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Gold Catalysis: Regio- and Stereoselective Total Synthesis of Xyloketals D and G and the Related Natural Product Alboatrin

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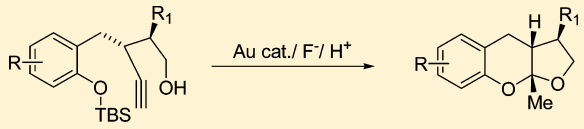
Supporting Information

ABSTRACT: A new and efficient one-pot desilylation−gold-catalyzed cycloisomerization of alkynes containing a silyl-protected phenolic −OH and a free alcoholic −OH unit leads selectively to the formation of tetrahydrofuranobenzopyran ring system. This approach has been used for the regio- and stereoselective synthesis of xyloketal D, xyloketal G, and the related natural product alboatrin.



INTRODUCTION

Xyloketals, originated from the mangrove fungus sp. (no. 2508), are a family of novel ketal compounds having a close biogenetic relationship.[1] The unique characteristics of this series of molecules is the *cis* disposition of three contiguous stereogenic centers embedded in the tetrahydrofuranobenzopyran moiety (Figure 1). Among them, xyloketal A (**1**) is most

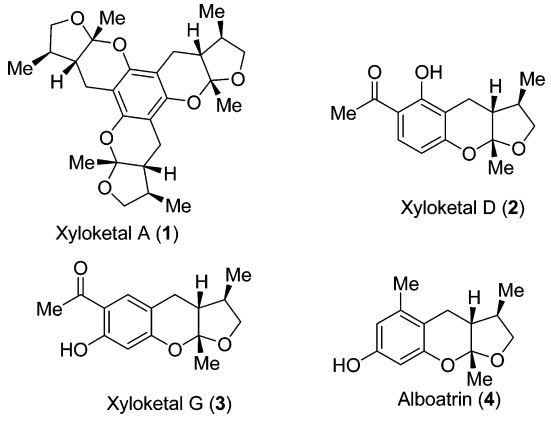


Figure 1. Structures of xyloketals A (**1**), D (**2**), and G (**3**) and alboatrin (**4**).

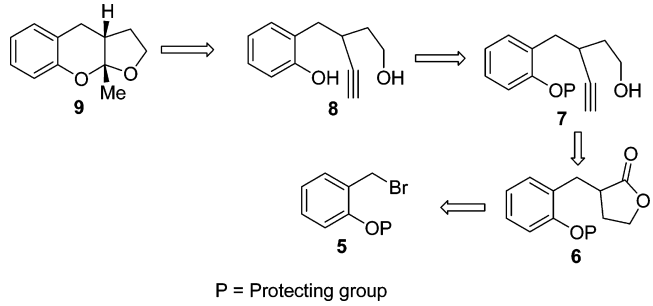
notable in view of its remarkable C_3 symmetry. Xyloketal D (**2**) and its regioisomer, xyloketal G (**3**),[2] represent simpler structural analogues of **1**. Both xyloketal A (**1**) and D (**2**) are known to inhibit acetylcholine esterase[3] and are considered potential lead compounds for the treatment of neurological disorders like Alzheimer's disease. Incidentally, a structurally related natural product alboatrin (**4**), isolated from the fungus *Verticillium albo-atrum*,[4] also shows significant biological activity in that it inhibits the root growth of the host plant (Maris Kabul) and causes vascular-wilt disease in alfalfa.[5] Over the years, the structural novelty and associated biological properties of xyloketals and alboatrin have triggered intense interest within the synthetic community.[6,15]

Recently, homogeneous catalysis using gold salts has emerged as one of the most dynamic fields in organic synthesis.[7] On the basis of their ability to activate C−C triple bonds as soft, carbophilic Lewis acids, gold salts are ideally suited for the formation of C−C and C−heteroatom bonds by nucleophilic attack to these activated substrates. One of the areas where gold has registered its supremacy over other transition metals is the catalytic cycloisomerization of alkynediols,[8] and this has emerged as an efficient strategy to build complex ketal systems in just one step.[9] In continuation of our work on gold-catalyzed organic transformations,[10] we report herein a novel gold-catalyzed cycloisomerization strategy for the synthesis of xyloketal natural products, e.g., xyloketal D (**2**), xyloketal G (**3**), and the related natural product alboatrin (**4**).

RESULTS AND DISCUSSION

At the outset, our focus was on the linear tricyclic tetrahydrofuranobenzopyran ring system **9** (Scheme 1) as enshrined in xyloketals and the related natural product, alboatrin (**4**). We thought a triple bond could be used as the oxidation-state equivalent to a ketone as has been documented in a number of recent publications.[11] Thus, the required

Scheme 1. Retrosynthetic Pathway for the Compound 9



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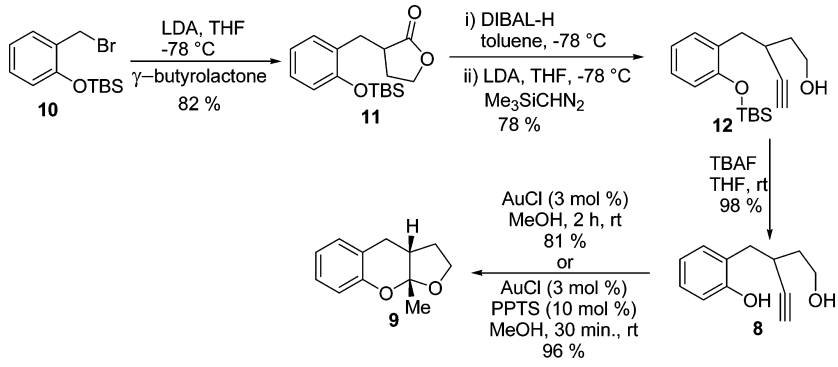
Scheme 2. Synthesis of Model Compound 9



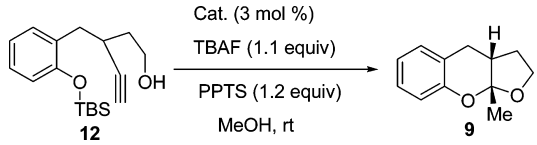
pendant alkyne **8** on activation by a gold catalyst may allow addition of two hydroxyl groups (an alcoholic −OH and a phenolic −OH) to the alkyne so as to form compound **9**. Because this cycloisomerization (**8** → **9**) is reversible, one would expect it to provide the thermodynamically more stable product having a *cis* ring junction. Compound **8** may be available from deprotection of protected phenol **7**. The alkyne **7** could be made via a DIBAL-H reduction of **6** to the corresponding lactol (not shown) followed by alkynylation. The lactone **6** is obtainable by alkylation of γ-butyrolactone with substituted benzyl bromide **5**.

The synthesis commenced with the known silyl-protected 2-hydroxybenzyl bromide **10**.[12] Thus, alkylation of γ-butyrolactone with **10** gave lactone **11** in 82% yield (Scheme 2). DIBAL-H reduction of **11** to lactol (not shown) followed by TMS-diazomethane-mediated alkynylation (Colvin rearrangement)[13] gave the alkyne **12** in 78% overall yield.[14] Deprotection of silyl group by TBAF gave phenol **8** in 98% yield. To test the gold-catalyzed cycloisomerization, AuCl (3 mol %) was added to a methanol solution of **8** at room temperature; after 2 h of stirring, it gave the tricyclic ketal **9**[15] incorporating the basic structural framework of the xyloketals in 81% isolated yield. Although metal-catalyzed spiroketalization of alkynes with alcohols are known in the literature,[8,9] this type of linear cyclic ketal formation namely, xyloketalization is uncovered for the first time. Note that the gold-catalyzed xyloketalization is highly stereoselective and furnished only the *cis*-diastereomer unaccompanied by even traces of *trans*-diastereomer. Furthermore, addition of a catalytic amount of PPTS increases the reaction rate such that the reaction was completed within 30 min with excellent yield (96%).

At this stage it occurred to us that isolation of **8** (Scheme 2) is avoidable and that conversion of **12** to **9** could be carried out as a one-pot reaction. Indeed, the literature is replete with cases where the gold−fluoride compatibility has been documented.[16] However, many authors continue to follow two-step strategies, first desilylation and then gold-catalyzed reaction, en route to their targets.[17] In the event, we added a methanol solution of alkyne **12** to a methanol solution of AuCl (3 mol %), TBAF (1.1 equiv), and PPTS (1.2 equiv) as proton source; after 1 h of stirring at room temperature the reaction yielded the tricyclic ketal **9** in 96% isolated yield.

