The Oxa-Pictet–Spengler Cyclization: Synthesis of Isochromans and Related Pyran-Type Heterocycles

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Abstract: Compounds bearing the isochroman ring system are found in natural and synthetic products of interest. The oxa-Pictet–Spengler condensation is a valuable tool for the preparation of polysubstituted isochromans and related oxygen-bearing heterocycles. The different stagings of the oxa-Pictet–Spengler reaction, as well as the scope and limitations of this transformation, are discussed.

Key words: oxa-Pictet–Spengler, cyclization, isochromans, natural products, chemical synthesis

1 Introduction

The isochroman template is present in structures of drugs (medicines, agrochemicals, etc.) and drug candidates, as well as among natural products. Compound **1**, found in the leaves of *Tectaria subtrifilla*[1] and stephaoxocanine (**2**), obtained from *Stephania cepharantha*[2] are selected examples of isochromans of vegetal origin (Figure 1) .

In addition, DMHI (**3a**), a plant growth regulator isolated from *Penicillium steckii* of terrestrial and marine origin,[3] the anticoccidial isochroman **3b**, originally found in a hybrid strain of *Penicillium citreo-vitride*, later in *Penicillium sp. FO-2295* and recently in *Penicillium expansum*,[4]

glucoside B (**4**), an aphid insect pigment derivative[5] and bioxanthracene **5**,[6] a promising antimalarial agent, constitute examples of natural isochromans obtained from insects and microorganisms.

Furthermore, the synthetic isochroman galaxolide (**6**)[7] and the tricyclic etodolac (**7**),[8] bearing the related pyrano[3,4-*b*]indole ring, are isochromans with commercial importance in the cosmetics and drug industries.

3a R[1] = R[4] = H, R[2] = R[3] = Me
3b R[1] = R[4] = Me, R[2] = R[3] = H
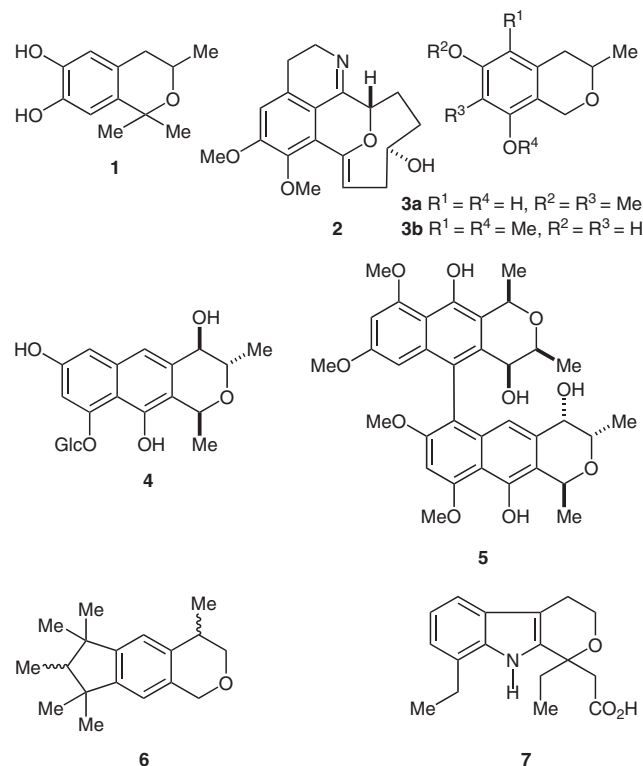
Figure 1

Isochromans can also be found among synthetic investigational drugs, such as the series of compounds related to **8** (Figure 2), which have been recently described as herbicides.[9]

There are also families of natural and synthetic products akin to the isochromans bearing a more oxidized heterocyclic ring. These include isochroman-3-ols[10a,b] and the related isochroman-3-ones, such as the antibiotic cytosporone D (**9**) which is an example of the phenylace-

tic acid lactone derivatives of rare occurrence in nature[10c] and relatively scarce among synthetic compounds.[10d]

The isochroman-1-ols, which include important natural products such as the topoisomerase II inhibitor CJ-12,373[11a] (**10a**) and the structurally similar antitumor and amiloid aggregation inhibitor **10b** isolated from *Penicillium simplicissimum* FERM BP-6357,[11b] constitute another group, while the related tetrahydroisocoumarins such as the inhibitor of pollen development 6-hydroxymellein (**11**)[12] are members of a third family of products bearing isochroman rings.
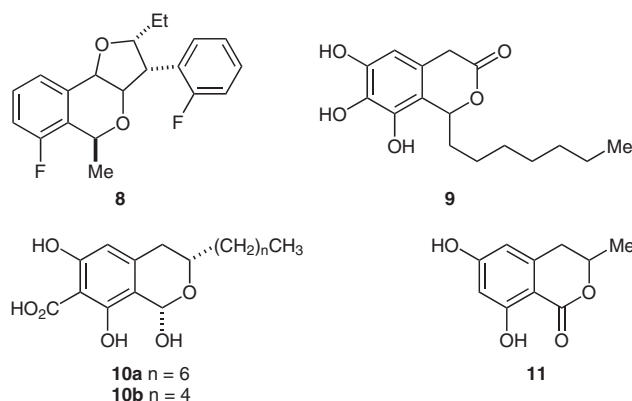

Figure 2

Isochroman derivatives are structural analogues of tetrahydroisoquinolines and have been repeatedly recognized as such.[13] This analogy has been exploited and several studies report on the use of isochromans as starting materials or intermediates for the synthesis of isoquinoline derivatives[14] and vice versa,[15] as well as for the preparation of other nitrogen-bearing heterocycles.[16]

Moreover, naturally occurring isochroman derivatives have been isolated and described as precursors of isoquinolines[17] and isochroman analogues of isoquinoline alkaloids have also been synthesized.[18]

Contrasting with the relative scarcity of isochromans in nature, the 1-substituted tetrahydroisoquinolines and 1-substituted β-carbolines are among the most abundant classes of natural products. This is the result of the metabolic systems present in many plants, which biosynthesize these compounds by complex enzymatic processes.[19]

Emulating nature, Pictet and Spengler devised a synthetic protocol which was initially employed towards the elaboration of tetrahydroisoquinolines,[20] but which later demonstrated to be useful for accessing β-carbolines.[21]

In its simplest form, this reaction consists in the cyclocondensation of a β-phenethylamine with a carbonyl compound under acidic conditions, to give a Schiff base which is protonated in situ generating an iminium salt; in turn, this undergoes an intramolecular electrophilic aromatic

Biographical Sketches

Enrique L. Larghi was born in Rosario (Santa Fe, Argentina). He received his BS in Chemistry in 1997 from the National University of Rosario (Argentina). He immediately started research work at the Universidade Federal de Santa María (Brazil) where he received his MSc in 1999 (with Dr. Claudio C. Silveira) and his PhD in chemistry in 2003 (with Dr. Ademir Farias Morel). After a short experience in the Argentine pharmaceutical industry, he joined Dr. Kaufman's group as a postdoctoral research fellow. His areas of research are organometallic chemistry and synthesis of heterocyclic natural products.

Teodoro S. Kaufman was born near Moises Ville (Santa Fe, Argentina). He graduated as Biochemist (1982) and Pharmacist (1985) from the National University of Rosario (Argentina). He received his PhD in organic chemistry from the same university (1987), working with Professor Edmundo A. Rúveda on the synthesis of geochemically interesting terpenoids. 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 analogues of the naturally occurring complement inhibitor K-76. In 1990, he returned to Argentina where 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, and Sub-Director of IQUIOS, the Institute of Synthetic Organic Chemistry (Rosario, Argentina), where he heads a small research group as Independent Research Scientist of CONICET. His areas of research are synthetic methodology, asymmetric synthesis and natural products synthesis. The work in his laboratory has been supported by ANPCyT, CONICET, Fundación Antorchas, IFS and TWAS.

substitution reminiscent of a Friedel–Crafts-type cyclization. The Pictet–Spengler condensation is currently an excellent and extensively exploited tool for the synthesis of isoquinolines, β-carbolines and other nitrogen-bearing heterocycles.

The oxygen version of the Pictet–Spengler reaction was termed the 'oxa-Pictet–Spengler reaction' for the first time by Wünsch and Zott in 1992.[22] In this reaction, a compound such as a 2-arylethanol reacts with an aldehyde or a ketone, as such or in masked form, to give an aromatic compound with a newly formed pyranic ring. In the case of 2-phenylethanols, 3,4-dihydro-1*H*-benzo[*c*]pyranic (isochromanic) structures are formed.

Because of their comparative scarcity, isochromans and related heterocycles are a relatively little-studied class of compounds and thus it is not surprising that the oxa-Pictet–Spengler condensation has received less attention than its nitrogen counterpart; however, this protocol constitutes a very important strategy for the synthesis of isochromans and other oxygenated heterocycles.

Interestingly, the analogy between isoquinolines (**12**) and isochromans (**13**) can be extended to β-carbolines (**14**) and 1,3,4,9-tetrahydropyrano[3,4-*b*]indoles (**15**) and other heterocycles, as shown in Figure 3; this offers the possibility of employing the oxa-Pictet–Spengler cyclization for the synthesis of different heterocycles.
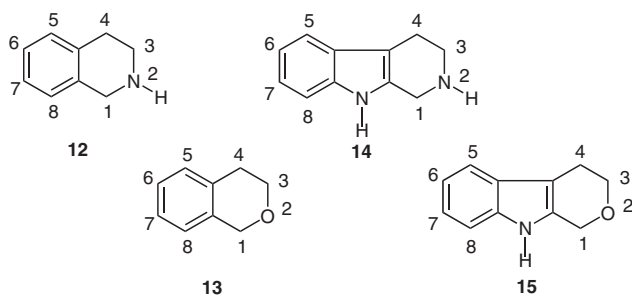

Figure 3

The oxa-Pictet–Spengler reaction seems to be relatively new; however, as this review will show, the use of this reaction for the preparation of isochromans is of long date and the transformation has been carried out under different names. The reaction has been classified in the literature as a special case of either the Friedel–Crafts alkylation, the Prins cyclization or the Mukaiyama reaction, among others.

It was found that activated substrates need moderately mild conditions;[23] the reaction has been described as taking place in the absence of added acid catalyst and it is known that sometimes only a weak promoter such as a carboxylic acid is sufficient. However, the literature records many examples in which the cyclization was accomplished under more difficult operative conditions, such as by the use of typical Lewis or Brönsted acids as catalysts, and several articles record the use of high reaction temperatures or prolonged reaction times.

The ease with which some activated β-phenethyl alcohols undergo the oxa-Pictet–Spengler cyclization induced Guiso to suppose that not all of the isolated isochromans may be truly natural products.[24,25] Among the artifacts, compound **1** isolated from the leaves of *Tectaria subtrifilla* by an acetone extraction procedure[1a] may be a likely example, in view of the abundance of the hydroxytyrosol[26] precursor in this plant.[27]

The chemistry of isochromans has been partially reviewed in short articles dating 15 years or more, covering their preparation, chemical properties and some selected applications.[28]

No recent reviews are available, however, despite that several important improvements, as well as new, more general and powerful methodologies have been described, aiming towards the synthesis of isochromans.

In this review, we provide an overview of the oxa-Pictet–Spengler reaction as a key synthetic tool towards the isochroman and related ring systems, including its application for the preparation of optically active compounds. However, the use of the so-synthesized oxa-heterocycles for the elaboration of more complex targets is not always fully covered.

2   Intermolecular Oxa-Pictet–Spengler Condensation

The oxa-Pictet–Spengler reaction has been implemented intermolecularly by reaction of β-arylethanols and aldehydes, ketones or their surrogates. Depending on the nature of the starting β-arylethanol and carbonyl components, this condensation has been used to provide 1-substituted (aldehydes) and 1,1-substituted (ketones) derivatives, as well as polysubstituted compounds with functionalization on C-3 and C-4. In the latter cases, the possibility of diastereoselective synthesis, particularly by 1,3-induction, has been observed and recorded.

2.1   Synthesis of 1-Substituted Isochromans

Campaigne informed that reaction of 3,4-dimethoxyphenethyl alcohol with aminoacetal in dioxane under hydrochloric acid catalysis gave 82% of the corresponding 1-aminomethylisochroman **16a**.[29]

Later, in an analogous fashion, the group of Macchia elaborated isochromans **16–19** as conformationally restricted analogues of the sympathomimetic catecholamines (Figure 4).[30] The syntheses were carried out by employing partial modifications of the protocols previously used by Kumar and co-workers in their preparation of **19a**.[30c]

More recently, the group of Guiso effected changes to the oxa-Pictet–Spengler reaction,[24] and proposed that their modified version could be generalized to obtain 1-benzylisochromans as oxygenated analogues of benzyltetrahydroisoquinoline alkaloids such as coclaurine (**20**).
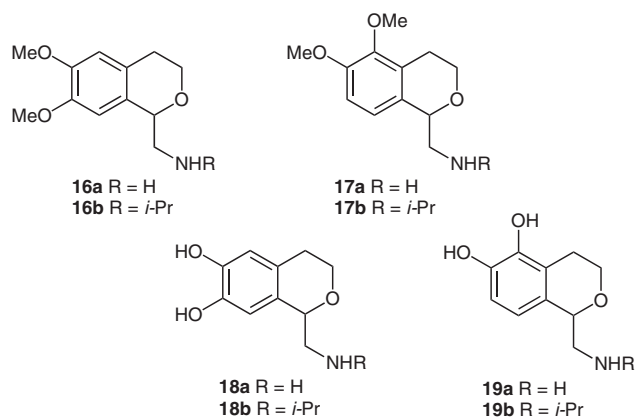
Figure 4

In order to test this hypothesis, Guiso and co-workers prepared several oxygenated analogues of 1-alkyl- and 1-phenyltetrahydroisoquinolines by the oxa-Pictet–Spengler protocol (Scheme 1).[25] This included 6,7-demethyloxacoclaurine (**21**), which was synthesized by condensation of 4-hydroxyphenylethanal (**22**), an oxidation product of tyrosol (**23**), and hydroxytyrosol (**24**). Interestingly, this transformation occurred in 80% yield, without the need for protecting groups.
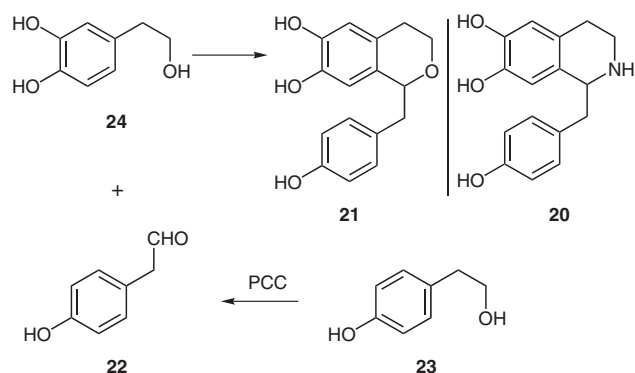
Scheme 1

According to these authors, the reaction has a three-step mechanism (Scheme 2) in which the first step consists of the acid-catalyzed formation of the hemiacetal **25** formed by condensation of the hydroxyethyl derivative **26** with an aldehyde or a ketone (**27**). This is followed by water loss, which provides the reactive intermediates **28a,b** that finally undergo intramolecular electrophilic aromatic substitution, in the activated position *para* to the hydroxyl group (**29**), furnishing the isochroman **30**.

In these activated systems, the group of Guiso[24,25] found that aldehydes react faster than ketones and that aromatic aldehydes gave higher yields than their aliphatic counterparts. This is probably because, for the aromatic aldehydes, the positive charge present in the reaction intermediate may give a resonance on the aromatic ring, thus increasing the stability of the intermediate cation;[31] alternatively, this can be explained as a consequence of the fact that these aldehydes cannot undergo enolization.
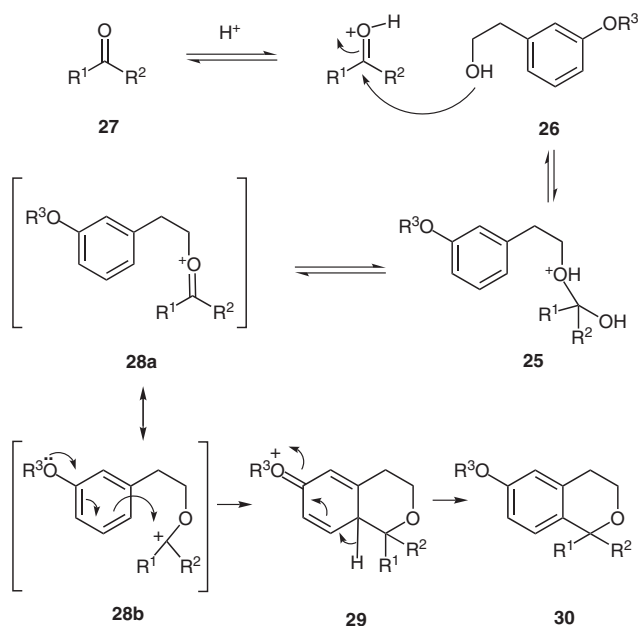
Scheme 2

Observation of the outcome of the reaction with different carbonyl components was also indicative that the water elimination step is of fundamental importance to the course of the reaction and the product yield.

In order to demonstrate the key role of the water elimination stage in the proposed mechanism, this group carried out reactions with and without dehydrating agents (Table 1). They found that the presence of a dehydrating agent was fundamental for achieving high yields; this effect was more pronounced in cyclizations involving aliphatic aldehydes.

In their stereocontrolled total synthesis of deoxyfrenolycin **31**, a natural product isolated from *Streptomyces roseofulvus*, Xu and co-workers[32] prepared the heterocyclic ring of this pyranonaphthoquinone antibiotic by means of an oxa-Pictet–Spengler reaction, as shown in Scheme 3.

The required alcoholic precursor **32** was elaborated by a highly regioselective benzannulation of chromium carbene complex **33** with terminal acetylene **34**,[33] available in turn from 3-buten-1-ol (**35**) via its protected derivative **36**, by ring opening of epoxide **37** with lithium acetylide (**38**) into alcohol **39**.[34]

Williamson methylation of the resulting **32** to the 1,4,5-trimethoxynaphthalene **40**[35] and deprotection of the alcoholic function (**41**) expedited the way to the oxa-Pictet–Spengler condensation to **42** which was carried out with formaldehyde dimethyl acetal under BF$_3$·Et$_2$O assistance.[36]

DDQ-induced oxidative coupling with allyl triphenylstannane stereospecifically gave the 1,3-*trans*-substituted allyl naphthopyran **43**.[37] This outcome was a distinctive characteristic of the synthesis, since previous approaches furnished the 1,3-*cis*-derivative.[38]

Table 1 Synthesis of 7-Hydroxyisochroman Derivatives by the Oxa-Pictet–Spengler Condensation

Entry	R^1	Carbonyl Compound	Yield (%)			R^2	R^3
			Protocol A[a]	Protocol B[b]	Protocol C[c]		
1	OH	Pentanal	80	60	50	H	n-Bu
2	OH	3-OH-C$_6$H$_4$-CHO	98	90	80	H	3-OH-C$_6$H$_4$-
3	OH	4-MeO-C$_6$H$_4$-CHO	98	90	80	H	4-MeO-C$_6$H$_4$-
4	OH	Benzaldehyde	95	80	60	H	Ph
5	OH	Isovaleraldehyde	90	73	62	H	2-Bu
6	OH	Propanal	95	80	72	H	Et
7	OH	Nonanal	95	90	75	H	n-Oct
8	H	Pentanal	80			H	n-Bu
9	H	Piperonal	98			H	3′,4′-OCH$_2$O-C$_6$H$_4$-
10	H	4-Cl-C$_6$H$_4$-CHO	95			H	4-Cl-C$_6$H$_4$-
11	H	4-MeO$_2$C-C$_6$H$_4$-CHO	90			H	4-MeO$_2$C-C$_6$H$_4$-
12	OH	4-HO-C$_6$H$_4$-CH$_2$CHO	80	75	60	H	4-OH-C$_6$H$_4$-CH$_2$-
13	OH	Acetone	95	80	63	Me	Me

[a] Protocol A: MeOH, activated MS, TsOH (cat.), 4 °C, 24–48 h.
[b] Protocol B: MeOH, anhydrous Na$_2$SO$_4$, TsOH (cat.), 4 °C, 24–48 h.
[c] Protocol C: MeOH, TsOH (cat.), 4 °C, 24–48 h.
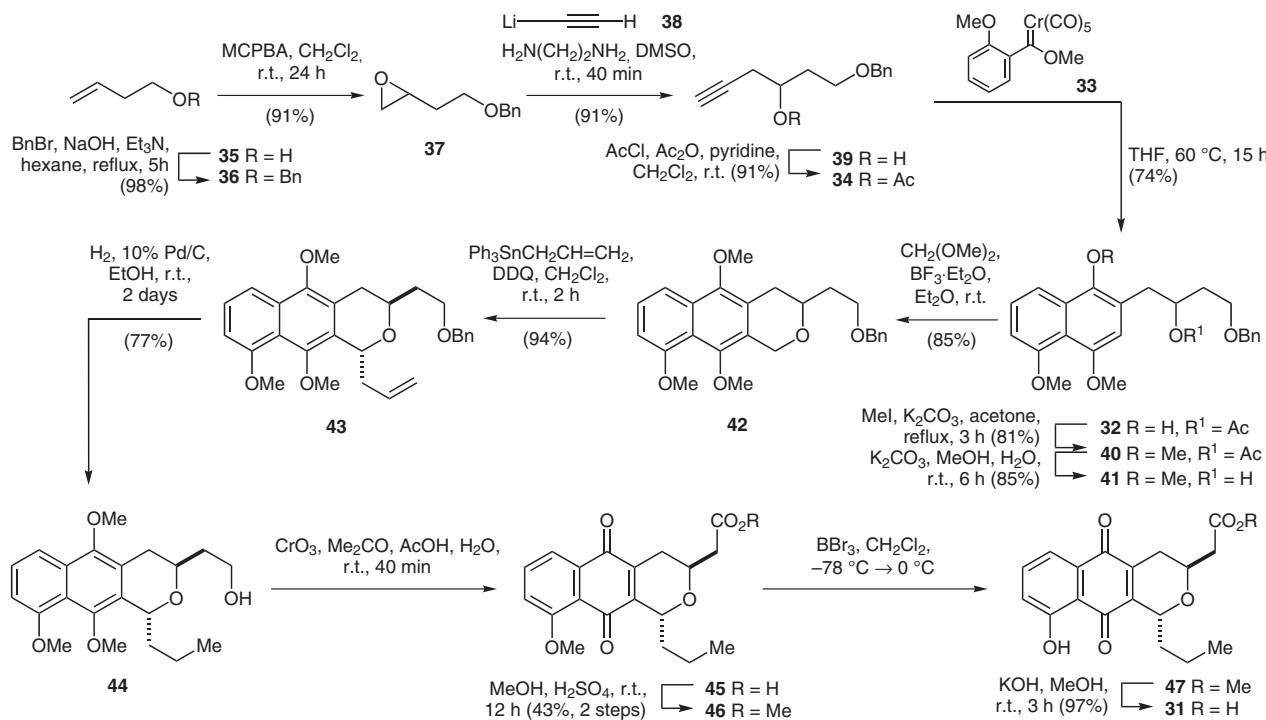
Scheme 3

The synthesis was completed with functional group transformations on the side chains (**43** → **44** and **45** → **46**) and on the aromatic moiety (**44** → **45** and **46** → **47**). These included double bond catalytic hydrogenation, the simultaneous oxidation of the primary alcohol to a carboxylic acid and of the central benzene ring to the corresponding quinone with CrO_3 in acetic acid,[39] and the boron tribromide assisted demethylation of the remaining methyl ether. Final saponification of the methyl ester in **46** furnished the natural product **31**.

