Ready Access to the Echinopines Skeleton via Gold(I)-Catalyzed Alkoxycyclizations of Enynes

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ABSTRACT: The [3,5,5,7] tetracyclic skeleton of echinopines has been stereoselectively accessed through a gold(I)-catalyzed alkoxycyclization of cyclopropyl-tethered 1,6-enynes. The key bicyclo[4.2.1]nonane core of the enyne precursors was readily assembled by means of a Co-catalyzed [6 + 2] cycloaddition. Furthermore, the attempted alkoxycyclization of 1,5-enyne substrates revealed an uncovered cyclopropyl rearrangement that gives rise to [3,6,5,7] tetracyclic structures.

INTRODUCTION

Echinopines A and B (1 and 2) were isolated in 2008 from the roots of Echinops spinosus and feature an unprecedented [3,5,5,7]-membered-ring tetracyclic skeleton (Scheme 1), which probably originates biosynthetically from a guaiane precursor. This complex carbon framework holds five contiguous stereogenic centers, two of them being adjacent quaternary stereocenters. Despite the fact that no biological activity has been reported to date for 1 and 2, the unique architecture of these sesquiterpenes has constituted an appealing challenge for the synthetic community and several syntheses of echinopines have been accomplished to date.8−12 However, the assembly of the complex polycyclic framework of the echinopines skeleton is not easily addressed by conventional methods, as evidenced by the lengthy existing syntheses, and it is in most of the cases delayed to one of the last steps of the sequence.

Gold(I) catalysis constitutes a powerful tool for the construction of complex polycyclic architectures from relatively simple enyne substrates under mild reaction conditions. A concise synthesis of the complex polycyclic framework of the echinopines skeleton could easily provide access to structural analogues for further evaluation of their biological properties. In this context, we envisioned a gold(I)-catalyzed alkoxycyclization of cyclopropyl-tethered tricyclic 1,5- (3) or 1,6-enynes (4) as the key step for the ready access to the tetracyclic skeleton of echinopines via 5-endo or 5-exo cyclization, respectively (Scheme 1).13−16 This transformation would stereoselectively lead to echinopine-based tetracyclic products bearing different groups suited for further functionalization.

RESULTS AND DISCUSSION

Our approach for the synthesis of tricyclic enynes 3 and 4 relied on a cobalt-catalyzed [6 + 2] cycloaddition between cycloheptatriene and an internal alkyne as the key step to build the bicyclo[4.2.1]nonane core.17,18 Thus, orthogonally protected diol 5a afforded cycloadduct 6a, which upon monodeprotection and cyclopropanation of the tetrasubstituted olefin from the less sterically hindered face gave rise to tricyclic compound 8a (Scheme 2). Oxidation of the primary alcohol and subsequent homologation employing the Ohira−Bestmann reagent provided 1,5-enyne 3a.
Initial attempts to perform the alkoxycyclization of 3a with methanol as the external nucleophile in the presence of different cationic gold(I) complexes A–D only provided methyl ketone 10 as a result of the formal hydration of the terminal alkyne (Scheme 3).

Moreover, when the reaction was performed under strictly anhydrous conditions, the corresponding dimethyl acetal 11 could be isolated, which rapidly decomposed to 10 under ambient conditions, thus demonstrating that the addition of methanol to the terminal alkyne of 3a is favored over the attack of the alkene moiety. Similar results were obtained when other alcohols were employed as the external nucleophiles.

The use of carbonucleophiles such as indole, 1,3-diketones, and electron-rich benzenes only resulted in the recovery of unreacted 3a. Nevertheless, when the reaction of 3a was performed with commercially available gold(I) complex A in the presence of acetic acid, complete conversion of 3a was achieved in 1 h, leading to the formation of rearranged product 12 in up to 61% yield (Scheme 4). A closer mechanistic inspection of this transformation suggested that the gold(I)-catalyzed reaction initially forms intermediate 14 that rearranges to form allyl cation 15, which is trapped by acetic acid. DFT calculations indicated that the formation of intermediate 16 that leads to 12 is thermodynamically favored over the formation of 17, which is predicted to be the driving force for the rearrangement to take place. This result further illustrates the influence of the cyclopropane functionality on the reaction pathways followed in the gold(I)-catalyzed cyclizations of cyclopropane-tethered 1,5-enynes and underscores the propensity of the strained tetracyclic system of echinopines to undergo rearrangements.

In order to unequivocally ensure the structure of 12, the acetate moiety was cleaved to form alcohol 18, which was converted into the corresponding crystalline p-nitrobenzoate derivative 19, whose structure was confirmed by X-ray diffraction (Scheme 5).

In addition, a related system having one of the double bonds reduced was also examined with the aim of promoting a rearrangement toward the echinopine skeleton on the basis of the higher stability of carbocation 24 over 22 predicted by DFT calculations. Thus, 18 could be selectively hydrogenated in the presence of Crabtree’s catalyst to give 20, which was converted into tertiary carbocation 22 via triolate 21. Nonetheless, the rearranged product was not observed and only nonrearranged elimination product 23 was isolated under different reaction conditions.

