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Stereocontrolled Synthesis of all-(*E*)- and (8*Z*)-Anhydroretinol

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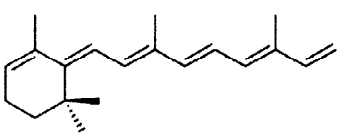
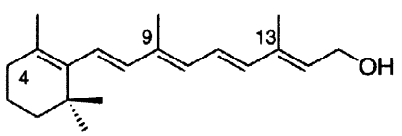
Abstract. Convergent syntheses of hexaenes anhydroretinol and its (8*Z*)-isomer are described. Despite the mild reaction conditions for the final step in both cases, a Stille coupling reaction between trienyl triflates and trienyl stannanes, the stereochemical integrity of anhydroretinol is not maintained, due to its intrinsic instability.

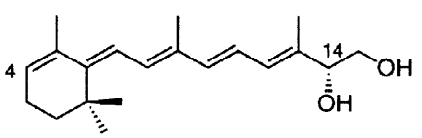
Anhydroretinol (AR, **1**) is a metabolite of retinol (vitamin A, **2**) that was first isolated from fish liver oils.[1] More recently it has been isolated from *Drosophila* Schneider S2M3 cells, and characterized in this cell line and several others from both Chordata and Arthropoda phyla.[2] Recent biochemical studies have shown that AR reversibly inhibits physiological effects regulated by **2** and by its messenger (14*R*)-14-hydroxy-4,14-*retro*retinol (14-HRR, **3**).[3] The latter was the first metabolite with a *retro*-retinoid structure isolated (from both mammalian and insect cell lines) and has since been found to be a potent intracellular agonist of retinol-dependent events in the immune system.[4] AR (**1**) inhibits these effects of 14-HRR (**3**), and blocks B lymphocyte proliferation and the activation of resting T lymphocytes. Accordingly, 14-HRR and AR are considered to be the first agonist/antagonist pair of lipid-signalling molecules.[3]



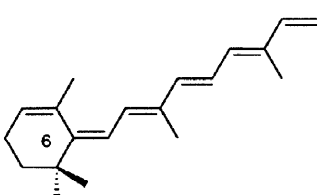
1 anhydroretinol (AR)



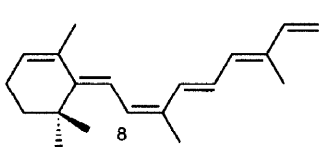
2 retinol (vitaminA)



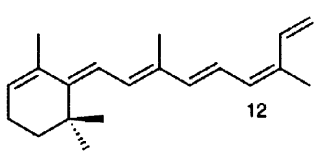
3 (14*R*)-14-hydroxy-4,14-*retro*retinol



4 (6*Z*)-anhydroretinol



5 (8*Z*)-anhydroretinol



6 (12*Z*)-anhydroretinol

Attempts at straightforward dehydration of vitamin A (**2**) into anhydroretinol (**1**) by treatment with acid afforded only a 10-30% yield of a complex mixture of anhydroretinol isomers.[5] In a recent re-examination of this reaction (HCl, EtOH, 25 °C, 30 min.)[2] additional spectroscopic data were obtained that allowed identification of three isomers of AR with *Z* double bonds (**4-6**), which were separated from **1** by HPLC. In view of the potential utility of these compounds in biochemical research, we thought it would be of interest to develop a stereocontrolled approach to AR (**1**) and AR-isomers **4-6** that gave improved yields and obviated the need for

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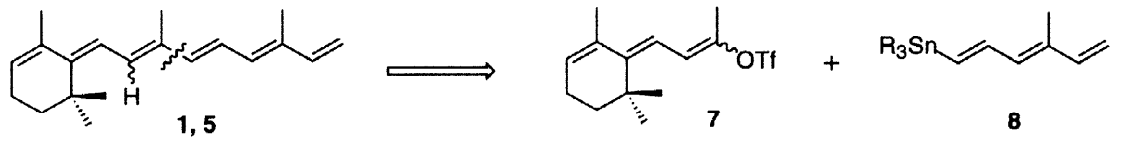
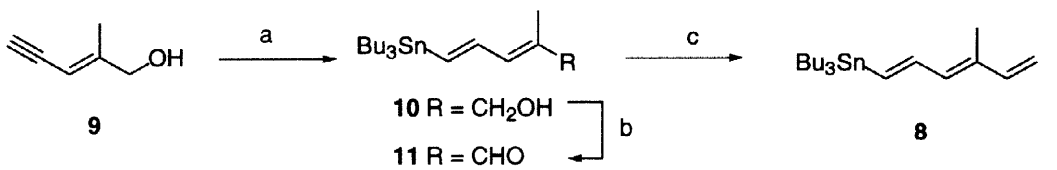
tedious HPLC purification. In addition, we were attracted to this endeavour by the stereochemical challenges involved in the synthesis of these rather unstable compounds,[2] and by the possibilities that such a stereocontrolled approach might offer for further modifying the polyene structure.

