Tetrahedron Vol. 40, No. 24, pp. 5185 to 5195, 1984
Printed in the U.S.A.

0040-4020/84 $5.00 + .00
Pergamon Press Ltd.

NADH MODELS—19[1]

CYCLOPROPANE RING AS A CHEMICAL PROBE IN THE STUDY OF THE MECHANISM OF HYDROGEN TRANSFER BY 1,4-DIHYDROPYRIDINE DERIVATIVES

LOUIS H. P. MEIJER,[2] JOHANNES C. G. VAN NIEL[3] and UPENDRA K. PANDIT*
Laboratory of Organic Chemistry, University of Amsterdam, Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

(*Received in UK* 31 *October* 1983)

Abstract—*N*-(Cyclopropylmethylene)phenylamines (**1a–c**), cyclopropyl 2-pyridyl ketones (**5a–c**) and ethyl cyclopropylmethylenepyruvate (**14**) have been subjected to reduction by 1,4-dihydropyridines [3,5-diethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridine (**2**) and/or 1-benzyl-1,4-dihydronicotinamide (**7**)] in the presence of magnesium ions, and by tin hydrides. The reactions with 1,4-dihydropyridines do not involve cleavage of the three-membered ring in the reduction step. The observed acyclic product from 2-pyridyl 2,2-dimethylcyclopropyl ketone (**5b**) is a consequence of ring cleavage prior to reduction of the carbonyl function. In contrast, reduction of **1a–c** and **5a–c** by tin hydrides leads to products in which the cyclopropane moiety has undergone ring-opening. These findings support a hydride transfer mechanism for reductions with NADH models.

The precise nature of the hydrogen which is transferred to and from the coenzyme in reactions mediated by pyridine nucleotide dependent dehydrogenases, has been the subject of considerable debate. Evidence has been presented in favour of both the hydride transfer mechanism,[4] and a mechanism involving three discrete steps, namely, an initial electron transfer, followed by successive proton and electron transfers.[5] Recently, use was made of the cyclopropane ring as a chemical probe in the study of enzyme-catalyzed redox reactions and biomimetic reductions with NADH models.[1,6,7] These investigations showed that no ring-cleavage was observed during the hydrogen transfer. It was therefore concluded that a mechanism involving radical intermediates [via a SET (single-electron-transfer) process] was not operative. Since in enzymatic reactions ring-opening of the cyclopropylmethyl radical can be prevented by steric constraints of the topology of the active site,[8] non-enzymatic reductions of cyclopropyl substrates, in which such factors are absent, by models of the reduced coenzyme, would be expected to provide valuable information on the mechanism of the hydrogen transfer process. The reduction of cyclopropaneglyoxylic acid was carried out by Suckling *et al.*[7] and that of the Schiffs base of cyclopropylaldehyde and aniline (**1a**)[1] was recently reported from this laboratory. We now report our results on the reduction of several cyclopropane derivatives by Hantzsch ester, 1-benzyl-1,4-dihydronicotinamide (NADH models) and by tin hydride reagents.

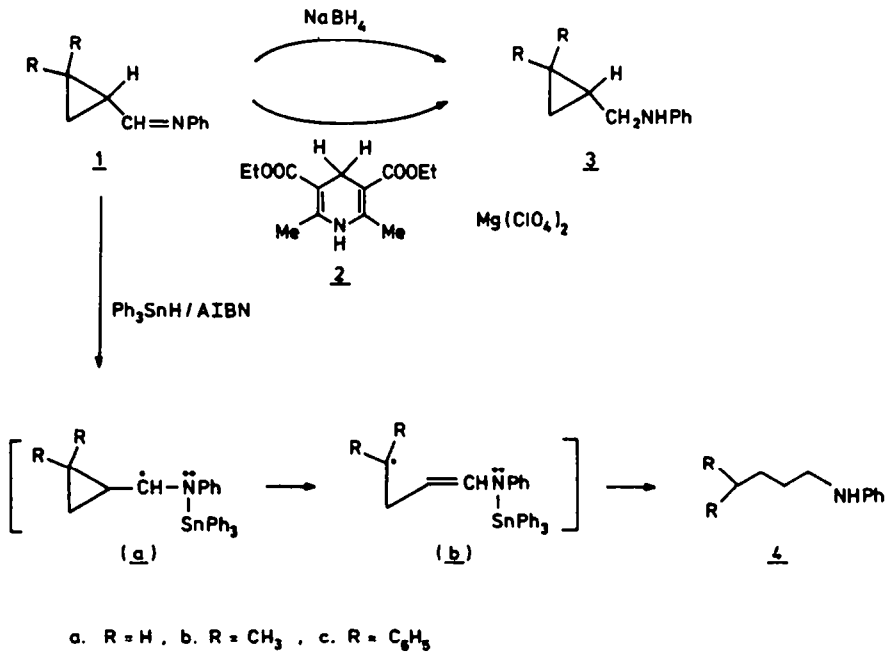
Typical unsaturated groups which are reduced by NADH-dependent enzymes include the C=N (e.g. glutamic dehydrogenase) the C=O (e.g. alcohol dehydrogenase) and the C=C (e.g. Δ^4-3-ketosteroidreductase) functionalities. It is also known that in the aforementioned cases an electrophile provided by the apoenzyme coordinates with the substrate and thereby activates it towards the hydrogen transfer step.[9–11] Consequently, it was considered necessary that the model reduction reactions of the cyclopropyl substrates (containing the C=N, C=O and C=C functional groups) be carried out in the presence of electrophiles such as metal ions.

Reduction of imines 1a–c

It has been demonstrated that imines can be reduced by Hantzsch ester (**2**) when the imine nitrogen coordinates with a proton,[12] an alkyl group[13] or a metal ion.[14] For the study of the hydrogen transfer mechanism the imines **1a–c** were regarded as substrates possessing suitable structural properties, since a mechanism involving an electron transfer to the imine function would generate a radical species which would be expected to undergo a ring-cleavage reaction.[15] A hydride transfer mechanism, would, on the other hand, result in a reduction product with an intact cyclopropane ring. In view of the fact that substituents on the cyclopropane ring enhance the ring-opening process, a comparison of the reactions of **1a** with **1b** and **1c** was considered pertinent to the investigation.

The imines **1a–c** were prepared from the corresponding aldehydes[16–18] and aniline. The reduction reaction (Scheme 1) was carried out by allowing **1a–c** to react with the Hantzsch ester (**2**), in acetonitrile, in the presence of $Mg(ClO_4)_2$. The products of the reactions of the three imines were identified as the corresponding amines **3a–c**, both by spectral data

(NMR) and by comparison (GLC) with the products obtained upon reduction of **1a–c** with $NaBH_4$. Significantly, no acyclic amines were detected in the chromatograms.



a. R = H , b. R = CH_3 , c. R = C_6H_5

Scheme 1.

In order to verify that the putative radical intermediate of the electron transfer mechanism, if formed, would have resulted in ring-cleavage, the substrates (**1a–c**) were reduced by triphenyltin hydride, in the presence of azoisobutyronitrile (AIBN). The results of the experiments showed that while in the case of **1a** the cyclic (**3a**) and the acyclic (**4a**) amines were formed, with **3a** predominating (**3a/4a** = 29%/13%); **1b** and **1c** gave increasing amounts of the corresponding acyclic amines (**3b/4b** = 8%/24%, **3c/4c** = 2%/15%). The cyclic amines were shown to be stable under the reaction conditions. Thus, in the case of **3b** it was demonstrated that the amine did not undergo ring-opening even upon heating with triphenyltin hydride and AIBN, for a period of 72 hr (NMR/GLC).

On the other hand, intermediates corresponding to the acyclic amines (viz. enamines **b**, Scheme 1) are expected to be diverted to non-isolable condensation/polymeric products. It follows that the reported yields of **4a–c** represent the lower limits for these compounds. The formation of **4a–c** follows from the expected radical mechanism of reduction by the tin hydride, especially in the presence of AIBN. The course of the reaction can be rationalized in terms of intermediates (**a**) and (**b**). The acyclic intermediate (**b**) being further reduced and hydrolyzed to **4a–c**. It should be pointed out that radical (**a**) will be stabilized by electron exchange with the electron-pair of the neighbouring nitrogen and, consequently, exhibit a retarded rate of ring-opening. A similar observation has been made in the ring-cleavage reaction of cyclopropylcarbaldehyde acetal.[19] Substituents on the three-membered ring should, however, make it more prone to cleavage. This effect explains the change in the ratios of the cyclic–acyclic amine products in the reduction of the series of imines **1a–c**.

Reduction of ketones **5a–c**

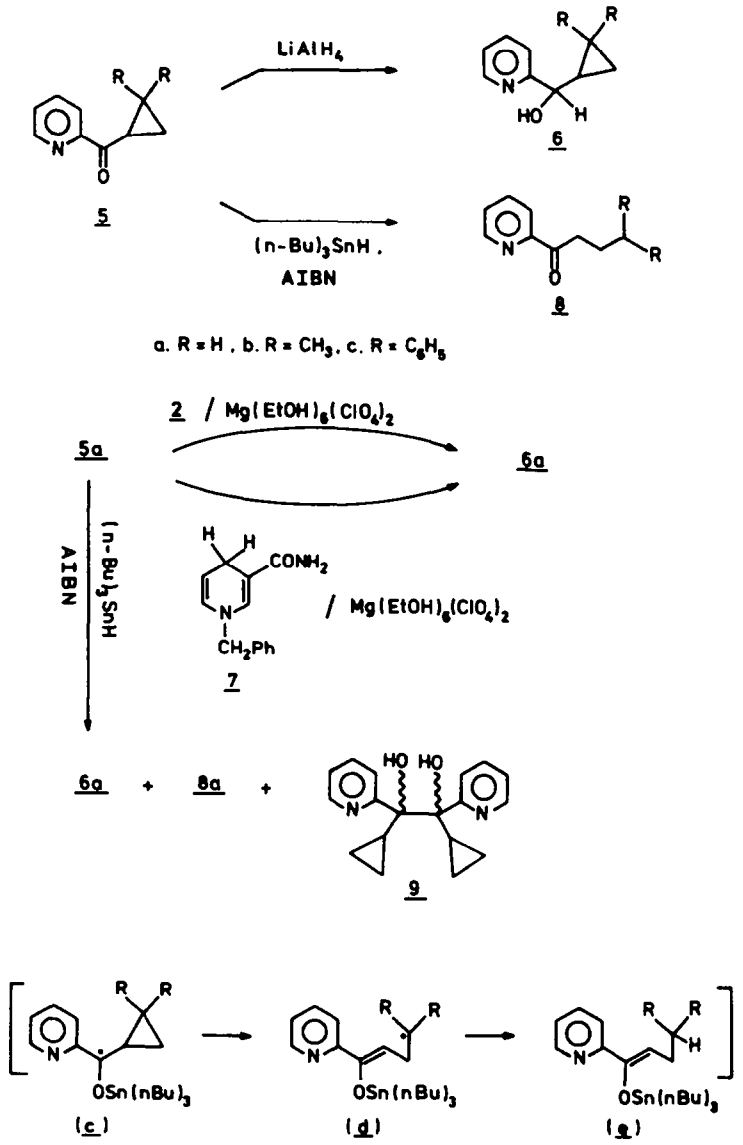
As models of a substrate containing the carbonyl function, the pyridyl ketones **5a–c** were selected. This choice was based on the observation that 2-acylpyridines are readily reduced by 1,4-dihydropyridines in the presence of metal ions.[20] The ketones were subjected to reduction by Hantzsch ester, 1-benzyl-1,4-dihydronicotinamide, lithium aluminium hydride and tri-n-butyltin hydride. The results of these experiments are described in Scheme 2.

