Regiodivergent electrophilic cyclizations of alkynylcyclobutanes for the synthesis of cyclobutane-fused *O*-heterocycles

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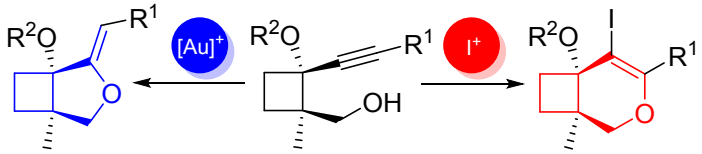
Supporting Information Placeholder



ABSTRACT: Cyclobutane-fused dihydropyrans and methylenetetrahydrofurans are highly interesting cores found in numerous natural products. Both these cores are selectively prepared from a common alkynylcyclobutane precursor bearing an appended hydroxyl group herein. Thus, cyclobutane-fused dihydropyrans can be obtained by a selective 6-*endo-dig* iodocyclization, whereas gold-catalyzed 5-*exo-dig* cycloisomerization provides a bicyclic core containing a methylenetetrahydrofuran moiety as major product. Several cyclobutane-fused *O*-heterocycles with diverse substituents are synthesized following the reported methodology.

INTRODUCTION

Four-membered carbocycles are widely found in natural products and other biologically active compounds, where they are frequently fused to heterocyclic moieties.[1] In particular, cyclobutane-fused dihydropyrans and methylenetetrahydrofurans are found in several natural products with biological activity (Figure 1A). For example, artocarpol A,[2] which has notable anti-inflammatory properties, and melicodenines C-E,[3] which can be isolated from the leaves of *Melicope denhamii*, include a cyclobutane-fused dihydropyran core in their structure, whereas cyclobutane-fused methylenetetrahydrofurans are present in hippolachnin A,[4] which has highly potent antifungal activity against several pathogenic fungi, and sinaspirolide[5] and neodiligustilide,[6] a pair of cytotoxic compounds extracted from the roots of *Angelica sinensis*. As such, the development of methodologies for the synthesis of these cyclobutane-fused heterocycles is of significant interest. In addition to the classical yet limited [2+2] cycloaddition approach,[7,8] functionalization of pre-existing cyclobutanes[9] or cyclobutenes[10] has been found to be a more efficient alternative.[11] In light of this, and based on our previous experience in the cyclization of functionalized alkynylcyclopropanes,[12] we envisioned that a useful way of accessing both substructures would be the electrophilic cyclization of alkynylcyclobutanes bearing an appended hydroxyl group (Figure 1B). Cyclization reactions of functionalized alkynes initiated by activation of the triple bond with electrophilic reagents or catalysts have been established as useful tools for the preparation of a wide number of carbo- and heterocycles,[13] with gold(I) complexes[14,15] and iodonium sources[16] being the main electrophilic partners in these processes.[17]

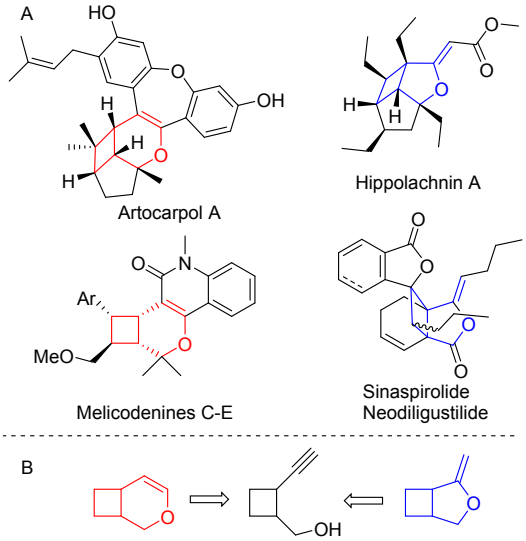


Figure 1. Selected natural products containing cyclobutane-fused dihydropyrans and methylenetetrahydrofurans (A) and proposed synthetic strategy (B).

In the proposed approach, a 5-*exo* cyclization would provide cyclobutane-fused methylenetetrahydrofurans, whereas the alternative 6-*endo* cyclization would render the corresponding

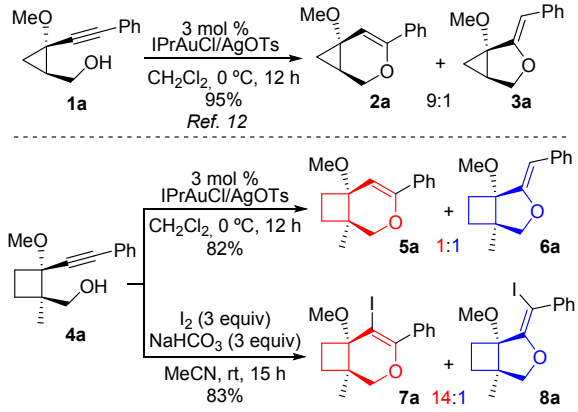
dihydropyrans. The development of divergent strategies in which different valuable structures can be accessed in a predictable way from a common precursor is challenging, but offers a unique opportunity for increasing the chemical space and facilitating drug discovery.[18, 19]

Herein, we report the selective synthesis of cyclobutane-fused dihydropyrans and methylenetetrahydrofurans from common alkynylcyclobutanes, by way of complementary gold-catalyzed and iodine-promoted cyclizations.

RESULTS AND DISCUSSION

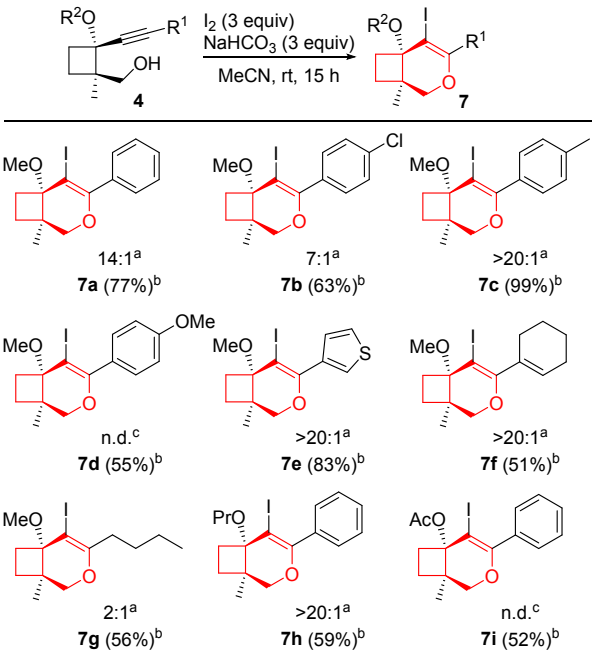
We initially selected alkynylcyclobutane **4a** as model substrate and tested its reaction under conditions we had previously reported to favour 6-*endo-dig* cyclizations for related alkynylcyclopropanes (Scheme 1, *top*). Thus, full conversion and high yield was achieved for the cycloisomerization of **4a** in the presence of 3 mol % of IPrAuCl/AgOTs in dichloromethane at 0 ºC, but an equimolecular mixture of bicycles **5a** and **6a**,[20] coming from 6-*endo-dig* and 5-*exo-dig* cyclizations respectively, was obtained (Scheme 1, *middle*). The high influence of the cycloalkane moiety in the regioselectivity could be atributed to its effect in the relative disposition of the alkynyl and hydroxy groups.[21] We subsequently explored the iodocyclization of **4a** and were delighted to find that, in the presence of I_2 and $NaHCO_3$ in acetonitrile as solvent, at room temperature, **4a** selectively gave cyclobutane-fused dihydropyran **7a** (Scheme 1, *bottom*).[22] The reaction of **4a** with NIS in dichloromethane led to a similar result.

Scheme 1. Preliminary results for the cyclization of 4a.



In view of the high selectivity of the iodocyclization of **4a** towards the formation of cyclobutane-fused dihydropyran **7a**, we decided to explore its scope. Scheme 2 shows the results obtained in the iodocyclization of alkynylcyclobutanes **4**, which gave a number of cyclobutane-fused dihydropyrans **7** in moderate to high yields. Compounds bearing phenyl rings with either electron-withdrawing or electron-donating groups (**7a-d**), heteroaromatic (**7e**) and alkenyl substituents (**7f**) were obtained from the corresponding alkynylcyclobutanes **4** in a reaction that proceeds with good to excellent selectivities in all cases. Under these conditions, an alkyl substituent was also well tolerated and, although the endo/exo selectivity of the process decreased to 2:1, dihydropyran **7g** was isolated in good yield. Substrates bearing bulkier or more electron-withdrawing alkoxy groups also provided the corresponding cyclobutane-fused dihydropyrans **7h** and **7i** as major products with high selectivities.

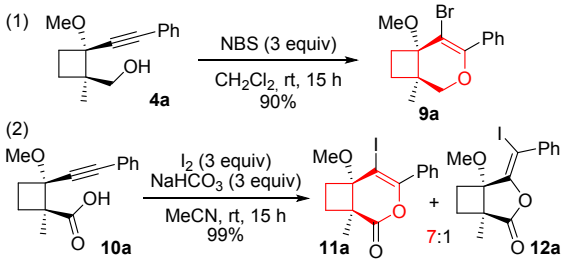
Scheme 2. Synthesis of cyclobutane-fused dihydropyrans 7 by 6-*endo-dig* iodocyclization of 4.



[a] **7**:**8** ratio determined by ^{1}H NMR in the crude reaction mixture
[b] yield of **7**
[c] **7**:**8** ratio could not be determined due to the presence of a byproduct

To further expand the scope of the reported halocyclization we performed some additional experiments. Gratifyingly, a related bromocyclization of **4a** with NBS provides bromine-functionalized dihydropyran **9a** in high yield and with excellent 6-*endo* selectivity (Scheme 3, eq 1). Moreover, we were interested in the iodocyclization of alkynylcyclobutanecarboxylic acid **10a**, in which the presence of the carboxylic acid together with the methoxy group confers push-pull character on the cyclobutane ring. Push-pull cyclobutanes are known to be prone to ring opening,[23] but it did not occur when **10a** was subjected to the conditions optimized for **4a**, and cyclobutane-fused dihydropyran **11a** was obtained in high yield and good selectivity (Scheme 3, eq 2).

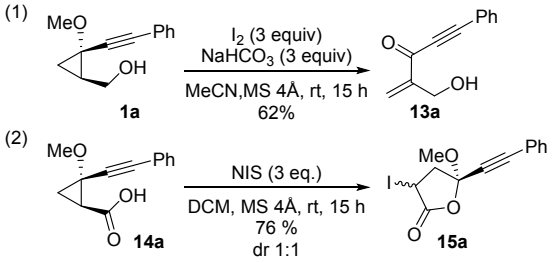
Scheme 3. Related halocyclizations.



On the other hand, alkynyl cyclopropanes **1a** and **14a** proceeded through different mechanistic pathways when subjected to identical conditions, which can be atributted to the higher reactivity of the cyclopropane ring compared to the cyclobutane one. Thus, alcohol **1a** provided and open chain product coming from the ring-opening of the cyclopropane moiety without participation of the hydroxy group (Scheme 4, eq 1). Furthermore, carboxylic acid **14a** yielded a mixture of products upon treatment with I_2 in the presence of $NaHCO_3$ in

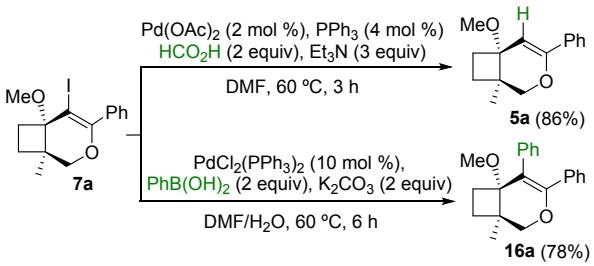
acetonitrile, whereas lactone **15a** was isolated in the reaction of **14a** with NIS in dichloromethane (Scheme 4, eq 2). The formation of **15a** can be explained by a carboxylic acid promoted cyclopropane ring-opening. The alkyne remained untouched in both of the transformations depicted in Scheme 4.

Scheme 4. Iodine-promoted reactions of alkynylcyclopropanes.



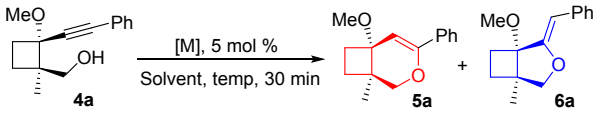
The presence of a C–I bond in cyclobutane-fused dihydropyrans **7** makes them highly useful synthetic intermediates, which can be easily modified via palladium-catalyzed cross-coupling reactions (Scheme 5). For example, for **7a**, reduction leads to compound **5a**, whereas straightforward Suzuki coupling provides diaryl-substituted dihydropyran **16a**, both in high yields. In this way, both 3-substituted and 3-unsubstituted cyclobutane-fused dihydropyrans can be prepared.

Scheme 5. Modification of cyclobutane-fused dihydropyran 7a.



With a method in hand for selectively synthesizing cyclobutane-fused dihydropyrans from alkynylcyclobutanes **4**, we next focused on developing a procedure for accessing the cyclobutane-fused dihydropyran skeleton from these common starting materials. To this end, we explored the effect of different factors on the cycloisomerization of **4a** (Table 1) with the final goal of increasing the regioselectivity for the formation of **6a.**

Table 1. Optimization of the gold-catalyzed cyclization of 4a for the synthesis of 6a.



