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Total Synthesis of (±)-Herbindole A, (±)-Herbindole B, and (±)-*cis*-Trikentrin A

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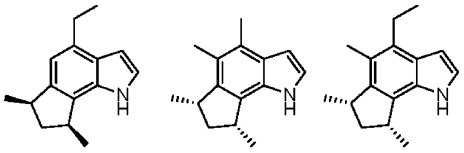

Herein we describe a divergent total synthesis of the title compounds utilizing Diels−Alder reactions of monoimine quinoids, followed by cyclization of the aromatized adducts to generate the tricyclic skeletons. Elaboration to iodinated or triflated indole derivatives allows for installation of the requisite alkyl substitution via cross-coupling reactions.

Introduction

The herbindole and trikentrin indoles comprise a series of structurally related polyalkylated cyclopent[*g*]indole natural products (Figure 1). Isolated from the orange colored Western Australian sponge, *Axinella sp*., the herbindoles were shown to exhibit cytotoxicity toward KB cells and act as general fish antifeedants.[1] Our contributions notwithstanding, Natsume's synthesis[2] of the herbindoles stands alone in the literature. The trikentrins, however, have received a great deal more attention from the synthetic community and differ from the herbindoles solely in the nature of the substitution at the 4- and 5-positions (indole numbering). Isolated from the marine sponge *Trikentrion flabelliforme*, these compounds show growth inhibitory activity toward the Gram-positive bacteria, *Bacillus subtilis*.[3] Successful synthetic strategies have employed aryl radical cyclizations,[4] intramolecular Heck coupling,[5] sequential heteroaromatic aza-diene Diels−Alder,[6] pyrrole indolization,[7] intramolecular Diels−Alder of allenic dienamides,[8] and, most recently, electrocyclic ring closure of divinylpyrrolines.[9]

The extensive substitution about the benzene nucleus of both the herbindoles and trikentrins lends a significant synthetic challenge to these compounds in that the typically more reactive 2- and 3-positions of the indole are unsubstituted. Moreover, the stereochemical disposition of the dimethylcyclopentyl unit adds to the difficulty in the design of an efficient synthesis of these unassuming compounds.

Recently, we reported a diastereoselective total synthesis of (±)-herbindole B and (±)-*cis*-trikentrin B relying on Diels−Alder chemistry of quinone monoimine derivatives.[10] In this paper, we present a full account of our studies toward a divergent synthetic strategy culminating in new syntheses of herbindole A, herbindole B, and *cis*-trikentrin A.

Results and Discussion

We have, in recent years, studied the Diels−Alder reaction of quinoid imines[11] and developed an efficient method to access highly substituted indoles.[12] The process, described in Scheme 1, relies on aromatization of Diels−Alder adducts such as **2** to dihydronaphthalenes **3**, oxidative cleavage, and subsequent Plieninger indolization[13] of the resulting bis-carbonyls of type **4**. By judicious choice of the starting diene and dienophile **1**, a

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(2) (a) Muratake, H.; Mikawa, A.; Seino, T.; Natsume, M. *Chem. Pharm. Bull.* **1994**, *42*, 854. (b) Muratake, H.; Mikawa, A.; Seino, T.; Natsume, M. *Chem. Pharm. Bull.* **1994**, *42*, 846.
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(12) (a) Banfield, S. C.; England, D. B.; Kerr, M. A. *Org. Lett.* **2001**, *3*, 3325. (b) Zawada, P. V.; Banfield, S. C.; Kerr, M. A. *Synlett* **2003**, 971.

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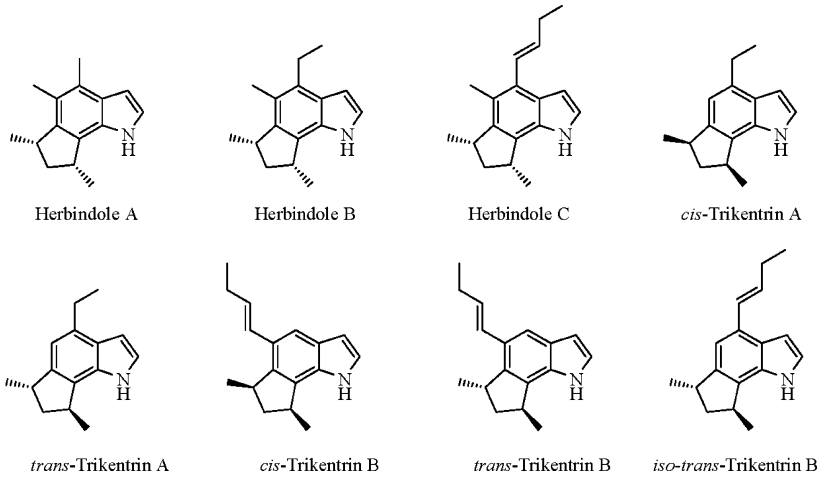
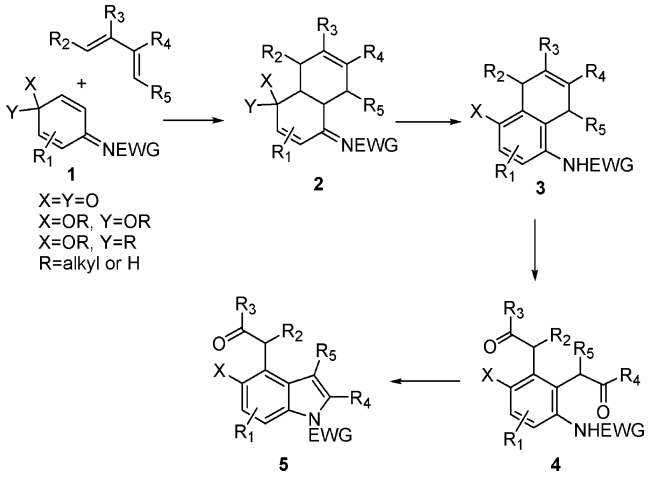


FIGURE 1. The herbindole and trikentrin indoles.

