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Enhancement of 5-Aminopenta-2,4-dienals Electrophilicity via Activation by *O*,*N*-Bistrifluoroacetylation. Application to an *N*-Acyl Pictet−Spengler Reaction†

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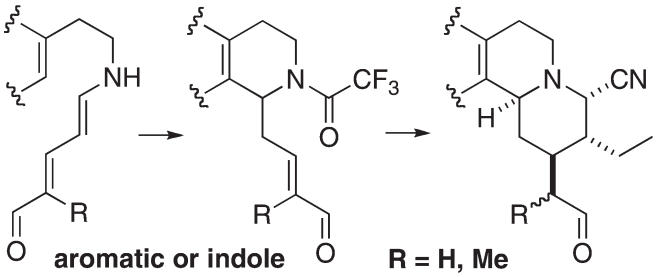
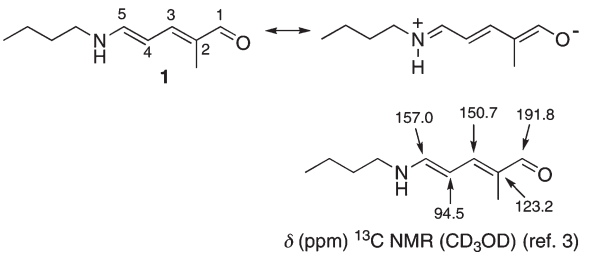


Aminopentadienals resulting from the condensation of tryptamine or homoveratrylamine with glutaconaldehydes were treated with trifluoroacetic anhydride, allowing the formation of tetrahydro-β-carbolines and tetrahydroisoquinolines bearing an enal function. In this *N*-acyl Pictet−Spengler reaction the electrophilicity of the aminopentadienals was dramatically increased by *O*,*N*-bistrifluoroacetylation. Recovery of the nitrogen nucleophilicity was achieved using a reductive process, and the heterocyclic amines were converted into aminonitriles by a Strecker reaction in the presence of butanal. Cyclization, by intramolecular Michael addition of the in situ generated enamines onto the enal moiety, was achieved in the presence of zinc triflate and involved cyanide ion trapping. In this manner, compounds related to protoemetine and dihydrocorynantheal were obtained, and a reduction step led to a short synthesis of (±)-protoemetinol.

Introduction

Our interest in the 5-alkylaminopenta-2,4-dienals[1] arose from the idea that manzamine alkaloids might originate from a biosynthetic pathway involving these species.[2] In this context, the nucleophilicity of both nitrogen and carbon C-4 of aminopentadienal **1** was exploited some years ago in our laboratory in its reaction with a 2,3-dihydropyridinium salt.[3]

However, aminopentadienals such as **1**, which are bisvinylogous formamides and donor−acceptor dienes, also have electrophilic sites located at positions 1, 3, and 5. The difference, from an electronic point of view, between these centers and the nucleophilic carbons C-2 and C-4 is evident from the values of the corresponding chemical shifts in the ^{13}C NMR spectrum.



δ (ppm) ^{13}C NMR (CD_3OD) (ref. 3)

The electrophilic character of *N*,*N*-disubstituted aminopentadienals (Zincke aldehydes), especially at C-1, was earlier shown

† This article is dedicated with respect to the memory of Christian Marazano to pay tribute to his contribution to the development of the Zincke reaction and of 5-aminopenta-2,4-dienal chemistry for biomimetic approaches to marine alkaloids.

(1) (a) For a review on aminopentadienals, see: Becher, J. *Synthesis* **1980**, 589–612. For recent work concerning aminopentadienal pericyclic reactions, see: (b) Steinhardt, S. E.; Silverston, J. S.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2008**, *130*, 7560–7561. (c) Steinhardt, S. E.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131*, 7546–7547.

(2) Kaiser, A.; Billot, X.; Gateau-Olesker, A.; Marazano, C.; Das, B. C. *J. Am. Chem. Soc.* **1998**, *120*, 8026–8034.

(3) Jakubowicz, K.; Ben Abdeljelil, K.; Herdemann, M.; Martin, M.-T.; Gateau-Olesker, A.; Al Mourabit, A.; Marazano, C.; Das, B. C. *J. Org. Chem.* **1999**, *64*, 7381–7387.

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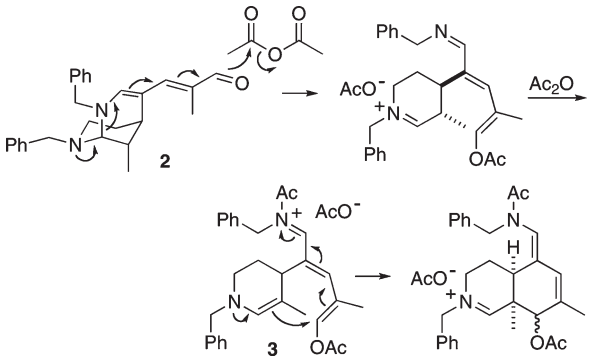
SCHEME 1. Rearrangement Occuring during Acetylation of Aminal 2



in condensation reactions with some nucleophilic reagents.[4] Very recently, Vanderwal reported an annelation reaction involving an intramolecular anionic cyclization onto the carbon C-5 of an aminopentadienal.[5]

In a study related to a biomimetic approach toward manzamine alkaloids, a rearrangement was observed during acetylation of the bicyclic aminal **2**.[6] This sequence might imply the intramolecular addition of an enamine onto an *N*, *O*-diacetylated aminopentadienal (see intermediate **3**) as illustrated in Scheme 1.[6]

These results prompted us to examine the possibility of increasing aminopentadienal electrophilicity by acylation and thereby of broadening the scope of their reactivity.

The activation of Zincke aldehydes with phosphorus oxychloride, for a Vilsmeier−Haack-type reaction, has been reported by Jutz.[7] *O*-Acylation of these aldehydes, leading to very reactive electrophilic compounds, was also described by Kröhnke and co-workers.[8] Starting from 5-(dialkylamino)-penta-2,4-dien-1-ones, *O*-activation and subsequent treatment by nucleophiles were used for the synthesis of pentamethine derivatives.[9] Very recently, 5-arylaminopenta-2,4-dienals were transformed into aminopentadieneiminiums via silylation.[9c] However, to the best of our knowledge, activation of *N*-monosubstituted aminopentadienals by acylation has not been reported. Our results in this area and their application in the context of the Pictet−Spengler reaction are presented here.[10]

Results and Discussion

Acylation of 5-Alkylaminopenta-2,4-dienals and the *N*-Acyl Pictet−Spengler Reaction. The behavior of the aminopentadienal **1** in the presence of an excess of acetic anhydride in $CDCl_3$, with monitoring by ^1H NMR spectroscopy, was examined, and no change was observed at room temperature. Only heating to reflux for several hours led to the disappearance of the signals corresponding to **1** with the formation of a complex mixture of presumed isomers of *O*, *N*-diacetylated products. With trifluoroacetic anhydride as an acylating agent, the transformation was very fast at room temperature, the presence of diacylated species being suspected (vide infra). Therefore, TFAA was chosen to increase the electrophilicity of aminopentadienals to promote the intramolecular additions of nucleophiles onto the activated intermediates, with the initial goal of achieving an *N*-acyl Pictet−Spengler reaction.[10,11]

With this aim in mind, the aminopentadienal **4** derived from tryptamine was prepared using 2-methylglutaconaldehyde potassium salt in the presence of trifluoroacetic acid (Scheme 2).[6] Reaction of **4** with TFAA was first tested in $CDCl_3$, in order to monitor it by ^1H NMR spectroscopy, and the formation of compounds probably corresponding to structure **8** was noted. Subsequent basic hydrolysis led to the isolation of the *N*-acylated tetrahydro-β-carboline **5** with an enal function and as the exclusive (*E*) isomer. It is interesting to note that the yield of **5** was only 47% when 1 equiv of anhydride was used but reached 82% with 2 equiv, suggesting that a diacylated species such as **7**, with an *N*-acyliminium moiety, is involved in the Pictet−Spengler-type reaction.[12,13] It is likely that *O*-trifluoroacetylation of **4** is the first step, with the imino compound (**6**) undergoing subsequent rapid acylation.

The reaction with **4** was therefore conducted using 2 equiv of TFAA and in CH_2Cl_2 as a solvent. The same procedure was applied to the aminopentadienal **9** obtained with 80% yield from tryptamine and glutaconaldehyde sodium salt.[1a,14] Basic hydrolysis of the enol esters led to the tetrahydro-β-carbolines **5** and **10** with, respectively, 87% and 58% yields (Scheme 3). It should be noted that the conjugation of the olefin with the carbonyl group was observed during this process with formation of the (*E*) isomer only.

