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

Enrique L. Larghi, Teodoro S. Kaufman*
Instituto de Química Orgánica de Síntesis (IQUIOS, CONICET-UNR) and Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Suipacha 531, (S2002LRK) Rosario, República Argentina
Fax +54(341)4370477; E-mail: tkaufman@fbioyf.unr.edu.ar
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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.

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 and stephaoxocanine (2), obtained from Stephania cepharantha are selected examples of natural isochromans of vegetal origin (Figure 1).

In addition, DMHI (3a), a plant growth regulator isolated from Penicillium stockii 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 derivative5 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 pyran[3,4-b]indole ring, are isochromans with commercial importance in the cosmetics and drug industries.

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 and relatively scarce among synthetic compounds. The isochroman-1-ols, which include important natural products such as the topoisomerase II inhibitor CJ-12,373 (10a) and the structurally similar antitumor and amiloid aggregation inhibitor 10b isolated from Penicillium simplicissimum FERM BP-6357, constitute another group, while the related tetrahydroisocoumarins such as the inhibitor of pollen development 6-hydroxymellein (11) 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. 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 and vice versa, as well as for the preparation of other nitrogen-bearing heterocycles. Moreover, naturally occurring isochroman derivatives have been isolated and described as precursors of isoquinolines and isochroman analogues of isoquinoline alkaloids have also been synthesized.

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.

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

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 Maria (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. 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-1H-benzo[e]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-tetrahydropyran[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](image-url)

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; 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. Among the artifacts, compound 1 isolated from the leaves of Tectaria subtrifilifolia by an acetone extraction procedure may be a likely example, in view of the abundance of the hydroxytyrosol precursor in this plant.

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.

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-arylethanol 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

Campagne informed that reaction of 3,4-dimethoxyphenethyl alcohol with aminocetal in dioxane under hydro chloric acid catalysis gave 82% of the corresponding 1-aminomethylisochroman 16a.

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

More recently, the group of Guiso effected changes to the oxa-Pictet–Spengler reaction and proposed that their modified version could be generalized to obtain 1-benzylisochromans as oxygenated analogues of benzyltetrahydroisoquinoline alkaloids such as couclaurine (20).
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).\textsuperscript{25} This included 6,7-demethoxyacoclaurine (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.

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\textsuperscript{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;\textsuperscript{31} alternatively, this can be explained as a consequence of the fact that these aldehydes cannot undergo enolization.

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 deoxyfrenolyacin (31), a natural product isolated from \textit{Streptomyces roseofulvus}, Xu and co-workers\textsuperscript{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) available in turn from 3-buten-1-ol (35) via its protected derivative (36), by ring opening of epoxide (37) with lithium acetylide (38). Williamson methylation of the resulting (32) to the 1,4,5-trimethoxynaphthalene (40) and deprotection of the aliphatic ring (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.\textsuperscript{36}

DDQ-induced oxidative coupling with allyl triphenylstannane stereospecifically gave the 1,3-trans-substituted allyl naphthopyran (43).\textsuperscript{35} This outcome was a distinctive characteristic of the synthesis, since previous approaches furnished the 1,3-cis-derivative.\textsuperscript{38}
Table 1  Synthesis of 7-Hydroxyisochroman Derivatives by the Oxa-Pictet–Spengler Condensation

