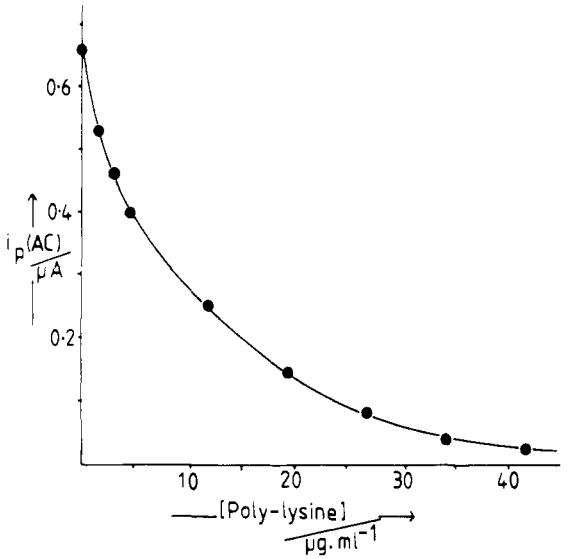

Figure 2. ac cyclic voltammetry peak current i_p(ac) against poly-L-lysine concentration, solution as in Figure 1. ac modulation frequency, 479 Hz: modulation amplitude, 8 mV.

ring disk indicate that the native cytochrome binds to the 4,4′-bipyridyl-modified gold electrode surface prior to electron transfer. Thus it appears that 4,4′-bipyridyl acts by forming a suitable surface at the electrode-solution interface to which the cytochrome can bind. The binding of the protein to the electrode may therefore be similar in kind to that observed in the cytochrome *c*-oxidase reaction, involving the ϵ-amino groups of lysine residues in the vicinity of the cytochrome *c* heme crevice. The observed similarities to the cytochrome *c*-oxidase reaction may result from a preferred orientation of the cytochrome when bound at the electrode surface or to cytochrome oxidase such that the exposed heme edge is adjacent to the electrode surface or the cytochrome oxidase thereby enabling rapid electron transfer to occur.

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(10) Prepared by the method of Wallace and Offord.[6]
(11) Prepared by the method of Hettinger and Harbury.[7]
(12) dc and ac cyclic voltammetry was carried out as previously described.[1]
(13) Prepared by the method of Fanger and Harbury.[8]
(14) Prepared by the method of Pettigrew et al.[9]
(15) Poly-L-lysine Type II, mol wt 3000, obtained from the Sigma Chemical Co. Ltd.
(16) The electrochemical measurements were made on 0.357 mM solutions of ferricytochrome *c* (Sigma, grade VI) in buffer (K_2HPO_4, 0.02 M; $NaClO_4$, 0.1 M) in a cell (5 cm^3) containing three electrodes: working, a gold wire (diameter, 5×10^{-4} m, length 5×10^{-3} m); counter, a cylindrical platinum net surrounding the working electrode; reference, an SCE, separated from the main compartment by a Luggin capillary. A Princeton Applied Research 173 potentiostat with a 179 coulometer was used. The amplitude of the ac modulation sine wave was 5 mV and the current responses in-phase and quadrature phase of the applied ac was measured by an Ortec Brookdeal 9503 lock-in amplifier. The impedence measurements were carried out at OV (vs SCE), the position of maximum ac current, and at 20–1000 Hz.
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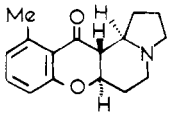
Elaeocarpus Alkaloids. Synthesis Using Nitrones

Sir:

The *Elaeocarpus* alkaloids comprise a relatively new and sizable group of natural products derived from the plant family Elaeocarpaceae, comprising several large, spreading trees found in New Guinea and India.[1,2] The leaves of these trees are rich in *dl*-elaeocarpine (**1**) and *dl*-isoelaeocarpine (**2**) as well as numerous other related indolizidine alkaloids. We report herein an extremely facile and pointedly direct synthesis[3] of two major (i.e., *dl*-elaeocarpine and *dl*-isoelaeocarpine) and one minor member (i.e., *dl*-isoelaeocarpicine, **3a**) of the *Elaeocarpus* family of alkaloids.



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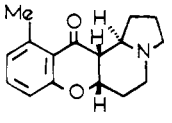

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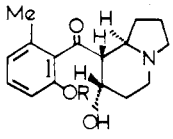
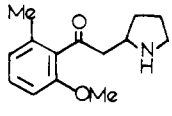


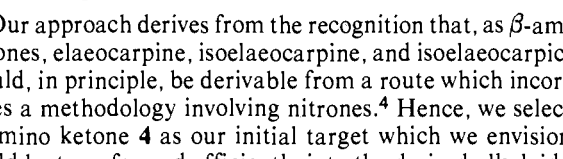
3a, R = H
b, R = Me



4

Our approach derives from the recognition that, as β-amino ketones, elaeocarpine, isoelaeocarpine, and isoelaeocarpicine would, in principle, be derivable from a route which incorporates a methodology involving nitrones.[4] Hence, we selected β-amino ketone **4** as our initial target which we envisioned could be transformed efficiently into the desired alkaloids.

