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# Synthesis of new quinuclidine derivatives via Pd-mediated cross-coupling and cross-benzannulation reactions

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ABSTRACT

New functionalized quinuclidines were prepared via palladium-catalyzed addition reactions of terminal alkynes (donors) to internal alkynes (acceptors). The enantiopure terminal alkynes were derivatives of quincoridine and quincorine, two semi-natural *Cinchona* alkaloids. The processes exhibited high chemoselectivity and excellent diastereoselectivity, the *E*-enynes being obtained as single products in almost all cases. The synthesis of new tetra and pentasubstituted benzene derivatives in good yields by [2+2+2] benzannulation of the diynes, obtained by the palladium-catalyzed homodimerization of 10,11-didehydro quincoridine and 10,11-didehydro quincorine, with terminal alkynes and in fair yield by [4+2] benzannulation of an enyne derivative of 10,11-didehydro quincoridine with 2,4-hexane-diyne are reported.



## 1. Introduction

Carbon–carbon bond-forming reactions are considered the most important processes in organic chemistry and represent key steps in the building of more complex molecules from simple precursors. In the last years, metal-catalyzed cross-coupling reactions have been extensively employed as 'direct' methodologies for carbon–carbon bond formation between unsaturated species such as vinyl, aryl and alkynyl moieties.[1–4]

*Cinchona* alkaloids and their derivatives, readily available in both pseudo-enantiomeric forms, are playing an important role as versatile chiral basic catalysts, ligands, chromatographic selectors and NMR discriminating agents; all of these applications having direct connection with asymmetric synthesis and chiral discriminators.[5] The Sharpless asymmetric dihydroxylation of olefins using various *Cinchona* alkaloid derivatives as chiral monodentate ligands for $OsO_4$ is one of the most known application.[6] The mechanism of this reaction was also extensively analyzed by Sharpless et al.[6,7] and Corey and Noe[8] and the most efficient ligands for promoting face-selective dihydroxylation of olefins were found to be derivatives of bis-*cinchona* alkaloids such as $(DHQD)_2PHAL$ and $(DHQD)_2PYDZ$ (Fig. 1).

Additionally, bidentate N,P-ligands have acquired a growing importance in the development of coordination chemistry and asymmetric catalysis. Lemaire et.al.[9] have developed a new family of N,P-ligands derived from quincoridine (QCD) and quincorine (QCI) with applications in hydroformylation, asymmetric hydrosilylation and asymmetric Grignard cross-coupling reactions.

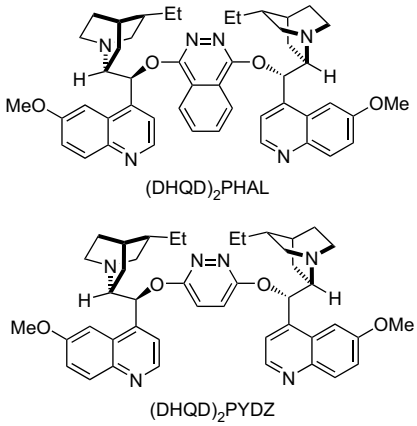


**Figure 1.** $(DHQD)_2PHAL$ and $(DHQD)_2PYDZ$, bis-*cinchona* alkaloids.

A remarkable number of functionalized quinuclidines are valuable chiral building blocks for pharmacology and medicinal chemistry (Fig. 2). They are selective agonists for a variety of receptors (e.g., neurokinin-1 ($NK_1$) **A**, 5-$HT_3$ **B**, 5-$HT_4$ **C**) and are able to act as squalene synthase inhibitors **D**.[10–13]

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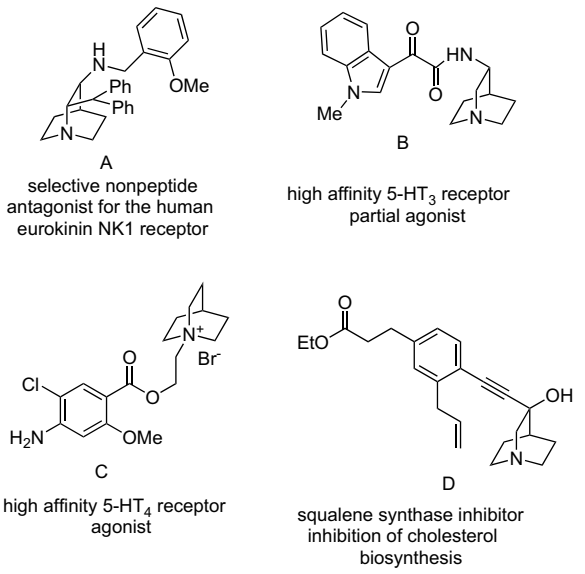
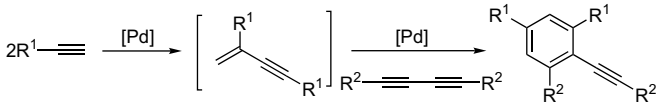



**Figure 2.** Medicinally relevant quinuclidine compounds.

Addition and cycloaddition reactions wherein the product is the simple sum of the reactants constitute an economical way to build more complex structures from simple building blocks.[2] Transition-metal-catalyzed cyclo-trimerization of alkynes is a useful method for the construction of substituted benzene derivatives and many transition-metal complexes have been employed as catalysts.[14–19] Yamamoto et al. have developed a procedure for the intermolecular palladium-catalyzed formal [2+2+2] trimerization of alkynes to give multisubstituted benzene derivatives. Homodimerization of terminal alkynes and subsequent [4+2] benzannulation with diynes allowed the formation of tetrasubstituted benzenes as a single reaction product in fair to good yields (Scheme 1).[20]



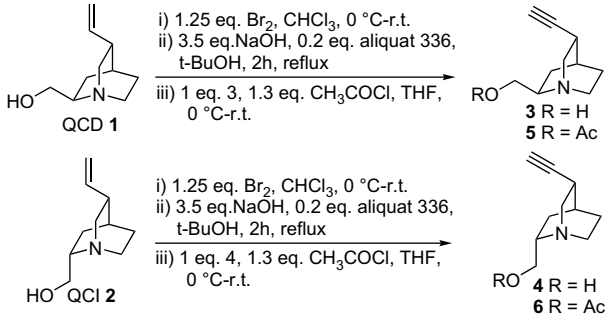
**Scheme 1.** Cyclo-trimerization of alkynes with diynes.

Herein, we considered it of interest to investigate the preparation of new 1,2,4-trisubstituted enyne, 1,2,3,5-tetra and 1,2,3,4,5-penta-substituted benzene functionalized quinuclidines, via palladium-catalyzed cross-coupling and cross-benzannulation reactions. These derivatives are obtained starting from enantiopure 10,11-didehydro QCD and 10,11-didehydro QCI and they are important candidates as ligands for chiral catalysts or chiral discriminating agents.

## 2. Results and discussion

Conjugated enynes are important units for a large variety of natural products and they are found in many man-made derivatives. Synthetic enynes are mainly obtained by palladium-catalyzed cross-coupling reactions between alkynes and vinyl halides or sulfonates.[21] Trost et al.[22] demonstrated that 1,2,4-trisubstituted enynes can be efficiently prepared via selective '*syn*'-addition of a terminal alkyne (donor alkyne) to an internal alkyne (acceptor alkyne) in the presence of catalytic amounts of palladium acetate and of an electron rich, sterically encumbered, ligand as tris(2,6-dimethoxyphenyl) phosphine (TDMPP).

In order to explore the applications of this addition reaction in the series of semi-natural *Cinchona* alkaloids we used 10,11-didehydro derivatives **3**, **4**, **5** and **6** of quincoridine (QCD) [(2*R*,4*S*,5*R*)-2-hydroxymethyl-5-vinyl-2-quinuclidine] **1** and quincorine (QCI) [(2*S*,4*S*,5*R*)-2-hydroxymethyl-5-vinyl-2-quinuclidine] **2** as terminal (donor) alkynes. These alkynes were prepared efficiently in two steps from **1** and **2** through a modified procedure based on the known literature method (Scheme 2).[23,24]

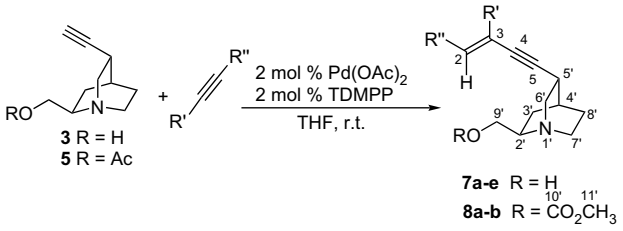



**Scheme 2.** The synthesis of terminal alkynes from QCD and QCI.

### 2.1. Trisubstituted enynes from 10,11-didehydro QCD

Coupling reactions between 10,11-didehydro quincoridine (QCD) derivatives **3** and **5** as donor alkynes with acceptor alkynes, which exhibit ester and ketone functionalities as electron withdrawing groups were investigated. When 1 equiv of **3** or **5** was treated with 1 equiv of acceptor alkyne in the presence of 2 mol % of $Pd(OAc)_2$ and 2 mol % of TDMPP in THF at room temperature (rt), the corresponding 1,2,4-trisubstituted enynes **7a–e** and **8a**,**b** were obtained in very good yields (Table 1). Except entries 4 and 5 (Table 1) all reactions proceeded smoothly and gave a single geometric isomer (assigned *E* on the basis of $^1$H NMR spectra and the reaction mechanism).[25,26] The vinylic hydrogen atom in **7a–c** and **8a**,**b** exhibits a low-field shift (Table 2) being at α-position referred to the anisotropic group (ester or ketone). Moreover, since in compounds **7b**,**c** and **8a** the vinylic hydrogen atom is

**Table 1**
Palladium-catalyzed addition of **3** and **5** to internal alkynes

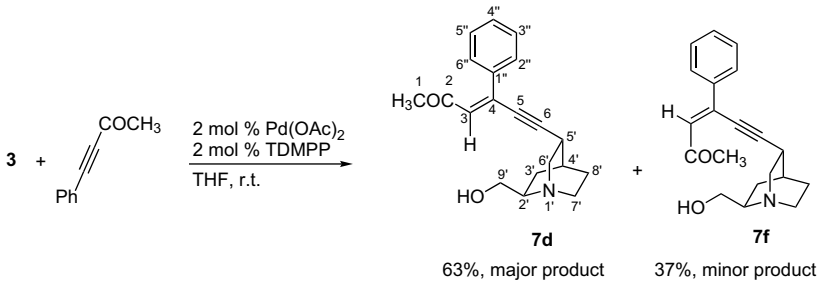



| Entry | Donor alkyne R | Acceptor alkyne | | Product | Yield [%] |
|---|---|---|---|---|---|
| | | R′ | R″ | | |
| 1 | H | $CH_3$ | $CO_2C_2H_5$ | **7a** | 94 |
| 2 | H | $C_6H_5$ | $CO_2C_2H_5$ | **7b** | 73 |
| 3 | H | $C_6H_5$ | $CO_2CH_3$ | **7c** | 84 |
| 4[a] | H | $C_6H_5$ | $COCH_3$ | **7d**, **7f** | 67 |
| 5[b] | H | $C_2H_5$ | $COCH_3$ | **7e** | 80 |
| 6 | Ac | $C_6H_5$ | $CO_2CH_3$ | **8a** | 81 |
| 7 | Ac | $C_2H_5$ | $COCH_3$ | **8b** | 53 |

[a] A mixture of *E*/*Z* isomers was obtained.
[b] Reaction performed 24 h at rt and 3 h at reflux, the transposition product **7f** was obtained.

