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FULL PAPER

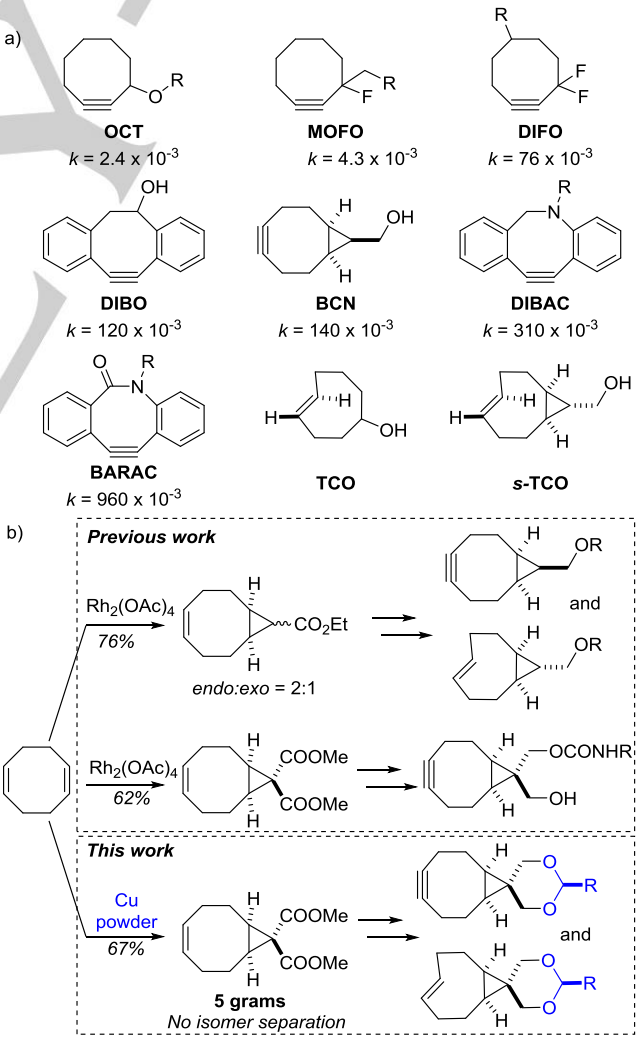
A practical synthesis of valuable strained 8-membered ring derivatives for click chemistry

Sabrina Bernard,[a] Ramar Arun Kumar,[a, b] Karine Porte,[a] Pierre Thuéry,[c] Frédéric Taran[a] and Davide Audisio*[a]

Abstract: A convenient and cost-effective synthetic access to cyclooctyne and *trans*-cyclooctene derivatives is described. A cyclopropanation step using copper powder *in lieu* of $Rh_2(OAc)_4$ as catalyst and a symmetric diazomalonate enabled to drastically reduce the overall cost of the synthesis. Further derivatizations allowed to characterize, for the first time, the structure of a BCN analogue by X-ray crystallography and obtain a library of derivatives potentially useful for applications in metal free click chemistry.

Introduction

Since the advent of click chemistry, a new golden age for cyclooctyl derivatives has emerged.[1] In the past, cyclooctynes have been largely overlooked by organic practitioners and were considered a mere curiosity with low synthetic value. Wittig and Krebs have first observed their remarkable reactivity with azides in 1961,[2] but the attention has been raised only in 2004 by the seminal work of C. Bertozzi.[3] For the first time, it was shown that this strained reagent with a bent geometry of a triple bond is an ideal partner for [3+2] cycloaddition with azides, thus avoiding the employment of copper in click chemistry and enabling the use of strain promoted transformations for bioorthogonal applications. Over the last decade, countless scientific advancements in this field have been reported.[4] In particular, in order to accelerate the rate of the cycloaddition, a great deal of attention was paid to find the ideal balance between ring strain and stability of the cyclooctyne derivatives. In 2016, Dommerholt et al. have reported a comprehensive review on the functionalization of cyclooctynes.[5] According to their definition, cyclooctynes can be recognized in two classes: an earlier generation of aliphatic, with rather low reactivity, and (di)benzoannulated cyclooctynes. To the first generation belong **OCT** and improved derivatives such as **MOFO** and **DIFO** bearing propargylic fluorine atoms (Scheme 1a). In the second generation of (di)benzoannulated cyclooctynes, an enhancement of the reactivity is caused by the increase in ring strain conferred by the sp^2-hybridized carbons. This phenomenon can also account for the reactivity order of **DIBAC** (a.k.a. **DBCO** or **ADIBO**) ca. 10 times more reactive than the first generation. **BARAC** derivatives (Scheme 1a) have shown remarkable reactivity with azides, but a challenging synthetic access has hampered their popularization.[6] One interesting exception to the (di)benzoannulated cyclooctyne rule is provided by **BCN**. Its excellent reactivity is induced by ring fusion of cyclooctyne to cyclopropane, leading to the typical bicyclo[6.1.0]non-4-yne structure. Reaction rate constants of **BCN** with aliphatic azides are in the same range of the second generation **DIBO** (Scheme 1a).[5]



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Scheme 1 a) Common cyclooctyne and *trans*-cyclooctene reagents for click reactions; reaction rate constants with aliphatic azides (M^{-1} s^{-1}) according to ref 5; b) Synthetic routes to functionalized BCN and TCO derivatives.

Among the myriad structures reported, only a few have received practical attention and are nowadays commonly found in bioorthogonal applications. The most common examples of cyclooctynes, regularly found in the literature for application in click and biorthogonal chemistries, are those commercially available: **DIBAC**[7] and *endo*-**BCN**[8] (Scheme 1a). Besides cyclooctynes, *trans*-cyclooctene (**TCO**) derivatives have also found large applications in chemical biology. **TCOs** have shown exquisite reactivity with tetrazines by means of an inverse electron demand Diels-Alder (IEDDA) process.[9] In particular, conformationally strained ***s*-TCO** (Scheme 1a) was reported to be one of the most reactive dienophiles for this ligation.[10]

Due to the *cis*-cyclopropyl ring fusion, which forces the **TCO** to adopt a 'half-chair' conformation higher in energy, ***s*-TCO** was shown to be a remarkable handle for biological applications including protein bioconjugation and in vivo chemistry.

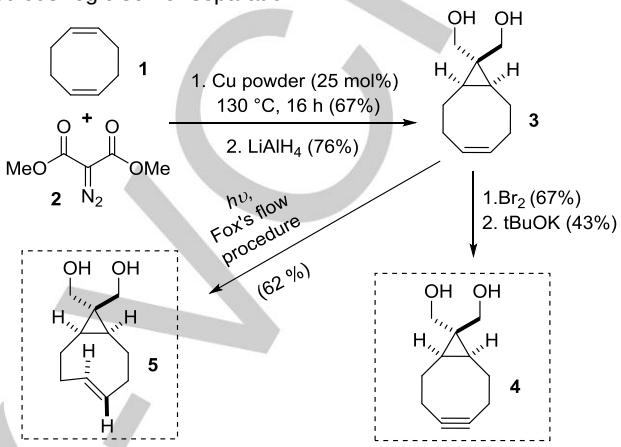
Recently, our group has reported a novel click and release transformation using imino-sydnones and strained alkynes, which enabled the access to a novel technology for proteins *trans* tagging under bioorthogonal conditions.[11] This original transformation was discovered through a large screening of mesoionic libraries in presence of cyclooctynes with more than hundred reactions performed. One major technical limitation we faced in our approach was the small amounts of strained alkynes available for the screening, discovery and optimization of the hit reactions. Despite their broad interest, **DIBAC**, *endo*-**BCN** and **TCOs** are expensive and can be purchased only on milligram scale amounts therefore limiting their practical synthetic use.

In this contribution, we describe a divergent synthetic route allowing the modular and scalable preparation of cyclooctyne and *trans*-cyclooctene derivatives (Scheme 1b), which enable to drastically reduce the overall cost of the synthetic process. This novel protocol should help the democratization of such useful reagents for click and bioorthogonal chemistry and are currently utilized in our group for discovery of new strained promoted transformations.

Results and Discussion

According to the original procedure described by van Delft, **BCN** is prepared from 1,5-cyclooctadiene by means of a rhodium acetate catalysed cyclopropanation in presence of ethyl diazoacetate.[8] In the reaction, a 2:1 mixture of *endo*:*exo* isomers is formed and, after a delicate column chromatography purification, the desired *endo* product is isolated in 50% yield (Scheme 1b). $Rh_2(OAc)_4$ is a very effective catalyst which enables the cyclopropanation to take place under mild reaction conditions but its cost is a limitation to the development of scalable processes.

