JOC The Journal of Organic Chemistry
Article
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Synthesis of Alkaloids by Stevens Rearrangement of Nitrile-Stabilized Ammonium Ylides: (±)-Laudanosine, (±)-Laudanidine, (±)-Armepavine, (±)-7-Methoxycryptopleurine, and (±)-Xylopinine

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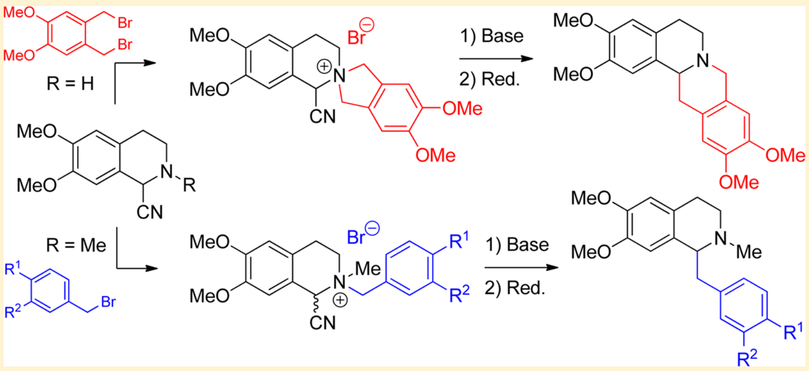
Supporting Information



ABSTRACT: The Stevens rearrangement of nitrile-stabilized ammonium ylides in conjunction with the reductive removal of the nitrile function permits the facile construction of *α*-branched amines from *α*-aminonitriles. We employed this reaction sequence for the preparation of (±)-laudanosine, (±)-laudanidine and (±)-armepavine, (±)-7-methoxycryptopleurine, and (±)-xylopinine from two closely related and readily accessible bicyclic *α*-aminonitriles. The final products were obtained in high to almost quantitative yields (71−98%) from the quaternary ammonium salts obtained by N-alkylation of these starting materials.

INTRODUCTION

Due to its strong anion-stabilizing capacity, the nitrile group can, for instance, be used for the preparation of stable *α*-aminocarbanions[1−3] carrying free NH-protons without the necessity of using a protecting group. We have employed this methodology for the preparation of various N-heterocycles and alkaloids but an additional conjugative stabilization of the anion is required to suppress the competing retro-Strecker reaction in the deprotonation step.[4−6] The same effect permits the facile generation of stabilized ammonium ylides by N-alkylation of *α*-aminonitriles and their subsequent deprotonation. Ylides of this type[7−10] have, e.g., been used in [2,3]-sigmatropic rearrangements involving allylic substituents[11−15] or in substitution and addition reactions.[16−20] In contrast, Stevens rearrangements of nitrile-stabilized ammonium ylides have only rarely been reported.[21−23] An interesting exception is the ring enlargement of Liu and Liang who combined the [1,2]-migration with a reductive decyanation.[24] The lability of the C−CN bond in the product of this rearrangement in a polar environment leads to the formation of small concentrations of the cyanide-iminium ion pair, the cation of which can easily be trapped by a hydride ion from a mild reductant such as $NaCNBH_3$ or $NaBH_4$.[25−29] The net result of this reaction sequence is the substitution of the nitrile group in the parent aminonitrile by the N-alkyl group with the highest migratory aptitude. Although the Stevens rearrangement of nonstabilized ylides prepared from 1,2,3,4-tetrahydrosoquinolinium salts was achieved by Grethe et al., harsh reaction conditions[30] were required and resulted in low yields.[31] In contrast, the nitrile group in the *α*-position of the isoquinolinium salt allows the use of milder reaction conditions and significantly improves purity and yield of the products (Scheme 1).[32−34] The method also compares favorably with the use of *α*-stannylated ammonium salts as recently exemplified by a five-step synthesis of the phenanthroindolizidine alkaloid (±)-tylophorine.[35,36]

RESULTS AND DISCUSSION

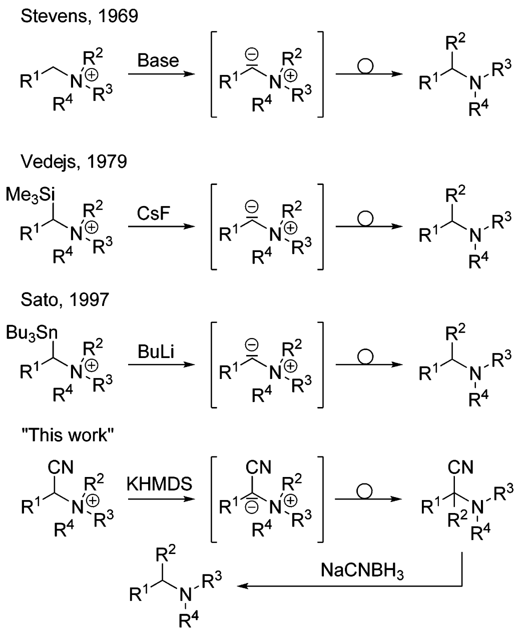
In continuation of our studies, we herein report on the application of the traceless N→C-shift of benzylic substituents for the preparation of benzylisoquinoline-, tetrahydroprotoberberine- and phenanthroquinolizidine-type alkaloids from readily available precursors.

Polycyclic alkaloids belonging to the above-mentioned structural classes play an important role in the world of biologically active alkaloids and have been demonstrated to possess anti-inflammatory,[37,38] antiallergic,[39,40] antiasthmatic,[39,40] antibacterial,[41] antifungal,[42] antitumor,[43] and antiviral[44] effects (Figure 1). In the phenanthro-alkaloids, the quinolizidine-based compounds regularly show a much higher

Received: March 28, 2013
Published: May 1, 2013

dx.doi.org/10.1021/jo400659n | *J. Org. Chem.* 2013, 78, 4985−4992

Scheme 1. Stevens Rearrangement/Reduction Sequence



potency in antiproliferative assays than their indolizidine counterparts.[45,46]

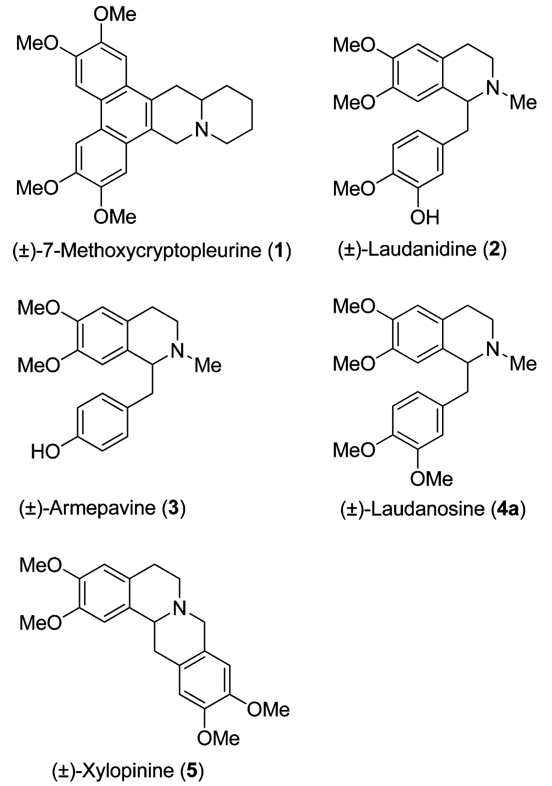
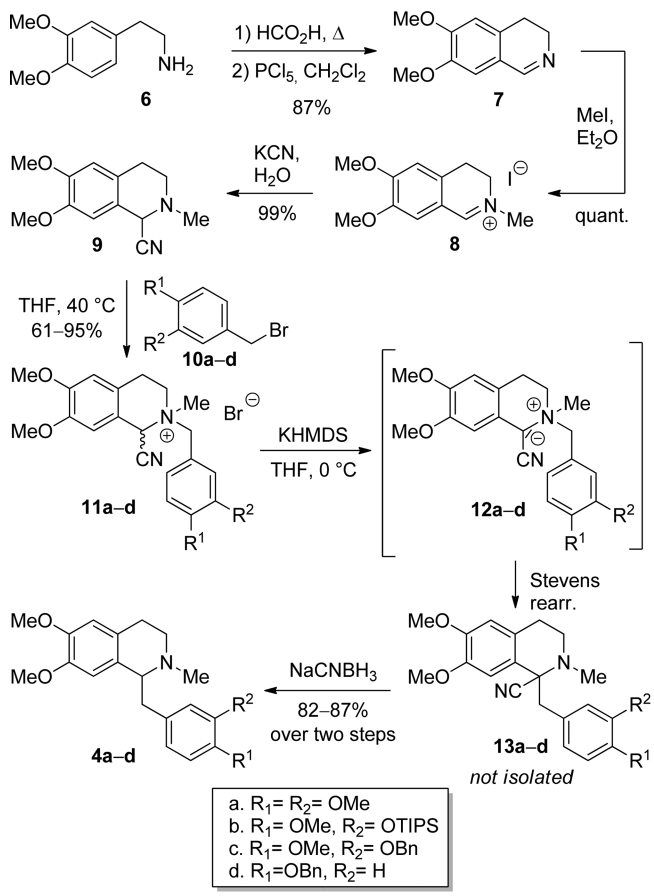


Figure 1. Alkaloid targets.

