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Synthetic approaches to 2-tetralones

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1. Introduction

The 2-tetralones, also known as 3,4-dihydro-1*H*-naphthalen-2-ones and β-tetralones (Fig. 1), are aromatic bicyclic ketones derived from tetraline (**1**). 2-Tetralone (**2**) is the simplest member of this family of useful ketones. The 2-tetralones are of great interest in organic synthesis, specially because of their high reactivity[1] and suitability as precursors of several natural products and their derivatives.[2,3] The 2-tetralones are also very useful as starting materials for synthetic compounds with biological activities and other useful properties, including steroids (specially estrogens and antiandrogens), prostaglandin analogs, dyes, heterocycles and pharmaceuticals.[4–7]

1 **2**

Figure 1. Chemical structures of tetraline (**1**) and 2-tetralone (**2**).

However, unlike their congeners the 1-tetralones, which are inexpensive substances, the 2-tetralones are usually more difficult to synthesize and some of them are highly unstable, requiring proper storage conditions, such as freezing, for their long-time preservation. In addition, preparation of 2-tetralones has long been hampered either by poor yields or difficulty accessible starting materials.

Chemists have been interested in 2-tetralones since the beginnings of the 20th century and even before.[8] However, after the Robinson's paper describing the use of 2-tetralones as starting materials for the preparation of steroids,[9] the increasing interest and application of 2-tetraline derivatives have stimulated the publication of a large number of articles describing aspects related to the preparation and reactivity of these valuable ketones.

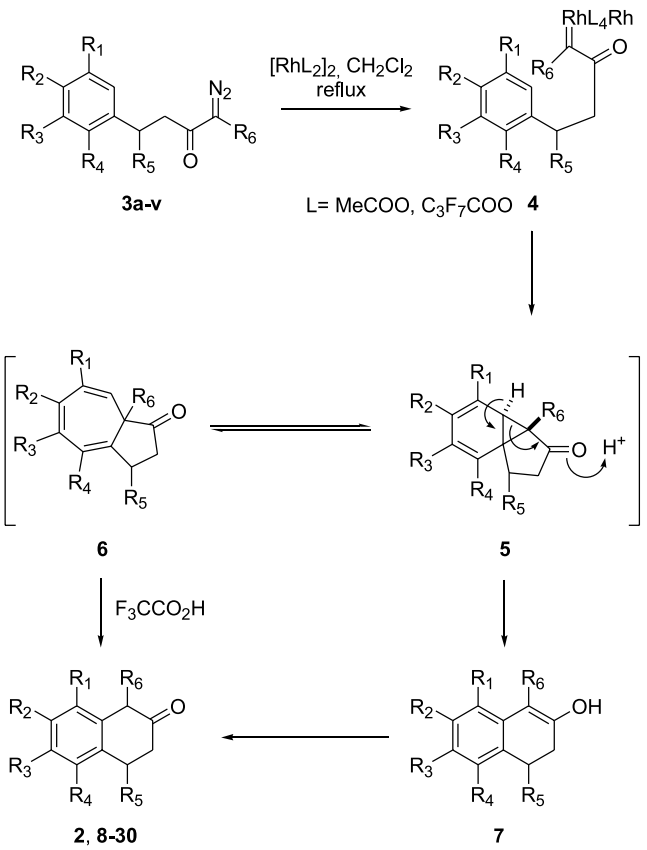
This allowed the synthesis of terpenes, novel aminoacids, benzomorphan derivatives, and bioactive compounds of interest in medicinal chemistry[10,11] and other fields. A simple chemical test has been designed for their detection, and 2-tetralones unsubstituted on C-1 give a characteristic reaction in the 'tetralone blue' test, first described by Cornforth.[12]

The only review article covering the preparation, chemical properties and some applications of 2-tetralones dates from 1966,[13] and since then several important improvements, as well as new, more general and powerful methodologies aiming towards the synthesis of 2-tetralones, have been described. In this review, we will provide an update on the different methods available for the synthesis of 2-tetralones. Aspects regarding the reactivity and use of 2-tetralones for the elaboration of more complex targets will not be covered, except for some specific examples.

For a better discussion, the arsenal of synthetic methodologies for the preparation of 2-tetralones has been divided here into three major groups: (a) methods involving the direct building of tetralines, generally from monocyclic aromatic precursors; (b) methods involving transformations within a pre-formed tetraline ring or a naphthalene type precursor, and (c) methods based on the ring-expansion of 1-indanones.

2. Methods involving the direct building of tetralines

Until the middle of the 1960s, the most frequently employed methods for the synthesis of 2-tetralones were those related to transformations of preformed precursors, specially those with a naphthalene framework (2-naphthol and/or 2-methoxynaphtalene, and their derivatives).[8,10,14,15] The main reason behind this preference was that this approach



Scheme 1. Rhodium(II)-catalyzed cyclization of α-diazoketones employing the Buchner reaction.

furnished the desired products either in pure form or with their isomeric composition unequivocally known in advance. At that time, this was an important synthetic aspect, considering the severe limitations of the methods available for characterization of the products.

However, with the advent of modern analytical techniques, specially high field NMR, together with the development of more selective methodologies for the direct building of polysubstituted tetralines, the de novo synthesis of tetraline derivatives, comprising the construction of the tetraline ring system from appropriately substituted benzenoid precursors, became one of the most widely employed approaches to 2-tetralones, specially for those carrying activating substituents on the aromatic ring.

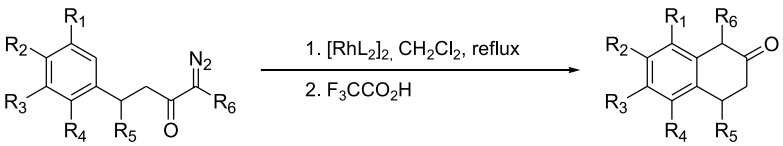
2.1. Intramolecular cyclization of α-diazo carbonyl compounds

The rhodium(II)-catalyzed decomposition of α-diazoketones **3** with concomitant rearrangement (Scheme 1), known as the Buchner reaction,[16] was first described as a convenient and general entry to polysubstituted 2-tetralones by McKervey and co-workers, in 1984.[17]

This was disclosed following the discovery of Teyssié that rhodium(II) carboxylates strongly facilitate nitrogen loss from diazo compounds, presumably by forming carbenoid species, such as **4**.[18] These authors synthesized several 2-tetralones (**2**, **8**–**30**) in very good yields (Table 1). It was observed that rhodium(II) acetate, as well as the corresponding heptafluorobutyrate can be used in this transformation, the latter forming more reactive, highly electrophilic carbenoids, compared with the former.

Several other groups employed this method to prepare 2-tetralones, as intermediates for their projected syntheses of natural alkaloids,[19] tetraline analogues of amphetamine[20a] topoisomerase I inhibitors,[21] melatonin analogues,[22] and a new series of α-adrenergic agonists.[23] The mechanistic aspects of the reaction have been exhaustively studied, as a consequence of the observation

Table 1. Synthesis of 2-tetralones employing the Buchner reaction



3a-v **2, 8-30**

Entry no.	Diazoketone	2-Tetralone	R_1	R_2	R_3	R_4	R_5	R_6	Yield (%)	Reference
1	**3a**	**2**	H	H	H	H	H	H	87	17a
									86	17b
2	**3b**	**8**	H	H	H	OMe	H	H	63	25d
									—[a]	25a
									13	25c
3	**3c**	**9**	H	H	OMe	H	H	H	65	25a
									86	17a
									—[a]	17b
4	**3d**	**10**	H	H	H	OMe	Me	H	60	24a
5	**3e**	**11**	H	Me	H	H	H	H	84	17a
									85	17b
6	**3f**	**12**	H	OMe	H	H	H	H	88	17a,b
7	**3g**	**13**	H	Oac	H	H	H	H	90	17a,b
8	**3h**	**14**	H	H	H	Me	H	H	86	17a,b
9	**3i**	**15**	OMe	H	H	H	H	H	84	17a,b
									20	22a
10	**3j**	**16**	H	H	OAc	H	H	H	77	17a
									80	17b
11	**3k**	**17**	H	H	OMe	H	H	Me	80	25a
12	**3l**	**18**	Me	H	H	H	H	H	87 (7:3)	17b
		19	H	H	Me	H	H	H		
13	**3m**	**20**	H	OMe	OMe	H	H	H	96 (8:2)	17a,b
		21	OMe	OMe	H	H	H	H		
14	**3n**	**22**	H	–OCH$_2$O–			H	H	97	17a,b
									35.5	20a
15	**3o**	**23**	–OCH$_2$O–		H	H	H	H	21	20a
16	**3p**	**24**	OMe	OMe	OMe	H	H	H	89	17a
									90	17b
17	**3q**	**25**	H	OMe	OAc	H	H	H	65	17a
18	**3r**	**26**	H	Oac	OAc	H	H	H	95	17a
19	**3s**	**27**	H	CF_3	H	H	H	H	61	23a
20	**3t**	**28**	H	Me	H	Me	H	H	—[a]	23a
21	**3u**	**29**	H	Me	H	OMe	H	H	—[a]	23a
22	**3v**	**30**	Cl	H	H	OMe	H	H	—[a]	23a

[a] Chemical yields were not informed.

of conflicting results regarding the nature of the intermediates and the products formed, when the starting diazoketone carried methoxy groups capable of participating in the reaction.[24,25]

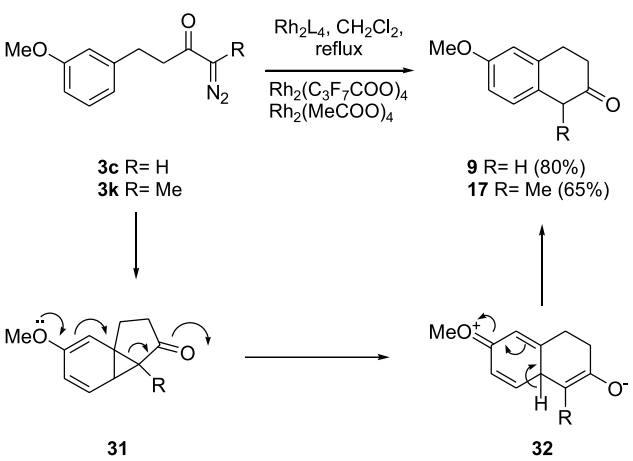
A salient feature of this transformation is the proposed equilibrium between the norcaradienone (**5**) and the cycloheptatrienone [3,8a-dihydroazulen-1(2*H*)-one, **6**] intermediates (Scheme 1).[17a,23a]

Under acidic conditions, the tricyclic intermediate **5** which is the kinetic product, can be protonated leading to a formal cyclopropyl carbenium ion. In turn, this rearranges[26] by the opening of a C–C bond to allow rearomatization, leading to the enolic form **7** of the product.

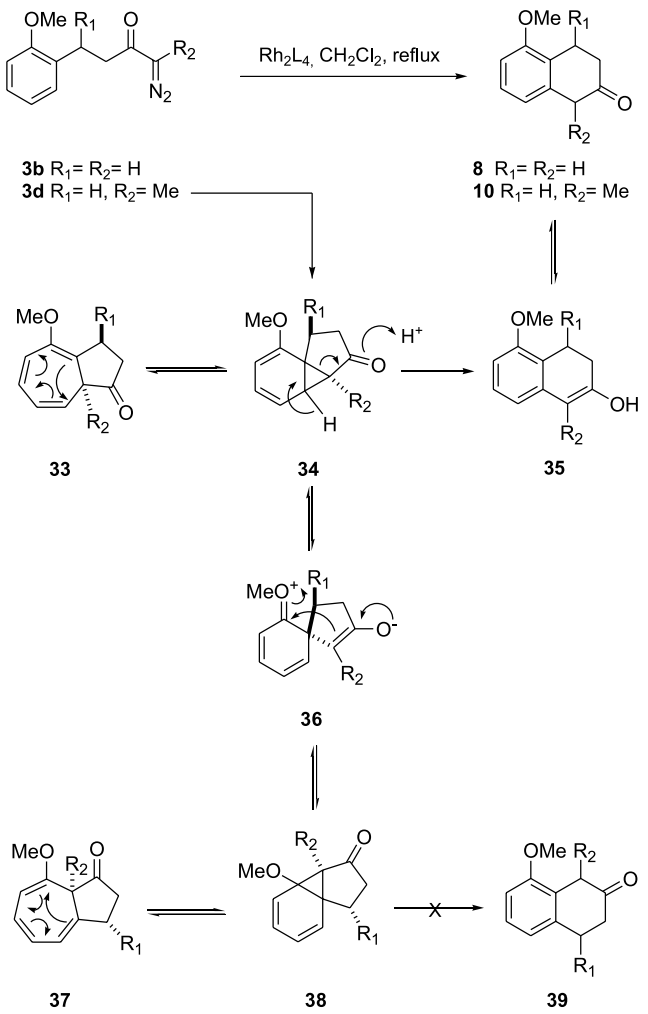
A similar mechanism was proposed to explain the rearrangement and the occurrence of 6-oxo-isopropylcyclohexene from a cyclopropyl ketone derivative.[27]

Interestingly, the methoxy substituent can affect the efficiency of the cyclization, and its regio- and stereoselectivity, having also some effect on the position of the equilibrium between the norcaradiene and the cycloheptatriene tautomers, by affecting their relative stabilities.[24]

Schemes 2 and 3 illustrate about the participation of the methoxy groups in the course of the reaction. In the first case, access to 2-tetralones **9** and **17** was carried out from the corresponding diazoderivatives **3c** and **3k** (Scheme 2). Presumably, in this reaction caradiene **31** is an intermediate which, aided by the methoxy group, provides enolate **32**. In the second case, 2-tetralones such as **8** and **10** can be obtained through the intermediacy of caradienone **34** and enol **35**, being cycloheptatriene derivative **33** one of the species in equilibrium with the caradienone. Other equilibria and products can be postulated for this reaction. Intermediate **34** can be in equilibrium with caradienone **38**, through spiro derivative **36**. The methoxy group plays here an important role, allowing the potential rearrangement of **36** to **38** and vice versa. In turn, **38** can be in equilibrium with cycloheptatrienone **37**; however, because of structural factors, it seems that **37** cannot rearrange to tetralone **39**, which is not observed in the reaction medium.



Scheme 2. Mechanism of the rhodium(II)-catalyzed cyclization of α-diazoketones. Participation of the *m*-methoxy group.



Scheme 3. Mechanism of the rhodium(II)-catalyzed cyclization of α-diazoketones. Participation of the *o*-methoxy group.

The starting α-diazoketones **3** can be conveniently accessed from the related phenylpropionic acids, by the reaction of their corresponding acid chlorides with diazomethane (R_6=H) or other diazo derivatives.[23a] The introduction of the R_5 substituent has been conveniently carried out in 45–73% yield, by conjugate addition of aryl Grignard reagents to buten-2-oic acid or aliphatic Grignards to cinnamic acid derivatives.[24a] It has been observed that sometimes, the Buchner reaction method is not selective, delivering more than one product; this is the case of some substituents and substitution patterns, (cf. Table 1, entries 12 and 13). Noteworthy, 5-methoxy-2-tetralone (**8**) and 6-methoxy-2-tetralone (**9**) accessed by this method, have been employed as starting materials for the synthesis of homosteroids.[23b]

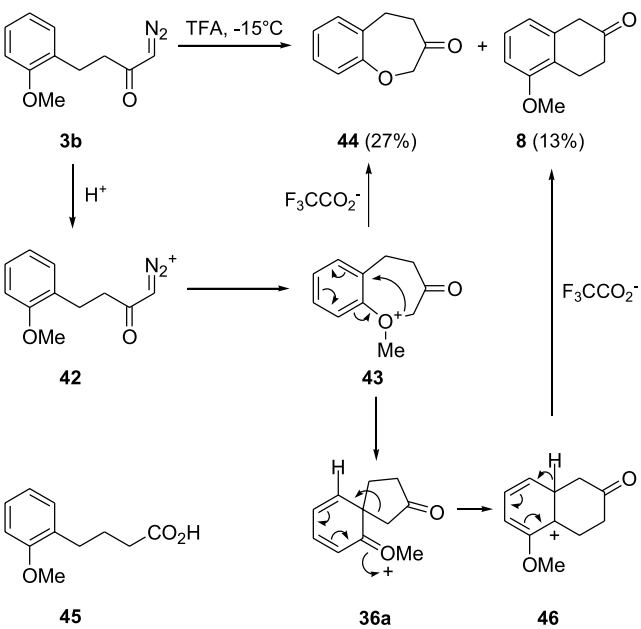
In an extension of the same transformation, 5,6a-dihydrocyclohepta[*a*]naphthalen-6-one **41** was prepared by rhodium catalyzed decomposition of biphenyl derivative **40** carrying a suitably placed α-diazoketone side chain, as shown in Scheme 4,[28] and the solid-phase synthesis of 7-hydroxy-2-tetralone in 60% overall yield, by the diazoketone cyclization methodology and employing the Wang resin, has been recently reported.[29]

Scheme 4. Synthesis of 5,6a-dihydro-cyclohepta[*a*]naphthalen-6-one **41**.

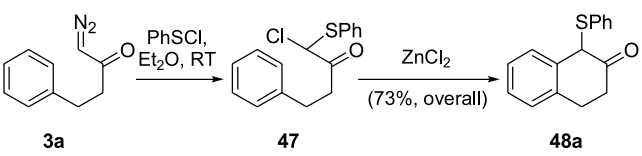
Interestingly, Ghosh and co-workers published the synthesis of 5-methoxy-2-tetralone (**8**) in 13% yield, by the trifluoroacetic acid-catalyzed cyclization of the corresponding α-diazoketone **3b**; in this process, however, the related benzo[*b*]-1-oxepan-3-one **44** was obtained as the main product, in 27% yield.

The postulated reaction mechanism, different from the rhodium-catalyzed decomposition of α-diazoketones, is shown in Scheme 5. It involves the participation of the methoxy group and the aromatic ring in the ketocarbocations **36a** and **46** successively produced from **43** by TFA-mediated (thermodynamic control) protonation of **3b** and attack of the resulting **42** to the methyl ether.[30] Interestingly, attempts to photochemically (254 nm or 365 nm) cyclize diazoketone **3b** met with failure, providing butyric acid derivative **45**.[31]

A somehow related transformation starting with α-diazoketones was disclosed by McKervey and Ratananukul (Scheme 6).[32] Employing phenylsulfenyl chloride, diazoketone **3a** was converted into the α-chloro-α-phenylsulfenyl ketone **47**. This adduct is a powerful electrophile for intramolecular cyclization, leading to tetralone **48a** upon reaction with a Lewis acid such as zinc chloride, as promoter.[33] The transformation **47→48a** bears some resemblance with the cyclization of β-ketosulfoxides, discussed in Section 2.5.



Scheme 5. Acid-catalyzed decomposition of α-diazocarbonyls. Proposed mechanism.

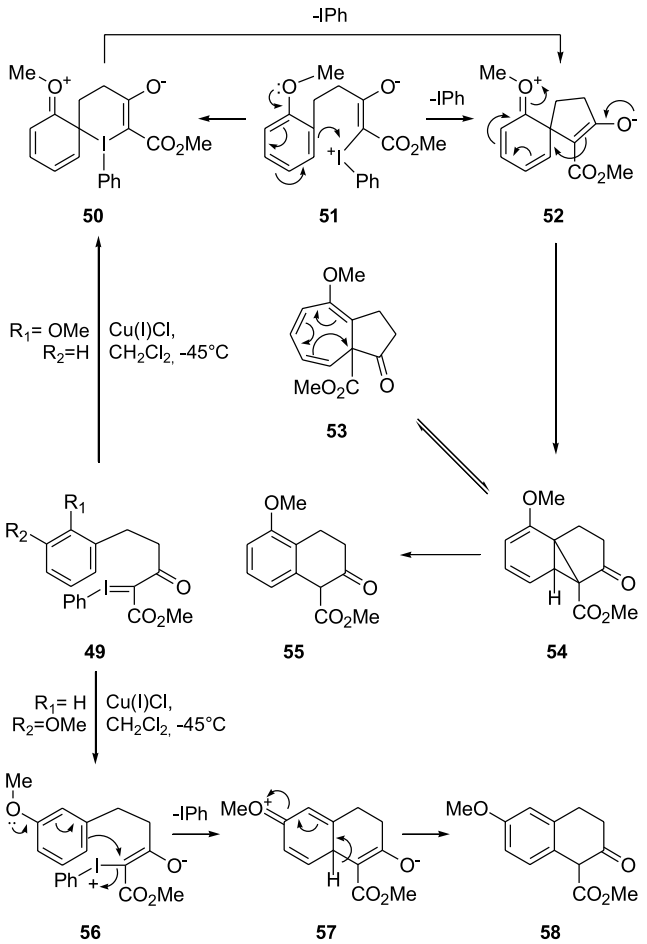


Scheme 6. Cyclization of α-halo-α-phenylthio ketones to 2-tetralone **48a**.