Further experimentation (Table 1) showed that AuCl and $AuCl_3$ (entries 1 and 9) are the catalysts of choice in presence of fluoride ion for this reaction. Absence of TBAF (entry 2), however, resulted in complete decomposition of the starting material, although absence of a proton source, e.g., PPTS (entry 3) does yield traces of product (TLC). When $HgCl_2$, $FeCl_3$, and $CuCl_2$ were used (entries 4−6), no traces of the desired product could be observed in the crude reaction mixtures by TLC analysis; only decomposition of starting material resulted. Other carbophilic Lewis acids such as AgOTf and $PtCl_2$ gave the desired product, albeit in lower yields (entries 7 and 8). In the absence of catalyst, this reaction yielded only the desilylated product **8** in excellent yield (entry 10). Other solvents, e.g., toluene, CH_2Cl_2, and THF, proved to be less efficient in this reaction (entry 1, Table 1) as under these conditions the desired product was obtained in 11%, 42%, and 80% yields, respectively.

Table 1. Xyloketalization of 12 under Various Catalytic Systems[a]



entry	catalyst	time (h)	yield[b] (%)
1	AuCl	1	96[c]
2	AuCl	12	0[d]
3	AuCl	12	traces[e]
4	$HgCl_2$	6	0
5	$FeCl_3$	6	0
6	$CuCl_2$	6	0
7	AgOTf	5	11
8	$PtCl_2$	2	44
9	$AuCl_3$	1	92
10		12	0[f]

[a]All of the reactions were performed using **12** (0.2 mmol), TBAF (0.22 mmol), and PPTS (0.24 mmol) in the presence of catalyst (3 mol %) in methanol (6 mL) at room temperature or as otherwise noted. [b]Isolated yield. [c]Isolated yield in toluene (11%), CH_2Cl_2 (42%), and THF (80%). [d]In the absence of TBAF. [e]In the absence of PPTS. [f]In the absence of catalyst.

With the verified success of our approach to the xyloketal core through a synthesis of the simple model compound, we decided to first apply the methodology to a synthesis of noralboatrin (**13**). We began our synthesis with the silyl-protected orcinol 2-carboxaldehyde **14**[18] (Scheme 3). Aldol condensation of **14** with γ-butyrolactone resulted in a complex mixture, probably resulting from further reactions of the initially formed aldol product including scrambling of the silyl groups. This problem was readily overcome when the aldol condensation was carried out with the known aldehyde **15** containing −OMe groups instead of −OTBS groups, thereby

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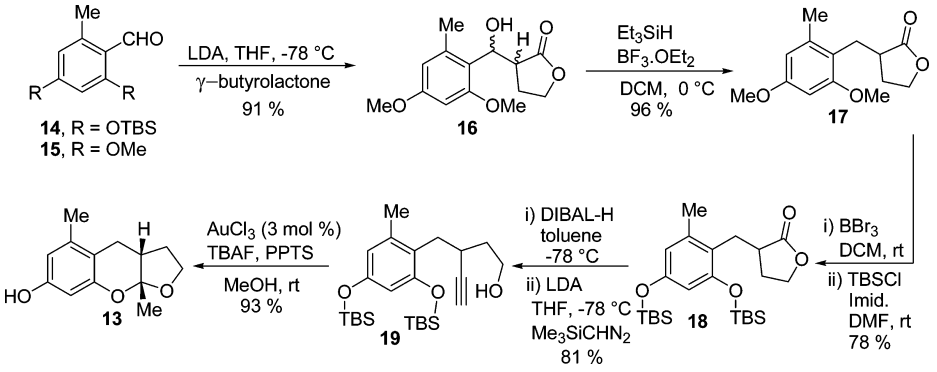
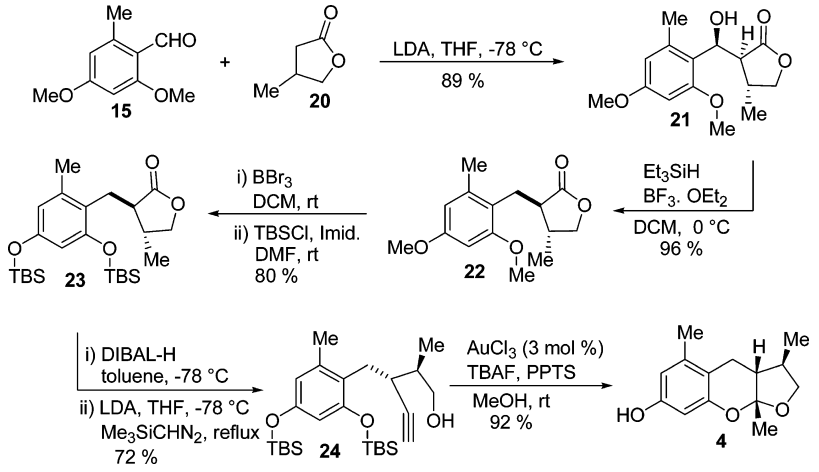
Scheme 3. Synthesis of Noralboatrin (13)



Scheme 4. Synthesis of Alboatrin (4)



providing **16** in 91% isolated yield as a single diastereomer; we made no attempt to determine its stereochemistry as it is irrelevant for the synthesis. Reduction of **16** with Et_3SiH in presence of boron trifluoride diethyl etherate afforded compound **17** in excellent yield. Demethylation of **17** gave a dihydroxy compound which, without purification, was protected with TBSCl by the usual way to give **18** in 78% overall yield. With **18** in hand, we then transformed it to **19** via DIBAL-H reduction to the corresponding lactol followed by TMS-diazomethane mediated alkynylation. Following our xyloketalization procedure, a methanol solution of alkyne **19** was added to a methanol solution of AuCl (3 mol %) and TBAF (2.1 equiv) in the presence of PPTS (2.2 equiv) and the mixture stirred for 2 h at room temperature: however, no desired product that is **13** could be obtained. Repeated efforts gave the same results. Incidentally, we discovered some shiny gold metal particles settling down in the reaction vessel, which instantly indicated that Au(I) was getting reduced to catalytically inactive Au(0) metal particles. Since Au(I) has a low reduction potential, it probably got reduced to Au(0) by a highly electron-rich substrate **19** or its desilylated product.

To overcome this problem, we decided to make use of a gold salt having comparatively high reduction potential, e.g., $AuCl_3$ instead of AuCl. Accordingly, treatment of a methanolic solution of **19** to a methanol solution of $AuCl_3$ (3 mol %) and TBAF (2.1 equiv) in presence of PPTS (2.2 equiv) afforded noralboatrin (**13**)[19] in 93% isolated yield.

Our next goal was the synthesis of the natural product alboatrin (**4**). In this context the racemic *γ*-butyrolactone **20**,[20] was subjected to aldol condensation with aldehyde **15** to give the *β*-hydroxy lactone **21** as a white solid in 89% isolated yield (Scheme 4). Interestingly, the aldol reaction is highly stereoselective and we obtained only one diastereomer; its stereochemistry was confirmed by a single-crystal X-ray analysis (CCDC 855274, see the Supporting Information). Reduction of **21** with Et_3SiH in the presence of boron trifluoride diethyl etherate afforded **22** in excellent yield, which was then transformed to **23** following the same procedure as described in the case of noralboatrin (**13**). The Colvin rearrangement of the lactol (not shown) obtained from **23** to **24** under a variety of conditions (stirring at low temperature, e.g., −78 °C for 12−18 h, and slowly warming to room temperature or carrying out the reactions at room temperature overnight) proved to be unfruitful, with the starting material being returned in each case in moderate yield. We ascribe this failure to a possible Thorpe−Ingold-type effect of the methyl substituent in the lactol, thereby preventing its ring-opening and generating enough of the free aldehyde in solution. However, heating the reaction mixture under reflux for 3 h and using excess reagents afforded the alkyne derivative **24** in 72% yield as a thick colorless liquid. Using our xyloketalization procedure, addition of a methanol solution of alkyne **24** to a methanol solution of $AuCl_3$ (3 mol %) and TBAF (2.1 equiv) in presence of PPTS (2.2 equiv) furnished alboatrin (**4**) in 92% yield. The melting point and spectral features (^1H and ^{13}C NMR) of our synthetic material are identical with those reported in the literature.[6f,19] This is a facile synthesis of racemic alboatrin with 45% overall yield using a seven-step procedure.