SCHEME 1. The Synthesis of Highly Substituted Indoles



number of highly substituted indoles with various substitution patterns have been prepared.

Our initially reported synthetic strategy toward *cis*-trikentrin B and herbindole B employed a variant of this method, as shown in Scheme 2.[10] Diels−Alder reaction of **6** with cyclopentadiene followed by acid catalyzed aromatization with concomitant cyclization afforded indole intermediate **7** in excellent yield. With the tricyclic skeleton in place, indole **7** was elaborated to the natural product through seven subsequent transformations, including Stille cross-coupling to install the 5-butenyl group, oxidative olefin cleavage, and reductive deoxygenation to reveal the *cis*-dimethylcyclopentyl moiety. Our synthesis toward herbindole B commenced with dienophile **8**, which was subjected to iterative Diels−Alder reactions with cyclopentadiene and butadiene (with appropriate reoxidation). Triflation of **10**, followed by osmylation, led to selective dihydroxylation of the more strained norbornenyl olefin. Protection of the diol, osmylation of the remaining olefin, oxidative cleavage of the resulting glycol, and treatment with acid catalyst afforded 5-trifloxy indole **12**, which was elaborated to the natural product through nine additional transformations.

With the synthesis of both *cis*-trikentrin B and herbindole B completed, we turned our attention toward the synthesis of other members of this natural product family. In particular, herbindole A and *cis*-trikentrin A were thought to be suitable targets. The sole difference between herbindole B and *cis*-trikentrin A is substitution at the 5-position of the indole (absolute stereochemistry notwithstanding). We therefore reasoned that the latter could be easily accessed by hydrogenolysis of the 4-ethyl derivative of indole **12**, an advanced intermediate from our herbindole B synthesis. Although this proved feasible, ultimately a more efficient synthesis leading to this substrate would be employed (vide infra).

At the outset, we reasoned that herbindole A, bearing a 4-methyl substituent, could be accessed by a one-carbon degradation of the 4-position side chain of a suitable intermediate from our herbindole B synthetic sequence. Thus, aldehyde **12** was reduced and converted to olefinic compound **13**, ultimately leading to 4,5-methyl indole **14** via olefin cleavage (Scheme 3). At this point, however, we were concerned with the overall efficiency of our synthetic sequence toward herbindole A, as one-carbon degradation involved excessive functional group manipulation, which proved to be lengthy and low yielding. This approach was therefore abandoned.

With the failure of this initial sequence in providing an efficient approach to the synthesis of the target compounds, we redesigned our synthetic strategy with a more divergent approach in mind. As shown in Scheme 4, we reasoned that an intermediate such as **16** would be suitably divergent in that the 4-iodo and 5-trifloxy substituents would provide handles for installation of the necessary R_1 and R_2 groups through cross-coupling reactions. The iodoindole intermediate **16** would arise from a similar Diels−Alder reaction between dienophile **18** and cyclopentadiene, as in our previously described synthesis of *cis*-trikentrin B (see Scheme 2). We initially attempted to construct derivatives of dienophile **18** bearing iodine functionalization at the appropriate position; however, this strategy was ultimately abandoned in favor of a later stage iodination.

Our revised synthesis of herbindole A commenced with indole **7**, an early intermediate in our *cis*-trikentrin B synthesis (see Scheme 2). Thus, osmylation of **7** afforded diol **19** (Scheme 5). To our delight, treatment of the latter with *N*-iodosuccinimide gave rise to 4-iodoindole **20** in superb yield. The selectivity of this reaction presumably arises from *o*-hydroxy activation coupled with deactivation of the 3-position by the tosyl

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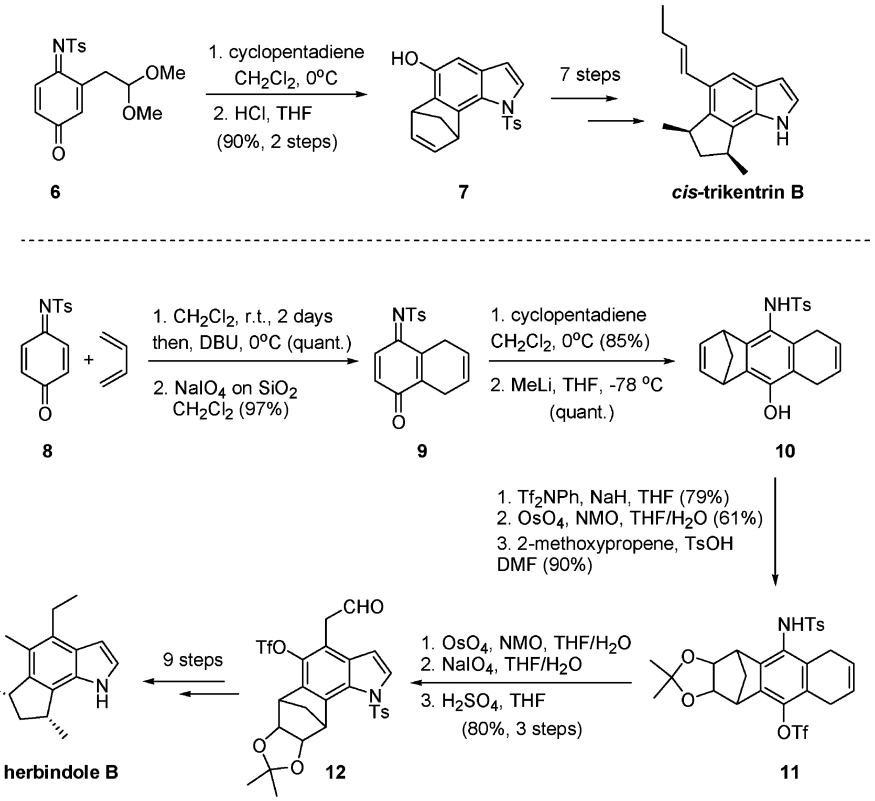
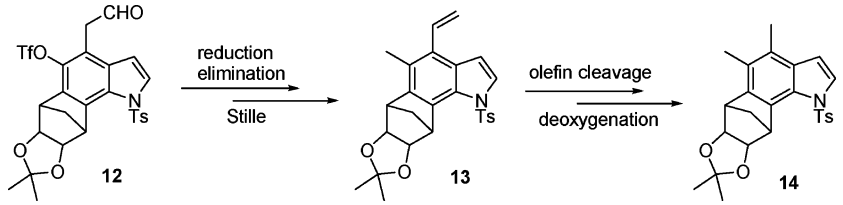
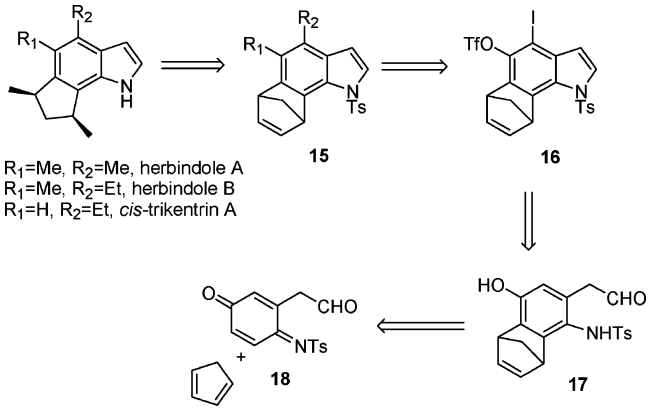
SCHEME 2. Initial Syntheses of *cis*-Trikentrin B and Herbindole B



