SCIENCE CHINA
Chemistry

• ARTICLES •

September 2010 Vol.53 No.9: 1921–1926
doi: 10.1007/s11426-010-4072-2

Synthesis of alkynes and alkynyl iodides bearing a protected amino alcohol moiety as functionalized amino acids precursors

AYED Charfedinne, PICARD Julien, LUBIN-GERMAIN Nadège, UZIEL Jacques* & AUGE Jacques*

Université de Cergy-Pontoise, Laboratoire de Synthèse Organique Sélective et Chimie bioOrganique-EA 4505, F-95000 Cergy-Pontoise, France

Received May 3, 2010; accepted June 23, 2010

Amino acid precursors in protected amino alcohol form are important synthons that can be used as building-blocks for the hemisynthesis of non-natural amino acids. Serine can be used as a common starting material for the synthesis of such compounds differently protected. Particularly, protected amino alcohols bearing an ethynyl and/or an iodoethynyl group can be used in cross-couplings, in 1,3-dipolar cycloadditions and/or in Nozaki-Hiyama-Kishi type reactions. We thus demonstrated that the efficiently protected amino alcohols derived from serine can be coupled to a sugar derivative by an indium mediated alkynylation reaction. The conditions of this coupling are compatible with such functionalized derivatives and allow envisaging an access to *C*-glycosylated amino acids.

amino alcohols, amino acids, oxazolidines, alkynyl iodides, *C*-glycoside, indium, alkynylation

1 Introduction

Amino acids present various important biological properties such as enzyme inhibitors or more general as therapeutic agents. Among the methods used for the synthesis of non-natural amino acids, the hemisynthesis [1] starting from natural chiral sources such as serine or other amino acids is a very interesting approach as it avoids the introduction of the chirality during the synthesis. It is indeed possible in many cases to take advantage of the fact that the configuration of the chiral center can be maintained during the synthetic sequence. Various building-blocks have received a large attention. Among them, those being amino alcohol derivatives have the advantage not to present an acidic α hydrogen atom and thus limit the risk of a racemization of the amino acid chiral center during a particular step of the synthetic pathway.

Oxazolidine **2** is one of the most interesting such building-blocks as it can be easily prepared from Garner's aldehyde **1** [2] itself derived from L- or D-serine. Meffre, Reginato *et al.* [3, 4] described its synthesis according to one-pot multicomponent process involving the *in situ* formation of the Ohira reagent [5].

Oxazolidines being a very efficient protection of amino alcohols, some other building-blocks seemed interesting to us. Thus, the protection of the amino group was changed and the synthons **7**, **8** and **11** were synthesized. In addition, iodoalkyne **13** bearing a silylated alcohol and a *N,N*-dibenzylated amine was also prepared.

This type of building-blocks could be used for the preparation of *C*-glycosylated amino acids through coupling with a sugar derivative. Introduced in peptide chains they can lead to interesting glycopeptides presenting a strong link between the sugar and the amino acid part.

We are particularly interested in the obtaining of such building-blocks bearing an α-ethynyl group and/or an α-iodoethynyl group as precursors of ethynylglycine and/or

*Corresponding author (email: jacques.auge@u-cergy.fr; jacques.uziel@u-cergy.fr)

iodoethynylglycine. This kind of synthons can be efficiently used in various reactions particularly Sonogashira cross-couplings or 1,3-dipolar cycloadditions in the case of terminal alkynes or Nozaki-Hiyama-Kishi (NHK) type alkynylations in the case of halogeno alkynes. We have recently described the indium mediated alkynylation of carbonyl derivatives with alkynyl iodides under Barbier conditions in chlorinated solvents [6, 7]. This reaction allows the easy obtaining of the corresponding propargylic alcohols. We have also extended it to the anomeric position of carbohydrates leading thus to the synthesis of *C*-glycosides [8–11]. In this case the possession of such iodoethynylglycine precursors allows us envisaging a pathway towards the synthesis of *C*-glycosylated amino acids, more stable analogues of Glc-Ser or other *O*-glycosylated amino acids.

In order to show the utility of the prepared building-blocks, we used them in two indium mediated alkynylation reactions of sugar derivatives, demonstrating that the conditions recently developed in our laboratory [8, 9] are compatible with such functionalized derivatives. We first showed that oxazolidine **3** in presence of indium reacts on the aldehyde of a formylglucose and leads to the corresponding propargylic alcohol **14**. In addition, we also realized the highly stereoselective alkynylation on the anomeric position of glucal with the iodoalkyne **13** leading exclusively to the α anomer of the corresponding *C*-glycoside **15**.

2 Experimental

2.1 General experimental

Infrared spectra were recorded on a Bruker Tensor 27 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 250 DPX and a JEOL ECX-400 spectrometers. Elemental analyses were done at the Central Service of Analysis (CNRS, Vernaison, France). High resolution mass spectra were obtained with a JEOL GC Mate II apparatus. Rotation values were recorded on a JASPO DIP 370 instrument. Melting points (uncorrected) were determined on a Büchi B-545.