While we considered that **4** could be obtainable from the isoxazolidine **5** derived from 1-pyrroline 1-oxide (**6**) and 6-methoxy-2-methylstyrene (**7**), the steric encumbrances in-



7 6 5

volved in such a cycloaddition were of some concern. Fortunately, we recognized that the steric crowding centered about the developing carbon-oxygen bond, while the nonsynchronous transition states probably involved in these [$_\pi 4_s + _\pi 2_s$] cycloadditions[5,6] appear to involve more extensive formation of

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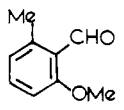
the carbon–carbon bond for most dipolarophiles.[7,8] This would suggest that nitrone cycloadditions would ordinarily be more subject to steric effects at the developing carbon–carbon bond, rather than at the developing carbon–oxygen bond.

The desired styrene **7** was prepared from 6-methoxy-2-methylbenzaldehyde (**8**) (generated from 6-hydroxy-2-meth-



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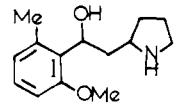
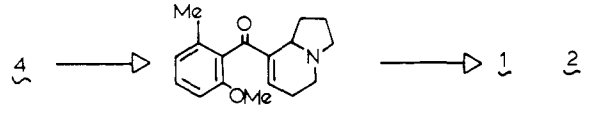


9

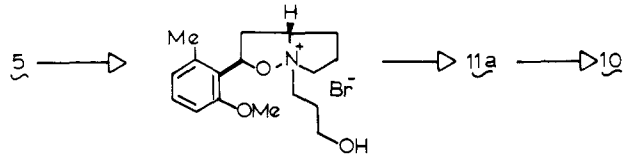
ylbenzaldehyde[9] by etherification with methyl iodide and base) by using Wittig methodology[10] (methyl triphenylphosphonium bromide, $MeSOCH_2Na$, 25 °C). The styrene **8** exhibits the expected two three-proton singlets at δ 2.31 and 3.68 ppm and a doublet of triplets (2 H, J = 13, 2.5 Hz) associated with the terminal methylene protons of the vinyl group at δ 5.40–5.72 ppm in its NMR spectrum. This compound, unlike its less crowded relatives,[11] is quite stable to prolonged storage. Moreover, it undergoes a smooth cycloaddition with 1-pyrroline 1-oxide (**6**) in toluene at 95 °C to afford in 85% yield a pale yellow isoxazolidine, mp 56–60 °C, displaying a crisp four-line pattern (X portion of an ABX array) at δ 5.64 ppm (J = 7, 10 Hz) associated with the α-oxabenzylic proton in **5.** The integration (1 H), apparent for this signal and the freedom of this region from competing signals, however minute, suggests that not only is high regioselectivity manifest in the formation of this adduct, but high stereoselectivity as well. This is predictable on the basis of recent regiochemical and stereochemical studies of related cycloadditions.[8,12] Thus, the preferential mode of attack is exo, using Diels–Alder notation, and the adduct can be assigned the stereochemistry denoted in **5.**

The cleavage of the nitrogen–oxygen bond was effected with Adams catalyst (PtO_2, H_2, EtOH) to produce the β-amino alcohol **9** (99%) exhibiting strong OH and NH absorption at 3.4 μ in the IR (KBr) spectrum and displaying its α-oxabenzylic proton at δ 5.08 ppm (dd, J = 10, 4 Hz). Conversion of amino alcohol **9** into the desired amino ketone **4** was accomplished by Jones oxidation. This amino ketone proved to be an easily decomposable yellow oil: IR (neat) 5.95 μ; mp (HCl salt) 171–174 °C (lit.[1b] mp 172–175 °C).

The amino ketone can be liberated from its hydrochloride salt by basification (K_2CO_3) and can undergo a Michael-aldol sequence not unlike the Robinson annulation procedure by exposure to acrolein (1 equiv) in benzene for 10 min at 25 °C. At this point, the reaction mixture was introduced by syringe into a benzene solution containing potassium *tert*-butylate (3 equiv) and stirred for 2 h to give unsaturated amino ketone **10**



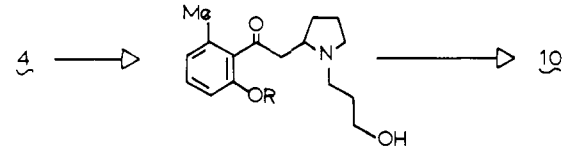
10



12

(34%) as a yellow oil, which exhibits its vinyl proton at δ 6.36 ppm (br t, 1) in the NMR spectrum and its carbonyl at 6.06 μ in the IR spectrum.

