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STEREOSELECTIVE SYNTHESIS AND RECEPTOR ACTIVITY OF CONFORMATIONALLY DEFINED RETINOID X RECEPTOR SELECTIVE LIGANDS

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Abstract: Retinoid X Receptor (RXR) specific ligands are currently being investigated for the treatment of metabolic diseases such as type II diabetes. We report the synthesis of conformationally locked retinoids, which are potent RXR selective ligands, and the attempted synthesis of 9-cyclopropyl locked analogs of RA and 9-*cis* RA.

Retinoids are natural and synthetic derivatives of retinoic acid (RA).[1] The retinoid receptors, which are members of the steroid/thyroid super family of nuclear receptors, consist of two classes, the retinoic acid receptors (RARα, RARβ, RARγ)[2] and retinoid X receptors (RXRα, RXRβ, RXRγ),[3] and mediate the biological effects of retinoids. The RXRs function as homodimers[4] or as heterodimers by partnering with RARs and other nuclear receptors, including peroxisome proliferator-activated receptors (PPARs), vitamin-D receptor (VDR) and thyroid hormone receptor (TR).[5] RA is the natural ligand for the RARs,[6] while 9-*cis* RA is the putative endogenous ligand for the RXRs (Figure 1).[7] However, 9-*cis* RA also binds and activates RARs, thus limiting its use as a tool to probe the biology of the RXRs. Due to the important role RXRs may play in various biological processes, there is an ongoing interest in the synthesis of RXR specific ligands which can be used as probes to delineate RXR biology.[8]

Recently, Curley et al. published their findings on conformationally restricted retinoic acid analogues.[9] Here, we disclose our research in the related area of 9-*cis* locked retinoids, which are designed to mimic 9-*cis* RA without the possibility of isomerization around the 9-10 double bond. These 9-*cis* locked retinoids have been shown to be good RXR selective ligands and the cyclopropyl group was found to be an ideal isostere for the 9-*cis* double bond.[8d,8e] Compounds **1** and **2** are selective RXR agonists, with the methyl substituted compound **1**, one of the most potent RXR ligands described to date, being of more than 50-fold higher affinity than the desmethyl analog **2** (Figure 1).[8e] In this regard, we targeted the 9-*cis* cyclopropyl analog **3** and the 9-*trans* cyclopropyl analog **4** as potential RXR and RAR selective ligands,

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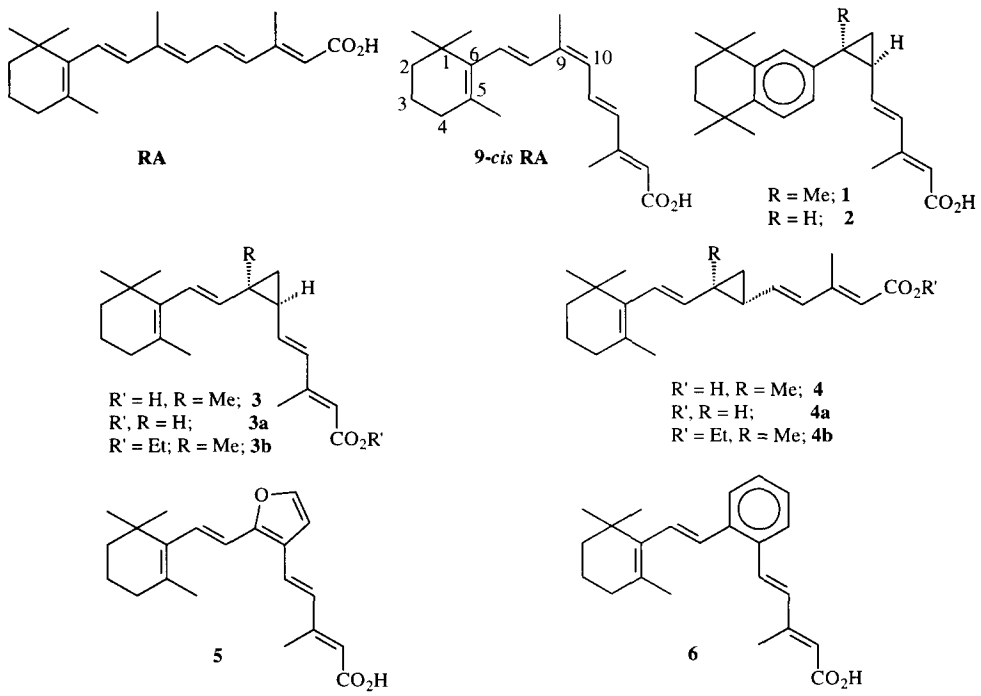
respectively. This report describes our synthetic efforts towards compounds **3** and **4** and the instability of these compounds because of rearrangement of the divinylcyclopropane moiety to a cycloheptadiene. We also describe the syntheses of 9-*cis* aryl locked analogs **5** and **6,** which are potent and selective RXR ligands.