Reduction of **5a** with Hantzsch ester (2) or 1-benzyl-1,4-dihydronicotinamide (7), in the presence of $Mg(EtOH)_6(ClO_4)_2$, or $LiAlH_4$, led in each case, to 2-pyridylcyclopropylcarbinol (**6a**) as the exclusive reduction product. In contrast, reaction of **5a** with $(n\text{-}Bu)_3SnH$/AIBN gave a mixture of **6a**, **8a** and **9**, in which **8a** constituted the major product (Scheme 2). The formation of **8a** is expected under the reaction conditions, since the $(n\text{-}Bu)_3SnH$ reagent would react with the ketone to yield a radical intermediate (**c**, R = H) which is prone to ring opening (**c** → **d**, R = H). Quenching of **d** (R = H) via uptake of a hydrogen radical, generates the tin enolate (**e**, R = H) which has been identified spectroscopically and which leads to **8a**, upon hydrolysis. This sequence of events was confirmed by carrying out the reaction with $(n\text{-}Bu)_3SnD$, whereupon deuterium incorporation was observed in **6a** and **8a** (see Experimental). The for-

mation of **6a** and **9** are consistent with the intermediacy of radical c (R = H). Delocalization of the odd electron in c (R = H), via resonance with the pyridine ring, would lend it stability, which would allow its dimerization to **9** or reduction to **6a**. The latter conclusions receive further support from results of the reduction of **5b** and **5c** by $(n\text{-Bu})_3SnH$. Since the substituents on the cyclopropane moiety are expected to augment the ring-opening of radical c (R = CH_3, C_6H_5), it was anticipated that, in comparison with **5a**, **5b** and **5c** should yield a greater proportion of products derived from intermediate **d** (R = CH_3, C_6H_5). In fact, the reduction of **5b** and **5c** (with $(n\text{-Bu})_3SnH$) gave, upon hydrolysis, the ketones **8b** and **8c**, respectively, as the sole reaction products. Reduction of **5b**, c with $LiAlH_4$, on the other hand, yielded the expected alcohols **6b**, c, containing the intact cyclopropane moiety. While **6b** was a single compound, m.p. 62–63°, **6c** consisted of a mixture of diastereomers (**6c′** + **6c″**).

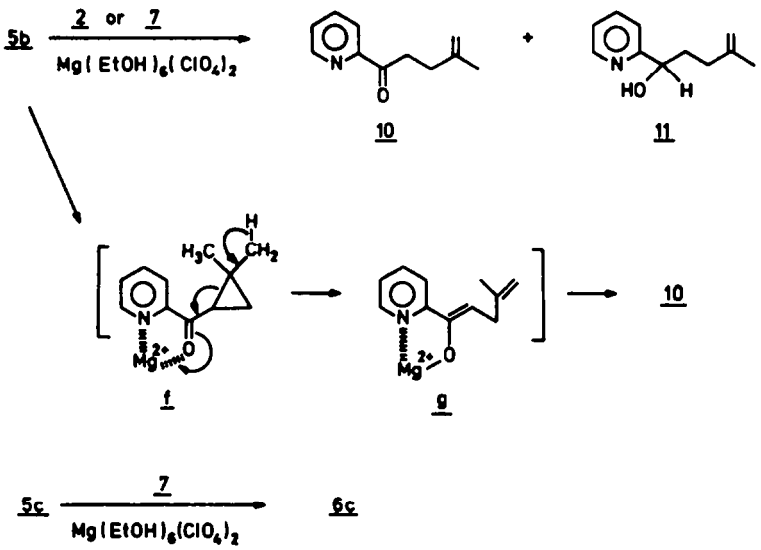
Reduction of **5b**, c with 1,4-dihydropyridines **2** and **7** exhibited features which were not encountered in the reduction of **5a**. Steric hindrance of the substituents on the cyclopropane ring, to the bulky and less reactive Hantzsch ester (**2**) led to only a slow reaction in the case of **5b**, while **5c** remained unaffected.[21] Furthermore, the reaction of **5b** followed a different course than **5a**, the products being identified as ketone **10** (53%) and alcohol **11** (43%) (Scheme 3). The more reactive 1,4-dihydronicotinamide (**7**), on the other hand, reacted with both **5b** and **5c**. In the case of the former substrate, once again a mixture of **10** and **11** was obtained, although under these conditions the relative amounts of the two products were widely different (**10** 4%; **11** 77%). Interestingly, the product of reaction of **5c** with **7** was the cyclopropylcarbinol **6c**.[21a] These observations deserve comment.

The question whether or not the formation of acyclic pyridyl derivatives **10** and **11** are mediated



Scheme 2.

by the dihydropyridine reagents is a critical one in the context of the present investigation. It is, however, plausible that ring-opening of the cyclopropane moiety (**5b** → **10**) is triggered by a metal ion catalyzed process, as the first step. An analogous acid catalyzed reaction of cyclopropyl ketones has been observed by Walborsky *et al.*[21b] A subsequent reduction reaction converts the ketone (**10**) to the corresponding alcohol (**11**). To check this possibility, the ketone **5b** and $Mg(EtOH)_6(ClO_4)_2$ were allowed to react under conditions (CH_3CN, reflux) which have been employed for the reduction reactions. The results of this control experiment showed that substrate **5b** is completely converted into **10**, under influence of Mg^{2+} ions. The mechanism of this conversion presumably follows the sequence **5b** → (**f**) → (**g**) → **10** (Scheme 3). Whether ring-opening and loss of proton in intermediate (**f**) are synchronous or stepwise is not known with certainty at this stage. However, the fact that substrate **5c** does not appear to undergo a facile ring cleavage,[21] despite the expected stability of the benzhydryl cation which would result from the diphenyl substituted analogue of complex (**f**), seems to suggest that a concerted ring-opening and deprotonation might be involved. The formation of **6c** upon reduction of **5c** is consistent with the rationalization that once again reduction with **7** proceeds without opening of the three-membered ring.

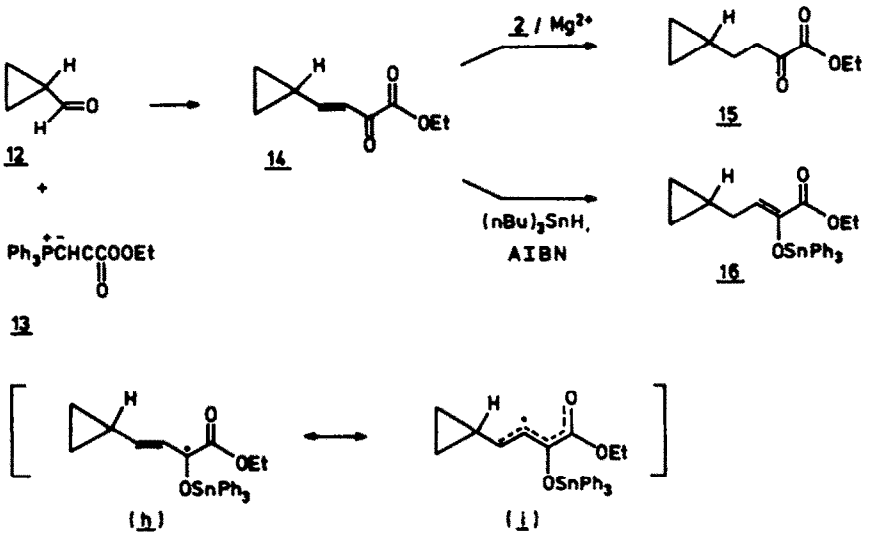


Scheme 3.

The above results reveal that reaction of cyclopropyl pyridyl ketones with dihydropyridines do not cause opening of the cyclopropane ring during the reduction process. The substrate **5b** constitutes a special case which incorporates structural features (methyl substituents) that promote the facile magnesium ion catalyzed ring opening. The final acyclic reduction product (**11**) is consequently derived from the initially generated ketone **10** and the ratio of the two [alcohol (**11**)/ketone (**10**)] is, as would be expected, dependent upon the activity of the reducing agents.

Reduction of α-keto-β,γ-unsaturated ester **14**

Carbon–carbon double bonds of acrylyl chloride,[22] α,β-unsaturated minimum salts[23] and cinnamoyl pyridines[24] can be reduced by the Hantzsch ester, the last class of substrates requiring the presence of magnesium or zinc ions. Furthermore, the reduction of α-keto-acids is well documented.[25] In a study of the reduction of α-keto-β,γ-unsaturated esters by NADH-models, it has been shown that the initial site of reduction is the C=C bond.[26] It appeared, therefore, that in the context of the present investigation keto ester **14** (Scheme 4) represented a suitable substrate for a study of the reduction of a C=C bond. The compound was obtained by a Wittig reaction of cyclopropylaldehyde **12** with the ylid **13**.[27] Reduction of **14** by one equivalent of **2**, with Mg^{2+} as catalyst, gave the dihydro-compound **15** as the exclusive reduction product, in accordance with the expected pattern of reaction observed thus far.[26] Surprisingly, however, when **14** was reduced by tri-n-butyltin hydride, and AIBN, only a single product, identified as the tin enolate **16**, was obtained in quantitative yield. The structure of **16** was established by spectral data (NMR, MS). An examination of the tin hydride mediated reduction was carried out under different reaction conditions, to see if the ring-cleavage product could be generated. This confirmed the lack of cyclopropane ring cleavage during reduction. This behavior of ester **14** can be rationalized in terms of the high resonance stabilization of radical (**h** ↔ **i**) and a consequential inertness towards ring-opening. The low density of the odd electron on the carbon-α to the cyclopropane moiety suppresses the ring-opening process so that such products are not observed.



Scheme 4.

