

262. Low Temperature *Grignard* Reactions with Pure Mg Slurries. Trapping of Cyclopropylmethyl and Benzocyclobutenylmethyl *Grignard* Reagents with CO₂

by Ernst Peter Kündig and Celia Perret

Département de Chimie Organique, Université de Genève, CH-1211 Genève 4

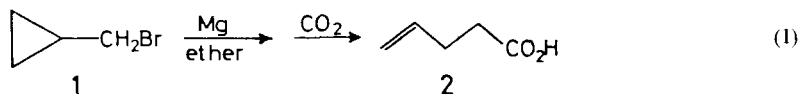
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Summary

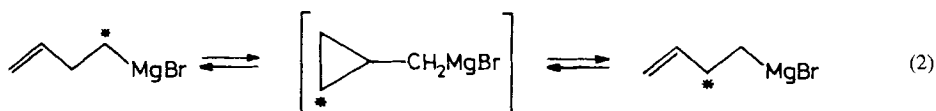
Cyclopropylmethyl bromide reacts readily at -75° with a Mg/THF slurry formed by evaporation of Mg in a rotating-solution reactor to yield after carbonation cyclopropyl acetic acid and 4-pentenoic acid in a ratio of 11:1. Addition of benzaldehyde to the *Grignard* solution again predominantly yields the addition product containing the cyclopropylmethyl unit. Using the same low temperature *Grignard* method, benzocyclobutenyl acetic acid is isolated upon carbonation of the *Grignard* reagent derived from the corresponding bromide, whereas under normal conditions *o*-vinylphenylacetic acid, the product corresponding to ring cleaved *Grignard* is obtained.

Active magnesium slurries for *Grignard* reagent preparations have been produced either by alkali metal reduction of magnesium halide [1-3] or by Mg-atom solvent cocondensation [4]. The latter method allows the formation of clean, alkali halide free, extremely reactive metal suspensions that have been shown to undergo *Grignard* reagent formation under very mild conditions. Apart from this early work by *Klabunde*, the method has not found wide-spread application in the organic laboratory, probably because of practical difficulties. However, over the past few years the apparatus design for metal vapour synthesis has developed considerably [5-7]. The rotating-solution reactor, originally designed by *Timms* [5], would particularly appear to present an ideal yet simple instrument for the formation of *Grignard* reagents difficult to obtain. In this paper we describe our results with cyclopropylmethyl and benzocyclobutenylmethyl *Grignard* reagents.

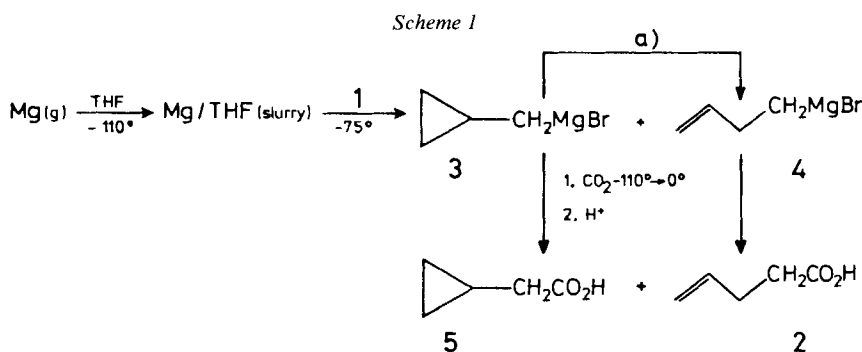
1. Preparation and reactions of cyclopropyl methyl magnesium bromide (3). - Cyclopropylmethyl bromide (**1**) reacts readily with magnesium in diethylether to yield, after carbonation, 4-pentenoic acid (**2**), the product corresponding to ring cleaved *Grignard* reagent (*Equ. 1*) [8] [9].



