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# A convenient synthesis of chiral 2-alkynyl-1,3-oxazolines

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**Abstract**

A general, high-yielding, two-step synthesis of chiral 2-alkynyl-1,3-oxazolines starting from 2-alkynoic acids and 2-aminoalcohols is disclosed. © 2000 Published by Elsevier Science Ltd.

## 1. Introduction

Chiral oxazolines have been extensively used in asymmetric synthesis, as both auxiliaries and ligands.[1] In the context of our study of the Pauson–Khand reaction of chiral, electron-deficient alkynes,[2] we needed to prepare a set of chiral 2-alkynyl-1,3-oxazolines. 2-Alkynyl-1,3-oxazolines, however, appear to be a practically unexplored class of compounds, and only a few examples of achiral or homochiral 2-alkynyl-1,3-oxazolines have been described.[3,4] Up to now, the only preparation of a chiral, alkyne-substituted oxazoline is the synthesis of *t*-leucinol-derived 2-alkynyl-1,3-oxazolines reported by Meyers and Kovachek.[4] This method requires the generation of the corresponding 2-hydro-1,3-oxazoline, which after metallation with *t*-butyl lithium is treated with dibromotetrafluoroethane to give an unstable 2-bromo-1,3-oxazoline. Palladium(0)-promoted coupling of this compound with a trimethylstannylacetylene finally affords the 2-alkynyl-1,3-oxazoline, in a process that takes place in overall moderate yields (25–28%) from the starting homochiral 2-aminoalcohol. We wish to report here a high-yield, convenient and general synthesis of homochiral 2-alkynyl-1,3-oxazolines that takes place in only two steps from a 2-aminoalcohol and a 2-alkynoic acid.

## 2. Results and discussion

Taking into account the ready availability of 2-alkynoic acids, we envisaged obtaining 2-alkynyl-1,3-oxazolines by the two-step process summarized in Scheme 1, involving the

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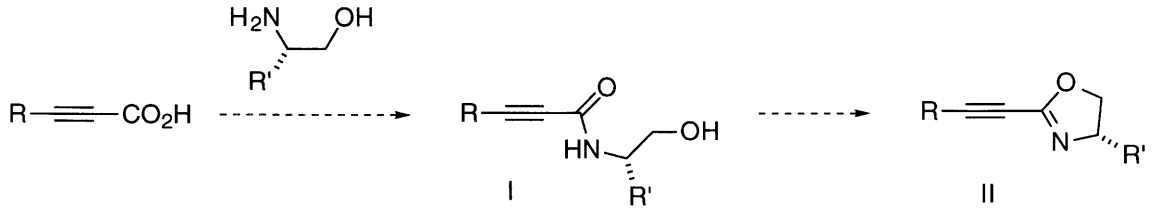
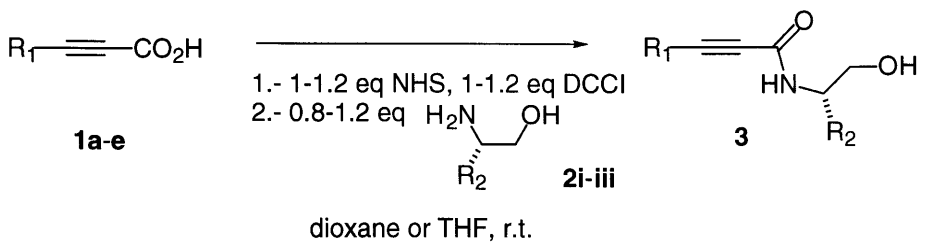
preparation of a 2-alkynoyl-derived β-hydroxyamide I and its subsequent cyclization to the corresponding oxazoline II: although this process is based on a well-established route for the preparation of chiral oxazolines from carboxylic acids,[5] it had up to now not been applied to 2-alkynoic acids.




Scheme 1.

After some experimentation,[6] we found that the most convenient conditions to perform the first step relied on the use of in situ generated *N*-hydroxysuccinimide esters[7] (Scheme 2 and Table 1). The reaction took place in very mild conditions (formation of the active ester and stirring with the aminoalcohol at room temperature), and the yields were generally high. The generation of the *N*-hydroxysuccinimide ester was performed by treatment of the 2-alkynoic acid, in 1,4-dioxane or in tetrahydrofuran, with *N*-hydroxysuccinimide and *N*,*N*′-dicyclohexylcarbodiimide and stirring for 2.5 h. After the addition of the homochiral aminoalcohol, stirring was maintained until total consumption of the starting products, and after filtering out the dicyclohexylurea the crude was purified by column chromatography. In this way, the β-hydroxyamides derived from phenylpropiolic acid **1a**, trimethylsilylpropiolic acid **1b** and tetrolic acid **1c** were obtained in excellent yields (84–93%). Somewhat lower yields were achieved with 9-decen-2-ynoic acid **1d**, and the hydroxyamide **3eii** could not be isolated from the reaction of propiolic acid **1e** with (*S*)-phenylglycynol **2ii**, probably owing to polymerization of the acid in the reaction medium.



