Biochimica et Biophysica Acta 1821 (2012) 3–9

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbalip

Review

Retinoid chemistry: Synthesis and application for metabolic disease ☆

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ARTICLE INFO

Article history:
Received 15 February 2011
Received in revised form 18 April 2011
Accepted 22 April 2011
Available online 30 April 2011

Keywords:
Retinoid
Synthesis
Structure–activity relationship
Metabolic disease
Obesity
Diabetes

ABSTRACT

In this review a discussion of the usual procedures used to synthesize retinoids is followed by an overview of the structure–activity relationships of these molecules. The discussion is then focused on the role and impact of retinoids on metabolic disorders with a particular emphasis on obesity, diabetes, and the metabolic syndrome. In these areas, both natural and synthetic retinoids that are being studied are reviewed and areas where likely future research will occur are suggested. This article is part of a Special Issue entitled Retinoid and Lipid Metabolism.

1. Introduction

While it has been known since at least 1500 B.C. that consuming certain foods can reverse night blindness, it was in 1913 [1] that what eventually became known as vitamin A or retinol (ROL; see **1** in Fig. 1) was established to be that essential dietary component needed for normal growth and vision in mammals. Subsequently, Wald determined [2] that it is actually the reversibly produced oxidative metabolite of ROL, retinal (RAL; **2**) that is the essential form of vitamin A that provides the chromophore for the formation of the visual pigment proteins (rhodopsin) in the eye. In a similar timeframe [3] it was recognized that vitamin A was also essential for the differentiation of epithelial tissues and slowly it was established that this activity mainly resides in the irreversibly produced further oxidized metabolite of RAL, retinoic acid (RA; **3**). While the aldehyde RAL is essential for vision and the alcohol ROL may play a role in aspects of mammalian reproduction and immune function, possibly as further metabolites, the profound impact of RA on epithelial tissue differentiation has focused interest on it and its analogs as potential treatments and preventives of various skin diseases and cancer. The origin of their uses in these two therapeutic areas, dermatology and cancer, has been nicely documented in the important volume "The Retinoids: Biology, Chemistry, and Medicine" [4–6]. While application of the natural vitamin A compounds and their analogs (retinoids) was prominently focused in these two areas through the early 1990s, it slowly began to be recognized that these compounds may play a role in other metabolic diseases as the understanding of the nuclear hormone receptors, that many of these substances interact with, blossomed. In this review, we will focus on the developments in the design and synthesis of retinoids and application of the retinoids in metabolic disease. While we will take a broad view of the definition of metabolic disease, the major focus will be in applications in diabetes, obesity, and the metabolic syndrome, where the majority of research has occurred.

2. Retinoid synthesis

2.1. General

The natural retinoids, as well as their carotenoid precursors, are prominently marked by the presence of a relatively long chain conjugated polyene unit. As a result of the presence of this type of unit, the molecules are fairly sensitive to oxidation as well as isomerization which can be effected primarily by acid, light, or heat. Because of the presence of the polyolefin unit, not too surprisingly olefin forming reactions feature prominently in the syntheses of retinoids. Classically, the Wittig reaction has been extensively employed in retinoid and carotenoid syntheses and reference [7] shows many of these early uses. For example, as shown in Scheme 1, the Wittig reaction of phosphonium salts with carbonyls can be used to prepare the ROL precursor retinyl acetate (**6**) as well as the ethyl ester of RA (**8**). One difficulty with employing the Wittig reaction in these processes is the tendency to form

Abbreviations: ROL, retinol; RAL, retinal; RA, retinoic acid; RXR, retinoid X receptor; HWE, Horner–Wadsworth–Emmons; TTNPB, 4-[(1*E*)-2-(5, 5, 8, 8-tetramethyl-5, 6, 7, 8-tetrahydro-2-naphthalenyl)-1-propen-1-yl]benzoic acid; RAR, retinoic acid receptor; 4-HPR, *N*-(4-hydroxyphenyl)retinamide; PPAR, peroxisome proliferator-activated receptor; RALdh1, retinal dehydrogenase-1; LXR, liver X receptor; 3-Cl-AHPC, (*E*)-4-[3-(1-Adamantyl)-4-hydroxyphenyl]-3-chlorocinnamic acid; SRBP, serum retinol bonding protein; ROR, retinoid-related orphan receptor

☆ This article is part of a Special Issue entitled Retinoid and Lipid Metabolism.

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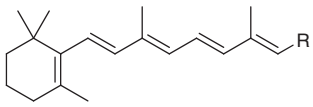
doi:10.1016/j.bbalip.2011.04.007



1 R=CH_2OH

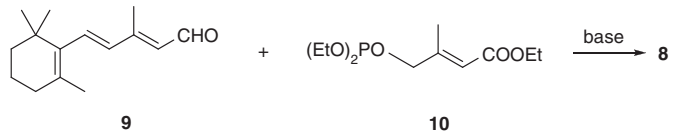
2 R=CHO

3 R=COOH

Fig. 1. Structures of natural retinoids.

isomer mixtures at the newly created olefinic linkage, often with the *cis* isomer predominating. While in the vision area, where 11-*cis*-retinal is critical, and with the more recent recognition that 9-*cis*-RA may be an important RA metabolite acting at the nuclear retinoid X receptor (RXR), *cis* olefin isomers are now also important; in most instances it is *trans* olefin linkages that are present in the natural retinoids, such as **1**–**3**. Thus, a number of modifications and alternatives to the Wittig olefination have been developed. For example, the replacement of the phosphonium salts such as in **4** with phosphonate esters, the Horner–Wadsworth–Emmons (HWE) modification, results in more nucleophilic phosphonate stabilized carbanions which in many retinoid syntheses can strongly favor formation of the *trans* or *E*-olefin. Thus, for example, the HWE modification can be used to prepare **8** as shown in Scheme 2. Conceptually similar processes have also been used in retinoid syntheses such as the Julia [13] and Peterson [14] olefinations.

