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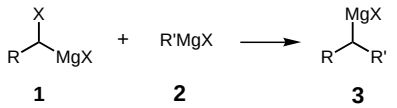
[19] The estimated coherent length of 6–8 is in accordance with other extensive measurements including excitation-wavelength- and porphyrin-number-dependent resonance Raman and laser-intensity dependent decay.[12]

Formation of Rearranged Grignard Reagents by Carbenoid-C-H Insertion**

Reinhard W. Hoffmann,* Oliver Knopff, and Andreas Kusche

Grignard compounds are standard carbanion reagents of classical organic synthesis. Most methods to generate Grignard reagents rely on the reaction of metallic magnesium with alkyl or aryl halides and are, hence, prone to the intermediate generation of free radicals and to side reactions caused by the latter. There are only few routes to alkylmagnesium reagents that are devoid of this risk.[1] One is the carbenoid–homologation reaction,[2] in which an α-haloalkylmetal Grignard reagent **1** is treated with another organometallic reagent, for example, a second Grignard reagent **2**, to generate a new Grignard reagent **3** by C–C bond formation.



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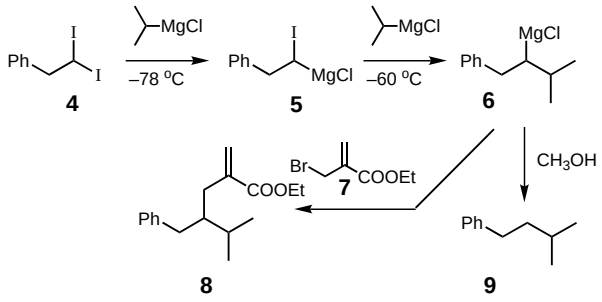
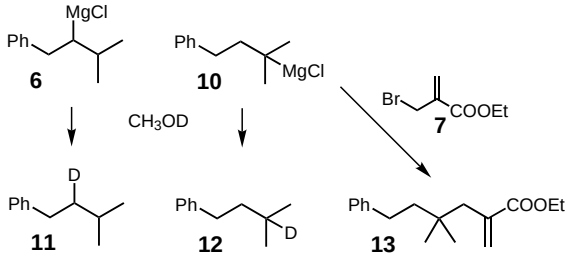
During model studies on this reaction we made some unexpected findings, which we report here. At first, the reaction of the diiodoalkane **4** with 3 equivalents of isopropylmagnesium chloride proceeded uneventfully in THF: The first equivalent of the Grignard reagent generated over one hour[3] the α-iodoalkylmagnesium compound **5**, which reacted slowly at $-78\,^{\circ}C$ and rapidly at temperatures up to $-60\,^{\circ}C$ with a further equivalent of isopropylmagnesium chloride to give the desired Grignard reagent **6**. The latter may be



trapped, for example, by the α-bromomethylacrylate **7** at -90 to $-78\,^{\circ}C$ over 30 min to give the adduct **8** in 79% yield (accompanied by 12% of a side product later identified as **13**). Protonation of the Grignard reagent **6** with methanol led to the hydrocarbon **9** in 92% yield.

Trapping of **6** with CH_3OD was therefore expected to give the deuterated hydrocarbon **11**. Inspection of the product by ^{2}D-NMR spectroscopy revealed, however, the presence of the isotopomer **12** in about 10% yield. This pointed to the formation of the tertiary Grignard reagent **10** as the immediate precursor of **12**.



This "side reaction" surprisingly became the main process when the reaction was carried out in diisopropyl ether or in diethyl ether as solvent (see Table 1). When the overall reaction was carried out in diethyl ether the "rearranged" Grignard reagent **10** could indeed be trapped by the α-bromomethylacrylate **7** to give **13** in 79% yield alongside **8** in 12% yield.

Similar observations were made when the diiodo compound **14** was treated with three equivalents of isopropylmagnesium bromide followed by trapping with allyl iodide. While when the reaction was carried out in THF as solvent the product **15** predominated over **16** by 10:1 (55% yield), the "rearranged" product (**16**) was again the main product (58%

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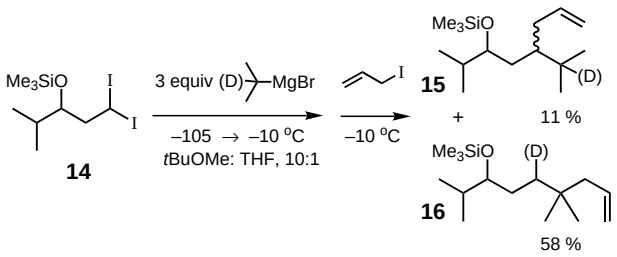
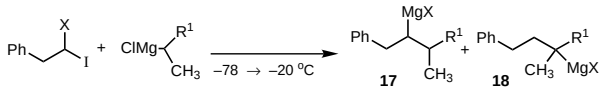


