Enantioselective Total Synthesis and X-ray Structures of the Tetrahydroprotoberberine Alkaloids (−)-(*S*)-Tetrahydropalmatrubine and (−)-(*S*)-Corytenchine

Ahmed L. Zein, Louise N. Dawe, and Paris E. Georghiou*

Department of Chemistry, Memorial University of Newfoundland, St. John's, Newfoundland and Labrador, A1B3X7, Canada

Received February 19, 2010

Enantioselective total syntheses and X-ray structures of both (*S*)-tetrahydropalmatrubine (**2**) and (*S*)-corytenchine (**3**) are reported for the first time. They were both derived from (*S*)-*N*-norlaudanidine, a benzyltetrahydroisoquinoline that was synthesized with high (>95% ee) enantioselectivity using a chiral auxiliary-assisted Bischler−Napieralski cyclization/reduction approach.

1-Benzyltetrahydroisoquinolines (BTHIQs) such as tetrahydropapaverine (**1**), in which the B ring is reduced at the C-1, C-2 and C-3, C-4 positions, are key biosynthetic precursors to many naturally occurring alkaloids. These include morphine and codeine, which are found in, or are derived from, the opium poppy, *Papaver somniferum* L.[1] BTHIQs are also biosynthetic precursors to the tetrahydroprotoberberines (THPBs),[2] a class of naturally occurring tetracyclic alkaloids that also contain an isoquinoline core,[3] and are a subclass of the protoberberine alkaloids.[4] These compounds are found in at least eight plant families and possess a variety of biological activities including, for example, anti-inflammatory, antimicrobial, antifungal, and antitumor properties.[5] The most common of these THPB derivatives, such as (*S*)-tetrahydropalmatrubine (**2**), have oxygen functionalities at the C-2, C-3 and C-9, C-10 positions on the A and D aromatic rings, respectively.[2] Less common is the class of "pseudo-THPBs" such as (*S*)-corytenchine (**3**) and (*S*)-xylopinine (**4**), for which oxygen functionalities are on the C-2, C-3 and C-10, C-11 positions (Figure 1).

We reported recently the enantioselective syntheses and X-ray structures of (*S*)-*N*-norlaudanidine (**5**) and its *R* enantiomer using a chiral auxiliary-assisted Bischler−Napieralski cyclization/reduction approach.[6] These BTHIQs are known to be trace opium constituents and, as a racemic mixture (also referred to in the literature as "(±)-norlaudanine"), have been shown also by Isawa et al.[2] to be bioconverted into stereoisomeric mixtures of both **2** and **3**. Interestingly, these authors concluded that the *R* isomer of **2** and the *S* isomer of **3** are the major enantiomers formed in their metabolic studies using cell cultures of *Macleaya* and *Corydalis* species, suggesting "stereospecific bioconversion".[2] In this study, however, a racemic mixture of (*S*)- and (*R*)-*N*-norlaudanidine, which was isolated from a mixture produced by an acid-mediated reaction of racemic tetrahydropapaverine (**1**), was employed. Herein, we report the enantioselective syntheses and X-ray structures of both (*S*)-tetrahydropalmatrubine (**2**) and (*S*)-corytenchine (**3**), which were derived directly from (*S*)-*N*-norlaudanidine.

Among the different strategies that have been used for the construction of a THPB core, the classical Pictet−Spengler[7] or the Bischler−Napieralski cyclization/reduction[8] procedures have been the most widely used. Although several racemic syntheses of THPBs have been reported, there are only a small number of asymmetric syntheses having the desired ring substitution patterns. Several of these asymmetric syntheses have been of (*S*)-(−)-xylopinine (**4**), using different approaches,[9] and also of (*S*)-tetrahydropalmatine (**6**).[10] These two compounds, however, are both tetramethoxylated, i.e., a 2,3,10,11- and a 2,3,9,10-tetramethoxyTHPB, respectively. Very recently, Cheng and Yang reported a >99% ee enantioselective synthesis of (*S*)-stepholidine (**7**), a compound that has attracted a great deal of attention since it was reported to display a unique pharmacological profile toward dopamine receptors.[11] This alkaloid has a 2,11-dihydroxy-3,10-dimethoxy substitution pattern on the A and D rings and was synthesized via an asymmetric Bischler−Napieralski cyclization/reduction approach.[12]