The synthesis of the homologous 1,6-enyne 4a commenced with the cobalt-catalyzed [6 + 2] cycloaddition between cycloheptatriene and alkyne 25 followed by treatment with N-iodosuccinimide, which afforded vinyl iodide 27 (Scheme 6). Kumada cross-coupling of 27 with (3-(trimethylsilyl)prop-2-yn-1-yl)magnesium bromide furnished 28, which was treated with HF·py to give allylic alcohol 29. Cyclopropanation of the tetrasubstituted olefin followed by deprotection of the terminal alkyne and protection of the primary alcohol gave rise to tricyclic 1,6-enyne 4a. However, all attempts to perform the alkoxycyclization of 4a in the presence of different gold(I) complexes provided only traces of the cyclized tetracyclic product and resulted in the formation of methyl ketone 31 as the major product.

Aldehydes 9a,b were next employed as the platform to access a series of tricyclic 1,6-enynes featuring different functionalities at the propargylic position. Thus, the addition of ethynylmagnesium bromide provided 4b,c as single diastereoisomers and their alkoxycyclization was investigated.
The X-ray crystal structure of tetracycles bearing NHC and phosphite ligands gave complex mixtures.26

The structure of tetracycles 32a

nucleophile from methanol to allyl alcohol in the reaction of single regioisomer, the analogous reaction of closely related system catalyzed cyclization process. In order to elucidate the order of substituent by a second molecule of alcohol in the gold(I)-[3,5,5,7] tetracyclic skeleton of echinopines ( Scheme 7 ).

while the reaction of 4b,c and their alkoxycyclization under the optimized reaction conditions provided mixtures of the two possible regiosomeric products 39a′,b′ and 39a″,b″, which could be separated by preparative chromatography ( Scheme 10 ). Water could also be used as the external nucleophile to afford inseparable mixtures of regiosomeric allylic alcohols 39c′,d′/39c″,d″ in moderate yields.

■ CONCLUSION

In summary, the [3,5,5,7] tetracyclic core of echinopines can be readily accessed through the gold(I)-catalyzed alkoxycyclization of tricyclic cyclopropyl-tethered 1,6-enynes bearing an O functionality at the propargylic position, giving access to functionalized echinopine analogues as single stereoisomers. Furthermore, the cyclization of 1,5-enyne 3a uncovered an unexpected migration of the cyclopropane functionality, thus providing access to the complex natural-product-like [3,6,5,7] tetracycle 12.

■ EXPERIMENTAL SECTION

General Remarks. Chemicals and solvents for chromatography were used as received. Solvents used in reactions under an inert atmosphere were dried by passing through an activated alumina column on a solvent purification system. Analytical thin-layer chromatography was carried out using TLC-aluminum sheets with 0.2 mm of silica gel (Merck FG254) with UV light as the visualizing agent or an acidic solution of vanillin in ethanol as the developing agent. Purifications by chromatography were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40–60 mm). Preparative TLC was performed on 20 cm × 20 cm silica gel plates. Organic solutions were concentrated under reduced pressure on a rotary evaporator. NMR spectra were recorded at 298 K on 300, 400, and 500 MHz devices. 1H and 13C chemical shifts (δ) are given in ppm relative to TMS, and coupling constants (J) in Hz. Mass spectra were recorded employing TOF mass analyzers (ESI, APCI). Melting points were determined by observation of the fusion of the solids placed in a capillary, through a magnifying glass. Crystal structure determinations were carried out using a diffractometer equipped with an APPEX 2-4K CCD area detector, an FR3PH rotating anode with Mo Kα radiation, Montel mirrors as the monochromator, and a Kryoslow low temperature device (T = −173 °C). Full-sphere data collection was used with ω and φ scans. Programs used: data collection APEX-2, data reduction Bruker Smart V/0.60A, and absorption correction SADABS. Structure solution and refinement: crystal structure solution was achieved using direct methods as implemented in SHELXTL. All non-hydrogen atoms were refined including anisotropic displacement parameters. tert-Butyl(4-methoxybut-2-yn-1-yl)oxy)dimethylsilane (5a). NaH (60% in mineral oil, 1.89 g, 47.2 mmol) was added to a solution of 4-(((tert-butyldimethylsilyl)oxy)but-2-yn-1-ol25 (8.60 g, 42.9 mmol)
in anhydrous THF (210 mL) under argon at 0 °C. The resulting suspension was stirred for 30 min, and then methyl iodide (3.2 mL, 51.5 mmol) was slowly added. The reaction mixture was warmed to room temperature and then stirred for 1.5 h. After it was diluted with Et₂O (100 mL), the mixture was washed with a saturated solution of NH₄Cl (150 mL) and water (150 mL), the aqueous layers were extracted with Et₂O (2 × 100 mL), and the combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The product was obtained after purification by flash
chromatography (cyclohexane/EtOAc 95/5) as a clear oil (8.00 g, 37.3 mmol, yield 87%). 1H NMR (400 MHz, CDCl3): δ 4.38 (t, J = 1.8 Hz, 2H), 4.15 (t, J = 1.8 Hz, 2H), 3.40 (s, 3H), 0.93 (s, 9H), 0.14 (s, 6H). 13C NMR (101 MHz, CDCl3): δ 85.1, 80.6, 60.0, 57.6, 51.7, 25.8, 18.3, −5.2. HRMS (ESI+): m/z calcd for C11H23NaO2Si [M + Na]+, 237.1281; found, 237.1278.

