C-Quaternary alkynyl glycinols via the Ritter reaction of cobalt complexed alkynyl glycols†

K. Grammatoglou,‡ J. Bolsakova‡ and A. Jirgensons*‡

A novel approach to C-quaternary alkynyl glycinols based on the Ritter reaction of acetonitrile with cobalt complexed alkynyl glycols is presented. The reaction is promoted by acids such as H2SO4 or BF3·Et2O to give oxazolines as the reaction products. These are subjected to cobalt complex cleavage in oxidative conditions and subsequent acidic hydrolysis providing amino alcohols. The substrates for the Ritter reaction can be easily assembled to introduce structural diversity at both variable positions. The Ritter reaction conditions for oxazoline formation is compatible with a range of substituents at the alkyne terminal position providing oxazolines in moderate to good yields. Methyl, hydroxymethyl and silyloxymethyl substituents at the reaction center of glycols are well tolerated, while a phenyl group in this position is detrimental to the reaction.

Introduction

C-Quaternary alkynyl glycinols 1 and synthetically equivalent alkynyl glycine 2 derivatives (Fig. 1) are versatile building blocks for the construction of complex biologically active molecules.1–7 While there is a good arsenal of methods for the synthesis of C-quaternary alkynyl glycines 2,1,2 the direct access to C-quaternary alkynyl glycinols 1 is limited to few alternatives avoiding the reduction of carboxyl groups in glycines 2. The literature search revealed only the Seyferth–Gilbert homologation of a serinal derivative,8 aminolysis of alkynyl epoxides7,9–12 and the insertion of a nitrene into a propargylic C–H bond13 as synthetically useful approaches. Thus, a short synthesis of glycinol derivatives 1 from readily available variable building blocks is very desirable.

We have recently reported the synthesis of alkynyl glycinols 1 (R1 = H) via intramolecular propargylic amination of bis-trichloroacetimidates derived from alkynyl glycols.14 Our attempts to extend this approach for the synthesis of C-quaternary derivatives were not successful. As an alternative, we turned our attention to the Ritter reaction of 1,2-diols which is a known method for the synthesis of oxazolines and oxazines involving carbenium ion A and nitrilium ion B intermediates.15–24 When alkynyl glycol 3 (R1 = Me, R2 = nPent) was directly subjected to the Ritter reaction conditions (MeCN, AcOH, H2SO4) the expected oxazoline 6 was obtained in a very low yield (<10%) (Scheme 1). This prompted us to explore the Ritter reaction of cobalt complexed alkynyl glycols 4 (ref. 25 and 26) which has better ability to stabilize the intermediate carbenium ion A27–29 providing oxazolines 5 as precursors of alkynyl glycinol derivatives 1. Such approach gave the expected results which are summarized in this article.

Results and discussion

Cobalt complexed alkynyl glycols 4a–j were prepared starting from hydroxy ketone derivatives 7a–j. Addition of lithium
acetylenides provided alkynyl diols 3a–j which were treated with Co$_2$(CO)$_3$ (Table 1).

If O-TBS protected starting materials 7l–n were used, the corresponding addition products 8a–c were deprotected before the complex 4l–m formation. Several O-TBS protected alkynyl glycols 8b–d were transformed to the corresponding cobalt complexes 9a–c.

Cobalt complexed alkynyl glycols 4a–d gave the expected oxazolines 5a–d in the Ritter reaction with acetonitrile using both H$_2$SO$_4$ and BF$_3$·Et$_2$O as acid promoters (Table 2, entries 1–4). Except for the substrate 4c, better yields were obtained under conditions involving BF$_3$·Et$_2$O. Using BF$_3$·Et$_2$O as acid, glycols 4e–h were transformed to oxazolines 5e–h (Table 2, entries 5–8). These results indicate that the Ritter reaction tolerates wide range of substituents at the terminal alkyne position in substrates 4. Diols 4i,j bearing Ph group at the reaction center were unsuitable substrates giving no yield of the expected oxazolines 5i,j (Table 2, entries 9 and 10). Secondary alcohol 4k could be successfully subjected to the Ritter reaction providing acetamide 5k (Table 2, entry 11). Hydroxymethyl substituent at the reaction center of the substrates 4l–m was tolerated to give the Ritter reaction products 5l,m in moderate and good yields (Table 2, entries 12 and 13).

Several reaction conditions for the cleavage of cobalt complex 5a were investigated to obtain the uncomplexed oxazolines 6a (ethylenediamine, THF, 65 °C, yield of 6a, 28%; NMO, CH$_2$Cl$_2$, r.t. yield of 6a, 42%; DDQ, CH$_2$Cl$_2$, r.t. yield of 6a, 84%).