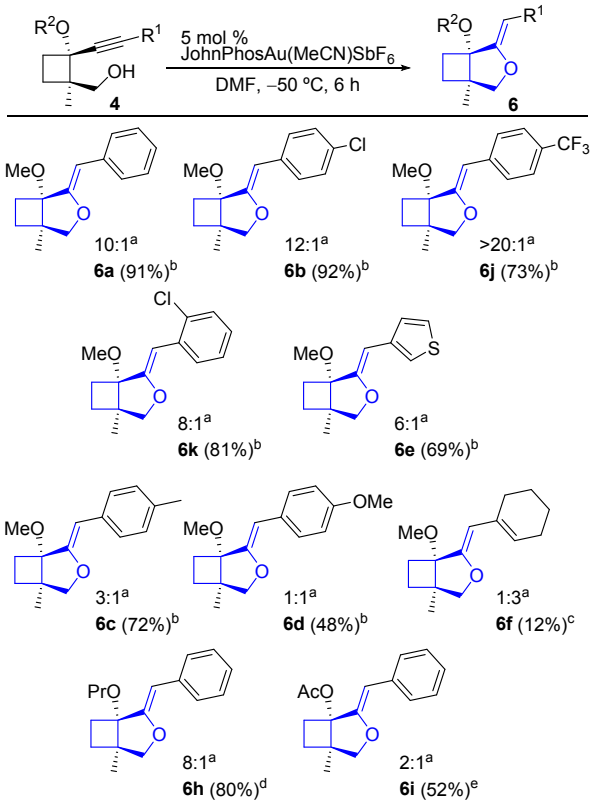
entry	[M]	solvent	temp	t	**5a**/**6a**[a]	yield **5a**+**6a**[b]
1	Ag_2CO_3	CH_2Cl_2	rt	0.5 h	-	-[c]
2	AgOTf	CH_2Cl_2	rt	0.5 h	1:17	29
3	PPh_3AuNTf_2	CH_2Cl_2	rt	0.5 h	1:1.3	67
4	$XPhosAuNTf_2$	CH_2Cl_2	rt	0.5 h	2.6:1	73
5	$MorDalPhosAuNTf_2$	CH_2Cl_2	rt	0.5 h	1:1.1	86
6	$t\text{-}Bu_3AuNTf_2$	CH_2Cl_2	rt	0.5 h	1.2:1	84
7	$PPh_3AuCl/AgNTf_2$	CH_2Cl_2	rt	0.5 h	1:1.1	66
8	$(p\text{-}CF_3\text{-}C_6H_4)_3AuCl/AgNTf_2$	CH_2Cl_2	rt	0.5 h	1:1.5	82
9	$PEt_3AuCl/AgNTf_2$	CH_2Cl_2	rt	0.5 h	1:1.1	97
10	$[(2,4\text{-}(t\text{-}Bu)_2C_6H_3O)_3P]AuCl/AgNTf_2$	CH_2Cl_2	rt	0.5 h	1.1:1	85
11	$IPrAuCl/AgNTf_2$	CH_2Cl_2	rt	0.5 h	1.2:1	66
12	$JohnPhosAu(MeCN)SbF_6$	CH_2Cl_2	rt	0.5 h	1:3.4	97
13	$JohnPhosAu(MeCN)SbF_6$	DMF	rt	0.5 h	1:3.4	99
14	$JohnPhosAu(MeCN)SbF_6$	THF	rt	0.5 h	1:3.9[d]	61
15	$JohnPhosAu(MeCN)SbF_6$	Et_2O	rt	0.5 h	1:1.9	99
16	$JohnPhosAu(MeCN)SbF_6$	Toluene	rt	0.5 h	1:1.7	97
17	$JohnPhosAu(MeCN)SbF_6$	MeCN	rt	0.5 h	1:1	99
18	$JohnPhosAu(MeCN)SbF_6$	CH_2Cl_2	0 °C	2 h	1:4.0	98
19	$JohnPhosAu(MeCN)SbF_6$	DMF	0 °C	2 h	1:4.6	97
20	$JohnPhosAu(MeCN)SbF_6$	DMF	–50 °C	6 h	1:10	99

[a] Determined by ^1H NMR spectroscopy of the crude mixture. [b] Determined by ^1H NMR of the crude mixture using CH_2Br_2 as internal standard. [c] Only starting material was recovered. [d] Formation of significant amount of subproducts is observed.

Silver salts, known to promote the cyclization of hidroxy-substituted acetylenes,[24,25] did not provide satisfactory results. Starting material was recovered after 30 minutes upon treatment with Ag_2CO_3 in DCM at room temperature (entry 1), whereas a low yield of cyclized products was obtained using AgOTf under anologous conditions (entry 2), which was attributed to decomposition of **5a** under the reaction conditions. We then focused on gold catalysts, which, in contrast to silver salts, provided full and clean conversion to **5a**/**6a** at room temperature in only 30 min. The counterion of the gold complex had only a minor effect on the **5a**/**6a** ratio, and due to the *in situ* promoted decomposition of **5a** observed in the presence of silver salts, preformed cationic catalysts were preferred for this transformation. Different ligands (entries 3-12) and solvents (entries 13-17) were tested, although their influence on the regioselectivity of the cyclization was found to be low. Among the catalysts tested, $XPhosAuNTf_2$ slightly favored the formation of **5a** (entry 4), whereas JohnPhosAu(MeCN)SbF_6 preferentially led to **6a** (entry 12). Use of the latter ligand and lowering the temperature to 0 ºC improved the regioselectivity slightly (entry 18), an effect that was more significant when DMF was used as solvent (entry 19). Finally, lowering the temperature to –50 ºC allowed the formation of cyclobutane-fused methylenetetrahydrofuran **6a** with a high 10:1 selectivity and an excellent combined yield (entry 20). Once we had established the conditions for selectively accessing the cyclobutane-fused methylenetetrahydrofuran, we embarked on analyzing the scope of this process. The results for the gold-catalyzed cyclization of diverse alkynylcyclobutanes **4** are collected in Scheme 6. Starting materials bearing a neutral or electron-withdrawing aromatic group were found to efficiently cyclize under the optimized conditions with good selectivities (≥ 8:1), thereby leading to the corresponding cyclobutane-fused methylenetetrahydrofurans **6a**,**b**,**j**,**k** in high yields. *Ortho*-substitution is well tolerated, as shown by the formation of compound **6k**. An alkynylcyclobutane with a heteroaromatic group is also a suitable substrate, as exemplified in the synthesis of **6e**, although the 5-*exo*/6-*endo* selectivity is slightly lower (6:1). This selectivity is significantly affected by the presence of electron-donating substituents. Thus, **6c**, which bears a *p*-methyl group, is obtained together with **5c** in a moderate 3:1 ratio, whereas an equimolecular mixture of **6d** and **5d** is formed when a highly electron-donating methoxy substituent is present. This selectivity decrease can be attributed to changes in the electronic distribution of the triple bond induced by the presence of the electron-donating substituent, thus favoring the 6-*endo* cyclization. Despite this lower selectivity, cyclobutane-fused methylenetetrahydrofurans **6c** and **6d** could still be isolated in synthetically useful yields. Moreover, when an alkynylcyclobutane having an alkenyl group is used the selectivity is reverted, and cyclobutane-fused dihydropyran **5h** is obtained as major product. On the other hand, alkynylcyclobutane **4g**, having an alkyl group at the alkyne terminus, lead to a complex mixture of products. Regarding the alkoxy group, a slight decrease in selectivity was observed for the bulkier OPr group, disfavouring the attack at the acetylenic carbon closer to this substituent, but **6h** can still be obtained in a high yield. On the other hand, a significantly lower selectivity was observed for the more electron-withdrawing OAc substituent.

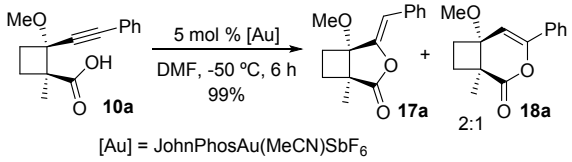
We were also interested in the cycloisomerization of push-pull cyclobutane **10a**, bearing a carboxylic acid. Altohugh gold-catalyzed reactions of alkynoic acids usually proceed through exo-cyclizations,[26] we have previously reported that related donor-aceptor alkynylcyclopropanes evolve through an *endo*-cyclization accompanied by ring opening.[12] Gratifyingly, we observed that when cyclobutane **10a** was subjected to the conditions optimized for **4a**, ring opening did not occur and cyclobutane-fused heterocycles **17a** and **18a** were obtained in high combined yield (Scheme 7). Moreover, **17a**, coming from an exo-cyclization, was the major product, although the selectivity was significantly lower than that observed in the analogous reactions of alcohol **4a**.

Scheme 6. Modification of cyclobutane-fused dihydropyran 7a.



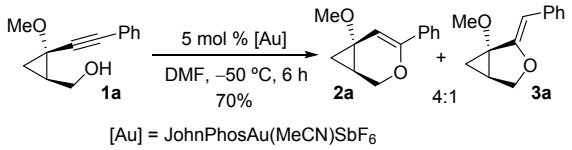
[a] **6**:**5** ratio determined by ^{1}H NMR in the crude reaction mixture
[b] yield of **6**
[c] isolated together with 36% of **5f**; [d] isolated together with 11% of **5h**;
[e] isolated together with 26% of **5i**

Scheme 7. Au-catalyzed cycloisomerization of alkynylcyclobutane carboxylic acid 10a.



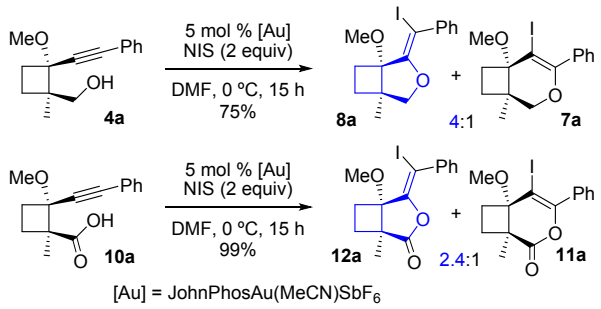
To check whether the ring size of the substrate was determinant in the regioselectivity of the gold-catalyzed cycloisomerization of **4** or the conditions were the major factor favouring the 5-*endo* cyclization, we performed the reaction of cyclopropane **1a** under the conditions we had optimized for cyclobutanes **4** (Scheme 8). We observed that for **1a** the cycloisomerization procedeed preferentially through a 6-*endo* cyclization, indicating that the ring size plays a definitive role.

Scheme 8. Gold-catalyzed cycloisomerization of alkynylcyclopropane 1a.



Finally we explored the possibility of synthesizing iodine-substituted cyclobutane-fused methylenetetrahydrofurans by performing the cyclization of **4a** and **10a** in the presence of both a gold catalyst and NIS.[27] Thus, the selectivity of the gold-catalyzed process could be retained whereas an iodine atom was introduced in the final product. Gratifyingly, we found that this approach was viable, and **8a** and **12a** could be obtained as major products, which represents a complementary regioselectivity to that observed in the direct iodocyclizations (Scheme 9). However the reactions were sluggish at –50 ºC and they should be performed at 0 ºC in order to achieve full conversion, thus leading to a moderate selectivity.

Scheme 9. Preliminary results in the selective synthesis of iodo-substituted cyclobutane-fused methylene-tetrahydrofurans.



CONCLUSIONS

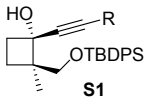
In conclusion, we have established appropriate complementary conditions for selectively accessing cyclobutane-fused dihydropyrans and methylenetetrahydrofurans from a common alkynylcyclobutane precursor functionalized with a pendant alcohol. Thus, iodocyclization occurs in a 6-*endo* fashion, giving rise to dihydropyrans with a C–I bond that can be further derivatized by palladium-catalyzed cross-coupling. Alternatively, gold-catalyzed cycloisomerization under optimized conditions proceeds selectively by 5-*exo* cyclization, providing the corresponding methylenetetrahydrofurans. Bromocyclization and reactions of a related alkynylcyclobutanecarboxylic acid also proceed under analogous conditions. The reactivity of alkynylcyclopropanes and alkynylcyclobutanes has been compared, unveiling significant differences atributed to the higher reactivity of the cyclopropane moiety and the different geometrical constrains. We consider that the reported methodologies provide an appealing alternative for the preparation of highly interesting bicyclic cores.

EXPERIMENTAL SECTION

General Experimental Details

All reactions involving air sensitive compounds were carried out under inert atmosphere (Ar). Starting materials sourced from commercial suppliers were used as received unless otherwise stated. Dry solvents, where necessary, were dried by a MBRAUN MB-SPS-800 apparatus. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60 F254, 70-200 mm) as the stationary phase. All melting points were determined in open capillary tubes on a Stuart Scientific SMP3 melting point apparatus. ^{1}H and ^{13}C spectra were recorded on either a Varian Mercury VX-300, Varian Unity 300 or Varian Unity 500 MHz spectrometer at room temperature. Chemical shifts are given in ppm (δ) downfield from TMS. Coupling constants (*J*) are in Hertz (Hz) and signals are described as follows: s, singlet; d doublet; t, triplet; bs, broad singlet; dd, double doublet; ddd, double doublet of doublet; dt, double triplet; td, triple doublet; ap t, apparent triplet; ap q, apparent quadruplet; ap dt, apparent double triplet; apparent triple doublet; m, multiplet. High-resolution analysis (HRMS) were performed on an Agilent 6210 time of-flight LC/MS.

General procedure for the synthesis of precursors S1: In a round bottom flask, the corresponding acetylene (3 equiv.) was dissolved in dry THF (0.7 M) and the resulting mixture was cooled to –78 ºC. Then, *n*-butyllithium (3 equiv.) was added dropwise and the reaction mixture was stirred 30 min at room temperature. The reaction mixture was cooled to –78 ºC and 2-(1-*tert*-butyldiphenylsilyloxymethyl)-2-methylcyclobutan-1-one[28] (1 equiv.) in dry THF (0.45 M) was added dropwise. The reaction mixture was stirred at room temperature until the cyclobutanone was completely consumed, which was determined by TLC analysis. Then, the reaction was quenched by addition of H_2O. The mixture was extracted with Et_2O and the combined organic layers were washed with saturated aqueous solution of NH_4Cl and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue, containing a mixture of **S1** and S1-diast, was purified by flash column chromatography on silica gel to give the corresponding acetylene **S1**.



(1R,2R*)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-2-methyl-1-(phenylethynyl)cyclobutanol (**S1a**):* following the general procedure, using phenylacetylene (1.9 mL, 17.0 mmol). Purification by flash column chromatography on silica gel (5 % EtOAc in Hexane) gave **S1a** (1.49 g, 3.3 mmol) as yellow oil in 58 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68–7.66 (m, 4H), 7.42–7.20 (m, 11H), 3.91 (d, *J* = 9.9 Hz, 1H), 3.63 (d, *J* = 9.9 Hz, 1H), 2.39 (ddd, *J* = 11.7, 8.8, 4.0 Hz, 1H), 2.29 (ddd, *J* = 11.6, 9.6, 9.0 Hz, 1H), 2.14 (s, 1H), 1.67 (ap dt, *J* = 11.1, 8.9 Hz, 1H), 1.54 (ddd, *J* = 11.2, 9.7, 4.0 Hz, 1H), 1.34 (s, 3H), 1.06 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 135.9 (2xCH), 135.8 (2xCH), 133.9 (C), 133.8 (C), 131.8 (2xCH), 129.7 (CH), 129.6 (CH), 128.30 (2xCH), 128.28 (CH), 127.72 (2xCH), 127.67 (2xCH), 122.9 (C), 91.0 (C), 85.7 (C), 71.5 (C), 70.1 (CH_2), 49.4 (C), 34.1 (CH_2), 27.0 (3xCH_3), 24.4 (CH_2), 19.5 (C), 18.0 (CH_3); HRMS (ESI-TOF) m/z:[M+H]$^+$ Calcd for $C_{30}H_{35}O_2Si$ 455.2401; Found 455.2400.

(1R,2R*)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-1-((4-chlorophenyl)ethynyl)-2-methylcyclobutanol (**S1b**):* following the general procedure, using 1-chloro-4-ethynylbenzene (2.7 g, 19.9 mmol). Purification by flash column chromatography on silica gel (1 % EtOAc in Hexane) gave **S1b** (1.63 g, 3.3 mmol) as yellow oil in 50 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70–7.64 (m, 4H), 7.45–7.26 (m, 6H), 7.25–7.22 (m, 2H), 7.16–7.13 (m, 2H), 3.89 (d, *J* = 9.9 Hz, 1H), 3.63 (d, *J* = 9.9 Hz, 1H), 2.39

(ddd, *J* = 11.7, 8.8, 4.0 Hz, 1H), 2.30 (ddd, *J* = 11.7, 9.6, 9.0 Hz, 1H), 2.09 (s, 1H), 1.67 (dt, *J* = 11.2, 8.9 Hz, 1H), 1.60–1.53 (m, 1H), 1.35 (s, 3H), 1.07 (s, 9H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 135.9 (2xCH), 135.8 (2xCH), 134.3 (C), 133.84 (C), 133.77 (C), 133.0 (2xCH), 129.72 (CH), 129.68 (CH), 128.6 (2xCH), 127.74 (2xCH), 127.70 (2xCH), 121.4 (C), 92.0 (C), 84.5 (C), 71.5 (C), 70.1 (CH_2), 49.4 (C), 34.0 (CH_2), 27.0 ($3xCH_3$), 24.4 (CH_2), 19.5 (C), 18.0 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{30}H_{34}ClO_2Si$ 489.2011; Found 489.2011.

