## General Strategy for the Asymmetric Synthesis of the Picrotoxanes

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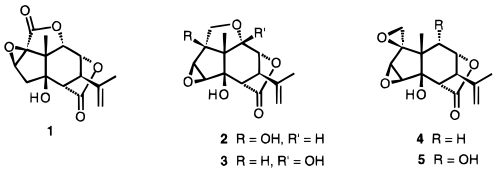
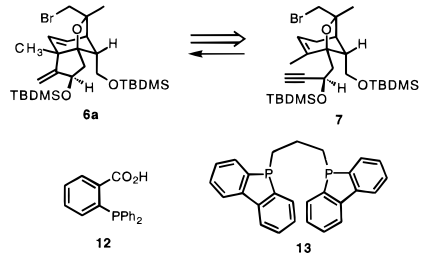
The important role of picrotoxinin (**1**) as a GABA antagonist has made it an invaluable tool for neurophysiology.[1] It is representative of a growing family of compounds represented by corianin (**2**), asteromurin A (**3**), coriamyrtin (**4**), tutin (**5**), and the novel structurally related picrodendrins, some of which show very similar biological functions.[2] The high potency of



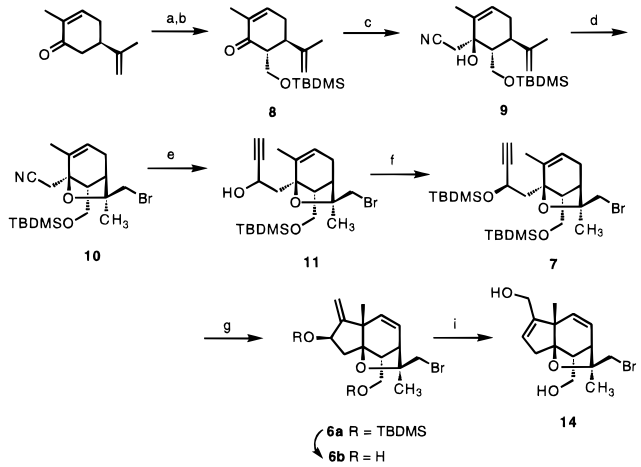

these compounds, the unusual pentacyclic structure, and the high density of functionality have made them challenging targets for synthesis.[3] In this communication, we develop a general strategy that provides flexibility to approach a number of members of this family. This strategy evolved from developments in metal-catalyzed Alder ene type reactions.[4]

Tricycle **6a** was envisioned to be a key intermediate since it possesses all of the carbons required and has appropriate functionality to adjust the oxidation level where needed to access each of the picrotoxanes illustrated. Its accessibility in enan-




tiopure form *via* an intramolecular Alder ene reaction from enyne **7** would provide a facile entry since the latter was readily available from carvone in seven steps as delineated in Scheme 1. The axial selectivity in the addition of the metalated acetonitrile to convert **8** to **9**, which sets the stereochemistry of

**Scheme 1.** Synthesis and Cyclization of Enyne **7**[a]




[a] (a) LDA, THF, −78 °C, $CH_2O$, 64%. (b) TBDMSCl, $C_3H_4N_2$, DMF, 60 °C, 95%. (c) $LiCH_2CN$, THF, −78 °C, 73%. (d) $C_5H_5N^+H$ $Br_3^-$, $C_5H_5N$, 0 °C, 96%. (e) (i) DIBAL-H, $PhCH_3$, −78 °C, workup with $NaHSO_4$, $H_2O$; (ii) HC≡CMgCl, THF, 0 °C. (f) TBDMSCl, $C_3H_4N_2$, DMF, 60 °C, 61% for steps e and f. (g) See text. (h) TBAF, THF, room temperature, 89%. (i) $SOCl_2$, $C_5H_5N$, ether, 0 °C, 66%; CsOAc, DMF, 60 °C, 79%; $K_2CO_3$, $CH_3OH$, room temperature, 97%.

the [6.5] ring junction, presumably derives from torsional strain rather than steric strain.[5] The addition of ethynylmagnesium chloride to the aldehyde generated from **10** gave a 2:1 diastereomeric mixture at the secondary alcohol **11**, a stereochemistry that is irrelevant with respect to the ultimate targets. Nonetheless, the minor epimer was converted to the major one using a Mitsunobu protocol so that **7** could be obtained diastereomerically pure.

