Total Synthesis of (–)-Picrotoxinin

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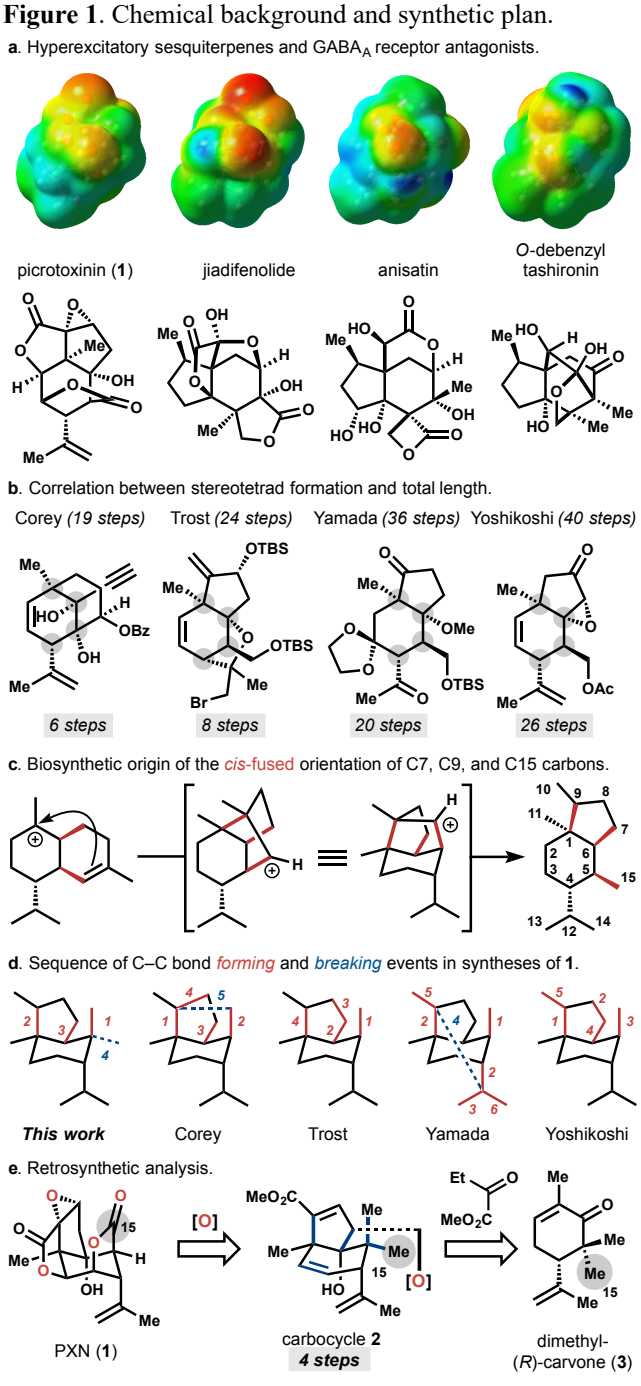
Supporting Information Placeholder

We report a concise, stereocontrolled synthesis of the neurotoxic sesquiterpenoid, (–)-picrotoxinin (**1**, PXN). The brevity of the route owes to regio- and stereoselective formation of the [4.3.0] bicyclic core by incorporation of a symmetrizing geminal dimethyl group at C5. A series of strong C–C and C–H bond oxidations convert the C5 *gem*-dimethyl group to the C15 lactone of PXN. This counterintuitive strategy features the first example of demethylation (C–C bond cleavage) in total synthesis.

