Synthesis and Biological Evaluation of 18-Methoxycoronaridine Congeners. Potential Antiaddiction Agents

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Variation of the methoxycarbonyl and C-18 substituents of the antiaddictive compound 18-methoxycoronaridine, and contraction of its isoquinuclidine ring segment, provided 15 congeners for SAR evaluation at opioid and α3β4 nicotinic acetylcholine receptors. The opioid activities were relatively low, and the α3β4 nicotinic acetylcholine receptor activities were found to correlate with in vivo antiaddictive activities.

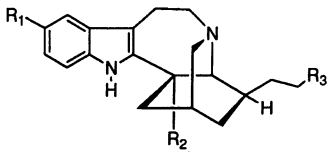
Introduction

While the natural product ibogaine (**1**) has been the subject of extensive studies with respect to its potential activity as an antiaddiction agent[1,2] and has even been clinically used, its stimulant and hallucinogenic activity and particularly its toxicity, manifested by tremors and its demonstrated destruction of Pukinje cells in the brain, exclude this alkaloid from consideration as a safe drug for the treatment of addiction to substance abuse (Figure 1).

With the observation that the related ester alkaloids voacangine, voacristine, and conopharyngine are not tremorigenic[3] and with our finding that racemic coronaridine (**2**) also has some antiaddictive activity in rats,[4] we launched a program of total synthesis to seek nontremorigenic structural variants of coronaridine having increased antiaddiction potency.[5] The best of our initial five coronaridine congeners,[5a] each with terminal oxygen substitution of the coronaridine ethyl group, was found to be 18-methoxycoronaridine (18-MC, **3**).[6] This compound showed good activity in overcoming demand for morphine,[7,8] cocaine,[7] alcohol,[9] methamphetamine,[10] and nicotine[10] in habituated rats, without affecting demand for water. It was found to be more potent than its major metabolite 18-hydroxycoronaridine (**4**,[5,11] albifloranine), the corresponding benzyl ether **5**,[5] or the MEM ether, or the acetate and lauryl ester derivatives of albifloranine.[5]

Since the methyl ester substituent in those initial five compounds was effective in elimination of tremorigenicity, it became important to determine if other corresponding ester, amide, or acid congeners of 18-MC would also support this protection from neurotoxicity and maintain the antiaddictive effect of 18-MC.

Although it could be shown that 18-methoxycoronaridine (**3**) reduces dopamine release in the nucleus accumbens[7] and binds with low affinity to several types of receptors,[1,6] its precise mechanism of action has been uncertain for a long time. Recently, however, using patch clamp methodology, 18-MC (**3**) was found to be a relatively selective antagonist at α3β4 nicotinic receptors, and it is now believed that this is 18-methoxycoronaridine's major mode of action.[12] Evidence pointing to the importance of this action was provided by data showing that low-dose combinations of 18-methoxycoronaridine (**3**) with other drugs known to have this same action (e.g., mecamylamine[13] and dextromorphan[14]) decreased both morphine and methamphetamine self-administration in rats at doses that were ineffective when administered alone. Not only were combinations of 18-MC with each of these agents effective, but a dextromorphan−mecamylamine combination was similarly effective. Because there are no agents available that are entirely specific for α3β4 receptors, the use of combinations of low doses of unrelated agents that act at this site was thought to be a potentially practical way of enhancing therapeutic efficacy (attributable to additive effects at the α3β4 site) while reducing side effects (attributable to the actions unique to each agent).



1 $R_1 = OCH_3$, $R_2 = H$, $R_3 = H$, ibogaine
2 $R = H$, $R_2 = CO_2CH_3$, $R_3 = H$, coronaridine
3 $R_1 = H$, $R_2 = CO_2CH_3$, $R_3 = OCH_3$, 18-methoxycoronaridine

Figure 1. Compounds with established antiaddiction activity.

Results and Discussion

In the present study, a series of coronaridine congeners was evaluated using patch clamp methodology to determine their key antagonist activity at α3β4 nicotinic receptors relative to the activity of 18-methoxycoronaridine (**3**) and to correlate this activity with in vivo antiaddiction activity. For comparison, activities at opioid receptors were measured.

Chemistry. For syntheses of new carbonyl derivatives of 18-MC, the latter compound had to be converted first to the corresponding carboxylic acid.Vigorous hy-

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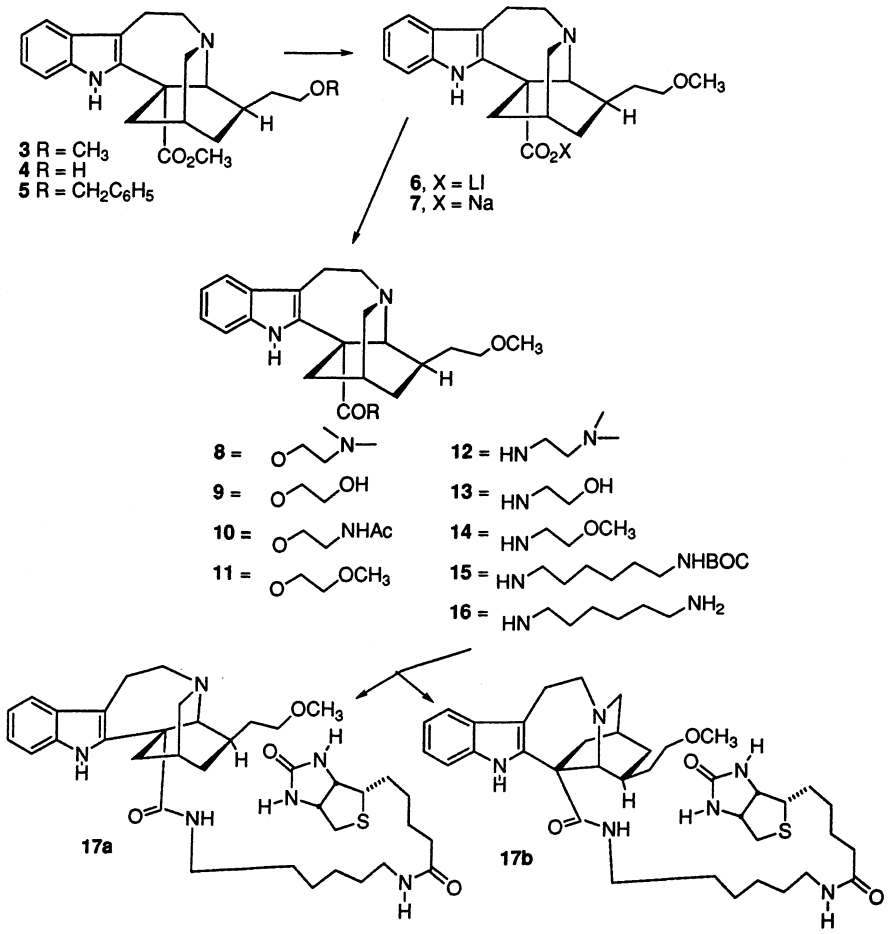
Scheme 1



drolysis of the tertiary ester **3** resulted in its decarbomethoxylation. Consequently, the ester was demethylated by treatment with lithium 1-propanethiolate. The resulting lithium salt **6** has low solubility in water, but it could be converted to the corresponding water-soluble sodium salt **7** by ion-exchange chromatography for biological evaluation.

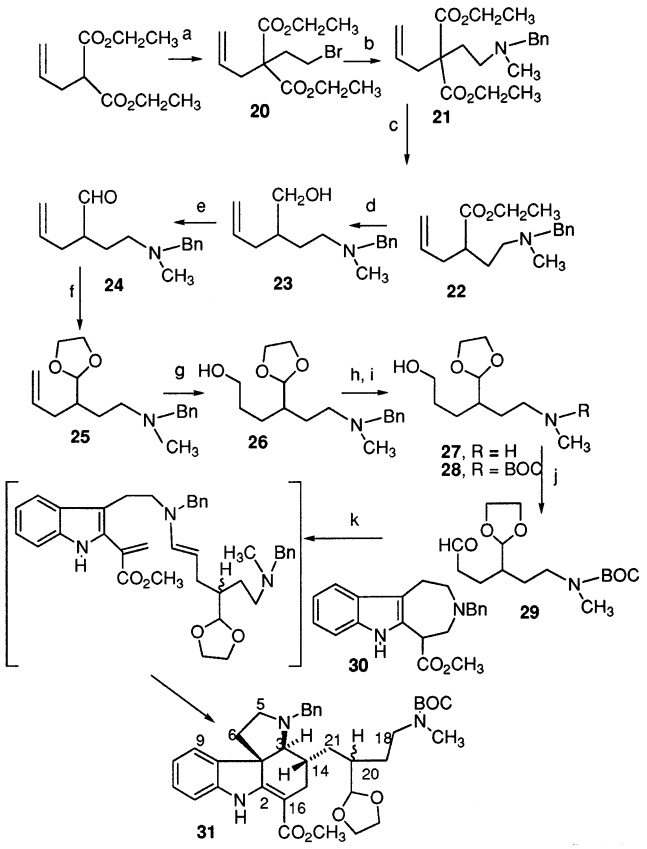
Generation of new ester and amide derivatives was then obtained by treatment of the lithium salt **6** with oxalyl chloride and reaction of the resulting acid chloride with the respective sodium alcoholates, or with amines, to furnish the esters **8**−**11** and amides **12**−**15**. Carbamate cleavage of the BOC derivative **15** provided the corresponding amine **16**. A reaction of the latter with (+)-biotin 4-nitrophenyl ester gave the biotinylated product **17a**,**b** as a mixture of two diastereomers. These could be separated on a chiral ODS HPLC column into the respective diastereomers **17a** and **17b** (Scheme 1).

An alternative to the 18-MC structure, which would maintain its skeleton and allow extensive variation of the key C-18 substitution, was expected for 18-aminocoronaridines. Such compounds, **18** and **19**, were generated by total synthesis (Schemes 2 and 3).

Alkylation of diethyl allylmalonate with dibromoethane provided the bromoethylmalonate **20** in 81% yield. Its reaction with *N*-benzylmethylamine gave the diester amine **21** in 56% yield. A Krapcho decarboethoxylation generated the monoester **22** in 97% yield. Reduction of the ester **22** with lithium aluminum hydride to the alcohol **23** (98%) and Swern oxidation furnished the aldehyde **24** (92%). For protection as an acetal, the methodology of Chan,[15] with trimethylsilyl chloride and ethylene glycol, was used (90%). Hydroboration of the olefin **25** with disiamylborane avoided the formation of a minor secondary alcohol product, which could not be detected by NMR in alcohol **26** (95%). Hydrogenolysis of the benzyl substituent (**27**, 79%) and ^{t}BOC carbamate formation with di-*tert*-butyl dicarbonate (**28**, 99%) was followed by another Swern oxidation (99%). The resulting aldehyde **29**, on condensation with the indoloazepine **30**,[16] neat at 130 °C, provided the key tetracyclic intermediate **31** as a mixture of C-20 epimers in 93% yield.

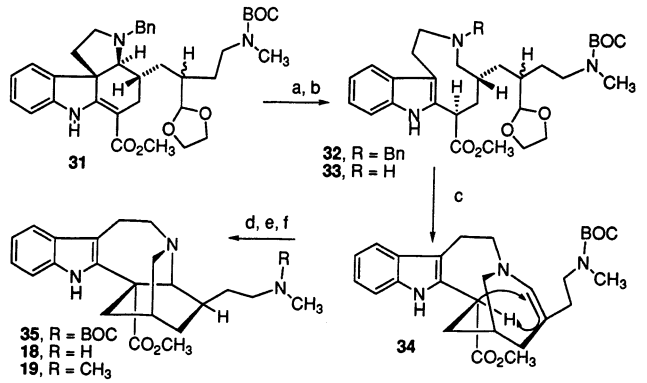
Reductive cleavage of the tetracyclic intermediate **31** with sodium borohydride in hot acetic acid gave the indoloazonines **32** (^{1}H NMR δ 5.6 for C-16 H) accompanied by about 10% of the C-16 ester epimeric product (^{1}H NMR δ 5.1 for C-16 H, total 93% yield). Hydrogenolysis of the *N*-benzyl substituent led to the C-20 epimeric but C-16 unique secondary amines **33** (94%). Epimerization of the methoxycarbonyl group under acidic conditions had been observed in our previous syntheses.[5,17] For cyclization to the enamine **34**, it was necessary to preserve the ^{t}BOC substituent in the hydrolysis of the acetal function of intermediates **33**. At −10 °C, this hydrolysis with 10% HCl in acetonitrile was slow but selective, forming on workup the enamine **34** in 91% yield. Its rearrangement on heating in benzene for 12 h gave the coronaridine congener **35** in 53% yield. Cleavage of the carbamate substituent with

Scheme 2[a]



[a] Reagents and conditions: (a) NaH, THF, $Br(CH_2)_2Br$, 81%; (b) Me(Bn)NH, K_2CO_3, acetone, 36 h reflux, 56%; (c) LiCl, DMSO/DMF, 190 °C, 6 h, 97%; (d) LAH, ether, 98%; (e) $(COCl)_2$, DMSO, −78 °C, then Et_3N, −78 °C, 10 h, 92%; (f) ethylene glycol, TMSCl, CH_2Cl_2, 72 h reflux, 90%; (g) disiamylborane, THF, −10 °C, 3 h, then H_2O_2, NaOH, 95%; (h) H_2, Pd/C, HOAc, 79%; (i) BOC_2O, CH_2Cl_2, 99%; (j) $(COCl)_2$, DMSO, then Et_3N, 92%; (k) 135 °C, neat, 30 min, 93%.

Scheme 3[a]

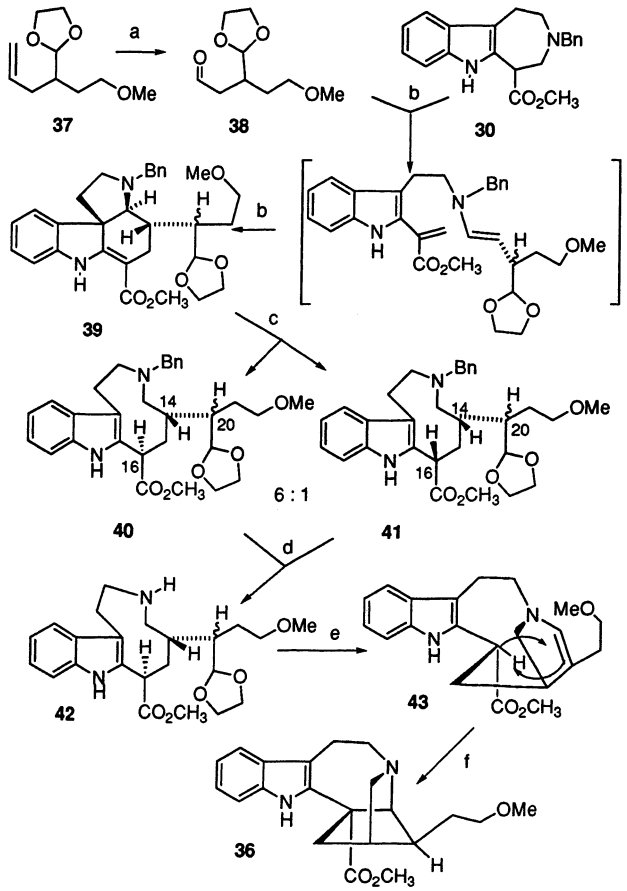


[a] Reagents and conditions: (a) $NaBH_4$, HOAc, 90 °C (93%); (b) H_2, Pd/C, HOAc (94%); (c) CH_3CN, 10% HCl, −10 °C, 72 h (91%); (d) benzene, reflux 12 h (53%); (e) HCl, MeOH, reflux 4 h (93%); (f) (1) CH_2O, MeOH, reflux 1 h, (2) $NaBH_4$ (45%).

methanolic HCl then provided the secondary amine **18** (93%). On reductive alkylation with formaldehyde and sodium borohydride, the 18-dimethylaminocoronaridine **19** was obtained.

With the syntheses of 18-MC congeners with variations of the ester and side chain substitution and their evaluation as potential antiaddiction agents (see below), it became of interest to see if the [2.2.2] bridged

Scheme 4[a]



[a] Reagents and conditions: (a) OsO_4 (cat.), $NaIO_4$, room temp, 24 h (90%); (b) neat, 130 °C, 1 h (76%); (c) $NaBH_4$, HOAc, 90 °C, 20 min (63%); (d) 10% Pd/C, H_2, HOAc (95%); (e) 10% HCl/CH_3CN, room temp, 45 min (94%); (f) toluene, reflux 24 h (64%).

isoquinuclidine core of 18-MC (**3**) is essential for its biological activity or if a [2.2.1] bridged compound **36** would still be active.This compound could be obtained (Scheme 4), starting from oxidative cleavage of the olefinic 18-MC precursor **37** (90%).[5] Condensation of the resulting aldehyde **38** with the melted indoloazepine **30**, at 130 °C, gave a 1:1 diastereomeric mixture of tetracyclic methoxyethyl epimers **39** in 76% yield.

