Rosenbrook Jr. (Abbott Laboratories, North Chicago) for samples of dihydrospectinomycin and spectinomycin for comparison. Thanks are due to R. Mayer for recording the 90-MHz NMR spectra.

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(31) Vicinal trans-disposed stannylidene acetals are also subject to oxidation by bromine.[28] In our case however, this would involve an axially oriented hydrogen atom at C-4 (4(*S*) isomer of **15**). Also, it is not ruled out that the C-7 and/or C-9 hydroxyl groups are transformed into alkoxytin derivatives in the treatment of **15** with Bu_2SnO, since dimeric and intermolecular structures are possible (see ref 28). Oxidation at these centers appears to be slower under our conditions presumably owing to steric reasons (at least at C-7).
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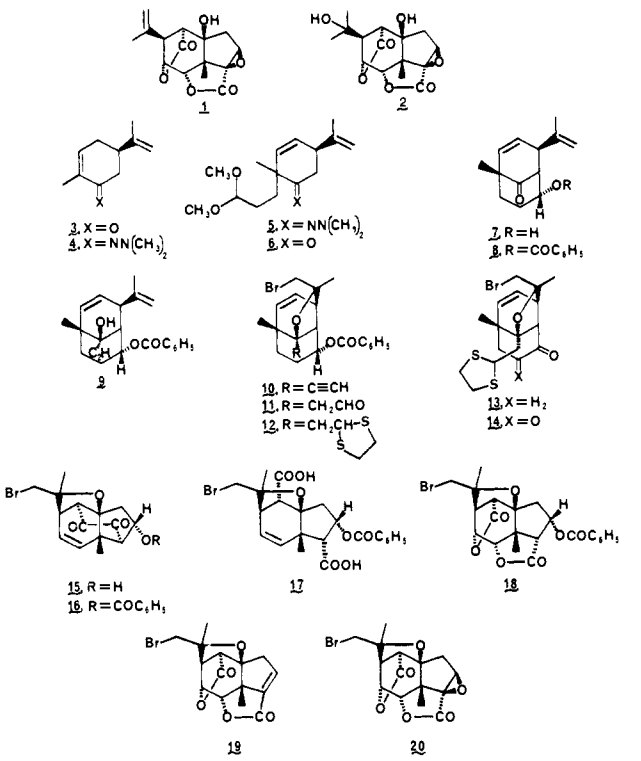
Total Synthesis of Picrotoxinin

Sir:

Picrotoxin, first isolated in 1811 from the berries of the plant *Menispermum cocculus*,[1] upon purification yields two closely related components, picrotoxinin (**1**) and picrotin (**2**). Despite intensive investigations, the molecular architecture of these substances remained obscure for almost 150 years, until the advent of modern techniques of structural analysis and, in particular, the brilliant and now classical investigations of Conroy,[2,3] whose conclusions were later confirmed by an X-ray crystallographic study.[4] In this report, we describe the first total synthesis of **1**, which is currently of considerable interest



because of its utility as an investigational tool in neuroscience (e.g., in antagonism of the inhibitory action of γ-aminobutyric acid (GABA) at synapses).[5] It is remarkable that there seem to have been no reports of progress toward the synthesis of picrotoxins in the literature of the past 25 years.[6]

The first step in our synthetic plan required an α-alkylation of the γ-extended enolate derived from commercially available (−)-carvone (**3**).[7] In accord with past experience,[8] we found that this type of transformation of carvone could not be realized

