

MORPHINANDIENONE ALKALOIDS

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Abstract - Morphinandienone, homomorphinandienone and related alkaloids are reviewed with respect to their isolation, structure elucidation, spectroscopy and synthesis.

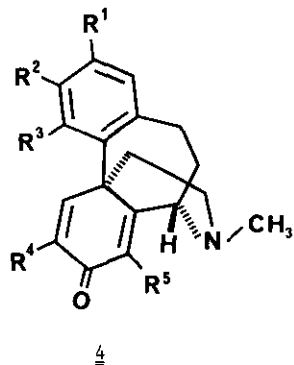
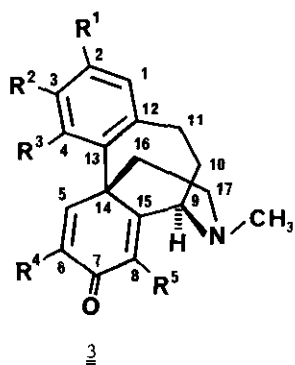
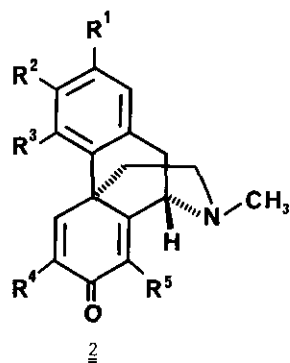
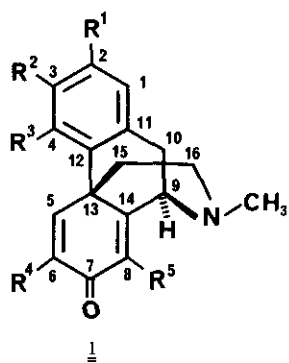
This paper is dedicated to Prof. Csaba Szántay, The Technical University of Budapest, Hungary on the occasion of his 60th birthday.

INTRODUCTION

Morphinandienone alkaloids are widely distributed in many plants of the Papaveraceae and Menispermaceae families, and they play an important role as biosynthetic intermediates in the biogenesis of pharmacologically active morphinan alkaloids¹. However, a number of characteristic properties of the morphinandienones set them apart from the morphinanes, and they are therefore considered as an individual class of the β -phenylethylamine-derived alkaloids.

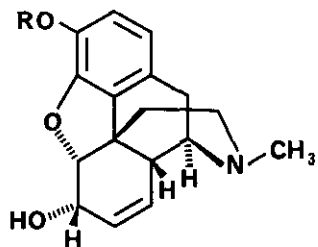
The occurrence, physical data, spectroscopic properties and syntheses of the morphinandienone (1-2) and homomorphinandienone (3-4) alkaloids were last reviewed by Stuart², and Kametani and Fukumoto³, in 1971. Increasing interest focussed on the development of suitable synthetic methodology to produce morphinanes has resulted in substantial advances in the chemistry of the morphinandienone alkaloids during the past sixteen years. In addition, the recently discovered antitumor activity of some morphinandienone alkaloids⁴ has enhanced the importance of this class of alkaloids.

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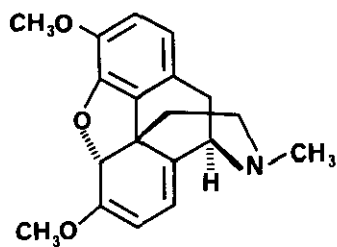
According to their absolute configuration, morphinandienone alkaloids with an R or S configuration at C-9 may be represented by expressions 1 and 2, respectively. Expressions 3 and 4 then represent the corresponding homomorphinandienone alkaloids possessing the R or S absolute configuration at C-9, respectively.

Since the morphinandienones are the experimentally determined biosynthetic precursors of morphine (5), codeine (6), thebaine (7) and sinomenine (8), and the homomorphinandienone alkaloids are believed to be precursors of homomorphine alkaloids, e.g. kreysignine (9), the critical role of these alkaloids in the biosynthetic milieu is well-established.

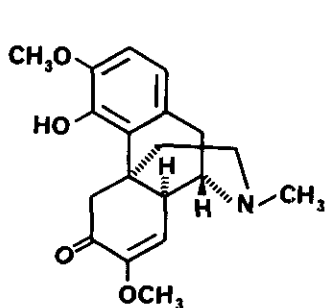


5 Morphine R = H

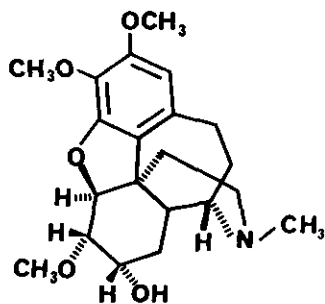
6 Codeine R = CH₃



7 Thebaine



8 Sinomenine



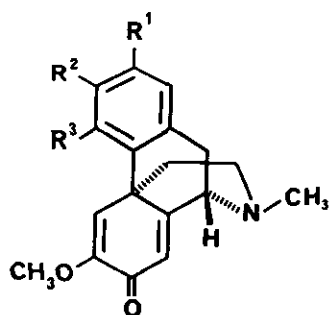
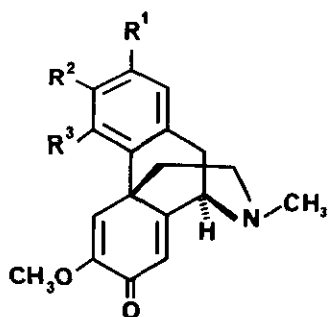
9 Kreysignine

The chemistry of the morphinandienone and homomorphinandienone alkaloids has developed concurrently with the recent investigations to find a reasonable synthetic route to produce natural morphinans, e.g. morphine and codeine, or semisynthetic derivatives such as naloxone, naltrexone and nalbuphine, on a large scale for pharmaceutical applications.

We report here on developments in the isolation, structure elucidation, spectroscopy, and synthesis of morphinandienone and related alkaloids, covering the literature since 1971.

I. ISOLATION AND STRUCTURE ELUCIDATION

The previously known morphinandienone alkaloids (10–16) isolated from new natural sources are summarized in Table 1.



10 Amurine $R^1 + R^2 = OCH_2O$, $R^3 = H$

11 Flavinantine $R^1 = OCH_3$, $R^2 = OH$, $R^3 = H$

12 O-Methylflavinantine $R^1 = R^2 = OCH_3$, $R^3 = H$

14 Salutaridine $R^1 = H$, $R^2 = OCH_3$, $R^3 = OH$

13 Pallidine $R^1 = OH$, $R^2 = OCH_3$, $R^3 = H$

15 Sebiferine $R^1 = R^2 = OCH_3$, $R^3 = H$

16 Sinoacutine $R^1 = H$, $R^2 = OCH_3$, $R^3 = H$

Table 1. ISOLATION OF PREVIOUSLY KNOWN MORPHINANDIENONE ALKALOIDS

<u>Alkaloid</u>	<u>Source</u>	<u>Ref.</u>
Amurine (<u>10</u>)	<u>Meconopsis cambrica</u> Vig.	5
	<u>Papaver pilosum</u> Sibth. et Smith	6
	<u>P. spicatum</u> Boiss. et Bal.	7
	<u>P. strictum</u> Boiss. et Bal.	7
	<u>P. trinifolium</u> Boiss.	8
Flavinantine (<u>11</u>)	<u>Meconopsis cambrica</u> Vig.	5
	<u>Papaver spicatum</u> Boiss. et Bal.	7
	<u>P. strictum</u> Boiss. et Bal.	7
O-Methylflavinantine (<u>12</u>)	<u>Cocculus laurifolius</u> DC.	9
	<u>Nemuaron vicillardii</u> Baill.	10
	<u>Papaver bracteatum</u> Lindl.	11
	<u>Rhigiocarya racemifera</u> Miers	12,13
Pallidine (<u>13</u>)	<u>Chasmanthera dependens</u> Hochst	14
	<u>Corydalis insica</u> Pers.	15
	<u>C. koidzumiana</u> Ohwi	16
	<u>Desmos tiebaghiensis</u> (Däniker) R.E.Fr.	17
	<u>Monodora crispata</u> Engl.	18
	<u>Ocotea acutangul</u> Mez.	19
	<u>O. brachybotra</u> (Meiss) Mez.	20,21
	<u>Rollinia mucosa</u> Baill.	22
	<u>Thalictrum dioicum</u> L.	23,24
	<u>T. faberi</u> Ulbr.	25
Salutaridine (<u>14</u>)	<u>Croton salutaris</u> Casar	26
	<u>Glaucium vitellinum</u> Boiss. et Buhse.	27
	<u>Papaver bracteatum</u> Lindl.	28,29,30
	<u>P. lasiothrix</u> Fedde	28,29,30
	<u>P. pseudoorientale</u> Fedde	28
	<u>P. trinifolium</u> Boiss.	8
	<u>Stephania brachyandra</u> Diels	31

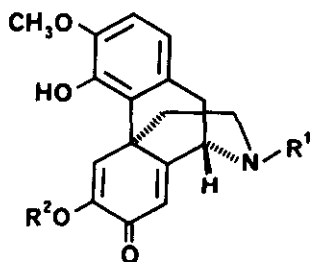
Table 1. (cont.)

Sebiferine (<u>15</u>)	<u>Polyalthia cauliflora</u> var. <u>beccarii</u> King	32
Sinoacutine (<u>16</u>)	<u>Cocculus carolinus</u> DC.	33
	<u>Corydalis incisa</u> Pers.	15
	<u>C. koidzumiana</u> Ohwi	16
	<u>Nandina domestica</u> Thunb.	34
	<u>Ocotea brachybotra</u> (Meiss) Mez.	20,21
	<u>Stephania elegans</u> Hook.f.et Thoms.	35
Norsinoacutine (<u>17</u>)	<u>Croton bonplandianus</u> Baill.	36

New morphinandienone alkaloids are listed in tabular form in Table 2 along with their physical and spectroscopic properties and their natural source(s).

