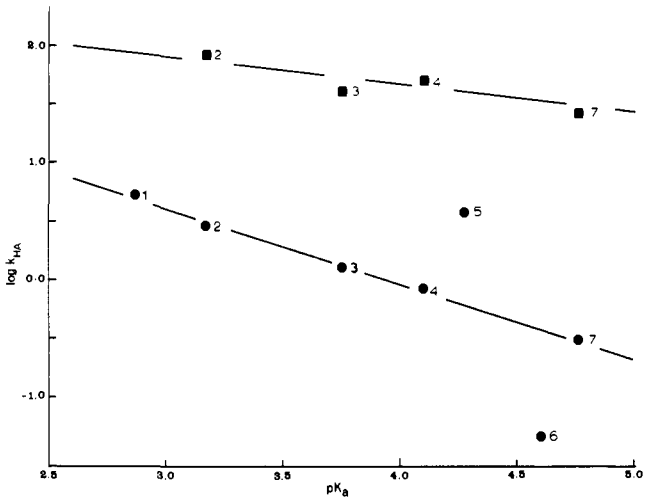

Figure 3. Brønsted plot for the general acid catalyzed dissociation of $Ca[2.2.2]^{2+}$ (■) and $Li[2.1.1]^{+}$ (●). Catalyzing acids are as follows: 1, CH_2ClCO_2H; 2, CH_2ICO_2H; 3, HCO_2H; 4, $CH_2ClCH_2CO_2H$; 5, $HO_2C{\cdot}CO_2^-$; 6, $C_6H_5NH_3^+$; 7, CH_3CO_2H.

pK_a(HA). For a given acid catalyst, the dissociation of $Ca[2.2.2]^{2+}$ is more strongly catalyzed than that of $Li[2.1.1]^{+}$, but it is significantly less sensitive to acid strength (Brønsted α values[17] are 0.25 and 0.64, respectively). The very striking difference between the uncharged substituted acetic acids and the charged acids (monooxalate ion, $HCO_2{\cdot}CO_2^-$, and anilinium ion, $C_6H_5NH_3^+$) when used as catalysts for $Li[2.1.1]^{+}$ is also clearly apparent. It would seem that, although the cations are contained within the cavity of the ligands, the relative charge of the complex and the catalyzing acid plays an important part in these reactions. The catalytic constant, k_H, for proton catalysis is not shown, but log k_H falls well below lines extrapolated from those shown in Figure 3, particularly for $Li[2.1.1]^{+}$. This may be partly a consequence of the positive charge on the proton, but a relatively low reactivity of the proton in general acid catalyzed reactions is frequently observed.[17]

A detailed mechanism for the acid catalyzed pathway is uncertain. A rate law of the form shown in eq 1 and 2 could arise either from a rate-determining proton transfer from HA to $MCry^{n+}$ (followed by, or even possibly coincidental with, loss of the cation), or a rate-determining dissociation of M^{n+} from an $AH{\cdots}CryM^{n+}$ complex. It has been claimed,[18] on the basis of a positive kinetic salt effect on the H^+ catalyzed dissociation, that the rate-determining step for this reaction is the protonation of the cryptate complex. However, this conclusion seems to be of doubtful validity, as catalysis by H^+ should show a positive salt effect whether the mechanism involved a preequilibrium protonation or a rate-determining proton transfer. It is hoped that kinetic hydrogen isotope effect studies, and studies of the proton-transfer reactions between HA and the monoprotonated cryptand, $CryH^+$, might help to resolve this mechanistic question.

