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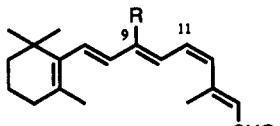
Stereospecific Synthesis of 9-Demethylretinoids via Palladium-Catalyzed Vinylboronic Acid-Vinyl Iodide Cross Coupling

Angel R. de Lera,* Alicia Torrado, Beatriz Iglesias and Susana López

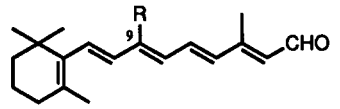
Departamento de Química Orgánica. Universidade de Santiago de Compostela. 15706 Santiago de Compostela. SPAIN

Abstract: A stereospecific synthesis of 9-demethylretinoids with either *trans* or 11-*cis* geometries, based on the thallium-accelerated palladium-catalyzed cross-coupling reactions of an (E)-1-alkenylboronic acid and (E) or (Z)-alkenyl iodides, is described.

Artificial rhodopsins and bacteriorhodopsins,[1] obtained by replacing the native chromophore (11-*cis*-retinal **1** in rhodopsin and *trans*-retinal **2** in the light-adapted form of bacteriorhodopsin) with a synthetic retinal analog have been instrumental in the present knowledge of the visual cycle and the bacteriorhodopsin photocycle. It has been recently shown that pigments derived from 11-*cis*-9-demethylretinal **3** fail to produce the biochemically active form of rhodopsin (meta II) upon photoisomerization.[2a] This result led to the suggestion[2a,b] that the C9-methyl group in rhodopsin connects the isomerization of the retinal to later events in the visual cycle by triggering a *cis-trans* isomerization of the peptide bond adjacent to the amino terminal side of a proline residue during the lumi-meta I transition, necessary for G-protein activation of the visual process. On the other hand, it is well-known that *trans* isomers of side-chain demethylretinals such as **4** modulate the proton-pumping activity of bacteriorhodopsin.[2c]



1 R= -CH_3
3 R= -H



2 R= -CH_3
4 R= -H

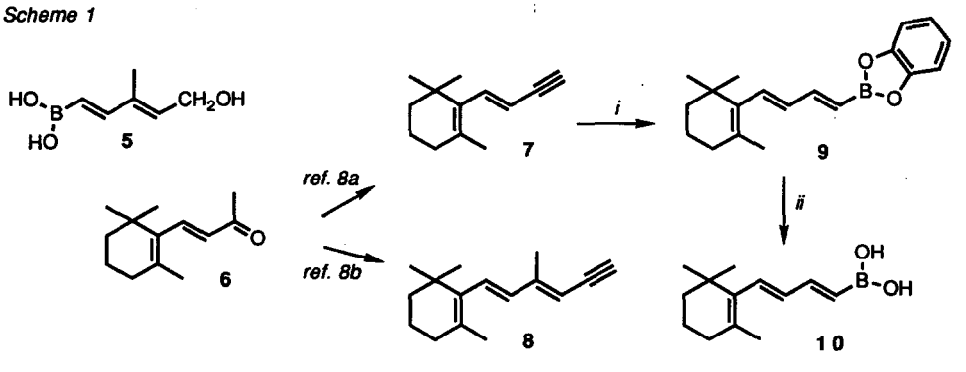
The dependence of biological profiles on the stereochemically defined structure of the polyene side chain makes it necessary to develop synthetic approaches to retinoids with high chemo-, regio- and stereoselectivities. Existing syntheses of mixtures of side-chain 11-*cis*- and *trans*-demethylretinoids rely on Wittig[3a] and Horner-Emmons reactions.[3b] Alternatively, isolation of the 11-*cis* congeners following photochemical isomerization[3a] requires their separation from the more abundant *trans* and other retinal isomers with *cis*-geometries about the most substituted double bonds. In this regard, coupling of stereochemically pure vinylic fragments seems a most reasonable approach, provided that the cross-coupling reaction takes place with retention of the stereochemistry. An in-depth study describing some palladium-catalyzed alkenyl-alkenyl coupling reactions for the synthesis of derivatized vitamin A has recently been published.[4] In contrast to the efficient coupling between alkenylzinc and

alkenyl iodides described in Negishi's paper[4], alkenylboronic esters performed rather poorly under the classical conditions developed by Suzuki.[5]

