DOI: 10.1002/anie.201209833

Heterolytic Fragmentation

C–C Fragmentation: Origins and Recent Applications

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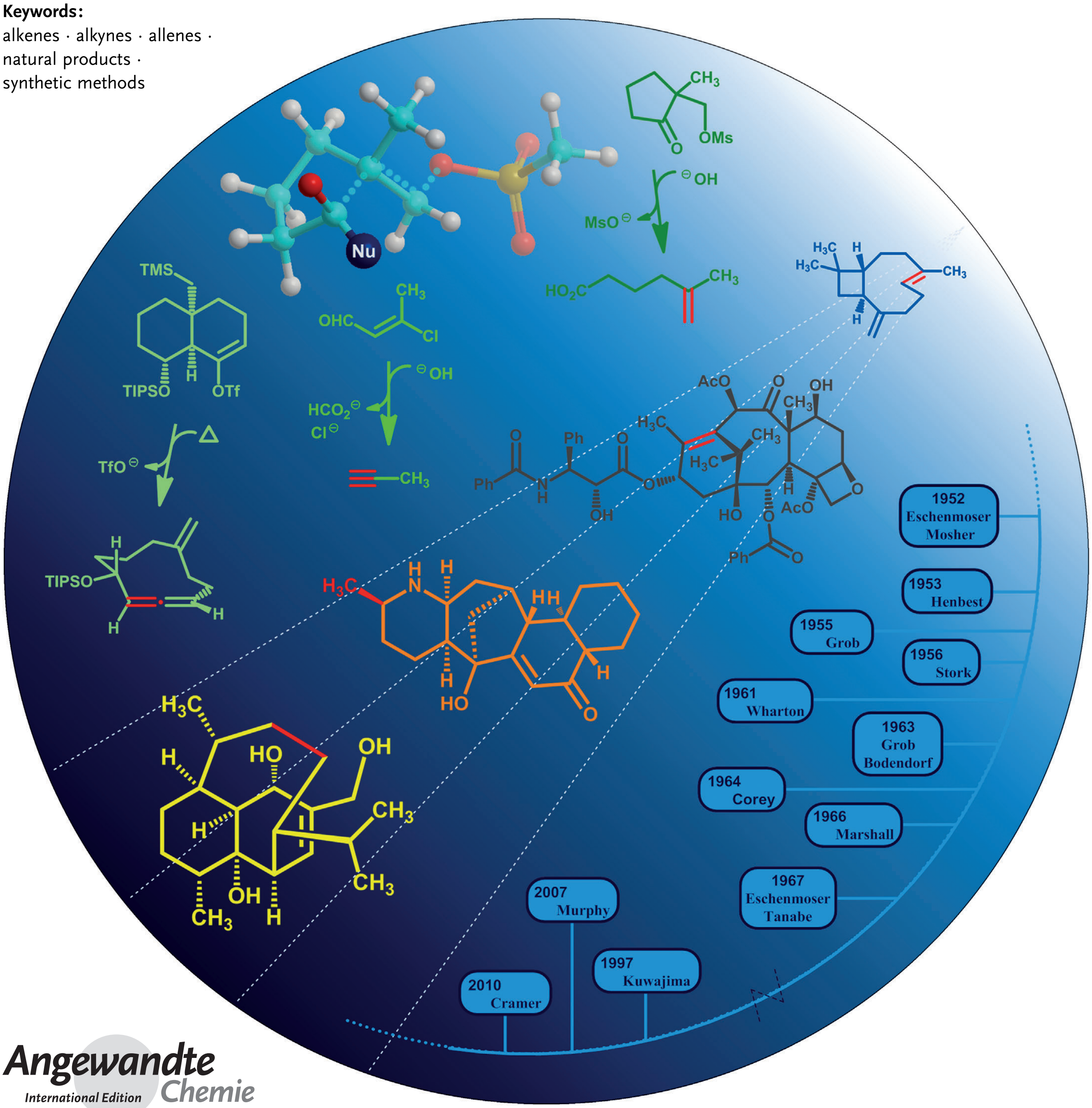
Keywords:
alkenes · alkynes · allenes · natural products · synthetic methods



Angewandte Chemie International Edition

It has been 60 years since Eschenmoser and Frey disclosed the archetypal C–C fragmentation reaction. New fragmentations and several variants of the original quickly followed. Many of these variations, which include the Beckmann, Grob, Wharton, Marshall, and Eschenmoser–Tanabe fragmentations, have been reviewed over the intervening years. A close examination of the origins of fragmentation has not been described. Recently, useful new methods have flourished, particularly fragmentations that give alkynes and allenes, and such reactions have been applied to a range of complex motifs and natural products. This Review traces the origins of fragmentation reactions and provides a summary of the methods, applications, and new insights of heterolytic C–C fragmentation reactions advanced over the last 20 years.

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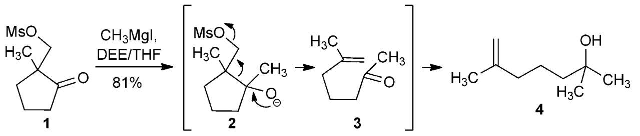
1. Introduction

Most synthetic methods focus on direct means to establish carbon–carbon (C–C), carbon–heteroatom (C–X), or heteroatom–heteroatom (X–Y) bond connectivity, to effect oxidation and reduction, or to achieve some combination of these. Direct chemical methods are powerful tools for synthesis. However, the immense variety of invented and naturally occurring molecules includes many structural motifs and motif combinations that are difficult to access directly.

Fragmentation reactions constitute distinctly different sorts of transformations. They effect bond cleavage and require the recognition of indirect synthetic planning strategies. As shown in Scheme 1, for example, in the archetypal C–C fragmentation, several objectives are achieved (**1**→**4**): creation of two π bonds (one of them transient, see **3**), scission of one C–C σ bond, and expulsion of a leaving group. Addition of a nucleophile to establish new connectivity constitutes an elegant embellishment that renders the overall process a cascade sequence. However, C–C cleavage is the key feature of the transformation and the lynchpin that enables the nucleophilic addition to leverage site-selective introduction of the C–C double bond. This contribution emanated from the Eschenmoser laboratories and appeared in 1952.[1] The report, and its complement of 1953,[2] contains all the features most closely associated with C–C fragmentation reactions. These include a mechanistic framework, applications in the selective preparation of otherwise difficult to form alkenes, and a review of the scattered antecedent observations of the reactivity principle, which to that point had not been mechanistically rationalized but which, given the author's insight, were clearly best understood as fragmentations.



Scheme 1. The original designed C–C fragmentation by Eschenmoser (1952).[1] DEE, Ms = mesyl.

Additional contributions that further established the Eschenmoser fragmentation as a general reaction paradigm were supplied by many. Strategically creative, mechanistically insightful, and otherwise useful developments were evident from the studies of Henbest, Grob, Stork, Wharton, and others within years of the landmark publication. Since most studies in this field find strong precedent in early reports, this Review presents a chronological examination of the antecedents (Section 2). Hence, we begin with the Beckmann fragmentation, which appeared in the German literature in the late 19th century, but was not generally recognized as such until the mid-20th century, and proceed through the first designed anionic fragmentation, which was advanced by Eschenmoser. This is followed by a brief history of cationic fragmentations and a detailed discussion of the early studies. The majority of the Review describes recent examples of C–C fragmentation from the past two decades (Section 3). The organization of this section parallels that of Section 2, with the addition of sp^2–sp^1 bond-forming fragmentations. We conclude with a reflection on remaining challenges in the field (Section 4).

The present Review does not aim to cover the entire field of fragmentations, or even the entirety of C–C fragmentations, but only its most elementary and recent divisions. There are a number of reactions that share the general features of heterolytic C–C fragmentation; nevertheless, they are more appropriately discussed elsewhere. For the purposes of this Review, therefore, the following reaction classes will not be

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covered: free-radical homolytic C–C fragmentation,[3] C–X fragmentations,[4] decarboxylative eliminations,[5] eliminations in general,[6] retro-Michael,[2] retro-aldol,[2] retro-Mannich,[7] and related processes.

Most schemes in this Review are accompanied by the year in which the work appeared and a framed illustration of the reactive intermediate in a conformation that approximates the presumed transition structure. The bonds directly involved in fragmentation are shown in bold. These figures are intended to facilitate an understanding of these transformations.

Several reviews on fragmentation have appeared over the years.[8] In most cases, these emphasize one aspect of the reaction class. For example, the first and most important review of the field, by Grob and Schiess,[8a] emphasized cationic pathways, nitrogen heterocycle substrates, and the mechanistic framework, and did not describe Eschenmoser's contributions,[9] whereas the most recent review by Prantz and Mulzer[8i] emphasized carbonyl-forming fragmentations that generated C–C double bonds. The most recent comprehensive review appeared in 1991.[8g]

2. Origins

In the 1950s, organic chemistry went through a period of explosive growth in understanding molecular structure and reactivity as well as in demonstrating this understanding in complex settings. A short, and only partial, list of fundamentally important findings with broad implications that were reported in—or directly traceable to—that decade includes such iconic achievements as ground- and transition-state conformational analysis of cyclic systems,[10] models for stereoinduction in acyclic systems,[11,12] recognition of rate-accelerating anchimeric effects,[13] mechanistic and stereochemical models for polyene cyclizations,[14] the discovery of important natural substances such as erythromycin,[15] formulation of the double-helical structure of DNA,[16] the application of nuclear magnetic resonance spectroscopy to the study of organic compounds,[17] and an organon for designing the synthesis of complex target molecules.[18]

Natural product synthesis, ever at the forefront of organic chemistry, took on an entirely new level of sophistication in this decade (Figure 1). Ground-breaking syntheses were

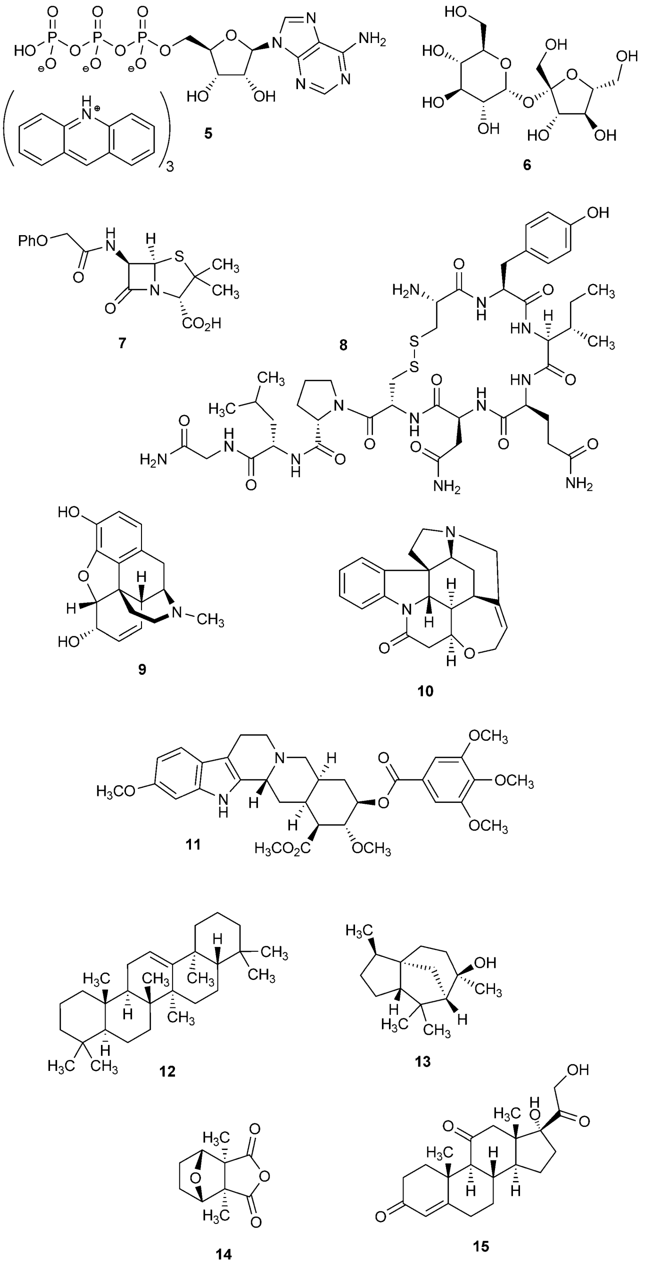

Figure 1. Selected natural products synthesized in the 1950s.[19–29]

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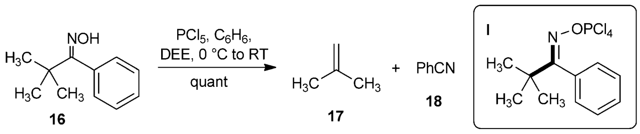
reported across structural classes, such as those for ATP (triacridinium salt **5**),[19] sucrose (**6**),[20] penicillin V (**7**),[21] oxytocin (**8**),[22] morphine (**9**),[23] strychnine (**10**),[24] reserpine (**11**),[25] pentacyclosqualene (**12**),[26] cedrol (**13**),[27] cantharadin (**14**),[28] and cortisone (**15**).[29]

This was the exciting period during which Eschenmoser put forth his fragmentation. The broad development of C–C fragmentation included reactions that produce sp^1–sp^1 connectivity as well as sp^2–sp^2 connectivity, but did not extend to producing the sp^2–sp^1 connectivity present in cumulenes until much later. Although they were originally misinterpreted, the earliest recorded fragmentations fall in the sp^1–sp^1 category. Accordingly, we describe these developments first and then return to the early work of sp^2–sp^2 bond-forming fragmentations.

2.1. sp^1–sp^1 Bond-Forming Fragmentations

The first C–C fragmentation reaction, the Beckmann fragmentation, was conducted unknowingly by Wallach at the end of the 19th century and gives a nitrile as the signature product (Scheme 2).[30] This cleavage process is often encountered as an undesired side reaction of a Beckmann rearrangement, which had been discovered by Beckmann in 1886.[31] Wallach's 1890 reaction[30a] was optimized, though still not interpreted correctly, by Schroeter in 1911.[32] It was not until 1955, when Brown and co-workers repeated Schroeter's work, that a correct mechanistic formulation of the Wallach transformation was recorded in the literature.[33] In this optimization, the competing Beckmann pathways are controlled by the activating reagent. Thus, treatment of pivalophenoxime (**16**) with phosphorous pentachloride under mild conditions gives a quantitative yield of benzonitrile (see also **I**).



Scheme 2. The optimized Wallach nitrile synthesis (1911).[30a,32,33]

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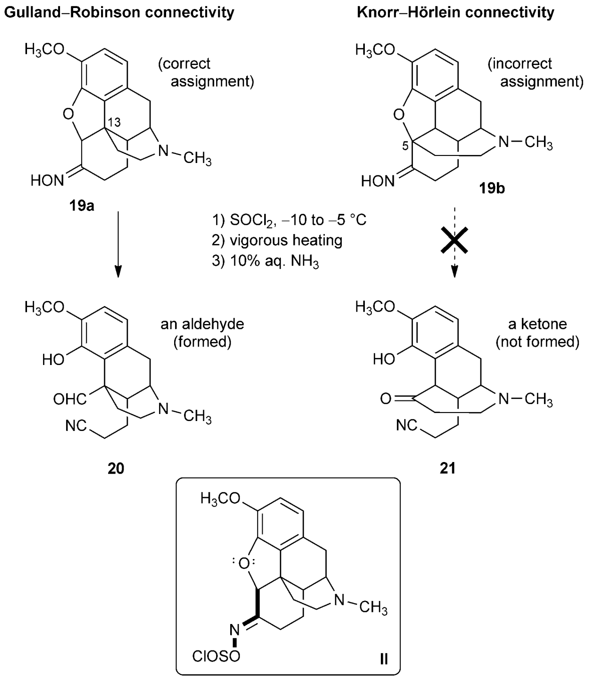
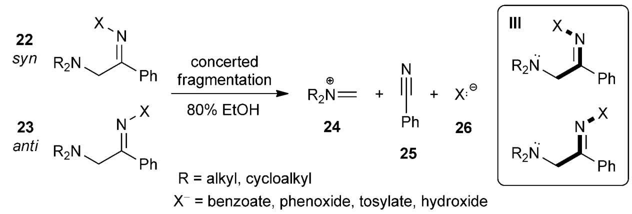
The Beckmann fragmentation was recognized as a useful transformation long before 1955. Perhaps the most astute early use of the reaction was in the context of determining the structure of morphine. For more than a century, chemists aimed at elucidating the structure of morphine and related opium alkaloids. The proposals of Gulland and Robinson in the early 1920s,[34] which contradicted the long-accepted Knorr–Hörlein formula,[35] were strongly supported by Schöpf's degradation studies of 1927 (Scheme 3).[36] Schöpf sought to determine whether the C-terminus of the ethylamine bridge was located at C13 or C5 by subjecting dihydrocodeinone oxime (**19 a/b**) to Beckmann conditions. After further degradation, the Beckmann fragmentation product was assigned as aldehyde nitrile **20**, not ketonitrile **21**. The 1952 synthesis of morphine by Gates and Tschudi proved these assignments to be correct.[23]



Scheme 3. Morphine degradation studies by Schöpf (1927).[34–36]

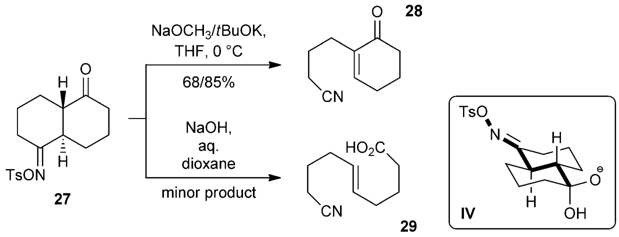
For most of its history, this reaction had been referred to by various names, including "Beckmann fission," "abnormal Beckmann rearrangement," and "second-order Beckmann rearrangement."[8c] It was not until the 1960s, after the mechanistic studies of Grob and Fischer,[37] that the synthetic community adopted the term Beckmann fragmentation.

