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Elaboration of the Side-Chain of Amino Acid Derivatives by Palladium Catalysed Couplings

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Abstract: The palladium-catalysed couplings of aryl halides and triflates with propargyl amino amides and the couplings of aryl and vinyl halides and triflates with an ethynyl oxazolidine are reported. © 1997 Elsevier Science Ltd.

INTRODUCTION

Unnatural and non-proteinogenic α-amino acids are important as components in bioactive peptides, enzyme inhibitors, therapeutic agents and chiral synthons.[1] In addition to these well established uses for such amino acids recent interest in understanding the details of molecular recognition has led to the development of methodologies for the construction of elaborate scaffolds based on amides and carboxylic acids.[2] The two principle methods for the preparation of amino acids containing modified aryl side chains have involved either electrophilic or nucleophilic substitutions [3] or palladium catalysed couplings. We have been interested in the preparation of amino acids containing aromatic and heteroaromatic side chains via palladium catalysed protocols.[4] Amino acids containing these side chains have been prepared by a variety of routes including modifications to existing phenylalanine derivatives by Suzuki couplings for the preparation of chemotactic peptides[5], angiotensin II antagonists[6] and mimics for tyrosine phosphates and sulfates[7]. An alternative palladium catalysed method involves the coupling of aryl electrophiles with organozinc derivatives of alanine and homoalanine.[8]

The preparation of arylalkyne bridges between amino acid components by the palladium mediated coupling of 4-iodophenylalanine derivatives with various terminal alkynes has led to the formation of structurally unique molecules for nonlinear optical studies.[9] The ethynylgylcine synthon 4-ethynyloxazolidine has also been coupled to a limited number of organic electrophiles[10,11] and the Stille and Suzuki couplings of a bromoallylglycine derivative have also been reported[12].

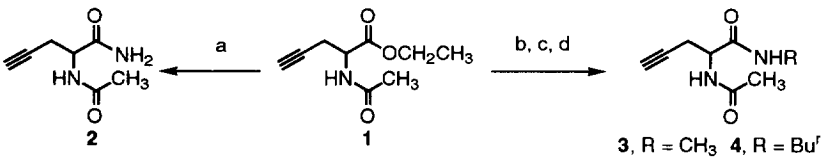
As part of our program of understanding the factors influencing molecular recognition in extensive amido hydrogen bonded networks, we have explored the palladium catalysed couplings of propargylglycine amides and 4-ethynyloxazolidine in order to prepare a series of arylalkynes amino acidates.

RESULTS AND DISCUSSION

Propargylglycine Derivatives

The known propargyl ester[13] **1** was readily converted into the amide **2** in 84% yield by treatment with a methanolic solution of ammonia (Scheme 1). The analogous alkylamides could not be prepared by reaction of

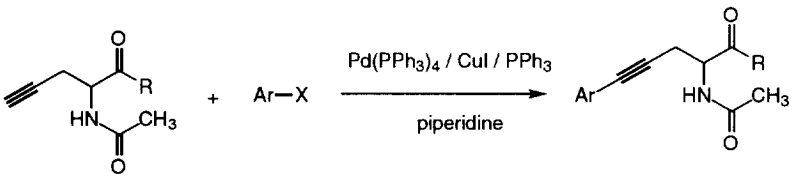
1 with primary amines, however, the indirect method of initial hydrolysis of **1** to the corresponding carboxylic acid and conversion to the *p*-nitrobenzyl ester proceeded readily and the labile ester could be displaced by the appropriate alkylamine (Scheme 1).



a. NH_3 / CH_3OH 84%
b. NaOH / CH_3OH 76%
c. *p*-nitrobenzyl bromide, NEt_3, DMF 73%
d. RNH_2 R = CH_3 96%, R = Bu^n 94%

Scheme 1

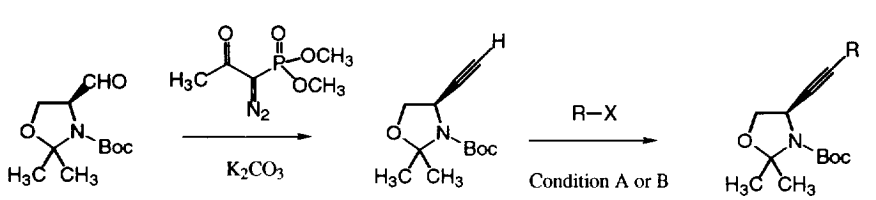
The optimum conditions for the palladium-catalysed coupling between the propargylglycine derivatives **2** and **3** and the aryl iodides or triflates used the standard protocol of $Pd(PPh_3)_4$ (5%), CuI (10%), PPh_3 (10%) in piperidine at reflux (Scheme 2 and Table 1).[4,14] Homocoupling of the propargylglycines occurred to a minor extent in all of the reactions. The amido derivatives **6-10** were all prepared as racemic mixtures from racemic precursors. The naphthalene derivative **11** was readily prepared from 2,7-dihydroxynaphthalene by a standard set of transformations (see Experimental). The amido complex **10** caused gelation of common organic solvents such as chloroform, toluene and acetonitrile. The gels were stable at room temperature and formed when the adducts were dissolved in warm solvent and later cooled. This cycle could be repeated many times without loss of gel formation.



2 R = NH_2 **3** R = $NHCH_3$ Scheme 2 **6 - 10**

Ethynylglycine Analogues

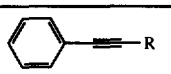
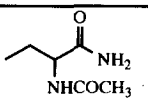
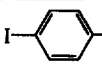
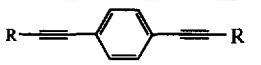
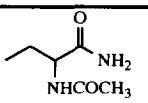
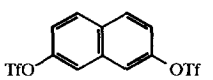
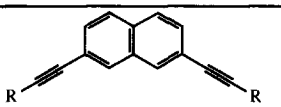
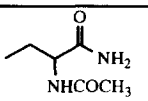
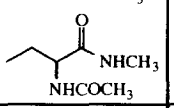
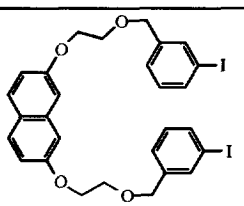
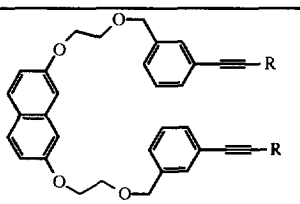
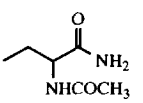
Ethynyloxazolidine (**12**)[10,11] was conveniently prepared from Garner's aldehyde (**13**)[15] and dimethyl (1-diazo-2-oxopropyl)phosphonate[16]. Compound **12** could also be readily coupled with a variety of aromatic[11] and vinylic halides and triflates using palladium catalysis (Scheme 3 and Table 2). For these couplings vinyl bromides and less reactive aryl triflates required more vigorous conditions compared to aryl iodides and vinyl triflates.