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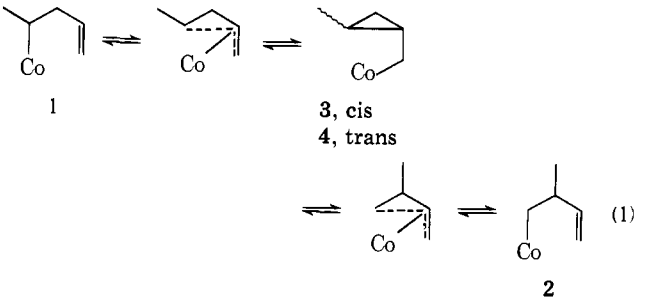
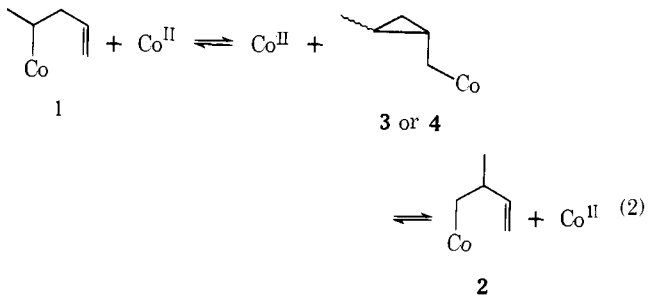
$^3\eta$-Homoallylcobalt Complexes in the Intramolecular Rearrangements of But-3-enylcobaloximes

Sir:

We reported[1,2] the thermal and acid-catalyzed equilibrium of 1-methylbut-3-enyl(pyridine)cobaloxime (**1**) with 2-methylbut-3-enyl(pyridine)cobaloxime (**2**). Cyclopropylcarbinylcobalt complexes such as **3** and **4** were postulated as intermediates in this and related rearrangements. Thus **3** and **4** might arise from **1** or **2** either in a unimolecular process (eq 1) via a $^3\eta$-homoallylic imtermediate or transition state or in





a bimolecular process (eq 2) whereby the C=C of **1** or **2** is attacked by a cobaloxime(II) species. We now report the syntheses and rearrangements of racemic **3** and **4**, studies of the stereochemical course of the acid-catalyzed equilibration of **1** and **2**, and an investigation of the skeletal rearrangement of isotopically labeled but-3-enylcobaloximes. We demonstrate that the acid-catalyzed equilibration of **1** and **2** is stereospecific and intramolecular, and that methylcyclopropylcarbinylcobalt species are plausible intermediates in this process. This is the first demonstration of the stereospecific and intramolecular character of the rearrangement of a but-3-enyl group attached to a metal.

Cobaloximes **3** and **4** were obtained by reacting (pyridine)-

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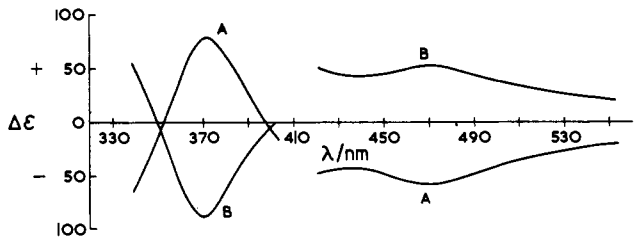
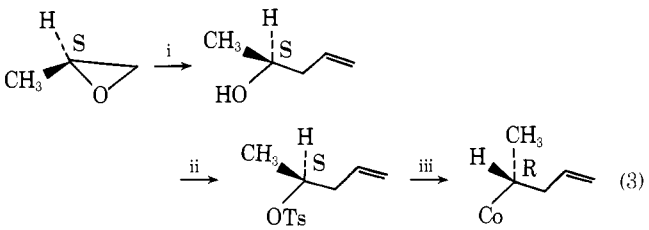


Figure 1. Circular dichroism spectra of (*S*)-**1** (A) and (*R*)-**1** (B).