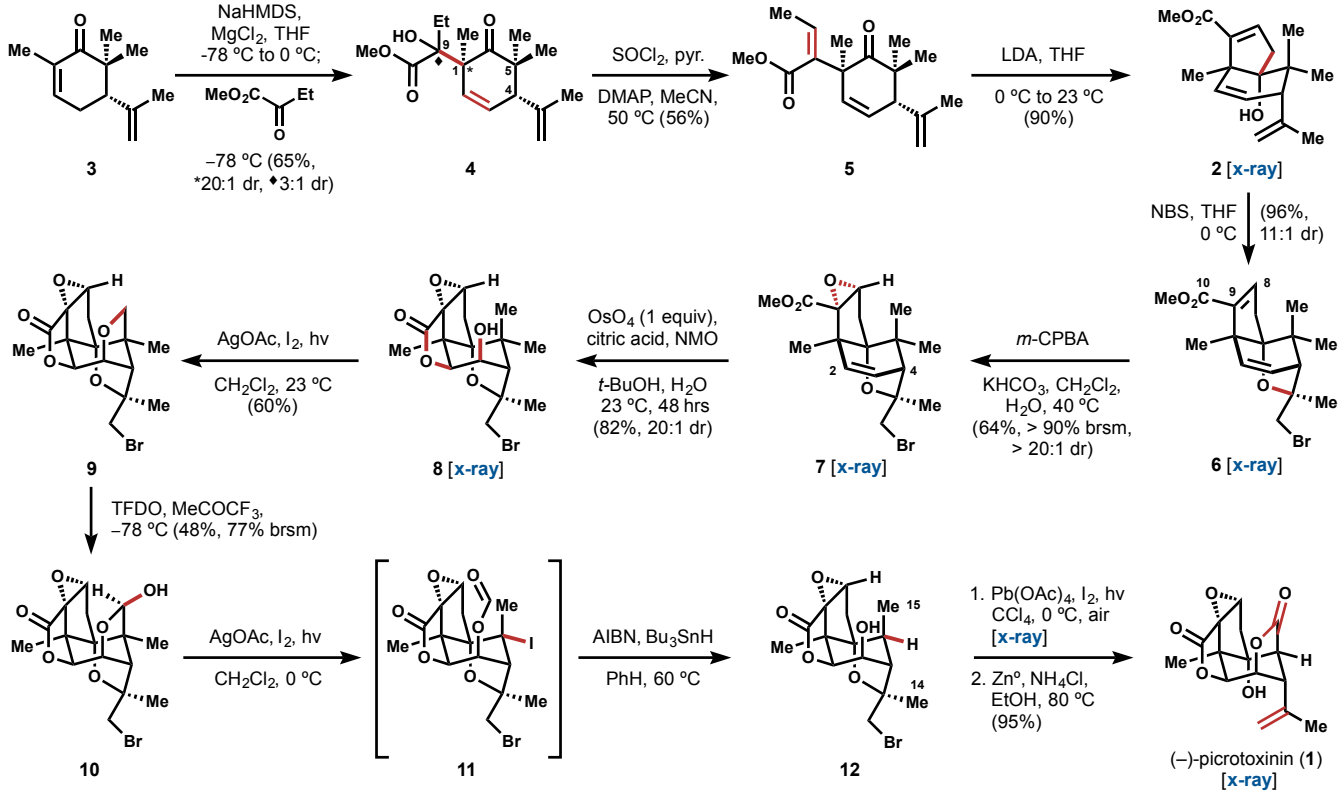
Picrotoxinin (**1**, PXN) is the flagship member of the picrotoxane family of natural products and continues to attract considerable attention from the synthesis community[1–8] due to its stereochemically-dense polyoxygenated structure and its use as a tool compound in neuroscience.[9–11] Picrotoxin (PTX), which consists of an equimolar mixture of PXN and its less-active C12 hydrate, picrotin (PTN), can exhibit useful therapeutic properties: chronic dosing of Down's syndrome model mice (Ts65Dn) normalizes memory performance by reducing overactivity of GABAergic neurons.[12] However, the therapeutic window of PTX is narrow: lethal convulsion through hyperexcitatory $GABA_A$ receptor antagonism occurs at low dose (LD_{50} = 2 mg/kg, rat, I.P.).[13] In contrast, $GABA_AR$ antagonists like bilobalide[14] can share the therapeutic properties, target, and binding site of PXN yet avoid acute toxicity.[15] Our group has identified 'neurotrophic' sesquiterpenes jiadifenolide[16] and *O*-debenzyltashironin[17] as sharing the hyperexcitatory effects of convulsant $GABA_AR$ antagonists anisatin[17] and PXN, yet jiadifenolide displays no convulsive signature in mice (Figure **1a**).[15,18] A short synthetic route might allow interrogation of analogs of PXN that similarly reduce its toxicity yet still antagonize $GABA_A$ receptors.