yield) using a solvent mixture rich in *tert*-butyl methyl ether (*t*BuOMe/THF = 10/1). When this reaction was repeated with $(CH_3)_2CDMgBr$ the deuterium atom could be shown by ^{13}C NMR spectroscopy to be located at the indicated position in **16**. At first glance, this looks like a rearrangement of a secondary Grignard reagent of the type **6** to a tertiary Grignard reagent of the type **10**, a process, in which the magnesium and a hydrogen atom swap places. This process, on the other hand, appeared highly unlikely since it is energetically unfavorable! Indeed, when a solution rich in secondary Grignard reagent **6** was generated in THF and the solvent was changed to diethyl ether the amount of the "rearranged" tertiary Grignard did not increase. Vice versa, when a solution rich in **10** was generated in diethyl ether, the Grignard reagent **10** was not converted to **6** on change of the solvent to THF. Therefore the Grignard reagents **6** and **10** do not interconvert, rather it appears that the Grignard reagents **6** and **10** are formed from the α-iodoalkyl Grignard reagent **5** and isopropylmagnesium chloride by two independent and concurring pathways, which show a different solvent dependence of the reaction rate.

Further experiments show that the tendency to form the "rearranged" Grignard reagent **10** depends not only on the solvent, but also on the nature of the halogen in the α-haloalkyl Grignard reagents **1** and on the nature of the second Grignard reagent **2** (Table 1). Changing the halogen in **1** from iodine to bromine or chlorine increases the amount of the unexpected product **12**. The more electrophilic (reactive) the carbenoid **1**, the higher the proportion of **12** that is formed. Regarding the Grignard reagent **2** used to initiate the reaction, the tendency to form the unexpected product **12** is clearly higher with isopropyl than with ethyl Grignard as the reaction partner.

Table 1. Formation of rearranged Grignard reagents.

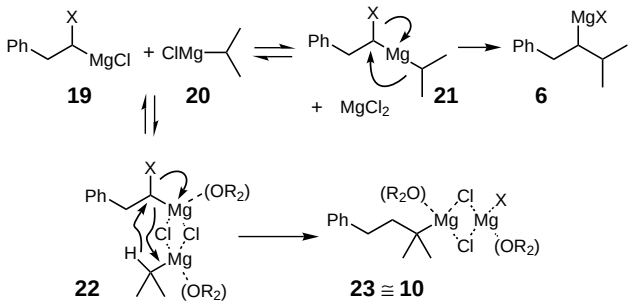


X	R^1	Solvent	**17**:**18**[a]	Yield [%] of deuterated hydrocarbons
I	Me	THF	90:10	92
		$MeOCMe_3$	31:69	82
		Et_2O	25:75	91
		iPr_2O	19:81	93
Br	Me	THF	18:82	85
		Et_2O	34:66	65
Cl	Me	THF	23:77	95
		Et_2O	35:65	81
I	H	THF	100:0	72
		Et_2O	100:0	71
Br	H	THF	89:11	74
		Et_2O	85:15	72
Cl	H	THF	97:3	76
		Et_2O	94:6	81

[a] Ratio determined by ^2H NMR spectroscopy after quenching with CH_3OD.

For the formation of the "expected" Grignard reagent **6** a conventional mechanism can be proposed, for example similar to the reaction of α-haloalkyl-boronates with Grignard reagents,[4] involving a dialkylmagnesium intermediate **21**. When the dialkylmagnesium species **21** was generated in diethyl ether from the α-iodoalkylmagnesium compound **5** and two equivalents of isopropyllithium,[5] only the regular substitution product **6** was formed (70%).

It is therefore unlikely that the dialkylmagnesium compound **21** is a precursor of the unexpected product **12**. We rather propose that the tertiary Grignard product **10** is derived from a mixed aggregate **22** that is formed from the two Grignard reagents **19** and **20**. The formation of such a halide-bridged aggregate should be favored in less coordinating solvents such as diethyl ether or *tert*-butyl methyl ether.[1] Moreover, it is known that lithium carbenoids R–CHX–Li are stabilized by THF, whereas they decompose much more rapidly in diethyl ether.[6] The tendency to generate carbenes or at least the electrophilic reactivity of carbenoids is apparently increased in these nonpolar solvents. We therefore propose that the carbenoid moiety in **22** undergoes an intra-aggregate C–H insertion (direct or indirect) into the α-C–H bond of the second Grignard reagent **20** to generate the product aggregate **23**, that is the tertiary Grignard reagent **10**.



This proposed mechanism is in line with the finding that the tertiary α-C–H bond in the isopropyl Grignard reagent should be more reactive towards electrophilic attack than the secondary α-C–H bond in an ethyl Grignard reagent. Furthermore, it is in accord with the effect exerted by the halogen atom in the α-haloalkyl Grignard reagent **1**, that is the iodo compounds are less inclined to undergo carbenoid insertion reactions than the other halo compounds.

