137. Asymmetric Catalysis by Vitamin B_{12}. The Mechanism of the Cob(I)alamin-Catalyzed Isomerization of 1,2-Epoxycyclopentane to (*R*)-Cyclopent-2-enol

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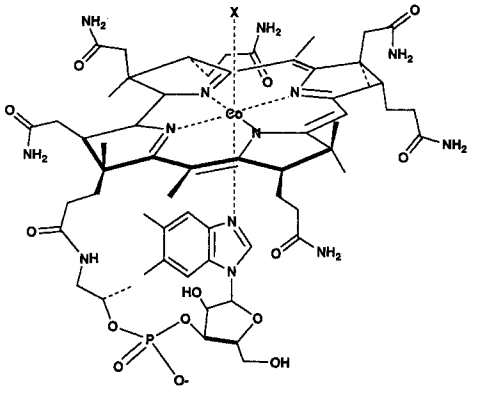
The isomerization of 1,2-epoxycyclopentane (**1**) to enantiomerically enriched (*R*)-cyclopent-2-enol (**2**) in protic solvents is catalyzed by cob(I)alamin. The enantiomeric excess (e.e.) of (*R*)-**2** is usually *ca.* 60%; it is only slightly dependent on the temperature, but increases with decreasing dielectric constant ε of the solvent. Standard kinetic methods show the reaction to be first order in vitamin B_{12} and zero order in **1**. The rate constant increases exponentially with increasing ε of the solvent. An *Arrhenius* plot at $\varepsilon = 40$ gives activation parameters $\Delta H^{\neq} = 78 \pm 4$ kJ·mol^{-1} and $\Delta S^{\neq} = -49 \pm 1$ J·mol^{-1}·K^{-1}. The isomerization **1** → **2** proceeds in two steps (*Schemes 2* and *7*): *i*) The epoxide ring is first opened by the proton-assisted fast and irreversible nucleophilic attack of the chiral Co^{I} catalyst to form diastereoisomeric (1*R*,2*R*)- and (1*S*,2*S*)-(2-hydroxycyclopentyl)cob(III)alamins **6** in a ratio of *ca.* 4:1 which are the dominant species in the steady state; *ii*) The intermediates **6** then decompose in the rate-limiting step to form **2** and recycled catalyst. Experiments with specifically ^{2}H-labeled **1** showed the hydro-cobalt elimination **6** → **2** to be non-stereoselective. It proceeds *via* reversible Co–C bond homolysis to a free 2-hydroxycyclopentyl radical from which stereoelectronically controlled H-abstraction by Co^{II} takes place.

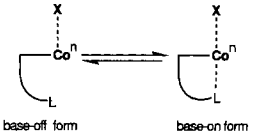
1. Introduction. – Recently, we reported on the isomerization of achiral epoxides to optically active allylic alcohols with catalytic amounts of cob(I)alamin (= vitamin B_{12s})[2])

[1]) Part of the Ph. D. thesis of *P. B.*, University of Berne, 1991; presented in part by *P. B.* at the Autumn Meeting of the Swiss Chemical Society, October 20, 1989, Berne, and at the VIIth EUCHEM Conference of Organic Free Radicals, 17–21 September 1990, Arles, France.

[2]) For convenience, we use the following short forms for vitamin-B_{12} derivatives: 'B_{12s}' for cob(I)alamin (Co^{I}, no *Coβ*-ligand, only base-off form), 'B_{12r}' for cob(II)alamin (Co^{II}, no *Coβ*-ligand, base-on or base-off form), 'B_{12a}' for hydroxocob(III)alamin hydrochloride (Co^{III}, *Coβ*-OH, base-on or base-off form), and 'alkylcobalamin' for alkylcob(III)alamin (Co^{III}, *Coβ*-R, base-on or base-off form).



Vitamin B_{12} (= cyanocob(III)alamin) X = CN



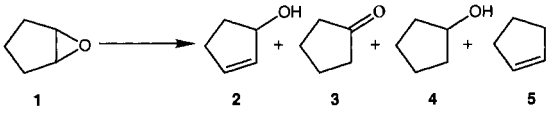
in protic polar solvents [1]. This enantioselective isomerization is specially suited for the efficient preparation of (*R*)-cycloalk-2-enols, simply by stirring a methanolic solution of the corresponding 1,2-epoxycycloalkane in presence of 1–3 mol-% of hydroxocobalamin hydrochloride (= vitamin B_{12a})[2]), some metallic Zn, and NH_4Cl for 2–4 days at room temperature under Ar. Although the enantiomeric excesses (e.e.'s) of the 5- and 6-membered allylic alcohols were moderate (65 and 40%, resp.) [1], they are comparable to, or better than those obtained by other methods, like the isomerization of epoxides with chiral Li-amides [2] or the kinetic resolution of racemic cyclic allylic alcohols by the *Sharpless* epoxidation [3]. The moderate e.e. in the exceedingly simple cob(I)alamin-catalyzed isomerization might be tolerated, if the enantiomerically enriched alcohol may be transformed efficiently to pure (crystalline) compounds as, *e.g.*, in the three-step synthesis of the enantiomerically pure prostaglandin intermediate (+)-(3a*S*,6a*R*)-3,3a,6,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one, obtained in 32% overall yield from (*R*)-cyclopent-2-enol (e.e. 62%) [4].

The cob(I)alamin-catalyzed isomerization of epoxides to allylic alcohols is also of interest from the point of view of its mechanism. Two main problems have to be addressed: *i*) the enantioselective nucleophilic opening of the epoxide with the formation of alkylcobalamin intermediates and *ii*) their olefin-forming decomposition with regeneration of the catalyst. With regard to the enantioselective ring-opening, *Golding et al.* have shown, that the reaction of cob(I)alamin with 10 mol-equiv. of racemic epoxypropane yields a 3:1 mixture of the diastereoisomeric (2*R*)- and (2*S*)-(2-hydroxypropyl)cobalamins [5]. In both compounds, the alkyl groups are attached to the Co-atom at the β(upper)-side of the corrin, as proven by X-ray analysis of (*R*)- and (*S*)-(2,3-dihydroxypropyl)cobalamin [6]. This is not obvious *a priori*, since alkylation of cob(I)alamin – even with sterically bulky secundary alkylation agents, containing electron-withdrawing substituents – may also take place at the α-side [7].

Concerning the olefin-forming decomposition of alkyl-Co^{III} derivatives of cobalamin and vitamin-B_{12}-related complexes containing H in 2-position relative to the Co-atom, a large body of information has been reviewed [8]. Hydro-cobalt-elimination and hydro-cobalt-addition are inverse processes; their regioselectivity and reversibility strongly depends on the reaction conditions (type of Co-complex, pH of the medium, *etc.*) [9]. Nevertheless, there is no clear-cut picture about the mechanism of the olefin-forming reaction. Interpretations are ranging from concerted *syn*-β-elimination [10], concerted β-elimination [11], β-H-transfer between a [R·,Co^{II}] geminate radical pair [12], sequential R–Co bond homolysis followed by a rapid β-H-transfer to Co^{II} [13] to concurrent and competitive Co–C bond homolysis and β-H-elimination [14].

The mechanism of the cob(I)alamin-catalyzed conversion of achiral epoxides to optically active allylic alcohols was now studied in the case of the isomerization of 1,2-epoxycyclopentane (**1**). Under standard conditions (1 mol-% of hydroxocobalamin hydrochloride, Zn^0, NH_4Cl, MeOH, 3 d at r.t. under Ar), **1** was converted to (*R*)-cyclopent-2-enol

Scheme 1



1 **2** **3** **4** **5**

(**2**; 64% yield, 62% e.e.; *Scheme 1*). As by-products, cyclopentanone (**3**; 5.5%), cyclopentanol (**4**; 0.5%), and cyclopentene (**5**; *ca.* 30%) were detected. It was intended to get an insight into factors operating in the enantioselective epoxide-ring opening, the stereochemistry of the olefin-forming step, and the generation of the by-products.

2. Kinetics and Thermodynamics. – The rate and the enantioselectivity of the isomerization of 1,2-epoxycyclopentane (**1**) to (*R*)-cyclopent-2-enol (**2**) and the by-product cyclopentanone (**3**) was determined at different temperatures and in different solvents. Solutions of red B_{12a}[2]) were first reduced by an excess of metallic Zn in presence of NH_4Cl under Ar, until the colour of green B_{12s}[2]) appeared (after some min). In the dark, a large excess of **1** (30–100 equiv. with respect to B_{12s}) was then added, whereby the colour turned immediatly to orange. Samples were taken and the concentrations of **2** and **3** determined quantitatively by GC (cyclohexanol as internal standard); what is referred as the 'observed rate' (k_{obs}) of the isomerization is the sum of the rates of formation of the allylic alcohol **2** and the ketone **3** formed in a ratio of *ca.* 11:1. The e.e. of (*R*)-**2** was measured by GC on a chiral stationary phase. Towards complete consumption of **1**, the colour changed gradually back to green ($\rightarrow B_{12s}$).