The results of these experiments show that the course of the Hantzsch ester reduction of substrates **1a–c**, **5a–c** and **14** are fully in accord with a hydride transfer mechanism. That the putative intermediates of a SET mechanism, namely, cyclopropylmethyl radicals, do undergo the expected ring-opening, has been demonstrated in the case of the first two classes of substrate. Furthermore, the lack of such a ring-cleavage in the case of **14** can be adequately rationalized.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were recorded on a Perkin–Elmer 257 spectrometer. PMR spectra were run on a Varian Associates Model A-60D and XL-100 or Bruker WM 250 instruments, using TMS as an internal standard. Unless stated otherwise, IR and PMR spectra were taken in $CHCl_3$ and $CDCl_3$, respectively. Mass spectra (EI, 70 eV, unless mentioned otherwise) were obtained with a Varian Mat-711 spectrometer. GLC was performed on a Varian Aerograph 200 provided with a TC detector and connected to a Philips recorder PM 8000, helium being used as carrier.

N-Cyclopropylmethylideneaniline (**1a**). Cyclopropylcarbaldehyde was prepared as described by Smith and Rogier.[16] In a typical experiment the aldehyde (1.40 g, 20 mmol) was stirred together with 20.2 mmol of aniline, in 25 ml of toluene, over 11 g of mol. sieves (3Å) previously activated by heating at 300° for 3 h. The drying agent was filtered off and washed with 20 ml of dry toluene. Further freshly activated mol. sieve (11 g) was added to the filtrates, the mixture allowed to stand for several hours and then filtered to remove the mol. sieves. Evaporation of the solvent yielded a faint yellow oil 1.91 g (65%). This product was purified by distillation in a kugelrohr apparatus. IR (neat) 1630 cm^{-1} (C=N); PMR: δ 0.75–1.00 (4 H, m, cyclopropyl 2 × CH_2), 1.5–2.1 (1 H, m, cyclopropyl CH), 6.75–7.45 (6 H, m, Ar-H + CH=N); MS: *m/e* calc for $C_{10}H_{11}N$: 145.0891; found: 145.0892.

N-(2,2-Dimethylcyclopropyl)methylidineaniline (**1b**). The starting aldehyde was obtained via a modification of the procedure described in the literature.[17] Ethyl acetate (4.59 g, 52 mmol) was added slowly (45 min) to a filtered, titrated solution of $LiAlH_4$ (1.32 g, 34.7 mmol) in 60 ml of ether, with cooling by an ice-salt mixture bath. After stirring for 0.5 h, the mixture was cooled to −50°, and 2,2-dimethylcyclopropyl cyanide[28] (3.3 g) was added in 3 min. The mixture was then allowed to warm to 15° and once again cooled in an ice-bath. At this stage the reaction mixture became very viscous. It was allowed to stand at 0° for 50 min and then carefully hydrolyzed with 40 ml ice-cold sulfuric acid (4.5 N). After separation of the layers, the aqueous phase was rapidly washed three times with ether. The combined organic layers were washed twice with sat. $NaHCO_3$, sat. NaCl, dried over sodium sulphate and the solvent removed. Yield of the aldehyde, 53%.

Substrate **1b** was obtained from this aldehyde and aniline as described for **1a**. Yield: 30%. IR (neat): 1630 cm^{-1}, (C=N); PMR: δ 0.9–1.35 (2 H, m, cyclopropyl CH_2), 1.17 and 1.22 (6 H, 2 s, 2 × CH_3), 1.55–2.00 (1 H, m, cyclopropyl CH), 6.55–7.75 (5 H, m, Ar-H), 7.52 (1 H, d, CH=N); MS: *m/e* calc for $C_{12}H_{15}N$: 173.1204; found: 173.1206.

N-(2,2-Diphenylcyclopropyl)methylideneaniline (**1c**). 2,2-Diphenylcyclopropylcarbaldehyde was prepared according to Vaidyanathaswamy.[18] Compound **1c** was prepared from this aldehyde on a 2-millimolar scale as described for **1a**. Yield 80%. IR (neat): 1630 cm^{-1} (C=N); PMR: δ *ca* 1.9 (2 H, m, cyclopropyl CH_2), 2.8 (1 H, m, cyclopropyl CH), 6.45–7.8 (16 H, m, Ar-H + CH=N); MS: *m/e* calc for $C_{22}H_{19}N$: 297.1517; found: 297.1517.

N-Cyclopropylmethylaniline (**3a**). Imine **1a** (144 mg, 0.99 mmol) in 10 ml absolute ethanol was treated with 2 equiv of sodium borohydride in an ice-bath. After standing overnight at room temperature the mixture was acidified with dil. HCl, with cooling, to pH 1–2 in an ice-bath. The pH was raised to 14 by means of dilute sodium hydroxide and the mixture was extracted three times with ether. The combined organic layers were dried over sodium sulphate and evaporated. Yield: 81 mg (56%). This product contained a small amount (<5%, GLC) of aniline as contaminant. PMR: δ 0.07–0.67 (4 H, m, cyclopropyl 2 × CH_2), 0.80–1.37 (1 H, m, cyclopropyl CH), 2.96 (2 H, d, N-CH_2), 6.50–6.84 (3 H, m, Ar-H, 7.04–7.33 (2 H, m, Ar-H), 3.40 (1 H, NH); MS: *m/e* calc for $C_{10}H_{13}N$: 147.1048; found: 147.1059.

N-(2,2-Dimethylcyclopropyl)methylaniline (**3b**). Imine **1b** (346 mg, 2 mmol) was reduced by 1 mmol of sodium borohydride in 10 ml absolute ethanol at 0°. The reaction mixture was allowed to stand overnight at room temperature and then worked up by treatment with saturated NH_4Cl

and basification with 50% NaOH while cooling in an ice-bath. It was then washed three times with ether, the organic layer was dried over sodium sulphate and evaporated, yielding 192 mg (55%) of **3b** as an oil. GLC revealed the presence of about 5% aniline as the sole contaminant. PMR δ 0.0–1.46 (3 H, m, cyclopropyl CH_2 + CH), 1.03 and 1.13 (6 H, 2 s, 2 × CH_3), 3.118 (2 H, d × d, N–CH_2), 6.58–6.77 (3 H, m, Ar–H), 7.08–7.36 (2 H, m, Ar–H); MS: *m/e* calc for $C_{12}H_{17}N$: 175. 1361; found: 175.1361.

N-(2,2-*Diphenylcyclopropyl*)*methylaniline* (**3c**). Imine **1c** (322 mg, 1.08 mmol) was reduced as already mentioned for the conversion of **1b** to **3b**. Yield of 275 mg (85%) of **3c**. PMR: δ 1.22–1.50 (2 H m, cyclopropyl CH_2), 1.83–2.13 (1 H, m, cyclopropyl CH), 2.94 (2 H, ABX N–CH_2 with restricted rotation), 6.50–6.80 and 6.98–7.53 (15 H, m, Ar–H), 1.65 (1 H, NH); MS: *m/e* calc for $C_{22}H_{21}N$: 299.1674; found: 299.1644.

N-*Butylaniline* (**4a**). PMR δ 1.95 (3 H, t, CH_3), 1.42 (2 H, m, $\underline{CH_2}CH_3$), 1.59 (2 H, m, $\underline{CH_2}CH_2CH_3$), 3.08 (2 H, t, N–CH_2), 6.55–6.81 and 7.10–7.44 (5 H, m, Ar–H); MS: *m/e* calc for $C_{10}H_{15}N$: 149.1204; found: 149.1204.

N-(4-*Methylpentyl*)*aniline* (**4b**). The amine was prepared by the general procedure described by Rice and Kohn.[29] Aniline (2.5 ml), Raney nickel (1.5 g) and 4-methylpentanol (10 ml) were refluxed overnight under water-free conditions. The catalyst was removed by filtration and washed with ethanol. The filtrate was concentrated and distilled in vacuo to remove trace amounts of the catalyst. The starting alcohol was removed by distillation at 20 mm/60°, the product was distilled at 20 mm/140°, yielding 4.38 g (88%) of crude **4b**.

This crude product (1.0 g) was dissolved in 25 ml of absolute ether and treated with gaseous HCl. The solution turned yellow. After addition of hexane 576 mg of a white crystalline precipitate could be filtered off. This was dissolved in a few drops of methanol, rendered alkaline with saturated carbonate, extracted three times with dichloromethane; the organic layers were dried over sodium sulphate and evaporated to yield 380 mg of the pure *N-alkylaniline* **4b**. PMR: δ 0.93 (6 H, d, 2 × CH_3), 1.11–1.83 (5 H, m, CH_2CH_2CH), 3.02 (2 H, t, N–$\underline{CH_2}CH_2$), 6.50–6.82 (3 H, m, arom. *m*- and *p*-protons), 7.03–7.32 (2 H, m, arom. *o*-protons); MS: *m/e* calc for $C_{12}H_{19}N$: 177.1517; found: 177.1517.

N-(4,4-*Diphenylbutyl*)*aniline* (**4c**). This compound was isolated by preparative GLC from the Ph_3SnH reduction of substrate **1c**. It was identified by its PMR and mass spectra. PMR: δ 1.53 (3 H, broad s, N–CH_2–CH_2–$\underline{CH_2}$ + NH), 2.18, (2 H, m, N–CH_2–$\underline{CH_2}$–), 3.15 (2 H, t, $\underline{N}$–CH_2), 3.85 (1 H, t–$CH(C_6H_5)_2$), 6.56–7.97 (15 H, m, Ar–H). MS: *m/e* calc for $C_{22}H_{23}N$: 301.1830, found: 301.1835.

Reduction of imines **1a–c** *with Hantzsch ester* (**2**). A mixture of 2 mmol of a substrate, equimolar amounts of **2** and magnesium perchlorate in 20 ml dry CH_3CN was refluxed under nitrogen until the reductant had disappeared (TLC). The reaction mixture was analyzed by GLC (described in the sequel). All the components of the reaction mixture were isolated via GLC and analysed by comparison of their PMR spectra with spectra of reference samples. A quantitatively measured amount of the mixture was worked up by thick layer chromatography (silica gel, eluent petroleum ether 60–80°/ethyl acetate 8/1). The product was scraped from the plate and eluted with ethyl acetate. After evaporation of the solvent some CCl_4 was added and evaporated to remove residual amounts of ethyl acetate. This was repeated several times. Yields of the amines: **3a** 90%, **3b** 82%, **3c** 58%. No ring-opened products were detected in the mixtures.

Reduction of imines **1a–c** *with triphenyltin hydride*. The substrate (1 mmol) in dry cyclohexane (10 ml) with a catalytic amount of azabisisobutyronitrile (AIBN) were frozen in liquid nitrogen. The flask containing the mixture was connected to the collector of a vacuum distillation apparatus. Triphenyltin hydride (4 mmol) was distilled in vacuum into the deep-frozen reaction mixture. The reaction mixture was then heated to reflux until all the substrate had reacted (GLC). The mixture was analyzed by GLC and all the components were isolated and their retention times and PMR spectra compared with those of reference compounds. Yields of the reaction products were determined by comparison of the peak areas of the components in the chromatograms of the reaction mixtures with those of known amounts of the reference compounds.

Reduction of **1a** yielded **3a** (29%) and **4a** (13%).

Reduction in **1b** yielded **3b** (8%) and **4b** (24%).

