Recovery of Carbonyl Compounds from *N,N*-Dialkylhydrazones

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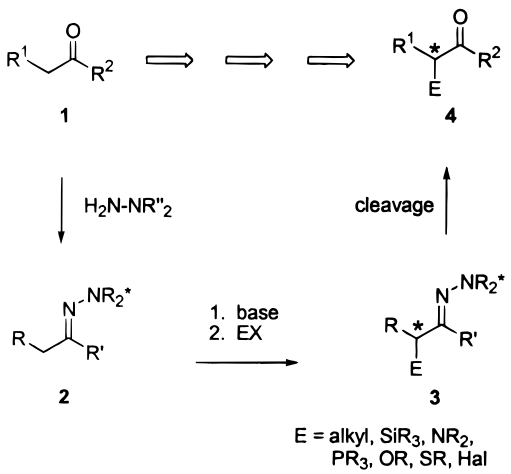
ABSTRACT

Deprotonation of enantiomerically pure hydrazones and subsequent trapping with suitable electrophiles generates new stereogenic centers with excellent stereoselectivity. To liberate the original carbonyl functionality in the final products, it is necessary to cleave the hydrazone moiety. In recent years, many reagents have been developed to regenerate carbonyl compounds from the corresponding dialkylhydrazones which are compatible with a wide range of functionalities. This has allowed the use of hydrazones in the total synthesis of complex natural products. This Account is meant to be an overview of methods which are classified as oxidative, hydrolytic, and reductive cleavage procedures.

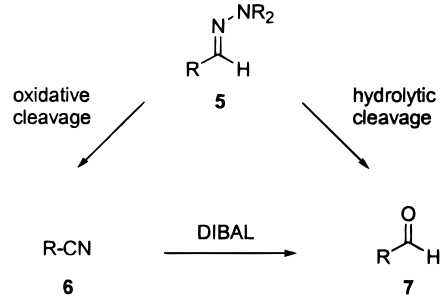
Introduction

The development of efficient and highly selective methods for C−C and C−X bond formation has been, and continues to be, a challenging and exciting endeavor in organic chemistry. Procedures that allow the construction of C−C and C−X bonds α to the carbonyl group via electrophilic substitution are among the most important synthetic operations. Most of the problems in classical carbonyl chemistry, such as aldol-type self-condensation, di- and polyalkylation, control of regiochemistry, side reactions of products, and lack of reactivity of the corresponding enolates, have been solved by the use of *N,N*-dialkylhydrazones **2** as equivalents of the parent ketones and aldehydes **1**.[1] Deprotonation of enantiomerically pure hydrazones **2** and subsequent trapping with suitable electrophiles EX generates new stereogenic centers with excellent stereoselectivity. To liberate the original carbonyl functionality in the final products **4**, it is necessary to cleave the hydrazones **3**. Many new cleavage reagents have been developed over the past four decades which are compatible with a wide range of other functionalities. In general, cleavage procedures can be classified into oxidative, hydrolytic, and reductive methods. In the case of aldehyde dialkylhydrazones **5**, the removal of the hydrazone can lead to two different cleavage products (Scheme 2). Hydrolysis of **5** gives rise to the corresponding aldehydes **7** in a manner similar to the ketone cases. Another pathway is via oxidation or elimination, which leads to the corresponding nitriles **6**. As the nitrile functionality can be easily transformed into the corresponding aldehyde **7** by simple DIBAL reduction,[2] this Account will also mention reagents leading to the nitriles **6**.

Scheme 1



Scheme 2



Oxidative Cleavage Procedures

Ozone (O_3). *N,N*-Dimethylhydrazones (DMHs) and SAMP/RAMP hydrazones **8** [SAMP and RAMP = (*S*)- and (*R*)-1-

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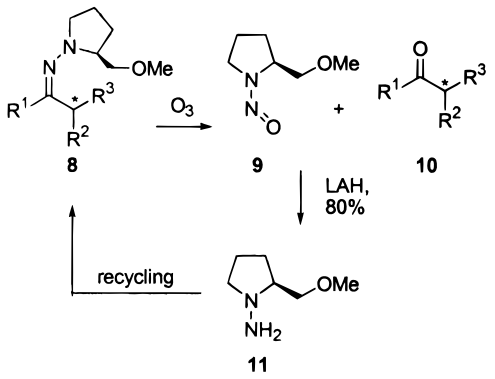
Scheme 3



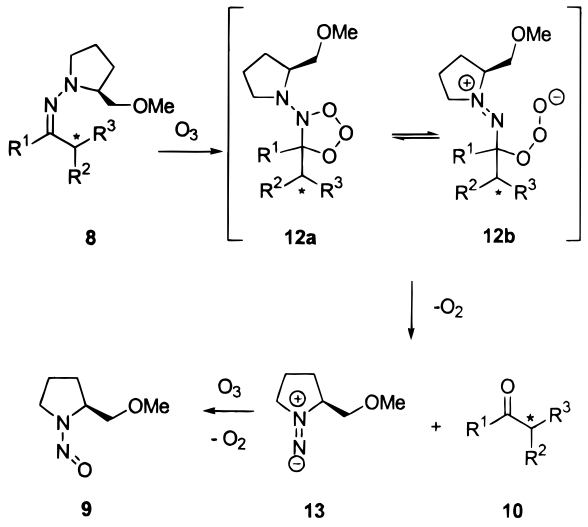
amino-2-methoxymethylpyrrolidine] of aldehydes and ketones may be oxidatively cleaved by ozonolysis in dichloromethane at −78 °C.[3] This reaction is very clean, and the only products formed are the desired carbonyl compounds **10** and 1 equiv of nitrosamine **9** in quantitative yield. The formation of the latter allows recycling of the chiral auxiliary RAMP or SAMP (**11**) after separation by distillation or chromatography and subsequent LAH reduction (Scheme 3).

Although the chemical yield of the recycling step is good (~80%), a partial racemization of up to 10% of the chiral auxiliary was observed in rare cases. Advantages of the oxidative cleavage by ozonolysis are extremely mild reaction conditions, low temperature (−78 °C), neutral pH, short reaction times and the ease of detecting the end of the reaction (appearance of a green-colored mixture of yellow nitrosamine **9** and blue ozone or by addition of an indicator such as Sudan red), the excellent, almost quantitative yields, and the lack of any racemization of the sensitive aldehydes (R^1 = H) and ketones **10** during the operation. Of course, the method cannot be applied in the presence of other functional groups that are not compatible with ozone under these reaction conditions. However, because the C=N double bond is highly reactive toward ozone, it is possible to obtain the desired carbonyl compounds chemoselectively, even in the presence of functional groups that are sensitive to oxidation, such as thioethers,[4] protected α-hydrazino and aminoketones,[5] and borane-protected phosphines,[6] by TLC control or by the addition of certain diazo dyes as indicators.

