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Efficient Synthetic Approach to Potent Antiproliferative Agent Hippuristanol via Hg(II)-Catalyzed Spiroketalization

Kontham Ravindar,[†] Maddi Sridhar Reddy,[†] Lisa Lindqvist,[‡] Jerry Pelletier,[‡] and Pierre Deslongchamps*,[†]

Département de Chimie, Université de Sherbrooke, Sherbrooke, QC, J1K 2R1, Canada, and Department of Biochemistry and Oncology, McIntyre Medical Sciences Building, McGill University, Montreal, QC H3G 1Y6, Canada

pierredeslongchamps@omegachem.com

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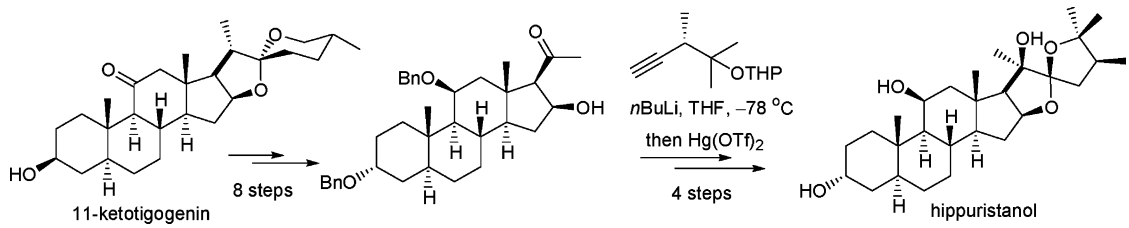
ABSTRACT



The steroidal natural product hippuristanol targets eukaryotic translation initiation factor (eIF)4A which plays a pivotal role in translation in eukaryotic cells. Now an efficient synthesis of hippuristanol from 11-ketotigogenin is reported. The synthesis features a rapid construction of a spiroketal unit via $Hg(OTf)_2$-catalyzed oxidation/spiroketalization of the 3-alkyn-1,7-diol motif.

The mechanism of eukaryotic translation initiation has received increasing attention owing to its potential as an anticancer drug target. The rate-limiting step of translation initiation involves the binding of ribosomes to mRNAs catalyzed by distinct trans-acting factors that differ in their affinity for different mRNA species. Of note is the eukaryotic initiation factor (eIF)4A (the prototypical DEAD-box RNA helicase) which is required to unwind the secondary structure within the mRNA 5′ untranslated region to prepare the ribosome landing pad. We have previously identified[1] hippuristanol (**1**), a polyoxygenated steroid from the gorgonian coral *Isis hippuris*, as a potential candidate to target the eukaryotic translation initiation factor eIF4A.[2] Hippuristanol (**1**) efficiently blocks translation and shows significant cytotoxic activities against several cultured cell tumor lines.[2] The identification of hippuristanol (**1**) demonstrates proof-of-concept that RNA helicases can be selectively targeted and highlights the anticancer potential of this approach. There is thus an urgent need for a practical synthetic route to hippuristanol (**1**) with the high feasibility of making analogues with considerable variation in structure and stereochemistry both for improving the affinity for eIF4A and for possibly developing inhibitors for other RNA helicases. Most recently, Yu and co-workers reported the first synthesis of hippuristanol (**1**) (from commercially available hydrocortisone) and showed the importance of structure and stereochemistry of the spiroketal appendage,[3] consistent with what had been previously reported.[1] Herein

[†] Université de Sherbrooke.
[‡] McGill University.

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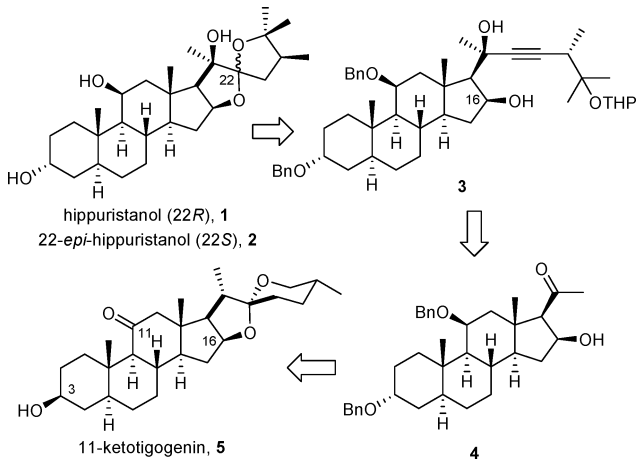
we report a practical synthesis of hippuristanol (**1**) from commercially available 11-ketotigogenin (**5**) via unprecedented $Hg(OTf)_2$-catalyzed spiroketalization, which can potentially lead to the synthesis of vast varieties of analogues for further insights into the structure−activity relationships.

