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Remote Intramolecular Free Radical Functionalizations: An Update.

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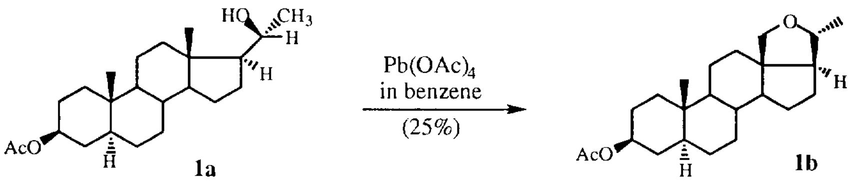
Contents

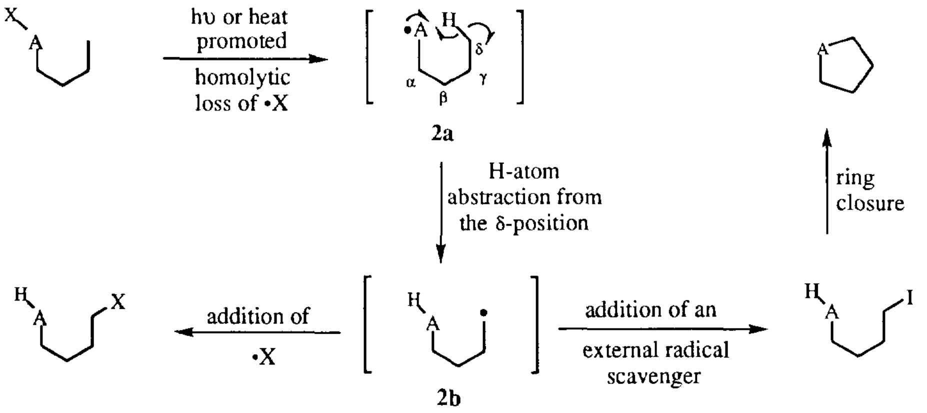
1. Introduction

In 1959 Arigoni and co-workers reported that treatment of **1a** with lead tetraacetate in benzene produced tetrahydrofuran derivative **1b** in 25% yield (Eq. 1).[1] Over the past 30 years, several preparatively useful procedures have been developed for the functionalization of unactivated carbons. Although a variety of reagents



(1)

and conditions are employed, each of these procedures relies on the same underlying mechanism, generalized in Eq. 2. The first step of this pathway is homolysis of the X—A bond to form either an oxygen or a nitrogen free radical (cf. **2a**). Hydrogen abstraction from the δ-position, normally via a *quasi*-chair-like six-atom transition state, generates a new carbon radical, **2b**, which in the absence of competing processes can be captured by the radical species produced by cleavage of the X—A bond. The addition of a good competing radical source, such as iodine, diverts the reaction to give an iodohydrin, which can cyclize to form a tetrahydrofuran derivative. Occasionally, tetrahydropyran derivatives are obtained in low yields. The most common means of generating the requisite oxygen radical (i.e., **2a**) is by thermolysis or photolysis of a hypochlorite (**2c**), a nitrite ester (**2d**), or a hypoiodite (**2e**). Nitrogen radicals are generated by heating appropriate *N*-haloamines with sulfuric acid to give pyrrolidines or piperidines (the Hofmann-Löffler-Freytag reaction). Extensive work has determined that these functionalizations work best with fairly rigid substrates that hold the reacting atoms in fixed geometries. Many of these intramolecular free radical-based functionalizations were comprehensively reviewed in 1964 by Heusler and Kalvoda.[2] This review surveys more recent applications of these functionalizations to organic synthesis and is organized in terms of the reagent(s) used to initiate the overall process.[3]

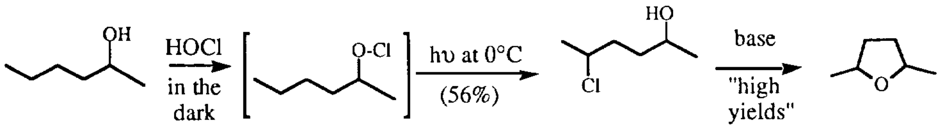


(2)

A = O; X = Cl (**2c**) Photolysis of a hypochlorite
= O; = NO (**2d**) "The Barton reaction"
= O; = I (**2e**) Photolysis of a hypoidite ["The Hypoiodite reaction"]
= O; = H (**2f**) Lead tetraacetate-iodine variation of the hypoiodite reaction
= O; = H (**2g**) Mercuric oxide-iodine variation of the hypoiodite reaction
= N; = Cl (**2h**) "The Hofmann-Löffler-Freytag reaction"

2. Photolysis of Hypochlorites

In 1961, Walling and Padwa reported that photolysis or thermolysis of alkyl hypochlorites derived from either primary or secondary aliphatic alcohols gives δ-chlorohydrins, which can cyclize under basic conditions (Eq. 3).[4a] The utility of this protocol, however, was severely handicapped by the need to isolate the often unstable alkyl hypochlorites. The photolysis of hypochlorites derived from tertiary alcohols was preparatively useful and conveniently achieved without special precautions by preformation of the hypochlorite from the alcohol and hypochlorous acid (in dim light and at room temperature). Without isolation, this substrate could then be added to carbon tetrachloride and photolyzed (Eqs. 4 and 5).[4b]



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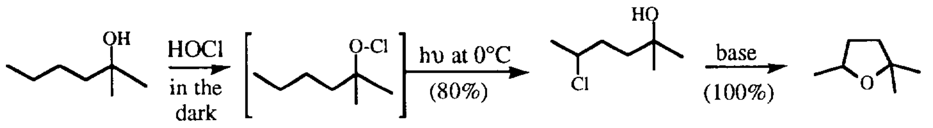

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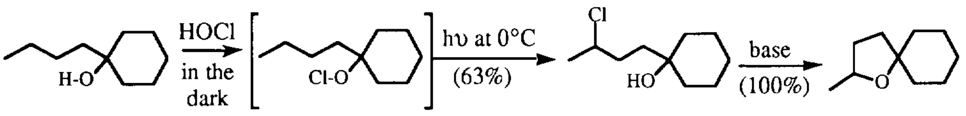
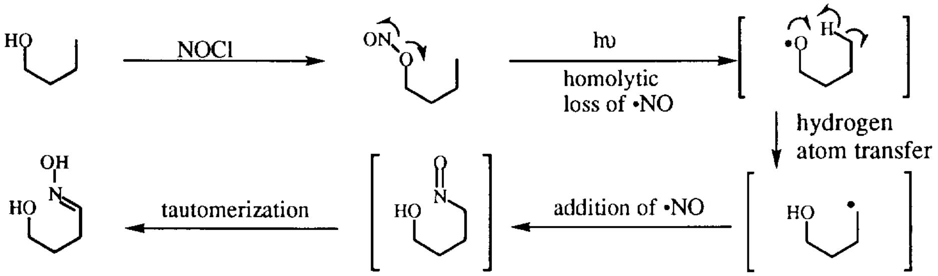


(5)

3. Photolysis of Nitrite Esters (The Barton Reaction)

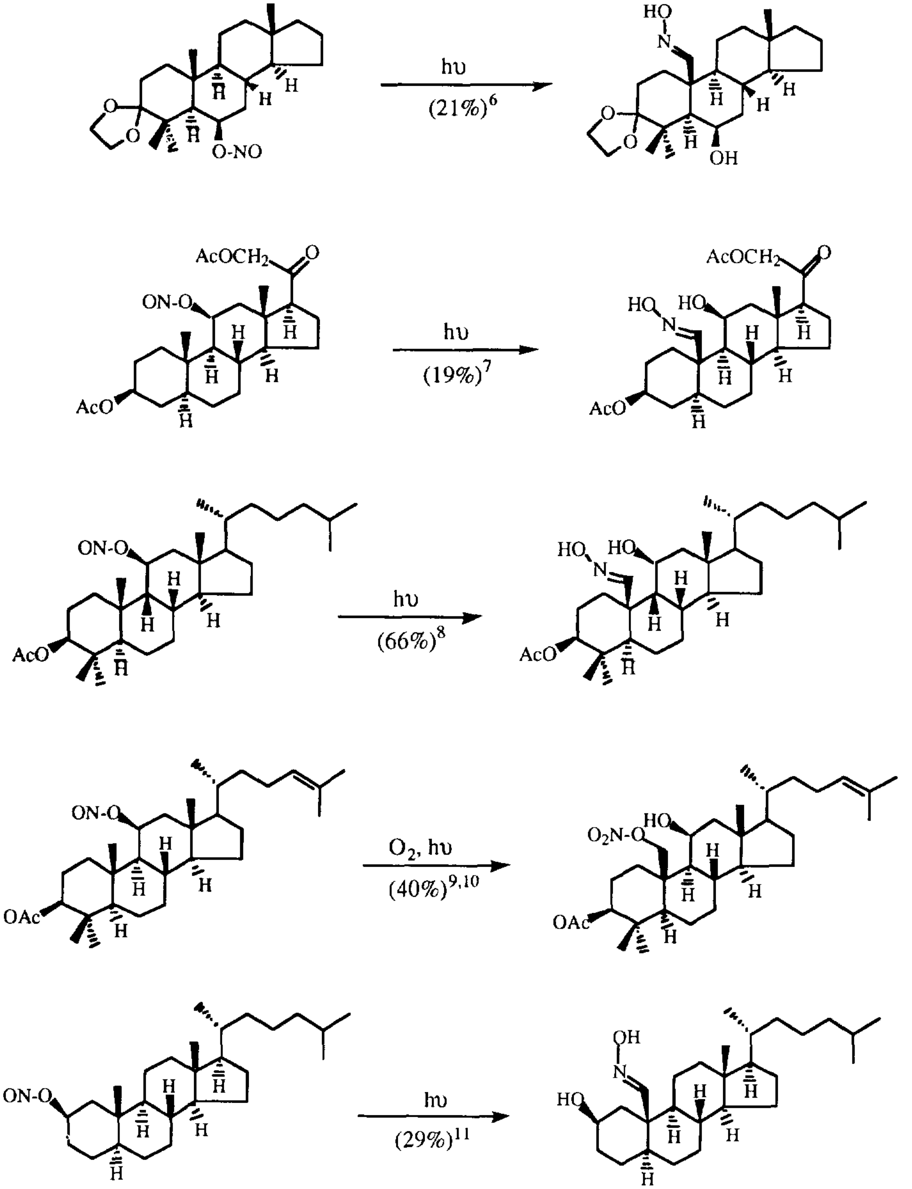
In 1961 Barton and co-workers discovered that photolysis of a nitrite ester generates an oxygen radical, which abstracts a hydrogen atom from a δ-carbon followed by capture of the carbon radical with the nitric oxide liberated upon the original homolysis (Eq. 6).[5]



(6)

Skeletons with several fused rings, such as steroids, are well suited to these remote functionalizations. Chart I contains twelve recent steroid functionalizations that use traditional Barton conditions. While most of these examples are straightforward applications of this procedure,[6-17] two cases are particularly noteworthy. The reaction shown in Eq. 10 was carried out in the presence of oxygen and produced a nitrate instead of the usual oxime.[9,10] The Barton reaction in Eq. 18 generated the expected oxime at C(18), which then reacted with the hydroxyl at C(11) to produce a hydroxylamine group (cf. **18a**). The amine condensed with the C(20) carbonyl, forming nitrone **18b**.[17] Further work showed that the yield of the nitrone varied with the choice of solvent used in the photolysis.