Aminopentadienals **11** and **12**, readily prepared from homoveratrylamine, led in the same conditions to the tetrahydroisoquinolines **13** and **14** with 78% and 62% yields, respectively. It should be emphasized that, for both series, the reaction was less efficient with the unsubstituted dienal moiety. This is a general problem with aminopentadienals without a substituent at C-2, which are more prone to cyclization to pyridiniums salts under acidic conditions.

This new use of aminopentadienals with a Pictet−Spengler-type reactivity supplements Vanderwal's recent work in the indole field.[5]

(4) (a) Jutz, C. *Chem. Ber.* **1958**, *91*, 1867–1880. (b) Malhotra, S. S.; Whiting, M. C. *J. Chem. Soc.* **1960**, 3812–3822. (c) Grewe, R.; von Bonin, W. *Chem. Ber.* **1961**, *94*, 234–241. (d) Köbrich, G.; Breckoff, W. E. *Liebigs Ann. Chem.* **1967**, *704*, 42–50. (e) Michels, T. D.; Rhee, J. U.; Vanderwal, C. D. *Org. Lett.* **2008**, *10*, 4787–4790.

(5) Martin, D. B. C.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131*, 3472–3473.

(6) Wypych, J.-C.; Nguyen, T. M.; Nuhant, P.; Bénéchie, M.; Marazano, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 5418–5421.

(7) Jutz, C. *Chem. Ber.* **1958**, *91*, 850–861.

(8) (a) Dickoré, K.; Kröhnke, F. *Chem. Ber.* **1960**, *93*, 1068–1074. (b) Nordmann, H. G.; Kröhnke, F. *Liebigs Ann. Chem.* **1970**, *731*, 80–90.

(9) (a) Jutz, C.; Wagner, R.-M.; Kraatz, A.; Löbering, H.-G. *Liebigs Ann. Chem.* **1975**, 874–900. (b) Voitenko, Z.; Mazières, M. R.; Sanchez, M.; Wolf, J. G. *Tetrahedron* **2001**, *57*, 1059–1066. (c) Korinek, M.; Rybackova, M.; Böhm, S. *Synthesis* **2009**, 1291–1296.

(10) For reviews, see: (a) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797–1842. (b) Youn, S. W. *Org. Prep. Process Int.* **2006**, *38*, 505–591.

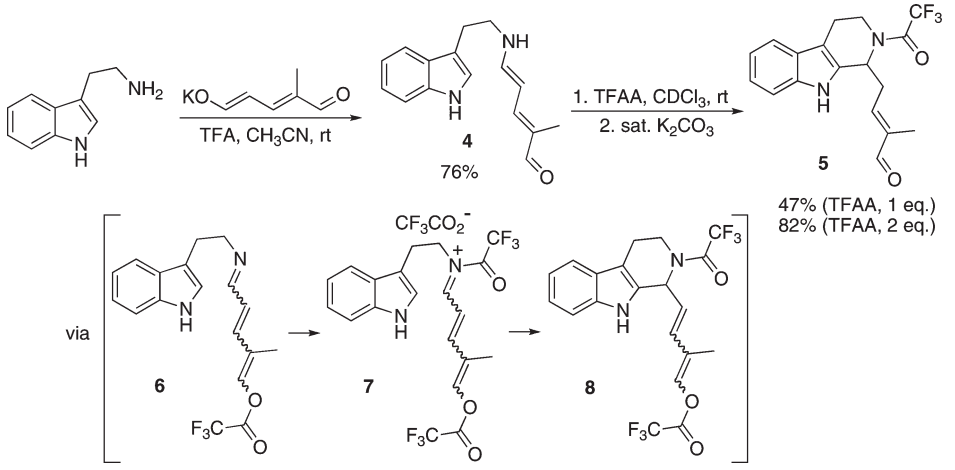
(11) For reviews, see: (a) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431–1628. (b) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311–2352.

(12) In an attempt to realize a Diels−Alder reaction with a Zincke aldehyde derived from tryptamine, with catalysis by Brønsted or Lewis acids, Vanderwal recently raised the possibility of Pictet−Spengler-like reactivity, but no details were reported (see ref 5).

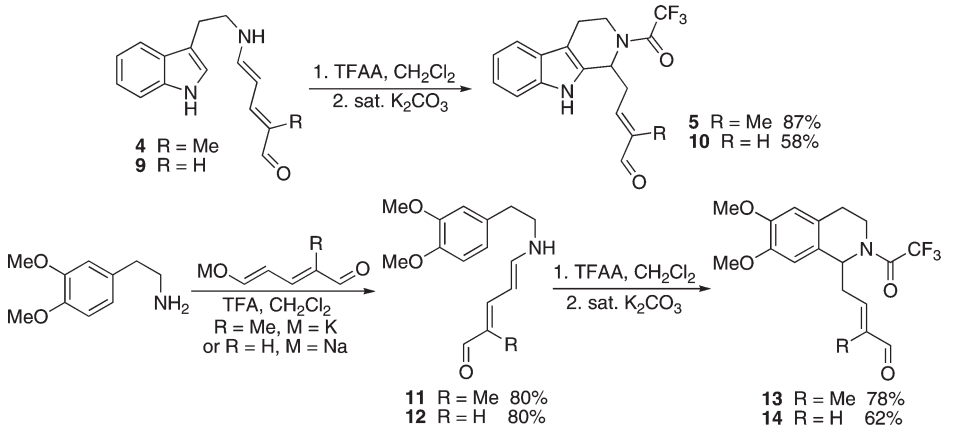
(13) The behavior reported here is reminiscent of Pictet−Spengler reactions observed with *N*-acylated enaminoketones, in the presence of Brønsted or Lewis acids, or by treatment of a 2-(3-acetamidoallylidene)malonate with $BF_3 \cdot Et_2O$, see: (a) Tietze, L. F.; Schimpf, R.; Wichmann, J. *Chem. Ber.* **1992**, *125*, 2571–2576. (b) Rosenmund, P.; Hosseini-Merescht, M.; Bub, C. *Liebigs Ann. Chem.* **1994**, 151–158.

(14) Becher, J. *Organic Synthesis*; Wiley: New York, 1988; Collect. Vol. VI, pp 640−644.

SCHEME 2. Formation of Aminopentadienal 4 and Its Reaction with TFAA

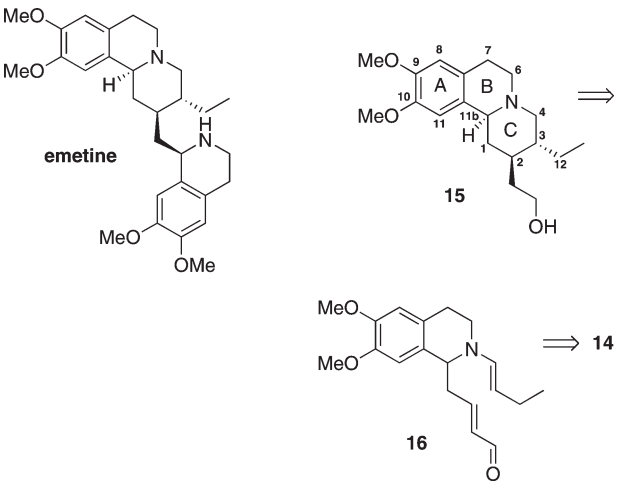


SCHEME 3. *N*-Acyl Pictet−Spengler Reaction by Treatment of Tryptamine and Homoveratrylamine Derived Aminopentadienals with TFAA



Application to Syntheses of Protoemetinol and of Tetrahydroisoquinoline and Indole Alkaloids Homologues. As the Pictet−Spengler reaction is a useful transformation for the synthesis of indole and tetrahydroisoquinoline alkaloids,[10] an application of the present methodology to this field was envisioned. Initially the construction of (±)-protoemetinol (**15**),[15] which is a pivotal intermediate in total syntheses of emetine and related biologically active alkaloids, was chosen.[16] Thus, it was considered that compound **14** might be a precursor for C-ring formation, possibly by an intramolecular Michael addition of an enamine onto the enal moiety of **16** (Scheme 4).

SCHEME 4. Retrosynthetic Scheme for Protoemetinol (15)



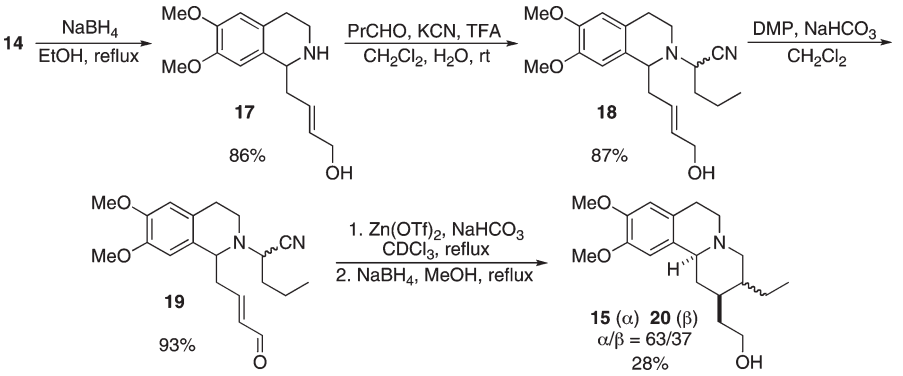
To avoid a vinylogous retro-Michael reaction, under basic conditions, or the liberation of the secondary amine in the presence of the enal function, a reductive procedure was used for the removal of the trifluoroacetyl moiety.[17] A protected

(15) (a) For isolation of (−)-protoemetinol, see: Battersby, A. R.; Kapil, R. S.; Bhakuni, D. S.; Popli, S. P.; Merchant, J. R.; Salgar, S. S. *Tetrahedron Lett*. **1966**, 4965–4971. (b) For a recent total synthesis of (±)-protoemetinol, see: Chang, J.-K.; Chang, B.-R.; Chuang, Y.-H.; Chang, N.-C. *Tetrahedron* **2008**, *64*, 9685–9688.