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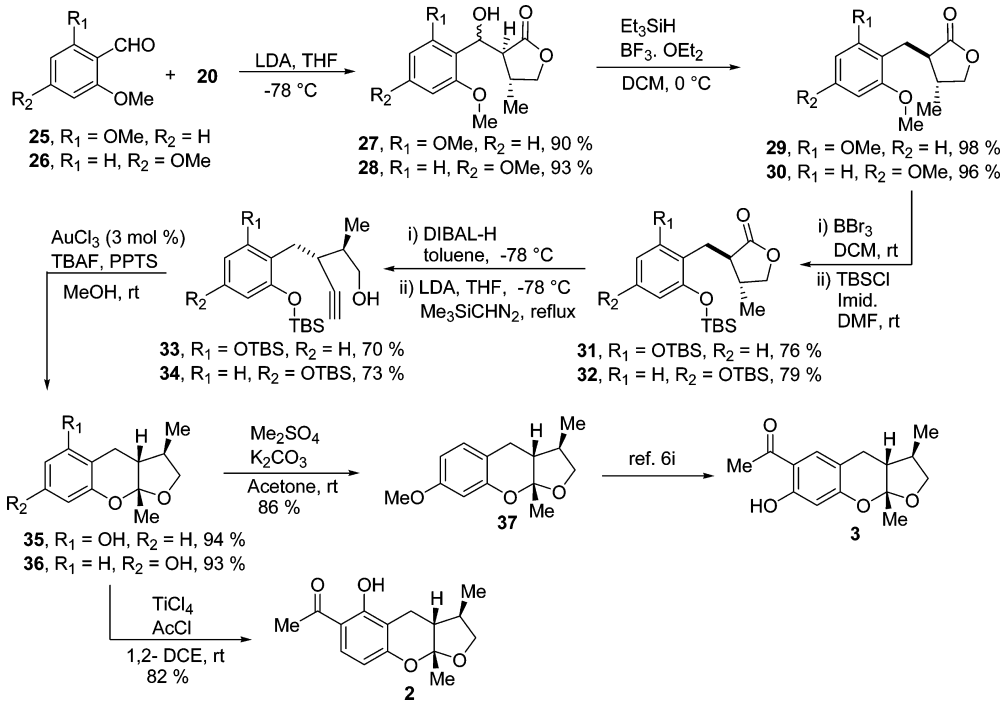
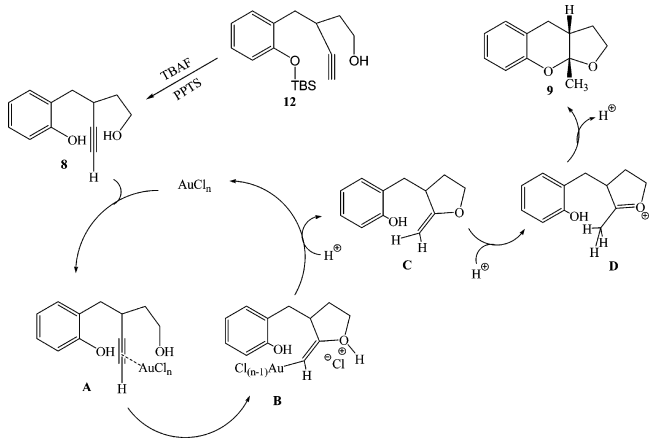
Scheme 5. Synthesis of Xyloketal D (2) and Xyloketal G (3)



The successful synthesis of noralboatrin (**13**) and alboatrin (**4**) propelled us to apply the same strategy to the synthesis of xyloketals D (**2**) and G (**3**). Xyloketals D (**2**) and G (**3**) are regioisomers. For their synthesis, we started our journey from the known aromatic aldehydes **25** and **26** (Scheme 5). Unlike in the case of alboatrin (**4**), aldol reactions of **25** and **26** were not completely stereoselective. Thus, while each of the carbinols **27** and **28** was formed in high yield with *trans* stereochemistry of the two side chains of the lactone ring, there was no stereocontrol in the formation of the remaining stereocenter. This was of course of no concern as reduction of **27** and **28** yielded compounds **29** and **30** as single diastereomers. Demethylation followed by silyl protection furnished **31** and **32**, which were then transformed into **33** and **34**, the ultimate precursors for xyloketalization. Xyloketalization of **33** and **34** then took place smoothly under the previously mentioned conditions described for noralboatrin (**13**) or alboatrin (**4**) to **35** and **36** in near-quantitative yields. $TiCl_4$-mediated selective acylation of **35** afforded our target molecule *rac*-xyloketal D (**2**)[6b] as white solid in 82% yield. The melting point and spectral features (^1H and ^{13}C NMR) of this synthetic material were identical with those reported in the literature.[6b] On the other hand, **36** was converted to the methyl ether **37** (86%), a precursor in an earlier synthesis of *rac*-xyloketal G (**3**).[6i] Thus, we have achieved a formal total synthesis of *rac*-xyloketal G (**3**) as well.

A plausible mechanism for the gold-catalyzed xyloketalyzation is shown in Scheme 6. TBAF deprotects the phenol silyl ether of compound **12** to phenoxide which receives the proton from PPTS to give compound **8**. Then the cycloisomerization reaction may be initiated by the formation of the alkynyl complex **A** via the complexation of triple bond of **8** to the Au catalyst. The coordination of the triple bond enhances the electrophilicity of the alkyne as advocated for metal-catalyzed reactions of alkynes. The addition of alcohol (5-*exo*-*dig*) may then occur, giving the vinyl gold intermediate **B**. Now proto-

Scheme 6. Proposed Mechanism for the Gold-Catalyzed Xyloketalization



deauration furnishes the enol ether **C** (along with regeneration of gold catalyst), which leads to oxonium ion **D**. Subsequent nucleophilic attack of phenolic OH group furnishes the tricyclic ketal **9**. Here, PPTS plays two roles. In the first place, it acts as proton source to yield **8** from the corresponding phenolate. Second, it also promotes proto-deauration followed by oxonium ion formation for the conversion of **B** to **D**.

CONCLUSION

In conclusion, we have developed a novel route for the synthesis of xyloketal natural products, namely xyloketal D, xyloketal G, and the related natural product alboatrin, based on gold-catalyzed xyloketalization in the key step. Notably, our approach is adaptable to chiral synthesis of these targets if the known chiral lactone, that is (*R*)-**20**,[6b,c,21] is employed in the initial condensation steps.

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EXPERIMENTAL SECTION

3-[2-(*tert*-Butyldimethylsilanyloxy)benzyl]dihydrofuran-2-one (11). To a stirred solution of LDA (4.8 mmol, 1.2 equiv) (prepared from diisopropylamine (1.3 mL, 9.6 mmol) and nBuLi (1.5 M in hexane, 3.2 mL, 4.8 mmol)) in THF (30 mL) was added a solution of γ-butyrolactone (413 mg, 4.8 mmol) in 5 mL of THF at −78 °C. After 20 min of stirring at that temperature, a solution of benzyl bromide **10** (1.20 g, 4 mmol) in 5 mL of THF was added dropwise over 10 min, and stirring was continued at −78 °C for 2 h. After completion (TLC), the reaction was quenched with saturated aq NH_4Cl solution, extracted with diethyl ether (2 × 30 mL), dried over anhyd Na_2SO_4, filtered, and evaporated. Purification by column chromatography on silica gel gave the α-benzyl lactone **11**(1.01 g, 82%) as a colorless liquid: IR (neat) 1774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15−7.10 (m, 2H), 6.89 (t, 1H, *J* = 7.4 Hz), 6.81 (d, 1H, *J* = 8.0 Hz), 4.26 (dt, 1H, *J* = 7.0 Hz, *J* = 3.0 Hz), 4.16−4.12 (m, 1H), 3.32 (dd, 1H, *J* = 13.4 Hz, *J* = 4.0 Hz), 2.92 (m, 1H), 2.61 (dd, *J* = 13.6 Hz, *J* = 10.0 Hz), 2.16 (m, 1H), 1.99 (m, 1H), 1.01 (s, 9H), 0.25 (s, 3H), 0.24 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.1, 154.0, 131.0, 129.4, 128.0, 121.5, 118.9, 66.7, 40.0, 31.3, 28.4, 26.0, 18.5, −3.8, −4.0; HRMS (CI MS) *m*/*z* for $C_{17}H_{27}O_3Si$ $(M + H)^+$ calcd 307.1724, found 307.1695; TLC R_f 0.30 (10% EtOAc/petroleum ether) (UV, I_2).