13 **12** **14-22**

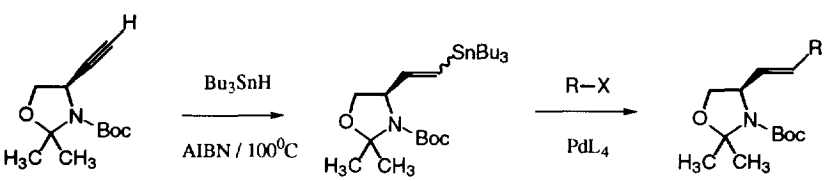
Scheme 3

Table 1. Reaction between propargylglycine derivatives **2** - **4** and aryl electrophiles.

Propargyl glycine	Aryl electrophile	Product	R	Yield %
2		 **6**		95
2		 **7**		73
2		 **8**		95
3		**9**		94
2	 **11**	 **10**		84

Vinylglycine Analogues

The synthetic versatility of **12** was further demonstrated by the formation of the vinylglycine precursors **E-23** and **Z-23** through the AIBN initiated hydrostannylation of **12**. The two stereoisomers could be separated by flash chromatography and were isolated in a combined yield of 94% and a 85:15 ratio (Scheme 4). The optimum conditions for the Stille[17] couplings between **E-23**[11] and aryl iodides were $Pd(PPh_3)_4$, CuI in N-methylpyrrolidinone at 40-50°C (Scheme 4 and Table 3).

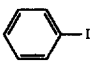
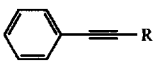
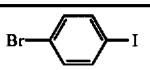
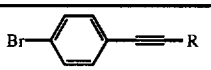
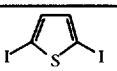
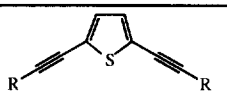
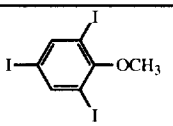
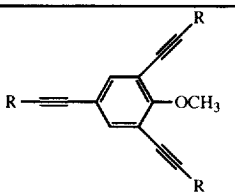
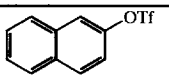
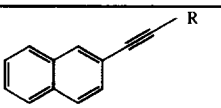
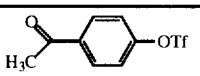
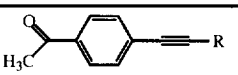
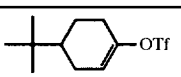
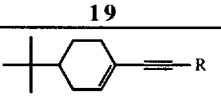
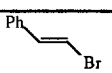
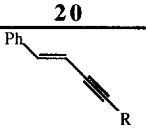
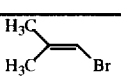
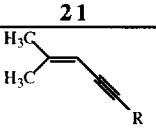


12 **23-E** **23-Z** **24-26**

Scheme 4

Although we have not deprotected the substituted oxazolidines **14-26** there is ample literature precedent for their conversion to carboxylic acid derivatives.[11,18] Thus a wide variety of arylalkyne amino acidates can be conveniently prepared using palladium catalysis and we will report in a separate paper the hydrogen bonding properties of some of these complexes.

Table 2. Reaction between ethynyloxazolidine **12** and aryl or vinyl electrophiles.

Condition	Aryl electrophile	Product	Yield %
A		 **14**	62
A		 **15**	75
A		 **16**	80
A		 **17**	72
A		 **18**	85
B		 **19**	73
A		 **20**	91
B		 **21**	77
B		 **22**	74

Condition A: $Pd(PPh_3)_4$ 10%, CuI 20%, Et_3N, DMF, RT

Condition B: $Pd(PPh_3)_4$ 5%, PPh_3 10%, CuI 10%, piperidine, 100°C

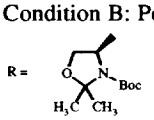
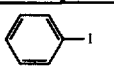
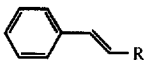
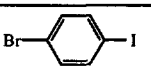
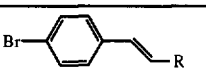
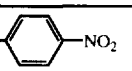
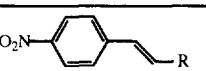
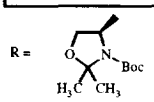
R = 

Table 3. Reaction between vinylstannane **E-23** and aryl iodides

Aryl electrophile	Product	Yield %
	 **24**	79
	 **25**	27
	 **26**	55

R = 

EXPERIMENTAL

^1H (300 MHz) and ^{13}C (50 MHz) NMR spectra were measured as dilute solutions in $CDCl_3$. Flash and squat chromatography was carried out using *Merck* silica gel 60 (230-400 mesh). Thin layer chromatography was carried out on *Merck* Alufolien Kieselgel 60 PF_{254} plates, which were visualised by ultraviolet light (254 nm) or by staining with a 5% ethanolic solution of phosphomolybdic acid. Compounds containing tin were visualised using iodine vapour. Reagents and solvents were purified and dried according to standard methods.[19] Dimethylformamide (DMF) was distilled from calcium sulphate under reduced pressure and stored over 4Å molecular sieves. Organic extracts were dried with magnesium sulphate or sodium sulphate.

The following compounds were prepared according to known procedures: tetrakis (triphenylphosphine)palladium(0),[20] (S)-(1,1-dimethylethyl)-4-formyl-2,2-dimethyl-3-oxazolidine carboxylate[15] dimethyl(1-diazo-2-oxopropyl)phosphonate,[16] 9,10-diiodoanthracene[21] and ethyl 2-(acetyl amino)-4-pentynoate (**1**)[13].