An interesting oxa-Pictet–Spengler cyclization leading to 1-alkylisochromans was disclosed by Jung and co-workers.[40a] In this case (Scheme 4), starting β-phenethyl alcohol was protected as a silyl ether (**48**) and the TMSI adduct of acetaldehyde (**49**) was employed as a masked carbonyl component.
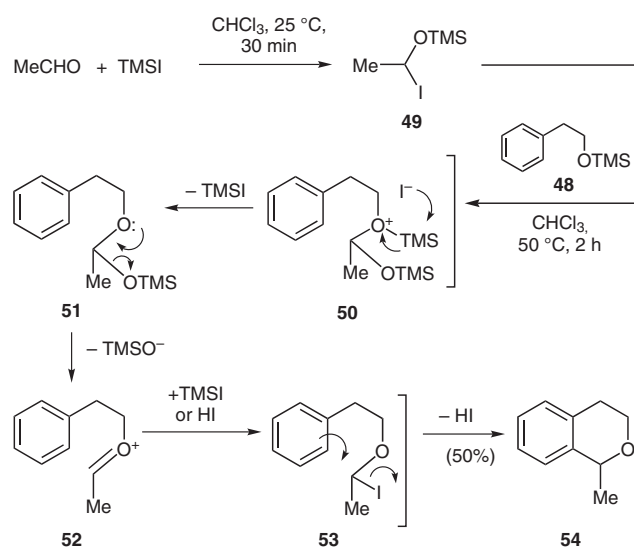
Scheme 4

This process seems to entail a first step that consists in the complexation or association of the iodo derivative and the silyl ether moiety originally tethered to the aromatic ring, with concomitant loss of TMSI (**50** → **51**), because no *para*-substituted products, the typical Friedel–Crafts byproducts, were observed.

Next, loss of trimethylsilyloxy anion to form hexamethyldisiloxane and subsequent nucleophilic attack by iodide to **52** would furnish iodo intermediate **53**, capable of cyclizing to the final isochroman **54**. However, since the reaction occurs with formation of HI, which is a Brönsted acid and useful catalyst, it is likely that the mechanistic picture may be more complex.

2.2   Synthesis of 1,1-Disubstituted Isochromans

The use of ketones in place of aldehydes gives rise to 1,1-disubstituted oxacycles. In addition to the example provided by Guiso (Table 1, entry 13), a few others have been recorded. 1,1-Dialkylisochroman derivatives **55** have been synthesized from 3,4-methylenedioxy β-phenethyl

alcohol and described as non-steroidal antiinflammatory agents.[41]

Among other 1,1-disubstituted pyran-type heterocycles with the same activity, etodolac (**7**)[42] and pemedolac (**56**)[43] have prominent importance (Figure 5). These are clinically effective as antiinflammatories, with the activity related to the presence of the dihydropyran acetic subunit. Interestingly, conformational changes in the oxygen ring, such as those produced by the introduction of the benzyl moiety in pemedolac, have been observed. These changes have an effect on the biological activity.[44]
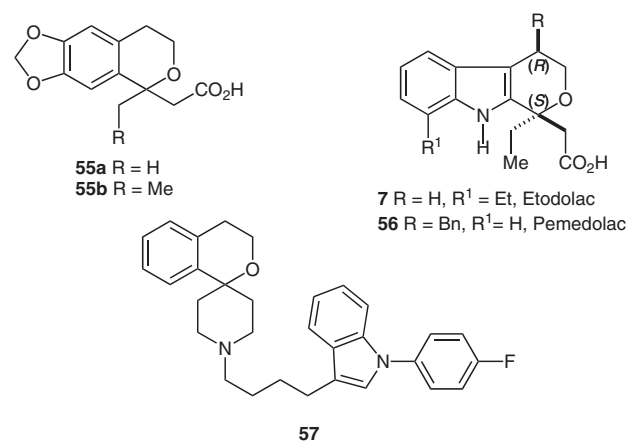

Figure 5

In addition, compound **57** and analogues have been prepared by Moltzen and co-workers, employing the oxa-Pictet–Spengler reaction of β-phenethyl alcohol with piperidin-4-one.[45] This Danish team demonstrated that **57** has subnanomolar affinity and preference for the brain σ_2 binding sites ($IC_{50} = 0.9$ nM). The σ ligands have potential as therapeutic agents for the treatment of psychosis.

Using safrole (**58**) as starting material, Da Silva and Barreiro were able to synthesize the 1,1-disubstituted isochroman derivatives **59** and **60** (Scheme 5),[46] which relate to the pyran-type antiinflammatories but have some conformational restrictions.[47]

Thus, safrole (**58**) was reductively ozonolyzed and the resulting aldehyde was further reduced to β-phenethyl alcohol **61**.[48] When submitted to boron trifluoride assisted cyclization with β-ketoesters **62a** and **62b**,[49] tricyclic compounds **63** and **64** were obtained, respectively. In turn, these were hydrolyzed to the corresponding acids with hydroalcoholic potassium hydroxide.[50]

Interestingly, the reaction did not proceed under *p*-toluenesulfonic acid assistance, which is a useful reagent for the acyclic congeners, and $BF_3\cdot Et_2O$ was chosen after a systematic promoter search.[51]

Products were obtained as diastereomeric mixtures, with prevalence (9:1) of one diastereomer. The observed diastereoselectivity was ascribed (Scheme 6) to a preferential attack of the regioactivated pro-C-6 position of the methylenedioxy phenyl group to the oxonium intermediate
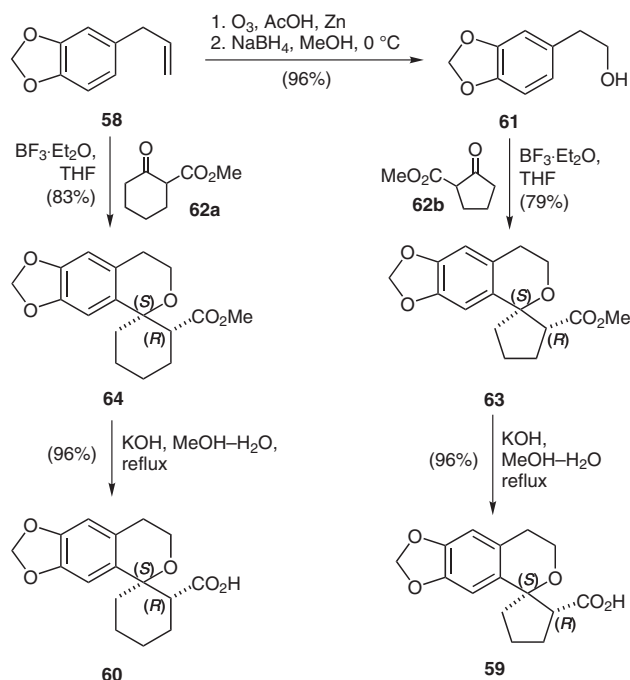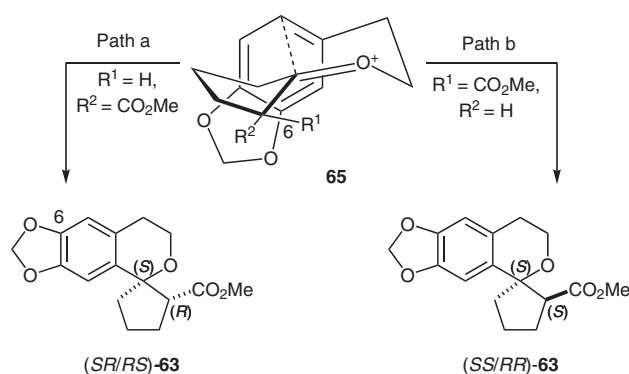
Scheme 5

Scheme 6

through its less-hindered face (**65**), opposite to the methoxycarbonyl moiety.

In agreement with the proposed hypothesis on the activity of these compounds, they showed poor antiinflammatory activity but powerful analgesic properties,[52] with the five membered ring analogue being the most potent.

2.3 Diastereoselective Synthesis of 1,3-Disubstituted Isochromans

The group of Jung[40a] disclosed that the self-condensation of the TMSI adduct of phenylacetaldehyde (**66**) gave the dibenzocyclooctadiene derivative **67** (Scheme 7), pre-

sumably through a mechanism similar to that shown in Scheme 4.

Here, displacement of iodide from one molecule of **66** by the oxygen atom of a second molecule of **66** led to the silylated oxonium iodide **68**, which upon loss of trimethylsilyl iodide afforded the iodo acetal **69**. In turn, this compound was converted into the iodo ether **70** by either of two pathways: (a) initial oxa-Pictet–Spengler cyclization with loss of hydrogen iodide to give the acetal **71** which is then converted into the iodo ether **70** by hydrogen iodide or TMSI; or (b) initial conversion of the acetal function to the symmetrical diiodo ether **72** followed by the oxa-Pictet–Spengler cyclization to **70**.

The iodo ether **70** is then transformed into **67** by a second intramolecular oxa-Pictet–Spengler condensation. Ether **67** was transformed into dibenzo[a,e]cycloocta-1,5-dien-3-one **73** through a reductive ring opening by sodium in liquid ammonia, followed by oxidation of the resulting alcohol. Ketone **73** is a useful starting material for compounds with antiinflammatory or psychotropic activity.[40b]

Wünsch and Zott[22,53a] reported that the condensation of several optically active phenyllactic acids **74** with benzaldehyde and butyraldehyde under acid catalysis gave mix-
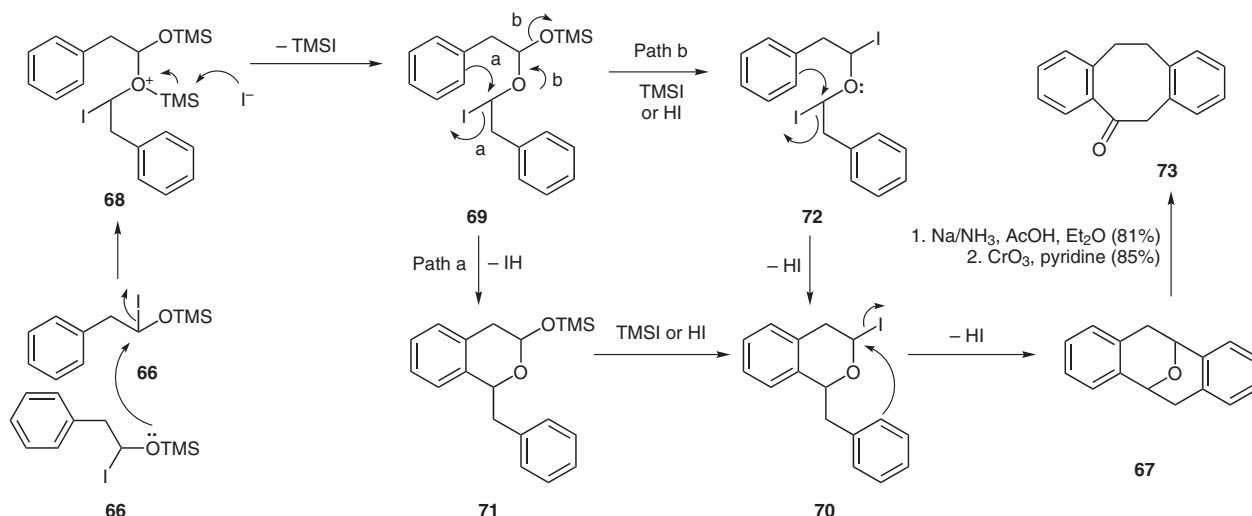
Scheme 7

Table 2 Synthesis of 1,3-Disubstituted Isochromans Employing the Oxa-Pictet–Spengler Condensation Protocol

Entry	R	R^1	R^2	R^3	Conditions	*cis/trans*	Yield (%)
1	H	H	Ph	H	HCl, ZnCl$_2$, r.t., 12 h	90:10	67
2	OH	Me	Ph	H	HCl, MeOH, r.t., 14h	61:39	71
3	OH	Me	Pr	H	TsOH, CHCl$_3$, 66 h	58:42	48
4	OH	Me	–H$_2$C-(CH$_2$)$_3$CH$_2$–		TsOH, CHCl$_3$, 3 h	–	85
5	OH	Me	–(CH$_2$)$_2$NMe(CH$_2$)$_2$–		TsOH, Cl(CH$_2$)$_2$Cl, 48 h	–	57
6	OH	Me	–(CH$_2$)$_2$NAc(CH$_2$)$_2$–		TsOH, Cl(CH$_2$)$_2$Cl, 16 h	–	32
7	OMe	Me	–(CH$_2$)$_2$NMe(CH$_2$)$_2$–		HCl, dioxane, r.t., 48 h	–	27

tures of 1,3-*cis*- and 1,3-*trans*-disubstituted isochromans **75**, with the *cis* diastereomers being favored (Table 2).

A similar observation was recently made by Chinese investigators.[53b] Compounds **76** were occasionally isolated as side products of these transformations. In addition, spirocyclic compounds related to **75** were obtained in fair-to-good yields when ketones were employed as the carbonyl components.

D$_1$ dopaminergic agonists with 1,3-disubstituted isochroman skeletons are among the few D$_1$ agonists known to date. Dopamine receptors have been divided into several classes on the basis of their pharmacological differences, and selective dopaminergic agents show promise for the treatment of extended conditions such as Parkinson's disease, and as probes to better understand the role of these receptors.[54]

Michaelidis and co-workers[55] reported the synthesis of 3-cyclohexylisochroman derivatives **77**, **78** and **79** following the synthetic route shown in Scheme 8. Lateral metallation of phenolic ether **80**, followed by reaction with cyclohexane carboxaldehyde gave the required β-phenethyl alcohol **81**, which was cyclocondensed in an oxa-Pictet–Spengler reaction either with *N*-formyl aminoacetal **82a** to furnish **83**, or with bromoacetal **82b** to give **84**.

The former 1,3-*cis*-disubstituted isochroman was then submitted to formyl-group reduction and hydrobromic acid assisted demethylation, providing compound **77**, while the second heterocycle was transformed into the primary amine **85** by nucleophilic substitution with lithium azide and reduction of the resulting azide **86**. After demethylation to phenol **87**, alkylation of the amino group furnished the final compounds **78** and **79**.

A slight variation of this strategy led to the preparation of 3-phenyl derivative **88**. To this end, benzylic bromide **89** was reacted with the lithium species **90** to furnish thioketal **91**, which was oxidatively deprotected to unveil ketone

92, and further reduced to β-phenethyl alcohol **93**. Cyclization of the latter with bromoacetal **82b** to 1,3-*cis* isochroman **94**, followed by transformation of the bromide into the corresponding amine **95** by way of azide **96**, and
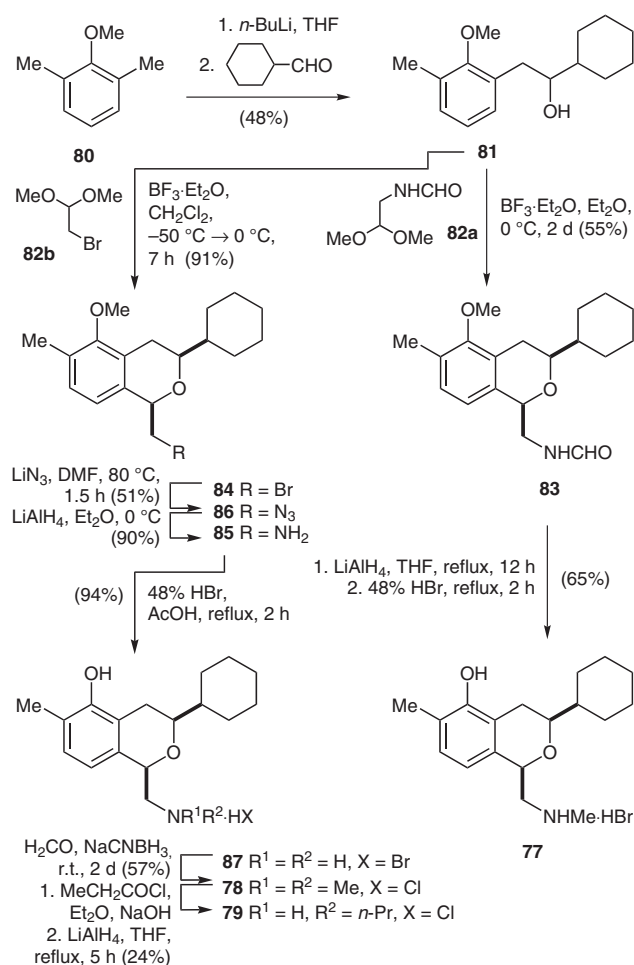
Scheme 8

final catalytic debenzylation culminated in **88** to complete the synthetic sequence, shown in Scheme 9.

These compounds made it possible to deduce that a primary amine was the best functional group for inducing the tested activity, and that the 3-phenyl analogues are more potent than their 3-cyclohexyl congeners. It was also concluded that the 6-methoxy substitution decreases the binding affinity, while a 6-methyl functionalization exhibits a lack of selectivity, with increased affinity towards 5-HT$_{1A}$ and 5-HT$_{1C}$ receptors.

More recently, Unterhalt and Heppert[56] reported the synthesis of 3′-phenyl-1′-isochromanyl-2-ethylamines related to fluoxetine by oxa-Pictet–Spengler condensation of 1,2-diphenylethanols with 3-chloropropanal diethylacetal under BF$_3$·Et$_2$O assistance and nucleophilic displacement of the resulting chlorides with amines. The affinities of the synthetic compounds towards the 5-HT$_{2A}$ receptor and the serotonin transporter were tested, and the authors synthesized 1-aryl analogues as well.
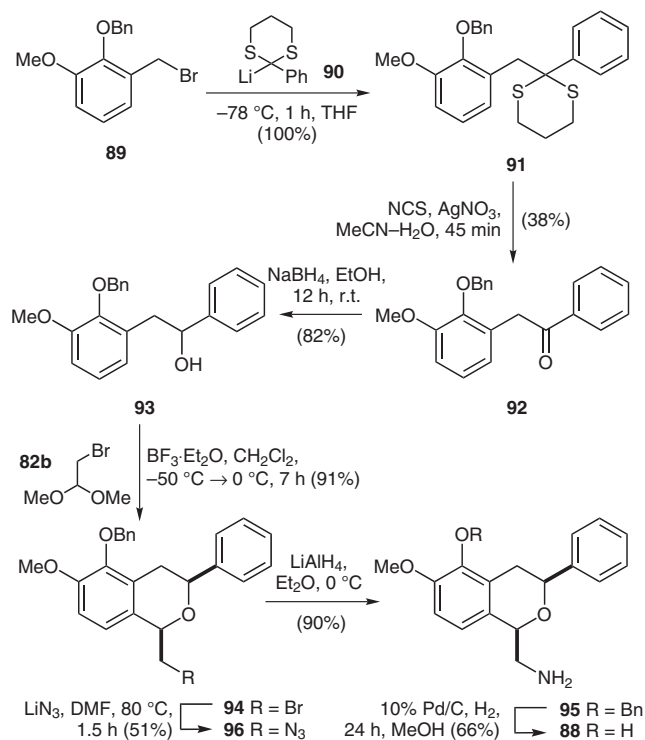
Scheme 9

While these oxa-Pictet–Spengler cyclizations selectively provided the 1,3-*cis* diastereomers, during their study of prospective antitumor agents, Grasso and co-workers[57] recently reported the oxa-Pictet–Spengler synthesis of the 1,3-*trans*-disubstituted isochroman derivative **97** from alcohol **98** (Scheme 10).[58]

Interestingly, however, the amine **99**, prepared by catalytic hydrogenation of **97**, did not pass the National Cancer Institute (U.S.A.) criteria for activity in the primary assay.
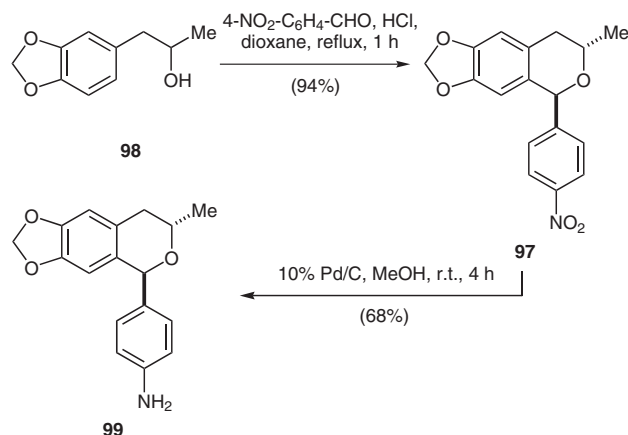
Scheme 10

2.4 Synthesis of 3-Substituted Isochromans

During the synthesis of the ochratoxins A and B (**100**), metabolites of the toxicogenic strains of the fungus *Aspergillus ochraceus* Wilh,[59] Steyn and Holzapfel[60] prepared 3-methylisochroman derivatives **101–104** from 3-bromophenol (**105**). Thus, the starting phenol was protected as a THP ether (**106**), and after preparation of the corresponding Grignard reagent, it was reacted with propylene oxide, furnishing β-phenethyl alcohol derivative **107** in good yield (Scheme 11).

Acid deprotection to **108**, followed by chlorination according to Campbell,[61] gave monochloride **109** and dichloride **110**, among other nuclearly mono- and di-chlorinated compounds. Williamson etherification furnished methyl ethers **111** and **112**, and upon reaction with the MOMCl–ZnCl$_2$ reagent, dihalogenated heterocycle **112** gave isochroman **101**; analogously, **102** was obtained quantitatively from **111** after treatment with MOMCl under ZnCl$_2$ catalysis at room temperature.

However, prolonged heating of **111** under reflux yielded chloromethyl derivative **103**, which was hydrolyzed to alcohol **104** and then selectively dechlorinated with Raney nickel under basic conditions to afford **113**. In turn, this was oxidized to carboxylic acid **114**, and demethylated by acid treatment, furnishing salicylic acid derivative **115**, which is analogous to the isochroman accessed by hydrolysis of natural ochratoxin B (**100**).

From chiral **115**, obtained by hydrolysis of the natural product, ochratoxin B (**100**) was reconstructed in 26% yield by reaction of the related acyl azide and L-phenylalanine.

The procedure of Singh[62] is very useful for the synthesis of simple 3-alkylisochromans (**116** → **117**); however, attempts to employ this strategy for accessing 3-phenyl or 3-vinyl derivatives met with failure, with the benzylic (**118**) and allylic (**119, 120**) chlorides being the major reaction products (Scheme 12).[63]

Interestingly, Rama[64] disclosed that 1,3-dimethyl-6,8-dimethoxyisochroman, as well as 1-methyl-, 1-ethyl-, 1-
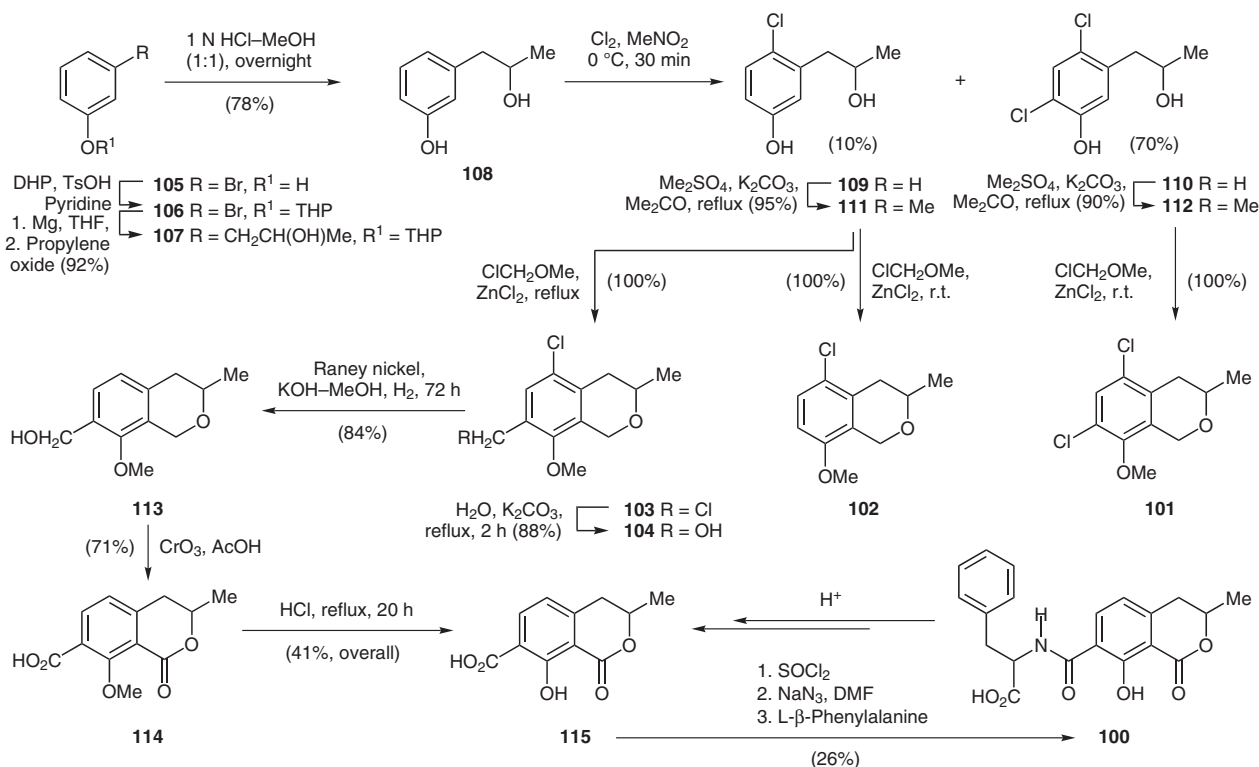
Scheme 11

propyl- and 1-isopropyl-6,8-dimethoxyisochromans, were prepared in 80–85% yield from the corresponding 3,5-dimethoxyphenyl alkanols **121a** and **121b** in nitromethane under BF$_3$·Et$_2$O catalysis, without dimerization.

