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# Total Synthesis of Methyl Picrotoxate *via* the Palladium Catalyzed Enyne Cycloisomerization Reaction

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***Abstract***: Bifurcation of the synthetic pathway affording total syntheses of picrotoxinin, picrotin and corianin from a common synthetic intermediate derived *via* the palladium catalyzed enyne cycloisomerization leads to the total synthesis of the picrotoxane sesquiterpene methyl picrotoxate.


We have previously reported 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, corianin, and dendrobine.[1,2] To further demonstrate the efficacy of this approach, we now describe the total synthesis of methyl picrotoxate (also known as picrotoxic acid methyl ester) *via* divergence of a synthetic intermediate in our approach to the picrotoxane sesquiterpenes (Figure 1).

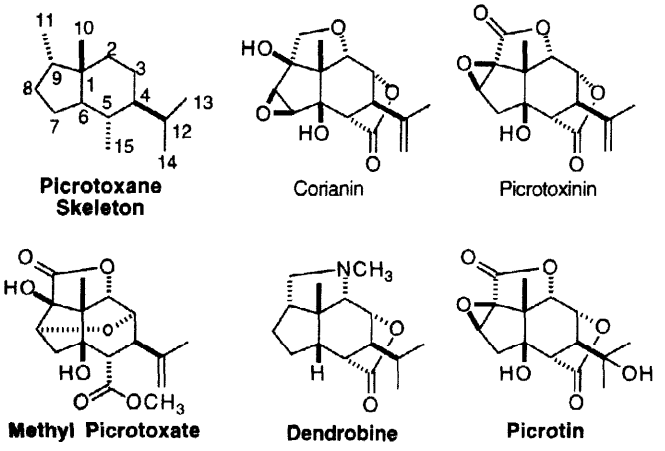


**Fig. 1.** Picrotoxane Natural Products Accessed *via* Palladium Catalyzed Cyclosiomerization

Methyl picrotoxate, first identified as a degradation product of picrotoxinin,[3] also occurs naturally as a constituent of the sea sponge *spirastrella inconstans*.[4] Structurally, methyl picrotoxate differs from other picrotoxane sesquiterpenes due to the presence of a transannular ether linkage bridging C3 and C8 of the *cis*-hydrindane ring system in lieu of the lactone moiety typically bridging C3 and C5 (see Figure 1). Retrosynthetically, we envisioned that its novel polycyclic skeleton could be accessed *via* bifurcation of an intermediate in our synthetic approach

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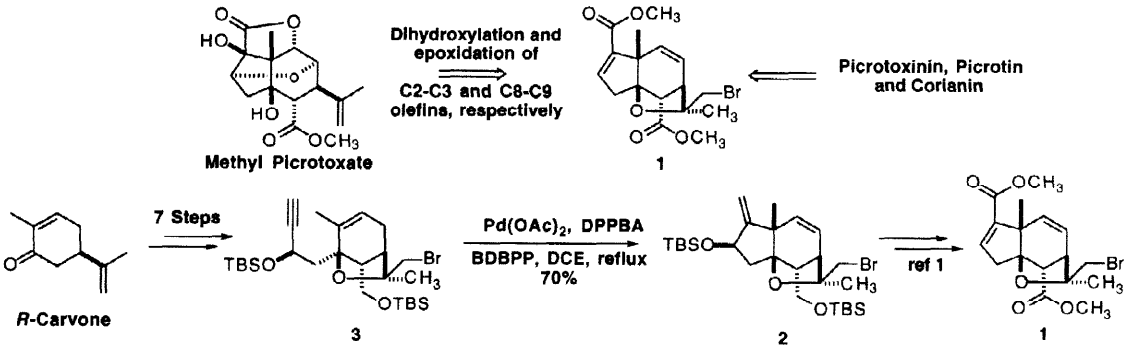
to the picrotoxane sesquiterpenes picrotoxinin, picrotin, and corianin. Specifically, diester diene **1**, which possesses all carbons of the picrotoxane skeleton and is readily prepared from enyne cycloisomerization product **2**, could be converted to methyl picrotoxate *via* stereoselective dihydroxylation and epoxidation of the C2-C3 and C8-C9 olefins, respectively (Scheme 1).

