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Synthesis of the Antiproliferative Agent Hippuristanol and Its Analogues via Suárez Cyclizations and Hg(II)-Catalyzed Spiroketalizations

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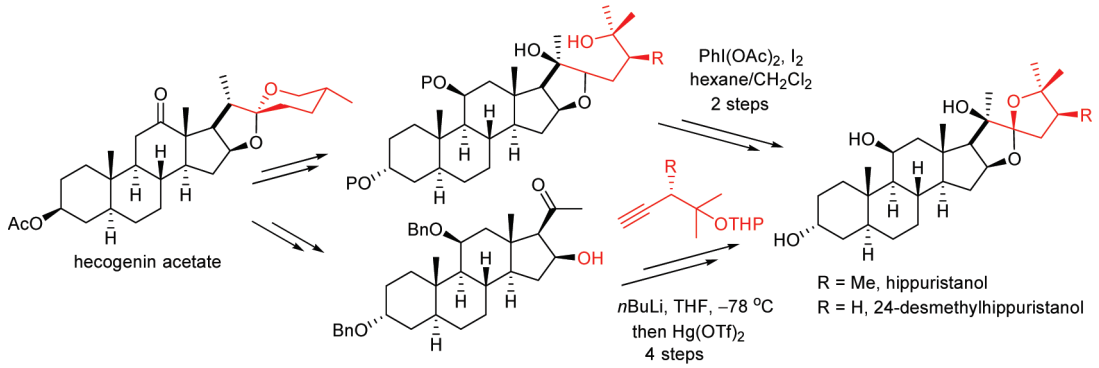

A full account of the synthesis of hippuristanol and its analogues is described. Hecogenin acetate was identified as a suitable and economical starting material for this work, and substrate-controlled stereoselection was obtained throughout the construction of the key spiroketal unit. Suárez cyclization was first used, but Hg(II)-catalyzed spiroketalization of the 3-alkyne-1,7-diol motif was finally identified as the most convenient strategy.

Introduction

Hippuristanol (**1**), a steroid isolated from coral *Isis hippuris*, has been identified as a selective and potent inhibitor of eukaryotic initiation factor(eIF)4A RNA-binding activity that can be used to distinguish between eIF4A-dependent and eIF4A-independent modes of translation initiation in vitro and in vivo.[1] It was also shown that poliovirus replication was delayed when infected cells were exposed to hippuristanol.[2] Recently, there has been much interest in targetting protein translation initiation as an anticancer therapy.[2d] Indeed, the use of other eIF4A activity modulators, such as silvestrol, has shown striking activity in preclinical mouse lymphoma models.[2e] Clearly, inhibiting eIF4A with hippuristanol may provide similar activity, and thus, there is a large unmet need to develop an easy access to hippuristanol and its analogues. While our efforts were under progress, Yu and co-workers reported a synthesis of hippuristanol and a few closely related analogues in order to study the effect of stereochemistry and substitution pattern on spiroketal appendage in relation to the biological activity.[3] We, most recently, disclosed our synthetic route to hippuristanol via an unprecedented $Hg(OTf)_2$-catalyzed cascade spiroketalization.[4] Herein, we give a full account of the synthetic efforts on hippuristanol and some

(1) (a) Bordeleau, M. E.; Mori, A.; Oberer, M.; Lindqvist, L.; Chard, L. S.; Higa, T.; Wagner, G. J.; Belsham, G.; Tanaka, J.; Pelletier, J. *Nat. Chem. Biol.* **2006**, *2*, 213–220. (b) Lindqvist, L.; Oberer, M.; Reibarkh, M.; Cencic, R.; Bordeleau, M. E.; Voqt, E.; Marintchev, A.; Tanaka, J.; Fagotto, F.; Altmann, M.; Wagner, G.; Pelletier, J. *PLoS One* **2008**, *3*, e1583. (c) Lindqvist, L.; Oberer, M.; Reibarkh, M.; Cencic, R.; Bordeleau, M.-E.; et al. *PLoS One* **2008**, *3*, e1583.

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(4) Ravindar, K.; Reddy, M. S.; Lindqvist, L.; Pelletier, J.; Deslongchamps, P. *Org. Lett.* **2010**, *12*, 4420–4423.

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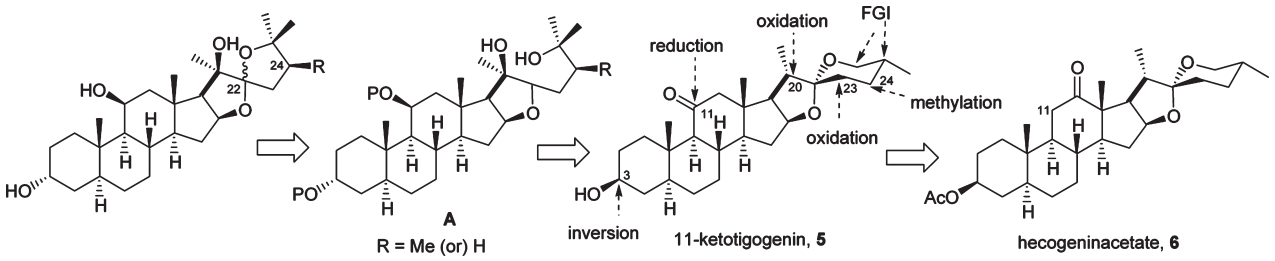
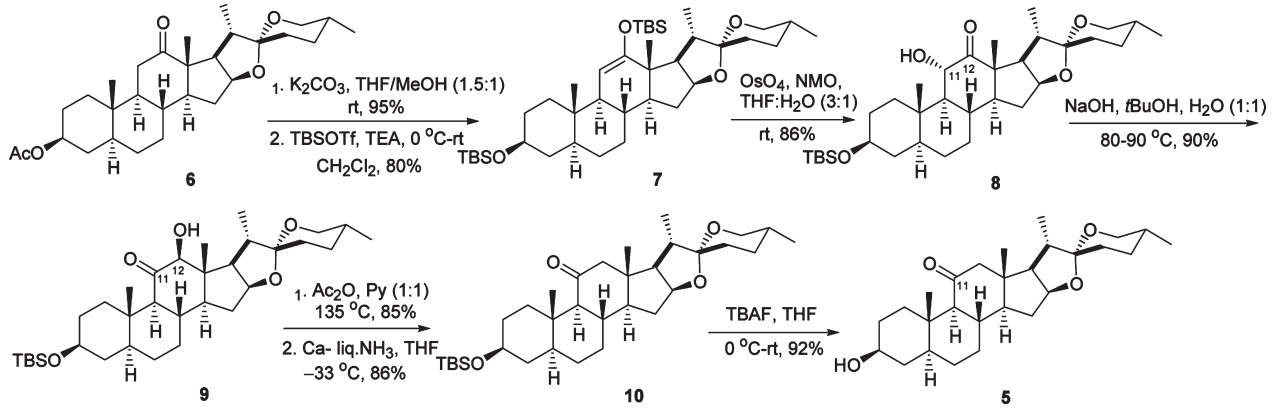
SCHEME 1. Retrosynthetic Analysis of Hippuristanol and Analogues via Suárez Cyclization



1 (22 *R*, R = Me, hippuristanol)
2 (22 *S*, R = Me, 22-*epi*-ihippuristanol)
3 (22 *R*, R = H, 24-desmethylhippuristanol)
4 (22 *S*, R = H, 24-desmethyl-22-*epi*-hippuristanol)

SCHEME 2. Synthesis of 11-Ketotigogenin 5 from Hecogenin Acetate 6



analogues via the Suárez cyclization and the $Hg(OTf)_2$-catalyzed cascade spiroketalization.

Results and Discussion

In the initial retrosynthetic analysis, as described in Scheme 1, we envisioned the synthesis of hippuristanol and its analogues (**2**, **3**, and **4**) from the suitable intermediate **A** via Suárez cyclization.[5] 11-Ketotigogenin **5**[6] was considered the best choice of material to derive intermediate **A** as it contains the favorable steric rigidity as well as suitable groups. Though 11-ketotigogenin is commercially available, it could be easily obtained from the cost-effective and commercially available plant-derived steroid material hecogenin acetate **6**.[6]

Thus, our synthetic efforts were begun from hecogenin acetate, as shown in Scheme 2. Though there is literature precedent for the bulk synthesis of 11-ketotigogenin **5** from hecogenin acetate **6**,[6] we adopted a slightly modified and practical approach to overcome the difficulty associated with selective bromination of the later at the C11 position. Thus, hecogenin acetate **6** was hydrolyzed using K_2CO_3 in THF–MeOH to get hecogenin, which, on exposure to TBSOTf and TEA in CH_2Cl_2, afforded TBS enol ether **7**. OsO_4-catalyzed dihydroxylation of **7** produced the 11-α-hydroxy-12-one **8**, which was rearranged to 12-*β*-hydroxy-11-one **9** using NaOH in *t*BuOH/H_2O (1:1). Acylation of **9** with Ac_2O in pyridine and reductive cleavage of the resulting α-ketoacetate using calcium in liquid NH_3 cleanly afforded 3-OTBS-11-ketotigogenin **10**. TBS deprotection of **10** afforded the 11-ketotigogenin **5**, which was obtained in 40% overall yield from **6** through seven steps.

The reaction of **5** under Mitsunobu conditions[7] (BzOH, DIAD, TPP) gave the corresponding inverted benzoate, which, on exposure to $LiAlH_4$ in THF, underwent reductive deprotection of the C3-benzoyl group and exclusive stereoselective reduction of the C11-keto group to produce diol **11** having the desired stereochemistry (see Scheme 3).

Having converted the A and C rings suitable for hippuristanol **1** and its analogues, the stage was set for working on the E and F rings. Initially, we wanted to evaluate the Suárez cyclization before introducing a methyl group at C24 and a hydroxyl group at C20. Also, we were interested to study the effect of these two groups on the biological activity by synthesizing 20-deshydroxy-24-desmethylhippuristanol and its 22-epimer. Accordingly, protection of **11** as its dibenzoate **12**, followed by reductive opening of the cyclic spiroketal of **12** using $NaCNBH_3$ in AcOH[8], cleanly yielded the alcohol

(5) (a) Betancor, C.; Freire, R.; Perez-Martin, I.; Prange, T.; Suarez, E. *Tetrahedron* **2005**, *61*, 2803–2814. (b) Phillips, S. T.; Shair, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 6589–6598.

(6) (a) McCarthy, P. A.; DeNinno, M. P.; Morehouse, L. A.; Chandler, C. E.; Bangerter, F. W.; Wilson, T. C.; Urban, F. J.; Walinsky, S. W.; Cosgrove, P. G.; Duplantier, K.; Etienne, J. B.; Fowler, M. A.; Lambert, J. F.; O'Donnell, J. P.; Pezzullo, S. L.; Watson, H. A.; Wilkins, R. W.; Zaccaro, L. M.; Zawistoski, M. P. *J. Med. Chem.* **1996**, *39*, 1935–1937. (b) DeNinno, M. P.; McCarthy, P. A.; Duplantier, K. C.; Eller, C.; Etienne, J. B.; Zawistoski, M. P.; Bangerter, F. W.; Chandler, C. E.; Morehouse, L. A.; Sugarman, E. D.; Wilkins, R. W.; Woody, H. A.; Zaccaro, L. M. *J. Med. Chem.* **1997**, *40*, 2547–2554. (c) Zhou, L. B.; Chen, T. H.; Bastow, K. F.; Shibano, M.; Lee, K. H.; Chen, D. F. *J. Nat. Prod.* **2007**, *70*, 1263–1267.

(7) (a) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380–2382. (b) Mitsunobu, O. *Synthesis* **1981**, 1–28. (c) Hughes, D. L. *Org. React.* **1992**, *42*, 335–656.

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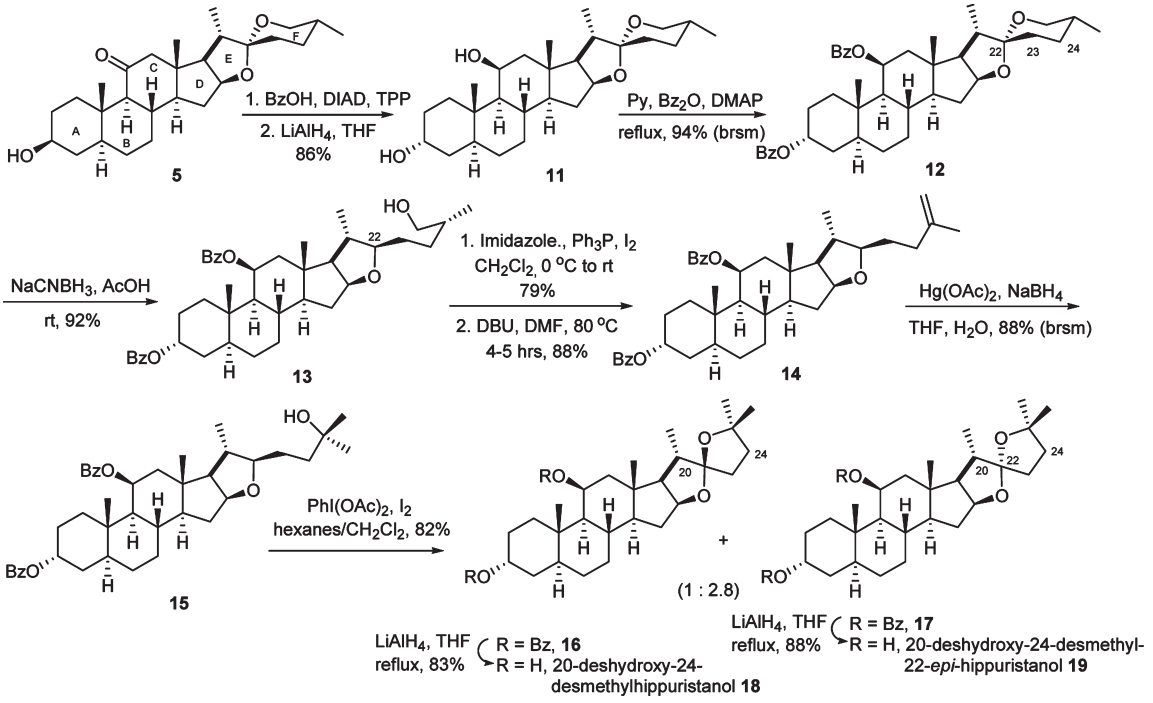
SCHEME 3. Synthesis of 20-Deshydroxy-24-desmethylhippuristanol 18 and Its 22-Epimer 19



13. Conversion of the hydroxyl group in **13** using TPP, I_2, and imidazole, followed by DBU-mediated elimination of the resulting iodide, produced olefin **14** in 70% yield in two steps. Introduction of the tertiary hydroxyl group at C25 to obtain **15** was easily achieved by oxymercuration and demercuration[5b] using $Hg(OAc)_2$ and $NaBH_4$ in aqueous THF. In the standard Suárez cyclization conditions ($PhI(OAc)_2$, I_2, hexanes/CH_2Cl_2),[5] alcohol **15** neatly underwent cyclic ketalization to afford ketals **16** and **17** in a 1:2.8 ratio in 82% yield. Benzoyl groups in **16** and **17** were removed through reduction using $LiAlH_4$ to afford 20-deshydroxy-24-desmethylhippuristanol **18** and its 22-epimer **19** in 83% and 88% yields, respectively. The stereochemistry was assigned on the basis of the analogy of the data (R_f values, ^{13}C spectra, and sensitivity to acidic and basic mediums) from previous similar work (vide infra). Compounds **18** and **19** were found to be biologically inactive by comparison with hippuristanol (**1**), indicating the importance of the role of hydroxyl and methyl groups at C20 and C24, respectively.