**Table 2**
$^1$H NMR data (δ, $CDCl_3$) for the vinylic H atom in **7a–c** and **8a**,**b**

| Compound | **7a** | **7b** | **7c** | **8a** | **8b** |
|---|---|---|---|---|---|
| δ (ppm) | 5.92 | 6.27 | 6.13 | 6.18 | 6.29 |

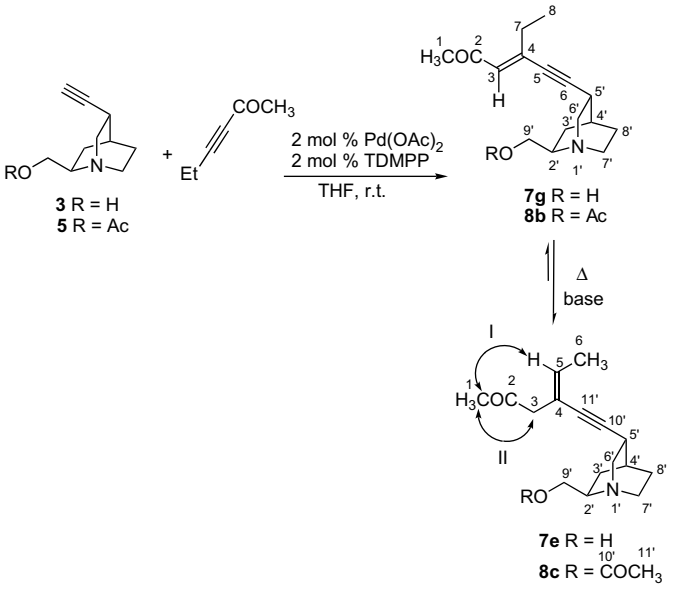



**Scheme 3.** Cross-coupling of **3** with 4-phenyl-3-butyn-2-one.

not affected by the anisotropy of the phenyl group, it is trans to this anisotropic unit.

The vinyl methyl unit in **7a** is also deshielded ($\delta$=2.20 ppm) by the ester group and that means it adopts the cis-position to this anisotropic substituent. When 4-phenyl-3-butyn-2-one was employed as acceptor (Table 1, entry 4), using 1:1 ratio of reactants under the standard conditions, the reaction lead to a mixture of *E* and *Z* isomers, which couldn't be separated by column chromatography on silica gel (Scheme 3). The *E*/*Z* ratio was found to be 63:37 from $^1$H NMR spectrum, which showed two singlets for the vinylic hydrogen atoms at 6.78 ppm (minor product) and 6.46 ppm (major product), respectively. These data are consistent with the proposed geometry, because in the *Z*-isomer the vinylic hydrogen is more deshielded due to the influence of both anisotropic groups (ketone and phenyl) than in the *E*-isomer, which is affected only by the anisotropy of the ketone.

Using 4-ethyl-3-butyn-2-one as acceptor (Table 1, entry 5) under the standard conditions, the reaction was not completed after 24 h. Raising the temperature to 60 °C to enforce full conversion with 1:1 ratio of the reactants, the isomerization of the product was observed and the isolated mixture contained 3% of **7g** and 97% of **7e**, respectively (from $^1$H NMR spectra) (Scheme 4). It is known that unsaturated aldehydes, ketones, carboxylic acids, carboxylic acid esters, carboxylic acid amides and nitriles isomerize using triethyl amine, sodium hydroxide or sodium methoxide as catalysts, in an equilibrium that normally lies on the side of the conjugated isomer.[27] In our case we assumed that the isomerization is due to the strong basicity of the bridgehead nitrogen atom. In order to prove this a pure sample of **8b** was heated to reflux in THF for 5 h. The equilibrium mixture contained >99% of compound **8c** (from $^1$H NMR), this being more stable than its conjugated isomer **8b**. The configurations of olefins **7e** and **8c** were assigned through NOE experiments. Upon irradiation of the ketone methyl group, large NOE's were recorded for the vinylic hydrogen atom (Scheme 4, arrow I) and the protons of the methylene group (Scheme 4, arrow II), suggesting their closed position. These observations confirmed the *Z* configurations of the olefins. The isomerization processes proceeded stereo-selectively, only the *Z*-isomers being obtained.

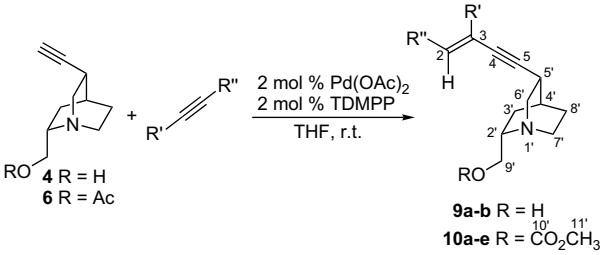



**Scheme 4.** Cross-coupling reactions of **3** and **5** with 4-ethyl-3-butyn-2-one.

## 2.2. Trisubstituted enynes from 10,11-didehydro QCI

Changing the donor alkynes from **3** and **5** to **4** and **6** the cross-coupling reactions with acceptor alkynes furnished the desired enynes in moderate yields (Table 3). In the case of alkyne **4** O-protection of the 1,2-aminoalcohol was necessary. Low conversions were recorded (Table 3, entries 1 and 2) even at high temperatures or by increasing the ratio of catalyst. The diminished yields are mainly due to the influence of the free OH group. This consideration is supported by the much better yields of the addition reactions (Table 3, entries 3–7) carried out with the *O*-acylated derivative **6**. Except entry 2 all reactions afforded a single geometric isomer *E* illustrating the high chemoselectivity and diastereoselectivity of the process. In $^1$H NMR spectra of **9a** and **10a–e** the vinylic hydrogen atom is deshielded by the ester or ketone group (Table 4). For entry 2 the ratio *E*/*Z* was 85:15 (from $^1$H NMR spectrum) and the low diastereoselectivity is perhaps due to high temperature required for the conversion of reactants. The conjugated enyne **10d**

**Table 3**
Palladium-catalyzed addition of **4** and **6** to internal alkynes



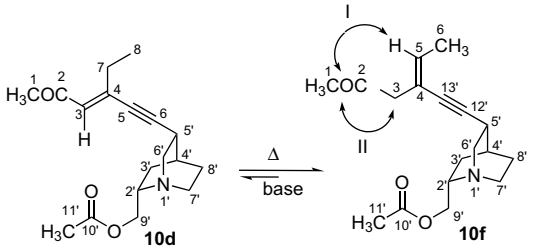

| Entry | Donor alkyne R | Acceptor alkyne | | Product | Yield [%] |
|---|---|---|---|---|---|
| | | R′ | R″ | | |
| 1 | H | $CH_3$ | $CO_2C_2H_5$ | **9a** | 26 |
| 2[a] | H | $C_6H_5$ | $CO_2C_2H_5$ | **9b**, **9c** | 31 |
| 3 | Ac | $CH_3$ | $CO_2C_2H_5$ | **10a** | 70 |
| 4 | Ac | $C_6H_5$ | $CO_2C_2H_5$ | **10b** | 67 |
| 5 | Ac | $C_6H_5$ | $CO_2CH_3$ | **10c** | 68 |
| 6 | Ac | $C_2H_5$ | $COCH_3$ | **10d** | 59 |
| 7 | Ac | $C_6H_5$ | $COCH_3$ | **10e** | 61 |

[a] A mixture of *E* and *Z* isomers was obtained.

**Table 4**
$^1$H NMR data ($\delta$, $CDCl_3$) for the vinylic H atom in **9a** and **10a–e**

| Compound | **9a** | **10a** | **10b** | **10c** | **10d** | **10e** |
|---|---|---|---|---|---|---|
| $\delta$ (ppm) | 5.93 | 5.94 | 6.18 | 6.18 | 6.28 | 6.39 |

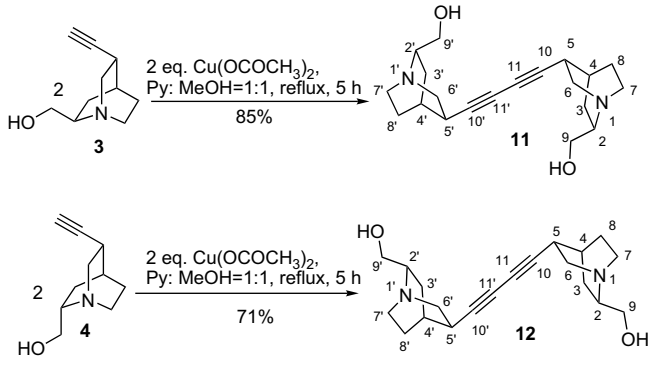
could be again smoothly transformed in its more stable isomer **10f** by self-base-catalyzed isomerization due to the strong basicity of the bridgehead nitrogen atom by heating a pure sample of **10d** to reflux in THF for 5 h (Scheme 5). The ratio **10d**/**10f** was 5:95 from the $^1$H NMR spectrum. The NOE experiment confirmed the *Z* configuration of the olefin **10f**. Large NOE effects were recorded for the vinylic hydrogen atom (Scheme 5, arrow I) and for the methylene group (Scheme 5, arrow II) upon irradiation of the ketone methyl group.