The best yield of 6a was obtained in oxidative conditions with DDQ which to our knowledge has not yet been reported as

### Table 1 Synthesis of cobalt complexed alkynyl diols 4 and 9

| Entry | R$^1$ | R$^2$ | Y   | 3 or 8, yield% | 4, yield% | 9, yield% |
|-------|-------|-------|-----|---------------|-----------|-----------|
| 1     | Me    | nPent | H   | 3a, 98        | 4a, 98    | —         |
| 2     | Me    | tBu   | H   | 3b, 47        | 4b, 75    | —         |
| 3     | Me    | TMS   | H   | 3c, 86        | 4c, >99   | —         |
| 4     | Me    | Ph    | H   | 3d, >99       | 4d, 94    | —         |
| 5     | Me    | 2-ClPh | H   | 3e, 90       | 4e, 90    | —         |
| 6     | Me    | 4-MeOPh | H   | 3f, 60       | 4f, 83    | —         |
| 7     | Me    | CH$_2$OBn | H   | 3g, 39       | 4g, 70    | —         |
| 8     | Me    | Me    | H   | 3h, 47       | 4h, 70    | —         |
| 9     | Ph    | nPent | H   | 3i, 96       | 4i, 56    | —         |
| 10    | Ph    | Ph    | H   | 3j, 97       | 4j, 82    | —         |
| 11    | H     | nPent | TBS | 8a, 82       | 4k, 40    | —         |
| 12    | CH$_2$OTBS (CH$_2$OH)$^a$ | nPent | TBS | 8b, 78       | 4l, 78    | 9a, 73 |
| 13    | CH$_2$OTBS (CH$_2$OH)$^a$ | Ph     | TBS | 8c, 95       | 4m, 73    | 9b, 79 |
| 14    | CH$_2$OTBS | Me     | TBS | 8d, 75       | —         | 9c, 86 |

$^a$ R$^1$ = CH$_2$OTBS in compounds 8 was transformed to R$^1$ = CH$_2$OH in compounds 4. $^b$ Reagents and conditions: (a) alkyn, nBuLi, LiBr, THF, −40 °C-r.t.; (b) Co$_2$(CO)$_3$, CH$_2$Cl$_2$, r.t.; (c) TBAF, THF, 0 °C-r.t.
the reagent for the decomposition of alkyne cobalt complexes. Other cobalt complexes 5a–h,l–m were also cleaved with DDQ to give uncomplexed oxazolines 6a–h,l–m typically in good yields. The only exception was substrate 5m which gave product 6m in poor yield. For the cleavage of the complex 5m, NMO was better suited as oxidant to provide product 6m more efficiently.

O-TBS protected alkyln glycols 9a–c could also be used as substrates for the Ritter reaction (Table 3). The reaction proceeded with concomitant deprotection of O-TBS group to give oxazolines 5i–n. The cleavage of cobalt complex 5n was performed with DDQ to give uncomplexed oxazoline 6n (Table 3, entry 3).

Selected oxazolines 6d,g,h,l,m were transformed to amino alcohols 1 by using acidic hydrolysis in mild conditions (Table 4). The hydrolysis proceed with good yields of product 1d,g,h,l,m formation which were puriﬁed by the trituration with EtOAc.

Experimental

General information

Commercially available reagents were used without further purification. All air or moisture-sensitive reactions were carried out under an argon atmosphere using oven-dried glassware. Flash chromatography was carried out using Merck Kieselgel 60 (230–400 mesh). Thin layer chromatography was performed on silica gel and was visualized by staining with KMnO4. NMR spectra were recorded on a Varian Mercury spectrometer (400 MHz) and a Bruker Fourier spectrometer (300 MHz) with chemical shift values (δ) in ppm relative to TMS using the residual chloroform signal as an internal standard. Elemental analyses were performed using a Carlo-Erba EA1108 Elemental Analyser. HRMS were obtained using a Q-TOF micro high resolution mass spectrometer with ESI (ESI+/ESI−).

Preparation of diols/triols 3 and 8

Alcohols 3 and 8 were prepared according to the procedure described in the literature starting from the corresponding ketones. 7,14

Alcohols 3a,3b,3c,3e,3f,3g,3h,3i,3j,3k,3l,3m,3n,3o,3p,3q,3r,3s,3t,3u,3v,3w,3x,3y were known in literature.

Table 3 The Ritter reaction of cobalt complexed alkyln diols 9a–c and the cleavage of cobalt complex in intermediate 5n

| Entry | R² | 5, yield% | 6, yield% |
|-------|-----|-----------|-----------|
| 1     | 9a, nPent | 5l, 37 | See Table 2 |
| 2     | 9b, Ph | 5m, 78 | See Table 2 |
| 3     | 9c, Me | 5n, 63 | 6n, 73 (C) |

* Reagents and conditions: (a) BF₃·Et₂O, MeCN, 0 °C; method C: DDQ, CH₂Cl₂, 0 °C.

