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Synthesis of the Antiproliferative Agent Hippuristanol and Its Analogues from Hydrocortisone via Hg(II)-Catalyzed Spiroketalization: Structure−Activity Relationship

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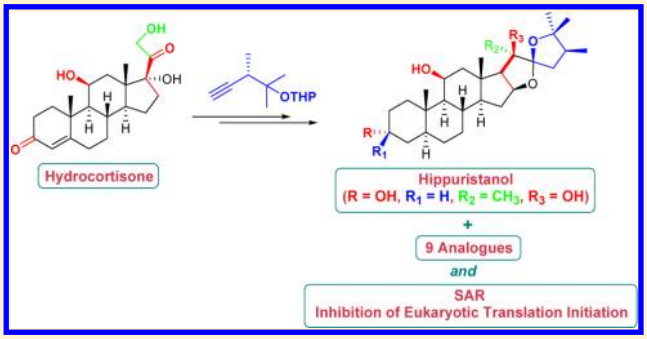
Supporting Information

ABSTRACT: An efficient synthesis of hippuristanol (**1**), a marine-derived highly potent antiproliferative steroidal natural product, and nine closely related analogues has been accomplished from the commercially available hydrocortisone utilizing Hg(II)-catalyzed spiroketalization of 3-alkyne-1,7-diol motif as a key strategy. This practical synthetic sequence furnished **1** in 11% overall yield from hydrocortisone in 15 linear steps. Modifications to the parent molecule **1** encompassed changing the functional groups on rings A and E. Each analogue was screened for their effects on inhibition of cap-dependent translation, and the assay results were used to establish structure−activity relationships. These results suggest that the stereochemistry and all substituents of spiroketal portion (rings E and F) and C3-α and C11-β hydroxyl functional groups on rings A and C, respectively, are critical for the inhibitory activity of natural product **1**.

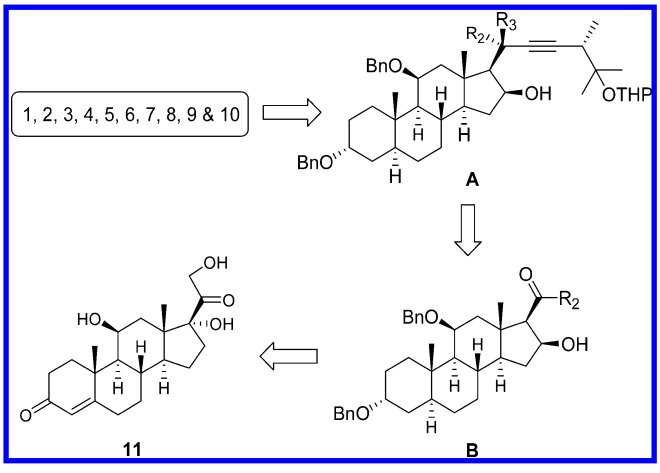


INTRODUCTION

Hippuristanol (**1**), a polyoxygenated marine-derived steroidal natural product, was isolated from the Gorgonian *Isis hippuris*.[1] We have previously identified hippuristanol as a highly potent candidate for the selective inhibition of eukaryotic initiation factor (eIF)4A-RNA binding activity that can be used to distinguish between eIF4A-dependent and independent modes of translation initiation in vitro and in vivo.[2] Eukaryotic protein synthesis is regulated at the level of initiation; here, a 40s ribosomal subunit and associated factors (43s preinitiation complex) are recruited to an mRNA by four initiation factors, namely, the eIF4F complex, which comprises the cap-binding protein, eIF4E, a large scaffolding protein, eIF4G, and an RNA helicase, eIF4A. Eukaryotic initiation factor (eIF)4A is the prototypical member of the DEAD-box family of RNA helicases, and it is required to unwind local secondary structure proximal to the 5′ m7GpppN cap structure. Compound **1** binds to eIFA and inhibits its RNA binding activity, thus inhibiting translation initiation.[2] Because of the selective translation inhibition activity of **1** and its effects on cellular proliferation, it is considered a promising lead for the development of anticancer chemotherapeutic agents.

Inspired by fascinating structural features and promise as an anticancer and antiviral lead structure and in combination with lowest natural abundance, we have recently disclosed synthetic routes for **1** (in 5.54% overall yield in 12 steps) and its structurally close analogues of spiroketals appendage (E and F rings, Scheme 1) including structure−activity relationship (SAR) studies, starting from hecogenin acetate via 11-ketotigogenin, employing our own protocol of Hg(II)-catalyzed

Scheme 1. Retrosynthetic Analysis of Hippuristanol (1) and Analogues 2−10



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cascade spiroketalization of semiprotected 3-alkyne-1,7-diol motifs and Suarez cyclizations.[3] Yu and co-workers reported the synthesis of **1** and some interesting analogues in order to verify the effect of size, stereochemical aspects, and different substitution patterns of spiroketal appendage (E and F rings, Scheme 1) in relation to the biological activity.[4] We and Yu previously have concluded that the hydroxyl group at C20, the "*R*" configuration at C_{22} spiroketal carbon, the three methyl groups on ring F, and the size (5/5) of the spiroketal portion were crucial for the inhibitory activity of **1** (Figure 1).[3,4]

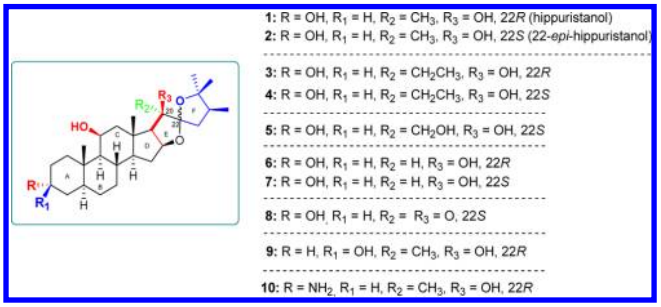


Figure 1. Hippuristanol and its analogues.

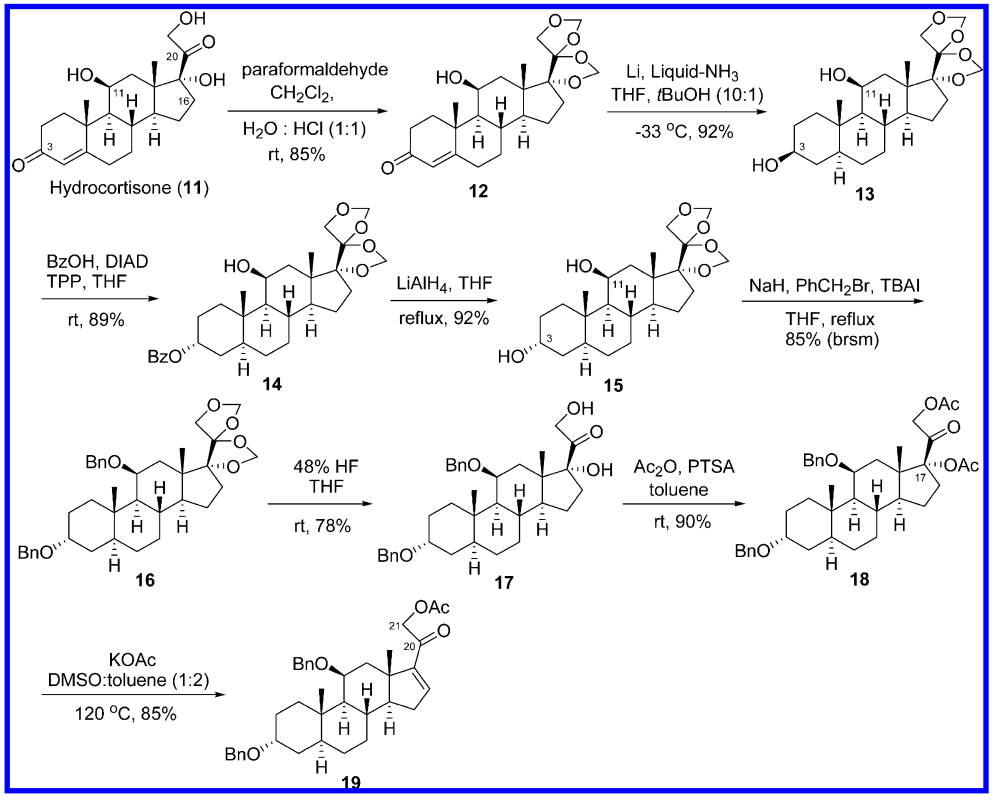
In this study we aimed to develop a practical synthetic route for natural product **1** and understand further the importance of the functional groups/substituents on rings A, C, and E for inhibitory activity as well as to identify analogues with enhanced biological activity. Herein, we report an efficient synthetic route for **1** and nine closely related new series of analogues, starting from commercially available and cost-effective hydrocortisone[4] employing our own protocol of Hg(II)-catalyzed cascade spiroketalization of semiprotected 3-alkyne-1,7-diol motif along with several unique transformations. Modifications to the parent molecule **1** included removal or changing the substituents and functional groups of rings A, C, and E. Structure–activity relationships of all analogues were established based on the screening results.

RESULTS AND DISCUSSION

In the retrosynthetic analysis, as described in Scheme 1, we envisioned the synthesis of **1** and its analogues (**2**–**10**) from the advanced suitable semiprotected 3-alkyne-1,7-diol intermediate **A**, via Hg(II)-catalyzed cascade spiroketalization. Hydrocortisone (**11**) was considered the best choice of commercially available and cost-effective starting material to produce intermediate **A**, via β-hydroxy ketone **B**, as it contains the favorable steric rigidity along with suitably positioned functional groups.

Synthesis of Hippuristanol (1) and 22-*epi*-Hippuristanol (2). As described in retrosynthetic analysis in Scheme 1, all analogues of natural product **1** were to be synthesized from the advanced suitable semiprotected 3-alkyne-1,7-diol intermediate **A**, via Hg(II)-catalyzed cascade spiroketalization, which could be readily prepared from the versatile enone intermediate **19**. Thus, our synthetic efforts began from **11** as shown in Scheme 2. Thus, natural product **11** was transformed into its bis-methyleneketal derivative **12** using paraformaldehyde in CH_2Cl_2, H_2O, and HCl, in good yield of 85%. Reduction of enone **12** under Birch conditions[5] (lithium, liquid NH_3, *t*-BuOH, THF, −33 °C) furnished C3-β-hydroxyl product (steroid numbering) **13** with trans ring juncture in excellent yield of 92%. Selective inversion of C3-β-hydroxyl group of diol **13** under Mitsunobu conditions[6] (DIAD, TPP, BzOH, THF) and subsequent $LiAlH_4$ reduction of benzoate **14** in anhydrous THF provided 3α-11β-diol **15** in 89% and 92% yields,

Scheme 2. Synthesis of Enone 19



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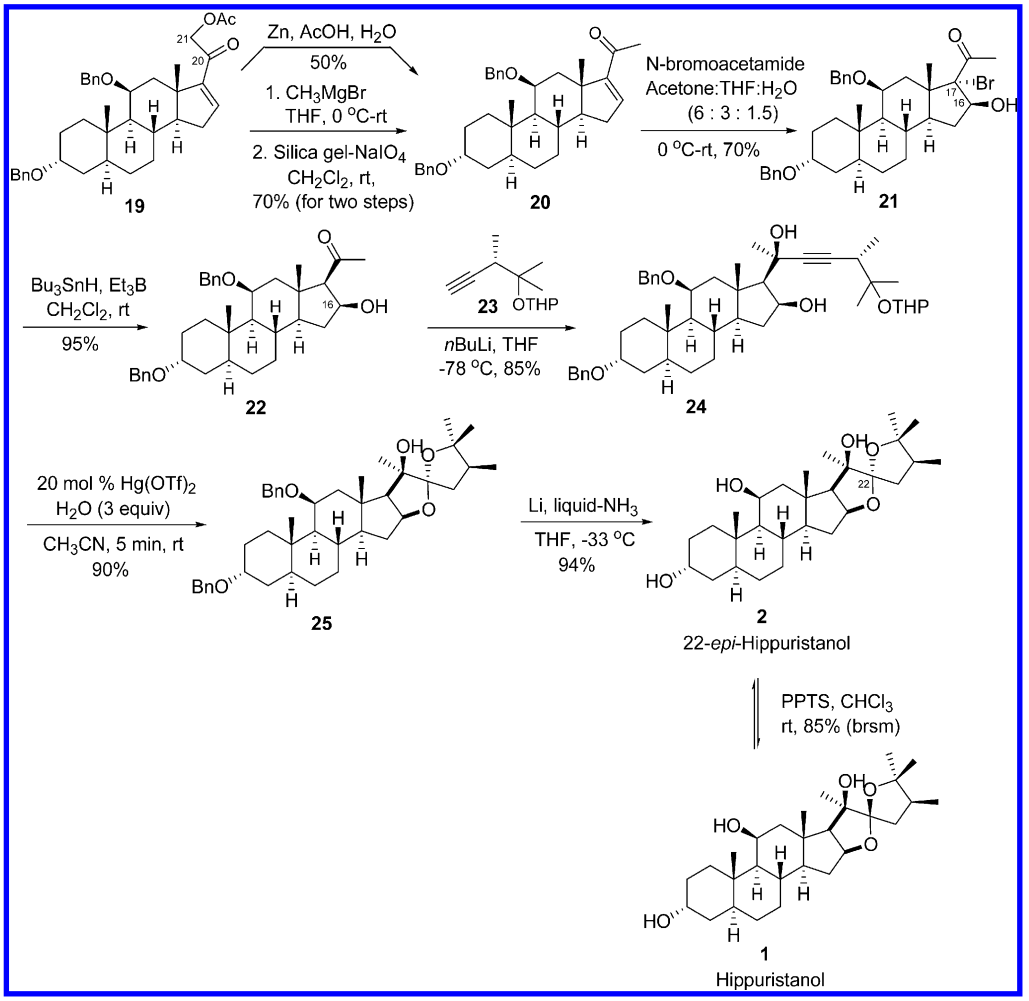
Scheme 3. Synthesis of Hippuristanol (1)



respectively.[3] Then diol **15** was protected as its dibenzyl ether **16** using standard conditions (NaH, $PhCH_2Br$, TBAI, THF, reflux). Deprotection[7] of bis-methylene ketal group in compound **16** using 48% aqueous HF in THF cleanly furnished corresponding dihydroxy ketone **17** in 78% yield. Dihydroxy ketone **17** was converted to bisacetoxy ketone **18** using standard reaction conditions (Ac_2O, PTSA, toluene), and then pyrolytic elimination[8] of the 17α-acetoxy group of **18** was carried out to obtain α,β-unsaturated 21-acetoxy ketone **19** in 85% yield (Scheme 2).

