DOI: 10.1002/ejoc.201100271

Synthesis of Oxacycles Employing the Oxa-Pictet–Spengler Reaction: Recent Developments and New Prospects

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Dedicated to Professor Manuel González Sierra on the occasion of his 65th birthday

Keywords: Natural products / Synthetic methods / Synthesis design / Oxygen heterocycles / Cyclization

The oxa-Pictet–Spengler cyclization is the oxygen variation of the Pictet–Spengler reaction, in which an aromatic alcohol component (generally a β-arylethyl alcohol) reacts with a carbonyl component (aldehyde, ketone or their masked derivatives), to yield a 1-substituted (or 1,1′-disubstituted) pyran fused to the aromatic ring system found in the starting alcohol. The transformation is usually promoted by Brønsted and Lewis acids. Intramolecular versions of the reaction are also known, where both components are mutually masked as an acetal. Discussed here are aspects concerning the most recent developments and new applications of this useful reaction, including the scope and limitations of new promoters, and new mechanistic pictures of this transformation. The use of novel stereochemical control strategies and the application of the reaction to the synthesis of natural products and their analogs, as well as to accessing fully synthetic bioactive compounds and new ring systems are presented, and chiral versions of the oxa-Pictet–Spengler are also analyzed.

1. Introduction

The 3,4-dihydro-1*H*-benzo[*c*]pyran (isochroman, **1**) motif constitutes the framework of many natural products, as well as that of synthetic and semisynthetic compounds of interest. Molecules belonging to this small family, have been synthetically studied at least since 1912, when Schmidlin and Garcia-Banùs, first reported the unexpected formation of 1,3-diphenylisochroman from the reaction of benzaldehyde with benzylmagnesium chloride.[1]

A statistical analysis of the number of indexed publications on the topic "isochroman" since 1910 counted about 900 articles, 300 of them published during the last decade and 35 in 2010 alone; Figure 1 displays a small selection of compounds embodying the isochroman motif. This includes excentricine (**2a**) and *N*-methylexcentricine (**2b**), alkaloids from the roots of *Stephania excentrica* carrying the tetracyclic stephaoxocane skeleton,[2] ilexchromane (**3**) obtained from the dried roots of *Ilex pubescens* Hook et Arn,[3] the

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penicisochromans D (**4a**) and E (**4b**) from *Penicillium* PSU-F40[4] and the structurally unique Cytosporolides A–C (**5a**–**c**), recently isolated from *Cytospora sp.*[5]

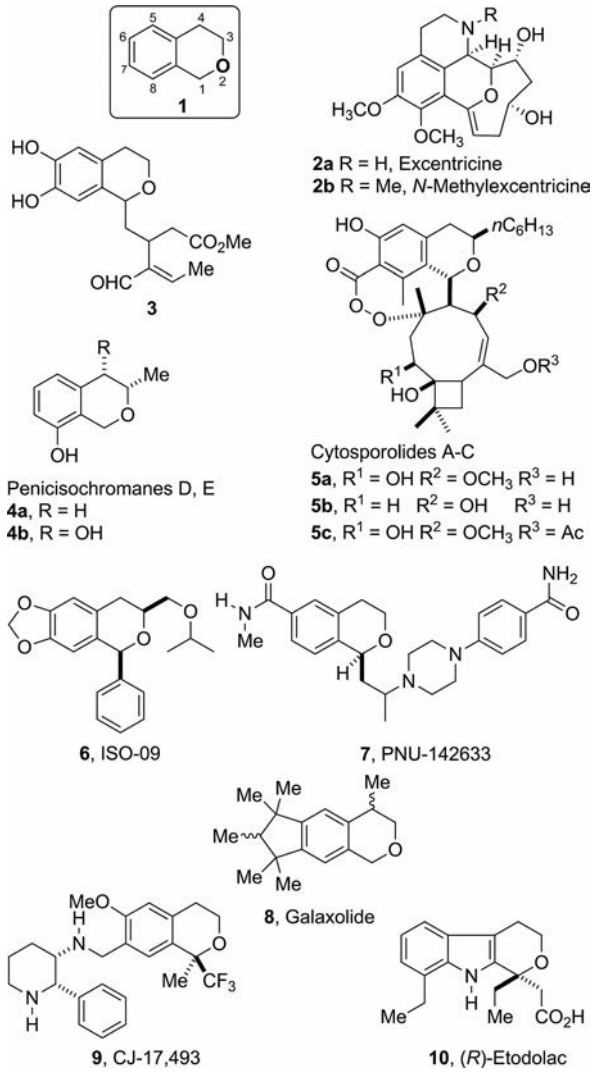

Figure 1. Structures of natural and synthetic isochromans, and the NSAID etodolac.

On the other hand, synthetic isochromans are exemplified by the apoptosis inhibitor of vascular endothelial cells ISO-09 (**6**),[6] the anti-migraine drug PNU-142633 (**7**),[7] the commercial fragrance galaxolide (**8**)[8] and the novel neurokinin-1 receptor antagonist CJ-17,493 (**9**),[9] while the non-steroidal anti-inflammatory drug etodolac (**10**)[10] is an example of a synthetic commercial aryl pyran other than a benzo-fused heterocyclic derivative.

Isochromans are also useful intermediates for the synthesis of isocoumarins, benzophenones, benzodiazepine-4-ones and other compounds.[11]

Among the arsenal of synthetic resources available for the synthesis of isochroman derivatives, the oxa-Pictet–Spengler reaction has emerged as a powerful and versatile tool. This is the oxygen variation of the Pictet–Spengler reaction, in which a properly activated aromatic carbinolic component (generally a β-arylethyl alcohol) is condensed with a carbonyl component (aldehyde, ketone or their masked derivatives), to yield a 1-substituted (also unsubstituted and 1,1′-disubstituted) 2-arylpyran derivative. Intramolecular versions of the reaction are also known, where both components are mutually masked as an acetal or related moiety or tethered to the same aromatic ring, such as in Marson's type cyclization or in the Mukaiyama-type acetal rearrangement extensively studied by Giles and co-workers.[12]

While in the classical Pictet–Spengler a β-arylethylamine (β-phenethylamine, tryptamine, and the like) derivative reacts with a carbonyl compound, generating an imine, which undergoes cyclization via an intramolecular electrophilic aromatic substitution process (yielding isoquinoline, β-carboline and similar derivatives), in the oxa-Pictet–Spengler reaction oxygen analogs of the amine yield the analogous oxygen-bearing heterocycles.

1.1. Early Applications of the oxa-Pictet–Spengler Cyclization

The reaction name was coined by Wünsch and co-workers in 1992;[13] however, syntheses of isochroman itself and isochroman derivatives employing this strategy have carried out long before and the reaction conditions have been the subject of continuous improvement.

The origins of the oxa-Pictet–Spengler cyclization strategy towards isochromans can be traced back to 1935, when two German patents described the chloromethylation of 2-phenylethanol with paraformaldehyde and HCl, with subsequent cyclisation in 50% yield upon treatment with inorganic acids, preferably at 100 °C.[14] In 1954, the method was improved by Maitte[15] who reported the AcOH-promoted cyclocondensation of (1-phenylcyclopentyl)methanol with formaldehyde at 100 °C during 1 h. Under these conditions, the yield of the corresponding spirocyclic isochroman derivative neared 90%.

The first application of the oxa-Pictet–Spengler cyclization to the synthesis of natural products was reported in 1949, when Warren and co-workers described the synthesis of dihydrocitrinin by reaction of a β-phenethyl alcohol resulting from degradation of the antibiotic citrinin and methylal in benzene under dry HCl promotion. The procedure was later extended to citrinin and dihydrocitrinin analogs by the use of different aldehydes, ketones and acetals.[16] Crude yields were 50–80%.

At the beginning of the 1970s, Micheel and Schleifstein described the cyclocondensation of benzene and glyceraldehyde in liquid hydrogen fluoride to furnish L-(1′,2′-dihydroxyethyl)-3-hydroxymethyl-4-phenylisochroman in 35–40% yield. Two molecules of glyceraldehyde were required for the process; one of them performed the acid-catalyzed acylation of benzene leading to an intermediate β-phenethyl alcohol derivative which cyclized when reacted with a second molecule of the aldehyde. Interestingly, apparently only one diastereomer was obtained.[17]

In 1975, by analogy with their "phenolic cyclization" where activated β-phenethylamines cyclised to yield 1,2,3,4-

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tetrahydroisoquinolines without acidic catalysts, Kametani and co-workers developed an alternative procedure to that of Warren's towards isochromans. The strategy employed an activated β-phenethyl alcohol derivative and did not require an acidic promoter.[18] Thus, heating *anti*-2-(3-hydroxyphenyl)cyclohexanol with cyclohexanone in a sealed tube for 15 h furnished 28% of spiro[1,2,3,4,4a,10b-hexahydrobenzo[*c*]chromene-6,1′-cyclohexan]-9-ol. However, cyclization of less active substrates required HCl or TsOH assistance.

Concomitantly, a limited number of synthetic approaches, reminiscing variations of the analogous thia-Pictet–Spengler cyclization, have been also developed for the synthesis of the structurally related isothiochromans, including the intramolecular cyclization of phenylethanethiol chloromethyl ethers in the presence of catalytic amounts of Lewis acids[19] and the intramolecular cyclization of thioacetal[20] derivatives.[21] Isothiochromans are useful precursors for the synthesis of analogs of tetrahydronaphthalenes, isoquinolines and isochromans.[22]

The chemistry of the isochromans has been reviewed[23] and two publications specifically addressed the uses and applications of the oxa-Pictet–Spengler reaction.[24] However, since publication of these reports in 2006, the oxa-Pictet–Spengler has been taken an increasingly central role in 2-aryl-1*H*-pyran synthesis. New promoters and reaction conditions have expanded its scope, which currently extends not only to pyran-type oxacycles but also to five- and seven-membered oxacycles. These developments allowed the syntheses of natural and bioactive compounds, as racemates and in their optically active forms.

This review examines these major developments, along with new insights into the reaction mechanism and an update of chalcogeno-Pictet–Spengler metodologies, closing with a brief conclusion and a prospect on the usefulness of the reaction in the near future.

2. New Promoters and New Reaction Control Elements

For the preparation of oxacycles from β-arylethanols and carbonyl derivatives, different Brønsted and Lewis acids have been employed.

Typically, aqueous HCl[25] as well as $BF_3{\cdot}Et_2O$,[26] HCl gas,[27] TsOH,[28] $ZnCl_2$,[29] $AlCl_3$,[30] $TiCl_4$[31] and $SnCl_4$[32] in organic solvents have been used to promote the reaction, sometimes along with high reaction temperatures.

However, more recently some new and milder promoters and conditions have been described; for example, the use of catalytic amounts of TsOH in MeOH at 4 °C,[33] oleic acid in MeOH at 21 °C, or using dehydrating agents (molecular sieves or anhydrous Na_2SO_4) besides the promoter.[34]

During the last five years, the performance of new promoters has been explored, some times with a view at environmental friendliness and application of green chemistry concepts. In this context, the use of different sulfonic acid derivatives has been tested, while bismuth triflate and other triflates have been proposed as new promoters, in organic solvents.

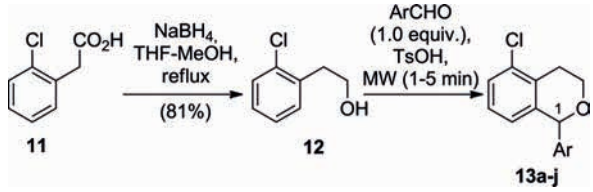
On the other hand, the performance of TsOH and perfluorooctanesulfonic acid in aqueous media has also been explored. In addition, tin and silicon chemistry has shown to be helpful in providing key alcohol components for the reaction, acting as control elements. Details of these investigations are given below.

2.1. New Promoters of the Oxa-Pictet–Spengler Cyclization

Saeed and Mumtaz[35] reported the clean and environmentally benign one-pot synthesis of 1-aryl-5-chloroisochromans (**13a**–**j**).

The synthesis took place by cyclocondensation of 2-(2-chlorophenyl)ethanol (**12**), a non-activated oxa-Pictet–Spengler alcoholic precursor, with aromatic aldehydes in a stoichiometric ratio, under microwave irradiation (Table 1). TsOH was employed to promote the reaction and the cyclization took place in the absence of solvent. The starting β-phenethyl alcohol was conveniently prepared in 81% yield by the sodium borohydride-mediated reduction of *o*-chlorophenylacetic acid (**11**). Yields of the cyclised product ranged from good to excellent.

Table 1. Synthesis of 1-arylisochromans under microwaves assistance.



Entry	Time [s]	Ar	% Yield
1	90	C_6H_5	78
2	60	4-F-C_6H_4	88
3	80	2-Cl-C_6H_4	80
4	90	3-Cl-C_6H_4	87
5	120	3-Br-C_6H_4	82
6	90	4-Br-C_6H_4	84
7	80	4-MeO-C_6H_4	92
8	60	3,4-$(MeO)_2$-C_6H_3	81
9	60	3,4,5-$(MeO)_3$-C_6H_2	91
10	90	α-furyl	69

On the other hand, Lherbet and co-workers[37] reported the use of bismuth triflate as a nontoxic and easy to handle promoter for the oxa-Pictet–Spengler synthesis of isochromans. Bi^{III} salts are known to catalyze Mannich reactions, which constitute an intermolecular version of the oxa-Pictet–Spengler cyclization.[38]

During reaction optimization, with 3,4-dimethoxy-β-phenethyl alcohol and 4-nitrobenzaldehyde, it was observed that in the absence of promoter the reaction mixture only provided 16% product when heated in toluene at 80 °C for 18 h. Addition of 0.01 equiv. $Bi(OTf)_3$ raised yields to over 99%, concomitantly reducing the reaction time to 0.5 h. The addition of activated molecular sieves inhibited the re-

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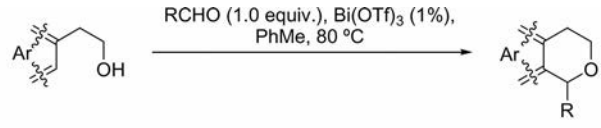
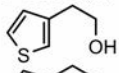
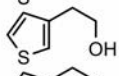
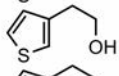
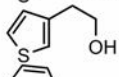
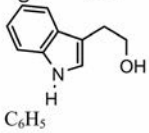
action, while incorporation of 2.5% water yielded 91% of the isochroman after heating for 1 h.

Neither $Bi(NO_3)_3$ nor $BiBr_3$ gave satisfactory product yields, while 0.1 equiv. TfOH almost quantitatively furnished the expected product. These results established the conditions for studying the generality of the reaction and provided hints regarding its mechanism.

Reaction of activated 3,4-dimethoxy-β-phenethyl alcohol (entries 1–6), 3-methoxy-β-phenethyl alcohol (entries 7–10), as well as (2-thienyl)ethanol (entries 11–14) gave high yields of the corresponding heterocycles (Table 2). Tryptophol (entry 15) gave a slightly lower yield, while aliphatic aldehydes performed as well as their aromatic congeners (entry 7).

Table 2. Synthesis of 1-substituted isochromans under $Bi(OTf)_3$ promotion.

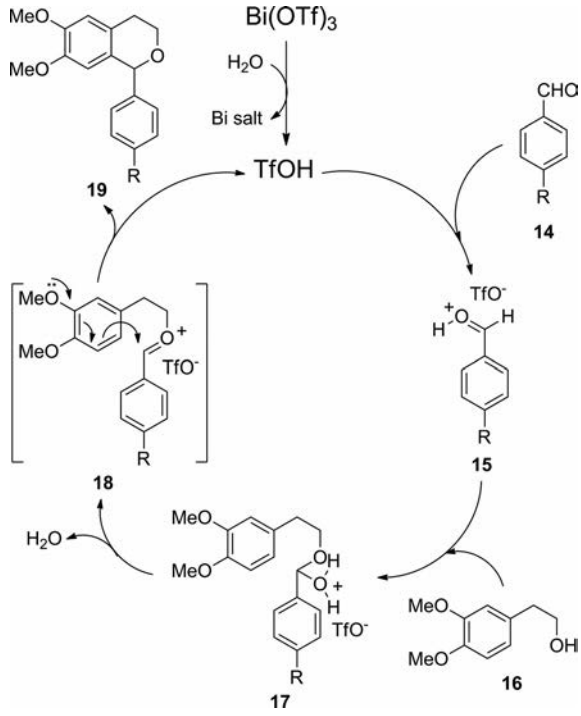


Entry	Time (h)	Ar	R (**14a–g**)	Yield (%)
1	0.5	3,4-MeO-C_6H_3	4-NO_2-C_6H_4	>99
2	0.5	3,4-MeO-C_6H_3	3-NO_2-C_6H_4	>99
3	1	3,4-MeO-C_6H_3	4-CN-C_6H_4	98
4	0.5	3,4-MeO-C_6H_3	4-Me-C_6H_4	97
5	1.5	3,4-MeO-C_6H_3	4-MeO-C_6H_4	92[d]
6	2[a]	3,4-MeO-C_6H_3	6-MeO-2-$C_{10}H_6$	99
7	1	3,4-MeO-C_6H_3	$Me(CH_2)_4$	>99
8	1.5	3-MeO-C_6H_4	4-NO_2-C_6H_4	>99
9	1	3-MeO-C_6H_4	4-CN-C_6H_4	95
10	1	3-MeO-C_6H_4	4-MeO-C_6H_4	98
11	1		4-NO_2-C_6H_4	>99
12	1		4-MeO-C_6H_4	84
13	1		4-CN-C_6H_4	92
14	1		$Me(CH_2)_4$	81
15	2[b]		4-NO_2-C_6H_4	53
16	6[c]	C_6H_5	4-NO_2-C_6H_4	84

[a] 2% $Bi(OTf)_3$ was employed. [b] The reaction was performed at 50 °C. [c] The reaction was performed at 110 °C, employing 10% $Bi(OTf)_3$. [d] The X-ray crystallographic data of this product have been disclosed.[36]

These observations suggested that residual water is an important factor for catalytic efficiency and that $Bi(OTf)_3$ behaves as a handy source of TfOH,[39] being product yields correlated to acid strength.

A mechanism was proposed (Scheme 1), where the in situ generated triflic acid protonates the aldehyde component (**14**) of the reaction. In turn, the activated carbonyl derivative **15** reacts with the β-phenethyl alcohol (**16**) to yield a protonated hemiacetalic intermediate (**17**), which becomes dehydrated to the related oxocarbenium ion (**18**), which is finally cyclized to give **19**. Most probably, the assistance of the electron lone pairs of the methoxy group *para* to the cyclization site plays a role in facilitating cyclization, as reaction of β-phenethyl alcohol requires harsher conditions and proceeds with slightly lower yield.



Scheme 1. The $Bi(OTf)_3$-assisted synthesis of isochromans. Proposed reaction mechanism.

Use of ketones or ketals yielded the corresponding 1,1′-substituted isochromans (Table 3). Interesingly, protected carbonyl derivatives (acetals, ketals) can be obtained with the aid of bismuth triflate.[40] Being more reactive, the ketals furnished better product yields than their ketonic parents, being the preferred substrates for this transformation. The dimethyl ketal of cyclohexanone clearly outperformed the related 1,3-dioxolane. Tryptophol and 2-(2-thienyl)ethanol also afforded the isochroman ring products in good yields.

This group also studied the related thia-Pictet–Spengler cyclization of phenylethanethiol (**20**) and aromatic aldehydes under bismuth triflate promotion, leading to isothiochromans, like **22**.[41] The reactions proceeded in 40–94% yield after 2–15 h of heating in toluene at 100 °C, in the presence of 0.1 equiv. bismuth triflate.

The authors observed that dithioacetals, exemplified by **21**, are intermediates of the reaction, being bismuth triflate responsible for their formation (Scheme 2). Interestingly, despite promoting the formation of dithioacetals, $BiCl_3$ was unable to assist the cyclization stage leading to thioisochromans. These findings complement a previous intramolecular cyclization of [2-(2-methoxy-ethoxymethylselenyl)ethyl]-aryl derivatives described by Yoshimatsu and co-workers, leading to fused aryl selenopyrans and the synthesis of analogs of prodolic acid.[42]

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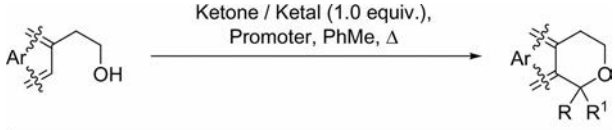
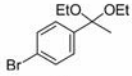
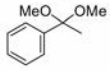
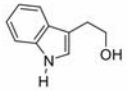
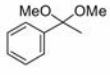
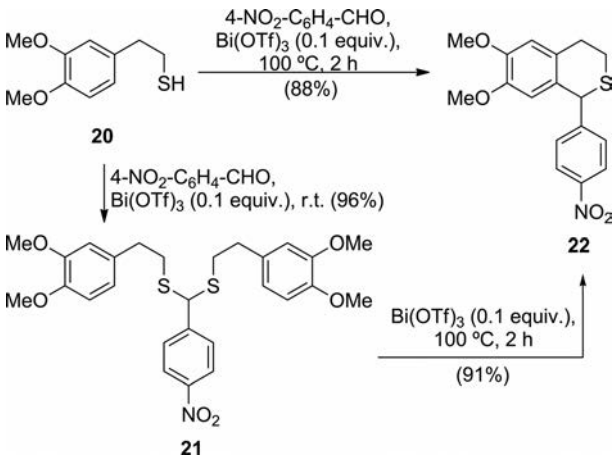
Table 3. Synthesis of 1,1′-disubstituted isochromans under $Bi(OTf)_3$ and TfOH promotion.



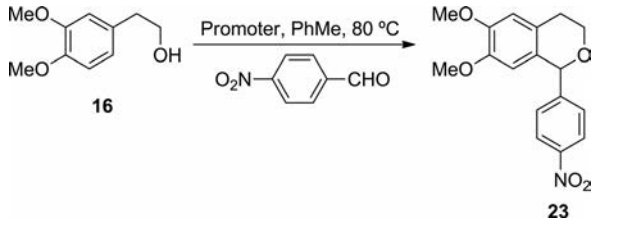
Conditions, [Promoter, mol-%]	Ar	R, R^1 ketone/ketal	Yield (%)
16h, 110 °C [$Bi(OTf)_3$, 10%]	3,4-MeO-C_6H_3		15
1h, 80 °C [TfOH, 10%]	3,4-MeO-C_6H_3		91
1h, 80 °C [$Bi(OTf)_3$, 1%]	3,4-MeO-C_6H_3		98
1h, 80 °C [$Bi(OTf)_3$, 1%]	3,4-MeO-C_6H_3		>99
3h, 80 °C [$Bi(OTf)_3$, 1%]	3,4-MeO-C_6H_3		60
18h, 80 °C [$Bi(OTf)_3$, 1%]	3,4-MeO-C_6H_3		34
4h, 80°C [$Bi(OTf)_3$, 1%]	3,4-MeO-C_6H_3		71
4h, 80 °C [TfOH, 10%]	3,4-MeO-C_6H_3		31
1h, 80 °C [$Bi(OTf)_3$, 1%]			94
1h, 80 °C [$Bi(OTf)_3$, 1%]			98
1.5h, 80 °C [$Bi(OTf)_3$, 1%]			81



Scheme 2. $Bi(OTf)_3$-promoted thia-Pictet–Spengler cyclization of 2-(3,4-dimethoxyphenyl)ethanethiol. Thioacetals as intermediates.

More recently, the same group studied the performance of the reaction between alcohol **16** and *p*-nitrobenzaldehyde with different metal triflates, demonstrating that the latter are useful promoters of the cyclocondensation to **23** (Table 4).[43]

Table 4. Synthesis of 1-arylisochromans under metal triflate promotion.



