Advances in the Krapcho decarboxylation

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This review provides a brief description of the Krapcho dealkoxycarbonylation and its recent applications in the synthesis of organic compounds and natural products. The general features of the Krapcho reaction, its mechanism and several modifications of the Krapcho reaction are discussed.

Keywords: decarboxylation, β-vetivone, cassine, β–silylethanol, vetiselinene

It was observed by Krapcho *et al.*[1,2] that geminal diethoxy compound **1** suffer-dealkoxycarbonylation on heating with sodium cyanide (NaCN) in dimethylsulfoxide (DMSO) yielding the monoester **2** in high yield. The discovery of this interesting transfor-mation[3] occurred serendipitously during the attempted conversion of the ditosylate **3** to the corresponding dinitrile **4** in DMSO with excess potassium cyanide at 90 °C. The resulting product was identified as the demethoxycarbonylated dinitrile **5**, not the expected compound **4**.

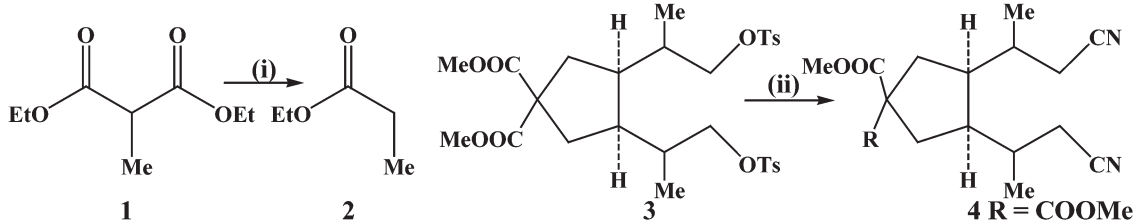
Later it was found that the dealkoxycarbonylation[4] of diesters can be accomplished by heating with NaCl in wet DMSO at temperatures of 140–186 °C. This interesting modification avoided the hazardous use of NaCN.The dealkoxycarbonylation of β-keto esters, α-cyano esters, malonate esters and α-alkyl or arylsulfonyl esters to the corresponding ketones, nitriles and alkyl or arylsulfones is known as *Krapcho dealkoxycarbonylation* or *Krapcho decarboxylation* or *Krapcho reaction.*

1. Modifications

Several modifications have been made to the original method for the Krapcho decarboxylation.

Some of these are described below.

A variety of mono and disubstituted diethyl malonates β-keto esters and α-cyanoesters have been decarboxylated in excellent yield by NaCl in wet DMSO. The effect of the NaCl is catalytic as has been observed from the study of the decarboxylation of a large number of esters. The decarboxylation process has been successfully accomplished using alkali metal fluorides, bromides, chlorides, sodium azide, sodium phosphate and hydrated lithium acetate in wet DMSO. In addition Triton B (benzyl trimethylammonium hydroxide) in wet DMSO has been utilised[5] to achieve the de-ethoxycarbonylation of some α-sulfonyl malonate esters to obtain the corresponding α-sulfonyl esters in good yield. The α-alkyl substituted malonic esters undergo de-ethoxycarbonylation with Triton B in DMSO at 50–80 °C affording the corresponding esters in satisfactory yield. The Krapcho decarboxylation of malonic esters can be efficiently carried out under solvent-free solid: liquid phase transfer catalytic condition[6] and a microwave irradiation in a focussed-open vessel microwave digestion system. It is pertinent to mention that microwave heating accelerates decarboxylation[7] (15 min, 80–98% isolated yield) of malonic acids in water by employing a microwave



Reagents: (i) NaCN, DMSO; (ii) DMSO, KCN, 90ºC

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autoclave and higher reaction temperature and power (190 °C; 800 watts). Not only DMSO, but other aprotic solvents such as dimethylacetamide (DMA), hexamethyl-phosphortriamide (HMPT) and dimethylformamide (DMF) have been frequently utilised to accomplish decarboxylation.[1,2]

2. General features

(a) The Krapcho decarboxylation is general for methyl or ethyl esters of carboxylic acids which have an electron withdrawing groups (–CO_2 alkyl, –CN, –CO–alkyl, SO_2–alkyl, attached).