2.2. Intramolecular cyclization of aryl substituted iodonium ylides with copper(I) chloride

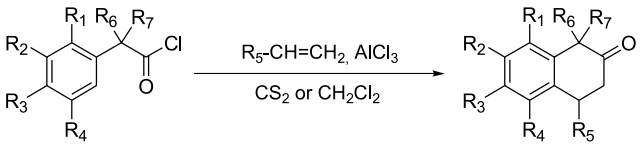
Iodonium ylides derived from β-dicarbonyl compounds are synthetically equivalent to the corresponding diazo β-dicarbonyl compounds in certain reactions. For example, the hypervalent iodine derivatives formed from β-ketoesters participate in the copper(I) chloride promoted intramolecular cyclopropanation of alkenes if the double bonds are appropriately positioned within the molecule.[34] Iodonium ylides of β-ketoesters also effect intramolecular C–H insertion upon decomposition by $Rh_2(OAc)_4$[35] and the group of Padwa has used iodonium ylides as diazo equivalents in intramolecular cycloadditions of carbonyl ylides.[36]

This analogy was exploited by Moriarty and co-workers in the design of a cyclization strategy, which is very similar to the Buchner reaction, where a C=N unit was substituted by



Scheme 7. Synthesis of 2-tetralones by intramolecular cyclization of aryl substituted iodonium ylides.

Table 2. Preparation of 2-tetralones by cyclization of phenyl acetyl chlorides with different alkenes, under Friedel–Crafts reaction conditions



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Entry no.	Phenylacetyl chloride	Product (2-tetralone)	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Yield (%)	References
1	**59a**	**60**	H	H	H	H	Bn	H	H	26	48a
2	**59a**	**61**	H	H	H	H	Ph	H	H	56	50c
3	**59b**	**62**	H	H	Cl	H	H	H	H	70	46a
										84	49e
4	**59c**	**63**	Cl	H	H	H	H	H	H	69	49b
5	**59d**	**64**	H	Cl	H	H	H	H	H	47	46a
										61	49e
6	**59d**	**63**	H	Cl	H	H	H	H	H	—[a]	49b
		65	H	H	H	Cl	H	H	H	**63**+**65** (7:3)	
7	**59e**	**66**	H	Cl	H	Cl	H	H	H	58	46a
8	**59f**	**67**	H	Cl	Cl	H	H	H	H	58	46a
9	**59g**	**11**+**14** (2:1)								95	46b
		11	H	Me	H	H	H	H	H	—[a]	46c
		14	H	H	H	Me	H	H	H	52	38b
10	**59h**	**18**	Me	H	H	H	H	H	H	80	46b
		14	H	H	H	Me	H	H	H	**18**+**14** (1:2)	
11	**59i**	**19**	H	H	Me	H	H	H	H	86	46b
12	**59j**	**68**	H	Me	Me	H	H	H	H	—[a]	46c
		69	H	H	Me	Me	H	H	H	**68**+**69** (4:1)	
13	**59k**	**70**	Br	H	H	H	H	H	H	68	46d
										64	49b
14	**59k**	**71**	H	Br	H	H	H	H	H	68	46c
15	**59l**	**72**	H	H	Br	H	H	H	H	—[a]	48c
16	**59m**	**9**	H	H	OMe	H	H	H	H	68	49a
										85	49b
17	**59n**	**20**	H	OMe	OMe	H	H	H	H	50	49d
										—[a]	49e
18	**59o**	**73**	H	H	OEt	H	H	H	H	—[a]	49e
19	**59p**	**74**	H	H	O^{n}Pr	H	H	H	H	—[a]	49e
20	**59q**	**75**	H	H	I	H	H	H	H	37	50b
21	**59r**	**76**	–N(Ts)CH=CH–							62	48d
22	**59s**	**77**	H	H	H	H	H	Me	1-Phthalimide	14	48e

[a] Product yield was not informed.

a C=IPh group.[37] The advantages of this substitution are important, since it avoids potential carcinogenicity hazards associated with diazo compounds, allows the multigram preparation of the starting materials under safe conditions and synthesis of the iodonium ylides is simply done by treatment of the β-dicarbonyl compounds with $PhI(OAc)_2$ and KOH.

The proposed cyclization mechanism is somehow reminiscent to that of the α-diazoketones and is depicted in Scheme 7. Attack to **49** may be at the iodonium center with subsequent loss of iodobenzene from **51**, or from the tricoordinated iodane intermediate **50**, forming spirocyclic compound **52**. In the case of 5-MeO and 7-MeO derivatives, the reaction mechanism involves intramolecular cyclopropanation of the arene ring, furnishing intermediate **54**. In turn, this can eventually be in equilibrium with the corresponding Buchner type cycloheptatriene ketone **53** or be transformed into 2-tetralone **55**.

Only the *meta*-methoxy derivative **56** can directly aromatize to 2-tetralone **58** by simple deprotonation of the intermediate **57**. Employing this approach, three different 2-tetralones were synthesized in 75–82% yield; curiously, however, the role of Cu(I)Cl in the generation of the dipolar intermediates **51** and **56** is unknown. 5-Methoxy derivative **55** has been employed as precursor for the synthesis of a benzidine analog of prostacyclin.[38]

2.3. Synthesis of 2-tetralones using a Friedel–Crafts acylation–cycloalkylation sequence with simple alkenes

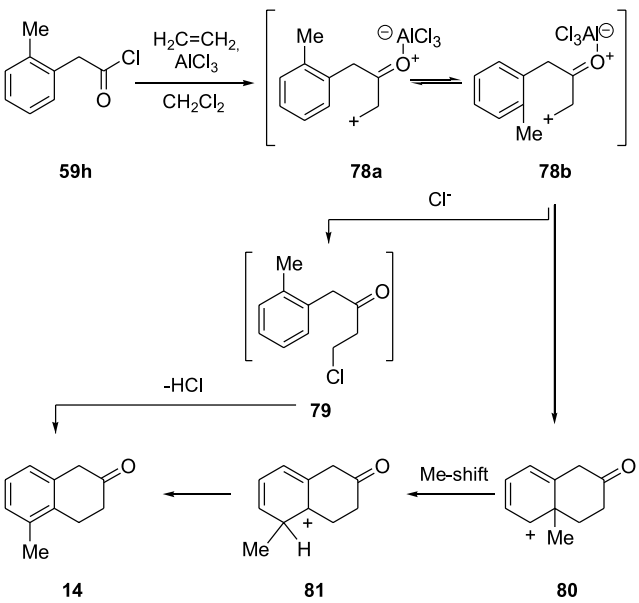
Carboannulation processes are among the most important reactions in organic synthesis.[39] The Friedel–Crafts type electrophilic substitution reactions are one of the most common carboannulation strategies available to the synthetic chemist.[40,41] The Friedel–Crafts acylation followed by cycloalkylation, through the reaction of aryl acetyl chlorides with olefins in the presence of $AlCl_3$, was initially reported by Cologne and Chambion in 1947.[42] Burckhalter and Campbell were the first in using ethylene for this kind of transformation, in 1961,[43] following the observations made in 1958 by Matsumoto, Hata and Nishida, that benzoyl chloride and ethylene formed 3-chloro-3-methyl butyrophenone in the presence of aluminum chloride as catalyst.[44] The reaction of acyl chlorides with ethylene to give ketones

is also known as the Darzens reaction.[45] Nowadays, this is one of the preferred methods for the preparation of 2-tetralones and since the original description, several publications have focused on the scope of the reaction (Table 2), reporting improvements and limitations.[23,46–50]

The best performance of the transformation was obtained with the use of an excess of $AlCl_3$ (3 equiv.) and the in situ generation of the acyl chloride. Sometimes, CH_2Cl_2 was found to be a better solvent than CS_2,[46b] being this attributed to the ability of the solvent to dissolve the acyl chloride–aluminum chloride complex.[46f] It was also demonstrated that the reaction can be carried out at room temperature and even at lower temperatures, depending on the activation degree of the aromatic ring.

Analogously to the Buchner cyclization, and despite the ready availability of the starting chlorides and the moderate to good yields obtained, this method suffers from low selectivity for some substrates, such as 3-chloro-phenylacetyl chloride (**59d**), 2- and 3-methylphenylacetyl chloride (**59g** and **59h**) and 3,4-dimethylphenylacetyl chloride (**59j**). The reaction mechanism, depicted in Scheme 8, provides the basis for rationalizing some interesting observations, such as the fact that 2-methyl phenylacetyl chloride **59h** gave rise to two isomeric 2-tetralones, **14** and **18**. Formation of unexpected 2-tetralone **14** occurs through a methyl migration (**80**→**81**).[46b] In this type of transformation, β-chloroethyl ketones like **79**, related to **78a** and **78b** have been isolated as intermediates.[49e,51]

It is accepted that the aluminum catalyst forms an acylium intermediate, which losses halide ion to form a carbocation which may react with a suitably placed π-system, such as ethylene, to furnish cationic intermediates (**78a**, **78b**); in turn, the latter may add chloride ion, to provide β-chloro-ketones such as **79**,[48a] or cyclize intramolecularly to yield the 2-tetralone products.

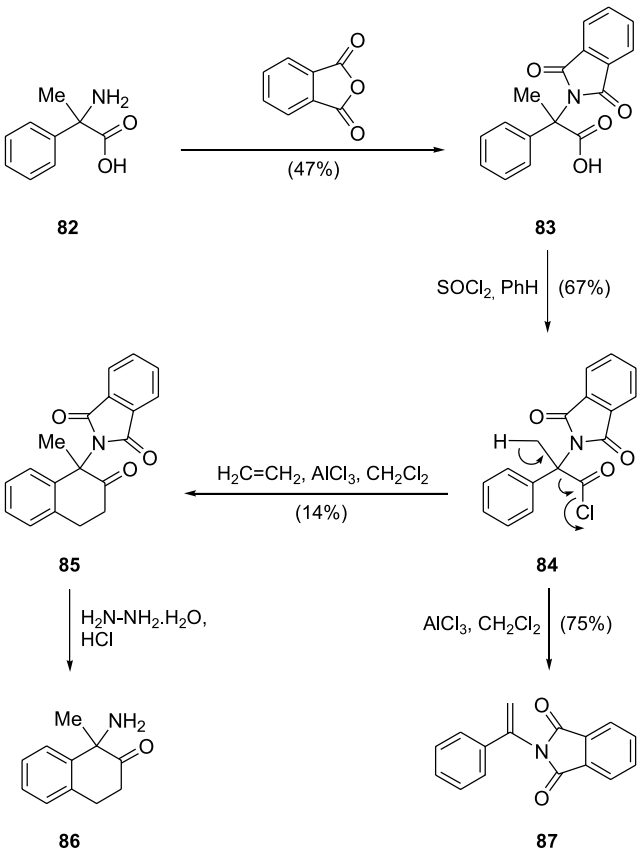


Scheme 8. Proposed mechanism for the formation of 5-methyl-2-tetralone **14** from 2-methyl-phenylacetyl chloride **59h**.[35b]

Chlorinated tetralone **62** and the related 1-methyl-6-chloro-2-tetralone[47a] were employed for the syntheses of the benzoquinolinones LY191704 and LY266111, which act as human type 1 steroid 5-α-reductase inhibitors,[47b] as well as for the elaboration of other benzoquinolinones with similar activity.[47c] Interestingly, however, the related 6-bromo-2-tetralone **72** was employed for the evaluation of an electrochemical reactor system in the biotransformation to the corresponding 2-tetralol,[47d] and in the synthesis of conformationally constrained phosphotyrosyl mimetics.[47e]

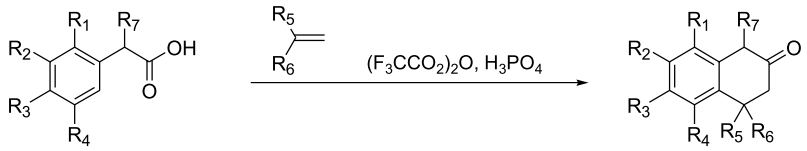
The intermediacy of **80** and a methyl shift explain the formation of rearranged 2-tetralone **14**. As expected, the reaction fails with some substrates carrying electron-withdrawing groups such as nitro on the aromatic moiety; nevertheless, some chlorinated derivatives have been obtained in fairly good yields following this method. It appears that the halogens retard the reaction rate to some extent, without affecting the preparative usefulness of the process.[52] The 6-nitro and 7-nitro 2-tetralones were simultaneously obtained by nitration of a preformed 2-tetralone.[50a] Similarly, nitration of 6-chloro-2-tetralone furnished the 7-nitro derivative.[50b] On the other hand, in case of *ortho* disubstituted ethers next to the acetyl side chain, an unusual reaction takes place, furnishing 2[3*H*]-benzofuranone derivatives, due to ether cleavage and intramolecular cyclization, instead of reaction with ethylene.[43]

When compared with older but not less effective methods, resorting to the reduction of naphthalene derivatives, the



Scheme 9. Friedel–Crafts type synthesis of 1-amino-2-tetralone **86**.

Table 3. Synthesis of 2-tetralones employing an environmentally friendly Friedel–Crafts reaction



85 **86**

Entry no.	Arylacetic acid	2-Tetralone	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Yield (%)
1	**88a**	**89a**	H	H	H	H	*n*-Bu	H	H	55
2	**88b**	**89b**	H	H	F	H	*n*-Bu	H	H	37
3	**88c**	**89c**	H	H	Me	H	*n*-Bu	H	H	74
4	**88d**	**89d**	H	H	OMe	H	*n*-Bu	H	H	62
5	**88e**	**89e**	H	OMe	OMe	H	*n*-Bu	H	H	76
6	**88f**	**89f**	H	H	H	H	*n*-Bu	H	Me	51
7	**88a**	**89g**	H	H	H	H	$CH_2CH_2CH_2Br$	H	H	55
8	**88c**	**89h**	H	H	Me	H	Me	Me	H	70

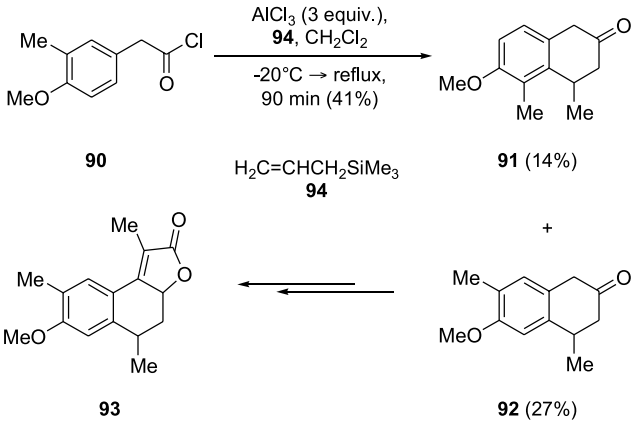
most attractive advantages of the Friedel–Crafts approach to 2-tetralones are that halogenated tetralones can be conveniently prepared, and that the starting acyl chlorides are readily available, against the relative inaccessibility of polysubstituted 2-methoxy naphthalene derivatives.

The Burckhalter and Campbell protocol was also employed for the synthesis of 1,1-disubstituted 2-tetralones. As part of a study on hypnotic and locomotive properties of ketamine analogs, Yang and Davisson[48e] prepared 1-methyl-1-amino-2-tetralone **86** from α-methyl phenylglycine **82**. Their synthesis is depicted in Scheme 9. The acyl chloride **84**, obtained by reacting the phthalimido derivative **83** with either thionyl chloride or phosphorus pentachloride, was treated with ethylene in the presence of aluminum chloride to give the expected *N*-protected aminotetralone **85** in good overall yield. Cyclization of the latter, however, proceeded in no more than 15% yield, constituting α-phthalimido styrene **87** more than 75% of the recovered products. Unfortunately, no improvement was recorded when reaction time, temperature and the sequence of addition of the reagents were changed. Conventional hydrazinolysis of the phthalimide **85** provided the required aminotetralone **86**.

An eco-friendly version of the Burckhalter and Campbell reaction was developed recently by Gray and Smith.[53] In this cleaner approach, the trifluoroacetic anhydride/H_3PO_4 system was used instead of the more contaminating metal-based ($AlCl_3$) methodology. In this way, 2-tetralones **89a–h** were prepared from starting phenylacetic acid derivatives **88a–f**.

Additional advantages of this green methodology are the use of an arylacetic acid as starting material instead of the related acyl chloride, which is very unpleasant to work with, and the avoidance of dichlorometane, employed as solvent in the former procedure. The reaction involves the in situ formation of a mixed anhydride of the arylacetic acid, a process that takes place near to room temperature, furnishing the 2-tetralones in good yields, as shown in Table 3.

An interesting modification of the Friedel–Crafts acylation–cycloalkylation approach with simple alkenes consists in the use of an allylsilane as the alkene moiety. Recently, Silveira and co-workers performed this type of study involving the use of allyltrimethylsilane (**94**) as the olefinic component of the cyclization. This allowed the preparation of several aryl-substituted (Cl, Br, OMe, Me)-4-methyl-2-tetralones. A mixture of 2-tetralones **91** and **92** was obtained in 41% combined yield from acid chloride **90**.[42] The 6-methoxy-4,7-dimethyl-2-tetralone **92**, prepared by this new allylsilane methodology, was employed as a key intermediate in a total synthesis of heritonin **93**, a tricyclic lactone isolated from *Heritiera littoralis*, which acts as a powerful natural piscicide (Scheme 10).[54]

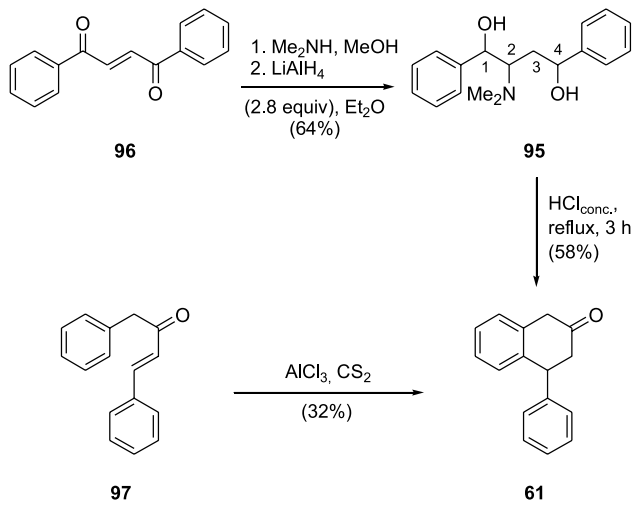


Scheme 10. Synthesis of 6-methoxy-4,7-dimethyl-2-tetralone **92**, through an allylsilane mediated Friedel–Crafts type cyclization.

2.4. Friedel–Crafts intramolecular alkylation

There are scattered examples reported about this approach, which provides 4-phenyl-substituted 2-tetralones. Exposure of 2-(*N*,*N*-dimethylamino)-1,4-diphenyl-1,4-butanediol (**95**) to refluxing concentrated HCl was used to prepare 4-phenyl-2-tetralone **61**, in up to 58% yield (Scheme 11).[55]

The starting diol **95** was easily obtained by reduction of 2-(*N*,*N*-dimethylamino)-1,4-diphenyl-1,4-butanedione **96** with excess of $LiAlH_4$. On the other hand, other aqueous mineral acids such as HBr, or H_2SO_4 can be employed in place of HCl.[56] This transformation probably proceeds through a Friedel–Crafts-type intramolecular alkylation

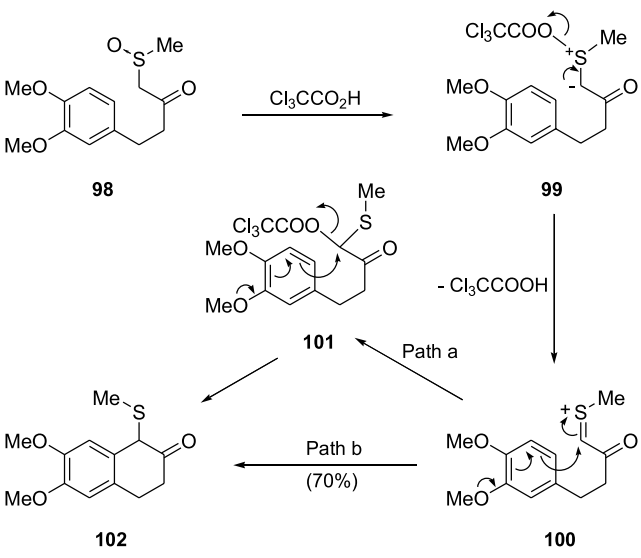


Scheme 11. Intramolecular Friedel–Crafts cyclization for the synthesis of 4-phenyl-2-tetralone (**61**).