The formation of the cyclopropylmethyl *Grignard* reagent **3** was demonstrated by *Roberts et al.* [10]. *In situ* acidolysis of the *Grignard* reagent derived from **1** (*Barbier* reaction [11]) at low temperature (-24°) yields 55% methylcyclopropane. It thus appears that substantial ring-opening occurs during *Grignard* formation, probably *via* a radical mechanism. In diethyl ether unrearranged *Grignard* **3** (*Scheme 1*) that is formed is then rapidly converted to **4**, unless trapped immediately by protolysis. In separate experiments in dimethyl ether this rearrangement was shown to be a comparatively slow process ($t_{1/2} = 121$ min) at -24° . Interest in the *Grignard* reagent **3** has been considerable because of its likely intermediacy in the 3-butenyl *Grignard* rearrangement (*Equ. 2*). Since its discovery by *Roberts et al.* [12] this rearrangement, which involves formally a 1.2 vinyl shift, has been the subject of very detailed mechanistic studies by several research groups [12-14]. From the foregoing discussion it is evident that a high yield synthesis of **3** and its reaction with C-electrophiles under conservation of the three-membered ring is an adequate test for a *Grignard* method.



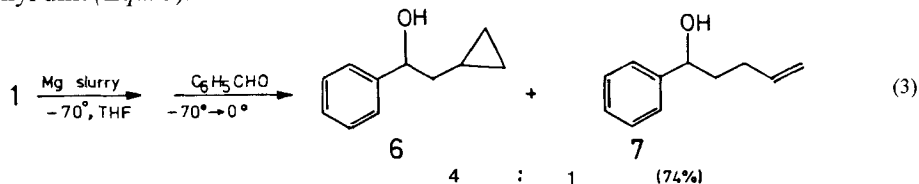
1.1. *Results and Discussion.* Condensation of Mg-atoms into tetrahydrofuran (THF) (-110° , $5 \cdot 10^{-3}$ Torr) in a simple rotating-solution reactor yields a black Mg-slurry. Slow addition of cyclopropylmethyl bromide (dissolved in THF) at -75° followed by condensation of gaseous CO_2 into the reaction mixture (-110°) and slow warm-up yields after work-up a mixture of cyclopropyl acetic acid and 4-pentenoic acid in a ratio of 11 to 1 (*Scheme 1*). The amount of cyclic product varies considerably from run to run (80 to 92%) depending on concentration, rate of addition of halide, and temperature. No problems are encountered, however, with initiation of *Grignard* reagent formation at low temperature. In order to ensure complete reaction as well as to account for loss of Mg through deposition on the poles of the reaction flask and the electrodes, a two- to three-fold excess of Mg was evaporated in all runs.



a) $k_{(10^\circ, \text{THF})} = 2.9 \cdot 10^{-5} \text{ s}^{-1}$

Alternatively, the acids **2** and **5** are obtained in a ratio of 1 to 7 upon carbonation of the *Grignard* solution prepared by direct evaporation of magnesium into a THF solution of **1** at -110° . Reaction is instantaneous as evidenced by the transparency of the solution. Black metal aggregates form only when all bromide has reacted. The drawback of this method is that side reactions (e.g. *Wurtz* coupling) due to excess halide in solution during *Grignard* formation become important. This results in relatively low yield of acids (45%).

Addition of benzaldehyde to the *Grignard* solution prepared from the Mg-slurry and **1** again predominantly yields the product containing the cyclopropylmethyl unit (*Equ.* 3).



In order to avoid reductive coupling of the aldehyde by excess Mg, the solutions of **3** were filtered prior to reaction. Surprisingly, the manipulation of the reagent solution and the warm-up associated with it did not alter the ratio of cyclic **6** to ring-opened product **7**. Subsequently, a solution of **3** was left to warm-up to -20° for 2 h prior to CO_2 -quenching. Product distribution was identical to that of an aliquot quenched prior to warm-up. Under these conditions more than 50% of **3** was observed to rearrange when the solvent was dimethyl ether [10]. Our experiments indicate a stabilization of the (cyclic) *Grignard* reagent **3** in THF. This situation was corroborated by a kinetic study of the ring opening reaction. Measurement of the rate of conversion of **3** to **4** at 10° was accomplished by following the time dependence of the ratio of the acids **5** and **2** formed upon quenching with CO_2 . The ratios were determined by GC. of the methyl esters, formed by reaction with excess diazomethane. The ring opening showed first-order kinetics with $k(10^\circ) = 2.9 \times 10^{-5} \text{ s}^{-1}$ ($t_{1/2}(10^\circ) = 400 \text{ min}$).