On the basis of our recent synthetic studies,[6,13] we targeted the synthesis of a 2,3,10-trimethoxy-11-hydroxy-functionalized THPB, i.e., (*S*)-corytenchine (**3**), using the chiral auxiliary (*S*)-α-methylbenzylamine, in an asymmetric Bischler−Napieralski cyclization/reduction sequence, as shown in Scheme 1.

Isovanillin (**8**) was converted into benzylic substance **9** in five steps in an overall 78% yield using Kim's methodology.[14] For the isoquinoline fragment, vanillin (**10**) was converted into **5** via the (*S*)-α-methylbenzylamine chiral auxiliary-protected amide, **13**, in 70% overall yield from **10**. As ascertained from its ^{1}H NMR spectrum, **12** was formed in ca. 95% de. Conversion of **5** into (*S*)-corytenchine (**3**) was then effected by reaction at 0 °C with formaldehyde (37% formalin) in acetonitrile, followed by addition of $NaBH_3CN$ and then by acetic acid.[13a] The reaction afforded almost quantitative formation of **3**, for which the NMR spectroscopic properties are generally in agreement with those reported by da Silva[15] and Martinez-Vazquez,[16] who, respectively, isolated **3** from *Xylopia langsdorffiana* A. St.-Hil. & Tul. (Annonaceae) and from the roots of *Annona cherimolia* Mill. (Annonaceae). Earlier, Kametani reported the isolation of **3** from *Corydalis ochotensis* Turcz[17] but had previously synthesized a "dibenzo[*a,g*]quinolizine", which they called "*O*-demethyltetrahydroxylopine", having the same substitution pattern as **3**, presumably as a racemate, by a similar procedure from racemic **5** using formalin in ethanol "without acid".[18] In this paper, the authors reported that they were unable to obtain a compound having the same substitution pattern as tetrahydropalmatrubine (**2**).

Since the product obtained in the present study had physical properties similar to those reported above but with slight differences in several of the NMR assignments, unequivocal evidence from X-ray crystallography was sought. The X-ray structure shown in Figure 2 confirmed the structure as (*S*)-corytenchine (**3**), based upon the absolute structure of the precursor **5**, for which the X-ray structure was previously established.[6]

When Kametani's methodology was employed as described,[18] a mixture was obtained that by its ^{1}H NMR spectroscopic data showed approximately 70% of **3** and 30% of the regioisomeric product, for which the spectroscopic properties and X-ray structure (Figure 3, as the hydrochloride salt) showed it to be (*S*)-tetrahydropalmatrubine (**2**).

Compound **3** has also been named "schefferine" in several publications in the literature, and in some cases this is confusing.

* To whom correspondence should be addressed. Phone: +1-709-7378517. Fax: +1-709-737-3702. E-mail: parisg@mun.ca.

