A Polymer-Assisted Solution-Phase Strategy for the Synthesis of Fused [2,1-*b*]Quinazolinones and the Preparation of Optically Active Vasicinone

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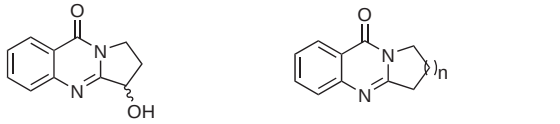
Abstract: An efficient preparation of fused [2,1-*b*]quinazolinones has been developed utilizing polymer-supported reagents. (±)-Vasicinone was converted into its dione by oxidation with poly (4-vinylpyridiniumdichromate). An efficient method has been developed for the synthesis of (*d*)- and (*l*)-vasicinone via asymmetric reduction of pyrrolo[2,1-*b*]quinazoline-3,9-dione by employing $NaBH_4/Me_3SiCl$ as the reducing agent and polymer-supported chiral sulfonamide as catalyst.

Key words: polymer-supported reagents, fused [2,1-*b*]quinazolinones, oxidations, vasicinone

A major role has been played by solid-phase chemistry in revolutionizing certain areas of chemistry, particularly combinatorial synthesis. Solid-phase synthesis is instrumental in building compound libraries efficiently. However, progress of the reaction and compound loading determination on the polymer usually require specialized techniques and analytical equipment. Furthermore, cleavage of the compound from the polymer at the final step is also a requirement. Therefore, an attractive alternative is the use of polymer-supported material as reagents instead as anchors for the substrates. Polymer-assisted solution-phase (PASP)[1] synthesis has many advantages over conventional solution-phase and solid-phase chemistry. Some of these include monitoring of the reaction in real-time by conventional methods, easy reaction optimization, and no residual functionality from bead attachment in the final product.

A number of quinazolinone alkaloids have been isolated from various plants, animals, and microorganisms and also synthesized because of their well-known biological properties.[2] The development of a new, practical, synthetic strategy employing polymer-supported reagents to the synthesis of such bioactive quinazolinone alkaloids is an important and challenging task. Deoxyvasicinone (**6a**) and vasicinone (**10**) and pyrido[2,1-*b*]quinazolinone (**7a**) alkaloids (Figure 1) have been isolated from the aerial parts of *Adhatoda vasica*[3] (from the family Acanthacea, Sankrit-Vasaka), an evergreen subherbaceous bush. Some synthetic routes have been reported for the preparation of deoxyvasicinone,[4] which possesses antimicrobial, antiinflammatory and antidepressant activities.[5] Vasicinone exhibits antitumour,[6a,b] bronchodilatory, hypotensive,[6c] anthelmintic,[6d] and antianaphylactic[6e] activities. Moreover, it is used extensively as a remedy to cold, cough, bronchitis and asthma[6f] in the *Indian Ayurvedic System of Medicine*. 3*S*-(–)-Vasicinone has been claimed to have better bronchodilatory activity than its racemic form and has been synthesized in this laboratory[4a] by a chemoenzymatic method and lipase-catalyzed resolution of the racemic mixture. An approach developed by Argade and co-workers[4b] employed (*S*)-acetoxysuccinic anhydride as one of the starting materials.



(±)-Vasicinone (**10**)
α-OH, (*d*)-Vasicinone (**10***S*)
β-OH, (*l*)-Vasicinone (**10***R*)

n = 1: Deoxyvasicinone (**6a**)
n = 2: 6,7,8,9-Tetrahydropyrido-[2,1-*b*]quinazolin-11-one (**7a**)

Figure 1 Biologically active fused [2,1-*b*]quinazolinones

Enantiopure or enantioenriched *sec*-alcohols are important building blocks for the synthesis of natural products, chiral ligand auxiliaries, biologically active compounds and catalysts. However, a method for their preparation, which usually involves an asymmetric reduction of prochiral ketones, that does not need the use of column chromatography is highly desirable.

