Tetrahedron 64 (2008) 5336–5344

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A novel entry to cyclopenta[*b*]quinolines via thermal ring-expansion of (2-aminophenyl)-ethynyl-substituted squaric acid derivatives

Peter S. Zehr [a], Reem Kayali [a], Eduardo Peña-Cabrera [b], Omar Robles-Resendiz [b], Alma D. Villanueva-Rendon [b], Björn C.G. Söderberg [a,*]

[a] *C. Eugene Bennett Department of Chemistry, West Virginia University, Morgantown, WV 26505-6045, USA*
[b] *Department of Chemistry, Universidad de Guanajuato, Col. Noria Alta S/N, Guanajuato, GTO 36050, Mexico*

ARTICLE INFO

Article history:
Received 17 October 2007
Received in revised form 25 February 2008
Accepted 7 March 2008
Available online 12 March 2008

ABSTRACT

Substituted cyclopenta[*b*]quinolin-1-ones were prepared by thermal ring-expansion of substituted *N*-Boc protected 4-(2-aminophenylethynyl)-4-hydroxy-2-cyclobuten-1-ones forming the corresponding 2-aminophenylmethylidene substituted 4-cyclopentene-1,3-diones. Deprotection of the amine resulted in spontaneous condensation giving cyclopenta[*b*]quinolin-1-ones. Sodium borohydride reduction of these products produced cyclopenta[*b*]quinolin-1-ols.

1. Introduction

Thermally induced ring-expansions of 4-alkynyl-4-hydroxy-2-cyclobuten-1-ones giving 1,4-benzoquinones and/or 5-alkylidenecyclopentenediones have been reported in a number of cases.[1,2] In general, alkyl-substituted alkynes offer a clean conversion to quinones.[3–9] In contrast, ethynyl trimethylsilane, alkynes with electron-withdrawing groups or alkenyl-substituted alkynes affords only five-membered products[10] and alkynes with electron-donating groups, and aryl-substituted alkynes afford mixtures of five- and six-membered rings. Ring-expansions of 4-alkynyl-4-hydroxy-2-cyclobuten-1-ones giving 5-alkylidenecyclopentenediones have also been reported using electrophilic reagents such as palladium(II),[11] NBS,[12] and iodine in the presence of an oxidizing reagent.[13]

Thermal reaction of **2** was examined as part of a project to prepare complex heterocyclic compounds via ring-expansion of 4-hydroxy-2-cyclobuten-1-ones having heteroatoms tethered to the cyclobutenone, in the 4-position, via an alkyne or an alkene (Scheme 1). Compound **2** was obtained via dilithiation of the *N*-protected 2-aminophenylalkyne **1** followed by alkylation with 2,3-bis(1-methylethoxy)-2-cyclobuten-1,4-dione (diisopropyl squarate). Cyclobutenone **2** was dissolved in toluene and heated at reflux overnight. Workup and purification by chromatography on silica gel gave a new compound that was initially thought to be the 1,4-quinone **3** based on ^{1}H and ^{13}C NMR data. Deprotection of the putative compound produced a new product seemingly derived from the formation of a quinone-imine **4**. However upon attempted sodium borohydride reduction of **4**, the spectral data of the product did not correspond to the expected hydroxycarbazole **5**. A new methine having a carbon resonance at 68.7 ppm and the corresponding proton resonance at 5.02 ppm was observed. These resonances cannot be assigned to any of the carbons or protons of the hydroxycarbazole **5**. Subjecting the product obtained from the reduction of **4** to gHMBC and gHMQC NMR experiments revealed that the product was in fact the fused quinolinol **8** and not **5**. This in turn meant that the initial ring-expansion did not yield **3** but the five-membered counterpart **6** (Scheme 2). Subsequent removal of the Boc-group gave the fused quinoline **7**. The ring-expansion was very selective with regard to ring-size, and only the five-membered ring was observed by ^{1}H NMR of the crude reaction mixture.

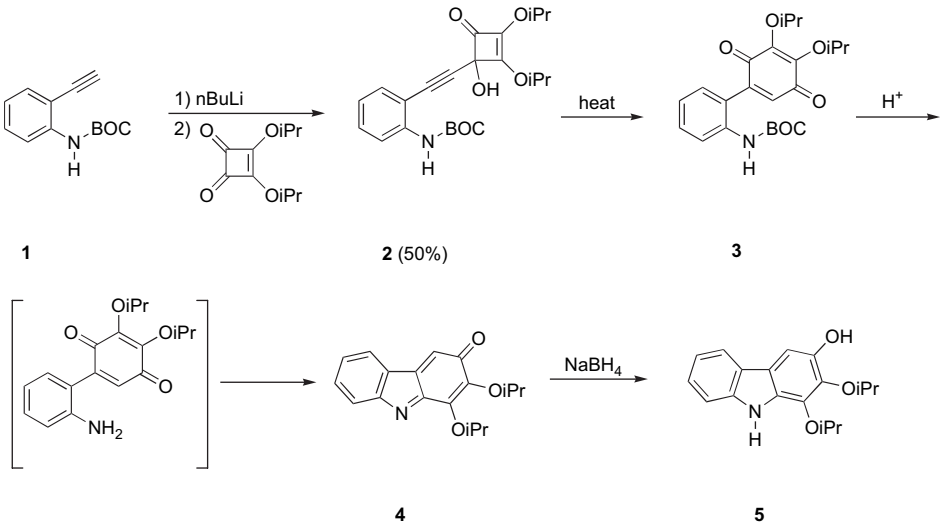
The Friedländer reaction, that is acid- or base-mediated reaction between 2-aminobenzaldehydes or 2-aminobenzoketones and an aldehyde or ketone bearing an α-methylene group, is arguably the most commonly used methodology for the preparation of quinolines including 2,3-fused quinolines.[14] For example, the Friedländer quinoline synthesis was used to prepare the indeno[1,2-*b*]quinolin-11-one tetracyclic ring system of a new class of DNA-binding agents (Scheme 3).[15] Similar tetracyclic compounds having a fused five-membered ketone have been examined as antiinfective agents.[16] Herein, we report a novel synthesis of a number of related fused quinolines, cyclopenta[*b*]quinolines, based on the preliminary results described in Scheme 2.

2. Results and discussion

A number of additional examples of this novel cyclopenta[*b*]quinoline synthesis were examined. The starting materials were prepared from 2-iodoarylamines via a sequence of steps consisting of *N*-Boc protection of the amino group, Sonogashira

* Corresponding author. Tel.: +1 3042933435; fax: +1 3042934904.
E-mail address: bjorn.soderberg@mail.wvu.edu (B.C.G. Söderberg).

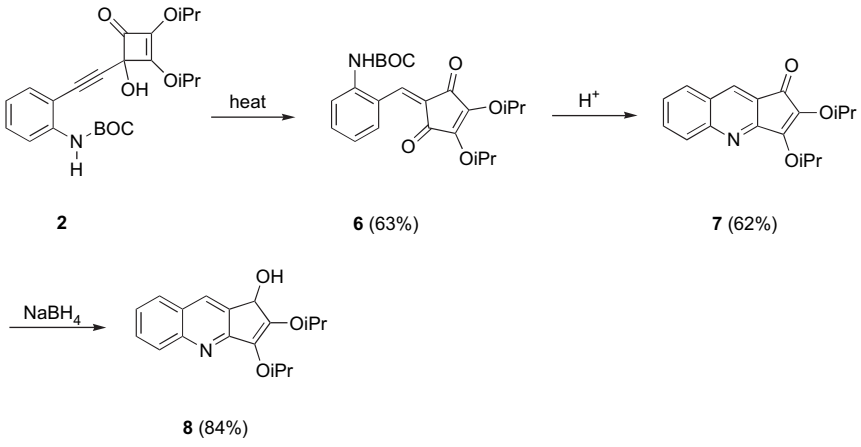
0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.03.025



1 **2** (50%) **3**

4 **5**

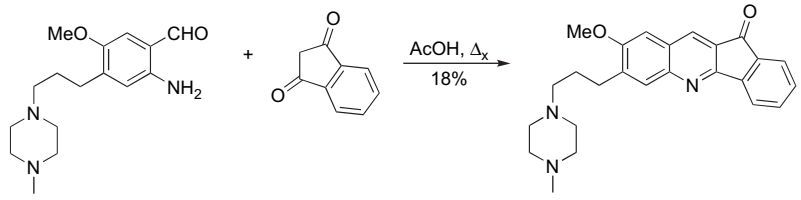
Scheme 1.



2 **6** (63%) **7** (62%)

8 (84%)

Scheme 2.

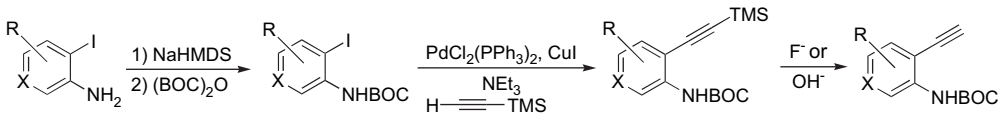


Scheme 3.

coupling using ethynyl trimethylsilane, desilylation, and alkylation. The first three steps proceeded smoothly in good to excellent yields in all the five cases examined (Scheme 4).

Alkylation of diisopropyl squarate was, however, more problematic and a significant amount of the alkyne starting material was often recovered (Scheme 5). For the 5-methoxy-substituted substrate, an inseparable mixture of the expected alkylation product **12b** and alkylation of the squarate with excess butyllithium was isolated. The 4-bromo-substituted substrate **11e** was also examined with the idea that the bromine could be replaced in the final product using the very rich palladium-catalyzed cross-coupling chemistry. Unfortunately, no alkylation product was observed for this compound, a result initially thought to be the result of a non-productive metal–halogen exchange. However, treatment of **11e** with *n*-BuLi followed by addition of benzaldehyde gave the expected alkylation product **16** (Scheme 6). We have presently no explanation for this. In addition to the alkylation route described above, Sonogashira coupling of alkyne **13** with a selection of aryl iodides **1**, **9b**, **9c**, **9e**, and **9f** was examined. This reaction also proved difficult and a satisfactory yield of product (**12b**) was only isolated from **9b**. All other substrates either failed to couple or gave a low yield.