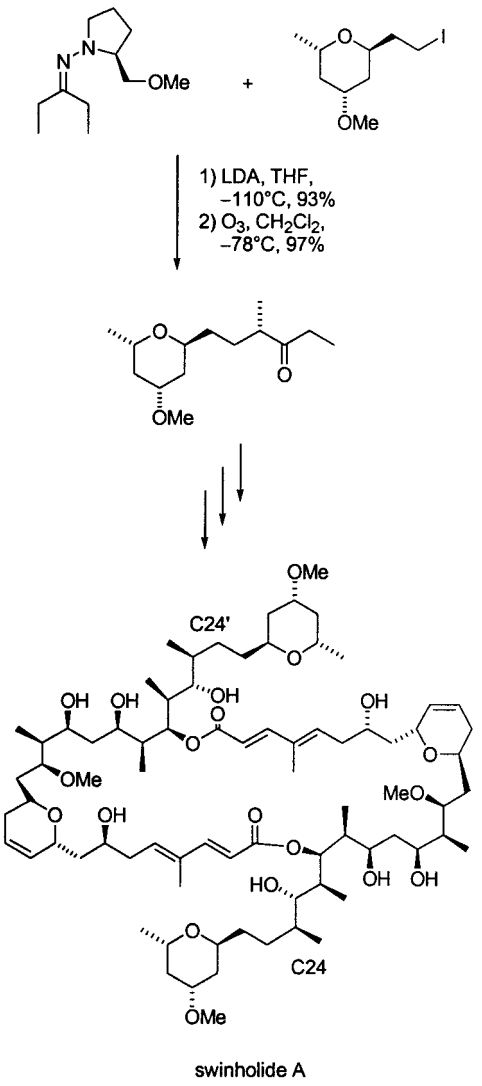
Although the mechanism of the ozonolysis is not exactly known, it is conceivable that the oxidative C=N bond cleavage starts with intermediates of type **12a** or **12b**, which directly decompose to carbonyl compound **10** and diazene **13**, which is further oxidized under the reaction conditions to the nitrosamine **9**. Indeed, 2 equiv of ozone per hydrazone are consumed (Scheme 4).[7]

Out of the manifold applications of SAMP hydrazone cleavage by ozonolysis, we would like to focus on some recent highlights in total synthesis of bioactive compounds. Swinholide A[8] was impressively synthesized by Nicolaou et al. Our hydrazone methodology followed by ozonolysis was used to build up stereogenic centers at C-24 and C-24′ (Scheme 5).

Scheme 4

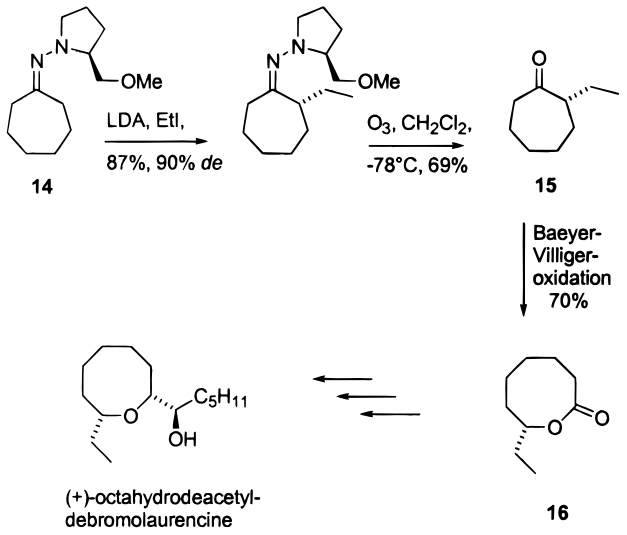


Scheme 5

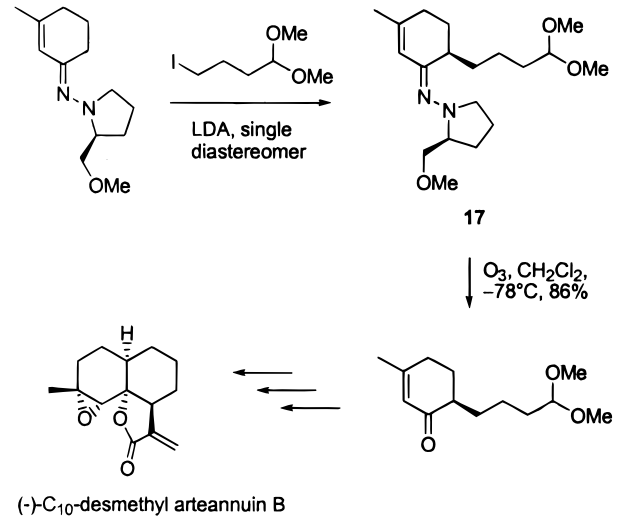


Holmes et al. used the SAMP/RAMP hydrazone method in their synthesis of medium-ring ethers such as model-compound (+)-octahydrodeacetyldebromolaurencin

Scheme 6



Scheme 7



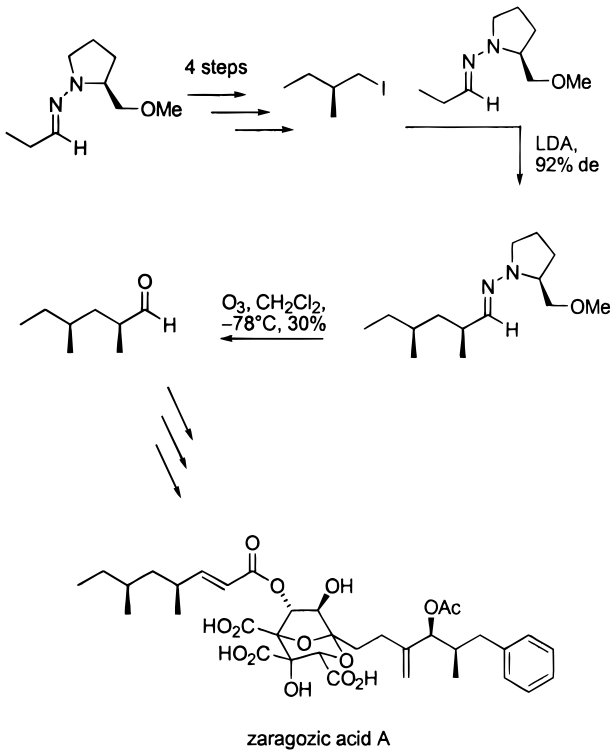
(Scheme 6).[9] After asymmetric alkylation (de = 90%) of the cycloheptanone SAMP hydrazone **14** followed by ozonolysis, chiral ketone **15** underwent a Baeyer−Villiger oxidation by treatment with trifluoroperacetic acid to yield key intermediate **16**.

At an early stage of the total synthesis of (−)-C_{10}-desmethyl arteannuin B, the SAMP/RAMP hydrazone method made it possible to install a key stereogenic center to yield **17** as a single diastereomer (Scheme 7).[10] During the ozonolysis, the conjugated double bond and dimethylacetal were resistant to the reaction conditions.

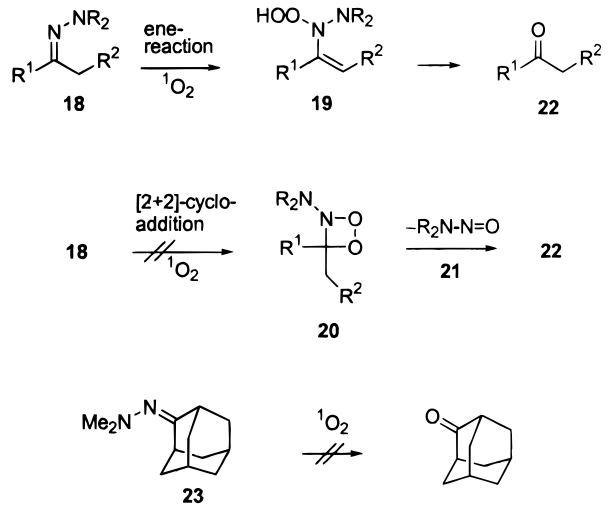
An elegant example of an iterative alkylation was used in the total synthesis of zaragozic acid A (Scheme 8) by Nicolaou et al.[11]

Singlet Oxygen ($^1O_2$). The dye-sensitized photooxygenation of a variety of *N,N*-dimethylhydrazones and SAMP hydrazones in MeOH, THF, or dichloromethane at −78 to 20 °C followed by reduction with Ph_3P or DMS and hydrolysis yielded the parent carbonyl compounds **22** in moderate to good yields.[12] This method appears to have broad applicability for the regeneration of aldehydes and