(16) For reviews, see : (a) Fujii, T.; Ohba, M. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 51, pp 271−321. (b) *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1983; Vol. 22, pp 1−50. For selected syntheses, see: (c) Hirai, Y.; Terada, T.; Hagiwara, A.; Yamazaki, T. *Chem. Pharm. Bull*. **1988**, *36*, 1343–1350. (d) Fujii, T.; Ohba, M.; Yoshifuji, S. *Heterocycles* **1988**, *27*, 1009–1033. (e) Ihara, M.; Yasui, K.; Taniguchi, N.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1469–1476. (f) Takacs, J. M.; Boito, S. C. *Tetrahedron Lett*. **1995**, *36*, 2941–2944. (g) Tietze, L. F.; Rackelmann, N.; Müller, I. *Chem.−Eur. J*. **2004**, *10*, 2722–2731. (h) Itoh, T.; Miyazaki, M.; Fukuoka, H.; Nagata, K.; Ohsawa, A. *Org. Lett*. **2006**, *8*, 1295–1297.

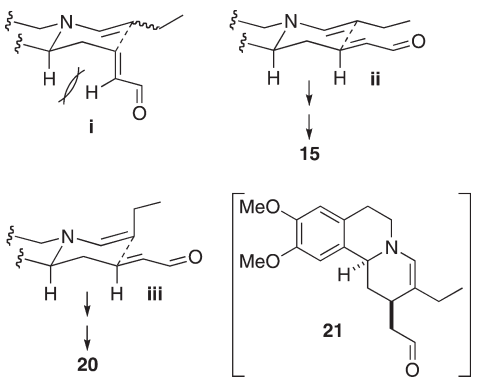
(17) Weygang, F.; Frauendorfer, E. *Chem. Ber*. **1970**, *103*, 2437–2449.

SCHEME 5. Access to Protoemetinol via Intramolecular Michael Addition



form of the labile open-chain enamine was introduced before restoring the correct oxidation level. This goal was achieved by the formation of an aminonitrile via a Strecker reaction. Transformation of the allylic alcohol **18** into the enal **19** was problematic, but use of the Dess−Martin periodinane in the presence of $NaHCO_3$ proved to be a good solution. To the best of our knowledge, no Michael-type addition involving an enal and an open chain aminonitrile has been described.[18,19] In the case of the desired reaction, in which the sensitive enamine **16** might be an intermediate, a Lewis acid could also increase the enal electrophilicity by oxygen coordination. A method was therefore developed for the gradual generation of the enamine and the achievement of the 1,4-addition. It was found that the treatment of **19** with 0.5 equiv of $Zn(OTf)_2$, in the presence of $NaHCO_3$ (a complex mixture was obtained without base) and in refluxing $CDCl_3$, led to cyclization with trapping of the intermediate iminium salt, by the cyanide ion, as an aminonitrile (^{1}H NMR spectroscopic assessment).[20] However, the product was not stable in these conditions and could not be isolated; therefore, both the aldehyde and the masked iminium functions were reduced by the addition of methanol and $NaBH_4$ (Scheme 5).

Following this procedure, a concise synthesis of (±)-protoemetinol (**15**)[15b] and its C-3 epimer (**20**)[21] was established, albeit with a moderate 28% overall yield, which is attributed to the low stability of the intermediates. However, **15** was the major product and its ^{1}H and ^{13}C NMR spectral data fit well with the values reported recently for this compound.[15b] The stereochemistry of **20** was deduced from its ^{13}C NMR spectra by the upfield shift, relative to **15**, of C-1 and C-12, due to the γ-effect of the axial ethyl group.[22] The formation of C-ring is considered to proceed via the transition states **ii** or **iii** (rather than **i**) or by equilibration of iminium ions involving B-ring opening.[23] The position of the ethyl group (equatorial for **15** and axial for **20**) can be considered as resulting from reduction of the iminium ions obtained by cyclization via **ii** and **iii**, respectively, or after their epimerization via the enamine **21**.



Other conditions aimed at transforming the aminonitrile **19** into the enamine **16** (via an iminium ion), such as treatment with $AgBF_4$,[24] TMSOTf,[25] $BF_3 \cdot Et_2O$[26] or alumina,[27] were unsuccessful.[28]

If the methyl at C-2 of the aminopentadienal has a beneficial effect on the yield of the Pictet−Spengler reaction (see Scheme 3), its influence is also positive for the cyclization by Michael addition, as illustrated by the synthesis of homologues of 4-cyano-protoemetine from the tetrahydroisoquinoline **13** (Scheme 6). It should be noted that, in a sequence that is analogous to those depicted in Scheme 5, addition of $NaHCO_3$ was not necessary either for the oxidation step or for the treatment of the aminonitrile **25** with $Zn(OTf)_2$. Here, unlike the reaction with **19**, the tricyclic aminonitrile **26** could be isolated. Moreover, only two epimers, differing in the relative position of the methyl on the oxoethyl side chain, were obtained, although five stereogenic centers are present in the molecule.

(18) An intermolecular Michael-type addition, involving a cyclic enamine, protected as an aminonitrile, and methyl vinyl ketone has been reported: Mitch, C. H. *Tetrahedron Lett*. **1988**, *29*, 6831–6834.

(19) A related enantioselective organocatalytic intramolecular Michael addition involving an enal was reported recently, but only for the case of the relatively unreactive enamine of indoles: (a) Li, C.-F.; Liu, H.; Liao, J.; Cao, Y.-J.; Liu, X.-P.; Xiao, W.-J. *Org. Lett*. **2007**, *9*, 1847–1850. (b) For a recent review on iminium catalysis, see: Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev*. **2007**, *107*, 5416–5470.

(20) Baldwin showed that the use of zinc bromide allowed the in situ formation of a 2,3-dihydropyridinium from the corresponding aminonitrile and that the cyanide ion, released in that process, was reintroduced in the product structure after a Diels−Alder reaction: Baldwin, J. E.; Spring, D. R.; Whitehead, R. C. *Tetrahedron Lett*. **1998**, *39*, 5417–5420.

(21) Kametani, T.; Suzuki, Y.; Terasawa, H.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1211–1217.

(22) Reimann, E.; Renz, M. *Monatsh. Chem*. **2007**, *138*, 211–218.

(23) Takano, S.; Hatakeyama, S.; Takahashi, Y.; Ogasawara, K. *Heterocycles* **1982**, *17*, 263–284.

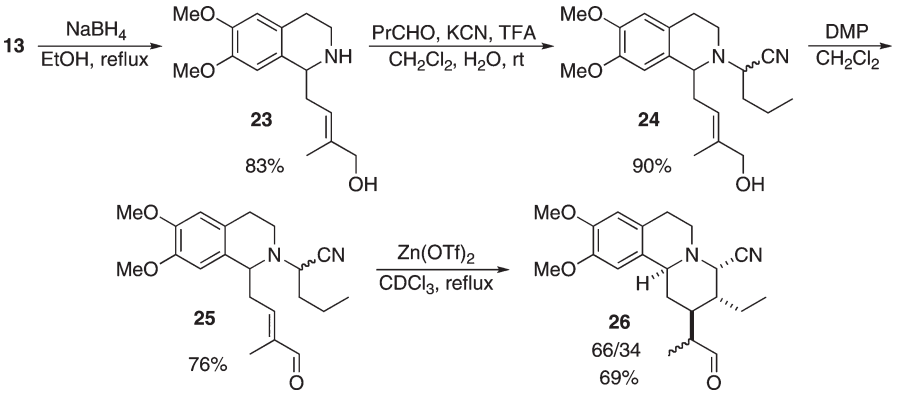
(24) Kempe, U. M.; Das Gupta, T. K.; Blatt, K.; Gygax, P.; Felix, D.; Eschenmoser, A. *Helv. Chim. Acta* **1972**, *55*, 2187–2198.

(25) Yue, C.; Royer, J.; Husson, H.-P. *J. Org. Chem*. **1992**, *57*, 4211–4214.