On reductive cleavage with sodium borohydride in hot acetic acid, these tetracycles furnished a 6:1 ratio of trans/cis substituted indoloazonines **40** and **41** (63%). The ^1H NMR signal of the hydrogen α to the methoxycarbonyl group is shifted downfield (δ 5.58) in the major epimer **40** relative to that in the minor epimer **41** (δ 4.57) because of proximity of the former hydrogen to N^b. Debenzylation (95%) of the indoloazonines by hydrogenolysis in acetic acid, with concomitant epimerization of the minor precursor **41**, gave the secondary amine C-20 diastereomers **42** (95%). Acetal hydrolyis with aqueous HCl in acetonitrile and workup produced the enamine **43** in 94% yield.

Of particular interest in this synthesis was the cyclization of the enamine **43** by a thermal electrocyclic rearrangement. In comparison to formation of the [2.2.2] bicyclic core of 18-MC, formation of the [2.2.1] ring system would be expected to increase ring strain. The rearrangement was found to be slow, taking 24 h in refluxing toluene to produce the 18-MC congener **36** in 64% yield.

Table 1. Percent Inhibition of μ, δ, and κ Opioid Binding to Guinea Pig Brain Membranes by 1 μM of the Following Compounds[a]

	% inhibition ± SE		
compd	0.25 nM [^{3}H]DAMGO (μ)	0.2 nM [^{3}H]naltrindole (δ)	1 nM [^{3}H]U69,593 (κ)
3	50 ± 6	35 ± 6	20 ± 2
4	15 ± 3	14 ± 2	4 ± 1
5	12 ± 0	8 ± 3	6 ± 4
6	11 ± 1	3 ± 3	7 ± 4
8	16 ± 0	28 ± 2	78 ± 1
9	8 ± 5	9 ± 1	8 ± 2
10	0 ± 16	10 ± 0	3 ± 1
11	5 ± 2	11 ± 1	24 ± 1
12	4 ± 1	14 ± 2	11 ± 2
13	7 ± 1	10 ± 1	9 ± 2
14	10 ± 0	7 ± 2	6 ± 1
17a,**b**	19 ± 4	9 ± 2	9 ± 5
18	24 ± 1	55 ± 5	7 ± 0
19	15 ± 2	49 ± 1	11 ± 1
36	18 ± 4	19 ± 4	10 ± 2

[a] For control data, see ref 18. Guinea pig brain membranes, 0.5 mg of protein/sample, were incubated with 1 μM of the compounds in the presence of receptor-specific radioligands at 25 °C in a final volume of 1 mL of 50 mM Tris-HCl, pH 7.5. Nonspecific binding was determined using 10 μM naloxone. Data are the mean value ± SE from three separate experiments performed in triplicate.

Biological Evaluation. a. Opioid Receptors. Like ibogaine, 18-MC (**3**) showed low micromolar affinity for the three opioid receptors (μ, δ, κ) with $K_i(\mu) = 1.1$, $K_i(\delta) = 3.5$, and $K_i(\kappa) = 5.1$ μM.[7b] Modest opioid binding inhibition by the present congeners of 18-MC (Table 1) further supports the view that these compounds, as a class, derive their antiaddiction potential from a different mechanism of action. Only the dimethylaminoethyl ester **8** stood out with its maximum 78% binding inhibition for the κ opioid receptor, at 1 μM concentration.

Because compound **8** produced 78% inhibition of binding to the κ opioid receptor, it was titrated and a K_i value was determined. Twelve different concentrations of compound **8** were titrated against 1 nM [^{3}H]-U69,593. Compound **8** had a K_i value of 188 ± 19 nM for binding to the κ opioid receptor. This compound has the highest affinity for the κ receptor. For comparison, K_i values, obtained by the same methodology for U50,-488, EKC, cyclazocine, and levorphanol, have been reported.[18]

Biological Evaluation. b. α3β4 Nicotinic Acetylcholine Receptor Binding Studies. HEK293 cells expressing α3 and β4 subunits of nicotinic acetylcholine (ACh) receptors were voltage-clamped to −70 mV and examined by whole-cell patch clamp recording with fast perfusion of ACh and drug solutions. Application of 1 mM ACh produced a large inward current, which turned on and off rapidly and was present for the length of the ACh pulse (Figures 2 and 3). However, the magnitude of the current decreased slowly with persistent application of agonist. This desensitization is common for neurotransmitter receptor currents. Coapplication of 20 μM 18-MC (**3**) produced a rapid and nearly complete inhibition (98% on average) of the ACh-evoked currents (Figure 2A), which recovered slowly and only partially (12 ± 3%) within 1 s after the removal of 18-MC. This is consistent with our previous studies showing that ibogaine and 18-MC potently inhibit ACh evoked currents at α3β4 receptors.[12]

Table 2. Inhibition of α3β4 Nicotinic Acetylcholine Receptor Binding[a]

compd	% inhibition	rate of inhibition (s^{-1})	% recovery	*n*	RI
3 (18-MC)	98 ± 0	5.5 ± 0.4	12 ± 3	6	1.0
4	98 ± 1	6.5 ± 0.7	73 ± 1	5	5.4
5	64 ± 7	2.2 ± 0.3	0 ± 0	3	na
7	59 ± 1	5.1 ± 0.1	27 ± 10	4	2.4
8	98 ± 2	10.3 ± 2.5	16 ± 10	3	0.7
9	97 ± 1	7.6 ± 0.7	20 ± 3	4	1.2
10	95 ± 3	6.7 ± 1.6	45 ± 4	3	3.1
11	99 ± 0	6.0 ± 0.5	8 ± 4	6	0.6
12	93 ± 3	9.5 ± 0.7	81 ± 5	5	3.9
13	85 ± 3	7.9 ±0.7	80 ± 16	5	4.7
14	96 ± 1	9.2 ± 0.9	46 ± 9	5	2.3
18	98 ± 1	8.5 ± 1.9	21 ± 3	5	1.1
19	99 ± 1	8.0 ± 2.4	16 ± 3	3	0.9
36	94 ± 3	4.1 ± 0.8	14 ± 5	4	1.6

[a] For methodology, see ref 12.Values are the mean ± SEM for inhibition of 1 mM ACh-evoked responses. Drug concentrations were 20 μM except for compound **4**, which was 18 μM. K_i for 18-methoxycoronaridine (**3**) is 0.7 μM as determined from kinetic measures of k_{off}/k_{on}. The relative inhibition index (RI) was calculated as the percent recovery/(rate of inhibition) and is expressed relative to 18-methoxycoronaridine (**3**). RI values less than 1.0 reflect lower K_i (more potent), and RI values greater than 1.0 reflect higher K_i (less potent). Vehicle alone, including 1% DMSO, did not produce any inhibition.

To extend these findings, we tested a series of 18-MC congeners for inhibition of ACh-evoked currents at α3β4 receptors. Results are presented in Figure 2, and a summary of these findings is given in Table 2. Of the 13 compounds tested, all inhibited the inward currents produced by application of ACh; however, they differed in their potencies (Figure 2B). The esters **8**, **9**, **11**, **18**, **19**, and **36** in particular were very potent. On average, each of these compounds inhibited ACh evoked currents by greater than 94% while the currents slowly recovered less than 25% when the drug was removed. Of these, compounds **8**, **9**, and the 18-amino coronaridines **18** and **19** had fast inhibition rates ranging from 7.6 to 10.3 s^{-1}. The ester **11** had a somewhat slower inhibition rate of 6.0 s^{-1}, whereas the compound with a ring-contracted isoquinuclidine, **36**, was considerably slower at 4.1 s^{-1}. The ester bearing an amide substituent, **10**, and the 18-MC amide derivatives **12**−**14** inhibited the ACh evoked currents by 85% or more; however, the currents recovered by more than 45% when the drug was removed. These compounds had relatively fast inhibition rates ranging from 6.7 to 9.5 s^{-1}, suggesting that they bind rapidly to the receptors, whereas their fast recovery suggests they also unbind rapidly, accounting for the reduced overall level of inhibition. Finally, the benzyl ether **5** and the sodium salt **7** corresponding to 18-MC inhibited the ACh-evoked currents by less than 65%; both were relatively slow to block, but they differed in the rate of block (2.2 and 5.1 s^{-1}) and the extent of recovery at 1 s after removal of the compounds.

The nature of the inhibition assay is such that supersaturating drug concentrations must be used to measure inhibition during the agonist application. The rate of drug binding and inhibition (k_{on}) is concentration-dependent and, for practical reasons, must be maintained at a faster rate than the natural decay of the ACh-evoked response that occurs by desensitization. The 20 μM concentration was selected as appropriate on the basis of 18-methoxycoronaridine (**3**) inhibition kinetics (note the IC_{50} for parent congener **3** is less than

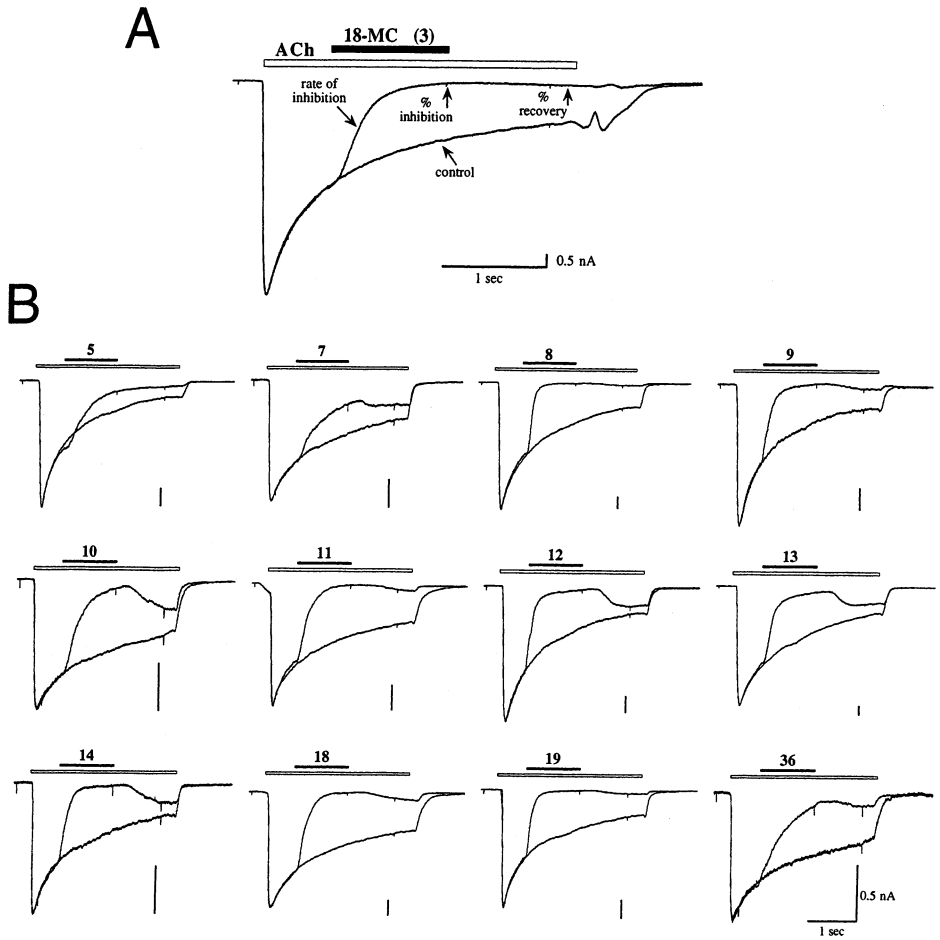


Figure 2. Inhibition of nicotinic α3β4 receptors by 18-methoxycoronaridine (18-MC) and 18-MC-like compounds. Recombinant receptors were expressed in HEK293 cells and examined by whole-cell patch clamp recordings with rapid application of acetylcholine (ACh) and drug solutions. (A) Whole-cell current evoked by application of 1 mM ACh in transfected cells was nearly eliminated by coapplications of 20 μM 18-MC. Current traces for the control and drug co-application are superimposed. Open bar depicts the timing of ACh application. Solid bar depicts the timing of coapplication of 18-MC. Arrows point to measurements presented in Table 2. (B) Inhibition of 1 mM ACh-evoked currents by various 18-MC like compounds. Conventions are as in part A. Horizontal scale bar applies to all traces. Vertical bars are 0.5 nA for all traces.

1 μM). Our goal in these studies was to gauge the relative potencies of the congeners in comparison to 18-methoxycoronaridine. Relative effective concentrations of 18-methoxycoronaridine and the various congeners can be inferred from the data in Table 2, where the more potent congeners produce nearly 100% inhibition, inhibit more quickly, and/or recover less completely than the parent **3**.

It is possible kinetically to estimate the equilibrium inhibition constants (K_i) for these compounds from the equation

$$K_i = [\text{drug}]\frac{k_{off}}{k_{on}}$$

where k_{off} is given by the rate of recovery and k_{on} is given by the rate of inhibition. The IC_{50} for 18-methoxycoronaridine (**3**) is approximately 0.75 μM,[12] close to the K_i estimate (0.67 mM) obtained from measurements of k_{off}/k_{on} at 20 μM drug. The congeners showing the least recovery following their removal are generally expected to have lower K_i values reflecting their slower unbinding from the nicotinic receptor. However, we did not estimate K_i values for all of the congeners in part because recovery time constants were too slow to resolve for some of them; this was particularly true for the most promising compounds, i.e., compounds **8**, **9**, **11**, **18**, and **19**. To facilitate comparisons between the drugs, Table 2 gives a relative inhibition index (RI) that was calculated as the percent recovery/rate of inhibition (similar to k_{off}/k_{on}) and that reflects the altered affinities of the congeners relative to 18-methoxycoronaridine (i.e., for 18-MC, **3**, it is 1).

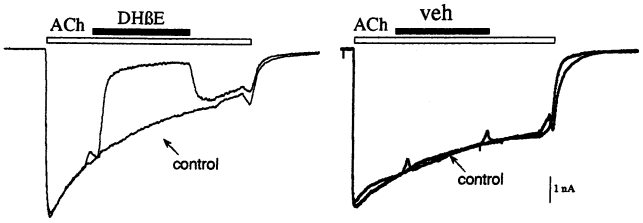


Figure 3. Controls for experiments shown in Figure 2.

Several of the congeners (depending on the amounts available) were subsequently tested on morphine self-administration in rats using well-established procedures.[7a,12] Nine compounds were examined, all administered (ip) at 20 mg/kg (a dose at which 18-methoxycoronaridine (**3**) reduces morphine self-administration to 40% of baseline). All of these compounds significantly reduced morphine self-adminstration (Ns = 4−6;

$p < 0.05-0.001$). Of the nine compounds, five (18-methoxycoronaridine (**3**), **8**, **11**, **18**, **19**) had relatively high nicotinic affinities (RI = 0.86 ± 0.09) and four (**4**, **10**, **13**, **36**) had relatively low nicotinic affinities (RI = 3.70 ± 0.85). The higher affinity compounds had a significantly larger effect than the lower affinity compounds (for morphine self-administration, percent of baseline is 35.0 ± 4.8 vs 65.0 ± 11.5; $p < 0.04$). In addition, four of the higher potency compounds were tested at a dose of 5 mg/kg, which is less than the minimally effective dose of 18-methoxycoronaridine (**3**).[7a] The most potent compound, and the only one producing a significant effect at 5 mg/kg, was the methoxyethyl ester **11**. Compound **11** also had the highest affinity index (RI, from Table 2).[19]

The pharmacokinetics of 18-methoxycoronaridine (**3**) have been previously studied.[7b] The compound appears to be sequestered in fat and slowly released. Concentrations of 18-methoxycoronaridine in discrete brain regions have not been determined, so it is difficult to definitively determine whether the affinity of 18-methoxycoronaridine at this nicotinic site is pharmacologically relevant to its antiaddictive property. However, relative to the many other receptor sites examined,[7b,12] 18-methoxycoronaridine appears to be most potent at the α3β4 nicotinic site.

Conclusion

A comparison of 18-methoxycoronaridine (**3**), currently being advanced as a potential treatment for multiple forms of drug abuse, with 13 congeners for the key activity as antagonists at α3β4 nicotinicacetylcholine receptors, indicated that the coronaridine methoxycarbonyl group can be replaced by other ester functions with retention of similar levels of activity.

The corresponding amides showed relatively fast binding but also fast unbinding from this receptor.

The carboxylic acid, administered as its sodium salt **7**, was the least active compound in the α3β4 nicotinic-acetylcholine receptor assay.

