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Synthesis of Cyclohexene Derivatives from 1,5-Enynes *via* Gold-Catalysis and Iodocyclization: A Comparative Study and Applications in the Synthesis of 7/5- or 8/5-Fused Rings and Biaryls†

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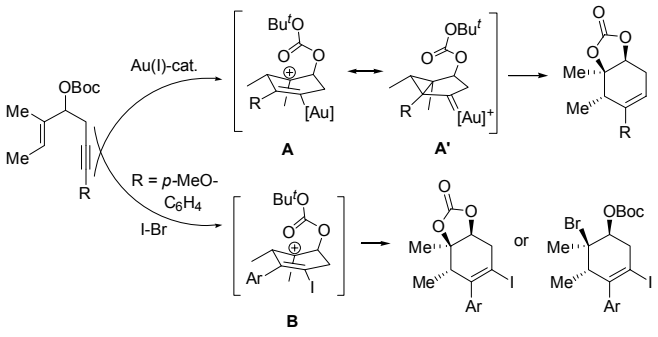
A comparative study on the Au(I)-catalyzed and IBr-promoted tandem cyclization of 1,5-enyne was reported. This study provides a meaningful mechanistic insight to the concerted nature of this tandem reaction and also provides interesting applications in the synthesis of 7/5- or 8/5-fused bicycles and biaryls.

Key Words: Gold catalysis, Iodocyclization, Tandem reaction, 1,5-Enyne, Carbocycles

Introduction

Tandem reactions are highly efficient means of enhancing synthetic efficiency in the synthesis of complex molecules.[1] Recent explosive developments in homogeneous gold catalysis is due to the ability of Au(I) or Au(III)-species to activate unsaturated π-bonds, where gold generates formal carbocationic intermediates and catalyze various tandem cyclizations.[2] We and others have recently reported Au(I)-catalyzed tandem cyclization, terminating with *t*-Boc trapping,[3] where the cationic vinyl gold species **A** is proposed to be stabilized by back-bonding interaction of gold as in **A'**. On the other hand, this stereochemical outcome can be emulated by iodine-induced cyclization of 1,5-enyne, where the metal back-bonding interaction is absent.[4] In the latter case, a concerted C-C and C-O bond formation can be invoked to rationalize the stereochemical outcome. However, in some cases, liberated bromide acts as a competing nucleophile, which stands contradictory to the concerted pathway (Scheme 1). Therefore, a comparative study on the Au-catalyzed cyclization and iodocyclization would give a meaningful insight as to tandem 1,5-enyne cyclization mechanism. In addition, we report herein two synthetic manipulations of the resulting cyclohexene derivatives that are potentially useful in the synthesis of natural products as well as biaryl ligands.

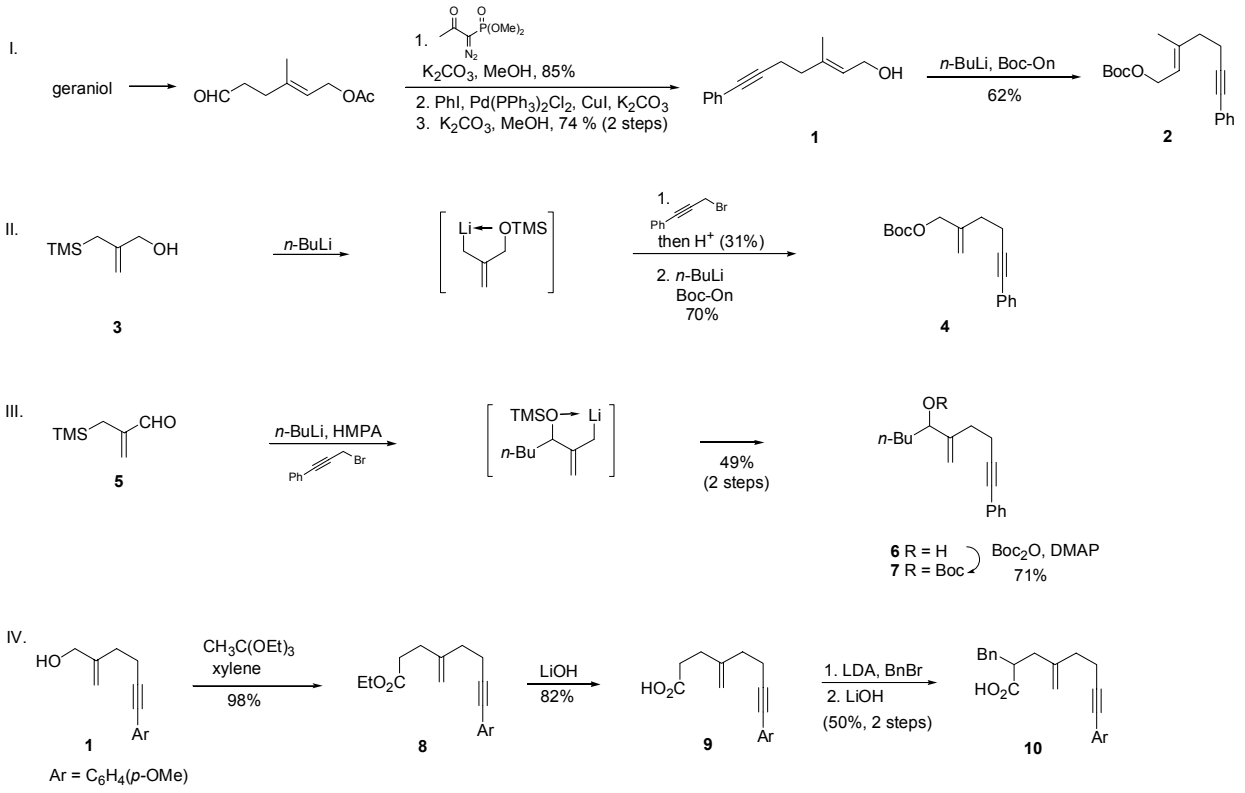


Scheme 1. Au(I)-catalyzed and iodonium-promoted tandem cyclization of 1,5-enyne

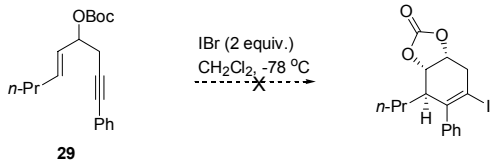
To expand the synthetic utility and also to provide a mechanistic insight as to the tandem cyclization, we prepared substrates having *t*-BocO trap elsewhere in the molecule rather than at C3 of 1,5-enyne. The synthesis of these substrates is depicted in Scheme 2. For example, the synthesis of substrate **2** started from a known aldehyde derived from geraniol,[5a] which was homologated by Bestmann reagent into the 1,5-enyne. Subsequent Sonogashira coupling followed by attaching *t*-Boc group on the resulting alcohol provided **2**. Treating 2-(trimethylsilylmethyl) prop-2-ene-1-ol **3** with *n*-BuLi induced silyl group transfer to form an allyl lithium species,[5b] which was reacted with a propargyl bromide derivative to form **4**. A similar sequence starting from aldehyde **5** led to a secondary alcohol **6** that was then converted into the carbonate **7**. We also planned to explore 1,5-enyne cyclization trapped with a carboxylic acid. For this purpose, 1,5-enyne alcohol **1** was first converted into the γ,δ-unsaturated acid **8**, which subsequently was alkylated and/or hydrolyzed to provide substrates **9** or **10**.