4-(2-Chlorophenyl)-2-methyl-3-yn-1,2-diol (3e). White powder. M.p. 63–65 °C. ¹H NMR (400 MHz, CD₂OD) δ 7.50 (dd, J = 7.3, 2.1 Hz, 1H, −C₆H₄Cl), 7.43 (dd, J = 7.7, 1.6 Hz, 1H, −C₆H₄Cl), 7.30 (td, J = 7.2, 2.0 Hz, 1H, −C₆H₄Cl), 7.26 (td, J = 7.5, 1.5 Hz, 1H, −C₆H₄Cl), 3.63 (d, J = 11.0 Hz, 1H, −CH₂O−), 3.60 (d, J = 11.0 Hz, 1H, −CH₂O−), 1.54 (s, 3H, −CH₃). ¹³C NMR (100 MHz, CD₂OD) δ 138.2, 135.9, 132.1, 131.7, 129.2, 125.4, 99.7, 82.5, 72.4, 71.1, 27.5. Anal. calcd for C₁₂H₁₀O₂: C, 62.72%; H, 5.26%; found: C, 62.71%; H, 5.23%.

4-(4-Methoxyphenyl)-2-methyl-3-yn-1,2-diol (3f). Off white powder. M.p. 74–77 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.36 (d, J = 8.9 Hz, 2H, −C₆H₄Cl), 6.83 (d, J = 8.9 Hz, 2H, −C₆H₄Cl), 3.81 (s, 3H, −OCH₃), 3.74 (dd, J = 11.0, 5.0 Hz, 1H, −CH₂O−), 3.56 (dd, J = 11.0, 8.8 Hz, 1H, −CH₂O−), 2.66 (s, 1H, −OH), 2.13 (dd, J = 8.8, 5.0 Hz, 1H, −OH), 1.55 (s, 3H, −CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 159.9, 133.4, 114.3, 114.1, 89.0, 84.7, 71.0, 69.2, 55.4, 20.2. Anal. calcd for C₁₂H₁₀O₂: C, 69.89%; H, 6.84%; found: C, 69.56%; H, 6.86%.

2-Methyl-pent-3-yn-1,2-diol (3h). Colourless oil. ¹H NMR (300 MHz, CDCl₃) δ 2.76 (d, J = 10.9 Hz, 1H, −CH₂O−), 2.61 (d, J = 10.9 Hz, 1H, −CH₂O−), 1.72 (s, 1H, −OH), 1.28 (s, 1H, −OH), 1.00 (s, 3H, −CH₃), 0.58 (s, 3H, −CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 109.9, 80.8, 70.9, 68.6, 25.5, 3.5. In HRMS conditions no signal observed. GC-MS (EI): m/z: 83 [M − CH₃–].

6-(Hept-1-yn-1-yl)-2,3,3,9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-ol (8b). Colourless oil. ¹H NMR (300 MHz, CDCl₃) δ 3.61 (d, J = 9.5 Hz, 2H, −CH₂O−), 3.51 (d, J = 9.5 Hz, 2H, −CH₂O−), 2.80 (s, 1H, −OH), 2.11 (t, J = 2.1 Hz, 2H, −CH₂(CH₃)₂CH₃), 1.52–1.37 (m, 2H, −CH₂(CH₂CH₂CH₂CH₂)₂CH₃), 1.29–1.14 (m, 4H, −CH₂CH₂CH₂CH₂CH₂CH₂), 0.82 (s, 18H, −Si(CH₃)₃), 0.81–0.77 (m, 3H, −CH₂(CH₂CH₂CH₂)₂CH₃), 0.00 (d, J = 1.1 Hz, 12H, −Si(CH₃)₃). ¹³C NMR (100 MHz, CDCl₃) δ 85.6, 79.8, 71.1, 65.9, 31.0, 28.2, 25.8, 22.2, 18.7, 13.8, 13.9, −5.4. In HRMS conditions no signal observed. GC-MS (EI): m/z: 357 [M − 2Bu]⁻.

Deprotection of silyl groups gave 2-hept-1-yn-1-yl)propane-1,2,3-triol (3k). Colourless oil. ¹H NMR (400 MHz, CDCl₃) δ 3.70 (s, 4H, −CH₂OH), 2.18 (ddt, J = 9.2, 7.1, 3.7 Hz, 2H, −CH₂CH₂CH₂CH₂CH₂), 1.59–1.44 (m, 2H, −CH₂CH₂CH₂CH₂CH₂), 1.30 (qd, J = 3.6, 3.1, 1.5 Hz, 4H, −CH₂CH₂CH₂CH₂CH₂), 0.96–0.81 (m, 3H, −CH₂CH₂CH₂CH₂). ¹³C NMR (100 MHz, CDCl₃) δ 87.9, 78.3,
Deprotection of silyl groups gave 4-(phenylthio)propan-1,2,3-triol (3f). Colourless oil. 1H NMR (300 MHz, CDCl₃) δ 7.52–7.41 (m, 2H, 6H-C₆H₄), 7.39–7.31 (m, 3H, m-p-C₆H₄), 3.92–3.82 (m, 4H, –CH₂OH), 3.08 (s, 1H, –OH), 2.18 (dd, J = 8.6, 4.8 Hz, 2H, –CH₂O). 13C NMR (100 MHz, CDCl₃) δ 131.1, 127.9, 127.9, 122.6, 88.9, 84.5, 71.5, 65.3. In HRMS conditions no signal observed. GC-MS (EI): m/z: 161 [M + Na]+.

