219. Cob(I)alamin-Catalyzed Skeletal Migrations Observed during the Reduction of 4β-(*tert*-Butyl)-1α-(1-methylvinyl)cyclohexanecarbaldehyde[1])

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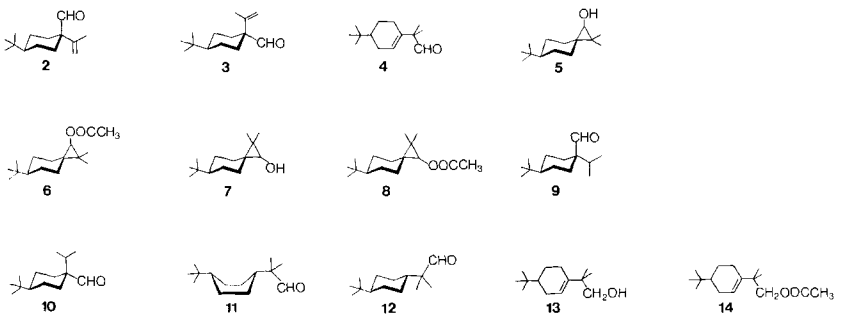
(2.IV.84)

Summary

The cob(I)alamin(**1(I)**)-catalyzed[2]) transformation of the aldehyde **2** has been studied (*cf. Table 1*). Kinetic examinations showed a rapid isomerization of **2** to **3** (*cf. Fig. 1* and *2*). From the transformations in glacial AcOH, the two cyclopropanols **5** and **7** were isolated as main products (*cf. Tables 1–3* and *Fig. 1* and *2*). Using large amounts of **1(I)**, the aldehyde **4** was very slowly transformed. Accepting the intermediate formation of 6 interconnected Co-complexes, *i.e.* **A**, **B**, **C**, **D**, **E**, and **F** (*cf. Scheme*), the generation of all the products observed can be explained.

1. Reductions Mediated by Cob(I)alamin (1(I))[2]) Starting from 2 and 4. – Varying the solvent and the amount of granular Zn present, the β,γ-unsaturated aldehyde **2**, *i.e.* 4β-(*tert*-butyl)-1α-(1-methylvinyl)cyclohexanecarbaldehyde, was reduced using cob(I)alamin **(1(I))**[2]) as catalyst (*cf. Table 1, Exper. 1–3*).



In *Exper. 1*, the two cyclopropanols **5** (41%) and **7** (30%) were the main products, and the saturated aldehyde **9** was detected in 15.1% yield. In *Exper. 2*, the same derivatives, *i.e.* **5** (44.1%) and **7** (33.4%), were again isolated as the main products. The saturated aldehyde **9** was present in 2.7% yield only; this small amount of **9** can be explained by the small quantities of granular Zn present (*cf. Chap. 4*). Interestingly, in *Exper. 3*, the saturated aldehyde **9** (45.2%) was the main product, the two cyclopropa-

[1]) 14th Communication in the series 'Cob(I)alamin as Catalyst'; for the preceeding paper, see [1a].

[2]) For the structural formulae of cob(I)- and cob(III)alamin (**1(I)**, **1(III)**) *cf. Scheme 1* in [1a].

Table 1. *Cob(I)alamin-Dependant Reductions and Blank Experiments with* **2** *and* **4**

Exper. No.	Starting material	Reaction conditions[a])	Reaction time	Products yield [%]												
				2	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
1	**2**	A	18 h	1.2	0.4	3.8	41	0.15	30	0.15	15.1	2.5	2	0.2	–	– [b])
				0.7	0.25	3.5	36.2	< 0.1	28.1	< 0.1	13	2.2	1.7	< 0.1	–	– [c])
2	**2**	B	18 h	10.6	3.5	2.7	44.1	< 0.1	33.4	< 0.1	2.7	0.4	0.4	–	–	– [b])
3	**2**	C	18 h	0.3	0.1	2.5	25.7	–	14.2	–	45.2	6.5	4	0.3	–	– [b])
4	**2**	D	18 h	99.4	–	–	–	–	–	–	–	–	–	–	–	– [b])
5	**2**	E	18 h	99.6	–	–	–	–	–	–	–	–	–	–	–	– [b])
6	**2**	F	18 h	99.4	–	–	–	–	–	–	–	–	–	–	–	– [b])
7	**4**	A	18 h	–	–	99	–	–	–	–	–	–	–	–	0.6	– [b])
				–	–	89	–	–	–	–	–	–	–	–	0.5	– [c])
8	**4**	G	7 d	–	–	98	–	–	–	–	–	–	–	–	1.8	– [b])
9	**4**	H	7 d	–	–	90	1.1	< 0.1	0.7	< 0.1	3.7	0.5	0.4	–	2.7	0.2[b])
						81	1	–	0.5	–	2	< 0.1	< 0.1	–	2	< 0.1[c])