However, under the same conditions, bis(isochroman)s such as **122a–c** were isolated (Scheme 13) when the preparation of 6,8-dimethoxyisochroman derivatives was attempted from the corresponding β-phenethyl alcohols **121a–c** with formaldehyde or formaldehyde diethyl acetal as the carbonyl component.

A report by Bird and co-workers[65] confirmed some of these observations, indicating that when 3,5-dimethoxy-β-phenyl alkanols were submitted to condensation either with dimethoxymethane and boron trifluoride or with

formaldehyde and hydrochloric acid, in addition to the expected oxa-Pictet–Spengler condensation, a side reaction took place, furnishing bis(isochroman-5-yl)methanes in high yield.

These condensing agents have been previously employed for the synthesis of 5,6-,[66] 5,7-[67] and 6,7-dimethoxyisochromans;[68] thus, this is a result of the characteristics of the starting material. Interestingly, NMR studies were unable to detect rotation restrictions along the C_{Ar}–C axes of these rare compounds.[69]

Exceptionally, however, Cutler and co-workers[70] were able to synthesize the plant growth regulator **3a**, through 6,8-dimethoxyisochroman intermediate **123** without dimerization (Scheme 14). In their approach, starting phenolic acid **124** was methylated to **125** and converted into bromide **126** by way of alcohol **127**.
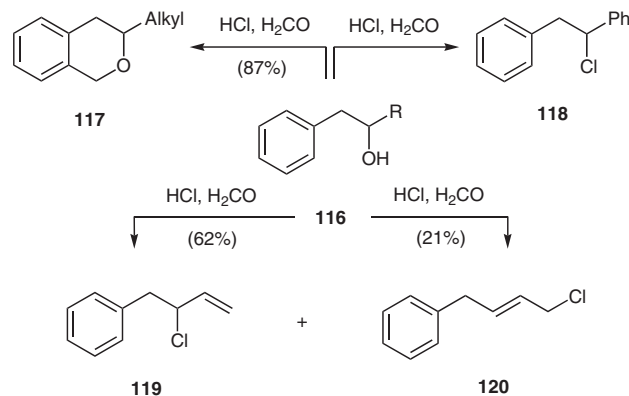
Scheme 12
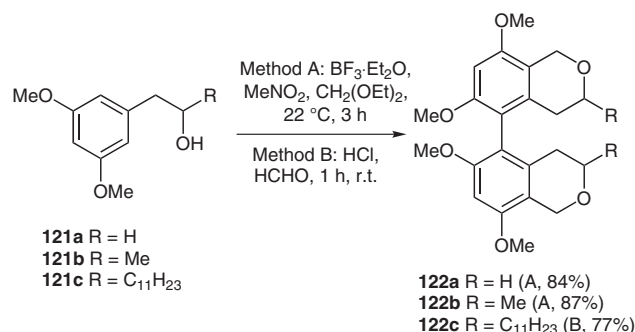
Scheme 13

Scheme 14

Next, vinyl Grignard addition produced compound **128**, which, once submitted to an oxymercuration–demercuration, afforded secondary alcohol **129**. Upon treatment with methoxymethyl chlor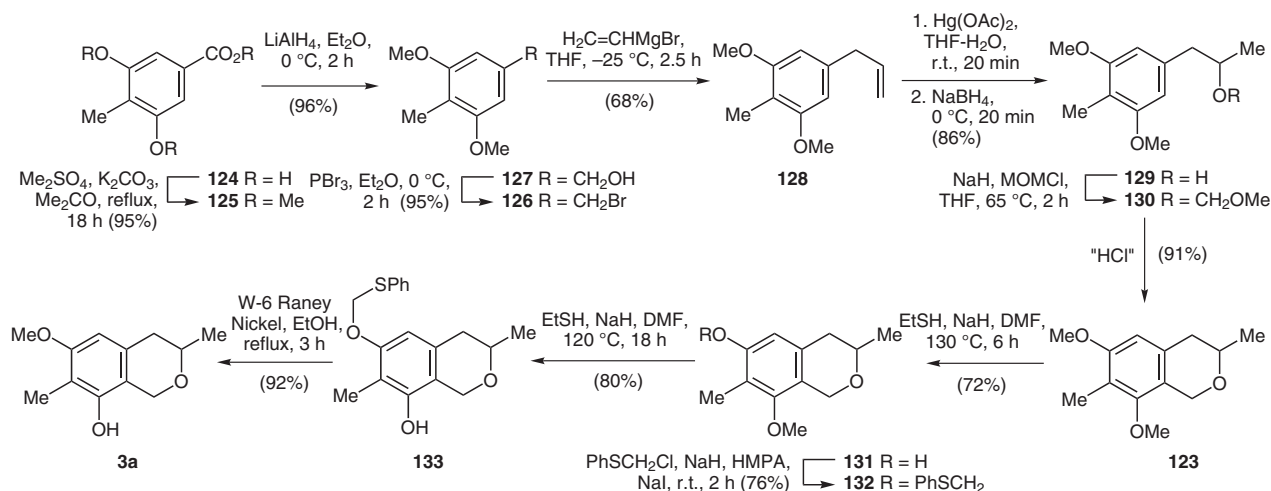ide (MOMCl), the alcohol furnished isochroman **123**, presumably by in situ acid-catalyzed (from excess MOMCl) oxa-Pictet–Spengler cyclization of intermediate **130**, which was not isolated.

Because the 8-methoxy group could not be selectively removed, the synthesis took advantage of the comparatively easy selective demethylation of the 6-methoxy moiety of **123**. Therefore, the resulting **131** was protected as the benzylthiomethyl ether derivative and the so-obtained **132** was submitted to demethylation to furnish **133**. Finally, reductive desulfurization afforded the target structure **3a**.

Compounds **3** and **131**, as well as some of their esters and ethers, were active in the wheat coleoptile assay. In addition, **3a** and **131** were demonstrated to inhibit the enzyme aldose reductase.[71]

2.5   Synthesis of C-4-Substituted Isochroman Derivatives

For the synthesis of 5-spirobenzodiazepinones, Gatta and Settimij[72] prepared cyclopentyl β-phenethyl alcohol **134a** and N-methylamino derivative **134b**[73] from ethyl phenylacetate **135**, by intermediacy of **136**.

As shown in Scheme 15, alcohols **134** were condensed with benzaldehyde under hydrochloric acid catalysis to furnish 1-phenylisochromans **137**. Chromium trioxide oxidation of the latter[74] followed by reaction of the resulting δ-ketoacids **138** with substituted hydrazines afforded the required benzodiazepine derivatives **139**. The isochroman-3-ones **140** seemed to be reaction intermediates, because once heated under vacuum they were smoothly converted into the products **139**.

Interestingly, a different oxa-Pictet–Spengler reaction strategy (Scheme 16) had to be employed for the synthesis of the related spirocyclic 1-phenylisochroman derivative
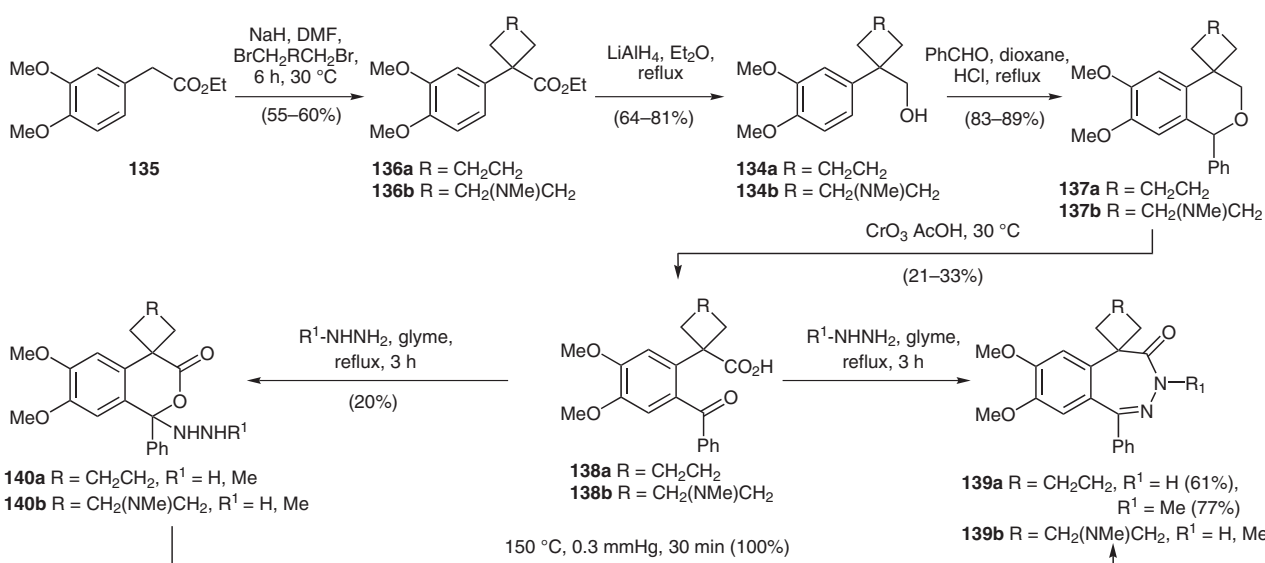
Scheme 15

141. This entailed the cyclization of **142**, analogous to **134a**, with formaldehyde in acetic acid to furnish **143**, which, once halogenated with chlorine to α-haloether **144**, was reacted with phenylmagnesium bromide to furnish the desired 1-phenylisochroman **141**.[75]
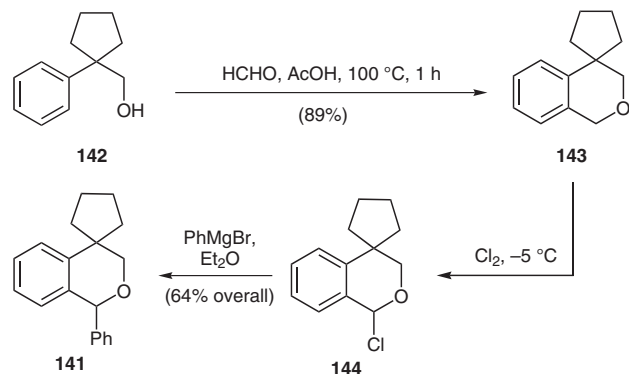
Scheme 16

The 4,4-disubstituted isochroman **145** was prepared in 45% yield by the team of Yamato,[76] who employed **146** as starting alcohol component (Scheme 17). Upon oxidation of **145** to the corresponding tetrahydroisocoumarin **147**, the ability of both heterocycles to inhibit the release of histamine was tested; however they were determined to be inactive.

Scheme 17

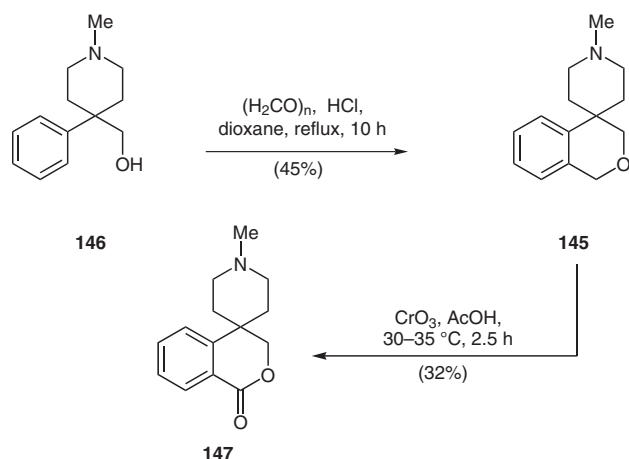Analogously, the same Japanese group prepared open-ring analogue **148** from γ-chloronitrile **149** (Scheme 18), which was aminated and then subjected to a Pinner-type acid-catalyzed methanolysis to furnish ester **150**.

The latter was reduced to β-phenethyl alcohol **151**, which was then submitted in situ to an oxa-Pictet–Spengler cyclization with paraformaldehyde and hydrochloric acid. Unfortunately, compound **148** was found to be inactive as a histamine release inhibitor.

It is also worth mentioning that during the work on hypotensive agents with peripheral and central action, McCall and co-workers[77] synthesized a series of 1,1,4,4-
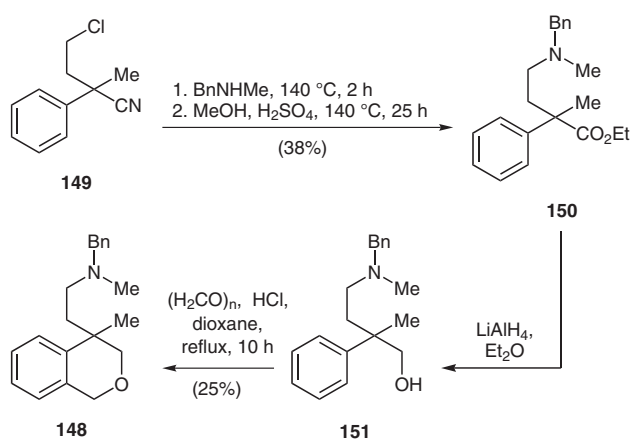
Scheme 18

(**152**) and 1,1,3,3-tetrasubstituted isochromans (**153**) in moderate to good yields (Scheme 19).

This was carried out by the oxa-Pictet–Spengler reaction of the corresponding β-phenethyl alcohols **154** and **155** with ethyl acetoacetate. In turn, alcohols **155** and **154** were accessed in high yields from ester **135** by methyl Grignard addition or LDA-mediated α-carbonyl alkylation (to **156**) and borane reduction, respectively.
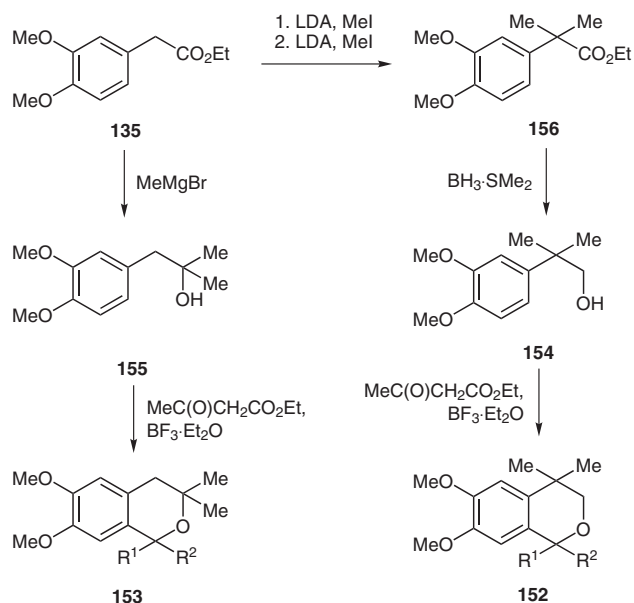
Scheme 19

Catechin (**157**) is a phenolic pigment of vegetal origin which acts as a natural antioxidant by the mechanism of oxygen-radical scavenging. Its activity is rather poor compared to that exhibited by the flavonoid quercetin (**158**), which due to its planar geometry, is able to delocalize the radical through the entire molecule.

Taking into account that the A and B rings of catechin are perpendicular,[78] the group of Fukuhara synthesized the planar analogue of catechin, **159**, by reaction of the natural product with acetone under BF₃·Et₂O catalysis (Scheme 20).[79]
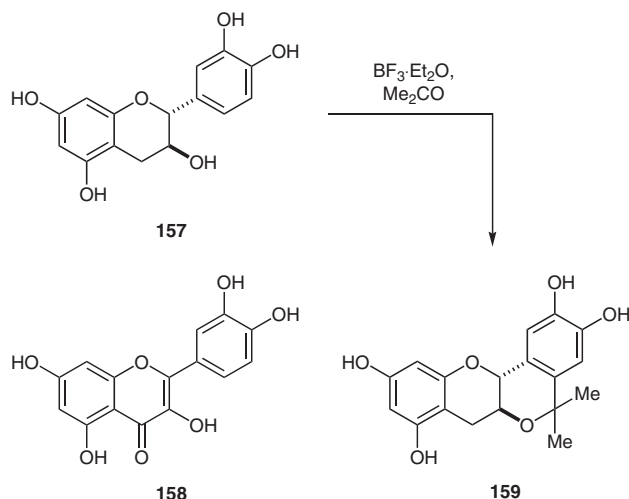
Scheme 20

This compound protected DNA from Fenton-reaction-mediated damage, and exhibited marked hydroxyl-radical scavenging ability, exceeding that of catechin.[80]

3 Intramolecular Oxa-Pictet–Spengler Cyclizations

The intramolecular versions of the oxa-Pictet–Spengler cyclization comprise reactions in which the carbonyl component is attached to the β-aryl-ethanol in the form of a mixed acetal, a vinyl ether, an α-acetoxy ether or a halomethyl ether.

Other versions include 1,3-dioxolanes as masked carbonyls, in which case 4-hydroxyisochromans are the resulting products, unless a reducing agent is employed during the cyclization process. In the latter situation, isochromans are produced.

The presence of substituents on the carbinolic or the benzylic positions of the alcohol moiety allows the preparation of compounds with different substitution patterns on the heterocyclic ring. There are no recorded examples of 1,1-disubstituted isochromans prepared by this intramolecular cyclization protocol; however, the diastereoselective synthesis of 1,3- and 1,4-disubstituted compounds is possible, especially in the case of the former substitution motif.

3.1 Synthesis of 1-Substituted Isochromans

The synthesis of 6-methoxyisochroman from the methoxymethyl ether of 3-methoxyphenethyl alcohol was reported by Meyer and Turner.[81a] U-54537 (**160**; Scheme 21) is an antihypertensive agent, working through the α-adrenergic receptors.[81b,c]

Removal of the two methoxy groups of **160** gave **161a**, which exhibited an increased preference for the D_4 over the D_2 receptor, while retaining significant binding to other CNS receptors.

The synthesis of analogues **161a** and **161b** started with β-phenethyl alcohol (**162**), which was reacted with chloroacetal **163** to give mixed acetal **164**; this was isolated and subjected to an oxa-Pictet–Spengler cyclization to isochroman **165** with aluminum chloride as the Lewis acid promoter (Scheme 21).
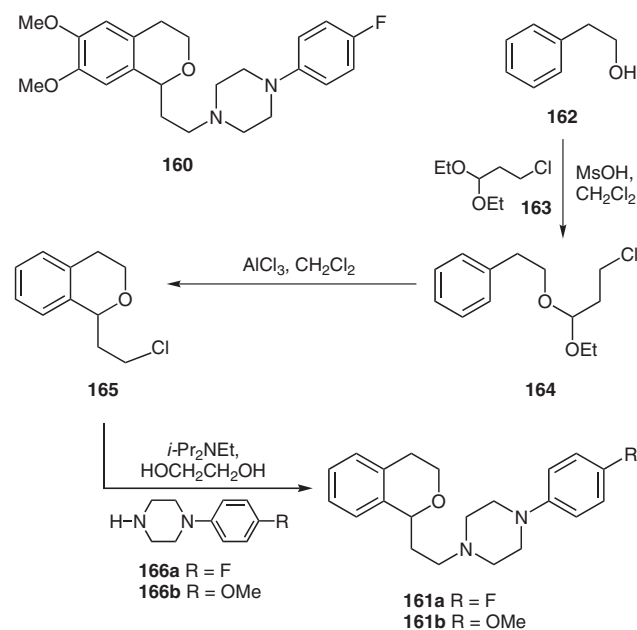
Scheme 21

Displacement of the halogen with different aryl piperazines (**166a** and **166b**) gave final products **161a** and **161b**. Compound **161b** was found to have a 400-fold preference for D_4 versus D_2 receptors. Other piperazine and related derivatives were later prepared by Combourieu and co-workers, by way of the same general strategy.[82]

3.2 Synthesis of 1,3- and 1,4-Disubstituted Isochromans

The reaction of β-phenethyl alcohols with paraldehyde or paraformaldehyde in the presence of acids to form isochroman derivatives has been reported by several groups.[83] These reactions most likely proceed through α-chloroethers or hemiacetals. A related transformation, occurring via an iodoacetal, was also reported by Jung.[40a]

Mohler and Thompson[84] disclosed an approach to isochromans under mild conditions that involved the prior preparation of acetals or enolethers derived from β-phenethyl alcohols employing MEM chloride and ethyl vinyl ether, respectively, and their cyclization with titanium tetrachloride as Lewis acid promoter. Before their breakthrough, only two reports mentioned the synthesis of mixed acetals towards isochromans.[60,85]

This group proposed a boat-like transition state for the ring-closure process. In this reaction (Scheme 22), cyclization of the acetals presumably starts by alkoxide abstraction by the Lewis acid from **167a**, leaving a stabilized

oxocarbocation (**167b**) which undergoes electrophilic attack on the aromatic ring to afford species **167c**. Final elimination of a proton produces the isochroman nucleus **168**.
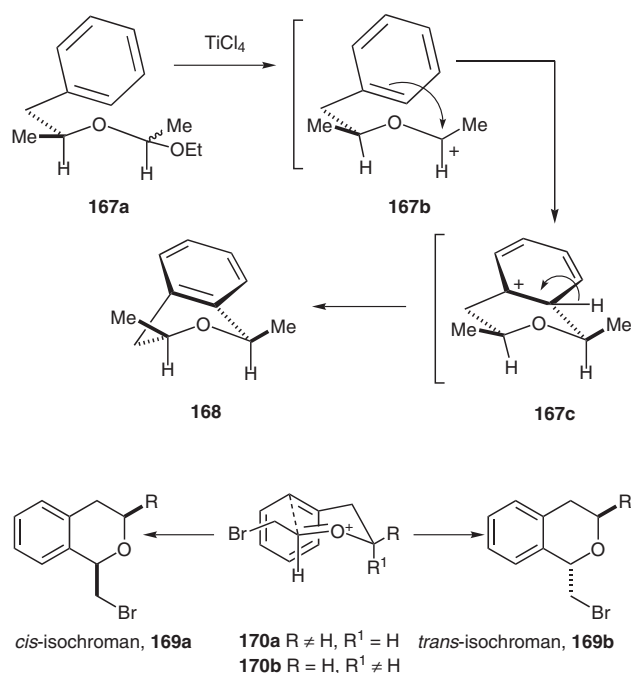
Scheme 22

Cyclization of a 52:48 mixture of acetals **167a** derived from 1-phenyl-2-propanol and ethyl vinyl ether gave a 4:1 mixture of *cis-* and *trans*-1,3-dimethylisochroman. The product distribution may be attributable to the fact that the *cis* isomer **168** has both of its methyl groups adopting a pseudoequatorial orientation, which minimizes the 1,3-diaxial interaction across the oxygen – a feature already observed in other pyran derivatives.[86]

Analogously, the outcome of the cyclizations reported by DeNinno, preferentially or exclusively leading to the 1,3-*cis*-isomers **169a**, has been explained on the basis of analysis of the reaction intermediates.[87]

Assuming that the reaction takes place through a chair-like transition state, 1,3-*trans*-isochromans **169b** are generated when the bulky pro-C-3 substituent is located pseudoaxially in the *E*-oxonium ion intermediate (**170b**). On the other hand, the corresponding *cis* isomers arise from intermediates bearing the pro-C-3 substituent located in the more favorable pseudoequatorial position (**170a**). Interestingly, transition states involving *Z*-oxonium ions are disfavored due to severe 1,3-diaxial interactions.

