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Haller–Bauer Reaction Revisited: Synthetic Applications of a Versatile C–C Bond Scission Reaction

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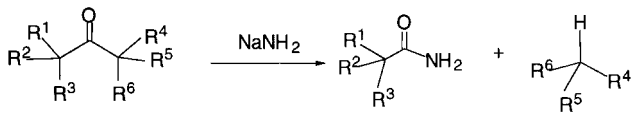
1. Introduction

The base-induced cleavage of non-enolisable ketones leading to a carboxylic acid derivative and a neutral fragment in which the carbonyl group is replaced by a hydrogen, is referred to as the Haller–Bauer (HB) reaction (Eq. (1)). This C–C bond cleavage reaction was first discovered by Semmler[1] in 1906, during his classical studies on the degradation of the monoterpene fenchone, which on treatment with sodamide furnished a cyclopentanecarboxylic acid amide (Eq. (2)). Haller and Bauer[2] followed up on this novel observation and explored its generality employing a variety of relatively simple aliphatic and aromatic ketones. In this early phase, concern was mainly to study the mode of cleavage in simple aliphatic and aromatic ketones (Eqs. (3) and (4)) and the reactions were traditionally carried out in sodamide in boiling benzene. Although this simple C–C bond cleavage reaction came to light at the beginning of this century and early work had firmly demonstrated its preparative utility, interest in the reaction has remained fairly low key. Indeed, the first comprehensive review[3] on the subject, which appeared half a century later in 1957, had less than 100 references. However, the 1960s saw a revival of interest in the HB cleavage as a result of the contributions of Gassman et al.,[4,5] who systematically investigated the C–C bond cleavage reaction in several norbornanone derivatives and also explored various reaction media to impart preparative efficiency to this reaction. These efforts were followed by extensive and incisive studies by Paquette et al.[6–13] on the regio- and stereoselectivity of the HB cleavage, which aided a clearer mechanistic understanding of the reaction and were essential for its applications in modern synthesis. Gilday and Paquette[14] have reviewed their own extensive investigations and those of others on the steric course of the HB reaction.



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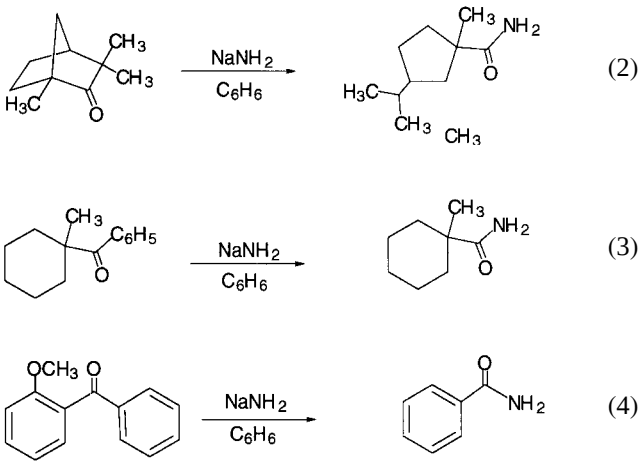
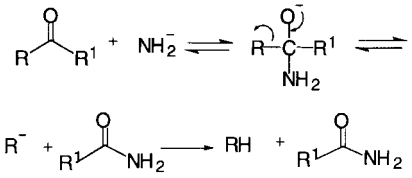


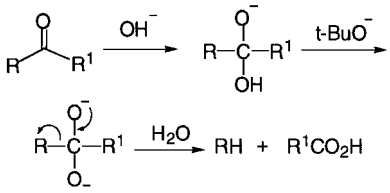
The developments involving improvements in preparative aspects and the predictability of stereochemical outcome have rekindled interest in the HB reaction. In addition, the fact that C–C bond cleavage can be affected in a range of ketones, on simple exposure to base, makes this reaction unique, and amenable to varied synthetic applications. In some respects, the promising synthetic possibilities with the HB cleavage reaction remain to be adequately harnessed and our intention in preparing this review is to summarise the developments thus far and stimulate fresh activity around this classical reaction of an earlier era. It is hoped that this effort will serve a useful purpose in drawing the attention of synthetic chemists to explore successfully the latent potential of this protocol in their synthetic procedures with complex organic molecules.

2. Reaction Conditions and Mechanism

The initial reaction conditions employed for the HB cleavage were sodamide in boiling benzene or toluene. Subsequently, it has been reported that yields in the HB reaction employing classical sodamide conditions can be substantially improved either in the presence of DABCO[15] or by removing the toluene-soluble impurities from the commercial sample of sodamide prior to use.[16] The generally accepted mechanism for this reaction, under these conditions, involves nucleophilic addition of the amide to furnish a tetrahedral intermediate, which cleaves to a carboxamide and a carbanion. Intermolecular proton transfer leads to a hydrocarbon product and an amide salt. Aqueous work-up delivers the observed products of the HB reaction (Eq. (5)). The direction of cleavage is largely determined by the carbanion stabilising abilities of R and R^1. Subsequent investigations of this reaction have shown that other bases, particularly hydroxides, can be equally efficiently employed to obtain the carboxylic acids directly.[4,5]

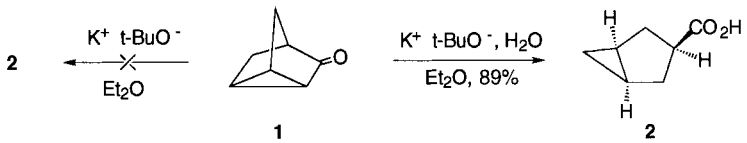


The other reaction conditions that are routinely employed in a synthetically useful manner include a combination of potassium *t*-butoxide and water in various solvents such as ether, glyme, HMPA, DMSO, *t*-butanol, DME etc.[4,5,17]; aqueous sodium or potassium hydroxide in benzene in a biphasic medium[18]; sodium methoxide in methanol[19] and methanolic or ethanolic sodium or potassium hydroxide.[20] In some cases, cleavage of benzophenones has also been observed even on heating with potassium *t*-butoxide in the absence of solvent, but the yields have been low.[21] Thus, it should be noted that the HB reaction efficiency and product profile exhibit a strong dependency on the reaction conditions. For example, Gassman et al.[5] have observed that nortricyclanone **1** is inert towards potassium *t*-butoxide in organic solvents like DMSO, diethyl ether etc., but addition of 3 equivalents of water to the solution leads to a facile regio- and stereoselective cleavage to furnish the bicyclo[3.1.0]hexane carboxylic acid **2** in high yield (Scheme 1). The presence as well as concentration of water was crucial for the cleavage to occur. On basis of these studies, it was proposed that the mechanism of the HB cleavage involves an initial addition of OH^- to the ketone to furnish a tetrahedral intermediate, which is further deprotonated by base to a dianionic species with an enhanced proclivity towards C–C bond cleavage (Eq. (6)).[5] From the large number of examples that have appeared over the years, it is quite apparent that the cleavage process is essentially anionic in character and the reaction is fairly facile in strained polycyclic systems, where the relief of strain is the main driving force.

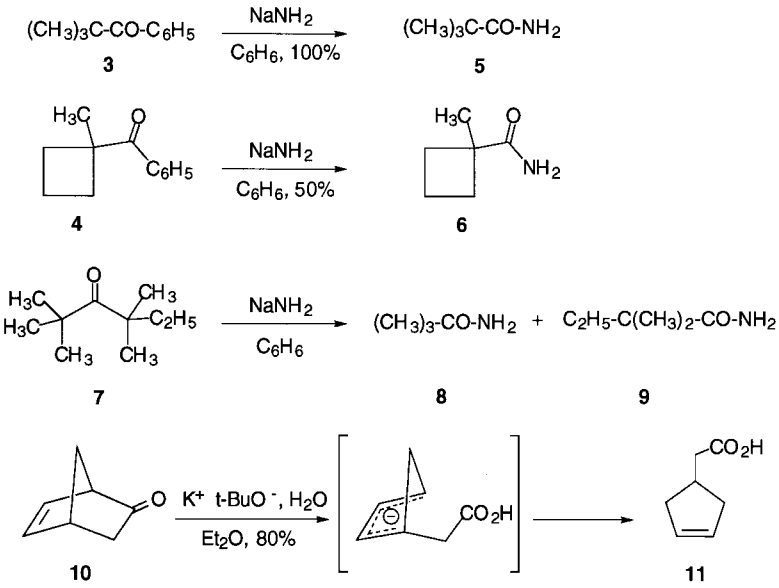


3. Regio- and Stereoselectivity

Mechanistic considerations to a large extent determine the regiochemical outcome of the HB cleavage reaction and enable rationalisation of the large body of examples reported in the literature. C–C bond cleavage in the HB reaction takes place in the direction that results in the



Scheme 1.

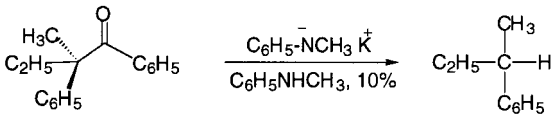


Scheme 2.

formation of the more stable carbanion. For instance, the HB cleavage in the case of aliphatic **3** or alicyclic **4** phenyl ketones gives the aliphatic **5** or alicyclic **6** carboxamides, respectively (Scheme 2), in keeping with the greater propensity of the benzene ring to stabilise the negative charge. However, simple unsymmetrical aliphatic ketones like **7** exhibit little selectivity and both carboxamides **8** and **9** are produced.[3] In the case of 2-norbornenone **10**, base-mediated cleavage leads regioselectively to the cyclopentene-4-carboxylic acid **11**,[5] the direction of the C–C bond cleavage being dictated by the formation of the intermediate allyl carbanion (Scheme 2).

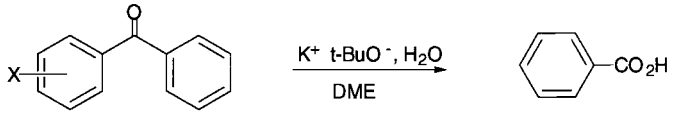
In the case of diaryl ketones, regioselectivity is determined by the substitution pattern on the aromatic rings (Scheme 3). For example, in the case of 2-chloro substitution, there is a near total cleavage of the substituted phenyl ring bond and chlorobenzene and benzoic acid are produced. However, in the case of 4-chloro substitution, regioselectivity is diminished and *p*-chlorobenzoic acid and benzene are also produced. The approximate order in which the substituents can induce cleavage of the proximal bond in benzophenones is: 2-Cl or 2-OMe>3-Cl>2-CO_2^->2-Me>4-Cl>3-MeO>4-Ph>H>4-MeO or 4-Me>3-Me>4-CO_2^-.[22]

As indicated above, the direction of HB cleavage is dependent on the substrate structure. In the case of alkyl–aryl ketones, the direction of cleavage is pre-determined by the stability of the arenide ion and alkyl carboxylic acids are formed. However, this may be completely reversed by incorporating an anion stabilising group (phenyl, cyclopropyl, allyl, trimethylsily etc.) into the alkyl chain.[14,23,24] Substitution of the alkyl chain at the α-position relative to the carbonyl group, besides influencing the regioselectivity, introduces an important stereochemical element as an asymmetric centre is installed. HB cleavage in such chiral precursors can therefore have an additional stereochemical outcome in terms of retention, inversion or racemisation. In one of the earliest examples of its kind, Cram et al.[23] observed 63% retention during the base-mediated cleavage of optically active **12** to the hydrocarbon **13**.



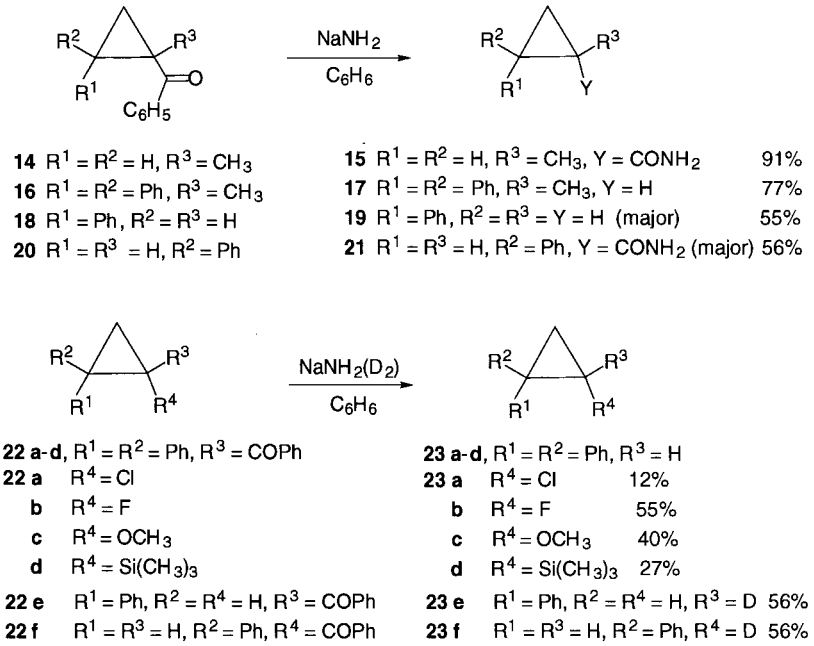
(−) **12** (+) **13** (7)

Haller, during his seminal studies on the reaction that bears his name, reported[25] that the sodamide-induced cleavage of 1-methylcyclopropyl phenyl ketone **14** furnished benzamide and methylcyclopropane. However, while reinvestigating this reaction Bumgardner[26] found that this cleavage in fact proceeded to give 1-methylcyclopropanecarboxamide **15** and not benzamide. The stability of the arenide



X = 2- Cl 92%
= 3- Cl 88%
= 2- CO_2H 87%
= 2- OCH_3 92%

Scheme 3.