<table>
<thead>
<tr>
<th>Entry</th>
<th>R(^1)</th>
<th>Carbonyl Compound</th>
<th>Yield (%)</th>
<th>R(^2)</th>
<th>R(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Protocol A(^\text{a})</td>
<td>Protocol B(^\text{b})</td>
<td>Protocol C(^\text{c})</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>OH</td>
<td>Pentanal</td>
<td>80</td>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>OH</td>
<td>3-OH-C(_6)H(_5)-CHO</td>
<td>98</td>
<td>90</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>OH</td>
<td>4-MeO-C(_6)H(_5)-CHO</td>
<td>98</td>
<td>90</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>OH</td>
<td>Benzaldehyde</td>
<td>95</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>OH</td>
<td>Isovaleraldehyde</td>
<td>90</td>
<td>73</td>
<td>62</td>
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<tr>
<td>6</td>
<td>OH</td>
<td>Propanal</td>
<td>95</td>
<td>80</td>
<td>72</td>
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<td>7</td>
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<td>8</td>
<td>H</td>
<td>Pentanal</td>
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<td></td>
</tr>
<tr>
<td>9</td>
<td>H</td>
<td>Piperonal</td>
<td>98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>H</td>
<td>4-Cl-C(_6)H(_5)-CHO</td>
<td>95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>H</td>
<td>4-MeO(_2)-C(_6)H(_5)-CHO</td>
<td>90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>OH</td>
<td>4-HO-C(_6)H(_2)-CH(_2)-CHO</td>
<td>80</td>
<td>75</td>
<td>60</td>
</tr>
<tr>
<td>13</td>
<td>OH</td>
<td>Acetone</td>
<td>95</td>
<td>80</td>
<td>63</td>
</tr>
</tbody>
</table>

\(^\text{a}\) Protocol A: MeOH, activated MS, TsOH (cat.), 4 °C, 24–48 h.
\(^\text{b}\) Protocol B: MeOH, anhydrous Na\(_2\)SO\(_4\), TsOH (cat.), 4 °C, 24–48 h.
\(^\text{c}\) 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 CrO3 in acetic acid,39 and the boron tribromide assisted demethylation of the remaining methyl ether. Final saponification of the methyl ester in mide assisted demethylation of the remaining methyl ester.40a In this case (Scheme 4), starting 1-alkylisochromans was disclosed by Jung and co-workers.40b An interesting oxa-Pictet–Spengler cyclization leading to the natural product may be more complex.

An interesting oxa-Pictet–Spengler cyclization leading to 1-alkylisochromans was disclosed by Jung and co-workers.40b 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.

This process seems to entail a first step that consists in the complexation or association of the iodo derivative and the central benzene ring to the corresponding quinone with CrO3 in acetic acid,43 and the boron tribromide assisted demethylation of the remaining methyl ether. Final saponification of the methyl ester in mide assisted demethylation of the remaining methyl ether.40a In this case (Scheme 4), starting 1-alkylisochromans was disclosed by Jung and co-workers.40b An interesting oxa-Pictet–Spengler cyclization leading to the natural product 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

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 σ2 binding sites (IC50 = 0.9 nM). The σ2 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-toluene-sulfonic acid assistance, which is a useful reagent for the acyclic congeners, and BF3·Et2O 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.
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,\textsuperscript{52} with the five membered ring analogue being the most potent.

2.3 Diastereoselective Synthesis of 1,3-Disubstituted Isochromans

The group of Jung\textsuperscript{40a} disclosed that the self-condensation of the TMSI adduct of phenylacetaldehyde (66) gave the dibenzocyclooctadiene derivative 67 (Scheme 7), presumably 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[\textit{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.\textsuperscript{40b}

Wünsch and Zott\textsuperscript{22,53a} reported that the condensation of several optically active phenyllactic acids 74 with benzaldehyde and butylaldehyde under acid catalysis gave mix-
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. 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.

D1 dopaminergic agonists with 1,3-disubstituted isochroman skeletons are among the few D1 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.

Michaelidis and co-workers reported the synthesis of 3-cyclohexylisochroman derivatives 77, 78 and 79 following the synthetic route shown in Scheme 8. Lateral metalation 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 aminal 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 thiokeetal 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