At medium or high epoxide concentration, the rate of isomerization of **1** is independent of **1** but linearly dependent on the concentration of B_{12}. The kinetics is thus

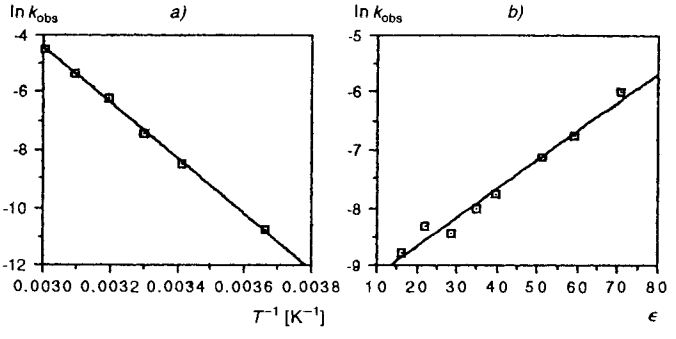


Fig. 1. *Logarithm of the observed rate constant* k_{obs} *of the isomerization of* **1** vs. a) *the reciprocal temperature* T^{-1} ($\ln k_{obs} = 9656 \cdot T^{-1} + 24.5$) *and* b) *the dielectric constant* ε *of the solution* ($\ln k_{obs} = 0.050\ \varepsilon + 9.7$)

Table 1. *Isomerization* **1**→**2** + **3** *at Different Temperatures*[a])

T [°C]	T^{-1} [10^{-3} K^{-1}]	k_{obs} [10^{-3} s^{-1}][b])	in k_{obs}	e.e. [%] of **2**[c])
0	3.66	0.0211	–10.8	52
20	3.41	0.209	–8.47	52
30	3.30	0.597	–7.42	51
40	3.19	2.04	–6.19	51
50	3.10	4.84	–5.33	49
60	3.00	11.1	–4.50	49

[a]) Conditions: 0.347M **1**, 0.18M NH_4Cl in MeOH/H_2O 82:18 (*v*/*v*; ε = 40), 0.01M B_{12}, Zn powder, 20° in the dark.
[b]) Initial first-order (in B_{12}) rate constant of the formation of the sum of **2** and **3** (ratio 2:3 ≈ 11).
[c]) Same conditions as[a]), but in MeOH/H_2O 57:43 (*v*/*v*, ε = 52).

first-order in B_{12} and zero-order in **1**[3]). The observed rate constant k_{obs} is an exponential function of the reciprocal temperature (*Table 1, Fig. 1a*) and of the dielectric constant ε of the solution (*Table 2, Fig. 1b*). The rate constant also increases by irradiation with light and with increasing pH of the solution: under slightly acidic conditions (0.4M NH_4Cl in MeOH at 20°C) in the dark, k_{obs} is $0.22 \cdot 10^{-3}$ s^{-1}; under the same conditions, but under irradiation with a high-pressure mercury lamp, k_{obs} amounts to $3 \cdot 10^{-3}$ s^{-1}; in slightly basic solution (0.2M NH_4Cl 0.2M ethylenediamine in MeOH at 20°C) in the dark, k_{obs} is $1.2 \cdot 10^{-3}$ s^{-1}. Within the temperature range 0–60°C, the e.e. of (*R*)-**2** is only very slightly decreasing (*Fig. 2b*), but it increases strongly with decreasing ε of the solvent (*Fig. 2a*). In dioxane/MeOH *ca.* 4:1 ($\varepsilon \approx 9$), the e.e. reaches 76.5%; in less polar solvents, the solubility of B_{12a} is too low.

Table 2. *Isomerization* **1**→**2** + **3** *in Different Solvents*[a])

Solution composition (*v*/*v*/*v*) [ml]	Dielectric constant ε[b])	k_{obs}[c]) [10^{-3} s^{-1}]	ln k_{obs}	e.e. [%] of **2**	k_a[d]) [10^{-3} M^{-1} s^{-1}]
Dioxane/MeOH/**1** 38:11:0.2	9			76.5	
Dioxane/H_2O/**1** 12: 3:2	16	0.151	–8.80	71	0.343
Dioxane/H_2O/**1** 7: 3:2	22	0.240	–8.33	67	
MeOH/**1** 10: 2:2	28.5	0.216	–8.44	63	0.758
Dioxane/H_2O/**1** 5: 5:2	34.5	0.333	–8.01	60	
MeOH/H_2O/**1** 7: 3:2	40	0.429	–7.75	57	2.70
MeOH/H_2O/**1** 4: 6:2	51.5	0.794	–7.14	54	11.2
MeOH/H_2O/**1** 2: 8:2	59	1.17	–6.75		18.2
H_2O/**1** 10: 1	71	2.49	–6.00	45	

[a]) In 0.4M NH_4Cl/solvent, *ca.* 1 mol-% B_{12} with respect to **1**, Zn powder, 20° in the dark.
[b]) Calculated as the weighted mean [15] on the ε of pure solvents [16] and added epoxide **1** ($\varepsilon \approx 7$).
[c]) Initial first-order (in B_{12}) rate constant of the formation of the sum of **2** and **3** (ratio 2:3 ≈ 11).
[d]) Calculated according to *Eqn. 4*.

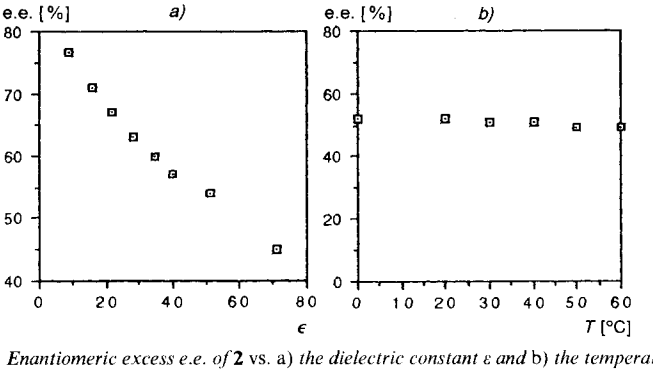


Fig. 2. *Enantiomeric excess e.e. of* **2** vs. a) *the dielectric constant* ε *and* b) *the temperature*

[3]) The kinetics depends on the epoxide concentration. If it is sufficiently high, a zero-order in **1** is observed. If the concentration decreases under a certain limit, the kinetics switches to first-order in **1**. The limit concentration depends on the dielectric constant of the solution (see below, *Fig. 5a*). At high ε (as *e.g.* in MeOH/H_2O), the zero-order in **1** is observed down to 0.05M **1**.

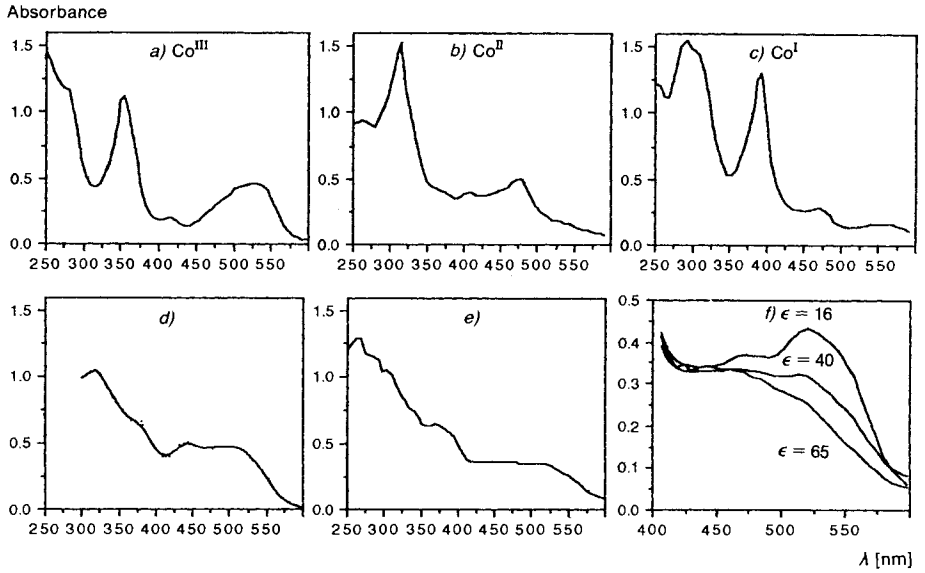
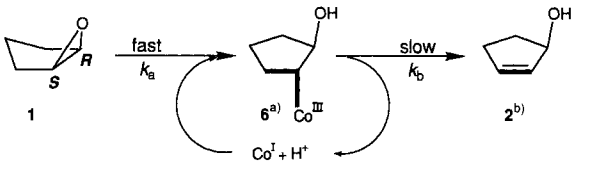


Fig. 3. *UV/VIS Spectra of cobalamins* (absorbance *vs.* wavelength). *a*) $2.8 \cdot 10^{-4}$ M B_{12a} in 0.1M $LiClO_4$/MeOH, $d = 0.2$ cm; *b*) same as *a*), but after exhaustive electroreduction at −0.30 V *vs.* SCE [18]; *c*) same as *a*), but after exhaustive electroreduction at −1.20 V *vs.* SCE [18]; *d*) spectrum of (cyclopentyl)cobalamin (60% base-on), calculated from published spectra of the base-off and the base-on forms [17]; *e*) same as *c*), but after addition of **1** (1M); *f*) same as *c*), but reduction by Zn powder in 0.1M NH_4Cl; solvents: H_2O/MeOH/**1** (*v*/*v*/*v*) 76:19:5 ($\varepsilon = 65$) and 58:25:17 ($\varepsilon = 40$), dioxane/H_2O/**1** 71:17:11 ($\varepsilon = 16$).

The UV/VIS spectra of the orange solution during the isomerization of **1** is shown in *Fig. 3e*. It may not be interpreted as a linear combination of the spectra of cob(I)-, cob(II)-, and cob(III)alamins (*Fig. 3a–c*), but it resembles the spectrum of (cyclopentyl)cob(III)alamin obtained from cob(I)alamin and bromocyclopentane in the same solvent (*Fig. 3d*). The intensity of the absorption band at 520nm, attributed to the base-on form of the organocobalamin [17] decreases with increasing dielectric constant ε of the solvent (*Fig. 3f*); the coordinated form of the base-on ⇄ base-off equilibrium is preferred in solutions of low ε.

It follows from these data that the isomerization of **1** proceeds in two steps *via* intermediate organocobalamins as the dominant species in the steady state (*Scheme 2*): In the first step, the epoxide ring of **1** is opened in a proton-assisted S_N2-type displacement of the O-atom by the chiral Co^I nucleophile to afford a mixture **6** of the two diastereoiso-

Scheme 2



a) Only the (1*R*,2*R*)-diastereoisomer is shown. b) Only the (*R*)-enantiomer is shown.

meric (1*R*,2*R*)- and (1*S*,2*S*)-*Coβ*-(2-hydroxycyclopentyl)cob(III)alamins in different amounts (ratio under standard conditions, *ca.* 4:1). This step is responsible for the enantioselectivity, the absolute configuration at the OH-substituted C-atom being already fixed in the alkylcobalamins **6**. The intermediates decompose in the second step to give **2** as well as recycled Co^{I} and H^{+}. At sufficiently high concentration of **1**, the first step is much faster than the decomposition of **6** which is thus rate-limiting. The activation parameters observed under conditions where the second step is rate-limiting, obtained from the data in *Table 1* ($\varepsilon = 40$), are $\Delta G^{\neq}_{obs,293K} = 92 \pm 5$ kJ·mol^{-1} with $\Delta H^{\neq}_{obs} = 78 \pm 4$ kJ·mol^{-1} and $\Delta S^{\neq}_{obs} = -49 \pm 1$ J·mol^{-1}·K^{-1}.

