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Communication

Synthesis of (−)-Picrotoxinin by Late-Stage Strong Bond Activation

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ABSTRACT: We report a concise, stereocontrolled synthesis of the neurotoxic sesquiterpenoid (−)-picrotoxinin (**1**, PXN). The brevity of the route is due to regio- and stereoselective formation of the [4.3.0] bicyclic core by incorporation of a symmetrizing geminal dimethyl group at C5. Dimethylation then enables selective C−O bond formation in multiple intermediates. A series of strong bond (C−C and C−H) cleavages convert the C5 *gem*-dimethyl group to the C15 lactone of PXN.

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] because of 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 ($GABA_AR$) antagonism occurs at low doses (LD_{50} = 2 mg/kg, rat, ip).[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 the "neurotrophic" sesquiterpenes jiadifenolide[16] and *O*-debenzyltashironin[17] as sharing the hyperexcitatory effects of the 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 analogues of PXN that similarly reduce its toxicity yet still antagonize $GABA_A$ receptors.[19]

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 stereodense 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 (see Supporting Information).[20,21] 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 classic palladium-catalyzed cycloisomerization to make the C1/C9 junction. Yet all syntheses concede some C−C disconnections within and about the bicyclo[4.3.0]nonane rather than directly accessing the core by disconnections solely *between* the [4.3.0] ring junctions (Figure 1c). We found brevity of stereotetrad formation in the literature to correlate with overall synthesis

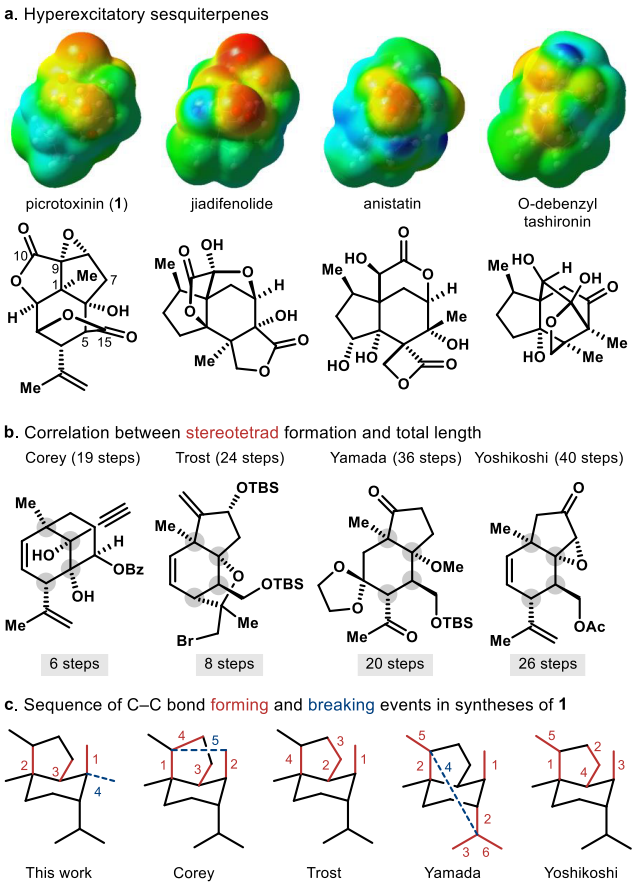

Figure 1. Chemical background and synthetic plan.

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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 encoded the oxidations of **1** with alkenes to arrive at carbocycle **2**, which might derive from (*R*)-carvone[1,3,5,22] via annulation of methyl 2-oxobutanoate (Figure 2). Most of the oxidation patterns were

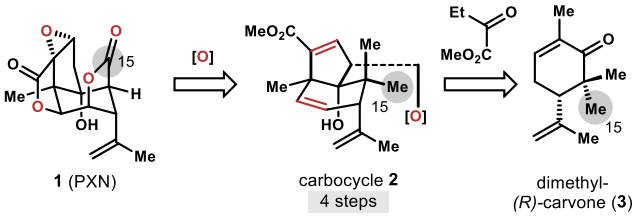

Figure 2. Chemical background and synthetic plan.