Then we turned our attention to establish suitable reaction conditions to access the required α,β-unsaturated methyl ketone **20** from α,β-unsaturated-21-acetoxy enone **19**. Thus, we first explored zinc in acetic acid mediated reductive cleavage[9] of the 21-acetoxy group in compound **19** to give **20**. We obtained only 50% yield which could be due to overreduction of C20-keto group. To overcome this problem, we adopted a two-step procedure for this conversion. Thus, we first treated compound **19** with methylmagnesium bromide in anhydrous THF to acquire the corresponding diol, which was subsequently subjected to silica gel supported $NaIO_4$[10] mediated cleavage in anhydrous CH_2Cl_2 to obtain the required enone intermediate **20** in good yield of 70%, for two steps (Scheme 3).

Having key enone intermediate **20** in hand, we adopted our own reported[3] synthetic sequence to furnish the natural product **1** as illustrated in Scheme 3. Accordingly, enone **20** was subjected to bromohydroxylation using *N*-bromoacetamide (NBA)[11] in aqueous acetone/THF to provide the 16β-hydroxy-17α-bromide **21** in 70% yield, which on subsequent treatment with *n*-Bu_3SnH and triethylborane (Et_3B) in anhydrous CH_2Cl_2 resulted in debrominated product **22** in 95% yield. This synthetic sequence provided hydroxy ketone **22** in 15% overall yield in 11 steps from commercially available natural product **11**, which was compared with our previous synthesis in 3% overall yield in 21 steps starting from hecogenin acetate.[3] Addition of lithiated alkyne coupling partner **23** (which was prepared using our own method)[3] onto 16β-hydroxyketone **22** provided exclusively the expected Cram's product **24** in 85% yield. Hg(II)-catalyzed cascade spiroketalization[3] of semi-protected alkynediol **24** provided the desired spiroketal **25** in excellent yield of 90%, which on debenzylation with lithium in liquid ammonia resulted in analogue **2** as a single diastereomer (22*S*) in 94% yield. Analogue **2** was converted to natural product **1** using pyridine *p*-toluenesulfonate (PPTS) mediated epimerization in $CHCl_3$ at room temperature in 85% yield (brsm, based on recovered starting material).[3] ^1H, ^{13}C, and remaining analytical data of the synthetic material were in good accordance with those of the natural product as well as with the reported data.[2−4]

With the above promising results, we then decided to expand our research toward the synthesis of various analogues of natural product **1** using the chemistry similar to that employed for the synthesis of **1** as shown in Scheme 2. Enone **19** was

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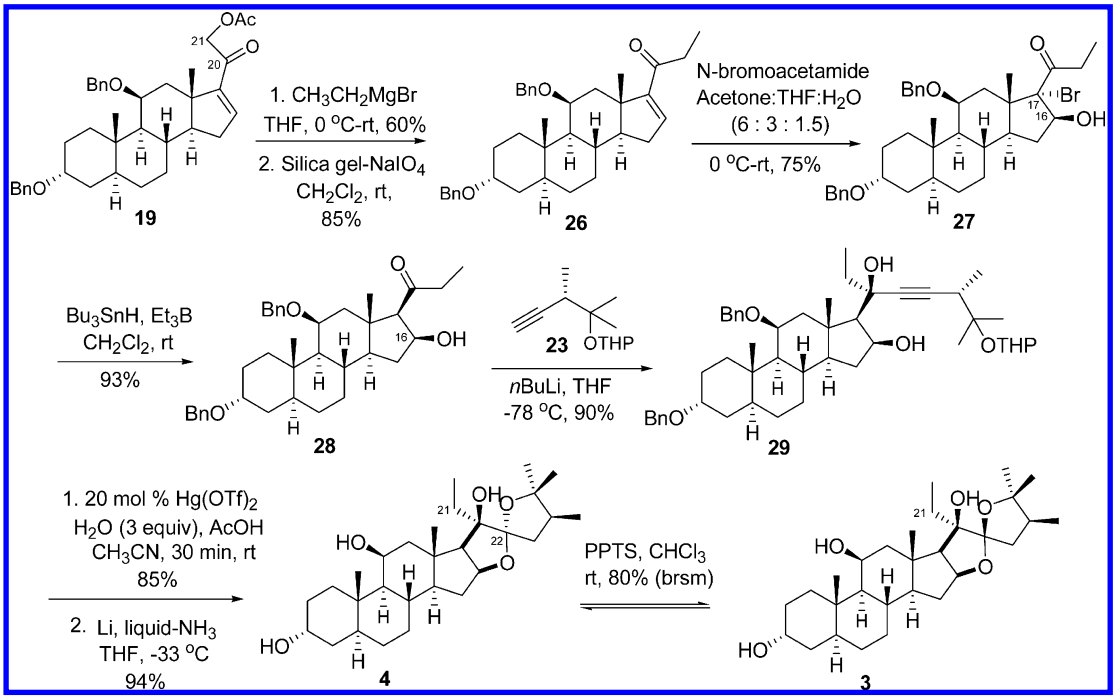
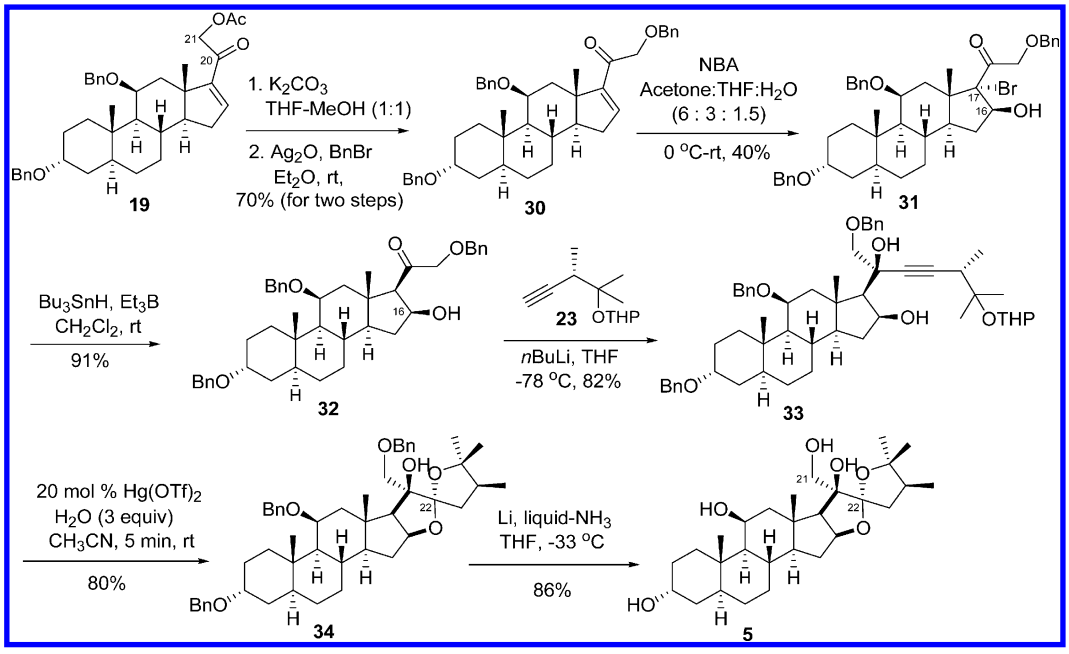
Scheme 4. Synthesis of 21-Methylhippuristanol (3) and Its 22-Epimer 4



Scheme 5. Synthesis of 21-Hydroxy-22-*epi*-hippuristanol (5)



used as a versatile building block for the synthesis of analogues related to E ring (**3**–**8**), whereas synthetic compound **1** was used as a precursor for analogues related to A and C rings (**9** and **10**) (Figure 1).

Synthesis of Analogues 3 and 4. Synthesis of 21-methylhippuristanol **3** (hippuristanol numbering) and its 22-epimer **4** was started from enone **19**. Addition of ethylmagnesium bromide to acetoxyenone **19** and subsequent silica supported $NaIO_4$ cleavage provided ethyl vinyl ketone **26**. Bromohydroxylation of **26** using *N*-bromoacetamide in aqueous acetone and THF gave the corresponding bromohydrin **27** in 75% yield. *n*-Bu_3SnH and Et_3B mediated debromination of **27** gave the required *β*-hydroxy ketone **28** in 93% yield. Lithiated alkyne **23** addition onto hydroxy ketone **28** furnished exclusively the desired Cram's product **29** in excellent yield of 90%. As was observed above, exposure of semiprotected 3-alkyn-1,7-diol **29** to $Hg(OTf)_2$ in aqueous acetonitrile and acetic acid at ambient temperature cleanly provided the spiroketal, which upon debenzylation with lithium in liquid ammonia resulted in analogue **4** as a single diastereomer. Epimerization of spiroketal **4** at C22 using PPTS in anhydrous $CHCl_3$ at room temperature furnished analogue **3** in 80% yield (brsm). Here slow epimerization was observed compared to the conversion of **2** into **1** (Scheme 4).

Synthesis of Analogue 5. In order to verify the effect of a more polar hydroxyl group in the vicinity of spiroketal segment

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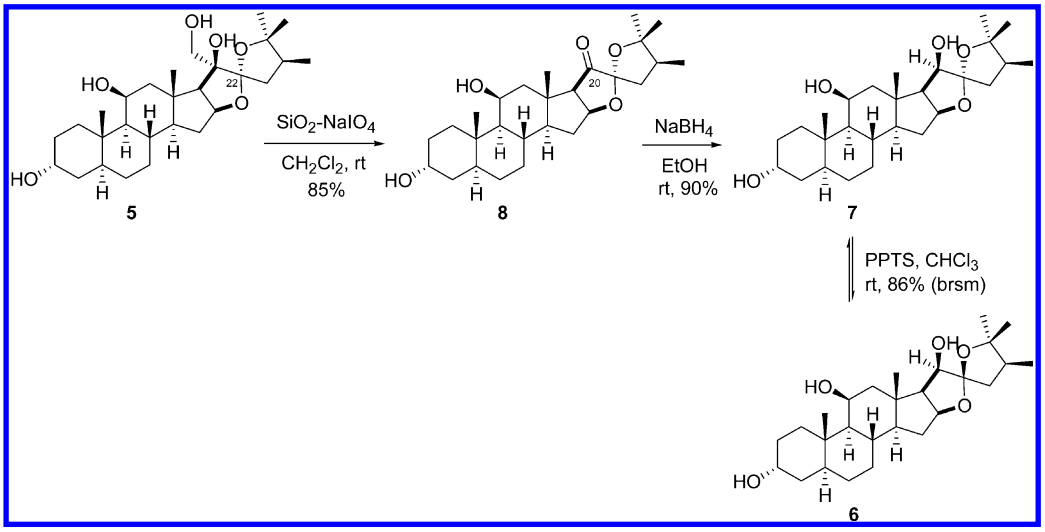
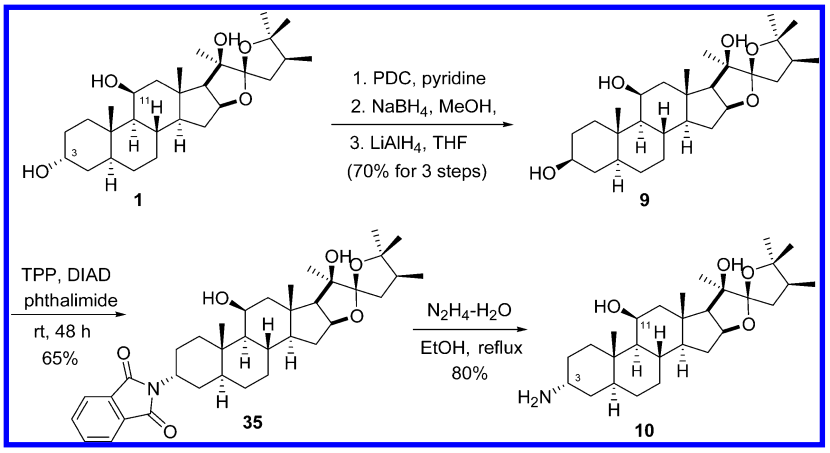
Scheme 6. Synthesis of Analogues 6−8



Scheme 7. Synthesis of Analogues 9 and 10



on inhibitory activity and the relative orientation of the spiroketal unit, we planned to prepare the 21-hydroxy derivative of **1** (hippuristanol numbering) from acetate intermediate **19** which has all the skeletal requirements. Hence, hydrolysis of acetate **19** using K_2CO_3 in MeOH−THF and subsequent benzyl protection using Ag_2O and benzyl bromide in anhydrous Et_2O [12] resulted in benzyl ether **30**. Compound **30** on exposure to *N*-bromoacetamide (NBA) in aqueous acetone/THF underwent bromohydroxylation to give 16β-hydroxy-17α-bromide **31** in moderate yield, which on treatment with Bu_3SnH/Et_3B in anhydrous CH_2Cl_2 resulted in debrominated product **32**. The addition of lithiated alkyne **23** onto β-hydroxy ketone **32** cleanly furnished the propargyl alcohol **33** in excellent yield of 82%. As was observed in prior experiments, exposure of semiprotected 3-alkyn-1,7-diol **33** to $Hg(OTf)_2$ in aqueous acetonitrile at room temperature cleanly furnished the spiroketal **34**, which on debenzylation using lithium in liquid ammonia resulted in the 22*S* spiroketal analogue **5** as a single diastereomer in a cascade manner. The stereochemistry of **5** was assigned on the basis of the analogy of the data (^{1}H and ^{13}C spectra) and from previous similar work (vide infra). PPTS mediated C22-epimerization of **5** was not observed, which could be due to the more favorable intramolecular hydrogen bonding between spiroketal oxygen (ring F) and α-oriented primary C20-hydroxymethylene group of the spiroketal **5** (Scheme 5).

