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Stereospecificity of the Au(I)-catalyzed reaction of 1-alkynyl-bicyclo[4.1.0]-heptan-2-ones with nucleophiles

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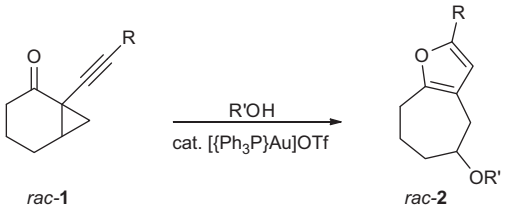
Dedicated to Professor Henri Kagan on the occasion of his 80th birthday

ABSTRACT

The stereospecificity of the Au(I)-catalyzed reaction of 1-alkynyl-bicyclo[4.1.0]-heptan-2-ones with nucleophiles was investigated. The substrates were prepared in non-racemic form (up to 88% ee) through parallel kinetic resolution (CBS reduction) and reoxidation of the separated diastereomeric alcohols. The key Au-catalyzed reaction was then found to proceed without significant loss of absolute stereochemical information; this way, an achiral carbocationic intermediate could be excluded. Thus, a bicyclobutonium-type intermediate seems to be attacked in a S_N2-type fashion by the nucleophile in accordance with computational predictions.

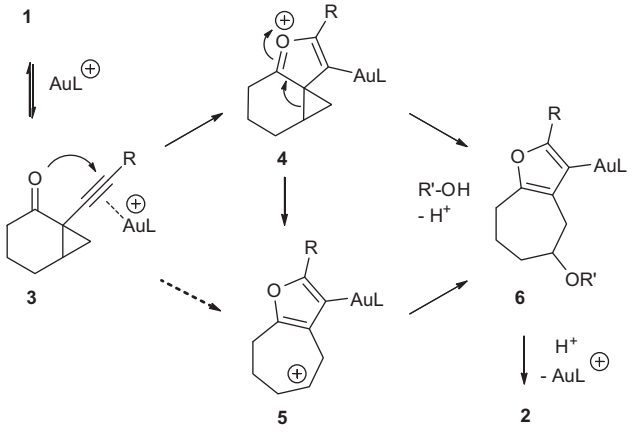
1. Introduction

In the past decade, homogeneous Au-catalysis has attracted much attention and a variety of powerful new synthetic methods have been developed to exploit the activation of an alkyne or an allene substructure towards nucleophilic attack by means of Au(I) or Au(III) species.[1] In particular, Au-catalyzed cyclizations have been frequently exploited in the synthesis of furans and other heterocycles.[2] As a contribution to this rapidly growing research field, we recently reported the gold-catalyzed reaction of 1-(1-alkynyl)-cyclopropyl ketones with nucleophiles to give substituted furans under mild conditions.[3] In a typical case, a 1-alkynyl-bicyclo[4.1.0]-heptan-2-one derivative *rac*-**1** was reacted with an alcohol in the presence of an in situ prepared phosphane-stabilized Au(I) catalyst to give a cycloheptено-[*b*]furane of type *rac*-**2** (Scheme 1).



Scheme 1. The basic reaction system of this study.

Initially, we proposed two mechanistic alternatives for this transformation both starting with the (possibly reversible) formation of a primary Au(I)-alkyne complex **3** and leading to a late furanyl gold intermediate of type **6** (Scheme 2).[3] Subsequent computational studies based on density functional theory suggested the key nucleophilic attack to take place on a cationic intermediate of type **4** leading directly to **6**.[4]



Scheme 2.

Nevertheless, the possibility that the primarily formed cyclopropyl-oxenium species **4** undergoes ring opening (to form a secondary carbocation of type **5**) prior to nucleophilic attack could not be ruled out. This is because the energy difference between **4** and **5** was predicted to be small and the formation of cationic intermediates of type **5** was postulated by Zhang et al. to mechanistically rationalize Au-catalyzed [4+2] annulation reactions of related substrates.[5]

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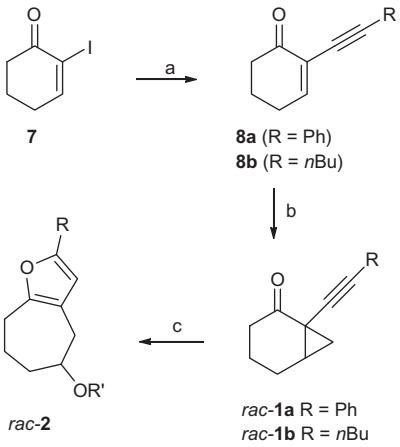
While theoretical investigations provide meaningful insights into possible reaction mechanisms, we feel that experimental probes should always complement such studies. To distinguish between the two mechanistic pathways discussed above (Scheme 2), we decided to probe the stereospecificity of the process. The basic consideration was that the nucleophile attack on a (chiral) intermediate **4** should proceed in a stereospecific (S_N2-type) fashion, while the absolute stereochemical information would be lost if an achiral intermediate of type **5** was involved. Herein, we disclose the results of a study using non-racemic substrates, which indeed demonstrated the reaction to proceed with a high degree of stereospecificity.

2. Results and discussion

2.1. Synthesis of racemic substrates as reference samples

Starting from 2-iodo-cyclohexenone **7**[6] the two alkynylated compounds **8a** and **8b** were prepared by standard Sonogashira coupling[7,2a] and further converted into the racemic substrates *rac*-**1a** and *rac*-**1b**, respectively, through Corey–Chaykovsky cyclopropanation[8] (Scheme 3).



Scheme 3. Reagents and conditions: (a) phenylacetylene or 1-hexyne, $Cl_2Pd(PPh_3)_2$ (1 mol %), CuI (2 mol %), diisopropylamine, 2–4 h, THF, 0 °C to rt, 82% **8a**; 53% **8b**; (b) NaH, trimethylsulfoxonium iodide, DMF, 14–16 h, rt, 70% (*rac*-**1a**), 43%, *rac*-**1b**; (c) Au[PPh_3]OTf (1 mol %), R'OH, (2 equiv), CH_2Cl_2, 15 min, rt, 80–91%.

The key Au(I)-catalyzed reaction then proceeded smoothly under the established conditions (CH_2Cl_2, rt, 15 min) employing (Au[PPh_3]OTf)[9] as a catalyst, which was generated in situ from Au[PPh_3]Cl and AgOTf after filtering off the AgCl precipitate formed. Using methanol, *tert*-butanol or 2-propanol as a nucleophilic reaction partner the expected (racemic) furans of type *rac*-**2** were obtained in good yield as summarized in Table 1. By means of chiral GC and HPLC, respectively, suitable conditions were then elaborated to analytically separate the racemic mixtures in almost all cases as a precondition for the planned investigations using non-racemic compounds. Only in the case of *rac*-**2by** did we fail to analytically resolve the enantiomers with the set of columns available.