Copper catalysis is a desirable and cheaper alternative to rhodium and it has found large applications in cyclopropanation of olefins with diazo derivative in the literature.[12,13] When, 1,5-COD and readily available diazomalonate **2** were reacted in presence of catalytic amounts of copper powder (25 mol%) the desired cyclopropyl product was isolated in 67% yield. The protocol turned out to be highly reliable and could be easily performed on a 5 gram scale. It is worth mentioning, that the use of diazomalonate in place of the diazoacetate has the sharp advantage to avoid tedious regioisomer separation.[14]



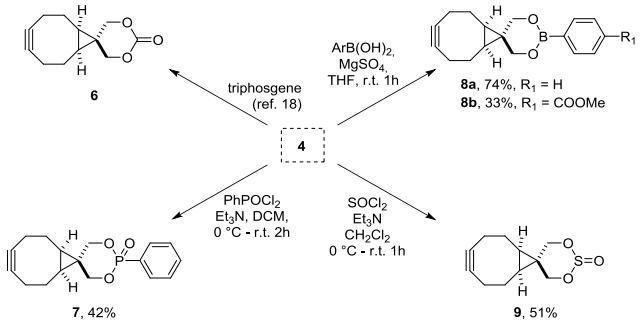
Scheme 2 Cheap synthesis of cyclooctyne **4** and *trans*-cyclooctene **5**.

The methyl esters were readily converted into the desired cyclooctene **3** in 76% yield. Further bromination (67% yield) and elimination (43% yield) afforded the strained alkyne **4**.

Interestingly with the current synthetic route, **4** can be obtained on 0.5 gram scale in a straightforward and cost-effective manner.[15]

We next investigated the derivatization of intermediate **3** to the corresponding *trans*-cyclooctene **5**. ***s*-TCO** is classically prepared according to the same procedure as **BCN** and the tedious isomer separation in part reduced the appeal of this compound and its derivatives.[16] Following the photochemical procedure described by the Fox group,[17] to our delight **3** could be smoothly converted to **5** in 62 % yield.

With a cost-effective approach to **4** and **5** secured, we next investigated the possible derivatizations of the diol motif present in these molecules. Van Delft previously described the preparation of **4** using Rh catalysis and showed that its treatment with triphosgene delivers the cyclic carbonate **6**, which was further opened upon treatment with an amine at elevated temperature (Scheme 3).[18] To develop more practical and reactive derivatives we envisaged the preparation of sulfoxide, phosphonate and boronate cyclooctyne derivatives.



Scheme 3 Functionalization of cyclooctyne **4.**

When **4** was reacted with phenylphosphonic dichloride with an excess of triethylamine the corresponding phosphonate **7** was isolated in 42% yield after column chromatography (Scheme 3). The boronic esters **8a-b** could be isolated in 74 and 33% yield by mixing **4** with the corresponding boronic acid under dehydrating conditions.[19] It is worth mentioning, that compound **8b** showed moderate stability on silica and the diol **4** was regenerated during the purification. Cyclic sulphite **9** was obtained upon thionyl chloride treatment of diol **4** with thionyl chloride and Et_3N at 0 °C in dichloromethane. Spirocyclic compound **9** is particularly intriguing, bearing a six and three membered rings further fused with a strained cyclooctyne. Its unconventional structure could be unambiguously confirmed by single-crystal X-ray diffraction (Figure 1). A large number of cyclooctynes have been described to date, nevertheless X-ray crystallography data are available only for a limited number of them.[20] In particular, for **BCN** derivatives, we are aware of only a single report describing the cobalt-hexacarbonyl-protected alkyne, where the geometry of the molecule differs largely from regular **BCN**.[21] As depicted in Figure 1, the crystal structure of **9** shows that the length of the triple bond, 1.190(4) Å, is in agreement with previous literature reports. On the other hand, the C(sp)–C(sp)–C(sp^3) angles of 153.4(3)° and 155.5(3)° are rather interesting and smaller than those in classic cyclooctynes such as **DIMAC** (157.53(16)°, 157.00(17)°), **MOFO** (159.9(2)°, 155.33(17)°), **DIFO2** (150.64(14)°, 161.96(14)°).[20] The presence of the fused cyclopropyl ring renders the angles of the triple bond closer to strained **BARAC** derivatives (153.02(16), 153.07(16)°).[20] On the other side of the molecule, the cyclic sulphite adopts a chair conformation with the exocyclic S=O in axial position.[22]

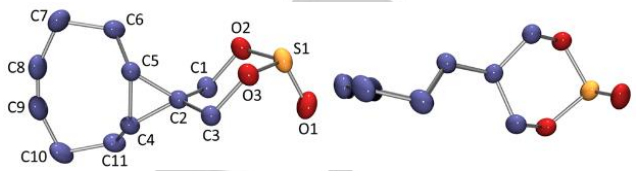
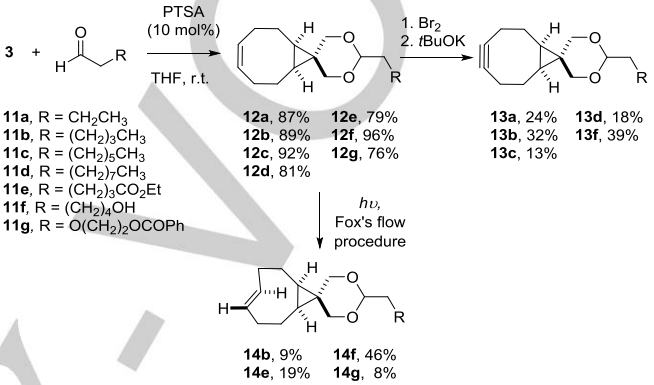


Figure 1 Molecular structure of **9** (side and top views). Displacement ellipsoids are drawn at the 40% probability level; hydrogen atoms are omitted for clarity.

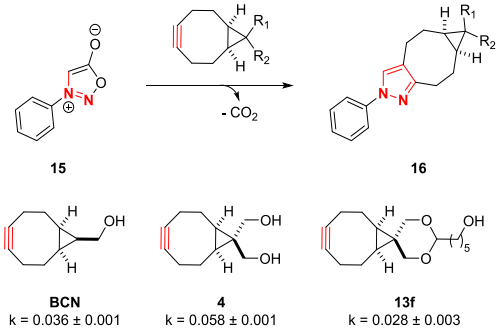
We then decided to investigate other derivatizations of the 1,3-diol moiety. Recently, **TCO** functionalized acetals were shown to be suitable partners for site-specific protein labelling[16] and pretargeted *in vivo* PET imaging.[23] The combination of **3** with different aldehydes **11a-g** under acidic conditions delivered the corresponding acetals **12a-g** in good yields (76-96%). Interestingly, spirocyclic scaffold **12** is chiral, and a racemic mixture of enantiomers is formed during the reaction. Compounds **12** were subsequently converted into the desired cycloalkynes following the classical bromination/elimination procedure. **BCN** analogues **13** were isolated in 13% to 39% yield over two steps. It is worth noting, that spiro compounds **13** are unique examples of chiral cyclooctyne structures (Scheme 4).



Scheme 4 Acetal functionalization of diol **3.**

Not surprisingly, **12e** and **12g** bearing a fragile ester moiety were not stable under the strong basic conditions required for the double elimination step. Despite our attempts to modify parameters such as the base (LDA, LiHMDS), the number of equivalents of base, temperature and time of the reaction, we were unable to obtain these derivatives. On the other hand, the conversion of acetals **12b, 12e, 12f** and **12g** into the corresponding **TCO**s **14** was achieved, albeit in moderate yields. The isomerization procedure was found compatible with the presence of an ester function (compound **14e**). In all cases, a 1:1 mixture of diastereoisomers was obtained. 8-membered rings derivatives **13** and **14** possess useful handles for further derivatizations and could be highly interesting in the contest of biomolecule and materials functionalization.

With a handful of derivatives synthesized, we next turned our attention to their reactivity. Compound **4** has been previously shown to react with azides with kinetic values very close to those of the parent **BCN**.[18] Due to our longstanding interest with sydnone chemistry, we decided to investigate the reactivity of **BCN**, **4** and **13f** with N-phenylsydnone **15**.[24] We recently reported sydnones as unconventional dipoles for [3+2]-cycloadditions with strained cyclooctynes, such as **BCN**, under remarkably mild conditions. As shown in scheme 5, the second order rate constants are in the same range of values as commercially available **BCN**, between 0.028 and 0.058 $M^{-1}sec^{-1}$.



Scheme 5 Rate constant of the reactions at RT in DMSO/PBS (10mM) (8:2) between *N*-phenylsydnone.

On the other hand, the reaction rate of stable **TCO 5**[17,25] with commercially available 3,6-diphenyl-1,2,4,5-tetrazine was not surprisingly very fast. UV measurements showed the disappearance of the reagent within few seconds in a very similar fashion compared to **s-TCO** (see supporting information for further details).