We next turned our attention to introduce the C20-hydroxyl group to obtain 24-desmethylhippuristanol and its 22-epimer. Protection of **11** as its dibenzylether **20** was carried out in standard conditions, and regioselective opening of the spiroketal in **20**, as a part of Marker's degradation,[9] was achieved using Py·HCl in refluxing Ac_2O to obtain enol ether **21** (see Scheme 4). A clean and stereospecific epoxidation of **21** using dimethyldioxirane[10] afforded epoxide **22**. The same transformation using *m*CPBA proved unfruitful, leading to complete degradation of the E ring.[11] Regioselective reductive opening of epoxide **22** using $NaCNBH_3$ in AcOH[8] produced alcohol **23** as a mixture of C22-epimers. Though separable, we took forward the mixture as such as this epimeric center will be eventually destroyed. Thus, kinetic dehydration of **23** using $SOCl_2$ in pyridine gave exoolefin **24**. Oxidative cleavage of the exoolefinic group in **24** using OsO_4, followed by $NaIO_4$, and treatment of the resulting ketone **25** with MeMgBr resulted in both the hydrolysis of the acetate group as well as the exclusive substrate-controlled addition of the methyl group to the ketone group to furnish inverted alcohol **26**. The primary hydroxyl group of **26** was eliminated via iodination to get olefin **27,** which, on oxymercuration and demercuration,[5b] produced ditertiary alcohol **28**. Exposure of **28** to standard Suárez cyclization conditions[5] cleanly furnished the diastereomeric spiroketal mixture (4.5:5.5, *R*/*S*), which, on separation and subjection to debenzylation, furnished 24-desmethylhippuristanol **3** and its 22-epimer **4**. In our hands, these isomers of hippuristanol were devoid of biological activity; Yu and co-workers reported also that these isomers were much less biologically active compared with the natural product.[3]

We then tried to introduce the missing methyl group at C24 from intermediate **20** (via oxidation of C23), followed by the same reaction sequence described in Scheme 5. Oxidation of C23 of the hecogenin congeners is well-documented.[12] We followed the same conditions ($BF_3 \cdot OEt_2$, $NaNO_2$, AcOH) for the oxidation of **20** to **29**, but the yield of the product was unsatisfactory due to side reactions through the deprotection of benzyl groups. The same oxidation of **12** (obtained from benzoylation of **11**) cleanly yielded 23-ketone **29a**. After several failures with LDA and KHMDS, LiHMDS was found suitable for methylation of ketone **29a** to get **30** as a

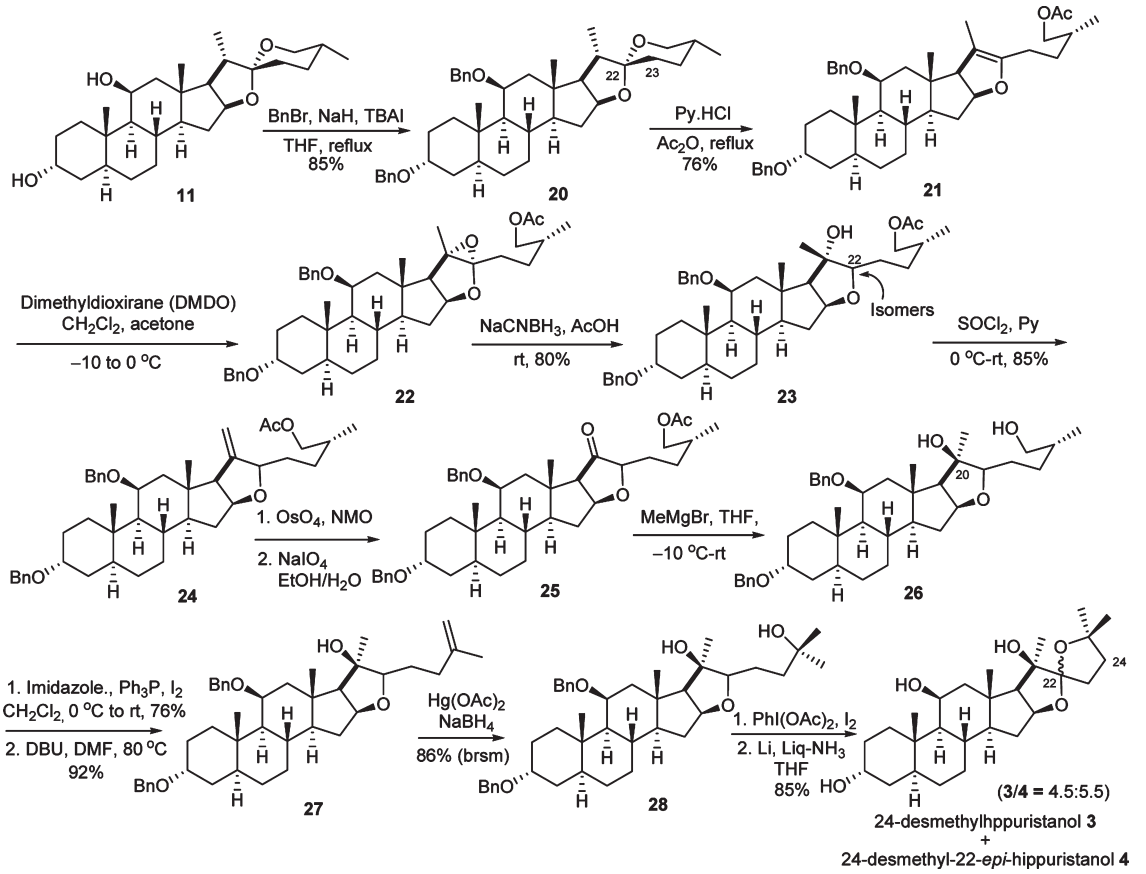
(9) (a) Dauben, W. G.; Fonken, G. J. *J. Am. Chem. Soc.* **1954**, *76*, 4618–4619. (b) Kemp, S. J. Ph.D. Thesis, University of California, Berkeley, CA, 1995. (c) Yamamoto, K.; Heathcock, C. H. *Org. Lett.* **2000**, *2*, 1709–1712. (d) Kongkathip, N.; Kongkathip, B.; Noimai, N. *Synth. Commun.* **2006**, 865–874.

(10) Moilanen, S. B.; Potuzak, J. S.; Tan, D. S. *J. Am. Chem. Soc.* **2006**, *128*, 1792–1793.

(11) Jastrzebska, I.; Katrynski, K. S.; Morzycki, J. W. *ARKIVOC* **2002**, *iX*, 46–54.

(12) Iglesias-Arteaga, M. A.; Gil, R. P.; Martinez, C. S. P.; Manchado, F. C. *J. Chem. Soc., Perkin Trans. 1* **2001**, 261–266.

SCHEME 4. Synthesis of 24-Desmethylhippuristanol 3 and Its 22-Epimer 4



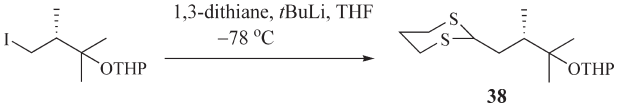
1:2 diastereomeric mixture in favor of the equatorial isomer. The **24-*S*** isomer was converted to the **24-*R*** isomer using NaOMe in refluxing MeOH, and the hydrolysis of the C3-benzoate group took place concurrently with the isomerization and provided **S6**. Surprisingly, the anticipated reductive decarbonylation of **30** and **S6** were unsuccessful through Wolff–Kishner and modified Wolff–Kishner (Huang–Minlon) conditions.[13] We obtained only the corresponding reduced product triol, which was characterized by the derivitization to its triacetate **31**. We then subjected **29** to Wolff–Kishner reaction conditions to get, to our surprise, the decarbonylated product **20** cleanly. When we tried the same reduction on **29a**, the reduction was also observed with concomitant hydrolysis of the benzoate groups to give back **11**. A literature example supports the formation of reduction product **31** from **30** under alcoholic KOH conditions.[14] If the reduction of **30** to **32** worked well, our next sequence of reactions, as described from **20** to **3** or **4** as in Scheme 4, would have led to hippuristanol (**1**) through intermediate **33**.

Because of failure of direct deoxygenation of **30** together with the low yield of oxidation of **20** to **29** and unwanted deprotections during the isomerization of **30**, we were forced to seek a new approach to produce the spiroketal and not consider alternative methods for deoxygenation of **30** through reduction and elimination reactions. Therefore, we considered the new retrosynthetic analysis (depicted in Scheme 6) with the degradation and elimination of the E ring completely, and reconstruct with all prerequisites. Accordingly, we envisioned the construction of the E and F rings of hippuristanol via spiroketalization of suitably constructed intermediates **34** or **35**. Regioselective spiroketalization of **34** with the assistance of C16-OH was anticipated with the support of some relevant literature. Intermediates **34** and **35** were convergently expected from hydroxy ketone **37** through the Cram's addition of organometallates of **36** and **38**, respectively. Intermediate **37** would be easily obtained from **21** via Marker's degradation.[9]

Thus, a new synthetic route began by the oxidative degradation of **21** to **39** using CrO_3 in AcOH (see Scheme 7).[9] However, addition of lithiated **38**[15] to the ketodiester **39** did not result in the expected addition product, but only the conjugated ketone **40** through the elimination of the side-chain ester. Much of the literature also shows that the congeners of **39** are very sensitive to both acidic and basic conditions, resulting in the conjugated ketones like **40**. We then decided to hydrolyze the ester side chain prior to addition of the required moiety to the ketone group. The direct hydrolysis of **39** proved to be insurmountable, in both acidic and basic conditions, leading to either the corresponding conjugated

(13) (a) Huang-Minlon *J. Am. Chem. Soc.* **1949**, *71*, 3301–3303. (b) Callow, R. K.; Massy-Beresford, P. N. *J. Chem. Soc.* **1957**, 4482–4488.
(14) Fisher, H.; Zeile, K.; Liebigs *J. Ann. Chem.* **1929**, *468*, 98.

(15) Tsuji, M.; Yokoyama, S.; Tachibana, Y.; Ikekawa, N. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2233–2238.



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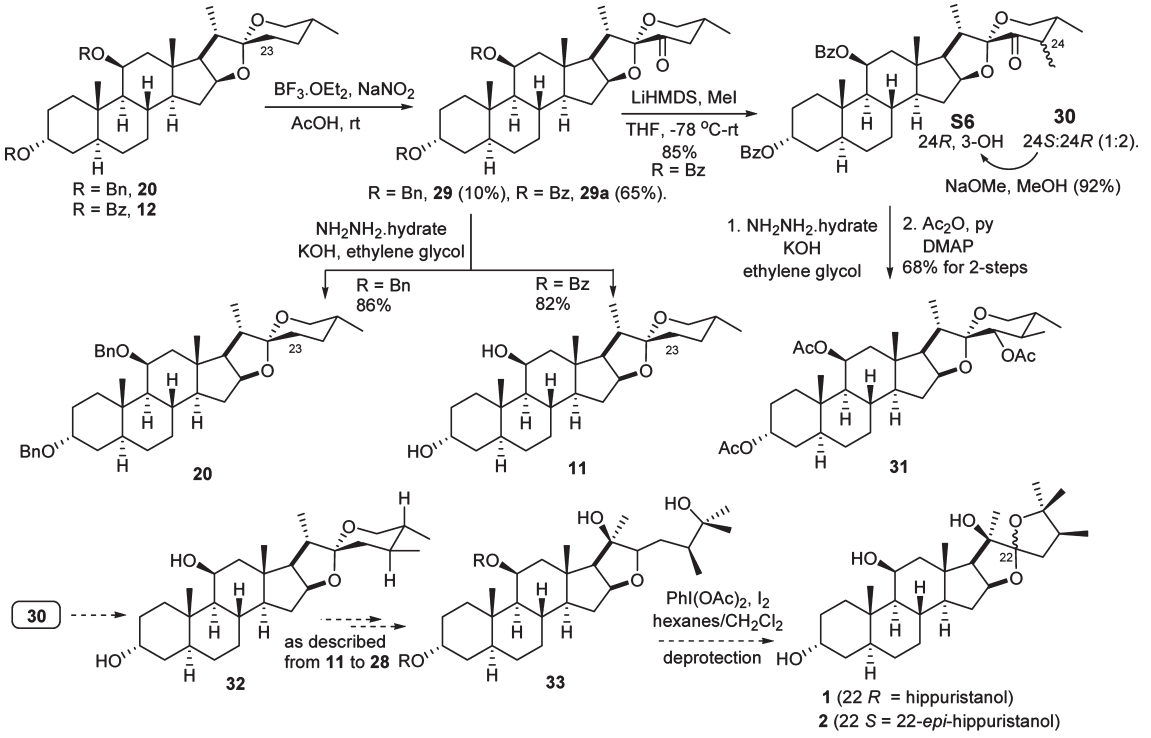
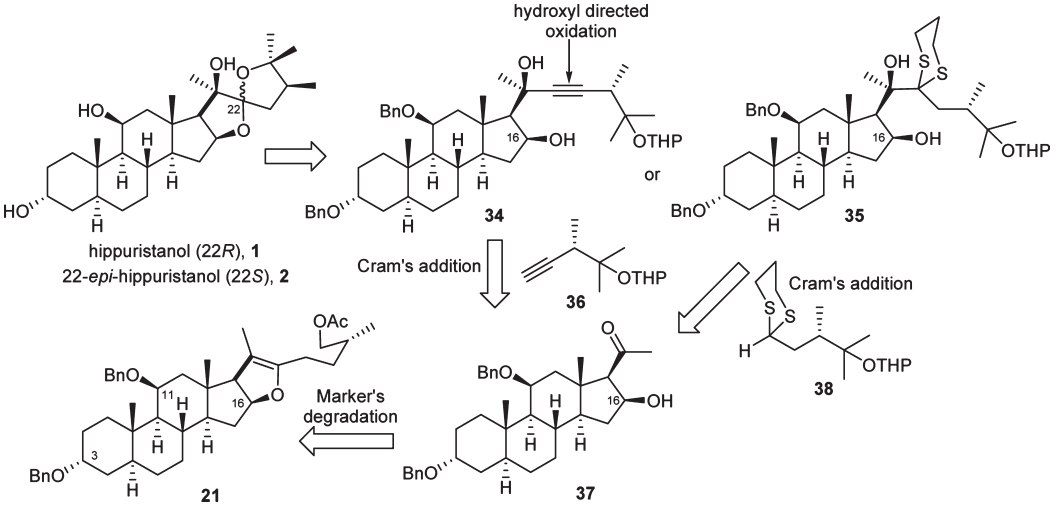
SCHEME 5. Efforts toward the Synthesis of Hippuristanol 1 and Its 22-Epimer 2 via Suárez Cyclization



SCHEME 6. New Retrosynthetic Analysis of Hippuristanol 1 and Its 22-Epimer 2 via Spiroketalization



methyl ketone **40** or decomposition (Table 1). We then adopted a roundabout procedure for hydrolysis. Thus, vinyl Grignard addition to **39** resulted in alkylative cleavage of the ester group and vinylation of the keto group to give diol **41**. OsO_4-mediated dihydroxylation of the olefin group in **41**, followed by oxidative cleavage, cleanly afforded the requisite β-hydroxy ketone **37**. Another parallel practical way was evaluated for **37** via **40**.[3] Thus, conjugated ketone **40** was synthesized in high yield from **39** using basic alumina (Al_2O_3) in benzene. Enone **40** on exposure to *N*-bromoacetamide (NBA) in aqueous acetone/THF underwent bromohydroxylation to give 16β-hydroxy-17α-bromide, which, on immediate treatment with Bu_3SnH/Et_3B, resulted in radical mediated debrominated product **37**. Again, the addition of lithiated **38** to hydroxy ketone **37** proved to be unsuccessful (to give **42**), though the excess of reagent was added. This failure could be due to the Thorpe−Ingold effect (gem dialkyl effect), as described in a literature precedent by Smith et al.[16] Hence, we decided to slightly alter the strategy by choosing a coupling partner, which is less sterically hindered.

This strategy is described in Scheme 8. Initially, we constructed 24-desmethylhippuristanol **3** using the known alkyne partner **43**.[17] Pleasingly, addition of lithiated **43** to ketone **37** cleanly furnished the propargyl alcohol **44** as a

(16) Smith, A. B., III; Adams, C. M. *Acc. Chem. Res.* **2004**, *37*, 365–377.
(17) Beszant, S.; Giannini, E.; Zanoni, G.; Vidari, G. *Eur. J. Org. Chem.* **2003**, 3958–3968.

SCHEME 7. Some Synthetic Efforts for the Coupling of 38 and for the Preparation of 37

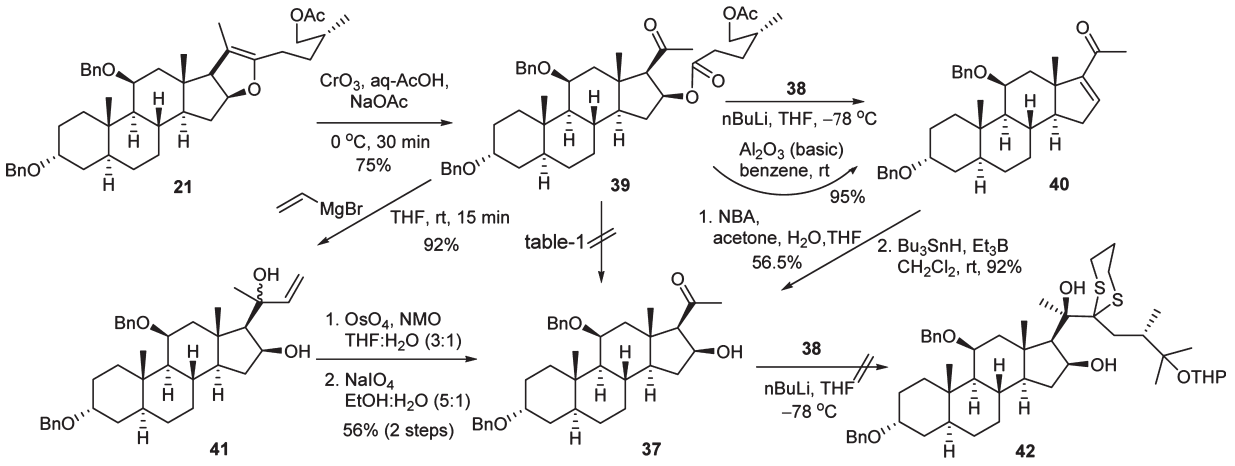
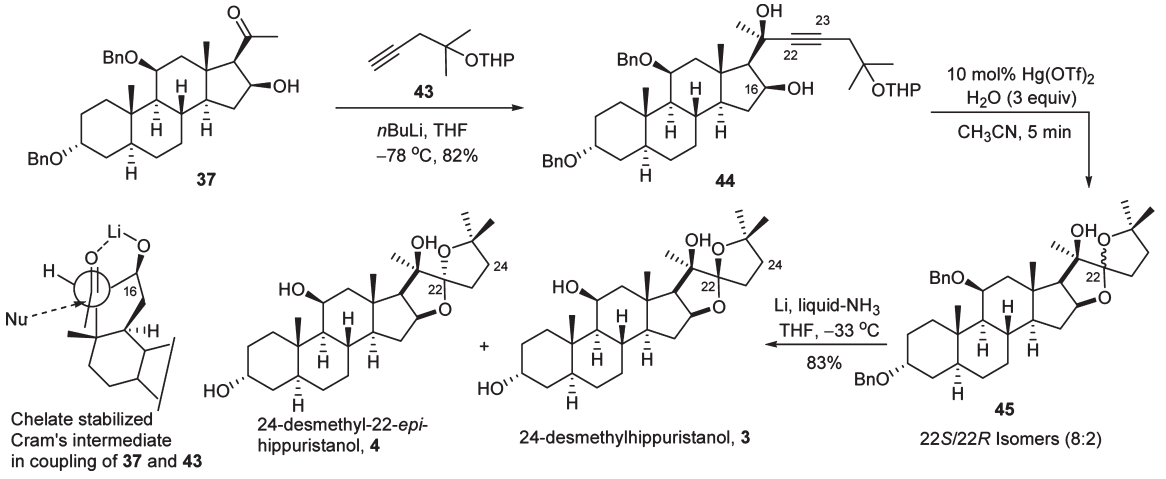


TABLE 1. Efforts on the Hydrolysis of 39 to 37

entry	conditions	result
1	K_2CO_3, MeOH, rt	enone (**40**)
2	K_2CO_3, MeOH/THF (1:1), rt	enone (**40**)
3	1 N HCl, THF, rt	decomposition
4	40% AcOH, THF, 45 °C	decomposition
5	PLE (pig liver esterase), phosphate buffer (pH = 7.0), Et_2O, rt	starting material + decomposition

SCHEME 8. Synthesis of 24-Desmethylhippuristanol 3 and Its 22-Epimer 4 via Hg(II)-Catalyzed Spiroketalization



single diastereomer. The exclusive formation of a single isomer must be due to the hydroxyl group mediated chelate stabilization of the Cram's intermediate, as shown in Scheme 8. At this stage, our aim was the regioselective hydration of **44** at C22 over C23 with the assistance of C16-OH, as described in a recent literature precedent, and later OTHP deprotection would lead to spiroketalization. Unprecedentedly, exposure of semiprotected 3-alkyn-1,7-diol **44** to $Hg(OTf)_2$ in aqueous acetonitrile[18] at room temperature, within no time, cleanly furnished directly the desired spiroketal **45** (in 8:2 22*S*/22*R* diastereomers) in a cascade manner. The mechanistic sequence of this cascade reaction is detailed in our communication.[4] Intermediate **45**, on debenzylation with lithium in liquid ammonia, resulted in 24-desmethylhippuristanol (**3**) and 24-desmethyl-22-*epi*-hippuristanol (**4**) in 83% yield (Scheme 8).[3]

With the above promising results, we then targeted the synthesis of hippuristanol (**1**). The suitable alkyne coupling partner **36** was synthesized from known diol **46** as shown in Scheme 9. Diol **46**[19] was oxidized with PDC to give hydroxy aldehyde **47**, which, on homologation under various conditions of Corey−Fuchs[20] and Ohira−Bestmann[21] protocols, proved to be unfruitful, revealing the substrate's high sensitivity to basic conditions. The Miwa protocol[22] using excess

(18) (a) Yamamoto, H.; Imagawa, H. *Synlett* **2009**, *7*, 1175–1179. (b) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617–1661.

