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Synthesis of natural quinazolinones and some of their analogues through radical cascade reactions involving *N*-acylcyanamides

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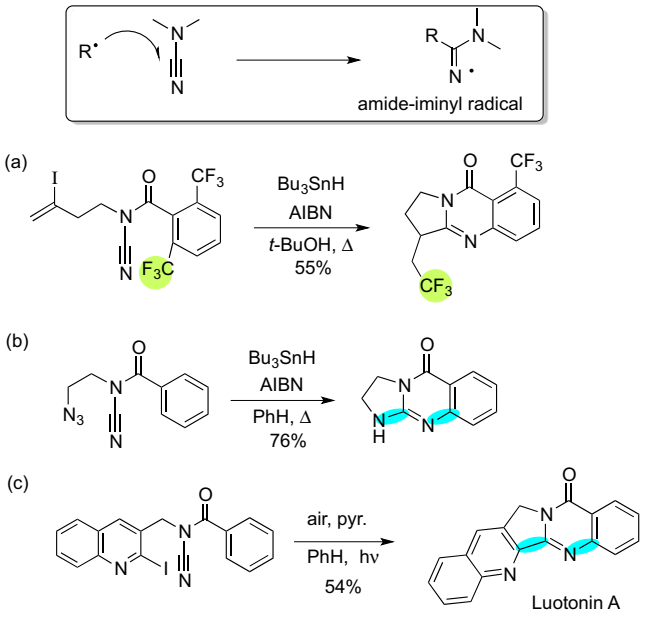
ABSTRACT

Two natural quinazolinones and two analogues can be prepared from the cascade cyclizations of alkyl-substituted *N*-acylcyanamide radicals, including 5-*exo*-*dig* or 6-*exo*-*dig* cyclizations onto the cyano group, followed by radical arylations of the resulting amidyl radicals. The fact that one can carry out the cascades from alkyl radicals in addition to aryl, vinyl and aminyl ones, shows the versatility of the method to rapidly access nitrogen-containing polycyclic structures.

1. Introduction

One of the great features of radical processes is that they allow the rapid increase of molecular complexity in one controlled operation. This is achieved via the stepwise formation of bonds in programmed substrates and obeys the principles of atom economy and step economy. Thus, radical cascades have been applied in various contexts,[1] and they are at the root of valuable strategies for the total synthesis of natural products.[2] Despite a broad spectrum of existing functional partners amenable to the design of cascades, there remains however a need for new building blocks and functions to be added to the palette.

Recently, we have been interested in the use of *N*-acylcyanamides as relay partners in radical cascades.[3] The principle of this approach relies on the fact that this function can have a dual role as radical acceptor (addition of R•) on the carbon atom of the N–CN group and that the resulting amide–iminyl radical can be engaged in a cyclization as well. This allowed us to discover an intriguing radical cascade initiated by vinyl radicals (Scheme 1a). It featured a homolytic aromatic substitution step followed by the formal addition on the vinyl moiety of the radicals generated by the rearomatization of the intermediate cyclohexadienyl radical.[3b] We could also devise a very versatile route to guanidines using an aminyl radical to initiate the cascade (Scheme 1b).[3c]



Scheme 1. Radical cascades involving *N*-acylcyanamides.

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The cascades proved useful in a total synthesis context. Starting with an initially formed 2-quinolyl radical the serial cyclization process provided Luotonin A (Scheme 1c).[3a] Herein, we broaden the cascade scope to the synthesis of additional natural products, as well as some of their analogues, using alkyl radicals as triggers.

2. Results and discussion

2.1. Synthetic targets

Four synthetic targets were defined. Two of them were natural quinazolinones (Fig. 1).

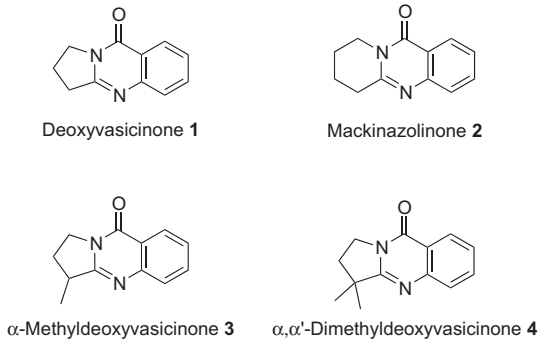


Fig. 1. Quinazolinones synthetic targets.

Deoxyvasicinone **1** is a natural alkaloid, which was isolated in 1957 from the leaves of *Adhatoda vasica*.[4] This compound possesses anti-depressive, antibacterial and anti-inflammatory properties.[5] Various methodologies have been developed for its synthesis, such as a Pd-catalyzed carbonylation/cyclization tandem reaction,[6] a transition metal complex-catalyzed reductive N-heterocyclization[7] or a tandem intramolecular Staudinger/aza-Wittig reaction.[8] In 2007, Bowman reported the first radical synthesis of deoxyvasicinone. It used an alkyl radical generated by treatment of the corresponding alkyl iodide with BEt_3 and O_2 and its oxidative cyclization on the 3*H*-quinazolin-4-one core.[9]

Mackinazolinone **2** is another natural quinazolinone. It is fused with a piperidine ring and can be viewed as the 1C homologue of **1**. This compound was isolated in 1965 in New Guinea from the leaves of *Mackinlaya subulata*[10] and has also shown a large spectra of pharmaceutical activities.[11] Numerous synthetic methodologies similar to those developed for deoxyvasicinone have been applied to the construction of mackinazolinone **2**.[8,9]

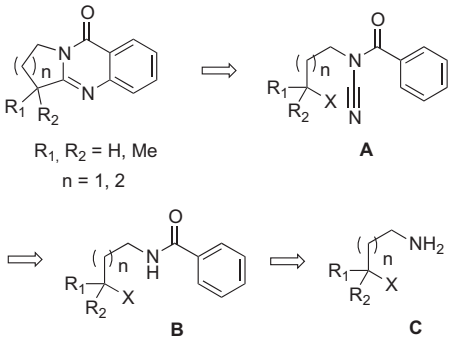
α-Methyldeoxyvasicinone **3** is an unnatural analogue of deoxyvasicinone **1** presenting a bronchodilator activity.[12]

Six syntheses of **3** have been reported,[13] but none of them included a radical step. To the best of our knowledge, the quaternary analogue of α,α′-dimethyldeoxyvasicinone **4** has never been described.