**Scheme 5.** The base-catalyzed isomerization of the enyne **10d**.

## 2.3. Synthesis of dimers

To examine the application of [2+2+2] cyclo-trimerization of alkynes to *Cinchona* alkaloid derivatives we used the dimers **11** and **12** as diynes. These dimers were reported for the first time by Hoffmann and co-workers and were obtained using a self-coupling reaction in the presence of $PdCl_2(PPh_3)_2$, CuI, $I_2$ (0.5 equiv) and $Et_3N$.[28] Eglinton reaction[29] for the homocoupling of the enantiopure 10,11-didehydro quincoridine (QCD) **3** and 10,11-didehydro quincorine (QCI) **4** afforded the desired diynes **11** and **12** in very good yields and without the formation of by-products (Scheme 6).




**Scheme 6.** Homocoupling reactions of 10,11-didehydro QCD **3** and 10,11-didehydro QCI **4**.

Colourless crystals suitable for X-ray analysis (Figs. 3 and 5) were obtained through slow diffusion of *n*-hexane into a concentrated $CH_2Cl_2$ solution of **11** and **12**. The molecular structure of **11** reveals the slightly bent behaviour of the diyne fragment, which is obvious from the angles C(2)–C(1)–C(14) 176.05(19), C(1)–C(2)–C(3) 179.0(2), C(2)–C(3)–C(4) 179.0(2) and C(3)–C(4)–C(24) 177.9(2) (Fig. 3).

In the lattice of **11** the hydrogen atom of one –OH group of a molecule is directed towards the oxygen atom of another

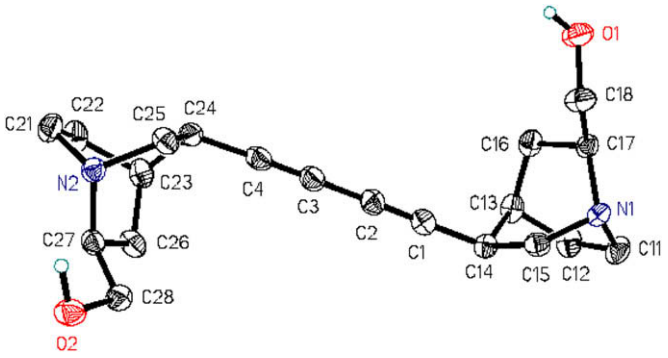



**Figure 3.** The molecular structure of **11** (H-atoms are omitted for clarity; ellipsoids at 50% probability level).

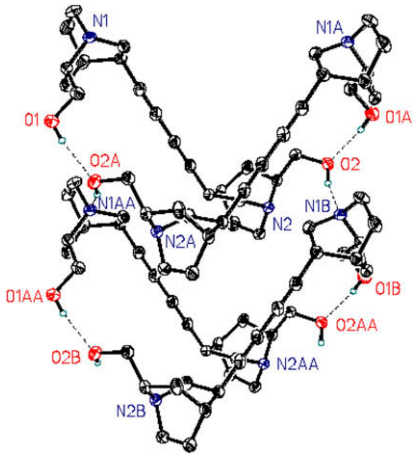



**Figure 4.** Hydrogen-bonded chains in the lattice of **11**.

molecule and vice versa in order to give dimer units by hydrogen bonds. On the other hands these dimeric units form a helix through hydrogen bonds, which involve the nitrogen atoms and the protons of the non participating (to the formation of the dimer) –OH groups of the dimers (Fig. 4).

In **12** the diyne fragment is also slightly bent, which is pointed out from the angles C(2)–C(1)–C(14) 179.6(2), C(1)–C(2)–C(3) 178.6(2), C(2)–C(3)–C(4) 177.9(2), C(3)–C(4)–C(24) 174.3(2) (Fig. 5).

In the lattice, the molecules of **12** are linked into infinite chains through hydrogen bonds (Fig. 6).

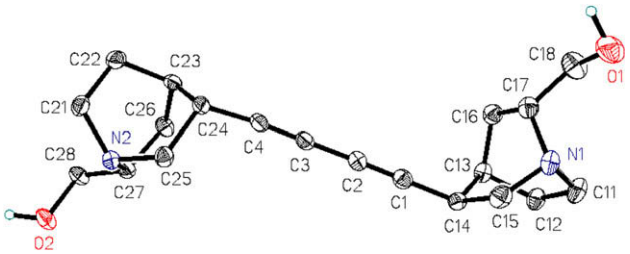



**Figure 5.** The molecular structure of **12** (H-atoms are omitted for clarity; ellipsoids at 50% probability level).

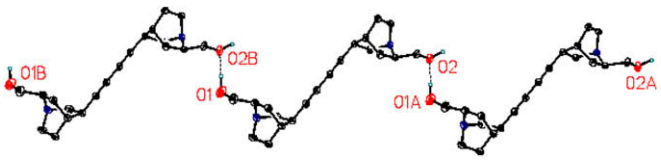
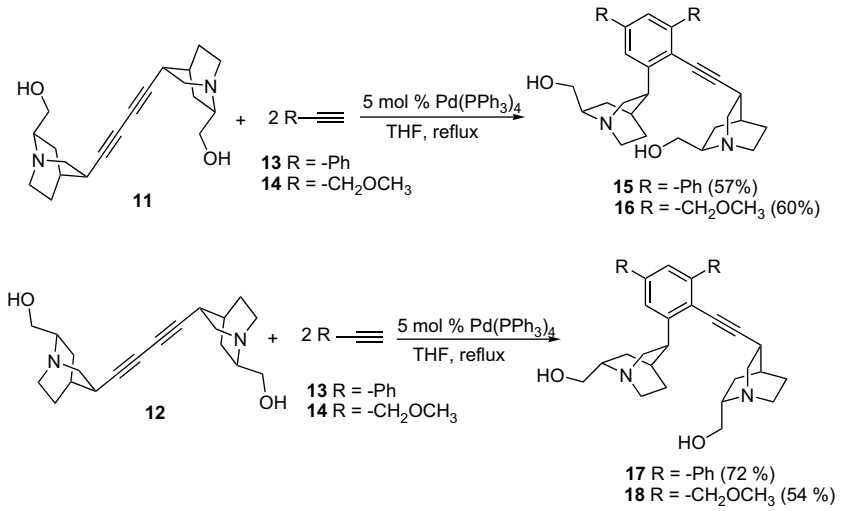



**Figure 6.** View of the lattice of **12**.



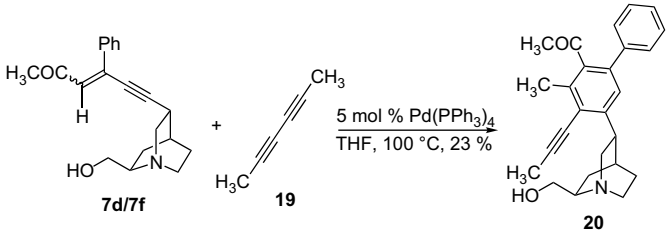

**Scheme 7.** The synthesis of tetrasubstituted benzene derivatives.

### 2.4. Synthesis of tetrasubstituted benzene derivatives

Reactions of terminal alkynes **13** and **14** with diynes **11** and **12** in the presence of 5 mol % of $Pd(PPh_3)_4$ in THF at reflux furnished the tetrasubstituted benzenes in good yields (Scheme 7). These derivatives were obtained as single reaction products and the $^1H$ NMR and mass spectra were in full agreement with the proposed structures.

### 2.5. Synthesis of pentasubstituted benzene derivative

The cross-benzannulation reaction of the mixture of *E*/*Z* enynes **7d**/**7f** with 2,4-hexadiyne **19** gave the pentasubstituted benzene **20** in fair yield (Scheme 8). The moderate yield of this reaction can be reasonably explained based on literature data.[20] The benzannulation process requires the migration of a hydrogen atom from the *E*-position of an enyne moiety and the *E*-isomer **7d** must be converted into *Z*-isomer **7f**. While, the inversion proceeds thermally, thereby explaining the high temperature required (100 °C) and therefore the lower yield.




**Scheme 8.** The synthesis of pentasubstituted benzene derivative **20**.

Slow diffusion of diethyl ether into a concentrated $CH_2Cl_2$ solution of **20** produced colourless crystals and the single crystal X-ray analysis provided the molecular structure of the target pentasubstituted benzene derivative (Fig. 7). The torsion angle of the aromatic rings of the biphenyl unit is 42.2(5).

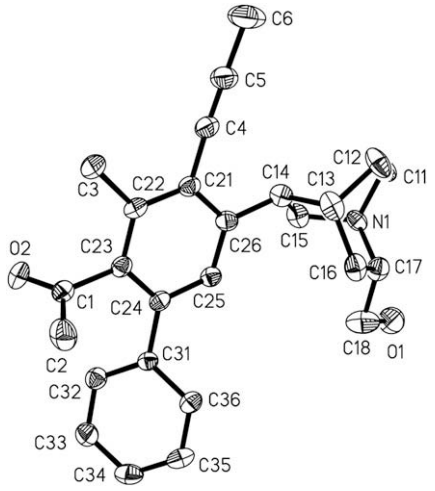



**Figure 7.** The molecular structure of **20** (H-atoms are omitted for clarity; ellipsoids at 50% probability level).

## 3. Conclusions

In summary, the addition reactions of terminal alkynes to internal alkynes allowed the formation, under mild conditions, of new quinuclidine derivatives in very good yields. The process exhibited high regio- and diastereoselectivity, the *E*-enynes being obtained as single products in almost all cases. 10,11-Didehydro quincorine **4** has failed as donor, but its *O*-acylated analogue **6** gave very good results in the cross-coupling reactions. The formal [2+2+2] intermolecular trimerization of alkynes via palladium-catalyzed cross-benzannulation reactions affords tetra- and pentasubstituted benzene derivatives, which are not easily available using conventional methods. The presented highly functionalized quinuclidines will find an application particularly in pharmaceutical industry and medicinal chemistry. The pharmaceutical importance of the *Cinchona* alkaloids through the centuries and the various receptor qualities of well known quinuclidines are focused in the new enantiopure quinuclidine building blocks.

## 4. Experimental section

### 4.1. General

All reactions were performed under a dry nitrogen atmosphere using standard Schlenk techniques. Tetrahydrofuran (THF) was freshly distilled under nitrogen from sodium/benzophenone. $Pd(OAc)_2$ and tris-(2,6-dimethoxyphenyl) phosphine (TDMPP)

were purchased from Fluka and Aldrich, respectively. $Pd(PPh_3)_4$ was prepared using the literature procedure.[30] Quincorine (QCI) and quincoridine (QCD) were donated from Buchler GmbH. Preparative column chromatography was performed on Fluka silica gel (particle size 30–60 μm). Analytical TLC was carried out on Polygram Sil G/$UV_{254}$ plates (0.2 mm silica gel).