14 $R^1 = R^2 = H$, $R^3 = CH_3$
16 $R^1 = R^2 = Ph$, $R^3 = CH_3$
18 $R^1 = Ph$, $R^2 = R^3 = H$
20 $R^1 = R^3 = H$, $R^2 = Ph$

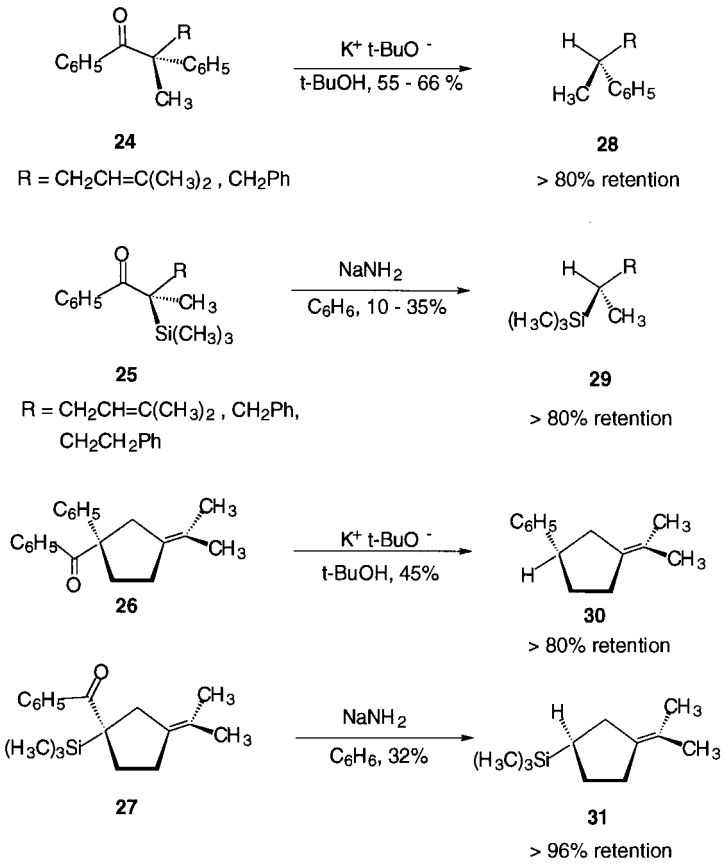
15 $R^1 = R^2 = H$, $R^3 = CH_3$, $Y = CONH_2$ 91%
17 $R^1 = R^2 = Ph$, $R^3 = CH_3$, $Y = H$ 77%
19 $R^1 = Ph$, $R^2 = R^3 = Y = H$ (major) 55%
21 $R^1 = R^3 = H$, $R^2 = Ph$, $Y = CONH_2$ (major) 56%

22 a-d, $R^1 = R^2 = Ph$, $R^3 = COPh$
22 a $R^4 = Cl$
b $R^4 = F$
c $R^4 = OCH_3$
d $R^4 = Si(CH_3)_3$
22 e $R^1 = Ph$, $R^2 = R^4 = H$, $R^3 = COPh$
22 f $R^1 = R^3 = H$, $R^2 = Ph$, $R^4 = COPh$

23 a-d, $R^1 = R^2 = Ph$, $R^3 = H$
23 a $R^4 = Cl$ 12%
b $R^4 = F$ 55%
c $R^4 = OCH_3$ 40%
d $R^4 = Si(CH_3)_3$ 27%
23 e $R^1 = Ph$, $R^2 = R^4 = H$, $R^3 = D$ 56%
23 f $R^1 = R^3 = H$, $R^2 = Ph$, $R^4 = D$ 56%

Scheme 4.

ion still determined the regioselectivity in this case (Scheme 4). The groups of Walborsky and Bumgardner,[24,26,27] on the contrary, came across an interesting finding while studying HB cleavage in 1-methyl-2,2-diphenylcyclopropyl phenyl ketone **16**. They observed the formation of 1-methyl-2,2-diphenylcyclopropane **17** and benzamide, through a complete reversal in the regiochemistry compared to **14**. It was further demonstrated that this was a general mode of cleavage of 2,2-diphenylcyclopropyl ketones and even (*Z*)-2-phenylcyclopropyl phenyl ketone **18** exhibited the same regiochemistry to furnish **19**. The reversal in regiochemistry in the case of **16** and **18** has been explained in terms of relief



24
R = $CH_2CH{=}C(CH_3)_2$, CH_2Ph

28
> 80% retention

25
R = $CH_2CH{=}C(CH_3)_2$, CH_2Ph, CH_2CH_2Ph

29
> 80% retention

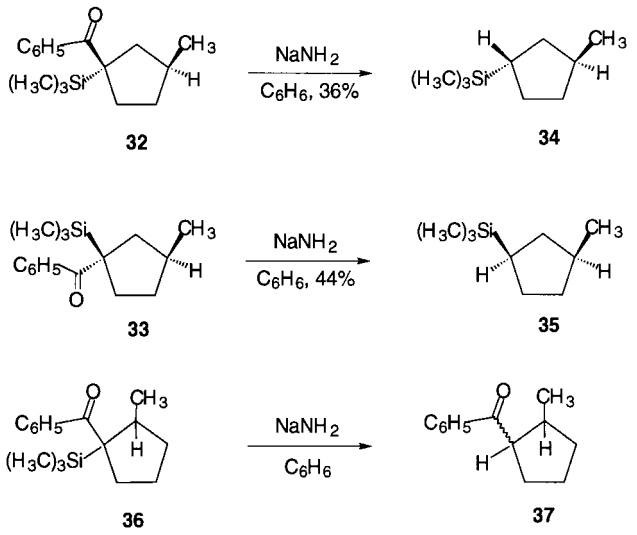
26

30
> 80% retention

27

31
> 96% retention

Scheme 5.

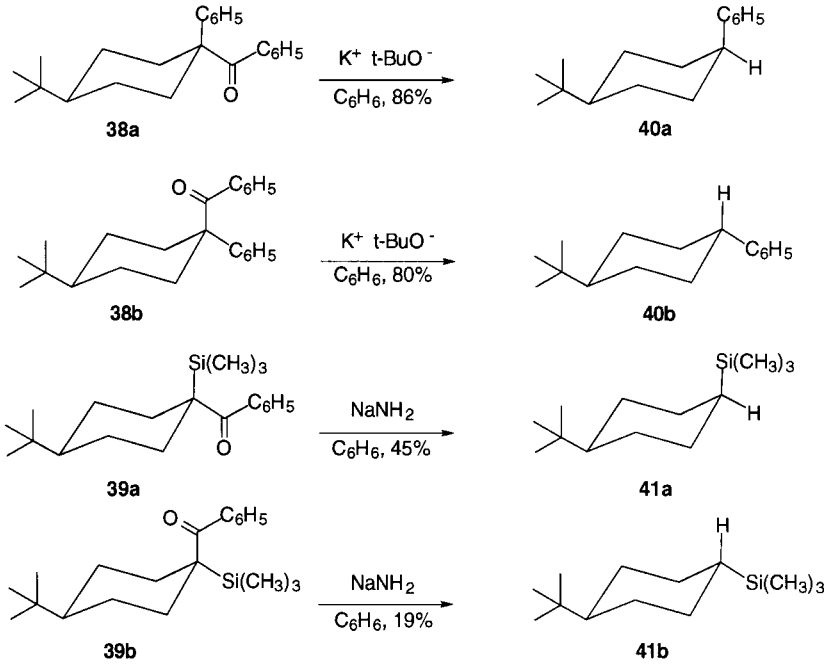


Scheme 6.

of the steric interaction between the phenyl group in the 2-position and the carbonyl group in the 1-position. In accordance with this interpretation, it was observed that (*E*)-2-phenylcyclopropylphenyl ketone **20**, in which the steric interaction between the phenyl group in the 2-position and the carbonyl group in the 1-position is substantially relaxed, furnished the cyclopropylcarboxamide **21** as the major product with the same regiochemistry as **14** (Scheme 4).

Walborsky et al.[27] also studied HB cleavage in several enantiomerically pure cyclopropylphenyl ketones **16** and **22a**–**c** and found a net retention of configuration and optical activity in the products **17** and **23a**–**c**, respectively (Scheme 4). The proposed mechanism involved the intermediacy of a cyclopropyl carbanion, which due to its inherent pyramidal nature was non-invertible and ensured a net retention of configuration. The inductive effect of the substituents at the 1-position in **22a**–**c** further facilitated the formation of the carbanion intermediate and provided additional leverage for the observed selectivity. Drawing on the above analogy, Paquette et al.[6] probed the efficiency of the trimethylsilyl group in enhancing the stereochemical outcome of the HB cleavage reaction. Employing a 1-silylated-cyclopropyl phenyl ketone **22d**, it was shown that **23d** was obtained with complete retention (Scheme 4). The retention of stereochemistry in the HB cleavage of the 2-substituted-cyclopropyl phenyl ketones **22e**,**f** has been made use of by Berson et al.[28] for the synthesis of the optical antipodes of 2-deuterophenylcyclopropanes **23e**,**f** (Scheme 4).

Expanding on the theme of employing phenyl and trimethylsilyl groups as anion stabilising functionalities, Paquette et al. have demonstrated impressive levels of configurational retention in several chiral acyclic phenylalkyl **24**, **25** and cyclopentylphenyl ketones **26**, **27** (Scheme 5).[7–12] Although a variety of bases could be employed for the cleavage reaction, in the case of the trimethylsilyl derivatives **25** and **27** only amide bases could be used due to desilylation with other bases. In all cases, HB cleavage was regioselective and generally high levels of retention were observed to furnish the products **28**–**31**, respectively. It may be noted, however, that the degree of retention shows a marked dependence on the nature of the base employed and particularly on the counterion. An interesting example of deviation from the usually encountered retention has been observed due to a solvent effect with the acyclic ketone **24**. When the cleavage in **24** was performed with potassium ethylene glycolate in ethylene glycol, an inversion was observed due to metal ion complexation and resultant steric crowding on one face in the transition state.[9]



Scheme 7.

The steric demand of a 2-substituent in channeling the mode of cleavage in cyclopropyl phenyl ketones has been amply illustrated (see Scheme 4). The possible effect of similar additional substituents in the case of certain cyclopentyl phenyl ketones has also been investigated.[12] The two cyclopentyl phenyl ketones **32** and **33** on the HB cleavage using sodium or potassium amide furnished the products **34** and **35**, respectively, with net retention. This response of **34** and **35** was almost identical to that observed for the related ketone **27**, indicating that a 3-substituent in the ring had virtually no effect on the steric course of the reaction. The isomeric 2-methyl derivative **36**, in which one face of the carbonyl group is effectively shielded by the methyl substituent, on exposure to amide bases, however, furnished only the desilylated ketone **37**. Apparently, the steric congestion around the carbonyl centre effectively directs the attack by base towards silicon and desilylation to **37** results (Scheme 6). The susceptibility of the HB reaction to subtle steric variations was thus highlighted.

The response of conformationally locked cyclohexyl phenyl ketone pairs **38a**,**b** and **39a**,**b** bearing α-phenyl or trimethylsilyl substituents is in keeping with the general trends observed with other substrates described earlier.[10] The C–C bond scission is regioselective and the dominant stereochemical outcome is retention to furnish **40a**,**b**–**41a**,**b,** respectively (Scheme 7). These results additionally corroborate the previous conclusions relating to higher levels of retention when the intermediate carbanion is stabilised by silicon rather than by phenyl. In the cyclohexyl substrates, the nature of the base, counterion and solvent also cause deviations in the levels of selectivity, but a definitive trend is not discernible.

The observations in the previous two sections reveal a number of interesting facets of the HB reaction.

1. The reaction is essentially anionic in character.
2. There is a net retention of configuration, and activity is retained in optically active substrates. An inversion is possible through a proper choice of solvent.
3. The regiochemistry of the cleavage can be controlled by placing an appropriate substituent at the α-position that will stabilise the resultant carbanion.
4. The cleavage is sensitive to steric compression at the reaction site.
5. The reaction is very sensitive to the reaction conditions. There is no generalised set of reaction conditions for any particular substrate and appropriate conditions may have to be evolved through trial and error.