The synthesis of the 1-benzyltetrahydroisoquinolines **4a–d** was achieved by condensation of homoveratrylamine (**6**) with formic acid followed by Bischler–Napieralski cyclization, providing 6,7-dimethoxy-3,4-dihydroisoquinoline (**7**) in 87% yield, followed by N-methylation with methyl iodide to obtain iminium salt **8** in quantitative yield. Treatment of this compound with aqueous KCN affords *α*-aminonitrile **9** as a universal building block. N-Benzylation of **9** with different benzyl bromides **10a–d** leads to the corresponding tetrahydroisoquinolinium salts **11a–d** in moderate to very high yield. These materials were treated with KHMDS in THF at 0 °C to generate the nitrile-stabilized ammonium ylides **12a–d**, which readily undergo a Stevens rearrangement at that temperature to lead to the C-alkylated *α*-aminonitriles **13a–d**.[47]

These compounds are prone to the spontaneous liberation of cyanide. However, the attempted isolation of the related enamines resulted in side reactions. In contrast, in situ reduction of the crude rearrangement products **13a–d** with $NaCNBH_3$ gave compounds **4a–d** in 82–87% yield and high purity. Desilylation of **4b** and hydrogenolytic debenzylation of **4c** afforded (±)-laudanidine (**2**) in 85% and 98% yield, respectively, while debenzylation of **4d** produced (±)-armepavine (**3**) in 97% yield (Scheme 2).

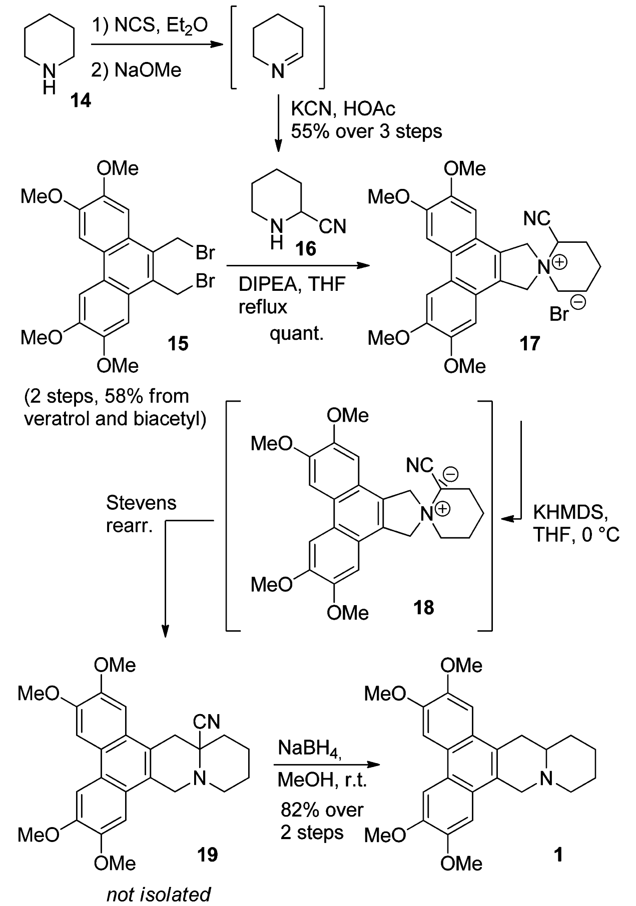
Scheme 2. Synthesis of Benzyltetrahydroisoquinolines 4a–d



For the preparation of 7-methoxycryptopleurine (**1**), spiro ammonium salt **17** was prepared in quantitative yield by reaction of pyrrolidine-2-carbonitrile **16**, prepared from piperidine (**14**) by N-chlorination and basic dehydrochlorination followed by HCN addition,[48,49] with dibromide **15**.[36] It could be converted to **1** in 82% yield over two steps without isolation of the intermediate aminonitrile **19** (Scheme 3). The isolation of **17** can be circumvented if a one-pot procedure is applied to **15**, generating **1** in 53% yield.

Reaction of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**21**)[50,51] with dibromide **23** obtained by double bromomethylation of vertatrole (**22**) according to Tayama et al.

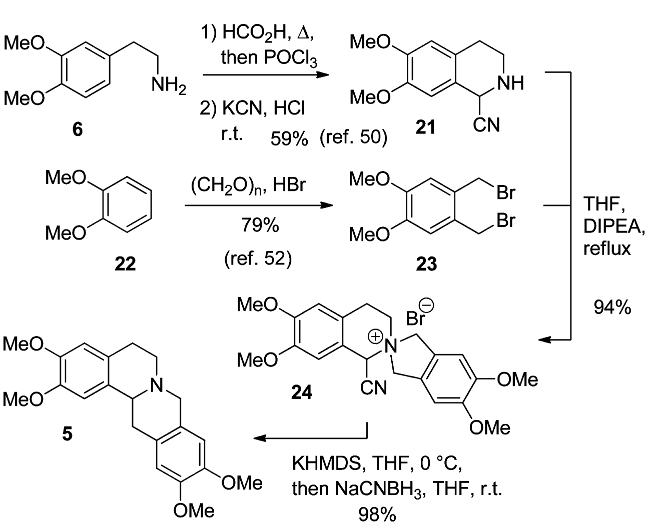
Scheme 3. Synthesis of (±)-7-Methoxycryptopleurine



gave the spirocyclic ammonium salt **24** (94%).[52] Xylopinine (**5**) was obtained after Stevens rearrangement followed by reduction of the crude α-aminonitrile with $NaCNBH_3$ in 98% yield over two steps. By combining the N-alkylation with the rearrangement/reduction sequence in a one-pot procedure, the overall yield of **5** could be increased to 97% (Scheme 4).[32]

In summary, the Stevens rearrangement of nitrile-stabilized ammonium ylides in combination with the reductive removal of the nitrile group provides an efficient method for the construction of polycyclic alkaloids from simple precursors. In the case of (±)-7-methoxycryptopleurine (**1**), this represents the shortest synthesis of this compound reported so far. The nitrile group allows the unambiguous selection of the end point of the 1,2-migration, being an advantage over the direct deprotonation of ammonium salts which may result in the formation of product mixtures if more than one site for a thermodynamically feasible proton abstraction exists. No products resulting from a competing Sommelet–Hauser rearrangement,[23,53] a [1,4]-migration[54] or Hofmann elimination[47] were detected in our reactions. Compared to the use of α-stannylated or α-silylated ammonium salts,[34,55,56] α-aminonitriles are more easy and economical to prepare. Currently, we are investigating asymmetric reductions for the enantioselective synthesis of α-branched amines.

Scheme 4. Synthesis of (±)-Xylopinine



■ EXPERIMENTAL SECTION

General Methods. All reactions requiring anhydrous conditions were performed in dried glassware under argon atmosphere. Reactions requiring a temperature of 0 °C were performed using a water/ice bath. All reagents and solvents were obtained from commercial suppliers without further purification. Anhydrous THF was distilled from potassium/benzophenone under argon. Melting points were determined in open capillary tubes and are uncorrected. NMR spectra were recorded with a 300 MHz spectrometer (300 MHz ^{1}H and 75.5 MHz ^{13}C), a 400 MHz (400 MHz ^{1}H and 100.6 MHz ^{13}C), or a 600 MHz spectrometer (600 MHz ^{1}H and 151 MHz ^{13}C). Deuterated solvents were used as internal standard. The spectra were measured in $CDCl_3$ and DMSO-d_6, the chemical shifts were referenced to the residual solvent signal ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm; DMSO-d_6: δ_H = 2.50 ppm, δ_C = 39.52 ppm).[57] IR spectra were recorded using a diamond ATR unit or NaCl plates and are reported in terms of frequency of absorption (ν, cm^{-1}). ESI-HRMS spectra were recorded on a Q-TOF instrument with a dual source and a suitable external calibrant. Thin-layer chromatography was carried out on 0.25-mm silica gel plates with fluorescence indicator. Substance bands were detected by illumination with UV light (254 and 360 nm).

6,7-Dimethoxy-3,4-dihydroisoquinoline (7). Under ice cooling, formic acid (3.48 g, 75.6 mmol) was added to 3,4-dimethoxyphenylethylamine **6** (10.0 g, 55.2 mmol). The reaction mixture was heated to reflux over 2 h or until TLC indicated complete conversion.[58] After cooling and following the methodology of Rohloff and co-workers,[59] the yellow reaction mixture was diluted with dichloromethane (10 mL) and PCl_5 (12.9 g, 61.8 mmol) was added in small portions over 90 min while maintaining the temperature between 35–40 °C. The HCl generated was collected in a gas scrubber with a 1 N NaOH solution. After the addition, the reaction mixture was stirred for additional 30 min at the same temperature. After cooling, a mixture of ice (30 g) and hexane (10 mL) was added, and the aqueous layer was separated. The organic residue was washed with water (2 × 50 mL) and the combinated aqueous layers were adjusted to pH > 12 by careful addition of NaOH (cooling). The mixture was extracted with diethyl ether (4 × 50 mL), the extracts were dried over Na_2SO_4, and the solvent was removed in vacuo to give **7** (10.5 g, 87%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.21 (s, 1H, H-1), 6.79 (s, 1H, H-8), 6.66 (s, 1H, H-5), 3.90, 3.88 (2s, 2 × 3H, C^6–OCH$_3$, C^7–OCH$_3$), 3.71 (t, J = 7.8 Hz, 2H, H-4), 2.66 (t, J = 7.8 Hz, 2H, H-3) ppm.

3,4-Dihydro-3,4-dimethoxy-2-methylisoquinolinium iodide (8). Methyl iodide (1.14 mL, 18.3 mmol) was added dropwise to a solution of compound **7** (2.01 g, 9.21 mmol) in dry diethyl ether. The reaction mixture was stirred overnight at room temperature. The precipitate was filtered off and washed several times with diethyl ether. After drying in vacuo, compound **8** (3.05 g, quantitative yield) was obtained as a yellow solid. Mp: 198–200 °C dec (lit.[60] mp 200–201 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.67 (s, 1H, H-1), 7.55 (s, 1H, H-8), 6.86 (s, 1H, H-5), 4.01(t, J = 8.4 Hz, 2H, H-3), 3.98 (s, 3H, C^6-

OCH_3), 3.87 (s, 3H, N-CH_3), 3.85 (s, 3H, C^7-OCH_3), 3.28 (t, J = 8.4 Hz, 2H, H-4) ppm.