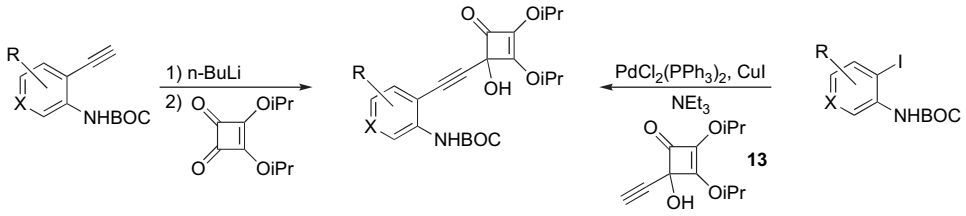
Thermal ring-expansion of **12a**–**12d** gave the expected cyclopentenediones **15a**–**15d**. Removal of the Boc-group gave the cyclopenta[*b*]quinoline-1-ones (**16a**–**16d**) and, finally, sodium borohydride reduction furnished the cyclopenta[*b*]quinoline-1-ols (**17a**–**17d**). Although easy to isolate, the cyclopenta[*b*]quinoline-1-ols (**17a**–**17d**) slowly oxidized to the corresponding cyclopenta[*b*]quinoline-1-ones (**16a**–**d**) upon standing in air (Scheme 7).



a R=4-Cl; X=CH	**9a** (81%)	**10a** (89%)	**11a** (92%)
b R=5-OMe; X=C	**9b** (88%)	**10b** (quant.)	**11b** (70%)
c R=5-Me; X=C	**9c** (92%)	**10c** (80%)	**11c** (79%)
d R=H, X=N	**9d**[a]	**10d** (quant.)	**11d** (94%)
f R=4-Br; X=CH	**9e**[a]	**10e** (88%)	**11e** (99%)

a) Known compound see experimental section.

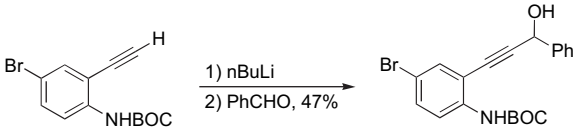
Scheme 4.



11a R=4-Cl; X=CH	**12a** (45%)	**9a**
11b R=5-OMe; X=C	**12b** (from **11b**,[b]*64%*)[a]	**9b**
11c R=5-Me; X=C	**12c** (21%, not observed from **9c**)	**9c**
11d R=H, X=N	**12d** (57%)	**9d**
11e R=4-Br; X=CH	**12e** (not observed from **9**/**11e**)	**9e**
14 R=H; X=CH	**2** (50%,*37%*)[a]	**1**

a) The yield in italicis is for the Sonogashira coupling. b) Not calculated, an inseparable 4:1 mixture with 4-butyl-4-hydroxy-2,3-di(1-methylethoxy)-2-cyclobuten-1-one.

Scheme 5.



Scheme 6.

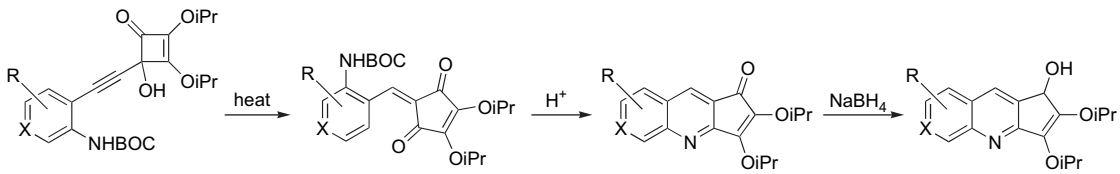
As a final example, 3-(1-methylethoxy)-4-methyl-3-cyclobutene-1,2-dione was allowed to react with the dianion formed from **1** giving the expected alkylation product **18** as a single regioisomer in 41% (59% based on recovered **1**, Scheme 8). Ring-expansion of **18** furnished the expected cyclopentenedione **19** as an 8.3:1 *E*/*Z* mixture. The *E*-isomers have previously been shown to be the kinetic products from ring-expansions of related compounds.[1] Although condensation of the carbonyl having a vinylogous alkoxide is expected to be much slower, we were somewhat surprised to observe only one quinoline isomer (**20**) upon removal of the Boc-protecting group. The product is derived from cyclization of the thermodynamically more stable *Z*-isomer. This observation can be explained by a facile *E* to *Z* isomerization of the alkene prior to cyclization. Isomerization of *E*-**19** to *Z*-**19** was observed by ^{1}H NMR by allowing the NMR sample to sit for a few hours at ambient temperature.

In conclusion, a novel route to cyclopenta[*b*]quinolin-1-ones and -ols has been developed. The key step in the sequence is a thermally induced ring-expansion of 4-(2-aminophenylethynyl)-4-hydroxy-2-cyclobuten-1-ones.

3. Experimental section

3.1. General procedures

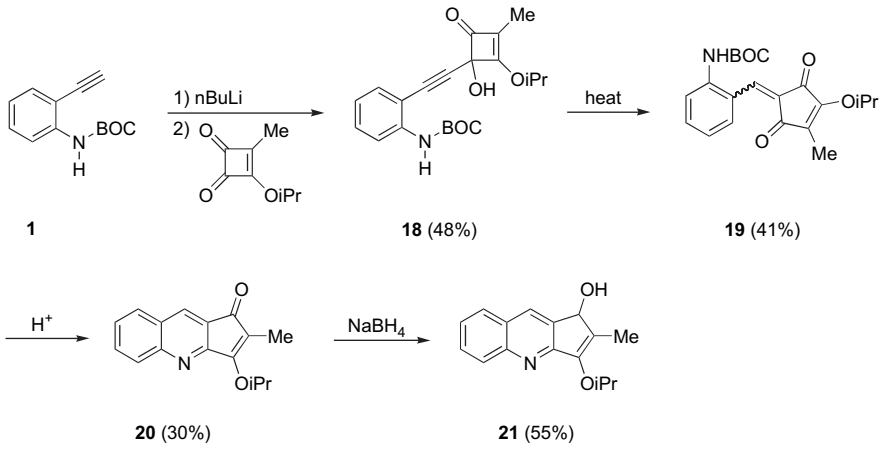
All NMR spectra were determined in $CDCl_3$ at 600 MHz (^{1}H NMR) and 150 MHz (^{13}C NMR) if not otherwise stated. The chemical shifts are expressed in δ values relative to Me_4Si (0.0, ^{1}H and ^{13}C) or $CDCl_3$ (77.0, ^{13}C) internal standards. Results of DEPT-^{13}C NMR experiments are shown in parentheses where, relative to $CDCl_3$, (−) denotes CH_3 or CH and (+) denotes CH_2 or C.



12a	**15a** (60%)	**16a** (54%)	**17a** (68%)
12b	**15b** (25%)[a]	**16b** (78%)	**17b** (70%)
12c	**15c** (81%)	**16c** (70%)	**17c** (70%)
12d	**15d** (47%)	**16d** (84%)	**17d** (51%)

a) Yield in two steps from **11b**.

Scheme 7.



Scheme 8.

Tetrahydrofuran (THF), toluene, dichloromethane, triethylamine, and diethyl ether were dried by passing through a steel column filled with activated alumina (8×14 mesh, Sorbent Technology) using argon pressure. Hexanes, EtOAc, and 1,2-dichloroethane were distilled from calcium hydride. Chemicals prepared according to literature procedures were referenced the first time used; all other reagents were obtained from commercial sources and used as-received. All reactions were performed in oven-dried glassware under a nitrogen atmosphere. Solvents were removed on a rotary evaporator at water aspirator pressure unless otherwise stated.

*3.1.1. (4-Chloro-2-iodophenyl)-carbamic acid 1,1-dimethylethyl ester (**9a**)*

To a solution of 4-chloro-2-iodo-1-aminobenzene (1.44 g, 5.67 mmol) in THF (5 mL) was added sodium bis(trimethylsilyl)amide (1.0 M in THF, 12.5 mL, 12.5 mmol) via syringe over a 15 min period. To the reaction mixture was added dropwise a solution of Boc_2O (1.24 g, 5.67 mmol) in THF (5 mL). The reaction mixture was stirred at ambient temperature (24 h). The solvent was removed under reduced pressure and the residue was partitioned between HCl (aq, 0.1 M, 50 mL) and EtOAc (20 mL). The layers were separated and the aqueous layer was treated with sodium bicarbonate (saturated aq, 10 mL). The resulting aqueous phase was extracted with EtOAc (2×20 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The crude product was purified by chromatography (hexanes/EtOAc, 95: 5) to give **9a** (1.63 g, 4.60 mmol, 81%) as an off-white solid. Mp 42–45 °C; ^{1}H NMR δ 8.00 (d, 1H, J=8.9 Hz), 7.72 (d, 1H, J=2.4 Hz), 7.28 (dd, 1H, J=8.9, 2.4 Hz), 6.79 (br s, 1H), 1.53 (s, 9H); ^{13}C NMR δ 152.3 (+), 137.7 (−), 137.6 (+), 129.1 (−), 128. 4 (+), 120.4 (−), 88.2 (+), 81.4 (+), 28.2 (−); IR (CCl_4) 3400, 2980, 1738, 1157 cm^{-1}; HRMS calcd for $C_{11}H_{14}NO_2ClI$ (M+H$^+$) 353.9758, found 353.9753.

*3.1.2. (2-Iodo-5-methoxyphenyl)-carbamic acid 1,1-dimethylethyl ester (**9b**)*

Reaction of 2-iodo-5-methoxyaniline[17] (409 mg, 1.64 mmol), sodium bis(trimethylsilyl)amide (1.0 M in THF, 3.60 mL, 3.60 mmol), and Boc_2O (355 mg, 1.63 mmol) in THF, as described above for **9a** (24 h), gave after workup and chromatography (hexanes/EtOAc, 8:2) **9b** (528 mg, 1.51 mmol, 92%) as an off-white solid. Mp 37–39 °C; ^{1}H NMR δ 7.79 (d, 1H, J=2.8 Hz), 7.57 (d, 1H, J=8.9 Hz), 6.83 (br s, 1H), 6.40 (dd, 1H, J=8.9, 2.9 Hz), 3.80 (s, 3H), 1.54 (s, 9H); ^{13}C NMR δ 160.7 (+), 152.4 (+), 139.6 (+), 138.7 (−), 111.7 (−), 105.1 (−), 81.1 (+), 55.4 (−), 28.3 (−), 0.0 (−); IR (CCl_4) 3396, 2981, 1734, 1158 cm^{-1}; HRMS calcd for $C_{12}H_{17}NO_3I$ (M+H$^+$) 350.0253, found 350.0251.

