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Pentoxygenated berbines: Total synthesis of (±) O-methylcapauridine and (±) O, O'-dimethylstephabinamine

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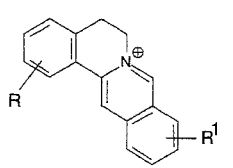
Abstract

A convenient total synthesis of pentaoxygenated berbine alkaloids; (±)-O-methylcapauridine(**15a**), (±) O,O'-dimethylstephabinamine(**15c**) and a berbine(**15b**) is described from 3,4,5-trimethoxy-β-phenylethylamine (mescaline **12**). Condensation of mescaline (**12**) with isochroman-3-ones (**13a–c**) in refluxing ethanol gives hydroxy amides (**14a–c**) which on Bischler–Napieralski cyclisation with $POCl_3$ in refluxing toluene, followed by $NaBH_4$ reduction, provides the berbine alkaloids **15a**, **15c** and berbine **15b**.

Key words : Heteroatom-directed lithiation reaction, Bischler–Napieralski cyclisation, mescaline, isochroman-3-ones, berbine alkaloids.

1. Introduction

The protoberberines form an important class of isoquinoline alkaloids[1–3] which commonly occur in plants belonging to Berberidaceae, Ranunculaceae, Manispermaceae and Rutaceae families. The first alkaloid of this series, berberine, was isolated in 1837. These tetracyclic alkaloids occur in nature in two forms, *e.g.*, the form of quaternary salt (**1**) or as tertiary bases (**2**). The skeleton **2** is commonly known as berbine[4] skeleton and the corresponding alkaloids as berbine alkaloids.



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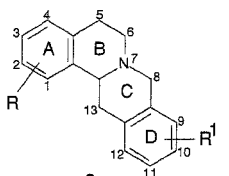

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Most of the berbine alkaloids contain four oxygen functions, two each in ring A and D as shown in structures **3–6**. Some pentaoxygenated berbine alkaloids have also been isolated

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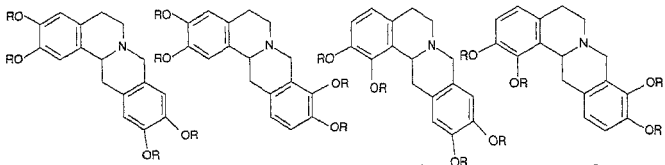
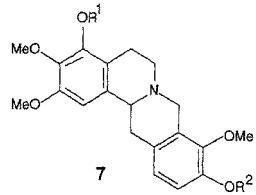


3 4 5 6

from natural sources. These alkaloids have three oxygen functions at 2, 3 and 4 positions in ring A and two oxygen functions at 9 and 10 positions in ring D. Thus, (–) thaicanine[5],(**7a**), O-methylthaicanine[5] (**7b**) and (–)thaipetaline[6] (**7c**) have oxygen functions at 2, 3, 4, 9, 10 positions. The N-methyl salts of **7a** and **7b** have recently been isolated from natural sources[7].



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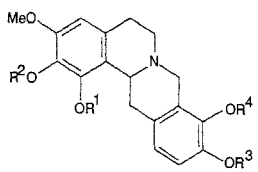
7a R^1 = H, R^2 = Me
7b R^1 = R^2 = Me
7c R^1 = R^2 = H

A few pentaoxygenated berbine alkaloids have three oxygen functions at 1, 2, 3 positions in ring A and two oxygen functions in ring D. Thus, in (–) capaurine[9] (**8a**), (±) capauridine[9] (**8a**), (–) capaurimine[10] (**8b**) and (–)govadine (**8c**) the oxygen functions are at 1, 2, 3, 9, 10 positions. The alkaloid (–) stephabinamine[11] (**9**) has three oxygen functions in ring A and two oxygen functions at 10, 11 positions in ring D.