(b) The one-pot procedure eliminates the need for the traditional method of the conversion of geminal diester to monoester which involves hydrolysis (acidic or basic) followed by thermal decarboxylation of the diacid and esterification of the final carboxylic acid.

(c) As the reaction condition is neutral, acetals, esters, lactams and lactones, which are sensitive either to acids or bases, the reaction and thus hydrolysis or rearrangements induced by acid or base are avoided.

(d) Double bonds are not isomerised and in most of the cases labile stereocentres are not racemised.

(e) The chemoselectivity and stability of functional groups in this context are noteworthy.

(f) The selection of reaction condition depends on the substitution pattern of the substrate.

(g) Monosubstituted malonic esters are dealkoxycarbonylated in a hot dipolar aprotic solvent containing at least one equivalent of water but disubstituted malonic esters are onlydealkoxycarbonylated in the presence of at least one equivalent of a salt (*e.g.*, KCN, LiCl, *etc*.) in wet DMSO at reflux. If the substrate has at least one proton at the α-position dealkoxycarbonylation can be achieved with wet DMSO at reflux in the absence of a salt.

(h) Methyl esters are dealkoxycarbonylated faster than the ethyl esters.

(i) Vinylogous β-ketoesters are also dealkoxycarbonylated in high yield.

(h) De-*tert*-butoxycarbonylation occurs more readily[8] than the de-ethoxycarbonylation in water/Me_2SO in the absence of salts such as LiCl. Thus this method is important for the easy chemoselective removal of tertiary ester groups using only water in dipolar aprotic solvents.

3. Mechanism

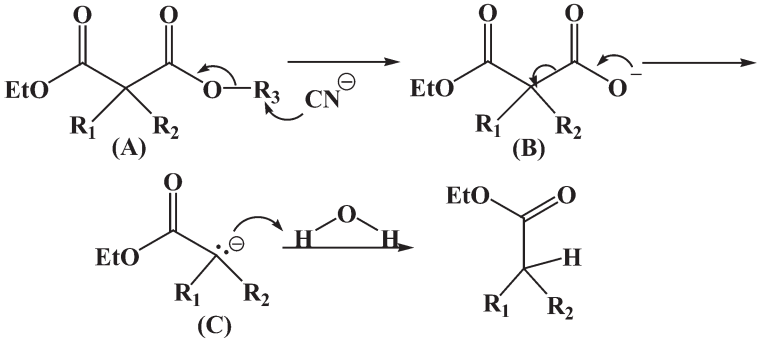
The mechanism of the Krapcho decarboxylation[9] is dependent on the structure of the substrate ester and the type of anion used. The decarboxylation probably proceeds *via* a nucleophilic catalytic mechanism. In the case of the α,α-disubstituted ester (A) (especially methyl esters) the anion CN^- from the salt NaCN attacks the alkyl group of the disubstituted ester in a S_N2 type fashion yielding an intermediate (B) whose decarboxylation forms the intermediate (C) which is protonated by water to yield the product (Scheme 1).

In the case of α-monosubstituted esters (D) (Scheme 2), the anion CN^- attacks the carbonyl group to form a tetrahedral intermediate (E) which breaks down to the carbanionic intermediate (F) as in Scheme 1 and a cyanoformate (G) which is hydrolysed to give carbon dioxide and alcohol. The intermediate (F) is similarly protonated to provide the decarboxylated product.

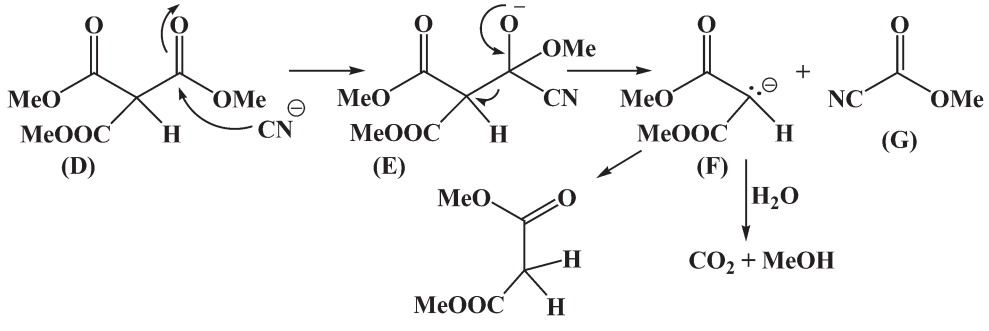
4. Synthetic applications

The Krapcho decarboxylation has received extensive application in organic synthesis and synthesis of natural products.[1,2,10] In the present review, we cite a few examples to indicate the importance of the Krapcho reaction.