(1R,2R*)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-2-methyl-1-(p-tolylethynyl)cyclobutanol* ***(S1c)****: f*ollowing the general procedure, using 4-ethynyltoluene (1.4 mL, 10.8 mmol). Purification by flash column chromatography on silica gel (5 % EtOAc in Hexane) gave **S1c** (0.76 g, 1.6 mmol) as orange oil in 45 % yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70–7.65 (m, 4H), 7.42–7.30 (m, 4H), 7.25–7.21 (m, 2H), 7.18–7.13 (m, 2H), 7.11–7.05 (m, 2H), 3.91 (d, *J* = 9.8 Hz, 1H), 3.64 (d, *J* = 9.8 Hz, 1H), 2.46–2.24 (m, 2H), 2.37 (s, 3H), 2.09 (bs, 1H), 1.69 (ap dt, *J* = 11.1, 8.7 Hz, 1H), 1.60–1.51 (m, 1H), 1.35 (s, 3H), 1.08 (s, 9H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 138.4 (C), 135.9 (4xCH), 133.90 (C), 130.87 (C) 131.7 (2xCH), 129.7 (C), 129.6 (C), 129.1 (2xCH), 127.73 (2xCH), 127.69 (2xCH), 119.8 (C), 90.2 (C), 85.8 (C), 71.5 (C), 70.1 (CH_2), 49.4 (C), 34.1 (CH_2), 27.0 ($3xCH_3$), 24.4 (CH_2), 21.6 (CH_3), 19.5 (C), 18.0 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for$C_{31}H_{37}O_2Si$ 469.2557; Found 469.2564.

(1R,2R*)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-1-((4-methoxyphenyl)ethynyl)-2-methylcyclobutanol* ***(S1d)****: f*ollowing the general procedure, using 4-ethynylanisole (2.2 mL, 17.0 mmol). Purification by flash column chromatography on silica gel (5 % EtOAc in Hexane) gave **S1d** (1.74 g, 3.6 mmol) as yellow oil in 63 % yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73–7.66 (m, 4H), 7.45–7.32 (m, 4H), 7.29–7.24 (m, 2H), 7.22–7.16 (m, 2H), 6.83–6.77 (m, 2H), 3.91 (d, *J* = 9.9 Hz, 1H), 3.82 (s, 3H), 3.64 (d, *J* = 9.9 Hz, 1H), 2.39 (ddd, *J* = 11.8, 8.8, 4.0 Hz, 1H), 2.29 (ap dt, *J* = 11.6, 9.3 Hz, 1H), 2.08 (s, 1H), 1.67 (ap dt, *J* = 11.0, 8.8 Hz, 1H), 1.55 (ddd, *J* = 11.1, 9.9, 4.1, 1H), 1.34 (s, 3H), 1.07 (s, 9H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 159.6 (C), 135.88 (2xCH), 135.87 (2xCH), 133.94 (C), 133.89 (C), 133.3 (2xCH), 129.7 (CH), 129.6 (CH), 127.73 (2xCH), 127.69 (2xCH), 115.1 (C), 113.9 (2xCH), 89.5 (C), 85.5 (C), 71.5 (C), 70.2 (CH_2), 55.4 (CH_3), 49.4 (C), 34.1 (CH_2), 27.0 ($3xCH_3$), 24.4 (CH_2), 19.6 (C), 18.0 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{31}H_{37}O_3Si$ 485.2506; Found 485.2506.

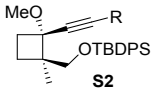
(1R,2R*)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-2-methyl-1-(thiophen-3-ylethynyl)cyclobutanol* ***(S1e)****: f*ollowing the general procedure, using 3-ethynylthiophene (1.26 mL, 12.8 mmol). Purification by flash column chromatography on silica gel (5 % EtOAc in Hexane) gave **S1e** (0.8 g, 1.74 mmol) as yellow oil in 41 % yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72–7.64 (m, 4H), 7.44–7.21 (m, 8H), 6.95 (dd, *J* = 4.3, 1.9 Hz, 1H), 3.90 (d, *J* = 9.9 Hz, 1H), 3.61 (d, *J* = 9.8 Hz, 1H), 2.39 (ddd, J = 11.6, 8.8, 4.0 Hz, 1H), 2.28 (ddd, *J* = 11.7, 9.7, 8.9 Hz, 1H), 2.07 (s, 1H), 1.66 (ap dt, *J* = 11.2, 8.8 Hz, 1H), 1.54 (ddd, *J* = 11.1, 9.6, 4.0 Hz, 1H), 1.33 (s, 3H), 1.07 (s, 9H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 135.91 (2xCH), 135.90 (2xCH), 133.9 (C), 133.8 (C), 130.1 (CH), 129.74 (CH), 129.69 (CH), 128.9 (CH), 127.8 (2xCH), 127.7 (2xCH), 125.2 (CH), 122.0 (C), 90.6 (C), 80.8 (C), 71.6 (C), 70.1 (CH_2), 49.5 (C), 34.0 (CH_2), 27.1 ($3xCH_3$), 24.4 (CH_2), 19.6 (C), 18.0 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{28}H_{33}O_2SSi$ 461.1965; Found 461.1964.

(1R,2R*)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-1-(cyclohex-1-en-1-ylethynyl)-2-methylcyclobutanol* ***(S1f)****: f*ollowing the general procedure, using 1-ethynylcyclohexene (2.0 mL, 17.0 mmol). Purification by flash column chromatography on silica gel (2 % EtOAc in Hexane) gave **S1f** (1.5 g, 3.3 mmol) as yellow oil in 58 % yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79–7.75 (m, 4H), 7.49–7.41 (m, 6H), 6.00–5.99 (m, 1H), 3.89 (d, *J* = 9.9 Hz, 1H), 3.69 (d, *J* = 9.9 Hz, 1H), 2.38–2.26 (m, 2H), 2.24 (s, 1H), 2.13–2.09 (m, 2H), 2.04–2.00 (m, 2H), 1.73–1.67 (m, 1H), 1.66–1.56 (m, 5H), 1.36 (s, 3H), 1.15 (s, 9H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 135.81 (2xCH), 135.79 (2xCH), 134.7 (CH), 134.0 (C), 133.9 (C), 129.6 (CH), 129.5 (CH), 127.62 (2xCH), 127.61 (2xCH), 120.3 (C), 88.0 (C), 87.4 (C), 71.2 (C), 70.1 (CH_2), 49.2 (C), 34.1 (CH_2), 29.1 (CH_2), 27.0 ($3xCH_3$), 25.7 (CH_2), 24.5 (CH_2), 22.4 (CH_2), 21.6 (CH_2), 19.5 (C), 17.9 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{30}H_{39}O_2Si$ 459.2714; Found 459.2701.

(1R,2R*)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-1-(hex-1-yn-1-yl)-2-methylcyclobutanol* ***(S1g)****: f*ollowing the general procedure, using 1-hexyne (1.0 mL, 8.5 mmol). Purification by flash column chromatography on silica gel (5 % EtOAc in Hexane) gave **S1g** (0.57 g, 1.31 mmol) as yellow oil in 46 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71–7.66 (m, 4H), 7.44–7.36 (m, 6H), 3.79 (d, J = 9.8 Hz, 1H), 3.60 (d, J = 9.8 Hz, 1H), 2.32–2.11 (m, 4H), 1.89 (s, 1H), 1.58 (ap dt, *J* = 10.9, 8.8 Hz, 1H), 1.48 (ddd, *J* = 11.9, 9.5, 4.3 Hz, 1H), 1.40–1.28 (m, 4H), 1.26 (s, 3H), 1.07 (s, 9H), 0.83 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 135.9 (4xCH), 134.2 (C), 134.1 (C), 129.65 (CH), 129.63 (CH), 127.69 (2xCH), 127.67 (2xCH), 86.3 (C), 81.7 (C), 71.2 (C), 70.1 (CH_2), 49.0 (C), 34.2 (CH_2), 30.9 (CH_2), 27.1 ($3xCH_3$), 24.5 (CH_2), 22.1 (CH_2), 19.6 (C), 18.6 (CH_2), 17.8 (CH_3), 13.7 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{28}H_{39}O_2Si$ 435.2714; Found 435.2717.

(1R,2R*)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-2-methyl-1-((4-(trifluoromethyl)phenyl)ethynyl)cyclobutanol* ***(S1j)****: f*ollowing the general procedure, using 1-ethynyl-4-(trifluoromethyl)benzene (2.8 mL, 17.0 mmol). The resulting residue was filtered over a plug of silica gel eluting with 5 % EtOAc in Hexane and was employed in the next step without further purification.

(1R,2R*)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-1-((2-chlorophenyl)ethynyl)-2-methylcyclobutanol* ***(S1k)***: following the general procedure, using 1-chloro-2-ethynylbenzene (2.1 mL, 17.0 mmol). Purification by flash column chromatography on silica gel (5 % EtOAc in Hexane) gave **S1k** (1.27 g, 2.6 mmol) as yellow oil in 46 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70–7.64 (m, 4H), 7.43–7.28 (m, 6H), 7.27–7.20 (m, 3H), 7.19–7.14 (m, 1H), 3.97 (d, *J* = 10.0 Hz, 1H), 3.69 (d, *J* = 9.9 Hz, 1H), 2.44 (ddd, *J* = 11.8, 8.8, 3.9 Hz, 1H), 2.33 (ap dt, *J* = 11.6, 9.3 Hz, 1H), 2.18 (s, 1H), 1.74 (ap dt, *J* = 11.0, 8.9 Hz, 1H), 1.58 (ddd, *J* = 11.1, 9.7, 3.9 Hz, 1H), 1.36 (s, 3H), 1.07 (s, 9H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 135.84 (2xCH), 135.80 (2xCH), 133.9 (2xC), 133.3 (C), 129.7 (CH), 129.6 (CH), 129.3 (2xCH), 127.7 (2xCH), 127.6 (2xCH), 126.4 (CH), 122.9 (C), 96.4 (C), 82.5 (C), 71.5 (C), 70.1 (CH_2), 49.5 (C), 34.1 (CH_2), 27.0 ($3xCH_3$), 24.5 (CH_2), 19.5 (C), 18.0 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{30}H_{34}ClO_2Si$ 489.2011; Found 489.2013.



General procedure for the synthesis of S2a-g,j,k: In a round bottom flask, the corresponding derivative **S1** (1 equiv.) was dissolved in dry DMF (0.4 M). Then, sodium hydride (60 % dispersion mineral oil) (1.5 equiv.) was added at 0 ºC and the reaction mixture was stirred 1 h at room temperature. Iodomethane (4 equiv.) was then added, and the reaction mixture was stirred at room temperature until **S1** derivative was completely consumed, which was determined by TLC analysis. The reaction was quenched by addition of brine and the mixture was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel to give the corresponding derivatives **S2a-g**,**j** and **k**.

Tert-butyl(((1R,2R*)-2-methoxy-1-methyl-2-(phenylethynyl)cyclobutyl)methoxy)diphenylsilane **(S2a)**:* following the general procedure, starting with compound **S1a** (1.49 g, 3.3 mmol). Purification by flash column chromatography on silica gel (5 % EtOAc in Hexane) gave **S2a** (1.46 g, 3.1 mmol) as yellow oil in 95 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72–7.69 (m, 4H), 7.46–7.38 (m, 2H), 7.37–7.29 (m, 7H), 7.21–7.17 (m, 2H), 3.96 (d, *J* = 10.1 Hz, 1H), 3.51 (s, 3H), 3.50 (d, *J* = 10.1 Hz, 1H), 2.36–2.28 (m, 2H), 1.61–1.55 (m, 1H), 1.41 (ddd, *J* = 11.1, 8.9, 3.7 Hz, 1H), 1.37 (s, 3H), 1.06 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 135.9 (2xCH), 135.8 (2xCH), 133.8 (C), 133.7 (C), 131.9 (2xCH), 129.7 (CH), 129.6 (CH), 128.3 (2xCH), 128.2 (CH), 127.73 (2xCH), 127.67 (2xCH), 123.1 (C), 88.7 (C), 87.8 (C), 77.4 (C), 69.7 (CH_2), 53.6 (CH_3), 49.7 (C), 32.2 (CH_2), 27.0 (3xCH_3), 23.7 (CH_2), 19.5 (C), 17.8 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{31}H_{37}O_2Si$ 469.2557; Found 469.2559.

Tert-butyl(((1R,2R*)-2-((4-chlorophenyl)ethynyl)-2-methoxy-1-methylcyclobutyl)methoxy)diphenylsilane **(S2b)**: f*ollowing the general procedure, starting with compound **S1b** (1.63 g, 3.3 mmol). Purification by flash column chromatography on silica gel (1 % EtOAc in Hexane) gave **S2b** (0.57 g, 1.13 mmol) as yellow oil in 34 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72–7.67 (m, 4H), 7.45–7.33 (m, 4H), 7.29–7.25 (m, 2H), 7.24–7.19 (m, 4H), 3.91 (d, *J* = 10.1 Hz, 1H), 3.50 (d, *J* = 10.1 Hz, 1H), 3.48 (s, 3H), 2.38–2.24 (m, 2H), 1.61–1.52 (m, 1H), 1.45–1.38 (m, 1H), 1.36 (s, 3H), 1.05 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 135.9 (2xCH), 135.8 (2xCH), 134.2 (C), 133.8 (C), 133.7 (C), 133.1 (2xCH), 129.7 (CH), 129.6 (CH), 128.7 (2xCH), 127.74 (2xCH), 127.69 (2xCH), 121.6 (C), 89.8 (C), 86.6 (C), 77.3 (C), 69.7 (CH_2), 53.6 (CH_3), 49.7 (C), 32.0 (CH_2), 26.9 (3xCH_3), 23.7 (CH_2), 19.5 (C), 17.8 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{31}H_{36}ClO_2Si$ 503.2168; Found 503.2166.

Tert-butyl(((1R,2R*)-2-methoxy-1-methyl-2-(p-tolylethynyl)cyclobutyl)methoxy)diphenylsilane **(S2c)**: f*ollowing the general procedure, starting with compound **S1c** (0.76 g, 1.6 mmol). Purification by flash column chromatography on silica gel (1 % EtOAc in Hexane) gave **S2c** (0.45 g, 0.93 mmol) as yellow oil in 58 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71–7.67 (m, 4H), 7.43–7.39 (m, 1H), 7.36–7.32 (m, 3H), 7.24–7.17 (m, 4H), 7.11–7.08 (m, 2H), 3.93 (d, *J* = 10.1 Hz, 1H), 3.49 (d, *J* = 10.1 Hz, 1H), 3.48 (s, 3H), 2.37 (s, 3H), 2.34–2.24 (m, 2H), 1.59–1.51 (m, 1H), 1.38 (ddd, *J* = 11.1, 8.9, 3.7 Hz, 1H), 1.34 (s, 3H), 1.04 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 138.3 (C), 135.92 (2xCH), 135.86 (2xCH), 133.82 (C), 133.78 (C), 131.8 (2xCH), 129.7 (CH), 129.6 (CH), 129.1 (2xCH), 127.73 (2xCH), 127.68 (2xCH), 120.1 (C), 87.87 (C), 87.85 (C), 77.4 (C), 69.7 (CH_2), 53.6 (CH_3), 49.7 (C), 32.2 (CH_2), 27.0 (3xCH_3), 23.8 (CH_2), 21.7 (CH_3), 19.5 (C), 17.8 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{32}H_{39}O_2Si$ 483.2714. Found 483.2720.

