A New Approach to the Synthesis of Aristolactams. Total Synthesis of Cepharanone A and B

Axel Couture,* Eric Deniau, Pierre Grandclaudon, Stéphane Lebrun

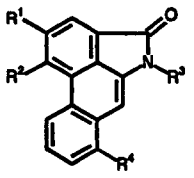
Laboratoire de Chimie Organique Physique, Associé au CNRS (URA n° 351), Université des Sciences et Technologies de Lille I, F-59655 Villeneuve d'Ascq Cedex, France

Fax (+33) 03 20 43 65 61; e-mail Axel.Couture@univ-lille1.fr

Received 11 September 1997

Abstract: An efficient, concise and tactically new synthesis of aristolactams is described. The key step is the aryne-mediated cyclization of an amino carbanion derived from a phosphorylated halobenzamide derivative. Horner reaction, radical cyclization and ultimate deprotection complete the synthesis of the phenanthrene lactam alkaloids. The viability of the strategy is further illustrated by the synthesis of cepharanone A and B.

Aristolactams, as exemplified by cepharanone A **1**, cepharanone B **2**, velutinam **3**, taliscanine **4** and enterocarpam **5**, are phenanthrene lactam alkaloids structurally and biogenetically related to aporphines[1-4] (Scheme 1). The richest source of this family of alkaloids is undoubtedly the Argentinian plant, *Aristolochia argentina* (Aristolochiaceae)[5-7] but some of them have been also isolated from Bornean[8] (Annonaceae) and Formosan[9] plants. In addition, *N*-methyl aristolactam **6** has been recently extracted from *Piper ribesioides* (Piperaceae).[10] Despite receiving considerable attention owing to their pharmacological activities, particularly as fertility-regulating,[11] cyclooxygenase inhibitor[12] and cytotoxic[13] agents, there are few satisfactory syntheses of these alkaloids which often are laborious and low-yielding.[14-16] This is probably due to the generation of a strained frame where a five-membered heterocycle is fused to a polysubstituted phenanthrene unit. The most convenient and elegant routes to these polycyclic lactam compounds involve (i) the lactone ring contraction of a dibenzochromanone and subsequent lactamisation of the resulted five-membered lactone,[17] (ii) the photocyclization of arylmethylidene phthalimidine,[14] (iii) the inter[15] and intramolecular[16] Diels-Alder cycloaddition between an aromatic enamide or dienamide respectively with a benzyne and (iv) the metallation followed by carboxylation of a bromophenanthrylamine.[18]