Surprisingly, the protocol that effected smooth cycloisomerization of a related monocyclic enyne failed.[6] However, one of the advantages of transition metal catalyzed reactions stems from the prospect of tailoring the active site to overcome such failures. Using a variety of monodentate (i.e., $Ph_3P$ or $Ph_3As$) or bidentate [i.e., dppe or 2-(diphenylphosphino)benzoic acid (**12**)] ligands gave 20−37% yields of **6a**. A promising yield of 43% was obtained when the bidentate ligand dppe and a ligand that could internally deliver a proton, **12**, was employed. Assessing the difficulty as steric in nature because of the creation of a 1,3-diaxial interaction between the silyloxymethyl substituent and one of the cyclopentyl ring bonds, we designed the bis-phosphole ligand **13** that ties back the diphenylphosphino moiety, thereby opening up the catalytic active site. Indeed, the combination of **13** and an internal proton delivery system, **12**, with catalytic palladium acetate (DCE, 60 °C) gave a 70% yield of **6**. The latter was converted straightforwardly to the diol **14** as in Scheme 1.[7] Both alcohols were simultaneously oxidized[8] [$(COCl)_2$, DMSO, $(C_2H_5)_3N$, $CH_2Cl_2$, −78 °C; $NaClO_2$, $(CH_3)_2C{=}CHCH_3$, $NaH_2PO_4$, *t*-$C_4H_9OH$, 0 °C; $CH_2N_2$, ether, 0 °C, 79% overall] to the diester **15**.

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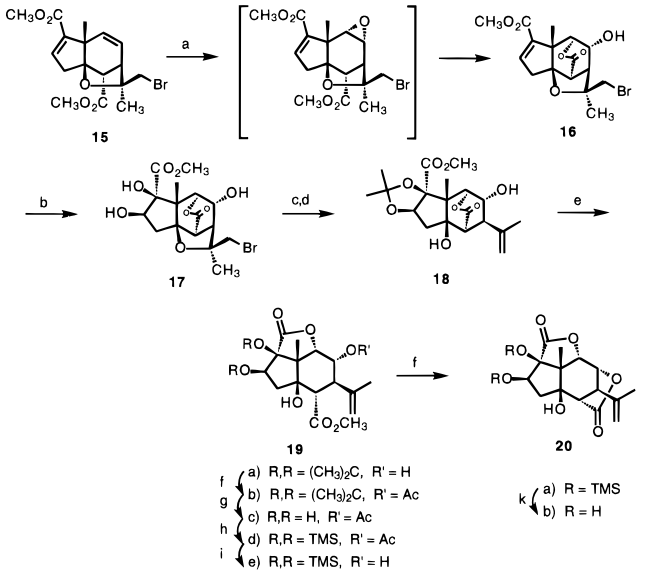
**Scheme 2** Synthesis of a Pivotal Intermediate[a]

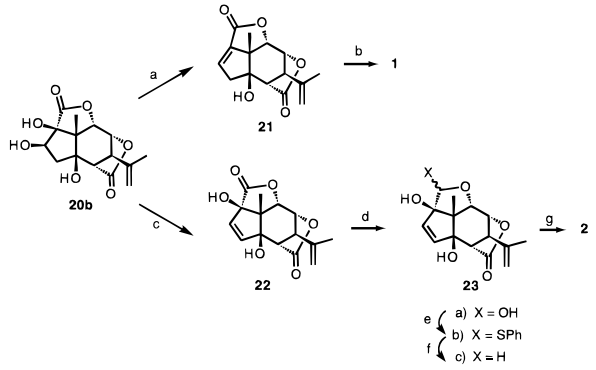



[a] (a) $CF_3CO_3H$, CSA, $CH_2Cl_2$, reflux, 63%. (b) $OsO_4$, $C_5H_5N$, room temperature, 75%. (c) Zn, HOAc, $CH_3OH$, 60 °C, 96%. (d) $(CH_3)_2C(OCH_3)_2$, $CH_3COCH_3$, TsOH, 70%. (e) KOH, $CH_3OH$, $H_2O$, room temperature then $CH_2N_2$, ether, 0 °C, 91%. (f) $CH_3COCl$, $(C_2H_5)_3N$, DMAP, $CH_2Cl_2$, 86%. (g) HCl, $H_2O$, THF, room temperature, 67%. (h) $TMSOSO_2CF_3$, lutidine, DCE, room temperature, 85%. (i) NaCN, $CH_3OH$, THF, room temperature, 90%. (j) *t*-$C_4H_9OLi$, *t*-$C_4H_9OH$, $PhCH_3$, 100 °C, 68%. (k) HF, $H_2O$, $CH_3CN$, 100 °C, 92%.