Our research group's experience in the development of new approaches to polyenes of biological interest[6] led us to consider convergent synthesis of the hexaene structure by palladium-catalysed coupling (Stille reaction)[7] of triene fragments of comparable complexity. Use of trienyl triflates **7** was suggested by the ready availability of precursors containing the cyclohexenyl fragment, and meant that the metalated fragment had fewer carbon atoms.



1, 5 **7** **8**

The right-hand triene fragment **8** was obtained by stannylcupration [$(Bu_3Sn)_2Cu(CN)Li_2$, THF, -30 °C][8] of known enynol **9**,[9] which took place efficiently (94% yield) with complete regio- and stereocontrol, followed by allylic oxidation of alcohol **10** to aldehyde **11** (MnO_2, CH_2Cl_2, 25 °C, 2h; 89% yield) and Wittig olefination of **11** under the mild conditions developed by Stork[10] ($CH_3PPh_3^+Br^-$, $NaN(TMS)_2$, HMPA/THF, -78 °C; 80% yield). Purification of the stannanes described was achieved by reverse-phase column chromatography, to avoid protodestannylation ocurring under acidic conditions.[11]



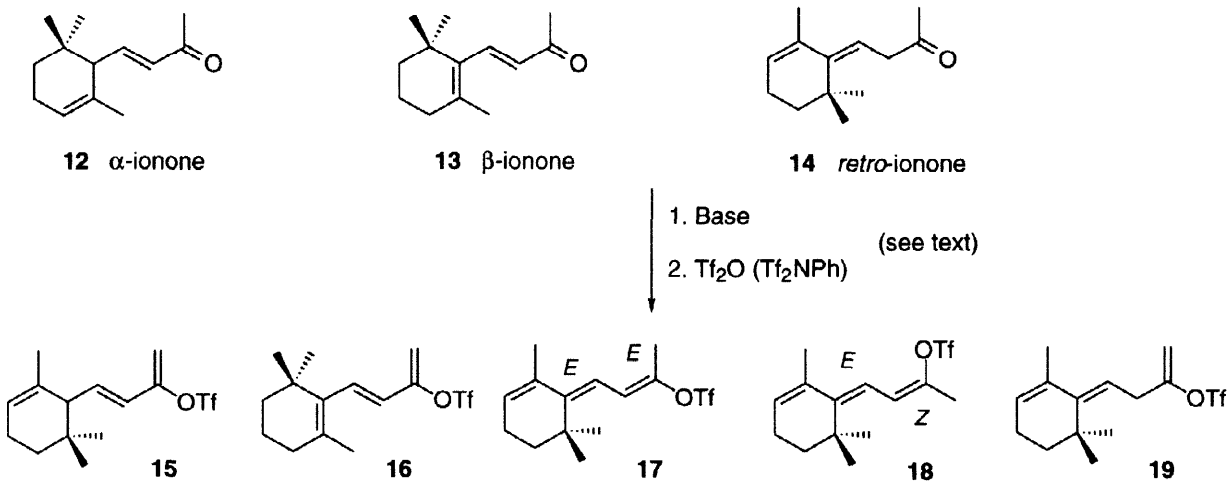
9 **8**

(a) CuCN, *n*-BuLi, *n*-Bu_3SnH, THF, -30 °C (94%); (b) MnO_2, CH_2Cl_2, 25 °C (89%); (c) $CH_3PPh_3^+Br^-$, $NaN(TMS)_2$, THF, HMPA, -78 -> 25 °C (80%).

Commercially available α-ionone **12** and β-ionone **13** were chosen as starting materials for the direct preparation of trienyl triflates **7**. Firstly, conditions for generation of kinetic and thermodynamic enolates from saturated cyclic ketones were examined, using bases iPr_2NLi[12a] and iPr_2NMgBr[12b], respectively, and trapping with either triflic anhydride or *N*-phenyltriflimide. The results were disappointing, however, since there was either no reaction or the undesired triflate **15** or **16** was formed. Alternative use of Et_3N as base gave only decomposition products, while di-*tert*-butylmethylpyridine (DBMP)/triflic anhydride, which has been successfully used for generation of dienyl triflates from conjugated cyclic ketones,[12c] gave mixtures of **15** or **16** and the desired triflate **7**, the latter as a mixture of *E* and *Z* isomers **17** and **18**.