NMR spectra were recorded with a Bruker DRX-400 spectrometer in $CDCl_3$ using the residual solvent signal at $\delta$=7.26 ($^1$H) or 77.0 ($^{13}$C) ppm as the internal standard. Mass spectra were recorded using a Finnigan MAT 90 spectrometer operating in EI or FAB mode. Melting points were determined on a Büchi 510 Melting Point apparatus and are uncorrected.

## 4.2. General procedure for the cross-couplings of terminal alkynes with internal alkynes

A mixture of $Pd(OAc)_2$ (0.02 equiv) and TDMPP (0.02 equiv) in 50 ml of absolute THF was stirred at rt for 15 min and then the acceptor alkyne (1.2 equiv) was added. After 5 min the donor alkyne (1 equiv) was added and stirring was continued until TLC analysis indicated complete consumption of the reactants. The reaction mixture was then concentrated in vacuo and the resulting crude product was purified by column chromatography to give the pure product.

### *4.2.1. 5-((1′S,2′R,4′S,5′S)-2′-Hydroxymethyl-1′-azabicyclo [2.2.2]oct-5′-yl)-3-methyl-(E)-2-penten-4-ynoic acid ethyl ester (**7a**)*

Prepared according to general procedure from 0.6 g (3.63 mmol) of **3**, 0.40 g (4.35 mmol) of ethyl-2-butynoate, 16.32 mg (2 mol %) of $Pd(OAc)_2$ and 32.17 mg (2 mol %) of TDMPP. The residue was purified by column chromatography with *t*-Bu-Me-ether/acetonitrile/$NH_3$ (25%)=1:1:0.1 as eluent to give 1 g of **7a** (94%) as a pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ 1.20 (t, *J*=7.1 Hz, 3H, C*H*$_3$CH$_2$–), 1.29–1.36 (m, 1H, H-3′), 1.44–1.64 (m, 3H, H-3′, 2H-8′), 1.86–1.89 (m, 1H, H-4′), 2.20 (d, *J*=1.4 Hz, –C*H*$_3$), 2.57–2.61 (m, 1H, H-5′), 2.75–3.00 (m, 6H, 2H-6′, 2H-7′, –OH, H-2′), 3.41 (dd, *J*=11.3, 4.9 Hz, 1H, H-9′), 3.50–3.55 (m, 1H, H-9′), 4.09 (q, *J*=7.1 Hz, 2H, CH$_3$C*H*$_2$–), 5.92 (d, *J*=1.4 Hz, 1H, H-2); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ 14.23 (*C*H$_3$CH$_2$–), 20.13 (*C*H$_3$–), 24.26 (C-3′), 25.42 (C-8′), 27.27 (C-4′), 29.09 (C-5′), 47.64 (C-6′), 48.41 (C-7′), 57.14 (C-2′), 59.90 (CH$_3$*C*H$_2$–), 62.03 (C-9′), 84.02 (C-4), 97.37 (C-5), 123.63 (C-2), 138.15 (C-3), 166.09 (*C*O). MS (EI) *m*/*z* (%): 277 (100) [M]$^+$, 260 (6) [M−OH]$^+$, 248 (89) [M−$C_2H_5$]$^+$, 246 (66) [M−$CH_2OH$]$^+$, 232 (24) [M−$C_2H_5O$]$^+$, 204 (31) [M−$C_2H_5CO_2$]$^+$. Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.12; H, 8.42; N, 5.10.

### *4.2.2. 5-((1′S,2′R,4′S,5′S)-2′-Hydroxymethyl-1′-azabicyclo [2.2.2]oct-5′-yl)-3-phenyl-(E)-2-penten-4-ynoic acid ethyl ester (**7b**)*

Prepared according to general procedure from 0.6 g (3.63 mmol) of **3**, 0.85 g (4.88 mmol) of ethyl-phenylpropiolate, 16.32 mg (2 mol %) of $Pd(OAc)_2$ and 32.17 mg (2 mol %) of TDMPP. The residue was purified by column chromatography with *t*-Bu-Me-ether/acetonitrile/$NH_3$ (25%)=1:1:0.1 as eluent to give 0.9 g of **7b** (73%) as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.16 (t, *J*=7.1 Hz, 3H, –CH$_2$C*H*$_3$), 1.38–1.44 (m, 1H, H-3′), 1.54–1.73 (m, 3H, 2H-8′, H-3′), 2.00–1.99 (m, 1H, H-4′), 2.69–2.74 (m, 1H, H-5′), 2.85–3.09 (m, 6H, 2H-6′, 2 H-7′, H-2′, –OH), 3.49 (dd, *J*=11.4, 4.9 Hz, 1H, H-9′), 3.57–3.63 (m, 1H, H-9′), 4.10 (q, *J*=7.1 Hz, 2H, –C*H*$_2$CH$_3$), 6.27 (s, 1H, H-2), 7.35–7.39 (m, 3H, H-3″, H-4″, H-5″), 7.41–7.44 (m, 2H, H-2″, H-6″); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ 13.90 (–CH$_2$*C*H$_3$), 24.30 (C-3′), 25.36 (C-8′), 27.25 (C-4′), 29.24 (C-5′), 47.56 (C-6′), 48.39 (C-7′), 57.11 (C-2′), 60.26 (–*C*H$_2$CH$_3$), 62.00 (C-9′), 82.89 (C-4), 99.30 (C-5), 124.19 (C-2), 127.76 (C-3″, C-5″), 128.27 (C-2″, C-6″), 128.72 (C-4″), 136.85 (C-1″), 138.41 (C-3), 165.35 (*C*O). MS (EI) *m*/*z* (%): 339 (100) [M$^+$], 310 (94) [M−$C_2H_5$]$^+$, 308 (54) [M−$CH_2OH$]$^+$, 266 (32) [M−$C_2H_5CO_2$]$^+$. Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N 4.13. Found: C, 74.23; H, 7.32; N, 4.18.

### *4.2.3. 5-((1′S,2′R,4′S,5′S)-2′-Hydroxymethyl-1′-azabicyclo [2.2.2]oct-5′-yl)-3-phenyl-(E)-2-penten-4-ynoic acid methyl ester (**7c**)*

Prepared according to general procedure from 0.6 g (3.63 mmol) of **3**, 0.69 g (4.31 mmol) of methyl-phenylpropiolate, 16.32 mg (2 mol %) of $Pd(OAc)_2$ and 32.17 mg (2 mol %) of TDMPP. The residue was purified by column chromatography with *t*-Bu-Me-ether/acetonitrile/$NH_3$ (25%)=1:1:0.1 as eluent to give 0.99 g of **7c** (84%) as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.29–1.35 (m, 1H, H-3′), 1.45–1.64 (m, 3H, 2H-8′, H-3′), 1.90–1.91 (m, 1H, H-4′), 2.61–2.65 (m, 1H, H-5′), 2.76–3.01 (m, 5H, 2H-6′, 2H-7′, H-2′), 3.14 (br s, 1H, –OH), 3.40 (dd, *J*=11.4, 4.9 Hz, 1H, H-9′), 3.47–3.53 (m, 1H, H-9′), 3.54 (s, 3H, –OC*H*$_3$), 6.17 (s, 1H, H-2), 7.25–7.34 (m, 5H, $H_{Ph}$); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ 24.25 (C-3′), 25.26 (C-8′), 27.23 (C-4′), 29.19 (C-5′), 47.51 (C-6′), 48.36 (C-7′), 51.38 (–O*C*H$_3$), 57.24 (C-2′), 61.94 (C-9′), 82.99 (C-4), 99.23 (C-5), 123.58 (C-2), 127.81 (C-2″, C-6″), 128.27 (C-3″, C-5″), 128.86 (C-4″), 136.66 (C-1″), 138.82 (C-3), 165.72 (*C*O). MS (EI) *m*/*z* (%): 325 (12) [M$^+$], 310 (6) [M−$CH_3$]$^+$, 294 (10) [M−$CH_2OH$]$^+$. Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.91; H, 7.03; N, 4.27.

### *4.2.4. 6-((1′S,2′R,4′S,5′S)-2′-Hydroxymethyl-1′-azabicyclo [2.2.2]oct-5′-yl)-4-phenyl-(E)-3-hexen-5-yn-2-one (**7d**)*

Prepared according to general procedure from 0.4 g (2.42 mmol) of **3**, 0.45 g (3.12 mmol) of 4-phenyl-3-butyn-2-one, 10.86 mg (2 mol %) of $Pd(OAc)_2$ and 21.41 mg (2 mol %) of TDMPP. The residue was purified by column chromatography with *t*-Bu-Me-ether/acetonitrile/$NH_3$ (25%)=1:1:0.1 as eluent to give 0.50 g of *E*/*Z* (63:37) mixture (67%) as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ 1.34–1.41 (m, 1H, H-3′), 1.50–1.72 (m, 3H, 2H-8′, H-3′), 1.97 (s, 3H, –C*H*$_3$), 1.91–1.98 (m, 1H, H-4′), 2.67–2.71 (m, 1H, H-5′), 2.81–3.07 (m, 5H, 2H-6′, 2H-7′, H-2′), 3.39–3.70 (m, 3H, 2H-9′, –OH), 6.46 (s, 1H, H-3), 7.38 (s, 5H, $H_{Ph}$); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ 24.31 (C-3′), 25.32 (C-8′), 27.22 (C-4′), 29.29 (C-5′), 30.41 (C-1), 47.56 (C-6′), 48.33 (C-7′), 57.04 (C-2′), 62.01 (C-9′), 69.16 (C-5), 100.32 (C-6), 128.20 (C-2″, C-6″), 128.40 (C-3″, C-5″), 129.11 (C-4″), 133.41 (C-3), 136.08 (C-1″), 137.01 (C-4), 199.22 (C-2). MS (EI) *m*/*z* (%): 309 (80) [M$^+$], 292 (8) [M−OH]$^+$, 278 (100) [M−$CH_2OH$]$^+$, 266 (17) [M−$CH_3CO$]$^+$. Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.51; H, 7.56; N, 4.57.