10.1021/np1001169
Published on Web 07/09/2010

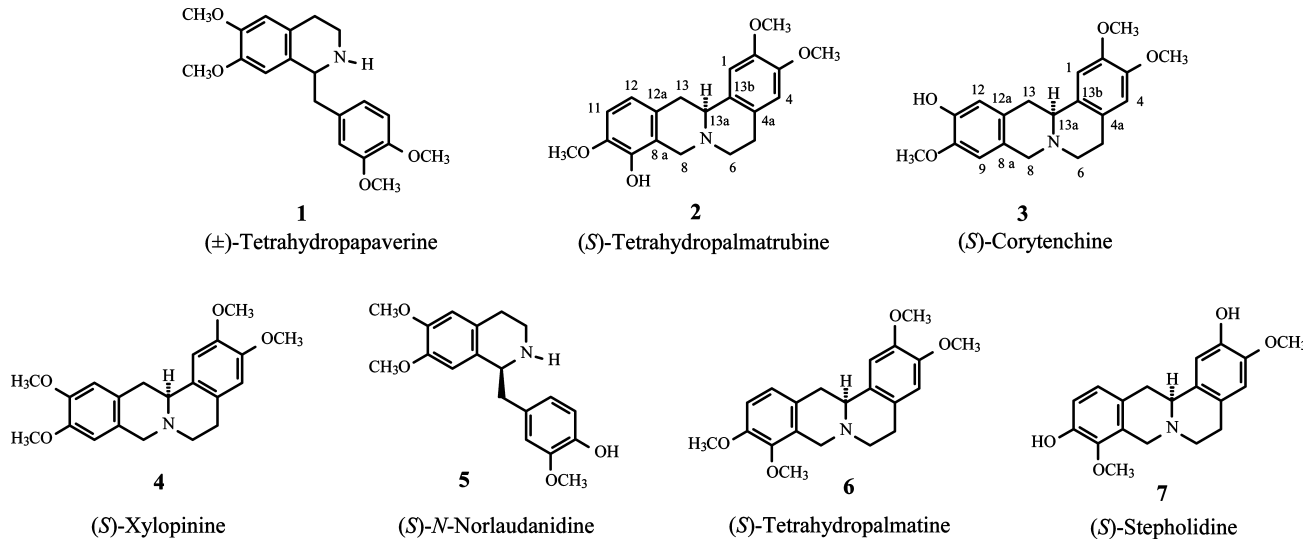
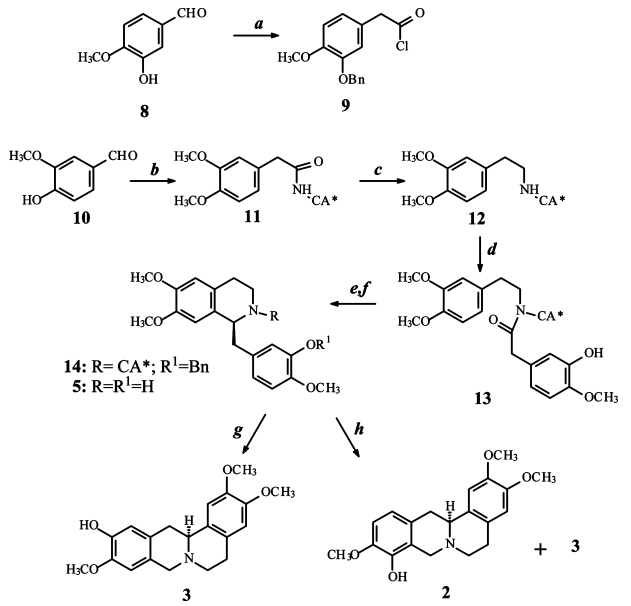


Figure 1. (±)-Tetrahydropapaverine (**1**) and THPB alkaloids **2**−**7**.

Scheme 1. Synthesis of (*S*)-Tetrahydropalmatrubine (**2**) and (*S*)-Corytenchine (**3**)[a]



[a] Reagents and conditions: ***a***: 1. BnBr, DMSO, 98%; 2. CBr_4, PPh_3, CH_2Cl_2, 93%; 3. pyrrolidine, H_2O, rt, 91%; 4. 1.0 M HCl_{aq}/dioxane; 5. $(COCl)_2$, benzene, 94%. ***b***: 1. $(CH_3)_2SO_4$, K_2CO_3, acetone, 95%; 2. CBr_4, PPh_3, CH_2Cl_2, 92%; 3. pyrrolidine, H_2O, rt, 91%; 4. 1.0 M HCl_{aq}/dioxane; 5. $(COCl)_2$, benzene, 96%; 6. CA* = (*S*)-α-methylbenzylamine, 5% $NaOH_{aq}$, CH_2Cl_2, 92%; ***c***: B_2H_6, THF, $BF_3 \cdot Et_2O$, 86%. ***d***: **9**, 5% $NaOH_{aq}$, CH_2Cl_2, 72%; ***e***: 1. $POCl_3$, benzene; 2. $NaBH_4$, MeOH, 89%, (95% ee); ***f***: H_2, 10% Pd/C, EtOH, 10% HCl_{aq}: **5** ~72%; ***g***: 1. HCHO, CH_3CN; 2. $NaBH_3CN$; CH_3CO_2H, 95%; ***h***: 1. HCHO, MeOH; 2. $NaBH_4$, ~70% **3** and ~30% **2**.