With these 1,5-enyne substrates in hand, we explored gold-catalyzed and iodonium-induced cyclizations. Previously, we have shown that the alkyne substituent has strong impact on the course of iodocyclization of 1,5-enyne. 1,5-Enynes having alkyne substituents such as H, TMS, Br, *o*-$NO_2C_6H_4$, and Me, induces monocyclization with alkene to form C-I and C-O bonds, while phenyl or electron-rich aryl ring at alkyne induces tandem cyclization with both alkene and alkyne, where C-I, C-C and C-O bonds form simultaneously.[4a] Therefore, all substrates in this comparitive study utilized aryl substituted alkynes. In Au(I)-catalyzed reaction, substrates **2** and **4** with a primary *O*-Boc group and the carboxylic acid **9'** (Ph derivative of **9**) underwent a smooth tandem cyclization into the respective carbonates or lactones, **11**, **12**, and **13**. Electron-density on the aryl substituted alkyne did not affect the course of the cyclization and both **14** and **16** reacted with more or less similar efficiency and diastereoselectivity (entries 4 and 5).

†This paper is dedicated to Professor Sunggak Kim on the occasion of his honorable retirement.



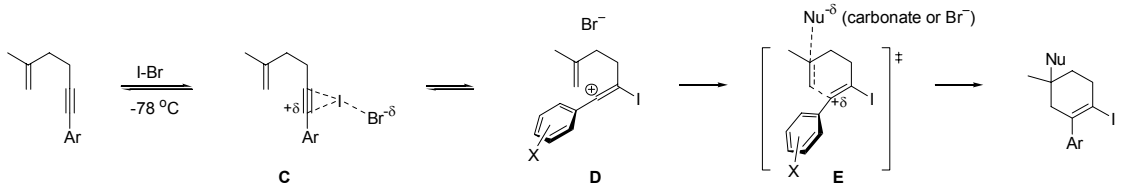
Scheme 2. Synthesis of substrates **2**, **4**, **7**, **9**, and **10**



Scheme 3. Failed cyclization of substrate **29**

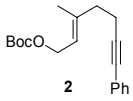
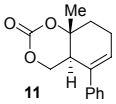
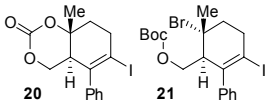
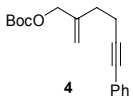
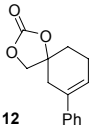
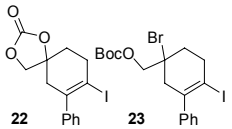
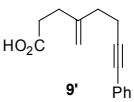
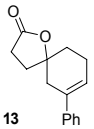
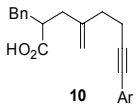
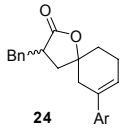
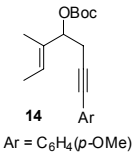
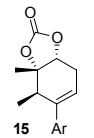
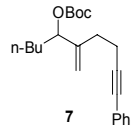
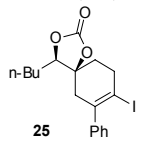
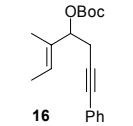
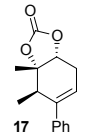
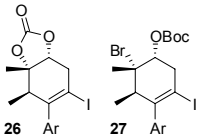
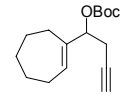
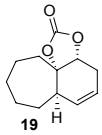
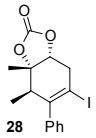
In contrast, IBr-promoted reaction of substrate **2** and **4** led to a mixture of products arising from *O*-Boc trapping (**20** and **22**) as well as bromide trapping (**21** and **23**) in about 1:2 ratio (entries 7 and 8). IBr-promoted cyclization of **9** led to a low yield of desired product from a messy reaction (not shown). Therefore, α-substituted **10**, aided by Thorp-Ingold effect, was expected to result in a more efficient cation-trapping by carboxylic acid. As expected, the cyclization of **10** led to isolation of the product **24** in 56% yield and none of the iodobromination product was observed in the reaction mixture. Similarly, secondary *O*-Boc group also efficiently trapped the forming carbocation and **25** was obtained as a sole product in 64% yield. A competing iodobromination product can also be observed in the reaction of **14**. While Au(I)-catalyzed cyclization led to a smooth formation of **15**, IBr-promoted cyclization led to a mixture of **26** and **27** (entries 4 and 11). Interestingly, when there is less electron-density on the aryl ring, the formation of iodobromination product is minimized (entry 12). Also in this iodocyclization, presence of cation-stabilizing substituent at the olefin in the starting substrate was crucial for the successful cyclization. For example, substrate **29** (Scheme 3) failed to cyclize under the standard condition.

The above results in Table 1 shows a surprisingly high diastereoselectivity that could not be fully answered only on the basis of stereoelectronic arguments. We interpreted these results on the basis of the mechanistic model shown in Scheme 4. It is well known that coordination of aryl-substituted alkyne with iodonium reagents results in formation of the open vinyl cation **D** that has linear coordination geometry.[6] The stability of this open vinyl cation **D** relative to the cyclic complex **C** correlates well with the electron-donating ability of alkynyl substituent, both computationally and experimentally. Thus the presence of C_6H_4(*p*-OMe) at Ar position (entry 11, Table 1) seem to increase the lifetime of **D**, and a fully dissociated bromide ion develops in the mixture and competes with the intramolecular carbonate as a cation-trapping nucleophile. This is also true when the intra-