We are reporting a stereo-defined approach to retinoids, based on the modified Suzuki cross-coupling reaction of an (E)-1-alkenylboronic acid and stereochemically pure vinyl iodides catalyzed by palladium at room temperature, which complements nicely the above study, and is of practical application to the preparation of the unstable and difficult-to-obtain 11-*cis* isomers.

In a first approach to retinoids we prepared the known[6] boronic acid **5** via direct treatment of (E)-3-methyl-2-penten-4-yn-1-ol with catecholborane followed by hydrolysis. Although compound **5** has been used for the preparation of smaller fragments in the synthesis of side chain retinoid analogs,[7] the low yields in the difficult separation of the catechol byproduct called for a change of functionality of the different coupling partners. At this point, we faced the problem of the lack of reactivity of dienynes such as **7**[8a] and trienynes such as **8**[8b] with catecholborane, even under forced conditions (starting material being recovered after prolonged heating in C_6D_6 as solvent, as proved by NMR monitoring). Fortunately, the catalytic effect[9] of the borane-N,N-diethylaniline complex allowed the efficient preparation of vinylboronate **9** from dienyne **7** at room temperature (Scheme 1).[10]

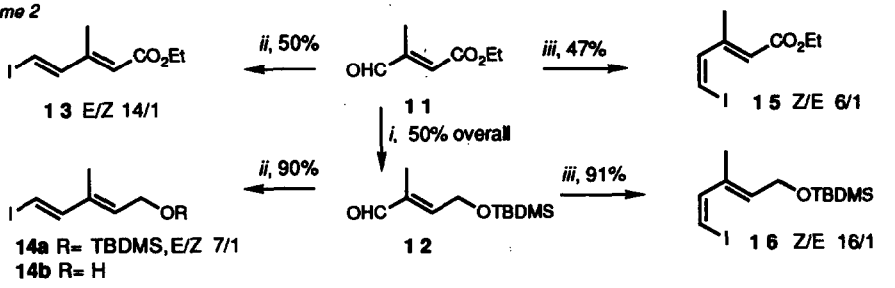
Scheme 1



Scheme 1. Reagents and reaction conditions
i. 1. Catecholborane (1.1 equiv), borane-N,N-diethylaniline complex (0.11 equiv), benzene, rt, 9 h.
ii. H_2O, rt, 3 h; 81% overall yield.

On the other hand, highly stereoselective routes to vinyl iodides (Scheme 2) relied upon well-known alkenylation reactions of aldehydes. (E)-Vinyl iodides (**13** and **14a**) were obtained from ester **11** or protected alcohol **12** by the CHI_3-$CrCl_2$ reaction developed by Nakai[11]. (Z)-Vinyl iodides (**15** and **16**) were prepared by Wittig reactions of the same substrates with iodomethylenetriphenylphosphorane as described independently by Stork[12a] and Bestmann[12b]. The major isomer in each case, obtained after careful chromatographic separation (appreciable amounts of the *trans* isomers were obtained in the purification of the *cis* isomers if the silica gel was not pretreated with pyridine), was subjected to the coupling reaction with the boron-functionalized fragment.