Reduction of **1c** yielded **3c** (2%) and **4c** (15%).

Reduction mixtures obtained by reactions of **1a–c** with **2** or Ph_3SnH were analyzed gas chromatographically under the following conditions. **1a**: 15% Silicone DC 550 on Chromosorb W-AW 45–60 mesh (450 × 0.7 cm) t = 135°, gas flow = 83 ml/min; **1b**: 15% Silicone DC 550 on Chromosorb W-AW 45–60 mesh (450 × 0.7 cm) t = 157°; gas flow = 60 ml/min; **1c**: 15% SE 30 on Chromosorb W-AW 45–60 mesh (300 × 0.7 cm) t = 200°, gas flow = 60 ml/min).

Cyclopropyl 2-pyridyl ketone (**5a**). This compound was prepared with minor modifications of the literature procedures.[30,31] The reaction was carried out in a 500 ml jacketed reaction vessel cooled by a cryomat, equipped with a magnetic stirrer, nitrogen inlet, and a dropping funnel. 2-Bromopyridine (31.6 g, 200 mmol) was added dropwise over a 10 min period to a cooled (−50°) solution of n-butyllithium (125 ml, 1.6 M in n-hexane, 200 mmol) in 100 ml dry ether. Stirring was continued for an additional 30 min followed by cooling to −60°, after which 13.42 g (200 mmol) cyclopropyl cyanide in 30 ml dry ether was added dropwise over 15 min. The cooling system was removed, and the solution allowed to attain room temperature (45 min). Hydrolysis was carried out by refluxing 30 min with 60 ml of a HCl (10%) solution. After cooling, an additional 150 ml HCl (10%) solution was added with vigorous stirring. The aqueous layer was removed and the ether layer washed twice with 50 ml HCl (10%). The combined aqueous layers were made alkaline (pH 13–14) with a NaOH (20%) solution and extracted with 3 × 150 ml ether. The solution was dried over Na_2SO_4 and evaporation of the solvent *in vacuo* gave, after repeated crystallizations, 12.0 g of pure ketone (**5a**) m.p. 37° (lit.[30] m.p. 36–37°). Purification of the mother liquor by column chromatography [Silica gel, ethyl acetate–hexane (1:10)] followed by distillation (b.p. 108°/10 mm) yielded another 6.45 g of ketone (**5a**). Total yield 18.45 g (125.4 mmol) 62.7% (lit.[30] 32%). IR 1680 cm^{-1} (C=O) 1588, 1572 cm^{-1} (pyridyl); PMR δ 0.95–1.35 (4 H, m, cyclopropyl CH_2), 3.57 (1 H, m, cyclopropyl CH), 7.47 (1 H, m, pyr 5-H), 7.83 (1 H, m, pyr 4-H), 8.05 (1 H, m, pyr 3-H), 8.74 (1 H, m, pyr 6-H); MS: *m/e* 147 (M), 146, 118 (100%) 78, 69, 51; *m/e* calc for C_9H_9NO: 147.0684; found: 147.0685.

The ether layer containing the neutral components gave, after distillation, butyl bromide and 1.40 g (11.1 mmol) of n-butyl cyclopropyl ketone (5.5%) IR 1690 cm^{-1} (C=O); PMR: δ 0.70–1.05 (4 H, m, cyclopropyl CH_2), 0.92 (3 H, t, butyl CH_3), 1.10–1.70 (4 H, m, –CH_2–CH_2–CH_2–CH_3), 1.94 (1 H, m, cyclopropyl CH), 2.55 (2 H, t, O=C–$\underline{CH_2}$); MS: *m/e* 126 (M), 84 (65%, (McLafferty rearr.), 69 (100%), 41; *m/e* calc for $C_8H_{14}O$: 126.1045; found: 126.1042.

2,2-*Dimethylcyclopropyl 2-pyridyl ketimine* (**5b'**). The procedure used was essentially that employed for the unsubstituted ketone (**5a**); using 140 ml (0.224 mol) of 1.6 M n-butyllithium in hexane and 22.0 ml (36.0 g, 0.227 mol) 2-bromopyridine. The addition was completed in 20 min and the mixture was stirred for 1 h (−60°). Then, 18.5 g (194.4 mmol) of 2,2-dimethylcyclopropyl cyanide[28] was added with stirring over 5 min, the stirring was continued for another 10 min (−60°), and the mixture allowed to warm to room temperature (1 h). The dark brown reaction mixture was decomposed by stirring (1 h) with 30 g $Na_2SO_4 \cdot 10H_2O$, whereupon it became much clearer (yellow-brown). The solution was filtered and the solvent was removed *in vacuo*. Careful distillation (30 cm vacuum-jacketed vigreux column) yielded successively: pyridine; n-butyl bromide; 4.78 g (31.6 mmol) 1-butyl-2,2-dimethylcyclopropyl cyanide (16%), b.p.

100° (20 mm); 12.84 g (73.7 mmol) 2,2-dimethylcyclopropyl 2-pyridyl ketimine (**5b'**) (38%), b.p. 86° (1 mm), and 2.12 g (12.2 mmol) 3-methyl-3-butenyl 2-pyridyl ketimine (6.25%) b.p. 90° (1 mm). These isomeric ketimines were very difficult to separate, but after two more distillations (purity > 91%), followed by crystallizations the purity of ketimine (**5b'**) was better than 95%; m.p. 28°. IR cm^{-1}: 3300 (N–H), 1620 (C=NH), 1583 and 1570 (pyridyl) J_{vic}: 8 Hz, J_{gem}: 4.5 Hz H of cyclopropyl CH_2, trans to ketimine), 0.96 (3 H, s, CH_3 trans to ketimine), 1.35 (1 H, broad s, H of cyclopropyl CH_2, cis to ketimine), 1.37 (3 H, s, CH_3 cis to ketimine), 2.11 (1 H, broadened dd, cyclopropyl CH), 7.34 (1 H, m, pyr 5-H), 7.70–7.95 (2 H, m, pyr 3-H, 4-H), 8.70 (1 H, m, pyr 6-H), 11.1 (1 H, broad s, C=NH). MS (FI-omA) 174.3 (100%), 175.3 (91%). (Anal. Found: C, 74.4; H, 8.1; N, 15.3. Calc for $C_{11}H_{14}N_2$: C, 75.8; H, 8.1; N, 16.1%.) The isomeric 3-methyl-3-butenyl 2-pyridyl ketimine was identified by PMR: δ 1.81 (3 H, s, CH_3), 2.43 (2 H, t, $-CH_2-C(:CH_2)-CH_3$) 3.06 (2 H, t, $C(:NH)-CH_2$), 4.80 (2 H, s, $C=CH_2$), 7.35 (1 H, m, pyr 5-H), 7.60–7.90 (2 H, m, pyr 3-H, 4-H), 8.70 (1 H, m, pyr 6-H). After hydrolysis we indeed obtained the ketone (10) which was identical to the compound obtained in the Mg^{2+}-mediated isomerisation of ketone (**5b**).

2,2-Dimethylcyclopropyl 2-pyridyl ketone (**5b**). A solution of the ketimine **5b'** in ethanol was diluted with the maximum amount of water which allowed a homogeneous solution to be maintained. After standing at room temperature for 24 h the solution was evaporated in vacuo, taken up in ether and dried over Na_2SO_4. After removal of the solvent in vacuo, the ketone **5b** was obtained in quantitative yield. Distillation, b.p. 90° (2 mm) and successive crystallizations reduced the contamination by the isomeric ketone **10** to less than 1% m.p. 24°. IR cm^{-1}: 1670 (C=O) 1585 and 1570 (pyridyl). PMR: δ 1.04 (1 H, dd, J_{vic}: 8 Hz, J_{gem}: 3.5 Hz, H of cyclopropyl CH_2, trans to C=O), 1.20 (3 H, s, CH_3 trans to C=O) 1.35 (3 H, s, CH_3 cis to C=O), 1.50 (1 H, dd, J_{vic}: 6 Hz, J_{gem}: 3.5 Hz, H of cyclopropyl CH_2 cis to C=O), 3.40 (1 H, dd J = 8 Hz, J = 6 Hz, cyclopropyl CH), 7.45 (1 H, m, pyr 5-H), 7.82 (1 H, m, pyr 4-H), 8.05 (1 H, m, pyr 3-H), 8.73 (1 H, m, pyr 6-H); MS: *m/e* 175 (M), 160 (100%), 146, 132, 117, 106, 95, 78; *m/e* calc for $C_{11}H_{13}NO$ 175.0997, found: 175.1029. (Anal. Found: C, 75.3; H, 7.9; N, 8.1; 0, 8.6%.) $C_{11}H_{13}NO$ requires C, 75.4; H, 7.5; N, 8.0; O, 9.1).

2,2-Diphenylcyclopropyl 2-pyridyl ketimine (**5c'**). The procedure followed was similar to that employed for ketimine **5b'** using 35 ml (56 mmol) of 1.6 M n-butyllithium in hexane, and 5.3 ml (8.70 g, 55 mmol) 2-bromopyridine. The addition of 11.00 g (50 mmol) 2,2-diphenylcyclopropyl cyanide[32] was carried out at −60° in 5 min. Hydrolysis was performed with 9.0 $Na_2SO_4 \cdot 10H_2O$, the solution was filtered and the solvent was removed in vacuo, whereupon ketimine (**5c'**) crystallized from the solution. After the volume of the solution was reduced to 50 ml, the ketimine was filtered off, washed with 10 ml cold ether–hexane 1:1, yield 3.99 g (13.4 mmol) of ketimine (**5c'**) (27%) m.p. 115°. IR cm^{-1}: 3300 (N–H), 1620 (C=N), 1600 (Ph), 1583 and 1569 (pyridyl). PMR: δ 1.64 (1 H, dd, J_{vic}: 8 Hz, J_{gem}: 5 Hz, H of cyclopropyl CH_2 trans to C=NH), 3.55 (1 H, broad, cyclopropyl CH), 7.0–7.6 (11 H, m, Ar–H + pyr 5-H), 7.69 (1 H, m, pyr 4-H), 7.91 (1 H, m, pyr 3-H), 8.70 (1 H, m, pyr 6-H). MS: *m/e* 298 (M), 297, 221, 165, 129, 115, 81, 54, 38, (100%); *m/e* calc for $C_{21}H_{18}N_2$: 298.1470, found: 298.1448. (Anal. Found: C, 84.4; H, 6.2; N, 9.3. $C_{21}H_{18}N_2$ requires C, 84.5; H, 6.1; N, 9.4%.) The mother liquor was distilled by short path distillation (Kugelrohr) temp 150–200° (0.005 mm) to give 7.11 g (25.8 mmol) 1-butyl-2,2-diphenylcyclopropylcyanide (52%).

