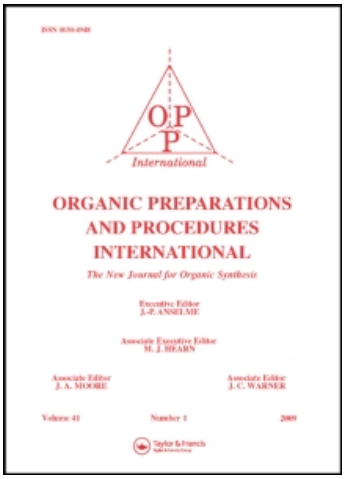

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DIBENZO[*bf*]OXEPINES: SYNTHESES AND APPLICATIONS. A REVIEW

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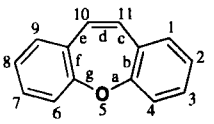
INTRODUCTION

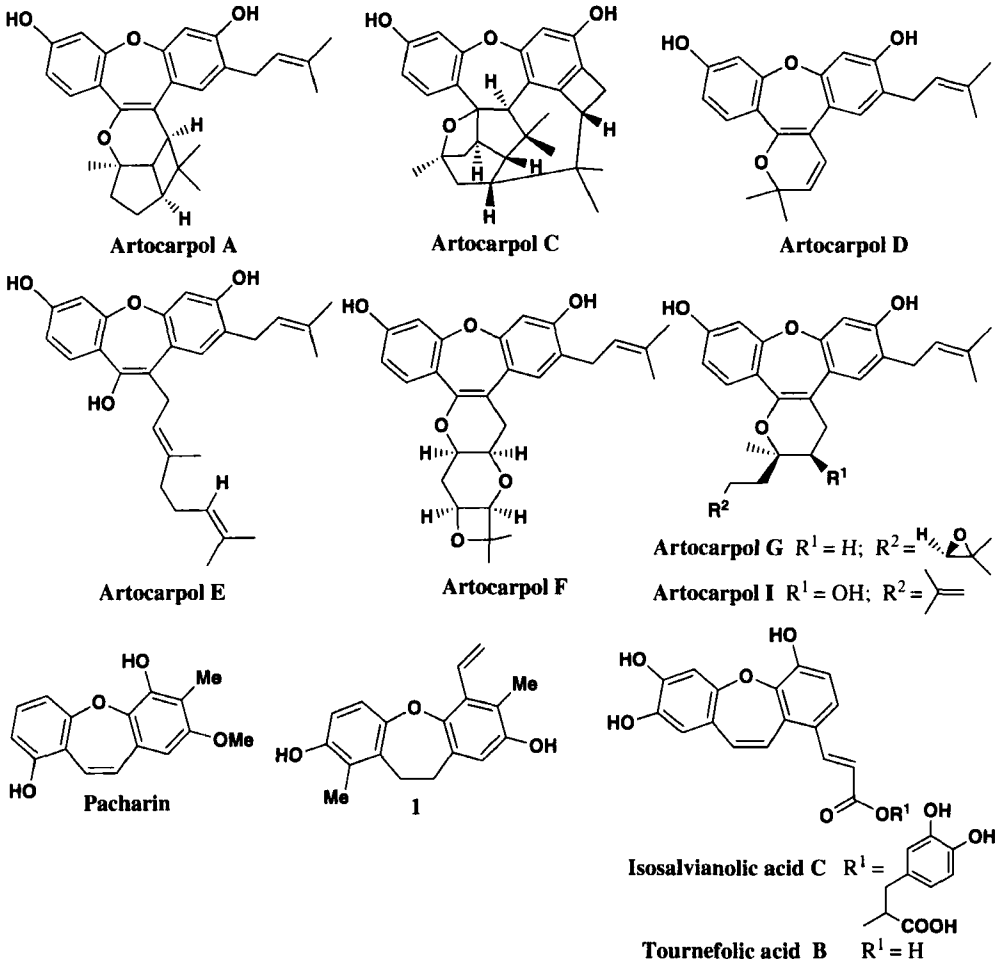
Since the initial discovery in 1911 by Pschorr and Knöffler of the first dibenzo[*b,f*]oxepine during nitration of α,β-diarylacrylic acids, this relatively little known scaffold has found synthetic utility in the construction of pharmaceutical drugs and an important number of bioactive synthetic products. Until quite recently, the long-standing problems associated with the synthesis of diarylethers kept the progress of research on dibenzoxepines rather limited since the most practical synthetic approaches relied on precursors containing the preformed ether linkage, therefore, restricting the molecular diversity of the target unit.



To date, very few surveys and monographs on this heterocyclic unit have been published,[1-9] and it is our aim to make a compilation of the most relevant information concerning this relatively underexploited heterocycle. At this point, it must be underlined that the present review is mainly focussed on dibenzo[*b,f*]oxepines and occasionally dibenzoxepino[*d*]heterocycles, and, therefore, more specific systems with other ring fusion (e.g. cularine alkaloids) will not be considered. For the purpose of this review, a first section describing the most relevant industrial applications over the last 30 years, including a brief outline of the outstanding dibenzo[*b,f*]oxepines developed so far, will be presented. The second section details the common synthetic pathways for the preparation of dibenzoxepines, focusing especially on novel approaches and practical methods appearing in the patent literature. For the reader's clarity, only one reference for a patent family is given in each case, preferably in the English language. In pertinent cases, whenever some precise information is not fully contained in a patent document, the appropiate references for the related patent family will be listed.

I. OCCURRENCE IN NATURE. TECHNOLOGICAL APPLICATIONS AND USES OF DIBENZO[*b,f*]OXEPINES

It is known that the oxepine ring, in its native as well as in its reduced form, occurs only in a small number of natural products, except in the closely related family of the cularine alkaloids. In the last three years, Lin and coworkers have increased the number of natural products containing this skeleton with the isolation of Artocarpols from the rootbark of *Artocarpus Rigida* (*Moraceae*) (*Scheme 1*).[10-13] In point of fact, Artocarpol G has exhibited a strong inhibition of the



Natural Products Containing Dibenzo[*b,f*]oxepine Nucleus

Scheme 1

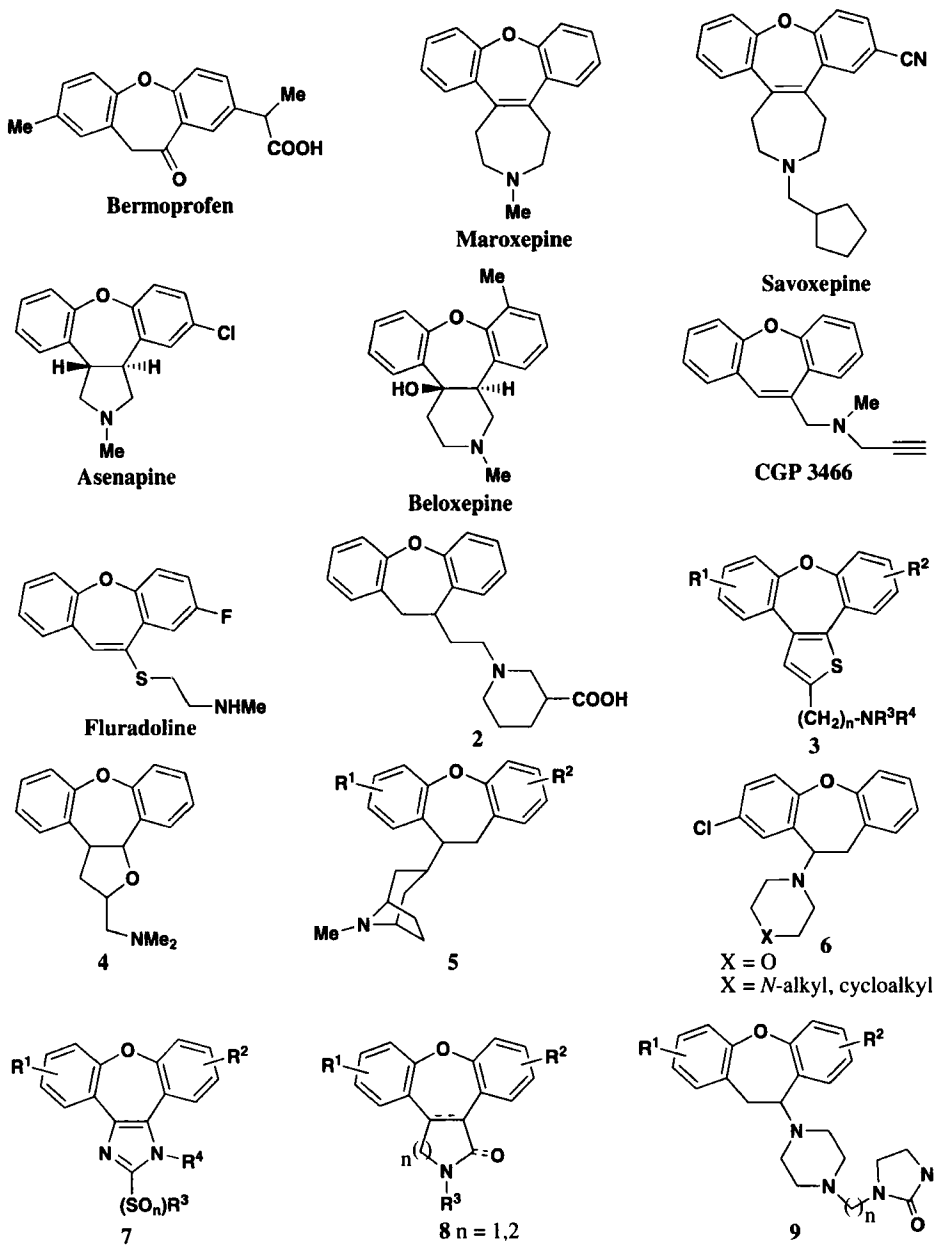
release of β-glucuronidase and histamine from mast cell degranulation,[13a] which constitutes important data for the development of potential leads with antiinflammatory activity. Other polyphenolic oxepines such as the depside isosalvianolic acid C and tournefolic acid B,[15] found in the stems of *Tournefortia sarmentosa* (*Boraginaceae*), exhibited a higher potency than the

hypoholesterolemic drug probucol,[15a] suggesting that they may indirectly protect LDL cholesterol from oxidative modification. Among the original caprices of nature, pacharin, isolated from the heartwood of *Bauhinia racemosa Lank*,[14] and the cytotoxic polyphenol **1**,[16] extracted from *Juncus effusus*, constitute the whole family of this unit discovered thus far.

