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Palladium Catalysed Tandem Cyclisation–Anion Capture. Part 6:[1] Synthesis of Sugar, Nucleoside, Purine, Benzodiazepinone and β-lactam Analogues via Capture of in situ Generated Vinylstannanes

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Abstract—The regioselective palladium catalysed hydrostannylation of alkynes bearing a β-heteroatom affords mainly α-vinyltin(IV) compounds that are used as terminating species in palladium catalysed cyclisation–anion capture processes. The pharmacophore attached to the alkyne moiety permits the synthesis of sugars, nucleosides, purines, benzodiazepinones and β-lactams analogues in good yields.

Organotin(IV) reagents ($RSnBu_3$) are, in general, readily prepared, stable to air and moisture and capable of a wide variation of the R group. The Stille coupling reaction[2] is the most important and versatile transformation involving such species. We have shown that organotin(IV) reagents are excellent anion capture agents in our intramolecular[1,3] and intermolecular[4] palladium catalysed cascade cyclisation–anion capture processes. Our published work on the intermolecular version of these processes[4] employs previously prepared or commercially available organotin(IV) reagents, whilst the intramolecular version can be achieved by in situ generated vinyltin species via the ready Pd(0) catalysed hydrostannylation of alkynes.[3,5] The latter cascade processes also permit easy access to the unexplored intermolecular sp^2–sp^3 Stille coupling. Moreover, this synthetic sequence permits activation of a wide variety of pharmacophores by attachment of the tributyltin(IV) moiety.

These features prompted us to prepare propargylic derivatives of a range of key pharmacophores which would serve, after the corresponding Pd(0) catalysed hydrostannylation reaction, as terminating species in our palladium(0) catalysed cascades.[4]

Initially, we therefore prepared a series of *O*- and *N*-propargylic derivatives of protected sugars (**2a**, **2b**), nucleosides (**2c**, **2d**), purines (**2e**, **2f**), benzodiazepinones (**2g**) and β-lactam (**2h**) (Scheme 1).

The alkynes **2a**–**h** have at least one heteroatom located β to the triple bond to take advantage of the well known regioselectivity of the palladium(0) catalysed hydrostannylation in the presence of a β- or γ-heteroatom.[3,5] Thus **2a**–**h** are typical anion capture agents for our methodology and these, together with appropriate reactants containing starter/relay species such as **4a**–**c**, allow the catalytic cascade cyclisation–anion capture to proceed (Scheme 2).

The palladium(0) catalysed hydrostannylation of **2a**–**h** was performed in toluene at 0°C for 1 h using tributyltin hydride and a catalyst comprised of 5 mol% $Pd_2(dba)_3$ and 20 mol% tris(2-furyl)phosphine. When the reaction was judged complete (TLC monitoring) the ratio of vinyltributylstannanes **3a**:**3b** was determined by ^1H NMR. In all cases **3a** was the major regioisomer (Scheme 3 and Table 1). Aryl iodide **4** was then added and the temperature increased to 110°C to initiate a 5-*exo*-*trig* cyclisation followed by sp^3–sp^2 Stille coupling of **5** with the appropriate α-vinylstannane **3a** (Scheme 3). The selected catalyst gave the best results for this coupling process.[3,6] Other catalysts [$Pd(PPh_3)_4$, $Pd(AcO)_2/PPh_3$, $Pd_2(dba)_3/AsPh_3$)],[6] solvents (NMP, acetonitrile, DMF) and additives (CuI,[7] CuCl,[8] CuO[9]) were tested without any noticeable improvement of yield.

The coupling reaction of the corresponding β-vinylstannanes **3b** furnished small amounts of **7** that were discarded during isolation of the desired major compounds **6**.

Keywords: cascade reactions; palladium catalysis; hydrostannylation; Stille coupling; cyclisation.
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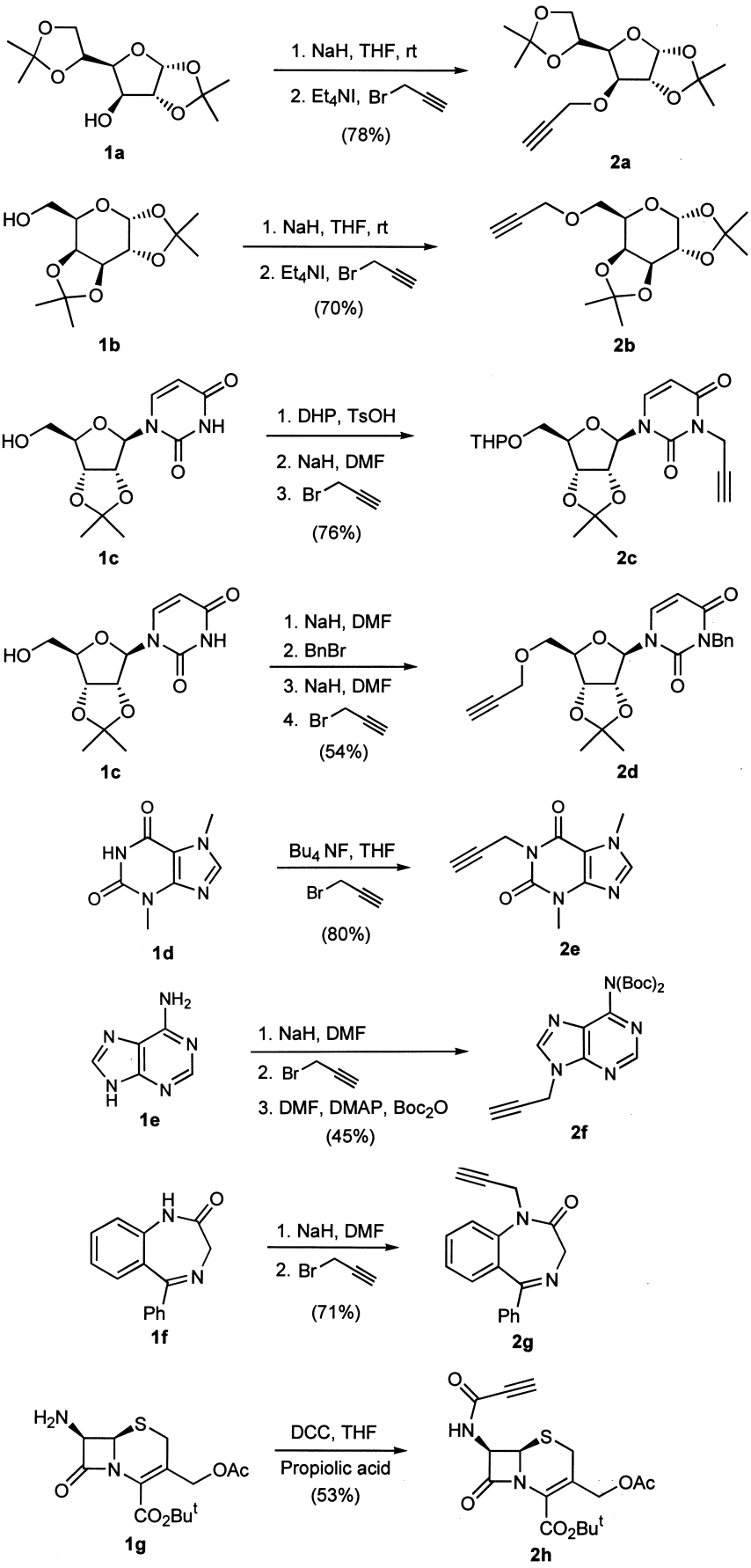
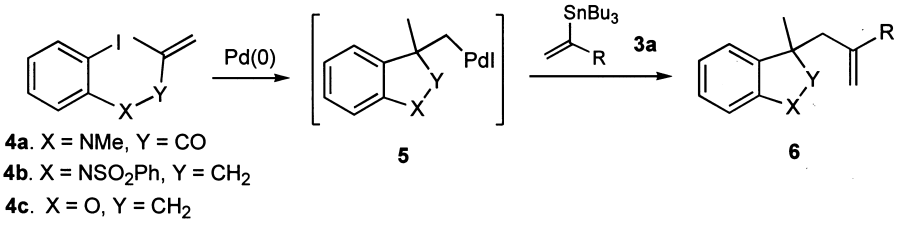
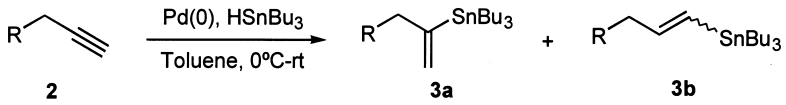

