Synthetic approaches to 2-tetralones

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1. Introduction

The 2-tetralones, also known as 3,4-dihydro-1H-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 and suitability as precursors of several natural products and their derivatives. 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.

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. However, after the Robinson’s paper describing the use of 2-tetralones as starting materials for the preparation of steroids, 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 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.

The only review article covering the preparation, chemical properties and some applications of 2-tetralones dates from 1966, 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-methoxynaphthalene, and their derivatives). The main reason behind this preference was that this approach...
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 tetrailines, the de novo synthesis of tetrailine derivatives, comprising the construction of the tetrailine ring system from appropriately substituted benzenoid precursors, became one of the most widely employed approaches to 2-tetrailones, specially for those carrying activating substituents on the aromatic ring.

2.1. Intramolecular cyclization of \( \alpha \)-diazo carbonyl compounds

The rhodium(II)-catalyzed decomposition of \( \alpha \)-diazo ketones 3 with concomitant rearrangement (Scheme 1), known as the Buchner reaction,\(^{16}\) was first described as a convenient and general entry to polysubstituted 2-tetrailones by McKervey and co-workers, in 1984.\(^{17}\)

This was disclosed following the discovery of Teyssiet 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-tetrailones (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-tetrailones, 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 \( \alpha \)-adrenergic agonists.\(^{23}\) The mechanistic aspects of the reaction have been exhaustively studied, as a consequence of the observation

### Table 1. Synthesis of 2-tetrailones employing the Buchner reaction

<table>
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<tr>
<th>Entry no.</th>
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<th>R(_3)</th>
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\(^{a}\) 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(2H)-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 rearranges26 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-isopropyl-cyclohexene from a cyclopropyl ketone derivative.27

Interestingly, the methoxy substituent can affect the efficiency of the cyclization, and its regio- and stereo-selectivity, 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.

The starting α-diazoketones 3 can be conveniently accessed from the related phenylpropionic acids, by the reaction of their corresponding acid chlorides with diazomethane (R6=H) or other diazo derivatives.23a The introduction of the R5 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 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.
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. 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, diazo-ketone 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.

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 Rh2(OAc)4 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...
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 \( \beta \)-dicarbonyl compounds with PhI(OAc)\( _2 \) and KOH.

The proposed cyclization mechanism is somehow reminiscent to that of the \( \alpha \)-diazoketones and is depicted in Scheme 7. Attack to \( 59 \) 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.

### 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. The Friedel–Crafts type electrophilic substitution reactions are one of the most common carboannulation strategies available to the synthetic chemist. The Friedel–Crafts acylation followed by cycloalkylation, through the reaction of acyl chloride with ethylene in the presence of \( \text{AlCl}_3 \), was initially reported by Cologne and Chambion in 1947. Burckhalter and Campbell were the first in using ethylene for this kind of transformation, in 1961, 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.

The reaction of acyl chlorides with ethylene to give ketones
is also known as the Darzens reaction. 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.

The best performance of the transformation was obtained with the use of an excess of AlCl₃ (3 equiv.) and the in situ generation of the acyl chloride. Sometimes, CH₂Cl₂ was found to be a better solvent than CS₂, being attributed to the ability of the solvent to dissolve the acyl chloride–aluminum chloride complex. 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 gave rise to two isomeric 2-tetralones, 14 and 18. Formation of unexpected 2-tetralone occurs through a methyl migration (80→81). In this type of transformation, β-chloroethyl ketones like 79, related to 78a and 78b have been isolated as intermediates.

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, 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.

Chlorinated tetralone 62 and the related 1-methyl-6-chloro-2-tetralone were employed for the syntheses of the benzoquinoliones LY191704 and LY266111, which act as human type 1 steroid 5α-reductase inhibitors, as well as for the elaboration of other benzoquinoliones with similar activity. 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, and in the synthesis of conformationally constrained phosphotyrosyl mimetics.