Conclusions

In conclusion, we have reported an efficient and cost-effective synthesis of cyclooctyne **4** and *trans*-cyclooctene **5**. The originality of this approach is the utilization of inexpensive copper powder as an effective catalyst for the cyclopropanation and the employment of a symmetric diazomalonate. The current method enables to obtain significant amounts of desired compounds in a much convenient manner compared to what is described in the literature. In addition, a number of useful derivatives were obtained and the unusual structure of the spirocyclic scaffold could be determined by X-ray diffraction. Discovery research using such strained alkynes and **TCOs** are currently undergoing in our laboratory. We believe this practical and low-cost approach might encourage new efforts and discoveries in the exciting field of strain promoted click chemistry.

Experimental Section

General Methods. FT-ATR-IR spectra were recorded on a Perkin-Elmer UAR Two Spectrum spectrometer and are reported as wavelength numbers (cm^{-1}). ^1H NMR (400 MHz), ^{13}C NMR (100 MHz) were measured on a Brucker Avance 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm, δ) downfield from residual solvents peaks and coupling constants are reported as Hertz (Hz). Splitting patterns are designated as singlet (s), doublet (d), triplet (t), broad singlet (br. s). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m). Electrospray mass spectra were obtained using an ESI-Quadripole autopurify, Waters (pompe 2545, mass: ZQ2000) mass Spectrometer. Silica gel 60H (40-63 µm) manufactured by Merck (Germany) was used for general chromatography unless otherwise specified. Thin-layer chromatographies were done on pre-coated silica gel 60 F254 plates (Merck). Unless otherwise noted, all other commercially available reagents and solvents (Aldrich) were used without further purification.

Dimethyl 2-diazomalonate (2).[26] Dimethyl malonate (5.86 g, 44.3 mmol, 1 eq.), triethylamine (9.16 mL, 72.2 mmol, 1.5 eq.) and 4-acetamidobenzenesulfonyl azide (9.00 g, 45.7 mmol, 1 eq.) were dissolved in acetonitrile (120 mL) at room temperature. After stirring the resulting mixture overnight, the suspension was filtered through a frit funnel and the solvent was removed under reduced pressure. The crude product was partitioned between dichloromethane (150 mL) and water (150 mL) and the two layers (aqueous and organic) filtered through a frit funnel again. The two layers were separated and the aqueous layer was extracted with dichloromethane (150 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Filtration over a plug of silica eluting with EtOAc/heptane (1/1), 300 mL, afforded dimethyl 2-diazomalonate (**2**) as pale yellow oil) (6.32 g, 90% yield). The crude product was used for the next step without further purification. The spectral data (^1H NMR) was consistent with literature report.[26] ^1H-NMR (400 MHz, $CDCl_3$): δ 3.85 (s, 6H) ppm.

(Z)-dimethyl bicyclo[6.1.0]non-4-ene-9,9-dicarboxylate.[13] Copper powder (0.5 g, 8 mmol, 0.3 eq.) was added into the 1,5-cyclooctadiene (27 mL, 221 mmol, 6.5 eq.) under argon atmosphere. The suspension was heated to 130 °C and dimethyl 2-diazomalonate (2) (5.0 g, 31.6 mmol, 1 eq.) was added dropwise through automatic syringe pump for 1 hour and the reaction mixture was stirred at the same temperature overnight. After overnight stirring, the reaction mixture was cooled down to room temperature. The crude reaction mixture was directly loaded to column chromatography and eluted first with 100% heptane until remove excess of cyclooctadiene and then eluted from 7 % to 10 % EtOAc in heptane to afford (Z)-dimethyl bicyclo[6.1.0]non-4-ene-9,9-dicarboxylate as colorless oil (4.970 g, 66 %). The spectral data (^1H NMR) was consistent with literature report.[13] ^1H-NMR (400 MHz, $CDCl_3$): δ 5.61–5.59 (m, 2H), 3.77–3.74 (m, 3H), 3.73–3.70 (m, 3H), 2.36–2.17 (m, 2H), 2.12-2.07 (m, 4H), 2.06–1.82 (m, 2H), 1.73–1.71 (m, 2H) ppm.

(Z)-bicyclo[6.1.0]non-4-ene-9,9-diyldimethanol (3).[8b] To a suspension of $LiAlH_4$ (0.865 g, 22.8 mmol, 1.8 eq.) in Et_2O (75 mL) was added dropwise at 0 °C a solution of (Z)-dimethyl bicyclo[6.1.0]non-4-ene-9,9-dicarboxylate (3.0 g, 12.6 mmol, 1 eq.) in Et_2O (75 mL) under argon atmosphere. Then, the reaction mixture was stirred for 2 hours at room temperature. Again the reaction mixture cooled to 0 °C and water was added very carefully with constant stirring until the grey solid had turned into white. Then $MgSO_4$ (12 g) was added, the solid was filtered off and washed thoroughly with Et_2O (600 mL). The filtrate was concentrated in vacuo. The crude product was recrystallized from EtOAc to afford **3** as a white crystalline solid (1.62 g, 70%). Crude product also can be used for the next step without further purification. The spectral data (^1H NMR) was consistent with reported one.[8b] ^1H NMR (400 MHz, $CDCl_3$): δ 5.64–5.57 (m, 2H), 3.85 (d, *J* = 5.1 Hz, 2H), 3.55 (d, *J* = 5.0 Hz, 2H), 2.63–2.60 (m, 2H), 2.41–2.33 (m, 2H), 2.12–1.99 (m, 4H), 1.69–1.60 (m, 2H), 0.92–0.85 (m, 2H) ppm.

(4R,5R)-4,5-dibromobicyclo[6.1.0]nonane-9,9-diyl-dimethanol.[8b] The dimethanol-cyclooctene **3** (2.3 g, 12.6 mmol, 1 eq.) was dissolved in dry dichloromethane (80 mL). At 0 °C a solution of Br_2 (839 µL, 16.4 mmol, 1.3

eq.) in dry dichloromethane (15 mL) was added dropwise until the yellow color of Br_2 persisted. The reaction mixture was quenched with 10 % solution of $Na_2S_2O_3$ and extracted with dichloromethane (2 x 100mL). The organic layer was dried over $MgSO_4$ and concentrated in *vacuo*. The crude product was recrystallized from dichloromethane to afford *(4R,5R)-4,5-dibromobicyclo[6.1.0]nonane-9,9-diyl-dimethanol* as a white solid (2.870 g, 67%). Crude product also can be used for the next step without further purification. The spectral data (^{1}H NMR) was consistent with reported one.[8b] ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.86–4.78 (m, 2H), 3.91–3.59 (m, 2H), 3.59–3.50 (m, 2H), 2.73–2.63 (m, 2H), 2.36–2.00 (m, 4H), 1.99–1.93 (m, 2H), 1.69–1.58 (m, 2H), 1.12–1.00 (m, 2H) ppm.

Bicyclo[6.1.0]non-4-yne-9,9-diyldimethanol (4).[8b] To a solution of the dibromide cyclooctane dimethanol (2.3 g, 6.76 mmol, 1 eq.) in dry THF (115 mL) was added dropwise at 0 °C a solution of *t*BuOK (42 mL, 1 M in THF, 42.0 mmol, 6.2 eq.). Then the solution was refluxed for 2 hours. After cooling down to room temperature the mixture was quenched with a saturated NH_4Cl solution and extracted with dichloromethane. The organic layer was dried over $MgSO_4$ and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel eluting 100% EtOAc to afford dimethanol-cyclooctyne **4** as a white solid (520 mg, 43%). The spectral data (^{1}H NMR) was consistent with reported one.[8b] ^{1}H-NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 2H), 3.64 (s, 2H), 2.33–2.17 (m, 8H), 1.69–1.60 (m, 2H), 0.89–0.82 (m, 2H) ppm.

General procedure A to isomerize cis-alkene to trans-alkene. The (Z)-cyclooctene (0.55 mmol, 1 eq.) and methyl benzoate (1.1 mmol, 2 eq.) were dissolved in a mixture ether/dichloromethane (13/1, 20 mL) in a quartz flask that was equipped with a magnetic stirrer. The quartz flask was placed in a Rayonnet® (10 UV lamp 254 nm) connected to a column (Isco, 40 g) and a Berthold HPLC pump via PTFE tubing. The setup used for the general photolysis was described inhere.[17] The bottom of the column was packed with dry silica (60-250 mesh, 2 cm) and the top of the column was packed with silver nitrate impregnated silica (3.1 g). The column was flushed with the mixture ether/dichloromethane (13/1). The flow rate was 10 mL/min. The lamp was turned on at 254 nm and photolysis of the stirring mixture was carried out for 13 hours. The column was washed with additional solvent for 30 min and then dried by a stream of compressed air. The column was emptied into an Erlenmeyer flask and the silica gel was stirred with ammonium hydroxide (40 mL) and dichloromethane (40 mL) for 5 min. The silica gel was filtered and the filtrate cake was washed with additional ammonium hydroxide (40 mL) and dichloromethane (40 mL). The filtrate was transferred to a separatory funnel. The organic layer was separated and the aqueous layer was washed with dichloromethane (2x50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The product purified by column chromatography with the adapted eluant to provide the desired *trans*-cyclooctene product.