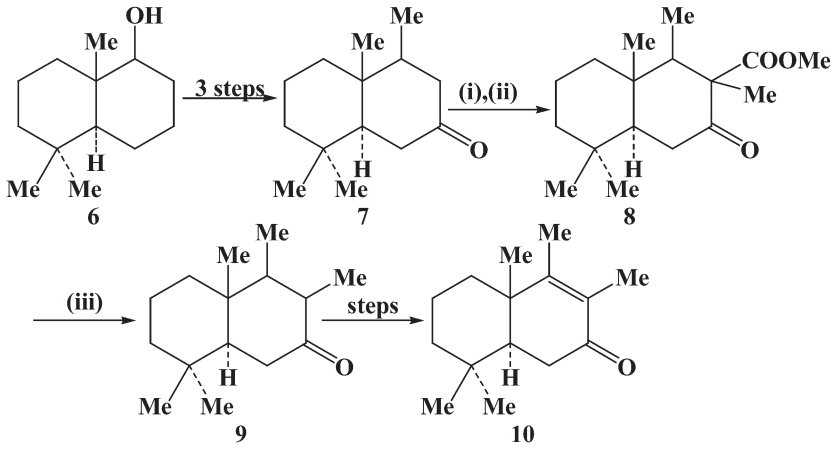
In order to achieve the synthesis of sesquiterpene (±)-drim-8-en-7-one **10**, Banerjee and coworkers[11] converted the previously reported[12] alcohol **6** into the ketone **7** in three steps (dehydration, oxidation and conjugate methylation). Ethoxycarbonylation of the ketone **7** followed by methylation afforded