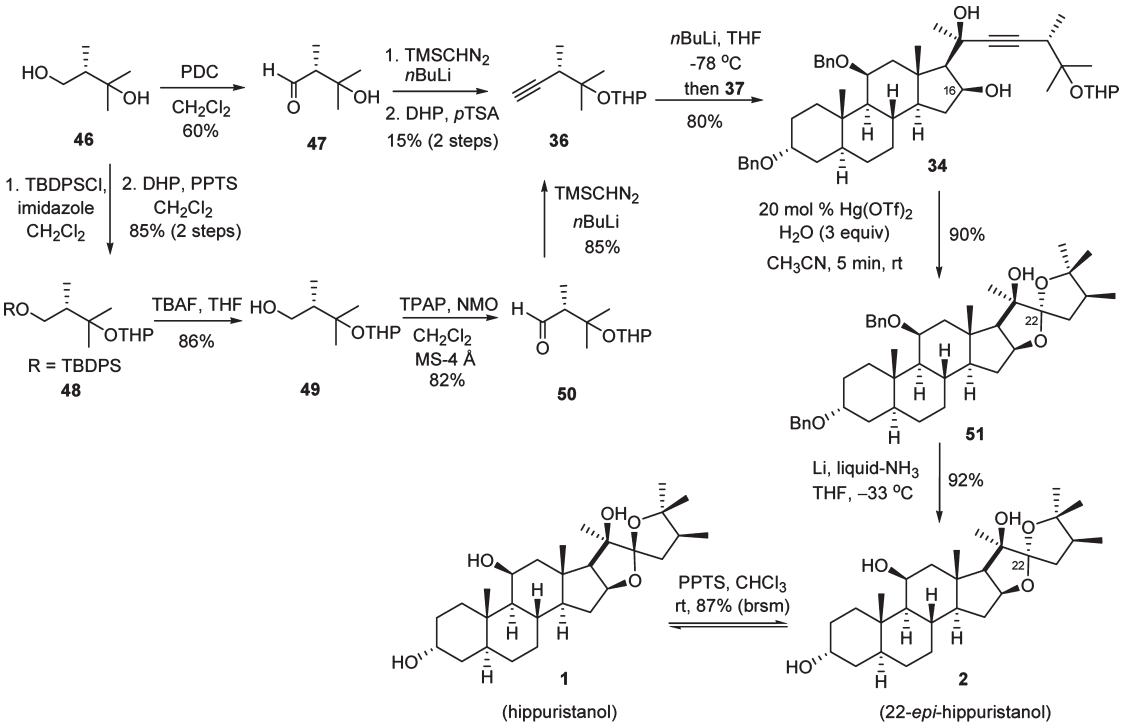
(19) Beszant, S.; Giannini, E.; Zanoni, G.; Vidari, G. *Eur. J. Org. Chem.* **2003**, 3958–3968.

(20) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769–3772.

(21) (a) Muller, S.; Liepold, B.; Roth, G.; Bestmann, H. J. *Synlett* **1996**, *06*, 521–522. (b) Toth, G.; Liepold, B.; Muller, S.; Bestmann, H. J. *Synthesis* **2004**, *1*, 59–62.

(22) Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, 107–108.

SCHEME 9. Completion of the Synthesis of Hippuristanol 1



$TMSCHN_2$ in combination with substoichiometric *n*BuLi at reduced temperatures produced the desired product, but in low yield, and the resulting alkyne was protected as its THP ether **36**. Unsatisfied with the yield, we developed a slightly longer, but convenient, route to **36** from diol **46**. Thus, the primary and tertiary hydroxyl groups of **46** were protected as TBDPS and THP ethers, respectively, in standard conditions to obtain **48**, which, upon treatment with TBAF, relieved the primary hydroxyl group to give alcohol **49**.[15] Oxidation of alcohol **49** with TPAP-NMO gave aldehyde **50**, which, under Miwa's conditions, cleanly furnished alkyne **36** in 85% yield.

Now, the stage was set for the completion of the synthesis of hippuristanol (**1**). Addition of lithiated alkyne **36** to hydroxy ketone **37** yielded exclusively the desired and expected Cram's product **34** in excellent yield.[23] As was observed above, exposure of semiprotected 3-alkyn-1,7-diol **34** to $Hg(OTf)_2$ in aqueous acetonitrile[4] at room temperature cleanly furnished the desired spiroketal **51**, which, on debenzylation with lithium in liquid ammonia, resulted in 22-*epi*-hippuristanol (**2**) as a single diastereomer in 82% overall yield. Stereochemistry of the spiroketal unit of both **51** and 22-*epi*-hippuristanol (**2**) was confirmed by the appearance of C22 spirocarbon ^{13}C NMR signals above δ 118 (122.53 and 118.66, respectively).[2b,c] Further, the analytical data of our 22-*epi*-hippuristanol (**2**) were in good agreement with those of the literature.[3] Ultimately, the 22-*epi*-hippuristanol (**2**) was converted to hippuristanol (**1**) using PPTS in $CHCl_3$ (aprotic system) at room temperature in a good yield of 87% (brsm). Initial observation of the R_f value on TLC and lowering of the δ value of C22 spirocarbon (δ 115.61) in ^{13}C NMR confirmed the inversion of the spirocenter. The remaining analytical data of the synthetic material were in good agreement with those of the natural product as well as with the reported data.[3]

Conclusion

In conclusion, an efficient synthesis of hippuristanol (**1**) and some of the close analogues has been achieved from readily available hecogenin acetate through an unprecedented $Hg(OTf)_2$-catalyzed cascade spiroketalization. Suárez cyclization was well studied for the synthesis of hippuristanol and was successfully applied for some of its analogues, that is, 20-deshydroxy-24-desmethylhippuristanol (both C22-epimers) and 24-desmethylhippuristanol (both C22-epimers). It has been revealed that the C20-OH and C24-methyl groups are important for the biological activity of hippuristanol. This novel construction of spiroketal motifs via the facile coupling of readily available acetylenic intermediates with hydroxy ketones, followed by Hg(II) treatment, should allow the preparation of hippuristanol analogues for further biological studies. Overall, our successful synthetic sequence produced hippuristanol (**1**) in 5.54% overall yield from 11-ketotigogenin **5** in 12 steps, compared with Yu's synthesis in 3.6% overall yield in 16 steps from hydrocortisone. Further study on the structure−activity relationships of hippuristanol and its analogues and the extension of the spiroketalization method are in progress and will be reported shortly.

Experimental Section

General Procedures. All reactions were performed under a nitrogen atmosphere with oven (80 °C) or flame-dried glassware. Tetrahydrofuran (THF) and ether were distilled from sodium-benzophenone under a nitrogen atmosphere immediately prior to use. Dichloromethane, toluene, *N*,*N*-dimethylformamide, and acetonitrile were freshly distilled over calcium

(23) (a) Hedtmann, U.; Klintz, R.; Hobert, K.; Frelek, J.; Vlahov, I.; Welzel, P. *Tetrahedron* **1991**, *47*, 3753–3772. (b) Kerb, U.; Wiechert, R. *Tetrahedron Lett*. **1968**, *40*, 4277–4280.

hydride under an 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; and br, broad. Chemical shifts are reported in values relative to the solvent used ($CHCl_3$: 7.26 ppm for ^1H NMR and 77.0 ppm for ^{13}C NMR) as an 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 are numbered starting from **S1**.

Hecogenin S1: Hecogenin acetate **6** (2.0 g, 4.231 mmol) was first dissolved in THF (15 mL) by stirring for 15 min at rt. MeOH (10 mL) and powdered K_2CO_3 (1.17 g, 8.46 mmol) were then added sequentially, and the reaction mixture was stirred at rt for 12 h. After completion, the reaction was filtered through Celite and washed with EtOAc, CH_2Cl_2, and 5% MeOH in CH_2Cl_2. Purification by flash chromatography (30/70% EtOAc/hexanes) using a small band of silica gel afforded hecogenin **S1** as a white solid (1.73 g, 95%). The product was confirmed by the comparison of its spectroscopic data with the literature.[6a,c]

TBS Enol Ether 7: To a mixture of Et_3N (2.0 mL) and CH_2Cl_2 (2.0 mL) was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (7.85 mL, 29.72 mmol) dropwise at 0 °C. To this mixture was added hecogenin (1.60 g, 3.71 mmol) in anhydrous CH_2Cl_2 at the same temperature. The mixture was warmed to room temperature and stirred at this temperature for 24 h. It was then quenched with isopropanol (2.0 mL) and H_2O (10 mL) at 0 °C. It was then diluted with CH_2Cl_2, washed with brine solution, and dried over Na_2SO_4. Purification by flash chromatography (5% EtOAc/hexanes) using silica gel gave TBS enol ether **7** (1.96 g, 80%) as a white solid. R_f = 0.8 (SiO_2, 10% EtOAc/hexanes); mp 190−193 °C; $[\alpha]_D^{20}$ −46.3 (c = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 4.51 (d, 1H, J = 1.64 Hz), 4.47−4.37 (m, 1H), 3.62−3.42 (m, 2H), 3.42−3.31 (m, 1H), 2.11−1.81 (m, 3H), 1.78−0.77 (m, 20H), 1.04 (d, 3H, J = 7.13 Hz), 0.93 (s, 9H), 0.90 (s, 3H), 0.88 (s, 9H), 0.78 (d, 3H, J = 6.58 Hz), 0.75 (s, 3H), 0.17 (s, 3H), 0.14 (s, 3H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 159.4, 109.0, 100.68, 80.8, 72.1, 66.8, 58.1, 56.1, 53.8, 46.3, 44.6, 42.9, 38.6, 36.6, 36.3, 33.4, 31.9, 31.7, 30.7, 30.4, 30.3, 29.2, 28.9, 26.1, 26.0, 18.6, 18.4, 18.3, 17.2, 14.0, 13.0, −3.7, −4.2, −4.6; IR (NaCl): cm^{-1} 2955.7, 2925.0, 1472.0, 1370.5, 1252, 1084; HRMS (ESI) m/z calcd for $C_{39}H_{70}O_4Si_2$ $[M]^+$ 658.4812, found 658.4818 ± 0.0020.

11-Hydroxy-12-ketone 8: To a stirred solution of silyl enol ether **7** (1.5 g, 2.27 mmol) in THF/water (3:1, 10 mL) were added 4-methylmorpholine-*N*-oxide (0.533 g, 4.55 mmol), followed by a solution of OsO_4 in H_2O (4% in H_2O, 0.01 mL, 0.455 mmol). The resulting solution was stirred for 5 h at room temperature. The mixture was as such concentrated without further workup and subjected to silica gel column chromatography (7% EtOAc/hexanes) to afford the α-hydroxy ketone **8** as a white solid (1.092 g, 86%). R_f = 0.6 (SiO_2, 10% EtOAc/hexanes); mp 225−228 °C; $[\alpha]_D^{20}$ −16.2 (c = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 4.41−4.30 (m, 2H), 3.95 (d, 1H, J = 2.74), 3.54 (sept, 1H, J = 4.94 Hz), 3.52−3.43 (m, 1H), 3.40−3.27 (m, 1H), 2.70−2.60 (m, 1H), 2.20−2.05 (m, 2H), 2.03−1.86 (m, 1H), 1.83−0.83 (m, 25H), 1.05 (d, 3H, J = 7.13 Hz), 0.88 (s, 9H), 0.79 (d, 3H, J = 6.03 Hz), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 213.6, 109.1, 79.3, 73.1, 71.4, 67.0, 63.5, 55.7, 53.6, 45.0, 42.1, 38.9, 38.0, 37.9, 34.3, 32.0, 31.7, 31.4, 31.3, 30.1, 28.8, 28.7, 25.9, 18.3, 17.1, 15.4, 13.3, 12.6, −4.5, −4.6; IR (NaCl): cm^{-1} 2955.7, 2935.0, 1708, 1462, 1063; HRMS (ESI) m/z calculated for $C_{29}H_{47}O_5Si$ $[M - C_4H_9]^+$ 503.3193, found 503.3196 ± 0.0015.

12-Hydroxy-11-ketone 9: To the ketol **8** (1.2 g, 2.14 mmol) in *tert*-BuOH (5 mL) and water (5 mL) was added powdered NaOH (0.599 g, 14.9 mmol), and the mixture was refluxed (80−90 °C) for 12 h. After completion of the reaction, *tert*-BuOH was removed under reduced pressure, and then more water was added and extracted with CH_2Cl_2. The crude product was dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purification of the crude product by flash chromatography (5% EtOAc/hexanes) using silica gel afforded the isomerized ketol **9** (1.08 g, 90%) as a white solid. R_f = 0.5 (SiO_2, 10% EtOAc/hexanes); mp 274−276 °C; $[\alpha]_D^{20}$ −32.8 (c = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 4.57−4.43 (m, 1H), 3.84−3.75 (m, 1H), 3.66−3.43 (m, 3H), 3.43−3.28 (m, 1H), 2.45−2.30 (m, 1H), 2.25−2.05 (m, 2H), 1.93−0.75 (m, 20H), 1.05 (d, 3H, J = 7.13 Hz), 1.04 (s, 3H), 0.88 (s, 9H), 0.79 (d, 3H, J = 6.58 Hz), 0.56 (s, 3H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 210.7, 109.4, 84.3, 80.5, 71.6, 66.8, 62.8, 60.5, 52.9, 50.0, 44.9, 42.4, 38.0, 37.1, 35.7, 35.2, 32.6, 31.5, 31.3, 30.9, 30.1, 28.7, 27.9, 25.9, 18.2, 17.1, 13.3, 12.4, 11.3, −4.6; IR (NaCl): cm^{-1} 2931.4, 2852.5, 1690.1, 1446.9, 1374.6, 1059.1; HRMS (ESI) m/z calcd for $C_{33}H_{56}O_5Si$ $[M]^+$ 560.3897, found 560.3896 ± 0.0017.

3-OTBS-11-ketotigogenin 10: To the ketol **9** (1.0 g, 1.78 mmol) in a single-neck, round-bottom flask was added pyridine (5 mL), followed by Ac_2O (5 mL), and the reaction mixture was refluxed at 135 °C for 2.5 h. After completion of the reaction, the contents were cooled to 0 °C and cold water and EtOAc were added. It was then extracted with EtOAc (3 × 10 mL), and combined extracts were washed with water and brine solution, dried over anhydrous Na_2SO_4, and concentrated under vacuum. Purification by silica gel column chromatography (5% EtOAc/hexanes) afforded the corresponding acetate **S2** (910 mg, 85%) as a white solid. R_f = 0.45 (SiO_2, 10% EtOAc/hexanes); mp 232−235 °C; $[\alpha]_D^{20}$ −51.8 (c = 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 4.82−4.67 (m, 1H), 4.57−4.41 (m, 1H), 3.59−3.42 (m, 2H), 3.42−3.23 (m, 1H), 2.40−2.24 (m, 1H), 2.22−1.98 (m, 2H), 2.15 (s, 3H), 1.97−0.64 (m, 20H), 1.03 (s, 3H), 0.93 (d, 3H, J = 7.13 Hz), 0.87 (s, 9H), 0.79 (d, 3H, J = 6.58 Hz), 0.72 (s, 3H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 203.9, 170.1, 109.3, 85.8, 80.4, 71.7, 66.9, 63.1, 60.0, 54.2, 47.8, 44.9, 42.3, 37.9, 36.6, 35.6, 35.2, 32.6, 31.5, 31.2, 30.8, 30.1, 28.7, 27.9, 25.9, 20.7, 18.3, 17.1, 13.5, 12.4, 12.4, −4.4, −4.6; IR (NaCl): cm^{-1} 2931.4, 2852.5, 1742.7, 1716.4, 1453.5, 1368.0, 1052.5; HRMS (ESI) m/z calcd for $C_{35}H_{58}O_6Si$ $[M]^+$ 602.4002, found 602.4003 ± 0.0018. Calcium (96.2 mg, 22.9 mmol) was placed in a flask topped with a dry ice condenser. The system was flushed with argon. The flask was cooled to −78 °C and the condenser filled with a dry ice/acetone mixture. Ammonia was condensed until no further calcium was seen. The cooling bath was removed, and the system was allowed to equilibrate to the refluxing temperature (−33 °C). THF (5 mL) was added to disperse the newly formed reagent, followed by a slow addition of a solution of the above acetate **S2** (500 mg, 2.29 mmol). A cautious addition is needed to ensure a regular and smooth ammonia reflux. The reaction mixture was then stirred at −33 °C for 20 min, carefully, and bromobenzene was slowly added at −33 °C to quench the reaction, followed by water. Ammonia was allowed to evaporate under a stream of air. To the reaction mixture was added water and a small amount of aqueous NH_4Cl (2 mL), and it was extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by silica gel column chromatography (6% EtOAc/hexanes) to afford the ketone **10** (910 mg, 86%) as a white solid. R_f = 0.6 (SiO_2, 20% EtOAc/hexanes); mp 235−238 °C; $[\alpha]_D^{20}$ −22.3 (c = 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): δ 4.54−4.42 (m, 1H), 3.59−3.42 (m, 2H), 3.42−3.27 (m, 1H), 2.48−2.36 (m, 1H), 2.23 (s, 2H), 2.17−2.03 (m, 1H), 2.01−1.91 (m, 1H), 1.90−0.71 (m, 20H), 1.01 (s, 3H), 0.93 (d, 3H, J = 7.13 Hz), 0.87 (s, 9H), 0.78 (d, 3H, J = 6.58 Hz), 0.70 (s, 3H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 210.1, 109.2, 80.6, 71.8, 67.0, 64.6, 60.7, 57.7, 55.8, 45.0, 44.4, 41.8, 38.1, 37.0, 35.9, 35.1, 32.8, 31.7, 31.3,

31.2, 30.2, 28.7, 28.1, 25.9, 17.1, 14.2, 12.2, −4.5, −4.6; IR (NaCl): cm^{-1} 2918.3, 2852.5, 1690.1, 1453.5; HRMS (ESI) m/z calcd for $C_{33}H_{56}O_4Si$ $[M]^+$ 544.3901, found 544.3902 ± 0.0016.