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>Conditions</th>
<th>cis/trans</th>
<th>Yield (%)</th>
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<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>HCl, ZnCl2, r.t., 12 h</td>
<td>90:10</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>OH</td>
<td>Me</td>
<td>Ph</td>
<td>H</td>
<td>HCl, MeOH, r.t., 14 h</td>
<td>61:39</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>OH</td>
<td>Me</td>
<td>Pr</td>
<td>H</td>
<td>TsOH, CHCl3, 66 h</td>
<td>58:42</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>OH</td>
<td>Me</td>
<td>–H2C-(CH2)3CH2 –</td>
<td>TsOH, CHCl3, 3 h</td>
<td>–</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>OH</td>
<td>Me</td>
<td>–(CH3)2NMe(CH2)3 –</td>
<td>TsOH, Cl(CH2)2Cl, 48 h</td>
<td>–</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>OH</td>
<td>Me</td>
<td>–(CH3)2NaC(CH2)3 –</td>
<td>TsOH, Cl(CH2)2Cl, 16 h</td>
<td>–</td>
<td>32</td>
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</tr>
<tr>
<td>7</td>
<td>OMe</td>
<td>Me</td>
<td>–(CH3)2NMe(CH2)3 –</td>
<td>HCl, dioxane, r.t., 48 h</td>
<td>–</td>
<td>27</td>
<td></td>
</tr>
</tbody>
</table>

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-HT1A and 5-HT1C receptors.

More recently, Unterhalt and Heppert56 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 BF3·Et2O assistance and nucleophilic displacement of the resulting chlorides with amines. The affinities of the synthetic compounds towards the 5-HT2A receptor and the serotonin transporter were tested, and the authors synthesized 1-aryl analogues as well.

While these oxa-Pictet–Spengler cyclizations selectively provided the 1,3-cis diastereomers, during their study of prospective antitumor agents, Grasso and co-workers57 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.

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 Holzapfel60 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–ZnCl2 reagent, dihalogenated heterocycle 112 gave isochroman 101; analogously, 102 was obtained quantitatively from 111 after treatment with MOMCl under ZnCl2 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 Singh62 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 benzyl (118) and allylic (119, 120) chlorides being the major reaction products (Scheme 12).63

Interestingly, Rama64 disclosed that 1,3-dimethyl-6,8-dimethoxyisochroman, as well as 1-methyl-, 1-ethyl-,
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 BF₃·Et₂O 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-; 65 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 CAr–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.
Next, vinyl Grignard addition produced compound 128, which, once submitted to an oxymercuration-demercuration, afforded secondary alcohol 129. Upon treatment with methoxymethyl chloride (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.

2.5 Synthesis of C-4-Substituted Isochroman Derivatives

For the synthesis of 5-spirobenzodiazepinones, Gatta and Settimi prepared cyclopentyl β-phenethyl alcohol 134a and N-methylamino derivative 134b 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 followed by reaction of the resulting d-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.
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-workers77 synthesized a series of 1,1,4,4-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 acetate. In turn, alcohols 155 and 154 were accessed in high yields from ester 135 by methyl Grignard addition or LDA-mediated α-carbonyl alkyla- tion (to 156) and borane reduction, respectively.

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
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-hydroxisochromans 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 D₄ versus D₂ receptors. Other piperazine and related derivatives were later prepared by Combourieu and co-workers, by way of the same general strategy.82

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 D₄ versus D₂ receptors. Other piperazine and related derivatives were later prepared by Mohler and Thompson.84

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

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 22

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-haloethers or hemiacetals. A related transformation, occurring via an iodoacetal, was also reported by Jung.40a

Mohler and Thompson 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
oxocarboxation (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-dimethylishochromans. The product distribution may be attributable to the fact that the cis isomer 168 has both of its methyl groups adopting a pseudoaxial 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 derivatives88 and involves the coupling of homoallylic alcohols with several equivalents of simple aldehydes, under acid catalysis.89 Acetals can be used in place of aldehydes90 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 Kaufman93 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 TiCl₄, with other Lewis acids such as BF₃·Et₂O 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

