Table I. Hyperfine Coupling Constants for PBN Adducts (in gauss)

	A_N	A_H	A_D
H_2 or D_2 on ZnO	14.8	7.41	1.08
CO/H_2 irradiation[a]	15.0	7.5	
irradiation of liquid alkanes[b]	14.8	7.0	

[a] Reference 3. [b] Reference 2.

tained with the desorbed material permits the radical species to be identified (Figure 2). The spectrum obtained with adsorbed H_2 (trace a) is attributed to the addition of H· to I; the hyperfine pattern consists of a 1:1:1 triplet due to ^{14}N, further split into 1:2:1 triplets due to two equivalent β protons. With D_2 (trace b), the addition product of D· to I gives a triplet-doublet-triplet splitting pattern, with the smaller triplet due to the β deuteron.

Figure 2 (b) also shows small amounts of the hydrogen addition product and another unidentified radical which was not present if a non-hydrogen-containing solvent such as carbon tetrachloride was used. A sample of ZnO was exchanged with D_2O and then outgassed in the usual way. Adsorption of hydrogen on this sample gave a spectrum showing the hydrogen addition product with a very small contribution from the deuterium addition product.

Table I compares the hyperfine splitting constants that we have observed with those reported in the literature for the addition products of H· and D· to I. The solution spectra are certainly those of II with R = H· or D·. The similarity of the adsorbed phase spectra to those from solution indicates that the addition products are formed on the ZnO surface by reaction of I with adsorbed hydrogen or deuterium.

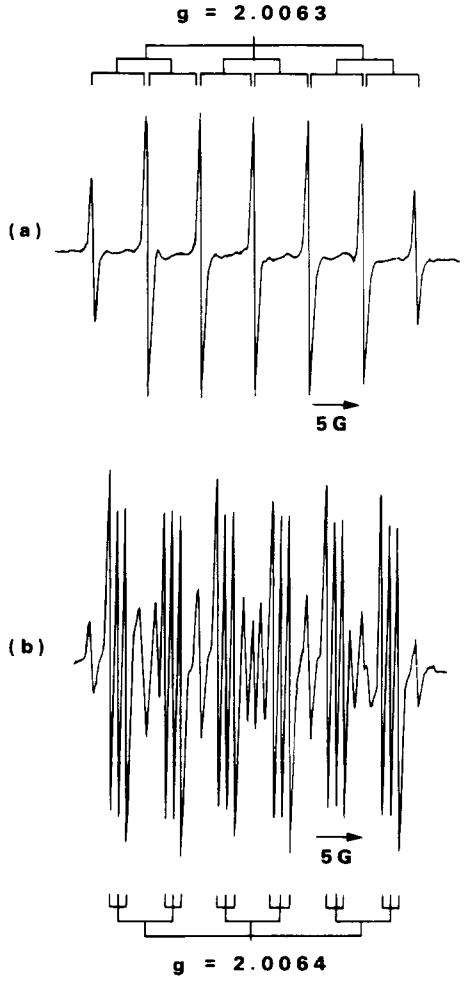

Figure 2. EPR solution spectra of PBN adducts desorbed from ZnO containing (a) adsorbed H_2 and (b) adsorbed D_2.

It has been shown by infrared spectroscopy that adsorption of H_2 on ZnO at room temperature involves a reversible dissociative chemisorption to form Zn–H and O–H species.[5,6] Our experiments indicate that hydrogen adsorbed on ZnO can be abstracted by PBN. Further experiments are needed to determine which hydrogen is abstracted and to determine the mechanism of abstraction. Trapping of the adsorbed hydrogen by PBN does not necessarily imply the presence of free hydrogen atoms on the ZnO surface, but does indicate that the reactivity of adsorbed hydrogen resembles that of hydrogen atoms produced in radiolysis[2] or electrolysis[4] experiments. The question of the extent of the radical character of hydrogen adsorbed on ZnO has still to be answered. Nevertheless, PBN is clearly a valuable spin trap to use in studying surface species having radical character. We envisage many systems of catalytic importance in which the presence of radical intermediates may be investigated by this technique.