1,2,3,9,9,10,10-Octamethyl-6-(prop-1-yn-1-yl)-4,8-dioxo-3,9-disilaundecan-6-ol (8d). Colourless oil. 1H NMR (400 MHz, CDCl₃) δ 3.67 (dd, J = 9.5 Hz, 2H, –OCH₂), 3.58 (dd, J = 9.5 Hz, 2H, –CH₂O), 2.85 (s, 1H, –OH), 1.81 (s, 3H, –CH₃), 0.89 (s, 18H, –Si(CH₃)₃), 0.66 (dd, J = 1.7 Hz, 12H, Si(CH₃)₃). 13C NMR (100 MHz, CDCl₃) δ 81.1, 79.2, 71.1, 65.8, 25.8, 18.3, 3.5, –5.3, –5.4. HR-MS (ESI-TOF) m/z: calculated for C₁₄H₃₀O₂Si₃Na 381.2247; found [M + Na]+ 381.2257.

General procedure for the preparation of cobalt-complexed propargyl alcohols 4 and 9

To a solution of alkyne (1 mmol) in CH₂Cl₂ (5 mL), Co₂(CO)₈ (1.1 mmol) was added under argon atmosphere. The solution was stirred at room temperature until no evolution of CO₂ was observed (TLC showed the formation of the complex to be completed). The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel eluting with a mixture of ethyl acetate and petroleum ether (1:30–1:4) to yield the Co₂(CO)₈-alkyne complex.

13C-NMR for compounds 4 and 9 was not possible to record due to Co induced line broadening. Typically compounds 4 and 9 were not stable under conditions used for HRMS.

Hexacarboxonyl[μ-η⁴-{2-(methyl-4-phenylbut-3-ene-1,2-diol)}dicobalt (4a). Red powder. 1H NMR (300 MHz, CDCl₃) δ 7.30 (d, J = 4.7 Hz, 2H, –CH₂O), 2.90–2.73 (m, 2H, –CH₂(CH₂)₃CH₃), 2.26 (s, 1H, –OH), 2.06–1.95 (m, 1H, –OH), 1.73–1.31 (m, 9H, –CH₃, –CH₂CH₂ (CH₂)₂CH₃, –CH₂(CH₂)₂CH₃, –CH₂(CH₂)₃CH₃), 0.93 (t, J = 6.2 Hz, 3H, –(CH₂)₃CH₃). Not stable under HRMS conditions.

Hexacarboxonyl[μ-η⁴-{2-(5,5-trimethylhex-3-ene-1,2-diol)}dicobalt (4b). Red powder. 1H NMR (300 MHz, CDCl₃) δ 3.72 (d, J = 5.3 Hz, 2H, –CH₂O), 2.25 (s, 1H, –OH), 2.15–2.02 (m, 1H, –OH), 1.62 (s, 3H, –CH₃), 1.35 (s, 9H, –C(CH₃)₃). Not stable under HRMS conditions.

Hexacarboxonyl[μ-η⁴-{2-(methyl-4-(trimethylsilyl)but-3-ene-1,2-diol)}dicobalt (4c). Red powder. 1H NMR (300 MHz, CDCl₃) δ 3.66 (d, J = 5.9 Hz, 2H, –CH₂O), 2.04 (s, 1H, –OH), 2.04 (t, J = 5.9 Hz, 1H, –OH), 1.57 (s, 3H, –CH₃), 0.33 (s, 9H, –Si(CH₃)₃). Not stable under HRMS conditions.

Hexacarboxonyl[μ-η⁴-{2-(methyl-4-phenylbut-3-ene-1,2-diol)}dicobalt (4d). Red powder. 1H NMR (400 MHz, CDCl₃) δ 7.69–7.56 (m, J = 6.8 Hz, 2H, o-C₆H₄), 7.40–7.29 (m, 3H, p,p-C₆H₄), 3.89–3.74 (br, 2H, –CH₂O), 2.58 (s, 1H, –OH), 2.08–1.99 (br, 1H, –OH), 1.67 (s, 3H, –CH₃). Not stable under HRMS conditions.