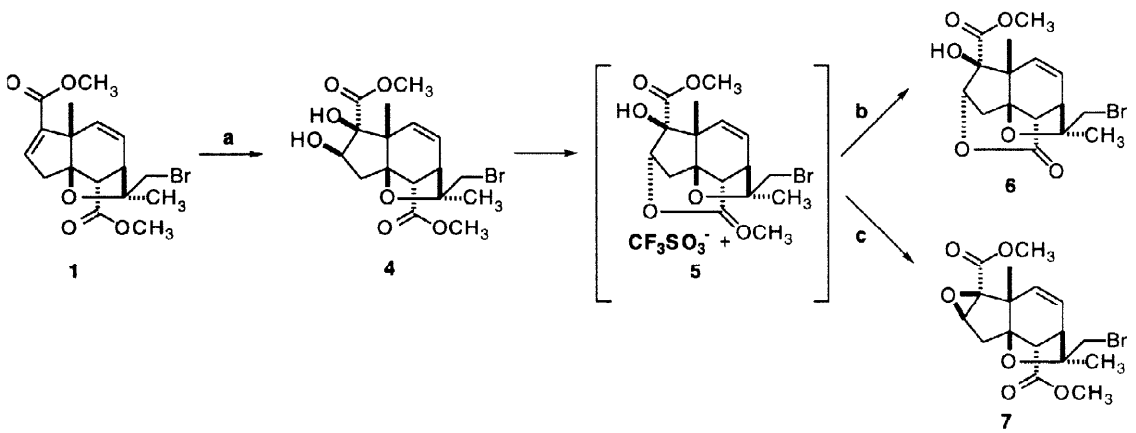



**Scheme 1.** Retrosynthetic Analysis

DPPBA=2-(diphenylphosphino)benzoic acid, BDBPP=1,3-bis-(dibenzophospholyl)propane, DCE=dichloroethane

The unusual stereoelectronic aspects of the bicyclic core of the bromoether containing intermediates quickly became apparent. As enone **1** was not susceptible to nucleophilic epoxidation, it was subjected to conditions for dihydroxylation.[5] Contrary to the electronic predisposition of the system, osmium tetroxide mediated dihydroxylation of **1** exclusively favored attack of the electron deficient olefin, presumably on the basis of steric hindrance around the C2-C3 alkene, to yield the crystalline diol **4** (mp = 169-170°C) in 89% yield as a single stereoisomer (Scheme 2). Combustion analysis and the appearance of an infrared absorbance at 3400 $cm^{-1}$ confirm the presence of the diol functionality. The retention of two olefinic resonances in the $^1H$ NMR at δ 5.98 (dd, $J$ = 9.6, 6.9 Hz, 1H) and 5.70 (d, $J$ = 9.8 Hz, 1H) corresponding to the C8-C9 olefin supports the chemoselectivity of the dihydroxylation. Remarkably, the olefin **4** and its corresponding acetonide or cyclic carbonate derivatives were inert to stoichiometric quantities of osmium tetroxide at high pressures and temperature (100°C, 16 kbar) or neat bromine. We surmised that conversion of the diol **4** to the desired glycidic epoxide **7** might be facilitated by participation of the axially oriented C15 carbomethoxy moiety which, *via* the intermediacy of the methoxycarbenium ion **5**, could allow for a double inversion mechanism in the activation of the C8 hydroxyl. Thus, whereas treatment of **4** with triflic anhydride in a dealkylating media such as

pyridine provides the product of dealkylative lactonization **5**, in the absence of a dealkylating agent internal attack of the vicinal C9 hydroxyl predominates to afford the glycidic epoxide **7** in 88% yield. The structural assignment of **7** is verified by its conversion to the picrotoxane degradation product β-bromopicrotoxinic acid methyl ester (*vida supra*) (Scheme 2).