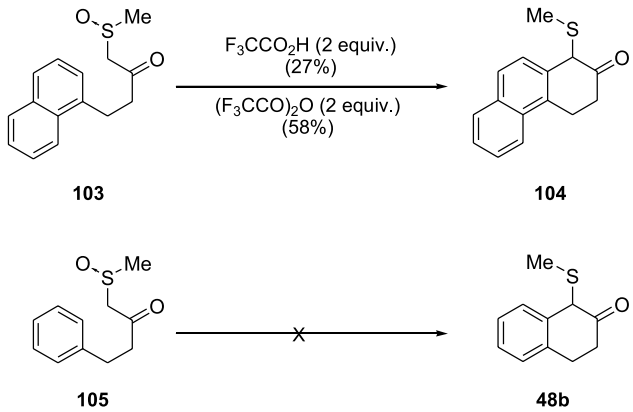
with C-4. In a second stage, dehydration of the benzyl alcohol on C-1, next to the amine moiety, yields an enamine, which readily hydrolyzes in the reaction medium, furnishing the product. In one alternative approach, the synthetically equivalent α,β-unsaturated ketone **97**[57] was converted into the same 2-tetralone (**61**) by Friedel–Crafts reaction with $AlCl_3$ in CS_2, albeit in only 32% yield; 2-tetralone **61** was also prepared in 45% overall yield from benzaldehyde, by reaction of trimethyl-styrylsilane with phenylacetyl chloride, under $AlCl_3$ catalysis (Table 2, entry 2).[50c]

2.5. Cyclization of β-ketosulfoxides

β-Ketosulfoxides are easily available by the well-known reaction of methylsulfinyl carbanion with the corresponding lower homologous esters.[58] The β-ketosulfoxides can undergo cyclization under acid catalysis to yield 2-tetralones, as illustrated in Scheme 12. The transformation takes place by protonation of the sulfinyl oxygen of the starting material (**98**) to form ylide **99**, which in turn can readily form the ylene intermediate **100** and rearrange to the α-acyl-α-thio acetal **101** upon attack by an appropriate nucleophile. This transformation is known as the Pummerer rearrangement. A nucleophile existing at a suitable position may attack intramolecularly the mixed acetal resulting from the rearrangement. Employing aromatic rings as internal nucleophiles (path a), 1-methylthio-2-tetralones **102** and **104** were prepared by cyclization of β-ketosulfoxides **98** and **103**, respectively (Schemes 12 and 13). An alternative route (path b) can be devised, by which the ylene intermediate **100** suffers intramolecular nucleophilic attack to furnish the product. Interestingly, while the cyclization is a first order process, the rearrangement is a second order reaction. Experimental evidence pointed to an acid catalyzed cyclization of the ylene (**100**), without rearrangement taking place, when trichloroacetic acid was employed.



Scheme 12. Mechanism of the synthesis of 2-tetralone derivatives employing the Pummerer rearrangement of β-ketosulfoxides.



Scheme 13. Synthesis of 2-tetralones by acid-catalyzed cyclization of β-ketosulfoxides.

In fact, cyclized products could be obtained in the presence of relatively weak acids, such as dichloroacetic acid and although rearranged products (mixed acetals) were isolated under certain conditions, they could not be converted into cyclized products following the cyclization protocol. However, the mechanism changed to a Pummerer rearrangement mediated cyclization when trifluoroacetic anhydride was employed as cyclization agent.[59a]

In the case of **98**, use of tricloroacetic acid furnished the product in 70% yield, while the same amount of trifluoroacetic acid provided 64% of the 2-tetralone **102**.[60] For the cyclization of **103**, trifluoroacetic acid yielded only 27% of the product **104**, while trifluoroacetic anhydride raised the yield to 58%.[59a] These reactions proceed in the presence of 2 equiv. of a trihalo-acid or trihalo-anhydride, under reflux during 1–2 h. The 1-methylthio-6,7-dimethoxy-2-tetralone **102** thus produced was desulfurized with hydrogen and Pd/C to give the expected 6,7-dimethoxy-2-tetralone **20** in 60% yield.[61] The cyclization of β-ketosulfoxides to 2-teralone derivatives was used for the preparation of starting materials for the elaboration of benzacridines as mammalian topoisomerase poisons. The method, however, is not suitable for the elaboration of 2-tetralones containing unsubstituted or deactivated aromatic rings, such as **48b**, by cyclization of the corresponding sulfoxide **105** (Scheme 13).

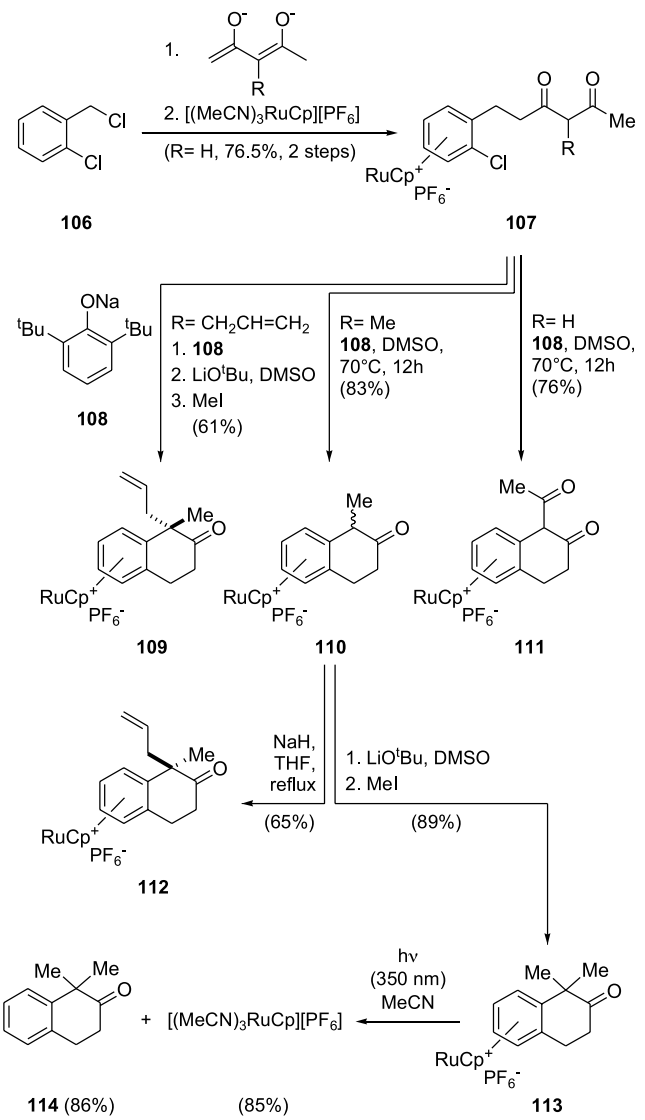
2.6. Intramolecular S_NAr reaction of (η^6-arene) ruthenium complexes

Cationic (η^6-arene)ruthenium(II) complexes are easily prepared and behave as useful air and moisture stable materials. The coordinated arene ring in this organometallic species exhibits a unique and potentially useful reactivity pattern, due to the activating effect exerted by the CpRu(II) fragment.[62]

(Chloroarene)Ru–Cp (Cp=cyclopentadienyl) moieties have been shown to be excellent electrophilic partners for nucleophilic aromatic substitution reactions. Despite the high cost of the transformations requiring stoichiometric amounts of ruthenium, this expense is somewhat mitigated by the availability of methods to recover the CpRu(II) fragment in forms suitable for reuse after removal of the arene ligand.[63]

Stabilized enolates generated from δ-aryl-β-dicarbonyl compounds **107** were induced to participate in a series of intramolecular S_NAr reactions assisted by the (arene)Ru moiety attached to it. The β-dicarbonyl compounds were prepared by first reacting the dianion of acetylacetone with 2-chlorobenzyl chloride **106**,[64] being this followed by introduction of the CpRu(II) fragment, using [$(MeCN)_3$-RuCp][PF_6] as a ruthenium transfer reagent.[63] Despite the possibility of coordinating to the acac moiety, it was found that the ruthenium coordinates solely with the arene ring.[65] Using hindered sodium phenoxide derivative **108** as base, acetyl tetralone **111** was conveniently isolated. Employing δ-aryl-β-dicarbonyl compounds functionalized between the carbonyls, different 1-substituted- (**110**) and 1,1-disubstituted-2-tetralones (**109** and **113**) were obtained in good yields (Scheme 14).[66] Monosubstituted 2-tetralones were regioselectively alkylated and the bulk of the CpRu(II) fragment allowed the stereocontrolled synthesis of 1,1-disubstituted 2-tetralones (compare **112** with **109**).[67]

The CpRu(II) moiety was easily removed under mild photochemical conditions, by irradiation at 350 nm in acetonitrile, and recovered in a reusable form in excellent yield, such as in **113→114**. The scope and limitations of the reaction have not been fully explored, since this methodology was employed only for the preparation of 2-tetralones functionalized at C-1 and unsubstituted on the aromatic ring. Interestingly, however, it is expected that the use of planar chiral (arene)Ru complexes may lead to useful chiral 1,1-disubstituted tetralones.



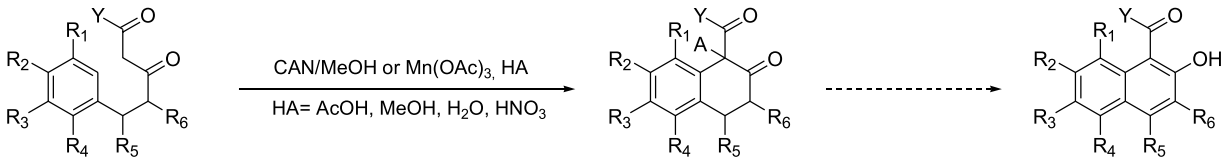
Scheme 14. Synthesis of 2-tetralones employing an intramolecular S_NAr reaction of (η^6-arene) ruthenium complexes.

2.7. Radical-mediated oxidative cyclization of δ-aryl-β-dicarbonyl compounds with Mn(III) and Ce(IV) salts

2-Tetralone derivatives were also prepared from δ-aryl-β-dicarbonyl compounds[64] by reaction with Mn(III) and with Ce(IV) salts. This entailed an intramolecular homolytic aromatic substitution reaction, with the α-dicarbonyl radicals generated by inner-sphere electron transfer from high-valent metal complex to the β-dicarbonyl compounds.[68] The transformation, which yielded tetralones **116a–116j** as examples, was initially developed with the aim of synthesizing 2-hydroxy-1-naphthoic acids, being the reaction conducing to the latter a four electron oxidation process. The cyclization proceeded only when the aromatic ring was sufficiently electron-rich. Cerium ammonic nitrate (CAN) performed better that Mn(III) acetate, not requiring, as the latter, electron releasing groups on the aromatic ring, *meta* to the dicarbonyl substituent.[69] The β-acyl-2-tetralones **116a–116c** were prepared with the aid of CAN, while their congeners **116d–116j** were synthesized employing Mn(III) acetate (Table 4).

In many cases, the 1-substituted 2-tetralones thus prepared, could not be isolated as such, being readily oxidized in situ by excess of reagent to the related 1-acetoxy (also hydroxy or methoxy) derivatives **116**, through the corresponding enolic form of the 2-tetralone.[70] They furnished the expected naphthoic acids **117** upon dehydration with silica gel in hot benzene or prolonged chromatography. It has been shown that the reaction can be stopped at the tetralone stage when the enol content of the latter is low.

Table 4. Synthesis of 2-tetralones employing the Ce(IV) or Mn(III)-mediated oxidative cyclization of δ-aryl-β-dicarbonyl compounds



115 **116** **117**

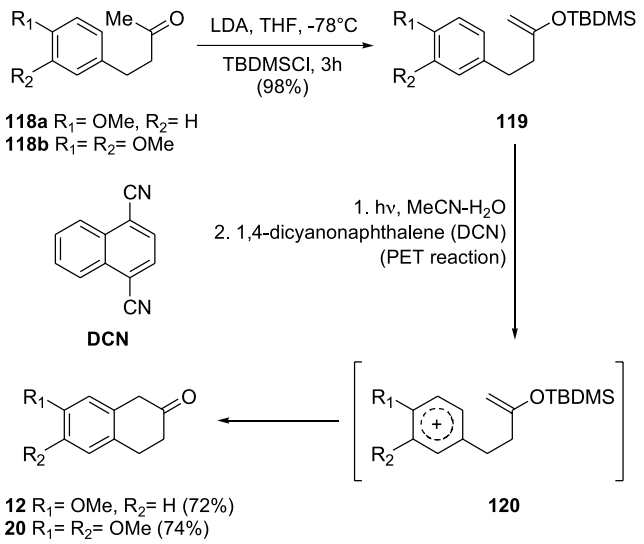
Entry no.	β-Dicarbonyl	2-Tetralone	R_1	R_2	R_3	R_4	R_5	R_6	A	Y	Yield (%)	Reference
1	**115a**	**116a**	H	H	H	H	H	H	OMe	OEt	22	69
2	**115a**	**116b**	H	H	H	H	H	H	ONO_2	OEt	26	69
3	**115b**	**116c**	H	H	OMe	H	H	Me	OAc	OMe	29	69
4	**115c**	**116d**	H	H	H	H	H	Me	OAc	Et	9	70
5	**115d**	**116e**	H	H	OMe	OBn	H	Me	OAc	Et	56	70
6	**115e**	**116f**	OBn	H	Obn	H	H	Me	OAc	Et	93	70
7	**115f**	**116g**	OBn	H	NHAc	H	H	Me	OAc	Et	93	70
8	**115g**	**116h**	OMe	H	OMe	H	H	H	OAc	Me	71	70
9	**115h**	**116i**	OMe	H	OMe	H	OH	H	OAc	Me	95	70
10	**115i**	**116j**	H	H	OMe	OBn	H	H	OAc	OEt	81	70

2.8. Intramolecular addition of silylenol ethers to PET-generated arene radical cations

The carboannulation reaction involving the intramolecular nucleophilic addition of silyl enol ethers to photochemically generated arene radical cations, was employed to synthesize two different 2-tetralones in good yields.[71] The intermediate radical cations were obtained by a 1,4-dicyanonaphthalene photosensitized electron transfer (PET) reaction. Starting ketones **118** were converted into the corresponding kinetic silyl enol ethers **119** by treatment with LDA and capture of the enolates with TBDMS chloride.[72]

After irradiation of the enol ether in a 4:1 MeCN–H_2O mixture for 3 h, through a Pyrex filter (>280 nm), without removing dissolved oxygen, 7-methoxy- (**12**, 72% yield) and 6,7-dimethoxy-2-tetralone (**20**, 74% yield) were prepared through the intermediacy of cations **120** (Scheme 15).

The 1,4-dicyanonaphthalene sensitizer was recovered almost quantitatively.[73] The synthesis seems to be flexible enough to incorporate other functionalities. In case of **118b** two products are possible; however, the regioselectivity observed is in accordance with the calculated electron densities (Huckel or MNDO) at the carbons of the HOMO of the arene radical cation.

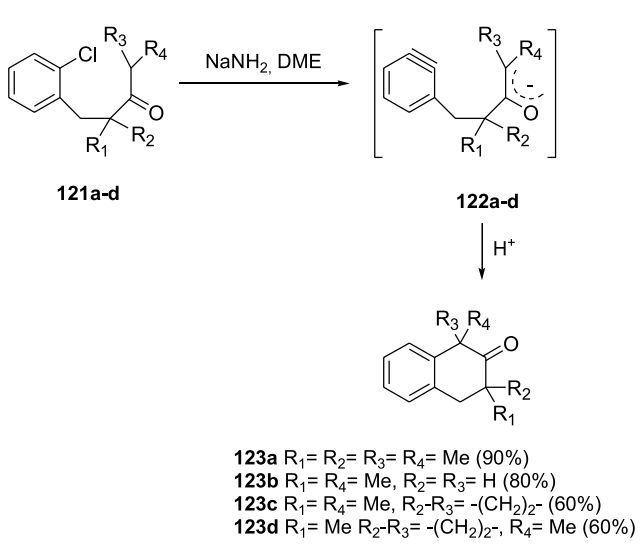


Scheme 15. Preparation of 2-tetralones **12** and **20** via intramolecular addition of silylenol ethers to PET-generated arene radical cations.

2.9. Intramolecular cyclization via benzyne intermediates

Several 1- and 3-substituted 2-tetralones were prepared by means of the intramolecular condensation of 2-chloro-benzyl acetone enolates.[74,75]

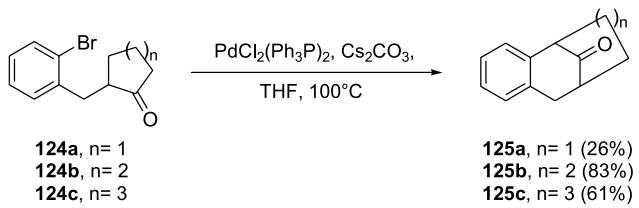
The reaction proceeded via the benzyne intermediates **122a–d**, generated by treatment of 2-chlorobenzyl acetone derivatives, **121a–d**, with a strong base in THF/HMPA or DME. The transformation was completed after ca. 12 h at 40–45 °C, and four different 1- and 3-substituted 2-tetralones (**123a–d**), were prepared in 60–90% yield (Scheme 16).



Scheme 16. Synthesis of 2-tetralones by intramolecular cyclization through benzyne intermediates.

2.10. Palladium-catalyzed intramolecular α-arylation of aliphatic ketones

The cyclization of 2-(2′-halobenzyl)-substituted cycloalkanones to bridged 2-tetralones was effected under promotion of palladium complexes. This is an intramolecular version of the widely studied α-arylation reaction of aliphatic ketones.[71,76,77] As examples, the 2-bromo cycloketones **124a–c** were submitted to intramolecular cyclization to afford bridged tricyclic 2-tetralones **125a–c** in 26–83% yield.[78] The reaction takes place in the presence of catalytic amounts of $PdCl_2(Ph_3P)_2$, with Cs_2CO_3 (3 equiv.) as base, and requires heating at 100 °C during 13–16 h (Scheme 17). While enones, formed by palladium-catalyzed dehydrogenation of the ketones (cyclized and uncyclized), have occasionally been found in the reaction mixture, the debrominated starting ketones are the main side products of this transformation. In another application of palladium reagents, Lipshutz described the synthesis of 1-aryl 2-tetralone derivatives by palladium(II) catalyzed hydrolysis of dioxolane acetals/ketals of 2-tetralones in moist acetonitrile.[79]

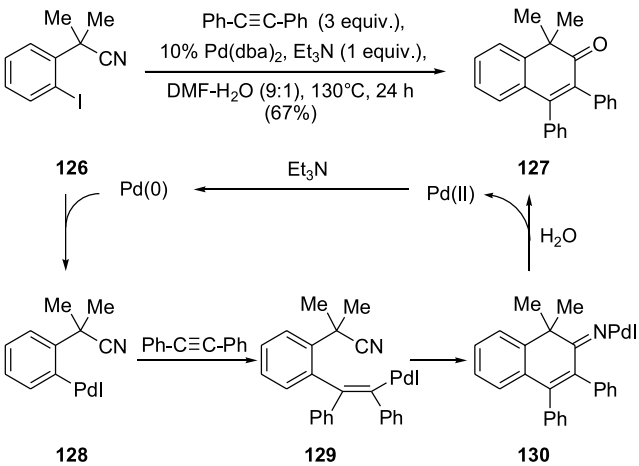


Scheme 17. Synthesis of 2-tetralones employing a palladium-catalyzed intramolecular α-arylation of aliphatic ketones.

2.11. Carbopalladation of aromatic nitriles in the presence of acetylenes

The carboannulation of 2′-iodophenyl-2-methyl-propanenitrile **126** with diphenylacetylene was effected under palladium catalysis, affording the unsaturated 1,1-dimethyl-3,4-diphenyl-2-tetralone **127** in 67% yield.[80]

For the only example available, 10% $Pd(dba)_2$ was employed as catalyst (Scheme 18). The process appears to involve formation of arylpalladium **128** and subsequent alkyne insertion (**129**) to produce a vinylic palladium imine intermediate (**130**), which hydrolyzes to the corresponding ketone. This is a catalytic process that requires reduction of the palladium(II) salt produced. This is probably carried out by the triethylamine added to the reaction. The protocol can afford only 1,1-disubstituted 2-tetralones; when it was applied to 2-iodophenyl acetonitrile, the intermediate imine aromatized and β-naphthylamines were obtained instead.