embedded into the starting materials,[23] with the exception of the C15 carboxylate. 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 on carvone led to the incorrect stereoisomer (**13** → **14**; see Figure 3a). Instead, we found that geminal dimethylation enabled the efficient synthesis of **2** in only four steps. The challenge then became discovery of a late-stage stereoselective cleavage of a strong C−C bond—a counterintuitive[24] but in this case enabling tactic. Here we report its successful implementation in a concise synthesis of **1** (Scheme 1).

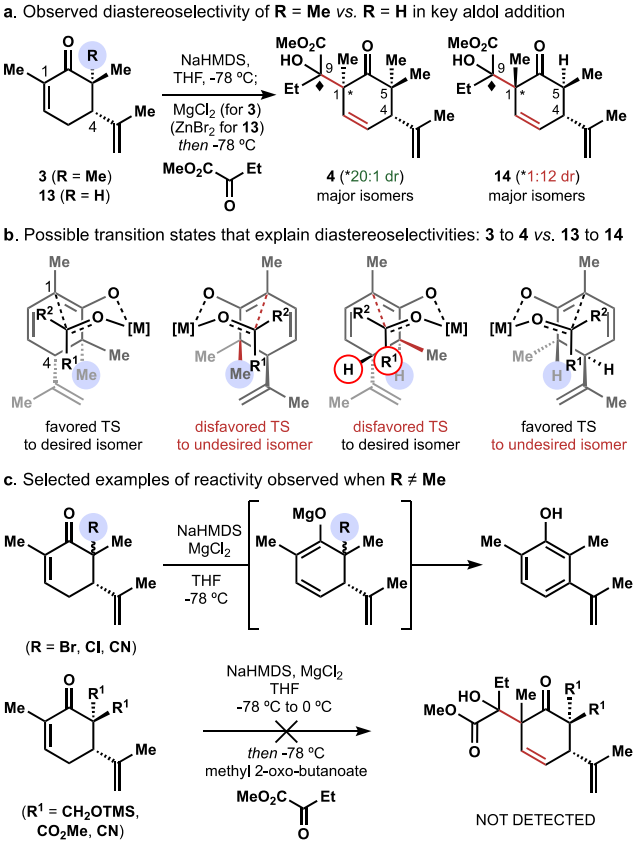

Figure 3. Importance of the extra methyl group in **2**.

Dimethylation of (*R*)-carvone was achieved in one[25] or two[26] steps, although the latter procedure was employed on a 30 g (200 mmol) 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 67% yield with excellent diastereoselectivity (>20:1) at C1 and inconsequential 3.3:1 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 of a 1,3-diaxial interaction between the axial C5 methyl group and methyl 2-oxobutanoate in the aldol addition transition state (Figure 3b). 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-methylcarvone, and use of Corey's hydrazone alkylation procedure[1] gave no aldol addition product.

Alternative tactics that replaced one of the Me groups with a Br, Cl, or CN group were plagued by poor stereocontrol in the formation of the C5 stereocenter and subsequent failure of the aldol addition through proton transfer, elimination, and aromatization pathways (Figure 3c). Symmetrical substitution at C5 with silylhydroxymethylene (R_3SiOCH_2-),[6] methyl ester, or nitrile groups required multiple steps for installation, and the aldol addition 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 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 $SOCl_2$-induced elimination.[27] 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 °C and warming to 23 °C. This reaction failed with the alkene derived from **14** because of 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 metal peroxides) 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 the use of $KHCO_3$ with *m*CPBA in a biphasic mixture of CH_2Cl_2 and H_2O at 23 °C afforded **7** with high diastereoselectivity in 84%