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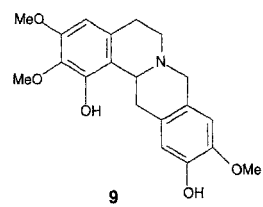
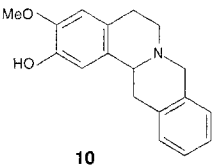


9

8a R^1 = H, R^2 = R^3 = R^4 = Me
8b R^1 = R^3 = H, R^2 = R^4 = Me
8c R^1 = R^2 = R^3 = H, R^4 = Me

Though a large number of tetra- and penta-oxygenated berbine alkaloids having oxygen functions in both A and D rings have been isolated from natural sources, (±) bharatamine[8] (**10**) is the only alkaloid which is unoxygenated in ring D.



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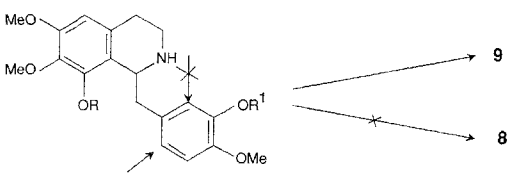
2. Synthesis of berbine alkaloids

Though several methods are known for the synthesis of berbine alkaloids, it is reported that berbine alkaloids having oxygen functions at 9, 10 positions pose problems in their synthesis[12]. Thus, benzylisoquinolines like **11** on Mannich or Bischler–Napieralski cyclisation give[13] 10,11-oxygenated berbines **9** and not the 9, 10 oxygenated berbines **8**. To



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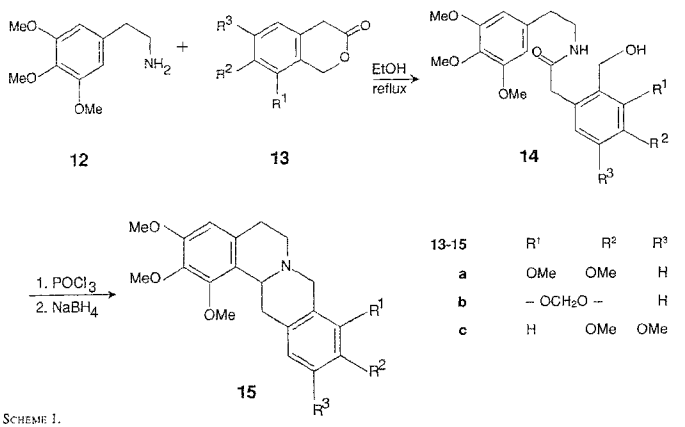
achieve the synthesis of the desired 9, 10-oxygenated berbines **8**, the reactive para position in **11** is blocked by bromine before cyclisation which is removed in the end[12, 14, 15]. After blocking the reactive position also, in some cases the desired products like **8** are obtained in poor yield[12] along with unwanted products like **9**.

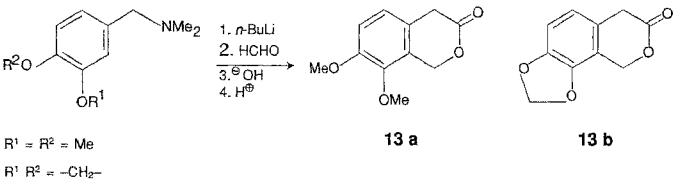
3. Isochromanone approach

We report herein a convenient synthesis of (±), O-methylcapauridine(**15a**), (±)1, 2, 3-trimethoxy-9, 10-methylenedioxyberbine(**15b**) and (±) O,O'-dimethylstephabinamine(**15c**) from 3,4,5-trimethoxy-β-phenylethylamine(**12**) as shown in Scheme 1. The 3, 4, 5-trimethoxy-β-phenylethyl amine (mescaline, **12**) was prepared[16] from 3,4,5-trimethoxybenzaldehyde through nitrostyrene. Isochroman-3-ones **13a** and **13b** required for the synthesis of 9,10-oxygenated berbines (**15a,b**) were synthesised from the corresponding N,N-dimethylbenzylamines using heteroatom-directed lithiation reaction[17]. 6,7-Dimethoxyisochroman-3-one[18] (**13c**) required for **15c** was prepared from 3,4-dimethoxy phenylacetic acid using normal hydroxymethylation approach.



SCHEME 1.