1-Cyano-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (9). A solution of KCN (1.76 g, 27.0 mmol) in water (5 mL) was added to a solution of the isoquinolinium salt **8** (2.09 g, 8.99 mmol) in water (20 mL). The reaction mixture was stirred overnight at room temperature and was extracted with dichloromethane (3 × 20 mL). The combined organic layers were washed with water and dried over Na_2SO_4, and the solvent was evaporated in vacuo to afford the compound **9** (2.06 g, 99%) as a yellow solid. Mp: 126−128 °C dec (lit.[61] mp 127−128 °C). R_f = 0.61 (cyclohexane/EtOAc/HNEt$_2$ = 5/3/1). IR (NaCl): 2940 (m), 2805 (m), 2217 (w), 1612 (m), 1518 (s), 1464 (m), 1256 (s), 1227 (s), 1140 (s), 1103 (s), 1012 (s) cm^{-1}. ^1H NMR, COSY (400 MHz, $CDCl_3$) δ = 6.64 (s, 1H, H-8), 6.59 (s, 1H, H-5), 4.63 (s, 1H, H-1), 3.83, 3.84 (2s, 2 × 3H, C^6-OCH_3, C^7-OCH_3), 3.0−2.90 (m, H_b-4), 2.89−2.82 (m, H_a-3), 2.74 (dd, J = 11.0, 4.0 Hz, 1H, H_b-3), 2.71−2.64 (m, 1H, H_b-4), 2.57 (s, 1H, N−CH_3) ppm. ^{13}C NMR, HMBC, HSQC (100,6 MHz, $CDCl_3$) δ = 149.2 (C7), 147.8 (C6), 126.2 ($C8_a$), 121.3 ($C4_a$), 116.8 (CN), 111.5 (C5), 109.4 (C8), 56.6 (C1), 56.0 (C^6−OMe), 55.9 (C^7−OMe), 48.4 (C3) 43.7 (N−CH_3), 28.1 (C4) ppm.

Synthesis of Benzyl Bromides 10a−d. 3,4-Dimethoxybenzyl bromide (**10a**), 4-methoxy-3-(triisopropylsilanyloxy)benzyl bromide (**10b**), 4-methoxy-3-(benzyloxy)benzyl bromide (**10c**), and 4-(benzyloxy)benzyl bromide (**10d**) were prepared according to known procedures.[62−65]

General Procedure for the Preparation of *cis/trans*-2-Aryl-1-cyano-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium Salts (11a−d). The benzylic bromide (1.72 mmol) was added to a stirred solution of **9** (0.860 mmol) in dry THF (6 mL). The mixture was heated to 40 °C for 1−3 days. The precipitate formed was filtered and washed several times with THF to afford the title compounds.

***cis/trans*-1-Cyano-2-(3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium bromide (11a).** The reaction was carried out during 24 h using isoquinoline **9** (200 mg, 0.861 mmol) and bromide **10a** (397 mg, 1.72 mmol). The isoquinolinium salt **11a** was obtained as a diastereomeric mixture in a 12:88 *cis/trans*-ratio (^1H NMR) in the form of a pale yellow solid (378 mg, 95%) which was used in the next step without further purification. IR (ATR): 2959 (w, br), 2836 (w), 2566 (w), 1728 (w), 1606 (m), 1518 (s), 1465 (m), 1262 (s), 1119 (m), 817 (m) cm^{-1}. ^1H NMR, COSY, NOESY (600 MHz, DMSO-d_6) *trans*-**11a**: δ = 7.12 (s, 2H, H-5′, H-2′), 7.06 (s, 1H, H-6′), 7.04 (s, 1H, H-5), 7.03 (s, 1H, H-8), 6.37 (s, 1H, H-1), 4.87 (d, J = 12.9 Hz, 1H, N-CH_a-Ar), 4.75 (d, J = 12.9 Hz, 1H, N-CH_b-Ar), 3.98−3.91 (m, 1H, H_a-3), 3.90−3.84 (m, 1H, H_b-3), 3.82−3.80 (3s, 3 × 3H, $C^{4'}$-OCH_3, C^6-OCH_3, C^7-OCH_3), 3.79 (s, 3H, $C^{3'}$-OCH_3), 3.26 (s, 3H, N-CH_3), 3.26−3.19 (m, 2H, H-4) ppm. Characteristic signals for *cis*-**11a**: δ = 6.20 (s, 1H, H-1), 4.94 (d, J = 12.9 Hz, 1H, N-CH_a-Ar), 4.90 (d, J = 12.9 Hz, 1H, N-CH_b-Ar) ppm. ^{13}C NMR, HMBC, HSQC (150.6 MHz, DMSO-d_6) δ = 150.8 (C6), 150.3 (C4′), 148.7 (C3′), 148.4 (C7), 126.4 (C2′), 122.6 ($C4_a$), 118.1 (C1′) 116.0 (C6′), 114.1 ($C8_a$), 113.7 (CN), 112.1 (C5), 111.8 (C5′), 109.5 (C8), 65.8 (N-CH_2-Ar), 59.3 (C1), 56.8 (C3), 55.8 (C^6-OMe), 55.7 (C^7-OMe), 55.6 ($C^{4'}$-OMe), 55.5 ($C^{3'}$-OMe), 46.2 (N-CH_3), 22.5 (C4) ppm. ESI-MS (m/z): 206.0 (100) $[M - C_{10}H_{11}NO_2]^+$, 383.1 (65) $[M]^+$, 356.2 (14.8) $[M - HCN]^+$. ESI-HRMS: calcd for $[C_{22}H_{27}N_2O_4]^+$ 383.1971, found 383.1958.

***cis/trans*-1-Cyano-6,7-dimethoxy-2-(4-methoxy-3-(triisopropylsilyloxy)benzyl)-2-methyl-1,2,3,4-tetrahydroisoquinolinium Bromide (11b).** The reaction was carried out during 48 h using isoquinoline **9** (200 mg, 0.861 mmol) and bromide **10b** (642 mg, 1.72 mmol). The isoquinolinium salt **11b** was obtained as a diastereomeric mixture in a *cis/trans*-ratio of 13:87 (^1H NMR), in the form of a pale yellow solid (442 mg, 85%) which was used in the next step without further purification. IR (ATR): 2941 (w, br), 2865 (w), 2562 (w), 1658 (w), 1602 (m), 1513 (s), 1442 (m), 1268 (s), 1166 (m), 810 (m) cm^{-1}. ^1H NMR, COSY, NOESY (400 MHz, DMSO-d_6) *trans*-**11b**: δ = 7.14 (s, 2H, H-5′, H-2′), 7.02 (s, 1H, H-5), 7.00 (s, 1H, H-6′), 6.99 (s, 1H, H-8), 6.37 (s, 1H, H-1), 4.86 (d, J = 12.8 Hz, 1H, N-CH_a-Ar), 4.75 (d, J = 12.8 Hz, 1H, N-CH_b-Ar), 3.99−3.89 (m, 1H, H_a-3), 3.88−3.81 (m, 1H, H_b-3), 3.81, 3.80 (2s, 2 × 3H, $C^{4'}$-OCH_3, C^6−OCH_3), 3.79 (s, 3H, C^7-OCH_3), 3.24 (s, 3H, N-CH_3), 3.24−3.13 (m, 2H, H-4), 1.29−1.16 (m, 3H, TIPS-CH), 1.04 (d, J = 7.5 Hz, 3 × 6H, TIPS-CH_3) ppm. Characteristic signal of *cis*-**11b**: δ = 7.19 (s, 2H, H-5′, H-2′), 6.18 (s, 1H, H-1), 4.95 (d, J = 12.8 Hz, 1H, N-CH_a-Ar) ppm. ^{13}C NMR, HMBC, HSQC (100.6 MHz, DMSO-d_6) δ = 152.6 (C4′), 150.1 (C6), 148.5 (C7), 144.5 (C3′), 127.3 (C2′), 124.4 (C6′), 122.6 ($C4_a$), 118.1 (C1′), 114.5 ($C8_a$), 113.4 (CN), 112.6 (C5′), 112.1 (C5), 109.4 (C8), 65.5 (N-CH_2-Ar), 59.2 (C1), 56.7 (C3), 55.8 (C^6-OMe), 55.7 ($C^{4'}$-OMe), 55.2 (C^7-OMe), 46.8 (N-CH_3), 22.6 (C4), 17.8 (6 × CH_3), 12.3 (3 × CH) ppm. ESI-MS (m/z): 498.3 (100) $[M - HCN]^+$, 206.0 (82) $[M - C_{18}H_{29}NO_2Si]^+$, 525.20 (39) $[M]^+$. ESI-HRMS: calcd for $[C_{30}H_{45}N_2O_4Si]^+$ 525.3149, found 525.3156.