**Scheme 6.** Cobalt (306.1 mg, 1.40 mmol), Zn (366.1 mg, 5.60 mmol), and ZnI2 (1.79 g, 5.60 mmol) were suspended in anhydrous 1,2-dichloroethane (20 mL) under argon. Then P(OiPr)3 (0.69 mL, 4.18 mmol) was added, followed by cycloheptatriene (4.36 mL, 41.98 mmol) and a solution of S8 (27.99 mmol) in dry 1,2-dichloroethane (8 mL). The resulting mixture was stirred at 50 °C for 16 h and then filtered through a pad of Celite and concentrated under reduced pressure. Purification of the resulting crude by flash chromatography (cyclohexane/EtOAc 1/0 to 95/5) afforded compounds 6.

tert-Butyl[(1R*,6S*)-8-(methoxymethyl)bicyclo[4.2.1]nona-2,4,7-trien-7-yl]methoxy(dimethyl)silane (6a). Yellow oil (6.69 g, 21.33 mmol, yield 78%). 1H NMR (300 MHz, CDCl3): δ 6.29−6.11 (m, 2H), 5.84−5.74 (m, 2H), 4.35 (d, J = 13.1 Hz, 1H), 4.23 (d, J = 13.1 Hz, 1H), 4.12 (d, J = 12.3 Hz, 1H), 3.92 (d, J = 12.3 Hz, 1H), 3.41 (t, J = 7.1 Hz, 1H), 3.32 (d, J = 7.1 Hz, 1H), 3.27 (s, 3H), 2.29−2.17 (m, 1H), 1.61 (d, J = 11.6 Hz, 1H), 0.93 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H). 13C NMR (75 MHz, CDCl3): δ 139.8, 139.8, 138.4, 132.1, 124.3, 124.2, 66.2, 57.8, 57.2, 45.4, 44.7, 30.0, 25.9, 18.4, −5.3, −5.4. HRMS (ESI+): m/z calcd for C24H34NaO2Si [M + Na]+, 392.1907; found, 392.1904.

((1R*,6S*)-8-(Benzyloxy)methyl)bicyclo[4.2.1]nona-2,4,7-trien-7-yl)methanol (7a). Colorless oil (1.62 g, 8.4 mmol, yield 74%). 1H NMR (400 MHz, CDCl3): δ 6.30−6.14 (m, 2H), 5.89−5.78 (m, 2H), 4.30 (dd, J = 13.2, 6.3 Hz, 1H), 4.24 (dd, J = 13.2, 4.9 Hz, 1H), 4.17 (d, J = 12.6 Hz, 1H), 4.00 (d, J = 12.4 Hz, 1H), 3.38−3.26 (m, 2H), 3.32 (s, 3H), 2.26 (dt, J = 11.5, 6.8, 1.3 Hz, 1H), 1.95 (t, J = 5.7 Hz, 1H), 1.61 (d, J = 11.4 Hz, 1H). 13C NMR (101 MHz, CDCl3): δ 139.3, 139.3, 137.6, 133.3, 124.6, 125.6, 66.5, 58.1, 57.6, 45.7, 45.7, 30.0. HRMS (ESI+): m/z calcd for C24H34NaO2 [M + Na]+, 215.1043; found, 215.1042.

((1R*,6S*)-8-(Benzyloxy)methyl)bicyclo[4.2.1]nona-2,4,7-trien-7-yl)methanol (7b). Colorless oil (2.29 g, 8.55 mmol, yield 75%). 1H NMR (500 MHz, CDCl3): δ 7.41−7.30 (m, 3H), 6.28−6.16 (m, 2H), 5.86−5.84 (m, 1H), 5.84−5.81 (m, 1H), 4.52 (d, J = 11.8 Hz, 1H), 4.46 (d, J = 11.8 Hz, 1H), 4.31−4.19 (m, 3H), 4.11 (d, J = 12.5 Hz, 1H), 3.35 (t, J = 7.0 Hz, 2H), 2.27 (dtt, J = 11.5, 6.8, 1.2 Hz, 1H), 1.76 (s, 1H), 1.63 (d, J = 11.4 Hz, 1H). 13C NMR (101 MHz, CDCl3): δ 139.4, 139.4, 139.1, 137.7, 133.5, 128.4, 127.8, 127.7, 124.6, 124.6, 72.2, 63.9, 57.5, 45.7, 45.7, 30.0. HRMS (ESI+): m/z calcd for C24H34NaO2 [M + Na]+, 291.1356; found, 291.1365.

**Synthesis of 8.** Diiodomethane (0.61 mL, 7.57 mmol) and ZnEt2 (1.0 M in hexanes, 15.75 mL, 15.75 mmol) were added to a solution of 7 (6.30 mmol) in anhydrous CH2Cl2 (210 mL) at 0 °C. The resulting mixture was warmed to room temperature and stirred until TLC analysis showed complete disappearance of the starting material (5−12 h). The reaction mixture was quenched by the slow addition of a saturated aqueous Na2/K-tartrate solution (100 mL), and after it was stirred for 30 min the organic layer was separated, the aqueous layer was extracted with CH2Cl2 (100 mL), and the combined organic phases were dried over MgSO4 and concentrated under reduced pressure. Purification by flash chromatography (cyclohexane/EtOAc 7/3) afforded products 8.