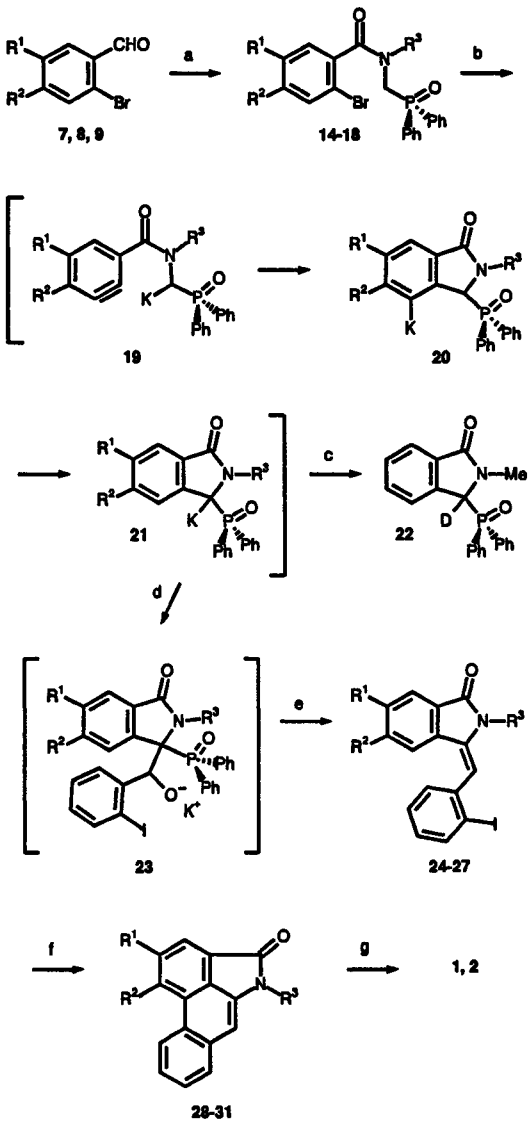


1 R^1, R^2= CH_2OCH_3, R^3= R^4= H
2 R^1= R^2= OMe, R^3= R^4= H
3 R^1= R^2= OMe, R^4= OH, R^3= H
4 R^1= R^2= R^4= OMe, R^3= H
5 R^1= OH, R^2= R^3= OMe, R^4= H
6 R^1= OMe, R^2= OH, R^4= H, R^3= Me

Scheme 1

Herein, we report an alternative and conceptually new approach to these highly conjugated systems which hinges upon the aryne-mediated cyclization of a phosphorylated amino carbanion deriving from a halobenzamide derivative. Subsequent Horner reaction with *o*-iodobenzaldehyde and construction of the phenanthrene nucleus by radical cyclization give rise to the target lactams as shown in Scheme 2.

In order to test the viability of the strategy the bromo-*N*-phosphorylmethylbenzamides **14**, **15** were initially chosen as models. These were conveniently prepared from the suitable aldehyde **7** and phosphorylated amines **10**, **11** by adapting a recently described procedure for the conversion of aromatic aldehydes into tertiary carboxamides (Scheme 2, Table).[19,20] Initially the phosphorylated amines **10**, **11** were obtained by treatment of the corresponding triazines[21] with diphenylphosphine oxide.[22]



Scheme 2. Reagents and conditions: a) NBS, AIBN cat., CCl_4 then $R_3NHCH_2P(O)Ph_2$ **10-13**; b) KHMDS (2 equiv), THF, -78°C to -30°C, 3 h; c) D_3O^+; d) *o*-iodobenzaldehyde, THF, -30°C; e) -30°C to rt, 30 min then aqueous NH_4Cl; f) Bu_3SnH, AIBN cat., benzene, reflux, 5 h; g) TFA, anisole, $ClCH_2CH_2Cl$, reflux, 24 h

The presence of the diphenylphosphinoyl group in the parent models reveals to be critical for the success of the strategy. Indeed, it is a temporary activating group for the regioselective generation of the required α-amino carbanionic species **19**. Addition of the suitably placed carbon nucleophile across the aryne moiety results in the formation of the metallated isoindolinone **20**. Noteworthy, the direct intramolecular arylation of the α-position of an amine is usually carried out by reaction of an α-amino carbanion with an epoxide[23] or by α-arylation and isomerisation of a cyclic enamide.[24]

Table. Compounds Prepared

R^1	R^2	R^3	*o*-Bromo-benzaldehyde	Phosphorylated Amine	Phosphorylated Benzamide (Yield %)		Arylmethylene Isoindolinone (*E*/*Z* ratio; Yield %)		Aristolactam (Yield %)		Cepharanone (Yield %)	
H	H	Me	7	10	14	(83)	24	(45/55; 81)	28	(56)	-	
H	H	Bn	7	11	15	(79)	25	(84/16; 78)	29	(49)	-	
CH_2-O-CH_2		4-$MeOC_6H_4CH_2$	8	12	16	(75)	26	(49/51; 71)	30	(46)	1	(91)
OMe	OMe	4-$MeOC_6H_4CH_2$	9	12	17	(82)	27	(53/47; 74)	31	(52)	2	(87)
H	H	$C_6H_5CH(Me)$	7	13	18	(63)	-		-		-	

Moreover examples of intramolecular trapping of a benzyne intermediate with an adjacent side-chain nucleophile vicinal to a nitrogen atom are very rare.[25]