***cis/trans*-2-(3-(Benzyloxy)-4-methoxybenzyl)-1-cyano-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium Bromide (11c).** The reaction was carried out during 48 h using isoquinoline **9** (200 mg, 0.861 mmol) and bromide **10c** (528 mg, 1.72 mmol). The isoquinolinium salt **11c** was obtained as a diastereomeric mixture in a *cis/trans*-ratio of 6:94 (^1H NMR) in the form of a beige solid (339 mg, 73%) which was used in the next step without further purification. The NMR spectra showed the presence of some remaining THF, the attempted removal of which led to beginning decomposition. IR (ATR): 2943 (w, br), 2838 (w), 2564 (w), 1663 (w), 1606 (m), 1521 (s), 1443 (m), 1263 (s), 1121 (m), 815 (m) cm^{-1}. ^1H NMR, COSY, NOESY (600 MHz, DMSO-d_6) *trans*-**11c**: δ = 7.45 (d, J = 7.5 Hz, 2H, H-2″, H-6″), 7.41 (t, J = 7.5 Hz, 2H, H-3″, H-5″), 7.35 (t, J = 7.5 Hz, 1H, H-4″), 7.17−7.11 (m, 3H, H-6′, H-5′, H-2′), 7.05 (s, 1H, H-5), 7.03 (s, 1H, H-8), 6.30 (s, 1H, H-1), 5.16 (d, J = 11.7 Hz, 1H, O-CH_a-Ph), 5.11 (d, J = 11.7 Hz, 1H, O-CH_b-Ph), 4.80 (d, J = 12.9 Hz, 1H, N-CH_a-Ar), 4.72 (d, J = 12.9 Hz, 1H, N-CH_b-Ar), 3.97−3.91 (m, 1H, H_a-3), 3.90−3.83 (m, 1H, H_b-3), 3.83 (s, 3H, $C^{4'}$-OCH_3), 3.82 (s, 3H, C^6-OCH_3, 3.78 (s, 3H, C^7-OCH_3), 3.21 (s, 3H, N-CH_3), 3.27−3.17 (m, 2H, H-4) ppm. Characteristic signal for *cis*-**11c**: δ = 7.07 (s, 1H, H-5), 7.01 (s, 1H, H-8), 6.15 (s, 1H, H-1) ppm. ^{13}C NMR, HMBC, HSQC (150.6 MHz, DMSO-d_6) δ = 151.1 (C4′), 150.3 (C6), 148.5 (C7), 147.7 (C3′), 136.6 (C1″), 128.5 (C3″, C5″), 128.0 (C4″), 127.9 (C2″, C6″), 126.7 (C2′), 122.6 ($C4_a$), 117.9 (C1′), 117.7 (C6′), 114.1 ($C8_a$), 113.7 (CN), 112.1 (C5), 111.8 (C5′), 109.5 (C8), 69.8 (O-CH_2-Ar), 66.0 (N-CH_2-Ar), 59.3 (C1), 56.8 (C3), 55.8 (C^6-OMe, C^7-OMe), 55.7 ($C^{4'}$-OMe), 46.1 (N-CH_3), 22.5 (C4) ppm. ESI-MS (m/z): 206.0 (100) $[M - C_{16}H_{15}NO_2]^+$, 432.2 (94) $[M - HCN]^+$, 559.1 (91) $[M]^+$. ESI-HRMS: calcd for $[C_{28}H_{31}N_2O_4]^+$ 459.2284, found 459.2283.

***cis/trans*-2-(4-(Benzyloxy)benzyl)-1-cyano-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolinium Bromide (11d).** The reaction was carried out during 72 h using isoquinoline **9** (200 mg, 0.861 mmol) and bromide **10d** (528 mg, 1.72 mmol) of. The isoquinolinium salt **11d** was obtained as a diastereomeric mixture in a *cis/trans*-ratio of 3:97 (^1H NMR) in the form of a beige solid (267 mg, 61%) which was used in the next step without further purification. The NMR spectra showed the presence of some remaining THF, the attempted removal of which led to beginning decomposition. IR (ATR): 2972 (w), 2838 (w), 2564 (w), 1662 (w), 1610 (m), 1516 (s), 1454 (m), 1237 (s), 1119 (s), 811 (m) cm^{-1}. ^1H NMR, COSY, NOESY (600 MHz, DMSO-d_6) *trans*-**11d**: δ = 7.50 (d, J = 8.4 Hz, 2H, H-2′, H-6′), 7.47 (d, J = 7.5 Hz, 2H, H-2″, H-6″), 7.41 (t, J = 7.5 Hz, 2H, H-3″, H-5″), 7.35 (t, J = 7.5 Hz, 1H, H-4″), 7.18 (d, J = 8.4 Hz, 2H, H-3′, H-5′), 7.02 (s, 1H, H-5), 6.99 (s, 1H, H-8), 6.36 (s, 1H, H-1), 5.17 (s, 2H, O-CH_2-Ph), 4.85 (d, J = 12.9 Hz, 1H, N-CH_a-Ar), 4.78 (d, J = 12.9 Hz, 1H, N-CH_b-Ar), 3.97−3.91 (m, 1H, H_a-3), 3.90−3.81 (m, 1H, H_b-3), 3.80 (2s, 2 × 3H, C^6−OCH_3, C^7-OCH_3), 3.23 (s, 3H, N-CH_3), 3.27−3.17 (m, 2H, H-4) ppm. Characteristic signals for *cis*-**11d**: δ = 7.18 (d, J = 8.6 Hz, 2H, H-3′, H-5′), 6.91 (s, 1H, H-5), 6.90 (s, 1H, H-8), 6.14 (s, 1H, H-1), 4.94 (d, J = 13.1 Hz, 1H, N-CH_a-Ar), 4.90 (d, J = 13.1 Hz, 1H, N-CH_b-Ar) ppm. ^{13}C NMR, HMBC, HSQC (150.6 MHz, DMSO-d_6) δ = 160.8 (C4′), 150.6 (C6), 148.9 (C7), 137.1 (C1″), 135.3 (C2′, C6′) 129.0 (C3″, C5″) 128.6 (C4″), 128.3 (C2″, C6″), 123.0 ($C4_a$), 118.6 (C1′), 115.9 (C3′, C5′), 114.5 ($C8_a$), 114.1 (CN), 112.4 (C5), 110.0 (C8), 69.9 (O-CH_2-Ph), 66.4 (N-CH_2-Ar), 60.0 (C1), 56.9 (C3), 56.3 (C^6-OMe), 56.2 (C^7-OMe), 46.2 (N-CH_3), 23.0 (C4) ppm. ESI-MS (*m*/*z*): 206.0 (100) [M − $C_{15}H_{13}NO$]$^+$, 402.2 (82) [M − HCN]$^+$, 429.1 (31) [M]$^+$. ESI-HRMS: calcd for [$C_{27}H_{29}N_2O_3$]$^+$ 429.2178, found 429.2191.

General Procedure for the Stevens Rearrangement and Reductive Decyanation.[36] A solution of KHMDS (56 mg, 0.28 mmol) in dry THF (1 mL) was added to a stirred suspension of the corresponding salt (0.26 mmol) in dry THF (7 mL) at 0 °C. After the solution was stirred for 1.5−3 h at this temperature, EtOH (1 mL) and $NaCNBH_3$ (57 mg, 0.91 mmol) were added, and the mixture was allowed to reach room temperature. Acetic acid (85 μL, 1.5 mmol) was added dropwise, and the mixture was stirred for 12 h. Saturated aq $NaHCO_3$ (15 mL) was added, and the product was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The products **4a**−**d** were purified by recrystallization or column chromatography.

(±)-Laudanosine (4a). According to the general procedure and after 14 h of reaction time, compound **4a** (77 mg, 83%) was obtained from the isoquinolinium salt **11a** (120 mg, 0.259 mmol) as a white solid after recrystallization from ethanol. Mp: 114−116 °C dec (lit.[66] mp 114−115 °C). R_f = 0.4 ($CHCl_3$/MeOH = 10/1). IR (ATR): 2932 (m, br), 2832 (m), 1608 (w), 1511 (s), 1463 (m), 1226 (s), 1138 (s), 1101 (m), 1027 (s), 861 (m) cm^{-1}. ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 6.74 (d, *J* = 8.1 Hz, 1H, H-5′), 6.61 (dd, *J* = 8.1, 1.9 Hz, 1H, H-6′), 6.58 (d, *J* = 1.9 Hz, 1H, H-2′), 6.54 (s, 1H, H-5), 6.03 (s, 1H, H-8), 3.82, 3.81 (2s, 2 × 3H, C^6-OCH_3, $C^{4'}$-OCH_3), 3.76 (s, 3H, $C^{3'}$-OCH_3), 3.68 (dd, *J* = 7.7, 4.9 Hz, 1H, H-1), 3.55 (s, 3H, C^7-OCH_3), 3.19 − 3.13 (m, 1H, H_a-3), 3.13 (dd, *J* = 13.7, 4.9 Hz, 1H, Ar-CH_a), 2.87− 2.69 (m, 2H, H_a-4, H_b-3), 2.75 (dd, *J* = 13.7, 7.7 Hz, 1H, Ar-CH_b), 2.57 (dt, *J* = 14.9, 4.0 Hz, 1H, H_b-4), 2.52 (s, 3H, N-CH_3) ppm. ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 148.5 (C4′), 147.3, 147.2 (C6, C3′), 146.3 (C7), 132.4 (C1′), 129.1 ($C8_a$), 125.9 ($C4_a$), 121.8 (C6′), 112.9 (C2′), 111.1 (C5), 111.0 (C8), 110.9 (C5′), 64.8 (C1), 55.9, 55.8 (C^6-OCH_3, $C^{4'}$-OCH_3), 55.7 ($C^{3'}$-OCH_3), 55.5 (C^7-OCH_3), 46.9 (C3), 42.6 (N-CH_3), 40.8 (Ar-CH_2), 25.5 (C4) ppm. ESI-MS (*m*/*z*): 358.1 (100) [M + H]$^+$. ESI-HRMS: calcd for [$C_{21}H_{27}NO_4$ + H]$^+$ 358.2018, found 358.2010. The spectroscopic data are in accordance with those reported in the literature.[67]