As described in the retrosynthetic analysis in Scheme 1, the cascade construction of the spiroketal unit of hippuristanol (**1**) and/or 22-*epi*-hippuristanol (**2**) can be achieved from suitably functionalized 3-alkyn-1,7-diol intermediate **3**. This intermediate comes from β-hydroxy ketone **4** which is readily available from 11-ketotigogenin (**5**)[4] through Marker's degradation along with some functional group manipulations.

Scheme 1. Retrosynthetic Analysis of Hippuristanol (**1**)



As depicted in Scheme 2, our synthesis starts with 11-ketotigogenin (**5**), which is commercially available and can also be obtained in bulk quantity from hecogenin acetate (**6**).[4] We have also prepared **5** on a moderate scale, using a slightly modified procedure which is described in the experimental section (Supporting Information). To begin the synthesis of hippuristanol (**1**), the hydroxyl group at C3 of 11-ketotigogenin (**5**) was inverted under Mitsunobu conditions[5] to afford the 3α-benzoate which upon treatment with $LiAlH_4$ underwent reductive removal of the benzoyl group and a highly stereocontrolled reduction of the 11-keto group to yield 3α,11β-diol **7**. Dibenzyl derivative **8** was then obtained under standard conditions. Following Marker's degradation,[6] treatment of **8** successively with pyridine hydrochloride in acetic anhydride followed by CrO_3 in acetic acid and sodium acetate gave keto diester **10** (via **9**) in good yield. Direct hydrolysis of ester **10** could not be achieved, and all the acidic and basic conditions proved to be unsuccessful, giving either the corresponding conjugated methyl ketone or an unidentified mixture of products. Then, we adopted a round away procedure for hydrolysis. Thus, vinyl grignard addition to **10** resulted in hydrolytic cleavage of the ester group and vinylation of the keto group to give diol **11**. OsO_4-mediated dihydroxylation of the olefin group in **11** followed by oxidative cleavage cleanly afforded the requisite β-hydroxy ketone **4**.

Synthesis of an alkyne coupling partner is depicted in Scheme 3. The known diol **12**[7] was oxidized with PDC to give hydroxy aldehyde **13**. Homologation of **13** under various conditions of Corey−Fuchs[8] and Ohira−Bestmann[9] protocols proved to be unfruitful revealing the substrate's high sensitivity in basic conditions. The Miwa protocol[10] using excess $TMSCHN_2$ 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 **14**. Unsatisfied with the yield, we have developed a slightly longer but convenient route to **14** from diol **12**. Thus, the primary and tertiary hydroxyl groups of **12** were protected as TBDPS and THP ethers, respectively, in standard conditions to obtain **15**, which upon treatment with TBAF relieved the primary hydroxyl group to give alcohol **16**. Oxidation of alcohol **16** with TPAP−NMO gave aldehyde **17** which under Miwa's conditions cleanly furnished alkyne **14** in 85% yield (Scheme 3).

Completion of the synthesis of hippuristanol (**1**) is described in Scheme 4. Addition of lithiated alkyne **14** to β-hydroxy ketone **4** yielded exclusively the desired and expected Cram's product **3** in excellent yield.[11] The stage was now set for the key cascade sequence, oxidation of alkyne, hemiketalization, deprotection of THP ether, and spiroketalization. Unprecedented, exposure of semiprotected 3-alkyn-1,7-diol **3** to $Hg(OTf)_2$ in aqueous acetonitrile at room temperature,[12] within no time, cleanly furnished directly the desired ketal **18** which on debenzylation with lithium in liquid ammonia resulted in 22-*epi*-hippuristanol (**2**) as a major diastereomer (22*S*/22*R*, 99.9:0.1) in 82% overall yield (Scheme 4). Stereochemistry of the spiroketal unit of both **18** and 22-*epi*-hippuristanol (**2**) was confirmed by the appearance of spirocarbon ^{13}C signals above δ 118 (122.53 and 118.66, respectively).[2b,c] Further, the analytical