Chart I: Steroid Functionalization using the Barton Reaction



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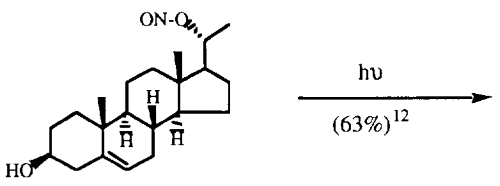

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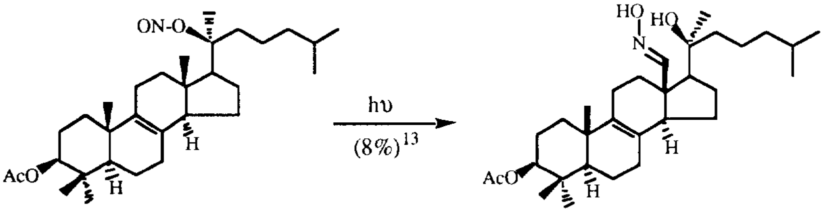

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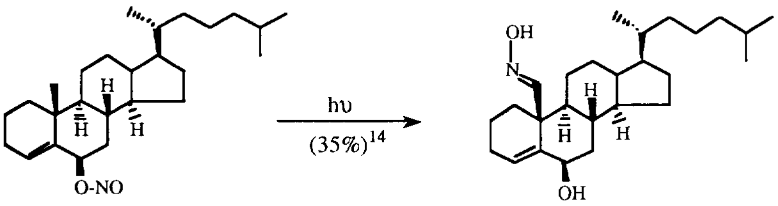

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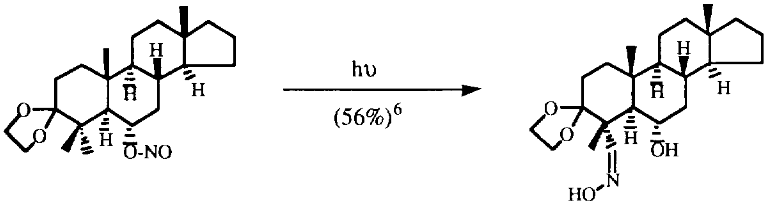

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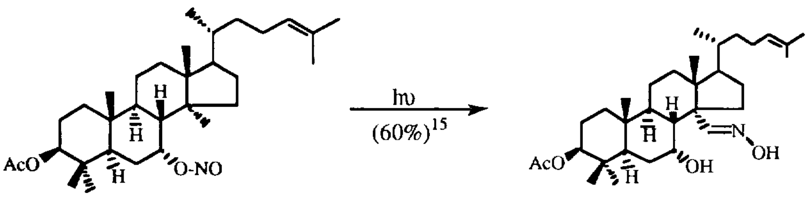

(16)

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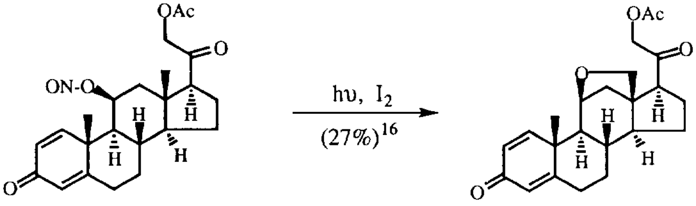

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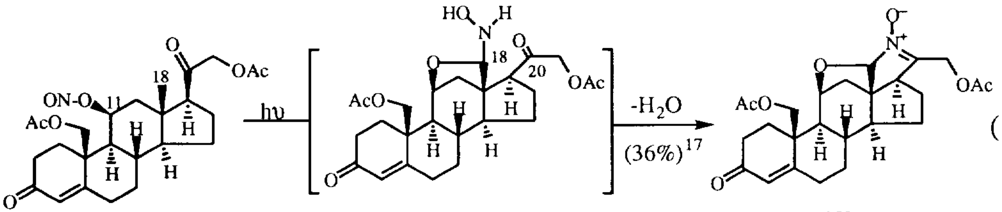
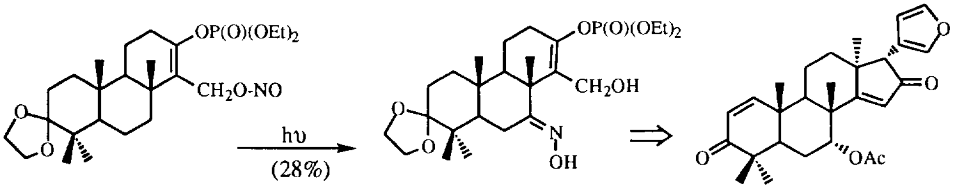


18a **18b**

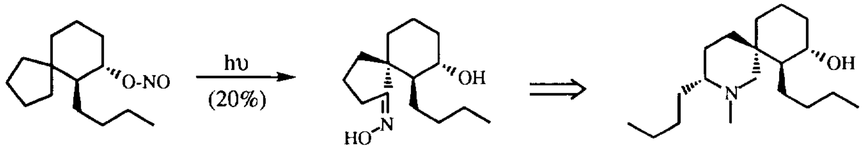
(18)

The Barton reaction has played a pivotal role in terpene synthesis and also in elucidation of terpene structure.[18] For example, in Corey's syntheses of azadiradione (Eq. 19)[19a] and perhydrohistrionicotoxin (Eq. 20),[19b] selective functionalization by means of the Barton reaction was *the* crucial step. Similarly, Masamune and co-workers oxidized the angular methyl group of **21a** using a nitrite photolysis, thereby facilitating a synthesis of rishitin (Eq. 21).[20]



azadiradione

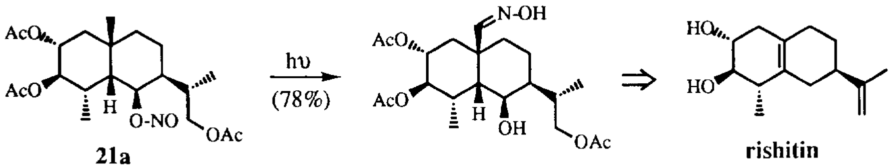
(19)



76a

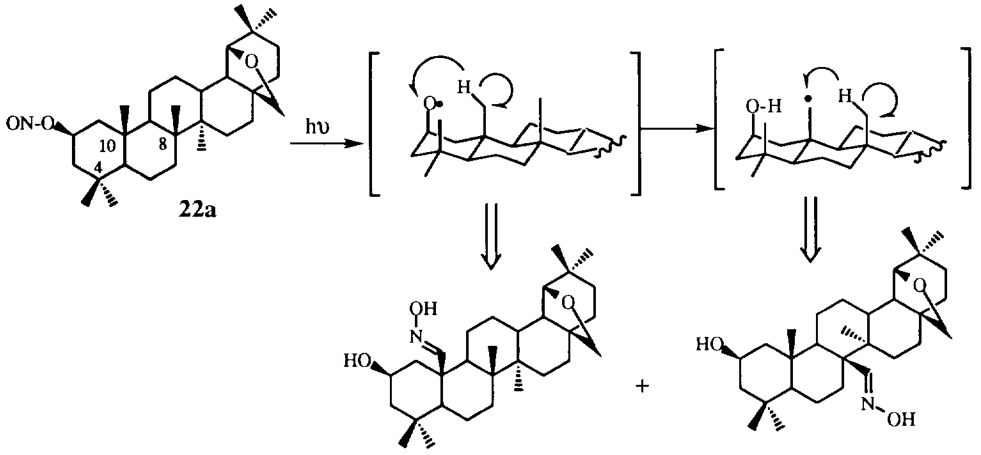
perhydrohistrionicotoxin

(20)



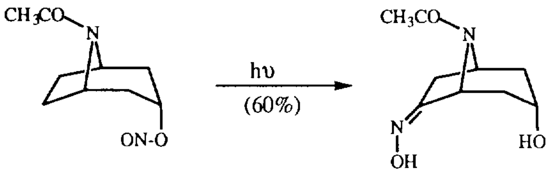
21a **rishitin** (21)

The Barton reaction does not always give a single major product. For example, in the functionalization of compound **22a**, reaction at either (or both) the C(4) and C(10) methyls was expected,[21] but oxidation of the C(8) methyl was not (cf. **22c**). This remote functionalization occurs via two consecutive 1,5 H-atom transfers.[22]



22a **22b** (39%) **22c** (38%) (22)

Although remote functionalization in alkaloids is usually associated with the Hofmann-Löffler-Freytag reaction, the Barton protocol is often useful. Two recent examples are shown in Eqs. 23 and 24, where photolysis of the nitrites afforded the corresponding oximes in good yield.[23,24]



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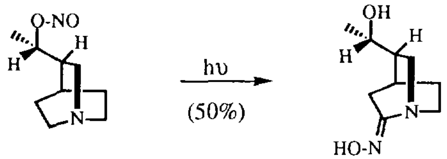
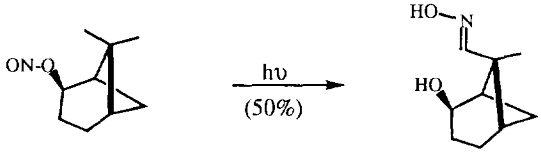


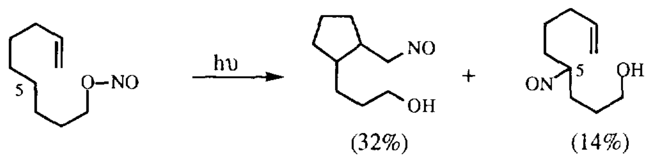
(24)

Although Barton reactions occur more easily with rigid structures (cf. Eq. 25),[25] flexible molecules can also be functionalized by this method. The reaction of the acyclic system shown in Eq. 26 must involve a rapid



(25)

hydrogen atom abstraction from C(5), since cyclic products derived from the addition of the oxygen radical to the double bond are not observed.[26,27] Equation 27 depicts a selective functionalization of the proximal methyl of a geminal dimethyl group.[28]



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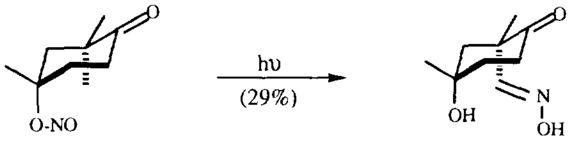
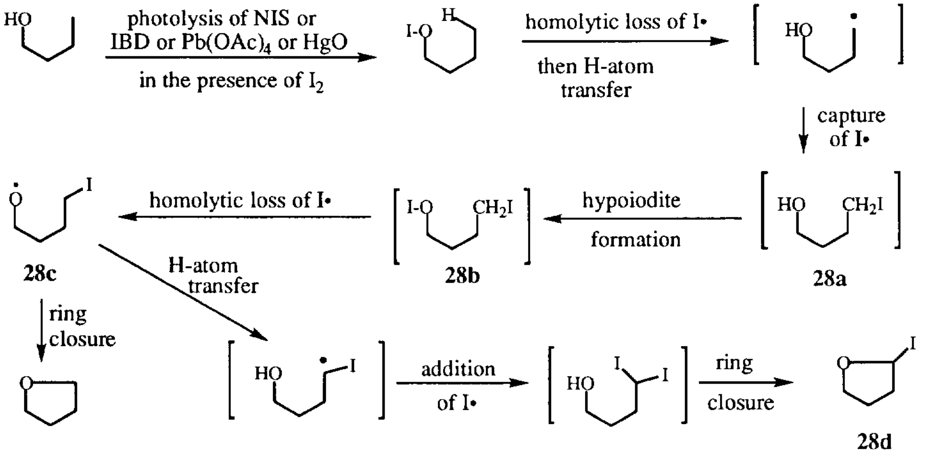