In 1972, Gellert and Rudzats[19] isolated two THPBs from *Schefferomitra subaequalis* Diels, of which one was named "schefferine" and with the same structure represented as **2**. However, Brochmann-Hanssen[20] later reassigned this structure as being the regioisomeric compound having the substitution pattern on the D ring transposed, with the hydroxy group at C-10 and the methoxy group at C-9, and indicated that it was the same as "kikemanine". Kikemanine was so named by Kametani,[21] who isolated it from *Corydalis pallida* Pers. in 1970, and was also equivalent to "corydalmine", previously isolated by Imaseki and Taguchi[22] from another *Corydalis* species (named as "engosan"). This was obtained also by Cava[23] in 1968 from *Stephania glabra* Miers. Corydalmine was synthesized by Bradsher[24] in 1965. In 1977, Kametani's group also

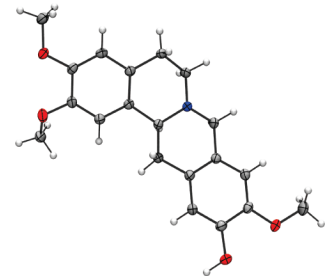


Figure 2. X-ray structure of **3** with 50% probability ellipsoids.

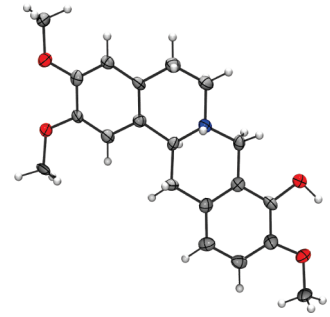


Figure 3. X-ray structure of **2** with 50% probability ellipses. Solvent water molecules and chloride ion omitted for clarity.

reported the synthesis of schefferine via a photochemical route[25a] and stated it to be "identical with an authentic sample", although the compound they were referencing it to was ambiguous with respect to the ring-D substitution pattern.[25b] In 2000, Bianchi and Kaufman[26] published two papers in which they reported the synthesis via a tosyliminium ion-based route, of "(±)-schefferine", to which was assigned the substitution pattern of **2**. However, their NMR spectroscopic data were not consistent with the proposed structure and are at odds with those determined herein for (*S*)-tetrahydropalmatrubine (**2**). ^{13}C NMR spectra were also reported by Kametani et al. for a series of dibenzo[*a,g*]quinolizidines, which included a structure (identified only as compound "16") identical to **2**.[27]

Experimental Section

General Experimental Procedures. Optical rotations were recorded on a JASCO DIP-370 polarimeter. ^1H and ^{13}C NMR spectra, HSQC, and COSY spectra were recorded on a Bruker 500 MHz NMR

spectrometer and were referenced to the solvent ($CDCl_3$) and TMS. LC-MS and HRMS were conducted using a GCT Premier Micromass spectrometer. X-ray structures were measured with a Rigaku Saturn CCD area detector equipped with a SHINE optic using Mo Kα radiation. Silicycle Ultrapure silica gel (0−20 μm) G and F-254 was used for the preparative-layer TLC, and Silicycle Silia-P Ultrapure Flash silica gel (40−63 μm) was used for flash column chromatography. TLC was conducted on Polygram SIL G/UV_{254} precoated plastic sheets. Solvents were purified using standard conditions before use.

