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Transformations of the Picrotoxanes: The Synthesis of Corianin and Structural Analogues From Picrotoxinin‡

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Abstract: The neurochemically active picrotoxane sesquiterpene corianin and several structural analogues have been prepared from inexpensive, commercially available picrotoxin.

One of the most toxic substances of plant origin known (LD_{50}=3.0 mg/Kg),[1] picrotoxinin, is a potent and specific antagonist against the neurotransmitter suppressor γ-aminobutyric acid (GABA)[2] and inhibits the opening of chloride ion channels *in vivo*.[3] To date, over 50 picrotoxane related compounds possessing similar biological activity have been isolated not only from plants, but from marine and terrestrial animals as well. Their ubiquity, novel structure and potent neurochemical properties have prompted intense investigations which have been reviewed by chemists[4] and biologists[5] alike.

In the course of our synthetic studies involving the use of the palladium catalyzed enyne cycloisomerization reaction in a general synthetic approach to both alkaloids and, more recently, sesquiterpenes of the picrotoxane skeleton (illustrated by total syntheses of picrotoxinin, picrotin, and corianin,[6] methyl picrotoxate[7] and dendrobine[8]), we undertook degradation studies of picrotoxinin to obtain model systems that could allow insight into the reactivity and conformational aspects of these highly oxygenated caged structures and provide structural proofs for some of our advanced synthetic intermediates. We soon realized that picrotoxinin, itself an indispensable neuropharmacological tool,[9] could be converted to other potentially useful analogues that would otherwise be difficult to obtain. Moreover, structure activity relationships related to the picrotoxanes have, to date, been

‡ *Dedicated to our colleague and friend, Professor Madeleine Joullié in celebration of forty years of distinguished teaching and research at the University of Pennsylvania.*

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restricted to those compounds that occur naturally or degradation products that invariably fail to retain the C3-C5 bridged lactone—a structural feature that is known to be essential for high levels of biological activity. Herein we present a means of preparing analogues of picrotoxinin that retain both lactone units while allowing for the introduction of functionality in the cyclopentane portion of the *cis*-hydrindane core. Most importantly, we present a facile preparation of corianin,[10] which shows promise as a possible therapeutic agent for schizophrenia,[11] *via* degradation of the naturally abundant picrotoxinin (Figure 1).

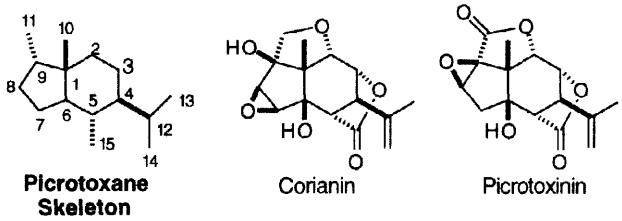
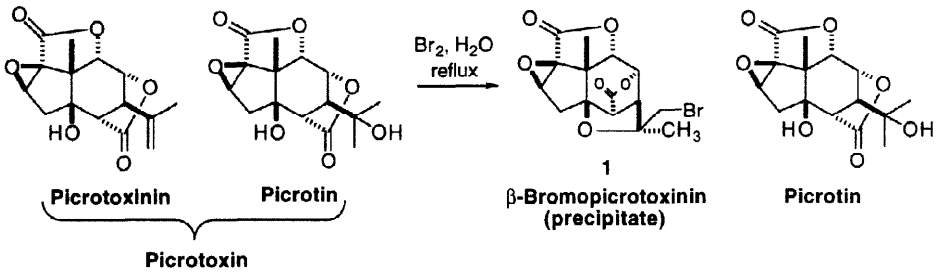


Figure 1: Carbocyclic Skeletons of the Picrotoxane Sesquiterpenes Picrotoxinin and Corianin

