Chemoenzymatic Synthesis of Pyrrolo[2,1-*b*]quinazolinones: Lipase-Catalyzed Resolution of Vasicinone†

Ahmed Kamal,* K. Venkata Ramana, and Maddamsetty V. Rao

Division of Organic Chemistry-I, Indian Institute of Chemical Technology, Hyderabad-500 007, India

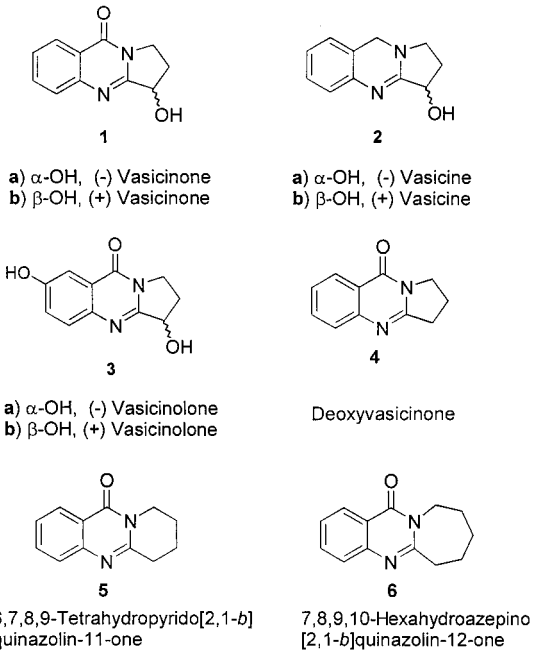
ahmedkamal@iict.ap.nic.in

Received July 28, 2000

A facile synthesis of bronchodilatory pyrrolo[2,1-*b*]quinazoline alkaloids by azidoreductive cyclization strategy employing TMSCl−NaI and bakers' yeast is described. Both the chemical and enzymatic methods are mild and take place at room temperature in good yields. Further, synthesis and resolution of vasicinone has been carried out by employing different lipases. It has been observed that lipase PS provides acetate of (*S*)-vasicinone in 98% ee.

Introduction

Vasicinone (**1**) is a pyrrolo[2,1-*b*]quinazoline alkaloid isolated from the aerial parts of *Adhatoda vasica* (family: Acanthaceae; Sanskrit-Vasaka), an evergreen subherbaceous bush used extensively in indigenous medicine for cold, cough, bronchitis, and asthma.[1] The related pyrrolo[2,1-*b*]quinazoline alkaloids namely, vasicine (**2**), vasicinolone (**3**), and 3-deoxyvasicinone (**4**) have also been reported to be isolated from these types of plants.[2] Most of these quinazoline alkaloids (examples **5** and **6**) are known to possess a broad spectrum of pharmacological activity particularly bronchodilatory activity. A series of analogues of vasicinone have recently been synthesized and evaluated for their bronchodilatory activity.[3] Deoxyvasicinone, though obtained in nature, may be considered as a precursor for the synthesis of vasicinone, and the former has been prepared by various methods such as carbonylation catalyzed by palladium,[4] coupling *O*-methyl butyrolactim with anthranilic acid,[5] cycloaddition of anthranilic acid iminoketene to a methyl butyrolactam (via sulfinamide anhydride),[6] and intramolecular aza-Wittig reaction using PPh_3 and PBu_3.[7] (±) Vasicinone has also been synthesized from deoxyvasicinones by bromination with NBS followed by acetoxylation with NaOAc−AcOH treatment and lead tetraacetate free radical oxidation.[5] (3*S*)-(−)-Vasicinone has been claimed to have better bronchodilation activity than the racemic form and has been recently synthesized by asymmetric hydroxylation using Davis reagent.[7a]



We have been interested in structural modification for synthetic analogues of vasicinone and exploration of convenient and efficient synthetic methods by the azido reductive processes employing TMSCl−NaI and bakers' yeast. Furthermore, resolution of vasicinone employing different lipases has also been investigated.

Results and Discussion

Azido Reductive Cyclization Employing TMSCl−NaI. The intramolecular aza-Wittig reaction has been used extensively for the synthesis of five- to seven-

* To whom correspondence should be addressed. Fax: 91-40-7173757.

† IICT Commun. No. 4592.

(1) Amin, A. H.; Mehta, D. R. *Nature* **1959**, *183*, 1317.

(2) (a) Joshi, B. S.; Newton, M. G.; Lee, D. W.; Barber, A. D.; Pelletier, S. W. *Tetrahedron*: *Asymmetry* **1996**, *7*, 25. (b) Atal, C. K. In *Chemistry and Pharmacology of Vasicine*; Raj Bandu Industrial Co.: Delhi, 1980. (c) Ghosal, S.; Chauhan, P. S. R. B.; Mehta, R. *Phytochemistry* **1975**, *14*, 830. (d) Chatterjee, A.; Ganguly, M. *Phytochemistry* **1968**, *7*, 307.

