β-Phenylethylamines and the isoquinoline alkaloids

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This review covers β-phenylethylamines and isoquinoline alkaloids and compounds derived from them, including further products of oxidation, condensation with formaldehyde and rearrangement, some of which do not contain an isoquinoline system, together with naphthylisoquinoline alkaloids, which have a different biogenetic origin. The occurrence of the alkaloids, with the structures of new bases, together with their reactions, syntheses and biological activities are reported. The literature from July 2001 to June 2002 is reviewed, with 581 references cited.

1 β-Phenylethylamines

β-Phenylethylamines and amides have been isolated from the following plant species, the ten marked with asterisks being new alkaloids:

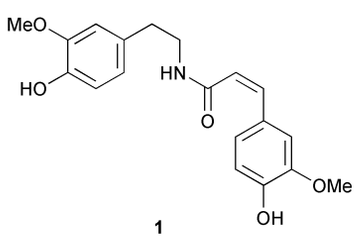
Aristolochia gehrtii[1]
N-cis-feruloyl-3-*O*-methyldopamine* (3-*O*-methyltuberosine A) **1**

Lindera glauca[2]
N-p-coumaroyltyramine, *N-cis*-feruloyltyramine, *N-trans*-feruloyltyramine, *N-cis*-sinapoyltyramine* **2** and *N-trans*-sinapoyltyramine* **3**

Oxytropis (unspecified)[3]
N-benzoylphenylethylamine* **4a**, (*S*)-*N*-benzoyl-2-hydroxy-2-phenylethylamine* **4b** and (*R*)-*N*-nicotinoyl-2-hydroxy-2-phenylethylamine* **5**

Oxytropis myriophylla[4]
N-benzoylphenylethylamine, (*S*)-*N*-benzoyl-2-hydroxy-2-phenylethylamine, *N-cis*-cinnamoylphenylethylamine* **6**, *N-trans*-cinnamoylphenylethylamine* **7a** and (*S*)-*N-trans*-cinnamoyl-2-hydroxy-2-phenylethylamine* **7b**

Zizyphus jujuba[5]
jubanine C* **8**, scutianine C and zizyphine A



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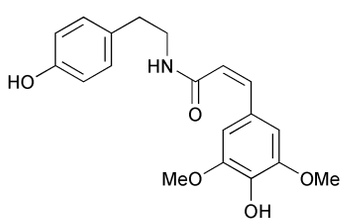

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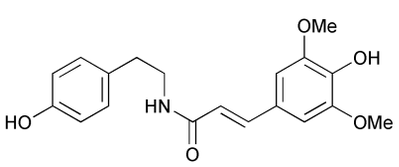

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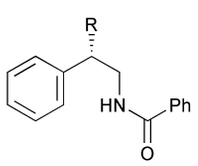
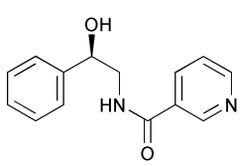


4a R = H
4b R = OH



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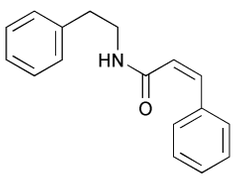
Jubanine C **8** is a new alkaloid similar to waltherines A, B and C, of the paracyclophane group, and a total synthesis of sanjoinine G1 **13b**, of this group, has been reported. The pentafluorophenyl ester of (*S*,*S*)-*N*,*N*-dibenzylhydroxyleucine **9** was condensed with the amine **10**, to give the dipeptide **11**,

 DOI: 10.1039/b111626f



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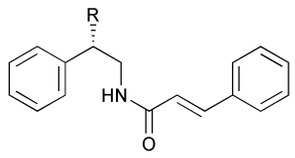
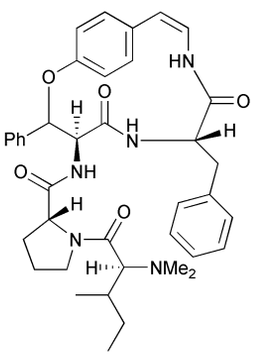
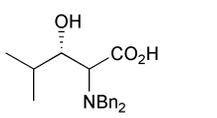


7a R = H
7b R = OH



8

which was cyclised to the cyclophane **12a**. Removal of the nitro group yielded **12b**, which was hydrolysed to the amine and this was condensed with L-*N*,*N*-dimethylphenylalanine to give *O*-acetylsanjoinine G1 **13a**, hydrolysed by potassium carbonate in aqueous methanol to give sanjoinine G1 **13b**.[6] An asymmetric synthesis of the marine phenylethylamine (*S*)-(+)-chelonine B **14** has been reported.[7]



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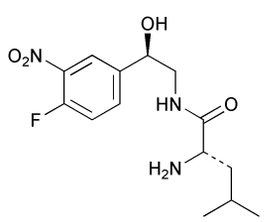

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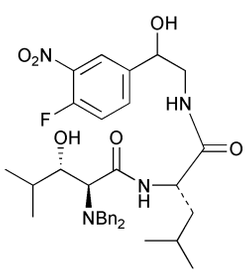

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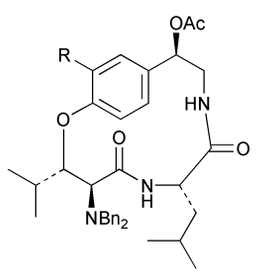
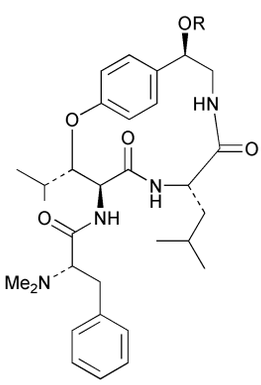
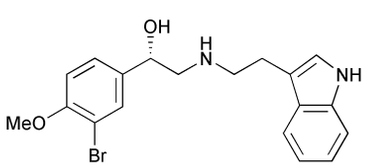


12a R = NO_2
12b R = H

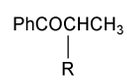


13a R = Ac
13b R = H

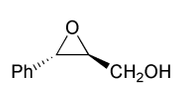


14

(±)-Ephedrine and (±)-pseudoephedrine have been synthesised by the bromination of ethyl phenyl ketone, amination of the resulting **15a** to give **15b** and reduction of the carbonyl group.[8] An asymmetric synthesis of (−)-pseudoephedrine **20** has been achieved from (*S*,*S*)-3-phenyloxiran-2-ylmethanol **16** by amination to **17**, followed by silylation and treatment with dibenzyl carbonate and sodium iodide, which proceeds with a stereospecific interchange of the amino and alcohol functions *via* the intermediate aziridine **18**, to give **19**, previously converted into (−)-pseudoephedrine.[9] In approaches to the commercial preparation of ephedrine the biosynthesis of phenyl acetyl carbinol by immobilised *Saccharomyces Sc-5* yeast cells has been studied.[10,11] The conversion of (+)-pseudoephedrine into (−)-ephedrine in 85% yield has been achieved by heating with glacial acetic acid in the presence of catalytic amounts of acetic anhydride.[12,13] Methods for the separation[14,15] and estimation[14–17] of the *Ephedra* alkaloids have been described.



15a R = Br
15b R = NHMe



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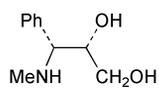

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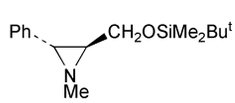

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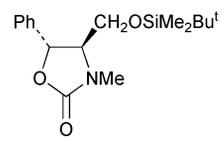

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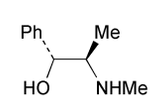

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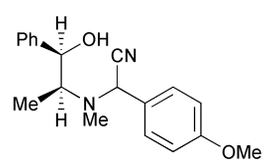
Reaction of ephedrine with 4-methoxybenzaldehyde and sodium cyanide has afforded the cyano-amine **21**, hydrolysis of which by acid yielded the (5*S*,6*R*) morpholinone **22**.[18] Ephedrine and pseudoephedrine have been reacted with the dihalodihydrofuranones **23a**–**23d** to give the dihydrofuranones **24a**–**24b** and **25a**–**25b**.[19] Acylation of pseudoephedrine with substituted phenylacetyl chlorides has given the amides **26a**–**26c**, the enolates of which reacted with di-*tert*-butyl azodicarboxylate to give the chiral compounds **27a**–**27c**, which have been hydrolysed to arylglycines in high optical purity.[20] The preparation of pseudoephedrine salicylate has been described.[21]



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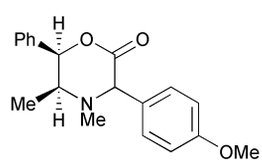

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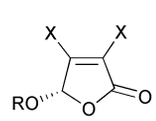
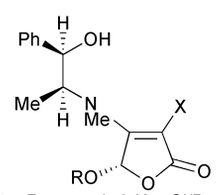
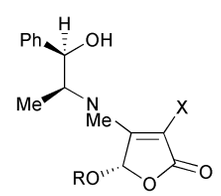


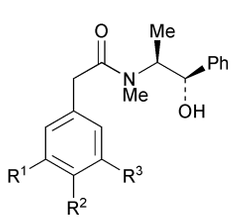
23a R = menthyl, X = Cl
23b R = menthyl, X = Br
23c R = bornyl, X = Cl
23d R = bornyl, X = Br



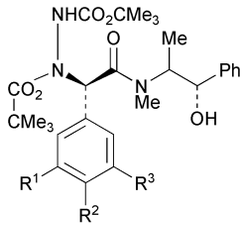
24a R = menthyl, X = Cl/Br
24b R = bornyl, X = Cl/Br



25a R = menthyl, X = Cl/Br
25b R = bornyl, X = Cl/Br

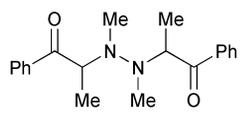


26a R^1 = H, R^2 = R^3 = OMe
26b R^1 = H, R^2 R^3 = OCH_2O
26c R^1 = R^2 = R^3 = OMe



27a R^1 = H, R^2 = R^3 = OMe
27b R^1 = H, R^2 R^3 = OCH_2O
27c R^1 = R^2 = R^3 = OMe

The photochemical oxidation of ephedrine by singlet oxygen has been shown to give the symmetrically substituted hydrazine **28**, resulting from a radical pairing process, together with the dihydroindole **29**, formed by an internal radical substitution.[22] The resolution of (±)-ephedrine has been described[23] and the crystallographic forms of the diastereoisomeric salts of ephedrine and of deoxyephedrine with (+)-and (−)-4′-fluoromandelic acid have been compared.[24] The pharmacological properties and physiological effects of ephedrine[25–37] and of pseudoephedrine[28,38] have been studied.



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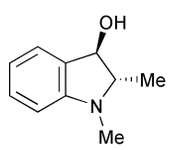
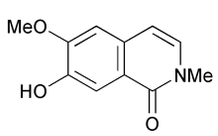


29

2 Isoquinolines

The new isoquinoline alkaloid cherianoine **30** has been isolated from *Annona cherimola*.[39]

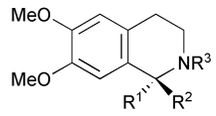


30

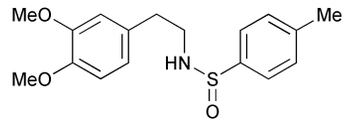
(*S*)-(−)-Salsolidine (**31a**) has been obtained in 40% enantiomeric excess by the reaction of methyllithium with 6,7-dimethoxy-3,4-dihydroisoquinoline in the presence of (−)-sparteine as a chiral ligand. The dihydroisoquinoline methiodide under the same conditions afforded the (*R*)-tetrahydroisoquinolines (+)-carnegine **31b** and **31c** with methyl lithium and phenyllithium respectively.[40] Syntheses of both (*R*)- and (*S*)-salsolidine in high enantiomeric excess have also been achieved by the Pictet–Spengler cyclisations of the homoveratrylamide **32** using the (*R*)- and (*S*)-forms of Andersen's reagent.[41] The thiazolino[2,3-*a*]isoquinolines **33a** and **33b** have been oxidised to the sulfoxides and then desulfurised to give the *N*-acetyltetrahydroisoquinolines **31d** and **31e**, which gave heliamine **31f** and (±)-salsolidine on hydrolysis.[42] A further synthesis of (±)-salsolidine and of (±)-salsoline is involved in the syntheses of bernumicine and bernumidine (section 4).