*3.1.3. (2-Iodo-5-methylphenyl)-carbamic acid 1,1-dimethylethyl ester (**9c**)*

Reaction of 2-iodo-5-methyl-1-aminobenzene[18] (897 mg, 3.84 mmol), sodium bis(trimethylsilyl)amide (1.0 M in THF, 4.2 mL, 8.4 mmol), and Boc_2O (846 mg, 3.88 mmol) in THF, as described for **9a** (24 h), gave after workup and chromatography (hexanes/EtOAc, 8:2) **9c** (1.122 g, 3.38 mmol, 88%) as an off-white solid. Mp 79.5–82 °C; ^{1}H NMR δ 7.91 (s, 1H), 7.59 (d, 1H, J=8.2 Hz), 6.79 (br s, 1H), 6.60 (dd, 1H, J=8.1, 1.6 Hz), 2.31 (s, 3H), 1.54 (s, 9H); ^{13}C NMR δ 152.5 (+), 139.4 (+), 138.4 (+), 138.3 (−), 125.7 (−), 120.6 (−), 84.6 (+), 80.9 (+), 28.3 (−), 21.3 (−); IR (CCl_4) 3396, 2979, 2360, 1736, 1160 cm^{-1}; HRMS calcd for $C_{12}H_{17}NO_2I$ (M+H$^+$) 334.0300, found 334.0304.

*3.1.4. (4-Chloro-2-(trimethylsilylethynyl)phenyl)-carbamic acid 1,1-dimethylethyl ester (**10a**)*

A mixture of **9a** (681 mg, 1.9 mmol), bis(triphenylphosphine)palladium dichloride (13 mg, 0.019 mmol), copper iodide (7 mg, 0.037 mmol), and ethynyl trimethylsilane (0.29 mL, 1.93 mmol) in triethylamine (20 mL) was stirred at ambient temperature (24 h). The reaction was diluted with water (50 mL) and the resulting biphasic mixture was extracted with diethyl ether (3×50 mL). The combined organic layers were washed with NH_4OH (10% aq, 25 mL), dried ($MgSO_4$), filtered, and the solvent were removed under reduced pressure. The crude product was purified by chromatography (hexanes/EtOAc, 95:5) to give **10a** (378 mg, 1.50 mmol, 89%) as a yellow solid. Mp 72–76 °C; ^{1}H NMR δ 8.08 (d, 1H, J=9.1 Hz), 7.34 (d, 1H, J=2.6 Hz), 7.31 (br s, 1H), 7.25 (dd, 1H, J=8.9, 2.4 Hz), 1.53 (s, 9H), 0.29 (s, 9H); ^{13}C NMR δ 152.1 (+), 138.8 (+), 130.7 (−), 129.8 (−), 126.6 (+), 118.3 (−), 112.3 (+), 103.4 (+), 99.0 (+), 80.9 (+), 28.2 (−), −0.3 (−); IR (CCl_4) 3400, 2977, 2152, 1737, 1157 cm^{-1}; HRMS calcd for $C_{16}H_{23}NO_2ClSi$ (M+H$^+$) 324.1187, found 324.1187.

*3.1.5. (5-Methoxy-2-trimethylsilylethynylphenyl)-carbamic acid 1,1-dimethylethyl ester (**10b**)*

Reaction of **9b** (504 mg, 1.44 mmol), bis(triphenylphosphine)palladium dichloride (54 mg, 0.077 mmol), copper iodide (14 mg, 0.074 mmol), and ethynyl trimethylsilane (230 μL, 1.59 mmol) in triethylamine (30 mL), as described for **10a** (ambient temperature, 24 h), gave after workup and chromatography (hexanes/EtOAc, 95:5) **10b** (360 mg, 1.16 mmol, 80%) off-white solid. Mp 39–41 °C; ^{1}H NMR δ 7.78 (s, 1H), 7.39 (s, 1H), 7.26 (d, 1H, J=9.0 Hz), 6.49 (dd, 1H, J=9.0, 2.4 Hz), 3.82 (s, 3H), 1.53 (s, 9H), 0.28 (s, 9H); ^{13}C NMR δ 160.9 (+), 152.3 (+), 141.9 (+), 132.2 (−), 108.9 (−), 103.0 (+), 102.1 (−), 100.8 (+), 100.5 (+), 80.6 (+), 55.4 (−), 28.3 (−), −0.1 (−);

IR (CCl_4) 3395, 2963, 2347, 2144, 1734, 1157 cm^{-1}; HRMS calcd for $C_{17}H_{26}NO_3Si$ ($M+H^+$) 320.1682, found 320.1679.

3.1.6. (5-Methyl-2-trimethylsilylethynylphenyl)-carbamic acid 1,1-dimethylethyl ester (**10c**)

Reaction of **9c** (450 mg, 1.36 mmol), bis(triphenylphosphine)palladium dichloride (48 mg, 0.068 mmol), copper iodide (16 mg, 0.084 mmol), and ethynyl trimethylsilane (200 μL, 1.42 mmol) in triethylamine (10 mL), as describe for **10a** (ambient temperature, 24 h), gave after workup and chromatography (hexanes/EtOAc, 95:5) **10c** (409 mg, 1.35 mmol, 100%) as a colorless oil. ^1H NMR δ 7.96 (s, 1H), 7.40 (br s, 1H), 7.15 (d, 1H, J=7.5 Hz), 6.75 (d, 1H, J=7.7 Hz), 2.34 (s, 3H), 1.53 (s, 9H), 0.28 (s, 9H); ^{13}C NMR δ (150 MHz) 152.4 (+), 140.5 (+), 140.1 (+), 131.0 (−), 122.8 (−), 117.7 (−), 108.1 (+), 101.3 (+), 100.8 (+), 80.5 (+), 28.3 (−), 22.0 (−), −0.1 (−); IR (CCl_4) 3396, 2977, 2348, 2148, 1736, 1159 cm^{-1}; HRMS calcd for $C_{17}H_{26}NO_2Si$ ($M+H^+$) 304.1733, found 304.1742.

3.1.7. (4-Trimethylsilylethynyl-3-pyridinyl)-carbamic acid 1,1-dimethylethyl ester (**10d**)

Reaction of (4-iodo-3-pyridinyl)-carbamic acid 1,1-dimethylethyl ester[19] (1.96 g, 6.14 mmol), bis(triphenylphosphine)palladium dichloride (65 mg, 0.093 mmol), copper iodide (17 mg, 0.89 mmol), and ethynyl trimethylsilane (1.33 mL, 6.45 mmol) in triethylamine (20 mL), as described for **10a** (ambient temperature, 24 h), gave after workup and chromatography (hexanes/EtOAc, 1:1) **10d** (1.78 g, 6.14 mmol, 100%) as a brown solid. Mp 59–61 °C; ^1H NMR δ 9.39 (s, 1H), 8.24 (d, 1H, J=4.9 Hz), 7.21 (d, 1H, J=4.9 Hz), 7.12 (br s, 1H), 1.55 (s, 9H), 0.31 (s, 9H); ^{13}C NMR 151.8 (+), 142.9 (−), 139.9 (−), 135.8 (+), 124.2 (−), 118.2 (+), 106.9 (+), 97.6 (+), 81.4 (+), 28.1 (−), −0.4 (−); IR (CCl_4) 3389, 2978, 2155, 1736, 1155 cm^{-1}; HRMS calcd for $C_{15}H_{23}N_2O_2Si$ ($M+H^+$) 291.1529, found 291.1541.

3.1.8. (4-Bromo-2-(trimethylsilylethynyl)phenyl)-carbamic acid 1,1-dimethylethyl ester (**10e**)

A mixture of **9e**[20] (724 mg, 1.82 mmol), bis(triphenylphosphine)palladium dichloride (66 mg, 0.094 mmol), copper iodide (18 mg, 0.095 mmol), and ethynyl trimethylsilane (243 mg, 2.47 mmol) in triethylamine (20 mL) was stirred at ambient temperature (24 h). The reaction was diluted with water (50 mL) and the resulting biphasic mixture was extracted with diethyl ether (3×50 mL). The solvent was removed and the crude product was purified by chromatography (hexanes/EtOAc, 95:5) to give **10e** (591 mg, 1.60 mmol, 88%) as a pale yellow solid. Mp 81–84 °C; ^1H NMR δ 8.03 (d, 1H, J=8.9 Hz), 7.49 (d, 1H, J=2.4 Hz), 7.39 (dd, 1H, J=8.9, 2.4 Hz), 7.31 (br s, 1H), 1.52 (s, 9H); 0.29 (s, 9H); ^{13}C NMR 152.0 (+), 139.3 (+), 133.5 (−), 132.6 (−), 118.6 (−), 113.8 (+), 111.7 (+), 103.5 (+), 98.8 (+), 80.9 (+), 28.2 (−), −0.3 (−); IR (CCl_4) 3395, 2964, 2154, 1739, 1507, 1154 cm^{-1}; HRMS calcd for $C_{16}H_{22}BrNNaO_2Si$ ($M+Na^+$) 390.0495, found 390.0502.

3.1.9. (4-Chloro-2-ethynylphenyl)-carbamic acid 1,1-dimethylethyl ester (**11a**)

To a solution of **10a** (924 mg, 2.85 mmol) in absolute ethanol/THF (1:1, 30 mL) was added a solution of NaOH (1 M, 3 mL) and the resulting reaction mixture was allowed to stir (ambient temperature, 2 h). The solvents were removed at reduced pressure and the residue was suspended in water (10 mL) and extracted with diethyl ether (3×50 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The crude product was purified by chromatography (hexanes/EtOAc, 9:1) to give **11a** (664 mg, 2.64 mmol, 92%) as an off-white solid. Mp 61–63 °C; ^1H NMR δ 8.13 (d, 1H, J=9.1 Hz), 7.39 (d, 1H, J=2.4 Hz), 7.29 (dd, 1H, J=9.1, 2.6 Hz), 7.21 (br s, 1H), 3.52 (s, 1H), 1.53 (s, 9H); ^{13}C NMR δ 152.1 (+), 138.9 (+), 131.5 (−), 130.1 (−), 126.7 (+), 118.7 (−), 111.2 (+), 85.1 (+), 81.2 (+), 77.9 (+), 28.2 (−); IR (CCl_4) 3411, 3305, 2980, 2361, 1737, 1156 cm^{-1}; HRMS calcd for $C_{13}H_{15}NO_2Cl$ ($M+H^+$) 252.0791, found 252.0790.