Undoubtedly, one of the areas wherein the dibenzoxepines have been of research interest is the field of analgesics and antiinflammatories. In fact, bermoprofen (Dibenon®) is one of such compounds developed at Dainippon Pharmaceuticals in the 1980s as a non-steroidal anti-inflammatory drug (NSAID), twice as potent as indomethacin in inhibiting prostaglandine synthesis and exerting a strong antipyretic action (*Scheme 2*).[17-20] Despite the excellent results in the treatment of orthopedic post-operative pain in preclinical trials and its wide safety margin, ulcerogenic activity typical of other NSAIDSs and the availabity of other drugs of novel pharmacological profiles in the market,[21] led to cancellation of preregistration of bermoprofen in June 2000. Nevertheless, novel compounds with the dibenzoxepinone framework are currently being patented as intermediates for the preparation of sedatives and analgesics.[22] Likewise, the employment of dibenzoxepines as antiinflammatories has also been claimed in the preparation of a variety of dental and orthopedic prosthesis.[23]

The introduction of tetracyclic antidepressants such as mianserin in the 80s entailed a new era in the field of pharmacotherapy, providing a different outlook for the treatment of depression, compulsive behaviour and, in particular, schizophrenic psychoses.[24] In this new approach, based on the mechanism of action that remains on the monoaminergic hypothesis, dibenzoxepines have expanded the scope, resulting in optimization of both action and side effects. In the middle of the 1970s initial steps were taken by Akzo Nobel and Yamanochi Pharm. with nitrogenated heterocycles such as **8**, as dibenzoxepinopyrroles and pyridines in different levels of oxidation,[25,26] to be developed as antidepressants and sedatives (*Scheme 2*). Around the same time, Ciba-Geigy described CNS depressant compositions based on dibenzoxepino-10-piperazinylalkylimidazolidinones **9**.[27] Previously, a short patent by Tanabe Seiyaku Co. had covered the preparation of aziridine derivatives as CNS estimulators.[28] Later, Novartis developed maroxepin and savoxepin, later abandoned in phase I and II respectively, as two potent dopamine D_2 receptor antagonists that exhibited antipsychotic effects in preclinical studies with minimal extrapyramidal side-effects (*Scheme 2*).[29] Currently, Organon is working on asenapine, a promising compound in phase III which could be prescribed against psychotic disorders. Asenapine has a high affinity for dopamine ($D_{1\text{-}2}$), serotonin (5-HT_2) and α_1-adrenergic receptors and unlike other antipsychotics, it does not impair cognitive performance.[30] Likewise, another lead from Organon, beloxepin, is a selective norepinephrine uptake inhibitor (SNUI) that in 2001 was abandoned in phase III as a potential antidepressant (*Scheme 2*).[31]

On the other hand, the hypothesis emerged that drugs preventing neuronal apoptosis may slow or halt neurodegenerative diseases[3] (Parkinson's, Huntington's disease and ALS, mainly) progression has propelled the projection of novel dibenzoxepines such as CGP3466



Selected Dibenzo[b,f]oxepines with Industrial Applications

Scheme 2

(*Scheme 2*).[32] This Novartis candidate whose development is still in progress, has shown a neurorescuing effect in preclinical assays and is currently being investigated for the treatment of motoneuron diseases.[33] Very recently, 10-aminoalkyldibenzo[*b,f*]oxepines closely related to CGP3466 have been utilized at Nordic Bioscience for the preparation of compositions for the modulation of IAMT activity and prevention of autoimmune response/disease in mammals,

which illustrates the broad range of activity of CGP3466 as a molecular lead.[34] Tetracyclic systems of this type are not only related to CNS diseases, in fact, the earliest synthesized dibenzoxepino-fused heterocycles, such as imidazoles **7**, were originally designed as antiarthritics at DuPont.[35]

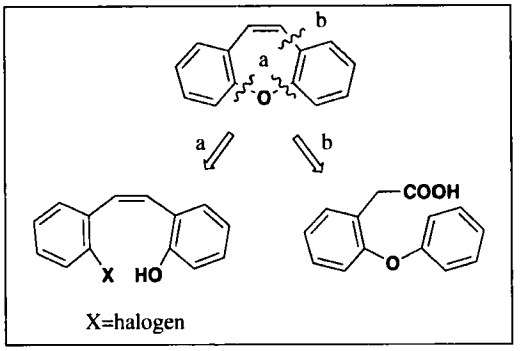
Fluradoline is another example of a dibenzoxepine often applied as a useful analgesic, and, at the same time with antidepressant activity, based on blocking the reuptake of norepinephrine and serotonin. However, the displacement of modern antidepressants toward different pharmacological profiles meant that fluradoline was not exploited extensively in such directions (*Scheme 2*).[36]

Other promising dibenzoxepines encompassed by the patent literature are noteworthy to mention, such as piperidine **2**, claimed as a clinically useful antiinflammatory for the treatment of neurogenic pain.[37] 1-Thiadibenzoazulenes **3** are potent inhibitors of cytokynes and other inflammation mediators such as interleukin 1 (IL-1), which makes them potentially specific analgesics.[38] A structurally related furan derivative **4** has exhibited moderate binding affinity for 5-HT2C receptor, and is claimed as a therapeutic agent for the prevention of CNS and cardiovascular disorders (*Scheme 2*).[39] Neurogen Corp. provides novel diazabicyclo compounds **5**, inhibitors of dopamine D2 receptors, with excellent properties to treat extrapyramidal effects of classical neuroleptic antipsychotics.[40] 9-Piperazinyldibenzoxepines **6** have aroused considerable interest, as proved by a patent of BASF Aktiengesellschaft, that claims their use as new ready-to-use insecticides, acaricides and nematocides or as potentiators of other common herbicides and plaguicides (*Scheme 2*).[41] Finally, the relevance of research in dibenzo[*b,f*]oxepines is disclosed by a diverse number of applications such as glutamic acid receptor blockers,[42] intimately involved in the treatment of nervous diseases or nerve degeneration, respiratory tract hypersensitiviness inhibitors as novel antiasthmatics,[43] antihistaminics,[44] antiestrogenics,[45] antioxidants,[46] neuroleptics,[47] or even as photoreceptors.[48]

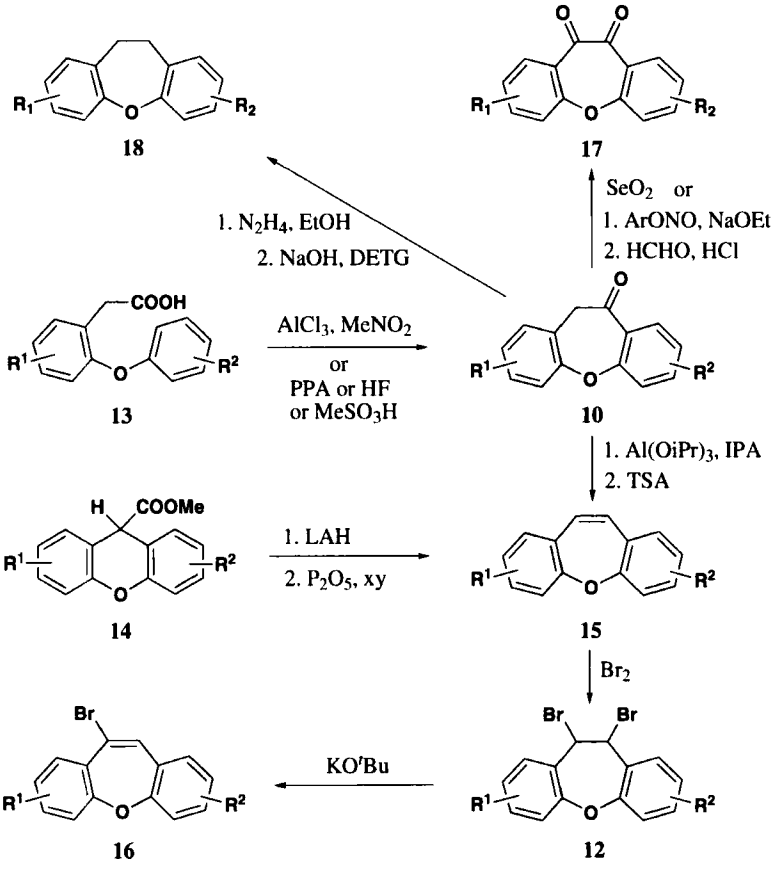
II. SYNTHESIS OF DIBENZO[*b,f*]OXEPINES

1. General Considerations

Despite the demands of medicinal chemistry investigations, a limited number of approaches to the synthesis of dibenzoxepines have been developed to date. Most methods fall within one of the two classical synthetic pathways; a) intramolecular C-O bond formation via Ullmann-ether reaction or S_NAr, or b) cyclodehydration of intermediates with a preformed diaryl ether framework. Many of these procedures involve strongly acidic conditions, longer reaction times and yields are markedly dependent on the nature of the aromatic substituents. In fact, to the best of our knowledge, all the revised patent literature relies on the original methods for the preparation of previously reported 10- or 11-functionalized dibenzoxepines to construct complex *d*-fused derivatives.



In practice, dibenzo[*b,f*]oxepin-10(11*H*)-ones **10**, 10- and/or 11-hydroxysubstituted derivatives **11** or bromo analogues **12** have served as the points of departure for most of the synthetic pathways carried out so far. Selected key transformations are depicted in *Scheme 3*.



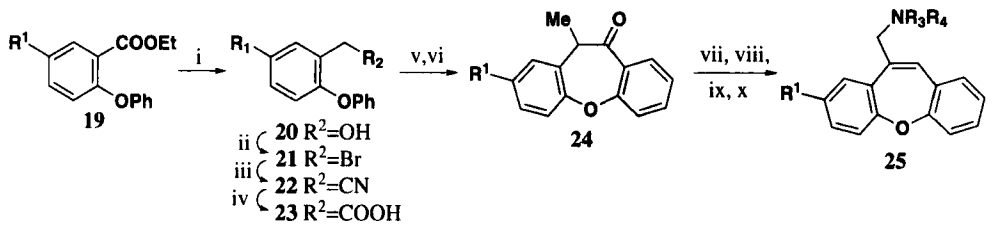
Common Transformations of the Dibenzo[*b,f*]oxepine Framework

Scheme 3

Friedel-Crafts acylation of *o*-phenoxyphenylacetic acids **13** in nitromethane or cyclodehydration in HF, $MeSO_3H$ or, more commonly, in PPA allows for easy access to the dibenzoxepine

nucleus, and constitutes the most straightforward approach.[49] Dibenzo[*b,f*]oxepines were also originally prepared by Meerwein-Pondorff-Verley reduction of dibenzoxepinones and dehydration with TSA of the resulting alcohol. Alternatively, dibenzoxepines were prepared by Wagner-Meerwein rearrangement of xanthene-10-methoxycarbonyl **14** in the presence of P_2O_5. Dibromination of dibenzo[*b,f*]oxepines **15** occurs upon treatement with bromine.[50] Subsequent dehydrobromination using an alkoxide-type base led to 10-bromodibenzo[*b,f*]oxepines **16**. Useful transformations at C-10 are based on nucleophilic displacement of bromo atoms, such as cyanation and attack of Grignard reagents. Oxidation of oxepinones **10** with selenium dioxide or by means of an oximation-formylation sequence,[44] provides diketo derivatives **17** quantitatively, which are key products for the heterocyclization of dibenzoxepines.[4] Finally, reduction of the keto group in dibenzoxepinones **10** to yield 10,11-dihydrodibenzoxepines **18** is easily carried out by Wolff-Kishner reduction.[51]

The synthetic pathway detailed below illustrates the synthesis of 10-(aminomethyl/ethyl)oxepines **25**, taking advantage of the previously described classical approach starting from a phenoxybenzoic acid (*Scheme 4*).[49b] A common feature of most of these

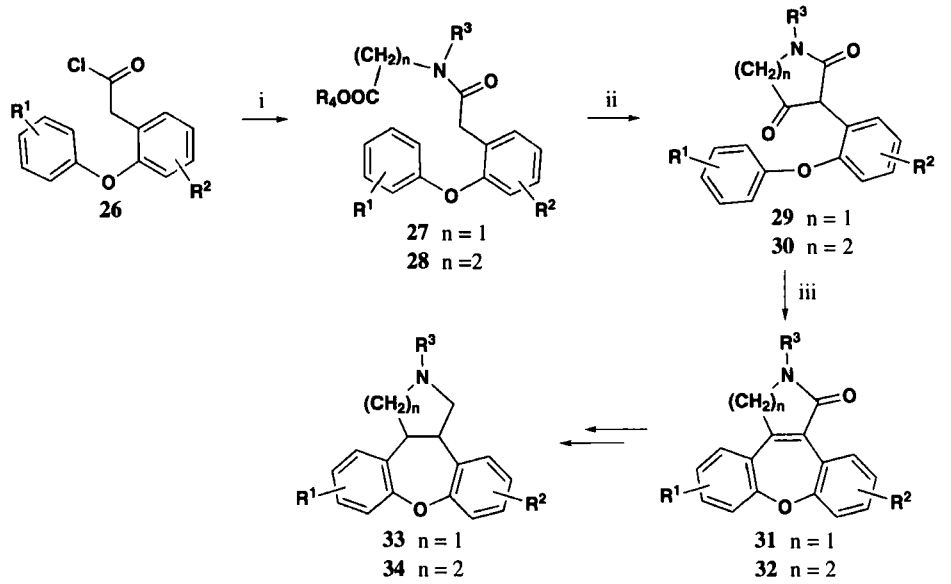


i) LAH, Et_2O, 15°C; ii) PBr_3, PhH, 55°C; iii) KCN, EtOH, reflux; iv) KOH, EtOH; v) PPA, 90°C; vi) a) $NaNH_2$, PhMe, reflux; b) MeI, reflux; vii) $SOCl_2$, PhH, Py, 50°C; viii) KO^{t}Bu, PhMe, reflux; ix) NBS, CCl_4, reflux,*hv*; x. HNR^3R^4, PhH, reflux