(27)

4. Hypoiodite Reactions

Heusler and Kalvoda popularized the term "hypoiodite reaction" to describe the homolytic cleavage of alkyl hypoiodites. Unlike the photolysis of hypochlorites or nitrite esters, in which only a single functionalization occurs, hypoiodite reactions can produce several products by multiple functionalizations and they also differ in the preparation of the requisite radical precursors. While nitrite esters and most hypochlorites must be isolated prior to decomposition, alkyl hypoiodites are generated *in situ* from the appropriate alcohol by the action of reagents such as *N*-iodosuccinimide (NIS), acyl hypoiodites or iodobenzene diacetate (IBD). The overall mechanism in these cases is similiar to the basic pathway presented in Eq. 2; iodine is added to the reaction mixture to accelerate the hypoiodite decomposition. However, under the reaction conditions, the 1,5-iodohydrin (28a) initially produced can react further to form a new hypoiodite species (cf. 28b), which



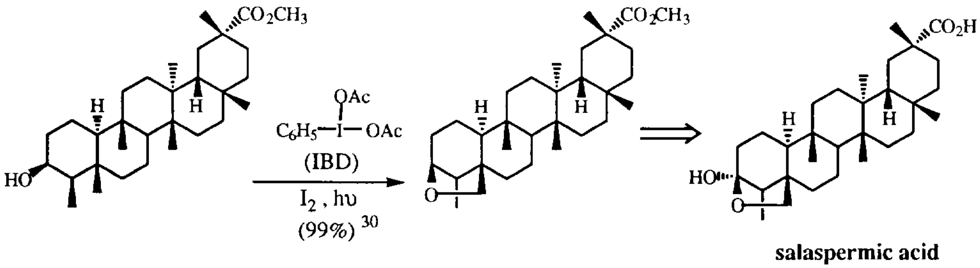
(28)

solvolyzes to produce iodo alkoxy radical **28c**. This reactive species can either cyclize to produce a tetrahydrofuran or can undergo a second H-atom abstraction to doubly functionalize the δ-position, leading to the formation of an iodo ether (**28d**). Heavy metal salts, such as the acetates of Pb(IV), Hg(II), Ag(I) or mercuric oxide, in combination with iodine, generate hypoiodite intermediate **28b** *in situ* and thus also hypoiodite reactions.[29]

(4.1) Iodobenzene Diacetate and Iodine-Promoted Hypoiodite Reactions.

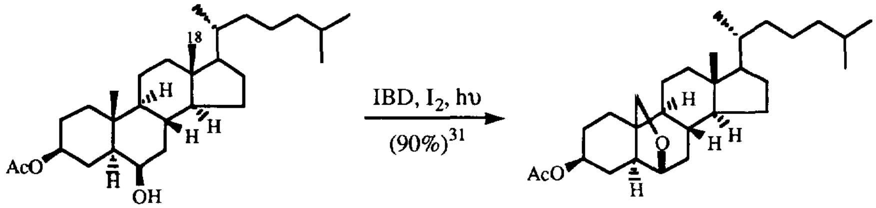
Reagents such as iodobenzene diacetate (IBD) limit hypoiodite reactions to tetrahydrofuran formation, whereas other reagents, such as lead tetraacetate or mercuric oxide, can form more highly oxidized products. Four recent applications of IBD-catalyzed hypoiodite reactions are shown in Chart II.[30-32] Although most of these applications have been in steroid research, this methodology has also been useful in terpene synthesis (cf. Eq. 32). Suarez and co-workers have used this methodology to form the spiroketal shown in Eq. 32. Deuterium labeling showed that this reaction goes through an unusual (seven-atom) transition state.

Chart II: Iodobenzene Diacetate and Iodine-Promoted Hypoiodite Reactions



(29)

Chart II continued:



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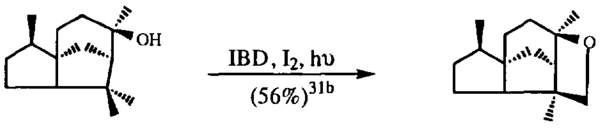

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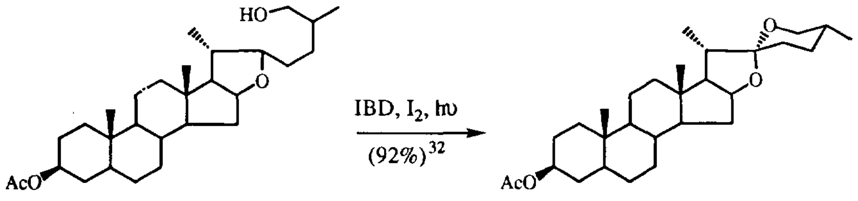
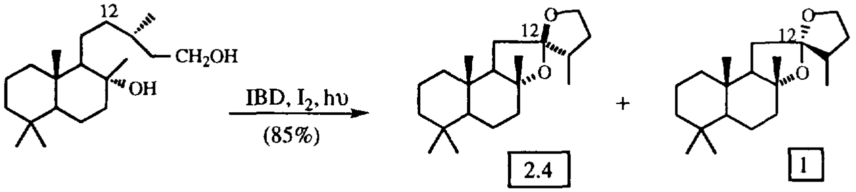


(32)

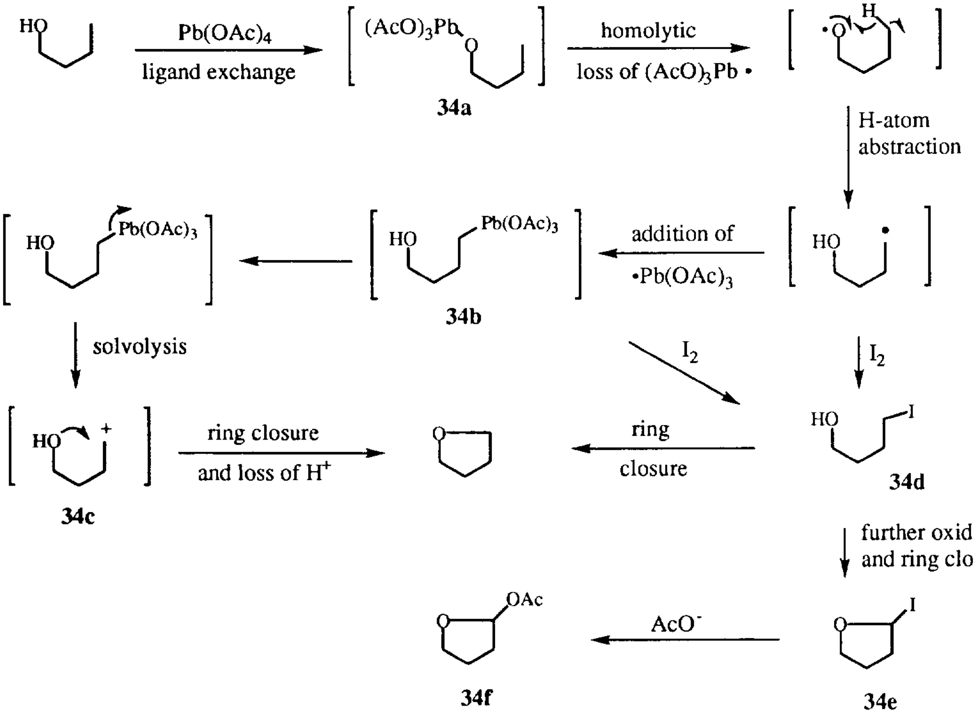
Equation 33 depicts the use of two hypoiodite reactions to doubly oxidize the C(12) position of a labdane derivative.[33] In this case, not only is the yield high, but the product mixture is significantly enriched in the *R*-C(12) epimer.



(33)

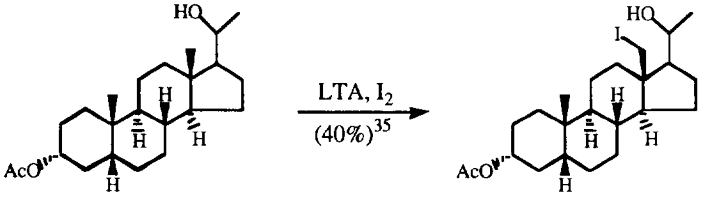
(4.2) Lead Tetraacetate and Iodine-Promoted Hypoiodite Reactions.

The use of lead tetraacetate (LTA) and iodine for oxidative cyclization of appropriate alcohols is an extremely powerful method for preparation of tetrahydrofuran derivatives. Although the mechanism of this process is complex and is thought to proceed via several possible transition states, a greatly simplified view is presented in Eq. 34.[34] The initial step of the sequence is the exchange of ligands to generate a lead(IV) alkoxide (**34a**), which is not isolable. Preferential cleavage of the (RO)—Pb bond, versus the less labile (RCO-O)—Pb bond, generates an alkoxy radical, which leads to H-atom abstraction. Most of the mechanistic uncertainty of this process centers on whether or not the organolead intermediate **34b** is formed and its subsequent role (i.e., the formation of carbenium ion **34c** or iodohydrin **34d**). Higher yields of the tetrahydrofuran products are obtained when the oxygen, carbon and iodine atoms can be colinear. However, if the alkoxy radical and the relevant C–H bond are conformationally flexible, elimination products are produced derived from intermediates with carbenium ion character. Since these reactions require large excesses of LTA and iodine, further oxidation often occurs and results in formation of an iodotetrahydrofuran, such as **34e**, or a hemiacetal acetate (cf. **34f**).



(34)

Iodohydrins can be isolated when the reaction times are short (e.g., the reaction time was 45 minutes for Eq. 35) and / or the quantities of the reagents are limited, as was the case in Eq. 36.



