Reactivity of 2-Ethoxy-5-alkyl-3,4-dihydro-2*H*-pyrans toward Aluminum Alkyls: Stereoselective Preparation of Cyclobutyl Derivatives

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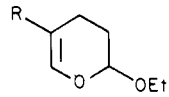
Aluminum trialkyls regioselectively react with 2-ethoxy-5-alkyl-3,4-dihydro-2*H*-pyrans to give as main products *trans*-cyclobutylmethanols or -carbinols and 2-alkyl-5-ethoxyheptanals. The parameters ruling the reaction course have been established, and on the basis of the dynamic and stereochemical results, some reasonable mechanistic hypotheses have been proposed.

As part of a more general research line on the synthesis[1] of heterocyclic substrates we have recently undertaken a study on the reactivity of such compounds with organometallic derivatives. This paper deals with an investigation on the behavior of aluminum trialkyls toward 2-ethoxy-5-alkyl-3,4-dihydro-2H-pyrans (1). Some preliminary



1a, R = H
b, R = Me
c, R = *i*-Pr
d, R = (*S*)-*sec*-Bu

results showed the dependence of the reaction on the nature of the aluminum alkyls and on the structure of the heterocyclic compounds 1.[2] We describe herein some additional examples of this reaction, clarify its stereochemical course, point out the parameters on which the product distribution depends, and suggest some mechanistic hypotheses.

Results and Discussion

Compounds 1[1a] were reacted in *n*-heptane with triisobutylaluminum (*i*-Bu_3Al), triethylaluminum (Et_3Al), or the corresponding etherate ($Et_3Al{\cdot}OEt_2$). The reaction times suitable to warrant the best conversion of 1 were established in some preliminary experiments, following the reaction progress by GLC. The experimental conditions adopted and the main results obtained in the reactions (Scheme I) are reported in the Table I. The reaction products (Scheme I) were isolated from the reaction mixtures and their structures were established by IR, ^1H, ^{13}C NMR, and mass spectra (see Experimental Section). The structure and the stereochemistry of the alcohols **3a** and **3b** were determined by comparison (GLC retention time and mass spectra) with authentic trans isomers[3] obtained as described.[4] By using the same IR spectroscopy approach employed by d'Angelo,[3] we also concluded that alcohols **2a–d** were pure trans stereoisomers. ^{13}C NMR spectroscopy proved useful in confirming such a deduction at least for **2c** and **2d**. The theoretical chemical shifts of **2a** and **2b** carbon atoms, evaluated by means of the additivity rule,[5] were in good agreement with those obtained by off-resonance decoupling experiments (see Table III; supplementary material); in the case of **2c** an appreciable deviation between the observed and calculated chemical shifts for C_2 and C_4 was found (28.10 and 76.64 ppm vs. 21.00 and 72.00 ppm, respectively); for these carbon atoms, supplementary increments had to be invoked.

In our opinion the C_2 increment is sterically induced and can be evaluated as ≈8 ppm,[6] taking into account the steric compression between the closely spaced hydrogens of C_2 and C_9 or C_{10}. In this way the actual theoretical shift (29.00 ppm) is in satisfactory agreement with the experimental one.

Moreover, the correct value of the chemical shift for C_4 can be evaluated only if one supposes a trans configuration for **2c**. In such a configuration the interaction between the hydrogens of the alcoholic function and of C_4 (γ effect) is possible (Figure 1); since this interaction results in ≈5 ppm[8] of additional increment, the effective chemical shift value of C_4 becomes 77.00 ppm, in very good agreement with the experimental data.

As regards **2d**, a theoretical chemical shift (76.94 ppm) for C_4 close to that experimentally determined (76.57 ppm) can be evaluated, once again, only if one considers a trans configuration for this compound.

The chemical shift of C_2 in **2d** (21.30 ppm) calculated with the sole contribution of the formal parameters, contrary to that we have seen for **2c**, agrees with the experimental value (20.28 ppm). This could be due to a particular conformation of the (*S*)-*sec*-butyl group. Moreover, the C_8 atom of this compound appears to be more deshielded than the corresponding carbon atom of **2c**, probably owing to such a conformation.