3.1.10. (2-Ethynyl-5-methoxyphenyl)-carbamic acid 1,1-dimethylethyl ester (**11b**)

To a solution of **10b** (603 mg, 1.89 mmol) in methanol/THF/water (5:5:1, 11 mL) was added anhydrous potassium fluoride (334 mg, 5.75 mmol) and the resulting mixture was stirred (ambient temperature, 1 h). The reaction was diluted with water (50 mL) and extracted with diethyl ether (3×50 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and the solvents were removed at reduced pressure. The crude product was purified by chromatography (hexanes/EtOAc, 95:5) to give **11b** (314 mg, 1.3 mmol, 70%) as a colorless solid. Mp around ambient temperature; ^1H NMR δ 7.83 (d, 1H, J=2.4 Hz), 7.32 (d, 1H, J=8.5 Hz), 7.29 (br s, 1H), 6.51 (dd, 1H, J=8.7, 2.6 Hz), 3.83 (s, 3H), 3.42 (s, 1H), 1.53 (s, 9H); ^{13}C NMR δ 161.1 (+), 152.3 (+), 141.8 (+), 133.1 (−), 109.1 (−), 102.4 (−), 101.8 (+), 82.8 (+), 80.9 (+), 79.5 (+), 55.4 (−), 28.3 (−); IR 3407, 3309, 2980, 2360, 1734, 1157 cm^{-1}; HRMS calcd for $C_{14}H_{18}NO_3$ ($M+H^+$) 248.1287, found 248.1280.

3.1.11. (2-Ethynyl-5-methylphenyl)-carbamic acid 1,1-dimethylethyl ester (**11c**)

Reaction of **10c** (400 mg, 1.32 mmol) with NaOH (1 M aq, 4 mL) in ethanol/THF (1:1, 20 mL), as described for **11a** (ambient temperature, 2 h), gave after workup and chromatography (hexanes/EtOAc, 9:1) **11c** (241 mg, 1.05 mmol, 79%) as a yellow solid. Mp 75–77 °C; ^1H NMR δ 8.01 (s, 1H), 7.31 (d, 1H, J=7.9 Hz), 7.24 (br s, 1H), 6.78 (d, 1H, J=7.9), 3.4 (s, 1H), 2.35 (s, 3H), 1.53 (s, 9H); ^{13}C NMR δ 152.4 (+), 140.7 (+), 140.1 (+), 131.9 (−), 122.9 (−), 117.9 (−), 106.9 (+), 83.4 (+), 80.7 (+), 79.5 (+), 28.3 (−), 21.9 (−); IR (CCl_4) 3408, 3309, 2978, 2926, 2347, 1735, 1157 cm^{-1}; HRMS calcd for $C_{14}H_{18}NO_2$ ($M+H^+$) 232.1338, found 232.1333.

3.1.12. (4-Ethynyl-3-pyridinyl)-carbamic acid 1,1-dimethylethyl ester (**11d**)

Reaction of **10d** (1.78 g, 6.14 mmol) with potassium fluoride dihydrate (1.72 g, 18.3 mmol) in methanol/THF (1:1, 15 mL), as described for **10b** (ambient temperature, 20 min), gave after workup and chromatography (hexanes/EtOAc, 1:1) **11d** (1.25 g, 5.8 mmol, 94%) as a brownish solid. Mp 77–80 °C; ^1H NMR δ 9.40 (s, 1H), 8.26 (d, 1H J=4.9 Hz), 7.28 (d, 1H, J=5.1 Hz), 7.09 (br s, 1H), 3.69 (s, 1H), 1.57 (s, 9H); ^{13}C NMR δ 151.9 (+), 143.0 (−), 140.4 (−), 136.0 (+), 125.2 (−), 117.3 (+), 88.1 (+), 88.0 (+), 81.7 (+), 28.2 (−); IR (CCl_4) 3407, 3298, 2982, 2248, 1727, 1160 cm^{-1}; HRMS calcd for $C_{12}H_{15}N_2O_2$ ($M+H^+$) 219.1134, found 219.1135.

3.1.13. (4-Bromo-2-ethynylphenyl)-carbamic acid 1,1-dimethylethyl ester (**11e**)

Reaction of **10e** (869 mg, 2.36 mmol) with NaOH (1 M aq, 4.4 mL) in ethanol/THF (1:1, 20 mL), as described for **11a** (ambient temperature, 3 h), gave after workup and chromatography (hexanes/EtOAc, 95:5) **11e** (693 mg, 2.34 mmol, 99%) as a pale yellow solid. Mp 65–67 °C; ^1H NMR δ 8.08 (d, 1H, J=9.1 Hz), 7.53 (d, 1H, J=2.4 Hz), 7.42 (dd, 1H, J=9.1, 2.4 Hz), 7.21 (br s, 1H), 3.52 (s, 1H), 1.53 (s, 9H); ^{13}C NMR δ 152.1 (+), 139.4 (+), 134.4 (−), 133.0 (−), 119.0 (−), 113.9 (+), 111.6 (+), 85.2 (+), 81.2 (+), 77.9 (+), 28.2 (−); IR (CCl_4) 2985, 2255, 1727, 1509, 1156 cm^{-1}; HRMS calcd for $C_{13}H_{15}BrNO_2$ ($M+H^+$) 296.0281, found 296.0286.

3.1.14. [2-(1-Hydroxy-2,3-bis(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)phenyl]-carbamic acid 1,1-dimethylethyl ester (**2**)

To a −5 °C cold solution of (2-ethynylphenyl)-carbamic acid 1,1-dimethylethyl ester (**1**)[21,22] (155 mg, 0.71 mmol) in THF (10 mL) was slowly added *n*-BuLi (1.6 M in THF, 1.1 mL, 1.8 mmol) via syringe. After 15 min, a −5 °C cold solution 3,4-bis(1-methylethoxy)-

3-cyclobutene-1,2-dione (141 mg, 0.71 mmol) in THF (10 mL) was added to the dilithiated compound via a cannula. The resulting reaction mixture was stirred (ambient temperature, 30 min) followed by the addition of water (40 mL). The biphasic mixture was extracted with diethyl ether (3×50 mL) and the combined organic layers were dried ($MgSO_4$), filtered, and the solvents were removed under reduced pressure. The crude product was purified by chromatography (hexanes/EtOAc, 8:2) to afford **2** (149 mg, 0.35 mmol, 50%) as a brown oil. ^{1}H NMR δ 8.14 (d, 1H, J=8.3 Hz), 7.40 (dd, 1H, J=7.7, 1.4 Hz), 7.32 (dt, 1H, J=8.7, 1.6 Hz), 7.14 (br s, 1H), 6.95 (dt, 1H, J=7.5, 1.0 Hz), 5.02 (heptet, 1H, J=6.1 Hz), 4.92 (heptet, 1H, J=6.1 Hz), 3.07 (br s, 1H), 1.53 (s, 9H), 1.48 (d, 3H, J=6.3 Hz), 1.47 (d, 3H, J=6.1 Hz), 1.33 (d, 3H, J=6.1 Hz), 1.32 (d, 3H, J=6.1 Hz); ^{13}C NMR δ 180.4 (+), 164.1 (+), 152.4 (+), 139.7 (+), 133.8 (+), 132.2 (−), 130.1 (−), 122.0 (−), 117.8 (−), 109.9 (+), 90.2 (+), 83.8 (+), 80.9 (+), 78.9 (+), 78.1 (−), 74.3 (−), 28.3 (−), 22.7 (−), 22.6 (−), 22.5 (−); IR (CCl_4) 3402, 2980, 2933, 1734, 1158 cm^{-1}; HRMS calcd for $C_{23}H_{30}NO_6$ (M+H$^+$) 416.2073, found 416.2081.

Alternative procedure: A solution of **1** (394 mg, 1.23 mmol), bis(triphenylphosphine)palladium dichloride (44 mg, 0.063 mmol), copper iodide (238 mg, 1.24 mmol), and 4-ethenyl-4-hydroxy-2,3-di(1-methylethoxy)-2-cyclobuten-1-one[23] (272 mg, 1.21 mmol) in triethylamine (30 mL) was stirred at ambient temperature (20 h). The reaction was diluted with water (50 mL) and the resulting biphasic mixture was extracted with diethyl ether (3×50 mL). The combined organic phases were washed with NH_4OH (10%-aqueous, 20 mL), dried ($MgSO_4$), filtered, and the solvent was removed. The crude product was purified by chromatography (hexanes/EtOAc, 8:2) giving **12b** (189 mg, 0.45 mmol, 37%) as a yellow-orange solid in addition to **1** (155 mg, 0.49 mmol).

3.1.15. *(4-Chloro-2-(1-hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)phenyl)-carbamic acid 1,1-dimethylethyl ester (**12a**)*

Reaction of **11a** (250 mg, 0.99 mmol), *n*-BuLi (2.65 M in THF, 0.93 mL, 2.4 mmol), and 3,4-bis(1-methylethoxy)-3-cyclobutene-1,2-dione (198 mg, 1.00 mmol) in THF (20 mL total), as described for **2** (30 min), gave after workup and chromatography (hexanes/EtOAc, 8:2), **12a** (200 mg, 0.44 mmol, 45%) as a yellow solid and **11a** (97 mg, 0.39 mmol). Mp 123–125 °C; ^{1}H NMR δ 8.08 (d, 1H, J=8.9 Hz), 7.34 (d, 1H, J=2.4 Hz), 7.25 (dd, 1H, J=8.9, 2.6 Hz), 7.15 (br s, 1H), 5.02 (heptet, 1H, J=6.1 Hz), 4.89 (heptet, 1H, J=6.1 Hz), 3.74 (br s, 1H), 1.53 (s, 9H), 1.48 (d, 3H, J=6.1 Hz), 1.47 (d, 3H, J=6.1 Hz);1.32 (d, 6H, J=6.1 Hz); ^{13}C NMR δ 180.6 (+), 164.2 (+), 152.3 (+), 138.4 (+), 133.8 (+), 131.4 (−), 130.1 (−), 126.8 (+), 119.1 (−), 111.4 (+), 91.3 (+), 82.4 (+), 81.2 (+), 78.6 (+), 78.2 (−), 74.3 (−), 28.2 (−), 22.7 (−), 22.6 (−), 22.5 (−); IR (CCl_4) 3424, 2968, 2355, 1734, 1157 cm^{-1}; HRMS calcd for $C_{23}H_{29}NO_6Cl$ (M+H$^+$) 450.1683, found 450.1687.