In conjunction with our earlier studies on the use of polymer-supported reagents for the preparation of the pyrrolo[2,1-*c*][1,4]benzodiazepine ring system,[7] we herein investigated the synthesis of fused [2,1-*b*]quinazolinones and related analogues, including vasicinone, employing polymer-supported reagents. In the first step 2-azidobenzoic acids (**1a**–**c**) were coupled with different lactams **2** employing *N*-cyclohexylcarbodiimide *N*′-methyl polystyrene (**A**)[8a,b] to give *N*-(2-azidobenzoyl)lactams (**3**–**5**) (Scheme 1).[9] Convieniently, the excess of acid and the urea by-products can be simply filtered off from the azido lactams **3**–**5**. Upon intramolecular azidoreductive cyclization of the azido-lactams employing polymer-supported triphenylphosphine (**B**),[8c] the fused [2,1-*b*]quinazolinones are formed in good overall yields (Table 1, **6**–**8**, 90–98%).[10]

Bromination of deoxyvasicinones **6a**–**c** by employing the polymer-bound brominating agent **C** (Amberlyst A-26, Br_3^- form)[8d] gives allylic monobromo derivatives **9a**–**c**[11] in excellent yields (>98%). These bromo-substituted

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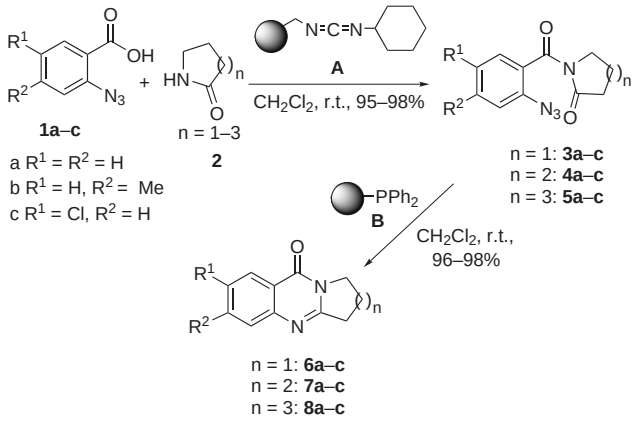
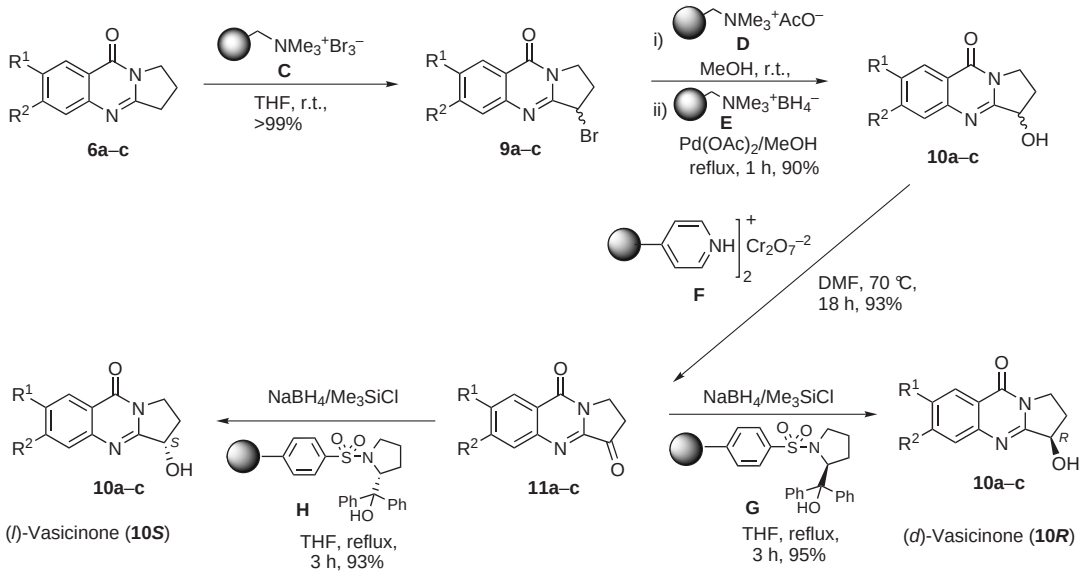