Although Grob was not the first to deliberately design substrates to undergo useful C–C fragmentation or to recognize the reactivity principle, he was the greatest protagonist and made manifold contributions to the field. He was instrumental in advancing the generality of fragmentation for sp^1–sp^1 and sp^2–sp^2 systems, C–C and C–X linkages, homolytic and heterolytic reactions, and cationic, anionic, and neutral pathways. Grob also advocated that fragmentations be considered distinct from other reactions, for example, eliminations. His 1967 review is especially noteworthy in this regard.[8a,9] Grob's first work on the Beckmann fragmentation appeared in 1963, in which he reported the fragmentation kinetics of α-aminoacetophenone oxime derivatives (e.g. **22** and **23**, Scheme 4).[37b] Throughout his studies, he favored the term nucleofuge, which refers to the leaving group of a fragmentation (e.g. X in Scheme 4), and the term electrofuge, which refers to the group that donates electrons in the fragmentation (e.g. the amine nitrogen atom).



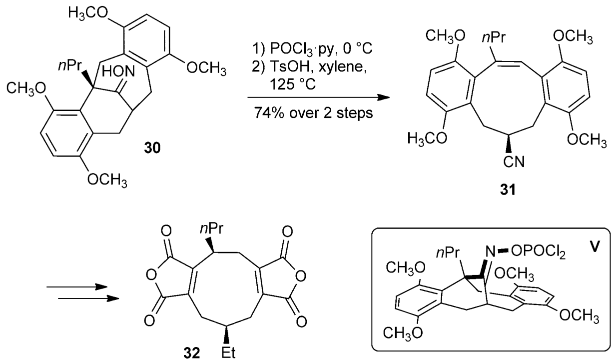
Scheme 4. Grob's oxime fragmentation studies (1963).[37b]

Also in 1963, Grob and co-workers extended the Beckmann fragmentation to include the formation of ene-nitriles (Scheme 5).[37c] Ketotosylate **27** was shown to give **28** or **29** depending on the reaction conditions. Nitrile **28** was formed cleanly upon treatment with a bulky base, whereas **29** was formed, albeit inefficiently, upon treatment with hydroxide. By this time the use of hydroxide to promote fragmentation had clear precedent.[1] It should be noted that the reactive intermediates were not characterized, as is often the case, and the structure shown (**IV**) is meant as a qualitative guide only.

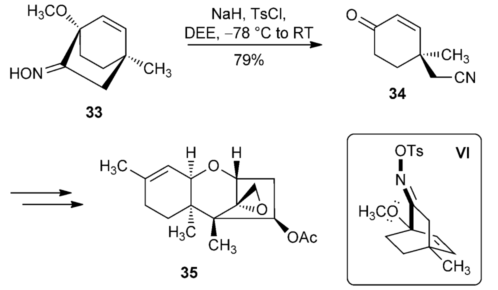


Scheme 5. Grob's ene-nitrile synthesis (1963).[37c]

The first applications of the Beckmann fragmentation to complex molecule synthesis continue to stand as the central paradigm for its strategic use. In 1972 Stork reported the first total synthesis of byssochlamic acid (**32**, Scheme 6), a nonadride mold metabolite.[38] The nine-membered ring was constructed by fragmentation of oxime **30**. Acid-induced isomerization of the exocyclic olefin intermediate gave endocyclic olefin **31** in good yield. In 1973 Colvin and co-workers utilized a heteroatom-assisted Beckmann fragmentation that is reminiscent of Schöpf's work on opium alkaloids (Scheme 7; cf. **II** and **VI**).[39] Under ionizing conditions, the oxime tosylate derived from **33** fragmented to furnish derivative **34**, an early stage intermediate in their synthesis of the sesquiterpene antibiotic trichodermine (**35**).[40]

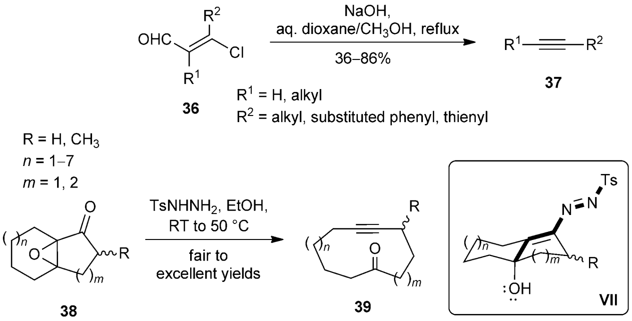


Scheme 6. Stork's ring expansion in the total synthesis of (±)-byssochlamic acid (**32**; 1972).[38] Py = pyridine.

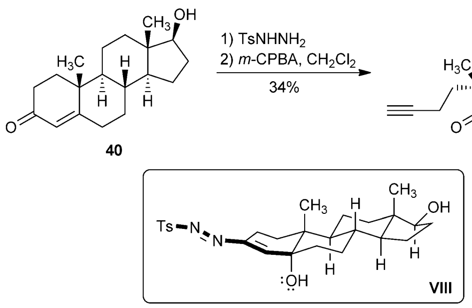


Scheme 7. Colvin's heteroatom-assisted fragmentation in the total synthesis of (±)-trichodermine (**35**; 1973).[39] Ts = toluene-4-sulfonyl.

The earliest sp^1–sp^1 bond-forming fragmentation reactions that did not give nitrile products were reported by Bodendorf in the early 1960s.[41] Substituted β-chloroacroleins were shown to fragment in the presence of aqueous sodium hydroxide to acetylenes and formic acid (e.g. **36**→**37**, Scheme 8). In 1967 Eschenmoser disclosed an α,β-epoxyketone fragmentation that gave cyclic alkynes (**38**→**39**).[42,43] Shortly after Eschenmoser's first report on this transformation appeared, Tanabe et al. disclosed essentially the same reaction[44] and followed up with a study on its application to secosteroids from testosterone (**40**, Scheme 9).[45] To circumvent the problem of the epoxidation of α,β-unsaturated ketones, the ketone was activated first to the *p*-toluenesulfo-



Scheme 8. The original alkyne synthesis by Bodendorf (1963),[41] and Eschenmoser's and Tanabe's cyclic alkyne syntheses (1967).[42,44]

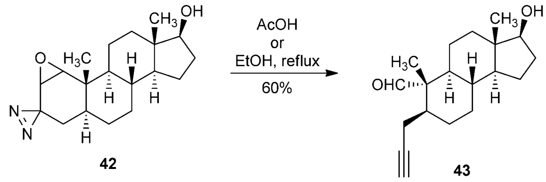


Scheme 9. Tanabe's secosteroid synthesis (1967).[45] *m*-CPBA = *meta*-chloroperbenzoic acid.

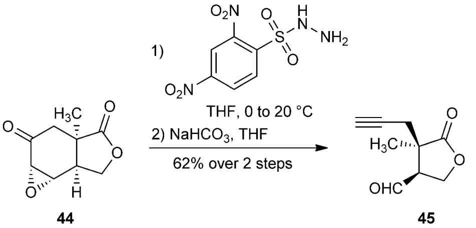
nylhydrazone (**VIII**), then treated with *m*-CPBA to effect fragmentation.

Creative extensions and important improvements followed shortly after the original findings. In 1968 Borrevang et al. extended the mechanistic framework to include epoxydiazirines to give acetylenic aldehydes (e.g. **42**→**43**, Scheme 10).[46]

In 1975 Corey and Sachdev showed that 2,4-dinitrobenzenesulfonylhydrazine is superior to *p*-toluenesulfonylhydrazine in the synthesis of acetylenic aldehydes (Scheme 11).[47]



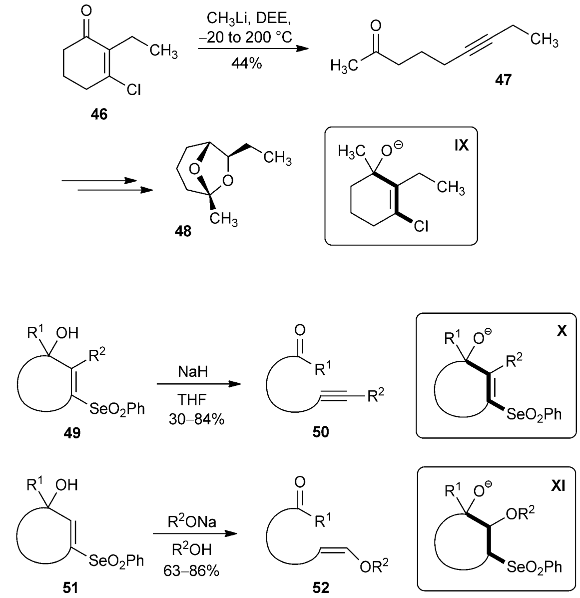
Scheme 10. Borrevang's A-norsteroid synthesis (1968).[46]



Scheme 11. Corey's acetylenic aldehyde synthesis (1975).[47]

The increased electron-withdrawing nature of this reagent renders the corresponding sulfinate a better leaving group, and thereby enables fragmentation to occur under conditions more compatible with the product (e.g. **45**). This early modification of the Eschenmoser–Tanabe fragmentation remains in use.

The 1977 report by Coke et al. is particularly relevant to much of the alkyne-forming fragmentations reported in recent years (**46**→**47**, Scheme 12).[48] The method was applied to the synthesis of *exo*-brevicomin (**48**), a pheromone produced by the western pine beetle. The addition of alkyllithium reagents to β-halo-α,β-unsaturated ketones followed by warming promotes fragmentation (see **IX**). This advance can be viewed as the fusion of the Bodendorf[41] and Eschenmoser[1] studies. This reaction modality was also demonstrated to include selenones as the leaving group.[49] Treatment of cyclic 3-hydroxyvinylphenyl selenones (**49** and **51**) with base at room temperature leads to fragmentation. Bases of low nucleophilicity (NaH, *t*BuOK, LDA) promote direct fragmentation. Alkoxides, however, add to the vinyl selenone, which is followed by proton transfer, and then fragmentation. Although the formation of **52** formally belongs to the sp^2–sp^2 category, the finding is relevant here, since the selection of the base determines the product distribution.



Scheme 12. Coke (1977)[48] and Kuwajima's (1981)[49] acetylenic ketone syntheses.

2.2. sp^2–sp^2 Bond-Forming Fragmentations

The 1952 Eschenmoser disclosure described alkene synthesis by fragmentation under basic conditions so as to ensure proper placement of the resultant C–C double bond.[1] The report included a comprehensive collection of the relevant anionic pathways that had been recorded as otherwise isolated and unrelated. These observations were summarized together in the context of a unified mechanistic framework, which provided insight as to likely product structures. Hence, certain reactions of halide-substituted monoterpenes with alkali reportedly produced ene-acids, such as β-bromocamphor (**53**, Figure 2),[50] monobromofenchone (**54**, the constitutional structure of which had not yet been fully assigned),[51] and a pulegone dibromide (**55**).[52] The product structures could then be readily formulated in light of the suggested mechanism. Certain β-bromo acids and α-tosyloxy-β,β-dimethylbutyrolactone were noted to undergo base-promoted decarboxylative or decarbonylative elimination.[53,54] The final

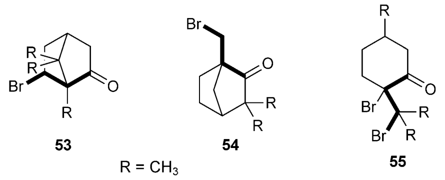
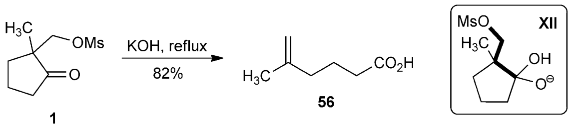


Figure 2. Monoterpene fragmentation substrates from Forster (**53**; 1902), Czerny (**54**; 1900), and Wallach (**55**; 1896).[50–52]



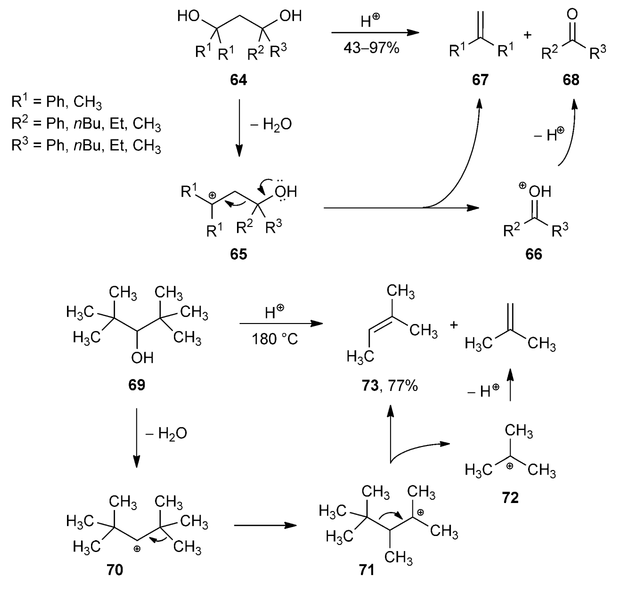
Scheme 13. Eschenmoser's original alkene synthesis (1952).[1]

observation cited was a 1951 report on the reaction of β-chloroketones with Grignard reagents.[55]

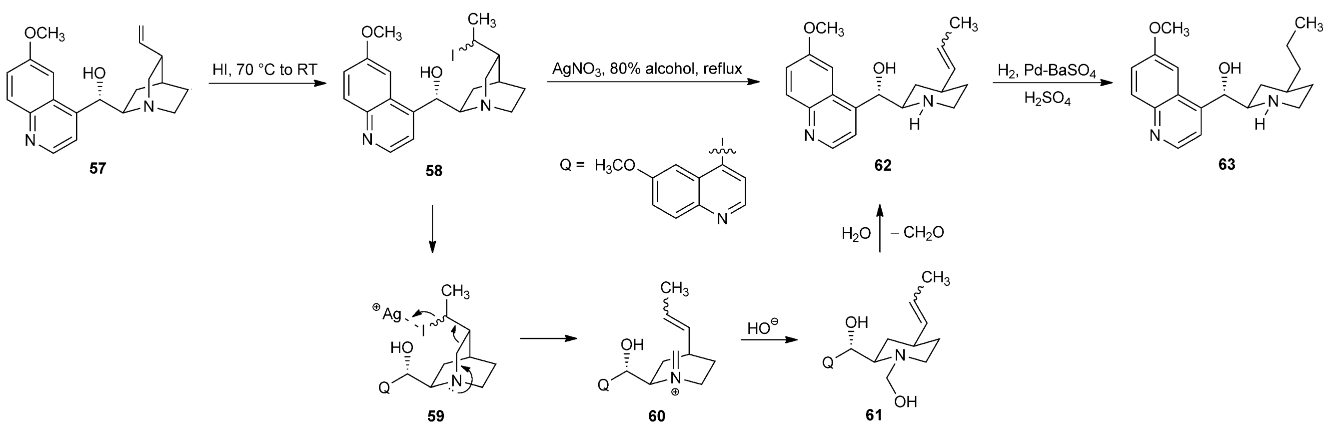
To illustrate the potential of the revealed reactivity, Eschenmoser designed substrate **1** (Scheme 13) for the selective preparation of a 1,1-disubstituted alkene (**56**).[1] The C–C cleavage (*spaltung*, according to Wallach) offered an improvement over existing methods of alkene synthesis,[56] which often required vigorous conditions and resulted in mixtures of products usually favoring the more-substituted double bond. Base-induced C–C cleavage and loss of the properly positioned leaving group guaranteed site-selective introduction of the alkene.

One antecedent not mentioned in Eschenmoser's original report was the degradation reactions of cinchona alkaloids under neutral conditions. Although initially interpreted incorrectly, the fragmentation of a quinine derivative was first reported by Skraup in 1892.[57–59] In the late 1930s, Gibbs and Henry confirmed the loss of formaldehyde in an analogous degradation of quinidine (**57**) to niquidine (**62**) and provided constitutional formulas of the isomeric products and the subsequent single hydrogenation product, dihydroniquidine (**63**, Scheme 14).[60] In a 1952 synthetic study, Mosher et al. offered a sound mechanism to explain the conversion of **57** into **62**.[61] However, this appeared in the same timeframe as the Eschenmoser report and could not have been included as a citation.