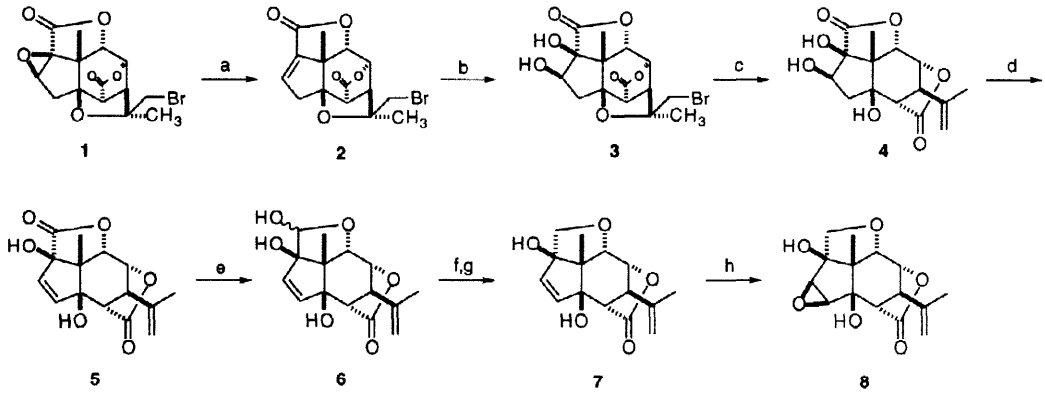
Picrotoxinin, commercially available as an equimolar mixture with picrotin, can be reacted with bromine water to afford β-bromopicrotoxinin as a white precipitate.[12] This reaction is not only a means of conveniently separating picrotoxinin from picrotin, but also introduces the bromoether function as a single isomer. β-Bromopicrotoxinin (**1**) was recrystallized from ethanol to give clear, prismatic crystals (mp = 273-275°C, lit. mp = 259-260°C,[13] 280°C[14] (Scheme 1).



Scheme 1. Bromination of Picrotoxin

Upon exposure to low valent tungsten,[15] β-bromopicrotoxinin chemoselectively undergoes deoxygenation of the glycidic epoxide in the presence of the bromoether moiety to give **2**. The chemoselectivity is noteworthy and contrasts to dissolving metal reductions wherein reductive elimination of the bromoether precedes epoxide deoxygenation (*vide infra*). Dihydroxylation[16] of the crude unsaturated lactone **2** proceeds readily to give the diol **3** whose structural assignment is supported by the infrared absorbance at 3400 cm^{-1}

corresponding to the hydroxyl functionality and the observance of the molecular ion in the mass spectrum. Subjection of **3** to conditions for zinc induced β-haloether fragmentation provides the *bis*-lactone triol **4**. We have reported the syntheses of both corianin and picrotoxinin from (*R*)-carvone *via* bifurcation of our synthetic route from material identical to compound **4**.[6] Thus, the preparation of **4** from picrotoxinin not only represents a structural proof for **4**, but also a total synthesis of the rare picrotoxane corianin **8** from the naturally abundant picrotoxane picrotoxinin as indicated in Scheme 2.

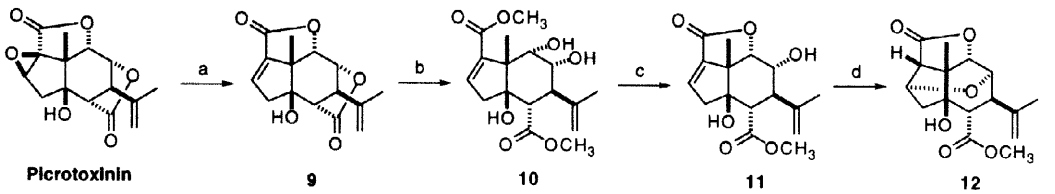


Scheme 2. Preparation of Corianin from Picrotoxinin

a) WCl_6, 2 equiv. BuLi, THF-Et_2O, room temperature, 52%. b) OsO_4, Pyr, then aq. $NaHSO_3$, 73%. c) Zn, MeOH, AcOH, 60°C, 88%. d) *N*-methylimidazole, Tf_2O, 100°C, 85%. e) $LiBH_4$, AcOH, THF, 0°C, 71%. f) PhSH, cat. TMSCl, CH_3CN, room temperature, 98%. g) Ph_3SnH, cat. AIBN, $PhCH_3$, reflux, 84%. h) MCPBA, DCM, 0°C, 87%.

Picrotoxinin itself is subject to low valent tungsten mediated deoxygenation to provide the unsaturated lactone **9**, "deoxypicrotoxinin," which contains a bridgehead olefin. Compound **9** has been independently synthesized from (*R*)-carvone thus constituting a structural proof of this material.[6] Sodium cyanide catalyzed transesterification[17] of **9** provides the diester **10**, the deoxygenated analogue of dimethyl picrotoxinin dicarboxylate. The structural assignment of **10** is supported by the ^1H NMR resonances at δ 3.75 (s, 3H) and 3.68 (s, 3H) indicating the presence of the two methyl esters and the resonance at 7.00 (bs, 1H) indicating the presence of the enoate function. Exposure of the enoate **10** to basic conditions for lactonization gave the monoester monolactone **11**. The observance of only one methyl ester resonance at δ 3.74 in the ^1H NMR and the two infrared absorptions at 1719 cm^{-1} and 1708 cm^{-1} indicate that the monoester monolactone **11** had formed. Compound **11** is the only picrotoxane degradation product to possess the indicated monoester monolactone (Scheme 3). An alternative six-membered ring lactone **15** (see Scheme 4), which was prepared