(±)-*O*-(Triisopropylsilyl)laudanidine (4b). According to the general procedure and after 15 h of reaction time, compound **4b** (109 mg, 84%) was obtained from the isoquinolinium salt **11b** (157 mg, 0.259 mmol) as a pale yellow oil after purification by column chromatography (cyclohexane/EtOAc/$HNEt_2$ = 10/3/1). R_f = 0.60 (cyclohexane/EtOAc/$HNEt_2$ = 5/3/1). IR (ATR): 2940 (m, br), 2864 (m), 1608 (w), 1510 (s), 1463 (m), 1227 (s), 1136 (s), 1102 (m), 1032 (m), 882 (m) cm^{-1}. ^{1}H NMR, COSY (600 MHz, $CDCl_3$) δ = 6.71 (d, *J* = 2.1 Hz, 1H, H-2′), 6.70 (d, *J* = 8.2 Hz, 1H, H-5′), 6.55 (dd, *J* = 8.2, 2.1 Hz, 1H, H-6′), 6.54 (s, 1H, H-5), 6.13 (s, 1H, H-8), 3.83 (s, 3H, C^6-OCH_3), 3.76 (s, 3H, $C^{4'}$-OCH_3), 3.62 (dd, *J* = 7.5, 4.7 Hz, 1H, H-1), 3.60 (s, 3H, C^7-OCH_3), 3.14 (ddd, *J* = 12.4, 8.7, 5.1 Hz, 1H, H_a-3), 3.07 (dd, *J* = 13.7, 4.7 Hz, 1H, Ar-CH_a), 2.80 (ddd, *J* = 15.9, 8.7, 5.6 Hz, 1H, H_a-4), 2.76−2.69 (m, 1H, H_b-3), 2.73 (dd, *J* = 13.7, 7.5 Hz, 1H, Ar−CH_b), 2.58 (dt, *J* = 15.9, 4.8 Hz, 1H, H_b-4), 2.51 (s, 3H, N-CH_3), 1.26−1.17 (m, 3H, TIPS-CH), 1.07 (d, *J* = 7.4 Hz, 18H, TIPS-CH_3) ppm. ^{13}C NMR, HMBC, HSQC (150.6 MHz, $CDCl_3$) δ = 149.3 (C4′), 147.3 (C6), 146.5 (C7), 145.3 (C3′), 132.6 (C1′), 129.6 ($C8_a$), 126.1 ($C4_a$), 122.8 (C2′), 121.9 (C5′), 111.9 (C6′), 111.1 (C5), 110.9 (C8), 65.1 (C1), 55.8, 55.7 (C^6-OCH_3, $C^{4'}$-OCH_3), 55.6 (C^7-OCH_3), 47.3 (C3), 42.9 (N-CH_3), 40.6 (Ar-CH_2), 25.8 (C4), 18.0 (6 × CH_3), 13.0 (3 × CH) ppm. ESI-MS (*m*/*z*): 500.2 (100) [M]$^+$. ESI-HRMS: calcd for [$C_{29}H_{45}NO_4Si$ + H]$^+$ 500.3196, found 500.3179.

(±)-*O*-Benzyllaudanidine (4c). According to the general procedure and after 15 h of reaction time, compound **4c** (112 mg, 82%) was obtained from the isoquinolinium salt **11c** (140 mg, 0.260 mmol) as a white solid after recrystallization from ethanol. Mp: 90−92 °C dec (lit.[68] mp 90.5−91.5 °C). R_f = 0.69 (cyclohexane/EtOAc/$HNEt_2$ = 5/3/1). IR (ATR): 2937 (m, br), 2860 (m), 1610 (w), 1510 (s), 1463 (m), 1275 (s), 1131 (s), 1101 (m), 1015 (m), 863 (m) cm^{-1}. ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.41 (d, *J* = 7.0 Hz, 2H, H-6″, H-2″), 7.34 (t, *J* = 7.3 Hz, 2H, H-5″, H-3″), 7.28 (m, 1H, H-4″), 6.77 (d, *J* = 8.1 Hz, 1H, H-5′), 6.66 (d, *J* = 2.0 Hz, 1H, H-2′), 6.60 (dd, *J* = 8.1, 2.0 Hz, 1H, H-6′), 6.54 (s, 1H, H-5), 5.99 (s, 1H, H-8), 5.07 (s, 2H, Ph-CH_2), 3.84, 3.83 (2s, 2 × 3H, C^6-OCH_3, $C^{4'}$-OCH_3), 3.59 (dd, *J* = 7.7, 5.1 Hz, 1H, H-1), 3.16 − 3.07 (m, 1H, H_a-3), 3.06 (dd, *J* = 13.7, 5.1 Hz, 1H, Ar-CH_a), 2.84−2.77 (m, 1H, H_a-4), 2.76−2.69 (m, 1H, H_b-3), 2.72 (dd, *J* = 13.7, 7.7 Hz, 1H, Ar-CH_b), 2.54 (dt, *J* = 15.6, 4.6 Hz, 1H, H_b-4), 2.48 (s, 3H, N-CH_3) ppm. ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 148.1 (C4′), 147.8 (C3′), 147.3 (C6), 146.4 (C7), 137.4 (C1″), 132.5 (C1′), 129.4 ($C4_a$), 128.6 (C3″, C5″), 127.9 (C4″), 127.4 (C2″, C6″), 126.1 ($C8_a$), 122.7 (C6′), 115.9 (C2′), 111.7 (C5′), 111.2 (C5), 111.0 (C8), 71.1 (Ph-CH_2), 64.9 (C1), 56.2, 55.9 (C^6-OCH_3, $C^{4'}$-OCH_3), 55.6 (C^7-OCH_3), 47.1 (C3), 42.8 (N-CH_3), 40.8 (Ar-CH_2), 25.7 (C4) ppm. ESI-MS (*m*/*z*): 434.2 (100) [M + H]$^+$. ESI-HRMS: calcd for [$C_{27}H_{31}NO_4$ + H]$^+$ 434.2331, found 434.2329. The spectroscopic data are in accordance with those reported in the literature.[68]

(±)-*O*-Benzylarmepavine (4d). According to the general procedure and after 13 h of reaction time, compound **4d** (91 mg, 87%) was obtained from the isoquinolinium salt **11d** (132 mg, 0.259 mmol) as a viscous yellow oil after purification by column chromatography (cyclohexane/EtOAc/$HNEt_2$ = 10/3/1). R_f = 0.58 (cyclohexane/EtOAc/$HNEt_2$ = 5/3/1). IR (ATR): 2926 (m, br), 2858 (m), 1612 (w), 1511 (s), 1463 (m), 1250 (s), 1101 (m), 1066 (m), 1015 (m), 862 (m) cm^{-1}. ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.44−7.35 (m, 4H, H-6″, H-5″, H-3″, H-2″), 7.34−7.29 (m, 1H, H-4″), 7.01 (d, *J* = 8.5 Hz, 2H, H-6′, H-2′), 6.88 (d, *J* = 8.5 Hz, 2H, H-5′, H-3′), 6.55 (s, 1H, H-5), 6.00 (s, 1H, H-8), 5.04 (s, 2H, Ph-CH_2), 3.83 (s, 3H, C^6-OCH_3), 3.67 (dd, *J* = 7.9, 5.0 Hz, 1H, H-1), 3.52 (s, 3H, C^7-OCH_3), 3.24−3.13 (m, 1H, H_a-3), 3.14 (dd, *J* = 13.7, 5.0 Hz, 1H, Ar-CH_a), 2.88−2.81 (m, 1H, H_a-4), 2.80−2.71 (m, 1H, H_b-3), 2.75 (dd, *J* = 13.7, 7.9 Hz, 1H, Ar-CH_b), 2.59 (dt, *J* = 15.5, 4.5 Hz, 1H, H_b-4), 2.53 (s, 3H, N-CH_3) ppm. ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 157.2 (C4′), 147.3 (C6), 146.3 (C7), 137.3 (C1″), 132.3 (C1′), 130.8 (C6′-C2′), 129.4 ($C8_a$), 128.7 (C5″, C3″), 128.0 (C4″), 127.5 (C6″, C2″), 126.0 ($C4_a$), 114.7 (C5′, C3′), 111.2 (C5), 111.1 (C8), 70.1 (Ph-CH_2), 65.0 (C1), 56.0 (C^6-OCH_3), 55.6 (C^7-OCH_3), 46.9 (C3), 42.3 (N-CH_3), 40.5 (Ar-CH_2), 25.6 (C4) ppm. ESI-MS (*m*/*z*): 404.2 (100) [M + H]$^+$. ESI-HRMS: calcd for [$C_{26}H_{29}NO_3$ + H]$^+$ 404.2226, found 404.2212.