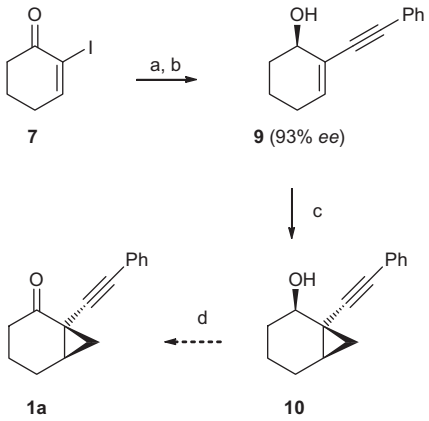
Table 1
Results of the Au-catalyzed transformations in the racemic series according to step c in Scheme 3

Entry	R	R′	Product	Yield[a] (%)
1	Ph	Me	*rac*-**2ax**	91
2	Ph	*tert*-Bu	*rac*-**2ay**	85
3	Ph	Propargyl	*rac*-**2az**	82
4	*n*-Bu	Me	*rac*-**2bx**	86
5	*n*-Bu	*tert*-Bu	*rac*-**2by**	80
6	*n*-Bu	Propargyl	*rac*-**2bz**	80

[a] Isolated yield after chromatographic purification.

2.2. Synthesis of non-racemic substrates of type 1

In the first approach (Scheme 4) towards the synthesis of substrates of type **1** in enantiomerically enriched form we employed the literature-reported[10] CBS reduction[11] of **7** as the chirogenic step. Using a CBS catalyst derived from (*S*)-diphenyl-prolinol and *n*-butyl boronic acid the (*R*)-configurated alcohol was obtained with 93% ee (GC). Subsequent Sonogashira coupling[7] afforded the enyne **9** in high yield. Unfortunately, our attempts to diastereoselectively convert **9** into the cyclo-propanated product **10** in a Simmons–Smith-type reaction did not lead to satisfying results. Even in the best case (Et_2Zn/CH_2I_2)[12] the reaction proceeded rather sluggishly to give **10** in only low yield (⩽25%).



Scheme 4. Reagents and conditions: (a) *n*Bu-(*S*)-CBS (15 mol %), $BH_3{\cdot}Me_2S$ (1.2 equiv, slow addition over 1.5 h), 15 min, THF, 0 °C, then quench with MeOH, 95%; (b) $Cl_2Pd(PPh_3)_2$ (3 mol %), CuI (6 mol %), phenylacetylene, diisopropylamine, overnight, THF, 0 °C to rt, 85%; (c) Et_2Zn (2 equiv), $ClCH_2I$ (4 equiv), $ClCH_2CH_2Cl$, 45 min, 0 °C, 25%; (d) oxidation.

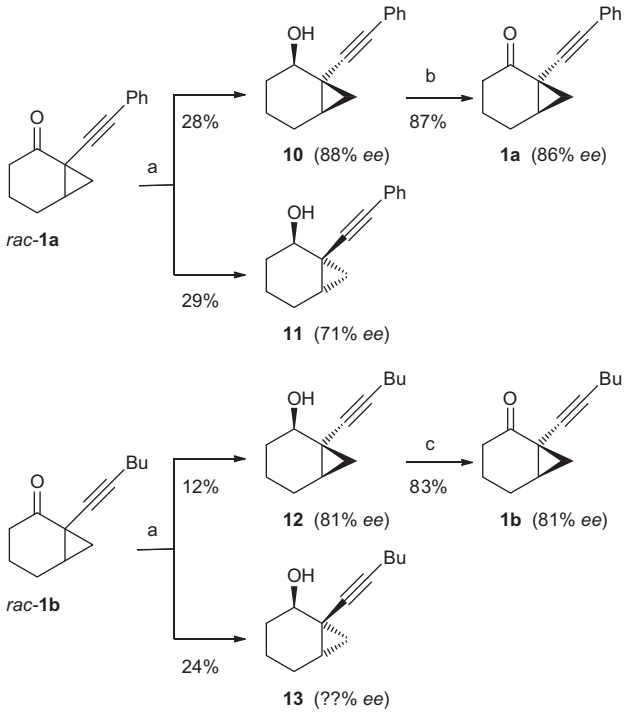
As an alternative entrance to non-racemic substrates of type **1** we then probed the kinetic resolution[13] of the racemic ketones (*rac*-**1a** and *rac*-**1b**, respectively) again using the CBS reduction. We were glad to find that a parallel kinetic resolution[14] took place to give a separable mixture of non-racemic diastereomeric alcohols in both cases (Scheme 5). Under optimized conditions (30 mol % of CBS catalyst, THF, 0 °C, slow addition of 1.2 equiv of BH_3–SMe_2) the (*R*)-configurated alcohols (**10**/**11** and **12**/**13**, respectively) were isolated with up to 88% ee albeit in rather low yields after careful chromatographic separation of the diastereomers. To avoid severe separation problems it proved to be important to ensure full conversion of the starting ketones.

The two *endo*-configurated alcohols **10** (88% ee) and **12** (81% ee) were then oxidized using either Jones or Dess–Martin reagent[15] to afford the desired ketones (+)-**1a** and (+)-**1b**, respectively, in good yields and unchanged enantiomeric purity within the limits of analytical accuracy (Scheme 5).

2.3. Configurational assignments

The relative configuration of the diastereomeric alcohols (**10**/**11** and **12**/**13**, respectively) was unambiguously determined by means of an X-ray crystal structure analysis of **10** (Fig. 1) and correlation of NMR data.

The absolute configuration of the chiral ketones **1a** and **1b** was assigned by comparison of the experimental and calculated CD



Scheme 5. Synthesis of the non-racemic ketones **1a** and **1b**, respectively, through parallel kinetic resolution. Reagents and conditions: (a) *n*Bu-(*S*)-CBS (30 mol %), $BH_3{\cdot}Me_2S$ (1.2 equiv, slow addition over 2 h), THF, 0 °C, then quench with MeOH; chromatographic separation of diastereomers; (b) Jones reagent, acetone, 20 min, 0 °C to rt; (c) Dess–Martin periodane (1.6 equiv), CH_2Cl_2, 3.5 h, rt.

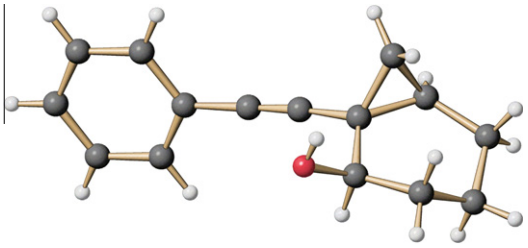


Figure 1. Structure of **10** in the crystalline state.

spectra (Fig. 2).[16,17] In addition, it could be shown by chiral GC that compound **10** prepared from *rac*-**1a** according to Scheme 5 was identical to the sample obtained by cyclopropanation of (*R*)-**9** (Scheme 4).