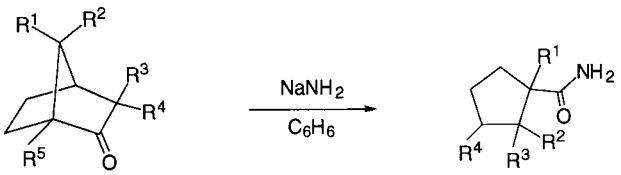
4. Synthetic Applications

While methodologies for C–C bond formation abound and continue to draw the widespread attention of synthetic chemists, the C–C bond-breaking processes are relatively less common and have not yet been fully exploited in complex synthesis by incorporating them within a synthetic sequence. The main reason for this is that for effecting C–C bond cleavage at a desired site, the substrate has to be properly set (for example a W–C–C–X arrangement is required for C–C bond cleavage where W is an electrofuge and X is a nucleofuge), requiring several additional steps. It is in this context that the HB reaction holds a special opportunity for synthetic chemists, as C–C bond cleavage can be affected in a single-pot operation, using common reagents. Of major importance is the fact that, in this reaction, no great site preparation is required, the chemical operation being performed on a simple, non-enolisable, keto–carbonyl group, which is a routinely encountered functionality. In the HB reaction, the two ends of the cleaved C–C bond are left with different functionalities at divergent oxidation levels (see Eq. (1)). HB cleavage, particularly in carbocyclic systems, can have considerable synthetic applications as it not only decomplexes the framework but also provides a versatile handle in the form of a carboxylic acid-derived functionality for further elaboration. A valuable feature of the HB cleavage from the synthetic point of view is that it is amenable to regio- and stereochemical controls in a predictable manner. We describe below many examples in which the HB reaction has been successfully applied to a wide range of substrates, and these have been further exploited in complex synthesis.

4.1. Cleavage in bridged ring systems

As already mentioned, the HB cleavage of non-enolisable ketones had its origin in the cleavage of the monoterpene fenchone with sodamide (Eq. (2)).[3] Indeed, several bicyclo[2.2.1]heptan-2-one (2-norbornanone) based bridged systems **42a**–**c** undergo facile HB cleavage to furnish functionalised cyclopentanes **43a**–**c**, respectively (Scheme 8).[3]

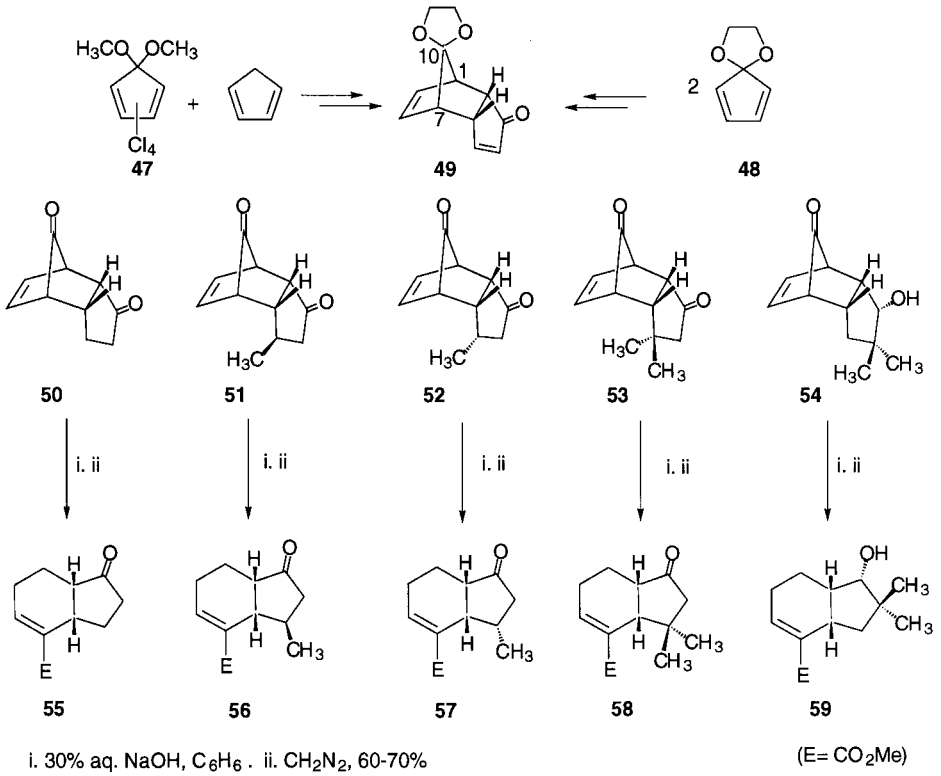
Since most of these precursors are of natural product origin, the examples cited in Scheme 8 constitute a convenient entry into chiral cyclopentanoids. Subsequently, Gassman et al.[5] demonstrated that 7-norbornenone **44** could be readily unbridged via the HB reaction to yield the isomeric cyclohexenecarboxylic acids **45** and **46**. This reaction, in which the bridge keto-carbon is removed from the bridged system simply by exposure to base, opened some interesting



42a $R^1 = R^2 = R^5 = H$; $R^3 = R^4 = CH_3$
b $R^1 = R^2 = R^3 = R^4 = R^5 = CH_3$
c $R^1 = R^2 = R^5 = CH_3$; $R^3 = R^4 = CH_2Ph$

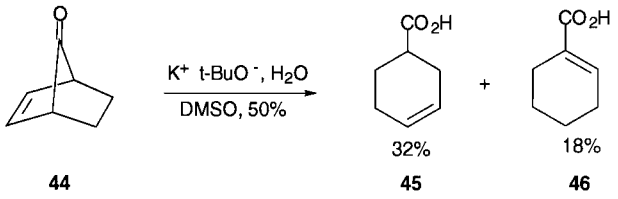
43a $R^1 = R^2 = R^3 = H$, $R^4 = CH(CH_3)_2$
b $R^1 = R^2 = R^3 = CH_3$, $R^4 = CH(CH_3)_2$
c $R^1 = R^2 = R^3 = CH_3$, $R^4 = CH(CH_2Ph)_2$

Scheme 8.



Scheme 9.

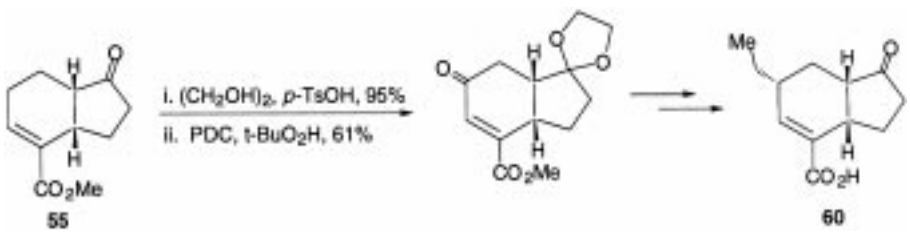
possibilities, which have been successfully exploited for a general synthesis of *cis*-hydrindanes.



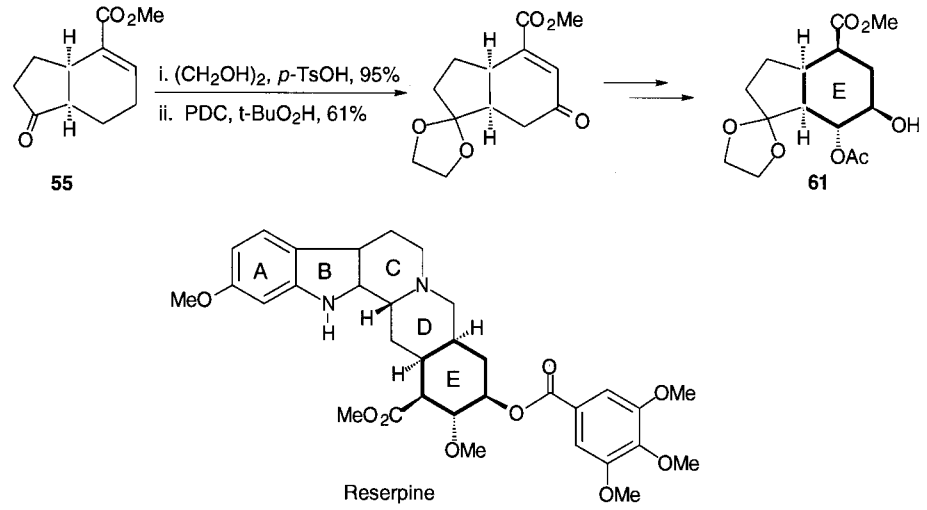
(8)

The *endo*-tricyclo[5.2.1.$0^{2,6}$]deca-4,8-diene-3,10-dione derivative **49**, incorporating a 7-norbornenone moiety, is conveniently accessible via a Diels–Alder reaction between readily available starting materials like 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene **47** and cyclopentadiene or through the dimerisation of cyclopentadienone ketal **48**, respectively (Scheme 9). Routine functional group transformations, particularly in the isolated five-membered ring of **49**, provide a range of *endo*-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-3,10-dione derivatives **50**–**54**, in which HB cleavage was applied to remove the C-10 bridge and unravel the *cis*-hydrindane moiety. Consequently, **50**–**54** were subjected to HB conditions involving a biphasic medium of 30% aqueous sodium hydroxide in benzene to furnish the bicyclic esters **55**–**59** after esterification (Scheme 9).[18] In all cases, HB cleavage was regioselective with preferential C1–C10 bond cleavage and the double bond migrated under the reaction conditions to an advantageous position to give α,β-unsaturated esters. Interestingly, the regioselectivity observed during the HB cleavage in these substrates seems to be emanating through the influence of the bystander C3-electron withdrawing substituent.

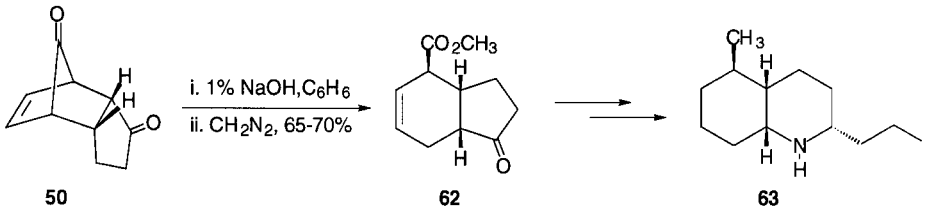
The *cis*-hydrindane based unsaturated esters **55**–**59** have substitution patterns reminiscent of many natural products. It was effectively demonstrated that these *cis*-hydrindanes, obtained via HB cleavage, can indeed be converted into several natural products. Thus, **55** was elaborated to the natural product coronofacic acid **60** in a stereoselective fashion (Scheme 10).[18] Recently, employing a chiral



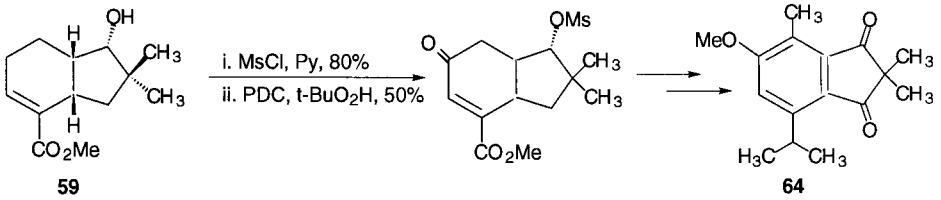
Scheme 10.



Scheme 11.

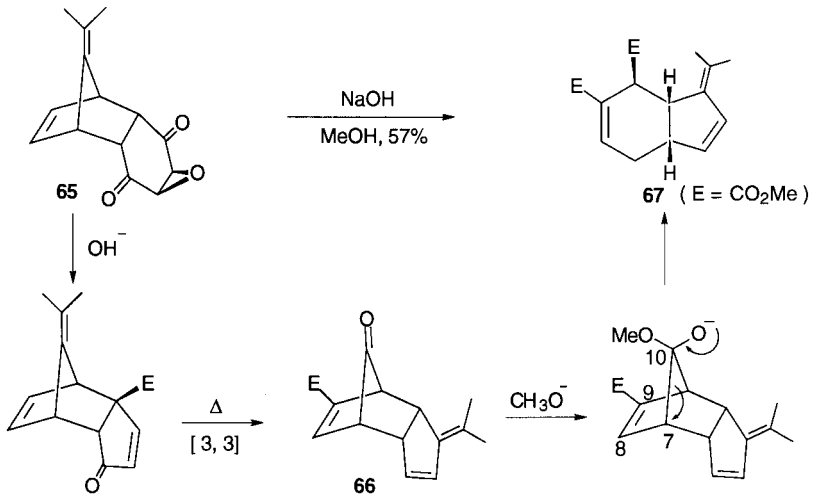


Scheme 12.