cobaloxime(I) with *cis*- and *trans*-2-methylcyclopropylcarbinyl bromide,[3] respectively, and were purified by chromatography at 0 °C using an eluant containing pyridine to inhibit their rearrangements. The ^1H and ^{13}C NMR spectra[4] of **3** and **4** are distinctive, prove their stereochemical homogeneity, and allow their rearrangement to be monitored accurately. For **3** and **4** in $CDCl_3$, rapid rearrangement occurs under both aerobic and anaerobic conditions, at similar rates, with first-order kinetics[5a] over 4 half-lives, to essentially the same mixture of **1** and **2** (~1:9) which is, within the limits of detection, the equilibrium mixture.[6] The rates of these rearrangements, and of the equilibration of **1** and **2**, are decreased by pyridine, are not significantly affected by up to 5 mol % aquocobaloxime(II), and are increased by trifluoroacetic acid.[5b] Under comparable conditions the rate constant for the acid-catalyzed rearrangement of **4** is ~25 times larger than that for the acid-catalyzed equilibration of **1** and **2**.[5c] Therefore, **3** and **4** are kinetically competent intermediates for the interconversion of **1** and **2**.

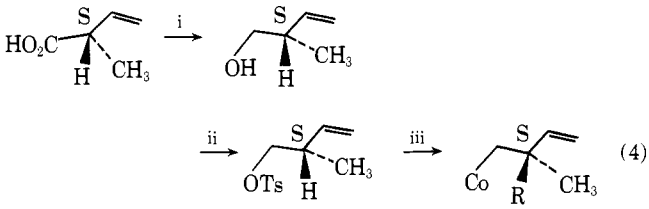
Under conditions of catalysis by TFA in $CDCl_3$,[5] (*R*)-**1** and (*S*)-**1**,[7] prepared from (*S*)- and (*R*)-epoxypropane,[8] respectively (e.g., eq 3)[9] equilibrate[10] *stereospecifically* with (*S*)-**2**



(3)

(i) CH_2=CHMgBr/Cu(I) cat./ether; (ii) *p*-toluenesulfonyl chloride-pyridine; (iii) (pyridine)cobaloxime(I)/ethanol

and (*R*)-**2**, respectively. An authentic sample of (*S*)-**2** (63% enantiomeric excess) was prepared from (*S*)-2-methylbut-3-enoic acid[11] (63% enantiomeric excess) via 2-methylbut-3-en-1-ol and its *p*-toluenesulfonate (eq 4). The circular di-



(4)

(i) $LiAlH_4$–ether; (ii) *p*-toluenesulfonyl chloride/pyridine; (iii) (pyridine)cobaloxime(I)/ethanol

chroism spectra of the optically active cobaloximes are shown in Figures 1 and 2.[12] The rate of TFA-catalyzed equilibration of **1** and **2** in $CDCl_3$ was not significantly affected by the presence of up to 10 mol % diaquocobaloxime(II) and optically pure (*S*)-**2** was still obtained from (*R*)-**1**. This finding rules out the bimolecular mechanism of eq 2, under these conditions.

The character of the equilibration of **1** and **2** as a C-1–C-2 interchange is confirmed by the observations that [1-^{13}C]-

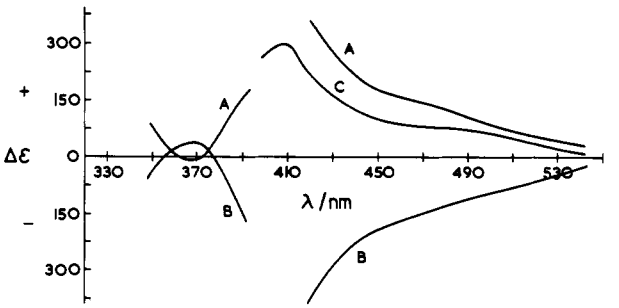
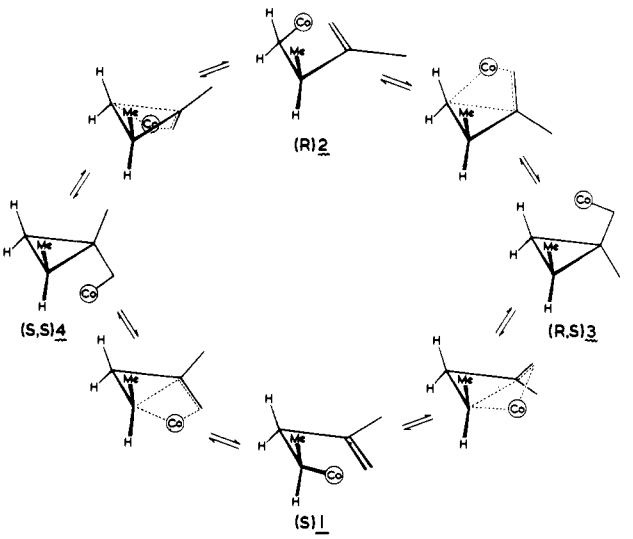
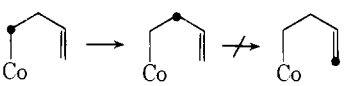