**Table 3** An Intramolecular Oxa-Pictet–Spengler Cyclization

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(CH₃)₂CO₂Et</td>
<td>CH₃Br</td>
<td>TiCl₄, CH₂Cl₂, -30 °C → r.t., 2 h</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td>(CH₃)₂CH₂OBn</td>
<td>CH₃SPh</td>
<td>TiCl₄, CH₂Cl₂, -60 °C → -30 °C, 2 h</td>
<td>26</td>
</tr>
<tr>
<td>3</td>
<td>(CH₃)₂CN</td>
<td>CH₃SPh</td>
<td>TiCl₄, CH₂Cl₂, -30 °C, 2 h</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>(CH₃)₂CN</td>
<td>(CH₂)₂SO₂Ph</td>
<td>TiCl₄, CH₂Cl₂, -78 °C, 1.5 h</td>
<td>59</td>
</tr>
<tr>
<td>5</td>
<td>(CH₃)₂CN</td>
<td>(CH₂)₂OTBDPS</td>
<td>TiCl₄, CH₂Cl₂, -45 °C, 4 h</td>
<td>60</td>
</tr>
</tbody>
</table>
acetal 177, leading to 178, where ring opening of the dioxolane 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-enolendo-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-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 team98 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 forms (183–d), the rearrangement of which provided 1-deuteroisochromans 184–d. Unfortunately, reported yields of isochromans were in the range of 5–30%.

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.

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 phthalazines102 and tetrahydroisoquinolines.103
Kametani also reported that mixing 2-(3-methoxyphenyl)ethanol (191), prepared from 192, with methyl pyruvate without an acid catalyst gave no reaction and allowed recovery of the starting material, 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 with several carbonyl compounds, accessing in this way hexahydro-6H-dibenzopyrans (Scheme 28). Yields, however, were less than 30%.

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-6H-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 in the trimer fraction of pine wood (from Pinus taeda) degraded by the DFRC (degradation followed by reductive procedure) protocol. 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.

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...
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 amounts108 (Scheme 30). The antioxidant and platelet aggregating 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 prepared 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 (−)-(15)-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 SnCl4 seemed to always outperform BF3·Et2O.

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-workers111 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-toluensulfonic 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 Catharanthus 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-

Figure 6
ject 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 D1 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 BF3·Et2O promotion, and the resulting 1,3-cis substituted 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 D1/D2 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).

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

| Entry | R* of 217 from 214 | Lewis Acid | Product | Yield (%) | de (%) | [α]D
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>213a</td>
<td>BF3·Et2O</td>
<td>216a</td>
<td>87</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>213b</td>
<td>BF3·Et2O</td>
<td>216b</td>
<td>81</td>
<td>40</td>
<td>−8.54</td>
</tr>
<tr>
<td>3</td>
<td>213b</td>
<td>SnCl4</td>
<td>216b</td>
<td>70</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>213c</td>
<td>BF3·Et2O</td>
<td>216c</td>
<td>68</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>213c</td>
<td>SnCl4</td>
<td>216c</td>
<td>61</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>213d</td>
<td>BF3·Et2O</td>
<td>216d</td>
<td>58</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>213d</td>
<td>SnCl4</td>
<td>216d</td>
<td>57</td>
<td>84</td>
<td>−18.0</td>
</tr>
<tr>
<td>8</td>
<td>213e</td>
<td>BF3·Et2O</td>
<td>216e</td>
<td>85</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>213e</td>
<td>SnCl4</td>
<td>216e</td>
<td>73</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>213f</td>
<td>BF3·Et2O</td>
<td>216f</td>
<td>61</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>213f</td>
<td>SnCl4</td>
<td>216f</td>
<td>59</td>
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<td></td>
</tr>
<tr>
<td>12</td>
<td>213g</td>
<td>BF3·Et2O</td>
<td>216g</td>
<td>80</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>213g</td>
<td>SnCl4</td>
<td>216g</td>
<td>78</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>213h</td>
<td>BF3·Et2O</td>
<td>216h</td>
<td>65</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>213h</td>
<td>SnCl4</td>
<td>216h</td>
<td>59</td>
<td>&gt;95</td>
<td>−20.2</td>
</tr>
</tbody>
</table>
Interestingly, this led to the demonstration 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 EC50 of 8580 nM, while the \((1R,3S)-225\) enantiomer displayed a \(D_1\) binding \(K_i\) of 1.6 nM and EC50 of 1.95 nM. Furthermore, the bulky phenyl ring was very important for achieving good activity, since the desphenyl analogue \(19\) 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 \(\beta\)-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-
triamolecular 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.