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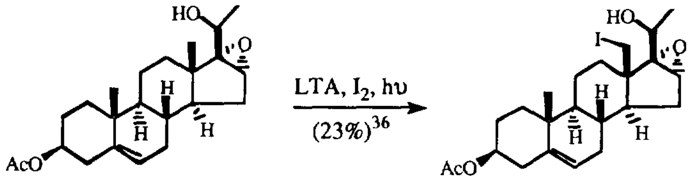
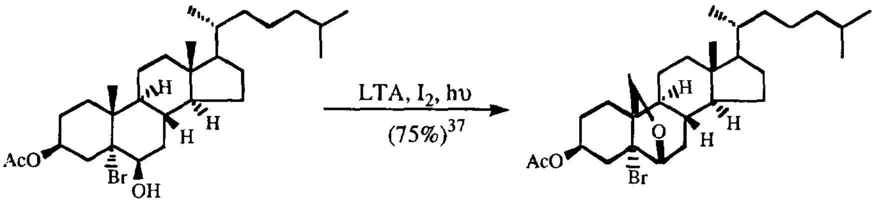


(36)

As mentioned earlier, the lead tetraacetate-iodine reagent has found broad applicability for the formation of tetrahydrofuran derivatives. Nine recent applications in which angular methyl groups are functionalized are presented in Chart III.[37-43]

Chart III: Lead Tetraacetate and Iodine-Promoted Tetrahydrofuran Preparations



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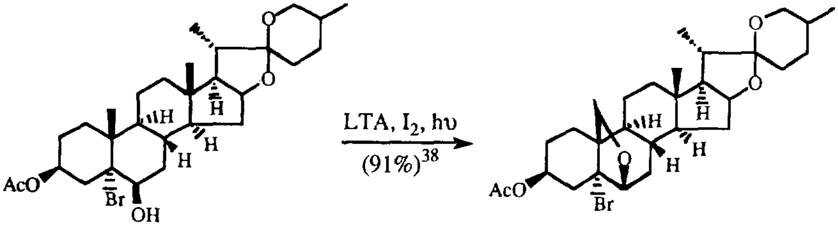

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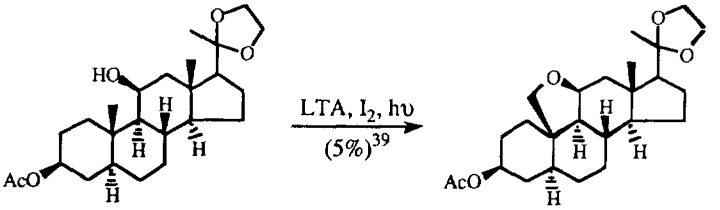

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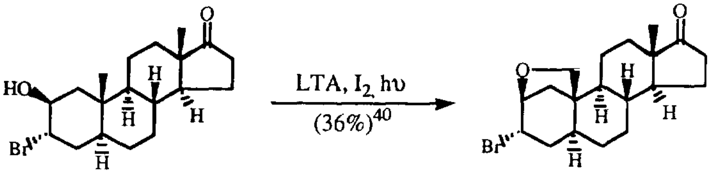

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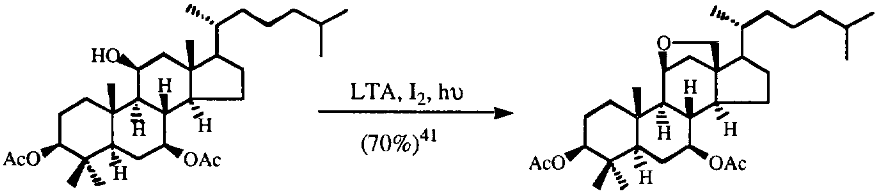

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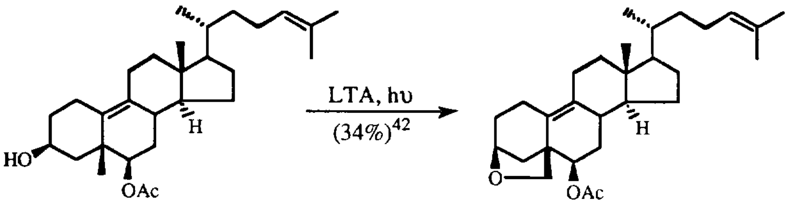

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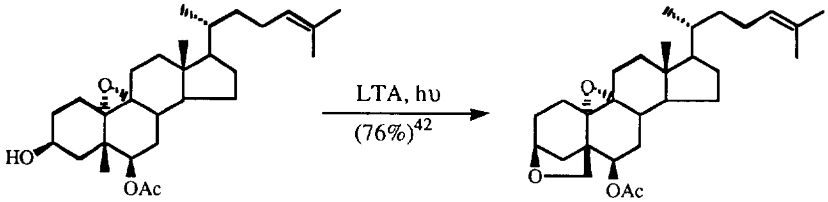

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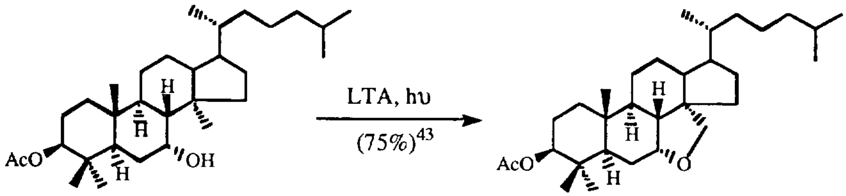

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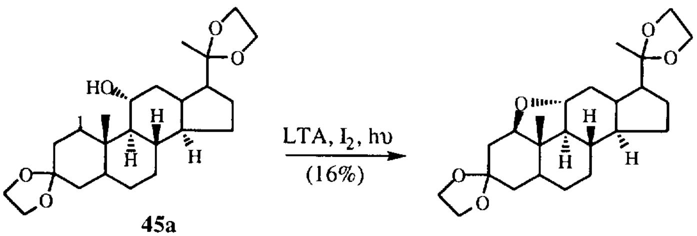
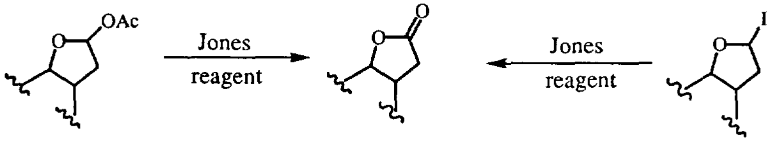


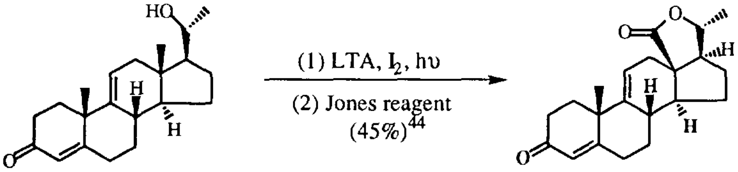
45a

(45)

A limitation of the hypoiodite reaction involving lead tetraacetate and iodine is the formation of hemiacetals, and / or α-iodo-ethers. Fortunately, treatment of the crude reaction mixture with Jones reagent



directly provides the corresponding lactone. Equations 46 through 48 depict three recent applications of this oxidative sequence.[44,45] Unfortunately, lactone formation occurs in only modest yield.



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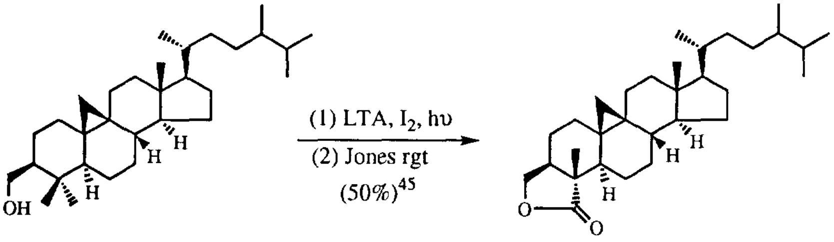

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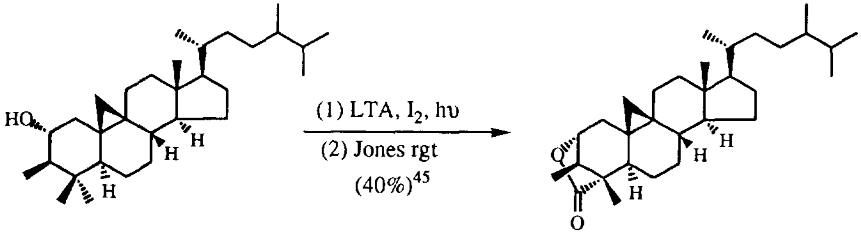
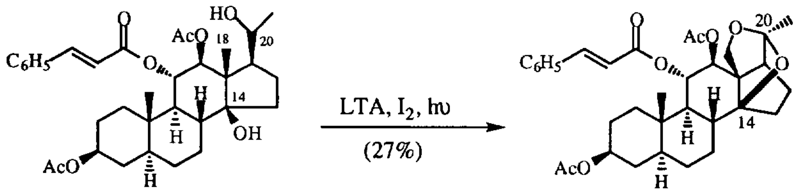


(48)

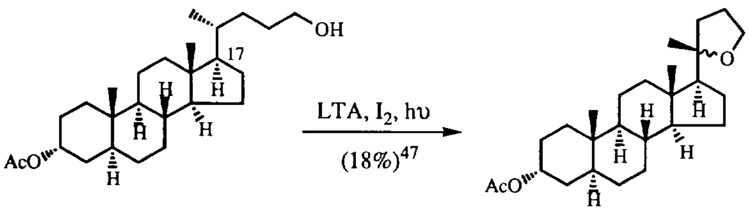
The photolysis of diol **49a** with lead tetraacetate and iodine forms ketal **49b** in low yield (Eq. 49).[46] This transformation involves two sequential hypoiodite reactions. Here, functionalization of the C(18) methyl group first occurs from the C(20) hydroxyl to generate a tetrahydrofuran, which then undergoes further oxidation at C(20) because of the close spatial proximity of the C(14) alcohol moiety.



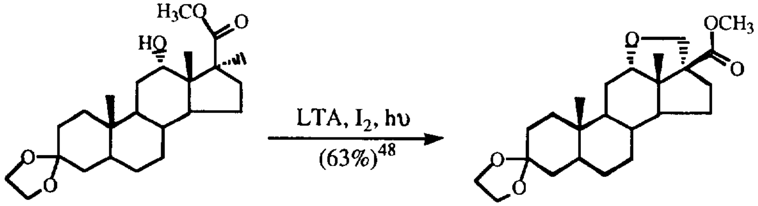
49a **49b**

(49)

The atoms on an alkyl chain at C(17) can be functionalized using a lead tetraacetate-iodine-promoted hypoiodite reaction to produce cyclic ethers that are fused to or attached to the steroid D ring. Three recent examples are shown in Eqs. 50 through 52.[47-49]



(50)



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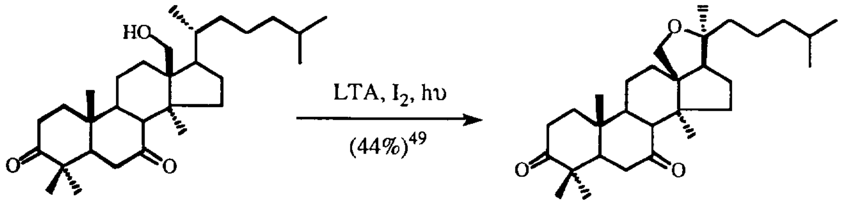
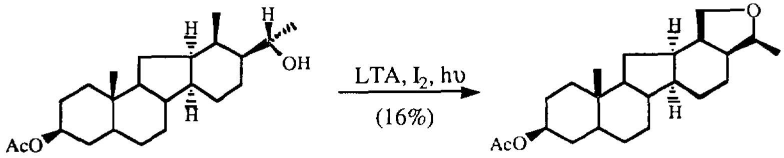


(52)

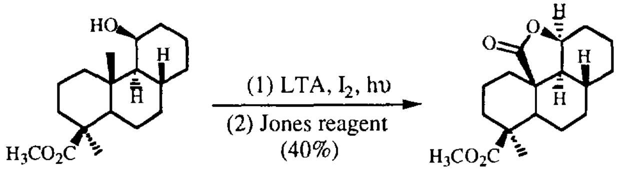
Recently, Masaumune and co-workers extended the lead tetraacetate and iodine photolysis procedure to norsteroids in their syntheses of jerveratum alkaloid derivatives (Eq. 53).[50]