These assignments are also in accordance with the empirical octand rule[18] considering the Cotton effects at ca. 280 nm (corresponding to the ketone n-π^* transition). Note that one has to be aware that a common simplification of the octand rule (reduction to a quadrant rule by looking along the carbonyl bond axis and only considering the four rear quadrants) would lead to the wrong assignment here (Fig. 3, left). Thus, looking from a bird's eye perspective on the ketone (Fig. 3, right) reveals that the octand occupied by the alkynyl substituent actually has a (+)-sign. Thus, a positive Cotton effect is predicted for both (*S*,*S*)-configured ketones **1a** and **1b**, respectively.

2.4. The Au-catalyzed key reaction in the non-racemic series

Finally, the stereospecificity of the Au-catalyzed title reaction was probed by subjecting the non-racemic ketones **1a** and **1b**, respectively, to the established reaction conditions (Scheme 6).

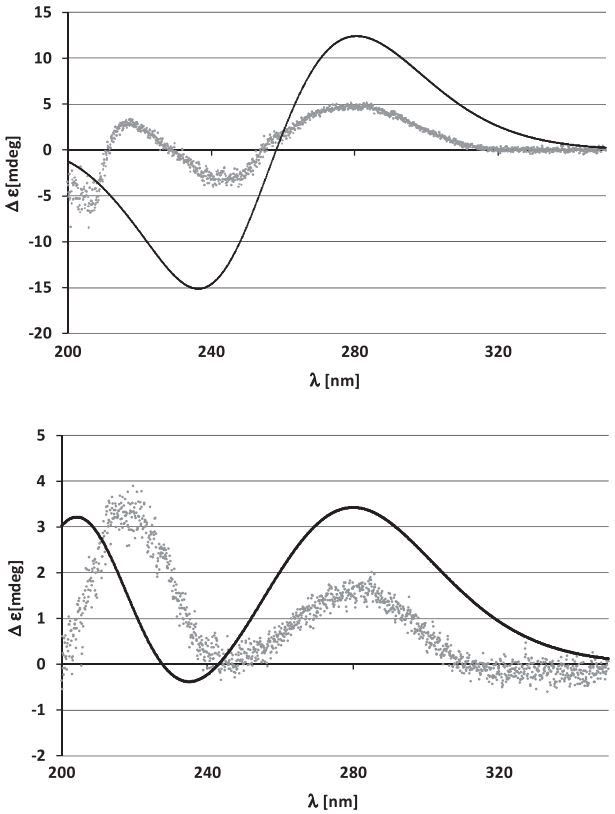


Figure 2. Experimental (grey) and calculated (black) CD spectra of compounds **1a** (top) **1b** (bottom) in MeCN.

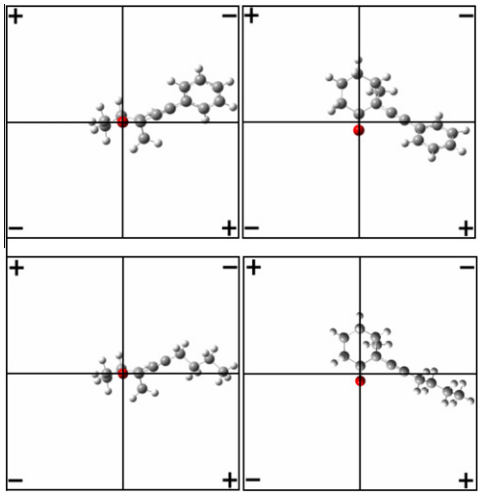
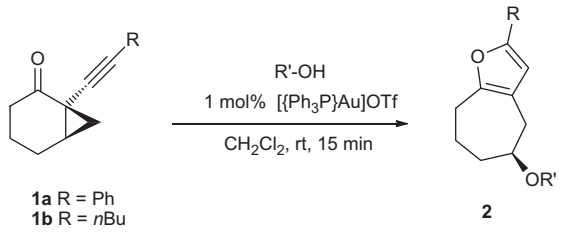


Figure 3. Application of the octand rule to ketones **1a** (top) and **1b** (bottom). Left side: common view along the C=O axis with the sign of the rear octands indicated. Right: view from above with the signs of the upper octands indicated. Thus, both compounds are predicted to exhibit a positive Cotton effect at ca. 280 nm because the alkynyl substituent occupies the (positive) upper front octand in both cases.

Using either methanol, *tert*-butanol or propargylic alcohol we were pleased to obtain the addition products (furans) of type **2** without any significant loss of absolute stereochemical information (Table 2).

While we did not explicitly prove the absolute configuration of the resulting compounds of type **2**, we confidently assume them to be (*S*)-configurated because the observed stereospecificity can only be explained through a S_N2-type attack of the alcohol nucleophile



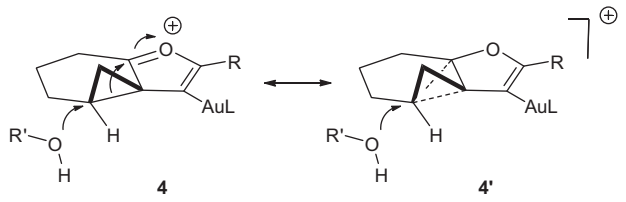
Scheme 6. Stereospecific Au-catalyzed transformation of ketones **1** into furans of type **2** (compare Table 2).

Table 2
Results of the Au-catalyzed furan synthesis in the non-racemic series according to Scheme 6

Entry	Substrate	ee (%)	R'OH	Product	ee (%)	Yield[a] (%)
1	**1a**	85	MeOH	**2ax**	83	63
2	**1a**	86	^{t}BuOH	**2ay**	83	97
3	**1a**	78	HC≡CCH$_2$OH	**2az**	77	68
4	**1b**	79	MeOH	**2bx**	79	65
5	**1b**	79	HC≡CCH$_2$OH	**2bz**	80	26

[a] Isolated yield after chromatographic purification.

onto a cationic intermediate of type **4**, which might also be regarded as a bicyclobutonium-type species **4'** (Scheme 7).[19]



Scheme 7. Stereospecific attack of an alcohol (R′OH) to a bicyclobutonium-type intermediate **4**/**4′** affording furans of type **2**.

The fact that the reaction (Scheme 6) proceeded with a very high degree of stereospecificity even in the case of *tert*-butanol (as a sterically demanding nucleophile) suggests that the formation of a secondary carbenium ion of type **5** (Scheme 2) is disfavoured under the conditions applied. This is in accordance with the observation that no conversion of the substrate **1** occurs in the absence of a nucleophile or in the presence of Et_3SiH (as a hydride source known to react with carbenium cations).[3]

3. Conclusions

By preparing the 1-alkynyl-bicyclo[4.1.0]-heptan-2-ones **1a** and **1b** in non-racemic form, we were able to demonstrate the stereospecificity of their Au(I)-catalyzed transformation into cyclohepteno[*b*]furans of type **2**. This result not only sheds some light to the mechanistic pathways of the reaction (by excluding an achiral cationic intermediate) but also opens new perspectives for possible applications of the methodology in the synthesis of non-racemic molecules.