Method *a*. Formalin (37% HCHO(aq), 2.0 mL) was added to a solution of **14**[6] (250 mg, 0.75 mmol) in MeOH (6.0 mL). After the mixture had been stirred at 25 °C for 3 h, $NaBH_4$ (319 mg, 8.44 mmol) was slowly added. Subsequently, the reaction mixture was stirred at 25 °C for an additional 16 h. Then, aqueous saturated NH_4Cl (25 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, and after filtering, the solvent was evaporated under a vacuum to afford a mixture of **2** and **3**, which was purified by preparative TLC (silica gel, 20% EtOH in hexane) to give **2** (78 mg) as a colorless solid, mp 178−179 °C (as the hydrochloride), and **3** (181 mg) as a colorless solid, mp 257−258 °C.

Method *b*. To a stirred solution of **14** (180 mg, 0.54 mmol) and formalin (37% HCHO(aq), 2.0 mL) in MeCN (1 mL) was added $NaBH_3CN$ (0.294 mg, 0.892 mmol). The reaction mixture was stirred for 1 h, and HOAc was then added. After being stirred for 1 h, the reaction mixture was quenched with water and neutralized to pH 8 with aqueous saturated $NaHCO_3$, and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, and after filtering, the solvent was evaporated under a vacuum to afford **3** (175 mg) as a colorless solid, mp 257−258 °C (245−246 °C).[16]

(*S*)-(−)-Tetrahydropalmatrubine (2): colorless solid that slowly developed color on standing, mp 178−179 °C (as the hydrochloride); $[\alpha]^{25}_D$ −115 (*c* 0.09, MeOH) (as the hydrochloride); ^{1}H NMR δ 6.74 (1H, d, *J* = 8.5 Hz, H-11), 6.74 (1H, s, H-1), 6.68 (1H, d, *J* = 8.5 Hz, H-12), 6.62 (1H, s, H-4), 4.25 (1H, d, *J* = 15.0 Hz, H-8ax), 3.89 (3H, s, OCH_3; C-2), 3.87 (6H, s, OCH_3; C-3, C-10), 3.58 (1H, dd, *J* = 12.0 and 3.5 Hz, H-13a), 3.53 (1H, d, *J* = 15.0 Hz, H-8eq), 3.26 (1H, dd, *J* = 15.5 and 3.5 Hz, H-13eq), 3.23−3.12 (2H, m, H-6eq and H-5eq), 2.84 (1H, dd, *J* = 15.5 and 12.0 Hz, H-13ax), 2.69−2.64 (2H, m, H-6ax and H-5ax); ^{13}C NMR δ 147.5 (C-11), 147.4 (C-10), 144.0 (C-2), 141.5 (C-3), 129.8 (C-13b), 128.1 (C-4a), 126.9 (C-8a), 121.3 (C-12a), 119.3 (C-4), 111.4 (C-12), 108.9 (C-9), 108.7 (C-1), 59.3 (C-13a), 56.2 (OCH_3; C-2), 56.1 (OCH_3; C-3), 55.9 (OCH_3; C-10), 53.5 (C-8), 51.4 (C-6), 36.4 (C-13), 29.1 (C-5); APCIMS *m*/*z* 342.1 (M^+ + 1, 100); HREIMS *m*/*z* 341.1620 (calcd for $C_{20}H_{23}NO_4$, 341.1614).

Crystal data for 2: $(C_{20}H_{24}NO_4)\cdot Cl\cdot 2(H_2O)$, prism crystals (of the hydrochloride) from methanol/HCl, *M* = 413.90, monoclinic, *a* = 11.197(6) Å, *b* = 7.218(4) Å, *c* = 12.421(7) Å, β = 99.841(11)°, *V* = 989.2(9) Å^3, *T* = 153(1) K, space group $P2_1$ (#4), *Z* = 2, μ(Mo Kα) = 0.230 mm^{-1}, 8699 reflections measured, 4013 independent reflections (R_{int} = 0.0451). The final R_1 values were 0.0962 ($I > 2\sigma(I)$), and the final $wR(F^2)$ values were 0.2646 (all data). The goodness of fit on F^2 was 1.051. Flack parameter = 0.07(18). Non-hydrogen atoms were refined anisotropically, while all hydrogen atoms were located in difference map positions and refined on a geometry-constrained (riding) model. CCDC #766063.