Our general synthetic strategy is outlined in Scheme 2, which relies on a radical cascade involving *N*-acylcyanamides. Thus, the appropriate substrates with alkyl radical precursors (**A**) might be prepared from benzamides **B** and finally amines **C**, i.e., the cyanation is envisaged as the last step. The order for the two steps can be reversed.

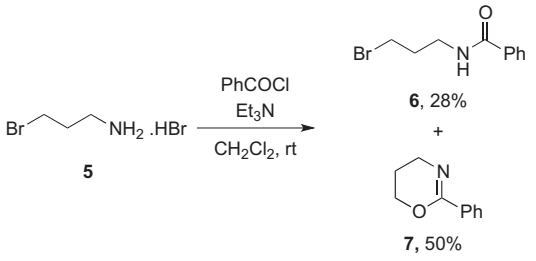
2.2. Synthesis of cascade precursors

*2.2.1. Preparation of the substrates for the synthesis of deoxyvasicinone (**1**) and mackinazolinone (**2**).* Our initial plan was to use a bromide as radical source. However, the benzoylation of



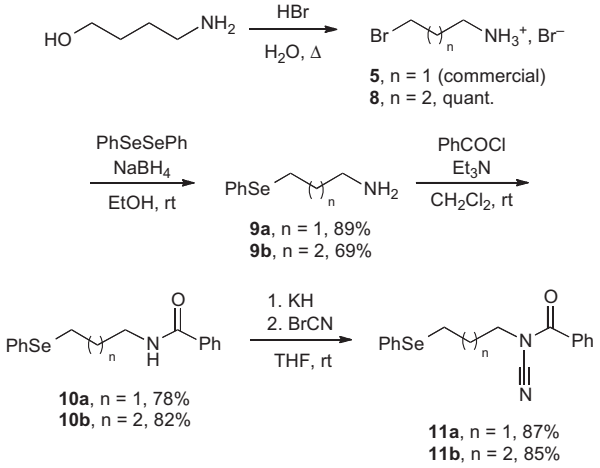
Scheme 2. Retrosynthetic analysis for the preparation of the target compounds.

3-bromopropylamine (**5**) led to only 28% of the desired amide **6**. The major product **7** resulted from an intramolecular O-alkylation side-reaction (Scheme 3).



Scheme 3. Attempt for direct benzoylation of bromoamine **5**.

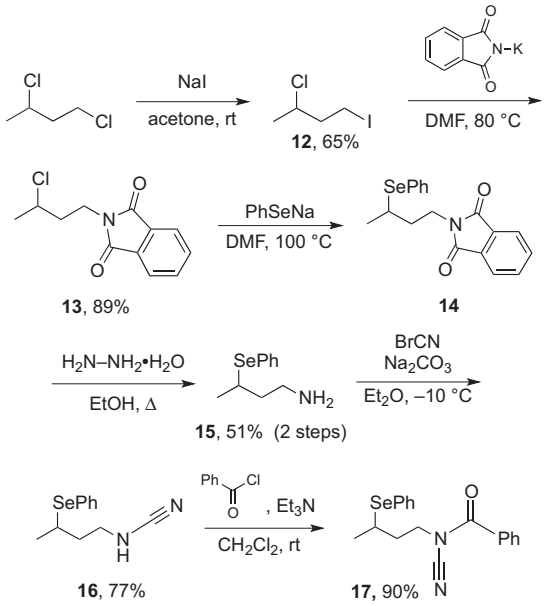
We thus replaced the bromine with a phenylselenyl group, which is cleaved by tin radicals as quickly as bromine atoms,[14] but is a poor nucleofuge (Scheme 4). Accordingly, 3-bromoammoniums **5** and **8** were converted to their seleno derivatives **9a** and **9b** by nucleophilic substitutions with sodium phenylselenoate (obtained by reduction of diphenyldiselenide).[15] Compound **8** was obtained by bromination of commercial 4-amino-butan-1-ol.[16] Selenoamines **9a** and **9b** were benzoylated, affording the corresponding selenoamides **10a** and **10b** in 89% and 69% yields, respectively. Cyanation of **10a**,**b** was first carried out with 3 equiv of BrCN and



Scheme 4. Synthesis of the substrates for the synthesis of **1** and **2**.

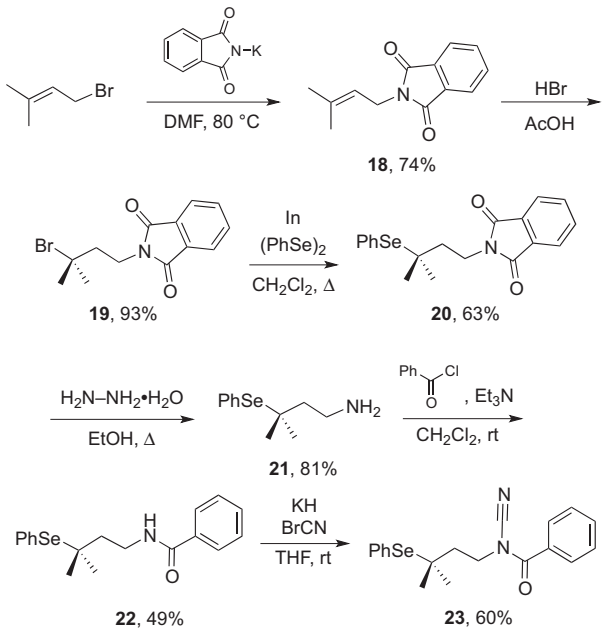
1 equiv of sodium hydride.[3a] However, the yields were low (about 20%). The replacement of sodium hydride with potassium hydride to generate more nucleophilic amidyl anions led to the desired *N*-acylcyanamides **11a** and **11b** in much better yields (87% and 85%, Scheme 4).

*2.2.2. Preparation of the substrate for the synthesis of α-methyldeoxyvasicinone (**3**).* The *N*-acylcyanamide substrate for the cascade leading to **3** was obtained in six steps from commercially available 1,3-dichlorobutane (Scheme 5). The latter was selectively mono-iodinated to afford 3-chloro-1-iodobutane **12**, which was reacted with potassium phthalimide to provide **13**. Selenylation of the secondary chloride was achieved by treatment with the in situ generated sodium phenylselenoate to give **14**, which was directly deprotected with hydrazine to afford selenoamine **15** in 51% yield over two steps. Amine **15** was cyanated first to **16** according to Harrison's methodology,[17] then acylated to obtain the desired *N*-acylcyanamide **17** in 90% yield.