Replacement of the 18-methoxy substituent of 18-methoxycoronaridine by a dimethylamine amine function (**19**) provided high α3β4 inhibition at a relatively fast rate and slow recovery.

The ring-contracted isoquinuclidine **36** showed a slight drop in α3β4 percent inhibition relative to 18-methoxycoronaridine (**3**).

18-Methoxycoronaridine (**3**) behaves neither as an agonist nor as an antagonist at opiate receptors.[3] We showed that 18-methoxycoronaridine shifts the whole morphine self-administration dose−response curve lower[8] rather than to the left or to the right, as would be expected of an agonist or antagonist, respectively (i.e., 18-methoxycoronaridine (**3**) reduces the efficacy of morphine). Consistent with the opiate data presented here, there is no evidence that 18-methoxycoronaridine and related congeners work in vivo directly via an opiate action, but their α3β4-nicotinic receptor binding is a likely mechanism of their antiaddiction activity.

Experimental Section

Chemical Methodology. The synthetic route for 18-methoxycoronaridine (**3**) was similar to that reported[5a] except for the synthesis of intermediates **10b** and **19b** of that publication. The new procedures for those two compounds follow below.

All reactions were carried out under nitrogen or argon. NMR spectra were obtained with a Bruker 500 MHz instrument. Mass spectrometry was performed with a Finnegan 4610 quadrupole instrument. IR spectra were obtained using a Perkin-Elmer system 2000 FT-IR instrument. TLC was performed on Art. 5554 DC-Alufolien Kieselgel 60 F_{254} silica gel on aluminum sheets and developed with ceric ammonium sulfate (CAS) or phosphomolybdic acid (PMA) spray reagents. For flash chromatography, 60−200 mesh silica gel was used. HPLC data were obtained with Star Chromatography Workstation, version 5.50, using a ProStar/Dynamax (2 v) detector and aVarian Microsorb-MV 100 Å C5 silica column or an ASTEC Cyclobond I 2000 (cyclodextrins linked to silica) column.

4-(1,3-Dioxolan-2-yl)-6-methoxyhexan-1-ol (10b).[5a] To a stirred solution of borane−THF (1 M, 8.1 mL, 8.1 mmol) at −10 °C, was added, dropwise, a solution of 2-methyl-2-butene in THF (2 M, 8.1 mL, 16.2 mmol) over 30 min. The mixture was stirred for 3 h at −10 °C. A solution of 4-(1,3-dioxolan-2-yl)-6-methoxy-1-hexene (1.0 g, 5.4 mmol)[5a] in dry THF (20 mL) was added dropwise over 10 min at −10 °C, and the mixture was stirred for 2 h at 0 °C. Then 15% NaOH (2.2 mL, 8.3 mmol) and 30% H_2O_2 (2.20 mL, 19.4 mmol) were added dropwise. The reaction mixture was heated at reflux for 1 h, cooled to room temperature, and concentrated under reduced pressure. To the residue was added saturated NH_4Cl solution (50 mL). Extraction with dichloromethane (4 × 30 mL), washing of the combined organic layers with saturated brine (2 × 30 mL), drying over $MgSO_4$, concentration under reduced pressure, and chromatography on a silica gel column, eluting with hexane/ethyl acetate (1:4), gave the title compound **10b** (1.04 g, 95%).

Enamine (19b).[5a] Secondary amine acetal **18b**[5a] (3.089 g, 7.2 mmol) was dissolved in acetonitrile (35 mL) and degassed, and 10% HCl (35 mL) was degassed and transferred into the above acetonitrile solution. Shielded from light, the mixture was stirred for 4 h at room temperature under argon, then poured into crushed ice, basified with 15% aqueous NH_3, and extracted with ether (7 × 150 mL). The extracts were dried over powdered 4 Å molecular sieves for 30 min, concentrated, then dried in a desiccator with P_2O_5 under vacuum overnight. The crude enamine was used directly for thermal isomerization to 18-methoxycoronaridine.

18-Methoxyibogamine 16-Lithiumcarboxylate (6). To a solution of *n*-butyllithium in hexane (1.6 M, 6.80 mL, 10.9 mmol) in dry THF (40 mL) at 0 °C were added dropwise 1-propanethiol (1.20 mL, 13.3 mmol) and dry HMPA (1.80 mL, 10.4 mmol). After the mixture was stirred for 1 h at room temperature, 18-methoxycoronaridine (**3**, 1.0 g, 2.7 mmol) in dry THF (60 mL) was added. The mixture was stirred for 68 h at room temperature, water (0.25 mL, 14 mmol) was added, and the mixture was concentrated at 32 °C under reduced pressure. The residue was chromatographed on silica gel (SM/silica gel = 1:400), eluting with dichloromethane/methanol (2:1) to give the title compound **6** (0.955 g, 98%) as a yellow solid: mp 183−184 °C; TLC R_f = 0.42 (silica gel, dichloromethane/methanol, 2:1, CAS yellow); UV (EtOH) λ_{max} 224, 284 nm; IR (KBr) ν_{max} 3420, 3184, 2923, 1606, 1464, 1363, 1334, 1320, 1110, 1093, 1048, 1011, 979 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.03−1.07 (m, 1 H), 1.58−1.77 (m, 6 H), 2.59 (d, J = 5 Hz, 1 H), 2.67 (d, J = 5 Hz, 1 H), 2.67 (d, J = 8 Hz, 1 H), 2.83 (m, 1 H), 2.95−3.03 (m, 3 H), 3.21 (s, 3 H), 3.32−3.37 (m, 4 H), 6.92 (t, J = 8 Hz, 1 H), 6.98 (t, J = 8 Hz, 1 H), 7.26 (d, J = 8 Hz, 1 H), 7.38 (d, J = 8 Hz, 1 H), 10.34 (s, 1 H); ^{13}C NMR (DMSO-d_6) δ 21.4, 26.9, 31.7, 32.7, 34.1, 35.6, 53.0, 53.3, 54.3, 56.8, 57.9, 70.1, 108.6, 111.1, 117.7, 120.6, 127.9, 135.6, 135.8, 138.4, 175.1; MS (CI), *m/z* (rel intensity) 367 (M^+ + Li, 0.2), 355 (M^+ − Li + 2, 0.48), 312 (1), 311 (4), 279 (0.5), 232 (100), 157 (4). Anal. ($C_{21}H_{25}N_2O_3Li$) C, H, N.

18-Methoxyibogamine 16-Sodiumcarboxylate (7). To a solution of the lithium salt **6** (0.25 g, 0.69 mmol) in THF/HMPA (1:1, 4 mL) was added Amberlite IR-120 (plus) ion-exchange resin (sodium form), and the mixture was stirred for 0.5 h,

filtered, and concentrated at 32 °C under reduced pressure. The residue was chromatographed on silica gel (SM/silica gel = 1:400), eluting with dichloromethane/methanol (2:1) to give the sodium salt **7** (0.21 g, 80%) as a yellow powder: mp 159−160 °C; TLC $R_f = 0.42$ (silica gel, dichloromethane/methanol, 2:1, CAS yellow); UV (EtOH) λ_{max} 224, 284 nm; IR (KBr) ν_{max} 3409, 2925, 2362, 1606, 1462, 742 cm^{-1}; ^{1}H NMR (DMSO-d_6 + D_2O) δ 1.03−1.04 (m, 1 H), 1.56−1.81 (m, 6 H), 2.55 (d, J = 13 Hz, 1 H), 2.63 (d, J = 9 Hz, 1 H), 2.86 (d, J = 9 Hz, 1 H), 2.94−3.05 (m, 3 H), 3.19 (s, 3 H), 3.29−3.37 (m, 4 H), 6.91(t, J = 7 Hz, 1 H), 6.98 (t, J = 7 Hz, 1 H), 7.24 (d, J = 8 Hz, 1 H), 7.36 (d, J = 8 Hz, 1 H), 10.23 (s, 1 H); ^{13}C NMR (DMSO-d_6 + D_2O) δ 21.5, 27.1, 31.8, 33.1, 34.2, 36.0, 53.5, 53.7, 54.5, 57.3, 58.3, 70.5, 108.9, 112.0, 118.0, 122.0, 128.3, 136.0, 136.1, 138.7, 176.0; MS (CI), m/z (rel intensity) 356 (15), 355 (M^+ − Na + 2, 100), 311 (21), 277 (7), 221 (10), 209 (11), 207 (15), 195 (17). HPLC: (a) silica C5, 68 bar, 1 mL/min, hexane/2-propanol/triethylamine (1:1:0.02), injection in 20 μL of THF, retention time of 55.52 min; (b) Cyclobond I 2000, 146 bar, 3 mL/min, hexane/ethanol/triethylamine (60:40:0.2), injection in 20 μL of THF, retention time of 27.44 min.

18-Methoxycoronaridine *N,N*-Dimethylethylenediamine Amide (12). The lithium salt **6** (0.10 g, 0.30 mmol) was suspended in dry THF (15 mL), and dry pyridine (0.03 mL, 0.4 mmol) was added at 0 °C, followed by oxalyl chloride (2 M, 0.6 mL, 1.2 mmol). The mixture was stirred for 42 h at room temperature and concentrated at 32 °C. The acid chloride residue was dissolved in dry dichloromethane (25 mL), and at 0 °C *N,N*-dimethylethylenediamine (0.3 mL, 2.6 mmol) was added dropwise. The mixture was stirred for 1 h (0 °C to room temperature), the organic phase was washed with water (3 × 20 mL), the combined aqueous phases were extracted with dichloromethane (3 × 30 mL), and the combined organic layers were washed to neutral with brine, dried over sodium sulfate, concentrated, and chromatographed on silica gel, eluting with dichloromethane/methanol (2:1) to give the amide **12** (0.11 g, 87%) as a yellow solid: mp 69−70 °C; TLC $R_f = 0.26$ (silica gel, dichloromethane/methanol, 2:1, CAS blue); UV (EtOH) λ_{max} 228, 286 nm; IR (KBr) ν_{max} 3320, 2925, 2857, 1653, 1521, 1461, 1347, 1290, 1186, 1118, 740, 668 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10 (m, 1 H), 1.65−1.68 (m, 2 H), 1.78−1.90 (m, 4 H), 2.28 (s, 6 H), 2.32−2.36 (m, 1 H), 2.45−2.49 (m, 1 H), 2.87−2.92 (m, 4 H), 3.17−3.21 (m, 2 H), 3.30 (s, 3 H), 3.29−3.31 (m, 3 H), 3.41 (t, J = 7 Hz, 2 H), 3.61−3.65 (m, 1 H), 5.91 (s, 1 H), 7.06 (dt, J = 7, 1 Hz, 1 H), 7.11 (dt, J = 8, 1 Hz, 1 H), 7.22 (dd, J = 8, 1 Hz, 1 H), 7.47 (d, J = 8 Hz, 1 H), 9.18 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.9, 27.1, 31.6, 33.4, 34.5, 35.6, 37.5, 45.4, 50.7, 53.5, 55.7, 58.45, 58.47, 60.8, 71.4, 110.6, 110.9, 118.2, 119.0, 121.7, 129.0, 135.8, 139.5, 174.3; MS (CI), m/z (rel intensity) 426 (M^+ + 2, 10), 425 (M^+ + 1, 100), 392 (3), 255 (7), 114 (4), 88 (4). HRMS calcd for $C_{25}H_{36}N_4O_2Li$: 431.2998. Found: 431.2997. HPLC: (a) silica C5, 39 bar, 1 mL/min, hexane/2-propanol/triethylamine (4:1:0.05), injection in 20 μL of 2-propanol, retention time of 13.16 min; (b) Cyclobond I 2000, 96 bar, 2 mL/min, hexane/ethanol (6:4), injection in 20 μL of ethanol, retention time of 9.05 min.

18-Methoxycoronaridine 2-Methoxyethylamide (14). Following the above procedure, the reaction of the 18-methoxycoronaridine-derived acid chloride with 2-methoxyethylamine and chromatography, twice on silica gel, first eluting with dichloromethane/methanol (15:1) and then with hexane/ethyl acetate (1:3), gave the title compound **14** (95%) as a white solid: mp 155−156 °C; TLC R_f = 0.4 (silica gel, dichloromethane/methanol, 15:1, CAS blue); UV (EtOH) λ_{max} 228, 286 nm; IR (KBr) ν_{max} 3271, 2931, 1645, 1533, 1461, 1360, 1293, 1197, 1090, 1011, 748 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.13−1.15 (m, 1 H), 1.61−1.65 (m, 1 H), 1.74−1.93 (m, 5 H), 2.78−2.84 (m, 2 H), 2.92−3.0 (m, 2 H), 3.21−3.24 (m, 2 H), 3.27 (s, 3 H), 3.32 (s, 3 H), 3.36−3.45 (m, 8 H), 6.05 (s, 1 H), 7.07 (t, J = 8 Hz, 1 H), 7.13 (t, J = 8 Hz, 1 H), 7.22 (d, J = 8 Hz, 1 H), 7.47 (d, J = 8 Hz, 1 H), 8.24 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.2, 27.2, 32.1, 33.8, 35.5, 39.8, 51.4, 53.3, 55.3, 58.5, 58.7, 59.8, 71.1, 71.8, 110.2, 110.4, 118.3, 119.1, 121.9, 128.8, 135.7, 138.3, 174.6; MS (CI), m/z (rel intensity) 412 (M^+ + 1, 18), 411 (M^+, 100). Anal. ($C_{24}H_{33}N_3O_3$) C, H, N.

18-Methoxycoronaridine 2-Hydroxyethylamide (13). Following the above procedure, the reaction of the 18-methoxycoronaridine-derived acid chloride with ethanolamine for 1.5 h at 0 °C, regular workup, and chromatography on silica gel, eluting with ethyl acetate/methanol (25:1), gave compound **13** (82%) as a white solid: mp 205 °C (dec); TLC R_f = 0.26 (silica gel, ethyl acetate/methanol, 25:1, CAS blue); UV (EtOH) λ_{max} 226, 286 nm; IR (KBr) ν_{max} 3303, 2923, 1653, 1624, 1559, 1522, 1458, 1259, 1107, 742, 668 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10−1.11 (m, 1 H), 1.61−1.64 (m, 1 H), 1.73−1.76 (m, 1 H), 1.82−1.85 (m, 1 H), 1.89−1.93 (m, 4 H), 2.82−2.86 (m, 2 H), 2.93−3.02 (m, 2 H), 3.06−3.15 (m, 1 H), 3.22−3.27 (m, 3 H), 3.33 (s, 3 H), 3.36−3.47 (m, 3 H), 3.56−3.68 (m, 4 H), 6.12 (s, 1 H), 7.08 (t, J = 8 Hz, 1 H), 7.14 (t, J = 8 Hz, 1 H), 7.23 (d, J = 8 Hz, 1 H), 7.46 (d, J = 8 Hz, 1 H), 8.17 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.3, 27.3, 32.2, 33.2, 33.6, 35.4, 42.9, 51.6, 53.5, 55.2, 58.1, 59.8, 61.5, 71.3, 110.1, 110.5, 118.3, 119.2, 122.1, 128.7, 135.7, 138.1, 175.3; MS (CI), m/z (rel intensity) 398 (M^+ + 1, 25), 397 (M^+, 100), 178 (19), 92 (12). HRMS calcd for $C_{23}H_{31}N_3O_3$: 397.2365. Found: 397.2359. HPLC: (a) silica C5, 34 bar, 1 mL/min, hexane/2-propanol/triethylamine (9:1:0.1), injection in 20 μL of 2-propanol, retention time of 11.11 min (97.6% purity), retention time of 13.74 min (2.4% impurity); (b) Cyclobond I 2000, 32 bar, 1 mL/min, hexane/ethanol (9:1), injection in 20 μL of ethanol, retention time of 12.06 min.