Synthesis of Analogues 6, 7, and 8. Silica-supported $NaIO_4$ cleavage of glycol **5** in anhydrous CH_2Cl_2 cleanly furnished the desired ketone analogue **8** in 85% yield, which was used as a precursor for the synthesis of analogues 20-desmethylhippuristanol (**6**) and 20-desmethyl-22-*epi*-hippuristanol (**7**). Therefore, $NaBH_4$/EtOH reduction of ketone **8** at room temperature resulted in analogue **7** as single diastereomer, which was confirmed by the comparison of ^{1}H (δ_{16H} = 4.42) and ^{13}C NMR (δ_{C22} = 113.0) data with data of analogue **2** and natural product **1**. PPTS mediated epimerization at spiroketal carbon of analogue **7** at room temperature afforded analogue **6** in 86% yield (brsm). Initial observation of the R_f value on TLC and lowering of the δ value of C22 spirocarbon (δ 112.7 ppm) in ^{13}C NMR and δ at 4.15 ppm in ^{1}H NMR confirmed inversion of the stereochemistry at spiroketal carbon (Scheme 6).

Synthesis of Analogues 9 and 10. Synthetic compound **1** was used as a precursor for the synthesis of analogues **9** and **10** as illustrated in Scheme 7. Oxidation of **1** using pyridinium dichromate (PDC) in anhydrous pyridine furnished 3,11-diketone in 75% yield. $NaBH_4$ mediated selective C3-ketone reduction followed by C11-ketone reduction using $LiAlH_4$ in anhydrous THF afforded the desired 3β,11β-diol analogue **9**

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Table 1. Correlation of the ^{1}H and ^{13}C NMR Data and the $[\alpha]_D$ Values between the Diastereomeric Analogues

compd with the "*R*" stereochemistry at C22 (hippuristanol numbering)				compd with the "*S*" stereochemistry at C22 (hippuristanol numbering)			
compd	$\delta_{H\text{-}16}$ (ppm)	$\delta_{C\text{-}22}$ (ppm)	$[\alpha]_D^{20}$	compd	$\delta_{H\text{-}16}$ (ppm)	$\delta_{C\text{-}22}$ (ppm)	$[\alpha]_D^{20}$
1 (hippuristanol)	4.15	115.2	+31.0	**2** (22-*epi*-hippuristanol)	4.33	118.6	−45.2
3	3.94	115.5	+10.3	**4**	4.14	118.4	−15.4
6	4.15	112.7	+43.5	**7**	4.42	113.0	−55.3
9	4.01	115.0	+38.5	**5**	4.15	117.5	−23.5
10	4.28	115.3	+28.5	**8**	4.88	109.0	−20.5

with complete substrate controlled stereoselection.[13] 3β-Hydroxyl group of **9** was selectively converted to the 3α-phthalimide **35** using Mitsunobu conditions (phthalimide, diisopropyl azodicarboxylate (DIAD) and triphenylphosphine) and then converted to the corresponding 3α-amine analogue **10** by treating with hydrazine hydrate in absolute ethanol at reflux temperature.[14]

Structural Correlations between C22 Diastereomers of Analogues. Structural and stereochemical elucidation of **1** and **2** was unambiguously reported by Higa and co-workers using extensive spectroscopic analysis and X-ray diffraction studies.[1] We and Yu have successfully assigned the stereochemistry of spiroketal appendage (E/F rings) of several analogues of natural product **1** on the basis of the correlation of R_f values, specific rotation, and ^{1}H NMR ($\delta_{H\text{-}16}$) and ^{13}C NMR ($\delta_{C\text{-}22}$) data with data reported for **1** and its 22-epimer **2**.[3,4] Using the above analogy, herein we assigned the stereochemistry of spiroketal appendage (E and F rings) of analogues **3**−**10**. Analogues **3** and **6**, having the same configuration as **1** at C22 (*R*), have their $\delta_{H\text{-}16}$ and $\delta_{C\text{-}22}$ chemical shifts at lower values of 3.94, 4.15 ppm and 115.5, 112.7 ppm, while their C-22 epimers (*S*) **4** and **7** have those signals at higher values of 4.14, 4.42 ppm and 118.4, 113.0 ppm, respectively, and this was attributed to the data reported for **1** and **2**. Analogues **9** and **10** have their $\delta_{C\text{-}22}$ values 115 and 115.3, respectively, and are very close to the compound **1** data. Analogues **5** and **8** have $\delta_{C\text{-}22}$ values of 117.5 and 109, respectively, which are very close to the observed compound **2** data. Analogues **3**, **6**, **9**, and **10** ("*R*" stereochemistry at spiroketal carbon) have shown diagnostic specific rotation values compared to those of **4**, **5**, **7**, and **8** ("*S*" stereochemistry at spiroketal carbon) (Table 1).

Biological Activity of Analogues 3−10. Earlier it was found that analogues possessing "*S*" stereochemistry at spiroketal carbon (C22) had less inhibitory activity compared to their C22 "'*R*" diastereomers.[1−4] The similar stereochemical requirement at spiroketal carbon is observed in the new series of analogues **3**−**10**. For analogue **4** with a methyl group extension at C21 and analogue **7** with the lack of C21 methyl group and in combination with C22, "*S*" stereochemistry showed less activity compared to their epimers (C22, "*R*") **3** and **6**, respectively. Hence, we conclude that "*R*" stereochemistry at the spiroketal carbon (C22) and C21 methyl group is crucial for the inhibitory activity. Methyl group extension onto the C21 carbon in analogue **3** resulted in a decrease in the activity compared to natural product **1**. Analogue **5** with polar hydroxyl functionality extension at C21 together with 22*S* stereochemistry showed less activity compared to **1** and **2**. Analogue **6** that lacks the methyl group at C20 is also less active, which suggests that the C20 methyl substitution is also essential for the activity. C20 ketone analogue **8**, possessing "*S*" stereochemistry at spiroketal carbon, which lacks the methyl and the hydroxyl groups at C20, displayed low activity compared to **1** and **2**. Replacement of the C3-α-hydroxyl group with β-OH or α-NH_2 functional group resulted in the less active analogue **9** or **10**, respectively. These results show that the C3 α-OH (hippuristanol numbering) can greatly influence the activity of the molecule **1** (Figure 2).

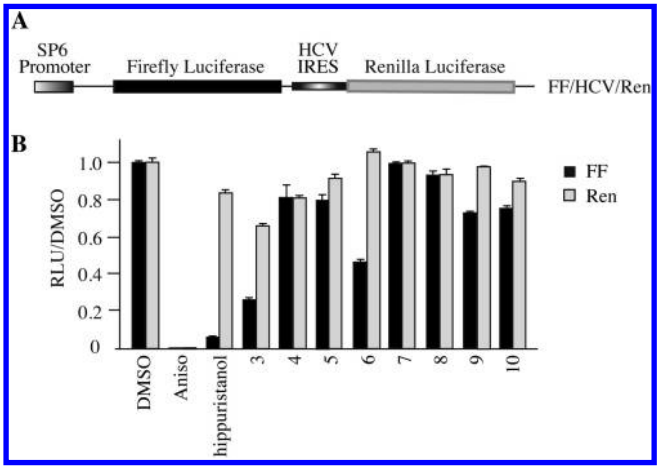

Figure 2. Evaluation of analogues of **1** as inhibitors of eukaryotic translation initiation. (A) Schematic representation of bicistronic FF/HCV/Ren construct used to evaluate the inhibitory potential of analogues of natural product **1** in in vitro translations. (B) Effect of analogues of **1** on cap-dependent (FF) in vitro translations. Cap-independent (HCV-Ren) translation serves as internal standard. Anisomycin (Aniso) is included as control compound inhibiting cap-dependent as well as cap-independent eukaryotic translation. Compounds were tested at a final concentration of 10 μM. The activity relative to DMSO is presented. Results are the average of duplicates with the error of the mean shown.

CONCLUSION

We have developed an efficient synthetic route featuring Hg(II)-catalyzed cascade spiroketalization using the semi-protected 3-alkyne-1,7-diol motif **24** to produce natural product **1** and nine closely related analogues **2**−**10**. This synthetic sequence produced **1** in 11% overall yield from commercially available **11**, which was compared with Yu's synthesis in 3.6% overall yield in 16 steps and our own previously reported synthetic route in 5.54% overall yield in 12 steps starting from 11-ketotigogenin. These results suggest that the "*R*" stereochemistry at spiroketal carbon (C22) and all substituents of 5,5-spiroketal portion (rings E and F) and C3-α and C11-β hydroxyl functional groups on ring A and C, respectively, are critical for the inhibitory activity of **1**. Further study on the structure−activity relationships of **1** and its analogues is under progress to increase the bioavailability while maintaining or even increasing the inhibitory activity and will be reported in due course.

EXPERIMENTAL SECTION

In Vitro Transcriptions and Translations. The bicistronic mRNA construct FF/HCV/Ren (Novac et al.) was linearized with *BamHI,* followed by in vitro transcription using SP6 RNA polymerase. The resulting mRNA was in vitro translated at a concentration of 4 ng/μL in rabbit reticulocyte lysate (RRL) from Promega according to the instructions of the manufacturer. In vitro translations were performed in the presence of 0.5% DMSO or 10 μM of the indicated compounds. Firefly (FF) and renilla (Ren) luciferase activities were measured on a Berthold Lumat LB 9507 luminometer, and values obtained were normalized against vehicle control, which was set at 1.

General Procedures. All reactions were performed under argon atmosphere with oven (80 °C) or flame-dried glassware. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone under argon atmosphere immediately prior to use. Dichloromethane, toluene, *N*,*N*-dimethylformamide, and acetonitrile were freshly distilled over calcium hydride under argon atmosphere. For the NMR spectra assignments, the following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, ABq, AB quartet; br, broad. Chemical shifts are reported in values relative to the solvent used ($CHCl_3$: 7.26 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR) as internal standard. Optical rotations were measured at the sodium D line (589 nm) with a 1.00 dm path length cell. Infrared spectra were recorded as neat liquid films, and only the most significant absorption bands are reported (in cm^{-1}). Experimental procedures for all the new compounds and known compounds without published experimental procedures are described below. Compounds that are not presented in the main text (manuscript) are numbered starting from **S1**. The HPLC purities of all analogues to be tested were determined with a Shimadzu Prominence apparatus (Kyoto, Japan) equipped with a Shimadzu LCMS-2020 mass spectrometer, an APCI (atmospheric pressure chemical ionization) probe, and an Alltima HP C18 analytical reversed-phase column (250 mm × 4,6 mm, 5 μm) and with a solvent gradient of MeOH/water. All final compounds showed a purity of ≥95% (96.4−99.5%) except for compounds **3**, **4**, **5**, and **6** (88.0−94.4%). The IUPAC nomenclature was used in the Experimental Section, and the names of steroid derivatives were generated using ACD/Laboratories (Chemist's version) software.

(8*S*,9*S*,10*R*,11*S*,13*S*,14*S*)-11-Hydroxy-10,13-dimethyl-1,6,7,8,9,10,11,12,13,14,15,16-dodecahydrodispiro-[cyclopenta[*a*]phenanthrene-17,4′-[1,3]dioxolane-5′,4″-[1,3]-dioxolan]-3(2*H*)-one (12). To a solution of water (450 mL) and concentrated HCl (450 mL) was added paraformaldehyde (150 g), and the mixture was stirred for 4 h at room temperature. Then hydrocortisone **11** (15 g, 41.4 mmol) and CH_2Cl_2 (750 mL) were added and stirred for an additional 4 h at room temperature. The mixture was placed overnight (without stirring) and extracted with CH_2Cl_2 (3 × 100 mL). Organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure. Purification by silica gel column chromatography (40% EtOAc/hexanes) afforded bis-methylene ketal **12** (14.17 g, 85%) as a white solid. $[\alpha]_D^{20}$ +24.5 (*c* 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.64 (s, 1H), 5.19 (s, 1H), 5.01 (s, 1H), 5.0 (s, 1H), 4.99 (s, 1H), 4.38 (m, 1H), 3.96 (q, 2H, *J* = 9.2 Hz), 2.55−0.9 (m, 18H), 1.42 (s, 3H), 1.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.6, 172.4, 122.2, 109.9, 94.8, 91.6, 91.4, 70.2, 68,5, 56.1, 52.6, 45.6, 40.6, 39.2, 34.9, 33.8, 32.5, 32.0, 31.3, 30.9, 23.7, 21.0, 15.2; IR (NaCl) cm^{-1} 3615.3, 3490.4, 3010, 2990, 1725, 1675, 1631.5, 1452, 1232. HRMS (ESI) *m*/*z*: $[M]^+$ calcd for $C_{23}H_{32}O_6$ 404.2199; found 404.2202 ± 0.0012.