By reacting *i*-Bu_3Al and 1 [1]/[*i*-Bu_3Al] = 0.5, only the corresponding cyclobutylmethanols **2a–d** were recovered, in high yields (60–91%; Scheme I, path A; Table I); when **1d** was employed the **2d** obtained is an optically active mixture of an erythro and threo pair of trans stereoisomers. The reaction of 1 with Et_3Al, in the same molar ratio, generally gave a more complex reaction mixture (Scheme I, path B), even considering that compounds **2–5** were obtained only when **1b** was used (Table I, entry 6).

A more detailed inspection of Table I shows that in the mentioned experimental conditions, alcohols **2** and aldehydes **4** are always present (entries 2, 6, 10, 14) and alcohols **3** are formed only when **1a** and **1b** were reacted (entries 2, 6). Moreover, in the reaction of **1a**, the alcohol **3a** is the main component of the reaction mixture (entry

(1) (a) Menicagli, R.; Botteghi, C.; Marchetti, M. *J. Heterocyc. Chem.* **1980**, *17*, 57. (b) Menicagli, R.; Malanga, C.; Lardicci, L. *Ibid.* **1979**, *16*, 667. (c) Menicagli, R.; Wis, M. L.; Lardicci, L.; Botteghi, C.; Caccia, G. *J. Chem. Soc., Perkin Trans 1* **1979**, 847 and references cited therein.

(2) Menicagli, R.; Malanga, C.; Lardicci, L.; Tinucci, L. *Tetrahedron Lett.* **1980**, 4525.

(3) D'Angelo J. *Bull. Soc. Chim. Fr.* **1969**, 181.

(4) (a) Quelet, R.; D'Angelo, J. *C. R. Acad. Sci.* **1967**, *264*, 216. (b) *Bull. Soc. Chim. Fr.* **1967**, 3390.

(5) Breitmaier, E.; Voelter, W. In "^{13}C NMR Spectroscopy", 2nd ed.; Verlag Chemie: New York, 1978; pp 131.

(6) An analogous effect can be observed for the methoxy group of the methyl ethyl ether with respect to that one of the dimethyl ether;[7] in the former compound a conformational situation similar to that of **2c** can be supposed.

(7) Christl, M.; Reich, H. J.; Roberts, J. D. *J. Am. Chem. Soc.* **1971**, *93*, 3463.

(8) See ref 5, pp 74, 153–155 and references cited therein.

0022-3263/82/1947-2288$01.25/0

Scheme I

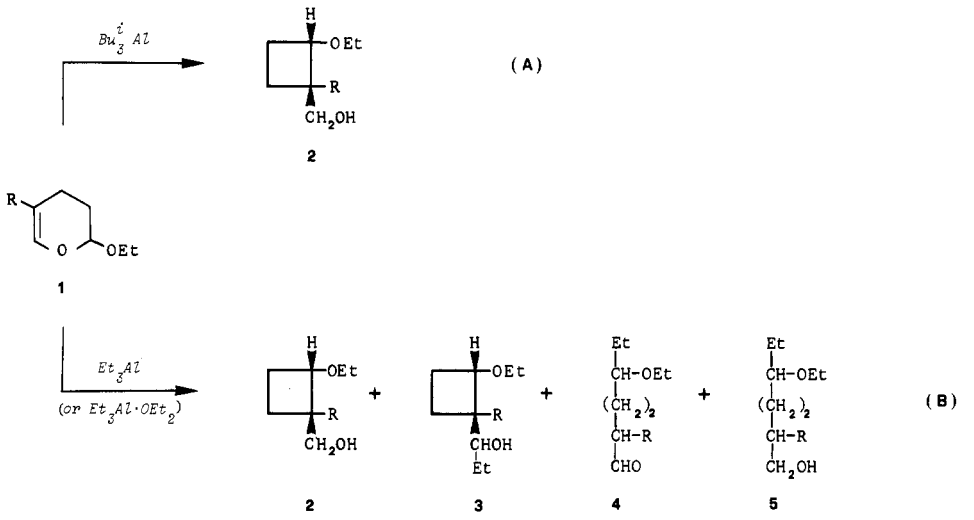


Table I. Reactions of 2-Ethoxy-5-alkyl-3,4-dihydro-2*H*-pyrans 1a-d with Aluminum Trialkyls (R_3Al)[a]