Table 2. NEW MORPHINANDIENONE ALKALOIDS

3-Methoxy-4,6-dihydroxymorphinandien-7-one (18)



mp: 143 °C (MeOH-EtOAc)

UV (MeOH): λ_{\max} 238 nm

IR (KBr): ν_{\max} 3400, 3215, 1665, 1634, 1608 cm^{-1}

$^1\text{H-NMR}$ (CDCl_3): δ 3.83 (OCH_3), 6.15 (H-8), 6.56 (H-1), 6.83 (H-2), 7.63 (H-5).

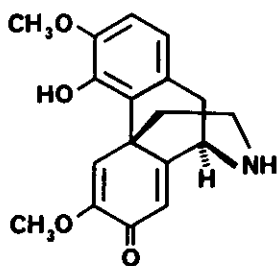
17 $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{CH}_3$

18 $\text{R}^1 = \text{CH}_3$, $\text{R}^2 = \text{H}$

MS: m/z 299 (M^+), 284, 277, 266, 256

The isolation of 3-methoxy-4,6-dihydroxymorphinandien-7-one (18), a compound isomeric to norsinoacutine (17), has been reported independently from two different sources; Croton bonplandianus Baill.³⁶ and Monodora crispata Engl.¹⁸ Physical and spectroscopic data of 18 are listed according to Ref. 36. The absolute configuration of 18 was established by comparison of its N,O-trimethylmethiodide derivative with N,O-dimethylnorsinoacutine methiodide³⁶.

N-Norsalutaridine (19)



19

mp: n.a.

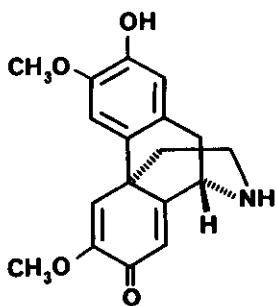
$[\alpha]_{589} +38.6^\circ$, $[\alpha]_{578} +40.7^\circ$, $[\alpha]_{546} +48.4^\circ$ (c 3.4).

$^1\text{H-NMR}$ (CDCl_3): δ 3.78 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.32 (s, 1H, H-8), 6.72 (AB pattern 2H, H-1 and H-2), 7.58 (s, 1H, H-5).

MS: m/z 313 (M^+).

Source: Croton salutaris Casar²⁶.

N-Norpallidine (20)



20

mp: 102 °C (CHCl_3)

$[\alpha]_{\text{D}} -10^\circ$ (c 1.9, MeOH)

UV (EtOH): λ_{max} 238 (3.93), 281 (3.75) nm.

IR (CHCl_3): ν_{max} 1668, 1642, 1625 cm^{-1} .

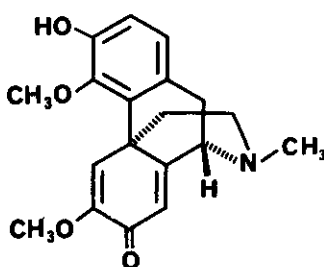
CD (MeOH): $[\theta]_{\text{max}} -1,346$, $[\theta]_{294} +7,068$, $[\theta]_{282} +6,058$, $[\theta]_{262} +33,656$.

$^1\text{H-NMR}$ (CDCl_3): δ 3.73 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 6.22 (s, 1H, H-8), 6.30 (s, 1H, H-1), 6.62 (s, 1H, H-4), 6.73 (s, 1H, H-5).

MS: m/z 313 (M^+), 296, 285, 270

Source: Fumaria vailanti Loisel var. Schrammii³⁷.

Isosinoacutine (21)



21

mp: 120 °C

$[\alpha]_{\text{D}} -41^\circ$ (CHCl_3), $[\alpha]_{\text{D}} -82^\circ$ (90% EtOH).

UV (MeOH): λ_{max} 235 (4.08), 283 (3.81) nm.

IR (KBr): ν_{max} 3458, 1668, 1642, 1625 cm^{-1} .

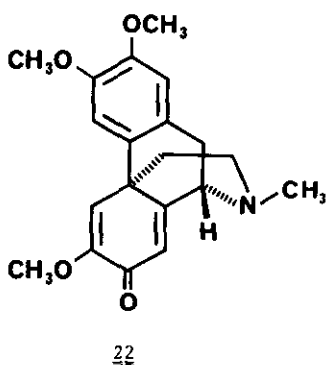
CD (MeOH): $[\theta]_{291} +17,660$, $[\theta]_{270} +9,370$, $[\theta]_{262} 0$, $[\theta]_{237} 55,610$.

$^1\text{H-NMR}$ (CDCl_3): δ 2.33 (s, 3H, N- CH_3), 3.74 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 6.26 (s, 1H), 6.73 (s, 2H), 7.25 (s, 1H).

MS: m/z 312 (M^+-15), 299, 284.

Source: Stephania elegans Hook.f. et. Thoms.³⁵.

O-Methylpallidine (22)



mp: 118-120 °C (diethyl ether)

$[\alpha]_D +25.2^\circ$ (CHCl₃).

UV (MeOH): λ_{max} 208 (4.49), 238 (4.19), 280 (3.82) nm.

IR (KBr): ν_{max} 1660, 1640, 1615 cm.⁻¹

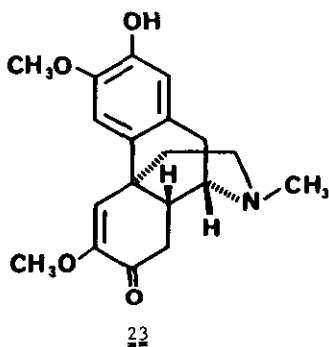
CD (MeOH): $[\theta]_{312} +3,760$, $[\theta]_{310} +3,640$, $[\theta]_{296} +5,580$, $[\theta]_{286} 0$,
 $[\theta]_{280} -2,230$, $[\theta]_{271} 0$, $[\theta]_{265} +880$, $[\theta]_{260} 0$, $[\theta]_{252} -750$,
 $[\theta]_{246} -450$, $[\theta]_{233} -32,370$.

¹H-NMR (CDCl₃): δ 2.45 (s, 3H, NCH₃), 3.75 (s, 3H, OCH₃), 3.81 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 6.25 (s, 1H, H-8), 6.33 (s, 1H, H-1), 6.59 (s, 1H, H-4), 6.78 (s, 1H, H-5).

MS: m/z 341 (M⁺), 326, 313, 298, 282, 270.

Source: *Ocotea acutangula* Mez.¹⁹.

Pallidine (23)



mp: 234-236 °C

$[\alpha]_D -80^\circ$ (c 0.5, CHCl₃)

UV (MeOH): λ_{max} 205 (4.45), 228 (sh), 260 (3.99) nm.

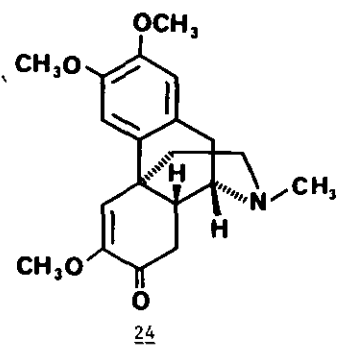
IR (KBr): ν_{max} 1688, 1685, 1620 cm.⁻¹

¹H-NMR (CDCl₃): δ 2.36 (s, 3H, NCH₃), 3.70 (s, 3H, OCH₃), 3.90 (s, 3H, OCH₃), 6.38 (s, 1H, H-1), 6.71 (s, 1H, H-4), 6.86 (s, 1H, H-5).

MS: m/z 329 (M⁺), 314, 286, 243, 218, 192

Source: *Ocotea acutangula* Mez.¹⁹.

O-Methylpallidine (24)



mp: n.a.

UV (MeOH): λ_{max} 206 (4.51), 228 (3.98), 262 (3.99) nm.

IR(KBr): ν_{max} 1690, 1620 cm.⁻¹

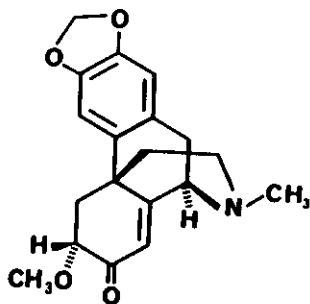
¹H-NMR (CDCl₃): δ 2.37 (s, 3H, NCH₃), 3.69 (s, 3H, OCH₃), 3.85 (s, 3H, OCH₃), 3.89 (s, 3H, OCH₃), 6.32 (s, 1H, H-1), 6.62 (s, 1H, H-4), 6.85 (s, 1H, H-5).

MS: m/z 343 (M⁺), 328, 312, 300, 257, 232, 215, 203, 192, 165, 59.

Source: *Ocotea acutangula* Mez.¹⁹.

24 HCl has mp: 195-200 °C (acetone) and $[\alpha]_D = -50^\circ$ (MeOH).

Amurinine (25)



25

mp: n.a.

$[\alpha]_D^{+42}$ (c 0.18, CHCl_3), $[\alpha]_D^{+42}$ (c 0.18, MeOH).

UV (MeOH): λ_{max} 235 (4.27), 294 (3.85) nm.

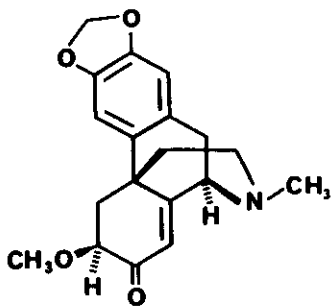
IR (CHCl_3): ν_{max} 1695, 1645 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): δ 2.27 (dd, $J = 13, 14$ Hz, 1H, $\text{H}_{\text{ax}}-5$), 2.46 (s, 3H, NCH_3), 2.67 (dd, $J = 6, 13$ Hz, 1H, $\text{H}_{\text{eq}}-5$), 2.96 (dd, $J = 6, 18$ Hz, 1H, $\text{H}_{\alpha}-10$), 3.24 (d, $J = 18$ Hz, 1H, $\text{H}_{\beta}-10$), 3.56 (d, $J = 6$ Hz, 1H, H-9), 3.61 (s, 3H, OCH_3), 4.07 (dd, $J = 6, 14$ Hz, $\text{H}_{\text{ax}}-6$), 5.93 (s, 2H, OCH_2O), 5.95 (s, 1H, H-8), 6.57 (s, 1H, H-1), 6.65 (s, 1H, H-4).