Scheme 8



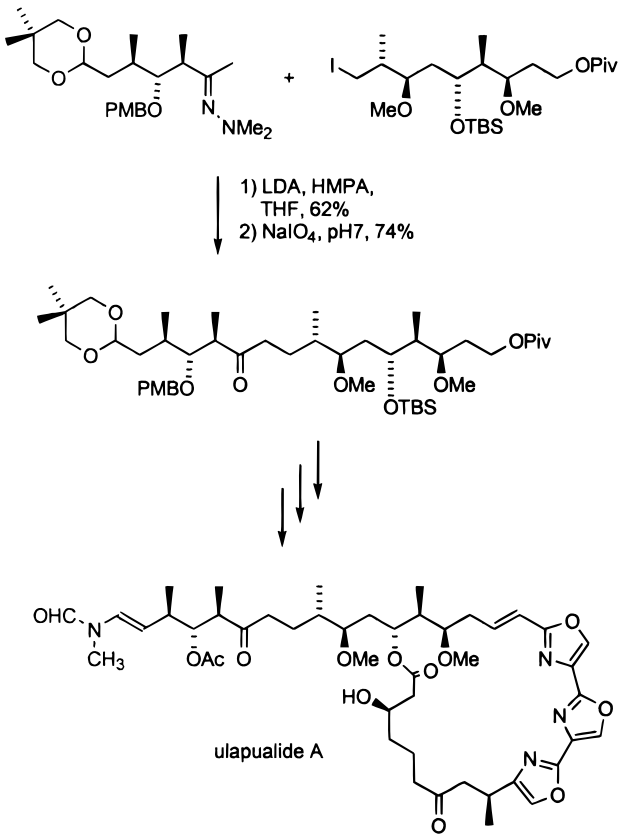
Scheme 9



ketones, as well as polyfunctional and relatively sensitive carbonyl compounds such as aldol adducts. Mechanistically, there are two obvious possibilities for the course of the oxidative cleavage, an ene-type reaction via a hydroperoxide **19** or a cycloaddition reaction via the dioxazetidine **20** as an intermediate (Scheme 9). Since dimethylnitrosamine **21** is not formed and the hydrazones **18** do not react in the absence of a sensitizer, the cycloaddition route and an autoxidation process can be excluded. Further evidence for the proposed ene-type reaction via **19** comes from the fact adamantanone-*N,N*-dimethylhydrazone **23** remains unchanged under the reaction conditions (Bredt's rule).

$NaIO_4$ and H_5IO_6. Dimethylhydrazones can be cleaved to the corresponding ketones in high yields under mild

Scheme 10

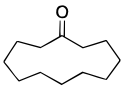
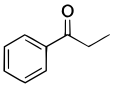
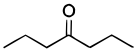
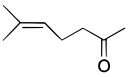


conditions using aqueous sodium periodate at pH 7 and room temperature.[1b,c] The neutral periodate hydrolysis procedure is not satisfactory for the cleavage of dimethylhydrazone derivatives of aromatic or α,β-unsaturated aldehydes, since these usually afford mixtures of aldehydes and nitriles. However, under modified conditions, by the use of periodic acid H_5IO_6, nonconjugated aldehydes can be obtained in high yield from the corresponding dimethylhydrazones. In general, the production of nitrile at the expense of aldehyde is favored at higher pH. This method tolerates a variety of sensitive functional groups within the molecule such as acetals, silyl ethers, esters, and PMB ethers, as demonstrated in the total synthesis of ulapualide A by Panek et al. (Scheme 10).[13]

$NaBO_3$. *N,N*-Dimethylhydrazones and SAMP hydrazones are efficiently cleaved back to the parent ketones **24**−**30** under mild conditions at pH 7.[14] The oxidative hydrolysis is effected in good yields (Table 1) with the very cheap bulk chemical sodium perborate in buffer solution and *tert*-butanol as cosolvent. Whereas DMH and SAMP hydrazones underwent smooth oxidative hydrolysis in 4−24 h, the cleavage of aromatic ketone hydrazones took 2−3 d. The procedure is also chemoselective, leaving a C=C double bond intact.

Tetrabutylammonium Peroxydisulfate. Tetrabutylammonium peroxydisulfate ($(TBA)_2S_2O_8$) has been shown to be a good source of a sulfate anion radical, which has the potential to be widely applicable in organic reactions.[15] This radical anion is considered to oxidize the C=N double bond. It has been found that treatment of DMHs with

Table 1. Yields of *N,N*-Dialkylhydrazone Cleavages with $NaBO_3$

No.	Product	Hydrazone	Yield [%]
24		DMH	70
25		DMH	91
25		SAMP	86
26		DMH	95
27		DMH	85
28		DMH	90
29		SAMP	87
30		DMH	94

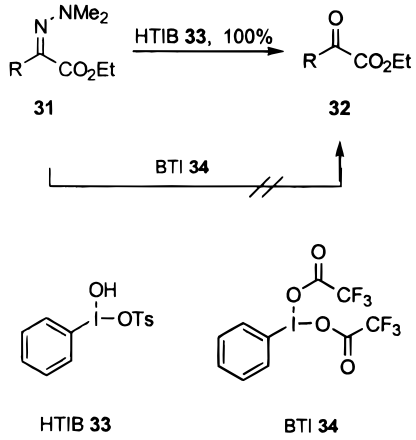
$(TBA)_2S_2O_8$ gave the parent ketones in excellent yields (89−97%). Because the reaction medium is at pH close to neutral, cleavage reactions have been found to proceed for hydrazones which contain sensitive functional groups, such as acetal and olefin moieties. Although the reaction mechanism is not yet clear, the cleavage appears to be initiated via the addition of sulfate radical to the carbon of C=N, and the oxygen of the carbonyl product probably originates from the peroxysulfate.

[Hydroxy(tosyloxy)iodo]benzene (HTIB or Koser's Reagent). The carbonyl groups of various hydrazone derivatives of α-keto esters **31** were readily regenerated in high yield through oxidative hydrolysis using hypervalent organoiodine(III) reagent [hydroxy(tosyloxy)iodo]-benzene (HTIB, **33**; Scheme 11).[16] In contrast to **33**, the α-ketoesterdimethylhydrazones **31** were not cleaved by treatment with [bis(trifluoracetoxy)iodo]benzene (BTI, **34**).

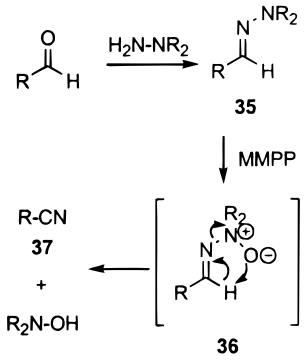
Magnesium Monoperoxyphthalate (MMPP). MMPP, a reagent with high stability at ambient temperature, has been shown to oxidize a wide range of substrates under milder conditions than MCPBA: the substrates include alkenes, ketones, sulfides and sulfoxides, and pyridine.[17]

N,N-Dimethylhydrazones and SAMP hydrazones of aliphatic or aromatic ketones undergo oxidative cleavage