entry	1	R	molar ratio of 1/R_3Al	rctn time, h	% conversion[b,c]	% product distribution[b-d] 2	3	4	5
1	a	*i*-Bu	0.5	22	100	100 (60)[e]			
2		Et	0.5	4.5	100	34	51 (15)[f]	15	
3		Et	1	4.5	96	17	83		
4		Et[g]	0.5	20.5	100	9	91		
5	b	*i*-Bu	0.5	22	100	100 (80)			
6		Et	0.5	4.5	100	53	11	20 (14)[h]	16 (14)[h]
7		Et	1	4.5	86	40	58	2	
8		Et[g]	0.5	42	100	59	41		
9	c	*i*-Bu	0.5	22	100	100 (79)			
10		Et	0.5	4.5	100	23		66 (55)[h]	
11		Et	1	87	91	69		11	
12		Et[g]	0.5	56	100	64		14	
13	d	*i*-Bu	0.5	41	100	100 (91)			
14		Et[i]	0.5	20.5	100	18		75 (60)[h]	
15		Et[i]	1	135	65	48		19	
16		Et[g,i]	0.5	91	77	21		20	

[a] The reactions were performed at 65-68 °C (*i*-Bu_3Al) and at 95-98 °C (Et_3Al and $Et_3Al·OEt_2$) and they were repeated at least twice. [b] Evaluated as medium values. [c] Determined by GLC analyses. [d] The numbers in parentheses are isolated yields. [e] The product was recovered by continuous extraction of the reaction mixture. [f] Referred to the recovery by preparative GLC of only one of the two diastereoisomeric components. [g] Diethyl etherate. [h] Obtained by preparative GLC. [i] Unidentified products were present in the reaction mixture.

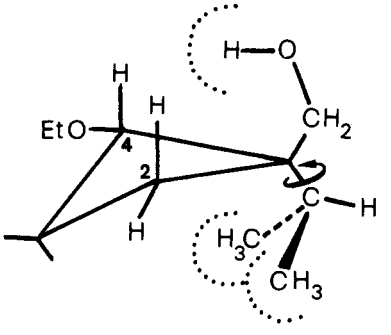


Figure 1. Perspective view of *trans*-**2c**, showing some possible steric interactions.

2) and alcohols **5** were detected only when **1b** and **1c** were reacted (entries 6, 10).[2] The formation of aldehydes **4** is closely related to the nature of **1**; in fact, **4** becomes the main product in the case of **1c** and **1d** (entries 10, 14).

To test if a dependence of the product distribution on the reagent molar ratios exists, we carried out a set of reactions with [1]/[Et_3Al] = 1.0 (entries 3, 7, 11, 15). The main observation is that the conversions decrease and the reaction times increase in relation to the C_5 substituent of **1** [(*S*)-*sec*-Bu ≫ *i*-Pr > Me ≃ H] and in the reaction mixtures of **1c** and **1d** an appreciable amount of side products was detected (entries 11, 15). No traces of alcohols **5** were present in the reaction mixtures; as regards aldehydes **4**, **4a** did not form and in any case only small amounts of **4b–d** were detected (entries 7, 11, 15). In these reaction conditions alcohol **3a** is obtained in a good overall yield (83%) even if an appreciable amount of **2a** (17%) is also formed (entry 3). The use of $Et_3Al·OEt_2$ in this kind of reaction allows formation of alcohol **3a** in an almost quantitative yield (entry 4); in all the other cases the composition of the reaction mixture was comparable with that obtained by using [1]/[Et_3Al] = 1.0 (Table I).