MS: m/z (M^+), 312, 299, 297, 296, 268, 242, 241, 240, 228, 198.

Source: Papaver pilosum Sibth et Smith⁶.

Epiamurinine (26)



26

mp: n.a.

$[\alpha]_D^{-68}$ (c 0.58, CHCl_3)

UV (MeOH): λ_{max} 230 (4.12), 290 (3.85) nm.

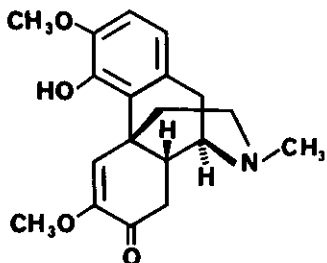
IR (CHCl_3): ν_{max} 1695, 1645 cm^{-1} .

$^1\text{H-NMR}$ (CDCl_3): δ 2.12 (dd, $J = 12.5, 14$ Hz, 1H, $\text{H}_{\text{ax}}-5$), 2.48 (s, 3H, N-CH_3), 2.79 (dd, $J = 4.5, 14$ Hz, 1H, $\text{H}_{\text{eq}}-5$), 2.91 (dd, $J = 6, 18$ Hz, 1H, $\text{H}_{\alpha}-10$), 3.35 (d, $J = 18$ Hz, 1H, $\text{H}_{\beta}-10$), 3.55 (s, 3H, OCH_3), 3.60 (d, $J = 6$ Hz, 1H, H-9), 3.68 (dd, $J = 4.5, 12.5$ Hz, 1H, $\text{H}_{\text{ax}}-6$), 5.89 (s, 1H, H-8), 5.97 (s, 2H, OCH_2O), 6.63 (s, 1H, H-1), 6.88 (s, 1H, H-4).

MS: m/z (M^+), 312, 299, 296, 268, 242, 241, 240, 228, 138.

Source: Papaver pilosum Sibth et Smith⁶.

Ocobotrine (27)



27

mp: 97-99 °C (EtOAc-diethyl ether)

$[\alpha]_D^{-93}$ (c 1, CHCl_3).

UV (MeOH): λ_{max} 264 (4.01), 210 (4.52) nm.

IR (CHCl_3): ν_{max} 3500, 1680, 1620 cm^{-1} .

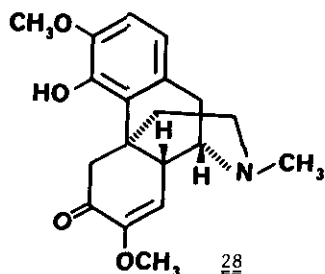
$^1\text{H-NMR}$ (CDCl_3): δ 2.35 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 6.35 (br, 1H, 4-OH), 6.73 and 6.75 (s, s, 2 x 1H, H-1 and H-2), 7.76 (s, 1H, H-5).

Ocobotrine (27) (cont.)

MS: m/z 329 (M^+), 314, 286, 271, 192, 189, 157, 115.

Source: *Ocotea brachybotra* (Meiss.) Mez.^{20,21}

14-Episinomenine (28)



mp: 118-120 °C (C_6H_6)

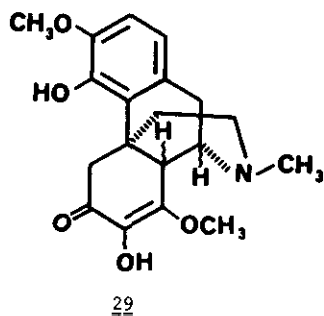
$[\alpha]_D^{20}$ -40° (c 1, $CHCl_3$)

UV (MeOH): λ_{max} 2722 (3.87), 211 (4.41) nm.

IR (KBr): ν_{max} 3500, 1675, 1625 cm^{-1} .

Source: *Ocotea brachybotra* (Meiss.) Mez.^{20,21}

Carococculine (29)



mp: 219-220 °C (EtOH)

$[\alpha]_D^{20}$ -29.5° (c 0.715, $CHCl_3$)

UV (EtOH): λ_{max} 215 (4.25), 292 (3.69) nm.

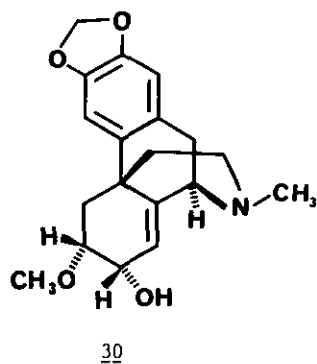
IR (KBr): ν_{max} 3500, 2940, 2843, 1660, 1630, 1490, 1235, 1052 cm^{-1} .

1H -NMR ($CDCl_3$): δ 2.46 (s, 3H, NCH_3), 3.81 (s, 3H, OCH_3), 4.09 (s, 3H, OCH_3), 4.46 and 2.36 (d d, $J = 14$ Hz, 2H, H-5), 6.72 (s, 2H, H-1 and H-2).

MS: m/z 345 (M^+), 330, 314, 273, 258, 208, 178, 146, 115.

Source: *Cocculus carolinus* DC.³⁸

Dihydronudaurine (30)



mp: n.a.

$[\alpha]_D^{20}$ +100° (c 0.32, $CHCl_3$)

UV (MeOH): λ_{max} 233 (3.97), 292 (3.85) nm.

IR ($CHCl_3$): ν_{max} 3560 cm^{-1}

1H -NMR ($CDCl_3$): δ 2.12 (dd, $J = 3.7$ Hz, 12 Hz, 1H, H_{eq}^{-5}), 2.28 (dd, $J = 12, 12$ Hz, 1H, H_{ax}^{-5}), 2.61 (s, 3H, NCH_3), 3.45 (s, 3H, OCH_3), 3.57 (ddd, $J = 3.7, 4, 12$ Hz, 1H, H_{ax}^{-6}), 4.40 (dd, $J = 4, 5.5$ Hz, 1H, H_{eq}^{-7}), 5.92 (s, 2H, OCH_2O), 5.98 (dd, $J = 1.5, 5.5$ Hz, 1H, H-8), 6.55 (s, 1H, H-1), 6.70 (s, 1H, H-4).

MS: m/z 329 (M^+), 314, 312, 298, 280, 270, 255, 254, 242, 241, 240, 228, 199, 135, 59.

Dihydronudaurine (30) (cont.)

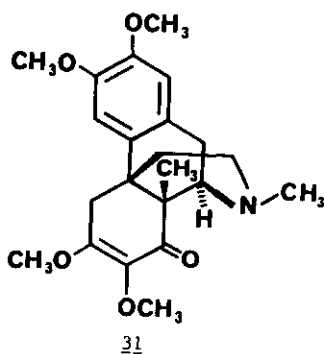
Source: *Papaver pannonum* O. Schwarz³⁹

P. pilosum Sibth. et Smith^{6,7}

P. strictum Sibth. et Smith⁷

When dihydronudaurine (30) was initially isolated,³⁹ the position of the C=C double bond was not established. The stereochemistry of C-7 hydroxyl group was determined according to Ref. 40. Physical and spectral data for 21 are from Ref. 6.

Tridictophylline (31)



mp: 204 °C (MeOH)

$[\alpha]_D^{25} +159^\circ$ (c 0.16, CHCl₃)

UV (MeOH): λ_{max} 230 sh (4.08), 279 (4.12) nm.

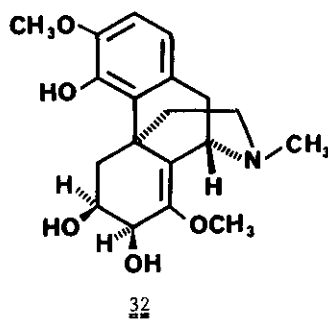
IR (CHCl₃): ν_{max} 3380, 2930, 1665, 1610, 1510, 1495, 1450, 1360, 1338, 1295, 1250, 1202, 1145, 1118, 1075, 1045, 990, 945, 920 cm⁻¹.

¹H-NMR (CDCl₃): δ 2.45 (s, 3H, NCH₃), 3.43 (s, 3H, OCH₃), 3.85 (s, 6H, 2 x OCH₃), 4.00 (s, 3H, OCH₃), 6.53 (s, 1H, ArH), 6.64 (s, 1H, ArH).

MS: m/z 389 (M⁺), 374, 358, 356, 303, 261, 206.

Source: *Triclisia dictyophylla* Diels⁴¹.

Sinococuline (32)



mp. n.a.

$[\alpha]_D^{25} -77^\circ$ (c 0.1, MeOH)

UV (EtOH): λ_{max} 234 (3.90), 283 (3.43) nm.

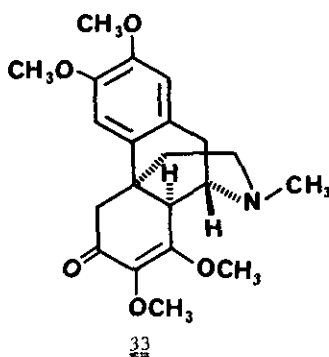
CD (MeOH): $[\theta]_{238} +62,100$ positive maximum.