3-[2-(*tert*-Butyldimethylsilanyloxy)benzyl]pent-4-yn-1-ol (12). To the α-benzyl lactone **11** (918 mg, 3 mmol) in toluene (30 mL) at −78 °C was added DIBAL-H (1 M in toluene, 3.6 mL, 3.6 mmol, 1.20 equiv) dropwise over 45 min. After being stirred at −78 °C for 30 min (TLC shows consumption of starting material), the reaction was quenched by the addition of methanol (1 mL) at −78 °C. Saturated aq NH_4Cl solution was added, and the reaction was allowed to warm to room temperature. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. The resulting clear oil was directly subjected to the next reaction step. LDA (10.5 mmol, 3.5 equiv) was freshly prepared from diisopropylamine (3 mL, 21 mmol, 7 equiv) and nBuLi (1.5 M in hexane, 7 mL, 10.5 mmol, 3.5 equiv) in THF (28 mL) at −78 °C. After 20 min of stirring, $TMSCHN_2$ (2 M in Et_2O, 3 mL, 6 mol, 2 equiv) was added dropwise over 1 h at −78 °C. After being stirred at −78 °C for 30 min, the solution of the crude lactol in THF (7 mL) was added dropwise over 20 min. The reaction was warmed slowly to 0 °C over 5 h. After completion (TLC) of the reaction, it was recooled to −78 °C and quenched with saturated aq NH_4Cl solution. The reaction mixture was allowed to warm to room temperature. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried (anhyd Na_2SO_4), and concentrated in vacuo. The crude product was purified by flash column chromatography (PET/AcOEt 20:1−15:1) to yield alkyne **12** (712 mg, 78%) as a colorless oil: ^1H NMR (200 MHz, $CDCl_3$) δ 7.22−7.04 (m, 2H), 6.89−6.74 (m, 2H), 3.78 (t, 2H, *J* = 6.3 Hz), 2.78 (m, 2H), 2.06 (s, 1H), 1.81−1.56 (m, 2H), 0.99 (s, 9H), 0.21 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.0, 131.7, 130.0, 127.6, 120.9, 118.4, 87.2, 70.2, 60.6, 37.5, 36.8, 28.5, 26.1, 18.4, −0.3, −3.9; HRMS (ESI-TOF) *m*/*z* for $C_{18}H_{28}NaO_2Si$ $(M + Na)^+$ calcd 327.1751, found 327.1749; TLC R_f 0.8 (10% EtOAc/petroleum ether) (UV, I_2).

2-[2-(2-Hydroxyethyl)but-3-ynyl]phenol (8). $TBAF{\cdot}3H_2O$ (694 mg, 2.2 mmol) was added to a THF (20 mL) solution of **12** (609 mg, 2 mmol) at room temperature, and stirring was continued for 1 h. After complete conversion (TLC), it was quenched by addition of saturated aq NH_4Cl solution. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried (anhyd Na_2SO_4), and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel to give **8** (372 mg, 98%) as a colorless liquid: ^1H NMR (200 MHz, $CDCl_3$) δ 7.17−7.07 (m, 2H), 6.90−6.77 (m, 2H), 3.99−3.72 (m, 2H), 2.98−2.73 (m, 3H), 2.14 (d, 1H, *J* = 1.4 Hz), 1.79−1.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 131.7, 128.2, 125.7, 120.7, 116.2, 87.2, 70.9, 61.1, 35.8, 35.8, 29.6; HRMS (CI MS) *m*/*z* for $C_{12}H_{15}O_2$ $(M + H)^+$ calcd 191.1067, found 191.1064; TLC R_f 0.32 (20% EtOAc/petroleum ether) (UV, I_2).

9a-Methyl-3,3a,4,9a-tetrahydro-2*H*-furo[2,3-*b*]chromene (9). TBAF (1 M in THF, 1.1 mL, 1.1 mmol), PPTS (301 mg, 1.2 mmol), and AuCl (7 mg, 0.03 mmol) were added to a stirred solution of alcohol **12** (304 mg, 1 mmol) in methanol (6 mL) under argon atmosphere. After the reaction mixture had been stirred for 1 h, the solvent was removed and the residue purified by flash chromatography on silica gel (hexane/ethyl acetate, 3:1 v/v) to give **9** (182 mg, 96%) as a white solid: mp 48−50 °C (lit.[6i] mp 44−47 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 7.14−7.06 (m, 2H), 6.88−6.82 (m, 2H), 4.02−3.97 (m, 1H), 3.96−3.90 (m, 1H), 3.06 (dd, 1H, *J* = 16.6 Hz, *J* = 5.8 Hz), 2.80 (d, 1H, *J* = 16.0 Hz), 2.50−2.43 (m, 1H), 2.08−2.01 (m, 1H), 1.81−1.73(m, 1H), 1.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 129.5, 127.9, 120.9, 119.6, 117.2, 107.5, 67.0, 41.2, 29.0, 26.5, 23.4; HRMS (CI MS) *m*/*z* for $C_{12}H_{15}O_2$ $(M + H)^+$ calcd 191.1067, found 191.1053; TLC R_f 0.72 (20% EtOAc/petroleum ether) (UV, I_2).

2,4-Bis(*tert*-butyldimethylsilanyloxy)-6-methylbenzaldehyde (14). A mixture of orcinol-2-carboxaldehyde (900 mg, 5.9 mmol), imidazole (2.4 g, 35.5 mmol), and TBSCl (4.5 g, 29.6 mmol) in anhydrous DMF (6.0 mL) was stirred at rt for about 24 h under N_2 atmosphere. The mixture was then diluted with ethyl acetate (100 mL) and H_2O (30 mL). The organic layer was separated, washed with H_2O (4 × 30 mL) and brine, dried over anhyd Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 50:1) to give **14** (2.0 g, 89%) as a colorless oil: ^1H NMR (200 MHz, $CDCl_3$) δ 10.47 (s, 1H), 6.29 (s, 1H), 6.17 (d, 1H, *J* = 2.2 Hz), 2.52 (s, 3H), 1.00 (s, 9H), 0.97 (s, 9H), 0.26 (s, 6H), 0.23 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 191.2, 162.3, 161.1, 144.4, 120.3, 117.2, 108.7, 25.9, 25.7, 22.2, 18.5, 18.4, −4.1, −4.1; HRMS (CI MS) *m*/*z* for $C_{20}H_{37}O_3Si_2$ $(M + H)^+$ calcd 381.2276, found 381.2271; TLC R_f 0.64 (5% EtOAc/petroleum ether), (UV, I_2).

3-[(2,4-Dimethoxy-6-methylphenyl)hydroxymethyl]-dihydrofuran-2-one (16). A mixture of aldehyde **15** (1.8 g, 10 mmol) and γ-butyrolactone (1.29 g, 15 mmol) in THF (15 mL) was added to a THF (30 mL) solution of LDA (15 mmol) prepared from 10 mL of nBuLi (1.5 M) and iPr_2NH (4.2 mL, 30 mmol) at −78 °C. The reaction mixture was warmed to 0 °C over a period of 7 h. After completion, the reaction was quenched with saturated aq NH_4Cl and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure, and the residue on chromatographic purification (silica gel) gave 2.42 g of product **16** as a white solid in 91% yield: mp 94−96 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 6.33 (s, 2H), 5.27−5.20 (m, 1H), 4.34 (dt, 1H, *J* = 8.5 Hz, *J* = 3.2 Hz), 4.19 (q, 1H, *J* = 16.1 Hz), 4.08 (d, 1H, *J* = 5.2 Hz), 3.82 (s, 3H), 3.79 (s, 3H), 3.42 (q, 1H, *J* = 18.8 Hz), 2.41 (s, 3H), 2.09−1.80 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.7, 159.8, 159.0, 138.8, 118.4, 107.9, 96.8, 68.6, 66.8, 55.5, 55.1, 44.1, 26.1, 20.6; HRMS (ESI-TOF) *m*/*z* for $C_{14}H_{18}NaO_5$ $(M + Na)^+$ calcd 289.1046, found 289.1045; TLC R_f 0.28 (20% EtOAc/petroleum ether) (UV, I_2).