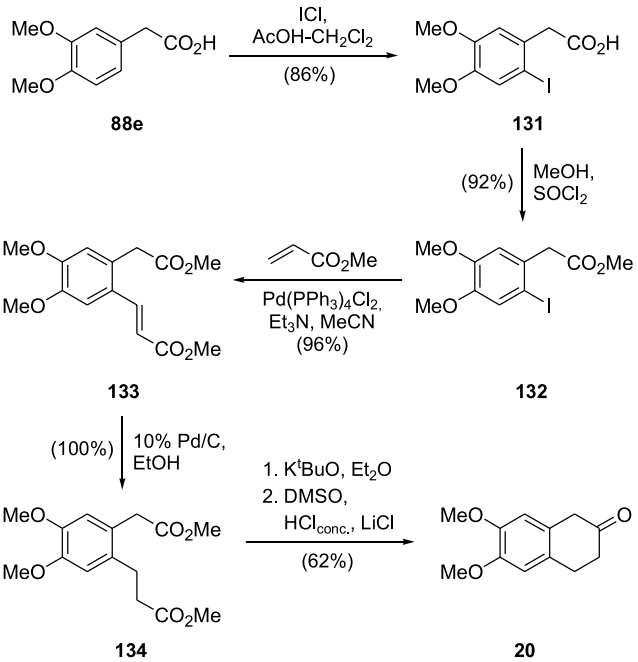


Scheme 18. Palladium catalysis for the preparation of 1,1-dimethyl-3,4-diphenyl-2-tetralone **127**.

2.12. Dieckmann condensation followed by decarboxylation

The highly useful 6,7-dimetoxy-2-tetralone **20** was synthesized in reasonable overall yield by a Dieckmann condensation protocol, employing 3,4-dimethoxy-phenylacetic acid **88e** as starting material.[81]

This 2-tetralone has been employed as starting material for the elaboration of the known dopamine agonist dihydrexidine and some of its derivatives,[82] as well as various aminotetralines,[49d,83,84] isoquinoline derived dopaminergic agents,[85] catecholamine mimicking agents,[86] naturally occurring alkaloids[19] and cyclic aminoacids.[87] The method involved the preparation of iodide **131** by selective iodination of the starting acid. This was esterified in over 70% overall yield to iodoester **132**[88] and then submitted to a Heck cross-coupling reaction[89] with methyl acrylate and 1 mol% of dichlorobis (triphenylphosphine) palladium(II) as catalyst, furnishing 96% of cinnamate **133**. Dichlorobis (triphenylphosphine) palladium(II) is a highly stable and low-cost form of palladium.[90] The so obtained cinnamate **133** was converted quantitatively to the dihydrocinnamate derivative intermediate **134**, by catalytic hydrogenation with Pd/C, which in turn was submitted to a Dieckmann condensation with potassium *tert*-butoxide, followed by decarboxylation of the resulting potassium salt under mild conditions,[91] to afford the desired 2-tetralone **20** in 62%

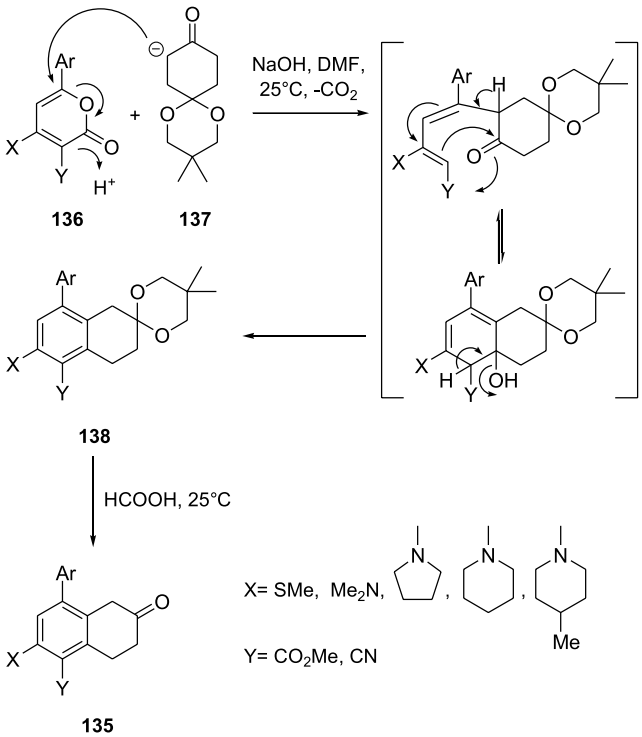


Scheme 19. 6,7-Dimetoxy-2-tetralone **20** prepared by a Dieckmann condensation strategy.

yield (Scheme 19). The tetralone was conveniently purified through its bisulfite adduct.

2.13. Carbanion-induced condensation of 2*H*-pyran-2-ones with 1,4-cyclohexanedione monoketal

Recently, the preparation of several functionalized 2-tetralones (**135a–o**) by means of the carbanion induced reaction of 6-aryl-3-methoxycarbonyl-4-methylsulfanyl- and 6-aryl-3-cyano-4-*sec*-amino-2*H*-pyran-2-ones **136** with 1,4-cyclohexanedione mono-(2,2-dimethyl trimethylene) ketal **137**, was described (Scheme 20, Table 5).[92]



Scheme 20. Synthesis of 2-tetralones by condensation of 2*H*-pyran-2-ones **136** with 1,4-cyclohexanedione monoketal **137**.

The reaction yielded 8-aryl-5-methoxycarbonyl-6-methylsulfanyl-3,4-dihydro-2(1*H*)-naphthalenone (2,2-dimethyltrimethylene) ketals **138** and the related nitriles. Mild acid hydrolysis of the ketals yielded exclusively the expected 2-tetralones **135**. The method is highly suitable for the introduction of diverse functionalities at positions 5, 6 and 8. The mechanism of the reaction can be rationalized by assuming an initial attack of the carbanion generated from **137** by the base in DMF at position 6 of the pyran ring of the pyrone **136**. The reaction then proceeds with ring opening followed by decarboxylation and condensation–cyclization involving the carbonyl functionality and C-3 of the pyran ring, leading to **138**. The latter compounds may also arise through an inverse electron-demand Diels–Alder cycloaddition of the enolate to the 2*H*-pyran-2-one **136**, but this mechanism is not very likely, taking into account previous precedents[93] and the mildness of the reaction conditions (Scheme 20). This is a very useful method for the preparation of 2-tetralones with electron-withdrawing groups in the aromatic ring (CN, CO_2Me).

2.14. One-pot annulation through an alkylation–acylation and decarboxylation sequence

A regioselective one-pot annulation process involving the bifunctional (nucleophilic and electrophilic centers within the same molecule) bromosulfone **139** and deprotonated malonate esters was reported by Ghera and Ben-David.[94]

The protocol is advantageous for the synthesis of 3-susbtituted 2-tetralones, because the starting materials are readily available.

In this transformation, the bromosulfone **139** acted as a 1,4-dipole, and the reaction took place by an alkylation–acylation sequence, providing the 1-phenylsulfonyl-2-tetralones **140a–e**. During the transformation, self-reactivity was avoided. When submitted to an in situ hydrolysis and decarboxylation, **140b** allowed access to 1-phenylsufonyl-3-alkyl-2-tetralone **141** in good yield (Scheme 21).

It has been demonstrated that, alternatively, deprotonated lactones (**142**)[95] can be used in the ring closure process instead malonate anions. In this case, γ- and δ-hydroxy-2-tetralones **143a**,**b** were obtained in good yields from bromosulfones **139** (Scheme 22).[94]

A more sophisticated version of this cyclization entailed the use of bromosulfone **145**, prepared from **139** through the intermediacy of olefin **144**. Carrying phenylsulfonyl and diester groups within the same molecule, bromosulfone **145** furnished the tricyclic 2-tetralone derivative **146** in 71% yield and 90% d.e. In this case, generation of the malonate and α-sulfonyl carbanions produced a double cyclization, leading to the product (Scheme 23).

2.15. Miscellaneous syntheses of 2-tetralones

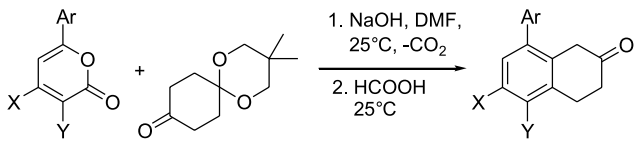
The preparation of 1,1,4,4-tetramethyl 2-tetralone **148** by the intermolecular Friedel–Crafts-type reaction of 2,2,5,5-tetramethyl tetrahydro-3-ketofuran (**147**) with benzene, as reactant and solvent in the presence of $AlCl_3$ as catalyst, was described (Scheme 24).[75b]

The compound was employed, as part of a series of photochemical studies of 2-tetralones in which it gave aldehyde **149** as the only photoproduct.[75a] The scope of the reaction remains unexplored.

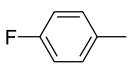
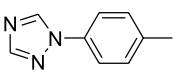
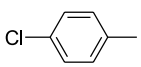
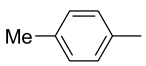
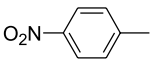
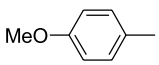
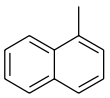
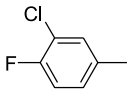
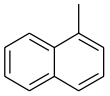
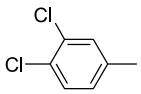
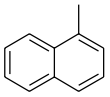
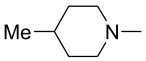
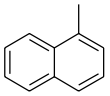
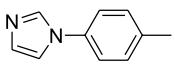
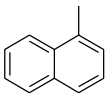
3. Methods involving transformations in a pre-formed tetralinic ring or a naphthalene precursor

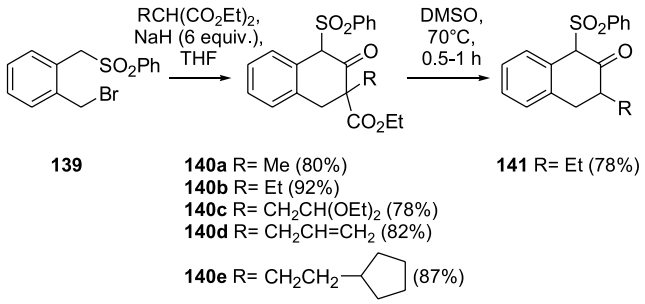
One of the most frequently used methods for the preparation of functionalized 2-tetralones involves chemical transformations of a pre-formed tetraline derivative. Despite the requirement of preparing the appropriate tetraline or naphthalene precursor before obtaining the 2-tetralone, this approach is very useful for accessing substituted 2-tetralones with their structure unequivocally known in advance. Mixtures of isomers, which are a serious problem when ring-closing methods are employed for some

Table 5. Polysubstituted 2-tetralones **135a**–**o** obtained by carbanion induced condensation of 2*H*-pyran-2-ones **136** with 1,4-cyclohexanedione monoketal (**137**)



136 **137** **135**

2-Tetralone	X	Y	Ar	Yield (%)	2-Tetralone	X	Y	Ar	Yield (%)
135a	SMe	CO_2Me		31	**135i**	SMe	CO_2Me		38
135b	SMe	CO_2Me		39	**135j**		CN		42
135c	SMe	CO_2Me		43	**135k**		CN		40
135d	SMe	CO_2Me		41	**135l**	Me_2N	CN		51
135e	SMe	CO_2Me		34	**135m**		CN		49
135f	SMe	CO_2Me		30	**135n**		CN		51
135g	SMe	CO_2Me		46	**135o**		CN		47
135h	SMe	CO_2Me		38	**135p**		CN		52

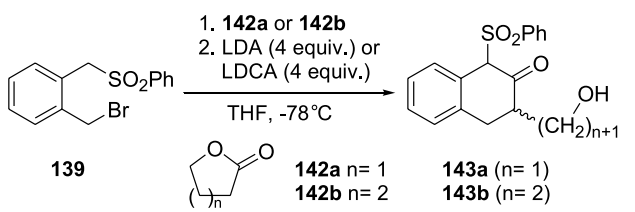


139

140a R= Me (80%)
140b R= Et (92%)
140c R= $CH_2CH(OEt)_2$ (78%)
140d R= $CH_2CH{=}CH_2$ (82%)
140e R= CH_2CH_2 (87%)

141 R= Et (78%)

Scheme 21. Synthesis of 2-tetralones by annulation of bromosulfone **139** and malonate anion derivatives.

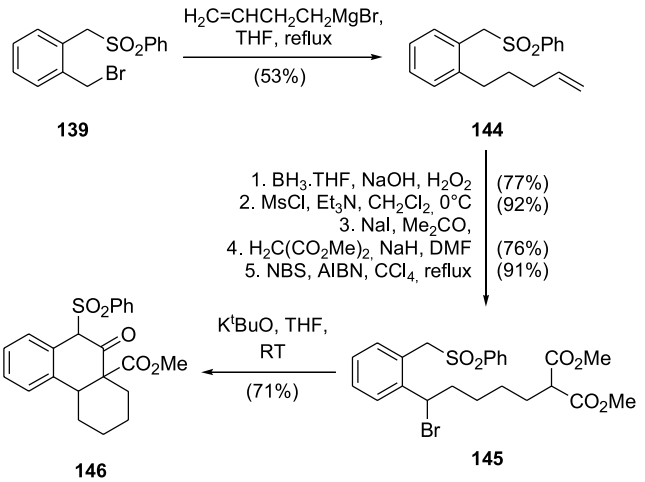


139

142a n= 1
142b n= 2

143a (n= 1)
143b (n= 2)

Scheme 22. Synthesis of 2-tetralones **143a**,**b** by annulation of bromosulfone **139** with deprotonated lactones **142a**,**b**.



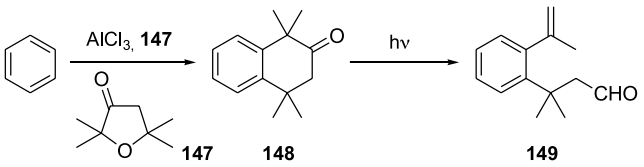
139 **144**

145

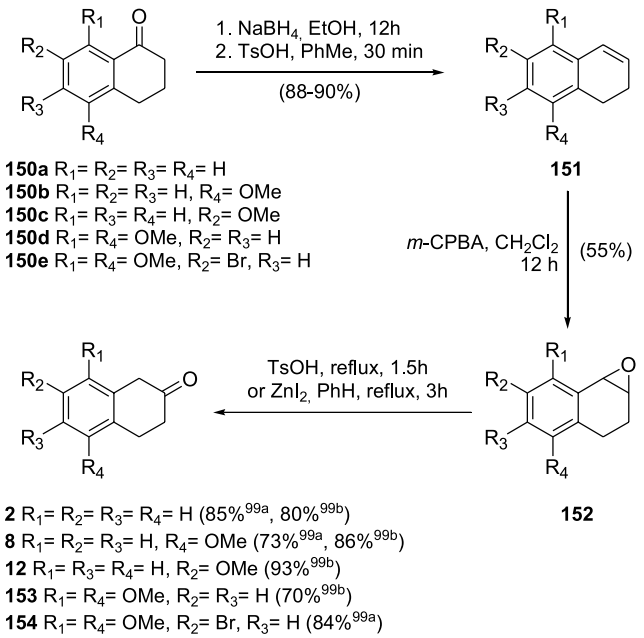
146

Scheme 23. Preparation of 2-tetralone **146** from bromosulfone **139** by a double annulation reaction.

substrates, are thus avoided. Another aspect that turns more useful this approach, is the possibility to synthesize 2-tetralones with electron-withdrawing groups attached to the aromatic ring.



Scheme 24. Synthesis and photodegradation of 2-tetralone **148**.



Scheme 25. Synthesis of 2-tetralones employing $NaBH_4$-generated 1-tetralols as intermediates.

3.1. 1,2-Carbonyl transposition of 1-tetralones

Being a key function in organic synthesis, a number of methods exist for the transposition of a carbonyl group in sequences ranging from 3 to 10 steps.[96] The 1,2-carbonyl transposition of 1-tetralones is one of the two most frequently employed methods for the elaboration of 2-tetralones from precursors having an already preformed tetraline ring system.[97] This strategy takes advantage of the ready availability of polysubstituted 1-tetralones. Several techniques to achieve the 1,2-transposition have been developed during the last decades; the most successfully employed ones and those with a more general scope, will be covered here.

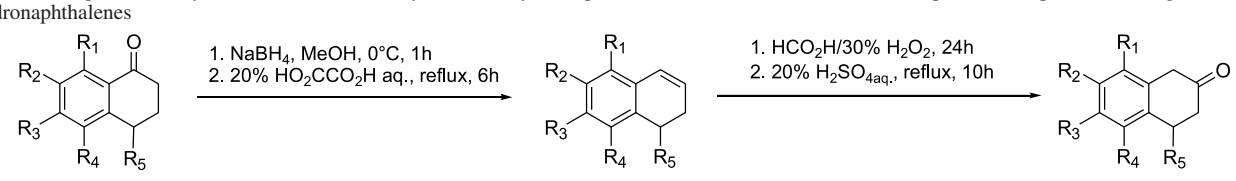
3.1.1. Carbonyl transposition by rearrangement of epoxides. The rearrangement of epoxides to ketones has been repeatedly used in organic synthesis.[98] The first reports on the use of epoxide rearrangements in the synthesis of 2-tetralones date from the 1940s,[13] where simple oxiranes derived from the inexpensive 1-tetralones were rearranged in good yields to 2-tetralones. However, several improvements were achieved during the last decades and the scope of the reaction was widened, making this a very useful and efficient methodology, especially for the selective preparation of 1- and 3-substituted 2-tetralones.

There are several ways to convert 1-tetralones into the respective epoxides and the most frequently used method is the epoxidation of an olefin, generated by dehydration of the corresponding 1-tetralol. The requisite alcohol, in turn, can be easily obtained by direct hydride reduction or by addition of an alkyl- or aryl Grignard (or organolithium) reagent to the carbonyl group of the starting 1-tetralone. The reaction sequence exploits the enhanced propensity of benzylic alcohols, compared to their aliphatic counterparts, to undergo acid-catalyzed dehydration.

Several 2-tetralones unsubstituted on C-1 were prepared from 1-tetralones **150a–e** through the intermediacy of the corresponding 1-tetralols, conveniently synthesized by $NaBH_4$ reduction of the 1-tetralones. After dehydration of the 1-tetralols with *p*-TsOH,[48a] the resulting olefins **151** were transformed into the corresponding epoxides **152** and then isomerized to the respective 2-tetralones **2**, **8**, **12**, **153** and **154** in good yields under acid catalysis of TsOH or ZnI_2 (Scheme 25).[99]

A slightly different procedure, involving oxalic acid for the

Table 6. Examples of the synthesis of 2-tetralones by 1,2-carbonyl transposition of the related 1-tetralones via epoxidation-apoxide rearrangement of 3,4-dihydronaphthalenes

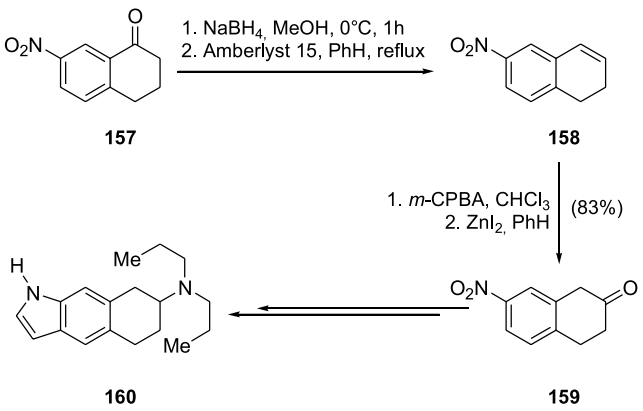


Entry no.	1-Tetralone	2-Tetralone	R_1	R_2	R_3	R_4	R_5	Yield (%)	Reference
1	**150c**	**12**	H	OMe	H	H	H	76	100
2	**150f**	**15**	OMe	H	H	H	H	93	100
3	**150g**	**156a**	H	H	H	H	Me	75	100
4	**150h**	**61**	H	H	H	H	Ph	71	100
5	**150i**	**14**	H	H	H	Me	H	74	100
								—[a]	46c
6	**150j**	**156b**	H	H	H	Ph	H	78	100
7	**150k**	**156c**	H	H	H	Me	Me	73	100
								74	46c
8	**150l**	**156d**	Me	H	Me	H	H	—[a]	46c

[a] Product yields were not informed.

dehydration of the 1-tetralol intermediate to **155** and the use of HCO_2H/H_2O_2 reagent as oxidant for the preparation of several 2-tetralones in good yields (Table 6) was also reported.[100]

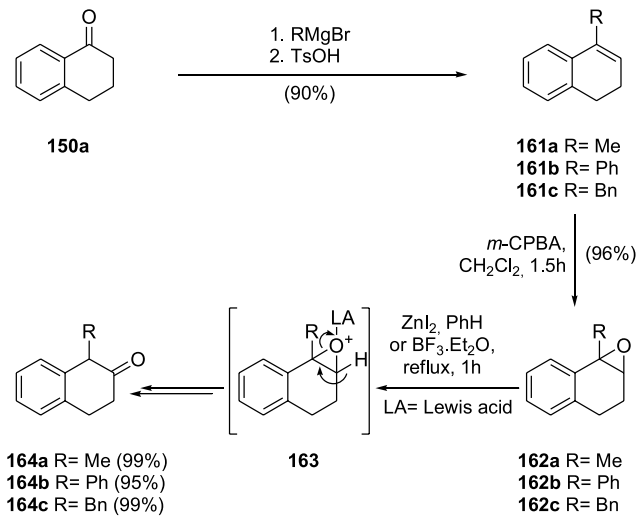
Several other acids were employed to catalyze the dehydration of the 1-tetralol precursors.[101] Thus, Amberlyst 15 was used for dehydration of the 1-tetralol derivative of 7-nitro-1-tetralone **157**, in the synthesis of 7-nitro-2-tetralone **159**, which occurred in 74% yield via dihydronaphthalene **158** (Scheme 26).[101a] Compound **159** was employed as key intermediate during the synthesis of *N*,*N*-di-*n*-propyl- 5,6,7,8- tetrahydro-benz[*f*]indol-7-amine **160**, an interesting dopaminergic agonist.[101a]



Scheme 26. Synthesis of 7-nitro-2-tetralone by 1,2-carbonyl transposition of the related 1-tetralone **157**.