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 aminoaetal.

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 diastereomer (1S,3S)-242 was submitted to a Dieckmann condensation, while the dextrorotatory diastereomer was first epimerized at C-3 to (1R,3R)-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)\(^{116d}\) and passed through phantolide (246).

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 (4RS,7SR)-6 and (4RS,7RS)-6 through the formation of chromium carbonyl complexes 247, as shown in Scheme 36.\(^ {120}\)
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 (4S,7R)-6, which proved to be the most powerful compound, closely followed by (4S,7S)-6. The 4R isomers were demonstrated to be much weaker and to not contribute to the odor profile of galaxolide.

A more recent synthesis of diastereomers of galaxolide on C-7 was described by the group of Scrivanti.123 These Italian scientists prepared compound (4S)-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

These authors120 also synthesized all four of its isomers (Scheme 37) through a strategy that consisted of reacting 1,1,2,3,3-pentamethyl indane (249), with chiral propylene oxides (R)-249 and (S)-249 under Friedel–Crafts-type conditions122 promoted by titanium tetrachloride.

A more recent synthesis of diastereomers of galaxolide on C-7 was described by the group of Scrivanti.123 These Italian scientists prepared compound (4S)-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%.

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In a short communication of their results on the synthesis of selective dopamine D₄ 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). 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 isochromans and naphthopyrans, the oxa-Pictet–Spengler cyclization was extensively employed for the synthesis of pyranoidoles, 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; however, recently the group of Miles reported the oxa-Pictet–Spengler reaction of 1-(3-furyl)alkan-2-ols.

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), were cyclocondensed with various aldehydes 261 and acetone. Good yields were obtained of the highly acid-sensitive 5,7-disubstituted 4,5-dihydro-7H-furano[2,3-c]pyrans 262, potentially useful starting materials for the preparation of complex pyran-type natural products.

**Scheme 39**

**Scheme 40**

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 reaction being applied to the synthesis of furan derivatives; however, recently the group of Miles reported the oxa-Pictet–Spengler reaction of 1-(3-furyl)alkan-2-ols.
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–Spengler134 condensation of different heterocyclic β-ethanols 264a–d (Figure 9) 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).

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 substituted on both heterocyclic rings as well as on the aromatic moiety, have been prepared by...
the oxa-Pictet–Spengler condensation of β-phenethyl alcohols with ketones and aromatic aldehydes using HBr in dioxane as catalyst. Noteworthy, the same group prepared the 4-oxo analogue of etodolac; related compounds were synthesized by Kreft and co-workers, employing BF₃·Et₂O as catalyst.

Analogously, Fréter and Fuchs prepared pyrido[3,4-b]pyranoindoles, employing the oxa-Pictet–Spengler condensation of aldehydes and ketones, under BF₃·Et₂O catalysis (Table 7).

In the latter case, the starting materials were prepared by cycloalkenylation of properly substituted indoles to give prodolic acid (270, R = R¹ = H) was initially prepared as a lead; further studies, in which 36 other related compounds were synthesized (Scheme 41), led to the discovery of etodolac. The derivatives were prepared by reaction of various tryptophols 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’, condensation of thio-tryptophol with ethyl oxovalerate furnished as a sulfur analogue of prodolic acid (Scheme 42). Other analogues were obtained from different β-ketoesters; all of them

![Diagram](image_url)

Figure 10

Table 6 Synthesis of Different Heterocycles Employing the Oxa-Pictet–Spengler Condensation