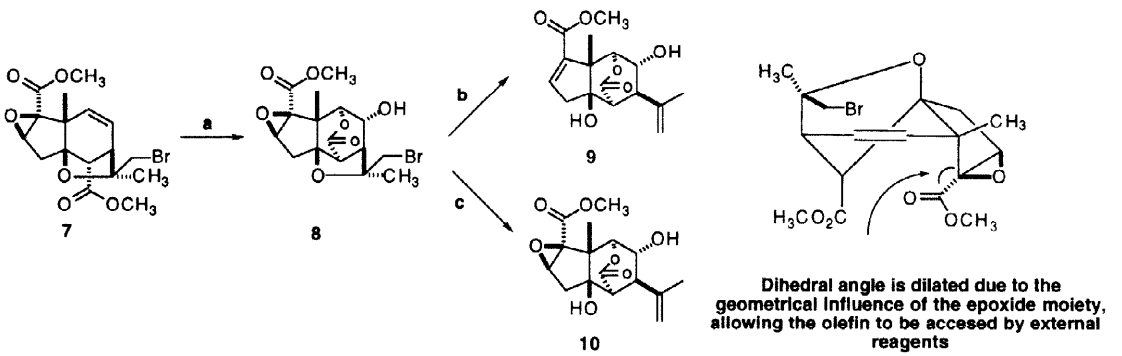



**Scheme 2.** Assistance of the C15 Carboxyl in the Formation of the Glycidic Epoxide 7

Reagents: a) $OsO_4$, Pyr, 25°C, 89%. b) $Tf_2O$, Pyr, 25°C, 89%. c) $Tf_2O$, DMAP, DCM, 25°C, 88%.

With the epoxy olefin **7** in hand, we reexamined the dihydroxylation of C2-C3 olefin and were pleased to observe the formation **8**, which is identical in all respects to β-bromopicrotoxinic acid methyl ester prepared *via* independent synthesis from picrotoxinin.[6] The presence of the bromoether bridge directs the π-facial selectivity of the dihydroxylation to exclusively favor attack of the olefin from its concave face with respect to the *cis*-hydrindane ring system. The spontaneous formation of the lactone confirms the introduction of the hydroxyl groups cis to the C-5 ester. The formation of a single isomeric monoester monolactone is consistent with the results of our degradation studies which demonstrate that β-bromopicrotoxinic acid methyl ester possesses the thermodynamic monoester monolactone configuration.[7] That the C2-C3 olefin of epoxide **7** is susceptible to dihydroxylation, while the corresponding olefin of diol **4** is not, may be rationalized in terms of the geometric influence of the glycidic epoxide. With the glycidic epoxide intact, the angle defined by C11-C1 and C9 becomes dilated relative to when the C8-C9 *cis*-vicinal diol functionality is present as in **4**, thus allowing the approach of external reagents. Zinc induced bromoether cleavage[8] of **8** was complicated by competitive deoxygenation[9] of the glycidic epoxide. Eventually, through modulation of the temperature and stoichiometry, conditions were determined that allowed access to either the desired glycidic monoester monolactone **10**, identical in all

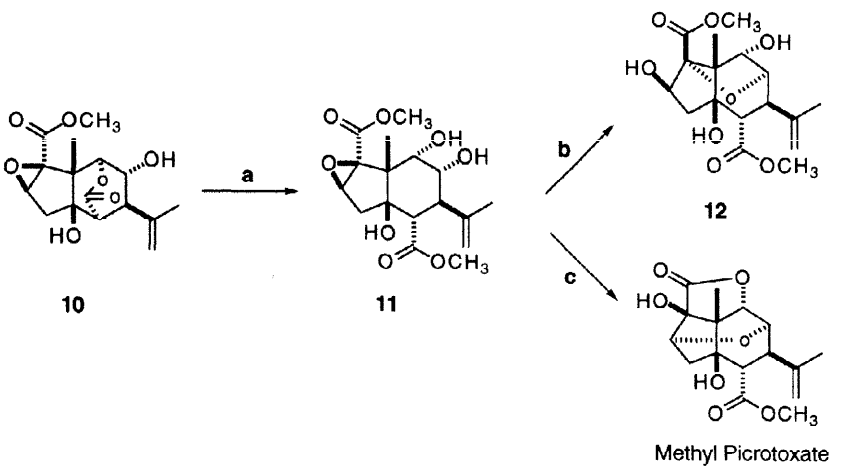
respects to α-picrotoxinic acid methyl ester prepared *via* independent synthesis from picrotoxinin,[10] or the corresponding deoxygenated compound **9** in 79% and 96% yields respectively (Scheme 3).