Conditions	Time [h]	% Yield
No catalyst	18	16
$Bi(OTf)_3$ (0.01 equiv.)	1	>99
$In(OTf)_3$ (0.01 equiv.)	1	>99
$Sc(OTf)_3$ (0.01 equiv.)	1	>99
$Zn(OTf)_2$ (0.01 equiv.)	1	91
$Yb(OTf)_3$ (0.01 equiv.)	1	>99
$Y(OTf)_3$ (0.01 equiv.)	1	>99
$Cu(OTf)_2$ (0.01 equiv.)	1	94
TfOH (0.1 equiv.)	1	>99
$M(OTf)_n$ (0.01 equiv.)[a]	1	>99
$M(OTf)_n$ (0.01 equiv.),[a] 4 Å mol. sieves	1	traces
$Bi(OTf)_3$ (0.01 equiv.), $MgSO_4$ (2 equiv.)	–	22
$M(OTf)_n$ (0.01 equiv.),[a] TTBP (0.1 equiv.)	1	0

[a] M = Bi, In, Sc, Yb, Y.

It was observed that yields were affected by the presence of dehydrating agents such as 4 Å molecular sieves and $MgSO_4$, and that when 2,4,6-tri-*tert*-butylpyridine (TTBP), a very hindered base, known to not interact with metal catalysts,[44] was added in order to neutralize traces of TfOH, no product was observed in the presence of various metal triflates.

The generality of the transformation was studied with different alcohols and aldehydes (Table 5). In the case of tryptophol, the yields of isochroman were around 50%, and a second product [a 2,2′-bis(indoyl)-4-nitrophenylmethane derivative] was formed concomitantly. In general, however, scandium and copper triflates were less efficient than the previously studied bismuth triflate. It was also observed that reaction with benzaldehydes bearing electron-rich substituents such as the 4-methoxy derivative proceeded slower than for benzaldehydes bearing electron-poor substituents such as 4-nitro.

Taking into consideration the human health and environmental concerns, the "Green Chemistry" approach to organic synthesis intends to decrease or preferably eliminate the use or generation of hazardous substances during chemical reactions. Nowadays, this paradigm is receiving much attention.

Solid acids and bases (natural and modified clay minerals, montmorillonites, zeolites, mixed oxides, layered double hydroxides) have been widely studied, resulting in efficient catalysts in organic synthesis.[45] These have excellent activity and selectivity even on industrial scales, and also good ability to be recovered from the reaction mixtures and reused while retaining good activity with concommitant production of less waste. Being these central ques-

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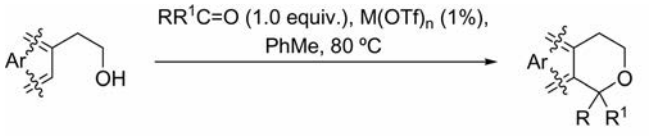
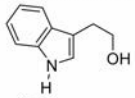
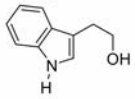
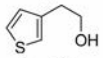
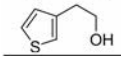
Table 5. Synthesis of 1-substituted isochromans under $M(OTf)_n$ promotion.



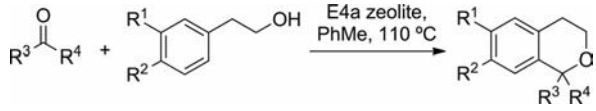
Alcohol	Carbonyl compd.	Triflate	Time (h)	Yield (%)
3,4-MeO-C_6H_3	4-NO_2-C_6H_4CHO	$Cu(OTf)_2$	1.5	>99
3,4-MeO-C_6H_3	4-MeO-C_6H_4CHO	$Cu(OTf)_2$	3	86
3,4-MeO-C_6H_3	Me-$(CH_2)_4$CHO	$Cu(OTf)_2$	3	90
3,4-MeO-C_6H_3	$MeCOCH_2CO_2Et$	$Cu(OTf)_2$	2	67
	4-NO_2-C_6H_4CHO	$Cu(OTf)_2$	3	40
	4-NO_2-C_6H_4CHO	$Sc(OTf)_3$	2	48
	4-MeO-C_6H_4CHO	$Sc(OTf)_3$	1.5	66
	$MeCOCH_2CO_2Et$	$Sc(OTf)_3$	2	85

tions from environmental point of view, Hegedüs and Hell recently proposed the use of Ersorb-4 (E4), a clinoptylolite-type zeolite material with high silicon content (Si/Al ratio = 5:1),[46] as promoter of the oxa-Pictet–Spengler reaction.[47]

The original mineral was modified by ion exchanges and with other water-phase technologies followed by a thermal treatment, yielding a Ca–K mixed cation-based adsorbent with 4 Å pore size. The composition of Ersorb-4 is: SiO_2 73.0%, Al_2O_3 11.2%, Fe_2O_3 1.17%, K_2O 5.12%, Na_2O 0.38%, CaO 2.20% and MgO 0.44%. E4 can adsorb small molecules (H_2O, HCl, NH_3, MeOH); it is stable until 500–600 °C, environmentally friendly, nontoxic, recoverable, reusable and inexpensive. The more acidic modification of Ersorb-4 (E4a, the pH of its aqueous suspension is ca. 3) demonstrated to be useful for the preparation of 1-substituted tetrahydroisoquinolines via the Pictet–Spengler reaction.[48]

When optimizing the reaction conditions for the oxa-Pictet–Spengler reaction, the best results were obtained using 0.5 g E4a and 2 mmol of 2-phenylethanol in PhMe 110 °C (Table 6). The weaker acidic E4 showed no activity and no reaction was observed using the strongly acidic KSF/0 montmorillonite alone or in a mixture with molecular sieves (4 Å). This result may be due to the fact that in the Ersorb catalysts both acidic sites and pores for binding water are present; thus, liberated water can be immediately fixed in the pores of the catalyst. The optimal reaction time was 15 h for aromatic aldehydes and 20 h for their aliphatic counterparts (at a lower temperature, due to their lower boiling points) and 35h for ketones. For 2-phenylethanol, the required reaction times were 40 h for aldehydes and 48 h for ketones, perhaps because of the lack of the activating groups.

Table 6. Synthesis of 1-substituted and 1,1′-disubstituted isochromans promoted by the E4a zeolite.



Entry	R^1	R^2	R^3	R^4	Time [h]	% Yield
1	MeO	MeO	4-Cl-C_6H_4	H	15	97[a]
2	MeO	MeO	4-Cl-C_6H_4	H	15	95
3	MeO	MeO	4-Cl-C_6H_4	H	15	95
4	MeO	MeO	4-MeO-C_6H_4	H	15	92
5	MeO	MeO	C_6H_5	H	15	83
6	MeO	MeO	C_6H_5	H	15	83
7	MeO	MeO	4-$(Me)_2N$-C_6H_4	H	15	89
8	MeO	MeO	3-NO_2–C_6H_4	H	15	85
9	MeO	MeO	2-Br-C_6H_4	H	15	77
10	MeO	MeO	Me-CH_2	H	20	70
11	MeO	MeO	Me-$(CH_2)_2$	H	20	79
12	O–CH_2–O		4-MeO-C_6H_4	H	15	91
13	O–CH_2–O		C_6H_5	H	15	86
14	H	H	C_6H_5	H	40	81
15	H	H	4-Cl-C_6H_4	H	40	88
16	H	H	4-MeO-C_6H_4	H	40	90
17	H	H	3-NO_2–C_6H_4	H	40	84
18	MeO	MeO	C_6H_5	Me	35	83
19	MeO	MeO	C_6H_5	Me	35	80
20	MeO	MeO	4-MeO-C_6H_4	Me	35	87
21	MeO	MeO	4-Me-C_6H_4	Me	35	90
22	MeO	MeO	4-Cl-C_6H_4	Me	35	91
23	MeO	MeO	3-MeO-C_6H_4	Me	35	77
24	MeO	MeO	2-Me-C_6H_4	Me	35	75
25	MeO	MeO	Me-CH_2	Me	35	64
26	H	H	C_6H_5	Me	48	77
27	H	H	4-MeO-C_6H_4	Me	48	82

[a] Crystallographic data of this compound have been published.[49]

The authors also studied the reaction mechanism, finding that the diphenylmethanol is an intermediate of the cyclization.[50] The intermediate was isolated, characterized by ^1H NMR and converted into the expected isochroman derivative upon refluxing over zeolite E4a in toluene.

According to these observations, a two-step mechanism was proposed which is at least operative for the oxa-Pictet–Spengler reaction catalyzed by zeolite (Scheme 3). The first step is an electrophilic aromatic substitution which involves reaction of the β-arylethanol **27** with the protonated form **25** of the carbonyl component **26**. Then, the thus formed diol intermediate **28** loses water to yield the isochroman **29**. Acid-catalyzed dehydration of homophthalic alcohols is at the hearth of one of the earliest general syntheses of isochromans.[51] The proposed cyclization sequence differs from the previously accepted mechanistic picture involving aromatic ring attack to an oxocarbenium intermediate[33,52] and was proposed to be operative during the synthesis of berkelic acid and in the silicon group-directed oxa-Pictet–Spengler cyclization reported by the group of Zhang.[68,170]

Interestingly, the group leaded by Ivanov[53] recently disclosed the application of *ortho*-acylated phenylacetic acid esters to the synthesis of 1-substituted isochromans through the intermediacy of alkyl-arylmethanol or diarylmethanol derivatives.

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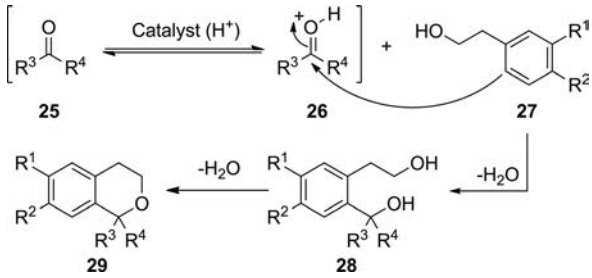
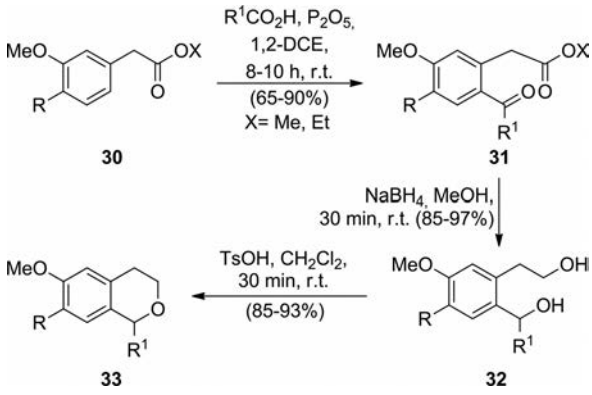


Scheme 3. Alternative reaction mechanism proposed for the oxa-Pictet–Spengler cyclization. Homophthalic alcohols as intermediates.

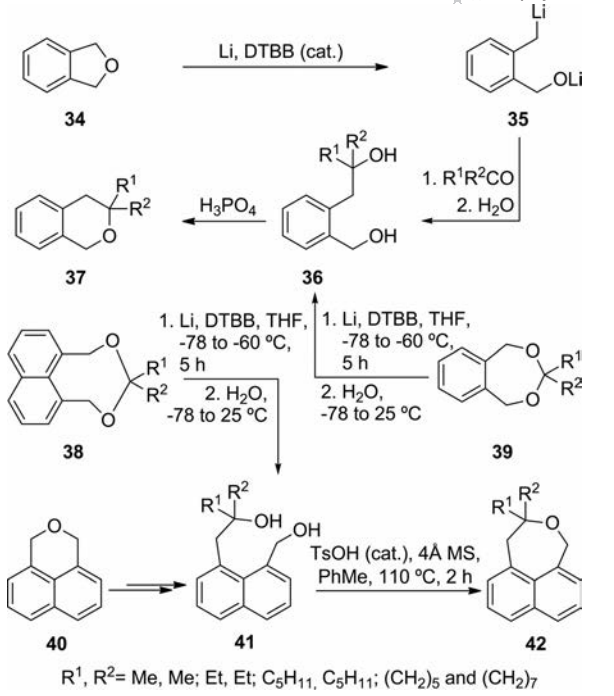
In this three-step sequence, the phenylacetic esters **30** were submitted to a Friedel–Crafts type acylation with different carboxylic acids, under assistance of P_2O_5, yielding ketones **31**, which were reduced to the corresponding key diols **32** with $NaBH_4$, which in turn were cyclized to **33** with TsOH in CH_2Cl_2 at room temperature (Scheme 4). The versatile strategy was able to accommodate a wide variety of substituents at C1.



Scheme 4. Oxa-Pictet–Spengler based cyclization sequence leading to isochromans from *ortho*-acylated phenylacetic acid esters.

Quite similar transformations leading to isochroman and 1,3,4,5-tetrahydro-benzo[*c*]oxepine derivatives were described by Foubelo and co-workers.[54] This group developed an efficient methodology to perform lithiations under mild reaction conditions, employing lithium powder and catalytic amounts (< 10%) of an arene, being 4,4′-di-*tert*-butylbiphenyl (DTBB) the most commonly used.[55] The reductive opening of phthalan (**34**) (Scheme 5) allowed the generation of the corresponding functionalised organolithium intermediates **35**, which once trapped with ketones yielded diols **36**, suitable precursors of isochromans **37**. The overall process entails a one-carbon ring expansion.

Analogously, the diol **41** was obtained in good yields from 1*H*,3*H*-benzo[*de*]isochromene **40**;[56] submission of the diol to cyclodehydration in refluxing toluene, to which catalytic amounts of TsOH were added, furnished the expected seven-membered oxacycles **42** in high yield. Access to the required diols **41** by ring opening and rearrangement of cyclic acetals **38**, **39** has also been reported.[57]



Scheme 5. Synthesis of six- and seven-membered oxacycles by ring expansion and cyclization of tertiary benzylic alcohols.

Saeed has recently disclosed a clean synthesis of isochromans in an environmentally friendly aqueous medium.[58] Reactants and products are poorly soluble in water; therefore, the mixture of the suspended organic reagents is refluxed and a biphasic system is present during the reaction.

The reaction conditions were optimized (Table 7) for the cyclocondensation of 3-methoxybenzaldehyde with 2-(3,4-dimethoxyphenyl)ethanol (**16**), and TsOH was found to be the best promoter.

Table 7. Optimization of the synthesis of isochromans in aqueous medium.

Entry	Solvent	Catalyst	Temp. [°C]	Time [h]	% Yield
1	–	TsOH	–	0.5	85
2	H_2O	–	room temp. to reflux	>300	–
3	H_2O	HCl/H_2SO_4	40–60	150	55
4	H_2O	HCl	60–80	120	60
5	H_2O	HCl	reflux	40	87
6	H_2O	TsOH	reflux	40	81
7	MeOH	TsOH	reflux	120	89
8	MeOH	TsOH	room temp.	>300	60

Employing an activated β-phenethyl alcohol, yields were above 80% (Table 8); however, in case of substrates like β-phenethyl alcohol itself, with no activating substituents on the phenyl ring, the reaction did not take place to an appreciable extent; therefore, β-phenethyl alcohols with electron-withdrawing groups are not expected to react under these conditions.

The reaction in water shows several advantages such as short reaction times, high yields, inexpensive catalyst, lack of side-product formation and minimum work up require-

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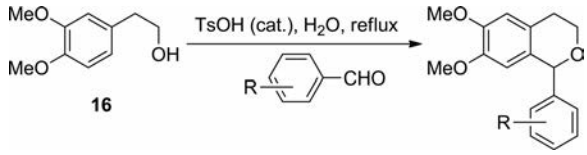
Table 8. Synthesis of isochromans under TsOH catalysis in aqueous medium.



Entry	R	Time [min]	% Yield
1	H	40	91
2	$C_6H_5C=CH$	45	88
3	3-MeO	45	98
4	4-MeO	40	87
5	3-MeO,4-OH	40	89
6	3,4-$(MeO)_2$	40	90
7	3,4,5-$(OMe)_3$	40	94
8	2-F	40	89[a]
9	3-F	45	88
10	4-F	45	97
11	2-Cl	50	86
12	3-Cl	50	97
13	4-Cl	50	98
14	4-$(Me)_2N$	45	98
15	3-NO_2	55	80
16	4-NO_2	55	81
17	3-HO	50	86
18	4-HO	55	81
19	4-Cl	60	58[b]
20	3-pyridyl	65	71[b]
21	3-NO_2	80	56[b]

[a] Crystallographic data of this isochroman derivative have been published.[59] [b] With 2-(3,4-dimethoxyphenyl)ethanethiol. Product is a isothiochroman.

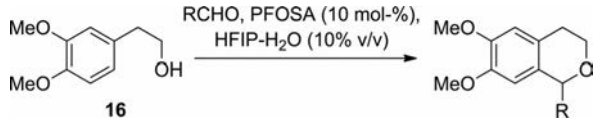
ments, as the insoluble products can be separated by direct filtration from the reaction medium.

The scope of method was also extended to a thia-Pictet–Spengler reaction. Condensation of 4-chlorobenzaldehyde, nicotinaldehyde and 3-nitrobenzaldehyde with 2-(3,4-dimethoxyphenyl) ethanethiol[60] afforded the corresponding isothiochromans in yields ranging between 56 and 71%, requiring 60–80 min. for completion.

Saito and co-workers[61] established the efficiency of perfluorooctanesulfonic acid (PFOSA) in 10% 1,1,1,3,3,3-hexafluoro-2-propanol HFIP–water as promoter for the Pictet–Spengler reaction of β-arylethyl carbamate derivatives, later extending the scope of the use of this reagent system to the oxa-Pictet–Spengler reaction of β-arylethyl alcohol (Table 9). The reagent system proved to be superior to TsOH, when aliphatic aldehydes such as heptanal were employed as carbonyl components and the amount of HFIP in the solvent mixture was optimized for this transformation.

However, while the cyclization yields with activated alcohols such as 3,4-dimethoxy-β-phenethyl alcohol (**16**) and 3-methoxy-β-phenethyl alcohol were high, the reaction of β-phenethyl alcohol itself with aliphatic and aromatic aldehydes gave no cyclized products. This cyclization was demonstrated not to proceed through the homophthalic alcohol path, as 1,2-dimethoxybenzene did not react with heptaldehyde under PFOSA promotion, even at high temperature; on the contrary, the related β-phenethyl alcohol furnished the corresponding isochroman in 93% yield (Entry 2).

Table 9. Optimization of the synthesis of isochromans with a perfluorosulfonic acid in HFIP-H_2O medium.



Entry	Aldehyde (equiv.)	Temp. [°C]	Time [h]	% Yiel
1	$nC_6H_{13}CHO$ (1.2)	room temp.	2	34[a]
2	$nC_6H_{13}CHO$ (1.2)	room temp.	48	93
3	$nC_{11}H_{23}CHO$ (1.8)	room temp.	48	91
4	EtCHO (1.8)	room temp.	96	87
5	37% formalin (3.6)	60	72	86
6	PhCHO (2.4)	90	18	95
7	$cC_6H_{11}CHO$ (4.8)	90	4	84
8	*i*PrCHO (4.8)	90	24	60

[a] Along with 58% of recovered alcohol.

Khorsandi and co-workers[62] disclosed the use of nanosilica sulfuric acid, a solid recoverable and recyclable reagent easily prepared by reaction of nanosilica with chlorosulfonic acid, as a superior reagent for the synthesis of phthalans.

On the other hand, Kenkin and Newman[63] studied the oxidative cleavage of primary alcohols with the acidic $H_5PV_2Mo_{10}O_{40}$ of the Keggin structure. Primary alcohols were treated with the phosphovanadomolybdate at 80 °C for 5h in sulfolane under strictly anaerobic conditions to yield the reduced polyoxometalate and the products in a 1:1 ratio.

When β-phenethyl alcohol was subjected to the standard reaction conditions, a mixture of benzaldehyde and isochroman was obtained in 41% yield. Since the reactions were carried out under anaerobic conditions it can be assumed the new oxygen atom in the products originated from the phosphovanadomolybdate, which also catalyzed the cyclization. The formaldehyde required for isochroman formation resulted from oxidative cleavage of the starting alcohol to the lower homologous aldehyde. In all, this is a two-electron oxidation coupled with oxygen transfer and the release of two protons, which can be defined as an electron and oxygen transfer (ET-OT) reaction.[64]

2.2. Tin and Silicon Moieties as Control Elements

An oxa-Pictet–Spengler reaction gave rise to an unexpected product during the study of the enantiospecific $BF_3{\cdot}OEt_2$-promoted S_E2' reactions of α-chiral allylic stannanes with aldehydes.[65] Reaction of the allylic benzoate **43** with $(Bu_3Sn)_2Zn$ to give **44** was expected to yield alcohol **45** upon reaction of the organostannane with excess 3-anisaldehyde under $BF_3{\cdot}Et_2O$ promotion (Scheme 6). However, this homoallylic alcohol could not be isolated; instead, remaining 3-anisaldehyde reacted with the expected product **45** in the presence of $BF_3{\cdot}Et_2O$, to give 50% of isochroman

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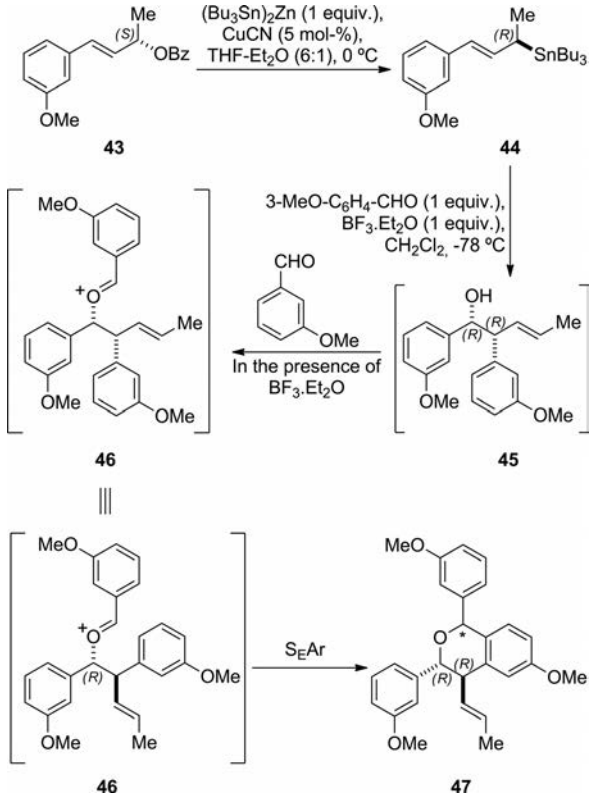
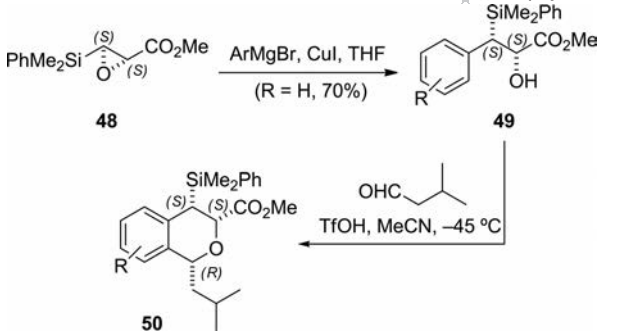
derivative **47** (through the intermediacy of **46**) as a 97:3 diastereomeric mixture. The stereochemistry of the newly formed stereogenic center was not assigned; however, the tin moiety controlled the generation of both stereocenters of the key homobenzylic alcohol **45**, which led to the final product, acting as a stereocontrol element.



Scheme 6. Unexpected oxa-Pictet–Spengler cyclization by over-reaction of intermediate **45**, yielding a polysubstituted isochroman during the reaction of a α-chiral allylic stannane with *meta*-anisaldehyde.