Three different 1-substituted 2-tetralones (**164a**–**c**) were obtained by selective acid-catalyzed isomerization of 1-organyl-1,2-epoxytetralines **162a**–**c**.[102]

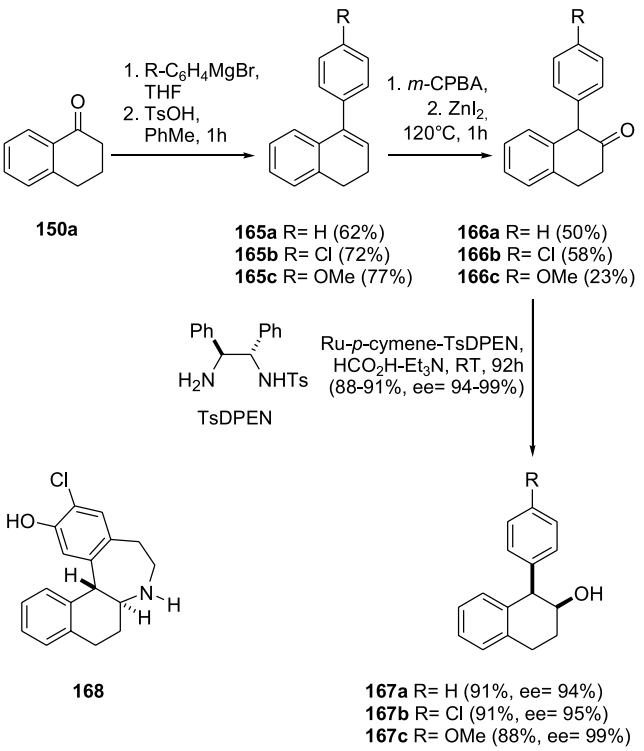
Coordination of the oxygen atom of the oxirane with the Lewis acid (**163**) is necessary for the reaction to take place. The olefinic precursors **161a**–**c** were obtained by dehydration of the tertiary alcohols generated by the attack of Grignard reagents to the 1-tetralone **150a** (Scheme 27).



Scheme 27. Synthesis of 2-tetralones employing epoxytetralines as intermediates.

The authors used $BF_3{\cdot}Et_2O$ and ZnI_2[101a] to perform the isomerization, with no relevant difference in yields.

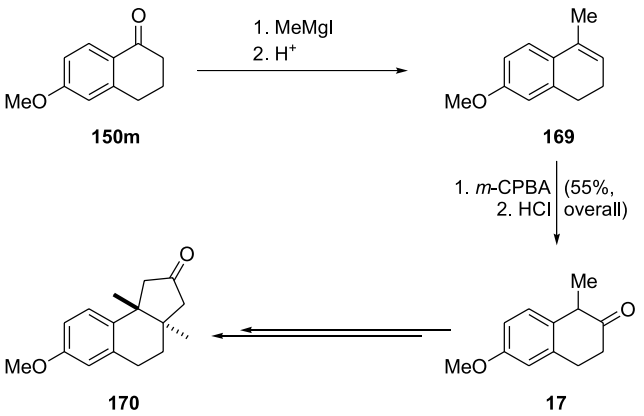
1-Aryl-2-tetralones **166a**–**c**, prepared by ZnI_2-assisted epoxide isomerization, have been employed for the dynamic kinetic resolution-asymmetric transfer hydrogenation to yield chiral 1-aryl-2-tetralols **167a**–**c**. The oxiranes were prepared by epoxidation of 3,4-dihydronaphthalene derivatives **165a**–**c** and the methodology was considered relevant for the synthesis of the benzodiazepine type dopamine D_1 agonist Sch-39166, **168** (Scheme 28).[103] The use of 1,2-diols and their monoester derivatives instead of the related epoxide were explored, with somewhat better results for substituted tetralones.[102] This variant of 1,2-carbonyl transposition will be discussed below (Section 3.1.6).



Scheme 28.

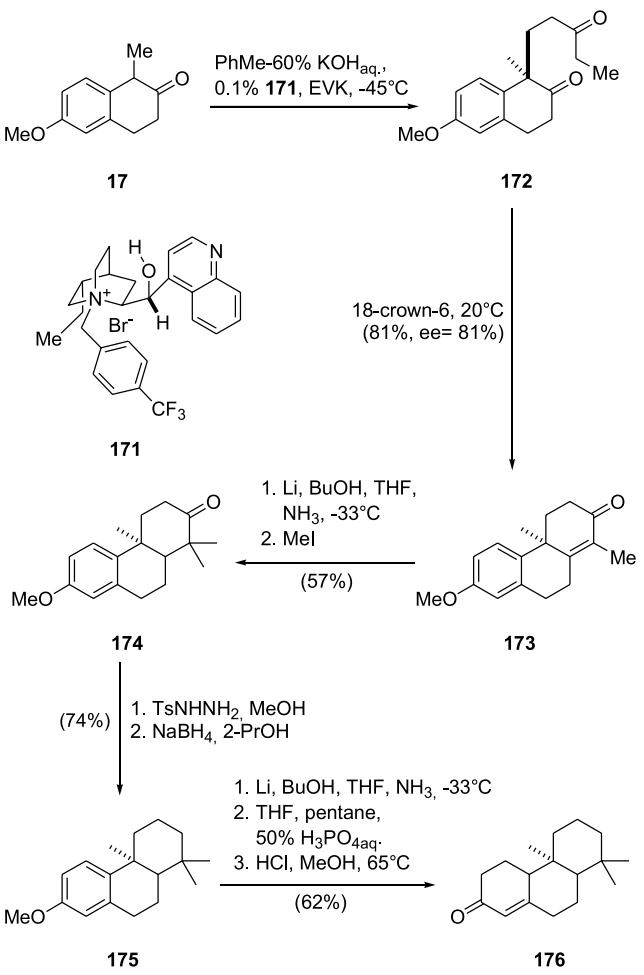
Alternatively, indium(III) chloride catalysis[104] and the ion exchange resin Dowex-50W[105] were used to promote the rearrangement of epoxides. For example, when the epoxide **162a** was stirred with a suspension of $InCl_3$ in THF at room temperature for 45 min, 1-methyl-2-tetralone **164a** was obtained in 87% yield.[104]

During a study of the synthesis of tetracyclic triterpenes, 6-methoxy-1-methyl-2-tetralone **17** was accessed in 55% yield using a similar alkylative transposition procedure from 1-tetralone **150m**. This was done through the intermediacy of **169**, employing HCl to effect the epoxide rearrangement (Scheme 29).[106] Tetralone **17** was recently employed for a study of the asymmetric alkylation of α-aryl substituted carbonyl compounds employing chiral phase transfer catalysts.[107] When mono perphthalic acid was used instead of *m*-CPBA for the epoxidation step, the yield was unsatisfactory (16%). In this sequence, the epoxide intermediate was not isolated and the 2-tetralone **17** was



Scheme 29. Synthesis of 6-methoxy-1-methyl-2-tetralone **17** employing the *m*-CPBA-mediated 1,2-carbonyl transposition of **169**.

used directly for the preparation of the B–C–*trans*-D benzindanone **170**, a potential intermediate for the synthesis of triterpenes of the lanostane–cycloartane group. The 2-tetralone **17** also served as starting material for the synthesis of podocarpenone **176**, as shown in Scheme 30. Robinson annulation of **17** with ethyl vinyl ketone (EVK) under phase transfer catalysis of the dihydrocinchoninium derivative **171** gave tricyclic compound **173** through the intermediacy of 1,5-diketone **172**. Reductive alkylation of **173**, followed by carbonyl desoxygenation of **174** through

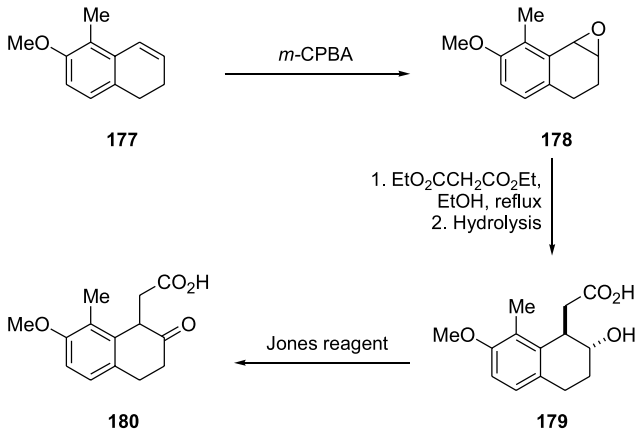


Scheme 30. Enantioselective synthesis of podocarpenone **176** from 2-tetralone **17**.

the corresponding tosylhydrazone furnished aromatic intermediate **175**; in turn, this was subjected to Birch reduction with lithium in liquid ammonia, and final conjugation of the double bond with the carbonyl.

The oxidation described in Scheme 27 was also performed using peroxyacetamidic acid (PAA) instead of *m*-CPBA, during 24 h,[108] furnishing 6-methoxy-1-methyl-2-tetralone **17** in 68% yield. PAA was prepared in situ by reacting acetonitrile, 30% H_2O_2, and $KHCO_3$ (pH 7.5).

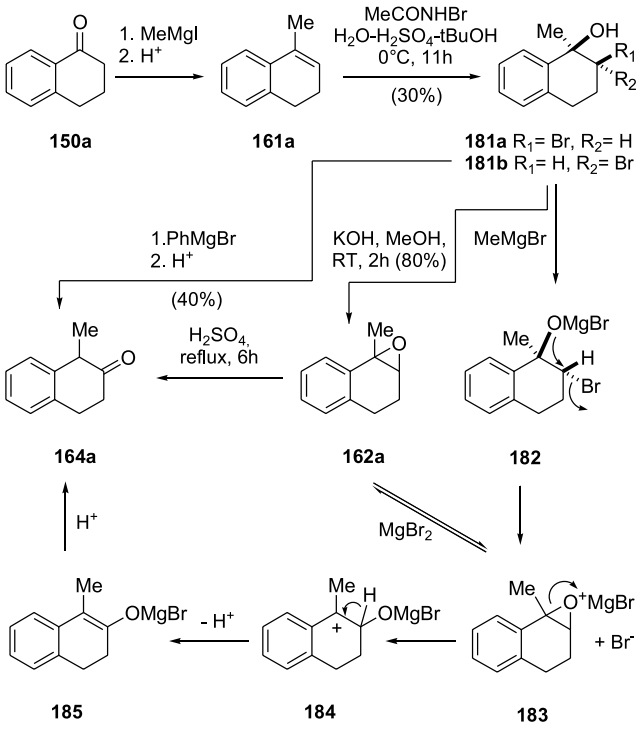
A variation on the epoxide strategy leading to 1-substituted 2-tetralones from the related 1-tetralones was disclosed by Chatterjee and co-workers.[108b] Analogous to other syntheses, their protocol involved reduction of the 1-tetralone, dehydration of the resulting 1-tetralol to the corresponding 3,4-dihydronaphthalene **177** and epoxidation of the latter to **178**. However, instead of epoxide rearrangement, the epoxidation stage was followed by nucleophilic ring opening of the oxirane ring with malonate derivatives in refluxing anhydrous ethanol. This furnished *cis* or *trans* lactones (or hydroxyacids such as **179**) or mixtures of both. Finally, Jones oxidation of the hydroxyacids/lactones provided 1-substituted 2-tetralone derivatives such as **180**, as shown in Scheme 31.



Scheme 31. Synthesis of 1-substituted 2-tetralones by ring opening of epoxides.

The epoxide **162a**, was also prepared by KOH treatment of *trans*-2-bromo-1-methyl-1-tetralol **181b**, that was obtained by hydrobromination of 1-methyl-3,4-dihydronaphthalene **161a**.[109] This procedure was used to convert 1-tetralone **150a** into 1-methyl-2-tetralone **164a**.[110]

When the bromohydrin **181b** was treated with PhMgBr as base, a rearrangement took place, converting directly the 1-methyl-1-tetralol **181b** into 1-methyl-2-tetralone **164a**, in 40% yield (Scheme 32). This was explained as being a consequence of the formation of an oxonium ion (**183**) upon nucleophilic attack of the halomagnesium derivative (**184**) to the carbon atom supporting the bromine atom, followed by its rearrangement through internal displacement to **184** and the related enolate **185**. This reaction mechanism also explains why between **181b** and the related *cis* bromohydrin **181a**, only the *trans* bromohydrin **181b**, which is the only diastereomer capable of furnishing the oxonium



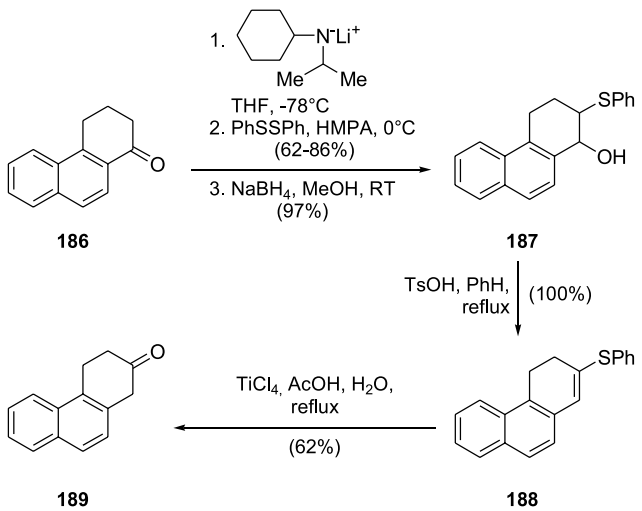
Scheme 32. Bromohydrins as epoxide precursors. Synthesis of 2-tetralone **164a** from 2-bromo-1-tetralol **181b**.

intermediate **183**, is capable of undergoing rearrangement to the 2-tetralone **164a**.

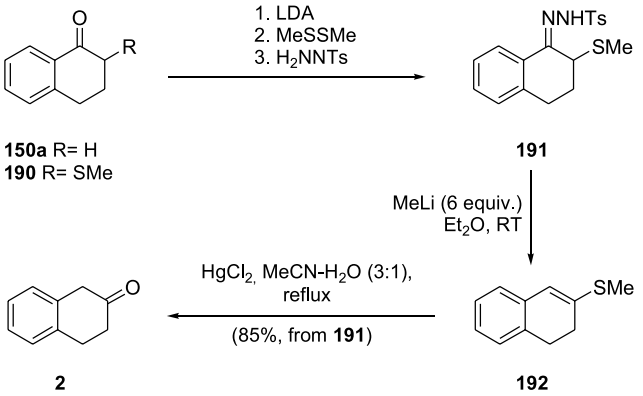
3.1.2. Carbonyl transposition via vinyl sulfides. An interesting and general procedure for carbonyl transposition has been provided by Trost and co-workers in 1975.[111]

The 1,2-carbonyl transposition was accomplished by monosulfenylation of a starting ketone, like **186**[112] followed by reduction of the resulting α-thio ketone to the corresponding β-hydroxy thioether **187** and dehydration of the alcohol so produced to give the vinyl sulfide **188**.

A final step consisting in the hydrolysis of the vinyl



Scheme 33. Synthesis of 2-tetralones employing a 1,2-carbonyl transposition with vinyl sulfides as intermediates.



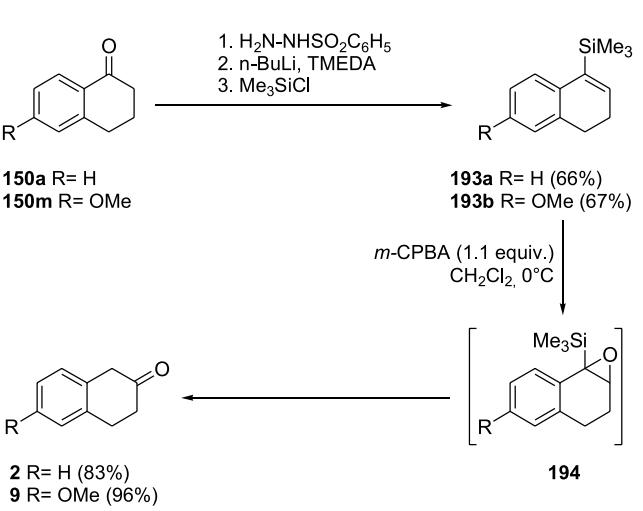
Scheme 34. Synthesis of 2-tetralone **2** by intermediacy of *p*-toluenesulfonylhydrazone **191**.

sulfide,[113] yielded the expected transposed ketone **189** in good yield (Scheme 33). A slightly different sequence for carrying out the carbonyl transposition was employed by Kano and co-workers.[114]

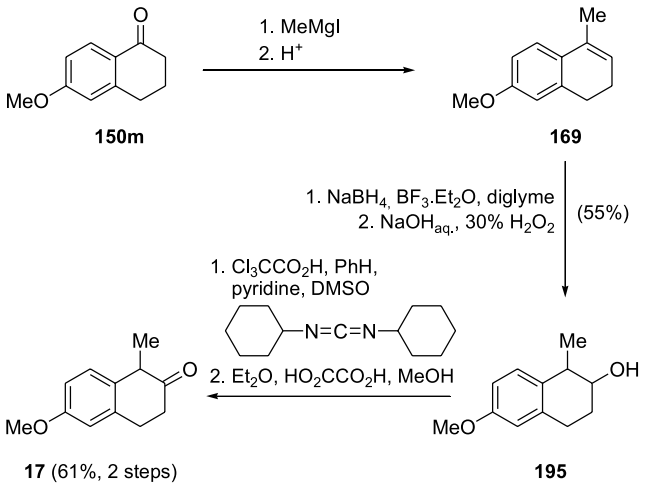
The α-thioketone **190**, derived from α-tetralone **150a**, on treatment with *p*-toluene-sulfonylhydrazide furnished *p*-toluenesulfony-lhydrazone **191**. Further reaction of **191** with methyllithium produced the vinyl sulfide **192**, which upon hydrolysis gave the β-tetralone **2** (Scheme 34).

3.1.3. Carbonyl transposition via vinylsilanes. The use of a vinylsilane as relay intermediate for the 1,2-carbonyl transposition was developed by Fristad and co-workers.[115] Vinylsilanes **193a**,**b** derived from α-tetralones **150a** and **150m**, were generated through reaction of ketone arene-sulfonyl-hydrazones with alkyllithium reagents and condensation of the resulting vinyl carbanions with chlorotrimethylsilane.[116]

They were next submitted to epoxidation, furnishing the non-isolated epoxysilanes **194**, when exposed to buffered ($NaHCO_3$) *m*-chloroperbenzoic acid in dichloromethane.[117] Contrary to other systems where carbonyl transposition requires $LiAlH_4$ reduction of the epoxide and chromic acid



Scheme 35. Synthesis of 2-tetralones by epoxidation–epoxide rearrangement of vinylsilanes.