(53)

Five diterpenoid functionalizations are presented in Chart IV. These examples include Herz's study of resin acid derivatives (Eqs. 54 and 55)[39] and Ceccherelli's work toward manool (Eqs. 56 and 57) and cafestol (Eq. 58).[22]

Chart IV: Lead-Tetraacetate and Iodine-Promoted Diterpenoid Functionalizations



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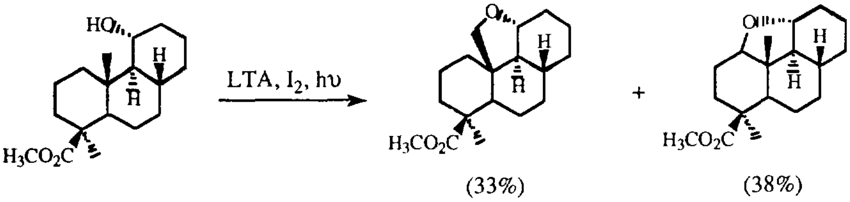
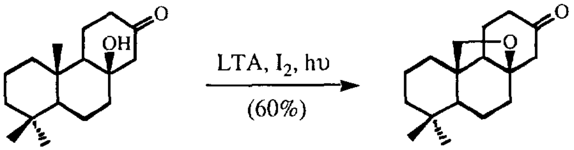
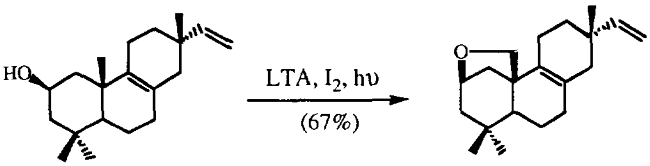


(55)

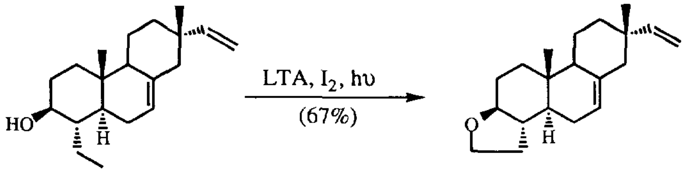


(56)



(57)

Chart IV continued

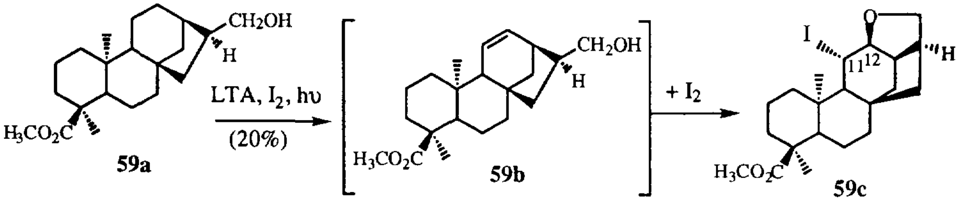


(58)

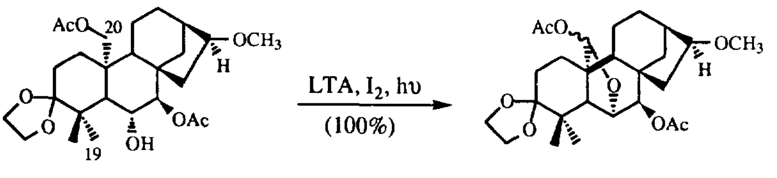
McCrindle[51] and Node[52] have used remote oxidative functionalizations in their studies of kauranes, norkauranes, and their derivatives (Chart V). Reaction of kauranol ester (**59a**) with lead tetraacetateand iodine results in the oxidation of two adjacent sites [cf. C(11) and C(12)] of iodide **59c**. McCrindle speculated that this product results from the loss of HI from the expected iodohydrin; resulting in the formation of a C(11),C(12)-double bond (cf. **59b**). The presence of iodine in the reaction mixture should account for the formation of iodide **59c**. Other free radical-based mechanisms were also postulated.[51]

The outcome of many of the functionalizations found in Chart V is the result of subtle conformational nuances. In Eqs. 60 and 61, although attack at C(19) was desired, when either reactant was photolyzed functionalization took place only at C(20). Remarkably, reversing the stereochemistry at C(6) gave the desired lactone in good yield as shown in Eq. 62. A similar strategy was employed in the syntheses of norkauranes (Eqs. 64 and 65).

Chart V: Lead Tetraacetate and Iodine-Promoted Functionalization of Kauranes and Norkaurane Derivatives

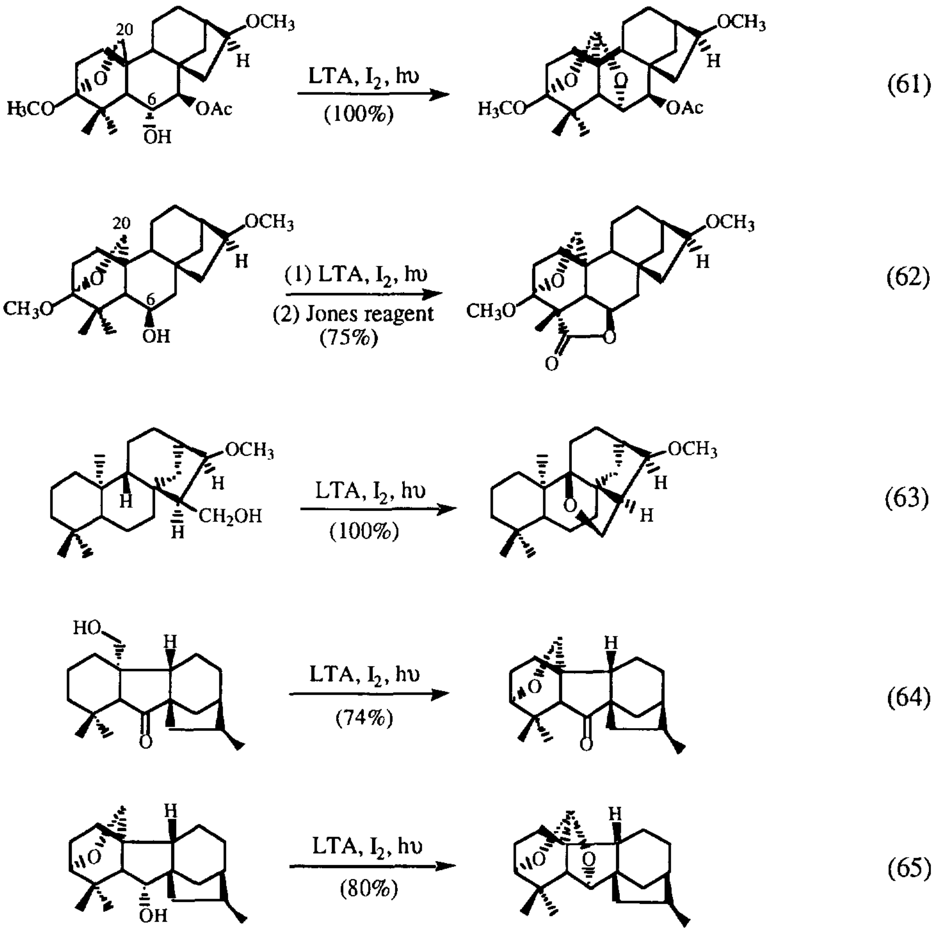


(59)

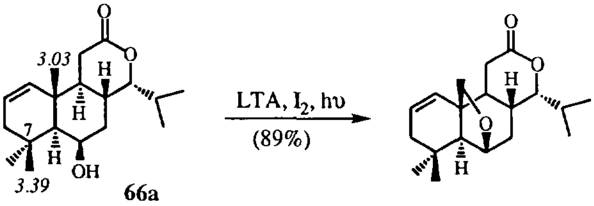


(60)

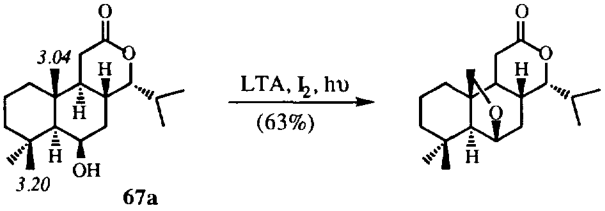
Chart V continued



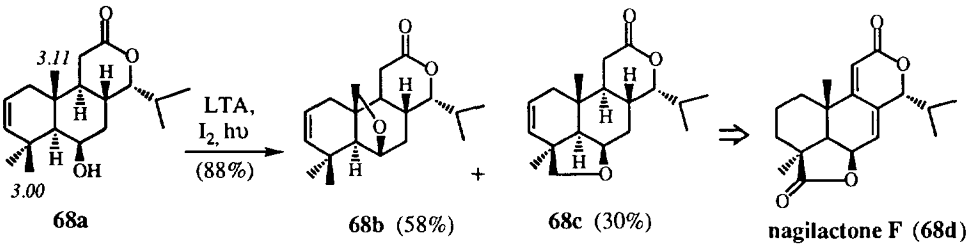
Burke relied on lead tetraacetate and iodine-promoted free radical oxidations to complete his synthesis of nagilactone F (cf. **68d**).[53] Although the methyl at C(7) was the target of selective functionalization, the methyl group at C(10) was preferentially oxidized (Eq. 66). For two other derivatives (Eqs. 67 and 68) the modeling program MacroModel was used to predict which carbon would be attacked. [The italicized numbers on structures **66a, 67a** and **68a** are the calculated distances in Angstroms from the alcohol oxygen to the methyl carbon.] These calculations confirmed that in Eqs. 66 and 67 the closest methyl group was oxidized preferentially. However, this selectivity was not observed when substrate **68a** was oxidized, as tetrahydrofuran **68b** predominated. Nevertheless, the isolation of ether **68c** allowed Burke and co-workers to complete a total synthesis of **68d**.



(66)

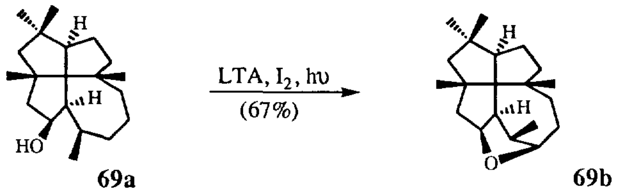


(67)



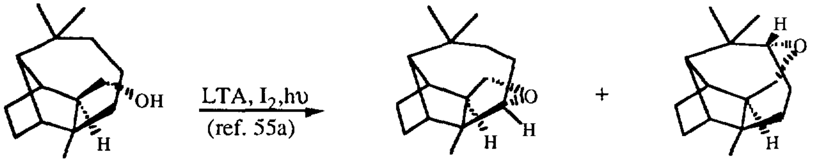
(68)

The three-dimensional structure of laurenene derivative **69a** is quite complex; several sites are positioned correctly for 1,5-hydrogen abstraction, and it was unclear even from the X-ray structure which carbon atom would be attacked under free radical functionalization conditions. Experimentally, only one product was obtained (cf. **69b**).[54]



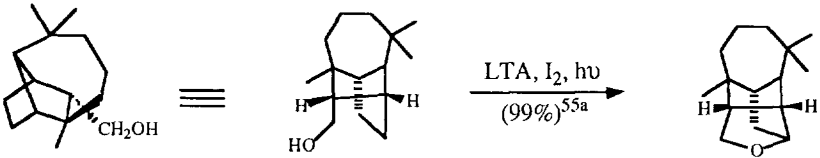
(69)

Nayak and co-workers found in their functionalization of longifolol derivatives that a pair of epimers produces quite different products: a mixture in the case of **70a** and a near-quantitative yield of a single product in the case of the other isomer (i.e., **71a**). A related longifolane derivative gave the cyclic ether shown in Eq. 72 in 84% yield.