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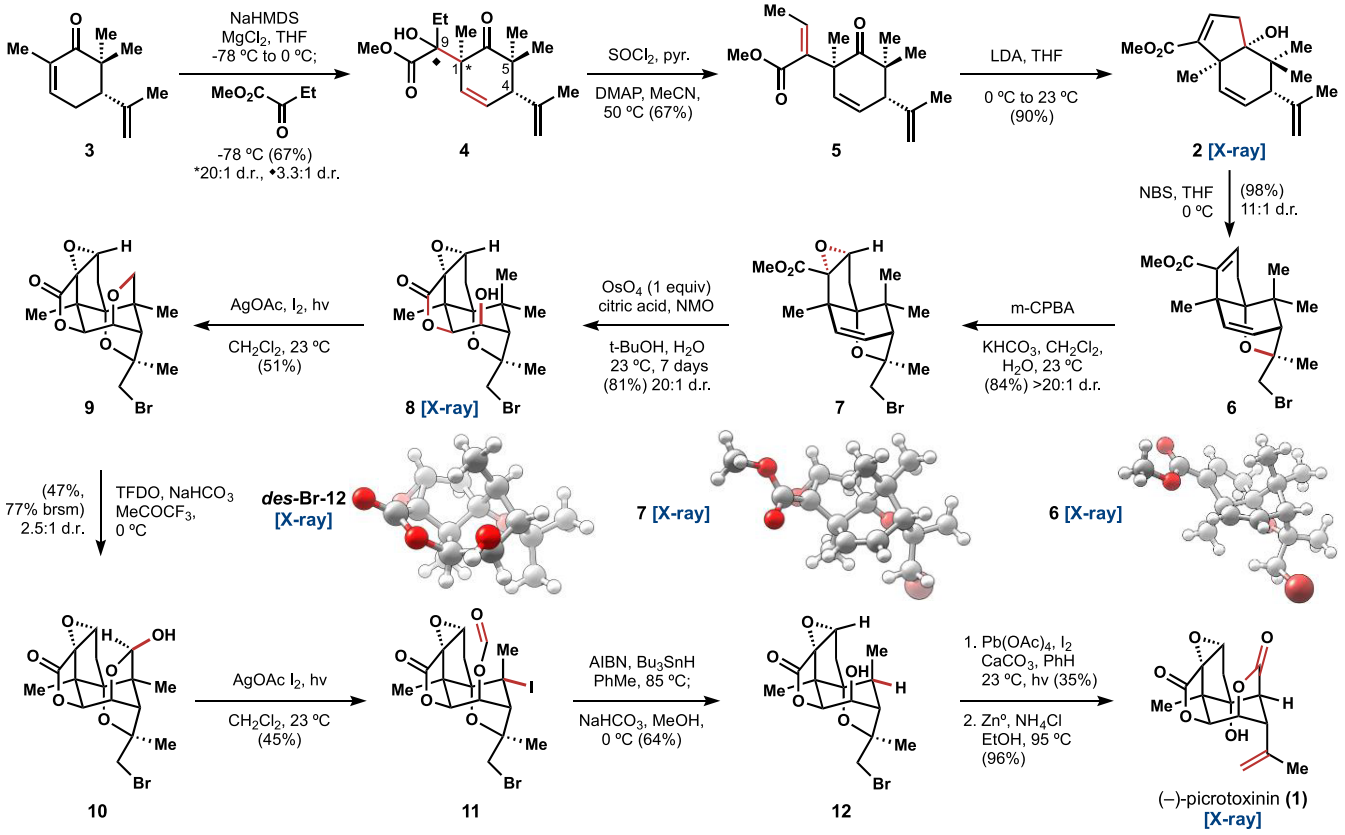
Scheme 1. Synthesis of (−)-Picrotoxinin (PXN, 1)



yield. 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 (stoichiometric OsO_4, pyridine). We eventually found that addition of citric acid to prevent off-pathway osmium sequestration[28] enabled full conversion of **7** to **8**. Steric congestion about the $\Delta^{2,3}$ alkene of **7**, however, slowed conversion, such that 1 equiv of OsO_4 still required 7 days to elicit an 81% yield.[29] 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.