((1R*,6S*,7R*,9S*)-9-[Methoxymethyl]tricyclo[4.3.1.02,6]deca-4,7-dien-7-yl)methanol (8a). Colorless oil (1.22 g, 5.92 mmol, yield 94%). 1H NMR (500 MHz, CDCl3): δ 6.11−6.00 (m, 2H), 5.85−5.74 (m, 2H), 4.01 (dd, J = 10.0, 1.2 Hz, 1H), 3.84 (d, J = 11.7 Hz, 1H), 3.67 (d, J = 11.7 Hz, 1H), 3.38 (s, 3H), 3.10 (d, J = 10.0 Hz, 1H), 2.86−2.78 (m, 2H), 2.01 (dt, J = 12.8, 6.3, 1.3 Hz, 1H), 1.78 (d, J = 13.1 Hz, 1H), 1.73 (d, J = 13.0 Hz, 1H), 0.81 (d, J = 5.6 Hz, 1H), 0.26 (d, J = 5.6 Hz, 1H). 13C NMR (101 MHz, CDCl3): δ 137.3, 136.5, 125.9, 125.0, 73.4, 64.2, 58.8, 42.1, 42.0, 39.6, 26.6, 14.4. HRMS:
Synthesis of 9. Dess–Martin periodinane (2.67 g, 6.30 mmol) was added to a solution of 8 (4.85 mmol) in CH2Cl2 (50 mL). After the addition of 1 drop of water the resulting suspension was stirred at room temperature for 1 h and then washed with a 1:1 mixture of a saturated solution of Na2S2O3/Na2CO3 (40 mL). The organic layer was filtered, and concentrated under reduced pressure. Purified by flash chromatography (cyclohexane/EtOAc 7/3).

(1R*,6S*,7R*,9S*)-9-((Benzyloxy)methyl)tricyclo[4.3.1.07,9]deca-2,4-diene-7-carbaldehyde (9a). Colorless oil (871.7 mg, 4.27 mmol, yield 88%). 1H NMR (500 MHz, CDCl3): δ 13.5, 136.3, 136.6, 138.6, 127.7, 127.6, 125.9, 125.0, 72.9, 70.9, 64.3, 42.1, 42.1, 41.5, 27.9, 26.6. 14.6. HRMS (ESI+): m/z calc for C13H18NaO2 [M + Na]+, 205.1512; found, 205.1517.

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benzoate (19). 4-Nitrobenzoyl chloride (30.6 mg, 0.16 mmol) was added to a solution of 18 (30 mg, 0.23 mmol), Et3N (38 µL, 0.27 mmol), and DMAP (1.2 mg, 0.01 mmol) in anhydrous CH2Cl2 (3 mL), and the mixture was stirred at room temperature for 1 h and then washed with H2O (2 × 5 mL). The organic layer was dried over MgSO4, filtered, and concentrated under reduced pressure. Purification by column chromatography (cyclohexane/EtOAc 9/1) afforded the product as a white solid (51.3 mg, 0.14 mmol, yield quantitative).

Mp: 136−138 °C. 1H NMR (500 MHz, CDCl3): δ 8.32−8.29 (m, 2H), 8.24−8.20 (m, 2H), 6.63 (dt, J = 5.9, 0.9 Hz, 1H, 5.84 (dd, J = 5.9, 3.1 Hz, 1H), 5.68 (dd, J = 12.5, 8.0, 2.1 Hz, 1H), 5.34 (dd, J = 12.4, 4.2, 1.1 Hz, 1H), 3.32 (q, J = 10.0 Hz, 1H), 3.25 (3H, 1H, 3.10 (m, 1H), 1.11 (s, 1H, 1H), 1.92−1.23 (m, 5H, 1H), 1.23 (m, 5H, 1H), 1.28−1.09 (m, 5H, 1H). 13C NMR (126 MHz, CDCl3): δ 163.9, 150.7, 137.0, 136.9, 134.0, 130.6, 126.7, 123.7, 123.5, 88.0, 81.3, 88.2, 47.5, 42.7, 32.0, 28.1, 24.5, 21.7, 19.3. HRMS (ESI+): m/z calcd for C14H20NaO2 [M + Na]+, 348.1353; found, 348.1352.