2.2 Synthesis of the *tert*-butyl (*R*)-4-iodoethynyl-2,2-dimethyloxazolidine-3-carboxylate (3)

*tert-Butyl (R)-4-ethynyl-2,2-dimethyloxazolidine-3-carboxylate (**2**)*

In a vigorously stirred solution of dimethyl 2-oxopropylphosphonate (4.98 g, 30 mmol) in $CHCl_3$ (70 mL) were added at 0 °C 4-acetamidobenzenesulfonyl azide (7.2 g, 30 mmol) and potassium carbonate (4.2 g, 30.5 mmol). The solution was stirred at this temperature for 48 h as a white suspension was formed. Potassium carbonate (1.93 g, 14 mmol) was then added at 0 °C followed by a solution of Garner's aldehyde **1** (2 g, 8,72 mmol) in MeOH (70 mL). After stirring for 24 h more, a saturated solution of NH_4Cl (200 mL) was added. The organic layer was washed with a saturated solution of NH_4Cl (200 mL) and with H_2O (2 × 200 mL). Each aqueous layer was extracted with $CHCl_3$ (100 mL). The organic layers were assembled and dried over $MgSO_4$. The obtained product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate: 9/1), leading to **2**; yield 67% (1.32 g), R_f = 0.6 (cyclohexane/ethyl acetate: 8/2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.49 (m, 1H), 3.95 (m, 2H), 2.21 (s, 1H, C≡CH), 1.5 (s, 3H), 1.45 (s, 12H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 151.4 (CO), 94.5 (C^{quat} isopropyl), 82.7 (C^{quat} Boc), 80.4 (C^{quat} C≡C), 70.1 (C≡CH), 68.6 (CH_2), 48.3 (CH), 28.4, 26.8, 25.8, 25.1, 24.3 (5 × CH_3).

*tert-Butyl (R)-4-iodoethynyl-2,2-dimethyloxazolidine-3-carboxylate (**3**)*

In a mixture obtained by stirring for 30 min iodine (1.64 g, 6.46 mmol) and morpholine (1.53 mL, 17.57 mmol) in benzene (7 mL) was added a solution of the above alkyne **2** in benzene (10 mL). The mixture was stirred for 24 h at 45 °C, then filtered and washed with diethyl ether (30 mL). The filtrate was washed with a saturated solution of NH_4Cl (15 mL), with a saturated solution of $NaHCO_3$ (15 mL), with H_2O (15 mL) and then dried over $MgSO_4$. The obtained product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate: 9/1), leading to **3**; yield 90% (1.85 g), R_f = 0.6 (cyclohexane/ethyl acetate: 9/1). mp 61 °C. $[\alpha]_D = -104$ (c = 3.4, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.62 (m, 1H), 4.01 (m, 2H), 1.62 (s, 3H), 1.49 (s, 12H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 151.4 (CO), 94.3 (C^{quat} isopropyl), 92.9 (C^{quat} C≡C), 80.4 (C^{quat} Boc), 68.5 (CH_2), 50.0 (CH), 28.3, 26.8, 25.7, 24.9, 24.4 (5 × CH_3), −1.3 (≡C–I). IR: ν = 1677, 2980 cm^{-1}. Anal. calcd for $C_{12}H_{18}INO_3$: C, 41.04; H, 5.17; N, 3.99; found: C, 41.10; H, 5.27; N, 3.84.

2.3 Synthesis of the (*R*)-3-(*o*-phenylbenzoyl)-4-iodo ethynyl-2,2-dimethyl oxazolidine (8)

*(R)-3-(o-Phenylbenzoyl)-2,2-dimethyloxazolidine-4-methanol (**5**)*

Into a suspension of calcium chloride (3.44 g, 30.96 mmol) in anhydrous THF (18 mL) was added a solution of methyl (*S*)-3-(*o*-phenylbenzoyl)-2,2-dimethyloxazolidine-4-carboxylate **4** (1.38 g, 4.05 mmol) in anhydrous ethanol (30 mL). Sodium borohydrate (2 g, 52.86 mmol) was then added in small portions at −20 °C. The mixture was stirred at room temperature overnight. After addition of ethyl ether (60 mL) the medium was hydrolyzed at −20 °C with a saturated solution of Na_2SO_4. The organic layer was then washed with brine (2 × 10 mL) and dried over $MgSO_4$. The obtained product **5** was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate: 4/6); yield 93% (1.28 g).