Figure 2. Circular dichroism spectra of (*S*)-**2** from (*R*)-**1** (A), (*R*)-**2** from (*S*)-**1** (B), and (*S*)-**2** prepared from 2-methyl-but-3-enoic acid (63% enantiomeric excess) (C). Concentrations in methanol: [**1**] = 7.8 × 10^{-4} mol dm^{-3}; [**2**] = 2.4 × 10^{-4} mol dm^{-3}.

Scheme I



but-3-enyl(pyridine)cobaloxime[13] and [1,1-$^2H_2$]but-3-enyl(pyridine)cobaloxime[13] equilibrate with [2-^{13}C]but-3-enyl(pyridine)cobaloxime and [2,2-$^2H_2$]but-3-enyl(pyridine)cobaloxime, respectively, without forming [4-^{13}C] or [4,4-$^2H_2$] cobaloximes (cf. eq 5). Transition states or intermediates in which C-1, C-2, and C-4 become equivalent (e.g., via cyclobutylcobalt species) are therefore excluded for these arrangements.



(5)

● = $^{13}C^1H_2$ or C^2H_2

The results with optically active **1** exclude dissociative mechanisms involving homolysis or heterolysis of the alkyl–Co bond. Comparison of the relative rates and products of the rearrangements of **3** and **4** with those of **1** and **2** supports the intermediacy of *both* methylcyclopropylcarbinylcobalt species in equilibrations of **1** and **2**. A mechanism for the equilibration of **1** and **2** consistent with all of the results is shown in Scheme I in which four distinct $^3\eta$-homoallylcobalt complexes (intermediates or transition states) connect **1** to **2**. It is envisaged that the formation of the $^3\eta$-homoallylcobalt complexes requires a thermally induced and/or trifluoracetic acid assisted dissociation of pyridine. Studies of equilibria in the protonation of alkyl(pyridine)cobaloximes with TFA and kinetic studies of the TFA-catalyzed equilibration of **1** and **2** suggest that TFA both protonates a dioximato ligand *and* removes pyridine.[14] A possible reactive intermediate in the TFA-catalyzed reaction is therefore a *protonated* five-coordinate organocobaloxime.