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArCH₂CH₂OH</th>
<th>Carbonyl component</th>
<th>R¹</th>
<th>R²</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>264a</td>
<td>H₂NCH₂CH₂(OEt)₂</td>
<td>CH₃NH₂</td>
<td>H</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>264a</td>
<td>MeCOCH₂CO₂Et</td>
<td>CH₃CO₂Et</td>
<td>Me</td>
<td>63</td>
</tr>
<tr>
<td>3</td>
<td>264a</td>
<td>N-Methyl-4-piperidone</td>
<td>-H₂C-</td>
<td>Me</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>264b</td>
<td>Cl(CH₂)₂CH(OEt)₂</td>
<td>(CH₂)₂Cl</td>
<td>H</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>264b</td>
<td>MeCOCH₂CO₂Et</td>
<td>CH₃CO₂Et</td>
<td>Me</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>264c</td>
<td>MeCOCH₂CO₂Et</td>
<td>CH₃CO₂Et</td>
<td>Me</td>
<td>50</td>
</tr>
<tr>
<td>7</td>
<td>264d</td>
<td>H₂NCH₂CH₂(OEt)₂</td>
<td>CH₃NH₂</td>
<td>H</td>
<td>74</td>
</tr>
<tr>
<td>8</td>
<td>264g (R = Cl)</td>
<td>MeCOCH₂CO₂Et</td>
<td>CH₃CO₂Et</td>
<td>Me</td>
<td>30</td>
</tr>
<tr>
<td>9</td>
<td>264g (R = H)</td>
<td>EtCOCH₂CO₂Et</td>
<td>CH₃CO₂Et</td>
<td>Et</td>
<td>13</td>
</tr>
<tr>
<td>10</td>
<td>264h (R = Me)</td>
<td>MeCOCH₂CO₂Et</td>
<td>CH₃CO₂Et</td>
<td>Me</td>
<td>65</td>
</tr>
<tr>
<td>11</td>
<td>264h (R = Me)</td>
<td>n-PrCOCH₂CO₂Et</td>
<td>CH₃CO₂Et</td>
<td>n-Pr</td>
<td>59</td>
</tr>
<tr>
<td>12</td>
<td>264h (R = Et)</td>
<td>MeCO(CH₂)₂CO₂Et</td>
<td>CH₃CH₂CO₂Et</td>
<td>Me</td>
<td>42</td>
</tr>
<tr>
<td>13</td>
<td>264h (R = Me)</td>
<td>MeCO(CH₂)₂CO₂Et</td>
<td>(CH₂)₂CO₂Et</td>
<td>Me</td>
<td>92</td>
</tr>
<tr>
<td>14</td>
<td>264i (R = H)</td>
<td>Me₂CO</td>
<td>Me</td>
<td>Me</td>
<td>73</td>
</tr>
<tr>
<td>15</td>
<td>264i (R = Cl)</td>
<td>MeCOCH₂CO₂Et</td>
<td>CH₃CO₂Et</td>
<td>Me</td>
<td>34</td>
</tr>
<tr>
<td>16</td>
<td>264i (R = NO₂)</td>
<td>MeCOCH₂CO₂Et</td>
<td>CH₃CO₂Et</td>
<td>Me</td>
<td>59</td>
</tr>
<tr>
<td>17</td>
<td>264i (R = H)</td>
<td>MeCOCO₂Et</td>
<td>CO₂Et</td>
<td>Me</td>
<td>57</td>
</tr>
</tbody>
</table>

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.