At 10° the ring opening of **3** is more than three times slower in THF than at -24° in dimethyl ether. Although we were surprised by the magnitude of the decrease in rate, the result is not totally unexpected. It is consistently found that the more polar and more basic THF leads to rates of *Grignard* rearrangement slower than those in dialkyl ethers [14]. *Maercker & Streit* suggested that the difference in rate arises from the increased solvation and therefore decreased aggregation of the *Grignard* compound in THF solutions [13 b]. These solvent effects are generally quite moderate in magnitude (rate decreases by factors between 2 and 6 are typical) but larger effects have been reported in a few systems, particularly in allylmethyl rearrangements [14] in which **3** is a probable intermediate. Our results illustrate that the *Grignard* reagent **3**, once formed, can be efficiently trapped by electrophiles without rearrangement. The ring opening encountered in cyclopropylmethyl bromide reaction with magnesium below 0° is thus shown to arise exclusively during *Grignard* formation. Evidence has been presented that outer-sphere-electron transfer from the magnesium to the halide is rate-determining in the *Grignard*

reaction [15] [16]. Assuming this mechanism, our results indicate that the subsequent collapse of the resulting radical ion pair to the *Grignard* reagent has a slightly lower activation energy than the ring opening reaction of the cyclopropylmethyl radical.

2. Preparation and reactions of benzocyclobutenylmethyl magnesium bromide (9). - In contrast to cyclopropylmethyl *Grignard* reagents the synthesis of the cyclobutylmethyl analogues is straightforward and accompanied by only little rearrangement [10] [17]. Ring cleavage does occur at higher temperatures ($> 50^\circ$) in an analogous fashion to the three-membered ring systems [17]. In benzocyclobutenyl derivatives, however, ring opening is observed under mild conditions. Thus, reaction of **8** with magnesium followed by hydrolysis yields *o*-methylstyrene [18]. No evidence for formation of the unrearranged *Grignard* was reported. More recently, the intermediacy of **9** was inferred in the [2+2]-cycloaddition reaction of benzyne with allyl *Grignard* reagent [19]. Again, upon hydrolysis only the ring-opened product, *o*-methylstyrene was isolated together with products derived from [2+4]-cycloaddition.

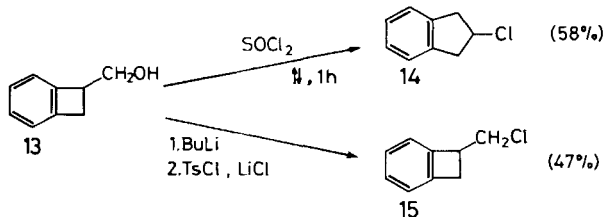
Results and Discussion. The acid **12** is the only product isolated from the reaction of **8** with magnesium turnings in THF at 30° followed by carbonation. The same reaction, at -75° , using a suspension of magnesium in THF prepared as described above yields the acids **11** and **12** in a ratio of 1:1.2 (*Scheme 2*).