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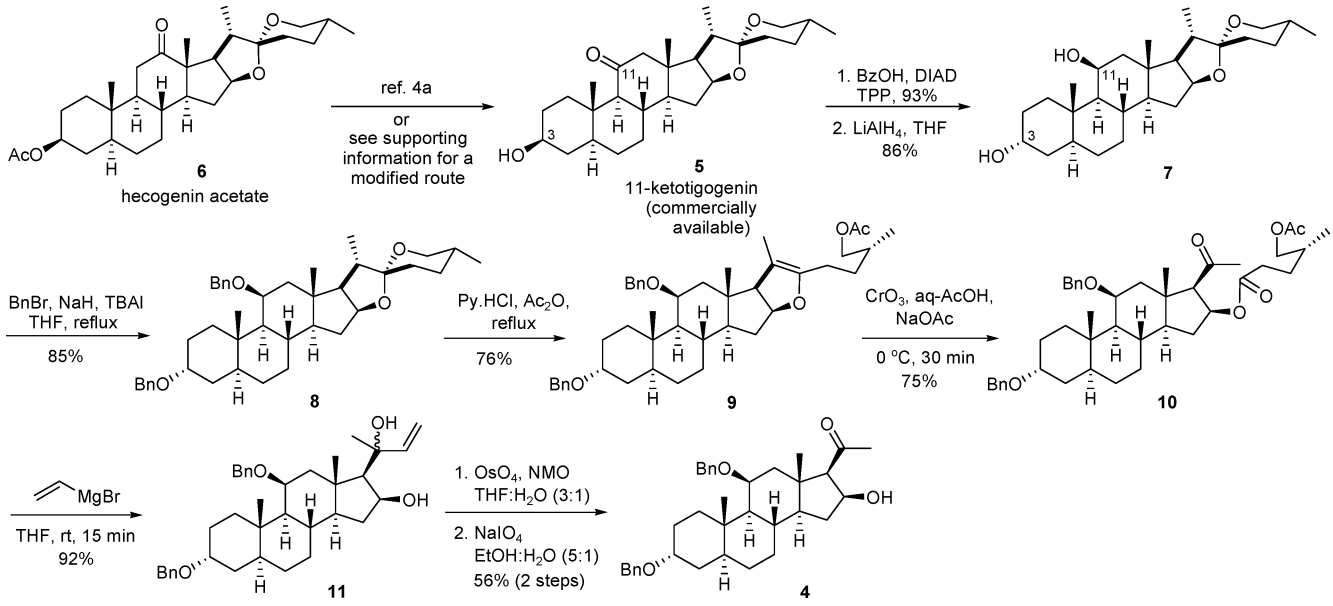
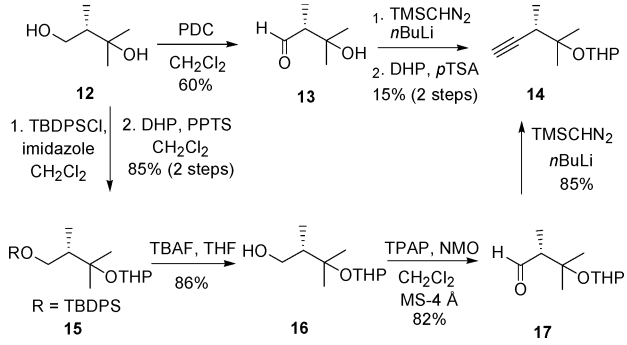
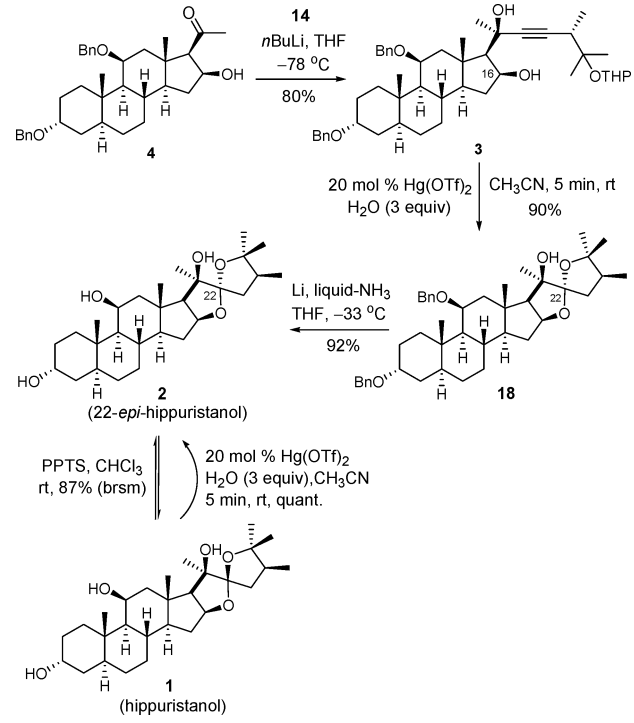
Scheme 2. Synthesis of Key Intermediate **4**