(S)-(−)-Corytenchine (3): colorless, cubic crystals; mp 257−258 °C; $[\alpha]^{25}_D$ −271 (*c* 0.09, MeOH); ^{1}H NMR δ 6.74 (1H, s, H-1), 6.72 (1H, s, H-4), 6.62 (1H, s, H-12), 6.56 (1H, s, H-9), 3.93 (1H, d, *J* = 14.5 Hz, H-8ax), 3.90 (3H, s, OCH_3; C-2), 3.87 (3H, s, OCH_3; C-10), 3.86 (3H, s, OCH_3; C-3), 3.68 (1H, d, *J* = 14.5 Hz, H-8eq), 3.57 (1H, dd, *J* = 11.5 and 3.5 Hz, H-13a), 3.21 (1H, dd, *J* = 15.5 and 3.5 Hz, H-13eq), 3.17−3.13 (2H, m, H-6eq and H-5eq), 2.81 (1H, dd, *J* = 15.5 and 11.5 Hz, H-13ax), 2.69−2.60 (2H, m, H-6ax and H-5ax); ^{13}C NMR δ 147.5 (C-11), 147.5 (C-10), 145.1 (C-2), 144.1 (C-3), 129.8 (C-13b), 127.1 (C-4a), 126.7 (C-8a), 125.8 (C-12a), 114.3 (C-4), 111.4 (C-12), 108.6 (C-9), 108.3 (C-1), 59.6 (C-13a), 58.4 (C-8), 56.1 (OCH_3; C-2), 56.0 (OCH_3; C-3), 55.9 (OCH_3; C-10), 51.4 (C-6), 36.2 (C-13), 29.1 (C-5); APCIMS *m*/*z* 342.1 (M^+ + 1, 100); HREIMS *m*/*z* 341.1627 (calcd for $C_{20}H_{23}NO_4$, 341.1627).

Crystal data for 3: $C_{20}H_{23}NO_4$, colorless prisms from methanol, *M* = 341.41, orthorhombic, *a* = 7.2621(12) Å, *b* = 8.0445(13) Å, *c* = 28.318(5) Å, *V* = 1654.3(5) Å^3, *T* = 153(1) K, space group $P2_12_12_1$ (#19), *Z* = 4, μ(Mo Kα) = 0.095 mm^{-1}, 22 912 reflections measured, 3418 independent reflections (R_{int} = 0.0245). The final R_1 values were 0.0325 ($I > 2\sigma(I)$), and the final $wR(F^2)$ values were 0.0844 (all data). The goodness of fit on F^2 was 1.057. Flack parameter = 0.0(8). Non-hydrogen atoms were refined anisotropically, while all hydrogen atoms were located in difference map positions and refined on a geometry-constrained (riding) model. CCDC #766064.

Acknowledgment. This work was supported by Memorial University of Newfoundland, the Natural Sciences and Engineering Research Council of Canada (NSERC), and the Ministry of Higher Education of Egypt (for a scholarship to A.L.Z.).

Supporting Information Available: Copies of the spectra and the crystallographic information files (CIF). This material is available free of charge via the Internet at http://pubs.acs.org. Crystallographic data for **2** (CCDC 766063) and **3** (CCDC 766064) have been deposited with the Cambridge Data Centre.

References and Notes

(1) (a) Shamma, M. In *The Isoquinoline Alkaloids: Chemistry and Pharmacology*; Blomquist, A. T.; Wasserman, H., Eds.; Academic Press: New York, 1972; pp 44−152. (b) Brochmann-Hanssen, E.; Furuya, T. *J. Pharm. Sci.* **1964**, *53*, 575. (c) Brochmann-Hanssen, E.; Nielsen, B. *Tetrahedron Lett.* **1965**, 1271–1274. (d) Brochmann-Hanssen, E.; Nielsen, B.; Utzinger, G. E. *J. Pharm. Sci.* **1965**, *54*, 1531–1532. (e) Toske, S. G.; Cooper, S. D.; Morello, D. R.; Hays, P. A.; Casale, J. F.; Casale, E. *J. Forensic Sci.* **2006**, *51*, 308–320.