2,2-Diphenylcyclopropyl 2-pyridyl ketone (**5c**). Ketimine **5c'** was hydrolyzed in the same way as its dimethyl substituted homolog **5b'**, whereupon the ketone (**5c**) was obtained in quantitative yield. Recrystallization from absolute ethanol gave colorless needles, m.p. 135–136°. IR cm^{-1}: 1685 (C=O), 1600 (Ph), 1585 and 1570 (pyridyl); PMR: δ 1.72 (1 H, dd, J_{vic}: 4.5 Hz H of cyclopropyl CH_2 trans to C=O), 2.52 (1 H, dd, J_{vic} 6.5 Hz. J_{gem} 4.5 Hz, H of cyclopropyl CH_2 cis to C=O) 4.40 (1 H, dd, J_1 = 8 Hz, J_2 6.5 Hz, cyclopropyl CH), 7.05–7.60 (1 H, m, Ar–H + pyr 5-H), 7.74 (1 H, m, pyr 4-H), 7.86 (1 H, m, pyr 3-H), 8.80 (1 H, m, pyr 6-H); MS: *m/e* 299 (M), 282, 280, 271, 222, 193, 180, 178, 165, 152, 121, 115 (100%), 106, 91, 79, 78; *m/e* calc for $C_{21}H_{17}NO$: 299.1310. found: 299.1292. (Anal. Found: C, 84.2; H, 5.7; N, 4.9; O, 5.3. $C_{21}H_{17}NO$ requires C, 84.2; H, 5.7; N, 4.7; O, 5.3%.)

Cyclopropyl(2-pyridyl)carbinol (**6a**). To a cooled (0°) and stirred suspension of 125.0 mg (3.29 mmol) lithium aluminium hydride in 30 ml anhydrous ether was added, over 10 min, 1.00 g (6.79 mmol) cyclopropyl 2-pyridyl ketone (**5a**) in 10 ml dry ether. After stirring for 1 h at room temperature, the solution was decomposed by careful addition of 20 ml water, followed by 10 ml of a NaOH (10%).

The ether layer was removed, and the aqueous layer was extracted twice with 20 ml ether. The combined organic layers were dried (Na_2SO_4); the solvent was removed *in vacuo*, whereupon the alcohol **6a** was obtained in nearly quantitative yield. Subsequent distillation by Kugelrohr (100°/1 mm) yielded 801.5 mg (5.37 mmol) 79% of the alcohol (**6a**). The product proved to be unstable at higher temperatures. IR cm^{-1}: 3390 (OH), 1598 and 1573 (pyridyl); PMR: δ 0.45–0.65 (4 H, m, cyclopropyl CH_2), 0.95–1.40 (1 H, m, cyclopropyl CH), 4.16 (1 H, d, J: 7.5 Hz, CHOH), 4.40 (1 H, broad, CHOH), 7.22 (1 H, m, pyr 5-H), 7.42 (1 H, m, pyr 3-H), 7.70 (1 H, m, pyr 4-H), 8.55 (1 H, m, pyr 6-H); MS: *m/e* 149 (M), 148, 134, 132, 120, 108 (100%), 93, 80, 79, 78, 53, 52, 51; *m/e* calc for $C_9H_{11}NO$: 149.0841, found: 149.0841.

2,2-Dimethylcyclopropyl(2-pyridyl)carbinol (**6b**). Ketone **5b** (876.1 mg, 5.00 mmol) and lithium aluminium hydride (190.0 mg, 5.00 mmol) were reacted as described for alcohol **6a**. After work up, the product was purified by column chromatography (silica gel, ethyl acetate–hexane 1:1, TLC R_f: 0.35). Recrystallization of the product from hexane yielded 223 mg of the alcohol **6b** as colorless needles, m.p. 62–63°. The remaining mother liquor was distilled by Kugelrohr (temp 100°, 1–0.5 mm) to give another 399 mg of the alcohol (**6b**). Total yield of **6b** was 622 mg (3.51 mmol) 71%. IR cm^{-1}: 3390 (OH), 1593 and 1570 (pyridyl); PMR: δ 0.35–0.65 (2 H, m, cyclopropyl CH_2), 0.90 (1 H, m, cyclopropyl CH), 1.15 (3 H, s, CH_3 trans to C=O), 1.35 (3 H, s, CH_3 cis to C=O), 4.29 (1 H, dd, J_{HH}: 9.5 Hz, J_{HOH}: 4 Hz CHOH), 4.55 (1 H, d, J_{HOH}: 4 Hz, CHOH), 7.20 (1 H, m, pyr 5-H), 7.41 (1 H, m, 3-H), 7.69 (1 H, m, pyr 4-H), 8.56 (1 H, m, pyr 6-H); MS: *m/e* 177 (M), 176, 160, 144, 121, 118, 109, 108 (100%), 93, 78, *m/e* calc for $C_{11}H_{15}NO$: 177.1154. Found: 177.1155. (Anal. Found: C, 74.4; H, 8.4; N, 7.7; O, 9.0. $C_{11}H_{15}NO$ requires C, 74.5; H, 8.5; N, 7.90; O, 9.1%.)

2,2-Diphenylcyclopropyl(2-pyridyl)carbinol (**6c**). Ketone **5c** (150.0 mg, 0.50 mmol) and lithium aluminium hydride (19.0 mg, 0.50 mmol) were reacted as described previously for the alcohol **6a**. The PMR spectrum of the crude reaction product showed 2 diastereoisomeric alcohols, which could be separated by thick layer chromatography (silica gel, ethyl acetate–hexane 1:1, TLC R_f: 0.45 minor, 0.60 major diastereoisomer). Of the minor diastereomeric alcohol (**6c'**) 19.1 mg (0.06 mmol, 12%) was isolated m.p. 131°. IR: cm^{-1}, 3380 (OH), 1592 and 1540 (pyridyl); PMR: δ 1.29 (1 H, t, J_{vic} 5.5 Hz, J_{gem} 5.5 Hz, H of cyclopropyl CH_2 cis to CHOH) 1.91 (1 H, dd, J_{vic} 9.0 Hz, J_{gem} 5.5 Hz, H of cyclopropyl CH_2 trans to CHOH), 2.18 (1 H, sextet, $J_{H,CHOH}$ 9.5 Hz, J_{vic} 9.0 Hz, J_{vic} 5.5 Hz, cyclopropyl CH), 3.52 (1 H, broad, CHOH), 4.00 (1 H, d, J 9.5 Hz, CHOH), 6.89 (1 H, m, pyr 3-H), 7.10–7.25 (11 H, m, Ar–H + pyr 5-H), 7.54 (1 H, m, pyr 4-H), 8.52 (1 H, m, pyr 6-H); MS: *m/e* 301 (M), 206, 193, 165, 121, 115, 108 (100%), 91, 78, *m/e* calc for $C_{21}H_{19}NO$: 301.1467; found: 301.1450. The major diastereomeric alcohol (**6c'**), m.p. 60°, was obtained in 56% yield (85.2 mg, 0.28 mmol). IR cm^{-1}: 3390 (OH) 1592 and 1540

(pyridine), (Ph under 1592 peak); PMR δ 1.31 (1 H, dd, J_{vic} 9.0 Hz, H_{gem} 5.5 Hz, H of cyclopropyl CH_2 cis to CHOH), 1.56 (1 H, t, J_{vic} 5.5 Hz, J_{gem} 5.5 Hz, H of cyclopropyl CH_2, trans to CHOH), 1.95 (1 H, sextet, $J_{N,CHOH}$ 9.5 Hz, J_{vic} 9.0 Hz, J_{vic} 5.5 Hz, cyclopropyl CH), 3.0–4.0 (1 H, broad CHOH), 3.92 (1 H, d, J 9.5 Hz, CHOH) 7.0–7.75 (13 H, m, Ar–H and pyr 3,4,5-H), 8.52 (1 H, m, pyr 6-H); *MS: m/e* 301 (M), 206, 193, 178, 165, 134, 121, 115, 108 (100%), 91, 78, *m/e* calc for $C_{21}H_{19}NO$: 301.1467; found: 301.1508.

Reduction of ketone **5a** *by tri-n-butyltin hydride.* A mixture of 1.00 g (6.8 mmol) of ketone **5a** and 2.75 ml (10.22 mmol) tri-*n*-butyltin hydride in 30 ml dry benzene was refluxed for 48 h under argon. During the initial 2 h of the reduction catalytic amounts of azobisisobutyronitrile (AIBN, recrystallized from dry methanol) were added after each 30 min. The reaction was followed by taking samples, evaporation of the benzene, and recording PMR spectra in benzene-d_6. Clean spectra were obtained and, despite obscuration of the butyl region (0.7–2.00 ppm), all the significant information could be obtained. Products were observed as their tin adducts, although small amounts of hydrolytic products could also be detected. PMR (benzene-d_6) of the tri-n-butyltin adduct of the alcohol **6a** δ: 4.70 (1 H, d, J = 6 Hz, CH–OSnBu_3), the tri-n-butyl tin enolate of the ketone **8a**; δ: 5.39 (1 H, t, J = 7 Hz, C=CH–CH_2), 2.73 (2 H, q, J = 7 Hz, =CH–CH_2–CH_3).

After 48 h, the presence of unreacted tri-n-butyltin hydride was observed. A few drops of water were added, the mixture allowed to attain room temperature and filtered to give 166 mg of diol **9**. The products in the filtrate were taken up in 10 ml HCl (10%), the organic (benzene) layer separated and washed with 10 ml HCl (10%). The combined aqueous layers were washed with 25 ml benzene, made alkaline (pH 13–14) with an NaOH (10%) solution and the white colloidal suspension thus obtained was extracted three times with 100 ml ether. After drying over Na_2SO_4 and removal of the solvent *in vacuo*, 750 mg of product was obtained. Product ratios in the worked up mixture and the crude reaction mixture (benzene-d_6) were identical (PMR). Ketone **5a**, alcohol **6a**, ketone **8a**, and diol **9** were found in the ratio 5:34:52:9 (total 100%). Isolation of these compounds was carried out by column chromatography (silica gel, ethyl acetate–hexane 1:10); the order of elution was determined by the R_f values of the components: (TLC, silica gel, ethyl acetate–hexane 1:3) diol **9**: 0.43, ketone **8a**: 0.35, ketone **5a**: 0.30, alcohol **6a**: 0.10.

Another 35.0 mg of **9** were isolated, bringing the total yield of the diol **9** to 201 mg (0.68 mmol, 20% relative to **5a**), colorless needles, m.p. 172–173°, recryst from benzene. Ketone **8a** (399 mg, 2.68 mmol, 39%) was the second component to be eluted, followed by 35 mg (0.23 mmol, 3.5%) of unreacted ketone **5a**. After change of eluent to a 1:3 mixture (ethyl acetate:hexane), 248 mg (1.66 mmol, 25%) of the alcohol **6a** was recovered. The material from the column was distilled by Kugelrohr at 120° (10 mm) to give **8a**; IR cm^{-1} 1695 (C=O), 1585 and 1540 (pyridine); PMR: δ 1.02 (3 H, t, J = 7 Hz, CH_3), 1.78 (2 H, sext, J = 7 Hz, CH_2–CH_2–CH_3), 3.22 (2 H, t, J = 7 Hz, C(:O)–CH_2), 7.46 (1 H, m, pyr 5-H), 7.84 (1 H, m, pyr 4-H), 8.05 (1 H, m, pyr 3-H), 8.70 (1 H, m, pyr 6-H); MS *m/e* 149 (M), 134, 121 (McLafferty), 106, 93, 79 (100%), 78, 51, *m/e* calc for $C_8H_{11}NO$: 149.0840, found: 149.0841.