Scheme 36. Synthesis of 6-methoxy-1-methyl-2-tetralone (**17**) by direct oxidation of 6-methoxy-1-methyl-2-tetralol **195**.

oxidation of the resulting alcohol, with concomitant desilylation, in these cases the corresponding β-tetralones **2** and **9** were accessed directly and in high yields (Scheme 35).[115] This result was attributed to the high activation of the system. The precise mechanistic details of this one-pot reaction have not been elucidated, but it is assumed that the procedure takes advantage of the properties associated with covalently bonded silicon.

3.1.4. Hydroboration–oxidation of dihydronaphthalene derivatives. Hydroboration–oxidation of trisubstituted alkenes (formed by Grignard addition to 1-tetralones and subsequent dehydration of the so produced tertiary alcohols), followed by oxidation of the resulting secondary alcohol constitutes an alternative to the epoxidation–epoxide rearrangement sequence for effecting the (alkylative)-1,2-carbonyl transposition.

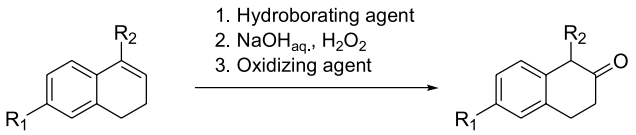
Thus, hydroboration–oxidation of 7-methoxy-4-methyl-1,2-dihydronaphthalene **169** with diborane, generated in situ from sodium borohydride and boron trifluoride and a Pfitzner–Moffatt oxidation, were employed to convert this trisubstituted olefin into **17** (61% yield from 1-tetralone **169**).[106] The reaction took place through the 6-methoxy-1-methyl-tetralin-2-ol intermediate **195** (Scheme 36). A similar approach to 2-tetralols was used by Parker during the synthesis of an inhibitor of the β-amiloid$_{1-42}$ aggregation,[118] and by Reddy and co-workers, the latter employing the chiral monoisopinocamphenyl borane for the hydroboration step.[119] Several other hydroborating reagents, such as 9-BBN and BH_3, have been reported for a similar reaction sequence,[120] and different oxidation systems have been tested for the oxidation of selected 2-tetralols. Unfortunately, CrO_3/H_2O/acetone, CrO_3/H_2O/pyridine, pyridine–chlorine complex, and the standard Oppenauer conditions, all met with failure. However, oxidation with the *N*-chlorosuccinimide–dimethyl sulfide complex provided **17**, albeit in modest yield (30%)[115] and the $Na_2Cr_2O_7/H_2SO_4$ reagent allowed the preparation of 1-organyl-2-tetralones in 53–73% yield,[120] as shown in Table 7.

A synthesis of **205**, an advanced intermediate towards triptoquinone employing the strategy of hydroboration–oxidation of dihydronaphthalene derivatives, was recently described by Shishido and co-workers. This natural product inhibits interleukin I release. As shown in Scheme 37, Claisen rearrangement of the allyl ether derivative **197** of bromophenol **196**, furnished allyl phenol **198**, which was conveniently manipulated to produce 1-tetralone **202** by a Friedel–Crafts type ring closure of intermediate **201**. The latter was produced by oxidative fission of the allyl moiety of **199** and oxidation of the resulting aldehyde **200**. Alkylation and dehydration of the tetralone furnished 1-methyl dihydronaphthalene **203**, which was hydroborated and oxidized, furnishing the expected 2-tetralol **204**. Finally, Swern oxidation of the 2-tetralol gave access to the natural product.

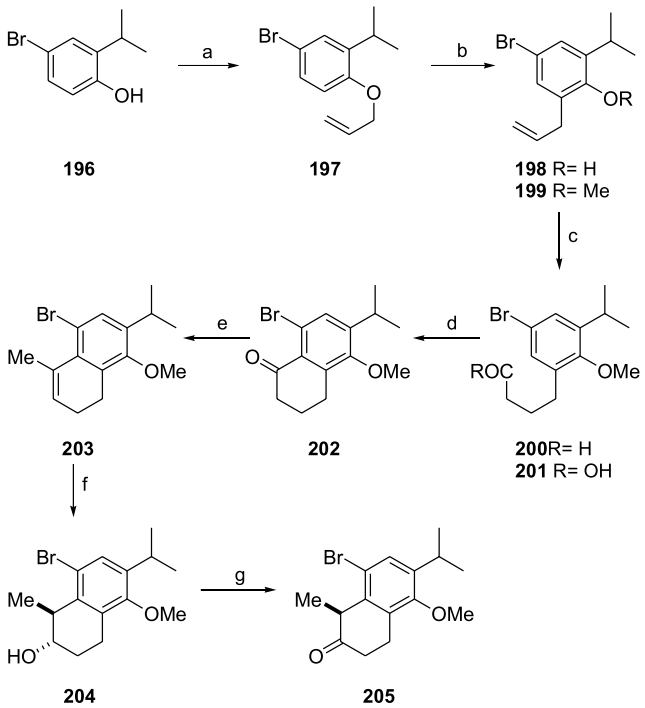
Miller and Shi reported the use of an hydroboration–oxidation strategy for the conversion of a 1,1-disubstituted 2-tetralone into a 4,4-disubstituted 2-tetralone, as depicted in Scheme 38. To this end, the starting 2-tetralone **206** was converted into dihydronaphthalene **207** by intermediacy of the related tosylhydrazone; in turn, this was submitted to an hydroboration–oxidation protocol, employing the bulky disiamyl borane reagent. Chromic oxidation of the resulting 2-tetralol **208** afforded the transposed 2-tetralone **209**.

Exposure of the 2-tetralone **209** to phosphorus pentabromide transformed the latter into 2-hydroxy-naphthalene derivative **213** by the bromoketone–phenol rearrangement. In this rearrangement, the tetralone was first α-brominated at the C-1 position, leading to compound **210**. Compound **211**, the enolic form of **210**, then favored migration of the

Table 7. Synthesis of 2-tetralones by hydroboration-oxidation of 1-organyl-3,4-dihydronaphthalenes and further oxidation of the resulting 2-tetralols



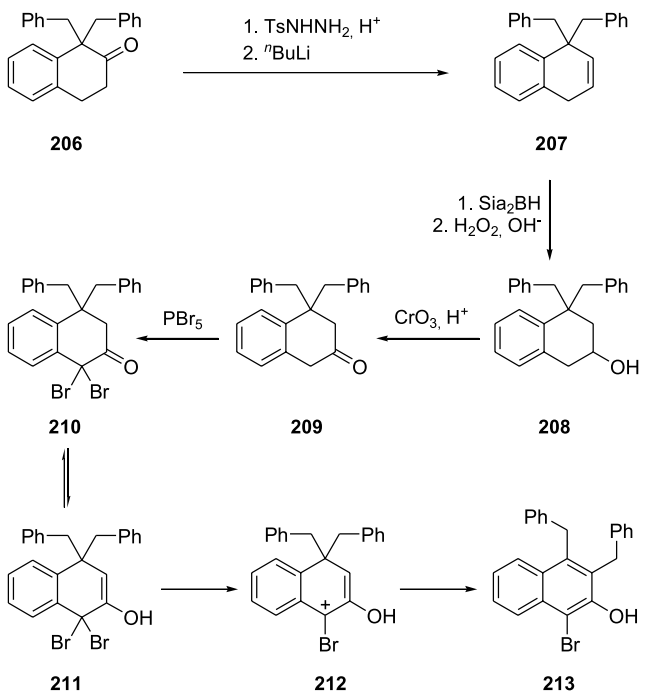
Entry no.	Hydro-borating agent	Oxidizing agent	Product	R_1	R_2	Yield (%)
1	$NaBH_4$, BF_3·Et_2O diglyme	Cl_3CCO_2H, DCC	**17**	OMe	Me	61
2	9-BBN, 0 °C→rt overnight	$K_2Cr_2O_7$, H_2SO_4, reflux, 7 h	**17**	OMe	Me	69
3	BH_3·THF	$K_2Cr_2O_7$, H_2SO_4, reflux, 7 h	**164a**	H	Me	73
4	9-BBN, 0 °C→rt overnight	$K_2Cr_2O_7$, H_2SO_4, reflux, 7 h	**164b**	H	Ph	53
5	BH_3·THF	$K_2Cr_2O_7$, H_2SO_4, reflux, 7 h	**164d**	H	Et	55
6	9-BBN, 0 °C→rt overnight	$K_2Cr_2O_7$, H_2SO_4, reflux, 7 h	**164e**	OMe	Ph	59



Scheme 37. (a) 1. $H_2C{=}CHCH_2Br$, K_2CO_3, DMF (78%); 2. NaOMe, CuI, MeOH, DMF (92%); (b) 1. 200 °C (91%); 2. Me_2SO_4, K_2CO_3, Me_2CO (99%); (c) 1. 9-BBN, CO, $LiAlH(t\text{-}BuO)_3$, HOO^- (58%); 2. H_2NSO_3H, $NaClO_2$, dioxane–H_2O (97%); (d) PPA (78%); (e) 1. MeMgI, PhH, Et_2O; 2. TsOH, PhH (88%); (f) $BH_3{\cdot}SMe_2$, HOO^- (87%); (g) $(COCl)_2$, DMSO, Et_3N (90%).

benzyl group through the carbocationic intermediate **212**. The rearrangement is spontaneous, since isolated dibromo tetralone **210** gives the bromonaphthol **213** on standing.[121a]

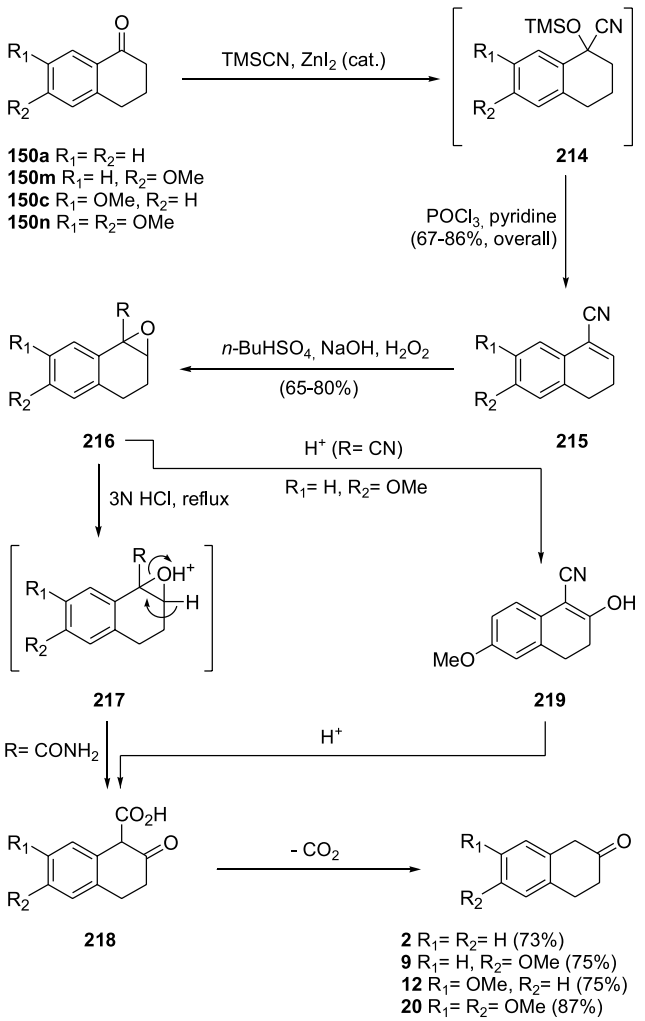
Unlike the known dienone–phenol rearrangement[121b] in which the migrating group is initially located *ortho* or *para* to the carbonyl, in this rearrangement the migrating group is originally located *meta* to the carbonyl function.



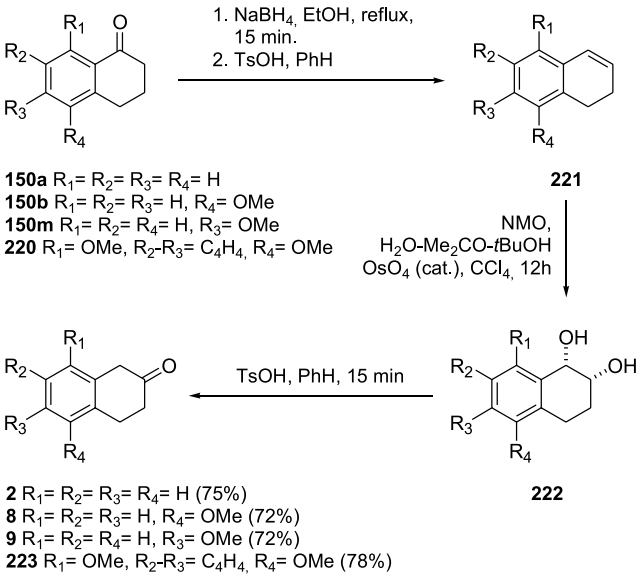
Scheme 38.

3.1.5. Carbonyl transposition via acid-catalyzed rearrangement of epoxyamides and epoxynitriles. Epoxynitriles **216** (R=CN), have been accessed by the Strecker silylcyanation of 1-tetralones **150a**, **150c**, **150m**, and **150n**,[122] followed by elimination of the resulting tertiary silyl ethers (**214**) and phase-transfer epoxidation[123] of the thus formed α,β-unsaturated nitriles **215**.

By refluxing with 3 N HCl, rearrangement of the epoxides took place, with concomitant partial hydrolysis of the nitrile moiety to the amide, furnishing the corresponding 2-tetralones in good yields, through the corresponding epoxyamides **217** (R=$CONH_2$) as intermediates. Four different congeners (**2**, **9**, **12** and **20**) were prepared by this procedure (Scheme 39).[124] It was observed that the epoxynitriles **216** (R=CN) themselves, prepared under non-hydrolytic conditions,[125] also rearranged to the 2-tetralones, albeit in very low yields (8%), being the enol **219** the major product (25%). The overall sequence is shown in Scheme 39. Apparently, epoxidation occurs before nitrile hydrolysis, being both relatively rapid processes. In acidic media, protonation of the epoxide **217**, was followed by ring opening and proton loss; final hydrolysis leads to the



Scheme 39. Synthesis of 2-tetralones by hydrolysis of epoxyamides.



Scheme 40. Preparation of 2-tetralones by selective partial dehydration of 1,2-diols **222**.

β-ketoacid **218**, which readily decarboxylates in situ to the corresponding tetralone. The protocol requires the development of a positive charge at the benzylic carbon which bears the nitrile or amide group (**217**);[126] this probably explains why the sequence does not seem to be effective with compounds carrying electron withdrawing groups on C-6, located *para* to C-1.

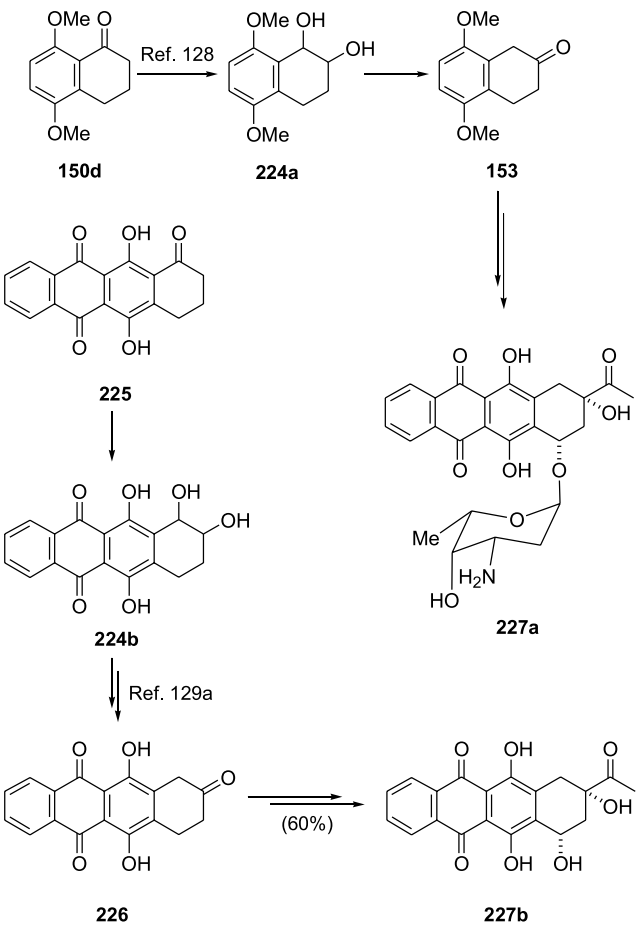
3.1.6. Carbonyl transposition by selective dehydration of 1,2-diols derived from 1-tetralones. This strategy takes advantage of the relative ease of benzylic alcohols to dehydrate under acid catalysis. Several 3,4-dihydronaphthalenes **221** were synthesized in a sequence starting with 1-tetralones **150a**, **150b**, **150m** and **220** and involving dehydration of the benzylic alcohol moiety of their corresponding 1-tetralols.

This was followed by dihydroxylation with a catalytic amount of osmium tetraoxide in the presence of *N*-methylmorpholine–*N*-oxide[127] or trimethylamine *N*-oxide as stoichiometric co-oxidants, furnishing diols **222**.[111] The diols were rearranged with *p*-toluenesulfonic acid in benzene to the transposed ketones in overall yields of approximately 70% (Scheme 40).

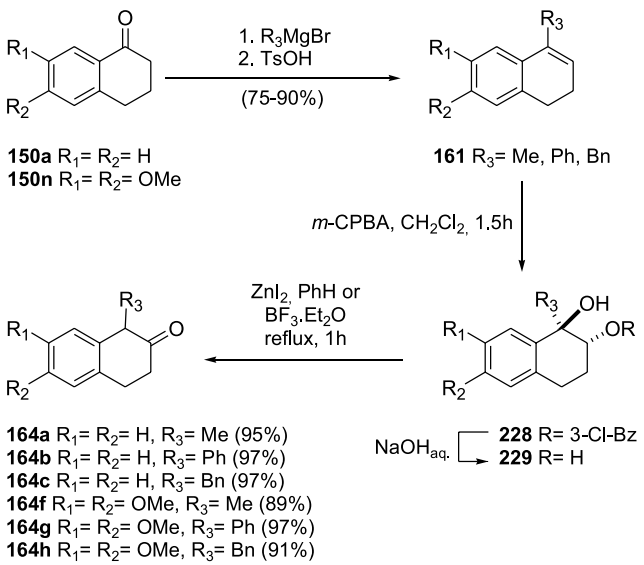
The strategy described in Scheme 40 was used during the total synthesis of idarubicine **227a**,[128] an antileukemic glycoside, and (±)-daunomycinone **227b**,[129] a potent antibiotic with anticancer activity.

In these syntheses, the 2-tetralone intermediates **153** and **226**, generated from the respective 1-tetralones **150d** and **225** through diols **224a** and **224b**, were involved (Scheme 41).

Despite previous reports indicating that the hydroxylation of dihydronaphthalenes with peracids often gives complex product mixtures as well as overoxidation products,[130] the sequence described in Scheme 40 was performed by several other reagents, such as the *m*-CPBA/NaOH reagent combination, for the generation of 1,2-diols **229** from their glycol monobenzoate intermediates **228**, and with ZnI_2 or BF_3 for their dehydration to 2-tetralones (Scheme 42).[102]



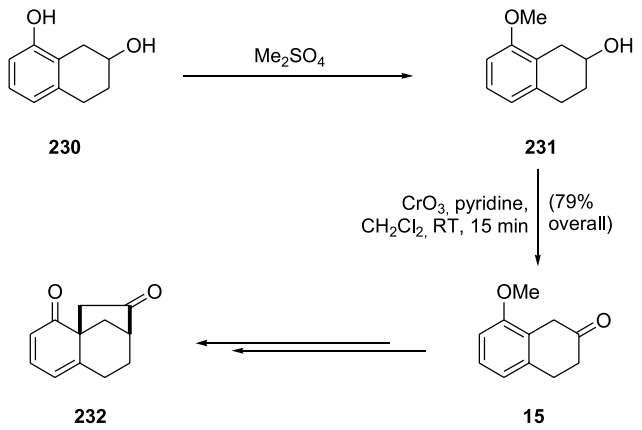
Scheme 41. Examples of the synthesis and use of 2-tetralones **153** and **226** employing the strategy of dehydration of 1,2-diols **224a** and **224b**.



Scheme 42. Synthesis of 1-organyl-2-tetralones **164a–c** and **164f–h** by 1,2-carbonyl transposition, through the intermediacy of 1,2-diols **229**.