**tert-Butyl diphenyldithiophenyl(1R,6S)-8-(3-trimethylsilylprop-2-ynyl)-1 bicyclo[4.2.1]- nona-2,4,7-trien-5-yl)methanol (26)**. ColBr (258.6 mg, 1.09 mmol), MnCl2 (13.9 N, 4.36 mmol) were suspended in anhydrous 1,2-dichloroethane (35 mL) under argon. Then (P(O)(OR)3)2 (0.54 mL, 2.18 mmol) was added, followed by cycloheptatriene (3.40 mL, 32.73 mmol) and a solution of 25 (8.00 g, 21.82 mmol) in anhydrous 1,2-dichloroethane (9 mL). The resulting mixture was stirred at 50 °C for 30 h and then filtered through a short pad of silica gel and concentrated under reduced pressure. Purification by flash chromatography (cyclohexane/EtOAc 1/0 to 95/5) afforded the product as a colorless oil (528.1 mg, 1.06 mmol, yield over two steps 44%). 1H NMR (400 MHz, CDCl3): δ 7.72−7.67 (m, 4H, 7.47−7.36 (m, 6H), 6.27−6.18 (m, 1H, 6.17−6.09 (m, 1H), 5.83−5.71 (m, 2H), 4.33 (d, J = 12.8 Hz, 1H), 4.20 (d, J = 13.0 Hz, 1H, 3.42 (t, J = 7.0 Hz, 1H), 3.36 (t, J = 7.0 Hz, 1H), 2.95 (d, J = 19.4 Hz, 1H), 2.85 (d, J = 18.6 Hz, 1H), 2.26 (dtt, J = 11.3, 6.7, 1.2 Hz, 1H), 1.61 (d, J = 13.8 Hz, 1H, 1.06 (s, 9H), 0.16 (s, 9H)). 13C NMR (101 MHz, CDCl3): δ 145.7, 139.1, 138.1, 135.6, 133.4, 133.4, 129.7, 127.7, 125.4, 124.9, 84.5, 60.3, 52.9, 44.1, 30.8, 26.9, 19.3. HRMS (ESI+): m/z calcd for C30H34NaO3 [M + Na]+, 535.0925; found, 535.0919.

**tert-Butyl diphenyldithiophenyl(1R,6S)-8-(3-trimethylsilylprop-2-ynyl)-1 bicyclo[4.2.1]- nona-2,4,7-trien-5-yl)methanol (26)**. ColBr (258.6 mg, 1.09 mmol), MnCl2 (13.9 N, 4.36 mmol) were suspended in anhydrous 1,2-dichloroethane (35 mL) under argon. Then (P(O)(OR)3)2 (0.54 mL, 2.18 mmol) was added, followed by cycloheptatriene (3.40 mL, 32.73 mmol) and a solution of 25 (8.00 g, 21.82 mmol) in anhydrous 1,2-dichloroethane (9 mL). The resulting mixture was stirred at 50 °C for 30 h and then filtered through a short pad of silica gel and concentrated under reduced pressure. Purification by flash chromatography (cyclohexane/EtOAc 1/0 to 95/5) afforded the product as a colorless oil (528.1 mg, 1.06 mmol, yield over two steps 44%). 1H NMR (400 MHz, CDCl3): δ 7.72−7.67 (m, 4H, 7.47−7.36 (m, 6H), 6.27−6.18 (m, 1H, 6.17−6.09 (m, 1H), 5.83−5.71 (m, 2H), 4.33 (d, J = 12.8 Hz, 1H), 4.20 (d, J = 13.0 Hz, 1H, 3.42 (t, J = 7.0 Hz, 1H), 3.36 (t, J = 7.0 Hz, 1H), 2.95 (d, J = 19.4 Hz, 1H), 2.85 (d, J = 18.6 Hz, 1H), 2.26 (dtt, J = 11.3, 6.7, 1.2 Hz, 1H), 1.61 (d, J = 13.8 Hz, 1H, 1.06 (s, 9H), 0.16 (s, 9H)). 13C NMR (101 MHz, CDCl3): δ 145.7, 139.1, 138.1, 135.6, 133.4, 133.4, 129.7, 127.7, 125.4, 124.9, 84.5, 60.3, 52.9, 44.1, 30.8, 26.9, 19.3. HRMS (ESI+): m/z calcd for C30H34NaO3 [M + Na]+, 535.0925; found, 535.0919.
slow addition of a saturated aqueous Na/K-tartrate solution (100 mL), and after the mixture was stirred for 30 min, the organic layer was separated, the aqueous layer was extracted with CH2Cl2 (100 mL), and the combined organic phases were dried over MgSO4 and concentrated under reduced pressure. Purification by flash chromatography (cyclohexane/EtOAc 8/2) afforded the product as a pale yellow oil (378.0 mg, 1.39 mmol, yield 94%). 1H NMR (400 MHz, CDCl3): δ 7.04 (d, J = 7.1 Hz, 1H), 6.81 (d, J = 7.3 Hz, 1H), 3.82 (s, 3H), 2.93 (s, 3H), 2.76 (t, J = 7.2 Hz, 1H), 2.73 (t, J = 6.7 Hz, 1H), 2.18 (s, 3H), 2.14 (d, J = 16.0 Hz, 1H), 2.04–1.95 (m, 1.9H), 1.71 (d, J = 13.0 Hz, 1H), 0.91 (s, 9H), 0.79 (d, J = 5.7 Hz, 1H), 0.21 (d, J = 5.7 Hz, 1H), 0.06 (s, 3H), 0.06 (s, 3H). 13C NMR (100 MHz, CDCl3): δ 208.9, 136.6, 136.5, 125.2, 125.1, 63.1, 43.7, 42.9, 41.8, 41.0, 35.6, 30.2, 26.4, 25.9, 18.3, 13.9, −5.2, −5.4. HRMS (ESI+): m/z calcd for C27H31O5Na [M + Na]+, 497.2292; found, 496.2269.