¹H-NMR (CD₃OD): δ 3.68 (s, 3H, 8-OCH₃), 3.82 (s, 3H, 3-OCH₃), 2.73 (dd, $J = 4.7, 13.1$ Hz, 1H, H_a-16), 2.63 (ddd, $J = 3.4, 12.5, 13.1$ Hz, 1H, H_b-16), 1.88 (ddd, $J = 4.7, 12.5, 12.7$ Hz, 1H, H_a-15), 2.01 (dd, $J = 3.4, 12.7$ Hz, 1H, H_b-15), 3.15 (dd, $J = 6.1, 17.7$ Hz, 1H, H_a-10), 2.89 (d, $J = 17.7$ Hz, 1H, H_b-10), 4.35 (d, $J = 6.1$ Hz, 1H, H-9), 4.28 (d, $J = 3.5$ Hz, 1H, H-7), 3.84 (ddd, $J = 3.5, 3.7, 13.3$ Hz, 1H, H-6), 2.17 (dd, $J = 13.3, 13.3$ Hz, 13.3 Hz, 1H, H_a-5), 2.90 (dd, $J = 3.7, 13.3$ Hz, 1H, H_b-5), 6.75 (d, $J = 8.3$ Hz, 1H, H-2), 6.53 (d, $J = 8.3$ Hz, 1H, H-1).

MS (high res.): 333.3527

Source: *Cocculus trilobus* DC.⁴²

Isostephodeline (33)



mp. 184–185 °C (C₆H₆)

[α]_D +160° (c 2, EtOH)

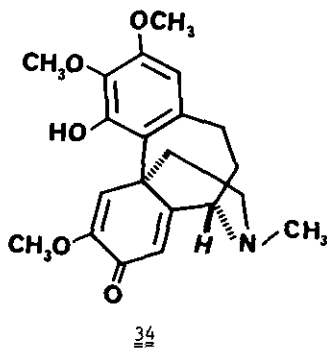
UV (EtOH): λ_{max} 226 (3.78), 275 (3.70) nm.

IR (CHCl₃): ν_{max} 1661, 1615, 1522 cm⁻¹.

¹H-NMR (CDCl₃): δ 2.36 (s, 3H, NCH₃), 2.56 (d, J = 3.1 Hz, 1H, H-11), 2.78 (br, 1H, H_{eq}-10), 2.78 (d, J = 5.6 Hz, 1H, H_{ax}-10), 3.58 (dd, J = 3.1, 5.6 Hz, 1H, H-9), 2.62 (d, J = 17 Hz, 1H, H_{ax}-5), 3.05 (d, J = 17, Hz, 1H, H_{eq}-5), 3.26 (s, 3H, 7-OCH₃), 3.72 (s, 3H, OCH₃), 3.74 (s, 3H, OCH₃), 3.88 (s, 3H, 8-OCH₃), 6.56 (s, 1H, H-4), 6.45 (s, 1H, H-1).

Source: *Stephania delavayi* Diels⁴³.

Collutine (34)



mp: 192–194 °C

[α]_D: -182° (c 1.7, CHCl₃)

UV (EtOH): λ_{max} 238 (4.3), 275 sh (2.81) nm.

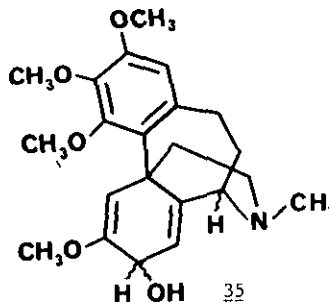
IR (KBr): ν_{max} 3450, 2940, 1660, 1630, 1600, 1560, 1455 cm⁻¹

¹H-NMR (CDCl₃): δ 2.35 (s, 3H, NCH₃), 3.59 (s, 3H, OCH₃), 3.80 (s, 3H, OCH₃), 3.98 (s, 3H, OCH₃), 6.22 (s, 2H), 6.77 (s, 1H).

MS: m/z 371 (M⁺), 356, 340, 328, 210.

Source: *Colchicum luteum* Baker⁴⁴.

Szovitsidine (35)



mp: n.a.

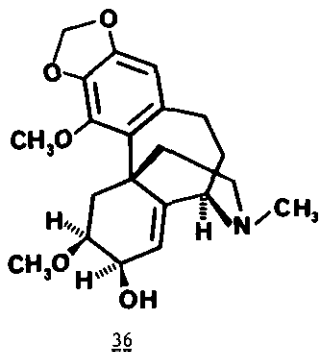
¹H-NMR: δ 2.32 (s, 3H, NCH₃), 3.52 (s, 3H, OCH₃), 3.74 (s, 3H, OCH₃), 3.83 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 6.26 (s, 2H), 6.40 (s, 1H), 6.50 (s, 1H).

MS: m/z 387 (M⁺), 372, 356, 344, 316, 149

Source: *Colchicum szovitsii* Fisch⁴⁵.

The reported data on szovitsidine are incomplete for the unambiguous structure confirmation. It may only be assumed that szovitsidine is a reduced derivative of *O*-methylandrocybine (63) whose structure and absolute stereochemistry have previously been elucidated together with that of androcybine (62)⁴⁶.

Alkaloid CC-2 (36)



mp: 172-174 °C (EtOAc)

$[\alpha]_D +40 \pm 4^\circ$ (c 0.48, CHCl₃)

UV (MeOH): λ_{max} 236 sh (3.80), 289 (3.30) nm.

¹H-NMR (CDCl₃): δ 2.24 (s, 3H, N-CH₃), 2.85 (s, 3H, OCH₃), 3.89 (s, 3H, OCH₃), 5.80 (s, 2H, OCH₂), 6.16 (s, 1H, H-1), 3.60 (m, 1H, H 10), 4.10 (t, $J = 4$ Hz, 1H, H-9), 5.50 (d, $J = 4$ Hz, 1H, H-8).

MS (high res.): 373.188⁹

Source: Colchicum cornigerum (Sweinf.) Tackh. et Drar.⁴⁷

Together with the previously known 12 alkaloids, reviewed by Stuart², the morphinandienones and related compounds now comprise 28 members and the number of the known homomorphinandienones has risen to 5. It should be noted that (+)-salutaridine (14) and (-)-sinoacutine (16), found separately in different plant sources, are two antipodes with different names. Pallidine (13) could also be named as isosalutaridine.

II. SPECTROSCOPY

A. Ultraviolet and Infrared

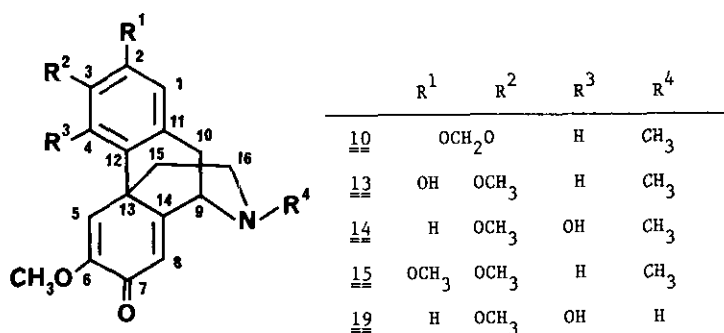
The uv absorption bands of morphinandienones are observed at 235-240 and 275-290 nm in approximately a 2:1 ratio with respect to their molecular extinction coefficients. Compounds substituted at C-2 and C-3 usually have a uv absorption around 290 nm, however, derivatives with C-3 and C-4 substituents this absorption is near to 275 nm.

The cyclohexandienone moiety of morphinandienones shows characteristic ir absorption bands in the region 1665, 1635 and 1615 cm⁻¹, while the dihydroderivatives show absorption bands at 1690 and 1645 cm⁻¹.

B. Nuclear Magnetic Resonance

The proton nmr spectroscopic data and available assignments of all new morphinandienone and related alkaloids are listed in Table 2.

The limited available data on the carbon-13 nmr spectral assignments of morphinandienones are shown in Tables 3 and 4.


 Table 3. ¹³C NMR DATA OF MORPHINANDIENONE ALKALOIDS

Compound	<u>N</u> -Norsalutaridine	Salutaridine	Pallidine	Amurine	Sebiferine
Carbon	(<u>19</u>) ⁴⁸	(<u>14</u>) ⁴⁸	(<u>13</u>) ⁴⁹	(<u>10</u>) ⁴⁹	(<u>15</u>) ⁴⁹
1	118.7	118.5	113.7	107.2	110.2
2	109.4	109.2	145.0	146.5 ^c	147.8 ^d
3	145.3	145.3	145.9	146.6 ^c	148.1 ^d
4	143.3	143.2	107.6	104.9	108.5
5	120.4 ^a	120.4	119.0	118.6	118.7
6	150.7	150.7	151.4	151.1	151.2
7	181.4	181.2	180.9	180.6	180.7
8	120.9 ^a	121.9	122.2	121.8	121.9
9	54.6	60.9	60.8	60.4	60.7
10	38.8 ^b	32.5	32.4	32.6	32.5
11	129.6	129.4	129.3	129.3	128.6
12	123.6	123.8	129.5	130.7	129.8
13	44.1	43.6	42.3	42.2	42.1
14	163.7	161.5	161.8	161.2	161.2
15	39.6 ^b	37.6	41.3	41.0	41.0
16	42.9	46.9	45.7	45.4	45.5
NCH ₃	-	41.5	41.7	41.4	41.6
2-OCH ₃	-	-	-	-	55.7 ^e
3-OCH ₃	56.2	56.1	56.2	-	56.1 ^e
6-OCH ₃	54.4	54.7	55.1	54.8	54.9
2,3-OCH ₂ O	-	-	-	100.9	-

^{a-e}Indicates assignments may be reversed.