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. The 6-nitro and 7-nitro 2-tetralones were simultaneously obtained by nitration of a preformed 2-tetralone. Similarly, nitration of 6-chloro-2-tetralone furnished the 7-nitro derivative. On the other hand, in case of ortho disubstituted ethers next to the acetyl side chain, an unusual reaction takes place, furnishing [2H]-benzofuranone derivatives, due to ether cleavage and intramolecular cyclization, instead of reaction with ethylene.

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

The 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 prepared 1-methyl-1-amino-2-tetralone from α-methyl phenylglycine. Their synthesis is depicted in Scheme 9. The acyl chloride, obtained by reacting the phthalimido derivative with either thionyl chloride or phosphorus pentachloride, was treated with ethylene in the presence of aluminum chloride to give the expected N-protected aminotetralone in good overall yield. Cyclization of the latter, however, proceeded in no more than 15% yield, constituting a phthalimido styrene 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 provided the required aminotetralone.

An eco-friendly version of the Burckhalter and Campbell reaction was developed recently by Gray and Smith. In this cleaner approach, the trifluoroacetic anhydride/H₃PO₄ system was used instead of the more contaminating metal-based (AlCl₃) methodology. In this way, 2-tetralones were prepared from starting phenylacetic acid derivatives.

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 dichloromethane, 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 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 and was obtained in 41% combined yield from acid chloride. The 6-methoxy-4,7-dimethyl-2-tetralone, prepared by this new allylsilane methodology, was employed as a key intermediate in a total synthesis of heritonin, a tricyclic lactone isolated from Heritiera littoralis, which acts as a powerful natural piscicide (Scheme 10).

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

<table>
<thead>
<tr>
<th>Entry no.</th>
<th>Arylacetic acid</th>
<th>2-Tetralone</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>R₅</th>
<th>R₆</th>
<th>R₇</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>88a</td>
<td>89a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>n-Bu</td>
<td>H</td>
<td>H</td>
<td>55</td>
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<tr>
<td>2</td>
<td>88b</td>
<td>89b</td>
<td>H</td>
<td>H</td>
<td>F</td>
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<tr>
<td>4</td>
<td>88d</td>
<td>89d</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>OMe</td>
<td>n-Bu</td>
<td>H</td>
<td>H</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>88e</td>
<td>89e</td>
<td>H</td>
<td>OMe</td>
<td>OMe</td>
<td>H</td>
<td>n-Bu</td>
<td>H</td>
<td>H</td>
<td>76</td>
</tr>
<tr>
<td>6</td>
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<td>51</td>
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<tr>
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<td>88a</td>
<td>89g</td>
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<td>H</td>
<td>H</td>
<td>H</td>
<td>CH₂CH₂CH₂Br</td>
<td>H</td>
<td>H</td>
<td>55</td>
</tr>
<tr>
<td>8</td>
<td>88c</td>
<td>89h</td>
<td>H</td>
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<td>Me</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>70</td>
<td></td>
</tr>
</tbody>
</table>

Scheme 10. Synthesis of 6-methoxy-4,7-dimethyl-2-tetralone 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-butandiol to refluxing concentrated HCl was used to prepare 4-phenyl-2-tetralone in up to 58% yield (Scheme 11).

The starting diol was easily obtained by reduction of 2-(N,N-dimethylamino)-1,4-diphenyl-1,4-butandione with excess of LiAlH₄. On the other hand, other aqueous mineral acids such as HBr, or H₂SO₄ can be employed in place of HCl. This transformation probably proceeds through a Friedel–Crafts-type intramolecular alkylation.
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 \( \alpha,\beta \)-unsaturated ketone \( \text{97} \) was converted into the same 2-tetralone (61) by Friedel–Crafts reaction with \( \text{AlCl}_3 \) in \( \text{CS}_2 \), albeit in only 32% yield; 2-tetralone \( \text{61} \) was also prepared in 45% overall yield from benzaldehyde, by reaction of trimethyl-styrylsilane with phenylacetyl chloride, under \( \text{AlCl}_3 \) catalysis (Table 2, entry 2).

2.5. Cyclization of \( \beta \)-ketosulfoxides

\( \beta \)-Ketosulfoxides are easily available by the well-known reaction of methylsulfinyl carbanion with the corresponding lower homologous esters. The \( \beta \)-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 \( \alpha \)-acetyl-\( \alpha \)-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 \( \beta \)-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.