Scheme 1 PASP synthesis of fused [2,1-*b*]quinazolinones

deoxyvasicinones gave the acetylated derivatives upon treatment with the AcO^- form of Amberlyst A-26 (**D**). Racemic vasicinones (**10a–c**)[12] were then obtained by treatment of these acetylated intermediates with borohydride exchange resin **E** in the presence of $Pd(OAc)_2$.[8e] Oxidation of the racemic vasicinones **10a–c** was then effected by using poly(vinylpyridinium dichromate) (**F**) to give diones **11a–c**.[8f,13] Enantioselective reduction of the diones **11a–c** by using polymer-supported chiral sulfonamide **H** in the presence of $NaBH_4/Me_3SiCl$[8g] afforded the optically active (*l*)-vasicinones (**10*S*)a–c**.[14] Alternatively, enantioselective reduction of the diones by using polymer-supported chiral sulfonamide **G** afforded the (*d*)-vasicinones (**10*R*)a–c**[14] in good yield (Scheme 2) with >90% of ee as determined by chiral HPLC.[15] All results are illustrated in Table 2. These polymer-supported chiral reagents have been recovered and reused.



Scheme 2 PASP synthesis of optically active vasicinones

Table 1 Yields and Observed Molecular Ions for Fused [2,1-*b*]quinazolinones **6–8**

Compound	R^1	R^2	n	Time (h)	Yield (%)[a]	MS[b]
6a	H	H	1	3.5	95	186
6b	H	Me	1	4.0	93	200
6c	Cl	H	1	6.0	90	220
7a	H	H	2	4.0	96	200
7b	H	Me	2	5.0	92	214
7c	Cl	H	2	6.0	91	234
8a	H	H	3	5.0	97	214
8b	H	Me	3	5.2	98	228
8c	Cl	H	3	6.0	92	248

[a] Isolated Yields.
[b] Determined by EI mass spectrometry.

Table 2 Products and Yields for the Preparation of Optically Active Vasicinones

Substrate	PS-Reagent	Product,[a] Yield (%)[b]
6a–c	**C**	**9a** (>99) **9b** (98) **9c** (99)
9a–c	**D**+**E**	**10a** (95) **10b** (86) **10c** (89)
10a–c	**F**	**11a** (92) **11b** (90) **11c** (87)
11a–c	**H**	**(10*S*)a** (93) **(10*S*)b** (90) **(10*S*)c** (90)
11a–c	**G**	**(10*R*)a** (95) **(10*R*)b** (91) **(10*R*)c** (90)

[a] Characterized by ^{1}H NMR and EI mass spectra.
[b] Isolated yields.

In conclusion, a clean preparation of fused [2,1-*b*]quinazolinones and enantioselective preparations of (*d*)- and (*l*)-vasicinone has been developed by employing polymer-supported reagents. This synthetic strategy is readily amenable for designing and preparing a combinatorial library. It is noteworthy that in the entire process, the work-up has been simplified to filtration and evaporation for all the steps and all the reagents could be reused, thus addressing the problems of environmental and economical sustainability.