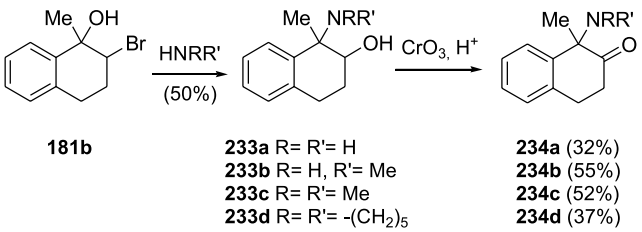
3.2. Direct oxidation of 2-tetralols

The CrO_3/pyridine/CH_2Cl_2 system was employed for the preparation of 8-methoxy-2-tetralone **15** from 8-methoxy-2-tetralol (**231**), in 85% yield.[131] The 2-tetralone **15** so obtained was used in the synthesis of the tricyclic dione **232**, a suitable intermediate for the preparation of tetracyclic terpenoids following the BC+D+A approach (Scheme 43). The partially methylated tetralol **231** is easily accessed by selective Williamson etherification of **230**.



Scheme 43. Synthesis of 8-methoxy-2-tetralone **15** by direct oxidation of the corresponding 8-methoxy-2-tetralol **231**.

1,1-Disubstituted 2-tetralols **233a–d**, accessed by regioselective ring opening of the epoxide formed by base treatment of bromohydrin **181b**, were converted to the respective 1,1-diorganyl-2-tetralones **234a–d** in modest yields, with Jones reagent (Scheme 44).[48e]

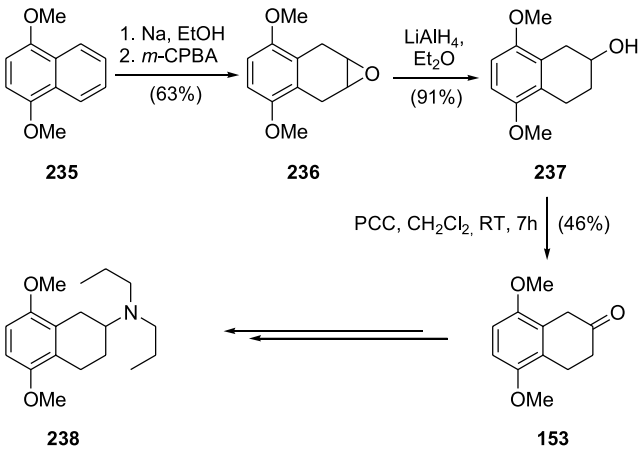


Scheme 44. Synthesis of 1-methyl-1-amino-2-tetralones **234a–d** from bromohydrin **181b** by epoxide formation, nucleophilic epoxide ring opening and direct oxidation of 1,1-disubstituted 2-tetralols **233a–d**.

The 1-methyl-1-amino-2-tetralones were synthesized to evaluate their hypnotic and locomotive properties in mice. They proved to be devoid of hypnotic activity, but showed to depress spontaneous locomotive activity.

The synthesis of 5,8-dimethoxy-2-(di-*n*-propylamino) tetralin **238**, a dopamine agonist (Scheme 45) demanded the preparation of 5,8-dimethoxy-2-tetralone **153**. This was effected in 46% yield through the oxidation of 5,8-dimethoxy-2-tetralol **237** with PCC in dichloromethane.[132]

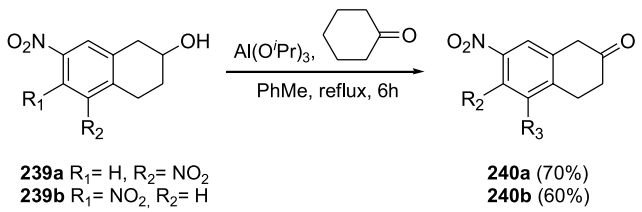
The intermediate 2-tetralol **237** was conveniently accessed by a three-step sequence involving partial reduction of 5,8-dimethoxynaphthalene **235**, followed by epoxidation of the resulting alkene and reduction of the oxirane group (**236**) with lithium aluminum hydride in ether. The 2-tetralone **153**



Scheme 45. 5,8-Dimethoxy-2-tetralone **153** via direct oxidation of 5,8-dimethoxy-2-tetralol.

was also employed for a study on anthracyclinone derivatives.[133]

The Oppenauer oxidation was employed for the preparation of 6,7- and 5,7-dinitro-2-tetralones (**240a**,**b**) from the respective 2-tetralols **239a**,**b**.[134] The 2-tetralones were obtained in good yields after refluxing the 2-tetralols with $Al(O^iPr)_3$ in the presence of a large excess of cyclohexanone during 6 h (Scheme 46). The oxidation of 2-tetralols was also discussed in Section 3.1.4.

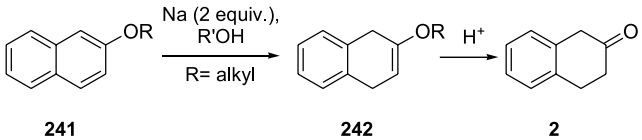


Scheme 46. Synthesis of 2-tetralones **240** by Oppenauer oxidation of 2-tetralols **239**.

3.3. Reduction of 2-alkoxynaphthalenes and 2-naphthols

3.3.1. Reduction of naphthalene derivatives with sodium in alcohol (Na/ROH). The Na/ROH reduction of 2-alkoxynaphthalenes, first described 60 years ago by Cornforth and co-workers,[12,15c] remains as one of the most important methodologies used for the syntheses of 2-tetralones. Several minor changes in the original reaction conditions have been made in order to optimize the transformation and adjust conditions to specific substrates.[20,21,46b,49d,135–137]

Basically, the procedure consists in reacting an alcoholic (ethanol, 2-propanol, isoamyl alcohol, etc.) solution of 2-alkoxynaphthalene (**241**) with 2 equiv. of sodium metal; submission of the resulting enol-ether **242** to acid hydrolysis yields the 2-tetralone product (Scheme 47).

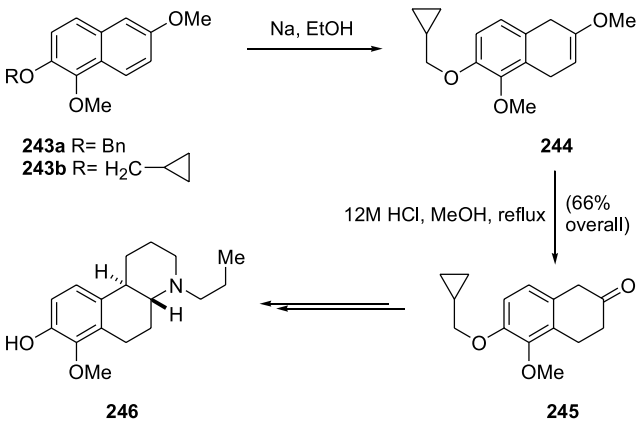


Scheme 47. Synthesis of 2-tetralone by Na/ROH reduction of 2-alkoxynaphthalenes.

The required alkoxynaphthalenes are not always easily available. Sometimes, they have been accessed from the related bromonaphthalenes employing an Ullman type coupling reaction with sodium methoxide, from sulfonic acids, and even from other 2-tetralones. It has been observed that the presence of a methoxy group in the α-position of one ring enhanced the reduction of the other ring, while the presence of the same substituent on the β-position enhanced the reduction of the ring the substituent was attached to. Amino and hydroxy groups display the same effects.

The Na/ROH reduction of alkoxynaphthalenes was employed for the preparation of a large number of 2-tetralones, precursors of compounds with biological and pharmacological activities,[22,38,49d,138–141] including dopaminergic agonists,[49d] benzoquinolines,[138] antiulcer agents,[38] radiolabelled compounds[140] and (−)-morphine.[141]

The 2-tetralone **245**, a key intermediate in the synthesis of *trans*-8-hydroxy-7-methoxy-4-*n*-propyl-1,2,3,4,4a,5,6,10b-octahydro-benzo[*f*]quinoline **246**, was also prepared by this method.[138] Attempts to effect the reduction of 2,5-dimethoxy-6-(benzyloxy)naphthalene (**243a**) to 5-methoxy-6-(benzyloxy)-2-tetralone, resulted in concomitant cleavage of the benzyl ether moiety. However, when the benzyl protecting group was replaced by a cyclopropylmethyl moiety, as in **243b**, the 2-tetralone enol ether derivative **244** was obtained, furnishing **245** in 66% overall yield after acid hydrolysis (Scheme 48).

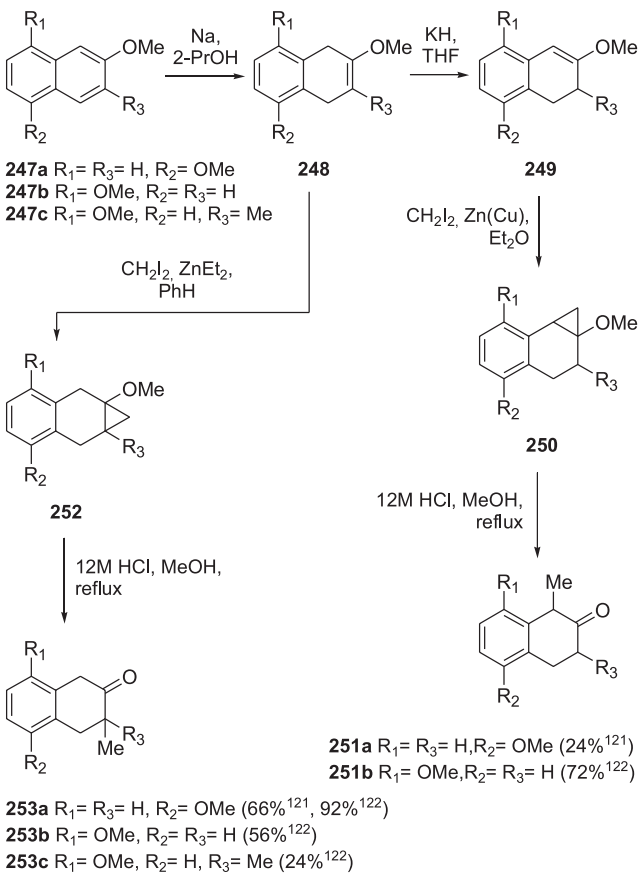


Scheme 48. Synthesis of 2-tetralone **245** by the Na/EtOH reduction of dimethoxynaphthalene **244**.

The naphthol ether reduction strategy was also considered very important to solve the problem of poor selectivity of the methods involving alkylation of 2-tetralones, for the preparation of 1- and 3-substituted 2-tetralones.[75]

While it is easy to prepare C-1[142] substituted 2-tetralones, C-3 substituted 2-tetralones are more difficult to access. The main synthetic route towards C-3-alkyl-substituted 2-tetralones involve specific carboxylation on C-3 with magnesium methyl carbonate, followed by alkylation of the resulting ketoester and final hydrolysis and decarboxylation;[143] however, this sequence is only moderately efficient. An alternative consists in protecting the more reactive C-1, alkylating the less acidic C-3 position and finally removing the protecting group. Unfortunately, introduction and removal of the protecting group add two steps to the route and reduces its efficiency in approximately 50%.[144] The formation of the dianion of 1-carboxymethyl-2-tetralones has been disclosed as another alternative that permits the efficient alkylation of C-3,[38] and condensation of 2-(phenylsulfonylmethyl)benzyl bromide **139** with the anion of monosubstituted malonates regioselectively provided C-3 substituted 2-tetralones, as discussed in Section 2.7,[145] offering additional possibilities.

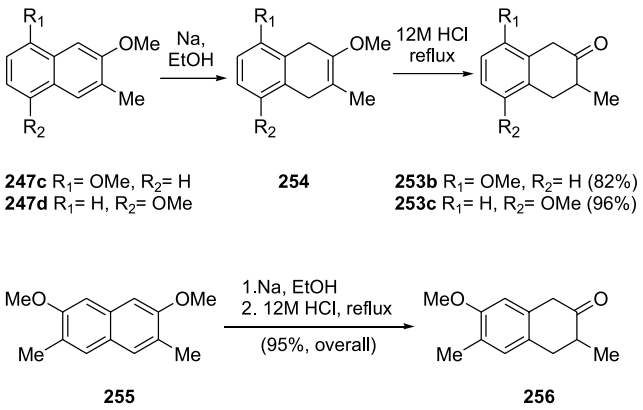
On the other hand, when the enol ether intermediate **248** was isomerized with strong base to **249** before the cyclopropanation step to **250**, it was possible to obtain 1-methyl-5-methoxy-2-tetralones **251a** selectively and in good yield (Scheme 49).



Scheme 49. Selective preparation of 1-methyl- and 3-methyl-2-tetralones **251a**,**b** and **253a**–**c** by the Na/ROH reduction of naphthalene derivatives **247a**–**c**.

When the solvent was changed to ethanol, and 3-methyl dimethoxynaphthalenes **247c** and **247d** were submitted to the dissolving-metal reduction, 3-methyl-2-tetralones **253b** and **253c** were prepared in good yields. Enol ethers **254** were intermediates of this transformation (Scheme 50).[146] By using the sodium in alcohol reduction of the symmetrical naphthalene **255**, the 7-methoxy-3,6-dimethyl-2-tetralone **256** was also successfully prepared, in 95% yield (Scheme 50).[148]

Exhaustive studies on the regioselective preparation of C-3 substituted 2-tetralones through the reduction of dimethoxynaphthalenes **247a**–**c** with Na/ROH have been

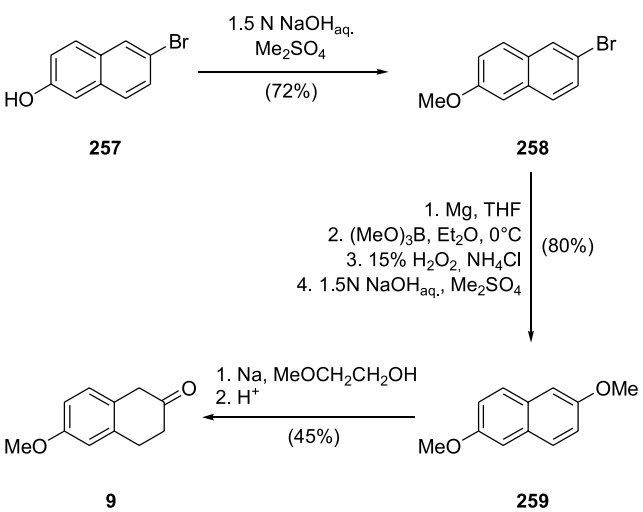


Scheme 50. Synthesis of 3-methyl-2-tetralones by reduction of naphthalene derivatives with Na/EtOH.

described.[145,146] Several experimental conditions were tested and the authors concluded that it was possible to control the regiochemistry of the reaction with the appropriate choice of the solvent system, which avoids the simultaneous formation of **248** and **249**.

Thus, 3-methyl-5-methoxy-2-tetralone (**253a**) was successfully obtained when the easily available 1,6-dimethoxy naphthalene **247a** was submitted to reduction with the Na/2-PrOH reagent system to give almost exclusively **248**. This was followed by a Simmons–Smith cyclopropanation to **252** with $CH_2I_2/Zn(Et)_2$ and an acid-catalyzed cyclopropane ring opening with MeOH/HCl.[147]

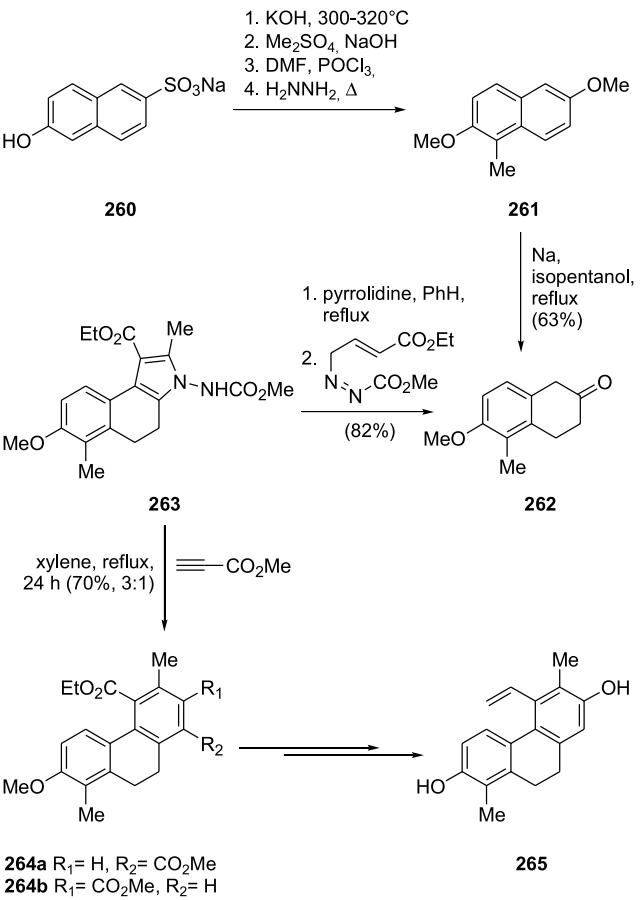
The Na/2-methoxyethanol system served to synthesize 6-methoxy-2-tetralone **9** in 70% yield from **259**. The starting symmetrical dimethoxynaphthalene was prepared in several steps from bromonaphthol **257**, being Williamson etherification to **258** the first of them (Scheme 51).[149] The same approach was employed for the preparation of a tyrosine analog of pharmacological interest.[150]



Scheme 51. Preparation of dimethoxynaphthalene **259** and its reduction with Na/2-methoxyethanol to 2-tetralone **9**.

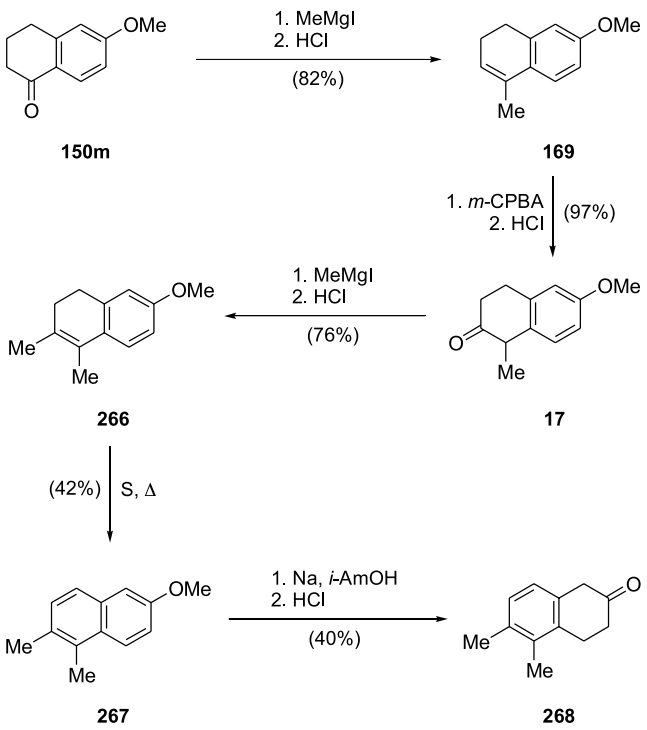
During their studies on the bio-reduction of 2-tetralones with Baker's yeast, Speranza and co-workers[151] synthesized several 2-tetralones employing the Na/EtOH system for the reduction of 2-methoxy-naphthalenes. Interestingly, recent publications disclosed the reverse path, reporting on the use of 2-tetralones as starting materials for the preparation of 1-substituted 2-naphthol derivatives.[152]

A further refinement of this reverse path is seen in the recent formal total synthesis of Emmotin G methyl ether from 5,8-dimethyl 2-tetralone (**153**), through its conversion into 6-methoxy-7-acetyl-1,4-dimethylnaphthalene.[153] The 2-tetralone derivative **262** was prepared in five steps and 72% overall yield from commercially available 2,6-dihydroxynaphthalene (**259**), in turn available from sodium 6-hydroxynaphthalene-2-sulfonate **260**. This compound was employed in a formal total synthesis of the cytotoxic phytoalexin juncusol (**265**), a natural product active against human nasopharynx carcinoma (Scheme 52).[154]



Scheme 52. Synthesis and use of the 2-tetralone **262** in the formal total synthesis of juncusol.

Condensation of **262** with pyrrolidine in benzene under reflux conditions, followed by reaction of the resulting enamine with ethyl 3-carbomethoxyazo-2-butenoate in THF gave pyrrole **263** in 82% yield. A Diels–Alder reaction with butyn-2-one in xylene at reflux temperature gave 70% of a 3:1 mixture of **264a** and **264b**. Functional group transformations lead to a previously synthesized juncusol precursor.[155] On the other hand, Rosowsky[46c] reported the joint use of the carbonyl transposition of a 1-tetralone (**150m**) to access a 2-tetralone intermediate (**17**) which, in turn was converted into a different 2-tetralone (**268**) by way of functionalization (**266**), aromatization (**267**) and sodium in isoamyl alcohol reduction, as shown in Scheme 53.