1. NaH, THF, rt
2. Et4NI, Br
(78%)
1a
2a
1. NaH, THF, rt
2. Et4NI, Br
(70%)
1b
2b
1. DHP, TsOH
2. NaH, DMF
3. Br
(76%)
1c
2c
1. NaH, DMF
2. BnBr
3. NaH, DMF
4. Br
(54%)
1c
2d
Bu4 NF, THF
Br
(80%)
1d
2e
1. NaH, DMF
2. Br
3. DMF, DMAP, Boc2O
(45%)
1e
2f
1. NaH, DMF
2. Br
(71%)
1f
2g
DCC, THF
Propiolic acid
(53%)
1g
2h

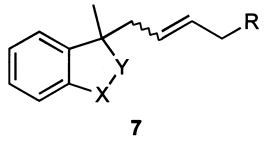
Scheme 1.



Scheme 2.



Scheme 3.



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In all cases, except when **2e**, **2f** and **2g** were employed, a 1:1 mixture of diastereoisomers was obtained according to ^{1}H NMR data. A similar ratio was observed in the earlier stages of the reaction, even at lower temperatures.

Selective deprotection of the THP group of the primary alcohol in the product arising from **2c** and **4b** to afford **6e** was achieved after treatment of the crude product with 0.2N hydrochloric acid/THF at room temperature for 1 day. However, the same deprotection was not possible in **6f** in the product arising from **2c** and **4c**. In this case, to afford **6f**, total deprotection of primary and secondary alcohols was carried out by treatment with 2N hydrochloric acid/THF at room temperature for 1 day.

Finally, *N*-propargylbenzodiazepinone **2g** needed 2 mol equiv. of tributyltin hydride in order to obtain a good yield of corresponding vinylstannanes and also 2 mol equiv. of **4b** and **4c** to generate products **6m** and **6n** in good yield.

In conclusion, a wide variety of interesting compounds can be accessed through a simple one-pot cascade protocol proceeding via palladium(0) catalysed hydrostannylation followed by cyclisation–anion capture.

Experimental

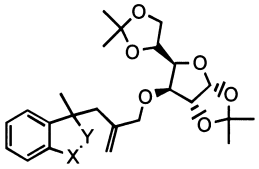
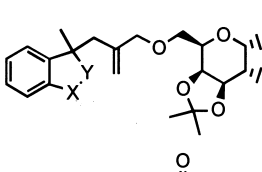
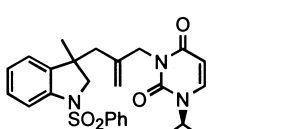
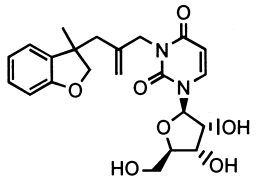
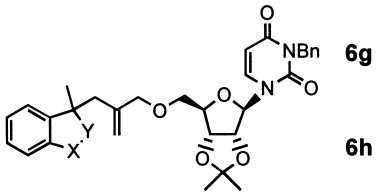
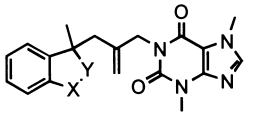
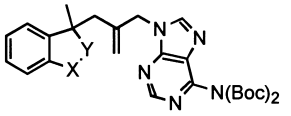
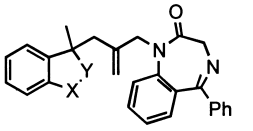
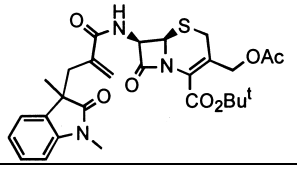
Melting points were determined on a Koffler hot-stage apparatus and are uncorrected. Mass spectral data were obtained from a VG Autospec mass spectrometer operating at 70 eV. Nuclear magnetic resonance spectra were recorded on Bruker QE300 and AM 400 machines operating at 300 and 400 MHz, respectively. Unless otherwise specified, deuterochloroform was used as solvent with tetramethylsilane as internal standard. Microanalyses were obtained using a Carlo Erba MOD 11016 instrument. Thin layer chromatography was carried out on Whatman PESIL G/UV polyester plates coated with a 0.2 mm layer of silica-gel 60 (Merck 9385). Column chromatography was performed with silica gel 60 (Merck 9385). Petroleum ether refers to the fraction with bp 40–60°C. Anhydrous DMF was commercially available (Aldrich), THF and toluene were sodium dried under a nitrogen atmosphere and *n*-hexane was distilled prior to use.