On the other hand, the diphenylphosphinoyl group survives the metallation-addition step and consequently induces a metal shift to the more acidic phosphorylated benzylic position thus giving rise to the phosphorylated amino carbanion **21**. This was evidenced by the regioselective introduction of deuterium at the 3-position of the isoindolinone ring of **22**[26] upon aqueous work-up (D_2O) at this step. Accordingly, applying the Horner protocol to **21** could be envisaged and as anticipated, addition of *o*-iodobenzaldehyde and subsequent dephosphorylation delivered the 2-alkyl-3-arylmethylene-2,3-dihydro-1*H*-isoindol-1-one **24**, **25** with excellent yields (Table). Finally the presence of the diphenylphosphinoyl group and of the weakly bound potassium counterion in the adduct **23** associated with the high degree of conjugation of the final compounds **24**, **25**[27] accounts for the efficiency of the process. It is worthy to point out that this protocol precludes isolation and purification of the intermediates, namely the phosphorylated isoindolinones such as **22**, and that the arylmethylene isoindolinones **24**, **25** are straightforwardly accessible from the "opened" phosphorylated *o*-bromobenzamides **14**, **15**. It is also worth mentioning that the final compound **24**, **25** are obtained in both *E* and *Z* forms (Table) but the stereochemistry about the central double bond is irrelevant for our purposes. Indeed, despite the strain which is developed during the bi-arylic bond formation, the tributyltin-mediated radical cyclization of compounds **24**, **25** as the final step in the construction of the phenanthrene nucleus afforded the aristolactams **28**, **29** with satisfactory yields[28] (Table).

We therefore proceeded to apply this strategy to the synthesis of cepharanone A and B, **1**, **2** respectively. Conversion of the 6-bromopiperonal **8**[29] and 6-bromoveratraldehyde **9**[30] to the required phosphorylated amides **16**, **17** was carried out through the reaction sequence shown in Scheme 2 (Table). As expected the 3-(aryl)methylene-1*H*-isoindolinones **26**, **27**[27,31] were readily obtained by basic treatment of the phosphorylated bromocarboxamides and subsequent addition of *o*-iodobenzaldehyde. The cyclization under radical conditions of compounds **26**, **27** proceeded uneventfully to afford the *N*-4-methoxyphenylmethyl aristolactams **30**, **31**[28,32]. Since there are only a few known examples of simple *N*-benzylated aromatic enamides which have been successfully deprotected,[33] we were cautiously optimistic about the possibility to overtake this difficulty. In order to solve the problem it has been recently reported that the usual benzyl protection could be advantageously replaced by the α-methylbenzyl[33] but unfortunately all our attempts to cyclize the suitable phosphorylated carboxamides **18**[20] under basic conditions were unrewarding. For the final removal of the 4-methoxyphenylmethyl group we then screened the commonly used debenzylating reagents including $Ce(NH_4)_2(NO_3)_6$, H_2O-MeCN;[34] H_2, $Pd(OH)_2$/C, EtOH;[35] $AlCl_3$, toluene;[36] $HCOONH_4$, Pd/C, MeOH;[37] Na, liq NH_3.[38] After numerous experimentations we found that treatment of the *N*-methoxybenzylated lactams **30**, **31** with trifluoroacetic acid-anisole in boiling 1,2-dichloroethane[39] ensured completion of the natural product synthesis and delivered the targeted cepharanone A and B, **1**, **2** respectively, with fairly good yields (Table).

In conclusion, by means of a tactically new synthetic approach involving an aryne-mediated cyclization of an α-amino carbanion deriving from a phosphorylated halobenzamide as the key step, it has been disclosed a convergent and concise synthesis of some aristolactam alkaloids. Owing to the efficiency and simplicity of the methodology, this process deserves attention and further work aimed at expanding the scope of these reactions to include other aporphinoid alkaloids are under way in our laboratory.

References and Notes

(1) Chang, Z. L.; Zhu, D-Y in *The Alkaloids*, Vol. 31, Brossi, A., Ed.; Academic Press, New York, 1987; p 29.

(2) Shamma, M.; Moniot, J. L. *Isoquinoline Alkaloid Research 1972-77*; Plenum Press, New York, 1978.

(3) Castedo, L.; Tojo, G. in *The Alkaloids*, Vol. 39; Brossi, A., Ed.; Academic Press, New York, 1990; p 99.

(4) Kametani, T. in *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley Interscience, New York, 1977.

(5) Han, D. S.; Chung, B. S.; Chi, H. J.; Lee, H. S. *Korean J. Pharmacogn.* **1989**, *20*, 1.

(6) Lee, H. S.; Han, D. S.; Won, D. K. *Korean J. Pharmacogn.* **1990**, *21*, 52.