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using any of the currently available conditions for direct alkylation (varying reagents, solvents, etc.) and that an indirect approach was necessary. The use of the *N,N*-dimethylhydrazone (**4**) provided a highly effective solution to the problem.[9] Reaction of (−)-carvone with 1.5 equiv of *N,N*-dimethylhydrazine and trifluoroacetic acid (0.05 equiv) in toluene (3 mL/g of **3**) at reflux for 6 h with removal of water (Dean-Stark trap) provided the dimethylhydrazone **4**, bp 89–91 °C at 6 Torr, in 95% yield.[10,11] Alkylation of **4** was accomplished by addition of 1 equiv each of lithium diisopropylamide and hexamethylphosphoric amide, together in 1 M solution in tetrahydrofuran (THF) to **4** in THF (5 mL/g of **4**) under argon at −78 °C, storage at −78 °C for 1 h, at −78 to 0 °C for 2.5 h, and then at 0 °C for 14.5 h, recooling to −60 °C, and reaction with 3-bromopropionaldehyde dimethyl acetal at −60 to 0 °C over 6 h to give in 85% yield a mixture of the desired acetal **5** (isopropenyl and methyl cis) and its geometrical isomer (isopropenyl and methyl trans) in ratio 6:4 by ^{13}C NMR, bp 105–110 °C at 0.15 Torr. It was convenient to defer separation until a later stage. Treatment of the mixture of **5** and its isomer with acetic acid–THF–water–sodium acetate (5:2:2:1 by weight)[12] at 25 °C for 24 h gave the corresponding ketones **6**, infrared ν_{max} ($CHCl_3$) 1710 cm^{-1}, in 95% yield, which upon direct exposure to 2.0 equiv of aqueous HCl in 5:1 THF–DME (dimethoxyethane) at 25 °C for 24 h afforded a 92% yield of the desired internal aldol product **7** and the geometrical isomer with methyl and isopropenyl trans (ratio 6:4; R_f values on silica gel plates[13] with 1:1 ether–petroleum ether were 0.21 and 0.25, respectively). The equatorial orientation of hydroxyl in the major isomer was indicated by the ^1H NMR spectrum of chromatographically purified material which revealed coupling of the carbinyl (>CH–O) proton to the three vicinal protons with J values of 3, 3, and 9 Hz. Benzoylation of the mixture of **7** and its diastereomer (1.5 equiv of benzoyl chloride, 0.7 M in pyridine, at 25 °C for 24 h) followed by chromatographic purification using a Waters Associates Model-500 preparative machine afforded pure **8**, mp 79–80 °C, $[\alpha]^{23}_D$ −72° (*c* 5, $CHCl_3$), in 58% yield along with the diastereomer in ~38% yield (R_f values were 0.064 and 0.15, respectively, using 1:1 methylene chloride–pentane). The benzoate **8** was then treated with 3 equiv of lithium acetylide[14] in THF at −78 °C for 0.5 h to produce in 99% yield a single acetylenic carbinol (**9**), mp 107–108 °C; R_f values for **8** and **9** were 0.62 and 0.46 (CH_2Cl_2), respectively. Reaction of **9** in THF (0.1 M) with 1.05 equiv of *N*-bromosuccinimide at 25 °C for 0.5 h produced stereospecifically the bromo ether **10** (99%); R_f values for **9** and **10** were 0.46 and 0.58 (CH_2Cl_2), respectively. Hydroboration of **10** in THF (0.1 M) with 4 equiv of dicyclohexylborane at 0 °C for 3 h followed by oxidation with 30 equiv of hydrogen peroxide (30%) and 0.5 equiv of sodium bicarbonate at 0 to 25 °C for 17 h gave, after extractive workup (1:1 ether–hexane), the *unstable* oily aldehyde **11**, which was used directly in the next step; R_f values of **10** and **11** (1% methanol in CH_2Cl_2) were 0.69 and 0.33, respectively. The aldehyde **11** was transformed into the oily thioketal **12** (68% yield from **10**) by reaction in 0.1 M methylene chloride solution with 2 equiv of ethanedithiol and 2 equiv of boron trifluoride etherate at 0 °C for 0.5 h and 25 °C for 3.5 h; R_f values of **11** and **12** were 0.58 and 0.45 (CH_2Cl_2), respectively. Cleavage of the benzoyl group in **12** was effected by exposure to 0.2 equiv of potassium carbonate in methanol (0.1 M in **12**) at 70 °C for 3 h to give the corresponding alcohol which, upon oxidation with 7 equiv of pyridinium dichromate in dimethylformamide[15] at 0 °C for 6 h, afforded the ketone **13** (95%), mp 157–158 °C, infrared ν_{max} 1700 cm^{-1} (KBr), $[\alpha]^{23}_D$ −67° (*c* 1.8, $CHCl_3$); R_f values of **13** and the precursor alcohol (CH_2Cl_2) were 0.53 and 0.14, respectively. The ketone **13** was oxidized by addition in THF solution together with 1.2 equiv of dimethyl disulfide to a solution of 2.2 equiv of potassium *tert*-butoxide[16] in *tert*-butyl alcohol under an atmosphere of oxygen at 23 °C and further reaction for 0.5 h to form the diketone **14** (92%) (existing mainly in the enolic form, infrared ν_{max} 1720, 1670 cm^{-1} in CH_2Cl_2) as a foam; R_f values for **13** and **14** were 0.63 and 0.51 (CH_2Cl_2),[a] respectively.