Synthesis of Alkynes (2)

2a. Sodium hydride (60% dispersion in mineral oil, 720 mg, 18 mmol) was added to a stirred solution of diacetone-D-glucose (5 g, 19 mmol) in dry THF (20 ml) and the mixture was stirred and boiled under reflux for 2 h. Tetraethylammonium iodide (1 g, 3.8 mmol, 20%) and a solution of propargyl bromide (80% solution in toluene, 4 g, 27 mmol) were then added and the mixture stirred at room temperature for 16 h, diluted with Et_2O (100 ml) and washed with water. The organic layer was separated, dried ($MgSO_4$), filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography eluting with 70:30 v/v hexane/ethyl acetate affording **2a** as a pale yellow oil (4.2 g, 78%). (Found: C, 60.10; H, 7.4. $C_{15}H_{22}O_6$ requires: C, 60.40; H, 7.5%). δ 1.32, 1.36, 1.43, 1.50 (4×s, 12H, 4×CH_3), 2.52 (t, J=2.0 Hz, 1H, CCH), 3.95–4.17 (m, 5H, 3×CCHO and $CH_2C{\equiv}C$), 4.28 (m, 2H, CH_2O),4.68 (d, J=3.5 Hz, 1H, CHO), and 5.92 (d, J=3.5 Hz, OCHO). *m/z* (%) 299 (M^++1, 4), 298 (M^+, 6), 283 (95), and 101 (100).

2b. Sodium hydride (60% dispersion in mineral oil, 308 mg, 7.7 mmol) was added slowly to a stirred solution of 1,2:3,4-di-*O*-isopropylidenegalactopyranose (194 mg, 7.7 mmol) in dry THF (10 ml) and the mixture stirred and heated under reflux for 2 h. Tetraethylammonium iodide (396 mg, 3.8 mmol, 20%) and a solution of propargylbromide (80% solution in toluene, 4 g, 27 mmol) were then added and the reaction stirred at room temperature for 16 h. Work up as above afforded **2b** (178 mg, 70%) as colourless prisms, mp 55–56°C. (Found: C, 60.45; H, 7.5. $C_{15}H_{22}O_6$ requires: C, 60.4; H, 7.5%). δ 1.28, 1.29, 1.40, 1.49 (4×s, 12H, 4×CH_3), 2.40 (t, J=2.4 Hz, 1H, CCH), 3.65 (m, 2H, CH_2O), 3.95 (m, 1H, CHOCO), 4.17 (dd, J=2.3 Hz, 2H, $C{\equiv}CCH_2O$), 4.21

Table 1. Cascade hydrostannylation–cyclisation–anion capture for the synthesis of **6a–o**

Alkyne	Aryl Iodide	$HSnBu_3$:**4** (equiv.)	**3a:3b**[a]	Time (h)	Product	Yield (%)[b]
2a	**4a**	1:1	80:20	2	 **6a**	(64)[c]
2a	**4c**	1:1	80:20	2	 **6b**	(66)[c]
2b	**4a**	1:1	80:20	3	**6c**	(65)[c]
2b	**4c**	1:1	80:20	3	 **6d**	(63)[c]
2c	**4b**	1:1	85:15	2	**6e**	(59)[c,d]
2c	**4c**	1:1	85:15	2	 **6f**	(59)[c,e]
2d	**4b**	1:1	70:30	2[f]	 **6g**	(60)[c]
2d	**4c**	1:1	70:30	2[f]	**6h**	(60)[c]
2e	**4a**	1:1	90:10	2	 **6i**	(67)
2e	**4c**	1:1	90:10	2	**6j**	(68)
2f	**4b**	1:1	90:10	4	 **6k**	(63)
2f	**4c**	1:1	90:10	4	**6l**	(66)
2g	**4b**	2:2	90:10	2	 **6m**	(72)
2g	**4c**	2:2	90:10	2	**6n**	(80)
2h	**4a**	1:1	(5:5	4	 **6o**	(64)[c]

[a] Calculated by ^{1}H NMR.
[b] Isolated compounds, based on **2**, after column chromatography.
[c] Obtained as a 1:1 mixture of diastereomers (^{1}H NMR).
[d] Isolated compound after treatment with 0.2 M HCl/THF, rt, 1 days.
[e] Isolated compound after treatment with 2 M HCl/THF, rt, 1 days.
[f] The cyclisation–anion capture reaction was carried out at 90°C.

(q, J=7.4, 1.8 Hz, 1H, CHO), 4.27 (q, J=5.0, 2.5 Hz, 1H, CHO), 4.56 (q, J=2.5, 7.9 Hz, 1H, CHO), and 5.48 (d, J=5.0 Hz, 1H, OCHO). m/z (%) 299 (M^++1, 4), 298 (M^+, 10), 283 (95), and 101 (100).