***N,N*-Dimethylaminoethyl 18-Methoxycoronaridinate (8).** The lithium salt **6** (50 mg, 0.14 mmol) was suspended in dry THF (25 mL), and dry pyridine (15 μL, 0.19 mmol) was added. At 0 °C, oxalyl chloride (280 μL, 0.56 mmol) was added. The mixture was stirred for 40 h at room temperature. Sodium hydride (90 mg, 60%, 2.25 mmol) was suspended in dry THF (10 mL), and at 0 °C *N,N*-dimethylethanolamine (0.46 mL, 4.58 mmol) was added. The mixture was stirred for 20 min at 0 °C and then for 1 h at room temperature. At 0 °C, the sodium alcoholate was dropped into the above acid chloride solution. After being stirred for 1 h at that temperature, the reaction mixture was quenched with buffer solution (pH 7), concentrated at 32 °C, and partitioned between dichloromethane and water. The aqueous layer was extracted with dichloromethane (3 × 20 mL), and the combined organic layers were washed with brine to neutral, dried over sodium sulfate for 1 h, and concentrated. Chromatography on silica gel, eluting with dichloromethane/methanol (17:1), gave the title compound **8** (46 mg, 78%) as a white solid: mp 112−113 °C; TLC R_f = 0.23 (silica gel, dichloromethane/methanol, 13:1, CAS blue); UV (EtOH) λ_{max} 228, 286 nm; IR (film) ν_{max} 2927, 2860, 1729, 1457, 1366, 1281, 1257, 1232, 1174, 1122, 1037, 950, 739 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.13 (d, J = 11 Hz, 1 H), 1.62−1.68 (m, 1 H), 1.75−1.78 (m, 3 H), 1.84−1.91 (m, 2 H), 2.40 (s, 6 H), 2.54−2.59 (m, 1 H), 2.65−2.70 (m, 1 H), 2.78−2.81 (m, 2 H), 2.92−2.94 (m, 1 H), 3.00−3.02 (m, 1 H), 3.24−3.29 (m, 1 H), 3.30 (s, 3 H), 3.32−3.43 (m, 5 H), 4.16−4.18 (m, 1 H), 4.59−4.60 (m, 1 H), 7.04 (t, J = 8 Hz, 1 H), 7.09 (t, J = 8 Hz, 1 H), 7.20 (d, J = 8 Hz, 1 H), 7.46 (d, J = 8 Hz, 1 H), 9.92 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.4, 27.0, 31.1, 33.7, 34.8, 36.6, 45.4, 49.9, 53.7, 55.6, 58.0, 58.6, 59.8, 61.6, 71.0, 110.6, 110.9, 118.1, 118.8, 121.3, 129.2, 135.7, 139.4, 174.0; MS (CI), m/z (rel intensity) 427 (M^+ + 2, 32), 426 (M^+ + 1, 100), 93 (5). HRMS calcd for $C_{25}H_{36}N_3O_3$: 426.2757. Found: 426.2738. HPLC: (a) silica C5, 32 bar, 1 mL/min, hexane/2-propanol/triethylamine (49:1:0.5), injection in 20 μL of 2-propanol, retention time of 14.95 min, 98.3%, 12.93 min, 1.7% impurity; (b) Cyclobond I 2000, 32 bar, 1 mL/min, hexane/ethanol (9:1), injection in 20 μL of THF, retention time of 10.96 min.

2-Methoxyethyl 18-Methoxycoronaridinate (11). Following the above procedure, the reaction of the 18-methoxycoronaridine-derived acid chloride with sodium 2-methoxyethanolate and chromatography on silica gel, eluting with hexane/ethyl acetate (1:1), gave compound **11** (83%) as a colorless oil: TLC R_f = 0.2 (silica gel, hexane/ethyl acetate, 1:1, CAS blue); UV (EtOH) λ_{max} 228, 286 nm; IR (film) ν_{max}

3327, 2929, 1729, 1653, 1559, 1460, 1368, 1346, 1228, 1198, 1122, 1029, 866, 743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15−1.17 (m, 1 H), 1.68−1.78 (m, 4 H), 1.86−1.90 (m, 3 H), 2.66 (d, J = 13 Hz, 1 H), 2.88−2.94 (m, 3 H), 3.23−3.28 (m, 2 H), 3.32 (s, 3 H), 3.33−3.35 (m, 1 H), 3.41 (s, 3 H), 3.42−3.44 (m, 1 H), 3.47 (s, H), 3.58−3.62 (m, 2 H), 4.27−4.29 (m, 1 H), 4.46−4.48 (m, 1 H), 7.06 (t, J = 7 Hz, 1 H), 7.12 (t, J = 7 Hz, 1 H), 7.21 (d, J = 8 Hz, 1 H), 7.46 (d, J = 8 Hz, 1 H), 8.37 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.8, 27.2, 31.6, 33.9, 34.4, 36.6, 50.7, 53.3, 55.3, 58.5, 58.8, 63.2, 70.3, 70.9, 110.4, 110.5, 118.3, 119.1, 121.7, 128.9, 135.5, 137.6, 174.3; MS (FAB), m/z (rel intensity) 413 (M^+ + 1, 10), 289 (4), 246 (12), 185 (36), 154 (74), 137 (64), 120 (12), 107 (24), 93 (100). HRMS calcd for $C_{24}H_{33}N_2O_4$: 413.2440. Found: 413.2449. HPLC: (a) silica C5, 32 bar, 1 mL/min, hexane/2-propanol/triethylamine (49:1:0.5), injection in 20 μL of 2-propanol, retention time of 9.06 min; (b) Cyclobond I 2000, 30 bar, 1 mL/min, hexane/ethanol (95:5) injection in 20 μL of EtOH, retention time of 6.27 min.

2-Hydroxyethyl 18-Methoxycoronaridinate (9). The acid chloride prepared from the lithium salt **6** (50 mg, 0.14 mmol), in dry THF (25 mL), dry pyridine (15 μL, 0.19 mmol), and oxalyl chloride (280 μL, 0.56 mmol), was added slowly at 0 °C to sodium ethylene glycolate [prepared from ethylene glycol (1.25 mL, 22.4 mmol) in dry THF (10 mL), at 0 °C, and sodium hydride (90 mg, 2.3 mmol), added slowly and stirred for 20 min at 0 °C and then 1 h at room temperature]. The mixture was stirred for 1 h at 0 °C, quenched with buffer solution (pH 7, 0.1 mL), concentrated at 32 °C, and partitioned between dichloromethane and water. The aqueous phase was extracted with dichloromethane (3 × 20 mL), and the combined organic layers were washed with brine to neutral, dried over sodium sulfate, concentrated, and chromatographed twice on silica gel, first eluting with dichloromethane/methanol (17:1), then with hexane/ethyl acetate (1:3), to give the title product **9** (55.3 mg, 100%) as a white solid: mp 143−144 °C; TLC R_f = 0.21 (silica gel, dichloromethane/methanol, 17:1, CAS blue); UV (EtOH) λ_{max} 228, 286 nm; IR (film) ν_{max} 3379, 2928, 1724, 1461, 1368, 1227, 1174, 1086, 742 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12−1.14 (m, 1 H), 1.68−1.76 (m, 1 H), 1.78−1.82 (m, 2 H), 1.88−1.92 (m, 3 H), 2.61−2.65 (m, 1 H), 2.86 (d, J = 8 Hz, 1 H), 2.92−3.00 (m, 2 H), 3.19−3.26 (m, 2 H), 3.33 (s, 3 H), 3.34−3.45 (m, 2 H), 3.50 (br s, 1 H), 3.56−3.61 (m, 2 H), 3.74−3.76 (m, 2 H), 3.96−3.98 (m, 1 H), 4.58−4.60 (m, 1 H), 7.07 (t, J = 7 Hz, 1 H), 7.13 (t, J = 7 Hz, 1 H), 7.23 (d, J = 9 Hz, 1 H), 7.46 (d, J = 8 Hz, 1 H), 7.99 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.1, 27.3, 32.0, 33.4, 34.1, 36.9, 51.2, 53.3, 55.1, 57.9, 58.1, 60.8, 67.2, 70.6, 110.3, 110.4, 118.4, 119.3, 122.0, 129.0, 135.5, 136.8, 175.5; MS (CI), m/z (rel intensity) 400 (M^+ + 2, 46), 399 (M^+ + 1, 100), 367 (12), 353 (20), 93 (65). Anal. ($C_{23}H_{30}N_2O_4$) C, H, N.

2-Acetylaminoethyl 18-Methoxycoronaridinate (10). A sodium alcoholate solution was prepared by addition of *N*-acetylethanolamine (0.42 mL, 4.6 mmol) to a suspension of sodium hydride (90 mg, 2.3 mmol) in 4 mL of dry DMF at 0 °C. After 1 h at room temperature, this solution was added at 0 °C to the acid chloride in THF, prepared from 50 mg (0.14 mmol) of the lithium salt **6**. After 1 h at 0 °C, the reaction mixture was quenched with buffer solution (pH 7, 0.1 mL), the THF was evaporated under reduced pressure at 32 °C, and then DMF was evaporated under vacuum at 39 °C. The residue was partitioned between dichloromethane and water and worked up as above. Two chromatographies, first eluting with dichloromethane/methanol (12.5:1), then ethyl acetate/methanol (25:1), gave the title product **10** (43 mg, 71%) as a colorless oil. TLC R_f = 0.3 (silica gel, dichloromethane/methanol, 12.5:1, CAS blue); UV (EtOH) λ_{max} 226, 286 nm; IR (film) ν_{max} 3300, 2929, 2859, 1726, 1661, 1548, 1461, 1371, 1223, 1174, 1118, 1036, 741 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (d, J = 7 Hz, 1 H), 1.76−1.79 (m, 3 H), 1.82 (s, 3 H), 1.84−1.93 (m, 3 H), 2.61 (m, 1H), 2.82 (d, J = 8 Hz, 1 H), 2.96−2.98 (m, 1 H), 2.99−3.03 (m, 1 H), 3.17−3.20 (m, 2 H), 3.34 (s, 3 H), 3.38−3.40 (m, 2 H), 3.44−3.48 (m, 2 H), 3.55−3.57 (m, 2 H), 3.98−4.05 (m, 1 H), 4.42−4.45 (m, 1 H), 6.67 (s, 1 H), 7.07 (t, J = 8 Hz, 1 H), 7.13 (t, J = 7 Hz, 1 H), 7.25 (d, J = 8 Hz, 1 H), 7.46 (d, J = 8 Hz, 1 H), 8.05 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.0, 22.5, 27.3, 31.7, 33.5, 34.3, 36.5, 38.8, 51.7, 53.2, 57.7, 58.1, 64.6, 70.4, 110.3, 110.5, 118.3, 119.2, 119.3, 121.9, 128.7, 135.5, 136.4, 170.7, 175.1; MS (FAB), m/z (rel intensity) 440 (M^+ + 1, 100), 355 (25), 154 (36), 93 (45). HRMS calcd for $C_{25}H_{34}N_3O_4$: 440.2549. Found: 440.2544. HPLC: (a) silica C5, 35 bar, 1 mL/min, hexane/2-propanol/triethylamine (9:1:0.1), injection in 20 μL of 2-propanol, retention time of 18.34 min; (b) Cyclobond I 2000, 32 bar, 1 mL/min, hexane/ethanol (9:1), injection in 20 μL EtOH, retention time 14.80 min.

18-Methoxycoronaridine 6-[(*tert*-Butyl)carbamyl]hexanamide (15). The lithium salt **6** (50 mg, 0.14 mmol) was suspended in dry THF (20 mL) and dry pyridine (15 μL, 0.19 mmol). At 0 °C, oxalyl chloride (280 μL, 0.56 mmol) was added, and the mixture was stirred for 40 h at room temperature. *tert*-Butyl *N*-(6-aminohexyl)carbamate hydrochloride (584 mg, 2.24 mmol) was suspended in dry THF (15 mL), triethylamine (0.63 mL, 4.5 mmol) was added, and then the mixture was dropped slowly into the above acid chloride solution at 0 °C. After being stirred for 2 h at 0 °C to room temperature, the mixture was concentrated at 32 °C and the residue was partitioned between dichloromethane and water. The aqueous layer was extracted with dichloromethane (3 × 20 mL), and the combined organic layers were washed with brine to neutral, dried over sodium sulfate, and concentrated. The crude material was directly used in the next reaction or chromatographed on silica gel, eluting with hexane/ethyl acetate (1:2) to give the title product **15** (38 mg, 50%) as a white solid: mp 117−119 °C; TLC R_f = 0.28 (silica gel, hexane/ethyl acetate, 1:2, CAS blue); UV (EtOH) λ_{max} 228, 286 nm; IR (film) ν_{max} 3303, 2930, 2857, 1691, 1648, 1521, 1462, 1391, 1366, 1252, 1172, 1117, 1010, 741 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12−1.26 (m, 5 H), 1.30−1.34 (m, 2 H), 1.42 (s, 9 H), 1.59−1.64 (m, 2 H), 1.80−1.95 (m, 6 H), 2.73−2.80 (m, 2 H), 2.90−2.93 (m, 1 H), 2.98−3.03 (m, 3 H), 3.17−3.26 (m, 4 H), 3.27−3.28 (m, 1 H), 3.32 (s, 3 H), 3.38−3.42 (m, 1 H), 3.46−3.48 (m, 2 H), 4.46 (br s, 1 H), 5.99 (br s, 1 H), 7.07 (t, J = 8 Hz, 1 H), 7.13 (t, J = 7 Hz, 1 H), 7.23 (d, J = 9 Hz, 1 H), 7.48 (d, J = 8 Hz, 1 H), 8.23 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.8, 26.6, 26.7, 27.8, 28.9, 29.8, 30.4, 32.9, 34.0, 34.5, 36.0, 40.4, 52.6, 53.7, 55.5, 58.9, 59.4, 72.6, 79.5, 110.2, 110.9, 118.8, 119.6, 122.4, 129.1, 136.1, 138.7, 156.5, 175.1; MS (CI), m/z (rel intensity) 554 (M^+ + 2, 36), 553 (M^+ + 1, 100), 507 (10), 497 (14), 382 (10), 310 (9), 257 (6), 199 (6), 189 (9), 187 (23), 143 (23), 93 (24), 91 (47), 85 (50), 81 (53). HRMS calcd for $C_{32}H_{49}N_4O_4$: 553.3754. Found: 553.3752.

18-Methoxycoronaridine 6-Aminohexanamide (16). Crude carbamate **15** (153 mg, 0.278 mmol) was dissolved in 3 N HCl/EtOAc (10 mL) at 0 °C. The reaction mixture was stirred for 1.5 h at room temperature and concentrated at 32 °C. Saturated sodium bicarbonate solution was added at 0 °C until pH 8−9 was obtained. The mixture was extracted with dichloromethane (3 × 40 mL), and the combined organic layers were washed with brine to neutral and concentrated to give the crude amine **16**, which was directly used in the next reaction.

Biotinoylamides 17a,b. To a solution of crude amine **16** (0.278 mmol) in pyridine (5 mL), (+)-biotin 4-nitrophenyl ester (100 mg, 0.274 mmol) was added at 0 °C. The reaction mixture was stirred overnight at room temperature, concentrated at 40 °C, then partitioned between dichloromethane and water. The aqueous layer was extracted with dichloromethane (3 × 40 mL), and the combined organic layers were washed with brine to neutral, dried over sodium sulfate, concentrated, and chromatographed twice on silica gel, first eluting with dichloromethane/methanol (7.3:1), then with ethyl acetate/methanol (4:1), to give the biotinylated products **17a**,**b** (135 mg, 72%, from lithium salt **6**, three steps) as a yellow powder.

Separation of Diastereomers 17a and 17b. The biotinylated products **17a**,**b** (10 mg) were loaded onto a semipreparative chiral ODS HPLC column and eluted with hexane/ethanol/diethylamine (10:1:0.01) to give the two diastereoisomers **17a** (50%, retention time of 180 min) as a white solid and **17b** (50%, retention time of 209 min) as a white solid.

17a: mp 119−120 °C; TLC $R_f = 0.18$ (silica gel, ethyl acetate/methanol, 4:1, CAS blue); $[\alpha]^{25}_D$ +50 (*c* 0.1, $CHCl_3$); UV (EtOH) λ_{max} 228, 286 nm; IR (film) ν_{max} 3288, 2928, 2857, 1700, 1646, 1540, 1461, 1265, 1116, 736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88−0.92 (m, 1 H), 1.13−1.20 (m, 4 H), 1.21−1.31 (m, 3 H), 1.35−1.44 (m, 6 H), 1.52−1.57 (m, 1 H), 1.60−1.68 (m, 4 H), 1.76−1.89 (m, 5 H), 2.11 (t, $J = 10$ Hz, 1 H), 2.64 (d, $J = 8$ Hz, 1 H), 2.78−2.83 (m, 3 H), 2.92−2.94 (m, 1 H), 2.98−3.02 (m, 1 H), 2.06−2.08 (m, 1 H), 3.11−3.24 (m, 5 H), 3.31 (s, 3 H), 3.38−3.42 (m, 1 H), 3.44−3.48 (m, 2 H), 4.28 (m, 1 H), 4.42 (m, 1 H), 5.55 (s, 1 H), 6.11 (s, 1 H), 6.28 (s, 1 H), 6.32 (s, 1 H), 7.04 (t, $J = 7$ Hz, 1 H), 7.10 (t, $J = 7$ Hz, 1 H), 7.28 (d, $J = 8$ Hz, 1 H), 7.45 (d, $J = 8$ Hz, 1 H), 9.09 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.4, 22.7, 25.4, 26.3, 27.3, 27.9, 28.0, 29.3, 29.5, 31.6, 32.3, 33.4, 33.8, 35.2, 35.6, 39.1, 39.9, 40.5, 52.4, 55.3, 55.9, 58.5, 59.0, 60.2, 62.2, 71.7, 109.8, 110.8, 118.1, 118.9, 121.6, 128.5, 136.1, 138.8, 164.0, 173.0, 174.9; MS (CI), *m*/*z* (rel intensity) 681 ($M^+ + 3$, 26), 680 ($M^+ + 2$, 54), 679 ($M^+ + 1$, 22), 647 (22), 633 (22), 148 (100), 147 (46), 99 (20), 93 (58), 91 (40), 85 (69), 83 (35), 81 (50), 79 (58), 77 (24). HRMS calcd for $C_{37}H_{55}N_6O_4S$: 679.4006. Found: 679.4012. HPLC: (a) silica C5, 57 bar, 1 mL/min, hexane/2-propanol/triethylamine (3:2:0.05), injection in 20 μL of 2-propanol, retention time of 13.76 min; (b) Cyclobond I 2000, 97 bar, 2 mL/min, hexane/ethanol (6:4), injection in 20 μL of EtOH, retention time of 5.89 min (98.7% purity), retention time of 1.62 min (1.3% impurity).