4. Experimental

4.1. General

Reactions were carried out under an atmosphere of argon in oven-dried glassware with magnetic stirring. THF and toluene were freshly distilled under an argon atmosphere from sodium/benzophenone. DMF was distilled from calcium hydride and stored over 3 Å molecular sieves. Methanol was distilled from magnesium turnings. Triethylamine was distilled and stored over potassium hydroxide. All other reagents were purchased from Aldrich, Merck, Acros, Fluka, MP, Chemetall or Strem and used without further purification, unless otherwise indicated. The CBS catalyst used was prepared from (*S*)-diphenylprolinol and *n*-butylboronic acid. Column chromatography was performed with Acros Silica Gel 60 (230–400 mesh). Analytical thin-layer chromatography (TLC) was performed with commercial aluminum plates coated with Silica Gel 60-F_{254} from Merck. Chromatograms were visualized by UV-light at 254 nm or by staining with a 'cerium reagent' (prepared from 2 g of phosphomolybdic acid, 1 g of cerium(IV) sulfate and 10 mL of concentrated H_2SO_4 in 90 mL of water) and subsequent heating. Melting points (mp) were determined with a Büchi 510 apparatus in open capillary tubes and are uncorrected. Nuclear magnetic resonance (NMR) spectra (^{1}H, ^{13}C) were recorded in $CDCl_3$ on Bruker instruments DPX 300, AC 300 or DRX 500. Chemical shifts (δ) are reported in delta (δ) units in parts per million (ppm) relative to tetramethylsilane (0.00 ppm). The fine structure of proton signals is given as s (singlet), d (doublet), t (triplet), m (multiplet) or br (broad). In the case of ^{13}C NMR, APT (attached proton test) spectra were used to determine the formal multiplicity C (s), CH (d), CH_2 (t), CH_3 (q). Infrared spectra (IR) were recorded on a Perkin–Elmer Paragon 1000 FT-IR spectrometer using the ATR technique. The intensity of absorption bands is given as s (strong), m (medium) or w (weak); b additionally indicates broad signals. Mass spectra (MS) and high resolution mass spectra (HRMS) were measured with a Varian MAT 711, Finnigan Incos 500 or Finnigan MAT 95 ST. The spectra were measured under electron impact (EI) with an ionization potential of 70 eV. Gas-chromatography with mass selective detection (GC–MS) was carried out using an Agilent instrument using a 5973 N detector on 30 m × 0.25 mm capillary columns (Optima-1-MS from Macherey-Nagel) with H_2 as a carrier gas (1.7 mL/min, 1.2 bar). As a routine, the following temperature programme was used: 50 °C (2 min), then heating with 25 °C/min to 300 °C (5 min), finally 320 °C (5 min). Enantiomeric analyses through GC were performed on an Agilent (HP 6890) instrument with FID detection using either a BGB-176SE column (A) or a 6TBDMS-2,3-Me-β-CD column (B). Enantiomeric analyses through High Performance Liquid Chromatography (HPLC) were conducted with HPLC units from Merck-Hitachi and Knauer (UV-detection at 220 nm and 254 nm) using one of the following columns: Diacel Chiracel OB-H (C), Diacel Chiracel OJ (D), Diacel Chiralpak AD-H (E), Macherey Nagel Nucleocell (F) and *n*-Hex/*i*-PrOH (90:10 or 95:5) as a solvent. Optical rotations were measured on a Perkin–Elmer 343 polarimeter at 20 °C using a 10 cm cell. The solvents and concentrations (in g/100 mL) are indicated.

4.2. 2-Iodocyclohex-2-enone 7

A round-bottomed flask was charged subsequently with 400 mL of THF/water 1:1, cyclohexenone (8 mL, 83 mmol), K_2CO_3 (13.7 g, 99 mmol), I_2 (31.6 g, 125 mmol) and 4-*N*,*N*-dimethylaminopyridine (2.02 g, 17 mmol). The mixture was stirred for 4.5 h, diluted with 800 mL of EtOAc and washed with satd aqueous $Na_2S_2O_3$ (800 mL) and 1 M aqueous HCl (600 mL). The organic layer was dried with $MgSO_4$, the solvent evaporated under reduced pressure and the solid residue was recrystallized from cyHex to yield 10.9 g of **7** as a colourless solid. The mother liquid was concentrated and the residue was purified by column chromatography (1:4 EtOAc/cyHex) to yield additional 5.0 g of **7** (overall yield 15.9 g, 87%). Compound **7** is thermally labile but could be stored in the freezer for several months without decomposition. Mp 49–51 °C. IR (neat): 2948 (w), 2866 (w), 1674 (s), 1583 (m), 1313 (m), 1119 (m), 965 (m) cm^{-1}. ^{1}H NMR: δ = 7.78 (m, 1H), 2.69–2.65 (m, 2H, CH_3), 2.48–2.43 (m, 2H), 2.15–2.05 (m, 2H). ^{13}C NMR: δ = 192.1 (s), 159.4 (d), 103.8 (s), 37.2 (t), 29.9 (t), 22.8 (t). GC–MS: 222 (M^+), 135 (100%).

4.3. 2-(Phenylethynyl)-cyclohex-2-enone 8a

A round-bottomed flask was charged with anhydrous THF (45 mL), enone **7** (4.4 g, 20 mmol), $Cl_2Pd(PPh_3)_2$ (140 mg, 0.2 mmol) and CuI (85 mg, 0.4 mmol) and the mixture was cooled to 0 °C before phenylacetylene (4 mL, 36 mmol) and diisopropylamine (8 mL, 57 mmol) were added. After 2 h at 0 °C the mixture was diluted with ether (450 mL) and washed with 1 M aqueous HCl (480 mL). The aqueous phase was extracted with ether (450 mL) and the combined organic layers were washed with brine (240 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the solid residue was purified by column chromatography (1:4 EtOAc/cyHex) to yield **8a** (3.2 g, 82%) as an orange solid. IR (neat): 3051 (w), 2947 (w), 2860 (w), 1681 (s), 1488 (m), 1353 (m), 1071 (m), 756 (s), 690 (s) cm^{-1}. ^1H NMR: δ = 7.51–7.48 (m, 2H), 7.36–7.29 (m, 4H), 2.55–2.46 (m, 4H), 2.09–2.01 (m, 2H). ^{13}C NMR: δ = 195.5, 154.1, 131.7, 128.3, 128.1, 125.2, 122.8, 92.0, 83.8, 38.1, 26.4, 22.4. GC–MS: 196 (M^+).