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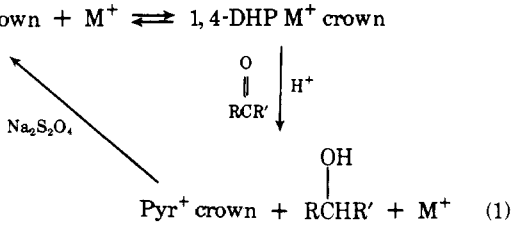
Asymmetric Reductions with a Chiral 1,4-Dihydropyridine Crown Ether[1]

Sir:

We are interested in the catalytic cycle shown in eq 1. A 1,4-dihydropyridine (DHP) is contained in a segment (for example a crown ether) capable of complexing a metal ion, M^+. The encapsulated M^+ then complexes with a carbonyl



compound, forming a ternary complex in which the carbonyl group is activated toward hydride acceptance through its complexation to M^+.[2,3] The pyridinium salt (Pyr^+) formed on reduction of the carbonyl group is reduced back to 1,4-DHP with $Na_2S_2O_4$.[4] Such a cycle has attractive synthetic and biomimetic aspects,[5] especially if the 1,4-DHP–crown combination is chiral and is capable of carrying out reductions with a significant degree of asymmetric induction.[6] We report here the preliminary results of work intended toward the achievement of the above goals.[7]

The synthetic route to the desired 1,4-DHP–crown compounds is shown in Scheme I. Chiral starting materials were the *tert*-butyl esters of optically pure L-alanine (**2a**) and L-

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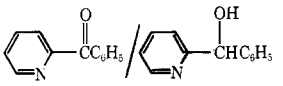
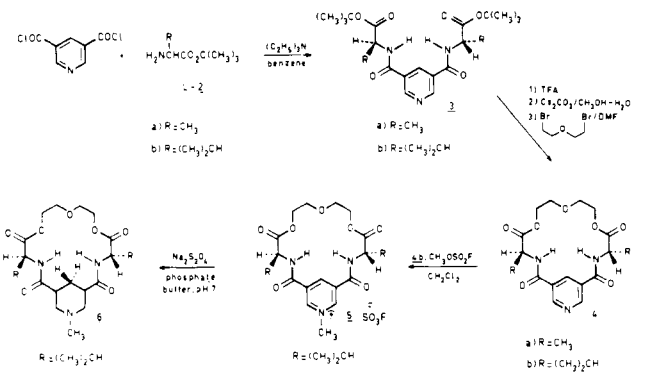
Table I

substrate/product	conditions (reaction time, h)	work-up procedure	NMR yield, %, of alcohol (**5**, ClO_4)	alcohol isolated yield,[s] %	$[\alpha]_D^T$, deg (concn)	$[\alpha]_D^T$, lit. deg (concn)	optical yield, %	absolute confign of excess enantomer
 **7** **8**	*a, b* (72)		65 (100)					
$C_6H_5COCF_3$ (**9**)/$C_6H_5CHOHCF_3$ (**10**)	*b, c* (100)	*d*	82 (100)	58	$[\alpha]^{22}_D$ + 9.7 (0.19)[j]	$[\alpha]^{24}_D$ + 14.2 [j,p,n]	68	*S*
$C_6H_5COCO_2C_2H_5$ (**11**)/$C_6H_5CHOHCO_2C_2H_5$ (**12**)	*c, e* (72)	*f, g*	80 (100)	61	$[\alpha]^{20}_D$ + 89.9 (0.76)[k]	$[\alpha]^{24}_D$ −104 [k,m,o]	86	*S*
$C_6H_5COCONH_2$ (**13**)/$C_6H_5CHOHCONH_2$ (**14**)	*c, e* (48)	*f, h*	67 (100)	69	$[\alpha]^{9}_D$ + 47.8 (0.55)[l]	$[\alpha]^{9}_D$ + 74.7 [l,p,q]	64	*S*
$C_6H_5COCONHC_2H_5$ (**15**)/$C_6H_5CHOHCONHC_2H_5$ (**16**)	*c, e* (75)	*f, i*	65 (100)	37	$[\alpha]^{20}_D$ + 26.5 (0.58)[k]	$[\alpha]^{16}_D$ − 34.4 [k,m,r]	78	*S*