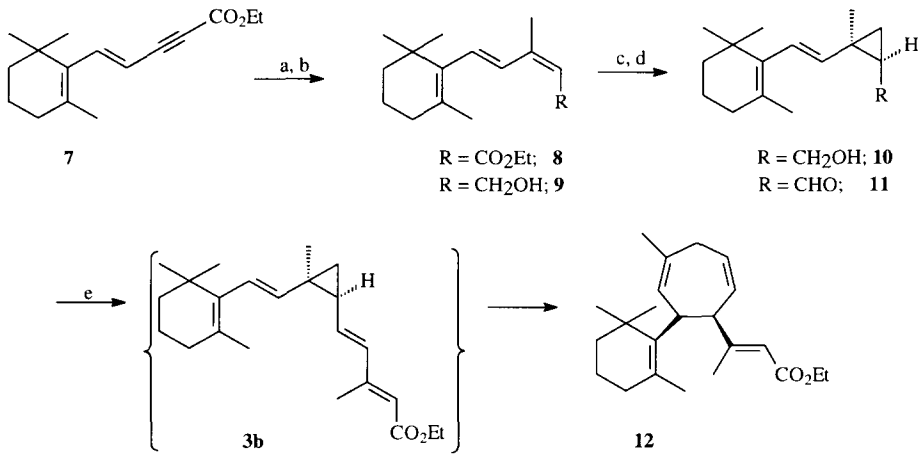
Figure 1



Scheme 1 delineates our attempts to synthesize **3**. Propargyl ester **7**[10] was converted to the Z-α,β-unsaturated ester **8** by reaction with Me_2CuLi at –78 °C. Compound **8** was reduced with DibAl-H to the Z-allylic alcohol **9**. Samarium mediated stereospecific cyclopropanation of **9** gave the *cis* cyclopropyl alcohol **10** in 85% yield. Compound **10** was oxidized to the aldehyde **11** by Swern oxidation. Aldehyde **11** was reacted with diethyl (*E*)-3-ethoxycarbonyl-2-methylallylphosphonate[11,8e] in the presence of LDA at –78 °C, to give a colorless oil in 80% yield. Spectral characterization of this product indicated that it was not the required compound **3b,** but the cycloheptadiene derivative **12**, which is presumably formed via the divinylcyclopropane - cycloheptadiene rearrangement of the initially formed **3b**.

The synthesis of the *trans* cyclopropyl analog **4b** also started from the propargyl ester **7**,[10] which was converted to a mixture of *E* and *Z* α,β-unsaturated esters, in a 10:1 ratio by reaction with Me_2CuLi at higher temperature (Scheme 2). The E isomer **13** was separated and reduced to the allylic alcohol **14**. Samarium mediated stereospecific cyclopropanation of the allylic alcohol **14** gave the cyclopropyl alcohol **15**.