(3) (a) Fitzgerald, J. S.; Johns, S. R.; Lamberton, J. A.; Redclife, A. H. *Aust. J. Chem*. **1966**, *19*, 151. (b) Stephen, T.; Stephen, H. *J. Chem. Soc*. **1956**, 4694. (c) Hermecz, I.; Vasvari-Debreczy, L.; Horvath, A.; Balogh, M.; Kokosi, J.; DeVos, C.; Rodriguez, L. *J. Med. Chem*. **1987**, *30*, 1543. (d) Dunn, A. D.; Kinnear, K. I.; Norrie, R.; Ringan, N.; Martin, D. *J. Heterocycl. Chem*. **1987**, *24*, 175. (e) Sharma, S. C.; Zutshi, U.; Gupta, O. P.; Dhar, K. L.; Atal, C. K. *Indian J. Chem*. **1996**, *35B*, 345. (f) Malhotra, S.; Koul, S. K.; Sharma, R. L.; Anand, K. K.; Gupta, O. P.; Dhar, K. L. *Indian J. Chem*. **1988**, *27B*, 937.

(4) Mori, M.; Kobayashi, H.; Kimura, M.; Ban, Y. *Heterocycles* **1985**, *23*, 2803.

(5) (a) Onaka, T. *Tetrahedron lett*. **1971**, 4387. (b) Morris, R. C.; Hanford, W. E.; Roger, A. *J. Am. Chem. Soc*. **1935**, *57*, 951.

(6) Kametani, T.; Loc, C. V.; Higa, T.; Koizumi, M.; Ihara, M.; Fukumoto, K. *J. Am. Chem. Soc*. **1977**, *99*, 2306.

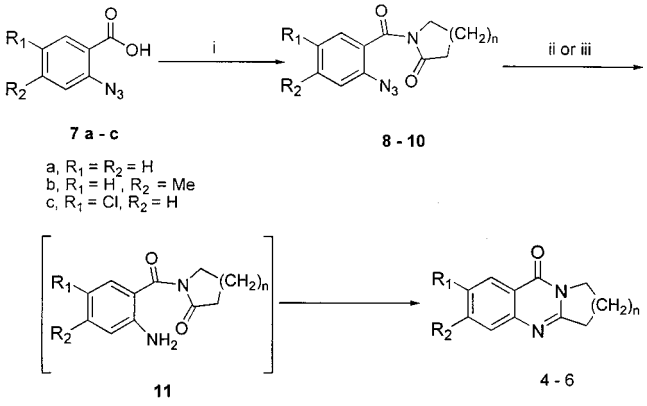
(7) (a) Eguchi, S.; Suzuki, T.; Okawa, T.; Matsushita, Y. *J. Org. Chem*. **1996**, *61*, 7316. (b) Takeuchi, H.; Hagiwara, S.; Eguchi, S. *Tetrahedron* **1989**, *45*, 6375.

10.1021/jo0011484 CCC: $20.00
Published on Web 01/13/2001

membered nitrogen heterocycles including vasicinone.[7] Cyclizations with triphenylphosphine usually takes place in about 5 h under reflux conditions in xylene. Tributylphosphine, a rather expensive reagent, takes about 2 h for the cyclization under reflux conditions in toluene. We have recently reported[8] the reduction of azides to amines employing TMSCl−NaI. This has prompted us to envisage an azidoreductive cyclization process to obtain the pyrrolo[2,1-*b*]quinazolinone system employing TMSCl−NaI under mild conditions in quantitative yield. This has been further generalized for the cyclization of similar azidobenzoyl lactams[7] to obtain the corresponding pyrido- and azepino-quinazolinones (**4**−**6**). The appropriate precursors 2-azidobenzoyl lactams have been prepared by coupling 2-azidobenzoic acids with respective lactams. Reductive cyclization with TMSCl−NaI provided the corresponding [2,1-*b*]quinazolinones in quantitative yields, and these reactions have been monitored by TLC. It is interesting to note that this process employing in situ generated TMSI is spontaneous (10−15 min), and the reaction takes place at room temperature.