(±)-Laudanidine (2). *Method A.* To a solution of silyl ether **4b** (90 mg, 0.18 mmol) in DMF (1 mL) was added a solution of KF (21 mg, 0.36 mmol) in water (0.1 mL). After the reaction mixture was stirred overnight at room temperature, satd aq NH_4Cl (8 mL) was added and the mixture was extracted with EtOAc (4 × 5 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. To remove the remaining silicon compounds, the crude material was dissolved in MeCN (3 mL) and extracted with *n*-hexane (6 mL). The MeCN layer was concentrated in vacuo to afford the title compound (53 mg, 85%) as a white solid. Mp: 165−166 °C dec (lit.[69] mp 164−165 °C). R_f = 0.26 (cyclohexane/EtOAc/$HNEt_2$ = 5/3/1). IR (ATR): 3437 (w, br), 2937 (m, br), 2835 (w), 1610 (w), 1510 (s), 1463 (m), 1253 (s), 1131 (m), 1015 (m), 863 (m) cm^{-1}. ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 6.78 (d, *J* = 2.1 Hz, 1H, H-2′), 6.72 (d, *J* = 8.2 Hz, 1H, H-5′), 6.55 (s, 1H, H-5), 6.53 (dd, *J* = 8.2, 2.1 Hz, 1H, H-6′), 6.06 (s, 1H, H-8), 3.85, 3.83 (2s, 2 × 3H, C^6-OCH_3, $C^{4'}$-OCH_3), 3.68 (dd, *J* = 7.7, 5.2 Hz, 1H, H-1), 3.57 (s, 3H, C^7-OCH_3), 3.19 (ddd, *J* = 12.5, 8.8, 5.1 Hz, 1H, H_a-3), 3.11 (dd, *J* = 13.7, 5.2 Hz, 1H, Ar-CH_a), 2.89−2.74 (m, 2H, H_a-4, H_b-3), 2.71 (dd, *J* = 13.7, 7.7 Hz, 1H, Ar-CH_b), 2.61 (dt, *J* = 15.4, 3.9 Hz, 1H, H_b-4), 2.51 (s, 3H, N-CH_3) ppm. ^{13}C NMR, HMBC, HSQC (100.6 MHz, $CDCl_3$) δ = 147.4 (C6), 146.4 (C7), 145.6 (C3′), 145.1 (C4′), 133.5 (C1′), 129.5 ($C8_a$), 125.8 ($C4_a$), 121.4 (C6′), 115.9 (C2′), 111.2 (C5), 111.1 (C8), 110.6 (C5), 64.9 (C1), 56.1 ($C^{4'}$-OCH_3), 55.9 (C^6-OCH_3), 55.6 (C^7-OCH_3), 46.8 (C3), 42.7 (N-CH_3), 40.9 (Ar-CH_2), 25.4 (C4) ppm. ESI-MS (*m*/*z*): 344.2 (100) [M + H]$^+$. ESI-HRMS: calcd for [$C_{20}H_{25}NO_4$ + H]$^+$ 344.1862, found 344.1856.

The spectroscopic data are in accordance with those reported in the literature.[70]

Method B. A mixture of benzyl ether **4c** (90 mg, 0.21 mmol) and 10% Pd/C (11 mg) in MeOH (8 mL) was stirred under a H_2 atmosphere at room temperature over 3 h. The reaction mixture was filtered through a pad of Celite, and the solvent was evaporated in vacuo to afford the title compound (71 mg, 98%) as a white solid. Mp: 164−166 °C dec. The spectroscopic data of the product are identical to those of the material obtained by method A.

(±)-Armepavine (3). A mixture of benzyl ether **4d** (100 mg, 0.248 mmol) and 10% Pd/C (13 mg) in MeOH (10 mL) was stirred under a H_2 atmosphere at room temperature over 2 h. The reaction mixture was filtered through a pad of Celite, and the solvent was evaporated in vacuo to afford the title compound (76 mg, 97%) as a white solid. Mp: 165−167 °C dec (lit.[71] mp 166 °C). R_f = 0.20 (cyclohexane/EtOAc/HNEt$_2$ = 5/3/1). IR (ATR): 3438 (w, br), 2924 (m), 2835 (w), 1611 (w), 1513 (s), 1463 (m), 1252 (s), 1115 (m), 1014 (m), 829 (m) cm^{-1}. ^{1}H NMR, COSY (600 MHz, CDCl$_3$) δ = 6.90 (d, J = 8.3 Hz, 2H, H-6′, H-2′), 6.63 (d, J = 8.3 Hz, 1H, H-5′, H-3′), 6.56 (s, 1H, H-5), 6.00 (s, 1H, H-8), 3.83 (s, 3H, C^6−OCH$_3$), 3.71 (dd, J = 8.1, 5.2 Hz, 1H, H-1), 3.55 (s, 3H, C^7-OCH$_3$), 3.25 (ddd, J = 12.6, 9.4, 5.3 Hz, 1H, H$_a$-3), 3.13 (dd, J = 13.7, 5.2 Hz, 1H, Ar-CH$_a$), 2.92−2.79 (m, 2H, H$_a$-4, H$_b$-3), 2.74 (dd, J = 13.7, 8.1 Hz, 1H, Ar-CH$_b$), 2.62 (dt, J = 15.9, 5.3 Hz, 1H, H$_b$-4), 2.53 (s, 3H, N-CH$_3$) ppm. ^{13}C NMR, HMBC, HSQC (150.6 MHz, CDCl$_3$) δ = 154.8 (C4′), 147.4 (C6), 146.4 (C7), 131.0 (C1′), 130.9 (C6′, C2′), 128.8 (C8$_a$), 125.3 (C4$_a$), 115.5 (C5′, C3′), 111.2 (C8, C5), 65.0 (C1), 55.9 (C^6-OCH$_3$), 55.6 (C^7-OCH$_3$), 46.2 (C3), 42.2 (N-CH$_3$), 40.6 (Ar-CH$_2$), 24.7 (C4) ppm. ESI-MS (m/z): 314.2 (100) [M+H]$^+$. ESI-HRMS: calcd for [C$_{19}$H$_{23}$NO$_3$ + H]$^+$ 314.1756, found 314.1749.

Piperidine-2-carbonitrile (16). The title compound was prepared in 55% yield from piperidine **14** by combining the protocol of Gravel et al.[48] for the preparation of 1-piperideine with the protocol of De Kimpe et al.[49] for the HCN addition. Colorless oil. Bp: 91−93 °C (16 mbar) (lit.[49] bp 91−95 °C (16 mbar)). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.97 (t, J = 4.2 Hz, CHN), 3.01−2.81 (m, 2H, NCH$_2$), 1.82− 1.41 (m, 6H, CH$_2$CH$_2$CH$_2$).

2′-Cyano-5,6,9,10-tetramethoxy-1,3-dihydrospiro[dibenzo-[*e,g*]isoindole-2,1′-piperidin]-1′-ium Bromide (17). A mixture of 9,10-bis(bromomethyl)-2,3,6,7-tetramethoxyphenanthrene[36] (**15**, 4.40 g, 9.09 mmol) and DIPEA (1.55 mL, 9.11 mmol, 1.0 equiv) in dry THF (100 mL) was heated under reflux with stirring while piperidine-2-carbonitrile (**16**, 1.00 g, 9.07 mmol, 1.0 equiv) was added dropwise. The mixture was heated to reflux for 20 h. It was cooled to room temperature, filtered, and washed with ice-cold water to afford the title compound (4.68 g, quant) as a white solid. Mp: 261−263 °C dec. IR (ATR): 2980 (w), 2866 (w), 1614 (w), 1522 (m), 1483 (s), 1422 (s), 1255 (s), 1160 (s), 857 (s), 770 (m), 624 (m) cm^{-1}. ^{1}H NMR, COSY, NOESY (400 MHz, DMSO-d_6): δ = 8.12 (s, 2H, 2 × Ar-H), 7.34 (s, 1H, Ar-H), 7.26 (s, 1H, Ar-H), 5.86−5.41 (m, 5H, H$_a$-1, H$_b$-1, H$_a$-3, H$_b$-3, H-2′), 4.06 (s, 6H, 2 × OCH$_3$), 3.98 (s, 3H, OCH$_3$), 3.97 (s, 3H, OCH$_3$), 3.95−3.93 (m, 1H), 3.89−3.83 (m, 2H), 2.24−2.10 (m, 1H), 2.09−1.97 (m, 1H), 1.90−1.79 (m, 2H) 1.31−1.20 (m, 1H) ppm. ^{13}C NMR, HMBC, HSQC (100.6 MHz DMSO-d$_6$): δ = 149.6 (C5, C10), 149.1 (C6, C9) 124.8 (Phen), 124.8 (Phen), 124.2 (Phen), 124.2 (Phen), 119.9 (Phen), 119.9 (Phen) 114.4 (CN), 105.5 (Phen), 105.3 (Phen), 104.7 (Phen), 104.7 (Phen), 69.0 (C1, C3) 61.9 (C6′), 60.9 (C2′), 56.1 (2 × OCH$_3$), 55.8 (2 × OCH$_3$) 25.3 (C3′), 20.2, 18.5 ppm. ESI-MS (m/z): 433.2 (100) [M]$^+$. ESI-HRMS: calcd for [C$_{26}$H$_{29}$N$_2$O$_4$]$^+$ 433.2127, found 433.2131.