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(4) **3**: ^{13}C NMR (^1H decoupled, in $CDCl_3$) δ 10.7, 13.5, 14.6 (cyclopropyl ring C's), 12.1 (4 dmg Me's), 18.6 (methyl), 33.2 (br, Co-CH_2), 125.4, 137.7, 149.4, and 149.7 ppm (pyr C's and 4 dmg C=N's). **4**: ^{13}C NMR (^1H decoupled, in $CDCl_3$) δ 12.1 (4 Me's) 14.4, 15.1, 18.9 (cyclopropyl ring C's), 22.8 (methyl), 38.0 (br, Co-CH_2), 125.3, 137.6, 149.3, and 149.6 ppm (pyr C's and 4 dmg C=N's).
(5) (a) In $CDCl_3$ with [cobaloxime] = 0.38 mol dm^3 at 298 K: for **3** $\rightarrow$ **1** + **2**, $10^4k_1 = 3.3 \pm 0.4\ s^{-1}$; for **4** $\rightarrow$ **1** + **2**, $10^5k_1 = 9.0 \pm 0.4\ s^{-1}$. (b) In $CDCl_3$ with [cobaloxime] = 0.39 mol dm^{-3} at 310 K: for **1** $\rightleftarrows$ **1** + **2**, $10^4k_1 = 4.6 \pm 0.2\ s^{-1}$, [TFA] = 0.78 M; $10^4k_1 = 2.1 \pm 0.1\ s^{-1}$, [TFA] = 0.52 M. (c) In $CDCl_3$ with [cobaloxime] = 0.52 mol dm^{-3} at 295 K: for **4** $\rightarrow$ **1** + **2**, $10^3k_1 = 9 \pm 1\ s^{-1}$; [TFA] = 0.21.
(6) It is not expected that the exact equilibrium mixture of **1** and **2** would be formed initially from **3** or **4** under kinetically controlled conditions. However, there is no detectable deviation from the equilibrium ratio of **1** and **2** at any stage of reactions starting from **3** or **4**.
(7) For (*R*)-**1**, $[\alpha]_D$ +60° (0.13 M, $CHCl_3$); for (*S*)-**1**, $[\alpha]_D$ −58° (0.13 M, $CHCl_3$).
(8) B. T. Golding, D. R. Hall, and S. Sakrikar, *J. Chem. Soc., Perkin Trans. 1*, 1214 (1973); B. T. Golding, P. J. Sellars, and A. K. Wong, *J. Chem. Soc., Chem. Commun.*, 570 (1977).
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(10) Equilibrations were carried out for 5–15 half-lives with 0.13 M solutions of (*R*)- and (*S*)-**1** and (*S*)-**2** (63% enantiomeric excess) in $CHCl_3$ containing 0.1 M TFA. After equilibrations, the mixture of **1** and **2** was purified, prior to measurement of circular dichroism, from ~5% unknown product(s) of decomposition by column chromatography on silica gel.
(11) Resolved by the method of R. Rossi, P. Diversi, and G. Ingrosso, *Gazz. Chim. Ital.*, **98**, 1391 (1968); see also G. T. Pearce, W. E. Gore, and R. M. Silverstein, *J. Org. Chem.*, **41**, 2797 (1976).
(12) We thank Dr. P. M. Scopes, Westfield College, for these spectra.
(13) The position of the label was confirmed by NMR spectroscopy.
(14) Unpublished results of the authors; see also M. P. Atkins, B. T. Golding, and P. J. Sellars, *Proc. Eur. Symp. Vitamin B_{12} Intrinsic Factors, 3rd, 1979*, 587 (1979).

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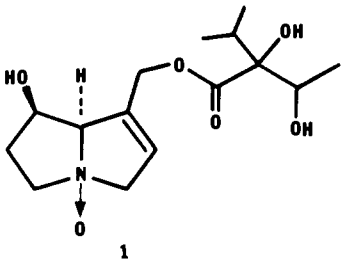
Synthetic Studies on Pyrrolizidine Alkaloids. 1. (±)-Heliotridine and (±)-Retronecine via Intramolecular Dienophile Transfer

Sir:

The pyrrolizidine alkaloids constitute an exceptionally large class of naturally occurring materials which have attracted the attention of synthetic organic chemists with increasing frequency in recent years.[1] The large number of such naturally occurring alkaloids, their deceptively simple structural features, and a remarkable range and potency of biological effects have all served to make these materials unusually attractive synthetic targets. Particularly intriguing are the changes in biological activity which accompany relatively minor modifications in structure. Thus, indicine *N*-oxide[2] [**1**, an oxidized trachelanthic acid ester of retronecine (**2**)] shows extremely promising antitumor activity, while the very similar heliotrine



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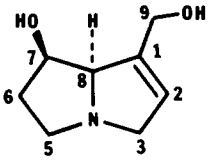

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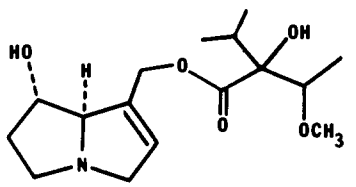

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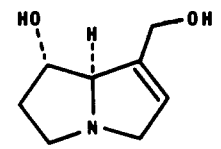

4

[**3**, an ester of heliotridine (**4**)] is an established carcinogen.