(26) Koskinen, A.; Lounasmaa, M. *J. Chem. Soc., Chem. Commun*. **1983**, 821–822.

(27) (a) Bonin, M.; Besselièvre, R.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett*. **1983**, *24*, 1493–1496. (b) Bonin, M.; Royer, J.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett*. **1986**, *27*, 1569–1572.

SCHEME 6. Access to Homologues of 4-Cyano-protoemetine



^{13}C NMR spectroscopy is the method of choice for structural analysis of these compound types, and it is clear from NMR analysis that the relative configurations at C-11b, C-2, C-3, and C-4 are the same for the two compounds. The chemical shifts for C-2 (δ_c 21.7 and 22.5) and the coupling constants for H-4 (J = 4.4 Hz) indicate an equatorial position for the ethyl group[22] and a *cis* relationship for H-3 and H-4 and, therefore, an axial cyano group.[30] In the case of the major compound, the coupling constants between H-2 and H-1ax and H-3 (12 Hz for both) showed a *trans*-diaxial relationship for these hydrogens, and therefore an equatorial position for the 1-oxopropan-2-yl group. The values of δ_c for C-11b being very close for both major and minor products (57.0 and 57.3, respectively), the position of the 1-oxopropan-2-yl group on C-ring is the same for the two compounds.[22] The relative stereochemistry of the C-ring is then the same as that of protoemetine. However, the configuration α to the carbonyl could not be determined.

The stereochemical outcome of the reaction might be attributed to a thermodynamically controlled process (equatorial ethyl and axial cyano groups), via an iminium-enamine equilibrium, with the relative configurations at C-11b and C-2 involving a transition state analogous to **ii**. The axial configuration for the cyano group is in accordance with a stabilizing anomeric-like effect.[31]

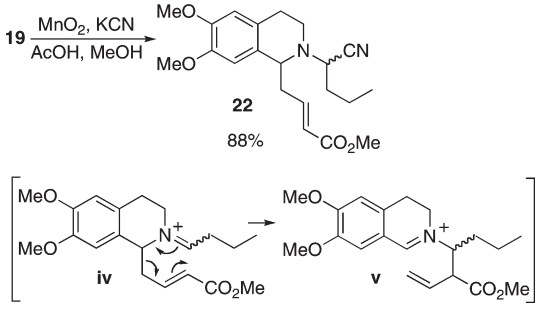
The aforementioned sequence could be applied in the indole series, starting from compound **5**, to give the homologues of 21-cyano-18,19-dihydrocorynantheal (**28**) (Scheme 7). In this case, the oxidation step was less efficient (42% yield), probably due to competitive indole participation, but as previously, only two epimers (**28**) were obtained after the Michael-type addition, which also proceeded with a lower yield (53%). Equilibration during the latter process is likely since four isomeric enals were detected by ^{1}H NMR spectroscopy after the Strecker reaction. The rationale developed for determining the relative configuration of aminonitriles **26** was also applied for **28**.[32] It is noteworthy that the major product has the same relative stereochemistry at C-3, C-15, and C-20 as that of corynantheal.[33]

The methodology reported here could be extended to the synthesis of alkaloids such as dihydroisoalangine[34] or 3-*epi*-antirhine.[35] It is also possible to envision the formation of the D- and E-rings of yohimbine and corynantheine derivatives,[36] starting from the Pictet−Spengler products, with the Michael addition procedure or using other methods.[37]

Conclusions

The scope of 5-alkylaminopenta-2,4-dienals reactivity has been broadened by increasing their electrophilicity via acylation with TFAA. *O*,*N*-Bistrifluoroacetylation was probably involved, and the putative *N*-acyliminium ions were used to realize *N*-acyl Pictet−Spengler reactions affording heterocycles

(28) An attempt to improve the effectiveness of the Michael addition was made using the more stable α,β-unsaturated ester **22**, which was readily prepared by Corey oxidation-esterification (Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616–5617.) of enal **19**. However, heating **22** in $CDCl_3$ in the presence of $Zn(OTf)_2$ did not lead to the desired cyclization, owing perhaps to the intervention of a cationic 2-aza-Cope [3,3] sigmatropic rearrangement[29] involving **iv** (signals corresponding to the vinyl and to the iminium moieties of **v** in the ^{1}H NMR spectrum of the reaction mixture).



(29) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352–359.

(30) For ^{13}C NMR of piperidine derived α-aminonitriles, see: Jokela, R.; Tamminen, T.; Lounasmaa, M. *Heterocycles* **1985**, *23*, 1707–1722.

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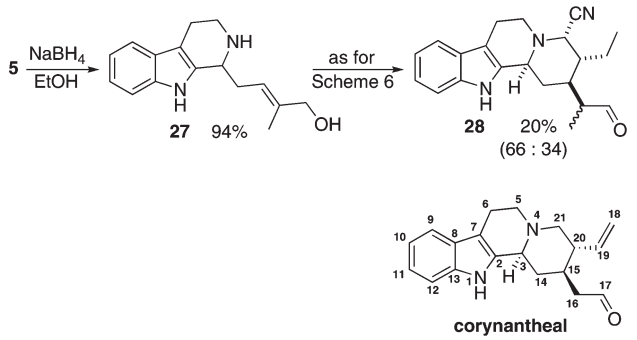
SCHEME 7. Access to Homologues of 21-Cyano-18,19-dihydrocorynantheal



with an enal function. Another advantage of the trifluoroacetyl moiety, as an activating group, is its easy removal from oxygen or nitrogen, allowing further transformations of the cyclized products. This feature was taken advantage of in an unprecedented intramolecular Michael addition of enamines, starting from their aminonitrile equivalents, onto enals. For the Pictet−Spengler reaction, as well as for the Michael addition, substitution at position 2 of the aminopentadienal moiety seems to be an important factor, since the procedures were less effective with unsubstituted compounds. Sequences combining these two reactions were applied in a short synthesis of (±)-protoemetinol and to access tetrahydroisoquinoline and indole alkaloid homologues. The *N*-acyl Pictet−Spengler reaction reported here could be useful for synthesis in the isoquinoline or indole alkaloids field. Finally, the aminonitrile moiety, present in intramolecular Michael addition products, might allow further functionalization.

Experimental Section

(2*E*,4*E*)-5-(2-(1*H*-Indol-3-yl)ethylamino)-2-methylpenta-2,4-dienal (4). To a solution of 98% tryptamine (500 mg, 3.06 mmol) in CH_3CN (31 mL) at 0 °C was slowly added TFA (236 μL, 3.06 mmol), and the mixture was brought to room temperature. 2-Methylglutaconaldehyde potassium salt[6] (482 mg, 3.21 mmol) was added, and the reaction mixture was stirred for 30 min. The mixture was taken up in CH_2Cl_2 and washed successively with saturated K_2CO_3 solution and brine, dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by flash chromatography on silica gel (CH_2Cl_2/AcOEt 70/30) to afford **4** (588 mg, 76%) as an orange gum: FTIR 3292, 1568, 1201 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.77 (s, 3 H), 3.07 (t, J = 6.5 Hz, 2 H), 3.48 (q, J = 6.5 Hz, 2 H), 4.87 (br s, 1 H), 5.48 (t, J = 12.5 Hz, 1 H), 6.78 (dd, J = 12.5, 8.0 Hz, 1 H), 6.82 (d, J = 12.5 Hz, 1 H), 7.05 (br s, 1 H), 7.14 (t, J = 7.0 Hz, 1 H), 7.22 (t, J = 7.0 Hz, 1 H), 7.39 (d, J = 8.0 Hz, 1 H), 7.59 (d, J = 8.0 Hz, 1 H), 8.65 (br s, 1 H), 9.17 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.1, 24.9, 44.6, 95.7, 111.5, 111.9, 118.4, 119.4, 122.2, 122.5, 126.4, 127.1, 136.5, 148.1, 154.3, 193.0; HRMS (ESI) m/z calcd for $C_{16}H_{19}N_2O$ $(M + H)^+$ 255.1497, found 255.1509.