(3*S*,5*S*,8*S*,9*S*,10*S*,11*S*,13*S*,14*S*)-10,13-Dimethylhexadeca-hydrodispiro[cyclopenta[*a*]phenanthrene-17,4′-[1,3]-dioxolane-5′,4″-[1,3]dioxolane]-3,11-diol (13). A flame-dried two-neck round-bottom flask was topped with a dry ice condenser. The system was flushed with argon. The condenser was filled with a dry ice/acetone mixture. Ammonia was condensed using a −78 °C trap, The hexane washed lithium metal (8.42 g) was added cautiously through the side neck of the round-bottom flask. The mixture was stirred at −33 °C until no further lithium was seen, and when bronze globules (golden liquid) started to appear, the system was allowed to equilibrate to the refluxing temperature (−33 °C). THF (10 mL) was added to disperse the newly formed reagent followed by a slow addition of a solution of enone **12** (14.95 g, 37.0 mmol) in anhydrous THF (100 mL) and *t*-BuOH (10 mL). A cautious addition is needed here to ensure a regular and smooth ammonia reflux. The reaction mixture was then stirred at −33 °C for 3 h. NH_4Cl powder was carefully and slowly added at −33 °C to quench the excess of unreacted lithium, and ammonia was allowed to evaporate under a stream of air with stirring for an additional 4 h. The resulting mixture was diluted with water, extracted with EtOAc, and washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel column chromatography (60% EtOAc/hexanes) provided the 3β,11β-diol **13** (14.02 g, 92%) as a white solid. Mp 238−243 °C; $[\alpha]_D^{20}$ −50.4 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.22 (s, 1H), 5.02 (s, 2H), 5.03 (s, 1H), 4.37 (m, 1H), 3.97 (q, 2H, *J* = 9.1 Hz), 3.58 (m, 1H), 2.10−0.7 (m, 22H), 1.07 (s, 3H), 1.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 109.9, 98.4, 92.8, 91.4, 70.3, 69.0, 66.3, 58.7, 53.0, 45.7, 40.0, 39.8, 37.1, 35.2, 32.2, 31.8, 31.2, 30.7, 28.6, 27.8, 23.6, 15.3, 14.2; IR (NaCl) cm^{-1} 3615, 3494, 3010, 2929, 1235. HRMS (ESI) *m*/*z*: $[M]^+$ calcd for $C_{23}H_{36}O_6$ 408.2512; found 408.2507 ± 0.0012.

(3*R*,5*S*,8*S*,9*S*,10*S*,11*S*,13*S*,14*S*)-11-Hydroxy-10,13-dimethyl-hexadecahydrodispiro[cyclopenta[*a*]phenanthrene-17,4′-[1,3]dioxolane-5′,4″-[1,3]dioxolan]-3-yl Benzoate (14). 3β,11β-Diol **13** (9.87 g, 24.2 mmol) was weighed in a flame-dried round-bottom flask and dissolved in anhydrous THF (359 mL) under argon atmosphere. Benzoic acid (BzOH, 4.83 g, 39.9 mmol) and triphenylphosphine (TPP, 15.52 g, 59.2 mmol) were added to the reaction mixture at 0 °C. After 5 min, diissopropylazodicarboxylate (DIAD, 11.69 mL, 59.4 mmol) was added at 0 °C. The mixture was allowed to stir at room temperature for 3 h. Then the reaction mixture was concentrated as such (without further workup) and subjected to silica gel column chromatography (20% EtOAc/hexanes) to afford the 3α-benzoate **14** (11 g, 89%) as a white foamy solid. $[\alpha]_D^{20}$ −54.4 (*c* 0.58, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.04−8.01 (m, 2H), 7.56−7.40 (m, 3H), 5.20 (m, 1H), 5.19 (s, 1H), 5.03 (s, 1H), 5.02 (s, 1H), 5.01 (s, 1H), 4.40 (m, 1H), 3.96 (q, 2H, *J* = 9.2 Hz), 2.10−0.8 (m, 21H), 1.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.8, 132.7, 131.0, 129.5, 129.4, 128.3, 109.9, 94.8, 91.9, 91.4, 70.5, 70.3, 68.2, 57.9, 53.4, 45.8, 41.2, 40.2, 36.0, 32.9, 32.4, 32.1, 31.3, 30.7, 27.7, 25.9, 23.6, 15.3, 15.2, 14.5. HRMS (ESI) *m*/*z*: $[M]^+$ calcd for $C_{30}H_{40}O_7$ 512.2774; found 512.2781 ± 0.0015.

(3*R*,5*S*,8*S*,9*S*,10*S*,11*S*,13*S*,14*S*)-10,13-Dimethyl-hexadecahydrodispiro[cyclopenta[*a*]phenanthrene-17,4′-[1,3]dioxolane-5′,4″-[1,3]dioxolane]-3,11-diol (15). 3α-Benzoate **14** (11.0 g, 21.5 mmol) was placed in a flame-dried two-necked round-bottom flask under argon. Anhydrous THF (27.5 mL) was added, and the system was cooled to 0 °C. $LiAlH_4$ solution (1.18 M in THF, 109 mL, 0.128 mmol) was added slowly and cautiously at 0 °C. After 30 min of stirring at 0 °C the mixture was slowly allowed to reflux for 4 h. The reaction mixture was then cooled to 0 °C and quenched with a minimum amount of cold water (10 mL) cautiously and very slowly. The reaction mixture was diluted with EtOAc (50 mL) and stirred for 2.5 h at room temperature and then filtered on Celite using EtOAc and CH_2Cl_2. The filtrate was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (50% EtOAc/hexanes) afforded 3α,11β-diol **15** (8.1 g, 92%) as a light yellow viscous liquid. $[\alpha]_D^{20}$ −65.9 (*c* 0.57, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.21 (s, 1H), 5.04 (s, 2H), 5.02 (s, 1H), 4.41 (m, 1H), 4.03 (m, 1H), 3.98 (q, 2H, *J* = 9.1 Hz), 2.15−0.8 (m, 22H), 1.07 (s, 3H), 1.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 109.9, 94.8, 91.8, 91.4, 70.3, 68.3, 66.3, 57.8, 53.2, 45.8, 40.1, 39.8, 36.2, 35.2, 32.2, 31.9, 31.3, 30.8, 28.6, 27.9, 23.7, 15.3, 14.3; IR (NaCl) cm^{-1} 3615.5, 3494, 3011, 2929, 1455, 1235, 1083. HRMS (ESI) *m*/*z*: $[M]^+$ calcd for $C_{23}H_{36}O_6$ 408.2512; found 408.2519 ± 0.0012.

(3*R*,5*S*,8*S*,9*S*,10*S*,11*S*,13*S*,14*S*)-3,11-Bis(benzyloxy)-10,13-dimethylhexadecahydrodispiro[cyclopenta[*a*]phenanthrene-17,4′-[1,3]dioxolane-5′,4″-[1,3]dioxolane] (16). To the 0 °C cooled suspension of NaH (60% dispersion in mineral oil, 2.62 g, 65.5 mmol) in anhydrous THF (15 mL) under argon atmosphere was

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added diol **15** (4.80 g, 11.7 mmol) in anhydrous THF (87 mL), and the mixture was stirred for 30 min at 0 °C and for 30 min at reflux temperature. Then it was cooled again to 0 °C, and to it was added TBAI (2.07 g, 5.6 mmol) followed by benzyl bromide (10.7 mL, 90.3 mmol). The reaction mixture was refluxed for 36 h and then cautiously quenched by adding cold water (dropwise) at 0 °C. Extraction was with Et_2O (3 × 100 mL), and washing was with brine solution. The organic fractions were dried over anhydrous Na_2SO_4, filtered using sintered funnel, and solvents were removed under vacuum. Purification of the crude product by silica gel column chromatography (6% EtOAc/hexanes) afforded the dibenzyl ether **16** (5.57 g, 85%) as a white foamy solid. $[\alpha]_D^{20}$ −17.1 (*c* 0.68, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38−7.26 (m, 10 H), 5.22 (s, 1H), 5.10 (s, 1H), 5.09 (1s, 1H), 5.08 (s, 1H), 4.67 (d, 1H, *J* = 11.5 Hz), 4.0 (q, 2H, *J* = 9.2 Hz), 4.03 (m, 1H), 4.0 (s, 2H), 3.64 (m, 1H), 2.45 (d, 1H, *J* = 12.1 Hz), 2.2−0.8 (m, 19H), 1.07 (s, 3H), 1.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.5, 139.3, 128.3, 128.2, 128.1, 127.6, 127.4, 127.3, 127.0, 110.1, 95.0, 94.9, 91.9, 91.5, 75.7, 73.2, 73.1, 72.8, 70.3, 69.6, 58.1, 53.8, 53.6, 46.1, 40.5, 36.1, 32.7, 32.5, 37.3, 31.5, 31.3, 28.1, 27.9, 25.4, 23.8, 23.7, 22.7, 14.3, 14.2; IR (NaCl) cm^{-1} 3011, 2930, 2875, 1700.2, 1453.8, 1356.3. HRMS (ESI) *m*/*z*: $[M]^+$ calcd for $C_{37}H_{48}O_6$ 588.3451; found 588.3456 ± 0.0017.

(3α,5α,11β)-3,11-Bis(benzyloxy)-17,21-dihydroxypregnan-20-one (17). To the solution of bismethylene ketal **16** (1.74 g, 2.9 mmol) in THF (15 mL) was added dropwise 48% HF (80 mL) in a plastic round-bottom flask at room temperature. The mixture was stirred for 6 h at room temperature. Then the contents were poured slowly into saturated aqueous $NaHCO_3$ solution, extracted with CH_2Cl_2 (3 × 100 mL), and washed with water and brine solution. Drying over anhydrous Na_2SO_4 and concentration under reduced pressure gave the crude product. Purification by silica gel column chromatography (40% EtOAc/hexanes) afforded the dihydroxy ketone **17** (1.25 g, 78%) as a white solid. $[\alpha]_D^{20}$ +62.8 (*c* 0.65, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.41−7.26 (m, 10H), 4.73 (s, 1H), 4.67 (d, 1H, *J* = 19.8 Hz), 4.58 (d, 1H, *J* = 11.4 Hz), 4.50 (q, 2H, *J* = 12 Hz), 4.32 (d, 1H, *J* = 19.8 Hz), 4.25 (d, 1H, *J* = 11.4 Hz), 4.05 (m, 1H), 3.64 (m, 1H), 2.67 (m, 1H), 2.1−0.8 (m, 20H), 1.0 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 212.5, 139.3, 138.7, 128.3, 128.2, 127.5, 127.4, 127.3, 127.1, 89.0, 75.3, 73.2, 70.3, 69.6, 67.4, 57.9, 52.6, 48.4, 40.4, 36.1, 34.2, 32.7, 32.6, 32.5, 31.8, 31.5, 28.0, 23.8, 16.8, 14.6; IR (NaCl) cm^{-1} 3608.3, 3489.6, 3011, 2928, 2858, 1660, 1357, 1278. HRMS (ESI) *m*/*z*: $[M]^+$ calcd for $C_{35}H_{46}O_5$ 546.3345; found 546.3334 ± 0.0016.

(3α,5α,11β)-3,11-Bis(benzyloxy)-20-oxopregnane-17,21-diyl Diacetate (18). To a solution of dihydroxy ketone **17** (1.96 g, 3.59 mmol) in toluene (37.3 mL) were added acetic anhydride (20.8 mL) and PTSA monohydrate (679 mg, 3.59 mmol) at room temperature, and the mixture was stirred at the same temperature for 24 h. After completion of the reaction, water was added and extracted with dichloromethane, and washing was with saturated aqueous $NaHCO_3$ solution. Drying over anhydrous Na_2SO_4, concentration under reduced pressure, and purification by silica gel column chromatography (15% EtOAc/hexanes) afforded the bisacetoxy ketone **18** (2.01, 90.6%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40−7.21 (m, 10 H), 4.99−4.18 (ABq, 2H, *J* = 16.7 Hz), 4.70−4.45 (m, 4H),4.07−4.02 (m, 1H), 3.65−3.60 (m, 1H), 2.83−2.74 (m, 1H), 2.30−2.24 (m, 1H), 2.17 (s, 3H), 2.11 (s, 3H), 1.96−0.87 (m, 18H), 0.98 (s, 3H), 092 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.7, 171.2, 170.5, 139.6, 138.0, 128.5, 128.3, 128.1, 129.9, 127.6, 127.5, 127.3, 95.0, 73.4, 73.0, 71.89, 70.4, 69.8, 58.0, 54.7, 53.3, 47.8, 40.6, 36.3, 32.7, 31.7, 30.8, 28.1, 25.5, 23.9, 21.5, 20.8, 15.5, 14.7; IR (NaCl) cm^{-1} 2927.3, 2863.6, 1736.4. HRMS (ESI) *m*/*z*: $[M]^+$ calcd for $C_{39}H_{50}O_7$ 630.3556; found 630.3569 ± 0.0019.

(3α,5α,11β)-3,11-Bis(benzyloxy)-20-oxopregn-16-en-21-yl Acetate (19). To a solution of bisacetoxy ketone **18** (2.05g, 3.25 mmol) in toluene (20 mL) and DMSO (10 mL) was added potassium acetate (1.26g, 12.89 mmol) at room temperature, and the mixture was stirred at 120 °C for 6 h. Contents were cooled to room temperature, water was added and extracted with EtOAc (3 × 100 mL). The sample was washed with brine solution, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel column chromatography (15% EtOAc/hexanes) afforded the monoacetoxy enone **19** (1.63g, 85%) as a viscous liquid. R_f = 0.5 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39−7.21 (m, 10H), 6.75−6.71 (m, 1H) 5.0−4.87 (ABq, 2H, *J* = 16.0 Hz), 4.55−4.43 (q, 2H, *J* = 12.4 Hz), 4.78−4.18 (ABq, 2H, *J* = 11.3 Hz), 4.0−3.94 (m, 1H), 3.65−3.60 (m, 1H), 3.01−2.94 (dd, 1H, *J* = 14.4, 1.9 Hz), 2.42−2.34 (m, 1H), 2.19 (s, 3H), 2.17−0.85 (m, 16 h), 1.17 (s, 3H), 1.03(s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.7, 170.6, 153.1, 144.2, 139.6, 139.2, 128.5, 128.3, 127.9, 127.5, 127.2, 75.6, 73.37, 70.3, 69.8, 65.81, 59.57, 58.0, 46.6, 40.9, 36.5, 36.1, 32.9, 32.5, 32.4, 30.87, 28.1, 25.4, 20.8, 17.8, 14.8; IR (NaCl) cm^{-1} 2928, 2856, 1746, 1682, 1460, 1200. HRMS (ESI) *m*/*z*: $[M]^+$ calcd for $C_{37}H_{46}O_5$ 570.3345; found 570.3322 ± 0.0012.