Enzyme-Catalyzed Reductive Cyclization by Bakers' Yeast. There has been a growing interest in biocatalysis and transformations mediated by bakers' yeast.[9] Reduction of carbonyl compounds has become a valuable strategy in organic synthesis, although the reduction or oxidation of other functionalities has not been investigated in detail. During our efforts to unravel newer applications of bakers' yeast,[10,11] we have recently observed the reduction[12] of aryl azides to arylamines employing bakers' yeast under extremely mild conditions. In continuation of this endeavor, the reductive cyclization of 2-azidobenzoyl lactams to pyrrolo[2,1-*b*]quinazolones has been accomplished by the application of bakers' yeast. Similarly, this yeast-mediated cyclization has been extended to obtain pyrido[2,1-*b*]quinazolinone and azepino-[2,1-*b*]quinazolinone ring systems in good yields. These reactions have been monitored by TLC. However, enzymatic cyclization of 4-chloro-2-azidobenzoyl lactams produced corresponding quinazolones in low yields (2%). Interestingly, cyclization with presonicated bakers' yeast[13] produced the cyclized product in improved yields (20%). It is presumed that the ultrasonic effect on yeast cells is associated with an enhancement of the diffusion process of the substrates on removal of the outer membrane. However, the increase in enzyme activity and membrane-associated factors can also play a role in this process. It is conceived that the cyclization of 2-azidobenzoyl lactams to [2,1-*b*]quinazolinones take place via the reduction of azido functionality to the amino group, although this intermediate (**11**) could not be isolated (Scheme1). A control incubation using a boiled yeast preparation afforded >95% recovery of the starting material **8**. The products have been characterized by mass spectrometry

Scheme 1[a]



Compd.	R_1	R_2	n
8a, 4a	H	H	1
8b, 4b	Me	H	1
8c, 4c	H	Cl	1
9a, 5a	H	H	2
9b, 5b	Me	H	2
9c, 5c	H	Cl	2
10a, 6a	H	H	3
10b, 6b	Me	H	3
10c, 6c	H	Cl	3

[a] Reaction conditions: (i) $SOCl_2$, benzene, lactam **6** or **7**; (ii) TMSCl−NaI, MeCN; (iii) bakers' yeast.

and other spectroscopic data, and the reactions are monitored by TLC. The enzymatic route described here suggests an alternative strategy for the preparation of this class of heterocyclic compounds by reductive cyclization approach under mild conditions without the use of heat or acid.

Synthesis and Lipase-Mediated Resolution of Vasicinone. Most of the synthetic methods reported for vasicinone and deoxyvasicinone have been targeted for their *dl* racemic mixture except for the recent asymmetric oxidation of deoxyvasicinone with the Davis oxidation reagent. However, no efforts have been made in the literature to resolve the racemic vasicinone, although the pharmacological activity has been shown to differ for the individual isomers of vasicinone. Therefore, we investigated the resolution of optically active vasicinone by employing various lipases. The lipase-catalyzed transesterification of an enantiomeric mixture of hydroxy compound in organic solvents is well established for obtaining enantiomerically pure compound.[14] For this purpose vasicinone has been obtained from deoxyvasicinone by its NBS bromination to obtain 3-bromovasicinone as described in the literature in about 57% yield. Treatment with KOAc in the presence of 18-crown-6 gave the desired acetylvasicinone in quantitative yields (Scheme 2), although the reported procedures[5] for acetyl vasicinone are low yielding. Acetyl vasicinone thus obtained has been

(8) Kamal, A.; Rao, N. V.; Laxman, E. *Tetrahedron Lett.* **1997**, *38*, 6945.
(9) (a) Servi, S. *Synthesis* **1990**, 1. (b) Czuk, R.; Glanzer, B. I. *Chem. Rev.* **1991**, *91*, 491.
(10) Kamal, A.; Rao, M. V.; Meshram, H. M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2056.
(11) Kamal, A.; Reddy, B. S. P. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 159.
(12) (a) Kamal, A.; Damayanthi, Y.; Laxminarayana, B.; Reddy, B. S. N. Indian Patent Appl., No. 108/DEL/98, Oct 1996. (b) Kamal, A.; Damayanthi, Y.; Reddy, B. S. N.; Laxminarayana, B.; Reddy, B. S. P. *Chem. Commun.* **1997**, 1015.
(13) (a) Bujons, J.; Guajardo, R.; Kyler, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 604. (b) Kamal, A.; Rao, M. V.; Rao, A. B. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2755.
(14) (a) Carreah, G.; Ottolina, G.; Riva, S. *Trends Biotechnol.* **1995**, *13*, 63. (b) Schmid, R. D.; Verger, R. *Angew. Chem. Int. Ed.* **1998**, *37*, 1609. (c) Theil, F. *Chem. Rev.* **1995**, *95*, 2203.