A sample of alkylcobalamins **6** was prepared as a solid material by the reaction of cob(I)alamin with **1** followed by fast precipitation. A solution of **6** in MeOH at room temperature decomposed to afford **2** and some **3** but no trace of **1**. This indicates that the first step (**1** → **6**) is irreversible and that the second occurs without previous reduction of **6**.

Isomerizations of **1** in CH_3O^2H/N^2H_4Cl, but otherwise under standard conditions, were performed. Alcohol **2** and the by-products **3** and **4** were analyzed by GC-MS. No detectable amount of ^2H attached to the carbocycle was found in **2**; **3** contained between none and 4 ^2H-atoms introduced *via* keto-enol tautomerism, and cyclopentanol (**4**) contained 1 ^2H attached to C(2). This indicates that the hydro-cobalt elimination **6** → **2** and **6** → **3** are irreversible processes under standard conditions and that **4** is formed by an ionic reductive cleavage of the Co–C bond of **6** [19]. Isomerization of **1** in C^2H_3OH, but otherwise under standard conditions, afforded **2**–**4** containing no detectable amount of ^2H. Abstraction of a H-atom from the solvent by a radical can thus be excluded.

According to *Scheme 2*, the reaction kinetics may be described by the steady-state approximation (*Eqn. 1*). [E] stands for the concentration of epoxide **1** and [I] for that of the intermediate **6**; k_a and k_b are the rate constants of the formation and decomposition of **6**, respectively. The dominant Co-containing species are cob(I)alamin (Co^{I}) and **6**; their concentrations are related by *Eqn. 2*, in which c_t is the total B_{12} concentration. *Eqn. 3* is deduced from *Eqns. 1* and *2*. Two limiting cases can be distinguished: if $k_a[E] \gg k_b$, then the observed rate ($k_b[I]$) becomes practically independent of the concentration of **1** (*Eqn. 3a*) and the reaction follows a first-order kinetics in B_{12} (zero-order in **1**); if $k_b \gg k_a[E]$, the rate depends on the concentration of **1** and follows a second-order kinetics (first-order in B_{12} and first-order in **1**; *Eqn. 3b*). The mid-position between the two limiting cases is reached, if $[E] = k_b/k_a$; below this limit, the kinetics changes from first- to second-order.

$$k_a[E]\,[Co^{I}] = k_b[I] \tag{1}$$

$$[I] = c_t - [Co^{I}] \tag{2}$$

$$k_b[I] = k_b\,k_a[E]\,c_t/(k_b + k_a[E]) \tag{3}$$

$$\text{if } k_a[E] \gg k_b, \text{ then } k_b[I] \approx k_b c_t \text{ and } k_{obs} = k_b, \tag{3a}$$

$$\text{if } k_b \gg k_a[E], \text{ then } k_b[I] \approx k_a[E]\,c_t \tag{3b}$$

From *Eqns. 1* and *2* results *Eqn. 4* saying that the reciprocal concentration of **6** and the reciprocal concentration of **1** are linearly related.

$$[I]^{-1} = (k_b/k_a c_t)[E]^{-1} + 1/c_t \tag{4}$$

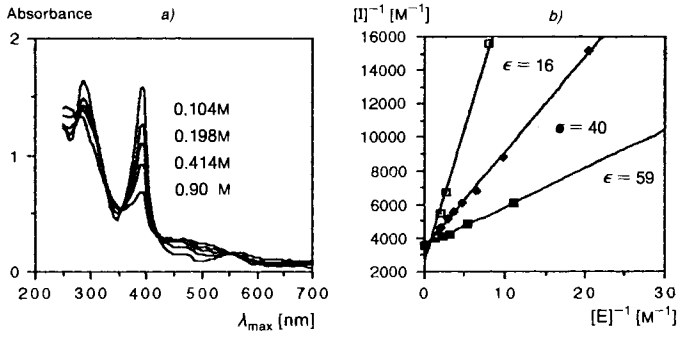


Fig. 4. a) *UV/VIS Spectra in the steady state.* Mixtures of $2.8 \cdot 10^{-4}$ M cob(I)alamin, 0.1M NH_4Cl in MeOH ($\varepsilon = 28.5$), Zn powder at different concentrations of **1** (0, 0.104, 0.198, 0.414, and 0.90M); $d = 0.2$ cm. b) *Reciprocal concentration of* **6** versus *reciprocal concentration of epoxide* **1** *in the steady state, at different dielectric constants* ε (calc. according to *Eqn. 2* and *4*).

The steady-state concentration of Co^I was measured by UV/VIS spectroscopy at λ_{max} 390 nm. It decreases with increasing concentration of **1** (*Fig. 4a*). As expected from *Eqn. 4*, the experimental values of $[I]^{-1}$ and $[E]^{-1}$ are linearly related (*Fig. 4b*). The slope is equal to $k_b/k_a c_t$, the intercept is $1/c_t$. Thus, knowing $k_{obs} \approx k_b$, k_a is indirectly obtained by *Eqn. 4* (*Table 2*). The activation energy of the formation of **6** at [E] = 1M and $\varepsilon = 40$ is $\Delta G^{\neq}_{a,293K} = 86 \pm 5$ kJ·mol^{-1}. The rate constant k_a increases exponentially with ε (*Fig. 5b*), accompanied by a decrease in enantioselectivity (*Fig. 2a*). As shown by *Fig. 5a*, the ratio k_b/k_a (unit: mol·l^{-1}) also depends on ε. From the e.e. of **2** and its temperature dependence (*Table 1* and *Fig. 2b*), the differences of activation parameters for the attack of Co^I at the enantiotopic (*R*)- and (*S*)-C-atoms of **1** are calculated: for an e.e. of 52% of (*R*)-**2** (see *Table 1*), the formation of (1*R*,2*R*)-**6** is favored over (1*S*,2*S*)-**6** by $\Delta\Delta G^{\neq}_{a,293K} = -2.7$ kJ·mol^{-1} with $\Delta\Delta H^{\neq}_a = -1.0 \pm 0.5$ kJ·mol^{-1} and $\Delta\Delta S^{\neq}_a = 5.7 \pm 1.7$ J·mol^{-1}·K^{-1}.

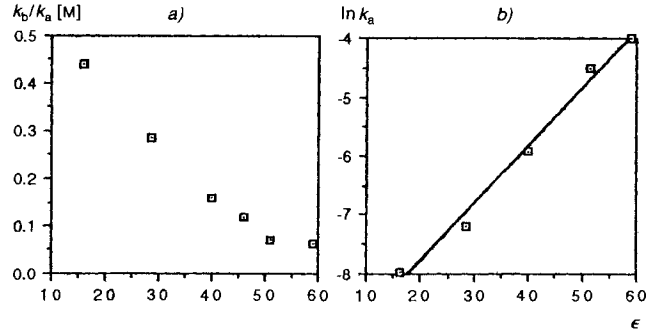


Fig. 5. a) *Ratio* k_b/k_a *of the rate constants of the decomposition* (k_b) *and formation* (k_a) of *alkylcobalamin* **6** vs. *dielectric constant* ε. b) *Logarithm of the rate constant* k_a *of formation of* **6** vs. *dielectric constant* ε.

In order to drive the system towards the thermodynamic equilibrium and to get an insight into the formation of the by-products, the reaction was carried out in boiling H_2O, but otherwise under the same conditions. Addition of **1** to the green Co^I solution caused an immediate color change to red, but after a few min, it turned back to green, indicating

Table 3. *Time-dependent Product Formation on Reaction of* **1** *in the Presence of Cob(I)alamin in Refluxing* H_2O[a])

Time [min]	Products concentration [%][b])					
	1	**2**	**7**	**3**	**4**	**5**[c])
0	100	0.0	0.0	0.0	0.0	0.0
10	3.5	61	1.9	2.5	0.8	30
30	0.3	46	9.2	3.4	2.0	39
60	0.0	36	14	4.1	4.0	42
125	0.0	30	15.5	5.4	5.9	43
240	0.0	27	16	7.8	7.9	42
300	0.0	27	16	7.8	8.0	42
5830	0.0	3.3	1.8	7.8	14	73

[a]) Conditions: 0.35M NH_4Cl, 0.012M B_{12} in H_2O, reflux (*ca.* 98°), Zn powder, 1.95M **1**.
[b]) Mol-% with respect to the initial conc. of **1** (= 100%), determined by GC.
[c]) Calculated (difference to 100%).

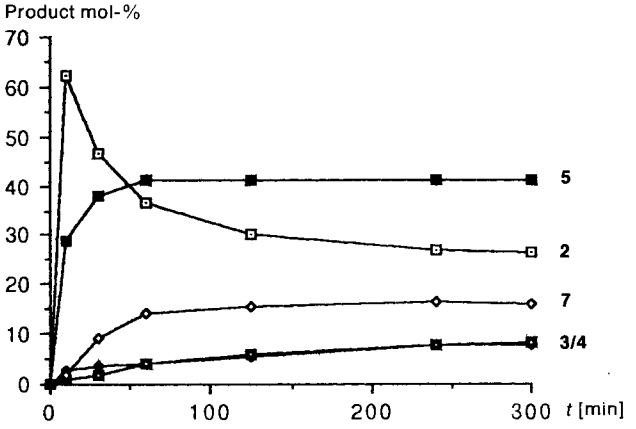


Fig. 6. *Towards the thermodynamic equilibrium: Time-dependent product formation on reaction of* **1** *in presence of cob(I)alamin in refluxing* H_2O

the total consumption of **1** and a very small concentration of organocobalamins. Reflux was maintained and the product composition monitored by GC (*Table 3* and *Fig. 6*). Already after 10 min, **1** was practically consumed, mainly by formation of the allylic alcohol **2** and cyclopentene (**5**), which escaped from the system. On further heating, the concentration of **2** decreased with increasing concentration of an isomer, whose structure was determined by GC-MS and NMR to be cyclopent-3-enol (**7**) [20]. After 3 h, the ratio **2**/**7** reached *ca.* 1.8 and remained constant (ratio close to the statistical value of 2, assuming the same thermodynamic stability of the isomers). The concentration of cyclopentanol (**4**) was increasing slowly, as well as the concentration of cyclopentanone (**3**), which is thermodynamically favored by *ca.* 69 $kJ \cdot mol^{-1}$ over the allylic alcohol **2** (calc. according to [21]).