SCHEME 3. Initial Approach to Herbindole A



SCHEME 4. Revised Retrosynthesis of Herbindole A, Herbindole B, and *cis*-Trikentrin A



protecting group. Protection of the diol as the acetonide and triflation of the phenolic oxygen afforded Stille substrate **21**. Double Stille reaction with tetramethylstannane proceeded without incident to install the 4,5-dimethyl substituents of compound **14** in excellent yield. Deprotection of the acetonide afforded glycol **22** in good yield. Periodate mediated glycol cleavage, with in situ reduction to avoid epimerization, afforded a diol that was bis-mesylated giving rise to **23** in moderate yield. Fujimoto reductive deoxygenation[14] and TBAF[15] promoted detosylation then completed the synthesis of (±)-herbindole A.

The synthesis of *cis*-trikentrin A is depicted in Scheme 6. Protection of diol **20** afforded **24** in good yield. At this point, we were inspired by Herbert's report[16] on the Negishi-type couplings of aryl bromides with dimethylzinc affording methyl−aryl coupled species. We were delighted to find that, without the need for phenol protection, 4-iodoindole **24** proved to be an excellent substrate for the analogous coupling reaction employing diethylzinc. In this manner, 4-ethylindole **25** was obtained in excellent yield. Triflation of phenol **25** led to a convergence with our original synthesis of herbindole B through compound **26**, this new synthesis being more efficient than initially reported. With the latter compound in hand, we turned our attention toward hydrogenolysis of the trifloxy group. Gratifyingly, treatment with ammonium formate under palladium catalysis afforded **27** in excellent yield.[17] Deprotection of the acetonide followed by diol cleavage, reduction and

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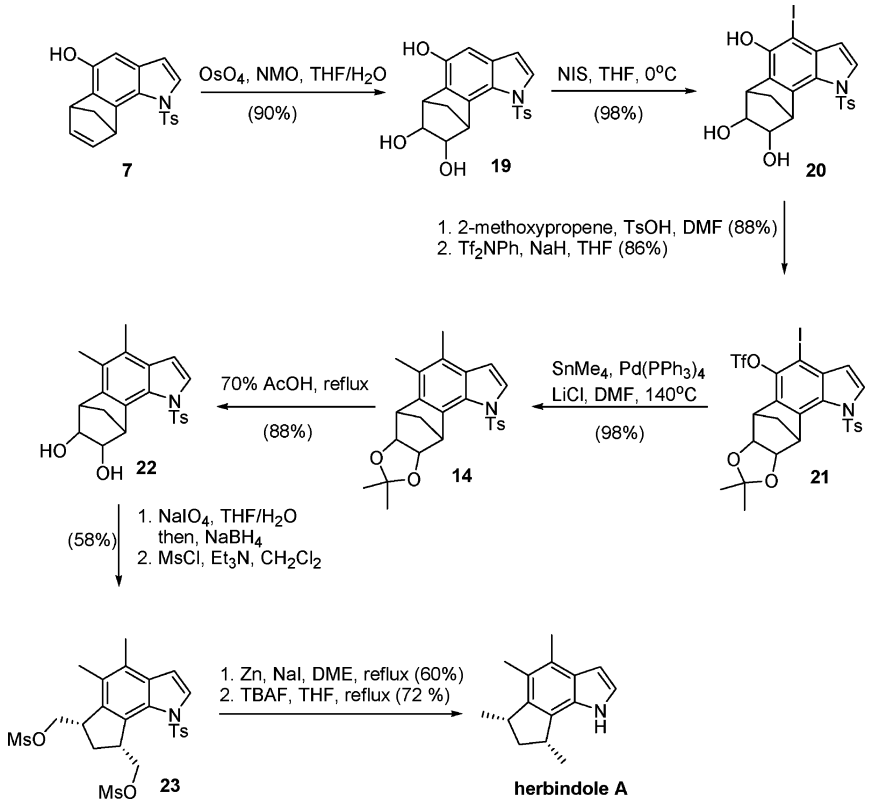
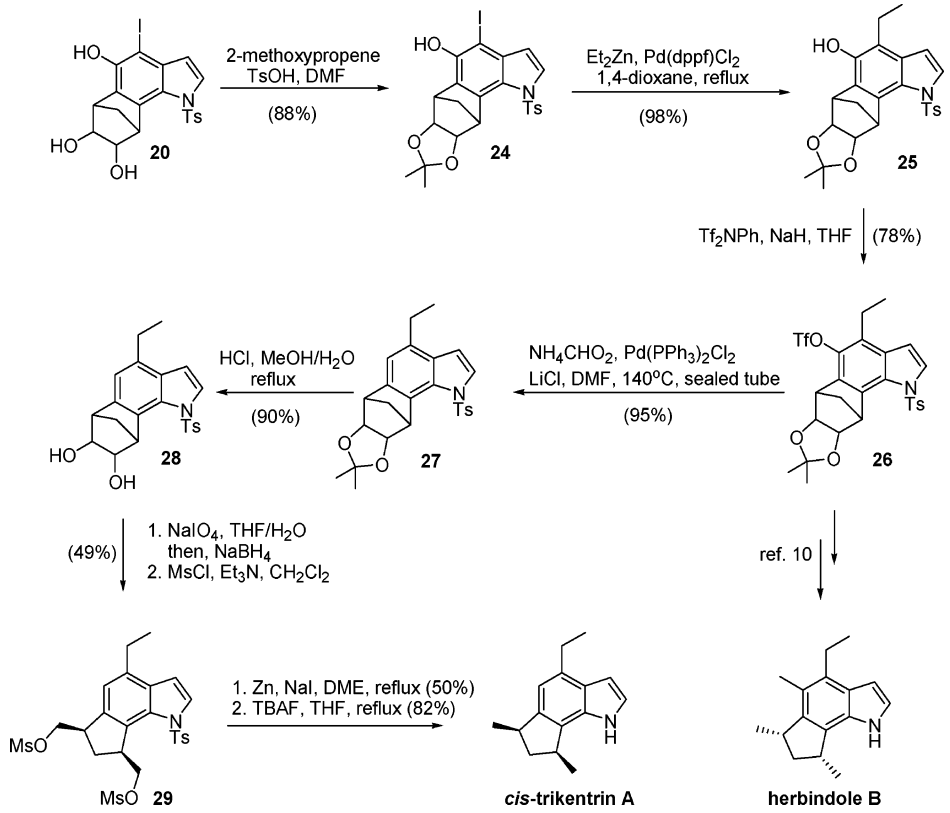
(17) England, D. B.; Kerr, M. A. *J. Org. Chem.* **2005**, *70*, 6519 and references therein.