Scheme 2

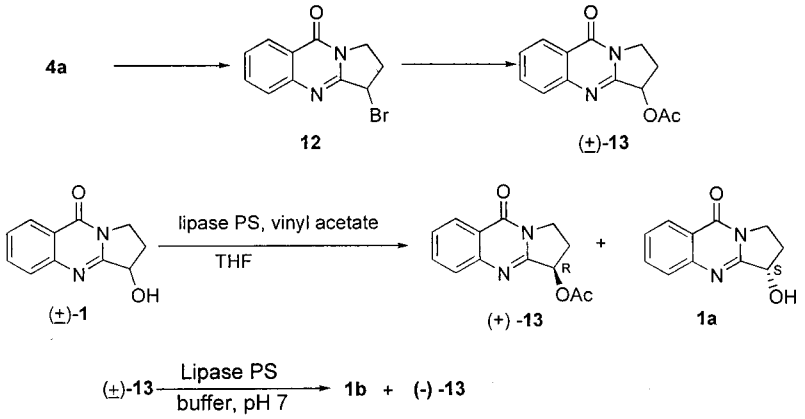


Table 1. Transesterfication of Vasicinone with Various Lipases in Diisopropyl Ether for 48 h

	lipases			**13**[b]
no.	name	amount (mg)	conversion (%)[a]	*R*:*S*
1	PS 'Amano'	250	50	96:4
2	*Candida rugosa*	100	51	62:38
3	porcine pancrease	150	53	66:34
4	liver acetone powder	500	52	54:46
5	wheat germ	270	15	49:51

Table 2. Resolution of (+) Vasicinone by Lipase PS 'Amano' Employing Different Solvents

				13[b]
no.	solvents	time (h)	conversion (%)[a]	*R*:*S*
1	toluene	46	48	98:2
2	THF	48	45	100:−
3	diisopropyl ether	48	51	96:4
4	1,2-dimethoxyethane	48	35	100:−
5	1,4-dioxane	48	28	93:7
6	*tert*-butylmethyl ether	48	25	100:−
7	dibutyl ether	48	38	95:5
8	acetonitrile	24	53	78:22
9	amyl alcohol	20	51	48:52

[a] Based on HPLC. [b] Enantiomeric ratio based on chiral HPLC analysis.[16]

enzymatically hydrolyzed employing lipase PS "Amano" to its (*R*)-alcohol and (*S*)-acetate in 98% ee. Alternately, acetylvasicinone has been chemically hydrolyzed to racemic vasicinone which has been resolved by transesterification with different lipases as shown in the Table 1. It has been observed that lipase PS gives the best results from the conversion as well as enantiomeric excess point of view. On the basis of these findings, a variety of solvents have been investigated for the resolution of vasicinone by transesterification using vinyl acetate to understand their role in this process, and the results are described in Table 2. It is observed that THF followed by toluene and diisopropyl ether provide good selectivity with good conversions, and interestingly (*R*)-acetate is obtained in >99% ee employing lipase PS in THF.

Conclusion

In conclusion, we have reported the synthesis of deoxyvasicinone from anthranilic acid and 2-pyrrolidinone with TMSCl−NaI as well as bakers' yeast utilizing the intramolecular azido reductive process. This method has been extended toward the preparation of racemic vasicinone. Further, we investigated the lipase-catalyzed resolution of vasicinone and its acetate, thus providing a convenient and practical route of preparation for both (*S*) and (*R*) isomers of vasicinone.

Experimental Section

General. Unless specified all solvents and reagents were reagent grade and used without purification. Benzene was dried and distilled over sodium while THF was dried and distilled from sodium benzophenone ketyl under nitrogen. Reactions involving moisture sensitive reagents were performed under an inert atmosphere of nitrogen in glassware that had been oven dried. Melting points have been recorded on an Electrothermal melting point apparatus and are uncorrected. Infrared spectra were recorded on KBr pellet and are reported in wavenumbers (cm^{-1}). ^1H NMR on a 200 MHz instrument was recorded as solutions in $CDCl_3$, and chemical shifts are reported in parts per million (ppm, δ). Coupling constants are reported in hertz (Hz). Spectral patterns are designated as s, single; br, broad; m, multiplet; and comp, complex multiplet. Low resolution mass spectra were recorded on a VG 7070H Micromass mass spectrometer at 200 °C, 70 eV, with a trap current of 200 μA and 4 kV acceleration voltage. HRMS were recorded on a VG Autospec N mass spectrometer at 200 °C, 70 eV, with a trap current of 200 μA and 7 kV acceleration voltage. Analytical TLC of all reactions was performed on Merck prepared plates (silica gel 60 F-254 on glass). Column chromatography was performed using Acme silica gel (60−120 mesh, unless otherwise mentioned). Percentage yields are given for compounds. HPLC analysis was performed on an instrument that consisted of a Shimadzu LC-6A system controller, SPD-6A fixed wavelength UV monitor as detector, FCV-100B fraction collector, and chromatopac C-R4A data processor as a recording integrator.