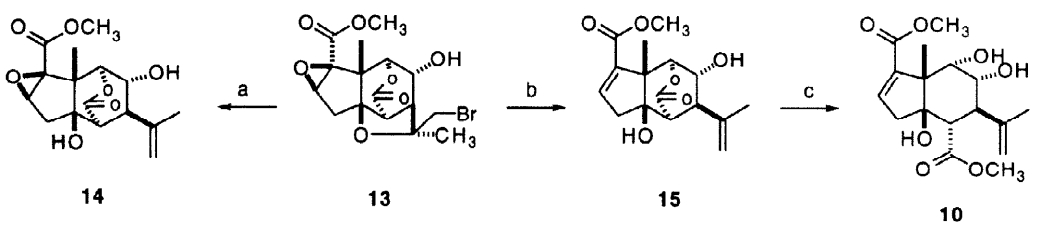
independently, can be ruled out. Further treatment with KH in THF at room temperature did not lactonize the remaining hydroxyester but led to disappearance of the double bond which tentatively suggests the cyclic ether **12**.



Scheme 3. Preparation of 8,9-Deoxygenated Analogues

a) WCl_6, 2 equiv. BuLi, TH-Et_2O, room temperature, 64%. b) MeOH, cat. NaCN, room temperature, 68%. c) KH, THF, 0°C, 64%.

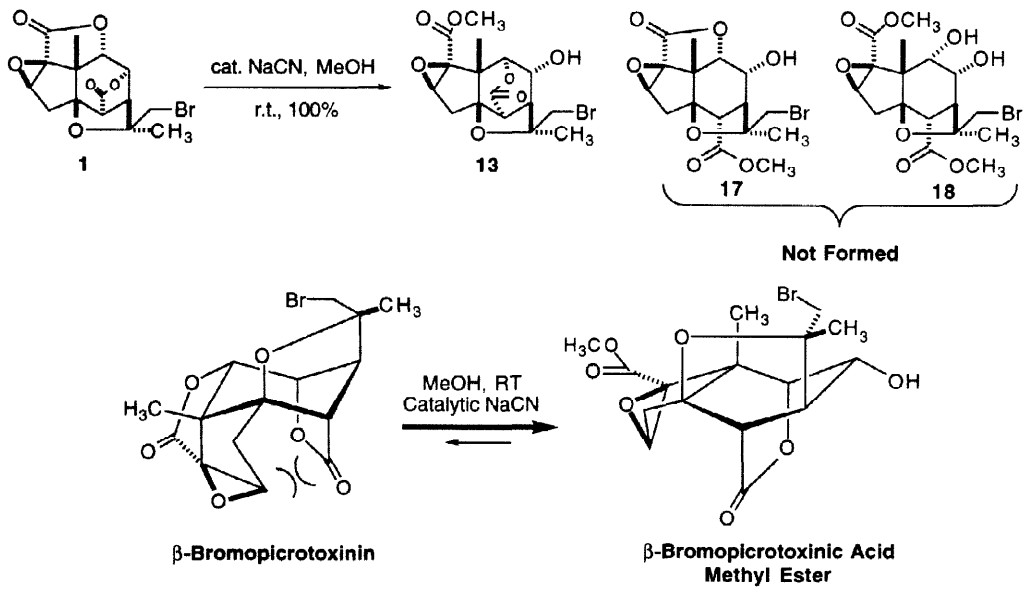
Unsaturated analogues may also be accessed *via* the zinc mediated reduction of β-bromopicrotoxinic acid methyl ester.[18] Treatment of **13** with Zn at 60° resulted only in bromoether cleavage to give **14**. However, raising the temperature to that of ethanol at reflux, led to fragmentation and deoxygenation producing the "deoxy α-picrotoxinic acid methyl ester" (**15**). That the bromoether had cleaved was evidenced by the resonances at δ 5.05 (bs, 1H) and 4.88 (bs, 1H) in the ^{1}H NMR of **15** and the absorbence at 1650 cm^{-1} in the infrared spectrum corresponding to the presence of the 2-propenyl moiety. That deoxygenatin of the epoxide had concomittantly occured was supported by the resonance at δ 6.68 in the ^{1}H NMR of **15** corresponding to the β-proton of the enoate moiety. The monoester monolactone **10** could be converted to "deoxy dimethyl picrotoxinin dicarboxylate" **10** by exposure to methanolic potassium cyanide (Scheme 4).