As chemists and biologists began to recognize that structures without the classic extended polyene chain could be effective retinoids, the range of structures that were synthesized expanded dramatically. The forerunner of this development is generally viewed to be the polycyclic structure known as TTNPB (4-[(1*E*)-2-(5, 5, 8, 8-tetramethyl-5, 6, 7, 8-tetrahydro-2-naphthalenyl)-1-propen-1-yl]benzoic acid; see **11** in Fig. 2) which was eventually found to be a highly potent ROL/RA mimic [15] due ultimately to its metabolism resistance and high affinity for retinoic acid receptors (RARs). Thus, a broadened array of structures and chemistry used to make analogs now exist for making molecules called retinoids. The outlines of the range of chemistry used to make these molecules have been extensively reviewed, again in the classic text



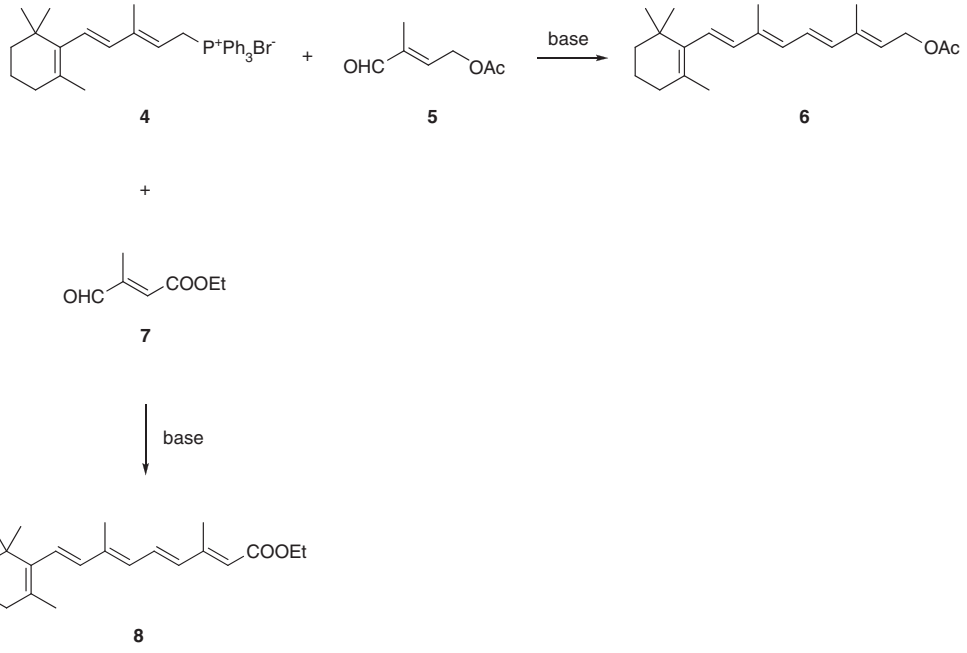
9 **10**

Scheme 2. Synthesis of retinoids via Horner–Wadsworth–Emmons reaction. While **10** is commercially available as an isomer mixture, example preparations of **9** and **10** can be found in references [11] and [12] respectively.

"The Retinoids: Biology, Chemistry, and Medicine" [16]. More recent very comprehensive updates of the chemistry used to synthesize retinoids and precursor carotenoids have been published [17,18]. Particularly useful for readers here may be the sections in reference [17] that describe the use of various modern metal-mediated coupling reactions being used in C—C bond forming processes in retinoid syntheses.

2.2. Structure–activity relationships—overview

As mentioned earlier, much of the analog development activity in the retinoid area has been focused on discovering agents for cancer therapy and prevention as well as applications in dermatological disease, not the purpose of this review. However, a number of the primary strategies which have had success have also eventually borne fruit in the use of these molecules for metabolic diseases, hence this overview section. As mentioned earlier, one of the important structurally rigid scaffolds which served to block metabolic inactivation was the highly potent TTNPB (**11**). Once the RARs were discovered, it was recognized that TTNPB also has the appropriate structural constraints to make it a high affinity RAR binder [19] and thus it is not resistance to metabolism alone that made TTNPB a useful lead. However, much like many of the natural retinoids, TTNPB can show considerable toxicities when used as a pharmacologic agent. As it was recognized that the RARs exist in at least three subtypes (α, β, and γ)with differential patterns of expression [20] and the same is true for the RXRs, efforts to develop subtype selective retinoids in the hopes of fine tuning activity and toxicity began in earnest. Many of the molecules developed can be viewed as TTNPB descendents with structural features that confer either RAR or RXR selectivity and, when most successful, desired isotype selectivity as has been reviewed in



Scheme 1. Syntheses of retinoids via Wittig reaction. For references to example preparations of building blocks **4**, **5**, and **7** see [8–10] respectively.