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. In the case of 98, use of trichloroacetic acid furnished the product in 70% yield, while the same amount of trifluoroacetic acid provided 64% of the 2-tetralone 102.

For the cyclization of 103, trifluoroacetic acid yielded only 27% of the product 104, while trifluoroacetic anhydride raised the yield to 58%. 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 \( \text{Pd/C} \) to give the expected 6,7-dimethoxy-2-tetralone 20 in 60% yield. The cyclization of \( \beta \)-ketosulfoxides to 2-tetralone 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 ($\eta^6$-arene) ruthenium complexes

Cationic ($\eta^6$-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 $\delta$-aryl-$\beta$-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 $\beta$-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 $\delta$-aryl-$\beta$-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 was found that the use of planar chiral (arene)Ru complexes may lead to useful chiral 1,1-disubstituted tetralones.

2.7. Radical-mediated oxidative cyclization of $\delta$-aryl-$\beta$-dicarbonyl compounds with Mn(III) and Ce(IV) salts

2-Tetralone derivatives were also prepared from $\delta$-aryl-$\beta$-dicarbonyl compounds,68 by reaction with Mn(III) and with Ce(IV) salts. This entailed an intramolecular homolytic aromatic substitution reaction, with the $\alpha$-dicarbonyl radicals generated by inner-sphere electron transfer from high-valent metal complex to the $\beta$-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 $\beta$-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.
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\(_2\)O 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.

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 derivatives.\(^74,75\) 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 15. Preparation of 2-tetralones 12 and 20 via intramolecular addition of silylenol ethers to PET-generated arene radical cations.](image)

![Scheme 16. Synthesis of 2-tetralones by intramolecular cyclization through benzyne intermediates.](image)

---

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

<table>
<thead>
<tr>
<th>Entry no.</th>
<th>β-Dicarbonyl</th>
<th>2-Tetralone</th>
<th>R(_1)</th>
<th>R(_2)</th>
<th>R(_3)</th>
<th>R(_4)</th>
<th>A</th>
<th>Y</th>
<th>Yield (%)</th>
<th>Reference</th>
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<tbody>
<tr>
<td>1</td>
<td>115a</td>
<td>116a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>22</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>115a</td>
<td>116b</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>26</td>
<td>69</td>
</tr>
<tr>
<td>3</td>
<td>115b</td>
<td>116c</td>
<td>H</td>
<td>H</td>
<td>HMe</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
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<td>69</td>
</tr>
<tr>
<td>4</td>
<td>115c</td>
<td>116d</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>9</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>115d</td>
<td>116e</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>56</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>115e</td>
<td>116f</td>
<td>OMe</td>
<td>H</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>OMe</td>
<td>93</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>115f</td>
<td>116g</td>
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<td>OMe</td>
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<td>70</td>
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<td>116h</td>
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<td>H</td>
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<td>OMe</td>
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<td>70</td>
</tr>
<tr>
<td>9</td>
<td>115h</td>
<td>116i</td>
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<td>OMe</td>
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<td>OMe</td>
<td>93</td>
<td>70</td>
</tr>
<tr>
<td>10</td>
<td>115i</td>
<td>116j</td>
<td>OMe</td>
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<td>OMe</td>
<td>OMe</td>
<td>H</td>
<td>OMe</td>
<td>81</td>
<td>70</td>
</tr>
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</table>
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. 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. The reaction takes place in the presence of catalytic amounts of PdCl₂(Ph₃P)₂, with Cs₂CO₃ (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.

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.

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.

2.12. Dieckmann condensation followed by decarboxylation

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

This 2-tetralone has been employed as starting material for the elaboration of the known dopamine agonist dihydroxycine and some of its derivatives, as well as various aminotetralines, isoquinoline derived dopaminergic agents, catecholamine mimicking agents, naturally occurring alkaloids, and cyclic aminoacids. 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 and then submitted to a Heck cross-coupling reaction with methyl acrylate and 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. 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, to afford the desired 2-tetralone 20 in 62% yield.