(±)-7-Methoxycryptopleurine (1). To a stirred solution of 2′-cyano-5,6,9,10-tetramethoxy-1,3-dihydrospiro[dibenzo[*e,g*]isoindole-2,1′-piperidin]-1′-ium bromide (**17**, 500 mg, 0.974 mmol) in dry THF (50 mL) was added KHMDS (214 mg, 1.07 mmol, 1.1 equiv) dissolved in dry THF (4 mL) at 0 °C. The reaction mixture was stirred at this temperature for 2.5 h before ethanol (20 mL) and NaBH$_4$ (120 mg, 3.17 mmol, 3.0 equiv) were added. The mixture was stirred at room temperature for 10 h, quenched with saturated aq. NaHCO$_3$ (40 mL), and extracted with CHCl$_3$ (3 × 100 mL). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO$_2$, CHCl$_3$ + 0.5% MeOH) to afford the title compound (326 mg, 82%) as a white solid. R_f = 0.27 (CH$_2$Cl$_2$/MeOH = 20:1). Mp 243−246 °C dec (lit.[72] mp 246−247 °C). IR (ATR): 2928 (m), 2829 (w, sh), 1614 (w), 1511 (m), 1466 (m), 1423 (s), 1244 (s), 1209 (m), 1149 (m), 1041 (m), 837 (m), 769 (m) 725 (s) cm^{-1}. ^{1}H NMR, COSY (400 MHz, CDCl$_3$): δ = 7.76 (s, 1H, Ar-H), 7.75 (s, 1H, Ar-H), 7.17 (s, 1H, Ar-H), 7.05 (s, 1H, Ar-H), 4.30 (d, ^2J = 15.4 Hz, 1H, H-9), 4.08 (s, 6H, 2 × OCH$_3$), 4.02 (s, 3H, OCH$_3$), 4.01 (s, 3H, OCH$_3$), 3.52 (d, ^2J = 15.4 Hz, 1H, H-9), 3.26 (d, J = 11.5 Hz, 1H, H-11), 3.06−2.95 (m, 1H), 2.90−277 (m, 1H), 2.37−2.22 (m, 2H, H-14a, H-11), 2.05−1.70 (m, 4H), 1.58−1.33 (m, 2H) ppm. ^{13}C NMR, HMBC, HSQC (100.6 MHz, CDCl$_3$): δ = 148.7 (2 × C$_q$-OMe), 148.5 (C$_q$-OMe), 148.3 (C$_q$-OMe), 125.2, 125.1, 124.8, 123.9, 123.5, 123.4 (6 × C$_q$), 103.9, 103.5, 103.3, 103.0 (4 × CH), 57.5 (C14a), 56.4 (C11), 56.2 (C9), 56.1 (2 × OCH$_3$), 56.0 (2 × OCH$_3$), 34.7, 33.7, 26.0, 24.4 ppm. ESI-MS (m/z): 408.3 (100) [M + H]$^+$. ESI-HRMS: calcd for [C$_{25}$H$_{30}$NO$_4$]$^+$ 408.2175, found 408.2166.

One-Pot Procedure. A mixture of 9,10-bis(bromomethyl)-2,3,6,7-tetramethoxyphenanthrene[36] (**15**, 500 mg, 1.03 mmol) and DIPEA (178 μL, 1.05 mmol, 1.0 equiv) in dry THF (30 mL) was heated under reflux with stirring while piperidine-2-carbonitrile (**16**, 121 mg, 1.10 mmol, 1.1 equiv) was added dropwise. The mixture was heated under reflux for 20 h. After cooling to 0 °C, a solution of KHMDS (658 mg, 3.30 mmol, 3.3 equiv) in dry THF (5 mL) was added. The reaction mixture was stirred at this temperature for 2 h before ethanol (20 mL) and NaBH$_4$ (240 mg, 6.34 mmol, 6.2 equiv) were added. The mixture was stirred at room temperature for 20 h, quenched with saturated aq NaHCO$_3$ (50 mL), and extracted with CHCl$_3$ (3 × 100 mL). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO$_2$, CHCl$_3$ + 0.5% MeOH) to afford the title compound (210 mg, 53%) as a white solid. The spectroscopic data of the product were identical to those of the sample prepared by the stepwise method.

1′-Cyano-5,6,6′,7′-tetramethoxy-3′,4′-dihydro-1′*H*-spiro-[isoindoline-2,2′-isoquinolin]-2-ium Bromide (24). A mixture of 1,2-bis(bromomethyl)-4,5-dimethoxybenzene[52] (**23**, 1.48 g, 4.57 mmol) and DIPEA (0.80 mL, 4.7 mmol, 1.0 equiv) in dry THF (50 mL) was heated under reflux with stirring while 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile[58] (**21**, 1.00 g, 4.58 mmol, 1.0 equiv) dissolved in dry THF (10 mL) was added dropwise. The mixture was heated to reflux for 20 h. It was cooled to room temperature, filtered, and washed with ice cooled chloroform (50 mL) to afford the title compound (1.98 g, 94%) as a beige solid. Mp: 205−208 °C dec. IR (ATR): 2995 (w), 2912 (w), 2835 (w), 1510 (s), 1465 (m), 1338 (m), 1260 (s), 1229 (s), 1123 (s), 1105 (m), 989 (m), 852 (m) cm^{-1}. ^{1}H NMR, COSY (400 MHz, DMSO-d_6): δ = 7.15 (s, 1H, Ar-H), 7.07 (s, 2H, 2 × Ar-H), 7.00 (s, 1H, Ar-H), 6.98 (s, 1H, H-1′), 5.32−5.16 (m, 2H, CH$_2$), 5.16 (d, J = 14.8 Hz, 1H, CH$_2$), 4.94 (d, J = 14.8 Hz, 1H, CH$_2$), 4.28−4.17 (m, 1H, H-3′) 4.17−4.04 (m, 1H, H-3′) 3.82 (s, 3H, OCH$_3$), 3.78 (s, 3H, OCH$_3$), 3.76 (s, 6H, 2 × OCH$_3$) 3.38−3.29 (m, 2H, H-4′) ppm. ^{13}C NMR, HMBC, HSQC (100.6 MHz DMSO-d_6): δ = 150.5 (C$_q$-OMe), 149.8 (2 × C$_q$-OMe), 148.3 (C$_q$-OMe), 123.8 (C$_q$), 123.5 (C$_q$), 122.6 (C$_q$), 114.6 (C$_q$), 113.9 (C$_q$), 112.1 (CH), 110.1 (CH), 106.8 (CH), 106.7 (CH), 68.2, 65.8, 59.6 (C1′), 56.3 (C3′), 55.9 (2 × OCH$_3$) 55.8 (OCH$_3$), 55.7 (OCH$_3$), 23.6 (C4′) ppm. ESI-MS (m/z): 381.2 (100) [M]$^+$. ESI-HRMS: calcd for [C$_{22}$H$_{25}$N$_2$O$_4$]$^+$ 381.1814, found 381.1815.

(±)-Xylopinine (5). To a stirred solution 1′-cyano-5,6,6′,7′-tetramethoxy-3′,4′-dihydro-1′*H*-spiro[isoindoline-2,2′-isoquinolin]-2-ium bromide (**24**, 500 mg, 1.08 mmol) in dry THF (50 mL) was added sa solution of KHMDS (239 mg, 1.20 mmol, 1.1 equiv) in dry THF (5 mL) at 0 °C. The reaction mixture was stirred at this temperature for 3.5 h. Ethanol (8 mL) and NaCNBH$_3$ (230 mg, 3.66 mmol, 3.4 equiv) were added, and the mixture was allowed to warm to room temperature before AcOH (1.6 mL) was added dropwise. The mixture was stirred at room temperature for 6 h, quenched with saturated aq NaHCO$_3$ (60 mL), and extracted with CHCl$_3$ (3 × 100 mL). The combined organic layers were washed with brine, dried over

Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, $CHCl_3$ + 2% MeOH) to afford the title compound (376 mg, 98%) as an pale orange solid. Mp: 150−153 °C dec (lit.[73] mp 150−151 °C). R_f = 0.40 (CH_2Cl_2/MeOH) = 19:1. IR (ATR): 2934 (w), 2833 (w), 1609 (w), 1513 (s), 1462 (m), 1257 (s), 1141 (m), 1099 (m), 855 (m), 768 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.73 (s, 1H, Ar-H), 6.66 (s, 1H, Ar-H), 6.60 (s, 1H, Ar-H), 6.57 (s, 1H, Ar-H), 3.93 (d, J = 14.6 Hz, 1H), 3.88 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.67 (d, J = 14.7 Hz, 1H), 3.58 (dd, J = 11.3, 3.9 Hz, 1H), 3.24 (dd, J = 15.8 Hz, 3.9 Hz, 1H), 3.19−3.08 (m, 2H), 2.83 (dd, J = 15.8 Hz, 11.3 Hz, 1H), 2.71−2.56 (m, 2H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 147.6 (C_q-OMe), 147.5 (C_q-OMe), 147.4 (C_q-OMe), 147.3 (C_q-OMe), 129.8, 126.7, 126.3, 126.2 (4 × C_q), 111.4 (2C), 109.0, 108.5 (4 × CH), 59.7, 58.4, 56.1 (4C) 51.5, 36.4, 29.2 ppm. ESI-MS (m/z): 356.2 (100) $[M + H]^+$. ESI-HRMS: calcd for $[C_{21}H_{26}NO_4]^+$ 356.1862, found 356.1852.

One-Pot Procedure. A mixture of 1,2-bis(bromomethyl)-4,5-dimethoxybenzene[52] (**23**, 500 mg, 1.54 mmol) and DIPEA (270 μL, 1.59 mmol, 1.0 equiv) in dry THF (50 mL) was heated under reflux with stirring while 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**21**, 337 mg, 1.54 mmol, 1.0 equiv) dissolved in dry THF (5 mL) was added dropwise. The mixture was heated under reflux for 15 h. After cooling to 0 °C, a solution of KHMDS (922 mg, 4.62 mmol, 3.3 equiv) in dry THF (8 mL) was added. The reaction mixture was stirred at this temperature for 2 h. Ethanol (15 mL) and $NaCNBH_3$ (774 mg, 12.3 mmol, 8.0 equiv) were added, and the solution was allowed to warm to room temperature before AcOH (5 mL) was added dropwise. The mixture was stirred at room temperature for 14 h, quenched with saturated aq $NaHCO_3$ (70 mL), and extracted with $CHCl_3$ (3 × 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, $CHCl_3$ + 2% MeOH) to afford the title compound (531 mg, 97%) as an pale orange solid, mp 149−152 °C dec. The spectroscopic data of the product were identical to those of the sample prepared by the stepwise procedure.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Rhineland-Palatinate Center for Integrated Natural Products Research for helpful discussions as well as Dr. J. C. Liermann (University of Mainz) for NMR spectroscopy and Dr. N. Hanold (University of Mainz) for mass spectrometry.