(7) Priestap, H. A. *Phytochemistry* **1985**, *24*, 849.

(8) Siraj, O.; Chang, L. C.; Fasihuddin, A.; Jiu, X. N.; Hasan, J.; Jinasheng, H.; Tetsuo, N. *Phytochemistry* **1992**, *31*, 4395.

(9) Wang, E-C; Shih, M-H; Liu, M-C; Chem, M-T; Lee, G. H. *Heterocycles* **1996**, *43*, 969.

(10) Nijsiri, R.; Sompop, P.; Lange, G. L.; Organ, M. G. *Phytochemistry* **1992**, *31*, 2397.

(11) Che, C. T.; Ahmed, M. S.; Kang, S. S.; Waller, D. P.; Bingel, A. S.; Martin, A.; Rajamahendran, P.; Bunyapraphatsara, N.; Lamkin, D. C. *J. Nat. Prod.* **1984**, *47*, 331.

(12) Proebstle, A.; Bauer, R. *Planta Med.* **1992**, *58*, 568.

(13) Sun, N. J.; Antoun, M.; Chang, C. J. *J. Nat. Prod.* **1987**, *50*, 843.

(14) Castedo, L.; Guitian, E.; Saa, J. M.; Suau, R. *Heterocycles* **1982**, *19*, 279.

(15) Castedo, L.; Guitian, E.; Saa, J. M.; Suau, R. *Tetrahedron Lett.* **1982**, *23*, 457.

(16) Estevez, J. C.; Estevez, R. J.; Guitian, E.; Villaverde, M. C.; Castedo, L. *Tetrahedron Lett.* **1989**, *30*, 5785.

(17) Estevez, J. C.; Estevez, R. J.; Castedo, L. *Tetrahedron* **1995**, *51*, 10801.

(18) Kupchan, S. M.; Wormser, H. C. *J. Org. Chem.* **1965**, *30*, 3933.

(19) Marko, I. E.; Mekhalfia, A. *Tetrahedron Lett.* **1990**, *31*, 7237.

(20) Satisfactory spectral data (IR, ^{13}C, ^{31}P and ^{1}H NMR) and elemental analyses were obtained for all compounds.
A typical procedure for the preparation of compounds **14-18** is illustrated by the preparation of **17**. To a preheated solution (95°C) of bromoveratraldehyde **9** (10 mmol) in CCl_4 (180 mL) were added AIBN (0.3 mmol) and NBS (11 mmol). The mixture was refluxed for 30 min, cooled to 0°C with an ice bath and a solution of the phosphorylated amine **12** (13 mmol) and Et_3N (18 mmol) in CCl_4 (20 mL) was then added dropwise with stirring. The reaction mixture was stirred at rt for 1 h, the solid was filtered and the organic phase was washed with water, brine and dried over $MgSO_4$. The phosphorylated amide **17** was purified by flash column chromatography on silica gel with acetone-hexane (2:1) as eluent and finally recrystallized from hexane-toluene. Pure **17** was obtained as a white powder; mp 177-178 °C; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 3.65 (3H, s), 3.75 (3H, s), 3.80 (3H, s), 4.38-4.57 (3H, m), 4.78 (1H, d, *J* 15.0 Hz), 6.19 (1H, s), 6.81 (2H, d, *J* 8.3 Hz), 6.90 (1H, s), 7.21 (2H, d, *J* 8.3 Hz), 7.40-7.57 (6H, m), 7.82-8.04 (4H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ : 42.1 (d, J_{CP} 76.5 Hz), 52.7, 55.2, 56.2, 110.0, 110.7, 114.0, 115.5, 127.2, 128.6 (d, J_{CP} 10.5 Hz), 128.7 (d, J_{CP} 11 Hz), 129.9, 131.3 (d, J_{CP} 8 Hz), 131.4 (d, J_{CP} 9.5 Hz), 132.2 (m), 148.4, 150.0, 159.3, 168.9; ^{31}P NMR ($CDCl_3$, 121 MHz) δ : 31.0; *m/z* (%): 595 and 593 (M^+, 65), 512 (50), 246 and 244 (100); Anal. Calcd for $C_{30}H_{29}BrNO_5P$: C, 60.62; H, 4.92; N 2.36. Found C, 60.61; H, 5.03, N, 2.34.