(E)-bicyclo[6.1.0]non-4-ene-9,9-diyldimethanol (5). Compound **5** was obtained in 62% yield, as a white powder (65.2 mg) starting from *cis*-isomer **3** (100 mg, 0.55 mmol) using the general procedure A and purified by column chromatography eluting 100% EtOAc. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.88 (ddd, *J* = 16.8 Hz, *J* = 9.3 Hz, *J* = 6.3 Hz, 1H), 5.19 (ddd, *J* = 16.8 Hz, *J* = 10.6 Hz, *J* = 3.9 Hz, 1H), 3.75 (qd, *J* = 12.0 Hz, *J* = 2.4 Hz, 2H), 3.61 (qd, *J* = 11.5 Hz, *J* = 2.4 Hz, 2H), 2.32–3.39 (m, 1 H), 2.24–2.31 (m, 2H), 2.15–2.20 (m, 2H), 2.04–2.09 (m, 1H), 1.87–2.00 (m, 2H), 1.11 (dddd, *J* = 12.9 Hz, *J* = 12.6 Hz, *J* = 11.2 Hz, *J* = 7.1 Hz, 1H), 0.84 (dtd, *J* = 14.1 Hz, *J* = 12.4 Hz, *J* = 2.5 Hz, 1H), 0.67 (ddd, *J* = 13.0 Hz, *J* = 8.8 Hz, *J* = 3.0 Hz, 1H), 0.55 (ddd, *J* = 12.3 Hz, *J* = 8.8 Hz, *J* = 4.5 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 138.3, 131.3, 73.8, 63.1, 34.7, 33.6, 30.1, 28.0, 27.1, 25.3, 24.2 ppm; IR (cm^{-1}) 3298, 2926, 1382, 1024, 1003, 972; HRMS (ESI) *m/z:* $[M+Na]^+$ Calcd for $C_{11}H_{18}NaO_2$: 205.1199; found: 205.1199; M_p. 138 °C.

2'-phenylspiro[bicyclo[6.1.0]non[4]yne-9,5'-[1,3,2] dioxaphosphinane] 2'-oxide (7). To a stirred solution of Et_3N (62 µL, 4.0 eq., 0.444 mmol) and (bicyclo[6.1.0]non-4-yne-9,9-diyl)dimethanol 4 (20 mg, 0.111 mmol, 1.0 eq.) in dichloromethane (2 ml) was added drop-wise phenylphosphonic dichloride (16 µL, 0.111 mmol, 1 eq.) at 0 °C under a nitrogen atmosphere. The mixture was allowed to warm at room temperature. After 2 hours, the mixture was washed with water (20 mL) and the aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic extract was washed with brine, dried in Na_2SO_4 and concentrated in *vacuo*. The crude was purified though flash chromatography (100% dichloromethane to 96% dichloromethane : 4% EtOAc) to afford the desired product **7** as a white powder (14 mg, 0.046 mmol, 42%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.84-7.79 (m, 2H), 7.58 (td, *J* = 14.9 Hz, 1.4 Hz, 1H), 7.52-7.47 (m, 2H), 4.59 (t, *J* = 10.4 Hz, 1H), 4.39 (t, *J* = 10.4 Hz, 1H), 4.22 (t, *J* = 10.4 Hz, 1H), 3.97(t, *J* = 10.4 Hz, 1H), 2.44 (dd, *J* = 13.5, 1.9 Hz, 2H), 2.37-2.24 (m, 4H), 1.64-1.54 (m, 2H), 1.28-1.01 (m, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 132.8 (d, J_{C-P} = 3.2 Hz, 1C), 131.6 (d, J_{C-P} = 10.9 Hz, 2C), 128.6 (d, J_{C-P} = 14.2 Hz, 2C), 127.0 (d, J_{C-P} = 192 Hz, 1C), 98.4, 98.0, 76.2 (d, J_{C-P} = 5.9 Hz, 1C), 67.3 (d, J_{C-P} = 5.9 Hz, 1C), 28.8, 28.5, 26.5 , 26.3, 25.1 (d, J_{C-P} = 7.9 Hz, 1C), 20.9, 20.8 ppm; ^{31}P-NMR (161 MHz, CDCl3): δ 16.2 ppm; IR (cm^{-1}) 2922, 1439, 1255, 1131, 1016, 993, 790, 519; LCMS (ESI) *m/z* $[M+H]^+$ 303.1, $[2M+H]^+$ 605.3. HRMS (ESI) *m/z:* $[M+H]^+$ Calcd $C_{17}H_{20}O_3P$: 303.1145; found: 303.1144;

2'-phenylspiro[bicyclo[6.1.0]non[4]yne-9,5'-[1,3,2]dioxaborinane] (8a). In a flame dried flask, (bicyclo[6.1.0]non-4-yne-9,9-diyl)dimethanol (**4**) (20 mg, 0.111 mmol, 1.0 eq.), phenylboronic acid (13 mg, 0.111 mmol, 1.0 eq.) and $MgSO_4$ (99.9% purity, 150 mg) were stirred in dry THF (1 mL) at room temperature. After 2 hours, the reaction mixture was diluted in EtOAc, filtered through Celite and concentrated under vacuum. The residue was subjected to flash column chromatography (heptane/EtOAc 9/1) to yield the desired product (22 mg, 0.083 mmol, 74%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 7.8 Hz, 2H), 7.42 (t, *J* = 7.0 Hz, 1H), 7.36-7.33 (m, 2H), 4.13 (s, 2H), 3.89 (s, 2H), 2.30-2.20 (m, 6H), 1.63-1.58 (m, 2H), 0.97-0.94 (m, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 133.9 (2C), 130.8, 127.8 (2C), 98.7 (2C), 72.5, 62.8, 29.0 (2C), 26.5, 26.0 (2C), 21.3 (2C), the quaternary carbon (C-B) missing, ppm; ^{11}B-NMR (128 MHz, $CDCl_3$): δ 31.8 ppm; IR (cm^{-1}) 2915, 1440, 1301, 1246, 1143, 1104, 907, 729, 699, 643.

Methyl (Z)-4-(spiro[bicyclo[6.1.0]non[4]yne-9,5'-[1,3,2]dioxaborinan]-4-en-2'-yl)benzoate (8b). The alkyne diol 4 (12 mg, 0.067 mmol, 1 eq.), 4-methoxycarbonylphenylboronic acid (12.0 mg, 0.066 mmol, 1eq.) and $MgSO_4$ (80 mg) were stirred in dry THF (1 mL) at room temperature for 1.5 hours. The reaction mixture was diluted with ethyl acetate, filtered through celite and concentrated under *vacuum*. The crude was purified by chromatography column eluting with heptane/EtOAc (1:1) to afford the product as a white powder (7.2 mg, 33%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ

8.00 (d, *J* = 7.2 Hz, 2H), 7.84 (d, *J* = 7.2 Hz, 2H), 4.14 (s, 2H), 3.92 (s, 3H), 3.90 (s, 2H), 2.34–2.21 (m, 6H), 1.70–1.58 (m, 2H), 1.01–0.94 (m, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 167.3, 133.6 (2C), 131.7, 128.4 (2C), 98.4 (2C), 72.3, 62.8, 52.0, 27.3 (2C), 26.2, 25.8 (2C), 21.0 (2C) ppm, note: one quaternary carbon missing; IR (cm^{-1}) 2917, 2850, 1722, 1426, 1347, 1322, 1304, 1275, 1249, 1144, 1115, 1022, 711, 642; Mp. 123–125 °C.