2-(Acetylamino)-4-pentynamide (2)

Propargylglycine ester **1** (4.24g, 23mmol) was added to ammonia saturated methanol (100mL) and stirred for 48h. The solvent was removed under vacuum and the residue recrystallised from methanol to give **2**, 2.14g (84%). Mp 172-173°C. ^1H NMR ($CD_3SOCD_3/CDCl_3$) δ 2.04 (s, 3H, CH_3), 2.14 (t, 1H, J=2.7 Hz, C≡C-H), 2.70 (m, 2H, CH_2), 4.64 (m, 1H, CH), 6.51 (s, 1H, NH_a), 7.19 (d, 1H, J=1.2 Hz, NH_b), 7.50 (d, 1H, J=7.0 Hz, NH). ^{13}C NMR ($CD_3SOCD_3/CDCl_3$) δ 20.53, 21.30, 49.94, 70.04, 78.94, 168.6, 170.9. IR (film) υ_{max} 3284, 1666 cm^{-1}. $[M+H]^+$ $C_7H_{10}N_2O_2$, Calc: 155.0821; Found: 155.0822.

*N*1-Methyl-2-(acetylamino)-4-pentynamide (3)

Propargylglycine ester **1** was hydrolysed with NaOH in methanol at room temperature. To a solution of the resultant acid (1.455g, 9.4mmol) in DMA (7.5mL) was added NEt_3 (2.63mL) and 4-nitrobenzylbromide (4,056g, 18.8 mmol). The reaction mixture was stirred for 3h at room temperature. The reaction mixture was

treated with water (20 mL), extracted with ethyl acetate and the organic layer washed with 2% $NaHCO_3$ solution, brine and dried. The residue was purified on silica gel (EtOAc:acetone, 19:1) to give 4-nitrobenzyl 2-(acetylamino)-4-pentynoate in 1.91g, 73%. Mp 113 - 115°C. ^1H NMR δ 2.03 (t, 1H, J=2.4 Hz, C≡CH), 2.08 (s, 3H, CH_3), 2.82 (m, 2H, CH_2), 4.84 (m, 1H, CH), 5.34 (m, 2H, OCH_2), 7.55 (dd J=1.8, 7.2 Hz, Ar), 8.26 (dd, 2H, J=2.4, 7.8 Hz, Ar). $[M+H]^+$ $C_{14}H_{14}N_2O_5$, Calc: 291.0981; Found: 291.0983. 4-Nitrobenzyl 2-(acetylamino)-4-pentynote (0.41g, 1.37 mmol) was added to methylamine saturated methanol (10mL) at 0°C and the mixture stirred overnight. The solvent was removed under vacuum and the residue purified on silica gel (EtOAc:acetone, 9:1) to give **3** in 0.23g, 99%. Mp 167-168°C. ^1H NMR δ 2.05 (s, 3H, CH_3), 2.10 (t, 1H, J=2.7 Hz, C≡CH), 2.57-2.78 (m, 1H, CH_2), 2.85(d, 3H, J=4.9 Hz, NCH_3), 4.51 (dd, 1H, J = 2.0, 5.6 Hz, CH), 6.19 (bs, 1H, NH), 6.29 (d, 1H, J=7 Hz, NH). ^{13}C NMR δ 20.20, 22.09, 23.06, 51.63, 71.47, 79.56, 170.37, 170.49. IR (film) υ_{max} 3280, 1635 cm^{-1}. Anal. Calc. for $C_8H_{12}N_2O_2$: C, 57.12; H, 7.19; N, 16.66%. Found: C, 56.88; H, 7.01; N, 16.53%.

_N_1-Butyl-2-(acetylamino)-4-pentynamide (4)

Prepared as described for **3** except butylamine was used instead of methylamine (94%). Mp 118-119°C. ^1H NMR δ 0.92 (t, 3H, J=7.3 Hz, CH_3), 1.37-1.51 (m, 4H, CH_2-CH_2), 2.04 (s, 3H, CH_3), 2.11 (t, 1H, J=2.4 Hz, C≡CH), 2.52-2.77 (m, 1H, CH_2), 3.28 (m, 2H, CH_2), 4.49 (m, 1H, CH), 6.14 (bs, 1H, NH), 6.32 (d, 1H, J=7 Hz, NH). ^{13}C NMR δ 13.56, 19.91, 22.30, 23.05, 31.40, 39.42, 51.69, 71.45, 79.66, 169.8, 170.3. IR (film) υ_{max} 3292, 1635 cm^{-1}. Anal. Calc. for $C_{11}H_{18}N_2O_2$: C, 62.84; H, 8.63; N, 13.32%. Found: C, 62.69; H, 8.48; N, 13.54%.

2-(Acetylamino)-5-phenyl-4-pentynamide (6)

To a stirred solution of iodobenzene (0.816g, 4.0mmol) and **2** (0.617g, 4mmol) in piperidine (40mL) under nitrogen, was added $Pd(PPh_3)_4$ (0.208g, 0.2mmol), PPh_3 (0.104g, 0.4mmol) and copper iodide (0.060g, 0.4mmol) respectively. The dark red solution was heated at reflux for 45 min. The solvent was evaporated *in vacuo* and the residue purified on silica gel ($CH_3OH/CHCl_3$, 20:80) to give **6**, 0.874g (95%). Mp 172-173°C. ^1H NMR ($CD_3SOCD_3/CDCl_3$) δ 2.04 (s, 3H, CH_3), 2.91(m, 2H, CH_2), 4.72 (m, 1H, CH), 6.18 (s, 1H, NH_a), 7.05 (s, 1H, NH_b), 7.27 - 7.41 (m , 6H, NH_a ArH). ^{13}C NMR ($CD_3SOCD_3/CDCl_3$) δ 22.7, 51.1, 82.3, 85.0, 122.74, 127.48, 127.74, 131.21, 169.8, 170.2. IR (film) υ_{max} 3199, 1703, 1682 cm^{-1}. Anal. Calc. for $C_{13}H_{14}N_2O_2$: C, 67.82; H, 6.13; N, 12.17%. Found: C, 67.73; H, 6.38; N, 12.28%.