Perhaps understandably, Beckmann and cationic pathways that led to overall fragmentation were not mentioned. Controlled alkene formation, germane to the Eschenmoser fragmentation, is compromised in cationic pathways. The discovery and study of what we now call cationic fragmentations began in the early 20th century and nearly coincided with the discovery of the reverse transformation: the Prins reaction (where the resultant cation is captured by a nucleophile).[62] The first report on a Prins-type reaction was published in 1899. Indeed, many cationic fragmentations could well be described as retro-Prins-type reactions. However, such transformations are now considered fragmentations. The etiology of this type of reaction is traceable to Slawjanov[63a] and Kalishev,[63b] who independently reported the acid-induced conversion of hexamethyl-1,3-propanediol into isobutylene and acetone (**64**→**67** and **68**, R^1, R^2, and $R^3 = CH_3$; Scheme 15). In 1933 Whitmore and Stahly demonstrated a similar process in the dehydration of di-*tert*-



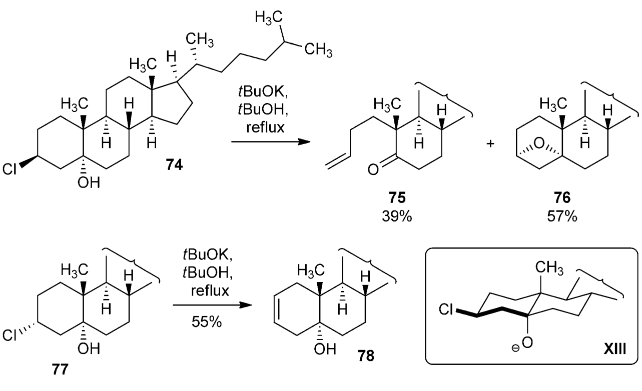
Scheme 15. Cationic fragmentations (1907–1952).[63,64,66]



Scheme 14. Gibbs–Henry degradation of quinidine (**57**; 1939)[60] and Mosher's mechanistic interpretation (1952).[61]

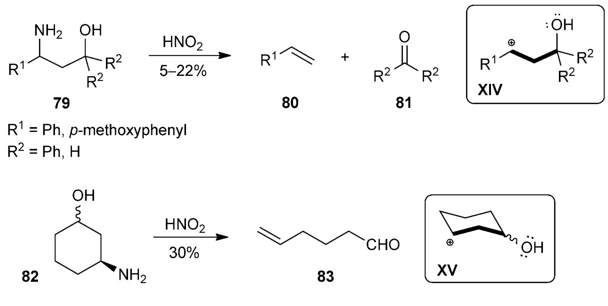
butylcarbinol (**69**).[64] Loss of water and formation of the secondary carbocation is followed by a 1,2-methyl shift and then C–C fragmentation to produce trimethylethylene (**73**) and isobutylene.[65]

After 1952, a treasure trove of discoveries and reactivity insights were published. The first such study emanated from the Henbest laboratories in 1953 (Scheme 16).[67] This research group explored the competing reaction pathways of 3-chloro-1-ols in basic solution.[67,68] Using monocyclic and steroidal substrates, they demonstrated that fragmentation depends on the relative stereochemical arrangement of the reaction centers. Treatment of *trans*-chlorocholestanol **74** with potassium *tert*-butoxide afforded significant quantities of the *seco*-ketone **75**; exposure of epimeric chlorocholestanol **77** to the same conditions predominantly gave the elimination product **78**. Clayton and Henbest were the first to assert that fragmentation is possible only when the bonds to be severed are in an antiparallel arrangement (see **XIII**).[67,68]



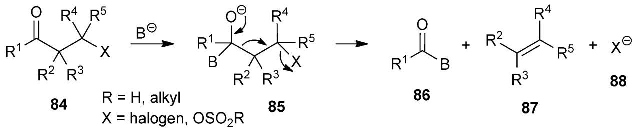
Scheme 16. The original stereochemical investigation on concerted C–C fragmentation by Henbest (1953).[67,68]

In the early 1950s English et al. expanded the scope of the acid-catalyzed cleavage reactions of 1,3-diols and singled out the importance of cationic intermediate **65** (Scheme 15).[66] In 1956, English and Bliss rationalized that other compounds capable of generating β-hydroxycarbocations should also undergo fragmentation.[69] Accordingly, they studied the deamination of 1,3-amino alcohols (e.g. **79**, Scheme 17) by nitrous acid. Shortly after this disclosure, Jefferies and coworkers reported the rupture of *cis*- and *trans*-3-aminocyclohexanol (**82**) under similar conditions.[70]



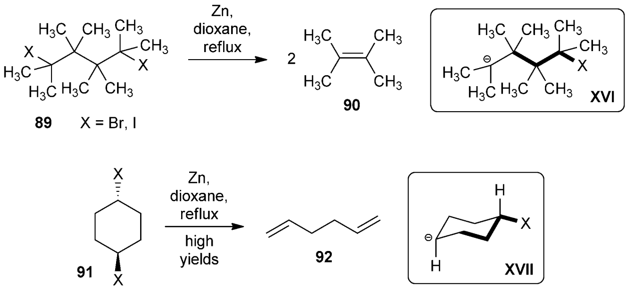
Scheme 17. English and Jefferies' cationic fragmentations (1956, 1957).[69,70]

Grob's first contribution to C–C fragmentation appeared in 1955.[71] In this report he introduced the term fragmentation (*fragmentierung*), presented the Eschenmoser mechanistic framework (Scheme 18) in a generalized form,[72,73] reviewed a series of 1,4-elimination reactions, including the zinc-mediated elimination of 1,4-dihalides (e.g. **89**), and converted 1,4-dihalocyclohexanes into hexa-1,5-diene in high yield (**92**, Scheme 19).

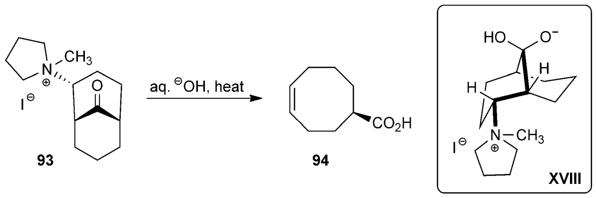


Scheme 18. The original C–C fragmentation mechanistic framework by Eschenmoser (1952).[1]

Stork and Landesman reported the first ring expansion by fragmentation in 1956 (**93**→**94**, Scheme 20).[74] However, beginning in 1961, Wharton demonstrated that site-selective olefin formation through C–C fragmentation could be stereospecific and could be used to generate medium-sized rings from bicyclic precursors (e.g. **95**→**96**, Scheme 21).[75] This strategic insight has been immensely useful for preparing cyclic alkenes of defined geometry.

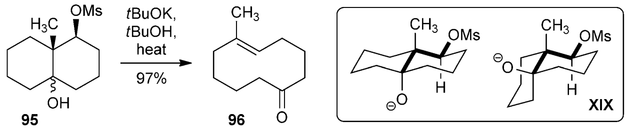


Scheme 19. Grob's 1,4-eliminations and diene synthesis (1955).[71]

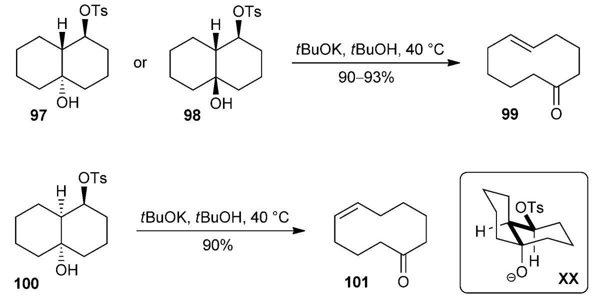


Scheme 20. The original C–C fragmentative ring expansion by Stork (1956).[74]

In 1965, Wharton and Hiegel reported numerous other examples of fragmentation in the decalindiol series, which are now considered classic studies. Importantly, these findings emphasize the efficiency of the method when the bonds to be broken are antiperiplanar.[76,77] Moreover, epimeric monoto-

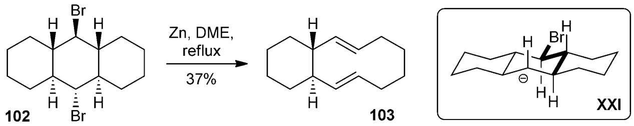


Scheme 21. Wharton's stereoconvergent ring expansion (1961).[75]



Scheme 22. Wharton's cyclodecene syntheses (1965).[76]

sylates **97** and **98** fragment under identical conditions to yield the same product, *trans*-5-cyclodecenone (**99**), in excellent yields (Scheme 22).[75] Thus, the stereochemistry of the procarbonyl carbon atom was suggested to be irrelevant in a fragmentation process (cf. **XIX**). The complementary *cis* isomer was obtained from the epimeric monotosylate **100**. Wharton et al. also executed the stereospecific fragmentation of dibromoperhydroanthracene **102** to bicyclo-[8.4.0]tetradecadiene **103** (Scheme 23).[78,79]



Scheme 23. Wharton's cyclodecadiene synthesis (1965).[78] DME = 1,2-dimethoxyethane.

Grob and Ostermayer reported in 1962 the solvolysis of acyclic, monocyclic, and bicyclic γ-amino halides **104**–**106** (Figure 3),[80] and thereby demonstrated that the degradative fragmentations of the cinchona alkaloids represent a general transformation.[57,58,60] They showed that fragmentation predominates over substitution and elimination in these systems. A series of *N*-methyldecahydroquinoline tosylates were also investigated (**107**, **109**, and **111**, Scheme 24).[81] In accordance with Clayton and Henbest,[67,68] Grob and Ostermayer confirmed that a concerted pathway is favored over a two-step mechanism provided both the C–OTs bond and nitrogen lone pair of electrons are antiperiplanar to the scissile C–C bond (see **XXV**–**XXVII**). Solvolysis of **107**, **109**, and **111** afforded products of stereospecific fragmentation exclusively, whereas the corresponding epimeric tosylates, which could not adopt an antiperiplanar arrangement, were much slower to solvolyze and yielded mixtures of fragmentation, substitution, and elimination products. Grob and co-workers argued that, although the *N*-methyl groups are predominantly in the equatorial position, concerted fragmentation occurs most readily when they are axial, thereby placing the nitrogen lone pair of electrons antiperiplanar to the rupturing bonds.[82–84]

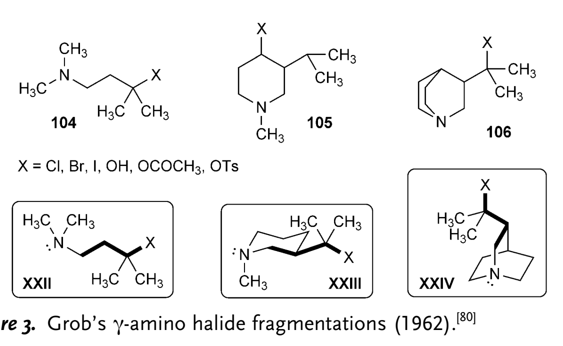
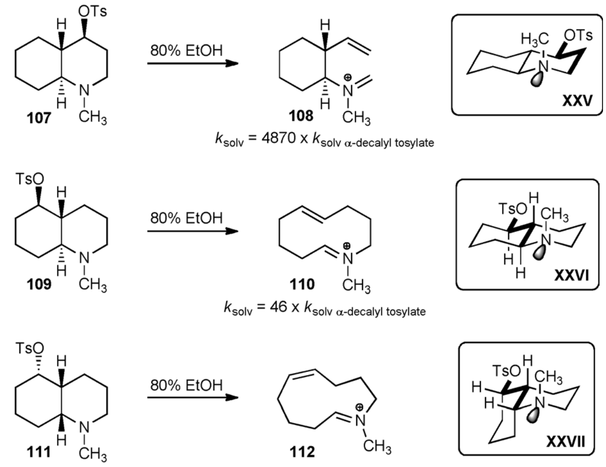
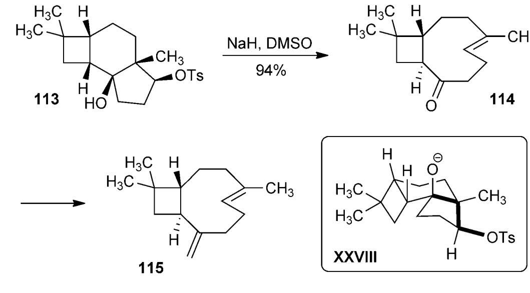


Figure 3. Grob's γ-amino halide fragmentations (1962).[80]

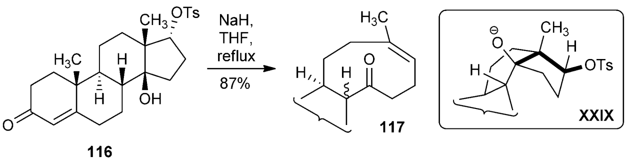


Scheme 24. Grob's kinetic studies (1964).[8b,81]

The 1963 and 1964 study by Corey et al. on caryophyllene stands as a classic in chemical synthesis (**115**, Scheme 25).[85] The authors noted that the contributions of Eschenmoser, Henbest, Jefferies, and Wharton provided the strategic foundation upon which this natural product and its isomers were prepared.[86] Indeed, the trisubstituted alkene was installed stereospecifically within this challenging context (**113**→**114**).



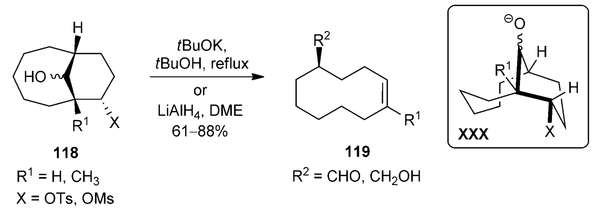
Scheme 25. The original total synthesis by C–C fragmentation by Corey (1963, 1964).[85]



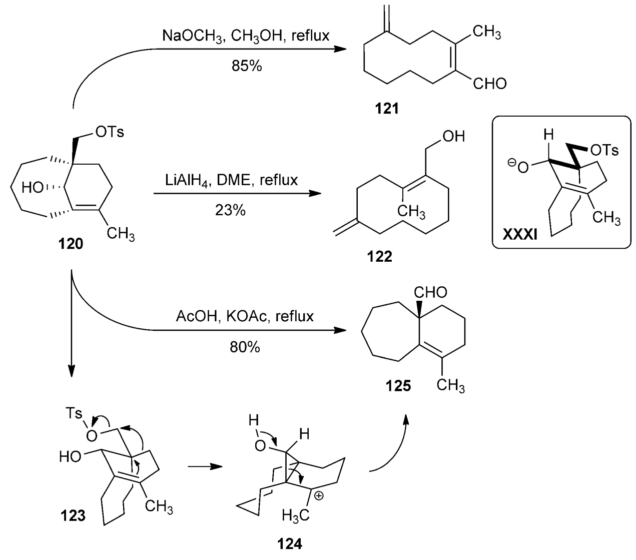
Scheme 26. Tanabe's cyclononene synthesis (1964).[87]

Concurrent with the syntheses of nine-membered rings by Corey et al., Tanabe and Crowe constructed the cyclononenone-containing 13,14-secosteroid **117** from hydroxytosylate **116** (Scheme 26).[87] Presumably, the *cis* relationship between the C17 hydrogen and C18 methyl group was retained (**XXIX**). The stereochemistry at C8 was not assigned because of the enolizability of this α-proton under the reaction conditions.

In a 1965 study reminiscent of the ring expansion by Stork and Landesman,[74] Marshall and Scanio prepared substituted *cis*-cyclodecenes from activated [5.3.1]bicycles (e.g. **118**→**119**, Scheme 27).[88] Similarly, the reactivity of hydroxytosylate **120** was studied (Scheme 28).[89] Under nucleophilic basic conditions, compound **120** fragmented and the *Z* olefin rearranged to the thermodynamic *E* olefin **121**. In the presence of hydride, **120** formed alcohol **122**. Under solvolytic conditions, however, the rearrangement product **125** was isolated. This product was rationalized in terms of cationic ring expansion and then fragmentation (**123**→**124**→**125**).

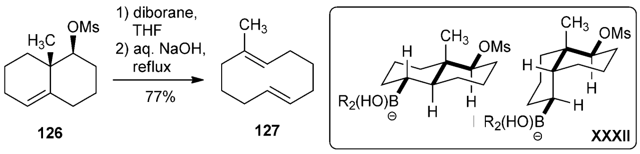


Scheme 27. Marshall's ring expansions (1965).[88]

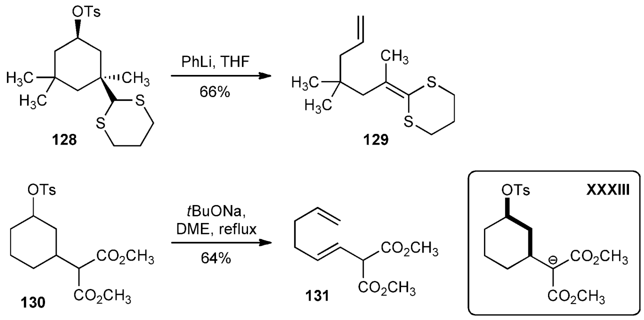


Scheme 28. Marshall's divergent fragmentations (1967).[89]

Marshall and Bundy ingeniously expanded the scope of the electrofuge. The first of these contributions appeared in 1966.[90] In it they showed that an in situ generated boronate, probably as a mixture of diastereomers, could serve as the electron source in a fragmentation through the stereospecific formation of **127** from **126** (Scheme 29).[91] The Marshall research group also introduced the use of stabilized dithianyl[92] and malonyl[93] anions, reminiscent of Grob's ene-nitrile work (Scheme 5). For example, **128** and **130** led to the corresponding products **129** and, after base-induced olefin migration, **131** (Scheme 30).



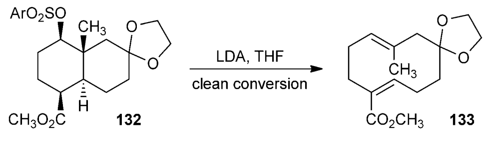
Scheme 29. The original boronate electrofuge by Marshall (1966).[90]



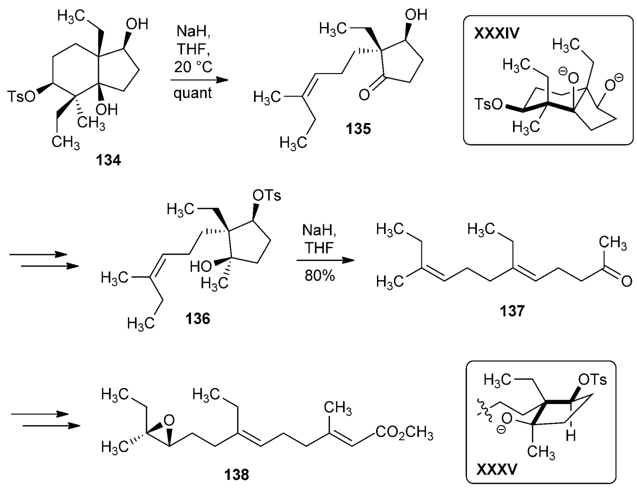
Scheme 30. The original dithianyl electrofuge and malonyl electrofuge by Marshall (1971).[92,93]

The Grob/Marshall-type electrofuge was used by Mander and co-workers to access complex germacranes and related sesquiterpenes.[94] The enolate of *trans*-decalin **132** underwent clean conversion into diene **133** (Scheme 31). Production of this single geometric isomer under non-isomerizing conditions implies that fragmentation occurred predominantly with the methyl ester in a pseudoaxial position.

Four years after the synthesis of caryophyllene (**115**),[85] a research group at Syntex reported the synthesis of a polyunsaturated acyclic system (**137**, Scheme 32).[95] In this classic synthesis, two challenging trisubstituted alkenes were



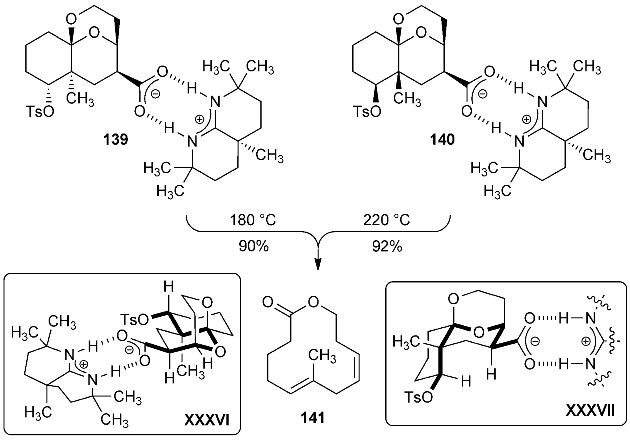
Scheme 31. Mander's germacrane scaffold synthesis (1977).[94] LDA = lithium diisopropylamide.



Scheme 32. The Syntex sequential fragmentation (1968).[95]

generated by way of a sequential fragmentation of a cyclic precursor. Bicycle **134** was designed to stereospecifically transform into **135** then **137**. This study constituted a formal synthesis of juvenile hormone I (**138**).