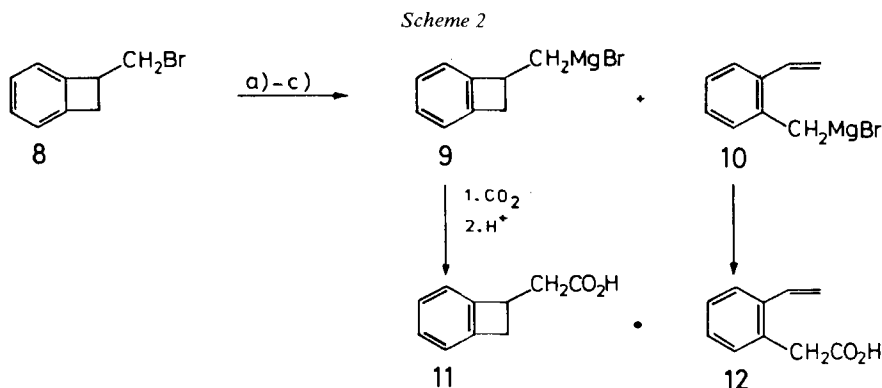
Variation of the reaction conditions¹⁾ did not improve the ratio of **11** to **12** when THF was used as solvent. In diethyl ether, however, **11** was the exclusive product, formed in good yield from the reaction of **8** with the Mg-slurry at -50° . Since organomagnesium rearrangements of this type are likely to occur *via* a single general mechanism with rates consistently lower in THF than in diethyl ether, we conclude that in THF at low temperature **10** is formed *during Grignard* formation rather than *via* rearrangement of **9**. In diethyl ether this rearrangement appears to be suppressed at low temperature and the difficultly accessible **9** can be trapped by reaction with CO_2 .

The formation of the Mg/diethyl ether slurry used in this reaction requires some specification:

Mg-Slurries in diethyl ether. Evaporation of magnesium into ether (-125° , 5×10^{-3} Torr) in the rotating solution reactor does not yield a black Mg-slurry.

¹⁾ Preliminary experiments with benzocyclobutenylmethyl chloride **15** and Mg-slurries led to unsatisfactory results; in the following we have limited our *Grignard* experiments to the bromide **8**. The chloride **15** is accessible from the alcohol **13** *via* the tosylate (method described by *Stork et al.* [20]), whereas reaction of **13** with SOCl_2 yields **14**. This reaction represents a good example of cationic rearrangement of the benzocyclobutenylmethyl skeleton resulting in ring expansion and contrasts with the products obtained *via* radical or anionic rearrangement (see above).





	% 11	% 12	Yield%
a) Mg-turnings/THF 30°	0	100	61
b) Mg-slurry/THF - 75°	45	55	82
c) Mg-slurry/ether - 50°	100	0	80

The ether phase remains colourless and on evaporation of solvent only traces of metal are found. In the absence of a strongly coordinating solvent or reactant, Mg-atoms appear to be reflected from the cold solvent surface and to be deposited mainly on the electrodes and on the poles of the reaction flask. Similar phenomena have been observed in experiments with other metals, particularly Zn [21] and Mn [22].

Mg/ether slurries are, however, readily produced *via* the cocondensation method [4] using the same simple apparatus (see *Exper. Part*). This technique, although more cumbersome since it involves cooling with liquid N₂, gives ready access not only to Mg/ether slurries but also to metal suspensions in less polar solvents such as arenes and alkanes. Magnesium reactions in these media are currently under study in our laboratory.