SCHEME 5. Synthesis of Herbindole A



SCHEME 6. Synthesis of *cis*-Trikentrin A and Herbindole B



mesylation afforded **29**. Reductive deoxygenation and detosylation completed the synthesis of (±)-*cis*-trikentrin A.

We have described our endeavors in the successful total syntheses of three natural products from the herbindole and trikentrin family of indole natural products. While we were initially successful with the synthesis of herbindole B, a redesigned synthesis not only allowed us to improve on our original strategy, but also allowed for the synthesis of herbindole

A and *cis*-trikentrin A. Herbindole B was initially synthesized in 4% overall yield over 19 steps. Our convergence with a late stage intermediate resulted in an improved herbindole B synthesis, completed in 15 steps and 7% overall yield. Herbindole A and *cis*-trikentrin A were completed in 7% yield over 14 steps and 5% yield over 16 steps, respectively. Key steps in our improved approach include Diels−Alder reactions of quinone monoimines and in situ indolization, selective ortho-iodination of a 5-hydroxyindole, and cross-coupling reactions allowing installation of the appropriate 4- and 5-position substituents of the natural products.

Experimental Section

4-Iodo-6,9-methano-1-(toluene-4-sulfonyl)-6,7,8,9-tetrahydro-1*H*-benzo[*g*]indole-5,7,8-triol (20). To a solution of olefin **7** (see ref 10 for preparation) (8.74 g, 24.9 mmol) in 150 mL of THF and 100 mL of H_2O was added NMO (4.37 g, 37.3 mmol) followed by a few crystals of OsO_4. The reaction was stirred at room temperature for 18 h or until TLC analysis showed complete consumption of starting material. Na_2SO_3 (15.7 g, 124 mmol) was added and the mixture was stirred for an additional 30 min. The reaction mixture was diluted with brine and extracted with EtOAc (4×). The combined organic fractions were washed with brine (1×), dried with $MgSO_4$, and concentrated. Typically, the diol was used in the subsequent step as the crude product; however, it could be purified by FC (70% EtOAc/hexanes) to afford 8.63 g (90%) of diol **19** as a white solid. The diol (5.05 g, 13.1 mmol) was dissolved in 82 mL of THF and cooled to 0 °C. *N*-Iodosuccinimide (3.10 g, 13.8 mmol) was added and the reaction was stirred at 0 °C for 3 h. The reaction was quenched with saturated $Na_2S_2O_3$ (aq) and extracted with EtOAc (3×). The combined organic fractions were washed with saturated $Na_2S_2O_3$ (1×) and brine (1×), dried with $MgSO_4$, and concentrated to afford 6.57 g (98%) of iodoindole **20** as a white solid requiring no further purification. Mp 100−104 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, J = 3.8 Hz, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 6.56 (d, J = 3.8 Hz, 1H), 6.22 (br s, 1H), 4.08 (br s, 1H), 3.73 (d, J = 5.8 Hz, 1H), 3.53 (br s, 1H), 3.43 (d, J = 5.8 Hz, 1H), 2.33 (s, 3H), 2.15 (d, J = 9.8 Hz, 1H), 1.77 (d, J = 9.8 Hz, 1H); ^{13}C NMR (150 MHz, d_6-acetone) δ 148.7, 146.2, 137.0, 136.6, 132.9, 131.4, 131.0, 130.0, 127.6, 124.6, 113.2, 75.5, 71.0, 70.5, 48.3 (2C), 43.2, 21.4; IR (thin film) 3360, 2951, 1701, 1595, 1576, 1374, 1171 cm^{-1}; HRMS calcd for $C_{20}H_{18}INO_5S$ 510.9950, exptl 510.9940.