2c. A solution of 2,3-*O*-isopropylideneuridine (2.84 g, 10 mmol), 3,4-dihydro-2*H*-pyran (1.0 ml, 11 mmol) an *p*-toluenesulfonic acid (90 mg) in THF (40 ml) was stirred at room temperature for 1 days. The solvent was removed under reduced pressure and the product was *N*-alkylated with propargyl bromide following the same procedure as that described for the synthesis of **2a**, furnishing **2c** (3.09 g, 76%) as a colourless sticky oil. (Found: C, 58.9; H, 6.3; N, 6.5. $C_{20}H_{26}N_2O_7$ requires: C, 59.1; H, 6.45; N, 6.85%). δ (1:1 mixture of diastereoisomers) 1.37, 1.38 (2×s, 3H, CH_3CO), 1.05–1.82 (m with s at 1.60, 9H, $CH_2CH_2CH_2CO$, CH_3CO), 2.10 (t, J=2.3 Hz, 1H, C≡CH), 3.51–3.61 (m, 2H, CH_2CH_2O), 3.68 (dd, J=11.0, 2.3 Hz, 1H, CH_2CHOCN), 3.85 (m, 2H, CH_2CHOCN), 3.98 (dd, J=11.0, 2.3 Hz, 1H, CH_2CHOCN), 4.44–4.87 (m, 6H, CH_2C≡C, 2×C*H*OCCH$_3$, OCHO and C*H*OCHN), 5.75, 5.78 (2×d, J=8.2 Hz, 1H, *H*C═CHN), 5.95 (d, J=2.7 Hz, 1H, OCHN), 7.69 and 7.75 (2×d, J=8.2 Hz, 1H, CH═C*H*N). m/z (%) 406 (M^+, 0.3), 150 (23), 88 (21), 86 (71), 85 (82), 84 (77), 71 (62), 57 (39), 56 (36), 55 (43), 47 (25), 43 (100), 42 (52), 41 (58) and 39 (32).

2d. A solution of 2,3-*O*-isopropylideneuridine (1.42 g, 5 mmol) in dry DMF (15 ml) was treated with sodium hydride (60% dispersion in mineral oil, 200 mg, 5 mmol), the reaction mixture was stirred at room temperature for 30 min when benzyl bromide (655 μl, 5.5 mmol) was added and stirring continued at room temperature for 1 h. After the usual work-up, the residue was chromatographed (SiO_2) affording *N*-benzyluridine (1.23 g, 73%). *O*-Alkylation was carried out as described for the synthesis of **2a** but in this case, the reaction mixture was stirred at room temperature for 1 day. Compound **2d** was isolated as a colourless sticky oil (740 mg, 54%). (Found: C, 64.2; H, 6.0; N, 6.55. $C_{22}H_{24}N_2O_6$ requires: C, 64.05; H, 5.85; N, 6.8%). δ 1.36, 1.58 (2s, 6H, 2×CH_3), 2.45 (t, J=2.2 Hz, 1H, C≡CH), 3.68 (dd, J=10.3, 3.8 Hz, 1H, OCH_2CO), 3.81 (dd, J=10.3, 2.5 Hz, 1H, OCH_2CO), 4.12, 4.18 (2×dd, J=16.0, 2.2 Hz, 2H, CH_2C≡C), 4.43 (ddd, J=3.8, 2.5, 2.5 Hz, 1H, CH_2CHO), 4.77 (dd, J=6.4, 2.0 Hz, 1H, OC*H*CHN), 4.80 (dd, J=6.4, 2.5 Hz, 1H, OC*H*CHN), 4.80 (dd, J=6.4, 2.5 Hz, 1H, OC*H*CHCH$_2$), 5.06, 5.14 (2×d, J=13.7 Hz, 2H, CH_2N), 5.76 (d, J=8.1 Hz, 1H, NCH═C*H*), 5.87 (d, J=2.0 Hz, 1H, OCHN), 7.22–7.49 (m, 5H, ArH), and 7.51 (d, J=8.1 Hz, 1H, NC*H*═CH). m/z (%) 412 (M^+, 28), 397 (25), 337 (22), 211 (31), 203 (24), 202 (43), 129 (53), 96 (45), 95 (20), 91 (100), 85 (30), 69 (52), 68 (36), 59 (30), 55 (32), 43 (52), 41 (39) and 39 (60).

2e. A solution of propargyl bromide in (80% solution in toluene, 2.4 g, 16.6 mmol) was added to a solution of 3,7-dimethylxanthine **1d** (1.5 g, 8.3 mmol) and tetra-*n*-butylammonium fluoride (1 M solution in THF, 16.6 ml) in dry THF (50 ml) and the mixture was stirred at room temperature for 16 h. The mixture was concentrated in vacuo, the residue dissolved in dichloromethane and washed with water. The organic layer was dried ($MgSO_4$), filtered and the filtrate concentrated in vacuo. Crystallisation of the residue from methanol yielded **2e** (1.45 g, 80%) as colourless needles, mp 209°C. (Found: C, 54.85; H, 4.35; N, 25.7. $C_{10}H_{10}N_4O_2$ requires: C, 55.05; H, 4.6, N, 25.7%). δ 2.19 (t, J=2.5 Hz, 1H, C≡CH), 3.59 (s, 3H, *3*-CH_3), 4.00 (s, 3H, *7*-CH_3), 4.78 (t, J=2.5 Hz, 2H, *5*-NCH_2), and 7.55 (s, 1H, ArH). m/z (%) 218 (M^+, 100), 190 (17), and 135 (10).

2f.[10] Sodium hydride (60% dispersion in mineral oil, 400 mg, 10 mmol) was added portionwise to a stirred suspension of adenine (1.35 g, 10 mmol) in dry DMF (40 ml) at 0°C and stirring continued at room temperature for 1 h. Propargyl bromide (80% solution in toluene, 2.23 ml, 20 mmol) was then added and stirring continued for 16 h. DMF was evaporated under reduced pressure and the residue partitioned between ethyl acetate (50 ml) and water (50 ml). The organic layer was separated, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was dissolved in DMF (100 ml), DMAP (3.65 g, 30 mmol) and di-*tert*-butyldicarbonate (6.5 g, 30 mmol) were added and the resulting mixture was stirred at room temperature for 1 days. After the usual work-up the residue was chromatographed eluting with 1:1 v/v *n*-hexane/ether affording product **2f** (1.76 g, 48%) as colourless needles from *n*-hexane/ether, mp 112–113°C. (Found: C, 57.9; H, 6.2; N, 18.8. $C_{18}H_{23}N_5O_4$ requires: C, 57.9; H, 6.2; N, 18.75%). δ 1.46 (s, 18H, 6×CH_3), 2.61 (t, J=2.3 Hz, 1H, C≡CH), 5.08 (d, J=2.3 Hz, 2H, CH_2C≡C), 8.32 (s, 1H, H-2), and 8.89 (s, 1H, H-8). m/z (%) 373 (M^+, 47), 274 (51), 218 (45), 200 (63), 174 (65), 173 (100), 146 (31), 144 (21), 57 (98), 41 (38) and 39 (20).