(3α,5α,11β)-3,11-Bis(benzyloxy)pregn-16-en-20-one (20). To the methylmagnesium bromide solution (3.0 M in THF, 2.92 mL, 8.76 mmol) in anhydrous THF (10 mL) was added monoacetoxy enone **19** (1.0 g, 1.75 mmol) in anhydrous THF (10 mL) at −10 °C (ice and salt mixture bath) under inert atmosphere. The mixture was stirred at 0 °C for 1 h and for an additional 1.5 h at room temperature. Then the reaction was quenched with saturated aqueous NH_4Cl (10 mL) solution cautiously in dropwise fashion at 0 °C. The resulting mixture was acidified with 3 N aqueous HCl (pH 6.0), extracted with EtOAc (3 × 50 mL), washed with brine solution, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude diol was used as such in the next step. Accordingly, the crude diol was dissolved in anhydrous CH_2Cl_2 and then treated with silica gel supported $NaIO_4$ (1.8 g) at room temperature under argon atmosphere. After completion of the reaction, the contents were filtered with sintered funnel and washed with CH_2Cl_2. Filtrate was concentrated under reduced pressure and the crude enone was subjected to silica gel column chromatography (10% EtOAc/hexanes) to afford the enone **20** (629 mg, 70% yield for two steps) as a white solid. $[\alpha]_D^{20}$ +95.6 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41−7.23 (m, 10H), 6.71−6.69 (m, 1H), 4.82−4.21 (ABq, 2H, *J* = 11.7 Hz), 4.50 (q, 2H, *J* = 12.1 Hz), 4.0−3.94 (m, 1H), 3.67−3.60 (m, 1H), 3.0−2.98 (dd, 1H, *J* = 14.0, 1.9 Hz), 2.38−2.30 (m, 1H), 2.27 (s, 3H), 2.13−0.82 (m, 17H), 1.16 (s, 3H), 1.0 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.0, 156.3, 144.4, 139.5, 139.2, 128.3, 128.1, 127.7, 127.4, 127.3, 126.9, 73.2, 70.2, 69.6, 59.4, 58.4, 45.8, 40.8, 36.4, 36.2, 32.7, 32.4, 32.3, 30.7, 27.9, 27.1, 25.3, 17.5, 14.7; IR (NaCl) cm^{-1} 2922, 2862.5, 1665.3, 1589.3, 1454, 1359, 1060. HRMS (ESI) *m*/*z*: $[M]^+$ calcd for $C_{35}H_{44}O_3$ 512.3290, found: 512.3291 ± 0.0015.

Enone 20 Using Zn-AcOH. To monoacetoxy **19** (1.0 g, 1.75 mmol) in AcOH (5 mL) and H_2O (1 mL) was added zinc dust (6.0 g) at 0 °C. The reaction was monitored by TLC. After completion of the reaction, the contents were filtered with sintered funnel and washed with MeOH. Filtrate was concentrated under reduced pressure. The crude enone was purified by silica gel column chromatography (8% EtOAc/hexanes) to obtain the enone **20** (449 mg, 50% yield) as a white solid. R_f = 0.7 (SiO_2, 20% EtOAc/hexanes); $[\alpha]_D^{20}$ +96.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40−7.22 (m, 10H), 6.71−6.66 (m, 1H), 4.82−4.20 (ABq, 2H, *J* = 11.7 Hz), 4.50 (q, 2H, *J* = 12.1 Hz), 4.0−3.95 (m, 1H), 3.65−3.60 (m, 1H), 3.0−2.97 (dd, 1H, *J* = 14.4, 2.3 Hz), 2.38−2.30 (m,1H), 2.26 (s, 3H), 2.12−0.93 (m, 17H), 1.15 (s, 3H), 1.0 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.0, 158.5, 144.6, 139.6, 139.4, 128.5, 128.2, 127.9, 127.6, 127.4, 127.1, 75.8, 73.4, 70.3, 69.8, 59.5, 58.5, 46.0, 41.0, 36.5, 32.9, 32.5, 32.48, 32.45, 30.9, 28.1, 27.3, 25.5, 17.7, 14.9.

(3α,5α,11β,16β)-3,11-Bis(benzyloxy)-17-bromo-16-hydroxypregnan-20-one (21). Enone **20** (252 mg, 0.49 mmol) was dissolved in acetone (6 mL), THF (3 mL) and H_2O (1.5 mL), and to the mixture was added NBA (*N*-bromoacetamide, 203.7 mg, 1.47 mmol) at room temperature. The mixture was stirred for 18 h in the dark, and additional NBA (135.7 mg, 0.98 mmol) was added at room temperature. The stirring continued for an additional 10 h at room temperature, and the mixture was diluted with EtOAc (30 mL). The organic layer was washed with saturated Na_2SO_3 solution and brine solution. The sample was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified

by silica gel column chromatography (10% EtOAc/hexanes) to get the α-bromo ketone **21** (208 mg, 70%) as a viscous liquid. $[\alpha]_D^{20}$ +17.4 (*c* 0.35, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36−7.25 (m, 10H), 4.95 (dd, 1H, *J* = 4.1 Hz), 4.68−4.30 (q, 2H, *J* = 11.4 Hz), 4.49 (q, 2H, *J* = 11.2 Hz), 4.04 (m, 1H), 3.62 (m, 1H), 2.39 (s, 3H), 2.9−1.0 (m, 19 H), 1.37 (s, 3H), 1.0 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.1, 139.4, 138.7, 128.3, 128.2, 127.6, 127.4, 127.3, 85.5, 82.0, 75.5, 73.1, 70.7, 69.7, 57.8, 50.6, 45.7, 40.4, 37.9, 36.1, 34.3, 32.7, 32.5, 32.2, 31.8, 28.5, 27.8, 25.4, 15.8, 14.6; IR (NaCl) cm^{-1} 3605, 3517, 2940.9, 2859.1, 1702, 1693.2, 1454, 1359, 1270. HRMS (ESI) *m/z*: $[M - OBr]^+$ calcd for $C_{35}H_{45}O_4Br$ 513.3368; found 513.3365 ± 0.0015.

(3α,5α,11β,16β)-3,11-Bis(benzyloxy)-16-hydroxypregnan-20-one (22). To a solution of bromide **21** (150 mg, 0.24 mmol) in anhydrous CH_2Cl_2 (3 mL) was added Bu_3SnH (0.651 mL, 2.46 mmol) followed by Et_3B (1 M in hexane, 0.24 mL, 0.48 mmol) and air (with empty syringe, 1.5 mL) under inert atmosphere. The mixture was allowed to stir for 45 min at room temperature and then concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (30% EtOAc/hexanes) to afford the hydroxy ketone **22** (123.6 mg, 95%) as a white solid. $[\alpha]_D^{20}$ +52.0 (*c* 0.5, $CHCl_3$); ^1H NMR (C_6D_6 + CCl_4 (1:9), 400 MHz) δ 7.11−6.96 (m, 10H), 4.43−3.39 (q, 2H, *J* = 11.3 Hz), 4.25−4.19 (m, 2H), 3.96−3.92 (m, 1H), 3.74−3.69 (m, 1H), 3.39−3.34 (m, 1H), 2.32−2.25 (m, 1H), 2.04−1.95 (m, 1H), 1.87 (s, 3H), 1.81−0.58 (m, 18H), 0.97 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (C_6D_6 + CCl_4 (1:9), 100 MHz) δ 210.0, 139.3, 138.4, 128.0,128.1, 127.9, 127.6, 127.5, 127.4, 127.2, 127.1, 127.0, 75.0, 73.0, 71.6, 70.5, 69.6, 67.0, 58.7, 55.7, 43.3, 40.4, 40.3, 36.7, 36.2, 32.7, 32.6, 32.4, 31.8, 31.38, 28.0, 25.6, 16.4, 14.7; IR (NaCl) cm^{-1} 3606.3, 3495.1, 2930.1, 2854.5, 1713.1, 1681.3, 1450, 1363.1. HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{35}H_{46}O_4$ 530.3396; found 530.3408 ± 0.0016.

Dihydroxyalkyne 24. To the known[3] terminal alkyne **23** (150 mg, 1.2 mmol) in anhydrous THF (2.5 mL) under argon was added *n*-butyllithium solution (1.6 M solution in hexane, 0.481 mL, 0.706 mmol) at −78 °C. The resultant mixture was stirred at −78 °C for 1.5 h, followed by the addition of hydroxy ketone **22** (135 mg, 0.253 mmol) in anhydrous THF (2.0 mL). The resultant mixture was stirred at −78 °C for 4 h. Then the reaction was quenched with saturated aqueous NH_4Cl solution at −78 °C. The mixture was warmed to 0 °C, diluted with water, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. Purification by flash column chromatography (silica gel, gradient elution with 4−20% EtOAc/hexanes) afforded the coupled product **24** (157 mg, 85%) as a viscous liquid. Here, we obtained the product as a mixture of diastereomers; hence, analytical data were not provided.

(3α,5α,11β,17ξ,22*S*,24*S*)-3,11-Bis(benzyloxy)-24-methyl-22,25-epoxyfurostan-20-ol (25). To a stirred mixture of dihydroxyalkyne **24** (117 mg, 0.159 mmol) and H_2O (14.5 mg, 0.799 mmol) in CH_3CN (2 mL) was added $Hg(OTf)_2$ (16 mg, 0.0319 mmol) at room temperature, and the mixture was stirred for 10 min at the same temperature. Reaction was quenched by the addition of Et_3N (65 μL). The resulting mixture was diluted with Et_2O (5 mL), extracted with Et_2O, and the combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was subjected to silica gel column chromatography (elution with 12% EtOAc/hexanes) to afford the spiroketal **25** (93 mg, 90%) as a white solid. ^1H NMR (C_6D_6 + CCl_4 (1:9), 400 MHz) δ 7.13−7.0 (m, 10H), 4.47−3.91 (ABq, 2H, *J* = 10.93 Hz), 4.25−4.14 (m, 3H), 3.63 (s br, 1H), 3.35 (br s, 1H), 2.31−2.21 (m, 2H), 1.89−1.68 (m,2H), 1.65−0.65 (m,19 H), 1.45 (d, 1H, *J* = 7.8 Hz), 1.23 (s, 3H), 1.0 (s, 3H), 1.0 (s,3H), 0.75 (s, 3H), 0.73 (s, 3H), 0.58−0.49 (dd, 1H, *J* = 11.32, 3.12 Hz). ^{13}C NMR (C_6D_6 + CCl_4 (1:9), 100 MHz) δ 139.4, 138.5, 128.1, 128.0, 127.9, 127.7, 127.4, 127.18, 127.15, 127.0, 119.7, 84.3, 82.4, 79.7, 74.7, 73.0, 70.5, 69.5, 66.7, 58.9, 58.2, 44.8, 42.7, 40.3, 36.1, 32.7, 32.59, 32.65, 31.6, 30.6, 31.0, 29.6, 28.3, 25.6, 23.0, 20.1, 14.6.