Reaction of the nitrostyrene **34a** with 4-benzyloxyphenylmagnesium bromide has given the diarylnitroethane **35a** which was reduced to the amine **35b**. This suffered Pictet–Spengler cyclisation and *N*-methylation when treated with formaldehyde and formic acid to give **36a**, which was debenzylated to (±)-cherylline **36b**. A similar synthesis of (±)-*O*,*O*-dimethylcherylline **36c** was achieved from **34b**.[43]

A patent for the synthesis of complex tetrahydroisoquinolines as potential medicinal agents has been published.[44]



31a R^1 = R^3 = H, R^2 = Me
31b R^1 = R^3 = Me, R^2 = H
31c R^1 = Ph, R^2 = H, R^3 = Me
31d R^1 = R^2 = H, R^3 = Ac
31e R^1 = H, R^2 = Me, R^3 = Ac
31f R^1 = R^2 = R^3 = H



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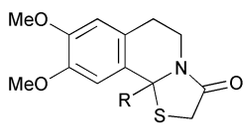
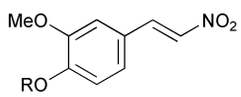
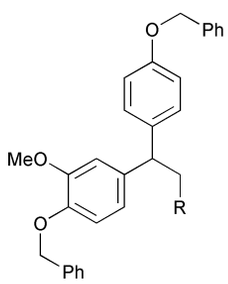


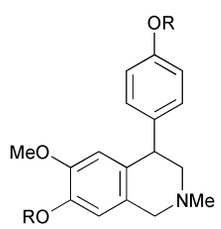
33a R = H
33b R = Me



34a R = CH_2Ph
34b R = Me



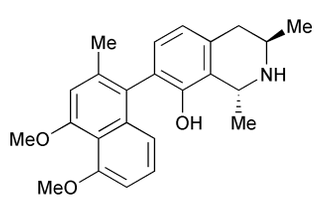
35a R = NO_2
35b R = NH_2



36a R = CH_2Ph
36b R = H
36c R = Me

3 Naphthylisoquinolines

Circular dichroism calculations for the assignment of the axial configuration to dioncophylline A **37** have been published.[45]

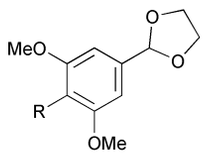


37

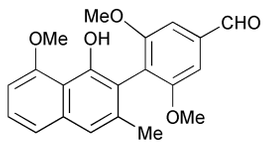
A first synthesis of the 7,3′-linked alkaloid ancistrocladidine has been reported. The highly hindered biaryl linkage was forged by the reaction of the lead compound **38c**, formed from **38a** *via* **38b**, with 8-methoxy-3-methyl-1-naphthol to give **39**. This aldehyde, protected as its methoxymethyl ether, was converted by the Wittig reaction into the allylic alcohol **40**, which was oxidised to the epoxide **41a**, the ester **41b** of which reduced to the alcohol **42**. This was aminated, with reversal of stereochemistry, to the amine **43a** and Bischler–Napieralsky cyclisation of the *N*-acetyl compound **43b** was accompanied by cleavage of the methoxymethyl ether to give ancistrocladidine **44** and its atropisomer.[46]

4 Benzylisoquinolines

Benzylisoquinoline alkaloids have been isolated from the following plant species, the five marked with asterisks being new alkaloids



38a R = I
38b R = $SnBu_3$
38c R = $Pb(OAc)_3$



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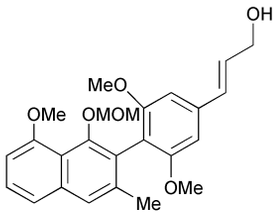

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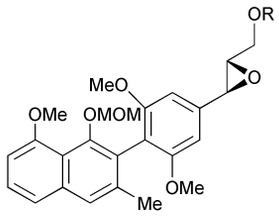
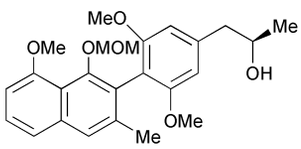
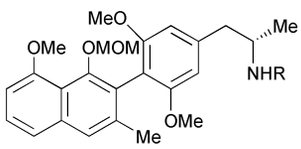


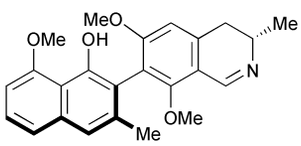
41a R = H
41b R = tosyl



42



43a R = H
43b R = $COCH_3$



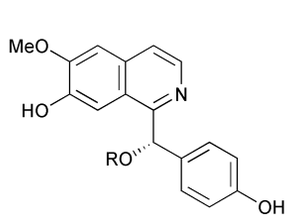
44

Annona cherimola[39]
anocherine A* **45a** and anocherine B* **45b**
Artabotrys uncinatus[47]
reticuline
Desmos yunanensis[48]
isococlaurine, *N*-methylisococlaurine and 7-deoxy-5-methoxymagnocurarine chloride* **46**
Doryphora sasafras[49]
N,*O*-dimethylneolitacumonine* **47**
Lindera qlauca[2]
norcinnamolaurine
Neolitsea acuminatissima[50]
neolitacumonine* **48a**

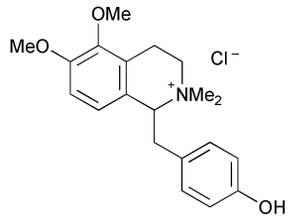
The new quaternary alkaloid **47** was previously prepared as the poorly characterised iodide by the *N*-methylation of *O*-methylneolitacumonine **48b** (then unnamed) isolated from *Ocotea macrophylla*.[51,52] Nymphaedaline, a phenoxybenzylisoquinoline alkaloid isolated from *Hernandia nymphaeifolia* (section 5) is clearly a degraded bisbenzylisoquinoline.

The structure of the alkaloid thalprzewalskiione, formerly believed to be **49a**, has been revised to **49b**, following the synthesis of these two positional isomers.[53]

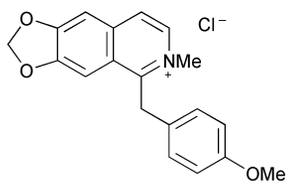
The potassium salt of armepavine has been reacted with acrylonitrile to give **50** and with dichloromethane to give the bimolecular compound **51**.[54] The photochemical oxidation of papaverine by singlet oxygen has been shown to give the 1,4-peroxide **52**,[21] and the thermal decomposition of *O*-methylarmepavine *N*-oxide to give the isoquinolone *N*-methylcorydaldine **53**.[55] The dihydroisoquinoline *N*-oxides **54a** and **54b** undergo [3+2]cycloaddition to the arylalkyne **55** to give the adducts **56a** and **56b**, which are rearranged by heat to the pyrroles **57a** and **57b** and these on treatment with aluminium chloride suffer cleavage of the isopropyl ether and ester groups, with concomitant lactonisation to give lamellarin I **58a** and lamellarin K **58b**.[56]



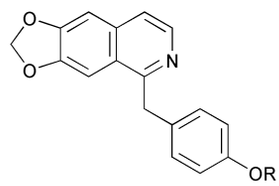
45a R = H
45b R = Me



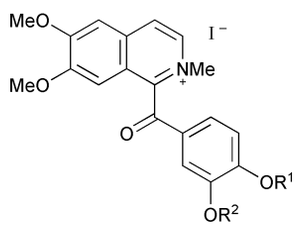
46



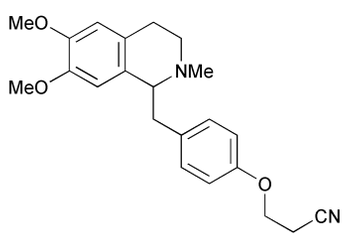
47



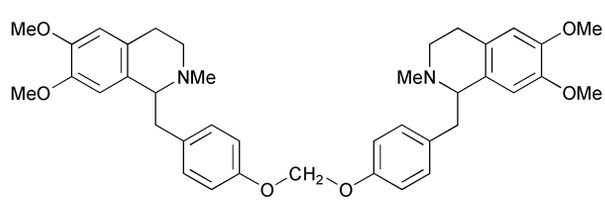
48a R = H
48b R = Me



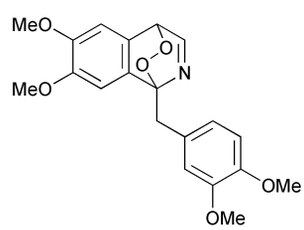
49a R^1 = H, R^2 = Me
49b R^1 = Me, R^2 = H



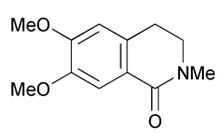
50



51

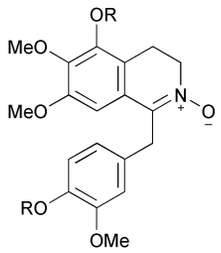


52

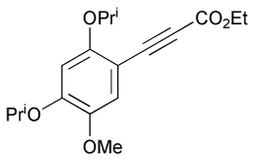


53

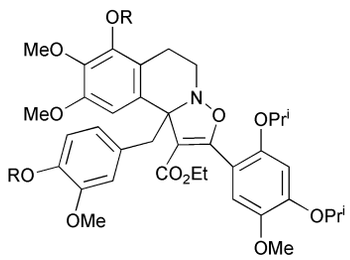
A synthesis of the *N*-benzylisoquinoline alkaloid bernumicine has been achieved *via* (±)-salsoline, prepared by Pictet–Spengler condensation of the phenylethylamine **59a** with acetaldehyde diethyl ketal and reductive debenzylation. Resolution of this with L-(+)-tartaric acid yielded (*R*)-(+)-salsoline **60**, which reacted with 3,4-dimethoxybenzyl toluenesulfonate to give (*R*)-(+)-bernumicine **61**, identical with the natural alkaloid. Similarly (±)-salsolidine, prepared from **59b** and



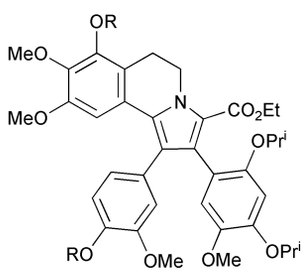
54a R = Pr^i
54b R = Me



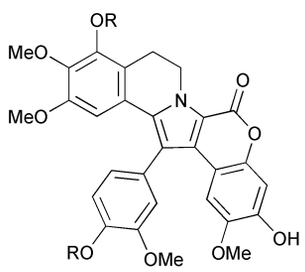
55



56a R = Pr^i
56b R = Me



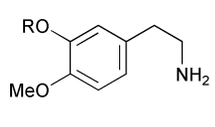
57a R = Pr^i
57b R = Me



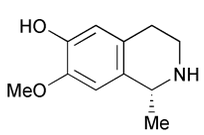
58a R = H
58b R = Me

resolved with D-(−)-tartaric acid, was converted into (*R*)-(+)-bernumidine **62**.[57]

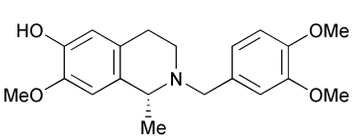
The pharmacological properties and physiological effects of papaverine,[58–64] of ethaverine[65] and of the bimolecular laudanosine derivative atracurium[66–73] have been studied.



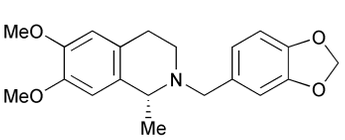
59a R = CH_2Ph
59b R = Me



60



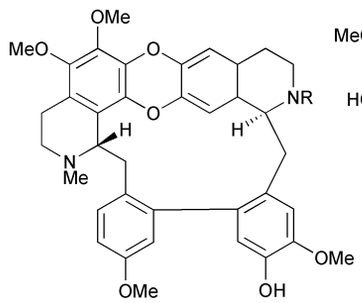
61



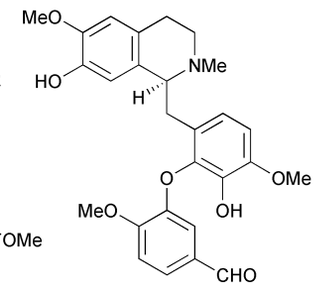
62

5 Bisbenzylisoquinolines

The new bisbenzylisoquinoline alkaloids tiliacosine **63a** and tiliasine **63b** have been isolated from *Tiliacora racemosa*, their structures being deduced from a comparison of their spectra with those of their close relatives tiliamosine, *N*-methyltiliamosine and tiliacorine.[74] The phenoxybenzylisoquinoline alkaloid nymphaedaline **64**, isolated from *Hernandia nymphaeifolia*,[75] is clearly an oxidised bisbenzylisoquinoline, probably derived from *O*-demethylateamine.