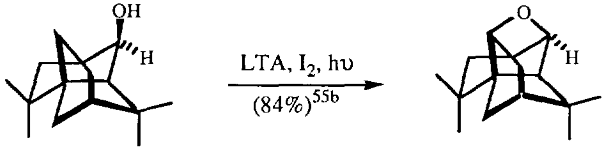
70a **70b** (40%) **70c** (40%)

(70)



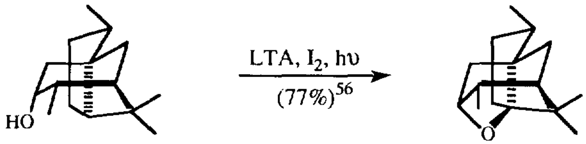
71a

(71)



(72)

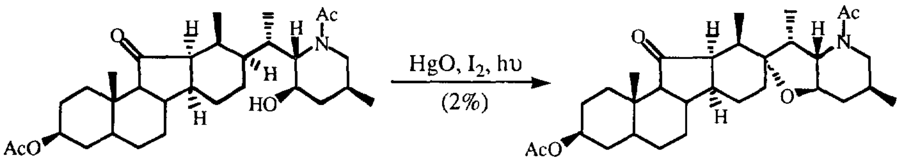
The rigid structure of cedrol and its derivatives is well suited to these remote functionalizations, as was confirmed by Waegell *et al* (Eq.73).[56]



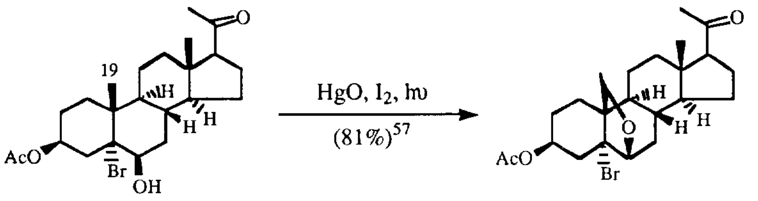
(73)

(4.3) Mercuric Oxide and Iodine-Promoted Hypoiodite Reactions

Hypoiodite reactions that use the combination of mercuric oxide and iodine afford tetrahydrofurans without overoxidation (cf. Eqs. 74 and 75). At the outset of the reaction the mercuric oxide and iodine form I_2O, which leads to hypoiodite formation *in situ*.[12] The remaining mechanistic steps parallel those discussed earlier in Eq. 34.

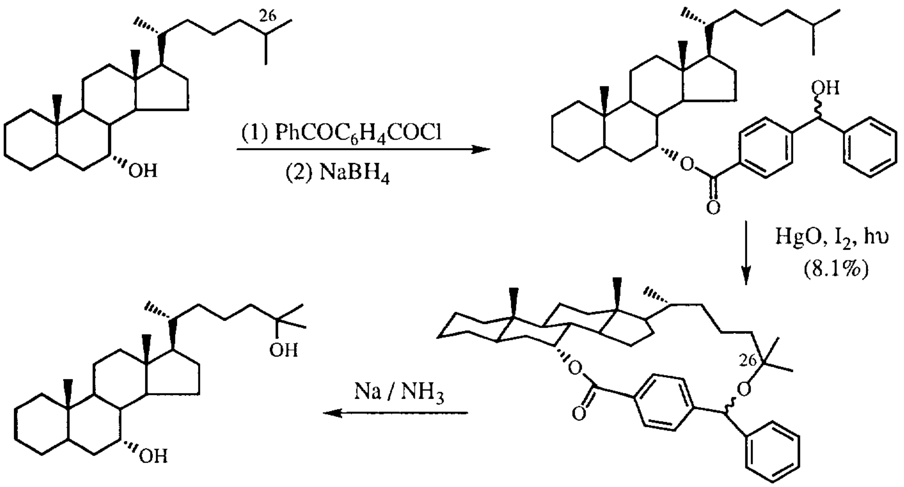


(74)



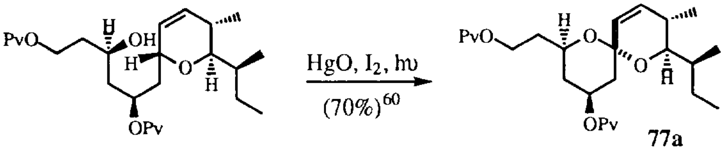
(75)

Masamune and co-workers have used mercuric oxide and iodine-based oxidations to functionalize the C(26) position of the alkyl side chain (Eq. 76). This type of reaction, pioneered by Breslow and co-workers using carbon radicals,[58] goes through a nineteen-atom cyclic transition state and selectively produces the C(26) functionalized product, albeit in low yield.[50,59]



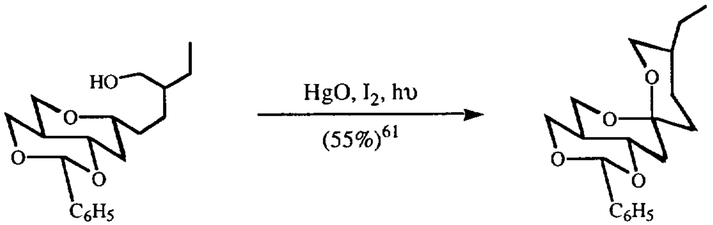
(76)

The formation of each of the spiroketals shown in Eqs. 77-79 requires a cyclic seven-membered transition state. These ring closures succeed, despite the larger than normal cyclic transition state, because a heteroatom-stabilized radical intermediate is generated. For example, in the formation of **77a**, a key intermediate in Danishefsky's synthesis of avermectin A_{1a}, ketal formation is the result of the abstraction of an allylic hydrogen atom. Recall that Suarez and co-workers studied the spiroketalization of a closely related system (cf. Eq. 31).

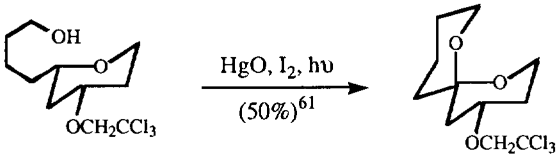


77a

(77)



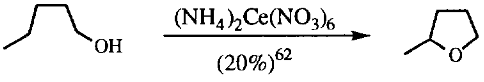
(78)



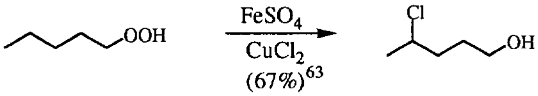
(79)

5. Other Useful Reagents for Oxygen Free Radical-Based Remote Functionalizations

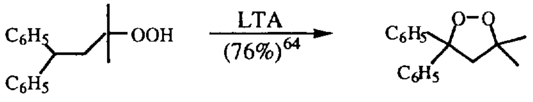
While the traditional procedures require photolysis of a nitrite or hypohalite species, there are alternative ways to produce the requisite oxygen radical. In 1969, Trahanovsky reported the use of cerium ammonium nitrate to produce the tetrahydrofuran shown in Eq. 80, in a yield comparable to that obtained with lead tetraacetate and iodine. To date, however, the use of this cerium reagent has not been widespread. Cekovic and Kropf discovered that peroxides and metal catalysts are also useful for remote functionalization, as illustrated in Eqs. 81 and 82.



(80)

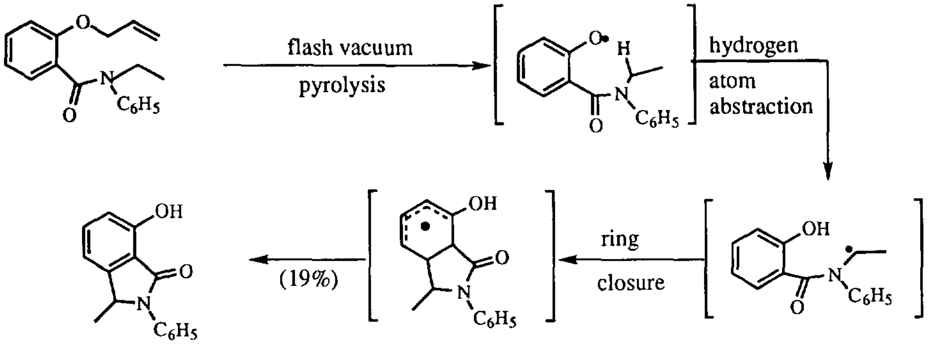


(81)



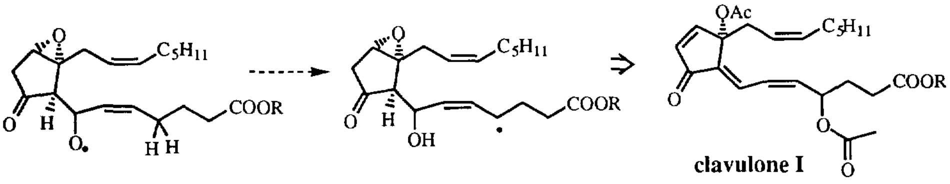
(82)

Early in 1994, Black, Cadogan, and McNab found that flash vacuum pyrolysis of allyl phenyl ethers can produce the necessary oxygen radical needed for further functionalization (Eq. 83).[65] Once again, the required H-atom transfer proceeds through an abnormal seven-atom transition state.



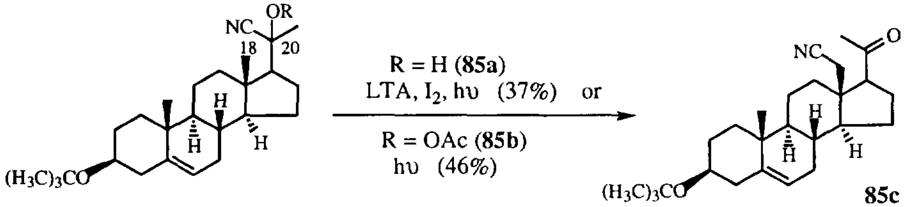
(83)

Remote intramolecular free-radical functionalizations may even occur in nature. Corey has proposed a variation of the oxygen free radical-based remote functionalization for the biosynthetic pathway to the clavulones (Eq. 84).[66]



(84)

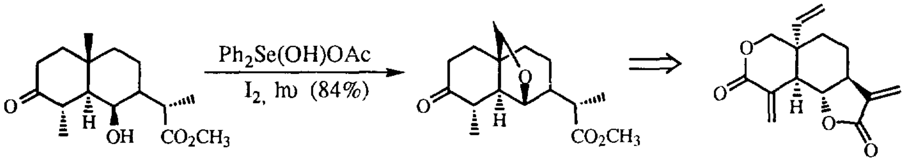
Photolysis of cyanohydrin **85a** gives a ketone instead of the expected alcohol (Eq. 85).[67] A recent modification of this reaction by Watt and co-workers used an acetyl peroxy group as the radical precursor (i.e., **85b**).[68] Although Watt's procedure gave an improved yield of **85c**, the starting acetyl peroxide required more steps to prepare.