Scheme 4. Deoxygenated Analogues *via* Elaboration of β-Bromopicrotoxinic Acid Methyl Ester

a) Zn, CH_3OH, HOAc, 60°C, 96%. b) Zn, EtOH, AcOH, reflux, 100%. c) MeOH, cat. KCN, 50°C, 50%.

Finally, the preparation of **13** from β-bromopicrotoxinin deserves some comment. Addition of 5 mol% of sodium cyanide to a methanolic solution of **1**, i.e., equilibrating conditions for translactonization/transesterification, results in its immediate and quantitative conversion to **13**. The other possible products of methanolysis, monoester monolactone **17** and diester **18** are not formed. Thus, it would appear that in the presence of the bromoether, the bridged [2,2,2]bicyclic structure found in β-bromopicrotoxinic acid methyl ester is thermodynamically preferred due to the relief of transannular steric interactions between substituents at C8 and C9 (Scheme 5).



Scheme 5. Determination of the Thermodynamic Lactone Isomer

In conclusion, we have presented an expedient means of preparing the neurochemically active picrotoxane natural product corianin *via* degradation of inexpensive, commercially available picrotoxin. The selective manipulation of the functionality of the five-membered ring portion of the hydrindane skeleton should allow for structure activity relationships of hitherto unavailable structural analogues to be determined. Most notably, the chemoselective deoxygenation of the epoxide sets the stage for structural variations.

EXPERIMENTAL SECTION:

All reactions were run under an atmosphere of nitrogen passed through a tube of calcium carbonate unless otherwise indicated. Anhydrous solvents were transferred by an oven-dried syringe or cannula. Flasks were flame-dried and cooled under a stream of nitrogen. Acetonitrile, benzene, dichloromethane, dichloroethane, hexane, pyridine,

triethylamine and diisopropylamine were distilled from calcium hydride. Dimethylsulfoxide (DMSO) was distilled at 60°C at 0.1 mmHg. Dimethylformamide (DMF) was distilled from barium hydroxide at reduced pressure. Ether, tetrahydrofuran (THF) and toluene were distilled from sodium benzophenone ketyl. Methanol and ethanol were distilled from magnesium methoxide and magnesium ethoxide respectively.

Analytical thin layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plates (DC-Fertigplatten Krieselgel 60 F_{254}). Preparative column chromatography employing silica gel was performed according to the method of Still.[19] Solvents for chromatography are listed as volume/volume ratios.

Melting points were determined on a Thomas-Hoover melting point apparatus in open capillaries and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1420 spectrophotometer or a Nicolet 205 1420 spectrophotometer. Elemental analyses were performed by Robertson Laboratories, Madison, New Jersey and M-H-W Laboratories Pheonix, Arizona. High resolution mass spectra (HRMS) were obtained from the Mass Spectrometry Resource, School of Pharmacy, University of California-San Francisco on a Kratos MS9 and are reported as m/e (relative intensity. Accurate masses are reported for the molecular ion (M^+) or a suitable fragment ion.

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded using a Varian XL-400 (400 MHz), Varian Gemini 200 (200 MHz) or Varian Gemini 300 (300 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, part per million (ppm) downfield from trimethylsilane. Coupling constants are reported in Hertz (Hz).

Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded using a Varian XL-400 (100 MHz), Varian Gemini 200 (50 MHz) or Varian Gemini 300 (75 MHz) spectrometer. Chemical shifts are reported in delta (δ) units, part per million (ppm) relative to the center line of the triplet at 77.00 ppm for deuteriochloroform. ^{13}C NMR spectra were routinely run with broadband decoupling.