Some intramolecular oxa-Pictet–Spengler cyclizations leading to 1,3- and 1,4-disubstituted isochroman derivatives have been described as particular cases of the Prins cyclization. This transformation is one of the most powerful methods for accessing tetrahydropyran derivatives[88] and involves the coupling of homoallylic alcohols with

several equivalents of simple aldehydes, under acid catalysis.[89] Acetals can be used in place of aldehydes[90] and allylsilane analogues of homoallylic alcohols facilitate the cyclizations.

In addition, α-acetoxy ethers, readily available from the corresponding esters by partial reduction and acetylation of the corresponding hemiacetal intermediates,[91] are also useful cyclization substrates for this reaction as demonstrated by Dahanukar and Rychnovsky. These authors used β-phenethyl alcohols in place of the homoallylic alcohol component in their modified Prins sequence, and obtained good yields of isochromans.[92]

In Rychnovsky's cyclization protocol (Scheme 23), the chloroacetate **171b**, derived from a β-substituted β-phenethyl alcohol, furnished exclusively 1,3-*cis*-isochroman **172b** in 90% yield through the intermediacy of **173b**. However, in the example involving the α-substituted congener **171a**, the same transformation from mixed acetal **173a** furnished 97% of **172a** as a 3:1 diastereomeric mixture.
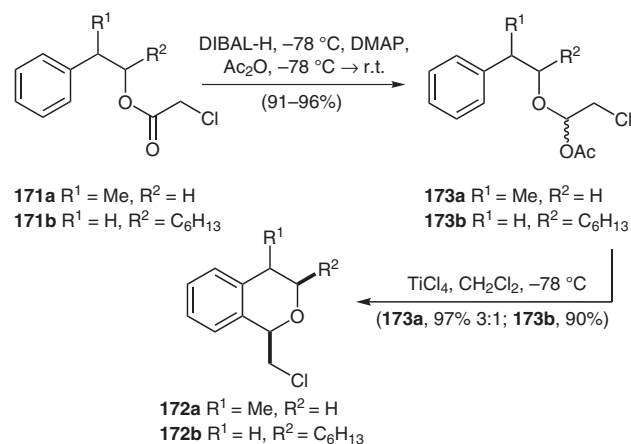
Scheme 23

Other examples of this kind of 1,3-induction during the intramolecular oxa-Pictet–Spengler reaction have been observed by the group of Kaufman[93] in similar systems, in which the isochroman ring is formed under different conditions.

3.3   Synthesis of 1,3,4-Trisubstituted Isochromans

The group of Giles reported the titanium tetrachloride promoted diastereoselective isomerization of 2,5-dimethyl-4-naphthyldioxolanes into benzoisochromans and examined this transformation in relation to natural product synthesis.[94]

The rearrangement, which has been regarded as an intramolecular version of the Mukaiyama reaction,[95] proved to be highly versatile. Subsequent studies by this Australian group explored the rearrangement's scope and limitations by converting the corresponding 2,5-dimethyl-4-phenyl-dioxolanes into isochromans in high yield.[96]

These studies demonstrated that the 4,5-stereochemistry of the parent dioxolanes was transferred intact to the corresponding 4,3-positions of the resulting isochromans, so that 4,5-*trans* dioxolanes afford 3,4-*cis* isochromans. The C-1 of the isochromans is derived from C-2 of the dioxolanes with a diastereoselectivity that seems to depend upon the aryl substitution and 4,5-stereochemistry of the substrate, and also upon the reaction temperature, when the C-1 substituent in the final compound is methyl.

In a further extension of this process, the authors also demonstrated the conversion of methyl 4,5-*trans*-4-aryl-dioxolan-5-yl acetates into methylisochroman-3-yl acetates and the corresponding isochroman-γ-lactones, a structural feature of the pyranonaphthoquinone antibiotics.[97]

In a systematic exploration, Kaufman's group more recently demonstrated that the oxa-Pictet–Spengler isomerization of acetals **174**, derived from *threo*-diols **175**, stereoselectively gives 1,3-*cis*-disubstituted isochromans **176** when the substituents are bulkier or more complex than simple methyl groups (Table 3).[93]

The rearrangement occurs under the promotion of TiCl$_4$, with other Lewis acids such as BF$_3$·Et$_2$O being ineffective; however, in some isolated cases, this transformation was demonstrated to take place under *p*-toluenesulfonic acid assistance.

The proposed reaction mechanism (Scheme 24) involves the initial protonation (when TsOH is employed) or coordination of titanium tetrachloride with O-3 of the starting
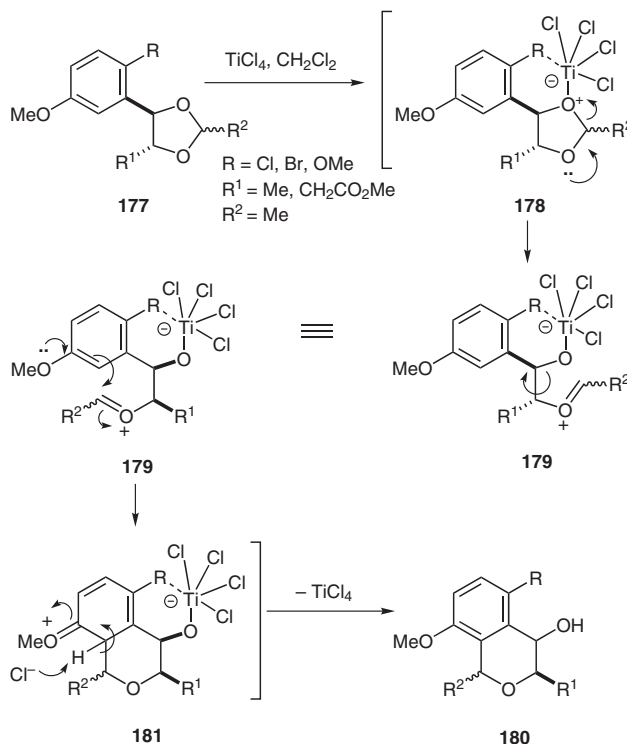
Scheme 24

Table 3 An Intramolecular Oxa-Pictet–Spengler Cyclization
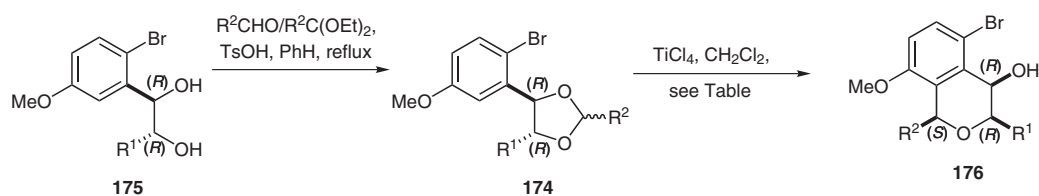
Entry	R^1	R^2	Conditions	Yield (%)
1	(CH$_2$)$_3$CO$_2$Et	CH$_2$Br	TiCl$_4$, CH$_2$Cl$_2$, –30 °C → r.t., 2 h	47
2	(CH$_2$)$_2$CH$_2$OBn	CH$_2$SPh	TiCl$_4$, CH$_2$Cl$_2$, –60 °C → –30 °C, 2 h	26
3	(CH$_2$)$_2$CN	CH$_2$SPh	TiCl$_4$, CH$_2$Cl$_2$, –30 °C, 2 h	87
4	(CH$_2$)$_2$CN	(CH$_2$)$_3$SO$_2$Ph	TiCl$_4$, CH$_2$Cl$_2$, –78 °C, 1.5 h	59
5	(CH$_2$)$_2$CN	(CH$_2$)$_3$OTBDPS	TiCl$_4$, CH$_2$Cl$_2$, –45 °C, 4 h	60

acetal **177**, leading to **178**, where ring opening of the di-oxolane ring C-2–O-3 bond, to afford the corresponding intermediate oxocarbenium ions **179**, takes place under assistance of O-1.

In turn, this intermediate undergoes an allowed 6-*enolen-do-endo-trig* type electrophilic cyclization to furnish the isochroman **180** by way of **181**. Alternatively, O-1 can be attacked; however, this leads to cleavage of the C-2–O-1 bond and furnishes an alternative oxocarbenium ion that cannot achieve the disallowed 5-*enolendo-endo-trig* type cyclization to dihydroisobenzofurans; therefore, these species usually revert to the parent dioxolanes.

The presence of an electron donor on the aromatic ring *ortho* to the dioxolanyl side chain blocks this otherwise favored cyclization position and offers a coordination site for the Lewis acid catalyst. In the absence of such a group in this position, low yields of isochromans are achieved. As shown in Scheme 25,[98] this kind of transformation was also employed by Cintrat and co-workers for the synthesis of 4-phenyl 3-substituted isochromans.

This French team[98] employed ortho esters such as **182** as acetal precursors; their reduction with tributyltin hydride gave the required acetals,[99] while use of tributyltin deuteride as reducing agent furnished deuterium-labeled formals (**183-d**), the rearrangement of which provided 1-deuteroisochromans **184-d**. Unfortunately, reported yields of isochromans were in the range of 5–30%.
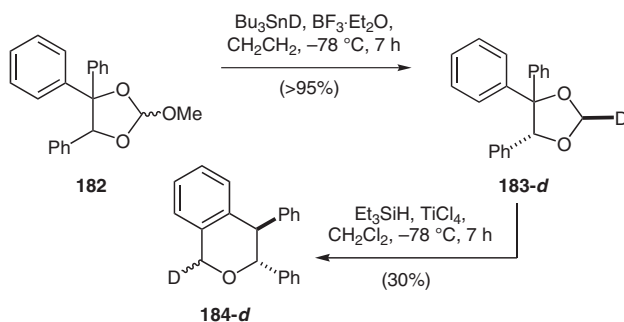
Scheme 25

Unlike Giles' protocol, the reaction does not take place in the absence of triethylsilane, which acts as a reducing agent, according to the proposed reaction mechanism shown in Scheme 26. There, the silane agent may act preferentially before the cyclization of the common intermediate **185**, formed by reaction of **183** with TiCl₄ according to the mechanism outlined in Scheme 26 (Path b, **185** → **186**). An alternative route (Path a), in which the reduction would occur after the cyclization of **185** to **187**, is also possible, but less likely to be operative.

The use of deuterated triethylsilane provides a C-4-labeled isochroman; in every case the 3,4-*trans* diphenyl derivative **184** was isolated through the intermediacy of **188**, presumably due to steric reasons.
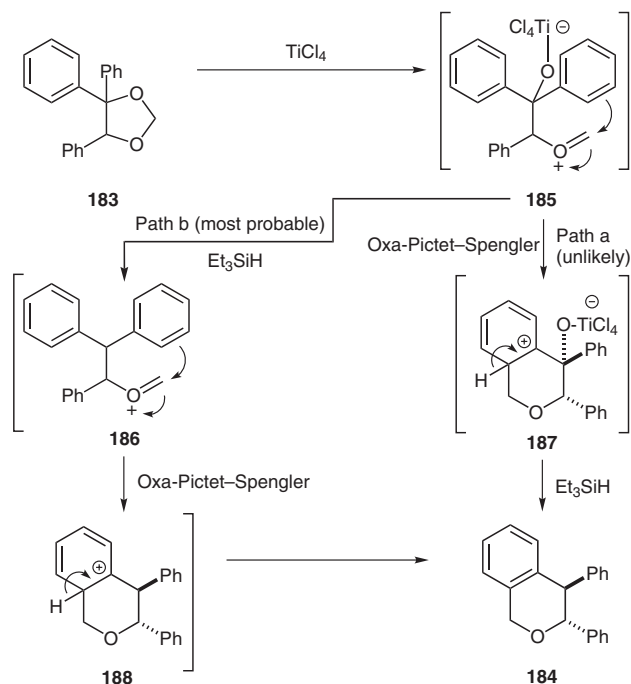
Scheme 26

4   The Oxa-Pictet–Spengler Condensation in the Absence of Acid Catalysts

The oxa-Pictet–Spengler condensation may proceed in the absence of an added acid catalyst in the case of highly activated substrates, like phenols.

Working with phenethylamines, Kametani demonstrated that 3-hydroxyphenethylamine (**189**) condensed with several aldehydes and ketones, without acid catalysis, to give the corresponding 6-hydroxy-1,2,3,4-tetrahydroisoquinolines **190**, carrying one or two substituents on C-1 (Scheme 27).[100] This transformation was designated as 'phenolic cyclization' because the phenolic moiety plays a key role in the cyclization process. The reaction was employed for the synthesis of 2-benzazepines,[101] phthalazines[102] and tetrahydroisoquinolines.[103]
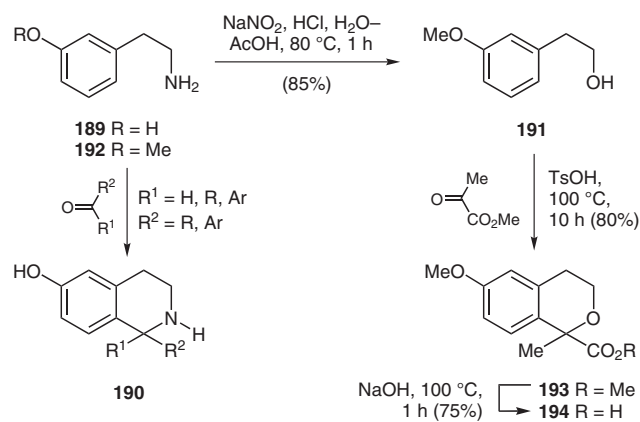
Scheme 27

Kametani also reported that mixing 2-(3-methoxyphen-yl)ethanol (**191**), prepared from **192**, with methyl pyruvate without an acid catalyst gave no reaction and allowed recovery of the starting material,[104] but isochroman **193** could be obtained in 80% yield by condensation of the former reagents in the presence of catalytic amounts of *p*-toluenesulfonic acid. Saponification of **193** gave 75% yield of **194** (Scheme 27).

The group of this Japanese scientist generalized and extended this reaction, studying the cyclization of *trans*-2-(3-hydroxyphenyl)cyclohexanol (**195**), easily available from the related ketone **196**[105] with several carbonyl compounds, accessing in this way hexahydro-6*H*-dibenzopyrans (Scheme 28). Yields, however, were less than 30%.
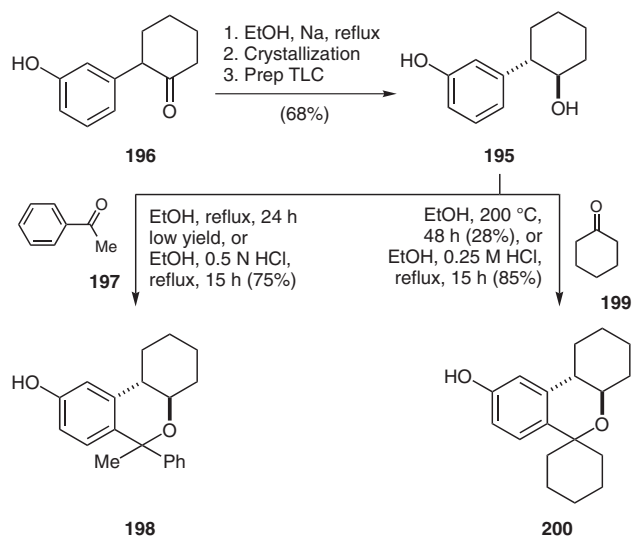
Scheme 28

Heating of **195** with acetophenone (**197**) in ethanol for 24 hours resulted in a poor yield of 1,2,3,4,4a,10b-hexahydro-6-methyl-6-phenyl-9-hydroxy-6*H*-dibenzo[*b,d*]pyran **198**; this increased to 75% upon addition of HCl. Analogously, reaction with cyclohexanone (**199**) gave the cyclohexyl derivative **200** (28%) which could be prepared in 85% yield when HCl was added as catalyst.

5 Naturally Occurring Oxa-Pictet–Spengler Cyclizations

Softwood lignins are produced principally from coniferyl alcohol via radical coupling reactions of **201** and **202**. Arylisochromans **203** were recently identified by NMR[106] in the trimer fraction of pine wood (from *Pinus taeda*) degraded by the DFRC (*d*egradation *f*ollowed by *r*eductive *p*rocedure) protocol.[107a,b] This implies a new pathway from **204** following the initial β-1 coupling between the coniferyl alcohol radical **201** and the lignin oligomer radical **202**, which traditionally is known to give **205** and **206**.[107c]

Whether arylisochromans are present as such in native lignins is not clear, but even if not, the internal trapping of a β-1 quinone methide intermediate **204** to give **207** suggests that it is presumably operating in vivo. The rationale for the formation of such arylisochromans through an oxa-Pictet–Spengler intramolecular condensation is given in Scheme 29.

Presumably, **207** undergoes ring opening to oxocarbenium ion **208** through the intermediacy of **209**; the mechanism furnishing **210** by way of **203** is analogous to other oxa-Pictet–Spengler cyclizations. Although the identification of the arylisochroman structure in isolated milled
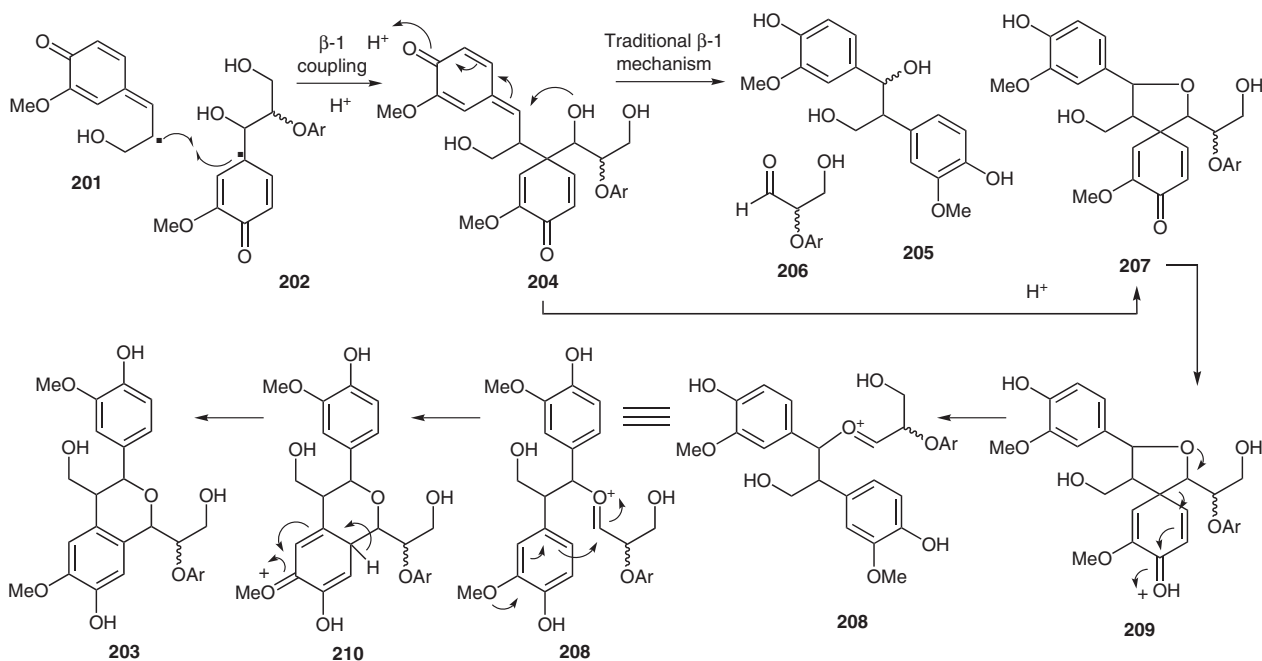
Scheme 29

wood lignins can be made firmly, the quantity visible in the NMR spectra is low. The possibility remains that **203** is a product of isolation and that its precursor **207**, for example, may be the true in situ natural product.

Either way, however, structure **203** provides compelling evidence for the occurrence of an internal cyclization pathway from β-1 intermediate **204**.

In addition, it is interesting to note that the presence of 1-(3-methoxy-4-hydroxy)phenyl-6,7-dihydroxyisochroman (L116, **211**) and 1-phenyl-6,7-dihydroxyisochroman (L117, **212**) in olive oil has been confirmed by chromatographic and spectroscopic means.

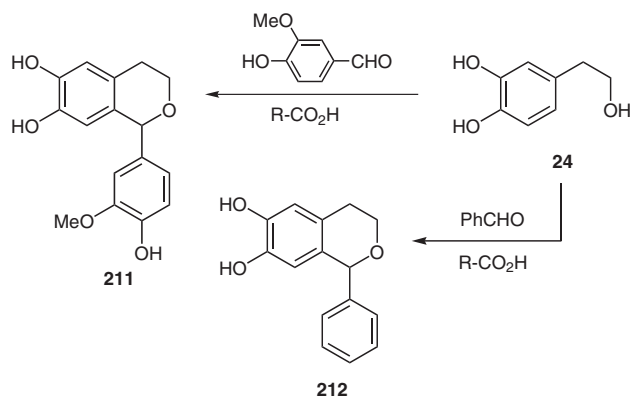These may be formed by an oxa-Pictet–Spengler cyclization of hydroxytyrosol (**24**) known to occur in olive oil, and the corresponding aldehydes, under catalysis of fatty acids always present there in small amounts[108] (Scheme 30). The antioxidant and platelet aggregation inhibiting properties of these isochromans have also been reported.[109]

Scheme 30

6   Oxa-Pictet–Spengler Reactions towards Optically Active Compounds

Few examples are available of optically active oxygen-bearing heterocycles accessed by way of the oxa-Pictet–Spengler condensation.

These can be either intermolecular or intramolecular processes which entail (a) the use of chiral carbonyl components, (b) condensation of chiral substrates with carbonyls or masked carbonyls with formation of a new asymmetric center, in a process involving 1,3-chirality transfer, (c) cyclization of chiral substrates with formaldehyde or its equivalents without formation of a new chiral center, and (d) the resolution of diastereomeric compounds formed through an oxa-Pictet–Spengler reaction.