In this section we summarized the foundational studies of C–C fragmentation and focused on the applications that presage much of the work in the field. We close with a final classic study and one of the boldest transformations of this sort. It appeared in 1979.[96] In an approach towards macrolides, Eschenmoser and co-workers designed diastereomeric amidinium carboxylates **139** and **140** to undergo extended fragmentation to produce macrolactone **141** (Scheme 33).



Scheme 33. Eschenmoser's extended decarboxylative elimination/C–C fragmentation (1979).[96]

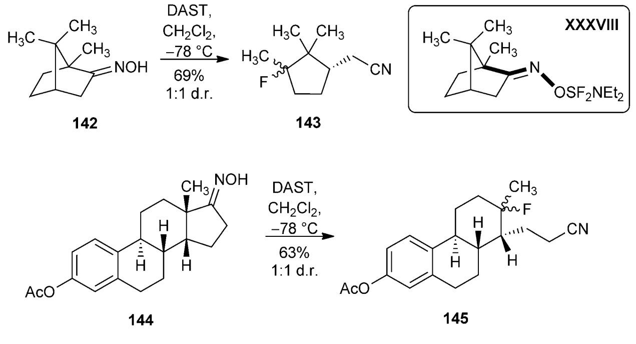
Although the mechanisms of these transformations were not studied, both were designed to effect tandem decarboxylative elimination and heterolytic C–C fragmentation processes that alter the connectivity of nine atoms of the substrate. Another pair of tricyclic substrates was also examined.[97]

3. Progress and Applications

The key findings described above have enabled many innovative advances in chemical synthesis. This section provides a comprehensive summary of C–C fragmentation reactions and methods that produce sp^1–sp^1, sp^2–sp^2, and sp^2–sp^1 connectivity described since the 1991 review of Weyerstahl and Marschall.[8g] These reactions are mechanistically novel and/or provide practical improvements over previous methods. The organization of this section parallels the preceding sections. Hence, fragmentations that generate sp^1–sp^1 bonds are discussed first. The more common sp^2–sp^2 examples are described next. Since fragmentations that generate sp^2–sp^1 bonds are a recent development, the sections on sp^1–sp^1 and sp^2–sp^2 formation are followed by a section that describes this fragmentation type. These sections begin with a description of ring-opening reactions and conclude with ring expansions. The possible use of a fragmentation may be difficult to discern in the planning stages of a synthesis owing to the subtleties associated with retrosynthesis[18] and pattern recognition.[98] Therefore, the final section summarizes the application of C–C fragmentation in the synthesis of complex molecules.

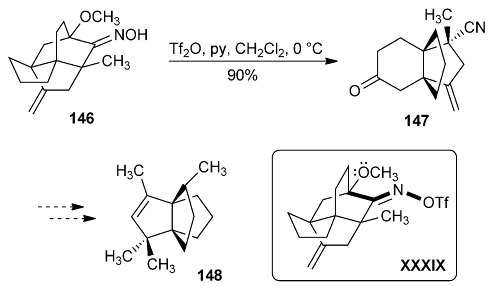
3.1. sp^1–sp^1 Bond-Forming Fragmentations

To date, C–C fragmentation reactions that give sp^1–sp^1 products give nitrile, alkyne, and nitrilium species. We begin with a discussion of nitrile-forming fragmentations. Several useful modifications and applications of the Beckmann fragmentation have appeared over the past several years. In 1997 Kirihara et al. reported that diethylaminosulfur trifluoride (DAST) effects the Beckmann fragmentation of cyclic ketoximes (e.g. **142** and **144**) and is accompanied by capture of the cationic intermediate with fluoride (Scheme 34).[99] This significant contribution is favored in substrates that possess electron-donating substituents α to the oximino carbon atom. The substrates evaluated were relatively complex, including both terpenes and steroids.

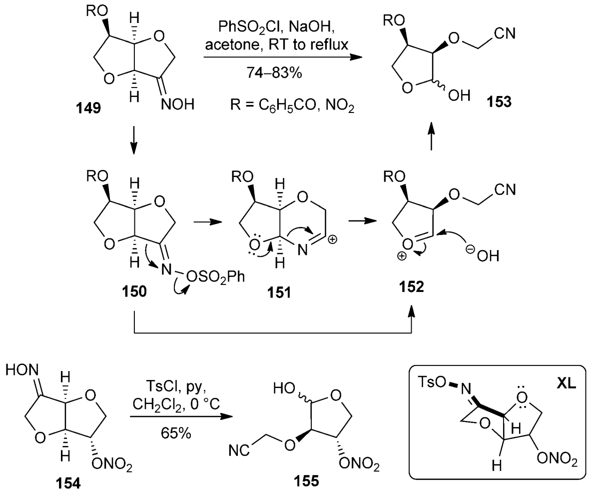


Scheme 34. Kirihara's fluorinative ketoxime fragmentations (1997).[99]

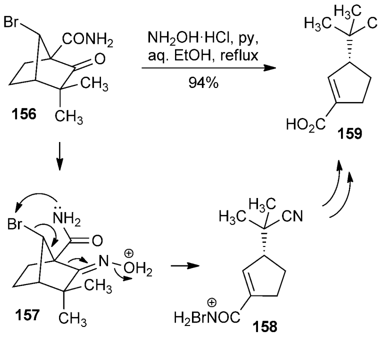
Reminiscent of the original morphine study,[36] Laxmisha and Subba Rao described an efficient heteroatom-assisted Beckmann fragmentation of **146**, which furnished the [4.3.3]propellane derivative **147** (Scheme 35).[100] This product



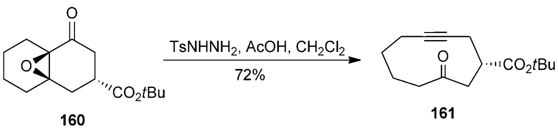
Scheme 35. Subba Rao's [4.3.3]propellane scaffold synthesis (2000).[100] Tf = trifluoromethanesulfonyl.



Scheme 36. Čeković's nitrile synthesis (2001).[101]



Scheme 37. Maroto's ring opening (2004).[102]



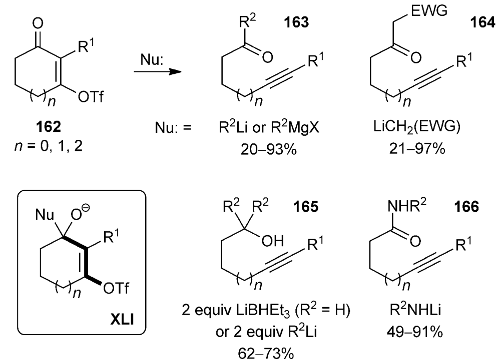
Scheme 38. de Meijere's cyclic alkynone synthesis (2001).[104]

is a potential intermediate en route to natural [3.3.3]propellanes such as modhephene (**148**). In related studies, Tokić-Vujošević and Čeković describe what they call Beckmann rearrangements on diastereomeric oximes **149** and **154** (Scheme 36).[101] They rationalize that the activated oxime, formulated as **150**, undergoes 1,2-migration to give a cation (e.g. **151**), which undergoes C–N bond cleavage instead of trapping with hydroxide. Of course, direct Beckmann fragmentation of the activated oxime in the usual way, **150**→**152** (cf. **XL**) may be the operative pathway.

An unexpected Beckmann fragmentation product of a C1-substituted-7-bromonorbornane-2-one was observed by Maroto and co-workers upon treatment of **156** with hydroxylamine (Scheme 37).[102] Further studies on this highly efficient transformation led to the suggestion that this process is driven by intramolecular activation of the bromo group by the amide nitrogen atom. Fragmentation did not take place when the amide was replaced by a methyl group. The reaction pathway appears to be oxime formation, fragmentation, and then amide hydrolysis. The fate of the bromo group and the role of the amide are intriguing.[103]

Fragmentations that give alkynes have been an area of much activity. In close analogy to the original Eschenmoser–Tanabe studies,[42,44] bicyclic epoxyketone **160** fragmented as expected to give cyclodecynone **161** in good yield (Scheme 38).[104] This was part of a study that demonstrated the utility of various 1,3,5-hexatrienes produced from a one-pot sequence of Stille and Heck coupling reactions.

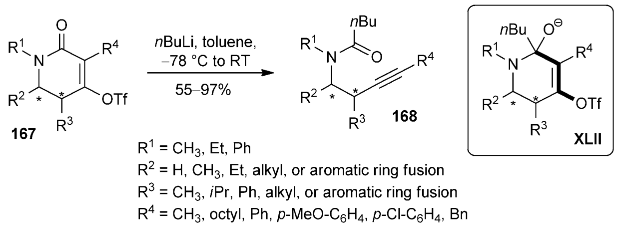
The most extensive and generally useful advance in this area has been registered by Dudley and co-workers. They have demonstrated thoroughly the synthetic versatility of cyclic vinylogous acyl triflates in mild nucleophilic addition/fragmentative ring-opening cascades (Scheme 39).[105] The use of triflates is a simplifying and efficiency-enhancing extension of the early studies on halides[48] and selenones.[49] Additionally, the cascade sequences, reminiscent as they are of the original fragmentation reaction,[1] are both elegant and useful. A wide array of nucleophiles, such as Grignard and organolithium reagents, stabilized lithium enolates, strong hydride donors, and primary lithium amides, reliably participate in the reaction and provide efficient and inexpensive access to acyclic acetylenic ketones (e.g. **163**), 1,3-diketones (**164**), tertiary alcohols (**165**), and amides (**166**). Deuterium-labeling experiments are consistent with their proposed mechanism:



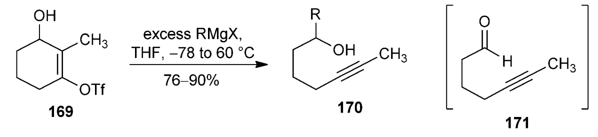
Scheme 39. Dudley's cascade synthesis of alkynes (2005, 2006, 2010).[105] EWG = electron-withdrawing groups.

fast 1,2-addition of the nucleophile to the carbonyl group forms a tetrahedral alkoxide (e.g. **XLI**), followed by a slow, irreversible fragmentation. Mild heating is required for certain substrates and/or nucleophiles. The scope of this method was further expanded with the conversion of dihydropyridone triflates (e.g. **167**) into homopropargylamines (**168**) with retention of stereochemistry (Scheme 40).[106]

Kamijo and Dudley also reported that cyclic vinylogous triflate hemiacetals can serve as stable synthetic equivalents for alkynyl aldehydes (e.g. **169**→**171**, Scheme 41).[107] The first



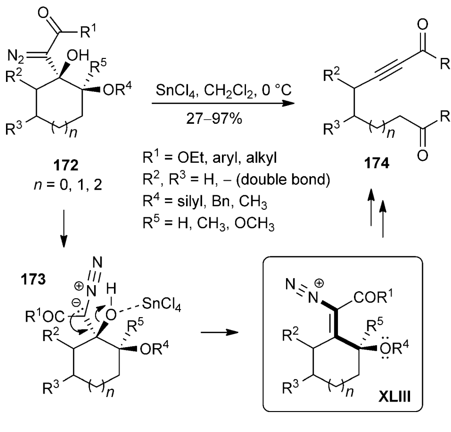
Scheme 40. Dudley's syntheses of homopropargyl amines (2011).[106]



Scheme 41. Dudley's in situ generation of alkynyl aldehydes (2006).[107]

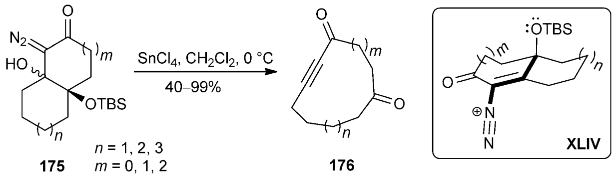
equivalent of the Grignard reagent deprotonates the alcohol, inducing fragmentation to an aldehyde, which undergoes nucleophilic attack from a second equivalent of Grignard to produce a secondary alkynol (e.g. **170**). This process is high-yielding for a variety of Grignard reagents, including aryl, vinyl, alkyl, allyl, and alkynyl variants.

As shown in Scheme 42, Brewer and co-workers advanced an insightful C–C fragmentation of cyclic γ-oxo-β-hydroxy-α-diazocarbonyl derivatives (e.g. **172**) in the presence of a stoichiometric amount of tin tetrachloride. The fragmentation products are either ynoates or ynones (**174**).[108] The ring size, γ-oxy group, and diazo portion of the starting material can all be varied. Thus, access to a wide range of functional-group-rich products should be possible. They hypothesize that the reaction proceeds via a vinyl diazonium species (e.g. **XLIII**) in which the C_β–C_γ and C–N bonds are antiperiplanar. Loss of nitrogen and C–C bond cleavage gives the corresponding oxocarbenium ion. Subsequent loss of the silyl, benzyl, or methyl substituent R^4 gives the observed product. This method was extended to the ring expansion of bicyclic γ-silyloxy-β-hydroxy-α-diazoketones to medium-sized cyclic 2-alkynones (e.g. **175**→**176**, Scheme 43).[109]

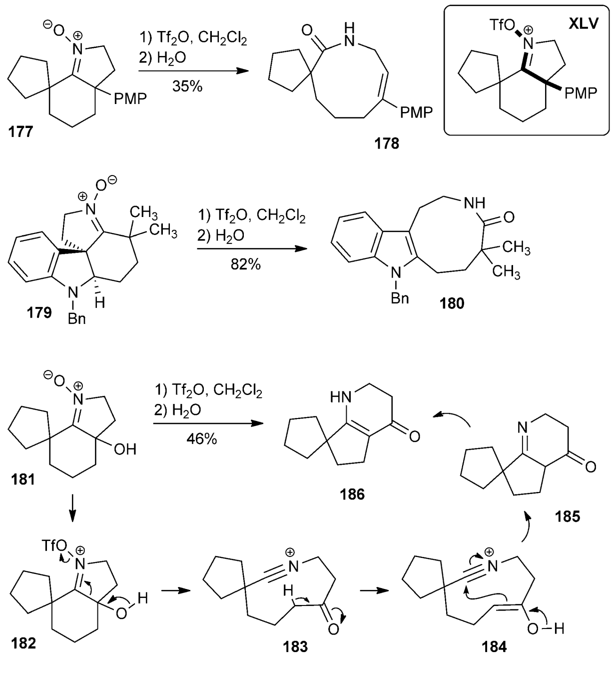


Scheme 42. Brewer's ynoate and ynone syntheses (2008, 2010).[108]

Recently, Murphy et al. designed a series of innovative fragmentation reactions of polycyclic nitrones, which lead initially to the formation of a nitrilium ion (e.g. **177**, **179**, and **181**; Scheme 44).[110] The transformation is induced by exposure of the nitrone to triflic anhydride. The nitrone triflate then undergoes spontaneous C–C and N–O bond cleavage. In one study, an enolate equivalent trapped the intermediate nitrilium species in a transannular fashion, and tautomerization gave the observed product (**186**). Hence, similar to oximes, nitrones can be induced to rearrange (Barton rearrangement)[111] or to fragment.



Scheme 43. Brewer's alkynone synthesis (2012).[109] TBS = *tert*-butyldimethylsilyl.

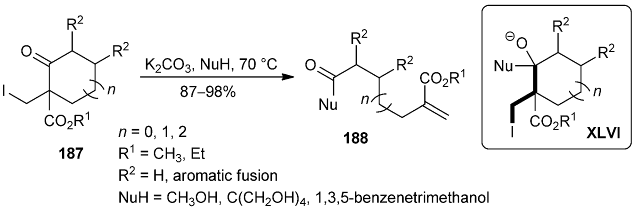


Scheme 44. The original C–C fragmentation of nitrones by Murphy (2007).[110]

3.2. sp^2–sp^2 Bond-Forming Fragmentations

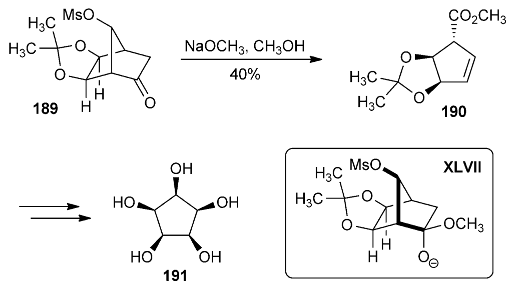
The bulk of the work in the C–C fragmentation field has focused on sp^2–sp^2 bond-forming transformations. Although these often closely follow the original precedent, many useful and instructive extensions of the method have been reported over the last 20 years. A recurring theme in these studies is that the nonfragmentation routes to these targets could be tedious or otherwise difficult. This is especially evident in cases where an intrinsic stereoselectivity of a temporary ring system enables construction of a particular arrangement of functionality. Subsequent fragmentation, be it ring opening or ring expansion, then gives the desired elaborated motif. The findings described in Schemes 46, 49, and 54 exemplify the ring-opening approach, whereas those in Schemes 47 and 48 exemplify the ring-expansion approach. Virtually all of the examples described in Section 3.4 exemplify this principle.

Lupton and co-workers optimized the fragmentation of systems of type **187** (Scheme 45, cf. Scheme 1), analogues of the original Eschenmoser substrate, and applied these to the divergent synthesis of modular dendrimers.[112] Six first generation dendrimers were thus prepared (e.g. **188**). Kinetic studies supported a concerted fragmentation over a retro-Dieckmann/elimination pathway. The presence of the electron-withdrawing ester appears to promote the fragmentation pathway. This method was reliable for five-, six-, and seven-membered rings with various electron-withdrawing groups and nitrogen- and oxygen-containing nucleophiles.[113]



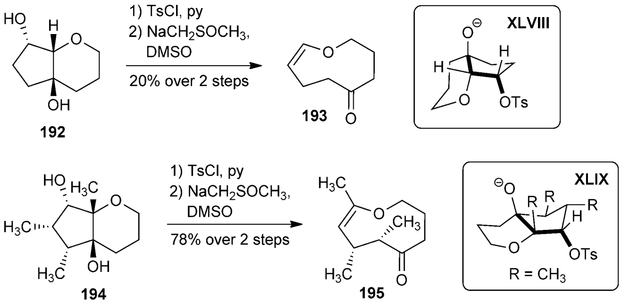
Scheme 45. Lupton's dendrimer core syntheses (2010).[112]

Similarly, the bridged norbornane **189** gave the versatile, stereochemically defined, cyclopentane scaffold **190**, from which a range of biologically active cyclopentitols are accessible (Scheme 46).[114] In this study, it was noted that displacement of the mesylate by methoxide (ca. 20% yield) competes with fragmentation.