### *4.2.5. 6-((1′S,2′R,4′S,5′S)-2′-Hydroxymethyl-1′-azabicyclo [2.2.2]oct-5′-yl)-4-phenyl-(Z)-3-hexen-5-yn-2-one (**7f**)*

Prepared according to general procedure from 0.4 g (2.42 mmol) of **3**, 0.45 g (3.12 mmol) of 4-phenyl-3-butyn-2-one, 10.86 mg (2 mol %) of $Pd(OAc)_2$ and 21.41 mg (2 mol %) of TDMPP. The residue was purified by column chromatography with *t*-Bu-Me-ether/acetonitrile/$NH_3$ (25%)=1:1:0.1 as eluent to give 0.50 g of *E*/*Z* (63:37) mixture (67%) as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ 1.50–1.72 (m, 4H, 2H-8′, 2H-3′), 2.10–2.12 (m, 1H, H-4′), 2.50 (s, 3H, –C*H*$_3$), 2.50–2.53 (m, 1H, H-5′), 2.81–3.07 (m, 5H, 2H-6′, 2H-7′, H-2′), 3.39–3.70 (m, 3H, 2H-9′, –OH), 6.78 (s, 1H, H-3), 7.40–7.42 (m, 3H, H-3″, H-4″, H-5″), 7.68–7.70 (m, 2H, H-2″, H-6″); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ 24.41 (C-3′), 25.43 (C-8′), 27.30 (C-4′), 28.06 (C-5′), 30.70 (C-1), 47.36 (C-6′), 48.40 (C-7′), 57.17 (C-2′), 62.06 (C-9′), 69.16 (C-5), 106.97 (C-6), 127.07 (C-2″, C-6″), 128.49 (C-3″, C-5″), 129.78 (C-4″), 131.28 (C-3), 134.20 (C-1″), 137.75 (C-4), 197.14 (C-2). MS (EI) *m*/*z* (%): 309 (80) [M$^+$], 292 (8) [M−OH]$^+$, 278 (100) [M−$CH_2OH$]$^+$, 266 (17) [M−$CH_3CO$]$^+$. Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.51; H, 7.56; N, 4.57.

#### 4.2.6. 4-((1′S,2′R,4′S,5′S)-2′-Hydroxymethyl-1′-azabicyclo [2.2.2]oct-5′-ylethynyl)-(Z)-4-hexen-2-one (**7f**)

Prepared according to general procedure from 0.6 g (3.63 mmol) of **3**, 0.42 g (4.36 mmol) of 3-hexyn-2-one, 16.32 mg (2 mol %) of $Pd(OAc)_2$ and 32.17 mg (2 mol %) of TDMPP. The residue was purified by column chromatography with *t*-Bu-Me-ether/acetonitrile/$NH_3$ (25%)=1:1:0.1 as eluent to give 0.76 g of **7e** (80%) as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ 1.42–1.50 (m, 1H, H-3′), 1.54–1.74 (m, 3H, 2H-8′, H-3′), 1.88 (d, *J*=6.7 Hz, 3H, H-6), 1.94–1.98 (m, 1H, H-4′), 2.21 (s, 3H, H-1), 2.67–2.72 (m, 1H, H-5′), 2.86–3.09 (m, 5H, 2H-6′, 2H-7′, H-2′), 3.17 (s, 2H, H-3), 3.23 (br s, 1H, –OH), 3.51 (dd, *J*=11.3, 5 Hz, 1H, H-9′), 3.60–3.65 (m, 1H, H-9′), 5.84 (q, *J*=6.7 Hz, 1H, H-5); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ 16.33 (C-6), 24.21 (C-3′), 25.47 (C-8′), 27.44 (C-4′), 29.08 (C-5′, C-1), 48.12 (C-6′), 48.42 (C-7′), 52.14 (C-3), 57.20 (C-2′), 62.04 (C-9′), 79.12 (C-11′), 97.92 (C-10′), 117.03 (C-4), 135.50 (C-5), 206.30 (CO). MS (EI) *m*/*z* (%): 261 (100) [$M^+$], 230 (84) [$M-CH_2OH]^+$, 218 (41) [$M-CH_3CO]^+$, 188 (13) [$M-CH_3CO_2CH_2]^+$. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 75.44; H, 8.96; N, 5.40.

#### 4.2.7. 5-((1′S,2′R,4′S,5′S)-2′-Acetoxymethyl-1′-azabicyclo [2.2.2]oct-5′-yl)-3-phenyl-(E)-2-penten-4-ynoic acid methyl ester (**8a**)

Prepared according to general procedure from 0.6 g (2.90 mmol) of **5**, 0.55 g (3.47 mmol) of methyl-phenylpropiolate, 13.00 mg (2 mol %) of $Pd(OAc)_2$ and 25.00 mg (2 mol %) of TDMPP. The residue was purified by column chromatography with *t*-Bu-Me-ether/acetonitrile/$NH_3$ (25%)=1:1:0.1 as eluent to give 0.86 g of **8a** (81%) as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ 1.41–1.60 (m, 4H, 2H-8′, 2H-3′), 1.92–1.93 (m, 1H, H-4′), 2.00 (s, 3H, H-11′), 2.61–2.65 (m, 1H, H-5′), 2.77–3.09 (m, 5H, H-2′, 2H-6′, 2H-7′), 3.53 (s, 3H, C*H*$_3$OCO–), 3.99 (dd, *J*=11.9, 4.8 Hz, 1H, H-9′), 4.07 (dd, *J*=11.9, 9.2 Hz, 1H, H-9′), 6.18 (s, 1H, H-2), 7.25–7.30 (m, 3H, H-2″, H-6″, H-4″), 7.31–7.36 (m, 2H, H-3″, H-5″); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ 21.03 (C-11′), 24.52 (C-3′), 24.94 (C-8′), 27.32 (C-4′), 29.11 (C-5′), 48.29 (C-6′), 48.51 (C-7′), 51.36 (*C*H$_3$OCO–), 54.46 (C-2′), 64.11 (C-9′), 82.99 (C-4), 99.27 (C-5), 123.62 (C-2), 127.81 (C-2″, C-6″), 128.28 (C-3″, C-5″), 128.83 (C-4″), 136.65 (C-1″), 138.82 (C-3), 165.70 (CH$_3$O*C*O–), 171.18 (C-10′). MS (EI) *m*/*z* (%): 367 (1) [$M^+$], 352 (1) [$M-CH_3]^+$. Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.83; H, 6.96; N, 3.72.

#### 4.2.8. 6-((1′S,2′R,4′S,5′S)-2′-Acetoxymethyl-1′-azabicyclo [2.2.2]oct-5′-yl)-4-ethyl-(E)-3-hexen-5-yn-2-one (**8b**)

Prepared according to general procedure from 0.44 g (2.12 mmol) of **5**, 0.25 g (2.60 mmol) of 3-hexyn-2-one, 10.00 mg (2 mol %) of $Pd(OAc)_2$ and 18.80 mg (2 mol %) of TDMPP. The residue was purified by column chromatography with *t*-Bu-Me-ether/acetonitrile/$NH_3$ (25%)=1:2:0.25 as eluent to give 0.34 g of **8b** (53%) as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ 1.04 (t, *J*=7.5 Hz, 3H, H-8), 1.42–1.61 (m, 4H, 2H-8′, 2H-3′), 1.89–1.94 (m, 1H, H-4′), 2.02 (s, 3H, H-11′), 2.13 (s, 3H, H-1), 2.59–2.65 (m, 3H, H-5′, H-7), 2.78–2.94 (m, 3H, H-6′, 2 H-7′), 3.0–3.10 (m, 2H, H-6′, H-2′), 4.01 (dd, *J*=11.9, 4.8 Hz, 1H, H-9′), 4.10 (dd, *J*=11.9, 9.3 Hz, 1H, H-9′), 6.29 (s, 1H, H-3); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ 12.85 (C-8), 21.04 (C-11′), 24.61 (C-3′), 25.05 (C-8′), 25.96 (C-7), 27.42 (C-4′), 29.14 (C-5′), 31.79 (C-1), 48.43 (C-6′), 48.51 (C-7′), 54.42 (C-2′), 64.21 (C-9′), 83.14 (C-5), 98.61 (C-6), 129.77 (C-3), 143.18 (C-4), 171.24 (C-10′), 197.68 (C-2). MS (EI) *m*/*z* (%): 303 (83) [$M^+$], 260 (26) [$M-CH_3CO]^+$, 244 (36) [$M-CH_3CO_2]^+$, 230 (100) [$M-CH_3CO_2CH_2]^+$. Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.33; H, 8.26; N, 4.58.

#### 4.2.9. 4-((1′S,2′R,4′S,5′S)-2′-Acetoxymethyl-1′-azabicyclo [2.2.2]oct-5′-ylethynyl)-(Z)-4-hexen-2-one (**8c**)

Enyne **8b** (0.15 g, 0.5 mmol) isomerized upon refluxing in THF for 5 h furnishing the enyne **8c** (99%). $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ 1.39–1.59 (m, 4H, 2H-8′, 2H-3′), 1.80 (d, *J*=6.8 Hz, 3H, H-6), 1.85–1.88 (m, 1H, H-4′), 2.02 (s, 3H, H-11′), 2.12 (s, 3H, H-1), 2.58–2.62 (m, 1H, H-5′), 2.78–2.94 (m, 3H, H-6′, 2 H-7′), 3.06–3.01 (m, 2H, H-2′, H-6′), 3.08 (s, 2H, H-3), 4.00 (dd, *J*=11.9, 5.0 Hz, 1H, H-9′), 4.09 (dd, *J*=11.9, 9.4 Hz, 1H, H-9′), 7.75 (q, *J*=6.8 Hz, 1H, H-5); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ 16.34 (C-6), 21.03 (C-11′), 24.49 (C-3′), 25.11 (C-8′), 27.47 (C-4′), 28.98 (C-5′), 29.08 (C-1), 48.51 (C-7′), 48.77 (C-6′), 52.08 (C-3), 54.46 (C-2′), 64.17 (C-9′), 79.22 (C-13′), 97.85 (C-12′), 116.99 (C-4), 135.51 (C-5), 171.23 (C-10′), 206.24 (C-2). MS (EI) *m*/*z* (%): 303 (17) [$M^+$], 260 (12) [$M-CH_3CO]^+$, 230 (16) [$M-CH_3CO_2CH_2]^+$. Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.19; H, 8.47; N, 4.55.