(Z)-spiro[bicyclo[6.1.0]non[4]yne-9,5'-[1,3,2]dioxathian]-4-ene 2'-oxide (9). To a solution of the alkyne-diol 4 (10.0 mg, 0.056 mmol, 1 eq.) and triethylamine (17 µL, 0.12 mmol, 2.2 eq.) in dry dichloromethane (1 mL) was added dropwise thionyl chloride (9.1 µL, 0.11 mmol, 2 eq.) at 0 °C. The reaction was stirred for 20 minutes (TLC completion) and was quenched at 0 °C with water. The phases were separated and the organic phase was washed with a saturated solution of hydrogenocarbonate sodium, dried over magnesium sulfate and concentrated under *vacuum*. The product was purified by column chromatography eluting with a mixture of heptane/EtOAc (95:5) to afford the desired product as a white powder (6.4 mg, 51%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.26 (d, *J* = 11.4 Hz, 1H), 5.18 (d, *J* = 11.9 Hz, 1H), 3.62 (dd, *J* = 11.9 Hz, *J* = 2.4 Hz, 1H), 2.99 (dd, *J* = 11.3 Hz, *J* = 2.4 Hz, 1H), 2.56 (ddt, *J* = 13.3 Hz, *J* = 3.2 Hz, *J* = 2.9 Hz, 1H), 2.43–2.34 (m, 1H), 2.32–2.18 (m, 3H), 2.17–2.11 (m, 1H), 1.72 (qd, *J* = 12.7 Hz, *J* = 4.1 Hz, 1H), 1.51–1.40 (m, 1H), 1.1 (ddd, *J* = 12.6 Hz, *J* = 9.0 Hz, *J* = 3.2 Hz, 1H), 0.74 (ddd, *J* = 12.9 Hz, *J* = 9.0 Hz, *J* = 3.2 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 98.6, 97.9, 67.1, 58.9, 29.3, 28.1, 27.2, 25.1, 24.4, 20.8 (2C) ppm; IR (cm^{-1}) 2919, 2851, 1455, 1184, 982, 953, 936, 715, 680; HRMS (ESI) *m/z:* $[M+Na]^+$ Calcd $C_{11}H_{14}NaO_3S$ 249.0556; found: 249.0554; Mp. 99–101 °C.

2-(2-oxoethoxy)ethyl benzoate (11g). In a flame dried flask, ethylene glycol monobenzoate synthesized according to the litterature[27] (688.8 mg, 3.28 mmol, 1 eq.) and Dess-Martin periodinane (1.67 g, 3.93 mmol, 1.2 eq.) were stirred at room temperature in dichloromethane (53 mL) for 3 hours. The reaction was quenched with sodium thiosulfate (2.4 eq.) in a saturated solution of hydrogenocarbonate (30 mL). The mixture was separated and the aqueous phase was extracted with dichloromethane (2 x 50 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated under *vacuum*. The residue was suspended in ether and filtered through *celite* to give the desired product as a colorless oil (264.4 mg, 37%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.75 (s, 1H), 8.07–8.05 (m, 2H), 7.60–7.56 (m, 1H), 7.47–7.44 (m, 2H), 4.55–4.53 (m, 2H), 4.20 (s, 2H), 3.93–3.91 (m, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 200.1, 166.4, 133.1, 129.6 (3C), 128.4 (2C), 76.5, 69.8, 63.8 ppm; IR (cm^{-1}) 3443, 2952, 2879, 1716, 1584, 1452, 1315, 1273, 1177, 1109, 1071, 1028, 712; HRMS (ESI) *m/z:* $[M+H]^+$ Calcd $C_{11}H_{13}O_4$ 209.0808; found: 209.0807;

General procedure B for acetal derivatives 12. The dimethanol-cyclooctene 3 (1 eq.) and the desired aldehyde (1.2 eq.) were solubilized in THF (10 mL). Paratoluenesulfonic acid monohydrate (0.1 eq.) was added. The resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with chloroform and washed with a saturated solution of sodium hydrogenocarbonate. The organic phase was dried over $MgSO_4$ and concentrated. The product was purified by column chromatography eluting with adapted eluant to give the desired product.

(Z)-2'-propylspiro[bicyclo[6.1.0]nonane-9,5'-[1,3]dioxan]-4-ene (12a). Compound **12a** was obtained in 87% yield, 112.7 mg (pale yellow oil) starting from dimethanol-cyclooctene **3** (100.0 mg, 0.55 mmol) and butyraldehyde (59.0 µL, 0.66 mmol) using the general procedure B and purified by column chromatography eluting heptane/EtOAc (96/4). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.63–5.52 (m, 2H), 4.53 (t, *J* = 5.2 Hz, 1H), 4.05 (d, *J* = 11.4 Hz, 1H), 3.90 (d, *J* = 11.8 Hz, 1H), 3.76 (dd, *J* = 11.8 Hz, *J* = 2.4 Hz, 1H), 3.06 (dd, *J* = 11.2 Hz, *J* = 2.3 Hz, 1H), 2.28–2.37 (m, 2H), 2.18–1.98 (m, 3H), 1.83–1.69 (m, 2H), 1.62–1.57 (m, 2H), 1.45–1.34 (m, 3H), 0.99–0.93 (m, 1H), 0.90 (t, *J* = 7.4 Hz, 3H), 0.60–0.67 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 129.7, 129.0, 102.5, 76.4, 67.4, 36.9, 27.6, 27.1, 26.5, 24.3, 22.8, 22.3, 22.0, 17.4, 13.9 ppm; IR (cm^{-1}): 2957.9, 2931.0, 2870.9, 2833.2, 1655.1, 1455.7, 1377, 1139.63, 1097.3, 1013.1, 935.3; LCMS (ESI) *m/z* $[M+Na]^+$ 259.2; HRMS (ESI) *m/z:* $[M+H^+]$ Calcd for $C_{15}H_{25}O_2$ 237.1849; found: 237.1850.

(1R,8S,Z)-2'-pentylspiro[bicyclo[6.1.0]non[4]ene-9,5'-[1,3]dioxane] (12b). Compound **12b** was obtained in 89% yield, 25.8 mg (pale yellow oil) starting from dimethanol-cyclooctene **3** (20.0 mg, 0.11 mmol) and hexanal (16.2 µL, 0.13 mmol) using the general procedure B and purified by column chromatography eluting heptane/EtOAc (95/5). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.63–5.52 (m, 2 H), 4.52 (t, *J* = 5.3 Hz, 1H), 4.05 (d, *J* = 11.3 Hz, 1 H), 3.91 (d, *J* =11.8 Hz, 1H), 3.76 (dd, *J* = 11.8 Hz, *J* = 2.4 Hz, 1H), 3.06 (dd, *J* = 11.3 Hz, *J* = 2.4 Hz, 1H), 2.38–2.28 (m, 2H), 2.19–1.98 (m, 3 H), 1.91–1.69 (m, 2H), 1.63–1.58 (m, 2H), 1.44–1.33 (m, 3H), 1,31–1.23 (m, 4H), 0.99–0.93 (m, 1H), 0.86 (t, *J* = 7.0 Hz, 3H), 0.67–0.61 (m, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 129.7, 129.0, 102.7, 76.4, 67.4, 34.2, 31.7, 27.6, 27.1, 26.5, 24.3, 23.8, 22.8, 22.5, 22.3, 22.0, 14.0 ppm; IR (cm^{-1}) 2953, 2929, 2859, 2836, 1140, 1104, 1016; HRMS (ESI) *m/z:* $[M+H]^+$ Calcd for $C_{17}H_{29}O_2$ 265.2162; found: 265.2158.

(Z)-2'-heptylspiro[bicyclo[6.1.0]nonane-9,5'-[1,3]dioxan]-4-ene (12c). Compound **12c** was obtained in 92% yield, 148.9 mg (pale yellow oil) starting from dimethanol-cyclooctene **3** (100.0 mg, 0.55 mmol) and octanal (103.0 µL, 0.66 mmol) using the general procedure B and purified by column chromatography eluting heptane/EtOAc (97/3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.65–5.55 (m, 2H), 4.54 (t, *J* = 5.3 Hz, 1H), 4.08 (d, *J* = 11.4 Hz, 1H), 3.93 (d, *J* = 11.9 Hz, 1H), 3.78 (dd, *J* = 11.9 Hz, *J* = 2.5 Hz, 1H), 3.09 (dd, *J* = 11.4 Hz, *J* = 2.5 Hz, 1H), 2.39–2.30 (m, 2H), 2.21–2.00 (m, 3H), 1.85–1.72 (m, 2H), 1.66–1.60 (m, 2H), 1.46–1.35 (m, 3H), 1.31–1.24 (m, 8H), 1.02–0.96 (m, 1H), 0.87 (t, *J* = 7.0 Hz, 3H), 0.70–0.63 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 129.7, 129, 102.7, 76.4, 67.4, 35, 31.7, 29.4, 29.2, 27.6, 27.1, 26.5, 24.3, 24.1, 22.8, 22.6, 22.3, 22.0, 14.0 ppm; IR (cm^{-1}): 2952, 2924, 2856, 1457, 1377, 1141, 1107, 1016, 940; LCMS (ESI) *m/z* $[M+Na]^+$ 315.3; HRMS (ESI) *m/z:* $[M+H]^+$ Calcd for $C_{19}H_{33}O_2$ 293.2475; found: 293.2475.