Scheme 46. Mehta's cyclopentitol scaffold synthesis (1999).[114]

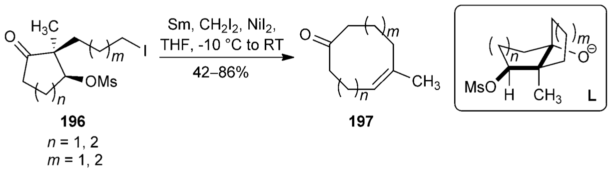
Medium-sized carbocycles and heterocycles are often difficult to access by direct ring closure.[115] Building on the studies of Wharton et al.,[75,76,78] West and co-workers have shown that an appropriately functionalized bicyclic ether is suitable for the preparation of delicate medium-sized oxacycles.[116] Subjecting the monotosylate of **192** to strongly basic conditions gave nine-membered ether **193** (Scheme 47).



Scheme 47. West's nine-membered oxacycle synthesis (1998).[116]

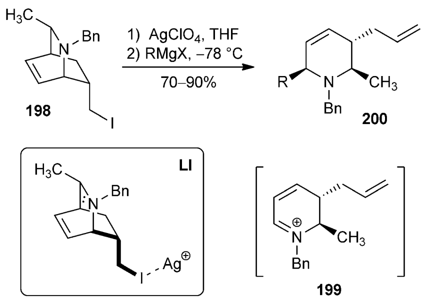
However, this product was accompanied by a similar amount of the elimination product. Elimination was not observed for **194**, which has a methyl group in place of the angular hydrogen atom, and consequently product **195** was obtained in excellent yield.

One of the most useful advances in fragmentation methods was reported by Molander et al.[117] They developed a conceptually simple and synthetically concise intramolecular Barbier-type cyclization/fragmentation cascade (e.g. **196**, Scheme 48). The method appears to be an excellent means by which to prepare functionalized and stereodefined eight-, nine-, and ten-membered carbocyclic *Z* alkenes (e.g. **197**).

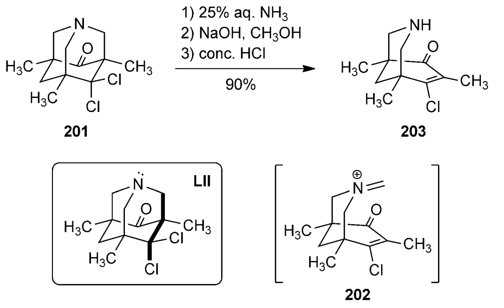


Scheme 48. Molander's cascade synthesis of medium-sized rings (2001).[117]

Charette and co-workers optimized the silver ion induced fragmentation of γ-amino halides (e.g. **198**, Scheme 49),[118] thereby extending and generalizing the early cinchona alkaloid fragmentation (Scheme 14). Additionally, this research group showed that 1,2-dihydropyridinium ion intermediates (e.g. **199**) can be trapped in situ with Grignard reagents in a highly regio- and diastereoselective fashion. The polysubstituted piperidine products (e.g. **200**) are of considerable interest in drug discovery and alkaloid synthesis. With the aim of avoiding the use of expensive silver salts, they showed that triflates are excellent alternatives to the corresponding iodo derivatives.[119]



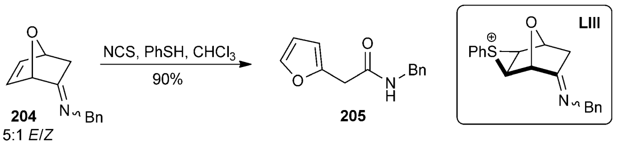
Scheme 49. Charette's γ-amino halide fragmentations (2008).[118] Bn = benzyl.



Scheme 50. Risch's γ-amino halide fragmentations (1991).[120]

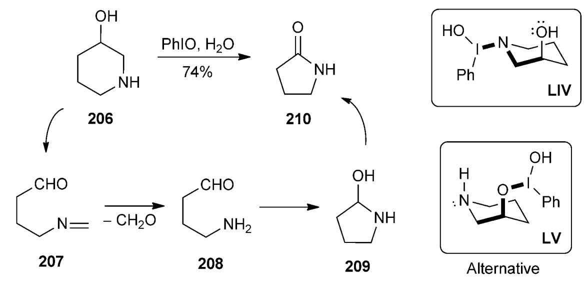
Functionalized 3-azabicyclo[3.3.1]nonane derivatives are readily accessible from azaadamantanones of type **201** through regioselective fragmentation (Scheme 50).[120] Exposure of the dichloride **201** to aqueous ammonia gives **203** (via **202**). The reaction mechanism is not altogether unambiguous. Nevertheless, the chloride axial to the carbocyclic ring is the presumed leaving group. Interestingly, the alternative fragmentation pathway, which would give the less thermodynamically stable β,γ-unsaturated product, was not observed.

Phenylsulfenyl chloride was used by Plumet and coworkers to effect fragmentation of imines of type **204** to amides of type **205** (Scheme 51).[121] This insight anticipates sulfonium-initiated fragmentation, nitrilium ion formation, and capture by chloride, which upon aromatization and hydrolysis gives the amide product.



Scheme 51. Plumet's sulfonium-initiated fragmentation (2001).[121] NCS = *N*-chlorosuccinimide.

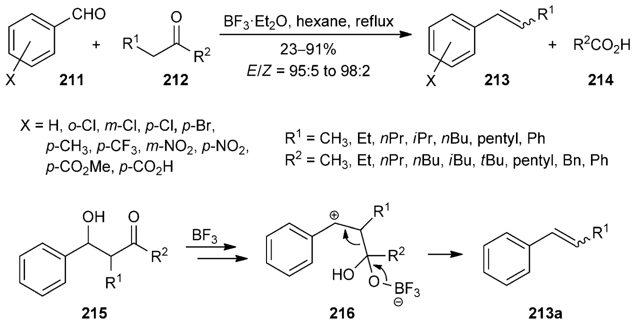
The oxidation of 3-hydroxypiperidine (**206**) with iodosylbenzene in water affords 2-pyrrolidinone (**210**, Scheme 52).[122] Ochiai and co-workers propose an initial ligand exchange at iodine(III) of the iodosylbenzene, thereby producing the labile aminoiodane and/or the cyclic iodane.



Scheme 52. Ochiai's oxidative fragmentation (2004).[122]

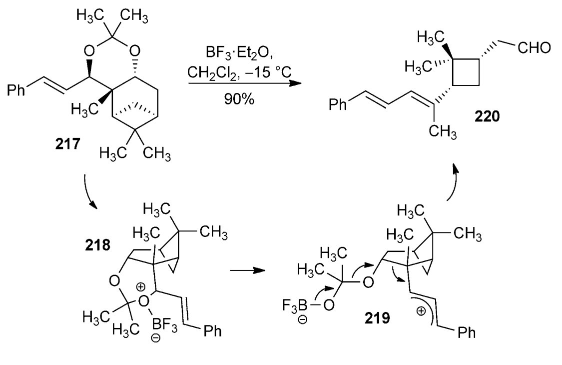
Alternative mechanisms with O- rather than N-activation are also plausible (see **LV**). Rapid oxidative fragmentation to iminoaldehyde **207** is followed by hydrolysis, cyclization, and then oxidation to give **210**.

Kabalka et al. developed an interesting tandem aldol/fragmentation sequence.[123] As shown in Scheme 53, aromatic aldehydes (e.g. **211**) and ketones (e.g. **212**) react in the presence of boron trifluoride to provide *E*-arylalkenes (e.g. **213**) with high stereoselectivity. This versatile one-pot alkene synthesis requires the combination of a strong Lewis acid and very low polarity solvent to prevent formation of the aldol condensation products.



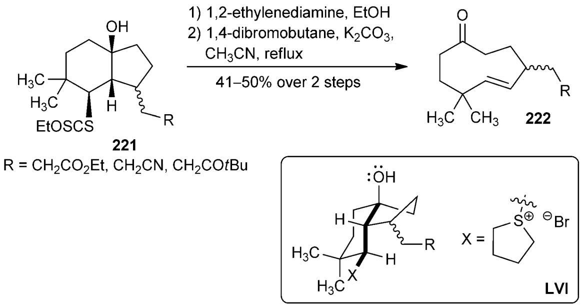
Scheme 53. Kabalka's cationic alkene synthesis (1998, 1999).[123]

Several other fragmentations are summarized in Schemes 54, 55, and 56. Suitably functionalized acetonides (e.g. **217**) undergo C–C fragmentation upon treatment with



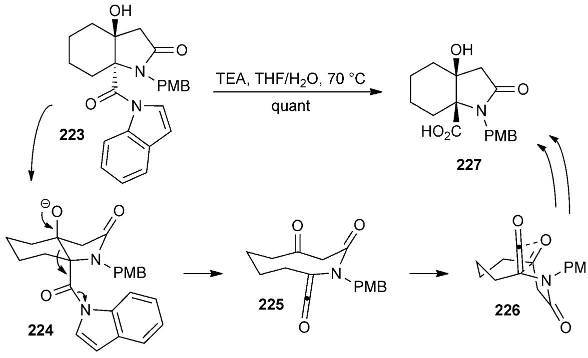
Scheme 54. Barluenga's terpene fragmentation (2003).[124]

a catalytic amount of a Brønsted or Lewis acid.[124] The terpene-derived substrates yield enantiopure aldehydes (e.g. **220**) that contain a cyclopropane or cyclobutane ring and an alkene or diene moiety. Barluenga et al. conducted several experiments that support a stepwise mechanism. The anticipated structure of oxonium ion **218** was suggested to lack the necessary orbital overlap for concerted fragmentation. Instead, the acetonide appears to open selectively to give the stabilized carbocation **219**, in accord with early cationic fragmentations/retro-Prins reactions (Schemes 15 and 17). Loss of acetone, C–C bond cleavage, and stereoselective alkene generation gives the observed product. Zard and coworkers have synthesized a series of strained nine-membered rings through fragmentation (e.g. **222**, Scheme 55).[125]



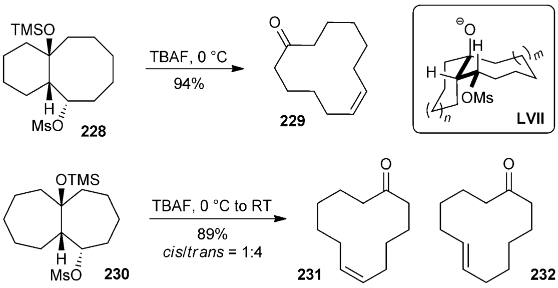
Scheme 55. Zard's cyclononene synthesis (1999).[125]

Although Molander et al. have provided a general method for direct entry into *Z*-alkene-containing nine-membered rings by fragmentation (Scheme 48), indirect multistep routes are still required in many cases. The approach by Zard and coworkers expands upon earlier ring-expansion studies and demonstrates the effectiveness of alternatives to the sulfonate nucleofuge. Hence, bicyclic xanthates (e.g. **221**) were selectively cleaved. The crude thiols were converted into the sulfonium products, which fragmented in situ. Bromide was also shown to be an effective leaving group. The reaction of *N*-acylindole **223** gave *syn*-bicyclic pyroglutamic acid **227** (Scheme 56).[126] The authors suggest that this transformation follows a pathway wherein a ketene is formed in a fragmentative ring expansion. The ketene intermediate is then suggested to undergo cycloaddition to give the β-lactone followed by hydrolysis to the observed product. The nonfragmentation pathway, by way of retro-aldol/aldol isomerization followed by hydrolysis, was not discussed, but may also be relevant.



Scheme 56. Kobayashi's *syn*-bicyclic pyroglutamic acid synthesis (2007).[126] PMB = *p*-methoxybenzyl.

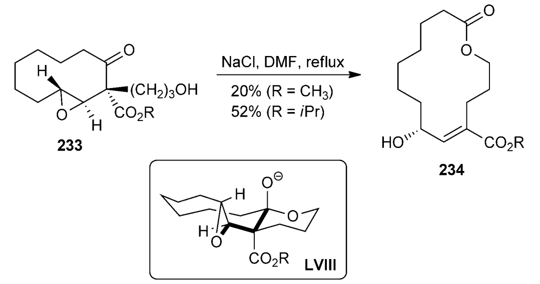
Fluoride-induced fragmentation of silyl-protected 1,3-hydroxysulfonates was shown be an excellent alternative to exposure of a 1,3-hydroxysulfonate to strong base. Hence, treatment of **228** with tetrabutylammonium fluoride gave the *cis*-cyclododecenone **229** as a single isomer (Scheme 57).[127]



Scheme 57. Dowd's fluoride-induced ring expansion (1996).[127] TBAF = tetrabutylammonium fluoride.

Unexpectedly, the silyl ether **230** afforded a mixture of *cis* and *trans* isomers (**231** and **232**). Zhang and Dowd pointed out the possibility of ionization of the sulfonate to account for the *trans* product.

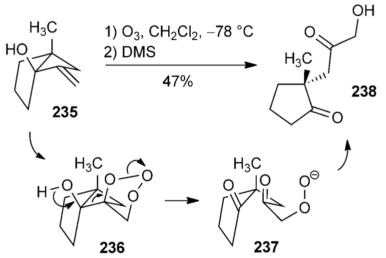
In contrast to the Eschenmoser–Tanabe fragmentation of α,β-unsaturated epoxyketones,[42,44] Stojanova and Hesse showed that appropriately functionalized cyclic β,γ-epoxyketones undergo fragmentation to give macrocyclic lactones (e.g. **233**→**234**, Scheme 58).[128] The product necessarily contains an allylic alcohol, present as a consequence of the fragmentative epoxide opening.



Scheme 58. Hesse's macrolactone synthesis (1995).[128] DMF = dimethylformamide.

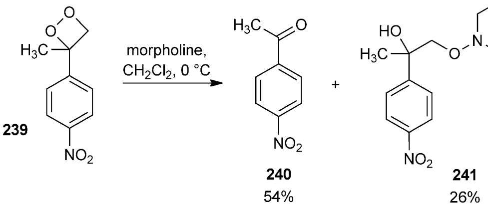
The vast majority of fragmentations reported to date involve common functional groups, as shown throughout this Review. In 2001, Jung and Davidov reported a remarkable fragmentation under ozonolysis conditions (**235**→**238**, Scheme 59).[129] They suggest that formation of the primary ozonide derived from the strained allylic alcohol provides a facile pathway for fragmentation. The release of angle strain in the cyclobutane ring combined with the weakness of the O–O bond facilitates the fragmentation.

Morpholine was shown to induce fragmentation of 3,3-disubstituted-1,2-dioxetanes to afford the corresponding ketones (e.g. **239**→**240**, Scheme 60).[130] The presence of *N*-oxide **241** was also noted. The reaction was rationalized as proceeding through the deprotonated form of **241**. Electron-withdrawing groups on the aryl ring appear to decrease the basicity of the intermediate alkoxide and to thereby promote fragmentation.



Scheme 59. Jung's ozonide fragmentation (2001).[129]

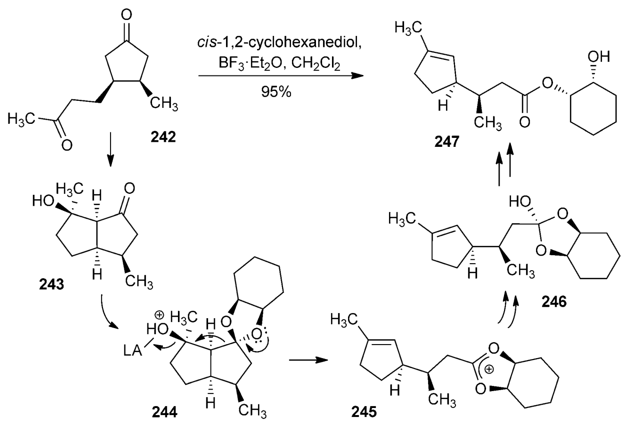
Sakai and co-workers showed that aldol products can be induced to fragment in the presence of a Lewis acid and a diol (Scheme 61).[131] Moreover, they effected the aldol reaction in situ. Hence, 1,6-diones (e.g. **242**) undergo a cascade reaction consisting of aldol addition, ketalization, C–C fragmentation, and then collapse of the resultant tetrahedral intermediate to give functionalized cyclopentenes (e.g. **247**). Mechanistic studies revealed that the sequence follows mainly the ketal pathway, but may partially proceed via the hemiketal.



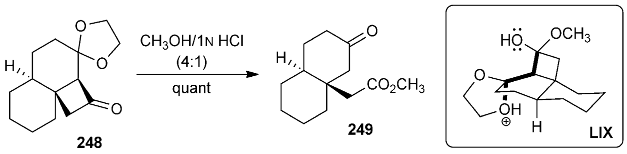
Scheme 60. Adam's peroxide fragmentation (1995).[130]

Bettolo and co-workers reported an analogous fragmentation (Scheme 62).[132] Exposure of 5-dioxolan-bicyclo-[4.2.0]octan-2-one **248** to acid yields 3-(methoxycarbonylmethyl)cyclohexanone **249**. Although the experimental data do not preclude a stepwise mechanism, the authors propose that the cyclobutane and protonated dioxolane rings open simultaneously. This method represents a strategy to introduce angular acetate to functionalized decalin systems.

Nickel and palladium catalysts have been used in the double ring opening of cyclic carbonates (e.g. **250**) to give ω-dienyl aldehydes (e.g. **251**, Scheme 63).[133] Carbonates possessing ring and/or torsional strain smoothly undergo fragmentation in the presence of monodentate phosphane ligands and [Ni(cod)$_2$]. The strain-free carbonates studied required the addition of bidentate phosphanes with bite angles of at least 95°. The synperiplanar arrangement of scissile bonds of the organometallic intermediate and the isolation of *E*/*Z* product mixtures suggest a stepwise cationic mechanism (**LXI**).