3-(2, 4-Dimethoxy-6-methylbenzyl)dihydrofuran-2-one (17). To a solution of the aldol product **16** (2.4 g, 9.0 mmol) and Et_3SiH (4.3 mL, 27 mmol) in CH_2Cl_2 (50 mL) was added $BF_3{\cdot}OEt_2$ (1.3 mL, 10 mmol) at 0 °C. After the reaction mixture was stirred at 0 °C for 2 h, saturated aqueous $NaHCO_3$ solution was added. The organic solution was separated, washed with brine, and dried (anhyd Na_2SO_4). The solvent was concentrated, and then the residue was subjected to silica gel column chromatography to give the benzyl lactone **17** (2.16 g, 96%) as a white solid: mp 86−88 °C; IR (neat) 1763 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.32 (s, 2H), 4.31 (dt, 1H, *J* = 8.35 Hz, *J* = 3.8 Hz), 4.11 (q, 1H, *J* = 15.7 Hz), 3.77 (s, 6H), 3.08 (q, 1H, *J* = 18.7 Hz), 2.82−2.76 (m, 2H), 2.30 (s, 3H), 2.19−1.94 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.6, 158.9, 158.7, 138.3, 118.1, 106.8, 96.1, 66.8, 55.4, 55.3, 39.6, 28.5, 26.1, 20.2; HRMS (ESI-TOF) *m*/*z* for $C_{14}H_{19}O_4$ $(M + H)^+$ calcd 251.1278, found 251.1277; TLC R_f 0.40 (20% EtOAc/petroleum ether) (UV, I_2).

3-[2,4-Bis(*tert*-butyldimethylsilanyloxy)-6-methylbenzyl]-dihydrofuran-2-one (18). BBr_3 (1 M solution in DCM) (32 mL, 32 mmol) was added dropwise to a precooled solution of **17** (2 g, 8

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mmol) at 0 °C in 100 mL of DCM. After being stirred at 0 °C for 1 h, the solution was warmed to room temperature and stirring was continued for 24 h at that temperature. On completion, the reaction mixture was poured into water, and dil HCl (10%, 50 mL) was added. The mixture was extracted with DCM; the organic layer was washed with water, dried over anhydrous Na_2SO_4, and evaporated. The residue thus obtained was used for the next step without purification

A mixture of residue, imidazole (3.25 g, 48 mmol), and TBSCl (6.1 g, 40 mmol) in anhydrous DMF (30 mL) was stirred at rt for about 24 h under N_2 atmosphere. The mixture was then diluted with ethyl acetate (200 mL) and H_2O (100 mL). The organic layer was separated, washed with H_2O (4 × 50 mL) and brine, dried over anhyd Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel column chromatography (hexane/ethyl acetate = 50:2) to give **18** (2.81 g, 78%) as a low-melting solid: mp 68−70 °C; IR (neat) 1774 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.31 (d, 1H, J = 2.0 Hz), 6.20 (d, 1H, J = 2.0 Hz), 4.31 (dt, 1H, J = 8.3 Hz, J = 3.8 Hz), 4.11(q, 1H, J = 16.8 Hz), 3.09 (d, 1H, J = 10.3 Hz), 2.87−2.68 (m, 2H), 2.25 (s, 3H), 2.14−2.03 (m, 1H), 0.99 (s, 9H), 0.97 (s, 9H), 0.24 (s, 3H), 0.23(s, 3H), 0.18 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.3, 154.7, 154.3, 138.5, 121.2, 115.5, 108.7, 66.8, 39.7, 28.5, 26.8, 26.1, 25.8, 20.4, 18.5, 18.4, −3.8, −3.9; HRMS (ESI-TOF) m/z for $C_{24}H_{42}NaO_4Si_2$ $(M + Na)^+$ calcd 473.2514, found 473.2519; TLC R_f 0.56 (10% EtOAc/petroleum ether) (UV, I_2).

3-[2,4-Bis(*tert*-butyldimethylsilanyloxy)-6-methylbenzyl]-pent-4-yn-1-ol (19). To the TBS ether **18** (1.35 g, 3 mmol) in toluene (30 mL) at −78 °C was added DIBAL-H (1 M in toluene, 3.6 mL, 3.6 mmol, 1.20 equiv) dropwise over 45 min. After being stirred at −78 °C for 30 min, the reaction was quenched by the addition of methanol (2 mL) at −78 °C. Saturated aq NH_4Cl solution was added, and the reaction was allowed to warm to rt. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried (anhyd Na_2SO_4), and concentrated in vacuo. The resulting clear oil was directly subjected to the next reaction step. LDA (10.5 mmol, 3.5 equiv) was freshly prepared from diisopropylamine (3 mL, 21 mmol, 7 equiv) and nBuLi (1.5 M in hexane, 7 mL, 10.5 mmol, 3.5 equiv) in THF (28 mL) at −78 °C. After 20 min of stirring, $TMSCHN_2$ (2 M in Et_2O, 3 mL, 6 mol, 2 equiv) was added dropwise over 1 h at −78 °C. After being stirred at −78 °C for 30 min, the solution of the crude lactol in THF (7 mL) was added dropwise over 20 min. The reaction was warmed slowly to 0 °C over 5 h. After completion (TLC) of the reaction, it was recooled to −78 °C and quenched with saturated aq NH_4Cl solution. The reaction mixture was allowed to warm to room temperature. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried (anhyd Na_2SO_4), and concentrated in vacuo. The crude product was purified by flash column chromatography (petroleum ether/AcOEt 20:1−15:1) to yield alkyne **19** (1. 09 g, 81%) as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 6.29 (s, 1H), 6.18 (s, 1H), 3.82−3.74 (m, 2H), 2.87−2.81 (m, 2H), 2.74−2.68 (m, 1H), 2.28 (s, 3H), 2.04(d, 1H, J = 1.2 Hz), 1.73−1.66 (m, 2H), 1.01 (s, 9H), 0.97 (s, 9H), 0.24 (s, 3H), 0.23 (s, 3H), 0.18 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 153.9, 138.9, 121.3, 114.8, 107.9, 87.4, 70.0, 61.5, 36.8, 32.1, 29.6, 28.5, 25.8, 25.6, 20.5, 18.2, 18.1, −4.1, −4.1, −4.4; HRMS (CI MS) m/z for $C_{25}H_{45}O_3Si_2$ $(M + H)^+$ calcd 449.2902, found 449.2890; TLC R_f 0.52 (10% EtOAc/petroleum ether) (UV, I_2).

Noralboatrin (13). TBAF (1 M in THF, 2.1 mL, 2.1 mmol), PPTS (552 mg, 2.2 mmol), and $AuCl_3$ (9 mg, 0.03 mmol) were added to a stirred solution of alcohol **19** (450 mg, 1 mmol) in methanol (6 mL) under argon atmosphere. After the reaction mixture had been stirred for 1 h, the solvent was removed and the residue purified by flash chromatography on silica gel to give noralboatrin **13** (205 mg, 93%) as a white solid: mp 146−148 °C (lit.[19] mp 148−149 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 6.29 (s, 1H), 6.22 (s, 1H), 4.75 (brs, 1H), 4.03 (dt, 1H, J = 9.0 Hz, J = 2.8 Hz), 3.94 (q, 1H, J = 16.4 Hz), 2.73 (s, 2H), 2.50−2.42 (m, 1H), 2.17 (s, 3H), 2.10−2.01 (s, 1H), 1.85−1.74 (m, 1H), 1.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 154.2, 138.5, 109.9, 109.8, 106.5, 101.8, 66.9, 40.9, 29.2, 23.3, 22.9, 19.5; HRMS (CI MS) m/z for $C_{13}H_{17}O_3$ $(M + H)^+$ calcd 221.1172, found 221.1169; TLC R_f 0.42 (20% EtOAc/petroleum ether) (UV, I_2).