The seminal work of Corey,[1,2] Yamada,[3] Yoshikoshi,[4] and Trost[5–7] illustrated the difficulty of the *contiguous stereotetrad* of **1** (Figure **1b**). Intermolecular formation of this stereo-dense motif is challenged by the *cis*-fused orientation of the C7, C9, and C15 carbons, which arises biosynthetically by an anti-Markovnikov cationic cyclization of a cadinyl cation and oxidative cleavage (Figure **1c**).[19] Corey[1] and Yamada[3] employed intramolecular cyclization/C–C oxidative cleavage steps to overcome this problem, while Trost[5–7] leveraged torsional strain with a small nucleophile to set the C7/C15 stereodiad and a palladium-catalyzed cyc-

Figure 1. Chemical background and synthetic plan.



Scheme 1. Synthesis of (–)-picrotoxinin (PXN, **1**).

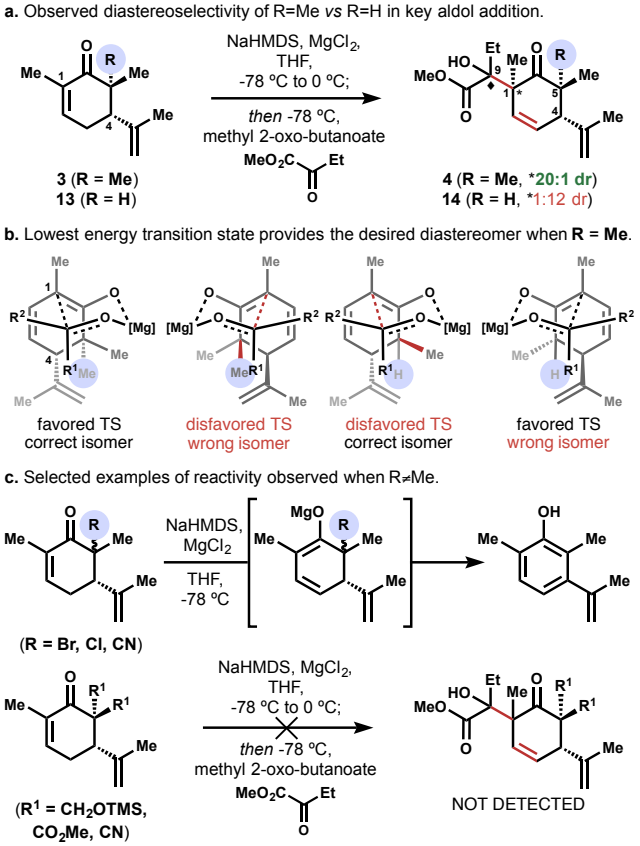


loisomerization to make the C7/C9 junction. Yet all syntheses concede some C–C disconnections within and about the [4.3.0]-bicyclononane, rather than directly accessing the core by disconnections solely between the [4.3.0] ring junctions (Figure **1d**). We found brevity of stereotetrad formation in the literature to correlate with overall synthesis length (Figure **1b**). Disconnections solely between the junctions of the bicyclic core should then promote a shorter synthesis of **1**.