Scheme 5. Synthesis of the precursor of α-methyldeoxyvasicinone (**17**).

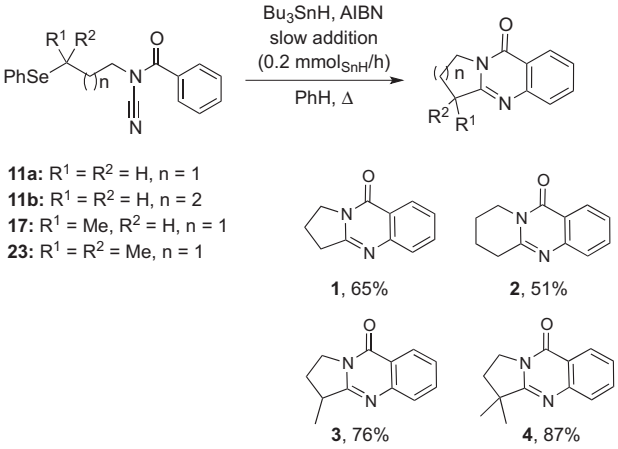
*2.2.3. Preparation of the substrate for the synthesis of α,α′-dimethyldeoxyvasicinone (**4**).* The *N*-acylcyanamide substrate for the cascade leading to **4** was also obtained in six steps, this time starting from commercially available 3,3-dimethylallyl bromide (Scheme 6). Potassium phthalimide was allylated by 3,3-dimethylallyl bromide at 80 °C, leading to phthalimide **18**. Hydrobromination of the double bond was then performed with an HBr solution in acetic acid, giving **19**. Several conditions were tested for the nucleophilic substitution on the quaternary carbon of **19** and the only successful strategy was the Barbier-type indium-mediated method developed by Jang et al.[18] This delivered selenoester **20** in 63% yield. Finally, the phthalimide in **20** was removed using hydrazine (yielding 81% of free amine **21**). In this case, the amine was first acylated to **22** (49%), then cyanated to the desired *N*-acylcyanamide **23** (60%).



Scheme 6. Synthesis of the precursor of α,α′-dimethyldeoxyvasicinone (**23**).

2.3. Radical cyclizations

In a typical cyclization (Scheme 7), Bu_3SnH (1.2 equiv) was slowly added to substrate **11a** in the presence of stoichiometric AIBN (1.5 equiv) in refluxing benzene (0.017 M). Quinazolinone **1** was easily purified owing to its high polarity. Noticeably, the tin byproduct $Bu_3SnSePh$ formed during the reaction is apolar and stable on silica gel, which contributes to its easy removal, as opposed to that of halogeno-stannanes. Thus, it was first eliminated by washing the column with pentane. Then elution with polar solvents allowed the isolation of pure **1** (65% yield). We attempted to replace the tin-based mediator with $(TMS)_3SiH$,[19] but the yield dropped to only 20%.



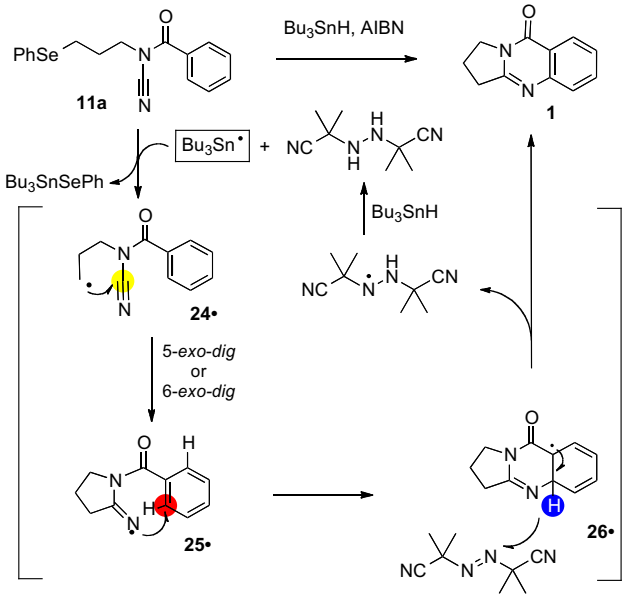
Scheme 7. Radical cyclization of *N*-acylcyanamides.

Using the procedure outlined above, substrate **11b** delivered mackinazolinone **2** in 51% yield together with the product of direct reduction (not isolated). The latter was observed because the initial 6-*exo*-*dig* cyclization is much slower than the 5-*exo*-*dig* cyclization leading to **1**. This also shows that the cascade can start with a 6-*exo*-*dig* cyclization from an alkyl radical, and not only with a 5-*exo*-*dig* process, or with 6-*exo*-*dig* steps from aminyl[3c] and vinyl radicals.[3b]

Similarly, α-methyldeoxyvasicinone **3** and α,α′-dimethyldeoxyvasicinone **4** were obtained in good 76% and 87% yields, respectively.

2.4. Mechanistic proposal

In the light of our previous mechanistic study,[3b] we propose the mechanism depicted in Scheme 8 for the formation of the cascade adducts. It is illustrated for the cyclization of **11a** to **1**, but can be easily extrapolated to the cases of **11b**, **17** and **23**. Phenylselenide abstraction by the tributyltin radical leads to the alkyl radical **24•**, which undergoes a 5-*exo*-*dig* cyclization to the cyanamide moiety. The intermediate amide–iminyl radical **25•** generated can then be trapped at the *ortho* position of the benzoyl phenyl ring, leading to cyclohexadienyl radical **26•**. Consistent with the Beckwith/Storey rearomatization mechanism, **26•** presumably rearomatized through bimolecular abstraction of the *ipso* hydrogen atom by AIBN (formal addition of H• to the N=N bond).[20] This step generates a new molecule of quinazolinone and consumes AIBN. The adduct radical is hydrogenated by Bu_3SnH to deliver the reduced AIBN and a new tin radical. The hydrogenation of AIBN explains why the reaction only works with a stoichiometric amount of initiator.



Scheme 8. Mechanistic proposal.