Synthesis of 4b.c. Ethynylmagnesium bromide (0.5 M in THF, 8.07 mL, 4.04 mmol) was added to a solution of 9 (3.67 mmol) in anhydrous THF (37 mL) at 0 °C. After it was stirred at room temperature for 30 min, the reaction mixture was diluted with Et2O (15 mL) and quenched by the addition of saturated NH4Cl aqueous solution (50 mL). The aqueous layer was extracted with Et2O (2 × 40 mL), the combined organic phases were dried over MgSO4, and concentrated under reduced pressure. Purification of flash chromatography (cyclohexane/EtOAc 8/2) afforded the pale yellow oil (769.2 mg, 3.34 mmol, yield 91%). 1H NMR (400 MHz, CDCl3): δ 7.04 (d, J = 7.1 Hz, 1H), 6.81 (d, J = 7.3 Hz, 1H), 3.82 (s, 3H), 2.93 (s, 3H), 2.76 (t, J = 7.2 Hz, 1H), 2.73 (t, J = 6.7 Hz, 1H), 2.18 (s, 3H), 2.14 (d, J = 16.0 Hz, 1H), 2.04–1.95 (m, 1.9H), 1.71 (d, J = 13.0 Hz, 1H), 0.91 (s, 9H), 0.79 (d, J = 5.7 Hz, 1H), 0.21 (d, J = 5.7 Hz, 1H), 0.06 (s, 3H), 0.06 (s, 3H). 13C NMR (100 MHz, CDCl3): δ 138.1, 137.3, 136.0, 128.4, 127.7, 127.6, 126.3, 125.0, 83.9, 73.6, 73.0, 69.7, 61.2, 43.8, 43.3, 43.0, 40.3, 26.4, 11.6. HRMS (APCI+): m/z calcd for C22H23NaO2 [M + Na]+, 253.1192; found, 252.1189.

Gold-Catalyzed Cyclization of 1,6-Enynes 4b,c. Gold(I) complex B (3.1 mg, 0.002 mmol) was added to a solution of 4b,c (0.1 mmol) in ROH (1 mL), and the resulting suspension was stirred at room temperature for 2 h before the addition of 1 drop of Et3N. Then the volatiles were removed under reduced pressure and the resulting crude product was purified by column chromatography to afford tetracycles 32.

(1H,4H,9H)-6,7-Dimethoxy-1a-(methylene)-5-methylen-1,1a,2,3,3a,4,5,6-octahydro-2,4-prop[1]encyclopropa[c]pentalene (32a). Purification: pentane/CH2Cl2 9:1. White solid (2.06 mg, yield 91%). 32a: δ 7.02 (d, J = 10.8 Hz, 1H, H1), 6.34 (d, J = 2.9 Hz, 1H, H3), 4.79 (dd, J = 7.3, 3.7 Hz, 1H), 3.70 (dd, J = 9.8, 1.6 Hz, 1H), 3.47 (s, 4H), 3.41 (s, 4H), 3.16–3.29 (m, 19H), 3.33 (s, 3H), 2.90 (dd, J = 9.7, 6.6 Hz, 1H), 2.84–2.80 (m, 2H), 2.50 (d, J = 13.7 Hz, 1H), 1.42 (d, J = 13.6, 1.7 Hz, 1H), 1.12 (dd, J = 5.8, 1.6 Hz, 1H), 1.08 (d, J = 5.8 Hz, 1H). 13C NMR (101 MHz, CDCl3): δ 151.6, 142.0, 127.8, 115.7, 107.3, 86.9, 84.7, 83.3, 78.9, 77.6, 77.5, 73.8, 67.6, 67.2, 58.3, 56.7, 56.6, 54.9, 45.6, 42.6, 40.9, 36.1, 30.3, 160. HRMS (ESI−): m/z calcd for C27H23NaO2 [M − Na]−, 249.1768; found, 249.1764. Note: This reaction could be scaled up to obtain 400 mg of 32a without any decrease in yield or selectivity. X-ray-quality single crystals were obtained by slow evaporation of a solution of 32a in CH2Cl2 at 5 °C.
Synthesis of 4d.e. Dess-Martin periodinane (47.88 mg, 1.13 mmol) was added to a solution of 4b,c (0.87 mmol) in CH$_2$Cl$_2$ (9 mL). After the addition of 1 drop of water, the resulting suspension was stirred at room temperature for 1 h and then washed with a 1/1 mixture of a saturated solution of Na$_2$SO$_4$/Na$_2$CO$_3$ (40 mL). The organic layer was dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The product was obtained after purification by flash chromatography (cyclohexane/EtOAc 7/3).