With this strategic goal in mind, we retrosynthetically decreased the oxidation state[20,21] of **1** to arrive at carbocycle **2**, which might derive from (*R*)-carvone[1,3,5,22] via annelation of methyl-2-oxo-butanoate (Figure **1e**). Our decision to decrease C15 to the methyl oxidation state was informed by problems encountered in the literature[4–7,9–11] with C10/C15 translactonization and intramolecular epoxide opening at higher oxidation states of C15. However, we quickly discovered that a single methyl group alone obstructed access to the *nor*-methyl-congener of **2** (see Figure **2a**). Instead, we found that geminal dimethylation enabled efficient synthesis of **2** in only 4 steps. The challenge then became discovery of a late-stage, stereoselective, cleavage of a strong C–C bond—a counterintuitive but, in this case, enabling tactic. Here we report its successful implementation in a concise synthesis of **1** (Scheme **1**).[23]

Dimethylation of (*R*)-carvone was achieved in one[24] or two[25] steps, although the latter procedure was employed on scale. The magnesium enolate of **3** was formed by deprotonation with NaHMDS in the presence of anhydrous $MgCl_2$; subsequent addition of methyl-2-oxobutanoate at -78 °C gave the aldol addition product **4** in 65% yield with excellent diastereoselectivity (>20:1) at C1 and inconsequential 3:1 diastereoselectivity at C9. Use of lithium, sodium, potassium, or zinc enolates gave diminished to no yield of **4**. The reaction was quenched at -78 °C to avoid retro-aldol decomposition that occurs above -20 °C. This unusual aldol reaction occurs with high regio- and diastereoselectivity to form a quaternary carbon (C1) and a neopentyl alcohol (C9). Our working model posits an efficient relay of stereochemical information from the C4 stereocenter to C1 by avoidance

Figure 2. Importance of the extra methyl group in **2**.



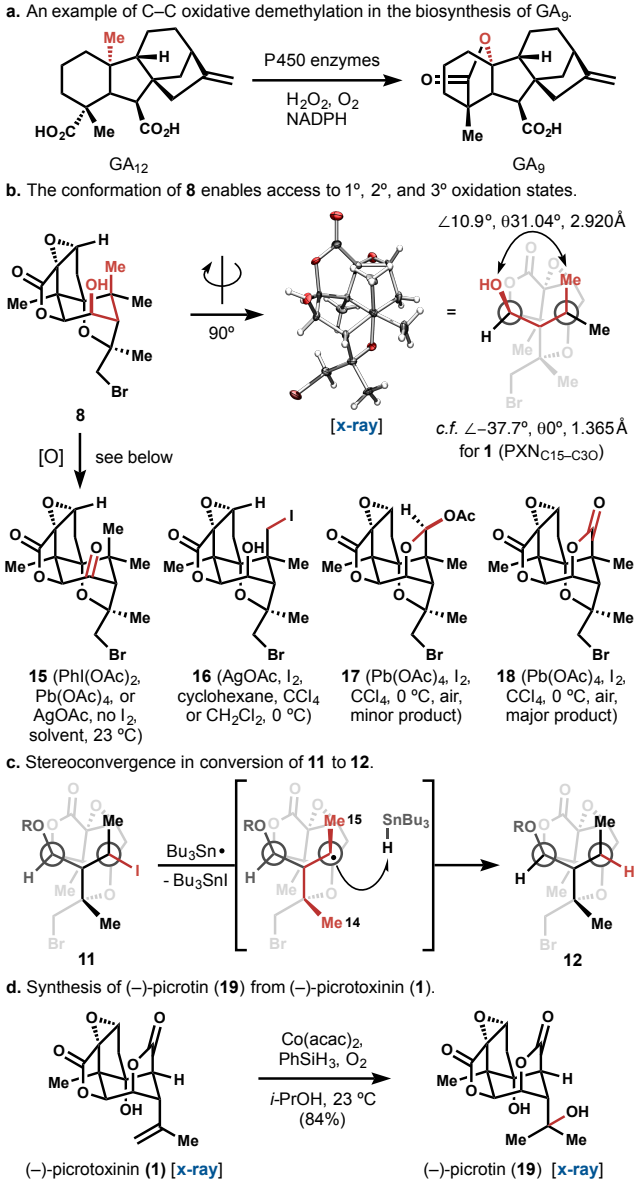
of a 1,3-diaxial interaction between the *axial* C5 methyl group and methyl-2-oxobutanoate in the aldol addition transition state (Figure **2b**). In contrast, use of *trans*-α-methylcarvone (**13**, *i.e.* mono methylation) resulted in a 1:12 diastereomeric mixture favoring the opposite and unproductive diastereomer (**14**). An extended enolate could not be formed with either (*R*)-carvone or *cis*-α-methyl-carvone, and use of Corey's hydrazone alkylation procedure[1] gave no aldol addition product.