While these mechanistic speculations may be superseded by other explanations, we have nevertheless established that the carbenoid homologation reaction may be diverted to a novel process that leads to a "rearranged" Grignard reagent.

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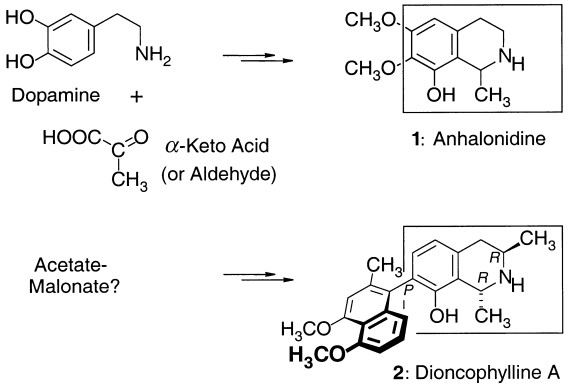
A New Biosynthetic Pathway to Alkaloids in Plants: Acetogenic Isoquinolines**

Gerhard Bringmann,* Michael Wohlfarth, Heiko Rischer, Matthias Grüne, and Jan Schlauer

Tetrahydroisoquinoline alkaloids constitute a large family of more than 2500 known,[1] mostly pharmacologically important, secondary plant metabolites—from simple 1-alkylisoquinolines like anhalonidine[2] (**1**, Scheme 1) to complex polycyclic benzylisoquinolines like the analgesic morphine.[3] Until now, it has been generally assumed that they are all derived from aromatic amino acids such as tyrosine through a common biosynthetic key step, the Pictet – Spengler condensation of 2-arylethylamines, like dopamine, with aldehydes (or α-keto acids). The ultimate structural diversity of isoquinolines found in nature[4] originates from the variation of the aldehyde precursor and subsequent transformations of the tetrahydroisoquinoline initially formed.



Scheme 1. Known biogenetic origin of tetrahydroisoquinolines such as anhalonidine (**1**) by Pictet – Spengler condensation[2] and the proposed novel pathway to dioncophylline A (**2**).

The structures of dioncophylline A (**2**, Scheme 1) and other naphthylisoquinoline alkaloids,[5] however, do not fit into this, hitherto, generally applicable biosynthetic scheme. In this paper, we report the discovery of a fundamentally different biosynthetic pathway to 1,2,3,4-tetrahydroisoquinoline alkaloids in higher plants; the entire carbon skeleton of dioncophylline A from *Triphyophyllum peltatum* (Dioncophyllaceae)[6] is unambiguously demonstrated to be synthesized by an acetate – polymalonate pathway.

Hints at the chemical plausibility of an acetogenic origin for naphthylisoquinoline alkaloids had already been obtained from early biomimetic polyketide cyclization reactions,[7] which had led to the efficient synthesis of both molecular parts from identical precursors and, thus, to first total syntheses of these compounds.[6]

Direct-feeding experiments with addition of [^{14}C]- and [^{13}C]-labelled acetate and malonate to cultivated or wild plants of the Ancistrocladaceae family did not yield significant incorporation rates. Cell cultures of *Ancistrocladus heyneanus* (Ancistrocladaceae) produced large amounts of naphthoquinones and tetralones[8] related to the naphthalene part of the alkaloids, but not the alkaloids themselves in sufficient quantities. More recently, we succeeded in establishing cell cultures of *T. peltatum* for the first time.[9] These proved to be capable of forming both naphthoquinones *and* naphthylisoquinolines, predominantly dioncophylline A (**2**).

The presumed precursor acetate was fed to these cultures in [$^{13}C_2$]-labelled form. After a previously optimized incubation time, **2** was isolated and investigated by high-field NMR spectroscopy.[10] The ^{1}H-decoupled ^{13}C NMR spectrum recorded on a 600 MHz system showed complex signal patterns. Due to overlapping signals and baseline noise obscuring the ^{13}C satellites, however, it was not possible to draw final conclusions. We addressed these problems by using the 2D INADEQUATE[11] experiment for the identification of direct C–C connectivities.[12] The signal-to-noise ratio was substantially improved by acquiring the data with a cryoprobe[13] on a 500 MHz NMR spectrometer.

The obtained spectrum (Figure 1) only displays clear pairwise C–C correlations which originate from the acetate units incorporated intact, without bond cleavage, into dioncophylline A (**2**).[14] Closer examination led to the conclusion that the entire carbon skeletons of both molecular halves of **2** are derived from acetate and that they exhibit an identical polyketide folding pattern with respect to the corresponding isocyclic rings. Furthermore, it is obvious that in both molecular halves decarboxylations occur at homologous positions, leaving the ultimate 1-methyl carbon atom and 3′-C.[15] These findings unambiguously prove our biosynthetic postulate[6] of the acetogenic origin of these alkaloids.

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