(*E*)-2-Methyl-4-(2-(2,2,2-trifluoroacetyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)but-2-enal (5). To a solution of **4** (235 mg, 0.92 mmol) in CH_2Cl_2 (3 mL) was added TFAA (276 μL, 1.94 mmol) over a period of 5 min at rt. The resulting solution was stirred for an additional 10 min at rt and quenched by the addition of 1 N HCl (3 mL). The mixture was stirred for 45 min and was quenched by solid K_2CO_3 until becoming basic, then diluted by CH_2Cl_2. The two phases were separated, and the organic phase was washed with brine and dried over Na_2SO_4. Concentration followed by flash chromatography on silica gel (heptane/EtOAc 60/40) afforded **5** (281 mg, 87%) as an orange gum: FTIR 3356, 2923, 1678, 1453, 1201, 1174, 1138 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.74 (s, 3 H), 2.93 (m, 2 H), 3.00 (m, 2 H), 3.58 (ddd, J = 14.0, 10.0, 6.0 Hz, 1 H), 4.28 (dt, J = 14.0, 2.5 Hz, 1 H), 5.87 (t, J = 7.0 Hz, 1 H), 6.59 (tq, J = 7.5, 1.0 Hz, 1 H), 7.15 (td, J = 8.0, 1.0 Hz, 1 H), 7.23 (td, J = 8.0, 1.0 Hz, 1 H), 7.35 (d, J = 8.0 Hz, 1 H), 7.49 (d, J = 8.0 Hz, 1 H), 8.19 (br s, 1 H), 9.39 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.4, 22.1, 33.9, 41.0, 50.2, 108.4, 111.2, 118.3, 120.2, 122.8, 126.1, 130.6, 136.3, 142.1, 146.8, 194.7 (the carbons of the trifluoroacetyl group were not detected); HRMS (ESI) m/z calcd for $C_{18}H_{17}F_3N_2NaO_2$ $(M + Na)^+$ 373.1140, found 373.1152.

(2*E*,4*E*)-5-(2-(1*H*-Indol-3-yl)ethylamino)penta-2,4-dienal (9). This compound was obtained with the procedure described for the preparation of **4**, using glutaconaldehyde sodium salt,[14] in 80% yield and as an orange gum: FTIR 3256, 1566, 1557, 1145 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.07 (t, J = 6.5 Hz, 2 H), 3.47 (q, J = 6.5 Hz, 2 H), 4.70 (br s, 1 H), 5.46 (t, J = 12.5 Hz, 1 H), 5.85 (dd, J = 14.0, 8.5 Hz, 1 H), 6.79 (dd, J = 12.5, 9.0 Hz, 1 H), 7.05 (br s, 1 H), 7.07 (dd, J = 14.0, 12.5 Hz, 1 H), 7.15 (t, J = 7.5 Hz, 1 H), 7.23 (t, J = 7.5 Hz, 1 H), 7.39 (d, J = 7.5 Hz, 1 H), 7.58 (d, J = 7.5 Hz, 1 H), 8.25 (br s, 1 H), 9.30 (d, J = 8.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.9, 44.5, 98.2, 111.4, 112.0, 118.5, 119.7, 120.9, 122.3, 122.4, 127.1, 136.4, 148.6, 156.5, 192.7; HRMS (ESI) m/z calcd for $C_{15}H_{17}N_2O$ $(M + H)^+$ 241.1341, found 241.1330.

(*E*)-4-(2-(2,2,2-Trifluoroacetyl)-2,3,4,9-tetrahydro-1*H*-pyrido-[3,4-*b*]indol-1-yl)but-2-enal (10). This compound was obtained using the procedure described for the preparation of **5**, starting from **9**, in 58% yield and as an orange gum: FTIR 3362, 2918, 1681, 1453, 1203, 1176, 1141 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.93 (m, 2 H), 3.00 (m, 2 H), 3.56 (ddd, J = 14.0, 11.0, 5.0 Hz, 1 H), 4.28 (dt, J = 14.0, 2.0 Hz, 1 H), 5.88 (dd, J = 8.5, 5.0 Hz, 1 H), 6.19 (ddt, J = 15.5, 8.0, 1.0 Hz, 1 H), 6.87 (dt, J = 15.5, 8.0 Hz, 1 H), 7.15 (td, J = 8.0, 1.0 Hz, 1 H), 7.23 (td, J = 8.0, 1.0 Hz, 1 H), 7.36 (d, J = 8.0 Hz, 1 H), 7.49 (d, J = 8.0 Hz, 1 H), 8.13 (br s, 1 H), 9.50 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.1, 37.8, 41.0, 50.1, 108.6, 111.2, 118.4, 120.2, 122.9, 126.2, 130.4, 135.6, 136.3, 151.0, 193.3 (the carbons of the trifluoroacetyl group were not detected); HRMS (ESI) m/z calcd for $C_{17}H_{15}F_3N_2NaO_2$ $(M + Na)^+$ 359.0983, found 359.0973.

(2*E*,4*E*)-5-(3,4-Dimethoxyphenylethylamino)-2-methylpenta-2,4-dienal (11). To a solution of homoveratrylamine (1.1 mL, 6.52 mmol) in CH_2Cl_2 (2 mL) at rt was added 2-methylglutaconaldehyde potassium salt[6] (1.0 g, 6.66 mmol). TFA (513 μL, 6.66 mmol) was added dropwise over a period of 5 min, and the reaction mixture was stirred for an additional 30 min at rt. The mixture was diluted by CH_2Cl_2, washed successively with a solution of saturated K_2CO_3 and with brine, dried over Na_2SO_4, filtered, and concentrated. The resulting residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH 95/5) to afford **11** (1.45 g, 80%) as a viscous light yellow colored oil: FTIR 3600, 1610, 1558, 1515, 1456, 1260, 1235, 1206, 1025, 763, 667, 608 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.72 (s, 3 H), 2.83 (t, J = 7.5 Hz, 2 H), 3.37 (q, J = 6.5 Hz, 2 H), 3.83 (s, 3 H), 3.84 (s, 3 H), 5.08 (br s, 1 H), 5.45 (t, J = 12.5 Hz, 1 H), 6.66−6.75 (m, 2 H), 6.76−6.87 (m, 3 H), 9.11 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.96, 34.6, 45.6, 55.8, 95.6, 111.3, 111.8, 120.6, 126.4, 130.6, 147.8, 149.0, 153.9, 192.8; HRMS (ESI) m/z calcd for $C_{16}H_{22}NO_3$ $(M + H)^+$ 276.1600, found 276.1593.

(*E*)-4-(6,7-Dimethoxy-2-(2,2,2-trifluoroethanoyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-2-methylbut-2-enal (13). To a solution of **11** (1.37 g, 4.98 mmol) in CH_2Cl_2 (16 mL) was added TFAA (1.51 mL, 10.69 mmol) over a period of 5 min at rt. The resulting solution was stirred for an additional 10 min at rt and quenched by the addition of 1 N HCl (15 mL). The mixture was stirred for 45 min and quenched by solid K_2CO_3 until becoming basic, then diluted by CH_2Cl_2. The two phases were separated, and the

organic phase was washed with brine and dried over Na_2SO_4. Concentration followed by flash chromatography on silica gel (heptane/EtOAc 60/40) afforded **13** (1.44 g, 78%) as viscous light yellow colored oil: FTIR 2939, 1690, 1681, 1611, 1519, 1462, 1256, 1196, 1141, 1116 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.68 (s, 3 H), 2.78 (dt, J = 16.0, 3.8 Hz, 1 H), 2.85−3.05 (m, 3 H,), 3.57 (ddd, J = 14.8, 11.2, 4.2 Hz, 1 H), 3.82 (s, 3 H), 3.84 (s, 3 H), 4.02 (br d, J = 15.0, 1 H), 5.66 (dd, J = 8.3, 5.4 Hz, 1 H), 6.52 (t, J = 7.1 Hz, 1 H), 6.60 (s, 1 H), 6.61 (s, 1 H), 9.36 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.2, 28.6, 35.7, 40.0, 52.8, 55.9, 56.0, 109.5, 111.2, 116.3 (q, J = 286.6 Hz), 124.8, 126.1, 141.3, 147.9, 148.1, 148.4, 156.2 (q, J = 34.6 Hz), 194.6; HRMS (ESI) m/z calcd for $C_{18}H_{20}F_3NNaO_4$ $(M + Na)^+$ 394.1242, found 394.1234.

(2*E*,4*E*)-5-(3,4-Dimethoxyphenylethylamino)penta-2,4-dienal (12). This compound was obtained using the procedure described for the preparation of **11**, using glutaconaldehyde sodium salt,[14] in 80% yield and as an orange gum: FTIR 3420, 1608, 1557, 1514, 1260, 1140, 1024, 763 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.81 (t, J = 7.1 Hz, 2 H), 3.34 (q, J = 7.0 Hz, 2 H), 3.83 (s, 3 H), 3.84 (s, 3 H), 5.17−5.29 (br s, 1 H), 5.43 (t, J = 11.8 Hz, 1 H), 5.79 (dd, J = 14.2, 8.3 Hz, 1 H), 6.66−6.86 (m, 4 H), 7.06 (dd, J = 14.1, 12.2 Hz, 1 H), 9.22 (d, J = 8.2 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.6, 45.6, 55.78, 55.82, 97.9, 111.4, 111.8, 120.2, 120.6, 130.4, 147.8, 149.0, 149.0, 157.0, 192.5; HRMS (ESI) m/z calcd for $C_{15}H_{20}NO_3$ $(M + H)^+$ 262.1443, found 262.1437.