11-Ketotigogenin 5: The TBS ether **10** (900 mg, 1.651 mmol) was placed in a flame-dried, two-neck, round-bottom flask, under an argon atmosphere. To this was added anhydrous THF (8 mL), and the mixture was cooled to 0 °C. TBAF (1.0 M in THF, 3.30 mL, 3.30 mmol) was then added slowly at the same temperature. The cooling bath was removed, and the system was allowed to stir at room temperature for 8 h. After complete conversion, the reaction mixture was as such concentrated and flashed on silica gel column chromatography (30−60% EtOAc/hexanes) to afford the 11-ketotigogenin **5** (654 mg, 92%) as a white solid. R_f = 0.25 (SiO_2, 60% EtOAc/hexanes); mp 220−223 °C; $[\alpha]_D^{20}$ −27.5 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.55−4.42 (m, 1H), 3.65−3.41 (m, 2H), 3.41−3.27 (m, 1H), 2.54−2.39 (m, 1H), 2.24 (s, 2H), 2.18−2.03 (m, 1H), 2.01−1.91 (m, 1H), 1.91−0.66 (m, 20H), 1.03 (s, 3H), 0.94 (d, 3H, J = 7.13 Hz), 0.79 (d, 3H, J = 6.58 Hz), 0.71 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 210.2, 109.2, 80.6, 70.9, 66.9, 64.5, 60.7, 57.7, 55.7, 44.8, 44.3, 41.8, 37.6, 37.0, 36.0, 35.1, 32.7, 31.3, 30.2, 28.7, 28.0, 17.1, 14.2, 12.1; IR (NaCl): cm^{-1} 3272.7, 2925.0, 1702.8, 1447.2, 1048.3; HRMS (ESI) m/z calcd for $C_{27}H_{42}O_4$ $[M]^+$ 430.3083, found 430.3084 ± 0.0013.

3-Benzoate S3: The hydroxy ketone **5** (600 mg, 1.39 mmol) was weighed in a flame-dried, round-bottom flask, connected to an argon supply, dissolved in anhydrous THF (5 mL), and cooled to 0 °C. Benzoic acid (BzOH, 169 mg, 1.39 mmol) and triphenylphosphine (TPP, 438 mg, 1.67 mmol) were added to the reaction mixture. After 5 min, diisopropyl-azodicarboxylate (DIAD, 0.34 mL, 1.67 mmol) was added at the same temperature. The mixture was allowed to stir at rt for 1.5 h. It was then concentrated as such (without any workup) and subjected to silica gel column chromatography (12% EtOAc/hexanes) to afford the corresponding benzoate **S3** (685 mg, 93%) as a white solid. R_f = 0.8 (SiO_2, 30% EtOAc/hexanes); mp 160−162 °C; $[\alpha]_D^{20}$ −20.8 (c = 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.10−7.99 (m, 2H), 7.61−7.37 (m, 3H), 5.26 (br s, 1H), 4.56−4.42 (m, 1H), 3.48 (dd, 1H, J = 10.97, 3.84 Hz), 3.36 (t, 1H, J = 10.97 Hz), 2.35 (dd, 1H, J = 13.17, 3.84 Hz), 2.26 (s, 2H), 2.18−2.04 (m, 1H), 2.02−0.84 (m, 20H), 1.08 (s, 3H), 0.94 (d, 3H, J = 6.58 Hz), 0.79 (d, 3H, J = 6.03 Hz), 0.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 210.1, 165.8, 132.7, 131.1, 129.5, 128.3, 109.2, 80.6, 70.4, 66.9, 64.5, 60.8, 57.7, 55.8, 44.4, 41.8, 40.3, 36.9, 35.6, 32.7, 32.2, 31.9, 31.2, 30.2, 28.7, 27.6, 26.1, 17.2, 17.1, 14.2, 11.1; IR (NaCl): cm^{-1} 2954.5, 2922.7, 1708, 1452, 1273.0, 114.8; HRMS (ESI) m/z calcd for $C_{34}H_{46}O_5$ $[M]^+$ 534.3345, found 534.3344 ± 0.0016.

Diol 11: The keto-ester **S3** (650 mg, 1.21 mmol) was placed in a flame-dried, two-neck, round-bottom flask under argon. Anhydrous THF (5 mL) was added, and the system was cooled to −10 °C (ice + NaCl mixture bath). $LiAlH_4$ (2.0 M in THF, 3.0 mL, 7.30 mmol) was added slowly and cautiously at −10 °C. After 30 min of stirring at −10 °C slowly, the mixture was allowed to reflux for 1.5 h. The reaction mixture was then cooled to −10 °C and quenched with a minimum amount of cold water (4 mL), cautiously and very slowly. After the completion of quenching, to the reaction mixture was added EtOAc (10 mL), and it was allowed stir for 2.5 h at rt, then filtered on Celite using EtOAc and CH_2Cl_2. The filtrate was dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. Purification of the crude product by column chromatography (50% EtOAc/hexanes) using silica gel afforded the diol **11** (451 mg, 86%) as a white solid. R_f = 0.35 (SiO_2, 30% EtOAc/hexanes); mp 247−250 °C; $[\alpha]_D^{20}$ −53.3 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.39 (q, 1H, J = 7.13 Hz), 4.30 (br s, 1H), 4.04 (br s, 1H), 3.54−3.26 (m, 2H), 2.12−1.96 (m, 1H), 1.95−1.76 (m, 4H), 1.75−0.72 (m, 20H), 1.03 (s, 3H), 0.99 (s, 3H), 0.96 (d, 3H, J = 6.58 Hz), 0.78 (d, 3H, J = 6.03 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 109.3, 80.6, 68.1, 66.8, 66.4, 62.8, 58.2, 57.9, 48.5, 41.6, 39.9, 39.6, 36.3, 35.3, 32.5, 31.8, 31.5, 31.3, 31.1, 30.3, 28.8, 28.6, 27.9, 19.2, 17.1, 14.5, 14.3; IR (NaCl): cm^{-1} 3441.5, 2930.1, 1452, 1048.3; HRMS (ESI) m/z calcd for $C_{27}H_{44}O_4$ $[M]^+$ 432.3239, found 432.3244 ± 0.0013.

Dibenzoate 12: To the diol **11** (560 mg, 1.29 mmol) in anhydrous pyridine (25 mL) under argon at room temperature was added DMAP (31.5 mg, 0.25 mmol), followed by benzoic anhydride (2.29 g, 12.96 mmol). The reaction mixture was refluxed (∼125 °C bath temperature) for 6 h, cautiously quenched with ice water at 0 °C, extracted with CH_2Cl_2, and washed with aqueous $NaHCO_3$ solution. The organic fractions were dried over anhydrous Na_2SO_4 and filtered using sintered funnel, and solvents were removed under vacuum. Purification of the crude product by silica gel column chromatography (5% EtOAc/hexanes) afforded the dibenzoate **12** (680 mg, 82%) as a white solid. R_f = 0.65 (SiO_2, 15% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.18−8.01 (m, 4H), 7.65−7.39 (m, 6H), 5.65 (s, 1H), 5.23 (s, 1H), 4.49−4.37 (m, 1H), 3.52−3.41 (m, 1H), 3.41−3.29 (m, 1H), 2.28−2.02 (m, 3H), 1.97−0.81 (m, 22H), 0.98 (s, 3H), 0.95 (s, 3H), 0.91 (d, 3H, J = 6.58 Hz), 0.77 (d, 3H, J = 6.03 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.9, 165.3, 132.9, 132.7, 129.7, 129.5, 128.5, 128.4, 109.4, 80.6, 70.3, 66.8, 62.8, 57.6, 57.1, 44.4, 41.6, 41.3, 39.6, 35.9, 33.1, 32.4, 31.9, 31.5, 31.3, 30.2, 28.7, 27.7, 26.1, 19.1, 17.1, 14.7, 14.4; IR (NaCl): cm^{-1} 2953, 2931, 1736, 1091, 1025; HRMS (ESI) m/z calcd for $C_{41}H_{52}O_6$ $[M]^+$ 640.3764, found 640.3771 ± 0.0019.

Primary Alcohol 13: To a solution of compound **12** (500 mg, 0.76 mmol) in acetic acid (2 mL) was added $NaCNBH_3$ (96 mg, 1.52 mmol). After 1.5 h, the mixture was quenched carefully with saturated aqueous sodium bicarbonate solution (15 mL) and then was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed with brine and dried over Na_2SO_4, and solids were removed by filtration. The solvent was removed in vacuo, and the crude material was purified by flash chromatography (30−45% EtOAc/hexanes) to provide the alcohol **13** (352 mg, 92%) as an oil. R_f = 0.25 (40% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12−8.02 (m, 4H), 7.64−7.41 (m, 6H), 5.68−5.62 (m, 1H), 5.23 (brs, 1H), 4.38−4.26 (m, 1H), 3.50−3.37 (m, 1H), 3.36−3.25 (m, 1H), 2.24−0.91 (m, 34H), 0.87 (d, 3H, J = 7.13 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.9, 165.6, 132.8, 132.7, 129.7, 129.5, 128.4, 128.2, 90.4, 83.0, 70.3, 68.1, 65.6, 57.9, 57.1, 44.2, 41.3, 40.2, 38.0, 35.6, 33.0, 32.4, 31.9, 30.4, 30.0, 27.6, 25.8, 19.4, 18.8, 16.6, 14.7; IR (NaCl): cm^{-1} 3521, 2952, 1736, 1734; HRMS (ESI) m/z calcd for $C_{41}H_{54}O_6$ $[M]^+$ 642.3920, found 642.3920 ± 0.0019.

Iodide S4: To a solution of alcohol **13** (350 mg, 0.54 mmol) in CH_2Cl_2 (10 mL) was added Ph_3P (430 mg, 1.6 mmol) and imidazole (148 mg, 2.1 mmol) at room temperature and I_2 (274 mg, 1.08 mmol) at 0 °C. The contents were stirred at rt for 3 h. When TLC showed the completion of the reaction, the reaction mixture was quenched with $Na_2S_2O_3$ solution and extracted with CH_2Cl_2 (3 × 8 mL). Combined extracts were washed with brine and concentrated to remove solvent. The residue was flashed on silica (20% EtOAc/hexanes) to get iodide **S4** (320 mg, 79%) as an oil. R_f = 0.6 (40% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10−8.03 (m, 4H), 7.62−7.43 (m, 6H), 5.68−5.63 (m, 1H), 5.28−5.22 (m, 1H), 4.37−4.28 (m, 1H), 3.55−3.25 (m, 1H), 3.22 (dd, 1H, J = 9.33, 3.84 Hz), 3.12 (dd, 1H, J = 9.33, 5.48 Hz), 2.26−2.80 (m, 3H), 1.96−1.80 (m, 2H), 1.75−0.92 (m, 32H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.9, 165.4, 133.9, 133.6, 132.9, 132.7, 132.2, 132.0, 129.8, 129.5, 128.7, 128.5, 128.4, 128.3, 90.2, 83.0, 70.2, 65.6, 57.9, 57.1, 44.2, 41.6, 38.0, 35.8, 34.8, 33.6, 33.1, 32.4, 31.8, 30.8, 27.6, 25.8, 20.4, 19.4, 18.8, 17.6, 14.8; IR (NaCl): cm^{-1} 2931.0, 2853.4, 1738, 1736, 1452.4, 1089.2, 1063.6; HRMS (ESI) m/z calcd for $C_{41}H_{53}IO_5$ $[M]^+$ 752.2938, found 752.2938 ± 0.0022.

Olefin 14: To a solution of the above iodide **S4** (300 mg, 0.39 mmol) in DMF (5 mL) was added DBU at rt, and the contents

were stirred at 80−90 °C for 4 h. When TLC showed the completion of the reaction, the contents were cooled to rt and diluted with water and extracted with EtOAc (3 × 8 mL). The combined extracts were washed with water and brine and concentrated to remove solvent. The residue was chromatographed on silica (15% EtOAc/hexanes) to get olefin **14** (228 mg, 88%) as a yellow oil. R_f = 0.5 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12−8.04 (m, 4H), 7.62−7.43 (m, 6H), 5.70−5.64 (m, 1H), 5.28−5.23 (m, 1H), 4.70−4.65 (m, 1H), 4.38−4.30 (m, 1H), 3.38−3.30 (m, 1H), 2.28−0.94 (m, 36H); IR (NaCl): cm^{-1} 2952, 1736, 1734, 1457.4, 1089, 1058; HRMS (ESI) m/z calcd for $C_{41}H_{52}O_5$ $[M]^+$ 624.3815, found 624.3815 ± 0.0018.

Tertiary Alcohol 15: Tetrahydrofuran (1 mL) was added to a solution of mercury(II) acetate (140 mg, 0.44 mmol) in water (0.8 mL). The flask was wrapped in aluminum foil to exclude light, and then a solution of olefin **14** (110 mg, 0.17 mmol) in tetrahydrofuran (1 mL) was added to the solution of mercury(II) acetate. After stirring at 23 °C for 16 h, $NaBH_4$ (133 mg, 5.0 mmol) was added in portions over 5 min, and the solution was stirred for 3 h. The reaction mixture was diluted with brine (2 mL) and was extracted with ethyl acetate (4 × 3 mL). The solution was dried over Na_2SO_4, the solids were removed by filtration, and the solvent was removed in vacuo. The crude material was purified by flash chromatography (25−50% EtOAc/hexanes) to afford tertiary carbinol **15** (60 mg, 53%) along with 40% starting material (44 mg). R_f = 0.2 (40% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10−8.02 (m, 4H), 7.62−7.42 (m, 6H), 5.68−5.62 (m, 1H), 5.26−5.21 (m, 1H), 4.38−4.28 (m, 1H), 3.38−3.28 (m, 1H), 2.68 (brs, 1H), 2.28−2.04 (m, 3H), 1.96−0.92 (m, 36H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.8, 165.4, 132.9, 132.8, 129.8, 129.5, 128.5, 128.3, 90.8, 83.1, 70.3, 70.0, 65.4, 58.0, 57.1, 44.1, 41.4, 40.9, 40.0, 38.0, 35.8, 33.1, 32.4, 32.3, 31.9, 29.8, 28.9, 27.9, 27.8, 25.9, 19.3, 18.6, 14.8; IR (NaCl): cm^{-1} 3410.8, 2930.1, 2848.3, 1447.2, 1094.3, 1058.5; HRMS (ESI) m/z calcd for $C_{41}H_{54}O_6$ $[M]^+$ 642.3920, found 642.3920 ± 0.0019.

Spiroketals 16 and 17: To a mixture of iodine (62 mg, 0.25 mmol) and iodobenzene diacetate (80 mg, 0.25 mmol) in hexanes (4 mL) was added a solution of compound **15** (80 mg, 0.12 mmol) in CH_2Cl_2 (4 mL) over 15 min via cannula. After 2 h, the reaction solution was quenched by addition of a saturated aqueous sodium thiosulfate solution (4 mL), and the resulting mixture was stirred for 20 min. The aqueous layer was extracted with ethyl acetate (3 × 5 mL), and the combined organic layers were dried over Na_2SO_4. Solids were removed by filtration, and the solvent was removed in vacuo. The crude material was purified by flash chromatography (10% EtOAc/hexanes) to provide clean spiroketals **16** (15 mg, 19%) and **17** (50 mg, 63%).

Spiroketal 16. R_f = 0.7 (50% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10−8.02 (m, 4H), 7.62−7.42 (m, 6H), 5.69−5.63 (m, 1H), 5.28−5.20 (m, 1H), 4.14−4.04 (m, 1H), 2.28−0.80 (m, 39H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.8, 165.5, 132.9, 132.7, 129.8, 129.5, 128.4, 128.3, 120.5, 81.6, 78.3, 70.3, 61.1, 57.3, 56.7, 44.8, 41.4, 39.9, 38.3, 36.9, 35.9, 33.1, 32.5, 32.4, 32.2, 31.8, 29.7, 29.3, 28.3, 27.7, 25.9, 19.4, 15.7, 14.7; IR (NaCl): cm^{-1} 2953, 2932, 1736, 1090, 1025; HRMS (ESI) m/z calcd for $C_{41}H_{52}O_6$ $[M]^+$ 640.3764, found 640.3771 ± 0.0018.