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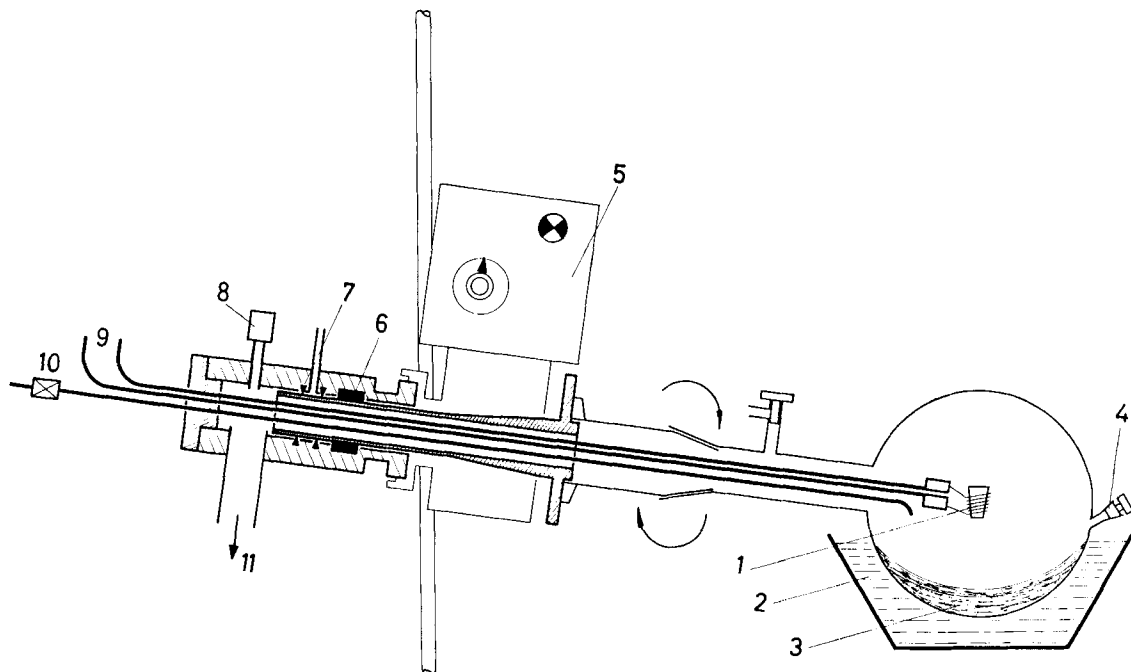
Experimental Part

All manipulations involving Mg-slurries and *Grignard* solutions were carried out in freshly distilled, dry, deoxygenated solvents in an atmosphere of dry N₂ or Ar. IR. spectra were recorded on a *Pye Unicam SP1100* spectrometer. ¹H-NMR. spectra were recorded on *Varian T60*, *XL 100* and *Bruker WH-360 E* spectrometers.

Starting materials. Cyclopropylmethyl bromide (**1**) and benzocyclobutenylmethyl bromide (**8**) were synthesized according to the methods described by *Meek & Rowe* [23] and *Horner et al.* [18], respectively.

Data of 8. - ¹H-NMR. (360 MHz, CDCl₃): 7.22 (*m*, 3 H); 7.09 (*d*, 1 H); 3.88 (*m*, 1 H, H-C(1)); 3.64 (*m*, 2 H, CH₂Br); 3.40 (*d* × *d*, *J* = 14.5 and 5.5 Hz, 1 H, H-C(2)); 2.88 (*d* × *d*, *J* = 14.5 and 2 Hz, 1 H, H-C(2)). Irradiation at 3.88: 3.64 (*AB*-system, *J* = 9.5 Hz); 3.40 (*d*, *J*_{gem} = 14.5 Hz); 2.88 (*d*, *J*_{gem} = 14.5 Hz).

Rotating solution reactor. The rotating solution reactor is based on a design by Timms [5]. The apparatus used in these experiments is schematically presented below with the following major modifications: cylindrical bearings (6) (ensuring stability of rotation); lubricated Viton Symerings (7) (the rotating vacuum seal enables pressures as low as $\sim 10^{-5}$ Torr), Pirani 12 pressure gauge (8) (Edwards) and substrate inlet tube with needle valve (10).



1. Preparation of cyclopropylmethylmagnesium bromide (3). - a) Preparation of Mg/THF-slurry. Mg (Alfa 99.95%, bloc) (1.02 g, 42 mmol) was evaporated over a period of 1.5 h from an alumina crucible (2 ml) (1) with embedded molybdenum wire (diameter 1.2 mm), resistance heated (22 A, 5.2 V) via water-cooled electrodes (9). The magnesium vapour was condensed into a layer of cold THF carried over continuously by rotation (60 rpm, rotatory drive (5) Büchi Rotavapor RE) of the reaction flask (1000 ml) containing 60 ml of solvent (3). The temperature of the cooling bath (petroleum ether) (2) was maintained at -110° . The pressure in the reactor was kept below 10^{-2} Torr during the reaction (via 11) by a 2-stage Hg diffusion pump (30 l s^{-1}) backed by a rotatory pump (Edwards ED 50). On evaporation of magnesium, the solution quickly turned black forming a fine slurry which was used directly for Grignard preparation²⁾.

