this paper represents one of the very few known photochemical reactions involving reduced flavin. Other examples include the photoalkylation of reduced flavin bound to lactate oxidase[32] and the photodehalogenation reactions observed with reduced 7- and 8-halogen-substituted flavins.[33]

Acknowledgment. We thank Drs. Wallace Ashton and Franz Müller for gifts of 1-deazariboflavin and 7,8-dimethyl-1,10-ethyleneisoalloxazium perchlorate, respectively. We are grateful to Dr. Richard Rest for the use of HPLC equipment. We also thank Juanita Yee-Foon Peck for skilled technical assistance.

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Communications to the Editor

Self-Reproduction of Chirality in C-C Bond Formation via Dipolar Intermediates Generated in Situ by [1,5] Hydrogen Transfer

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In this paper we describe the self-reproduction of chirality in the thermal isomerization of [[2-(1-pyrrolidinyl)phenyl]-methylene]propanedinitriles to pyrroloquinoline derivatives. During this conversion, which takes place via a 1,5-hydrogen shift and subsequent cyclization, the center of chirality in the starting material is lost in the corresponding dipolar intermediate but reproduced with retention of configuration upon cyclization. In addition the suprafacial 1,5-hydrogen shift offers the possibility to introduce a second novel chiral center with >98% enantioselectivity.

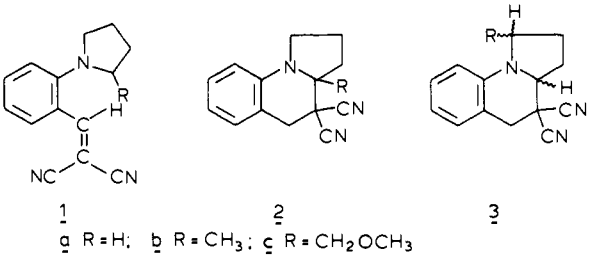
Recently, Seebach et al.[1] have described a novel method for the synthesis of chiral α-heterosubstituted carboxylic acids via α-alkylation at the chiral center. During this so-called "self-reproduction of chirality" the chirality at the reacting sp^3-C atom is temporarily lost. However, the chirality of this center is memorized by a novel chiral center that is constructed prior to reaction at the original chiral center, and conformational effects direct the alkylation of the intermediate. At the original chiral center a highly stereospecific reaction takes place.

In the course of our studies on the C-C bond formation via the "*tert*-amino effect"[2] we have previously described the thermal isomerization of [[2-(1-pyrrolidinyl)phenyl]methylene]propanedinitriles (**1a**) to pyrroloquinolines (**2a**).[2a]

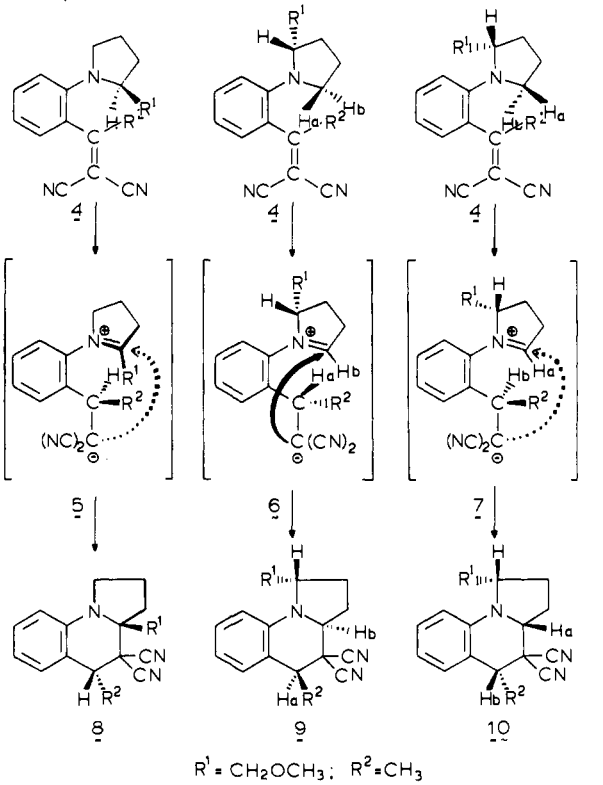
When we further studied the regioselectivity of this reaction we found that heating of **1b**[3] in refluxing 1-butanol (0.5 h) yielded selectively 1,2,3,3a,4,5-hexahydro-3a-methylpyrrolo[1,2-*a*]-quinoline-4,4-dicarbonitrile (**2b**) (85%) (Chart I). However, with a more bulky methoxymethyl substituent as in **1c**, the regioselectivity was lost.[3] Heating of **1c** in refluxing 1-butanol (2.5 h) gave a mixture of **2c** (46%) and two diastereomers of **3c** [(1α,3aα)-, 19%; (1α,3aβ)-, 17%].