Hexacarboxonyl[μ-η⁴-{4-(2-chlorophenyl)-2-methylbut-3-ene-1,2-diol]}dicobalt (4e). Red powder. 1H NMR (300 MHz, CDCl₃) δ 8.01–7.94 (m, 1H, C₆H₄Cl), 7.45–7.37 (m, 1H), 7.32–7.26 (m, 2H, C₆H₄Cl), overlapping with CHCl₃ signal, 3.82 (d, J = 5.8 Hz, 2H, –CH₂O), 2.87 (s, 1H, –OH), 2.05 (t, J = 5.8 Hz, 1H, –OH), 1.67 (s, 3H, –CH₃). Not stable under HRMS conditions.

Hexacarboxonyl[μ-η⁴-{4-(2-methylpropyl)-2-methylbut-3-ene-1,2-diol]}dicobalt (4f). Red powder. 1H NMR (300 MHz, CDCl₃) δ 7.61 (s, 2H, m-C₆H₄), 6.90 (s, 2H, o-MeO-C₆H₄), 4.14 (s, 2H, –CH₂O), 3.68 (d, J = 10.0 Hz, 1H, –CH₂O), 2.55 (s, 1H, –OH), 1.53 (s, 3H, –CH₃). Not stable under HRMS conditions.
1.66

A solution of the cobalt complex of diol under HR-MS conditions. The reaction mixture was diluted with a mixture of ethyl acetate and petroleum ether (1:20-1:10) to afford oxazoline cobalt complex.

Method B for the Ritter reaction

A solution of the cobalt complex 4 (0.15 mmol) in dichloromethane (2 mL) was added dropwise to a mixture of ethyl acetate and petroleum ether (5:1) to afford octamethyl-4,8-dioxa-3,9-disilaundecan-6-ol under HR-MS conditions.

Hexacarbonyl[m-η4-(4-(hept-1-yn-1-yl)-2,4-dimethylxazoline)]cobalt (5a).

Viscous colorless oil. 1H NMR (400 MHz, CDCl3) δ 4.28 (d, J = 8.4 Hz, 1H, -CH(O)-), 2.91 (dd, J = 8.4 Hz, 4H, -CH2O-), 1.97 (s, 3H, -CH3), 1.74-1.58 (m, 5H, -CH2), -CH2(=CH(CH2)3)CH3), 1.43 (q, J = 15.2, 7.4 Hz, 4H, -CH2=CH2(CH2)3)CH3), 0.93 (t, J = 7.1 Hz, 3H, -CH2(=CH2)CH3). Not stable under HR-MS conditions.

Hexacarbonyl[m-η4-(4-(3,3-dimethylbut-1-yn-1-yl)-2,4-dimethyl oxazoline)]cobalt (5b).

Viscous colorless oil with tendency to crystalize. 1H NMR (300 MHz, CDCl3) δ 4.28 (d, J = 8.4 Hz, 1H, -CH(O)-), 4.14 (d, J = 8.4 Hz, 1H, -CH(O)-), 1.97 (s, 3H, -CH3), 1.68 (s, 3H, -CH3). Not stable under HR-MS conditions.

Hexacarbonyl[m-η4-(2,4-dimethyl-4-(trimethylsilyl)ethynyl) oxazoline]cobalt (5c).

Viscous colorless oil. 1H NMR (400 MHz, CDCl3) δ 7.74-7.68 (m, 5H, -CH2), 7.41-7.27 (m, 3H, -C6H4), 4.40 (d, J = 8.4 Hz, 1H, -CH(O)-), 4.21 (d, J = 8.4 Hz, 1H, -CH(O)-), 2.02 (s, 3H, -CH3), 1.70 (s, 3H, -CH3). Not stable under HR-MS conditions.

Method A for the Ritter reaction

A solution of the cobalt complex 3 (2.2 mmol) in dichloromethane (3 mL) was added dropwise to a mixture of ethyl acetate and petroleum ether (1:20-1:10) to afford octamethyl-4,8-dioxa-3,9-disilaundecan-6-ol under HR-MS conditions.

Hexacarbonyl[m-η4-(4-(2-chlorophenylethynyl)-2,4-dimethyl oxazoline)]cobalt (5d).

Red oil. 1H NMR (300 MHz, CDCl3) δ 7.69 (2H, -CH=CH2), 6.92 (2H, -CH=CH2), 4.42 (1H, -CH(O)-), 2.14 (1H, -CH(O)-), 3.85 (3H, -OCH3), 2.03 (3H, -CH3), 1.71 (3H, -CH3). Not stable under HR-MS conditions.

Hexacarbonyl[m-η4-(4-(4-methylphenylenethynyl)-2,4-dimethyl oxazoline)]cobalt (5e).