Trifluoromethanesulfonic Acid 6,10-Methano-4-iodo-8,8-dimethyl-1-(toluene-4-sulfonyl)-6,6a,9a,10-tetrahydro-1*H*-7,9-dioxa-1-azadicyclopenta[*a*,*g*]naphthalen-5-yl Ester (21). To a solution of iodoindole **20** (6.57 g, 12.9 mmol) in 70 mL of DMF was added 2-methoxypropene (1.48 mL, 15.4 mmol) followed by *p*-TsOH (487 mg, 2.56 mmol). The flask was purged with argon and the reaction was stirred at room temperature until complete by TLC analysis. The reaction mixture was diluted with H_2O and extracted with EtOAc (3×). The combined organic fractions were washed with H_2O (3×) and brine (1×), dried with $MgSO_4$, and concentrated. The crude product was purified by FC (gradient elution, 15−30% EtOAc/hexanes) to afford 6.26 g (88%) of the acetonide as a white solid. To a chilled (0 °C) suspension of NaH (55 mg, 1.37 mmol) in 3 mL of THF was added via cannula a solution of the acetonide (580 mg, 1.05 mmol) in 15 mL of THF. The reaction mixture was stirred at 0 °C for 30 min. A solution of $PhNTf_2$ (489 mg, 1.37 mmol) in 5 mL of THF was added via cannula and the reaction mixture was warmed to room temperature and stirred overnight. The mixture was diluted with brine and extracted with EtOAc (3×). The combined organic fractions were washed with H_2O (1×) and brine (1×), dried with $MgSO_4$, and concentrated. Purification by FC (gradient elution, 10−20% EtOAc/hexanes) afforded 620 mg (86%) of the triflated product **21** as a white solid. Mp 83−85 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (d, J = 4.2 Hz, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 6.75 (d, J = 4.2, 1H), 4.19 (br s, 1H), 4.18 (d, J = 5.4 Hz, 1H), 3.62 (br s, 1H), 3.48 (d, J = 5.4 Hz, 1H), 2.40 (s, 3H), 2.25 (d, J = 9.6 Hz, 1H), 1.93 (d, J = 9.6 Hz, 1H), 1.52 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.5, 141.2, 137.7, 136.0, 135.5, 132.2, 130.6, 130.4, 129.5, 127.9, 126.8, 118.5 (q, J_{CF} = 319 Hz, 1C), 113.1, 112.4, 80.4, 80.2, 47.7, 46.6, 43.5, 25.7, 24.1, 21.6; IR (thin film) ν_{max} 3151, 3118, 3053, 2990, 2939, 1596, 1421, 1410, 1210, 1175 cm^{-1}; HRMS calcd for $C_{24}H_{21}F_3INO_7S_2$ 682.9756, exptl 682.9750.

4,5,8,8-Tetramethyl-6,10-methano-1-(toluene-4-sulfonyl)-6,6a,9a,10-tetrahydro-1*H*-7,9-dioxa-1-azadicyclopenta[*a*,*g*]naphthalene (14). To a solution of 4-iodo-5-trifloxyindole **21** (420 mg, 0.610 mmol) in 15 mL of dry DMF was added LiCl (129 mg, 3.05 mmol), $SnMe_4$ (0.256 mL, 1.84 mmol), and $Pd(PPh_3)_4$ (142 mg, 0.0920 mmol). The reaction flask was fitted with a condenser, purged with argon, and brought to reflux until TLC analysis showed complete consumption of starting material. The cooled reaction mixture was filtered through a short pad of Celite and rinsed with EtOAc (3×), then the filtrate was washed with H_2O (3×) and brine (1×). The organic fraction was dried with $MgSO_4$ and concentrated in vacuo. Purification by FC (gradient elution, 5−20% EtOAc/hexanes) afforded 261 mg (98%) of the title compound as a pale orange solid. Mp 93−95 °C; ^{1}H NMR (600 MHz, CDl_3) δ 7.67 (d, J = 3.6 Hz, 1H), 7.63 (d, J = 8.4, 2H), 7.25 (d, J = 8.4 Hz, 2H), 6.69 (d, J = 3.6 Hz, 1H), 4.15 (br s, 1H), 4.02 (d, J = 5.4 Hz, 1H), 3.51 (d, J = 5.4 Hz, 1H), 3.42 (br s, 1H), 2.37 (s, 3H), 2.36 (s, 3H), 2.27 (s, 3H), 2.20 (d, J = 9.6 Hz, 1H), 1.80 (d, J = 9.6 Hz, 1H), 1.53 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 142.0, 136.3, 130.8, 130.0, 128.2, 127.3, 127.0, 126.7, 126.0, 125.7, 112.5, 106.8, 81.3, 80.8, 46.8, 46.0, 42.2, 25.9, 24.1, 21.5, 15.4, 15.3; IR (thin film) ν_{max} 2987, 2935, 2873, 1457, 1372, 1170, 1137 cm^{-1}; HRMS calcd for $C_{22}H_{27}NO_4S$ 437.1661, exptl 437.1666.