Subsequently the stereoselectivity of the C-C bond formation was studied. Cyclization of the *chiral* (*S*)-[1-[2-[2-(methoxymethyl)-1-pyrrolidinyl]phenyl]ethylidene]propanedinitrile (**4**),[3] in which the α-carbon atom of the vinyl moiety is a *prochiral center*, in refluxing 1-butanol (5 h) gave three compounds. Compound **8**[4] was obtained in a yield of 33% together with two

Chart I



Scheme I



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(3) Compounds **1b** and **1c** were synthesized from 2-methyl- and (±)-2-(methoxymethyl)pyrrolidine, respectively, 2-fluorobenzaldehyde, and malonitrile. For the procedure see ref 2a. Compound **4** was synthesized from (*S*)-(+)-2-(methoxymethyl)pyrrolidine, 2-fluoroacetophenone, and malonitrile.[2a]

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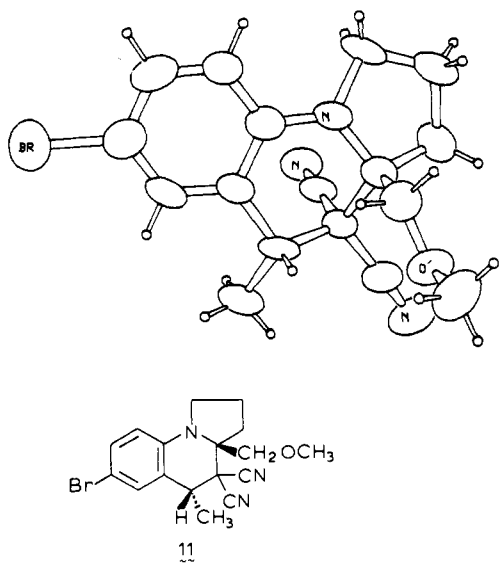

Figure 1. Crystal structure of compound **11**.

diastereomers, **9** and **10**, in yields of 35% and 6%, respectively. The quinoline derivative **8** was obtained as one enantiomer. ^{1}H NMR spectroscopy, 200 MHz, of **8** in the presence of the chiral shift reagent ytterbium tris[3-[(trifluoromethyl)hydroxymethylene]-*d*-camphorato], ($Yb(tfc)_3$), proved an ee of >98%[5] (Scheme I).

In order to determine the absolute configuration of **8** by X-ray analysis, this compound was brominated with NBS in CCl_4 at room temperature to give **11** [78%, mp 128–130 °C (MeOH)]. X-ray analysis of **11**[6a] showed that the cyclization had taken place with retention of configuration at the chiral center, with the methoxymethyl group at the bridgehead carbon atom and the methyl group at the new chiral center in the trans position (Figure 1).

From these results we concluded that, first, the 1,5-hydrogen shift proceeds *enantioselectively* and that, second, in the chiral dipolar intermediate **5** the carbanion is forced to add to the iminium double bond from below because the upper side is shielded by the methoxymethyl group (Scheme I). The chirality at the carbon atom with the methoxymethyl substituent in **4** is lost upon the intramolecular hydrogen transfer but a new chiral center is created. In the cyclization step the original chiral center is formed enantioselectively because the chirality in **4** is memorized in the form of a unique chiral "anticlockwise" helical dipolar intermediate.