(*E*)-4-(6,7-Dimethoxy-2-(2,2,2-trifluoroethanoyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)but-2-enal (14). This compound was obtained using the procedure described for the preparation of **13**, starting from **12**, in 62% yield and as a yellow gum: FTIR 2938, 1681, 1611, 1518, 1462, 1252, 1194, 1173, 1115, 1137 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.78 (dt, J = 15.9, 3.2 Hz, 1 H), 2.84−3.06 (m, 3 H), 3.54 (ddd, J = 15.9, 12.0, 4.4 Hz, 1 H), 3.85 (s, 6 H), 4.05 (br d, J = 15.8, 1 H), 5.68 (dd, J = 9.0, 5.1 Hz, 1 H), 6.10 (dd, J = 15.6, 7.8 Hz, 1 H), 6.61 (s, 2 H), 6.82 (ddd, J = 15.4, 8.1, 6.7 Hz, 1 H), 9.49 (d, J = 7.7 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.5, 39.8 (2C), 52.5, 55.9, 56.0, 109.4, 111.3, 116.3 (q, J = 289.0 Hz), 124.7, 125.9, 135.2, 148.2, 148.5, 151.9, 156.3 (q, J = 35.3 Hz), 193.2; HRMS (ESI) m/z calcd for $C_{17}H_{18}F_3NNaO_4$ $(M + Na)^+$ 380.1086, found 380.1034.

(*E*)-4-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)but-2-en-1-ol (17). To a solution of **14** (460 mg, 1.29 mmol) in ethanol (5 mL) at rt was added 96% $NaBH_4$ (254 mg, 6.44 mmol). The mixture was heated at reflux overnight and quenched by the addition of 1 N HCl. Unreacted **14** and other neutral impurities were removed by extracting the reaction mixture with CH_2Cl_2. The aqueous phase was neutralized by the addition of saturated K_2CO_3 solution and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to afford **17** (291 mg, 86%) as a viscous colorless oil. Further purification was not necessary since the product was found to be sufficiently pure by spectral analysis: FTIR 3520, 2930, 1608, 1511, 1450, 1255, 1220, 1111, 1010, 974, 855, 786, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.96−2.23 (br s, 2 H), 2.38−2.51 (m, 1 H), 2.56−2.81 (m, 3 H), 2.92 (ddd, J = 11.8, 4.9, 2.4 Hz, 1 H), 3.19 (dt, J = 11.8, 5.0 Hz, 1 H), 3.84 (s, 6 H), 3.96 (dd, J = 9.0, 3.5 Hz, 1 H), 4.10 (d, J = 4.6 Hz, 2 H), 5.65−5.85 (m, 2 H), 6.56 (s, 1 H), 6.63 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.4, 39.1, 41.0, 54.9, 55.8, 56.0, 63.2, 109.0, 111.8, 127.3, 129.0, 130.4, 132.6, 147.2, 147.4; HRMS (ESI) m/z calcd for $C_{15}H_{22}NO_3$ $(M + H)^+$ 264.1600, found 264.1589.

(*E*)-2-(1-(4-Hydroxybut-2-enyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)pentanenitrile (18). To a solution of **17** (490 mg, 1.86 mmol) in CH_2Cl_2 (6 mL) at rt were added butyraldehyde (200 μL, 2.22 mmol), H_2O (70 μL), and 97% KCN (250 mg, 3.72 mmol). TFA (310 μL, 4.17 mmol) was added, and the reaction mixture was stirred for 3 h. CH_2Cl_2 was added, and the mixture was washed with saturated K_2CO_3 solution, dried over Na_2SO_4, and concentrated. The crude residue was purified by flash chromatography on neutral alumina (heptane/EtOAc 50/50) to afford **18** (557 mg, 87%) as a viscous colorless oil. Only the major product is described by ^1H and ^{13}C NMR: FTIR 3480, 2931, 1609, 1513, 1462, 1355, 1252, 1224, 1113, 1007, 973, 858, 732 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (t, J = 7.3 Hz, 3 H), 1.49 (sextet, J = 7.4 Hz, 2 H), 1.75−1.88 (m, 2 H), 2.49−2.57 (m, 2 H), 2.58−2.70 (m, 3 H), 3.08 (dt, J = 10.8, 4.6 Hz, 1 H), 3.84−3.87 (m, overlapping s at 3.84 and 3.85, 8 H), 3.98 (br t, J = 5.0 Hz, 2 H), 5.45−5.59 (m, 2 H), 6.56 (s, 1 H), 6.57 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 19.2, 29.0, 33.5, 38.9, 42.7, 53.9, 55.8, 56.0, 60.6, 63.3, 109.9, 110.8, 118.4, 127.3, 128.3, 128.5, 131.5, 147.2 (2C); HRMS (ESI) m/z calcd for $C_{20}H_{28}N_2NaO_3$ $(M + Na)^+$ 367.1998, found 367.1996.

(*E*)-2-(6,7-Dimethoxy-1-(4-oxobut-2-enyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)pentanenitrile (19). To a solution of **18** (163 mg, 0.47 mmol) in CH_2Cl_2 (0.5 mL) was added $NaHCO_3$ (400 mg, 4.76 mmol) followed by the addition of Dess−Martin periodinane (15% solution in CH_2Cl_2, 1.97 mL, 0.95 mmol) dropwise over a period of 5 min. The mixture was stirred for 10 min and quenched by the addition of a saturated solution of $NaHCO_3$ (26 mL), a saturated solution of $Na_2S_2O_3$ (26 mL), and ether (52 mL). The mixture was stirred for 45 min whereupon the initially formed precipitate dissolved and the phases became clear. The two phases were separated, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford **19** (151 mg, 93%) as a viscous colorless oil: FTIR 2958, 1685, 1610, 1514, 1463, 1250, 1222, 1136, 1113, 1025, 981, 862 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, J = 8.0 Hz, 3 H), 1.46 (sextet, J = 7.3 Hz, 2 H), 1.72−1.90 (m, 2 H), 2.66 (td, J = 10.9, 4.0 Hz, 1 H), 2.64−2.87 (m, 4 H,), 3.09 (dt, J = 10.8, 4.0 Hz, 1 H), 3.81 (t, J = 8.0 Hz, 1 H), 3.83 (s, 3 H), 3.85 (s, 3 H), 4.06 (br t, J = 4.0 Hz, 1 H), 6.00 (dd, J = 15.4, 7.8 Hz, 1 H), 6.49−6.63 (m, overlapping s at 6.55 and 6.57, 3 H), 9.34 (d, J = 7.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.4, 19.2, 28.5, 33.4, 38.3, 42.5, 53.8, 55.8, 56.0, 60.0, 109.5, 111.0, 118.0, 127.1, 127.9, 134.7, 147.7 (2C), 154.2, 193.4; HRMS (ESI) m/z calcd for $C_{20}H_{26}N_2NaO_3$ $(M + Na)^+$ 365.1841, found 365.1848.

(±)-Protoemetinol (15) and (±)-3-*epi*-Protoemetinol (20). To a solution of **19** (427 mg, 1.24 mmol) in $CDCl_3$ (4.1 mL) were added $NaHCO_3$ (1.04 g, 12.4 mmol) and 98% $Zn(OTf)_2$ (230 mg, 0.62 mmol). The mixture was heated at 70 °C for 1 h (reaction monitored by NMR) and then cooled to room temperature. MeOH (2 mL) and 96% $NaBH_4$ (122 mg, 3.10 mmol) were added, and the mixture was heated at 70 °C for 1 h. The mixture was cooled again to room temperature, washed with saturated K_2CO_3 solution, dried over Na_2SO_4, and concentrated. The crude residue was flash chromatographed on silica gel (acetone/EtOAc/heptane 5/3/2) to afford **15** (70 mg, 17.6%) and **20** (41 mg, 10.4%) as viscous colorless oils. **15**: FTIR 3344, 2932, 1512, 1463, 1253, 1228 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J = 7.0 Hz, 3 H), 1,12 (m, 1 H), 1.25 (m, 1 H), 1.43 (m, 2 H), 1.67 (m, 1 H), 1.94 (m, 2 H), 2.01 (t, J = 11.0 Hz, 1 H), 2.33 (dt, J = 13.0, 3.0 Hz, 1 H), 2.47 (td, J = 11.5, 4.0 Hz, 1 H), 2.61 (br dd, J = 16.0, 4.0 Hz, 1 H), 2.96 (ddd, J = 11.5, 6.0, 1.5 Hz, 1 H), 3.06 (m, 2 H), 3.10 (ddd, J = 16.0, 11.0, 6.0 Hz, 1 H), 3.75 (t, J = 7.0 Hz, 2 H), 3.83 (s, 3 H), 3.84 (s, 3 H), 6.56 (s, 1 H), 6.68 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.1, 23.5, 29.1, 35.9, 37.2, 37.6, 41.3, 52.4, 55.8, 56.1, 60.5, 61.4, 62.7, 108.3, 111.5, 126.7, 130.0, 147.1, 147.4; HRMS (ESI) m/z calcd for $C_{19}H_{30}NO_3$ $(M + H)^+$ 320.2226, found 320.2223. **20**: FTIR 3331, 2932, 1513, 1462, 1259, 1227 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J = 7.5 Hz, 3 H), 1,30 (m, 2 H), 1.46 (m, 1 H), 1.60 (m, 1 H), 1.61 (m, 2 H), 1.90 (m, 1 H), 2.00 (ddd, J = 13.0, 3.5, 2.0 Hz, 1 H), 2.27 (dd, J = 11.5, 2.4 Hz, 1 H), 2.43 (td, J = 11.5, 4.0 Hz, 1 H), 2.56 (br dd, J = 16.0, 4.0 Hz, 1 H), 2.83 (dd, J = 11.5, 6.0 Hz, 1 H), 2.98 (dd, J = 11.5, 6.0 Hz, 1 H), 3.07 (m, 1 H), 3.09 (m, 1 H), 3.75 (t, J = 7.0 Hz, 2 H), 3.84 (s, 3 H), 3.85 (s, 3 H), 6.57 (s, 1 H), 6.69 (s, 1 H); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 12.6, 17.6, 29.4, 33.3, 36.4, 36.7, 39.1, 53.1, 55.9, 56.1, 59.1, 60.9, 63.4, 108.1, 111.6, 127.1, 130.7, 147.1, 147.3; HRMS (ESI) m/z calcd for $C_{19}H_{30}NO_3$ $(M + H)^+$ 320.2226, found 320.2223.