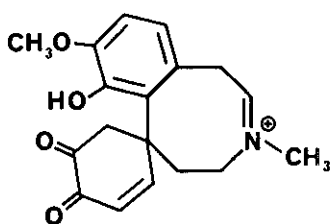
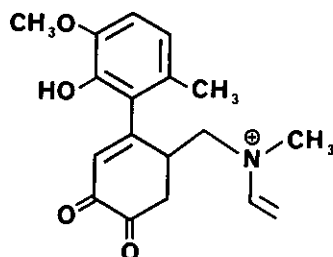
Table 4. ^{13}C -NMR DATA OF PARTIALLY SATURATED MORPHINANDIENONE ALKALOIDS

Compound	Dihydronodaurine	O-Methylpallidine	Tridictophylline	Sinococculin
Carbon	(<u>30</u>) ⁶	(<u>24</u>) ⁴¹	(<u>31</u>) ⁴¹	(<u>32</u>) ⁴²
1	106.9	114.4	109.2	119.5
2	146.1	147.4	148.1	111.0
3	146.8	147.8	148.1	147.6 ^a
4	104.5	107.7	110.5	145.7
5	30.2	121.4	34.6	36.8
6	76.5	150.8	135.0	68.5
7	61.5	194.5	161.9	66.5
8	130.6	39.1	n.a.	147.7 ^a
9	62.8	56.4	60.3	47.2
10	33.3	27.2	29.6	36.1
11	127.7	132.5	129.4	130.4
12	134.7	129.7	129.4	121.5
13	38.7	36.9	40.5	39.6
14	141.3	40.1	66.7	129.9
15	38.7	36.2	34.6	37.2
16	47.1	45.8	45.8	41.0
NCH ₃	41.2	42.8	42.6	-
OCH ₃	56.3	55.0	55.8	57.0
OCH ₃	56.3	56.0	55.8	57.3
OCH ₃	-	56.7	57.6	-
OCH ₃	-	-	58.7	-
OCH ₂ O	100.8	-	-	-

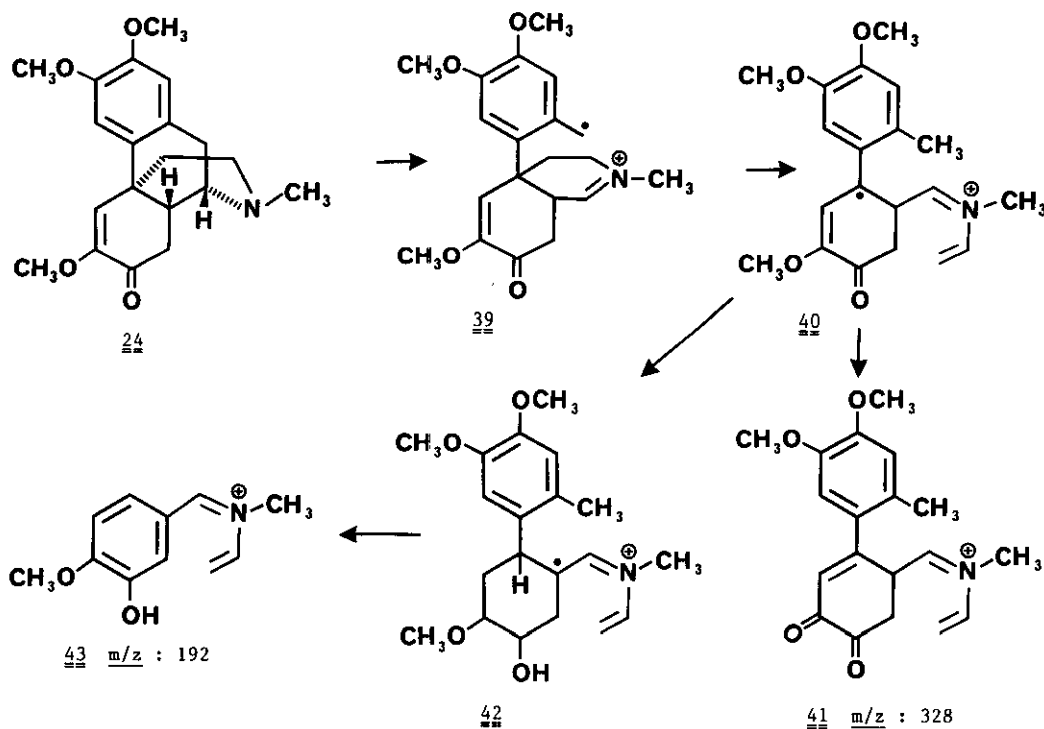
^aIndicates assignments may be reversed.

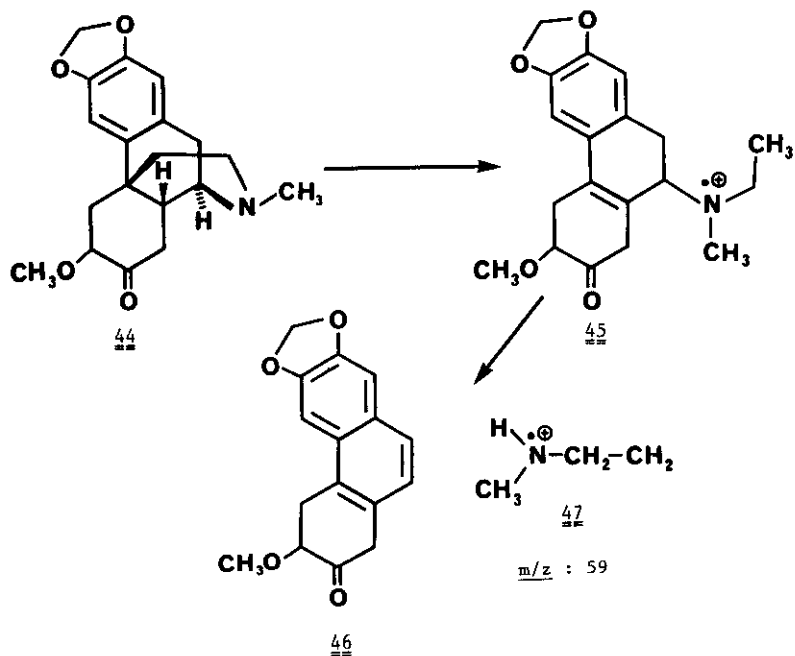
C. Mass Spectrometry

It has been demonstrated⁵⁰ that the mass spectrometric fragmentation of salutaridine (14) shows initial cleavage at an allylic or benzylic bond followed by the loss of a methyl group leading to the conjugated even-electron ions 37 and 38 (Scheme 1). The simultaneous loss of CO and methyl is also a common fragmentation of morphinandienones resulting in a strong peak at M^+-43 .

37 m/z : 31438 m/z : 314Scheme 1. Major fragments of salutaridine (14)

In the case of 8,14-dihydro or 5,6,8,14-tetrahydro derivatives, mass spectrometry is a suitable method for determination of the stereochemistry of the B/C ring anellation. In the B/C *cis* series, *N*-methyl compounds shows an intense peak at m/z 59, whereas the B/C *trans* compounds give no fragmentation, or only a very weak ion at m/z 59. The difference is attributed to the spatial arrangement of H-14 and the nitrogen-containing side-chain which is involved in the key fragmentation step. As an illustrative example, the fragmentations of *O*-methylpallidine (24)¹⁹ and tetrahydroamurine (44)⁵¹ are shown in Schemes 2 and 3, respectively.

Scheme 2. Fragmentation of *O*-Methylpallidine (24)¹⁹



Scheme 3. Fragmentation of Tetrahydroamurine (44)⁵¹

D. X-Ray Crystallography

The only complete X-ray crystallographic analyses of alkaloids in this series are of O-methylflavinantine (12)⁵² and alkaloid CC-2 (36).⁵³

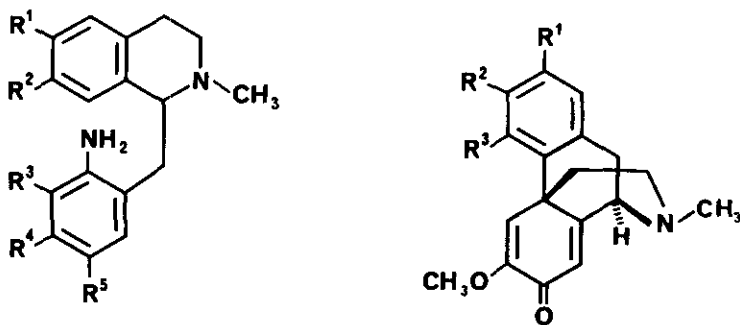
SYNTHESIS

The synthesis of morphinandienones and related compounds is discussed in this review by the methods utilized. Among them the classic Pschorr-, benzene-, and photocyclization approaches, the biomimetic phenolic oxidative coupling, as well as the recently improved Greve cyclization and electrochemical coupling methods are presented.

A. Pschorr-type syntheses

Kametani and co-workers performed a pioneering work on the total syntheses of morphinandienone alkaloids, and some of their efforts have previously been reviewed.³ The key reaction step of their approach is a Pschorr-type cyclization of an appropriately substituted 6-aminobenzylisoquinoline leading to the target morphinandienone. The typical low yield is the consequence of numerous side reactions, e.g. deamination, formation of an isomeric coupled product (aporphine-type compound), etc. Morphinandienones which have been synthesized via Pschorr cyclization utilizing either thermal decomposition (Method A) or photochemical decomposition of a diazonium intermediate (Method B) are listed in Table 5.