R_f = 0.1 (cyclohexane/ethyl acetate: 4/6). $[\alpha]_D = -185$ (c = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (m, 9H, Ph), 3.69 (d, J = 8.7 Hz, 1H, CH_2), 3.29 (dd, J = 8.7, 8.2 Hz, 1H, CH_2OH), 3.21 (m, 1H, CH), 3.16 (m, 1H, CH_2OH), 3.01 (dd, 1H, J = 8.7, 5.0 Hz, CH_2), 1.66 (s, 3H, CH_3), 1.49 (sl, 1H, OH), 1.23 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1 (CO), 139.5, 137.8, 136.6, 129.7, 129.1, 128.8, 128.1, 127.9, 127.7 (Ph), 95.5 (C^{quat} isopropyl), 65.0 (CH_2), 62.1 (CH_2OH), 58.9 (CH), 27.0 (CH_3), 21.9 (CH_3). IR: ν = 1610, 2982, 3409 cm^{-1}. HRMS calcd for $C_{19}H_{21}NO_3$: 311.1521; found: 311.1534.

*(R)-3-(o-Phenylbenzoyl)-2,2-dimethyloxazolidine-4-formal dehyde (**6**)*

Into a solution of oxalyl chloride (3.6 mL, 42.4 mmol) in CH_2Cl_2 (85 mL) was added dropwise at −78 °C a solution of DMSO (6 mL, 84.8 mmol) in CH_2Cl_2 (15 mL). After 10 min the (*R*)-3-(*o*-phenylbenzoyl)-2,2-dimethyloxazolidine-4-methanol **5** (8.8 g, 28.25 mmol) in CH_2Cl_2 (25 mL) was added dropwise and the mixture was stirred for 30 min at −60 °C. Triethylamine (19.6 mL, 141 mmol) in CH_2Cl_2 (15 mL) was then added dropwise and after return to room temperature water (45 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were assembled and washed with water (3 × 140 mL) and brine (140 mL) and then dried over $MgSO_4$. The obtained product was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate: 7/3), leading to **6**; yield 76% (6.65 g), R_f = 0.1 (cyclohexane/ethyl acetate: 7/3). $[\alpha]_D = -84$ (c = 10.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.23 (s, 1H, CHO), 7.44 (m, 9H, Ph), 3.88 (dd, J = 7.5, 1.8 Hz 1H, CH_2), 3.65 (dl, J = 6.8 Hz, 1H, CH), 3.28 (dd, J = 7.5, 6.8 Hz, 1H, CH_2), 1.71 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.9 (CO), 168.2 (CO), 139.3, 137.6, 136.2, 130.1, 129.6, 129.0, 128.3, 128.0 (Ph), 96.8 (C^{quat} isopropyl), 65.8 (CH), 63.9 (CH_2), 25.8, 22.4 (2 × CH_3). IR: ν = 1641, 1735, 2177, 2984, 3061 cm^{-1}. HRMS calcd for $C_{19}H_{19}NO_3$: 309.1379; found: 309.1365.

*(R)-3-(o-Phenylbenzoyl)-4-ethynyl-2,2-dimethyloxazolidine (**7**)*

In a vigorously stirred solution of aldehyde **6** (5.26 g, 17 mmol) in MeOH (360 mL) were added at 0 °C potassium carbonate (4.4 g, 31.8 mmol) and a solution of dimethyl 1-diazo-2-oxopropylphosphonate (5.53 g, 28.8 mmol) in MeOH (5 mL). After 16 h stirring at room temperature the medium was diluted with ethyl ether (400 mL), washed with a 5% solution of sodium bicarbonate (50 mL) and dried over $MgSO_4$. The crude product was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate: 9/1), leading to **7**; yield 97% (5.05 g), R_f = 0.9 (cyclohexane/ethyl acetate: 9/1). $[\alpha]_D = -6$ (c = 1.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (m, 9H, Ph), 3.81 (sl, 1H, CH), 3.70 (d, J = 7.8 Hz, 1H, CH_2), 3.16 (sl, 1H, CH_2), 2.10 (d, J = 1.8 Hz, 1H, C≡CH), 1.74 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7 (C=O), 139.5, 136.5, 129.7, 129.3, 128.9, 128.7, 128.1, 128.0, 127.7 (Ph), 96.1 (C^{quat} isopropyl), 81.4 (C^{quat} C≡C), 71.7 (C≡CH), 68.9 (CH_2), 49.6 (CH), 26.2, 22.7 (2 × CH_3). IR: ν = 1613, 1739, 2176, 2983, 3058, 3287 cm^{-1}. HRMS calcd for $C_{20}H_{19}NO_2$: 305.1416; found: 305.1414.