Recently, the group of Panek presented the development of a new class of benzylsilane reagents, prepared by nucleophilic opening of silyl glycidates.[66] The *syn*-organosilanes undergo stereoselective oxa-Pictet–Spengler reactions under kinetically controlled conditions, providing 1,3,4-trisubstituted isochromans with 1,3-*syn* selectivity (Scheme 7), where the silicon group promotes electrophilic aromatic substitution and simultaneously acts as a stereocontrol element.

The required *trans*-silanoglycidate **48**[67] was prepared in 63% yield in four steps, including sodium-assisted hydrosilylation of propargyl alcohol with $PhMe_2SiH$ in refluxing THF in the presence of Chandra's platinum catalyst, followed by Sharpless epoxidation of allylic alcohols with (+)-DET, $RuCl_3$-mediated oxidation of the epoxy alcohol to the related acid and final Steglich esterification with MeOH/DCC-DMAP. The glycidate **48** was ring-opened with different Normant reagents in 70–92% yield, providing the *syn*-silyl α-hydroxy esters **49**. Reaction of **49** (R = H) with isovaleraldehyde allowed optimization of the reaction conditions. Under TfOH promotion in MeCN at –45 °C, 82% yield of a 20:1 mixture of isochromans **50** was obtained, favouring the *syn* diastereomer.



Scheme 7. Stereoselective oxa-Pictet–Spengler reaction of a benzylsilane derivative.

As expected, aromatic rings carrying electron withdrawing substituents (Cl, NO_2) did not cyclize, and a control experiment with methyl α-hydroxy-β-phenylpropionate furnished the cyclised product in 13% yield, as a 5:1 *syn*/*anti* diasteromeric mixture, while cyclization of **49** with various aldehydes (aromatic, aliphatic, alicyclic), acetals and ketals produced the expected isochromans **50** as > 20:1 diastereomeric mixtures in 64–91% yields.

It was demonstrated that TsOH in CH_2Cl_2 at room temperature is also capable to provide cyclised products in good yields (77–93%), especially those that were not formed under TfOH promotion; however, lower diastereomeric relationships (10:1 to 4:1) were observed. This reagent system was also effective when ketones were employed as the carbonyl component.

The analogous *cis*-glycidate was prepared in 45% overall yield by a more complex sequence involving DIBAL-H-mediated stereoselective reduction of phenyldimethylsilyl-protected propargyl alcohol THP ether, *m*-CPBA epoxidation of the deprotected *Z*-olefin and lipase PS-D resolution of the epoxyalcohols with the aid of vinyl acetate. While ring-opening of the glycidate was successfully accomplished with phenyllithium under $BF_3{\cdot}Et_2O$ promotion (76%), the oxa-Pictet–Spengler cyclization of the resulting (*R*)-β-phenethyl alcohol proceeded in low yields (< 20%), furnishing several side products. Interestingly, 1,3-*anti*-isochromans were obtained.

Zhang and co-workers[68] reported a new form of silicon-based control of oxa-Pictet–Spengler reactions through the disclosure of a silicon-terminated oxa-Pictet–Spengler strategy towards tetrahydropyrano[3,4-*b*]indoles (**57**). The starting tryptophols **54** were prepared in moderate yields after Larock's protocol,[69] by coupling the corresponding *o*-iodoanilines **52** (synthesized by selective iodination of anilines **51** with NIS) with the silyl homopropargyl alcohol **53**. The oxa-Pictet–Spengler cyclization of **54** was more consistently performed with CF_3CO_2H as a promoter, which furnished the required pyrano-indoles **57** in 50–90% yield. Isolation of the desilylated tryptophol **58** and other side products allowed the proposal of two different reaction mechanisms. In the conventional reaction pathway (Scheme 8) the

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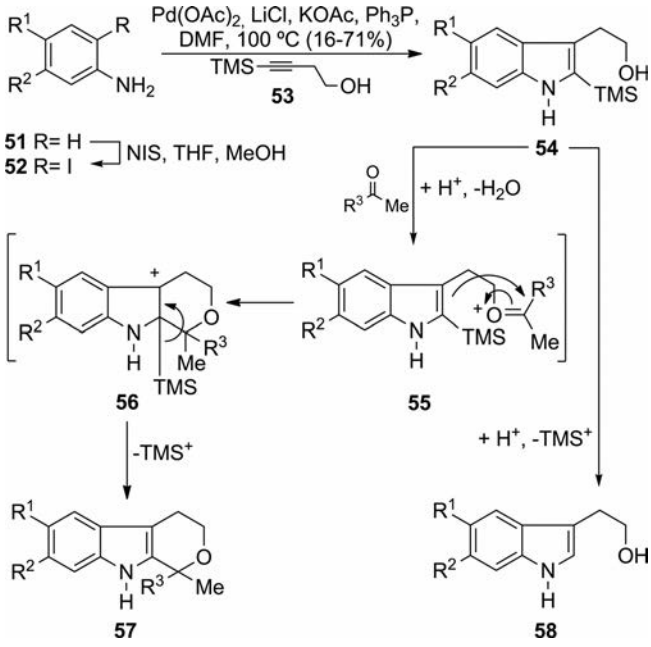
oxacycle is formed through the intermediacy of an oxocarbenium ion **55**, followed by loss of TMS cation from cyclized intermediate **56**.



Scheme 8. Silicon-controlled oxa-Pictet–Spengler cyclization.

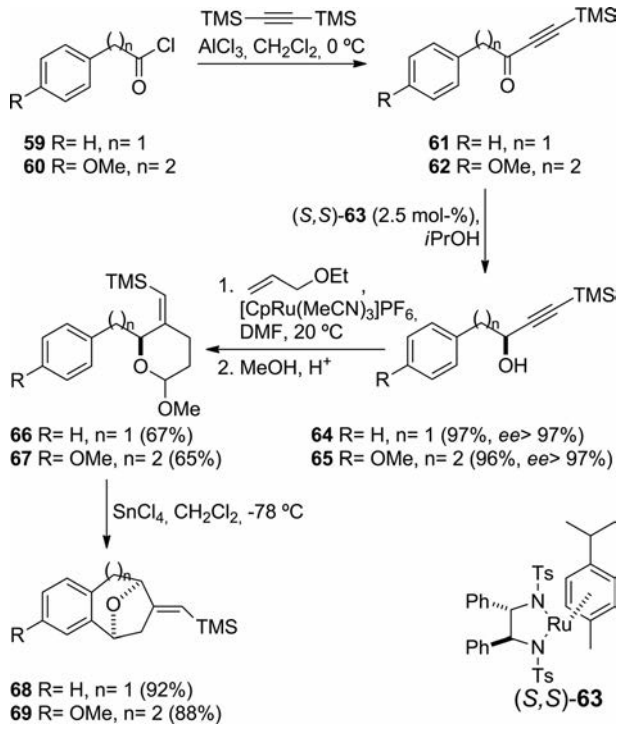
Alternatively, paralleling Mukayama aldol condensation, the TMS moiety may assist the reaction between the carbonyl and the indole nucleus yielding an alcoholic intermediate (analogous to the homophthalic alcohols shown above) which cyclizes after losing the TMS directing group. The reaction is sensitive to steric bulk and no cyclization was observed when benzophenone and cyclohexanone were employed as the carbonyl components.

The stereochemical outcome of the oxa-Pictet–Spengler cyclization can be affected by reaction conditions, such as the nature of the carbonyl component (aliphatic, aromatic) and the structure of the alcohol component. This is illustrated through several examples in the syntheses of six- and seven-membered oxacycles discussed below.

3. Synthesis and Reactions of Oxacycles with Different Ring Sizes or as Part of Various Ring Systems

Typically, oxa-Pictet–Spengler cyclizations were carried out to obtain polysubstituted isochromans; however, analogous protocols have been recently devised for the preparation of aryl-fused oxacycles carrying five- and seven-membered oxygenated rings. In addition variations in the nature of the aromatic alcohol moiety and intramolecular versions have been devised, extending the scope of the reaction.

Recently, Mascareñas and co-workers[70] reported an asymmetric approach to the assembly of enantiopure, oxa-bridged, medium-sized carbocyclic systems employing ruthenium catalysis and a Marson-type intramolecular oxa-Pictet–Spengler cyclization as key steps, as shown in Scheme 9. The required ketones **61** and **62** were prepared from acid chlorides **59** and **60** by addition of bis(trimethylsilylacetylene) under $AlCl_3$ catalysis.[71] Catalytic asymmetric hydrogen transfer reduction of the ketones with Noyori's ruthenium complex **63** in *i*PrOH provided the desired alkynols **64** and **65** with excellent chemical and optical yields.[72] Treatment of the chiral alcohols with allyl ethyl ether in the presence of $[CpRu(MeCN)_3]PF_6$, followed by in situ acid-catalyzed acetalization with MeOH gave pyrans **66** and **67** in 67% and 65% yield, respectively. Finally, oxa-Pictet–Spengler cyclization of the acetals under $SnCl_4$ promotion furnished the tricycles **68** and **69**. The analogous Prins cyclization with acetals tethered to olefins also yielded up to nine-membered oxa-bridged carbocyles.



Scheme 9. Intramolecular oxa-Pictet–Spengler cyclization towards substituted 12-oxatricyclo[7.2.1.$0^{2,7}$]dodeca-2,4,6-triene and 13-oxatricyclo[8.2.1.$0^{2,7}$]trideca-2,4,6-triene derivatives.

Zheng and Zhang[73] disclosed an oxa-Pictet–Spengler synthesis of 1,3-*syn*-disubstituted 1,3,4,5-tetrahydrobenzo-[*c*]oxepines **71** prepared from alcohols **70** under either $BF_3{\cdot}Et_2O$ or MsOH promotion in dioxane or CH_2Cl_2, observing an unexpected internal redox ring cleavage reaction of the product towards **72**. The heterocycles **71** have demonstrated activity as antianaphylactic agents and also as central and peripheral α-blockers.[74]

It was found that $BF_3{\cdot}Et_2O$ (200 mol-%) in dioxane at room temperature was the most effective condition for the oxa-Pictet–Spengler reaction to produce the desired oxepine, while ring cleavage took place in the presence of acids such as $BF_3{\cdot}Et_2O$ (20 mol-%), MsOH, and TsOH, under reflux (Table 10).

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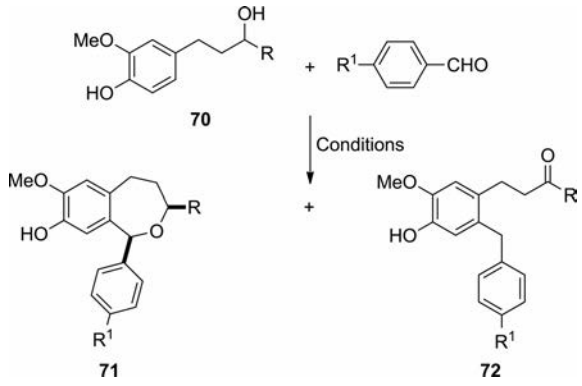
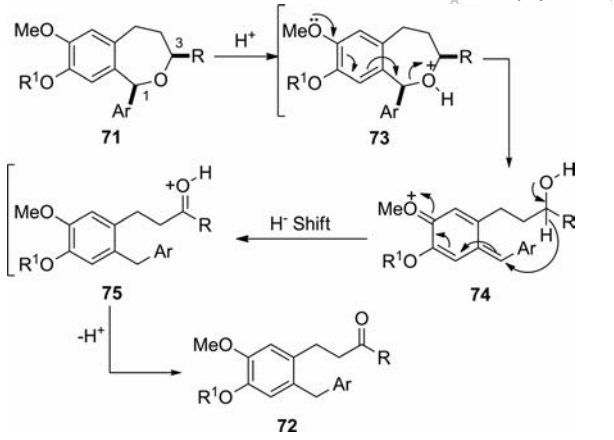
Table 10. Oxa-Pictet–Spengler-mediated synthesis and ring-cleavage of 1,3-*syn*-1,3,4,5-tetrahydrobenzo[*c*]oxepines.



R^1	Solvent	Catalyst (temp.)	R	% Yield **71**	% Yield **72**
NO_2	CH_2Cl_2	$BF_3{\cdot}Et_2O$ (room temp.)	Me	52	16
NO_2	CH_2Cl_2	$BF_3{\cdot}Et_2O$ (reflux)	Me	0	84
NO_2	dioxane	$BF_3{\cdot}Et_2O$ (room temp.)	Me	62	0
NO_2	dioxane	$BF_3{\cdot}Et_2O$ (reflux)	Me	23	65
H	CH_2Cl_2	$BF_3{\cdot}Et_2O$ (room temp.)	Me	0	57
H	CH_2Cl_2	$BF_3{\cdot}Et_2O$ (reflux)	Me	0	45
H	dioxane	$BF_3{\cdot}Et_2O$ (room temp.)	Me	32	9
H	dioxane	$BF_3{\cdot}Et_2O$ (reflux)	Me	0	38
H	CH_2Cl_2	MsOH (room temp.)	Me	7	20
H	CH_2Cl_2	MsOH (reflux)	Me	0	74
H	dioxane	MsOH (room temp.)	Me	0	0
H	dioxane	MsOH (reflux)	Me	3	27
NO_2	dioxane	$BF_3{\cdot}Et_2O$ (room temp.)	Ph	22	
NO_2	dioxane	$AlCl_3$ (room temp.)	H	47	
NO_2	1,2-DCE	MsOH (reflux)	Ph		47
NO_2	1,2-DCE	MsOH (reflux)	H		0
Cl	1,2-DCE	TsOH (reflux)	Me		89

Milder acids such as AcOH and benzoic acid do not promote the ring opening reaction and no ring-opened products were observed when a 3-arylpropanol derivative was employed as substrate. The cyclization was remarkably stereoselective,[75] furnishing **71** as single 1,3-*syn*-stereoisomers. The stereochemistry of the heterocycle was assigned by nOe enhancement experiments and further confirmed by X-ray crystallography. This is in contrast with the results of Xiang and co-workers, who obtained 50–90% yields of *syn*-*anti* mixtures (55:45 to 80:20) of 1-alkyl/phenyl-3-alkoxymethyl-6,7-methylenedioxy-isochromans upon reaction of the monoprotected glycols with aldehydes under TsOH in refluxing MeOH.[76]

A mechanism for the cleavage reaction of **71** was proposed (Scheme 10), whereby protonation of oxygen atom in the seven-membered ring **73** provides an oxonium ion, which then undergoes cleavage of a C–O single bond to give a conjugated carbocation **74**. Intramolecular hydride migration to the carbocation provides a stable protonated ketone **75**, which upon loss of a proton gives the final product **72**. No similar ring cleavage process has been reported among the analogous six-membered oxacyles; however, since phenylacetones are prone to self-condense under acid conditions,[77] the occurrence of this transformation cannot be fully discarded.



Scheme 10. Proposed mechanism for the ring-cleavage of 1,3-*syn*-1,3,4,5-tetrahydrobenzo[*c*]oxepines.

Guiso and co-workers[78] recently also reported the synthesis of 1,3,4,5-tetrahydro-benzo[*c*]oxepines (homoisochromans) through the oxa-Pictet–Spengler reaction of 3-(3,4-dihydroxyphenyl)-1-propanol and 3-(3-hydroxyphenyl)-1-propanol with various aromatic aldehydes in MeOH under TsOH promotion at 37 °C for one week. Yields ranged from 20 to 45%, being higher with the more activated alcohol. The low yields were attributed to the difficulties of the intermediaries involved in achieving the required molecular orientation.

Chou and Chen reported the oxa-Pictet–Spengler synthesis of 1-chloromethyl-tetrahydropyrano[3,4-*b*]indoles and their unusual hydrolytic cleavage, which takes place with 1,2-alkyl chain migration, upon heating with water and base in DMF. The authors proposed a 1,2-alkyl chain migration mechanism for the formation of the 2-succinoyl tryptophols and a ring-expansion sequence for the observed dihydro-oxepine fused indoles. The ring cleavage reaction was not observed when a structurally related 1-(chloromethyl)isochroman (**76**), obtained through the oxa-Pictet Spengler cyclization of **16** with ethyl 4-chloro-3-oxobutyrate dimethyl acetal was submitted to analogous conditions which, however, led to ring expansion to **79**.[79]

The outcome of the ring-expansion rearrangement was explained (Scheme 11) as being the result of the initial formation of a strained oxonium ion intermediate **77**, which is able to undergo attack by the solvent yielding an unstable seven-membered oxacycle **78**, which finally furnishes the product **79** after deprotonation and dehydration.

Zhang and Duan reported the oxa-Pictet–Spengler reactions of sydnones **80** as an approach to 4,6-diaryl-4,6,7,8-tetrahydro-1,4-oxazepino[4,3-*c*]sydnones **81**, seven-membered ring-fused sydnones.[80] Since sydnones are unstable to both acidic and basic aqueous media, the reaction was carried out at room temperature in dioxane or DME. $BF_3{\cdot}Et_2O$ was found to be the most efficient catalyst while TsOH was completely ineffective and electron-rich aromatic aldehydes did not react at all (Table 11).

The reaction took place with slight to marked *syn*-selectivity (2:1 to 12:1)[81] and only the 4,6-*syn* derivative was

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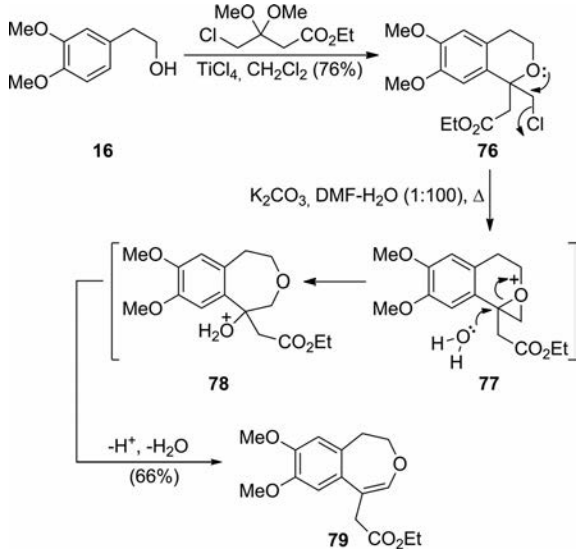
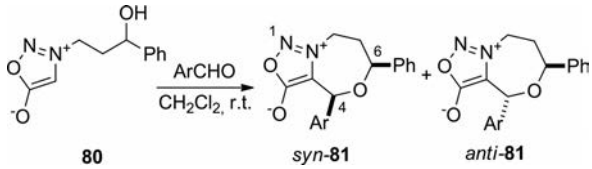


Scheme 11. Synthesis and hydrolytic ring expansion of 1-(chloromethyl)isochromans.

Table 11. Synthesis of tetraydro-1,4-oxazepino[4,3-*c*]sydnones employing the oxa-Pictet–Spengler cyclization.

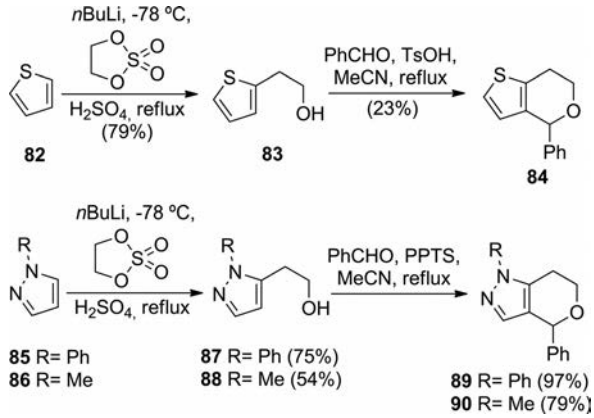


Entry	Ar	*syn*/*anti*	% Yield
1	C_6H_5	71:19	73.4
2	4-Br-C_6H_4	69:31	67
3	3-Br-C_6H_4	84:16	64.6
4	2-O_2N-C_6H_4	100:0	45.2
5	4-O_2N-C_6H_4	92:8	86
6	3-O_2N-C_6H_4	92:8	84.4
7	2,6-Cl_2–C_6H_3	88:12	76
8	2-Cl-C_6H_4	100:0	56
9	4-MeO-C_6H_4	–	0

isolated when 4-nitro- and 4-chlorobenzaldehyde were employed. The resulting tetrahydro-1,4-oxazepino[4,3-*c*]sydnones are potentially useful precursors for the synthesis of fused pyrazole derivatives by the [3+2] cycloaddition with alkenes or alkynes.[82]

Wünsch and co-workers[83] recently developed a facile protocol for the synthesis of β-arylethanols, which is complementary to other existing alternatives,[84] particularly those employing ethylene oxide as a two-carbon synthon,[85] which overcome some of their limitations.[86]

The strategy (Scheme 12) entails metalation (or halogen–metal exchange) of the starting material, followed by quenching of the organolithium species with ethylene sulfate.[87] In this fashion, thienyl alcohol **83**[88] and pyrazoles **87** and **88** were obtained in a one pot reaction from **82**, **85** and **86** in 79%, 75% and 54% yield, respectively. The corresponding oxacycles were accessed through an oxa Pictet–Spengler cyclization, which included reaction with benzaldehyde under TsOH or PPTS promotion.



Scheme 12. Synthesis and oxa-Pictet–Spengler cyclization of heterocyclic β-arylethanols.

The thienyl derivative **84** was accessed in 23%; however, TsOH failed to provide cyclised products with the pyrazole derivatives **87** and **88**. This was interpreted as being a consequence of the basicity of the pyrazole.[89] Therefore, PPTS was employed instead, leading to **89** and **90** in high yields. These results complement previous efforts by the groups of Miles and Gopalsami on other heterocycles.[75,90]

Phthalans are very important heterocycles with interesting applications in diverse fields.[91] Guiso and co-workers[78] demonstrated that the oxa-Pictet–Spengler reaction is also useful for the synthesis of polysubstituted phthalans; these authors also investigated and discussed the effects of the substituents on the aromatic rings of the alcoholic moiety and on the aldehyde on the course of the reaction. 3-Hydroxybenzyl alcohol, as well as the symmetrically substituted 3,5-dihydroxybenzyl alcohol, and 3,5-dimethoxybenzyl alcohol were employed, in conjunction with aromatic and aliphatic aldehydes, and the reaction was carried in MeOH, employing catalytic amounts of TsOH.

In general, yields were moderate (Table 12) and the so obtained phthalans were always accompanied by aldehyde acetals (methyl and mixed acetals).

The use of aprotic solvents instead of methanol decreases the yields. In addition, when the strongly activated dihydroxy and the dimethoxy benzyl alcohols were employed, the heterocycles were also accompanied by diarylation side products arising from electrophilic aromatic substitution (25–33%). Their formation was prevented when the milder chloroacetic acid was employed as catalyst. When aliphatic aldehydes were employed as carbonyl components, the comparative more difficult closure of the phthalan ring shifted the equilibrium to the formation of the less-hindered acetals and of the arylation products.

The substituted benzaldehydes may experience less steric hindrance during the closure. Those with electron-withdrawing substituents yield only the oxa-Pictet–Spengler reaction while those carrying electron-donating substituents may concomitantly also form arylation products, probably due to the marked stability of the intermediate carbocation.

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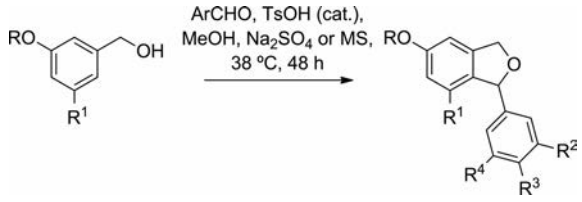
Table 12. Synthesis of 1-arylphthalans from activated benzylic alcohols under TsOH catalysis.