An experiment in refluxing ^2H_2O, under the same conditions, was performed. After 6 h, the compounds **2**, **3**, **4**, and **7** were analyzed by GC-MS. As shown in *Table 4*, all these

Table 4. *Reaction of* **1** *in Presence of Cob(I)alamin in Refluxing* ^2H_2O[a]: *Distribution of the* ^{2}*H-Labeled Products* [%][b]

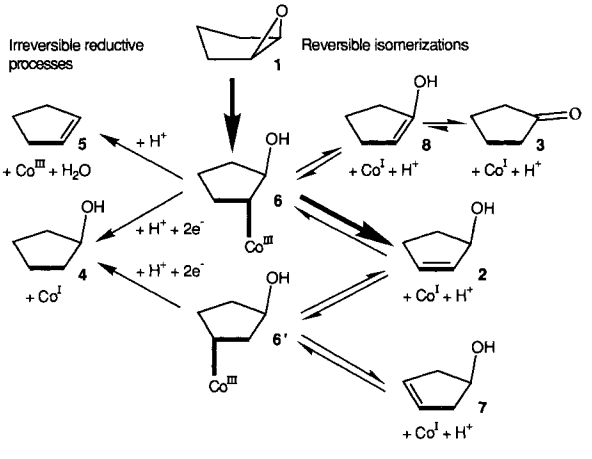
Number of ^{2}H attached to C	**2**	**7**	**3**[c]	**4**
0	2	3	36	0
1	9	8	26	0
2	30	25	21	14
3	42	37	13	15
4	10	21	4	20
5	7	6	0	34
6	0	0	0	17

[a]) Conditions: 0.18M N^2H_4Cl, $7.2 \cdot 10^{-3}$M B_{12} in ^2H_2O, Zn powder, 2M **1**, 6 h reflux under Ar.
[b]) Evaluated from GC-MS.
[c]) In addition to the 4 ^{2}H-atoms incorporated *via* the enol form.

compounds contain one or more ^{2}H-atoms attached to the carbocycle. Most molecules of the olefinic alcohols **2** and **7** bear 2 or 3 ^{2}H-atoms at the C-skeleton, whereas the molecules of ketone **3** contain mainly none, 1, or 2 ^{2}H-atoms more than the 4 in α-position to the carbonyl group (introduced *via* the keto-enol tautomerism).

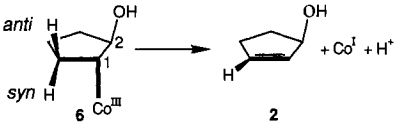
Under standard conditions, the isomerization **1** → **2** + **3** occurs under kinetic control. It can, however, be driven towards the thermodynamic equilibrium, as observed in refluxing H_2O. This and the incorporation of ^{2}H (*Table 4*) during the B_{12s}-catalyzed reaction in boiling ^2H_2O is explained by reversible hydro-cobalt addition/hydro-cobalt elimination processes (*Scheme 3*). It must be noted that hydro-cobalt addition to olefins is negligible as long as **1** is still present, since it reacts much faster with cob(I)alamin than the olefins. Irreversible processes are the formation of volatile cyclopentene (**5**) and H_2O by fragmentation of **6** under reducing conditions [8] [22] and the formation of cyclopentanol (**4**) by reductive protonation of **6** or **6′** [19] (*Scheme 3*).

Scheme 3. *Reactions of 1,2-Epoxycyclopentane* (**1**) *with* B_{12} (cat.), *Zn, and* NH_4Cl *in Protic Solvents* (shown only for one diastereoisomer of **6** and **6′** and for one enantiomer of **2**). Bold arrows, main irreversible reactions in MeOH at 20°; light arrows, reactions in boiling H_2O.



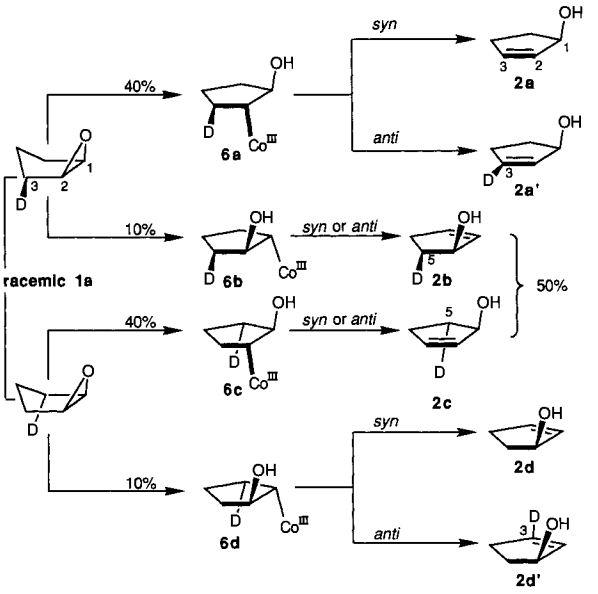
3. Stereochemistry. – The isomerization **1** → **2** occurs *via* the diastereoisomeric (1*R*,2*R*)- and (1*S*,2*S*)-(2-hydroxycyclopentyl)cob(III)alamins **6**. These intermediates decompose to **2**, Co^{I}, and H^{+}. The hydro-cobalt elimination may occur in a concerted or stepwise manner either in an *anti-*, *syn-*, or a nonspecific mode (*Scheme 4*).

Scheme 4[a])



a) Hydro-cobalt elimination shown only for the (1*R*,2*R*)-diastereoisomer **1**.

Scheme 5



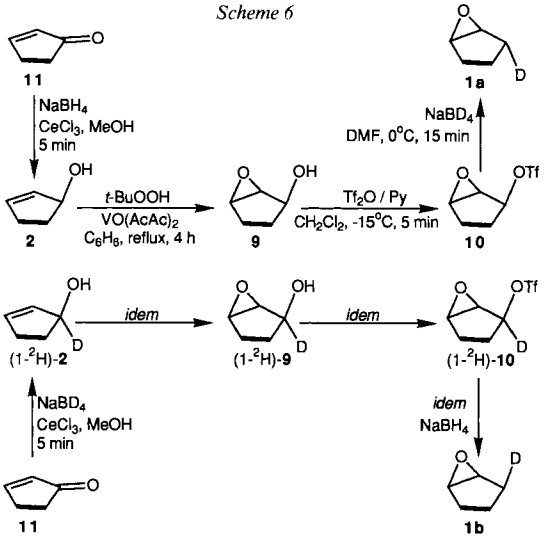
To determine the stereochemical course of the elimination, the isomerization of racemic *trans-* as well as of racemic *cis*-1,2-epoxy(3-$^{2}H_{1}$)cyclopentane (**1a** and **1b**, resp.) was studied. The expected ^{2}H-distribution in the allylic alcohol **2** starting from **1a** and resulting from either a clean *syn-* or *anti*-elimination is outlined in *Scheme 5;* an e.e. of 60% is assumed for **2**; the content and position of labeling in **2** is, however, independent of the e.e. It is further assumed that the influence of the label in **1a** on the rate of formation of the four diasteroisomeric alkylcobalamins **6a–d** is negligible.

In the two diastereoisomeric alkylcobalamins **6b** and **6c** formed by $S_{N}2$-type ring opening of epoxide **1a** by cob(I)alamin, the ^{2}H-label is not located in β-position relative to the Co-atom. Thus, independent of the stereochemistry of the elimination, 50% of the resulting allylic alcohol **2** will be labeled at C(5) (**2b** and **2c**). The two other alkylcobal-

amins **6a** and **6d** bearing the label in β-position relative to the Co-atom lose ^2H on *syn*-elimination and the other 50% of **2** will not be labeled (**2a** and **2d**); on *anti*-elimination, the label is retained and 50% of **2** will be labeled at C(3) (**2a'** and **2d'**). The expected isotopic composition of **2** obtained from **1a** and **1b**, *via* either a clean *syn*- or *anti*-elimination, is given in *Table 6* (see below).

The required racemic ^2H-labeled epoxides **1a** and **1b** were obtained as shown in *Scheme 6*. Vanadium-catalyzed epoxidation of racemic cyclopent-2-enol (**2**) according to *Teranishi et al.* [23] afforded practically pure *cis*-epoxyalcohol **9** which was then converted to the trifluoromethanesulfonate **10** and reacted with NaB^2H_4 in DMF to give pure **1a** (18% overall yield). For the preparation of **1b**, cyclopent-2-enone (**11**) was reduced with NaB^2H_4 in presence of $CeCl_3$ [24] affording racemic (1-^2H)-**2**. As described above, but using $NaBH_4$ instead of NaB^2H_4 in the last step, this allylic alcohol was transformed to **1b**.

Scheme 6



The configuration of the compounds **1a** and **1b** (purity > 96%, GC and MS) was determined by NMR. *Fig. 7* shows the relevant parts of the ^1H-NMR spectra of non-labeled **1** as well as of **1a** and **1b**. The assignment of the signals of H-atoms located *cis* or *trans* with respect to the O-atom is based on Eu-shift experiments (*Fig. 8*). *Table 5* gives the δ-values and integrals of the relevant signals, *Fig. 9* the $^{13}C,^1H$-shift-correlation NMR of **1a** and **1b**.