General Procedure for the Preparation of *N*-(2-Azidobenzoyl) Lactams (8−10). 2-Azidobenzoic acid (0.01 mol) was suspended in dry benzene (15 mL) under nitrogen, and $SOCl_2$ (0.05 mol) was added. To this was added a catalytic amount of DMF and stirred at room temperature for 5 h. The solvent was removed under vacuum to obtain an oily residue of the acid chloride. This was taken up in dry THF (20 mL) and added dropwise under nitrogen to the corresponding lactam (0.01 mol) and Et_3N (0.02 mol) also taken up in dry THF (20 mL). The mixture was stirred for 2 h, and the solvent was removed under reduced pressure to obtain a viscous residue. The residue was taken up into EtOAc (50 mL) and washed with water (2 × 25 mL). The organic layer was separated and dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue thus obtained was purified by silica gel column chromatography (60−120 mesh, 1:4 EtOAc−hexane) to obtain the *N*-(2-azidobenzoyl) lactams **8**−**10** in 75−83% yields.

***N*-(2-Azidobenzoyl)pyrrolidin-2-one (8a):** mp 81−83 °C; IR (KBr) 2150, 1750, 1680 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.2 (q, 2H, J = 6.8, 8.0 Hz), 2.6 (t, 2H, J = 8 Hz), 4.0 (t, 2H, J = 7.6 Hz), 7.2 (m, 3H), 7.5 (t, 1H); MS (EI) m/z 230 (M^+).

***N*-(2-Azido-5-methylbenzoyl)pyrrolidin-2-one (8b):** ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.1 (q, 2H, J = 7.5, 6.8 Hz), 2.4 (s, 3H), 2.6 (t, 2H, J = 6.3 Hz), 4.0 (t, 2H, J = 8.0 Hz), 7.0 (s, 1H), 7.1−7.3 (m, 2H).

***N*-(2-Azido-4-chlorobenzoyl)pyrrolidin-2-one (8c):** mp 137−139 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.2 (q, 2H, J = 7.6, 6.8 Hz), 2.6 (t, 2H, J = 8 Hz), 4.0 (t, 2H, J = 7.6 Hz), 7.1−7.3 (m, 3H); MS (EI) m/z 264 (M^+).

***N*-(2-Azidobenzoyl)-δ-valerolactam (9a):** mp 92−94 °C; IR (KBr) 2130, 1706, 1664 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.9 (m, 4H), 2.5 (t, 2H, J = 6.4 Hz), 3.9 (t, 2H, J = 6.0 Hz) 7.2 (m, 2H), 7.5 (t, 1H).

***N*-(2-Azido-5-methylbenzoyl)-δ-valerolactam (9b):** mp 128−130 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.0 (m, 4H), 2.4 (s, 3H), 2.6 (t, 2H, J = 6.5 Hz), 3.9 (t, 2H, J = 6.0 Hz), 7.0 (s, 1H), 7.1−7.3 (m, 2H); MS (EI) m/z 230 (M^+ − 28); HRMS m/z (M^+ − 28) calcd for $C_{13}H_{14}N_2O$ 230.105528, found 230.105300.

***N*-(2-Azido-4-chlorobenzoyl)-δ-valerolactam (9c):** mp 114−118 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.0 (m, 4H), 2.5 (t, 2H, J = 6.4 Hz), 3.85 (t, 2H, J = 6.0), 7.1−7.4 (m, 3H); MS (EI) m/z 250 (M − 28).

***N*-(2-Azidobenzoyl)-∈-caprolactam (10a):** mp 70−72 °C; IR (KBr) 2127, 1707, 1671 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.9 (s, 6H), 2.6 (d, 2H), 4.0 (d, 2H), 7.1−7.5 (m, 4H); MS (EI) m/z 230 (M^+ − 28).

***N*-(2-Azido-5-methylbenzoyl)-∈-caprolactam (10b):** mp 98−100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.9 (m, 6H), 2.3 (s, 3H), 2.7 (d, 2H), 4.0 (d, 2H), 7.0 (d, 1H, J = 11 Hz), 7.1 (s, 1H), 7.2 (d, 1H, J = 2.5 Hz).

***N*-(2-Azido-4-chlorobenzoyl)-∈-caprolactam (10c):** mp 104−106 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.9 (s, 6H), 2.7 (d, 2H), 4.0 (d, 2H), 7.0−7.3 (m, 3H); MS (EI) m/z 264 (M^+ − 28).