Scheme 1

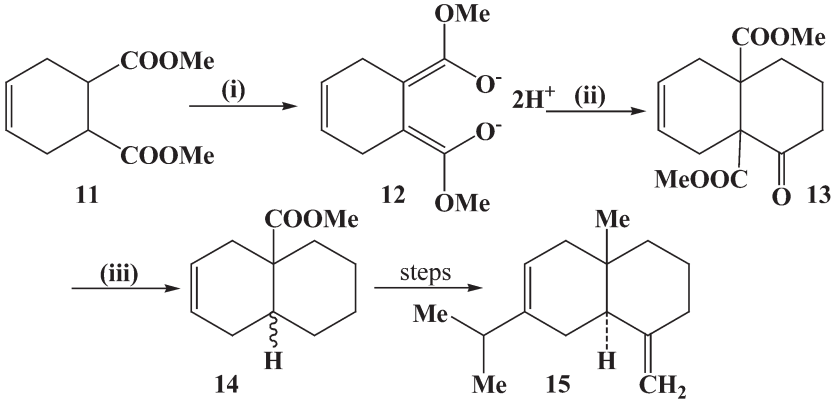


Scheme 2



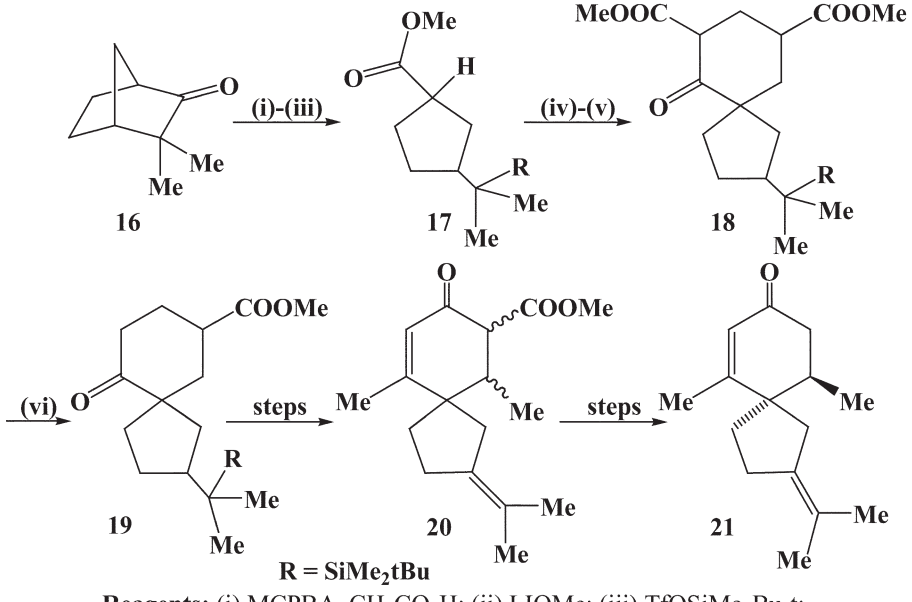
Reagents: (i) $CO(OEt)_2$, NaH; (ii) MeI; (iii) LiCl, DMSO, H_2O

Scheme 3



Reagents: (i) LDA; (ii) $Br(CH_2)_3COOEt$; (iii) NaCl, DMSO, 16ºC

Scheme 4

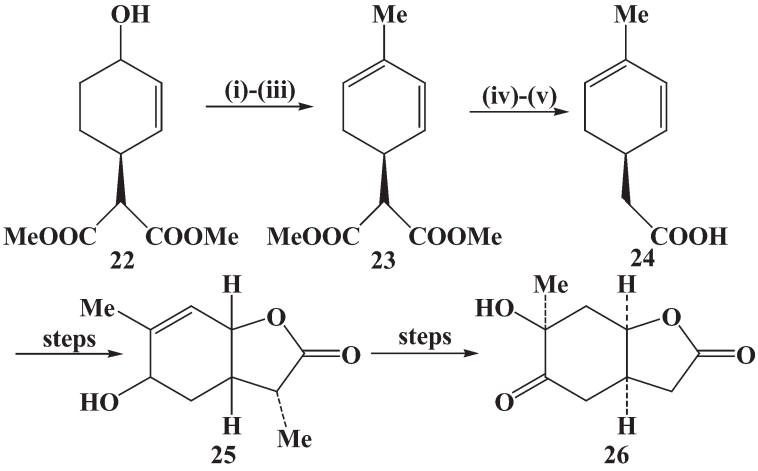


Reagents: (i) MCPBA, CH_3CO_2H; (ii) LIOMe; (iii) $TfOSiMe_2Bu$-t; (iv) LDA; (v) CH_2=CH-COOMe; (vi), NaCl, DMSO

Scheme 5

the keto-ester **8**. It was subjected to a Krapcho decarboxylation to obtain **9** which was finally converted into the sesquiterpene drim-8-en-7-one **10** (Scheme 3).

The Krapcho decarboxylation was applied by Garratt and Porter[13] during the synthesis of the sesquiterpene vetiselinene **15**. The anion **12**, prepared from the ester **11** (Scheme 4), on treatment with ethyl-4-bromo-butanoate gave the diester **13** in 40% yield. Krapcho decarboxylation with NaCl and Me_2SO afforded the keto-ester **14** which proved to be a potential intermediate for the synthesis of vetiselinene **15**.



Reagents: (i) CrO_3-Py, CH_2Cl_2; (ii) LDA, Tf_2NPh, THF; (iii) CuI (cat), MeMgBr, THF; (iv) NaCN, wet DMSO; (v) KOH, MeOH

Scheme 6

Posner and Shulman-Roskes,[14] used the Krapcho-decarboxylation reaction in order to accomplish a new synthesis of the sesquiterpene (±) β-vetivone **21**. The synthetic route is depicted in Scheme 5.

The cyclopentane carboxylate ester **17 was** prepared from 3,3-dimethylnorcamphor **16** in three steps, and subjected to the Michael–Dieckmann cyclisation to obtain the spirobicyclic compound **18**. Krapcho decarboxylation produced the cyclohexanone **19** which was converted into β-ketoester **20**. The conversion of this compound into β-vetivone **21** was accomplished by a Krapcho decarboxylation.