![Scheme 17. Synthesis of 2-tetralones employing a palladium-catalyzed intramolecular α-arylation of aliphatic ketones.](image)

![Scheme 18. Palladium catalysis for the preparation of 1,1-dimethyl-3,4-diphenyl-2-tetralone 127.](image)

![Scheme 19. 6,7-Dimethoxy-2-tetralone 20 prepared by a Dieckmann condensation strategy.](image)
yield (Scheme 19). The tetralone was conveniently purified through its bisulfite adduct.

### 2.13. Carbanion-induced condensation of 2H-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-2H-pyran-2-ones 136 with 1,4-cyclohexanedione mono-(2,2-dimethyl trimethylene) ketal 137, was described (Scheme 20, Table 5).

The reaction yielded 8-aryl-5-methoxycarbonyl-6-methylsulfanyl-3,4-dihydro-2(1H)-naphthalenone (2,2-dimethyl-trimethylene) 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 2H-pyran-2-one 136, but this mechanism is not very likely, taking into account previous precedents 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, CO₂Me).

### 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.

The protocol is advantageous for the synthesis of 3-substituted 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-phenylsulfonyl-3-alkyl-2-tetralone 141 in good yield (Scheme 21).

It has been demonstrated that, alternatively, deprotonated lactones (142) 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).

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 AlCl₃ as catalyst, was described (Scheme 24).

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. 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 2H-pyran-2-ones 136 with 1,4-cyclohexanedione monoketal (137)

<table>
<thead>
<tr>
<th>2-Tetralone</th>
<th>X</th>
<th>Y</th>
<th>Ar</th>
<th>Yield (%)</th>
<th>2-Tetralone</th>
<th>X</th>
<th>Y</th>
<th>Ar</th>
<th>Yield (%)</th>
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<td>135i</td>
<td>SMeth</td>
<td>CO₂Me</td>
<td></td>
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</tr>
<tr>
<td>135b</td>
<td>SMeth</td>
<td>CO₂Me</td>
<td></td>
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<td>135j</td>
<td>CN</td>
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</tr>
<tr>
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<td></td>
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<td>CN</td>
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<td>40</td>
</tr>
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<td>SMeth</td>
<td>CO₂Me</td>
<td></td>
<td>41</td>
<td>135l</td>
<td>Me₂N</td>
<td>CN</td>
<td></td>
<td>51</td>
</tr>
<tr>
<td>135e</td>
<td>SMeth</td>
<td>CO₂Me</td>
<td></td>
<td>34</td>
<td>135m</td>
<td>CN</td>
<td></td>
<td></td>
<td>49</td>
</tr>
<tr>
<td>135f</td>
<td>SMeth</td>
<td>CO₂Me</td>
<td></td>
<td>30</td>
<td>135n</td>
<td>CN</td>
<td></td>
<td></td>
<td>51</td>
</tr>
<tr>
<td>135g</td>
<td>SMeth</td>
<td>CO₂Me</td>
<td></td>
<td>46</td>
<td>135o</td>
<td>CN</td>
<td></td>
<td></td>
<td>47</td>
</tr>
<tr>
<td>135h</td>
<td>SMeth</td>
<td>CO₂Me</td>
<td></td>
<td>38</td>
<td>135p</td>
<td>CN</td>
<td></td>
<td></td>
<td>52</td>
</tr>
</tbody>
</table>


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

Scheme 23. Preparation of 2-tetralone 146 from bromosulfone 139 by a double annulation reaction.
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. 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. 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. The first reports on the use of epoxide rearrangements in the synthesis of 2-tetralones date from the 1940s, 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 through the intermediacy of the corresponding 1-tetralols, conveniently synthesized by NaBH₄ reduction of the 1-tetralones. After dehydration of 1-tetralols with p-TsOH, the resulting olefins were transformed into the corresponding epoxides in good yields under acid catalysis of TsOH or ZnI₂ (Scheme 25).