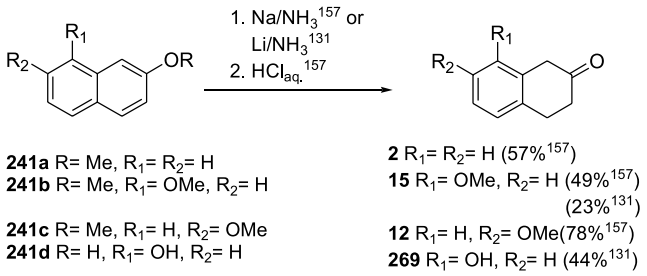


Scheme 53.

3.3.2. Reduction of naphthalene derivatives with dissolving metals in liquid ammonia (M/NH_3).

The dissolving metal reduction in liquid ammonia (Birch–Dryden reaction) has been reported as an efficient methodology for the synthesis of 2-tetralones. Similarly to the Na/ROH reduction methodology previously described, the M/NH_3 reduction of 2-naphthols and 2-methoxynaphthalenes is not new.[13,156,157]

Thus, lithium[131] and sodium[158] dissolved in NH_3 were employed for the conversion of 2-hydroxy-[131] and 2-methoxynaphtalenes (**241a–d**)[131,158a,b] into 2-tetralones **2**, **12**, **15** and **269** in reasonable to good yields (Scheme 54).



Scheme 54. Synthesis of 2-tetralones employing the M/NH_3 reduction of 2-methoxynaphthalenes and 2-naphthols.

By using the procedure described in Scheme 54, key 2-tetralones were produced and several 3-amino-2-tetralones were synthesized and biologically evaluated for their ability to selectively inhibit the membrane-bound zinc-dependent aminopeptidase-M, isolated from porcine kidney. The 1-phenethyl-3-amino-2-tetralone hydrochloride **270** and the tricyclic tetralone **271** were the most active among the tested 2-tetralones-based inhibitors (Fig. 2).[131,158]

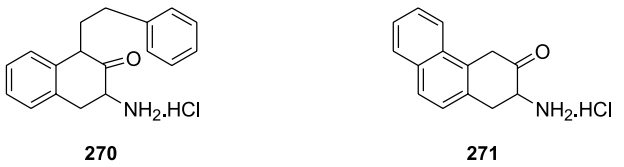
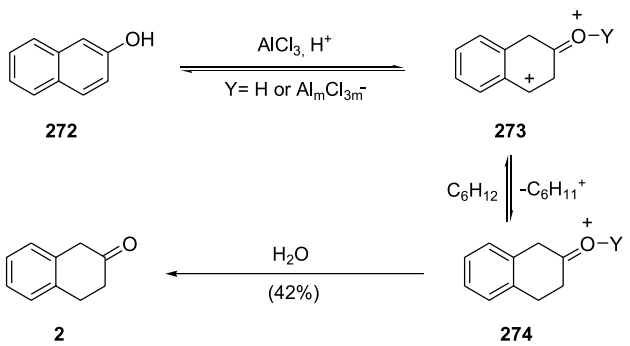


Figure 2. Structures of 3-amino-2-tetralones with potent and selective activity as inhibitors of aminopeptidase-M.

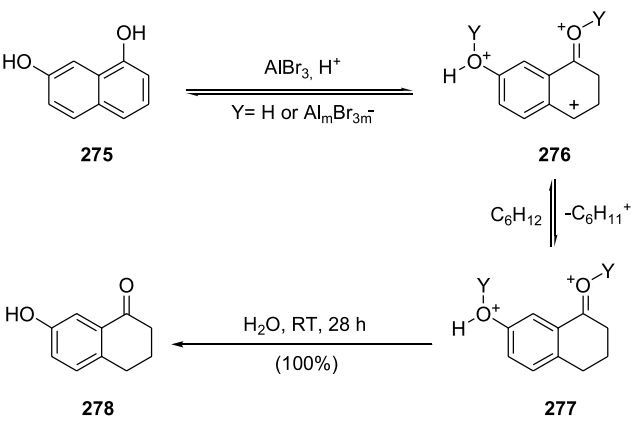
3.4. Ionic hydrogenation of 2-naphthols

2-Naphthol (**272**) was transformed into 2-tetralone **2** in 42% yield by means of an ionic hydrogenation with cyclohexane in the presence of $AlCl_3$ and HCl, as shown in Scheme 55.[158b] Compounds **273** and **274** have been postulated as reaction intermediates of this process.



Scheme 55. Ionic hydrogenation of 2-naphthol **272** with cyclohexane–$AlCl_3$. Synthesis of 2-tetralone (**2**).

The method, however, has some known limitations. For example and not unexpectedly, when 1,7-dihydroxynaphthalene **275** was submitted to the same conditions, replacing $AlCl_3$ with $AlBr_3$, 7-hydroxy-1-tetralone **278** was the only isolated product and none of **269** was observed. The tetralone **278** was formed through the intermediacy of **276** and **277** (Scheme 56). Interestingly, the thermolysis of 2-naphthol is known to produce 2-tetralone (**2**) as the major product.[159]



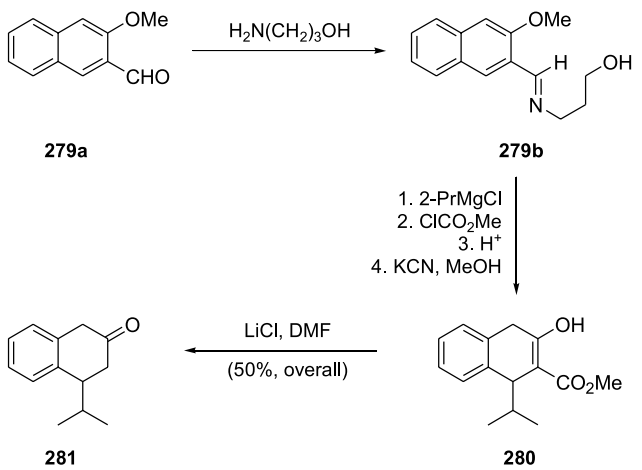
Scheme 56. Ionic hydrogenation of 7-hydroxy-1-naphthol **275** with cyclohexane/$AlBr_3$, yielding 1-tetralone **278**.

3.5. Tandem Grignard addition to 2-methoxynaphthyl imines. Synthesis of chiral 2-tetralones

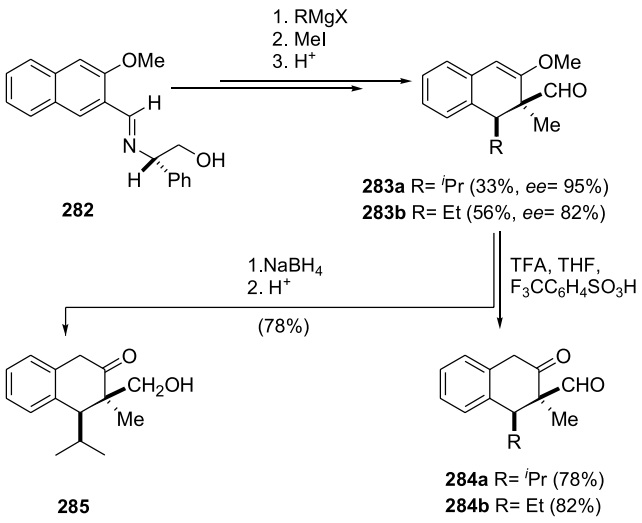
Recently, an elegant methodology that allows the preparation of 4-alkyl-, 3,4-dialkyl-, 3,4-disubstituted and 3,3,4-trisubstituted 2-tetralones with different substitution patterns, was described.[160]

The strategy involves the tandem addition of Grignard reagents to naphthalene derived imine **279** and it is suitable for the preparation of chiral 2-tetralones.

By this procedure, 4-isopropyl-2-tetralone **281** was obtained in 50% yield from **279b** (which is easily available from **279a**), being **280** the enolic form of a β-ketoester, an intermediate of this synthetic protocol (Scheme 57). When 2-PrMgCl and EtMgBr where added to the (*R*)-phenylglycinol imine **282**, chiral 3,3,4-trisubstituted 2-tetralones **284a**, **284b** and **285**, were obtained in good yields (Scheme 58).



Scheme 57. Synthesis of 2-tetralones employing the tandem addition of Grignard reagents to 2-methoxynaphthyl imines and acid hydrolysis.



Scheme 58. Synthesis of chiral 2-tetralones **284a**,**b** and **285** by tandem addition of Grignard reagents to 2-methoxynaphthyl imine **282** and subsequent α-carbonyl alkylation.

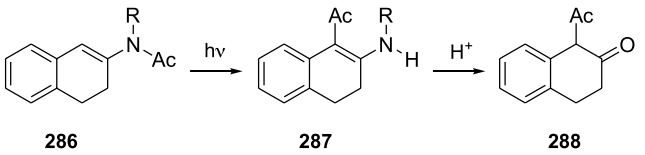
Reduction of the aldehyde moiety of intermediate **283a** prior to acid hydrolysis allowed differentiation of the carbonyl functions, as in **285**.

3.6. Photochemical reactions leading to polysubstituted 2-tetralones

Besides the intramolecular addition of silylenol ethers to PET-generated arene radical cations as a strategy for the synthesis of 2-tetralones, discussed in Section 2.8, other photochemical processes have been disclosed, the products of which are substituted 2-tetralones.

For example, Ninomiya and co-workers[161] reported that the photochemical reaction of *N*-acylenamines of aromatic systems **286** affords acyl migrated products. Thus, irradiation of *N*-acetyl enamines **286a**–**d** furnished 1-acyl-2-tetralone **288**, after acid hydrolysis of the *C*-acyl enamine intermediates **287a**–**d**. Table 8 shows the yields of the transformation employing different enamines.

Table 8. Photochemical reactions of *N*-acylenamines **286a**–**d**. Synthesis of 1-acetyl-2-tetralone **288**



Entry no.	Enamine	R	**287**, Yield (%)	**288**, Yield (%)
1	**286a**	$CH_2CH{=}CH_2$	60	70
2	**286b**	Me	67	65
3	**286c**	Bn	46	55
4	**286d**	n-C_4H_9	50	60

In another research work, a photocycloaddition reaction has been reported, by which in the presence of Lewis acids, 2-naphthols **290** add ethylene, furnishing [2+2] cycloadducts **292**, when irradiated with a high pressure mercury lamp through a Pyrex filter, at −78 °C.

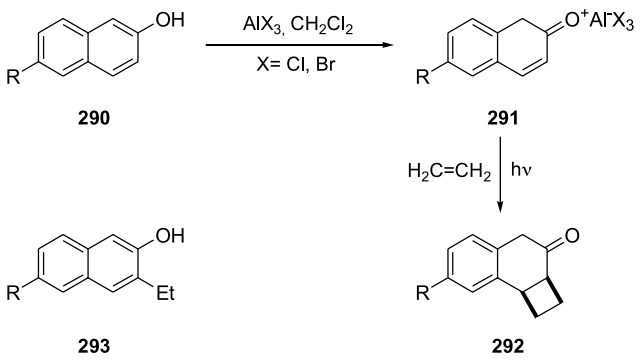
The reaction formally proceeds through the keto tautomer form (**291**) of the naphthol, formed under the assistance of the Lewis acid. Table 9 displays the results of the cycloaddition, employing different starting naphthols.[162] Interestingly, only $AlCl_3$ (5 equiv.) and $AlBr_3$ proved to be effective, and minor amounts of the ethyl substituted 2-naphthol **293** as well as 3-ethyl-2-tetralone, were isolated as side products.

4. Thallium(III)-promoted ring-expansion of 1-indanone exo-methylene derivatives

There are many publications[23,138,146] describing the preparation of several 2-tetralones from 1-indanones **294**. The reaction, originally developed by Taylor and co-workers[163] involves an initial Wittig reaction with $Ph_3PCH_3^+Br^-$ on the indanones, which yields the exocyclic methylene derivatives **295**.

The subsequent ring expansion/oxidation with $Tl(NO_3)_3$ in

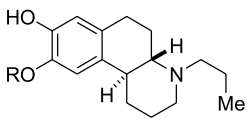
Table 9. Photoreaction of 2-naphthols with ethylene under the assistance of Lewis acids



Entry no.	R	Lewis acid	Yield (%)
1	H	$AlCl_3$	70
2	OH	$AlCl_3$	49
3	OMe	$AlCl_3$	66
4	Br	$AlCl_3$	68
5	CO_2Me	$AlCl_3$	68
6	H	$AlBr_3$	63

MeOH/$CHCl_3$ furnishes the corresponding 2-tetralones (**298**) in reasonable to good yields (Table 10). The use of a mixture of methanol and trimethyl orthoformate as solvent leads to the formation of the dimethylketal of the 2-tetralone product, from which the ketone can be obtained by acid hydrolysis, while the use of methanol alone as solvent conduces directly to the 2-tetralone. The starting indanones are easily available in high yield by means of short synthetic sequences.[164]

The protocol has been employed for the preparation of a differentially protected 2-tetralone, which served as an intermediate for the synthesis of aminotetraline derivative **300a**, a catechol *O*-methyltransferase metabolite (Fig. 3). This compound when evaluated in the cat cardioaccelerator nerve assay showed 50% inhibition at a dose of 300 μg/kg, 1000 times less potent than the related catechol **300b**.[118a]



300a R= Me
300b R= H

Figure 3.

The overall transformation, depicted in Scheme 59, is initiated by an oxythallation of the double bond of the exo-methylene derivative **295**, followed by a 1,2-rearrangement of the aryl group, as shown in the conversion of **296** to **297**; the carbon atom to which the aryl group was originally attached emerges in the final product as a carbonyl (**298**) or protected carbonyl (**299**), depending on the reaction conditions.

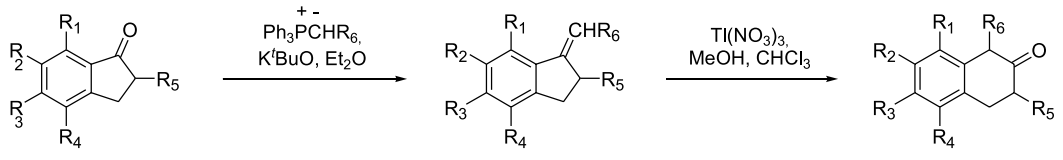
In an interesting example of carbonyl functionalization, compound 2**98i** was recently used as starting material for the synthesis of Wy-16225 (**306**),[118] a potent analgesic drug, as shown in Scheme 60.

Enantioselective alkylation of **298i** with 1,5-dibromo-pentane, under phase transfer catalysis of cinchoninium derivative **301** furnished bromide **302**, which was subjected to intramolecular cyclization, yielding **303**. Elaboration of the amine intermediate **305** through oximation (**304**) was followed by boron tribromide-assisted demethylation, efficiently providing the final product.

5. Conclusions

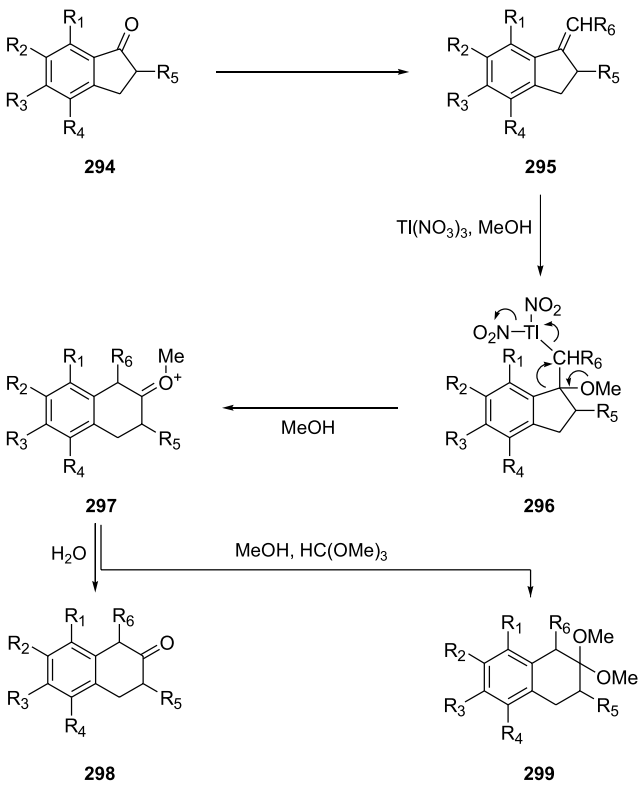
Known to chemists for over a century, 2-tetralones have become increasingly useful intermediates for the synthesis of natural products and their derivatives, as well as for the elaboration of novel, interesting and structurally accessible pharmacologically active compounds.

Table 10. The synthesis of 2-tetralones **253a** and **298a–j** employing the thallium(III)-promoted ring expansion of 1-indanones **294a–k**

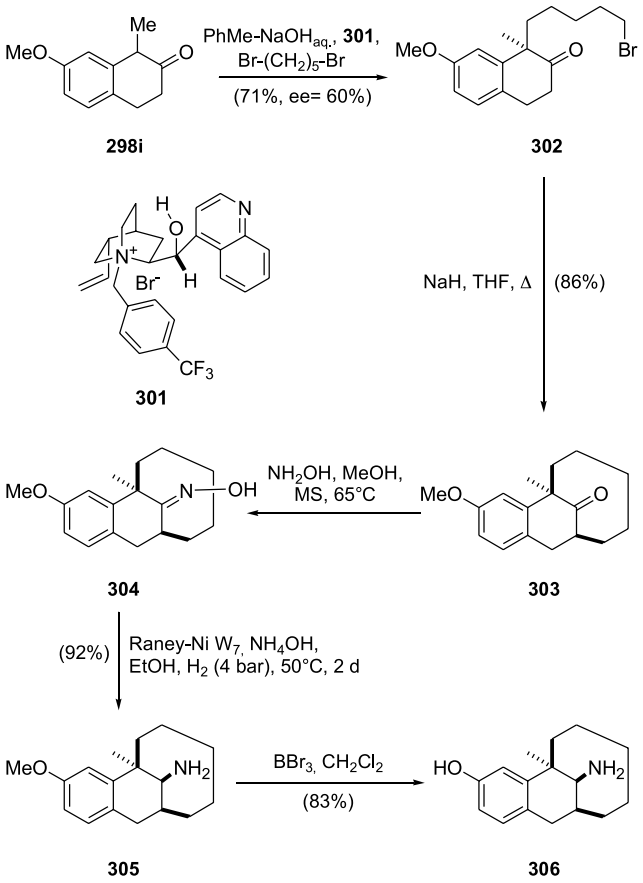


Entry no.	1-Indanone	2-Tetralone	R_1	R_2	R_3	R_4	R_5	R_6	Yield (%)	Reference
1	**294a**	**253a**	H	H	H	OMe	Me	H	46	122
2	**294b**	**298a**	H	OMe	H	H	Me	H	45	122
3	**294c**	**298b**	H	Et	H	H	H	H	36	16
4	**294d**	**298c**	H	^{i}Pr	H	H	H	H	—[a]	16
5	**294e**	**298d**	H	^{t}Bu	H	H	H	H	—[a]	16
6	**294f**	**298e**	OMe	H	H	OEt	H	H	—[a]	16
7	**294g**	**298f**	Oet	H	H	OEt	H	H	—[a]	16
8	**294h**	**298g**	H	OMe	Obn	H	H	H	27	118a
9	**294i**	**298h**	H	OBn	OMe	H	H	H	13	118a
10	**294j**	**298i**	H	OMe	H	H	H	Me	93	132
11	**294k**	**298j**	H	H	Me	H	H	H	96[b]	132

[a] Yields were not reported.
[b] Obtained as the dimethylketal derivative.



Scheme 59.



Scheme 60. Synthesis of analgesic agent Wy-16225 (**306**).

Many strategies were designed during the first half of the 20th century for the preparation of 2-tetralones; however, during the last 40 years, a number of new, cleaner and atom-efficient methods for the synthesis of 2-tetralones have been devised and a series of important improvements to previously existing methodology have been disclosed. In addition, methods for the regio- and enantioselective synthesis of polysubstituted 2-tetralones have been reported, especially in recent times and chiral 2-tetralone derivatives have been used as key intermediates of complex enantioselective syntheses.

Although a few strategies seem to be rather narrow in scope or their scope has not been exhaustively studied to date, others are general and of broad application and some of them have been thoroughly studied even from the mechanistic point of view, being their advantages and limitations known in good detail.

These advances have made readily available many members of this class of compounds, some of which were difficult to prepare not long ago and discouraged chemists from using them as starting materials of devising syntheses carrying 2-tetralones as key intermediates.

It is beyond doubt that the current arsenal of synthetic approaches to the elaboration of 2-tetralones will continue to increase and diversify, and methods will improve, as more demanding synthetic targets will continue to capture organic chemists' imagination.

Acknowledgements

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