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(9) **Typical Procedure: Preparation of Compound 3a**. *N*-Cyclohexylcarbodiimide *N*-methyl polystyrene **A** (1.32 mmol, 1.30 mmol/g) was added to a dry reaction vessel. Compound **1a** (163 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) was added to the dry resin and the resulting mixture was stirred at r.t. for 5 min before the corresponding lactam **2** (56 mg, 0.66 mmol) in CH_2Cl_2 (2 mL) was added and the stirring continued at r.t. for 10 h. The resin was removed by filtration and washed with CH_2Cl_2. Evaporation of the filtrate provided **3a** in 97% yield. Mp 81–83 °C; IR (KBr): 2150, 1750, 1680 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.19 (q, *J* = 6.8 Hz, 2 H), 2.62 (t, *J* = 7.5 Hz, 2 H), 4.0 (t, *J* = 7.5 Hz, 2 H), 7.2 (m, 3 H), 7.5 (t, *J* = 7.5 Hz, 1 H); MS (EI): *m*/*z* = 230 [M$^+$].

(10) **Typical Procedure: Preparation of Compound 6a**. Triphenylphosphine-impregnated polystyrene **B** (3.2 mmol, 3 mmol/g) was suspended in anhydrous CH_2Cl_2 (10 mL) and the 2-azidobenzoyl lactam **3a** (150 mg, 0.65 mmol) was added and the suspension was stirred for 5 h at r.t. The resin was removed by filtration and washed with CH_2Cl_2 and evaporation of the filtrate afforded **6a** in 98% yield. Mp 104–106 °C; IR (KBr): 1675 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.32 (q, *J* = 7.5 and 8.0 Hz, 2 H), 3.22 (t, *J* = 8.0 Hz, 2 H), 4.19 (t, *J* = 7.5 Hz, 2 H), 7.5 (t, *J* = 7.4 Hz, 1 H), 7.6–7.8 (m, 2 H), 8.31 (d, *J* = 8.0 Hz, 1 H); MS (EI): *m*/*z* = 186 [M$^+$].

(11) **Typical Procedure: Preparation of Compound 9a**. To a stirred solution of compound **6a** (115 mg, 0.61 mmol) in dry THF was added the Br_3^- form of Amberlyst A-26 **C** (515 mg, 0.65 mmol, 1.26 mmol/g). The mixture was allowed to stir at r.t. for 18–20 h. After completion of the reaction as indicated

by TLC the reaction was filtered and the resin washed with CH_2Cl_2 and EtOH. The filtrate was concentrated under reduced pressure to afford **9a** in >99% yield. Mp 141–142 °C; IR (KBr): 1684, 776 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 2.50–2.90 (m, 2 H), 4.10–4.30 (m, 1 H), 4.30–4.50 (m, 1 H), 5.20 (dd, *J* = 4.6, 1.8 Hz, 1 H), 7.40–7.60 (m, 2 H), 7.60–7.80 (m, 1 H), 8.30 (d, *J* = 8.0 Hz, 1 H); MS (EI): *m*/z = 264 [M^+].

(12) **Typical Procedure: Preparation of Compound 10a**. To a stirred solution of 3-bromo-3-deoxyvasicinone **9** (134 mg, 0.50 mmol) in MeOH (5 mL) was added Amberlyst A-26 in the AcO^- form **D** (275 mg, 1.00 mmol, 3.65 mmol/g). The mixture was stirred at r. t. for 1 h then a MeOH (5 mL) solution of $Pd(OAc)_2$ (56 mg, 0.25 mmol) and boron hydride exchange resin **E** (500 mg, 1.5 mmol) was added to the reaction flask under a nitrogen atmosphere and the mixture was held at reflux for 1 h. After completion of the reaction as indicated by TLC the reaction was filtered the resin was washed with CH_2Cl_2 and EtOH. The filtrate was concentrated under reduced pressure to afford **10a** in 95% yield. Mp 203–204 °C; ^1H NMR (200 MHz, $CDCl_3$): δ = 2.30–2.50 (m, 1 H), 2.60–2.80 (m, 1 H), 4.00–4.20 (m, 1 H), 4.30–4.50 (m, 1 H), 5.10–5.30 (m, 2 H), 7.50–7.60 (m, 1 H), 7.70–7.80 (m, 2 H), 8.40 (d, *J* = 8.1 Hz, 1 H). MS (EI): *m*/*z* = 202 [M^+].