Scheme 4

sequences is the concatenation of high yielding, well-known tranformations to effect the homologation of the benzylic position of the starting phenyl ether *via* a bromination/cyanation/hydrolysis sequence (**21**→**22**→**23**), in such a way that, at best, the overall yield is low, thus constituting an expensive approach in terms of chemical/atom economy. In an effort to shorten the sequence for the homologation, when synthetic necessities find suitable commercial sources, homologation of benzoic acids may be conveniently by-passed by synthesizing the homoacids from acetophenones by the Willgerodt reaction, as will be illustrated in the following sections.[52a]

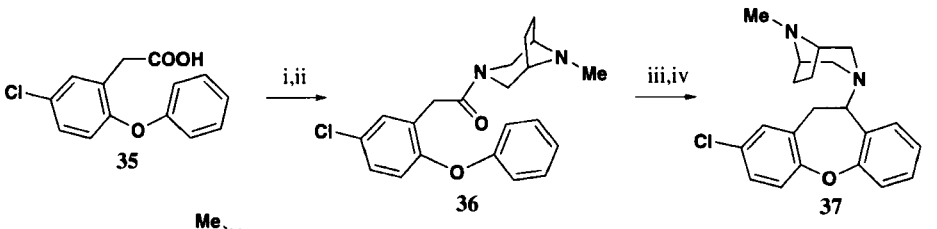
A major limitation of this approach is the necessity associated with bearing a reactive functionality at the C-10 or C-11 position for further manipulation. However, if such functionality is suitably transformed, as in the synthetic path reported by van der Burg at Akzona Inc., it can lead to asenapine-like dibenzoxepinopyrrolidine and pyperidine structures **33** and **34**. As shown in *Scheme 5*, starting from acyl chloride **26**, two sequentially conducted intramolecular cyclizations provided dibenzoxepine derivatives **31** and **32**, which were finally reduced to target

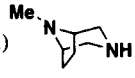


i) $R^3NH(CH_2)_nCOOR^4$, TEA, DMF; ii) KO^{t}Bu, PhMe, 0°C; iii) PPA, 125°C

Scheme 5

3 and **34**.[52b] In certain cases, as in the synthesis of the potential neuroleptic **37**,[40] transformation of the precursor phenoxyaryl acetic acid **35** into the diazabicyclo compound **36** yields a reactive enough intermediate to undergo a straighforward cyclodehydration by the action of $POCl_3$ (*Scheme 6*).

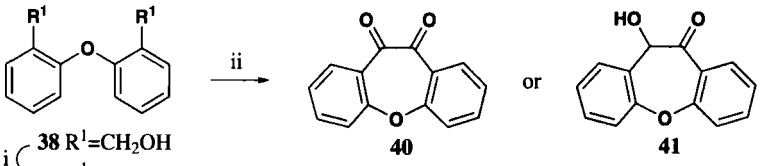


i) $SOCl_2$, reflux; ii)  , DIPEA, 0°C; iii) $POCl_3$, reflux; iv) $NaCNBH_3$, HOAc, EtOH

Scheme 6

Interestingly, a straightforward and alternative mode of cyclization to form 10,11-dihydro-dibenzo[*b,f*]oxepin-10-ones which avoids the common methods discussed above, involves an intramolecular benzoin condensation of a preformed dialdehyde **39**. As originally defined by Wong *et al.* (*Scheme 7*), treatment with potassium cyanide of aldehyde **39**, easily obtained by Jones oxidation of an appropriate diol **38**, yields diketone **40** or hydroxy derivative **41** depending on the reaction time.[53]

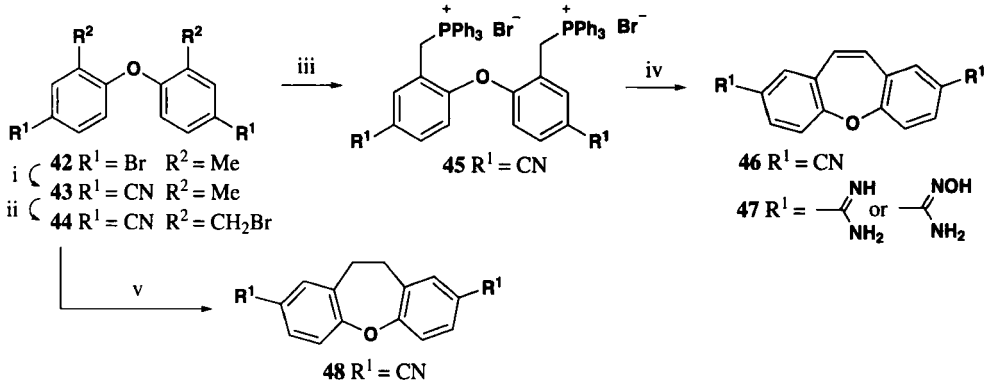
A strategy reported occasionally concerning an alternative dibenzoxepine ring closing method is based on an intramolecular Wittig reaction on dibromo diphenyl ethers, and enables the preparation of molecules with an important degree of functionalization. As an illustration,



i) CrO_3, H_2SO_4, Me_2CO, 0°C; ii) KCN, DMSO (N_2)

Scheme 7

this method was applied by Iyer to the synthesis of 2,8-diamidinodibenzo[*b,f*]oxepines **47**, which showed antileishmanial *in vitro* activity (*Scheme 8*).[54] As such, easily obtainable diphenyl ether **42** was subjected to bromination at the methyl groups after manipulation of peripheral functionalities, and transformed into the triphenylphosphorane **45**, which was oxidized to the desired oxepine **46** by oxygen. It is noteworthy that dibromo derivative **44** successfully underwent monometal halogen exchange and intramolecular alkylation to the dihydrodibenzoxepine **48**,[55] but disappointingly, all efforts to dehydrogenate the system did not work.



i) CuCN, py, 130°C; ii. NBS, Bz_2O, CCl_4, *hv*; iii) TPP, DMF, 160°C; iv) a) PhLi, THF, 0°C; b) O_2, PhH; v) PhLi, THF, 0°C

Scheme 8

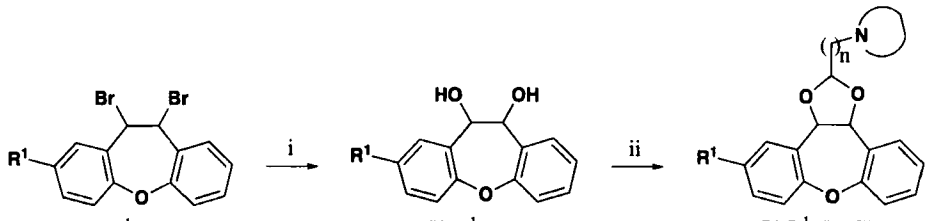
2. Synthesis of Dibenzo[*b,f*]oxepines from a Preformed Central Core

Transformations of the dibenzo[*b,f*]oxepine nucleus are well represented in the literature and the versatility of this approach has been demonstrated in a number of eminent examples, providing efficient routes to attractive tetracyclic systems.

Thus, Monforte transformed dibromodibenzoxepines **49** to the *cis*-hydroxyderivatives **50** by treatment with silver acetate (*Scheme 9*).[56] The resulting diols were reacted with suitable haloaldehyde acetals and aminated to yield 2-substituted dioxolanes **51**, which showed a modest antispasmodic activity.

Metal-halogen exchange occurs quantitatively with 10-bromodibenzoxepine **52**, and this has been employed in the successful synthesis of analogues **53-55** of the atypical antipsychotic clozapine (*Scheme 10*).[57] Earlier, Boris *et al.*, had envisioned the preparation of one deriv-

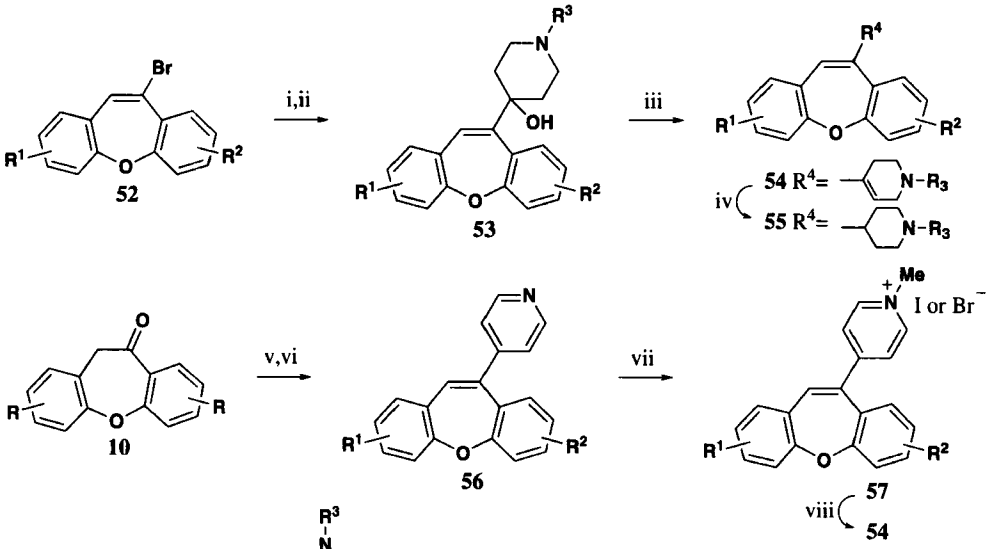
ative of **54** as a topic antiinflammatory reversing the eletronic nature of the functionalities on the starting products, *via* attack of lithiopyridine on dibenzoxepinone **10** and dehydration, followed by quaternization of pyridine ring and partial nuclear reduction (*Scheme 10*).[58]

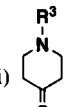


49 R^1=H, Cl **50** R^1=H, Cl **51** R^1=H, Cl (n = 1,2)

i) CH_3COOAg, HOAc, 80°C; ii) $XCH_2CH(OEt)_2$, 155°C (X=Cl, Br); iii) *sec*-amine, PhMe, 110°C

Scheme 9

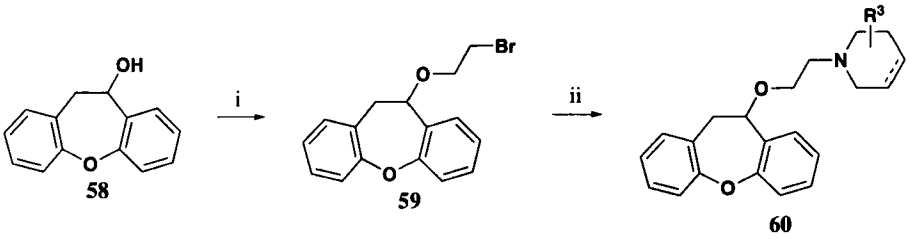


i) *n*-BuLi, Et_2O, -78°C; ii)  , -78°C → rt; iii) HCl, EtOH, rt; iv) H_2, PtO_2, EtOH; v) PyLi, -45°C; vi) $MeSO_3H$ or TFA, reflux; vii) MeI or MeBr, ACN, reflux; viii) $NaBH_4$, MeOH, 0°C

Scheme 10

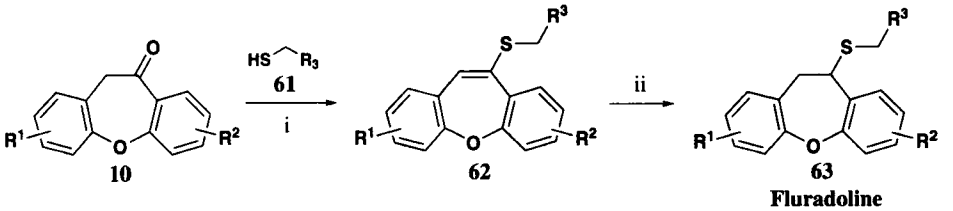
Lewis acid-catalyzed alkylation of the hydroxy group of 10,11-dihydrodibenzo[*b,f*]oxepin-10-ol **58** leads to useful branched dibenzoxepines **59** (*Scheme 11*), incorporated as radicals in a number of complex structures **60**[59] or targeted as potential drugs.[37]