Red oil. 1H NMR (300 MHz, CDCl3) δ 7.45-7.29 (m, 5H, -C6H4), 6.92 (2H, -CH=CH2), 6.92 (2H, -CH=CH2), 4.42 (1H, -CH(O)-), 3.85 (3H, -OCH3), 2.03 (3H, -CH3), 1.71 (3H, -CH3). Not stable under HR-MS conditions.

Hexacarbonyl[m-η4-(4-(4-benzoxylethynyl)prop-1-yn-1-yl)-2,4 dimethyl-oxazoline]cobalt (5f).

Red oil. 1H NMR (300 MHz, CDCl3) δ 7.40-7.50 (m, 5H, -C6H4), 7.28 (br, 3H, -CH3), 1.96 (s, 3H, -CH3), 1.63 (s, 3H, -CH3). Not stable under HR-MS conditions.

Hexacarbonyl[m-η4-(2,4-dimethyl-4-(prop-1-yn-1-yl)-2,4 dimethyl-oxazoline)]cobalt (5g).

Red oil. 1H NMR (300 MHz, CDCl3) δ 7.45-7.29 (m, 5H, -C6H4), 6.92 (2H, -CH=CH2), 6.92 (2H, -CH=CH2), 4.42 (1H, -CH(O)-), 2.14 (1H, -CH(O)-), 3.85 (3H, -OCH3), 2.03 (3H, -CH3), 1.71 (3H, -CH3). Not stable under HR-MS conditions.
4.02 (d, J = 8.0 Hz, 1H, -CH₂O⁻), 1.97 (s, 3H, -CH₃), 1.45 (s, 3H, -CH₃), 1.18 (s, 9H, -C(CH₃)₃). ¹³C NMR (100 MHz, CDCl₃) δ 164.7, 91.2, 81.8, 79.8, 64.3, 31.2, 29.6, 27.4, 14.2. HR-MS (ESI-TOF) m/z: caleed for C₁₃H₁₈NO 120.1388; found 180.1389 [M + H]⁺.

2.4-Dimethyl-4-(((trimethylsilyl)ethynyl)oxazoline (6c). Colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 4.32 (d, J = 8.2 Hz, 1H, -CH₂O⁻), 4.03 (d, J = 8.2 Hz, 1H, -CH₂O⁻), 1.98 (s, 3H, -CH₃), 1.49 (s, 3H, -CH₃), 0.14 (s, 9H, -Si(CH₃)₃). ¹³C NMR (100 MHz, CDCl₃) δ 164.4, 100.7, 86.3, 83.8, 28.1, 13.2, -0.9. HR-MS (ESI-TOF) m/z: caleed for C₁₃H₁₉SiO₃ 232.2388; found 232.2388 [M + H]⁺.

2.4-Dimethyl-4-((phenylethynyl)oxazoline (6d). Colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.06 (dd, J = 7.7, 1.7 Hz, 1H, -CH₃), 6.65 (d, J = 6.0 Hz, 1H, -CH₂O⁻), 4.09 (d, J = 5.3 Hz, 2H, -CH₂O⁻), 1.99 (s, 3H, -CH₃), 1.58 (s, 3H, -CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 165.3, 131.8, 128.3, 128.9, 91.7, 83.5, 79.5, 64.9, 29.1, 14.2. HR-MS (ESI-TOF) m/z: caleed for C₁₃H₁₈NO 206.1205; found 206.1209 [M + H]⁺.

4-((2-Chlorophenyl)ethyl)2,4-dimethoxalol (6e). Colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.73 (dd, J = 8.2 Hz, 1H, -CH₂O⁻), 7.43 (d, J = 7.7, 1.7 Hz, 1H, -CH₂O⁻), 4.11 (d, J = 8.2 Hz, 1H, -CH₂O⁻), 1.93 (s, 3H, -CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 167.0, 131.9, 129.0, 128.9, 128.6, 122.8, 96.9, 80.4, 79.4, 65.0, 28.9, 14.2. HR-MS (ESI-TOF) m/z: caleed for C₁₃H₁₈ClO 266.0884; found 266.0884 [M + H]⁺.

4-(4-Methoxyphenethyl)2,4-dimethoxalol (6f). Colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.33 (d, J = 8.9 Hz, 2H, -CH₂O⁻), 6.79 (d, J = 8.9 Hz, 2H, -CH₂O⁻), 4.41 (d, J = 8.1 Hz, 1H, -CH₂O⁻), 4.41 (d, J = 8.1 Hz, 1H, -CH₂O⁻), 3.78 (s, 3H, -OCH₃), 2.00 (s, 3H, -CH₃), 1.58 (s, 3H, -CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 165.5, 137.6, 132.4, 129.4, 127.0, 124.6, 122.8, 96.9, 80.4, 79.4, 65.0, 28.9, 14.2. HR-MS (ESI-TOF) m/z: caleed for C₁₉H₂₄NO 329.1781; found 329.1785 [M + H]⁺.