Scheme 4. Mechanistic model for the iodocyclization

Table 1. Gold-catalyzed and iodonium-promoted cyclization of 1,5-enyne

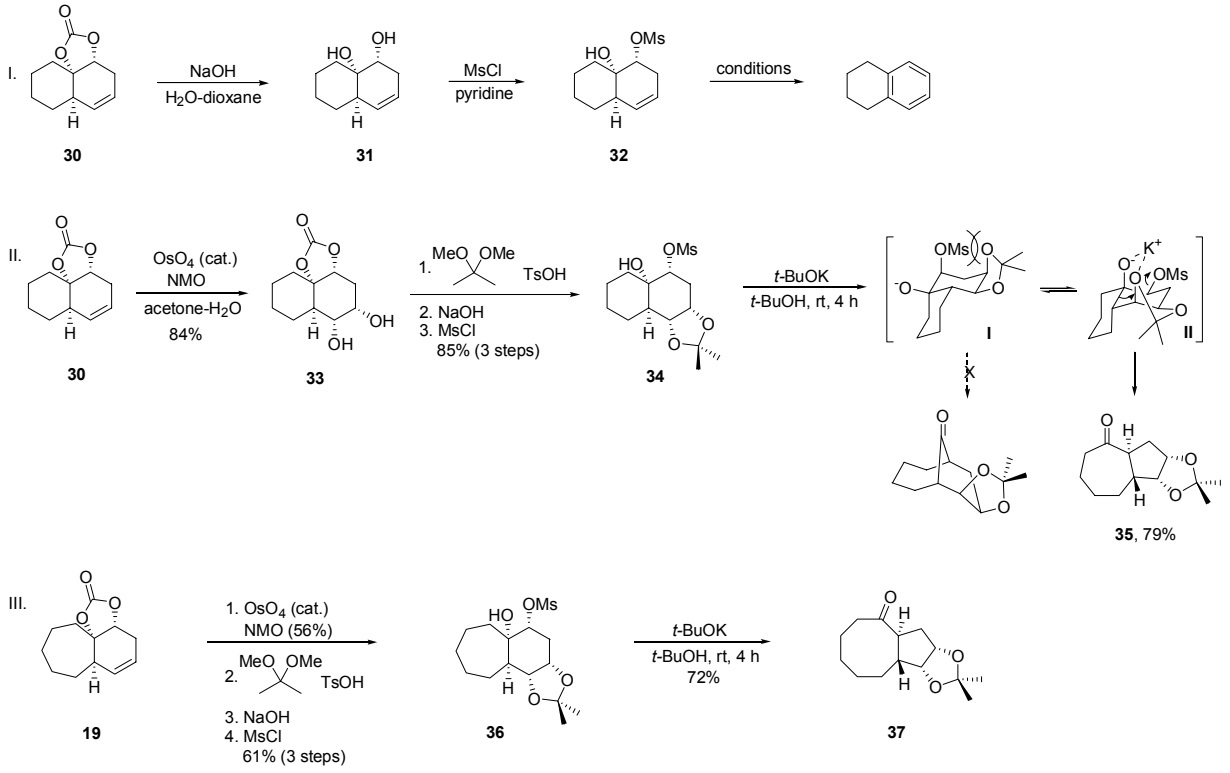
entry	substrate	cond[a]	product[b]	entry	substrate	cond[a]	product[b]
1	 **2**	A	 **11** 58%	7[e]	**2**	B	 **20** 30%[c] **21** 60%
2	 **4**	A	 **12** 91%	8[e]	**4**	B	 **22** 39% **23** 58%
3	 **9'**	A	 **13** 85%	9[e]	 **10**	B	 **24** Ar = C_6H_4(*p*-OMe) 56% (3:1)
4	 **14** Ar = C_6H_4(*p*-OMe)	A	 **15** 88%	10[e]	 **7**	B	 **25** 64%[c]
5[d]	 **16**	A	 **17** 73% (10:1)	11[e]	**14**	B	 **26** 29% **27** 60%
6	 **18**	A	 **19** 76%	12	**16**	B	 **28** 64%

[a]Condition A: Au[*t*-Bu_2P(*o*-biphenyl)]SbF_6 (2 mol %) in DCE at rt; Condition B: IBr (2.0 equiv.) in CH_2Cl_2 at −78 °C. [b]Isolated yield after chromatography; A single diastereomer unless diastereomeric ratio was noted in parenthesis. [c]NOE experiments supports this stereochemical assignment. [d]ref. 3a. [e]ref. 4a.

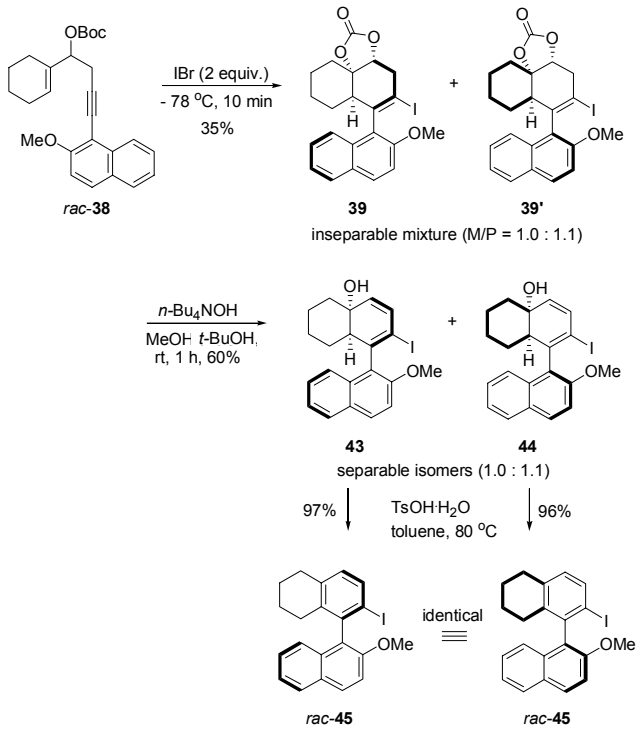
molecular *t*-Boc carbonate is placed at the less effective position for nuclepophilic trapping (entries 7 and 8). The following concerted transition state (**E**) for the C-C and C-Br bond formations explains the high diastereoselectivity observed. On the other hand, when the Ar group is less donating (such as with Ph) or when the more effective intramolecular nucleophilic attack becomes feasible (entries 9, 10 and 12, Table 1), the open vinyl cation **C** is less fully developed and the nucleophilic attack seems to be concerted with the vinyl cation formation as well as nucleophilic trapping.

We next examined the synthetic utility of the cyclohexene products obtained in the gold-catalyzed and iodonium-promoted tandem cyclization (Scheme 5). 7,5-Fused carbocycles are abundantly found in guainane family of natural products and we inspected the ring expansion of our cyclohexane-1,2-diol derivatives **30**.[3a] First, the carbonate **30** was deprotected with base, and was treated with methanesulfonyl chloride to get **32** which was selectively mesylated on the secondary alcohol. We examined a variety of conditions for the proposed ring expansion chemistry. However, after extensive trials, we failed to get the desired 7,5-fused ring and instead we obtained tetrahydronaphthalene as a major side reaction product. Having noted the presence of endocyclic double bond led to a facilitation of the undesired elimination, we then converted the olefin into a diol **33** *via* osmium catalyzed dihydroxylation. Protection of newly formed secondary 1,2-diol, followed by hydrolysis of carbonate and mesylation of the resulting alcohol led to **34** in 85% yield (over 3 steps). After some screening of reaction conditions (base, solvent and temperature), we found that treatment of **34** with potassium *t*-butoxide at room temperature led to a clean formation of the desired 7,5-trans-fused carbocycle **35** in gratifying 79% yield. A selective formation of 7,5-fused rings instead of [4,3,1]-bicyclodecane ring could be explained by the chelation model in a conformer **II**, while conformer **I** suffers a severe 1,3-diaxial interaction. Similar sequence of reactions also led to a 8,5-fused ring **37** in 72 % yield, starting from **19** that was synthesized *via* gold-catalyzed tandem cyclization (entry 6, Table 1).

We next explored the synthetic application of the iodocycliza-



Scheme 5. Synthesis of 7,5- and 8,5-fused carbocycles



Scheme 6. Synthesis of atropisomeric biaryls and their transformations

tion product. When the 1,5-enyne **38** bearing a bulky 2-methoxy-1-naphthyl group reacted with IBr, an inseparable mixture of isomeric products formed (ratio = 1.0:1.1) in 35% yield. We assigned this isomeric mixture as atrop-diastereomeric pair **39**/**39'** (Scheme 6). At this point, however, the structural identity

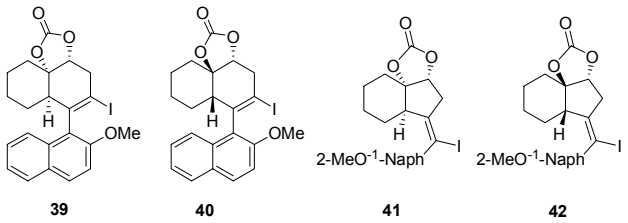


Figure 1. Possible structures for the isomeric products from the tandem iodocyclization of **38**.

of this mixture was uncertain and several possible isomeric forms could also account for the observed spectra (Figure 1).