In view of the low regio- and stereoselectivity obtained in the preparation of trienyltriflates **17** and **18** from conjugated ketones **12** or **13**, we decided to examine the use of the alternative unconjugated ketone with a preformed terminal diene system. The required ketone was efficiently prepared by allylic deprotonation and deconjugation of β-ionone **13** using *t*-BuOK in DMSO, which gave a 7:1 mixture of *E* and *Z* isomers of *retro*-ionone **14** in 96% yield.[13] The desired (*E*)-**14** was isolated from the mixture by a selective low temperature (-30 °C) crystallization.[13]

With **14** in hand, conditions were sought for stereoselective generation of (*E,E*)- and (*Z,E*)-trienyl triflates. The conditions tried with the conjugated ketones **12** and **13** were likewise unproductive, leading mainly to recovery of starting material. After extensive experimentation, varying the base, solvent/cosolvent, temperature and order of addition, we developed conditions allowing regio- and stereoselective generation of either trienyl triflate. Thus (*Z,E*)-triflate **18** was obtained in 94% yield as a single stereoisomer by treating ketone **14** with LiHMDS in 4:1 THF/HMPA at 0 °C for 1 h, and then trapping the enolate with Tf_2NPh; whereas (*E,E*)-triflate **17** was the major component (4:1 **17/18** ratio, 83% yield) when **14** was enolized using Et_2NLi in THF at -78 °C for 1 h, and then treated sequentially with HMPA and triflating agent. Although up to 14:1 **17/18** ratios could be obtained by adding the enolate in THF to a solution of Tf_2NPh in 4:1 THF/HMPA, this led to loss of regioselectivity and formation of the undesired triflate **19** in amounts that made this approach unacceptable for preparation of **17**. Note also that enolate generation in the presence of HMPA (Et_2NLi in 4:1 THF/HMPA, -78 °C, 1 h) caused reversal of stereselectivity and formation of the (*Z,E*)-trienyl triflate **18** as major product (2:1 **18/17** ratio; 83% yield).[14]



The critical palladium-catalysed coupling step was performed using the optimal conditions developed by Farina.[15] Thus, a mixture of triflate **18** and stannane **8**, in the presence of catalytic amounts of $Pd_2(dba)_3$ and $AsPh_3$, were stirred in *N*-methylpyrrolidinone (NMP) at 25 °C for 2 h, saturated aqueous KF solution was added, and the mixture was extracted with ether, from which (8*Z*)-anhydroretinol (**5**) was isolated as a single stereoisomer (stereochemistry was confirmed by NOE experiments) in 70% yield. The inseparable 4:1 mixture of trienyl triflates **17/18** was likewise smoothly coupled (2.5 h, 75% yield) with stannane **8**, affording, to our surprise, a crude product containing a *ca.* 2:1 mixture of AR **1** and its (8*Z*)-isomer **5**, as determined by ^{1}H-NMR spectroscopy, rather than the expected 4:1 mixture. The two products were separated by preparative reversed-phase HPLC (6 μm particle size, 19 x 300 mm, C18 column; eluant CH_3CN, 4.25 mL/min), and then identified by comparison of their spectroscopic data with those described in the literature.[2] This result was most puzzling, since it has been well documented that the Stille cross-coupling proceeds with retention of the stereochemical integrity of the coupling partners.[7] To our knowledge, AR **1** and its (8*Z*)-isomer **5** are the longest substituted polyenes ever prepared by Stille-type processes,[16] and it is possible that their length favored loss of their stereochemical integrity under the reaction conditions. To confirm this, AR **1**, freshly isolated by HPLC, was stirred in NMP at 25 °C for 2 h either in the presence or in the absence of catalyst $Pd_2(dba)_3/AsPh_3$. Whereas

stirring in NMP alone provided compounds **1** and **5** in a 3:2 ratio, the presence of the palladium catalyst resulted in the same 2:1 obtained above. Therefore, isomerization of AR **1** appears to occur at the product stage, despite the rather mild reaction conditions, although it is not yet clear whether it is catalyzed by palladium.[17]

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17. Satisfactory spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, UV) were obtained for all new substances reported in this paper. Elemental compositions were determined by high resolution mass spectroscopy after purification by HPLC.