*(R)-3-(o-Phenylbenzoyl)-4-iodoethynyl-2,2-dimethyloxazolidine (**8**)*

In a mixture obtained by stirring for 45 min iodine (6.28 g, 24.7 mmol) and morpholine (4.4 mL, 0.5 mmol) in benzene (60 mL) was added a solution of the above (*R*)-3-(*o*-phenylbenzoyl)-4-ethynyl-2,2-dimethyloxazolidine **7** in benzene (15 mL). The mixture was stirred for 48 h at 45 °C, then filtered and washed with diethyl ether (100 mL). The filtrate was concentrated up to 30 mL and then washed with a saturated solution of NH_4Cl (2 × 20 mL), with a saturated solution of $NaHCO_3$ (20 mL), with H_2O (20 mL) and then dried over $MgSO_4$. The obtained product was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate: 9/1), leading to **8**; yield 73% (5.2 g), R_f = 0.9 (cyclohexane/ethyl acetate: 9/1). $[\alpha]_D = -5$ (c = 1.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (m, 9H, Ph), 3.87 (sl, 1H, CH), 3.70 (d, J = 6.9 Hz, 1H, CH_2), 3.23 (sl, 1H, CH_2), 1.73 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9 (C=O), 139.6, 137.6, 136.6, 129.8, 129.4, 128.9, 128.7, 128.3, 128.1, 127.7 (Ph), 96.2 (C^{quat} isopropyl), 91.7 (C^{quat} C≡C), 68.8 (CH_2), 51.2 (CH), 26.1, 22.9 (2 × CH_3), 1.3 (≡C–I). IR: ν = 1613, 2177, 2982 cm^{-1}. HRMS calcd for $C_{20}H_{18}INO_2$: 431.0383; found: 431.0379.

2.4 Synthesis of the (*S*)-3-benzyl-4-ethynyl-2,2-dimethyl-oxazolidine (11)

*(R)-3-Benzyl-2,2-dimethyloxazolidine-4-formaldehyde (**10**)*

Into a solution of oxalyl chloride (2.6 mL, 30 mmol) in CH_2Cl_2 (60 mL) was added dropwise at −78 °C a solution of DMSO (4.6 mL, 64.8 mmol) in CH_2Cl_2 (10 mL). After 10 min, the (*S*)-3-benzyl-2,2-dimethyloxazolidine-4-methanol **9** (5.5 g, 25 mmol) in CH_2Cl_2 (30 mL) was added dropwise and the mixture was stirred for 30 min at −60 °C. Triethylamine (18 mL, 190 mmol) in CH_2Cl_2 (10 mL) was then added dropwise and after return to room temperature water (30 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The organic layers were assembled and washed with water (3 × 100 mL) and brine (100 mL) and then dried over $MgSO_4$. The obtained product **10** (4.65 g, 84%) was used in the next step without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.87 (d, 1H, J = 4.6 Hz, CHO), 7.23 (m, 5H, Ph), 4.01 (dd, J = 9.2, 8.7 Hz, 1H, CH_2), 3.91 (d, J = 12.8 Hz 1H, CH_2Ph), 3.80 (dd, J = 9.2, 6.0 Hz, 1H, CH_2), 3.39 (d, J = 12.8 Hz 1H, CH_2Ph), 3.29 (ddd, J =

8.7, 6.0, 4.6 Hz, 1H, CH), 1.39 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.3 (CO), 138.4, 129.5, 128.7, 128.0 (Ph), 96.9 (C^{quat} isopropyl), 70.6 (CH), 64.0 (CH_2), 53.9 (CH_2Ph), 27.1, 20.6 ($2\times CH_3$).

*(S)-3-Benzyl-4-ethynyl -2,2-dimethyloxazolidine (**11**)*

Into a solution of (*R*)-3-benzyl-2,2-dimethyloxazolidine-4-formaldehyde **10** (1.4 g, 6.4 mmol) in methanol (95 mL) was added K_2CO_3 (1.17 g, 8 mmol) under vigorous stirring. Then dimethyl 1-diazo-2-oxopropylphosphonate (1.4 g, 7.6 mmol) in MeOH (5 mL) was added at 0 °C. After 16 h at room temperature, the medium was diluted with ethyl ether (150 mL) and washed with a 10% $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$ and the product was purified by flash chromatography on silica gel (triethylamine/cyclohexane: 1/1) leading to **11**; yield 40% (0.55 g); R_f = 0.85 (cyclohexane/ethyl acetate: 9/1). mp 48 °C. $[\alpha]_D$ = −2 (c = 10.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (m, 5H, Ph), 4.04 (dd, J = 7.3, 6.0 Hz, 1H, CH_2), 3.98 (dd, J = 7.3, 3.2 Hz 1H, CH_2), 3.87 (d, J = 13.3 Hz, 1H, CH_2Ph), 3.83 (d, J = 13.3 Hz 1H, CH_2Ph), 3.76 (ddd, J = 6.0, 3.2, 2.3, Hz, 1H, CH), 2.36 (d, J = 2.3 Hz, 1H, C≡CH), 1.38 (s, 3H), 1.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.3, 128.9, 128.4, 127.2 (Ph), 95.4 (C^{quat} isopropyl), 82.3 (C≡CH), 74.1 (C≡C), 70.6 (CH), 69.5 (CH_2), 50.9 (CH), 49.0 (CH_2Ph), 26.6, 24.1 ($2\times CH_3$). HRMS calcd for $C_{14}H_{17}NO$: 215.1310; found: 215.1321.