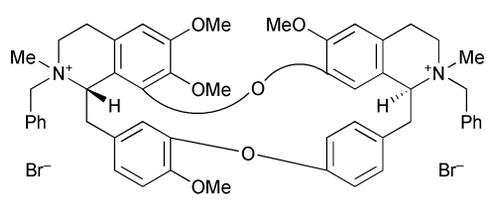


63a R = Me
63b R = H



64

The NMR spectra of fangchinoline have been studied.[76] The *N*,*N*-dibenzyl quaternary salt of (*S*,*S*)-(+)-tetrandrine **65** has been prepared and shown to dimerise in aqueous solution. Physicochemical studies have shown strong binding of the salt to succinate and aromatic carboxylate ions and to nucleotides.[77]

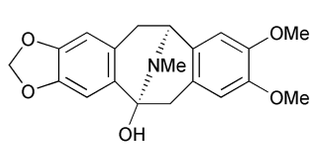


65

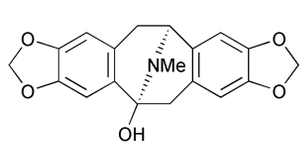
The pharmacological properties and physiological effects of berbamine,[78,79] of cepharanthine,[80,81] of dauricine,[82–84] of tetrandrine[82,85–101] and of tubocurarine[102] have been studied.

6 Pavines and isopavines

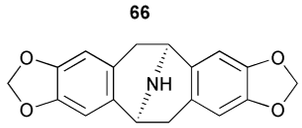
Five new alkaloids of the pavine group, 12-hydroxy-*O*-methylcaryachine **66**, 12-hydroxycrychine **67**, *N*-demethylcrychine **68**, escholzidine *N*-oxide **69a** and isocaryachine *N*-oxide **69b** have been isolated from *Cryptocarya chinensis*.[103,104]



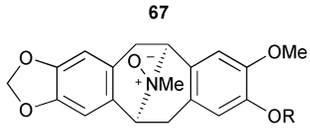
66



67



68

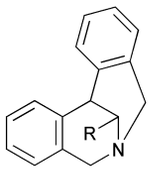


69a R = Me
69b R = H

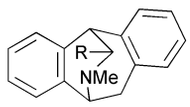
N-Methylation of the base **70a**, followed by heating of the quaternary salt with potassium *tert*-butoxide effects a Stevens rearrangement to give the isopavine **71**. Similar rearrangements of the internal quaternary salts formed from **70b** and **70c** affords the more complex isopavines **72** and **73** respectively.[105]

7 Berberines and tetrahydroberberines

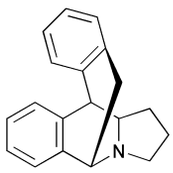
Alkaloids of the berberine group have been isolated from the following plant species, the four marked with asterisks being new alkaloids:



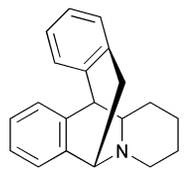
70a R = Me
70b R = CH_2Br
70c R = CH_2CH_2Br



71



72



73

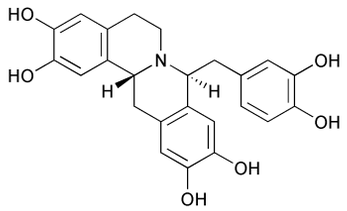
Artabotrys uncinatus[47]
10-*O*-demethyldiscretine
Chelidonum majus[106]
stylopine
Corydalis turtschaninowii[107]
tetrahydrocorydaline
Desmos yunanensis[48]
demethylcordalmine and spinosine
Phoenicanthus obliqua[108]
pseudocolumbamine
Talinum paniculatum[109]
javaberine A* **74**, javaberine B* **75** and 3′-deoxyjavaberine A* **76**
Thalictrum wanqii[110]
berberine and thalibealine* **77**

A glucoside of the 3-*O*-methyl ether of **76** and its *cis N*-oxide have previously been isolated as alkaloids from *Aristolochia gigantea*.[111] Two berberine–benzylisoquinoline dimers, longiberine and *O*-methyllongiberine have recently been discovered[112] and thalibealine is the second recorded berberine–aporphine dimer, being isomeric with acutioporberine **78**,[113] the structure of which was incorrectly drawn in the previous review. The only other dimeric alkaloids containing the berberine system are the beberine dimers bisjatrorrhizine,[114] berpodine[115] and ilicifoline.[116]

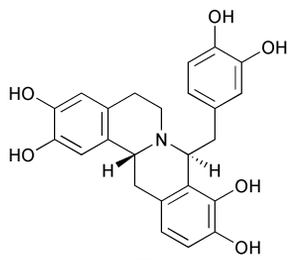
A patent for a procedure for the extraction of acutioporberine from *Thalictrum acutifolium* and for its use as an antitumour agent has been published.[117] The molecular and crystal structures of berberine azide **79a**, of berberine thiocyanate **79b** and of 8-cyanodihydroberberine **80a** have been studied,[118]

Berberine chloride **79c** has been reduced to tetrahydroberberine **81** by indium in aqueous ammonium chloride[119] and converted into 8-aminodihydroberberine **80b** by liquid ammonia. Coptisine reacts in a similar manner with ammonia.[120] Reaction of the lithium salt **82** with the enantiomerically pure **83** affords the adduct **84** which, when treated with dibutylaluminium hydride, is converted into the dihydroisoquinoline **85** and this has been reduced and cyclised to (*S*)-(+)-xylopinine **86**.[121] A review of methods of synthesis of tetrahydroberberines[122] and patents for the synthesis of berberine[123] and palmatine[107] and their derivatives[107,124] have been published.

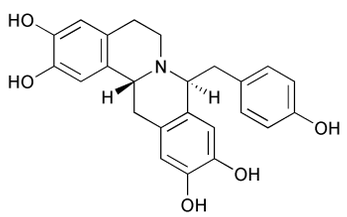
The pharmacological properties and physiological effects of berberine,[125–136] of tetrahydroberberine,[137] of coptisine,[138] of tetrahydropalmatine[139] of stepholidine[140,141] and of stylopine[106] have been studied. The new alkaloid javaberine A **74** has been shown to be a strong inhibitor of the lipopolysaccharide induced production of tumour necrosis factor and nitric oxide from mouse peritoneal macrophages, though it is less potent in this respect than some thiazolidinediones.[108]



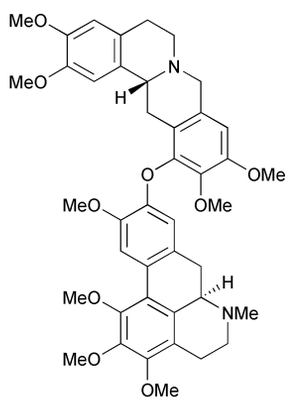
74



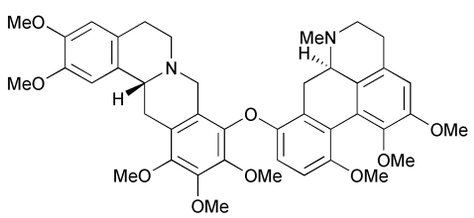
75



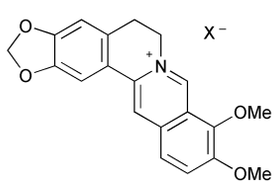
76



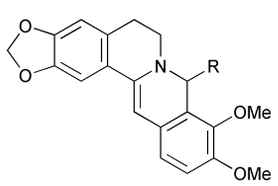
77



78



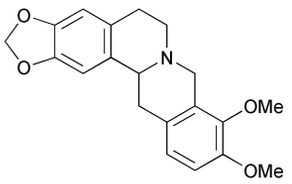
79a X = N_3
79b X = SCN
79c X = Cl



80a R = CN
80b R = NH_2

8 Secoberberines

Torulosine and the four new secoberberine alkaloids, dihydroleptopine **87**, 8-oxohypecorinine *N*-oxide **88**, demethyltorulosine *N*-methochloride **89** and hypecoleptopine **90** have been



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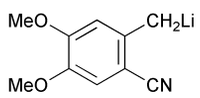

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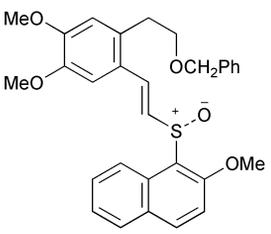

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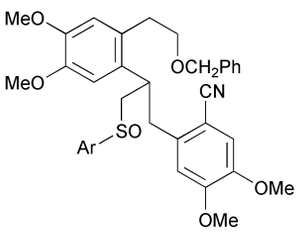

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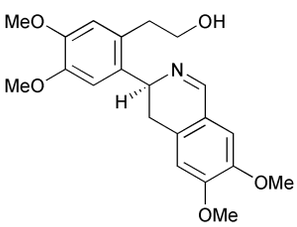

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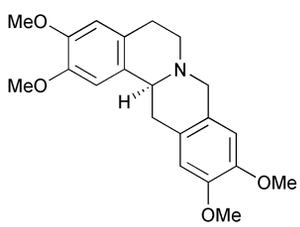
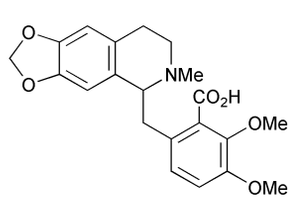


86

isolated from *Hypecoum leptocarpum*.[142] Structures were derived for these new alkaloids on the basis of their NMR spectra, but it should be noted that that assigned to hypecoleptopine does not bear an obvious relationship to that of any alkaloid of the berberine or benzylisoquinoline groups, containing in its skeleton four additional carbon atoms in a naphthalene system.



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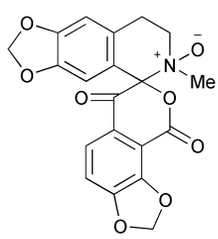

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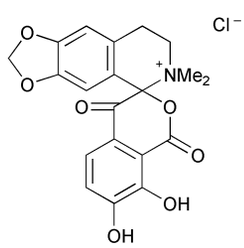

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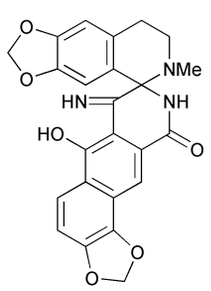


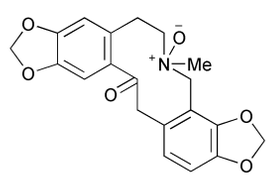
90

9 Protopines

Protopine has been isolated from *Fumaria schleicheri*.[143] The pyrolysis of protopine *N*-oxide **91** has afforded the oxamine **92**, resulting from a Meisenheimer rearrangement, together with the phenylnaphthalene **93**.[144]

10 Phthalide–isoquinolines

The phthalide–isoquinoline alkaloids adlumidiceine and *N*-methylhydrasteine have been isolated from *Fumaria*



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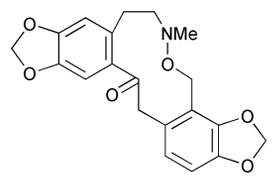

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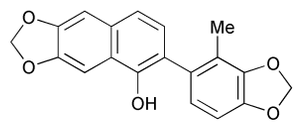
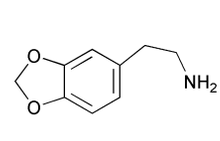


93

schleicheri.[143] The pharmacological properties and physiological effects of bicuculline have been studied.[145–149]

11 Other modified berberines

A novel synthesis of (±)-lennoxamine has been achieved. Homopiperonylamine **94** was condensed with 5-oxo-1,3-dioxine **95** and the resulting imine was acylated with the acid chloride **96** to give the enamide **97**. This, on treatment with boron trifluoride etherate, suffered a retrocycloaddition to afford **98**, which then cyclised to the benzazepine **99a**. Oxidation of this aldehyde gave the acid **99b**, which, when subjected to a Kochi reaction, gave the enamide **100** and free-radical cyclisation of this with tributyltin hydride yielded (±)-lennoxamine **101**.[150] A related synthesis of (±)-aphanorphine is described in section 19.