Another example of simple manipulations of the dibenzo[*b,f*]oxepine nucleus leading to bioactive derivatives is exemplified by the synthesis of fluradoline (*Scheme 12*).[60] Thus, Ong *et al.*, carried out the direct reaction of mercaptoacetic derivatives **61** with dibenzoxepinones **10** under dehydrating conditions which, after reduction with magnesium metal, gave the desired tetrahydro derivatives **63**, thus avoiding the preliminary manipulations of the keto group of the substrate illustrated in *Schemes 10* and *11*.



i) BF_3•OEt_2, 2-bromoethanol, PhH, 10°C; ii) K_2CO_3, HNR^1R^2, DMF, 45°C

Scheme 11

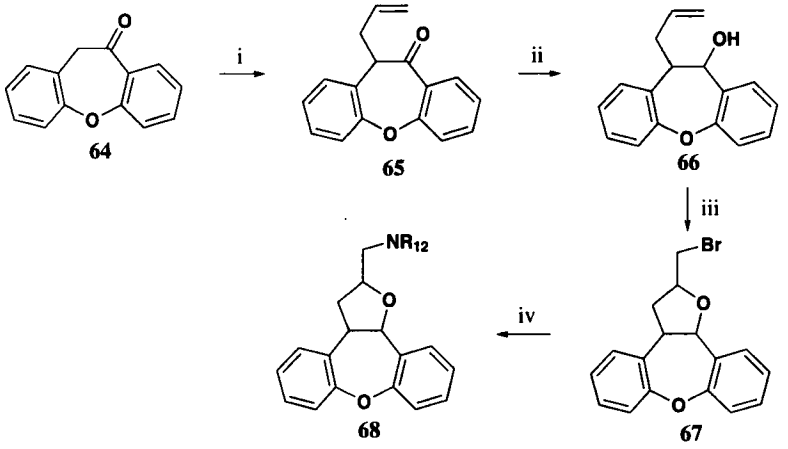


i) BF_3•OEt_2, HOAc, 65°C; ii) Mg, MeOH

R^1 = H; R^2 = 3-F; R^3 = CH_2NHMe

Scheme 12

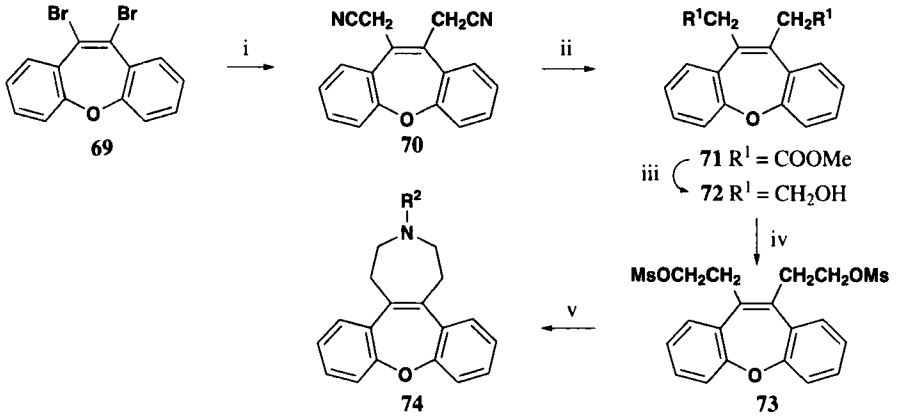
Intramolecular cyclization strategies to generate fused heterocycles at the C_{10}-C_{11} bond are not numerous. Workers at Janssen Pharmaceutica explored successfully the access to dibenzofurooxepines **68** *via* 11-allyl-dibenzoxepinone **65** (*Scheme 13*).[39] Alkylation of the versatile dibenzo[*b,f*]oxepin-10(11*H*)-one **64** with allyl bromide and reduction led to **66**, which was cyclized in a sequential process during the bromination step, affording the furan **67**. Direct reaction with secondary amines under pressure completed the sequence to the desired tetracycle.



i) 3-bromopropene, K^{t}OBu, ^{t}BuOH, 80°C; ii) $NaBH_4$, EtOH, 60°C; iii) Br_2, py, CCl_4, 0°C; iv) $HNR^1{}_2$, ΔP, DMSO, $CHCl_3$, 65°C or $HNR^1{}_2$, 120°C

Scheme 13

Among several dibenzoxepines reported, Blattner and Storni claimed the formulation of novel azatetracyclic **74** tranquilizers (*Scheme 14*).[61a-b] The construction of the azaheterocyclic ring was approached by converting a series of the known dibromodibenzoxepine **69** into the acetonitrile derivatives **70** and further transformation into the diol **72**. Activation of the diethanolic functionalities by mesylation and double consecutive amination with suitable secondary amines completed the sequence to the azepine system in quite good yield.



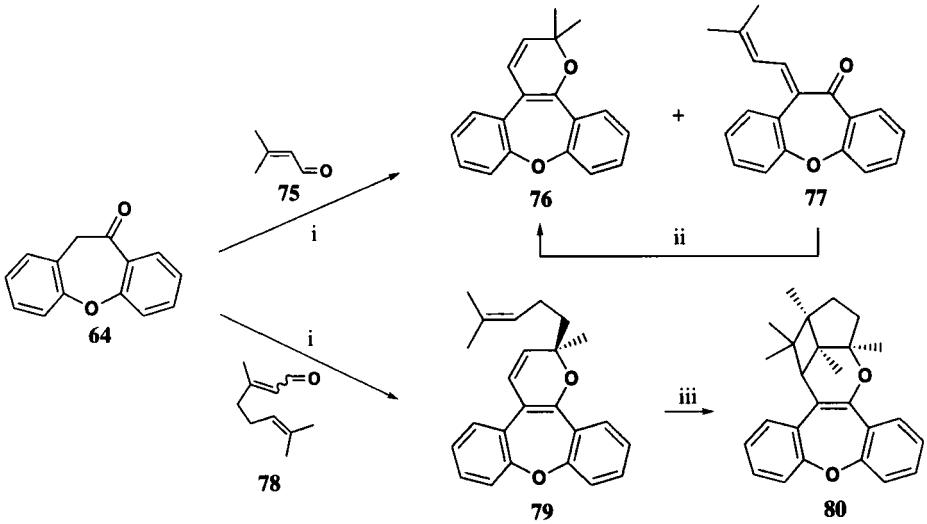
i) NaH, ACN, reflux; ii) HCl(g), MeOH, H_2O; iii) LAH, Et_2O, 0°C; iv) MsCl, py; v) HNR^2_2, DIPEA, EtOH, reflux

Scheme 14

Very recently, a straightforward transformation of preformed dibenzo[*b,f*]oxepin-10(11*H*)-one **64** provided the first synthesis of the polycyclic ring systems of artocarpols A and D. Indeed, when precursor **64** was reacted with senecialdehyde **75**, a mixture of 2*H*-pyran derivative **76** and unsaturated ketone **77** was obtained. A slight modification of the reaction conditions applied to the latter ketone provided the target artocarpol D analogue **76**. In a similar fashion, condensation of oxepinone **64** with citral **78** afforded the corresponding pyran **79**, which on subsequent irradiation underwent cyclization, thus forming the polycyclic system of artocarpol A **80** (*Scheme 15*). The authors speculated that the mechanism for the formation of the 2*H*-pyran ring, involved nucleophilic attack of the enol form of oxepinone to the corresponding imines of the aldehydes.[61c]

3. Synthesis of Dibenzo[*b,f*]oxepines by Formation of the C-O Biaryl Ether Bond

The introduction of a specific substitution pattern on the dibenzoxepine nucleus usually involves a formidable problem, since the commercial availability of phenoxybenzoic acids is rather limited and their functionalization often lacks regioselectivity. In spite of the recent advances in the chemistry of the formation of the biaryl ether linkage,[62] a vast majority of the revised methods based on the diaryl ether Ullmann reactions or the aromatic nucleophilic substitution of fluoroarenes by phenols/phenoxides to implement direct closure of the dibenzoxepine ring.



i) allylamine (6 eq.), $MgSO_4$, THF, reflux; ii) allylamine (3 eq.), $MgSO_4$, THF, reflux; iii) benzophenone, PhH, *hv*

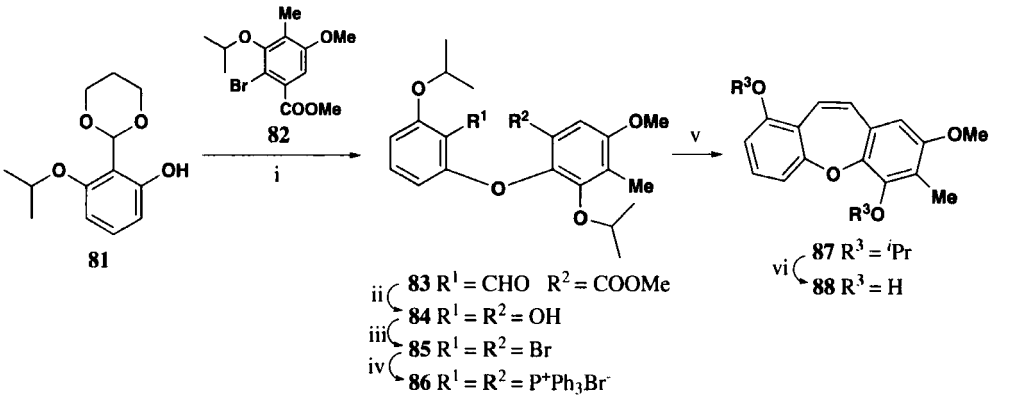
Scheme 15

a. Formation of the Dibenzoxepine Nucleus via the Ullmann-ether Reaction

Particularly appealing aspects of the Ullmann-ether reaction are the simplicity in operation and inexpensive copper reagents employed. Copper(II) oxide is often the reagent of choice, in substitution to the classical Ullmann reaction conditions that applied mixtures of metallic copper with copper(I,II) oxides. Application of the latter reagents and, to a lesser extent, other copper complexes, permits accomplishment of this transformation at moderate temperatures and expansion of the range of functionalities present on the substrate, which are traditionally the main drawbacks of the Ullmann reaction.

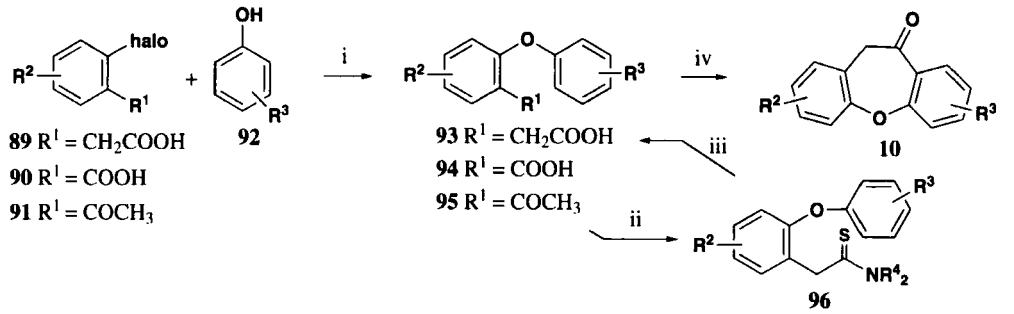
The synthesis of pacharin by Sargent illustrates a classical approach to a dibenzoxepine derived from the condensation of rather elaborated phenol and bromoarene counterparts **81-82** mediated by CuO (*Scheme 16*).[14a] Interestingly, further interconversion of functional groups led to the *bis*-ylide **86**, which on exposure to an oxygen atmosphere and subsequent deprotection step afforded pacharin **88**.