2.5 Synthesis of the (*S*)-1-iodo-3-dibenzylamino-4-(*tert*-butyldiphenylsiloxy)but-1-yne (13)

After complete dissolution of iodine (1.22 g, 4.8 mmol) in benzene (30 mL), morpholine (1.2 mL, 12 mmol) was added and the mixture was stirred for 45 min until appearance of an orange precipitate. The compound **12** (2.04 g, 4 mmol) in benzene (10 mL) was then added and the mixture was heated at 50 °C for 48 h. The medium was cooled, diluted with ethyl ether (100 mL) and filtered. The filtrate was reduced to 20 mL by evaporation under vacuum. The organic layer was washed with a saturated solution of NH_4Cl (2×15 mL), a saturated solution of $NaHCO_3$ (15 mL), water (20 mL) and then dried over $MgSO_4$. The crude product was purified on silica gel (cyclohexane/ethyl acetate: 95/5) leading to **13**; yield 70% (1.77 g); R_f = 0.8 (cyclohexane/ethyl acetate: 9/1); mp 156 °C. $[\alpha]_D$ = +9 (c = 2.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (m, 20H, Ph), 3.96 (d, J = 13.7 Hz, 2H, CH_2Ph), 3.94 (m, 1H, CH), 3.88 (dd, J = 10.1, 6.9 Hz, 1H, CH_2), 3.79 (dd, J = 10.1, 6.0 Hz, 1H, CH_2), 3.54 (d, J = 14.2 Hz, 2H, CH_2Ph), 1.12 (s, 9H, *tert*Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ 129.8, 128.8, 128.4, 127.8, 127.1 (Ph), 91.7 (C≡C), 65.1 (CH), 65.1 (CH), 56.3 (CH_2Ph), 55.7 (CH_2), 26.9 (CH_3 *tert*Bu), 19.3 (C^{quat} *tert*Bu), –0.1 (≡CI). IR: ν = 1588, 2247, 2929, 3067 cm^{-1}. HRMS calcd for $C_{34}H_{36}NOISi$: 629.1611; found: 629.1627.

2.6 Coupling reactions

*tert-Butyl(R)-4-[3-hydroxy-3-(2,3,4,6-tetra-O-benzyl-D-gluco-β-C-pyranosyl)prop-1-ynyl]-2,2-dimethyloxazolidine-3-carboxylate (**14**)*

Indium (0.28 g, 2.4 mmol) was stirred during 1 h under vacuum under vacuum/argon in a sealed tube. Then, a solution of *tert*-butyl (*R*)-4-iodoethynyl-2,2-dimethyloxazolidine-3-carboxylate **3** (0.70 g, 2 mmol) and 2,3,4,6-tetra-*O*-benzyl-1-formyl-β-D-glucopyranose (0.55 g, 1 mmol) in anhydrous CH_2Cl_2 (15 mL) was introduced to the medium which was refluxed overnight. The medium was then hydrolyzed with a saturated solution of $NaHCO_3$ (10 mL). The aqueous layer was extracted with dichloromethane (2×10 mL). The organic layers were assembled and dried over $MgSO_4$. The obtained product was obtained as a mixture of two diastereomers in a 2/1 ratio that were separated by flash chromatography on silica gel (petroleum ether/ethyl acetate: 8.5/1.5) leading to **14**; yield 66% (0.51 g). Major diastereomer R_f = 0.5 (cyclohexane/ethyl acetate: 7/3). $[\alpha]_D$ = −12 (c = 2.0, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.14 (m, 20H, Ph), 5.12–4.62 (m, 10H, CH_2Ph, CHN and CHOH), 3.88 (m, 2H, CH_2O), 3.68–3.28 (m, 7H, 1-H, 2-H, 3-H, 4-H, 5-H, 6-H), 1.54 (s, 3H), 1.40 (s, 12H). ^{13}C NMR (62.9 MHz, $CDCl_3$): 151.4 (CO), 138.4–137.7, 128.4–127.5 (Ph), 94.2 (C^{quat} isopropyl), 93.8 (C≡C), 86.7 (1-C), 83.9 (C≡C), 81.0 (C^{quat} Boc), 80.4, 78.9, 78.1, 77.9 (2-C, 3-C, 4-C, 5-C), 75.3, 75.2, 74.9, 73.3 (CH_2Ph), 68.5 (6-C, CH_2O), 61.4 (CHOH), 48.5 (CHN), 28.3, 26.8, 25.9, 25.2, 24.3 (CH_3). IR: ν = 1496, 1697, 2922, 3401 cm^{-1}. HRMS $[M+NH_4]^+$ calcd for $C_{47}H_{59}N_2O_9$: 795.4221; found: 795.4211. Minor diastereomer R_f = 0.3 (cyclohexane/ethyl acetate: 7/3). $[\alpha]_D$ = −14 (c = 2.1, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.14 (m, 20H, Ph), 4.81–4.44 (m, 10H, CH_2Ph, CHN and CHOH), 3.85 (m, 2H, CH_2O), 3.66–3.39 (m, 7H, 1-H, 2-H, 3-H, 4-H, 5-H, 6-H), 1.52 (s, 3H), 1.37 (s, 12H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 151.3 (CO), 138.4–137.9, 128.3–127.5 (Ph), 94.3 (C^{quat} isopropyl), 93.8 (C≡C), 86.7 (1-C), 85.6 (C≡C), 80.5 (C^{quat} Boc), 80.2, 79.9, 78.9, 78.3 (2-C, 3-C, 4-C, 5-C), 75.4, 75.2, 75.0, 73.1 (CH_2Ph), 68.8, 68.4 (6-C, CH_2O), 61.5 (CHOH), 48.5 (CHN), 28.4, 26.9, 26.1, 25.1, 24.1 (CH_3). IR: ν = 1496, 1702, 2923, 3405 cm^{-1}. HRMS $[M+NH_4]^+$ calcd for $C_{47}H_{59}N_2O_9$: 795.4221; found: 795.4216.