The B_{12}-catalyzed isomerization of **1a** as well as of **1b** by the standard procedure in the dark afforded two samples of cyclopent-2-enol (**2**) which were isolated by prep. GC. In both cases, these optically active alcohols **2** (e.e. *ca.* 60%) were mixtures of compounds differing only in chirality and ^2H-labeling. Their analyses were performed by MS (total amount of ^2H-labeling) and ^1H-NMR (amount, constitution, and configuration of ^2H-labeling). Results of two independent experiments, starting from both isomers **1a** and **1b**, are presented in *Table 6*. Both reactants gave mixtures of **2** with practically the same isotopic composition: total amount of mono-^2H-labeling *ca.* 75%; ratio (3-^2H)-**2**/(5-^2H)-**2**/unlabeled **2** *ca.* 1:2:1.

It follows from these experimental results that the vicinal hydro-cobalt-elimination from the intermediates **6** takes place in a non-stereospecific manner, in which products

resulting from a formal *syn*- or *anti*-elimination are formed in practically equal amounts. Furthermore, no indication for the operation of a thermodynamic or kinetic isotope effect was observed. This indicates that hydro-cobalt elimination from **6** does *not* proceed *via* an intramolecular concerted mechanism.

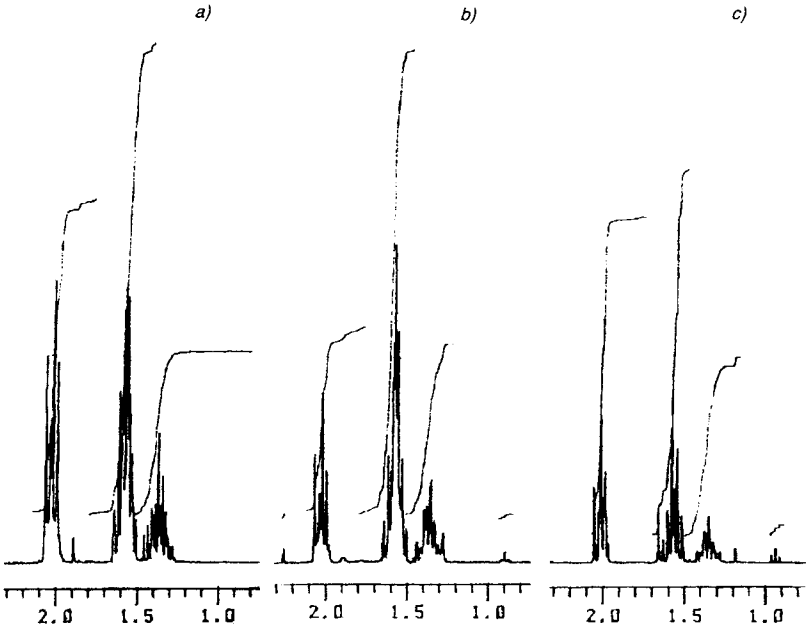


Fig. 7. *Part of the* ^{1}*H-NMR spectra* (300 MHz, $CDCl_3$) *of* a) *1,2-epoxycyclopentane* **1**, b) *(±)*-cis-*1,2-epoxy(3-*$^2H_1$*)-cyclopentane* (**1b**) *and* c) *(±)*-trans-*1,2-epoxy(3-*$^2H_1$*)cyclopentane* (**1a**)

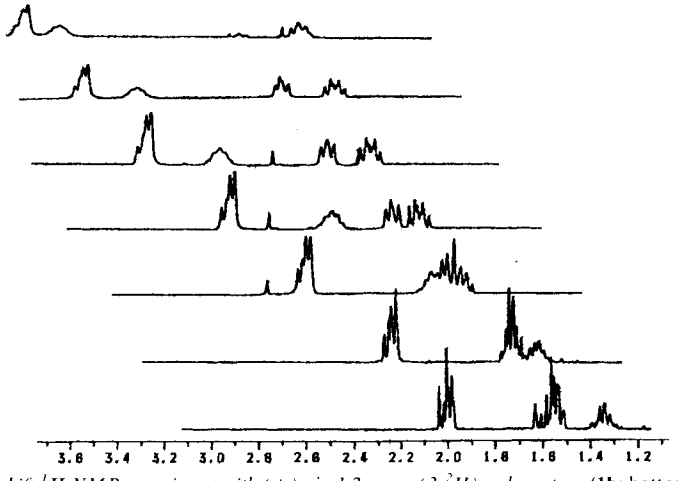


Fig. 8. *Europium-shift* ^{1}*H-NMR experiment with (±)*-cis-*1,2-epoxy(3-*^2H*)cyclopentane* (**1b**; bottom) *on successive additions of [Eu(fod)*$_3$*] reagent.* The signals of H-atoms located *cis* with respect to the O-atom at $\delta = 1.35$ and 2.01 ppm are strongly shifted.

Table 5. *^{1}H-NMR Data of 1,2-Epoxycyclopentane* (**1**) *and of Its* trans- *and* cis-*(3-^{2}H)-Labeled Derivatives* **1a** *and* **1b**

δ [ppm]		Assignment	Number of H-atoms (from integral)		
			1	**1b**	**1a**
3.46 (*s*)		H–C(1)	2	2	2
2.01 (*m*)	*cis*	H–C(3), H–C(5)	2	1	2
1.53, 1.58 (2*m*)	*trans*	H–C(3), H–C(4), H–C(5)	3	3	2
1.35 (*m*)	*cis*	H–C(4)	1	1	1

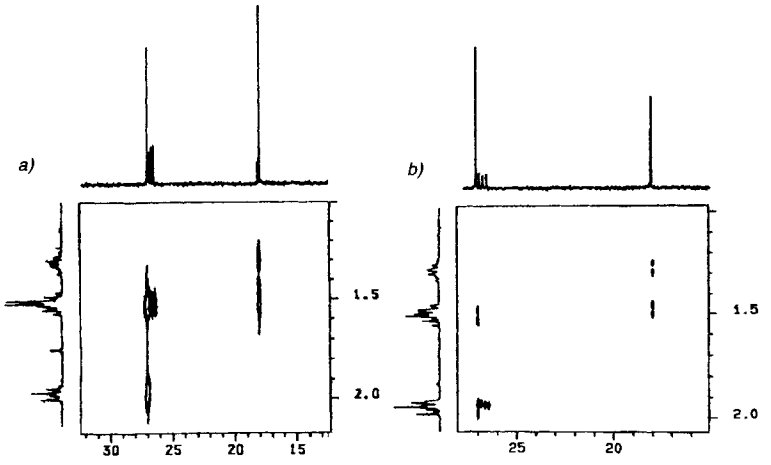


Fig. 9. *^{1}H,^{13}C-NMR correlation spectra of* a) *(±)-*cis*-1,2-epoxy(3-$^2H_1$)cyclopentane* (**1b**) *and* b) *(±)-*trans*-1,2-epoxy(3-^{2}H)cyclopentane* (**1a**). The ^{2}H-bearing C-atom (*t*) is in the first case correlated with a *trans* H-atom and in the second case with a *cis*-H-atom.

Table 6. *Expected* (for clean *syn-* and *anti*-elimination) *and Experimentally Determined Isotopic Composition of Cyclopent-2-enols from the B_{12}-Catalyzed Isomerization of* **1a** *and* **1b**[a]. Results of two experiments (*Exper. 1* and *2*).

Location of label in the product	Isotopic composition [%] of cyclopent-2-enols							
	Expected		Result		Expected		Result	
	syn	*anti*	*Exper. 1*	*Exper. 2*	*syn*	*anti*	*Exper. 1*	*Exper. 2*
non-labeled	50	0	27	30	0	50	21	28
^{2}H at C(3)[b])	0	50	27	26	50	0	26	29
^{2}H at C(5)[b])[c])	50 (*trans*)	50 (*trans*)	46 (*trans*)	44 (*trans*)	50 (*cis*)	50 (*cis*)	53 (*cis*)	43 (*cis*)
Total ^{2}H[d])	50	100	73	70	100	50	79	72

[a]) $3 \cdot 10^{-2}$M B_{12}, 0.1M NH_4Cl in MeOH, Zn powder, initial conc. of **1a** and **1b** 2M, 4 d, r.t. in the dark.
[b]) Taken from ^{1}H-NMR (error ± 5%).
[c]) Configuration of ^{2}H at C(5) with respect to OH.
[d]) Taken from MS (error ± 5%) and ^{1}H-NMR (error ± 5%).

4. Discussion. – The occurrence of **6** as the intermediate in the cob(I)alamin-catalyzed isomerization **1** → (*R*)-**2** has been shown by spectroscopic evidence and kinetic behaviour as well as by the isolation of **6**. Due to the inherent instability of secondary alkycobalamins, the ratio of the configurational isomers **6** and their structure could not be directly

determined yet. The assumption that **6** is formed in an S_N2 reaction as a *ca.* 4:1 mixture of *Coβ*-substituted (1*R*,2*R*)- and (1*S*,2*S*)-(2-hydroxycyclopentyl)cob(III)alamin is based on the e.e. of (*R*)-**2**, the kinetics of **1** → **6**, and the known stereochemistry of alkylation of Co^I derivatives of B_{12} by alkylating agents containing an O-atom as C-bound leaving group like epoxides [5] and 4-toluenesulfonates [25].

The activation process of the alkylation is not governed by dipolar interactions between reactants, otherwise k_a would decrease with increasing ε. In the transition state of the considered S_N2 process **1** → **6**, the Co-, C-, and O-atoms are expected to be close and colinear, keeping the carbocycle in a cavity at the upper(*β*) side of the corrin. Thereby, the B_{12} undergoes probably a strong bending [26], causing a large contribution to the activation energy. The observed increase of k_a with increasing ε can be interpreted as a gain in flexibility of the B_{12} part since intramolecular dipolar interactions become weaker. Furthermore, the fact that $\Delta\Delta H_a^{\neq} = -1.0 \pm 0.5$ kJ·mol^{-1} and $\Delta\Delta S_a^{\neq} = 5.7 \pm 1.7$ J·mol^{-1}·K^{-1} ($-T\Delta\Delta S_a^{\neq} = -1.7 \pm 0.5$ kJ·mol^{-1}) contribute in the same direction to $\Delta\Delta G_{a,293K}^{\neq} = -2.7$ kJ·mol^{-1} excludes an outer-sphere electron-transfer process where desolvatation processes would make the largest contribution to the activation energy [27]. The inner-sphere process by which the alkylation then proceeds (and, therefore, the enantioselection) is probably controlled to a large extent by deformations of the reactants on the way to the transition state. The decreasing e.e. of **2** with increasing ε of the protic solvent may also be explained by an activation of the epoxide by competing H-bonding with the solvent or with the *β*-oriented acetamide side chains of B_{12} [28]. H-Bonding of (2-hydroxyalkyl)cobalamins to the acetamide O-atom of the side chain *c* is known [6].