Scheme 3. Synthesis of Alkyne Intermediate **14**



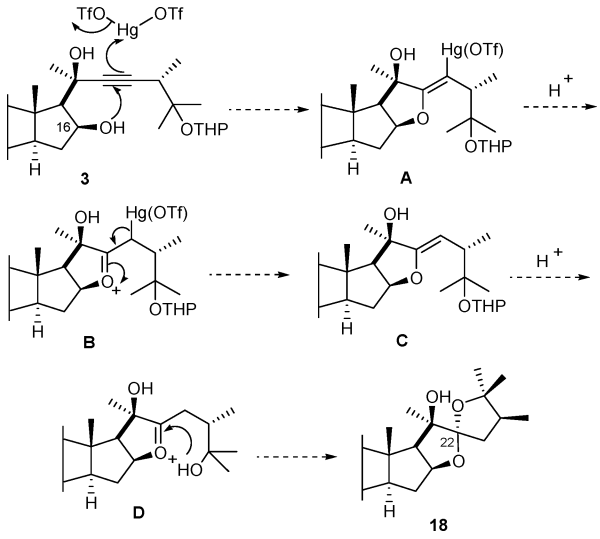
Scheme 4. Synthesis of Hippuristanol (**1**)



data of our 22-*epi*-hippuristanol (**2**) was in good agreement with that of the literature.[3] The mechanistic sequence that we presume for the completely stereocontrolled cascade spiroketalization is depicted in Scheme 5. Oxymercuration of the triple bond in **3** involving the 16-hydroxyl group presumably led to intermediate **A** which on olefin isomerization (to give **B**) followed by demercuration formed cyclic enol ether **C**.[12] Protonation of **C** to produce **D**, followed by ketalization, furnished the cyclic ketal **18**. The reason for the exclusive formation of one isomer at the end of the cascade process might be due to approach of the hydroxyl group in **D** from the less hindered α-side (*anti* to the neighboring tertiary hydroxyl group at C21), or the other isomer of **18** formed in the reaction might be converted to **18** due to the acidic (and protic) nature of the reaction medium (vide infra).

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 spirocarbon (115.61) in ^{13}C NMR confirmed the inversion of the spirocenter. Surprisingly, in contrast to the previous reports,[3] we observed that hippuristanol (**1**) (both synthetic and natural product) quickly isomerized in $CDCl_3$ to 22-*epi*-hippuristanol (**2**), and hence it was necessary to take ^1H and ^{13}C NMRs in the CCl_4/C_6D_6 (9:1) solvent system. Data of synthetic material were in good agreement with those of the natural product as well as with the reported data.[3]

Scheme 5. Proposed Mechanism for Cascade Spiroketalization



The 22-*epi*-hippuristanol (**2**) was inactive, while synthetic hippuristanol (**1**) inhibited translation to an extent similar to the natural compound.

To further understand the complete stereocontrolled formation of dibenzyl *epi*-hippuristanol (**18**), we treated hippuristanol (**1**) under the same reaction conditions ($Hg(OTf)_2$, H_2O (3 equiv), and CH_3CN) and found that it underwent a complete isomerization to 22-*epi*-hippuristanol (**2**). Of course, upon treatment of 22-*epi*-hippuristanol (**2**) under the same aqueous acidic conditions, no isomerization occurred. The existence of hippuristanol (**1**) and 22-*epi*-hippuristanol (**2**) in equilibrium is thus possible only in aprotic acidic medium. This indicates that the conversion of **3** to **18** is a thermodynamically controlled process. In addition, the appearance of hipppuristanol (**1**) along with *epi*-hippuristanol (**2**) in *aprotic acidic medium* is likely due to the presence of an intramolecular hydrogen bond with the neighboring tertiary hydroxyl group at C20 with one of the spiroketal oxygens. In conclusion, an efficient synthesis of hippuristanol (**1**) has been achieved from readily available 11-ketotigogenin (**5**) through an unprecedented $Hg(OTf)_2$-catalyzed cascade spiroketalization. This novel spiroketal synthesis via the facile coupling of readily available acetylenic intermediates with hydroxy ketones should allow the preparation of hippuristanol analogues for further biological studies. Further study on structure−activity relationships of hippuristanol (**1**) and its analogues and the extension of the spiroketalization method are in progress and will be reported shortly.

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Supporting Information Available: Experimental section and physical and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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