(3α,5α,11β,17ξ,22*S*,24*S*)-24-Methyl-22,25-epoxyfurostan-3,11,20-triol (2). A flame-dried two-neck round-bottom flask was topped with a dry ice condenser, and the system was flushed with argon. The condenser was filled with a dry ice/acetone mixture. Ammonia was condensed, and the lithium metal (16 mg, 2.611 mmol, washed with hexanes) was added cautiously through the side neck of the round-bottom flak. The contents were stirred at −33 °C until no further lithium was seen. When bronze globules (golden liquid) started to appear, the system was allowed to equilibrate to the refluxing temperature (−33 °C). THF (1.5 mL) was added to disperse the newly formed reagent, and then to the mixture was added slowly a solution of dibenzyl ether **25** (84 mg, 0.130 mmol). A cautious addition is needed to ensure a regular and smooth ammonia reflux. The reaction mixture was then stirred at −33 °C for 2 h, and to the mixture was carefully and slowly added NH_4Cl powder at −33 °C to quench the excess of lithium. Ammonia was allowed to evaporate under a stream of air. To the residue was added H_2O (5 mL), and extraction was with EtOAc (5 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography (15% acetone/hexanes) afforded 22-*epi*-hippuristanol (**2**) (56.4 mg, 94%) as a white solid. $[\alpha]_D^{20}$ −45.2 (*c* 1.0, $CHCl_3/CH_3OH$ (1:1)); ^1H NMR ($CDCl_3$ + 2% CD_3OD, 400 MHz) δ 4.37−4.28 (m, 1H),4.17 (br s, 1H), 3.98 (br s, 1H), 2.17−2.08 (m,1H), 2.08−2.0 (m, 1H), 1.99−0.74 (m, 19H), 1.20 (s, 3H), 1.18 (s, 3H), 1.17 (s, 3H), 1.25 (s, 3H), 1.23 (s, 3H), 0.98 (s, 3H), 0.94 (s, 3H), 0.89 (d, 3H, *J* = 7.0 Hz), 0.70−0.63 (dd, 1H, *J* = 10.93, 3.1 Hz); ^{13}C NMR ($CDCl_3$ + 2% CD_3OD, 100 MHz) δ 118.6, 84.5, 82.3, 79.4, 67.8, 66.5, 58.5, 58.1, 48.3, 42.1, 41.0, 39.9, 36.3, 35.2, 32.5, 31.7, 31.6, 30.3, 28.9, 28.4, 28.0, 27.1, 22.9, 19.1, 14.0, 13.9. HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{28}H_{46}O_5$ 462.3345; found 462.3348. LRMS for $C_{28}H_{47}O_5$ $[M + H]^+$ = 463.45. HPLC purity of 96.4% (retention time = 15.8)

(3α,5α,11β,17ξ,22*R*,24*S*)-24-Methyl-22,25-epoxyfurostan-3,11,20-triol (1). 22-*epi*-Hippuristanol (**2**) (63 mg, 0.135 mmol) was dissolved in $CHCl_3$ (2 mL) in a single neck round-bottom flask, and to this solution was added pyridine *p*-toluenesulfonate (PPTS, 5.3 mg, 0.021 mmol) at room temperature. After the mixture was stirred for 12 h at room temperature, the solvent was removed under reduced pressure. Chromatography of the residue (without further workup) on silica gel (15% acetone/hexanes) afforded hippuristanol (**1**) (18.4 mg, 85% brsm (based on recovered starting material of 42%)) as a white solid. $[\alpha]_D^{20}$ +31.0 (*c* 0.5, CCl_4); ^1H NMR (400 MHz, 9:1 CCl_4/C_6D_6) δ 4.05−3.96 (m, 2H), 3.73−3.68 (m, 1H), 2.69 (s, 1H), 2.15−2.07 (m, 1H), 1.98−1.91 (m, 1H), 1.80−0.55 (m, 18H), 1.15 (s, 3H), 1.05 (s, 3H), 1.0 (s, 3H), 1.0 (s, 3H), 1.0 (s, 3H), 0.81(s, 3H), 0.79 (s, 3H), 0.53−0.46 (m, 1H); ^{13}C NMR (75 MHz, 9:1 CCl_4/C_6D_6) δ 115.2, 84.1, 80.0, 79.2, 68.0, 66.4, 66.0, 58.6, 57.6, 50.6, 42.5, 42.1, 41.1, 40.0, 36.0, 34.4, 34.4, 33.1, 31.7, 30.6, 29.4, 29.1, 28.4, 23.6, 18.9, 15.4, 14.3. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{28}H_{46}O_5Na$ 485.3238; found 485.3234. LRMS for $C_{28}H_{47}O_5$ $[M + H]^+$ = 463.45. HPLC purity of 99.5% (retention time = 17.0).

1-[(3*R*,5*S*,8*S*,9*S*,10*S*,11*S*,13*S*,14*S*)-3,11-Bis(benzyloxy)-10,13-dimethyl-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl]propan-1-one (26). To a stirred solution of ethylmagnesium bromide (3.0 M in THF, 1.61 mL, 4.8 mmol) in anhydrous THF (5 mL) was added acetoxy enone **19** (300 mg, 0.48 mmol) in anhydrous THF (5 mL) at −10 °C (ice and salt mixture bath) under argon atmosphere. The mixture was stirred at 0 °C for 1 h and for an additional 1.5 h at room temperature, then quenched with saturated aqueous NH_4Cl (10 mL) solution cautiously in dropwise fashion at 0 °C. The resulting mixture was acidified with 3 N aqueous HCl (pH 6.0), extracted with EtOAc (3 × 30 mL), washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. This crude diol was used as such in the next step without further purification. Accordingly, the crude diol (176 mg, 0.29 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) and then treated with silica gel supported $NaIO_4$ (629 mg) at room temperature under argon atmosphere. After completion of the reaction, the contents were filtered with sintered funnel and washed with CH_2Cl_2. Filtrate was concentrated under reduced pressure and the crude enone was subjected to silica gel column chromatography (8% EtOAc/hexanes) to afford the desired enone **26** (141 mg, 85% yield) as a white solid. R_f = 0.7 (SiO_2, 20% EtOAc/hexanes); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.39−7.2 (m, 10 H), 6.72−6.63 (m, 1H), 4.81−4.19 (ABq, 2H, *J* = 11.32 Hz), 4.49 (q, 2H, *J* = 12.1 Hz), 4.0−3.94 (m,

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1H), 3.65−3.59 (m, 1H), 3.07−2.99 (m, 1H), 2.7−2.56 (m, 2H), 2.37−0.93 (m,17 H), 1.15 (s, 3H), 1.08 (t, 3H, J = 7.02 Hz), 1.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.8, 155.7, 142.7, 139.4, 139.1, 128.2, 128.0, 127.7, 127.3, 127.2, 126.9, 75.5, 73.1, 70.0, 69.5, 59.3, 58.2, 45.9, 40.7, 36.3, 36.2, 32.7, 32.3, 32.2, 32.1, 32.0, 30.7, 27.9, 25.2, 17.5, 14.6, 8.2. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{36}H_{47}O_3$ 527.352; found 527.3512.

1-[(3*R*,5*S*,8*S*,9*S*,10*S*,11*S*,13*S*,14*S*,16*S*,17*S*)-3,11-Bis(benzyloxy)-17-bromo-16-hydroxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl]propan-1-one (27). Enone **26** (141 mg, 0.26 mmol) was dissolved in acetone (6 mL), THF (3 mL), and H_2O (1.5 mL). Then to the mixture was added NBA (*N*-bromoacetamide, 110.7 mg, 0.80 mmol) at room temperature. The mixture was stirred for 6 h in the dark at room temperature. Then the mixture was diluted with EtOAc (20 mL). The organic layer was washed with saturated Na_2SO_3 solution and brine solution, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (10% EtOAc/hexanes) to give the α-bromo ketone **27** (125 mg, 75%) as a viscous liquid. R_f = 0.6 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39−7.24 (m, 10H), 5.0−4.95 (m, 1H), 4.66−4.32 (ABq, 2H, J = 11.7 Hz), 4.51−4.48 (m, 2H), 4.47−4.44 (m, 1H), 4.07−4.02 (m, 1H), 3.66−3.62 (m, 1H), 3.05−2.97 (m, 1H), 2.48−2.34 (m, 2H), 2.05−0.84 (m, 17 H), 1.37 (s, 3H), 1.16 (t, 3H, J = 7.0 Hz), 1.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 207.1, 139.3, 138.6, 128.5, 128.9, 128.2, 127.6, 127.3, 127.2, 127.2, 85.8, 82.0, 75.6, 73.1, 70.7, 69.6, 57.7, 50.6, 45.6, 40.3, 38.0, 36.1, 34.2, 33.6, 32.6, 32.4, 32.1, 31.7, 27.8, 25.4, 15.8, 14.5, 8.5.

1-[(3*R*,5*S*,8*S*,9*S*,10*S*,11*S*,13*S*,14*S*,16*S*,17*R*)-3,11-Bis(benzyloxy)-16-hydroxy-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl]propan-1-one (28). To a solution of bromide **27** (125 mg, 0.20 mmol) in anhydrous CH_2Cl_2 (5 mL) were added Bu_3SnH (0.53 mL, 2.0 mmol) followed by Et_3B (1 M in hexane, 0.32 mL, 0.32 mmol) and air (with empty syringe, 5 mL) under inert atmosphere. The mixture was allowed to stir for 45 min at room temperature and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (20% EtOAc/hexanes) to afford the desired hydroxy ketone **28** (101.5 mg, 93% yield) as a white solid. R_f = 0.5 (SiO_2, 30% EtOAc/hexanes). ^{1}H NMR (C_6D_6 + CCl_4, 400 MHz) δ 7.14−6.95 (m, 10H), 4.42−3.98 (ABq, 2H, J = 11.3 Hz), 4.26−4.18 (m, 3H), 3.74−3.70 (m, 1H), 3.39−3.34 (m, 1H), 2.27−1.96 (m, 3H), 1.87−0.61 (m, 14H), 0.96 (s, 3H), 0.84 (t, 3H, J = 7.41 Hz), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 212.4, 139.1, 138.2, 127.7, 127.4, 127.6, 127.4, 127.3, 127.2, 126.96, 126.91, 126.8, 74.9, 72.7, 71.5, 70.4, 69.3, 65.8, 58.4, 55.4, 43.4, 40.2, 37.5, 35.9, 32.4, 32.3, 32.2, 31.1, 27.8, 26.6, 25.4, 16.3, 14.5; IR (NaCl) cm^{-1} 3606.3, 3495.1, 2930.1, 2854.5, 1713.1, 1681.3, 1450, 1363.1. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{36}H_{49}O_4$ 545.3625; found 545.3622.

(2*S*,2′*R*,4*S*,4a′*S*,4b′*S*,5′*S*,6a′*S*,7′*R*,9a′*S*,10a′*S*,10b′*S*,12a′*S*)-7′-Ethyl-4,4a′,5,5,6a′-pentamethylicosahydro-3*H*-spiro[furan-2,8′-naphtho[2′,1′:4,5]indeno[2,1-*b*]furan]-2′,5′,7′-triol (4). To the known terminal alkyne **23** (109 mg, 0.18 mmol) in anhydrous THF (2.5 mL) under argon was added *n*-butyllithium solution (1.6 M solution in hexane, 0.29 mL, 0.46 mmol) at −78 °C. The resultant mixture was stirred at −78 °C for 1.5 h, followed by the addition of hydroxy ketone **28** (101.5 mg, 0.18 mmol) in anhydrous THF (2 mL). The resultant mixture was stirred at −78 °C for 6 h. Then the reaction was quenched with saturated aqueous NH_4Cl solution at −78 °C. The mixture was warmed to 0 °C, diluted with water, extracted with EtOAc (3 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (gradient elution with 5−15% EtOAc/hexane) to afford the desired coupled product **29** (139 mg, 90%) as a mixture of diastereomers and was used as such in the next reaction. To a stirred mixture of dihydroxyalkyne **29** (139 mg, 0.18 mmol) and H_2O (16.8 mg, 0.93 mmol) in CH_3CN (2.0 mL) was added $Hg(OTf)_2$ (18.7 mg, 0.037 mmol) at room temperature. Then 0.1 mL of acetic acid was added and the mixture was stirred for 10 min at the same temperature. Reaction was quenched by the addition of Et_3N (0.5 mL), and the resulting mixture was diluted with Et_2O (5 mL) and water (5 mL) and extracted with Et_2O (3 × 10). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (elution with 10% EtOAc/hexanes) to afford the corresponding spiroketal (104 mg, 85%) which was used directly in next step.

A flame-dried two-neck round-bottom flask was topped with a dry ice condenser, and the system was flushed with argon. The condenser was filled with a dry ice/acetone mixture. Ammonia was condensed, and the lithium metal (9.4 mg, 1.58 mmol, washed with hexanes) was added cautiously through the side neck of the round-bottom flak. The contents were stirred at −33 °C until no further lithium was seen. When bronze globules (golden liquid) started to appear, the system was allowed to equilibrate to the refluxing temperature (−33 °C). THF (1.5 mL) was added to disperse the newly formed reagent, and then to the mixture was added slowly a solution of the above dibenzyl ether (104 mg, 0.15 mmol). A cautious addition is needed to ensure a regular and smooth ammonia reflux. The reaction mixture was then stirred at −33 °C for 2 h, and to the mixture was carefully and slowly added NH_4Cl powder at −33 °C to quench the excess of lithium. Ammonia was allowed to evaporate under a stream of air. To the residue was added H_2O (5 mL), and extraction was with EtOAc (5 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography (20% acetone/hexanes) afforded 21-methyl-22-*epi*-hippuristanol **4** (71 mg, 94%) as a colorless solid. R_f = 0.45 (SiO_2, 30% acetone/hexanes); $[\alpha]_D^{20}$−15.4 (c 0.25, CH_2Cl_2); ^{1}H NMR (C_6D_6 + CCl_4, 400 MHz) δ 4.19−4.09 (m, 1H), 4.04−3.98 (m, 1H), 3.74−3.67 (m, 1H), 2.13−2.01 (m, 1H), 1.85−0.65 (m, 21H), 1.08 (s, 3H), 1.06 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (C_6D_6 + CCl_4, 100 MHz) δ 118.4, 84.8, 83.2, 78.6, 67.4, 65.5, 64.0, 58.5, 57.8, 48.8, 41.6, 40.3, 39.4, 36.0, 35.4, 32.3, 31.4, 31.2, 30.7, 30.0, 29.3, 28.6, 27.8, 23.2, 19.34, 13.83, 14.04, 8.6. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{29}H_{49}O_5$ 477.3575; found 477.3571. LRMS for $C_{29}H_{49}O_5$ [M + H] = 477.45. HPLC purity of 94.4% (retention time = 17.2).