Table 5. MORPHINANDIENONES SYNTHESIZED BY PSCHORR CYCLIZATION



	R ¹	R ²	R ³	R ⁴	R ⁵		R ¹	R ²	R ³
<u>48</u>	OCH ₃	OCH ₃	H	OCH ₂ O		<u>10</u>	OCH ₂ O		H
<u>49</u>	OCH ₃	OC ₂ H ₅	H	OCH ₂ O		<u>11</u>	OCH ₃	OH	H
<u>50</u>	OCH ₃	OCH ₃	H	OH	OH	<u>12</u>	OCH ₃	OCH ₃	H
<u>51</u>	OCH ₃	OCH ₃	H	OCH ₂ ∅	OCH ₃	<u>14</u>	H	OCH ₃	OH
<u>52</u>	OCH ₃	OCH ₃	H	OCH ₃	OCH ₃	<u>59</u>	OCH ₃	OCH ₂ ∅	H
<u>53</u>	OCH ₃	OC ₂ H ₅	H	OCH ₃	OCH ₃	<u>60</u>	OCH ₂ ∅	OCH ₃	H
<u>54</u>	OCH ₃	OCH ₃	H	OCH ₃	OCH ₂ ∅				
<u>55</u>	OCH ₃	OCH ₃	OCH ₂ ∅	OCH ₃	H				

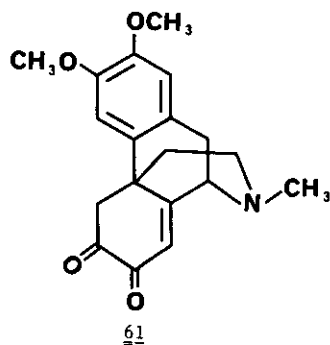
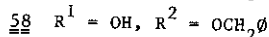
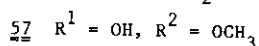
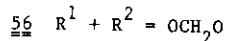
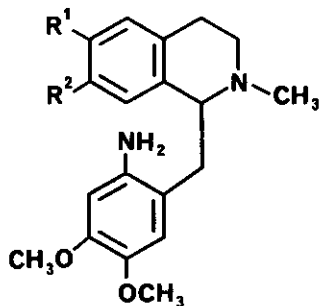
Starting material	Method	Product	Yield %	Ref.
(<u>48</u>)	A	(+)-Amurine (<u>10</u>)	1.2	54,55
(<u>49</u>)	A	(+)-Amurine (<u>10</u>)	2.0	54,55
(<u>50</u>)	B	(+)-Flavinantine (<u>11</u>)	2.0	56
(<u>51</u>)	A	(+)-Benzylflavinantine (<u>59</u>) ^a	8.4	57
(<u>52</u>)	A	(+)-Methylflavinantine (<u>12</u>)	1.4	58,59
(<u>53</u>)	A	(+)-Methylflavinantine (<u>12</u>)	1.4	58,59
(<u>54</u>)	A	(+)-O-Benzylisosalutaridine (<u>60</u>) ^a	10	60
(<u>55</u>)	A	(+)-Salutaridine (<u>14</u>) ^{b,c}	1.1	61

^a O-Benzylflavinantine (59) and O-Benzylisosalutaridine (60) were debenzylated to (+)-flavinantine (11) and (+)-isosalutaridine [(+)-pallidine] (13), respectively by acid treatment.

^b Debzylolation takes place during the Pschorr reaction resulting in (+)-salutaridine (14) directly.

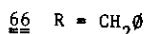
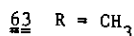
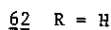
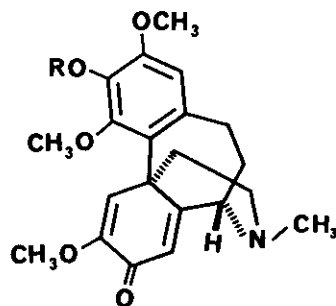
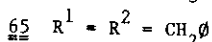
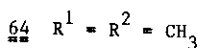
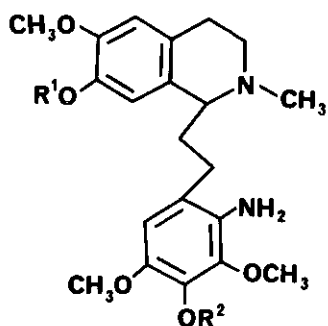
^c (+)-Salutaridine (14) was also obtained starting from (-)-5. On the other hand, cyclization of (+)-5 resulted in the (-)-enantiomer, sinoacutine (16)

Model studies have been performed for application of the Pschorr cyclization aimed at the synthesis of the sinomenine (8) type compounds. During the course of this work dehydrosinomenol (61) was prepared in low yield from three different 6'-aminobenzylisoquinolines (56-58).⁶²⁻⁶⁴



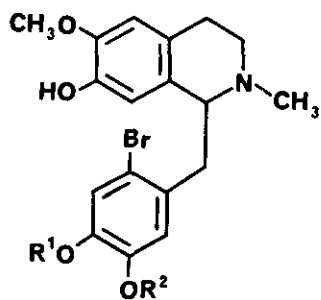
61

The total synthesis of (+)-androcymbine (62), as well as *O*-methylandrocymbine (63) has been reported by Kametani and co-workers.⁶⁵⁻⁶⁷ Diazotisation of 1-(2-aminophenethyl)isoquinolines 64 and 65 followed by photolysis with Hanovia 450 W mercury lamp gave (+)-*O*-methylandrocymbine (63) and *O*-benzylandrocymbine (66), respectively in less than 1% yield. The latter was debenzylated to afford (+)-androcymbine (62).



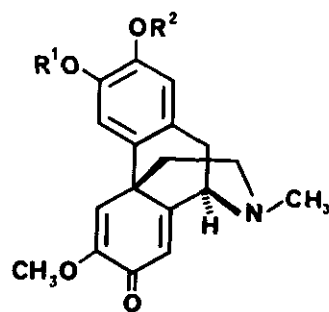
B. Benzyne cyclization

The benzyne reaction of 1-(2-bromobenzyl)isoquinoline derivatives 67 and 68 with sodium amide in liquid ammonia afforded complex reaction mixtures from which the morphinandienone amurine (10) and *O*-methylflavinantine (12), respectively, the aporphines domesticine (69) and thaliporphine (70) respectively, as well as tetrahydrodibenzopyrrocoline type compounds cryptowoline (71) and cryptaustoline (2), respectively, could be isolated in low yield.⁶⁸⁻⁷⁰



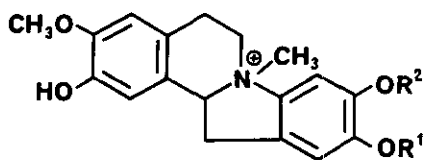
$$\underline{67} \quad R^1 + R^2 = \text{CH}_2$$

$$\underline{68} \quad R^1 + R^2 = \text{CH}_3$$



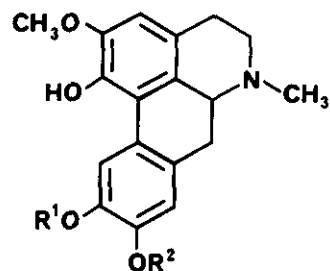
$$\underline{10} \quad R^1 + R^2 = \text{CH}_2$$

$$\underline{12} \quad R^1 + R^2 = \text{CH}_3$$



$$\underline{71} \quad R^1 + R^2 = \text{CH}_2$$

$$\underline{72} \quad R^1 + R^2 = \text{CH}_3$$

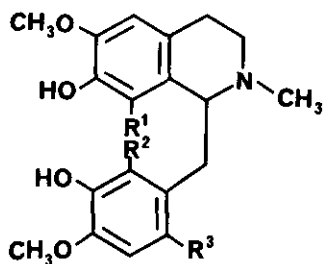


$$\underline{69} \quad R^1 + R^2 = \text{CH}_2$$

$$\underline{70} \quad R^1 + R^2 = \text{CH}_3$$

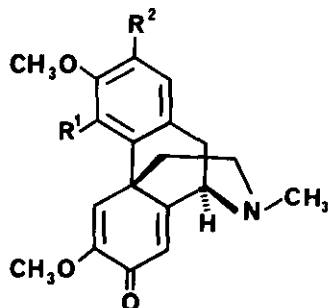
C. Photocyclization

Irradiation of 2'-bromo-reticuline (73) with a 400 W mercury lamp in the presence of NaOH/NaI afforded (+)-salutaridine (14) in 1% yield, together with 1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-2-methylisoquinolone (75).^{71,72} Interestingly, irradiation of the 6',8-dibromo derivative 74 gave (+)-pallidine (13) in low yield as the only isolable product.⁷²



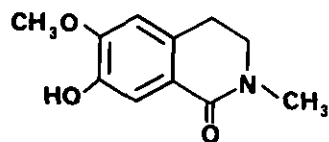
$$\underline{73} \quad R^1 = R^3 = \text{H}, R^2 = \text{Br}$$

$$\underline{74} \quad R^1 = R^3 = \text{Br}, R^2 = \text{H}$$



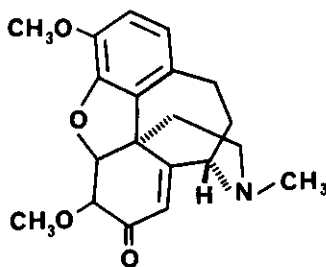
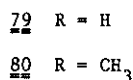
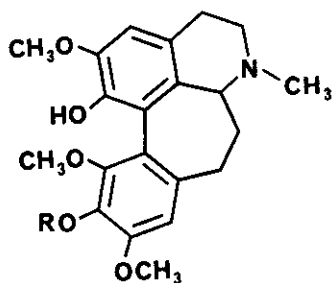
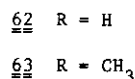
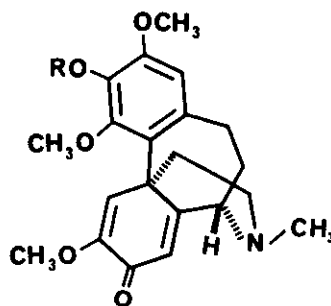
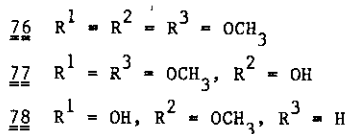
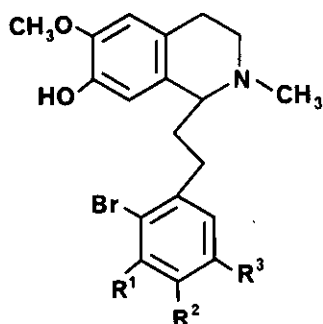
$$\underline{13} \quad R^1 = \text{H}, R^2 = \text{OH}$$