3. Conclusion

To conclude, we have shown that natural products can be prepared from *N*-acylcyanamides using a radical cascade strategy, which was extended to alkyl radical triggers. A new array of quinazolinones should now be open for testing, using our methodology. Future work will seek to extend the cascades using intermolecular bond forming events. This should side-step the issue of the preparation of the all-intramolecular cascade substrate and provide a faster access to the molecules.

4. Experimental section

4.1. General remarks

Reactions were carried out under argon, with magnetic stirring and redistilled solvents. THF and Et_2O were distilled from sodium/benzophenone. CH_2Cl_2, DMF and NEt_3 were distilled from CaH_2. Benzene was distilled from sodium/potassium amalgam. 2,2-Azobis(2-methylpropionitrile) (AIBN) was purified by precipitation in acetone at 0 °C. Thin layer chromatography (TLC) was performed on Merck 60 F_{254} silica gel. Merck Geduran SI 60 Å silica gel (35–70 mm) was used for column chromatography. The melting points reported were measured with a Reichert hot stage apparatus and are uncorrected. IR spectra were recorded with a Bruker Tensor 27 ATR diamant PIKE spectrometer. Optical rotations were measured using a Perkin–Elmer 341 polarimeter. ^1H, ^{13}C and ^{19}F NMR spectra were recorded at 400, 100 and 377 MHz, respectively, using a Bruker 400 AVANCE spectrometer fitted with a BBFO probehead. Chemical shifts are given in parts per million using the $CDCl_3$ or the MeOD-d_4 signal as reference (^1H=7.26 ppm, ^{13}C=77.16 ppm and ^1H=3.31 ppm, ^{13}C=49.00 ppm, respectively). Unless noted, NMR spectra were recorded in $CDCl_3$ at 300 K. The terms m, s, d, t, q, quint. and sext. represent multiplet, singlet, doublet, triplet, quadruplet, quintuplet, and sextuplet, respectively, and the term br means a broad signal. Exact masses were recorded by Structure et Function de Molecules Bioactives (UMR 7201) of Université Pierre et Marie Curie (electrospray source).

4.2. Preparation and cyclization of alkyl precursors

4.2.1. General procedures

4.2.1.1. General procedure 1 (GP1). 4.2.1.1.1. Conversion of alkyl bromides into phenylseleno derivatives.[15] To a solution of diphenyldiselenide (0.5 equiv) in EtOH (0.02 M) at rt was added $NaBH_4$ (1 equiv). The reaction mixture was stirred at rt during 30 min, then a solution of the amine bromide hydrobromide (1 equiv) in EtOH (0.2 M) was added. The reaction mixture was stirred under reflux during 4 h. Aqueous NaOH 1 M was added and the amine was extracted two times with CH_2Cl_2. The combined organic layers were washed with water, dried over $MgSO_4$ and concentrated in vacuo to afford the desired phenylseleno derivative as orange oil.

4.2.1.2. General procedure 2 (GP2). 4.2.1.2.1. Preparation of phthalimides. To a solution of halide (1 equiv) in DMF (0.6 M) was added potassium phthalimide (1.5 equiv). After 3 h at 90 °C, the mixture was quenched with water. The aqueous layer was then extracted with Et_2O. The organic extracts were combined, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford the desired phthalimide.

4.2.1.3. General procedure 3 (GP3). 4.2.1.3.1. Preparation of amines from phthalimides. To a solution of phthalimide (1 equiv) in EtOH (0.1 M) was added hydrazine monohydrate (2 equiv). After refluxing for 2 h, a solution of HCl 6 M was added. The mixture was filtered and the filtrate was neutralized by a solution of NaOH 2 M. The aqueous layer was then extracted with Et_2O. The organic extracts were combined, dried over $MgSO_4$ and concentrated under reduced pressure to afford the desired amine.

4.2.1.4. General procedure 4 (GP4). 4.2.1.4.1. Benzoylation of selenoamines. To a solution of selenoamine (1 equiv) in CH_2Cl_2 (0.1 M) at 0 °C was added NEt_3 (2 equiv), and 15 min later, benzoyl chloride (1.1 equiv). The reaction mixture was stirred at rt during 14 h, then hydrolyzed by a saturated solution of NH_4Cl. The aqueous layer was extracted two times with CH_2Cl_2. The combined organic layers were washed with water, dried over $MgSO_4$ and concentrated in vacuo. Purification by flash column chromatography afforded the seleno amide as a white solid.

4.2.1.5. General procedure 5 (GP5). 4.2.1.5.1. Preparation of N-acylcyanamides. To freshly degreased KH (1.2 equiv) was added a solution of seleno amide (1 equiv) in THF (0.14 M) at rt. The reaction mixture was stirred during 45 min, then a solution of BrCN (3 equiv) in CH_2Cl_2 (3.0 M) was added. The resulting reaction

mixture was stirred at rt during 24 h and filtered through a short pad of silica. The filtrate was concentrated under reduced pressure and purified by flash column chromatography to afford the cyanamide as a pale yellow oil. *Caution*: Cyanogen bromide is a very toxic reagent and must be carefully manipulated under a ventilated hood. All the glassware must be washed with a NaOH solution (0.5 M) and bleach (10%).

4.2.1.6. General procedure 6 (GP6). 4.2.1.6.1. Cyclization of N-acylcyanamides. To a degassed solution of *N*-acylcyanamide (1 equiv) and AIBN (0.3 equiv) in benzene (final concentration=0.017 M, 75% final volume) under reflux were added Bu_3SnH (2 equiv) and AIBN (1.2 equiv) in benzene (25% final volume) over 2 h (0.2 mmol Bu_3SnH/h). The reaction mixture was refluxed for an additional hour, cooled to rt and concentrated under reduced pressure. Purification of the residue by flash column chromatography afforded the cyclization product.

4.2.2. Alkyl seleno precursors

*4.2.2.1. 3-Phenylselanyl-1-propylamine (**9a**).* Following GP1 with 3-bromopropylamine hydrobromide (7 mmol; 1.53 g), **9a** was isolated as an orange oil (1.33 g; 89%). Spectral data are in accordance with those reported in the literature.[16] ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.46 (br s, 2H, NH_2), 1.79–1.86 (m, 2H, PhSe–CH_2–CH_2), 2.78 (t, J=7.2 Hz, 2H, PhSe–CH_2), 2.94 (t, J=7.1 Hz, 2H, NH_2–CH_2), 7.21–7.26 (m, 3H, arom.), 7.47–7.49 (m, 2H, arom.); ^{13}C NMR (100 MHz, $CDCl_3$): δ=25.0 (PhSe–CH_2–CH_2), 29.7 (PhSe–CH_2), 41.6 (NH_2–CH_2), 126.8 (CH arom.), 129.2 (2CH arom.), 130.2 (C arom.), 132.4 (2CH arom.).