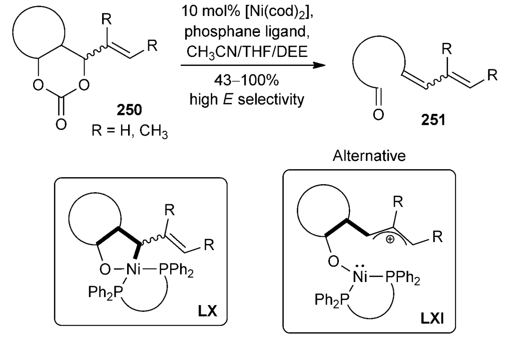


Scheme 61. Sakai's in situ aldol product C–C fragmentation (1991).[131]



Scheme 62. Bettolo's angular acetate synthesis (1997).[132]

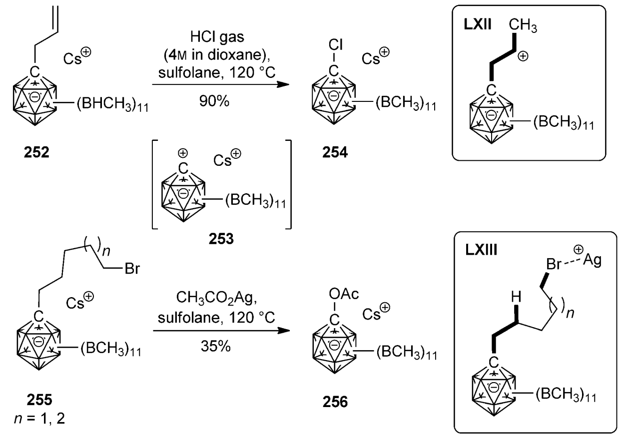
The most exotic C–C fragmentations reported to date are shown in Scheme 64. In this case, substituted icosahedral carba-*closo*-dodecaborate anions undergo C–C bond cleavage (e.g. **252** and **255**→**253**).[134] Moreover, the C–C bond cleavage of alkyl halide substituted derivative **255** apparently involves intramolecular hydride transfer via a five- or six-membered transition state (cf. **LXIII**). Isotopic labeling experiments demonstrated that the double bond in the side products is located at the terminus originally attached to the carborane cage. Although the likelihood of this reaction



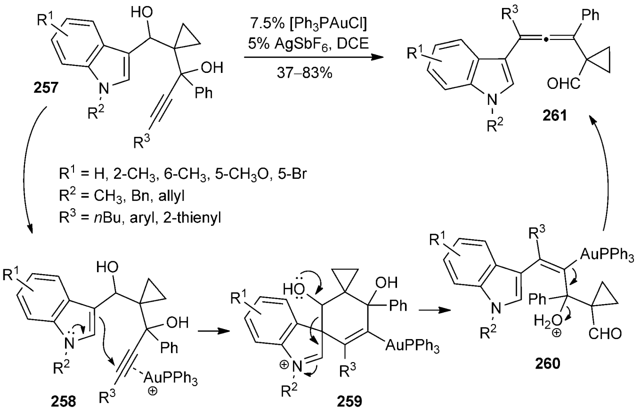
Scheme 63. Tamaru's nickel-mediated fragmentation (2006).[133] cod = 1,5-cyclooctadiene.

becoming a useful synthetic method seems remote at present, it remains a fascinating example of what technically can be classified as a C–C fragmentation.

In closing this section, we note that fragmentation may be buried within more complex rearrangements. This is especially true of certain organometallic transformations. We have deliberately not delved into such areas. The mechanisms are obscured by a lack of relevant data and are nuanced and layered with speculation. This notwithstanding, the reactions are not fundamentally fragmentations. For example, Li and Liu optimized a gold-catalyzed reaction of 3-alkynylindolediols (e.g. **257**→**261**, Scheme 65).[135] The reaction has good substrate scope. It was rationalized as proceeding through cationic gold activation of the alkyne followed by intramolecular nucleophilic attack by the indole. Fragmentation of the spirocyclic iminium cation regenerates the indole. Elimination of the Au^I catalyst and water gives the allene. Buried within the speculation by Li and Liu are the recognizable fragmentation elements: an electron source, an electron sink, and a cleaved C–C bond (**259**). This step can also be considered the reverse of electrophilic aromatic substitution. We suggest that the transformation by Li and Liu be considered a gold(I)-catalyzed rearrangement.[136]



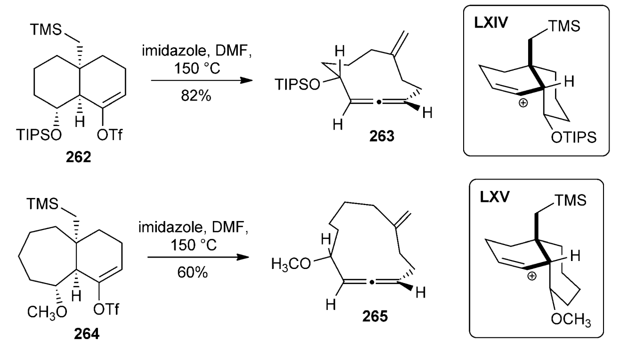
Scheme 64. Michl's carba-*closo*-dodecaborate fragmentation (2004).[134]



Scheme 65. Liu's allene synthesis (2010).[135] DCE = 1,2-dichloroethane.

3.3. *sp²–sp¹* Bond-Forming Fragmentations

The synthesis of allenes by way of C–C fragmentation is an exciting area of recent development that has not previously been reviewed. The structural and reactive properties of allenes complement the chemistry of alkynes and alkenes.[137] Importantly, however, this transformation is not altogether new. Three key antecedents presage much of the work in this area: Kuwajima's thermolysis studies on vinyl triflates (see Scheme 66), Dudley's demonstration of the general utility of vinyl triflates for anionic fragmentations (see Section 3.1, Schemes 39–41), and the cumulative studies—first demonstrated by Eschenmoser—that fragmentations can be initiated by nucleophiles.

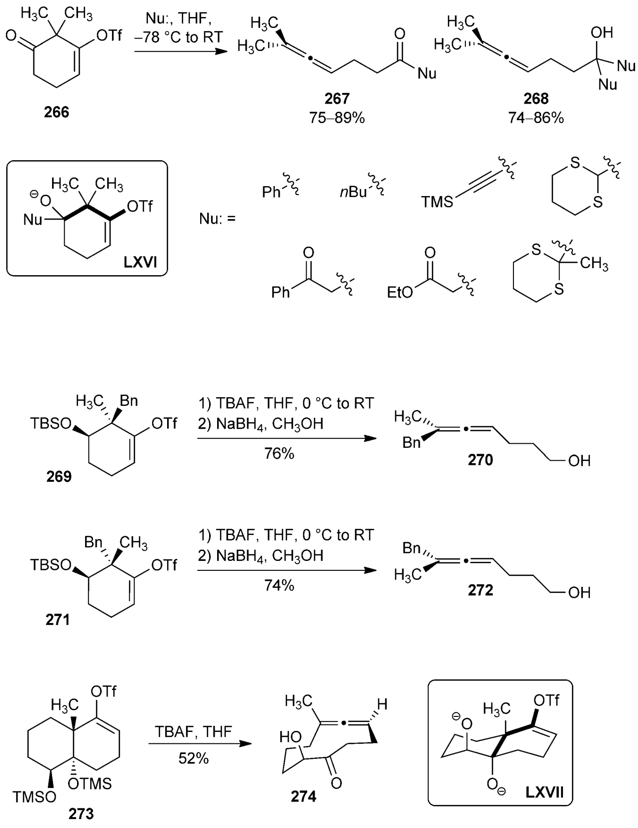


Scheme 66. The original allene synthesis through C–C fragmentation by Kuwajima (1997).[139]

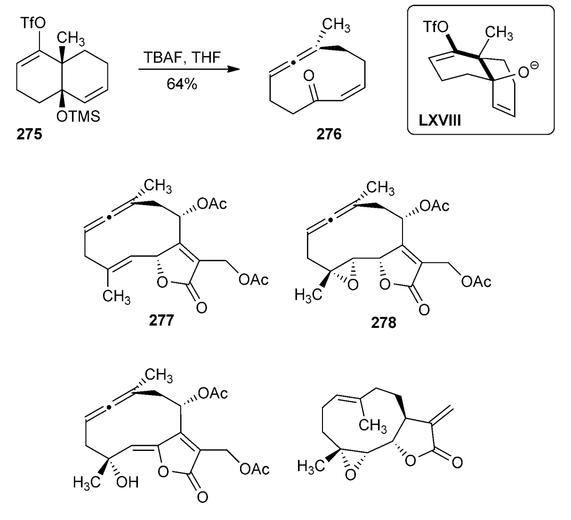
Numerous elimination processes are known to give allenes;[4b,138] however, Kuwajima and co-workers reported the first fragmentation process that gave allenes.[139] Thermolytic ring expansion of enol triflates **262** and **264** gave medium-sized cyclic allenes **263** and **265** (Scheme 66). Since high temperature and high polarity were required, it was reasoned that the rate-determining step is ionization of the triflate and that the fragmentation is cationic. These original experiments provided difficult-to-form cyclic allenes from bicyclic precursors.

Our research group realized a new synthesis of allenes based on the concerted fragmentation of functionalized vinyl triflates.[140] Nucleophilic addition to a ketone of type **266** generates allenic ketones by way of fragmentation of the in situ generated alkoxide (e.g. **267**, Scheme 67). Use of excess nucleophile gave the corresponding tertiary alcohols (e.g. **268**). Fragmentation appears rate-limiting and was shown to be stereospecific (cf. **269**→**270** and **271**→**272**).[141] Consistent with earlier studies,[127] fluoride was shown to promote fragmentation. Hence, upon exposure to fluoride, bicyclic silyl ether **273** fragments to ten-membered endocyclic allene **274**, presumably via the dianion.

We also reported that this mild method appears reliable for *cis*-decalin-derived substrates.[142] Treatment of bicyclic vinyl triflate **275** with TBAF afforded the ten-membered endocyclic allenone **276** (Scheme 68). This simplified scaffold is related to the germacrane terpenes, especially the vernonia



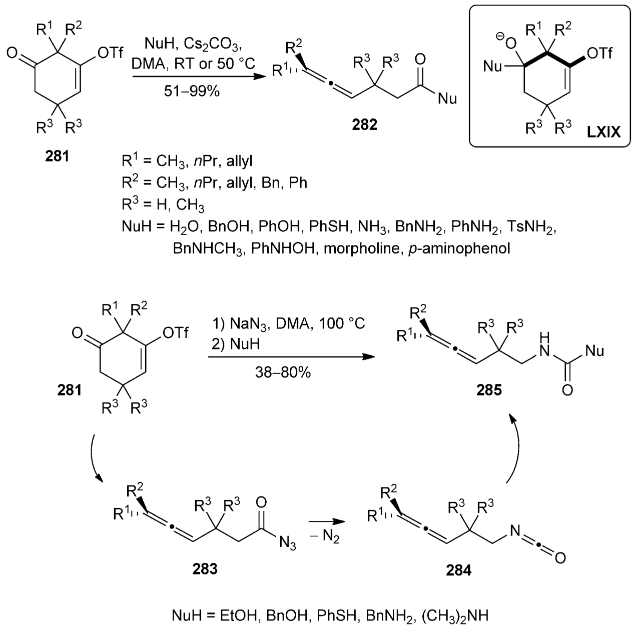
Scheme 67. Fragmentations of vinyl triflates to allenes (2009).[140] TMS = trimethylsilyl.



Scheme 68. Synthesis of an endocyclic allene related to the germacranolides (2011).[142]

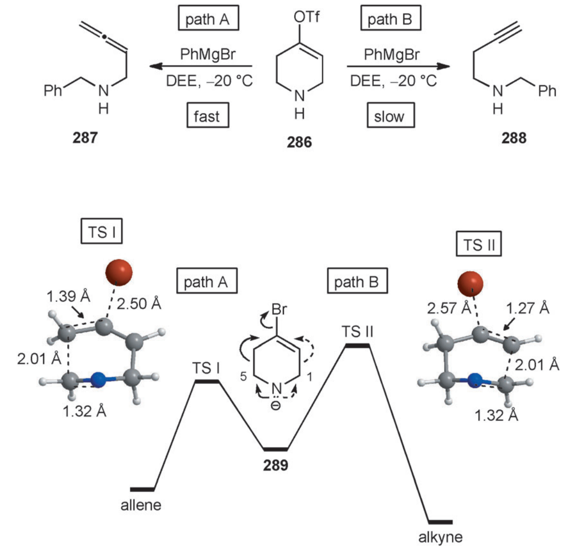
allenes (**277**–**279**), the only known endocyclic allene containing natural products.

Saget and Cramer reported a series of complementary fragmentations.[143] They used heteroatom nucleophiles to access trisubstituted allenes (e.g. **282**, Scheme 69). Fragmentation of vinyl triflates (**281**) is highly favored in polar aprotic solvents with an excess of base. In some cases mild heating is beneficial. Some of the substrates were designed to undergo domino reactions to form even more structurally diverse motifs. For example, vigorous heating of the vinyl triflate in the presence of sodium azide generated a carbamate **285** through a designed in situ Curtius rearrangement of the acyl azide fragmentation product **283**.



Scheme 69. Saget and Cramer's allene synthesis (2010).[143] DMA = *N*,*N*-dimethylacetamide.

There is only one study where divergent fragmentation pathways are compared in a single substrate both experimentally and computationally. Triflate **286** was designed to be able to fragment to give an alkyne or an allene (Scheme 70).[140] Remarkably, base induces **286** to undergo C–C fragmentation to give allene **287** significantly faster than



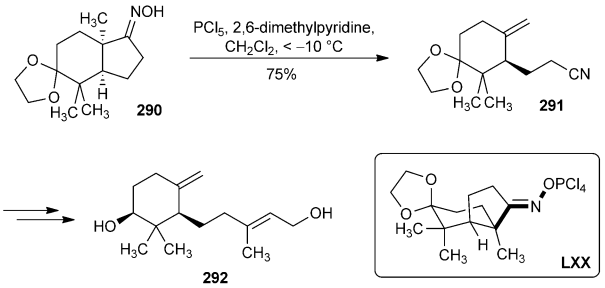
Scheme 70. Fragmentation favors the allene over the alkyne (2009).[140]

alkyne **288**. Computational evaluation of bromide **289** indicates that a greater positive charge builds up on C5 than on C1. This suggests that the sp^3 network of **286** is more polarized by the triflyl group than the sp^2 network. The greater positive charge leads to a stronger interaction with the negatively charged nitrogen atom and a lower barrier to the allene product, despite proper stereoelectronic alignment for both pathways.

3.4. Complex Molecule Synthesis

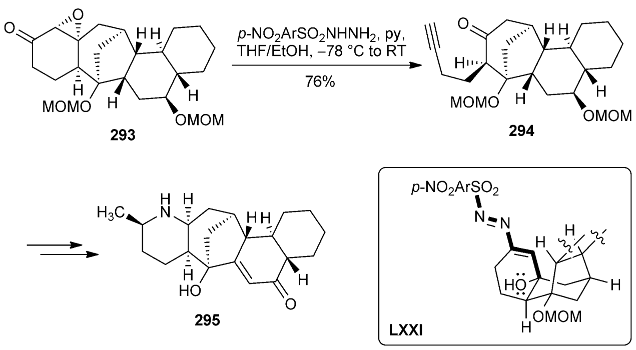
The synthesis of natural products is a unique test for the utility of a synthetic method or strategy. Consequently, the syntheses of natural products and natural product core structures that have appeared over the last twenty years and that rely upon the use of a fragmentation are described here as distinct from motif-building studies described in the previous sections. The strategic application of C–C fragmentation has found the widest use in terpene natural products and has been used to effect ring openings and ring expansions. Fragmentation reactions of complex substrates that give sp^1–sp^1 connectivity are rare (Scheme 71–74), whereas those that give sp^2–sp^2 connectivity are common (Scheme 75–96). Fragmentations leading to sp^2–sp^1 connectivity have not been applied to complex targets other than those mentioned above.

Ring-opening reactions achieved by C–C fragmentation that give sp^1–sp^1 products are shown below. Beckmann fragmentation of oxime **290** provided *exo*-olefin **291** regioselectively en route to (−)-elegansidiol (**292**), a monocarbocyclic sesquiterpene (Scheme 71).[144] The fragmentation is especially interesting because the least sustituted alkene was formed. Hu and co-workers note that a bulky, non-nucleophilic base at reduced temperature was required for this product to be obtained in high yield.



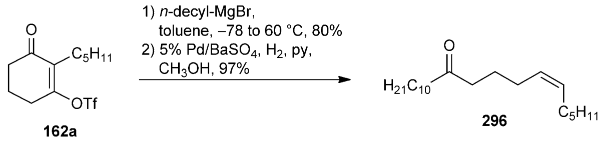
Scheme 71. Hu's ring-opening fragmentation en route to elegansidiol (**292**; 2007).[144]

A modified Eschenmoser–Tanabe fragmentation was utilized in the racemic total synthesis of GB-13 (**295**), a complex polycyclic alkaloid isolated from the rainforest tree *Galbulimima belgraveana* (Scheme 72).[145] In this synthesis by Mander and McLachlan, epoxyketone **293** was converted into alkynone **294**, a late-stage intermediate.



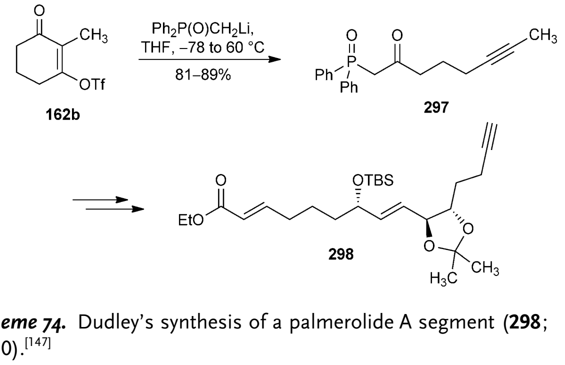
Scheme 72. Mander's synthesis of (±)-GB-13 (**295**) made use of a late-stage fragmentation (2003).[145] MOM = methoxymethyl.

Dudley and co-workers extended their ring-opening cascade to target several natural products. The reaction of vinylogous acyl triflate **162a** with *n*-decylmagnesium bromide afforded the keto alkyne, which upon semireduction gave the sex attractant of the Douglas fir tussock moth *Orgyia pseudotsugata* (**296**, Scheme 73).[146] More recently they used fragmentation to expedite the synthesis of the "eastern hemisphere" of the macrolide palmerolide A, a potent inhibitor of vacuolar ATPase and a selective anti-skin-cancer agent.[147] Treatment of **162b** with a lithiated phosphine oxide provided β-keto phosphine oxide **297** and subsequently **298** (Scheme 74).