Diol **9**; IR cm^{-1}: 3240 (OH), 1590 and 1565 (pyridyl); PMR: δ (−)0.40–(+)0.10 (8 H, m, cyclopropyl CH_2), 1.14 (2 H, m, cyclopropyl CH), 6.99 (2 H, broad, OH), 7.26 (2 H, m, pyr 5-H), 7.75 (2 H, m, pyr 4-H), 7.90 (2 H, m, pyr 3-H), 8.48 (2 H, m, pyr 6-H); ^{13}C-NMR: δ −1.46 (cyclopropyl CH_2), 2.07 (cyclopropyl CH_2), 16.73 (broadened signal, cyclopropyl CH), 77.22 (–C(OH)–), 121.71 (pyr 5-C), 121.87 (broadened signal pyr 3-C), 136.65 (pyr 4-C), 145.87 (pyr 6-C), 164.95 (broadened signal, pyr 2-C) MS (FD omA-2nA, sample in PEO 4000)[33] *m/e* (abundance): 298 (1), 297 (3), 151(1), 150 (1), 149 (29), 148 (100), 147 (7), 146 (1); normal FD and EI, 70 eV, showed only fragment ions. (Anal. Found: C, 72.7; H, 6.9; N, 9.4; O, 10.9. $C_{18}H_{20}N_2O_2$ requires C, 73.0; H, 6.8; N, 9.4; O, 10.8%.)

1-(2-*Pyridyl*)-1-*butanone* (4-d_1). Isolated by column chromatography after reduction of **5a** with tri-n-butyl deuteride. PMR, identical to **8a**, except for the following: 1.02 (2 H, nine line splitting pattern, $J_{NH,vic}$: 7.0 Hz, $J_{HD,gem}$: 2.0 Hz, CH_2D) 1.78 (2 H, quint, –CH_2–CH_2D); MS (EI, 70 eV) 150 (M), 134 (M–CH_2D), 122 (McLafferty), 106, 93, 79 (100%), 78, 51.

4-*Methyl*-1-(2-*pyridyl*)-1-*pentanone* (**8b**). Ketone **5b** (350.4 mg, 2.0 mmol) and 0.56 ml (2.1 mmol) tri-n-butyltin hydride were refluxed overnight in 20 ml benzene under the same conditions as for ketone **5a**. PMR analysis of the crude reaction mixture in benzene-d_6 showed the characteristic lines of the tin enolate of **8b**, δ 2.62 (2 H, t, J = 7 Hz, =CH–CH_2–CHMe_2), 5.41 (1 H, t, J = 7.0 Hz, =CH–CH_2–), 6.55 (1 H, m, pyr 5-H), 6.98 (1 H, m, pyr 4-H), 7.35 (1 H, m, pyr 3-H), 8.03 (1 H, m, pyr 6-H), as well as traces of hydrolyzed product **8b**.

Work up was carried out as described in the reduction of ketone **5a** by tri-n-butyltin hydride. The product was directly distilled in a Kugelrohr apparatus temp 100° (1 mm), to yield 238.0 mg (1.34 mmol) of ketone **8b** 67%. IR cm^{-1} 1695 (C=O), 1588 and 1570 (pyridyl); PMR δ 0.95 (3 H, t, CH_3), 1.5–1.8 (3 H, m, CH_2–CHMe_2), 3.23 (2 H, t, C(:O)–CH_2), 7.45 (1 H, m, pyr 5-H), 7.83 (1 H, m, pyr 4-H), 8.05 (1 H, m, pyr 3-H), 8.69 (1 H, m, pyr 6-H); MS (EI, 70 eV): *m/e* 177 (M), 162, 149, 134, 121 (McLafferty), 106, 93, 79 (100%), 51, *m/e* calc for $C_{11}H_{15}NO$: 177.1153. Found: 177.1138.

4,4-*Diphenyl*-1-(2-*pyridyl*)-1-*butanone* (**8c**). Ketone **5c** (299.4 mg, 1.0 mmol) and 0.30 ml (1.1 mmol) of tri-n-butyltin hydride were refluxed overnight in 20 ml benzene, under the same conditions as ketone **5a**. PMR analysis of the crude reaction mixture (benzene-d_6) showed the characteristic lines of the tin enolate of **8c** δ 3.46 (2 H, t, J = 7 Hz, =CH–CH_2–$CHPh_2$), 4.36 (1 H, t, J = 7 Hz, –$CHPh_2$), 5.36 (1 H, t, J = 7 Hz, =CH–CH_2), 6.43 (1 H, m, pyr 5-H), 6.75 (1 H, m, pyr 4-H), 6.9–7.2 (10 H, m, Ar–H), 7.39 (1 H, m, pyr 3-H), 7.91 (1 H, m, pyr 6-H), as well as traces of hydrolyzed product **8c**. Hydrolysis was carried out by 10 ml HCl 10% and stirring for 30 min. The hydrochloride of ketone **8c** could not be transferred to the aqueous layer, so the benzene layer was washed with 10 ml NaOH (10%) in order to obtain the free base, the solvent was removed *in vacuo*, whereupon ketone **8c** partially crystallised from the mixture. The remaining ketone was obtained from the mother liquor by thick layer chromatography (silica gel, ethyl acetate–hexane 1:2). Recrystallization from absolute ethanol yielded 238 mg (0.79 mmol) of ketone **8c** 79% m.p. 76–77°. IR cm^{-1}: 1690 (C=O), 1598 (Ph), 1582 and 1570 (pyridine) PMR: δ 2.54 (2 H, q, J = 7 Hz, –CH_2–$CHPh_2$), 3.23 (2 H, t, J = 7 Hz, C(=O)–CH_2–), 4.07 (1 H, t, J = 7 Hz, –$CHPh_2$), 7.1–7.35 (10 H, m, Ar–H), 7.40 (1 H, m, pyr 5-H), 7.78 (1 H, m, pyr 4-H), 8.00 (1 H, m, pyr 3-H), 8.62 (1 H, m, pyr 6-H); MS (EI, 70 eV): *m/e* 301, 283, 282, 180, 167, 165, 152, 134, 121 (77%, McLafferty), *m/e* calc for $C_{21}H_{19}NO$: 301.1467. Found: 301.1449. (Anal. Found: C, 82.8; H, 6.4; N, 4.3; O, 5.3. Calc for $C_{21}H_{19}NO$: C, 83.68; H, 6.35; N, 4.65; O, 5.31%.)

Reduction of ketone **5a** *by Hantzsch ester* (**2**). Ketone **5a** (1.00 g, 6.8 mmol) and 1.72 g (6.8 mmol) Hantzsch ester (**2**) were refluxed in 30 ml dry acetonitrile in presence of 1 equiv. $Mg(ClO_4)_2$ (6.8 ml of a 1 M sol in CH_3CN) under inert atmosphere (N_2). A second equiv. Hantzsch ester was added after 8 h and a third after 24 h. A PMR spectrum of a sample after 32 h showed the ketone **5a** and the alcohol **6a** in the ratio 1:3; after 48 h, besides the alcohol **6a** only traces of the ketone could be detected. The acetonitrile was removed *in vacuo*, followed by successive addition of 100

ml $CHCl_3$ and 50 ml H_2O under vigorous stirring. The chloroform layer was separated and the water layer extracted once more with 50 ml $CHCl_3$. The combined chloroform layers were dried (Na_2SO_4) and the solvent removed *in vacuo*. Kugelrohr distillation of the product gave in a first fraction (100°/1 mm) 1.046 g of colorless material composed (by PMR) of 838 mg (5.62 mmol, 83%) alcohol **6a**, 125 mg (0.85 mmol, 12%) ketone **5a** and 83 mg of the oxidized Hantzsch ester. Further distillation yielded only oxidized Hantzsch ester. Reaction with 1 equiv. Hantzsch ester **2** gave, after 24 h, the ketone **5a** and the alcohol **6a** in the ratio 3:1. No unreacted Hantzsch ester was present at this stage.

Reduction of ketone **5a** *by* 1-*benzyl*-1,4-*dihydronicotinamide* (**7**). Ketone **5a** (1.00 g, 6.8 mmol) and 2.18 g (10.2 mmol) of the 1,4-dihydropyridine **7**, were refluxed for 8 h under N_2 atmosphere in 30 ml dry acetonitrile and in presence of 1 equiv. $Mg(EtOH)_6(ClO_4)_2$ (6.8 ml of a 1 M sol in CH_3CN). The acetonitrile (in a sample of the mixture) was removed in vacuo, followed by working up at a smaller scale but in a similar way to that used in the reduction of **5a** by Hantzsch ester. PMR analysis showed a clean spectrum, where ketone **5a** and alcohol **6a** were present in the ratio 45:55, as well as 0.64 equiv (4.33 mol) unreacted 1,4-dihydropyridine **7**. After 24 h the ratio was unchanged, while after 48 h the ratio changed to 55:45, probably due to the instability of the alcohol **6a**.

Reduction of ketone **5b** *by Hantzsch ester* **2**. Ketone **5b** (525.7 mg, 3.0 mmol) and 760.0 mg (3.0 mmol) Hantzsch ester **2** were refluxed for 24 h under N_2 atmosphere in 30 ml dry acetonitrile, in presence of 1 equiv $Mg(ClO_4)_2$ (3 ml of a 1M sol in CH_3CN). After work-up similar to that used for the reduction of **5a** by Hantzsch ester, the products were separated by column chromatography (silica gel, ethyl acetate–hexane 1:5 (fraction 1), 1:1 (fraction 2). The first fraction to be eluted was composed of (PMR) 486 mg (1.94 mmol) of oxidized Hantzsch ester and 279 mg (1.59 mmol, 53%) of 4-methyl-1-(2-pyridyl)-4-penten-1-one (**10**). In a second fraction 226 mg (1.28 mmol, 43%) of 4-methyl-1-(2-pyridyl)-4-penten-1-ol (**11**) was recovered.