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-apioxide rearrangement of 3,4-dihyronaphthalenes

<table>
<thead>
<tr>
<th>Entry no.</th>
<th>1-Tetralone</th>
<th>2-Tetralone</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>R₅</th>
<th>Yield (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>150c</td>
<td>12</td>
<td>H</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>76</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>150f</td>
<td>15</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>74</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>150g</td>
<td>156a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>73</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>150h</td>
<td>61</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>74</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>150i</td>
<td>14</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>74</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>150j</td>
<td>156b</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>74</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>150k</td>
<td>156c</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>74</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>150l</td>
<td>156d</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>74</td>
<td>100</td>
</tr>
</tbody>
</table>

*Product yields were not informed.
dehydration of the 1-tetralol intermediate to \( \text{HCO}_2\text{H}/\text{H}_2\text{O}_2 \) 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 dihydro-naphthalene \(^{158}\) (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. \(^{101a}\)

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 26. Synthesis of 7-nitro-2-tetralone by 1,2-carbonyl transposition of the related 1-tetralone 157.](image)

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 \(\alpha\)-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
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 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, furnishing 6-methoxy-1-methyl-2-tetralone 17 in 68% yield. PAA was prepared in situ by reacting acetonitrile, 30% H2O2, and KHCO3 (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. 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 29. Synthesis of 6-methoxy-1-methyl-2-tetralone 17 employing the m-CPBA-mediated 1,2-carbonyl transposition of 169.

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

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. This procedure was used to convert 1-tetralone 150a into 1-methyl-2-tetralone 164a.

When the bromohydrin 181 was treated with PhMgBr as base, a rearrangement took place, converting directly the 1-methyl-1-tetralol 181 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
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.\textsuperscript{111} The 1,2-carbonyl transposition was accomplished by monosulfenylation of a starting ketone, like 186 followed by reduction of the resulting \( \alpha \)-thio ketone to the corresponding \( \beta \)-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 sulfide\textsuperscript{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.\textsuperscript{114}

The \( \alpha \)-thioketone 190, derived from \( \alpha \)-tetralone 150a, on treatment with \( p \)-toluene-sulfonylhydrazide furnished \( p \)-toluenesulfonyl-hydrazone 191. Further reaction of 191 with methylolithium produced the vinyl sulfide 192, which upon hydrolysis gave the \( \beta \)-tetralone 2 (Scheme 34).

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

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.\textsuperscript{115} Vinylsilanes 193a, \( b \) derived from \( \alpha \)-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.\textsuperscript{116}

They were next submitted to epoxidation, furnishing the non-isolated epoxysilanes 194, when exposed to buffered (\( \text{NaHCO}_3 \)) \( m \)-chloroperbenzoic acid in dichloromethane.\textsuperscript{117} Contrary to other systems where carbonyl transposition requires \( \text{LiAlH}_4 \) reduction of the epoxide and chromic acid

Scheme 34. Synthesis of 2-tetralone 2 by intermediacy of \( p \)-toluenesulfonylhydrazone 191.

Scheme 35. Synthesis of 2-tetralones by epoxidation–epoxide rearrangement of vinylsilanes.
Thus, hydroboration–oxidation of 7-methoxy-4-methyl-1,2-carbonyl transposition of the epoxide rearrangement sequence for effecting the (alkyl-alcohol constitutes an alternative to the epoxidation–alcohols), followed by oxidation of the resulting secondary 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.

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). The reaction took place through the 6-methoxy-1-methyl-2-tetralol intermediate 195 (Scheme 36). A synthesis of 2-tetralones by hydroboration-oxidation of 1-organyl-3,4-dihydronaphthalenes and further oxidation of the resulting 2-tetralols 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-tetralone 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