Tert-butyl(((1R,2R*)-2-methoxy-2-((4-methoxyphenyl)ethynyl)-1-methylcyclobutyl)methoxy)diphenylsilane **(S2d)**: f*ollowing the general procedure, starting with compound **S1d** (1.6 g, 3.4 mmol). Purification by flash column chromatography on silica gel (5 % EtOAc in Hexane) gave **S2d** (1.28 g, 2.6 mmol) as yellow oil in 76 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74–7.67 (m, 4H), 7.46–7.39 (m, 1H), 7.38–7.34 (m, 3H), 7.30–7.25 (m, 2H), 7.24–7.20 (m, 2H), 6.86–6.80 (m, 2H), 3.95 (d, *J* = 10.1 Hz, 1H), 3.84 (s, 3H), 3.50 (d, *J* = 10.1 Hz, 1H), 3.48 (s, 3H), 2.36–2.24 (m, 2H), 1.61–1.52 (m, 1H), 1.39 (ddd, *J* = 11.1, 9.1, 3.5 Hz, 1H), 1.35 (s, 3H), 1.05 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 159.6 (C), 135.92 (2xCH), 135.86 (2xCH), 133.84 (C), 133.77 (C), 133.3 (2xCH), 129.7 (CH), 129.6 (CH), 127.72 (2xCH), 127.69 (2xCH), 115.3 (C), 114.0 (2xCH), 87.6 (C), 87.1 (C), 77.4 (C), 69.7 (CH_2), 55.5 (CH_3), 53.6 (CH_3), 49.7 (C), 32.2 (CH_2), 27.0 (3xCH_3), 23.8 (CH_2), 19.5 (C), 17.8 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{32}H_{39}O_3Si$ 499.2663; Found 499.2672.

Tert-butyl(((1R,2R*)-2-methoxy-1-methyl-2-(thiophen-3-ylethynyl)cyclobutyl)methoxy)diphenylsilane **(S2e)**: f*ollowing the general procedure, starting with compound **S1e** (0.8 g, 1.7 mmol). Purification by flash column chromatography on silica gel (1 % EtOAc in Hexane) gave **S2e** (0.71 g, 1.5 mmol) as pale yellow oil in 86 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74–7.65 (m, 4H), 7.46–7.31 (m, 5H), 7.29–7.19 (m, 3H), 7.00 (dd, *J* = 4.9, 1.2 Hz, 1H), 3.92 (d, *J* = 10.1 Hz, 1H), 3.47 (s, 3H), 3.46 (d, *J* = 10.1 Hz, 1H), 2.37–2.22 (m, 2H), 1.61–1.48 (m, 1H), 1.39 (ddd, J = 11.1, 9.0, 3.7 Hz, 1H), 1.34 (s, 3H), 1.05 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 135.92 (2xCH), 135.86 (2xCH), 133.8 (C), 133.7 (C), 130.2 (CH), 129.7 (CH), 129.6 (CH), 128.8 (CH), 127.74 (2xCH), 127.69 (2xCH), 125.2 (CH), 122.1 (C), 88.2 (C), 82.8 (C), 77.4 (C), 69.6 (CH_2), 53.6 (CH_3), 49.7 (C), 32.1 (CH_2), 27.0 (3xCH_3), 23.7 (CH_2), 19.5 (C), 17.8 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{29}H_{35}O_2SSi$ 475.2122; Found 475.2130.

Tert-butyl(((1R,2R*)-2-(cyclohex-1-en-1-ylethynyl)-2-methoxy-1-methylcyclobutyl)methoxy)diphenylsilane **(S2f)**: f*ollowing the general procedure, starting with compound **S1f** (0.24 g, 0.56 mmol). Purification by flash column chromatography on silica gel (1 % EtOAc in Hexane) gave **S2f** (0.15 g, 0.33 mmol) as yellow oil in 59 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79–7.68 (m, 4H), 7.47–7.35 (m, 6H), 6.03–6.00 (m, 1H), 3.87 (d, *J* = 10.0 Hz, 1H), 3.48 (d, *J* = 10.0 Hz, 1H), 3.41 (s, 3H), 2.31–2.20 (m, 1H), 2.19 (ddd, *J* = 11.5, 8.7, 2.9 Hz, 1H), 2.14–2.08 (m, 2H), 2.07–2.02 (m, 2H), 1.68–1.57 (m, 4H), 1.56–1.48 (m, 1H), 1.37 (ddd, *J* = 11.0, 9.6, 3.0 Hz, 1H), 1.32 (s, 3H), 1.08 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 135.9 (4xCH), 134.5 (CH), 134.0 (C), 133.9 (C), 129.63 (CH), 129.55 (CH), 127.69 (2xCH), 127.67 (2xCH), 120.5 (C), 89.6 (C), 85.6 (C), 77.2 (C), 69.8 (CH_2), 53.4 (CH_3), 49.5 (C), 32.2 (CH_2), 29.4 (CH_2), 27.0 (3xCH_3), 25.7 (CH_2), 23.8 (CH_2), 22.5 (CH_2), 21.7 (CH_2), 19.5 (C), 17.7 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{31}H_{41}O_2Si$ 473.2870; Found 473.2853.

Tert-butyl(((1R,2R*)-2-(hex-1-yn-1-yl)-2-methoxy-1-methylcyclobutyl)methoxy)diphenylsilane (**S2g**): f*ollowing the general procedure, starting with compound **S1g** (0.56 g, 1.3 mmol). The resulting residue was filtered over a plug of silica gel eluting with 1 % EtOAc in Hexane and was employed in the next step without further purification.

Tert-butyl(((1R,2R*)-2-methoxy-1-methyl-2-((4-(trifluoromethyl)phenyl)ethynyl)cyclobutyl)methoxy)diphenylsilane (**S2j**):* following the general procedure, starting with compound S1j (0.76 g, 1.45 mmol). Purification by flash column chromatography on silica gel (5 % EtOAc in Hexane) gave **S2j** (0.26 g, 0.48 mmol) as yellow oil in 33 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68–7.64 (m, 4H), 7.55–7.51 (m, 2H), 7.44–7.32 (m, 6H), 7.21–7.16 (m, 2H), 3.89 (d, *J* = 10.2 Hz, 1H), 3.49 (d, *J* = 10.2 Hz, 1H), 3.48 (s, 3H), 2.36–2.25 (m, 2H), 1.60–1.52 (m, 1H), 1.43 (ddd, *J* = 11.1, 9.3, 3.4 Hz, 1H), 1.36 (s, 3H), 1.04 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 135.9 (2xCH), 135.8 (2xCH), 133.7 (C), 133.6 (C), 132.1 (2xCH), 129.74 (CH), 129.65 (CH), 127.8 (CH), 127.74 (2xCH), 127.66 (2xCH), 125.3 (q, *J* = 3.8 Hz, CH), 91.5 (2xC), 86.4 (C), 77.3 (C), 69.7 (CH_2), 53.7 (CH_3), 49.8 (C), 32.0 (CH_2), 26.9 (3xCH_3), 23.7 (CH_2), 19.5 (C), 17.8 (CH_3). The signals corresponding to the CF_3 and the quaternary aromatic carbons are not observed; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{32}H_{36}F_3O_2Si$ 537.2431; Found 537.2409.

Tert-butyl(((1*R**,2*R**)-2-((2-chlorophenyl)ethynyl)-2-methoxy-1-methylcyclobutyl)methoxy)diphenylsilane *(**S2k**)*: following the general procedure, starting with compound **S1k** (1.27 g, 2.6 mmol). Purification by flash column chromatography on silica gel (5 % EtOAc in Hexane) gave **S2k** (0.3 g, 0.6 mmol) as yellow oil in 23 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70–7.63 (m, 4H), 7.43–7.37 (m, 2H), 7.36–7.24 (m, 5H), 7.22–7.17 (m, 1H), 7.13 (ap t, *J* = 7.5 Hz, 2H), 3.96 (d, *J* = 10.2 Hz, 1H), 3.52 (s, 3H), 3.51 (d, *J* = 10.2 Hz, 1H), 2.36–2.30 (m, 2H), 1.65–1.57 (m, 1H), 1.45–1.38 (m, 1H), 1.35 (s, 3H), 1.03 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 136.1 (C), 135.9 (2xCH), 135.8 (2xCH), 133.8 (2xC), 133.4 (CH), 129.7 (CH), 129.5 (CH), 129.3 (CH), 129.2 (CH), 127.7 (2xCH), 127.6 (2xCH), 126.5 (CH), 123.1 (C), 94.3 (C), 84.7 (C), 77.4 (C), 69.6 (CH_2), 53.8 (CH_3), 49.8 (C), 32.2 (CH_2), 27.0 (3xCH_3), 23.8 (CH_2), 19.5 (C), 17.8 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{31}H_{36}ClO_2Si$ 503.2168; Found 503.2166.

Synthesis of tert-butyl(((1R*,2R*)-1-methyl-2-(phenylethynyl)-2-propoxycyclobutyl)methoxy)diphenylsilane (S2h): in a round bottom flask, **S1a** (40.0 mg, 0.0880 mmol) was dissolved in dry DMF (0.4 M). Then, sodium hydride (60 % dispersion mineral oil) (5.3 mg, mmol, 1.5 equiv.) was added at 0 ºC and the reaction mixture was stirred 1 h at room temperature. Iodopropane (34.3 µL, mmol, 4 equiv.) was then added, and the reaction mixture was stirred at room temperature until **S1a** derivative was completely consumed, which was determined by TLC analysis. The reaction was quenched by addition of brine and the mixture was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (1 % EtOAc in Hexane) to give **S2h** (28.1 mg, 0.0566 mmol) as a yellow oil in 64 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71–7.66 (m, 4H), 7.44–7.38 (m, 2H), 7.37–7.27 (m, 7H), 7.16 (ap t, *J* = 7.5 Hz, 2H), 3.97 (d, *J* = 10.1 Hz, 1H), 3.70 (dt, *J* = 9.2, 6.8 Hz, 1H), 3.67–3.60 (m, 1H), 3.45 (d, *J* = 10.1 Hz, 1H), 2.38–2.26 (m, 2H), 1.67 (h, *J* = 7.2 Hz, 2H), 1.63–1.50 (m, 1H), 1.41–1.33 (m, 1H), 1.35 (s, 3H), 1.05 (s, 9H), 0.98 (t, *J* = 7.7 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 135.93 (2xCH), 135.85 (2xCH), 133.80 (C),133.76 (C), 131.9 (2xCH), 129.7 (CH), 129.5 (CH), 128.3 (2xCH), 128.2 (CH), 127.72 (2xCH), 127.66 (2xCH), 123.3 (C), 89.6 (C), 87.4 (C), 77.4 (C), 69.7 (CH_2), 67.8 (CH_2), 50.0 (C), 32.6 (CH_2), 26.9 (3xCH_3), 23.7 (CH_2), 23.4 (CH_2), 19.5 (C), 17.9 (CH_3), 11.0 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{33}H_{41}O_2Si$ 497.2870; Found 497.2880.

Synthesis of (1R*,2R*)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-2-methyl-1-(phenylethynyl)cyclobutyl acetate (S2i): in a round bottom flask, 4-(dimethylamino)pyridine (5 mol%), Et_3N (0.37 mL, 2.64 mmol) and **S1a** (0.40 g, 0.8797 mmol) were dissolved in dry CH_2Cl_2 (1.5 M). Then, acetic anhydride (0.17 mL, 1.7595 mmol) was added dropwise and the reaction mixture was stirred at room temperature overnight. After, the reaction was quenched by addition of satured aqueous solution of NH_4Cl. The aqueous layer was extracted with Et_2O, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (5 % EtOAc in Hexane) to give **S2i** (0.4365 g, 0.8796 mmol) as a yellow oil in 99 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76–7.72 (m, 4H), 7.46–7.40 (m, 2H), 7.39–7.36 (m, 2H), 7.35–7.32 (m, 2H), 7.31–7.28 (m, 1H), 7.27–7.25 (m, 4H), 4.04 (d, *J* = 9.9 Hz, 1H), 3.93 (d, *J* = 9.9 Hz, 1H), 2.63 (ddd, *J* = 12.0, 8.8, 3.2 Hz, 1H), 2.54 (dt, *J* = 12.3, 9.9 Hz, 1H), 2.12 (s, 3H), 1.90 (ap q, *J* = 9.2 Hz, 1H), 1.68 (ddd, *J* = 11.3, 9.8, 3.0 Hz, 1H), 1.42 (s, 3H), 1.14 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.2 (C), 135.82 (2xCH), 135.77 (2xCH), 134.0 (2xC), 131.9 (2xCH), 129.61 (CH), 129.56 (CH), 128.3 (CH), 128.1 (2xCH), 127.67 (2xCH), 127.65 (2xCH), 122.7 (C), 87.4 (C), 86.8 (C), 75.2 (C), 69.9 (CH_2), 49.0 (C), 33.3 (CH_2), 27.0 (3xCH_3), 25.6 (CH_2), 21.3 (CH_3), 19.6 (C), 18.6 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{32}H_{37}O_3Si$ 497.2506; Found 497.2517.

General procedure for the synthesis of 4: to a solution of the corresponding derivative **S2** (1 equiv.) in dry THF (0.45 M) was added tetrabutylammonium fluoride (4 equiv.) and the reaction mixture was stirred overnight at room temperature. Then, the mixture was concentrated under reduced pressure and the residue was mixed with brine and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel to give the corresponding derivatives **4**.

((1R,2R*)-2-methoxy-1-methyl-2-(phenylethynyl)cyclobutyl)methanol (**4a**): f*ollowing the general procedure, starting with compound S2a (2.9 g, 6.3 mmol). Purification by flash column chromatography on silica gel (20 % EtOAc in Hexane) gave **4a** (1.3 g, 5.7 mmol) as yellow oil in 91 % yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.43 (m, 2H), 7.36–7.30 (m, 3H), 3.91 (dd, *J* = 11.4, 5.8 Hz, 1H), 3.57 (dd, *J* = 11.4, 7.4 Hz, 1H), 3.39 (s, 3H), 2.36–2.26 (m, 2H), 1.92 (dd, *J* = 7.4, 5.9 Hz, 1H), 1.75 (ap dt, *J* = 11.1, 9.0 Hz, 1H), 1.57–1.50 (m, 1H), 1.28 (s, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 131.8 (2xCH), 128.7 (CH), 128.5 (2xCH), 122.4 (C), 88.3 (C), 87.9 (C), 76.5 (C), 69.4 (CH_2), 52.6 (CH_3), 49.2 (C), 31.0 (CH_2), 23.6 (CH_2), 17.6 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{19}O_2$ 231.1380; Found 231.1375.

((1R,2R*)-2-((4-chlorophenyl)ethynyl)-2-methoxy-1-methylcyclobutyl)methanol (**4b**):* following the general procedure, starting with compound **S2b** (0.57 g, 1.1 mmol). Purification by flash column chromatography on silica gel (30 % EtOAc in Hexane) gave **4b** (0.19 g, 0.72 mmol) as yellow oil in 64 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.34 (m, 2H), 7.29–7.25 (m, 2H), 3.85 (d, *J* = 11.4 Hz, 1H), 3.54 (d, *J* = 11.4 Hz, 1H), 3.35 (s, 3H), 2.29–2.23 (m, 2H), 2.17 (bs, 1H), 1.68 (ap dt, *J* = 11.1, 9.1 Hz, 1H), 1.49 (ddd, *J* = 11.2, 7.3, 6.4 Hz, 1H), 1.23 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 134.6 (C), 133.0 (2xCH), 128.7 (2xCH), 120.9 (C), 89.3 (C), 86.7 (C), 76.5 (C), 69.2 (CH_2), 52.6 (CH_3), 49.1 (C), 30.9 (CH_2), 23.6 (CH_2), 17.5 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{18}ClO_2$ 265.0990; Found 265.0989.