17b: mp 119−120 °C; TLC $R_f = 0.18$ (silica gel, ethyl acetate/methanol, 4:1, CAS blue); $[\alpha]^{25}_D$ +10 (*c* 0.1, $CHCl_3$); UV (EtOH) λ_{max} 206, 228, 286 nm; IR (film) ν_{max} 3289, 2927, 1670, 1653, 1540, 1458, 1265 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88−0.92 (m, 1 H), 1.14−1.28 (m, 8 H), 1.36−1.43 (m, 6 H), 1.66−1.69 (m, 4 H), 1.74−1.78 (m, 1 H), 1.82−1.88 (m, 4 H), 2.15−2.18 (m, 1 H), 2.64 (d, $J = 10$ Hz, 1 H), 2.76−2.85 (m, 2 H), 2.92−2.94 (m, 1 H), 3.03−3.20 (m, 7 H), 3.23−3.27 (m, 1 H), 3.31 (s, 3 H), 3.41−3.47 (m, 3 H), 4.26 (m, 1 H), 4.37 (m, 1 H), 5.37 (s, 1 H), 6.11 (s, 2 H), 6.32 (s, 1 H), 7.05 (t, $J = 7$ Hz, 1 H), 7.11 (t, $J = 7$ Hz, 1 H), 7.28 (d, $J = 8$ Hz, 1 H), 7.45 (d, $J = 7$ Hz, 1 H), 9.07 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.3, 22.7, 25.8, 26.0, 27.4, 28.1, 29.2, 29.3, 31.6, 32.2, 33.4, 33.8, 35.0, 36.1, 38.9, 39.7, 40.6, 52.8, 53.2, 55.2, 55.5, 58.4, 58.8, 60.1, 61.8, 71.7, 109.7, 110.8, 118.1, 118.9, 121.7, 128.4, 136.0, 138.6, 163.9, 173.1, 174.8; MS (CI), *m*/*z* (rel intensity) 682 (31), 681 (80), 680 ($M^+ + 2$, 100), 679 (29), 678 (M^+, 15), 633 (22), 171 (10), 148 (44), 147 (31), 93 (89), 91 (65), 85 (77), 83 (61), 81 (78), 79 (65), 77 (42). HRMS calcd for $C_{37}H_{55}N_6O_4S$: 679.4006. Found: 679.3981. HPLC: (a) silica C5, 56 bar, 1 mL/min, hexane/2-propanol/triethylamine (3:2:0.05), injection in 20 μL of 2-propanol, retention time of 14.12 min; (b) Cyclobond I 2000, 97 bar, 2 mL/min, hexane/ethanol (60:40), injection in 20 μL of ethanol, retention time of 5.93 min (98.3% purity), retention time of 1.72 min (1.7% impurity).

Total Synthesis of 18-Methylaminocoronaridine and 18-Dimethylaminocoronaridine (18 and 19). A. 6-Bromo-4,4-di(ethoxycarbonyl)hex-1-ene (20). A solution of diethyl allylmalonate (75.0 g, 0.370 mol) in dry THF (100 mL) was added dropwise at room temperature to a stirred suspension of sodium hydride (60% dispersion in mineral oil, 18.2 g, 0.456 mol) in dry THF (100 mL) over a period of 30 min. The mixture was stirred for 1 h at room temperature, and a solution of 1,2-dibromoethane (64.0 mL, 0.740 mol) in dry THF (100 mL) was added dropwise over 30 min. The mixture was stirred for 15 h at room temperature and then poured into water (750 mL). The mixture was concentrated under reduced pressure, and the concentrate was extracted with ether (5 × 200 mL). The combined ether extracts were washed with brine (250 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield a yellow oil. Excess 1,2-dibromoethane and unreacted diethylallyl malonate were removed by Kugelrohr distillation to yield the bromoester as a viscous yellow oil (91.50 g, 0.2979 mol, 81%). Fractional distillation under high vacuum yielded a colorless oil (bp 114−116 °C, 0.19 mmHg). IR (NaCl) ν_{max} 3081, 2983, 2938, 2908, 1732, 1643, 1466, 1446, 1391,1369, 1336, 1299, 1273, 1244, 1204, 1175, 1161, 1097, 1032, 924, 859, 749, 641 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, $J = 7$ Hz, 6 H), 2.45 (t, $J = 7$ Hz, 2 H), 2.67 (d, $J = 7$ Hz, 2 H), 3.37 (t, $J = 7$ Hz, 2 H), 4.21 (q, $J = 7$ Hz, 4 H), 5.13 (s, 1 H), 5.17 (d, $J = 7$ Hz, 1 H), 5.62−5.69 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 27.0, 36.3, 37.8, 57.5, 61.6, 119.6, 131.8, 170.2; MS (CI, isobutane, 100 eV), *m*/*z* (rel intensity) 309 ($M + 1^+$, 100), 307 (71), 217 (40), 192 (11).

B. 6-(*N*-Benzyl-*N*-methylamino)-4,4-di(ethoxycarbonyl)hex-1-ene (21). To a solution of bromide **20** (20.0 g, 65.1 mmol) in dry acetone (250 mL), *N*-benzylmethylamine (8.40 mL, 65.1 mmol) and anhydrous K_2CO_3 (40 g) were added, and the mixture was heated at reflux for 36 h with vigorous stirring. The mixture was filtered, and the precipitate was washed with acetone (3 × 100 mL). The filtrate was concentrated under reduced pressure, water (250 mL) was added, and the layers were separated. The aqueous layer was extracted with ether (6 × 100 mL), and the combined organic layers were washed with 10% HCl (250 mL). The acid layer was washed with ether (3 × 100 mL) and made basic with 10% NaOH. The basic mixture was extracted with ether (5 × 100 mL), and the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure to yield an orange oil. The crude product was purified by flash chromatography on silica gel, eluting with hexanes/ethyl acetate (1:1) to yield amine **21** as a pale-yellow oil (12.63 g, 36.4 mmol, 56%). The product can be distilled under vacuum to yield a pale-yellow oil (bp 148−156 °C, 0.31 mmHg); TLC $R_f = 0.32$ (hexanes/ether, 3:1, 1% TEA, I_2); IR (NaCl) ν_{max} 3082, 3064, 3028, 2981, 2940, 2907, 2873, 2842, 2788, 1732, 1642, 1602, 1586, 1495, 1464, 1453, 1420, 1389, 1367, 1283, 1227, 1203, 1151, 1096, 1077, 1057, 1023, 921, 860, 738, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (t, $J = 7$ Hz, 6 H), 2.13 (t, $J = 7$ Hz, 2 H), 2.19 (s, 3 H), 2.35 (t, $J = 7$ Hz, 2 H), 2.62 (d, $J = 7$ Hz, 2 H), 3.48 (s, 2 H), 4.14 (q, $J = 7$ Hz, 4 H), 5.01−5.07 (m, 2 H), 5.57−5.66 (m, 1 H), 7.24−7.31 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.9, 39.3, 36.8, 42.0, 51.9, 56.1, 61.0, 62.5, 118.7, 126.8, 128.0, 128.9, 132.4, 138.9, 170.9; MS (CI, isobutane, 100 eV), *m*/*z* (rel intensity) 348 ($M + 1^+$, 24), 276 (11), 167 (5), 134 (12), 91 (5). Anal. ($C_{20}H_{29}NO_4$) C, H, N.

C. 6-(*N*-Benzyl-*N*-methylamino)-4-ethoxycarbonyl-1-ene (22). A solution of diester **21** (12.0 g, 34.6 mmol) and LiCl (3.2 g, 76 mmol) in DMSO (32 mL), DMF (6.5 mL), and water (0.5 mL) was heated at 180 °C for 6 h under nitrogen. The resulting dark-brown reaction mixture was cooled to room temperature and poured into water (150 mL). The mixture was extracted with dichloromethane (5 × 100 mL), and the combined organic phases were washed with ice/water (3 × 100 mL) and brine (100 mL). Drying over sodium sulfate and condensation under reduced pressure gave a brown oil, which was purified by flash chromatography on silica gel, eluting with hexanes/ethyl acetate (1:1) to yield a yellow oil (9.26 g, 33.6 mmol, 97%), which was distilled under vacuum to yield a colorless oil (bp 143−146 °C, 0.11 mmHg). TLC $R_f = 0.54$ (ether/hexanes, 1:1); IR (NaCl) ν_{max} 3064, 3028, 2979, 2951, 2841, 2790, 1733, 1642, 1495, 1454, 1374, 1261, 1177, 1145, 1026, 916, 860, 738, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (t, $J = 7$ Hz, 3 H), 1.63−1.69 (m, 1 H), 1.83−1.90 (m, 1 H), 2.16 (s, 3 H), 2.19−2.25 (m, 1 H), 2.31−2.40 (m, 3 H), 2.50−2.56 (m, 1 H), 3.46 (s, 2 H), 4.05−4.15 (q, $J = 7$ Hz, 2 H), 4.99−5.05 (m, 2 H), 5.69−5.77 (m, 1 H), 7.20−7.33 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 14.2, 15.2, 29.1, 36.4, 41.9, 43.1, 54.9, 60.0, 62.5, 65.7, 116.7, 126.8, 128.1, 128.9, 135.4, 139.2, 175.3; MS (EI, 70 eV), *m*/*z* (rel intensity) 275 (M^+, 14), 230 (4), 202 (4), 134 (97), 91 (100). Anal. ($C_{17}H_{25}NO_2$) C, H, N.

D. 2-(2-*N*-Benzyl-*N*-methylaminoethyl)pent-4-enol (23). To a solution of the ester **22** (6.80 g, 24.7 mmol) in dry ether (75 mL) was added dropwise a 1 M solution of lithium aluminum hydride in ether (12.3 mL, 12.3 mmol) at 0 °C over 5 min. The mixture was stirred for 1.5 h at room temperature and then cooled to 0 °C and quenched with water (1 mL), followed by 15% NaOH (1 mL) and water (3 mL). The white precipitate was filtered and washed with ether (4 × 25 mL). The filtrate was dried over sodium sulfate and concentrated under reduced pressure to yield a pale-yellow viscous oil, which was distilled (bp 134−136 °C, 0.090 mmHg) to yield alcohol

23 (5.62 g, 24.1 mmol, 98%). TLC $R_f = 0.46$ (2% TEA in ethyl acetate); IR (NaCl) ν_{max} 3392, 3073, 3065, 3029, 2974, 2919, 2840, 2800, 1640, 1495, 1454, 1366, 1073, 1045, 996, 912, 738, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.52−1.57 (m, 1 H), 1.65−1.75 (m, 2 H), 1.92−1.97 (m, 1 H), 2.03−2.09 (m, 1 H), 2.15 (s, 3 H), 2.47 (t, $J = 6$ Hz, 2 H), 3.36−3.40 (m, 1 H), 3.47−3.60 (m, 3 H), 4.97−5.00 (m, 2 H), 5.71−5.79 (m, 1 H), 6.59 (s, 1 H), 7.24−7.32 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 31.0, 36.7, 41.1, 41.2, 55.9, 62.5, 66.4, 116.0, 127.3, 128.3, 129.3, 136.8, 137.2; MS (CI, isobutane, 100 eV), *m/z* (rel intensity), 234 ($M + 1^+$, 100), 134 (34), 91 (30) Anal. ($C_{15}H_{23}NO$) C, H, N.

E. 2-(2-*N*-Benzyl-*N*-methylaminoethyl)pent-4-enal (24). A solution of dry DMSO (4.3 mL, 60 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise to a stirred 2 M solution of oxalyl chloride in CH_2Cl_2 (15 mL, 30 mmol) at −78 °C over 10 min. After the mixture was stirred for 30 min at −78 °C, dry DMF (three drops) was added. The mixture was stirred for another 10 min, and a solution of alcohol **23** (5.56 g, 23.8 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise over 20 min. Then the mixture was stirred an additional 45 min at −78 °C, and a solution of dry triethylamine (9.95 mL, 71.4 mmol) in dry CH_2Cl_2 (25 mL) was added dropwise over 10 min. The mixture was stirred overnight, warming gradually from −78 °C to room temperature over 10 h. The reaction mixture was quenched by adding water (25 mL) dropwise, with stirring, over 5 min. The mixture was poured into CH_2Cl_2 (200 mL), and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic phases were washed with ice/water (3 × 100 mL) and brine (200 mL). Drying over sodium sulfate and condensation under reduced pressure gave a yellow oil (5.08 g, 22.0 mmol, 92%), which was used in the next step without further purification. TLC $R_f =$ 0.53 (hexanes/ethyl acetate/TEA, 2:1:0.1); IR (NaCl, neat) ν_{max} 3064, 3028, 2977, 2929, 2841, 2795, 2718, 1724, 1641, 1602, 1495, 1453, 1419, 1366, 1354, 1301,1257, 1209, 1153, 1126, 1076, 1027, 995, 916, 738, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65−1.72 (m, 1 H), 1.83−1.91 (m, 1 H), 2.15 (s, 3 H), 2.16−2.19 (m, 1 H), 2.30−2.44 (m, 4 H), 3.47 (s, 2 H), 4.99−5.05 (m, 2 H), 5.67−5.73 (m, 1 H), 9.63 (d, $J = 2$ Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 26.7, 32.8, 41.6, 49.1, 54.1, 62.4, 116.9, 126.8, 128.0, 128.8, 134.9, 138.7, 203.4; MS (CI, isobutane, 100 eV), *m/z* (rel intensity) 232 ($M + 1^+$, 100), 203 (8), 134 (34), 91 (17).

F. 4-(1,3-Dioxolan-2-yl)-6-(*N*-benzyl-*N*-methylamino)-1-hexene (25). Crude aldehyde **24** (13.1 g, 21.2 mmol) was added to a stirred solution of dry ethylene glycol (6.97 mL, 125 mmol) in dry CH_2Cl_2 (300 mL). Chlorotrimethylsilane (31.7 mL, 250 mmol) was added dropwise over 5 min. The mixture was heated at reflux under nitrogen for 72 h and concentrated under reduced pressure. The oily residue was subjected to flash chromatography on silica gel, eluting with hexanes/ethyl acetate (2:1) to yield the product as a yellow oil (14.02 g, 50.9 mmol, 90%). Distillation under vacuum gave a colorless oil (bp 140−142°C, 0.12 mmHg). TLC $R_f = 0.62$ (hexanes/ethyl acetate, 1:1, I_2); IR (NaCl, neat) ν_{max} 3064, 3027, 2976, 2946, 2881, 2840, 2786, 1949, 1825, 1640, 1495, 1453, 1417, 1400, 1366, 1313, 1254, 1212, 1123, 1074, 1027, 997, 946, 913, 827, 781, 738, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.49−1.56 (m, 1 H), 1.67−1.74 (m, 1 H), 1.81−1.86 (m, 1 H), 2.05−2.12 (quint, $J = 7$ Hz, 1 H), 2.18 (s, 3 H), 2.20−2.26 (m, 1 H), 2.39−2.46 (m, 2 H), 3.47−3.48 (d, $J = 4$ Hz, 2 H), 3.80−3.86 (m, 2 H), 3.88−3.94 (m, 2 H), 4.80−4.81 (d, $J = 4$ Hz, 1 H), 4.96−5.03 (m, 2 H), 5.75−5.83 (m, 1 H), 7.21−7.31 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 26.1, 33.7, 39.3, 42.1, 55.1, 62.3, 64.9, 65.0, 106.2, 116.0, 126.8, 128.1, 129.0, 136.9, 139.4; MS (EI, 70 eV) *m/z* (rel intensity) 275 (M^+, 3), 202 (5), 160 (3), 134 (85), 120 (13), 91 (100). Anal. ($C_{17}H_{25}NO_2$) C, H, N.