$$\underline{14} \quad R^1 = \text{OH}, R^2 = \text{H}$$



$$\underline{75}$$

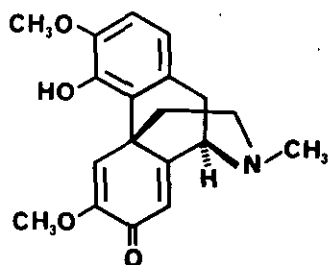
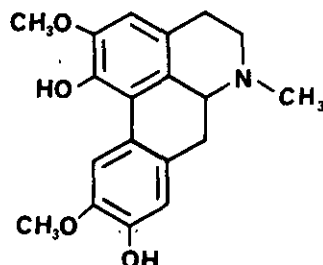
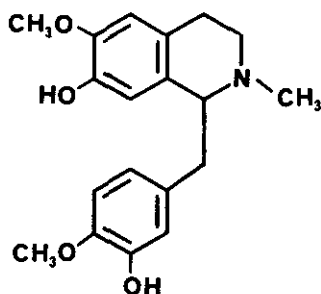
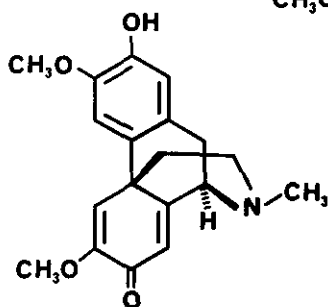
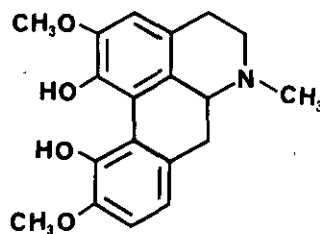
Photolysis of 1-(2-bromo-phenethyl)isoquinoline 76 afforded the homomorphinandienone (+)-0-methylandrocybine (63) and the homoaporphine (+)-kreysigine (80),⁷³ while irradiation of 77 resulted in (+)-androcybine (62) and (+)-multifloramine (79).⁷⁴ Irradiation of 78, on the other hand, led to the kreysigine-type enone 81, indicating that after phenolic coupling reaction ring closure to the enone had occurred.⁷⁵



D. Phenolic oxidative coupling

The importance of phenolic oxidative coupling as a biosynthetic process is well established.⁷⁶ For example morphine (5) is produced through modification of salutaridine (14) formed through the phenolic oxidative coupling of reticuline (82), as originally suggested by Gulland and Robinson,⁷⁷ and further refined by Barton and Cohen.⁷⁸ The first successful *in vitro* transformation of reticuline (82) into salutaridine (14) was performed by Barton and co-workers^{79,80} through potassium ferricyanide oxidation of tritium-labeled (+)-reticuline (82) which gave (+)-salutaridine (14) in 0.03% yield as detected by an isotope-dilution technique. Other attempts to effect para-ortho oxidative coupling of (+)-reticuline (82) afforded only the para-para coupled

product (+)-isosalutaridine (13)⁸¹ and/or the ortho-para coupled product (+)-isoboldine (83)⁸¹⁻⁸³ and the ortho-ortho coupled product (+)-isoboldine (83)⁸¹⁻⁸³ and the ortho-ortho coupled product (+)-corytuberine (84).⁸⁴

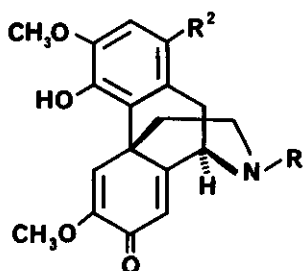
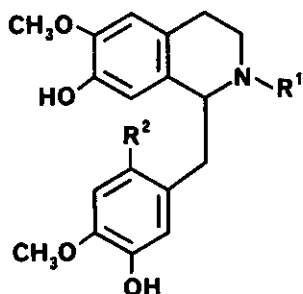

13

83

82

14

84

A substantial improvement in the biomimetic approach to the morphinandienones was achieved by Schwartz and Mami^{85,86} when N-acylnorreticulines 85 - 87 were used as starting materials and thallium tris(trifluoroacetate) was utilized as the oxidative reagent resulting in N-acylnorsalutaridines 96, 97 and 98, respectively in 16-35% yield. The high regioselectivity of the reaction was attributed to the chelating effect of the thallium ion.

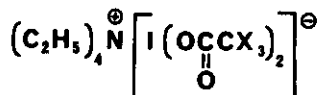
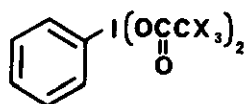
A feasible and effective cyclization method was also developed by Szántay and co-workers^{87,88} for the regio-selective para-ortho coupling of N-acylnorreticulines 86 - 92 utilizing lead tetraacetate (LTA) or isodosobenzene diacetate (106) in the presence of strong organic acids, isodosobenzene bis(trichloroacetate) (107), or tetraethylammonium [bis(trihalogen-acyloxy)-iodate(I)] type reagents (109, 110).

Results of these systematic experimentations and the N-acylnorsalutaridine derivatives prepared are listed in Table 6.

Table 6. PHENOLIC OXIDATIVE COUPLING OF *N*-ACYLNORRETICULINE DERIVATIVES



	Starting Material		Oxidant 1 mol equiv.	Additive	Product	Yield		
	R ¹	R ²				R ¹	R ²	%
<u>86</u>	CHO	H	Pb(OAc) ₄	CCl ₃ COOH	<u>97</u>	CHO	H	17.5
<u>86</u>	CHO	H	<u>106</u>	CCl ₃ COOH	<u>97</u>	CHO	H	15.3
<u>87</u>	CO ₂ C ₂ H ₅	H	Pb(OAc) ₄	CCl ₃ COOH	<u>98</u>	CO ₂ C ₂ H ₅	H	24.4
<u>87</u>	CO ₂ C ₂ H ₅	H	<u>106</u>	CCl ₃ COOH	<u>98</u>	CO ₂ C ₂ H ₅	H	14.0
<u>87</u>	CO ₂ C ₂ H ₅	H	<u>107</u>	-	<u>98</u>	CO ₂ C ₂ H ₅	H	16.5
<u>87</u>	CO ₂ C ₂ H ₅	H	<u>109</u>	-	<u>98</u>	CO ₂ C ₂ H ₅	H	6.2
<u>88</u>	CO ₂ C(CH ₃) ₃	H	Pb(OAc) ₄	CCl ₃ COOH	<u>99</u>	CO ₂ C(CH ₃) ₃	H	37.3
<u>89</u>	CHO	Br	<u>107</u>	-	<u>100</u>	CHO	Br	19.5
<u>89</u>	CHO	Br	<u>109</u>	-	<u>100</u>	CHO	Br	35.1
<u>91</u>	CO ₂ C ₂ H ₅	Br	Pb(OAc) ₄	CCl ₃ COOH	<u>102</u>	CO ₂ C ₂ H ₅	Br	32.5
<u>91</u>	CO ₂ C ₂ H ₅	Br	<u>107</u>	-	<u>102</u>	CO ₂ C ₂ H ₅	Br	32.7
<u>91</u>	CO ₂ C ₂ H ₅	Br	<u>109</u>	-	<u>102</u>	CO ₂ C ₂ H ₅	Br	58.0
<u>91</u>	CO ₂ C ₂ H ₅	Br	<u>110</u>	-	<u>102</u>	CO ₂ C ₂ H ₅	Br	52.7
<u>92</u>	CO ₂ C ₂ H ₅	Cl	<u>107</u>	-	<u>103</u>	CO ₂ C ₂ H ₅	Cl	31.5



106 X = H

107 X = Cl

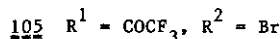
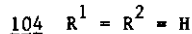
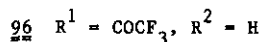
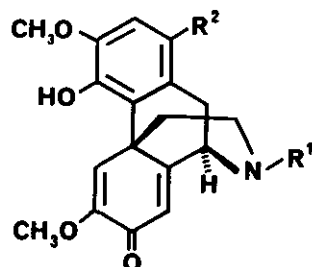
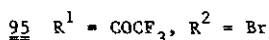
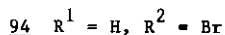
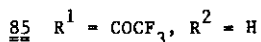
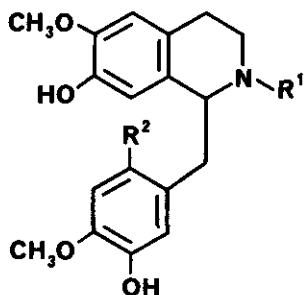
108 X = F

109 X = Cl

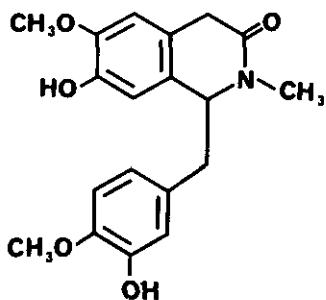
110 X = F

The above findings on phenolic oxidative coupling were successfully adopted for the *in vitro* conversion of (+)-reticuline (82) to (+)-salutaridine (14) on a preparative scale.⁸⁹ Using LTA in the presence of trichloroacetic acid afforded (+)-salutaridine (14) in 2.7% yield. (+)-Salutaridine (14) was also obtained by Eschweiler-Clarke methylation of (+)-N-nonsalutaridine (104) obtained either from (+)-N-formylnorsalutaridine (97) via deformylation in aqueous acidic media or from (+)-N-*tert*-butoxycarbonylnorsalutaridine (99) by removing the protecting group with *p*-toluenesulfonic acid in C₆H₆.⁸⁸

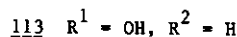
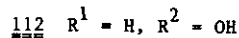
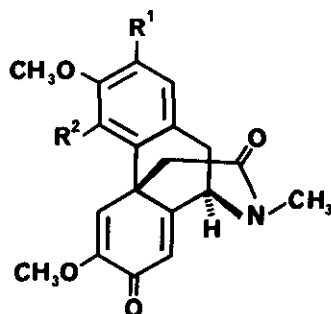
White and co-workers⁹⁰ further developed the phenolic oxidative coupling reaction during their total synthesis of (-)-codeine (6). (+)-Norreticuline (93) was resolved, as previously described by Rice and Brossi⁹¹, and brominated to afford (-)-6'-bromo-N-norreticuline (94). The secondary nitrogen of (-)-(94) was protected by trifluoroacetylation and the product 95 was cyclized with iodosobenzene bis(trifluoroacetate) (108) to 105 in 21% yield.