Alternative tactics that replaced one of the methyls with Br, Cl, or CN groups were plagued by *poor stereocontrol in formation of the C5 stereocenter and subsequent failure* of the aldol addition reaction through proton-transfer, elimination and aromatization pathways (Figure **2c**). Symmetrical substitution at C5 with silylhydroxymethylene (R_3SiOCH_2-),[6] methyl ester, or nitrile groups required multiple steps for installation and the aldol addition reaction still failed. Since the inclusion of an extra C5 methyl group enabled installation of all 15 carbon atoms of the picrotoxinin skeleton with the correct regio- and stereochemistry in just two steps and without need for C5 stereocontrol, we continued forward with a plan to excise the extra C5 methyl group at a late stage—a risky, but ultimately successful decision.

Neopentyl alcohol **4** was converted to **5** by a $SOCl_2$-induced elimination.[26] These conditions proved uniquely able to eliminate both diastereomers of the sterically congested C9 alcohol **4**. A vinylogous intramolecular 5-*exo*-*trig* aldol addition reaction yielded **2** in 90% yield upon treatment of **5** with LDA at 0 ºC and warming to 23 ºC. This reaction failed with the alkene derived from **14** due to competitive deprotonation and epimerization pathways.

Facile and scalable access to **2** allowed extensive interrogation of the remaining alkene oxidations. First, bromoetherification[1,5,9] with NBS proved entirely selective for the isopropene group and delivered an 11:1 diastereomeric mixture of **6**. This dual-purpose bromoetherification served to protect the $\Delta^{12,13}$ isopropenyl alkene and lock the conformation of **2** to promote lactonization at C10 and directed oxidation of the C5 methyl groups. Epoxidation of **6** initially suffered poor diastereocontrol under nucleophilic epoxidation conditions (*e.g.* alkali metalperoxides) and low conversion with electrophilic epoxidation reagents (*e.g.* DMDO, trifluoroperacetic acid). Although *m*CPBA alone was insufficient to react with **6**, we found that use of $KHCO_3$ with *m*CPBA in a biphasic mixture of CH_2Cl_2 and H_2O at 40 ºC afforded **7** with high diastereoselectivity in 64% yield (90% brsm). We had anticipated that dihydroxylation of **7** might be facile by analogy with Yoshikoshi's OsO_4/pyridine oxidation of a similar substrate,[4] but no more than 30% conversion could be obtained under these conditions (OsO_4, pyridine). We eventually found that addition of citric acid to prevent off-pathway osmium sequestration[27] enabled full conversion of **7** to **8**. Steric congestion about the $\Delta^{2,3}$ alkene, however, slowed conversion such that one equivalent of OsO_4 still required 48 hours to elicit an 82% yield. This drawback was mitigated by excellent diastereoselectivity (>20:1) at C2 and C3 and spontaneous lactonization at C10. For comparison, the strong oxidant dimethyldioxirane reacted exclusively with the electron-deficient $\Delta^{8,9}$ alkene in **6** to provide **7**, which did not react further.

Figure 3. Further details and synthesis of (–)-picrotin (**19**).