3.1.16. *(2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methoxyphenyl)-carbamic acid 1,1-dimethylethyl ester (**12b**)*

Reaction of **11b** (192 mg, 0.80 mmol), *n*-BuLi (1.4 M in THF, 1.43 mL, 2.01 mmol), and 3,4-bis(1-methylethoxy)-3-cyclobutene-1,2-dione (106 mg, 0.81 mmol) in THF (25 mL total), as described for **2** (30 min), gave after workup and chromatography (hexanes/EtOAc, 8:2) an inseparable mixture of **12b** and 4-butyl-4-hydroxy-2,3-di(1-methylethoxy)-2-cyclobuten-1-one (215 mg, 4:1 ratio). ^{1}H NMR δ 7.80 (d, 1H, J=2.2 Hz), 7.28 (d, 1H, J=8.3 Hz), 7.17 (br s, 1H), 6.50 (dd, 1H, J=8.5, 2.6 Hz), 5.02 (heptet, 1H, J=6.1 Hz), 4.90 (heptet, 1H, J=6.3 Hz), 3.82 (s, 3H), 3.21 (br s, 1H), 1.53 (s, 9H), 1.48 (d, 3H, J=6.3 Hz), 1.46 (d, 3H, J=6.1 Hz), 1.32 (d, 3H, J=6.1 Hz), 1.31 (d, 3H, J=6.1 Hz); ^{13}C NMR δ 180.7 (+), 164.3 (+), 161.1 (+), 152.3 (+), 141.3 (+), 133.7 (+), 133.1 (−), 109.1 (−), 102.5 (−), 101.9 (+), 89.1 (−), 83.9 (+), 80.9 (+), 78.9 (+), 74.2 (−), 28.3 (−), 22.7 (−), 22.6 (−), 22.5 (−), 22.3 (−); IR (CCl_4) 3565, 2989, 2942, 1731, 1161 cm^{-1}.

Alternative procedure: A solution of **9b** (912 mg, 2.61 mmol), bis(triphenylphosphine)palladium dichloride (91 mg, 0.13 mmol), copper iodide (496 mg, 2.60 mmol), and **13** (581 mg, 2.59 mmol) in triethylamine (30 mL) was stirred at ambient temperature (20 h). The reaction was diluted with water (50 mL) and the resulting biphasic mixture was extracted with diethyl ether (3×50 mL). The combined organic phases were washed with NH_4OH (10%-aqueous, 20 mL), dried ($MgSO_4$), filtered, and the solvent was removed. The crude product was purified by chromatography (hexanes/EtOAc, 8:2) giving **12b** (747 mg, 1.68 mmol, 64%) as a yellow-orange solid. Mp 38–42 °C; HRMS calcd for $C_{24}H_3NNaO_7$ (M+Na$^+$) 468.1993, found 468.1992.

3.1.17. *(2-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-5-methylphenyl)-carbamic acid 1,1-dimethylethyl ester (**12c**)*

Reaction of **11c** (217 mg, 0.94 mmol), *n*-BuLi (1.6 M in THF, 1.47 mL, 2.36 mmol), and 3,4-bis(1-methylethoxy)-3-cyclobutene-1,2-dione (187 mg, 0.94 mmol) in THF (30 mL total), as described for **2** (30 min), gave after workup and chromatography (hexanes/EtOAc, 8:2) **12c** (89 mg, 0.21 mmol, 21%) as a yellow oil and **11c** (89 mg, 0.39 mmol). ^{1}H NMR δ 7.98 (s, 1H), 7.26 (d, 1H, J=7.9 Hz), 7.12 (br s, 1H), 6.77 (d, 1H, J=7.9 Hz), 5.02 (heptet, 1H, J=6.1 Hz), 4.90 (heptet, 1H, J=6.1 Hz), 3.16 (br s, 1H), 2.34 (s, 3H), 1.53 (s, 9H), 1.48 (d, 3H, J=6.3 Hz), 1.46 (d, 3H, J=6.1 Hz), 1.32 (d, 3H, J=6.1 Hz), 1.31 (d, 3H, J=6.1 Hz); ^{13}C NMR δ 180.3 (+), 164.1 (+), 152.4 (+), 140.9 (+), 139.6 (+), 133.9 (+), 131.9 (−), 123.0 (−), 118.3 (−), 106.9 (+), 89.6 (+), 84.1 (+), 80.8 (+), 78.9 (+), 78.0 (−), 74.3 (−), 28.3 (−), 22.7 (−), 22.6 (−), 22.5 (−), 21.9 (−); IR (CCl_4) 3424, 2978, 1731, 1637, 1161 cm^{-1}; HRMS calcd for $C_{24}H_{32}NO_6$ (M+H$^+$) 430.2230, found 430.2242.

3.1.18. *(4-(1-Hydroxy-2,3-di(1-methylethoxy)-4-oxo-cyclobut-2-enylethynyl)-pyridin-3-yl)-carbamic acid 1,1-dimethylethyl ester (**12d**)*

Reaction of **11d** (1.05 g, 4.81 mmol), *n*-BuLi (2.89 M in THF, 4.16 mL, 12.04 mmol), and 3,4-bis(1-methylethoxy)-3-cyclobutene-1,2-dione (0.96 g, 4.83 mmol) in THF (40 mL total), as described for **2**, gave after workup and chromatography (hexanes/EtOAc, 1:1) to give **12d** (1.14 g, 2.74 mmol, 57%) as a brown oil. ^{1}H NMR δ 9.40 (s, 1H), 8.24 (d, 1H, J=4.9 Hz), 7.24 (d, 1H, J=4.9 Hz), 6.99 (br s, 1H), 5.02 (heptet, 1H, J=6.1 Hz), 4.91 (heptet, 1H, J=6.1 Hz), 4.57 (br s, 1H), 1.53 (s, 9H), 1.47 (d, 3H, J=6.3 Hz), 1.46 (d, 3H, J=6.1 Hz), 1.32 (d, 3H, J=6.1 Hz), 1.31 (d, 3H, J=6.1 Hz); ^{13}C NMR δ 180.0 (+), 164.0 (+), 151.8 (+), 142.3 (−), 139.9 (−), 139.8 (−), 135.7 (+), 133.8 (+), 125.3 (−), 118.0 (+), 95.5 (+), 81.6 (+), 80.5 (+), 78.5 (+), 78.1 (−). 78.0 (−), 74.3 (−), 74.2 (−), 28.1 (−), 22.6 (−), 22.5 (−), 22.4 (−); IR (CCl_4) 3405 (br), 2978, 2360, 1737, 1158 cm^{-1}; HRMS calcd for $C_{22}H_{29}N_2O_6$ (M+H$^+$) 417.2026, found 417.2027.

3.1.19. *(2-(3-Hydroxy-3-phenyl-1-propynyl)-4-bromophenyl)-carbamic acid 1,1-dimethylethyl ester*

A THF (5 mL) solution of compound **11e** (108 mg, 0.44 mmol) was reacted with *n*-BuLi (1.8 M in THF, 610 μL, 1.10 mmol) as described for **2**. Benzaldehyde (39 mg, 0.54 mmol) was added via a syringe at −78 °C and the resulting mixture was stirred for 30 min. The solvent was removed under reduced pressure and the crude product was purified by chromatography (hexanes/EtOAc, 9:1) to give in order of elution **11e** (28 mg, 0.11 mmol) and the title compound (85 mg, 0.21 mmol, 48%) as a red-brown oil. ^{1}H NMR (270 MHz) δ 8.05 (d, 1H, J=9.1 Hz), 7.60 (dd, 2H, J=8.1, 1.8 Hz), 7.52 (d, 1H, J=3.4 Hz), 7.48–7.24 (m, 4H), 7.13 (br s, 1H), 5.75 (d, 1H, J=5.9 Hz), 2.39 (d, 1H, J=6.1 Hz), 1.51 (s, 9H); ^{13}C NMR δ 152.1, 140.2, 139.0, 134.2, 132.9, 128.9, 128.8, 126.5, 119.2, 114.1, 112.1, 96.9, 81.3, 80.6, 65.1, 28.3; IR (neat) 3400, 1732, 1710, 1508 cm^{-1}; HRMS calcd for $C_{20}H_{20}BrNNaO_3$ (M+Na$^+$) 424.0519, found 424.0525.

*3.1.20. (2-(3,4-Di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl)-carbamic acid 1,1-dimethylethyl ester (**6**)*

A solution of **2** (291 mg, 0.70 mmol) in toluene (20 mL) was heated at reflux overnight. The reaction was cooled to ambient temperature and the solvent was removed under reduced pressure. The crude residue was purified by chromatography (hexanes/EtOAc, 95:5) to give **6** (184 mg, 0.44 mmol, 63%) as an orange solid. Mp 93–96 °C; ^{1}H NMR δ 7.91 (dd, 1H, J=7.9, 1.6 Hz), 7.80 (d, 1H, J=8.1 Hz), 7.44 (s, 1H), overlapping 7.40 (t, 1H, J=8.7 Hz), 7.13 (t, 1H, J=7.5 Hz), 6.54 (br s, 1H), 5.59 (m, 2H), 1.51 (s, 9H), 1.40 (d, 6H, J=6.3 Hz), 1.37 (d, 6H, J=6.1 Hz); ^{13}C NMR δ 185.9 (+), 184.4 (+), 152.8 (+), 151.9 (+), 149.4 (+), 137.8 (+), 131.7 (−), 131.5 (−), 130.8 (−), 127.3 (+), 124.2 (+), 123.4 (−), 122.2 (−), 80.9 (+), 74.9 (−), 74.8 (−), 28.2 (−), 22.9 (−), 22.6 (−); IR ($CDCl_3$) 3326 (br), 2980, 2933, 1733, 1156 cm^{-1}; HRMS calcd for $C_{23}H_{30}NO_6$ (M+H$^+$) 416.2073, found 416.2073.

Alternative procedure: Compound **2** (95 mg, 0.23 mmol) was transferred to an airless flask. The compound was heated neat in an oil bath at 140 °C for 30 min. The residue was purified by chromatography (hexanes/EtOAc, 8:2) to afford **6** (80 mg, 0.19 mmol, 85% yield).

*3.1.21. (4-Chloro-2-(3,4-di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl)-carbamic acid 1,1-dimethylethyl ester (**15a**)*

Reaction of **12a** (452 mg, 1.00 mmol) in toluene (20 mL), as described for **6**, gave after workup and chromatography (hexanes/EtOAc, 8:2) **13a** (268 mg, 0.60 mmol, 60%) as a yellow solid. Mp 57–62 °C; ^{1}H NMR δ 7.93 (d, 1H, J=2.4 Hz), 7.79 (d, 1H, J=8.5 Hz), 7.34 (dd, 1H, J=8.7, 2.4 Hz), 7.32 (s, 1H), 6.48 (br s, 1H), 5.59 (m, 2H), 1.51 (s, 9H), 1.40 (d, 6H, J=5.5 Hz), 1.38 (d, 6H, J=5.9 Hz); ^{13}C NMR δ 185.4 (+), 184.0 (+), 152.7 (+), 152.6 (+), 149.8 (+), 136.3 (+), 131.2 (−), 131.0 (−), 128.9 (+), 128.7 (−), 128.5 (+), 81.3 (+), 75.2 (−), 75.1 (−), 65.8 (+), 28.2 (−), 23.0 (−), 23.0 (−), 15.2 (−); IR ($CDCl_3$) 3149, 2982, 2254, 1727, 1160 cm^{-1}; HRMS calcd for $C_{23}H_{29}NO_6Cl$ (M+H$^+$) 450.1683, found 450.1683.