[a]) A: Cob(I)alamin from 0.1 mol-equiv. of **1**, 20 mol-equiv. of Zn, AcOH, Ar, r.t.
B: Cob(I)alamin from 0.1 mol-equiv. of **1**, 2 mol-equiv. of Zn, AcOH, Ar, r.t.
C: Cob(I)alamin from 0.1 mol-equiv. of **1**, 20 mol-equiv. of Zn, AcOH/H_2O 4:1, Ar, r.t.
D: 20 mol-equiv. of Zn, AcOH, Ar, r.t.
E: Cob(II)alamin from 0.1 mol-equiv. of **1**, $SnCl_2 \cdot 2H_2O$ (5 mol-equiv.), AcOH, Ar, r.t.
F: Cob(II)alamin from 0.1 mol-equiv. of **1**, $SnCl_2 \cdot 2H_2O$ (2 mol-equiv.), AcOH/H_2O 4:1, Ar, r.t.
G: 60 mol-equiv. of Zn, AcOH, Ar, r.t.
H: Cob(I)alamin from 0.5 mol-equiv. of **1**, 60 mol-equiv. of Zn, AcOH, Ar, r.t.

[b]) GC data from the crude product.

[c]) Yield of product after chromatography.

nols **5** and **7** being produced in 25.7 and 14.2% yield, respectively. In all three experiments, the aldehydes **2** and **3** as well as the cyclopropanols **5** and **7** have been formed in similar proportions, *i.e.* **2**/**3** = 3.0, **5**/**7** = 1.32–1.81.

A cob(I)alamin-catalyzed reduction of 2-[4-(*tert*-butyl)-1-cyclohexenyl]-2-methylpropionaldehyde (**4**; *Exper. 7*) caused almost no consumption of the starting aldehyde. Even in the presence of high amounts of **1(I)**, **4** was very slowly reduced *(Exper. 9)*. *Inter alia*, traces of the cyclopropanols **5** (1.1%) and **7** (0.7%) and of the alcohol **13** (2.7%) could be detected.

2. Blank Experiments. – As **1(I)** formed in our experiments from Zn in AcOH was shown to be metastable under acidic conditions [2], it was necessary to establish which oxidation state, *i.e.* **1(I)** and/or **1(II)**, is accounting for the transformations observed starting from **2**. A blank experiment omitting the cobalamin catalyst led to unreacted starting material (99.4%; *cf. Table 1, Exper. 4*). Two experiments, one using AcOH (glacial) and the other AcOH/H_2O, running under conditions excluding the presence of **1(I)**, *i.e.* applying $SnCl_2$ to reduce **1(III)** to **1(II)** [3], also led to the starting material **2** (99.6 and 99.4%, resp.; *Exper 5* and *6*). Therefore, the transformations of *Exper. 1–3* must be brought about by **1(I)**.

A blank experiment starting from **4** using a larger excess of Zn and running for 7 d caused almost no transformation *(Exper. 8)*; in low yield, the alcohol **13** was detected. This alcohol as well as the corresponding acetate **14** present in the product mixture from *Exper. 9* are, therefore, assumed to be formed by direct interaction of Zn with the aldehyde **4**.