Spiroketal 17. R_f = 0.75 (50% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10−8.02 (m, 4H), 7.62−7.42 (m, 6H), 5.68−5.62 (m, 1H), 5.26−5.21 (m, 1H), 4.54−4.44 (m, 1H), 2.25−0.80 (m, 39H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.9, 165.4, 132.8, 132.7, 129.7, 129.5, 128.4, 128.3, 120.0, 82.1, 80.2, 70.3, 70.2, 62.5, 57.4, 57.0, 44.4, 41.3, 39.6, 38.3, 37.0, 35.9, 33.7, 33.0, 32.3, 31.9, 31.6, 30.2, 28.4, 27.6, 25.9, 19.0, 19.0, 14.7, 14.5; IR (NaCl): cm^{-1} 2952, 2931, 1734, 1091, 1025; HRMS (ESI) m/z calcd for $C_{41}H_{52}O_6$ $[M]^+$ 640.3764, found 640.3771 ± 0.0021.

3,11-Dihydroxy-spiroketal 18: $LiAlH_4$ (5 mg, 0.12 mmol) was added to a solution of **16** (20 mg, 0.031 mmol) at 0 °C, and the contents were slowly heated to reflux for 1 h. After cooling to room temperature, the mixture was slowly quenched with water and the solids were filtered off. The filtrate was concentrated, and the residue was chromatographed (33% EtOAc/hexanes) to get diol **18** (11 mg, 83%) as a white solid. R_f = 0.25 (40% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.25−4.28 (m, 1H), 4.16−4.00 (m, 2H), 2.24−0.78 (m, 39H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 119.3, 77.1, 76.4, 67.1, 65.4, 59.9, 57.2, 56.0, 47.8, 38.9, 37.2, 35.9, 35.3, 34.3, 31.6, 31.0, 30.7, 30.0, 28.7, 28.3, 28.2, 27.6, 27.3, 26.9, 18.6, 14.6, 13.2; IR (NaCl): cm^{-1} 3441.5, 2930.1, 1452, 1048.3; HRMS (ESI) m/z calcd for $C_{27}H_{44}O_4$ $[M]^+$ 432.3239, found 432.3244 ± 0.0013.

3,11-Dihydroxy-spiroketal 19: The preparation of **19** from **17** followed the same procedure as that described for the conversion of **16** to **18**. The yield of **19** was 88%. R_f = 0.3 (40% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.44 (dd, 1H, J = 15.3, 7.6 Hz), 4.30 (brs, 1H), 4.04 (brs, 1H), 2.13−0.76 (m, 39H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 120.0, 82.0, 80.3, 68.1, 66.3, 62.4, 58.1, 57.8, 48.6, 39.9, 39.7, 38.3, 37.0, 36.2, 35.3, 33.6, 32.5, 31.8, 31.0, 30.2, 28.6, 28.4, 27.9, 19.0, 14.6, 14.3; IR (NaCl): cm^{-1} 3442, 2930, 1452, 1049; HRMS (ESI) m/z calcd for $C_{27}H_{44}O_4$ $[M]^+$ 432.3239, found 432.3244 ± 0.0018.

Dibenzyl Ether 20: To a suspension of NaH (60% dispersion in mineral oil, 248 mg, 6.240 mmol) in anhydrous THF (5 mL) under argon at 0 °C was added diol **11** (450 mg, 1.040 mmol) in anhydrous THF (2 mL), and the mixture was stirred for 30 min at 0 °C and for 30 min at rt. The mixture was then cooled again to 0 °C, and TBAI (768 mg, 2.08 mmol) was added, followed by benzylbromide (0.310 mL, 2.60 mmol). The reaction mixture was refluxed for 10 h, cautiously quenched with cold water at 0 °C, extracted with Et_2O, and washed with brine solution. The organic fractions were dried over anhydrous Na_2SO_4 and filtered using a 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 **20** (541 mg, 85%) as a low-melting white foamy solid. R_f = 0.75 (SiO_2, 10% EtOAc/hexanes); mp 65−68 °C; $[\alpha]_D^{20}$ −16.3 (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.43−7.27 (m, 10H), 4.69−4.18 (ABq, 2H, J = 11.52 Hz), 4.48 (q, 2H, J = 13.17 Hz), 4.44−4.33 (m, 1H), 3.90 (br s, 1H), 3.61 (br s, 1H), 3.53−3.27 (m, 2H), 2.34−2.20 (m, 1H), 2.12−1.92 (m, 2H), 1.92−0.82 (m, 22H), 1.02 (s, 3H), 0.98 (s, 3H), 0.97 (d, 3H, J = 6.58 Hz), 0.78 (d, 3H, J = 6.03 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 139.4, 139.1, 128.3, 128.1, 127.3, 126.9, 109.4, 80.7, 75.1, 73.2, 70.0, 69.6, 66.8, 62.7, 58.3, 58.2, 41.5, 40.8, 40.4, 39.9, 36.1, 32.7, 32.6, 31.6, 31.5, 31.3, 30.3, 28.8, 27.9, 25.4, 18.2, 17.1, 14.5; IR (NaCl): cm^{-1} 2918.3, 2839.4, 1446.9, 1354.9, 1046.0; HRMS (ESI) m/z calcd for $C_{41}H_{56}O_4$ $[M]^+$ 612.4178, found 612.4188 ± 0.0018.

Acetate 21: In a flame-dried, single-neck, round-bottom flask was placed spiroketal **20** (500 mg, 0.815 mmol). The flask was fitted with a reflux condenser, and Ac_2O (5.0 mL) was added. Pyridine hydrochloride (757 mg, 6.526 mmol) (Py·HCl; must be a white crystalline solid, otherwise, yields are low) was then added, and the mixture was refluxed at 135 °C for 2 h. The mixture was then cooled to 0 °C, some ice and water were added to quench the reaction, and the mixture was diluted with CH_2Cl_2 and extracted with CH_2Cl_2. The organic layer was washed three times with water, and aqueous $NaHCO_3$ solution was added cautiously at 0 °C. The mixture was stirred for 30 min. It was then separated using a separating funnel, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. Purification of the crude product by silica gel column chromatography (5% EtOAc/hexanes) afforded the acetate **21** (405 mg, 76%) as a colorless viscous liquid. R_f = 0.55 (SiO_2, 10% EtOAc/hexanes); $[\alpha]_D^{20}$ +39.4 (c = 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.41−7.21 (m, 10H), 4.77−4.68 (m, 1H), 4.67−4.19 (ABq, 2H, J = 11.52 Hz), 4.49 (q, 2H, J = 12.62 Hz), 3.97−3.82 (m, 3H),

3.61 (br s, 1H), 2.47−2.38 (d, 1H, J = 10.42 Hz), 2.34 (dd, 1H, J = 14.27, 2.19 Hz), 2.26−1.89 (m, 4H), 2.02 (s, 3H), 1.88−1.70 (m, 3H), 1.65−0.82 (m, 18H), 1.01 (s, 3H), 0.92 (d, 3H, J = 6.58 Hz), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.3, 151.6, 139.4, 139.2, 128.3, 128.1, 127.4, 127.3, 126.9, 103.8, 84.2, 75.2, 73.2, 70.1, 69.6, 69.2, 64.8, 58.4, 56.7, 42.9, 40.7, 40.5, 36.2, 33.8, 32.9, 32.7, 32.6, 32.1, 31.4, 30.8, 27.9, 25.4, 23.2, 20.9, 16.7, 15.6, 14.6, 11.8; IR (NaCl): cm^{-1} 2919.9, 2848.3, 1743.8, 1452.3, 1232.4, 1058.5; HRMS (ESI) m/z calcd for $C_{43}H_{58}O_5$ $[M]^+$ 654.4284, found 654.4292 ± 0.0019.

Tertiary Alcohols 23 and 23A: A stirred solution of olefin **21** (600 mg, 0.91 mmol) in dichloromethane/acetone (4 mL/2 mL, 2:1) was treated with a cold (0 °C) solution of dimethyldioxirane (DMDO) (1.37 mmol in 5 mL of acetone) at −10 °C. The reaction was continued for 4 h at 0 °C. After completion of the reaction, solvents were removed under reduced pressure (at room temperature). The resulting crude epoxide **22** was immediately dissolved in glacial AcOH, treated with $NaBH_3CN$ (172.8 mg, 2.75 mmol) at room temperature, and stirred for 1.5 h. It was then quenched with ice water and extracted with CH_2Cl_2 (3 × 15 mL), and the organic layer was washed with water and aqueous $NaHCO_3$ (25 mL) solution, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. Purification of the crude product using Al_2O_3 (neutral) column chromatography (30 → 40% EtOAc/hexanes) afforded the diastereomeric (C-22) mixture of alcohols (diastereomer **23**, 197 mg, 32%, R_f = 0.38 (SiO_2, 40% EtOAc/hexanes); diastereomer **23A**, 296 mg, 48%, R_f = 0.36 (SiO_2, 40% EtOAc/hexanes)) in a 4:6 ratio as colorless viscous liquids. These two diastereomers are used individually in subsequent transformations. Analytical data of diastereomer **23**: $[\alpha]_D^{20}$ +2.8 (c = 0.55, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.43−7.13 (m, 10H), 4.75−4.55 (m, 2H), 4.54−4.39 (m, 2H), 4.33−4.17 (m, 1H), 4.02−3.77 (m, 3H), 3.77−3.51 (m, 2H), 2.53−2.33 (m, 1H), 2.04 (s, 3H), 2.20−1.94 (m, 2H), 1.93−0.73 (m, 21H), 1.38 (s, 3H), 1.19 (s, 3H), 1.01 (s, 3H), 0.95 (d, 3H, J = 6.58 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.3, 139.4, 139.0, 128.3, 128.2, 127.4, 127.3, 127.1, 87.7, 81.7, 80.3, 75.2, 73.2, 70.3, 70.2, 69.6, 69.3, 58.2, 40.6, 40.5, 40.4, 36.2, 34.1, 32.9, 32.56, 30.9, 27.9, 26.9, 25.4, 21.0, 20.2, 16.9, 15.5, 14.6; IR (NaCl): cm^{-1} 3461.9, 2919.9, 2331.8, 1733.5, 1447.1, 1247.7; HRMS (ESI) m/z calcd for $C_{43}H_{58}O_5$ $[M - H_2O]^+$ 654.4284, found 654.4279 ± 0.0019. Analytical data of diastereomer **23A**: $[\alpha]_D^{20}$ +19.2 (c = 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.43−7.15 (m, 10H), 4.73−4.58 (m, 1H), 4.54−4.38 (m, 3H), 4.34−4.18 (m, 1H), 4.01−3.78 (m, 3H), 3.74−3.50 (m, 2H), 2.54−2.35 (m, 1H), 2.04 (s, 3H), 2.18−1.93 (m, 2H), 1.90−1.69 (m, 5H), 1.60−0.0.81 (m, 16H), 1.39 (s, 3H), 1.15 (s, 3H), 1.01 (s, 3H), 0.93 (d, 3H, J = 6.58 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.3, 139.4, 139.11, 128.3, 128.1, 127.4, 127.3, 127.0, 92.3, 81.4, 81.3, 75.1, 73.2, 72.1, 70.2, 69.6, 69.3, 59.3, 58.2, 40.9, 40.4, 36.1, 32.7, 32.5, 32.4, 31.9, 31.3, 30.9, 27.9, 25.4, 21.2, 20.9, 18.0, 16.9, 14.5; IR (NaCl): cm^{-1} 3461.6, 2930.1, 1738.6, 1467.6, 1247.7; HRMS (ESI) m/z calcd for $C_{43}H_{58}O_5$ $[M - H_2O]^+$ 654.4284, found 654.4292 ± 0.0019.

Exocyclic Olefins 24 and 24A: The alcohol **23** (350 mg, 0.52 mmol) was dissolved in anhydrous pyridine (4.5 mL) and cooled to 0 °C. To this stirring solution was added $SOCl_2$ (0.432 mL, 5.2 mmol) dropwise over 10 min. After stirring for 10 min, the ice bath was removed, and the solution was stirred for 45 min. After completion of the reaction, the contents were slowly and cautiously poured into ice, and water (2.0 mL) and Et_2O (5.0 mL) were added. The solution was extracted with Et_2O, washed with water and brine solution, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the crude product by Al_2O_3 (neutral) column chromatography (10% EtOAc/hexanes) afforded the exocyclic olefin **24** (260 mg, R_f = 0.52 (SiO_2, 15% EtOAc/hexanes)) and enolether **21** (28.9 mg, R_f = 0.55 (SiO_2, 15% EtOAc/hexanes) in a 9:1 ratio, 85%) as colorless viscous liquids. Analytical data for **24**: $[\alpha]_D^{20}$ −15.2 (c = 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.41−7.18 (m, 10H), 4.96−4.82 (m, 2H), 4.65 (Abq, 1H, J = 11.52 Hz), 4.60−4.38 (m, 4H), 4.21 (Abq, 1H, J = 11.52 Hz), 4.01−3.79 (m, 3H), 3.61 (s, 1H), 2.54−2.33 (m, 2H), 2.05 (s, 3H), 2.20−1.90 (m, 2H), 1.88−1.71 (m, 3H), 1.68−0.84 (m, 20), 0.99 (s, 3H), 0.93 (d, 3H, J = 6.58 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.3, 153.4, 139.4, 139.0, 128.3, 128.1, 127.5, 127.4, 127.3, 127.0, 104.8, 84.6, 82.8, 75.2, 73.2, 70.1, 69.6, 69.3, 62.1, 58.4, 58.1, 42.9, 40.5, 39.5, 36.2, 33.9, 33.6, 32.7, 32.6, 31.9, 29.7, 29.3, 27.9, 25.4, 21.0, 17.0, 15.7, 14.6; IR (NaCl): cm^{-1} 2978.3, 1739.1; HRMS (ESI) m/z calcd for $C_{43}H_{58}O_5$ $[M]^+$ 654.4284, found 654.4292 ± 0.0019. The procedure described above for the preparation of compound **24** was employed as such for the preparation of **24A** from **23A**. Analytical data of **24A**: $[\alpha]_D^{20}$ +15.8 (c = 0.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.42−7.17 (m, 10H), 4.93−4.79 (m, 2H), 4.66 (ABq, 1H, J = 10.97 Hz), 4.56−4.32 (m, 3H), 4.22 (ABq, 1H, J = 10.97 Hz), 4.22−4.14 (m, 1H), 4.01−3.80 (m, 3H), 3.60 (s, 1H), 2.57−2.33 (m, 2H), 2.04 (s, 3H), 2.22−1.92 (m, 2H), 1.88−1.71 (m, 3H), 1.69−0.81 (m, 17H), 0.96 (s, 3H), 0.99 (s, 3H), 0.93 (d, 3H, J = 6.58 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.3, 152.9, 139.4, 139.1, 128.3, 128.1, 127.4, 127.3, 126.9, 104.2, 84.1, 82.7, 76.2, 73.2, 70.0, 69.6, 69.4, 61.8, 58.8, 58.3, 42.6, 40.5, 39.9, 36.2, 32.8, 32.7, 32.6, 32.6, 31.9, 30.4, 30.2, 27.9, 25.4, 21.0, 17.0, 16.7, 14.6; IR (NaCl): cm^{-1} 2919.9, 1753.5, 1452, 1242.6, 1063.6; HRMS (ESI) m/z calcd for $C_{43}H_{58}O_5$ $[M]^+$ 654.4284, found 654.4279 ± 0.0019.

Diols 26 and 26A: To a stirred solution of olefin **24** (250 mg, 0.381 mmol) in THF/water (3:1, 4.0 mL) wase added 4-methylmorpholine-*N*-oxide (105 mg, 0.894 mmol), followed by a solution of OsO_4 in H_2O (4% in H_2O, 0.56 mL, 0.0025 mmol). The resulting mixture was stirred for 12 h at rt. After the complete conversion, THF was removed under reduced pressure. To this crude diol was added EtOH/H_2O (5:1, 5 mL), and the mixture was cooled to −10 °C. $NaIO_4$ (383 mg, 1.788 mmol) was then added, and the mixture was stirred for 30 min at 0 °C and 15 min at rt. EtOH was then removed under reduced pressure, and water (2.5 mL) and brine solution (2.5 mL) were added. The mixture was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, and concentrated. To this crude ketone **25** in anhydrous THF (4.0 mL) was added methyl magnesium bromide solution (3.0 M in THF, 0.761 mL, 2.28 mmol) dropwise at −10 °C. The mixture was then slowly allowed to warm to 0 °C, stirred for 30 min, quenched with aqueous NH_4Cl solution (2 mL) at 0 °C, extracted with EtOAc (5 mL), washed with brine solution, dried over anhydrous Na_2SO_4, and filtered, and solvents were removed under reduced pressure. Purification of the crude product by silica gel column chromatography (40 → 60% EtOAc/hexanes) afforded the diol **26** (132.5 mg, 55% for three steps). R_f = 0.30 (SiO_2, 50% EtOAc/hexanes); $[\alpha]_D^{20}$ +14.2 (c = 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.40−7.18 (m, 10H), 4.67 (ABq, 1H, J = 11.52 Hz), 4.57−4.40 (m, 3H), 4.22 (ABq, 1H, J = 11.52 Hz), 4.01−3.85 (m, 2H), 3.61 (s, 1H), 3.53−3.36 (m, 2H), 2.64−2.52 (m, 1H), 2.17−1.88 (m, 2H), 1.87−1.65 (m, 6H), 1.66−0.78 (m, 18H), 1.27 (s, 3H), 1.01 (s, 3H), 0.92 (d, 3H, J = 6.58 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 139.4, 139.1, 128.3, 128.1, 127.5, 127.4, 127.3, 127.0, 85.8, 81.9, 80.5, 75.1, 73.2, 70.1, 69.6, 68.0, 67.3, 58.3, 57.7, 42.3, 40.8, 40.5, 36.2, 36.0, 34.9, 32.7, 32.2, 30.7, 30.4, 28.2, 27.9, 26.2, 25.4, 16.7, 16.2, 14.5; IR (NaCl): cm^{-1} 3405.7, 2919.9, 2853.4, 1452.3, 1094.3, 1063.6; HRMS (ESI) m/z calcd for $C_{40}H_{55}O_5$ $[M - CH_3]^+$ 615.4049, found 615.4061 ± 0.0018. The procedure described above for the preparation of compound **26** was employed as such for the preparation of **26A** from **24A**. Analytical data of **26A**: $[\alpha]_D^{20}$ +18.8 (c = 0.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48−7.12 (m, 10H), 4.76−4.56 (m, 1H), 4.56−4.33 (m, 2H), 4.31−4.02 (m, 2H), 3.98−3.76 (m, 1H), 3.69−3.25 (m, 4H), 2.69−2.41 (m, 1H), 2.23−1.94 (m, 4H),

1.92−0.68 (m, 19H), 1.34 (s, 3H), 1.27 (s, 3H), 1.01 (s, 3H), 0.91 (d, 3H, J = 6.58 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 139.4, 139.1, 128.3, 128.1, 127.4, 127.7, 126.9, 90.1, 81.9, 80.4, 74.9, 73.1, 70.0, 69., 68.9, 67.8, 59.1, 58.2, 42.2, 40.9, 40.4, 36.0, 35.6, 32.6, 32.4, 31.9, 31.1, 30.9, 30.0, 27.9, 26.2, 25.3, 18.5, 16.7, 14.5; IR (NaCl): cm^{-1} 3400.6, 2919.9, 2858.5, 1452.3, 1094.3, 1068.8; HRMS (ESI) m/z calcd for $C_{40}H_{55}O_5$ $[M - CH_3]^+$ 615.4049, found 615.4061 ± 0.0018.