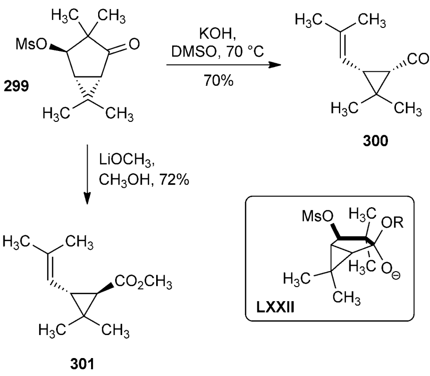


Scheme 73. Dudley's synthesis of moth pheromone **296** (2006).[146]

Ring-opening fragmentations that give acyclic alkene (sp^2–sp^2) motifs have been used to generate a diverse range of natural product related compounds. Among the many creative approaches to the iconic chrysanthamates, Krief and Surleraux demonstrated that functionalized cyclopentanone **299** is a suitable substrate for fragmentation that grants access to both *cis*- and *trans*-chrysanthemic acids (Scheme 75).[148]

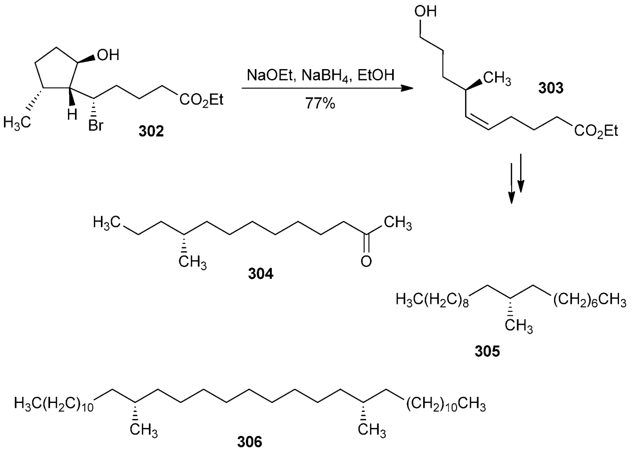


Scheme 74. Dudley's synthesis of a palmerolide A segment (**298**; 2010).[147]



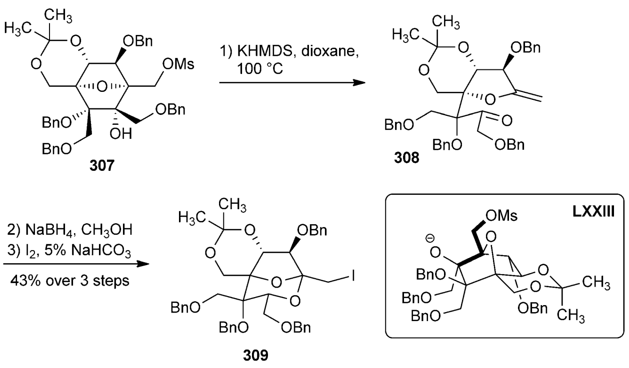
Scheme 75. Krief and Surleraux's *cis*- and *trans*-chrysanthemic carboxylate syntheses (**300** and **301**; 1991).[148]

These are common intermediates in the production of pyrethroid insecticides. The action of potassium hydroxide gives retention of stereochemistry, whereas lithium methoxide induces epimerization to the thermodynamic *trans* carboxylate. A related and mechanistically complementary fragmentation of hydroxy bromide **302** gave, after reduction of the unstable aldehyde, *Z* olefin **303** in good yield (Scheme 76).[149] From this intermediate, de Groot and co-workers completed the synthesis of three related insect pheromones: (R)-10-methyl-2-tridecanone (**304**), (S)-9-methylnonadecane (**305**), and (*meso*)-13,23-dimethylpentatriacontane (**306**).



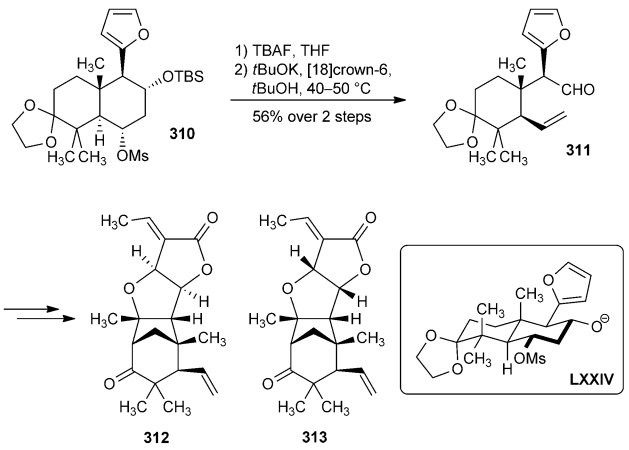
Scheme 76. de Groot's divergent synthesis of insect pheromones (2003).[149]

The zaragozic acids (squalestatins) are fungal metabolites that inhibit squalene synthase and farnesyl-protein transferase.[150] These complex natural products challenge the art and science of synthesis and continue to inspire new synthetic studies. The 2,8-dioxabicyclo[3.2.1]octane core (**309**) of this family was constructed by Nagaoka and co-workers through the strategic use of fragmentation (**307**→**308**), followed by reduction/iodo acetalization (Scheme 77).



Scheme 77. Nagaoka's zaragozic acid core synthesis (**309**; 1999).[150] KHMDS = potassium hexamethyldisilazide.

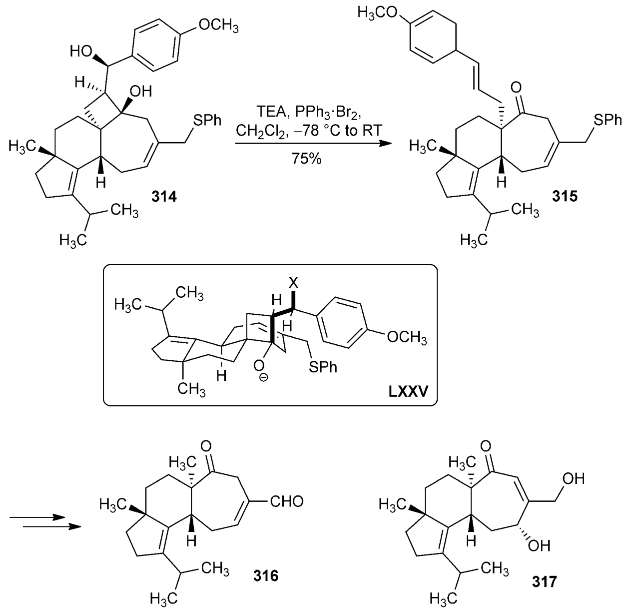
Recently, a C–C fragmentation strategy was applied to the racemic total syntheses of pallavicinin (**312**) and neopallavicinin (**313**) by Peng and Wong (Scheme 78).[151] These modified labdane diterpenoids exhibit bioactivities ranging from fever reduction to muscle regeneration and detoxification. Heating the free secondary alcohol derived from **310** with strong base produced **311**, the key intermediate for a planned biomimetic intramolecular aldol sequence.



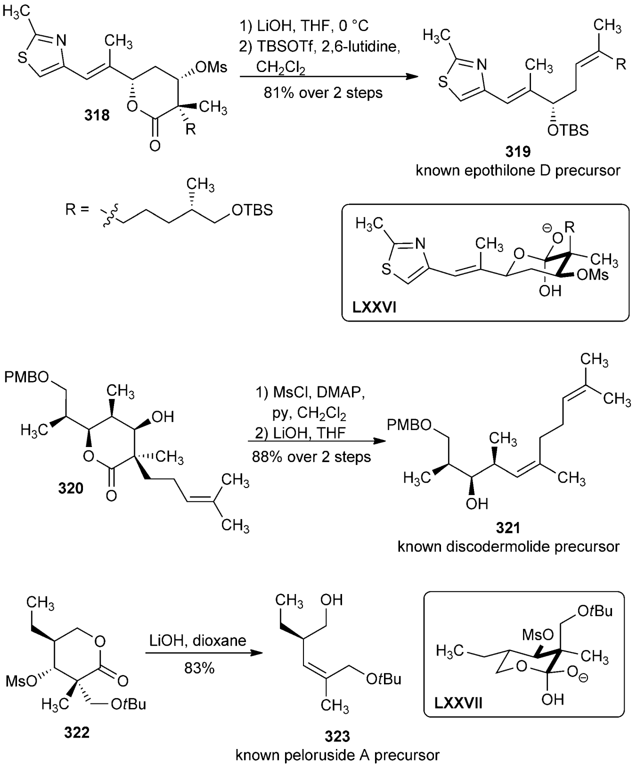
Scheme 78. C–C fragmentation in the syntheses of(±)-pallavicinin (**312**) and (±)-neopallavicinin (**313**) by Peng and Wong (2006).[151]

Release of ring strain was used to leverage fragmentation in the recent racemic synthesis of cyathin B_2 (**316**) and cyathin A_3 (**317**, Scheme 79) by Kim and Cha.[152] Several members of this tricyclic diterpene family of natural products exhibit antimicrobial and anticancer properties.

In a series of studies, Prantz and Mulzer developed stereocontrolled syntheses of methyl-branched trisubstituted *Z* olefins (**319**, **321**, and **323**) by hydroxide-mediated fragmentation of mesyloxylactones (**318**, **320**, and **322**, Scheme 80).[153] This was applied to the formal syntheses of anticancer polyketides epothilone D, discodermolide, and peloruside A. Sodium, potassium, and lithium hydroxides were equally effective in the conversion of **318** into **319** in tetrahydrofuran. When the stereoelectronic requirements for

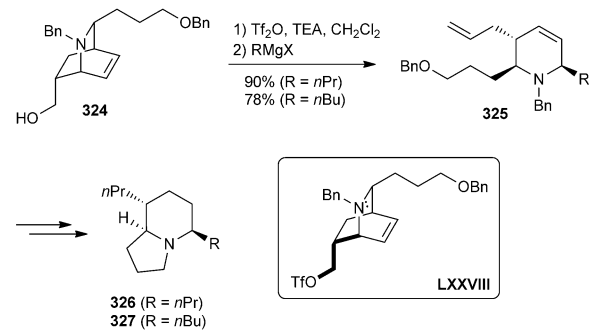


Scheme 79. A C–C fragmentation in the syntheses of (±)-cyathin B$_2$ (**316**) and (±)-cyathin A$_3$ (**317**) by Kim and Cha (2009).[152] TEA = triethylamine.



Scheme 80. The C–C fragmentations in Mulzer's formal syntheses of epothilone D, discodermolide, and peloruside A polyketides (2009, 2010).[153] DMAP = 4-dimethylaminopyridine.

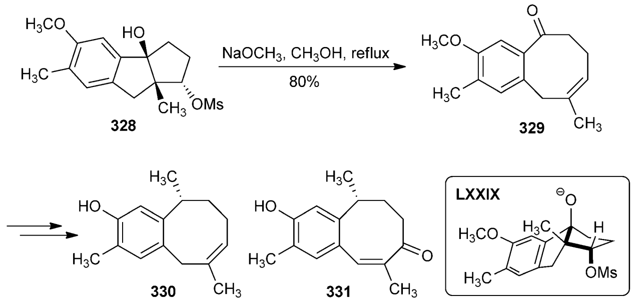
fragmentation are satisfied (e.g. **LXXVI**), fragmentation appears to precede hydrolysis. These reactions may follow a decarboxylative pathway. Both pathways would give the observed product.



Scheme 81. Key steps in Charette's enantioselective total syntheses of 209I (**326**) and 223 J (**327**; 2010).[154]

Charette's triflic anhydride mediated method (Scheme 49) was applied in a ring-opening fragmentation of γ-amino hydroxide **324** (Scheme 81). This intermediate was used to advance the stereoselective total syntheses of frog skin indolizidine alkaloids 209I (**326**) and 223 J (**327**).[154]

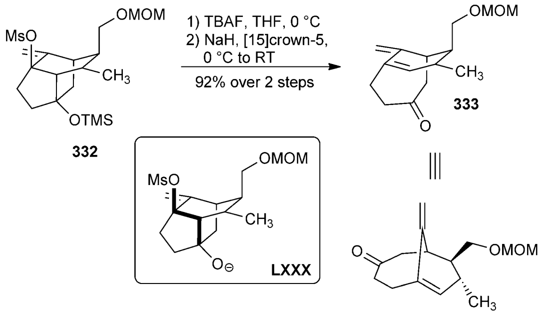
The power of C–C fragmentation is especially evident in ring-expansion strategies. Direct methods for the preparation of functionalized, or otherwise complex, eight-, nine-, and ten-membered rings can be particularly challenging. In these contexts, C–C fragmentation has found its most important application. The functionalized eight-membered ring skeleton of parvifoline (**330**) and isoparvifolinone (**331**) was constructed by fragmentative ring expansion from the racemic *trans*-hydroxymesylate **328** (Scheme 82).[155] The *Z* olefin **329** was then advanced to access both sesquiterpenes.



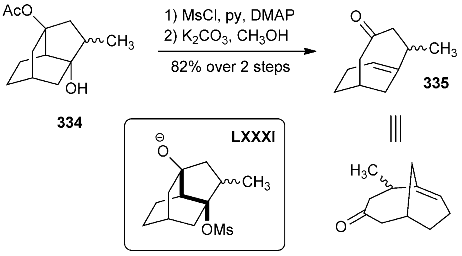
Scheme 82. Key fragmentation of Joseph-Nathan's syntheses of (±)-parvifoline (**330**) and (±)-isoparvifolinone (**331**) (1995).[155]

The bridgehead olefin **333**, which includes a nine-membered ring and constitutes the core of the novel *ras*-farnesyl transferase and squalene synthase inhibitor CP-263,114, was accessed by fragmentation of tricycle **332** (Scheme 83).[156] Nagaoka and co-workers suggested that sequestration of the sodium cation from the alkoxide electrofuge drives this transformation. In an alternative approach towards the natural product, Njardarson and Wood designed a mesylate derived from isotwistane **334**, which underwent ring expansion upon mild methanolysis to give the related bicycle **335** (Scheme 84).[157]

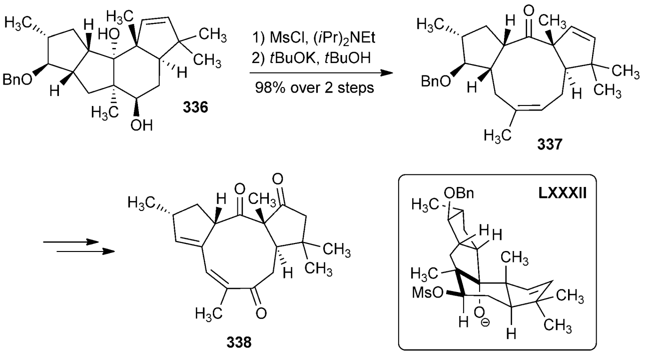
Following detailed preliminary studies,[158] Paquette et al. achieved the first total synthesis of the antileukemic agent



Scheme 83. Nagaoka's approach to CP-263,114 (1999).[156]



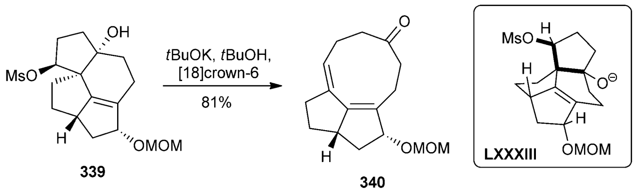
Scheme 84. Wood's approach to CP-263,114 (2001).[157]



Scheme 85. The key fragmentation in Paquette's synthesis of (±)-jatrophatrione (**338**; 2002).[159]

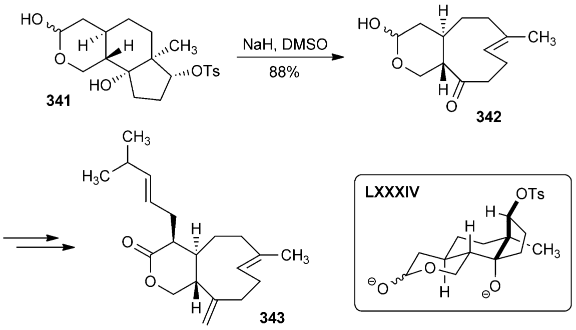
jatrophatrione (**338**, Scheme 85).[159] The unique nine-membered ring-containing diterpene framework of this natural product was revealed upon fragmentation of the complex monomesylate derived from tetracycle **336** (see **LXXXII**).

The aquariane carbocyclic ring system (**340**) was also synthesized successfully through ring expansion (Scheme 86).[160] The gorgonian diterpene natural product target molecules exhibit cytotoxicity against human breast cancer cells. Thornton and Burnell prepared this scaffold from tetracycle **339**. Base-induced C–C fragmentation gave the nine-membered ring fused to the diquinane core.