(2) Iwasa, K.; Cui, W.; Sugiura, M.; Takeuchi, A.; Moriyasu, M.; Takeda, K. *J. Nat. Prod.* **2005**, *68*, 992–1000, and references therein.

(3) (a) Bhakuni, D. S.; Jain, S. In *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: New York, 1986; Vol. 28, pp 95−181. (b) Sÿantavy, F. In *The Alkaloids: Chemistry and Physiology*; Manske, R. H. F., Rodrigo, R. G. A., Eds.; Academic Press: New York, 1979; Vol. 17, pp 385−544.

(4) Hesse, M. *Alkaloids: Nature's Curse or Blessing*; Wiley-VCH: Weinheim; Chichester, UK, 2002.

(5) (a) Memetzidis, G.; Stambach, J. F.; Jung, L.; Schott, C.; Heitz, C.; Stoclet, J. C. *Eur. J. Med. Chem.* **1991**, *26*, 605–611. (b) Cushman, M.; Dekow, F. W.; Jacobsen, L. B. *J. Med. Chem.* **1979**, *22*, 331–333. (c) Wilson, W. D.; Gough, A. N.; Doyle, J. J.; Davison, M. W. *J. Med. Chem.* **1976**, *19*, 1261–1263. (d) Zee-Cheng, R. K. Y.; Cheng, C. C. *J. Med. Chem.* **1976**, *19*, 882–886.

(6) Zein, A. L.; Otman, O. O.; Dawe, L. N.; Georghiou, P. E. *Tetrahedron Lett.* **2010**, *51*, 177–180, and references therein.

(7) For a review on Pictet−Spengler cyclization, see: Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797–1842. For examples, see: Munchoff, M. J.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 4607–4610. Miller, R. B.; Tsang, T. *Tetrahedron Lett.* **1988**, *29*, 6715–6718. Meyers, A. I.; Dickman, D. A.; Boes, M. *Tetrahedron* **1987**, *43*, 5095–5108. Meyers, A. I.; Boes, M.; Dickman, D. A. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 458–459. McMurtrey, K. D.; Meyerson, L. R.; Cashaw, J. L.; Davis, V. E. *J. Org. Chem.* **1984**, *49*, 947–948. Kametani, T.; Nakano, K.; Shishido, K.; Fukumoto, K. *J. Chem. Soc. C* **1971**, 3350–3354.

(8) See, for example: (a) Venkov, A. P.; Ivanov, I. I. *Tetrahedron* **1996**, *52*, 12299–12308. (b) Larsen, R. D.; Reamer, R. A.; Corley, E. G.; Davis, P.; Grabowski, E. J. J.; Reider, P. J.; Shinkai, I. *J. Org. Chem.* **1991**, *56*, 6034–6038. (c) Pandey, G. D.; Tiwari, K. P. *Heterocycles* **1980**, *14*, 59–82. (d) Patra, A.; Mukhopadhyay; Mitra, A. K. *Indian J. Chem., Sect. B* **1980**, *19*, 561–562. (e) Pai, B. R.; Natarajan, S.; Manikumar, G.; Rajaraman, R.; Suguna, H. *J. Org. Chem.* **1978**, *43*, 1992–1994. (f) Rajaraman, R.; Pai, B. R.; Premila, M. S.; Suguna, H. *Indian J. Chem., Sect. B* **1977**, *15*, 876–879.

(9) (a) Mujahidin, D.; Doye, S. *Eur. J. Org. Chem.* **2005**, 2689–2693. (b) Davis, F. A.; Mohanty, P. K. *J. Org. Chem.* **2002**, *67*, 1290–1296. (c) Kametani, T.; Takagi, N.; Toyata, M.; Honda, T.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2830–2834. (d) Czarnocki, Z.; Arazny, Z. *Heterocycles* **1999**, *51*, 2871–2879. (e) Comins, D. L.; Thakker, P. M.; Baevsky, M. F.; Badawi, M. M. *Tetrahedron* **1997**, *53*, 16327–16340.