Preparation of "8,9-Deoxy-β-bromopicrotoxinin," 2 and "8,9-Dihydroxy-β-bromopicrotoxinin," 3:

To a flask charged with ether (33.6 mL, 0.2 M with respect to WCl_6) at -78°C was added tungsten(VI)chloride (2.67 g, 6.7 mmol, 500 mol%) followed by *n*-butyllithium (10.3 mL of a 1.3 M solution in hexane, 13.3 mmol, 1000 mol%). The mixture was allowed to stir for 5 min. at which point the cooling bath was removed. Once at 0°C, β-bromopicrotoxinin (500 mg, 1.34 mmol, 100 mol%) was added as a solution in THF (26.9 mL, 0.05 M). The reaction mixture was stirred at room temperature for 4 h. at which point the reaction mixture was filtered through a pad of silica gel with the aid of ethyl acetate. The solution was then evaporated onto silica gel. Column chromatography (SiO_2; 40→50% ethyl acetate in hexane) afforded the enoate **2** (183 mg, 0.51 mmol) in 38% yield

along with returned starting material (183 mg, 36%) as an inseparable mixture. The yield of enoate **2** based on recovered starting material is 52%.

The enoate **2** (100 mg, 0.28 mmol) prepared by this protocol was dissolved in pyridine (2.8 mL, 0.1 M) and osmium tetroxide (178 mg, 0.7 mmol, 250 mol%) was added. The reaction mixture was allowed to stir for 6 h. at which point $NaHSO_{3(aq)}$ was added. The reaction mixture was allowed to stir for an additional 16 h. at which point the reaction mixture was partitioned between chloroform and water. The aqueous layer was extracted with chloroform and the combined organic extracts were dried ($MgSO_4$), filtered and evaporated onto silica gel. Column chromatography (SiO_2; 35→50% ethyl acetate in hexane) afforded the diol **3** (80 mg, 0.21 mmol) in 73% yield as a white foam. R_f = 0.25 (50% ethyl acetate in hexane). $[\alpha]_D$ = -70.5 (1.5% in acetone). IR (neat): 3400, 1770, 1340, 1190 cm^{-1}. ^1H NMR (200 MHz, d4-methanol): δ 5.10 (dd, $J_1 = J_2$ = 5.6 Hz, 1H), 4.82 (d, J = 5.7 Hz, 1H), 4.46 (dd, J_1 = 10.8, J_2 = 6.6 Hz, 1H), 3.74 (d, J = 11.3 Hz, 1H), 3.60 (m, 2H), 3.23 (d, J = 5.0 Hz, 1H), 2.26 (m, 2H), 1.46 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (100 MHz, d^4-methanol): δ 178.2, 174.6, 86.1, 82.5, 81.2, 79.9, 79.4, 69.0, 59.3, 55.4, 55.2, 43.2, 38.0, 28.0, 19.6. Mass Spec.: 390(5.2), 388(5.5), 372(3.8), 370(3.5), 333(4.1), 3.28(7.2), 309(27.4), 163(100). HRMS: Calcd for $C_{15}H_{17}Br^{81}O_7$: $[M^+]$ = 390.0137. Found: 390.0137.

"8,9-Dihydroxypicrotoxinin," 4:

To a methanolic solution (8.3 mL, 0.1 M) of the bromoether diol **3** (325 mg, 0.835 mmol, 100 mol%) was added acetic acid (477 μL, 8.35 mmol, 1000 mol%). The reaction vessel was placed in a 60°C oil bath and zinc dust (1.09 g, 16.67 mmol, 2000 mol%) was added. The reaction mixture was allowed to stir in the oil bath for 2 h. at which point the solution was decanted from the zinc salts with the aid of ethyl acetate. The solution was evaporated onto silica gel and subjected to collum chromatography (SiO_2; 40→60% ethyl acetate in hexane) to afford the *bis*-lactone triol **4** (230 mg, 0.74 mmol) in 88% yield. Material prepared by this protocol is identical in all respects to material prepared from (*R*)-carvone. R_f = 0.3 (60% ethyl acetate in hexane). $[\alpha]_D$ = -15.3° (1.6% in CH_2Cl_2). IR (neat): 3400, 1777, 1770, 1648, 1454, 1307, 1208, 1176, 1012 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.11 (bs, 1H), 5.07 (dd, $J_1 = J_2$ = 4.28 Hz, 1H), 4.92 (bs, 1H), 4.66 (d, J = 3.97 Hz, 1H), 4.15-4.19 (dd, J = 12.01, 6.27 Hz, 1H), 3.40 (bs, 1H), 3.06 (d, J = 4.28 Hz, 1H), 2.80-2.85 (A part of ABX system, dd, J = 13.29, 6.31 Hz, 1H), 195-2.02 (B part of ABX system, dd, J = 12.2, 13.3 Hz, 1H), 1.93 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (100 MHz, d^5-Pyridine): δ 177.4, 176.3, 140.5, 113.2, 82.7, 81.8, 77.7, 74.7, 70.9, 53.1, 52.4, 49.0, 48.4, 22.9, 20.6. Mass Spec.: 310(71), 292(8.3), 181(60), 95(100). HRMS: Calcd for $C_{15}H_{18}O_7$: $[M^+]$ = 310.1053; found: 310.1042.