Entry	R	R^1	R^2	R^3	R^4	% Yield
1	H	H	H	H	H	60
2	H	H	H	Cl	H	56
3	H	H	H	OMe	H	62
4	H	H	OMe	OMe	H	55
5	H	H	H	H	H	60
6	H	H	H	NO_2	H	61
7	H	H	NO_2	H	H	61
8	H	H	OMe	OMe	OMe	55
9	H	OH	H	NO_2	H	61
10	H	OH	H	Cl	H	57
11	H	OH	NO_2	H	H	61
12	H	OH	H	OH	H	29
13	H	OH	H	OMe	H	48
14	H	OH	OMe	H	OMe	57
15	H	OH	OMe	OMe	OMe	58
16	Me	OMe	H	NO_2	H	45
17	Me	OMe	OMe	H	OMe	47

The comparative lower yields observed when compared to isochromans were explained in terms of the Baldwin rules[92] which favour 6-*endo-trig* and the 6-*exo-tet* ring closure. However, for the synthesis of the phthalans, the 5-*endo-trig* path is not favoured.

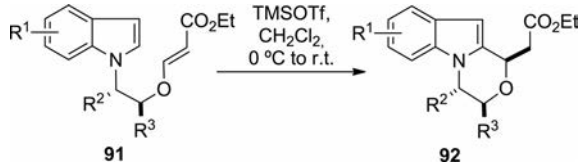
Taking into account this work, Khorsandi and coworkers[62] disclosed a modification of this synthesis of phthalans, employing nanosilica sulfuric acid. The transformation was run in EtOH (0.1 mL/mmol) under thermal (80 °C, 20–90 min) and microwave (90–300 s) heating, being the products recovered in moderate to excellent yields. Under the reaction conditions, silica-sulfuric acid-promoted the reaction but yields were notoriously lower, while use of nanosilica alone did not result in cyclized product.

Very recently, Gharpure and Sathiyanarayanan[93] reported the intramolecular oxa-Pictet–Spengler reaction of indoles bearing *N*-tethered vinylogous carbonates (**91**) for the stereoselective synthesis of oxazino[4,3-*a*]indoles **92** (Table 13). Synthetic studies on these heterocycles are scarce,[94] despite they have been examined for their antidepressant and antitumor properties.[95]

Vinylogous carbonates can react similarly to enol ethers, acting as a source of oxo-carbenium in the Prins-type cyclization.[96] The transformation was carried out under promotion of TMSOTf, which outperformed other acidic promoters in model experiments. The intramolecularity of the reaction ensured preferential electrophilic substitution of indole at less nucleophilic C2 position and the products could be manipulated further to yield tetracyclic oxazinoindole derivatives.

Furthermore, addition of a suitable electrophile (acid anhydride, acyl chloride, Michael acceptor) before quenching the cyclization allowed the development of a one-pot, tandem oxa-Pictet–Spengler cyclization Friedel–Crafts acylation for the synthesis of oxazinoindoles substituted at the C3 position of the indole nucleus in good to excellent yields (68–95%).

Table 13. Stereoselective synthesis of oxazino[4,3-*a*]indoles.



Entry	R^1	R^2	R^3	% Yield	*dr*
1	H	H	Ph	85	≥ 19:1
2	H	H	CH2OBn	60	≥ 19:1
3	H		$-(CH_2)_4-$	56	≥ 19:1
4	H		$-(CH_2)_3-$	32	≥ 19:1
5	5-OMe	H	Me	92	≥ 19:1
6	5-OMe	H	Ph	72	≥ 19:1
7	5-Br	H	Me	54	≥ 19:1
8	5-Br	H	Ph	64	≥ 19:1
9	3-Me	H	Me	85	10:1
10	3-Me	H	Ph	75	7:1
11	3-Ph	H	Ph	74	5:1

4. Synthesis of Natural and Bioactive Products and Related Compounds

Berkelic acid, the pseudoanguillosporins, 8-hydroxy-6-methoxy-3,7-dimethylisochroman, the arohynapenes C and D, the bruguierols A and C, brussonol and the tri- and tetracycles belonging to the widespread family of the pyrano-naphthoquinones are examples of natural products carrying the isochroman motif. Other non-isochromanic natural products can be modified, grafting an oxacycle to adjust their properties.

Similarly, bioactive synthetic compounds such as sonepiprazole, PNU-109291, HCV-371 and other simple isochromans and pyrano-indoles are relevant to the continuously improving drug discovery endeavor. The search of new avenues towards these and related compounds or the need to synthesize more potent or structurally simplified analogs has often been solved by the use of oxa-Pictet–Spengler based strategies.

4.1. Syntheses of Isochromans and Naphtho-Pyrans Related to the Pyrano-Naphthoquinone Antibiotics

Lactoquinomycin (**93**, medermycin), a naturally occurring pyrano-naphthoquinone antibiotic (Figure 2) and frenolycin B (**96**), were found to selectively inhibit the serine-threonine kinase AKT (protein kinase B, PKB).[97] Constitutively activated AKT has been found in several human tumor types, and its presence has been correlated with poorer prognoses.[98]

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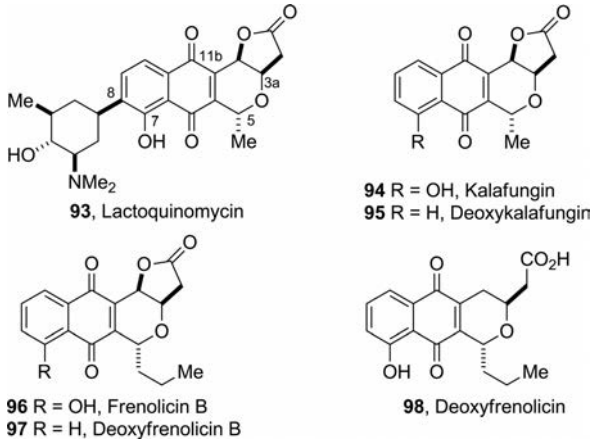
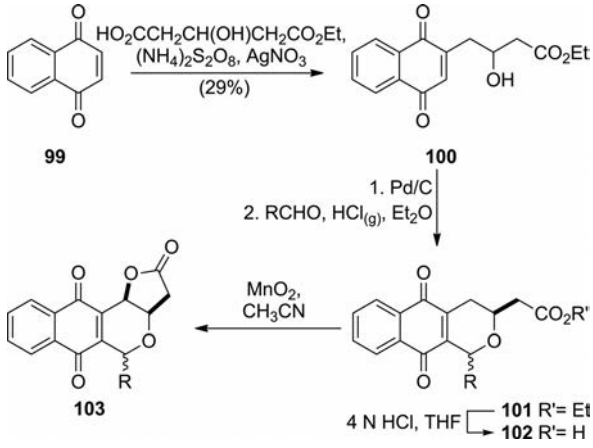


Figure 2. Pyrano-naphthoquinones **93** and **96**, which inhibit the enzyme serine-threonine kinase (AKT) and related compounds.

This moved the interest of the group of Salaski towards the related aglycones, including kalafungin (**94**),[99] deoxykalafungin (**95**), deoxyfrenolycin B (**97**) and deoxyfrenolycin (**98**).[100] This group prepared a set of simplified synthetic pyrano-naphthoquinone analogs resorting to the oxa-Pictet–Spengler cyclization with various aliphatic and aromatic aldehydes and ketones to provide diversity (Scheme 13).[101]



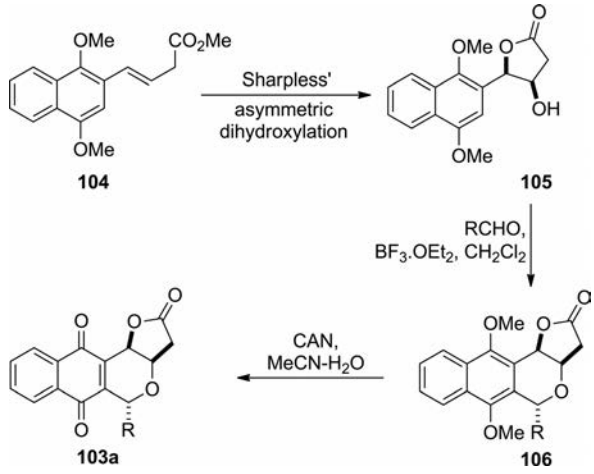
Scheme 13. Synthesis of deoxyfrenolycin B analogs.

Alkylation of 1,4-naphthoquinone (**99**) yielded hydroxy ester **100** through the reaction with the radical derived from the silver nitrate/ammonium peroxydisulfate reagent in the presence of monoethyl 3-hydroxypentanedioate.[102] The latter was reduced to the corresponding hydroquinone with Pd/C before being oxa-Pictet–Spengler cyclised with different aldehydes, employing 2 N HCl in Et_2O as promoter. The resulting tricyclic hydroquinones spontaneously reoxidized to the related quinones **101** upon exposure to air.

The authors observed that aromatic aldehydes yielded only *syn* diastereomers, while aliphatic aldehydes furnished ca. 3:1 mixtures of *syn* and *anti* diastereomers, depending on the reaction conditions, as the initially formed *syn* derivatives tended to equilibrate with the *anti* congeners.[103]

Acid hydrolysis of **101** yielded the corresponding acids **102**, which upon allylic oxidation with activated MnO_2 in MeCN furnished the deoxyfrenolycin analogs, the lactones **103**. This process is also known to spontaneously take place among these tricyclic acids by exposure to air.[104]

A chiral version of the synthesis of the lactones **103** was also devised (Scheme 14), starting with the Sharpless' asymmetric dihydroxylation[105] of β,γ-unsaturated ester **104**.[106] In one case, the oxa-Pictet–Spengler cyclization of the resulting β-hydroxylactone **105** under $BF_3{\cdot}Et_2O$ assistance in CH_2Cl_2 furnished the pyranolactones **106** as *anti* diastereomers, regardless the nature of the aldehyde.[107] Final oxidation with ceric ammonium nitrate (CAN) afforded the *anti*-pyrano-naphthoquinone lactone **103a**. Interestingly, this sequence not only allows access to individual enantiomers of the lactones, but also complements the racemic, *syn*-selective route (Scheme 13).



Scheme 14. Asymmetric dihydroxylation/oxa-Pictet–Spengler cyclization strategy towards deoxyfrenolicin B (**103a**).

The synthetic compounds proved to inhibit the proliferation of human tumour cell lines containing constitutively activated AKT and showed the expected effects on cellular biomarkers (Table 14). A mechanism, based on the bioreductive alkylation was proposed.[108] Details on the interaction of lactoquinomycin with certain cystine residues of AKT1 were also disclosed.[109]

The same group developed the enantioselective syntheses[110] of (+)-kalafungin (**94**) and (–)-nanaomycin D (**111**)[111] along the same lines, employing trimethoxynaphthalene derivative **107**. This was asymmetrically dihydroxylated following Sharpless' protocol with both AD-mix reagent systems, furnishing enantiomeric γ-butyrolactones in good yield,[112] which were subjected to oxa-Pictet–Spengler cyclizations with acetal under $BF_3{\cdot}Et_2O$ (3 equiv.) promotion and then submitted to CAN oxidation to furnish **108** and **109** (Scheme 15).

The authors discovered that during the BBr_3-mediated demethylation (CH_2Cl_2, –50 °C, 2h) stage, these tetracycles epimerized, presumably as a consequence of enone-dienol tautomerism involving **110**, giving diastereomeric mixtures enriched in the *anti*-diastereomers kalafungin (**94**) and (–)-

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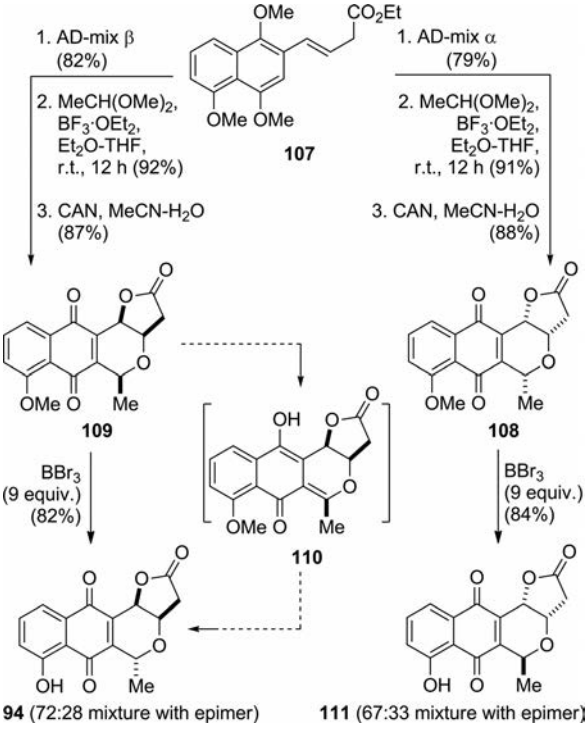
Table 14. Results of enzyme (AKT) and cell proliferation (MDA468) inhibitory activity of the racemic and enantiopure pyrano-naphthoquinone lactones **103**.

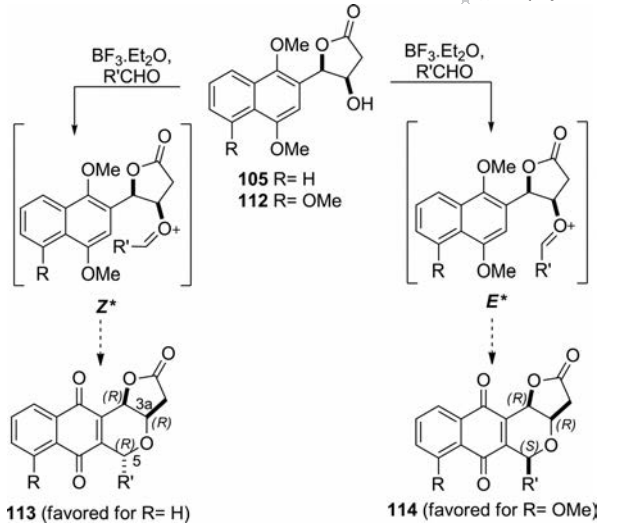
Entry	R	Stereochemistry	AKT IC_{50} (μM)	MDA468 IC_{50} (μM)
1	H	(+)	0.044	0.80
2	2-thienyl	(+)-*anti*	0.057	0.60
3	CH_2OBn	(±)-*anti*	0.072	1.00
4	4-hydroxyphenyl	(±)-*syn*	0.080	0.55
5	3-thienyl	(–)-*anti*	0.099	0.41
6	3-thienyl	(+)-*anti*	0.122	0.30
7	Me	(+)-*anti*	0.150	0.48
8	*n*-propyl	(±)-*anti*	0.163	0.60
9	$–(CH_2)_4–$	(±)	0.295	1.60
10	3-hydroxyphenyl	(±)-*syn*	0.350	1.00
11	*n*-propyl	(±)-*syn*	0.383	1.30
12	4-aminophenyl	(±)-*syn*	0.850	0.55
13	*gem*-dimethyl	(±)	1.440	0.23



Scheme 15. Enantioselective total syntheses of (+)-kalafungin (**94**) and (–)-nanaomycin D (**111**).

nanaomycin D (**111**). The same transformation could be better accomplished employing concentrated H_2SO_4 for 30 min, which furnished epimeric relationships of 93:7 and 94:6 for products **94** and **111**, respectively.[113]

The syntheses of (+)-7-deoxyfrenolicin B (**97**) and (+)-7-deoxykalafungin (**95**) reported by Eid and co-workers[107] takes place along the same reaction sequence as for **94** and **111** (Scheme 16), where the β,γ-unsaturated ester was prepared in 80% yield by Heck coupling between 2-bromo-1,4-dimethoxynaphthalene and isobutyl but-3-enoate employing $Pd(tBu_3P)_2$ and dicyclohexyl methylamine.[114]



Scheme 16. Synthesis of 3a,5-*syn*- and 3a,5-*anti*-pyrano-naphthoquinono lactones.

The critical oxa-Pictet–Spengler cyclizations which established the stereochemistry of the newly formed stereogenic centre were performed with butyraldehyde (88% yield) and acetaldehyde (98% yield) as carbonyl components. This directly produced the *anti* diastereomers as the main products (*de* > 99%), a stereochemistry in agreement with that found in these natural products.

Computational efforts[107] made on the intermediate oxocarbenium ions derived from **105** and **112**[115] to explain the stereochemical outcome of the reaction evidenced that the geometry and distance of the ***Z**** intermediate which lead to the *anti* product, are predefined for a favourable eventual ring-forming reaction (Scheme 16). The ***E**** isomer appears to be more stable because it can relieve much of the crowding necessitated by ***Z****. However, in so doing, the double bond moves farther from the nucleophilic center, which will need to come closer together to react.

With the conformations organized for a chair transition state, the HOMO and LUMO of both isomeric intermediates appear qualitatively to overlap appropriately. The ring forming reaction would cause the hydrogens attached to the newly formed bond to lie *gauche* for ***Z**** and *anti* for ***E****. For the tetracycles, the energies were in favour of the (11a*R*,3a*R*,5*R*)-*anti* product **113**.

In contrast, the (3a,5)-*syn*-substituted dihydropyrans **114** were synthesized directly from the more electron-rich trimethoxynaphthyl systems **112**. The former would be derived from an ***E**** isomer. The increased nucleophilicity of the naphthyl ring would be reflected in an earlier transition state favouring the ***E**** intermediate over the ***Z**** isomer. Furthermore, the additional methoxy group may indirectly crowd the ***Z**** isomer, favoring the ***E**** isomer and ultimately leading to **114**.

Hongconin[116] was isolated from *Eleutherine americana* Merr. et Heyne (Iridaceae), a plant used in folk medicine for treating cardiac diseases (angina pectoris). Fernandes and Chavan[117] developed short asymmetric syntheses of

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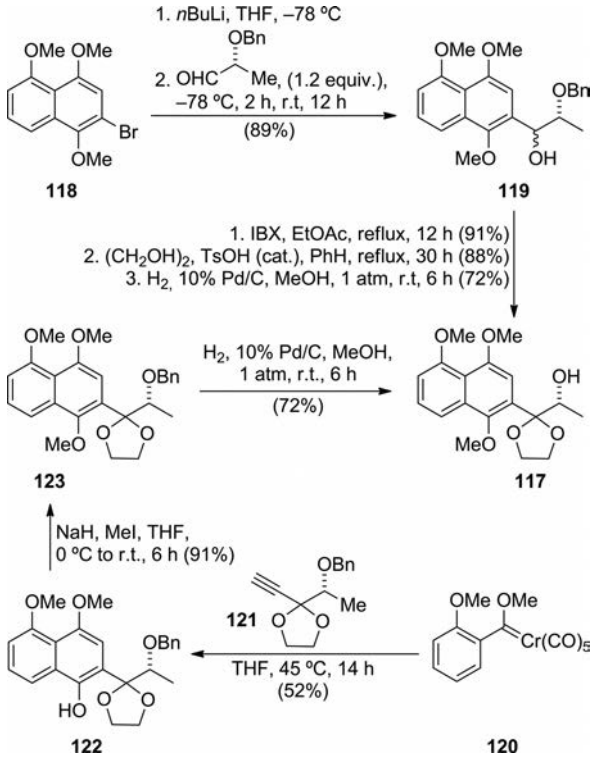
(–)-hongconin (**115**) and (–)-1-*epi*-hongconin (**116**), which complement previous approaches to racemic and enantioselective syntheses of the natural product, its enantiomer and C3 epimer.[118,119] The synthesis took place by means of the oxa-Pictet–Spengler cyclization of key intermediate **117**, which was accessed either by lactaldehyde arylation[120] or by Dötz benzannulation.[121]

In the first case (Scheme 17), the carbanion generated from trimethoxy bromonaphthalene (**118**) was added to lactaldehyde benzyl ether furnishing 89% of alcohol **119**. This was transformed into the desired key intermediate **117** in 57% yield, by a three step procedure which included IBX oxidation to the related ketone, ketalyzation with ethyleneglycol under TsOH catalysis and hydrogenolysis of the benzyl ether with 10% Pd/C.

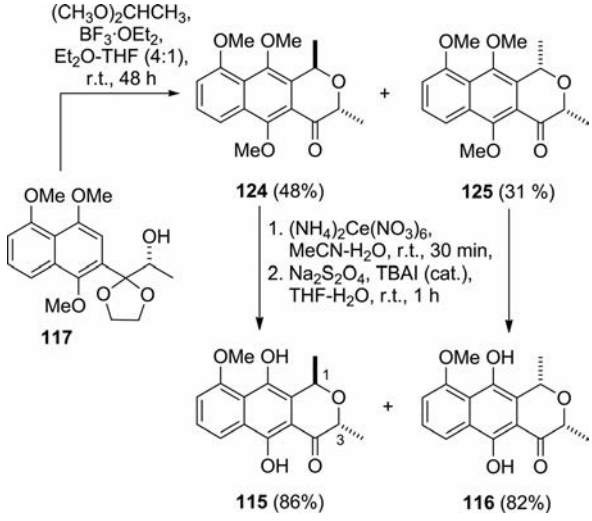


Scheme 17. Lactaldehyde arylation and Dötz benzannulation strategies leading to key intermediate **117** towards (–)-hongconin (**115**) and (–)-1-*epi*-hongconin (**116**).

In the Dötz benzannulation-based synthesis, Fischer carbene complex **120** derived from 2-bromoanisole[122] was condensed with chiral alkyne **121** (prepared in six steps and 32% overall yield from *R*-methyl lactate) to provide 52% of substituted naphthol **122**.

Methylation of the phenolic OH group in **122** gave **123** in 91% yield, which was hydrogenolyzed to **117** as before (72%).

The key oxa-Pictet–Spengler cyclization[123] was performed on **117** with acetal under promotion by $BF_3{\cdot}Et_2O$ (Scheme 18); the reaction took place with concomitant deprotection of the ketal, furnishing a 3:2 separable mixture of *anti* and *syn* diastereomers **124** and **125** in 79% overall yield, respectively. Finally, CAN-mediated oxidation to the quinones followed by sodium dithionite reduction to the corresponding hydroquinones completed the synthetic sequence, furnishing **115** (86%) and **116** (82%).



Scheme 18. Final steps of the syntheses of (–)-hongconin (**115**) and (–)-1-*epi*-hongconin (**116**).

Eleutherin (**126**)[124] is a pyrano-naphthoquinone isolated from the bulbs of *Eleutherin bulbosa*, which exhibits activity against *Bacillus subtilis*.[125] Extracts of *E. americana* of which eleutherin and isoeleutherin are the major constituents have been used to treat angina pectoris[126] and (+)-eleutherin is a reversible inhibitor of topoisomerase II, a target for anticancer agents.[127] This tricycle has been repeatedly targeted as a synthetic objective, in racemic[128] and chiral forms.[129]

Employing an analogous strategy (Scheme 19), the same group performed the stereodivergent syntheses of (+)-**126**[122a] and (+)-*allo*-eleutherin (**127**). The required alcohol **131** was synthesized in 56% overall yield by Dötz benzannulation of **120** with acetylene **128** [prepared in 3 steps and 82% overall yield from ethyl (*S*)-3-hydroxybutyrate], furnishing **129**, followed by methylation to **130** and TBAF-mediated desilylation.