2g. Benzodiazepinone **1f**[11] was alkylated by the same experimental procedure as that used for the synthesis of **2a**. Compound **2g** (73%) was obtained as colourless needles from *n*-hexane/ether, mp 46–48°C. (Found: C, 78.6; H, 4.9; N, 10.25. $C_{18}H_{14}N_2O$ requires: C, 78.8; H, 5.1; N, 10.2%). δ 2.28 (t, J=2.4 Hz, 1H, C≡CH), 3.81 (d, J=10.6 Hz, 1H, CH_2CO), 4.51, 4.69 (2×dd, J=17.4, 2.4 Hz, 2H, CH_2C≡C), 4.82 (d, J=10.6 Hz, 1H, CH_2CO) and 7.21–770 (m, 9H, ArH). m/z (%) 274 (M^+, 99), 273 (93), 247 (48), 246 (100), 234 (25), 205 (33), 91 (39), 77 (27) and 39 (25).

2h.[12] Propiolic acid (62 mg, 0.89 mmol) was added dropwise to a solution of cephalosporin **1g** (300 mg, 0.9 mmol) and *N*,*N*′-dicyclohexylcarbodiimide (206 mg, 1 mmol) in of dry THF (2 ml) at 0°C and the mixture was stirred for 16 h at room temperature. The solvent was removed in vacuo, the residue dissolved in dichloromethane and washed with water. The organic layer was separated, dried ($MgSO_4$), filtered and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography eluting with 70:30 v/v hexane/ethyl acetate to yield **2h** (180 mg, 53%) as light brown prisms, mp 76°C. (Found: C, 53.5; H, 5.2; N, 7.3; S, 8.3. $C_{17}H_{20}N_2O_6S$ requires: C, 53.6; H, 5.3, N, 7.3; S, 8.4%). δ 1.52 (s, 9H, *t*-Bu), 2.07 (s, 3H, $OCOCH_3$), 3.03 (s, 1H, C≡CH), 3.37 (d, J=18.5 Hz, 1H, *2*-H_a), 3.56 (d, J=18.5 Hz, 1H, *2*-$H_{b)}$, 4.79 (d, J=18.4 Hz, 1H, *2*-CH_aOAc), 4.96 (d, J=4.8 Hz, 1H, *8*-H), 5.10 (d, J=18.4 Hz, 1H, *2*-CH_bOAc), 5.81 (t, J=4.8 Hz, 8.7 Hz, 1H, *7*-H), and 7.55 (d, J=8.7 Hz, 1H, NH). m/z (%) 380 (M^+, 3), 216 (64), 156 (100).

Synthesis of 2-iodoarylalkenes 4

4a. Sodium hydride (60% dispersion in mineral oil, 960 mg, 24 mmol) was added slowly to a stirred solution of *N*-*o*-iodophenyl acrylamide (7 g, 24 mmol) in dry DMF (20 ml). After 2 h at room temperature the mixture was cooled to 0°C followed by the addition of iodomethane (3.4, 24 mmol) and stirring continued at room temperature for further 2 h. The mixture was diluted with Et_2O (200 ml) and washed with water. The organic layer was separated, dried ($MgSO_4$), filtered and the filtrate concentrated in vacuo. Purification of the residue by column chromatography afforded **4a** (5.36 g, 78%) as colourless prisms from benzene, mp 75°C. (Found: C, 43.9; H, 3.8; N, 4.4; I, 42.2. $C_{11}H_{12}$ INO requires: C, 43.8; H, 4.0; N, 4.6; I, 42.1%). δ 1.80 (s, 3H, CCH_3), 3.22 (s, 3H, NCH_3), 4.98 and 5.03 (2×s, 2H, C═CH_2), 7.03 (t, 1H, ArH), 7.18 (d, 1H, ArH), 7.38 (t, 1H, ArH) and 7.92 (d, 1H, ArH). *m*/*z* (%) 301 (M^+, 0.3), 203 (4), and 174 (100).

4b. Sodium hydride (60% dispersion in mineral oil, 880 mg, 22 mmol) was added slowly to a solution of *N*-sulphonyl-2-iodoaniline (3.9 g, 10 mmol) in dry DMF (25 ml). After 2 h at room temperature, the mixture was cooled to 0°C, 3-chloro-1-methylpropene (1.1 g, 10 mmol) added and stirring continued at 0°C for 4 h. The mixture was then diluted with Et_2O (200 ml) and washed with water. The organic layer was separated, dried ($MgSO_4$) filtered and the filtrate concentrated in vacuo. Purification of the residue by column chromatography eluting with 5:1 v/v hexane/ether yielded **4b** (3.3 g, 75%) as a colourless oil. (Found: C, 43.1; H, 3.6; N, 3.2. $C_{16}H_{16}INO_2S$ requires: C, 43.2; H, 3.6; N, 3.3%). δ 1.84 (s, 3H, CH_3), 3.96 (s, 2H, CH_2N), 5.10, 5.24 (2×s, 2H, C═CH_2), and 7.00–7.68 (m, 9H, ArH). *m*/*z* (%) 445 (M^+, 11), 304 (42), 141 (100), 123 (18), 77 (40), and 55 (54).

4c. Prepared as for **4b** but using 2-iodophenol. The product (79%) was obtained as a colourless oil. (Found: C, 43.8; H, 4.0; I, 46.4. $C_{10}H_{11}IO$ requires: C, 43.6; H, 4.3; I, 46.1%). δ 1.84 (s, 3H, CH_3),4.42 (s, 2H, CH_2), 4.96, 5.18 (2×s, 2H, C═CH_2), 6.65 (t, 1H, ArH), 6.75 (d, 1H, ArH), 7.21 (m, 1H, ArH), and 7.88 (d, 1H, ArH). *m*/*z* (%) 274 (M^+, 58.5), 220 (32), and 147 (60).