**Scheme 3.** Geometrical Influence of the Glycidic Epoxide in the Dihydroxylation of Epoxyolefin 7

a) $OsO_4$, Pyridine 70°C, 3 days, then $H_2S$, $CHCl_3$, 88%. b) Zinc dust, EtOH, AcOH, reflux, 96%. c) Zinc dust, MeOH, AcOH, 60°C, 79%.

In principal, the total synthesis of methyl picrotoxate may be achieved through the isomerization of **10**. This was realized in a two step procedure. Sodium cyanide catalyzed methanolysis of the lactone grouping[11] affords the diester **11** which is identical in all respects to dimethyl picrotoxinin dicarboxylate prepared independently from picrotoxinin.[12] Finally, base induced cyclization of **11** provides methyl picrotoxate in 73% yield, the structure of which was confirmed *via* x-ray crystallographic analysis (Figure 2).[13] Interestingly, attempted acid promoted cyclization led to the formation of the regioisomeric product of epoxide ring opening, tetrahydrofuran **12**. The disappearance of the characteristic C8 glycidic methine resonance at δ 4.43 (dd, $J_1 = J_2 = 3.0$ Hz, 1H) in the $^1$H NMR and retention of two methyl ester resonances at δ 3.90 and 3.67 indicate the formation of **12**. The regiochemical outcome of the acid and base induced cyclizations derives *via* differential stabilization of the leaving group. In basic aprotic media the C3 alkoxide attacks at C8 such that the developing alkoxide leaving group is stabilized in a cyclic metal chelate with the ester. In acidic protic media, protonation of the epoxide precedes attack and internal coordination is not needed because the leaving group may be solvated externally (Scheme 4). The activating influence of a carbonyl group with respect to $S_N2$ displacements then controls the regioselectivity of the epoxide ring opening.




**Scheme 4.** Regiochemistry in the Cyclization-Epoxide Opening of Epoxytriol **11**

a) MeOH, 50°C, 52% Catalytic KCN. b) TsOH, PhH, reflux, 57%. c) KH, THF, 0°C, 73%

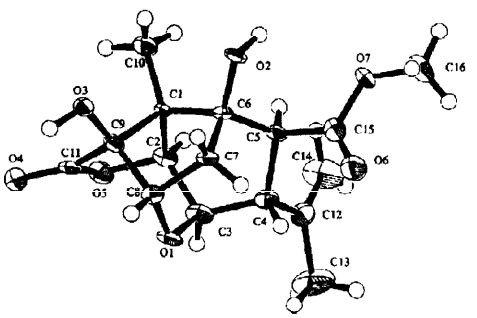



**Figure 2.** X-Ray Structure of Methyl Picrotoxate

Through the use of the palladium catalyzed enyne cycloisomerization reaction we have achieved the most rapid entry to the bicyclic core of the picrotoxane skeleton to date. Conditions for cycloisomerization are sufficiently mild to allow high levels of functionality to be tolerated in our cyclization substrates such that each carbon of the core structure can be modified to permit entry to the myriad forms comprising the picrotoxane family. The total syntheses of dendrobine, picrotoxinin, picrotin, corianin and methyl picrotoxate illustrate this point. The occurrence of natural products possessing the picrotoxane skeleton and exhibiting similar biological activities is

noted in an increasingly diverse range of plant, animal, terrestrial and marine life. Such ubiquitous distribution in such a diverse range of organisms underscores the fundamental role of the picrotoxanes in neurochemistry. Our efforts in this field are now directed toward extending our synthetic approach toward the recently discovered family of picrotoxane diterpenes, the picrodendrins.[14] Picrodendrin Q is the most potent picrotoxane to date. With $IC_{50}$ values of 0.0075-6.0 μM for the inhibition of specific binding of [$^{35}$S]*t*-butylbicyclophosphorothionate to rat brain cell membranes, picrodendrin Q is 27 fold more potent than picrotoxinin.[15]

## EXPERIMENTAL SECTION

### Synthesis of Methyl Picrotoxate, β-Bromopicrotoxic Acid Methyl Ester, α-Picrotoxinic Acid Methyl Ester and Dimethyl Picrotoxinin Dicarboxylate

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 Still.[16] 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 tetramethylsilane. 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.