*4.2.2.2. 4-Phenylselanyl-butylamine (**9b**).* 4-Aminobutan-1-ol (3.9 mmol; 350 mg) was refluxed for 3 h in an aqueous solution of HBr 48% wt (30 mL). After concentration in vacuo, 4-bromobutylamine hydrobromide was obtained as a white solid. Following GP1 with crude 4-bromobutylamine hydrobromide, **9b** was isolated as an orange oil (606 mg; 69%). Spectral data are in accordance with those reported in the literature.[16] ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.22 (br s, 2H, NH_2), 1.45–1.49 (m, 2H, PhSe–CH_2–CH_2), 1.62–1.70 (m, 2H, NH_2–CH_2–CH_2), 2.60 (t, J=7.0 Hz, 2H, PhSe–CH_2), 2.84 (t, J=7.3 Hz, 2H, NH_2–CH_2), 7.12–7.18 (m, 3H, arom.), 7.40–7.42 (m, 2H, arom.); ^{13}C NMR (100 MHz, $CDCl_3$): δ=27.3, 27.5 (PhSe–CH_2–CH_2+NH_2–CH_2–CH_2), 33.6 (PhSe–CH_2), 41.4 (NH_2–CH_2), 126.5 (CH arom.), 128.8 (2CH arom.), 130.3 (C arom.), 132.2 (2CH arom.).

*4.2.2.3. 2-(3-Chloro-butyl)-isoindole-1,3-dione (**13**).* To a solution of sodium iodide (60 mmol; 1 equiv; 8.99 g) in acetone (20 mL) was added 1,3-dichlorobutane (60 mmol; 1 equiv; 6.83 mL). The reaction mixture was stirred for 2 h at rt and filtrated. The filtrate was concentrated under reduced pressure and Et_2O (30 mL) was added to precipitate inorganic salts. After a second filtration, the filtrate was concentrated under pressure to afford 3-chloro-1-iodobutane (8.50 g; 65%) as a yellow oil.[21] Following GP2 with the latter (8.72 mmol, 1.90 g), 2-(3-chloro-butyl)-isoindole-1,3-dione **13** (petroleum ether/Et_2O=10:1; 1.84 g; 89%) was isolated as a white solid. IR (ATR): ν=2922, 1764, 1698, 1494, 1443, 1401, 1380, 1290, 1085, 959, 712 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.55 (d, J=6.6 Hz, 3H, Me), 2.02–2.12 (m, 2H, N–CH_2–CH_2), 3.77–3.91 (m, 2H, N–CH_2), 3.99–4.08 (m, 1H, MeC*H*), 7.69–7.71 (m, 2H, arom.), 7.81–7.84 (m, 2H, arom.); ^{13}C NMR (100 MHz, $CDCl_3$): δ=25.4 (Me), 35.8 (N–CH_2–CH_2), 38.8 (N–CH_2), 55.7 (MeCH), 123.4 (2CH arom.), 132.2 (2C arom.), 134.1 (2CH arom.), 168.3 (2CO); HRMS calcd for $C_{12}H_{12}NO_2ClNa$ ([M+Na]$^+$) 260.0449, found 260.0449.

*4.2.2.4. 3-Phenylselanyl-butylamine (**15**).* To a solution of sodium phenylselenolate (8.4 mmol; 1 equiv; 1.50 g) in DMF (8 mL) was added chloride **13** (8.4 mmol; 1 equiv; 2.00 g). After 14 h at 110 °C, the mixture was quenched with water. The aqueous layer was then extracted with CH_2Cl_2 (15 mL). The organic extracts were combined, dried over $MgSO_4$ and concentrated under reduced pressure to afford 2-(3-phenylselanyl-butyl)-isoindole-1,3-dione **14** (2.02 g; 67%) as a pale yellow oil. Following GP3 with **14** (4.5 mmol; 1.63 g), 3-phenylselanyl-butylamine **15** (780 mg; 76%) was isolated as a pale yellow oil. IR (ATR): ν=3295, 3024, 2950, 2917, 2860, 1649, 1578, 1476, 1436, 1375, 1253, 1066, 1021, 739, 691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.31 (s, 2H, NH_2), 1.45 (d, J=6.8 Hz, 3H, Me), 1.72–1.84 (m, 2H, N–CH_2–CH_2), 2.84–2.91 (m, 2H, N–CH_2), 3.39 (sextet, J=6.9 Hz, 1H, Se–CH), 7.25–7.30 (m, 3H, arom.), 7.55–7.57 (m, 2H, arom.). ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.6 (CH–*Me*), 37.2 (Se–CH), 40.6 (N–CH_2–CH_2), 41.6 (N–CH_2), 127.6 (2CH arom.), 129.1 (CH arom.), 129.2 (C arom.), 135.2 (2CH arom.); HRMS calcd for $C_{10}H_{16}NSe$ ([M+H]$^+$) 230.0442, found 230.0440.

*4.2.2.5. 2-(3-Methyl-3-phenylselanyl-butyl)-isoindole-1,3-dione (**20**).* Following GP2 with 3,3-dimethylallyl bromide (20.0 mmol; 2.66 mL), **18** (petroleum ether/Et_2O=6:2; 3.20 g; 74%) was isolated as a white solid.[22] A solution of **18** (12.5 mmol; 1 equiv; 2.70 g) and HBr (33% in AcOH, 20 mL) was stirred at rt for 2 h. Water was then added and the aqueous layer was extracted with Et_2O. The organic extracts were combined, dried over $MgSO_4$ and concentrated under reduced pressure to afford **19** (3.45 g; 93%) as a white solid. To a solution of indium (2.7 mmol; 1.3 equiv; 313 mg) and diphenyldiselenide (2.7 mmol; 1.3 equiv; 844 mg) in CH_2Cl_2 (30 mL), was added **19** (2.1 mmol; 616 mg). The reaction mixture was refluxed for 1 h, then hydrolyzed with a 1 M HCl solution. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water, dried over $MgSO_4$ and concentrated in vacuo. Purification by flash column chromatography (petroleum ether/EtOAc=10:3) afforded **20** (490 mg; 63%) as a white solid.[18] IR (ATR): ν=1767, 1705, 1396, 1365, 1331, 1143, 722 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.43 (s, 6H, C*Me*$_2$), 1.78–1.82 (m, 2H, N–CH_2–CH_2), 3.93–3.97 (m, 2H, N–CH_2), 7.30–7.36 (m, 3H, arom.), 7.68–7.76 (m, 4H, arom.), 7.83–7.85 (m, 2H, arom.); ^{13}C NMR (100 MHz, $CDCl_3$): δ=29.9 (C*Me*$_2$), 35.6 (N–CH_2–CH_2), 40.9 (*C*Me$_2$), 44.9 (N–CH_2), 123.3 (2CH arom.), 127.4 (C arom.), 128.8 (3CH arom.), 132.3 (2C arom.), 134.0 (2CH arom.), 138.5 (2CH arom.), 168.3 (2CO); HRMS calcd for $C_{19}H_{19}NO_2SeNa$ ([M+Na]$^+$) 396.0473, found 396.0470.