1-(1R*,6S*,7R*,9S*)-9-(Benzoxymethyl)tricyclo[4.3.1.0$^7,9$]dec-2,4-dien-7-yl-prop-2-yn-1-one (4d). Yellow oil (121.2 mg, 0.53 mmol, yield 61%). 1H NMR (400 MHz, CDCl$_3$): δ 6.32 (dd, J = 11.4, 7.4, 1.1 Hz), 6.02 (dd, J = 11.2, 7.7, 0.9 Hz, 1H), 5.79 (dd, J = 11.5, 7.4, 0.8 Hz, 1H), 5.70 (dd, J = 11.4, 7.4, 0.8 Hz, 1H), 4.02 (dd, J = 10.1, 1.5 Hz, 1H), 3.82 (d, J = 10.1 Hz, 1H), 3.42 (3H, 3.26 (1H), 3.12–3.06 (m, 1H), 2.91 (t, J = 7.0 Hz, 1H), 2.06–1.98 (m, 1H), 1.85 (dd, J = 13.2, 0.6 Hz, 1H), 1.34 (d, J = 5.5, 14 Hz, 1H), 1.26 (d, J = 5.5 Hz, 1H). 13C NMR (126 MHz, CDCl$_3$): δ 185.7, 136.9, 134.8, 125.5, 124.1, 82.0, 79.1, 71.4, 58.8, 52.3, 45.4, 41.7, 40.4, 25.6, 22.5. HRMS (ESI+): m/z calcd for C$_{26}$H$_{23}$NaO$_3$ [M + Na]$^+$, 425.1034; found, 425.1035.

Gold-Catalyzed Cyclizations of 1,6-Enynes 4d.e. Gold(I) complex B (3.1 mg, 0.002 mmol)$^{37}$ was added to a solution of 4d.e (0.1 mmol) in ROH (1 mL) or a 2/1 dioxane/H$_2$O mixture (2 mL), and the resulting suspension was stirred at room temperature for the appointed time before the addition of 1 drop of Et$_3$N. Then the volatiles were removed under reduced pressure and purification by preparative TLC afforded the tetracyclic products 39/39'.

1-(1R*,6S*,7R*,9S*)-9-(Benzoxymethyl)-7-methoxy-5-methylene-1a,2,3,3a,4,5-hexahydro-2-prop-1-enocyclopropapentalene (39). General procedure starting from 4e and methanol. Reaction time: 1 h. Purification: cyclohexane/EtOAc 95/5 (eluted three times). White solid (15.1 g, 4.85 mmol, yield 45%). Mp: 59–61 ºC. 1H NMR (400 MHz, CDCl$_3$): δ 7.40–7.28 (m, 5H), 6.14–6.07 (m, 2H), 5.72 (dd, J = 11.8, 7.2 Hz, 1H), 5.33 (dd, J = 2.2, 0.6 Hz, 1H), 4.58 (d, J = 11.9 Hz, 1H), 4.44 (d, J = 12.0 Hz, 1H), 3.82 (dd, J = 7.3, 3.1, 0.7 Hz, 1H), 3.68 (dd, J = 10.0, 1.9 Hz, 1H), 3.54–3.48 (m, 1H), 3.34 (3H, 3.30 (t, J = 9.9 Hz, 1H), 3.03 (t, J = 6.6 Hz, 1H), 2.89 (dd, J = 9.3, 7.2 Hz, 1H), 2.74 (d, J = 13.9 Hz, 1H), 1.87 (d, J = 5.7 Hz, 1H), 1.68 (dt, J = 13.9, 6.9, 1.7 Hz, 1H), 1.52 (d, J = 5.8, 1.8 Hz, 1H). 13C NMR (101 MHz, CDCl$_3$): δ 201.7, 147.6, 140.4, 138.3, 128.4, 127.7, 127.1, 112.8, 82.7, 73.1, 70.5, 56.6, 52.7, 47.5, 45.6, 42.4, 42.0, 31.5, 22.4. HRMS (ESI+): m/z calcd for C$_{26}$H$_{28}$NaO$_3$ [M + Na]$^+$, 359.1618; found, 359.1617.

1-(1R*,6S*,7R*,9S*)-9-(Benzoxymethyl)-9-methoxy-5-methylene-1a,2,3,3a,4,5-hexahydro-4,2-prop-1-enocyclopropapentalene (39'). General procedure starting from 4e and methanol. Reaction time: 1 h. Purification: cyclohexane/EtOAc 95/5 (eluted three times). White solid (9.7 mg, yield 29%). Mp: 70–72 ºC. 1H NMR (400 MHz, CDCl$_3$): δ 7.40–7.26 (m, 5H), 6.14–6.07 (m, 2H), 5.72 (dd, J = 11.8, 7.2 Hz, 1H), 5.33 (dd, J = 2.9, 0.8 Hz, 1H), 4.58 (d, J = 11.9 Hz, 1H), 4.44 (d, J = 12.0 Hz, 1H), 3.82 (dd, J = 7.3, 3.1, 0.7 Hz, 1H), 3.68 (dd, J = 10.0, 1.9 Hz, 1H), 3.54–3.48 (m, 1H), 3.34 (3H, 3.30 (t, J = 9.9 Hz, 1H), 3.03 (t, J = 6.6 Hz, 1H), 2.89 (dd, J = 9.3, 7.2 Hz, 1H), 2.74 (d, J = 13.9 Hz, 1H), 1.87 (d, J = 5.7 Hz, 1H), 1.68 (dt, J = 13.9, 6.9, 1.7 Hz, 1H), 1.52 (d, J = 5.8, 1.8 Hz, 1H). 13C NMR (101 MHz, CDCl$_3$): δ 201.7, 147.6, 140.4, 138.3, 128.4, 127.7, 127.1, 112.8, 82.7, 73.1, 70.5, 56.6, 52.7, 47.5, 45.6, 42.4, 42.0, 31.5, 22.4. HRMS (ESI+): m/z calcd for C$_{26}$H$_{28}$NaO$_3$ [M + Na]$^+$, 359.1618; found, 359.1617.
5.4 Hz, 1H), 1.68−1.61 (m, 1H), 1.34 (dd, J = 5.5, 1.7 Hz, 1H). 13C NMR (101 MHz, CDCl3): δ 202.1, 149.7, 138.1, 131.5, 128.4, 127.9, 127.8, 121.1, 115.5, 78.2, 73.1, 69.3, 56.9, 47.5, 47.1, 44.8, 43.6, 26.7, 21.0. HRMS (ESI+): m/z calculated for C22H31NO5 [M + Na]+, 359.1618; found, 359.1616.