Condensation of amine **12** with isochroman-3-ones (**13a-c**) in refluxing ethanol provided the hydroxyamides **14a–c** in 91, 80 and 83% yield, respectively. These amides (**14a–c**) on Bischler–Napieralski cyclisation with $POCl_3$ in refluxing toluene, followed by $NaBH_4$ reduction



$R^1 = R^2 = Me$

$R^1\ R^2 = -CH_2-$

of the iminium salt, furnished (±) O-methylcapauridine(**15a**), (±)1,2,3-trimethoxy-9, 10-methylenedioxyberbine (**15b**) and (±) O,O'-dimethylstephabinamine (**15c**). The structures of amides (**14a–c**) and berbines (**15a–c**) were determined on the basis of their spectral and analytical data.

It is reported[19] in literature that the C_8-H equatorial appears downfield in berbines having oxygen function at 9, 10 positions as compared to the C_8-protons of berbines having oxygen function at 10, 11 positions. Thus, one of the C_8-H in **15a** and **15b** appears at δ 4.3 and 4.2, respectively, and the other one is merged in the multiplet (δ 2.5–3.65). In the case of **15c**, both the C_8-protons are merged in the multiplet (δ 2.45–3.78). The PMR spectral data for the berbines **15a** and **15c** are in agreement with the literature values[20,21].

4. Experimental

All mps are uncorrected. IR spectra were obtained in $CHCl_3$ solution on a Nicolet FT 20s IR instrument and ^{1}HNMR spectra in $CDCl_3$ on a Jeol FX 90Q instrument. Chemical shifts are expressed in δ (ppm) downfield from TMS as an internal standard and coupling constants in Hz.

N[2-(3,4,5-Trimethoxyphenyl)ethyl] (3,4-dimethoxy-2-hydroxymethyl)phenylacetamide ***(14a)***

A solution of mescaline[16](**12**, 0.650 g, 0.0031 mol) and 7,8-dimethoxyisochroman-3-one[17] (**13a**, 0.60 g, 0.0028 mol) in absolute ethanol (15 ml) was refluxed for 3 h. Excess of ethanol was removed under reduced pressure to give a gummy mass. It was cooled to 0°, dry ether (5 ml) added and scratched to get a white solid which was filtered, dried and recrystallised from chloroform-*n*-hexane to yield amide **14a** (1.2 g, 93%), mp 112°, IR: 3450, 3340, 1635 cm^{-1}; ^{1}HNMR: 2.70 (2H, t, *J*=7Hz, N-CH_2-CH_2-Ar), 3.37(2H, t, *J*=7Hz, -N-CH_2), 3.57 (2H, s, ArCH_2CO), 3.88 and 3.98 (15H, 2xs, 5xOMe), 4.67 (2H, s, –CH_2OH), 6.32 (2H, b s, exchangeable with D_2O, OH/NH), 6.45–6.98 (4H, m, ArH); MS (*m/z*): 419 (M^+); 211, 208, 182, 164, 149. (Found: C, 62.87, H, 6.66. $C_{22}H_{29}NO_7$ requires C,62.99, H,6.97%).

N[2-(3,4,5-Trimethoxyphenyl) ethyl] (3,4-methylenedioxy-2-hydroxymethyl) phenylacetamide ***(14b)***

A solution of **12** (0.650 g, 0.0031 mol) and 7,8-methylenedioxy isochroman-3-one[17] (**13b**, 0.60 g, 0.0031 mol) in absolute ethanol (15 ml) was refluxed for 28 h. On workup as described above, the amide **14b** was obtained (1.0 g, 81%), mp 135°, IR: 3420, 3320, 1640 cm^{-1}; ^{1}HNMR: 2.67(2H, t, *J*=7Hz, N–CH_2–CH_2–Ar), 3.43 (2H, t, *J*=7Hz,–N–CH_2–), 3.49 (2H, s, Ar CH_2CO), 3.87 (9H, s, 3xOMe), 4.70 (2H, s, –CH_2OH), 5.97 (2H, s –OCH_2O–), 6.58 (2H, s, exchangeable with D_2O, OH/NH), 6.64–6.88 (4H, m, ArH); MS (*m/z*): 403 (M^+), 192, 182, 167, 148. (Found: C, 62.78, H, 6.42. $C_{21}H_{25}NO_7$ requires C, 62.52, H, 6.25%).