*3.1.22. (2-(3,4-Di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)-5-methoxy-phenyl)-carbamic acid 1,1-dimethylethyl ester (**15b**)*

Reaction of a 4:1 mixture of **12b** and 4-butyl-4-hydroxy-2,3-di(1-methylethoxy)-2-cyclobuten-1-one (215 mg) in toluene (20 mL), as described for **6** (reflux, overnight), gave after chromatography (hexanes/EtOAc, 8:2) **13b** (87 mg, 0.20 mmol, 25% from **11b**) as an orange-yellow solid. Mp 99–102 °C; ^{1}H NMR δ 8.15 (d, 1H, J=9.0 Hz), 7.48 (br s, 1H), 7.38 (s, 1H), 6.79 (s, 2H), 6.68 (dd, 1H, J=8.4, 2.4 Hz), 5.53 (m, 2H), 3.85 (s, 3H), 1.52 (s, 9H), 1.39 (d, 6H, J=6.0 Hz), 1.38 (d, 6H, J=6.0 Hz); ^{13}C NMR δ (150 MHz) 186.8 (+), 185.0 (+), 162.9 (+), 152.5 (+), 151.4 (+), 148.4 (+), 140.3 (+), 133.8 (−), 130.5 (−), 124.5 (+), 116.0 (+), 110.1 (−), 106.3 (+), 81.1 (+), 74.8 (−), 74.7 (−), 55.4 (−), 28.2 (+), 22.9 (+); IR (CCl_4) 3445, 2980, 2933, 1733, 1670, 1156 cm^{-1}; HRMS calcd for $C_{24}H_{32}NO_7$ (M+H$^+$) 446.2179, found 446.2180.

*3.1.23. (2-(3,4-Di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-methylidene)-5-methyl-phenyl)-carbamic acid 1,1-dimethylethyl ester (**15c**)*

Reaction of **12c** (59 mg, 0.14 mmol) in toluene (20 mL), as described for **6** (reflux, overnight), gave after chromatography (hexanes/EtOAc, 8:2) **13c** (48 mg, 0.11 mmol, 81%) as a colorless oil. ^{1}H NMR δ 7.89 (d, 1H, J=8.1 Hz), 7.65 (s, 1H), 7.42 (s, 1H), 6.95 (d, 1H, J=7.1 Hz), 6.56 (br s, 1H), 5.57 (m, 2H), 2.37 (s, 3H), 1.51 (s, 9H), 1.40 (d, 6H, J=6.1 Hz), 1.37 (d, 6H, J=6.1 Hz); ^{13}C NMR δ 186.3 (+), 184.7 (+), 152.8 (+), 151.8 (+), 149.1 (+), 142.8 (+), 137.9 (+), 131.8 (−), 130.8 (−), 126.4 (+), 124.5 (−), 122.5 (−), 121.3 (+), 80.9 (+), 74.9 (−), 74.8 (−), 29.7 (+), 28.3 (−), 23.0 (−), 21.8 (−); IR (CCl_4) 3437, 2980, 2360, 1734, 1672, 1157 cm^{-1}; HRMS calcd for $C_{24}H_{32}NO_6$ (M+H$^+$) 430.2230, found 430.2236.

*3.1.24. (4-(3,4-Di(1-methylethoxy)-2,5-dioxo-3-cyclopenten-1-ylmethyl)-3-pyridinyl)-carbamic acid 1,1-dimethylethyl ester (**15d**)*

Reaction of **12d** (107 mg, 0.26 mmol) in 1,2-dichloroethane (20 mL), as described for **6** (reflux, 18 h), gave after chromatography (hexanes/EtOAc, 6:4) **13e** (50 mg, 0.12 mmol, 47%) as a brown solid. Mp 117–119 °C; ^{1}H NMR δ 8.99 (s, 1H), 8.40 (d, 1H, J=5.3 Hz), 7.66 (d, 1H, J=5.2 Hz), 7.30 (s, 1H), 6.45 (br s, 1H), 5.61 (m, 2H), 1.51 (s, 9H), 1.41 (d, 6H, J=6.3 Hz), 1.38 (d, 6H, J=6.3 Hz); ^{13}C NMR δ (150 MHz) 184.5 (+), 183.6 (+), 153.1 (+), 152.6 (+), 150.8 (+), 144.8 (−), 144.3 (−), 133.1 (+), 132.3 (+), 130.7 (+), 127.3 (−), 124.2 (−), 81.6 (+), 75.5 (−), 75.4 (−), 28.1 (−), 23.0 (−); IR (CCl_4) 3000, 2960, 1740, 1690, 1160 cm^{-1}; HRMS calcd for $C_{22}H_{29}N_2O_6$ (M+H$^+$) 417.2026, found 417.2034.

*3.1.25. 2,3-Di(1-methylethoxy)cyclopenta[b]quinolin-1-one (**7**)*

A solution of **6** (169 mg, 0.41 mmol) in EtOAc/HCl (1:1, 3 M aq HCl, 20 mL) was stirred at ambient temperature (6 d). The solvents were removed under reduced pressure and the resulting residue was suspended in water (20 mL) and extracted with diethyl ether (3×50 mL). The organic layers were washed with $NaHCO_3$ (aq saturated 25 mL), dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. The crude product was purified by chromatography (hexanes/EtOAc, 8:2) to give **7** (75 mg, 0.25 mmol, 62%) as a yellow-orange solid. Mp 59–61 °C; ^{1}H NMR δ 8.05 (d, 1H, J=8.3 Hz), 7.79 (s, 1H), 7.71 (dd, 1H, J=7.9, 1.4 Hz), 7.62 (dt, 1H, J=7.1, 1.4 Hz), 7.42 (dt, 1H, J=8.1, 1.2 Hz), 5.68 (heptet, 1H, J=6.3 Hz), 5.26 (heptet, 1H, J=6.1 Hz), 1.50 (d, 6H, J=6.1 Hz), 1.35 (d, 6H, J=6.1 Hz); ^{13}C NMR δ 187.2 (+), 158.0 (+), 156.8 (+), 149.2 (+), 138.2 (+), 130.6 (−), 129.8 (−), 129.7 (−), 127.7 (+), 126.8 (−), 126.3 (−), 123.7 (+), 76.5 (−), 73.8 (−), 22.9 (−), 22.8 (−); IR (CCl_4) 3436, 2978, 1695, 1102 cm^{-1}; HRMS calcd for $C_{18}H_{20}NO_3$ (M+H$^+$) 298.1443, found 298.1438.

*3.1.26. 7-Chloro-2,3-di(1-methylethoxy)cyclopenta[b]quinolin-1-one (**16a**)*

Reaction of **15a** (163 mg, 0.44 mmol) in EtOAc/HCl (1:1, 3 M aq HCl, 30 mL), as described for **7** (ambient temperature, 3 d), gave after workup and chromatography (hexanes/EtOAc, 8:2), **14a** (71 mg, 0.24 mmol, 54%) as an orange solid. Mp 104–106 °C; ^{1}H NMR δ 7.99 (d, 1H, J=8.9 Hz), 7.69 (s, 1H), 7.68 (s, 1H) overlapping 7.61 (d, 1H, J=2.3 Hz), 7.55 (dd, 1H, J=8.7,2.3 Hz), 5.66 (heptet, 1H, J=6.1 Hz), 5.28 (heptet, 1H, J=6.1 Hz), 1.51 (d, 6H, J=6.3 Hz), 1.36 (d, 6H, J=6.3 Hz); ^{13}C NMR δ 186.5 (+), 158.5 (+), 156.7 (+), 147.5 (+), 138.4 (+), 132.4 (+), 131.0 (−), 128.6 (−), 128.5 (−), 125.2 (−), 124.6 (+), 75.3 (−), 73.9 (−), 22.9 (−), 22.8 (−); IR (CCl_4) 3410, 2982, 2931, 2360, 1700, 1101 cm^{-1}; HRMS calcd for $C_{18}H_{19}NO_3Cl$ (M+H$^+$) 332.1053, found 332.1054.

*3.1.27. 2,3-Di(1-methylethoxy)-6-methoxycyclopenta[b]quinolin-1-one (**16b**)*

Reaction of **15b** (154 mg, 0.35 mmol) in EtOAc/HCl (4:3, 3 M aq HCl, 35 mL), as described for **6** (ambient temperature, 2 d), gave after workup and chromatography (hexanes/EtOAc, 8:2) **14b** (88 mg, 0.27 mmol, 78%) as a yellow oil. ^{1}H NMR δ 7.73 (s, 1H), 7.60 (d, 1H, J=8.7 Hz), 7.48 (d, 1H, J=2.6 Hz), 7.05 (dd, 1H, J=8.7, 2.6 Hz), 5.62 (heptet, 1H, J=6.1 Hz), 5.23 (heptet, 1H, J=6.1 Hz), 3.92 (s, 3H), 1.49 (d, 6H, J=6.1 Hz), 1.34 (d, 6H, J=6.1 Hz); ^{13}C NMR δ 187.6 (+), 161.6 (+), 159.2 (+), 156.1 (+), 151.0 (+), 137.1 (+), 130.6 (−), 126.1 (−), 121.9 (+), 121.2 (+), 117.9 (−), 109.9 (−), 74.8 (−), 73.7 (−), 55.5 (−), 22.8 (−), 22.7 (−); IR (CCl_4) 2980, 2932, 2359, 1701, 1108 cm^{-1}; HRMS calcd for $C_{19}H_{22}NO_4$ (M+H$^+$) 328.1549, found 328.1537.