2.4-Dimethyl-4-((prop-1-yn-1-yl)oxazoline (6h). Colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 4.26 (d, J = 8.1 Hz, 1H, -CH₂O⁻), 3.98 (d, J = 8.1 Hz, 1H, -CH₂O⁻), 1.95 (s, 3H, -CH₃), 1.79 (s, 3H, -CH₃), 1.44 (s, 3H, -CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 164.9, 81.8, 79.4, 79.3, 64.2, 29.0, 13.9, 3.6. HR-MS (ESI-TOF) m/z: caleed for C₁₄H₁₉NO 237.1091; found 237.1091 [M + H]⁺.

4-(Hept-1-yn-1-yl)-2-methoxalol (6k). Colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 4.68 (d, J = 8.0 Hz, 1H, -CH₂O⁻), 4.33 (dd, J = 10.0, 8.0 Hz, 1H, -CH₂O⁻), 4.11-3.99 (m, 1H, -CH₂O⁻), 2.12 (td, J = 7.1, 2.0 Hz, -CH₂⁻), 1.93 (s, 3H, -CH₃), 1.49–
Aqueous 6 M HCl (1 mL) was added dropwise to a solution of more time. The residue was suspended in EtOAc and filtered to give the desired product. The reaction mixture was stirred at room temperature for another 1 h.

1-Hydroxy-2-(hydroxymethyl)non-3-yn-2-aminium chloride (1m). Amorphous compound. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.53–7.43 (m, 2H, \(\text{CH}_2\text{O}\)), 7.43–7.33 (m, 3H, \(p\)-m-C\(_6\)H\(_4\)), 3.87 (d, \(J = 11.4\) Hz, 2H, –CH\(_2\text{OH}\)), 3.83 (d, \(J = 11.4\) Hz, 2H, –CH\(_2\text{OH}\)). \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 131.5, 129.1, 128.2, 121.1, 87.5, 82.8, 62.7, 57.4. HR-MS (ESI-TOF) m/z: calcul. for \(\text{C}_{10}\text{H}_{18}\text{NO}_2\) 186.1494; found 186.1494 [M + H\(^+\)].

1-Hydroxy-2-(hydroxymethyl)-4-phenylbut-3-yn-2-aminium chloride (1m). Amorphous compound. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.53–7.43 (m, 2H, \(\text{CH}_2\text{O}\)), 7.43–7.33 (m, 3H, \(p\)-m-C\(_6\)H\(_4\)), 3.87 (d, \(J = 11.4\) Hz, 2H, –CH\(_2\text{OH}\)), 3.83 (d, \(J = 11.4\) Hz, 2H, –CH\(_2\text{OH}\)). \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 131.5, 129.1, 128.2, 121.1, 87.5, 82.8, 62.7, 57.4. HR-MS (ESI-TOF) m/z: calcul. for \(\text{C}_{10}\text{H}_{18}\text{NO}_2\) 186.1494; found 186.1494 [M + H\(^+\)].

Conclusions

In summary, we have developed a novel approach to \(\text{C}\)-quaternary alkynyl glucinols. This is based on the Ritter reaction of acetoniitride with cobalt complexed alkynyl glycols to give oxazolines. The substrates can be easily assembled to introduce the structural diversity at both variable positions. The Ritter reaction is compatible with a range of substituents at the alkyne terminal position providing oxazolines in moderate to good yields. Hydroxymethyl substituent at the reaction center in both unprotected or O-TBS protected form was well tolerated. The Ritter reaction proceeds also with bis-O-TBS protected alkynyl glycerols with concomitant cleavage of the TBS groups. However, the phenyl group at the reaction center of glycols was detrimental inducing low or no yield of the product formation. Cobalt alkynyl complexes in the oxazolines produced by the Ritter reaction can be cleaved in oxidative conditions using DDQ, or NMO as reagents. Hydrolysis of oxazoline ring in mild acidic conditions efficiently provides amino alcohols. We believe that method presented in this paper will find an application for the synthesis of complex amino alcohol derivatives. A version based on catalytic amount of cobalt additive or a protocol for efficient cobalt recovery needs to be developed in the future. This would enable the use of the method for economic and eco-friendly manufacturing processes.

Acknowledgements

Financial support from the EU H2020 Marie Curie Skłodowska Curie ETN program, project INTEGRATE (Contract No. 642620), is gratefully acknowledged.

Notes and references

1 J. Bolsakova and A. Jirgenson, \textit{Eur. J. Org. Chem.}, 2016, 4591.
2 T. Boibessot, D. Bénimélis, P. Meffre and Z. Benfodda, *Amino Acids*, 2016, 48, 2081.