Scheme 11



Scheme 12



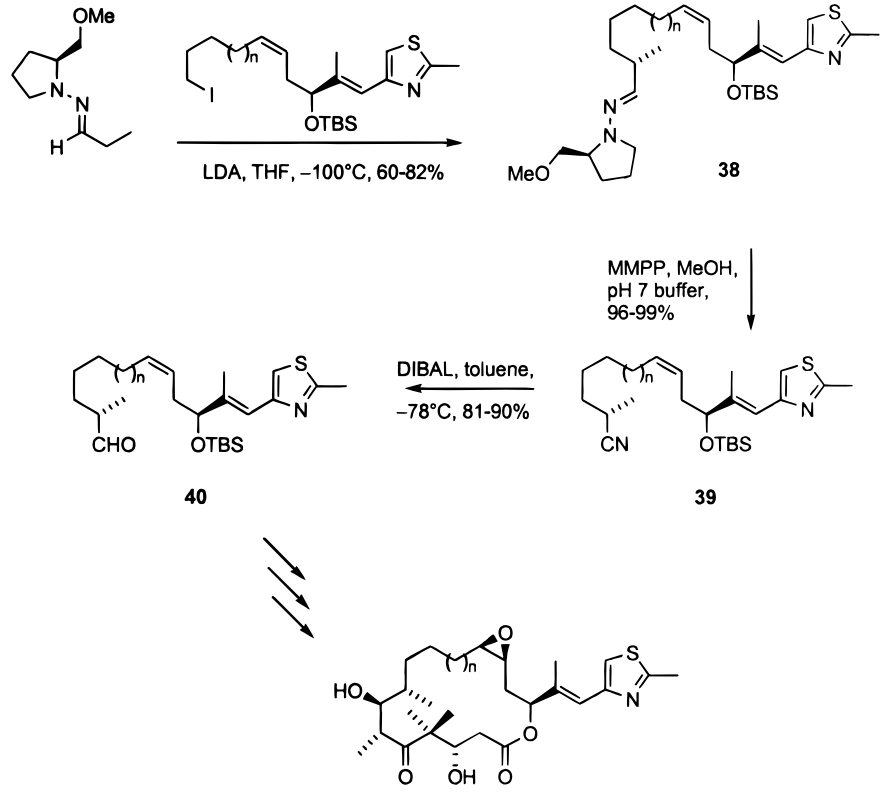
on reaction with MMPP hexahydrate under mild conditions.[18,19] The reaction is high-yielding (76−94%) and chemoselective and proceeds without racemization (>97%). In contrast, aldehyde hydrazones **35**, bearing a stereogenic center α to the hydrazone moiety, give rise to the parent nitriles **37** in good yields and without racemization via an oxy-Cope-type elimination via **36** (Scheme 12).[20]

The broad applicability of this method has been demonstrated in several natural product syntheses, such as the enantioselective synthesis of a library of epothilones by Nicolaou et al., as depicted in Scheme 13.[21] Key intermediate **38**, containing an isolated and conjugated double bond as well as a silyl ether group and a highly oxidation-sensitive thiazole moiety, was smoothly converted to the corresponding nitrile **39**, which could be further transformed into aldehyde **40** in excellent yield (81−90%).

In the first total synthesis of stigmatellin A, a strong inhibitor of the electron transport in chloroplasts and mitochondria, intermediate **41** was cleaved with MMPP to **42** in the presence of the paramethoxbenzyl ether moiety as an alcohol protecting group (Scheme 14).[22]

MCPBA and $MeCO_3H$. The 3-chloroperoxybenzoic acid (MCPBA) oxidation of DMHs of aromatic aldehydes gives the corresponding nitriles (**43**−**51**) in good yields (Table 2).[23] The oxidation of aliphatic DMHs, however, gave rise to the formation of mixtures of nitriles and aldehydes (see **51**) and is therefore of no synthetic value. A further disadvantage is the long reaction time (several days). MCPBA was successfully used to cleave DMH **52** on a large

Scheme 13



Scheme 14

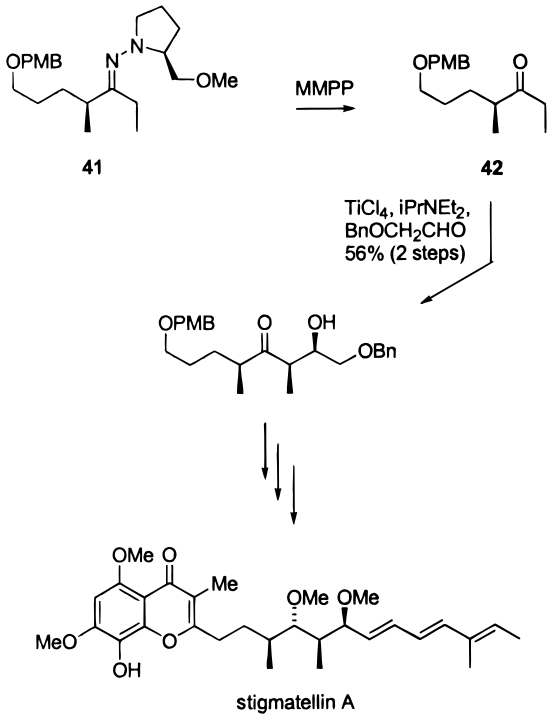
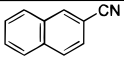
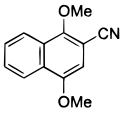
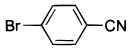
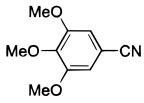
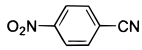
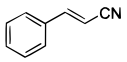
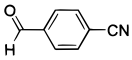
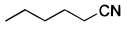


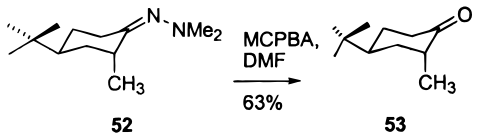
Table 2. Comparison of MCPBA, H_2O_2/SeO_2, and H_2O_2/2-NBSeA

Product nitrile		MCPBA	H_2O_2/SeO_2	H_2O_2/2-NBSeA
		Yield [%]	Yield [%]	Yield [%]
43		78	95	97
44		71	88	92
45		76	82	91
46		77	93	97
47		75	78	84
48		55	58	65
49		50	64	73
50		83	87	95
51		65	45	83 (aldehyde)

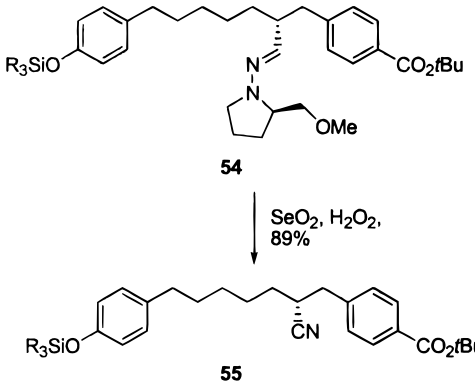
scale to ketone **53** without any epimerization of the axial methyl group (Scheme 15).[24]

In a similiar manner, peracetic acid has been used for aromatic aldehyde dimethylhydrazone cleavage at low temperatures, whereas at high temperatures undefined

Scheme 15



Scheme 16



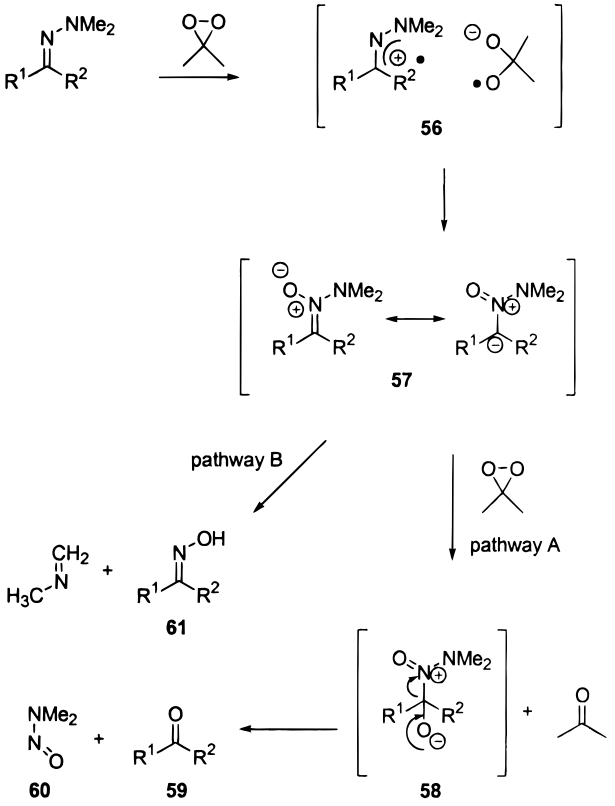
product mixtures were obtained. The corresponding nitriles could be isolated in moderate yields.[25]