2-(Acetylamino)-5-{4-[4-(acetylamino)-5-amino-5-oxo-1-pentynyl]phenyl}-4-pentynamide (7)

As described for **6** using 1,4-diiodobenzene and **2**, yield 73%. Mp >320°C. ^1H NMR ($CD_3SOCD_3/CDCl_3$) δ 1.94 (s, 3H, CH_3), 2.81 (m, 2H, CH_2), 4.55 (m, 1H, CH), 7.11 (s, 1H, NH_a), 7.32 (s, 4H, Ar), 7.46 (s, 1H, NH_b), 8.09 (d, 1H, J=8.2 Hz, NH). ^{13}C NMR ($CD_3SOCD_3/CDCl_3$) δ 20.94, 21.28, 49.65, 79.80, 86.76, 120.96, 129.59, 167.72, 170.26. IR (film): υ_{max} 3379, 3291, 3192, 1650 cm^{-1}. $[M]^+$ $C_{20}H_{22}N_4O_4$, Calc: 382.1641; Found: 382.1635.

2-(Acetylamino)-5-{7-[4-(acetylamino)-5-amino-5-oxo-1-pentynyl]-2-naphthyl}-4-pentynamide (8)

As described for **6** using 2,7-bis(trifluoromethanesulfonyl)naphthalene and **2**, yield 95%. Mp 198-200°C.

^{1}H NMR ($CD_3SOCD_3/CDCl_3$) δ 1.97 (s, 3H, CH_3), 2.85 (m, 2H, CH_2), 4.60 (m, 1H, CH), 7.14 (s, 1H, NH_a), 7.43 (dd, 1H, J=1.2, 8.7 Hz, Ar), 7.51 (s, 1H, NH_b), 7.79 (d, 1H, J=8.7 Hz, Ar), 7.87 (s, 1H, Ar), 8.13 (d, 1H, J=8.1 Hz, NH). ^{13}C NMR ($CD_3SOCD_3/CDCl_3$) δ 20.98, 21.34, 49.84, 80.33, 85.88, 119.63, 126.02, 127.30, 128.70, 129.54, 130.50, 167.94, 170.47. IR (film) υ_{max} 3286, 3194, 1624 cm^{-1}. $[M+H]^+$ $C_{24}H_{24}N_4O_4$, Calc: 433.1876; Found: 433.1880.

N1-Methyl-2-(acetylamino)-5-{7-[4-(acetylamino)-5-(methylamino)-5-oxo-1-pentynyl]-2-naphthyl}-4-pentynamide (9)

As described for **6** using 2,7-bis(trifluoromethanesulfonyl)naphthalene and **3**, yield 94%. Mp 278-279°C. ^{1}H NMR ($CD_3SOCD_3/CDCl_3$) δ 1.95 (s, 3H, CH_3), 2.69 (d, 3H, J=4.5 Hz, CH_3), 2.85 (m, 2H, CH_2), 4.58 (m, 1H, CH), 7.41 (d, 1H, J=8.7 Hz, Ar), 7.81 (d, 1H, J=8.7 Hz, Ar), 7.89 (s, 1H, Ar), 8.01 (q, 1H, J=4.8 Hz, $NHCH_3$), 8.22 (d, 1H, J=8.4 Hz, NHAc). ^{13}C NMR ($CD_3SOCD_3/CDCl_3$) δ 20.81, 21.22, 23.89, 49.97, 80.16, 85.87, 119.44, 125.99, 127.14. IR (film) υmax 3285, 1645 cm^{-1}. $[M+H]^+$ $C_{26}H_{28}N_4O_4$, Calc: 461.2189; Found: 461.2190.

2-(Acetylamino)-5-(3-{[2-({7-[2-({3-[4-(acetylamino)-5-amino-5-oxo-1-pentynyl] benzyl}oxy)ethoxy]-2-naphthyl}oxy)ethoxy]methyl}phenyl)-4-pentynamide (10)

As described for **6** using **2** and **12** and recrystallised from ethanol, yield 84%. Mp 116-118°C. ^{1}H NMR ($CD_3SOCD_3/CDCl_3$) δ 1.93 (s, 3H, CH_3), 2.81 (m, 2H, CH_2), 3.86 (m, 2H, CH_2), 4.26 (t, 2H, J=3.9 Hz, CH_2), 4.52 (m 1H, CH), 4.58 (s, 2H, CH_2), 7.02 (dd, 1H, J=2.4, 9.0 Hz, Ar), 7.16 (d, 1H, J=2.4 Hz, Ar), 7.28 (m, 4H, ArH), 7.39 (s, 1H, NH_a), 7.66 (s, 1H, NH_b), 7.70 (d, 1H, J=9.0 Hz, Ar), 8.15 (d, 1H, J=8.4 Hz, NHAc). ^{13}C NMR ($CD_3SOCD_3/CDCl_3$) δ 20.85, 21.14, 49.72, 65.28, 66.64, 70.10, 80.09, 84.88, 104.31, 114.26, 121.37, 122.13, 125.24, 126.48, 127.16, 128.54, 128.62, 133.87, 136.74, 167.74, 170.34. IR (film) υ_{max} 3282, 3181, 1629 cm^{-1}. $[M+H]^+$ $C_{42}H_{44}N_4O_8$, Calc: 733.3237; Found: 733.3254

2,7-Di{2-[(3-iodobenzyl)oxy]ethoxy}naphthalene (11)