(13) **Typical Procedure: Preparation of Compound 11**. To a stirred solution of compound **10a** (75 mg, 0.036 mmol) in DMF (5 mL) was added poly(vinylpyridinium dichromate) **F** (190 mg, 0.14 mmol). The reaction mixture was stirred at 70 °C until the completion of the reaction. The resin was removed by filtration and washed with CH_2Cl_2. Evaporation of the filtrate provided **11a** in 92% yield. Mp 165–170 °C; IR (KBr): 1744, 1656, 1600 cm^{-1}; ^1H NMR (200 MHz, $CDC1_3$): δ = 3.05 (t, *J* = 6.7 Hz, 2 H), 4.41 (t, *J* = 6.7 Hz, 2 H) 7.63 (ddd, *J* = 7.8, 7.6, 1.5 Hz, l H), 7.85 (d, *J* = 7.8, 1.5 Hz, 1 H), 7.98 (ddd, *J* = 8.3, 7.6, 1.5 Hz, 1 H), 8.37 (dd, *J* = 8.3, 1.5 Hz, lH); MS (EI): *m*/*z* = 200 [M^+].

(14) **Typical Procedures: Preparations of (*d*)-Vasicinone (10*R*)a and (*l*)-Vasicinone (10*S*)a.** A solution of Me_3SiCl (132 mg, 1.2 mmol) was added to a suspension of $NaBH_4$ (45 mg, 1.2 mmol) in THF (10 mL) and the resulting suspension held at reflux for 1 h. The polymer-supported chiral sulfonamide **G** (50 mg, 0.12 mmol) was added and the suspension was treated with a solution of compound **11a** (100 mg, 0.5 mmol) in THF (10 mL) at rate of 3 mL h^{-1}. After completion of the reaction, the mixture was treated with water and filtered. The resulting aqueous solution was extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and evaporated to afford the **(10*R*)a** in 93% yield and 94% ee (as determined by chiral HPLC[15]). Mp 202–203 °C; $[\alpha]_D^{22}$ +102 (*c* 1, $CHCl_3$), Lit.[16a] $[\alpha]_D^{22}$ +148 (*c* 1.35, EtOH); IR (KBr): 3140, 1668 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 2.21–2.42 (m, 1 H), 2.63–2.79 (m, 1 H), 3.92–4.11 (m, 1 H), 4.30–4.49 (m, 1 H), 4.82 (s, 1 H), 5.19 (t, *J* = 7.35 Hz, 1 H), 7.43–7.62 (m, 1 H), 7.68–7.77 (m, 2 H), 8.33 (d, *J* = 7.35 Hz, 1 H); MS (EI): *m*/*z* = 202 [M^+]. Alternatively, polymer-supported chiral sulfonamide **H** (98 mg, 0.25 mmol) suspension was treated with compound **11a** (200 mg, 1.0 mmol) to give **(10*S*)a** in 95% yield and 94% ee (as determined by chiral HPLC[15]). Mp 200–202 °C; $[\alpha]_D^{22}$ –85 (*c* 0.5, $CHCl_3$), Lit.[16b] $[\alpha]_D^{22}$ –90 (*c* 0.5, $CHCl_3$); IR (KBr): 3135, 1648 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 2.21–2.39 (m 1 H), 2.62–2.83 (m, 1 H), 4.0–4.1 (m, 1 H), 4.32–4.53 (m, 1 H), 4.75 (s, 1 H), 5.19 (t, *J* = 7.15 Hz, 1 H), 7.39–7.58, (m, 1 H), 7.71–7.82 (m, 2 H), 8.29 (d, *J* = 7.15 Hz, 1 H); MS (EI): *m*/*z* = 202 [M^+].

(15) Conditions: Chiracel OD column employing hexane-2-propanol (85:15) as the mobile phase at 0.7 mL/min flow rate and monitored at 254 nm wavelength.

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