The pivotal oxa-Pictet–Spengler cyclization was next carried out on **131** with acetal and 3 equivalents of $BF_3{\cdot}Et_2O$ as promoter, yielding diastereomeric mixtures of **132** and **133** in yields ranging from 78 to 92% and proportions (32–43%) depending on the reaction time (2–14 h) and temperature (0 °C and room temp.), with higher temperatures and/or prolonged reaction times increasing the overall yield and favouring the production of (+)-*allo*-eleutherin. Chromatographic separation of the diastereomers, followed by CAN-mediated oxidation yielded the corresponding naphthoquinones **126** and **127** in 86–89% yield. Interestingly, *allo*-eleutherin has been previously prepared by isomerization of eleutherin with H_3PO_4.[130]

Cardinalin 3 (**134**), isolated from the New Zealand toadstool *Dermocybe cardinalis*,[131] is an important cytotoxic compound. It has been shown that the crude ethanolic ex-

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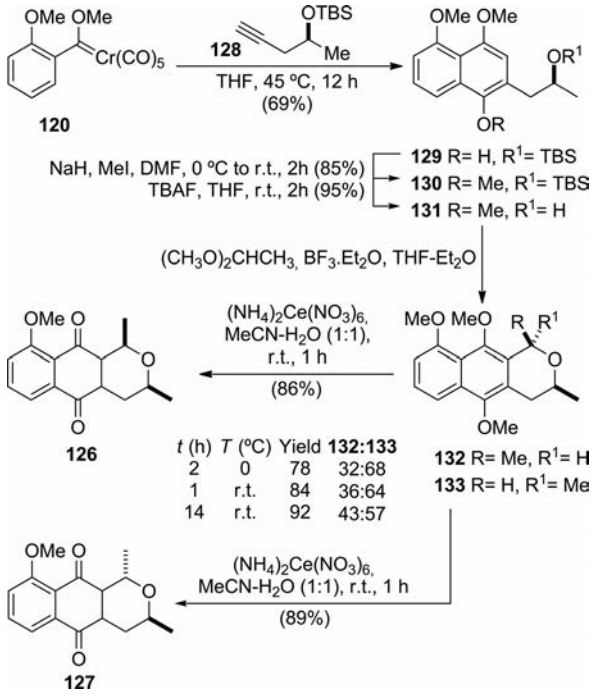
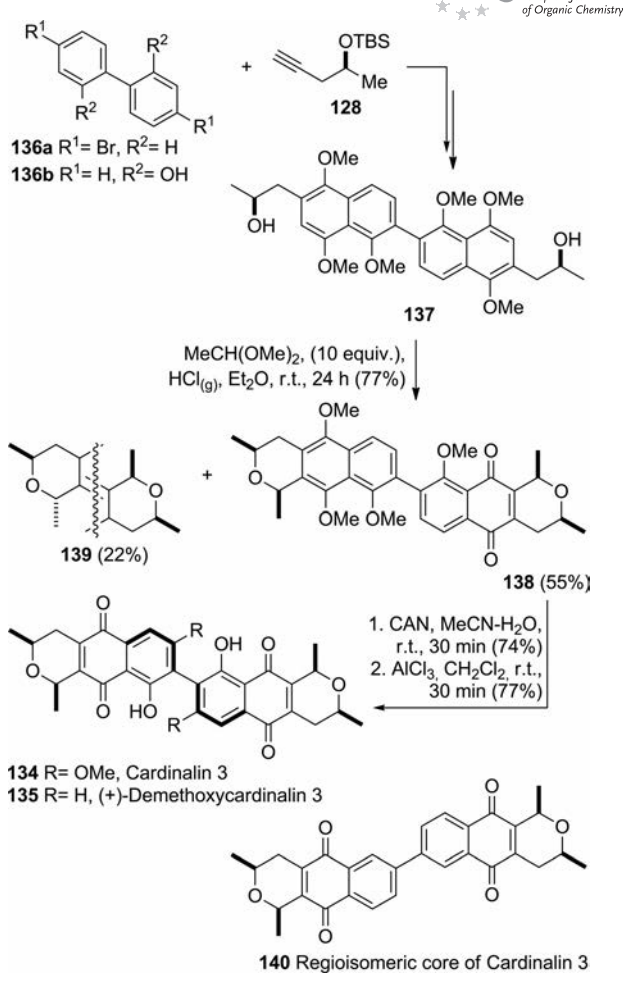


Scheme 19. Stereodivergent Dötz benzannulation/oxa-Pictet–Spengler cyclization syntheses of (+)-eleutherin (**126**) and (+)-allo-eleutherin (**127**).



Scheme 20. Double Dötz benzannulation/oxa-Pictet–Spengler cyclization-based synthesis of (+)-demethoxycardinalin 3 (**135**).

tract of *Dermocybe cardinalis* inhibits the growth of P388 murine leukemia cells (IC_{50} 0.47 μg/mL). Structurally, cardinalin 3 showed no evidence of asymmetric doubling in either the ^1H or ^{13}C NMR spectra, suggesting that it occurs as discrete atropisomers. From CD spectra it is believed that the cardinalins possess (*S*)-axial chirality (as shown in Scheme 20).

Complementing the racemic synthesis of **134**[132] and previous efforts in the field,[133] the group of Fernandes[134] employed the Fischer carbene/Dötz benzannulation oxa-Pictet–Spengler cyclization strategy for the preparation of the regioisomeric core of the natural product (Scheme 20) as well as for a rapid and convenient access to (+)-demethoxycardinalin 3 (**135**).

The required dimeric Fischer carbenes were prepared from 4,4′-dibromobiphenyl (**136a**) and 2,2′-dihydroxybiphenyl (**136b**), respectively, while the chiral acetylenic component **128** was synthesized from ethyl (*S*)-3-hydroxybutyrate and ethyl acetoacetate, respectively; in the latter case, a five-steps sequence was employed, providing the alkyne in 75% overall yield. The synthesis of the regioisomeric core of cardinalin 3 (**140**) was achieved in six steps and 7.4% overall yield, and acetal was used for the double oxa-Pictet–Spengler cyclization step.

The synthesis of (+)-demethoxy cardinalin 3 (**135**) was developed along a similar strategic line. While $BF_3{\cdot}Et_2O$ produced different amounts (16–82%) and proportions (1.5–2.6) of the undesired isomers of desoxycardinalin 3, none of the natural product was obtained. However, bubbling HCl gas[135] into an ethereal solution of the diol, furnished 55% of **138**, together with 22% of the *syn-anti* epimer **139** after 24 h at room temperature. CAN-mediated oxidation of **138** (74%) followed by $AlCl_3$-promoted bis-demethylation in CH_2Cl_2 gave **135** in 77% yield.

The same outcome was observed during the synthesis of the regioisomeric core of cardinalin 3, where analogous conditions provided the desired bis-naphthopyran in 56% yield, along with 16% of the *syn-anti* epimer after 36 h at room temperature.

Waghmode and co-workers[136] employed an L-proline-catalyzed asymmetric α-aminooxylation[137] of an aldehyde in conjunction with inter- and intramolecular oxa-Pictet–Spengler cyclizations for the synthesis of deoxy analogs of several pyrano-naphthoquinones (Figure 3), including (+)-nanaomycin A methyl ester (**141**), (+)-eleutherin (**126**), (+)-*allo*-eleutherin (**127**), and (+)-thysanone (**142**), and a formal synthesis of (1*R*,3*S*)-thysanone (**143**).[138]

Nanaomycin A (**144**) was isolated from *Streptomyces rosa*;[139] it displays significant antitumor activity and inhibitory activity against mycoplasma, fungi, and Gram-positive bacteria, being also an inhibitor of platelet aggregation. Several syntheses of the racemate, its methyl ester and deoxy analog have been reported.[140]

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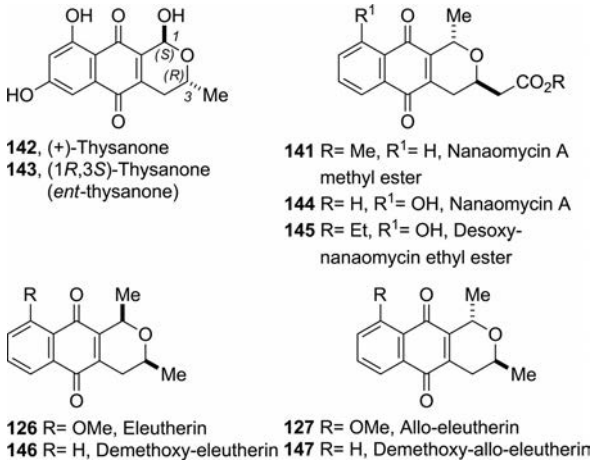


Figure 3. Naturally-occurring pyrano-naphthoquinones and synthesized analogs.

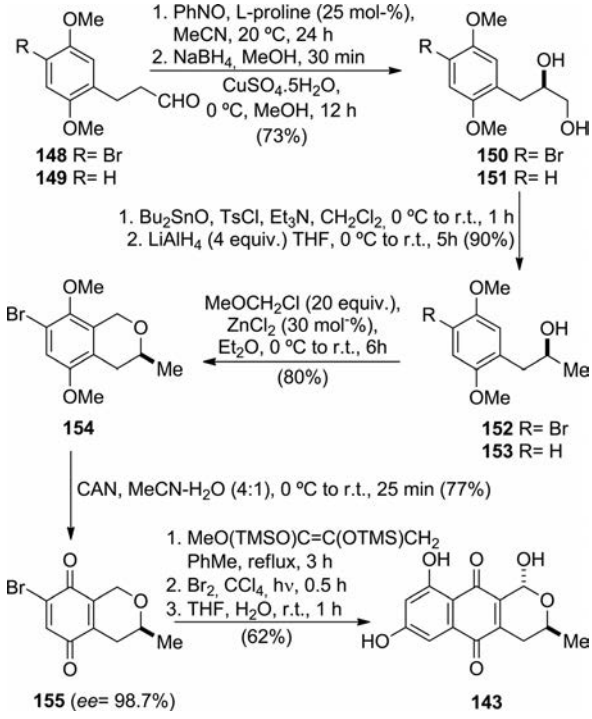
On the other hand, thysanone (**142**) was isolated from the fungus *Thysanophora penicilloides*.[141] The natural product is one of the effective inhibitors of human rhinovirus 3C-protease, a valid target for the development of chemotherapeutic agents for the common cold. Several racemic[142] and enantioselective[143] approaches to thysanone (**143**) and its analogs have been reported.

The organocatalyzed enantioselective synthesis of (1*R*,3*S*)-thysanone commenced with the L-proline-catalyzed α-aminooxylation of brominated phenylpropanal **148** (available in 3 steps and 68% yield from 2,5-dimethoxybenzaldehyde) to furnish 73% of diol **150** after reduction of the intermediate α-hydroxy aldehyde and the aminooxy alcohol (Scheme 21). The terminal carbon was deoxygenated in 90% yield by selective tosylation of the primary hydroxy moiety with TsCl and a catalytic amount of dibutyltin oxide,[144] followed by reduction with $LiAlH_4$ to give **152**.

Next, the pyran ring was built employing an oxa-Pictet–Spengler reaction with MOMCl in presence of $ZnCl_2$ (30 mol-%) in Et_2O, which provided 80% of isochroman **154**.[145] The oxidative demethylation of the isochroman with CAN in aqueous MeCN furnished quinone **155** in 77% yield and *ee* > 98.7%. The conversion of **155** into **143** was performed according to a previously reported method, through a regioselective Diels–Alder reaction with 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene, followed by radical bromination and final hydroxylation.[146]

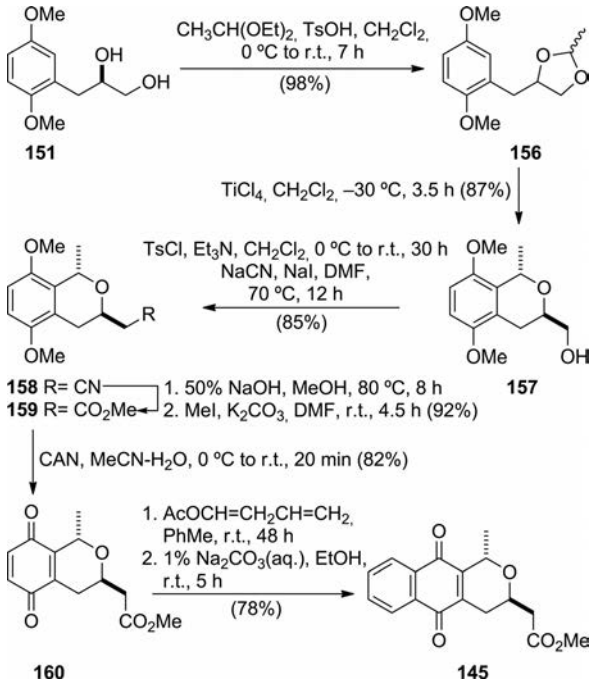
The related alcohol **153**, prepared in 72% overall yield from (2,5-dimethoxyphenyl)propanal (**149**), was employed for the syntheses of the analogs of (+)-eleutherin and (+)-*allo*-eleutherin.[147] Oxa-Pictet–Spengler cyclization of **153** with acetal in the presence of $BF_3{\cdot}Et_2O$ gave a 25:75 separable mixture of isochromans in combined 86% yield. Their oxidative demethylation, followed by Diels–Alder reaction with 1-acetoxy-1,3-butadiene furnished the final compounds.

The synthesis of desoxynanaomycin A methyl ester (**145**) was carried out along the same general lines (Scheme 22). The starting diol **151** was acetalyzed with acetal under



Scheme 21. Organocatalytic α-aminooxylation oxa-Pictet–Spengler-mediated synthesis of (1*R*,3*S*)-thysanone (**143**).

TsOH catalysis and the product **156** was subjected to a $TiCl_4$-catalyzed intramolecular oxa-Pictet–Spengler cyclization,[148] which installed the relative 1,3-*anti* stereochemistry of the oxacycle **157**.



Scheme 22. Organocatalytic α-aminooxylation intramolecular oxa-Pictet–Spengler-mediated synthesis of desoxynanaomycin methyl ester.

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Homologation of the alcohol to the nitrile by way of the tosylate and hydrolysis of the nitrile **158**, followed by esterification of the resulting acid furnished ester **159** in 92% yield. The oxidative demethylation of **159** with CAN (82%) followed by Diels–Alder reaction of **160** with 1-acetoxy-1,3-butadiene, finally yielded the nanaomycin A analog **145**.

Reductive cleavage of the aphid insect pigments (Figure 4) the protoaphins-*fb* and *sl* affords glucoside quinone A (**161**) and quinone A′ (**162**). The group of Giles disclosed the complementary diastereoselectivity (**163**–**165**) observed when titanium or magnesium naphtholates react with ethoxyethyl-protected (*R*)-lactaldehyde.[149]

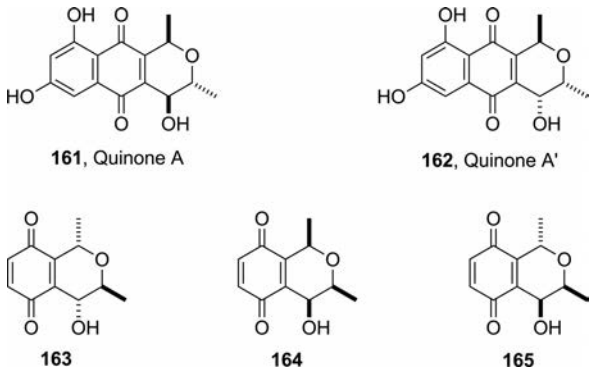
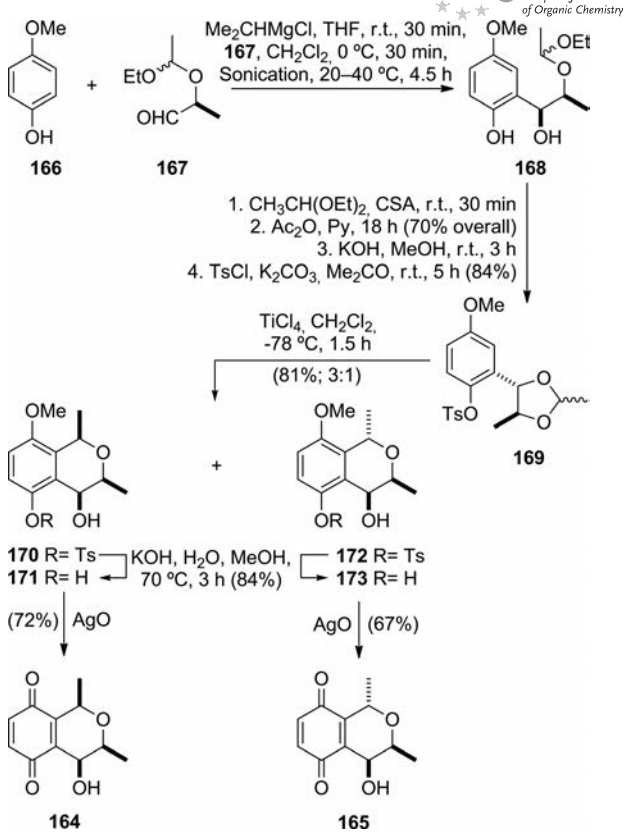


Figure 4. Quinones resulting from the reductive cleavage of aphid insect pigments (**161**, **162**) and related 4-hydroxypyranoquinones (**163**–**165**).



Scheme 23. Magnesium naphtholate-mediated lactaldehyde arylation oxa-Pictet–Spengler cyclization syntheses of pyranoquinones **164** and **165**.

The authors prepared enantiopure (1*S*,3*S*,4*R*)-, (1*R*,3*S*,4*S*)- and (1*S*,3*S*,4*S*)-3,4-dihydro-4-hydroxy-1,3-dimethyl-2-benzopyrans in short reactions sequences and good overall yield from 4-methoxyphenol, employing (2*S*,1′*R*)- and (2*S*,1′*S*)-1′-ethoxy ethoxypropanal as source of asymmetry.

The syntheses of **164** and **165** (Scheme 23) are illustrative of the synthetic sequences. First, the magnesium alkoxide of **166** was prepared and added to the protected lactaldehyde **167**, furnishing alcohol **168** as a diastereomeric 93:7 mixture. Treatment of the latter with acetal under CSA catalysis furnished dioxolane **169** as a mixture of C2 epimes, which were protected as the corresponding aryl tosylates **169** by way of the related acetates, on account that the latter did not withstand the cyclization conditions of the next step.

Although cyclization of the mixed acetal would also entail an intramolecular oxa-Pictet–Spengler, its stereochemical outcome could be different. This strategy provided a convenient method to achieve selective loss of the elements of ethanol. Exposure of the mixture of dioxolanes to $TiCl_4$ at –78 °C effected the intramolecular oxa-Pictet–Spengler cyclization, furnishing the isochromans **170** and **172** along with deprotected starting material, which could be recycled to the mixture of dioxolanes. Separation of the isochroman-4-ols was followed by basic hydrolysis of the tosyl esters to **171** and **173** and oxidative dealkylation with AgO in the same medium to the target quinones **164** and **165**. The remaining oxa-heterocycle **163** was similarly prepared, by way of the titanium alkoxide, prepared from phenol **166** and $Ti(OiPr)_4$.

The same group prepared enantiomerically pure naphthyl dioxolane **174** and, when submitted to the intramolecular oxa-Pictet–Spengler cyclization, it gave a mixture of the diol related to the starting dioxolane and tricycle **175** (65% based on consumed dioxolane).[150] The transformation (Scheme 24) presents two unusual aromatic substitution reactions; in one, the tosyloxy moiety is lost, and in the other, aromatic chlorination takes place being $TiCl_4$ the source of chlorine.

In the proposed reaction mechanisms, the stereochemistry at C4 and C5 in the starting dioxolane is transferred unaltered to C4 and C3, respectively, in the resulting naphthopyran.[151] When the $TiCl_4$ is coordinated to O3 of the dioxolane[152] the allowed 6-enol *endo-endo-trig* ring closure (***i***) takes place.[153] Cleavage of the C2–O3 dioxolane bond and coordination of titanium to both oxygens would require the conformation depicted at the vicinal carbons in the derived oxonium ion ***ii***. Intramolecular electrophilic aromatic substitution by this oxonium ion could occur either *ortho*- or *para*- to the activating methoxy substituent; however, there is a preference for naphthalenes to undergo α-electrophilic substitution, particularly at low temperatures, which would lead to ***iii***. Regioselective nucleophilic attack of the chloride anion (***iv***) at C10 (the predicted site

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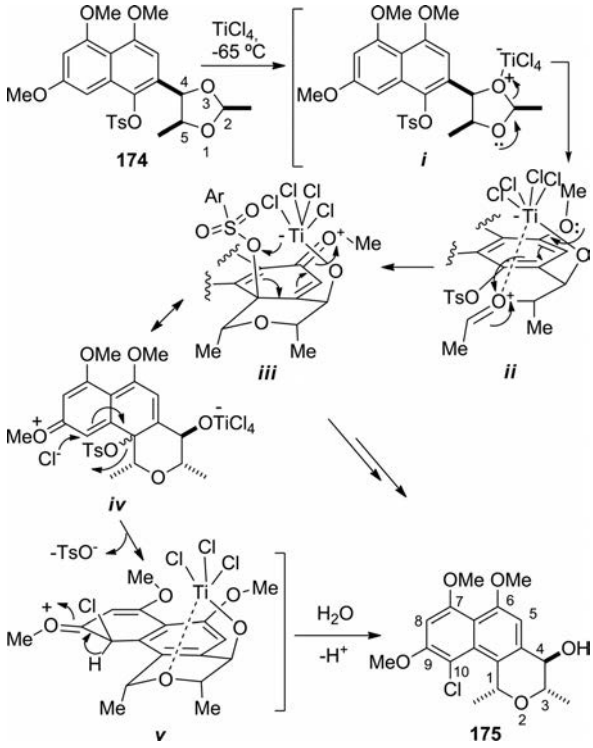

Scheme 24. Intramolecular oxa-Pictet–Spengler cyclization. Proposed mechanism for the synthesis enantiomerically pure angular naphthopyran **175** from acetal **174**.

for electrophilic chlorination of the naphthalenic aromatic system[154]) with loss of tosylate would lead to intermediate ***v***, which after losing a proton during the aqueous work up would finally furnish **175**.

An alternative mechanism from the negatively charged titanium σ complex was proposed, where the titanium facilitates tosyloxy removal and provides the chloride, which is abstracted under assistance of the free electron pair of the oxygen atom bound to C9. Loss of coordination with titanium takes place during workup, causing the product to undergo a conformational inversion which allows its substituents to assume the *pseudo*-equatorial orientations.[155]

Previous research of the same group demonstrated that, in analogous systems, such as *rel*-(2*R*,4*S*,5*R*)-4-(1′-bromo-4′-methoxynaphthalen-2′-yl)-2,5-dimethyl-1,3-dioxolane, cyclization is unsuccessful; however, the intramolecular $TiCl_4$-mediated oxa-Pictet–Spengler reaction of the related compound lacking the bromine atom easily furnished angular naphthopyrans in 60% yield; however, a 3:1 mixture of *syn*- and *anti*-dimethyl derivatives was obtained.[156] The role of methoxy groups in product distribution resulting from the intramolecular oxa-Pictet–Spengler reaction of naphthyl- and phenyl-dioxolanes has been recently studied by Green and October.[157]

4.2. Synthetic Studies on 3-Substituted Isochromans

3-Substituted alkylisochromans are quite rare as natural products and their absolute configuration has either not been determined or has been inferred merely based on biogenetic considerations. These include (Figure 5) the antifungic pseudoanguillosporins A and B (**176**, **177**),[158] the antibacterial bruguierols A and C (**178**, **179**), the anticoccidial arohynapenes C and D (**180**, **181**), (3*S*)-6-hydroxy-8-methoxy-3,5-dimethylisochroman (**182**),[159] and the micotoxin 8-hydroxy-6-methoxy-3,7-dimethylisochroman, also known as DHMI (**183**), a plant growth regulator isolated from *Penicillium corylophilium*.[160]

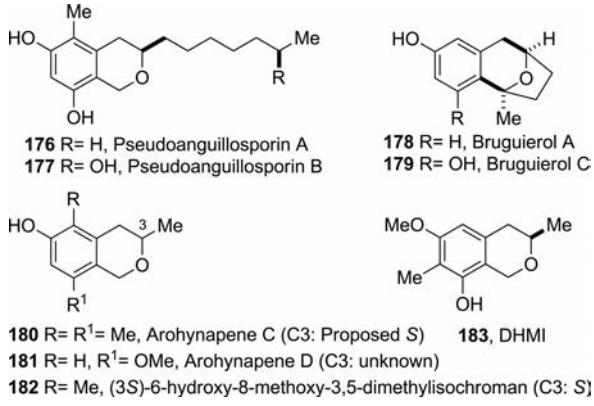

Figure 5. Some naturally occurring 3-substituted isochromans.