2,6-Dihydroxynaphthalene (8.0g, 0.05mol) and methyl bromoacetate (15.3g, 0.10mol) were heated at reflux in acetone (200mL) with potassium carbonate (69g) for 24h. The resulting mixture was then filtered, evaporated *in vacuo* and the white solid recrystallised from ethanol to give methyl 2-{[7-(2-methoxy-2-oxoethoxy)-2-naphthyl]oxy} acetate (11.8g, 78%. Mp 129-130°C. ^{1}H NMR δ 3.84 (s, 3H, CH_3), 4.75(s, 2H, CH_2), 6.99 (d, 1H, J=2.5 Hz, Ar), 7.14 (dd, 1H, J=2.5, 9.2 Hz, Ar), 7.73 (d, 1H, J=9.2 Hz, Ar) [M$^+$] 304) which was reduced with lithium aluminium hydride to give 2-{[7-(2-hydroxyethoxy)-2-naphthyl]oxy}-1-ethanol (97% yield, Mp 152-153°C. ^{1}H NMR δ 3.63 (t, 1H, J=5.8 Hz OH), 3.91 (m, 2H, CH_2OH), 4.14 (t, 2H, J=4.4 Hz CH_2O), 7.03 (d, 1H, J=2.4 Hz, Ar), 7.14 (dd, 1H, J=2.4, 8.6 Hz, Ar), 7.70 (d, 1H, J= 8.6 Hz, Ar). [M$^+$] 248). NaH (60% dispersion in paraffin oil, 2.08g, 52mmol) was suspended in THF (10mL) and 2-{[7-(2-hydroxyethoxy)-2-naphthyl]oxy}-1-ethanol in THF (50mL) was added dropwise at 0°C after which 3-iodobenzyl bromide (3.56g, 12mmol) and Bu_4NI (0.1g) were added. After 2h at room temperature the THF was removed and DMA (10mL) was added and the mixture heated at 50°C for 15h. The resulting mixture was decomposed with ethanol and water, extracted with ethyl acetate and dried. The solvent was removed under vacuum, the residue purified on silica gel with hexanes as an eluant to remove excess 3-iodobenzylbromide and ethyl acetate:acetone (19:1) to give **11** (2.84g, 82%). Mp 58-60°C. ^{1}H NMR δ 3.88

(t , 2H, J=4.8 Hz CH_2), 4.26 (t, 2H, J=4.6 Hz CH_2), 4.59 (s, 2H, CH_2), 7.75-7.03 (m, 10H, ArH). ^{13}C NMR δ 67.30, 68.73, 72.36, 106.23, 116.41, 126.75, 127.69, 128.40, 129.14, 130.13, 135.69, 136.50, 136.67, 140.48. $[M]^+$ $C_{24}H_{24}N_4O_4$, Calc: 679.9924; Found: 679.9906.

Tert-butyl (4R)-4-(1-ethynyl)-2,2-dimethyl-1,3-oxazolane-3-carboxylate (12)

To a solution of dimethyl (1-diazo-2-oxopropyl)phosphonate[16] (2.51 g, 13.1 mmol) and **13**[15] (2.0 g, 8.7 mmol) in dry methanol (50 mL) was added potassium carbonate (2.41 g, 17.5 mmol) at 0 °C under a nitrogen atmosphere for 30 min and warmed to room temperature for 3h. After addition of aqueous saturated NH_4Cl (50 mL) and pentane (2 x 75 mL), the organic layer was separated, dried and evaporated to yield 1.53 g (78%) of **12** as a clear oil. ^1H NMR δ 1.49 (s, 9H, $C(CH_3)_3$), 1.49 (s, 3H, H_3CCCH_3), 1.63 (s, 3H, H_3CCCH_3), 2.31 (d, 1H, J=2.2 Hz, C≡C-H), 4.05 (m, 2H, CH_2), 4.53 (m, 1H, CH). ^{13}C NMR δ 24.35, 26.24, 28.38, 48.32, 68.65, 70.15, 80.33, 82.60, 92.07, 151.61. IR (neat) ν_{max} 3268, 2112, 1700 cm^{-1}. FABMS ($[M+H]^+$) 226 . $[\alpha]_D$ = -81.3°, (T=20°C, $CHCl_3$, c 2.43), lit.[10] -81.3°, (T=20°C, $CHCl_3$, c 2.43).

Tert-butyl (4R)-2,2-dimethyl-4-[2-(2-phenyl-1-ethynyl]-1,3-oxazolane-3-carboxylate (14)

Condition A

Iodobenzene (0.072 g, 0.35 mmol) and **12** (0.120 g, 0.53 mmol) were added to a degassed mixture of dry DMF (2 mL) and dry triethylamine (0.5 mL). $Pd(PPh_3)_4$ (0.038 g, 0.035 mmol) and CuI (0.013 g, 0.070 mmol) were added respectively. After having been stirred overnight at room temperature the reaction mixture was filtered through a thin layer of silica and the filtrate was evaporated *in vacuo*. Flash chromatography of the residue on silica gel (hexane:EtOAc, 85:15), gave **14** as yellow / orange crystals (0.065 g, 62%). Mp 106-107°C. ^1H NMR δ 1.51 (s, 9H, $C(CH_3)_3$), 1.54 (s, 3H, H_3CCCH_3), 1.67(s, 3H, CH_3CCH_3), 4.10 (m, 2H, CH_2), 4.73 (m, 1H, CH), 7.40 (m, 5H). ^{13}C NMR δ 24.70, 26.03, 28.47, 49.16, 68.92, 80.37 82.02, 88.09, 94.08, 122.93, 128.22, 131.70, 151.61. IR (nujol) ν_{max} 1702 cm^{-1}. MS: $[M]^{+\cdot}$ 301. $[\alpha]_D$ = -100.7°, (T=20°C, $CHCl_3$, c 0.18). $[M]^+$ $C_{18}H_{23}NO_3$, Calc: 301.1678; Found: 301.1680.