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.[30] Modification of *gem*-dimethyls, including their excision, can be effected with iron−oxo enzymes to produce biologically active scaffolds (Figure 4a).[31] 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.[32] In this example we found an exception to the rule.

Molecular modeling, which was later confirmed by analysis of the crystal structure of **8**, indicated that the strain conferred upon the cyclohexane core by the one bridged and two fused pentacycles causes the C3 alcohol to tilt about 11° away from a parallel orientation to the C15 methyl group, with a dihedral angle (θ) of 31° (Figure 4b). This subtle shift in conformation places the C3 alcohol oxygen 2.920 Å (X-ray) away from the axial methyl group, such that ether formation is slow because of torsional strain in the transition state (cf. $\angle$ −37.7°, θ = 0°, 1.365 Å (X-ray) for the C15 lactone C−O bond of **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 4b). These oxidation states were accessible by generating IOAc[33] with different reagents and temperatures, although acetal **17** was never formed as a major product (Figure 4b). Thus, the use of AgOAc/I_2 in methylene chloride at 23 °C under ambient light provided ether **9** in 51% yield (Scheme 1), whereas 1° iodide **16** was obtained at 0 °C in cyclohexane as the major product (Figure 4b). Notably, ketone **15** formed readily in the absence of iodine and was observed as a persistent byproduct. Treatment of **9** with TFDO at 0 °C generated hemiacetal **9** as a 2.5:1 diastereomeric mixture, a distribution that may occur because the outward-facing C−H bond not only is less sterically hindered but also experiences better hyperconjugative donation from the C3 ether oxygen than its inward-facing counterpart. The same conditions for formation of **16** (AgOAc, I_2, CH_2Cl_2, 23 °C) applied here led to Suárez fragmentation[34] of the adjacent strong C−C bond in **10** to form **11** as a single stereoisomer. The tertiary iodide of **11** was removed with AIBN/Bu_3SnH to form a single isomer of **12** after cleavage of the formyl group in a basic workup. 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 concave 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 4c). Finally, the use of

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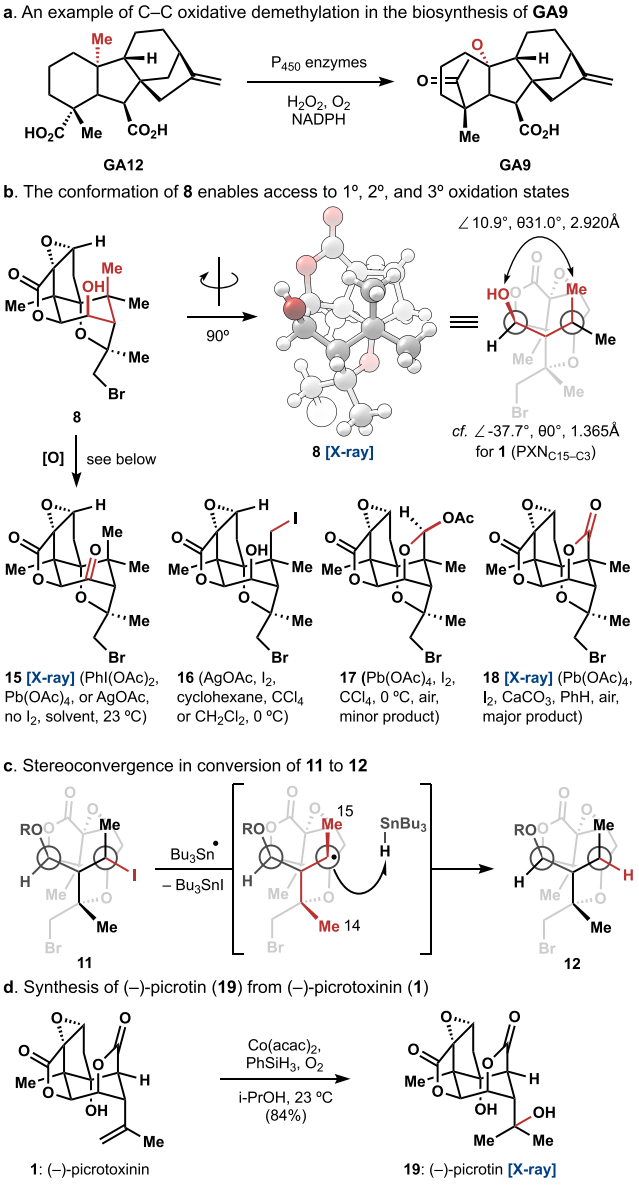