Although considerable progress has been made recently, by a number of groups,[3] in developing synthetic approaches to somewhat simpler, less oxidized pyrrolizidines, little progress has been described toward more complex examples such as heliotridine and retronecine. Presently we report the synthesis of retronecine and heliotridine by a route which relies heavily on the previously described intramolecular dienophile transfer technique[4] to simultaneously form one key carbon nitrogen bond ($N-C_8$, pyrrolizidine numbering), establish the $\Delta_{1,2}$ double bond, and functionalize C_3 appropriately for eventual formation of the $N-C_3$ bond.

The known,[5] readily available acetylenic ester **5**, upon addition to 1.2 equiv of lithium divinylcuprate at −78 °C in tetrahydrofuran, reaction at −78 °C for 4.25 h, and quenching with methanol (−78 °C), affords, after dilution with ether, filtration through Florisil, and normal extractive workup, diene ester **6** as a single isomer in quantitative yield: ^1H NMR (90 MHz, $CDCl_3$) δ 6.42 (dd, J = 18, 10 Hz, 1 H, C_4 vinyl), 5.93 (s, 1 H, C_2 vinyl), 5.80 (d, 1 H, J = 18 Hz, C_5 vinyl), 5.40 (d, 1 H, J = 10 Hz, C_5 vinyl), 4.83 (s, 2 H, CH_2), 4.69 (br s, 1 H, OCHO), 3.72 (s, 3 H, OCH_3), 4.00–3.33 (m, 4 H, CH_2O), 1.59 (m, 4 H, CH_2CH_2); mass spectrum (CI, methane) *m/e* 227. Ester **6** was reduced (2.0 equiv of i-Bu_2AlH in ether, 0 °C, 0.25 h) to dienol **7**, which was oxidized with excess active manganese dioxide[8] in benzene containing anhydrous Celite (23 °C, 48 h) to afford the labile dienal **8**, used immediately in the subsequent step after filtration and concentration under reduced pressure.

Addition of aldehyde **8** to a cold (−78 °C) solution of the lithium enolate[4] of **9** (prepared by addition of **9** to 1.1 equiv of lithium diisopropylamide in 4:1 THF-hexamethylphosphoramide at −78 °C), followed by warming to −25 °C over 45 min, quenching (−25 °C) with methanol, and normal extractive workup, cleanly afforded alcohol **10** [IR (film, partial) 3400 (br), 1650 (br); NMR (90 MHz, $CDCl_3$, partial) δ 7.87–7.18 (m, 8 H, aromatic), 6.20 (dd, J = 18, 11 Hz, 1 H, CH=CH_2), 5.54 (d, J = 9 Hz, 1 H, vinyl), 5.33 (d, J = 18 Hz, 1 H, CH=CH_2), 5.03 (d, 1 H, J = 11 Hz, CH=CH_2), 4.79 (br q, J = 6 Hz, 1 H, methine), 2.69 (s, 3 H, CH_3), 2.44 (d, J = 6 Hz, 2 H, CH_2C=O), 2.15 (s, 3 H, CH_3)] which was readily converted[10] (*tert*-butyldimethylchlorosilane, imidazole, dimethylformamide, 23 °C, 12 h) into its *tert*-butyldimethylsilyl ether derivative **11**. This key intermediate, formed in 64% overall yield from **7** after purification by column (MPLC) chromatography,[9] now contains all carbons and the nitrogen destined to appear in the final alkaloid products, as well as differentially protected hydroxyl moieties destined to appear at C_7 and C_9.

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