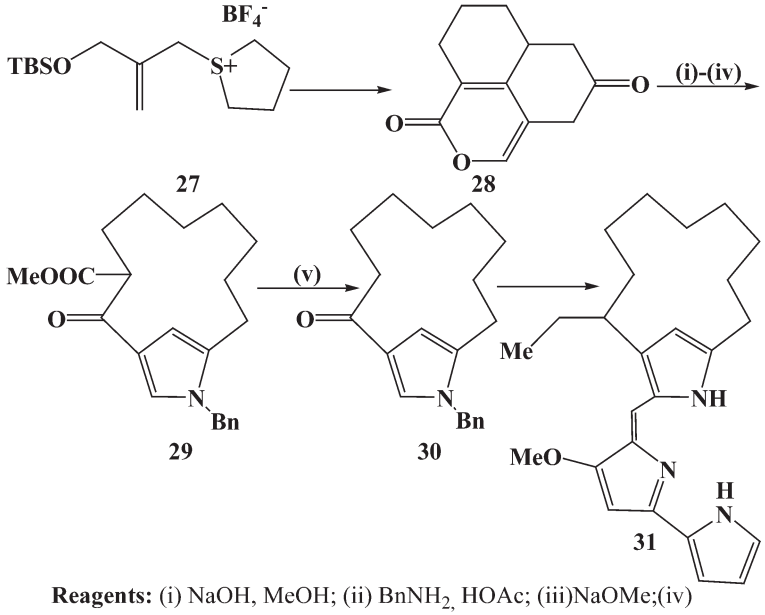
The importance of a Krapcho decarboxylation has been described by Backvall and collaborators[15] in their efforts to develop an enantioselective route to paeonilactone A (Scheme 6).

The allylic alcohol **22** was converted to 2-methyl-1,3-diene **23** in three steps (oxidation, transformation to triflate and copper-catalysed Grignard coupling). Krapcho decarboxylation and subsequent alkaline hydrolysis produced the diene acid **24** which was converted into the lactone **25**. It was utilised for the synthesis of paeonilactone A **26** which has been isolated from paeony root (*Paeonia Albiflora* Pallas).[16]

A Krapcho decarboxylation was also used during the development of a new approach to the synthesis of the immunosuppressive alkaloid metacycloprodigiosin **31** and its functional derivatives.[17] The α-pyrone **28**, prepared from the sulfonium salt **27**, was converted into the compound **29** in four steps (Scheme 7). The Krapcho decarboxylation of compound **29** with NaCl, in aq. DMSO at 180 °C led to the formation of compound **30** which is a potential intermediate for the synthesis of metacycloprodigiosin **31**.

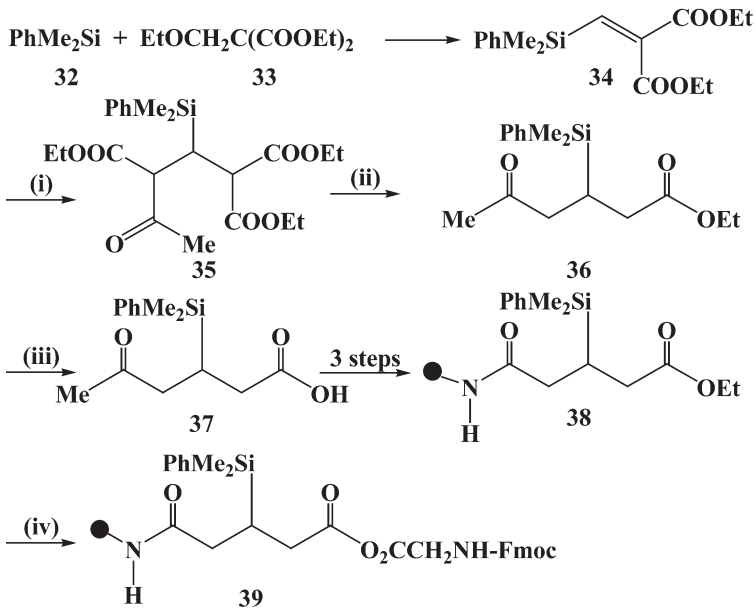
The application of the Krapcho decarboxylation can be seen in the synthesis of aa β-silylethanol anchoring group on an aminomethylated Merrifield resin developed by Iyer and Ghosh,[18] as shown in Scheme 8.