In one of the rare examples described of chiral oxa-Pictet–Spengler cyclizations, Costa and co-workers disclosed their strategy to synthesize chiral analogues of etodolac (**214**). Based on the original synthesis, which relies on the oxa-Pictet–Spengler condensation of 7-ethyltryptophol (**215b**) with methyl β-ketobutyrate, these scientists pre-
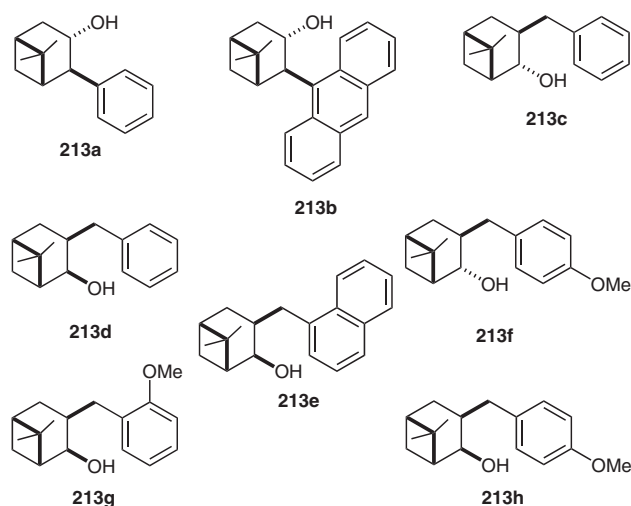
Figure 6

pared chiral β-ketoesters **216a–h** by reaction of acetoacetates **217a–h** with **215a**. The esters were synthesized by acetoacetylation of the chiral secondary alcohols **213a–h** shown in Figure 6, which are derived from (–)-(1S)-β-pinene.[110]

Regardless of the Lewis acid employed (Table 4), esters prepared with **213c** and **213f** gave racemic products (**216c** and **216f**), while chiral auxiliaries **213e**, **213g** and **213h** furnished either racemic or chiral esters **216e, 216g** and **216h**, respectively, depending on the Lewis acid employed. This effect was dramatically noticeable in the case of **213h**. It was also observed that SnCl$_4$ seemed to always outperform BF$_3$·Et$_2$O.

Excellent yields of the final acids **214** were obtained by saponification of the thus-obtained esters. In addition, by means of the oxa-Pictet–Spengler cyclization, Brenna and co-workers[111] synthesized several esters and alcohols related to etodolac, that were found to be difficult to resolve enzymatically. However, classical resolution with (+)-(R)-α-methylbenzylamine afforded a poorly soluble salt from which the pharmacologically active S enantiomer could be made free.

The same Italian researchers demonstrated that the unwanted enantiomer remaining in the mother liquors could be recycled, since it completely racemized by a 'retro' oxa-Pictet–Spengler after refluxing two hours in toluene with a catalytic amount of p-toluenesulfonic acid.[111]

An oxa-Pictet–Spengler cyclization was employed by the group of Lesma during their synthesis of (+)-(20R)-15,20-dihydrocleavamine (**218**).[112] This tetracyclic alkaloid is structurally related to 16-β-carbomethoxyvelbanamine, the indole 'upper half' of the antitumoral bisindole alkaloids occurring in *Catharantus roseus*, such as vinblastine and vincristine.

To this end, this Italian group enzymatically desymmetrized *meso*-piperidine-3,5-dimethanol and transformed the *R,R* enantiomer into enol ether **219**. Chiral enol ether **219** was protected as its benzoate **220**, and then was sub-

Table 4 Oxa-Pictet–Spengler Mediated Synthesis of Optically Active Analogues of Etodolac: Condensation of **215a** with Chiral Esters **217**

215a R = H
215b R = Et

KOH, MeOH–H$_2$O,
reflux (90–96%) **216** R = R*
 214 R = H
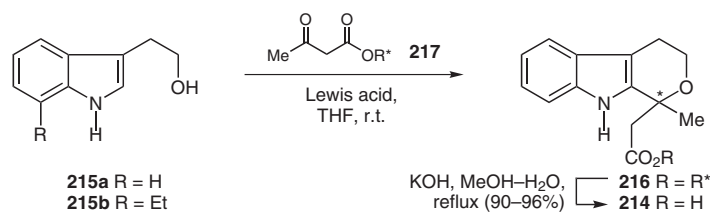
Entry	R* of **217** from	Lewis Acid	Product	Yield (%)	de (%)	$[\alpha]_D$
1	**213a**	BF$_3$·Et$_2$O	**216a**	87	10	
2	**213b**	BF$_3$·Et$_2$O	**216b**	81	40	−8.54
3	**213b**	SnCl$_4$	**216b**	70	36	
4	**213c**	BF$_3$·Et$_2$O	**216c**	68	0	
5	**213c**	SnCl$_4$	**216c**	61	0	
6	**213d**	BF$_3$·Et$_2$O	**216d**	58	73	
7	**213d**	SnCl$_4$	**216d**	57	84	−18.0
8	**213e**	BF$_3$·Et$_2$O	**216e**	85	10	
9	**213e**	SnCl$_4$	**216e**	73	0	
10	**213f**	BF$_3$·Et$_2$O	**216f**	61	0	
11	**213f**	SnCl$_4$	**216f**	59	0	
12	**213g**	BF$_3$·Et$_2$O	**216g**	80	0	
13	**213g**	SnCl$_4$	**216g**	78	24	
14	**213h**	BF$_3$·Et$_2$O	**216h**	65	0	
15	**213h**	SnCl$_4$	**216h**	59	>95	−20.2

jected to oxa-Pictet–Spengler condensation with tryptophol (**215a**), yielding 74% of **221** as a mixture of diastereomers (Scheme 31).

Reductive opening of the pyran ring of **221** provided 44% of **222**, which was transformed into mesylate **223**. This set the stage for the intramolecular alkylation of the piperidine ring, which afforded **224** after hydrogenolytic deprotection of the piperidine moiety. Benzoate **224** was finally homologated to **218** in 62% yield from **223**, through the use of organocopper chemistry.

In search of potent and selective D$_1$ agonists, DeNinno and co-workers[113] prepared 3-arylisochroman derivative A68930 (**225**) by employing the oxa-Pictet–Spengler condensation of a polysubstituted β-phenethyl alcohol with bromoacetal (**82b**).

In one of the same group's published sequences (Scheme 32), cyclohexylidene-protected catechol **226** was *ortho*-metallated and the resulting organolithium species was employed to nucleophilically open styrene oxide (**227**) and furnish alcohol **228**.

This was stereospecifically cyclized with bromoacetal under BF$_3$·Et$_2$O promotion, and the resulting 1,3-*cis* disub-

stituted isochroman **229** was transformed into the primary amine **230** by nucleophilic displacement of the primary bromide by azide anion and subsequent reduction of the azide.

Finally, mild acidic deprotection gave the target molecule **225**. Interestingly, these compounds are prone to epimerization upon prolonged exposure to organic acids such as TFA, such that this process results in a prevalence of the corresponding *trans* isomers, which are thermodynamically more stable. In vitro, compound **225** exhibited D$_1$/D$_2$ selectivity greater than 1500:1 and was more potent than the reference compound SKF38393 (**231**).

Since the stereochemistry of the chiral center formed at C-1 is controlled by the center at C-3, in order to prepare this target compound in optically active form, ketone **232**, easily available from **228** by oxidation with PCC, was employed as starting material.

Once subjected to reduction with Brown's chiral (–)- and (+)-diisopinocampheyl chloroboranes **233**,[114] compound **232** gave chiral alcohols (*R*)-**228** and (*S*)-**228** in high enantiomeric excess (Scheme 33).
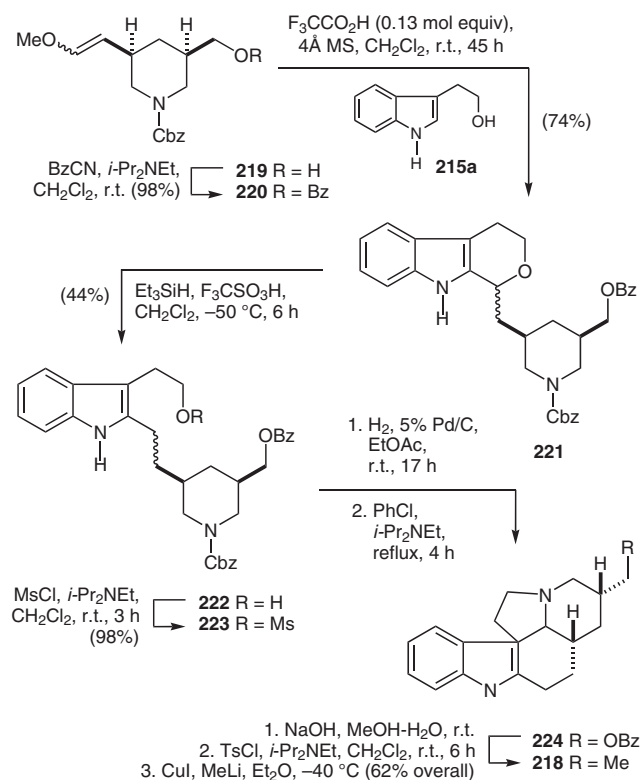
Scheme 31

Scheme 32

Interestingly, this led to the demontration that the activity of this isochroman resided mainly in one single enantiomer; thus, the (1S,3R)-**225** analogue exhibited a K_i of 7200 nM and EC_{50} of 8580 nM, while the (1R,3S)-**225** enantiomer displayed a D_1 binding K_i of 1.6 nM and an EC_{50} of 1.95 nM. Furthermore, the bulky phenyl ring was very important for achieving good activity, since the desphenyl analogue **19a**[28c,30c] was 200–400-fold less potent.

The compounds were also orally active in vivo. A related compound, **225a**, known as A-77636, was prepared by the same strategy.
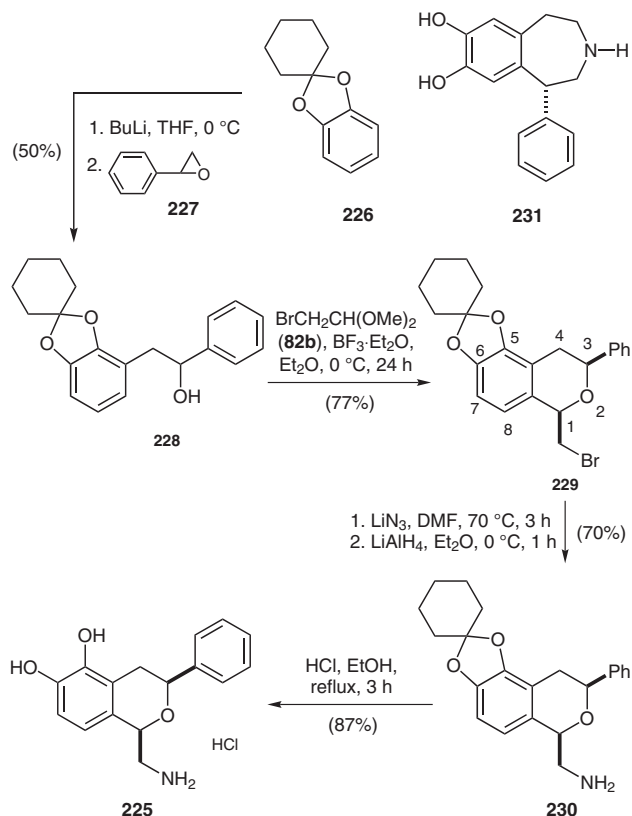
In addition, other *cis*-1,3-disubstituted isochroman derivatives were elaborated by the same group; the required chiral β-phenethyl alcohols were obtained by Corey's oxazaborolidine-mediated reduction of a ketone[115] prepared with the aid of chiral oxazaborolidines,[116] or by the nucleophilic opening of chiral epoxides (for a similar strategy, see Scheme 37).

Wünsch and Zott[117] (Scheme 34) reported the regioselective preparation of enantiopure 1,5-epoxy-3-benzazocines and 1,6-epoxy-4-benzazocines, structurally related to benzomorphans active as analgesics. They used an in-

tramolecular oxa-Pictet–Spengler condensation, with an acetal tether as the carbonyl moiety.

The starting acetal was prepared from tyrosine (**234**)[22] by its conversion to the corresponding (*S*)-3-(3,4-dihydroxyphenyl)lactate **74a**, methylation of the phenolic hydroxyls to give **74b**. *p*-Toluenesulfonic acid catalyzed aminolysis of the latter with aminoacetal provided the target **235**.

Scheme 34

Upon reaction with dioxane saturated with HCl, 60% yield of tricyclic lactam **236** was obtained, presumably through the intermediacy of acetal **237**. Final deoxygenation of the lactam with lithium aluminum hydride to **238**, followed by reductive methylation furnished the desired analogue **239**.

Similarly, the seven-membered heterocycle was prepared employing aminopropanal diethyl acetal in place of aminoacetal.

Wünsch[23] also reported that the oxa-Pictet–Spengler condensation of **74a** and methyl levulinate (**240**) gave mixtures of *cis* and *trans* 1,1,3-trisubstituted isochromans **241** (Scheme 35).

After Williamson etherification to **242** and chromatographic separation of the isomers, the levorotatory *cis*-diastereomer (1*S*,3*S*)-**242** was submitted to a Dieckmann condensation, while the dextrorotatory diastereomer was first epimerized at C-3 to (1*R*,3*R*)-**242** and then subjected to a Dieckmann condensation, leading to (*R*,*R*)-**243**. Enantiomeric ketones **244** were then prepared by saponification and decarboxylation of their corresponding β-ketoesters **243**.

Among the fragrances, Galaxolide (**6**), prepared and patented in 1967 by Heeringa and Beets,[118] is the ultimate result of the chemical evolution of the benzenoid musks (Figure 7) which began over 110 years ago with musk ketone (**245**)[118d] and passed through phantolide (**246**).
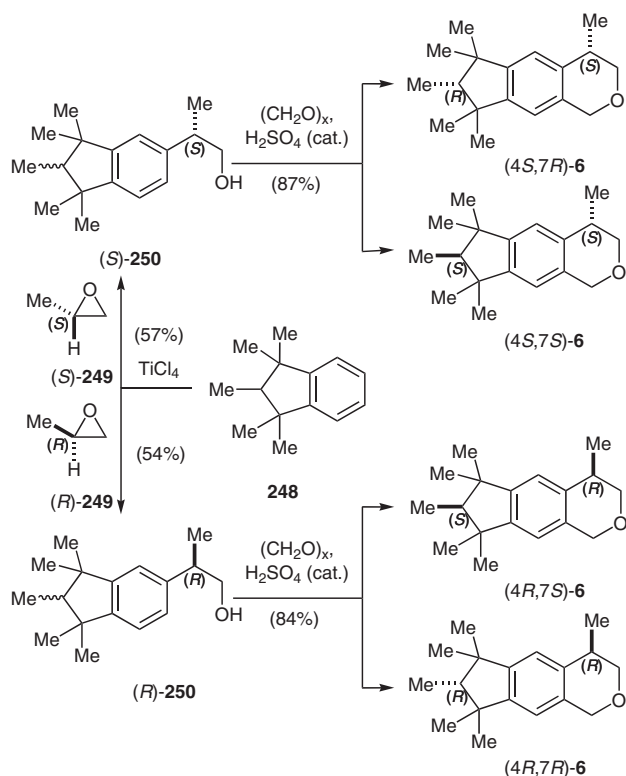

Figure 7

The current annual production of Galaxolide is around 3800 metric tons, and it has recently been detected in rivers and surface waters at μg/L levels.[119] Interestingly, only two of the four possible isomers of **6** are responsible for the valuable musk scent; this information is of high value in view of the low degradability of this product and increasing environmental concerns.

The group of Fráter was able to prepare and separate the diastereomers (4*RS*,7*SR*)-**6** and (4*RS*,7*RS*)-**6** through the formation of chromium carbonyl complexes **247**, as shown in Scheme 36.[120]

Scheme 35

Scheme 36

These authors[120] also synthesized all four of its isomers (Scheme 37) through a strategy that consisted of reacting 1,1,2,3,3-pentamethyl indane (**248**)[121] with chiral propylene oxides (*R*)-**249** and (*S*)-**249** under Friedel–Crafts-type conditions[122] promoted by titanium tetrachloride.
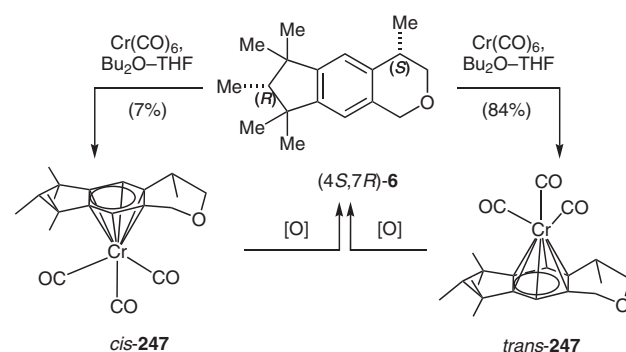

Scheme 37

This gave 54–57% yields of 1:1 diastereomeric mixtures of phenethyl alcohols (*R*)-**250** and (*S*)-**250**, respectively. Interestingly, complete configurational inversion of the oxiranyl chiral centers was observed.

Once submitted to the oxa-Pictet–Spengler cyclization with paraformaldehyde under sulfuric acid catalysis, the β-phenethyl alcohols **250** furnished two separate mixtures of galaxolide isomers in 84–87% yield. For these products, the stereochemistry of the C-4 methyl group was unequivocally established by correlation with the configuration of the starting oxiranes.

Each pair of diastereomers was separated through the use of the chromium complexes **247**; Scheme 38 shows the preferential formation of *trans*-**247** from (4*S*,7*R*)-**6**, which proved to be the most powerful compound, closely followed by (4*S*,7*S*)-**6**. The 4*R* isomers were demonstrated to be much weaker and to not contribute to the odor profile of galaxolide.

Scheme 38

A more recent synthesis of diastereomers of galaxolide on C-7 was described by the group of Scrivanti.[123] These Italian scientists prepared compound (4*S*)-**250**, also from **248**, by employing palladium chemistry coupled to a catalytic hydrocarbonylation and an enantioselective catalytic hydrogenation to build the 2-substituted hydroxypropyl side chain with the proper configuration on the methyl group. However, optical purities of the target compound were between 62% and 89%.

Racemic etodolac (**7**), prepared according to the original oxa-Pictet–Spengler synthesis of Humber,[42] was converted into its diastereomeric esters with (–)-borneol and the esters were separated by preparative HPLC. The enantiomers of the drug were then individually recovered (ee > 99.9%) after saponification.[124]

Bornyl esters also allowed the unequivocal establishment of the absolute configuration of etodolac (**7**). Thus, the *S* absolute configuration was assigned to the pharmacologically active (+)-etodolac (anti-inflammatory and analgesic), which is 2.6 times more potent than its enantiomer, on the basis of the crystallographic analysis of the *S*-(–)-bornyl ester of *R*-(–)-etodolac.[125] Interestingly, however, the *R* enantiomer of the drug has been proposed as a drug for treating hepatitis C.[126]

In a short communication of their results on the synthesis of selective dopamine D_4 antagonists, useful for treating schizophrenia and psychotic diseases, TenBrink and co-workers described the preparation of ester **251** by oxa-Pictet–Spengler condensation of β-phenethyl alcohol (**162**) and malonic acetal **252** (Scheme 39).[127] After hydrolysis to **253**, this was resolved enzymatically or by diastereomeric salt formation with the enantiomeric α-phenethyl amines **254**.

The resolved acids (*R*)-**253** and (*S*)-**253** were individually reduced to the corresponding alcohols **255** with borane, and these were coupled with different aryl piperazines **166b** and **256** through their mesylates. This allowed for the synthesis of chiral compounds (*R*)-**161b** and **257**, and their corresponding enantiomers. Isochroman derivative (*S*)-**257** (U-101387) is known as sonepiprazole.

An similar approach was followed by the same group in their synthesis of isochroman-6-carboxamides such as PNU-109291 (**258a**) and PNU-142633 (**258b**) (Figure 8).[128] These are both highly selective 5-HT$_{1D}$ agonists, useful for treatment of migraine, without cardiovascular side effects. The required chiral precursor was obtained by enzymatic resolution of a carboxylic acid analogous to **253**.
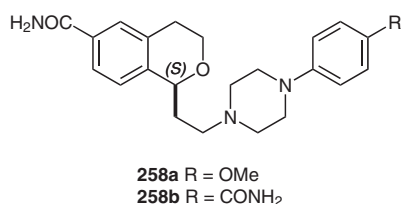
258a R = OMe
258b R = CONH$_2$

Figure 8

## 7 Synthesis of Heterocycles other than Isochroman Derivatives

In addition to being used in the synthesis of isochromans and naphthopyrans, the oxa-Pictet–Spengler cyclization was extensively employed for the synthesis of pyranoindoles, largely driven by the powerful pharmacological properties of etodolac. Other heterocycles have also been prepared following this strategy, thus extending the scope of the reaction.

There are few precedents on the oxa-Pictet–Spengler reaction being applied to the synthesis of furan derivatives;[129] however, recently the group of Miles reported the oxa-Pictet–Spengler reaction of 1-(3-furyl)alkan-2-ols.[130]
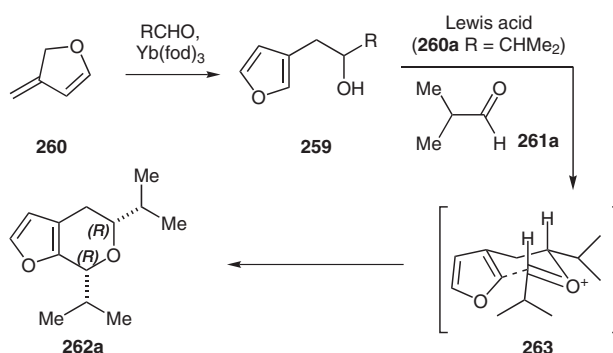
Scheme 40

In their protocol, the heterocyclic alkan-2-ols **259**, easily available through the carbonyl-ene reaction of 3-methylene-2,3-dihydrofuran **260** with different aldehydes (Scheme 40),[131] were cyclocondensed with various aldehydes **261** and acetone. Good yields were obtained of the highly acid-sensitive 5,7-disubstituted 4,5-dihydro-7*H*-furano[2,3-*c*]pyrans (**262**), potentially useful starting materials for the preparation of complex pyran-type natural products.[132]
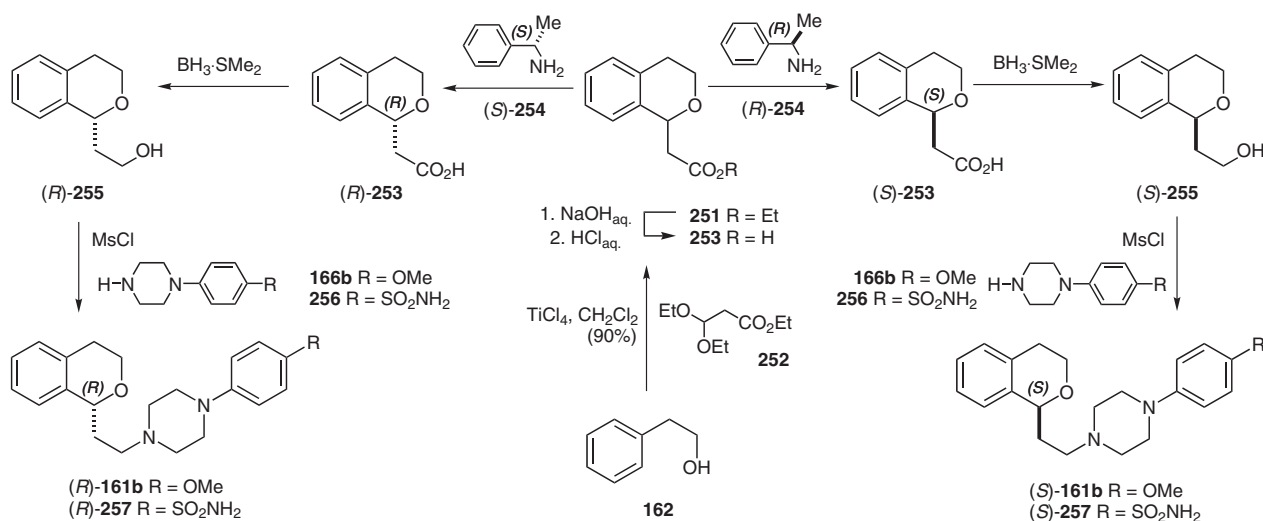
Scheme 39

It was found that *p*-toluenesulfonic acid is the most useful catalyst for this transformation (Table 5), but high catalyst loads were required for appropriate reaction rates when bulky carbonyls were used.