To confirm the identity of this mixture and to explore the synthetic application of the product, we converted the mixture **39**/**39'** into the alcohol **43**/**44** *via* deprotection of carbonate and base-promoted elimination. From this, two isomers **43** and **44** were obtained that were separable by silica gel chromatography (1.0:1.1 ratio), which eliminate the possibility of **39**/**40** or **41**/**42** pair for original isomers **39**/**39'**. The product **43** and **44** was then separately dehydrated to form an aromatized product **45**. In this sequence, both products from **43** and **44** had identical spectra and chromatographic property, which confirms that the original inseparable isomers (**39**/**39'**) were not **39**/**41** (or **39**/**42**), but an atropisomeric mixture having structures **39**/**39'** shown in Scheme 6. This atropisomerism in **39**/**39'** probably results from a restricted rotation around the axis connecting biaryls due to steric hindrance between the methoxy and the iodo group. In principle, upon the availability of a single enantiomer of **38**, both forms of enantiopure tetrahydrobinaphthyl iodide **45** would be available from one enantiomer of **38** and these products should

be potential precursors of modified MOP ligand.[7]

In summary, we reported herein the comparative study of 1,5-enyne cyclization terminating with *t*-Boc trapping, under the Au(I)-catalysis and IBr. From this study evolved a mechanistic model that successfully accounts for the observed high diastereoselectivity in both cyclization protocols. In addition, potential applications of the resulting products were explored and we have shown that these methods are effective for the synthesis of 7,5-*trans*-fused bicycle as well as atropisomeric biaryl compounds.

Experimental

Anhydrous dichloromethane and 1,2-dichloroethane (reagent grade) was purified by distillation over calcium hydride. Anhydrous THF was distilled over sodium-benzophenone ketyl. All commercially available reagents were used without further purification. Flash column chromatography was performed on Kieselgel 60 (230 - 400 mesh) and TLC analysis was carried out on Merck silica gel 60 F_{254} plates. ^{1}H and ^{13}C NMR spectra were recorded on a Varian (^{1}H at 400 MHz) spectrometer with TMS as an internal standard. 2D-NMR experiments were conducted on Varian (600 MHz) at Seoul National University. Elemental analyses and HRMS experiments were conducted at Sogang University, Korea Basic Science Institute, and Seoul National University.

Synthesis of substrates.

***(E)-tert*-Butyl 3-methyl-7-phenylhept-2-en-6-ynyl carbonate (2):** To a solution of aldehyde[5a] (470 mg, 2.76 mmol) in MeOH (10 mL) at 0 °C was added Bestmann reagent (795.7 mg, 4.14 mmol) and K_2CO_3 (762 mg, 5.52 mmol). The mixture was slowly warmed to rt over 2 h while stirring. The solvent was removed under vacuum and the residue was purified by chromatography (EtOAc:Hex = 1:3) to get 390 mg (85%) of the corresponding alkyne as a colorless oil; A solution of this alkyne (200 mg, 1.20 mmol), iodobenzene (368 mg, 1.80 mmol), CuI (9.2 mg, 0.048 mmol), $Pd(PPh_3)_2Cl_2$ (16.8 mg, 0.024 mmol) and K_2CO_3 (664 mg, 4.81 mmol) in THF (10 mL) was stirred at rt for 6 h. The solvent was removed and the crude oil of acetate was dissolved in MeOH (10 mL), then treated with K_2CO_3 (249.4 mg, 1.80 mmol) at rt. The mixture was stirred at rt for 4 h and was filtered through a Celite pad (3 cm), eluting with ether. The solvent was removed and the residue was purified by chromatography (EtOAc:Hex = 1:4) to give deprotected alcohol **1** (180.6 mg, 74%). The alcohol **1** (180.6 mg, 0.902 mmol) was dissolved in ether (2 mL) and was treated with *n*-BuLi (0.620 mL of 1.6 M solution in hexane) at −78 °C. After stirring for 30 min, the resulting lithium alkoxide solution was transferred to a solution of 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrine (Boc-On) (244.3 mg, 0.992 mmol) in THF (1.0 mL) at 0 °C. The resulting mixture was allowed to stir at rt overnight. The reaction was quenched by addition of aqueous saturated NH_4Cl (3 mL) and the aqueous layer was extracted with ether (3 mL × 3). The combined organic extracts were dried, evaporated and the residue was purified by chromatography (EtOAc:Hex = 1:12) to give 167 mg (62%) of **2** as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.35 (m, 2H), 7.31-7.24 (m, 3H), 5.48 (t, J = 5.9 Hz, H), 4.61 (d, J = 6.9 Hz, 2H), 2.53 (t, J = 7.3 Hz, 2H), 2.34 (t, J = 7.3 Hz, 2H), 1.76 (s, 3H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 141.4, 132.2, 128.8, 128.2, 124.4, 120.0, 90.0, 82.6, 81.8, 64.2, 39.0, 28.4, 18.8, 17.1.

***tert*-Butyl 2-methylene-6-phenylhex-5-ynyl carbonate (4):** To a solution of 2-($TMSCH_2$)prop-2-ene-1-ol **3**[5c] (288.6 mg, 2.00 mmol) in THF (3 mL) at 0 °C was added *n*-BuLi (1.25 mL of 1.6 M solution, 2.00 mmol). After 30 min at 0 °C, the color changes from pale yellow to orange. To the mixture was added 1-(3-bromo-1-propynyl)benzene (975.3 mg, 5.00 mmol) in THF (8 mL) at 0 °C and then the resulting dark brown solution was treated with 2 mL of HMPA. The mixture was allowed to stir overnight at rt. The reaction was quenched by addition of 0.5 N HCl (10 mL) and stirring at rt for 1 h. The aqueous layer was extracted with ether (10 mL × 4). After drying ($MgSO_4$) and evaporation of solvent, the residue was purified by chromatography (EtOAc:Hex = 1:4) to get 114.0 mg (31%) of the alcohol as a colorless oil. The *O*-Boc group was introduced following a similar procedure for **2** to give **4** (70% yield, a colorless oil). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.35 (m, 2H), 7.29-7.24 (m, 3H), 5.16 (s, H), 5.08 (s, H), 4.57 (s, 2H), 2.58 (t, J = 7.4 Hz, 2H), 2.40 (t, J = 7.3 Hz, 2H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 142.7, 132.2, 128.8, 128.3, 124.4, 114.7, 89.8, 82.8, 81.9, 69.8, 32.8, 28.4, 18.8.