It is striking to note the similarity between the dependences of both rate constants k_a and k_b towards ε (*Fig. 1* and *5b*). This could be due to the fact that the activation pathways for the formation (k_a) and the decomposition (k_b) of **6** are structurally related. Compared with other published data of alkyl-Co^{III} complexes, the activation enthalpy and entropy for the decomposition of **6** are particularly low, although well fitting *Halpern*'s correlation between $\Delta S^{\neq}$ and $\Delta H^{\neq}$ shown in *Fig. 10* [29]. Referring to *Hammond*'s theory [30], the transition state in the rate-determining step **6** → **2** can be characterized as more 'reactant-like' than for other alkyl-Co^{III} complexes. The low activation enthalpy

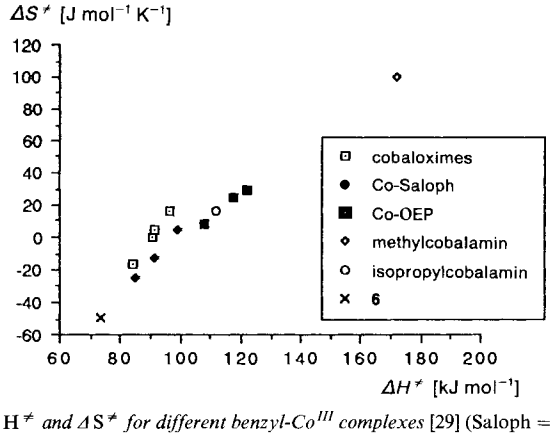
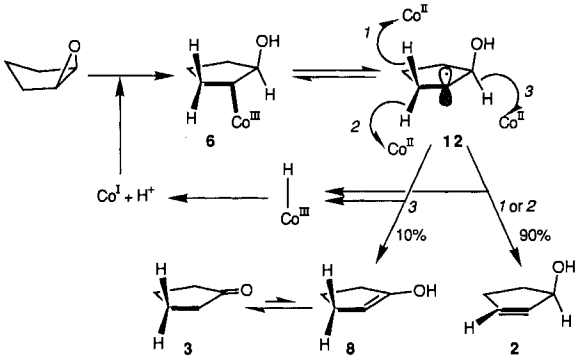


Fig. 10. *Correlation of* $\Delta H^{\neq}$ *and* $\Delta S^{\neq}$ *for different benzyl-*Co^{III} *complexes* [29] (Saloph = (*N*,*N*′-bis(salicylidene)-*o*-phenylenediamine, OEP = octaethylporphyrine), *methylcobalamin* [31], *isopropylcobalamin* [11], *and* **6**

$\Delta H^{\neq} = 78 \pm 4$ kJ·mol^{-1} corresponds to little Co–C bond lenghtening, while the low activation entropy $\Delta S^{\neq} = -49 \pm 1$ J·mol^{-1}·K^{-1} may reflect a loss of molecular flexibility of the B_{12} part. It seems, thus, that the B_{12} ligand deformation is the key event in the activation process for the decomposition of **6**.

The hydro-cobalt elimination from **6** has been shown to proceed non-stereoselectively and without H-isotope effect. To explain these findings, we are proposing a pathway as shown in *Scheme 7*. First, the alkylcobalamins **6** undergo a reversible homolytic cleavage to the transient C-centered radical **12** and the persistant radical Co^{II} (*i.e.* B_{12r}). The occurrence of a free C-radical during isomerization could not be detected by

Scheme 7



ESR measurements since its concentration is too low. Trapping experiments in presence of activated olefins (as *e.g.* acrylonitrile), however, showed the formation of products containing a new C–C bond (as *e.g.* 2-(2-cyanoethyl)cyclopentanol) and thus clearly indicate the intermediacy of a free C-radical (a detailed report is given in a subsequent paper). H-Atom transfer to another C-radical (dismutation) has to be excluded since no equivalent amount of cyclopentanol is formed (this compound is produced in small quantity by an ionic reaction, as discussed above). Low-spin Co^{II}-complexes, on the other hand, are known to abstract H-atoms located in α-position with respect to the radical center at a rate near to the diffusion limit [32]. The thus formed hydridocob(III)alamin may undergo reductive elimination to H^+ and Co^I who re-enter the catalytic cycle.

From the steady-state concentration of radical **12** ($[R\cdot] < 10^{-12}$ M as shown by trapping by acrylonitrile in a subsequent paper), the concentration of Co^{II} ($[Co^{II}] < 10^{-2}$ M, the total B_{12} concentration), and the observed rate constant $k_{obs} = 10^{-6}$ Ms^{-1}, we deduce from *Eqn. 5* a lower limit for the rate constant of the H-abstraction of 10^8 M^{-1}s^{-1}, what is indeed close to the diffusion limit.

$$k_{obs} = k_E [R\cdot] [Co^{II}] \tag{5}$$

The 2-hydroxycyclopentyl radical **12** bears three nonequivalent H-atoms in α-position with respect to the radical center. The abstraction of the H-atom located at the OH-substituted C(2) leads first to enol **8** and then to ketone **3** which was found as an isomerization product in minor quantity. The abstraction of either of the two H-atoms

(or 1 H and 1 ^{2}H) at C(5) leads to the main product **2**. Since ketone **3** is more stable than **2**, the reaction **12** → **2** or **3** is kinetically controlled. We propose a stereoelectronic control, based on a parallel arrangement of a H–C bond with the radical p orbital in the transition state. Stereoelectronic and energetic changes on the way to the transition state can be extrapolated from the known ESR spectra of related radicals.

The ESR spectrum of the cyclopentyl radical at room temperature is characterized by only one coupling constant of 3.50 mT [33]. This is due to the fast oscillation of both CH_2 groups next to the radical center between two energy minima which are symmetric with respect to the nodal plane of the p orbital. The ESR at 100 K, however, shows signals explained by two coupling constants of 2.44 and 4.69 mT, corresponding to a locked conformation characterized by dihedral angles of 49 and 12.5° between the p orbital and the H–C bonds of the two neighbouring CH_2 groups [33]. From the ESR of the 2-methoxycyclopentyl radical at 263 K, two coupling constants of 3.60 mT (H–C(5)) and 2.20 mT (H–C(2)) have been derived [34]. This can be explained by the fast oscillation of the CH_2 group described above and by a mean dihedral angle of 49° between the H–C(2) bond and the p orbital.

Based on these data, we assume that the free energy required to reach the transition state is essentially the energy needed to reach a conformation in which the linear arrangement of C, H, and Co^{II} is parallel to the radical p orbital. This accounts for the regioselectivity, since more energy is required to adjust the H–C(2) bond (dihedral angle 49° with

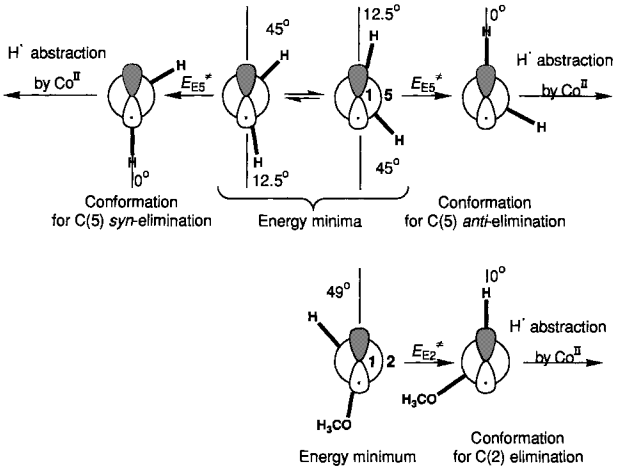
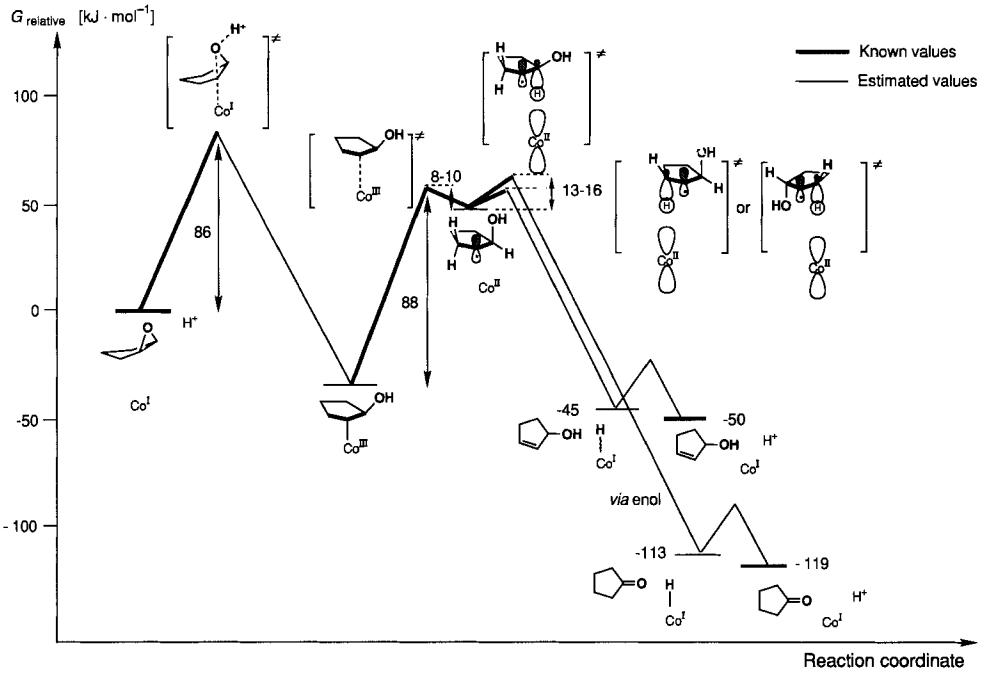


Fig. 11. Newman *projections C(1)–C(5)* (top) *and C(1)–C(2)* (bottom) *of the 2-methoxycyclopentyl radical;* energy minima and conformations enabling H-atom abstraction by Co^{II}

the p orbital) than the H–C(5) bond (12.5°; *Fig. 11*). It is further assumed that after this conformation has been reached, the H-atom transfer proceeds downhill in energy. The absence of an observable H-isotope effect is explained by an unsignificant C–H bond lengthening in the transition state. The non-stereoselectivity in the abstraction of either the *cis*- or the *trans*-oriented H-atom at C(5) has then to be explained by a long distance between Co^{II} and C in the transition state.