3-[(2,4-Dimethoxy-6-methylphenyl)hydroxymethyl]-4-methyldihydrofuran-2-one (21). Aldol product **21** was prepared from aldehyde **15** (1.8 g, 10 mmol) and lactone **20** (1.5 g, 15 mmol) in 89% yield exactly following the procedure described for the preparation of **16**: mp 98−100 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 6.27 (s, 2H), 5.19 (d, 1H, J = 9.6 Hz), 4.30 (t, 1H, J = 8.4 Hz), 4.25-4.06(m, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 3.65−3.61 (m, 1H), 2.96 (t, 1H, J = 9.8 Hz), 2.35 (s, 3H), 2.28−2.05 (m, 1H), 0.56 (d, 3H, J = 6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 180.4, 159.9, 159.3, 139.0, 118.1, 107.9, 96.7, 73.0, 68.3, 55.5, 55.2, 50.2, 33.7, 20.9, 16.3; HRMS (FAB-TOF) m/z for $C_{15}H_{20}O_5$ $(M)^+$ calcd 280.1305, found 280.1314; TLC R_f 0.34 (20% EtOAc/petroleum ether) (UV, I_2).

3-(2,4-Dimethoxy-6-methylbenzyl)-4-methyldihydrofuran-2-one (22). Reduction product **22** was prepared from **21** (2.8 g, 10 mmol) in 96% yield exactly following the procedure described for the preparation of **17**: mp 63−65 °C; IR (neat) 1777 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.30 (s, 2H), 4.30 (t, 1H, J = 7.9 Hz), 3.75 (s, 6H), 3.61 (t, 1H, J = 8.4 Hz), 3.06 (dd, 1H, J = 13.9 Hz, J = 4.7 Hz), 2.80 (dd, 1H, J = 13.8 Hz, J = 9.0 Hz), 2.44−2.34 (m, 2H), 2.29 (s, 3H), 0.74 (d, 3H, J = 5.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.4, 158.8, 158.6, 138.2, 117.6, 106.6, 95.9, 72.5, 55.2, 55.1, 46.0, 36.7, 25.9, 20.2, 16.7; HRMS (FAB-TOF) m/z for $C_{15}H_{21}O_4$ $(M + H)^+$ calcd 265.1434, found 265.1439; TLC R_f 0.46 (20% EtOAc/petroleum ether) (UV, I_2).

3-[2,4-Bis(*tert*-butyldimethylsilanyloxy)-6-methylbenzyl]-4-methyldihydrofuran-2-one (23). Compound **23** was prepared from **22** (2.38 g, 9 mmol) in 80% yield following the procedure described for the preparation of **18**: mp 123−125 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 6.31 (s, 1H), 6.20 (d, 1H, J = 2.2 Hz), 4.32 (t, 1H, J = 7.9 Hz), 3.62 (t, 1H, J = 8.9 Hz), 3.13 (dd, 1H, J = 13.9 Hz, J = 3.9 Hz), 2.80 (dd, 1H, J = 13.9 Hz, J = 10.4 Hz), 2.48−2.36 (m, 2H), 2.25 (s, 3H), 0.99 (s, 9H), 0.97 (s, 9H), 0.67(d, 3H, J = 6.0 Hz), 0.24 (s, 3H), 0.23 (s, 3H), 0.17 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.5, 154.7, 154.3, 138.5, 120.9, 115.5, 108.6, 72.7, 46.1, 36.9, 29.8, 26.8, 26.0, 25.8, 20.4, 18.4, 18.1, 16.8, −3.4, −3.9, −4.2; HRMS (CI MS) m/z for $C_{25}H_{45}O_4Si_2$ $(M + H)^+$ calcd 465.2851, found 465.2857; TLC R_f 0.74 (10% EtOAc/petroleum ether), (UV, I_2).

3-[2,4-Bis(*tert*-butyldimethylsilanyloxy)-6-methylbenzyl]-2-methylpent-4-yn-1-ol (24). To the TBS ether **23** (930 mg, 2 mmol) in toluene (20 mL) at −78 °C was added DIBAL-H (1 M in toluene, 2.4 mL, 2.4 mmol, 1.20 equiv) dropwise over 45 min. After being stirred at −78 °C for 30 min, the reaction was quenched by the addition of methanol (1 mL) at −78 °C. Saturated aq NH_4Cl solution was added, and the reaction was allowed to warm to room temperature. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried (anhyd Na_2SO_4), and concentrated in vacuo. The resulting clear oil was directly subjected to the next reaction step. LDA (20 mmol, 10 equiv) was freshly prepared from iPr_2NH (4.2 mL, 30 mmol, 15 equiv) and nBuLi (1.5 M in hexane, 13.3 mL, 20 mmol, 10 equiv) in THF (30 mL) at −78 °C. After continued stirring at the same temperature for 20 min, $TMSCHN_2$ (2 M in Et_2O, 10 mL, 20 mol, 10 equiv) was added dropwise over 1 h and the reaction mixture stirred for 1 h. Then the solution of crude lactol in THF (6 mL) was added dropwise over 20 min. The reaction was warmed slowly to room temperature over 1 h, and then it was refluxed for 3 h. After completion (TLC) of the reaction, it was recooled to −78 °C and quenched with saturated aq NH_4Cl solution. The reaction mixture was allowed to warm to room temperature. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried (anhyd Na_2SO_4), and concentrated in vacuo. The crude product was purified by flash column chromatography (petroleum ether/AcOEt 20:1−15:1) to yield alkyne **24** (666 mg, 72%) as a colorless oil: ^1H NMR (200 MHz, $CDCl_3$) δ 6.29 (s, 1H), 6.19 (s, 1H), 3.78−3.56 (m, 2H), 2.85−2.71 (m, 3H), 2.29 (s, 3H), 1.95 (s, 1H), 1.84−1.74 (m, 2H), 1.08 (d, 3H, J = 6.8 Hz), 1.00 (s, 9H), 0.97 (s, 9H), 0.24(s, 6H), 0.18 (s, 6H); ^{13}C

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NMR (50 MHz, $CDCl_3$) δ 154.8, 154.1, 139.2, 122.0, 115.1, 108.3, 86.1, 71.0, 66.0, 39.3, 35.3, 29.9, 26.1, 25.9, 20.8, 18.5, 18.4, 16.3, 1.24, −3.7, −4.1; HRMS (CI MS) m/z for $C_{26}H_{47}O_3Si_2$ $(M + H)^+$ calcd 463.3058, found 463.3062; TLC R_f 0.64 (10% EtOAc/petroleum ether) (UV, I_2).

Alboatrin (4). Alboatrin (**4**) was prepared from **24** (600 mg, 1.3 mmol) in 92% yield following the procedure described for the preparation of **13**: mp 148−149 °C (lit.[6f] mp 148−149 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (d, 1H, J = 2.0 Hz), 6.21(d, 1H, J = 2.4 Hz), 4.66 (brs, 1H), 4.18 (t, 1H, J = 8.2 Hz), 3.51 (t, 1H, J = 8.6 Hz), 2.70−2.68 (m, 2H), 2.19 (s, 3H), 2.15−2.09 (m, 1H), 1.93 (ddd, 1H, J = 11.0 Hz, J = 5.5 Hz, J = 2.0 Hz), 1.50 (s, 3H), 1.06 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 153.9, 138.4, 109.7, 109.6, 107.2, 101.7, 74.1, 48.2, 35.4, 22.9, 21.6, 19.5, 16.0; HRMS (CI MS) m/z for $C_{14}H_{19}O_3$ $(M + H)^+$ calcd 235.1329, found 235.1333; TLC R_f 0.14 (10% EtOAc/petroleum ether) (UV, I_2).