<table>
<thead>
<tr>
<th>Entry no.</th>
<th>Hydro-borating agent</th>
<th>Oxidizing agent</th>
<th>Product</th>
<th>R₁</th>
<th>R₂</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaBH₄, BF₃·Et₂O diglyme</td>
<td>Cl₂C₆H₄O₂H, DCC</td>
<td>17</td>
<td>OMe</td>
<td>Me</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>9-BBN, 0 °C→rt overnight</td>
<td>K₂Cr₂O₇, H₂SO₄ reflux, 7 h</td>
<td>17</td>
<td>OMe</td>
<td>Me</td>
<td>69</td>
</tr>
<tr>
<td>3</td>
<td>BH₃·THF</td>
<td>K₂Cr₂O₇, H₂SO₄ reflux, 7 h</td>
<td>164a</td>
<td>H</td>
<td>Me</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>9-BBN, 0 °C→rt overnight</td>
<td>K₂Cr₂O₇, H₂SO₄ reflux, 7 h</td>
<td>164b</td>
<td>H</td>
<td>Ph</td>
<td>53</td>
</tr>
<tr>
<td>5</td>
<td>BH₃·THF</td>
<td>K₂Cr₂O₇, H₂SO₄ reflux, 7 h</td>
<td>164d</td>
<td>H</td>
<td>Et</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>9-BBN, 0 °C→rt overnight</td>
<td>K₂Cr₂O₇, H₂SO₄ reflux, 7 h</td>
<td>164e</td>
<td>OMe</td>
<td>Ph</td>
<td>59</td>
</tr>
</tbody>
</table>
bензил групп через карбокатионный интермедиат 212. Расслоение происходит спонтанно, так как изолированное дигормо тетраол 210 дает бромонафтол 213 на стоянке.121а

Нет квинтсептации в известном диенон–фенольном расслоении 121б, в котором мигрирующий групп покаывает орто или пара относительно группы, которая мигрирует. В этом расслоении 3.1.5. Карбокси аттадиация через катализируемое расслоение эпоксидамидов и эпокситриллов. Эпокситриллы 216 (R=CN) были бы доставлены от Strecker silylcyanation of 1-tetralones 150a, 150c, 150m, and 150n,122 followed by elimination of the resulting tertiary silyl ethers (214) and phase-transfer epoxidation123 of the thus formed αβ-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=CONH₂) 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

carboxили в этом расслоении мигрирующий групп мигрирует meta по отношению к карбоксили.
\[ \text{β-ketoacid 218}, \text{ which readily decarboxylates in situ to the} \]
\[ \text{corresponding tetralone. The protocol requires the} \]
\[ \text{development of a positive charge at the benzylic carbon} \]
\[ \text{which bears the nitrile or amide group (217);126 this} \]
\[ \text{probably explains why the sequence does not seem to be} \]
\[ \text{effective with compounds carrying electron withdrawing} \]
\[ \text{groups on C-6, located para to C-1.} \]

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 dehydrogenation 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\textsuperscript{127} or trimethylamine \( N \)-oxide as stoichiometric co-oxidants, furnishing diols 222.\textsuperscript{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 \textsuperscript{227a,128} an antileukemic glycoside, and (±)-daunomycinone \textsuperscript{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,\textsuperscript{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 \( \text{ZnI}_2 \) or \( \text{BF}_3 \) for their dehydration to 2-tetralones (Scheme 42).\textsuperscript{102}
3.2. Direct oxidation of 2-tetralols

The CrO$_3$/pyridine/CH$_2$Cl$_2$ system was employed for the preparation of 8-methoxy-2-tetralone 15 from 8-methoxy-2-tetralol (231), in 85% yield. 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](image)

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).

![Scheme 44](image)

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. 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 was also employed for a study on anthracyclinone derivatives.

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. The 2-tetralones were obtained in good yields after refluxing the 2-tetralols with Al(OPr)$_2$ in the presence of a large excess of cyclohexanone during 6 h (Scheme 46). The oxidation of 2-tetralons was also discussed in Section 3.1.4.

![Scheme 45](image)

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

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, 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.

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](image)

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, including dopaminergic agonists, benzoxquinolines, antiulcer agents, radiolabelled compounds and (-)-morphine.

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. Attempts to effect the reduction of 2,5-dimethoxy-6-(benzoxynaphthalene (243a) to 5-methoxy-6-(benzoxyl)-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).

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. While it is easy to prepare C-1 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; 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%. The formation of the dianion of 1-carboxymethyl-2-tetralones has been disclosed as another alternative that permits the efficient alkylation of C-3, and condensation of 2-(phenysulfonylmethyl)benzyl bromide 139 with the anion of monosubstituted malonates regioselectively provided C-3 substituted 2-tetralones, as discussed in Section 2.7, 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).