(21) Amoroso, R.; Cardillo, G.. Tomasini, C. *Tetrahedron Lett.* **1990**, *31*, 6413.

(22) a) Couture, A.; Deniau, E.; Grandclaudon, P.; Lebrun, S. *Tetrahedron Lett.* **1996**, *37*, 7749. b) Couture, A.; Deniau, E.; Grandclaudon, P.; Woisel, P. *Tetrahedron* **1996**, *52*, 4433.

(23) Beak, P.; Wu, S.; Yum, E. K.; Jun, Y. M. *J. Org. Chem.* **1994**, *59*, 276.

(24) Nilsson, K.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 2464.

(25) Jaques, B.; Wallace, R. G. *Tetrahedron* **1977**, *33*, 581.

(26) Compound **22**: mp 197-198 °C; ^{1}H NMR ($CDCl_3$; 300 MHz) δ 3.04 (3H, s), 5.33 (1H, d, J_{HP} 11.1 Hz; signal absent upon aqueous work-up with D_2O), 6.84 (1H, d, *J* 7.5 Hz), 7.25-7.67 (13H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ : 30.4, 63.8 (d, J_{CP} 72.5 Hz), 123.7, 123.8, 128.7 (d, J_{CP} 12 Hz), 128.8 (d, J_{CP} 12 Hz), 131.2, 131.6 (d, J_{CP} 9 Hz), 131.8 (d, J_{CP} 9 Hz), 132.9 (d, J_{CP} 2.5 Hz), 133.0 (d, J_{CP} 3 Hz), 138.6, 168.8; ^{31}P NMR ($CDCl_3$, 121 MHz) δ : 30.6; *m/z* (%): 347 (M^+, 32), 201 (50), 146 (100); Anal. Calcd for $C_{21}H_{18}NO_2P$: C, 72.62; H, 5.22; N 4.03. Found C, 72.36; H, 5.24, N, 4.08.

(27) **General Procedure for the Synthesis of 24-27:**
A solution of KHMDS in toluene (0.5 M, 2 mmol) was added dropwise to a stirred solution of the phosphorylated amide **14-17** (1 mmol) in THF (20 mL) at -78°C under Ar. The solution was slowly warmed to -30°C (3 h) and a solution of *o*-iodobenzaldehyde (1 mmol) in THF (5 mL) was added and the reaction mixture was allowed to warm to rt over a period of 30 min. Usual work-up and flash chromatography on silica gel with AcOEt-hexane (1:4) as eluent afforded *Z* and *E* forms of the isoindolinones **24-27**.

(28) **General Procedure for the Synthesis of 28-31:**
AIBN (0.25 mmol) and tributyltin hydride (0.70 mmol) were added to a solution of the arylmethylene isoindolinones **24-27** (0.50 mmol) in dry benzene (250 mL) and refluxed for 5 h under Ar. The benzene was removed *in vacuo* and the residue was dissolved in acetonitrile (150 mL) which was washed with hexane (3 x 50 mL). Concentration *in vacuo* afforded a solid residue which was purified by flash chromatography eluting with AcOEt-hexane (2:3). Recrystallization from EtOH gave the condensed products **28-31** as lemon yellow crystals.

(29) a) Jung, M. E.; Lam, P. Y.; Mansuri, M. M.; Speltz, L. M. *J. Org. Chem.* **1985**, *50*, 1087. b) Khanapure, S. P.; Biehl, E. R. *J. Org. Chem.* **1990**, *55*, 1471.

(30) Charlton, J. L.; Alauddin, M. M. *J. Org. Chem.* **1986**, *51*, 3490.