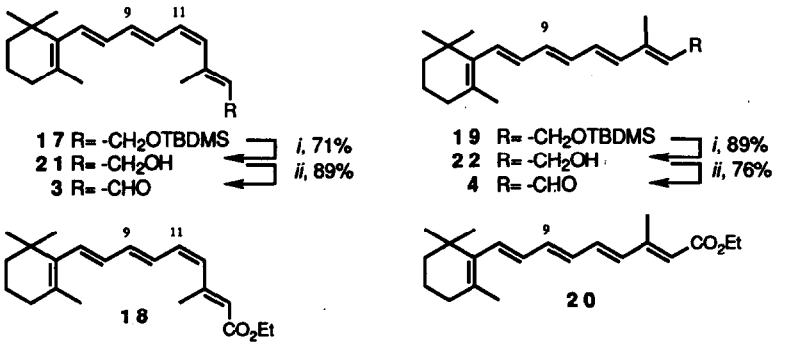
Scheme 2



Scheme 2. Reagents and reaction conditions
i. 1. ethylene glycol, PPTS, benzene, reflux, 12 h; 2. $LiAlH_4$, ether, 0 °C, 1 h; 3. TBDMSiCl, imidazol, DMF, rt, 1.5 h; 4. pTSA, acetone-H_2O, rt, 15 min. *ii.* $CrCl_2$, CHI_3, THF, 0 °C, 45 min. *iii.* $(Ph_3P^+CH_2I)I^-$, $NaN(TMS)_2$, THF, HMPA, -78 °C, 1 h.

For the coupling reaction we turned our attention to the TlOH modification of the Suzuki coupling developed by Kishi and coworkers for one of the critical steps in the synthesis of fully protected palytoxin carboxylic acid.[13] Even under those conditions, vinylboronates performed poorly in accordance with the above observation.[4] The boronic acid **10**, obtained by hydrolysis of boronate **9** (Scheme 1) gave reproducible coupling rates with the vinyl iodides used (probably due[6b] to the better quality of the reagent utilized) and acceptable yields of 9-demethylretinoids. A representative experiment involves stirring of a degassed THF solution of boronic acid **10** (1.0 equiv) and vinyl iodide (**13-16**, 0.67 equiv) in the presence of 10% TlOH (3.08 equiv) and $Pd(PPh_3)_4$ (0.07 equiv) under inert atmosphere for 30 min at rt. Under the described conditions, 11-*cis* -9-demethylretinoids **17** and **18** were obtained in 57% and 67% yields of purified product, respectively (Scheme 3). *Trans*-9-demethylretinoids **19** and **20** were prepared in 48 % and 31% yields, respectively, again with essential retention of configuration, both in (E)-1-alkenylboronic acid and in (E) or (Z)-alkenyl iodides, no other isomers being detected in the reaction mixture.[14]

Scheme 3



Scheme 3. Reagents and reaction conditions
i. $(n\text{-}Bu)_4NF$ (1M in THF), rt, 4 h. *ii.* MnO_2, Cl_2CH_2, rt, 2 h.

Finally, fluoride-induced deprotection of **17** and **19** to the 9-demethylretinols (**21** and **22**) followed by MnO_2 oxidation afforded the known 11-*cis*-9-demethylretinal **3** and *trans*-9-demethylretinal **4**, respectively (Scheme 3) whose spectroscopic data coincide with those published.[3a] A direct route to 11-*cis*-9-demethylretinol

21 (50 % overall yield) uses the direct coupling of boronic acid **10** and alcohol **14b**, itself obtained (Scheme 2) by DIBAL-H reduction of ester **13** (alternative preparation of **14b** by fluoride deprotection of **14a** led to some isomerization).

We believe that the mild conditions of the cross-coupling reaction (compatible with carboxylic esters and unprotected alcohols) make this procedure particularly useful for the highly efficient stereo- and regiospecific preparation of retinoids, especially the difficult-to-obtain 11-*cis* isomers, for their use in a variety of biological protocols. Extension of this methodology to the stereospecific synthesis of the parent system as well as a variety of retinoids with structural modifications at the cyclohexenyl ring will be reported in due course.

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10. The effect of the borane-N,N-diethylaniline complex, that is the hydroboration and exchange of the alkenyl/alkyl group with a diaryloxyborane such as catechol borane, was not observed with trienyne **8**. Compound **10** is, to our knowledge, the only reported example of a conjugated trienylboronic acid.
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14. Satisfactory spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, UV) was obtained for all the new substances reported in this paper. Their elemental composition was determined by high resolution mass spectroscopy.

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