The reaction probably proceeds through a chair-like transition state (**263**) in which the bulky substituents of the furan and the carbonyl component remain pseudo-equatorially oriented in order to minimize steric interactions.

Therefore, reaction with aliphatic aldehydes such as isobutyraldehyde **261a** proved to be remarkably stereoselective, giving exclusively the *cis* isomer **262a** in most cases.

Moreover, when a 1:1 mixture of diastereomeric furano[2,3-*c*]pyrans was subjected to the standard reaction conditions, the mixture was recovered unchanged, demonstrating the 'kinetic' origin of the *cis* selectivity observed. The mechanistically similar Prins reaction exhibits similar behavior.[133]

The oxa-Pictet–Spengler[134] condensation of different heterocyclic β-ethanols **264a–d** (Figure 9)[135] with appropriate acetals or ketones as carbonyl components, leading to the synthesis of a series of different pyrano-type compounds **265**, has also been disclosed (Table 6).
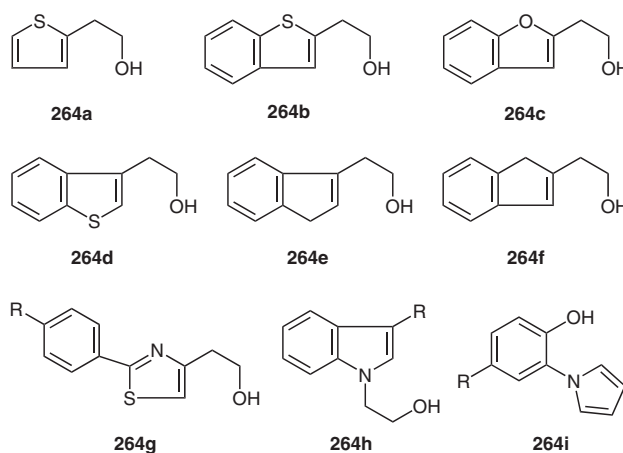
Figure 9

Reactions were carried out with HCl in dioxane, or with catalytic amounts of *p*-toluenesulfonic acid in refluxing benzene or toluene, with the assistance of a Dean–Stark trap to drive the reaction toward products. The transformations involving compounds **264h–i** operate by the same general mechanism.

In addition, [2]benzopyrano[3,4-*c*]pyridine derivatives **266a** (Figure 10)[136] substituted on both heterocyclic rings as well as on the aromatic moiety, have been prepared by

Table 5 Synthesis of 5,7-Disubstituted 4,5-Dihydro-7*H*-furano[2,3-*c*]pyrans Employing the Oxa-Pictet–Spengler Reaction

Entry	Furan (R^1)	Carbonyl (R^2, R^3)	Lewis acid, (mmol%)	Time	Temp.	Yield (%)
1	CHMe$_2$	CHMe$_2$, H	TsOH (1)	2	r.t.	76
2	CHMe$_2$	CHMe$_2$, H	Sc(OTf)$_3$ (1)	1	0 °C	45
3	CHMe$_2$	CHMe$_2$, H	Yb(OTf)$_3$ (1)	20	r.t.	56
4	CHMe$_2$	CHMe$_2$, H	TsOH (1)	1.25	r.t.	78
5	CHMe$_2$	4-Me-C$_6$H$_4$-, H	TsOH (10)	0.5	r.t.	14
6	(CH$_2$)$_8$Me	CHMe$_2$, H	TsOH (1)	2	r.t.	78^a
7	(CH$_2$)$_8$Me	CHMe$_2$, H	Sc(OTf)$_3$ (0.5)	0.5	0 °C	58
8	(CH$_2$)$_8$Me	CHMe$_2$, H	F$_3$CCO$_2$H (73)	1	r.t.	48
9	(CH$_2$)$_8$Me	(CH$_2$)$_3$Me, H	TsOH (1)	1.25	r.t.	63^b
10	(CH$_2$)$_8$Me	CMe$_3$, H	TsOH (10)	0.5	r.t.	95
11	(CH$_2$)$_8$Me	Me, Me (10 equiv)	TsOH (10)	0.5	r.t.	92
12	4-Me-C$_6$H$_4$-	CHMe$_2$, H	TsOH (19)	1	r.t.	82
13	4-Me-C$_6$H$_4$-	(CH$_2$)$_3$Me, H	TsOH (3)	5	r.t.	66

^{a} *Cis/trans* ratio = 14:1.
^{b} *Cis/trans* ratio = 15:1.

266a

266b

Figure 10

the oxa-Pictet–Spengler condensation of β-phenethyl alcohols with ketones and aromatic aldehydes[137] using HBr in dioxane as catalyst. Noteworthy, the same group prepared the 4-oxo analogue of etodolac **266b**;[138] related compounds were synthesized by Kreft and co-workers, employing $BF_3·Et_2O$ as catalyst.[139]

Analogously, Fréter and Fuchs[140] prepared pyrido[3,4-b]pyranoindoles **267**, employing the oxa-Pictet–Spengler condensation of **268** with aldehydes and ketones, under $BF_3·Et_2O$ catalysis (Table 7).

In the latter case, the starting materials were prepared by cycloalkenylation of properly substituted indoles to give

269, followed by hydroboration–oxidation of the double bond.[141]

The discovery of 1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acids as antiinflammatory agents triggered much research work on the synthesis of these compounds, which is best carried out following an oxa-Pictet–Spengler cyclization strategy on conveniently substituted tryptophols.[142]
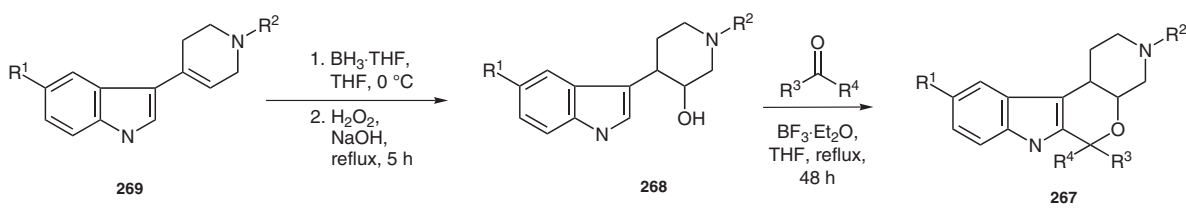
In this fashion, prodolic acid (**270**, R = R^1 = H) was initially prepared as a lead;[143] further studies, in which 36 other related compounds **270** were synthesized (Scheme 41), led to the discovery of etodolac. The derivatives were prepared by reaction of various tryptophols **271**[142] with β-ketoesters under p-toluenesulfonic acid catalysis in moderate to very good yields.

Employing an analogous strategy, which could be termed 'thia-Pictet–Spengler',[144] condensation of thio-tryptophol (**272**) with ethyl oxovalerate furnished **273** as a sulfur analogue of prodolic acid (Scheme 42). Other analogues were obtained from different β-ketoesters; all of them
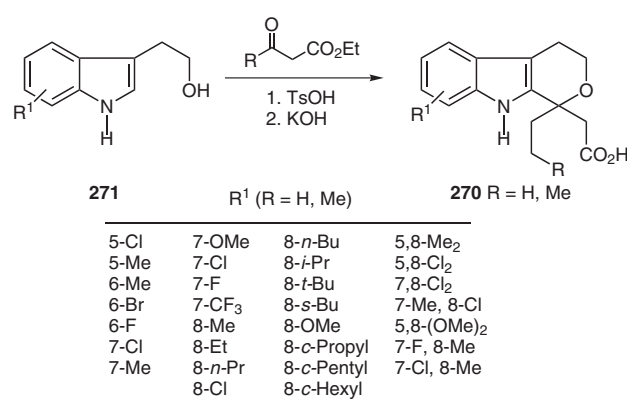
Table 6 Synthesis of Different Heterocycles Employing the Oxa-Pictet–Spengler Condensation

264 **265**
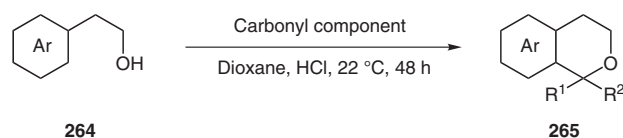
Entry	$ArCH_2CH_2OH$	Carbonyl component	R^1	R^2	Yield (%)
1	**264a**	$H_2NCH_2CH(OEt)_2$	CH_2NH_2	H	60
2	**264a**	$MeCOCH_2CO_2Et$	CH_2CO_2Et	Me	63
3	**264a**	N-Methyl-4-piperidone	$-H_2C\overset{}{\frown}N(Me)\overset{}{\frown}CH_2-$		37
4	**264b**	$Cl(CH_2)_2CH(OEt)_2$	$(CH_2)_2Cl$	H	70
5	**264b**	$MeCOCH_2CO_2Et$	CH_2CO_2Et	Me	50
6	**264c**	$MeCOCH_2CO_2Et$	CH_2CO_2Et	Me	50
7	**264d**	$H_2NCH_2CH(OEt)_2$	CH_2NH_2	H	74
8	**264g** (R = Cl)	$MeCOCH_2CO_2Et$	CH_2CO_2Et	Me	30
9	**264g** (R = H)	$EtCOCH_2CO_2Et$	CH_2CO_2Et	Et	13
10	**264h** (R = Me)	$MeCOCH_2CO_2Et$	CH_2CO_2Et	Me	65
11	**264h** (R = Me)	$n\text{-}PrCOCH_2CO_2Et$	CH_2CO_2Et	n-Pr	59
12	**264h** (R = Et)	$MeCO(CH_2)_2CO_2Et$	$CH_2CH_2CO_2Et$	Me	42
13	**264h** (R = Me)	$MeCO(CH_2)_3CO_2Et$	$(CH_2)_3CO_2Et$	Me	92
14	**264i** (R = H)	Me_2CO	Me	Me	73
15	**264i** (R = Cl)	$MeCOCH_2CO_2Et$	CH_2CO_2Et	Me	34
16	**264i** (R = NO_2)	$MeCOCH_2CO_2Et$	CH_2CO_2Et	Me	59
17	**264i** (R = H)	$MeCOCO_2Et$	CO_2Et	Me	57

**Table 7** Synthesis of Pyrido[3,4-*b*]pyranoindoles Employing the Oxa-Pictet–Spengler Condensation

Entry	R^1	R^2	Yield (%) of 268	R^3	R^4	Yield (%) of 267
1	H	Me	56	Me	Me	59
2	H	Ts	75	Me	Me	89
3	OMe	Me	73	Me	Me	31
4	H	Me	56	H	C_6H_5	13

Scheme 41

showed diminished activity, when compared with their oxygen counterparts.

An additional series of analogues of etodolac was restricted to 6-fluoro-7-substituted derivatives. Soll's group prepared these in moderate-to-excellent yields by the oxa-Pictet–Spengler condensation of appropriately substituted tryptophols with methyl-3-methoxypentenoate under $BF_3 \cdot Et_2O$ catalysis.[145]

During research work related to the synthesis of etodolac, Chou prepared chloro derivative 274 by oxa-Pictet–Spengler reaction of 7-ethyltryptophol 215b with ketal ester
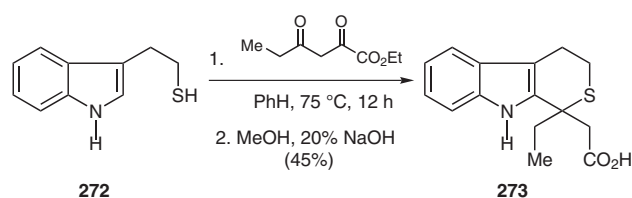
Scheme 42

275, while reaction with enol ether 276 gave diester 277a, which was converted into nitrile 277b by simple functional group transformations (Scheme 43).[146] Interestingly, upon submission to reaction with sodium cyanide in DMF, the γ-chloroester 274 produced a rearrangement–chain-extension reaction,[147] leading to cyanoester 278.

The reaction probably takes place through the intermediacy of oxonium ion 279, formed by pyrano oxygen nucleophilic attack to the chloride, and the rearranged ester 280, produced by indole ring-assisted chain migration to the electrophilic carbon center. The generality of this chain extension was explored with different tryptophols, and cyanoesters analogous to 278 were obtained in 43–82% yield.

On the other hand, hydroxypyranoindole 281 is a metabolite of etodolac, the preparation of which by microbial oxidation of etodolac with *Cunninghamella blackesleeama* is synthetically impractical due to the low yields of this process.[148]

Therefore, Soll and co-workers[49] decided to pursue the total synthesis of the compound. A heteroatom-facilitated *ortho* metallation on starting pivalamide 282, followed by reaction with acetaldehyde to 283 and catalytic hydrogenation, allowed the installation of the ethyl side chain to yield 284 (Scheme 44).

Next, reaction of 284 with ethyl oxalyl chloride was followed by hydrolysis of the ester to oxamic acid 285, and a $SnCl_4$-mediated cyclization of the acid chloride, formed with the aid of PCl_5, furnished isatine 286.

Demethylation of 286 with lithium iodide in DMF[149] to 287 was followed by the addition of lithium *tert*-butyl acetate to 288, and reduction of the carbonyl groups and dehydration of the tertiary alcohol gave hydroxytryptophol 289. In turn, this was subjected to the oxa-Pictet–Spengler cyclization with the methyl enol ether of 3-oxomethylpentanoate (290) under $BF_3 \cdot Et_2O$ promotion, to
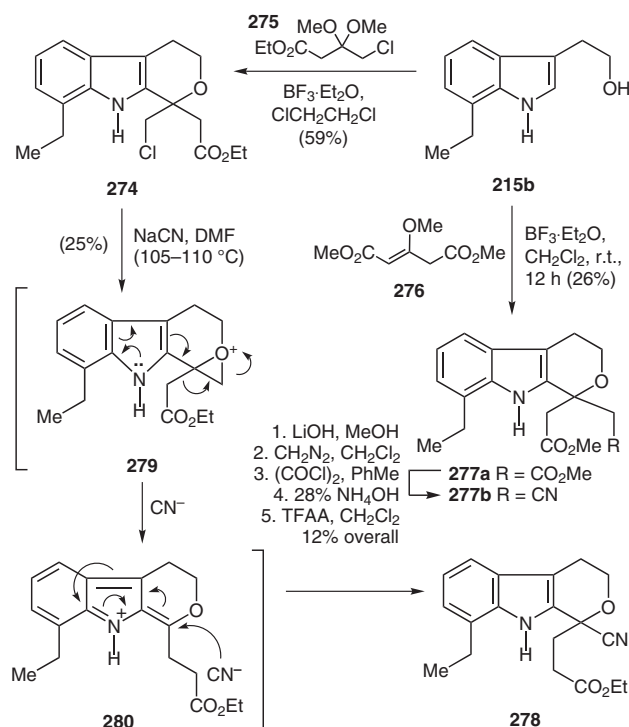
Scheme 43

yield methyl ester **291**. Final saponification of the ester gave the desired product **281**.

Resembling Thompson and Mohler's approach[84] to isochromans, an intermolecular version of the oxa-Pictet–Spengler reaction leading to a pyranoindole was disclosed by the group of Wilson[150] during their synthesis of the dehydrosecodine model **292** (Scheme 45), potentially useful for the elaboration of iboga and aspidosperma alkaloids.
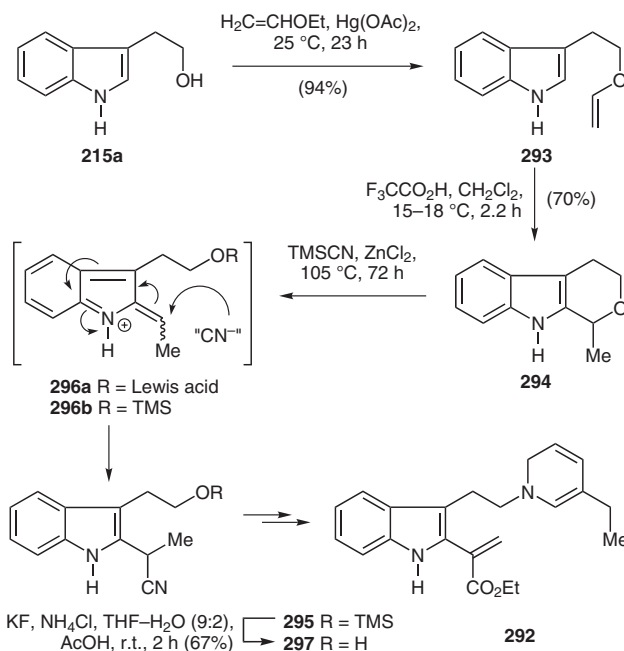
Scheme 45

This synthesis consisted of the mercury-assisted transetherification of ethyl vinyl ether with tryptophol (**215a**) to give enol ether **293**, followed by TFA-mediated cyclization to pyranoindole derivative **294** in 70% yield. Pyran ring opening with the TMSCN–ZnCl$_2$ reagent system to **295** through the intermediacy of **296**, and fluoride ion desilylation of the former furnished cyanoalcohol **297**, which was finally transformed into the projected [4,2]dehydrosecodine model **292**.

Very recently, Zhang and co-workers[151] designed a silicon-terminated oxa-Pictet–Spengler protocol towards tetrahydropyrano[3,4-*b*]indoles **298** (Scheme 46). The
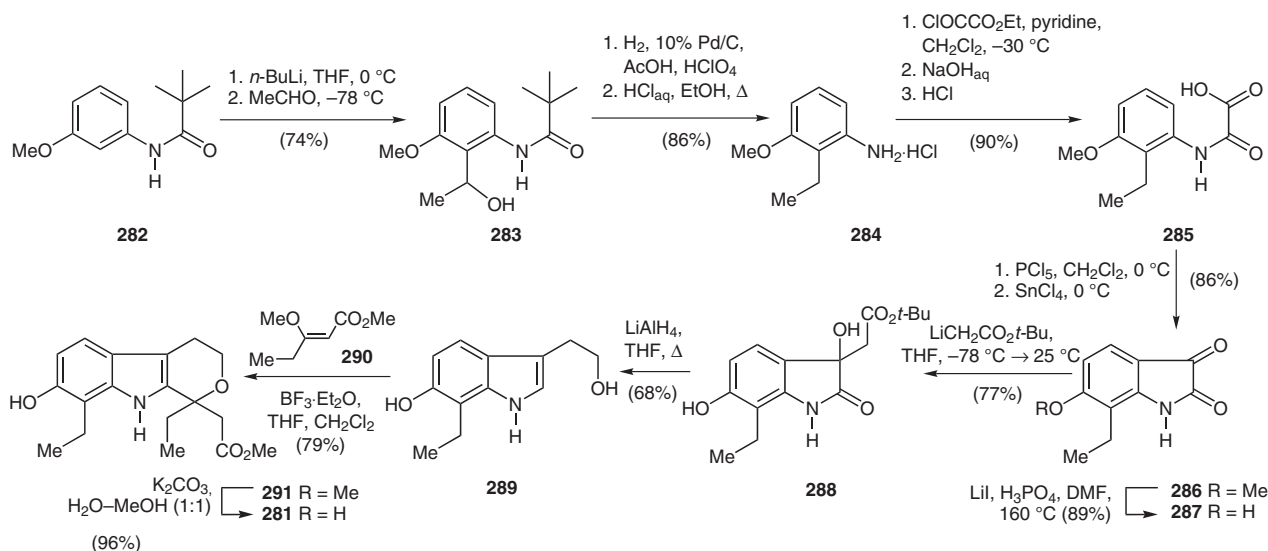
Scheme 44
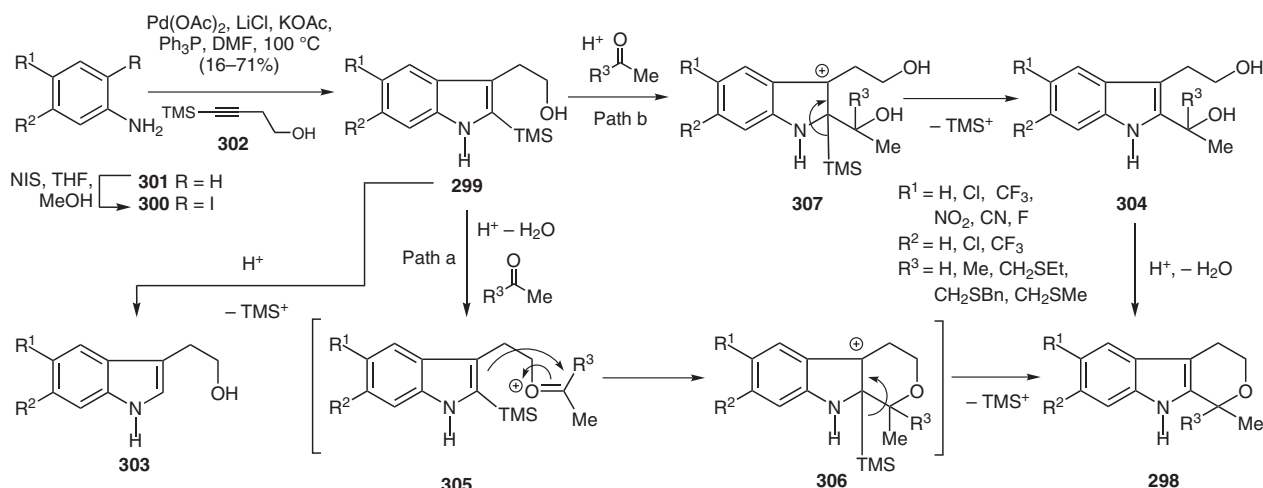
Scheme 46

required starting tryptophols **299** were prepared in moderate yields from the corresponding iodoanilines **300** by the method of Larock.[152] Thus, anilines **301** were selectively iodinated with *N*-iodosuccinimide and then subjected to coupling with silyl homopropargyl alcohol (**302**).

The oxa-Pictet–Spengler cyclization of **299** was explored with BF$_3$·Et$_2$O and trifluoroacetic acid as promoters; however, while the former usually gave good-to-excellent yields of product, it sometimes furnished complex mixtures. In contrast, trifluoroacetic acid consistently provided the required pyranoindoles in 50–90% yields.

Side products, such as the desilylated tryptophol **303** and uncyclized olefins, presumably resulting from dehydration of tertiary carbinol **304**, allowed for the proposal of two different reaction mechanisms. One of them (Path a) resembles the conventional oxa-Pictet–Spengler reaction pathway leading to isochromans through the oxocarbenium intermediate **305**, followed in this case by loss of TMS cation from intermediate **306**.

The other route (Path b) involves a TMS-assisted reaction of the carbonyl with the indole nucleus, as in a Mukaiyama aldol condensation, to furnish intermediate **307**, which yields **304** by loss of TMS cation prior to its final cyclization to **298**. Synthesis of isochromans by cyclodehydration of 1,5-diols has long been known.[153]

The reaction seems to be sensitive to steric bulk, since no cyclization was observed when benzophenone and cyclohexanone were employed as carbonyl components. While the former allowed for isolation of the desilylated tryptophol, the latter gave cyclohexenyl indole derivatives, which may arise from Path b.

A cyclization analogous to an oxa-Pictet–Spengler condensation was employed by the group of McCall[154] in their synthesis of tetrahydro-2-benzoxepines as potential hypotensive agents (Scheme 47).

In one of their synthetic strategies, **308** was condensed with different acetals under trifluoroacetic acid promotion to furnish **309**; further amination of the halides with pip-
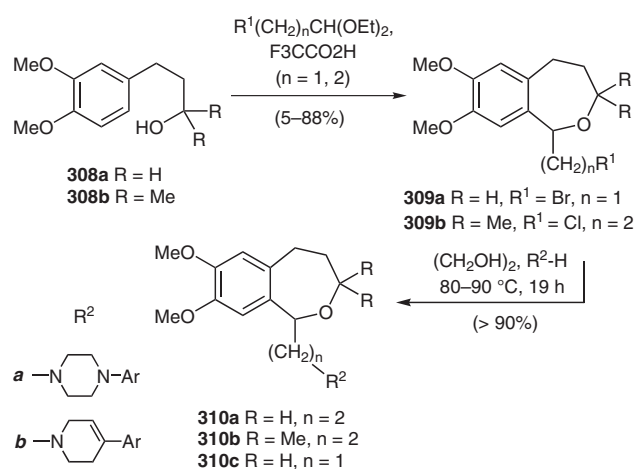
Scheme 47

erazine or piperidine derivatives gave **310**. Among them, 1-[2-(1,3,4,5-tetrahydro-7,8-dimethoxy-2-benzoxepin-1-yl)ethyl]-4-(4-fluorophenyl)piperidine (**310c**, R^2 = *a*, Ar = 4-CF$_3$-C$_6$H$_4$-) was shown to be an α-blocker with central and peripheral action.