Reduction of ketone **5b** *by* 1-*benzyl*-1,4-*dihydronicotinamide* (**7**). The experiment was carried out in the same way as the preceding reduction, except for the use of 642.0 mg (3 mmol) of 1-benzyl-1,4-dihydronicotinamide **7** and 3 ml of 1 M $Mg(EtOH)_6(ClO_4)_2$ in CH_3CN. Work-up and column chromatography gave a first fraction of 18.7 mg (0.11 mmol, 4%) of ketone **10**, and a second fraction of 410 mg (2.32 mmol, 77.3%) of 4-methyl-1-(2-pyridyl)-4-penten-1-ol (**11**). 4-methyl-1-(2-pyridyl)-4-penten-1-one (**10**): IR cm^{-1}: 1692 (s, C=O), 1650 (m, $C=CH_2$), 1585 and 1570 (pyridyl), 890 (s, $C=CH_2$, ν out of plane); PMR: 1.80 (3 H, s, broadened, CH_3), 2.45 (2 H, t, J = 7.5 Hz, broadened $-\underline{CH}_2-C(-CH_3)=CH_2$), 3.39 (2 H, t, J = 7.5 Hz, $-C(:O)-\underline{CH}-$), 4.75 (2 H, s, broadened, $C=\underline{CH}_2$), 7.46 (1 H, m, pyr 5-H), 7.83 (1 H, m, pyr 4-H), 8.05 (1 H, m, pyr 3-H), 8.70 (1 H, m, pyr 6-H). Broadening of signals by allylic coupling was observed and the PMR spectrum was completely resolved by double resonance. ^{13}C-NMR: δ 22.66 (CH_3), 31.88 ($-\underline{C}H_2-C(CH_3)=CH_2$), 35.98 ($C(=O)-\underline{C}H_2-$), 110.16 ($C=\underline{C}H_2$), 121.74 (pyr 3-C), 126.92 (pyr 5-C), 136.65 (pyr 4-C), 144.77 ($\underline{C}=CH_2$), 148.92 (pyr 6-C), 153.59 (pyr 2-C), 201.36 ($\underline{C}=O$), MS: *m/e* 175 (M), 160, 156, 147, 146, 132, 106, 91, 79 (100%), 78, 51, *m/e* calc. for $C_{11}H_{13}NO$: 175.0997, found: 175.0961.

4-*Methyl*-1-(2-*pyridyl*)-4-*penten*-1-*one* (**10**) was the only product of the magnesium perchlorate hexakisethanol (0.50 ml, 1 M sol. in CH_3CH) mediated isomerisation of ketone **5b** (70.0 mg, 0.40 mmol) after 16 h refluxing in 10 ml dry acetonitrile. The acetonitrile was removed *in vacuo*, followed by addition of 20 ml $CHCl_3$ and 10 ml H_2O. The chloroform layer was separated, and the water layer was extracted twice with 10 ml $CHCl_3$. The combined chloroform layers were dried (Na_2SO_4); evacuation of the chloroform followed by a Kugelrohr distillation (100°/0.5 mm) yielded the ketone **10** in quantitative yield.

4-*Methyl*-1-(2-*pyridyl*)-4-*penten*-1-*ol* (**11**) was obtained by distillation (100°/0.5 mm) (Kugelrohr) of the second chromatographic fraction; IR cm^{-1} 3400 (OH), 1650 ($C=CH_2$), 1598 and 1575 (pyridyl), 890 ($C=CH_2$) PMR δ: 1.67 (3 H, s, broadened, CH_3), 1.78 (1 H, m, H of $-CHOH-\underline{CH}_2-$), 1.92 (1 H, m, H of $-CHOH-\underline{CH}_2-$), 2.10 (2 H, t, broadened, $\underline{CH}_2-C(-CH_3)=CH_2$), 4.20 (1 H, broad, $O\underline{H}$), 4.65 (2 H, s, broadened, $C=\underline{CH}_2$), 4.70 (1 H, dd, J_{HH} 7.9 Hz, $J_{H,OH}$: 4.4 Hz, $C\underline{H}OH$), 7.13 (1 H, m, pyr 5-H), 7.24 (1 H, m, pyr 3-H), 7.62 (1 H, m, pyr 4-H), 8.46 (1 H, m, pyr 6-H). Peak broadening was caused by allylic coupling; double resonance resulted in line sharpening. ^{13}C–NMR δ 22.36 ($-\underline{C}H_3$), 33.32 ($C(=O)-\underline{C}H_2-$), 36.40 ($\underline{C}H_2-C(-CH_3)=CH_2$), 72.61 ($\underline{C}HOH$), 109.81 ($C=\underline{C}H_2$), 120.17 (pyr 3-C), 122.02 (pyr 5-C), 136.46 (pyr 4-C), 145.27 ($-\underline{C}(CH_3)=CH_2$), 148.05 (pyr 6-C), 162.41 (pyr 2-C); MS *m/e* 177 (M), 134, 122, 121, 99, 98 (100%), 93, 80, 79, 78, 69, 53, 52, 51, *m/e* calc for $C_{11}H_{15}NO$: 177.1153; found: 177.1145.

Reduction of ketone **5c** *by Hantzsch ester* **2**. A solution of 299.4 mg (1.0 mmol) ketone **5c**, 253.3 mg (1.0 mmol) Hantzsch ester **2** and 1 mmol $Mg(ClO_4)_2$ (as 1 ml of a 1 M sol in CH_3CN) in 15 ml dry acetonitrile were refluxed for 24 h under N_2 atmosphere. After work-up similar to the procedure described in the reduction of ketone **5a** by Hantzsch ester, PMR analysis showed a complex mixture of products, where, beside the oxidized Hantzsch ester, a small amount of starting ketone **5c** was present (<5%). Other products identified (PMR) were a small amount of 4,4-diphenyl-1-(2-pyridyl)-3-buten-1-one (<5%) as well as decomposition products of this ketone.

Reduction of ketone **5c** *by* 1-*benzyl*-1,4-*dihydronicotinamide* (**7**). A solution of 299.4 mg (1 mmol) of ketone **5c**, 214 mg (1 mmol) of 1,4-dihydropyridine **7**, and 1 ml of a 1 M sol of $Mg(EtOH)_6(ClO_4)_2$ in 15 ml dry acetonitrile were refluxed under N_2 atmosphere for 24 h. After work-up similar to the reduction of **5a** by Hantzsch ester, the presence of a substantial amount of alcohol **6c** was identified (PMR). Also present were small amounts of the starting ketone **5c** and 4,4-diphenyl-1-(2-pyridyl)-3-buten-1-one. Thick layer chromatography (Silica gel, ethyl acetate:hexane 1:1) yielded 5 mg (0.05 mmol, 5%) of ketone **5c**, and 115 mg (0.38 mmol, 38%) of the alcohol **6c**″.

Reaction of ketone **5c** *with* $Mg(EtOH)_6(ClO_4)_2$. Reaction of ketone **5c** (150 mg, 10.5 mmol) with 0.5 ml of the $Mg(EtOH)_6(ClO_4)_2$ (1 M sol in 7.5 ml acetonitrile) under the same conditions as in the preceding experiments led to the detection of the same small amount of 4,4-diphenyl-1-(2-pyridyl)-3-buten-1-one (<5%), as well as the same decomposition products as described in the last mentioned experiment (PMR). These conclusions were confirmed by following the reaction by PMR (CD_3CN). After 4.5 h a ratio of 5:40 for the mixture 4,4-diphenyl-1-(2-pyridyl)-3-buten-1-one/ketone **5c** was observed with almost no decomposition products. After 22 h approx a 1:1 mixture of decomposition products of ketone **5c**, with only a small amount of 4,4-diphenyl-1-(2-pyridyl)-3-buten-1-one, was observed. The last compound was identified via PMR, 3.68 (2 H, d, $C(=O)-\underline{CH}_2-$), 6.15 (1 H, t, $-\underline{CH}=CPh_2$).

Ethyl cyclopropylmethylenepyruvate (**14**). Cyclopropylcarbaldehyde (**12**) was prepared as described by Smith and Rogier.[16] Ethyl triphenylphosphoranylidenepyruvate (**13**) was prepared from ethyl bromopyruvate and triphenylphosphine according to the procedure of LeCorre.[27] A Carius tube containing 5.40 g (14.3 mmol) of the ylid **13**, 2.00 g (28.6 mmol) of the aldehyde **12** and 25 ml benzene[34] was introduced in an iron protection mantle and heated at 130° for 24 h. After cooling to room temperature, the reaction mixture was transferred to an evaporation flask and the solvent and excess of aldehyde were removed. The residue was taken up in ethyl acetate, and the triphenylphosphine oxide formed was precipitated by addition of hexane. After

removal of the solvent from the filtrate the process was repeated. After the final removal of the solvent the keto ester was selectively taken up in hexane. The brown viscous residue obtained after evaporation of the hexane was distilled (Kugelrohr) temp 100° (0.01 mm), to give keto ester **14**. Subsequent distillation gave pure **14**, b.p. 65° (0.01 mm), 955 mg (40%); IR cm^{-1}; 1728 (s), 1690 (s), 1660 (s), 1610 (s); PMR: δ 0.60–0.90 (2 H, m, H of cyclopropyl CH_2), 0.95–1.25 (2 H, m, H of cyclopropyl CH_2), 1.39 (3 H, t, J = 7 Hz, ester CH_3), 1.50–1.95 (1 H, m, cyclopropyl CH), 4.35 (2 H, q, J = 7 Hz, ester CH_2), 6.50–6.90 (2 H, m, –CH=CH–trans), ^{13}C-NMR: 10.16 (cyclopropyl CH_2), 14.07 (ester CH_3), 15.96 (cyclopropyl CH), 62.15 (ester CH_2), 122.34 (=CH–C(=O), 160.06 (–CH=CH–C(=O)), 162.66 (COOEt), 182.35 (C=O). MS: *m/e* 168 (M), 140, 122, 112, 96, 95 (100%), 67, 65, 55, 53, 51; *m/e* calc for $C_9H_{12}O_3$: 168.0786; found: 168.0764. (Anal. Found: C, 63.9; H, 7.2; O, 28.5. $C_9H_{12}O_3$ requires C, 63.9; H, 7.2; O, 28.5%.)

Ethyl 4-cyclopropyl-2-oxo-1-butanoate (**15**). Keto ester **14** (504.6 mg, 3 mmol) and 760 mg (3 mmol) Hantzsch ester **2** were stirred for 30 min at room temperature in 30 ml dry acetonitrile, in presence of 3 ml $Mg(ClO_4)_2$ (1 M in CH_3CN) solution and under N_2. After evaporation of acetonitrile under reduced pressure the work-up was carried out as for the reduction of ketone **5a** by **2**. Careful Kugelrohr distillation yielded in a first fraction 296.2 mg (1.74 mmol, 58%) of keto ester **15**, 90° (0.8–0.5 mm). IR cm^{-1}: 1730 (s, C=O); PMR: δ 0.03–0.09 (2 H, m, H of cyclopropyl CH_2), 0.41–0.48 (2 H, m, H of cyclopropyl CH_2), 0.73 (1 H, m, cyclopropyl CH), 1.37 (3 H, t, J = 7 Hz, ester CH_3), 1.54 (2 H, q, J = 7 Hz, CH–CH_2–CH_2), 2.94 (2 H, t, J = 7 Hz, CH_2–C(=O)–), 4.32 (2 H, q, J = 7 Hz, ester CH_2); ^{13}C-NMR 4.57 (cyclopropyl CH_2), 10.31 (cyclopropyl CH), 13.94 (ester CH_3), 28.26 (CH–CH_2–CH_2), 39.36 (CH_2–C(=O)–), 62.25 (ester CH_2), 161.13 (–C(=O)–OEt), 194.57 (C=O); MS m/e: 170, 141, 124, 97 (100%, M–CO_2Et), 91, 69, 55, 41, *m/e* calc for $C_9H_{14}O_3$: 170.0943; found: 170.0940.