N[2-(3,4,5-Trimethoxyphenyl)ethyl] (4,5-dimethoxy-2-hydroxymethyl)phenylacetamide ***(14c)***

A solution of **12** (0.650 g, 0.0031 mol) and 6,7-dimethoxy isochroman-3-one[18] (**13c**, 0.60 g, 0.0028 mol) in absolute ethanol (15 ml) was refluxed for 20 h. On usual workup as described above, the amide **14c** was obtained (1.1 g, 85%), mp 147–148°, IR: 3420, 3315, 1650 cm^{-1}; ^{1}HNMR: 2.65(2H t, *J*=7Hz, NCH_2-CH_2-Ar), 3.42 (2H, t, *J*=7Hz, -N–CH_2–), 3.54 (2H, s, Ar CH_2CO), 3.82, 3.86 and 3.92 (15H, s, 5xOMe), 4.58 (2H, s,–CH_2OH), 6.27(1H, s, exchangeable with D_2O, OH/NH), 6.57 (2H, m, ArH), 6.71 and 6.88 (1H each, s, ArH); MS (*m/z*): 419(M^+), 211, 208, 182, 167, 161, 149 and 121. (Found: C,62.77, H, 7.05. $C_{22}H_{29}NO_7$ requires C, 62.99, H, 6. 97%).

(±) O-methylcapauridine **(15a)**

To a solution of hydroxy amide **14a** (0.2 g, 0.00047 mol) in dry toluene (4 ml), phosphorus oxychloride (5 ml, 0.054 mol) was added and the reaction mixture was refluxed for 1 h. Solvent was removed under reduced pressure to give a syrupy liquid. It was dissolved in methanol (6 ml), sodium borohydride (0.5 g) added to it in lots and stirred at room temperature for 1 h and left overnight. Methanol was removed under reduced pressure to give a residue. Water (20 ml) was added to it and extracted with methylene chloride (3×10 ml).

It was then dried over Na_2SO_4 and evaporated under reduced pressure to give a thick mass which was chromatographed over neutral alumina using hexane–methylenechloride (1:1) as an eluant to give a solid. On recrystallisation from ethanol it furnished (±)-O-methylcapauridine (**15a**, 0.055 g, 30%), mp 140–142° (lit.[22,23] mp 140–142°, 142–144°), ^{1}HNMR: 2.48–3.52 (8H, m, methylene and methine protons and C_8-H), 3.90 and 3.92 (15H, 2xs, 5xOMe), 4.3 (1H, d, *J*=15.5Hz, C_8-H), 6.60 (1H, s, C_4-H), 6.80 (1H, d, *J*=8Hz, C_{11}-H), 6.88 (1H, d, *J*=8Hz, C_{12}-H); MS (*m/z*): 385 (M^+), 220, 164; (Found: C, 68.87, H,6.99. $C_{22}H_{27}NO_5$ requires C, 68.55, H,7.06%).

*(±) 1, 2, 3-Trimethoxy 9, 10-methylenedioxyberbine (**15b**)*

The hydroxy amide **14b** (0.4 g, 0.00099 mol) in dry toluene (8 ml) was reacted with phosphorus oxychloride (10 ml, 0. 107 mol) as described above to give a solid which on recrystallisation from ethanol yielded **15b** (0.15 g, 41.0%), mp 140°, ^{1}HNMR: 2.53–3.58 (8H, m, methylene and methine protons and C_8-H), 3.90 and 3.92 (9H, 2xs, 3xOMe), 4.2 (1H, d, *J*=15.5Hz, C8-H), 5.96 (2H, S, $-OCH_2O-$), 6.50 (1H, s, Ar-H), 6.62 (1H, d, *J*=8Hz,C_{11}-H), 6.77 (1H, d, *J*=8Hz, C_{12}-H); MS (*m/z*): 369 (M^+), 220, 148; (Found: C, 68.43, H, 6.48. $C_{21}H_{23}NO_5$ requires C, 68.28, H, 6.28%).