**(1R, 3R, 4S, 5R, 8R, 9S, 11S)-9-bromomethyl-4,11-dicarbomethoxy-3,4-dihydroxy-5,9-dimethyl-10-oxotricyclo[6,2,1,$0^{1,5}$]undec-6-ene, 4**

To a solution of diester diene **1** (92 mg, 0.24 mmol, 100 mol%) in pyridine (2.5 mL, 0.1 M) at room temperature was added osmium tetroxide (122 mg, 0.48 mmol, 200 mol%). The reaction mixture was allowed to stir for 20 h. at which point the reaction mixture was evaporated and the residue dissolved in (4:1) methanol-water. Sodium bisulfite (1.0 g) was added and the methanolic solution was heated to 70°C for 1 h. The reaction mixture was partitioned between dichloromethane and water and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$) and evaporated to give the crystaline diol **4** (90 mg, 0.21 mmol) in 89% yield. Material prepared by this protocol was pure by $^1H$ NMR. The diol **4** may be recrystallized from chloroform-hexane to give clear needles. $R_f$ = 0.3 (50% EtOAc in hexane). Mp = 169-172°C. $[\alpha]_D$ = -77.3° (0.59% in $CH_2Cl_2$). IR (neat): 3400, 1739, 1436, 1267, 1023 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ 5.97-6.02 (A part of ABX system, dd, *J* = 6.9, 9.6 Hz, 1H), 5.68-5.71 (B part of ABX system, d, *J* = 9.8 Hz, 1H), 4.89-4.94 (dd, *J* = 7.3, 10.3 Hz, 1H), 3.66 (s, 6H), 3.54-3.56 (A part of AB system, d, *J* = 9.5 Hz, 1H), 3.33-3.35 (B part of AB system, d, *J* = 9.5, 1H), 3.21 (d, *J* = 2.7 Hz, 1H), 2.79-2.81 (dd, *J* = 3.0, 6.9 Hz, 1H), 2.41-2.46 (A part of ABX system, dd, *J* = 7.3, 13.0 Hz, 1H), 2.14-2.21 (B part of ABX system, dd, *J* = 10.6, 13.0 Hz, 1H), 1.44 (s,3H), 1.09 (s, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 173.5, 169.7, 133.1, 125.9, 88.8, 84.2, 81.3, 69.8, 54.9, 54.6, 52.4, 51.8, 44.6, 39.6, 38.1, 25.7, 19.5. Anal.: Calc'd for $C_{17}H_{23}O_7Br$: C, 48.70%; H, 5.53%. Found: C, 48.80%, H, 5.61%.

**1R, 3R, 5S, 6R, 9R, 10S, 12S)-10-bromomethyl-5,12-dicarbomethoxy-6,10-dimethyl-4,11-dioxotetracyclo[7,2,1,$0^{1,6}$, $0^{3,5}$]dodec-7-ene, 7**

To a solution of the diol **4** (41 mg, 0.097 mmol, 100 mol%) in dichloroethane (977 μL, 0.1 M) at room temperature was added dimethylaminopyridine (59.6 mg, 0.488 mmol, 500 mol%) followed by triflic anhydride (21 μL, 0.12 mmol, 130 mol%). The reaction vessel was placed in a 70°C oil bath and the reaction mixture was allowed to stir for 2 h. at which point the reaction mixture was charged onto a column of silica gel ($SiO_2$; 20→30% ethyl acetate in hexane). The