#### 4.2.10. 5-((1′S,2′S,4′S,5′S)-2′-Hydroxymethyl-1′-azabicyclo [2.2.2]oct-5′-yl)-3-methyl-(E)-2-penten-4-ynoic acid ethyl ester (**9a**)

Prepared according to general procedure from 0.3 g (1.81 mmol) of **4**, 0.24 g (2.17 mmol) of ethyl-2-butynoate, 8.16 mg (2 mol %) of $Pd(OAc)_2$ and 16.00 mg (2 mol %) of TDMPP. The residue was purified by column chromatography with *t*-Bu-Me-ether/acetonitrile/$NH_3$ (25%)=1:1:0.1 as eluent to give 0.13 g of **9a** (26%) as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ 0.75–0.81 (m, 1H, H-3′), 1.20 (t, *J*=7.1 Hz, 3H, –$CH_2CH_3$), 1.34–1.49 (m, 2H, 2H-8′), 1.86–1.90 (m, 1H, 2H-4′), 1.93–2.00 (m, 1H, H-3′), 2.20 (d, *J*=1.4 Hz, 3H, –*C*H$_3$), 2.49–2.56 (m, 1H, H-7′), 2.61–2.65 (m, 1H, H-5′), 2.80–2.93 (m, 2H, H-6′, H-7′), 2.98–3.08 (m, 2H, H-2′, –OH), 3.22 (dd, *J*=13.3, 10.0 Hz, 1H, H-6′), 3.39–3.45 (m, 2H, 2H-9′), 4.08 (q, *J*=7.1 Hz, 2H, –*C*H$_2$CH$_3$), 5.93 (d, *J*=1.4 Hz, 1H, H-2); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ 14.16 (–$CH_2$*C*H$_3$), 20.08 (–*C*H$_3$), 24.90 (C-3′), 26.11 (C-8′), 26.54 (C-4′), 28.68 (C-5′), 39.51 (C-7′), 56.76 (C-6′), 56.91 (C-2′), 59.81 (–*C*H$_2$CH$_3$), 62.57 (C-9′), 83.32 (C-4), 98.19 (C-5), 123.49 (C-2), 138.23 (C-3), 166.04 (CO). MS (EI) *m*/*z* (%): 277 (73) [$M^+$], 248 (83) [$M-C_2H_5]^+$, 246 (65) [$M-CH_2OH]^+$, 232 (26) [$M-C_2H_5O]^+$. Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.37; H, 8.29; N, 4.95.

#### 4.2.11. 5-((1′S,2′S,4′S,5′S)-2′-Hydroxymethyl-1′-azabicyclo [2.2.2]oct-5′-yl)-3-phenyl-(E/Z)-2-penten-4-ynoic acid ethyl ester (**9b**/**9c**)

Prepared according to general procedure from 0.6 g (3.63 mmol) of **4**, 0.75 g (4.31 mmol) of ethyl-phenylpropiolate, 40.80 mg (5 mol %) of $Pd(OAc)_2$ and 80.43 mg (5 mol %) of TDMPP. The residue was purified by column chromatography with *t*-Bu-Me-ether/acetonitrile/$NH_3$ (25%)=1:1:0.1 as eluent to give 0.38 g of *E*/*Z* (85:15) mixture (30%) as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ 0.73–0.82 (m, 1H, H-3′), 1.05 (t, *J*=7.1 Hz, 3H, –$CH_2CH_3$), 1.32–1.48 (m, 2H, 2H-8′), 1.88–1.97 (m, 2H, H-3′, H-4′), 2.47–2.57 (m, 1H, H-7′), 2.63–2.68 (m, 1H, H-5′), 2.81–2.93 (m, 2H, H-6′, H-7′), 2.97–3.05 (m, 1H, H-2′), 3.21 (br s, 1H, –OH), 3.21 (dd, *J*=13.2, –10.0 Hz, 1H, H-6′), 3.35–3.43 (m, 2H, 2H-9′), 3.95–4.01/4.10–4.15 (q, *J*=7.1 Hz, 2H, –*C*H$_2$CH$_3$), 6.17/7.04 (s, 1H, H-2), 7.21–7.27 (m, 3H, H-3″, H-4″, H-5″), 7.31–7.36 (m, 2H, H-2″, H-6″); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ 13.71/13.83 (–$CH_2$*C*H$_3$), 24.91 (C-3′), 26.03 (C-8′), 26.54 (C-4′), 28.69/28.79 (C-5′), 39.48 (C-7′), 56.64 (C-6′), 56.72/56.91 (C-2′), 60.16/61.38 (–*C*H$_2$CH$_3$), 62.52 (C-9′), 82.20 (C-4), 95.75/99.99 (C-5), 124.08 (C-2), 127.68/128.11 (C-3″, C-5″), 128.21/128.50 (C-2″, C-6″), 128.64/128.76 (C-4″), 134.64/136.79 (C-1″), 138.45/142.45 (C-3), 165.29 (CO). MS (EI) *m*/*z* (%): 339 (15) [$M^+$], 310 (13) [$M-C_2H_5]^+$, 277 (29) [$M-C_2H_5O-OH]^+$, 262 (13) [$M-C_6H_5]^+$. Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.39; H, 7.35; N, 4.20.

#### 4.2.12. 5-((1′S,2′S,4′S,5′S)-2′-Acetoxymethyl-1′-azabicyclo [2.2.2]oct-5′-yl)-3-methyl-(E)-2-penten-4-ynoic acid ethyl ester (**10a**)

Prepared according to general procedure from 0.6 g (2.90 mmol) of **6**, 0.39 g (3.48 mmol) of ethyl-2-butynoate, 13.01 mg (2 mol %) of

$Pd(OAc)_2$ and 25.64 mg (2 mol %) of TDMPP. The residue was purified by column chromatography with *t*-Bu-Me-ether/acetonitrile/$NH_3$ (25%)=10:1:0.25 as eluent to give 0.64 g of **10a** (70%) as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ 0.88–0.93 (m, 1H, H-3′), 1.20 (t, $J$=7.1 Hz, 3H, $-CH_2CH_3$), 1.36–1.51 (m, 1H, 2H-8′), 1.90 (br s, 1H, H-4′), 2.02 (s, 3H, H-11′), 1.98–2.07 (m, 1H, H-3′), 2.21 (d, $J$=1.4 Hz, 3H, $-CH_3$), 2.57–2.65 (m, 2H, H-7′, H-5′), 2.83–2.97 (m, 2H, H-7′, H-6′), 3.11–3.19 (m, 1H, H-2′), 3.26 (dd, $J$=13.4, 10.0 Hz, 1H, H-6′), 3.96 (dd, $J$=11.8, 5.2 Hz, 1H, H-9′), 4.02 (dd, $J$=11.8, 9.2 Hz, 1H, H-9′), 4.08 (q, $J$=7.1 Hz, 2H, $-CH_2CH_3$), 5.94 (d, $J$=1.4 Hz, 1H, H-2). $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ 14.15 ($-CH_2CH_3$), 20.07 ($-CH_3$), 20.97 (C-11′), 25.15 (C-3′), 25.94 (C-8′), 26.64 (C-4′), 28.28 (C-5′), 40.21 (C-7′), 54.12 (C-2′), 56.79 (C-6′), 59.79 ($-CH_2CH_3$), 64.58 (C-9′), 83.33 (C-4), 98.10 (C-5), 123.50 (C-2), 138.20 (C-3), 166.00 (CO), 171.19 (C-10′). MS (EI) $m/z$ (%): 319 (59) [$M^+$], 290 (41) [$M-C_2H_5]^+$, 274 (14) [$M-C_2H_5O]^+$, 260 (11) [$M-CH_3CO_2]^+$, 246 (100) [$M-C_2H_5CO_2]^+$. Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.54; H, 7.96; N, 4.43.

#### 4.2.13. 5-((1′S,2′S,4′S,5′S)-2′-Acetoxymethyl-1′-azabicyclo [2.2.2]oct-5′-yl)-3-phenyl-(E)-2-penten-4-ynoic acid ethyl ester (**10b**)

Prepared according to general procedure from 0.5 g (2.41 mmol) of **6**, 0.50 g (2.87 mmol) of ethyl-phenylpropiolate, 10.08 mg (2 mol %) of $Pd(OAc)_2$ and 21.37 mg (2 mol %) of TDMPP. The residue was purified by column chromatography with *t*-Bu-Me-ether/acetonitrile/$NH_3$ (25%)=10:1:0.25 as eluent to give 0.62 g of **10b** (67%) as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ 0.87–0.92 (m, 1H, H-3′), 1.05 (t, $J$=7.1 Hz, 3H, $-CH_2CH_3$), 1.34–1.48 (m, 2H, 2H-8′), 1.91–1.92 (m, 1H, H-4′), 1.96–2.00 (m, 1H, H-3′), 2.02 (s, 3H, H-11′), 2.56–2.66 (m, 2H, H-5′, H-7′), 2.85–2.96 (m, 2H, H-7′, H-6′), 3.10–3.18 (m, 1H, H-2′), 3.25 (dd, $J$=13.4, 10.0 Hz, 1H, H-6′), 3.95 (dd, $J$=11.9, 5.2 Hz, 1H, H-9′), 3.98 (q, $J$=7.1 Hz, 2H, $-CH_2CH_3$), 4.00 (dd, $J$=11.9, 9.4 Hz, 1H, H-9′), 6.18 (s, 1H, H-2), 7.24–7.28 (m, 3H, H-3″, H-4″, H-5″), 7.30–7.35 (m, 2H, H-2″, H-6″); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ 13.88 ($-CH_2CH_3$), 21.01 (C-11′), 25.26 (C-3′), 25.95 (C-8′), 26.69 (C-4′), 28.48 (C-5′), 40.27 (C-7′), 54.20 (C-2′), 56.75 (C-6′), 60.21 ($-CH_2CH_3$), 64.63 (C-9′), 82.26 (C-4), 99.97 (C-5), 124.15 (C-2), 127.72 (C-3″, C-5″), 128.27 (C-2″, C-6″), 128.69 (C-4″), 136.84 (C-1″), 138.45 (C-3), 165.33 (CO), 171.22 (C-10′). MS (EI) $m/z$ (%): 381 (73) [$M^+$], 352 (60) [$M-C_2H_5]^+$, 308 (100) [$M-C_2H_5CO_2]^+$. Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.33; H, 7.19; N, 3.75.