4.4. 2-(Hex-1-ynyl)-cyclohex-2-enone 8b

Following the procedure described above for the synthesis of **8a**, 4.4 g (20 mmol) of **7** was reacted with 1-hexyne (3.2 mL, 26 mmol) for 4 h at rt to give 1.9 g (53%) of **8b** as a yellow oil after chromatography (6:1 toluene/CH_2Cl_2). IR (neat): 2948 (s), 2930 (s), 2866 (s), 2227 (w), 1683 (s), 1349 (m), 1117 (m) cm^{-1}. ^1H NMR: δ = 7.20 (t, J = 4.4 Hz, 1H), 2.50–2.35 (m, 6H), 2.06–1.97 (m, 2H), 1.58–1.37 (m, 4H), 0.94–0.89 (m, 3H). ^{13}C NMR: δ = 196.2 (s), 153.0 (d), 125.5 (s), 93.4 (s), 74.9 (s), 38.1 (t), 30.7 (t), 26.3 (t), 22.4 (t), 22.0 (t), 19.1 (t), 13.6 (q). GC–MS: 134 (100%), 176 (M^+).

4.5. 1-Phenylethynyl-bicyclo[4.1.0]heptan-2-one rac-1a

A round-bottomed flask was charged with DMF (200 mL), NaH (1.8 g, 44 mmol) and trimethylsulfoxonium iodide (11.5 g, 52 mmol). After 30 min at rt, the enone **8a** (7.8 g, 40 mmol) in DMF (30 mL) was added and stirring was continued for 16 h. Then 1000 mL of water was added, the aqueous phase was extracted with MTBE (3 × 200 mL) and the combined organic layers were washed with satd aqueous NH_4Cl (100 mL) and dried over $MgSO_4$. After removing the solvent under reduced pressure the remaining oil was purified by column chromatography (1:6 EtOAc/cyHex) to yield 5.9 g (70%) of *rac*-**1a** as a white solid. Mp= 52–53 °C. IR (neat): 3044 (w), 2939 (w), 2225 (w), 1693 (s), 1595 (w), 1091 (m), 757 (s), 692 (s) cm^{-1}. ^1H NMR: δ = 7.44–7.40 (m, 2H), 7.27–7.24 (m, 3H), 2.43–2.34 (m, 1H), 2.25–1.95 (m, 4H), 1.80–1.60 (m, 4H). ^{13}C NMR: δ = 203.7 (s), 131.8 (d), 128.0 (d), 123.2 (s), 89.2 (s), 79.7 (s), 36.3 (s), 29.4 (d), 27.0 (t), 21.3 (t), 21.2 (t), 18.2 (t). GC–MS: 210 (M^+).

4.6. 1-Hex-1-ynyl-bicyclo[4.1.0]heptan-2-one rac-1b

In analogy to the procedure described above for the synthesis of *rac*-**1a**, NaH (170 mg, 3.9 mmol) and trimethylsulfoxonium iodide (1.0 g, 4.6 mmol) were first reacted in DMF (15 mL) for 30 min before the enone **8b** (627 mg, 3.6 mmol) in 5 mL of DMF was added. After 14 h at rt the mixture was partitioned between water (50 mL) and MTBE (3 × 20 mL) before the combined organic layers were washed with satd aqueous NH_4Cl (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the remaining oil was purified by column chromatography (1:8 EtOAc/cyHex) to yield 297 mg (43%) of *rac*-**1b** as a yellow oil. IR (neat): 2927 (s), 2860 (m), 1690 (s), 1455 (w), 1350 (w), 1322 (w), 1238 (w), 1135 (w), 1089 (w), 1017 (w), 913 (w), 814 (w), 746 (w) cm^{-1}. ^1H NMR δ = 2.33 (ddd, J = 4.30 Hz, J = 5.49 Hz, J = 18.21 Hz, 1H), 2.20 (t, J = 6.99 Hz, 2H), 2.16–1.90 (m, 4H), 1.78–1.55 (m, 3H), 1.52–1.32 (m, 5H), 0.89 (t, J = 7.14 Hz, 3H). ^{13}C NMR δ = 204.7 (s), 80.2 (s), 79.4 (s), 36.2 (t), 30.9 (t), 29.0 (d), 26.7 (s), 21.9 (t), 21.27 (t), 20.95 (t), 18.56 (t), 18.35 (t), 20.95 (t), 13.6 (q). GC–MS: 91 (100%), 190 (M^+).

4.7. Kinetic resolution of rac-1b: Preparation of 1-phenylethynyl-bicyclo[4.1.0]heptan-2-ol 10 and 11

A solution of ketone *rac*-**1a** (1.05 g, 5 mmol) in 45 mL of THF was cooled to 0 °C and a 0.5 M solution of the CBS catalyst in toluene was added (3 mL, 1.5 mmol). Then a solution of $BH_3{\cdot}Me_2S$ in THF (3.0 mL, 6 mmol) was added slowly over a period of 2 h under stirring by means of a syringe pump. The reaction was then stopped by addition of a few mL of MeOH. Removal of all volatiles under reduced pressure and column chromatography (5:2 toluene/CH_2Cl_2) of the oily residue gave the two diastereomers **10** (296 mg, 28%, 88% ee (GC column A)) and **11** (311 mg, 29%, 71% ee (HPLC column F)).

Compound **11**: R_f (5:2 toluene/CH_2Cl_2) = 0.3. $[\alpha]_\lambda$ (20 °C, $CHCl_3$, c 1): $[\alpha]_{589}$ = +73.4, $[\alpha]_{546}$ = +88.4, $[\alpha]_{405}$ = +200.9, $[\alpha]_{365}$ = +280.4. IR (neat): 3388 (b-m), 3071 (w), 3010 (w), 2933 (m), 2857 (m), 2216 (m), 1949 (w), 1877 (w), 1809 (w), 1678 (w), 1696 (m), 1043 (s), 754 (s), 690 (s) cm^{-1}. ^1H NMR: δ = 7.41–7.38 (m, 2H), 7.28–7.25 (m, 3H), 4.16 (t, 1H, J = 3.67 Hz), 2.61 (s, 1H), 2.12–2.03 (m, 1H), 1.72–1.48 (m, 4H), 1.44–1.33 (m, 1H), 1.18 (dd, 2H, J = 4.68, J = 9.35 Hz) 0.61 (dd, 1H, J = 4.84 Hz, J = 6.22 Hz). ^{13}C NMR: δ = 131.7 (d), 128.1 (d), 127.8 (d), 123.2 (s), 92.9 (s), 79.2 (s), 66.2 (s), 27.7 (t), 22.4 (t), 20.0 (t), 18.6 (t), 14.8 (t). GC–MS: 194 (100%), 212 (M^+). HRMS: calcd for $C_{15}H_{16}O$ = 212.1201, found: 212.120.