*1-(4,6-di-O-Acetyl-2,3-dideoxy-D-erythrohex-2-enopyranosyl)-(S)-3-dibenzylamino-4-(tert-butyldiphenylsiloxy)but-1-yne (**15**):*

Indium bromide (0.36 g, 1.86 mmol) was stirred during 1 h under vacuum/argon in a sealed tube. Then, a solution of (*S*)-1-iodo-3-dibenzylamino-4-(*tert*-butyldiphenylsiloxy)butyne **13** (0.94 g, 1.5 mmol) and tri-*O*-acetyl-D-glucal (0.2 g, 0.74 mmol) in anhydrous CH_2Cl_2 (20 mL) was introduced to the medium which was refluxed for 24 h. The mixture

was filtered over celite and the crude was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate: 8/2), leading to **15**; yield 40% (0.53 g), R_f=0.4 (cyclohexane/ethyl acetate: 8/2). $[\alpha]_D$=+1 (c=6.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (m, 20H, Ph), 5.84 (ddd, J=10.1, 3.4, 1.4 Hz, 1H, 2-H), 5.72 (dd, J=10.1, 1.8 Hz, 1H, 3-H), 5.25 (ddd, J=8.2, 3.4, 1.8 Hz, 1H, 4-H), 5.01 (d, J=1.4 Hz, 1H, 1-H), 4.16 (m, 3H, 5-H, 6-H), 3.82 (d, J=14.0, 2H, CH_2Ph), 3.73 (m, 2H, CH_2), 3.65 (dd, J=7.1, 3.4 Hz, 1H, CH), 3.41 (d, J=14.0, 2H, CH_2Ph), 2.01 (s, 3H, Ac), 1.98 (s, 3H, Ac), 0.96 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 170.4 (CO), 139.5, 135.6, 133.3 (Ph), 129.8 (2-C), 129.7, 128.8, 128.4, 127.7, 127.1 (Ph), 125.3 (3-C), 83.2 (C≡C), 81.7 (C≡C), 70.0 (5-C), 65.0 (CH_2, 4-C), 64.3 (1-C), 63.3 (6-C), 55.7 (CH_2Ph), 54.4 (CH), 26.9 (CH_3 terbutyl), 21.1, 21.0 (2×CH_3, Ac), 19.3 (C^{quat} terbutyl). IR: ν=1742, 2932, 3029 cm^{-1}. HRMS calcd for $C_{44}H_{49}NO_6Si$: 715.3329; found: 715.3331.

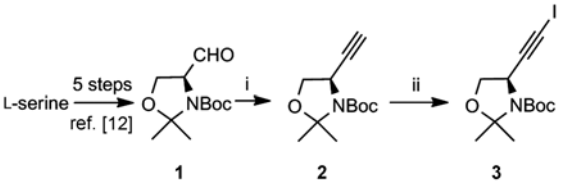
3 Results and discussion

3.1 Synthesis of the *tert*-butyl (*R*)-4-iodoethynyl-2,2-dimethyloxazolidine-3-carboxylate (3)

This alkynyl iodide was obtained starting from Garner's aldehyde **1**. This well known aldehyde presents the amino alcohol part protected as a *N*-Boc oxazolidine. We prepared it in five steps starting from L-serine according to the procedure described by Dondoni *et al.* [12]. The aldehyde was then homologated into the terminal alkyne **2** by the Seyferth-Colvin-Gilbert reaction using the Ohira-Bestman reagent *i.e.* the dimethyl 1-diazo-2-oxopropylphosphonate. We chose Meffre *et al*. modification [3] in which this diazo derivative is prepared *in situ* from *p*-acetamidobenzenesulfonyl azide and dimethyl 2-oxopropylphosphonate in presence of potassium carbonate. The iodination was then achieved with a high yield by reaction of iodine and morpholine in benzene heated at 45 °C (Scheme 1).