*4.2.2.6. 3-Methyl-3-phenylselanyl-butylamine (**21**).* Following GP3 with **20** (1.05 mmol; 390 mg), 3-methyl-3-phenylselanyl-butylamine **21** (205 mg; 81%) was isolated as a yellow oil. IR (ATR): ν=2922, 1577, 1465, 1435, 1364, 1121, 1022, 1000, 739, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.37 (s, 6H, C*Me*$_2$), 1.42 (s, 2H, NH_2), 1.68–1.72 (m, 2H, N–CH_2–CH_2), 2.89 (t, J=8.0 Hz, 2H, N–CH_2), 7.28–7.32 (m, 2H, arom.), 7.34–7.37 (m, 1H, arom.), 7.61–7.63 (m, 2H, arom.). ^{13}C NMR (100 MHz, $CDCl_3$): δ=30.2 (C*Me*$_2$), 39.2 (N–CH_2–CH_2), 46.0 (*C*Me$_2$), 47.5 (N–CH_2), 127.8 (C arom.), 128.7 (2CH arom.), 128.8 (CH arom.), 138.3 (2CH arom.); HRMS calcd for $C_{11}H_{18}NSe$ ([M+H]$^+$) 244.0599, found 244.0595.

*4.2.2.7. N-(3-Phenylselanyl-propyl)-benzamide (**10a**).* Following GP4 with **9a** (7.47 mmol; 1.60 g), **10a** was purified by flash column chromatography (petroleum ether/EtOAc=8:2) and isolated as a white solid (1.85 g; 78%). Spectral data are in accordance with those reported in the literature.[23] ^{1}H NMR (400 MHz, MeOD): δ=1.95–2.00 (m, 2H, PhSe–CH_2–CH_2), 2.97 (t, J=7.2 Hz, 2H, PhSe–CH_2), 3.47 (t, J=7.0 Hz, 2H, NH–CH_2), 7.22–7.26 (m, 3H, arom.), 7.42–7.47 (m, 2H, arom.), 7.49–7.57 (m, 3H, arom.), 7.78–7.80 (m, 2H, arom.), NH is missing; ^{13}C NMR (100 MHz, MeOD): δ=25.6 (PhSe–CH_2–CH_2), 31.2 (PhSe–CH_2), 40.9 (NH–CH_2), 127.9 (CH arom.), 128.3 (2CH arom.), 129.6 (2CH arom.), 130.2 (2CH arom.), 131.5 (C arom.), 132.6 (CH arom.), 133.7 (2CH arom.), 135.7 (C arom.), 170.3 (CO).

*4.2.2.8. N-(4-Phenylselanyl-butyl)-benzamide (**10b**).* Following GP4 with **9b** (1.07 mmol; 244 mg), **10b** was purified by flash column chromatography (petroleum ether/EtOAc=5:1) and isolated as a white solid (290 mg; 82%). Spectral data are in accordance with those reported in the literature.[23] ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.73–1.82 (m, 4H, PhSe–CH_2–CH_2–CH_2), 2.96 (t, J=6.9 Hz, 2H, PhSe–CH_2), 3.46 (q, J=6.8 Hz, 2H, NH–CH_2), 7.23–7.26 (m, 3H, arom.), 7.41–7.50 (m, 5H, arom.), 7.71–7.72 (m, 2H, arom.), NH is missing; ^{13}C NMR (100 MHz, $CDCl_3$): δ=27.5 (2CH_2, PhSe–CH_2–CH_2–CH_2), 29.8 (PhSe–CH_2), 39.5 (NH–CH_2), 127.0 (3CH arom.), 128.7 (2CH arom.), 129.2 (2CH arom.), 130.2 (C arom.), 131.5 (CH arom.), 133.8 (2CH arom.), 134.8 (C arom.), 167.7 (CO).

*4.2.2.9. N-Cyano-(3-Phenylselanyl-propyl)-benzamide (**11a**).* Following GP5 with **10a** (1.64 mmol; 524 mg), **11a** was purified by flash column chromatography (petroleum ether/EtOAc=3:1) and isolated as a pale yellow oil (491 mg; 87%). IR (neat): ν=2230, 1700, 1578, 1477, 1447, 1437, 1269, 1113, 1021, 691, 670 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.17–2.24 (m, 2H, PhSe–CH_2–CH_2), 2.98 (t, J=7.1 Hz, 2H, PhSe–CH_2), 3.89 (t, J=7.0 Hz, 2H, N–CH_2), 7.26–7.30 (m, 3H, arom.), 7.47–7.50 (m, 2H, arom.), 7.54–7.60 (m, 3H, arom.), 7.78–7.80 (m, 2H, arom.); ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.2 (PhSe–CH_2–CH_2), 28.2 (PhSe–CH_2), 47.7 (N–CH_2), 111.1 (CN), 127.6 (CH arom.), 128.7 (4CH arom.), 129.3 (2CH arom.), 129.4 (C arom.), 131.0 (C arom.), 133.3 (CH arom.), 133.4 (2CH arom.), 168.5 (CO); HRMS calcd for $C_{17}H_{16}N_2OSeNa$ ([M+Na]$^+$) 367.0321, found 367.0321.