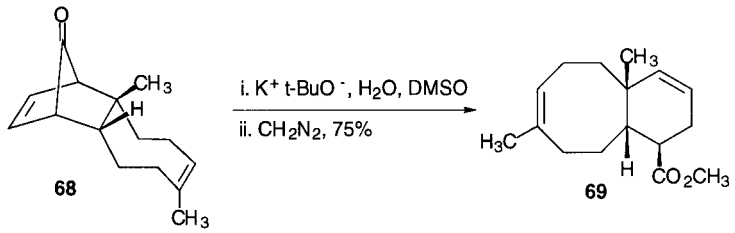


Scheme 13.

endo-tricyclo [5.2.1.$0^{2,6}$]dec-8-en-3,10-dione derivative and following the sequence depicted in Scheme 10, a synthesis of (+)-**60** has been achieved.[29] In another series of investigations, the same bicyclic ester **55** was transformed into a highly functionalised *cis*-hydrindane derivative **61**,[30] which embodies all of the requisite functionalities and stereochemical features present in the ring-E of the pentacyclic indole alkaloid reserpine (Scheme 11).



Scheme 14.



Scheme 15.

In a sequence emerging from the tricyclic dione **50**, HB cleavage was affected in a manner that arrested the isomerisation of the double bond to furnish **62** as the major-diastereomer.[31] Functional group transformations on **62** led to the *cis*-decahydroquinoline alkaloid natural product pumiliotoxin C **63** (Scheme 12).

For a synthetic approach directed towards marine natural products of the primnatriene-type, the requisite functionalisation pattern was built into the tricyclic ketone precursor **54**. HB cleavage furnished **59** which was elaborated to the natural sesquiterpenoid **64** (Scheme 13).[32]

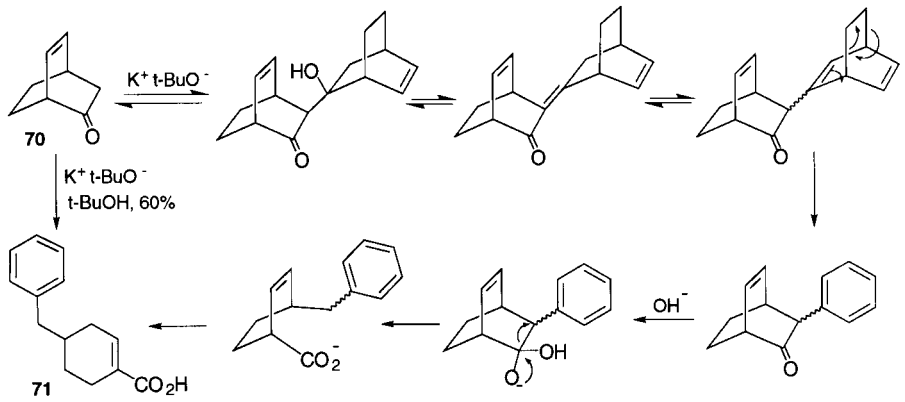
Guan et al.[33] have disclosed an example of tandem Favorskii-type ring contraction–Cope rearrangement in the tricyclic epoxy dione **65** to give the intermediate *endo*-tricyclo[5.2.1.$0^{2,6}$]dec-8-en-10-one derivative **66**. The HB cleavage in **66** on treatment with methanolic sodium hydroxide afforded the bicyclic *cis*-hydrindane diester **67** (Scheme 14). The regiochemical course in this reaction is determined by the preferential formation of the intermediate carbanion that can effectively delocalise on to the α,β-unsaturated ester moiety.

The *endo*-tricyclo[8.2.1.$0^{2,9}$]tridecan-10-one **68** is an interesting bridged system in which a medium ring is annulated to the 7-norbornenone moiety. Regioselectivity proved to be a key factor in the HB cleavage of **68** to furnish the *cis*-bicyclo[6.4.0]dodecane derivative **69** (Scheme 15).[34] The unexpected position of the cyclohexene double bond in **69** is a typical example of many double bond isomerisations that are encountered during the HB reaction conditions. The 6,4-fused bicyclic skeleton **69**, with its complement of methyl groups, is present in a number of natural products, particularly the taxane group of bioactive compounds.

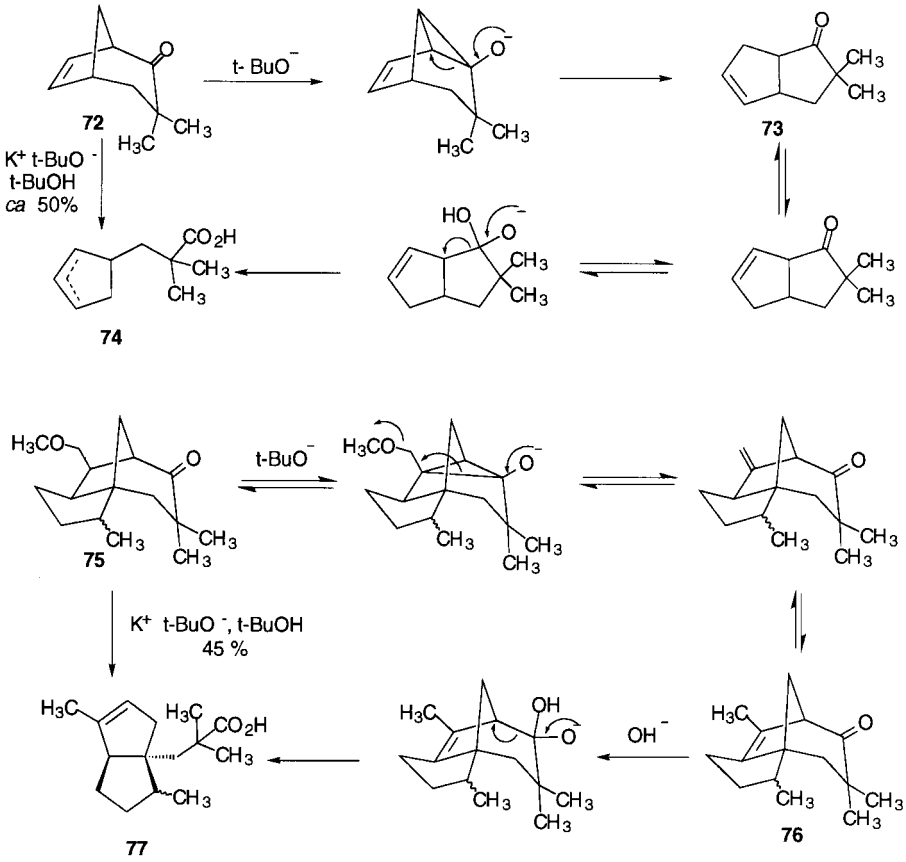
During their extensive investigations on the homoenolisation in sterically compressed bridged systems, Stothers et al.[35] have observed extensive intervention by the HB cleavage reaction to furnish interesting products. For example, when β-enolisation was attempted on the simple bicyclic[2.2.2]octenone **70** in the presence of potassium *t*-butoxide in *t*-butanol, the cyclohexenecarboxylic acid **71** was obtained as the major product through a cascade of base-catalysed processes in which HB cleavage was the terminal step leading to the observed product (Scheme 16). On the other hand, when the bicyclo[3.2.1]octenone **72** was treated with base, the contemplated β-enolisation to the bicyclo[3.3.0]octenone **73** did occur but, under the reaction conditions, this further underwent HB cleavage resulting in the isomeric cyclopentenylpropanoic acids **74** (Scheme 17).[36] In the case of the tricyclic annulated derivative **75** of **72**, a series of events beginning with homoenolisation–elimination–isomerisation leads to **76**, which undergoes HB cleavage to furnish the bicyclo[3.3.0]octene carboxylic acid derivative **77** (Scheme 17).[37] The higher homologue of **72**, the bicyclo[3.3.1]nonenone **78**, on exposure to base first undergoes double bond isomerisation to **79**, followed by competitive HB cleavage and aromatisation to give the arylpropanoic acid **80** (Scheme 18).[38]

Homoenolisation efforts in the benzobicyclo[2.2.2]octanone **81**, benzobicyclo[3.2.1]octanone **82** and benzobicyclo-[3.2.2]nonanone **83** also resulted in competitive, regioselective HB cleavage to furnish the ring-cleaved acids **84**–**86**, respectively (Scheme 19).[39]

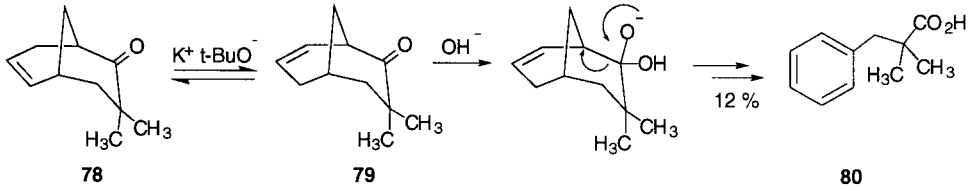
Saturated bicyclo[n.1.1]alkanones like **87** having a bridged cyclobutanone moiety have been found to be inert towards HB cleavage on exposure to base. However, when an unsaturation is introduced into the system such that the



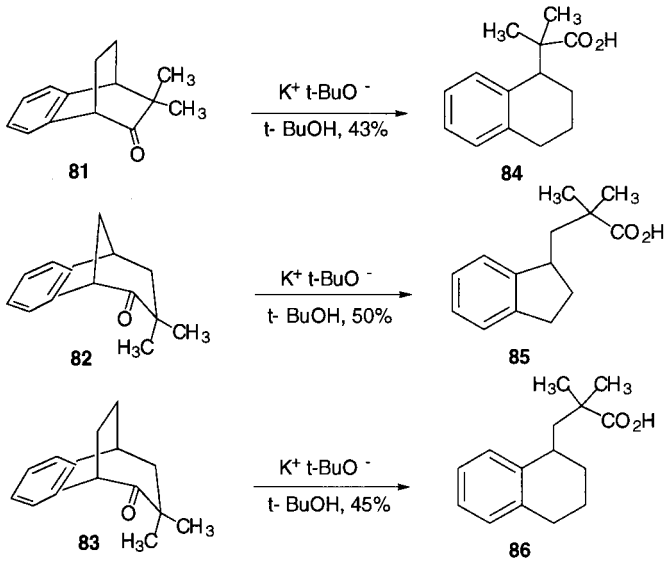
Scheme 16.



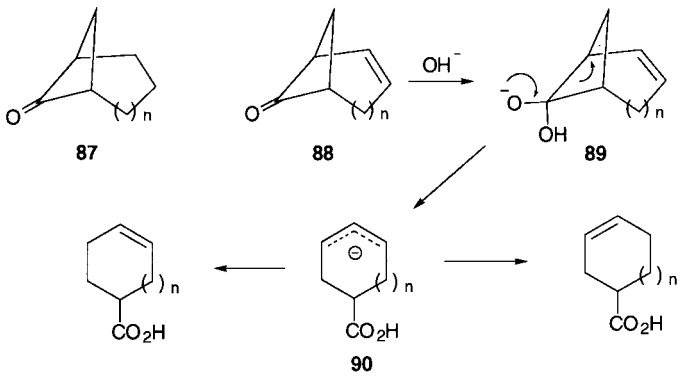
Scheme 17.



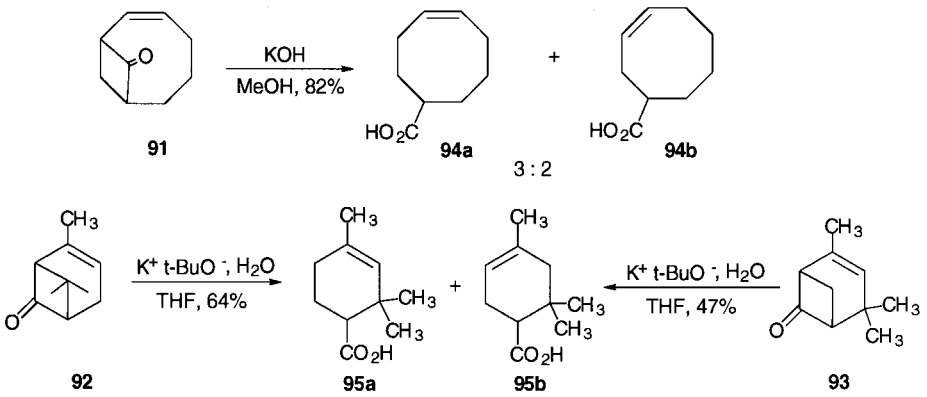
Scheme 18.



Scheme 19.



Scheme 20.

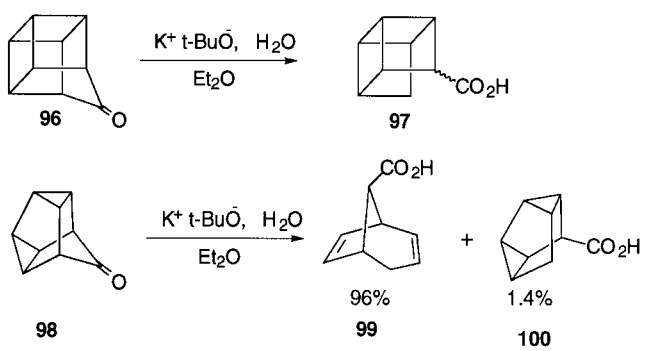


Scheme 21.