"8,9-Deoxypicrotoxinin," 9:

To a flask charged with ether (40 mL, 0.1 M with respect to WCl_6) at -78°C was added tungsten(VI)chloride (1.6 g, 4.03 mmol, 500 mol%) followed by *n*-butyllithium (6.8 mL of a 1.3 M solution in hexane, 8.8 mmol, 1100 mol%). The mixture was allowed to stir for 5 min. at which point the cooling bath was removed. Once at 0°C, picrotoxinin (236 mg, 0.80 mmol, 100 mol%) was added as a solution in THF (4 mL, 0.2 M). The reaction mixture was stirred at room temperature for 2 h. at which point the reaction mixture was filtered through a pad of silica gel with the aid of ethyl acetate. The solution was then evaporated onto silica gel. Column chromatography (SiO_2; 30→40% ethyl acetate in hexane) afforded "deoxy-picrotoxinin" **9** (108 mg, 0.39 mmol) in 49% yield along with returned starting material (71 mg, 30%). The yield of enoate **9** based on recovered starting material is 64%. Material prepared by this protocol is identical in all respects to that prepared from the *bis*-lactone triol **4.** R_f = 0.4 (60% ethyl acetate in hexane). $[\alpha]_D$ = 120° (2.75% in acetone). IR (neat): 3450, 2930, 1784, 1760, 1651, 980 cm^{-1}. ^1H NMR (400 MHz, CDCl3): δ 6.38 (bs, 1H), 5.06 (s, 1H), 4.97 (dd, J = 4.34, 3.66 Hz, 1H), 4.82 (s, 1H), 4.70 (d, J = 3.36 Hz, 1H), 3.38 (bs, 1H), 3.26-3.32 (A part of ABX system, dd, J = 17.88, 3.73 Hz, 1H), 3.07-3.12 (B part of ABX system, d, J = 17.94 Hz, 1H), 2.90 (d, J = 4.58 Hz,1H), 2.65 (bs, 1H), 1.93 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5, 163.6, 142.2, 140.0, 134.9, 113.3, 83.3, 79.3, 78.0, 53.6, 49.6, 49.3, 49.0, 23.2, 19.2. Mass Spec.: 276(36.0), 248(7.3), 163(16.1), 136(26.2), 95(100). HRMS: Calcd for $C_{15}H_{16}O_5$: $[M^+]$ = 276.0997. Found: 276.0998.

Preparation of "8,9-Deoxy Dimethyl Picrotoxinindicarboxylate," 10:

To a flask charged with a methanolic solution (3.2 mL, 0.05 M) of enoate **9** (50 mg, 0.162 mmol, 100 mol%) was added powdered potassium cyanide (3.2 mg, 0.046 mmol, 30 mol%). The reaction mixture was allowed to gently reflux for 19 h. at which point the reaction mixture was evaporated onto silica gel. Column chromatography (SiO_2; 40→50% ethyl acetate in hexane) afforded "dimethyl deoxy-picrotoxinindicarboxylate" **10** (21.1 mg, 0.062 mmol) in 38% yield along with returned starting material (15.4 mg, 30%). The yield of product **10** based on recovered starting material is 50%. R_f = 0.4 (60% ethyl acetate in hexane). $[\alpha]_D$ = 88.6° (1.6% in methanol). IR (neat): 3450, 2950, 1715, 1648, 1436, 1344, 1243 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.00 (bs, 1H), 5.02 (bs, 1H), 4.94 (bs, 1H), 4.12 (d, J = 2.7 Hz, 1H), 3.81 (dd, J_1 = 10.7, J_2 = 2.6 Hz, 1H), 3.75 (s, 3H), 3.68 (s, 3H), 3.14 (dd, A part of ABX system, J_1 = 18.3, J_2 = 2.0 Hz, 1H), 2.89 (d, J = 12.5 Hz, 1H), 2.78 (dd, J_1 = 12.7, J_2 = 10.9 Hz, 1H), 2.23 (dd, B part of ABX system, J_1 = 18.3, J_2 = 3.2 Hz, 1H), 1.79 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 165.0, 144.1, 142.4, 136.5, 116.6, 81.9, 74.4, 68.5, 56.4, 51.7, 51.4, 50.6, 45.5, 43.5, 18.5, 15.5. Mass Spec.: 340(3.7), 322(15.4), 290(30.9),

245(28.0), 209(31.5), 154(79.5), 127(90.9), 95(100). HRMS: Calcd for $C_{17}H_{24}O_7$: $[M^+]$ = 340.1522. Found: 340.1529.