(31) **Selected spectroscopic data:**
27 (*Z* + *E*) ^{1}H NMR ($CDCl_3$; 300 MHz) δ *Z*: 3.50 (3H, s), 3.77 (3H, s), 3.93 (3H, s), 5.04 (2H, s), 6.22 (1H, s), 6.43 (1H, s), 6.85 (2H, d, *J* 8.3), 7.00-7.05 (1H, m), 7.25-7.30 (4H, m), 7.46 (1H, d, *J* 7.3), 7.92 (1H, dd, *J* 8.0, 1.0); δ *E*: 3.69 (3H, s), 3.99 (3H, s), 4.02 (3H, s), 4.75 (2H, s), 6.30 (1H, s), 6.39 (2H, d, *J* 8.6), 6.60 (2H, d, *J* 8.6), 6.95-7.07 (1H, m), 7.14-7.40 (4H, m), 7.78 (1H, d, *J* 8.0); ^{13}C NMR ($CDCl_3$, 75 MHz) δ *Z*: 42.8, 55.3, 55.7, 56.3, 101.2, 104.9, 105.5, 113.5, 114.1, 123.3, 127.8, 128.5, 129.2, 129.3, 130.9, 136.4, 139.3, 139.8, 150.7, 152.1, 158.9, 166.9; δ *E*: 44.4, 55.3, 56.4, 56.6, 101.8, 104.8, 109.8, 113.7, 121.0, 127.3, 127.5, 128.7, 128.9, 131.3, 132.1, 134.8, 138.4, 132.9, 140.6, 151.1, 153.3, 158.6, 169.1; *m/z* (FAB, %): 528 (M^+ + 1, 40), 419 (45); Anal. Calcd for $C_{25}H_{22}INO_4$: C, 56.94; H, 4.20; N 2.66. Found C, 56.82; H, 3.95, N, 2.91.

(32) **Selected spectroscopic data:**
31; mp 190-191°C; ^{1}H NMR ($CDCl_3$; 300 MHz) δ: 3.75 (3H, s), 4.07 (3H, s), 4.10 (3H, s), 5.09 (2H, s), 6.83 (2H, d, *J* 8.7), 6.84 (1H, s), 7.32 (2H, d, *J* 8.7), 7.49-7.56 (2H, m), 7.71-7.74 (1H, m), 7.82 (1H, s), 9.18-9.23 (1H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ : 43.4, 55.2, 56.9, 60.3, 105.2, 109.7, 114.1, 120.8, 121.0, 125.9, 127.1, 127.4, 127.5, 128.7, 129.1, 134.7, 136.2, 154.4, 156.9, 161.0, 167.8; *m/z* (%): 399 (M^+, 100); Anal. Calcd for $C_{25}H_{21}NO_4$: C, 56.94; H, 4.20; N 2.66. Found C, 56.88; H, 4.12, N, 2.37.

(33) Gramain, J. C.; Troin, Y.; Mavel, S.; Vallee-Goyet, D. *Tetrahedron* **1991**, *47*, 7287.

(34) Barro, A.; Benetti, S.; Pollini, G. P.; Spatullo, G.; Zanirato, V. *Gazz. Chim. Ital.* **1993**, *123*, 185.

(35) Chung, K. H.; Cho, K. Y.; Asami, Y.; Takahashi, N.; Yoshida, S. *Heterocycles* **1991**, *22*, 99.

(36) Agostini, O.; Bonacchi, G.; Coppini, G.; Di Mareo, G.; Paoli, P.; Toja, A. *Arzneim Forsch.* **1995**, *45*, 684.

(37) Botta, M.; Summa, V.; Saladino, R.; Nicoletti, R. *Synth. Commun.* **1991**, *21*, 2181.

(38) Jacobi, P. A.; Brielmann, H. L.; Hauck, S. I. *J Org. Chem.* **1996**, *61*, 5013.

(39) **General Procedure for the Preparation of 1, 2:**
A solution of trifluoroacetic acid (1.5 mmol), anisole (1.5 mmol), aristolactam **30**, **31** (0.15 mmol) in dry 1,2-dichloroethane (1 mL) was refluxed for 24 h under an argon atmosphere. The solvents were evaporated under vacuum, the residue was dissolved in CH_2Cl_2 (10 mL) and then treated with NEt_3 (1 mL). Water was added and the organic layer was washed with brine and dried ($MgSO_4$). The solvent was removed *in vacuo*, leaving a solid residue which was recrystallized from EtOH to afford a yellow solid identified by comparison (IR, MS, ^{13}C and ^{1}H NMR) with literature data (see references [7, 9, 40]).

(40) a) Priestap, H. *Magn. Reson. Chem.* **1989**, *27*, 460. b) Eckhardt, G.; Urzua, A.; Cassels, B. K. *J. Nat. Prod.* **1983**, *46*, 92.