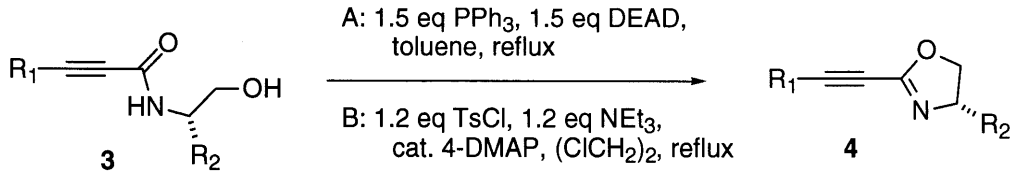

Scheme 2.

Two different sets of conditions were developed for the cyclization of the hydroxyamides **3** to the corresponding oxazolines **4** (Scheme 3 and Table 2).

Oxazolines **4ai**, **4aii**, **4cii** and **4dii** were best obtained under Mitsunobu reaction conditions[5f] (1.5 equiv. $PPh_3$, 1.5 equiv. DEAD, toluene, reflux; conditions A). The yield of the (*S*)-*tert*-leucinol-derived oxazoline **4aiii** was much improved by treatment of **3aiii** with tosyl chloride and triethylamine in the presence of DMAP in refluxing dichloroethane[5d] (conditions B). In this way, the overall yield (from **2iii**) for **4aiii** is 75%, three times higher than that previously described.[4] Conditions B, which involve the generation and in situ cyclization of the hydroxyamide tosylate, also led to somewhat better yields of oxazoline **4cii**. It is worth noting that fluoride-induced

Table 1
β-Hydroxyamides **3** from 2-alkynoic acids **1** and β-aminoalcohols **2**

| 2-Alkynoic acid ($R_1$) | β-Aminoalcohol ($R_2$) | β-Hydroxiamide, % yield |
|---|---|---|
| **1a** (Ph) | **2i** ($CH_2CH(CH_3)_2$) | **3ai**, 87 |
| **1a** (Ph) | **2ii** ($CH_2Ph$) | **3aii**, 84 |
| **1a** (Ph) | **2iii** ($C(CH_3)_3$) | **3aiii**, 92 |
| **1b** ($Si(CH_3)_3$) | **2ii** ($CH_2Ph$) | **3bii**, 93 |
| **1c** ($CH_3$) | **2ii** ($CH_2Ph$) | **3cii**, 93 |
| **1d** ($(CH_2)_5CH{=}CH_2$) | **2ii** ($CH_2Ph$) | **3dii**, 63 |
| **1e** (H) | **2ii** ($CH_2Ph$) | **3eii**, 0 |




Scheme 3.

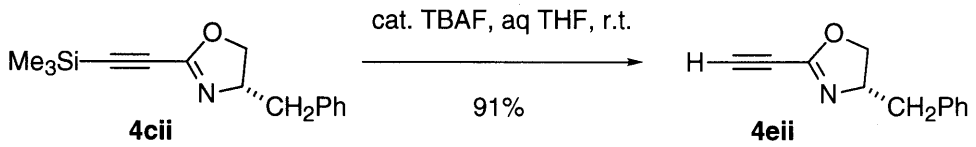
Table 2
2-Alkynyl-1,3-oxazolines **4** from *N*-(2-alkynoyl)hydroxyamides **3**

| β-Hydroxyamide | Reaction conditions[a] | Oxazoline ($R_1$, $R_2$) | Yield (%) |
|---|---|---|---|
| **3ai** | A | **4ai** (Ph, $CH_2CH(CH_3)_2$) | 81 |
| **3aii** | A | **4aii** (Ph, $CH_2Ph$) | 87 |
| **3aiii** | A | **4aiii** (Ph, $C(CH_3)_3$) | 23 |
| **3aiii** | B | **4aiii** (Ph, $C(CH_3)_3$) | 82 |
| **3bii** | A | **4bii** ($Si(CH_3)_3$, $CH_2Ph$) | 60 |
| **3bii** | B | **4bii** ($Si(CH_3)_3$, $CH_2Ph$) | 75 |
| **3cii** | A | **4cii** ($CH_3$, $CH_2Ph$) | 72 |
| **3cii** | B | **4cii** ($CH_3$, $CH_2Ph$) | 67 |
| **3dii** | A | **4dii** ($(CH_2)_5CH{=}CH_2$, $CH_2Ph$) | 60 |

[a] See Scheme 3.

desilylation of this compound afforded the 2-ethynyloxazoline **4eii** in 91% yield, thus overcoming the lack of accessibility of the β-hydroxyamides derived from propiolic acid (Scheme 4).

In summary, we have developed a practical and general route to 2-alkynyl-1,3-oxazolines, taking place in only two steps from readily available 2-alkynoic acids and 2-aminoalcohols. Preliminary experiments show that chiral 2-alkynyl-1,3-oxazolines readily participate in intermolecular Pauson–Khand reactions, leading regioselectively and in high yields to 3-(2-oxazolinyl)-2-cyclopentenones as chromatographically separable diastereomer mixtures; in contrast, intramolecular Pauson–Khand cycloadditions appear to be highly disfavoured for this kind of substrate. These results shall be reported in due time. We hope that other applications of 2-alkynyl-1,3-oxazolines will develop as a result of the present ready availability of these hitherto almost unknown homochiral substrates.




**4cii** **4eii**

Scheme 4.