(Z)-2'-nonylspiro[bicyclo[6.1.0]nonane-9,5'-[1,3]dioxan]-4-ene (12d). Compound **12d** was obtained in 81% yield, 70.6 mg (pale yellow oil) starting from dimethanol-cyclooctene **3** (50.0 mg, 0.27 mmol) and decylaldehyde (62.0 µL, 0.33 mmol) using the general procedure B and purified by column chromatography eluting heptane/EtOAc (97/3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.64–5.53 (m, 2H), 4.53 (t, *J* = 5.2 Hz, 1H), 4.07 (d, *J* = 11.3 Hz, 1H), 3.92 (d, *J* = 11.8 Hz, 1H), 3.77 (dd, *J* = 11.8 Hz, *J* = 2.4 Hz, 1H), 3.07 (dd, *J* = 11.4 Hz, *J* = 2.4 Hz, 1H), 2.39-2.30 (m, 2H), 2.20–2.00 (m, 3H), 2.40–2.30 (m, 2H), 1.84–1.71 (m, 2H), 1.67–1.61 (m, 2H), 1.45–1.34 (m, 3H), 1.30–1.24 (m, 12H), 1.01–0.95 (m, 1H), 0.86 (t, *J* = 6.8 Hz, 3H), 0.69–0.62 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 129.7,

129.0, 102.7, 76.4, 67.4, 35.0, 31.8, 29.5, 29.4 (2C), 29.2, 27.6, 27.1, 26.5, 24.3, 24.1, 22.8, 22.6, 22.3, 22.0, 14.0 ppm; IR (cm^{-1}): 2951, 2922, 2853, 1456, 1376, 1139, 1109, 1015, 937; LCMS (ESI) *m/z* $[M+H]^+$ 321.3. HRMS (ESI) *m/z:* $[M+Na]^+$ Calcd for $C_{21}H_{37}O_2$ 321.2788; found: 321.2788.

Ethyl 5-((1R,8S,Z)-spiro[bicyclo[6.1.0]non[4]ene-9,5'-[1,3]dioxan]-2'-yl)pentanoate (12e). Compound **12e** was obtained in 79% yield, 140.8 mg (pale yellow oil) starting from dimethanol-cyclooctene **3** (100.0 mg, 0.55 mmol) and ethyl 6-oxohexanoate (104.2 mg, 0.66 mmol) using the general procedure B and purified by column chromatography eluting heptane/EtOAc (95/5). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.65–5.53 (m, 2H), 4.54 (t, *J* = 5.3 Hz, 1H), 4.10 (q, *J* = 7.2 Hz, 2H), 4.06 (d, *J* = 11.3 Hz, 1H), 3.91 (d, *J* = 11.8 Hz, 1H), 3.76 (dd, *J* = 11.8 Hz, *J* = 2.4 Hz, 1H), 3.06 (dd, *J* = 11.3 Hz, *J* = 2.4 Hz, 1H), 2.38–2.26 (m, 4H), 2.19–1.99 (m, 3H), 1.83–1.70 (m, 2H), 1.68–1.59 (m, 4H), 1.47–1.36 (m, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.00–0.94 (m, 1H), 0.68–0.62 (m, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 173.6, 129.7, 129.0, 102.3, 76.3, 67.4, 60.1, 34.5, 34.2, 27.6, 27.1, 26.5, 24.7, 24.3, 23.7, 22.8, 22.3, 22.0, 14.2 ppm; IR (cm^{-1}) 1732, 1139, 1013; HRMS (ESI) *m/z:* $[M+H]^+$ Calcd for $C_{19}H_{31}O_4$ 323.2217; found: 323.2217.

4-((1R,8S,Z)-spiro[bicyclo[6.1.0]non[4]ene-9,5'-[1,3]dioxan]-2'-yl)butan-1-ol (12f). Compound **12f** was obtained in 96% yield, 84.9 mg (yellow oil) starting from dimethanol-cyclooctene **3** (57.5 mg, 0.315 mmol) and 6-hydroxypentanal, synthesized as described in the literature,[28] (44.0 mg, 0.38 mmol) using the general procedure B and purified by column chromatography eluting heptane/EtOAc (1/1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.63–5.52 (m, 2H), 4.54 (t, *J* = 5.2 Hz, 1H), 4.05 (d, *J* = 11.6 Hz, 1H), 3.91 (d, *J* = 11.8 Hz, 1H), 3.76 (dd, *J* = 11.8 Hz, *J* = 2.4 Hz, 1H), 3.61 (t, *J* = 6.4 Hz, 2H), 3.06 (dd, *J* = 11.6 Hz, *J* = 2.4 Hz, 1H), 2.37–2.29 (m, 2H), 2.18–1.98 (m, 3H), 1.83–1.51 (m, 7H), 1.44–1.32 (m, 5H), 0.98–0.92 (m, 1H), 0.66–0.61 (m, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 129.7, 129.0, 102.5, 76.3, 67.4, 62.9, 34.9, 32.6, 27.6, 27.1, 26.5, 25.6, 24.3, 23.9, 22.8, 22.3, 22.0 ppm; IR (cm^{-1}) 3402, 1139, 1041, 1011; HRMS (ESI) *m/z:* $[M+H]^+$ Calcd for $C_{17}H_{29}O_3$ 281.2111; found: 281.2113.

2-(((1R,8S,Z)-spiro[bicyclo[6.1.0]nonane-9,5'-[1,3]dioxan]-4-en-2'-yl)methoxy)ethyl benzoate (12g). Compound **12g** was obtained in 35% yield, as a transparent oil (64.5 mg) starting from dimethanol-cyclooctene **3** (89.6 mg, 0.492 mmol) and aldehyde 11g (122.9 mg, 0.590 mmol) using the general procedure B except that the reaction was heated at 50 °C and purified by column chromatography eluting heptane/EtOAc (85/15). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 7.8 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 2H), 5.65–5.61 (m, 2H), 4.81 (t, *J* = 4.6 Hz, 1H), 4.49 (t, *J* = 4.8 Hz, 2H), 4.11 (d, *J* = 11.3 Hz, 1H), 3.96 (d, *J* = 11.9 Hz, 1H), 3.88 (t, *J* = 4.9 Hz, 2H), 3.81 (dd, *J* = 11.9 Hz, *J* = 2.2 Hz, 1H), 3.64 (ddd, *J* = 12.2 Hz, *J* = 9.4 Hz, *J* = 4.8 Hz, 2H), 3.11 (dd, *J* = 11.4 Hz, *J* = 2.2 Hz, 1H), 2.38–2.31 (m, 2H), 2.20–2.00 (m, 3H), 1.86–1.70 (m, 2H), 1.46–1.36 (m, 1H), 1.02–0.96 (m, 1H), 0.71–0.65 (m, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 166.5, 132.9, 130.0, 129.7 (3C), 129.1, 128.3 (2C), 100.3, 76.3, 72.7, 69.7, 67.4, 64.1, 27.6, 27.0, 26.5, 24.3, 22.9, 22.3, 22.1 ppm; IR (cm^{-1}) 2931, 2860; HRMS (ESI) *m/z:* $[M+H]^+$ Calcd for $C_{22}H_{29}O_5$ 373.2010; found: 373.2006.

General procedure C for bicyclo[6.1.0]non[4]ene derivatives 13. The corresponding acetal 12 (1 eq.) was dissolved in dry dichloromethane (0.150 M). At 0 °C a solution of Br_2 (1.3 eq.) in dry dichloromethane (1.0 M) was added dropwise until the yellow color of Br_2 persisted. The reaction mixture was quenched with 10 % solution of $Na_2S_2O_3$ and extracted with dichloromethane (2 x 100 mL). The organic layer was dried over $MgSO_4$ and concentrated in *vacuo*. The crude product was directly engaged in the next step without further purification. To a solution of the crude in dry THF (0.60 M) was added dropwise at 0 °C a solution of *t*BuOK (1 M in THF, 3 eq.). Then the solution was refluxed for 2 hours except otherwise indicated. After cooling down to room temperature the mixture was quenched with a saturated NH_4Cl solution and extracted with duchloromethane. The organic layer was dried over $MgSO_4$ and concentrated in *vacuo*. The residue was purified by column chromatography on silica gel to afford desired alkyne.

2'-propylspiro[bicyclo[6.1.0]nonane-9,5'-[1,3]dioxan]-4-yne (13a). Compound **13a** was obtained in 24% yield, 23.1 mg (white solid) starting from acetal **12a** (178.7 mg, 0.42 mmol) using the general procedure C and purified by column chromatography eluting heptane/EtOAc (97/3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.54 (t, *J* = 5.2 Hz, 1H), 4.10 (d, *J* = 11.3 Hz, 1H), 3.92 (d, *J* = 11.8 Hz, 1H), 3.79 (dd, *J* = 11.8 Hz, *J* = 2.4 Hz, 1H), 3.13 (dd, *J* = 11.3 Hz, *J* = 2.4 Hz, 1H), 2.50–2.45 (m, 1H), 2.34–2.10 (m, 4H), 2.07–2.02 (m, 1H), 1.69–1.56 (m, 3H), 1.44–1.34 (m, 3H), 0.95–0.91 (m, 1H), 0.89 (t, *J* = 7.4 Hz, 3H), 0.62–0.56 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 102.6, 99.0, 98.1, 76.6, 67.3, 36.9, 29.7, 28.2, 27.7, 24.1, 23.0, 21.1, 21, 17.4, 13.9 ppm; IR (cm^{-1}) 2959, 2924, 2848, 1456, 1377, 1139, 1097, 1014, 938; LCMS (ESI) *m/z* $[M+H]^+$ 235.1; HRMS (ESI) *m/z:* $[M+Na]^+$ Calcd $C_{15}H_{22}O_2$ 235.1693; found: 235.1692; Mp. 66–67 °C.