H_2O_2/SeO_2 and H_2O_2/2-Nitrobenzeneselenic Acid (2-NBSeA). In comparison to the above-mentioned MCPBA procedure, H_2O_2 activated by SeO_2 or 2-nitrobenzeneselenic acid, respectively, resulted in shorter reaction times and higher yields. Surprisingly, no oxidation of aromatic aldehyde dimethylhydrazones was observed when the mixture was stirred with 30% H_2O_2, even for 12 d. Except for the more easily hydrolyzed aliphatic derivatives, all hydrazones were converted into nitriles in good yields (Table 2). The reaction catalyzed by SeO_2 was faster than that carried out in the presence of 2-nitrobenzeneselenic acid (2-NBSeA), but the yields were higher in the latter case. Oxidation of the aliphatic derivative with H_2O_2/2-NBSeA gave only the parent aldehyde, while the faster reaction with H_2O_2/SeO_2 produced a mixture of aldehyde and nitrile **51**. These results are in accordance with the tendency of aliphatic DMHs to undergo hydrolysis under the aqueous oxidation conditions. The H_2O_2/SeO_2 method was successfully applied to the cleavage of RAMP hydrazones **54** to provide chiral nitriles **55** for monomers in material science (Scheme 16).[26]

H_2O_2. The H_2O_2 oxidation of the DMHs of cinnamaldehyde, benzaldehyde, and alkoxy-substituted benzaldehydes gave the corresponding nitriles in good yields. Oxidation of DMHs of *p*-nitrobenzaldehyde, *p*-chlorobenzaldehyde, *n*-valeraldehyde, and *n*-octanal gave mixtures of nitrile-containing products.[27] In the synthesis of aldol products via SAMP hydrazones of ketones, this method was applied yielding the products in good yields.[28]

Dimethyldioxirane. The use of dimethyldioxirane (DMDO) is feasible for the cleavage of *N,N*-dimethylhydrazones, SAMP hydrazones, and aryl- and tosylhydrazones in high yields.[29] The procedure proceeds very rapidly; e.g., α-methylcyclohexanone SAMP hydrazone was cleaved within 5 min in 85% yield. Only minimal

Scheme 17

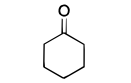
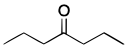
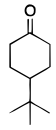
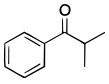
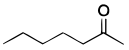
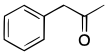


racemization could be detected (less than 2%, ee = 94%). Under the reaction conditions, C=C double bonds were not attacked and acetoxy groups not hydrolyzed. Mechanistic studies revealed the reaction pathway shown in Scheme 17.

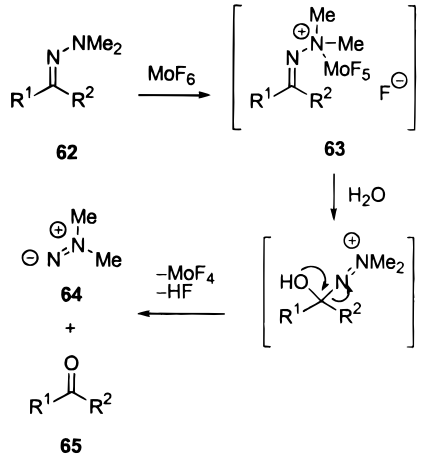
EPR studies suggested that the radical cation species in radical pair **56** was formed as an intermediate. Subsequent trapping of this with the bisoxyl radical anion in **56** (or direct electrophilic *O*-transfer from DMDO to the substrate) should provide **57**; the latter reacts with another equivalent of DMDO to give rise to the desired ketones **59** and nitrosamine **60** (pathway A). Pathway B explains the formation of small amounts of oxime **61** as side product.

MoF_6, CoF_3, WF_6, UF_6, and $MoOCl_3$. The covalent nature of transition metal fluorides in high oxidation states such as MoF_6,[30] CoF_3,[31] WF_6,[32] and UF_6[33] allows the use of nonaqueous solvents such as $CHCl_3$, CH_2Cl_2, and Freon 113 during the *N,N*-dimethylhydrazone cleavage. Although it is known that some of these compounds are fluorinating agents for carbonyl groups, no fluorinated products were observed. The reagents are easy to handle, and glass is not attacked. The desired carbonyl compounds may be obtained in moderate to excellent yields (Table 3). In the UF_6 case, it was demonstrated that ketone, ester, amide, nitrile, and nitro moieties were tolerated under the reaction conditions. The proposed mechanism of the MoF_6 cleavage is depicted in Scheme 18 and was shown to work similiarly for the other cases. MoF_6 attacks in an electrophilic manner at the dialkylated nitrogen of hydrazone **62**. The treatment of the activated hydrazonium salt

Table 3. Yields of Oxidative Transition Metal Halide-Mediated DMH Cleavages

Carbonyl Compound	MoF_6 Yield [%]	CoF_3 Yield [%]	WF_6 Yield [%]	UF_6 Yield [%]	$MoOCl_3$ Yield [%]
	78	-	73	46	85
	96	46	83	-	76
	85	74	93	41	80
	66	89	91	-	88
	95	-	85	50	96
	94	94	94	-	-
	-	67	-	56	78
	-	76	-	69	-
	50	-	-	-	-

Scheme 18



63 with water furnishes the carbonyl compound **65** and diazene **64** as byproduct.

In contrast to the ionic mechanism of the fluorides, the $MoOCl_3$ cleavage is proposed to proceed by a single electron transfer with intermediate radical cation **66**, which is trapped by the resulting Mo(IV) species (Scheme 19).[30]

$NOBF_4$, NO_2BF_4, and Clay-Supported Ferric Nitrate. Nitronium and nitrosonium salts are capable of mediating

Scheme 19

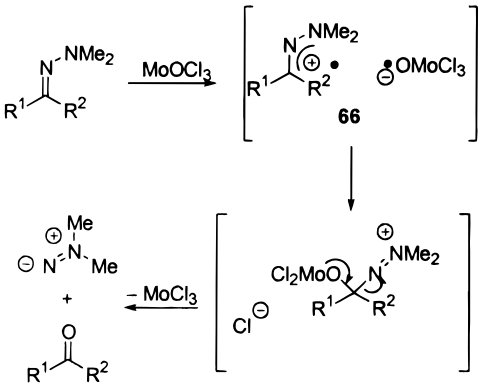
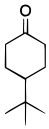
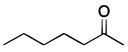
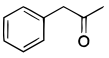
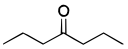


Table 4. Yields of DMH Cleavage Using $NOBF_4$, NO_2BF_4, and Clay-Supported Ferric Nitrate 4

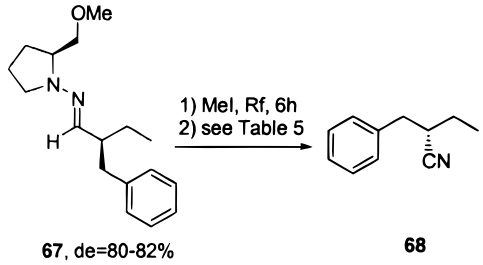
Carbonyl Compound	$NOBF_4$ Yield [%]	NO_2BF_4 Yield [%]	Clayfen Yield [%]
	75	73	87
	59	70	85
	82	50	-
	66	53	-
	86	80	-
	-	-	78
	-	-	80

hydrolysis either by electron transfer or by the nitrosylation route.[34] Accordingly, dimethylhydrazones were subjected to reaction with equimolar quantities of nitronium or nitrosonium tetrafluoroborate, yielding the corresponding ketones in moderate to good yields (Table 4).