General Procedure for the Synthesis of [2,1-*b*] Fused Quinazolones. Method A. To a solution of **8**−**10** (1 mmol) in MeCN (15 mL) were added NaI (5 mmol) and TMSCl (2 mmol) and stirred for 15 min at room temperature. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and washed with saturated aqueous $Na_2S_2O_3$ solution (2 × 10 mL) followed by brine (1 × 15 mL). The organic phase was separated and dried over anhydrous Na_2SO_4. Evaporation under reduced pressure afforded a solid which was purified over a short silica column (60−120 mesh, 1:1 EtOAc−hexane) to obtain the corresponding cyclized products **4**−**6** in quantitative yields.

Method B (Enzymatic). To a suspension of bakers' yeast (2 g) in water (15 mL) incubated for 30 min at 37.5 °C on a rotary shaker was added a solution of precursor **8**−**10** (0.1 mmol) taken up in 30% water in EtOH (1 mL). This was incubated for 24 h, and an additional amount of 2 g of bakers' yeast was added. The reaction was further continued for 24 h and extracted with EtOAc (3 × 20 mL) upon complete conversion (monitored on TLC, 1:1 EtOAc−hexane). The organic phase was washed with dilute aqueous Na_2CO_3 (4 × 15 mL) followed by brine (2 × 15 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to obtain a residue which was purified by flash column chromatography on silica gel (EtOAc−hexane, 1:1) to obtain the pure cyclized products **4**−**6** in 25−50% yields.

2,3-Dihydropyrrolo[2,1-*b*]quinazolin-9-one (4a): mp 104−106 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.3 (q, 2H, J = 7.5 and 8.0 Hz), 3.2 (t, 2H, J = 8.0 Hz), 4.2 (t, 2H, J = 7.5 Hz), 7.5 (t, 1H, J = 7.4 Hz), 7.6−7.8 (m, 2H), 8.3 (d, 1H, J = 8.0 Hz); MS (EI) m/z 186 (M^+); HRMS calcd for $C_{11}H_{10}N_2O$ 186.079313, found 186.078920.

3-Methyl-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9-one (4b): mp 99−101 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.3 (q, 2H, J = 7.3, 7.8 Hz), 2.5 (s, 3H), 3.2 (t, 2H, J = 7.8 Hz), 4.2 (t, 2H, J = 7.5 Hz), 7.5 (s, 2H), 8.0 (s, 1H); MS (EI) m/z 200 (M^+).

6-Chloro-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9-one (4c): mp 186−188 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.3 (q, 2H, J = 7.3, 7.8 Hz), 3.2 (t, 2H, J = 7.8 Hz), 4.2 (t, 2H, J = 7.5 Hz), 7.4 (d, 1H, J = 6.5 Hz), 7.6 (d, 1H, J = 2 Hz), 8.1 (d, 1H, J = 6.5 Hz); MS (EI) m/z 220 (M^+). HRMS calcd for $C_{11}H_9ClN_2O$ 220.040341, found 220.040296.

6,7,8,9-Tetrahydropyrido[2,1-*b*]quinazolin-11-one (5a): mp 96−98 °C; IR (KBr) 1657 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.0 (m, 4H), 3.0 (t, 2H, J = 6.4 Hz), 4.0 (t, 2H, J = 6.0 Hz), 7.4 (t, 1H, J = 7.4 Hz), 7.6 (d, 1H, J = 8.0 Hz), 7.7 (t, 1H, J = 7.4 Hz), 8.2 (d, 1H, J = 8.0 Hz); MS (EI) m/z 200 (M^+). HRMS calcd for $C_{12}H_{12}N_2O$ 200.94963, found 200.094511.

2-Methyl-6,7,8,9-tetrahydropyrido[2,1-*b*]quinazolin-11-one (5b): ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.0 (m, 4H), 2.5 (s, 3H), 3.0 (t, 2H, J = 5.0 Hz), 4.1 (t, 2H, J = 5.0 Hz), 7.5 (s, 2H), 8.0 (s, 1H); MS (EI) m/z 214 (M^+).

3-Chloro-6,7,8,9-tetrahydropyrido[2,1-*b*]quinazolin-11-one (5c): mp 132−133 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.0 (m, 4H), 3.0 (t, 4H, J = 8.0 Hz), 4.0 (t, 2H, J = 7.4 Hz), 7.4 (dd, 1H, J = 6.6 Hz), 7.6 (d, 1H, J = 1.6 Hz), 8.2 (d, 1H, J = 6.5 Hz); MS (EI) m/z 234 (M^+); HRMS calcd for $C_{12}H_{11}ClN_2O$ 234.0056418, found 234.055991.