(2*R*,2′*R*,4*S*,4a′*S*,4b′*S*,5′*S*,6a′*S*,7′*R*,9a′*S*,10a′*S*,10b′*S*,12a′*S*)-7′-ethyl-4,4a′,5,5,6a′-Pentamethylicosahydro-3*H*-spiro[furan-2,8′-naphtho[2′,1′:4,5]indeno[2,1-*b*]furan]-2′,5′,7′-triol (3). 21-Methyl-22-*epi*-hippuristanol **4** (71 mg, 0.14 mmol) was dissolved in $CHCl_3$ (2 mL), and to this solution was added pyridine *p*-toluenesulfonate (PPTS, 5.6 mg, 0.02 mmol) at room temperature. The mixture was stirred for 12 h. The solvent was removed under reduced pressure. The crude residue was purified (without further workup) by silica gel column chromatography using 15% acetone/hexanes to afford the desired 21-methylhippuristanol **3** (28.0 mg, 80% brsm (based on recovered starting material of 40%)) as a colorless liquid. R_f = 0.5 (SiO_2, 30% acetone/hexanes); $[\alpha]_D^{20}$ +10.3 (c 0.25, CH_2Cl_2); ^{1}H NMR (400 MHz, 9:1 CCl_4/C_6D_6) δ 4.05−3.89 (m, 2H), 3.71 (br s, 1H), 2.69 (s, 1H), 2.16−2.03 (m, 1H), 1.89 (dd, 1H, J = 13.6 Hz), 1.80−0.58 (m, 27H), 1.15 (s, 3H), 1.09 (s, 3H), 1.01 (s, 3H), 1.0 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, CCl_4/C_6D_6 (9:1)) δ 115.5, 83.4, 81.2, 80.0, 67.5, 65.6, 60.7, 58.2, 57.1, 49.7, 41.85, 41.83, 40.3, 39.6, 36.2, 35.4, 33.8, 32.5, 31.2, 30.0, 28.6, 28.3, 27.9, 22.9, 18.3, 14.8, 13.7, 8.4. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{29}H_{49}O_5$ 477.3575; found 477.3575. LRMS for $C_{29}H_{49}O_5$ [M + H] = 477.45. HPLC purity of 94.1% (retention time = 18.0).

(3α,5α,11β)-3,11-Bis(benzyloxy)-21-hydroxypregn-16-en-20-one (S1). To a stirred solution of ketoacetate **19** (500 mg, 0.87 mmol) in THF (5 mL), MeOH (5 mL), and H_2O (2 drops) was added K_2CO_3 (120 mg, 0.87 mmol) at room temperature, and the reaction was monitored by TLC. After completion of the reaction, solvent was removed under reduced pressure and the reaction mixture was diluted with EtOAc (20 mL) and washed with H_2O (2 × 20 mL) and brine. The sample was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (15% EtOAc/hexanes) to provide the corresponding alcohol **S1** (324 mg, 70%) as a colorless solid. R_f = 0.46 (30% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39−7.23 (m, 10 H), 6.75−6.71 (m, 1H), 4.81−4.23 (ABq, 2H, J = 11.32 Hz), 4.55−

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4.47 (ABq, 2H, J = 12.24 Hz), 4.45−4.35 (ABq, 2H, J = 16.13 Hz), 4.01−3.97 (m, 1H), 3.65−3.62 (m, 1H), 2.97 (dd, 1H, J = 14.44, 1.95 Hz), 2.43−2.33 (m, 1H), 2.19−1.98 (m, 2H), 1.88−1.76 (m, 2H), 1.62−0.91 (m, 14H), 1.19 (s, 3H), 1.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.7, 152.6, 144.8, 139.6, 139.2, 128.5, 128.3, 127.8, 127.5, 127.4, 127.2, 75.7, 73.3, 70.4, 69.8, 65.2, 59.61, 58.2, 46.5, 40.9, 36.5, 36.3, 32.8, 32.5, 32.4, 30.8, 28.0, 25.5, 17.9, 14.8. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{35}H_{45}O_4$ 529.3312; found 529.3306.

(3α,5α,11β)-3,11,21-Tris(benzyloxy)pregn-16-en-20-one (30). To a stirred solution of alcohol **S1** (324 mg, 0.61 mmol) in dry diethyl ether (10 mL) under argon at room temperature was added silver oxide (284 mg, 1.22 mmol) followed by benzyl bromide (0.087 mL, 0.73 mmol), and the mixture was allowed to stir for 48 h at room temperature. After completion of the reaction, the mixture was filtered through Celite pad and washed with Et_2O (20 mL). The original filtrate and Et_2O washings were combined and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (5% EtOAc/hexanes) to afford the benzyl ether **30** (303 mg, 80%) as a colorless foamy solid. R_f = 0.80 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42−7.25 (m, 15 H), 6.74−6.70 (m, 1H), 4.82−4.23 (ABq, 2H, J = 11.24 Hz), 4.67−4.34 (m, 4H), 4.02−3.97 (m, 1H), 3.66−3.62 (m, 1H), 3.08−3.01 (dd, 1H, J = 14.42, 1.95 Hz), 2.39−2.31 (m, 1H), 2.14−2.0 (m, 2H), 1.88−1.79 (m, 2H), 1.68−0.96 (m, 14H), 1.19 (s, 3H), 1.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 194.9, 153.4, 143.6, 139.4, 139.1, 137.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.3, 127.2, 126.9, 75.5, 73.2, 73.1, 72.5, 70.15, 69.6, 59.3, 57.9, 46.4, 40.7, 36.3, 36.1, 32.7, 32.6, 32.3, 32.2, 30.6, 27.9, 25.3, 17.6, 14.6. HRMS (ESI) m/z: $[M + H]^+$calcd for $C_{42}H_{51}O_4$ 619.3782; found 619.3779.

(3α,5α,11β,16β)-3,11,21-Tris(benzyloxy)-17-bromo-16-hydroxypregnan-20-one (31). To a stirred solution of enone **30** (303 mg, 0.48 mmol) in acetone (8 mL), THF (2 mL), and H_2O (4 mL) was added NBA (*N*-bromoacetamide) (202 mg, 1.46 mmol) at room temperature. The mixture was stirred for 5 h at room temperature. The mixture was diluted with EtOAc (20 mL). The organic layer was washed with saturated Na_2SO_3 solution and brine solution, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (10% EtOAc/hexanes) to get the desired hydroxy bromide **31** (140 mg, 40%) as a viscous liquid. R_f = 0.5 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41−7.20 (m, 15 H), 5.05−4.99 (m, 1H), 4.74−4.22 (ABq, 2H, J = 11.71 Hz), 4.67−4.21 (m, 5H), 3.99 (m, 1H), 3.62 (m, 1H), 2.49−2.32 (m, 2H), 2.05−0.83 (m, 18H), 1.38 (s, 3H), 0.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.8, 139.3, 138.7, 136.5, 128.6, 128.2, 128.13, 128.11, 127.6, 127.3, 127.2, 127.1, 85.3, 81.4, 75.0, 73.6, 73.1, 73.0, 70.3, 69.6, 57.6, 50.4, 46.5, 40.3, 37.4, 36.0, 34.3, 32.5, 32.59, 32.50, 31.5, 27.5, 25.3, 16.2, 14.5. HRMS (ESI) m/z: $[M + NH_4]^+$calcd for $C_{42}H_{55Br}NO_5$ 733.3292; found 733.3289.

(3α,5α,11β,16β)-3,11,21-Tris(benzyloxy)-16-hydroxypregnan-20-one (32). To a stirred solution of hydroxy bromide **31** (140 mg, 0.19 mmol) in anhydrous CH_2Cl_2 (5 mL) was added Bu_3SnH (0.51 mL, 1.9 mmol) followed by Et_3B (1 M in hexane, 0.31 mL, 0.31 mmol) and air (with empty syringe, 3 mL) under inert atmosphere. The mixture was allowed to stir for 45 min at room temperature, then directly concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (20% EtOAc/hexanes) to afford the desired hydroxy ketone **32** (113 mg, 91%) as a white solid. R_f = 0.4 (SiO_2, 30% EtOAc/hexanes); $[\alpha]_D^{20}$ +38.0 (c 0.3, CH_2Cl_2); ^{1}H NMR (C_6D_6 + CCl_4 (1:9), 400 MHz) δ 7.13−6.95 (m, 15 H), 4.40−3.91 (ABq, 2H, J = 11.32 Hz), 4.34−3.63 (m, 8H), 3.35 (br s, 1H), 3.27 (d, 1H, J = 3.51 Hz), 2.19−2.10 (m, 2H), 2.06−1.96 (m, 1H), 1.80−0.58 (m, 16H), 0.99 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (C_6D_6 + CCl_4 (1:9), 100 MHz) δ 209.1, 139.1, 138.3, 136.9, 128.1, 127.8, 127.7, 127.45, 127.41, 127.2, 126.9, 126.8, 75.7, 74.6, 72.7, 71.6, 70.1, 69.3, 63.0, 58.3, 55.3, 43.4, 40.1, 39.4, 37.0, 35.9, 32.43, 32.41, 32.3, 31.0, 27.69, 26.65, 16.82, 14.50. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{42}H_{53}O_5$ 637.3888; found 637.3903.

(3α,5α,11β,17ξ,22*S*,24*S*)-24-Methyl-22,25-epoxyfurostan-3,11,20,21-tetrol (5). To the alkyne **23** (104 mg, 0.53 mmol) in anhydrous THF (2.5 mL) under argon was added *n*-butyllithium solution (1.6 M solution in hexane, 0.27 mL, 0.44 mmol) at −78 °C. The resultant mixture was stirred at −78 °C for 1.5 h, followed by the addition of hydroxy ketone **32** (113 mg, 0.17 mmol) in anhydrous THF (2 mL). The resulting mixture was stirred at −78 °C for 6 h. Then the reaction was quenched with saturated aqueous NH_4Cl solution at −78 °C. The mixture was warmed to 0 °C, diluted with water, extracted with EtOAc (3 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (gradient elution with 5−15% EtOAc/hexane) to afford the desired coupled product **33** (121 mg, 82%) as an inseparable mixture of diastereomers (R_f = 0.6 (SiO_2, 30% EtOAc/hexanes)). This was used in the next reaction without further analysis. To a stirred mixture of dihydroxyalkyne **33** (121 mg, 0.14 mmol) and H_2O (0.013 g, 0.72 mmol) in CH_3CN (2.0 mL) was added $Hg(OTf)_2$ (14 mg, 0.029 mmol) at room temperature, and the mixture was stirred for 10 min at the same temperature. Reaction was quenched by the addition of Et_3N (90 μL). The resulting mixture was diluted with Et_2O (5 mL), extracted with Et_2O, and the combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product **34** (87 mg, 80%) was used as such for the next step. A flame-dried two-neck round-bottom flask was topped with a dry ice condenser, and the system was flushed with argon. The condenser was filled with a dry ice/acetone mixture. Ammonia was condensed, and the lithium metal (13.9 mg, 2.32 mmol, washed with hexanes) was added cautiously through the side neck of the round-bottom flask. The contents were stirred at −33 °C until no further lithium was seen. When bronze globules (golden liquid) started to appear, the system was allowed to equilibrate to the refluxing temperature −33 °C. THF (1.0 mL) was added to disperse the newly formed reagent, and then to the mixture was added slowly a THF solution of **34** (87 mg, 0.11 mmol). A cautious addition is needed to ensure a regular and smooth ammonia reflux. The reaction mixture was then stirred at −33 °C for 2 h, and to the mixture was carefully and slowly added NH_4Cl powder at −33 °C to quench the excess of lithium. Ammonia was allowed to evaporate under a stream of air. To the residue was added H_2O (10 mL), and extraction was with EtOAc (3 × 10 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by silica gel column chromatography (15% acetone/hexanes) afforded C-21-hydroxy-22-*epi*-hippuristanol (**5**) (47.8 mg, 86%) as a white solid. R_f = 0.5 (SiO_2, 30% acetone/hexanes); $[\alpha]_D^{20}$ −23.5 (c 1.0, acetone); ^{1}H NMR (C_6D_6 + CCl_4 (1:9), 400 MHz) δ 4.19−411 (m, 1H), 4.03 (br s, 1H), 3.75 (br s, 1H), 3.41 (d, 1H, J = 11.71 Hz), 3.19 (d, 1H, J = 11.32 Hz), 2.61−2.55 (br s, 1H), 2.24 (s, 1H), 2.14−2.04 (m, 1H), 1.93−0.60 (m, 29H), 1.83 (s, 3H), 1.09 (s, 3H), 0.98 (s, 3H); ^{13}C NMR ($C_6D_{6+}CCl_4$ (1:9), 100 MHz) δ 117.5, 83.1, 83.0, 79.5, 68.1, 67.3, 67.1, 63.4, 58.4, 58.1, 48.4, 41.6, 40.2, 39.6, 38.6, 36.1, 35.4, 32.3, 31.4, 30.4, 29.3, 28.5, 27.8, 23.4, 18.0, 14.0, 13.8. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{47}O_6$ 479.3367; found 479.3383. LRMS for $C_{28}H_{47}O_6$ $[M + H]$ 479.45. HPLC purity of 88.0 (retention time = 15.1).

(2*S*,2′*R*,4*S*,4a′*S*,4b′*S*,5′*S*,6a′*S*,9a′*S*,10a′*S*,10b′*S*,12a′*S*)-2′,5′-Dihydroxy-4,4a′,5,5,6a′-pentamethyloctadecahydro-3*H*-spiro[furan-2,8′-naphtho[2′,1′:4,5]indeno[2,1-*b*]furan]-7′(1′*H*)-one (8). To a vigorously stirred suspension of silica gel supported $NaIO_4$ reagent (0.198 g) in CH_2Cl_2 (5 mL) was added a solution of vicinal diol **5** (47.8 mg, 0.09 mmol) in anhydrous CH_2Cl_2 (10 mL). The reaction was monitored by TLC until disappearance of the diol. After completion of the reaction, the mixture was filtered through sintered glass funnel and silica gel and thoroughly washed with CH_2Cl_2 (3 × 15 mL). The filtrate was concentrated under reduced pressure and purified by silica gel column chromatography (10% acetone/hexanes) to afford the ketone **8** (37.9 mg, 85%) as a white solid. R_f = 0.7 (SiO_2, 30% acetone/hexanes). $[\alpha]_D^{20}$ −20.5 (c 1.0, acetone); ^{1}H NMR (C_6D_6 + CCl_4 (1:9), 400 MHz) δ 4.92−4.85 (m, 1H), 4.39−4.34 (m, 1H), 4.08−4.04 (m, 1H), 2.35 (d, 1H, J = 7.0 Hz), 2.31−0.80 (m, 24H), 1.31 (s, 3H), 1.03 (s, 3H), 1.02 (s, 3H), 0.98 (d, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 211.4, 109.0, 86.1, 79.5, 67.7, 66.3, 59.7, 58.0, 57.9, 47.8, 43.3, 41.7, 39.8, 38.9, 36.3, 35.2, 33.2, 32.3, 31.7, 31.0,

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28.6, 28.2, 27.7, 22.3, 17.4, 14.1, 13.9. HRMS (ESI) m/z: $[(M + H) + (-H_2O)]^+$ calcd for $C_{27}H_{41}O_4$ 429.2999; found 429.2997. LRMS for $C_{27}H_{41}O_4$ $[M + H - H_2O]$ = 429.40. HPLC purity of 99.4% (retention time = 16.2).