(1R,8S)-2'-pentylspiro[bicyclo[6.1.0]non[4]yne-9,5'-[1,3]dioxane] (13b). Compound **13b** was obtained in 32% yield, 7.1 mg (colorless oil) starting from acetal **12b** (30.80 mg, 0.117 mmol) using the general procedure C and purified by column chromatography eluting heptane/EtOAc (97/3). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.54 (t, *J* = 5.2 Hz, 1H), 4.11 (d, *J* = 11.4 Hz, 1H), 3.92 (d, *J* = 11.8 Hz, 1H), 3.80 (dd, *J* = 11.8 Hz, *J* = 2.5 Hz, 1H), 3.13 (dd, *J* = 11.4 Hz, *J* = 2.5 Hz, 1H), 2.48 (dq, *J* = 11.3 Hz, *J* = 3.0 Hz, 1H), 2.35–2.08 (m, 4H), 2.05 (dq, *J* = 13.3 Hz, *J* = 3.0 Hz, 1H), 1.70–1.58 (m, 3H), 1.45–1.34 (m, 3H), 1.30–1.23 (m, 4H), 0.93 (ddd, *J* = 12.5 Hz, *J* = 8.9 Hz, *J* = 3.4 Hz, 1H), 0.86 (t, *J* = 6.9 Hz, 3H), 0.60 (ddd, *J* = 12.8 Hz, *J* = 8.9 Hz, *J* = 3.4 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 102.8, 99.1, 98.1, 76.8, 67.3, 34.9, 31.7, 29.8, 28.3, 27.7, 24.1, 23.8, 23.0, 22.5, 21.1, 21.0, 14.0 ppm; IR (cm^{-1}) 2954, 2926, 2850, 1139, 1015; HRMS (ESI) *m/z:* $[M+H]^+$ Calcd for $C_{17}H_{27}O_2$ 263.2006; found: 263.2007.

2'-heptylspiro[bicyclo[6.1.0]nonane-9,5'-[1,3]dioxan]-4-yne (13c). Compound **13c** was obtained in 13% yield, 14.1 mg (colorless oil) starting from acetal **12c** (145 mg, 0.32 mmol) using the general procedure C and purified by column chromatography eluting heptane/EtOAc (98/2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.54 (t, *J* = 5.2 Hz, 1H), 4.10 (d, *J* = 11.4 Hz, 1H), 3.92 (d, *J* = 11.8 Hz, 1H), 3.80 (dd, *J* = 11.8 Hz, *J* = 2.4 Hz, 1H), 3.13 (dd, *J* = 11.4 Hz, *J* = 2.4 Hz, 1H), 2.51–2.45 (m, 1H), 2.35–2.11 (m, 4H), 2.08–2.03 (m, 1H), 1.70–1.57 (m, 3H), 1.45–1.33 (m, 3H), 1.29–1.23 (m, 8H), 0.96–0.90 (m, 1H), 0.85 (t, *J* = 7.0Hz, 3H), 0.62–0.56 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 102.8, 99.0, 98.1, 76.7, 67.3, 35.0, 31.7, 29.8, 29.4, 29.2 (2C), 28.2, 27.7, 24.1, 22.9, 22.6, 21.1, 21.0, 14.0 ppm; IR (cm^{-}

[1]) 2951, 2922, 2850, 1456, 1376, 1138, 1108, 1015, 918; HRMS (ESI) *m/z:* $[M+H]^+$ Calcd for $C_{19}H_{31}O_2$ 291.2319; found: 291.2324;

2'-nonylspiro[bicyclo[6.1.0]nonane-9,5'-[1,3]dioxan]-4-yne (13d). Compound **13d** was obtained in 18% yield, 12.1 mg (colorless oil) starting from acetal **12d** (90.0 mg, 0.19 mmol) using the general procedure C and purified by column chromatography eluting heptane/EtOAc (97/3). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.54 (t, *J* = 5.1 Hz, 1H), 4.10 (d, *J* = 11.4 Hz, 1H), 3.92 (d, *J* = 11.9 Hz, 1H), 3.80 (dd, *J* = 11.9 Hz, *J* = 2.5 Hz, 1H), 3.13 (dd, *J* = 11.4 Hz, *J* = 2.5 Hz, 1H), 2.51–2.46 (m, 1H), 2.36–2.12 (m, 4H), 2.08–2.03 (m, 1H), 1.69–1.58 (m, 3H), 1.45–1.34 (m, 3H), 1.29–1.23 (m, 12H), 0.96–0.90 (m, 1H), 0.85 (t, *J* = 7.0 Hz, 3H), 0.63–0.56 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 102.8, 99.0, 98.1, 76.6, 67.3, 35.0, 31.8, 29.8, 29.5 (4C), 29.2, 28.2, 27.7, 24.1, 23.0, 22.6, 21.1, 21.0, 14.1 ppm; IR (cm^{-1}) 2951, 2921, 2851, 1729, 1465, 1376, 1138, 1111, 1015, 938; HRMS (ESI) *m/z:* $[M+H]^+$ Calcd for $C_{21}H_{35}O_2$ 319.2632; found: 319.2631;

4-((1R,8S)-spiro[bicyclo[6.1.0]non[4]yne-9,5'-[1,3]dioxan]-2'-yl)butan-1-ol (13f). Compound **13f** was obtained in 30% yield, 8.3 mg (pale yellow oil) starting from acetal **12f** (88.0 mg, 0.314 mmol) using the general procedure C but only heated for 30 min and purified by column chromatography eluting heptane/EtOAc (1/1). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 4.57 (t, *J* = 5.2 Hz, 1H), 4.13 (d, *J* = 11.3 Hz, 1H), 3.94 (d, *J* = 11.8 Hz, 1H), 3.82 (dd, *J* = 11.9 Hz, *J* = 2.5 Hz, 1H), 3.63 (t, *J* = 6.5 Hz, 2H), 3.15 (dd, *J* = 11.3 Hz, *J* = 2.5 Hz, 1H), 2.50 (dq, *J* = 13.4 Hz, *J* = 3.1Hz, 1H), 2.38–2.15 (m, 4H), 2.04 (dq, *J* = 13.4 Hz, *J* = 3.1Hz, 1H), 1.73–1.54 (m, 6H), 1.48–1.36 (m, 5H), 0.95 (ddd, *J* = 12.7 Hz, *J* = 8.8 Hz, *J* = 3.2 Hz, 1H), 0.62 (ddd, *J* = 12.7 Hz, *J* = 8.8 Hz, *J* = 3.2 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 102.6, 99.1, 98.1, 67.3, 62.9, 53.4, 34.9, 32.6, 29.7, 28.2, 27.7, 25.6, 24.1, 23.8, 23.0, 21.1, 21.0 ppm; IR (cm^{-1}) 3424, 2927, 2852, 1723, 1456, 1404, 1377, 1137, 1040, 1011, 937; MS (ESI) *m/z* $[M+H]^+$ 279.4; HRMS (ESI) *m/z:* $[M+H]^+$ Calcd for $C_{17}H_{27}O_3$ 279.1955; found: 279.1953.