Intermediate **8** set the stage to explore *gem*-dimethyl modification, including C–C bond cleavage. Geminal dimethyl groups predominate in terpenoids as a result of their biosynthesis from polyprenyl- (dimethylallyl) pyrophosphates.[28] Modification of *gem*-dimethyls, including their excision, can be effected with iron-oxo enzymes to produce biologically active scaffolds (Figure **3a**).[29] Similar demethylations have not been employed in chemical synthesis since abiotic routes are not often constrained by biosynthetic building blocks, and retrosynthetic addition of an extra carbon-bound methyl group is seldom simplifying.[30] In this example we found an exception to the rule.

Molecular modeling of **8** indicated that the strain conferred upon the cyclohexane core by the two fused and one bridged pentacycles causes the C3 alcohol to tilt about 11º away from a parallel orientation to the C15 methyl group, with a dihedral angle (θ) of 31º (Figure **3b**). This subtle shift in conformation places the C3 alcohol oxygen 2.920 Å (x-ray) away from the axial methyl group and means that ether formation is slow due to torsional strain in the transition state (*cf.* ∠-37.7º, θ0º, 1.365 Å (x-ray) for the C15 lactone C–O bond of PXN (**1**)). Consequently, it was possible to directly

access the primary (ether **9** or iodide **16**), secondary (acetal **17**), or tertiary (lactone **18**) oxidation states of the axial methyl group in **8** (Figure **3b**). These oxidation states were accessible by generating IOAc[31] with different reagents and temperatures, although acetal **17** was never formed as a major product (Figure **3b**). Thus, use of AgOAc/I_2 in cyclohexane at 23 ºC under ambient light provided the ether **9** in 60% yield, whereas the 1º iodide **16** was obtained at 0 ºC as the major product (Figure **3b**). Notably, ketone **15** formed readily in the absence of iodine and was observed as a persistent byproduct. Treatment of **9** with TFDO generated a single hemiacetal diastereomer since the outward-facing C–H bond is both less sterically hindered and experiences better hyperconjugative donation from the C3 ether oxygen than its inward-facing counterpart. Conditions for formation of **16** (AgOAc, I_2, CH_2Cl_2, 0 ºC) applied here led to Suárez fragmentation[32] in **10** of the adjacent strong C–C bond to form **11** stereoselectively. The tertiary iodide of **11** was removed with AIBN/Bu_3SnH to form a single isomer of **12** after removal of the formyl group with basic work-up. A plausible explanation for this stereochemistry is that Bu_3SnH is too large a hydrogen atom donor for hydrogen atom transfer (HAT) to occur at the convex face of C5. A 1,3-diaxial interaction between the C15 and C14 methyl groups in the transition state for HAT at the concave face would further destabilize this pathway (Figure **3c**). Finally, use of $Pb(OAc)_4/I_2$ in CCl_4 at 0 ºC under an aerobic atmosphere led directly to formation of the C15 lactone. Reduction with zinc cleaved the bromoether linkage of **12** to deliver (–)-picrotoxinin (**1**). Conversion to (–)-picrotin (**19**) occurred in one step and 84% yield by a Mukaiyama hydration, which had not been reported previously.[2,4,6,7]

In summary, we disclose a concise synthesis of (–)-picrotoxinin (**1**) using a symmetrizing *gem*-dimethyl that allowed efficient annelation to form the [4.3.0]-bicyclononane core. The key stereotetrad was accessed in only 4-5 steps from (*R*)-carvone and correlated to an overall short synthesis. The facile, stereoselective annelation to form **2** benefitted from symmetrizing dimethylation—allowing stereochemical relay from the C4 β-isopropene of carvone and obviating the need for stereocontrol at C5. A series of C=C, C–C, C–H oxidations were leveraged to access **1** in the shortest sequence to date. This route provides the first example, to our knowledge, of an oxidative C–C demethylation sequence applied in total synthesis.

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