b) Preparation of the Grignard solution from cyclopropylmethyl bromide (1). The reaction flask containing the Mg-slurry was filled with Ar and an ampoule connected to 10 was charged with a solution of 1 (1.75 g, 13 mmol) in 40 ml of THF. This solution was added dropwise (via 10) to the Mg-slurry over a period of 2 h while maintaining rotation of the flask cooled by a bath of -75° . During the addition a slight underpressure was maintained in the reactor.

c) Carbonation. The Grignard solution prepared in b) was cooled to -120° , the system evacuated, and a stream of CO_2 condensed (via 10) into the solution for 5 min. The reaction mixture was left to warm-up to -30° and treated (via 10) with 10 ml of sat. NH_4Cl -solution³⁾. A large portion of THF

²⁾ Although our experiments were 'one-pot' reactions Klabunde reported that Mg/THF-slurries formed by cocondensation can be taken to dryness and stored under Ar without loss of Mg-activity [4].

³⁾ Care must be exercised in this operation as excess Mg reacts violently with water.

was removed *in vacuo* prior to extraction with ether. Work-up by standard methods yielded 1.01 g (78%) of a malodorous liquid product, consisting of a mixture of cyclopropylacetic acid (**5**) [8] and 4-pentenoic acid (**2**) in a ratio of 11:1 (by $^1\text{H-NMR}$).

Data of 5. - $^1\text{H-NMR}$. (100 MHz, CDCl_3): 11.1 (br. s, 1H); 2.25 (d, 2H); 0.8-1.3 (m, 1H); 0.43-0.65 (m, 2H); 0.08-0.27 (m, 2H). - MS.: 100 (16, M^+ , $\text{C}_5\text{H}_8\text{O}_2$), 84 (28), 55 (100).

d) *Reaction with benzaldehyde: (cyclopropylmethyl)phenyl methanol (6) [24] [25] and (3-buten-1-yl)phenylmethanol (7) [24].* A Grignard solution was prepared as described in b from 1.5 g (11.1 mmol) of **1** at -70° . The mixture was transferred *via* teflon tubing (septum cap at (4); see Fig.) and filtered at low temperature through a glass frit using standard airless techniques [26]. Benzaldehyde (1.12 ml, 11.1 mmol) was added rapidly dropwise at -70° ; the reaction mixture was left to warm-up to 0° , concentrated, treated with conc. NH_4Cl -solution (20 ml) and extracted with ether (3×20 ml). The combined ether phases were washed successively with NaHSO_3 -solution (3 g/10 ml; 2×5 ml), water and brine and dried over MgSO_4 . Ether was removed on a *Rotavapor* and the crude liquid product distilled *i.v.* in a *Kugelrohr* to yield 1.33 g (74%) of a mixture of the alcohols **6** and **7** in a ratio of ca. 4 to 1 (by $^1\text{H-NMR}$). The $^1\text{H-NMR}$. spectrum of **6** was identical to that reported by Trahanovsky *et al.* [25] of the compound prepared by a different route.

e) *Kinetics of ring opening reaction.* A Grignard solution of **3** was prepared and filtered as described in b and c. An aliquot of the solution (ca. 0.1 m) was poured at low temperature onto powdered dry ice under an atmosphere of Ar. The crude acid was extracted, the solution concentrated and treated with an excess of an ethereal solution of diazomethane. GC. analysis (*Carbowax 10%/chromosorb W*; $3 \text{ m} \times 2 \text{ mm}$; 70°) showed a ratio of the methyl esters of acids **5** and **2** of 85 to 15 (retention times 6.3 and 4.5 min respectively; assignment by independent synthesis of **2**). The Grignard solution was then brought to 10° , aliquots (**7**) removed at intervals and treated and analyzed as described above. Peak areas were determined by integration and a median value of 3 injections was taken for the analysis.