***tert*-Butyl 6-methylene-10-phenyldec-9-yn-5-yl carbonate (7):** To a solution of **3** (288 mg, 2.00 mmol) in ether (20 mL) was treated with MnO_2 (0.870 g, 10.0 mmol) at rt. After 10 h, the mixture was filtered through Celite pad and rinsed with ether. The solvent was removed by simple distillation apparatus under atmospheric pressure (bath temperature, 70 °C). The residue was re-dissolved in THF (10 mL) and *n*-BuLi (1.50 mL of 1.6 M soln, 2.40 mmol) was added to the mixture at −78 °C. After 30 min, it was treated with a solution of 1-(3-bromo-1-propynyl)benzene (1.17 g, 6.00 mmol) in THF/HMPA (10 mL/1.4 mL) dropwise at −78 °C. The mixture was warmed to rt over 20 min and quenched with 0.5 N HCl (20 mL). The aqueous layer was extracted with ether (20 mL × 3) and the combined organic layers were dried ($MgSO_4$), evaporated and the residue was purified by chromatography (EtOAc/Hex = 1:8) to give 198.3 mg (49%, over 2 steps) of **6** as pale yellow oil. The *O*-Boc group was introduced following a similar procedure for **2** to give **7** (71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.35 (m, 2H), 7.29-7.24 (m, 3H), 5.14 (s, H), 5.02 (s, H), 4.97 (t, J = 6.6 Hz, H), 2.62-2.55 (m, 2H), 2.37 (q, J = 6.6 Hz, 2H), 1.74-1.60 (m, 2H), 1.47 (s, 9H), 1.38-1.25 (m, 4H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 146.5, 132.2, 128.8, 128.2, 124.5, 113.1, 90.1, 82.5, 81.6, 80.7, 33.6, 31.4, 28.5, 28.3, 23.1, 18.8, 14.6.

8-Aryl-2-benzyl-4-methyleneoct-7-ynoic acid (10): The solution of **1** (330 mg, 1.53 mmol), triethyl orthoacetate (1.67 mL, 9.16 mmol) and propionic acid (5.6 mg, 0.076 mmol) in xylene (50 mL) was heated under reflux (bath temp, 135 °C). After 6.5 h, the mixture was washed with saturated $NaHCO_3$ (5 mL) and was evaporated to dryness. The residue was purified by chromatography (EtOAc:Hex = 1:6) to give **8** (428.2 mg, 98%) as an oil. To a solution of the ethyl ester **8** (57.3 mg, 0.200 mmol) dissolved in THF (3 mL) at −78 °C, was added dropwise LiHMDS (0.150 mL of 1.6 M soln, 0.240 mmol). After 30 min at −78 °C, benzyl bromide (30.9 μL, 0.260 mmol) was added. The mixture was slowly warmed to rt over 2 h. Purification by chromatography (EtOAc:Hex = 1:4) gave 37.3 mg (50%) of α-

benzylated ester. This ethyl ester (37.3 mg, 0.099 mmol) was hydrolyzed in THF/MeOH/water (1:1:1, 1 mL) using $LiOH·H_2O$ (4.6 mg, 0.11 mmol). After 1 h, the mixture was filtered through a short silica gel, rinsing with EtOAc. The solvent was removed and the residue was purified by chromatography (EtOAc:Hex = 1/2, 3% MeOH) to give 25.5 mg (74%) of **10**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7. 34-7.15 (m, 7H), 6.79 (d, J = 8.4 Hz, 2H), 4.91 (s, H), 4.89 (s, H), 3.78 (s, 3H), 3.02-2.86 (m, 2H), 2.85-2.76 (m, H), 2.58-2.40 (m, 3H), 2.38-2.22 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.4, 159.7, 145.3, 139.4, 133.5, 129.5, 129.1, 127.2, 116.6, 114.4, 113.1, 88.4, 81.4, 55.9, 46.6, 38.9, 38.6, 35.5, 18.8.

A representative procedure for Au(I)-catalyzed cyclization (12). To a solution of Au[*t*-Bu_2P(*o*-biphenyl)]Cl (3.1 mg, 0.0059 mmol) and $AgSbF_6$ (2.0 mg, 0.0059 mmol) in 1,2-dichloroethane (0.5 mL) at room temperature, was added a solution of enyne **4** (68.2 mg, 0.238 mmol) in 1,2-dichloroethane (0.6 mL). After stirring the mixture for 20 min, the reaction was quenched by the addition of triethylamine (~20 mg). Solvent was removed under vacuum and the residue was purified by flash chromatography (EtOAc:Hex = 1:9) to get **12** (49.9 mg, 91%) as off-white solid.

(11): A white solid (mp 129 - 131 °C); IR (NaCl) 2940, 2836, 1750, 1500, 1403, 1300, 1196, 1133, 1092 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.29 (m, 3H), 7.20-7.12 (m, 2H), 5.85-5.72 (m, H), 4.45 (dd, J = 5.9, 11.0 Hz, H), 3.97 (dd, J = 11.0, 13.2 Hz, H), 3.44-3.30 (m, H), 2.62-2.47 (m, H), 2.43-2.25 (m, H), 2.12-1.94 (m, 2H), 1.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140, 149.6, 139.3, 135.0, 129.2, 128.4, 128.0, 127.5, 81.2, 69.6, 40.7, 34.5, 24.9, 19.0; Anal Calcd for $C_{15}H_{16}O_3$: C 73.75, H 6.60; found: C 73.71, H 6.45.

(12): A white solid (mp 129 - 131 °C); IR (NaCl) 2933, 2843, 1791, 1438, 1383, 1182, 1064 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.31 (m, 4H), 7.30-7.24 (m, H), 6.20-6.12 (m, H), 4.24 (ABq, J = 8.4 Hz, 2H), 2.89 (ABq, J = 17.3 Hz, H), 2.72 (ABq, J = 17.3 Hz, H), 2.66-2.48 (m, H), 2.47-2.27 (m, H), 2.14 (td, J = 6.6, 12.8 Hz, H), 1.92 (td, J = 5.9, 12.5 Hz, H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.9, 133.3, 129.1, 128.1, 125.7, 124.1, 82.8, 74.9, 38.0, 31.2, 23.4; Anal Calcd for $C_{14}H_{14}O_3$: C 73.03, H 6.13; found: C 73.02, H 6.23.

(13): A colorless solid (mp 89 - 91 °C); IR (NaCl) 3033, 2913, 1770, 1493, 1445, 1230, 1175, 1064 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.29 (m, 4H), 7.28-7.20 (m, H), 6.20-6.08 (m, H), 2.86-2.74 (m, H), 2.74-2.62 (m, 3H), 2.58-2.46 (m, H), 2.45-2.28 (m, H), 2.13 (dt, J = 1.8, 8.4 Hz, 2H), 2.03 (td, J = 6.6, 12.8 Hz, H) 1.79 (td, J = 6.3, 12.9 Hz, H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 134.1, 129.0, 127.8, 125.6, 124.2, 85.6, 39.5, 33.0, 32.8, 29.2, 24.1; Anal Calcd for $C_{15}H_{16}O_2$: C 78.92, H 7.06; found: C 78.91, H 6.95.