Interestingly, yields were lower when unsubstituted alcohols **308a** were employed. The better performance of bromoacetal was explained by the ability of intermediate **311**, derived from bromoacetal, to form bromonium ion intermediate **312**, according to Scheme 48. This allowed for the isolation of **309a** in 37% yield and the recovery (30%) of **311**.

Unlike the analogous transformation leading to isochromans, this cyclization required harsher conditions and yields were comparatively lower, especially when chloropropanal diethyl acetal (5–10% yields) was employed.

Interestingly, Rosowsky was able to prepare benzoxepine **313**, bearing an improperly activated aromatic ring, in 40% yield by condensation of **314** with formaldehyde in the presence of aluminum chloride as catalyst (Scheme 49).[155]
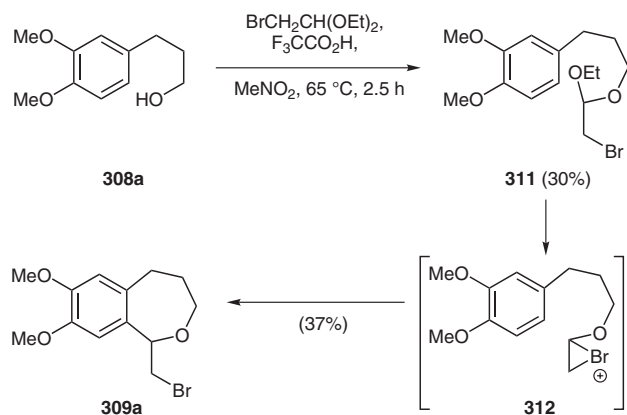
Scheme 48
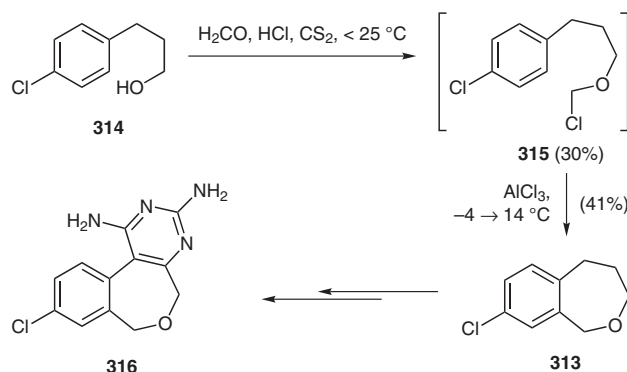
Scheme 48

Scheme 49

Scheme 49

The reaction was carried out in two stages and the inter-mediacy of chloromethyl ether **315** was invoked.[155] Compound **313** was further elaborated into rigid analogues of folic acid, such as 6,7-dihydro-5*H*-benzo[3,4]cyclohepta[1,2-*d*]pyrimidine derivative **316**.

By combining the intermolecular oxa-Pictet–Spengler protocol developed by Giles with the Jackson isoquinoline synthesis, the Kaufman and co-workers recently described the synthesis of **317**,[156] which embodies the oxaazaphenalene moiety which constitutes the ABC ring system of stephaoxocanidine (**318**) and eletefine (**319**). These are two structurally intriguing members of the new stephaoxocane family, isolated from *Stephania* and *Cissampelos* species of the Far East and Brazil.[157] Tricyclic analogues of stephaoxocanidine have been demonstrated to display potent activity as acetylcholinesterase inhibitors.[158]

In this approach (Scheme 50), bromoaldehyde **320** was subjected to a Wittig olefination, followed by olefin equilibration (to **321**) and osmium tetraoxide catalyzed dihydroxylation, to furnish *threo*-diol **322**. In turn, this was transformed into a mixture of acetals **323**, which was preferentially rearranged to *trans*-1,3-dimethylisochroman-3-ol **324** upon intramolecular oxa-Pictet–Spengler reaction catalyzed by TiCl$_4$.

Radical debromination to **325** and transformation to the inverted chloride **326** set the stage for implementing the Jackson protocol. This was carried out by nucleophilic displacement of the chloride with aminoacetal and trans-
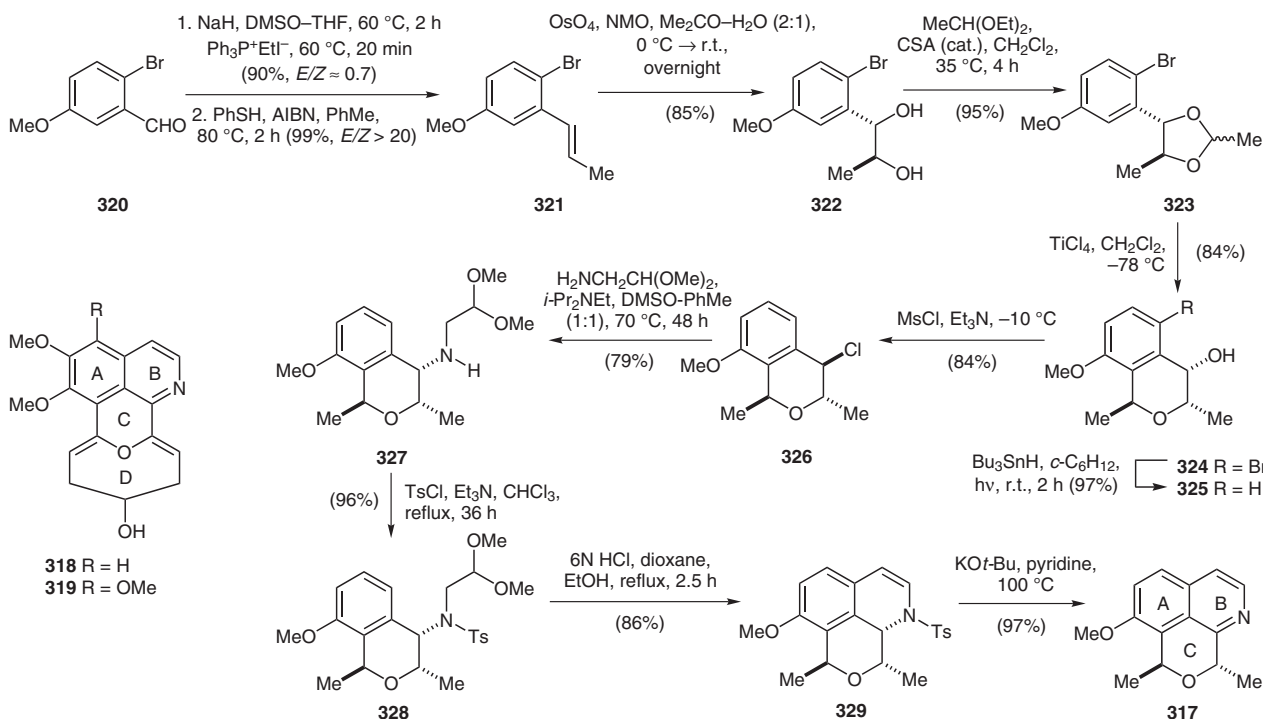
Scheme 50

Scheme 50

formation of the resulting secondary amine **327** into sulfonamide **328**, ready for cyclization to **329** with HCl in refluxing dioxane. Finally, β-elimination of sulfinate of **329** with potassium *tert*-butoxide in refluxing pyridine gave the required oxaazaphenalene **317**.

8   Conclusions

Six-membered ring oxygen-bearing aromatic heterocycles with the isochroman and related skeletons are found in nature and among bioactive compounds of interest. Many syntheses of natural and bioactive products bearing this core structure, as well as their analogues and derivatives, have been published during the last thirty years thanks to the use of the oxa-Pictet–Spengler cyclization protocol.

Despite the reaction scheme being half a century old, the analogy with the better-known Pictet–Spengler tetrahydroisoquinoline and β-carboline syntheses has emerged during the last decade.

Research in this field was driven not only by the desire to explore the scope and limitations of the reaction, but also by the need for concise and more efficient strategies for the synthesis of bioactive or commercially attractive compounds such as etodolac and galaxolide, as well as the permanent interest in a better characterization and improved knowledge of the dopamine receptors, which led to the preparation of potentially useful and selective dopamine D_1 and D_4 receptor agonists.

The multiple uses given to the oxa-Pictet–Spengler reaction during the last three decades have accompanied the remarkable progress in synthetic organic chemistry during this time, showing the continuous evolution of reactions, reagents and synthetic strategies.

Therefore, in view of the continuous development of more sophisticated, practical and powerful synthetic methods, it is expected that the oxa-Pictet–Spengler condensation will remain as an important synthetic tool for accessing pyran-type aromatic heterocycles. Original syntheses of new members of the isochroman family will continue to be disclosed in the future.

Acknowledgement

References

(1) (a) Hsu, F. L.; Chen, J. Y. *Phytochemistry* **1993**, *34*, 1625. (b) Ralph, J.; Peng, J.; Lu, F. *Tetrahedron Lett.* **1998**, *39*, 4963.

(2) Kashiwaba, N.; Morooka, S.; Kimura, M.; Ono, M.; Toda, J.; Suzuki, H.; Sano, T. *Nat. Prod. Lett.* **1997**, *9*, 177.

(3) (a) Cox, R. H.; Hernandez, O.; Dorner, J. W.; Cole, R. J.; Fennell, D. I. *J. Agric. Food Chem.* **1979**, *27*, 999. (b) Cutler, H. G.; Majetich, G.; Tian, X.; Spearing, P. US Patent 5922889, **1999**; *Chem. Abstr.* **1999**, *131*, 73559. (c) Malmstrom, J.; Christophersen, C.; Frisvad, J. C. *Phytochemistry* **2000**, *54*, 301.

(4) (a) Lai, S.; Shizuri, Y.; Yamamura, S.; Kawai, K.; Terada, Y.; Furukawa, H. *Chem. Lett.* **1990**, 589. (b) Masuma, R.; Tabata, N.; Tomoda, H.; Haneda, K.; Iwai, Y.; Omura, S. *J. Antibiot.* **1994**, *47*, 46. (c) Masuma, G.; Matsuura, H.; Takushi, T.; Kawano, S.; Yoshihara, T. *J. Nat. Prod.* **2004**, *67*, 1084.

(5) Cameron, D. W.; Cromartie, R. I. T.; Kingston, D. G. I.; Todd, A. R. *J. Chem. Soc.* **1964**, 51.

(6) Isaka, M.; Kongsaeree, P.; Thebtaranonth, Y. *J. Antibiot.* **2001**, *54*, 36.

(7) Specker, M. A.; Theimer, E. T. US Patent 4162256, **1986**.

(8) (a) Satoh, D.; Nishinomiya, H.; Aoyama, K.; Ibaraki, O. Ger. Offen. 2051496, **1971**; *Chem. Abstr.* **1971**, *75*, 49451. (b) Shaw, C. C.; Pelz, K. Eur. Pat. Appl. 306149, **1989**; *Chem. Abstr.* **1989**, *111*, 174074. (c) Demerson, C. A.; Humber, L. G.; Dobson, T. A.; Jirkovsky, I. L. Ger. Offen. 2226340, **1973**; *Chem. Abstr.* **1973**, *78*, 159581. (d) Mobilio, D.; Demerson, C. A.; Humber, L. G. US Patent 4687860, **1987**; *Chem. Abstr.* **1988**, *109*, 149346. (e) Katz, A. H.; Demerson, C. A.; Humber, L. G. US Patent 4670462, **1987**; *Chem. Abstr.* **1987**, *107*, 96704j.

(9) Kakimoto, T.; Koizumi, F.; Hirase, K.; Banba, S.; Tanaka, E.; Arai, K. *Pest Manag. Sci.* **2004**, *60*, 493.

(10) (a) Palusiak, M.; Matecka, M.; Rybarczyk-Pirek, A.; Epsztajn, J.; Bieniek, A.; Kowalska, J. A. *Acta Crystallogr., Sect. E* **2003**, *59*, 11. (b) Palusiak, M.; Grabowski, S. J.; Epsztajn, J.; Kowalska, J. A. *Acta Crystallogr., Sect. E* **2003**, *59*, 2000. (c) Brady, S. F.; Wagenaar, M. M.; Singh, M. P.; Janso, J. E.; Clardy, J. *Org. Lett.* **2000**, *2*, 4043. (d) Bianchi, D. A.; Kaufman, T. S. *ARKIVOC* **2003**, *(x)*, 178.

(11) (a) Inagaki, T.; Kaneda, K.; Suzuki, Y.; Hirai, H.; Nomura, E.; Sakakibara, T.; Yamauchi, Y.; Huang, L. H.; Norcia, M.; Wondrack, L. M.; Sutcli, J. A.; Kojima, N. *J. Antibiot.* **1998**, *51*, 112. (b) Hirai, H.; Ichiba, T.; Tonai, H. US Patent 6177458, **2000**; *Chem. Abstr.* **2000**, *133*, 88296.

(12) Shimada, A.; Kusano, M.; Takeuchi, S.; Fujioka, S.; Inokuchi, T.; Kimura, S. *Z. Naturforsch.* **2002**, *57c*, 459.

(13) Palmquist, U.; Nilsson, A.; Pettersson, T.; Ronlan, A.; Parker, V. D. *J. Org. Chem.* **1979**, *44*, 196.

(14) (a) Wiegrebe, W.; Friecke, J.; Budzikiewicz, P. L. *Tetrahedron* **1972**, *28*, 2849. (b) Wiegrebe, W.; Reinhart, H.; Frieke, J. *Pharm. Acta Helv.* **1973**, *48*, 420. (c) Stephan, H. M.; Langer, G.; Wiegrebe, W. *Pharm. Acta Helv.* **1976**, *51*, 164. (d) Wiegrebe, W.; Prior, S. *Chimia* **1978**, *32*, 256. (e) Wiegrebe, W.; Prior, S.; Mayer, K. K. *Arch. Pharm.* **1982**, *315*, 262. (f) Ambros, R.; Prior, S.; Wiegrebe, W. *Sci. Pharm.* **1982**, *51*, 179. (g) Prior, S.; Wiegrebe, W. *Arch. Pharm.* **1981**, *314*, 577. (h) Foubelo, F.; Gomez, C.; Gutierrez, A.; Yus, M. *J. Heterocycl. Chem.* **2000**, *37*, 1061. (i) Martinez, E.; Estévez, J. C.; Estévez, R. J.; Castedo, L. *Tetrahedron* **2001**, *57*, 1973.

(15) (a) Yamato, M.; Ishikawa, T.; Kobayashi, T. *Chem. Pharm. Bull.* **1981**, *29*, 720. (b) Rothenberg, A. S.; Yayatilake, G. S.; Hussain, S. F. *Heterocycles* **1976**, *5*, 41. (c) Yamato, M.; Hashigaki, K.; Ishikawa, S.; Qais, N. *Tetrahedron Lett.* **1988**, *29*, 6949. (d) Yamato, M.; Hashigaki, K.; Qais, N.; Ishikawa, S. *Tetrahedron* **1990**, *46*, 5909. (e) Lee, D.-U. *Bull. Korean Chem. Soc.* **2003**, *24*, 256.

(16) Meise, W.; Pfister, H. *Arch. Pharm.* **1977**, *310*, 501.

(17) Ogawa, A.; Murakami, C.; Kamisuki, S.; Kuriyama, I.; Yoshida, H.; Sugawara, F.; Mizushina, Y. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3539.

(18) (a) de Koning, C. B.; Michael, J. P.; van Otterlo, W. A. L. *Tetrahedron Lett.* **1999**, *40*, 3037. (b) de Koning, C. B.; Michael, J. P.; van Otterlo, W. A. L. *J. Chem. Soc., Perkin Trans. 1* **2000**, 799.

(19) Dewick, P. M. *Medicinal Natural Products*; Wiley: Chichester, **1998**.

(20) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030.

(21) Tatsui, G. *J. Pharm. Soc. Jpn.* **1928**, *48*, 92.

(22) Wünsch, B.; Zott, M. *Liebigs Ann. Chem.* **1992**, 39.

(23) Wünsch, B.; Zott, M.; Höfner, G. *Arch. Pharm. (Weinheim)* **1992**, *325*, 733.

(24) Guiso, M.; Marra, C.; Cavarischia, C. *Tetrahedron Lett.* **2001**, *42*, 6531.

(25) Guiso, M.; Bianco, A.; Marra, C.; Cavarischia, C. *Eur. J. Org. Chem.* **2003**, 3407.

(26) Bianco, A.; Righi, G.; Passacantilli, P. *Synth. Commun.* **1988**, *18*, 1765.

(27) Panizzi, L.; Scarpati, M. L.; Oriente, G. *Gazz. Chim. Ital.* **1960**, *90*, 1449.

(28) (a) Markaryan, E. A.; Samodurova, A. G. *Russ. Chem. Rev.* **1989**, *58*, 479. (b) Yamato, M. *Synth. Org. Chem.* **1983**, *41*, 958. (c) *Rodd's Chemistry of Carbon Compounds*, 2nd Ed., Vol. 4E; Coffey, S., Ed.; Elsevier: Amsterdam, **1977**. (d) Stannton, J. In *Comprehensive Organic Chemistry. The Synthesis and Reactions of Organic Compounds*, Vol. 4; Barton, D., Ed.; Pergamon Press: Oxford, **1979**, 607–626.

(29) Campaigne, E.; Heaton, B. G. *J. Org. Chem.* **1964**, *29*, 2372.

(30) (a) Macchia, B.; Balsamo, J. A.; Breschi, M. C.; Chiellini, G.; Lapucci, A.; Macchia, M.; Manera, C.; Martinelli, A.; Martini, C.; Scatizzi, R.; Uccello Barretta, G. *J. Med. Chem.* **1993**, *36*, 3077. (b) Kumar, A.; Khanna, J. M.; Jain, P. C.; Anand, N.; Srimal, R. C.; Kohli, J. D.; Goldberg, L. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1987**, *26*, 47. (c) Kumar, A.; Khanna, J. M.; Jain, P. C.; Anand, N. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1978**, *16*, 793.

(31) Schmitz, E.; Eichhorn, I. In *The Chemistry of the Ether Linkage: Acetals and Hemiacetals*; Patai, S., Ed.; John Wiley & Sons: New York, **1967**, 309–351.

(32) Xu, Y.-C.; Kohlman, D. T.; Liang, S. X.; Erikkson, C. *Org. Lett.* **1999**, *1*, 1599.

(33) Wulff, W. D.; Tang, P. C.; McCallum, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 7677.

(34) Takano, S.; Sekiguchi, Y.; Sato, N.; Ogasawara, K. *Synthesis* **1987**, 139.

(35) Koo, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1995**, *117*, 3389.

(36) DeNinno, M. P.; Perner, R. J.; Morton, H. E.; Didomenico, S. J. *J. Org. Chem.* **1992**, *57*, 7115.

(37) Xu, Y. C.; Roy, C.; Lebeau, E. *Tetrahedron Lett.* **1993**, *51*, 8189.

(38) (a) Li, T.; Ellison, R. H. *J. Am. Chem. Soc.* **1978**, *100*, 6263. (b) St. Pyrek, J.; Achmatowicz, O. Jr.; Zamojski, A. *Tetrahedron* **1977**, *33*, 673.

(39) Sita, L. R. *J. Org. Chem.* **1993**, *58*, 5285.

(40) (a) Jung, M. E.; Mossman, A. B.; Lyster, M. A. *J. Org. Chem.* **1978**, *43*, 3698. (b) Lombardino, J. G. *J. Heterocycl. Chem.* **1974**, *11*, 17.

(41) Humber, L. G. *Med. Res. Rev.* **1987**, *7*, 1.

(42) Demerson, G. A.; Humber, L. G.; Philipp, A. H.; Martel, R. R. *J. Med. Chem.* **1976**, *19*, 391.

(43) Katz, A. H.; Demerson, C. A.; Shaw, C. C.; Asselin, A.; Humber, L. G.; Conway, K. M.; Gavin, G.; Guinosso, C.; Jensen, N. P.; Mobilio, D.; Noureldin, R.; Schmid, J.; Shah, U.; Van Engen, D.; Chau, T. T.; Weichman, B. M. *J. Med. Chem.* **1988**, *31*, 1244.

(44) Mobilio, D.; Humber, L. G.; Katz, A. H.; Demerson, C. A.; Hughes, P.; Brigance, R.; Conway, K.; Shah, U.; Williams, G.; Labadia, F.; De Lange, B.; Schmid, J.; Asselin, A.; Newburger, J.; Jensen, N. P.; Weichman, B. M.; Chau, T.; Neuman, G.; Wood, D. D.; Van Engen, D.; Taylor, N. *J. Med. Chem.* **1981**, *31*, 2211.

(45) Moltzen, E. K.; Perregaard, J.; Meier, E. *J. Med. Chem.* **1995**, *38*, 2009.

(46) Da Silva, E. F.; Barreiro, E. J. *J. Braz. Chem. Soc.* **1993**, *4*, 40.

(47) Cabral, L. M.; Barreiro, E. J. *J. Heterocycl. Chem.* **1995**, *32*, 959.

(48) (a) de Farias, F. M. C.; Barreiro, E. J.; Coelho, F. A. S.; Costa, P. R. R. *Quim. Nova* **1984**, *7*, 111. (b) Barreiro, E. J.; Costa, P. R. R.; Coelho, F. A. S.; de Farias, F. M. C. *J. Chem. Res., Miniprint* **1985**, 2301.

(49) Soll, R. M.; Guinosso, C.; Asselin, A. *J. Org. Chem.* **1988**, *53*, 2844.

(50) Fraga, C. A. M.; Barreiro, E. J. *J. Heterocycl. Chem.* **1992**, *29*, 1667.

(51) DeNinno, M. P.; Schoenleber, R.; Asin, K. E.; MacKenzie, R.; Kebabian, J. W. *J. Med. Chem.* **1990**, *33*, 2950.

(52) Winter, C. A.; Risley, E. A.; Nuss, G. W. *Proc. Soc. Exp. Biol. Med.* **1962**, *111*, 544.

(53) (a) Wünsch, B.; Zott, M.; Höfner, G.; Bauschke, G. *Arch. Pharm. (Weinheim)* **1995**, *328*, 487. (b) Zhao, B.-X.; Sha, L.; Tan, W.; Zuo, H.; Wang, D.-W. *Chin. J. Org. Chem.* **2004**, *24*, 1300.

(54) Tomiyama, K.; McNamara, F. N.; Clifford, J. J.; Kinsella, A.; Koshikawa, N.; Waddington, J. L. *Eur. J. Pharmacol.* **2001**, *418*, 47.

(55) Michaelides, M. R.; Schoenleber, R.; Thomas, S.; Yamamoto, D. M.; Britton, D. R.; MacKenzie, R.; Kebabian, J. W. *J. Med. Chem.* **1991**, *34*, 2946.

(56) (a) Unterhalt, B.; Heppert, U. *Pharmazie* **2001**, *56*, 445. (b) Unterhalt, B.; Heppert, U. *Pharmazie* **2002**, *57*, 346.

(57) Micale, N.; Zappalà, M.; Grasso, S. *Farmaco* **2002**, *57*, 853.

(58) Zappalà, M.; Grasso, S.; Micale, N.; Polimeni, S.; De Micheli, A. *Synth. Commun.* **2002**, *32*, 527.

(59) van der Merwe, K. J.; Steyn, P. S.; Fourie, L. *J. Chem. Soc.* **1965**, 7083.