(*E*)-Methyl 4-(2-(1-cyanobutyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)but-2-enoate (22). To a solution of **19** (621 mg, 1.81 mmol) in MeOH (36 mL) were successively added activated MnO_2 (3.15 g, 36.2 mmol), 97% KCN (487 mg, 7.25 mmol), and glacial AcOH (114 μL, 1.99 mmol). The organic mixture was stirred for 3 h at ambient temperature and then filtered on Celite. The filtrate was diluted by CH_2Cl_2 and hydrolyzed with a solution of saturated K_2CO_3. The aqueous phase was extracted by CH_2Cl_2, and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated to afford **22** as a mixture of epimers (66/33) (603 mg, 88%) and as a viscous colorless oil. Only the major product is described by ^1H and ^{13}C NMR: FTIR 2957, 1716, 1514, 1463, 1251, 1226, 729 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, J = 7.5 Hz, 3 H), 1.50 (m, 2 H), 1.81 (m, 2 H), 2.63 (m, 1 H), 2.66 (m, 3 H), 2.80 (m, 1 H), 3.08 (dt, J = 10.8, 4.0 Hz, 1 H), 3.66 (s, 3 H), 3.78 (t, J = 8.0 Hz, 1 H), 3.82 (s, 3 H), 3.84 (s, 3 H), 3.96 (br t, J = 5.0 Hz, 1 H), 5.72 (dt, J = 16.0, 1.0 Hz, 1 H), 6.52 (s, 1 H), 6.57 (s, 1 H), 6.76 (dt, J = 16.0, 7.0 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 19.2, 28.3, 33.5, 38.5, 42.5, 51.3, 54.0, 55.8, 56.0, 60.3, 109.7, 111.0, 118.3, 122.9, 127.6, 127.9, 145.2, 147.5, 147.6, 166.5; HRMS (ESI) m/z calcd for $C_{20}H_{28}NO_4$ $(M - CN)^+$ 346.2018, found 346.2018.

(*E*)-4-(6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)-2-methylbut-2-en-1-ol (23). To a solution of **13** (50 mg, 0.14 mmol) in ethanol (2 mL) at rt was added 96% $NaBH_4$ (27 mg, 0.69 mmol). The mixture was heated at reflux for 6 h and quenched by the addition of 1 N HCl (5 mL). Unreacted **13** and other neutral impurities were removed by extracting the reaction mixture with CH_2Cl_2. The aqueous phase was neutralized by the addition of saturated K_2CO_3 solution and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to afford **23** (31 mg, 83%) as a viscous colorless oil. Further purification was not necessary since the product was found to be sufficiently pure by spectral analysis: FTIR 3455, 2905, 1609, 1513, 1462, 1356, 1325, 1258, 1222, 1111, 1017, 853 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.67 (s, 3 H), 2.41−2.59 (m, 1 H), 2.63−2.80 (m, 2 H), 2.87−3.05 (m, 4 H), 3.16 (dt, J = 12.6, 5.6 Hz, 1 H), 3.82 (s, 6 H), 3.97 (m, 3 H), 5.47 (t, J = 7.5 Hz, 1 H), 6.54 (s, 1 H), 6.61 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 29.0, 34.4, 40.6, 55.4, 55.9, 56.0, 68.2, 109.2, 111.8, 121.7, 127.0, 130.2, 138.1, 147.3, 147.5; HRMS (ESI) m/z calcd for $C_{16}H_{24}NO_3$ $(M + H)^+$ 278.1756, found 278.1745.

(*E*)-2-(1-(4-Hydroxy-3-methylbut-2-enyl)-6,7-dimethoxy-3,4-dihydroisoquinolin-2(1*H*)-yl)pentanenitrile (24). To a solution of **23** (30 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) at rt were added butyraldehyde (12 μL, 0.13 mmol), H_2O (4 μL), and 97% KCN (14 mg, 0.21 mmol). TFA (18 μL, 0.23 mmol) was added, and the reaction mixture was stirred for 2 h. CH_2Cl_2 (10 mL) was added, and the mixture was washed with a saturated K_2CO_3 solution, dried over Na_2SO_4, and concentrated. The crude residue was purified by flash chromatography on neutral alumina (heptane/EtOAc 50/50) to afford **24** as two epimers (83/17) (35 mg, 90%) as a viscous colorless oil. Only the major product is described by ^1H and ^{13}C NMR: FTIR 3495, 2933, 1611, 1514, 1463, 1331, 1251, 1227, 1133, 1116, 1013, 860 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, J = 7.3 Hz, 3 H), 1.45 (sextet, J = 7.3 Hz, 2 H) 1.51 (s, 3 H), 1.65−1.85 (m, 2 H), 2.47 (t, J = 5.5 Hz, 2 H), 2.60 (dd, J = 11.0, 3.0 Hz, 1 H), 2.73−2.91 (m, 2 H), 3.06 (dt, J = 11.0, 4.0 Hz, 1 H), 3.76−3.83 (m, overlapping s at 3.78 and 3.80, 8 H), 3.85 (s, 2 H), 5.30 (t, J = 7.0 Hz, 1 H), 6.53 (s, 1 H), 6.55 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.3, 13.8, 19.0, 28.3, 33.4, 33.7, 42.6, 53.9, 55.6, 55.8, 60.5, 68.4, 109.9, 110.4, 118.4, 121.6, 127.6, 128.8, 136.2, 147.13, 147.14; HRMS (ESI) m/z calcd for $C_{21}H_{30}N_2NaO_3$ $(M + Na)^+$ 381.2154, found 381.2160.

(*E*)-2-(6,7-Dimethoxy-1-(3-methyl-4-oxobut-2-enyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)pentanenitrile (25). To a solution of **24** (75 mg, 0.21 mmol) in CH_2Cl_2 (1 mL) was added dropwise Dess−Martin periodinane (15% solution in CH_2Cl_2, 0.89 mL, 0.43 mmol) over a period of 5 min. The reaction mixture was stirred for an additional 10 min and quenched by the addition of a saturated solution of $NaHCO_3$ (11 mL), a saturated solution of $Na_2S_2O_3$ (11 mL), and ether (22 mL). After the reaction mixture stirred for 45 min, the initially formed precipitate dissolved and the phases became clear. The two phases were separated, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography on neutral alumina (heptane/EtOAc 60/40) afforded **25** as two epimers (71/29) (57 mg, 76%) as a viscous colorless oil. Only the major product is described by ^1H and ^{13}C NMR: FTIR 2935, 1682, 1611, 1518, 1461, 1256, 1196, 1142, 1117, 1018 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 3 H), 1.34−1.54 (m, 2 H), 1.60 (s, 3 H), 1.70−1.87 (m, 2 H), 2.56−2.97 (m, 5 H), 3.07 (dt, J = 10.5, 3.7 Hz, 1 H), 3.75−3.84 (m, overlapping s at 3.76 and 3.81, 7 H), 4.05 (t, J = 4.3 Hz, 1 H), 6.32 (t, J = 6.5 Hz, 1 H), 6.54 (s, 1 H), 6.55 (s, 1 H), 9.21 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.4, 13.3, 19.0, 28.4, 33.3, 34.5, 42.4, 53.7, 55.6, 55.8, 59.7, 109.6, 110.8, 118.0, 127.4, 127.8, 140.1, 147.51, 147.53, 150.1, 194.5; HRMS (ESI) m/z calcd for $C_{21}H_{28}N_2NaO_3$ $(M + Na)^+$ 379.1998, found 379.1996.