Preparation of *mono*-Ester *mono*-Lactone 11:

To a flask charged with a suspension of potassium hydride (12 mg, 0.32 mmol, 200 mol%) in THF (1.6 mL, 0.1 M) at 0°C was added a THF solution of "dimethyl deoxypicrotoxinindicarboxylate" **10** (55.1 mg, 0.161 mmol, 100 mol%). The reaction mixture was allowed to stir for 30 min. at which point the reaction mixture was partitioned between diethyl ether and half-saturated $NH_4Cl_{(aq)}$. The aqueous layer was extracted with ether and the combined organic extracts were dried ($MgSO_4$), filtered and evaporated onto silica gel. Column chromatography (SiO_2; 40→50% ethyl acetate in hexane) afforded hydroxy ester **11** (31.7 mg, 0.103 mmol) in 64% yield. R_f = 0.45 (60% ethyl acetate in hexane). Mp = 196-199°C. $[\alpha]_D$ = 24.7 (1.1% in acetone). IR (neat): 3450, 2954, 1719, 1708, 1636, 1438, 1343, 1252 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.72 (bs, 1H), 5.25 (bs, 1H), 5.19 (bs, 1H), 5.14 (s, 1H), 4.59 (d, J = 5.8 Hz, 1H), 3.74 (s, 3H), 3.13 (d, J = 1.9 Hz, 1H), 2.82 (dd, A part of ABX system, J_1 = 20.8, J_2 = 2.8 Hz, 1H), 2.65 (dd, B part of ABX system, J_1 = 20.1, J_2 = 2.4 Hz, 1H), 2.55 (bs, 1H), 2.43 (bs, 1H), 1.97 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (75 MHz, d^6-acetone): δ 174.2, 164.2, 144.8, 142.3, 138.8, 110.4, 85.6, 80.2, 67.0, 55.7, 53.7, 51.6, 49.6, 47.8, 22.5, 15.9. Mass Spec.: 308(4.2), 293(62.5), 155(32.3), 154(100), 96(49.4), 95(50.9). HRMS: Calcd for $C_{16}H_{20}O_6$: $[M^+]$ = 308.1260. Found: 308.1251.

α-Picrotoxinic Acid Methyl Ester (14)

To a solution of bromoether **13** (110 mg, 0.27 mmol, 100 mol%) in methanol (5.5 mL, 0.05 M) was added acetic acid (156 μL, 2.72 mmol, 1000 mol%) followed by zinc dust (357 mg, 5.44 mmol, 2000 mol%). The heterogeneous mixture was refluxed for 30 min. at which point the reaction vessel was removed from the heating bath and the clear solution was decanted away from the zinc salts. The zinc salts were washed several times with methanol and the combined methanolic solutions were evaporated onto silica gel. Chromatography (SiO_2; 30→40% ethyl acetate in hexane) gave the title compound **14** in 79% yield (69.9 mg, 0.213 mmol) as a white crystalline solid. R_f = 0.35 (50% EtOAc in hexane). Mp = 179-181°C. $[\alpha]_D$ = -10.9° (1.5 in ethanol). IR (neat): 3432, 2956, 1736, 1440, 1327, 1066 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.49 (s, 1H), 5.15 (bs, 1H), 5.12 (bs, 1H), 4.58 (bd, J = 4.06 Hz, 1H), 3.90 (d, J = 2.35, 1H), 3.75 (s, 3H), 3.12 (d, J = 2.26 Hz, 1H), 2.45 (bs, 1H), 2.35-2.41 (A part of ABX system, dd, J = 2.41, 16.2 Hz, 1H), 2.26 (s, 1H), 2.15 (B part of ABX system, d, J = 16.2 Hz, 1H), 1.92 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (50 MHz, d^6-acetone): δ 173.7, 168.2, 144.2, 110.0, 85.9,

82.7, 69.6, 66.4, 63.7, 54.0, 52.6, 51.2, 48.8, 22.4, 13.5. HRMS: Calcd for $C_{16}H_{20}O_7$: C, 59.25%; H, 6.21%. Found: C, 59.10%, H, 6.19%.