(2*S*,2′*R*,4*S*,4a′*S*,4b′*S*,5′*S*,6a′*S*,7′*R*,9a′*S*,10a′*S*,10b′*S*,12a′*S*)-4,4a′,5,5,6a′-Pentamethylicosahydro-3*H*-spiro[furan-2,8′-naphtho[2′,1′:4,5]indeno[2,1-*b*]furan]-2′,5′,7′-triol (7). To a stirred solution of ketone **8** (37.9 mg, 0.084) in anhydrous ethanol (4.0 mL) was added $NaBH_4$ (6.4 mg, 0.16 mmol) at 0 °C, and the reaction mixture was allowed to stir at ambient temperature for 1 h. The resulting solution was poured into ice cold water, and to it was added Et_2O. Then the sample was extracted with Et_2O (3 × 10 mL), dried over anhydrous Na_2SO_4, filtered using sintered funnel, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (20% acetone/hexanes) to give the desired 20-desmethyl-22-*epi*-hippuristanol (**7**) (34.2 mg, 90%) as a colorless solid. R_f = 0.5 (SiO_2, 30% acetone/hexanes); $[\alpha]_D^{20}$ −55.3 (*c* 0.25, $CHCl_3$); ^1H NMR ($CDCl_3$ + 2% CD_3OD, 400 MHz) δ 4.45−4.37 (m, 2H), 4.24−4.18 (br s, 1H), 3.97−3.91 (br s, 1H), 2.23−0.79 (m, 22H), 1.20 (s, 3H), 1.19 (s, 3H), 0.95 (s, 3H), 0.92 (s, 3H), 0.88 (d, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$ + 2% CD_3OD, 100 MHz) δ 113.0, 79.3, 76.4, 76.1, 63.8, 62.0, 55.8, 54.5, 54.1, 44.0, 37.5, 37.1, 35.8, 35.5, 32.1, 31.1, 28.8, 28.3, 27.6, 26.5, 24.5, 24.3, 23.8, 19.0, 14.0, 10.07, 10.0. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{27}H_{45}O_5$449.3262; found 449.3252. LRMS for $C_{27}H_{45}O_5$ $[M + H]^+$ = 449.40. HPLC purity of 96.5% (retention time = 13.4)

(2*R*,2′*R*,4*S*,4a′*S*,4b′*S*,5′*S*,6a′*S*,7′*R*,9a′*S*,10a′*S*,10b′*S*,12a′*S*)-4,4a′,5,5,6a′-Pentamethylicosahydro-3*H*-spiro[furan-2,8′-naphtho[2′,1′:4,5]indeno[2,1-*b*]furan]-2′,5′,7′-triol (6). 20-Desmethyl-22-*epi*-hippuristanol (**7**) (34.2 mg, 0.076 mmol) was dissolved in $CHCl_3$ (1.0 mL) in a single-neck round-bottom flask, and to this solution was added pyridine *p*-toluenesulfonate (PPTS, 2.8 mg, 0.01 mmol) at room temperature. After the mixture was stirred for 12 h at room temperature, the solvent was removed under reduced pressure. The crude residue (without further workup) was purified by silica gel column chromatography (18% acetone/hexanes) to afford the 20-desmethylhippuristanol (**6**) (15.3 mg, 85% brsm (based on recovered starting material of 40%)) as a white solid. R_f = 0.6 (SiO_2, 30% acetone/hexanes); $[\alpha]_D^{20}$ +43.5 (*c* 0.2, CH_2Cl_2); ^1H NMR (400 MHz, CD_2Cl_2) δ 4.29−4.20 (m, 2H), 4.15 (dd, 1H, J = 17.17, 8.19 Hz), 3.99−3.94 (br s, 1H), 2.51 (d, 1H, J = 8.1 Hz), 2.16 (d, 1H, J = 5.46 Hz), 2.13−0.73 (m, 20H), 1.25 (s, 3H), 1.22 (s, 3H), 1.14 (s, 3H), 1.0 (s, 3H), 0.92 (d, 3H, J = 6.63 Hz); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 112.7, 84.6, 80.0, 78.5, 67.9, 66.1, 58.8, 58.1, 57.8, 49.0, 46.4, 42.0, 41.6, 39.8, 36.2, 35.3, 33.8, 32.4, 31.6, 30.2, 28.6, 27.9, 27.4, 22.2, 18.6, 13.8, 13.7. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{27}H_{45}O_5$ 449.3262; found 449.3252. LRMS for $C_{27}H_{45}O_5$ $[M + H]^+$ = 449.40. HPLC purity of 92.5% (retention time = 15.8).

(3*β*,5*α*,11*β*,17*ξ*,22*R*,24*S*)-24-Methyl-22,25-epoxyfurostan-3,11,20-triol (9). Hippuristanol (**1**) (100 mg, 0.2 mmol) was dissolved in pyridine (5.0 mL). PDC (325 mg, 0.86 mmol) was added at 0 °C under argon atmosphere. The reaction mixture was warmed to room temperature and stirred for 4 h at room temperature. After completion of the reaction, contents were poured into water, then extracted with ether, and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (20% acetone/hexanes) to afford a mixture of C3-mono ketone and 3,11-diketone, which was used as such in the next reaction. To a stirred solution of above mixture of ketones (63.0 mg, 0.13 mmol) in MeOH (2 mL) was added $NaBH_4$ (51.9 mg, 1.3 mmol) at 0 °C. After 10 min the reaction mixture was warmed to reflux temperature for 4 h and then cooled to 0 °C. Brine solution was added to the reaction mixture and warmed to room temperature and extracted with EtOAc (3 × 10 mL), dried over anhydrous Na_2SO_4, filtered using sintered funnel, and concentrated under reduced pressure. The crude residue was purified by a short pad of silica gel and further treated with $LiAlH_4$ solution (1.18 M in THF, 0.93 mL, 1.09 mmol) at 0 °C in THF under argon atmosphere. The mixture was stirred for 30 min at 0 °C and slowly allowed to reflux for 4 h. The reaction mixture was cooled to 0 °C and quenched with a minimum amount of cold water (5 mL) cautiously. The reaction mixture was diluted with EtOAc (5 mL) and stirred for 2.5 h at room temperature and then filtered using Celite-cintered funnel. The filtrate was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (30% acetone/hexanes) afforded 3-*β*,11-*β* diol **9** (38.0 mg, 75% yield) as a colorless solid. R_f = 0.4 (SiO_2, 30% Acetone/Hexanes). $[\alpha]_D^{20}$ +38.5 (*c* 1.0, acetone). ^1H NMR (C_6D_6 +CCl_4 (1:9), 400 MHz) δ 4.01−3.91 (m, 2H), 3.25−3.13 (m, 1H), 2.71−2.68 (br s, 1H), 2.15−2.07 (m, 1H), 1.93 (dd, 1H, J = 14.0, 2.3 Hz), 1.79−0.29 (m, 20H), 1.16 (s, 3H), 1.06 (s, 3H), 1.02 (s, 3H), 1.01 (s, 3H), 0.83 (s, 3H), 0.80 (d, 3H, J = 7.02 Hz); ^{13}C NMR (C_6D_6 + CCl4, 100 MHz) δ 115.0, 83.8, 79.9, 78.8, 70.4, 67.8, 66.0, 58.3, 57.0, 50.0, 45.79, 42.0, 41.5, 40.6, 36.3, 35.6, 34.0, 32.6, 31.4, 31.2, 30.1, 29.0, 28.5, 28.0, 23.0, 18.3, 14.9, 14.0; IR (NaCl) cm^{-1} 3615.5, 3494, 3011, 2929, 1455, 1235, 1083. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{47}O_5$ 463.3418; found 463.3433. LRMS for $C_{28}H_{47}O_5$ $[M + H]^+$ = 463.45. HPLC purity of 98.8% (retention time = 15.6).

2-[(3*α*,5*α*,11*β*,17*ξ*,22*R*,24*S*)-11,20-Dihydroxy-24-methyl-22,25-epoxyfurostan-3-yl]-1*H*-isoindole-1,3(2*H*)-dione (35). To a stirred solution of 3*β*,11*β*-hydroxyhippuristanol (**9**) (38.0 mg, 0.08 mmol) in dry THF (5 mL) was added TPP (22.4 mg, 0.08 mmol) and phthalimide (12.0 mg, 0.08 mmol) at 20 °C under nitrogen atmosphere. The resulting suspension was cooled to 5 °C and stirred for 10 min, and then DIAD (0.017 mL, 0.09 mmol) in THF (0.1 mL) was added slowly to the reaction mixture, which was slowly allowed to room temperature and was stirred for 48 h at room temperature. Methanol was added to the reaction mixture, and the resulting slurry was stirred for 1 h. The solid was filtered off and solid was washed with dichloromethane and combined filtrates were evaporated to give the phthalimide **35** (48.6 mg, 65% yield). R_f = 0.6 (SiO_2, 30% acetone/hexanes). ^1H NMR (C_6D_6 + CCl_4, 400 MHz) δ 7.53−7.48 (m, 2H), 7.29−7.26 (m, 2H), 4.31−4.24 (br s, 1H), 4.08−3.97 (m, 2H), 2.69−2.66 (br s, 1H), 2.15−2.07 (m, 1H), 1.92 (dd, 1H, J = 14..0, 2.3 Hz), 1.79−0.47 (m, 19H), 1.18 (s, 3H), 1.07 (s, 3H), 1.02 (s, 3H), 1.01 (s, 3H), 0.89 (s, 3H), 0.80 (d, 3H, J = 7.02 Hz); ^{13}C NMR (C_6D_6 + CCl_4 (1:9), 100 MHz) δ 167.9, 132.8, 132.2, 122.4, 115.0, 83.8, 80.0, 78.9, 67.5, 65.9, 58.1, 56.8, 50.0, 47.1, 42.0, 41.5, 41.1, 40.6, 38.7, 35.3, 33.9, 33.6, 32.3, 32.0, 30.0, 28.5, 27.9, 23.0, 21.4, 18.3, 14.9, 14.4.

(3*α*,5*α*,11*β*,17*ξ*,22*R*,24*S*)-3-Amino-24-methyl-22,25-epoxyfurostan-11,20-diol (10). To a stirred solution of phthalimide **35** (48.6 mg, 0.08 mmol) in dry EtOH (2 mL) was added hydrazine monohydrate (0.48 mL, 9.9 mmol) at room temperature under nitrogen atmosphere. The resulting suspension was heated to reflux for 24 h. The mixture was allowed to cool to 0 °C, and the solid was filtered off. The solid was washed with dichloromethane and combined filtrates were dried with anhydrous Na_2SO_4 and evaporated to give the crude residue. The crude residue was purified by Al_2O_3 (neutral) column chromatography (15% MeOH−CH_2Cl_2) to afford the desired amine **10** (30 mg, 80% yield). R_f = 0.3 (SiO_2, 20% MeOH/CH_2Cl_2) as a white solid. $[\alpha]_D^{20}$ +28.5 (*c* 0.25, CH_2Cl_2); ^1H NMR (CD_2Cl_2, 500 MHz) δ 4.32−4.24 (m, 2H), 3.36−3.28 (br s, 1H), 3.16−3.07 (br s, 1H), 2.41−2.34 (m, 2H), 2.18−2.10 (m, 1H), 2.06−0.82 (m, 18H), 1.36 (s, 3H), 1.30 (s, 3H), 1.23 (s, 3H), 1.20 (s, 3H), 1.04 (s, 3H), 0.99 (d, 3H, J = 7.1 Hz); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 115.3, 84.3, 79.9, 79.1, 68.0, 66.1, 57.8, 57.0, 49.74, 46.4, 42.1, 41.9, 40.8, 39.5, 36.4, 33.9, 33.7, 32.5, 31.2, 30.2, 28.9, 28.1, 28.0, 22.7, 21.6, 18.4, 14.4, 14.0; IR (NaCl) cm^{-1} 2920.35, 1455, 1260, 1018.1, 799.57. HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{28}H_{48}NO_4$ 462.3578; found 462.3591. LRMS for $C_{28}H_{48}NO_4$ $[M + H]^+$ = 462.45. HPLC purity of 96% (retention time = 4.8).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C spectra for all new 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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ABBREVIATIONS USED

RNA, ribonucleic acid; eIF, eukaryotic initiation factor; mRNA, messenger ribonucleic acid; DEAD, aspartic acid−glutamic acid−alanine−aspartic acid; G, glycine; N, asparagine; SAR, structure−activity relationship; THF, tetrahydrofuran; DIAD, diisopropyl azodicarboxylate; TPP, triphenylphosphine; TBAI, tetrabutylammonium iodide; PTSA, *p*-toluenesulfonic acid; NBA, *N*-bromoacetamide; PPTS, pyridinium *p*-toluenesulfonate; R_f, retention factor (in chromatography); TLC, thin-layer chromatography; NMR, nuclear magnetic resonance; PDC, pyridinium dichromate; FF, firefly; Ren, renilla; DMSO, dimethyl sulfoxide; HPLC, high-performance liquid chromatography; high-pressure liquid chromatography

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