Tert-butyl (4R)-2,2-dimethyl-4-[2-(4-bromophenyl)-1-ethynyl]-1,3-oxazolane-3-carboxylate (15)

Coupling of **12** (0.1 g, 0.44 mmol) with 1-bromo-4-iodobenzene (0.096 g, 0.34 mmol) under Condition A yielded, after flash chromatography on silica gel (85:15, hexane:EtOAc), **15** as an orange solid (0.095 g, 73%). Mp 68-69°C. ^1H NMR δ 1.49 (s, 9H, $C(CH_3)_3$), 1.52 (s, 3H, H_3CCCH_3), 1.66 (s, 3H, H_3CCCH_3), 4.08 (m, 2H, CH_2), 4.73 (m, 1H, CH), 7.24 (d, 2H, J=8.3 Hz), 7.42 (d, 2H, J=8.3 Hz). ^{13}C NMR δ 24.49, 25.97, 28.42, 49.09, 68.71, 80.33, 81.05, 89.30, 94.35, 121.81, 122.43, 131.47, 133.08, 151.50. IR (nujol) ν_{max} 1698 cm^{-1}. FABMS: 382/380 ($[M+H]^+$). $[\alpha]_D$= -131.9°, (T=20°C, $CHCl_3$, c 0.30). $[M]^+$ $C_{18}H_{22}NO_3Br^{79}$, Calc: 379.0783; Found: 379.0786.

Tert-butyl (4R)-4-[2-(5-{2-[(4S)-3-(tert-butoxycarbonyl)-2,2-dimethyl-1,3-oxazolan-4-yl]-1-ethynyl}-2-thienyl)-1-ethynyl]-2,2-dimethyl-1,3-oxazolane-3-carboxylate (16)

Coupling of **12** (0.1 g, 0.44 mmol) with 2,5-diiodothiophene (0.066g, 0.19 mmol) under Condition A yielded, after flash chromatography on silica gel (90:10, hexane:EtOAc), **16** as a yellow solid (0.082 g, 80%). Mp 147-150°C. ^1H NMR δ 1.49 (s, 18H, $C(CH_3)_3$), 1.52 (s, 6H, H_3CCCH_3), 1.64 (s, 6H, H_3CCCH_3), 4.08 (m, 4H, CH_2), 4.72 (m, 2H, CH), 6.99 (s, 2H). ^{13}C NMR δ 24.57, 25.89, 28.44, 48.98/49.26,

68.29/68.51, 75.03, 80.53, 92.78, 94.42, 123.98, 131.65, 151.48. IR (nujol) ν_{max} 1700 cm^{-1} FABMS: 531 ($[M+H]^+$). $[\alpha]_D$ = -183.2°, (T=20 °C, $CHCl_3$, c 0.25). $[M]^+$ $C_{28}H_{38}N_2O_6S$, Calc: 530.2450; Found: 530.2452.

Tert-butyl (4R)-4-[2-(3,5-di{2-[(4R)-3-(tert-butoxycarbonyl)-2,2-dimethyl-1,3-oxazolan-4-yl]-1-ethynyl}-2-methoxyphenyl)-1-ethynyl]-2,2-dimethyl-1,3-oxazolane-3-carboxylate (17)

Coupling of **12** (0.18 g, 0.82 mmol) with 2,4,6-triiodoanisole (0.1 g, 0.21 mmol) under Condition A yielded, after flash chromatography on silica gel, (75:25, hexane:EtOAc), **17** as a light orange oil (0.12 g, 72%). ^1H NMR δ 1.45 (s, 27H, $C(CH_3)_3$), 1.49 (s, 9H, H_3CCCH_3), 1.62 (s, 9H, H_3CCCH_3), 3.95 (s, 3H, OCH_3), 4.05 (m, 6H, CH_2), 4.72 (m, 3H, CH), 7.33 (br s, 2H). ^{13}C NMR δ 24.43/24.90, 25.89/26.52, 28.31, 48.97/49.15, 61.01, 68.71, 80.04, 80.31, 93.22, 94.27, 117.02, 118.07, 136.53, 151.37, 161.89. IR (neat) ν_{max} 2980, 2248, 1708 cm^{-1}. $[\alpha]_D$ = -151.3°, (T=20°C, $CHCl_3$, c 1.95). $[M]^+$ $C_{43}H_{59}N_3O_{10}$, Calc: 777.4110; Found: 777.4202.

Tert-butyl (4R)-2,2-dimethyl-4-[2-(2-naphthyl)-1-ethynyl]-1,3-oxazolane-3-carboxylate (18)

Coupling of **12** (0.1 g, 0.44 mmol) with 2-naphthyl triflate (0.094 g, 0.34 mmol) under Condition A yielded, after flash chromatography on silica gel (95:5, hexane:EtOAc), **18** as a white fluffy solid (0.102 g, 85%). Mp 130-132°C. ^1H NMR δ 1.53 (s, 9H, $C(CH_3)_3$), 1.56 (s, 3H, H_3CCCH_3), 1.72 (s, 3H, H_3CCCH_3), 4.15 (m, 2H, CH_2), 4.80 (m, 1H, CH), 7.42-7.84 (m, 6H), 7.94 (s, 1H). ^{13}C NMR δ 24.52, 25.00, 28.50 , 49.24, 68.95, 80.37, 82.49, 88.44, 94.21, 120.21, 126.50, 126.62, 127.69, 127.73, 127.89, 128.47 , 131.53, 132.79, 132.92, 151.64. IR (nujol) ν_{max} 1700 cm^{-1}. FABMS 352 ($[M+H]^+$). $[\alpha]_D$ = -164.1°, (T=20°C, $CHCl_3$, c 0.39. $[M]^+$ $C_{22}H_{25}NO_3$, Calc: 351.1834; Found: 351.1826

Tert-butyl (4R)-4-[2-(4-acetylphenyl)-1-ethynyl]-2,2-dimethyl-1,3-oxazolane-3-carboxylate (19)

Condition B

12 (0.05 g, 0.22 mmol), *p*-acetylphenyltriflate (0.04 g, 0.17 mmol), PPh_3 (0.0058 g, 0.017 mmol), and $Pd(PPh_3)_4$ (0.012 g, 0.008 mmol) were dissolved in degassed piperidine (12 mL). Copper iodide (0.0042 g, 0.017 mmol) was added and the clear light yellow solution rapidly went brown. The mixture was heated at reflux for 2 h. The solvent was evaporated *in vacuo* and the residue was initially purified by passing through a short column of silica gel (50:50, hexane:EtOAc), then by column chromatography (90:10, hexane:EtOAc) to yield **19** as a yellow oil (0.029 g, 73%). ^1H NMR δ 1.48 (s, 9H, $C(CH_3)_3$), 1.52 (s, 3H, H_3CCCH_3), 1.65 (s, 3H, H_3CCCH_3), 4.10 (m, 2H, CH_2), 4.74 (m, 1H, CH), 7.46 (d, 2H, J=8.1 Hz), 7.86 (d, 2H, J=8.1 Hz). ^{13}C NMR δ 24.66, 25.99, 26.55 , 28.43, 48.96/49.13, 68.27/68.68, 81.09, 81.39, 91.55, 94.35, 127.73, 128.13, 131.79, 136.29, 151.45, 197.21. IR (nujol) ν_{max} 1712 cm^{-1}. $[\alpha]_D$ = -67.4°, (T=20°C, $CHCl_3$, c 0.18). $[M+H]^+$ $C_{20}H_{25}NO_4$, Calc: 343.1783; Found: 343.1781.