By considering the nature of the products recovered from the reactions of **1** with aluminum trialkyls, we can draw the following general observations.

(i) The transfer of nucleophilic species to C_6 always causes the rearrangement of the dihydropyran ring to the cyclobutyl derivatives **2** and **3**.

(ii) By use of *i*-Bu_3Al, the hydride transfer to C_6 of the dihydropyran ring occurs. On the contrary, both Et_3Al and $Et_3Al·OEt_2$ give either reduction or alkylation products; however, the hydride transfer is quite regioselective for C_6, while the alkylation affects both C_2 and/or C_6; moreover, the alkylation to C_2 results in the cleavage of the endocyclic O–C_2 bond to give aldehydes **4**.

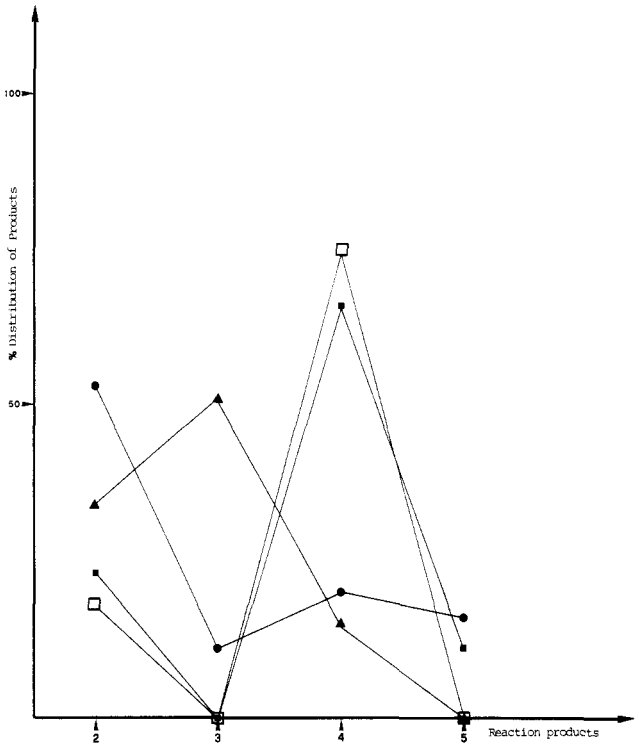


Figure 2. Reaction mixture composition obtained from **1a–d** with Et_3Al ([1]/[Et_3Al] = 0.5): **a**, R = H (▲); **b**, Me (●); **c**, *i*-Pr (■); **d**, (*S*)-*s*-Bu (□).

(iii) The formation of alcohols **2** and **3** is quite stereoselective; in fact, only the trans isomers are formed.

Moreover, the dynamic trend of the reaction of **1a–d** and Et_3Al depends on the experimental conditions adopted and on the structure of **1**. By use of [1]/[Et_3Al] = 0.5, the yields of ethoxy aldehyde **4** follow the order **1d** ≃ **1c** > **1b** > **1a** (Table I, entries 14, 10, 6, 2), and the drop of C_2 alkylation is accompanied by an increase of C_6 reduction and/or -alkylation. However, when the steric bulk of the substituent at C_5 is increased, the hydride transfer to C_6 is preferred (Table I, Figure 2). It is interesting that by use of a [1]/[Et_3Al] = 1.0 molar ratio, the alkylation to the C_2 remarkably drops, but, at the same time, the yields of alcohols **2** and **3** increase. Once again the formation of **3** depends on the C_5 substituent of **1**.