In an early report, Ehlers, at Hoechst-Russell Pharmaceuticals, accomplished the preparation of a variety of polyfunctionalized dibenzoxepinones **10** as precursors of more complex dibenzoxepines (*Scheme 17*).[63] As shown in the preceding sections, the initial step involved phenoxylation by Ullmann coupling of *o*-halosubstituted -benzoic, -phenylacetic acids or –acetophenones mediated by copper(II) oxide, -acetate or -chloride and subsequent cyclodehydration under some of the conditions cited previously. The notion of using *o*-haloacetophenones **91** as starting materials is particularly appealing since the corresponding phenoxyacetic acids **93** may be synthesized using the Willgerodt-Kindler protocol **95→96→93**, avoiding the cumbersome and low-yielding cyanation/hydrolysis sequence often used for the homologation step.



i) a) CuO, K_2CO_3, Py, reflux; b) H_3O^+, THF; ii) LAH, Et_2O, 0°C → rt; iii) PBr_3, DCM, py; iv) a) TPP, DMF; b) LiOMe, MeOH; v) O_2; vi) BCl_3, DCM, -10°C → 0°C

Scheme 16

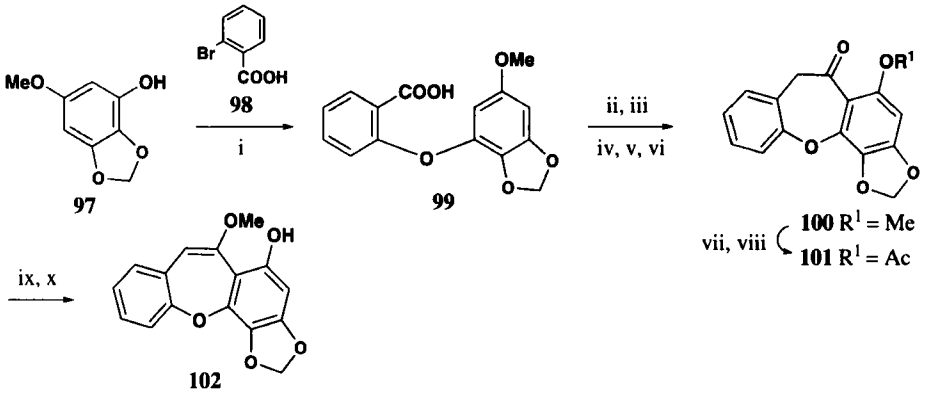


i) CuO or $CuAc_2$ or $CuCl_2$, KOH, reflux; ii) S_x, HNR^4_2; iii) H_3O^+; iv) $ZnCl_2$ or $AlCl_3$ or PPA, solvent, 40-80°C

Scheme 17

Okita prepared the oxepine **102**, a remarkably potent antioxidant isolated from *Saccharomyces cerevisiae*, by Ullmann coupling between phenolic component **97** and 2-bromobenzoic acid **98** using a mixture of metallic copper and copper(I) iodide substoichiometrically (*Scheme 18*).[64] Homologation of the resulting benzoic acid **99** to the corresponding phenylacetic derivative is conducted via the cyano derivative, through a well-established protocol broadly applied in the chemistry of dibenzoxepines. Subsequent intramolecular Friedel-Crafts acylation, accomplished by treatment with a mixture of TFAA and $BF_3{\cdot}OEt_2$, turned out to be a delicate task as a result of the unstable nature of the intermediates.

Ong *et al.* prepared a series of hydroxylated metabolites of fluradoline starting from phenoxybenzoic acids prepared in moderate yields *via* Ullmann coupling mediated by mixtures of copper(I) chloride/iodide and copper powder. In this report, they noted the difference in reactivity toward cyclodehydration under the standard Friedel-Crafts conditions among the phenylacetic acids prepared, rationalizing this fact by postulating the formation of stable quinoidal intermediates after decarbonylation of the initially formed aluminum complex.[65]



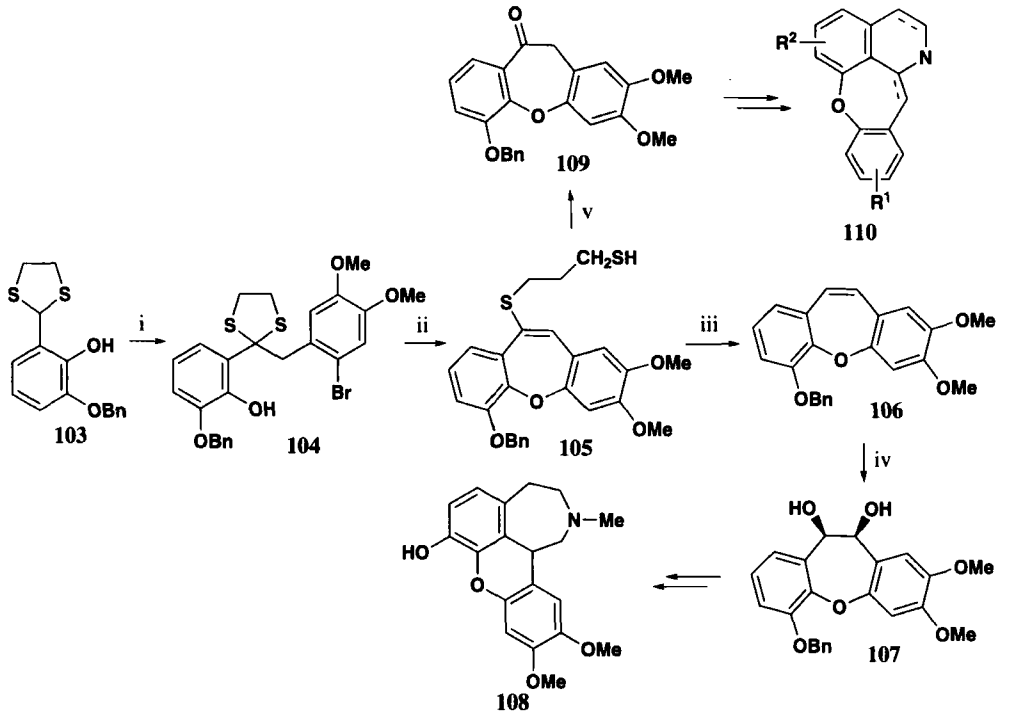
i) CuI, Cu (30 mol%), K_2CO_3, NMP, 120°C; ii) $NaBH_4$, BF_3•OEt_2 , THF, 0°C → rt; iii) PBr_3, DCM, 0°C; iv) NaCN, DMSO, 80°C; v) NaOH (aq), EtOH, THF, 110°C; vi) TFAA, BF_3•Et_2O, DCM, 0°C; vii) BBr_3, DMS, DCM, 0°C; viii) KO'Bu, AcCl, THF, -78 → -20°C; ix) $CH(OMe)_3$, CSA, MeOH, 80°C; x) $NaHCO_3$ (aq), MeOH

Scheme 18

An alternative protocol is exemplified by Burden's synthesis of the constrained 1,8-disubstituted-10,11-dihydrodibenzoxepin-10-ones, prepared as modulators of $GABA_A$ receptor with potentially anaesthetic activity.[66] Coupling of chloroarenes with sodium phenolates occurred preferentially over premature dehalogenation through the so-called substitutive reduction, by using copper(I) chloride catalysis to provide the desired diaryl ether. It is of interest to note that few methods start from such chloroarenes, due to the broadly accepted lack of reactivity of these substrates under Ullmann reaction conditions. In this context, investigators at Novartis described the preparation of 10-aminoaliphatyldibenzo[*b,f*]oxepines by reaction of chloroarenes preferably with a mixture of copper and copper(I) iodide.[32]

Only in certain cases, probably due to the strong activation of the aromatic ring bearing the chloro substituent, copper powder may be utilized in the absence of copper(I) salts, as proven by Hino (Dainippon Pharmaceutical) who prepared hydroxy/carboxy derivatives of bermoprofen applying such conditions.[20] These results highlight the importance of evaluating the possibility of applying activated chloroarenes instead of the less available iodide or bromide analogues.

In a series of reports, Castedo and Domínguez described an elegant route to the sole member of the dibenzopyranazepines alkaloids (-)-clavizepine **108** based on a dibenzoxepinediol **107** as main intermediate (*Scheme 19*).[67c-d] Alkylation of an appropriate 1,3-dithiane with a benzylic halide to give **104** was followed by an intramolecular Ullmann condensation driven by copper(II) oxide. Reduction of the dithioketal and hydroxylation of the resulting alkene by action of osmium yielded the target diol **107**. Further reaction on **107** involving ring contraction and heterocyclization led to the obtention of clavizepine in 17% overall yield (9 steps). Similar chemistry involving dithiane-type intermediates **104** allowed for the direct preparation of dibenzoxepinones **109** and their conversion into a variety of cularine alkaloids **110**.[67a-b]

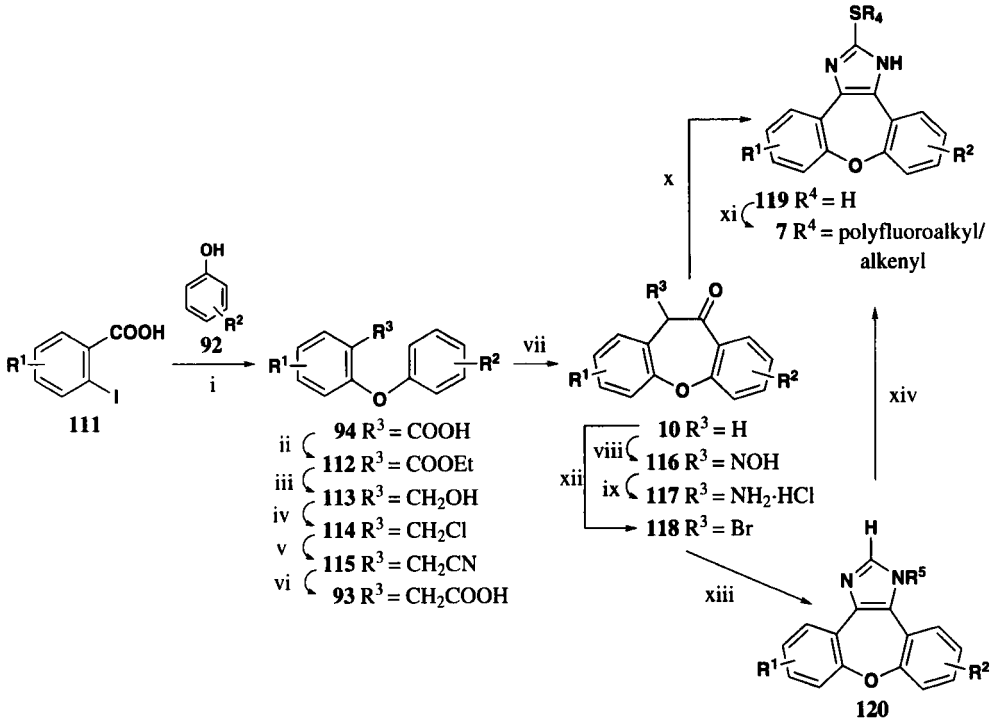


i) a) *n*-BuLi, THF, -78 → 0°C; b) $ArCH_2Cl$, THF; ii) CuO, K_2CO_3, py (argon), reflux; iii) Raney Ni, Me_2CO, 70°C; iv) OsO_4, THF, NMMO; v) HCl, EtOH, reflux

Scheme 19

Only in a very few cases, was the classical Ullmann reaction been performed using solely the mediation of copper powder.[35,68] A case in point is illustrated by the synthesis of anti-inflammatories **7** at Dupont, featured by an initial phenoxylation of *o*-iodobenzoic acids in the presence of copper powder (*Scheme 20*).[35] It must be noted that in such cases, enhancement of the reactivity of the haloarene is required; more reactive aryl iodides are necessary to obtain acceptable yields and high conversion. In practice, in the preparation of imidazoles **7**, after the initial homologation steps of phenoxybenzoic acid **94**, heterocyclization to the imidazole ring from dibenzoxepinone **10** was achieved via an oximation/reduction/heterocyclization sequence **116→117→119**, and ultimately by direct reaction of the intermediate thiol **119** with perfluoro-ralkenes under pressure. An alternative procedure involves the preparation of the imidazole ring **120** by conventional methods, deprotonation of the protected imidazole and reaction with disul-fides, alkenyl halides or sulfonic anhydrides.