Iodide S5 and S5-A: To the diol **26** (110 mg, 0.17 mmol) in anhydrous CH_2Cl_2 (2.5 mL) under an argon atmosphere was added triphenylphosphine (228 mg, 0.87 mmol) and imidazole (81 mg, 1.19 mmol), followed by iodine (129.5 mg, 0.51 mmol) at 0 °C. The reaction mixture was allowed to stir for 1.5 h at room temperature, and then it was quenched with aqueous $Na_2S_2O_3$ (5.0 mL) solution. It was then extracted with CH_2Cl_2 (5 mL) and washed with water and brine solution. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (12% EtOAc/hexanes) afforded iodide **S5** (98.15 mg, 76%). R_f = 0.50 (SiO_2, 20% EtOAc/hexanes); $[\alpha]_D^{20}$ +6.8 (c = 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.43−7.18 (m, 10H), 4.67 (ABq, 1H, J = 11.52 Hz), 4.57−4.37 (m, 3H), 4.22 (ABq, 1H, J = 11.52 Hz), 3.98−3.83 (m, 2H), 3.61 (s, 1H), 3.31−3.19 (m, 1H), 3.18−3.04 (m, 1H), 2.65−2.47 (m, 1H), 2.17−1.88 (m, 2H), 1.87−1.64 (m, 3H), 1.63−0.75 (m, 21H), 1.27 (s, 3H), 1.01 (s, 3H), 0.99 (d, 3H, J = 6.58 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 139.4, 139.0, 128.3, 128.1, 127.5, 127.8, 127.3, 127.0, 85.5, 81.9, 80.6, 75.1, 73.2, 70.1, 69.6, 67.3, 58.3, 57.7, 42.3, 40.9, 40.5, 36.2, 35.2, 34.9, 33.8, 32.7, 32.5, 30.7, 28.2, 27.9, 26.3, 25.4, 20.5, 17.5, 16.3, 14.5; IR (NaCl): cm^{-1} 3446.6, 2914.8, 2858.6, 1457.4, 1094.3, 1063.6; HRMS (ESI) m/z calcd for $C_{41}H_{57}IO_4$ $[M]^+$ 740.3301, found 740.3289 ± 0.0022. The procedure described above for the preparation of compound **S5** was employed as such for the preparation of **S5-A** from **26A**. Analytical data of **S5-A**: $[\alpha]_D^{20}$ +12.2 (c = 0.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.42−7.19 (m, 10H), 4.70 (ABq, 1H, J = 12.07 Hz), 4.53−4.39 (m, 2H), 4.24 (ABq, 1H, J = 12.07 Hz), 4.22−4.12 (m, 1H), 3.91 (s, 1H), 3.61 (s, 1H), 3.46−3.32 (m, 1H), 3.31−3.11 (m, 2H), 2.66−2.51 (m, 1H), 2.19−1.96 (m, 2H), 1.87−1.64 (m, 4H), 1.63−0.84 (m, 20H), 1.34 (s, 3H), 1.01 (s, 3H), 0.98 (d, 3H, J = 6.58 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 139.4, 139.1, 128.29, 128.1, 127.3, 127.3, 126.9, 89.9, 82.0, 80.4, 74.9, 73.2, 70.0, 69.6, 68.8, 59.1, 58.2, 42.2, 40.9, 40.4, 36.1, 34.9, 33.7, 32.7, 32.6, 32.4,31.9, 31.1, 30.9, 27.9, 26.6, 25.4, 20.6, 18.6, 17.8, 14.5; IR (NaCl): cm^{-1} 3477.3, 2930.1, 2853.4, 1452.3, 1089.2, 1063.6; HRMS (ESI) m/z calcd for $C_{41}H_{57}IO_4$ $[M]^+$ 740.3301, found 740.3289 ± 0.0022.

Terminal Olefins 27 and 27A: To a solution of iodide **S5** (75 mg, 0.10 mmol) in anhydrous DMF (1.5 mL) was added DBU (76.6 μL, 0.30 mmol), and the mixture was heated at 85 °C for 4.5 h. After completion of the reaction, water and EtOAc were added and the mixture was extracted with EtOAc, dried over anhydrous Na_2SO_4, and concentrated under vacuum. Purification of the crude product by flash chromatography (5% EtOAc/hexanes) using silica gel afforded the olefin **27** (57 mg, 92%) as a colorless liquid. R_f = 0.53 (SiO_2, 20% EtOAc/hexanes); $[\alpha]_D^{20}$ +12.5 (c = 0.42, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.42−7.17 (m, 10H), 4.76−4.61 (m, 3H), 4.57−4.40 (m, 3H), 4.30−4.18 (m, 1H), 4.01−3.86 (m, 2H), 3.61 (s, 1H), 2.65−2.53 (m, 1H), 2.27−1.91 (m, 4H), 1.86−1.68 (m, 3H), 1.72 (s, 3H), 1.66−0.80 (m, 18H), 1.28 (s, 3H), 1.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 145.9, 139.4, 139.1, 128.3, 128.1, 127.5, 127.4, 127.2, 127.0, 109.7, 85.2, 81.9, 80.6, 75.1, 73.2, 70.2, 69.6, 67.3, 58.3, 57.7, 42.3, 40.9, 40.5, 36.2, 35.1, 34.9, 32.7, 32.6, 32.5, 30.8, 29.1, 27.9, 26.3, 25.4, 22.6, 16.2, 14.5; IR (NaCl): cm^{-1} 3446.6, 2925, 2858.6, 1457.4, 1089, 1058; HRMS (ESI) m/z calcd for $C_{41}H_{56}O_4$ $[M]^+$ 612.4178, found 612.4188 ± 0.0018. The procedure described above for the preparation of compound **27** was employed as such for the preparation of **27A** from **S5-A**. Analytical data of **27A**: $[\alpha]_D^{20}$ +16.8 (c = 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.45−7.19 (m, 10H), 4.79−4.63 (m, 3H), 4.58−4.41 (m, 2H), 4.31−4.12 (m, 2H), 3.91 (s, 1H), 3.61 (s, 1H), 3.51−3.35 (m, 1H), 2.68−2.51 (m, 1H), 2.28−1.95 (m, 4H), 1.89−1.67 (m, 3H), 1.72 (s, 3H), 1.66−0.74 (m, 18H), 1.34 (s, 3H), 1.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 145.8, 139.4, 139.0, 128.3, 128.1, 127.4, 127.3, 126.9, 109.7, 89.5, 81.9, 80.5, 74.9, 73.2, 70.0, 69.6, 68.9, 59.2, 58.2, 42.2, 40.9, 40.4, 36.1, 34.7, 32.7, 32.6, 32.5, 31.9, 30.9, 27.9, 27.2, 25.4, 22.7, 18.6, 14.5; IR (NaCl): cm^{-1} 3448.6, 2930, 2858.6, 1457.4, 1094, 1063; HRMS (ESI) m/z calcd for $C_{41}H_{56}O_4$ $[M]^+$ 612.4178, found 612.4188 ± 0.0018.

Diols 28 and 28A: The procedure used here is the same as that described for the conversion of **14** to **15**. Purification by flash chromatography (35/45% EtOAc/hexanes) using silica gel gave the alcohol **28** (31.5 mg, 68%) as a colorless viscous liquid. R_f = 0.35 (SiO_2, 50% EtOAc/hexanes); $[\alpha]_D^{20}$ +18.6 (c = 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.43−7.17 (m, 10H), 4.67 (ABq, 1H, J = 11.52 Hz), 4.55−4.42 (m, 3H), 4.22 (ABq, 1H, J = 11.52 Hz), 4.02−3.86 (m, 2H), 3.61 (s, 1H), 3.47 (brs, 1H), 2.63−2.53 (m, 1H), 2.16−1.88 (m, 3H), 1.86−1.68 (m, 4H), 1.67−0.79 (m, 18H), 1.29 (s, 3H), 1.25 (s, 3H), 1.21 (s, 3H), 1.01 (s, 3H); IR (NaCl): cm^{-1} 3410.8, 2930.1, 2848.3, 1447.2, 1094.3, 1058.5; HRMS (ESI) m/z calcd for $C_{40}H_{55}O_5$ $[M - CH_3]^+$ 615.4049, found 615.4061 ± 0.0018. The procedure described above for the preparation of compound **28** was employed as such for the preparation of **28A** from **27A**. Analytical data of **28A**: $[\alpha]_D^{20}$ +21.6 (c = 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.42−7.18 (m, 10H), 4.69 (ABq, 1H, J = 11.52 Hz), 4.54−4.42 (m, 2H), 4.24 (ABq, 1H, J = 11.52 Hz), 4.23−4.16 (m, 1H), 3.90 (s, 1H), 3.60 (s, 1H), 3.46−3.38 (m, 1H), 2.64−2.54 (m, 1H), 2.13−1.99 (m, 3H), 1.84−0.79 (m, 19H), 1.36 (s, 3H), 1.34 (s, 3H), 1.21 (s, 6H), 1.01 (s, 3H); IR (NaCl): cm^{-1} 3410, 2930, 2844, 1446, 1094.1, 10582; HRMS (ESI) m/z calcd for $C_{40}H_{55}O_5$ $[M - CH_3]^+$ 615.4049, found 615.4061 ± 0.0018. ^{13}C NMR for compounds **28** and **28A** was not analyzed; both of these C22 diastereomers were used as such in subsequent transformations.

Ketone 29: To a well-stirred solution of compound **20** (500 mg, 0.81 mmol) in glacial acetic acid (8.5 mL) was added $BF_3 \cdot Et_2O$ (0.640 mL, 4.86 mmol) slowly dropwise, and the mixture was stirred for 5 min at room temperature. $NaNO_2$ (619 mg, 8.91 mmol) was then added in small portions over an hour. The stirring was maintained for 1 additional hour. The mixture was poured into cool water and extracted with CH_2C1_2 (2 × 30 mL). The organic layer was washed with water (2 × 10 mL), 5% NaOH (2 × 10 mL), and water (3 × 10 mL) and dried over anhydrous Na_2S0_4, and the solvent was evaporated under vacuum. The syrupy crude product was dissolved in benzene/hexanes (10 mL, 3:2) and allowed to stand in a chromatographic column packed with Brockmann activity-III (Al_2O_3 with 6.0 wt % of H_2O) before slow elution with 5−10% EtOAc/hexane. Evaporation of the solvent afforded the ketone **29** (51 mg, 10%) as a viscous liquid. R_f = 0.50 (SiO_2, 10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.44−7.20 (m, 10H), 4.62−4.57 (m, 1H), 4.55−4.50 (m, 2H), 4.27−4.15 (m, 1H), 3.90 (s, 1H), 3.85−3.72 (m, 1H), 3.62 (s, 1H), 3.59−3.52 (m, 1H), 2.97−2.83 (m, 1H), 2.49−2.51 (m, 2H), 2.38−2.19 (m, 2H), 2.13−1.94 (m, 2H), 1.88−1.66 (m, 4H), 1.64−0.72 (m, 14H), 0.94 (d, 3H, J = 6.58 Hz), 0.99 (s, 6H), 1.01 (s, 3H); IR (NaCl): cm^{-1} 2918.3, 2839, 1732; HRMS (ESI) m/z calcd for $C_{41}H_{55}O_5$ $[M + H]^+$ 627.4044, found 627.4052 (Diff(ppm) = 1.28).

Ketone 29a: The procedure described above for the preparation of the ketone **29** was employed as such in this reaction. The dibenzoate **12a** (620 mg, 0.96 mmol) was treated with $BF_3 \cdot Et_2O$ (0.785 mL, 5.76 mmol), followed by $NaNO_2$ (733 mg, 10.56 mmol), to afford the ketone **29a** (410 mg) in 65% yield. R_f = 0.45 (SiO_2, 15% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.13−7.95 (m, 4H), 7.62−7.38 (m, 6H), 5.66 (brs, 1H), 5.23 (brs,

1H), 4.73−4.54 (m, 1H), 3.86−3.68 (m, 1H), 3.64−3.49 (m, 1H), 2.92−2.74 (m, 1H), 2.46−2.35 (m, 2H), 2.33−2.01 (m, 4H), 1.97−0.75 (m, 16H), 0.98 (s, 3H), 0.96 (s, 3H), 0.91 (d, 3H, J = 6.58 Hz), 0.88 (d, 3H, J = 7.13 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 201.6, 165.9, 165.4, 132.9, 132.8, 131.0, 130.5, 129.72, 129.5, 128.5, 128.3, 109.9, 83.1, 70.3, 70.0, 65.6, 62.4, 57.6, 57.0, 45.2, 44.1, 41.3, 40.1, 35.9, 35.6, 34.7, 33.0, 32.3, 31.9, 31.6, 27.6, 25.9, 18.9, 17.1, 14.7, 14.3; IR (NaCl): cm^{-1} 2952, 2934, 1737, 1733, 1086, 1020; HRMS (ESI) m/z calcd for $C_{41}H_{51}O_7$ $[M + H]^+$ 655.3635, found 655.3648 ± 0.0020.

Methylated Ketone 30: To a solution of Li-HMDS (1.0 M in THF, 1.60 mL, 1.60 mmol) in THF at −78 °C was added a solution of ketone **29a** (350 mg, 0.53 mmol) slowly over 15 min, and the resulting mixture was stirred at −78 °C for 45 min. CH_3I (100 μL, 1.60 mmol) was added to the reaction mixture, and the resulting solution was stirred at −78 °C for 20 min and at room temperature for 2 h. The reaction mixture was quenched by addition of saturated NH_4Cl and extracted with Et_2O. Combined extracts were concentrated in vacuum. Purification of the crude product by silica gel column chromatography (8% EtOAc/hexanes) afforded the methylated compound **30** (equatorial/axial isomers in a 2:1 ratio, 304 mg, 85%) as a viscous liquid. R_f = 0.55 (SiO_2, 10% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.11−8.01 (m, 4H), 7.63−7.39 (m, 6H), 5.69−5.63 (m, 1H), 5.27−5.21 (m, 1H), 4.69−4.54 (m, 1H), 3.90−3.73 (m, 1H), 3.65−3.49 (m, 1H), 2.87−2.36 (m, 2H), 2.28−2.01 (m, 3H), 1.96−0.76 (m, 32H). ^{13}C NMR of this compound was not analyzed due to the diastereomeric mixture (equatorial/axial isomers). IR (NaCl): cm^{-1} 2956, 2932, 1736, 1734, 1086; HRMS (ESI) m/z calcd for $C_{42}H_{53}O_7$ $[M + H]^+$ 669.3791, found 669.3798 ± 0.0020.

Ketone S6: To a well-stirred solution of NaOMe (198 mg, 3.74 mmol) in MeOH was added a solution of the ketone **30** (250 mg, 0.37 mmol) in MeOH at room temperature, and the mixture was allowed to stir for 45 min. After the completion of the reaction, the solvent was removed under reduced pressure and the residue was diluted with ether and water at 0 °C and extracted with Et_2O. The combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. Purification of the analytical sample by silica gel column chromatography (30% EtOAc/hexanes) afforded the isomerized product **S6** (194 mg, 92%) as a white solid. R_f = 0.45 (SiO_2, 40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.09−7.99 (m, 2H), 7.62−7.38 (m, 3H), 5.69−5.60 (m, 1H), 4.71−4.56 (m, 1H), 4.01 (s, 1H), 3.85 (t, 1H, J = 11.52 Hz), 3.53 (dd, 1H, J = 11.52, 4.90 Hz), 2.80 (qt, 1H, J = 6.58 Hz), 2.58−2.45 (m, 1H), 2.23−2.04 (m, 3H), 1.85−1.80 (m, 2H), 1.79−1.66 (m, 2H), 1.65−0.79 (m, 16H), 0.88 (s, 3H), 1.02 (d, 3H, J = 6.58 Hz), 0.97 (d, 3H, J = 6.58 Hz), 0.91 (s, 3H). Only the analytical sample was purified due to the formation of byproducts (due to 3 and 11-OBz groups deprotection), hence ^{13}C NMR was not analyzed. IR (NaCl): cm^{-1} 3521, 2952, 2928, 1736, 1734; HRMS (ESI) m/z calcd for $C_{35}H_{48}O_6[M]^+$ 564.3468, found 564.3468 ± 0.0018.

