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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(10) Satisfactory proton magnetic resonance, infrared, and mass spectral data were obtained using chromatographically homogeneous samples with the exception of the unstable aldehyde **11.**
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(23) This research was assisted financially by a grant from the National Science Foundation.

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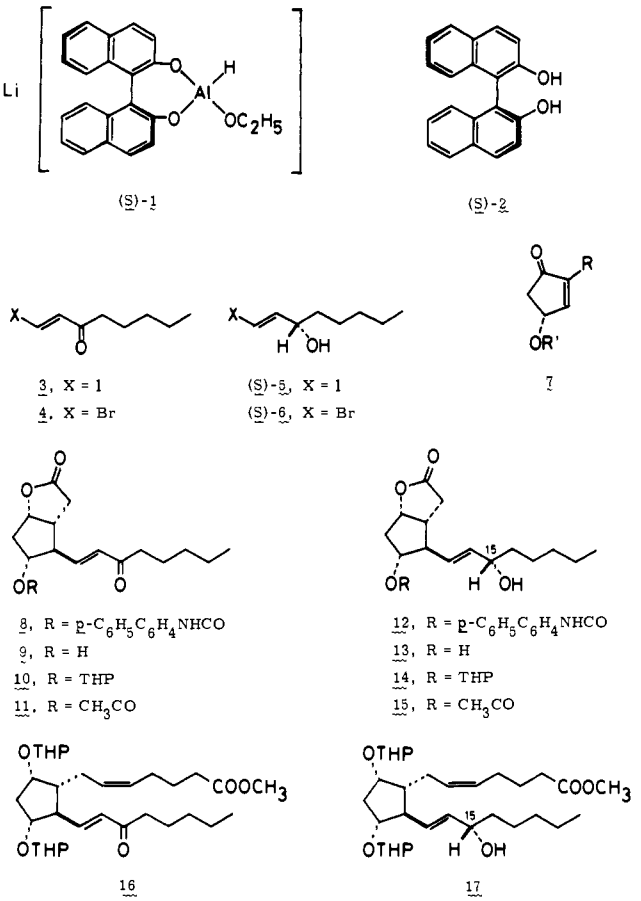
A Highly Efficient Synthesis of Prostaglandin Intermediates Possessing the 15*S* Configuration[1]

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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control in the construction of the functionalized cyclopentane framework. The only remaining stereochemical problem is to explore an effective method for allowing the highly selective conversion of the enone side chain into the allylic alcohols that possess the correct, 15*S* configuration. So far tremendous attempts have been made to solve this problem, and a 15*S*/15*R* ratio as high as 92:8 was recorded in the reaction of the enone having a *p*-phenylphenylcarbamoyl protective group and a bulky trialkylborohydride reagent (**8** → **12**)[12] or reduction of the hydroxy enone with diisobutylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide (**9** → **13**).[13] We found that the stereoselectivity displayed by (*S*)-**1** is far superior to that of any of the existing systems currently available. Thus, when the tetrahydropyranyloxy enone **10** was treated with 3 equiv of (*S*)-**1** in THF at −100 °C for 2 h and then at −78 °C for 1 h, there was obtained the 15*S* alcohol **14** of 99.5% stereoisomeric purity[14] in 95% yield. No 1,4-reduction product, the 13,14-saturated ketone, was formed under such conditions. In a like manner, the stereoselective reduction proceeded equally well with the acetoxy enone **10**[7] to afford **15** (99.4% stereochemically pure[14]) in 96% yield. The reaction of the unprotected hydroxy enone **9** gave rise to the 15*S* alcohol **13** *exclusively*, though the isolated yield was modest, 40% (97% yield based on the consumed starting enone).[7,14] Finally, the monocyclic substrate **16** under the standard reduction conditions[7] gave the $PGF_{2\alpha}$ derivative **17** as a single stereoisomer in 76% isolated yield.[14]

The sense and extent of the stereoselection is dependent on the absolute configuration of the binaphthyl moiety in **1**. In the reduction of the THF derivative **10**, for instance, (*S*)-**1** exhibited very high 15*S* stereoselection (15*S*/15*R*, 99.5:0.5), whereas the reduction with the enantiomeric reagent, (*R*)-**1**, showed only moderate, 15*R* selection (15*S*/15*R*, 32:68).[7,14] These observations, coupled with the results obtained with the prochiral substrates **3** and **4**, imply that both the excellent enantioface-recognizing ability of the hydride reagent **1** and diastereomeric influence of the functionalized cyclopentane moieties of the substrates are synergistically operating in exhibiting the exceptionally high stereocontrol.

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(7) The reaction was carried out in THF using 3 equiv of **1** at −100 °C for 2 h and then at −78 °C for 1 h.

(8) Pure (*S*)-(+)-**6** obtained by optical resolution[6] exhibited specific rotation $[\alpha]^{24}_D$ +13.1° (c 1.39, CH_3OH). The configuration assignment was made by comparison of the CD curve with that of (*S*)-(+)-**5**.

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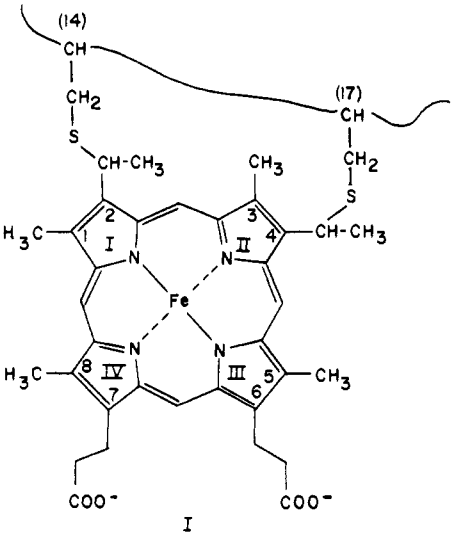
Detection of Localized Conformational Flexibility in Horse Heart Cytochrome *c* by Proton Nuclear Magnetic Resonance

Sir:

Proton nuclear magnetic resonance (^{1}H NMR) studies of hemoproteins have been found to be extremely useful in characterizing the protein structural and dynamic properties which may influence the heme prosthetic group and hence its function. This is particularly true of paramagnetic hemoproteins where the hyperfine shifted resonances can serve as sensitive probes of protein flexibility in the region surrounding the heme. In the case of ferricytochrome *c*, however, despite extensive NMR studies,[1,2] no direct evidence of protein conformational flexibility in the heme environment has been detected in the physiologically relevant pH range. Detecting and monitoring such flexibility could aid in current investigations devoted to elucidating the changes in conformation that may occur when the protein interacts with its associated oxidase, reductase, and/or peroxidase.

We report here on some preliminary studies on the high-field NMR spectra of horse heart ferricytochrome *c* (cyto c^{III}), which allow characterization of localized protein conformational flexibility in the heme region. The pertinent prosthetic group is depicted in **I**. The hyperfine shifted region of the 200-



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and 360-MHz spectra of cyto c^{III} are shown in Figure 1.[3] The heme methyl assignments have been proposed based on combined NOE and saturation transfer experiments.[4] The most striking feature of the comparison is the unique variation of line width, δ, of the single Lorentzian signal previously proposed to arise from 3-CH_3. A plot of line width vs. H_0^2 for this methyl is linear for data taken at 100, 200, and 360 MHz. At all fields the line width is independent of protein concentration

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