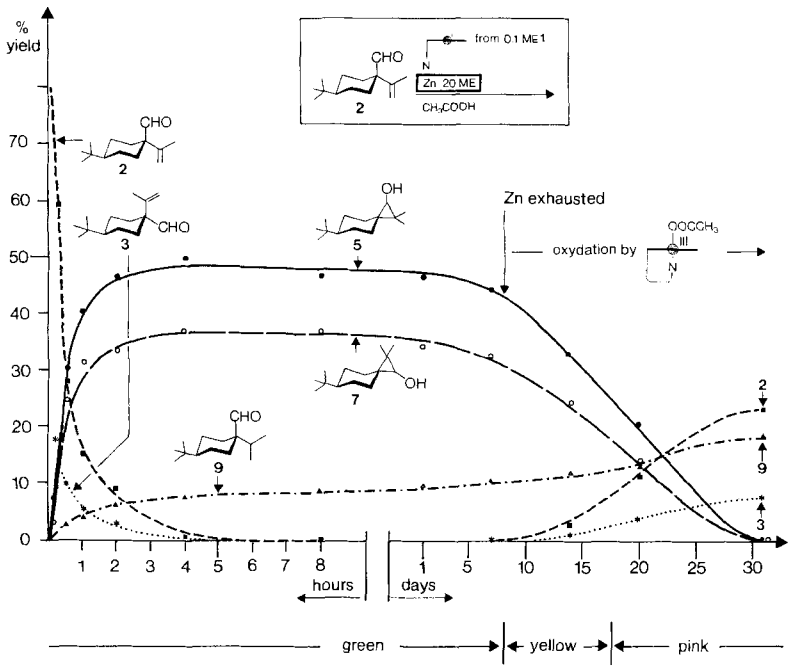


Fig. 1. *Kinetics of the* **1(I)***-catalyzed transformations starting from* **2** *in the presence of 20 mol-equiv. of Zn*

3. Kinetic Studies. – The kinetics of the **1(I)**-catalyzed transformations starting from **2** *(cf. Fig. 1)* were studied repeating *Exper. 1* under conditions guaranteeing a better control of the absence of H_2O *(cf. Exper. Part)*. From the reaction mixture, aliquots were withdrawn after ¼ h, ½ h, 1 h, 2 h, 4 h, 8 h, 24 h, 7 d, 14 d, 20 d, and 31 d. In *Fig. 1*, a synopsis is presented showing only the products **3**, **5**, **7**, **9**, and the starting material **2** (complete data in the *Exper. Part*). The aldehyde **2** is rapidly consumed disappearing after *ca.* 4 h. After 15 min, the β,γ-unsaturated aldehyde **3** was present in 18% yield; subsequently, **3** behaved like **2**, being completely consumed after *ca.* 4 h. The two major products **5** and **7** reached a top level at the time of almost complete consumption of **2** and **3**. In minor amounts, the aldehyde **9** was produced. After this starting phase ending at *ca.* 4 h, the reaction showed equal product composition for a long time. However, when the majority of Zn was consumed, *i.e.* after about 7 d, a new phase started characterized by a gradual colour change from green to yellow and then to pink. At the same time, consumption of the two cyclopropanols **5** and **7**, generation of **2** and **3**, and slightly increasing amounts of aldehyde **9** were observed.

As the aldehyde **3** was already formed after 15 min, its generation from **2** must be a fast process catalyzed by **1(I)**. The catalyst **1(I)** was prepared *in situ* from acetatocob(III)alamin and Zn; the use of small quantities of Zn should, therefore, allow to visualize the generation of **3** from **2**. Data from such an experiment, *i.e.* the transformation of **2** in the presence of only 1 mol-equiv. of Zn in AcOH, are presented in *Fig. 2* (samples withdrawn after ¼ h, ½ h, 1 h, 2 h, 4 h, 8 h, 24 h, 4 d, 7 d, 11 d, and 19 d; complete data in the *Exper. Part*). Again, a fast generation of **3** from **2** occurred. After