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 253a and 253c were prepared in good yields. Enol ethers 254 were intermediates of this transformation (Scheme 50).

Exhaustive studies on the regioselective preparation of C-3 substituted 2-tetralones through the reduction of dimethoxynaphthalenes 247a-c with Na/ROH have been
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 CH2I2/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

Condensation of 262 with pyrrolidine in benzene under reflux conditions, followed by reaction of the resulting enamine with ethyl 3-carbethoxyazo-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, Rosowsky46c 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.
3.3.2. Reduction of naphthalene derivatives with dissolving metals in liquid ammonia (M/NH₃). 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/NH₃ reduction of 2-naphthols and 2-methoxy-naphthalenes is not new. 13,156,157 Thus, lithium 131 and sodium 158 dissolved in NH₃ were employed for the conversion of 2-hydroxy 131 and 2-methoxynaphthalenes (241a–d)131,158a,b into 2-tetralones 2, 12, 15 and 269 in reasonable to good yields (Scheme 54).

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

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 AlCl₃ and HCl, as shown in Scheme 55.158b Compounds 273 and 274 have been postulated as reaction intermediates of this process.

The method, however, has some known limitations. For example and not unexpectedly, when 1,7-dihydroxynaphthalene 275 was submitted to the same conditions, replacing AlCl₃ with AlBr₃, 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
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 \(\beta\)-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.](image)

![Scheme 58. Synthesis of chiral 2-tetralones \(^{284a, b}\) and \(^{285}\) by tandem addition of Grignard reagents to 2-methoxynaphthyl imine \(^{282}\) and subsequent \(\alpha\)-carbonyl alkylation.](image)

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-acyl-2-tetralone \(^{288}\).](image)

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 \(-78^\circ C\).

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 \(\text{AlCl}_3\) (5 equiv.) and \(\text{AlBr}_3\) 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 \(\text{Ph}_3\text{PCH}_2\text{Br}^-\) on the indanones, which yields the exocyclic methylene derivatives \(^{295}\).

The subsequent ring expansion/oxidation with \(\text{Ti(NO}_3)_3\) in
MeOH/CHCl₃ 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. 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

The overall transformation, depicted in Scheme 59, is initiated by an oxythallation of the double bond of the exomethylene 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 298i was recently used as starting material for the synthesis of Wy-16225 (306),118a 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 9. Photoreaction of 2-naphthols with ethylene under the assistance of Lewis acids

<table>
<thead>
<tr>
<th>Entry no.</th>
<th>R</th>
<th>Lewis acid</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>AlCl₃</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>OH</td>
<td>AlCl₃</td>
<td>49</td>
</tr>
<tr>
<td>3</td>
<td>OMe</td>
<td>AlCl₃</td>
<td>66</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>AlCl₃</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>CO₂Me</td>
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<td>68</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>AlBr₃</td>
<td>63</td>
</tr>
</tbody>
</table>