3 H. Fukumoto, K. Takahashi, J. Ishihara and S. Hatakeyama, *Angew. Chem., Int. Ed.*, 2006, 45, 2731.

4 S. N. Osipov, P. Tsouker, L. Hennig and K. Burger, *Tetrahedron*, 2004, 60, 271.

5 K. Morisaki, M. Sawa, J. Nomaguchi, H. Morimoto, Y. Takeuchi, K. Mashima and T. Ohshima, *Chem. – Eur. J.*, 2013, 19, 8417.

6 V. M. Girijavallabhan, L. Chen, C. Dai, R. J. Feltz, L. Firmansjah, D. Li, S. H. Kim, J. A. Kozlowski, B. J. Lavey, A. Kosinski, et al., *Bioorg. Med. Chem. Lett.*, 2010, 20, 7283.

7 G. Pattenden and G. Rescourio, *Org. Biomol. Chem.*, 2008, 6, 3428.

8 Z. Benfodda, D. Bénimélis, M. Jean, J.-V. Naubron, V. Rolland and P. Meffre, *Amino Acids*, 2015, 47, 899.

9 G. Hattori, A. Yoshida, Y. Miyake and Y. Nishibayashi, *J. Org. Chem.*, 2009, 74, 7603.

10 U. Schmidt, M. Respondek, A. Lieberknecht, J. Werner and P. Fischer, *Synthesis*, 1989, 256.

11 S. Hatakeyama, H. Matsumoto, H. Fukuyama, Y. Mukugi and H. Irie, *J. Org. Chem.*, 1997, 62, 2275.

12 C. J. Brennan, G. Pattenden and G. Rescourio, *Tetrahedron Lett.*, 2003, 44, 8757.

13 R. D. Grigg, J. W. Rigoli, S. D. Pearce and J. M. Schomaker, *Org. Lett.*, 2012, 14, 280.

14 J. Sirotkina, L. Grigorjeva and A. Jirgensons, *Eur. J. Org. Chem.*, 2015, 6900–6908.

15 R. Bishop, in *Compr. Org. Synth. II*, Elsevier, Amsterdam, 2nd edn, 2014, pp. 239–295.

16 I. R. Morgan, A. Yazici, S. G. Pyne and B. W. Skelton, *J. Org. Chem.*, 2008, 73, 2943.

17 M. Vangala and G. P. Shinde, *Beilstein J. Org. Chem.*, 2015, 11, 2289.

18 J. L. Jiménez Blanco, E. M. Rubio, C. Ortiz Mellet and J. M. García Fernández, *Synlett*, 2004, 2230.

19 D. Noort, G. A. van der Marel, G. J. Mulder and J. H. van Boom, *Synlett*, 1992, 224.

20 D. M. Gordon and S. J. Danishefsky, *J. Org. Chem.*, 1991, 56, 3713.

21 L. W. Davies, C. H. Senanayake, R. D. Larsen, T. R. Verhoeven and P. J. Reider, *Tetrahedron Lett.*, 1996, 37, 813.

22 C. H. Senanayake, L. M. DiMichele, J. Liu, L. E. Fredenburgh, K. M. Ryan, F. E. Roberts, R. D. Larsen, T. R. Verhoeven and P. J. Reider, *Tetrahedron Lett.*, 1995, 36, 7615.

23 E.-J. Tillmanns and J. Ritter, *J. Org. Chem.*, 1957, 22, 839.

24 A. Toshimitsu, C. Hirosawa and K. Tamao, *Tetrahedron*, 1994, 50, 8997.

25 S. Top and G. Jaouen, *J. Chem. Soc., Chem. Commun.*, 1979, 224.

26 S. Top and G. Jaouen, *J. Org. Chem.*, 1981, 46, 78.

27 R. F. Lockwood and K. M. Nicholas, *Tetrahedron Lett.*, 1977, 18, 4163.

28 K. M. Nicholas, *Acc. Chem. Res.*, 1987, 20, 207.

29 B. J. Teobald, *Tetrahedron*, 2002, 58, 4133.

30 G. B. Jones, J. M. Wright, T. M. Rush, G. W. Plourde, T. F. Kelton, J. E. Mathews, R. S. Huber and J. P. Davidson, *J. Org. Chem.*, 1997, 62, 9379.

31 T. Sugihara, H. Ban and M. Yamaguchi, *J. Organomet. Chem.*, 1998, 554, 163.

32 D. Kalaitzakis, T. Montagnon, I. Alexopoulou and G. Vassilikogiannakis, *Angew. Chem., Int. Ed.*, 2012, 51, 8868.

33 B. Gabriele, R. Mancuso, V. Maltese, L. Veltri and G. Salerno, *J. Org. Chem.*, 2012, 77, 8657.

34 S.-T. Chen and J.-M. Fang, *J. Org. Chem.*, 1997, 62, 4349.

35 R. Spina, E. Colacino, J. Martinez and F. Lamaty, *Chem. – Eur. J.*, 2013, 19, 3817.