G. 4-(1,3-Dioxolan-2-yl)-6-(*N*-benzyl-*N*-methylamino)-hexan-1-ol (26). Disiamylborane reagent was prepared in situ by adding a 2 M solution of 2-methyl-2-butene in THF dropwise to a stirred 1 M solution of borane·THF in THF at −10 °C over a period of 30 min. The mixture was stirred for 3 h at −10 °C to complete the reaction. A solution of olefin **25** (4.03 g, 14.6 mmol) in dry THF (20 mL) was then added, and the mixture was stirred for 3 h at 0 °C. Aqueous sodium hydroxide (15%, 11 mL) and aqueous hydrogen peroxide (30%, 11 mL) were added dropwise at 0 °C, and the mixture was heated at reflux for 1 h. The reaction mixture was then cooled to room temperature, and the layers were separated. The aqueous layer was extracted with dichloromethane (5 × 50 mL). The combined organic layers were washed with brine (2 × 50 mL), dried over sodium sulfate, and concentrated to a pale-yellow oil. This was dissolved in benzene (20 mL), and triphenylphosphine (3.83 g, 14.6 mmol, 1.0 equiv) was added. The mixture was heated at reflux for 3 h to reduce any *N*-oxide present. Benzene was removed under reduced pressure to yield a yellow, viscous residue, which was purified by flash chromatography on silica gel, eluting with ether/methanol/TEA (98:2:1) to yield a viscous yellow oil (4.055 g, 13.8 mmol, 95%); TLC $R_f = 0.16$ (5% methanol in ether, PMA); IR (NaCl, neat) ν_{max} 3409, 3062, 3085, 3062, 3028, 2941, 2875, 2789, 1495, 1453, 1403, 1367, 1212, 1124, 1058, 1028, 947, 914, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32−1.39 (m, 1 H), 1.44−1.64 (m, 2 H), 1.72−1.80 (m, 2 H), 1.89 (br s, 1 H), 2.18 (s, 3 H), 2.37−2.43 (m, 1 H), 2.45−2.55 (m, 1 H), 3.44−3.52 (m, 2 H), 3.59−3.61 (t, $J = 6$ Hz, 2 H), 3.80−3.85 (m, 2 H), 3.88−3.95 (m, 2 H), 4.76−4.77 (d, $J = 4$ Hz, 1 H), 7.21−7.32 (m, 6 H, signal + solvent); ^{13}C NMR ($CDCl_3$) δ 25.2, 26.5, 30.1, 38.8, 42.0, 54.9, 62.1, 62.7, 64.8, 106.6, 126.9, 128.1; MS (CI, isobutane, 100 eV) *m/z* (rel intensity) 294 ($M + 1^+$, 100), 221 (6), 204 (6), 171 (1), 142 (4), 134 (25), 91 (12). Anal. ($C_{17}H_{27}NO_3$) C, H, N.

H. 4-(1,3-Dioxolan-2-yl)-6-(*N*-methylamino)hexan-1-ol (27). *N*-Benzylamine **26** (3.343 g, 11.39 mmol) was dissolved in glacial acetic acid (100 mL), and 10% palladium on activated carbon (dry, 1.4 g) catalyst was added. The mixture was degassed under high vacuum and purged with nitrogen and then with hydrogen. The reaction mixture was stirred for 12 h under 1 atm of hydrogen. It was then purged with nitrogen and filtered, and the filtrate was concentrated under reduced pressure to ca. 5 mL. At 0 °C, saturated NH_4OH was added dropwise until the mixture was basic. The mixture was extracted with dichloromethane (5 × 25 mL), and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to a pale-yellow, viscous oil (2.285 g, 11.24 mmol, 99%). The crude product was subjected to the following protection step without further purification. TLC $R_f = 0.25$ (10% methanol in dichloromethane, PMA); IR (NaCl, neat) ν_{max} 3371, 2945, 2880, 2782, 2448, 1710, 1665, 1597, 1471, 1404, 1273, 1228, 1211, 1132, 1102, 1056, 946, 775, 734, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39−1.80 (m, 9 H), 2.17 (br s, 3 H), 2.42 (s, 3 H), 2.64−2.71 (m, 2 H), 3.62−3.67 (m, 2 H), 3.83−3.88 (m, 2 H), 3.91−3.96 (m, 2 H), 4.77−4.78 (d, $J = 4$ Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.5, 28.2, 30.0, 35.4, 38.9, 49.4, 62.1, 64.7, 64.8, 106.5; MS (CI, isobutane, 100 eV) *m/z* (rel intensity) 204 ($M + 1^+$, 100), 184 (10), 170 (3), 158 (10), 142 (23), 131 (5), 114 (2), 101 (7).

I. 4-(1,3-Dioxolan-2-yl)-6-[*N*-(*tert*-BOC)-*N*-methylamino]hexan-1-ol (28). The crude amino alcohol **27** (1.202 g, 5.91 mmol) was dissolved in dry dichloromethane (50 mL) and cooled to 0 °C. Di-*tert*-butyl dicarbonate (1.63 mL, 7.09 mmol, 1.2 equiv) was added dropwise (gas evolution) via syringe over a period of 5 min. After the addition was complete, the ice bath was removed and the mixture was stirred for 13 h at room temperature. The mixture was concentrated under reduced pressure, and the residue was subjected to flash chromatography on silica gel, eluting with 5% methanol in dichloromethane to yield a highly viscous, deep-yellow oil (1.780 g, 5.866 mmol, 99%). TLC $R_f = 0.5$ (5% methanol in dichloromethane, PMA); IR (NaCl, neat) ν_{max} 3447, 2974, 2935, 2880, 2246, 1691, 1540, 1482, 1456, 1400, 1366, 1312, 1250, 1222, 1159, 1094, 1056, 945, 922, 880, 773, 733, 646 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45−1.74 (m, 18 H), 2.83 (s, 3 H), 3.24 (br s, 1.5 H), 3.46 (br s, 0.5 H), 3.83−3.88 (m, 2 H), 3.92−3.98 (m, 2 H), 4.78−4.79 (d, $J = 4$ Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.92, 25.4, 26.6, 27.2, 28.3, 31.0, 33.8, 38.0, 38.9, 46.1, 47.3, 62.1, 62.6, 64.8, 79.1, 106.3, 155.7; MS (CI, isobutane, 100 eV) *m/z* (rel intensity) 304 ($M + 1^+$, 13), 260 (6), 242 (100), 204 (4), 198 (8), 186 (37), 158 (3), 142 (92). Anal. ($C_{15}H_{29}NO_5$) C, H, N.

J. 4-(1,3-Dioxolan-2-yl)-6-[*N*-(*t*BOC)-*N*-methylamino]-hexan-1-al (29). The alcohol **28** (1.770 g, 5.838 mmol) was oxidized using 2 M $(COCl)_2$ (3.79 mL, 7.58 mmol), dry DMSO (1.08 mL, 15.2 mmol), dry DMF (1 drop), and dry triethylamine (2.43 mL, 17.4 mmol), analogous to the oxidation of alcohol **23**. Similar workup as for aldehyde **24** yielded aldehyde **29** (1.626 g, 5.395 mmol, 92%) as a yellow oil. TLC $R_f = 0.63$ (ethyl acetate/hexanes, 2:1; DNP yellow); IR (NaCl, neat) ν_{max} 2976, 2933, 2887, 2722, 1809, 1725, 1693, 1481, 1456, 1424, 1396, 1366, 1309, 1248, 1215, 1158, 1072, 947, 881, 846, 773, 736, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41−1.53 (m, 14 H, signal + solvent), 1.63−1.76 (m, 4 H), 1.79−1.87 (sextet, $J = 8$ Hz, 1 H), 2.54−2.57 (t, $J = 8$ Hz, 2 H), 2.83 (s, 3 H), 3.27 (br m, 2 H), 3.82−3.87 (m, 2 H), 3.93−3.96 (m, 2 H), 4.75−4.76 (d, $J =$ 4 Hz, 1 H), 9.76 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.3, 26.9, 26.2, 28.2, 33.8, 38.3, 38.7, 40.8, 41.5, 46.3, 46.8, 64.6, 64.6, 79.0, 106.0, 155.4, 201.9; GC−MS (CI, methane, 100 eV), *m/z* (rel intensity) 342 ($M + C_3H_5$), 302 ($M + 1^+$, 0.4), 286 (3), 274 (5), 246 (6), 202 (19), 184 (6), 168 (3), 140 (100).

K. Tetracycles (31). A mixture of *N*-benzylindoloazepine **30** (0.100 g, 0.300 mmol) and aldehyde **29** (0,132 g, 0.438 mmol, 1.5 equiv) was stirred (neat) in an open flask at 135 °C for 30 min, when TLC indicated that the condensation was complete. The gummy residue was dissolved in methanol/dichloromethane (1:5, 6 mL), and sodium borohydride (powder, 0.010 g) was added to reduce the excess aldehyde. The mixture was stirred for 15 min, and water (1 mL) was added. The layers were separated, and the aqueous layer was washed with dichloromethane (4 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over sodium sulfate, and concentrated under reduced pressure to yield a yellow foam, which was purified by centrifugal chromatography, eluting with hexanes/ether (4:1) to yield product **31**, an inseparable mixture of diastereomers, as a white foam (0.173 g, 0.280 mmol, 93%). TLC $R_f = 0.57$ (hexanes/ethyl acetate, 1:1, CAS blue-yellow); UV (EtOH) λ_{max} 204, 300, 330 nm; IR (NaCl, thin film) ν_{max} 3377, 3059, 3026, 2973, 2934, 2889, 2795, 2248, 1689, 1681, 1611, 1479, 1466, 1454, 1437, 1392, 1366, 1345, 1303, 1280, 1249, 1205, 1155, 1126, 1104, 1050, 946, 912, 880, 772, 745, 735, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70−0.74 (m, 1 H), 0.85−0.88 (m, 1 H), 1.00−1.04 (m, 1 H), 1.09−1.15 (m, 1 H), 1.24−1.72 (m, 20 H), 2.02−2.14 (m, 2 H), 2.58−2.86 (m, 7 H), 2.87−3.18 (m, 4 H), 3.68−3.85 (m, 9 H), 4.11−4.14 (m, 1 H), 4.60 (m, 0.5 H), 4.65 (m, 0.5 H), 6.79−6.83 (d, $J = 7$ Hz, 2 H), 7.11−7.14 (t, $J = 7$ Hz, 1 H), 7.24−7.46 (m, 8 H, signal + solvent), 8.96 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 28.1, 28.3, 28.4, 30.5, 30.8, 34.1, 36.4, 36.6, 42.2, 42.3, 50.5, 50.6, 50.9, 55.1, 58.1, 58.3, 64.7, 64.9, 72.1, 79.0, 90.4, 106.0, 106.7, 109.2, 120.5, 122.2, 127.0, 127.7, 128.3, 128.9, 137.9, 139.1, 142.0, 155.5, 165.2, 165.5, 169.0. HRMS (FAB) calcd for $C_{36}H_{48}N_3O_6$ (M^+): 618.3543. Found: 618.3551.

L. *N*-Benzylcleavamines (32). The tetracycles **31** (0.168 g 0.272 mmol) were dissolved in glacial acetic acid (1.5 mL), and the solution was heated to 90 °C. Sodium borohydride (0.051 g, 1.4 mmol, 5.0 equiv) was added in portions to the stirred mixture over a period of 15 min. The mixture was poured onto crushed ice and made basic with saturated ammonium hydroxide, and the resulting layers were separated. The aqueous phase was extracted with dichloromethane (4 × 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated to a gummy yellow residue, which was purified by centrifugal chromatography on silica gel, eluting with hexanes/ether (1:1) to yield the cleavamines **32** as a white foam (0.157 g, 0.253 mmol, 93%). TLC $R_f = 0.60$ (hexanes/ethyl acetate, 1:1, CAS yellow); UV (EtOH) λ_{max} 208, 228, 286 nm; IR (NaCl, thin film) ν_{max} 3381, 3058, 3027, 2974, 2928, 1728, 1692, 1483, 1462, 1453, 1433, 1392, 1365, 1340, 1248, 1216, 1161, 1067, 1027, 923, 881, 771, 740, 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92−1.72 (m, 26 H), 1.95−2.04 (m, 2 H), 2.27−2.49 (m, 8 H), 2.59−2.65 (t, $J = 12$ Hz, 2 H), 2.76−2.78 (d, $J = 10$ Hz, 1 H), 2.83−2.91 (m, 4 H), 3.02−3.17 (m, 1.5 H), 3.17−29 (m, 0.5 H), 3.33−3.38 (m, 1 H), 3.49−3.55 (m, 4 H), 3.64−3.66 (d, $J = 12$ Hz, 1 H), 3.74−3.94 (m, 7 H), 4.33 (d, $J = 4$ Hz, 0.5 H), 4.50−4.51 (d, $J = 4$ Hz, 0.5 H), 4.71−4.75 (m, 0.2 H), 5.08−5.09 (d, $J = 8$ Hz, 0.1 H), 5.59−5.62 (m, 1 H), 7.00−7.15 (m, 3 H), 7.24−7.43 (m, 11 H, signal + solvent), 8.58−8.90 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.0, 20.9, 24.9, 25.5, 26.0, 27.3, 27.7, 28.3, 30.8, 33.2, 36.0, 36.2, 40.2, 41.6, 45.9, 46.2, 46.6, 46.8, 51.9, 52.3, 56.1, 60.2, 70.0, 62.1, 63.1, 64.3, 64.4, 64.4, 64.7, 78.8, 105.4, 106.2, 110.4, 110.5, 111.4, 114.2, 117.5, 117.9, 118.7, 121.1, 126.8, 127.8, 128.1, 128.5, 129.3, 131.5, 133.8, 135.6, 135.8, 139.6, 155.4, 175.0, 175.6; MS (CI, isobutane, 100 eV) *m/z* (rel intensity) 620 ($M + 1^+$, 72), 530 (2), 334 (5), 133 (6), 107 (72), 91 (100). HRMS (FAB) calcd for $C_{36}H_{50}N_3O_6$ (M^+): 620.3699. Found: 620.3678.

M. *N*−H Cleavamines (33). Cleavamines **32** (1.399 g, 2.257 mmol) were dissolved in glacial acetic acid (30 mL), and 10% palladium on activated carbon (dry, 0.28 g) was added. The reaction flask was degassed under high vacuum and purged with nitrogen and then with hydrogen. The mixture was stirred for 4 h at room temperature under hydrogen (1 atm). After being purged with nitrogen, the mixture was filtered through Celite and the filter cake was washed with methanol. The filtrate was concentrated to ca. $^1/_8$ volume under reduced pressure, poured onto crushed ice, made basic with NH_4OH, and extracted with dichloromethane (5 × 20 mL). The combined organic layers were washed with brine (25 mL), dried over sodium sulfate, filtered, and concentrated to yield a yellow oil, which was purified by centrifugal chromatography on silica gel, eluting with ethyl acetate to yield the amines **33** as a white foam (1.121 g, 2.116 mmol, 94%). TLC $R_f = 0.47$ (10% methanol in dichloromethane, CAS yellow); UV (EtOH) λ_{max} 210, 228. 286 nm; IR (NaCl, thin film), ν_{max} 3366, 3055, 2974, 2927, 1730, 1691, 1608, 1485, 1462, 1398, 1366, 1339, 1307, 1247, 1160, 1052, 1032, 1012, 947, 880, 771, 740, 703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80−1.08 (m, 2 H), 1.08−1.22 (m, 2 H), 1.22−1.32 (m, 2 H), 1.32−1.65 (m, 19 H), 1.70−1.77 (m, 2 H), 2.00−2.10 (m, 2 H), 2.20−2.25 (t, $J = 13$ Hz, 2 H), 2.34−2.43 (m, 2 H), 2.44−2.52 (m, 3 H), 2.62−2.73 (m, 3 H), 2.76−3.01 (m, 4 H), 3.10−3.18 (m, 2 H), 3.21−3.32 (m, 1 H), 3.34−3.62 (m, 4 H), 3.70−3.77 (s, 3 H), 3.82−3.87 (m, 1 H), 3.90−3.96 (m, 1 H), 4.04−4.06 (t, $J = 7$ Hz, 0.3 H), 4.34−4.35 (d, $J = 4$ Hz, 0.5 H), 4.52−4.53 (d, $J = 4$ Hz, 0.5 H), 5.44−5.54 (m, 1 H), 7.02−7.05 (t, $J = 7$ Hz, 1 H), 7.08−7.11 (t, $J = 7$ Hz, 1 H), 7.28−7.30 (d, $J = 7$ Hz, 1 H), 7.45−7.47 (d, $J = 7$ Hz, 1 H), 8.60−8.94 (m, 0.5 H); ^{13}C NMR ($CDCl_3$) δ 27.1, 27.2, 28.3, 29.6, 31.3, 33.4, 33.9, 33.4, 33.9, 36.0, 36.4, 38.8, 39.3, 39.7, 41.7, 43.3, 45.9, 46.3, 46.9, 49.5, 50.0, 51.2, 51.9, 57.0, 64.4, 64.5, 64.6, 64.8, 105.4, 106.0, 106.2, 110.5, 110.6, 114.0, 117.7, 118.7, 121.2, 126.8, 127.7, 131.8, 135.6; MS (CI, isobutane, 100 eV) *m/z* (rel intensity) 530 ($M + 1^+$, 91), 498 (3), 472 (2), 290 (3), 239 (1), 184 (26), 162 (59), 93 (100). HRMS (FAB) calcd for $C_{29}H_{44}N_3O_6$ (M^+): 530.3230. Found: 530.3238.