3.2 Synthesis of the (*R*)-3-(*o*-phenylbenzoyl)-4-iodo ethynyl-2,2-dimethyl oxazolidine (8)

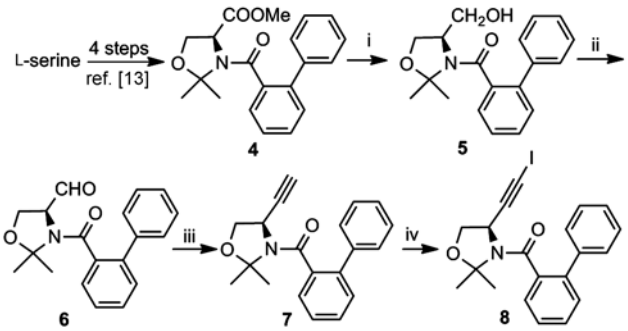
The interest of this building-block lies in the presence of the biphenylcarbonyl group that confers to the synthetic intermediates a particular stability. It is noteworthy that many of the compounds are crystalline making easier their manipulation. The preparation of this synthon is performed from ester **4** obtained in four steps from L-serine [13]. We selectively reduced the methyl ester by sodium borohydrate in the presence of calcium chloride at −20 °C, and then oxidized the obtained alcohol under Swern conditions. The aldehyde **6** was then transformed into the terminal alkyne and the corresponding iodo alkyne according to the same procedures used for the obtaining of **2** and **3** (Scheme 2).



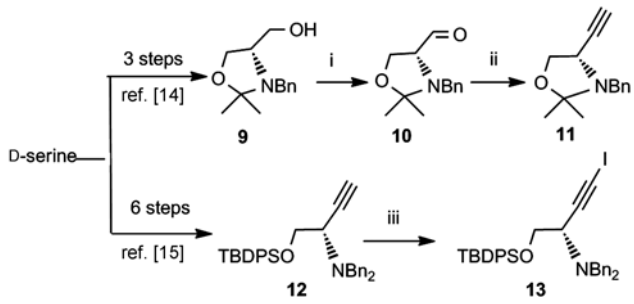
Scheme 1 Reaction conditions: (i) K_2CO_3, $CHCl_3$, *p*-$CH_3CONHC_6H_4SO_2N_3$, $CH_3COCH_2P(O)(OMe)_2$, 0 °C, 48 h then MeOH, 0 °C, 24 h, 67%; (ii) I_2, morpholine, benzene, 45 °C, 24 h , 90%.

3.3 Synthesis of the (*S*)-3-benzyl-4-ethynyl-2,2-dimethyloxazolidine (11) and (*S*)-1-iodo-3-dibenzylamino-4-(*tert*-butyldiphenylsiloxy)but-1-yne (13)

The precedent building-blocks bearing the amino group under a carbamate or an amide form, we wanted also to access to synthons with a tertiary amine functional group. Thus the above alkyne **11** and iodoalkyne **13** were also prepared. The first one was obtained by oxidation and homologation of alcohol **9** issued from D-serine after a three step transformation [14]. The second one was reached by iodination of the terminal alkyne **12** that results also from D-serine after a six step transformation [15] (Scheme 3).



Scheme 2 Reaction conditions: (i) $NaBH_4$, $CaCl_2$, EtOH, −20 °C, 2 h then rt, 16 h, 93%; (ii) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C then Et_3N, 76%; (iii) $CH_3COC(=N_2)P(O)(OMe)_2$, K_2CO_3, MeOH, 0 °C, 1 h then rt, 16 h, 97%; (iv) I_2, morpholine, benzene, 45 °C, 48 h , 73%.

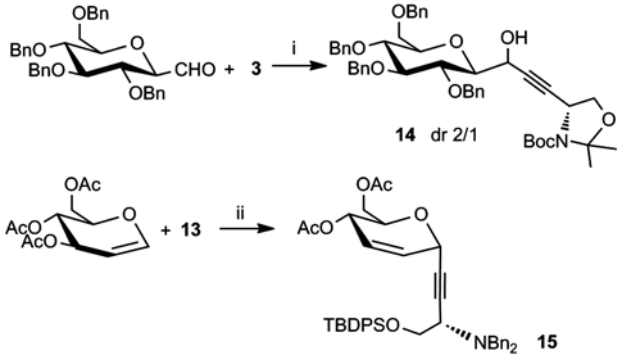


Scheme 3 Reaction conditions: (i) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C then Et_3N, 84%; (ii) $CH_3COC(=N_2)P(O)(OMe)_2$, K_2CO_3, MeOH, 0 °C, 1 h then rt, 16 h, 40%; (iii) I_2, morpholine, benzene, 45 °C, 48 h , 70%.