The stage was set for creation of the bis-lactone of picrotoxinin. All attempts to effect direct oxidative cyclizations using lead tetraacetate failed.[9] The sequence ultimately employed (see Scheme 2) revealed several interesting features of this unusual ring system. The transiently generated epoxide (which may be isolated) underwent facile ring opening with retention of configuration to lactone **16**, for which an X-ray structure confirmed its connectivity and stereochemistry. Formation of the six-membered-ring lactone (as in **16**−**18**) appears to be thermodynamically favored over either five-membered-ring lactone as long as the conformation is restricted in the form of the bromo ether. On the other hand, cleavage of the bromo ether allowed facile equilibration to the fused five-membered-ring lactone **19**. Surprisingly, closure of the bridged lactone proved to be extremely sensitive to the nature of the protecting groups on the five-membered-ring diol. A cyclic derivative like the acetonide failed to cyclize. Replacing the acetonide with acyclic TMS ethers permitted smooth cyclization under basic conditions to give our pivotal intermediate **20**.

To demonstrate the generality of this strategy, syntheses of both picrotoxinin[10] and corianin[11] were completed as outlined in Scheme 3. Dehydroxylation[12] occurred readily to form the strained alkene **21**, which was chemo- and diastereoselectively epoxidized under nucleophilic conditions[13] to give picrotoxinin,

**Scheme 3.** Bifurcation of Common Intermediate to Picrotoxinin and Corianin[a]




[a] (a) $(CH_3)_2NCH(OCH_3)_2$, $Ac_2O$, 100 °C, 68%. (b) LHMDS + *t*-$C_4H_9OOH$, THF, 0 °C, 77%. (c) $(CF_3SO_2)_2O$, *N*-methylimidazole, 100 °C, 85%. (d) $LiBH_4$, HOAc, THF, 0 °C, 71%. (e) PhSH, $CH_3CN$, TMS-Cl (catalytic), room temperature, 98%. (f) $Ph_3SnH$, AIBN, $PhCH_3$, reflux, 84%. (g) MCPBA, $CH_2Cl_2$, 0 °C, 87%.

identical in all respects to an authentic sample. The previous conversion of picrotoxinin to picrotin makes this route a formal synthesis of the latter as well.[3]

Adjustment of the oxidation pattern to form corianin began with a chemoselective dehydration of diol **20** to alkene **22**. Acid-promoted borohydride treatment chemoselectively reduced the α-hydroxy fused butyrolactone to lactol **23a**. Deoxygenation *via* radical desulfurization of the corresponding sulfide[14] **23b** followed by hydroxyl-directed epoxidation of diene[15] **23c** completed a synthesis of corianin, identical to an authentic sample.

The advent of a metal-catalyzed Alder ene reaction not only realized a more efficient strategy to the bicyclic core of the picrotoxanes than previously practiced but also highlights one of the strengths of catalytic versus thermal methods, that is, the ability to modify the catalytic system to achieve success if one protocol fails, an opportunity that is lacking in thermal processes. The result herein is the construction of intermediates possessing sufficiently differentially substituted carbons that each carbon of the core structure can be modified to permit entry to many members of the picrotoxane family, not just picrotoxinin itself. While syntheses of picrotoxinin and corianin illustrate this point, syntheses of asteromurin A, coriamyrtin, and tutin can all be envisioned to derive readily from intermediates reported herein. Efforts in this regard are the subject of future work.

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**Supporting Information Available:** Characterization data for **1**, **6a**, **7**−**10**, **15**−**18**, **19a**, **20b**, **21**, **22**, **23c**, and corianin and experimental procedure for conversion of **7** to **6** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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