((1R,2R*)-2-methoxy-1-methyl-2-(p-tolylethynyl)cyclobutyl)methanol (**4c**):* following the general procedure, starting with compound **S2c** (0.45 g, 0.92 mmol). Purification by flash column chromatography on silica gel (20 % EtOAc in Hexane) gave **4c** (0.21 g, 0.86 mmol) as yellow oil in 93 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.33 (m, 2H), 7.15–7.11 (m, 2H), 3.88 (d, *J* = 11.5 Hz, 1H), 3.55 (d, *J* = 11.5 Hz, 1H), 3.37 (s, 3H), 2.36 (s, 3H), 2.32–2.23 (m, 2H), 1.97 (bs, 1H), 1.73 (ap dt, *J* = 11.2, 9.0 Hz 1H), 1.52 (ddd, *J* = 11.2, 7.8, 5.6 Hz 1H), 1.25 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 138.9 (C), 131.7 (2xCH), 129.3 (2xCH), 119.4 (C), 88.1 (C), 87.6 (C), 76.5 (C), 69.6 (CH_2), 52.6 (CH_3), 49.3 (C), 31.0 (CH_2), 23.7 (CH_2), 21.6 (CH_3), 17.7 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{21}O_2$ 245.1536; Found 245.1532.

((1R,2R*)-2-methoxy-2-((4-methoxyphenyl)ethynyl)-1-methylcyclobutyl)methanol (**4d**):* following the general procedure, starting with compound **S2d** (1.24 g, 2.6 mmol). Purification by flash column chromatography on silica gel (30 % EtOAc in Hexane) gave **4d** (0.56 g, 2.15 mmol) as white solid in 84 % yield. M. p.: 59–60 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.37 (m, 2H), 6.87–6.82 (m, 2H), 3.87 (d, *J* = 11.5 Hz, 1H), 3.81 (s, 3H), 3.55 (d, *J* = 11.5 Hz, 1H), 3.36 (s, 3H), 2.31–2.24 (m, 2H), 2.02 (bs, 1H), 1.72 (ap dt, *J* = 11.2, 9.0 Hz, 1H), 1.55 (ddd, *J* = 11.2, 7.9, 6.1 Hz, 1H), 1.24 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 160.0 (C), 133.3 (2xCH), 114.5 (C), 114.1 (2xCH), 87.8 (C), 86.9 (C), 76.5 (C), 69.5 (CH_2), 55.5 (CH_3), 52.5 (CH_3), 49.3 (C), 31.0 (CH_2), 23.7 (CH_2), 17.7 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{21}O_3$ 261.1485; Found 261.1485.

((1R,2R*)-2-methoxy-1-methyl-2-(thiophen-3-ylethynyl)cyclobutyl)methanol (**4e**):* following the general procedure, starting with compound **S2e** (0.7 g, 1.5 mmol). Purification by flash column chromatography on silica gel (10 % EtOAc in Hexane) gave **4e** (0.3 g, 1.3 mmol) as yellow oil in 87 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 3.0, 1.1 Hz, 1H), 7.28 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.12 (dd, *J* = 5.0, 1.1 Hz, 1H), 3.86 (d, *J* = 11.4 Hz, 1H), 3.55 (d, *J* = 11.4 Hz, 1H), 3.36 (s, 3H), 2.30–2.24 (m, 2H), 2.01 (s, 1H), 1.71 (ap dt, *J* = 11.1, 9.1 Hz, 1H), 1.51 (ddd, *J* = 11.2, 7.6, 6.3 Hz, 1H), 1.24 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 130.0 (CH), 129.2 (CH), 125.6 (CH), 121.4 (C), 87.9 (C), 82.9 (C), 76.6 (C), 69.4 (CH_2), 52.6 (CH_3), 49.2 (C), 30.9 (CH_2), 23.7 (CH_2), 17.6 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{17}O_2S$ 237.0944; Found 237.0942.

((1R,2R*)-2-(cyclohex-1-en-1-ylethynyl)-2-methoxy-1-methylcyclobutyl)methanol (**4f**):* following the general procedure, starting with compound **S2f** (0.15 g, 0.33 mmol). Purification by flash column chromatography on silica gel (10 % EtOAc in Hexane) gave **4f** (0.046 g, 0.2 mmol) as yellow oil in 60 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.14–6.10 (m, 1H), 3.77 (d, *J* = 11.5 Hz, 1H), 3.47 (d, *J* = 11.5 Hz, 1H), 3.28 (s, 3H), 2.23–2.06 (m, 6H), 2.04 (bs, 1H), 1.70–1.54 (m, 5H), 1.45 (ddd, *J* = 11.2, 9.3, 4.8 Hz, 1H), 1.18 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 135.6 (CH), 120.0 (C), 89.8 (C), 85.5 (C), 76.3 (C), 69.5 (CH_2), 52.4 (CH_3), 49.2 (C), 31.0 (CH_2), 29.4 (CH_2), 25.7 (CH_2), 23.6 (CH_2), 22.3 (CH_2), 21.5 (CH_2), 17.6 (CH_3); HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{22}O_2Na$ 257.1512; Found 257.1509.

((1R,2R*)-2-(hex-1-yn-1-yl)-2-methoxy-1-methylcyclobutyl)methanol (**4g**):* following the general procedure, starting with compound **S2g** (0.33 g, 0.73 mmol). Purification by flash column chromatography on silica gel (10 % EtOAc in Hexane) gave **4g** (0.085 g, 0.41 mmol) as yellow oil in 55 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.76 (d, *J* = 11.5 Hz, 1H), 3.47 (d, *J* = 11.5 Hz, 1H), 3.27 (s, 3H), 2.28 (t, *J* = 7.1 Hz, 2H), 2.20–2.09 (m, 2H), 2.00 (bs, 1H), 1.64 (ap dt, *J* = 11.1, 9.0 Hz, 1H), 1.57–1.49 (m, 2H), 1.48–1.37 (m, 3H), 1.17 (s, 3H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 88.6 (C), 79.3 (C), 76.1 (C), 69.5 (CH_2), 52.2 (CH_3), 48.9 (C), 30.98 (CH_2), 30.97 (CH_2), 23.5 (CH_2), 22.1 (CH_2), 18.6 (CH_2), 17.6 (CH_3), 13.7 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{23}O_2$ 211.1693; Found 211.1696.

((1R,2R*)-1-methyl-2-(phenylethynyl)-2-propoxycyclobutyl)methanol (**4h**):* following the general procedure, starting with compound **S2h** (39.0 mg, 0.0786 mmol). Purification by flash column chromatography on silica gel (5 % EtOAc in Hexane) gave **4h** (13.2 mg, 0.0511 mmol) as yellow oil in 65 % yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.41 (m, 2H), 7.36–7.29 (m, 3H), 3.88 (d, J = 11.5 Hz, 1H), 3.57 (d, *J* = 11.5 Hz, 1H), 3.50 (t, *J* = 6.6 Hz, 2H), 2.37–2.25 (m, 2H), 1.89 (bs, 1H), 1.79–1.68 (m, 1H), 1.67–1.59 (m, 2H), 1.58–1.46 (m, 1H), 1.26 (s, 3H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 131.8 (2xCH), 128.6 (CH), 128.5 (2xCH), 122.6 (C), 89.2 (C), 87.5 (C), 75.5 (C), 69.6 (CH_2), 66.8 (CH_2), 49.5 (C), 31.6 (CH_2), 23.7 (CH_2), 23.3 (CH_2), 17.7 (CH_3), 11.0 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{23}O_2$ 259.1693; Found 259.1700.

((1R,2R*)-2-(hydroxymethyl)-2-methyl-1-(phenylethynyl)cyclobutyl) acetate (**4i**):* following the general procedure, starting with compound **S2i** (0.4365 g, 0.8796 mmol). Purification by flash column chromatography on silica gel (10 % EtOAc in Hexane) gave **4i** (0.1954 g, 0.7570 mmol) as yellow oil in 86 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48–7.43 (m, 2H), 7.34–7.26 (m, 3H), 4.16 (d, *J* = 11.5 Hz, 1H), 3.44 (bs, 1H), 3.31 (d, *J* = 11.6 Hz, 1H), 2.57–2.48 (m, 1H), 2.42 (ddd, *J* = 11,6, 8.8, 2.6 Hz, 1H), 2.09 (s, 3H), 1.69 (ap q, *J* = 10.9 Hz, 1H), 1.51 (td, *J* = 10.4, 2.6 Hz, 1H), 1.24 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 170.5 (C), 132.0 (2xCH), 128.8 (CH), 128.3 (2xCH), 122.2 (C), 88.1 (C), 86.4 (C), 75.5 (C), 68.8 (CH_2), 50.5 (C), 31.6 (CH_2), 23.7 (CH_2), 21.3 (CH_3), 17.5 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{19}O_3$ 259.1329; Found 259.1298.

((1R,2R*)-2-methoxy-1-methyl-2-((4-(trifluoromethyl)phenyl)ethynyl)cyclobutyl)methanol (**4j**):* following the general procedure, starting with compound **S2j** (0.25 g, 0.47 mmol). Purification by flash column chromatography on silica gel (10 % EtOAc in Hexane) gave **4j** (24.5 mg, 0.082 mmol) as yellow oil in 18 % yield ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61–7.54 (m, 4H), 3.88 (d, *J* = 11.4 Hz, 1H), 3.57 (d, *J* = 11.4 Hz, 1H), 3.38 (s, 3H), 2.34–2.27 (m, 2H),

1.81 (bs, 1H), 1.72 (ap dt, *J* = 11.2, 9.1 Hz, 1H), 1.54 (ap dt, *J* = 11.3, 6.9 Hz, 1H), 1.27 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 132.1 (2xCH), 130.5 (q, *J* = 32.9 Hz, C), 126.3 (C), 125.5 (q, *J* = 3.8 Hz, 2xCH), 124.0 (q, *J* = 272.2 Hz, C), 91.1 (C), 86.5 (C), 76.6 (C), 69.4 (CH_2), 52.8 (CH_3), 49.3 (C), 30.9 (CH_2), 23.7 (CH_2), 17.5 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{18}F_3O_2$ 299.1253; Found 299.1243.

((1R,2R*)-2-((2-chlorophenyl)ethynyl)-2-methoxy-1-methylcyclobutyl)methanol (**4k**):* following the general procedure, starting with compound **S2k** (0.3 g, 0.6 mmol). Purification by flash column chromatography on silica gel (20 % EtOAc in Hexane) gave **4k** (0.04 g, 0.15 mmol) as yellow oil in 25 % yield. ^1H NMR (500 MHz, $CDCl_3$) δ 7.50 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.42 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.28 (td, *J* = 7.7, 1.9 Hz, 1H), 7.23 (td, *J* = 7.7, 1.9 Hz, 1H), 3.96 (d, *J* = 11.6 Hz, 1H), 3.55 (d, *J* = 11.6 Hz, 1H), 3.42 (s, 3H), 2.38–2.26 (m, 2H), 2.03 (bs, 1H), 1.74 (ap dt, *J* = 11.2, 9.1 Hz, 1H), 1.53 (ddd, *J* = 11.2, 9.3, 4.6 Hz, 1H), 1.27 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 136.0 (C), 133.6 (CH), 129.7 (CH), 129.4 (CH), 126.7 (CH), 122.5 (C), 93.9 (C), 84.6 (C), 76.7 (C), 69.3 (CH_2), 52.9 (CH_3), 49.5 (C), 31.0 (CH_2), 23.7 (CH_2), 17.6 (CH_3); HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{17}ClO_2Na$ 287.0809; Found 287.0809.

Synthesis of (1*S,2*R**)-2-methoxy-1-methyl-2-(phenylethynyl)cyclobutanecarboxylic acid (10a):** in a round bottom flask, ((1*R**,2*R**)-2-methoxy-1-methyl-2-(phenylethynyl)cyclobutyl)methanol **4a** (0.42 g, 1.8 mmol), 4-methylmorpholine *N*-oxide (2.12 g, 18.1 mmol) and tetrapropylammonium perruthenate (10 mol %, 0.064 g, 0.18 mmol) were dissolved in MeCN (7 mL), and the resulting mixture was stirred 40 min at room temperature. The residue was concentrated under reduced pressure and without further purification, was dissolved in a mixture of THF/H_2O/^{t}BuOH (3:1:3) (28 mL). Then, sodium chlorite (0.49 g, 5.4 mmol), dibasic potassium phosphate (0.94 g, 5.4 mmol) and 2-methyl-2-butene (1.5 mL, 14.4 mmol) were added and the reaction mixture was stirred overnight at room temperature. The reaction mixture was quenched by the addition of HCl (1M), and the resulting mixture was extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (10 % EtOAc in Hexane) to give (1*S**,2*R**)-2-methoxy-1-methyl-2-(phenylethynyl)cyclobutanecarboxylic acid (0.24 g, 0.97 mmol) as yellow solid in 54 % yield. M. p.: 130-132 ºC; ^1H NMR (500 MHz, $CDCl_3$) δ 11.92 (bs, 1H), 7.41–7.36 (m, 2H), 7.31–7.21 (m, 3H), 3.48 (s, 3H), 2.52–2.44 (m, 1H), 2.39–2.22 (m, 2H), 1.62–1.52 (m, 1H), 1.48 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 181.1 (C), 132.0 (2xCH), 128.6 (CH), 128.3 (2xCH), 122.5 (C), 87.8 (C), 87.1 (C), 76.1 (C), 55.2 (C), 53.4 (CH_3), 31.7 (CH_2), 22.5 (CH_2), 18.1 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{17}O_3$ 245.1172; Found 245.1175.

Synthesis of cyclobutane-fused dihydropyrans 7 by iodocyclization of 4 (general procedure A): to a solution of the corresponding compound **4** (1 equiv.) in dry MeCN (0.05 M), iodine (3 equiv.) and sodium bicarbonate (3 equiv.) were added and the resulting mixture was stirred 15 h at room temperature and protected from light. The reaction was quenched by addition of saturated aqueous solution of $Na_2S_2O_3$. The mixture was extracted with Et_2O, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel to give the corresponding cyclobutane-fused dihydropyran derivative **7**.

(1R,6S*)-5-iodo-6-methoxy-1-methyl-4-phenyl-3-oxabicyclo[4.2.0]oct-4-ene (**7a**):* following the general procedure A, starting with compound **4a** (0.23 g, 1.0 mmol). Purification by flash column chromatography on silica gel (5 % EtOAc in Hexane), followed by semipreparative TLC (Toluene) gave **7a** (0.27 g, 0.77 mmol) as yellow oil in 77 % yield. ^1H NMR (500 MHz, $CDCl_3$) δ 7.52–7.46 (m, 2H), 7.43–7.33 (m, 3H), 3.97 (d, *J* = 11.3 Hz, 1H), 3.75 (d, *J* = 11.3 Hz, 1H), 3.32 (s, 3H), 2.28–2.18 (m, 1H), 1.91 (ddd, *J* = 10.7, 8.6, 1.9 Hz, 1H), 1.87–1.79 (m, 1H), 1.44–1.35 (m, 1H), 1.37 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 157.6 (C), 138.5 (C), 129.3 (2xCH), 129.1 (CH), 128.0 (2xCH), 83.7 (C), 76.9 (C), 72.0 (CH_2), 53.0 (CH_3), 44.7 (C), 34.3 (CH_2), 21.0 (CH_2), 17.9 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{18}IO_2$ 357.0346; Found 357.0343.