The unsaturated diester **34**, prepared from dimethyl(phenyl)-silyllithium **32** and diethyl ethoxymethylenemalonate **33** was made to react with ethyl acetoacetate in the presence of a catalytic amount of diethylamine gave the triester **35**. Krapcho decarboxylation provided the ester **36** in 61% overall yield. On alkaline hydrolysis this provided the keto-acid **37** in quantitative yield which was then utilised to prepare a resin bound β-silyl alcohol **38** in three steps (reaction with aminomethylated Merrifield resin, Baeyer–Villiger oxidation and



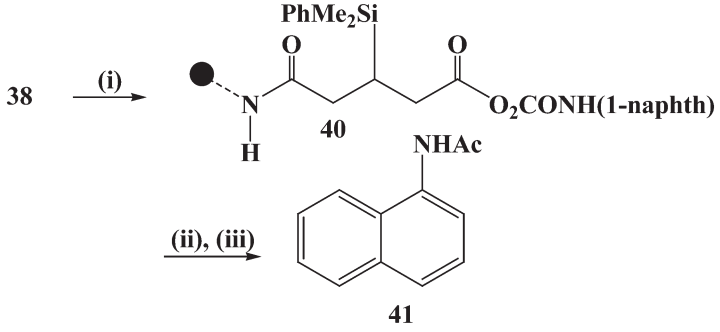
Reagents: (i) NaOH, MeOH; (ii) $BnNH_2$, HOAc; (iii)NaOMe;(iv) PO_4NRuO_4; (v) NaCl, aq.DMSO, 180 ºC

Scheme 7



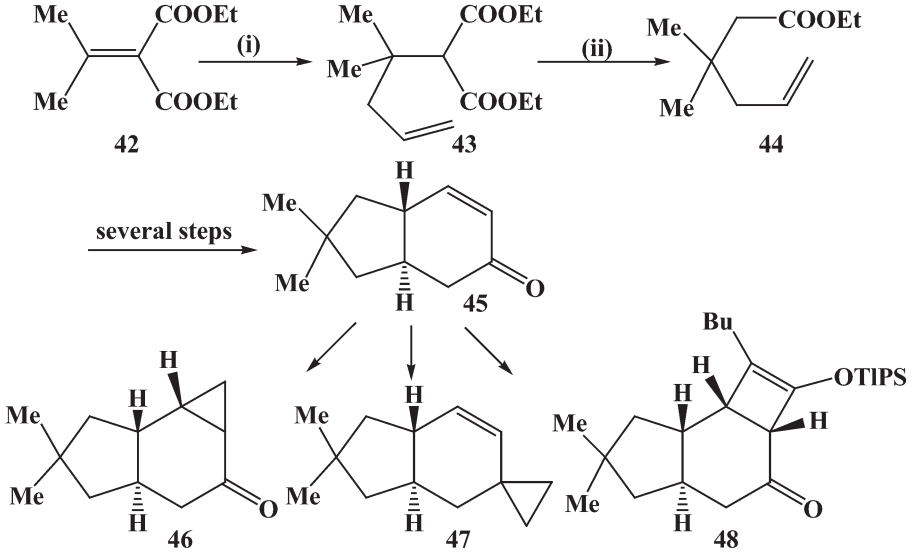
Reagents: (i) EtO_2CCH_2COMe, Et_2NH, rt; (ii) NaCl, DMSO, H_2O; (iii) NaOH, MeOH, H_2O;(iv) Fmoc-Gly,DIC,1-OHBt, DMAP, 0°C to rt.