Clayfen (ferric nitrate impregnated on K-10 bentonite clay) is a nitrosonium ion source comparable to $NOBF_4$ and is capable of effecting cleavage of the dimethylhydrazone group. The reaction is fast and exothermic, giving the corresponding carbonyl compounds in very good yields (Table 4).[35]

$MeReO_3/H_2O_2$. The rhenium(VII)-catalyzed oxidative cleavage of aliphatic or aromatic DMH's with H_2O_2 gives the corresponding nitriles in good yields (83−89%).[36] Double bonds are resistant to the reaction conditions.

Scheme 20



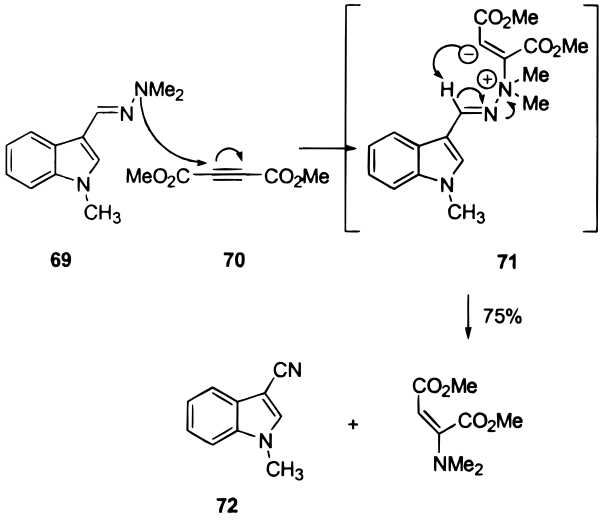
67, de=80-82% **68**

Table 5. Effects of Base and Temperature on Chemical Yield and Enantiomeric Excess

solvent	base (equiv)	*T* (°C)	reaction time (h)	yield (%)[a]	ee (%)
CH_2Cl_2	DABCO (5.0)	40	2	nr	
CH_2Cl_2	DMAP (2.0)	40	12	nr	
	DBU (5.5)	20	0.2	83	28
CH_2Cl_2	DBU (4.0)	0	5.5	68	46
THF	DBU (1.2)	0	3.0	77−85	75−80

[a] nr, no reaction.

Scheme 21



69 **70** **71** **72**

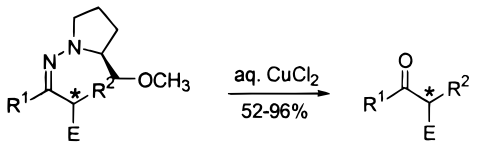
Methyl Iodide and DBU. Stupp et al. reported a convenient procedure to transform methiodide derivatives to nitriles under mildly basic conditions.[37] Furthermore, the application of this procedure to the synthesis of nitriles with absolute stereocontrol was demontrated. To convert diastereomerically enriched hydrazone **67** (de = 80−82%) to the corresponding chiral nitrile **68** without racemization (Scheme 20), the reaction conditions were optimized as depicted in Table 5.

Chloroformates. Aliphatic aldehyde dimethylhydrazones have been shown to yield the parent nitriles by oxidative elimination of the carbomethoxyhydrazonium salts (cy = 64−90%).[38]

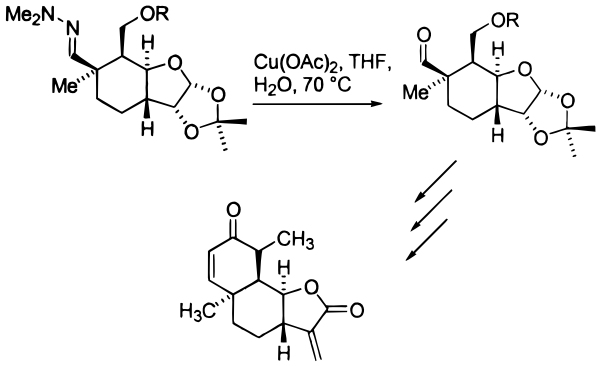
Methyl Propiolate and Dialkyl Acetylenedicarboxylate. During attempts to carry out [4 + 2] cycloaddition reactions with indole-3-carboxaldehyde *N,N*-dimethylhydrazone **69** with methyl propiolate or dimethyl acetylenedicarboxylate **70**, unexpectedly indole-3-carbonitriles **72** were formed (Scheme 21).[39]

The proposed mechanism proceeds via aza-Michael

Scheme 22



Scheme 23



addition of the hydrazone dimethylamino group at methyl propiolate to form hydrazonium salt **71** with subsequent oxidative elimination to the nitrile **72**.[40]

Hydrolytic Cleavage Procedures

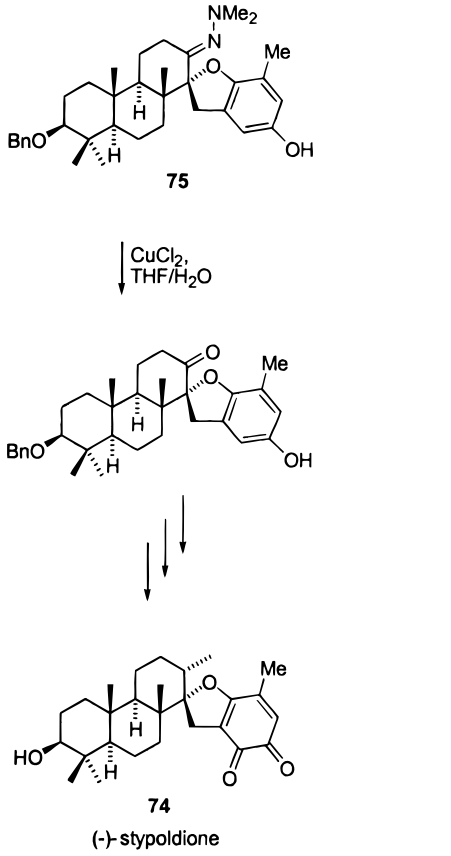
$CuCl_2$ and $Cu(OAc)_2$. The Cu(II)-mediated hydrolysis is applicable to ketone and aldehyde DMHs.[41] In the latter case, the formation of nitriles is not a significant side reaction. The hydrolysis is irreversible, since the resulting hydrazine is oxidized to the diazene by Cu(II).[42]

Treatment of α-branched ketone SAMP hydrazones **3** with an aqueous $CuCl_2$ solution affords the parent ketones **4** in highly enantiomerically pure form (ee = 89−99%) and in moderate to excellent yields (52−94%, Scheme 22).[43] The cleavage conditions do not affect functionalities sensitive to oxidation or strong acids. For example, amines, alkenes, and thioethers as well as acid-labile protecting groups such as acetals and silyl ethers are compatible with this procedure. Compounds with these functionalities usually give low yields when subjected to other typical procedures, such as ozonolysis and the salt method. The alkylation/cleavage protocol can be carried out in one pot and affords the products without racemization. In addition, the Cu(II) method avoids the formation of nitrosamine byproducts. In contrast to the case with aldehyde DMHs, this method is not applicable to the cleavage of aldehyde SAMP hydrazones.