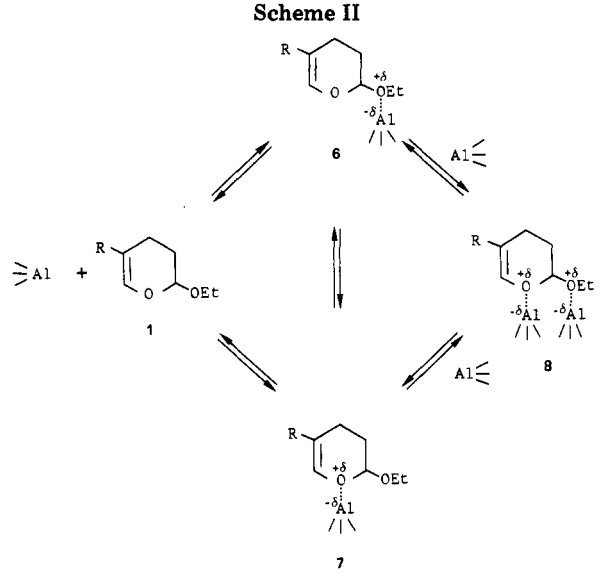
An interpretation of the overall results from a mechanistic point of view is not a simple matter because of the complex phenomena that are to be considered. The initial attack of the aluminum alkyl on **1** can be thought to cause a series of preequilibria in which the complex species **6–8** are formed (Scheme II).

In fact, the coordination bond might affect the exo- and/or the endocyclic oxygen atom even if it is reasonable to suppose that **7** is favored for a stabilizing electronic effect of the double bond. On the other hand, the exocyclic oxygen atom plays a determinant role to promote the reactivity of **1**: in fact, 3,4-dihydro-2*H*-pyran is strongly coordinated by *i*-Bu_3Al and Et_3Al, but under the usual experimental conditions, no reaction occurs.[9]

Hence, the reactivity of **1** must be related to the electronic effects of the exocyclic oxygen atom on C_2; such an activation effect should be strongly increased in complex

(9) A sample of 3,4-dihydro-2*H*-pyran, in heptane solution, was reacted both with *i*-Bu_3Al and Et_3Al (molar ratio of the reactants, 0.5) at 65–68 °C and 95–98 °C, respectively for 48 h. The solvent was removed at 25–35 °C (0.5 torr) and only traces of 3,4-dihydro-2*H*-pyran were present in it (GLC). After hydrolysis, the unchanged heterocyclic compound was almost quantitatively recovered.

Scheme II



8, whose formation should depend on the nature of the aluminum alkyl and on the reagent molar ratio.

The subsequent reaction step is the hydride or ethyl transfer, the former process occurring from the carbon atom in the β position to the aluminum atom both in the case of *i*-Bu_3Al and Et_3Al, because isobutene and ethylene, respectively, are formed during the reaction.

The question arises on the alkylation mechanism for which, in principle, two hypotheses can be proposed: (i) 1 mol of **1** might react with 2 mol of Et_3Al; whereas the former coordinates, the latter alkylates the dihydropyran ring to C_2 and/or C_6; (ii) the alkylation process might involve only 1 mol of Et_3Al in a concerted four-center mechanism.

In our opinion this last mechanistic pathway is more reasonable because it should be hard to explain the almost quantitative conversion of **1** obtained by using a [1]/[Et_3Al] = 1.0 molar ratio with respect to that reached when a 0.5 molar ratio of the reagents is used (Table I).

Moreover, taking into account that alcohols **2** and **3** are formed in a trans configuration, the hydride or the ethyl transfer to C_6 causes a stereochemically controlled rearrangement. Starting from such an observation the proposed dipolar intermediate **9**[2] (Scheme III) must be rejected; on the contrary, the concerted internal alkylation ($C_5 \rightarrow C_2$), which occurs by starting from the intermediates **7** or **8**, should warrant such a complete stereochemical control (Scheme III).

We are continuing our active investigation to establish the mode of coordination of the aluminum atom to the dihydropyran ring and to gain a deeper insight into the mechanism of the internal $C_5 \rightarrow C_2$ alkylation.

Experimental Section

Materials and Instrumentation. Triethylaluminum and triisobutylaluminum (Fluka A.G. Co) were redistilled under argon and stored in sealed capillary glass vials, in weighed amounts. 2-Ethoxy-3,4-dihydro-2*H*-pyran (**1a**) was a commercial sample (Aldrich), and the other 2-ethoxy-5-alkyl-3,4-dihydro-2*H*-pyrans (**1b–d**) were synthesized in 60–85% overall yields according procedures reported elsewhere.[1c] Compounds **1** were purified by distillation under argon from Na and then from $LiAlH_4$ before use. Heptane was commercial reagent grade material and it was purified by a standard method and redistilled under argon from $LiAlH_4$ before use.