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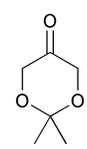

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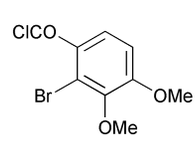

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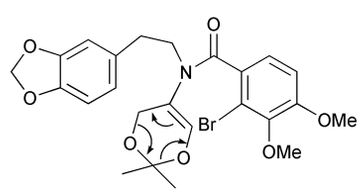

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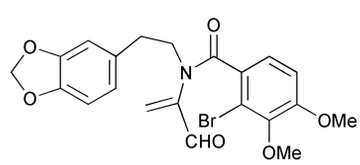

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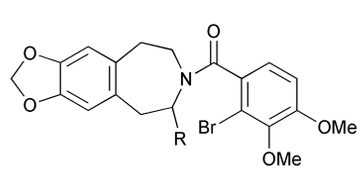
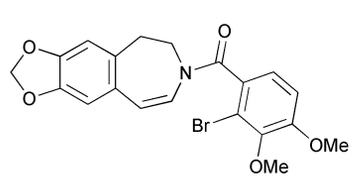


99a R = CHO
99b R = CO_2H



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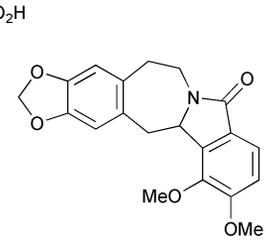


101

12 Benzophenanthridines

Benzophenanthridine alkaloids have been isolated from the following plant species:

Chelidonum majus[106]
sanguinarine and oxosanguinarine

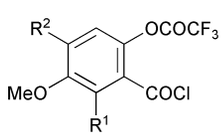
Zanthoxylum caudatum[151]
8-acetonyldihydroavicine, 8-acetonyldihydronitidine and decarine

Zanthoxylum piasezkii[152]
N-demethylchelerythrine

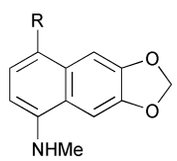
Zanthoxylum tetraspermum[151]
8-acetonyldihydroavicine, 8-acetonyldihydronitidine and decarine

The amines **103a** and **103b** have been acylated with the acid chlorides **102a** and **102b** to give the amides **104a**–**104c**, which were cyclised to oxochelerythrine **105a**, oxonitidine **105b** and 12-methoxyoxochelerythrine **105c** by palladium diacetate in the presence of the bidentate ligand 1,3-bis(diphenylphosphino)-propane and triphenylphosphine. Similar results were obtained with analogues of **104** in which the trifluoroacetoxy group was replaced by bromine or by iodine.[153]

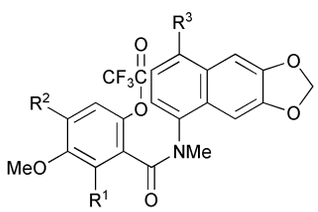
The pharmacological properties and physiological effects of chelerythrine,[154–156] of sanguinarine,[157,158] of 8-acetonyl-dihydroavicine[151] and of 8-acetonyldihydronitidine[151] have been studied.



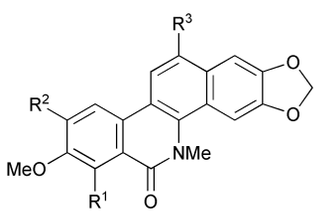
102a R^1 = OMe, R^2 = H
102b R^1 = H, R^2 = OMe



103a R = H
103b R = OMe



104a R^1 = OMe, R^2 = R^3 = H
104b R^1 = R^3 = H, R^2 = OMe
104c R^1 = R^3 = OMe, R^2 = H



105a R^1 = OMe, R^2 = R^3 = H
105b R^1 = R^3 = H, R^2 = OMe
105c R^1 = R^3 = OMe, R^2 = H

13 Emetine and related alkaloids

Five new tetrahydroquinoline–monoterpene glycosides, demethylisoalangiside **106**, demethylalangiside 2-*O*-β-D-glucoside **107**, (4*R*)-4-hydroxyipecoside **108**, ipecoside 6″-*O*-β-D-glucoside **109** and ipecoside 6″-*O*-α-D-glucoside **110** have been isolated as new alkaloids, together with the known alkaloids demethylalangiside and ipecoside, from *Cephaelis acuminata*.[159]

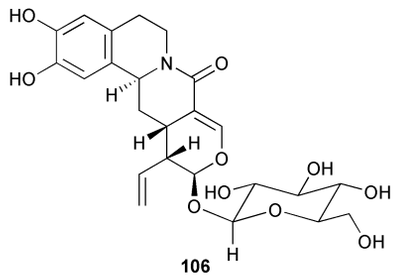
14 Aporphinoid alkaloids

14.1 Proaporphines

Proaporphine alkaloids have been isolated from the following plant species, the seven marked with asterisks being new alkaloids:

Artabotrys uncinatus[47]
stepharine

Cryptocarya chinensis[103,104]
1-*O*-demethylcryprochine* **111**, isoamuronine* **112a**, isocryprochine* **113**, pro-oxocryprochine* **114** and 8,9-dihydrostepharine* **112b**



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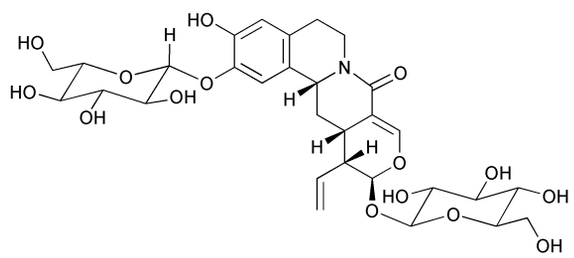

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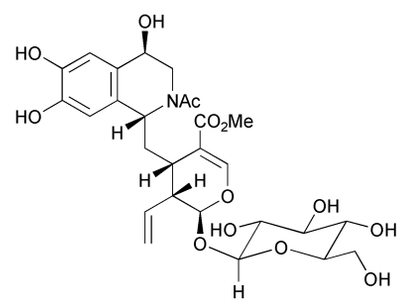

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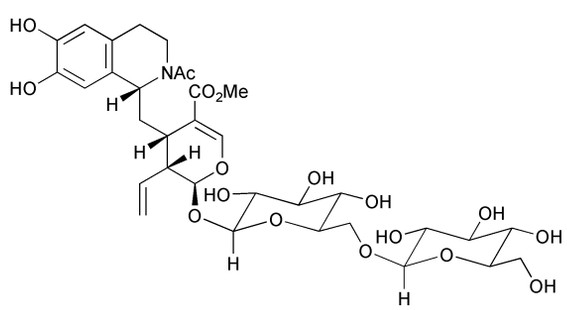

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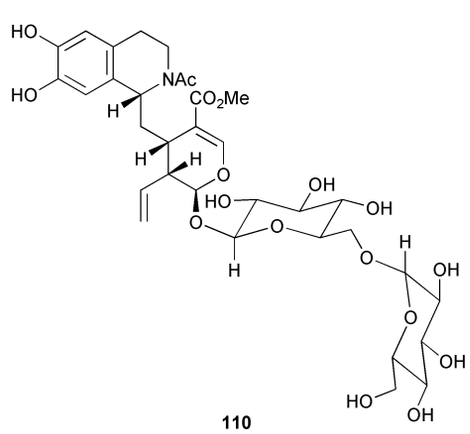
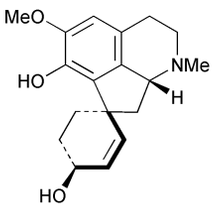


110

Roemeria hybrida[160]
roehybridine α-*N*-oxide* **115** and roehybramine β-*N*-oxide* **116**

14.2 Aporphines

Aporphine alkaloids have been isolated from the following plant species, the four marked with asterisks being new alkaloids:



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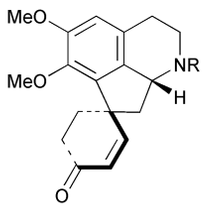
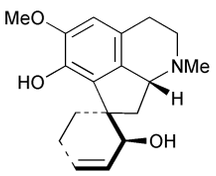


112a R = Me
112b R = H



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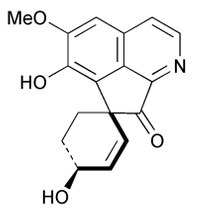

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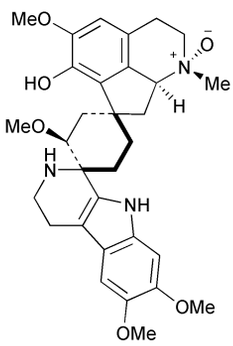

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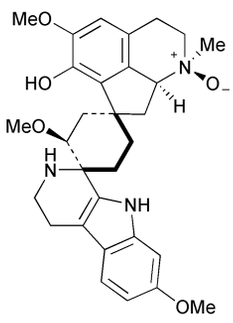

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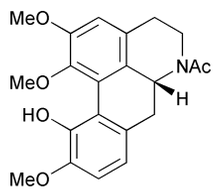

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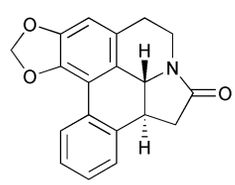

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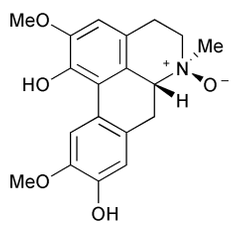

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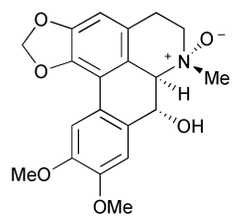
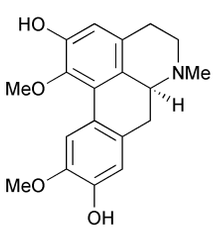


120

Annona cherimola[39]
artabonatine B and romucosine H* **117**
Artabotrys uncinatus[47]
anonaine, artabonatine D* **118**, asimilobine, cissaglaberimine, isocorydine, isopiline, *N*-methylisopiline, norisocorydine, *O*-methylnorlirinine, nornuciferine, norstephalgine, *N*-acetylnorstephalgine, norushinsunine, roemerine and stephalgine
Cryptocarya chinensis[103,104]
glaucine and isoboldine β-*N*-oxide* **119**
Desmos dasymachalus[161]
dasymachaline and dasymachaline α-*N*-oxide* **120**
Desmos yunanensis[48]
anonaine
Duguetia flagellaris[162]
calycinine, duguetine, duguevanine, isopiline, *O*-methylisopiline nornuciferine, oliveridine, oliveroline, oliveroline β-*N*-oxide and pachypodanthine
Hernandia nymphaeifolia[75]
laetine
Lindera glauca[2]
isoboldine, laetanine, norisocorydine and *N*-methyllarotetanine
Phoebe formosana[163]
laurolitsine
Phoenicanthus obliqua[107]
glaucine
Thalictrum wangii[109]
magnoflorine

The heterocyclic compounds **122** and **123** have been prepared from boldine **121**[164] and *O*,*O*′-methylenebisisofugipavine **124** has been obtained by heating the sodium salt of the alkaloid with dichloromethane.[54] Patents have appeared on the conversion of laurolitsine through glaucine into thaliporphine and the formation from this of the derivatives **125a**–**125d** for use as treatments for cardiac arrhythmias[163] and on the preparation of 3-*O*-esters of apomorphine.[165] Details of the synthesis of (*R*)-11–2′,6′disubstitutedphenylaporphines *e.g.* **12b** as serotonin receptor antagonists[166] have been published.