Scheme 8



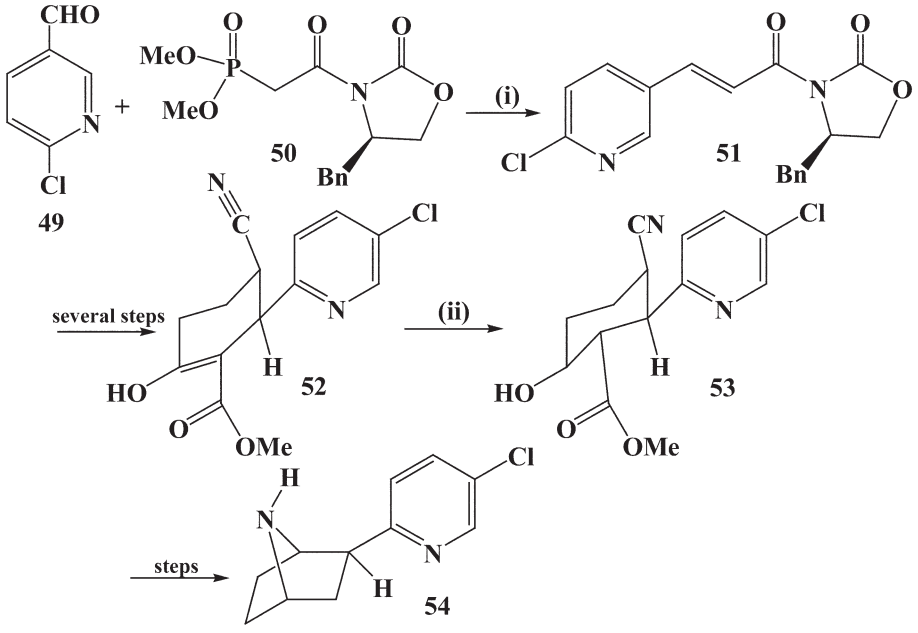
Reagents: (i) 1-naphthylisocyanate, DMAP, Et_3N, $CHCl_3$, reflux; (ii) $TBAF.3H_2O$, CH_2Cl_2; (iii) Ac_2O, Py, CH_2Cl_2

Scheme 9



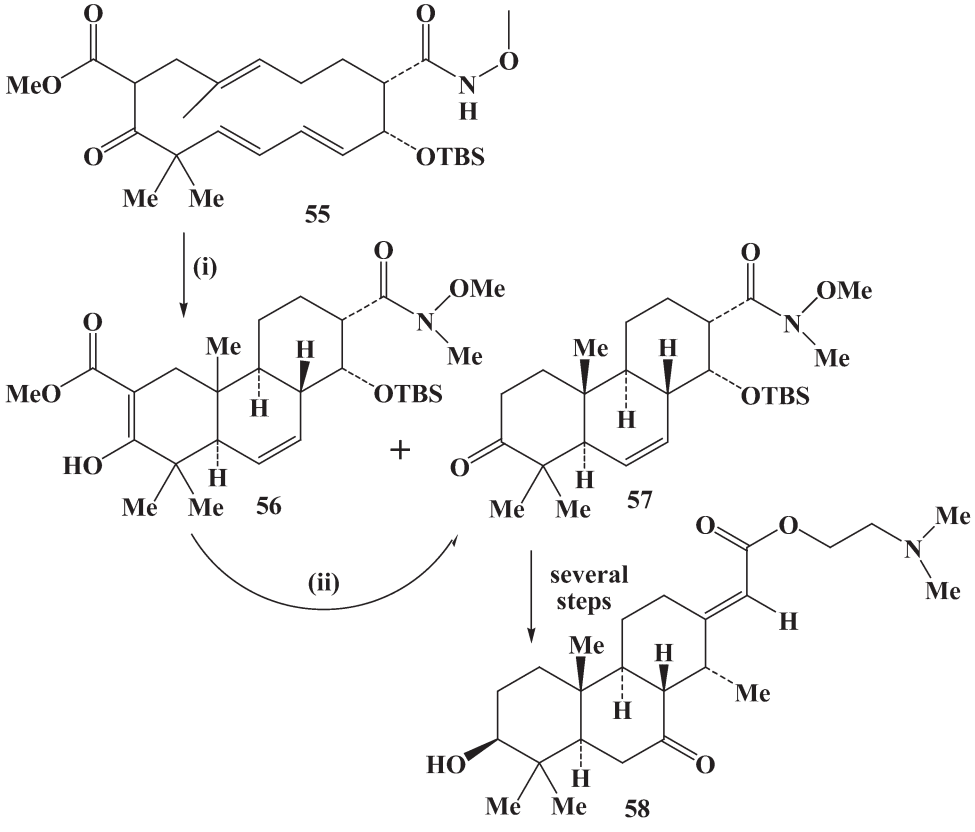
Reagents: (i) allylMgBr, CuI; (ii) Δ, DMSO