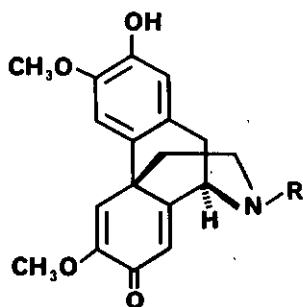
When the oxidative coupling of 3-oxoreticuline (111) was performed with iodosobenzene diacetate (106) in the presence of trifluoroacetic acid, 16-oxosalutaridine (112) and 16-oxopallidine (113) were obtained in yields of 27% and 8%, respectively.⁹²



111



Interestingly enough, the phenolic oxidative coupling of different *N*-acylnorreticulines 86 - 87 with manganese tris (acetylacetonate) resulted in regioselective *para-para* coupling leading to the *N*-acyl-norisosalutaridine 114 and 115, respectively.⁹³ In this way the total synthesis of (+)-pallidine (13) was accomplished through deformylation of 114 and subsequent methylation of (+)-norpallidine (116) by an Eschweiler-Clarke methylation process.⁹³

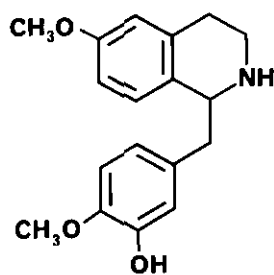


- 114 R = CHO
115 R = CO₂C₂H₅
116 R = H
13 R = CH₃

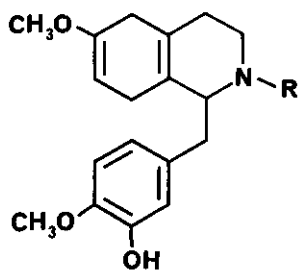
E. Greve cyclization

The classical Greve cyclization of hexahydro-, or octahydro-1-benzylisoquinolines can only supply dihydrothebainone type products, which may be considered as saturated derivatives of morphinandienones. This approach is therefore reviewed here because it presently represents the most feasible route for the production of morphinans ranging from the most well-known natural alkaloids to the clinically valuable synthetic derivatives^{94,95}.

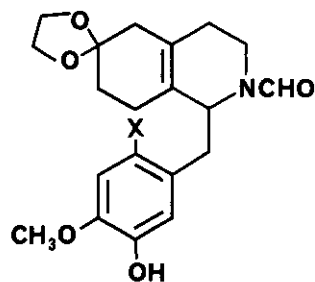
(+)-Dihydrothebainone (117) was synthesized by Rice⁹⁶ in high overall yield from the readily available 1-benzylisoquinoline 118. Birch reduction of 118 with lithium in liquid ammonia afforded pure 119 which was formylated to 120 in 94% yield. Cleavage of the enol ether of 120 and protection of the carbonyl group was achieved in THF containing methanesulfonic acid and ethylene glycol to yield ketal 121 which could be brominated quantitatively with *N*-bromoacetamide to 122. Deketalization of 122 and subsequent Greve cyclization in dry CF₃SO₃H in the presence of NH₄F·HF afforded 1-bromo-*N*-formyl-nordihydrothebainone (123) in 60% isolated yield. (+)-Dihydrothebainone (117) was obtained directly and quantitatively from 123 through acid catalyzed deformylation and hydrogenation of the product over palladium catalyst in acetic acid in the presence of aqueous formaldehyde. In view of the above results and the high-yielding conversion of 117 to codeine (6) and thebaine (7),⁹⁷ as well as the facile *O*-demethylation of codeine (6) to morphine (5)⁹⁸, the practical total synthesis of these alkaloids and their semisynthetic derivatives was achieved. Subsequently, resolution of racemic 118 permitted extension of this route to the total synthesis of both the natural and unnatural series of morphinans.^{99,100}



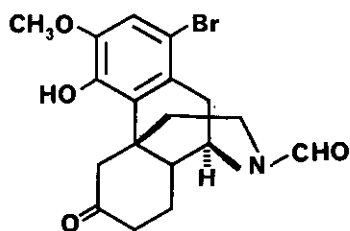
118



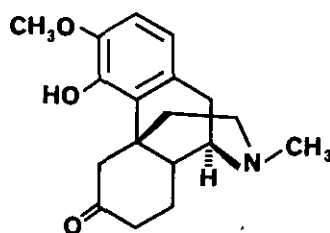
119 R = H
120 R = CHO



121 X = H
122 X = Br

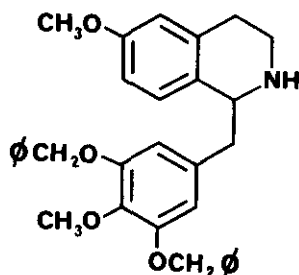


123

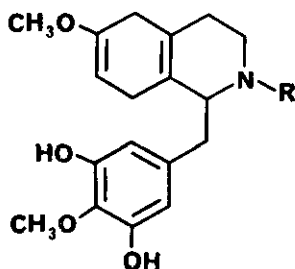


117

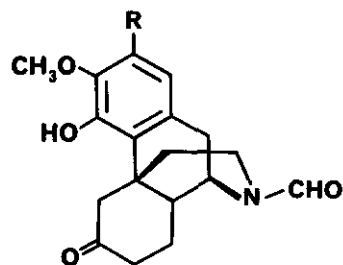
A similar approach was reported for the synthesis of dihydrothebainone (117) by Beyerman and co-workers¹⁰¹⁻¹⁰⁴ utilizing 1-(3,5-dibenzyloxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-6-methoxyisoquinoline (124) as the starting material. The advantage of 134 as the starting material is the exclusive formation of 127 in the Greve cyclization step, however, removal of the additional hydroxyl group requires additional synthetic steps. The reaction sequence was performed on racemic as well as optically active compounds.



124



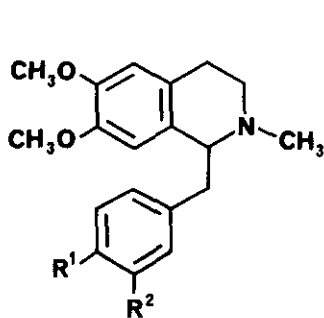
125 R = H
126 R = CHO



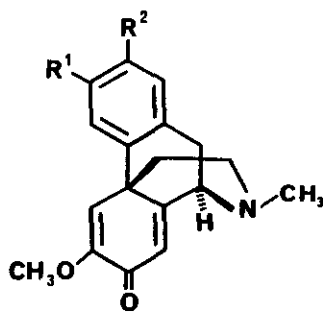
127 R = OH
128 R = OCN₄-φ
129 R = H

F. Electrochemical coupling

The application of an intramolecular, nonphenolic, anodic cyclization of laudanosine (130) to the morphinandienone, *O*-methylflavinantine (12) has been extensively studied.¹⁰⁵⁻¹¹² The electrochemical oxidation of 130 is usually performed in acetonitrile containing HBF₄ to afford protection of the tertiary nitrogen. Experiments were conducted at constant electrode potential and also at constant current. Both methods afforded virtually the same yields (70-85%) for the coupling reaction. However, the constant current method could be successfully applied at higher substrate concentrations than the constant potential method.



	R ¹	R ²
<u>130</u>	OCH ₃	OCH ₃
<u>131</u>	OCH ₂ ∅	OCH ₃
<u>132</u>	OCH ₃	OCH ₂ ∅
<u>133</u>	OCH ₂ O	



	R ¹	R ²
<u>12</u>	OCH ₃	OCH ₃
<u>59</u>	OCH ₂ ∅	OCH ₃
<u>60</u>	OCH ₃	OCH ₂ ∅
<u>10</u>	OCH ₂ O	

O-Benzylflavinantine (59) *O*-benzylpallidine (60) and amurine (10) have been synthesized by nonphenolic anodic oxidation starting from the corresponding appropriately substituted 1,2,3,4-tetrahydro-1-benzylisoquinolines 31, 132 and 133, respectively^{105,110}.

G. Miscellaneous methods

The total synthesis of (+)-salutaridine (14) has been reported by Ludwig and Schafer¹¹³ starting with the lithiated formamidine 134 and the protected cyclohexenone derivative 135. Cyclization of 136 to 137 could be achieved by different Lewis acids such as SnCl₄ or BF₃·Et₂O, in 46% yield. Compound 137 was dehydrogenated with DDQ to (+)-salutaridine (14) in 53% yield. Applying a chiral auxiliary group on the imine nitrogen of 134, the condensation led to a 1-alkyltetrahydroisoquinoline with high stereoselectivity possessing the absolute configuration of 15. This compound was later transformed to (-)-sinoacutine (16)¹¹³.

PHARMACOLOGY

Salutaridine (14) exerts antitumor activity⁴ against the Walker 256 carcinosarcoma,¹¹⁶ and naloxone, a semisynthetic derivative of morphine, increases the survival time of mice treated with neuroblastoma.¹¹⁷ Sinococculine (32) shows antitumor activity against Sarcoma 180A and P-388 lymphocytic leukemia in mice.⁴²

Pharmacodynamic investigation of salutaridine (14) suggests that this alkaloid can be considered as a partial agonist of the GABA/benzodiazepine receptor complex.¹¹⁸

ACKNOWLEDGEMENT

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