Methanesulfonic Acid 6-Methanesulfonyloxymethyl-4,5-dimethyl-1-(toluene-4-sulfonyl)-1,6,7,8-tetrahydro-1-aza-*as*-indacen-8-yl Methyl Ester (23). Acetonide **14** (127 mg, 0.290 mmol) was suspended in 10 mL of 70% aqueous AcOH. The flask was fitted with a condenser and refluxed for 24 h. The reaction mixture was cooled to room temperature and diluted with H_2O and EtOAc. The mixture was then neutralized by portionwise addition of solid Na_2CO_3 until gas evolution ceased. The aqueous layer was extracted with EtOAc (3×) and the combined organic layers were washed with brine (1×) and dried with $MgSO_4$. Concentration of the solution afforded 101 mg (88%) of the crude glycol **22**, which was taken up in 12 mL of THF/H_2O (3:1). $NaIO_4$ (380 mg, 1.78 mmol) was added and the reaction mixture was vigorously stirred until TLC analysis showed complete starting material consumption. The mixture was diluted with 10 mL of THF and cooled to 0 °C, then $NaBH_4$ (142 mg, 3.75 mmol) was cautiously added. When completed by TLC, the mixture was diluted with 15 mL of brine and extracted with EtOAc (3×). The combined organic fractions were washed with H_2O (1×) and brine (1×) and dried with $MgSO_4$. Concentration of the solution yielded the crude diol that was used directly in the subsequent step. The crude diol was taken up in 5 mL of dry CH_2Cl_2 and NEt_3 (0.279 mL, 2.00 mmol) was added followed by MsCl (0.0780 mL, 1.00 mmol) under argon. The reaction mixture was stirred until complete by TLC analysis. The mixture was diluted with CH_2Cl_2 and washed with 10% HCl (aq) (3×) and neutralized with saturated $NaHCO_3$ (aq). The organic layer was dried with $MgSO_4$ and concentrated in vacuo. Purification by FC (40% EtOAc/hexanes) afforded 80 mg (58% from **22**) of bismesylate **23** as a white solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, J = 3.6 Hz, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 6.73 (d, J = 3.6 Hz, 1H), 4.75 (dd, J = 9.6, 3.6 Hz, 1H), 4.53 (dd, J = 9.6, 3.6 Hz, 1H), 4.49 (adt, 1H), 4.25 (at, 1H), 4.08 (at, 1H), 3.72 (adt, 1H), 3.05 (s, 3H), 2.98 (s, 3H), 2.51−2.45 (m, 1H), 2.38 (d, J = 13.8 Hz, 1H), 2.33 (s, 3H), 2.32 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.9, 139.1, 134.9, 133.4, 130.6, 130.0, 129.9, 129.4, 129.2, 126.4, 124.9, 109.9, 72.7, 71.8, 43.9,

43.8, 37.3, 36.8, 29.9, 21.6, 16.2, 15.5; IR (thin film) ν_{max} 3153, 3062, 2943, 1596, 1457, 1354, 1174, 1091, 976, 955 cm^{-1}; HRMS calcd for $C_{24}H_{29}NO_8S_2$ 555.1055, exptl 555.1053.

Herbindole A. To a solution of bis-mesylate **23** (80.0 mg, 0.140 mmol) in 5 mL of DME was added NaI (324 mg, 2.16 mmol) and activated Zn dust (141 mg, 2.16 mmol). The flask was fitted with a condenser and brought to reflux for 24 h. The mixture was cooled to room temperature, filtered to remove the Zn, and diluted with EtOAc. The solution was washed with H_2O (3×) and brine (1×), dried with $MgSO_4$, and concentrated. Purification by preparative TLC (5% EtOAc/hexanes) afforded 31 mg (60%) of *N*-tosylherbindole A. To a solution of *N*-tosylherbindole A (27 mg, 0.073 mmol) in 10 mL of THF was added TBAF (0.514 mL of a 1.0 M solution in THF, 0.514 mmol). The flask was purged with argon and brought to reflux for 24 h. The mixture was cooled to room temperature, diluted with brine and extracted with EtOAc (3×). The combined organic fractions were washed with H_2O (3×) and brine (1×), dried with $MgSO_4$, and concentrated in vacuo. Purification by preparative TLC (5% EtOAc/hexanes, double elution) afforded 11 mg (72%) of herbindole A. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.14−7.13 (m, 1H), 6.57−6.56 (m, 1H), 3.51−3.45 (m, 1H), 3.45−3.40 (m, 1H), 2.71 (dt, J = 12.6, 9.0 Hz, 1H), 2.49 (s, 3H), 2.34 (s, 3H), 1.56 (dt, J = 12.6, 2.4 Hz, 1H), 1.46 (d, 7.2 Hz, 3H), 1.37 (d, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.0, 130.4, 127.7, 126.6, 126.4, 123.2, 122.8, 101.6, 41.8, 39.1, 37.1, 23.8, 22.8, 15.5, 15.3; IR (thin film) ν_{max} 3414, 2958, 2928, 2868, 1448, 1126, 724 cm^{-1}; HRMS calcd for $C_{15}H_{19}N$ 213.1518, exptl 213.1518.

4-Iodo-8,8-dimethyl-6,10-methano-1-(toluene-4-sulfonyl)-6,-6a,9a,10-tetrahydro-1*H*-7,9-dioxa-1-azadicyclopenta[*a*,*g*]naphthalen-5-ol (24). To a solution of diol **20** (6.70 g, 13.1 mmol) in 70 mL of DMF was added 2-methoxypropene (1.50 mL, 15.7 mmol) and *p*-TsOH (498 mg, 2.62 mmol). When complete by TLC analysis, the mixture was diluted with H_2O and extracted with EtOAc (3×). The combined organic extracts were washed with H_2O (3×), saturated $NaHCO_3$ (aq) (1×), and brine (1×). The solution was dried with $MgSO_4$ and concentrated in vacuo. Purification by FC (gradient elution, 15−30% EtOAc/hexanes) afforded 6.36 g (88%) of acetonide **24** as a white solid. Mp 194−196 °C (d); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 3.8 Hz, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 6.56 (d, J = 3.8 Hz, 1H), 5.35 (s, 1H), 4.15 (br s, 1H), 4.08 (d, J = 5.4 Hz, 1H), 3.57 (br s, 1H), 3.47 (d, J = 5.4 Hz, 1H), 2.36 (s, 3H), 2.21 (d, J = 9.6, 1H), 1.86 (d, J = 9.6, 1H), 1.52 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0, 144.9, 135.9, 135.5, 131.4, 130.1, 129.2, 128.9, 126.7, 124.2, 112.9, 111.4, 80.9, 80.5, 75.5, 47.1, 44.6, 42.9, 25.9, 24.1, 21.5; IR (thin film) ν_{max} 3482, 3148, 2987, 2935, 1374, 1206, 1172, 1161 cm^{-1}; HRMS calcd for $C_{23}H_{22}INO_5S$ 551.0263, exptl 551.0271.