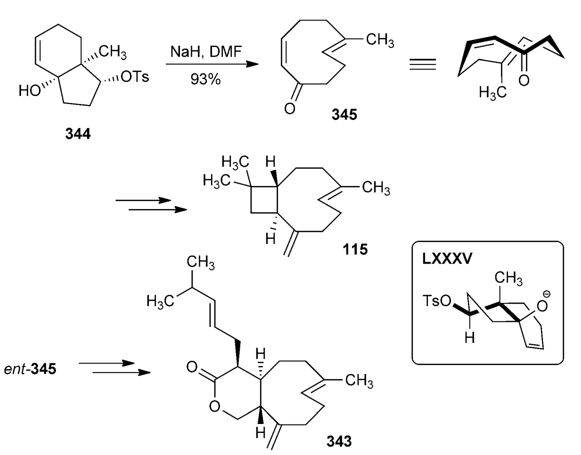


Scheme 86. Thornton's approach to the aquariolide core (**340**; 2006).[160]

Many members of the xenicane diterpene superfamily have been described and the majority has been found to be bioactive. These compounds have captured the attention of several research groups. Studies that utilize C–C fragmentation reactions have appeared over the past decade from the research groups of Leumann and Corey, as well as our group. Leumann and co-workers successfully completed the first total synthesis of optically active coraxeniolide A (**343**, Scheme 87), one of many challenging targets in this class.[161] The strategy was related to Corey's original synthesis of caryophyllene.[85] Fragmentation of hydroxytosylate **341** was pivotal for the stereospecific elaboration of the strained cyclononene **342**. Larionov and Corey revisited the caryophyllene problem with a new approach.[162] They reported the synthesis of enantioenriched cyclononadienone **345** (Scheme 88). This versatile atropisomeric intermediate granted access to β-caryophyllene (**115**), and its enantiomer was used to access coraxeniolide A (**343**). Concurrent with Corey's investigations, we evaluated the structure and reac-

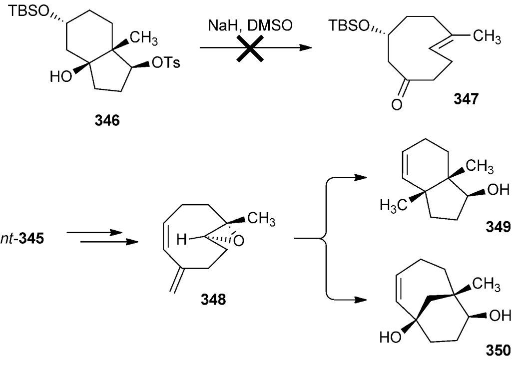


Scheme 87. Key fragmentation in Leumann's synthesis of coraxeniolide A (**343**; 2000).[161]



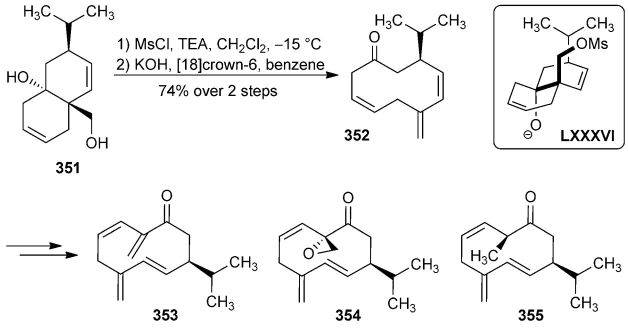
Scheme 88. Enantioenriched **344** gives enantioenriched **345** by fragmentation in Corey's syntheses of β-caryophyllene (**115**) and coraxeniolide A (**343**; 2008).[162]

tivity of dissymmetric *ent*-**345** as a potential scaffold for the synthesis of complex xenicanes.[163] The initial fragmentation target, silyl-protected cyclononenone **347**, was inaccessible from hydroxytosylate **346**, as this precursor failed to fragment (Scheme 89). Computational modeling indicated that the reactive centers of **346** were not fully antiperiplanar. Installation of the olefin was calculated to improve this geometry and facilitated fragmentation. Hence, a geometry very close to antiperiplanar appears to be critical. Intrinsically slow racemization of *ent*-**345** ($t_{1/2} = 32$ h) permitted the synthesis of highly enantioenriched nine-membered ring derivatives. From *ent*-**345**, a divergent stereoselective route to the core carbon frameworks of the xeniolide (**348**), xenibellol (**349**), and florlide (**350**) natural product classes was realized.[164]



Scheme 89. Failed fragmentation and divergent synthesis of three xenicane core structures (2009, 2011).[163,164]

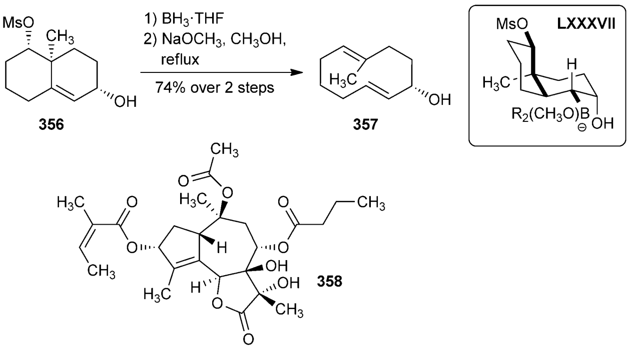
The classic periplanone targets, highly unsaturated sesquiterpenes and sex pheromones of the American cockroach, were also prepared by C–C fragmentation (Scheme 90).[165]



Scheme 90. Saicic's key fragmentation en route to the synthesis of (±)-periplanones **353**–**355** (2004).[165]

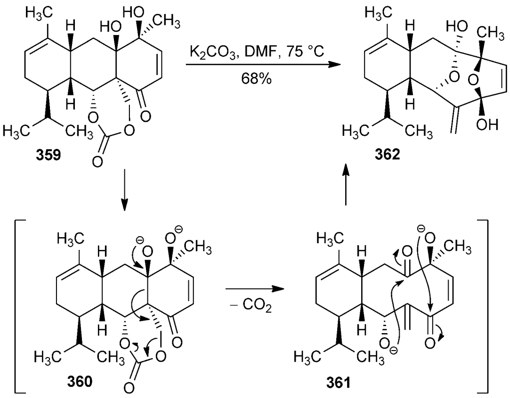
The key reaction gave an *exo*-olefin and the desired ten-membered ring. Saicic and co-workers designed the primary mesylate derived from **351** to undergo hydroxide-promoted fragmentation late in the synthesis. Subsequent arrival at periplanone C (**353**) also constituted formal syntheses of periplanones A (**354**) and D (**355**).

Ley et al. used a variation of the Marshall embodiment of C–C fragmentation in an exploratory route towards thapsigargins such as nortrilobolide (**358**, Scheme 91).[166] This family of complex guaianolide terpenes exhibits a range of biological activities, including potent and selective Ca^{2+} modulation and apoptosis induction in prostate cancer cells. Face-selective hydroboration of **356** gave the α-alkylborane intermediate. Ring expansion, through fragmentation of the boronate promoted by methoxide (see **LXXXVII**), proceeded smoothly to yield cyclodecadiene **357**.



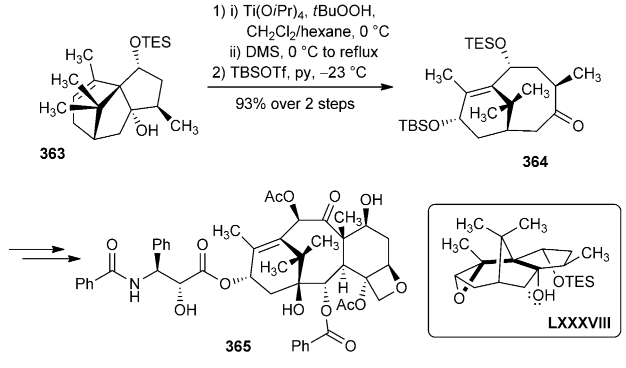
Scheme 91. Ley's approach towards the thapsigargins (2004).[166]

Winkler and co-workers reported the synthesis of the core carbon framework of eleutherobin, a diterpene glycoside with robust antitumor activity, by way of a regioselective fragmentation/decarboxylation/double hemiketal formation process (Scheme 92).[167] Heating **359** in the presence of potassium carbonate in DMF furnished **362** as the only product. The authors did not comment on the possibility of a stepwise process, that is, retro-aldol/β-elimination. Lupton's findings (Scheme 45) may be relevant to the selective cleavage of the primary carbonate C–O bond over the secondary carbonate C–O (**360**). Regardless, this selectivity and the elegant strategy are especially noteworthy.



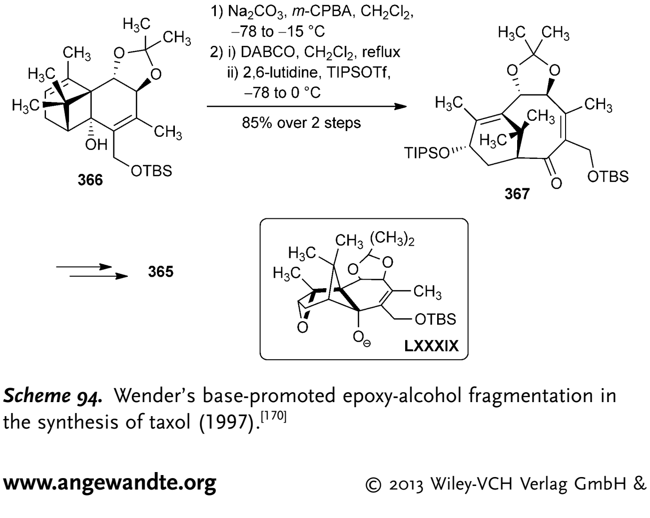
Scheme 92. Winkler's fragmentation cascade to the eleutherobin core (**362**; 2003).[167]

Perhaps the most complex natural products prepared to date using fragmentation as the key step are those housing highly functionalized ten-membered rings in a challenging context. For example, Holton et al. achieved the total synthesis of the potent anticancer drug taxol (**365**) by using this transformation (Scheme 93).[168] A Lewis acid promoted epoxy-alcohol fragmentation of bicyclo[3.2.1]octane **363** unveiled the AB ring system **364**. The apparent syn-periplanar orientation of the fragmentation is noteworthy (**LXXXVIII**). This planned reaction was also evaluated in model studies that confirmed that the stereochemical arrangement accommodates facile fragmentation, whereas the corresponding *exo* epoxides in the model study did not give clean conversion into the target alkenes.[169]

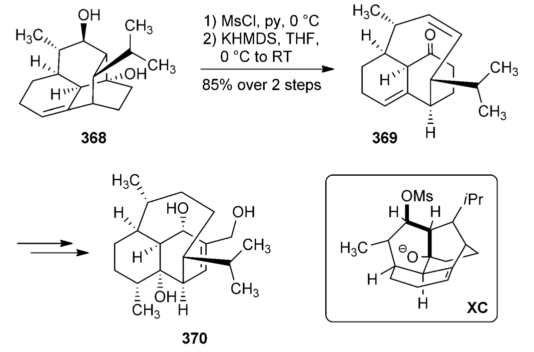


Scheme 93. Holton's Lewis acid promoted epoxy-alcohol fragmentation in the synthesis of taxol (**365**; 1994).[168]

This phenomenon might be best understood through a stepwise mechanism in which the epoxide ionizes first to reveal a tertiary carbocation. In another, now classic, synthesis of this target, Wender et al. realized an even more concise route via the related epoxide derived from bicyclo[3.1.1]heptane **366** (Scheme 94).[170] Interestingly, this fragmentation (**LXXXIX**), which was also the subject of several model studies,[171] was performed under mild basic conditions.



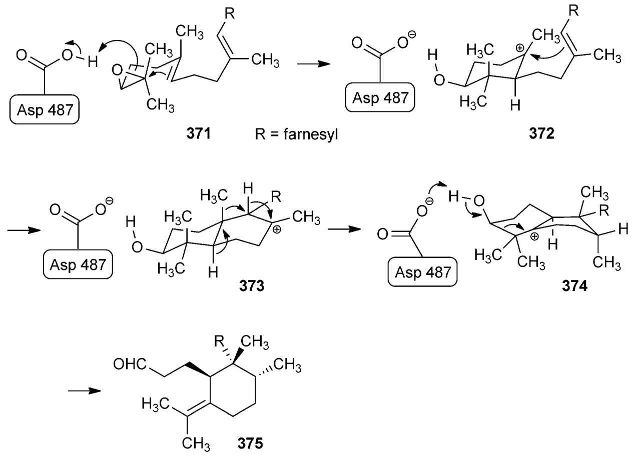
Scheme 94. Wender's base-promoted epoxy-alcohol fragmentation in the synthesis of taxol (1997).[170]



Scheme 95. The key fragmentation in Baran's synthesis of (±)-vinigrol (**370**; 2009).[173]

The structurally intricate diterpene vinigrol (**370**, Scheme 95) is an antihypertensive, a tumor necrosis factor antagonist, and an inhibitor of platelet activating factor induced platelet aggregation. Baran and co-workers developed a concise approach to the challenging core structure through base-induced fragmentation.[172] They also applied this maneuver to the total synthesis of vinigrol.[173] In this ring expansion, deprotonation of the tertiary alcohol of the monomesylate derived from tetracycle **368** was accompanied by clean fragmentation to tricycle **369**, which was properly functionalized for completion of the synthesis.

The final entry in this section is the C–C fragmentation recently discovered in triterpene biosynthesis.[174] Synthase At5g42600, from the small flowering plant *Arabidopsis thaliana*, was shown to catalyze the conversion of oxidosqualene (**371**) into marneral (**375**), a carbocyclic precursor to more complex triterpenes (Scheme 96). Oxidosqualene appears first to be protonated by aspartate 487 and then to undergo carbocationic cyclizations (**371**→**373**). Following a series of 1,2-hydride and methyl shifts (**373**→**374**), fragmentation of tertiary carbocation **374**, facilitated in part by aspartate 487, produces seco-aldehyde **375**.



Scheme 96. *Arabidopsis* oxidosqualene cyclase fragmentation in the biosynthesis of marneral (**375**), identified by Matsuda (2006).[174]

4. Summary and Outlook

In a decade of iconic achievements in the field of organic chemistry, Eschenmoser advanced a reaction that simultaneously accomplished the cleavage of a carbon–carbon single bond and the site-specific formation of a carbon–carbon double bond.[1] In this parvum opus the relevant antecedent data from the previous 50 years were collected and rationalized under a new, single mechanistic umbrella, and the new transformation was used in a ring-opening cascade sequence that illustrated the effectiveness of the advance. The scope and limitations of the reaction manifold were evaluated by many. Early key contributors included the research groups of Henbest,[67,68] Grob,[71,80,81] Stork,[74] and especially Marshall,[90,92,93] who demonstrated that many synthetically useful anion equivalents will participate in the reaction, Wharton, who significantly extended the strategy to include ring expansion,[75,76,78] and Corey, who first demonstrated that this transformation can be powerfully simplifying in natural product total synthesis.[85] The contributions by Grob and coworkers were instrumental to developing a clear understanding of the reaction. He introduced the terms electrofuge, nucleofuge, and fragmentation, and categorized the transformation-type as distinct from additions, eliminations, substitutions, and rearrangements.[8a,b] He also studied the cinchona alkaloid-type C–C fragmentations, and others not reviewed here, and showed that the mechanism for the formation of nitriles under Beckmann conditions fell within this framework.[37a–d] Fragmentation methods that resulted in the formation of alkynes were advanced by the research groups of Bodendorf,[41] Eschenmoser,[42,43] and Tanabe.[44,45] Practical refinements were advanced by Corey and Sachdev[47] as well as others. Hence, heterolytic C–C fragmentation emerged as a powerful ring-opening and ring-expansion method for the selective preparation of functionalized nitriles, alkynes, and especially alkenes.

Many new and modified methods and total syntheses that rely on C–C fragmentation and several important mechanistic insights have been advanced over the past 20 years. These reports broaden the substrate scope, expand the reaction range from alkene to alkyne, allene, and related functional groups, and demonstrate new insights through concise syntheses.

Opportunities abound for discovery and creativity in the C–C fragmentation field. Additional mechanistic studies would provide useful insight into the stereoelectronic requirements of these reactions. Probably the most restrictive aspect of concerted C–C fragmentation is the structural constraint required for reaction. Although the ideal angle between the leaving group and the C–C bond that is cleaved is recognized to be 180°, the minimum angle necessary for fragmentation and the role of other functionality in facilitating or attenuating this process has not been established fully.[142,163] Experimental and computational mechanistic studies would increase our understanding of these less conspicuous, but important, features of fragmentation and thereby increase the reliability of proposed fragmentations. Moreover, C–C fragmentation would find expanded utility through inclusion of a broader set of electron sources (electrofuges) and new electron sinks (nucleofuges). Murphy's nitrone investigation is an exceptional example;[110] Dudley's demonstration that triflates are convenient and reliable is another.[105] Several studies reported within the past few years point to the advantages of using ring-strain release and cleavage of weak bonds to facilitate fragmentation. These principles are not widely used nor have they been fully explored. Jung's work is especially noteworthy in this regard.[129] Concerted C–C fragmentation as a means to generate multiple sites of C–C unsaturation has the potential to further expedite organic synthesis; however, the designed synthesis of multiple carbon–carbon π bonds by way of extended fragmentation has been described in only a few instances.[97] Admittedly, fragmentation reactions have strict limitations. At a minimum, five substrate atoms are involved in the transformation. These restrictions necessarily increase in cases where multiple sites of C–C unsaturation are targeted, and these challenges of design and execution would have to be addressed. Fragmentation methods would be significantly enhanced by broadening the scope of cascade sequences used to promote C–C fragmentation, especially those products that are not obviously derived from fragmentation precursors. The successful designs of Cramer are fine illustrations of this insight and are also remarkable since they give allenes as the fragmentation product.[143] The new alkyne and allene methods have been used to prepare natural products in only a limited set of instances. The demonstration of the value of these advances to prepare natural products remains to be shown convincingly, especially in the case of allenes. Within the alkene scenario, however, fragmentation reactions remain exceptionally useful for complex molecule synthesis. Corey's preparation of coraxeniolide A—by the stereospecific creation of a dissymmetric scaffold—is one of many outstanding recent examples.[162] In most C–C fragmentation studies, the well-understood intrinsic reactivity of common ring systems is often parleyed into structures with enhanced stereochemical or functional complexity and then the common ring connectivity is shed by fragmentation to give acyclic or cyclic arrays, including medium and large carbocyclic and heterocyclic targets. Given the vastness of structure space and the need to gain access to specific substances, the benefits of improving and expanding the utility of C–C fragmentation are substantial.

Clearly, the C–C fragmentation reaction remains indispensably useful. The exciting developments of the past 20 years continue in the tradition set forth in the early years of fragmentation—infused with creative insight and applied to problems that challenge the science of synthesis. Indeed, one can scarcely study this transformation without experiencing the inquisitive tug to consider new possibilities, which, pleasingly, are far from exhausted.

The National Institutes of Health (GM-078145), the National Science Foundation (CHE-1012379), Bristol-Myers Squibb (for hosting a sabbatical leave for L.J.W. and for stimulating discussions with BMS scientists), and Rutgers, The State University of New Jersey (Louis Bevier Dissertation Fellowship for M.A.D.) are gratefully acknowledged for their support.

Received: December 9, 2012

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[9] Grob cited Eschenmoser's contributions twice: in his first report (Ref. [71]) and in his second review (Ref. [8b]). Grob did not credit Eschenmoser for being the first to collect the relevant anionic antecedents, for being the first to formulate the correct mechanism, for recognizing the utility of the transformation, or for being the first to design a fragmentation reaction that selectively gave an otherwise difficult to form product. Taken together, this may have served to promulgate the notion that Grob invented this reaction.

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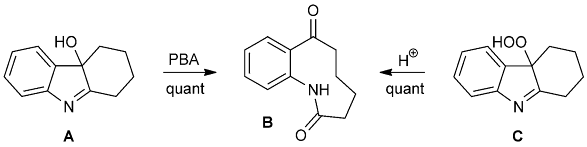

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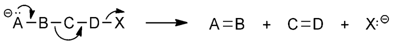

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