3.4 Coupling reactions

Indium-promoted organometallic reactions have elicited considerable attention since the discovery of the remarkable reactivity of this metal [16]. Indium-mediated alkynylation of carbonyl compounds and sugar derivatives was largely developed in our laboratory [6–11]. In order to extend this reactivity to more functionalized molecules, we first explored the reaction of alkynyl iodide **3** with 2,3,4,5-tetra-*O*-benzyl-1-formylglucopyranose that was prepared in three steps starting from *per*benzylgluconolactone [17]. The coupling proceeded efficiently in dichloromethane in presence of metallic indium and the corresponding propargylic alcohol was obtained in 66% yield as a 2/1 mixture of two diastereomers that can be easily separated by flash chromatography. In another hand, we also checked the *C*-glycosylation by an alkynylation on the 1-position of tri-*O*-acetylglucal. In this case, the Ferrier-type reaction with iodide **13** in presence of 2.4 equivalents of indium (I) bromide in refluxing dichloromethane led to the corresponding *C*-glycoside in 40% yield exclusively under the α anomer form (Scheme 4).

These results are very promising as they allow envisaging the access to carbonated analogues of glycosyl serines or homoserines after deprotection of the amino acid part and functionalization of the sugar moiety in the second case.



Scheme 4 Reaction conditions: (i) In, CH_2Cl_2, reflux, overnight, 66%; (ii) InBr, CH_2Cl_2, reflux, 24 h, 40%.

4 Conclusions

We described herein the synthesis of some alkynes and iodoalkynes bearing a protected amino alcohol moiety as amino acid precursors. As the described building-blocks present diversely protected functional groups, they could be introduced in reactions that use different conditions. As an example we introduced two of these synthons in an indium mediated alkynylation reaction of sugar derivatives demostrating the compatibility of the coupling conditions with such functionalized compounds.

1 Duthaler R. Recent developments in the stereoselective synthesis of α-aminoacids. *Tetrahedron*, 1994, 50: 1539–1650
2 Garner P, Park JM. The synthesis and configurational stability of differentially protected β-hydroxy-α-amino aldehydes. *J Org Chem*, 1987, 52: 2361–2364
3 Meffre P, Hermann S, Durand P, Reginato G, Riu A. Practical one-pot synthesis of ethynylglycine synthon from Garner's aldehyde. *Tetrahedron*, 2002, 58: 5159–5162
4 Reginato G, Meffre P, Gaggini F. Ethynylglycine synthon from Garner's aldehyde: A useful precursor for the synthesis of non-natural amino acids. *Amino Acids*, 2005, 29: 81–87
5 Ohira S. Methanolysis of dimethyl(1-diazo-2-oxopropyl)phosphonate. Generation of (diazomethyl) phosphonate ansd reaction with carbonyl compounds. *Synth Commun*, 1989, 19: 81–87
6 Augé J, Lubin-Germain N, Seghrouchni L. Indium-mediated carbonyl alkynylation. *Tetrahedron Lett*, 2002, 43: 5255–5256
7 Augé J, Lubin-Germain N, Seghrouchni L. Indium-mediated formation of propargyl ketones from aldehydes or acylchlorides. *Tetrahedron Lett*, 2003, 44: 819–821
8 Picard J, Lubin-Germain N, Uziel J, Augé J. Indium mediated alkynylation in *C*-glycoside synthesis. *Synthesis*, 2006, 979–982
9 Lubin-Germain N, Hallonet A, Huguenot F, Palmier S, Uziel J, Augé J. Ferrier-type alkynylation reaction mediated by indium. *Org Lett*, 2007, 9: 3679–3682
10 Lubin-Germain N, Baltaze JP, Coste A, Hallonet A, Lauréano H, Legrave G, Uziel J, Augé. Direct *C*-glycosylation by indium-mediated alkynylation on sugar anomeric position. *Org Lett*, 2008, 10: 725–728
11 Aït Youcef R, Dos Santos M, Roussel S, Baltaze JP, Lubin-Germain N, Uziel J. Huisgen cycloaddition reaction of *C*-alkynyl ribosides under micellar catalysis: Synthesis of ribavirin analogues. *J Org Chem*, 2009, 74: 4318–4323
12 Dondoni A, Perrone D. Synthesis of 1,1-dimethylethyl-(*S*)-4-formyl-2,2-dimethyl-3-oxazolidine carboxylate by oxidation of the alcohol. *Org Synth*, 2000, 77: 64–77
13 Wanyoike GN, Onomura O, Maki T, Matsumura Y. Highly enhanced enantioselectivityin the memory of the chirality via acyliminium ions. *Org Lett*, 2002, 4: 1875–1877
14 Barco A, Benetti S, Spalluto G, Casolari A, Pollini GP, Zanirato V. A new approach to kainoids through tándem Michael reaction methodology: Application to the enantioselective synthesis of (+)- and (–)-α-allokainic acid and to the formal synthesis of (–)-α-kainic acid. *J Org Chem*, 1992, 57: 6279–6286
15 Salvador BA, Solis FC. Derivatives of fusarochromanone as therapeutic agents. WO 2004/103985. 2004-2-12
16 Augé J, Lubin-Germain N, Uziel J. Recent advances in indium-promoted organic reactions. *Synthesis*, 2007, 1739–1764
17 Lasterra-Sanchez ME, Michelet V, Besnier I, Genêt JP. Convenient methods for the synthesis of β-*C*-glycosides. *Synlett*, 1994, 705–708