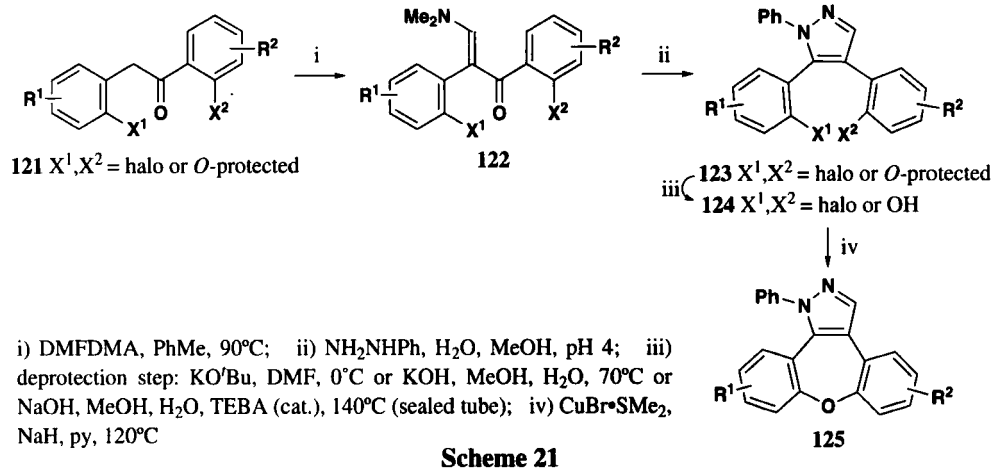
Aside from the reagents and strategies previously mentioned, in the author's laboratories a direct method to heterocyclofused dibenzoxepines **125**, based on the postponement of the C-O bond generation, which constitutes a scarcely applied route, was recently developed. Concretely, this synthetic pathway required the preparation of halohydroxy diarylpyrazoles **124**, efficiently obtained starting from accessible deoxybenzoins **121** subjected to aminomethylenation and



i) K_2CO_3, Cu, $PhNO_2$, 150°C; ii) EtOH, H_2SO_4, reflux; iii) LAH, Et_2O, reflux; iv) $SOCl_2$, py, 30°C → rt; v) NaCN, H_2O, EtOH, reflux; vi) KOH, EtOH, reflux; vii) PPA, 125°C; viii) a) $NaNO_2$, H_2O, H_2SO_4, MeOH, rt; b) Et_2O, HCl; ix) H_2(g), PtO_2 (cat.), THF; x) KSCN, HOAc, reflux; xi) ^{i}PrNH, $CF_2 = CF_2$, 50°C, DP; xii) bromination in HOAc; xiii) a) $HCONH_2$; b) protection of imidazole; xiv) a) *n*-BuLi, THF, -78°C; b) R^4SSR^4 or R^4SCl or $(R^4SO_2)_2O$

Scheme 20

subsequent regioselective heterocyclization with hydrazines in a simple and high yielding protocol (*Scheme 21*).[69] Suitable protective group removal and Ullmann etheration in the presence of



i) DMFDMA, PhMe, 90°C; ii) NH_2NHPh, H_2O, MeOH, pH 4; iii) deprotection step: KO^{t}Bu, DMF, 0°C or KOH, MeOH, H_2O, 70°C or NaOH, MeOH, H_2O, TEBA (cat.), 140°C (sealed tube); iv) CuBr•SMe_2, NaH, py, 120°C

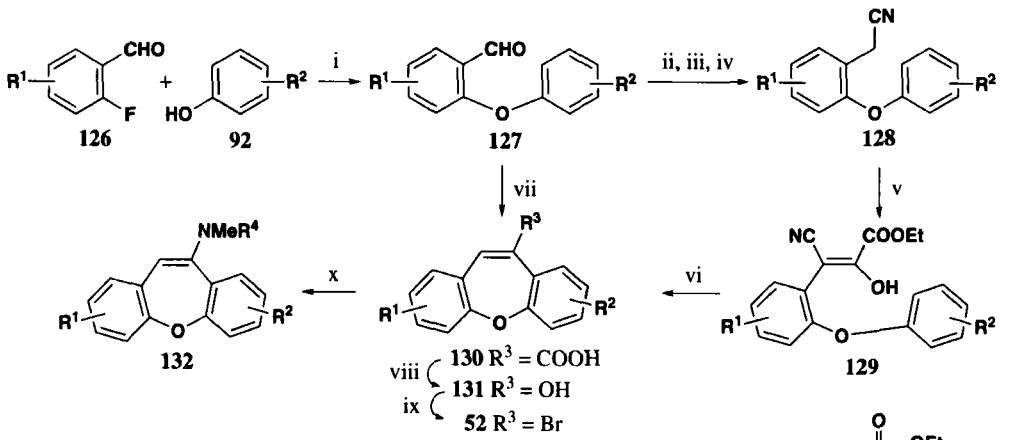
Scheme 21

$CuBr{\cdot}SMe_2$ complex was carried out at relatively mild temperatures. A reagent screening for the Ullmann coupling was assayed concluding that etheration could be successfully achieved by a discrete number of systems based on copper(I). Despite the constraint of the structure subjected to heterocyclization, our results tempt us to speculate that the thermodynamic stability of the ultimately formed oxepine ring may favour the cyclization step, which should be taken into account in complicated systems wherein harsh conditions for Ullmann coupling are needed in earlier synthetic stages.

b. Formation of the Dibenzoxepine Nucleus via Aromatic Nucleophilic Substitution

As mentioned previously, complementary to the Ullmann coupling is a widely applied approach to construct the dibenzoxepine nucleus relying on the S_NAr of adequately *ortho*-substituted aryl fluorides with phenols under mild alkaline conditions.[33a] The selection of one of these methods depends on the availability of adequate substrates and the compatibility and endurance of the chemical functionalities to the reaction conditions especially in the case of utilizing Ullmann-ether coupling. In general, most reactions conditions for S_NAr directed to generate dibenzo[*b,f*]oxepines are limited to heating the reactants in the presence of an inorganic base, calcium carbonate preferably.

An eminent example that complies with this statement is the preparation of derivatives of the antiapoptotic and neurorescuer compound CGP3466 at Novartis (**132** in *Scheme 22*).[33c,70]



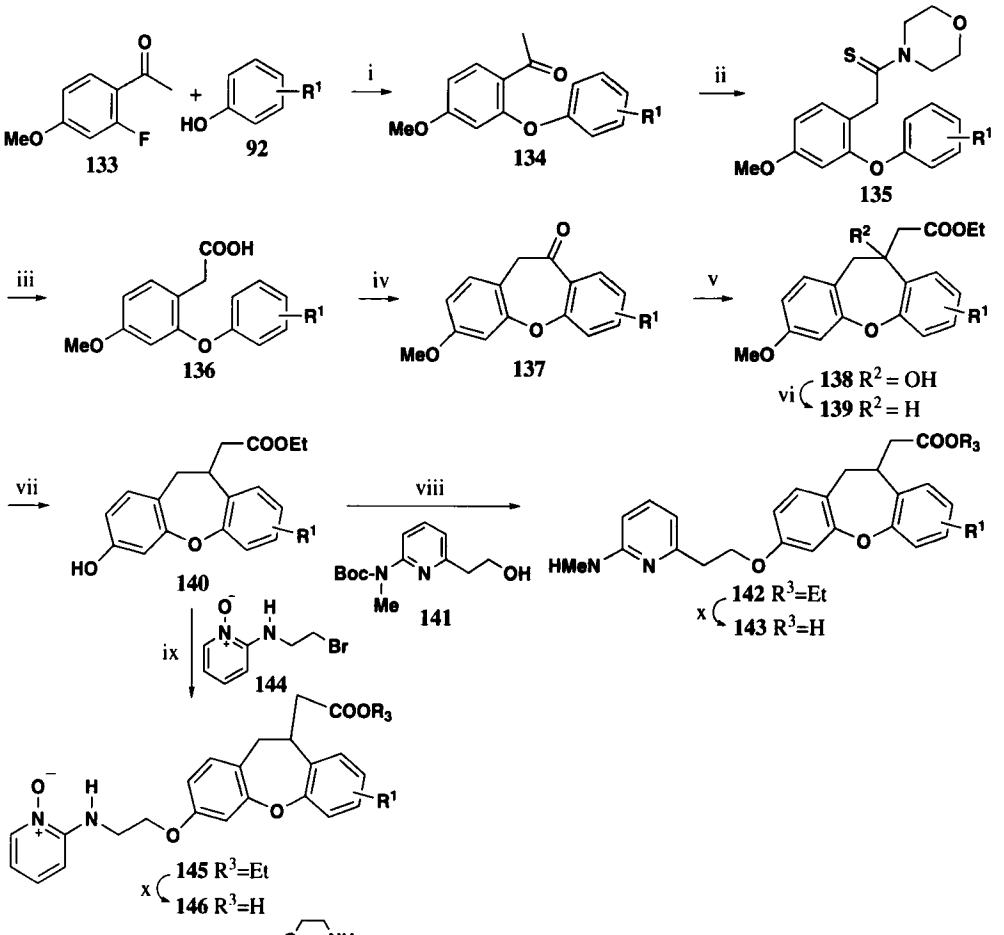
i) K_2CO_3, DMA, 110°C; ii) LAH, Et_2O; iii) HBr, HOAc; iv) NaCN, DMF; v) Na, ; vi) H_2SO_4; vii) $C_6H_5CONHCH_2COOH$, NaOAc, Ac_2O, H_2SO_4, 80°C; viii) a) $^iBuOCOCl$, NMMO, DME, -15°C; b) $NaBH_4$, H_2O, 10°C; ix) NBS, TPP, THF; x) $HNMeR^4$, DMF

Scheme 22

After initial implementation of condensation of *ortho*-fluorobenzaldehydes with different phenols, the azalactonization with hippuric acid, followed by ring-closure under strongly acidic conditions, led to the dibenzo[*b,f*]oxepin-10-carboxylic acids **130**. Depending on the substitutents on the aryl rings, highly variable yields were obtained, such that the azalactone route should be replaced by a

cyano homologation sequence and intramolecular Friedel-Crafts type acylation of derivative **129**. Reduction of the carboxylic acids **130** by forming mixed aldehydes in the presence of isobutyl chloroformate gave dibenzoxepinols **131**. Finally, formation of bromides **52** followed by amination with primary or secondary amines gave 10-aminomethyldibenzoxepines **132**.