*(±)O,O'-Dimethylstephabinamine (**15c**)*

The hydroxy amide **14c** (0.2 g, 0.00047 mol) in dry toluene (4 ml) was reacted with phosphorus oxychloride (5 ml, 0.054 mol) as described above to give a solid. On recrystallisation from ethanol it provided **15c** (0.078 g, 42.4%), mp 150–152° (lit.[21] mp 151–152°), ^{1}HNMR: 2.45–3.79 (9H, m, methylene and methine protons), 3.81 (15H, m, 5x OMe), 6.50 (1H, s, Ar-H), 6.68 (2H, m, Ar-H); MS (*m/z*): 385 (M^+), 220, 164; (Found: C, 68.54, H, 7.33. $C_{22}H_{27}NO_5$ requires C, 68.55, H, 7.06%).

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References

1. SANTAVY, F. — *The alkaloids: Chemistry and physiology* (Manske, R.H.F. and Rodrigo, R.G.A. (eds)), Vol.17, Ch.4, pp. 439–461, 1979, Academic Press.

2. KAMETANI, T. — *The chemistry of the isoquinoline alkaloids*, Ch.10, pp. 109–128, 1969, Hirokawa Pub. Co.

3. PAI, B. R., NAGARAJAN, K. AND NATARAJAN, S. — *Heterocycles*, 1977, **6**, 1377–1439.

4. PANDEY, G. P. AND TIWARI, K. P. — *Synth. Commun.*, 1979, **9**, 895–900.

5. RUANGRUNGSI, N., LANGE, G.L. AND LEE, M. — *J. Nat. Prod.*, 1986, **49**, 253–258.

6.	LAVAULT, M., GUINAUDEAU, H., BRUNETON, J., SEVENET, T. AND HADI, H. A.	*Phytochemistry*, 1990, **29**, 3845–3847.
7.	KANYINDA, B., VANHAELEN–FASTRE, R., VANHAELEN, M. AND OTTINGER, R.	*J. Nat Prod.*, 1992, **55**, 607–612.
8	PAKRASHI, S. S., MUKHOPADHYAYA, R., DASTIDAR, P. P. G., BHATTACHARJYA, A. AND ALI, E.	*J. Indian Chem Soc*, 1985, **62**, 1003–1007.
9.	MANSKE, R. H. F. AND HOLMES, H. L.	*J. Am. Chem Soc.*, 1945, **67**, 95–98.
10.	KANEKO, H. AND NARUTO, S.	*Yakugaku Zasshi*, 1971, **91**, 101–108.
11.	CHEN, C.-H., CHEN, T.-M. AND LEE, C.	*J. Pharmac Sci.*, 1980, **69**, 1061–1065.
12.	GOVINDACHARI, T. R.	*J. Indian Chem Soc*, 1985, **57**, 353–358.
13.	SHAMMA, M.	*The isoquinoline· Chemistry and pharmacology*, Ch. 16, pp. 271–280, 1972, Academic Press.
14.	KAMETANI, T., IIDA, H., KIKUCHI, T., OHKUBO, K. AND FUKUMOTO, K.	*Chem. Pharmac Bull*, 1969, **17**, 1051–1054.
15.	KAMEGAYA, T.	Japan 74 20,800. *Chem. Abstr.*, 1975, **82**, 73291y.
16.	BENINGTON, F.	*J. Am Chem. Soc*, 1953, **73**, 1353.
17.	NARSIMHAN, N. S., MALI, R. S. AND KULKARNI, B. K.	*Tetrahedron*, 1983, **39**, 1975–1982.
18.	FINKELSTEIN, J. AND BROSSI, A.	*Org. Synth.*, 1976, **55**, 45–48.
19.	CHEN, C. Y. AND MACLEAN, D. B.	*Can J. Chem.*, 1968, **46**, 2501–2506.
20.	TOURWE, D., BINST, G. V. AND KAMETANI, T.	*Org. Magn. Resonance*, 1977, **9**, 341–346
21.	DEAN, R.T. AND RAPOPORT, H.	*J. Org. Chem.*, 1978, **43**, 2115–2122.
22.	KAMETANI, T., IIDA H., HONDA, T. AND IHARA, M.	*J Heterocycl. Chem.*, 1970, **7**, 491–493.
23.	KAMETANI, T., FUKUMOTO, K., IHARA, M., VIITE, A. AND KOIZUMI, H.	*J. Org. Chem.*, 1975, **40**, 3280–3283.