tf_2O, 2,6-lutidine, CH_2Cl_2, −40 °C, (98%); (i) bis(pinacolato)diboron, $PdCl_2$(dppf), KOAc, dioxane, 80 °C, (**19**, 85%); (j) diethanolamine, 2-propanol, Et_2O, (78%); (k) aq 1 M HCl, THF, rt (**15**, 85%).

sequence. An isopropyl group[7] was employed as the protecting group since this allowed for selectivity in the removal of protecting groups in the final step of the total synthesis. $Cu(OAc)_2$-mediated[8] diaryl ether coupling of **14** with boronic acid **15** afforded **16**, which was hydrolyzed to the free carboxylic acid synthon **7**, using conditions that did not affect the other two protecting groups.

Boronic acid **15** was synthesized via conversion of methyl (4-hydroxyphenyl)acetate (**17**) to the triflate **18**, followed by $PdCl_2$(dppf)-catalyzed coupling with bis(pinacolato)diboron[9] to form the intermediate arylboronate **19**. Conversion to **15** could only be efficiently accomplished using a procedure similar to that described by Jung and Lazarova:[9] reaction of **19** with diethanolamine formed the corresponding cyclic aminoboronate intermediate, which could be more easily hydrolyzed than **19**, under acidic conditions, to **15** (Scheme 3).

Diastereoselective[6] Bischler−Napieralski cyclization to form synthon **4** was accomplished by the reactions shown in Scheme 4: the chiral auxiliary-bearing synthon **6** condensed smoothly with **7** using HOBt/EDCI conditions[10] to form amide **20**. A four-step sequence converted **20** into **22b** in 60% overall yield. Cyclization of **22b** using typical Bischler−Napieralski conditions, with $POCl_3$ in benzene,

(2) For reviews, see: (a) Guha, K. P.; Mukherjee, B.; Mukherjee, R. *J. Nat. Prod.* **1979**, *42*, 1−84. (b) Schiff, P. L., Jr. *J. Nat. Prod.* **1983**, 46, 1−43. (c) Schiff, P. L., Jr. *J. Nat. Prod.* **1987**, *50*, 529−599. (d) Schiff, P. L., Jr. *J. Nat. Prod.* **1991**, *54*, 645−749. (e) Schiff, P. L., Jr. *J. Nat. Prod.* **1997**, *60*, 934−953.

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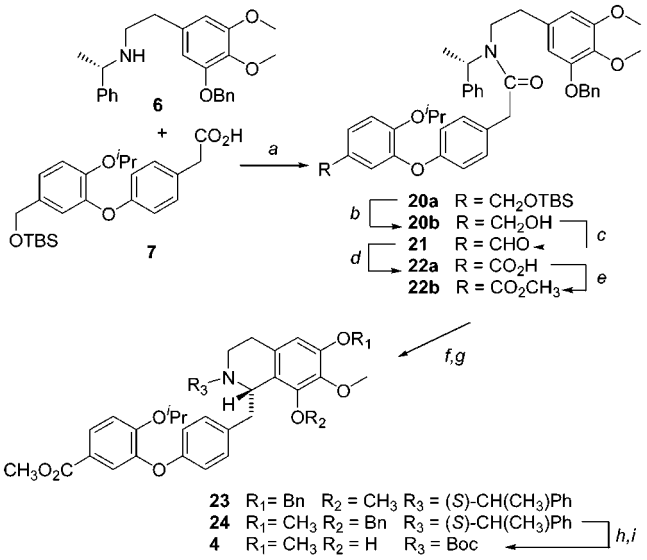
(10) Evans, D. A.; Wood, M. R.; Trotter, B. W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2700−2704.

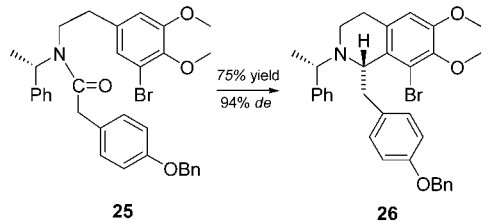
Scheme 4[a]



[a] Reagents and conditions: (a) HOBt/EDCI, DMF, 0 °C, 48 h (73%); (b) TBAF, THF, 0 °C, 1 h, (quant); (c) Dess−Martin periodinane oxidation, 1 h; (d) $NaClO_2$, Na_2HPO_4, resorcinol, DMSO, rt, 12 h; (e) $TMSCHN_2$, MeOH, benzene, rt, 1 h (60% from **20a**); (f) $POCl_3$, benzene, reflux, 12 h; (g) $NaBH_4$/MeOH, −78 °C, 5 h (**23**, 45%; **24**, 40%); (h) H_2, Pd/C, EtOH, EtOAc, aq HCl, rt, 15 h; (i) $(Boc)_2O$, Et_3N, −78 °C→rt, 12 h (**4**, 80%).

followed by $NaBH_4$ reduction afforded a pair of regioisomers **23** and **24** in 45 and 40% yields, respectively. The regioisomer **24**, which was required for the synthesis of (−)-tejedine, was formed in approximately 99% de, as determined by ^1H NMR spectroscopy. Pd/C-catalyzed hydrogenation effected smooth removal of both the chiral auxiliary and the benzyl groups. The secondary amine of the tetrahydroisoquinoline was then selectively protected as the Boc derivative to afford **4**.