Scheme 1

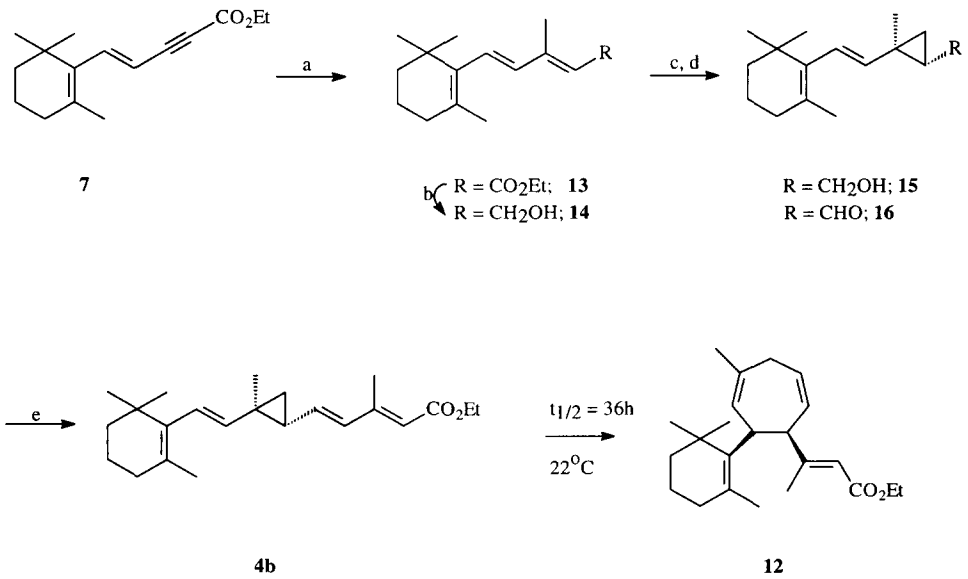


Reagents and conditions: (a) Me_2CuLi, -78 °C, 85%. (b) DibAl-H, -78 °C, 90% (c) Sm, CH_2I_2, 85% (d) Oxalyl chloride, DMSO, Et_3N, 70% (e) LDA, diethyl (*E*)-3-ethoxycarbonyl-2-methylallylphosphonate, 80%.

Compound **15** was oxidized to the aldehyde **16** by Swern oxidation, and the aldehyde was allowed to react with the anion of diethyl (*E*)-3-ethoxycarbonyl-2-methylallylphosphonate to give compound **4b** in 80% yield. The structure of **4b** was confirmed by spectral characterization. Interestingly, **4b** also underwent rearrangement to the cycloheptadiene **12** with a $t_{1/2}$ of 36 h at ambient temp. This precluded the conversion of **4b** to **4** by standard hydrolytic procedures. The surprisingly low stability of **4b** and the contrasting stability of the desmethyl analog **4a**[9] is quite interesting. There are several literature reports for this rearrangement,[12] and the facility with which the *cis*-divinyl cyclopropane rearranges to a cycloheptadiene is

dictated by the substitution pattern on the cyclopropane ring and on the two olefinic bonds. The suggested mechanism for the *cis* divinyl cyclopropane rearrangement is via a concerted pathway, but the rearrangement of the *trans* analog is suggested to follow a diradical pathway under thermal conditions.[12] The relative stereochemistry of the substituents on the cycloheptadiene ring of **12** was assigned based on literature precedence.[13]