## 3. Experimental

### 3.1. General methods

Optical rotations were measured at room temperature (23°C) on a Perkin–Elmer 241 MC polarimeter (concentration in g/100 ml). Melting points were determined on a Gallenkamp apparatus and have not been corrected. Infrared spectra were recorded on a Nicolet 510 FT-IR instrument. NMR spectra were acquired on Varian-Gemini 200 or Varian Unity 300 instruments in $CDCl_3$. $^1H$ NMR spectra were obtained at 200 or 300 MHz (s = singlet, d = doublet, t = triplet, q = quartet, h = heptuplet, m = multiplet and b = broad) using tetramethylsilane (TMS) as an internal standard in $CDCl_3$, and $^{13}C$ NMR spectra were obtained at 50.3 or 75.3 MHz, referenced to residual $CHCl_3$ ($\delta = 77.00$ ppm) in $CDCl_3$. Carbon multiplicities ($CH_3$, $CH_2$, CH, Cq) have been assigned by DEPT experiments. Low-resolution mass spectra were recorded on a Hewlett–Packard 5988 A spectrometer; ammonia was used for chemical ionization (CI). High-resolution mass spectra were performed by the 'Unidade de Espectrometria de Masas de la Universidade de Santiago de Compostela', using the FAB+ technique. Elemental analyses were performed by the 'Servei d'Anàlisis Elementals del CSIC de Barcelona'. Chromatographic separations were carried out using $SiO_2$ (230–400 mesh) eluting with hexanes–ethyl acetate mixtures. Chromatographic analyses were performed on a Helwett–Packard 1050 HPLC instrument equipped with a Nucleosil 120 C18 (20 cm) column. Dichloromethane, 1,2-dichloroethane and dioxane were distilled over calcium hydride and preserved on 4 Å molecular sieves. Tetrahydrofuran was distilled over sodium benzophenone ketyl before use. Toluene was distilled over sodium immediately prior to use. Triethylamine was distilled over calcium hydride and preserved on KOH pellets. 8-Nonen-2-ynoic acid **1d** was prepared as previously described,[2c] and (*S*)-2-amino-3-phenyl-1-propanol **2ii** was obtained from the corresponding amino acid according to the methodology of McKennon and Meyers.[8] All of the remaining starting materials were obtained from commercial suppliers and used without purification. Reactions were generally performed in flame- or oven-dried glassware under nitrogen.

### 3.2. Preparation of N-(2-hydroxyethyl)ynamides *3*

#### 3.2.1. N-[(1S)-2-Hydroxy-1-(2-methylpropyl)ethyl]-3-phenylprop-2-ynamide, *3ai*

To a stirred solution of 2.67 g (18.3 mmol) of phenylpropiolic acid **1a** in 120 ml of anhydrous dioxane, 2.12 g (18.4 mmol) of *N*-hydroxysuccinimide and 3.79 g (18.4 mmol) of *N*,*N*′-dicyclohexylcarbodiimide were added sequentially. After 2.5 h of stirring at room temperature, 2.10 ml (1.92 g, 16.3 mmol) of (*S*)-(+)-leucinol **2i** were added via a syringe; stirring was maintained for an additional 5 h until completion of the reaction (TLC monitoring). After this time, the

precipitated *N*,*N*′-dicyclohexylurea was filtered off, and the solvent was eliminated at reduced pressure. The residue was taken up in 100 ml of ethyl acetate, and the solution was washed twice with 30 ml of a saturated NaCl solution. After extracting the aqueous phase with ethyl acetate (20 ml), the combined organic extracts were dried over sodium sulfate and the solvents removed in vacuo. The crude product was purified by column chromatography (hexane/ethyl acetate 70/30) to give 3.49 g (87% yield) of **3ai** as a colourless solid. Colourless crystals, mp 102–3°C. $[\alpha]_D^{23} = -44.4$ (*c* 1.26 $CHCl_3$). IR (KBr) 3250, 2950, 2217, 1630 $cm^{-1}$. $^1H$ NMR (300 MHz) $\delta = 7.55$–7.27 (m, 5H), 6.20 (d, $J = 8.8$ Hz, 1H), 4.18 (m, 1H), 3.65 (m, 2H), 2.58 (b, 1H), 1.70 (m, 1H), 1.40 (m, 2H), 0.96 (d, $J = 6.9$ Hz, 6H). $^{13}C$ NMR (75 MHz) $\delta = 153.8$ (Cq), 132.4 (CH), 129.9 (CH), 128.5 (CH), 120.0 (Cq), 85.2 (Cq), 82.9 (Cq), 65.1 ($CH_2$), 50.3 (CH), 39.9 ($CH_2$), 24.8 (CH), 23.0 ($CH_3$), 22.2 ($CH_3$). MS (CI-$NH_3$) $m/e = 246$ ($[M+1]^+$, 100%). Elemental analysis: calculated for $C_{15}H_{19}NO_2$: C, 73.43%; H, 7.81%; N, 5.71%; found: C, 73.63%; H, 7.84%; N, 5.66%.