Figure 4. Further details and synthesis of (−)-picrotin (**19**).

$Pb(OAc)_4/I_2$ in benzene with $CaCO_3$ at 23 °C under an aerobic atmosphere led directly to the 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,[35] which had not been reported previously.[2,4,6,7]

Geminal dimethylation of carvone at C5 expedited forward entry to the carbocyclic core of PXN but revised our initial retrosynthesis, amounting to a "nonsense" methylation transform (**1** ⇒ **20** or **8**; see Figure 5) in search of a forward solution. The complexity of **1** versus **20** was not diminished by methylation since information content was added and no stereocenter was removed (C_m = 468 vs 480 mcbits).[36] Symmetrization of C5 in intermediate targets like **8**, however, greatly simplified entry into chemical space very close to **1**. Interestingly, 5-methylpicrotoxinin (**20**) retained modest antagonism of the $GABA_A$ receptor (IC_{50} = 9 μM vs [^{3}H]TBOB@rat cerebral cortex) and slightly improved upon the aqueous stability of **1** at pH 8, more than halving the pseudo-first-order rate constant.[37] Ongoing biological studies

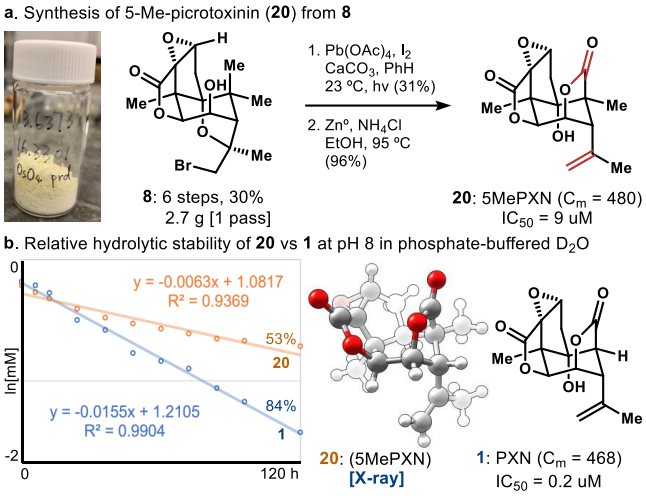

Figure 5. 5-Methylpicrotoxinin (**20**) is equal in complexity, more stable, and less antagonizing than picrotoxinin (**1**).

intended for this Communication that leveraged the quick entry into picrotoxinin chemical space (eight steps to **20**) have been delayed by recent events.

In summary, we have disclosed a concise synthesis of (−)-picrotoxinin (**1**) via incorporation of a symmetrizing *gem*-dimethyl moiety that allows efficient annulation to form the bicyclo[4.3.0]nonane core. The key stereotetrad was accessed in only four or five steps from (*R*)-carvone and correlated to an overall short synthesis. The facile stereoselective annulation to form **2** benefited from symmetrizing dimethylation, allowing stereochemical relay from the C4 *β*-isopropene of carvone and obviating the need for stereocontrol at C5. High oxidation states in the starting materials were encoded by unsaturation and 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. We aim to use this short entry into PXN chemical space to continue our probe of selectivity within the ligand-gated ion channel (LGIC) superfamily of receptors.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c05042.

CIF files (ZIP)

Materials and methods, details related to synthesis and experiments, X-ray data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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