4-Ethyl-8,8-dimethyl-6, 10-methano-1-(toluene-4-sulfonyl)-6,-6a,9a,10-tetrahydro-1*H*-7,9-dioxa-1-azadicyclopenta[*a*,*g*]naphthalen-5-ol (25). To a solution of 4-iodoindole **24** (3.00 g, 5.44 mmol) in 50 mL of dry 1,4-dioxane sparged with argon was added Et_2Zn (19.4 mL of a 1.0 M solution in hexanes, 19.4 mmol) and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (660 mg, 0.816 mmol). The reaction mixture was refluxed under argon until TLC analysis showed complete consumption of the starting material. The reaction mixture was cooled to 0 °C and quenched by the dropwise addition of MeOH. The mixture was filtered through a pad of Celite and rinsed with EtOAc (3×). The layers were separated and the aqueous fraction was extracted with EtOAc (3×). The combined organic fractions were washed with 10% aqueous HCl (1×), $NaHCO_3$ (1×), and brine (1×) and dried with $MgSO_4$. The solution was concentrated to afford 2.42 g (98%) of the title compound as a white solid requiring no further purification. Mp 218−220 °C (d); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (d, J = 3.6 Hz, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 6.64 (d, J = 3.6 Hz, 1H), 4.81 (br s, 1H), 4.13 (br s, 1H), 4.09 (d, J = 5.4 Hz, 1H), 3.55 (d, J = 5.4 Hz, 1H), 3.41 (br s, 1H), 2.83−2.72 (m, 2H), 2.36 (s, 3H), 2.22 (d, J = 9.6 Hz, 1H), 1.84 (d, J = 9.6 Hz, 1H), 1.52 (s, 3H), 1.21 (s, 3H), 1.19 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 136.3, 131.5, 130.0, 128.8, 128.2, 127.2, 126.7, 124.8, 120.2, 112.8, 106.5, 81.3, 80.7, 47.0, 43.6, 42.7, 25.8, 24.1, 21.5, 20.0, 14.3; IR (thin film) ν_{max} 3447, 2977, 2936, 2873, 1373, 1169, 1139, 1061 cm^{-1}; HRMS calcd for $C_{25}H_{27}NO_5S$ 453.1610, exptl 453.1605.

Trifluoromethanesulfonic Acid 4-Ethyl-6,10-methano-8,8-dimethyl-1-(toluene-4-sulfonyl)-6,6a,9a,10-tetrahydro-1*H*-7,9-dioxa-1-azadicyclopenta[*a*,*g*]naphthalen-5-yl ester (26). To a chilled (0 °C) suspension of NaH (261 mg, 6.53 mmol) in 15 mL of THF was added a solution of 5-hydroxyindole **25** (2.47 g, 5.44 mmol) in 30 mL of THF via cannula. The mixture was stirred for 30 min at 0 °C and a solution of $PhNTf_2$ (2.33 g, 6.53 mmol) in 15 mL of THF was added via cannula. The mixture was warmed to room temperature and stirred for 18 h. The mixture was diluted with brine and extracted with EtOAc (3×). The combined organic fractions were washed with H_2O (1×) and brine (1×), dried with $MgSO_4$, and concentrated in vacuo. Purification by FC (20% EtOAc/hexanes) afforded 2.50 g (78%) of 5-trifloxyindole **26** as a white solid. Mp 168−170 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (d, J = 4.2 Hz, 1H), 7.66 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 6.75 (d, J = 4.2 Hz, 1H), 4.18 (d, J = 4.8 Hz, 1H), 4.15 (s, 1H), 3.55 (s, 1H), 3.51 (d, J = 4.8 Hz, 1H), 2.96−2.85 (m, 2H), 2.40 (s, 3H), 2.25 (d, J = 9.6 Hz, 1H), 1.90 (d, J = 9.6 Hz, 1H), 1.51 (s, 3H), 1.24 (t, J = 7.8 Hz, 3H), 1.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 137.8, 135.9, 135.4, 132.1, 130.3, 129.5, 129.3, 129.0, 128.0, 126.9, 118.6 (q, J_{CF} = 319.7 Hz, 1C), 112.9, 106.5, 80.6, 80.6, 47.6, 45.8, 43.4, 25.8, 24.2, 21.6, 20.9, 14.4; IR (thin film) ν_{max} 3152, 2984, 2938, 2881, 2360, 1617, 1494, 1455, 1406, 1374 cm^{-1}; HRMS calcd for $C_{26}H_{26}F_3NO_7S_2$ 585.1103, exptl 585.1239.

4-Ethyl-8,8-dimethyl-6,10-methano-1-(toluene-4-sulfonyl)-6,-6a,9a,10-tetrahydro-1*H*-7,9-dioxa-1-azadicyclopenta[*a*,*g*]naphthalene (27). 5-Trifloxyindole **26** (2.41 g, 4.11 mmol) was dissolved in 15 mL of dry DMF sparged with argon in a tube. To the solution was added LiCl (871 mg, 20.6 mmol), ammonium formate (5.19 g, 82.3 mmol), and $Pd(PPh_3)_2Cl_2$ (288 mg, 0.410 mmol). The tube was purged with argon, sealed, immersed in an oil bath at 140 °C, and stirred for 18 h. The tube was cooled to 0 °C and cautiously opened. The mixture was diluted with H_2O and extracted with EtOAc (3×). The combined organic fractions were washed with H_2O (3×) and brine (1×), dried with $MgSO_4$, and concentrated in vacuo. Purification by FC (gradient elution, 5−20% EtOAc/hexanes) afforded 1.71 g (95%) of the title compound as a white solid. Mp 164−166 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, J = 4.2 Hz, 1H), 7.64 (d, J − 8.4 Hz, 2H), 7.25 (d, J = 4.2 Hz, 1H), 6.96 (s, 1H), 6.71 (d, J = 4.2 Hz, 1H), 4.10 (br s, 1H), 4.04 (d, J = 5.4 Hz, 1H), 3.51 (d, J = 5.4 Hz, 1H), 3.23 (br s, 1H), 2.83−2.77(m, 2H), 2.35 (s, 3H), 2.20 (d, J = 9.6 Hz, 1H), 1.84 (d, J = 9.6 Hz, 1H), 1.51 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.18 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 144.5, 143.1, 136.4, 135.4, 130.0 (2C), 129.9, 127.3, 126.9, 126.2, 117.3, 112.5, 106.3, 81.5, 81.2, 47.9, 46.6, 42.9, 25.9 (2C), 24.1, 21.5, 14.8; IR (thin film) ν_{max} 3049, 2977, 2936, 2874, 1371, 1266, 1175, 1130 cm^{-1}; HRMS calcd for $C_{25}H_{27}NO_4S$ 437.1661, exptl 437.1653.