Bondinell, at Glaxo Smithkline Beecham, as a part of a patent comprising antagonists of vitronectin receptors, useful for treating osteolytic lesions such as osteoporosis or Paget's disease, prepared a series of 3-aminopyridinyl-10,11-dihydrodibenzo[*b,f*]oxepine-10-acetic acid derivatives **143** or their corresponding *N*-oxides **146** (*Scheme 23*).[71] The synthesis starts by



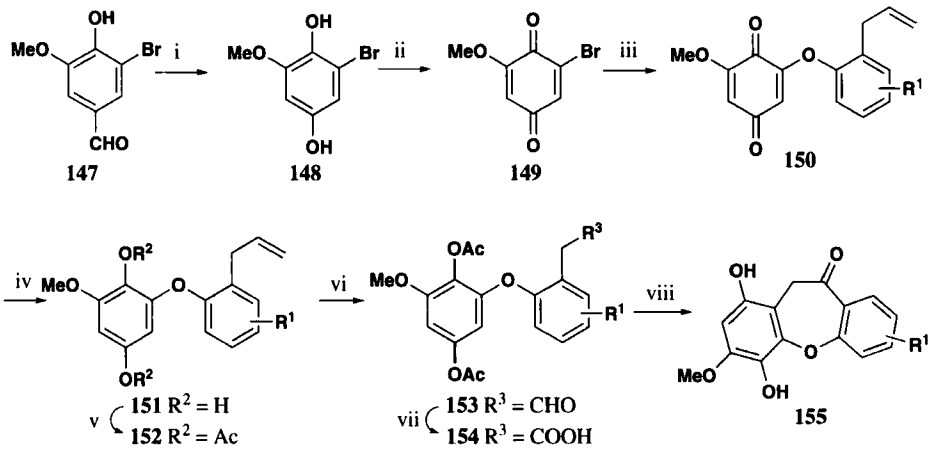
i) K_2CO_3, DMF, 90°C; ii) S_x,  ; iii) KOH, H_2O, IPA, reflux; iv) a) $SOCl_2$, PhMe, reflux; b) $AlCl_3$, DCM, reflux; v) LHMDS, EtOAc, TMEDA, THF, -78°C → -40°C; vi) a) Et_3SiH, BF_3•OEt_2, DCM, 0°C; b) H_2 (50 psi), Pd/C, EtOH, reflux; vii) BBr_3, DCM, MeOH, 0°C; viii) a) DIAD, TPP, DCM; b) HCl, diox., DCM; ix) NaOH, ACN; x) NaOH, EtOH, 50°C

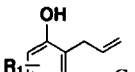
Scheme 23

reacting commercially available 2-fluoro-4-methoxyacetophenone **133** with phenols in the presence of potassium carbonate to give the diarylether **134**. Willgerodt-Kindler reaction with

sulphur using morpholine as solvent yielded the thioamide **135**, which underwent basic hydrolysis leading to the corresponding phenylacetic acid **136**. Friedel-Crafts conditions allowed the closure of the oxepine ring, and subsequent reaction of the resulting dibenzoxepinone **137** with the enolate of ethylacetate in an aldol-type reaction completed the desired functionality on the oxepine counterpart **138**. Elimination of the hydroxy group at C-11 position, reduction and demethylation of the methoxy group rendered the key dibenzoxepine **140**. A Mitsunobu protocol on **140** with hydroxyalkyl-2-aminopyridines **141** or, alternatively, alkylation with bromoalkyl-2-aminopyridine *N*-oxydes **144** under standard conditions, led to the esterified derivatives **142** and **145** of the target products.

Other alkali metal carbonates have been used occasionally, as in the case of glutamic acid receptor blockers[42] or antioxidants,[72] applied in the prevention of nervous or arteriosclerotic diseases, respectively. In this case, a concise and versatile synthetic sequence leading to polyhydroxylated dibenzoxepinones was envisioned at Nippon Suisan Kaisha. This process took advantage of the more reactive 2-bromo-1,4-benzoquinones, suitable for reaction with phenols in the presence of cesium carbonate; avoiding the use of the less available fluoro analogues (*Scheme 24*). Starting from

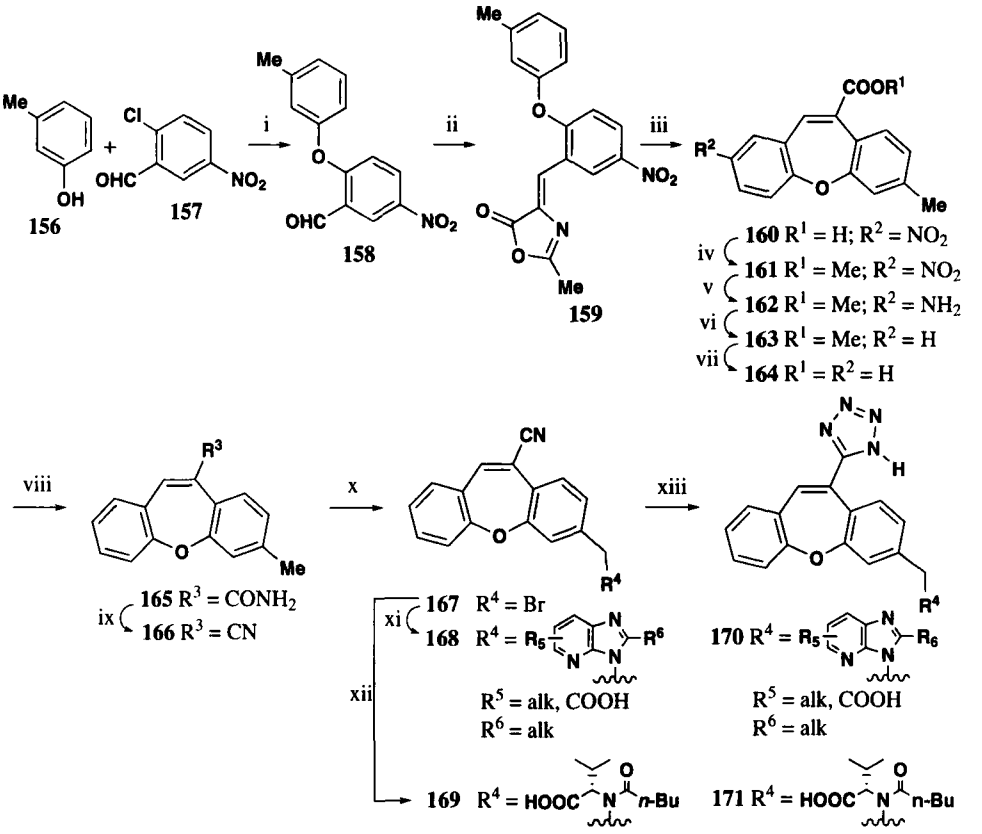


i) MCPBA, DCM, 50°C; ii) CAN, ACN; iii)  , Cs_2CO_3, DMF; iv) ascorbic acid, H_2O; v) Ac_2O, py; vi) a) O_3, DCM, MeOH, HOAc, -78°C; b) DMS, -78°C → rt; vii. NaClO, NaH_2PO_4, H_2O, tBuOH, 2-methyl-2-butene; viii. $MeSO_3H$

Scheme 24

the inexpensive 5-bromovanillin **147**, direct conversion to benzoquinone **149** was effected by oxidation with MCPBA and subsequent treatment with CAN. Phenoxylation with 2-allylphenol afforded benzoquinone **150** which, after rearomatization and ozonization of the allyl residue, gave intermediate **153**. Hypochlorite mediated oxidation and cyclodehydration with methanesulfonic acid led to the corresponding dibenzoxepinone derivatives **155** which, after appropiate conversion to the partially reduced or the 10,11-dihydroderivatives according to the procedures discussed in previous sections, were converted into the real target products of those patents.

When suitable substituents are present on the haloarene, the application of less expensive chloroarenes as starting materials have been reported in the literature. Kiyama *et al.* prepared several 1-tetrazolyldibenzo[*b,f*]oxepines **170** and **171**, derived from a 3D substructure search, with subnanomolar *in vitro* activity (0,7-9,6 nM) against angiotensin II receptor, but devoid of antihypertensive activity (*Scheme 25*).[73] The preparation of these derivatives was initiated by coupling of *m*-cresol **156** with 2-chloro-5-nitrobenzaldehyde **157** in aqueous NaOH to



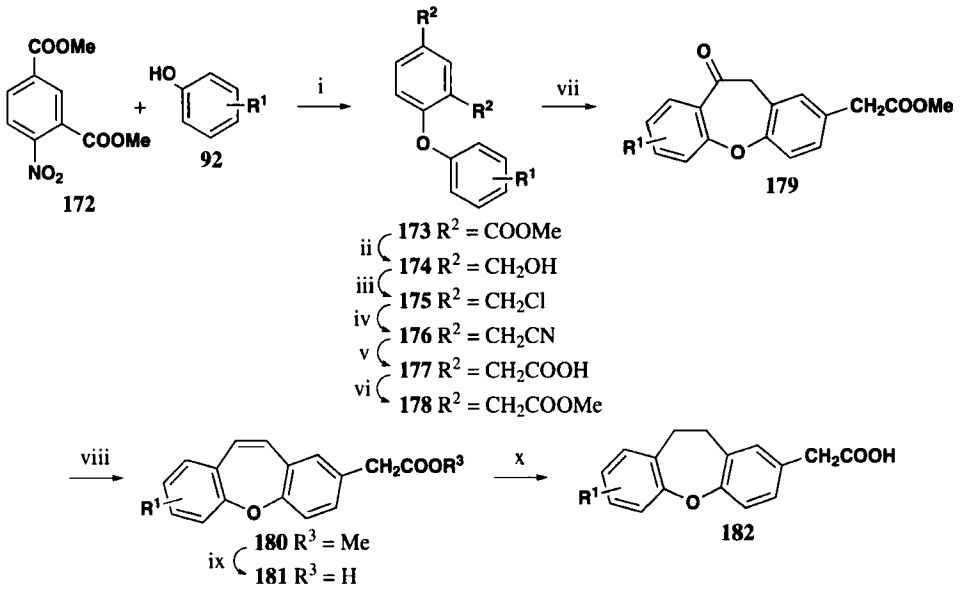
i) NaOH, H_2O, reflux; ii) *N*-acetylglycine, $KHCO_3$, HOAc, 40°C; iii) HCl, H_2O, reflux; iv) a) DMF, SOCl2, PhH, reflux; b) MeOH, py; v) $FeSO_4 \cdot 7H_2O$, TEA, H_2O, MeOH, diox.; vi) a) HCl, H_2O; b) $NaNO_2$, H_2O, 0°C; c) H_3PO_4; vii) NaOH, MeOH, reflux; viii) a) DMF, $SOCl_2$, PhH, reflux; b) NH4OH; ix) $SOCl_2$, reflux; x) NBS, DCE, Bz_2O, reflux; xi) NaH, DMF, 5,7-dimethyl-2-alkylimidazo[4,5-*b*]pyridine, -20 → -40°C → rt; xii) a) L-valine, DMAP, DCM, ACN; b) *n*-BuCOCl; c) LiOH, MeOH, py; xiii) a) Me_3SnN_3, DMF, 110°C; b) HCl, EtOH

Scheme 25

give the diphenylether **158**. After construction of the oxazolone intermediate **159** by reaction of **158** with *N*-acetylglycine, cyclization to the dibenzoxepine ring **160** was effected under mild conditions. Removal of the activating nitro group was achieved after reduction and decomposition of the diazonium salt derived from of the resulting amino group on **162**. Conversion of the 11-ester group into a cyano derivative **166** concluded the implementation of specific substitution

on the oxepine ring. Further manipulation at peripheral positions allowed for easy introduction of the imidazo[4,5-*b*]pyridine framework.

In this context, dibenzoxepine-2-acetic and -propionic acids were prepared at Syntex as antiinflammatories, by phenoxylation of 4-nitroisophthalates.[74] The nitro group proved to be reactive enough to undergo substitution under mild conditions when treated with an excess of phenol in the presence of an alkali metal hydride to produce 4-phenoxyisophthalates **173** (*Scheme 26*). Conventional homologation of **173** *via* the cyano derivative **176** gave a



i. NaH, DMF; ii. LAH, DME; iii. $SOCl_2$, DCM; iv. NaCN, DMF; v. HOAc, H_3PO_4, reflux; vi. HCl(g), MeOH; vii. $AlCl_3$, DCM, $PhNO_2$; viii. $NaBH_4$, DME, MeOH; ix. NaOH, H_2O, MeOH, reflux; x. H_2, Pd/C (cat.), DME

Scheme 26

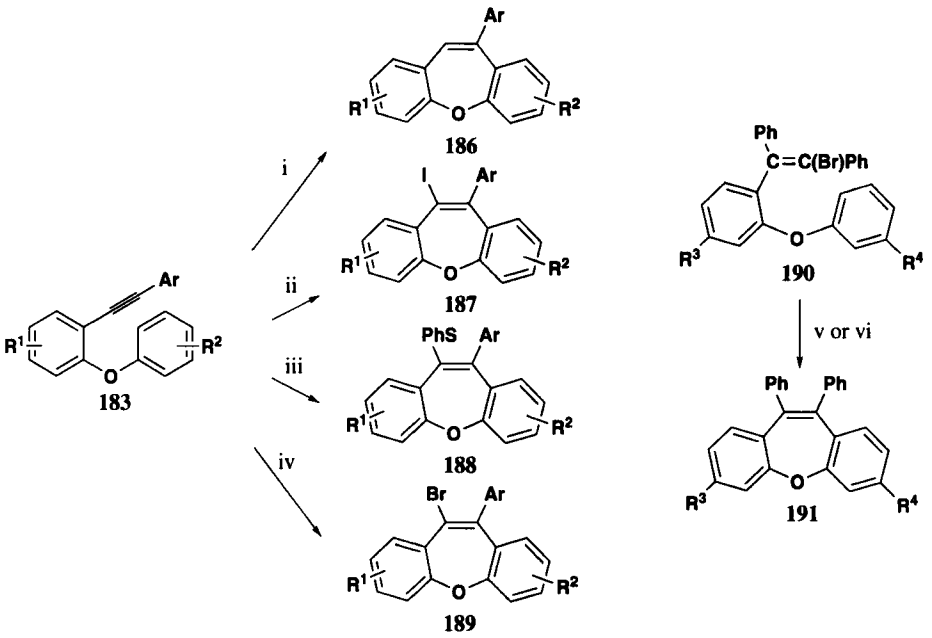
phenoxyphenylacetic acid **177**, that allowed the obtention of dibenzoxepinone **179** under Friedel-Crafts acylation conditions. Reduction of the carbonyl group on **179** led to a variety of reduced products **180-182** that formed a part of the family of compounds covered by the patent.