#### 4.2.14. 5-((1′S,2′S,4′S,5′S)-2′-Acetoxymethyl-1′-azabicyclo [2.2.2]oct-5′-yl)-3-phenyl-(E)-2-penten-4-ynoic acid methyl ester (**10c**)

Prepared according to general procedure from 0.40 g (1.93 mmol) of **6**, 0.37 g (2.31 mmol) of methyl-phenylpropiolate, 8.67 mg (2 mol %) of $Pd(OAc)_2$ and 17.10 mg (2 mol %) of TDMPP. The residue was purified by column chromatography with *t*-Bu-Me-ether/acetonitrile/$NH_3$ (25%)=10:2:0.25 as eluent to give 0.48 g of **10c** (68%) as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ 0.87–0.92 (m, 1H, H-3′), 1.37–1.47 (m, 2H, 2H-8′), 1.91 (br s, 1H, H-4′), 1.95–1.99 (m, 1H, H-3′), 2.01 (s, 3H, H-11′), 2.55–2.65 (m, 2H, H-5′, H-7′), 2.84–2.95 (m, 2H, H-7′, H-6′), 3.09–3.17 (m, 1H, H-2′), 3.24 (dd, $J$=13.4, 10.1 Hz, 1H, H-6′), 3.53 (s, 3H, $-CH_3$), 3.94 (dd, $J$=11.7, 5.1 Hz, 1H, H-9′), 4.00 (dd, $J$=11.7, 9.3 Hz, 1H, H-9′), 6.18 (s, 1H, H-2), 7.24–7.28 (m, 3H, H-3″, H-5″, H-4″), 7.30–7.35 (m, 2H, H-2″, H-6″); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ 20.91 (C-11′), 25.17 (C-3′), 25.84 (C-8′), 26.60 (C-4′), 28.39 (C-5′), 40.16 (C-7′), 51.22 ($-CH_3$), 54.09 (C-2′), 56.60 (C-6′), 64.53 (C-9′), 82.20 (C-4), 100.07 (C-5), 123.37 (C-2), 127.67 (C-3″, C-5″), 128.19 (C-2″, C-6″), 128.70 (C-4″), 136.58 (C-1″), 138.82 (C-3), 165.60 (CO), 171.09 (C-10′). MS (EI) $m/z$ (%): 367 (100) [$M^+$], 352 (43) [$M-CH_3]^+$, 308 (98) [$M-CH_3CO_2]^+$, 294 (63) [$M-CH_3CO_2CH_2]^+$. Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 72.05; H, 6.93; N, 3.70.

#### 4.2.15. 6-((1′S,2′S,4′S,5′S)-2′-Acetoxymethyl-1′-azabicyclo [2.2.2]oct-5′-yl)-4-ethyl-(E)-3-hexen-5-yn-2-one (**10d**)

Prepared according to general procedure from 0.88 g (4.25 mmol) of **6**, 0.49 g (5.09 mmol) of 3-hexyn-3-one, 19.08 mg (2 mol %) of $Pd(OAc)_2$ and 37.60 mg (2 mol %) of TDMPP. The residue was purified by column chromatography with *t*-Bu-Me-ether/acetonitrile/$NH_3$ (25%)=10:2:0.25 as eluent to give 0.75 g of **10d** (59%) as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ 0.89–0.95 (m, 1H, H-3′), 1.05 (t, $J$=7.5 Hz, 3H, $-CH_2CH_3$), 1.36–1.51 (m, 2H, 2H-8′), 1.86–1.96 (m, 1H, H-4′), 2.02 (s, 3H, H-11′), 1.99–2.06 (m, 1H, H-3′), 2.12 (s, 3H, $-CH_3$), 2.58–2.66 (m, 4H, H-7′, H-5′, $-CH_2CH_3$), 2.83–2.98 (m, 2H, H-7′, H-6′), 3.12–3.20 (m, 1H, H-2′), 3.28 (dd, $J$=13.5, 10.0 Hz, 1H, H-6′), 3.97 (dd, $J$=11.7, 5.5 Hz, 1H, H-9′), 4.02 (dd, $J$=11.7, 9.3 Hz, 1H, H-9′), 6.28 (s, 1H, H-3); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ 12.81 (C-8), 20.99 (C-11′), 25.25 (C-3′), 25.96 (C-8′, C-7), 26.74 (C-4′), 28.46 (C-5′), 31.74 (C-1), 40.24 (C-7′), 54.20 (C-2′), 56.89 (C-6′), 64.61 (C-9′), 82.46 (C-5), 99.44 (C-6), 129.63 (C-3), 143.31 (C-4), 171.21 (C-10′), 197.61 (C-2). MS (EI) $m/z$ (%): 303 (95) [$M^+$], 260 (47) [$M-CH_3CO]^+$, 244 (27) [$M-CH_3CO_2]^+$, 230 (100) [$M-CH_3CO_2CH_2]^+$. Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.33; H, 8.29; N, 4.56.

#### 4.2.16. 6-((1′S,2′S,4′S,5′S)-2′-Acetoxymethyl-1′-azabicyclo [2.2.2]oct-5′-yl)-4-phenyl-(E)-3-hexen-5-yn-2-one (**10e**)

Prepared according to general procedure from 0.43 g (2.07 mmol) of **6**, 0.36 g (2.49 mmol) of 4-phenyl-3-butyn-2-one, 9.30 mg (2 mol %) of $Pd(OAc)_2$ and 18.37 mg (2 mol %) of TDMPP. The residue was purified by column chromatography with *t*-Bu-Me-ether/acetonitrile/$NH_3$ (25%)=10:2:0.25 as eluent to give 0.44 g of **10e** (61%) as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ 0.90–0.95 (m, 1H, H-3′), 1.37–1.55 (m, 2H, 2H-8′), 1.89 (s, 3H, $-CH_3$), 1.94–1.95 (m, 1H, H-4′), 2.03 (s, 3H, H-11′), 1.97–2.05 (m, 1H, H-3′), 2.60–2.70 (m, 2H, H-5′, H-7′), 2.87–2.99 (m, 2H, H-6′, H-7′), 3.13–3.21 (m, 1H, H-2′), 3.28 (dd, $J$=13.4, 10.1 Hz, 1H, H-6′), 3.95–4.05 (m, 2H, 2H-9′), 6.39 (s, 1H, H-2), 7.30 (s, 5H, $H_{Ph}$); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ 21.05 (C-11′), 25.20 (C-3′), 25.84 (C-8′), 26.71 (C-4′), 28.52 (C-5′), 30.50 (-$CH_3$), 40.29 (C-7′), 54.30 (C-2′), 56.66 (C-6′), 64.49 (C-9′), 77.20 (C-4), 82.45 (C-5), 128.32 (C-2″, C-6″), 128.50 (C-3″, C-5″), 129.22 (C-4″), 133.63 (C-2), 136.10 (C-1″), 137.04 (C-3), 171.25 (C-10′), 199.35 (CO). MS (EI) $m/z$ (%): 351 (100) [$M^+$], 308 (26) [$M-CH_3CO]^+$, 292 (28) [$M-CH_3CO_2]^+$, 278 (73) [$M-CH_3CO_2CH_2]^+$. Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 75.26; H, 7.13; N, 3.82.

#### 4.2.17. 4-((1′S,2′S,4′S,5′S)-2′-Acetoxymethyl-1′-azabicyclo [2.2.2]oct-5′-ylethynyl)-(Z)-4-hexen-2-one (**10f**)

Enyne **10d** (0.2 g, 0.6 mmol) isomerized upon refluxing in THF for 5 h furnishing the enyne **10f** (95%). $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ 0.87–0.93 (m, 1H, H-3′), 1.35–1.50 (m, 2H, 2H-8′), 1.80 (d, $J$=6.8 Hz, 3H, H-6), 1.86–1.91 (m, 1H, H-4′), 2.02–2.08 (m, 1H, H-3′), 2.02 (s, 3H, H-11′), 2.12 (s, 3H, H-1), 2.57–2.64 (m, 2H, H-5′, H-7′), 2.83–2.97 (m, 2H, H-7′, H-6′), 3.08 (s, 2H, H-3), 3.13–3.20 (m, 1H, H-2′), 3.26 (dd, $J$=13.4, 10.0 Hz, 1H, H-6′), 3.96 (dd, $J$=11.8, 5.2 Hz, 1H, H-9′), 4.01 (dd, $J$=11.8, 9.3 Hz, 1H, H-9′), 5.75 (q, $J$=6.8 Hz, 1H, H-5); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ 16.26 (C-6), 20.98 (C-11′), 25.18 (C-3′), 26.02 (C-8′), 26.77 (C-4′), 28.30 (C-5′), 29.03 (C-1), 40.25 (C-7′), 52.07 (C-3), 54.13 (C-2′), 57.23 (C-6′), 64.63 (C-9′), 78.52 (C-13′), 98.56 (C-12′), 117.04 (C-4), 135.35 (C-5), 171.21 (C-10′), 206.22 (C-2). MS (EI) $m/z$ (%): 303 (8) [$M^+$], 260 (27) [$M-CH_3CO]^+$, 230 (12) [$M-CH_3COCH_2]^+$. Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.18; H, 8.38; N, 4.69.

### 4.3. General procedure for the Eglinton reaction

To a solution of finely powdered cupric acetate monohydrate (1.5 equiv) in pyridine/methanol (1:1) (2 ml/1.5 mmol alkyne) was

added terminal alkyne (1 equiv) **3** or **4**. The deep blue suspension becomes green when heated under reflux. After 3–5 h of heating, the solution was cooled and the solvent removed in vacuo. The residue was treated with an aqueous solution of $NH_3$ (25%) and extracted with $CH_2Cl_2$. The organic layer was dried over $Na_2SO_4$ and the solvent removed in vacuo. The resulting crude product was purified by column chromatography (*t*-Bu-Me-ether/MeOH/$NH_3$ (25%)=10:3:0.25) to afford the desired dimeric alkynes **11** and **12**. The spectral data for these are in agreement with that already reported in literature.[28]

### 4.4. General procedure for the synthesis of tetrasubstituted benzene derivatives 15–18

A mixture of alkyne **13** or **14** (2 equiv), diyne **11** or **12** (1 equiv) and $Pd(PPh_3)_4$ (0.05 equiv) in absolute THF (10 ml) was stirred under reflux until TLC analysis indicated complete consumption of the reactants. The reaction mixture was concentrated in vacuo and the crude product was purified by column chromatography.