General procedure for cyclisation–anion capture

Tri-*n*-butyltin hydride (0.5 or 1 mmol, see Table 1) was added dropwise to a stirred solution of **2** (0.5 mmol), $Pd_2(dba)_3$ (11.2 mg, 0.025 mmol), and tri-(2-furyl)phosphine (11.6 mg, 0.10 mmol) in anhydrous toluene (5 ml) at 0°C, and the mixture stirred at room temperature for 1 h. Aryl iodide **4** (0.5 or 1 mmol, see Table 1) and toluene (2 ml) were then added and the mixture boiled under reflux for the time indicated in Table 1. The reaction mixture was cooled to room temperature, ethyl acetate (10 ml) and 2 M aqueous solution of potassium fluoride (10 ml) added and the resulting mixture vigorously stirred for 1 h. The mixture was then filtered, the organic layer separated, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash chromatography eluting with mixtures of *n*-hexane/ether or *n*-hexane/ethyl acetate to furnish **6a**–**o**. Yields and reaction times are collected in Table 1. Products **6a**–**h** and **6o** were obtained as 1:1 mixtures of diastereomers.

6a. Pale yellow oil. (HRMS found: 473.2403. $C_{24}H_{35}NO_7$ requires: 473.2403). δ (mixture of diastereoisomers) 1.20–1.60 (m, 15H, 5×CH_3), 2.65 (q, *J*=16.5 Hz, 2H, CH_2C═C), 3.18 (s, 2H, NCH_3), 3.35, 3.45, 3.52, 3.63 (4×d, *J*=13.5 Hz, 2H, C═CCH_2O), 3.60–4.40 (m, 7H, 5×CHO and CH_2OCO), 4.75, 4.79, 4.88, 4.92 (4×s, 2H, C═CH_2), and 6.80–7.20 (m, 4H, ArH). *m*/*z* (%) 473 (M^+, 1), 214 (91), 160 (100).

6b. Pale yellow oil. (HRMS found: 447.2308. $C_{25}H_{34}O_7$ requires: 447.2338). δ (mixture of diastereoisomers) 1.30, 1.36, 1.39, 1.42, 1.48 (5×s, 15H, 5×CH_3), 2.37, 2.51 (2×d, *J*=13.8 Hz, 1H, CCH_2C═C), 2.38, 2.49 (2×d, *J*=13.0 Hz, 1H, CCH_2C═C), 3.57, 3.78 (2×d, *J*=12 Hz, 2H, C═CCH_2O), 4.16, 4.53 (2×d, *J*=8 Hz, 2H, ArOC*H*$_2$), 3.70–4040 (m, 7H, 5×OCH and CH_2OCO), 4.91, 5.15 (2×s, 2H, C═CH_2), and 6.73–7.20 (m, 4H, ArH). *m*/*z* (%) 446 (M^+, 0.4), 314 (5), and 133 (100).

6c. Pale yellow oil. (HRMS found: 473.2414. $C_{26}H_{35}NO_7$ requires: 473.2414). δ (mixtures of diastereoisomers) 1.30–1.60 (5×s, 15H, 5×CH_3), 2.38 (m, 2H, CCH_2C═C), 3.18 (s, 3H, NCH_3), 3.35 (m, 2H, $OCCH_2O$), 3.65–5.60 (m, 7H, 5×CHO, and C═CCH_2O), and 6.80–7.15 (m, 4H, ArH). *m*/*z* (%) 473 (M^+, 0.8), 313 (26), and 245 (92).

6d. Pale yellow oil. (Found: C, 67.5; H, 7.8. $C_{25}H_{34}O_7$ requires: C, 67.25; H, 7.65%). δ (mixture of diastereoisomers) 1.32, 1.35, 1.43, 1.44, 1.53 (5×s, 15H, 5×CH_3), 2.38, 2.51 (2×d, *J*=13.8 Hz, 2H, CCH_2C═C), 3.45 (m, 2H, $OCCH_2O$), 3.62, 3.78 (2×d, *J*=15 Hz, 2H, ArOC*H*$_2$); δ 3.72 (s, 2H, CH_2O), 3.95 (m, 1H, CHO), 4.16 (dq, *J*=9.95, 1.2 Hz, CHO), 4.27 (d, *J*=9.8 Hz, 1H, C═CCH_2O), 4.31 (dd, *J*=5.0, 2.3 Hz, CHO), 4.52 (d, *J*=9.8 Hz, 1H, C═CCH_2O), 4.59 (dd, *J*=10.0, 2.3 Hz, 1H, CHO), 4.21, 4.87 (2× s, 2H, C═CH_2), 5.52 (d, *J*=5.0 Hz, 1H, OCHO), and 6.67–7.18 (m, 4H, ArH). *m*/*z* (%) 446 (M^+, 0.5), 314 (1), and 133 (100).

6e. Colourless prisms from *n*-hexane/ether, mp 49–51°C. (Found: C, 61.15; H, 5.5; N, 6.6; S, 5.05. $C_{31}H_{35}N_3O_8S$ requires: C, 61.1; H, 5.9; N, 6.9; S, 5.25%). δ (mixture of diastereoisomers) 1.21 (s, 3H, CH_3CCN), 1.37, 1.58 (2×s, 6H, 2×CH_3CO), 2.21, 2.28 (2×d, *J*=14.0 Hz, 2H, CCH_2C═C), 2.59 (br. s, 1H, OH), 3.53, 3.54 (2×d, *J*=10.3 Hz, 1H, C*H*$_2$NAr), 3.88 (dd, *J*=12.0, 3.3 Hz, 1H, CH_2O), 3.93 (dd, *J*=12.0, 2.5 Hz, 1H, CH_2O), 4.00 (d, *J*=10.3 Hz, 1H, C*H*$_2$NAr), 4.18, 4.25 (2×m, 2H, NCH_2C═C), 4.32 (br. s, 1H, C*H*CH_2O), 4.59, 4.61, 4.66 (3×s, 2H, CH_2═C), 5.00 (br. s, 2H, 2×C*H*$OCCH_3$), 5.58 (d, *J*=1.6 Hz, 1H, OCHN), 5.76 (d, *J*=8.0 Hz, 1H, NCH═C*H*) and 6.98–7.96 (m with d at 7.47, *J*=8.0 Hz, 10H, NC*H*═CH and ArH). *m*/*z* (%) 609 (M^+, 3), 468 (22), 338 (27), 273 (34), 272 (100), 184 (31), 166 (60), 141 (48), 132 (42), 131 (30), 130 (59) and 77 (58).