### *3.2.2.* N-*[(1*S*)-1-Benzyl-2-hydroxyethyl]-3-phenylprop-2-ynamide*, ***3aii***

To a stirred solution of 3.29 g (22.5 mmol) of phenylpropiolic acid (**1a**) in 120 ml of anhydrous dioxane, 2.41 g (20.9 mmol) of *N*-hydroxysuccinimide and 4.26 g (20.7 mmol) of *N*,*N*′-dicyclohexylcarbodiimide were added sequentially. After 2.5 h of stirring at room temperature, 3.05 g (20.2 mmol) of (*S*)-(−)-2-amino-3-phenyl-1-propanol (**2ii**) were added in one single portion; stirring was maintained for 8 h until completion of the reaction (TLC monitoring). After this time, the precipitated *N*,*N*′-dicyclohexylurea was filtered off, and the solvent was eliminated at reduced pressure. The residue was taken up in 100 ml of ethyl acetate, and the solution was washed twice with 30 ml of a saturated NaCl solution. After extracting the aqueous phase with ethyl acetate (20 ml), the combined organic extracts were dried over sodium sulfate and the solvents removed in vacuo. The crude product was purified by column chromatography (hexane/ethyl acetate 65/35) to give 4.76 g (84% yield) of **3aii** as a colourless solid. Colourless crystals, mp 113–4°C. $[\alpha]_D^{23} = -68.8$ (*c* 1.65 $CHCl_3$). IR (KBr) 3287, 2950, 2217, 1630, 1329, 1055, 758, 692 $cm^{-1}$. $^1H$ NMR (200 MHz) $\delta = 7.50$–7.21 (m, 10H), 6.67 (d, $J = 8.0$ Hz, 1H), 4.25 (m, 1H), 3.95 (b, 1H), 3.60 (m, 2H), 2.93 (d, $J = 7.4$ Hz, 2H). $^{13}C$ NMR (50 MHz) $\delta = 153.7$ (Cq), 137.3 (Cq), 132.5 (CH), 129.2 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 126.2 (CH), 120.0 (Cq), 85.4 (Cq), 82.9 (Cq), 62.9 ($CH_2$), 53.1 (CH), 36.8 ($CH_2$). MS (CI-$NH_3$) $m/e = 280$ ($[M+1]^+$, 100%), 297 ($[M+18]^+$, 39%). Elemental analysis: calculated for $C_{18}H_{17}NO_2$: C, 77.43%; H, 6.09%; N, 5.02%; found: C, 77.25%; H, 6.18%; N, 4.85%.

### *3.2.3.* N-*[(1*S*)-1-(*tert*-Butyl)-2-hydroxyethyl]-3-phenylprop-2-ynamide*, ***3aiii***

Obtained by the method described above starting from 0.438 g (3.00 mmol) of phenylpropiolic acid **1a**, 0.450 g (3.91 mmol) of *N*-hydroxysuccinimide, 0.713 g (3.46 mmol) of *N*,*N*′-dicyclohexylcarbodiimide and 0.390 g (3.33 mmol) of (*S*)-*tert*-leucinol **2iii** in 30 ml of anhydrous dioxane. The reaction was complete after 15 h of stirring at room temperature. Working up and column chromatography (hexane/ethyl acetate 3/1) afforded 0.677 g (92% yield) of hydroxyamide **3aiii**. Colourless crystals, mp 119–21°C. $[\alpha]_D^{23} = -20.6$ (*c* 1.63 $CHCl_3$). IR (KBr) 3226, 3064, 2965, 2213, 1632, 1329, 1310, 1053, 754 $cm^{-1}$. $^1H$ NMR (200 MHz) $\delta = 7.56$–7.37 (m, 5H), 6.32 (d, $J = 9.0$ Hz, 1H), 4.00–3.50 (m, 3H), 2.60 (b, 1H), 1.00 (s, 9H). $^{13}C$ NMR (50 MHz) $\delta = 154.0$ (Cq), 132.4 (CH), 129.9 (CH), 128.4 (CH), 120.0 (Cq), 85.7 (Cq), 82.5 (Cq), 62.4 ($CH_2$), 59.8 (CH), 33.9 (Cq), 26.9 ($CH_3$). MS (CI-$NH_3$) $m/e = 246$ ($[M+1]^+$, 100%), 263 ($[M+18]^+$, 36%).

*3.2.4.* N-*[(1*S*)-1-Benzyl-2-hydroxyethyl]-3-trimethylsilylprop-2-ynamide*, ***3bii***

Obtained by the method described above starting from 0.235 g (1.65 mmol) of trimethylsilylpropiolic acid **1b**, 0.242 g (2.10 mmol) of *N*-hydroxysuccinimide, 0.406 g (1.97 mmol) of *N*,*N*′-dicyclohexylcarbodiimide and 0.285 g (1.88 mmol) of (*S*)-(−)-2-amino-3-phenyl-1-propanol **2ii** in 30 ml of anhydrous dioxane. The reaction was complete after 15 h of stirring at room temperature. Working up and column chromatography (hexane/ethyl acetate 70/30) afforded 0.424 g (93% yield) of hydroxyamide **3bii**. Colourless crystals, mp 85–87°C. $[\alpha]_D^{23} = -49.6$ (*c* 1.10 $CHCl_3$). IR (KBr) 3208, 3060, 2185 (very weak), 1624, 1312, 1252, 1051, 847 $cm^{-1}$. $^1H$ NMR (200 MHz) $\delta = 7.10–7.00$ (m, 5H), 6.08 (d, $J = 7.8$ Hz, 1H), 4.00 (m, 1H), 3.40 (m, 2H), 2.69 (d, $J = 7.0$ Hz, 2H), 0.00 (s, 9H). The signal corresponding to the OH group could not be identified. $^{13}C$ NMR (50 MHz) $\delta = 153.7$ (Cq), 137.9 (Cq), 129.8 (CH), 129.3 (CH), 127.3 (CH), 98.0 (Cq), 92.7 (Cq), 63.5 ($CH_2$), 53.6 (CH), 37.4 ($CH_2$), 0.0 ($CH_3$). MS (CI-$NH_3$) $m/e = 276$ ($[M+1]^+$, 100%), 293 ($[M+18]^+$, 72%).