Scheme 8



In conclusion, the results of the studies on the mechanism of the isomerization of 1,2-epoxycyclopentane (**1**) to the enantiomerically enriched (*R*)-cyclopent-2-enol (**2**) is summarized in *Scheme 8* (experimentally determined and known energy differences are marked by bold lines).

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Experimental Part

General. Hydroxocobalamin hydrochloride (B_{12a}; pyrogen-free *Fr. Ph. BP.*, 10.7% loss on drying, < 2% cyanocobalamin) from *Roussel Uclaf* and 1,2-epoxycyclopentane ('für Synthese') from *Merck* (purification, see preparation of **1**). MeOH (*puriss.*) from *Fluka* was flushed with Ar before use. NH_4Cl (*purum*) from *Siegfried*. Zn powder (*puriss.*) from *Fluka*, activated before use by sequential washing with 2M HCl, H_2O, and MeOH and drying. Cyclopentene (*puriss.*) from *Fluka* and 30% H_2O_2 soln. (*Ph. Hvi.*) from *Siegfried*. Cyclohexanol (*puriss.*), $C^2H_3O^2H$ (*puriss., ca.* 99.8% ^2H), CH_3O^2H (*puriss.*, > 99.5% ^2H), ^2H_2O (> 99.8% ^2H), and $CeCl_3 \cdot 7H_2O$ (*purum*) all from *Fluka*. Cyclopent-2-enone and NaB^2H_4 from *Aldrich*. Vanadyl acetoacetate ($VO(AcAc)_2$; *puriss.*) and *t*-BuOOH (*pract.*, 80%) from *Fluka*. Pyridine (*Ph. Hvi.*) from *Siegfried*. Trifluoromethanesulfonic anhydride (*purum*), $NaBH_4$ (*purum*), DMF (*puriss.*; over 4 Å molecular sieve), and acrylonitrile (*puriss.*) from *Fluka*. The electrochemical procedure was carried out in a H-type cell with glass-frit separation using graphitized carbon felt as cathode material under potentiostatic conditions [35]. GC: He as carrier gas; *Perkin-Elmer Sigma 3*, FID, and

Hewlett-Packard HP5790A and *HP5890A*, with 25-m capillary column coated with *OV1701* (int. diameter 0.2–0.3 mm), *Carbowax 20 M* (int. diameter 0.4 mm), or *PEG* (int. diameter 0.3 mm), t_R in min; e.e. determinations on 25-m capillary column (int. diameter 0.2 mm) coated with *OV1701* containing 43% heptakis[2,3,6-(tri-*O*-propyl)-β-cyclodextrin], 35°. Prep. GC: *Perkin-Elmer-F21*, 5% *Carbowax 20 M* on *Chromosorb G-AW-DMCS*, 60–80 mesh, 1 × 43 cm. UV/VIS: diode-array spectrophotometer *HP8451A*. IR (cm^{-1}): *Perkin-Elmer 782*. NMR: *Bruker-AM-400-WB* (400-MHz) and *Bruker-AC300* (300-MHz) spectrometers; δ in ppm with TMS (= 0 ppm) as internal standard, in $CDCl_3$; shift reagent [Eu(fod)$_3$] (europium tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate)) from *Merck*. MS: *Varian MAT CH-7A*, 70 eV. GC-MS: *Varian MAT 44S*, 70 eV.

1. Kinetics and Thermodynamics. – 1.1. *1,2-Epoxycyclopentane (= 6-Oxabicyclo[3.1.0]hexane;* **1**). Modified procedure according to [36]: Cyclopentene (264 ml, 204 g, 3.0 mol) and benzyltriphenylphosphonium pertungstate (33 g, 26 mmol, prepared according to [36]) were dissolved in CH_2Cl_2 (2 l). Within 2 h, 30% H_2O_2 soln. (500 ml) was added dropwise under strong mechanical stirring. The mixture was then heated to reflux with stirring for 24 h. The org. phase was separated, washed repeatedly with 1M Na_2SO_3 in H_2O (*ca.* 3 × 200 ml) until the I_2/starch-paper test for peroxides was negative, and dried (Na_2SO_4). The solvent was slowly distilled off over a 1-m *Vigreux* column, keeping the vapor temp. at 38°/715 Torr. The remaining crude epoxide was then distilled on a 40-cm *Vigreux* column (b.p. 99°/715 Torr): 126.5 g (50%) of **1**. Colourless liquid purity (GC) 96%. For the B_{12}-catalyzed reactions, this material (as well as the commercially available **1** from *Merck*) had to be redistilled on a *Fischer*-'Spaltrohr' column, in order to remove all traces of CH_2Cl_2. ^{1}H-NMR (*Table 5* and *Fig. 7*): 3.46 (*s*, H–C(1), H–C(2)); 2.01 (*m*, H–C(3) and H–C(5) *cis* to O); 1.53, 1.58 (*m*, H–C(3), H–C(5), and H–C(4) *trans* to O); 1.35 (*m*, H–C(4) *cis* to O). MS: 84 (8.9, $M^{+\cdot}$), 83 (18), 56 (37), 55 (100), 42 (24), 41 (84).

1.2. *(R)-Cyclopent-2-en-1-ol* (**2**). *Preparative Isomerization (Standard Conditions)*. To vitamin B_{12a} (200 mg, 0.14 mmol) and NH_4Cl (0.2 g, 3.7 mmol) in MeOH (20 ml) under Ar, Zn powder (*ca.* 1 g) was added and the mixture stirred for several min, until the colour had turned from red to dark green (→ B_{12s}). Epoxide **1** (2.00 g, 24.0 mmol) was added by syringe. The colour immediately changed to orange-brown (→ alkyl-Co^{III}). Stirring at r.t. was continued for 4 d. GC (*OV1701*, 25 m, 0.3 mm, 40°, 1°/min) with cyclohexanol as internal standard and GC-MS of the crude mixture showed the presence of **2** (64% rel. to **1**; t_R 7.88), *cyclopentanone* (**3**; 5.5%; t_R 8.24), and *cyclopentanol* (**4**; 0.5%; t_R 8.44). (*Cyclopentene* (**5**; 30%) was determined by GC-MS from a reaction in dioxane/H_2O 1:1 (*v/v*) in a closed flask, but otherwise under the same conditions.) Et_2O (60 ml) was added, the precipitate (B_{12} and salts) filtered off, and the clear soln. evaporated. Distillation under reduced pressure over a 10-cm *Vigreux* column afforded **2** (b.p. 47°/12 Torr): 1.18 g (59%), e.e. 62%. GC on chiral phase: (*S*)-**2** at t_R 22.3, (*R*)-**2** at 23.8, base-line separated. ^{1}H-NMR (assigned by NOE): 5.98 (*m*, H–C(3)); 5.83 (*m*, H–C(2)); 4.82 (*s*, H–C(1)); 2.49 (*m*, H–C(4) *trans* to OH); 2.28–2.24 (2*m*, H–C(4) *cis* to OH, H–C(5) *trans* to OH); 2.0–1.8 (*s*, OH); 1.69 (*m*, H–C(5) *cis* to OH). GC-MS: 84 (41, $M^{+\cdot}$), 83 (100), 66 (16), 65 (14), 56 (25), 55 (75), 41 (31), 39 (34). GC-MS of **4**: 86 (3.0, $M^{+\cdot}$), 71 (3.4), 68 (5.2), 67 (4.6), 57 (100), 44 (42). GC-MS of **3**: 84 (29, $M^{+\cdot}$), 56 (29), 55 (100), 42 (16), 41 (32).

Kinetics. The reaction was carried out as described above, in the dark. Solvents and temp. are given in *Tables 1* and *2*. Samples were taken by syringe and analyzed by quant. GC using cyclohexanol as internal standard. The e.e. was determined by GC on chiral phase (see above).

1.3. *Preparation and Decomposition of (2-Hydroxycyclopentyl)cobalamins* (**6**). *Preparation*. To B_{12a} (2.00 g, 1.44 mmol) in MeOH (20 ml) under Ar, Zn powder (*ca.* 2 g) and ethylenediamine (2 drops) were added. The soln. rapidly turned green under stirring. Epoxide **1** (5.0 g, 60 mmol) was added at r.t. After 5 min, the orange soln. was decanted and poured into Et_2O (30 ml) with stirring. The precipitate was filtered off, washed with Et_2O (30 ml), and suspended in Et_2O (50 ml) with stirring for 30 min in the dark. After filtration, the orange solid was dried at r.t./200 Torr: 1.90 g (89%). This material is slowly decomposing at r.t.

Decomposition. At r.t., **6** (300 mg, 0.20 mmol) was dissolved under Ar in MeOH (3 ml) containing cyclohexanol (0.175M) as internal standard. After 1.2 h, **2** (30% rel. to **6** (GC)) and **3** (1%), but no epoxide **1** were detected by GC of the soln.