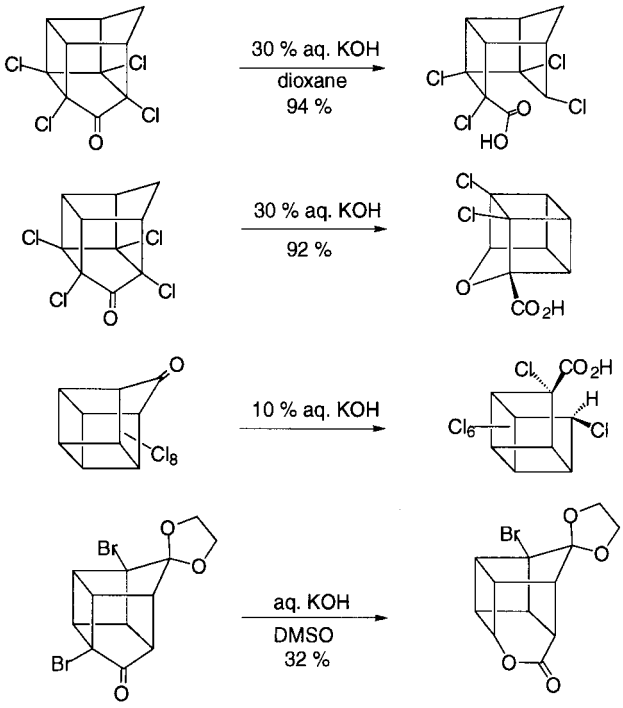
carbanion intermediate formed on C–C bond cleavage (**88** → **89**) can delocalise, then HB reaction leading to **90** is observed (Scheme 20).[40] Several βγ-unsaturated bicyclo[n.1.1]alkanones **91**–**93** undergo facile cleavage to give the regioisomeric acids **94a**,**b**–**95a**,**b**, respectively (Scheme 21).[40,41]

4.2. Cleavage in polycyclic caged systems

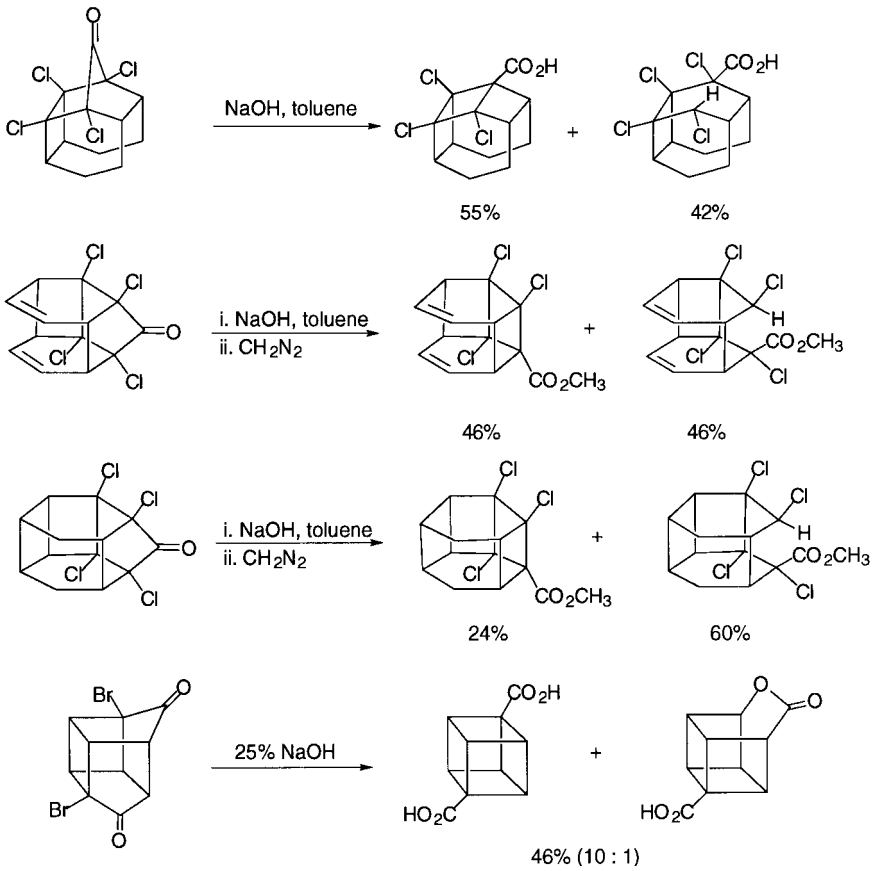
Polycyclic caged systems by their very constitution and their method of preparation are endowed with a non-enolisable carbonyl functionality in a strained environment, thus rendering them good candidates for effecting the HB reaction. Such a cleavage in complex polycyclic systems helps to demystify the structure and also to considerably relax the built-in strain. Two typical examples are the formation of the seco-cubanecarboxylic acid **97** from the homocubanone **96** and the decomplexing of the norsnoutanone **98** on exposure to base to yield the bicyclo[3.2.1]octadienecarboxylic acid **99** and the tetracyclo[3.3.0^{1,5}.0^{2,8}.0^{4,6}]octanecarboxylic acid **100** (Scheme 22).[42]



Scheme 22.

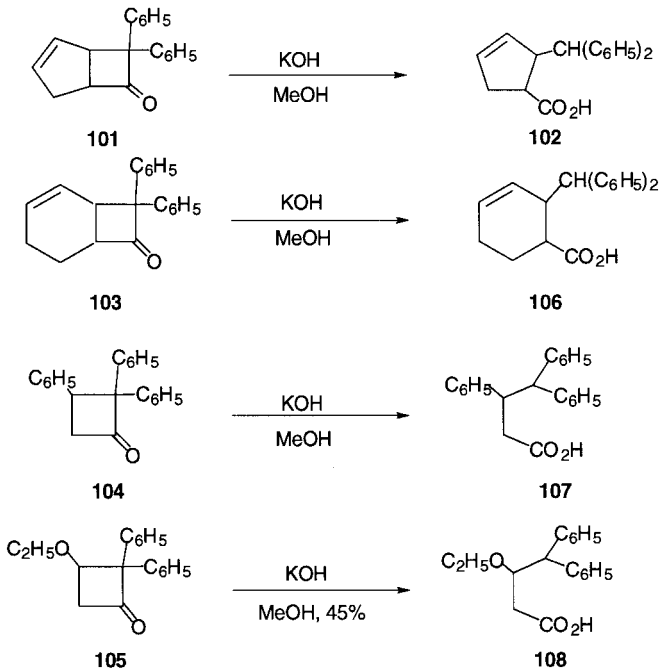


Scheme 23.

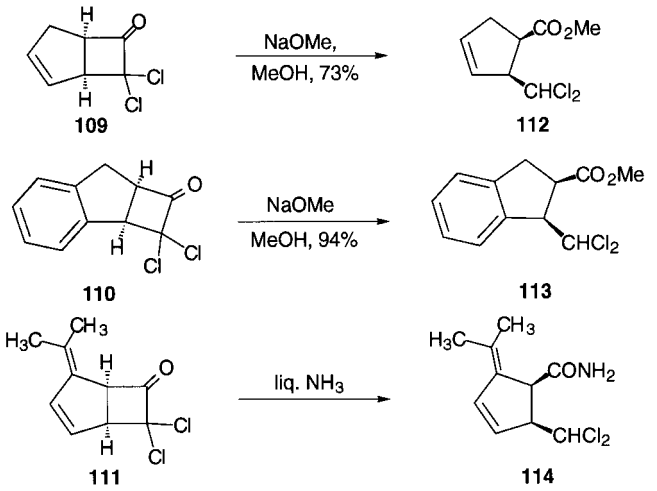


Scheme 24.

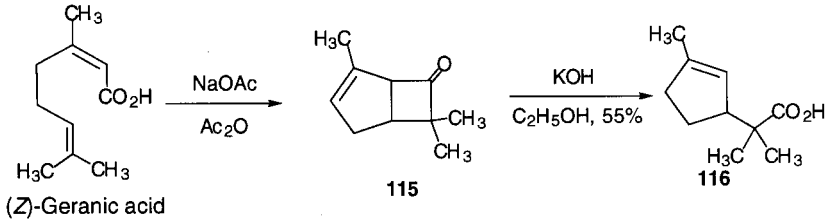
One of the key reactions in accessing the strained, high symmetry, cage systems like cubanes, prismanes etc., encompassing many fused cyclobutane rings, is a Favorskii-type ring contraction in an intermediate α-haloketone. The ring contraction is carried out in the presence of a base and, under these reaction conditions, HB cleavage products are invariably formed in different amounts depending on the substrate structure and the nature of the reaction medium.



Scheme 25.



Scheme 26.



Scheme 27.

In some cases, the HB cleavage product is exclusively formed or predominates (Scheme 23),[43–47] while in others it competes as an important side reaction. Four examples in which both HB cleavage and Favorskii-type ring contraction products are co-produced are collected in Scheme 24.[48–51] In the reactions given in Schemes 22–24 and earlier, the carbonyl moiety undergoing HB cleavage is located in the five-membered ring and, therefore, non-enolisable bridged cyclopentanones appear to be especially amenable to HB cleavage.

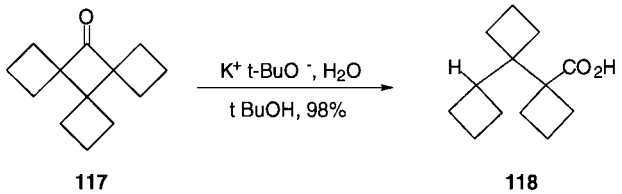
Despite the many examples presented above, it is still not possible to predict with certainty whether the HB or the ring contraction course will be favoured in a particular situation in the polycyclic, caged α-halo ketones, although strain considerations should be the main determinants of the outcome. It should also be pointed that HB products in polycyclic cage systems have been generally regarded as being of 'nuisance' value, as unwanted side products, and this has thwarted efforts towards exploiting the reaction in caged systems towards more useful purposes.

4.3. Cleavage in fused cyclobutanones

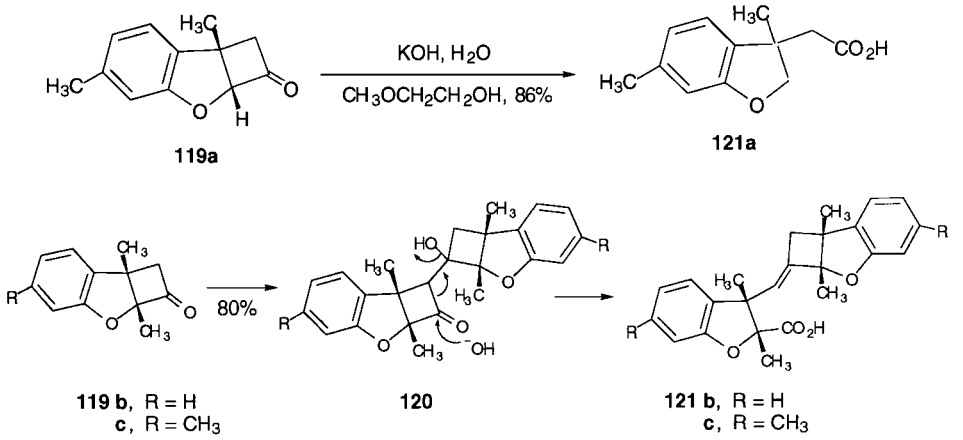
Although simple cyclobutanones have been found to be stable towards the typical conditions employed in HB cleavage, they have been observed to undergo cleavage when the α-carbon atom is suitably substituted by an anion stabilising group. One of the early examples of such a cleavage was reported[52,53] for the [2+2]-adduct **101** of diphenylketene and cyclopentadiene. On treatment with methanolic potassium hydroxide, the bicyclic cyclobutanone **101** furnished the cyclopentenecarboxylic acid **102** as a mixture of stereoisomers (Scheme 25). Subsequently, several [2+2]-adducts **103**–**105** from diphenylketene and various olefins have been found to display the same uni-directional cleavage to yield the carboxylic acids **106**–**108**, respectively (Scheme 25).[54,55] The [2+2]-adducts **109**–**111** of dichloroketene with various cyclic olefins, bearing the bicyclo[n.2.0]alkanone moiety, also respond similarly on exposure to base to give the corresponding ring-cleaved products **112**–**114**, respectively[56,57] (Scheme 26). Intervention by a stabilising allylic carbanion induces HB cleavage in the bicyclo[3.2.0]hept-2-en-7-one **115**, obtained from geranic acid via an intramolecular ketene–olefin [2+2]-cycloaddition, to furnish **116** (Scheme 27).[20]

Recently, an example of HB cleavage in a cyclobutanone, forming part of a cyclobutane-based polyspirane system, has been reported by Fitjer et al.[58] Thus, the polyspiranone **117** underwent a facile cleavage to furnish the interesting cyclobutanecarboxylic acid **118** (Scheme 28).