GLC analyses were performed on a Perkin-Elmer F 30 instrument (2 m × 0.29 cm columns packed with 8% CW 20M + 2% KOH on 80–100-mesh Chromosorb W) and on a Dani 300 instrument (30 m × 0.3 mm and 25 m × 0.25 mm columns filled

Scheme III

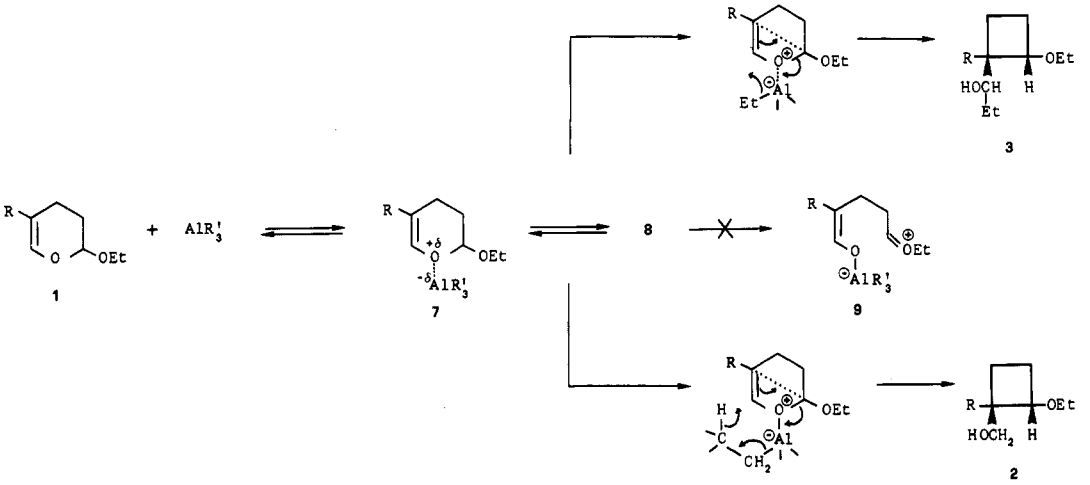


Table II. Physical Properties of Products Obtained from Reactions of 1a-d and Aluminum Trialkyls[a]

compd		formula (mol wt)	mp, °C (EtOH/H_2O) or bp °C (torr)
2a		$C_7H_{14}O_2$ (130.18)	69 (2)
2a	3,5-DNPB[b,c]	$C_{14}H_{16}N_2O_7$ (324.27)	67
2b	3,5-DNPB[b,c]	$C_{15}H_{18}N_2O_7$ (338.29)	72
2c	3,5-DNPB[b,c]	$C_{17}H_{22}N_2O_7$ (366.35)	60
2d[d,e]		$C_{11}H_{22}O_2$ (186.29)	102 (4)
2d	3,5-DNPB[b,c]	$C_{18}H_{24}N_2O_7$ (380.37)	43
3a		$C_9H_{18}O_2$ (158.23)	104 (20)[f]
3b		$C_{10}H_{20}O_2$ (172.26)	60 (0.5)[g]
4d[d,h]		$C_{13}H_{26}O_2$ (214.34)	134 (18)
4d	2,4-DNPI[i,c]	$C_{19}H_{30}N_4O_5$ (394.43)	42-47

[a] For physical and spectral properties of compounds **2b,c**, **4b,c**, and **5b,c**, see ref 2. [b] Dinitrophenyl benzoate. [c] Satisfactory analysis was obtained. [d] Starting from a sample of **1d** having $[\alpha]^{25}_D$ +43.07°. [e] The sample showed α^{25}_D (l = 1) −14.41°. [f] Reference 4a, bp 103-104 °C (20 torr). [g] Reference 4b, bp 58-62 °C (0.5 torr). [h] The sample showed $[\alpha]^{25}_D$ −6.77° (c 8.230, CCl_4). [i] (Dinitrophenyl)hydrazone.

with CW 20M and FFAP, respectively) equipped with flame-ionization detectors and N_2 as carrier gas.