(15): Pale yellow solid (mp 95 - 96 °C); IR (NaCl) 2982, 2926, 2850, 1784, 1597, 1514, 1459, 1355, 1251, 1113, 1043; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 5.94 (d, J = 5.1 Hz, H), 4.63 (d, J = 4.1 Hz, H), 3.81 (s, 3H), 3.09 (q, J = 7.4 Hz, H), 2.67 (dd, J = 7.0, 17.2 Hz, H), 2.52 (d br, J = 17.6 Hz, H), 1.64 (s, 3H), 1.09 (d, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 155.0, 144.1, 133.1, 127.4, 117.3, 114.5, 86.6, 81.1, 55.9, 41.1, 28.8, 25.5, 14.1; Anal Calcd for $C_{16}H_{18}O_4$: C 70.06, H 6.61; found: C 70.12, H 6.64.

(19): A colorless solid (mp 65-67 °C); IR (NaCl) 2926, 2850, 1791, 1445, 1362, 1237, 1189, 1036 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00-5.89 (m, H), 5.82-5.70 (m, H), 4.44 (t, J = 4.0 Hz, H), 2.63 (t, J = 7.0 Hz, H), 2.45 (td, J = 3.6, 16.9 Hz, H), 2.37 (d, J = 16.9 Hz, H), 2.16 (dd, J = 8.8, 15.0 Hz, H), 1.92-1,76 (m, 3H), 1.76-1.62 (m, 3H), 1.56-1.45 (m, 2H), 1.39-1.30 (m, H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 133.5, 122.5, 88.7, 82.8, 44.0, 40.3, 30.4, 29.8, 29.0, 27.0, 22.6; Anal Calcd for $C_{12}H_{16}O_3$: C 69.21, H 7.74; found: C 69.10, H 7.83.

A representative procedure for IBr-promoted cyclization (20/21). To a solution of **2** (60.0 mg, 0.200 mmol) in dichloromethane (1.0 mL) at −78 °C was added dropwise a solution of IBr (82.7 mg, 0.400 mmol) in dichloromethane (1.0 mL). The mixture was kept stirred at −78 °C for 20 min, then aqueous saturated $Na_2S_2O_3$ (4 mL) was added at once. The mixture was allowed to warm to room temperature with stirring. Layers were separated and the aqueous layer was extracted with dichloromethane (4 mL × 3). The combined organic layers were dried ($MgSO_4$), evaporated, and the residue was purified by silica gel chromatography (EtOAc:Hex = 1:6) to yield 22.1 mg of **20** (30%) along with 60.8 mg of **21** (60 %).

(20): A white solid (mp 138 - 140 °C); IR (NaCl) 2916, 2845, 1748, 1393, 1190, 1100 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46-7.36 (m, 3H), 7.08 (d, J = 7.3 Hz, H), 7.00-6.95 (m, H), 4.10 (dd, J = 11.1, 13.2 Hz, H), 3.87 (dd, J = 6.0, 11.0 Hz, H), 3.28-3.19 (m, H), 3.09 (dd, J = 7.2, 18.9 Hz, H), 2.96-2.84 (m, H), 2.27-2.18 (m, H), 1.97 (dd, J = 6.9, 12.6 Hz, H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 141.3, 139.3, 129.7, 129.3, 129.1, 129.0, 127.6, 101.4, 79.7, 69.4, 43.5, 40.1, 37.6, 19.2; HRMS-ES: *m/z* calculated for $C_{15}H_{15}IO_3Na$ $[M+Na]^+$: 392.9964, found 392.9959. (Structure was based on COSY and 1D-NOE spectra. The selected NOE contacts as well as vicinal $J_{1,2}$ constants of OCH_2 protons (H_a: J = 13.6 Hz, H_e: J = 5.9 Hz) supports trans-ring junction.)

(21): A pale yellow liquid; IR (NaCl) 2978, 2926, 1743, 1450, 1365, 1270, 1246, 1161, 1104 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.42-7.30 (m, 3H), 7.16 (d, J = 6.6 Hz, 2H), 4.00 (d, J = 4.0 Hz, 2H), 3.24 (s br, H), 3.14-3.02 (m, H), 2.92 (dd, J = 6.2, 18.3 Hz, H), 2.22-2.10 (m, H), 2.02-1.96 (m, H), 1.96 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 145.4, 141.3, 129.1, 128.9, 128.3, 102.2, 83.1, 68.0, 65.0, 56.4, 41.0, 39.2, 32.5, 28.4; LRMS (CI+) calcd for $C_{19}H_{24}{}^{79}BrIO_3$ $[M^+]$ 506, found 451(1) $[M^+$+H-C_4H_8,^{79}Br], 453(1) $[M^+$+H-C_4H_8,^{81}Br], 389(14) $[M^+$-BocO,^{79}Br], 391(15) $[M^+$-BocO,^{81}Br], 371(67) $[M^+$-C_4H_8-Br], 309(100) $[M^+$-BocOH-Br].

(22): A pale yellow solid (mp 113 - 114 °C) IR (NaCl): 2926, 2850, 1790, 1492, 1436, 1388, 1232, 1175, 1062 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.42-7.30 (m, 3H), 7.16-7.12 (m, 2H), 4.27 (d of AB q, J = 8.8 Hz, H), 4.20 (d of AB q, J = 8.5 Hz, H), 3.15-3.04 (m, H), 2.96-2.82 (m, 2H), 2.76-2.67 (m, H), 2.18-2.10 (m, H), 2.05-1.96 (m, H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 145.1, 139.9, 129.2, 128.5, 128.4, 97.1, 81.5, 74.6, 43.3, 38.3, 34.2; Anal Calcd for $C_{14}H_{13}IO_3$: C 47.21, H 3.68; found: C 47.21, H 3.84.

(23): A pale yellow liquid; IR (NaCl) 2973, 2921, 2850, 1738, 1369, 1275, 1256, 1161 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.40-7.28 (m, 3H), 7.17-7.12 (m, 2H), 4.36 (ABq, J = 11.4, 14.9 Hz, 2H), 3.18-3.02 (m, 2H), 3.00-2.95 (m, 2H), 2.16-2.06 (m, H), 2.04-1.96 (m, H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 153.6, 145.9, 140.6, 129.0, 128.5, 128.2, 96.9, 83.5, 74.1, 63.6, 45.6, 40.0, 36.2, 28.4; LRMS (CI+) calcd for $C_{18}H_{22}{}^{79}BrIO_3$ [M^++H] 493, found 493(2) [M^++H,^{79}Br], 495(2) [M^++H,^{81}Br], 375(64) [M^+-BocO,^{79}Br], 377(59) [M^+-BocO,^{81}Br], 357(46) [M^+-Br-C_4H_8], 295(100) [M^+-Br-BocOH].

(24): (obtained as an inseparable 3:1 mixture of diastereomers): A pale yellow solid; IR (NaCl) 2926, 2845, 1771, 1606, 1511, 1454, 1242, 1180, 1038 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.36-7.28 (m, 2H), 7.25-7.16 (m, 3H), 7.07-7.02 (m, 2H), and 6.91-6.85 (m, 2H) for aromatic protons (major and minor), 3.81 and 3.80 (s, 3H, 3:1 ratio) for -OMe of major and minor, 3.29 (dd, J = 4.4, 14.0 Hz, H), 3.15-3.04 (m, H), 3.04-2.92 (m, H), 2.85-2.76 (m, 2H), 2.59-2.49 (m, 2H), 2.23-2.15 (m, H), 1.96-1.86 (m, H), 1,85-1.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 159.5, 140.4, 139.0, 138.2, 129.7/129.6, 129.5, 129.4, 127.5, 114.3/114.2, 97.4, 82.3/82.2, 55.8, 46.0, 42.4, 39.2, 39.0, 37.3/37.2, 35.0 (underlined peaks are from the minor isomer); HRMS-ES: *m/z* calculated for $C_{23}H_{23}IO_3Na$ [M+Na]$^+$: 497.0590, found 497.0591.