3-[(2,6-Dimethoxyphenyl)hydroxymethyl]-4-methyldihydrofuran-2-one (27). Aldol product **27** was prepared from aldehyde **25** (1.66 g, 10 mmol) and lactone **20** (1.5 g, 15 mmol) in 90% yield following the procedure described for the preparation of **16**: mp 62−63 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.16 (t, 2H, J = 8.4 Hz), 6.49 (d, 4H, J = 8.4 Hz), 5.57−5.49 (m, 1H), 5.32(t, 1H, J = 7.9 Hz), 4.34−4.22 (m, 2H), 3.76 (s, 12 H), 3.71−3.58 (m, 2H), 2.86(t, 1H, J = 8.3 Hz), 2.81−2.70 (m, 1H), 2.51(dd, 1H, J = 7.6 Hz, J = 5.4 Hz), 2.27−2.13(m, 1H), 0.86 (d, 3H, J = 6.6 Hz), 0.68 (d, 3H, J = 6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 178.9, 177.0, 158.3, 157.6, 129.5, 129.1, 116.0, 116.0, 104.4, 104.3, 72.9, 72.7, 67.0, 66.4, 55.8, 55.7, 53.2, 51.3, 33.5, 31.6, 18.2, 17.0; HRMS (ESI-TOF) m/z for $C_{14}H_{18}NaO_5$ $(M + Na)^+$ calcd 289.1046, found 289.1046; TLC R_f 0.48 (30% EtOAc/petroleum ether) (UV, I_2).

3-(2, 6-Dimethoxybenzyl)-4-methyldihydrofuran-2-one (29). Reduction product **29** was prepared from **27** (2.4g, 9 mmol) in 98% yield following the procedure described for the preparation of **17**: mp 71−72 °C, IR (neat) 1771 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.16 (t, 1H, J = 8.3 Hz), 6.53 (d, 2H, J = 8.4 Hz), 4.31 (dd, 1H, J = 8.7 Hz, J = 7.6 Hz), 3.80 (s, 6H), 3.63 (t, 1H, J = 8.5 Hz), 3.17 (dd, 1H, J = 13.2 Hz, J = 5.0 Hz), 2.92 (dd, 1H, J = 13.2 Hz, J = 10 Hz), 2.59−2.43 (m, 1H), 2.40−2.27 (m, 1H), 0.71 (d, 3H, J = 6.4 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.8, 158.6, 127.8, 115.0, 103.7, 72.8, 55.7, 45.8, 36.3, 23.3, 17.2; HRMS (CI MS) m/z for $C_{14}H_{19}O_4$ $(M + H)^+$ calcd 251.1278, found 251.1281; TLC R_f 0.72 (20% EtOAc/petroleum ether), (UV, I_2).

3-[2,6-Bis(*tert*-butyldimethylsilanyloxy)benzyl]-4-methyldihydrofuran-2-one (31). Compound **31** was prepared from **29** (2.0g, 8 mmol) in 76% yield following the procedure described for the preparation of **18**: mp 111−112 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.95 (t, 1H, J = 8.2 Hz), 6.46 (d, 2H, J = 8.2 Hz), 4.32 (t, 1H, J = 8.1 Hz), 3.62 (t, 1H, J = 8.7 Hz), 3.17 (dd, 1H, J = 13.2 Hz, J = 4.0 Hz), 2.88 (dd, 1H, J = 11.9 Hz, J = 10.6 Hz), 2.58 (ddd, 1H, J = 10.1 Hz, J = 9.7 Hz, J = 4.2 Hz), 2.50−2.39 (m, 1H), 1.01 (s, 18H), 0.68 (d, 3H, J = 6.2 Hz), 0.26 (s, 6H), 0.24 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.4, 155.3, 127.0, 120.4, 111.8, 72.7, 45.7, 36.8, 26.1, 25.9, 25.1, 18.5, 17.1, −3.9; HRMS (CI MS) m/z for $C_{24}H_{43}O_4Si_2$ $(M + H)^+$ calcd 451.2694, found 451.2697; TLC R_f 0.44 (5% EtOAc/petroleum ether) (UV, I_2).

3-[2,6-Bis(*tert*-butyldimethylsilanyloxy)benzyl]-2-methylpent-4-yn-1-ol (33). Compound **33** (colorless liquid) was prepared from **31** (1.35 g, 3 mmol) in 70% yield following the procedure described for the preparation of **24**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.95−6.87 (m, 1H), 6.44−6.38 (m, 2H), 3.94−3.86 (m, 1H), 3.53−3.41 (m, 1H), 3.09−2.88 (m, 2H), 2.67−2.59 (m, 1H), 1.80 (d, 1H, J = 2.4 Hz), 1.80−1.62 (m, 1H), 1.07 (d, 3H, J = 6.8 Hz), 1.01 (s, 18H), 0.24 (s, 6H), 0.23 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.4, 126.6, 121.6, 111.4, 85.5, 70.2, 65.3, 39.5, 34.4, 27.6, 26.2, 18.5, 16.3, 1.25, 0.39, −0.25, −3.8, −3.9; HRMS (ESI-TOF) m/z for $C_{25}H_{44}NaO_3Si_2$ $(M + Na)^+$ calcd 471.2721, found 471.2722; TLC R_f 0.82 (10% EtOAc/petroleum ether) (UV, I_2).

3,9a-Dimethyl-2,3,3a,9a-tetrahydro-4*H*-1,9-dioxacyclopenta[*b*]naphthalen-5-ol (35). Compound **35** was prepared from **33** (896 mg, 2 mmol) in 94% yield following the procedure described for the preparation of **13**: mp 122−123 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.96 (t, 1H, J = 8.1 Hz), 6.44 (d, 1H, J = 8.0 Hz), 6.37 (d, 1H, J = 7.8 Hz), 5.53 (brs, 1H), 4.21 (t, 1H, J = 8.3 Hz), 3.54 (t, 1H, J = 8.4 Hz), 2.90 (dd, 1H, J = 24.3 Hz, J = 1.4 Hz), 2.74 (dd, 1H, J = 17.5 Hz, J = 6.2 Hz), 2.24−2.06 (m, 1H), 2.00−1.90 (m, 1H), 1.53 (s, 3H), 1.07 (d, 3H, J = 6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.6, 154.3, 127.7, 109.8, 107.4, 107.0, 106.4, 74.2, 47.7, 35.6, 23.0, 19.0, 16.1; HRMS (CI MS) m/z for $C_{13}H_{17}O_3$ $(M + H)^+$ calcd 221.1172, found 221.1178; TLC R_f 0.44 (20% EtOAc/petroleum ether) (UV, I_2).

Xyloketal D (2). To a solution containing **35** (220 mg, 1 mmol) in 7 mL of 1,2-dichloroethane at −10 °C was added 4 mL (4 mmol) of $TiCl_4$ (1.0 M in CH_2Cl_2). The reaction mixture was stirred for 5 min at −10 °C, and 1.2 mL (120 mg, 1.5 mmol) of acetyl chloride solution in DCE (from stock solution: 1.1 mL acetyl chloride dissolved in 10 mL DCE) was added. The reaction mixture was stirred at room temperature for 24 h. Then the reaction mixture was poured into 50 mL of 2 N HCl (aq), filtered through a pad of Celite, and washed with 30 mL of ethyl acetate. The organic phase was separated, and the aqueous phase was extracted with (3 × 10 mL) ethyl acetate. The combined organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to afford a crude residue. The residue was purified by flash chromatography on a silica gel column. Elution with 1:5 ethyl acetate−hexanes gave **2** as a white solid: yield 214 mg (82%): mp 78−79 °C (lit.[6b] mp 82 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.12 (s, 1H), 7.52 (d, 1H, J = 9.2 Hz), 6.37 (d, 1H, J = 8.8 Hz), 4.21 (t, 1H, J = 8.4 Hz), 3.57 (t, 1H, J = 8.6 Hz), 2.96 (d, 1H, J = 18.0 Hz), 2.72 (dd, 1H, J = 17.8 Hz, J = 6.0 Hz), 2.55 (s, 3H), 2.10−1.96 (m, 2H), 1.53 (s, 3H), 1.08 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 163.1, 159.7, 130.2, 113.3, 109.0, 108.5, 106.3, 74.5, 47.1, 35.3, 26.4, 22.9, 18.2, 16.0; HRMS (ESI-TOF) m/z for $C_{15}H_{18}NaO_4$ $(M + Na)^+$ calcd 285.1097, found 285.1102; TLC R_f 0.28 (20% EtOAc/petroleum ether) (UV, I_2).