[a] NMR experiment. [b] 55 °C. [c] 0.14 M in **6**, substrate, and $Mg(ClO_4)_2 \cdot 1.5H_2O$ in CH_3CN (CD_3CN). Reaction was carried out under N_2. [d] The reaction mixture was concentrated, ether was added, and the precipitated **5** ClO_4 was filtered off. This procedure was repeated twice with the residue. Thereafter the combined ether extracts were concentrated, filtered, and subjected to preparative TLC (silica gel, C_6H_6). After Kugelrohr distillation the ^1H NMR spectrum of the alcohol **10** still showed some minor impurities. A sample was subjected to LC (silica gel, 82:18 CH_2Cl_2–hexane) and distilled again before measuring rotation. No impurities were detectable by either ^1H NMR spectroscopy or LC. [e] Room temperature. [f] Water was added to the reaction mixture. After 30 min the solvent was evaporated; and the residue was dissolved in dry CH_3CN, filtered, and concentrated. [g] The residue was subjected to preparative TLC (silica gel, 9:1 C_6H_6–$(C_2H_5)_2O$). Ethyl mandelate (**12**) was isolated and distilled in a Kugelrohr apparatus. No impurities in **12** could be detected either by ^1H NMR or LC. [h] The alcohol was isolated by column chromatography (silica gel, 4:1 CH_2Cl_2–CH_3COCH_3) and further purified by LC (silica gel, 4:1 CH_2Cl_2–CH_3COCH_3). The compound was pure by LC and ^1H NMR and melted at 113.7–121.3 °C (lit. 122–122.5 °C for the pure enantiomer). [i] The alcohol was isolated by column chromatography (silica gel, 9:1 CH_2Cl_2–CH_3COCH_3) and further purified by LC (silica gel, 9:1 CH_2Cl_2–CH_3COCH_3), colorless oil (lit. mp 65.5–66.5 °C for the pure enantiomer), and was pure by both ^1H NMR and LC. [j] In C_6H_6. [k] In C_2H_5OH. [l] In CH_3COCH_3. [m] For optically pure material (*R*). [n] Reference 15. [o] Reference 16. [p] For optically pure material (*S*). [q] Reference 17. [r] Reference 18. [s] Corrected for recovered substrate.

Scheme I



valine (**2b**). Reactions of these amino acid esters with **1** gave, respectively, **3a** (80% yield, mp 137.3–138.6 °C, $[\alpha]^{21}_D$ +26.8° (*c* 1.00, $C_2H_5O_2CCH_3$)) and **3b** (88% yield, mp 170.1–170.4 °C, $[\alpha]^{21}_D$ +37.7° (*c* 1.00, $C_2H_5O_2CCH_3$)). For the crucial ring-closure reaction **3a** and **3b** were first deblocked with trifluoroacetic acid (TFA) and were then converted to their dicesium salts and allowed to react with 1,5-dibromo-3-oxopentane in DMF. The cesium salt method, first developed for peptide chemistry, and known not to involve racemization,[8] has recently been applied by us for the synthesis of crown ethers[9] and macrolides.[10] There was obtained **4a** (22% yield overall, 26% for ring closure, mp 259.1–262.3 °C dec, $[\alpha]^{23}_D$ −94.0° (*c* 0.95, DMF)) and **4b** (32% yield overall, 48% for ring closure, mp 251.4–254.3 °C, $[\alpha]^{20}_D$ −126.8° (*c* 1.02, DMF)). Thus far only **4b** has been used for further experiments. Methylation with methyl fluorosulfonate gave pyridinium salt **5** (80% yield, nonreproducible decomposition point, $[\alpha]^{22}_D$ −159.6° (*c* 1.00, CH_3OH)). Reduction at room temperature with sodium dithionite in a pH 7 phosphate buffer afforded **6** (98% yield, mp 140.5–142.4 °C, UV (CH_2Cl_2) 352 nm (ϵ 2500), $[\alpha]^{25}_D$ −133.9° (*c* 1.04, CH_3CN)). This reduction method is a large improvement over literature procedures, which call for basic conditions;[11] excellent yields of very pure product are obtained in 10–20 min. Analytical data for all new compounds are good and spectral data are in accord with the proposed structures. We believe that all pyridine compounds reported here are optically pure (note that inversion at one asymmetric center produces a meso diastereomer). As far as we are aware this is the first report of the synthesis of amino acid containing "crown ethers".

The results of several reductions with **6** are given in Table I. Reactions were carried out under nitrogen in acetonitrile with equimolar amounts of **6**, substrate, and $Mg(ClO_4)_2 \cdot 1.5H_2O$.[12] In the presence of oxygen, **6** was completely oxidized to the perchlorate salt of **5** without detectable reduction of substrate. We observed a direct correlation between the sensitivity of **6** to oxidation and the ease of reduction of the substrate. In the absence of $Mg(ClO_4)_2 \cdot 1.5H_2O$ either with or without oxygen no significant oxidation of **6** or reduction of substrate occurred.

Reduction by **6** of 2-benzoylpyridine (**7**) to alcohol **8** proceeded only slowly (72 h) even at the relatively high temperature of 55 °C. Data for the maximum rotation of **8** as well as its absolute configuration have not been reported and therefore this reaction was not examined further. Optical data are, however, available for the alcohol **10** derived from trifluoroacetophenone (**9**), which is a popular substrate for reductions by 1,4-dihydropyridines. We found the reaction to be very sluggish, taking 5 days at 55 °C to go to completion. The degree of asymmetric induction in **10**, 68%, is, however, quite satisfying. The reductions of the ethyl ester (**11**) and amide (**13**) of phenylglyoxylate proceeded exceptionally smoothly. The optical inductions in **12** and **14** of, respectively, 86 and 64% are also very good indeed considering that the chiral centers in **6** are five bonds removed from the site of hydride donation.[13] The reduction of the *N*-ethylamide **15** to alcohol **16** has been attended thus far by experimental difficulties: the isolated chemical yield is poor but the optical induction is high with the same stereochemical result (*S* configuration; see below) as observed in other reductions.