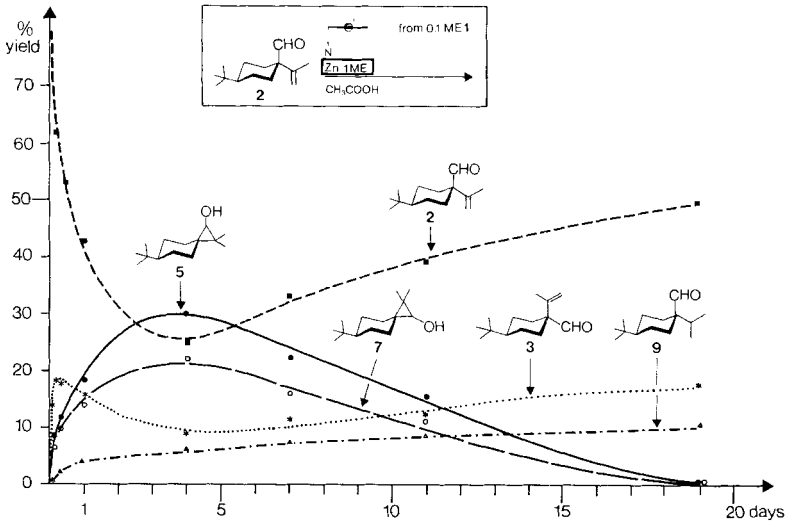


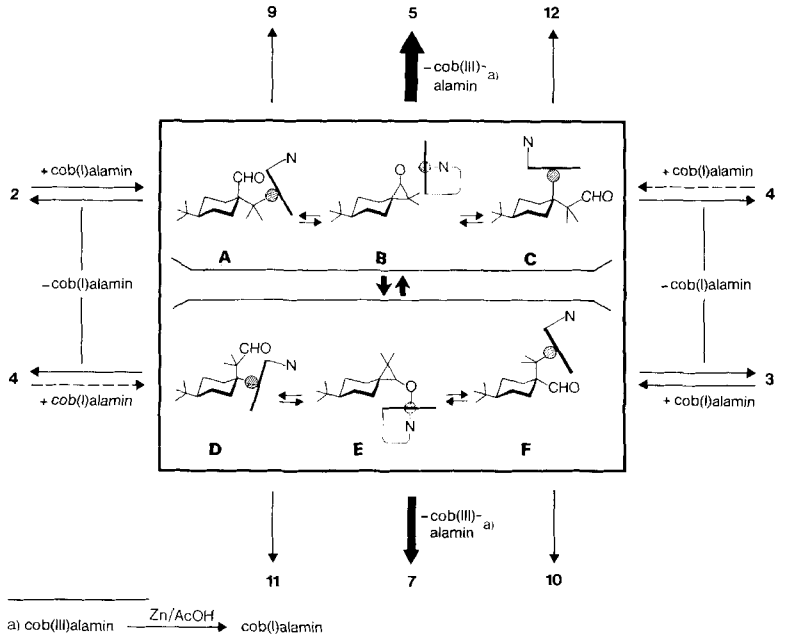
Fig. 2. *Kinetics of the* **1(I)***-catalyzed transformations starting from* **2** *in the presence of 1 mol-equiv. of Zn*

4 d, the Zn was consumed and a maximal yield of the two cyclopropanols **5** and **7** and a minimal amount of **2** and **3** were observed. The initial phase, lasting for the first 4 d, was characterized by the fast formation and subsequent consumption of **3** as well as by a decrease of **2** and by the formation of **5** and **7**; the saturated aldehyde **9** was present in minor amounts. In the terminal phase initiating after 4 d, the two cyclopropanols **5** and **7** were consumed and increasing amounts of **2** and **3** were present. The saturated aldehyde **9** was found in slightly increasing amounts during this phase. Obviously, there was not enough Zn present to consume **2** and **3** completely. The initial and the terminal phase in this experiment parallel the starting and terminal phase in the experiment presented in *Fig. 1*.

In both kinetic experiments, **3** was produced from **2**. Subsequently, **2** and **3** were consumed, and at the same time **5** and **7** were formed. After consumption of the Zn working under conditions not excluding the invasion of O_2, the two cyclopropanols **5** and **7** are oxidized back to the two β,γ-unsaturated aldehydes **2** and **3** [1a]. Observing the amounts of the saturated aldehyde **9** present, such a reversibility was not detected in the above two experiments. A detailed study of the cob(III)alamin-mediated transformation starting from **5** and **7** has been published [1a].