As this annulation procedure proceeded in modest yield, we chose to examine an alternate, but related process to **10.** Thus, the amino ketone **4** was alkylated with 3-bromo-1-propanol in refluxing methylene chloride to give **11a** (89%). The amino



11a, R = Me
b, R = H

ketone **11a** (4.05 mmol) was immediately exposed to a solution of potassium *tert*-butylate (15 mmol) and benzophenone[13,14] (50 mmol) in refluxing benzene (2.5 h) to afford **10** in 71% yield. Finally, in a sequence of optimal efficiency, isoxazolidine **5** was alkylated with 3-bromo-1-propanol to give a quaternary salt (i.e., **12**), which on exposure to benzene containing potassium *tert*-butylate and benzophenone at reflux, produces **10** directly. This one-flask operation involves base-induced isoxazolidine ring opening[15] to **11a** and modified Oppenauer oxidation to the aldehyde, followed by an aldol closure to the unsaturated ketone **10.**

The methyl ether function of **10** was cleaved with BBr_3[2b] in CH_2Cl_2 (25 °C) to give the phenolic ketone **11b,** which was directly cyclized with dilute sodium hydroxide solution, thereby giving an ~1:1 ratio of a readily separable mixture (Al_2O_3, 50:50 benzene–hexane) of *dl*-elaeocarpine (**1**) and *dl*-isoelaeocarpine (**2**), confirmed by comparison with spectral properties recorded in the literature[1] and displayed by authentic samples. Mixture melting point behavior with an authentic sample confirmed the former assignment, while the latter was bolstered by the similar melting point behavior of the picrates of authentic and synthetic *dl*-isoeleaocarpine (mp 233–235 and 235–237 °C, respectively).

Finally, the first total synthesis of *dl*-isoelaeocarpicine (**3a**) was accomplished by treating the Michael product derived from **4** and acrolein with acid (concentrated aqueous HCl) rather than base. Such treatment gave in 36% yield, after basification with aqueous potassium carbonate, *dl*-isoelaeocarpicine methyl ether (**3b**), which was converted into *dl*-isoelaeocarpicine (**3a**), mp 143–145 °C, in 80% yield by cleavage of the ether function with BBr_3 (CH_2Cl_2). NMR and IR comparisons revealed the identity of the synthetic material with the natural product, save for the absence of optical activity in the former.

We note that the synthesis of *dl*-elaeocarpine (and *dl*-isoelaeocarpine) involving quaternary salt **12** involves only four steps from the substituted styrene (i.e., **7**).

Acknowledgment. We thank the Institute for General Medical Sciences of the National Institutes of Health for financial assistance (GM25303) and Dr. J. A. Lamberton of the CSIRO (Melbourne) for authentic samples of *dl*-elaeocarpine, *dl*-isoelaeocarpine picrate, *dl*-isoelaeocarpine hydrobromide, *dl*-eleacarpine hydrobromide, and natural *d*-isoelaeocarpicine. Moreover, we thank Dr. Ikuo Iijima (Tanabe Seiyaku Co., Japan) for IR and NMR spectra of natural and synthetic elaeocarpine and isoelaeocarpine.

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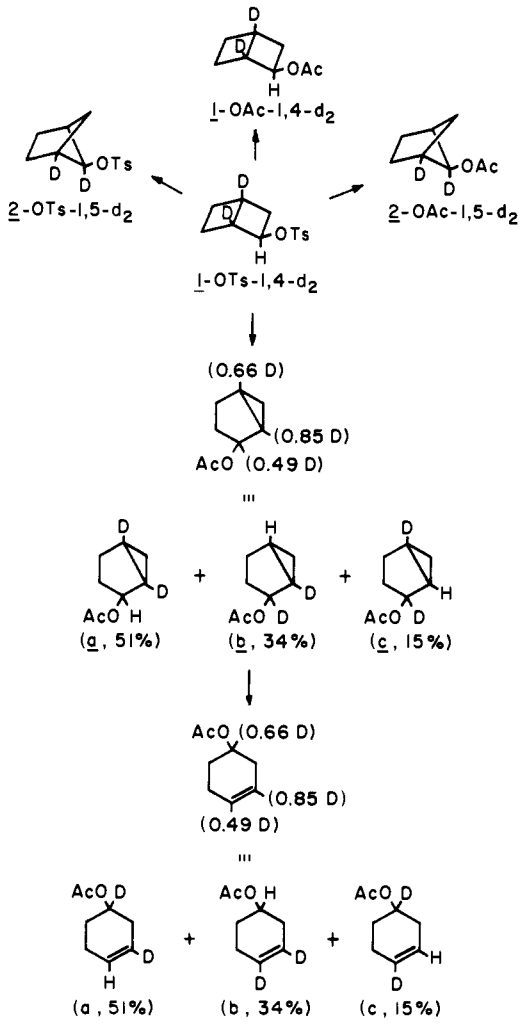
Strained Ring Systems. 18.[1] Determination of the Rearrangement Pathways in the Buffered Acetolysis of Bicyclo[2.2.0]hex-*exo*-2-yl Tosylate with Specific Deuterium Labeling and Optical Purity Probes