*4.2.2.10. N-Cyano-(3-phenylselanyl-propyl)-benzamide (**11b**).* Following GP5 with **10b** (0.85 mmol; 283 mg), **11b** was purified by flash column chromatography (petroleum ether/EtOAc=7:3) and isolated as a pale yellow oil (258 mg; 85%). IR (neat): ν=2928, 2232, 1705, 1438, 1329, 1279, 730, 711, 686, 652 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.78–1.97 (m, 4H, PhSe–CH_2–CH_2–CH_2), 2.96 (t, J=7.1 Hz, 2H, PhSe–CH_2), 3.77 (t, J=7.1 Hz, 2H, N–CH_2), 7.25–7.28 (m, 3H, arom.), 7.44–7.61 (m, 5H, arom.), 7.74–7.77 (m, 2H, arom.); ^{13}C NMR (100 MHz, $CDCl_3$): δ=26.9, 27.1 (PhSe–CH_2–CH_2–CH_2), 27.8 (PhSe–CH_2), 47.3 (N–CH_2), 111.1 (CN), 127.2 (CH arom.), 128.7 (4CH arom.), 129.3 (2CH arom.), 129.8 (C arom.), 131.1 (C arom.), 133.2 (2CH arom.), 133.3 (2CH arom.), 168.5 (CO); HRMS calcd for $C_{18}H_{18}N_2O$-SeNa ([M+Na]$^+$) 381.0477, found 381.0481.

*4.2.2.11. 3-Phenylselanyl-butyl-cyanamide (**16**).* To a solution of cyanogen bromide (1.9 mmol; 1.2 equiv; 219 mg) in Et_2O (3 mL) at −15 °C were added Na_2CO_3 (3.18 mmol; 2 equiv; 337 mg) and amine **15** (1.59 mmol; 363 mg). The reaction mixture was stirred for 2 h at −15 °C, allowed to reach rt, and filtered through a short pad of silica. The filtrate was concentrated under reduced pressure and purified by flash column chromatography (petroleum ether/Et_2O=1:2) to afford cyanamide **16** as a pale yellow oil (310 mg; 77%). This product proved unstable and was immediately used for the next step. IR (neat): ν=3198, 2918, 2217, 1578, 1476, 1436, 1375, 1246, 1158, 1066, 1021, 999, 738, 691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.42 (d, J=7.0 Hz, 3H, Me), 1.81–1.87 (m, 2H, N–CH_2–CH_2), 3.17–3.21 (m, 2H, N–CH_2), 3.24–3.32 (m, 1H, Se–CH), 4.35 (br s, 1H, NH), 7.23–7.29 (m, 3H, arom.), 7.52–7.54 (m, 2H, arom.); ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.5 (Me), 36.1 (Se–CH), 37.1 (N–CH_2–CH_2), 44.5 (N–CH_2), 116.4 (CN), 127.9 (CH arom.), 128.1 (C arom.), 129.1 (2CH arom.), 135.3 (2CH arom.); HRMS calcd for $C_{11}H_{14}N_2SeNa$ ([M+Na]$^+$) 277.0214, found 277.0215.

*4.2.2.12. N-Cyano-(3-phenylselanyl-butyl)-benzamide (**17**).* To a solution of cyanamide **16** (0.75 mmol; 190 mg) in CH_2Cl_2 (20 mL) at 0 °C were added NEt_3 (1.5 mmol; 2 equiv; 211 μL) and benzoyl chloride (0.97 mmol; 1.3 equiv; 113 μL). The reaction mixture was stirred for 15 min at 0 °C and 14 h at rt, concentrated under reduced pressure and purified by flash column chromatography (petroleum ether/Et_2O=10:2), to afford *N*-acylcyanamide **17** as a white solid (240 mg; 90%). Mp: 62–63 °C; IR (neat): ν=2954, 2230, 1701, 1579, 1476, 1448, 1345, 1272, 1074, 1022, 909, 788, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.51 (d, J=7.0 Hz, 3H, Me), 1.99–2.17 (m, 2H, N–CH_2–CH_2), 3.30 (sext., J=6.9 Hz, 1H, Se–CH), 3.86–4.04 (m, 2H, N–CH_2), 7.27–7.36 (m, 3H, arom.), 7.44–7.52 (m, 2H, arom.), 7.56–7.64 (m, 3H, arom.), 7.80–7.76 (m, 2H, arom.); ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.5 (Me), 35.2 (N–CH_2–CH_2), 36.1 (Se–CH), 46.7 (N–CH_2), 111.1 (CN), 127.9 (C arom.), 128.2 (CH arom.), 128.7 (4CH arom.), 129.2 (2CH arom.), 131.0 (C arom.), 133.3 (CH arom.), 135.8 (2CH arom.), 168.4 (CO); HRMS calcd for $C_{18}H_{18}ON_2SeNa$ ([M+Na]$^+$) 381.0477, found 381.0479.

*4.2.2.13. N-cyano-N-(3-methyl-3-(phenylselanyl)butyl)benzamide (**23**).* Following GP4 with **21** (0.71 mmol; 172 mg), amide **22** was purified by flash column chromatography (petroleum ether/Et_2O=1:1) and isolated as a white solid (120 mg; 49%). Following GP5 with **22** (0.29 mmol; 100 mg), acylcyanamide **23** was purified by flash column chromatography (pentane/Et_2O=5:1) and isolated as a pale yellow oil (65 mg; 60%). IR (neat): ν=2956, 2230, 1702, 1599, 1579, 1448, 1345, 1270, 1075, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.45 (s, 6H, 2Me), 1.93–1.97 (m, 2H, N–CH_2–CH_2), 4.02–4.06 (m, 2H, N–CH_2), 7.33–7.42 (m, 3H, arom.), 7.48–7.50 (m, 2H, arom.), 7.57–7.61 (m, 1H, arom.), 7.67–7.69 (m, 2H, arom.), 7.78–7.80 (m, 2H, arom.); ^{13}C NMR (100 MHz, $CDCl_3$): δ=30.1 (2Me), 40.3 (N–CH_2–CH_2), 44.2 (Me_2C), 46.0 (N–CH_2), 111.2 (CN), 127.2 (C arom.), 128.7 (2CH arom.), 128.7 (2CH arom.), 129.1 (3CH arom.), 131.1 (C arom.), 133.3 (CH arom.), 138.4 (2CH arom.), 168.4 (CO); HRMS calcd for $C_{19}H_{20}N_2OSeNa$ ([M+Na]$^+$) 395.0633, found 395.0633.