The broad applicability of this method has been demonstrated in the total synthesis of several complex natural products, such as the sesquiterpene lactone (+)-tuberiferine **73**[44] by Fraser-Reid et al. (Scheme 23).[45]

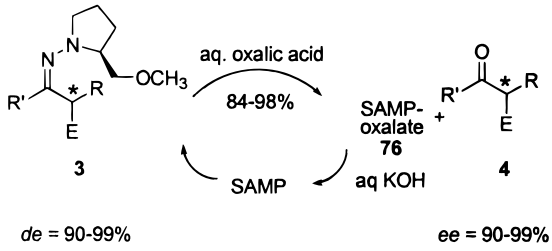
In the total synthesis of complex pentacyclic marine diterpenoid (−)-stypoldion (**74**), characterized by a benzoquinone furan moiety, the quaternary stereogenic center was introduced with excellent diastereoselectivity by direction of the neighboring dimethylhydrazone moiety followed by deprotection of the DMH **75** with $CuCl_2$ (Scheme 24).[46]

Scheme 24



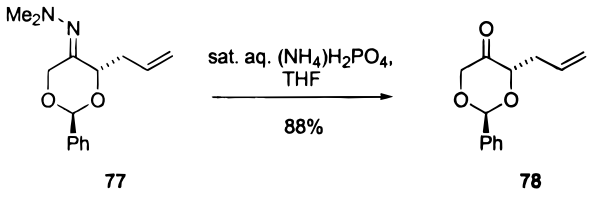
Oxalic Acid. Cleavage of ketone SAMP hydrazones **3** with saturated aqueous oxalic acid solution gives the corresponding ketones **4** in excellent yields (84−98%) and with high enantiomeric purity (ee = 90−99%, Scheme 25).[47]

Scheme 25



This racemization-free cleavage procedure is compatible with functionalities that are sensitive to oxidative cleavage conditions, such as C=C double bonds, or to strong acids, such as ketal groups. SAMP can be easily recovered from the corresponding oxalate salt **76** (cy = 80−90%) without any detectable racemization of the auxiliary. The SAMP hydrazones are hydrolyzed by aqueous oxalic acid in a short time. The acid-sensitive acetonide group was not hydrolyzed, and racemization was avoided by performing the reaction in a two-phase system

Scheme 26



(water/ether or pentane). Usually, the ketone products **4** do not require chromatographic purification. This method is therefore suitable for large-scale reactions. No carcinogenic nitrosamine byproduct is formed as is the case in the ozonolysis method, and no toxic methylating agents are needed as in the salt method (vide infra). Oxalic acid has turned out to be the most versatile reagent of those our group has studied for the cleavage of ketone SAMP hydrazones **3**. Unfortunately, this method is not compatible for the hydrolysis of aldehyde SAMP hydrazones.

$(NH_4)H_2PO_4$. For the cleavage of dioxanone DMH **77** containing the acid-labile acetal moiety, conditions had to be carefully selected. Treatment with a saturated aqueous ammonium dihydrogen phosphate buffer at ambient temperature smoothly converted **77** into the ketone **78** in good yield (Scheme 26).[48]

Methyl Iodide/HCl (Salt Method). According to Levisalles et al., DMHs are hydrolyzed under much milder conditions if they are first transformed to their corresponding trimethylhydrazonium iodides (MeI, EtOH, H_2O).[49] For the conversion of SAMP/RAMP hydrazones **3** of aldehydes and ketones to optically active carbonyl compounds **4**, a two-phase variant was developed.

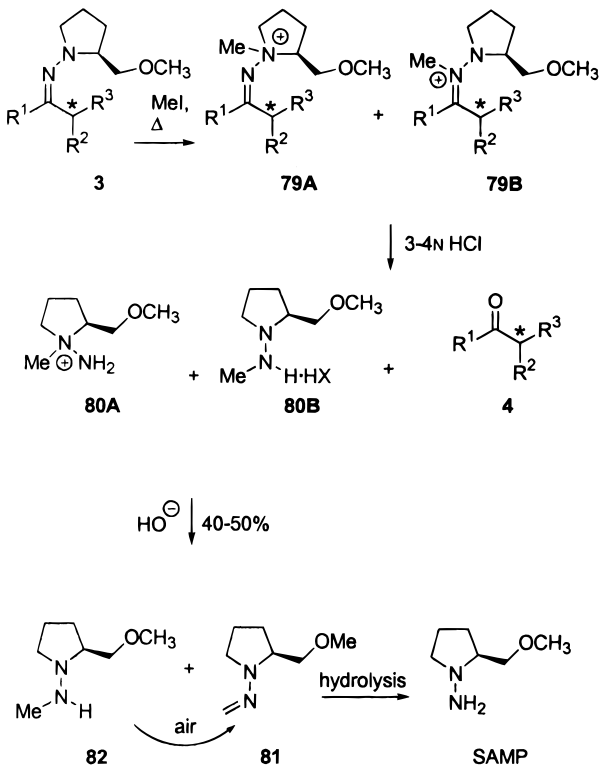
Treatment of **3** with excess methyl iodide at 60 °C leads quantitatively to a mixture of the methiodides **79A** and **79B** (Scheme 27), which are hydrolyzed without further purification in a two-phase system (3−4 N HCl, *n*-pentane) to afford the parent carbonyl compounds **4** in good to excellent yields and in short reaction times (15−60 min).

This procedure also occurs without any racemization. Obviously the carbonyl compounds **4** are rapidly transferred with vigorous stirring into the pentane phase, which is free of acid. Chiral aldehydes and ketones bearing a stereogenic center in the position α to the carbonyl moiety are unexpectedly resistant against racemization in an acidic environment. Traces of base, however, lead to rapid and complete racemization.

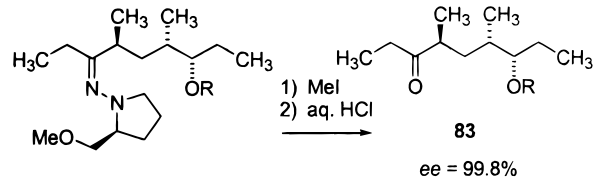
When the aqueous layer, expected to contain the auxiliary in the form of salts **80**, is neutralized and extracted, SAMP hydrazone **81**, the hydrazine **82**, and SAMP were isolated in a mixture of 1:7:2 (yield = 40−50%). While the ammonium salts **80A** remain in the aqueous phase, trisubstitued hydrazines such as **82** are known to easily undergo air oxidation to formaldehyde hydrazones such as **81**, which itself is hydrolyzed to SAMP. In this way, at least a partial recycling of SAMP or RAMP is possible.

The procedure was employed in the synthesis of several natural products. For example, serricornin **83**, the sex pheromone of the female cigarette beetle, was synthesized in almost enantiomerically pure form (Scheme 28).[50]

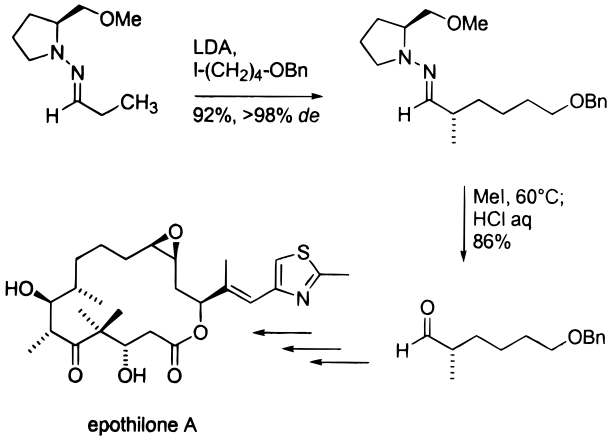
Scheme 27



Scheme 28



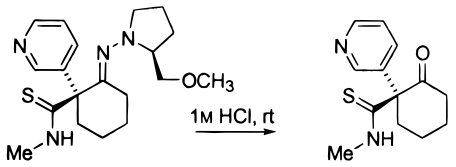
Scheme 29



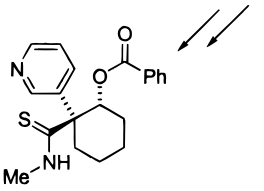
Nicolaou et al. have demonstrated the usefulness of the salt method by the total synthesis of epothilones A and B (Scheme 29).[51] Compared to ozonolysis, the MeI/HCl method resulted in higher yields (O_3, 77%; MeI/HCl, 86%).