At this point, the hydroindene nucleus of picrotoxinin was established by reaction of **14** with 2.5 equiv of mercuric oxide and 2.5 equiv of boron trifluoride etherate[17] in THF–H_2O (6:1) for 3.5 h at 25 °C which effected both dithiolane cleavage and aldol cyclization to give stereospecifically the hydroxy diketone **15** (65%): mp 196–200 °C dec; infrared ν_{max} 1748, 1729 cm^{-1} ($CHCl_3$); R_f values for **14** and **15** (3% acetone in CH_2Cl_2) were 0.66 and 0.06, respectively.[18] The orientation of the hydroxyl group in the aldol product, which was demonstrated conclusively to be as indicated in **15** by a chemical correlation with naturally derived picrotoxinin (to be discussed in a separate paper), is a point of special interest. Treatment of the aldol **15** in pyridine (0.5 M) with 2 equiv of benzoyl chloride and 0.1 equiv of 4-dimethylaminopyridine at 25 °C for 15 h produced the diketo benzoate **16** (79%): mp 70–75 °C; infrared ν_{max} 1740, 1730, 1725 cm^{-1} ($CHCl_3$); $[\alpha]^{23}_D$ +49° (*c* 0.78, $CHCl_3$); R_f values for **15** and **16** were 0.07 and 0.47 (3% acetone in CH_2Cl_2), respectively. Oxidative cleavage of the diketone **16** was accomplished by exposure to 20 equiv of 0.7 M sodium hypochlorite (commercial bleach) in H_2O–THF (2:1) at 25 °C for 24 h to yield 96% of the diacid **17**, infrared ν_{max} 1715 cm^{-1} ($CHCl_3$), R_f 0.58 using 20:10:1 benzene–dioxane–acetic acid.

Much effort was expended on the transformation of the diacid **17** to the dilactone **18** using a wide variety of approaches. Iodo- and bromolactonization processes could not be realized either in aqueous or nonaqueous media with sodium, tetrabutylammonium, thallium, or silver salts.[19] The surprising resistance of salts of the diacid **17** to reaction with these halogens may be due to the pronounced steric shielding of the olefinic bond by the substituents on the six-membered ring. Attempts to convert the disalt of **17** into the dilactone **18** by anodic oxidation provided encouraging results. Electrolysis of a methanolic solution of the tetra-*n*-butylammonium salt of **17** at 0 °C using platinum electrodes afforded the desired product **18**, but only in ~15% yield; other conditions of electrolysis were even less satisfactory. Finally, success was achieved by the use of another oxidative lactonization process which turned out to be remarkably effective. Reaction of the diacid **17** with 6 equiv of lead tetraacetate in acetonitrile at 25 °C for 1.5 h gave dilactone **18** in 99% yield: mp 208–210 °C dec; infrared ν_{max} 1808, 1725 cm^{-1} ($CHCl_3$); $[\alpha]^{23}_D$ −89° (*c* 0.38, $CHCl_3$); R_f 0.66 with benzene–dioxane–acetic acid (20:10:1) vs. 0.58 for **17**. The scope and mechanism of this interesting double-lactonization reaction, which has some precedent,[20] are now under further investigation.

Elimination of the benzoate group in **18** was accomplished by heating with excess diisopropylethylamine in DME at 50 °C for 18 h to give in 67% yield the unsaturated dilactone **19**: mp 205–210 °C dec; infrared ν_{max} 1802, 1788 cm^{-1} ($CHCl_3$); $[\alpha]^{23}_D$ −37° (*c* 2.53, $CHCl_3$); R_f 0.14 using ethyl acetate–hexane (1:3, two developments) compared with 0.077 for **18**; ^1H NMR peak due to a single olefinic proton at 6.10 ppm ($CDCl_3$). Epoxidation of **19** with excess peroxytrifluoroacetic acid in chloroform in the presence of disodium hydrogen phosphate powder at 50 °C for 4 h provided stereospecifically the epoxy bromo ether dilactone **20** (96% yield), identical in all respects (TLC, IR, ^1H NMR) with the major (β)[4,21] bromo ether prepared by the action of *N*-bromosuccinimide–THF on picrotoxinin, mp 280 °C dec, $[\alpha]^{23}_D$ −126° (*c* 0.21, $CHCl_3$).[21] Reaction of the dilactone bromo ether **20** with 5 equiv of zinc dust and 2.5 equiv of ammonium chloride in ethanol containing a little water at reflux for 0.5 h afforded *synthetic* picrotoxinin (**1**), identical with naturally derived picrotoxinin, mp and mmp

198–199 °C,[21] $[\alpha]^{23}_D$ −6.3° (*c* 0.27, $CHCl_3$), in 99% yield. Synthetic and naturally derived **1** exhibited identical infrared, ^1H NMR, ^{13}C NMR, circular dichroism, and optical rotatory dispersion spectra,[22] and showed identical TLC mobilities with several different solvent systems. Picrotoxinin now joins the list of long-known but fiercely defiant naturally occurring substances which have been produced by total synthesis.