Reduction of keto ester **14** *with tri-n-butyltin hydride.* Reduction of keto ester **14** (336.4 mg, 2 mmol) with tri-n-butyltin hydride (582.1 mg, 2 mmol) was carried out under several different reaction conditions. Whether the reaction was carried out with one or two equivalents of tri-n-butyltin hydride, in the presence or absence of a catalytic amount of azobisisobutyronitrile (AIBN), in 10 ml benzene or without solvent, at room temperature or with heating at 80°, the reaction product was the same tin enolate **16**, irrespective of the conditions employed. After evacuation of the solvent, the tin enolate **16** was obtained in quantitative yield. IR cm^{-1}: 1690 (C=O ester), 1625 (C=C–OSn); PMR: δ (benzene-d_6): 0.10–0.50 (4 H, m, cyclopropyl CH_2), 0.80–1.90 (31 H, m, butyl cyclopropyl CH, ester CH_3), 2.42 (2 H, t, J = 7 Hz, CH–CH_2–CH=), 3.97 (2 H, q, J = 7 Hz, ester CH_2), 6.04 (1 H, t, J = 7 Hz, CH_2–CH=C). Assignments were confirmed by double resonance and use of tri-n-butyltin deuteride: PMR δ 2.38 (1 H, broadened t, J = 7 Hz, CH–CHD–CH=), 6.02 (1 H, d, J = 7 Hz, CH–CHD–CH=). MS (FDMS) *m/e*: no molecular ion was observed, however, peaks centered at 401 (M–Bu), 170 (100%), MH^+ with subsequent loss of $^{\cdot}Sn\,Bu_3$), attested to the enolate structure.

Acknowledgement—This work was carried out in part under the auspices of the Netherlands Foundation of Chemical Research (S.O.N.) and with financial support from The Netherlands Organisation of Pure Research (Z.W.O.).

REFERENCES

[1]NADH Models Part 18. J. C. G. van Niel and U. K. Pandit, *J. Chem. Soc. Chem. Commun.* 149 (1983).

[2]Taken in part from the forthcoming doctoral dissertation of L. H. P. Meijer, University of Amsterdam.

[3]Taken in part from the forthcoming doctoral dissertation of J. C. G. van Niel, University of Amsterdam.

[4a]H. Sund, In *Biological Oxidations* (Edited by T. P. Singer), pp. 621–624. Wiley Interscience, New York (1968); [b]D. S. Sigman, J. Hajdu and D. J. Creighton, *Bioorganic Chemistry* (Edited by E. E. van Tamelen), Vol. 4, p. 385. Academic Press, New York (1978); [c]R. J. Kill and D. A. Widdowson, *Ibid.*, p. 239; [d]J. W. Bunting and S. Sindhuatmadia, *J. Org. Chem.* **46**, 4211 (1981); [e]J. M. Bunting, V. S. F. Chew and G. Chu, *Ibid.* **47**, 2303 (1982); [f]R. Sirinivasan, R. T. Medary, H. F. Fisher, D. J. Norris and R. Stewart, *J. Am. Chem. Soc.* **104**, 807 (1982); [g]M. F. Powell and T. C. Bruice, *Ibid.* **104**, 5834 (1982); **105**, 1014 (1983).

[5a]A. Ohno, H. Yamamoto and S. Oka, *J. Am. Chem. Soc.* **103**, 2041 (1981); [b]A. Ohno, T. Shio, H. Yamamoto and S. Oka, *Ibid.* p. 2045; [c]S. Shinkai, T. Tsuno and O. Manabe, *J. Chem. Soc. Chem. Commun.* 592 (1982); [d]S. Oae, T. Nagata, T. Yoshimura and K. Fujimori, *Tetrahedron Letters* **23**, 3189 (1982); [e]N. Ono, R. Tamura and A. Kaji, *J. Am. Chem. Soc.* **105**, 4017 (1983). The two last mentioned groups provide evidence for electron-transfer chain reactions.

[6]I. MacInnes, D. C. Nonhebel, S. T. Orszulik and C. J. Suckling, *J. Chem. Soc. Chem. Commun.* 121 (1982).

[7]D. C. Nonhebel, S. T. Orszulik and C. J. Suckling, *J. Chem. Soc. Chem. Commun.* 1146 (1982).

[8]S.-K. Chung and A.-U. Park, *J. Org. Chem.* **47**, 3197 (1982).

[9a]I. I. Holbrook, A. Liljas, S. I. Steindel and M. G. Rossmann, *The Enzymes* (Edited by P. Boyer), 3rd Edn, Vol. XI, pp. 191–293. Academic Press, New York (1975); [b]C.-I. Bränden, H. Jörnvall, H. Eklund and B. Furugren, *Ibid.* pp. 107–190.

[10a]L. I. Banaszak and R. A. Bradshaw, *The Enzymes* (Edited by P. Boyer), 3rd Edn, Vol. XI, pp. 369–496. Academic Press, New York (1975). [b]W. S. Verma, D. Sharma and K. G. Gollakota, *Ind. J. Biochem. Biophys.* **13**, 99 (1976); [c]M. Pandey, G. S. Sirohi and G. C. Sirivastava, *Ind. J. Exp. Biol.* **14**, 719 (1976).

[11a]C. T. Angelis, M. F. Dunn, D. C. Muchmore and R. M. Wing, *Biochemistry* **16**, 2922 (1977); [b]M. C. Traglia, J. Schmidt, M. F. Dunn and J. T. McFarland, *J. Biol. Chem.* **252**, 3493 (1977).

[12a]S. Singh and V. K. Sharma, *Tetrahedron Letters* 2733 (1979); [b]S. Singh and I. Singh, *J. Chem. Soc. Chem. Commun.* 100 (1982).

[13a]U. K. Pandit, R. A. Gase, F. R. MasCabré and M. J. de Nie-Sarink, *J. Chem. Soc. Chem. Commun.* 211 (1975); [b]S. Shinkai and T. Kunitake, *Chem. Lett.* 1113 (1976); [c]N. Baba, K. Nishiyama, I. Oda and Y. Inouye, *Agr. Biol. Chem.* **40**, 1441 (1976); [d]M. J. de Nie-Sarink and U. K. Pandit, *Recl. Trav. Chim. Pays-Bas* **98**, 162 (1979).

[14a]U. K. Pandit, H. van Dam and J. B. Steevens, *Tetrahedron Letters* 913 (1977); [b]J. B. Steevens and U. K. Pandit, *Tetrahedron* **39**, 1395 (1983); [c]U. K. Pandit, M. J. de Nie-Sarink, A. v.d. Burg, J. B. Steevens and R. F. M. van Dokkum, *Recl. Trav. Chim. Pays-Bas* **97**, 121 (1978).

[15a]B. Maillard, D. Forest and K. U. Ingold, *J. Am. Chem. Soc.* **98**, 7024 (1976); [b]A. Effio, D. Griller, K. U. Ingold, A. L. K. Beckworth and A. K. Serelis, *Ibid.* **102**, 1734 (1980).

[16]L. I. Smith and E. R. Rogier, *J. Am. Chem. Soc.* **73**, 4047 (1951).

[17a]M. Julia, S. Julia and J. A. Amaudric Du Chaffaut, *Bull. Soc. Chim. Fr.* 1735 (1960); [b]H. C. Brown, *Tetrahedron Letters* **3**, 9 (1959).

[18]R. Vaidyanathaswamy, *Ind. J. Chem.* **14B**, 30 (1976).

[19]L. R. C. Barclay, D. Griller and K. U. Ingold, *J. Am. Chem. Soc.* **104**, 4399 (1982).

[20a]M. Hughes and R. H. Prince, *Chem. Ind. (London)* 648 (1975); [b]R. A. Gase, G. Boxhoorn and U. K. Pandit, *Tetrahedron Letters* 2889 (1976); [c]A. Ohno, S. Yasui and

S. Oka, *Bull. Chem. Soc. Jpn.* **53**, 3244 (1980) and papers cited therein.

[21a]A small amount of 4,4-diphenyl-1-(2-pyridyl) 3-buten-1-one has been spectrally identified in the reaction of **5c** with $Mg(EtOH)_6(ClO_4)_2$. This ring-opened product has, as expected, also been detected in reactions of **5c** with **2** and **7**; [b]H. M. Walborsky and L. Plonsker, *J. Am. Chem. Soc.* **83**, 2138 (1961).

[22]U. K. Pandit, J. B. Steevens and F. R. MasCabré, *Bioorganic Chem.* **2**, 293 (1973).

[23a]U. K. Pandit, F. R. MasCabré, R. A. Gase and M. J. de Nie-Sarink, *J. Chem. Soc. Chem. Commun.* 627 (1974); [b]M. J. de Nie-Sarink and U. K. Pandit, *Tetrahedron Letters* 2449 (1979).

[24]R. A. Gase and U. K. Pandit, *J. Am. Chem. Soc.* **101**, 7059 (1979).

[25]S. Shinkai, H. Hamada, Y. Kusano and O. Manabe, *Tetrahedron Letters* 3511 (1979) and references cited therein.

[26]L. H. P. Meijer, Unpublished results from this laboratory.

[27]M. LeCorre, *C.R. Acad. Sci. Paris, Serie C* **270**, 1312 (1970).

[28]E. R. Nelson, M. Maienthal, L. A. Lane and R. A. Benderly, *J. Am. Chem. Soc.* **79**, 3467 (1957).

[29]R. G. Rice and E. J. Kohn, *J. Am. Chem. Soc.* **77**, 4052 (1955).

[30]F. J. McCarty, C. H. Tilford and M. G. van Campen Jr., *J. Am. Chem. Soc.* **79**, 472 (1957).

[31]R. V. Stevens, M. C. Ellis and M. P. Wentland, *J. Am. Chem. Soc.* **90**, 557b (1968).

[32]H. M. Walborsky and J. M. Motes, *J. Am. Chem. Soc.* **92**, 2445 (1970).

[33]Field Desorption Mass Spectrometry using polyethylene oxide (PEO) 4000 as matrix; [a]K. H. Ott, Thesis, University of Bonn (1981); [b]J. J. Zwinselman, Thesis, University of Amsterdam (1983).

[34]Reaction in toluene or xylene gave lower yields and increasing amounts of intractable by-products.