HCl. In some cases, the dialkylhydrazones are hydrolyzed efficiently even without the formation of methiodides. In the synthesis of RP 66471, a potent potassium channel opener, the SAMP/RAMP methodology was applied to build up the quaternary center α to the carbonyl

Scheme 30

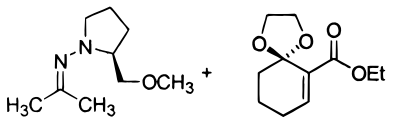


84



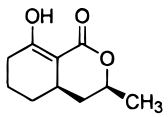
RP 66471

Scheme 31



86 **87**

1. LDA, THF, TMEDA
2. **87**, BF_3 OEt_2, THF, –78°C
3. 6N HCl, Et_2O, rt
4. L-selectride, THF, –78°C



85

ramulosin

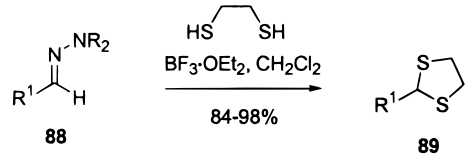
group. By acidic hydrolysis, the key intermediate **84** was obtained (Scheme 30).[52]

Our group used acidic hydrolysis to synthesize ramulosin **85** and its analogues (Scheme 31).[53] After Michael addition of acetone SAMP hydrazones **86** to the unsaturated ester **87**, the auxiliary was removed by stirring in a two-phase system (Et_2O, 6 N HCl).

Silica Gel. The cleavage of hydrazones using acidic reagents suffers from the lack of selectivity in the presence of acid-sensitive groups. Using silica gel for the cleavage of DMHs gives the corresponding ketones containing other acid-sensitive functionalities such as THP groups, benzyl ether moieties, and acetal groups, which remain intact.[54] However, this method seems to be less versatile for the cleavage of α-branched ketones.

$BiCl_3$ and Microwave Irradiation. Hydrolytic cleavage of the C=N bond of DMHs by the use of catalytic quantities of $BiCl_3$ in wet THF under microwave irradiation yields the corresponding ketones or aromatic aldehydes.[55] The reaction proceeds efficiently in high yields (75−98%) at ambient pressure within a few minutes. For example, benzophenone DMH was cleaved in 2 min in 98% yield.

Scheme 32



88 **89**

The corresponding control reaction, performed by refluxing for 8 h, produced only a 50% yield.

$Pd(OAc)_2$ and $SnCl_2$. Ketone DMHs undergo cleavage to the parent ketones by a catalytic amount of $Pd(OAc)_2$/$SnCl_2$ in moderate to good yields.[56] The reaction proceeds without using acidic or oxidative reagents. Even α,β-unsaturated ketone DMHs can be hydrolyzed without rearrangement using this catalyst system. Functionalities such as halogen or nitro groups are also inert.

BF_3·OEt_2. BF_3·OEt_2 is a suitable Lewis acid to promote the hydrolysis of DMHs,[57] which is also applicable to the racemization-free cleavage of SAMP hydrazones of α-branched 2-oxoesters by stirring in acetone/water under addition of paraformaldehyde in an exchange reaction. Compared to the ozonolytic cleaveage (yields = 80−90%), BF_3·OEt_2 gave higher yields (81−97%), but with longer reaction times.[58] Direct dithioketalization of *N,N*-dimethylhydraxones or SAMP hydrazones **88** of aliphatic, aromatic, and α,β-unsaturated aldehydes promoted by BF_3·OEt_2 or *p*-TsOH and 1,2-ethanedithiol in dry medium affords the corresponding dithiolanes **89** in nearly quantitative yields (Scheme 32).[59]

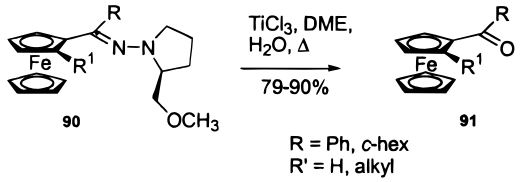
Baker's Yeast. Ketones and aromatic aldehydes have been regenerated biocatalytically from their corresponding phenyl- and *N,N*-dimethylhydrazones in quantitative yield on incubating with baker's yeast.[60] In the case of the DMHs, no cleavage of α-branched carbonyl compounds has been reported.

Reductive Cleavage Procedures

Reductive cleavage procedures have been used in several cases to regenerate carbonyl compounds from their derivatives, such as oximes, 2,4-dinitrophenylhydrazones, tosylhydrazones, etc. However, in the case of dialkylhydrazone cleavage, very few studies have been carried out employing reductive methods. We were interested in recovering ferrocenyl ketones from their corresponding SAMP hydrazones by a reductive manner, as these compounds are often sensitive to oxidative and acidic reaction conditions. It could be demonstrated that some of these methods, known for related compounds, are also applicable to the cleavage of SAMP hydrazones.

$TiCl_3$. Titanium(III) is well known for its ability to cleave the N−O bond of oximes and nitro compounds as well as the S−O bond of sulfoxides. Therefore, the cleavage of the N−N hydrazone bond was considered to be analogous. Trivalent titanium has been used frequently for deoximination procedures[61] and for the cleavage of tosyl-[62] and 2,4-dinitrophenylhydrazones.[63] The resulting imines generated from reduction are easily hydrolyzed to the carbonyl compounds. This method has also been applied

Scheme 33



to the cleavage of ferrocenyl ketone SAMP hydrazones **90** (Scheme 33).[64]

In some cases, the cleavage was accompanied by a small degree of racemization. Cp−Si bonds are cleaved under the reaction conditions, and hydroxy groups α to the ferrocenyl backbone are removed to form the corresponding alkyl group. Compounds containing Ph_2P in the *ortho* position do not yield the ketone **91**, but the corresponding methylene compound is formed by overreduction. This means that, for this special case, its applicability is limited to only a few functional groups.

$SnCl_2$. $SnCl_2$ has been used to recover carbonyl compounds from their 2,4-dinitrophenylhydrazones.[65] This method has been applied to cleave ferrocenyl ketone SAMP hydrazones **90** in good yields (70−85%).[64] The procedure tolerates many functionalities in the *ortho* position, such as alkyl, hydroxyalkyl, or halogen groups; however, the Cp−Si bonds are cleaved.

$Cr(OAc)_2$ and VCl_2. $Cr(OAc)_2$ effects reductive deoximation reactions which are highly efficient, even in the presence of acid- and base-sensitive functional groups such as ketals, hemiketals, esters, and epoxides.[66] The selection of the reagent was based on the premise that it would cause reductive fission of the oxime N−O linkage to give an imine which would suffer rapid hydrolysis to ketone at pH 5. $Cr(OAc)_2$ is also able to cleave ferrocenyl ketone SAMP hydrazones in good to excellent yields (65−99%), tolerating a thiophene moiety as R. An advantage is that the reaction products are obtained very pure by simple filtration.

VCl_2 is also an efficient deoximation reagent.[67] In comparison to Cr(II), for the cleavage of ferrocenyl ketone SAMP hydrazones **90**, V(II) gives lower yields (ca. 70%) but also very pure products.[64b]

Conclusion

Many reagents have been developed to regenerate carbonyl compounds from the corresponding dialkylhydrazones which are compatible with a wide range of functionalities. This has allowed the use of hydrazones in the total synthesis of complex natural products. However, owing to the importance of hydrazone methodology, there is still an interest in designing new and mild reagents for hydrazone cleavage.

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