(25): A white solid (mp 65 - 67 °C); IR (NaCl) 2959, 2940, 2865, 1795, 1360, 1275, 1185 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.30 (m, 3H), 7.18-7.13 (m, 2H), 4.24 (dd, J = 2.6, 10.3 Hz, H), 3.10-3.00 (m, H), 2.99-2.89 (m, H), 2.76-2.62 (s br, 2H), 2.05-1.96 (m, H), 1.94-1.86 (m, H), 1.83-1.72 (m, H), 1.62-1.55 (m, 2H), 1.46-1.36 (m, 3H), 0.92 (t, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.4, 145.2, 139.7, 129.1, 128.48, 128.46, 97.5, 85.3, 83.7, 43.0, 37.7, 29.3, 28.9, 28.8, 23.0, 14.4; Anal Calcd for $C_{18}H_{21}IO_3$: C 52.44, H 5.13; found: C 52.42, H 5.69. Structure was based on COSY and 1D-NOE spectra. The selected NOE contact for CHO proton (δ 4.24, dd) and isolated methylene (δ 2.69, m) indicates the relative stereochemistry shown below.

(26): A white solid (mp 105 - 107 °C); IR (NaCl) 2916, 2850, 1790, 1601, 1511, 1350, 1246, 1057 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 4.55 (t, J = 3.7 Hz, H), 3.82 (s, 3H), 3.24-3.16 (m, 2H), 2.95 (q, J = 7.3 Hz, H), 1.58 (s, 3H), 1.07 (d, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 154.6, 149.6, 136.7, 130.0, 129.8, 114.4, 89.0, 86.0, 81.9, 55.9, 46.3, 43.8, 25.0, 13.4; HRMS-ES: *m/z* calculated for $C_{16}H_{17}IO_4Na$ [M+Na]$^+$: 423.0069, found 423.0068.

(27): A pale yellow liquid; IR (NaCl) 2916, 2930, 1743, 1601, 1506, 1365, 1279, 1242, 1156 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.16 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 5.49 (dd, J = 3.3, 7.7 Hz, H), 4.03 (q, J = 6.9 Hz, H), 3.82 (s, 3H), 3.37 (dd, J = 7.7, 17.3 Hz, H), 2.77 (dd, J = 3.3, 17.2 Hz, H), 1.70 (d, J = 7.0 Hz, 3H), 1.51 (s, 9H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 153.6, 152.8, 131.2, 129.5, 114.3, 95.2, 83.1, 78.3, 60.4, 57.4, 55.8, 50.7, 28.4, 21.8, 18.7; LRMS (CI+) calcd for $C_{20}H_{26}{}^{79}BrIO_4$ [M^++H] 537, found 537 (22) [M^++H,^{79}Br], 539 (22) [M^++H,^{81}Br], 481(26) [M^++H-C_4H_8,^{79}Br], 483(24) [M^++H-C_4H_8,^{81}Br], 419(52) [M^+-BocO,^{79}Br], 421(51) [M^+-BocO,^{81}Br], 401(100) [M^+-Br-C_4H_8,^{79}Br].

(28): A white solid (mp 137 - 139 °C); IR (NaCl) 2982, 2921, 1795, 1440, 1350, 1208, 1057 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.45-7.30 (m, 3H), 7.22-7.14 (m, 2H), 4.56 (t, J = 3.6 Hz, H), 3.30-3.14 (m, 2H), 2.98 (q, J = 7.4 Hz, H), 1.58 (s, 3H), 1.09 (d, J = 7.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 150.1, 144.4, 129.1, 128.5, 128.4, 89.1, 85.9, 81.8, 46.1, 43.8, 25.0, 13.4; HRMS-ES: *m/z* calculated for $C_{15}H_{15}IO_3Na$ [M+Na]$^+$: 392.9964, found 392.9963.

Ring expansion and the formation of 7,5-fused bicycle (35). A solution of *t*-BuOK (1.0 M solution in *t*-BuOH) was added to a magnetically stirred solution of the monomesylate **34** (15 mg, 0.0468 mmol) in *t*-BuOH at rt. The reaction mixture was stirred at rt for 14h and then diluted with water. The product was extracted with ether. The ether extract was washed with water, dried over $MgSO_4$, concentrated and purified by column chromatography to give a colorless solid **35** (8.2 mg, 79%)

(33): A white solid (mp 150 - 152 °C); IR (NaCl) 3508, 2985, 2937, 2867, 1454, 1332, 1220, 1173, 1052, 935 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 4.23 (d, J = 2.6 Hz, H), 4.06 (d, J = 2.9 Hz, H), 3.63 (dd, J = 2.2, 11.4 Hz, H), 2.98 (s br, H), 2.87 (s br, H), 2.53 (td, J = 2.6, 16.5 Hz, H), 2.31 (d br, J = 11.0 Hz, H), 2.03 (d br, J = 10 Hz, H), 1.88 (td, J = 4.0, 16.5 Hz, H), 1.79 (d br, J = 12.1 Hz, H), 1.75-1.55 (m, 5 H), 1.46-1.37 (m, H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 85.7, 81.0, 39.0, 68.0, 38.1, 30.9, 30.0, 22.6, 21.5, 20.6.

(34): A white solid (mp 153 - 155 °C); IR (NaCl) 3420, 2923, 2854, 1774, 1450, 1355, 1290, 1221 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.91 (dd, J = 4.7, 11.3 Hz, H), 4.31-4.22 (m, H), 4.00 (q, J = 2.2 Hz, H), 3.73 (s br, H), 3.07 (s, 3H), 2.42-2.22 (m, 3H), 2.10-2.04 (m, H), 1.82-1.67 (m, 3H), 1.56 (s, 3H), 1.51-1.36 (m, 3H), 1.33 (s, 3H), 1.18-1.10 (m, H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.5, 79.0, 76.5, 72.5, 72.4, 43.8, 39.7, 33.9, 32.3, 29.3, 27.6, 26.7, 25.3, 21.8.

(35): A white solid (mp 63 - 65 °C); IR (NaCl) 2929, 2857, 1708, 1464, 1384, 1221, 1149, 1055 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.54 (t, J = 2.9 Hz, H), 4.31 (d, J = 6.3 Hz, H), 2.82-2.72 (m, H), 2.65-2.54 (m, H), 2.32 (ddd, J = 1.8, 10.2, 15.4 Hz, H), 2.19 (ddd, J = 3.3, 8.4, 15.4 Hz, H), 2.14-2.08 (m, H), 1.86-1.75 (m, 2H), 1.74-1.66 (m, 2H), 1.63-1.55 (m, H), 1.35 (s, 3H), 1.29 (s, 3H), 1.20-1.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.6, 81.7, 72.3, 54.4, 44.1, 30.1, 27.2, 26.7, 26.3, 26.2, 26.0, 25.4; HRMS (CI+) calcd for $C_{13}H_{21}O_3$ [M^++H] 225.1491 found 225.1489.