Triacetate 31: A mixture of ketone **S6** (45 mg, 0.079 mmol) and hydrazine hydrate (60 μL, 1.19 mmol) and powdered KOH (100 mg, 1.99 mmol) in ethylene glycol (2 mL) was heated at 180 °C for 4 h. After cooling to room temperature, water was added, and the mixture was extracted with CH_2Cl_2, washed with brine solution, and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The crude product was dissolved in anhydrous pyridine and treated with Ac_2O, followed by DMAP. The resulting reaction mixture was allowed to stir at room temperature for 24 h. It was then diluted with water, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, and concentrated under vacuum. Purification of the crude product by Al_2O_3 (neutral) column chromatography (12% EtOAc/hexanes) afforded the triacetate **31** (31.8 mg, 68% for two steps). R_f = 0.45 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.29 (s, 1H), 4.99 (s, 1H), 4.91 (d, 1H, J = 2.19 Hz), 4.54−4.43 (m, 1H), 3.52 (dd, 1H, J = 10.97, 4.94 Hz), 3.43 (t, 1H, J = 10.97 Hz), 2.12 (s, 3H), 2.04 (s, 3H), 2.01 (s, 3H), 2.16−1.94 (m, 4H), 1.89−0.71 (m, 18H), 0.97 (d, 3H, J = 7.13 Hz), 0.91 (s, 3H), 1.89 (s, 3H), 0.83 (d, 3H, J = 6.03 Hz), 0.77 (d, 3H, J = 6.58 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.8, 170.6, 170.1, 109.4, 108.4, 81.2, 74.6, 69.7, 69.5, 66.4, 64.5, 57.6, 56.6, 52.3, 43.8, 40.9, 40.0, 39.9, 36.5, 35.7, 32.7, 32.2, 31.7, 31.0, 27.6, 26.5, 25.7, 21.9, 21.5, 20.9, 18.4, 15.9, 14.2, 14.1, 13.9; IR (NaCl): cm^{-1} 2956, 2931, 1738, 1241, 1091, 1051, 1025; HRMS (ESI) m/z calcd for $C_{34}H_{52}O_8$ $[M]^+$ 588.3712, found 588.3712 ± 0.0012.

Acyloxy Ketone 39: The cyclic enol ether **21** (400 mg, 0.610 mmol) was dissolved in AcOH (2.5 mL) and cooled to 10 °C. To this stirring solution was added CrO_3 solution (1.4 M in 9:1 Ac_2O/H_2O, 0.760 mL, 1.067 mmol) dropwise over 10 min and NaOAc (87.6 mg, 1.067 mmol). After stirring for 30 min, the ice bath was removed, water (2.0 mL) and Et_2O (5.0 mL) were added, and the mixture was extracted with Et_2O, washed with water and brine solution, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (20/30% EtOAc/hexanes) afforded compound **39** (314 mg, 75%) as a colorless viscous liquid. R_f = 0.71 (SiO_2, 40% EtOAc/hexanes); $[\alpha]_D^{20}$ +40.6 (c = 2.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48−7.09 (m, 10H), 5.59−5.37 (m, 1H), 4.78−4.62 (m, 1H), 4.48 (q, 2H, J = 12.07 Hz), 4.27−4.17 (m, 1H) 4.01−3.78 (m, 3H), 3.61 (br s, 1H), 2.72−2.57 (m, 1H), 2.56−2.13 (m, 4H), 2.07 (s, 3H), 2.04 (s, 3H), 2.12−0.74 (m, 19H), 1.25 (s, 3H), 0.99 (s, 3H), 0.92 (d, 3H, J = 6.58 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 205.5, 173.0, 171.2, 139.4, 138.9, 128.3, 128.1, 127.7, 127.4, 127.3, 127.0, 74.7, 74.2, 73.1, 70.2, 69.6, 68.8, 67.2, 58.5, 55.8, 42.1, 40.4, 39.0, 36.1, 34.9, 32.5, 32.3, 32.0, 31.9, 30.8, 30.6, 28.3, 27.8, 25.3, 20.9, 16.3, 15.1, 14.5; IR (NaCl): cm^{-1} 2927.3, 2850.1, 1736.4, 1709.1, 1450, 1231.8, 1063.6; HRMS (ESI) m/z calcd for $C_{36}H_{52}O_7$ $[M - C_7H_6]^+$ 596.3713, found 596.3716 ± 0.0018.

Diol 41: In a flame-dried, two-neck, round-bottom flask under an argon atmosphere was placed keto-diester **39** (300 mg, 0.436 mmol) in anhydrous THF (2.0 mL). Vinylmagnesium bromide solution (1.0 M in THF, 4.36 mL, 4.360 mmol) was added dropwise at ambient temperature. After 30 min, the reaction was quenched with aqueous NH_4Cl solution (2 mL) at 0 °C. The mixture was extracted with EtOAc (5 mL), washed with brine solution, dried over anhydrous Na_2SO_4, and filtered. The solvents were removed under reduced pressure. Purification of the crude product by silica gel column chromatography (10/20% EtOAc/hexanes) afforded a C20-diastereomeric mixture of allylalcohol (major/minor (8:2), 224 mg, 92%). The major diastereomer **41** had a slightly higher R_f value (TLC) than that of the minor diasteromer, and it was only separated partially from the minor isomer. Major diastereomer: R_f = 0.70 (SiO_2, 40% EtOAc/hexanes); $[\alpha]_D^{20}$ +25.4 (c = 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.42−7.22 (m, 10H), 6.10 (dd, 1H, J = 17.01, 10.42 Hz), 5.33 (dd, 1H, J = 17.01, 1.64 Hz), 5.03 (dd, 1H, J = 10.42, 1.64 Hz), 4.76−4.19 (ABq, 2H, J = 10.97 Hz), 4.55−4.42 (m, 3H), 3.92 (br s, 1H), 3.62 (br s, 1H), 2.94 (br s, 1H), 2.75−2.65 (m, 1H), 2.28−2.15 (m, 1H), 2.05−1.89 (m, 1H), 1.88−1.71 (m, 2H), 1.61−0.72 (m, 17H), 1.38 (s, 3H), 0.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 148.1, 139.4, 139.0, 128.3, 128.1, 127.7, 127.4, 127.3, 127.1, 110.4, 76.5, 75.4, 74.5, 73.3, 70.4, 69.6, 61.6, 58.5, 55.9, 43.0, 41.5, 40.5, 36.2, 32.5, 32.4, 30.8, 28.4, 27.9, 25.3, 16.7, 14.5; IR (NaCl): cm^{-1} 3339.2, 2919.9, 2853.4, 1355.1, 1094.9, 1063.6, 910.23, 731.25; HRMS (ESI) m/z calcd for $C_{37}H_{48}O_3$ $[M - H_2O]^+$ 540.3603, found 540.3604 ± 0.0016.

Hydroxy Ketone 37: To a stirred solution of olefin **41** (250 mg, 0.447 mmol) in THF/water (3:1, 3.0 mL) was added 4-methylmorpholine-*N*-oxide (105 mg, 0.894 mmol), followed by a solution of OsO_4 in H_2O (4% in H_2O, 0.59 mL, 0.003 mmol). The resulting mixture was stirred for 12 h at rt. After the complete conversion, THF was removed under reduced pressure.

To this crude tetrol was added EtOH/H_2O (5:1), and the mixture was cooled to 0 °C. $NaIO_4$ (383 mg, 1.788 mmol) was then added, and the mixture was stirred for 30 min at 0 °C and 15 min at rt. Water (2.5 mL) and brine solution (2.5 mL) were then added, and the mixture was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, and concentrated. Purification of the crude product by silica gel column chromatography (20/30% EtOAc/hexanes) afforded the β-hydroxy ketone **37** (132 mg, 56%) as a white solid. R_f = 0.52 (SiO_2, 40% EtOAc/hexanes); mp 156−158 °C; $[\alpha]_D^{20}$ +52.5 (c = 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.40−7.25 (m, 10H), 4.68−4.28 (q, 2H, J = 11.3 Hz), 4.50 (q, 2H, J = 11.10 Hz), 4.62−4.50 (m, 1H), 3.99 (m, 1H), 3.62 (m, 1H), 2.56−2.51 (m, 1H), 2.40−0.79 (m, 18H), 2.21 (s, 3H), 1.12 (s, 3H), 1.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 213.3, 139.4, 138.8, 128.3, 128.2, 127.7, 127.4, 127.3, 127.2, 75.2, 73.2, 72.2, 70.6, 69.7, 66.5, 58.5, 55.5, 43.8, 40.5, 40.3, 36.9, 36.2, 32.7, 32.5, 32.4, 31.4, 27.9, 25.4, 16.5, 14.6; IR (NaCl): cm^{-1} 3606.3, 3495.1, 2930.1, 2854.5, 1713.1, 1681.3, 1450, 1363.1; HRMS (ESI) m/z calcd for $C_{35}H_{46}O_4$ $[M]^+$ 530.3396, found 530.3408 ± 0.0016.

Enone 40: Compound **39** (300 mg, 0.43 mmol) was dissolved in benzene (10 mL). To this mixture was added Al_2O_3 (basic, 1.0 g), and it was stirred at rt for 2.5 h. After completion of the reaction, the contents were filtered using Celite and washed with CH_2Cl_2. The solvents were removed under reduced pressure. Purification by silica gel column chromatography (10% EtOAc/hexanes) afforded the enone **40** (212 mg, 95%) as a colorless oil. R_f = 0.55 (SiO_2, 20% EtOAc/hexanes); $[\alpha]_D^{20}$ +95.6 (c = 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.39−7.27 (m, 10H), 6.69 (m, 1H), 4.81−4.22 (q, 2H, J = 11.4 Hz), 4.26 (q, 2H, J = 11.1 Hz), 3.98 (m, 1H), 3.63 (m, 1H), 3.01 (m, 1H), 2.26 (s, 3H), 2.3−0.8 (m, 17 H), 1.16 (s, 3H), 1.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 196.8, 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 calcd for $C_{35}H_{44}O_3$ $[M]^+$ 512.3290, found 512.3291 ± 0.0015.

α-Bromo Ketone S7: The enone **40** (210 mg, 0.41 mmol) was dissolved in acetone (5 mL), THF (1 mL), and H_2O (0.5 mL), and NBA (*N*-bromoacetamide, 169.78 mg, 1.23 mmol) was added at room temperature. The mixture was stirred for 18 h in the dark, and another portion of NBA (113.14 mg, 0.82 mmol) was added. The stirring continued for an additional 10 h, and the mixture was diluted with EtOAc (25 mL). The organic layer was washed with saturated Na_2SO_3 and brine solution, dried over anhydrous Na_2SO_4, and filtered, and then the solvent was removed under vacuum. The crude product was purified by silica gel column chromatography (10% EtOAc/hexanes) to afford the α-bromo ketone **S7** (141 mg, 56.5%) as a viscous liquid. R_f = 0.60 (SiO_2, 30% EtOAc/hexanes); $[\alpha]_D^{20}$ +17.4 (c = 0.35, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36−7.25 (m, 10H), 4.95 (m, 1H), 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), 2.40 (s, 3H), 2.39−1.0 (m, 19 H), 1.37 (s, 3H), 1.01 (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} 36.05, 3517, 2940.9, 2859.1, 1702, 1693.2, 1454, 1359, 1270; HRMS (ESI) m/z calcd for $C_{35}H_{45}O_4Br$ $[M - OBr]^+$ 513.3368, found 513.3365 ± 0.0015.

Compound 37: To a solution of bromide **S7** (125 mg, 0.20 mmol) in anhydrous CH_2Cl_2 (2.5 mL) was added Bu_3SnH (0.543 mL, 2.05 mmol), followed by Et_3B (1 M in hexane, 0.2 mL, 0.4 mmol) and air with an empty syringe (1 mL). The reaction was allowed to stir for 35 min at rt and then concentrated. The resulting residue was purified by silica gel column chromatography (25/30% EtOAc/hexanes) to afford the **37** (100 mg, 92%) as a white solid. R_f = 0.35 (SiO_2, 30% EtOAc/hexanes). Analytical data were in good agreement with the literature, and a copy of the ^{1}H NMR spectrum is provided in the Supporting Information to demonstrate the purity.

24-Desmethylhippuristanol 3 and 24-desmethyl-22-*epi*-hippuristanol 4 via Suarez Cyclization: To a mixture of **Iodine** (23.9 mg, 0.095 mmol), and iodobenzene diacetate (30.6 mg, 0.095 mmol) in hexanes (1 mL) was added a solution of **28, 28A** (30 mg, 0.047 mmol) in CH_2Cl_2 (1 mL). After 2 h, the reaction solution was quenched by addition of a saturated aqueous sodium thiosulfate solution (2 mL), and the resulting mixture was stirred until clear. The aqueous layer was extracted with ethyl acetate (3 × 2 mL), and the combined organic layers were dried over Na_2SO_4. Solids were removed by filtration, and the solvent was removed under reduced pressure. To the crude material was added to Li (metal) (5.64 mg, 0.94 mmol) in liquid ammonia at −35 °C in anhydrous THF. After 30 min of stirring at −35 °C, the mixture was quenched with solid NH_4Cl, and then excess NH_3 was evaporated using a constant air flow. The material was diluted with water, extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (15/20% acetone/hexanes) using silica gel afforded 22-*epi*-24-desmethylhippuristanol **4** (9.95 mg, R_f = 0.36 (SiO_2, 30% acetone/hexanes)) and 24-desmethylhippuristanol **3** (8.15 mg, R_f = 0.38 (SiO_2, 30% acetone/hexanes)) in 5.5:4.5 isolated (85% for two steps) ratios as white solids. Analytical data of 24-desmethyl-22-epi-hippuristanol **4**: $[\alpha]_D^{20}$ −36.8 (c = 0.65, $CHCl_3$/MeOH (1:1)); ^{1}H NMR ($CDCl_3$ + 5% CD_3OD, 300 MHz): δ 4.36 (dd, 1H, J = 12.62, 7.68 Hz), 4.22 (br s, 1H), 3.94 (br s, 1H), 2.20−2.04 (m, 2H), 2.04−0.76 (m, 20H), 1.26 (s, 3H), 1.24 (s, 3H), 1.23 (s, 3H), 1.10 (s, 3H), 0.95 (s, 3H), 0.71 (dd, 1H, J = 10.97, 2.74 Hz); ^{13}C NMR ($CDCl_3$ + 5% CD_3OD, 300 MHz): δ 120.9, 82.6, 82.2, 79.2, 67.74 66.2, 66.5, 58.3, 57.9, 48.3, 41.9, 39.8, 36.8, 36.1, 35.0, 32.3, 31.9, 31.6, 31.4, 30.2, 29.7, 28.3, 28.1, 27.4, 26.8, 19.2, 13.9; HRMS (ESI) m/z calcd for $C_{27}H_{45}O_5$ $[M + H]^+$ 449.3267, found 449.3273 ± 0.0013.Analytical data of 24-desmethylhippuristanol **3**: $[\alpha]_D^{20}$ +60.4 (c = 0.45, $CHCl_3$/MeOH (1:1)); ^{1}H NMR ($CDCl_3$ + 5% CD_3OD, 300 MHz): δ 4.32−4.16 (m, 2H), 3.96 (br s, 1H), 2.19−2.06 (m, 1H), 2.07−1.94 (m, 1H), 1.94−0.86 (m, 20H), 1.32 (s, 6H), 1.26 (s, 3H), 1.11 (s, 3H), 0.97 (s, 3H), 0.86−0.70 (m, 1H); ^{13}C NMR ($CDCl_3$ + 5% CD_3OD, 100 MHz): δ 116.4, 83.1, 80.6, 78.6, 68.12, 66.4, 66.3, 58.4, 57.4, 49.7, 42.3, 39.9, 37.2, 36.5, 35.4, 34.3, 33.8, 32.6, 31.8, 30.4, 30.3, 28.7, 28.4, 28.3, 27.9, 18.5, 14.1; HRMS (ESI) m/z calcd for $C_{27}H_{45}O_5$ $[M + H]^+$ 449.3267, found 449.3273 ± 0.0013.

Hydroxy Alkyne 44: To the terminal alkyne **43** (87.5 mg, 2.24 mL, 0.480 mmol) in anhydrous THF (1.5 mL) under argon was added *n*-butyllithium solution (1.6 M solution in hexane, 0.292 mL, 0.480 mmol) at −78 °C. The resultant mixture was stirred at −78 °C for 1 h, followed by the addition of ketone **37** (85 mg, 0.160 mmol) in anhydrous THF (1.2 mL). The resultant mixture was stirred at −78 °C for 2 h, then quenched with saturated aqueous NH_4Cl solution at −78 °C, 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 10/20% EtOAc/hexane) afforded the coupled product **44** (93.6 mg, 82%) as a viscous liquid. R_f = 0.65 (SiO_2, 40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) mixture of (OTHP) diastereomers: δ 7.43−7.20 (m, 10H), 4.94−4.75 (m, 1H), 4.74−4.60 (m, 2H), 4.60−4.41 (m, 2H), 4.25−4.17 (m, 1H), 4.03−3.85 (m, 2H), 3.61 (s, 1H), 3.52−3.39 (m, 1H), 2.73−2.57 (m, 1H), 2.52−0.75 (m, 29H), 1.31 (s, 6H), 1.27 (s, 3H), 0.98 (s, 3H). ^{13}C NMR was not analyzed; the diastereomeric (OTHP ether) mixture was used as such in the next step. IR (NaCl): cm^{-1} 3390, 2919.6, 2852.2, 1446, 1348, 1156.31, 1060. We could not obtain HRMS data for this

compound after several attempts. This may be due to the instability of the OTHP group; hence, the LRMS (low-resolution mass spectrum) is provided. LRMS (ESI-MS) m/z: $[M - H_2O]^+ = 696$.