glycidic ester **7** (34.6 mg, 0.085 mmol) was obtained in 88% yield as a colorless oil. $R_f$ = 0.5 (40% EtOAc in hexane). $[\alpha]_D$ = -69.9° (1.0% in $CDCl_3$). IR (neat): 2982, 1740, 1437, 1040 $cm^{-1}$. $^1H$ NMR (400 MHz, $d^6$-benzene): δ 6.26 (A part of ABX system, d, *J* = 9.5 Hz, 1H), 6.02 (B part of ABX system, dd, *J* = 7.8, 9.7 Hz, 1H), 3.91 (d, *J* = 3.7 Hz, 1H), 3.36 (s, 3H), 3.33 (A part of AB system, d, *J* = 9.5 Hz, 1H), 3.29 (s, 3H), 3.05 (B part of AB system, d, *J* = 9.52 Hz, 1H), 2.84 (d, *J* = 3.4 Hz, 1H), 2.69 (dd, *J* = 3.4, 6.7 Hz, 1H), 2.1 (A part of ABX system, d, *J* = 14.0 Hz, 1H), 1.95 (B part of ABX system, dd, *J* = 3.7, 14.3 Hz, 1H), 1.23 (s, 3H), 1.21 (s, 3H). $^{13}$NMR (100 MHz, $d^6$-benzene): δ 169.2, 167.9, 134.0, 125.7, 95.6, 85.6, 66.3, 63.2, 56.4, 51.4, 51.3, 48.6, 44.2, 38.4, 35.7, 25.4, 18.6. Mass Spec.: 402(1.8), 400(1.9), 264(36.6), 249(24.0), 205(61), 145(100). HRMS: Calc'd for $C_{17}H_{21}Br^{81}O_6$: $[M^+]$ = 402.0501: Found: 402.0504.

**β-Bromopicrotoxinic Acid Methyl Ester, 8**

To a pyridine solution (500 μL, 0.04 M) of the glycidic ester **7** (7.5 mg, 0.018 mmol, 100 mol%) was added osmium tetroxide (47 mg, 0.18 mmol, 1000 mol%). The reaction vessel was placed in a 70°C oil bath and allowed to stir for 3 days at which point the reaction mixture was evaporated and the residue dissolved in chloroform. The chloroform solution was placed under an atmosphere of $H_2S$ (1 atm) and allowed to stir for 10 min. The solution was filtered through a plug of celite with the aid of ethyl acetate, evaporated and chromatographed ($SiO_2$; 30-50% ethyl acetate in hexane). The title compound **8** was obtained in 40% yield (3.0 mg) as a colorless oil along with 55% recovered starting material (4.1 mg) to give an overall 88% yield based on recovered starting material. $R_f$ = 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* = 1.9 Hz, 1H), 3.74 (s, 3H), 3.48 (A part of AB system, d, *J* = 11.4 Hz, 1H), 3.40 (B part of AB system, d, *J* = 10.7 Hz, 1H), 3.20 (d, *J* = 3.6 Hz, 1H), 2.46 (d, *J* = 4.1 Hz, 1H), 2.24-2.30 (B part of ABX system, dd, *J* = 3.0, 15.3 Hz, 1 H), 2.17 (A part of ABX system, d, *J* = 15.34 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). HMRS: Calc'd for $C_{16}H_{19}Br^{81}O_7$: $[M^+]$ = 404.0294: Found: 404.0293.

**α-Picrotoxinic Acid Methyl Ester, 10**

To a solution of bromoether **8** (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 **10** 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* = 2.4, 1H), 3.75 (s, 3H), 3.12 (d, *J* = 2.3 Hz, 1H), 2.45 (bs, 1H), 2.35-2.41 (A part of ABX system, dd, *J* = 2.4, 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, 44.8, 22.4, 13.5. Anal.: Calc'd for $C_{16}H_{20}O_7$: C, 59.25%; H, 6.21%. Found: C, 59.10%, H, 6.19%.

**Dimethyl Picrotoxinindicarboxylate, 11**

To a methanolic solution (5.5 mL, 0.05 M) of **10** (90.0 mg, 0.277 mmol, 100 mol%) was added potassium cyanide (3.6 mg, 0.055 mmol, 20 mol%). The reaction vessel was placed in a 50°C oil bath and allowed to stir for 5.5 hours at which point the reaction mixture was absorbed onto silica and chromatographed ($SiO_2$; 30→40% ethyl acetate in hexane) to afford the title compound **11** (51.3 mg, 0.144 mmol) in 52% yield a white crystalline solid. $R_f$ = 0.5 (60% EtOAc in hexane). Mp = 189-191°C. $[\alpha]_D$ = 33.5° (2.3% in ethanol). IR (neat): 3525, 3450, 2948, 1725, 1436 $cm^{-1}$. $^1H$ NMR (400 MHz, $s^6$-acetone): δ 4.79 (s, 1H), 4.71 (s, 1H), 4.30 (dd, $J_1 = J_2$ = 3.0 Hz, 1H), 4.01 (s, 1H), 3.87 (d, *J* = 3.3 Hz. 1H), 3.77 (m, 1H), 3.70 (s, 3H), 3.65 (d, *J* = 6.2 Hz, 1H), 3.51 (s, 3H), 3.07 (s, 1H), 2.84 (s, 1H), 2.73 (A part of AB system, d, *J* = 15.0 Hz, 1H), 2.68 (m, 1H), 1.92 (B part of AB system, d, *J* = 15.0 Hz, 1H) 1.72 (s, 3H), 1.61 (s, 3H). $^{13}C$ NMR (75 MHz, $d^6$-acetone): δ 172.5, 168.2, 144.2, 114.9, 79.4, 75.7, 69.4, 67.4, 64.3, 52.2, 51.7, 51.0, 50.8, 46.1, 38.7, 18.6, 13.6. Mass Spec.: 356(0.4), 338(10.2), 167(34.2), 151(34.1), 140(100), 126(99.4), 95(69.5). HMRS: Calc'd for $C_{17}H_{24}O_8$: $[M^+]$ = 356.1471. Found: 356.1475.