Compound **10**: R_f (5:2 toluene/CH_2Cl_2) = 0.12. $[\alpha]_\lambda$ (20 °C, $CHCl_3$, c 1): $[\alpha]_{589}$ = −90.5, $[\alpha]_{546}$ = −108.8, $[\alpha]_{405}$ = −242.9, $[\alpha]_{365}$ = −338.2, $[\alpha]_{334}$ = −470.1. IR (neat): 3388 (b-m), 3071 (w), 3010 (w), 2933 (m), 2857 (m), 2216 (m), 1949 (w), 1877(w), 1809 (w), 1678 (w), 1696 (m), 1043 (s), 754 (s), 690 (s) cm^{-1}. ^1H NMR: δ = 7.40–7.36 (m, 2H), 7.28–7.24 (m, 3H), 4.33 (dd, 1H, J = 5.69, J = 9.12 Hz, H-6), 2.06–1.95 (m, 2H), 1.79–1.71 (m, 1H), 1.67–1.59 (1H, H-2), 1.52–1.40 (m, 2H), 1.35–1.21 (m, 2H), 1.10 (dd, 1H, J = 4.64, J = 9.28 Hz), 0.93 (dd, 1H, J = 4.80, J = 6.52 Hz). ^{13}C NMR: δ = 131.7 (d), 128.2 (d), 127.6 (d), 123.6 (s), 95.4 (s), 76.6 (s), 70.9 (d), 28.9 (t), 24.6 (d), 22.7 (t), 20.0 (t), 19.3 (s), 17.6 (t). GC–MS: 194 (100%), 212 (M^+). HRMS: calcd for $C_{15}H_{16}O$ = 212.1201, found: 212.120. For X-ray structure analysis, colourless crystals were obtained from wet CH_2Cl_2 containing traces of isopropylamine.[20]

4.8. 1-(Phenylethynyl)-bicyclo[4.1.0]heptan-2-one 1a

A solution of alcohol **10** (135 mg, 0.64 mmol) in 5 mL of acetone was cooled to 0 °C. Jones reagent was added dropwise until the orange colour persisted. Stirring was continued for 15 min at 0 °C before the cooling bath was removed and, after five more minutes, the reaction was stopped by addition of a little *i*-PrOH. The mixture was concentrated under reduced pressure and the residue was partitioned between water and MTBE. The organic layers were washed with satd aqueous $NaHCO_3$ and dried over $MgSO_4$. After solvent evaporation under reduced pressure the residue was purified by column chromatography (1:10 EtOAc/cyHex) to give **1a** as a white solid (117 mg, 0.55 mmol, 87%, 86% ee (HPLC column C)). $[\alpha]_\lambda$ (20 °C, $CHCl_3$, c 1): $[\alpha]_{589}$ = -23.2, $[\alpha]_{546}$ = -24.3, $[\alpha]_{405}$ = 16.6, $[\alpha]_{365}$ = 115.5, $[\alpha]_{334}$ = 419.3.

4.9. Kinetic resolution of rac-1b: preparation of 1-hex-5-ynyl-bicyclo[4.1.0]heptan-2-ol 12 and 13

A solution of ketone *rac*-**1b** (1.91 g, 10 mmol) in anhydrous THF (90 mL) was cooled to 0 °C and a 0.5 M solution of the CBS catalyst

in toluene was added (6 mL, 3 mmol). Then a solution of $BH_3{\cdot}Me_2S$ in THF (6.0 mL, 12 mmol) was added slowly over a period of 2 h under stirring by means of a syringe pump. The reaction was then stopped by addition of a few mL of MeOH. Removal of all volatiles under reduced pressure and column chromatography (5:2 toluene/CH_2Cl_2) of the oily residue gave the two diastereomers **12** (239 mg, 12%, 81% ee (GC column A)) and **13** (461 mg, 24%).

Compound **12**: $[\alpha]_\lambda$ (20 °C, $CHCl_3$, *c* 1): $[\alpha]_{589} = -38.1$, $[\alpha]_{546} = -44.8$, $[\alpha]_{405} = -88.3$, $[\alpha]_{365} = -113.5$. IR (neat): 3384 (b-m, OH), 2932 (s), 2860 (m), 1455(m), 1330 (w), 1253 (w), 1046 (w), 990 (w), 916 (w), 853 (w), 766 (w) cm^{-1}. ^1H NMR: $\delta = 4.17$ (dd, 1H, $J = 5.68$, $J = 9.47$ Hz), 2.15 (t, 2H, $J = 9.94$), 1.96–1.90 (m, 2H), 1.75–1.66 (m, 1H), 1.51–1.18 (m, 9H), 1.00–0.88 (m, 5H), 0.75 (dd, 1H, $J = 4.72$, $J = 6.22$ Hz). ^{13}C NMR: $\delta = 85.4$ (s), 76.8 (s), 71.4 (d), 31.1 (t), 28.7 (t), 23.8 (d), 22.7 (t), 21.9 (t), 20.3 (t), 19.0 (s), 18.5 (t), 17.2 (t), 13.6 (q). GC–MS: 91 (100%) 192 (M^+). HRMS: calcd for $C_{13}H_{20}O$ = 192.1514, found: 192.151.

Compound **13**: $[\alpha]_\lambda$ (20 °C, $CHCl_3$, *c* 1): $[\alpha]_{589} = 46.3$, $[\alpha]_{546} = 83.6$, $[\alpha]_{405} = 121.1$, $[\alpha]_{365} = 163.0$. IR (neat): 3388 (bm), 3071 (w), 2932 (s), 2853 (m), 1456 (w), 1393 (w), 1333 (w), 1253 (w), 1176 (w), 1116 (w), 1086 (w), 1063 (w), 991 (w), 843 (w) cm^{-1}. ^1H NMR: $\delta = 4.03$ (t, 1H, $J = 3.95$ Hz), 2.54 (s, 1H), 2.18 (t, 1H, $J = 6.94$ Hz), 2.05–2.0 (m, 1H), 1.59–1.26 (m, 9H), 1.13–1.11 (m, 1H), 1.00 (dd, 1H, $J = 4.71$, $J = 9.29$ Hz), 0.90 (t, 3H, $J = 7.17$ Hz), 0.46 (dd, 1H, $J = 4.76$, $J = 6.27$ Hz). ^{13}C NMR: $\delta = 82.9$ (s), 79.9 (s), 66.2 (d), 31.1 (t), 27.6 (t), 22.6 (t), 22.0 (t), 20.9 (d), 19.5 (t), 18.5 (t), 18.2 (s), 14.3 (t), 13.6 (q). GC–MS: 91 (100%) 192 (M^+). HRMS: calcd for $C_{13}H_{20}O$ = 192.1514, found: 192.151.

4.10. 1-Hex-1-ynyl-bicyclo[4.1.0]heptan-2-one 1b

To a solution of alcohol **12** (212 mg, 1.1 mmol) in 35 mL of CH_2Cl_2 were added water (35 μL, 1.2 mmol) and Dess–Martin periodane (763 mg, 1.8 mmol) and the mixture was stirred for 3 h before a second portion of Dess–Martin periodane was added (254 mg, 0.6 mmol). After 0.5 h the solution was filtrated through a small pad of silica and concentrated in vacuo to give the ketone **1b** as a yellow oil (174 mg, 0.9 mmol, 83%, 79% ee (GC column A)); $[\alpha]_\lambda$ (20 °C, $CHCl_3$, *c* 1): $[\alpha]_{589} = -13.0$, $[\alpha]_{546} = -13.8$, $[\alpha]_{405} = -1.9$, $[\alpha]_{365} = +29.6$.