85c

(85)

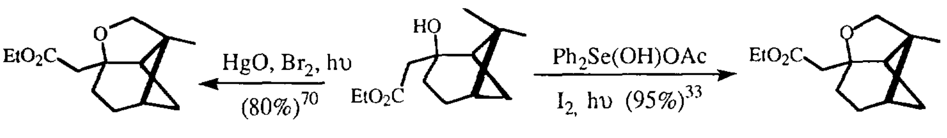
Suarez and co-workers began with **86a** to functionalize the angular methyl group in their synthesis of deoxyvernolepin.[69] Here, diphenylhydroxyselenium acetate was used to promote formation of ether **86b** in high yield; use of iodobenzene diacetate to promote the transformation decreased the yield to 65%.



86a **86b** **deoxyvernolepin**

(86)

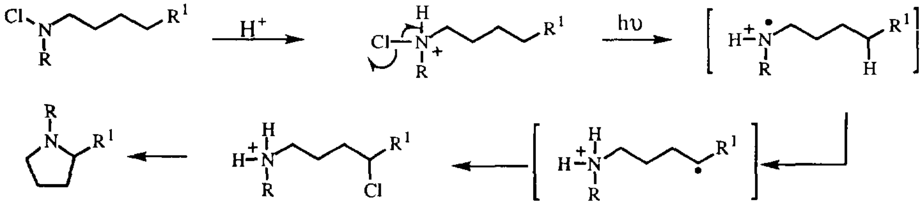
Diphenylhydroxyselenium acetate has proved useful for the synthesis of pinane derivatives. The efficiency of this reagent is best appreciated when compared with traditional conditions for the same transformation (Eq. 87).[70] In contrast to the outcome with other reagents, iodohydrins or products arising from a second H-atom abstraction reaction were not detected when diphenylhydroxyselenium acetate was used.



(87)

6. Hofmann-Löffler-Freytag Reactions

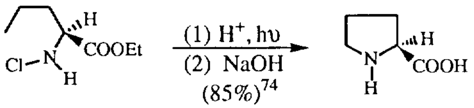
The Hofmann-Löffler-Freytag reaction works on the same principle as the Barton reaction but involves a 1,5-hydrogen atom transfer to a nitrogen radical. Although the reaction was discovered in 1887,[71] its mechanism was not fully understood until 1960 (Eq. 88).[72] It is generally accepted that the first step is the formation of a chloroammonium salt from the *N*-chloramine and the acid present. Irradiation then converts this salt to a nitrogen radical cation. Hydrogen atom transfer is followed by capture of the carbon radical by chlorine, and finally by ionic cyclization. The Hofmann-Löffler-Freytag reaction was reviewed previously in 1963 by Wolff.[73]



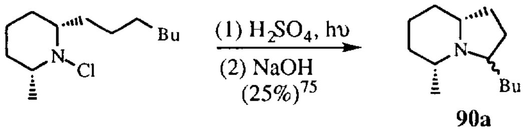
(88)

The Hofmann-Löffler-Freytag reaction has been applied to acyclic molecules more widely than have alkoxy radical-based processes, usually to form substituted pyrrolidines. The procedure traditionally requires strong acidic conditions, which limits its appeal. Nevertheless, even under the acidic conditions normally required, structurally diverse molecules can be functionalized by this procedure as typified by the seven examples in Chart VI.[74-80] In the first example, Lavergne used this methodology to produce L-proline (Eq. 89). Sonnet and Oliver's preparation of potential ant sex pheromone precursors (i.e., octahydroindolizine **90a**) and Waegell's synthesis of azabicyclo[3.2.1]octane derivatives (Eq. 91) are examples of the construction of bicyclic amines through this procedure. Equation 92 presents another case of the preparation of a bridged product. More specifically, pentacycle **92b** was produced on photolysis of chloramine **92a**. This intermediate proved to be useful for the preparation of the kobusine-type alkaloids. After much effort, Deshpande and Nayak proved it was possible to prepare pyrrolidines containing a longifolene nucleus (cf. Eq. 93). [We discussed a similar functionalization earlier, producing a tetrahydrofuran instead of a pyrrolidine (Eq. 73). That reaction gave a much higher yield (77% versus 10%), presumably because the O—I bond is more easily cleaved homolytically than the analogous N—Cl bond.] Since derivatives of adamantane have a rigid framework, the yields of the Hofmann-Löffler-Freytag abstration in these systems are quite good. Note that the tertiary nature of chloride **94b** precludes cyclization by an SN2 displacement, whereas secondary bromide **95b** does undergoes an SN2 ring closure. Nevertheless, pyrrolidine **94c** can be formed under forcing conditions.

Chart VI: Recent Hofmann-Löffler-Freytag Reactions Under Acidic Conditions

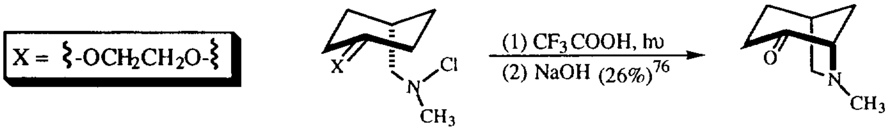


(89)

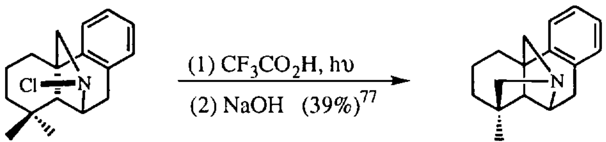


90a

(90)



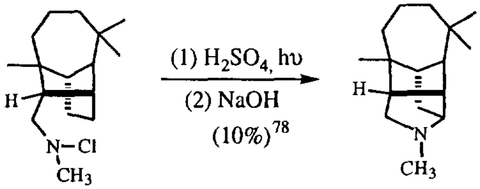
(91)



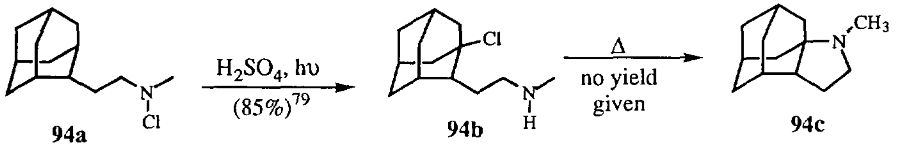
92a **92b**

(92)

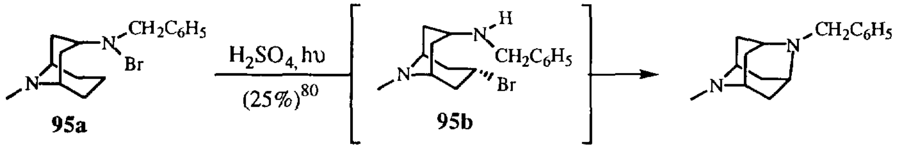
Chart VI continued:



(93)

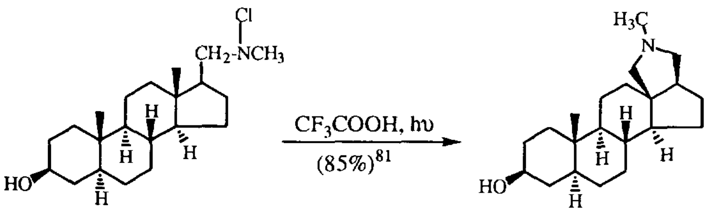


(94)



(95)

Although the Hofmann-Löffler-Freytag reaction has not been extensively applied to steroid syntheses, Hora and Van de Woude used this procedure in their syntheses of conessine derivatives as shown in Eqs. 96-98.



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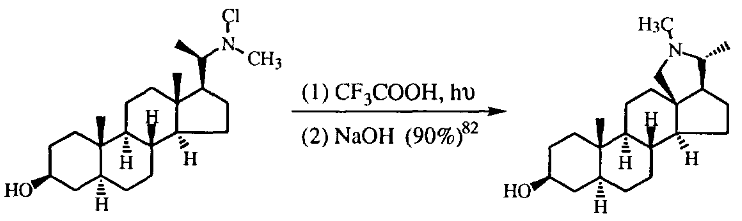
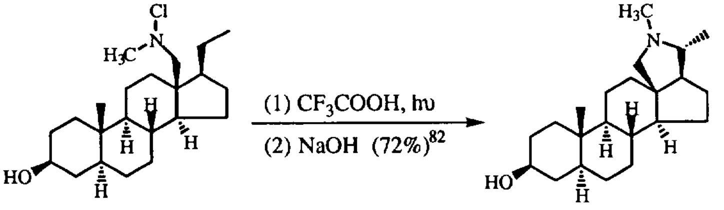


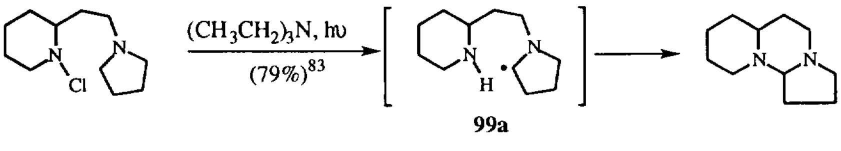
(97)



(98)

Recent work has revealed that acidic conditions are not always necessary for a Hofmann-Löffler-Freytag reaction to proceed; instead, the stability of the alkyl radical that is generated *in situ* is more important. For example in Equations 99 and 100, the nitrogen atoms of **99a** or **100a**, stabilize the radical species generated by H-atom abstraction and permit this step to take place even under weakly basic conditions (Chart VII);[83-85] the

Chart VII: Hofmann-Löffler-Freytag Reactions Under Mild Conditions



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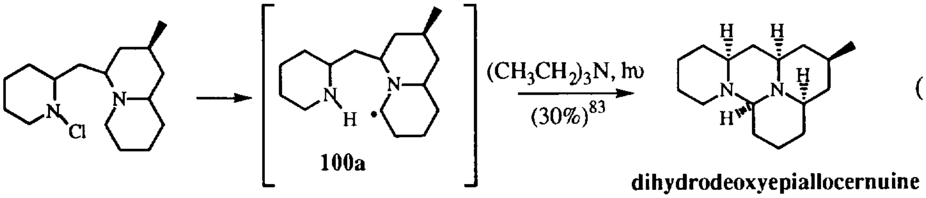

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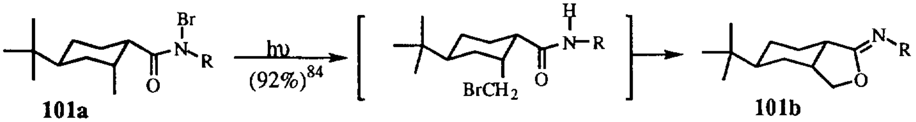
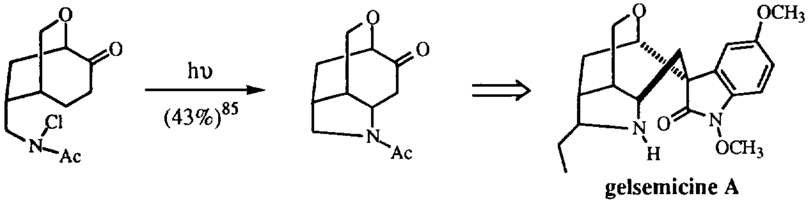