24-Desmethylhippuristanol 3 and 24-desmethyl-22-*epi*-hippuristanol 4 via $Hg(OTf)_2$-Catalyzed Spiroketalization: To a stirred mixture of hydroxy alkyne **44** (60 mg, 0.084 mmol) and H_2O (4.54 mg, 0.252 mmol) in CH_3CN (1.5 mL) was added $Hg(OTf)_2$ (8.38 mg, 0.0168 mmol) at room temperature, and the mixture was stirred for 20 min at the same temperature. The reaction was quenched by the addition of Et_3N (40 μL). The resulting mixture was diluted with Et_2O (2 mL) and extracted with Et_2O, and the combined extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product **45** was subjected to Birch reduction. 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 (10.08 mg, 1.68 mmol) (washed with hexane) 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, and 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 a solution of crude dibenzylether was added slowly. A cautious addition is needed to ensure a regular and smooth ammonia reflux. The reaction mixture was then stirred at −33 °C for 1.5 h and NH_4Cl powder was carefully and slowly added 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 it was extracted 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*-24-desmethylhippuristanol **4** (25.04 mg) and 24-desmethylhippuristanol **3** (6.26 mg) (22*S*/22*R* in an 8:2 ratio, respectively, 83% for two steps) as white solids. Analytical data were in good agreement with the literature and with data obtained via Suarez cyclization, and a copy of the ^{1}H NMR spectrum is provided in the Supporting Information.

TBDPS Ether S8: To an ice-cold solution of diol **46** (500 mg, 4.231 mmol) and imidazole (576 mg, 8.462 mmol) in anhydrous CH_2Cl_2 (4.0 mL) was added TBDPS-Cl (1.30 mL, 5.077 mmol) in CH_2Cl_2 (1.0 mL). After stirring for 15 min at 0 °C, the reaction mixture was brought to room temperature, and the stirring was continued for 1 h. It was then quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by silica gel column chromatography (100% hexanes to 10% EtOAc/hexanes) to afford the pure primary monosilylether **S8** (1.417 g, 94%) as a viscous liquid. $R_f = 0.8$ (SiO_2, 40% EtOAc/hexanes); $[\alpha]_D^{20}$ +5.8 (c = 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.77−7.60 (m, 4H), 7.50−7.32 (m, 6H), 3.78−3.61 (m, 2H), 1.97−1.79 (m, 1H), 1.23 (s, 3H), 1.19 (s, 3H), 1.06 (s, 9H), 0.80 (d, 3H, J = 6.58 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.7, 129.9, 127.8, 67.9, 43.9, 29.1, 26.8, 24.6, 12.9; IR (NaCl): cm^{-1} 3456.8, 3083.5, 2965.9, 2930.1, 2858.5, 1472.7, 1426.7, 1114.8, 1058.5, 823.3; HRMS (ESI) m/z calcd for $C_{18}H_{23}O_2Si$ $[M - C_4H_9]^+$ 299.1467, found 299.1468 ± 0.0009.

TBDPS-THP Ether 48: To the alcohol **S8** (1.25 g, 3.505 mmol) in anhydrous CH_2Cl_2 (8.0 mL) under an argon atmosphere was added 3,4-dihydro-2*H*-pyran (DHP, 0.639 mL, 7.011 mmol), followed by pyridine-*p*-toluenesulfonate (PPTS, 176 mg, 0.701 mmol). The reaction mixture was allowed to stir for 2.5 h at room temperature and then quenched with aqueous $NaHCO_3$ (5.0 mL) solution. It was then extracted with CH_2Cl_2 and washed with water and brine solution. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (5% EtOAc/hexanes) afforded the THP ether **48** (1.390 g, 90%, mixture of diastereomers obtained due to OTHP group) as a yellow oil. $R_f = 0.82$ (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) mixture of diastereomers: δ 7.71−7.64 (m, 4H), 7.47−7.32 (m, 6H), 4.75−4.69 (m, 1H), 3.92−3.78 (m, 1H), 3.56−3.45 (m, 1H), 3.45−3.32 (m, 1H), 1.92−1.79 (m, 1H), 1.79−1.65 (m, 1H), 1.94−0.98 (m, 24H); ^{13}C NMR ($CDCl_3$, 75 MHz) mixture of diastereomers: δ 135.7, 129.5, 127.6, 93.2, 93.0, 65.5, 65.4, 62.8, 62.71, 45.7, 45.4, 32.3, 26.9, 26.8, 25.5, 25.2, 24.1, 22.9, 20.4, 20.3, 19.4, 19.3, 12.8, 12.6; IR (NaCl): cm^{-1} 2940.3, 2858.5, 1427.7, 1421.6, 1358.8, 1114.8, 1079.0, 981.8, 823.3, 700.5; HRMS (ESI) m/z calcd for $C_{23}H_{31}O_3Si$ $[M - C_4H_9]^+$ 383.2042, found 383.2044 ± 0.0011.

Alcohol 49: TBDPS ether **48** (1.3 g, 2.949 mmol) was placed in a flame-dried, round-bottom flask under an argon atmosphere. To this was added anhydrous THF (10 mL), followed by TBAF (1.0 M in THF, 5.89 mL, 5.899 mmol) at 0 °C. The cooling bath was removed, and the system was allowed to stir at room temperature for 3 h. After complete conversion, the reaction mixture was as such concentrated and flashed through silica gel column chromatography (30% EtOAc/hexanes) to afford the alcohol **49** (506 mg, 86%) as a colorless oil. $R_f = 0.12$ (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) mixture of diastereomers: δ 4.95−4.82 (m, 1H), 4.05−3.86 (m, 1H), 3.80−3.39 (m, 4H), 2.01−0.81 (m, 16H); ^{13}C NMR ($CDCl_3$, 75 MHz) mixture of diastereomers: δ 93.4, 93.1, 81.0, 65.8, 62.9, 62.9, 44.5, 44.4, 32.2, 26.4, 25.2, 25.1, 22.0, 20.8, 20.3, 20.2, 13.0; IR (NaCl): cm^{-1} 3431.3, 2976.1, 2950.6, 1442.2, 1467.6, 1365.3, 1130.1, 1022.7, 986.9.

Aldehyde 50: Anhydrous powdered molecular sieves (4 Å, 200 mg) were placed in a flame-dried, round-bottom flask under an argon atmosphere. It was then cooled to 0 °C, and anhydrous CH_2Cl_2 (5 mL) was added. Alcohol **49** (300 mg, 1.478 mmol) in anhydrous CH_2Cl_2 (3 mL) was added, and the content was stirred for 10 min. 4-Methylmorpholine-*N*-oxide (347 mg, 2.966 mmol) was then added, followed by tetrapropylammonium-perruthenate (TPAP) at 0 °C, and it was allowed to stir at room temperature for 1 h. After the completion of the reaction, some silica gel was added to the reaction mixture and it was directly subjected to column chromatography (12% EtOAc/hexanes) to afford the aldehyde **50** (245 mg, 82%) as an oily liquid. $R_f = 0.4$ (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) mixture of diastereomers: δ 9.93−6.87 (m, 1H), 4.93−4.83 (m, 1H), 3.99−3.87 (m, 1H), 3.53−3.42 (m, 1H), 2.62−2.41 (m, 1H), 1.91−1.01 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz) mixture of diastereomers: δ 205.8, 205.5, 93.6, 93.1, 63.0, 62.8, 55.7, 55.4, 32.05, 25.9, 25.3, 24.6, 24.2, 22.9, 20.2, 20.0, 9.4; IR (NaCl): cm^{-1} 2981.3, 2945.5, 2868.8, 1723.3, 1452.1, 1390.9, 1380.7, 1130.1, 1073.9, 1027.8, 981.8, 869.3; HRMS (ESI) m/z calcd for $C_{11}H_{20}O_3$ $[M]^+$ 200.1412, found 200.1412 ± 0.0006.

Alkyne 36: To trimethylsilyldiazomethane (2.0 M solution in Et_2O, 2.24 mL, 4.488 mmol) in anhydrous THF (1.5 mL) under argon was added *n*-butyllithium solution (1.6 M solution in hexane, 2.33 mL, 3.744 mmol) at −78 °C. The resultant mixture was stirred at −78 °C for 45 min, and aldehyde **50** (150 mg, 0.748 mmol) in anhydrous THF (1.2 mL) was added. The resultant mixture was stirred at −78 °C for 30 min and warmed to 0 °C over 40 min. The reaction mixture was recooled to −78 °C, quenched with saturated aqueous NH_4Cl solution, warmed to 0 °C, diluted with water, extracted with Et_2O, dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. Purification of the crude product by flash column chromatography (silica gel, 4% EtOAc/hexane) afforded terminal alkyne **36** (125 mg, 85%) as a pale yellow oil. $R_f = 0.75$ (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) mixture of diastereomers: δ 4.87−4.74 (m, 1H), 4.03−3.88 (m, 1H), 3.55−3.36 (m, 1H), 2.73−2.54 (m, 1H), 2.05−2.04 (m, 1H), 1.97−1.93 (m, 1H),

1.74−1.60 (m, 1H), 1.59−1.14 (m, 13H); ^{13}C NMR ($CDCl_3$, 75 MHz) mixture of diastereomers: δ 94.1, 93.5, 69.4, 63.2, 62.9, 36.9, 32.2, 29.7, 25.9, 25.5, 24.4, 22.3, 21.6, 20.6, 20.2, 15.6; IR (NaCl): cm^{-1} 2931, 2860.5, 1448.9, 1360.8, 1243.7, 1149.3, 1125.7, 1020, 984.7. We could not obtain HRMS data for this compound after several attempts; this may be due to the instability of the OTHP group. LRMS (ESI-MS) m/z $[M - C_5H_9O]^+$: 113.

Dihydroxy Alkyne 34: To the terminal alkyne **36** (99.8 mg, 2.24 mL, 0.508 mmol) in anhydrous THF (1.5 mL) under argon was added *n*-butyllithium solution (1.6 M solution in hexane, 0.321 mL, 0.508 mmol) at −78 °C. The resultant mixture was stirred at −78 °C for 1 h, followed by the addition of ketone **37** (90 mg, 0.169 mmol) in anhydrous THF (1.2 mL). The resultant mixture was stirred at −78 °C for 2 h and then quenched with saturated aqueous NH_4Cl solution at −78 °C, 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/hexane) afforded the coupled product **34** (98.5 mg, 80%) as a viscous liquid. R_f = 0.73 (SiO_2, 40% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) mixture of diastereomers: δ 7.45−7.20 (m, 10H), 4.95−4.61 (m, 3H), 4.59−4.39 (m, 2H), 4.31−4.13 (m, 1H), 4.01−3.83 (m, 2H), 3.73−3.57 (m, 1H), 3.54−3.35 (m, 1H), 2.76−2.56 (m, 1H), 2.29−2.11 (m, 1H), 2.08−1.73 (m, 4H), 1.72−0.73 (m, 38H); ^{13}C NMR ($CDCl_3$, 75 MHz) mixture of diastereomers: δ 139.4, 138.8, 128.9, 128.1, 127.5, 127.4, 127.3, 127.1, 94.1, 93.4, 86.5, 83.6, 77.7, 77.6, 75.4, 73.2, 72.8, 70.4, 69.6, 67.7, 63.2, 62.7, 59.7, 58.5, 56.9, 42.5, 40.6, 36.7, 36.1, 35.3, 32.5, 32.4, 32.2, 31.0, 29.7, 27.9, 27.9, 25.9, 25.5, 25.4, 25.4, 24.4, 22.9, 21.8, 20.6, 20.2, 15.8, 15.6, 15.6, 15.4, 14.6, 7.7, 7.6, 7.5; IR (NaCl): cm^{-1} 3389.3, 2919.2, 2848.2, 1448.9, 1349.1, 1155.1, 1061.1, 1020.2, 762.2. We could not obtain HRMS data for this compound after several attempts; this may be due to the instability of the OTHP group. LRMS (ESI-MS) m/z $[M - C_5H_6O]^+$: 644.

Spiroketal 51: To a stirred mixture of dihydroxy-alkyne **34** (90 mg, 0.123 mmol) and H_2O (11.13 mg, 0.615 mmol) in CH_3CN (1.5 mL) was added $Hg(OTf)_2$ (12.3 mg, 0.0246 mmol) at room temperature, and the mixture was stirred for 10 min at the same temperature. The reaction was quenched by the addition of Et_3N (50 μL). The resulting mixture was diluted with Et_2O (2 mL) and 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 **51** (71.5 mg, 90%) as a white solid. R_f = 0.48 (SiO_2, 20% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$ + 5% CD_3OD, 300 MHz): δ 7.38−7.18 (m, 10H), 4.66−4.13 (ABq, 2H, J = 10.97 Hz), 4.50−4.39 (m, 2H), 4.39−4.30 (m, 1H), 3.88−3.81 (m, 1H), 3.61−3.54 (m, 1H), 2.48 (dd, 1H, J = 13.72, 1.64 Hz), 2.11−1.92 (m, 2H), 1.81−1.68 (m, 3H), 1.55−0.83 (m, 21H), 1.28 (s, 3H), 1.11 (s, 3H), 1.10 (d, 3H, J = 6.03 Hz), 0.92 (s, 3H), 0.82−0.74 (m, 1H); ^{13}C NMR ($CDCl_3$ + 5% CD_3OD, 75 MHz): δ 139.3, 138.9, 128.2, 128.1, 127.6, 127.4, 127.3, 127.0, 122.5, 83.7, 82.1, 79.0, 74.7, 73.20, 70.2, 69.6, 67.3, 58.8, 58.0, 49.0, 42.8, 40.4, 36.1, 32.6, 32.4, 31.2, 30.7, 307, 29.7, 29.6, 27.8, 25.3, 22.4, 19.7, 18.9, 14.3; IR (NaCl): cm^{-1} 3612.6, 3001.5, 2954.5, 2919.2, 1448.9, 1378.4, 1357.9, 1243.3, 1161.0, 1084.6, 1061.4, 1046.4, 1025.9, 964.2, 917.1, 879.1; HRMS (ESI) m/z calcd for $C_{42}H_{58}O_5$ $[M]^+$ 642.4284, found 642.4284 ± 0.0019.

22-*epi*-hippuristanol 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 (13 mg, 2.176 mmol) (washed with hexane) 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, and 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 a solution of dibenzylether **51** (70 mg, 0.109 mmol) was added slowly. A cautious addition is needed to ensure a regular and smooth ammonia reflux. The reaction mixture was then stirred at −33 °C for 1.5 h, and NH_4Cl powder was carefully and slowly added 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 the mixture was extracted 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** (45.95 mg, 92%) as a white solid. R_f = 0.38 (SiO_2, 30% acetone/hexanes); $[\alpha]_D^{20}$ −45.8 (c = 0.5, $CHCl_3/CH_3OH$ (1:1)); ^{1}H NMR ($CDCl_3$ + 2% CD_3OD, 300 MHz): δ 4.46−4.34 (m, 1H), 4.24 (br s, 1H), 3.98 (br s, 1H), 2.29−2.16 (m, 1H), 2.16−2.07 (m, 1H), 2.06−0.79 (m, 19H), 1.27 (s, 3H), 1.25 (s, 3H), 1.23 (s, 3H), 0.98 (s, 3H), 0.94 (s, 3H), 0.89 (d, 3H, J = 6.58 Hz), 0.79−0.69 (dd, 1H, J = 10.97, 3.29 Hz); ^{13}C NMR ($CDCl_3$ + 2% CD_3OD, 75 MHz): δ 118.7, 84.3, 82.33, 79.1, 67.7, 66.3, 66.1, 58.3, 57.9, 48.3, 41.9, 40.9, 39.7, 36.1, 35.0, 32.3, 31.6, 31.4, 30.2, 28.9, 28.3, 27.8, 26.9, 22.8, 19.1, 13.9, 13.8; HRMS (ESI) m/z calcd for $C_{28}H_{46}O_5$ $[M]^+$ 462.3345, found 462.3348 ± 0.0014.

Hippuristanol 1: 22-*epi*-Hippuristanol **2** (45 mg, 0.097 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, 3.74 mg, 0.015 mmol) at rt. After stirring for 8.5 h at room temperature, the solvent was removed under the reduced pressure. Chromatography of the residue (without further workup) on silica gel (15% acetone/hexanes) afforded hippuristanol **1** (18.9 mg, 87% brsm (based on recovered starting material of 42%) as a white solid. R_f = 0.4 (SiO_2, 30% acetone/hexanes); $[\alpha]_D^{20}$ +31.7 (c = 0.45, CCl_4); ^{1}H NMR (300 MHz, 9:1 CCl_4/C_6D_6): δ 4.15−4.03 (m, 2H), 3.80 (br s, 1H), 2.71 (s, 1H), 2.25−2.13 (m, 1H), 2.07−1.96 (m, 1H), 1.94−0.65 (m, 19H), 1.24 (s, 3H), 1.18 (s, 3H), 1.14 (s, 3H), 1.10 (s, 3H), 0.90 (s, 3H), 0.86 (d, 3H, J = 7.13 Hz), 0.62−0.54 (m, 1H); ^{13}C NMR (75 MHz, 9:1 CCl_4/C_6D_6): δ 115.6, 84.4, 80.5, 79.4, 68.1, 66.6, 66.2, 58.7, 57.6, 50.6, 42.6, 42.1, 41.2, 40.2, 36.8, 36.0, 34.5, 33.1, 31.8, 30.6, 29.6, 29.1, 28.5, 23.6, 18.9, 15.5, 14.3; HRMS (ESI) m/z calcd for $C_{27}H_{43}O_5$ $[M - CH_3]^+$ 447.3110, found 447.3113 ± 0.0013.

Assessment of Biological Activity. The biological activity of the compounds was tested in *in vitro* translation reactions using rabbit reticulocyte lysates as per the manufacturer's instructions (Promega Corp.) (Bordeleau et al. 2006).[1a] The compound was added to translation reactions to a final concentration of 5 μM. Translation reactions were programmed with FF/HCV/Ren mRNA (8 μg/mL) and contained a final concentration of 135 mM KCl. After 1 h at 30 °C, aliquots were removed and monitored with a Berthold Lumat LB 9507 luminometer following addition of the Firefly or Renilla luciferase substrate. Data for Firefly luciferase were normalized to Renilla luciferase readings (since translation of the latter is resistant to hippuristanol) and compared to vehicle controls. Experiments were always performed alongside reactions containing 5 μM hippuristanol purified from natural sources as a positive control.[1a]

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Supporting Information Available: ^{1}H and ^{13}C spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.