#### *4.4.1. 1,5-Diphenyl-2-((1′S,2′S,4′S,5′S)-2′-hydroxymethyl-1′-azabicyclo[2.2.2]oct-5′-ylethynyl)-3-((1″S,2″S,4″S,5″S)-2″-hydroxymethyl-1″-azabicyclo[2.2.2]oct-5″-yl)-benzene (**15**)*

Prepared according to general procedure from 0.3 g (0.91 mmol) of **11**, 0.20 g (1.96 mmol) of **13**, 52.00 mg (5 mol %) of $Pd(PPh_3)_4$. The residue was purified by column chromatography with *t*-Bu-Me-ether/MeOH/$NH_3$ (25%)=10:3:0.25 as eluent to give 0.30 g of **15** (57%) as a white solid. Mp=212–213 °C. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 0.98–1.03 (m, 1H), 1.21–1.32 (m, 2H), 1.40–1.55 (m, 3H), 1.66–1.73 (m, 3H), 2.04–2.05 (m, 1H), 2.54–2.58 (m, 1H), 2.62–2.80 (m, 4H), 2.83 (dd, *J*=13.8, 10.3 Hz, 1H), 2.88–2.97 (m, 1H), 3.10 (dd, *J*=13.9, 10.2 Hz, 1H), 3.16–3.25 (m, 3H), 3.45–3.49 (m, 2H), 3.61 (t, *J*=10.7 Hz, 1H), 7.26–7.39 (m, 7H), 7.42–7.45 (m, 3H), 7.51 (s, 1H), 7.53 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 23.63, 24.27, 25.55, 27.33, 27.80, 28.06, 29.52, 39.59, 45.45, 47.40, 48.41, 48.84, 57.31, 58.19, 62.03, 62.40, 79.49, 101.03, 121.72, 123.22, 126.10, 127.03 (2C), 127.30, 127.66, 127.80, 128.92 (2C), 129.30 (2C), 139.78, 140.55, 141.48, 145.48, 146.04. MS (EI) *m*/*z* (%): 532 (100) [$M^+$], 503 (64) [$M-CHO]^+$. Anal. Calcd for $C_{36}H_{40}N_2O_2$: C, 81.17; H, 7.57; N, 5.26. Found: C, 81.09; H, 7.61; N, 5.30.

#### *4.4.2. 1,5-Dimethoxymethyl-2-((1′S,2′R,4′S,5′S)-2′-hydroxymethyl-1′-azabicyclo[2.2.2]oct-5′-ylethynyl)-3-((1″S,2″R,4″S,5″S)-2″-hydroxymethyl-1″-azabicyclo[2.2.2] oct-5″-yl)-benzene (**16**)*

Prepared according to general procedure from 0.3 g (0.91 mmol) of **11**, 0.126 g (1.80 mmol) of **14**, 52.00 mg (5 mol %) of $Pd(PPh_3)_4$. The residue was purified by column chromatography with *t*-Bu-Me-ether/MeOH/$NH_3$ (25%)=1:1:0.1 as eluent to give 0.25 g of **16** (60%) as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.10–1.13 (m, 1H), 1.34–1.69 (m, 7H), 1.96 (br s, 2H), 2.74–2.96 (m, 8H), 3.01–3.13 (m, 3H), 3.31 (s, 3H), 3.36 (s, 3H), 3.28–3.36 (m, 3H), 3.37–3.59 (m, 4H), 4.38 (s, 2H), 4.50 (s, 2H), 7.13 (s, 1H), 7.20 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 23.44, 25.52, 27.57, 27.74, 27.84, 29.51, 39.04, 45.40, 47.97, 48.40, 48.69, 57.10, 57.42, 58.15, 58.58, 62.16, 62.19, 73.14, 74.43, 77.50, 102.07, 121.63, 123.58, 124.24, 137.41, 141.05, 144.61. MS (FAB) *m*/*z* (%): 469 [$M+H]^+$. Anal. Calcd for $C_{28}H_{40}N_2O_4$: C, 71.76; H, 8.60; N, 5.98. Found: C, 71.68; H, 8.65; N, 6.01.

#### *4.4.3. 1,5-Diphenyl-2-((1′S,2′S,4′S,5′S)-2′-hydroxymethyl-1′-azabicyclo[2.2.2]oct-5′-ylethynyl)-3-((1″S,2″S,4″S,5″S)-2″-hydroxymethyl-1″-azabicyclo[2.2.2]oct-5″-yl)-benzene (**17**)*

Prepared according to general procedure from 0.2 g (0.60 mmol) of **12**, 0.13 g (1.27 mmol) of **13**, 34.00 mg (5 mol %) of $Pd(PPh_3)_4$. The residue was purified by column chromatography with *t*-Bu-Me-ether/MeOH/$NH_3$ (25%)=10:3:0.25 as eluent to give 0.23 g of **17** (72%) as white a solid. Mp=110–112 °C. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 0.54–0.59 (m, 1H), 0.70–0.74 (m, 1H), 1.27–1.44 (m, 2H), 1.54–1.79 (m, 5H), 2.00 (br s, 1H), 2.42–2.49 (m, 1H), 2.58–2.60 (m, 1H), 2.65–2.85 (m, 4H), 3.05–3.58 (m, 10H), 3.60–3.66 (m, 1H), 7.26–7.39 (m, 7H), 7.44 (s, 1H), 7.46 (s, 1H), 7.52 (s, 1H), 7.54 (s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 24.29, 24.82, 26.21, 26.61, 27.39, 28.58, 29.01, 39.54, 39.72, 40.42, 55.16, 56.56, 56.77, 57.69, 62.53, 63.13, 78.82, 101.59, 121.65, 123.15, 126.04, 127.08 (2C), 127.28, 127.64, 127.74 (2C), 128.88 (2C), 129.27 (2C), 139.88, 140.51, 141.55, 145.88, 146.43. MS (EI) *m*/*z* (%): 532 (100) [$M^+$], 501 (26) [$M-CH_3O]^+$. Anal. Calcd for $C_{36}H_{40}N_2O_2$: C, 81.17; H, 7.52; N, 5.26. Found: C, 81.24; H, 7.47; N, 5.19.

#### *4.4.4. 1,5-Dimethoxymethyl-2-((1′S,2′S,4′S,5′S)-2′-hydroxymethyl-1′-azabicyclo[2.2.2]oct-5′-ylethynyl)-3-((1″S,2″S,4″S,5″S)-2″-hydroxymethyl-1″-azabicyclo[2.2.2] oct-5″-yl)-benzene (**18**)*

Prepared according to general procedure from 0.3 g (0.91 mmol) of **12**, 0.13 g (1.89 mmol) of **14**, 52.00 mg (5 mol %) of $Pd(PPh_3)_4$. The residue was purified by column chromatography with *t*-Bu-Me-ether/MeOH/$NH_3$ (25%)=1:1:0.1 as eluent to give 0.26 g of **18** (54%) as a white solid. Mp=173–175 °C. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 0.64–0.69 (m, 1H), 0.82–0.88 (m, 1H), 1.35–1.64 (m, 5H), 1.91–1.92 (m, 1H), 1.97 (br s, 1H), 2.04–2.09 (m, 1H), 2.53–2.60 (m, 1H), 2.67–2.75 (m, 1H), 2.80–2.89 (m, 1H), 2.90–2.95 (m, 2H), 3.32 (s, 3H), 3.37 (s, 3H), 3.05–3.55 (m, 19H), 4.40 (s, 2H), 4.51 (s, 2H), 7.22 (s, 1H), 7.24 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C): $\delta$ 24.03, 25.22, 26.30, 26.97, 27.34, 28.34, 29.10, 39.30, 36.62, 40.43, 54.73, 57.08, 57.27, 57.54, 58.18, 58.65, 62.65, 62.98, 73.21, 74.47, 102.71, 121.65, 123.65, 124.21, 137.57, 140.92, 145.49. MS (EI) *m*/*z* (%): 468 (100) [$M^+$], 453 (85) [$M-CH_3]^+$, 423 (46) [$M-CH_3COCH_2]^+$. Anal. Calcd for $C_{28}H_{40}N_2O_4$: C, 71.76; H, 8.60; N, 5.98. Found: C, 71.70; H, 8.63; N, 6.05.

### 4.5. General procedure for the synthesis of pentasubstituted benzene derivative 20

A mixture of enyne (**7d**/**7f**) (0.35 g, 1.13 mmol) and diyne **19** (0.1 g, 1.28 mmol) and 65.00 mg (5 mol %) $Pd(PPh_3)_4$ in absolute THF (10 ml) was stirred at 100 °C until TLC analysis indicated complete consumption of the reactants. The solution was concentrated in vacuo and the residue was purified by column chromatography with *t*-Bu-Me-ether/MeOH/$NH_3$ (25%)=10:3:0.25 as eluent to give 0.1 g (23%) of **20** as a white solid.

#### *4.5.1. [5-((1′S,2′R,4′S,5′S)-2′-Hydroxymethyl-1′-azabicyclo[2.2.2]oct-5′-yl)-3-methyl-4-prop-1-ynyl-biphenyl-2-yl]-methylketone (**20**)*

Mp=183–185 °C. $^1$H NMR (400 MHz, $CDCl_3$, 25 °C) $\delta$ 1.12–1.18 (m, 1H), 1.39–1.45 (m, 1H), 1.69–1.82 (m, 2H), 1.86 (s, 3H), 2.02–2.04 (m, 1H), 2.11 (s, 3H), 2.31 (s, 3H), 2.93–3.03 (m, 4H), 3.08–3.18 (m, 2H), 3.42–3.48 (m, 2H), 3.50–3.56 (m, 1H), 7.02 (s, 1H), 7.22–7.25 (m, 2H), 7.28–7.36 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$, 25 °C) $\delta$ 4.70, 18.26, 23.42, 27.33, 27.84, 32.25, 39.17, 45.12, 48.68, 57.73, 62.05, 77.20, 96.42, 124.48, 124.75, 127.94, 128.75 (2C), 128.85 (2C), 136.59, 136.63, 139.73, 140.17, 144.63, 207.45. MS (EI) *m*/*z* (%): 387 (100) [$M^+$], 372 (57) [$M-CH_3]^+$, 356 (63) [$M-CH_3O]^+$. Anal. Calcd for $C_{26}H_{29}NO_2$: C, 80.59; H, 7.54; N, 3.61. Found: C, 80.65; H, 7.48; N, 3.65.

### 4.6. Crystal structure analyses

The crystal structure data for **11**, **12** and **20** were collected on a Bruker SMART 1000CCD area detector (graphite-monochromated Mo K$\alpha$ radiation, $\lambda$=71.073 pm) at −140 °C in the $\omega$- and $\varphi$-scan mode. Empirical absorption corrections were applied using the program SADABS. The structures were solved by direct methods using SHELXS-86/97,[31] and subjected to full-matrix least-squares

refinement on $F^2$ using SHELXL-93/97,[32] with anisotropic displacement parameters for non-H atoms.

CCDC-710575 (**12**), CCDC-710576 (**11**) and CCDC-710577 (**20**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223/336 033; e-mail: deposit@ccdc.cam.ac.uk].

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