**Methyl Picrotoxate**

To a flask charged with potassium hydride (7.6 mg, 0.189 mmol, 250 mol%) was added a THF solution (750 μL, 0.1 M) of triol **11** (27.0 mg, 0.0757 mmol, 100 mol%) at 0°C. The reaction mixture was allowed to stir for 30 min. at which point half-saturated $NH_4Cl_{(aq)}$ was added and the aqueous solution was extracted with ether. The combined ethereal extracts were evaporated onto silica and chromatographed ($SiO_2$; 30→40% ethyl acetate in hexane) to give methyl picrotoxate (18 mg, 0.138 mmol) in 73% yield as an opaque film. $R_f$ = 0.3 (60% EtOAc in

hexane). $[\alpha]_D$ = 74.8° (1% in $CH_2Cl_2$). IR (neat): 3446, 2955, 1793, 1731, 1646, 1439 1114 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 4.93 (s, 1H), 4.86 (s, 1H), 4.26 (d, *J* = 2.4 Hz, 1H), 4.11 (d, *J* = 3.6 Hz, 1H), 3.86 (d, *J* = 2.2 Hz, 1H), 3.75 (s, 3H), 3.10 (A part of ABX system, d, *J* = 14.8 Hz, 1H), 3.08 (A part of AB system, d, *J* = 11.3 Hz, 1H), 2.77 (B part of AB system, d, *J* = 11.3 Hz, 1H), 2.14-2.20 (B part of ABX system, dd, *J* = 3.9, 14.0 Hz, 1H), 1.81 (s, 3H), 1.25 (s, 3H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 175.9, 173.2, 141.6, 112.8, 85.5, 81.7, 80.3, 79.6, 72.7, 58.1, 52.4, 47.8, 47.0, 43.0, 22.1, 10.3. Mass Spec.: 324(13.9), 306(6.0), 293(12.9), 139(29.1), 127(100), 111(45.8), 95(49.0), 82(97.2). HRMS: Calc'd for $C_{16}H_{20}O_7$: $[M^+]$ = 324.1209. Found: 324.1213.

**Preparation of Furan, 12**

To a solution of dimethyl picrotoxinin dicarboxylate **11** (30 mg, 0.084 mmol, 100 mol%) in benzene (1.7 mL, 0.05 M) was added *p*-toluenesulfonic acid (1.6 mg, 0.008 mmol, 10 mol%). The reaction mixture was allowed to gently reflux for a period of 5 h. at which point the reaction mixture was evaporated onto silica gel. Column chromatography ($SiO_2$; 60→70% ethyl acetate in hexane) afforded the cyclic ether **12** (17.0 mg, 0.048 mmol) as a crystalline solid in 57% yield. $R_f$ = 0.2 (50% ethyl acetate in hexane). Mp = 165-178°C. $[\alpha]_D$ = 29.6° (1.4% in ethanol). IR (neat): 3500, 2952, 1735, 1648, 1437, 1012, 732 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ 4.99 (bs, 1H), 4.96 (bs, 1H), 4.42 (d, *J* = 2.7 Hz, 1H), 4.32 (bs, 1H), 3.90 (s, 3H), 3.67 (s, 3H), 3.51 (bd, *J* = 8.7 Hz, 1H), 3.11 (d, *J* = 15.3 Hz, 1H), 2.75 (m, 2H), 2.10 (dd, $J_1$ = 15.3, $J_2$ = 2.1 Hz, 1H), 1.78 (s, 3H), 1.11 (s, 3H). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ 172.2, 172.1, 141.4, 116.7, 87.4, 80.2, 78.6, 78.3, 68.4, 53.4, 53.1, 51.7, 48.7, 48.1, 43.0, 18.4, 7.2. Mass Spec.: 356(31.5), 338(33.9), 279(23.6), 209(34.7), 153(48.7), 111(81.7), 95(100). HRMS: Calc'd for $C_{17}H_{24}O_8$: $[M^+]$ = 356.1471. Found: 356.1460.