7,8,9,10-Hexahydroazepino[2,1-b]quinazolin-12(6*H*)-one (6a): mp 97−99 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.8 (s, 6H), 3.0 (d, 2H), 4.4 (d, 2H), 7.4 (t, 1H, J = 7.4 Hz), 7.6 (d, 1H, J = 8.0 Hz), 7.7 (t, 1H, J = 7.4 Hz), 8.2 (d, 1H, J = 8.0 Hz); MS (EI) m/z 214 (M^+).

2-Methyl-7,8,9,10-hexahydroazepino[2,1-*b*]quinazolin-12(6*H*)-one (6b): mp 68−70 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.8 (s, 6H), 2.4 (s, 3H), 3.0 (d, 2H, J = 6.0 Hz), 4.3 (d, 2H, J = 5 Hz), 7.4 (s, 2H), 8.0 (s, 1H); MS (EI) m/z 228 (M^+).

3-Chloro-7,8,9,10-hexahydroazepino[2,1-*b*]quinazolin-12(6*H*)-one (6c): mp 101−104 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.9 (s, 6H), 3.0 (d, 2H), 4.4 (d, 2H), 7.4 (d, 1H), 7.6 (d, 1H, J = 1.6 Hz), 8.1 (d, 1H, J = 6.5 Hz); MS (EI) m/z 248 (M^+); HRMS calcd for $C_{13}H_{13}ClN_2O$ 248.071641, found 248.071641.

Synthesis of Vasicinone. 3-Bromo-3-deoxyvasicinone (12). To a solution of **4a** (1.8 g, 0.01mol) in dry CCl_4 (50 mL) were added NBS (1.7 g, 0.01mol) and benzoyl peroxide (24 mg, 0.01 mmol). The reaction mixture was refluxed for 5 h and filtered after cooling to room temperature. The filtrate was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel (60−120 mesh, 7:3 EtOAc−hexane) to obtain **12** (1.2 g, 52%): mp 141−142 °C; IR (KBr) 1684, 776 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.5−2.9 (m, 2H), 4.1−4.3 (m, 1H), 4.3−4.5 (m, 1H), 5.2 (dd, 1H, J = 4.6, 1.8 Hz), 7.4−7.6 (m, 2H), 7.6−7.8 (m, 1H), 8.3 (d, 1H, J = 8 Hz); MS (EI) m/z 264 (M^+ − 1); HRMS calcd for $C_{11}H_9N_2O$ 263.989824, found 263.990046.

(±)-Acetylvasicinone (13). To a solution of **12** (2.6 g, 0.01 mol) in MeCN (20 mL) were added KOAc (3.92 g, 0.04 mol) and 18-crown-6 (0.2 g, 0.001 mol) and stirred at room temperature for 1 h. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and filtered through Celite. The filtrate was concentrated, and the residue was purified through a short column (silica gel 60−120 mesh, 1:1 EtOAc−hexane) to afford 2.2 g (90%) of (±)-**13**: mp 137−139 °C; IR (KBr) 1732, 1681, 1465 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.2 (s, H), 2.2−2.4 (m, 1H), 2.7−2.9 (m, 1H), 4.1−4.4 (m, 2H), 6.0 (t, 1H, J = 7.6, 5.4 Hz), 7.4−7.6 (m, 1H), 7.7 (d, 2H, J = 3 Hz), 8.3 (d, 1H, J = 8 Hz); MS (EI) m/z 244 (M^+ − 1).

(±)-Vasicinone (1). To a solution of (±)-**13** (2.4 g, 0.1 mol) in EtOAc was added a solution of NaOH in 50% aqueous MeOH and stirred vigorously for 15 min. The reaction mixture was diluted with EtOAc and washed with water. The combined EtOAc layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain 2 g (97%) of (±)-**1**: mp 203−204 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.3−2.5 (m, 1H), 2.6−2.8 (m, 1H), 4.0−4.2 (m, 1H), 4.3−4.5 (m, 1H), 5.1−5.3 (m, 2H), 7.5−7.6 (m, 1H), 7.7−7.8 (m, 2H), 8.4 (d, 1H, J = 8.1 Hz); MS (EI) m/z 202 (M^+).