3-[(2,4-Dimethoxyphenyl)hydroxymethyl]-4-methyldihydrofuran-2-one (28). Aldol product **28** was prepared from aldehyde **26** (1.66 g, 10 mmol) and lactone **20** (1.5 g, 15 mmol) in 93% yield following the procedure described for the preparation of **16**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.39 (t, 2H, J = 8.1 Hz), 6.54−6.45 (m, 4H), 5.53 (brs, 1H), 5.16 (d, 1H, J = 8.2 Hz), 4.35 (t, 2H, J = 7.9 Hz), 3.81 (s, 12H), 3.68 (dt, 2H, J = 8.8 Hz, J = 3.4 Hz), 2.82−2.50 (m, 4H), 0.67 (d, 3H, J = 6.4 Hz), 0.65 (d, 3H, J = 6.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.1, 178.5, 160.1, 159.8, 157.0, 156.1, 128.3, 126.6, 121.9, 121.1, 104.2, 103.6, 97.7, 97.6, 72.9, 72.8, 67.6, 65.7, 54.9, 54.9, 52.4, 51.6, 33.0, 29.2, 20.5, 17.4, 16.2, 13.8; HRMS (ESI-TOF) m/z for $C_{14}H_{18}NaO_5$ $(M + Na)^+$ calcd 289.1046, found 289.1044; TLC R_f 0.22 (20% EtOAc/petroleum ether), (UV, I_2).

3-(2,4-Dimethoxybenzyl)-4-methyldihydrofuran-2-one (30). Reduction product **30** was prepared from **28** (2.4 g, 9 mmol) in 96% yield following the procedure described for the preparation of **17**: mp 92−93 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.05 (d, 1H, J = 7.8 Hz), 6.39(s, 1H), 6.37 (d, 1H, J = 7.6 Hz), 4.21(t, 1H, J = 8.2 Hz), 3.75 (s, 3H), 3.73 (s, 3H), 3.59 (t, 1H, J = 9.0 Hz), 3.15 (dd, 1H, J = 13.7 Hz, J = 5.2 Hz), 2.82−2.60 (m, 1H), 2.49−2.38 (m, 1H), 2.28−2.12 (m, 1H), 0.82 (dd, 3H, J = 6.4 Hz, J = 0.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.3, 159.8, 158.4, 131.3, 118.8, 104.0, 98.2, 72.5, 55.2, 55.1, 46.8, 35.7, 29.0, 16.5; HRMS (ESI-TOF) m/z for $C_{14}H_{18}NaO_4$ $(M + Na)^+$ calcd 273.1097, found 273.1096; TLC R_f 0.44 (20% EtOAc/petroleum ether) (UV, I_2).

3-[2,4-Bis(*tert*-butyldimethylsilanyloxy)benzyl]-4-methyldihydrofuran-2-one (32). Compound **32** was prepared from **30** (2.0 g, 8 mmol) in 79% yield following the procedure described for the preparation of **18**: mp 70−72 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.96 (d, 1H, J = 8.2 Hz), 6.38 (dd, 1H, J = 7.8 Hz, J = 2.4 Hz), 6.31 (d, 1H, J = 2.4 Hz), 4.23 (t, 1H, J = 8.3 Hz), 3.61 (t, 1H, J = 9.0 Hz), 3.34−3.21 (m, 1H), 2.60−2.41 (m, 2H), 2.35−2.23 (m, 1H), 0.98 (s, 9H), 0.94 (s, 9H), 0.71 (d, 3H, J = 6.6 Hz), 0.22 (s, 6H), 0.15 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.3, 155.2, 154.5, 131.2, 121.9, 113.3, 111.0, 72.7, 46.8, 36.2, 30.5, 25.9, 25.8, 18.3, 18.1, 17.0, −3.5, −3.9, −4.1, −4.3; HRMS (ESI-TOF) m/z for $C_{24}H_{42}NaO_4Si_2$ $(M + Na)^+$ calcd 473.2514, found 473.2514; TLC R_f 0.48 (10% EtOAc/petroleum ether), (UV, I_2).

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3-[2,4-Bis(*tert*-butyldimethylsilanyloxy)benzyl]-2-methylpent-4-yn-1-ol (34). Compound **34** was prepared from **32** (1.35 g, 3 mmol) in 73% yield following the procedure described for the preparation of **24**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.04 (dd, 1H, J = 8.2 Hz, J = 2.2 Hz), 6.39 (dd, 1H, J = 8.2 Hz, J = 2.4 Hz), 6.30 (t, 1H, J = 2.2 Hz), 3.86−3.72 (m, 1H), 3.50 (dd, 1H, J = 10.0 Hz, J = 7.8 Hz), 2.86−2.56 (m, 3H), 1.96 (d, 1H, J = 2.0 Hz), 1.87−1.75 (m, 1H), 1.05−0.96 (21H), 0.24 (s, 6H), 0.18 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.8, 154.2, 131.5, 123.2, 112.5, 110.6, 85.7, 70.7, 65.1, 38.6, 35.6, 25.9, 25.7, 18.3, 16.1, 15.9, 14.3, −0.4, −4.0, −4.3; HRMS (ESI-TOF) m/z for $C_{25}H_{44}NaO_3Si_2$ $(M + Na)^+$ calcd 471.2721, found 471.2726; TLC R_f 0.78 (10% EtOAc/petroleum ether) (UV, I_2).

3,9a-Dimethyl-2,3,3a,9a-tetrahydro-4*H*-1,9-dioxacyclopenta[*b*]naphthalen-7-ol (36). Compound **36** was prepared from **34** (448 mg, 1 mmol) in 93% yield following the procedure described for the preparation of **13**: mp 117−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (d, 1H, J = 8.0 Hz), 6.42−6.38 (m, 2H), 5.37 (brs, 1H), 4.15 (t, 1H, J = 8.2 Hz), 3.49 (t, 1H, J = 8.4 Hz), 2.93 (dd, 1H, J = 16.4 Hz, J = 6.0 Hz), 2.68 (d, 1H, J = 16.4 Hz), 2.16−2.04 (m, 1H), 1.95−1.91 (m, 1H), 1.56 (s, 3H), 1.04 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 154.0, 130.0, 108.3, 108.2, 104.1, 103.5, 74.2, 48.9, 35.2, 24.1, 23.9, 16.1; HRMS (ESI-TOF) m/z for $C_{13}H_{16}NaO_3$ $(M + Na)^+$ calcd 243.0992, found 243.0993; TLC R_f 0.34 (20% EtOAc/petroleum ether) (UV, I_2).

7-Methoxy-3,9a-dimethyl-2,3,3a,9a-tetrahydro-4*H*-1,9-dioxacyclopenta[*b*]naphthalene (37). To a solution of **36** (200 mg, 0.9 mmol) in 4 mL of acetone were added anhydrous K_2CO_3 (248 mg, 1.8 mmol) and dimethyl sulfate (227 mg, 1.8 mmol) and the mixture stirred at room temperature for 12 h. Then the reaction mixture was evaporated under reduced pressure, and H_2O (10 mL) was added. The reaction mixture was extracted with diethyl ether (10 mL × 3). The organic part was dried over anhyd Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/AcOEt 20:1−10:1) on a silica gel column to yield **37** (181 mg, 86%) as a white solid: mp 67−68 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.96 (d, 1H, J = 8.4 Hz), 6.48−6.39 (m, 2H), 4.15 (t, 1H, J = 8.3 Hz), 3.74 (s, 3H), 3.50 (t, 1H, J = 8.4 Hz), 2.95 (dd, 1H, J = 16.6 Hz, J = 5.8 Hz), 2.69 (d, 1H, J = 16.0 Hz), 2.16−2.03 (m, 1H), 1.96−1.90 (m, 1H), 1.55 (s, 3H), 1.04 (d, 1H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 154.1, 129.9, 111.1, 108.1, 107.7, 102.0, 74.2, 55.5, 48.8, 35.2, 24.1, 23.7, 16.2; HRMS (CI MS) m/z for $C_{14}H_{19}O_3$ $(M + H)^+$ calcd 235.1329, found 235.1332; TLC R_f 0.82 (20% EtOAc/petroleum ether) (UV, I_2).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

ORTEP diagram, crystallographic data, and CIF of compound **21**, ^{1}H and ^{13}C NMR spectra of all unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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