-25 °C, 15.5% 6aS, 7bR*−7-(Allyloxy)-1a-(benzoxymethyl)-5-methylene-1a,2,3,3a,4,5-hexahydro-2,4-prop[1]enocyclopropa[c]pentalen-6(1H)-one (39b). General procedure starting from 4e and allyl alcohol. Reaction time: 1.5 h. Purification: cyclohexane/EtOAc 95/5 (eluted three times). White solid (15.1 mg, 99.3, 7.2 Hz, 1H), 2.80 (d, J = 10.4, 1.8 Hz, 1H), 3.16 (d, J = 11.8 Hz, 1H), 4.44 (d, J = 12.6, 5.5, 1.5 Hz, 1H), 4.07 (dd, J = 12.6, 5.7, 1.4 Hz, 1H). 3.97 (dd, J = 3.3, 1.0 Hz, 1H), 3.68 (dd, J = 10.0, 1.8 Hz, 3H), 3.05 (d, J = 9.2, 2.5 Hz, 1H), 3.06 (d, J = 10.0 Hz, 1H), 3.06 (t, J = 6.7 Hz, 1H), 2.90 (dd, J = 9.3, 7.2 Hz, 1H), 2.80 (d, J = 13.9 Hz, 1H), 1.86 (d, J = 5.7 Hz, 1H). 1.69 (dd, J = 13.9, 6.9, 1.7 Hz, 1H), 1.52 (dd, J = 5.8, 1.7 Hz, 1H). 13C NMR (101 MHz, CDCl3): δ 201.7, 147.7, 140.3, 138.3, 135.1, 128.4, 127.7, 127.7, 127.5, 118.0, 117.2, 80.1, 73.1, 70.5, 69.3, 52.8, 47.3, 46.0, 42.4, 42.0, 31.6, 22.4. HRMS (ESI+): m/z calculated for C22H31NO5 [M + Na]+, 385.1774; found, 385.1780.

1aR, 3aS, 4aS, 4bS, 5bS, 5cS, 5dS, 6aS, 7bR*−7-(Allyloxy)-1a-(benzoxymethyl)-5-methylene-1a,2,3,3a,4,5-hexahydro-2,4-prop[1]enocyclopropa[c]pentalen-6(1H)-one (39c). General procedure starting from 4e and allyl alcohol. Reaction time: 1.5 h. Purification: cyclohexane/ EtOAc 95/5 (eluted three times). White solid (15.1 mg, 99.3, 7.2 Hz, 1H), 2.80 (d, J = 10.4, 1.8 Hz, 1H), 3.16 (d, J = 10.4, 1.8 Hz, 1H), 2.80 (d, J = 13.9 Hz, 1H), 1.86 (d, J = 5.7 Hz, 1H). 1.69 (dd, J = 13.9, 6.9, 1.7 Hz, 1H), 1.52 (dd, J = 5.8, 1.7 Hz, 1H). 13C NMR (101 MHz, CDCl3): δ 201.7, 147.7, 140.3, 138.3, 135.1, 128.4, 127.7, 127.7, 127.5, 118.0, 117.2, 80.1, 73.1, 70.5, 69.3, 52.8, 47.3, 46.0, 42.4, 42.0, 31.6, 22.4. HRMS (ESI+): m/z calculated for C22H31NO5 [M + Na]+, 385.1774; found, 385.1780.

1aR, 3aS, 4aS, 4bS, 5bS, 5cS, 5dS, 6aS, 7bR*−7-(Allyloxy)-1a-(benzoxymethyl)-5-methylene-1a,2,3,3a,4,5-hexahydro-2,4-prop[1]enocyclopropa[c]pentalen-6(1H)-one (39d). General procedure starting from 4e and water. Reaction time: 5 h. Purification: cyclohexane/ EtOAc 6/4 (eluted twice). Colorless oil (18.6 mg, yield 58%). 39d: 39d: 1aR, 3aS, 4aS, 4bS, 5bS, 5cS, 5dS, 6aS, 7bR*−7-(Allyloxy)-1a-(benzoxymethyl)-5-methylene-1a,2,3,3a,4,5-hexahydro-2,4-prop[1]enocyclopropa[c]pentalen-6(1H)-one (39d). General procedure starting from 4e and water. Reaction time: 5 h. Purification: cyclohexane/ EtOAc 6/4 (eluted twice). Colorless oil (18.6 mg, yield 58%).
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(25) Aldehydes 9b,c were prepared following a route analogous to that for the preparation of 9a shown in Scheme 2. See the Supporting Information for details.

(26) See the Supporting Information for details.

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