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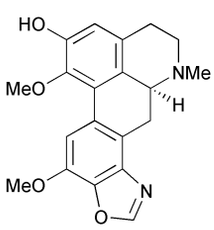

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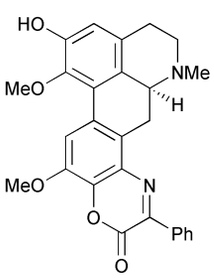

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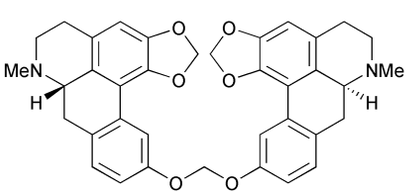

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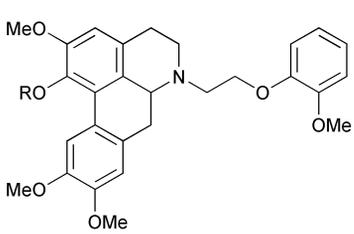
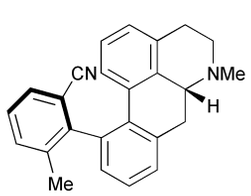


125a R = COMe
125b R = COEt
125c R = COPr^{n}
125d R = COOBu^{t}



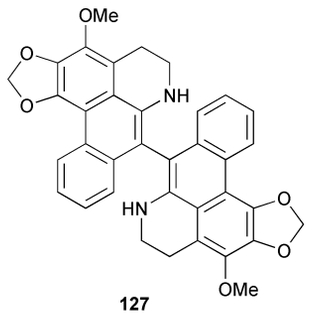
126

The pharmacological properties and physiological effects of apomorphine[167–201] and of laetine[75] have been studied.

14.3 Dimeric aporphines

A new 7,7′-bisdehydroaporphine, artabonatine F **127**, has been isolated from *Artabotrys uncinatus*[47] and its close analogues, the known alkaloids urabaine, 7,7′-bisdehydro-*O*-methylisopiline and 7-dehydronuciferyl-7′-dehydro-*O*-methylisopiline, have been isolated, together with the new alkaloid phoenicanthusine **128**, have been isolated from *Phoenicanthus obliqua*.[107] Phoenicanthusine, the structure of which was determined solely from its spectra, is a dimer of dehydronuciferine and dehydroglaucine and is the first dimeric aporphine to be discovered with

two linkages, 4,6′ and 5,7′, between the two units. The other known dimeric aporphines are 7,7′-linked as in **127**, 4,7′-linked as in polybeccarine and beccapoline,[202,203] 8,8′-linked as in 8,8′-bisisocorydine[204] or singly linked through oxygen as in the 8,11′-linked *O*-bisisocorydine **129**[205] and its 8,9′-linked isomer dehatripine.[204]



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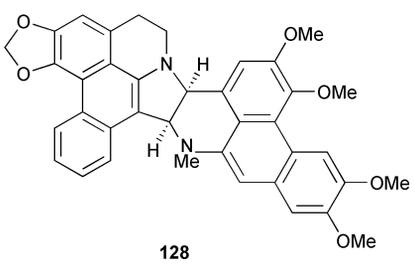

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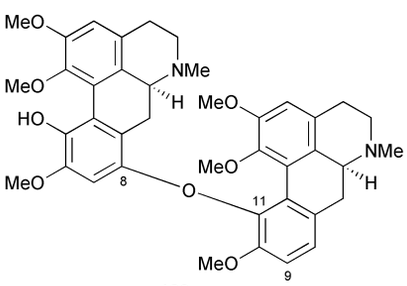


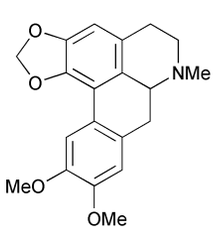
129

14.4 Aporphine–benzylisoquinoline dimers

The aporphine–benzylisoquinoline dimer thalmelatidine has been isolated from *Thalictrum wangii*.[109] Fifty-six alkaloids of this type are known and all except uskudaramine, which is a biphenyl, are linked through oxygen. The oxygen-linked aporphine dimers *O*-bisisocorydine **129** and dehatripine and the aporphine–berberine dimers thalibealine **77** and acutioporberine **78** are simply further members of this class.

14.5 Secoaporphines (phenanthrenes)

N-Methylsecoglaucine has been isolated from *Phoenicanthus obliqua*[107] Treatment of dicentrine **130** with ethyl formate has given the phenanthrene **131a**, and this has been converted into the tertiary amines **131b**–**131e**. All of these compounds exhibit strong cytotoxic effects on several cancer cell lines.[206]



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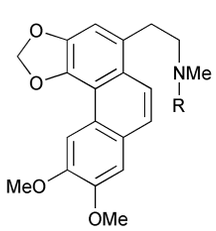
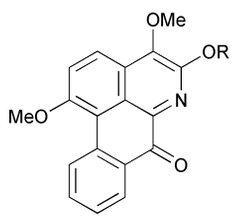


131a R = CO_2Et
131b R = Et
131c R = Bu
131d R = CH_2CN
131e R = CH_2CH_2OH

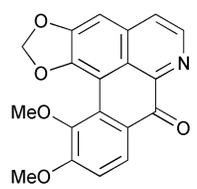
14.6 Oxoaporphines

Oxoaporphine alkaloids have been isolated from the following plant species, the three marked with asterisks being new alkaloids:

Artabotrys uncinatus[47]
artabonatine C* **132a**, artabonatine D* **132b**, artacinatine, atherospermidine, *O*-methylmoschatoline and oxoasimilobine
Desmos dasymachalus[161]
dicentrinone
Hernandia nymphaeifolia[75]
oxo-*O*-methylbulbocapnine* **133**
Zanthoxylum caudatum[151]
liriodenine
Zanthoxylum tetraspermum[151]
liriodenine



132a R = Me
132b R = H



133

Liriodenine has been found to have potent antifungal activity[151] and atherospermidine to have potent cytotoxic effects against hepatocarcinoma cell lines.[47]

14.7 Dioxoaporphines

A novel synthesis of *N*-methyluregidione has bee achieved. 3,4,5-Trimethoxybenzaldehyde and *N*-methylanisylamine afforded the carbinolamine **134**, which reacted with diphenylphosphane oxide to give **135**. Treatment of this with butyllithium and 2-bromobenzaldehyde gave the enamine **136**, which was cyclised by tributyltin hydride to the aminophenanthrene **137**. Reductive removal of the anisyl group and acylation of the resulting secondary amine with oxalyl chloride afforded the acid chloride **138**, which was cyclised by stannic chloride to *N*-methyluregidione **139**.[207]

14.8 Aristolactams

Aristolactam A-Ia **140a** and its 8-*O*-methyl ether **140b**, which is a new alkaloid, have been isolated from *Goniothalamus cheliensis*.[208]

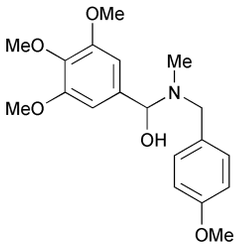
The azaaristolactam eupolauramine has been synthesised by a process similar to that leading to the amine **137**. Cyclisation of the amide **141** yielded the lactam **142**, the lithium salt of which condensed with 2-iodobenzaldehyde to give the benzylic alcohol, which was dehydrated to the *E*-olefin **143**. Cyclsation of this with tributyltin hydride afforded the azaphenanthrene **144a**, which was converted through the bromo and hydroxy compounds **144b** and **144c** into eupolauramine **144d**.[209]

14.9 Oxoisoaporphines

Four new oxoisoaporphine alkaloids, daurioxoisoporphines A **145**, B **146**, C **147** and D **148** have been isolated from *Menispermum dauricum*. Daurioxoisoporphines A and B show cytotoxic effects on certain cancer cell lines.[210]

15 Alkaloids of the morphine group

Alkaloids of the morphine and related groups have been isolated from the following plant species, the two marked with asterisks being new alkaloids:



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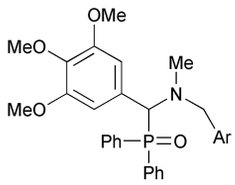

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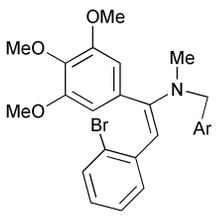

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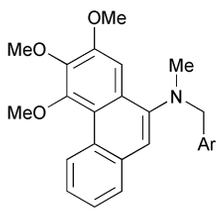

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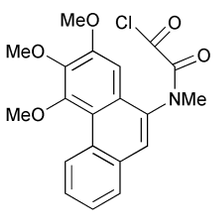

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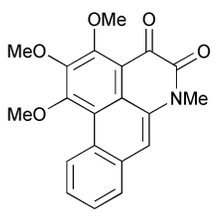

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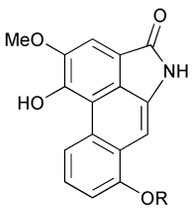
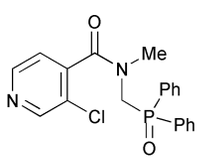


140a R = H
140b R = Me



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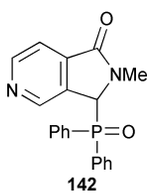

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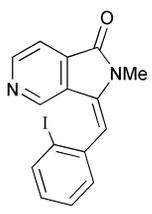

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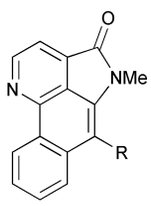


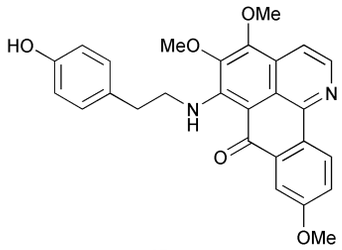
144a R = H
144b R = Br
144c R = OH
144d R = OMe

Artabotrys uncinatus[47]
flavinantine and salutaridine

Lindera glauca[2]
N-methylflavinantine and pallidine

Menispermum dauricum[211]
acutumine **149a**, acutumidine **149b**, dauricumine* **150a** and dauricumidine* **150b**

Dauricumine and dauricumidine are epimers of acutumine and acutumidine respectively and when the four alkaloids, labelled with chlorine-36, were fed to root cultures of *Menispermum dauricum* dauricumine was converted into acutumine and



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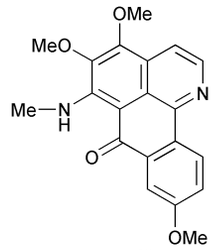

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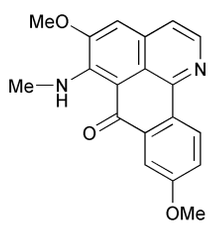

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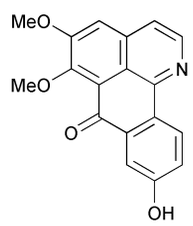
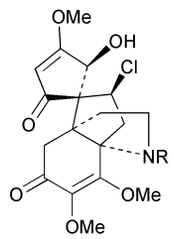
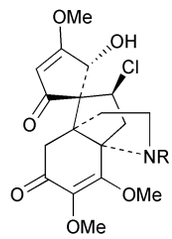


148



149a R = Me
149b R = H

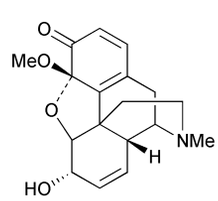


150a R = Me
150b R = H

acutumidine, but the reverse transformations were not observed, indicating that dauricumine is the first alkaloid to be produced; mutual interconversions between dauricumine and dauricumidine and between acutumine and acutumidine were observed, but dauricumine was not converted into acutumidine.[211]

The progress of the production of thebaine, codeine and morphine at various stages in the growth of *Papaver somniferum* plants has been studied[212] and a process for the extraction of sinomenine from *Sinomenium diels* has been published.[213]

The oxidation of morphine with phenyliodo(III) diacetate in the presence of methanol has afforded the *O*-quinone ketal **151**. The increased stereochemical flexibility in dihydromorphine allows the C-6 hydroxy group to participate in this reaction and oxidation of this compound afforded the ketal **152**, whereas dihydroisomorphine, in which such participation is not possible, behaves like morphine, giving **153**, as does naloxone, which is oxidised to **154**. The loss of aromaticity in ring A is accompanied by a marked diminution in antinociceptive properties in **151**–**153**.[214]