Tert-butyl (4R)-4-{2-[4-(tert-butyl)-1-cyclohexenyl]-1-ethynyl}-2,2-dimethyl-1,3-oxazolane-3-carboxylate (20)

Coupling of **12** (0.1 g, 0.44 mmol) with 4-tertbutylcyclohex-1-en-1-yl triflate (0.098 g, 0.34 mmol) under Condition A yielded, after flash chromatography on silica gel (95:5, hexane:EtOAc), **20** as a clear viscous oil

(0.11 g, 91%). ^{1}H NMR δ 0.83 (s, 9H, $C(CH_3)_3$), 1.24 (m, 3H, $CHCH_2CH_2$), 1.47 (s, 3H, H_3CCCH_3), 1.47 (s, 9H, $C(CH_3)_3$), 1.61 (s, 3H, H_3CCCH_3), 1.76 (m, 2H, CH_2CH=C), 2.13 (m, 2H, $CHCH_2CH_2$), 3.98 (m, 2H, CH_2), 4.61 (m, 1H, CH), 6.06 (bs, 1H, CH=C). ^{13}C NMR: δ 23.72, 24.66, 25.92, 27.09, 27.29, 28.43, 30.69, 32.13, 43.18, 49.09, 69.04, 80.02, 83.63, 85.52, 94.02, 120.07, 135.03, 151.57. IR (neat) ν_{max} 2964, 2216, 1706 cm^{-1}. $[\alpha]_D$ = -52.5°, (T=20 °C, $CHCl_3$, c 0.37). $[M]^+$ $C_{22}H_{35}NO_3$, Calc: 361.2617; Found: 361.2610.

Tert-butyl (4R)-2,2-dimethyl-4-[(E)-4-phenyl-3-buten-1-ynyl]-1,3-oxazolane-3-carboxylate (21)

Coupling of **12** (0.1 g, 0.44 mmol) with *E*-1-bromo-2-phenylethene (0.062 g, 0.34 mmol) under Condition B yielded, after flash chromatography on silica gel (94:6, hexane:EtOAc), **21** as bright yellow, needle-like crystals (0.085 g ,77%). Mp 81-83°C. ^{1}H NMR δ 1.51 (s, 9H, $C(CH_3)_3$), 1.51 (s, 3H, H_3CCCH_3), 1.66 (s, 3H, H_3CCCH_3), 4.06 (m, 2H, CH_2), 4.71 (m, 1H, CH), 6.15 (dd, 1H, J=1.8, 16.4 Hz), 6.92 (d, 1H, J=16.4 Hz), 7.31 (m, 5H). ^{13}C NMR δ 25.00, 25.97, 28.46, 49.26, 68.87, 80.45, 81.35, 90.09, 94.02, 107.82, 128.21, 128.35, 128.57, 128.67, 136.17, 141.49, 151.59. IR (nujol) ν_{max} 1710 cm^{-1}. $[\alpha]_D$ = -190.1°, (T=20°C, $CHCl_3$, c 0.26). $[M]^+$ $C_{20}H_{25}NO_3$, Calc: 327.1834; Found: 327.1818.

Tert-butyl (4R)-2,2-dimethyl-4-(4-methyl-3-penten-1-ynyl)-1,3-oxazolane-3-carboxylate (22)

Coupling of **12** (0.1 g, 0.44 mmol) with 1-bromo-2-methylpropene (0.046 g, 0.34 mmol) under Condition B yielded, after flash chromatography (94:6, hexane:EtOAc), **22** as a orange viscous oil (0.070 g, 74%) which later formed a solid. Mp 43-45°C. ^{1}H NMR δ 1.49 (s, 9H, $C(CH_3)_3$), 1.51 (s, 3H, H_3CCCH_3), 1.64 (s, 3H, H_3CCCH_3), 1.79 (s, 3H, $C{=}CCH_3$), 1.88 (s, 3H, $C{=}CCH_3$), 4.03 (m, 2H, CH_2), 4.69 (m, 1H, CH), 5.25 (m, 1H, HC=C). ^{13}C NMR δ 20.88, 24.69, 25.01, 25.81, 28.43, 49.15, 69.16, 80.22, 90.01, 94.09, 94.16, 104.85, 148.73, 151.58. IR (nujol) ν_{max} 1708 cm^{-1}. $[\alpha]_D$ = -132.9°, (T=20°C, $CHCl_3$, c 1.33). $[M+H]^+$ $C_{16}H_{25}NO_3$, Calc: 279.1834; Found: 279.1827.