Preparation of "8,9-Deoxy-α-picrotoxinic Acid Methyl Ester," 15:

To an ethanolic solution (13.2 mL, 0.1 M) of β-bromopicrotoxinic acid methyl ester **(13)** (535 mg, 1.32 mmol, 100 mol%) at reflux was added acetic acid (760 μL, 13.2 mmol, 1000 mol%) followed by zinc dust (3.47 g, 52.8 mmol, 4000 mol%). The reaction mixture was allowed to stir at reflux for 1.5 h. at which point the solution was decanted from the zinc salts with the aid of ethyl acetate. The reaction mixture was partitioned between ethyl acetate and brine-$NaHCO_{3(aq)}$ (1:1). The aqeous layer was extracted and the combined extracts were dried ($MgSO_4$), filtered and evaporated to give the enoate "deoxy-α-picrotoxinic acid" **15** (377 mg, 1.22 mmol) in 96% yield. Chromatography was not required as material prepared by this protocol was pure by ^1H NMR spectroscopy. R_f = 0.25 (60% ethyl acetate in hexane). Mp = 192-195°C. $[\alpha]_D$ = 18.6 (1.0% in methanol). IR (neat): 3436, 3340, 1721, 1648, 1440, 1348 cm^{-1}. ^1H NMR (400 MHz, d^6-acetone): δ 6.68 (bs, 1H), 5.05 (bs, 1H), 4.88 (s, 2H), 4.57 (dd, $J_1 = J_2$ = 5.7 Hz, 1H), 4.41 (d, J = 5.6 Hz, 1H), 4.12 (s, 1H), 3.69 (s, 3H), 3.08 (bs, 1H), 2.98 (s, 1H), 2.76 (dd, A part of ABX system, J_1 =2 0.0, J_2 = 2.8 Hz, 1H), 2.67 (dd, B part of ABX system, J_1 = 20.0, J_2 = 2.4 Hz, 1H), 2.30 (bs, 1H), 1.88 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (100 MHz, d^6-acetone): δ 174.0, 163.9, 144.5, 142.1, 138.5, 110.1, 85.4, 79.9, 66.7, 55.5, 53.4, 51.3, 49.3, 47.6, 22.2, 15.6. Mass Spec.: 308(3.6), 293(4.6), 276(3.7), 204(11.3), 188(12.9), 167(18.1), 154(100). HRMS: Calcd for $C_{16}H_{20}O_6$: $[M^+]$ = 308.1260. Found: 308.1261.

Preparation of β-Bromopicrotoxinic Acid Methyl Ester (13)

To a flask charged with a methanolic solution (67 mL, 0.1 M) of β-bromopicrotoxinin **1** (2.50 g, 6.73 mmol, 100 mol%) was added powdered sodium cyanide (16 mg, 0.326 mmol, 5 mol%). The reaction mixture was allowed to stir at room temperature for 45 min. at which point the reaction mixture was partitioned between ethyl acetate and half-saturated sodium bicarbonate. The aqueous layer was extracted with ethyl acetate and the combined organic extracts were dried ($MgSO_4$), filtered and evaporated to give **13** in 99.5% yield identical in all respects to that reported by Hormann.[12] Chromatography was not required as material prepared by this protocol was pure by ^1H NMR spectroscopy. R_f = 0.4 (50% EtOAc in hexane). Mp = 216-217°C $[\alpha]_D$ = -74.9° (1.0% in methanol). IR (neat): 3500, 2940, 1750, 1439, 1381, 1042 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.15 (d, J = 2.2 Hz, 1H), 4.24 (d, J = 1.92 Hz, 1H), 3.74 (s, 3H), 3.48 (A part of AB system, d, J = 11.39 Hz, 1H), 3.40 (B part of AB system, d, J = 10.72 Hz, 1H), 3.20 (d, J = 3.57 Hz, 1H), 2.46 (d, J = 4.12 Hz, 1H), 2.24-2.30 (B part

of ABX system, dd, J = 3.03, 15.33 Hz, 1 H), 2.17 (A part of ABX system, d J = 15.38 Hz, 1H), 1.47 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 166.8, 94.9, 84.4, 80.8, 77.2, 66.9, 65.4, 60.8, 53.3, 52.8, 48.2, 37.3, 35.2, 25.9, 13.1. Mass Spec.: 404(4.1), 402(4.2), 389(11.8), 387(13.9), 317(24.6), 315(19.6), 193(39.4), 111(45.9), 95(100). HRMS: Calcd for $C_{16}H_{19}Br^{81}O_7$: $[M^+]$ = 404.0294. Found: 404.0293.

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