A patent claimed optically active 3-substituted 1-arylisochroman derivatives to be intermediates towards the synthesis of chiral *N*-substitutes, 2,3-dihydrobenzodiazepines as useful AMPA receptor antagonists.[161] The synthesis employed chiral β-phenethyl alcohols, which were prepared through a bioreduction of the related ketones, preferably by yeasts of the genus *Zygosaccharomyces*.

As part of a circular dichroism study, Antus and coworkers[162] synthesized a series of chiral 3-methylisochroman derivatives with different substitution patterns on their aromatic rings, by oxa-Pictet–Spengler ring-closure of the corresponding (+)-(*S*)-1-arylpropan-2-ols **184** (Table 15). The starting alcohols were accessed through several ways, including the kinetic resolution of the racemate with the lipase from *Pseudomonas cepacia* (PCL). At approximately 50% conversion, the products (separated by column chromatography) exhibited *ee* > 95%. In a second alternative strategy, the alcohols leading to **185f** and **185g** were obtained by bioreduction of the corresponding phenyl ketone employing *Zygosaccharomyces rouxii* ketoreductase.[163]

The cyclizations were smoothly performed by reaction of the alcohols with MOMCl under $ZnCl_2$ (in Et_2O at 0 °C) promotion. Reactions furnishing **185e** and **185f** were highly stereoselective, producing only one product, while cyclization of the 3-methoxy derivative of entry 3 gave rise to a separable mixture of both possible isomers **185c** and **185d**, in 71% and 19% yield.

Compound **185g** resulted from cyclization of the corresponding alcohol of entry 8, together with small amounts of the intermediate MOM ether. Cyclization of (–)-(1*R*,2*S*)-2-phenylcyclohexanol yielded 76% of the *anti*-fused 1,2,3,4,6,10b-hexahydro-4a*H*-benzo[*c*]chromene.

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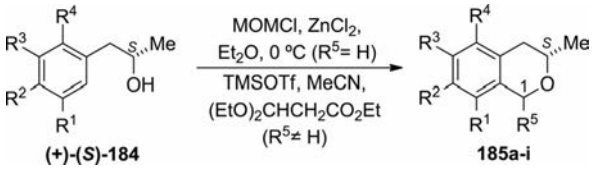
Table 15. Synthesis of enantiomerically pure 3-methylisochromans.



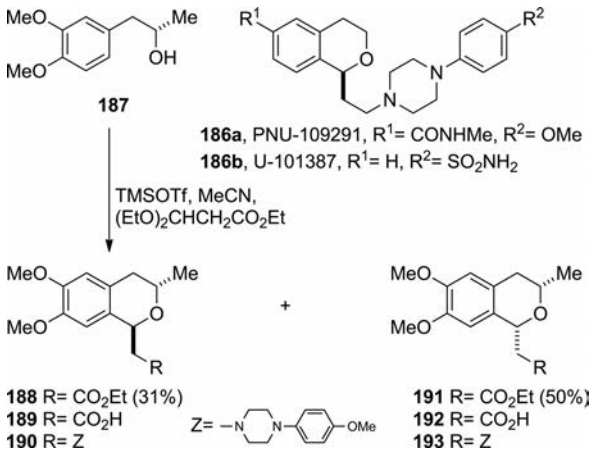
Entry	R^1	R^2	R^3	R^4	R^5	Product	% Yield
1	H	H	H	H	H	**185a**	74
2	OMe	H	OMe	H	H	**185b**	90
3	OMe	H	H	H	H	**185c**	19
	H	H	OMe	H	H	**185d**	71
4	H	OMe	OMe	H	H	**185e**	94[a]
5	H	OCH_2O		H	H	**185f**	77
6	OMe	H	H	Br	H	**185g**	73
7	H	OCH_2O		H	H	**185f**	77
8	OMe	H	H	Br	H	**185g**	73
9	H	OMe	OMe	H	CH_2CO_2Et	**185h**	31 (1*R*)
10	H	OMe	OMe	H	CH_2CO_2Et	**185i**	50 (1*S*)

[a] Yielded 81% **185e** when the cyclization was performed with formaldehyde dimethyl acetal in the presence of $BF_3{\cdot}Et_2O$.

The synthesized heterocycles allowed the establishment of a helicity rule for the unsubstituted isochroman chromophore and deduction of the absolute configuration of the pseudoanguillosporins A and B, from their CD spectrum.

These chiral 3-substituted isochromans are constituents of the endophytic fungus *Pseudoanguillospora* sp. 6577, isolated from the red algae *Polyides rotundus*. Use of $(EtO)_2CHCH_2CO_2Et$ as carbonyl component furnished a diastereomeric mixture of esters **185h** and **185i**.

Following the same strategy, with the use of (*S*)-**187** as starting alcohol, and in order to study the applicability of circular dichroism for the assignment of the configuration of 1,3-disubstituted isochromans, these researchers prepared the C1 epimers of the 3-methyl-6,7-dimethoxy analogs (Scheme 25) of the 5-HT1D agonist PNU-109291 (**186a**) and of the D4 antagonist sonepiprazole (**186b**, U-101387).

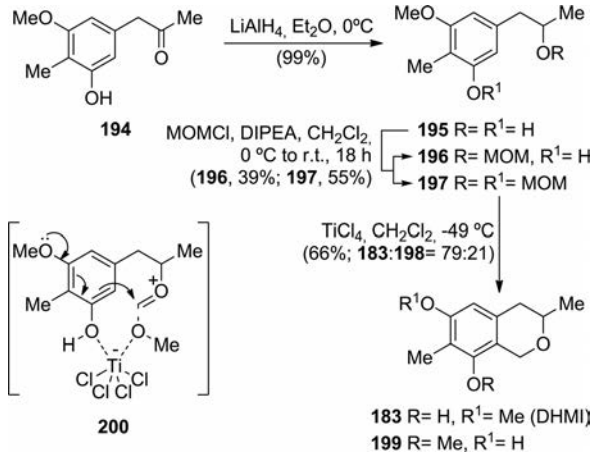


Scheme 25. Oxa-Pictet–Spengler synthesis of 1,3-disubstituted isochromans as analogs of PNU-109291 and U-101387.

Cyclization of (*S*)-**187** with TMSOTf in refluxing MeCN with ethyl 3,3-diethoxypropionate furnished a separable mixture of the expected isochroman esters **188** and **191** in 81% overall yield. The related acids **189** and **192** and (*p*-methoxyphenyl)piperazine derivatives **190** and **193** were obtained from esters **188** and **191**, respectively.[164]

Analysis of the CD spectra of the synthetic isochromans demonstrated that the isochroman helicity rule can be used for the configurational assignment of 1,3-disubstituted isochromans in the absence of an interacting C1 aromatic substituent. In the case of the piperazine derivatives, the near mirror image Cotton effects below 250 nm were indicative of the C1 absolute configuration of the epimers; thus, they can be used for the configurational assignment of C1 in analogous compounds.

The synthesis of DHMI (**183**) was studied by Suzuki and co-workers (Scheme 26).[165] Among the different alternatives, the authors proposed the use of oxa-Pictet–Spengler-based strategies. Thus, reduction of ketone **194**[166] furnished alcohol **195**, which was converted into the MOM derivative **196**, albeit in moderate yield (39%), mixed with 55% of the bis-MOM compound **197**.



Scheme 26. Total synthesis of the plant growth regulator DHMI (**183**).

Submission of **196** to reaction with $TiCl_4$ in CH_2Cl_2 at low temperature furnished a 79:21 mixture of DHMI and its regioisomer **199** in 66% overall yield. Preference for the 8-hydroxy derivative was explained by the authors on the basis of an interaction of the catalyst with the phenolic hydroxy (complex **200**). Compound **198** also yielded DHMI and **199** (53%, 88:12) under the same reaction conditions.

4.3. Synthetic Studies on Berkelic Acid

Berkelic acid (**215**) was isolated through a bioassay guided fractionation of the $CHCl_3$ extracts of a Penicillium species collected in the very hostile environment of Berkeley Pit Lake, a flooded former copper mine. The natural product is a tetracycle which possesses an all-carbon quaternary stereocenter and two contiguous stereogenic centers on an aliphatic chain.

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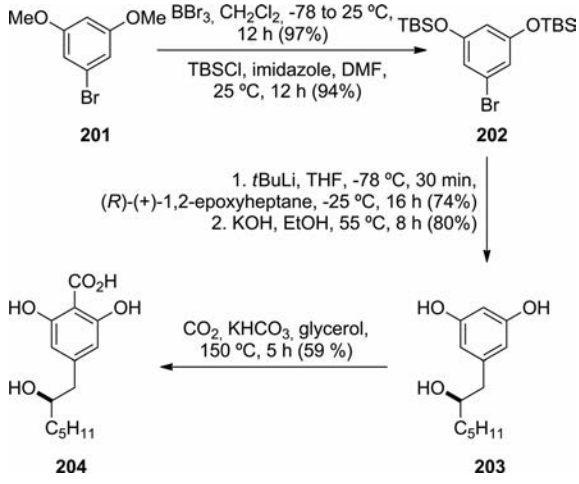
The relative configuration of berkelic acid was originally assigned based on NMR experiments;[167] then it was revised by Fürstner[168] and Snider established its absolute configuration by the total synthesis discussed below. Berkelic acid is selectively active against OVCA$R\bar{3}$ (GI_{50} = 91 nM) an ovarian cancer cell line and inhibited caspase-1 (GI_{50} = 0.098 mM) and the matrix metalloproteinase MMP3 (GI_{50} = 1.87 μM). MMP inhibitors hold the promise of being potencial leads for new therapies for acute and chronic inflammatory and vascular diseases.[169]

Snyder and co-workers performed model studies towards berkelic acid which allowed the biomimetic elaboration of its tetracyclic core[170] and facilitated the development of a convergent enantioselective total synthesis of the natural product. The strategy employed an oxa-Pictet–Spengler cyclization to join the key chiral β-phenethyl alcohol **204** and aldehyde fragments **209**.[171] Preparation of β-phenethyl alcohol unit **204** started with bis-demethylation of 1-bromo-3,5-dimethoxybenzene (**201**), followed by protection of hydroxy moieties as bis-TBS ether (**202**), continued by lithium–halogen exchange, regioselective ring opening of (*R*)-(+)-1,2-epoxyheptane and TBS deprotection[172] to render **203**. Final Kolbe-type carboxylation of **203** gives **204** in 59% yield (Scheme 27).[173]

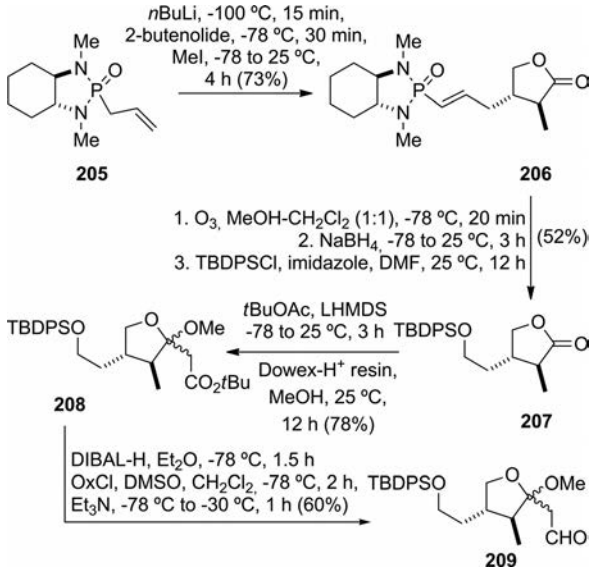


Scheme 27. Snyder's synthesis of the β-phenethyl alcohol fragment **204** for berkelic acid.

On the other hand, the aldehyde fragment **209** was prepared as shown in Scheme 28, by the procedure of Hanessian,[174] through addition of 2-butenolide to metallated **205**, followed by trapping of the resulting enolate with MeI (**206**, 73%).

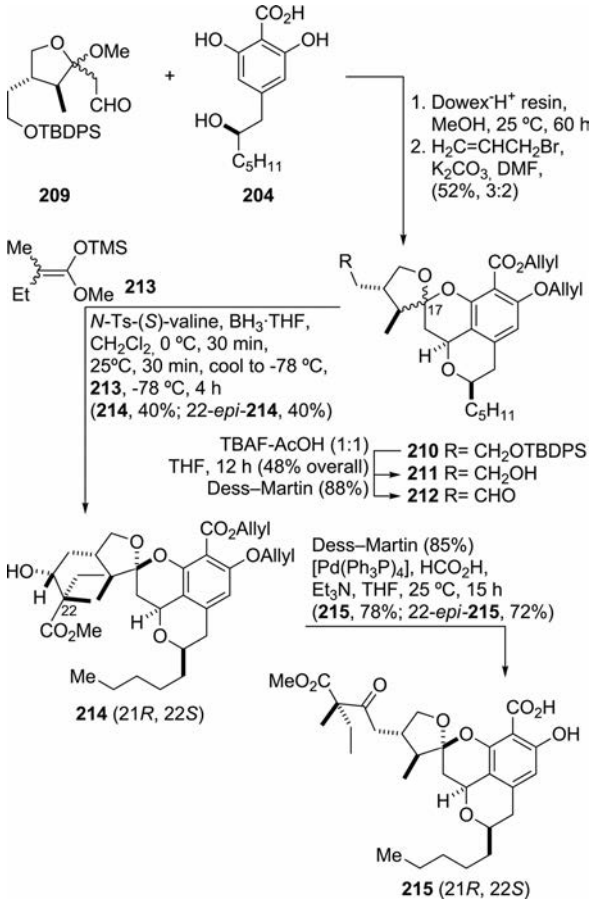
Reductive ozonolysis of the alkene and protection of the resulting alcohol gave **207** (52%). Addition of the lithium enolate of *tert*-butyl acetate and ketal formation with a protonated Dowex resin afforded 78% of **208**. DIBAL-H mediated reduction of the ester furnished mixtures of the desired aldehyde **209** and the related alcohol resulting from overreduction, which was re-oxidized to **209** in 60% overall yield.

Joining of the key fragments **204** and **209** was performed (Scheme 29) by means of a Dowex 50WX8-400-H^+ resin, which furnished the isochroman motif and concomitantly



Scheme 28. Synthesis of the carbonyl fragment for berkelic acid.

effected a transketalization yielding a separable 3:2 mixture of diastereomeric tetracycles **210** after K_2CO_3 in DMF-assisted allylation of the salicylic acid moiety.[175]



Scheme 29. Total synthesis of of berkelic acid. Advanced stages.

Desylilation of the primary alcohol **211** and Dess–Martin oxidation to the related aldehyde **212**, set the stage for extension of the side chain.

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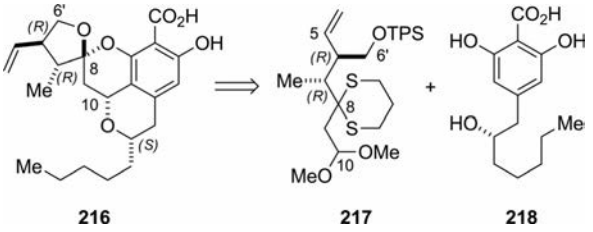
Reaction of the aldehyde **212** with ketene acetal **213** under Kiyooka's protocol,[176] with a chiral auxiliary prepared in situ from *N*-Ts-(*S*)-valine and BH_3·THF, was *Si* face-selective affording only two epimeric aldol adducts (**214** and 22-*epi*-**214**) at the C22 quaternary centre in 80% overall yield.

Next, Dess–Martin oxidation of the secondary alcohol and palladium-mediated removal of the allyl moieties furnished 78% of berkelic acid (**215**). The related 22-*epi*-berkelic acid was prepared in an analogous fashion in 72% yield, from 22-*epi*-**214**.

Stiasni and Hiersemann[177] also contributed to the chemistry of berkelic acid through the preparation of the C5–C8 fragment of berkelic acid (**217**). The authors proposed structure **216** as a key intermediate towards berkelic acid, which was projected as accessible by means of the key oxa-Pictet–Spengler-mediated construction of its isochroman moiety from acetal-thioketal **217** and β-phenethyl alcohol (**218**, *ent*-**204**) fragments (Scheme 30).



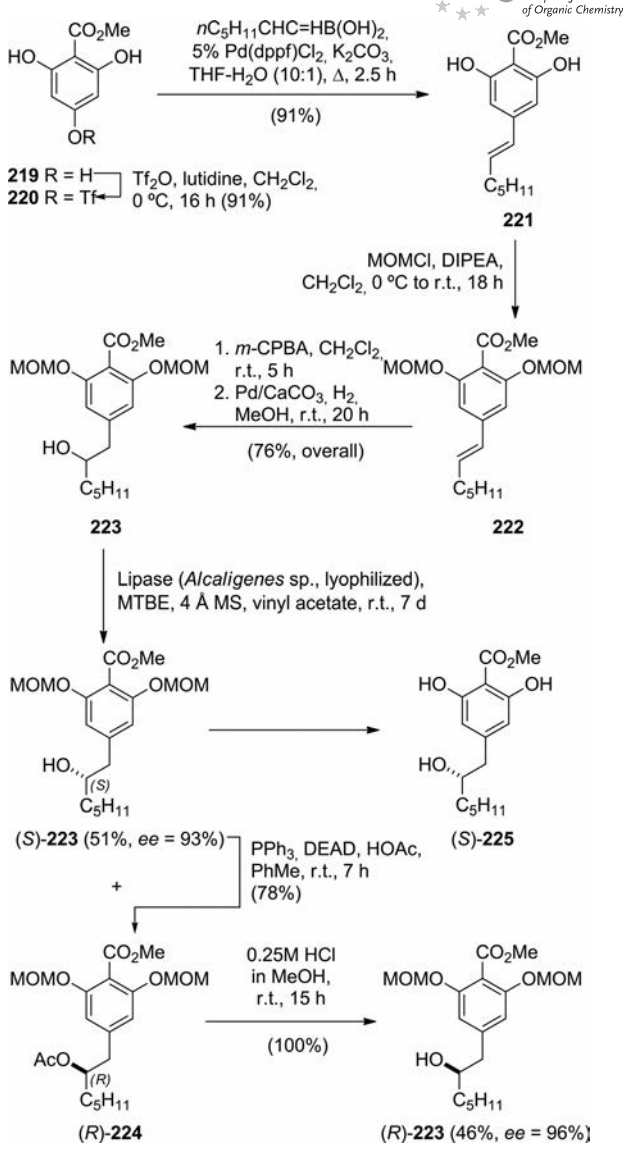
Scheme 30. Retrosynthetic analysis of **216**, a proposed advanced intermediate towards berkelic acid, based on an oxa-Pictet–Spengler transform between thioketal **217** and β-phenethyl alcohol derivative **218**.

Construction of the acetal-thioketal fragment **217** was carried out in ten steps and approximately 10% overall yield from (*Z*)-2-butene-1,4-diol and included a preparative HPLC separation of geometric isomers[178] of a key intermediate and a catalytic asymmetric Gosteli–Claisen rearrangement[179] with the bis-oxazoline copper complex [Cu{(*S*,*S*)-*t*Bu-Box}$(H_2O)_2$]$(SbF_6)_2$ as chiral Lewis acid.[180]

The enantioselective synthesis of the methyl ester (*S*)-**225** related to the proposed acid **218** was performed by the group of Brabander as part of their studies on berkelic acid.[181] As shown in Scheme 31, to that end, the commercially available methyl 2,4,6-trihydroxybenzoate (**219**) was converted into triflate **220** in 91% yield and this was coupled with 1-heptenylboronic acid to afford 91% of styrene derivative **221**, which was protected as the MOM derivative **222**.

The homobenzylic carbinol was installed by oxidation of the olefin moiety in **222** with *m*-CPBA, followed by selective hydrogenolysis of the benzylic C–O bond to yield 76% of racemic alcohol **223**. The desired chiral alcohol was obtained by kinetic resolution of **(±)-223** with the *Alcaligenes* sp. lipase,[182] which effected a highly selective transesterification of **223** with vinyl acetate, yielding a 51:46 mixture of (*S*)-**223** and (*R*)-**224** in *ee* = 93% and 96%, respectively.

The authors transformed alcohol (*S*)-**223** into (*R*)-**224** by means of a Mitsunobu inversion with AcOH as the acidic component, yielding 78% of the product. Finally, simultaneous hydrolysis of the acetate and MOM protecting groups in acidic MeOH quantitatively furnished the expected (*R*)-**223**.



Scheme 31. Synthesis of the β-phenethyl alcohol-type key fragments (*S*)-**225** and (*R*)-**224** employed in berkelic acid research.

4.4. Intramolecular Oxa-Pictet–Spengler Cyclization. Total Synthesis of (+)-Bruguierol C, Formal Total Syntheses of (±)-Brussonol and (±)-Abrotanone, and an Approach to (–)-Platensimycin

The bruguierols A–C (**178**, **179**) were isolated from the stem of the *Bruguiera gymmorrhiza* mangrove tree. The *meta*-substituted hydroxy group is crucial for the antimicrobial activity and only bruguierol C (**179**) exhibits interesting antimicrobial activity, especially against *Enterococcus faecalis* 1528 (resistant to gentamicin, teicoplanin, and vancomycin).[183]

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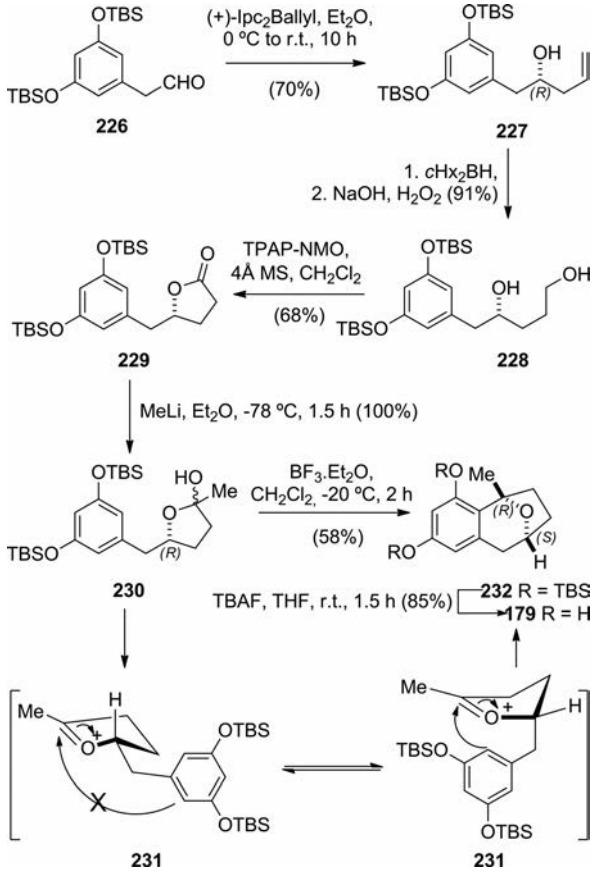
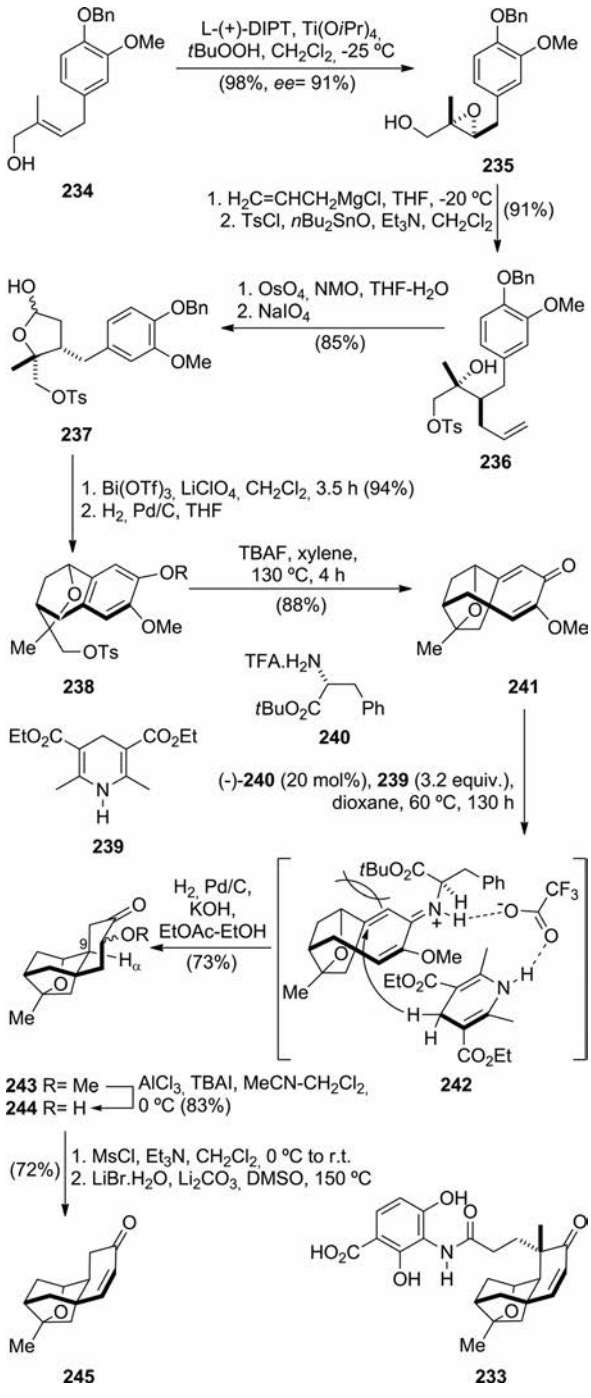
Martínez Solorio and Jennings recently completed the first total synthesis of (+)-bruguierol C, as shown in Scheme 32.[184] For that purpose, aldehyde **226** (prepared in 77% yield from the related methyl ester through $LiAlH_4$ reduction and PCC oxidation of the resulting alcohol)[185] was submitted to Brown's asymmetric allylboration with (+)-Ipc$_2$Ballyl[186] to furnish the homoallylic alcohol **227** (70% yield, *er* = 95:5).