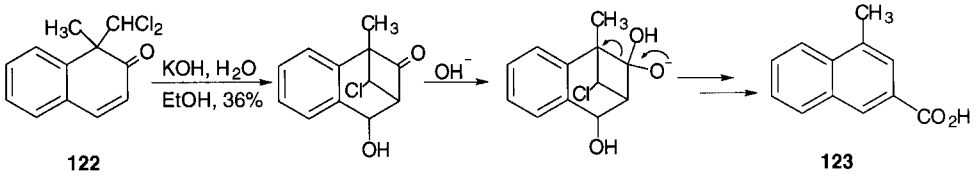
HB cleavage in cyclobutanones fused to benzofurans of the type **119** has been investigated by Venkateswaran et al.[59] They found that the product profile in these substrates was



Scheme 28.



Scheme 29.



Scheme 30.

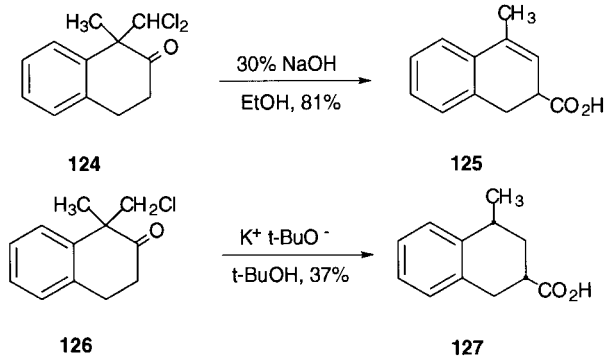
markedly dependent on the α-substitution at the angular position. On base treatment **119a** furnished the bicyclic acid **121a** through regioselective C–C bond cleavage directed by the furanoid oxygen. However, substrates with quaternary angular carbon centres **119b**, **c** took a multi-event route and furnished **121b**, **c** through aldol condensation to the ketol **120** followed by fragmentation of the cyclobutanone ring (Scheme 29). In these reactions, the biphasic medium of aqueous KOH and benzene was found to be ineffective and homogeneous reaction conditions had to be employed to effect ring cleavage.

Wenkert et al.[60,61] have developed a 'homo-Favorskii' rearrangement of β-haloketones in the presence of a base and the rearrangement has been postulated to involve an incipient cyclobutanone intermediate that undergoes HB cleavage. The naphthalenone **122**, for example, on treatment with aqueous KOH in ethanol furnished the naphthoic acid **123** as the major product. The reaction was suggested to proceed through a cyclobutanone intermediate which underwent a regioselective cleavage followed by elimination (Scheme 30). The saturated analogue **124** also charted a similar course and the expected unsaturated acid **125** was realised through an implied cyclobutanone pathway. That the presence of β-halogen was not imperative for ring opening has been established from a similar reaction on the monochloroketone **126** to yield the acid **127** (Scheme 31). Clearly, the anion-stabilising presence of the aromatic ring facilitates the ring opening.

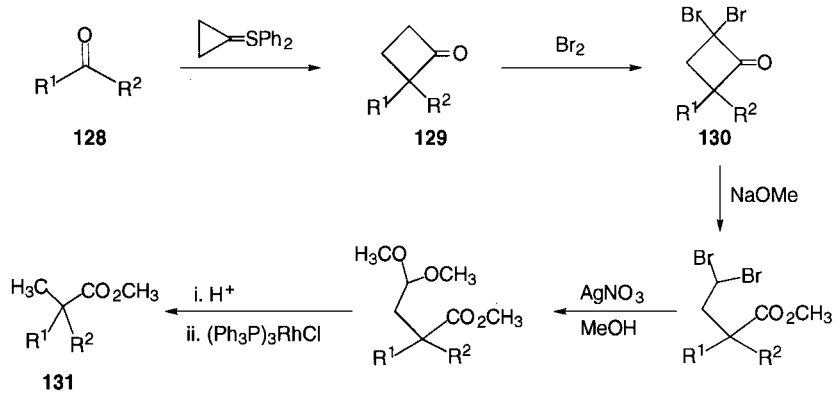
The HB cleavage of cyclobutanones has been elegantly exploited by Trost et al.[62,63] to develop a synthetically useful geminal alkylation protocol. The α,α-dialkylated cyclobutanone **129**, obtained from the carbonyl precursor **128** via 4-ring annulation, was brominated to the α,α-dibromo compound **130**. Sodium methoxide-mediated efficient HB cleavage and further transformations led to **131**, resulting in an overall geminal alkyl carboxylation of the starting carbonyl compound (Scheme 32). The utility of this methodology has been demonstrated by application to a synthesis of grandisol **134**, one of the synergistic components of the pheromone of boll weevil. The HB cleavage in **132** to furnish **133** constituted the key step in this synthesis (Scheme 33).[64] In an alternative methodology, the α,α-dialkylated cyclobutanone **135** was converted to an α-dithioacetal **136** which underwent facile HB cleavage in the presence of base to furnish **137** and this was further elaborated to a diterpene resin acid precursor **138**, Scheme 34.[65,66] Since spiro-fused cyclobutanones could be prepared in a stereospecific fashion making use of the Trost annulation procedure, the overall sequence, involving the HB cleavage as a critical step, is a potentially useful way of transforming a ketone into a *gem*-alkyl carboxylate.

4.4. Cleavage in condensed aromatics

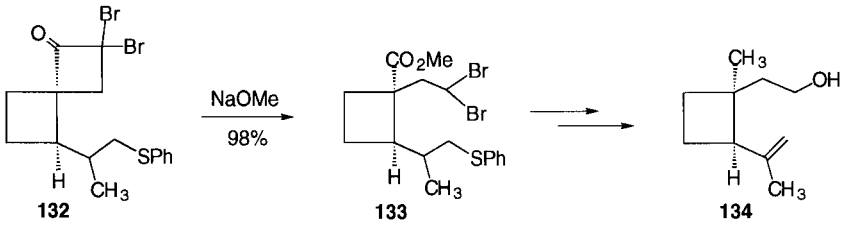
The amide base-induced cleavage of a typical condensed



Scheme 31.

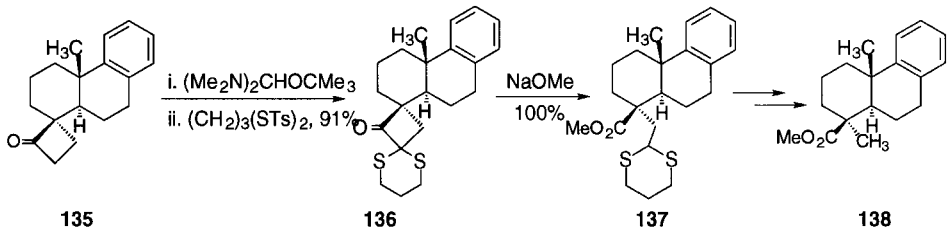


Scheme 32.

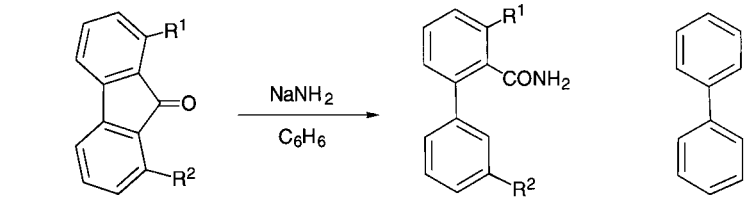


Scheme 33.

aromatic system represented by fluorenone **139a** was first reported by Haller and Bauer[2] to furnish 1-phenylcarboxamide **140a** (Scheme 35). Other workers have also reported this cleavage using a variety of bases, including the use of DABCO[15] to enhance the yield when commercial sodamide is used. Snieckus and Zhao[16] have recently carried out detailed studies on various substituted fluorenones in view of the possibility of utilisation of the resulting carboxamides as progenitors of substrates for studies on directed metallation. They have found that, by filtering the commercial sodamide as a suspension in toluene, the yields from the cleavage of fluorenones are greatly enhanced, even without the addition of DABCO. The yields in the HB cleavage of various fluorenones are preparatively useful. However, the reaction time needs to be monitored carefully as longer periods give rise to the formation of the unrequired biphenyl **141** as a decomposition product. The susbtituted fluorenones **139b**,**c** exhibited good regioselectivity with the C–C bond of the



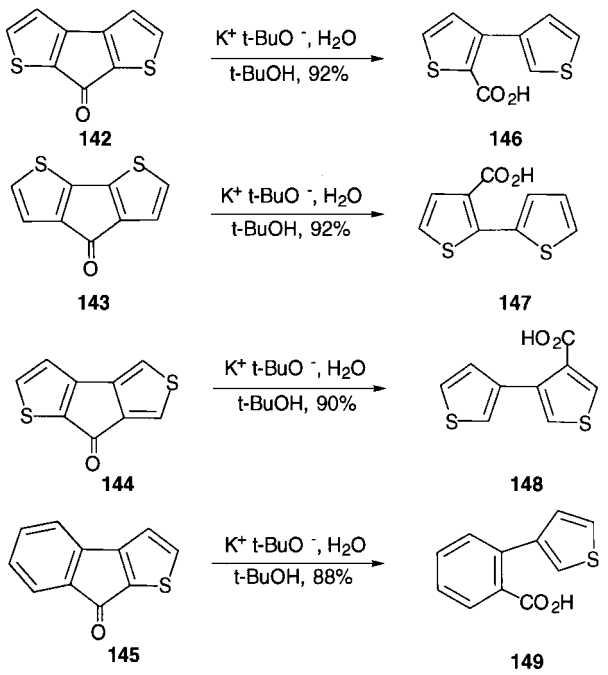
Scheme 34.



139 a, $R^1 = R^2 = H$
b, $R^1 = H$, $R^2 = OCH_3$
c, $R^1 = H$, $R^2 = C_6H_5$
d, $R^1 = H$, $R^2 = Si(C_2H_5)_3$

140 a, $R^1 = R^2 = H$ 65%
b, $R^1 = H$, $R^2 = OCH_3$ 68%
c, $R^1 = H$, $R^2 = C_6H_5$ 86%

Scheme 35.



Scheme 36.

substituted ring undergoing cleavage. This regioselectivity is in accordance with observations in the case of substituted benzophenones discussed earlier.[22] The silylated derivative **139d**, however, gave only the phenylcarboxamide **140a** through desilylation under the reaction conditions employed (Scheme 35).

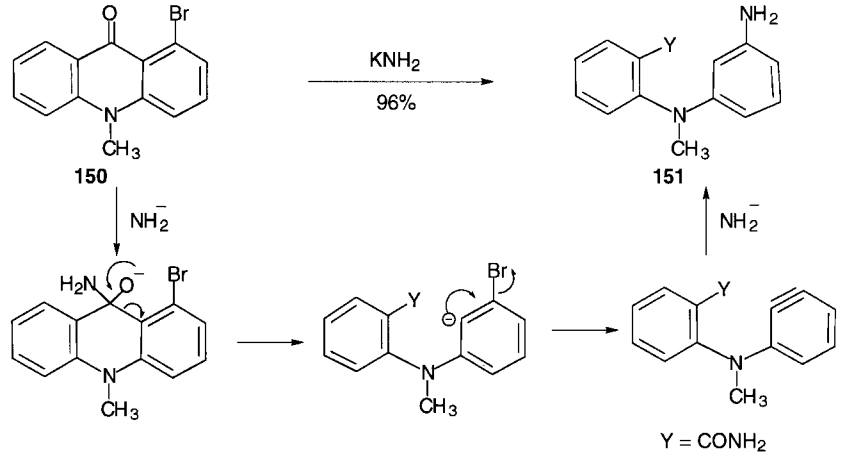
The HB cleavage of non-enolisable thienyl ketones has been investigated by Rawson and Wynberg[67] (Scheme 36). The thienyl derivatives **142**–**145** on base-induced cleavage furnished the products **146**–**149**, respectively. In all cases, the cleavage was regioselective in keeping with the relative stability of the resultant thienyl carbanion.

In connection with their studies on acridones, Gream et al.[68] found that the 1-bromo derivative **150** underwent a facile, regioselective HB cleavage to give the amide **151** through the sequence shown in Scheme 37.

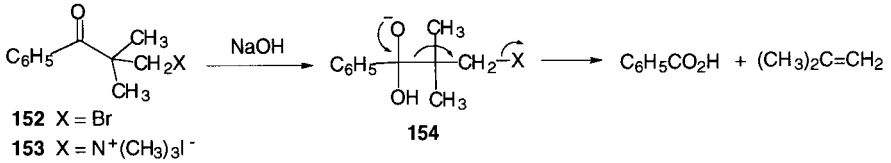
4.5. Fragmentation processes

The HB reaction is attributed to a process that involves a base-induced cleavage of a non-enolisable ketone into an acid derivative and a hydrocarbon through an intermediate carbanion and, if there is a nucleofugal group in the β-position of the ketone, there can then be a net fragmentation leading to an acid derivative and an olefin. Such processes can also be brought within the scope of the HB reaction as tandem HB reaction–fragmentation sequences. Nerdel et al.[69,70] reported that treatment of the bromoketone **152** or the methiodide **153** with alkali resulted in facile fragmentation via the adduct **154** to produce benzoic acid and isobutene (Scheme 38). Stork and Landesman[71] had previously reported an intramolecular variation of this process to provide a new ring expansion protocol. This involves treatment of the amino ketones **156** (obtained by condensation of the enamines **155** with acrolein) with methyl iodide followed by base to yield the medium ring carboxylic acids **158** via the fragmentation of the intermediate **157** (Scheme 39).