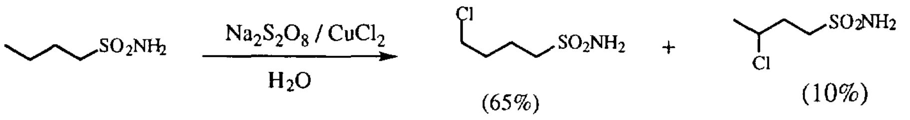
(101)



(102)

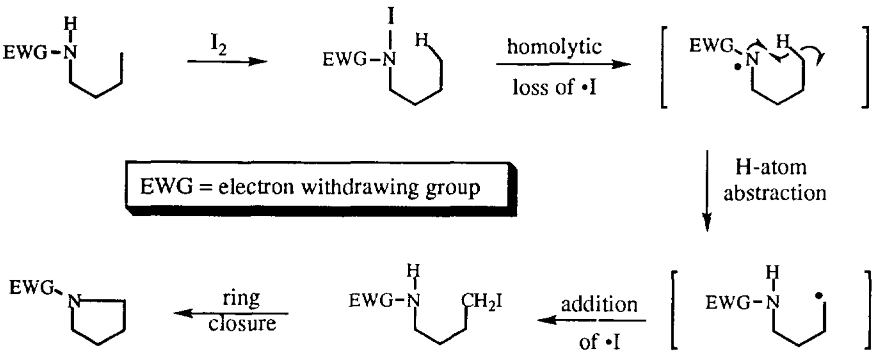
triethylamine present scavenges the hydrochloric acid produced by cyclization. The photolysis of *N*-bromamides has also been studied. Irradiation of *N*-bromamide **101a** gave iminolactone **101b** in 92% yield. In contrast, analogs of **101a** lacking the *tert*-butyl group gave complex mixtures. A modification of the Hofmann-Löffler-Freytag reaction facilitates the pyrrolidine formation shown in Eq. 102. Baldwin and Doll examined this pilot study with the hope that it would one day serve as the basis for a total synthesis of the alkaloid gelsemicine.[85]

Sulfonamides can also undergo intramolecular free-radical functionalization to produce γ- and δ-chloroalkanesulfonamides, usually without the addition of acid (Eq. 103).[86]



(103)

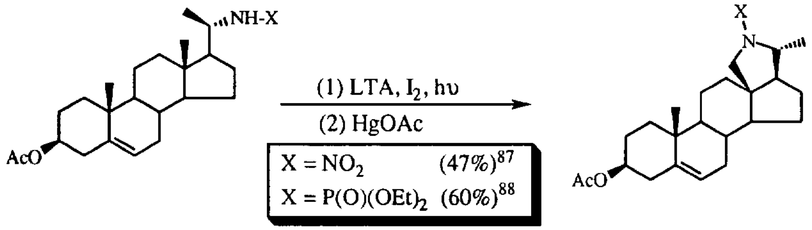
In 1983, Suarez and co-workers developed neutral conditions for the Hofmann-Löffler-Freytag reaction permitting its use with more sensitive molecules. The mechanism of this process, which is similar to the hypoiodite mechanism described earlier, is summarized in Eq. 104.



(104)

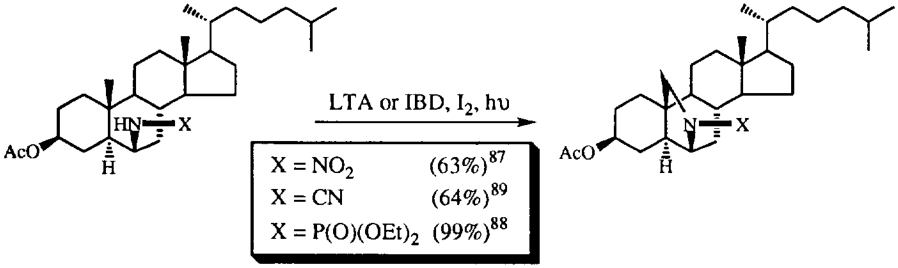
This modified procedure has been applied to a number of steroid and triterpene compounds as shown in Chart VIII.[87-91] Equations 105-108 illustrate that the photolysis of N-nitro or N-cyanamides give moderate yields of the expected Hofmann-Löffler-Freytag product, whereas the phosphoramidate-initiated functionalizations generally proceeded in excellent yield. Note that the direct oxidative conversion of an amide to a lactam is shown in part of Eq. 109.

Chart VIII: Recent Examples of the Suarez Modification of the Hofmann-Löffler-Freytag Reaction



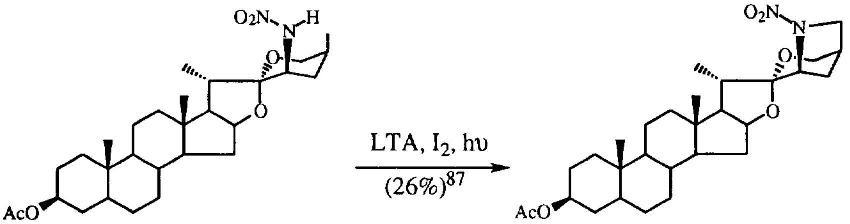
$X = NO_2$	(47%)[87]
$X = P(O)(OEt)_2$	(60%)[88]

(105)

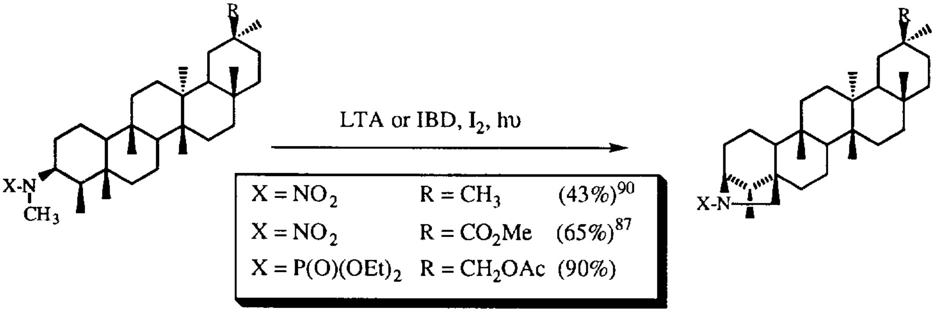


$X = NO_2$	(63%)[87]
$X = CN$	(64%)[89]
$X = P(O)(OEt)_2$	(99%)[88]

(106)



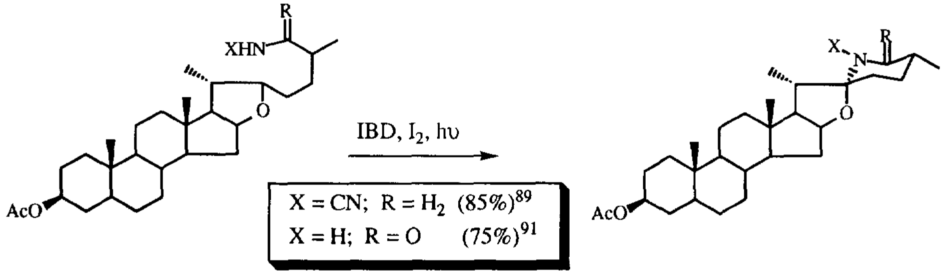
(107)



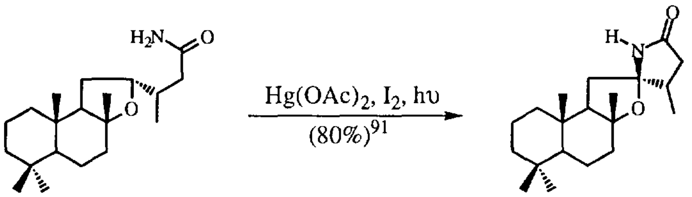
$X = NO_2$	$R = CH_3$	(43%)[90]
$X = NO_2$	$R = CO_2Me$	(65%)[87]
$X = P(O)(OEt)_2$	$R = CH_2OAc$	(90%)

(108)

Chart VIII continued



(109)



(110)

7. Closing Remarks

Several areas of remote functionalization requiring further work suggest themselves. First, although the need for rigid systems is well-documented, recent observations indicate that many acyclic systems can also give excellent yields. While traditional free radical conditions produce low yields of functionalized products, reagents such as iodobenzene diacetate or diphenylhydroxyselenium give high yields. One may ask whether these reagents are general or are their successes simply an artifact of the conformational nuances of the individual substrates studied? Similarly, the yields obtained for the Hofmann-Löffler-Freytag reactions with *N*-nitro or *N*-cyanamides and *N*-phosphoramidate derivatives suggest that these modified procedures have the potential to become as integral a part of alkaloid and amino acid chemistry as the Barton reaction has become for steroid and terpene chemistry. Given the diversity of free radical-based functionalizations shown to date this area will undoubtedly continue to be the focus of extensive activity.

8. Acknowledgments

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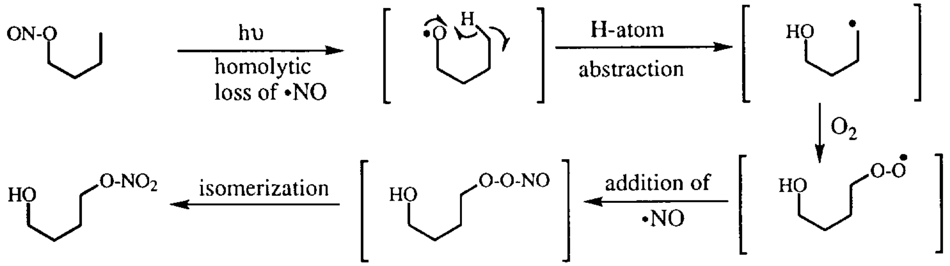

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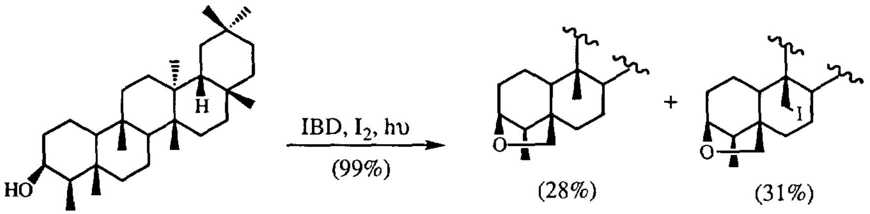

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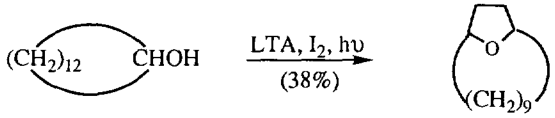

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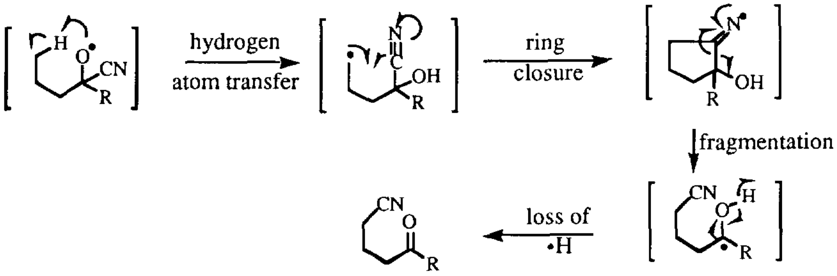

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