N. Enamine (34). A solution of 10% HCl (aqueous) in acetonitrile (1:1, 30 mL) was deoxygenated with a stream of nitrogen for 15 min. The solution was cooled to 0 °C and added to the NH cleavamines **33**, under nitrogen, at 0 °C. The mixture was stirred for 75 h at −10 °C in the dark, poured onto crushed ice, and made basic with saturated ammonium hydroxide. The resulting basic suspension was extracted with dichloromethane (5 × 5 mL), and the combined organic extracts were washed with brine (15 mL), dried over sodium sulfate, and concentrated under reduced pressure below 40 °C to give the enamine **34** as a pale-yellow foam (0.467 g, 0.999 mmol, 91%). Because it is sensitive, the enamine was used directly in the following rearrangement step without further purification. UV (EtOH) λ_{max} 206, 228, 286 nm; IR (NaCl, thin film) ν_{max} 3375, 3054, 2924, 2846, 1731, 1692, 1589, 1482, 1462, 1435, 1393, 1365, 1337, 1305, 1249, 1220, 1166, 1073, 1050, 1011, 883, 741 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41−1.54 (m, 15 H), 1.58−1.61 (t, $J = 7$ Hz, 1 H), 1.70−1.74 (m, 2 H), 1.80−1.85 (m, 1 H), 2.04−2.09 (m, 2 H), 2.10−2.14 (d, $J = 15$ Hz, 2 H), 2.22−2.25 (t, $J = 7$ Hz, 3 H), 2.48−2.55 (m, 4 H), 2.64−2.73 (m, 3 H), 2.77−2.93 (m, 7 H), 3.16−3.27 (m, 3 H), 3.29−3.32 (m, 2 H), 3.67 (s, 3 H), 3.73−3.74 (m, 1 H), 4.46−4.48 (d, $J =$ 10 Hz, 1 H), 5.92 (s, 1 H), 7.07−7.09 (t, $J = 7$ Hz, 1 H), 7.14−7.17 (t, $J = 7$ Hz, 1 H), 7.32−7.34 (d, $J = 7$ Hz, 1 H), 7.48−7.50 (d, $J = 7$ Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.6, 28.5, 28.6,

32.6, 34.2, 38.4, 38.8, 39.8, 41.7, 49.0, 51.4, 52.1, 52.6, 78.9, 101.3, 110.6, 118.1, 119.0, 121.7, 127.3, 130.1, 133.8, 155.7, 175.1, 175.5; MS (CI, isobutane, 100 eV) *m*/*z* (rel intensity) 468 (M + 1^+, 100), 410 (27), 368 (14), 324 (28), 265 (10).

O. 18-*N*-*tert*-BOC-*N*-methylcoronaridine (35). Crude enamine **34** (0.408 g, 0.873 mmol) was dissolved in dry, deoxygenated benzene (25 mL), and the mixture was heated at reflux for 12 h in the dark. The solvent was removed under reduced pressure, and the residue (0.494 g) was purified by centrifugal chromatography, eluting with hexanes/ethyl acetate (3:1) to yield the title product **35** as a white foam (0.218 g, 0.466 mmol, 53%). Recrystallization from ether gave white crystals (mp 164−165 °C). TLC R_f = 0.52 (hexanes/ethyl acetate, 1:1, CAS blue-yellow); UV (EtOH) λ_{max} 206, 228, 286 nm; ^{1}H NMR ($CDCl_3$) δ 1.13−1.23 (m, 1 H), 1.40−1.55 (m, 11 H), 1.61−1.73 (m, 2 H), 1.74−1.86 (m, 2 H), 1.87−1.98 (m, 2 H), 2.56−2.58 (d, J = 13 Hz, 1 H), 2.80−2.96 (m, 5 H), 2.97−3.07 (m, 1 H), 3.15−3.21 (m, 3 H), 3.26−3.35 (m, 1 H), 3.36−3.46 (m, 1 H), 3.49−3.54 (m, 1 H), 3.71 (s, 3 H), 7.07−7.10 (t, J = 7 Hz, 1 H), 7.13−7.16 (t, J = 7 Hz, 1 H), 7.23−7.25 (d, J = 7 Hz, 1 H), 7.46−7.48 (d, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.7, 27.3, 28.5, 29.7, 31.9, 34.0, 34.8, 36.5, 51.6, 52.6, 53.2, 54.9, 58.1, 60.3, 79.1, 110.3, 118.4, 119.3, 122.0, 128.8, 135.5, 136.4, 155.7, 171.1, 175.4; MS (CI, isobutane, 100 eV) *m*/*z* (rel intensity) 469 (M + 2^+, 34), 468 (M + 1^+, 100), 412 (27), 323 (7). HRMS (FAB, 3-NBA/Gly/TFA) calcd for $C_{27}H_{38}N_3O_4$: 468.2862. Found: 468.2888. For ^{13}C isotope peak, calcd: 469.2896. Found: 469.2922.

P. 18-Methylaminocoronaridine (18). The preceding compound **35** (0.647 g, 1.38 mmol) was dissolved in dry methanol (60 mL). Anhydrous ether saturated with dry hydrogen chloride (4.0 mL) was added dropwise to the stirred solution, and the resulting yellow solution was heated at reflux for 4 h. The mixture was then poured onto crushed ice in a 15% solution of ammonium hydroxide in brine (40 mL). The resulting basic mixture was extracted with dichloromethane (5 × 25 mL). The combined organic extracts were washed with brine (25 mL), dried over magnesium sulfate, and concentrated to afford the amine **18** as a light-yellow powder, which was recrystallized from 2-propanol to give light-yellow crystals (mp 208−210 °C). TLC R_f = 0.17 (25% methanol in dichloromethane, CAS yellow); UV (EtOH) λ_{max} 206, 226, 286 nm; IR (NaCl, thin film) ν_{max} 3323, 3060, 3022, 2985, 2922, 2855, 2818, 2793, 1719, 1501, 1464, 1451, 1429, 1339, 1307, 1266, 1257, 1231, 1206, 1191, 1164, 1127, 1093, 1073, 1057, 1031, 1010, 1003, 996, 983, 956, 929, 901, 866, 837, 734 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.16−1.23 (m, 1H), 1.52−1.83 (m, 7 H), 1.88−1.94 (m, 2 H), 2.45 (s, 3 H), 2.55−2.66 (m, 3 H), 2.80−2.82 (d, J = 8 Hz, 1 H), 2.91−2.93 (m, 1 H), 2.98−3.04 (m, 1 H), 3.14−3.21 (m, 2 H), 3.35−3.43 (m, 1 H), 3.54 (s, 1 H), 3.71 (s, 3 H), 7.06−7.09 (t, J = 7 Hz, 1 H), 7.12−7.15 (t, J = 7 Hz, 1 H), 7.23−7.24 (d, J = 7 Hz, 1 H), 7.46−7.48 (d, J = 7 Hz, 1 H), 7.85 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.1, 27.4, 32.0, 34.2, 35.0, 36.4, 36.5, 49.7, 51.7, 52.6, 53.1, 55.0, 57.7, 110.4, 118.4, 119.3, 122.0, 128.8, 135.5, 136.3, 175.5; MS (CI, isobutane, 100 eV) *m*/*z* (rel intensity) 368 (M + 1^+, 100), 337 (4), 323 (9). HRMS (FAB, 3-NBA/Gly/TFA) calcd for $C_{22}H_{30}N_3O_2$: 368.2338. Found: 368.2323. For ^{13}C isotope peak, calcd: 369.2372. Found: 369.2353. HPLC: (a) silica C5, 43 bar, 1 mL/min, hexane/2-propanol/triethylamine (3:1:0.04), injection in 20 μL of 2-propanol, retention time of 2.93 min; (b) Cyclobond I 2000, 169 bar, 3 mL/min, hexane/ethanol/triethylamine (50:50:1), injection in 5 μL of EtOH, retention time of 6.28 min.

Q. 18-Dimethylaminocoronaridine (19). Crude amine **18** (0.304 g, 0.827 mmol) was taken up in methanol (12 mL), aqueous formaldehyde (37%, 1.5 mL) was added, and the mixture was heated at reflux for 2 h. After the mixture was cooled to room temperature, sodium borohydride (0.50 g, 13.2 mmol, 16 equiv) was added, in portions, to the stirred mixture. The solvent was removed under reduced pressure to yield a yellow-white solid residue, which was taken up in water (20 mL). The mixture was extracted with dichloromethane (5 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield 0.275 g of crude product. Centrifugal chromatography, eluting with 10% methanol in dichloromethane, gave the title product **19** as a yellow solid (0.143 g, 0.3714 mmol). The product was recrystallized from methanol to give white crystals (mp 175−176 °C). TLC R_f = 0.30 (25% methanol in dichloromethane, CAS yellow); UV (EtOH) λ_{max} 208, 228, 286 nm; IR (NaCl, thin film) ν_{max} 3434, 3373, 3148, 3095, 3058, 3022, 2927, 2855, 2825, 2779, 1729, 1491, 1461, 1443, 1430, 1368, 1344, 1327, 1296, 1280, 1249, 1231, 1193, 1171, 1142, 1129, 1099, 1076, 1063, 1032, 1010, 973, 960, 926, 892, 857, 809, 738, 661 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.13−1.18 (m, 1 H), 1.48−1.54 (quint, J = 7 Hz, 1 H), 1.60−1.67 (m, 1 H), 1.72−1.82 (m, 3 H), 1.85−1.95 (m, 3 H), 2.23−2.40 (m, 12 H), 2.52−2.58 (d, J = 14 Hz, 1 H), 2.79−2.81 (d, J = 8 Hz,1 H), 2.90−2.93 (dt, J = 8, 3 Hz, 2 H), 2.98−3.04 (m, 4 H), 3.54 (m, 1 H), 3.72 (s, 3 H), 7.07−7.09 (t, J = 7 Hz, 1 H), 7.12−7.16 (t, J = 7 Hz, 1 H), 7.23−7.25 (d, J = 7 Hz, 1 H), 7.47−7.48 (d, J = 7 Hz, 1 H), 7.89 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.9, 27.2, 31.6, 31.9, 35.2, 36.3, 45.1, 51.5, 52.5, 53.0, 53.3, 54.8, 57.2, 57.7, 110.1, 110.3, 118.3, 119.0, 121.8, 128.6, 135.4, 136.3; MS (CI, isobutane, 100 eV) *m*/*z* (rel intensity), 382 (M + 1^+, 83), 337 (13), 323 (73), 278 (16), 150 (20), 123 (22), 102 (27), 93 (47), 83 (100). HRMS (FAB, 3-NBA/Gly/TFA) calcd for $C_{23}H_{32}N_3O_2$: 382.2494. Found: 382.2480. For ^{13}C isotope peak, calcd: 383.2528. Found: 383.2512. HPLC: (a) silica C5, 43 bar, 1 mL/min, hexane/2-propanol/triethylamine (3:1:0.04), injection in 20 μL of 2-propanol, retention time of 18.04 min; (b) Cyclobond I 2000, 99 bar, 2 mL/min, hexane/ethanol/triethylamine (60:40:0.2), injection in 20 μL of EtOH, retention time of 5.66 min.

Total Synthesis of 15-Nor-18-methoxycoronaridine (36). A. 4-(1,3-Dioxolan-2-yl)-6-methoxy-1-hexanal (38). 4-(1,3-Dioxolan-2-yl)-6-methoxy-1-hexene (**37**) (7.75 g, 41.6 mmol)[5a] was dissolved in 50% aqueous dioxane (1 L), and a catalytic amount of osmium tetroxide (0.50 g, 2.0 mmol, 5 mol %, toxic!) was added, followed by sodium periodate (17.8 g, 83.2 mmol, 2 equiv). The reaction mixture, initially black due to the presence of osmium(0), turned to a thick, white, milky suspension after 5 min. Stirring was continued for 24 h at room temperature. The suspension was filtered, and the white precipitate was washed with dichloromethane (2 × 100 mL). The filtrate was concentrated to ca. 500 mL under reduced pressure and extracted with dichloromethane (2 × 100 mL). The combined organic layers were dried over sodium sulfate and concentrated to an orange-yellow oil (5.953 g). Continuous extraction of the aqueous layer for 12 h furnished additional product (1.11 g) for a total yield (crude) of 90%. The aldehyde can be distilled under vacuum to give a colorless oil (bp 98−100 °C, 0.19 mmHg). TLC R_f = 0.60 (hexanes/ethyl acetate, 1:1, 2,4-DNP, yellow); IR (NaCl) ν_{max} 2930, 2886, 2835, 1722, 1477, 1462, 1453, 1439, 1394, 1274, 1209. 1194, 1131, 1153, 1120, 1032, 947, 735, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.57−1.64 (m, 1 H), 1.83−1.89 (m, 1 H), 2.34−2.38 (m, 1 H), 2.48−2.56 (m, 2 H), 3.31 (s, 3 H), 3.44−3.46 (t, J = 7 Hz, 2 H), 3.81−3.95 (m, 4 H), 4.86−4.87 (d, J = 3 Hz, 1 H), 9.69 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 29.9, 34.7, 42.8, 58.3, 64.7, 64.9, 70.1, 105.3, 201.3.

B. Tetracycles 39. A mixture of *N*-benzylindoloazepine **30** (1.06 g, 3.17 mmol) and aldehyde **38** (0.60 g, 3.2 mmol) was heated, neat, with stirring in an open flask for 30 min. Another 0.5 equiv of aldehyde (0.30 g, 1.6 mmol) was added, and heating continued for another 30 min. The residue was cooled to room temperature and dissolved in dichloromethane/methanol (5:1, 30 mL). Sodium borohydride (0.25 g, 6.6 mmol) was added in portions, with stirring, over 15 min to reduce the excess aldehyde. Stirring was continued for 20 min, and the mixture was poured into water (10 mL) and extracted with ether (4 × 20 mL). The combined ether layers were dried over sodium sulfate and concentrated to yield a yellow-orange residue. Flash chromotography on silica gel, eluting with hexanes/ethyl acetate (3:1), gave tetracycles **39**, an inseparable mixture of diastereomers, as a pale-yellow foam (1.22 g, 2.41 mmol, 76%). TLC R_f = 0.33 (hexanes/ethyl acetate, 1:1, CAS blue-yellow); UV (EtOH) λ_{max} 212, 232, 302, 330 nm; IR (NaCl) ν_{max} 3380, 2885, 2806, 1678, 1611, 1478. 1437, 1384, 1345,

1294, 1279, 1250, 1205, 1088, 915, 746, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34−1.40 (m, 3 H), 1.41−1.48 (m, 2 H), 1.48−1.79 (m, 10 H), 1.98−2.07 (m, 4 H), 2.12−2.16 (m, 1 H), 2.54−2.63 (m, 4 H), 2.65−2.66 (d, J = 4 Hz, 1 H), 2.79−2.83 (m, 2 H), 2.86−2.89 (m, 3 H), 2.95−2.99 (m, 5 H), 3.16−3.25 (m, 7 H), 3.28−3.30 (m, 1 H), 3.30−3.35 (m, 2 H), 3.41−3.46 (m, 1 H), 3.59−3.63 (m, 5 H), 3.66−3.71 (m, 3 H), 3.73−3.81 (m, 12 H), 3.86−3.90 (m, 1 H), 4.19−4.24 (m, 2 H), 4.63−4.64 (d, J = 3 Hz, 1 H), 4.67 (d, J = 3 Hz, 1 H), 6.79−6.81 (m, 2 H), 6.82−6.87 (q, J = 8 Hz, 2 H), 7.04−7.05 (d, J = 8 Hz, 1 H), 7.08−7.09 (d, J = 8 Hz,1 H), 7.11−7.15 (t, J = 8 Hz, 2 H), 7.26−7.29 (m, 5 H, signal + solvent), 7.32−7.35 (m, 6 H), 7.38−7.42 (m, 4 H), 8.85 (br s, 1 H), 8.94 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.2, 22.0, 27.4, 27.6, 29.9, 37.8, 38.1, 40.4, 41.5, 42.9, 43.0, 50.5, 55.7, 58.1, 58.4, 64.7, 65.1, 68.6, 69.6, 71.9, 72.7, 91.1, 91.4, 104.8, 105.6, 109.3, 109.4, 120.8, 122.2, 122.4, 127.2, 127.8, 127.9, 129.0, 138.3,139.9, 143.4, 169.0; MS (CI, isobutane, 100 eV), *m*/*z* (rel intensity), 506 (11), 505 (M + 1^+, 43), 473 (4), 431 (3), 290 (7), 227 (10), 201 (8), 171 (9), 157 (37), 127 (60), 91 (94), 84 (100), 73 (77), 61 (35), 59 (41). HRMS (FAB) calcd for $C_{30}H_{37}N_2O_5$: 505.2702. Found: 505.2702.