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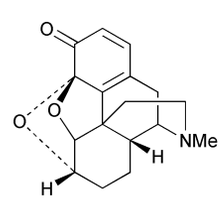

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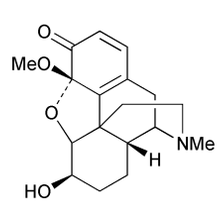

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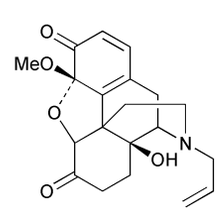
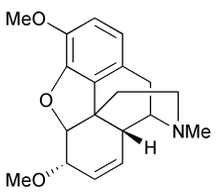


154

Codeine methyl ether **155** has been oxidised to thebaine **156** by manganese dioxide in 95% yield, using the ionic liquid l-butyl-3-methylimidazolinium tetrafluoroborate to remove excess of the oxide.[215] Rearrangement of thebaine by methanesulfonic acid in the presence of thiophenol has given the aporphine **157a** and, in the presence of thiosalicylic acid, the related acid **157b**, together with the ketone **158** and the ketal **159**. Hydrolysis of this ketal with acid yielded the thioxanthylium salt **160**.[216]



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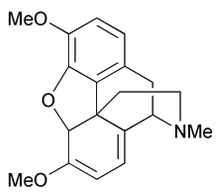

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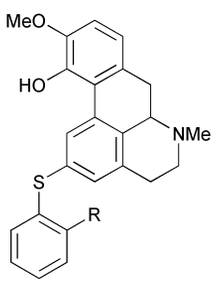
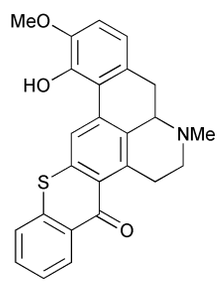


157a R = H
157b R = CO_2H



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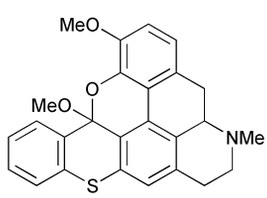

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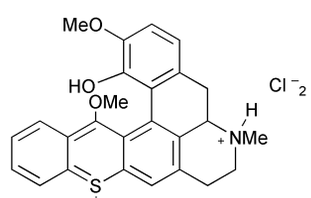
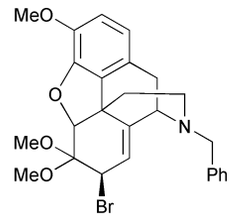


160

N-Benzyl-7-bromonorneopinone dimethyl ketal **161**, on treatment with 2-hydroxyethylamine, has been rearranged to the hasubanan derivative **162a**. The *N*-benzoyloxycarbonyl derivative of this **162b** has been hydrolysed to the oxazolidinone **163**, the structure of which was confirmed by X-ray crystallography.[217] 14-Hydroxydihydrocodeinone **164a** and its methyl ether **164b** suffer fission of the 4,5-oxygen bridge on treatment with toluenesulfonylmethyl isocyanide to give 6-cyano-14-hydroxydihydrodeoxycodeine C **165a** and its methyl ether **165b**.[218]



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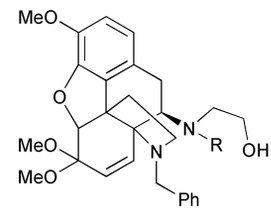
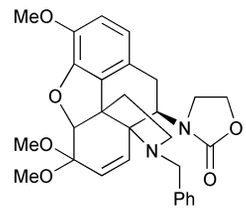


162a R = H
162b R = $COOCH_2Ph$



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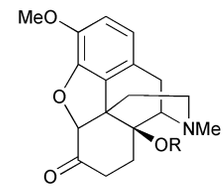
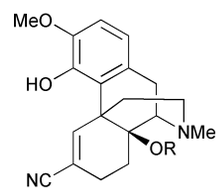


164a R = H
164b R = Me



165a R = H
165b R = Me

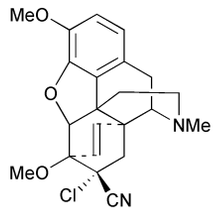
In the 6, 14-*endo*-ethenotetrahydrothebaine series an improved hydrolysis of the chloronitrile **166** to the ketone **167**, by sodium sulfide enneahydrate has been described.[219] The Diels–Alder adduct **168a** has been demethylated by hydrogen bromide successively to **168b** and **168c**. More prolonged treatment leads to the rearranged products **172** and **173**, the structure of **173** being determined by X-ray crystallography and of **172** by NMR spectroscopy. A reaction mechanism proceeding through the intermediates **168c**, **169**, **170**, and **171** to give **172**, with final dehydration of the carbinolamine to the imine **173** has been proposed.[220]

Details of the *N*-demethylation of codeine methyl ether through its *N*-oxide,[221] of the preparation of nalbuphine and its derivatives,[222] of diazoles such as **174** and **175**,[223] of pyrroles of general type **176**,[224] of indoles of type **177**[225–228] and of the 3-carboxamido-3-deoxymorphines **178a**–**178c** and **179**[229] have been published. A wide range of 6-sulfonylamino compounds of general structure **181** has been prepared by the reductive amination of naltrexone **180** bound on a solid support of Wang resin, with sulfonylation of the resulting amine before freeing it from the support.[230]

Methods of estimating morphine,[231–235] morphine glucuronides,[234,235] codeine[233,236] naltrexone[237] naltrexol[237] and buprenorphine[238–242] have been described.

A chiral synthesis of (−)-dihydrocodeinone has been achieved starting from the (−)-ketone **182**, in which the protecting group R is methoxymethyl. Reaction of this with 2,3-dimethoxyphenyllithium afforded the alcohol **183** which was oxidised to the enone **184** and this reacted with vinylmagnesium chloride, copper(I) bromide and trimethylsilyl chloride to give **185**. Treatment of **185** with *N*-bromosuccinimide gave the bromoketone **186**, which was cyclised to the benzodihydrofuran **187** as a single diastereoisomer. Protection of the carbonyl group as a cyclic ketal, followed by hydroboration, then afforded the diol **188a**, which was converted into the monopivalyl ester **188b**. When this was heated with ethylene glycol, benzene and toluenesulfonic acid, with removal of water by azeotropic distillation, it was converted, presumably *via* intermediates such as **189** and **190**, into the olefin **191a**. Conversion of this through **191b** into **191c**, followed by reduction with lithium and ammonia, afforded the cyclic ketal **192**, which can be hydrolysed to the ketone (−)-dihydrocodeinone.[243]

The analgesic action[244–303] pharmacokinetics[304–306] and metabolism[307,308] of morphine have been studied, as have the effects of the alkaloid on behaviour,[309–330] on respiration,[331–336] on the cardiovascular system,[335–338] on the gastrointestinal tract,[339–341] on immune responses,[342–345] on learning and memory,[346–349] on perception,[350] on locomotor activity,[351–355] on the brain,[356] on the pituitary[357] and thymus[358,359] glands, on neurones,[360] on synaptic transmission,[361–363] on hypersensitivity,[364] on temperature regulation,[365–367] on cell proliferation,[368] on smooth muscle cells,[369] on the progress of multiple sclerosis,[370] on glucose tolerance,[371] on retention of urine,[372] on pruritus,[373] on neonates,[374–377] on *status epilepticus*,[378] on dystonia,[379] on apoptosis,[380,381] on the pathogenesis of *Herpes simplex* virus,[382] on cholinergic activity,[383] and on levels of adrenocorticotropic hormone,[384] of calmodulin,[385] of cholecysto-



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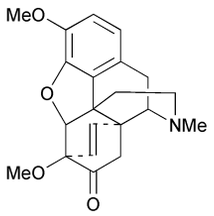

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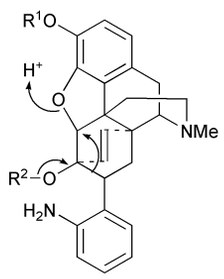
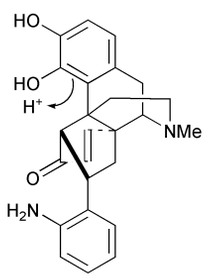


168a $R^1 = R^2 = Me$
168b $R^1 = Me$, $R^2 = H$
168c $R^1 = R^2 = H$



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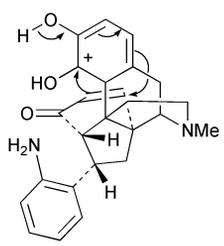

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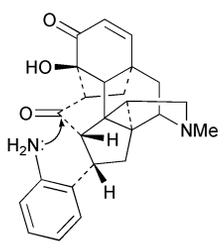

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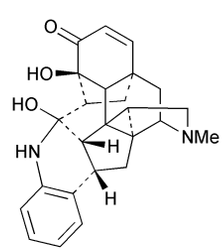

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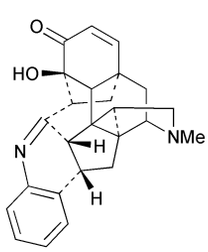


173

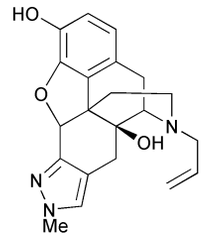
kinin,[386–388] of corticosterone,[389] of dynorphin A,[390] of enkephalins,[391] of oestrogens,[392] and gonadal hormones,[393] of interleukins,[394–397] of thyroxine,[398] of substance P[399,400] and of nitric oxide.[401–404]

The morphine antagonist actions of naolone[405–409] have been studied, as have the effects of this ketone on behaviour,[410–416] on the cardiovascular system,[417–420] on heat sugar intake[421] and glucose levels,[422] on the consumption of ethanol,[423] on heat stroke,[424] on the secretion of catecholamines[425] and serotonin,[426] on calcium turnover,[427,428] on glutamate transport,[429] on lymphocytes,[430] on sensitivity to profolol[431] and on fentanyl-induced brain damage.[432]

Studies have also been reported of the pharmacological properties and physiological effects of morphine 3-glucuronide,[433–436] morphine 6-glucuronide,[434–442] 6-*O*-acetylmorphine,[443] *O*,*O*-diacetylmorphine (heroin),[444–462] codeine,[463–471] dihydromorphinone,[472–477] dihydromorphinone glucuronide,[478] dihydrocodeinone,[479] 14-hydroxydihydrocodeinone,[479–482] naloxone benzoylhydrazone,[483] naltrexone,[484–491] methylnaltrexone,[492] nalbuphine,[493–497] naltrindole,[498] buprenorphine[499–531] and dihydroetorphine.[532]

16 Phenethylisoquinolines

The dibromoquinoline **193** has been reacted with the silyl enol ether **194** and the chiral substituted alanyl chloride **195** to give the (*S*)-1,2-dihydroisoquinoline **196**, with high stereoselectivity.



