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

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Abstract. Convergent syntheses of hexaenes anhydroretinol and its (8Z)-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. © 1998 Elsevier Science Ltd. All rights reserved.

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



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 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 interest⁶ 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.



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** (MnO₂, CH₂Cl₂, 25 °C, 2h; 89% yield) and Wittig olefination of **11** under the mild conditions developed by Stork¹⁰ (CH₃PPh₃+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



(a) CuCN, *n*-BuLi, *n*-Bu₃SnH, THF, -30 °C (94%); (b) MnO₂, CH₂Cl₂, 25 °C (89%); (c) CH₃PPh₃⁺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 *i*Pr₂NLi^{12a} and *i*Pr₂NMgBr^{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 Et₃N 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 Tf₂NPh; whereas (E,E)-triflate 17 was the major component (4:1 17/18 ratio, 83% yield) when 14 was enolized using Et₂NLi 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 Tf₂NPh 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 (Et₂NLi 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 AsPh₃, 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 ¹H-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 CH₃CN, 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 Pd₂(dba)₃/AsPh₃.

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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