1.4. *Isomerization of* **1** *in* CH_3O^2H. N^2H_4Cl was prepared by dissolving NH_4Cl (1.07 g, 20 mmol) in ^2H_2O (> 99.8% ^2H, 5 ml, 0.25 mol), and evaporation of the solvent *i.v.* This procedure was repeated 3 times. B_{12a} (200 mg) was treated in the same way. The isomerization of **1** in CH_3O^2H (> 99.8% ^2H, 10 ml) with B_{12a} (200 mg), Zn, and N^2H_4Cl (0.1 g) was done as described in *1.2*. After 4 d H_2O (30 ml) was added, the mixture extracted with Et_2O (3 × 20 ml) and washed with H_2O (3 × 10 ml) and the org. phase dried (K_2CO_3) and analyzed by GC-MS. MS and t_R of **2** and **3** from isomerization in CH_3OH and CH_3O^2H showed no difference. The fraction at t_R 8.44 corresponding to **4** showed MS: 87 (7.8, $M^{+\cdot}$), 86 (2.0), 69 (15), 68 (19), 58 (94), 57 (100), 45 (26), 44 (40).

1.5. *Isomerization of* **1** *in* C^2H_3OH. To $C^2H_3O^2H$ (*ca.* 99.8% ^2H, 10 ml, 0.22 mol) diluted in pentane (50 ml), Na (7 g, 0.30 mol) was added in small pieces under stirring. Once the $^2H_2$ evolution had stopped, H_2O (*ca.* 10 ml) and then 2M HCl (*ca.* 100 ml) were added dropwise with stirring. After 15 min, the org. phase was separated and

dried (K_2CO_3), the solvent removed, and the crude product distilled affording C^2H_3OH (5.7 g, 71%). The isomerization of **1** in C^2H_3OH was done as described in *1.2*. The crude mixture was analyzed by GC-MS. MS and t_R of **2–4** from isomerization in CH_3OH and C^2H_3OH showed no difference.

1.6. *Isomerization of* **1** *in* H_2O *under Reflux*. To a soln.of B_{12a} (500 mg, 0.36 mmol), NH_4Cl (500 mg, 9.3 mmol), and cyclohexanol (500 mg, 5.0 mmol; internal standard) in 25 ml H_2O under Ar, Zn powder (*ca.* 2 g) was added and the mixture heated (oil bath) to reflux temp. (98°). Epoxide **1** (5.00 g, 60 mmol) was added by syringe to the green, boiling soln. The colour first changed to orange-brown, but turned to green after *ca.* 10 min. Samples were taken in time intervals by syringe, extracted with Et_2O and quantitatively analyzed by GC (*PEG* phase): **1** at t_R 4.35, **2** at t_R 10.65, **3** at t_R 7.05, **5** at t_R 9.65, **7** at t_R 10.80 (*Table 3, Fig. 6*).

In a parallel experiment under the same conditions (10 g (0.12 mol) of **1**), after 6 h, the soln. was cooled to r.t., extracted with Et_2O (2 × 40 ml), and washed with H_2O (10 ml). The org. phase was dried ($MgSO_4$) and evaporated. Distillation of the 7.1 g of crude oil at 12 Torr afforded a fraction at b.p. 46–48°: 3.82 g (38%). GC: 2 main peaks at t_R 10.70 and 10.85 corresponding to **2**/**7** in a ratio of 1.8:1. ^{1}H-NMR: signals of **2**; additionally 2.65 (*q*, 2 H–C(2), 2 H–C(5)); 4.50 (*s*, H–C(1)); 5.72 (*s*, H–C(3), H–C(4)).

1.7. *Isomerization of* **1** *in* ^2H_2O *under Reflux*. Under the same conditions as described in *1.6*, B_{12a} (0.10 g), N^2H_4Cl (0.10 g), and **1** (0.30 g, 3.6 mmol) were reacted for 5 h in 10 ml of ^2H_2O. The soln. was then extracted with dry Et_2O (10 ml) and the org. phase directly submitted to GC-MS analysis. GC-MS of **2**: 89 (4), 88 (20), 87 (50), 86 (100), 85 (63), 84 (18), 83 (4). *GC-MS of cyclopent-3-enol* (**7**): 89 (2), 88 (16), 87 (39), 86 (51), 85 (30), 84 (10), 83 (3), 44 (100). GC-MS of **3**: 92 (3), 91 (10), 90 (15), 89 (19), 88 (24), 56 (100). GC-MS of **4**: 93 (2.40), 92 (4.80), 91 (3.10), 90 (2.25), 89 (1.98), 60 (100).

2. Stereochemistry. – 2.1. *(1-*$^2H_1$*)Cyclopent-2-enol* ((1-^{2}H)-**2**). According to [24], $CeCl_3 \cdot 7H_2O$ (22.3 g, 60 mmol) and cyclopent-2-enone (**11**; 4.90 g, 60 mmol) were dissolved in MeOH (150 ml). Under vigorous stirring, NaB^2H_4 (2.30 g, 55 mmol) was added in two portions, whereby a violent hydrogen evolution occurred. After 5 min, Et_2O (150 ml) was added, the precipitate filtered off, and the solvent evaporated. The crude product was diluted with Et_2O (100 ml), washed with H_2O (3 × 20 ml), and dried (K_2CO_3). After evaporation the residue was distilled over a 5-cm *Vigreux* column. At b.p. 47°/12 Torr, (1-^{2}H)-**2** (3.38 g, 67%) was obtained. ^{1}H-NMR: like **2**, without peak at 4.82. MS: 85 (73, M^+), 84 (100), 83 (40), 56 (51), 55 (32), 42 (30), 41 (25), 39 (23).

2.2. cis-*2,3-Epoxycyclopentanol* (**9**). According to [23], cyclopent-2-enol (3.95 g, 46.5 mmol) and $VO(AcAc)_2$ (0.20 g, 0.75 mmol) in benzene (50 ml; blue soln.) were heated to reflux, and *t*-BuOOH (5.73 g, 51.1 mmol) was added dropwise within 20 min. The colour first changed to yellow and after 4–5 h refluxing to green. The solvent was evaporated at 50°/150 Torr, and Et_2O (150 ml) was added to the remaining oil. The precipitate was filtered off over *Celite*, the solvent evaporated, and the oil distilled (b.p. 55–57°/0.8 Torr): 3.38 g (72%) of **9**. ^{1}H-NMR: 4.20 (*t*, J = 8, H–C(1)); 3.41 (*d*, J = 2.8, H–C(3)); 3.39 (*d*, J = 2.8, H–C(2)); 2.01 (*dd*, J = 8.4, 14.3, H–C(5) *trans* to O); 1.83 (*dd*, J = 8.6, 12.8, H–C(4) *cis* to O); 1.56 (*dddd*, J = 14.3, 10.1, 8.5, 1.3, H–C(4) *trans* to O); 1.18 (*m*, H–C(5) *cis* to O). MS: 100 (7.0, M^+), 81 (45), 57 (83), 44 (100), 43 (65), 41 (36), 39 (32).

cis-*2,3-Epoxy(1-*$^2H_1$*)cyclopentanol* ((1-^{2}H)-**9**). Prepared like **9**, but starting from (1-^{2}H)-**2**. ^{1}H-NMR: like **9**, but lacking the signal at 4.20. MS: 101 (5.2, M^+), 82 (46), 58 (55), 57 (58), 45 (97), 44 (100), 41 (38), 39 (27).

2.3. trans-*1,2-Epoxy(3-*$^2H_1$*)cyclopentane* (**1a**). A soln. of dry pyridine (2.60 g, 33 mmol) in dry CH_2Cl_2 (80 ml) under Ar was cooled to −15°, and trifluoromethanesulfonic anhydride (8.88 g, 31.5 mmol) was added in 1 portion under vigorous stirring (→ precipitate). Alcohol **9** (3.15 g, 31.5 mmol) was added dropwise by syringe at −15°, whereby most of the precipitate dissolved. The mixture was allowed to return to r.t., the precipitate filtered off, and the solvent evaporated *i.v.* at r.t. The remaining orange oil was diluted with dry Et_2O (30 ml) and added dropwise to a stirred soln. of NaB^2H_4 (1.21 g, 32 mmol) in dry DMF (20 ml) at 0°. After 15 min, the mixture was diluted with Et_2O (20 ml) and washed with brine (2 × 20 ml) and H_2O (20 ml), the org. phase dried (K_2CO_3), the solvent distilled off over a 40-cm *Vigreux* column, and the residue distilled over a 5-cm column (b.p. 46–48°/100 Torr): 837 mg (32%) of **1a**. Purity (GC) > 96%. ^{1}H-NMR: see *Table 5, Figs. 7* and *9*. MS: 85 (6.0, M^+), 84 (22), 83 (3.0), 57 (35), 56 (100), 55 (37), 42 (59), 41 (40).

cis-*1,2-Epoxy(3-*$^2H_1$*)cyclopentane* (**1b**). Prepared from (1-^{2}H)-**9** as described above, but with $NaBH_4$ instead of NaB^2H_4. ^{1}H-NMR: see *Table 5, Figs. 7–9*. MS: 85 (5.5, M^+), 84 (22), 83 (2.6), 57 (33), 56 (100), 55 (31), 42 (54), 41 (38).

2.4. *Isomerization of* **1a** *and* **1b**. Samples of **1a** (100–700 mg) were isomerized in two parallel experiments under the same conditions as described in *1.2*, in the dark. Alcohol **2** was isolated by prep. GC: e.e. 60%. ^{1}H-NMR: like **2** (see above), but differing in integrals for *Exper. 1* and *2* (values of the latter in parentheses); 5.98 (*m*, 0.73(0.74) H, H–C(3)); 2.24–2.28 (2*m*, 1.54(1.56) H, H–C(4) *cis* to OH, H–C(5) *trans* to OH). MS: 85 (35(40), M^+), 84 (100(100)), 83 (32(36)), 67 (10(17)), 66 (11(16)), 57 (8(20)), 56 (31(83)), 55 (12(42)), 43 (9(25)), 42 (12(39)), 41 (11(29)), 40 (9(25)), 39 (13(32)).

2 *from* **1b**: ^{1}H-NMR: like **2** (see above) but differing in integral; 5.98 (*m*, 0.74(0.71) H, H–C(3)); 1.69 (*m*, 0.47(0.57) H, H–C(5) *cis* to OH). MS: 85 (34(34), $M^{+\cdot}$), 84 (100(100)), 83 (23(24)), 67 (9(21)), 66 (11(20)), 57 (8(20)), 56 (31(81)), 55 (10(35)), 43 (9(27)), 42 (13(39)), 41 (12(32)), 40 (13(34)), 39 (15(33)).

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