(1R,6S*)-4-(4-chlorophenyl)-5-iodo-6-methoxy-1-methyl-3-oxabicyclo[4.2.0]oct-4-ene (**7b**):* following the general procedure A, starting with compound **4b** (80.0 mg, 0.3 mmol). Purification by flash column chromatography on silica gel (2 % EtOAc in Hexane), followed by semipreparative TLC (Toluene) gave **7b** (74.1 mg, 0.19 mmol) as yellow oil in 63 % yield. ^1H NMR (500 MHz, $CDCl_3$) δ 7.48–7.43 (m, 2H), 7.39–7.35 (m, 2H), 3.96 (d, *J* = 11.3 Hz, 1H), 3.73 (d, *J* = 11.3 Hz, 1H), 3.30 (s, 3H), 2.27–2.17 (m, 1H), 1.89 (ddd, *J* = 10.9, 8.6, 1.9 Hz, 1H), 1.83–1.75 (m, 1H), 1.43–1.36 (m, 1H), 1.37 (s, 3H); $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 156.5 (C), 136.8 (C), 135.0 (C), 130.9 (2xCH), 128.3 (2xCH), 84.2 (C), 76.9 (C), 72.0 (CH_2), 53.1 (CH_3), 44.7 (C), 34.2 (CH_2), 21.0 (CH_2), 17.9 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{17}ClIO_2$ 390.9956; Found 390.9952.

(1R,6S*)-5-iodo-6-methoxy-1-methyl-4-(p-tolyl)-3-oxabicyclo[4.2.0]oct-4-ene (**7c**):* following the general procedure A, starting with compound **4c** (85.5 mg, 0.35 mmol). Purification by flash column chromatography on silica gel (5 % EtOAc in Hexane) gave **7c** (125.0 mg, 0.34 mmol) as brown oil in 96 % yield. ^1H NMR (500 MHz, $CDCl_3$) δ 7.44–7.38 (m, 2H), 7.24–7.19 (m, 2H), 3.96 (d, *J* = 11.3 Hz, 1H), 3.74 (d, *J* = 11.3 Hz, 1H), 3.32 (s, 3H), 2.39 (s, 3H), 2.27–2.18 (m, 1H), 1.92 (ddd, *J* = 10.9, 8.6, 1.9 Hz, 1H), 1.86–1.78 (m, 1H), 1.43–1.36 (m, 1H), 1.37 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 157.6 (C), 139.0 (C), 135.6 (C), 129.2 (2xCH), 128.6 (2xCH), 83.5 (C), 76.9 (C), 71.9 (CH_2), 53.0 (CH_3), 44.7 (C), 34.2 (CH_2), 21.5 (CH_3), 21.0 (CH_2), 17.9 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{20}IO_2$ 371.0502; Found 371.0505.

(1R,6S*)-5-iodo-6-methoxy-4-(4-methoxyphenyl)-1-methyl-3-oxabicyclo[4.2.0]oct-4-ene (**7d**):* following the general procedure A, starting with compound **4d** (130.1 mg, 0.5 mmol). Purification by flash column chromatography on silica gel (10 % EtOAc in Hexane) gave **7d** (106.7 mg, 0.28 mmol) as yellow oil in 55 % yield. ^1H NMR (500 MHz, $CDCl_3$) δ 7.50–7.43 (m, 2H), 6.95–6.87 (m, 2H), 3.95 (d, *J* = 11.3 Hz, 1H), 3.83 (s, 3H), 3.73 (d, *J* = 11.3 Hz, 1H), 3.30 (s, 3H), 2.26–2.17 (m, 1H), 1.94–1.87 (m, 1H), 1.85–1.76 (m, 1H), 1.40–1.36 (m, 1H), 1.36 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.9 (C), 157.2 (C), 130.82 (C), 130.75 (2xCH), 113.2 (2xCH), 83.5 (C), 77.0 (C), 71.9 (CH_2), 55.3 (CH_3), 52.9 (CH_3), 44.6 (C), 34.2 (CH_2), 20.9 (CH_2), 17.8 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{20}IO_3$ 387.0452; Found 387.0439.

(1R,6S*)-5-iodo-6-methoxy-1-methyl-4-(thiophen-3-yl)-3-oxabicyclo[4.2.0]oct-4-ene (**7e**):* following the general

procedure A, starting with compound **4e** (118.2 mg, 0.5 mmol). Purification by flash column chromatography on silica gel (5 % EtOAc in Hexane) gave **7e** (150.1 mg, 0.41 mmol) as yellow oil in 83 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 3.0, 1.3 Hz, 1H), 7.43 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.30 (dd, *J* = 5.0, 3.0 Hz, 1H), 3.96 (dd, *J* = 11.6, 1H), 3.72 (d, *J* = 11.6 Hz, 1H), 3.28 (s, 3H), 2.26–2.17 (m, 1H), 1.89 (ddd, *J* = 10.8, 8.6, 1.9 Hz, 1H), 1.83–1.74 (m, 1H), 1.41–1.33 (m, 1H), 1.36 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 152.6 (C), 138.2 (C), 128.5 (CH), 127.2 (CH), 124.4 (CH), 83.9 (C), 77.1 (C), 71.7 (CH_2), 53.0 (CH_3), 44.6 (C), 34.3 (CH_2), 20.8 (CH_2), 17.9 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for$C_{13}H_{16}IO_2S$ 362.9910; Found 362.9910.

(1R,6S*)-4-(cyclohex-1-en-1-yl)-5-iodo-6-methoxy-1-methyl-3-oxabicyclo[4.2.0]oct-4-ene (**7f**):* following the general procedure A, starting with compound **4f** (30.2 mg, 0.13 mmol). Purification by flash column chromatography on silica gel (5 % EtOAc in Hexane) gave **7f** (23.5 mg, 0.065 mmol) as yellow oil in 51 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91–5.83 (m, 1H), 3.84 (d, *J* = 11.3 Hz, 1H), 3.57 (d, *J* = 11.3 Hz, 1H), 3.23 (s, 3H), 2.25–2.08 (m, 5H), 1.84 (ddd, *J* = 10.6, 8.5, 1.9 Hz, 1H), 1.75–1.57 (m, 5H), 1.35–1.23 (m, 1H), 1.29 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 160.0 (C), 136.6 (C), 130.9 (CH), 81.7 (C), 76.7 (C), 71.6 (CH_2), 52.8 (CH_3), 44.6 (C), 34.2 (CH_2), 26.5 (CH_2), 25.0 (CH_2), 22.5 (CH_2), 21.8 (CH_2), 20.9 (CH_2), 17.9 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{22}IO_2$ 361.0659; Found 361.0663.

(1R,6S*)-4-butyl-5-iodo-6-methoxy-1-methyl-3-oxabicyclo[4.2.0]oct-4-ene (**7g**):* following the general procedure A, starting with compound **4g** (20.0 mg, 0.095 mmol). Purification by flash column chromatography on silica gel (2 % EtOAc in Hexane) gave **7g** (11.2 mg, 0.03 mmol) as yellow oil in 56 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.82 (d, *J* = 11.3 Hz, 1H), 3.51 (d, *J* = 11.3 Hz, 1H), 3.21 (s, 3H), 2.59–2.47 (m, 2H), 2.19–2.05 (m, 1H), 1.82–1.72 (m, 1H), 1.69–1.50 (m, 3H), 1.48–1.34 (m, 2H), 1.33–1.22 (m, 1H), 1.30 (s, 3H), 0.96 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 159.5 (C), 82.9 (C), 76.7 (C), 71.3 (CH_2), 52.7 (CH_3), 44.4 (C), 37.8 (CH_2), 34.2 (CH_2), 29.4 (CH_2), 22.4 (CH_2), 20.9 (CH_2), 17.9 (CH_3), 14.2 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{22}IO_2$ 337.0659; Found 337.0653. From the same reaction, compound **8g** (7.8 mg, 0.0232 mmol) was obtained as yellow oil in 24 % yield, and was characterized from a mixture with **7g**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09 (d, *J* = 9.0 Hz, 1H), 3.88-3.78 (m, 1H), 3.17 (s, 3H), 2.48–2.06 (m, 4H), 1.81–1.33 (m, 9H) 1.00– 0.89 (m, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 157.3 (C), 83.7 (C), 79.6 (CH2), 76.0 (C), 53.4 (CH_3), 50.7 (C), 35.0 (CH_2), 33.0 (CH_2), 24.1 (CH_2), 22.5 (CH_2), 18.1 (CH_2), 16.2 (CH_3), 16.0 (CH_3). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{22}IO_2$ 337.0659; Found $[M+H]^+$: 337.0662.

(1R,6S*)-5-iodo-1-methyl-4-phenyl-6-propoxy-3-oxabicyclo[4.2.0]oct-4-ene (**7h**):* following the general procedure A, starting with compound **4h** (23.1 mg, 0.09 mmol). Purification by flash column chromatography on silica gel (5 % EtOAc in Hexane) gave **7h** (20.4 mg, 0.053 mmol) as yellow oil in 59 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50–7.47 (m, 2H), 7.42–7.35 (m, 3H), 3.96 (d, *J* = 11.3 Hz, 1H), 3.74 (d, *J* = 11.3 Hz, 1H), 3.50 (dt, *J* = 8.4, 6.5 Hz, 1H), 3.24 (dt, *J* = 8.4, 6.8 Hz, 1H), 2.25 (ap q, *J* = 10.5 Hz, 1H), 1.91 (ddd, *J* = 10.6, 8.5, 1.9 Hz, 1H), 1.86–1.78 (m, 1H), 1.70–1.60 (m, 2H), 1.44–1.32 (m, 1H), 1.35 (s, 3H), 0.97 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 157.1 (C), 138.6 (C), 129.4 (2xCH), 129.1 (CH), 128.0 (2xCH), 84.8 (C), 76.2 (C), 72.0 (CH_2), 66.9 (CH_2), 44.8 (C), 34.4 (CH_2), 23.6 (CH_2), 21.0 (CH_2), 17.9 (CH_3), 11.0 (CH_3). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{22}IO_2$ 385.0659; Found 385.0662.

(1R,6S*)-5-iodo-1-methyl-4-phenyl-3-oxabicyclo[4.2.0]oct-4-en-6-yl acetate (**7i**):* following the general procedure A, starting with compound **4i** (38.4 mg, 0.1488 mmol). Purification by flash column chromatography on silica gel (10 % EtOAc in Hexane) gave **7i** (29.6 mg, 0.0771 mmol) as yellow oil in 52 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50–7.46 (m, 2H), 7.38–7.35 (m, 3H), 4.26 (d, *J* = 10.8 Hz, 1H), 3.80 (d, *J* = 10.8 Hz, 1H), 2.45–2.36 (m, 1H), 2.13–2.10 (m, 3H), 2.05–1.96 (m, 1H), 1.59–1.53 (m, 1H), 1.40–1.31 (m, 1H), 1.28 (s, 3H) . ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.8 (C), 155.5 (C), 138.4 (C), 129.4 (2xCH), 129.1 (CH), 128.0 (2xCH), 80.1 (C), 78.4 (C), 70.2 (CH_2), 45.7 (C), 33.2 (CH_2), 21.34 (CH_2), 21.25 (CH_3), 18.1 (CH_3). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{18}IO_3$ 385.0295; Found 385.0305.

Synthesis of (1R*,6S*)-5-bromo-6-methoxy-1-methyl-4-phenyl-3-oxabicyclo[4.2.0]oct-4-ene (9a): in a round bottom flask, compound **4a** (115.2 mg, 0.5 mmol) in dry CH_2Cl_2 (10 mL) and N-bromosuccinimide (267.0 mg, 1.5 mmol) were added and the reaction mixture was stirred 15 h at room temperature and protected from light. The reaction was quenched by addition of saturated aqueous solution of $Na_2S_2O_3$. The mixture was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on neutral alumina (2 % EtOAc in Hexane) to give **9a** (138.6 mg, 0.45 mmol) as yellow oil in 90 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61–7.57 (m, 2H), 7.43–7.37 (m, 3H), 3.97 (d, *J* = 11.3 Hz, 1H), 3.72 (d, *J* = 11.3 Hz, 1H), 3.33 (s, 3H), 2.33–2.25 (m, 1H), 2.13 (ddd, *J* = 11.0, 8.5, 2.0 Hz, 1H), 1.87–1.79 (m, 1H), 1.44–1.37 (m, 1H), 1.34 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 154.8 (C), 136.1 (C), 129.12 (CH), 129.10 (2xCH), 128.0 (2xCH), 104.4 (C), 76.0 (C), 71.7 (CH_2), 53.1 (CH_3), 45.8 (C), 32.3 (CH_2), 20.9 (CH_2), 17.4 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{18}BrO_2$ 309.0485; Found 309.0483.

Synthesis of (1S*,6S*)-5-iodo-6-methoxy-1-methyl-4-phenyl-3-oxabicyclo[4.2.0]oct-4-en-2-one (11a): following the general procedure A, starting with compound **10a** (24.4 mg, 0.1 mmol). Purification by flash column chromatography on silica gel (5 % EtOAc in Hexane) gave **11a** along with **12a** (7:1) (36.3 mg, 0.098 mmol) as yellow solid in 98 % yield. M. p.: 131–134 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62–7.56 (m, 2H), 7.46–7.40 (m, 3H), 3.20 (s, 3H), 2.50–2.41 (m, 1H), 2.28–2.12 (m, 2H), 1.84–1.77 (m, 1H), 1.68 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, CDCl3) δ 169.0 (C), 152.1 (C), 135.1 (C), 130.1 (CH), 129.6 (2xCH), 128.2 (2xCH), 84.9 (C), 79.6 (C), 52.0 (CH_3), 44.8 (C), 36.3 (CH_2), 26.1 (CH_2), 17.0 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{16}IO_3$ 371.0139; Found 371.0139.

Synthesis of 2-(hydroxymethyl)-5-phenylpent-1-en-4-yn-3-one (13a): following the general procedure A, starting with compound **1a** (20.2 mg, 0.1 mmol). Purification by flash column chromatography on silica gel (10 % EtOAc in Hexane) gave **13a** (11.6 mg, 0.0623 mmol) as yellow oil in 62 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63–7.58 (m, 2H), 7.50–7.44 (m, 1H), 7.43–7.37 (m, 2H), 6.67–6.65 (m, 1H), 6.32–6.29 (m, 1H), 4.45–4.42 (m, 2H), 2.29 (bs, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 179.8 (C), 148.0 (C), 133.1 (2xCH), 131.0

(CH), 130.9 (CH_2), 128.8 (2xCH), 112.0 (C), 92.4 (C), 85.8 (C), 61.4 (CH_2). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{12}H_{11}O_2$ 187.0754; Found 187.0762.