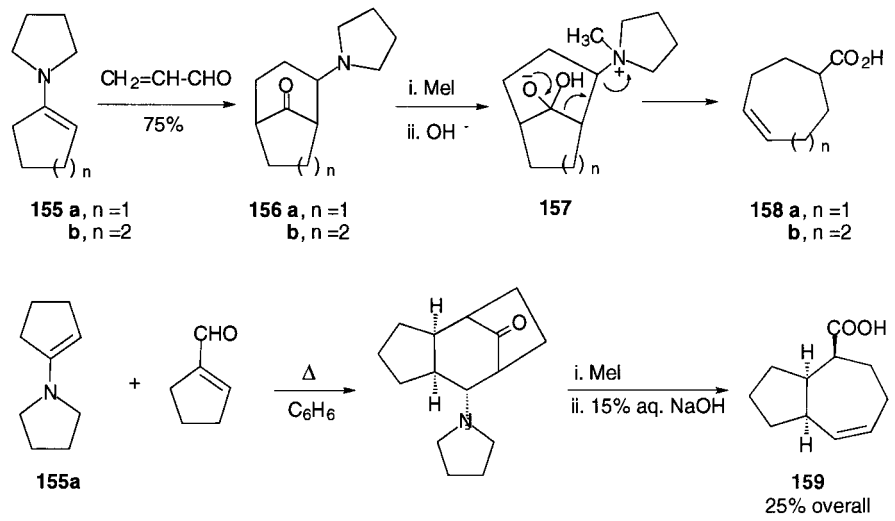
Hendrickson and Boeckman[72] adapted a similar sequence for a short, simple synthesis of perhydroazulene **159**, starting from the readily available cyclopentene-1-carboxaldehyde and the enamine **155a** derived from cyclopentanone (Scheme 39).



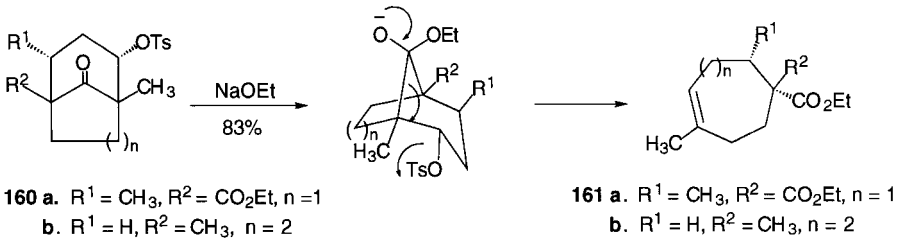
Scheme 37.



Scheme 38.



Scheme 39.



Scheme 40.

Toluene-*p*-sulphonate and methanesulphonate moieties have also been found to be very efficient in effecting the HB-fragmentation sequence. A facile route to generate cycloheptene and cyclooctene systems **161** from bicyclo-[3.n.1]alkane precursors **160** is shown in Scheme 40.[73,74] Very recently, Maldonado et al.[75] have applied the base-induced fragmentation of a bicyclo[3.3.1]nonane derived mesylate **162** to generate the benzocyclooctene framework **163** of the phenolic sesquiterpene parvifoline **164** (Scheme 41).

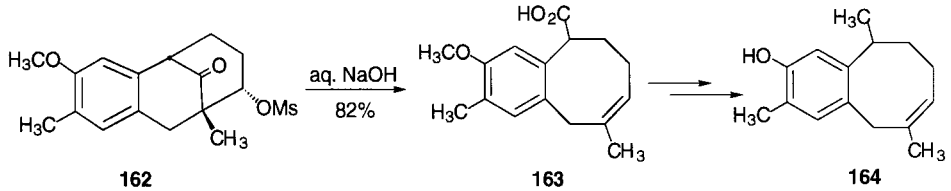
Dutta et al.[76] and Boeckman et al.[77,78] have synthesised the 5-8 fused core structure present in the ophiobolin and ceroplastol group of sesterterpenes and fusiccosin diterpenes having a 5-8-5 fused tricyclic ring system. Employing a base-induced HB fragmentation in the annulated bicyclo[3.3.1]nonanes **165** and **166**, the bicyclo[6.3.0]undecane derivatives **167** and **168**, respectively, were obtained (Scheme 42).

A synthesis of the hydroazulene sesquiterpene guaiol **171** described by Buchanan and Young[79] involved base-catalysed HB-type fragmentation as the key step. The diketone **169** on treatment with sodium methoxide underwent a fragmentation induced by the α,β-unsaturated ketone moiety acting as a nucleofuge to provide the intermediate hydroazulene ester **170** (Scheme 43).

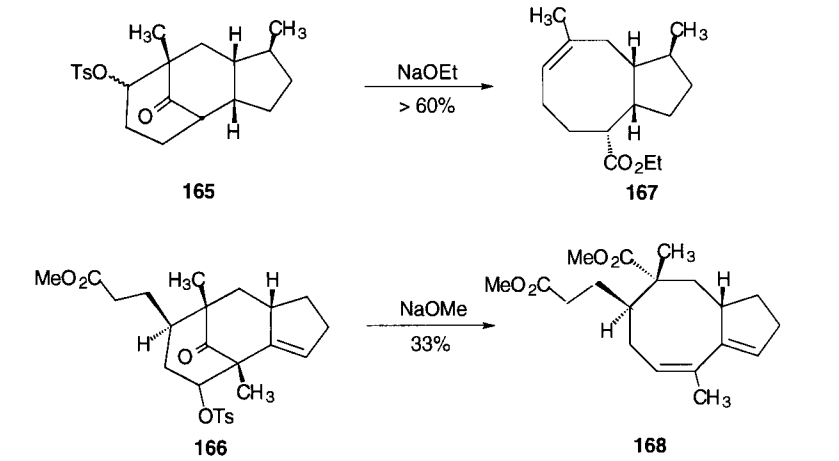
Larsen and Monti[80] have reported the amide-induced HB-type fragmentation of the tricyclic trimethylsilyl derivative **172** to generate a precursor **174** for further transformation to α-pinene and α-*trans* bergamotene **175** (Scheme 44). In this case, the OTMS group functions as a leaving group **173**.

Wender et al.[81] have carried out a base-induced fragmentation of the keto-tosylate **176** to furnish the lactone **177** (Scheme 45). This lactone served as the key intermediate in the synthesis of the fenestrane-type diterpene natural product, laurenene **178**.

During their approach to the synthesis of taxane derivatives, a facile HB-type cleavage in the polycyclic ketoether **179**

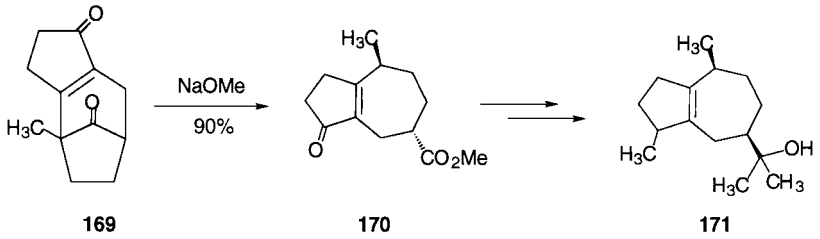


Scheme 41.



165 **167** **166** **168**

Scheme 42.



169 **170** **171**

Scheme 43.

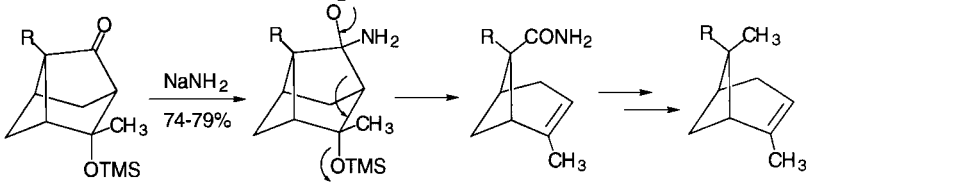
has been reported by Fetizon et al.[82] Treatment of **179** with sodamide afforded the lactam **182** through a fragmentation **180** followed by the ring opening of the ether linkage **181** (Scheme 46).

An interesting case of a tandem HB–Grob[83] fragmentation in the base treatment of some pentacyclo[4.3.0.$0^{2,4}$.$0^{3,8}$.$0^{5,7}$]-nonan-9-ones **183a–d** (norsnoutanones), substituted at the 4-position by electron-withdrawing groups, to produce a tricyclo[3.2.1.$0^{2,7}$]octane ring system has been recorded by Mehta and Ravikrishna.[84] Treatment of the pentacylic keto-ester **183a** with aqueous NaOH followed by esterification furnished the tricyclic diester **184** along with traces of the epimeric **185**. When potassium *tert*-butoxide was used as the base, **185** was formed exclusively and could be isomerised to **184**. The pentacyclic ketones **183b**,**c** under the conditions employed above furnished the tricyclic esters **184** and **186**, respectively (Scheme 47). The hydroxymethyl derivative **183d**, lacking a nucleofugal group, underwent simple HB cleavage to provide the epimeric diesters **187a**,**b** (Scheme 47). The pathway leading to the formation of the tricyclics **184**–**186** is thought to involve a tandem HB cleavage and higher order Grob fragmentation sequence in which two C–C bond scissions occur as depicted in Scheme 48. However, it is not clear whether the fragmentation is concerted (path a) or stepwise (path b).

4.6. Miscellaneous

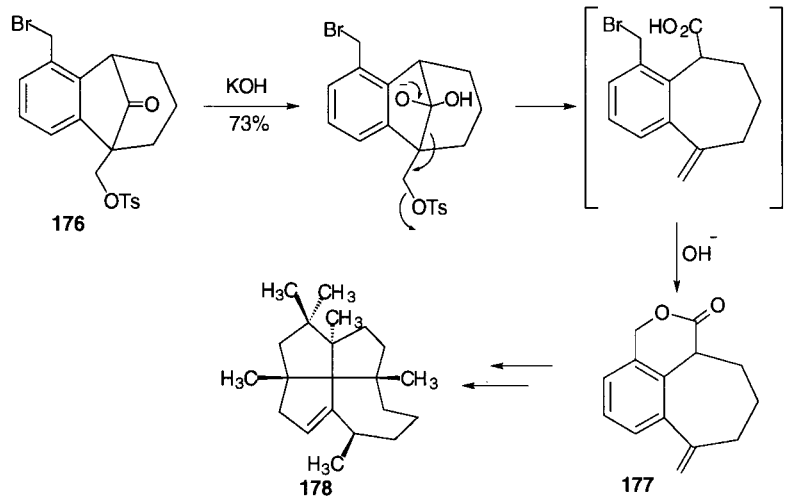
Although simple cyclohexanones have generally been found to be refractory towards HB type cleavage, their α-dithioacetal derivatives undergo ready cleavage in the presence of base. Marshall and Seitz[85] have demonstrated this in the case of the cycloalkanones **188** (6, 7 and 8-membered ring systems) to furnish the ω-functionalised carboxylic acids **189**. Similarly, the decalone **190** led to **191** (Scheme 49). An application of this methodology towards the synthesis of a prototype **192**, related to the vernolepin group of sesquiterpene antibiotics, has been reported (Scheme 49).[85]

Alexander and Tom[86] have developed a route to the 2-substituted bicyclo[1.1.1]pentane **194** employing HB cleavage in geminally substituted **193** (Scheme 50).