In this fashion, prodolic acid (270, R = R¹ = H) was initially prepared as a lead; further studies, in which 36 other related compounds were synthesized (Scheme 41), led to the discovery of etodolac. The derivatives were prepared by reaction of various tryptophols 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’, condensation of thio-tryptophol with ethyl oxovalerate furnished as a sulfur analogue of prodolic acid (Scheme 42). Other analogues were obtained from different β-ketoesters; all of them
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 oxo-Pictet–Spengler condensation of appropriately substituted tryptophols with methyl-3-methoxypentenoate under BF₃·Et₂O catalysis.¹⁴⁵

During research work related to the synthesis of etodolac, Chou prepared chloro derivative 274 by oxo-Pictet–Spengler reaction of 7-ethyltryptophol 215b with ketal ester 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-workers⁴⁹ 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 SnCl₄-mediated cyclization of the acid chloride, formed with the aid of PCl₃, furnished isatine 286.⁵⁰

Demethylation of 286 with lithium iodide in DMF¹⁴⁹ 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 oxo-Pictet–Spengler cyclization with the methyl enol ether of 3-oxomethylpentanoate (290) under BF₃·Et₂O promotion, to

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>Yield (%) of 268</th>
<th>R¹</th>
<th>R²</th>
<th>Yield (%) of 267</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>Me</td>
<td>56</td>
<td>Me</td>
<td>Me</td>
<td>59</td>
</tr>
<tr>
<td>2</td>
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<td>Ts</td>
<td>75</td>
<td>Me</td>
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<td>3</td>
<td>OMe</td>
<td>Me</td>
<td>73</td>
<td>Me</td>
<td>Me</td>
<td>31</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>Me</td>
<td>56</td>
<td>H</td>
<td>C₆H₅</td>
<td>13</td>
</tr>
</tbody>
</table>

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

![Scheme 41](image1)

![Scheme 42](image2)
yield methyl ester 291. Final saponification of the ester gave the desired product 281.

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

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–ZnCl₂ 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 designed a silycon-terminated oxa-Pictet–Spengler protocol towards tetrahydropyrano[3,4-b]indoles 298 (Scheme 46).
required starting tryptophols 299 were prepared in moderate yields from the corresponding iodoanilines 300 by the method of Larock. Thus, anilines 301 were selectively iodinated with N-iodosuccinimide and then subjected to coupling with silyl homopropargyl alcohol (302).

The oxo-Pictet–Spengler cyclization of 299 was explored with BF₃·Et₂O and trifluoroacetic acid as promoters; however, the former usually gave good-to-excellent yields of product, it sometimes furnished complex mixtures. In contrast, trifluoroacetic acid consistently provided the required pyranoidoless in 50–90% yields.

Side products, such as the desilylated tryptophol 303 and unsilylated 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 oxo-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.

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 oxo-Pictet–Spengler condensation was employed by the group of McCullough in their synthesis of tetrahydro-2-benzoepines as potential hypotensive agents (Scheme 47).

In one of their synthetic strategies, 308 was condensed with different acetics under trifluoroacetic acid promotion to furnish 309; further amination of the halides with piperazine 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, R² = Me, Ar = 4-CF₃-C₆H₄) 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 bromoacetol was explained by the ability of intermediate 311, derived from bromoacetol, 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 acetate (5–10% yields) was employed. Interestingly, Rosowsky was able to prepare benzoepine 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).
The reaction was carried out in two stages and the intermediacy of chloromethyl ether 315 was invoked.\textsuperscript{155} Compound 313 was further elaborated into rigid analogues of folic acid, such as 6,7-dihydro-5H-benzo[3,4]cyclohept[a,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,\textsuperscript{156} which embodies the oxazaphenalene 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 \textit{Stephania} and \textit{Cissampelos} species of the Far East and Brazil.\textsuperscript{157} Tricyclic analogues of stephaoxocanidine have been demonstrated to display potent activity as acetylcholinesterase inhibitors.\textsuperscript{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 \textit{threo}-diol 322. In turn, this was transformed into a mixture of acetals 323, which was preferentially rearranged to \textit{trans}-1,3-dimethylisochroman-3-ol 324 upon intramolecular oxa-Pictet–Spengler reaction catalyzed by TiCl\textsubscript{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
formation of the resulting secondary amine 327 into sulfonyamide 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 oxazaphenalene 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 D1 and D2 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 isochromen family will continue to be disclosed in the future.

Acknowledgement

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References