*3.2.5.* N-*[(1*S*)-1-Benzyl-2-hydroxyethyl]but-2-ynamide*, ***3cii***

Obtained by the method described above starting from 0.128 g (1.52 mmol) of tetrolic acid **1c**, 0.175 g (1.52 mmol) of *N*-hydroxysuccinimide, 0.361 g (1.75 mmol) of *N*,*N*′-dicyclohexylcarbodiimide and 0.285 g (1.88 mmol) of (*S*)-(−)-2-amino-3-phenyl-1-propanol (**2ii**) in 30 ml of anhydrous dioxane. The reaction mixture was stirred overnight at room temperature. Working up and column chromatography (hexane/ethyl acetate 40/60) afforded 0.307 g (93% yield) of hydroxyamide **3cii**. Colourless crystals, mp 70–72°C. $[\alpha]_D^{23} = -67.6$ (*c* 1.13 $CHCl_3$). IR (KBr) 3287, 2963, 2251, 1636, 1302, 1049 $cm^{-1}$. $^1H$ NMR (200 MHz) $\delta = 7.32–7.21$ (m, 5H), 6.10 (m, 1H), 4.20 (m, 1H), 3.60 (m, 2H), 2.89 (d, $J = 7.4$ Hz, 2H), 2.50 (b, 1H), 1.93 (s, 3H). $^{13}C$ NMR (50 MHz) $\delta = 149.9$ (Cq), 133.5 (Cq), 125.4 (CH), 124.9 (CH), 122.9 (CH), 86.0 (Cq), 80.2 (Cq), 59.3 ($CH_2$), 49.1 (CH), 32.9 ($CH_2$), 3.9 (weak, $CH_3$). MS (CI-$NH_3$) $m/e = 218$ ($[M+1]^+$, 100%), 235 ($[M+18]^+$, 97%).

*3.2.6.* N-*[(1*S*)-1-Benzyl-2-hydroxyethyl]oct-7-en-2-ynamide*, ***3dii***

Obtained by the method described above starting from 0.612 g (4.03 mmol) of 8-nonen-2-ynoic acid **1d**, 0.525 g (4.57 mmol) of *N*-hydroxysuccinimide, 0.930 g (4.50 mmol) of *N*,*N*′-dicyclohexylcarbodiimide and 0.680 g (4.50 mmol) of (*S*)-(−)-2-amino-3-phenyl-1-propanol (**2ii**) in 40 ml of anhydrous tetrahydrofuran. The reaction mixture was stirred overnight at room temperature. Working up and column chromatography (hexane/ethyl acetate 70/30) afforded 0.715 g (63% yield) of hydroxyamide **3dii**. Colourless solid, mp = 71–72°C. $[\alpha]_D^{23} = -44.8$ (*c* 1.02 $CHCl_3$). IR (KBr) 3284, 2932, 2247, 1624, 1327, 1283, 1030, 700 $cm^{-1}$. $^1H$ NMR (200 MHz) $\delta = 7.31–7.21$ (m, 5H), 6.11 (d, $J = 6.8$ Hz, 1H), 5.80 (m, 1H), 5.00 (m, 2H), 4.18 (m, 1H), 3.60 (m, 2H), 2.50 (s, 1H), 2.90 (d, $J = 7.4$ Hz, 2H), 2.26 (m, 2H), 2.05 (m, 2H), 1.60–1.40 (m, 4H). $^{13}C$ NMR (50 MHz) $\delta = 154.0$ (Cq), 138.1 (CH), 137.2 (Cq), 129.2 (CH), 128.6 (CH), 126.6 (CH), 114.8 ($CH_2$), 88.0 (Cq), 75.7 (Cq, 63.2 ($CH_2$), 52.9 (CH), 36.7 ($CH_2$), 33.2 ($CH_2$), 28.0 ($CH_2$), 27.1 ($CH_2$), 18.5 ($CH_2$). MS (CI-$NH_3$) $m/e = 286$ ($[M+1]^+$, 100%), 303 ($[M+18]^+$, 25%).

### 3.3. General procedures for the cyclization of N-(2-hydroxyethyl)ynamides **3** to 2-alkynyl-1,3-oxazolines **4**

#### 3.3.1. Method A

To a stirred solution of the ynamide **3** (1.0 mmol) and triphenylphosphine (1.5 mmol) in anhydrous toluene (10 ml), 1.5 mmol of diethyl azodicarboxylate (DEAD) were added at room temperature. The resulting mixture was heated to reflux until the disappearance of the starting amide (TLC monitoring), cooled and submitted directly to purification by column chromatography, eluting with hexane/ethyl acetate mixtures.