4.11. General procedure for the Au(I)-catalyzed key reaction

In a Schlenk-tube the ketone **1** (0.2 mmol) and the alcohol (0.4 mmol) were dissolved in anhydrous dichloromethane (0.1 mL) and a solution of freshly prepared $Au[PPh_3]OTf$ in CH_2Cl_2 (0.3 mL) was added. After stirring for 15 min at rt the solvent was removed under reduced pressure and the product was purified by column chromatography (1:10 EtOAc/cyHex).

4.12. (*S*)-2-Phenyl-5-methoxy-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]furan 2ax

The reaction of **1a** (41 mg, 0.2 mmol, 85% ee) with methanol (13 mg, 0.4 mmol) in the presence of $Au[PPh_3]OTf$ (0.00625 M, 0.3 mL, 0.002 mmol) afforded 30 mg (63%, 83% ee (HPLC column D)) of **2ax** as a liquid. R_f (1:10 EtOAc/cyHex) = 0.45. $[\alpha]_\lambda$ (20 °C, $CHCl_3$, *c* 1): $[\alpha]_{589} = -3.2$, $[\alpha]_{546} = -5.0$, $[\alpha]_{405} = -27.2$, $[\alpha]_{365} = -61.9$. IR (neat): 2932 (m), 2853 (w), 1697 (w), 1662 (w), 1602(w), 1447 (m), 1093 (s), 759 (s) cm^{-1}. ^1H NMR: $\delta = 7.59$–7.55 (m, 2H), 7.34–7.29 (m, 2H), 7.20–7.15 (m, 1H), 6.44 (s, 1H), 3.37 (s, 3H, OMe), 3.35–3.26 (m, 1H), 2.90–2.81 (m, 2H), 2.76–2.67 (m, 1H), 2.60–2.52 (m, 1H), 2.22–2.14 (m, 1H), 2.02–1.91 (m, 1H), 1.78–1.53 (m, 2H). ^{13}C NMR: $\delta = 153.1$ (s), 150.2 (s), 131.1 (s), 128.5 (d), 126.6 (d), 123.2 (d), 116.8 (s), 108.9 (d), 79.7 (d), 56.2 (q), 35.8 (t), 31.2 (t), 28.3 (t), 22.8. GC–MS: 242 (100%, M^+).

4.13. (*S*)-5-*tert*-Butoxy-5,6,7,8-tetrahydro-2-phenyl-4*H*-cyclohepta[*b*]furan 2ay

The reaction of **1a** (42 mg, 0.2 mmol, 86% ee) with *t*-butanol (27 mg, 0.4 mmol) in the presence of $Au[PPh_3]OTf$ (0.00625 M, 0.3 mL, 0.002 mmol) afforded 55 mg (97%, 83% ee (HPLC column D)) of **2ay** as a yellow liquid. $[\alpha]_\lambda$ (20 °C, $CHCl_3$, *c* 1): $[\alpha]_{589} = +7.1$, $[\alpha]_{546} = +7.7$, $[\alpha]_{405} = +4.6$. R_f (1:4 EtOAc/cyHex) = 0.75. IR (neat): 2969 (m), 2928 (m), 2852 (w), 1698 (w), 1601 (w), 1486 (w), 1447 (w), 1361 (m), 1698 (w), 1193 (s), 1053 (s), 1018 (m), 758 (w), 690 (m) cm^{-1}. ^1H NMR: $\delta = 7.60$–7.57 (m, 2H), 7.35–7.33 (m, 2H), 7.21–7.16 (m, 1H), 6.42 (s, 1H), 3.54 (m, 1H), 3.56–3.47 (m, 1H), 2.91–2.84 (m, 1H), 2.71–2.57 (m, 3H), 2.14–1.90 (m, 2H), 1.71–1.55 (m, 2H), 1.22 (s, 9H). ^{13}C NMR: $\delta = 153.2$ (s), 150.1 (s), 131.1 (s), 128.5 (d), 126.6 (d), 123.2 (d), 117.2 (s), 108.9 (d), 73.8 (s), 70.9 (d), 40.0 (t), 35.0 (t), 28.3 (q), 24.0 (t). GC–MS: 227 (100%), 284 (M^+)

4.14. Synthesis of (*S*)-5,6,7,8-tetrahydro-2-phenyl-5-(prop-2-ynyloxy)-4*H*-cyclohepta[*b*]furan 2az

The reaction of **1a** (32 mg, 0.15 mmol, 78% ee) with propargylic alcohol (17 mg, 0.3 mmol) in the presence of $Au[PPh_3]OTf$ (0.00625 M, 0.23 mL, 0.0015 mmol) afforded 27 mg (68%, 77% ee (HPLC column E)) of **2az** as a liquid. $[\alpha]_\lambda$ (20 °C, $CHCl_3$, *c* 1): $[\alpha]_{589} = -18.9$, $[\alpha]_{546} = -23.5$, $[\alpha]_{405} = -103.1$. R_f (1:10 EtOAc /cyHex) = 0.54. IR (neat): 3292 (w), 2927 (m), 2846 (w), 1676 (w), 1599 (w), 1553 (w), 1483 (w), 1446 (w), 1356 (w), 1080 (s), 932 (w), 932 (w), 813 (w), 759 (s), 691 (w) cm^{-1}. ^1H NMR: $\delta = 7.60$–7.57 (m, 2H), 7.36–7.31 (m, 2H), 7.22–7.17 (m, 1H), 6.45 (s, 1H), 4.22 (d, 2H, $J = 2.36$ Hz), 3.67 (tt, $J = 2.91$, $J = 9.37$ Hz), 2.90–2.83 (m, 2H), 2.77–2.71 (m, 1H), 2.68–2.58 (m, 1H), 2.41 (t, 1H, $J = 2.34$), 2.25–2.17 (m, 1H), 2.04–1.93 (m, 1H), 1.82–1.56 (m, 2H). ^{13}C NMR: $\delta = 153.1$ (s), 150.3 (s), 131.0 (s), 131.0 (d), 126.6 (d), 123.2 (d), 116.4 (s), 108.8 (d), 80.2 (s), 77.2 (d), 73.9 (d), 55.6 (t), 36.0 (t), 31.4 (t), 28.3 (t), 22.8 (t). GC–MS: 266 (100%, M^+). HRMS: calcd for $C_{18}H_{18}O_2$ = 266.1307, found: 266.131.