Scheme 32. Enantioselective total synthesis of bruguierol C (**179**).

Next, hydroboration–oxidation of the olefin moiety with dicyclohexyl borane gave diol **228** in 91% yield and Ley's oxidation of the primary alcohol moiety with TPAP-NMO gave 68% of lactone **229**.[187] The required methyl group was quantitatively introduced by reaction of lactone **229** with MeLi, yielding a mixture of lactols **230**. Sequential treatment of the lactols with $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at –20 °C and TBAF in THF first effected the oxa-Pictet–Spengler cyclization (**232**, 58% yield) and then, the phenol deprotection (85% yield) respectively, giving access to the desired product **179**. Attack of the oxocarbenium intermediate **231** was proposed to have taken place from the outside face of the envelope conformer.

(–)-Platensimycin (**233**) a structurally unique potent broad-spectrum antibiotic isolated from a *Streptomyces platensis* strain, has attracted the attention of many synthetic organic Chemists (Scheme 33).[188] Eey and Lear[189] recently reported a high yielding approach to the core or (–)-platensimycin, employing a Bi(OTf)$_3$-catalyzed intramolecular oxa-Pictet–Spengler-type cyclization of a lactol, to yield a seven-membered fused oxacycle.



Scheme 33. Oxa-Pictet–Spengler-mediated organocatalytic synthesis of a key intermediate towards (–)-platensimycin (**233**).

The synthesis (Scheme 33) began with the catalytic Sharpless epoxidation of the eugenol-derived allylic alcohol **234**, with L-(+)-DIPT, which afforded the epoxy alcohol **235** (98% yield, *ee* = 91%); in turn, the epoxide was regioselectively opened with allyl Grignard and the diol was subjected to Martinelli's regioselective catalytic monotosylation to to-

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sylate **236**.[190] Oxidative cleavage of the allyl moiety to the aldehyde with the OsO_4-NMO/$NaIO_4$ reagent system took place with spontaneous cyclization to the key lactol **237** in 85% yield.

The Marson-type intramolecular oxa-Pictet–Spengler cyclization of **238** proved problematic under $BF_3{\cdot}Et_2O$ and $SnCl_4$ promotion and unsuccessful with TfOH and TMSOTf, rising suspicion on the interference by the tosylate moiety. However, the 5% $Bi(OTf)_3$–$LiClO_4$ combination proved to be efficient, furnishing 94% of cyclised product. $LiClO_4$ alone is incapable of carrying out the cyclization, while $Bi(OTf)_3$ alone gave poor yields of product **238**. Competition of Li^+ for the Lewis basic sulfonate group to release any trapped Bi^{III} would allow a catalytic cycle to persist, while concomitant formation of a reactive oxocarbenium perchlorate intermediate, could explain the success of this cyclization.[191]

Hydrogenolytic cleavage of the benzyl ether was followed by a intramolecular alkylative dearomatization; this transformation took place efficiently when the phenol **238** was heated with TBAF in xylene, providing 86% of the caged ketone **241**.

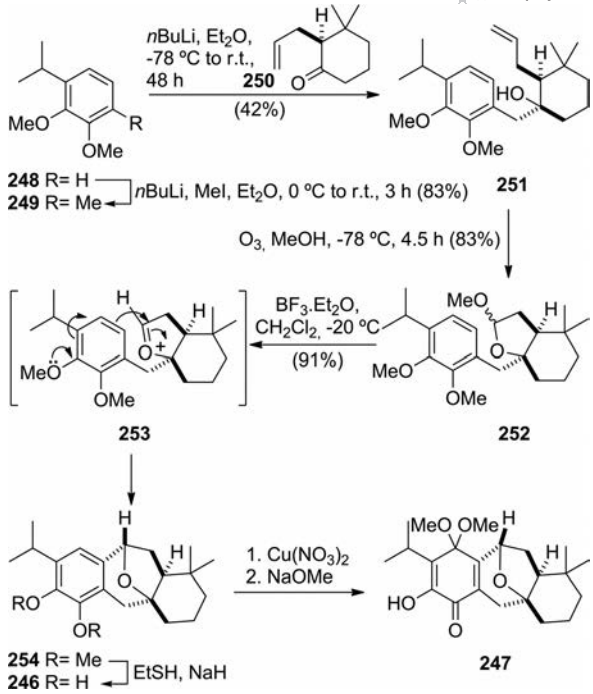
The chemo- and stereocontrolled Hantzsch conjugate reduction with **239** of the dienone system was achieved with D-phenylalanine derivative **240**, which yielded a 4:1 mixture of 9α-H:9β-H products **242**, which were subjected to catalytic hydrogenation over Pd/C to give **243** in 73% overall yield. Finally, $AlCl_3$/TBAI-mediated demethylation to **244**,[192] followed by alcohol elimination by way of the related mesylate furnished the target tetracyclic enone **245** in 57% yield.

The π-facial selectivity observed in the Hantzsch reduction was rationalized as being the result of hydride transfer to the less congested α-face of an *anti* iminium intermediate **242** formed by condensation of the ketone and the amine auxiliary. The bulky *tert*-butyl and benzyl moieties of the D-phenylalanine act providing steric congestion to the β-face, thus hindering hydride transfer. An additional counteranion hydrogen bonding network helps organizing the system.[193]

The icetexane diterpenoids are structurally unique and medicinally relevant compounds. Brussonol (**246**) was isolated from the root cultures of *Salvia broussoneti* and was shown to be cytotoxic toward insect and mammalian cell lines as well as against the P388 murine leukemia cell line (IC_{50} = 1.9 μg/mL).[194]

Martínez-Solorio and Jennings reported a convergent formal total synthesis of (±)-brussonol (**246**) and the related (±)-abrotanone (**247**), which hinged upon an intramolecular oxa-Pictet–Spengler reaction, as shown in Scheme 34.[195] The required starting 3-isopropylveratrol moiety (**248**) was prepared in 32% overall yield as reported by Majetich, by successive *ortho*-metallation reactions of 1,2-dimethoxy benzene and capture of the lithium species first with acetone and finally with MeI (**249**).

On the other hand, the cyclohexyl fragment (**250**) was synthesized in 55% overall yield by a Karasch-type reaction of 3-methylcyclohexenone, employing the conditions of



Scheme 34. Synthesis of an advanced intermediate towards (±)-brussonol (**246**) and (±)-abrotanone (**247**).

Reetz, which entailed the conjugate addition of a methyl organocuprate reagent under TMSCl promotion, followed by trapping of the enolate with allyl iodide.[196]

Joining of the fragments **249** and **250** was accomplished by lateral metallation of the aromatic moiety followed by addition of the latter to the ketone fragment. The synthetic route continued with ozonolytic cleavage of the allyl side chain of the resulting **251** in the presence of MeOH, which furnished acetal **252**, by cyclization of an intermediate aldehyde. Exposure of the acetal to $BF_3{\cdot}Et_2O$ furnished 91% of the cyclised product **254** through the intermediacy of oxocarbenium ion **253**, while thiolate anion-assisted cleavage of both methyl ethers provided brussonol **246**. Access to abrotanone (**247**) required copper(II)-assisted oxidation of **246** followed by basic hydrolysis.

4.5. Modification of Natural Antioxidants: Hydroxytyrosol, Lignins and Catechin

Hydroxy-1-arylisochromans are secondary metabolites identified in extra-virgin olive oil. These natural isochromans or their synthetic derivatives have been shown to exhibit beneficial antioxidant effects. The antiplatelet activity and antioxidant power of these isochromans were also evaluated, and found to be effective free radical scavengers, also being inhibitors of platelet aggregation and thromboxane release evoked by agonists.[197]

Lorenz and co-workers prepared a series of derivatives of hydroxytyrosol and their *O*-methyl derivatives (ISO 0, ISO 2–4) employing the oxa-Pictet–Spengler reaction with TsOH as promoter, in yields ranging from 46% to 85%,

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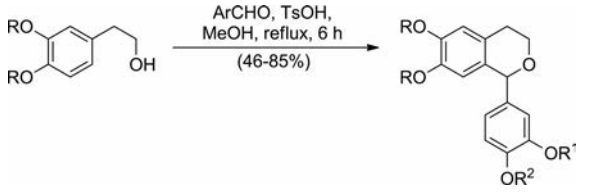
and tested their antioxidant ability in the 2,2-diphenylpicrylhydrazyl (DPPH) assay as well as their ability to scavenge superoxide and $ONOO^-$ radicals (Table 16).

Table 16. Hydroxytyrosol-derived 1-arylisochromans and their antioxidant activity.



	R	R^1	R^2	Scavenger activity, EC_{50}, mM DPPH	$O_2^{\cdot-}$	$ONOO^-$
ISO 0	Me	Me	Me	>250	–	–
ISO 2	H	Me	Me	25.2	91.8	55.6
ISO 3	H	Me	H	22.5	84.0	45.3
ISO 4	H	H	H	10.4	34.4	23.0

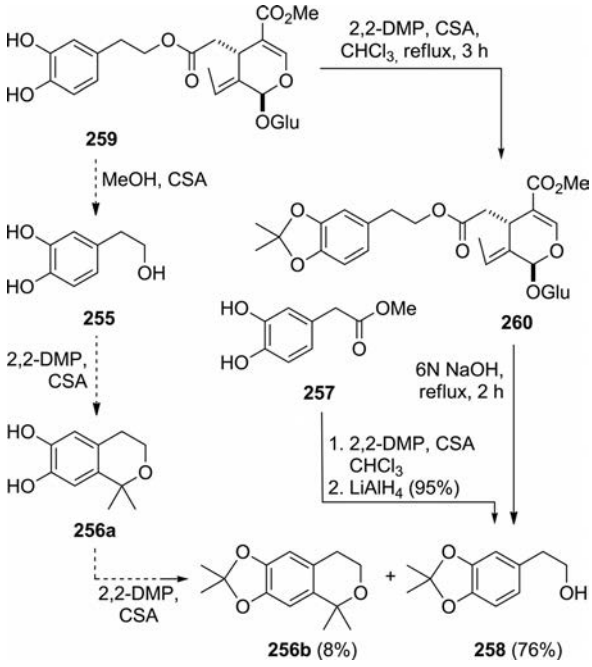
The compounds demonstrated to be effective radical scavengers, able to counteract the effect of intracellular hydrogen peroxide. In general, activity decreased with an increase of the number of blocked hydroxy groups. In addition, compounds with 2, 3 or 4 hydroxy substituents effectively scavenges reactive oxygen species released from mitochondria with activity comparable with that of the stilbene-like polyphenolic resveratrol.[198]

During the synthesis of hydroxytyrosol acetonide[199] as a stable derivative of the strong antioxidant hydroxytyrosol (**255**), Gambacorta and co-workers observed that hydroxytyrosol itself was not a suitable starting material, due to its propensity to undergo oxa-Pictet–Spengler cyclization to 1,1′-dimethyl-6,7-dihydroxyisochroman (**256a**), a natural product isolated from *Tectaria subtriphylla* and *Dioscorea cirrhosa*,[200] and previously prepared by the oxa-Pictet–Spengler reaction of hydroxytyrosol with acetone.[33]

These researchers synthesized this heterocycle in 60% yield by refluxing hydroxytyrosol (**255**) in acetone to which 14 mol-% TsOH was added. Therefore, the acetonide moiety was introduced in 91% yield on the related methyl (3,4-dihydroxyphenyl)acetate (**257**) by transacetalization with 2,2-DMP under CSA promotion in $CHCl_3$. Subsequent $LiAlH_4$ reduction gave 95% of hydroxytyrosol acetonide (**258**), which is stable to silica, and to air and light for 3 months. Unmasking of hydroxytyrosol from **258** was accomplished with Amberlyst 15 in MeOH (97%).

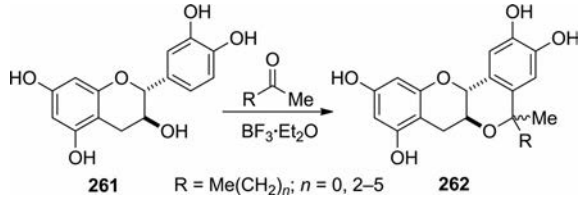
When the same procedure was applied on oleouropeine (**259**), a mixture containing acetonide **260** was obtained (Scheme 35); upon saponification of the mixture, it was observed the presence of an impurity (8%) to which structure **256b** was attributed.

This substance may be the result of acetonidation of the oxa-Pictet–Spengler product resulting from condensation of hydroxytyrosol with acetone; in turn, hydroxytyrosol could be formed in the reaction medium by transesterification of oleuropeine with the MeOH released from 2,2-DMP.



Scheme 35. Synthesis of protected hydroxytyrosol (**258**) from oleuropein (**259**) and possible chemical origin of its isochroman-type impurity, **256b**.

Following previous work in the field,[201] and taking into account that the 3-OH group of catechin (**261**) is not associated with its antioxidative activity and that lipophilic antioxidants and that catechin has limited solubility in lipidic substances, Poaty and co-workers[202] synthesized catechin derivatives **262** with increasing lipophilicity employing an optimized oxa-Pictet–Spengler reaction, promoted by $BF_3{\cdot}Et_2O$ under solventless conditions (Scheme 36).



Scheme 36. Oxa-Pictet–Spengler mediated derivatization of catechin towards lipophilic antioxidants.

These tetracyclic products **262** were obtained as a ca. 2:1 mixture of diastereomers (except when acetone was used) and the yields were in the range 30–95%, increasing with the increase in the number of carbons in the ketone. Interestingly, under the same conditions, 2-pentanone outperformed 3-pentanone as carbonyl component. The synthesized tetracycles retained the antioxidation ability of **261**, as proven by inhibition of the induced oxidation of methyl linoleate and by reactivity with the DPPH free radical.

Being water-soluble because of their structure containing many OH groups, tannins exhibit a limited solubility in lipids. To use them in these hydrophobic media, tannins need to be more lipophilic while preserving their antioxidant

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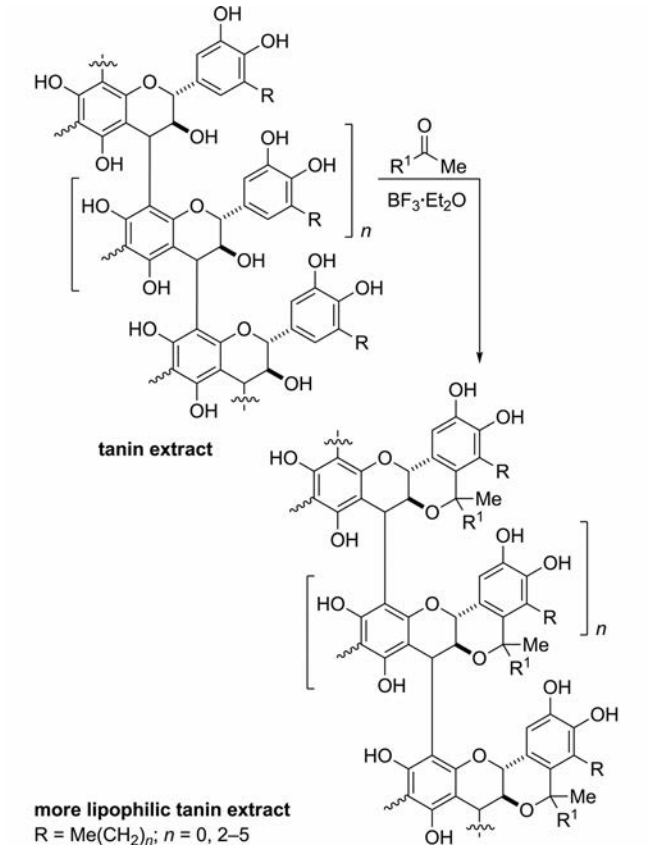
properties. In order to prove this concept, Poaty and coworkers carried out the same oxa-Pictet–Spengler transformation on plant tannins extracted from wood chestnut, oak, quebracho and grape seed, yielding more lipophilic extracts.[203]

After performing the oxa-Pictet–Spengler-mediated modification (Scheme 37), it was observed that the antioxidant properties of the resulting extracts were suitably preserved. These modified extracts should be cost-effective agents, useful to protect lipids from oxidation, which is usually carried out with synthetic antioxidant additives of petrochemical origin.[204]



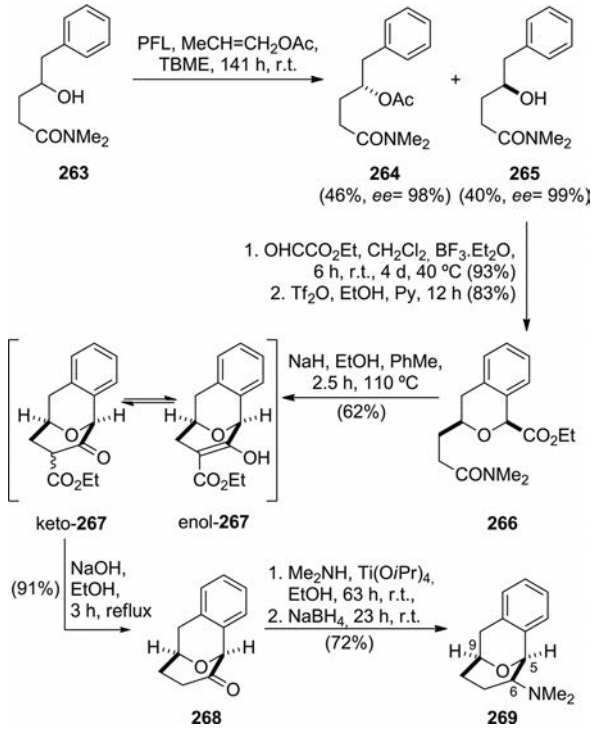
Scheme 37. Oxa-Pictet–Spengler-mediated derivatization of lignin extracts towards more lipophilic antioxidants.

The transformation did not produce a strong decrease of polarity for tannin derivatives as compared with lipophilic catechins, probably because unlike free catechin tannins do not have all their possible reaction sites available, which may lead to partial reaction.

4.6. Synthesis of Enantiomerically Pure Benzomorphans

The group of Wünsch[205] synthesized enantiomerically pure tricyclic amines analogous to benzomorphans. Depending on the stereochemistry of the tricyclic ring system and the *N*-substituent, benzomorphans can interact with opioid μ and/or κ receptors, σ receptors and the phencyclidine binding site of the NMDA receptor.[206]

One of the key steps of the synthetic sequence (Scheme 38) was the kinetic resolution of secondary alcohol **263** with the lipase from *Pseudomonas fluorescencens* (PFL), as a strategy to access the required chiral alcohol (*S*)-**265**. This and the related (*R*)-ester [(*R*)-**264**] were obtained in good yields and enantiomeric excesses (*S*-**265**, 40%, *ee* = 99%; *R*-**264**, 46%, *ee* = 98.4%). The tricyclic ring system was accessed by a highly diastereoselective oxa-Pictet–Spengler reaction of (*S*)-**265** with ethyl glyoxalate, which gave the *syn*-configured isochroman **266**, and subsequent alcoholysis of the amide to yield 77% of **266**.



Scheme 38. Oxa-Pictet–Spengler-based synthesis of an enantiomerically pure benzomorphan.

This was followed by a Dieckmann cyclization of **266** to diastereomeric β-keto esters **267**, which according to the NMR spectra, coexist in a thermodynamic equilibrium with the related enolester (25:15:65). Hydrolysis and decarboxylation of **267** furnished 91% of ketone **268**, which was condensed with dimethylamine under $Ti(OiPr)_4$ promotion[207] and subsequently diastereoselectively reduced, providing 72% of **269**.

The absolute configuration of the product was inferred from comparison of the quantum mechanically calculated specific optical rotation of the (*S*,*S*,*S*)-configured alcohol resulting from reduction of **268** with its measured specific rotation and X-ray crystal structure analysis. The enantiomerically pure dimethylamine **269** exhibited moderate affinity toward σ_2 receptors.

4.7. Simple Isochromans and Drug Discovery

4-Arylpiperazines are "privileged" templates in drug discovery.[208] This motif is found in dopaminergic, sero-

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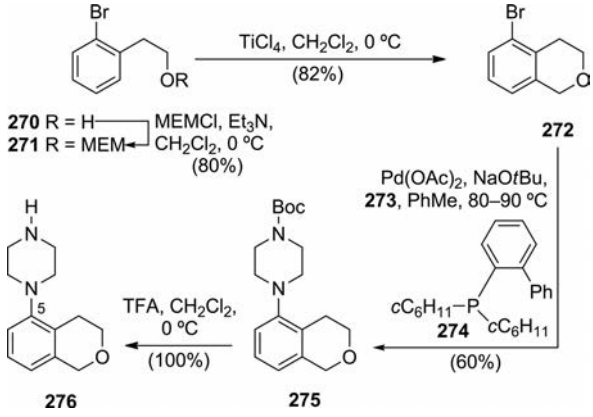
tonergic, and adrenergic agents and numerous other bioactive compounds.[209] Favor and co-workers[210] prepared a series of regioisomeric chromanyl, isochromanyl and dihydrobenzofuranyl piperazines employing novel methodologies.