4.2.3. Cyclized quinazolinones

*4.2.3.1. Deoxyvasicinone (**1**).* Following GP6 with *N*-acylcyanamide **11a** (1.41 mmol; 484 mg), **127** was purified by flash column chromatography (pentane then CH_2Cl_2/EtOAc=1:1) and isolated as a white solid (171 mg; 65%). Spectral data are in accordance with those described in the literature.[24] Mp: 105–106 °C; IR (neat): ν=2962, 2924, 1670, 1609, 1483, 1424, 1334, 770, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=2.25 (quint., J=7.8 Hz, 2H, N–CH_2–CH_2), 3.14 (t, J=7.9 Hz, 2H, C–CH_2), 4.17 (t, J=7.3 Hz, 2H, N–CH_2), 7.40 (ddd, J=7.4, 6.8, 1.3 Hz, 1H, arom.), 7.59–7.60 (m, 1H, arom.), 7.66–7.70 (m, 1H, arom.), 8.23 (dd, J=8.0, 1.4 Hz, 1H, arom.). ^{13}C NMR (100 MHz, $CDCl_3$): δ=19.5 (N–CH_2–CH_2), 32.6 (C–CH_2), 46.5 (N–CH_2), 120.5 (C arom.), 126.2 (CH arom.), 126.4 (CH arom.), 126.8 (CH arom.), 134.1 (CH arom.), 149.2 (C arom.), 159.5 (N–C–N), 161.0 (CO); HRMS calcd for $C_{11}H_{11}O_1N_2$ ([M+H]$^+$) 187.0866, found 187.0866.

*4.2.3.2. Mackinazolinone (**2**).* Following GP6 with *N*-acylcyanamide **11b** (0.46 mmol; 164 mg), **2** was purified by flash column chromatography (pentane, then CH_2Cl_2/EtOAc=1:1) and isolated as a white solid (47 mg; 51%). Spectral data are in accordance with those described in the literature.[24] Mp: 95–96 °C; IR (neat): ν=2955, 1658, 1610, 1583, 1564, 1467, 772 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.90–2.02 (m, 4H, N–CH_2–CH_2–CH_2), 2.97 (t, J=6.7 Hz, 2H, C–CH_2), 4.06 (t, J=6.3 Hz, 2H, N–CH_2), 7.39 (ddd, J=7.6, 7.0, 1.1 Hz, 1H, arom.), 7.55–7.58 (m, 1H, arom.), 7.66–7.69 (m, 1H, arom.), 8.23 (d, J=7.3, 1.4 Hz, 1H, arom.). ^{13}C NMR (100 MHz, $CDCl_3$): δ=19.4 (N–CH_2–CH_2), 22.2 (C–CH_2–CH_2), 32.1 (C–CH_2), 42.4 (N–CH_2), 120.5 (C arom.), 126.2 (CH arom.), 126.5 (CH arom.), 126.7 (CH arom.), 134.3 (CH arom.), 147.5 (C arom.), 155.0 (N–C–N), 162.3 (CO); HRMS calcd for $C_{12}H_{13}N_2O$ ([M+H]$^+$) 201.1022, found 201.1023.

*4.2.3.3. α-Methyldeoxyvasicinone (**3**).* Following GP6 with *N*-acylcyanamide **17** (0.45 mmol; 162 mg), **3** was purified by flash column chromatography (CH_2Cl_2/EtOAc=10:1 to 1:1) and isolated

as a white solid (68 mg; 76%). Spectral data are in accordance with those described in the literature.[25] Mp: 120–121 °C; IR (neat): ν=2965, 2928, 1663, 1609, 1560, 1468, 782, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=1.45 (d, J=7.0 Hz, 3H, Me), 1.83 (dq, J=12.9, 8.5 Hz, 1H, N–CH_2–C*H*H), 2.39–2.51 (m, 1H, N–CH_2–CH*H*), 3.23–3.33 (m, 1H, Me–C*H*), 3.91–4.01 (m, 1H, N–C*H*H), 4.23 (ddd, J=12.4, 8.7, 3.9 Hz, 1H, N–CH*H*), 7.40 (ddd, J=8.2, 6.7, 1.6 Hz, 1H, arom.), 7.62–7.70 (m, 2H, arom.), 8.22–8.25 (m, 1H, arom.). ^{13}C NMR (100 MHz, $CDCl_3$): δ=17.2 (Me), 28.6 (N–CH_2–CH_2), 38.8 (Me–CH), 44.6 (N–CH_2), 120.7 (C arom.), 126.2 (CH arom.), 126.4 (CH arom.), 127.0 (CH arom.), 134.1 (CH arom.), 149.4 (C arom.), 161.0 (N–C–N), 162.4 (CO); HRMS calcd for $C_{12}H_{12}N_2ONa$ ($[M+Na]^+$) 223.0842, found 223.0843.

*4.2.3.4. α,α′-Dimethyldeoxyvasicinone (**4**).* Following GP6 with *N*-acylcyanamide **23** (0.08 mmol; 30 mg), **130** was purified by flash column chromatography (CH_2Cl_2/EtOAc=10:1 to 1:1) and isolated as a white solid (15 mg; 87%). Spectral data are in accordance with those described in the literature. Mp: 128–129 °C; IR (neat): ν=2961, 1671, 1613, 1470, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=1.43 (s, 6H, 2Me), 2.10 (t, J=7.2 Hz, 2H, C–CH_2), 4.12 (t, J=7.2 Hz, 2H, N–CH_2), 7.41–7.43 (m, 1H, arom.), 7.70–7.72 (m, 2H, arom.), 8.28 (d, J=8.1 Hz, 1H, arom.). ^{13}C NMR (100 MHz, $CDCl_3$): δ=26.1 (2Me), 35.6 (N–CH_2–CH_2), 43.2 (N–CH_2), 43.6 (Me_2C), 120.9 (C arom.), 126.2 (CH arom.), 126.5 (CH arom.), 127.3 (CH arom.), 134.1 (CH arom.), 149.8 (C arom.), 161.3 (N–C–N), 165.1 (CO). HRMS calcd for $C_{13}H_{14}N_2ONa$ ($[M+Na]^+$) 237.0998, found 237.0995.

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Supplementary data

^1H and ^{13}C NMR spectra of substrates **11a**,**b**, **17**, **23** as well as polycyclic compounds **1**–**4**. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.05.058.

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