Synthesis of (5S)-3-iodo-5-methoxy-5-(phenylethynyl)dihydrofuran-2(3H)-one (15a): in a round bottom flask, compound **14a** (21.6 mg, 0.1 mmol) in dry CH_2Cl_2 (2 mL) and *N*-iodosuccinimide (67.5 mg, 0.3 mmol) were added and the reaction mixture was stirred at 15 h at room temperature and protected from light. The reaction was quenched by addition of saturated aqueous solution of $Na_2S_2O_3$. The mixture was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give **15a** (26.0 mg, 0.0760 mmol) as a brown oil in 76 % yield. The compound was characterized without further purification (decomposition was observed when purification by flash column chromatography was attempted). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52–7.48 (m, 2H, maj), 7.48–7.45 (m, 2H, min), 7.43–7.32 (m, 3H, maj + 3H, min), 4.86 (t, *J* = 8.5 Hz, 1H, maj), 4.77 (dd, *J* = 9.0, 4.5 Hz, 1H, min), 3.66 (s, 3H, min), 3.60 (s, 3H, maj), 3.27 (dd, *J* = 14.9, 9.0 Hz, 1H, min), 3.09 (dd, *J* = 14.1, 8.5 Hz, 1H, maj), 3.00 (dd, *J* = 14.1, 8.5 Hz, 1H, maj), 2.90 (dd, *J* = 14.9, 4.5 Hz, 1H, min). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 173.1 (C, min), 172.9 (C, maj), 132.0 (3xCH, maj + CH, min), 129.8 (2xCH, min), 128.63 (2xCH, min), 128.62 (2xCH, maj), 120.64 (C, maj), 120.57 (C, min), 103.2 (C, min), 102.9 (C, maj), 88.9 (C, maj), 88.4 (C, min), 82.4 (C, min), 81.2 (C, maj), 53.8 (CH_3, maj)), 53.5 (CH_3, min), 48.7 (CH_2, maj), 47.6 (CH_2, min), 7.0 (CH, maj), 4.9 (CH, min).

Synthesis of (1R*,6R*)-6-methoxy-1-methyl-4-phenyl-3-oxabicyclo[4.2.0]oct-4-ene (5a): to a Biotage microwave vial equipped with a stir bar were added $Pd(OAc)_2$ (2 mol %, 0.5 mg, 0.002 mmol), PPh_3 (4 mol %, 1.2 mg, 0.005 mmol) and **7a** (40.0 mg, 0.11 mmol). The vial was sealed with a cap line with a disposable Teflon septum and purged with argon. Then, formic acid (10 µL, 0.22 mmol), dry Et_3N (47 µL, 0.73 mmol) and dry DMF (1.5 mL) were added and the resulting mixture was stirred 4 h at 60 ºC. The reaction mixture was filtered on Celite washing with CH_2Cl_2. The solvents were evaporated under reduced pressure, and the resulting residue was purified by flash column chromatography on silica gel (5 % EtOAc in Hexane) to give **5a** (22.2 mg, 0.096 mmol) as yellow oil in 86 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69–7.63 (m, 2H), 7.41–7.32 (m, 3H), 5.53 (s, 1H), 3.96 (d, *J* = 11.0 Hz, 1H), 3.62 (d, *J* = 11.0 Hz, 1H), 3.29 (s, 3H), 2.38–2.25 (m, 1H), 1.97 (ddd, *J* = 10.4, 8.5, 1.8 Hz, 1H), 1.83–1.70 (m, 1H), 1.38–1.28 (m, 1H), 1.27 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 154.0 (C), 135.5 (C), 128.6 (CH), 128.3 (2xCH), 125.0 (2xCH), 101.4 (CH), 73.1 (C), 71.7 (CH_2), 52.7 (CH_3), 44.8 (C), 32.7 (CH_2), 20.4 (CH_2), 16.7 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{19}O_2$ 231.1380; Found 231.1377.

Synthesis of (1R*,6S*)-6-methoxy-1-methyl-4,5-diphenyl-3-oxabicyclo[4.2.0]oct-4-ene (16a): in a round bottom flask, **7a** (35.6 mg, 0.1 mmol) and K_2CO_3 (27.6 mg, 0.2 mmol) were dissolved in DMF/H_2O (5:1) (1.2 mL). Then, $PhB(OH)_2$ (25.7 mg, 0.2 mmol) was added and the reaction mixture was stirred 10 min at room temperature. $PdCl_2(PPh_3)_2$ (10 mol%, 7.0 mg, 0.01 mmol) was then added and the reaction mixture was stirred at 60 ºC 5 h. The resulting mixture was extracted with Et_2O, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (30 % EtOAc in Hexane) to give **16a** (23.8 mg, 0.078 mmol) as orange solid in 78 % yield. M. p.: 56–58 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28–7.25 (m, 2H), 7.19–7.14 (m, 5H), 7.13–7.06 (m, 3H), 4.00 (d, *J* = 10.8 Hz, 1H), 3.79 (d, *J* = 10.8 Hz, 1H), 3.03 (s, 3H), 2.63–2.55 (m, 2H), 2.03–1.94 (m, 1H), 1.45–1.38 (m, 1H), 1.36 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 154.1 (C), 138.3 (C), 137.0 (C), 130.8 (2xCH), 130.1 (2xCH), 128.1 (CH), 127.7 (2xCH), 127.6 (2xCH), 125.9 (CH), 115.4 (C), 76.0 (C), 72.1 (CH_2), 52.8 (CH_3), 46.6 (C), 33.8 (CH_2), 20.5 (CH_2), 17.3 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{23}O_2$ 307.1693; Found 307.1693.

Synthesis of cyclobutane-fused methylenetetrahydrofurans 6 by gold-catalyzed 5-*exo-dig* cyclization of 4 (general procedure B): a solution of the corresponding compound 4 (1 equiv.) in DMF (0.1 M) was cooled at –50 ºC. Then, JohnPhosAu(MeCN)SbF_6 (5 mol%) was added and the reaction mixture was stirred 6 h at this temperature. The resulting mixture was filtered over a plug of Celite eluting with CH_2Cl_2 and solvents were removed under reduced pressure. The crude reaction mixture was purified by flash chromatography on silica gel to give the corresponding cyclobutane-fused methylenetetrahydrofuran **6**.

(1S,5R*,Z)-2-benzylidene-1-methoxy-5-methyl-3-oxabicyclo[3.2.0]heptane (**6a**):* following the general procedure B, using compound **4a** (115.2 mg, 0.5 mmol). Purification by flash column chromatography on silica gel (5 % EtOAc in Hexane) gave **6a** (104.3 mg, 0.45 mmol) as yellow oil in 91 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66–7.62 (m, 2H), 7.34–7.29 (m, 2H), 7.16–7.12 (m, 1H), 5.47 (s, 1H), 4.23 (d, *J* = 8.9 Hz, 1H), 3.99 (d, *J* = 8.9 Hz, 1H), 3.24 (s, 3H), 2.32 (ap q, *J* = 10.6 Hz, 1H), 2.16 (ddd, *J* = 10.8, 8.1, 2.5 Hz, 1H), 1.70–1.55 (m, 2H), 1.33 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 159.5 (C), 136.5 (C), 128.4 (2xCH), 127.9 (2xCH), 125.5 (CH), 100.2 (CH), 85.5 (C), 81.2 (CH_2), 53.0 (CH_3), 47.0 (C), 30.6 (CH_2), 24.1 (CH_2), 15.6 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{19}O_2$ 231.1380; Found 231.1374.

(1S,5R*,Z)-2-(4-chlorobenzylidene)-1-methoxy-5-methyl-3-oxabicyclo[3.2.0]heptane (**6b**):* following the general procedure B, using compound **4b** (132.4 mg, 0.5 mmol). Purification by flash column chromatography on silica gel (2 % EtOAc in Hexane), followed by semipreparative TLC (5 % Et_2O in Toluene) gave **6b** (121.9 mg, 0.46 mmol) as yellow oil in 92 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60–7.53 (m, 2H), 7.30–7.23 (m, 2H), 5.42 (s, 1H), 4.24 (d, *J* = 8.9 Hz, 1H), 3.99 (d, *J* = 8.9 Hz, 1H), 3.22 (s, 3H), 2.32 (ap q, *J* = 10.9 Hz, 1H), 2.14 (ddd, *J* = 10.9, 8.0, 2.7 Hz, 1H), 1.70–1.55 (m, 2H), 1.33 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 160.1 (C), 135.0 (C), 130.7 (C), 129.1 (2xCH), 128.4 (2xCH), 99.1 (CH), 85.6 (C), 81.4 (CH_2), 53.0 (CH_3), 47.0 (C), 30.5 (CH_2), 24.1 (CH_2), 15.6 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{18}ClO_2$ 265.0990; Found 265.0992.

(1S,5R*,Z)-1-methoxy-5-methyl-2-(4-methylbenzylidene)-3-oxabicyclo[3.2.0]heptane (**6c**):* following the general procedure B, using compound **4c** (85.5 mg, 0.35 mmol). Purification by flash column chromatography on silica gel (5 % EtOAc in Hexane), followed by semipreparative TLC (5 % Et_2O in Toluene) gave **6c** (61.5 mg, 0.25 mmol) as white solid in 72 % yield. M. p.: 59–60 ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57–7.51 (m, 2H), 7.16–7.09 (m, 2H), 5.44 (s, 1H), 4.22 (d, *J* = 8.9 Hz, 1H), 3.97 (d, *J* = 8.9 Hz, 1H), 3.23 (s, 3H), 2.37–2.26 (m, 1H), 2.33 (s, 3H), 2.19–2.11 (m, 1H), 1.71–1.62 (m, 1H), 1.58 (ap td, *J* = 11.1, 2.5 Hz, 1H), 1.32 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 158.7 (C), 135.1 (C), 133.6 (C), 129.1 (2xCH), 127.8

(2xCH), 100.1 (CH), 85.4 (C), 81.1 (CH_2), 52.9 (CH_3), 47.1 (C), 30.6 (CH_2), 24.1 (CH_2), 21.3 (CH_3), 15.6 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{21}O_2$ 245.1536; Found 245.1539. From the same reaction, compound **5c** (20.6 mg, 0.084 mmol) was obtained as white solid in 24 % yield, and was characterized from a mixture with **6c**. M. p.: 62–64ºC. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60–7.55 (m, 2H), 7.20 (m, 2H), 5.50 (s, 1H), 3.95 (d, *J* = 11.0 Hz, 1H), 3.62 (d, *J* = 11.0 Hz, 1H), 3.29 (s, 3H), 2.39 (s, 3H), 2.38–2.35 (m, 1H), 1.97 (ddd, *J* = 10.4, 8.4, 1.9 Hz, 1H), 1.82–1.74 (m, 1H), 1.37–1.32 (m, 1H), 1.27 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 154.2 (C), 138.4 (C), 132.8 (C), 129.0 (2xCH), 125.0 (2xCH), 100.6 (CH), 73.0 (C), 71.5 (CH_2), 52.6 (CH_3), 44.7 (C), 32.6 (CH_2), 21.3 (CH_2), 20.3 (CH_3), 16.6 (CH_3). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{21}O_2$ 245.1536; Found 245.1534.

(1S,5R*,Z)-1-methoxy-2-(4-methoxylbenzylidene)-5-methyl-3-oxabicyclo[3.2.0]heptane **(6d)**:* following the general procedure B, using compound **4d** (130.1 mg, 0.5 mmol). Purification by flash column chromatography on silica gel (10 % EtOAc in Hexane), followed by semipreparative TLC (5 % Et_2O in Toluene) gave **6d** (62.4 mg, 0.24 mmol) as white solid in 48 % yield. M. p.: 59–61 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62–7.54 (m, 2H), 6.90–6.85 (m, 2H), 5.41 (s, 1H), 4.20 (d, *J* = 8.9 Hz, 1H), 3.95 (d, *J* = 8.9 Hz, 1H), 3.81 (s, 3H), 3.22 (s, 3H), 2.30 (ap q, *J* = 10.6 Hz, 1H), 2.14 (ddd, *J* = 10.7, 8.1, 2.5 Hz, 1H), 1.69–1.54 (m, 2H), 1.31 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 157.7 (C), 157.6 (C), 129.4 (C), 129.1 (2xCH), 113.9 (2xCH), 99.7 (CH), 85.4 (C), 81.0 (CH_2), 55.5 (CH_3), 52.9 (CH_3), 47.2 (C), 30.6 (CH_2), 24.1 (CH_2), 15.7 (CH_3). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{21}O_3$ 261.1485; Found 261.1481. From the same reaction, compound **5d** (62.0 mg, 0.24 mmol) was obtained as white solid in 48 % yield, and was characterized from a mixture with **6d**. M. p.: 61–62 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63–7.57 (m, 2H), 6.93–6.85 (m, 2H), 5.43 (s, 1H), 3.93 (d, *J* = 11.0 Hz, 1H), 3.83 (s, 3H), 3.60 (d, *J* = 11.0 Hz, 1H), 3.27 (s, 3H), 2.36–2.26 (m, 1H)1.94 (ddd, *J* = 10.4, 8.4, 1.9 Hz, 1H), 1.79–1.71 (m, 1H), 1.32–1.29 (m, 1H), 1.24 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 160.0 (C), 154.0(C), 128.3 (C), 126.4 (2xCH), 113.7 (2xCH), 99.7 (CH), 73.0 (C), 71.6 (CH_2), 55.3 (CH_3), 52.5 (CH_3), 44.6 (C), 32.6 (CH_2), 20.3 (CH_2), 16.6 (CH_3). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{21}O_3$ 261.1485; Found 261.1487.

(1S,5R*,Z)-1-methoxy-5-methyl-2-(thiophen-3-ylmethylene)-3-oxabicyclo[3.2.0]heptane **(6e)**:* following the general procedure B, using compound **4e** (118.2 mg, 0.5 mmol). Purification by flash column chromatography on silica gel (5 % EtOAc in Hexane), followed by semipreparative TLC (5 % Et_2O in Toluene) gave **6e** (81.5 mg, 0.35 mmol) as white solid in 69 % yield. M. p.: 86–89 ºC; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.31 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.26 (dd, *J* = 5.0, 3.0 Hz, 1H), 5.58 (s, 1H), 4.21 (d, *J* = 8.9 Hz, 1H), 3.97 (d, *J* = 8.9 Hz, 1H), 3.22 (s, 3H), 2.31 (ap q, *J* = 10.6 Hz, 1H), 2.13 (ddd, *J* = 10.7, 8.1, 2.5 Hz, 1H), 1.71–1.62 (m, 1H), 1.61–1.54 (m, 1H), 1.32 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 158.6 (C), 137.1 (C), 128.4 (CH), 124.7 (CH), 120.5 (CH), 95.1 (CH), 85.0 (C), 81.0 (CH_2), 52.9 (CH_3), 47.5 (C), 30.5 (CH_2), 24.1 (CH_2), 15.6 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{17}O_2S$ 237.0944; Found 237.0951.