*3.1.28. 2,3-Di(1-methylethoxy)-6-methylcyclopenta[b]quinolin-1-one (**16c**)*

Reaction of **15c** (185 mg, 0.43 mmol) in EtOAc/HCl (3:2, 3 M aq HCl, 25 mL), as described for **7** (ambient temperature, 2 d), gave

after workup and chromatography (hexanes/EtOAc, 8:2) **14c** (94 mg, 0.30 mmol, 70%) as a yellow-orange solid. Mp 78–80 °C; ^{1}H NMR δ 7.85 (s, 1H), 7.75 (s, 1H), 7.60 (d, 1H, J=8.1 Hz), 7.26 (dd, 1H, J=7.5, 1.4 Hz), 5.67 (heptet, 1H, J=6.1 Hz), 5.22 (heptet, 1H, J=6.1 Hz), 2.46 (s, 3H), 1.49 (d, 6H, J=6.1 Hz), 1.34 (d, 6H, J=6.1 Hz); ^{13}C NMR δ 187.3 (+), 158.5 (+), 156.5 (+), 149.2 (+), 141.2 (+), 137.8 (+), 129.5 (−), 129.4 (−), 128.5 (−), 126.2 (−), 125.3 (+), 122.8 (+), 74.9 (−), 73.7 (−), 22.9 (−), 22.7 (−), 21.7 (−); IR (CCl_4) 3000, 2950, 1715, 1645, 1155 cm^{-1}; HRMS calcd for $C_{19}H_{22}NO_3$ (M+H$^+$) 312.1600, found 312.1606.

3.1.29. 2,3-Di(1-methylethoxy)-6-aza-cyclopenta[b]quinolin-1-one (**16d**)

To a 0 °C cold solution of **15d** (273 mg, 0.66 mmol) in CH_2Cl_2 (15 mL) was slowly added trifluoroacetic acid (1.0 mL, 5.93 mmol). The reaction mixture was allowed to stir (0 °C, 4 h, then reflux, 1 h). The solvent was removed under reduced pressure and the residue was suspended in $NaHCO_3$ (aq saturated, 10 mL). The suspension was extracted with CH_2Cl_2 (100 mL) and the combined organic layers were, dried ($MgSO_4$), filtered, and the solvents were removed under reduced pressure. The crude product was purified by chromatography (hexanes/EtOAc, 1:1) to give **14d** (163 mg, 0.55 mmol, 84%) as an orange solid. Mp 73–76 °C; ^{1}H NMR δ 9.37 (s, 1H), 8.55 (d, 1H, J=5.3 Hz), 7.74 (s, 1H), 7.55 (d, 1H, J=5.2 Hz), 5.71 (heptet, 1H, J=6.1 Hz), 5.32 (heptet, 1H, J=6.1 Hz), 1.51 (d, 6H, J=6.1 Hz), 1.36 (d, 6H, J=6.1 Hz); ^{13}C NMR δ (150 MHz) 185.6 (+), 159.6 (+), 156.9 (+), 152.9 (−), 145.4 (−), 143.9 (+), 139.8 (+), 131.9 (+), 127.7 (+), 124.2 (−), 121.9 (−), 75.6 (−), 74.1 (−), 22.9 (−), 22.8 (−); IR ($CHCl_3$) 2985, 2348, 2254, 1704, 1094 cm^{-1}; HRMS calcd for $C_{17}H_{19}N_2O_3$ (M+H$^+$) 299.1396, found 299.1396.

3.1.30. 2,3-Di(1-methylethoxy)cyclopenta[b]quinolin-1-ol (**8**)

To a 0 °C cold solution of **7** (96 mg, 0.32 mmol) in THF (10 mL) was added $NaBH_4$ (130 mg, 3.44 mmol) and the resulting mixture was allowed to stir (3 h). Methanol (1.55 mL, 35.51 mmol) was added and the mixture was diluted with water (20 mL) and extracted with EtOAc (3×30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvents were removed under reduced pressure. The crude product was purified by chromatography (hexanes/EtOAc, 8:2) to afford **8** (81 mg, 0.27 mmol, 84%) as a pale yellow oil. ^{1}H NMR δ (600 MHz) 7.93 (d, 1H, J=7.8), 7.68 (s, 1H), 7.53 (m, 2H), 7.32 (dt, 1H, J=1.2, 7.8 Hz), 5.29 (heptet, 1H, J=5.4 Hz), 5.13 (heptet, 1H, J=6.0 Hz), 5.02 (br s, 1H), 2.75 (br s, 1H), 1.36 (d, 3H, J=5.4 Hz), 1.34 (d, 3H, J=6.0 Hz), 1.33 (d, 3H, J=6.0 Hz), 1.31 (d, 3H, J=6.0 Hz); ^{13}C NMR δ 159.8 (+), 151.5 (+), 148.2 (+), 133.8 (+), 131.1 (+), 128.7 (−), 128.5 (−), 128.1 (−), 127.9 (−), 126.4 (+), 124.8 (−), 72.9 (−), 72.3 (−), 68.7 (−), 22.91 (−), 22.90 (−), 22.64 (−), 22.61 (−); IR (CCl_4) 3277, 3061, 2979, 2935, 2360, 1317, 1104 cm^{-1}; HRMS calcd for $C_{18}H_{22}NO_3$ (M+H$^+$) 300.1600, found 300.1600.

3.1.31. 7-Chloro-2,3-di(1-methylethoxy)cyclopenta[b]quinolin-1-ol (**17a**)

Reaction of **16a** (80 mg, 0.27 mmol) with $NaBH_4$ (106 mg, 2.80 mmol), and methanol (1.30 mL, 29.58 mmol) in THF (10 mL), as described for **8** (3 h), gave after workup and chromatography (hexanes/EtOAc, 8:2) **15a** (55 mg, 0.18 mmol, 68%) as a light yellow oil. ^{1}H NMR δ (600 MHz) 7.83 (d, 1H, J=9.0 Hz), 7.58 (s, 1H), 7.51 (d, 1H, J=1.8 Hz), 7.47 (dd, 1H, J=8.4, 2.4 Hz), 5.24 (heptet, 1H, J=6.0 Hz), 5.15 (heptet, 1H J=6.0 Hz), 5.01 (br s, 1H), 2.75 (br s, 1H), 1.40 (d, 3H, J=6.0 Hz), 1.36 (d, 3H, J=6.0 Hz), 1.35 (d, 3H, J=6.0 Hz), 1.34 (d, 3H, J=6.0 Hz); ^{13}C NMR δ (150 MHz) 160.3 (+), 152.2 (+), 146.8 (+), 133.8 (+), 132.2 (+), 130.4 (−), 130.1 (−), 129.6 (+), 127.3 (−), 127.2 (−), 126.9 (+), 73.4 (−), 72.7 (−), 68.8 (−), 23.17 (−), 23.15 (−), 22.87 (−), 22.83 (−); IR ($CHCl_3$) 3366 (br.), 2976, 1313, 1104; HRMS calcd for $C_{18}H_{21}NO_3Cl$ (M+H$^+$) 334.1210, found 334.1205.

3.1.32. 2,3-Di(1-methylethoxy)-6-methoxycyclopenta[b]quinolin-1-ol (**17b**)

Reaction of **16b** (61 mg, 0.19 mmol), $NaBH_4$ (80 mg, 2.11 mmol), and methanol (0.91 mL, 20.95 mmol) in THF (10 mL), as described for **7** (overnight), gave after workup and chromatography (hexanes/EtOAc, 8:2) **15b** (43 mg, 0.13 mmol, 70%) as a yellow oil. ^{1}H NMR δ 7.78 (s, 1H), 7.56 (d, 1H, J=8.9 Hz), 7.40 (d, 1H, J=2.4 Hz), 7.03 (dd, 1H, J=8.7, 2.6 Hz), 5.34 (heptet, 1H, J=5.7 Hz), 5.12 (heptet, 1H, J=5.9 Hz), 5.06 (d, 1H, J=6.9 Hz), 3.92 (s, 3H), 1.38 (m, 12H); ^{13}C NMR δ 160.2 (+), 159.9 (+), 151.1 (+), 149.7 (+), 133.9 (+), 128.8 (+), 127.9 (−), 120.9 (+), 116.6 (−), 107.9 (−), 72.9 (−), 72.3 (−), 68.6 (−), 55.4 (−), 22.9 (−), 22.6 (−); IR (CCl_4) 3412, 2977, 2931, 1105 cm^{-1}; HRMS calcd for $C_{19}H_{24}NO_4$ (M+H$^+$) 330.1705, found 330.1707.

3.1.33. 2,3-Di(1-methylethoxy)-6-methylcyclopenta[b]quinolin-1-ol (**17c**)

Reaction of **16c** (94 mg, 0.30 mmol), $NaBH_4$ (118 mg, 2.80 mmol), and methanol (1.44 mL, 33.2 mmol) in THF (10 mL), as described for **8** (overnight), gave after workup and chromatography (hexanes/EtOAc, 8:2) **15c** (66 mg, 0.21 mmol, 70%) as a faint yellow oil. ^{1}H NMR δ 7.79 (s, 2H), 7.58 (d, 1H, J=7.9 Hz), 7.21 (d, 1H, J=9.1 Hz), 5.39 (heptet, 1H, J=6.1 Hz), 5.15, (heptet, 1H, J=6.1 Hz), 5.04 (d, J=5.1 Hz), 2.51 (s, 3H), 1.38 (m, 12H); ^{13}C NMR δ 159.6 (+), 151.4 (+), 148.1 (+), 138.8 (+), 133.7 (+), 130.2 (+), 127.9 (−), 127.7 (−), 127.5 (−), 126.6 (−), 124.1 (+), 72.8 (−), 72.2 (−), 68.5 (−), 22.9 (−), 22.6 (−), 21.6 (−); IR (CCl_4) 3400, 2978, 2933, 1105 cm^{-1}; HRMS calcd for $C_{19}H_{24}NO_3$ (M+H$^+$) 314.1756, found 314.1759.

3.1.34. 2,3-Di(1-methylethoxy)-6-azacyclopenta[b]quinolin-1-ol (**17d**)

To a 0 °C cold solution of **16d** (414 mg, 3.36 mmol) in THF/MeOH (1:1, 10 mL) was added $NaBH_4$ (110 mg, 2.91 mmol). The reaction was stirred for 10 min at 0 °C and subsequently quenched with water. The mixture was quickly extracted with ethyl acetate (3×50 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and the solvents were removed under reduced pressure. The residue was purified by chromatography (hexanes/EtOAc, 3:7) to give **15d** (212 mg, 0.71 mmol, 51%) as a white solid that quickly turned yellow. Tentative NMR assignments from a rapidly decomposing compound. ^{1}H NMR δ 9.25 (s, 1H), 8.39 (d, 1H, J=5.3 Hz), 7.77 (s, 1H), 7.46 (d, 1H, J=5.5 Hz), 5.25 (overlapping heptet, 2H), 5.07 (s, 1H), 1.46–1.32 (m, 12H); ^{13}C NMR δ 161.5 (+), 153.6 (+), 151.6 (−), 143.4 (+), 142.2 (−), 136.3 (+), 133.5 (+), 130.3 (+), 126.1 (−), 120.7 (−), 73.4 (−), 72.5 (−), 68.3 (−), 28.2 (−), 22.9 (−), 22.6 (−).