During the course of the above studies leading to a successful total synthesis of picrotoxinin a considerable amount of new information was generated on the chemistry of picrotoxinin. This work will be reported separately as will a related study on the synthesis of picrotin and coriamyrtin.[23]

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(23) This research was assisted financially by a grant from the National Science Foundation.

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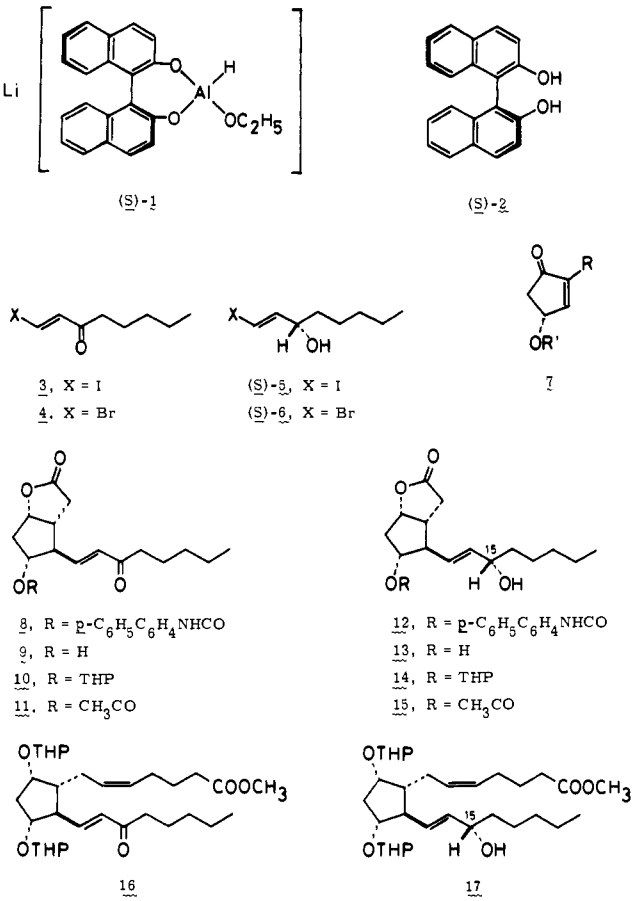
A Highly Efficient Synthesis of Prostaglandin Intermediates Possessing the 15*S* Configuration[1]

Sir:

With the demonstration of the extemely high stereoselection in carbonyl group reduction by a binaphthol-modified aluminum hydride reagent accomplished,[1] attention has been directed to the possibility of utilizing prostaglandin (PG) intermediates as the ketonic substrate. Reported herein is the realization of such expectation.

First, this method has proved to allow the enantioselective synthesis of the potential PG ω chain which is used in the conjugate addition approaches.[2-4] A THF solution of the reducing agent, (*S*)-**1,** was prepared by treating $LiAlH_4$ in THF



(0.97 M solution) with equimolar amounts of ethanol (1.0 M solution in THF) and optically pure (*S*)-(−)-2,2′-dihydroxy-1,1′-binaphthyl ((*S*)-**2**)[5] ($[\alpha]_D^{24}$ −37.8° (*c* 1.00, THF)) (0.60 M THF solution) for 1 h at room temperature. The iodovinyl ketone **3** was then mixed with 3 equiv of (*S*)-**1** in THF at −100 °C and allowed to stir at the same temperature for 2 h and at −78 °C for 1 h. The mixture was quenched by addition of moist ether, filtered through Celite 545, and concentrated. Recrystallization from hexane gave back ~90% of the chiral auxiliary ligand, (*S*)-**2,** without any noticeable loss of optical purity. Column chromatography of the residue on silica gel gave the allylic alcohol, (*S*)-**5,** in 95% yield. This product was 97% enantiomerically pure, as determined by the comparison of the magnitude of the optical rotation, $[\alpha]^{24}_D$ +9.53° (*c* 1.56, CH_3OH), with that of authentic sample.[6] The high enantioface differentiation was achieved also in the reaction of the bromovinyl ketone **4** and (*S*)-**1,** producing the allylic alcohol, (*S*)-**6,** in 96% ee, $[\alpha]^{24}_D$ +12.6° (*c* 1.40, CH_3OH) (96% yield).[7,8] Thus the present chemical transformation appears to be much more effective than the microbiological reduction of **3** (10% yield, 80% optical yield)[9] or optical resolution of the racemic alcohol.[6] Combination of these vinylic halides via the organometallic intermediates with the readily available (*R*)-4-hydroxy-2-cyclopentenone or its derivatives of type **7**[3,4,10] leads to PGs having the natural 15*S* configuration.

Even more important is the application of this reagent to the Corey synthesis via the bicyclic lactone intermediates.[2,11] A noteworthy feature of this route is the complete stereochemical

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