#### 3.3.2. Method B

To a stirred solution of the ynamide **3** (1.0 mmol), triethylamine (5.0 mmol) and 4-(dimethylamino)pyridine (4-DMAP, 0.05 mmol) in 1,2-dichloroethane (4 ml), 1.4 mmol of *p*-toluenesulfonyl chloride (TsCl) were added at room temperature. The resulting mixture was heated to reflux until the disappearance of the starting amide (TLC monitoring). After cooling, the solvent and the excess triethylamine were eliminated at reduced pressure, and the residue was purified by column chromatography, eluting with hexane/ethyl acetate mixtures.

#### 3.3.3. (4S)-4-(2-Methylpropyl)-2-(2-phenylethynyl)-1,3-oxazoline, **4ai**

Prepared according to general method A, starting from 0.494 g (2.01 mmol) of hydroxyamide **3ai**, 0.809 g (3.09 mmol) of triphenylphosphine and 0.47 ml (0.520 g, 3.00 mmol) of DEAD in 20 ml of anhydrous toluene. After heating to reflux for 24 h and chromatographic purification (92/8 hexane/ethyl acetate), 0.370 g (81% yield) of oxazoline **4ai** were obtained. Colourless crystals, mp 72–3°C. $[\alpha]_D^{23} = -84.1$ (*c* 1.17 $CHCl_3$). IR (KBr) 2954, 2234, 1628, 1362, 1163, 972, 762, 688 $cm^{-1}$. $^1H$ NMR (200 MHz) $\delta = 7.58$–7.34 (m, 5H), 4.40 (m, 2H), 3.90 (m, 1H), 1.90 (h, $J = 6.6$ Hz, 1H), 1.65 (m, 1H), 1.30 (m, 1H), 0.97 (d, $J = 6.6$ Hz, 3H), 0.95 (d, $J = 6.6$ Hz, 3H). $^{13}C$ NMR (50 MHz) $\delta = 149.5$ (Cq), 132.4 (CH), 129.9 (CH), 128.4 (CH), 120.3 (Cq), 97.0 (Cq), 89.0 (Cq), 73.0 ($CH_2$), 65.3 (CH), 45.2 ($CH_2$), 25.3 (CH), 23.0 ($CH_3$), 22.4 ($CH_3$). MS (CI-$NH_3$) $m/e = 228$ ( $[M+1]^+$, 100%). Elemental analysis: calculated for $C_{15}H_{17}NO$: C, 79.30%; H, 7.49%; N, 6.17%; found: C, 79.18%; H, 7.78%; N, 5.97%.

#### 3.3.4. (4S)-4-Benzyl-2-(2-phenylethynyl)-1,3-oxazoline, **4aii**

Prepared according to general method A, starting from 0.558 g (2.00 mmol) of hydroxyamide **3aii**, 0.785 g (3.00 mmol) of triphenylphosphine and 0.47 ml (0.520 g, 3.00 mmol) of DEAD in 20 ml of anhydrous toluene. After heating to reflux for 24 h and chromatographic purification (92/8 hexane/ethyl acetate), 0.454 g (87% yield) of oxazoline **4aii** were obtained. Colourless crystals, mp 75–6°C. $[\alpha]_D^{23} = +15.3$ (*c* 1.08 $CHCl_3$). IR (KBr) 2950, 2232, 1624, 1358, 1161, 970, 762, 689 $cm^{-1}$. $^1H$ NMR (200 MHz) $\delta = 7.55$–7.26 (m, 10H), 4.60 (m, 1H), 4.30 (m, 1H), 4.10 (m, 1H), 3.17 (dd, $J = 13.6$ Hz, $J' = 6.0$ Hz, 1H), 2.73 (dd, $J = 13.6$ Hz, $J' = 8.0$ Hz, 1H). $^{13}C$ NMR (50 MHz) $\delta = 150.0$ (Cq), 137.4 (Cq), 132.4 (CH), 130.0 (CH), 129.1 (CH), 128.6 (CH), 128.4 (CH), 126.6 (CH), 120.3 (Cq), 89.7 (Cq), 71.7 ($CH_2$), 70.0 (CH), 41.4 ($CH_2$). The signal around 97–98 ppm corresponding to the acetylenic carbon vicinal to the oxazoline ring was very weak and could not be observed. MS (CI-$NH_3$) $m/e = 262$ ( $[M+1]^+$, 100%). Elemental analysis: calculated for $C_{18}H_{15}NO$: C, 82.73%; H, 5.79%; N, 5.36%; found: C, 82.37%; H, 5.62%; N, 5.50%.