The synthesis of 1-(isochroman-5-yl)piperazine (**276**) was accomplished as shown in Scheme 39, through the intramolecular oxa-Pictet–Spengler cyclization of **271** [the MEM derivative of 2-(2-bromophenyl)ethanol (**270**)], by exposure to $TiCl_4$ in CH_2Cl_2 at 0 °C (82%).[211] The resulting aryl bromide **272** was subjected to Buchwald amination conditions[212] with *N*-Boc-piperazine (**273**) and employing **274** as ligand, yielding 60% of **275**. The *N*-Boc deprotection of **275** quantitatively afforded the target compound.



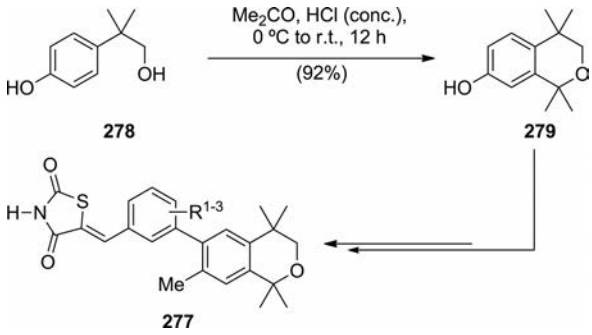
Scheme 39. Synthesis of a 1-(isochroman-5-yl)piperazine.

The related 1-(isochroman-8-yl)piperazine was synthesized following an analogous sequence through the intermediacy of 8-bromoisochroman prepared by the $TiCl_4$-promoted cyclization of 1-bromo-3-[2-((2-methoxyethoxy)-methoxy)ethyl]benzene. However, ring closure of the oxonium intermediate took place in 75% yield to form two different regioisomers 8-bromo-isochroman and 7-bromo-isochroman. The regioselectivity of this cyclization was ca. 3.4:1, favouring the undesired regioisomer, presumably due to steric reasons.

A recent patent contains information on 1,1′,4,4′-tetramethyl-substituted isochroman derivatives functionalized on C6 and C7 (**277**), which are potentially useful in antidiabetic therapy. These drugs are insulin sensitizers that resensitize patients to their own insulin, thereby reducing blood glucose levels, and thus reducing the requirement for exogenous insulin.[213]

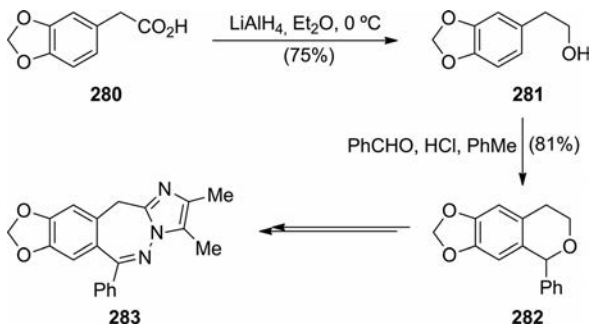
The pivotal intermediate 1,1′,4,4′-tetramethyl-isochroman-6-ol (**279**) was prepared in 92% yield by an oxa-Pictet–Spengler cyclization of 3-(2-hydroxy-1,1′-dimethylethyl)-phenol (**278**) with acetone under HCl promotion (Scheme 40).

On the other hand, a research group at Schering AG interested in novel α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate (AMPA) receptors, identified tetracyclic compound **283** as a valid candidate for AMPA receptor inhibition (IC_{50} = 3.4 μM). These receptors have been implicated



Scheme 40. Oxa-Pictet–Spengler-based synthesis of a key intermediate towards isochromane derivatives with potential application as antidiabetics.

in the onset of certain neurological disorders for which competitive antagonists may yield potential therapeutic treatments. The target compound **283** and some analogs were prepared from substituted phenylacetic acids **280**, employing as key intermediates isochromans **282** resulting from the oxa-Pictet–Spengler cyclization of β-phenethyl alcohols **281** (Scheme 41).[214]



Scheme 41. Oxa-Pictet–Spengler-mediated synthesis of an isochroman intermediate towards the AMPA receptor inhibitor **283**.

The group of Prasad[215] developed a series of isochroman mono-carboxylic acid derivatives as inhibitors of the protein tyrosine phosphatase 1B (PTP1B). Inhibitors of this enzyme are potential *anti*-diabetic agents. Analysis of structure–activity relationships led to the identification of compound **284**, which inhibited PTP1B with IC_{50} value of 51.63 ± 0.91 nM. In general, high potency was associated with a dithiolane ring with a spacer of five carbons to the isochroman ring.

For the synthesis (Scheme 42), L-phenylalanine was converted into L-(–)-3-phenyllactic acid (**285**) through diazotization,[216] and the latter was then cyclized using paraformaldehyde, furnishing (3*S*)-isochroman-3-carboxylic acid,[217] which was esterified in situ with MeOH in the presence of a catalytic amount of H_2SO_4, to yield 74% of **286**.

Nitration of **286** with fuming HNO_3 at –40 °C gave a ca. 1:1 mixture of the isomeric 6-nitro- and 7-nitroisochromans, which could be separated chromatographically after catalytic hydrogenation to the corresponding amines **287**. EDCI-Mediated coupling of amine **287** with [(3*R*)-1,2-dithiolan-3-yl]butylcarboxylic acid (lipoic acid, **288**) and sub-

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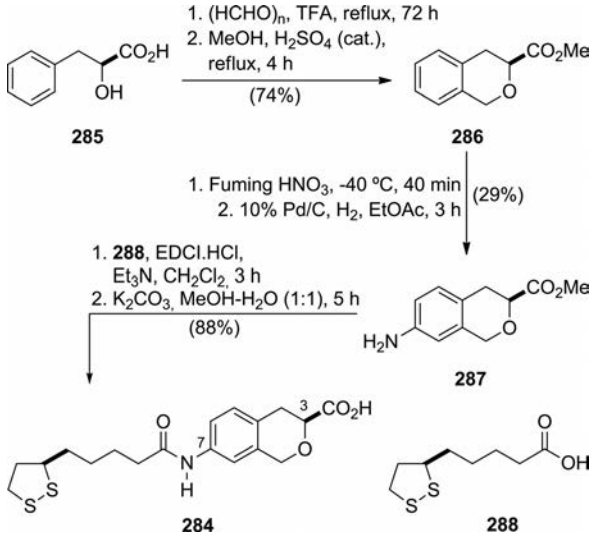


Scheme 42. Synthesis of an isochroman-3-carboxylic acid derivative as potential inhibitor of the protein tyrosine phosphatase 1B.

sequent saponification furnished **284**, the most potent compound of a library of twenty 6- and 7-aminoisochromans, in 88% yield.

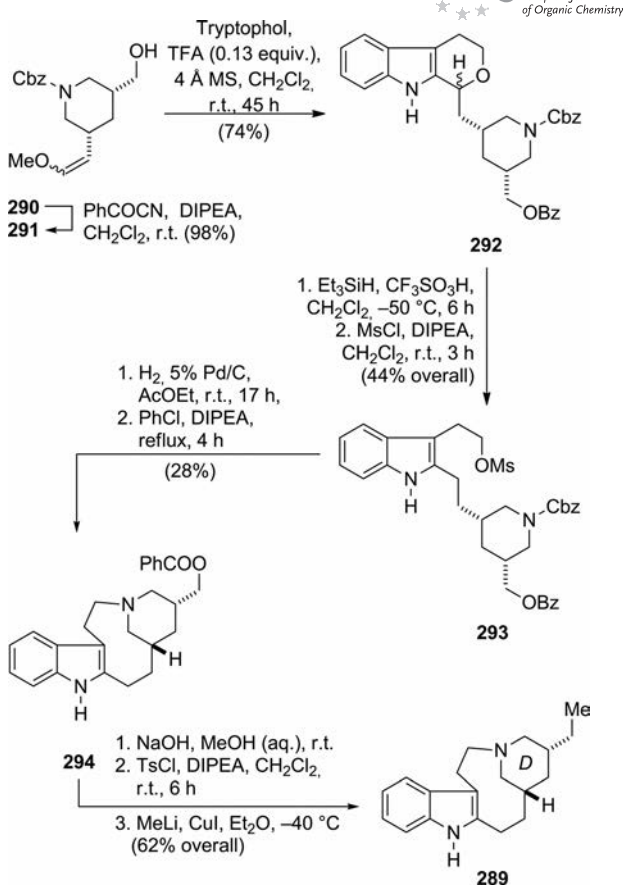
4.8. Syntheses and Reactions of Polysubstituted Pyrano-[3,4-*b*]indoles

Danieli and co-workers reported an approach to (+)-(14*S*,20*R*)-15,20-dihydrocleavamine (**289**),[218] which proceeds through an oxa-Pictet–Spengler cyclization taking advantage of the chemoenzymatically accessible piperidine **290**,[219] surrogative of the ring D of the target molecule (Scheme 43). The tetracyclic alkaloid is structurally related to 16-β-(methoxycarbonyl)velbanamine, the indole "upper half" of the antitumoral bis(indole) alkaloids occurring in *Catharantus roseus*, such as the pharmacologically useful vinblastine and vincristine.[220]

The fully protected piperidine **291** was prepared smoothly by benzoylation of **290**. Then, taking advantage of the enol methyl ether function of **291**, treatment with tryptophol in the presence of a catalytic amount of TFA and molecular sieves (4 Å), cleanly generated the tricyclic indole derivative **292** in 74% yield, which was isolated as an inseparable 1:1 mixture of diastereoisomers.

The ring opening of the oxygenated ring was performed with the Et_3SiH-CF_3SO_3H reagent, furnishing a tryptophol intermediate in modest 44% yield. For the cyclization step, a good leaving group was required; therefore, the alcohol was converted almost quantitatively into the corresponding mesylate **293**.

Subsequent hydrogenolytic deprotection over 5% Pd/C and intramolecular nucleophilic displacement in refluxing chlorobenzene afforded 28% of the tetracyclic derivative **294**. A final three-step sequence involving hydrolysis of the



Scheme 43. Oxa-Pictet–Spengler approach towards (+)-(14*S*,20*R*)-15,20-dihydrocleavamine (**289**).

benzoate, tosylation and displacement of the tosylate with lithium dimethylcuprate furnished the final product (**289**).[221]

Some 1,2,3,9-tetrahydropyrano[3,4-*b*]indoles belong to the family of analgesics. In addition, 1-acetic acid derivatives have been successfully tested as anti-inflammatory agents. Their scale-up preparation, which includes a key oxa-Pictet–Spengler cyclization of a suitably substituted tryptophol, was also disclosed.[222]

A patent on spirocyclic cyclohexane derivatives of 1,2,3,9-tetrahydropyrano-[3,4-*b*]indoles which act to a great extent on the nociceptin/ORL1 and are accessible through an oxa-Pictet–Spengler reaction, has also been recently issued.[223]

The group of Jacobsen developed a highly enantioselective organocatalyzed modification of the acyl-Pictet–Spengler reaction,[224] in which *N*-acyliminium ions undergo cyclization in the presence of chiral thiourea catalysts **296**, **297**. After noticing similarities between the Pictet–Spengler and the oxa-Pictet–Spengler reactions, Doyle and Jacobsen presented an extension of this strategy to reactions involving oxocarbenium ions.[225] This yielded an organocatalytic enantioselective version of the oxa-Pictet–Spengler reaction, enabling the access to enantio-enriched tetrahydropyrano-indoles **298** (Scheme 44).

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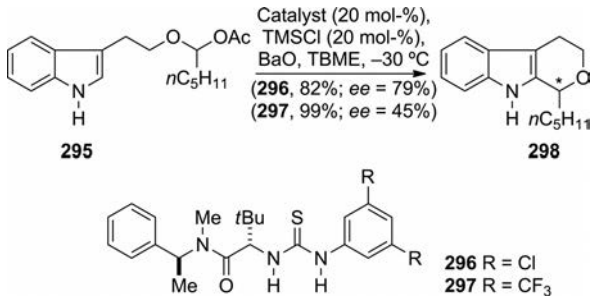


Scheme 44. Organocatalytic enantioselective oxa-Pictet–Spengler cyclization. Enantio-enriched 1,2,3,9-tetrahydropyrano[3,4-*b*]indoles.

Different catalysts and conditions were tested and no enantioinduction was observed for the condensation of tryptophol derivatives with various aldehydes, ketones, or their surrogates; however, the intramolecular cyclization of mixed acetal **295** provided good yields and moderate enantiomeric excesses after systematic optimization of the catalyst structure and the reaction conditions.

The starting acetal was prepared in 81% yield following Rychnovsky's reductive acetylation protocol.[226] TMSCl, added as a dehydrating agent, was found to accelerate the reaction, while protecting the indole nitrogen exerted a positive effect on optical and chemical yields.

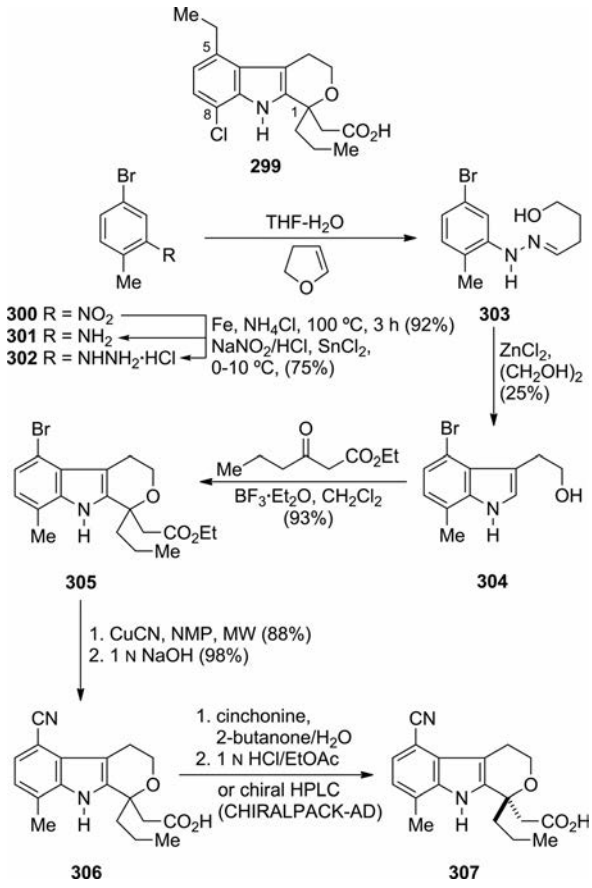
Other pyrano-heterocycles, having thiophene, pyrrole, benzofuran and benzo[*b*]thiophene aromatic components were similarly prepared, but chemical (20–35% conversion) and optical (16–55%) yields were rather low. Based on the experimental results, it was concluded that the thiourea catalyst participates in the rate-determining step (formation of the oxocarbenium ion) as well as in the *ee*-determining stage.

The group of Gopalsamy performed a high throughput screening (HTS) of various compound libraries with the aim of identifying a Hepatitis C virus (HCV) polymerase inhibitor. HCV is one of the most significant infections, with 150 million human carriers worldwide.[227] This represents a significant medical problem with negative economic implications.

Their efforts yielded pyrano-indole **299** as a lead (Scheme 45). This compound had an IC_{50} of 3.0 μM, being selective against human polymerase α ($IC_{50} > 100$ μM), calf thymus polymerase R ($IC_{50} > 100$ μM), helicase ($IC_{50} > 75$ μM), and HIV reverse transcriptase ($IC_{50} > 100$ μM). The compound was not cytotoxic in rapidly dividing and stationary Vero and Huh7 cells.[228]

This group prepared and tested a series of novel HCV NS5B RNA-dependent RNA polymerase inhibitors containing a pyrano[3,4-*b*]indole scaffold and established structure–activity relationships[229] which in turn lead to the discovery of compound **307**, as a highly potent and selective inhibitor that is active in the replicon system.

The pyrano-indole **307** was synthesized from the nitrobenzene **300**, which was reduced to the aniline **301** and transformed to the hydrazine **302** by diazotization with $NaNO_2$ and $SnCl_2$ reduction (Scheme 45). Reaction of the



Scheme 45. Synthesis of HCV-371 (**307**) as a potential RNA-dependent RNA polymerase inhibitor.

hydrazine with 2,3-dihydrofuran furnished alcohol **303**, which was cyclised with $ZnCl_2$ to the tryptophol **304**. Condensation of **304** with ethyl 3-oxohexanoate furnished 93% of the expected pyrano-indole **305**, which was transformed into nitrile-acid **306** (88%) by treatment with CuCN and saponification of the ester. The enantiomers were separated by resolution with cinchonine or by chiral HPLC yielding the *R*-enantiomer (**307**, HCV-371) with at least 99% enantiomeric excess.

Compound **307** displayed inhibitory activity against the NS5B enzyme derived from different HCV genotypes with IC_{50} values in the range 0.3–1.4 μM. It was demonstrated that it binds to the allosteric site of the enzyme.[230] The compound showed no inhibitory activity against a panel of human polymerases.

Unfortunately, HCV-371 failed to pass phase Ib of efficacy study, not demonstrating significant antiviral activity. This motivated the group of LaPorte to synthesize more complex analogs, of which **308** exhibited the most suitable properties.

Based on the previous experience and recognizing that the Fischer indolization approach was unreliable for the synthesis of large quantities of polysubstituted tryptophol, an alternative sequence to the key 3-hydroxypyrano-indole intermediate required for the synthesis of **308** was designed

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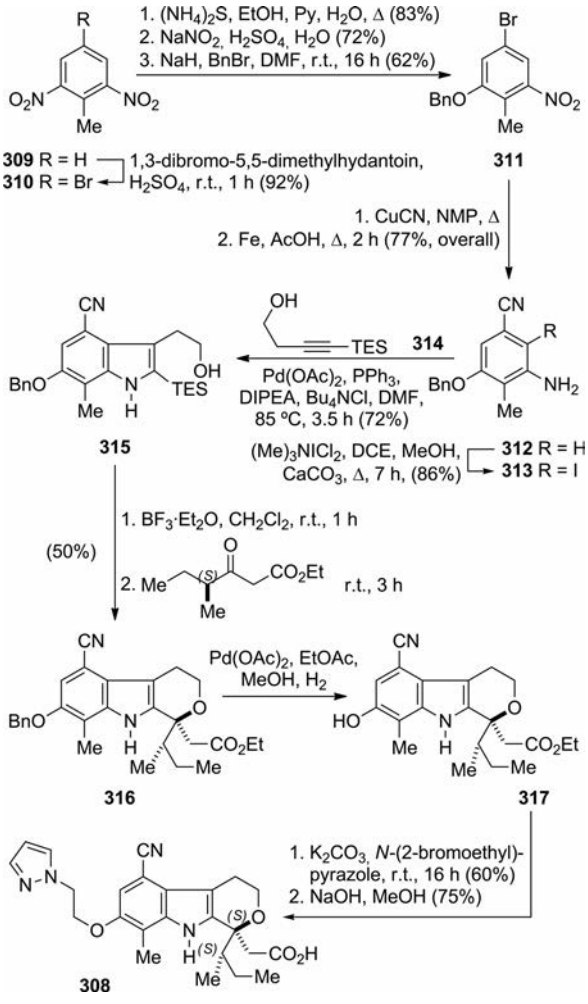
based on the use of Larock protocols[231] coupled to the Lewis-acid-catalyzed oxa-Pictet–Spengler reaction of the tryptophol with a suitable β-keto ester.[232]

To that end 2,6-dinitrotoluene (**309**) was brominated to **310** and then partially reduced to the monoaniline (83%), which upon diazotization and hydrolysis converted the amino moiety into a phenol (72%), which was ultimately protected as a benzyl ether giving **311** in 62% yield (Scheme 46). CuCN-mediated cyanation of **311** proceeded in low yield, but was followed by iron powder reduction of the remaining nitro group in AcOH, furnishing 36% of **312**. Iodination of **312** with benzyltrimethylammonium dichloroiodate exclusively afforded the required *o*-iodoaniline **313**.[233] Reaction of the latter with the TES-protected alkyne **314** gave 72% of TES-tryptophol **315** as the sole product.[234] An analogous sequence, employing Larock indole synthesis, was recently reported by Zheng and coworkers[68] in which a TES-tryptophol was prepared, the silicon group directing the subsequent oxa-Pictet–Spengler cyclization.



Scheme 46. Oxa-Pictet–Spengler synthesis of second generation pyrano-indole **308**, as RNA-dependent RNA polymerase inhibitors.

Following a previous observation suggesting that introduction of a (*S*)-*sec*-butyl substituent at the C1 position could effect a dramatic increase in cellular activity, **315** was subjected to the oxa-Pictet–Spengler cyclization with ethyl (4*S*)-methyl-3-oxohexanoate[235] yielding pyrano-indole **316** as a ca. 1:1 mixture of diastereomers.

This was catalytically debenzylated (**317**) and saponified for enantiomer resolution with cinchona alkaloids. Since this proved ineffective, the acid was re-esterified and separation was accomplished by chiral HPLC. Interestingly, heating with trimethyl orthoacetate in toluene in the presence of methanol and an acid caused concurrent esterification and racemisation,[236] which allowed recycling of the undesired enantiomer.

Final alkylation of the phenol moiety with *N*-(2-bromoethyl)pyrazole, followed by saponification of the ester, yielded the expected product **308**.

Conclusions

Aromatic heterocycles with the isochroman and related oxygen-bearing skeletons are scatteredly found in nature; however, many of them are bioactive, have important applications or have inspired the synthesis of bioactive compounds of interest.

The oxa-Pictet–Spengler cyclization is the oxygen variation of the better-known and widely used Pictet–Spengler tetrahydroisoquinoline and β-carboline synthesis, in which two components, an alcohol tethered to an aromatic ring and a carbonyl derivative, react usually under Lewis or Brønsted acid promotion to yield an oxacycle (typically a 2-arylpyran).

The general reaction scheme is now 75 years old, but its current name was coined in 1992. Despite still not being as popular as its sister reaction, during the last half decade or so, the oxa-Pictet–Spengler cyclization protocol has emerged as a highly useful and increasingly employed transformation with an identity of its own.

Many syntheses of natural and bioactive products bearing this core structure, as well as their analogs and derivatives, have been published during the last 5–7 years thanks to the use of this reaction. Research in this area was driven by curiosity, by the natural desire to acquire a more detailed map of the scope and limitations of the reaction, and also by the need of finding more efficient strategies towards highly complex bioactive natural products or compounds with pharmaceutical potential.

During this period, new insights into the reaction mechanism were acquired and new variations, and many extentions of the cyclization have been designed, including those yielding oxacycles with five and seven members and thus furnishing oxacycles attached to different aromatic moieties. Furthermore, new promoters have been developed and tested, some of them having into account green chemistry principles and environmental concerns.

In addition, the syntheses of 1-, 3- and 1,3-substituted chiral heterocycles was perfectioned and protocols includ-

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ing the oxa-Pictet–Spengler cyclization as key step were devised for the enantioselective elaboration of complex natural products and their derivatives. The stereochemical outcome of the cyclizations leading to some of these optically active compounds was studied, and reaction mechanisms for their rationalization have been proposed.

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. In view of the continuous development of the synthetic organic chemistry and its increasingly fruitful interactions with other branches of Science, it can be foreseen that the oxa-Pictet–Spengler cyclization will remain as a relevant synthetic tool for accessing 2-arylpyrans and related heterocycles.

Therefore, it is expected that novel syntheses of new members of the isochroman and related families will continue to be disclosed in the near future, having the oxa-Pictet–Spengler as one of their pivotal steps, while exploration of more elaborate, expedient and environmentally benign variations of this strategy will remain as the main challenge for the synthetic community.

Acknowledgments

The authors would like to acknowledge Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Agencia Nacional de Promoción Científica y Tecnológica (ANPCyT) and Secretary of Science and Technology, National University of Rosario (SECyT-UNR) for financial support.

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Received: February 26, 2011
Published Online: June 22, 2011

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