■ REFERENCES

(1) Albright, J. D. *Tetrahedron* **1983**, *39*, 3207.
(2) Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359.
(3) Shafran, Y. M.; Bakulev, V. A.; Mokrushin, V. S. *Usp. Khim.* **1989**, *58*, 250.
(4) Meyer, N.; Opatz, T. *Synlett* **2003**, 1427.
(5) Opatz, T.; Ferenc, D. *Org. Lett.* **2006**, *8*, 4473.
(6) Opatz, T. *Synthesis* **2009**, 1941.
(7) Jonczyk, A.; Lipiak, D. *J. Org. Chem.* **1991**, *56*, 6933.
(8) Langlois, Y.; Konopski, L.; Bac, N. V.; Chiaroni, A.; Riche, C. *Tetrahedron Lett.* **1990**, *31*, 1865.
(9) Gimranova, G. S.; Soldatova, S. A.; Prokudina, E. G.; Soldatenkov, A. T.; Polyanskii, K. B. *Russ. J. Org. Chem.* **2008**, *44*, 1399.
(10) Zdrojewski, T.; Jończyk, A. *J. Org. Chem.* **1998**, *63*, 452.
(11) Mander, L. N.; Turner, J. V. *J. Org. Chem.* **1973**, *38*, 2915.
(12) Buchi, G.; Wuest, H. *J. Am. Chem. Soc.* **1974**, *96*, 7573.
(13) Vanecko, J. A.; Wan, H.; West, F. G. *Tetrahedron* **2006**, *62*, 1043.
(14) Mander, L. N.; Turner, J. V.; Twitchin, B. *Tetrahedron Lett.* **1981**, *22*, 3017.
(15) Kametani, T.; Suzuki, T.; Sato, E.; Nishimura, M.; Unno, K. *J. Chem. Soc., Chem. Commun.* **1982**, *0*, 1201.
(16) Jończyk, A.; Konarska, A. *Synlett* **1999**, *1999*, 1085.
(17) Jończyk, A.; Kowalkowska, A. *Synthesis* **2002**, *2002*, 0674.
(18) Yang, Z.; Fan, M.; Mu, R.; Liu, W.; Liang, Y. *Tetrahedron* **2005**, *61*, 9140.
(19) Couty, F.; David, O.; Larmanjat, B.; Marrot, J. *J. Org. Chem.* **2007**, *72*, 1058.
(20) Bhattacharjee, S. S.; Ila, H.; Junjappa, H. *Synthesis* **1982**, *1982*, 301.
(21) Kowalkowska, A.; Jończyk, A. *Synth. Commun.* **2011**, *41*, 3308.
(22) Klunder, J. M. *J. Heterocycl. Chem.* **1995**, *32*, 1687.
(23) Kocharyan, S. T.; Ogandzhanyan, S. M.; Razina, T. L.; Babayan, A. T. *Zh. Org. Khim.* **1982**, *18*, 1861.
(24) Liu, Y. X.; Liang, X. T. *Chin. Chem. Lett.* **2001**, *12*, 7.
(25) Mattalia, J.-M.; Marchi-Delapierre, C.; Hazimeh, H.; Chanon, M. *ARKIVOC* **2006**, 90.
(26) Bonin, M.; Romero, J. R.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1982**, *23*, 3369.
(27) Yamada, S.; Akimoto, H. *Tetrahedron Lett.* **1969**, *10*, 3105.
(28) Baldwin, J. E.; Spring, D. R.; Whitehead, R. C. *Tetrahedron Lett.* **1998**, *39*, 5417.
(29) Meyer, N.; Werner, F.; Opatz, T. *Synthesis* **2005**, *2005*, 945.
(30) Kametani, T.; Huang, S.-P.; Koseki, C.; Ihara, M.; Fukumoto, K. *J. Org. Chem.* **1977**, *42*, 3040.
(31) Grethe, G.; Lin Lee, H.; R. Uskoković, M. *Tetrahedron Lett.* **1969**, *10*, 1937.
(32) Paton, J. M.; Pauson, P. L.; Stevens, T. S. *J. Chem. Soc. C* **1969**, *42*, 2130.
(33) Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1979**, *101*, 6452.
(34) Maeda, Y.; Sato, Y. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1491.
(35) Lin, Q.-X.; Ho, T.-L. *Tetrahedron* **2013**, *69*, 2996.
(36) Lahm, G.; Stoye, A.; Opatz, T. *J. Org. Chem.* **2012**, *77*, 6620.
(37) Yang, C. W.; Chuang, T. H.; Wu, P. L.; Huang, W. H.; Lee, S. J. *Biochem. Biophys. Res. Commun.* **2007**, *354*, 942.
(38) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669.
(39) Ganguly, T.; Sainis, K. B. *Phytomedicine* **2001**, *8*, 348.
(40) Yadav, M.; Dwivedi, P.; Singh, P.; Singh, V. K. *Indian J. Plant Physiol.* **2010**, *15*, 297.
(41) Krishna Reddy, B.; Balaji, M.; Uma Reddy, P.; Sailaja, G.; Vaidyanath, K.; Narasimha, G. *Afr. J. Biochem. Res.* **2009**, *3*, 393.
(42) Wang, K.; Su, B.; Wang, Z.; Wu, M.; Li, Z.; Hu, Y.; Fan, Z.; Mi, N.; Wang, Q. *J. Agric. Food. Chem.* **2010**, *58*, 2703.
(43) Iwasa, K.; Moriyasu, M.; Tachibana, Y.; Kim, H.-S.; Wataya, Y.; Wiegrebe, W.; Bastow, K. F.; Cosentino, L. M.; Kozuka, M.; Lee, K.-H. *Bioorg. Med. Chem.* **2001**, *9*, 2871.
(44) Wang, K.; Wu, M.; Liu, Z.; Su, B.; Li, L.; Liu, Y.; Huang, R.; Liu, Y.; Wang, Q. *Nongyaoxue Xuebao* **2010**, *12*, 507.
(45) Gao, W.; Chen, A. P.-C.; Leung, C.-H.; Gullen, E. A.; Fürstner, A.; Shi, Q.; Wei, L.; Lee, K.-H.; Cheng, Y.-C. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 704.
(46) Wang, Z.; Wu, M.; Wang, Y.; Li, Z.; Wang, L.; Han, G.; Chen, F.; Liu, Y.; Wang, K.; Zhang, A.; Meng, L.; Wang, Q. *Eur. J. Med. Chem.* **2012**, *51*, 250.
(47) Valpuesta, M.; Ariza, M.; Díaz, A.; Suau, R. *Eur. J. Org. Chem.* **2010**, *2010*, 4393.
(48) Gravel, E.; Poupon, E.; Hocquemiller, R. *Tetrahedron* **2006**, *62*, 5248.
(49) De Kimpe, N.; Stevens, C. *J. Org. Chem.* **1993**, *58*, 2904.

(50) Liermann, J. C.; Opatz, T. *J. Org. Chem.* **2008**, *73*, 4526.
(51) Kobor, J.; Koczka, K. *Szegedi Tanarkepzo Foiskola Tud. Kozl.* **1969**, 179.
(52) Tayama, E.; Takedachi, K.; Iwamoto, H.; Hasegawa, E. *Tetrahedron Lett.* **2012**, *53*, 1373.
(53) Weinreb, S. M.; Basha, F. Z.; Hibino, S.; Khatri, N. A.; Kim, D.; Pye, W. E.; Wu, T. T. *J. Am. Chem. Soc.* **1982**, *104*, 536.
(54) Jończyk, A.; Lipiak, D.; Sienkiewicz, K. *Synlett* **1991**, *1991*, 493.
(55) Vedejs, E.; West, F. G. *Chem. Rev.* **1986**, *86*, 941.
(56) Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1979**, *101*, 6452.
(57) Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. *Organometallics* **2010**, *29*, 2176.
(58) Werner, F.; Blank, N.; Opatz, T. *Eur. J. Org. Chem.* **2007**, 3911.
(59) Rohloff, J. C.; Dyson, N. H.; Gardner, J. O.; Alfredson, T. V.; Sparacino, M. L.; Robinson, J. *J. Org. Chem.* **1993**, *58*, 1935.
(60) Taylor, A. M.; Schreiber, S. L. *Org. Lett.* **2005**, *8*, 143.
(61) Pyman, F. L. *J. Chem. Soc., Trans.* **1909**, *95*, 1266.
(62) van Oeveren, A.; Jansen, J. F. G. A.; Feringa, B. L. *J. Org. Chem.* **1994**, *59*, 5999.
(63) Yamaguchi, S.; Tsuchida, N.; Miyazawa, M.; Hirai, Y. *J. Org. Chem.* **2005**, *70*, 7505.
(64) Yang, P.-Y.; Zhou, Y.-G. *Tetrahedron: Asymmetry* **2004**, *15*, 1145.
(65) Kurosawa, W.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 8112.
(66) Cava, M. P.; Afzali, A. *J. Org. Chem.* **1975**, *40*, 1553.
(67) Shinohara, T.; Takeda, A.; Toda, J.; Sano, T. *Heterocycles* **1998**, *48*, 981.
(68) Miller, L. L.; Stermitz, F. R.; Falck, J. R. *J. Am. Chem. Soc.* **1973**, *95*, 2651.
(69) Kuck, A. M.; Frydman, B. *J. Org. Chem.* **1961**, *26*, 5253.
(70) Hara, H.; Hashimoto, F.; Hoshino, O.; Umezawa, B. *Chem. Pharm. Bull.* **1986**, *34*, 1946.
(71) Marion, L.; Lemay, L.; Portelance, V. *J. Org. Chem.* **1950**, *15*, 216.
(72) Wang, Z.; Wang, Q. *Tetrahedron Lett.* **2010**, *51*, 1377.
(73) Kametani, T.; Ogasawara, K.; Takahashi, T. *Tetrahedron* **1973**, *29*, 73.