4.15. Synthesis of (*S*)-2-butyl-5,6,7,8-tetrahydro-5-methoxy-4*H*-cyclohepta[*b*]furan 2bx

The reaction of **1b** (38 mg, 0.2 mmol, 79% ee) with methanol (13 mg, 0.4 mmol) in the presence of $Au[PPh_3]OTf$ (0.00625 M, 0.3 mL, 0.002 mmol) afforded 29 mg (65%, 79% ee (GC column B)) of **2bx** as a liquid. $[\alpha]_\lambda$ (20 °C, $CHCl_3$, *c* 1): $[\alpha]_{589} = -2.9$, $[\alpha]_{546} = -3.8$, $[\alpha]_{405} = -13.8$, $[\alpha]_{365} = -23.7$. $R_f = 0.43$ (1:4 EtOAc / cyHex). IR (neat): 2929 (s), 2852 (m), 1574 (w), 1455 (w), 1369 (w), 1242 (w), 1188 (w), 1094 (s), 974 (w), 913 (w), 799 (w) cm^{-1}. ^1H NMR: $\delta = 5.75$ (s, 1H), 3.36 (s, 3H), 3.30–3.22 (m, 1H), 2.80–2.65 (m, 2H), 2.65–2.43 (m, 4H), 2.19–2.13 (m, 1H), 1.97–1.88 (m, 1H), 1.70–1.49 (m, 4H), 1.43–1.26 (m, 2H), 0.92 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR: $\delta = 152.8$ (s), 150.9 (s), 114.5 (s), 108.3 (d), 80.0 (d), 56.1 (q), 35.8 (t), 31.2 (t), 30.2 (t), 28.1 (t), 27.6 (t), 23.0 (t), 22.3(t), 13.8 (q). GC–MS: 147 (100%), 222 (M^+).

4.16. Synthesis of (*S*)-5-*tert*-butoxy-2-butyl-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]furan 2by

The reaction of **1b** (38 mg, 0.2 mmol, 79% ee) with *t*-butanol (27 mg, 0.4 mmol) in the presence of $Au[PPh_3]OTf$ (0.00625 M, 0.3 mL, 0.002 mmol) afforded 42 mg (80%) of **2by** as a liquid. $[\alpha]_\lambda$ (20 °C, $CHCl_3$, *c* 1): $[\alpha]_{589} = +7.5$; $[\alpha]_{546} = +9.2$; $[\alpha]_{405} = +16.0$. $R_f = 0.78$ (1:4 EtOAc/cyHex). IR (neat): 2962 (m), 2929 (s), 2855 (w), 1574 (w), 1455 (w), 1386 (w), 1360 (m), 1237 (w), 1194 (s), 1053 (s), 1018 (w), 865 (w), 799 (w) cm^{-1}. ^1H NMR: $\delta = 5.73$ (s, 1H), 3.50–3.42 (m, 1H), 2.78–2.71 (m, 1H), 2.60–2.47 (m, 5H),

2.10–2.04 (m, 1H), 1.92–1.85 (m, 1H), 1.65–1.53 (m, 4H), 1.43–1.31 (m, 2H), 0.94–0.89 (m, 3H). ^{13}C NMR: δ = 152.7 (s), 151.0 (s), 115.1 (s), 108.3 (d), 73.7 (s), 71.2 (d), 40.0 (t), 35.0 (t), 30.3 (t), 28.3 (q), 28.0 (t), 27.6 (t), 24.1 (t), 22.4 (t), 13.8 (q). GC–MS: 57 (100%), 264 (M^+). HRMS: calcd for $C_{17}H_{28}O_2$ = 264.2089, found: 264.209.

4.17. Synthesis of (*S*)-2-butyl-5,6,7,8-tetrahydro-5-(prop-2-ynyloxy)-4*H*-cyclohepta[*b*]furan 2bz

The reaction of **1b** (38 mg, 0.2 mmol) with propargylic alcohol (22 mg, 0.4 mmol) in the presence of Au[PPh_3]OTf (0.00625 M, 0.3 mL, 0.002 mmol) afforded 13 mg (26%, 80% ee (GC column A)) of **2bz** as a liquid. R_f (1:10 EtOAc/cyHex) = 0.52. $[\alpha]_\lambda$ (20 °C, $CHCl_3$, *c* 1): $[\alpha]_{589}$ = −2.2, $[\alpha]_{546}$ = −2.7, $[\alpha]_{405}$ = −9.6, $[\alpha]_{365}$ = −17.2, $[\alpha]_{365}$ = −31.8. IR (neat): 3293 (w), 3293 (s), 2853 (m), 1770 (w), 1574 (w), 1455 (m), 1360 (w), 1246 (w), 1082 (s), 963 (w), 803 (w) cm^{-1}. ^{1}H NMR: δ = 5.75 (s, 1H), 4.20 (d, 2H, *J* = 2.38 Hz), 3.60 (tt, *J* = 2.94, *J* = 9.51 Hz), 2.81–2.49 (m, 6H), 2.39 (t, 1H, *J* = 2.37 Hz), 2.22–2.14 (m, 1H), 1.98–1.88 (m, 1H), 1.74–1.52 (m, 4H), 1.36 (dt, 2H, *J* = 7.34 Hz, *J* = 14.28 Hz), 0.92 (t, 3H, *J* = 7.30). ^{13}C NMR: δ = 152.9 (s), 150.9 (s), 114.3 (s), 108.3 (d), 80.3 (s), 77.6 (d), 73.8 (d), 55.5 (t), 36.0 (t), 31.4 (t), 30.2 (t), 28.1 (t), 27.5 (t), 23.0 (s), 22.3 (t), 13.6 (q). GC–MS: 147 (100% peak), 246 (M^+). HRMS: calcd for $C_{16}H_{22}O_2$ = 246.1620, found: 246.162.

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16. The CD spectra were calculated through time-dependent density-functional theory (TDDFT) using GAUSSIAN 03W, the B3LYP functional and the 6-311++G(2d,2p) basis set.
17. For the calculation of the CD spectra shown in Figure 2 the lowest energy conformation was used. It should be noted that other low energy conformers of **1b** (resulting from rotations within the sidechain or from inversion of the pseudo-halfchair) also showed positive Cotton effects at 280 nm.
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20. X-ray crystal structure of **10**: Formula: C_{15} H_{16} O_1, crystal size: 0.3 × 0.1 × 0.03 mm; monocline; space group *P*21; 100 K; λ = 0.71073 Å; structure determination with direct methods (SHELXS); unit cell: *a* = 6.3332(3) Å, α = 90°, *b* = 20.8130(9) Å, β = 96.701(2)°, *c* = 14.0532(7) Å, γ = 90°; *Z* = 6; space group *P*21, *d* (calcd) = 1.150 mg/m^3; *F*(0 0 0) 684; Θ-range: 1.46–25.00°; 3347 independent reflexes; *R* indices [$1 > 2\sigma$ (1)]: R_1 = 0.0426, wR_2 = 0.0750; residual electron density: 0.174 and −0.223 eÅ^{-3}. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 772857.