(E)-2'-pentylspiro[bicyclo[6.1.0]non[4]ene-9,5'-[1,3]dioxane] (14b). Compound **14b** was obtained in 9% yield, 8.6 mg (pale yellow oil) starting from the isomer **12b** (100 mg, 0.378 mmol) using the general procedure A and purified by column chromatography eluting heptane/EtOAc (95/5). Both diastereosiomers were not separated. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.93–5.80 (m, 2H), 5.22–5.10 (m, 2H), 4.55–4.51 (m, 2H), 4.10 (dd, *J* = 11.2 Hz, *J* = 1.5 Hz, 2H), 3.82 (dd, *J* = 11.9 Hz, *J* = 3.6 Hz, 2H), 3.66 (dd, *J* = 21.1 Hz, *J* = 2.5 Hz, 1H), 3.63 (dd, *J* = 20.7 Hz, *J* = 2.5 Hz, 1H), 3.13 (dd, *J* = 11.2 Hz, *J* = 2.4 Hz, 2H), 2.47–2.19 (m, 6H), 2.05–1.81 (m, 6H), 1.65–1.59(m, 4H), 1.42–1.35 (m, 4H), 1.32–1.25 (m, 8H), 1.16–1.08 (m, 1H), 0.91–0.83 (m, 8H), 0.79–0.73 (m, 1H), 0.65–0.50 (m, 2H), 0.46–0.40 (m, 1H), 0.31–0.24 (m, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 138.8, 137.9, 131.9, 130.8, 102.8, 102.7, 67.1, 67.0, 35.2, 34.9, 33.4, 33.3, 33.0, 31.7 (2C), 28.3, 27.6, 27.0, 26.9, 26.6, 26.1, 23.8 (2C), 23.5, 22.5 (2C), 22.1, 21.0, 14.0 (2C), (2 peaks underneath $CDCl_3$ peak), quaternary carbons missing, ppm; IR (cm^{-1}) 2951, 2926, 2854, 1137, 1016; HRMS (ESI) *m/z:* $[M+H]^+$ Calcd for $C_{17}H_{29}O_2$ 265.2162; found: 265.2158.

(E)-ethyl 5-(spiro[bicyclo[6.1.0]non[4]ene-9,5'-[1,3]dioxan]-2'-yl)pentanoate (14e). Compound **14e** was obtained in 19% yield, 8.6 mg (pale yellow oil) starting from the isomer **12e** (70 mg, 0.21 mmol) using the general procedure A and purified by column chromatography eluting heptane/EtOAc (95/5). Both diastereoisomers were not separated. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.90–5.78 (m, 2H), 5.20–5.09 (m, 2H), 4.52–4.50 (m, 2H), 4.12 (q, *J* = 7.2 Hz, 4H), 4.08 (dd, *J* = 11.7 Hz, *J* = 1.7 Hz, 2H), 3.79 (dd, *J* = 11.8 Hz, *J* = 3.5 Hz, 2H), 3.65 (dd, *J* = 11.8 Hz, *J* = 2.3 Hz, 1H), 3.60 (dd, *J* = 11.7 Hz, *J* = 2.3 Hz, 1H), 3.10 (dd, *J* = 11.3 Hz, *J* = 2.4 Hz, 2H), 2.46–2.18 (m, 10H), 2.04–1.80 (m, 6H), 1.65–1.60 (m, 8H), 1.46–1.35 (m, 4H), 1.23 (t, *J* = 7.2 Hz, 6H), 1.14–1.04 (m, 1H), 0.92–0.81 (m, 2H), 0.77–0.70 (m, 1H), 0.62–0.48 (m, 2H), 0.44–0.38 (m, 1H), 0.30–0.22 (m, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 173.6, 138.7, 137.9, 131.8, 130.8, 102.4, 102.3, 67.1, 67.0, 60.2 (2C), 35.2, 34.5, 34.2 (2C), 33.4, 33.3, 33.0, 28.3, 27.6, 27.0, 26.9, 26.6, 26.1, 24.8 (2C), 23.7, 23.6(2C), 23.5, 22.1, 21.1, 14.2 (2C), (2 peaks underneath $CDCl_3$ peak), quaternary carbons missing, ppm; IR (cm^{-1}) 2953, 2927, 2855, 1731, 1455, 1404, 1376, 1138, 1102, 1056, 1016, 985, 939; HRMS (ESI) *m/z:* $[M+H]^+$ Calcd for $C_{19}H_{31}O_4$ 323.2217; found: 323.2217.

(E)-4-(spiro[bicyclo[6.1.0]non[4]ene-9,5'-[1,3]dioxan]-2'-yl)butan-1-ol (14f). Compound **14f** was obtained in 46% yield, 52.0 mg (pale yellow oil) starting from the isomer **12f** (112 mg, 0.40 mmol) using the general procedure A and purified by column chromatography eluting heptane/EtOAc (1/1). Both diastereoisomers were not separated. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.93–5.80 (m, 2H), 5.22–5.09 (m, 2H), 4.55 (m, 2H), 4.10 (dd, *J* = 11.2 Hz, *J* = 1.4 Hz, 2H), 3.81 (dd, *J* = 11.9 Hz, *J* = 3.6 Hz, 2H), 3.69–3.60 (m, 6H), 3.12 (dd, *J* = 11.2 Hz, *J* = 2.4 Hz, 2H), 2.46–2.19 (m, 6H), 2.04–1.79 (m, 6H), 1.65–1.52 (m, 8H), 1.45–1.34 (m, 8H), 1.31–1.23 (m, 2H), 1.16–1.05 (m, 1H), 0.94–0.82 (m, 2H), 0.79–0.73 (m, 1H), 0.65–0.50 (m, 2H), 0.47–0.40 (m, 1H), 0.32–0.25 (m, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 138.8, 137.9, 131.9, 130.8, 102.6, 102.5, 67.1, 67.0, 62.85 (2C), 35.2, 34.8 (2C), 33.4, 33.3, 33.0, 32.6 (2C), 28.3, 27.6, 27.0, 26.9, 26.6, 26.1, 25.6 (2C), 23.8 (2C), 23.7, 23.5, 22.1, 21.1, (2 peaks underneath $CDCl_3$ peak) ppm; IR (cm^{-1}) 3415, 2927, 2853, 1136, 1013; HRMS (ESI) *m/z:* $[M+H]^+$ Calcd for $C_{17}H_{29}O_3$ 281.2111; found: 281.2113.

(E)-2-(spiro[bicyclo[6.1.0]nonane-9,5'-[1,3]dioxan]-4-en-2'-ylmethoxy)ethyl benzoate (14g). Compound **14g** was obtained in 8% yield, as a colorless oil (5.3 mg) starting from the isomer **12g** (64.8mg, 0.17 mmol) using the general procedure A and purified by column chromatography eluting heptane/EtOAc (8/2). Both diastereoisomers were not separated. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.0 Hz, 4H), 7.53 (t, *J* = 7.4 Hz, 2H), 7.41 (t, *J* = 7.4 Hz, 4H), 5.89–5.77 (m, 2H), 5.19–5.07 (m, 2H), 4.77–4.74 (m, 2H), 4.45 (d, *J* = 4.5 Hz, 4H), 4.11 (dd, *J* = 11.2 Hz, *J* = 2.0 Hz, 2H), 3.86–3.81 (m, 6H), 3.70–3.58 (m, 6H), 3.13 (dd, *J* = 11.4 Hz, *J* = 2.2 Hz, 2H), 2.43–2.16 (m, 6H), 2.02–1.77 (m, 6H), 1.13–1.02 (m, 1H), 0.90–0.79 (m, 2H), 0.77–0.70 (m, 1H), 0.63–0.50 (m, 2H), 0.47–0.39 (m, 1H), 0.30–0.24 (m, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ 166.5, 138.7, 137.9, 132.9, 131.9, 130.9, 130.0, 129.7 (2C), 128.3 (2C), 100.4, 72.6, 69.7, 67.1, 67.0, 64.1, 35.2, 33.4, 33.3, 33.0, 28.3, 27.6, 27.0, 26.9, 26.6, 26.1, 23.8, 23.5, 22.2, 21.2, (2 peaks underneath $CDCl_3$ peak) ppm; IR (cm^{-1}) 2924, 2852, 1719, 1452, 1273, 1273, 1136, 1115, 1071, 1055, 713; HRMS (ESI) *m/z:* $[M+H]^+$ Calcd for $C_{22}H_{29}O_5$ 373.2010; found: 373.2006.

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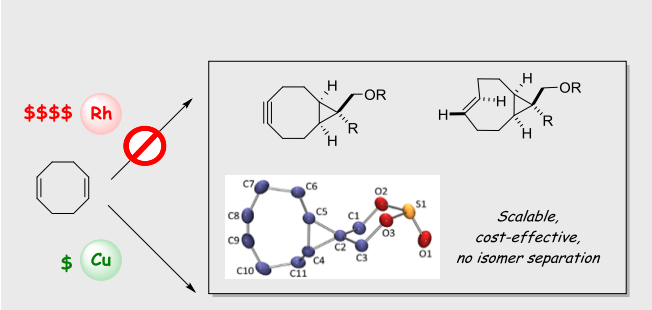

8-membered ring synthesis

*Sabrina Bernard, Ramar Arun Kumar, Karine Porte, Pierre Thuéry, Frédéric Taran, Davide Audisio**

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A scalable and cheap synthetic approach to valuable strained 8-membered ring derivatives for click chemistry

A convenient and cost-effective synthetic access to cyclooctyne and *trans*-cyclooctene derivatives is described. A cyclopropanation step using copper powder *in lieu* of $Rh_2(OAc)_4$ as catalyst and a symmetric diazomalonate enabled to drastically reduce the overall cost of the synthesis.