In all cases care was taken to avoid optical fractionation of the alcohol during workup.[14] The recovered perchlorate of pyridinium salt **5** could be reduced by dithionite back to **6** with undiminished rotation. This completes, albeit in two separate reactions, the catalytic cycle of eq 1.

These results represent some of the highest asymmetric in-

ductions ever achieved with optically active 1,4-dihydropyridines.[6] The consistent formation of an excess of the *S* enantiomer (the relative priorities of the groups are the same for all the optically active alcohols allowing direct comparison) strongly suggests structurally related transition states for reduction. ^{1}H NMR shielding effects in the presence of Mg^{2+} indicate complexation of Mg^{2+} close to the diethylene glycol bridge of **6.** Assuming that the oxygen of carbonyl group complexes to Mg^{2+} with the carbonyl carbon oriented toward the 4 position of the 1,4-dihydropyridine, that the phenyl substituent is the largest group, and that complexed α-dicarbonyl compounds assume a cis conformation for the carbonyl groups, the observed *S* configurations can be predicted. It is important to note that **6** is rather rigid owing to the two amide linkages.

Further experiments are in progress.[19]

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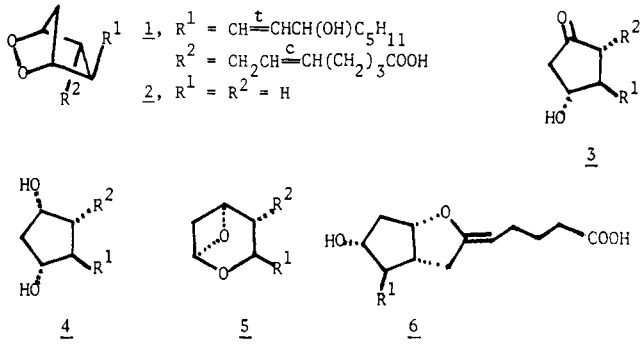
Extraordinary Reactivity of the Prostaglandin Endoperoxide Nucleus. Nonpolar Rearrangement of 2,3-Dioxabicyclo[2.2.1]heptane and -[2.2.2]octane

Sir:

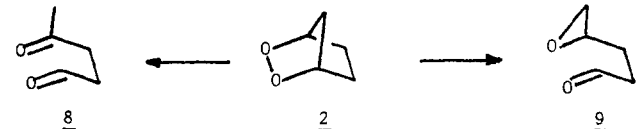
Occasionally Nature provides us with molecules which not only have unusual structures, but which also exhibit extraordinary chemical reactivity. Prostaglandin (PG) endoperoxides[1] (e.g., **1**) possess an unusual bicyclic peroxide nucleus **2**.[2] They are a branch point in the oxidative transformation of polyunsaturated fatty acids into a vast array of physiologically active metabolites.[3] The biological role of **1** depends in large measure on enzymatic conversion into prostaglandins (e.g., **3**, **4**), thromboxane A_2 (**5**),[4] and prostacyclin (**6**).[5] To provide a basis



3 4 5 6

for interpreting the complex biochemistry of **1**, we are studying the chemistry of the model endoperoxide **2** and homologues. We now report that the abnormally large solvent effects found for thermal decompositions of **2**[6] are not observed for decomposition of the less strained homologue, 2,3-dioxabicyclo[2.2.2]octane (**7**).[7] Furthermore, activation enthalpies and entropies for thermal decomposition of **2**, of the homologue **7**, and of *tert*-butyl peroxide in cyclohexane are remarkably different. $\Delta H^{\ddagger}$ increases with decreasing strain in the series.

Thermal decompositions of **2** and **7**[7] were monitored by ^{1}H NMR. Relative rates in various solvents are listed in Table I. Both reactions follow first-order kinetics. As reported previously, the rate of decomposition of **2** increases with solvent polarity and is exceptionally rapid in protic solvents owing primarily to an extraordinary dependence of the rate of rearrangement to levulinaldehyde (**8**) on solvent polarity.[6] The parallel first-order rearrangement of **2** to **9** is a nonpolar process which shows only a small dependence on solvent polarity.



8 2 9

In contrast, the rate of decomposition of **7** varies only slightly and erratically with changes in solvent polarity. The modest acceleration found for decomposition of **7** in protic solvents

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