MeOH/CHCl₃ 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

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

<table>
<thead>
<tr>
<th>Entry no.</th>
<th>1-Indanone</th>
<th>2-Tetralone</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>R₅</th>
<th>R₆</th>
<th>Yield (%)</th>
<th>Reference</th>
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<tr>
<td>1</td>
<td>294a</td>
<td>253a</td>
<td>H</td>
<td>H</td>
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<td>OMe</td>
<td>Me</td>
<td>H</td>
<td>46</td>
<td>122</td>
</tr>
<tr>
<td>2</td>
<td>294b</td>
<td>298a</td>
<td>H</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>45</td>
<td>122</td>
</tr>
<tr>
<td>3</td>
<td>294c</td>
<td>298b</td>
<td>H</td>
<td>Et</td>
<td>H</td>
<td>H</td>
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<tr>
<td>4</td>
<td>294d</td>
<td>298c</td>
<td>H</td>
<td>'Pr</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>—</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>294e</td>
<td>298d</td>
<td>H</td>
<td>'Bu</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>—</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>294f</td>
<td>298e</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>OEt</td>
<td>H</td>
<td>H</td>
<td>—</td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>294g</td>
<td>298f</td>
<td>OEt</td>
<td>H</td>
<td>H</td>
<td>OEt</td>
<td>H</td>
<td>H</td>
<td>—</td>
<td>16</td>
</tr>
<tr>
<td>8</td>
<td>294h</td>
<td>298g</td>
<td>OMe</td>
<td>H</td>
<td>OMe</td>
<td>Obn</td>
<td>H</td>
<td>H</td>
<td>27</td>
<td>118a</td>
</tr>
<tr>
<td>9</td>
<td>294i</td>
<td>298h</td>
<td>OMe</td>
<td>H</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>13</td>
<td>118a</td>
</tr>
<tr>
<td>10</td>
<td>294j</td>
<td>298i</td>
<td>H</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>93</td>
<td>132</td>
</tr>
<tr>
<td>11</td>
<td>294k</td>
<td>298j</td>
<td>H</td>
<td>OMe</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>96</td>
<td>132</td>
</tr>
</tbody>
</table>

* Yields were not reported.

* Obtained as the dimethylketal derivative.
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.

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References and notes


Biographical sketch

Claudio C. Silveira was born in 1962 in Bom Jesus (RS), Brazil. He received his undergraduate education at Federal University of Santa Maria (Brazil, 1983) and MSc from University of São Paulo under Professor J. V. Comasseto (1986). He completed PhD thesis in 1988 under the guidance of Professor J. V. Comasseto at University of São Paulo, during the course of which he spent one year in the group of Professor J. P. Marino at University of Michigan, USA. He began his independent academic at Londrina State University (1988) then moved to Federal University of Santa Maria in 1991. During 1994–1995, he spent one year at Georg-August Universität Göttingen, Germany, in the laboratory of Professor Armin de Meijere as a postdoctoral fellow. His research interests have centered around the development of new synthetic methodologies, based mainly on organophosphorus and organochalcogen chemistry and their application to the synthesis of natural products.

Teodoro S. Kaufman was born in Moises Ville (Santa Fe, Argentina). He graduated as Biochemist (1982) and Pharmacist (1985) from the National University of Rosario (Argentina) and received his PhD in Organic Chemistry from the same University, in 1987, working with Professor Edmundo A. Rüveda in the synthesis of terpenes of geochemical interest. From 1987 to 1989, he was a postdoctoral fellow in the laboratory of Professor Robert D. Sindelar at The University of Mississippi, working on the design and synthesis of analogs of the complement inhibitor K-76. In 1990, he became Assistant Research Scientist of the Argentine National research Council (CONICET) and Assistant Professor at the National University of Rosario. He is now Associate Professor, Independent Research Scientist of CONICET and Sub-Director of the Institute of Synthetic Organic Chemistry (Rosario, Argentina). Areas of research are synthetic methodology and natural products synthesis. The work in his lab has been supported by TWAS, IFS, CONICET, ANPCyT and Fundación Antorchas.

Antonio Luiz Braga was born in Tupã-SP (Brazil) and obtained his BSc in 1982 from the Federal University of São Carlos (SP State). He received his MS and PhD degrees from the University of São Paulo in 1984 and 1989, working under the direction of Professor J. V. Comasseto in the field of organic selenium chemistry. In 1985, he obtained a position at the Federal University of Santa Maria-RS (south Brazil) as Assistant Professor and currently is still at the same place as Professor of Organic Chemistry. His research interests are focused in the bioorganic chemistry and in the application of chiral organochalcogen compounds in organic synthesis.

Eder J. Lenardão was born in 1968 in Sabádua-PR, Brazil. He received his BS from State University of Londrina and MS degree from Federal University of Santa Maria-RS under the guidance of Professor Claudio C. Silveira. In 1997, he earned a PhD degree in organic chemistry at University of São Paulo, under the guidance of Professor Miguel J. Dabdoub and in 2003 he worked with Professor Antonio L. Braga at UFSM as a postdoctoral fellow. His research interest lie in the area of organic and green chemistry.