The configurations of **9** and **10**, were determined by ^{1}H NOE difference spectroscopy. Definite proof of the structure of **10** was obtained by X-ray analysis (Figure 2),[6b] assuming that the chiral center with the methoxymethyl group is retained. In the formation of **9** and **10** either one of the two hydrogen atoms (Ha or Hb) undergoes a 1,5-hydrogen shift, however, in the case of **9** and **10**

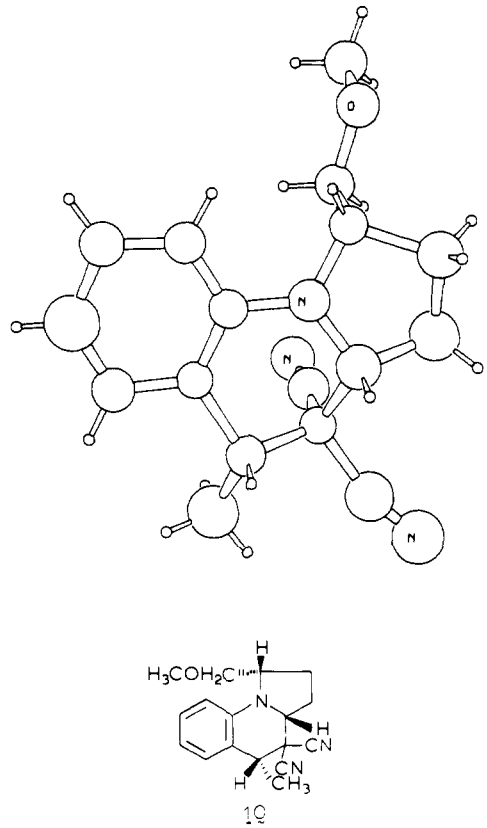

Figure 2. Crystal structure of compound **10**.

not in a 1:1 ratio.[7] CPK models reveal that in **4** the pyrrolidinyl group is out of plane with the phenyl group because of steric hindrance caused by the methyl group attached to the vinyl moiety. In the case that Hb undergoes the 1,5-hydrogen shift and **10** is formed, the position of the pyrrolidinyl ring causes severe steric hindrance between the methoxymethyl group and the aromatic ring. This is much less the case when Ha shifts and **9** is formed favorably.

The cyclization of the dipolar intermediates **6** and **7**, leading to **9** and **10**, respectively, can only take place from one side because otherwise the methyl group would have to turn inward where it would interfere with the pyrrolidine ring.

The difference between our reaction and the self-reproduction of chirality via α-alkylation as reported by Seebach et al.[1] is that *auxiliary reagents are not required.* The self-reproduction of chirality in the C–C bond formation to yield **8** is a direct consequence of the stereospecificity of a concerted [1,5] H transfer and of the quantitative storage of chiral information in the resulting dipolar intermediate although the original chiral center is lost.[8,9] We are currently studying the effects of the structure of the chiral (cyclo)dialkylamino group and of the influence of other groups R^2 in compounds like **4** on the regioselectivity.

Acknowledgment. We thank Prof. Dr. D. Seebach (ETH, Zürich) for stimulating discussions. This investigation was supported by the Netherlands Foundation of Chemical Research

(4) Satisfactory elemental analyses were obtained for all compounds. Compound **8**: mp 139–141 °C (MeOH); $[\alpha]^{25}_D$ +42.5° (*c* 0.4, $CHCl_3$). **9**: mp 123–125 °C (MeOH); $[\alpha]^{25}_D$ -158° (*c* 0.2, $CHCl_3$). **10**: mp 139–141 °C [petroleum ether (bp 60–80 °C)]; $[\alpha]^{25}_D$ -29.5° (*c* 0.17, $CHCl_3$).