Sir:

A prerequisite to defining the structures and number of carbonium ions produced in a solvolysis reaction is detailed knowledge of the various rearrangement channels leading from substrate to product(s). This is usually accomplished experimentally using structural probes (e.g., specific isotopic labeling and chirality) incorporated in the substrate and determining the overall changes following these probes in going to the product(s). We report herein the results of a study using three probes with the buffered acetolysis of bicyclo[2.2.0]hex-*exo*-2-yl tosylate (X-**1**-OTs) at 75 °C where the isolated products are bicyclo[2.1.1]hex-*exo*-5-yl OTs (X-**2**-OTs, 54%), X-**1**-OAc (2%), X-**2**-OAc (16%), bicyclo[3.1.0]hex-*exo*-2-yl OAc (X-**3**-OAc, 10%) and its endo epimer (N-**3**-OAc, 7%), cyclohex-3-enyl OAc (**4**-OAc, 10%), cyclohex-2-enyl OAc (**5**-OAc, 1%), and cyclopent-2-enylmethyl OAc (**6**-OAc, ~0.1%).

The first probe of the solvolytic rearrangements of X-**1**-OTs was carried out with X-**1**-OTs-*1,4-d*$_2$.[1,2] The products, dideuterated X-**2**-OTs, X-**1**-OAc, X-**2**-OAc, X- and N-**3**-OAc, and **4**-OAc. were separated and collected (GLC). The positions of deuterium substitution and the H and D content per position were then determined using ^{13}C NMR spectroscopy for each of these products. While X-**1**-OAc-d_2 showed no scrambling of its bridgehead deuteriums, both X-**2**-OTs-d_2 and X-**2**-OAc-d_2 were the result of a single Wagner–Meerwein rearrangement with no further equilibration (Scheme I). The dideuterated acetates X- and N-**3**-OAc[3] and **4**-OAc showed deuterium at three carbons, as shown in Scheme I, which are analyzed in terms of three isomeric dideuterated species. These latter results uniquely demonstrate the direct rearrangement pathway of the cationic precursors ([3.1.0]-**2**$^+$ → 3-cyclohexenyl$^+$) of these acetates.

Scheme I



The second and third probes were combined using X-**1**-OTs-*exo-3-d* of 86% optical purity.[4] The deuterium analysis by ^{13}C NMR spectroscopy readily identified the single sites of substitution in each of the above six products (Scheme II). The stereochemistry of the deuterium in X-**1**-OAc was clearly *exo*-3 by comparison of its ^{1}H NMR spectrum with that of authentic X-**1**-OAc-*exo-3-d*.[4,6] In X-**2**-OTs-*d* and X-**2**-OAc-*d*, the C_6 syn-D stereochemistry was assigned based on the observed "W" coupling of the C_6 anti-H and C_5 endo-H and integration in the ^{1}H NMR spectra.[7] In the ^{1}H NMR spectra of X- and N-**3**-OAc. the exo and endo H's at C_6 are well separated and clearly the deuterium was exo in both epimers.

The optical purity of X-**1**-OAc-*exo-3-d* ($[\alpha]^{27}_D$ 40.0° ($CHCl_3$)) was found to be 86% with Eu-Opt^R (Alfa-Ventron) shift reagent. Both hydrolysis and conversion of the alcohol to the tosylate ester (pyridine + TsCl) was assumed to occur without racemization. The optical purities of the GLC collected samples of the four chiral products are listed in Table I.

The results from all three probes establish that 6,2- and 3,2-hydride shifts do not occur in the carbonium-ion intermediates leading to X-**1**-OAc and X-**2**-OAc.[8,9] Further, an equilibrium involving classical chiral [2.2.0]-**2**$^+$ and achiral [2.1.1]-**5**$^+$ cations cannot be involved prior to solvent trapping and ion-pair return to yield these three solvolysis products. These same requirements must also be placed on the initially produced cations leading to X- and N-**3**-OAc and **4**-OAc.[9]

Equating the results from X-**1**-OTs-*1,4-d*$_2$ → X- and N-**3**-OAc (isomers a (51%), b (34%), and c (15%), Scheme III)

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