*3.3.5. (4S)-4-(*tert*-Butyl)-2-(2-phenylethynyl)-1,3-oxazoline*, ***4aiii***[4]

(a) Prepared according to general method A, starting from 0.150 g (0.61 mmol) of hydroxyamide **3aiii**, 0.478 g (1.82 mmol) of triphenylphosphine and 0.30 ml (0.332 g, 1.93 mmol) of DEAD in 6 ml of anhydrous toluene. After heating to reflux for 24 h and chromatographic purification (97/3 hexane/ethyl acetate), 0.032 g (23% yield) of oxazoline **4aiii** were obtained. (b) Following the general method B, 0.175 g (0.92 mmol) of TsCl were added to a solution of 0.128 g (0.52 mmol) of hydroxyamide **3aiii**, 0.35 ml (0.254 g, 2.5 mmol) of triethylamine and 0.006 g (0–05 mmol) of 4-DMAP in 2 ml of 1,2-dichloroethane. After heating to reflux for 24 h and chromatographic purification, 0.097 g (82% yield) of oxazoline **4aiii** were obtained. Colourless solid, mp 57–9°C. $[\alpha]_D^{23}=-69.3$ (*c* 1.19 $CHCl_3$). IR (KBr) 2959, 2869, 2230, 1634, 1354, 1163, 978, 756 $cm^{-1}$. $^1H$ NMR (200 MHz) $\delta=7.56$–7.35 (m, 5H), 4.40–4.00 (m, 3H), 0.96 (s, 9H). $^{13}C$ NMR (50 MHz) $\delta=149.2$ (Cq), 132.4 (CH), 129.9 (CH), 128.4 (CH), 120.5 (Cq), 89.0 (Cq), 76.4 (CH), 68.6 ($CH_2$), 33.8 (Cq), 25.9 ($CH_3$). The signal around 97–98 ppm corresponding to the acetylenic carbon vicinal to the oxazoline ring was very weak and could not be observed. MS (CI-$NH_3$) $m/e=228$ ($[M+1]^+$, 100%), 245 ($[M+18]^+$, 1%).

*3.3.6. (4S)-4-Benzyl-2-(2-trimethylsilylethynyl)-1,3-oxazoline*, ***4bii***

(a) Prepared according to general method A, starting from 0.424 g (1.50 mmol) of hydroxyamide **3bii**, 0.610 g (2.33 mmol) of triphenylphosphine and 0.36 ml (0.398 g, 2.30 mmol) of DEAD in 15 ml of anhydrous toluene. After heating to reflux for 15 h and chromatographic purification (99/1 hexane/ethyl acetate), 0.230 g (60% yield) of oxazoline **4bii** were obtained. (b) Following the general method B, 0.470 g (2.47 mmol) of TsCl were added to a solution of 0.446 g (1.60 mmol) of hydroxyamide **3bii**, 1.20 ml (0.871 g, 8.65 mmol) of triethylamine and 0.006 g (0.05 mmol) of 4-DMAP in 8 ml of 1,2-dichloroethane. After heating to reflux for 3 h and chromatographic purification, 0.310 g (75% yield) of oxazoline **4bii** were obtained. Colourless oil. $[\alpha]_D^{23}=-6.9$ (*c* 1.08 $CHCl_3$). IR (NaCl film) = 2961, 1624, 1346, 1252, 1221, 935, 847, 762, 700 $cm^{-1}$. $^1H$ NMR (200 MHz) $\delta=7.00$–6.99 (m, 5H), 4.20 (m, 1H), 4.00 m, 1H), 3.76 (m, 1H), 2.90 (dd, $J=14.0$ Hz, $J'=5.4$ Hz, 1H), 2.43 (dd, $J=14.0$ Hz, $J'=8.4$ Hz, 1H), 0.00 (s, 9H). $^{13}C$ NMR (50 MHz) $\delta=150.0$ (Cq), 138.0 (Cq), 129.8 (CH), 129.3 (CH), 127.3 (CH), 98.0 (Cq), 92.7 (Cq), 72.4 ($CH_2$), 68.6 (CH), 42.0 ($CH_2$), 0.0 ($CH_3$). MS (CI-$NH_3$) $m/e=258$ ($[M+1]^+$, 100%). HRMS (FAB+): calculated for $C_{15}H_{19}NOSi$: 257.1236; found: 257.1223.

*3.3.7. (4S)-4-Benzyl-2-(prop-1-ynyl)-1,3-oxazoline*, ***4cii***

(a) Prepared according to general method A, starting from 0.187 g (0.86 mmol) of hydroxyamide **3cii**, 0.436 g (1.66 mmol) of triphenylphosphine and 0.26 ml (0.288 g, 1.62 mmol) of DEAD in 10 ml of anhydrous toluene. After heating to reflux for 24 h and chromatographic purification (7/1 hexane/ethyl acetate), 0.124 g (72% yield) of oxazoline **4cii** were obtained. (b) Following the general method B, 0.366 g (1.92 mmol) of TsCl were added to a solution of 0.271 g (1.25 mmol) of hydroxyamide **3cii**, 1.00 ml (0.726 g, 7.22 mmol) of triethylamine and 0.006 g (0.05 mmol) of 4-DMAP in 6 ml of 1,2-dichloroethane. After heating to reflux for 12 h and chromatographic purification, 0.167 g (67% yield) of oxazoline **4cii** were obtained. Colourless solid, mp = 38–40°C. $[\alpha]_D^{23}=-17.4$ (*c* 1.10 $CHCl_3$). IR (NaCl film) = 3029, 2921, 2247, 1630, 1352, 1273, 1246, 1024, 955, 700 $cm^{-1}$. $^1H$ NMR (200 MHz) $\delta=7.27$–7.23 (m, 5H), 4.40 (m, 1H), 4.20 (m, 1H), 4.00 (m, 1H), 3.11 (dd, $J=13.4$ Hz, $J'=5.6$ Hz, 1H), 2.67 (dd, $J=13.4$ Hz, $J'=8.4$ Hz, 1H), 2.00 (s, 3H). $^{13}C$ NMR (50 MHz) $\delta=149.9$ (Cq), 137.4 (Cq), 129.1 (CH), 128.5 (CH), 126.5 (CH), 88.4 (Cq), 71.5 ($CH_2$), 67.6 (CH), 41.3 ($CH_2$), 4.1 ($CH_3$). The signal corresponding to the