Supporting evidence that the new stereogenic center in **24** had the same configuration as that in the target (−)-tejedine came from a model study: reaction of bromoarene **25** under the Bischler−Napieralski/$NaBH_4$ conditions gave **26** as the major diastereomer in 94% de. Its X-ray crystal structure[11] (Figure 1) established that the configuration of the new stereogenic center was the desired one.



Synthon **5** was synthesized via a five-step synthetic sequence from 4-fluoro-3-nitroacetonitrile (**27**)[12] (Scheme 5). Base-mediated S_NAr coupling of **5** with **4** produced **28**, which was transformed into the carbamate synthon in a sequence

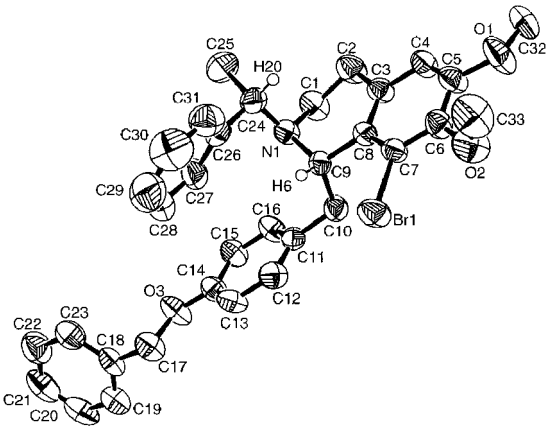
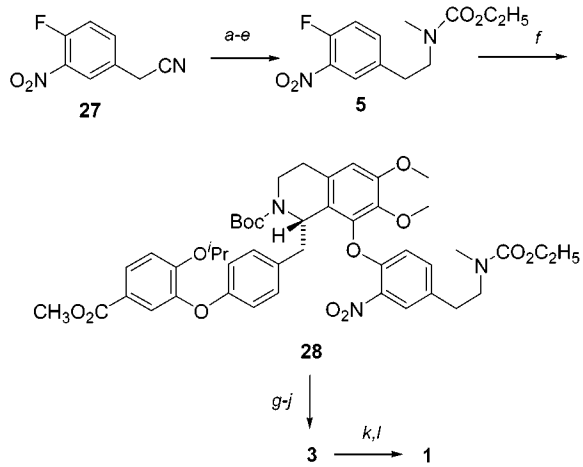


Figure 1. ORTEP X-ray structure of **26**.

that included the high-yield six-step nitro to methoxy group transformation,[13] followed by a two-step removal of the Boc group and N-methylation to form **3**. These steps were conducted in a "one-pot" reaction, not requiring purification of the intermediates. The penultimate step, in which **3** was cyclized to form the corresponding isoquinolone, was effected using Banwell's procedure.[14] Chemoselective removal of the isopropyl protecting group on the cyclized product using $AlCl_3$ gave **1**, which was identical in all respects with a sample of authentic (−)-tejedine.[15]

Scheme 5[a]



[a] Reagents and conditions: (a) 12 M, HCl, reflux 15 h (92%); (b) $(COCl)_2$, DMF, benzene, rt, 2 h; (c) $MeNH_3^+Cl^-$, aq 5% NaOH, rt, 2 h (80%); (d) B_2H_6·THF/BF_3·Et_2O, THF, reflux, 5 h; (e) $ClCO_2Et$, aq satd $NaHCO_3$, CH_2Cl_2/H_2O, rt, 12 h (80%); (f) **4** + **5**: CsF, DMSO, rt, (90%); (g) H_2/Pd−C, MeOH; (h) HBF_4, *i*-amylONO, CH_3CN, −20 °C, 0.5 h; aq satd KI, −45 °C→rt, 2 h; *i*-PrMgCl, THF, −60 → −40 °C, 2 h; $B(OCH_3)_3$, from −60 → −40 °C, 1 h; H_2O_2, aq 1 M NaOH, −20 → 0 °C, 1 h (85% from **28**); (i) CH_3I, DMF, 0 °C/TFA, THF; (j) aq 37% HCHO, $NaBH_3CN$, (95%); (k) Tf_2O, DMAP, CH_2Cl_2, 0 °C→rt, 12 h (80%); (l) $AlCl_3$, CH_2Cl_2, rt, 48 h, (56%).

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Supporting Information Available: ^{1}H NMR spectra (500 MHz) of synthetic and authentic tejedine and of the key intermediates **3**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) $C_{33}H_{34}O_3NBr$: monoclinic, space group $P2_1$ (#4), $a = 10.814$ (2) Å, $b = 9.818$ (1) Å, $c = 13.573$ (2) Å, $\beta = 97.61$ (1)°, V = 1428.3 (4) Å^3, $Z = 2$, $D_{calcd} = 1.331$ g/cm^3. Intensity data were measured at 299 "1 K on a Rigaku AFC6S diffractometer with graphite-monochromated Mo Kα radiation ($\lambda = 0.71069$ Å) to $2\theta_{max}$ (deg) 55.1°. A total of 7336 reflections were measured of which 3496 ($R_{int} = 0.056$) were unique. The final cycle of full-matrix least-squares refinement on F was based on 2284 observed reflections ($I > 2.00\sigma(I)$) and 343 variable parameters and converged with unweighted and weighted agreement factors of: $R = 0.038$ $R_w = 0.038$, GOF = 1.42. We thank David O. Miller, X-ray Crystallography Unit, Department of Chemistry, Memorial Univerity of Newfoundland for these measurements.

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(15) We thank Professor Rafael Suau of the University of Malaga, Spain for a sample of (−)-tejedine. The spectral and optical properties of synthetically derived tejedine and those of the sample provided by Professor Suau were identical.