6f. Colourless prisms from *n*-hexane/ether, mp 53–55°C. (Found: C, 61.6; H, 6.0; N, 6.3. $C_{22}H_{26}N_2O_7$ requires: C, 61.4; H, 6.1; N, 6.5%). δ (mixture of diastereoisomers) 1.26 (s, 3H, CH_3), 2.44, 2.49 (2×d, *J*=14.0 Hz, 2H,

$CCH_2C{=}C$), 2.23 (br. s, 1H, OH), 3.47, 3.86 (2×d, J=11.5 Hz, 2H, $NCH_2C{=}C$), 4.06–4.20 (m, 8H, C*H*$_2$OH, 3×CHO and 1H of C*H*$_2$OAr), 4.49 (d, J=8.6 Hz, 1H, C*H*$_2$OAr), 4.61, 4.70 (2×s, 2H, $CH_2{=}C$), 5.73 (d, J=3.2 Hz, 1H, OCHN), 5.75 (d, J=8.2 Hz, 1H, NCH=C*H*) and 6.77–7.27 (m, 4H, ArH) and 7.75 (d, J=8.2 Hz, 1H, NC*H*=CH). *m*/*z* (%) 430 (M^+, 1), 298 (36), 166 (46), 151 (21), 134 (22), 133 (100), 132 (14), 131 (13) and 105 (50).

6g. Colourless needles from *n*-hexane/ether, mp 58–59°C. (Found: C, 65.0; H, 5.9; N, 5.8; S, 4.6. $C_{38}H_{41}N_3O_8S$ requires: C, 65.2; H, 5.9; N, 6.0; S, 4.6%). δ (mixture of diastereoisomers) 1.13–1.43 (2×s, 3H, CH_3CCN), 1.37, 1.58 (2×s, 6H, 2×CH_3CO), 2.10–2.29 (m, 2H, $CCH_2C{=}C$), 3.31–3.53, (m, 5H, CH_2OCH_2 and 1H of C*H*$_2$NAr), 3.94, 3.92 (2×d, J=10.2 Hz, 1H, C*H*$_2$NAr), 4.32 (br. s, 1H, CH_2CHO), 4.67–4.79 (m, 3H, 2×C*H*OCCH$_3$ and 1H of $CH_2{=}C$), 4.92 (br. s, 1H, $CH_2{=}C$), 5.07, 5.13 (2×d, J=13.8 Hz, 2H, CH_2N), 5.63, 5.66 (2×d, J=8.0 Hz, 1H, NCH=C*H*), 5.86 (d, J=5.4 Hz, 1H, OCHN) and 6.94–7.83 (m with d at 7.62, J=8.0 Hz, 15H, ArH and NC*H*=CH). *m*/*z* (%) 669 (M^+, 1), 428 (29), 272 (100), 141 (39), 132 (34), 131 (25), 130 (63), 91 (47), 77 (56) and 43 (22).

6h. Colourless sticky oil. (Found: C, 68.2; H, 6.5; N, 4.7. $C_{32}H_{36}N_2O_7$ requires: C, 68.55; H, 6.5; N, 5.0%). δ (mixture of diastereoisomers) 1.34, 1.35 (2×s, 3H, CH_3CCN), 1.36, 1.57 (2×s, 6H, 2×CH_3CO_2), 2.24–2.38 (m, 2H, $CCH_2C{=}C$), 3.34–3.50, (m, 4H, $C{=}CCH_2OCH_2$), 4.13 (d, J=8.7 Hz, 1H, C*H*$_2$OAr), 4.33 (br. s, 1H, CH_2CHO), 4.44, 4.46 (2×d, J=8.7 Hz, 1H, C*H*$_2$OAr) 4.74 (m, 2H, 2×C*H*OCCH$_3$), 4.84, 5.05 (2 br. s, 2H, $CH_2{=}C$), 5.06, 5.12 (2×d, J=13.8 Hz, 2H, CH_2N), 5.67, 5.68 (2×d, J=8.0 Hz, 1H, NCH=C*H*), 5.86 (br. s, 1H, OCHN) and 6.82–7.48 (m, 10 H, ArH and NC*H*=CH). *m*/*z* (%) 560 (M^+, 0.1), 428 (27), 269 (25), 203 (17), 202 (16), 134 (22), 133 (100), 105 (63), 91 (47), 84 (18), 69 (15), 55 (20), 46 (36) and 41 (28).

6i. Colourless prisms from ethyl acetate/petroleum ether, mp 181°C. (Found: C, 64.1; H, 5.7; N, 17.8. $C_{21}H_{23}N_5O_3$ requires: C, 64.1; H, 5.9; N,17.8%). δ 1.44 (s, 3H, CCH_3), 2.70, 2.72 (d, J=13.2 Hz, 1H, $C{=}CCH_2$), 3.25 (s, 3H, NCH_3), 3.51 (s, 3H, $NCNCH_3$), 3.98 (s, 3H, $OCNCH_3$), 4.01, 4.18 (2×d, J=15.5 Hz, 1H, $NCH_2C{=}C$), 4.50, 4.62 (2×s, 2H, $C{=}CH_2$), 6.82–7.38 (m, 4H, ArH), and 7.49 (s, 1H, N=CH). *m*/*z* (%) 393 (M^+, 5), 233 (100), and 160 (32).

6j. Colourless prisms from pentane, mp 51°C. (HRMS found: 366.1697. $C_{20}H_{22}N_4O_3$ requires: 366.1697). δ 1.47 (s, 3H, *3*-CH_3), 2.55 (dd, J=13.1 Hz, 2H, $CCH_2C{=}C$), 3.58 (s, 3H, $NCNCH_3$), 3.98 (s, 3H, $OCNCH_3$), 4.23 (d, J=8.7 Hz, 1H, ArOC*H*$_2$), 4.37 (s, 2H, $NCH_2C{=}C$), 4.58 (d, J=8.7 Hz, ArOC*H*$_2$), 4.73, 4.79 (2×s, 2H, $C{=}CH_2$), 6.80–7.22 (m, 4H, ArH), and 7.53 (s, 1H, N=CH). *m*/*z* (%) 366 (M^+, 1), 234 (54), and 133 (100).