(2*S,3*R**,4*S**,11b*S**)-3-Ethyl-9,10-dimethoxy-2-(1-oxopropan-2-yl)-2,3,4,6,7,11b-hexahydro-1*H*-pyrido[2,1-*a*]isoquinoline-4-carbonitrile (26).** To a solution of **25** (57 mg, 0.16 mmol) in $CDCl_3$ (2 mL) was added 98% $Zn(OTf)_2$ (2 mg, 5.4 μmol), and the mixture was heated at 80 °C in a sealed tube for 4 h. The reaction mixture was washed with a saturated K_2CO_3 solution, dried over Na_2SO_4, and concentrated. The crude residue was subjected to flash chromatography on neutral alumina (heptane/EtOAc 70/30) to afford **26** as two epimers (66/34) (39 mg, 69%) and as a viscous colorless oil: FTIR 2934, 1719, 1610, 1513, 1462, 1381, 1360, 1336, 1250, 1231, 1209, 1153, 1106, 1011, 855, 735 cm^{-1}; HRMS (ESI^-) m/z calcd for $C_{21}H_{27}N_2O_3$ $(M - H)^-$ 355.2022, found 355.2029). **Major epimer**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.01 (d, J = 7.2 Hz, 3 H), 1.03 (t, J = 7.5 Hz, 3 H), 1.26 (m, 1 H), 1.39 (m, 1 H), 1.73 (m, 1 H), 1.76−1.92 (m, 2 H), 2.39 (tt, J = 12.0, 3.0 Hz, 1 H), 2.65 (br d, J = 16.2 Hz, 1 H), 2.73 (qd, J = 7.0, 3.0 Hz, 1 H), 2.81−2.94 (m, 2 H), 3.01−3.15 (m, 1 H), 3.71 (br d, J = 11.0 Hz, 1 H), 3.81 (s, 3 H), 3.83 (s, 3 H), 4.13 (d, J = 4.4 Hz, 1 H), 6.54 (s, 1 H), 6.57 (s, 1 H), 9.80 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 6.6, 11.1, 21.7, 29.1, 32.4, 37.5, 41.0, 46.2, 50.7, 55.8, 56.1, 57.0, 59.6, 108.3, 111.4, 115.1, 125.9, 128.4, 147.5, 147.7, 204.4. **Minor epimer**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.96 (t, J = 7.5 Hz, 3 H), 1.16 (d, J = 7.1 Hz, 3 H), 1.27 (m, 1 H), 1.46 (m, 1 H), 1.55 (m, 1 H), 1.76−1.92 (m, 1 H), 2.18−2.31 (m, 2 H), 2.54 (qd, J = 7.0, 2.0 Hz, 1 H), 2.65 (br d, J = 16.2 Hz, 1 H), 2.79−2.95 (m, 1 H), 2.99−3.16 (m, 2 H), 3.71 (br d, J = 11.0 Hz, 1 H), 3.84 (s, 3 H), 3.85 (s, 3 H), 4.08 (d, J = 4.4 Hz, 1 H), 6.57 (s, 1 H), 6.64 (s, 1 H), 9.78 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.4, 11.0, 22.5, 29.1, 35.9, 39.7, 41.4, 48.6, 50.5, 55.8, 56.1, 57.3, 59.3, 108.3, 111.4, 115.0, 126.0, 128.4, 147.5, 147.7, 204.3.

(*E*)-2-Methyl-4-(2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)-but-2-en-1-ol (27). To a solution of **5** (1.19 g, 3.40 mmol) in ethanol (34 mL) at rt was added 96% $NaBH_4$ (669 mg, 16.98 mmol). The mixture was heated at reflux for 6 h and quenched at 0 °C by the addition of 1 N HCl. Unreacted **5** and other neutral impurities were removed by extracting the reaction mixture with CH_2Cl_2. The aqueous phase was neutralized by the addition of saturated K_2CO_3 solution and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to afford **27** (814 mg, 94%) as an amorphous white solid. Further

purification was not necessary since the product was found to be sufficiently pure by spectral analysis: FTIR 3263, 2922, 1451, 907 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.66 (s, 3 H), 2.45 (ddd, J = 14.5, 7.0, 6.5 Hz, 1 H), 2.60 (ddd, J = 14.5, 7.0, 6.5 Hz, 1 H), 2.72 (m, 2 H), 2.97 (m, 1 H), 3.31 (dt, J = 13.0, 5.0 Hz, 1 H), 4.03 (s, 2 H), 4.08 (br t, J = 6.5 Hz, 1 H), 5.53 (br t, J = 7.0 Hz, 1 H), 7.09 (td, J = 7.0, 1.5 Hz, 1 H), 7.15 (td, J = 7.0, 1.5 Hz, 1 H), 7.30 (d, J = 7.0 Hz, 1 H), 7.47 (d, J = 7.0 Hz, 1 H), 8.31 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 22.5, 33.3, 42.4, 52.5, 67.9, 108.8, 110.8, 118.0, 119.2, 120.9, 121.5, 127.2, 135.6, 135.7, 138.4; HRMS (ESI) m/z calcd for $C_{16}H_{19}N_2O$ $(M - H)^+$ 255.1497, found 255.1497.

(2*S,3*R**,4*S**,12b*S**)- 3-Ethyl-2-(1-oxopropan-2-yl)-1,2,3,4,-6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-4-carbonitrile (28).** To a solution of **27** (714 mg, 2.79 mmol) in a mixture of MeOH and H_2O (1/1) (5.6 mL) at rt were successively added TFA (215 μL, 2.79 mmol), 97% KCN (187 mg, 2.79 mmol), and butyraldehyde (254 μL, 2.79 mmol). The reaction mixture was stirred overnight, diluted by CH_2Cl_2, and hydrolyzed by a solution of saturated K_2CO_3 until becoming basic. The two phases were separated, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford crude aminonitrile (841 mg, 90%). It was dissolved in CH_2Cl_2 (1.2 mL), and Dess−Martin periodinane (15% solution in CH_2Cl_2, 7.8 mL, 3.74 mmol) was added dropwise over a period of 5 min. The reaction mixture was stirred for an additional 10 min and quenched by the addition of a saturated solution of $NaHCO_3$ (70 mL), a saturated solution of $Na_2S_2O_3$ (70 mL), and CH_2Cl_2 (110 mL). After the reaction mixture was stirred for 45 min, the initially formed precipitate dissolved and the phases became clear. The two phases were separated, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated. Column chromatography on neutral alumina (heptane/AcOEt 8/2) afforded a mixture of four isomeric aldehydes (ratio ca. 5/2/2/1, as assessed by integration of the formyl peaks in the ^1H NMR spectrum) (351 mg, 42%). To a solution of these compounds (58 mg, 0.173 mmol) in $CDCl_3$ (1.7 mL) was added $Zn(OTf)_2$ (19 mg, 0.05 mmol), and the mixture was heated overnight at 80 °C in a sealed tube. The reaction mixture was washed with saturated K_2CO_3 solution, dried over Na_2SO_4, and concentrated to afford quantitatively **28**. However, the product was unstable during flash chromatography on neutral alumina (heptane/EtOAc 8/2), and it was just possible to obtain only a small amount of **28** as two epimers (66/34) (31 mg, 53%) and as a viscous colorless oil. Only the major product is described by ^1H and ^{13}C NMR: FTIR 3310, 2977, 2548, 1660, 1488, 1144 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.02 (d, J = 7.0 Hz, 3 H), 1.06 (t, J = 7.0 Hz, 3 H), 1.33−1.50 (m, 2 H), 1.72−1.82 (m, 2 H), 1.90 (tt, J = 11.2, 4.3 Hz, 1 H), 2.40 (tt, J = 11.7, 3.0 Hz, 1 H), 2.73−2.84 (m, 2 H), 2.92−3.17 (m, 3 H), 3.86 (br d, J = 11.5 Hz, 1 H), 4.20 (d, J = 4.0 Hz, 1 H), 7.10 (br t, J = 7.0 Hz, 1 H), 7.16 (br t, J = 7.0 Hz, 1 H), 7.31 (d, J = 7.0 Hz, 1 H), 7.47 (d, J = 7.0 Hz, 1 H), 7.82 (br s, 1 H), 9.78 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 6.7, 11.1, 21.6, 21.8, 30.6, 36.7, 41.3, 46.0, 51.4, 54.3, 58.8, 107.9, 110.9, 115.1, 118.2, 119.6, 121.9, 126.9, 133.1, 136.1, 204.3; HRMS (ESI) m/z calcd for $C_{20}H_{25}N_2O$ $(M - CN)^+$ 309.1967, found 309.1962.

Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra for compounds **4**, **5**, **9**−**15**, **17**−**20**, and **22**−**28**. This material is available free of charge via the Internet at http://pubs.acs.org.