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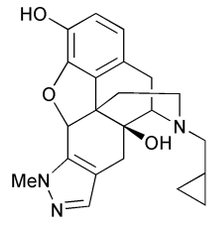

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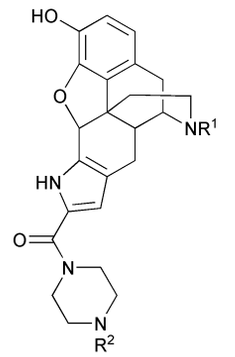

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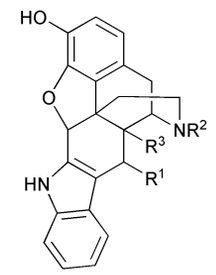

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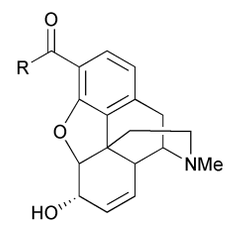
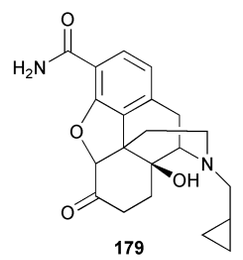


178a $R = NH_2$
178b R = NHMe
178c $R = NMe_2$



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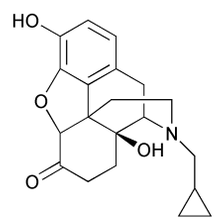
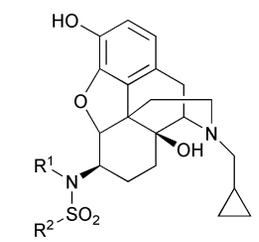
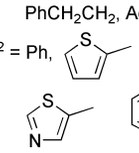
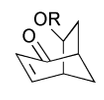


180



181 R^1 = Me, Et, $PhCH_2$, $PhCH_2CH_2$, $AcNHCH_2CH_2$
R^2 = Ph,





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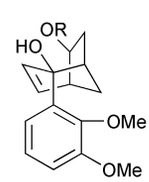

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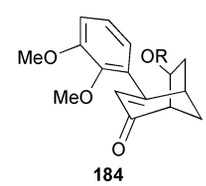

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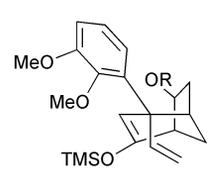

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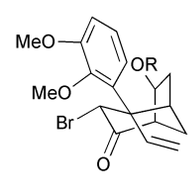

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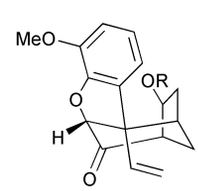

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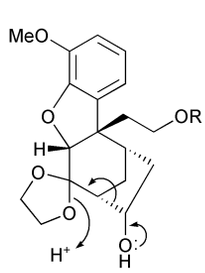
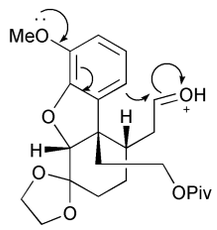


188a R = H
188b R = $COCMe_3$



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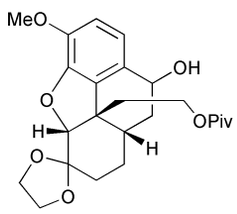

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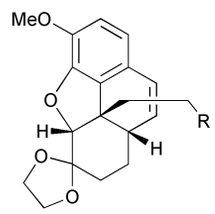
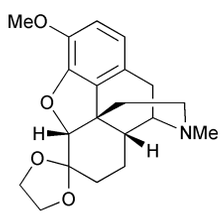
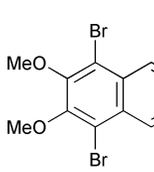


191a R = $OCOCMe_3$
191b R = OH
191c R = $NMeSO_2Ph$



192

Catalytic reduction of this removed the bromine to give the tetrahydroisoquinoline **197** and further reduction of the carbonyl group yielded **198a**, which could be cleaved by reduction with lithium aluminium hydride only in poor yield and with partial racemisation. Reduction of the amide **198b**, however, proceeded smoothly to give the phenethyltetrahydroisoquinoline **199a**, which was *N*-methylated to (*S*)-(+)-*O*,*O*-dimethylautumnaline **199b**, previously oxidised to the homoaporphine alkaloid (*S*)-(+)-*O*-methylkrysigine **200**. Cyclisation of the secondary base **199a** with formaldehyde yielded the homoberberine **201**, which is not a natural product.[533]



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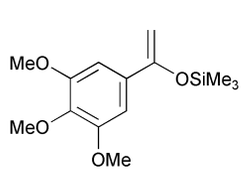

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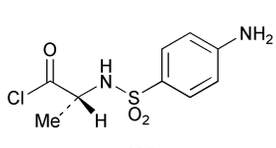

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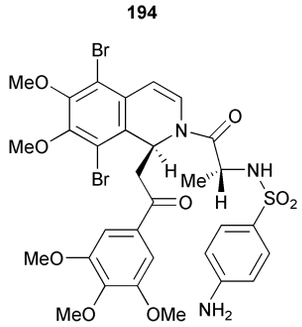

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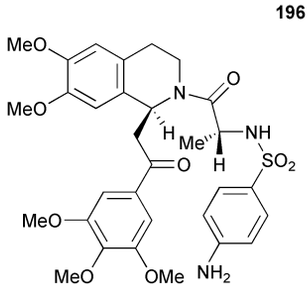

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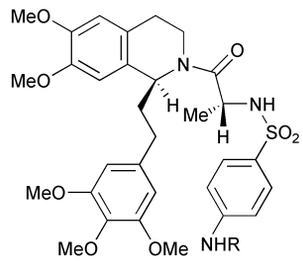
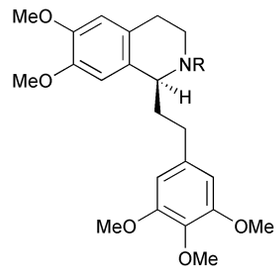
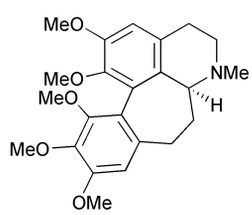


198a R = H
198b R = $COCF_3$



199a R = H
199b R = Me



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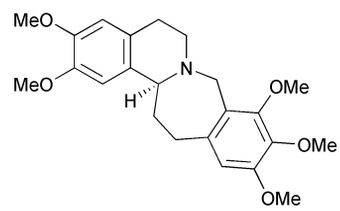
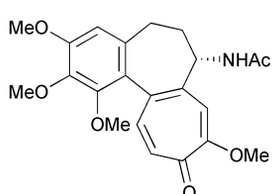


201

17 Colchicine and related alkaloids

Colchicine has been isolated from *Colchicum autumnale*.[534]

Photochemical oxidation of isocolchicine **202** with singlet oxygen has afforded the *endo* and *exo* peroxides **203** and **204** in a 1 : 7 ratio. Treatment of **204** with triethylamine afforded an inseparable mixture of the isomeric hemiketals **205** and **206**, which in ethyl acetate were converted by silica gel into the cyclic ether **207**.[535]



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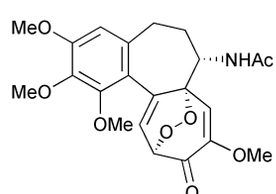

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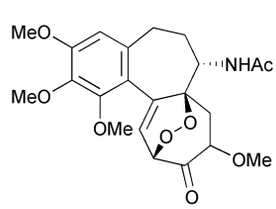

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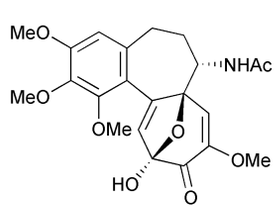

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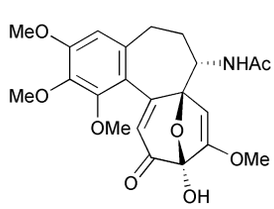

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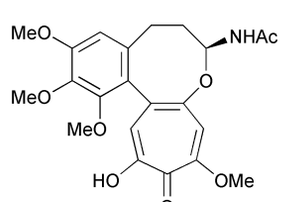
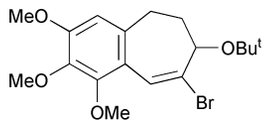


207

The carbene–chromium carbonyl complex **209**, formed from **208**, has been annulated to the allocolchinoid compound **210**.[536] Patents for the preparation of derivatives of *N*-deactylthiocolchicine[537,538] and of colchinol[539,540] have been published.

The pharmacological properties and physiological effects of colchicine have been studied.[541–551]



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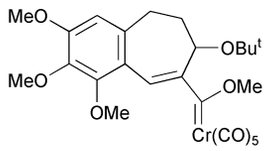

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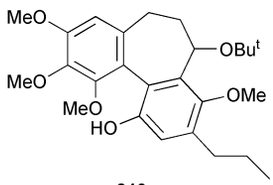
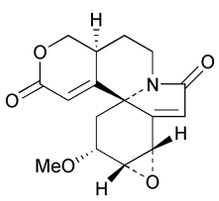


210

18 *Erythrina* alkaloids

18.1 Erythrinanes

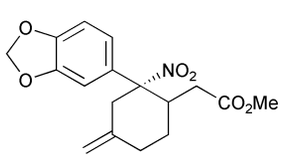
Erysodine, erysotrine, erythrartine and erythristemine have been isolated from *Erythrina lysistemon*.[552] 8-Oxo-α-erythroidine, together with the new alkaloid 8-oxo-α-erythroidine-1,2-α-epoxide **211**, have been isolated from *Erythrina poeppigiana*.[553]



211

Condensation of methylenedioxyphenylnitromethane with the methyl ester of 6-(acetoxymethyl)hepta-2,5-dienoic acid has given the nitro-ester **212**, which was reduced to the amine with simultaneous lactonisation to give **213** Addition of this to phenyl vinyl sulfoxide, followed by Pummerer cyclisation, afforded the tetrahydroisoquinoline **214**, Desulfurisation of this and oxidative cleavage of the methylene group yielded the ketone **215**, which was reduced with sodium borohydride and *O*-methylated to give (±)-dihydrocrystamidine **216**. This was reduced with lithium aluminium hydride to (±)-dihydroerythramine **217**.[554]

A first synthesis of (±)-cocculolidine has been achieved. The imine **218** was coupled with tetronic acid to give the amino-



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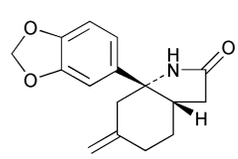

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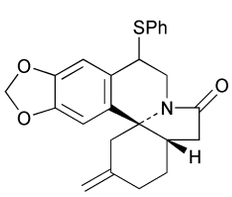

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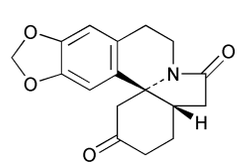

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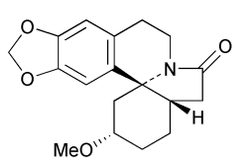

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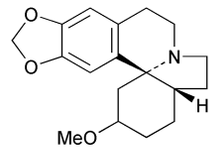
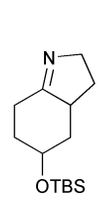


217

lactone **219**, the *N*-*t*-butoxycarbonyl-*O*-methanesulfonyl derivative of which with tributylvinyl tin gave the vinyl compound **220**. This was cyclised by trifluoroacetic acid to the amine **221**, which was oxidised to the ketone **222**. The enol ether **223** of this, when treated with benzeneselenenyl chloride yielded the enol ether **225**, which was oxidised by osmium tetroxide and hydrogen peroxide to the hydroxyketone **225**. The dithioketal of this was catalytically desulfurised and *O*-methylated to give (±)-cocculolidine **226**.[555]



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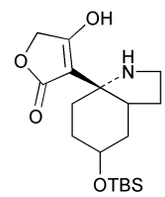

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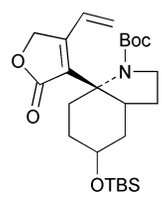

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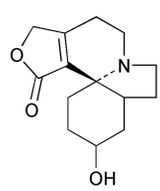

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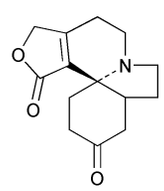

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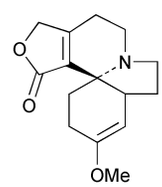

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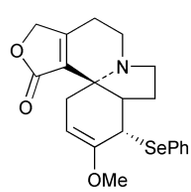

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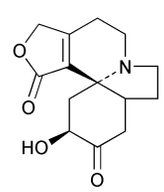

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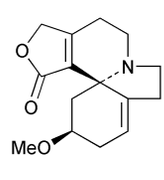


226

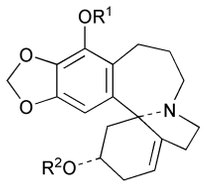
18.2 Homoerythrinanes

Dyshomoerythrine **227a** has been isolated from *Lagarostrobos colensoi* and demethylated to **227b** and **227c**. The allylic amine system of the alkaloid is cleaved on catalytic reduction to give **228** and by peracid oxidation to give **229**. The methiodide of the alkaloid resists Hofmann degradation under the most usual conditions, but with sodium iodide in acetone at 80 °C it is degraded to the dibenzazecine **230**. Dyshomoerythrine and compounds **228**–**230** show insecticidal activity.[556]