(10) (a) Enders, D.; Boudou, M. *J. Org. Chem.* **2005**, *70*, 9486–9494. (b) Meyers, A. I.; Matulenko, M. A. *J. Org. Chem.* **1996**, *61*, 573–580.

(11) Cheng, J.-J.; Yang, Y.-S. *J. Org. Chem.* **2009**, *74*, 9225–9228.

(12) (a) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341–3370. (b) Rozwadowska, M. D. *Heterocycles* **1994**, *39*, 903. For a recent enantioselective synthesis of some benzyltetrahydroisoquinolines via a Bischler−Napieralski approach, see: Pyo, M. K.; Lee, D.-H.; Kim, D.-H.; Lee, J.-H.; Moon, J.-C.; Chang, K. C.; Yun-Choi, H. S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4110–4114.

(13) (a) Wang, Y.; Georghiou, P. E. *Org. Lett.* **2002**, *4*, 2675–2678. (b) For earlier applications of (*S*)- and (*R*)-α-methylbenzylamine in a

Bischler−Napieralski cyclization see e.g.: Okawara, T.; Kametani, T. *Heterocycles* **1974**, *2*, 571–574.
(14) Huh, D. H.; Jeong, J. S.; Lee, H. B.; Ryu, H.; Kim, Y. G. *Tetrahedron* **2002**, *58*, 9925–9932.
(15) da Silva, M. S.; Tavares, J. F.; Queiroga, K. F.; Agra, M. deF.; Filho, J. M. B.; Almeida, J. R. G. daS.; da Silva, S. A. S. *Quim. Nova* **2009**, *32*, 1566–1570.
(16) Martinez-Vazquez, M.; Lozano, D. G. C.; Estrada-Reyes, R.; Gonzalez-Lugo, N. M.; Apan, T. R.; Heinze, G. *Fitoterapia* **2005**, *76*, 733–736.
(17) Lu, S.-T.; Su, T.-L.; Kametani, T.; Ujiie, A.; Ihara, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1976**, 63–68.
(18) Kametani, T.; Fukumoto, K.; Agui, H.; Yagi, H.; Kigasawa, K.; Sugahara, H.; Hiiragi, M.; Hayasaka, T.; Ishimaru, H. *J. Chem. Soc. C* **1968**, 112–118.
(19) Gellert, E.; Rudzats, R. *Aust. J. Chem.* **1972**, *25*, 2477–2482.
(20) Brochmann-Hanssen, E.; Chiang, H. C. *J. Org. Chem.* **1977**, *42*, 3588–3591.
(21) Kametani, T.; Ihara, M.; Honda, T. *J. Chem. Soc. C* **1970**, 1060–1064.
(22) Imaseki, I.; Taguchi, H. *J. Pharm. Soc. Jpn.* **1962**, *82*, 1214−1219.
(23) Cava, M. P.; Nomura, K.; Talaptra, S. K.; Mitchell, M. J.; Schlessinger, R. H.; Buck, K. T.; Beal, J. L.; Douglas, B.; Raffauf, R. F.; Weisbach, J. A. *J. Org. Chem.* **1968**, *33*, 2785–2789.
(24) Telang, S. A.; Bradsher, C. K. *J. Org. Chem.* **1965**, *30*, 752–754.
(25) (a) Kametani, T.; Sugai, T.; Shoji, Y.; Honda, T.; Satoh, F.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1151–1155. (b) Kametani, T.; Ihara, M.; Honda, T. *Chem. Commun.* **1969**, 1301.
(26) (a) Bianchi, D. A.; Kaufman, T. S. *Can. J. Chem.* **2000**, *78*, 1165–1169. (b) Bianchi, D. A.; Kaufman, T. S. *Synlett* **2000**, *6*, 801–804.
(27) Kametani, T.; Fukumoto, K.; Ihara, M.; Ujiie, A.; Koizumi, H. *J. Org. Chem.* **1975**, *40*, 3280–3283.

NP1001169