acetylenic carbon vicinal to the oxazoline ring was very weak and could not be observed. MS (CI-$NH_3$) $m/e=200$ ($[M+1]^+$, 100%). HRMS (FAB+): calculated for $C_{13}H_{14}NO$: 200.1075; found: 200.1071.

### 3.3.8. (4S)-4-Benzyl-2-(oct-7-en-1-ynyl)-1,3-oxazoline, **4dii**

Prepared according to general method A, starting from 0.695 g (2.43 mmol) of hydroxyamide **3dii**, 1.067 g (4.07 mmol) of triphenylphosphine and 0.57 ml (0.630 g, 3.60 mmol) of DEAD in 25 ml of anhydrous toluene. After heating to reflux for 32 h and chromatographic purification (98/2 hexane/ethyl acetate), 0.389 g (60% yield) of oxazoline **4dii** were obtained. Colourless dense oil. $[\alpha]_D^{23}=-3.8$ (*c* 1.07 $CHCl_3$). IR (NaCl film)=2929, 2245, 1630, 1352, 1242, 1028 $cm^{-1}$. $^1H$ NMR (200 MHz) $\delta=7.25$–7.17 (m, 5H), 5.80 (m, 1H), 5.00 (m, 2H), 4.40 (m, 1H), 4.20 (m, 1H), 3.95 (m, 1H), 3.10 (dd, $J=14.0$ Hz, $J'=5.6$ Hz, 1H), 2.65 (dd, $J=14.0$ Hz, $J'=8.4$ Hz, 1H), 2.31 (m, 2H), 2.05 (m, 2H), 1.54 (m, 4H). $^{13}C$ NMR (50 MHz) $\delta=149.8$ (Cq), 138.1 (CH), 137.4 (Cq), 129.0 (CH), 128.5 (CH), 126.5 (CH), 114.8 ($CH_2$), 92.3 (Cq), 71.5 ($CH_2$), 69.6 (Cq), 67.7 (CH), 41.3 ($CH_2$), 33.1 ($CH_2$), 27.9 ($CH_2$), 27.1 ($CH_2$), 18.8 ($CH_2$). MS (CI-$NH_3$) $m/e=268$ ($[M+1]^+$, 100%). HRMS (FAB+): calculated for $C_{18}H_{21}NO$: 267.1623; found: 267.1622.

### 3.3.9. (4S)-4-Benzyl-2-ethynyl-1,3-oxazoline, **4eii**

To a stirred solution of 0.106 g (0.40 mmol) of the 2-(trimethylsilylethynyl)-1,3-oxazoline **4bii** in 1 ml of tetrahydrofuran, 0.01 ml (0.01 mmol) of a 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran and 0.05 ml (2.78 mmol) of distilled water were added sequentially via a syringe, at room temperature. After 30 min, the reaction mixture was diluted with 20 ml of dichloromethane and washed with 20 ml of a saturated NaCl solution. The aqueous phase, after separation, was washed with dichloromethane (2×20 ml). The combined organic phase was dried over $Na_2SO_4$, and the solvent was removed at reduced pressure. The crude product was purified by column chromatography (1/1 hexane/ethyl acetate), to give 0.067 g (91% yield) of the 2-ethynyl-1,3-oxazoline **4eii**. Colourless solid, mp=53–7°C. $[\alpha]_D^{23}=-62.5$ (*c* 1.58 $CHCl_3$). IR (NaCl film)=3178, 3023, 2915, 2120, 1628, 1350, 1211, 976, 700 $cm^{-1}$. $^1H$ NMR (200 MHz) $\delta=7.28$–7.22 (m, 5H), 4.45 (m, 1H), 4.25 (m, 1H), 4.00 (m, 1H), 3.12 (dd, $J=13.8$ Hz, $J'=6.0$ Hz, 1H), 2.95 (s, 1H), 2.70 (dd, $J=13.8$ Hz, $J'=8.4$ Hz, 1H). $^{13}C$ NMR (50 MHz) $\delta=149.0$ (Cq, 137.1 (Cq), 129.1 (CH), 128.5 (CH), 126.6 (CH), 78.3 (Cq), 71.9 (CH), 71.8 ($CH_2$), 67.8 (CH), 41.1 ($CH_2$). MS (CI-$NH_3$) $m/e=186$ ($[M+1]^+$, 100%). HRMS (FAB+): calculated for $C_{12}H_{11}NO$: 185.0841; found: 185.0843.

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