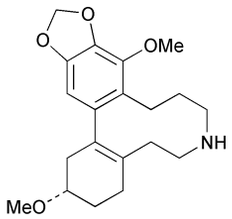
18.3 Cephalotoxine and related alkaloids

Cephalotoxine and homoharringtonine have been isolated from *Cephalotoxus sinensis*[557] and the new polycyclic alkaloid cephalocyclidin A **231** has been isolated from *Cephalotoxux harringtonia*, its structure and relative and absolute stereochemistry being deduced from spectroscopic and X-ray crystallographic data.[558]

The *Z*-olefinic lactam **232** has been oxidised in the presence of methanol to give the monomethyl ether of a diol, which was cyclised by boron trifluoride to the tetrahydroisoquinoline **233**, then dehydrated with rearrangement by thionyl chloride to give **234a**. This was converted through **234b** and **234c** into the keto-ester **234d**, which was cyclised to a diastereoisomeric mixture of the keto-ester **235**. Hydrolysis and decarboxylation of this gave



227a $R^1 = R^2 = Me$
227b $R^1 = Me$, $R^2 = H$
227c $R^1 = R^2 = H$



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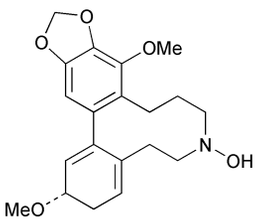

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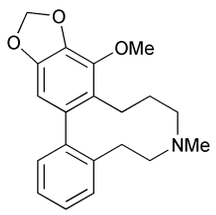

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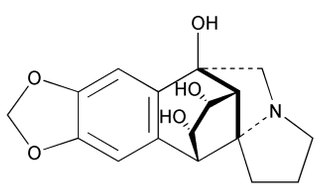
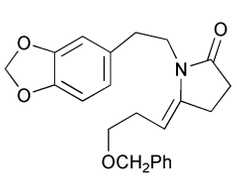


231

the *cis* ketone **236** as only a minor product, but when **234a** was treated with *N*-iodosuccinimide and titanium tetrachloride it was converted into the unsaturated keto-ester **237**, which on hydrogenolysis and decarboxylation gave the *cis* ketone **236** in high yield. Since **236** has been converted into (±)-cephalotoxine this process constitutes a formal synthesis of the racemic alkaloid.[559]



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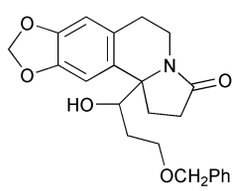

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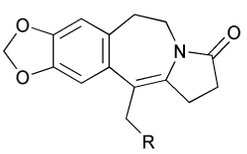
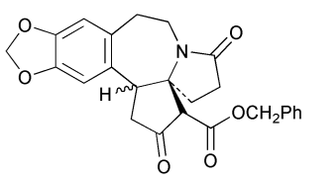


234a $R = CH_2OCH_2Ph$
234b $R = CH_2OH$
234c $R = CHO$
234d $R = COCH_2CO_2$



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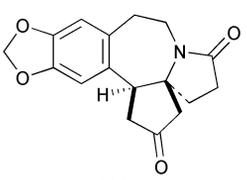

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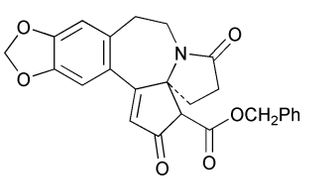
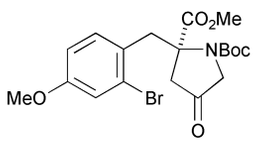


237

A patent for the preparation of esters of cephalotoxine has been published[560] and the physiological and antitimour effects of harringtonine[561,562] and of homoharringtonine[562–569] have been studied.

19 Other alkaloids

Two syntheses of (−)-aphanorphine **243**, an alkaloid isolated from the freshwater blue-green alga *Aphanizomenon flos-aquae*, which contains the elements of a β-phenylethylamine, have been achieved. *trans*-4-Hydroxy-*N*-benzyloxycarbonyl-L-proline was converted through **238** into **239**, which was cyclised by tributyltin hydride to **240a**. This was hydrolysed to the acid **240b**, which was decarboxylated easily only through **240c** to give **241**. Hydrogenolysis of this over Raney nickel afforded *O*-methylnoraphanorphine **242a**, which was *N*-methylated to **242b** and *O*-demethylated to (−)-aphanorphine **243**.[570]



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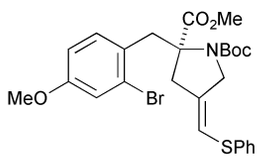

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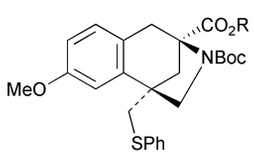
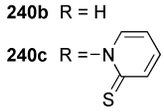
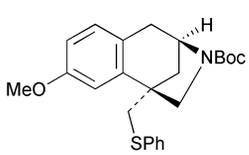


240a R = Me
240b R = H



240c



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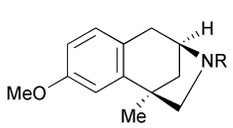
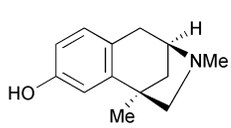


242a R = H
242b R = Me



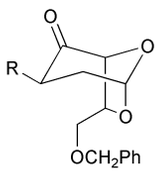
243

The chiral bicyclic keto-ketal **244a** was methylated to **244b**, which was condensed with 4-methoxyphenylhydrazine to give directly the carbinolamine **245** as a single product. Reductive diazotisation of this with sodium nitrite and hypophosphorous acid yielded a ketone, which was reduced in stages to **246a**. This was converted through **246b** and **246c** into the iodide **246d**, which was cleaved by zinc and acetic acid to the hemiacetal **247**, then oxidised to the lactone **248a**. Oxidation of the vinyl group and cleavage of the resulting diol gave the aldehyde **248b**, which was reduced by zinc and acetic acid to **249**. Cyclisation of this afforded the dihydronaphthalene **250a**, which was converted through **250b** into **250c**, an intermediate in a prior synthesis of (−)-aphanorphine **243**.[571]

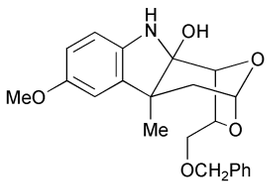
(±)-Aphanorphine has also been synthesised by a process similar to that used in the synthesis of (±)-lennoxamine described in section 11. Cyclisation of the enamide **251** gave the benzazepine **252a** as a single *trans* isomer, which was reduced to the alcohol **252b**. The methanesulfonyl ester of this was cyclised by potassium *tert*-butoxide to the lactam **253**, which was reduced to *O*-methylaphanorphine and demethylated to (±)-aphanorphine.[150]

A first synthesis of (±)-jamtine has been achieved. Cyclisation of **254** with camphorsulfonic acid afforded **255**, which was further cyclised through deprotonation with sodium hydride to give **256**. Oxidation of this to the sulfoxide, followed by elimination yielded the unsaturated lactam **257**, which was converted into the thiolactam and desulfurised to (±)-jamtine **258**.[572]

A total synthesis of (−)-tetrazomine, an antitumour agent closely related to quinocarcin and isolated from *Saccharothrix*



244a R = H
244b R = Me



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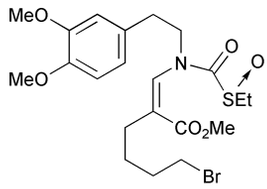

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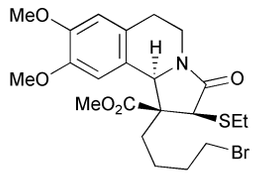

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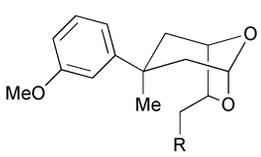
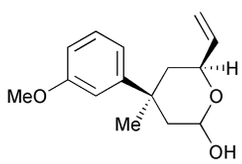


246a R = OCH_2Ph
246b R = OH
246c R = OMes
246d R = I



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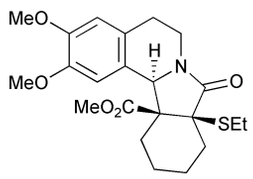
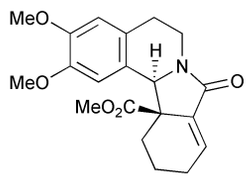
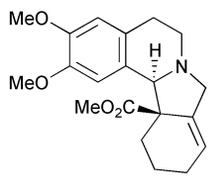


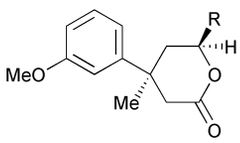
256



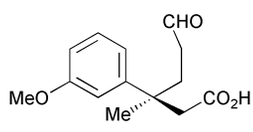
257



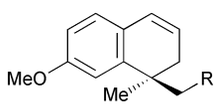
258



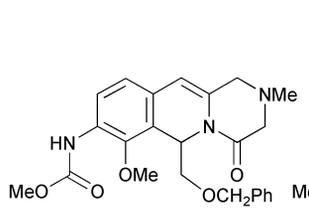
248a R = CH=CH_2
248b R = CHO



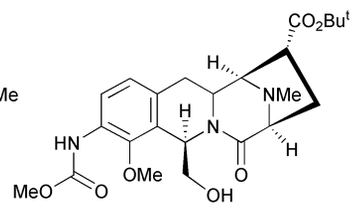
249



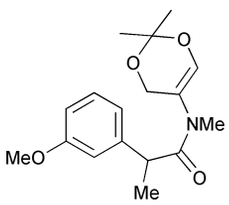
250a R = CO_2H
250b R = NCO
250c R = $NHCO_2Me$



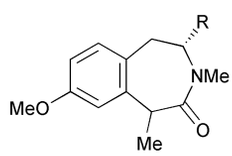
259



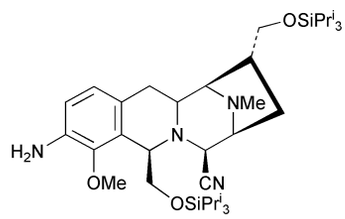
260



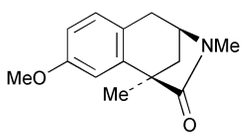
251



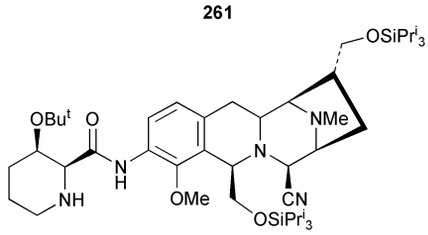
252a R = CHO
252b R = CH_2OH



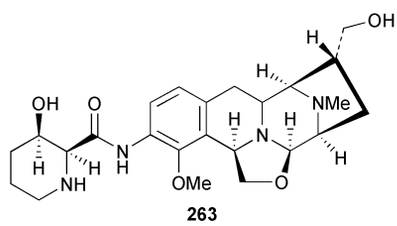
261



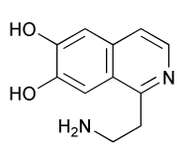
253



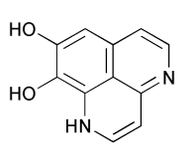
262



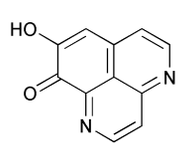
263



264



265



266

mutabilis, has been accomplished. The tertiary amine **259** was converted into the imine by *N*-bromosuccinimide and when this was deprotonated the resulting ylid added to *tert*-butyl acrylate and the product was catalytically reduced to **260**. This was reduced by lithium aluminium hydride, the product was trapped with potassium cyanide and the resulting aminonitrile converted into the triisopropylsilyl ether **261**, which was acylated to the amide **262**. Removal of the protecting groups gave the triol, treatment of which with silver trifluoroacetate effected the final cyclisation to give (−)-tetrazomine **263**.[573,574] Tetrazomine has substantial structural elements in common with the ecteinascidins and saframycins, approaches to the synthesis of which have also been studied.[575–580]

1-Aminoethyl-6,7-dihydroxyisoquinoline **264** has been oxidised by oxygen in alkaline solution and by potassium persulfate to *O*,*O*-demethylaaptamine **265** and *O*-demethyloxyaaptamine **266**.[581]

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