(5) When racemic **4** was reacted under the same conditions the racemic **8–10** were obtained. The 200-MHz ^{1}H NMR spectra of a mixture of each of the racemates and 1.5 equiv of $Yb(tfc)_3$ showed two doublets ($\Delta\nu$ = 4.2 Hz) whereas **8–10** obtained from the chiral starting material showed one doublet.

(6) (a) **11**: $C_{17}H_{18}BrN_3O$, monoclinic, space group $P2_1$, a = 7.680 (5) Å, b = 8.947 (5) Å, c = 12.527 (7) Å, β = 108.05 (5)°; Z = 2, d_c = 1.458 g cm^{-3}. Mo Kα radiation, $2 < \theta < 25°$. Structure determination (heavy atom method) and refinement (full matrix) based on 1586 reflections with $F_o^2 > 3\sigma(F_o^2)$. Absolute configuration determined from anomalous scattering of Br. Hydrogen atoms at calculated positions with fixed thermal parameters. Final R = 4.4%, R_w = 5.1%, 271 variables. (b) **10**: $C_{17}H_{19}N_3O$, orthorhombic, $P2_12_12_1$, a = 8.627 (5) Å, b = 13.443 (7) Å, c = 13.550 (7) Å. Z = 4, d_c = 1.139 g cm^{-3}. Mo Kα radiation, $2 < \theta < 25°$. Structure determination (direct methods) and refinement (full matrix) based on 978 reflections with $F_o^2 > 3\sigma(F_o^2)$. Absolute configuration not determined. Hydrogen positions refined. Final R = 3.0%, R_w = 3.8%, 267 variables.

(7) The product ratio of **9** and **10** is determined by the ratio of shifts of Ha and Hb, because the suprafacial [1,5] H shift is the rate-determining step.[2a]

(8) A thermal 1,5-carbon migration with inversion of configuration has been reported by: (a) Klaerner, F. G.; Brassel, D. *J. Am. Chem. Soc.* **1980**, *102*, 2469–2470. (b) Baldwin, J. E.; Broline, B. M. *J. Am. Chem. Soc.* **1982**, *104*, 2857–2865.

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(SON) with financial aid from the Netherlands Organization for Advancement of Pure Research (ZWO).

Supplementary Material Available: Stereodrawing and tables of bond lengths and angles and of positional and thermal parameters (3 pages). Ordering information is given on any current masthead page.

Ketonization of 1,3-Cyclohexadienol, a Conjugated Enol

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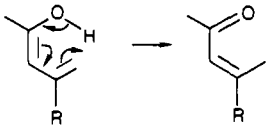
Although rates of enolization of aldehydes and ketones are fairly straightforward to measure,[1] determination of the rates of the reverse reaction has been hampered by the difficulty of obtaining solutions of the enols.[2] Recently, however, Kresge,[3] Capon,[4] and their collaborators have developed techniques to generate enols in greater than equilibrium concentrations, and they have been able to directly measure the rates of ketonization of a variety simple enols. In contrast to simple enols, however, the rates of ketonization of dienols remain largely unknown.[5] These compounds are of particular importance because they are intermediates in the conversion of β,γ-unsaturated ketones to their conjugated α,β-isomers.[6] Duhaime and Weedon[5d] have concluded, partly on the basis of the very rapid rates of uncatalyzed ketonization of **1a,b** (k = 40 s^{-1} for **1b** at 23 °C, $t_{1/2}$ = 17 ms), that dienols ketonize via a 1,5-sigmatropic hydrogen shift.