Preparative GLC was carried out on a Perkin-Elmer F21 chromatograph using 2 or 3 m × 0.95 cm columns packed with 8% CW 20M + 2% KOH on 80–100-mesh Chromosorb W.

IR spectra were obtained on a Perkin-Elmer 225 spectrophotometer by using liquid films; CCl_4 solutions (2×10^{-1} and 2×10^{-3} M) were employed to determine the stereochemistry of **1a–d**.[3]

^1H NMR spectra and ^{13}C NMR Fourier-transform spectra were obtained with JEOL PS 100 (100 MHz), Varian XL-100 (25.2 MHz) and Cameca RMN 250 (62.8 MHz) spectrometer in $CDCl_3$ solutions, unless otherwise stated; chemical shifts are reported as δ values with Me_4Si as internal reference.

Mass spectra were taken at 70 eV on a Varian Mat CH-7 GC-MS spectrometer.

Optical rotations were taken with a Perkin-Elmer 142 polarimeter and refer to pure liquid unless otherwise stated. Melting points were uncorrected. Microanalyses were carried out in the Microanalysis Laboratory of the Faculty of Pharmacy of the Pisa University.

General Procedure. All reactions were carried out at least in duplicate under dry argon. In a typical small-scale reaction a weighed amount of the trialkylaluminum (20 mmol) was transferred from the sealed capillary glass vial to a two-necked 50 mL round-bottom flask containing *n*-heptane (10 mL), equipped with a magnetic stirrer, a dropping funnel, and a reflux condenser. The vessel was cooled to 0 °C and the required amount of **1** in *n*-heptane (2 mL) was added dropwise. The reaction mixture was stirred for 30 min at room temperature and then heated by means of a previously thermostated oil bath for the required time (Table I). The hydrolysis was carried out at 0 °C with water and then with 10% H_2SO_4. The aqueous phase was extracted with ether (4 × 50 mL), and the ether extracts were washed with 10% $NaHCO_3$ (2 × 50 mL) water and dried (Na_2SO_4). The relative percentages of the reaction products were established by GLC of the crude hydrolysis mixture.

The products were characterized by their mass spectra and some of them identified by chromatographic comparison: in this context samples of **3a** and **3b** were prepared according to a previously reported procedure.[4]

All unknown compounds were isolated: chemically pure **2a–d** were obtained by distillation of the hydrolysis mixture and **3a** and **4d** were purified by preparative GLC.

Physical properties of the obtained compounds as well as those of the 3,5-dinitrobenzoate of **2a–d** and of the (2,4-dinitrophenyl)hydrazone of **4d** are reported in Table II; for spectral data, see Table IV (supplementary material).

Registry No. **1a**, 103-75-3; **1b**, 2397-94-6; **1c**, 71237-04-2; **1d**, 63003-02-1; **2a**, 81158-86-3; **2a** ester, 81158-87-4; **2b**, 81158-88-5; **2b** ester, 81158-89-6; **2c**, 81158-90-9; **2c** ester, 81158-91-0; (−)-**2d**, 81158-92-1; **2d** ester, 81158-93-2; **3a**, 17591-31-0; **3b**, 17591-18-3; **4a**, 81158-94-3; **4b**, 77299-83-3; **4c**, 77299-85-5; **4d**, 81158-95-4; **4d** hydrazone, 81158-96-5; **5b**, 77299-84-4; **5c**, 77299-86-6; *i*-Bu_3Al, 100-99-2; Et_3Al, 97-93-8; $Et_3Al{\cdot}OEt_2$, 15221-30-4.

Supplementary Material Available: Table III (observed and predicted ^{13}CNMR chemical shifts of compounds **2a–d**) and Table IV (spectral data of compounds reported in Table II) (2 pages). Ordering information is given on any current masthead page.