(36): A white solid (mp 100 - 101 °C); IR (NaCl) 3457, 2929, 2866, 1775, 1444, 1361, 1257, 1179, 1039 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (t, J = 3.6 Hz, H), 4.02-3.98 (m, H), 3.76 (s, H), 3.02 (s br, H), 2.83 (s br, H), 2.24 (td, J = 4.4, 14.6 Hz, H), 2.19-2.13 (m, H), 2.13-2.02 (m, 2H), 2.02-1.78 (m, 6H), 1.78-1.68 (m, H), 1.67-1.54 (m, H), 1.40-1.30 (m, H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 89.5, 85.5, 72.0, 66.9, 45.5, 36.4, 31.2, 30.1, 29.1, 25.3, 23.6.

(37): A pale yellow oil; IR (NaCl) 2933, 2867, 1699, 1462, 1371, 1207, 1169, 1041 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 (t, J = 5.5 Hz, H), 4.49 (t, J = 5.1 Hz, H), 3.17 (dt, J = 5.5, 11.3 Hz, H), 2.46-2.30 (m, 2H), 2.25-2.10 (m, H), 1.96 (dt, J = 5.1, 11.7 Hz, H), 1.88-1.76 (m, 3H), 1.74-1.62 (m, 2H), 1.62-1.52 (m, 2H), 1.48 (s, 3H), 1.29 (s, 3H), 1.20-1.01 (m, H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.7, 83.5, 79.8, 54.4, 49.3, 44.0, 36.5, 29.1, 26.7, 25.4, 24.7, 24.4, 22.9; HRMS (CI+) calcd for $C_{14}H_{23}O_3$ [M^++H] 239.1647 found 239.1648.

Synthesis of biaryl and structural confirmation (45). To a solution of *rac*-**38** (109.1 mg, 0.268 mmol) in dichloromethane (1.0 mL) at −78 °C was added dropwise a solution of IBr (111 mg, 0.537 mmol) in dichloromethane (1.5 mL). The mixture was

kept stirred at −78 °C for 20 min, then aqueous saturated $Na_2S_2O_3$ (4 mL) was added at once. The mixture was allowed to warm to room temperature with stirring. Layers were separated and the aqueous layer was extracted with dichloromethane (4 mL × 3). The combined organic layers were dried ($MgSO_4$), evaporated, and the residue was purified by silica gel chromatography (EtOAc:Hex = 1:4) to yield 43.3 mg of a mixture of atropdiastereomer **39**/**39'** (34 %).

(39/39'): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.88 (Ar-H), 7.62-7.59 (Ar-H), 7.56-7.50 (Ar-H), 7.50-7.40 (Ar-H), 7.40-7 .24 (Ar-H), 4.73-4.66 (H, major & minor), 3.98 (s, 3H, minor), 3.92 (s, 3H, major), 3.42-3.26 (2H, major & minor), 2.81-2.70 (H, major & minor), 2.18-1.95 (m), 1.90-1.70 (m), 1.68-1.52 (m), 1.52-1.25 (m), 1.16-1.02 (m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2/153.8, 145.2/143.4, 131.8, 130.7, 130.5, 129.6, 129.4, 129.1, 128.7, 128.0, 127.4, 127.1, 126.5, 125.3, 124.6, 124.5, 124.1, 114.5/113.6, 94.8/93.3, 85.2/84.6, 80.9/79.6, 57.3/56.8, 48.4/47.1, 44.0/43.9, 37.7/36.7, 28.6/27.5, 24.4/24.2, 23.1/22.9. (*major/minor)

To a solution of a mixture of **39/39'** (48 mg, 0.101 mmol) in THF (1 mL) was added a solution of *n*-Bu_4NOH (0.11 mL of 1.0 M in *t*-BuOH, 0.111 mmol). After stirring 30 min at rt, water was added and the mixture was extracted with ether. After usual workup and a careful chromatography on a silica gel (EtOAc: Hex = 1:0), 12.3 mg and 13.8 mg of **43**/**44** was separated (total yield, 60 %).

(43 or 44): (lower R_f isomer): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 9.1 Hz, H), 7.82 (d, J = 8.0 Hz, H), 7.74 (d, J = 8.4 Hz, H), 7.47 (t, J = 7.3 Hz, H), 7.37 (t, J = 7.4 Hz, H), 7.31 (d, J = 9.2 Hz, H), 6.52 (d, J = 9.2 Hz, H), 5.65 (dd, J = 1.4, 9.9 Hz, H), 3.98 (s, 3H), 2.43 (dd, J = 3.3, 12.4 Hz, H), 1.96 (d br, J = 12.5 Hz, H), 1.88 (d br, J = 13.2 Hz, H), 1.72 (d br, J = 11.3 Hz, H), 1.61-1.20 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 144.6, 134.6, 134.1, 131.0, 130.4, 129.5, 128.8, 127.9, 127.3, 126.0, 124.5, 113.6, 94.5, 70.5, 57.3, 53.4, 37.8, 29.2, 24.3, 23.5.

(43 or 44): (higher R_f isomer): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.4 Hz, H), 7.87 (d, J = 8.8 Hz, H), 7.80 (d, J = 8.4 Hz, H), 7.46 (t, J = 7.7 Hz, H), 7.35 (t, J = 7.0 Hz, H), 7.30 (d, J = 9.1 Hz, H), 6.59 (d, J = 9.5 Hz, H), 5.60 (d, J = 9.5 Hz, H), 3.95 (s, 3H), 2.56 (dd, J = 4.0, 12.1 Hz, H), 2.00-1.81 (m, 3H), 1.72 (d br, J = 13.2 Hz, H), 1.61.52-1.40 (m, 3H), 1.30-1.18 (m, H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 146.3, 136.7, 133.7, 131.6, 130.4, 129.6, 128.7, 127.5, 126.5, 125.2, 124.3, 113.8, 93.7, 71.6, 56.9, 53.0, 39.1, 28.6, 24.4, 24.2.

To a solution of **43** (7.2 mg, 0.0166 mmol, lower spot) in toluene was added $TsOH \cdot H_2O$ (1.5 mg, 0.5 equiv.) and the mixture was heated at 80 °C for 30 min. After simple filtration through a silica pad and evaporatio of volatile, *rac*-**45** was obtained in 6.5 mg (97%) yield. The upper R_f isomer was similarly treated with $TsOH \cdot H_2O$ to provide a compound having identical ^{1}H and ^{13}C spectra.

(45): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 9.2 Hz, H), 7.86-7.82 (m, H), 7.74 (d, J = 8.5 Hz, H), 7.37 (d, J = 8.8 Hz, H), 7.36-7.30 (m, 2H), 7.13-7.09 (m, H), 6.88 (d, J = 8.0 Hz, H), 3.90 (s, 3H), 2.82 (t, J = 6.2 Hz, 2H), 2.37-2.24 (m, 2H), 2.16-2.05 (m, 2H), 1.78-1.67 (m, 2H), 1.66-1.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 141.5, 139.2, 138.1, 136.2, 132.9, 131.1, 130.1, 129.7, 128.7, 127.5, 127.4, 124.7, 124.3, 114.3, 99.4, 57.2, 30.3, 29.0, 23.8, 23.1.

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