1a, R = Me
b, R = *t*-Bu

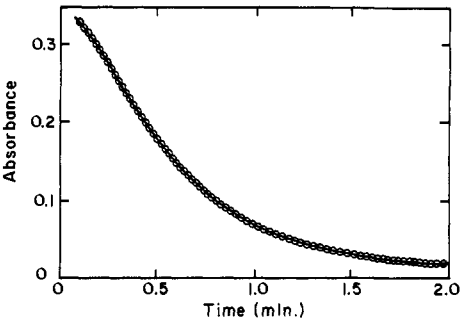
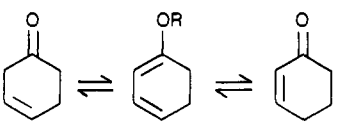


Figure 1. Plot of absorbance vs. time for the reaction of sweet potato acid phosphatase (0.0375 mg/mL) with 1,3-cyclohexadienol phosphate in D_2O solution (pD 4.70, [OAc^-] = 5 mM, 25.0 °C). The theoretical curve was calculated by using $k_1 = 7.26 \times 10^{-2}$ s^{-1} and $k_2 = 4.25 \times 10^{-2}$ s^{-1}. All experimental points are within ±0.0004 absorbance units of the theoretical line.

We have now examined the rate of water-catalyzed ketonization of 1,3-cyclohexadienol (**2a**), a dienol that is locked in a conformation such that a 1,5-sigmatropic rearrangement is impossible. In contrast to the rates of ketonization of **1a,b**, the uncatalyzed rate of ketonization of **2a** is relatively slow ($k_0 = 1.4 \times 10^{-2}$ s^{-1} in D_2O at 25 °C, $t_{1/2}$ = 48 s). In addition, this process leads



3 **2a**, R=H **4**
b, R=PO_3H_2

exclusively to the β,γ-unsaturated isomer, rather than the α,β-unsaturated compound observed with **1a,b**. These results confirm the mechanism suggested by Duhaime and Weedon for **1a,b**.

The dienol **2a** was generated in situ by the action of sweet potato acid phosphatase on the corresponding enol phosphate **2b**.[7] When **2b** is treated with acid phosphatase in deuterium oxide at pD 4.7–5.6 and the reaction is monitored at 265 nm, a first-order decay with a significant induction period is observed (Figure 1). An ultraviolet scan of the product shows no significant absorbance above 220 nm, demonstrating that the final product is exclusively 3-cyclohexenone (**3**). We confirmed this conclusion by adding a small quantity of 10 N sodium hydroxide to the product solution and observing an increase in absorbance at 232 nm due to formation of **4**.

This variation of absorbance with time is characteristic of a series reaction (eq 1). For k_1 and k_2 both pseudo first order, the

$$\mathbf{2b} \xrightarrow{k_1} \mathbf{2a} \xrightarrow{k_2} \mathbf{3} \qquad (1)$$

change in absorbance may be analyzed by least-squares fitting of the data to a double exponential.[8] At relatively high concentrations of enzyme and low buffer concentration, the system is described quite well. At low enzyme concentrations, where $k_1 \lesssim k_2$, the data give only a fair fit (presumably because the k_1 process is not strictly first order). Alternatively, the reaction was run at high enzyme concentrations where the formation of the intermediate is rapid relative to its breakdown to products ($k_1 \gg k_2$). The data were then analyzed by ignoring the first part of the reaction and treating the system as a pseudo-first-order process. In cases where both methods were used, agreement was good (±15%).

Since in two-step reactions it is not generally true that the slower decay corresponds to the second step in the reaction,[8] it is necessary to demonstrate that the exponential decay that we attribute to ketonization (k_2) is due to that reaction and not some process

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(5) Dienols have been generated and observed, although their rates of ketonization have rarely been examined. See, for example: (a) Schmidt, E. A.; Hoffmann, H. M. R. *J. Am. Chem. Soc.* **1972**, *94*, 7832. (b) Noyori, R.; Inoue, H.; Katô, M. *J. Am. Chem. Soc.* **1970**, *92*, 6699. (c) Noyori, R.; Inoue, H.; Katô, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3673. (d) Duhaime, R. M.; Weedon, A. C. *J. Am. Chem. Soc.* **1985**, *107*, 6723. (e) Tureček, F.; Havlas, Z. *J. Org. Chem.* **1986**, *51*, 4066.

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