Methanesulfonic Acid 4-Ethyl-6-methanesulfonyloxymethyl-1-(toluene-4-sulfonyl)-1,6,7,8-tetrahydro-1-aza-*as*-indacen-8-yl Methyl Ester (29). Acetonide **27** (320 mg, 0.730 mmol) was suspended in 25 mL of concentrated HCl/MeOH (1:3) and brought to reflux for 18 h. The solution was cooled to room temperature, neutralized with 1 N KOH, and extracted with EtOAc (3×). The combined organic fractions were washed with brine (1×), dried with $MgSO_4$, and concentrated to afford 261 mg (90%) of glycol **28** requiring no further purification. The glycol (261 mg, 0.660 mmol) was dissolved in 15 mL of THF/H_2O (3:2) and $NaIO_4$ (988 mg, 4.62 mmol) was added. When complete by TLC analysis, the mixture was diluted with 25 mL of THF and cooled to 0 °C. $NaBH_4$ (375 mg, 9.90 mmol) was added and the reaction mixture was stirred

until TLC showed complete consumption of starting material. The mixture was then diluted with brine and extracted with EtOAc (3×). The combined organic fractions were washed with brine (1×), dried with $MgSO_4$, and concentrated in vacuo to afford the crude diol, which was taken up in dry CH_2Cl_2. NEt_3 (0.570 mL, 4.09 mmol) and MsCl (0.123 mL, 1.58 mmol) were added under argon and the reaction was stirred at room temperature until complete by TLC. The mixture was diluted with CH_2Cl_2, washed with 10% aqueous HCl (3×) and saturated $NaHCO_3$ (1×), dried with $MgSO_4$, and concentrated in vacuo. Purification by FC (gradient elution, 30−40% EtOAc/hexanes) afforded 181 mg (49% from **28**) of bis-mesylate **29** as a white solid. Mp 56−60 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59 (d, J = 4.2 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 7.04 (s, 1H), 6.75 (d, J = 4.2 Hz, 1H), 4.71 (dd, J = 9.6, 3.0 Hz, 1H), 4.51−4.48 (m, 1H), 4.48−4.45 (m, 1H), 4.29 (at, 1H), 4.25 (at, 1H), 3.68−3.64 (m, 1H), 3.02 (s, 3H), 2.90 (s, 3H), 2.81−2.74 (m, 2H), 2.57 (adt, 1H), 2.32 (s, 3H), 2.18 (d, J = 15.0 Hz, 1H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.0, 140.9, 137.7, 134.7, 132.3, 132.1, 129.9, 129.2, 126.4, 125.1, 120.0, 109.5, 73.2, 73.1, 43.7, 43.6, 37.1, 36.7, 30.0, 25.7, 21.5, 14.5; IR (thin film) ν_{max} 3152, 3029, 2967, 2877, 2518, 2306, 1734, 1596, 1540, 1494, 1466, 1350, 4271, 1169, 1090, 954 cm^{-1}; HRMS calcd for $C_{24}H_{29}NO_8S_3$ 555.1055, exptl 555.1050.

***cis*-Trikentrin A.** To a solution of bis-mesylate **29** (181 mg, 0.330 mmol) in 20 mL of DME was added Zn dust (108 mg, 1.65 mmol) and NaI (943 mg, 6.60 mmol). The reaction flask was fitted with a condenser, purged with argon, and brought to reflux for 24 h. The flask was cooled to room temperature, filtered, and rinsed with EtOAc. The solution was washed with H_2O (3×) and brine (1×), dried with $MgSO_4$, and concentrated in vacuo. Purification by FC (0−5% EtOAc/hexanes) afforded 61 mg (50%) of *N*-tosyl-*cis*-trikentrin A. To a solution of *N*-tosyl-*cis*-trikentrin A (61.0 mg, 0.170 mmol) in 10 mL of dry THF was added TBAF (1.19 mL of a 1.0 M solution in THF, 1.19 mmol). The flask was fitted with a condenser, purged with argon, and brought to reflux for 18 h. The mixture was cooled to room temperature, diluted with brine, and extracted with EtOAc (3×). The combined organic fractions were washed with saturated $NaHCO_3$ (1×) and brine (1×), dried with $MgSO_4$, and concentrated in vacuo. Purification by preparative TLC (5% EtOAc/hexanes, triple elution) afforded 30 mg (82%) of *cis*-trikentrin A. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 (br s, 1H), 7.20, (at, 1H), 6.87 (s, 1H), 6.62 (dd, J = 3.6, 2.4 Hz, 1H), 3.49−3.43 (m, 1H), 3.28−3.22 (m, 1H), 3.01−2.91 (m, 2H), 2.63 (dt, J = 12.6, 7.8 Hz, 1H), 1.52 (d, J = 7.2 Hz, 3H), 1.40 (d, J = 7.2 Hz, 3H), 1.39 (t, J = 7.8 Hz, 3H), 1.34 (dt, J = 12.6, 8.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.9, 135.0, 132.3, 127.0, 126.3, 122.8, 114.0, 101.3, 44.6, 38.9, 37.1, 26.5, 21.0, 20.8, 15.0; IR (thin film) ν_{max} 3431, 2958, 2929, 2868, 1618, 1500, 1457, 1402, 1374, 1128, 1064 cm^{-1}; HRMS calcd for $C_{15}H_{19}N$ 213.1518, exptl 213.1520.

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Supporting Information Available: General experimental remarks and spectroscopic data for all compounds reported in the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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