4. Discussion. – Under the conditions of the experiment displayed in *Fig. 1*, the starting aldehyde **2** was consumed after *ca.* 4 h. Under identical experimental conditions, the structurally closely related double bonds in 4β-(*tert*-butyl)-1α-(1-methylvinyl)cyclohexanecarbonitrile and 4β-(*tert*-butyl)-1α-(1-methylvinyl)cyclohexanemethanol were saturated showing half-lifes of 1 and 4 h, respectively [1b]. This compares well with the rapid consumption of **2**. Contrasting these rapid transformations, **4**, 2-[4-(*tert*-butyl)-1-cyclohexenyl]-2-methylpropiononitrile, and 2-[4-(*tert*-butyl)-1-cyclohexenyl]-2-methylpropanol revealed to be rather inert towards **1(I)**. Under forcing conditions using high amounts of **1(I)** and Zn, these derivatives were only slowly trans-

Scheme



formed (*cf.* [1b]). In order to explain the products observed starting from the two β,γ-unsaturated nitriles and the two homoallylic alcohols, (*tert*-alkyl)cobalamins have been formulated [1b]. In analogy to such a mechanism, initial generation of the (*tert*-alkyl)cobalamins **A** from **2** and **C** and **D** from **4** is formulated in this paper as well (*cf. Scheme*). Alkylcobalamin **A** is one of the 6 Co-complexes, *i.e.* 4 alkylcobalamins **A**, **C**, **D**, and **F** and 2 (cyclopropanolo)cobalamins **B** and **E**, represented within the black frame in the *Scheme*. Studying the **1(III)**-mediated oxidation of **5** and **7** at room temperature in AcOH, these cobalamin complexes were shown to be in equilibrium [1a]. From these interconnected intermediates, the generation of all the products observed can be explained.

From **A**, **C**, **D**, and **F**, the aldehydes **2**, **3**, and **4** can be produced by reductive elimination. At the same time, **1(I)** is regenerated, which can rapidly attack **2** and **3** again. Initially, this leads to isomerization of **2** and ultimately to consumption of **2** and **3**. The aldehyde **4** produced in small amounts starting from **2** was shown to be rather stable in presence of **1(I)** (*cf. Exper. 7* and *9*). The slow accumulation of this derivative (see *Exper. Part*) can, therefore, easily be understood. The formation of the two cyclopropanols **5** and **7** can be explained as well, *e.g.* by ligand exchange from **B** and **E**. Under the conditions applied, cob(III)alamin produced after ligand exchange should rapidly be reduced to **1(I)**. Therefore, the cyclopropanols **5** and **7** should accumulate during the reaction. Our experiments show this to be the case (*cf. Fig. 1* and *2*). From the 4 (*tert*-alkyl)cobalamins **A**, **C**, **D**, and **F**, reductive cleavage (*cf. e.g.* [1b]) should lead to the corresponding saturated aldehydes. As this reaction has been shown to

follow retention of configuration [1e], **9**, **12**, **11**, and **10** should be produced from **A**, **C**, **D**, and **F**. The 4 saturated aldehydes **9**–**12** have shown to be present in the reaction mixtures (*cf. Table 1* and *Exper. Part*).

The 6 interconnected Co-complexes displayed within the black frame of the *Scheme* are arranged in two horizontal rows. Focussing on the two termini of each horizontal row, *i.e.* **A**, **C** and **D**, **F**, the rearrangements can be characterized as diretentive diatropic migrations.

The authors would like to thank their colleagues from the Central Research Units and in particular Dr. *A. Dirscherl* (microanalysis), Dr. *M. Vecchi* (GC), Drs. *Englert* and *Arnold* (NMR), *G. Oesterheld* (GC/MS) and *W. Meister* (MS) for analytical and spectroscopic data.

Experimental Part

General Remarks. See [1b]. The cob(I)alamin-catalyst was according to the procedure published in [1c].

A. Reductions Mediated by 1(I). – a) *Exper. 1.* To the catalyst prepared from 330 mg (0.1 mol-equiv.) of cyanocob(III)alamin (**1**) in 30 ml of AcOH and 3.1 g (20 mol-equiv.) of activated granular Zn were added 500 mg of **2** in 16 ml of AcOH. The suspension[3]) was stirred in the dark at r.t. for 18 h under Ar. After aq. extraction (Et_2O), 495 mg (99% recovery by weight of starting **2**) of a mixture was obtained and analyzed by NMR, TLC, and GC. Product distribution (GC): see *Table 1*. The crude product was purified by chromatography (SiO_2, Et_2O/hexane, the 7 aldehydes were eluted in 1 fraction); for yields, see *Table 1*. Data of **2**, **4**, **9**, **11**, and **12**: *cf.* [1b]. Data of **5**, **7**, and **10**: see [1d]. Data of **3**, **6**, and **8**: see [1a].