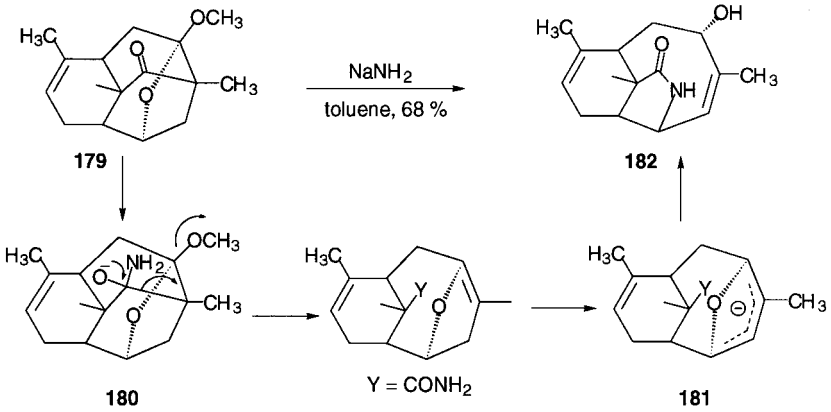


172a R = CH_3 **173** **174** **175a** R = CH_3
b R = $CH_2CH_2CH{=}C(CH_3)_2$ **b** R = $CH_2CH_2CH{=}C(CH_3)_2$

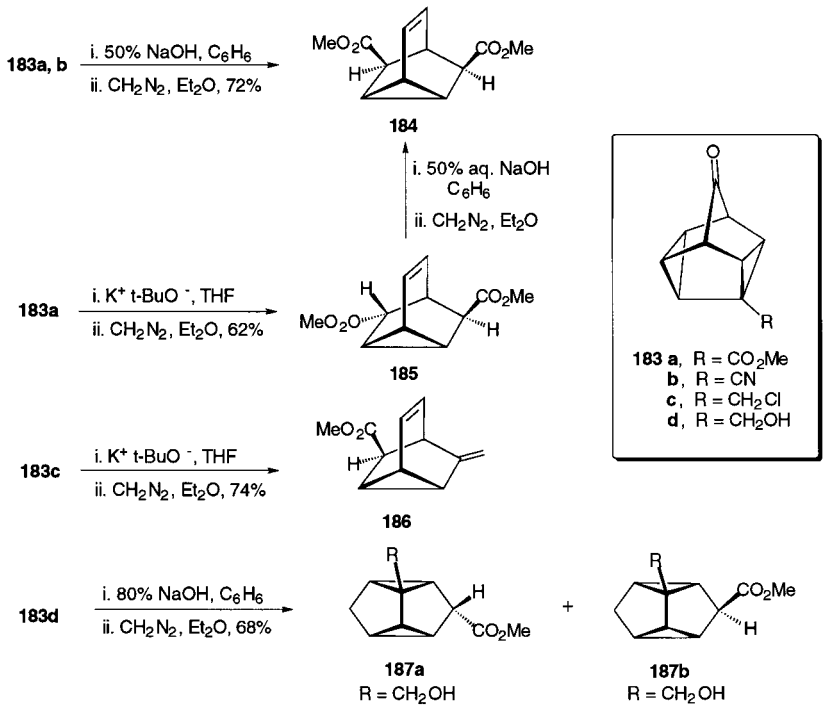
Scheme 44.



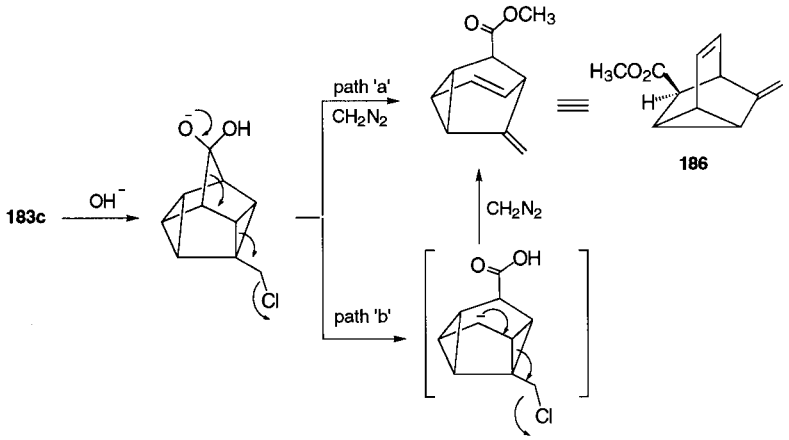
Scheme 45.



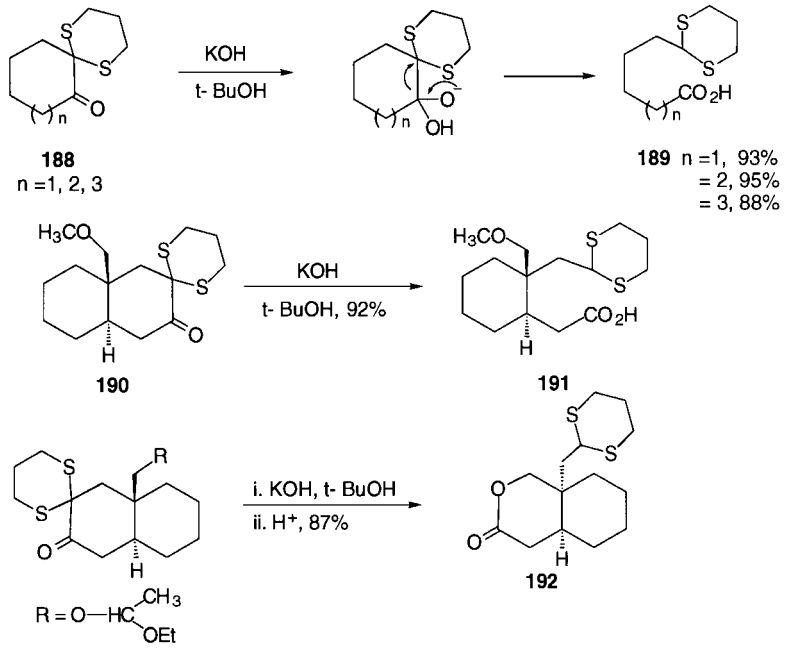
Scheme 46.



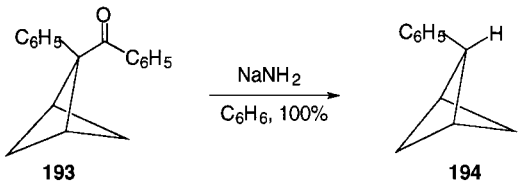
Scheme 47.



Scheme 48.



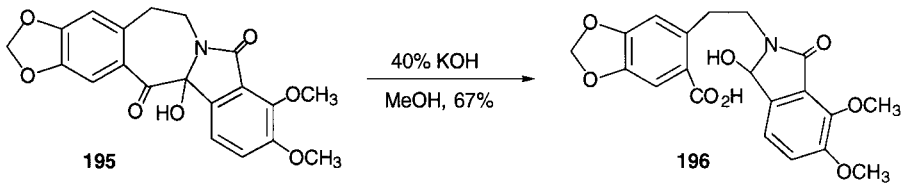
Scheme 49.



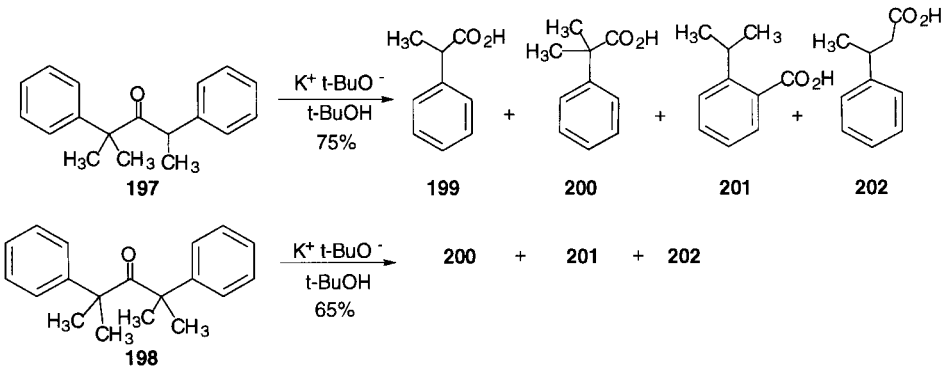
Scheme 50.

Investigating the chemistry of the highly functionalised aporhoeadane **195**, an unusual isoindolobenzazepine-based derivative of a natural product, Shamma et al.[87] have reported that, on treatment with aqueous methanolic KOH, it underwent a regioselective HB cleavage in ring C to produce the imidol **196** (Scheme 51).

During the course of their work on β-enolisation in α,α′-substituted ketones, Stothers et al.[88] found that the tri- and tetrasubstituted ketones **197** and **198**, respectively, under β-enolisation condition underwent a competitive HB



Scheme 51.



Scheme 52.

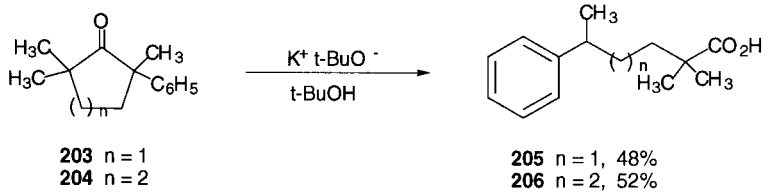
cleavage to give acidic products as shown in Scheme 52. While the acids **199** and **200** are derived through the normal HB cleavage, the acids **201** and **202** apparently arise from HB cleavage of the intermediate β-enolisation products. The fully substituted cyclopentanone **203** and cyclohexanone **204** also undergo competitive regioselective cleavage to furnish the acids **205** and **206**, respectively (Scheme 53).[89]

An interesting case of cleavage of a trifluoromethyl ketone has been reported by Kende et al.[90] The final step in the synthesis of the alkaloid altemicidin **208** involved an amide-induced cleavage of the trifluoromethylketone **207** to furnish the target compound (Scheme 54).

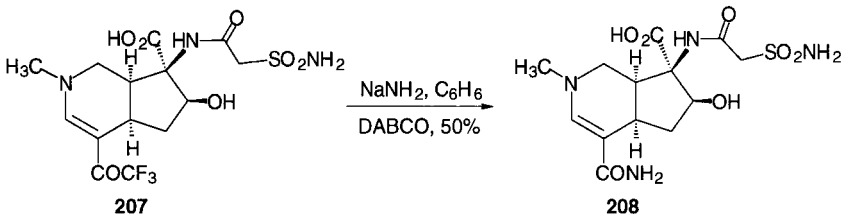
In a recent publication, Fitjer et al.[58] have disclosed a facile cleavage of a cyclohexanone which forms part of a polyspirane. The polyspiranone **209** on treatment with base leads to the opening of the cyclohexane ring to provide the interesting carboxylic acid **210** (Scheme 55).

5. Concluding Remarks

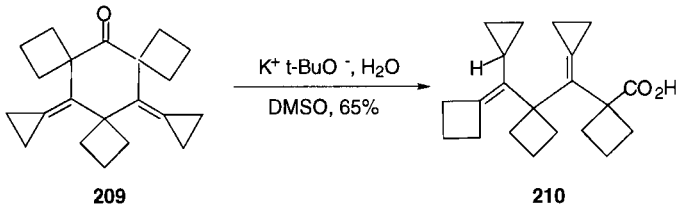
The unique aspect of the HB reaction is that a C–C bond cleavage can be affected by simply exposing a ketone to a base under the appropriate conditions. Despite such simplicity, the HB reaction has not found widespread use in synthesis, as its applicability is restricted to non-enolisable ketones. Its marked sensitivity to reaction conditions also hampers its routine use. The reaction needs to be pursued with a certain degree of persistence since small variations in the reaction conditions can make the vital difference between success and failure. One way of enhancing the preparative utility and the wider applicability of the HB reaction is to block the α,α′-positions by inert groups that



Scheme 53.



Scheme 54.



Scheme 55.

can either be disposed of or integrated with the synthetic scheme after the HB cleavage. The blocking groups can also serve as regio- and stereodirectors depending on their carbanion stabilising abilities. The success of the HB reaction with α,α'-dihalo- and α-dithioacetal-substituted ketones indicates that such blocking tactics can be exploited advantageously and amplifies the scope of this reaction. The combination of the HB reaction with Grob-like fragmentation, in tandem, offers several new opportunities in medium ring carbocyclic ring construction that need to be explored. Then, there are new possibilities like reductive decarboxylation with retention of configuration. Thus, conversion of an acid to a phenyl ketone followed by HB cleavage provides a synthetically useful methodology for a stereodefined decarboxylation with the proviso that the phenyl ketone should have a proper α-substituent to stabilise the resultant carbanion and regiodirect the reaction.

We think that the HB reaction offers many more opportunities in synthesis than have been recognised so far. It is hoped that this review will stimulate activity towards directed applications of this reaction in synthesis as opposed to the recording of incidental observations as has been generally the case.

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Biographical Sketch

Goverdhan Mehta was born in Jodhpur, India and obtained his Ph.D under the supervision of Dr Sukh Dev. His academic appointments include an Assistant Professorship (1970–77) at the Indian Institute of Technology, Kanpur and Professorship (1977–98) at the University of Hyderabad. In 1998, he accepted an invitation to become a Professor of Organic Chemistry at the Indian Institute of Science, Bangalore. He has been the recipient of numerous awards and honours for his research accomplishments and has extensively lectured in India and abroad. He is a Fellow of Science Academies in India and also of the Third World Academy of Sciences. In 1995, he was a recipient of the Humboldt Senior Scientist Award and in 1996 he received a Doctorate (h.c) from the University of Marseilles, France. His current research interests encompass the total synthesis of natural products, design of aesthetically pleasing molecular entities and devising incisive probes to study stereoelectronic control of diastereoselectivity.

R. V. Venkateswaran was born in Paalakkad, Kerala, India and obtained his Ph.D (1973) working at the Indian Association for the Cultivation of Science (I.A.C.S), Calcutta under Prof. P. C. Dutta. Subsequently, he joined the same institute as a faculty member. Later he did postdoctoral research with Dr E. W. Colvin at the University of Glasgow, U.K. He became a Professor in the Department of Organic Chemistry, I.A.C.S. in 1991 and, since 1997, he has been the Chairman of the Department. His research interests are in the total synthesis of natural products, particularly sesquiterpenoids and related compounds, and applications of photochemistry in organic synthesis.