6k. Colourless needles from *n*-hexane/ether, mp 57–58°C. (Found: C, 61.65; H, 6.0; N, 12.8; S, 4.9. $C_{34}H_{40}N_6O_6S$ requires: C, 61.8; H, 6.1; N, 12.7; S, 4.8%). δ 1.29 (s, 3H, CH_3CCN), 1.44 (s, 18H, 6×CH_3CO), 2.25, 2.31 (2×d, J=14.2 Hz, 2H, $CCH_2C{=}C$), 3.53, 4.04 (2×d, J=10.2 Hz, 2H, C*H*$_2$NAr), 4.24, 4.36 (2×d, J=16.4 Hz, 2H, $NCH_2C{=}C$), 4.51, 4.81 (2×s, 2H, $C{=}CH_2$) and 7.01–7.88 (m with s at 7.79, 10H, H-8 and ArH). *m*/*z* (%) 660 (M^+, 0.01), 345 (56), 272 (50), 215 (27), 214 (23), 185 (24), 184 (100), 141 (50), 131 (32), 130 (67), 77 (71), 59 (42), 44 (22), 41 (38) and 39 (20).

6l. Colourless oil. (Found: C, 64.55; H, 6.75; N, 13.85. $C_{28}H_{35}N_5O_5$ requires: C, 64.5; H, 6.75; N, 13.5%). δ 1.44 (s, 18H, 6×CH_3CO), 1.47 (s, 3H, CH_3CCN), 2.39 (s, 2H, $CCH_2C{=}C$), 4.23(d, J=8.9 Hz, 1H, CH_2O), 4.26, 4.42 (2×d, J=16.5 Hz, 2H, $NCH_2C{=}C$), 4.56 (d, J=8.9 Hz, 1H, CH_2O), 4.62, 4.97 (2×s, 2H, $C{=}CH_2$), 6.85–7.20 (m, 4H, ArH), 7.73 (s, 1H, H-8) and 8.84 (s, 1H, H-2). *m*/*z* (%) 521 (M^+, 6), 389 (45), 348 (27), 322 (31), 289 (23), 215 (71), 214 (30), 189 (84), 188 (50), 133 (100), 105 (63), 57 (64) and 41 (27).

6m. Colourless needles from *n*-hexane/ether, mp 59–60°C. (Found: C, 72.8; H, 5.55; N, 7.2; S, 5.7. $C_{34}H_{31}N_3O_3S$ requires: C, 72.7; H, 5.55; N, 7.5; S, 5.7%). δ 1.03–1.10 (2×s, 3H, CH_3), 2.03, 2.09 (m, 2H, $CCH_2C{=}C$), 3.40 (d, J=8.4 Hz, 1H, C*H*$_2$NAr), 3.77–3.83 (m, 2H, 1H of C*H*$_2$NAr and 1H of CH_2CO), 3.94–4.44 (m, 2H, $NCH_2C{=}C$), 4.50–4.82 (m, 3H, $CH_2C{=}C$ and 1H of CH_2CO) and 6.76–7.83 (m, 18H, ArH). *m*/*z* (%) 561 (M^+, 1), 421 (36), 290 (96), 289 (76), 272 (74), 184 (37), 141 (56), 132 (51), 131 (33), 130 (83), 91 (31) and 77 (100).

6n. Colourless prisms from *n*-hexane/ether, mp 37–38°C. (Found: C, 79.3; H, 6.1; N, 6.55. $C_{28}H_{26}N_2O_2$ requires: C, 79.6; H, 6.2; N, 6.65%). δ 1.30 (s, 3H, CH_3), 2.23 (m, 2H, $CCH_2C{=}C$), 3.78, 3.81 (2×d, J=9.5 Hz, 1H, CH_2CO), 3.98–4.56 (m, 4H, CH_2O and $NCH_2C{=}C$), 4.71–4.83 (m, 3H, $CH_2C{=}C$ and 1H of CH_2CO) and 6.70–7.62 (m, 13H, ArH). *m*/*z* (%) 422 (M^+, 2), 291 (35), 290 (100), 289 (80), 262 (19), 261 (22), 235 (17), 208 (16), 207 (17), 133 (80), 105 (53), 91 (22) and 77 (16).

6o. Colourless prisms from petroleum ether/ethyl acetate, mp 88°C. (HRMS found: 555.2034. $C_{28}H_{31}N_3O_5S$ requires: 555.2039). *m*/*z* (%) (mixed isomers) 555 (M^+, 0.3), 228 (81), and 160 (100). δ (*Isomer A*) 1.53 [s, 9H, $C(CH_3)_3$], 2.07 (s, 1H, $OCCH_3$), 2.90 (s, 2H, *17*-CH_2), 3.18 (s, 3H, NCH_3), 3.33 (d, J=19.9 Hz, 1H, *8*-H_a), 3.52 (d, J=19.9 Hz, 1H, *8*-H_b), 4.79 (d, J=12.7 Hz,, 1H, C*H*$_a$OAc), 4.88 (d, J=4.9 Hz, 1H, *18a*-H), 5.07 (d, J=12.7 Hz, 1H, C*H*$_b$OAc), 5.16, 5.20 (2×s, 2H, *9*-CH_2), 5.38 (dd, J=7.9, 4.9 Hz, 1H, *12*-H), 6.08 (d, J=7.9 Hz, 1H, *11*-NH), and 6.80–7.30 (m, 4H, ArH). δ (*Isomer B*) 1.54 [s, 9H, $C(CH_3)_3$], 2.08 (s, 1H, $OCCH_3$), 2.78 (d, J=13.3 Hz, 1H, *17*-H_a), 3.05 (d, J=13.3 Hz, 1H, *17*-H_b), 3.19 (s, 3H, NCH_3), 3.31 (d, J=19.8 Hz, 1H, *8*-H_a), 3.55 (d, J=19.8 Hz, 1H, *8*-H_b), 4.82 (d, J=18.6 Hz,, 1H, C*H*$_a$OAc), 4.91 (d, J=4.9 Hz, 1H, *18a*-H), 5.02 (d, J=18.6 Hz, 1H, C*H*$_b$OAc), 5.48, 5.56 (2×s, 2H, *9*-CH_2), 5.68 (dd, J=8.7, 4.9 Hz, 1H, *12*-H), 6.42 (d, J=8.7 Hz, 1H, *11*-NH), and 6.8–7.30 (m, 4H, ArH).

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