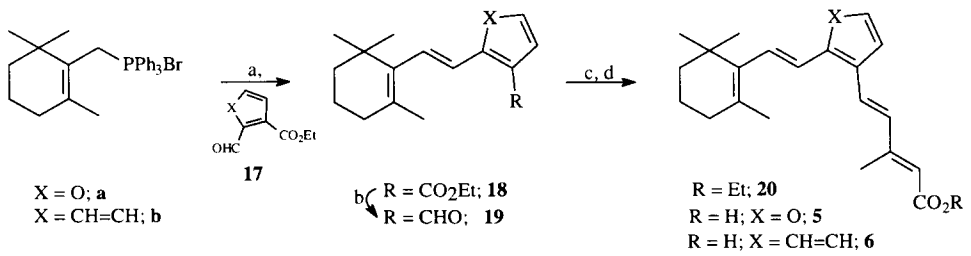
Scheme 2



Reagents and conditions: (a) Me_2CuLi, 0 °C, Flash chromatography, 85%. (b) DibAl-H, -78 °C, 90% (c) Sm, CH_2I_2, 85% (d) Oxalyl chloride, DMSO, Et_3N, 70% (e) LDA, diethyl (*E*)-3-ethoxycarbonyl-2-methylallylphosphonate, 80%.

Having failed to synthesize a strained 9-cyclopropyl locked retinoid as a stable analog, we targeted less strained ring systems (e.g., furyl and phenyl) as 9-*cis* locks, to design RXR selective retinoids. The synthesis of aryl locked target molecules **5** and **6** is described in Scheme 3. The cyclogeranyl phosphonium bromide[9] was reacted with the aldehyde derivatives **17**,[14] and the *E*-olefinic products **18** were purified and reduced to the corresponding to the aldehydes **19** using DibAl-H at –78 °C. Aldehydes **19** were converted to the ethyl esters **20** by reaction with diethyl (*E*)-3-ethoxycarbonyl-2-methylallylphosphonate in 80% yield. Compounds **20a** (X = O) and **20b** (X = CH=CH) were separately hydrolyzed to the acids **5** and **6**.

Scheme 3



Reagents and conditions: (a) n-BuLi, 0 °C, 85%. (b) DibAl-H, -78 °C, 90% (c) LDA, diethyl (*E*)-3-ethoxycarbonyl-2-methylallylphosphonate, 80% (d) KOH.

The binding affinities of the synthetic retinoids were determined by competition of 5 nM [^{3}H] RA (for RARs) and 5 nM [^{3}H] 9-*cis* RA (for RXRs) with unlabelled test retinoid for baculovirus expressed RARs and RXRs respectively (Table 1).[15] The furyl locked analog **5** binds with as high affinity[16] to the RXRs as the putative hormone, 9-*cis* RA. The phenyl analog **6**[16] is a somewhat lower affinity ligand for the RXRs indicating that a smaller lipophilic group is preferred in the ligand binding pocket which accomodates the 9-methyl group of 9-*cis* RA. Unlike 9-*cis* RA, both **5** and **6** are quite selective for the RXRs with neither showing detectable affinity for the RARs.

Table 1

Compound	RAR K_d (nM)			RXR K_d (nM)		
	α	β	γ	α	β	γ
RA	15 ±2	13 ±3	18 ±1	$>10^3$	$>10^3$	$>10^3$
9-*cis* RA	93 ±10	97 ±10	148 ±5	8 ±3	15 ±2	14 ±3
5	$>10^3$	$>10^3$	$>10^3$	7 ±2	15 ±7	14 ±13
6	$>10^3$	$>10^3$	$>10^3$	26 ±7	53 ±19	35 ±12

In summary, we have demonstrated that synthesis of 9-*cis* cyclopropyl locked RA analogs is not feasible due to the spontaneous rearrangement of the *cis*-divinyl cyclopropane moiety to a cycloheptadiene. We also show that the methyl substituted 9-*trans* cyclopropyl RA analog **4b** undergoes rearrangement at

higher temperature. Finally, we have synthesized potent, RXR-selective compounds in **5** and **6**, which will be useful probe compounds in further elucidating RXR biology.

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16. Compounds **5** and **6** are full agonists at all three RXRs tested in the cotransfection assay performed as described in reference 8e above. The potencies of the compounds in the transactivation assays are consistent with the observed binding affinities.