Scheme 10



Reagents: (i) LiCl, i-Pr_2EtN, MeCN; (ii) DMSO, H_2O

Scheme 11



Reagents: (i) Δ, 123°C; (ii) DMSO, H_2O

Scheme 12

hydrazinolysis in N-methylpyrrolidone). The alcohol **38** was coupled with N-Fmoc-Gly to yield the resin **39**. Similarly the alcohol **38** was reacted with 1-naphthylisocyanate to obtain the resin bound carbamate of 1-naphthylamine **40**. The cleavage of 1-naphthylamine **40** was achieved with 0.1M TBAF in dichloromethane. It was analysed and characterised as its acetate **41** (Scheme 9).

It can be seen that the synthesis of a β-silylethanol anchoring group on an aminomethylated Merrifield resin has been realised from 3-silyl-5-oxohexanoic acid **37** whose synthesis was easily accomplished by using the Krapcho decarboxylation.

The utility of the Krapcho decarboxylation in synthesis of the cycloenone **45** can be seen in the context of the synthesis

of *trans*-fused sesquiterpenoid analogues by zirconocene-mediated metallo-ene reaction.[19] This proved a potential intermediate for the preparation of sesquiterpene analogues with unnatural *trans*-[3.4.0]bicyclononane skeleton. The synthetic approach is described in Scheme 10.

The conjugate addition of alkylmagnesium bromide to the commercially available malonates **42** yielded **43** in 90% yield which on being subjected to aKrapcho decarboxylation in wet DMSO produced the ester **44** in 60% yield. Its conversion into the *trans*-fused bicyclo cycloenone **45** was achieved in several steps. The cycloenone served as a building block for the synthesis of the *trans*-marsmane **46** (53%), *trans*-illudane **47**(24%) and *trans*-protoilludine **48** (44%) skeleton.

The importance of the Krapcho decarboxylation has been described by Evans and collaborators[20] during the synthesis of the alkaloid (+)-epibatidine **54**, an alkaloid isolated from the skin of Ecuadorian frog *Epibatidores tricolour.* The synthetic route is shown in Scheme 11.

The aldehyde **49** was reacted with the phosphonate **50** to obtain the acyl oxazoldinone dienophile **51** in 81% yield. This was converted in several steps into the nitrile **52** which was isolated exclusively as the enol tautomer in 81% yield. Krapcho decarboxylation of **52** afforded the ketone **53** in 99% yield which was thenconverted into (–)–epibatidine **54** in 95% yield.

Deslongchamps and collaborators[22] have illustrateded the importance of Krapcho decarboxylation in the context of the synthesis of (+)-cassaine **58** via a transannular Diels-Alder reaction[21]. (+)-Cassaine is a nonsteroidal inhibitor of Na^+, K^+ -ATPase that is known to possess a pharmacological action similar to that of the digitals glycosides such as digitoxin. The synthetic route of (+)-cassaine is depicted in Scheme 12.

The previously decribed[23] macrocycle **55** on being heated at 123 °C in a sealed tube afforded the tricycle **56** and the decarboxylated derivative **57**. The tricycle **56** with DMSO, H_2O (Krapcho decarboxylation) at 150 °C yielded **57** in high yield. The transformation of **57** into cassaine **58** involved several further steps.

5. Conclusions

This review has focussed on the importance of the Krapcho decarboxylation in the synthesis of natural products. It has only selected some organic compounds whose decarboxylation has provided important intermediates for transformation into natural products. It can be concluded that in future, the Krapcho decarboxylation will be used to synthesise futher intermediates for natural and non-natural products. This review has not discussed all the recent examples on Krapcho decarboxylation but it is worthwhile considering the articles[24–26] which describe the application of Krapcho decarboxylation. We hope that the present review will attract the attention of the readers who are actively engaged in organic synthesis, especially of natural products.

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