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

To an ethanolic solution (13.2 mL, 0.1 M) of β-bromopicrotoxinic acid methyl ester **8** (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 aqueous layer was extracted and the combined extracts were dried ($MgSO_4$), filtered and evaporated to give the enoate "deoxy-α-picrotoxinic acid" **9** (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, $J_1 = 20.0$, $J_2 = 2.8$ 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). HMRS: Calc'd for $C_{16}H_{20}O_6$: $[M^+]$ = 308.1260. Found: 308.1261.

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## REFERENCES

1. Trost, B.M.; Krische, M.J. *J. Am. Chem. Soc.* **1996**, *118*, 233.
2. Trost, B.M.; Tasker, A.S.; Ruther, G.; Brandes, A. *J. Am. Chem. Soc.* **1991**, *113*, 670.
3. Conroy, H. *J. Am. Chem. Soc.* **1957**, *79*, 5550.
4. Sharma, N; Rambabu, M.; Sranjaneyulu, A. *Indian J. Chem.* **1987**, *26b*, 189.
5. Schroder, M. *Chem. Rev.* **1980**, *80*, 187.
6. Horrmann, P. *Ber.* **1913**, *46*, 2793. For β-bromopicrotoxinic acid see: Meyer, R.J.; Bruger, P. *Ber.* **1898**, *31*, 2958.
7. Krische, M.J.; Trost, B.M. manuscript in preparation.
8. House, H.O.; Ro, R.S. *J. Am. Chem. Soc.* **1957**, *80*, 182.
9. Sharpless, K.B. *J. Chem. Soc. Chem. Commun.* **1970**, 1450. Horrmann, P. *Ber.* **1913**, *46*, 2793.
10. Horrmann, P. *Ber.* **1913**, *46*, 2793.
11. Mori, K.; Tominaga, M.; Takigawa, T.; Matsui, M. *Synthesis* **1973**, 790.
12. Hormann, P. *Ann.* **1916**, *411*, 273.
13. X-Ray crystallographic analysis performed by Professor Dan Stack.
14. Picrodendrins C and D: Ohmoto, T.; Koike, K.; Fukuda, H.; Mitsunaga, K.; Ogata, K.; Kagei, K. *Chem. Pharm. Bull.* **1989**, *37*, 2988. Picrodendrins E, F, and I: Koike, K. Ohmoto, T.; Kawai, T.; Sato, T. *Phytochemistry* **1991**, *30*, 3353. Picrodendrins B,G,

and J: Koike, K.; Fukuda, H.; Mitsunaga, K.; Ohmoto, T. *Chem. Pharm. Bull.* **1991**, *39*, 934. Picrodendrins K-R: Suzuki, Y.; Koike, K.; Ohmoto, T. *Phytochemistry* **1992**, *31*, 2059. Picrodendrins S and T: Koike, K.; Suzuki, Y.; Ohmoto, T. *Phytochemistry* **1994**, *35*, 701. Picrodendrins U, V and W: Nagahisa, M.; Koike, K.; Narita, M.; Ohmoto, T. *Tetrahedron* **1994**, *50*, 10859.

15. Ozoe, Y.; Hasagawa, H.; Mochida, K.; Koike, K.; Suzuki, Y.; Nagahisa, M.; Ohmoto, T. Biosci. Biotech. Biochem. **1994**, *58*, 1506.
16. Perrin, D.D.; Armarego, W.L.F. *Purification of Laboratory Chemicals*, 3rd Ed. Permagon Press: New York, **1988**.