(1S,5R*,Z)-2-(cyclohex-1-en-1-ylmethylene)-1-methoxy-5-methyl-3-oxabicyclo[3.2.0]heptane **(6f)**:* following the general procedure B, using compound **4f** (23.4 mg, 0.1 mmol). Purification by flash column chromatography on silica gel (10 % EtOAc in Hexane) gave **6f** together with **5f** (1:3) (10.8 mg, 0.046 mmol) as yellow oil in 46 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.34–6.29 (m, 1H, maj), 5.89–5.85 (m, 1H, min), 4.98 (s, 1H, maj), 4.92 (s, 1H, min), 4.05 (d, *J* = 8.9 Hz, 1H, min), 3.81 (d, *J* = 8.9 Hz, 1H, min), 3.78 (d, *J* = 11.1 Hz, 1H, maj), 3.43 (d, *J* = 11.1 Hz, 1H, maj), 3.21 (s, 3H, maj), 3.18 (s, 3H, min), 2.42–2.29 (m, 2H, min), 2.28–2.20 (m, 1H, maj + 1H, min), 2.19–2.10 (m, 4H, maj + 2H, min), 2.05 (ddd, *J* = 10.7, 8.1, 2.4 Hz, 1H, min), 1.85 (ddd, *J* = 10.5, 8.3, 2.0 Hz, 1H, maj), 1.75–1.55 (m, 5H, maj + 5H, min), 1.52 (td, *J* = 11.2, 2.4 Hz, 1H, min), 1.29–1.21 (m, 1H, maj + 3H, min), 1.19 (s, 3H, maj). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 156.5 (C, min), 154.8 (C, maj), 134.0 (C, min), 131.3 (C, maj), 125.4 (CH, maj), 124.6 (CH, min), 102.9 (CH, min), 100.0 (CH, maj), 85.1 (C, min), 80.5 (C, maj), 72.9 (CH_2, min), 71.2 (CH_2, maj), 52.8 (CH_3, min), 52.6 (CH_3, maj), 47.0 (C, min), 44.6 (C, maj), 32.7 (CH_2, maj), 30.6 (CH_2, min), 29.0 (CH_2, min), 26.0 (CH_2, min), 25.6 (CH_2, maj), 24.8 (CH_2, maj), 24.1 (CH_2, min), 23.2 (CH_2, min), 22.8 (CH_2, maj), 22.4 (CH_2, min), 22.3 (CH_2, maj), 20.2 (CH_2, maj), 16.7 (CH_3, maj), 15.7 (CH_3, min). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{23}O_2$ 235.1693; Found 235.1688.

(1S,5R*,Z)-2-benzylidene-5-methyl-1-propoxy-3-oxabicyclo[3.2.0]heptane **(6h)**:* following the general procedure B, using compound **4h** (26.4 mg, 0.1 mmol). Purification by flash column chromatography on silica gel (1 % EtOAc in Hexane) gave **6h** together with **5h** (8:1) (24.0 mg, 0.093 mmol) as yellow oil in 91 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74–7.71 (m, 1H, min), 7.67–7.61 (m, 2H, maj + 1H, min), 7.55–7.51 (m, 1H, min), 7.39–7.34 (m, 2H, min), 7.33–7.29 (m, 2H, maj), 7.16–7.10 (m, 1H, 1 maj), 5.53 (s, 1H, min), 5.46 (s,1H, maj), 4.22 (d, *J* = 8.8 Hz, 1H, maj), 3.98 (d, *J* = 8.8 Hz, 1H, maj), 3.93 (d, *J* = 11.0 Hz, 1H, min), 3.61 (d, *J* = 11.0 Hz, 1H, min) 3.52–3.43 (m, 1H, maj + 1H, min), 3.32–3.25 (m, 1H, min), 3.17–3.10 (m, 1H, maj), 2.39–2.28 (m, 1H, maj), 2.16 (ddd, *J* = 10.7, 8.1, 2.4 Hz, 1H, maj), 1.95 (ddd, *J* = 10.5, 8.4, 2.0 Hz 1H, min), 1.78–1.70 (m, 1H, min), 1.69–1.61 (m, 1H, maj), 1.60–1.54 (m, 3H, maj + 3H min), 1.31 (s, 3H, maj), 1.24 (s, 3H, min), 0.95–0.82 (m, 3H, maj + 3H, min). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, major isomer) δ 160.4 (C), 136.6 (C), 128.4 (2xCH), 127.9 (2xCH), 125.4 (CH), 100.0 (CH), 84.9 (C), 81.2 (CH_2), 66.8 (CH_2), 47.2 (C), 30.8 (CH_2), 24.1 (CH_2), 23.5 (CH_2), 15.7 (CH_3), 10.8 (CH_3). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{23}O_2$ 259.1693; Found 259.1710.

(1S,5R*,Z)-2-benzylidene-5-methyl-3-oxabicyclo[3.2.0]heptan-1-yl acetate **(6i)**:* following the general procedure B, using compound **4i** (25.8 mg, 0.1 mmol). Purification by flash column chromatography on silica gel (5 % EtOAc in Hexane) gave **6i** together with **5i** (2:1) (20.5 mg, 0.0794 mmol) as yellow oil in 79 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 7.1 Hz, 2H, min), 7.60 (d, *J* = 7.8 Hz, 2H, maj), 7.38–7.31 (m, 3H, min), 7.30–7.25 (m, 2H, maj), 7.13–7.08 (m, 1H, maj), 5.82 (s, 1H, min), 5.41 (s, 1H, maj), 4.31 (d, *J* = 8.1 Hz, 1H, maj), 4.19 (d, *J* = 8.1 Hz, 1H, maj), 3.87 (d, *J* = 10.9 Hz, 1H, min), 3.75 (d, *J* = 10.9 Hz, 1H, min), 2.55–2.46 (m, 1H, maj + 1H, min), 2.36–2.26 (m, 1H, maj + 1H, min), 2.05 (s, 3H, maj), 2.03 (s, 3H, min), 1.93–1.80 (m, 1H, maj + 1H, min), 1.73–1.66 (m, 1H, maj), 1.50–1.44 (m, 1H, min), 1.23 (s, 3H, maj + 3H, min). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 170.2 (C, min), 169.5 (C, maj), 161.2 (C, maj), 152.9 (C, min), 136.5 (C, maj), 135.4 (C, min), 128.8 (CH, min), 128.32 (2xCH, maj), 128.31 (2xCH, min), 127.9 (2xCH, maj), 125.4 (CH, maj), 125.3 (2xCH, min), 100.2 (CH, min), 98.5 (CH, maj), 84.1 (C, maj), 80.9 (CH_2, maj), 74.8 (C, min), 69.9 (CH_2, min), 48.1

(C, maj), 44.3 (C, min), 33.9 (CH_2, min), 30.0 (CH_2, maj), 24.6 (CH_2, maj), 21.8 (CH_3, min), 21.7 (CH_2, min), 21.3 (CH_3, maj), 17.1 (CH_3, min), 15.5 (CH_3, maj). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{19}O_3$ 259.1329; Found 259.1337.

(1S,5R*,Z)-1-methoxy-5-methyl-2-(4-(trifluoromethyl)benzylidene-3-oxabicyclo[3.2.0]heptane (**6j**):* following the general procedure B, using compound **4j** (29.8 mg, 0.1 mmol). Purification by flash column chromatography on silica gel (10 % EtOAc in Hexane) gave **6j** (21.8 mg, 0.07 mmol) as yellow oil in 73 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.1 Hz, 2H), 7.54 (d, *J* = 8.2 Hz, 2H), 5.50 (s, 1H), 4.28 (d, *J* = 9.0 Hz, 1H), 4.03 (d, *J* = 9.0 Hz, 1H), 3.23 (s, 3H), 2.34 (ap q, *J* = 10.7 Hz, 1H), 2.16 (ddd, *J* = 10.9, 7.7, 2.9 Hz, 1H), 1.69–1.58 (m, 2H), 1.34 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 161.9 (C), 140.1 (C), 127.8 (2xCH), 127.0 (q, *J* = 32.3 Hz, C), 125.2 (q, *J* = 3.8 Hz, 2xCH), 124.6 (q, *J* = 271.4 Hz, C), 99.0 (CH), 85.8 (C), 81.8 (CH_2), 53.0 (CH_3), 46.9 (C), 30.5 (CH_2), 24.1 (CH_2), 15.6 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{18}F_3O_2$ 299.1253; Found 299.1241.

(1S,5R*,Z)-2-(2-chlorobenzylidene)-1-methoxy-5-methyl-3-oxabicyclo[3.2.0]heptane (**6k**):* following the general procedure B, using compound **4k** (24.8 mg, 0.1 mmol). Purification by flash column chromatography on silica gel (2 % EtOAc in Hexane), followed by semipreparative TLC (Toluene) gave **6k** (21.4 mg, 0.08 mmol) as white solid in 81 % yield. M. p.: 68–70 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.35 (d, *J* = 7.9, 1H), 7.26–7.18 (m, 1H), 7.12–7.00 (m, 1H), 5.91 (s, 1H), 4.23 (d, *J* = 8.9 Hz, 1H), 3.98 (d, *J* = 8.9 Hz, 1H), 3.26 (s, 3H), 2.35 (ap q, *J* = 10.8 Hz, 1H), 2.20 (ddd, *J* = 10.9, 8.0, 2.7 Hz, 1H), 1.73–1.55 (m, 2H), 1.32 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 161.1 (C), 134.1 (C), 132.0 (C), 129.6 (CH), 129.4 (CH), 126.6 (CH), 126.5 (CH), 95.8 (CH), 85.7 (C), 81.5 (CH_2), 53.0 (CH_3), 46.9 (C), 30.6 (CH_2), 24.1 (CH_2), 15.6 (CH_3); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{18}ClO_2$ 265.0990; Found 265.0989.

Synthesis of (1S*,5R*,Z)-4-benzylidene-5-methoxy-1-methyl-3-oxabicyclo[3.2.0]heptan-2-one (17a): following the general procedure B, using compound **10a** (122.1 mg, 0.5 mmol). Purification by flash column chromatography on silica gel (5 % EtOAc in Hexane) gave **17a** together with **18a** (2:1) (120.9 mg, 0.5 mmol) as yellow oil in 99 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75–7.65 (m, 2H, maj + 2H, min), 7.46–7.33 (m, 2H, maj + 3H, min), 7.28–7.23 (m, 1H, maj), 5.86 (s, 1H, maj), 5.70 (s, 1H, min), 3.22 (s, 3H, maj), 3.16 (s, 3H, min), 2.61–2.47 (m, 1H, maj + 1H, min), 2.33 (ddd, *J* = 11.1, 8.1, 2.8 Hz, 1H, maj), 2.16 (ddd, *J* = 11.2, 8.3, 1.8 Hz, 1H, min), 2.09–1.94 (m, 1H, maj + 1H, min), 1.87 (ddd, *J* = 12.3, 10.7, 2.7, 1H, maj), 1.71 (ddd, *J* = 11.2, 9.5, 1.8 Hz, 1H, min), 1.59 (s, 3H, min), 1.45 (s, 3H, maj); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 176.8 (C, maj), 170.1 (C, min), 151.1 (C, min), 150.8 (C, maj), 133.3 (C, maj), 132.1 (C, min), 129.7 (CH, min), 129.0 (2xCH, maj), 128.62 (2xCH, min), 128.59 (2xCH, maj), 127.5 (CH, maj), 125.2 (2xCH, min), 107.0 (CH, maj), 101.9 (CH, min), 80.2 (C, maj), 74.8 (C, min), 52.1 (CH_3, maj), 52.0 (CH_3, min), 45.5 (C, min), 45.1 (C, maj), 33.8 (CH_2, min), 30.9 (CH_2, maj), 26.0 (CH_2, min), 25.2 (CH_2, maj), 15.5 (CH_3, min), 13.2 (CH_3, maj); HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{17}O_3$ 245.1172; Found 245.1161.

Synthesis of (1S*,5R*,E)-2-(iodo(phenyl)methylene)-1-methoxy-5-methyl-3-oxabicyclo[3.2.0]heptane (8a): a solution of compound **4a** (23.0 mg, 0.1 mmol) in DMF (0.1 M) was cooled at 0 ºC. Then, NIS (45.0 mg, 0.2 mmol) and JohnPhosAu(MeCN)SbF_6 (5 mol%, 3.9 mg, 0.005 mmol) were added and the reaction mixture was stirred 15 h at this temperature. The resulting mixture was filtered over a plug of Celite eluting with CH_2Cl_2 and solvents were removed under reduce pressure. The crude reaction mixture was purified by flash chromatography on silica gel (5% EtOAc in Hexane), followed by semipreparative TLC (Toluene) to give **8a** (21.4 mg, 0.06 mmol) as yellow oil in 60 % yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62–7.58 (m, 2H), 7.35–7.29 (m, 2H), 7.22–7.16 (m, 1H), 4.08 (d, *J* = 9.0 Hz, 1H), 3.84 (d, *J* = 9.0 Hz, 1H), 3.26 (s, 3H), 2.47 (ddd, *J* = 10.9, 7.1, 3.9 Hz, 1H), 2.31 (dt, *J* = 11.6, 10.6 Hz, 1H), 1.67–1.62 (m, 2H), 1.34 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 156.5 (C), 140.5 (C), 130.0 (2xCH), 128.0 (2xCH), 127.5 (CH), 86.8 (C), 80.3 (CH_2), 68.5 (C), 53.2 (CH_3), 48.3 (C), 29.6 (CH_2), 24.5 (CH_2), 16.0 (CH_3). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{18}IO_2$ 357.0346; Found 357.0343.

Synthesis of (1S*,5S*,E)-4-(iodo(phenyl)methylene)-5-methoxy-1-methyl-3-oxabicyclo[3.2.0]heptan-2-one (12a): a solution of compound **10a** (24.4 mg, 0.1 mmol) in DMF (0.1 M) was cooled at 0 ºC. Then, NIS (45.0 mg, 0.2 mmol) and JohnPhosAu(MeCN)SbF_6 (5 mol%, 3.9 mg, 0.005 mmol) were added and the reaction mixture was stirred 15 h at this temperature. The resulting mixture was filtered over a plug of Celite eluting with CH_2Cl_2 and solvents were removed under reduce pressure. The crude reaction mixture was purified by flash chromatography on silica gel (5% EtOAc in Hexane) gave **12a** along with **11a** (2.4:1) (37.1 mg, 0.1 mmol) as a white solid in 99 % yield. M. p.: 140–142 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62–7.57 (m, 2H, min), 7.56–7.51 (m, 2H, maj), 7.47–7.40 (m, 3H, min), 7.39–7.32 (m, 2H, maj), 7.31–7.23 (m, 1H, maj), 3.26 (s, 3H, maj), 3.20 (s, 3H, min), 2.79 (ddd, *J* = 12.2, 8.3, 3.0 Hz, 1H, maj), 2.65–2.39 (m, 1H, maj, + 1H, min), 2.28–2.11 (m, 2H, min), 2.07–1.95 (m, 1H, maj), 1.93–1.76 (m, 1H, maj + 1H, min), 1.69 (s, 3H, min), 1.47 (s, 3H, maj). ^{13}C{^{1}H} NMR (75 MHz, CDCl3) δ 175.4 (C, maj), 169.0 (C, min), 152.1 (C, min), 148.0 (C, maj), 138.5 (C, maj), 135.1 (C, min), 130.2 (CH, min), 129.7 (2xCH, maj), 129.6 (2xCH, min), 128.8 (CH, maj), 128.3 (2xCH, maj), 128.2 (2xCH, min), 84.9 (C, min), 81.9 (C, maj), 79.6 (C, min), 78.3 (C, maj), 52.6 (CH_3, maj), 52.1 (CH_3, min), 45.6 (C, maj), 44.8 (C, min), 36.3 (CH_2, min), 30.1 (CH_2, maj), 26.1 (CH_2, min), 25.1 (CH_2, maj), 16.9 (CH_3, min), 13.6 (CH_3, maj). HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{16}IO_3$ 371.0139; Found 371.0127.

ASSOCIATED CONTENT

Supporting Information

NMR spectra for all new compounds (PDF).

The Supporting Information is available free of charge on the ACS Publications website.

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