Tert-butyl (4R)-2,2-dimethyl-4-[(E)-2-(1,1,1-tributylstannyl)-1-ethenyl]-1,3-oxazolane-3-carboxylate (23-E, 23-Z)

A solution of **12** (0.1 g, 0.44 mmol) and AIBN (0.022g) in dry toluene was added to a Schlenk apparatus under an atmosphere of dry nitrogen. Tri-n-butylstannane (0. 19g, 0.67 mmol) was added by syringe and the solution immersed in a preheated oil bath (120°C) for 15min. The solvent was removed by rotary evaporation and the residue purified by flash chromatography (95:5, hexane:EtOAc). **23-E**: R_f = 0.20, (0. 194 g, 85%). ^{1}H NMR δ 0.84-1.61 (m, 42H, $C(CH_3)_3$, H_3CCCH_3, $Sn((CH_2)_3CH_3)_3$), 3.78 (dd, 1H, CH_2, J=2.9, 8.6 Hz), 4.06 (dd, 1H, CH_2, J=4.0, 8.6 Hz), 4.25 (br m, 1H, CH), 5.98 (m, 2H, HC=CHSn). ^{13}C NMR δ 9.96, 13.77, 24.01, 26.54, 27.33, 28.41, 29.15, 62.50, 68.52, 79.69, 94.09,129.15, 146.98, 152.21. IR (neat): ν_{max} 2952, 1702 cm^{-1} ElMS 516 (M+1). **23-Z**: R_f = 0.28, (0.0216g, 9%). ^{1}H NMR δ 0.86-1.58 (m, 42H, $C(CH_3)_3$, H_3CCCH_3, $Sn((CH_2)_3 CH_3)_3$), 3.67(dd, 1H, CH_2, J=3.9, 8.0 Hz), 4.06 (m, 2H, CH_2, CH), 5.97 (br d, 1H, HC=CHSnu$_3$, J=12.5Hz), 6.47 (br dd, 1H, HC=CHSnBu$_3$, J=7.2, 12.5 Hz). $[M+H]^+$ $C_{24}H_{48}NO_3Sn^{120}$: 518.

Tert-butyl (4R)-2,2-dimethyl-4-[(E)-2-phenyl-1-ethenyl]-1,3-oxazolane-3-carboxylate (24)

$Pd(PPh_3)_4$ (0.01 g, 0.0097 mmol) was added to dioxane (5 mL) under nitrogen. Iodobenzene (0.033 mL, 0.289 mmol) and **23-E** (0. l0g, 0.193 mmol) were added with a further 5 mL of dioxane and the mixture heated at reflux for 3h. After cooling to room temperature, 10% potassium fluoride (30 mL) was added in a separatory funnel, and the mixture was extracted with diethyl ether (4 x 30 mL), dried and concentrated. The residue was purified by flash chromatography (90:10,hexane:EtOAc) to yield **24** as fine, cream crystals (0.046g, 79%).

Mp 62-65°C. ^{1}H NMR δ 1.43 (s, 9H, $C(CH_3)_3$), 1.54 (s, 3H, CH_3CCH_3), 1.65 (s, 3H, CH_3CCH_3), 3.83 (dd, 1H, CH_2, J=9.4, 2.4Hz), 4.11 (dd, 1H, CH_2, J=9.4, 6.5 Hz), 4.43 (m, 1H, CH), 6.16 (br dd, lH, HC=CHPh, J=15.6, 7.8 Hz), 6.50 (br d, 1H, HC=CHPh, J=15.6 Hz), 7.23-7.40 (m, 5H, Ph). ^{13}C NMR δ 24.39, 27.02, 28.69, 59.64, 68.42, 80.00, 94.19, 121.61, 128.18, 129.69, 130.68, 131.90, 135.89, 152.19 .IR(nujol) ν_{max} 2920, 1704, 1650, 1590 cm^1. $[\alpha]_D$ = 33.00, (T=18°C, $CHCl_3$, c 1.00). $[M]^+$ $C_{18}H_{25}NO_3$, Calc: 303.1834; Found: 303.1831.

Tert-butyl (4R)-4-[(E)-2-(4-bromophenyl)-1-ethenyl]-2,2-dimethyl-1,3-oxazolane-3-carboxylate (25)

Reaction of **23-E** 0.20g, 0.388 mmol) with 1-bromo-4-iodobenzene as described for **24** gave **25** as an orange-brown solid (0.0234g, 27%). Mp 76-79°C. ^{1}H NMR δ 1.44 (s, 9H, $C(CH_3)_3$), 1.55 (s, 3H, CH_3CCH_3), 1.66 (s, 3H, CH_3CCH_3), 3.83 (dd, 1H, J=2.0, 8.9 Hz, CH_2), 4.13 (dd, 1H, J=5.6, 8.9 Hz, CH_2), 4.43 (brm, 1H, CH), 6.16 (dd, 1H, J=7.8, 15.7 Hz, HC=CHPh), 6.46 (br d, 1H, HC=CHPh), 7.35 (m, 4H, Ph). ^{13}C NMR δ 23.67/24.68, 26.58/27.49, 28.35, 59.47, 68.28, 79.68, 94.00, 112.18, 126.48, 127.69, 128.64, 136.76, 131.72, 152.09. IR(nujol) ν_{max} 2952, 1704, 1655, 1500 cm^{-1}. $[\alpha]_D$ = -53.3°, (T=22°C, $CHC1_3$, c 0.61). $[M]^+$ $C_{18}H_{24}NO_3Br^{79}$, Calc: 381.0940; Found: 381.0942

Tert-butyl (4R)-2,2-dimethyl-4-[(E)-2-(4-nitrophenyl)-1-ethenyl]-1,3-oxazolane-3-carboxylate (26)

Reaction of **23-E** with 1-iodo-4-nitrobenzene as described for **24** gave **26** as a yellow solid (55%). ^{1}H NMR δ 1.41 (s, 9H, $C(CH_3)_3$), 1.49 (s, 3H, CH_3CCH_3), 1.65 (s, 3H, CH_3CCH_3), 3.85 (dd, 1H, J=2.4, 9.0 Hz, CH_2), 4.15 (dd, 1H, J=6.5, 9.4 Hz, CH_2), 4.53 (brm, 1H, CH), 6.37 (m, 1H, HC=CPh), 6.58 (m, 1H, C=CHPh), 7.50 (m, 2H, Ph), 8.20 (m, 2H, Ph). ^{13}C NMR δ 23.72, 26.64, 28.39, 59.23, 67.95, 79.68, 95.18, 123.70, 124.06, 126.99, 129.62, 133.56, 143.18, 147.12. IR(nujol) ν_{max} 1696, 1596, 1518 cm^{-1}. $[M]^+$ $C_{18}H_{25}N_2O_5$, Calc: 349.1763; Found: 349.1764.

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