3.1.35. (2-(1-Hydroxy-2-(1-methylethoxy)-3-methyl-4-oxo-cyclobut-2-enylethynyl)-phenyl)-carbamic acid 1,1-dimethylethyl ester (**18**)

Reaction of **1** (406 mg, 1.87 mmol), *n*-BuLi (1.6 M in THF, 2.90 mL, 4.67 mmol), and 3-methyl-4-(1-methylethoxy)-3-cyclobutene-1,2-dione[23] (290 mg, 1.88 mmol) in THF (30 mL total), as described for **2** (30 min), gave after workup and chromatography (hexanes/EtOAc, 8:2) **16** (33 mg, 0.89 mmol, 48%) as a yellow solid and **2** (81 mg, 0.37 mmol). ^{1}H NMR δ 8.11 (d, 1H, J=8.5 Hz), 7.33 (dt, 1H, J=1.6, 7.5 Hz), 7.21 (br s, 1H), 6.93 (dt, 1H, J=7.5, 1.0 Hz), 5.11 (heptet, 1H, J=6.3 Hz), 4.24 (br s, 1H), 1.71 (s, 1H), 1.53 (s, 9H), 1.49 (d, 6H, J=6.3 Hz); ^{13}C NMR δ 187.6 (+), 180.1 (+), 152.5 (+), 139.7 (+), 132.1 (−), 130.1 (−), 124.3 (+), 122.1 (−), 118.0 (−), 110.0 (+), 90.1 (+), 84.8 (+), 83.2 (+), 80.9 (+), 78.5 (−), 28.2 (−), 22.9 (−), 22.6 (−), 6.5 (−); IR (CCl_4) 3410, 2980, 2380, 1735, 1157 cm^{-1}; HRMS calcd for $C_{21}H_{26}NO_5$ (M+H$^+$) 372.1811, found 372.1808.

3.1.36. E- and Z-(2-(3-(1-Methylethoxy)-4-methyl-2,5-dioxo-3-cyclopenten-1-ylmethyl)phenyl)-carbamic acid 1,1-dimethylethyl ester (**19**)

Reaction of **16** (310 mg, 0.83 mmol) in 1,2-dichloroethane (20 mL), as described for **6** (reflux, 18 h), gave after chromatography

(hexanes/EtOAc, 8:2) an inseparable mixture of *E*- and *Z*-**19** (127 mg, 0.34 mmol, 8.3:1 ratio, 41%) as a yellow solid. Mp 132–136 °C; ^{1}H NMR δ 8.05 (dd, 1H, *J*=7.9, 1.6 Hz), 7.76 (d, 1H, *J*=8.3 Hz), 7.48 (s, 1H), 7.43 (dt, 1H, *J*=7.7, 1.6 Hz), 7.16 (t, 1H), 6.63 (br s, 1H), 5.73 (heptet, 1H, *J*=6.1 Hz), 1.99 (s, 3H), 1.51 (s, 9H), 1.41 (d, 6H, *J*=5.9 Hz); ^{13}C NMR δ (150 MHz) 189.3 (+), 188.2 (+), 164.8 (+), 152.9 (+), 138.1 (+), 137.5 (+), 132.7 (−), 132.2 (−), 131.9 (−), 131.5 (−), 127.9 (+), 123.7 (−), 122.6 (−), 80.9 (+), 74.8 (−), 74.7 (−), 28.2 (−), 23.2 (−), 7.2 (−); IR (CCl_4) 3400, 2978, 2931, 2359, 1733, 1156 cm^{-1}; HRMS calcd for $C_{21}H_{26}NO_5$ (M+H$^+$) 372.1811, found 372.1813.

3.1.37. 2-(1-Methylethoxy)-3-methylcyclopenta[b]quinolin-1-one (*20*)

Reaction of **19** (107 mg, 0.29 mmol) in EtOAc/HCl (3:2, 3 M aq HCl, 25 mL), as described for **7** (ambient temperature, 2 d), gave after workup and chromatography (hexanes/EtOAc, 8:2) **18** (22 mg, 0.087 mmol, 30%) as a yellow-orange solid. Mp 78–80 °C; ^{1}H NMR δ 7.94 (d, 1H, *J*=8.3 Hz), 7.93 (s, 1H), 7.71 (d, 1H, *J*=8.3 Hz), 7.63 (t, 1H, *J*=7.1 Hz), 7.39 (t, 1H, *J*=7.5 Hz), 5.28 (heptet, 1H, *J*=6.1 Hz), 2.19 (s, 3H), 1.34 (d, 6H, *J*=6.1 Hz); ^{13}C NMR δ (150 MHz) 189.4 (+), 163.9 (+), 156.1 (+), 150.1 (+), 139.0 (+), 131.3 (−), 130.5 (−), 129.6 (−), 128.1 (−), 127.5 (+), 126.6 (−), 123.3 (+), 73.9 (−), 23.2 (−), 8.3 (−); IR (CCl_4) 2988, 2254, 1707, 1636, 1102 cm^{-1}; HRMS calcd for $C_{16}H_{16}NO_2$ (M+H$^+$) 254.1181, found 254.1189.

3.1.38. 2-(1-Methylethoxy)-3-methylcyclopenta[b]quinolin-1-ol (*21*)

Reaction of **20** (90 mg, 0.36 mmol), $NaBH_4$ (140 mg, 3.70 mmol), and methanol (1.7 mL, 39.1 mmol) in THF (10 mL), as described for **8** (3 h), gave after workup and chromatography (hexanes/EtOAc) **19** (50 mg, 0.20 mmol, 55%) as a yellow oil. Tentative NMR assignments from a rapidly decomposing compound: ^{1}H NMR δ (600 MHz) 7.76 (d, 1H, *J*=8.4 Hz), 7.53 (dt, 1H, *J*=7.8, 2.4 Hz), 7.24 (dt, 1H, *J*=8.4, 1.8 Hz), 7.15 (dd, 1H, *J*=7.8, 1.8 Hz), 6.99 (s, 1H), 5.01 (heptet, 1H, *J*=5.4 Hz), 4.97 (t, 1H, *J*=1.8 Hz), 1.91 (d, 3H, *J*=1.2 Hz), 1.46 (d, 3H, *J*=6.6 Hz), 1.30 (d, 3H, *J*=6.6 Hz); ^{13}C NMR δ 167.3 (+), 164.7 (+), 147.7 (+), 132.1 (+), 128.8 (−), 128.3 (−), 127.5 (−), 127.4 (+), 126.3 (+), 124.1 (−), 115.8 (+), 72.7 (−), 69.6 (−), 23.3 (−), 23.1 (−), 6.9 (−); HRMS calcd for $C_{16}H_{18}NO_2$ (M+H$^+$) 256.1338, found 256.1335.

Acknowledgements

This work was supported by research grants from the National Science Foundation (CHE 0611096), the National Institute of General Medical Sciences, National Institutes of Health (RO1 GM57416), and the American Chemical Society Petroleum Research Fund (40665-AC1). NSF-EPSCoR (Grant #1002165R) is gratefully acknowledged for the funding of a 600 MHz Varian Inova NMR and a Thermo-Finnegan LTQ-FT Mass Spectrometer and the NMR and MS facilities in the C. Eugene Bennett Department of Chemistry at West Virginia University.

References and notes

1. Foland, L. D.; Karlsson, O.; Perri, S. T.; Schwabe, R.; Xu, S. L.; Patil, S.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 975–989.
2. For a review of cyclobutane derivatives in synthesis, see: Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485–1537.
3. Wipf, P.; Hopkins, C. R.; Phillips, E. O.; Lazo, J. S. *Tetrahedron* **2002**, *58*, 6367–6372.
4. Boullais, C.; Rannou, C.; Reveillere, E.; Mioskowski, C. *Eur. J. Org. Chem.* **2000**, 723–727.
5. Wipf, P.; Hopkins, C. R. *J. Org. Chem.* **1999**, *64*, 6881–6887.
6. Hergueta, A. R.; Moore, H. W. *J. Org. Chem.* **1999**, *64*, 5979–5983.
7. Sullivan, R. W.; Coghlan, V. M.; Munk, S. A.; Moore, H. W.; Reed, M. W. *J. Org. Chem.* **1994**, *59*, 2276–2278.
8. Liebeskind, L. S.; Foster, B. S. *J. Am. Chem. Soc.* **1990**, *112*, 8612–8613.
9. Karabelas, K.; Moore, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 5372–5373.
10. For examples of alkylidenecyclopentenediones, see: Zora, M.; Kokturk, M.; Eralp, T. *Tetrahedron* **2006**, *62*, 10344–10351 and references therein.
11. Liebeskind, L. S.; Mitchell, D.; Foster, B. S. *J. Am. Chem. Soc.* **1987**, *109*, 7908–7910.
12. Aoyama, Y.; Konoike, T.; Kanda, A.; Naya, N.; Nakajima, M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1695–1697.
13. Yamamoto, Y.; Ohno, M.; Eguchi, S. *Tetrahedron Lett.* **1995**, *36*, 5539–5542.
14. Cheng, C. C.; Yan, S. J. *Org. React.* **1982**, *28*, 37–201.
15. Malecki, N.; Carato, O.; Rigo, B.; Goossens, J.-F.; Houssin, R.; Bailly, C.; Henichart, J.-P. *Bioorg. Med. Chem.* **2004**, *12*, 641–647.
16. Zhu, X. Y.; Mardenborough, L. G.; Li, S.; Khan, A.; Fan, P.; Jacob, M.; Khan, S.; Walker, L.; Ablordeppy, S. Y. *Bioorg. Med. Chem.* **2007**, *15*, 686–695.
17. Sakamoto, T.; Kondo, Y.; Uchiyama, M.; Yamanaka, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1941–1942.
18. Fisher, T. H.; Meierhoefer, A. W. *J. Org. Chem.* **1978**, *43*, 220–224.
19. Crous, R.; Dwyer, C.; Holzapfel, C. W. *Heterocycles* **1999**, *51*, 721–726.
20. Wensbo, D.; Annby, U.; Gronowitz, S. *Tetrahedron* **1995**, *51*, 10323–10342.
21. McDonald, F. E.; Chatterjee, A. K. *Tetrahedron Lett.* **1997**, *38*, 7687–7690.
22. Ishizaki, M.; Zyo, M.; Kasama, Y.; Niimi, Y.; Hoshino, O.; Nishitani, K.; Hara, H. *Heterocycles* **2003**, *60*, 2259–2271.
23. Liebeskind, L. S.; Fengl, R. W.; Wirtz, K. R.; Shawe, T. T. *J. Org. Chem.* **1988**, *53*, 2482–2488.