b) *Exper. 2.* To the catalyst (from 66 mg (0.1 mol-equiv.) of **1**) in 7 ml of AcOH and 63 mg (2 mol-equiv.) of activated granular Zn were added 100 mg of **2** in 2 ml of AcOH. The suspension[3]) was stirred in the dark at r.t. for 18 h under Ar. After aqueous extraction (Et_2O), 94 mg (94% recovery by weight) of a mixture was obtained and analyzed as above. Product distribution (GC): see *Table 1*.

c) *Exper. 3.* Conditions exactly as in *Exper. 1*, but replacing AcOH by AcOH/H_2O 4:1 (97% recovery by weight). Product distribution (GC): see *Table 1*.

d) *Exper. 7.* Conditions exactly as in *Exper. 1*, but replacing **2** by **4** (96.5% recovery by weight). Product distribution (GC) and yields after chromatography (SiO_2, Et_2O/hexane): see *Table 1*. Data of **13**: *cf.* [1b].

e) *Exper. 9.* To the catalyst (from 1.63 g (0.5 mol-equiv.) of **1**) in 30 ml of AcOH and 9.4 g (60 mol-equiv.) of activated granular Zn were added 500 mg of **4** in 16 ml of AcOH. The green[3]) suspension was stirred in the dark at r.t. for 7 d under Ar and then treated as in *Exper. 1* (97.2% recovery by weight). Product distribution (GC) and yields after chromatography (SiO_2, Et_2O/hexane, the 4 aldehydes were eluted as one fraction): see *Table 1*.

*Data of 2-[4-(*tert*-butyl)-1-cyclohexenyl]-2-methylpropyl Acetate* (**14**): R_f 0.33 (CH_2Cl_2/hexane 2:1), t_R (GC, 50→330°) 13.2 min. IR (liq.): 1743 (C=O), 1392, 1365, 1290, 1244, 1038. ^{1}H-NMR: 0.86 (*s*, 9H, $(CH_3)_3C$); 0.86–2.2 (*m*, 7H, CH_2, CH); 1.04 (*s*, 6H, $(CH_3)_2C$); 2.04 (*s*, 3H, CH_3COO); 3.90 (*AB*('*q*'), J = 11, $\nu_{AB}/2$ = 6, 2H, CH_2OOC); 5.4–5.58 (*m*, 1H, =CH). MS: 252 (1, M^+), 206 (1), 192 (14, $M^+ - CH_3COOH$), 179 (19, $M^+ - CH_3COOCH_2$), 135 (49), 123 (57, $M^+ - CH_3COOCH_2 - CH_2{=}C(CH_3)_2$), 109 (36), 93 (29), 79 (25), 57 (100, $(CH_3)_3C^+$), 43 (50, CH_3CO^+).

B. Blank Experiments. a) *Exper. 4.* To 500 mg of **2** in 46 ml of AcOH were added 3.1 g (20 mol-equiv.) of activated granular Zn. The suspension was then treated as in *Exper. 1* (96% recovery). Product distribution: **2** (99.4%).

b) *Exper. 5.* To the catalyst (from 66 mg (0.1 mol-equiv.) of **1**) in 7 ml of AcOH were added 541 mg (5 mol-equiv.) of $SnCl_2 \cdot 2H_2O$. After stirring for 30 min at r.t. under Ar, 100 mg of **2** in 2 ml of AcOH were added. The suspension was stirred in the dark at r.t. for 18 h under Ar. A colourless solution and a yellow precipitate was formed. After extraction (Et_2O), 93 mg (93% recovery) of product was isolated. Product distribution (GC): **2** (99.6%).