(60) Steyn, P. S.; Holzapfel, C. W. *Tetrahedron* **1967**, *23*, 4449.

(61) Campbell, A.; Shields, D. J. *Tetrahedron* **1965**, *21*, 211.

(62) Singh, R.; Singh, R. P.; Srivastava, J. N. *J. Indian Chem. Soc.* **1991**, *68*, 276.

(63) Antonioletti, R.; Bovicelli, P.; Crescenzi, B.; Lupatelli, P. *Tetrahedron Lett.* **1998**, *39*, 6751.

(64) Rama, N. H.; Saeed, A. *J. Chem. Soc. Pak.* **1992**, *14*, 286; *Chem. Abstr.* **1993**, *119*, 225782g.

(65) Rama, N. H.; Saeed, A.; Bird, C. W.; Cobb, J. *J. Heterocycl. Chem.* **1995**, *32*, 1075.

(66) Srivasta, J. N.; Chaudhary, D. N. *J. Org. Chem.* **1962**, *27*, 4337.

(67) Srivasta, J. N.; Chaudhary, D. N. *J. Indian Chem. Soc.* **1963**, *40*, 865.

(68) Miyake, A.; Itoh, K.; Tada, N.; Oka, Y. *J. Takeda Res. Lab.* **1982**, *41*, 24.

(69) Mukherjee, J.; Chatterjee, J. N.; Sengupta, S. C. *Indian J. Chem.* **1975**, *13*, 879.

(70) Cutler, H. G.; Majetich, G.; Tian, X.; Spearing, P. *J. Agric. Food Chem.* **1997**, *45*, 1422.

(71) de la Fuente, J. A.; Manzanaro, S. *Nat. Prod. Rep.* **2003**, *20*, 243.

(72) Gatta, F.; Settimij, G. *J. Heterocycl. Chem.* **1983**, *20*, 1267.

(73) Iorio, M. A.; Gatta, F.; Menichini, E. *Farmaco, Ed. Sci.* **1977**, *32*, 212.

(74) Thibault, J.; Maitte, P. *Bull. Soc. Chim. Fr.* **1969**, 915.

(75) Maitte, P. *Ann. Chim. (Paris)* **1954**, *9*, 465.

(76) (a) Yamato, M.; Hashigaki, K.; Ikeda, M.; Ohtake, H.; Tasaka, K. *J. Med. Chem.* **1981**, *24*, 194. (b) Yamato, M.; Hashigaki, K.; Tsusumi, A.; Tasaka, K. *Chem. Pharm. Bull.* **1981**, *29*, 3494.

(77) McCall, J. M.; McCall, R. B.; TenBrink, R. E.; Kamdar, B. V.; Humphrey, S. J.; Sethy, V. H.; Harris, D. W.; Daenzer, C. *J. Med. Chem.* **1982**, *25*, 75.

(78) Van Acker, S. A. B. E.; de Groot, M. J.; van den Berg, D. J.; Tromp, M. N. L. J.; Doone-op den Kelder, G.; van der Vijgh, W. J. F.; Bast, A. *Chem. Res. Toxicol.* **1996**, *9*, 1305.

(79) Fukuhara, K.; Nakanishi, I.; Kansui, H.; Sugiyama, E.; Kimura, M.; Shimada, T.; Urano, S.; Yamaguchi, K.; Miyata, N. *J. Am. Chem. Soc.* **2002**, *124*, 5952.

(80) (a) Fukuhara, K.; Nakanishi, I.; Shimada, T.; Ohkubo, K.; Miyazaki, K.; Hakamata, W.; Urano, S.; Ozawa, T.; Okuda, H.; Miyata, N.; Ikota, N.; Fukuzumi, S. *Chem. Res. Toxicol.* **2003**, *16*, 81. (b) Nakanishi, I.; Ohkubo, K.; Miyazaki, K.; Hakamata, W.; Urano, S.; Ozawa, T.; Okuda, H.; Fukuzumi, S.; Ikota, N.; Fukuhara, K. *Chem. Res. Toxicol.* **2004**, *17*, 26.

(81) (a) Meyer, A. L.; Turner, R. B. *Tetrahedron* **1971**, *27*, 2609. (b) Oka, Y. J.; Miyake, A.; Tada, N.; Itoh, K. US Patent 4066648, **1978**; *Chem. Abstr.* **1978**, *88*, 37613. (c) Von Voigtlander, P. F.; Lahti, R. A.; Tang, A. H.; Sethy, V. H. *Arch. Int. Pharmacodyn. Ther.* **1983**, *266*, 23.

(82) Laigle, J.-C.; Combourieu, M.; Simbille, N. US Patent 5393759, **1991**; *Chem. Abstr.* **1992**, *116*, 151567.

(83) (a) Buschmann, H.; Michel, R. German Patent DE 614,461, **1935**; *Chem. Abstr.* **1936**, *30*, 492. (b) Maitte, P. *Ann. Chim. (Paris)* **1954**, *9*, 431. (c) Cologne, J.; Boide, P. *Bull. Soc. Chim. Fr.* **1956**, 1341. (d) Rieche, A.; Schmitz, E. *Chem. Ber.* **1956**, *89*, 1254. (e) Reiche, A.; Schmitz, E. *Chem. Ber.* **1956**, *89*, 2813. (f) Thibault, J. *Ann. Chim. (Paris)* **1971**, *6*, 253.

(84) Mohler, D. L.; Thompson, D. W. *Tetrahedron Lett.* **1987**, *28*, 2567.

(85) Antus, S.; Snatzke, G.; Steinke, I. *Liebigs Ann. Chem.* **1983**, 2247.

(86) Melany, M. L.; Lock, G. A.; Thompson, D. W. *J. Org. Chem.* **1985**, *50*, 3925.

(87) DeNinno, M. P.; Shoenleber, R.; Perner, R. J.; Lijewski, L.; Asin, K. E.; Britton, D. R.; MacKenzie, R.; Kebabian, J. W. *J. Med. Chem.* **1991**, *34*, 2561.

(88) Snider, B. B. *Comprehensive Organic Synthesis*, Vol. 2; Trost, B. M.; Fleming, I.; Heathcock, C. H., Eds.; Pergamon Press: New York, **1991**, 527–561.

(89) (a) Stapp, P. R. *J. Org. Chem.* **1969**, *34*, 479. (b) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661.

(90) (a) Blumenkopf, T. A.; Bratz, M.; Castaneda, A.; Look, G. C.; Overman, L. E.; Rodriguez, D.; Thompson, A. S. *J. Am. Chem. Soc.* **1990**, *112*, 4386. (b) Nikolic, N. A.; Gonda, E.; Longford, C. P. D.; Lane, N. T.; Thompson, D. W. *J. Org. Chem.* **1989**, *54*, 2748. (c) Winstead, R. C.; Simpson, T. H.; Lock, G. A.; Schiavelli, M. D.; Thompson, D. W. *J. Org. Chem.* **1986**, *51*, 275.

(91) Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, *61*, 8317.

(92) Rychnovsky, S. D.; Hu, Y.; Ellsworth, B. *Tetrahedron Lett.* **1998**, *39*, 7271.

(93) Bianchi, D. A.; Rúa, F.; Kaufman, T. S. *Tetrahedron Lett.* **2004**, *45*, 411.

(94) Giles, R. G. F.; Green, I. R.; Knight, L. S.; Lee Son, V. R.; Yorkea, S. C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 865.

(95) (a) Mukaiyama, T. *Org. React.* **1982**, *28*, 203. (b) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 817.

(96) (a) Giles, R. G. F.; Rickards, R. W.; Senanayake, B. S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2241. (b) Giles, R. G. F.; Rickards, R. W.; Senanayake, B. S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3361.

(97) Giles, R. G. F.; Rickards, R. W.; Senanayake, B. S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3949.

(98) Guyard, A.-L.; Valleix, A.; Rousseau, B.; Cintrat, J.-C. *J. Labelled Compd. Radiopharm.* **2001**, *44*, 529.

(99) Ando, M.; Ohhara, H.; Takase, K. *Chem. Lett.* **1986**, 879.

(100) (a) Kametani, K.; Fukumoto, K.; Agui, H.; Kigasawa, K.; Sugahara, H.; Hiiragi, M.; Hayasaka, T.; Ishimaru, H. *J. Chem. Soc.* **1968**, 112. (b) Kametani, T.; Shibuya, S.; Satoh, M. *Chem. Pharm. Bull.* **1968**, *16*, 953. (c) Kametani, T.; Agui, H.; Fukumoto, K. *Chem. Pharm. Bull.* **1968**, *16*, 1285. (d) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Ishimaru, H. *Chem. Pharm. Bull.* **1969**, *17*, 2353. (e) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Ishimaru, H.; Horie, S. *J. Heterocycl. Chem.* **1970**, *7*, 51. (f) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Ishimaru, H.; Wakisaka, K. *J. Chem. Soc. C* **1971**, 1805. (g) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Kusama, O.; Hayashi, E.; Ishimaru, H. *Chem. Pharm. Bull.* **1971**, *19*, 1150.

(101) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Ishimaru, H.; Haga, S. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2602.

(102) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Ishimaru, H.; Uryu, T.; Haga, S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 471.

(103) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Ishimaru, H.; Haga, S. *J. Pharm. Soc. Jpn.* **1975**, *95*, 1298.

(104) Kametani, K.; Kigasawa, K.; Hiiragi, M.; Ishimaru, H.; Wagatsuma, N.; Haga, S.; Kusama, O. *J. Heterocycl. Chem.* **1975**, *12*, 851.

(105) Cornubert, R.; Barraud, G.; Cormier, M.; Descharmes, M.; Eggert, H. G. *Bull. Soc. Chim. Fr.* **1955**, 400.

(106) Peng, J.; Lu, F.; Ralph, J. *Phytochemistry* **1999**, *50*, 659.

(107) (a) Peng, J.; Lu, F.; Ralph, J. *J. Agric. Food Chem.* **1998**, *46*, 553. (b) Lu, F.; Ralph, J. *J. Agric. Food Chem.* **1997**, *45*, 4655. (c) Lundquist, K.; Miksche, E. *Tetrahedron Lett.* **1965**, *25*, 2131.

(108) Bianco, A.; Coccioli, F.; Guiso, M.; Marra, C. *Food Chem.* **2001**, *77*, 405.

(109) Togna, G. I.; Togna, A. R.; Franconi, M.; Marra, C.; Guiso, M. *J. Nutr.* **2003**, *133*, 2532.

(110) (a) Vasconcellos, M. L. A. A.; d'Angelo, J.; Desmaele, D.; Costa, P. R. R.; Potin, D. *Tetrahedron: Asymmetry* **1991**, *2*, 353. (b) Dumas, F.; Alencar, K. G.; Mahuteau, J.; Barbero, M. J.; Miet, C.; Gérad, F.; Vasconcellos, M. L. A. A.; Costa, P. R. R. *Tetrahedron: Asymmetry* **1997**, *8*, 579. (c) Costa, P. R. R.; Cabral, L. M.; Alencar, K. G.; Schmidt, L. L.; Vasconcellos, M. L. A. A. *Tetrahedron Lett.* **1997**, *38*, 7021. (d) Cabral, L. M.; Costa, P. R. R.; Vasconcellos, M. L. A. A.; Barreiro, E. J.; Castro, R. N. *Synth. Commun.* **1996**, *26*, 3671.

(111) Brenna, E.; Fuganti, C.; Fuganti, D.; Grasselli, P.; Malpezzi, L.; Pedrocchi-Fantoni, G. *Tetrahedron* **1997**, *53*, 17769.

(112) (a) Danieli, B.; Lesma, G.; Passarella, D.; Silvani, A. *Tetrahedron Lett.* **2000**, *41*, 3489. (b) Van Beek, T. A.; Verpoorte, R.; Baerheim Svendsen, A. *Tetrahedron* **1984**, *40*, 737.

(113) DeNinno, M. P.; Schoenleber, R.; Asin, K. E.; MacKenzie, R.; Kebabian, J. W. *J. Med. Chem.* **1990**, *33*, 2948.

(114) Chandrasekharan, P. V.; Ramachandran, P. V.; Brown, H. C. *J. Org. Chem.* **1985**, *50*, 5446.

(115) DeNinno, M. P.; Perner, R. J.; Lijewski, L. *Tetrahedron Lett.* **1990**, *31*, 7415.

(116) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.

(117) Wünsch, B.; Zott, M. *Tetrahedron: Asymmetry* **1993**, *4*, 2307.

(118) (a) Heeringa, L. G.; Beets, M. G. J. US Patent 3360530, **1967**; retrievable from www.USPTO.gov. (b) Ford, R. A. *Soap Perfum. Cosmet.* **1999**, *(Feb.)*, 33. (c) Muermann, H.-E. *Parfuem. Kosmet.* **1999**, *80*, 12. (d) Teisseire, P. J. *Chemistry of Fragrant Substances*; VCH Publishers Inc.: New York, **1994**, 333–358.

(119) (a) Dsikowitzky, L.; Schwarzbauer, J.; Kronimus, A.; Littke, R. *Chemosphere* **2004**, *57*, 1275. (b) Bester, K. *Chemosphere* **2004**, *57*, 863. (c) Wollenberger, L.; Breitholtz, M.; Kusk, K. O.; Bengtsson, B.-E. *Sci. Total Environ.* **2003**, *305*, 53. (d) Ricking, M.; Schwarzbauer, J.; Franke, S. *Water Res.* **2003**, *37*, 2607. (e) Winkler, M.; Kopf, G.; Hauptvogel, C.; Neu, T. *Chemosphere* **1998**, *37*, 1139. (f) Luckenbach, T.; Corsi, I.; Epel, D. *Mar. Environ. Res.* **2004**, *58*, 215. (g) Heberer, T.; Gramer, S.; Stan, H.-J. *Acta Hydrochim. Hydrobiol.* **1999**, *27*, 150. (h) Franke, S.; Meyer, C.; Heinzel, N.; Gatermann, R.; Hühnerfuss, H.; Rimkus, G.; König, W. A.; Francke, W. *Chirality* **1999**, *11*, 795.

(120) Fráter, G.; Müller, U.; Kraft, P. *Helv. Chim. Acta* **1999**, *82*, 1656.

(121) Spoelstra, D. B.; Weber, S. H.; Kleipool, R. J. C. *Recl. Trav. Chim. Pays-Bas* **1963**, *82*, 1100.

(122) Nakajima, T.; Sugo, S.; Sugita, T.; Ichiawa, K. *Tetrahedron* **1969**, *25*, 1807.

(123) Ciappa, A.; Matteoli, U.; Scrivanti, A. *Tetrahedron: Asymmetry* **2002**, *13*, 2193.

(124) Demerson, C. A.; Humber, L. G.; Abraham, N. A.; Schilling, G.; Martel, R. R.; Pace-Asciak, C. *J. Med. Chem.* **1983**, *26*, 1778.

(125) Humber, L. G.; Demerson, C. A.; Swaminathan, P.; Bird, P. H. *J. Med. Chem.* **1986**, *29*, 871.

(126) Gopalsamy, A.; Ellingboe, J. W.; Mansour Tarek, S. WO Patent 03/099824, **2003**; *Chem. Abstr.* **2003**, *140*, 5039.

(127) TenBrink, R. E.; Bergh, C. L.; Duncan, J. N.; Harris, D. W.; Huff, R. M.; Lahti, R. A.; Lawson, C. F.; Lutzke, B. S.; Martin, I. J.; Rees, S. A.; Schlachter, S. K.; Sih, J. C.; Smith, M. W. *J. Med. Chem.* **1996**, *39*, 2435.

(128) (a) Ennis, M. D.; Ghazal, N. B.; Hoffman, R. L.; Smith, M. W.; Schlachter, S. K.; Lawson, C. F.; Im, W. M.; Pregenzer, J. F.; Svensson, K. A.; Lewis, R. A.; Hall, E. D.; Sutter, D. M.; Harris, L. T.; McCall, R. B. *J. Med. Chem.* **1998**, *41*, 2180. (b) McCall, R. B.; Huff, R.; Chio, C. L.; TenBrink, R.; Bergh, C. L.; Ennis, M. D.; Ghazal, N. B.; Hoffman, R. L.; Meisheri, K.; Higdon, N. R.; Hall, E. *Cephalalgia* **2000**, *22*, 799.

(129) (a) Satoh, D.; Hashimoto, T.; Aoyama, K. *Yakugaku Zasshi* **1974**, *94*, 774; *Chem. Abstr.* **1974**, *81*, 105333. (b) Satoh, D.; Hashimoto, T.; Aoyama, K. *Yakugaku Zasshi* **1975**, *95*, 1183; *Chem. Abstr.* **1976**, *84*, 17073.

(130) Miles, W. H.; Heinsohn, S. K.; Brennan, M. K.; Swarr, D. T.; Eidam, P. M.; Gelato, K. A. *Synthesis* **2002**, 1541.

(131) (a) Miles, W. H.; Berreth, C. L.; Smiley, P. M. *Tetrahedron Lett.* **1993**, *34*, 5112. (b) Miles, W. H.; Berreth, C. L.; Anderton, C. A. *Tetrahedron Lett.* **1996**, *37*, 7893. (c) Miles, W. H.; Fialcowitz, E. J.; Halstead, E. S. *Tetrahedron* **2001**, *57*, 9925.

(132) Bhatt, U.; Christmann, M.; Quitschalle, M.; Claus, E.; Kalesse, M. *J. Org. Chem.* **2001**, *66*, 1885.

(133) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679; and references cited therein.

(134) (a) Dobson, T. A.; Humber, L. G. *J. Heterocycl. Chem.* **1975**, *12*, 591. (b) Philipp, A. H.; Humber, L. G.; Martel, R. R. *J. Heterocycl. Chem.* **1978**, *15*, 413. (c) Jirkovsky, I.; Humber, L. G.; Noureldin, R. *Eur. J. Med. Chem.* **1976**, *11*, 571. (d) Demerson, C. A.; Santroch, G.; Humber, L. G.; Charest, M. P. *J. Med. Chem.* **1975**, *18*, 577. (e) Jirovsky, I.; Humber, L. G.; Baudy, R. *J. Heterocycl. Chem.* **1976**, *13*, 311.

(135) (a) Davies, W.; Porter, Q. N. *J. Chem. Soc.* **1957**, 4958. (b) Cagniant, P.; Kirsch, G. *C. R. Seances Acad. Sci., Ser. C* **1971**, *272*, 406. (c) Campaigne, E.; Neiss, E. S.; Pfeiffer, C. C.; Beck, R. A. *J. Med. Chem.* **1968**, *11*, 1049.

(136) Gauthier, J. A.; Humber, L. G.; Revesz, C. US Patent 4132710, **1979**; *Chem. Abstr.* **1979**, *90*, 152153y..

(137) Lyle, R. E.; Krueger, W. E. *J. Org. Chem.* **1965**, *30*, 394.

(138) (a) Humber, L. G.; Ferdinandi, E.; Demerson, C. A.; Ahmed, S.; Shah, U.; Mobilio, D.; Sabatucci, J.; Lange, B. D.; Labbadia, F.; Hughes, P.; Virgilio, J. D.; Neuman, G.; Chau, T. T.; Weichman, B. M. *J. Med. Chem.* **1988**, *31*, 1712. (b) Ferdinandi, E. S.; Mobilio, D.; Sabatucci, J. P.; Humber, L. G. US Patent 4686213, **1987**; *Chem. Abstr.* **1987**, *108*, 21869.

(139) Kreft, A. F.; Caufield, C. E.; Failli, A. A.; Caggiano, T. J.; Greenfield, A. A.; Kubrak, D. M. US Patent 5824699, **1988**; *Chem. Abstr.* **1998**, *129*, 122569.

(140) Fréter, K.; Fuchs, V. *J. Heterocycl. Chem.* **1982**, *19*, 377.

(141) (a) Fréter, K. *J. Org. Chem.* **1975**, *40*, 2525. (b) Beck, D.; Schenker, K. *Helv. Chim. Acta* **1968**, *51*, 260. (c) Bergman, J. *J. Heterocycl. Chem.* **1970**, *7*, 1071. (d) Audia, J. E.; Colocci, N. *Tetrahedron Lett.* **1991**, *32*, 3779.

(142) Garden, S. J.; da Silva, R. B.; Pinto, A. C. *Tetrahedron* **2002**, *58*, 8399.

(143) Demerson, C. A.; Humber, L. G.; Dobson, T. A.; Martel, R. R. *J. Med. Chem.* **1975**, *18*, 189.

(144) Jirovsky, I.; Humber, L. G.; Noureldin, R. *J. Heterocycl. Chem.* **1975**, *12*, 937.

(145) McKittrick, B.; Failli, A.; Steffan, R. J.; Soll, R. M.; Hughes, P.; Schmid, J.; Asselin, A. A.; Shaw, C. C.; Noureldin, R.; Gavin, G. *J. Heterocycl. Chem.* **1990**, *27*, 2151.

(146) Chou, S.-Y. *Heterocycles* **2003**, *60*, 1095.

(147) Chou, S.-Y.; Tseng, C.-L.; Chen, S.-F. *Heterocycles* **1999**, *51*, 1527.

(148) Ferdinandi, E. S.; Sehgal, S. N.; Demerson, C. A.; Dubuc, J.; Zilber, J.; Dvornik, D.; Cayen, M. N. *Xenobiotica* **1986**, *16*, 153.

(149) Dean, P. D. G. *J. Chem. Soc.* **1965**, 6655.

(150) Wilson, R. M.; Farr, R. A.; Burlett, D. J. *J. Org. Chem.* **1981**, *46*, 3293.

(151) Zhang, X.; Li, X.; Lanter, J. C.; Sui, Z. *Org. Lett.* **2005**, *7*, 2043.

(152) (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Ujjainwalla, F.; Warner, D. *Tetrahedron Lett.* **1998**, *39*, 5355. (c) Walsh, T.; Toupence, R.; Ujjainwalla, F.; Young, J.; Goulet, M. *Tetrahedron* **2001**, *57*, 5233.

(153) (a) Siegel, S.; Coburn, S. *J. Am. Chem. Soc.* **1951**, *73*, 5494. (b) Warnell, J. L.; Shriner, R. L. *J. Am. Chem. Soc.* **1957**, *79*, 3165.

(154) (a) TenBrink, R. E.; McCall, J. M. *J. Heterocycl. Chem.* **1981**, *18*, 821. (b) TenBrink, R. E.; McCall, J. M.; Pals, D. T.; McCall, R. B.; Orley, J.; Humphrey, S. J.; Wendling, M. G. *J. Med. Chem.* **1981**, *24*, 67. (c) TenBrink, R. E.; McCall, J. M.; Johnson, H. G. *J. Med. Chem.* **1980**, *23*, 1058.

(155) (a) Rosowsky, A.; Chen, K. K. N.; Lin, M.; Nadel, M. E.; St. Amand, R.; Yaeger, S. A. *J. Heterocycl. Chem.* **1971**, *8*, 789. (b) Rieche, A.; Gross, H. *Chem. Ber.* **1962**, *65*, 61. (c) Bott, R. W.; Eaborn, C.; Leyshon, K. *J. Chem. Soc.* **1964**, 1548.

(156) (a) Bianchi, D. A.; Cipulli, M. A.; Kaufman, T. S. *Eur. J. Org. Chem.* **2003**, 4731. (b) Kaufman, T. S.; Bernardi, C. R.; Cipulli, M.; Silveira, C. C. *Molecules* **2000**, *5*, 493.

(157) (a) Kashiwaba, N.; Morooka, S.; Kimura, M.; Ono, M. *J. Nat. Prod.* **1996**, *59*, 803. (b) da-Cunha, E. V. L.; Cornélio, M. L.; Barbosa-Filho, J. M.; Braz-Filho, R.; Gray, A. I. *J. Nat. Prod.* **1998**, *61*, 114.

(158) Bianchi, D. A.; Schemda-Hirschmann, G.; Theoduloz, C.; Bracca, A. B. J.; Kaufman, T. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2711.