2. *Preparation of benzocyclobutenylmethyl magnesium bromide.* - a) Grignard reaction in THF at 30° : *o-Vinylphenylacetic acid (12)*. A solution of the bromide **8** (0.6 g, 3 mmol) in THF (10 ml) was added dropwise and with stirring to magnesium turnings (86 mg, 3.5 mmol) in THF (10 ml). The reaction mixture was poured over powdered dry ice and then processed in the usual way. The crude product was recrystallized to yield **12** (0.3 g, 61%), m.p. $98-100^\circ$ (from hexane). - IR. (CHCl_3): 625w, 922m, 988w, 1245w, 1295m br., 1420m, 1490w, 1630w, 1715vs, 2400-3500m br. - $^1\text{H-NMR}$. (360 MHz, CDCl_3): 10.8 (br. s, 1H); 7.52 ($d \times d$, $J=7$ and 1.5 Hz, 1H); 7.18-7.32 (m, 3H); 6.93 ($d \times d$, $J=17$ and 11 Hz, 1H); 5.65 ($d \times d$, $J=17$ and 1.5 Hz, 1H); 5.34 ($d \times d$, $J=11$ and 1.5 Hz, 1H); 3.72 (s, 2H). - MS.: 162 (42, M^+ , $\text{C}_{10}\text{H}_{10}\text{O}_2$), 147 (13), 132 (9), 117 (100), 116 (29), 115 (55), 91 (30).

b) Grignard reaction in THF at -75° : *Benzocyclobutenylacetic acid (11)*. A Grignard solution was prepared as described in 1b from a Mg-slurry and bromide **8** (1 g, 5.1 mmol) and carbonated at low temperature (see 1c). Work-up yielded 670 mg (81.5%) of a mixture of the acids **11** and **12** in a ratio of 1:1.2 (by $^1\text{H-NMR}$). The two products were separated by fractional crystallization from hexane to yield first 370 mg of **12**, followed by 270 mg of **11**.

Data of 11. M.p. $63-65^\circ$ (from hexane). - IR. (CCl_4): 635w, 711m, 735m br., 1200w, 1220w, 1236m, 1280m, 1300m, 1410m, 1461m, 1714vs, 2400-3400 br., 2926m, 2960m. - $^1\text{H-NMR}$. (360 MHz, CDCl_3): 10.7 (br. s, 1H); 7.05-7.30 (m, 4H); 3.85 (m, 1H, H-C(1)); 3.47 ($d \times d$, $J=14$ and 5 Hz, 1H, H-C(2)); 2.88 ($d \times d$, $J=14.5$ and 2.5 Hz, 1H, H-C(2)); 2.80 (m, 2H, CH_2COOH). - Irradiation at 3.85: 3.47 (d, $J_{\text{gem}}=14$ Hz); 2.88 (d, $J_{\text{gem}}=14$ Hz); 2.80 (AB-system, $J=16.5$ Hz). - MS.: 162 (63, M^+ , $\text{C}_{10}\text{H}_{10}\text{O}_2$), 147 (25), 133 (14), 117 (100), 116 (87), 115 (100), 91 (54).

c) Grignard reaction of **8** *via Mg-slurry/ether*. The reaction flask (2 l) was evacuated to below 10^{-3} Torr, then rotated (5) (60 rpm) and placed in a liquid N_2 -bath ((2), see Fig.). A dropping funnel, connected to the inlet (10) was charged with ether (60 ml). Evaporation of Mg (0.5 g) was started and ether was concomitantly cocondensed into the reactor over a period of 45 min. During the cocondensation the pressure was kept below 10^{-2} Torr. Subsequently, the flask was filled with Ar, the cooling bath brought up to -50° and the bromide **8** (0.87 g, 4.4 mmol) in 30 ml ether added in the usual way over 1.5 h. Proceeding with carbonation and work-up as described in 1c yielded 0.57 g (80%) of pure **11**.

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