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[3]) After 5–10 min stirring under Ar, the colour turned to green.

c) *Exper. 6.* Conditions as in *Exper. 5*, but replacing AcOH by AcOH/H_2O 4:1 and using only 2 mol-equiv. of $SnCl_2 \cdot 2H_2O$ (clear dark yellow solution after addition of **2**; 95% recovery). Product distribution GC: **2** (99.4%).

d) *Exper.* 8. To a solution of 300 mg of **4** in 28 ml of AcOH were added 5.65 g (60 mol-equiv.) of activated granular Zn. The suspension was stirred in the dark at r.t. for 7 d under Ar. After aq. workup (Et_2O), 298 mg (99.5% recovery) of mixture was obtained. Product distribution (GC): see *Table 1.*

C. Kinetic Experiments. a) *Exper. presented in* Fig. 1 *and* Table 2. Conditions exactly as in *Exper. 1* (see *Chap. A*), but using AcOH from a fresh bottle. From the stirred suspension, aliquots of 2 ml were withdrawn using a syringe after 15 min, 30 min, 1 h, 2 h, 4 h, 8 h, 24 h, 7 d, 14 d, 20 d, and 31 d. After aq. extraction (Et_2O) of the aliquots, the weight recovery was 91–99%. The crude products were analyzed by TLC, NMR, and GC. Product distributions: see *Table 2.*

b) *Exper. of* Fig. 2 *and* Table 3. Conditions exactly as described in *Chap. A*, but using only 1 mol-equiv. of Zn. Aliquots of 2 ml after 15 min, 30 min, 1 h, 2 h, 4 h, 8 h, 24 h, 4 d, 7 d, 11 d, and 19 d (recovery 89–99%). Product distributions: *Table 3.*

Table 2. *Product Distributions in the Aliquots Obtained after Treatment of* **2** *with* **1(I)** *in the Presence of 20 mol-equiv. of Zn*

Yield	Time										
[%]	¼ h	½ h	1 h	2 h	4 h	8 h	24 h	7 d	14 d	20 d	31 d
2	59.1	29.1	15.3	8.7	0.6	0.6	0.35	0.8	3.5	11.5	24.9
3	18	9.6	5.2	3	0.2	0.2	0.1	0.25	1.1	4	8.6
4	0.8	1.3	1.5	1.6	1.6	1.7	1.7	2	2.6	3.2	3.3
5	7	30	40	46.7	50.3	46.6	47.1	44	33.7	20.7	–
6	–	–	–	–	–	–	0.2	2	5.8	8.7	10.5
7	3.7	25	32	32.6	38	37.2	36.7	33.8	26.3	16.7	–
8	–	–	–	–	–	–	0.2	2	5.9	9.0	10.6
9	2.2	3.1	4.0	5.5	6.7	9	9.6	10.9	12.3	16.3	19.8
10	0.5	0.5	0.7	0.8	0.9	1.4	1.4	1.5	2.3	2.7	3.4
11	0.2	0.2	0.2	0.4	0.9	0.8	1.1	1.2	1.7	2	2.5
12	–	–	–	–	–	–	–	0.1	0.2	0.3	0.3
2/3	3.28	3.03	2.94	2.9	3.0	3.0	3.5	3.2	3.18	2.88	2.90
5/7	1.89	1.2	1.25	1.43	1.32	1.25	1.28	1.30	1.28	1.24	–

Table 3. *Product Distributions in the Aliquots Obtained after Treatment of* **2** *with* **1(I)** *in the Presence of 1 mol-equiv. of Zn*

Yield	Time										
[%]	¼ h	½ h	1 h	2 h	4 h	8 h	24 h	4 d	7 d	11 d	19 d
2	99.3	97.2	88.4	80.0	62.5	52.8	42.5	25.0	32.7	38.0	49.3
3	–	2	9.3	12.9	18.3	17.6	15.2	8.8	11.3	12.3	17.3
4	–	–	0.15	0.35	0.95	1.7	3.4	3.35	3.5	4.0	4.4
5	–	–	0.7	2.0	8.0	12.9	18.1	30.2	22.3	15.4	0.4
6	–	–	–	–	–	–	0.1	0.8	1.4	2.4	3.3
7	–	–	0.5	1.5	6.1	10	14.6	21.8	15.9	11.1	0.3
8	–	–	–	–	–	–	0.1	0.85	1.4	2.4	3.1
9	–	–	0.1	0.3	0.9	1.7	3.6	5.7	7.3	7.7	10.1
10	–	–	–	–	–	0.2	0.5	0.9	1.0	1.1	1.5
11 + 12	–	–	–	–	–	–	–	0.8	0.9	0.9	0.9
2/3	–	48.6	9.5	6.2	3.41	3.0	2.80	2.84	2.89	3.09	2.85
5/7	–	–	1.4	1.33	1.31	1.29	1.24	1.39	1.40	1.39	1.33

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