C. *N*-Benzylcleavamines 40 and 41. To tetracycles **39** (4.244 g, 8.39 mmol), dissolved in glacial acetic acid (50 mL) at ∼92 °C, sodium borohydride (0.95 g, 25.1 mmol, 3 equiv) was added over a period of 20 min. The solution was cooled to room temperature, poured onto crushed ice, and made basic with saturated ammonium hydroxide (250 mL). The resulting basic suspension was extracted with ether (5 × 100 mL). The combined ether extracts were washed with brine (100 mL) and dried over sodium sulfate to yield the crude product as a viscous red oil (4.032 g). Flash chromatography on silica gel, eluting with hexanes/ether (3:1), afforded the diastereomeric products as a white foam (2.691 g, 5.30 mmol, 63%). TLC R_f = 0.40 (ether/hexanes, 5:2, CAS yellow); UV (EtOH) λ_{max} 232, 286 nm; IR (NaCl) ν_{max} 3441, 3392, 3058, 3027, 2923, 2888, 2246, 1727, 1488, 1462, 1436, 1340, 1248, 1192, 1213, 1162, 1112, 1026 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33−1.36 (m, 3 H), 1.46 (m, 1 H), 1.73−1.78 (m, 2 H), 2.02−2.08 (m, 3 H), 2.31−2.36 (m, 2 H), 2.40−2.47 (m, 2 H), 2.51−2.63 (m, 3 H), 2.74−2.86 (3 H), 2.90−2.93 (2 H), 3.00−3.01 (2s, 3 H), 3.07−3.13 (m, 2 H), 3.26−3.35 (m, 1 H), 3.55−3.58 (m, 2 H), 3.64−3.68 (m, 2 H), 3.70−3.72 (m, 2 H), 3.75−3.79 (m, 4 H), 3.81−3.85 (m, 2 H), 4.51−4.53 (m, 1 H), 4.57−4.58 (m, 0.2 H), 5.57−5.60 (m, 1 H), 7.02−7.05 (t, J = 7 Hz, 1 H), 7.07−7.10 (t, J = 7 Hz, 1 H), 7.24−7.28 (m, 5 H, signal + solvent), 7.31−7.35 (m, 3 H), 7.41−7.45 (m, 4 H), 8.66 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.1, 26.5, 29.7, 32.8, 33.5, 36.57, 37.8, 42.0, 42.4, 52.0, 56.3, 58.2, 60.7, 63.4, 64.5, 64.6, 64.8, 71.4, 105.5, 105.9, 110.4, 110.5, 117.8, 118.8, 121.2, 126.9, 127.9, 128.2, 129.6, 131.4, 135.7, 139.8, 176.0; MS (CI, isobutane, 100 eV), *m*/*z* (rel intensity) 508 (0.70), 507 (M + 1^+, 4), 391 (33), 279 (24), 233 (80), 201 (15), 183 (14), 171 (19), 167 (38), 149 (77), 113 (44), 91 (11), 83 (20), 73 (100).

D. Secondary Cleavamines 42. The mixture of diastereomeric cleavamines **40** and **41** (0.434 g, 0.855 mmol) was dissolved in glacial acetic acid (5 mL), and 10% palladium on carbon (0.12 g, dry) was added. The reaction mixture was degassed under high vacuum, and the system was purged with nitrogen and then hydrogen. The mixture was stirred at 25 °C for 25 h under hydrogen (1 atm). The black suspension was filtered through Celite, the filter cake was washed with methanol (3 × 10 mL), and the filtrate was concentrated to ca. $^1/_3$ volume under reduced pressure. The concentrate was poured onto crushed ice, made basic with saturated ammonium hydroxide (15 mL), and extracted with dichloromethane (5 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield the secondary amines **42** (0.338 g, 0.809 mmol, 95%). TLC R_f = 0.11 (ether/hexanes, 5:2, CAS blue-yellow); UV (100% EtOH) λ_{max} 244, 270, 298 nm; IR (NaCl) ν_{max} 3376, 2924, 2246, 1726, 1684, 1462, 1437, 1340, 1266, 1192, 1163, 1116, 1029, 946, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10−1.23 (m, 1 H), 1.24−1.35 (m, 1 H), 1.38−1.52 (m, 2 H), 1.60−1.68 (septet, J = 7 Hz, 1 H), 1.93−2.06 (m, 3 H), 2.08−2.14 (t, J = 13 Hz, 1 H), 2.19−2.27 (q, J = 13 Hz, 1 H), 2.60−2.68 (m, 2 H), 2.77−87 (m, 2 H), 2.89 (s, 1.5 H), 2.91−2.93 (m, 0.5 H), 2.94−2.96 (m, 0.5 H), 2.98 (br s, 0.5 H), 3.03 (s, 1.5 H), 3.08−3.17 (m, 1 H), 3.21−3.24 (m, 1 H), 3.33−3.35 (m, 1 H), 3.38−3.44 (m, 1 H), 3.44−3.50 (m, 1 H), 3.60−3.66 (m, 1 H), 3.68−3.79 (m, 6 H), 3.83−3.88 (m, 0.5 H), 3.91−3.97 (m, 0.5 H), 4.57 (d, J = 4 Hz, 0.5 H), 4.63−4.64 (d, J = 4 Hz, 0.5 H), 5.43−5.47 (m, 1 H), 7.04−7.07 (t, J = 7 Hz, 1 H), 7.10−7.13 (q, J = 7 Hz, 1 H), 7.28−7.32 (m, 1 H), 7.47−7.49 (d, J = 7 Hz, 1 H), 8.62 (br s, 0.5 H), 8.65 (br s, 0.5 H); ^{13}C NMR ($CDCl_3$) δ 10.8, 13.9, 22.8, 23.7, 26.2, 26.6, 27.5, 33.2, 33.8, 35.6, 37.3, 38.6, 41.8, 42.0, 42.4, 49.6, 51.8, 54.8, 58.1, 64.2, 64.6, 68.0, 70.4, 71.4, 105.3, 105.8, 110.3, 114.5, 117.7, 118.7, 121.2, 127.8, 128.7, 130.7, 131.6, 135.7, 175.7; MS (CI, isobutane, 100 eV), *m*/*z* (rel intensity) 417 (M + 1^+, 0.9), 358 (2), 233 (100), 201 (11), 173 (11), 144 (1). HRMS (FAB) calcd for $C_{23}H_{33}N_2O_5$: 417.2389. Found: 417.2381.

E. Enamine 43. A solution of acetonitrile and 10% HCl (1:1, 20 mL) was deoxygenated by bubbling nitrogen through the solution for 15 min and then added, under nitrogen, to the cleavamines **42** (0.845 g, 2.03 mmol). The solution was stirred for 1 h at 25 °C in the dark and was then poured onto crushed ice and made basic with saturated ammonium hydroxide (40 mL). The resulting white suspension was extracted with dichloromethane (5 × 15 mL). The combined organic extracts were washed with brine (20 mL), dried over sodium sulfate, filtered, and concentrated (below 50 °C) to yield the enamine **43** (0.675 g, 1.90 mmol, 94%). Owing to the sensitivity of this compound, it was used directly in the cyclization step without further purification. TLC R_f = 0.58 (ethyl acetate/hexanes, 4:1, CAS blue); UV (EtOH) λ_{max} 206, 294, 334 nm; IR (NaCl) ν_{max} 3327, 2922, 2863, 1731, 1660. 1584, 1482, 1462, 1435, 1387, 1305, 1240, 1193, 1166, 1103, 1057, 1018, 959, 931, 870, 743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43−1.46 (m, 1 H), 1.55−1.61 (m, 2 H), 1.63−1.72 (septet, J = 7 Hz, 2 H), 1.73−1.79 (m, 2 H), 1.89−1.95 (m, 3 H), 2.00−0.05 (m, 1 H), 2.09−2.20 (m, 4 H), 2.23−2.27 (m, 1 H), 2.28−2.37 (m, 3 H), 2.46−2.60 (m., 4 H), 2.83−2.94 (m, 5 H), 3.02−3.04 (m, 2 H), 3.15−3.25 (m, 5 H), 3.29−3.42 (m, 10 H), 3.44−3.45 (m, 1 H), 3.49−3.54 (m, 3 H), 3.71−3.77 (m, 7 H), 3.79−3.81 (d, J = 11 Hz, 1 H), 4.17−4.19 (d, J = 11 Hz, 1 H), 5.86 (s, 1 H), 6.76−6.78 (d, J = 7 Hz, 1 H), 6.88−6.91 (t, J = 7 Hz, 1 H), 7.08−7.23 (m, 5 H), 7.28−7.31 (m, 1 H), 7.34 (s, 1 H), 7.48−7.51 (d, J = 7 Hz, 1 H), 8.75 (br s, 1 H), 10.24 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 24.3, 26.6, 30.9, 33.5, 34.9, 37.2, 38.3, 39.4, 40.2, 41.6, 42.4, 44.2, 48.6, 50.9, 52.1, 52.7, 54.7, 58.4, 59.7, 65.2, 70.8, 71.0, 72.0, 72.2, 78.6, 90.6, 108.3, 110.4, 113.7, 119.1, 121.3, 121.8, 131.5, 135.3, 136.3, 137.8, 140.5, 141.0, 142.3, 153.8, 166.4, 170.4, 174.7, 184.1, 184.8; GC−MS (CI, methane, 100 eV), *m*/*z* (rel intensity), 396 (M + $C_3H_6^+$), 383 (M + $C_2H_5^+$), 355 (M + 1^+), 323, 309, 297.

F. 15-*nor*-18-Methoxycoronaridine (36). Enamine **43** (0.053 g, 0.15 mmol) was dissolved in dry, deoxygenated toluene (10 mL), and the mixture was heated in the dark at reflux for 24 h. The mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel, eluting with hexanes/ethyl acetate (4:1) to yield product **36** as a white foam (0.034 g, 0.096 mmol, 64%). The product can be recrystallized from ether to yield colorless crystals (mp 110−111 °C). TLC R_f = 0.43 (hexanes/ethyl acetate, 3:1, CAS blue-yellow); UV (EtOH) λ_{max} 206, 228, 286 nm; IR (NaCl) ν_{max} 3446, 3367, 3054, 2955, 2926, 2853, 2303, 1719, 1488, 1462, 1435, 1382, 1366, 1344, 1304, 1265, 1236, 1212, 1193, 1172, 1125, 1111, 1083, 1056, 1011, 896, 807, 740, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.64−1.75 (m, 5 H), 1.86−1.91 (m, 1 H), 2.21 (br s, 1 H), 2.41−2.42 (d, J = 8 Hz, 1 H), 2.80−2.83 (m, 1 H), 2.90−2.96 (m, 1 H), 3.19−3.24 (m, 1 H), 3.35 (s, 3 H), 3.40−3.47 (m, 2 H), 3.51−3.58 (m, 1 H), 3.72 (s, 3 H), 4.02 (br s, 1 H), 7.06−7.09 (t, J = 7 Hz, 1 H), 7.11−7.25 (t, J = 7 Hz, 1 H), 7.22−7.24 (d, J = 7 Hz, 1 H), 7.46−7.48 (d, J = 7 Hz, 1 H), 7.87 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.0, 26.4, 40.6, 43.9, 46.9, 49.6, 52.7, 58.5, 60.2, 66.4, 72.1, 111.7, 119.2, 121.6, 128.4, 135.0, 135.3, 175.3; MS (CI, isobutane, 100 eV), *m*/*z* (rel intensity) 355 (M + 1^+, 100), 323 (9), 296 (61), 233 (23), 171 (20), 147 (12), 129 (23). HRMS (FAB, 3-NBA/Gly/

TFA) calcd for $C_{21}H_{27}N_2O_3$: 355.2021. Found: 355.2017. For ^{13}C isotope peak, calcd: 356.2055. Found: 356.2056. HPLC: (a) silica C5, 34 bar, 1 mL/min, hexane/2-propanol/triethylamine (98.5:1.5:1), injection in 20 μL of 2-propanol, retention time of 8.88 min; (b) Cyclobond I 2000, 31 bar, 1 mL/min, hexane/ethanol (95:5), injection in 20 μL of EtOH, retention time of 6.46 min.

Biological Receptor Studies. Receptor functional analyses were performed as previously described.[12−14] Briefly, human embryonic kidney 293 fibroblasts (HEK293, ATCC CRL1573) were cultured in MEM supplemented with 10% fetal bovine serum and 2 mM glutamine (Life Technologies). Cells were plated at (2−3) × 10^4 cells per milliliter on poly-D-lysine coated 35 mm nunc dishes. Cells were transfected with the cDNA cells for nicotinic acetylcholine receptor (nAChR) subunits nAChR-a3 (accession no. L31621), nAChR-b4 (accession no. U42976), and enhanced green fluorescent protein (EGFP, 10% of total cDNA) using the Lipofectamine PLUS method (Life Technologies). We performed functional analyses between 12 and 36 h after transfection. Transfected cells were selected for EGFP expression and examined by voltage-clamp recording at −70 mV in the whole-cell configuration using an Axopatch 200B patch clamp amplifier (Axon Instruments). Thin-walled borosilicate glasss microelectrodes (TW150F, World Precision Instruments) had resistances of 3−5 MS when filled with an internal solution containing the following: 135 mM CsCl, 10 mM CsF, 10 mM HEPES, 5 mM EGTA, 1 mM $MgCl_2$, 0.5 mM $CaCl_2$, pH 7.2. Current responses were filtered at 1 kHz with an eight-pole Bessel filter (Cygnus Technologies), digitized at 1 kHz, and stored on a Macintosh PowerPC-G3 computer using an ITC-16 interface (Instrutech) under control of the data acquisition and analysis program Synapse (Synergy Research). Cells were continuously superfused with extracellular solution containing the following: 150 mM NaCl, 3 mM KCl, 5 HEPES, 1 mM $MgCl_2$, 1.8 mM $CaCl_2$, 10 mM glucose, and 0.1 mg/mL phenol red, pH 7.3. ACh stock was made up in extracellular solution at 1 M. Compound stocks were made up in DMSO at 20 mM except compound **5**, which was made up at 18 mM. ACh and the various compounds were diluted 1 to 1000 in extracellular solution immediately prior to use. The final concentration of DMSO was 0.1%, which we found to have no effect on its own. Control, ACh, and drug solutions were applied to individual cells by rapid perfusion. Solutions were driven by a syringe pump through a flowpipe having four inputs that converge at a single common output of approximately 100 mm diameter. Rapid switching between inputs was achieved using a set of upstream solenoid valves (Lee Co.) under computer control. The rate of solution exchange was approximately 5 ms as determined from liquid junction current measures.

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593, respectively. For (−)-cyclazocine, they are 0.10 ± 0.03, 0.58 ± 0.06, and 0.052 ± 0.001 for [^{3}H]DAMGO, [^{3}H]naltrindole, and [^{3}H]U69,593, respectively. For levorphanol, they are 0.21 ± 0.02, 4.2 ± 0.5, and 2.3 ± 0.3 for [^{3}H]DAMGO, [^{3}H]naltrindole, and [^{3}H]U69,593, respectively.

(19) It is extremely unlikely that the effects of these compounds on drug self-administration are due to a nonspecific action (e.g., a sedative effect). Neither 18-methoxycoronaridine (**3**) nor 18-hydroxycoronaridine (**4**), or its hydroxyl derivatives,[5a] at the same dosage (20 mg/kg), affected responding for a nondrug reinforcer (water). Although we did not have sufficient quantities of the other compounds to test in this model, 18-methoxycoronaridine was one of the most potent whereas 18-hydroxycoronaridine was one of the least potent compounds at the $\alpha 3\beta 4$ site. The possibility of there being a correlation between the effects of these compounds at $\alpha 3\beta 4$ receptors and effects on responding for water is therefore quite remote. Compounds **3**, **4**, **11**, and **18** were also evaluated in a sucrose solution response and found to show no significant effect. Also, 18-methoxycoronaridine (**3**) does not affect food intake in rats.[9]

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