Enzymatic Hydrolysis of (±)-Acetylvasicinone. To a solution of acetylvasicinone (200 mg, 1 mmol) in MeCN (18 mL) and phosphate buffer pH 7 (20 mL) was added 80 mg of lipase PS and stirred on a rotary shaker for 7 h at room temperature. The reaction mixture was extracted with EtOAc (3 × 20 mL). The organic layer was separated and dried over anhydrous Na_2SO_4. Filtration and evaporation under reduced pressure gave a crude solid, which was purified by column chromatography (silica gel, 60−120 mesh, 1:1 EtOAc−hexane) to afford (*R*)-**1** and (*S*)-**13**. Further, (*S*)-**13** was hydrolyzed to (*S*)-**1** as mentioned in the above procedure at 0 °C. The enantiomeric purity of these products were determined by

chiral HPLC.[16] (*R*)-**1:** 80 mg, mp 200−201 °C; $[\alpha]^{22}_D = +105$ (*c* 1, $CHCl_3$), lit.[17a] $[\alpha]^{22}_D = +148$ (*c* 1.35 mg mL^{-1}, EtOH); IR 3131, 1664 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.2−2.4 (m, 1H), 2.6−2.8 (m, 1H), 3.9−4.1 (m, 1H), 4.3−4.5 (m, 1H), 4.8 (s, 1H), 5.2 (t, 1H, $J = 7.4$ Hz), 7.4−7.6, (m, 1H), 7.7−7.8, (m, 2H), 8.3 (d, 1H, $J = 7.4$ Hz); MS (EI) *m*/*z* 202 (M^+); HRMS calcd for $C_{11}H_{10}N_2O$ 202.074228, found 202.074030. (*S*)-**13**: ^1H NMR (200 MHz, $CDCl_3$) δ 2.2 (s, 3H), 2.2−2.4 (m, 1H), 2.6−2.9 (m, 1H), 4.1−4.4 (m, 2H), 6.0 (t, 1H, $J = 5.8$ Hz), 7.4−7.6, (m, 1H), 7.7−7.8, (s, 2H), 8.3 (d, 1H, $J = 7.9$ Hz); MS (EI) *m*/*z* 244 (M^+); HRMS calcd for $C_{13}H_{12}N_2O_3$ 244.084792, found 244.085651. (*S*)-**1**: mp 200−201 °C; $[\alpha]^{22}_D = -87$ (*c* 0.5, $CHCl_3$), lit.[17b] $[\alpha]^{22}_D = -90$ (*c* 0.5, $CHCl_3$); IR 3132, 1644 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.2−2.4 (m 1H), 2.6−2.8 (m, 1H), 4.0−4.1 (m, 1H), 4.3−4.5 (m, 1H), 4.7 (s, 1H), 5.2 (t, 1H, $J = 7.2$ Hz), 7.4−7.6, (m, 1H), 7.7−7.8, (m, 2H), 8.3 (d, 1H, $J = 7.4$ Hz); MS (EI) *m*/*z* 202 (M^+); HRMS calcd for $C_{11}H_{10}N_2O$ 202.0474228, found 202.074528.

(15) Jaen, J. C.; Gregor, V. E.; Lee, C.; Davis, R.; Emmerling, M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 737.

(16) Determined by chiral HPLC (Chiracel OD column, Diacel) employing hexane−2-propanol (85:15) as mobile phase, 0.7 mL/min flow, and monitored at 254 nm wavelength.

(17) (a) Rajlakshmi, P.; Aditya, N. C. *J. Ind. Chem. Soc.* **1988**, *65*, 814. (b) Mehta, D. R.; Naravane, J. S.; Desai, R. M. *J. Org. Chem.* **1963**, *28*, 445.

Enzymatic Transesterification of Vasicinone. A mixture of (±)-**1** (200 mg, 1 mmol), vinyl acetate (2 mL), and triethylamine (2 mL) in an organic solvent (as mentioned in Table 2) was stirred for 10 min in the presence of 4 Å molecular sieves (1 g) to which was added lipase (e.g., PS "Amano" 250 mg) as shown in the Table 1. The reaction mixture was stirred at 50 °C and was monitored by HPLC. After about 50% conversion, the reaction mixture was filtered to remove the enzyme and the molecular sieves. The filtrate was evaporated under reduced pressure, and the crude mixture was purified by column chromatography (silica gel, 60−120 mesh, 1:1 EtOAc−hexane) to obtain (+)-**13** and (−)-**1**. The products thus obtained were analyzed by HPLC.[16] The results are summarized in Tables 1 and 2. (*R*)-**13**: ^1H NMR (200 MHz, $CDCl_3$) δ 2.2 (s, 3H), 2.2−2.4 (m, 1H), 2.6−2.8 (m, 1H), 4.1−4.4 (m, 2H), 6.0 (t, 1H, $J = 5.8$ Hz),7.4−7.6 (m, 1H), 7.7 (m, 2H), 8.3 (d, 1H, $J = 7.9$ Hz); MS (EI) *m*/*z* 244.

Acknowledgment. One of the authors (K.V.R.) is thankful to CSIR, New Delhi, for the award of Senior Research Fellowship.

Supporting Information Available: Copies of ^1H NMR, IR, EIMS, HRMS spectra, and HPLC chromatograms of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0011484