4. Miscellaneous Synthetic Methods for the Preparation of Dibenzoxepines

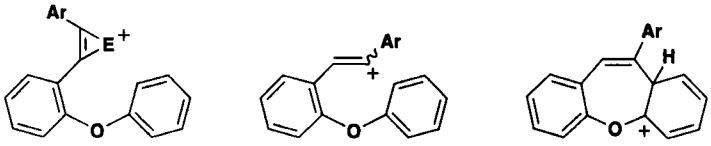
Apart from the main methodologies to prepare dibenzo[*b,f*]oxepines presented so far, the synthesis of this interesting heterocyclic system has been conducted occasionally in other uncommon, but attractive ways. Although barely explored in comparison in the previous approaches, such protocols feature some advantages over the existing procedures that are worth examining.

For example, an original entry to the dibenzo[*b,f*]oxepine framework, based on the use of vinyl cations as synthetic intermediates, was established by Kitamura and Taniguchi in a

series of reports showing several aspects of this relatively unexplored strategy.[75] The authors developed different procedures for the generation of such cationic species **184-185**. In a first approach, 11-aryldibenzoxepines **186** were prepared by protonation of acetylenic derivatives **183**, which, on treatment with other electrophiles (ICl, PhSCl, Br_2), provided 10,11-disubstituted heterocycles **187-189**.[75b,d] Alternatively, 10,11-diphenylderivatives **191** were formed either by photolysis or silver-assisted solvolysis of substituted vinyl bromides **190** (*Scheme 27*).[75a,c] In



i) $HClO_4$ or HBF_4, DCM, AcOH; ii) ICl, DCM; iii) PhSCl, DCM; iv) Br_2, DCM; v) hv / Pyrex, DCM; vi) AgOAc, AcOH, reflux

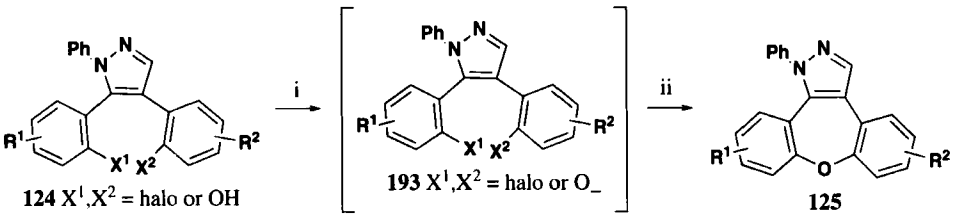


Scheme 27

addition, a brief mechanistic study was showed that the intramolecular cyclization of β-[*o*-(aryloxy)phenyl]vinyl cation **185** is favoured by the considerably higher relative stability of intermediate **192**. Despite the feasibility of the presented non-conventional approach, several structural limitations, such as the need for specific stabilizing groups of the resulting cation (Ar = *p*-$MeOC_6H_4$ in **183** and Ph in **190**), cannot be omitted.

Closely related to the Ullmann-type approach shown in *Scheme 21*, our group envisaged that oxepine ring closure could be carried out as the final step by a palladium-catalyzed biaryl ether formation.[69] Such a process, with several advantages in terms of a more sustainable chemistry and milder conditions over more classical *O*-arylation methodologies, would provide

dibenzoxepinopyrazoles **125** from halophenolic derivatives **124** using catalytic amounts of palladium. After an initial deprotonation step, the corresponding halophenoxide intermedates **193** were intramolecularly coupled *in situ* by a Buchwald-Hartwig reaction, affording tetracycles **125** with comparable yields using either BINAP or DPPF bidentate ligands (*Scheme 28*).[69,76]



124 X^1,X^2 = halo or OH

193 X^1,X^2 = halo or O_

125

i) NaOH, PhMe, reflux; ii) $Pd_2(dba)_3$/L (4-9 mol%), PhMe, THF, 100°C
L=BINAP, DPPF

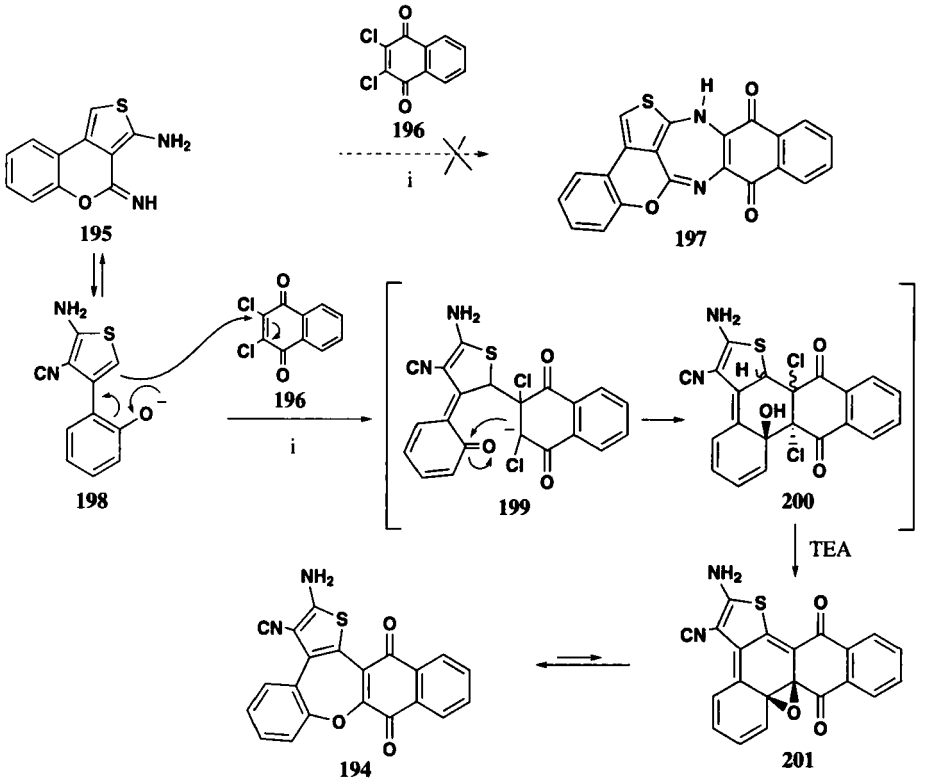
Scheme 28

Although it constitutes an isolated case, the serendipitous formation of pentacyclic oxepine **194** reported by Nyiondi-Bonguen *et al* is worthy of comment, considering the few existing synthetic strategies for the preparation of the dibenzoxepine core. The initial aim on treating 3-amino-4-iminothienobenzopyran **195** with 2,3-dichloro-1,4-naphhoquinone **196** was to effect a cycloaddition leading to the [1,4]diazepine **197**. However, oxepine **194** was isolated as the main product, and the mechanistic path that could explain its unexpected formation, as depicted in *Scheme 29*, relies on the cyclization of the isomer **198** (generated *in situ* from **195**) with quinone **196**. Subsequent loss of HCl by intermediate **200** would lead to the unstable arene oxide **201** which rapidly rearranges to its oxepine counterpart **194**.[77]

Given the mild conditions and tolerability of functional groups, the ingenious ring closure of substituted acetophenones reported by Hiroto *et al.* provides a promising entry to dibenzoxepinones **203**. Indeed, irradiation of *o*-(2-bromoaryloxy)acetophenones **202** in liquid ammonia, in the presence of potassium *tert*-butoxide, afforded the corresponding dibenzoxepine derivatives **203** in good yields (*Scheme 30*). Such cyclization, effected by means of a high-pressure mercury-vapor lamp, was also applicable to the synthesis of thiepine analogs.[78]

III. CONCLUSIONS

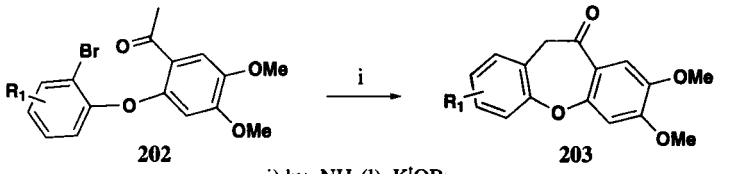
Despite their scarcity in nature, the plethora of pharmaceutical and industrial applications of dibenzo[*b,f*]oxepines has promoted extensive research on their synthesis. However, apart from the unusual protocols featured as miscellaneous methods, and probably due to the difficulty involved in diaryl ether bond formation, most existing procedures rely either on a cyclodehydration of aryloxylated intermediates or on an intramolecular C-O bond formation via Ullmann coupling or S_NAr. All these methodologies provide dibenzoxepines bearing several substitution patterns, even heterocyclic rings fused to the 10,11- positions. It is particularly in the synthesis of such compounds where recent, meaningful advances have been made, supplying catalytically



i) TEA, THF, reflux

Scheme 29

conducted diaryl ether formation procedures and new heterocyclization reactions. In this context, it is likely that factors such as the continuous discovery of biological properties associated with the dibenzo[*b,f*]oxepine framework and the relatively limited number of synthetic paths available will determine a research area where contributions can still be made.



i) hν, NH_3(l), K^{t}OBu

Scheme 30

LIST OF ABBREVIATIONS

ALS	Amyotrophic lateral sclerosis
ACN	Acetonitrile
BINAP	2,2'-bis(Diphenylphosphino)-1,1'-binaphthyl

BOC	*tert*-Butoxycarbonyl
CAN	Ammonium cerium(IV) nitrate
cat.	Catalytic
CNS	Central nervous system
CSA	(+)-10-Camphorsulfonic acid
D	Dopamine
dba	Dibenzylideneacetone
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DETG	Diethylene glycol
DIAD	Diisopropyl azodicarboxylate
diox.	1,4-Dioxane
DIPEA	*N*,*N*-Diisopropylethylamine
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMFDMA	Dimethylformamide dimethyl acetal
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
DPPF	1,1'-*bis*(Diphenylphosphino)ferrocene
eq.	Equivalent
GABA	γ-Aminobutyric acid
5-HT	5-Hydroxytriptamine (serotonin)
IAMT	*L*-Isoaspartyl(*D*-aspartyl)-*O*-methyltransferase
IL	Interleukin
IPA	Isopropanol
LAH	Lithium aluminum hydride
LDL	Low-density lipoprotein
LHMDS	Lithium bis(trimethylsilyl)amide
MCPBA	*m*-Chloroperbenzoic acid
NBS	*N*-bromosuccinimide
NMMO	*N*-methylmorpholine
NMP	*N*-methyl-2-pyrrolydinone
NSAID	Non-steroidal antiinflammatory drug
PPA	Polyphosphoric acid
py	Pyridine
SNUI	Selective norepinephrine uptake inhibitor

TEA	Triethylamine
TEBA	Triethyl benzyl ammonium chloride
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
TPP	Triphenylphosphine
TSA	*para*-Toluenesulfonic acid
xy	Xylene

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