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A Novel Synthesis of 9,13-di*cis* Double Bonds Locked Retinoids

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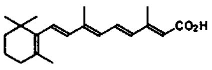
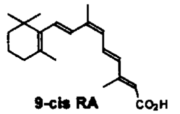
Abstract: Synthesis of two retinoids in which the 9,13-dicis double bonds were locked in cycloalkene or thiophene was described. The key step was carbonylation of vinyl bromide **9** and **16** with carbon monoxide in the presence of $Pd(PPh_3)_4$. © 1997 Elsevier Science Ltd.

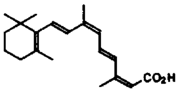
Retinoids are natural and synthetic analogs of Vitamin A . Because of their far ranging biological effects, retinoids have found clinical applications in dermatology, oncology and show promise in other diverse therapeutic areas including arthritis, dyslipidemias, and the prevention of HIV-induced lymphopenia. Cumulative evidence has indicated that retinoids may exert their functions by regulating gene expression mediated by two classes of nuclear receptors: the retinoic acid receptor family (RAR) [1] and the retinoid X receptor family (RXR) [2]. The physiological hormones for the RAR and RXR are proposed to be all-*trans* -retinoic acid (RA) and 9-*cis* -retinoic acid (9-*cis* RA) respectively. However, 9-*cis* RA can bind to and transcriptionally activates the RAR as well [3]. Unfortunately , use of the retinoids is associated with a number of significant side effects and therefore widespread clinical use of retinoids is severely limited . In view of the related, but clearly distinct, nature of these receptors, ligands which are selective for the RAR or RXR family would provide the capacity for independent control of the physiologic processes mediated by the RAR or RXR and further offer the possibility of improved therapeutic indices and reduced toxicity[4]. Recently, identification of 9,13-di*cis*-retinoic acid as a major plasma metabolite of 9-*cis*-RA has been reported[5]. In order to investigate the function of 9,13-di*cis* RA and obtain the selective substances for RXR or RAR receptor, we were interested in designing and preparing compounds **1** and **2** in which the 9-*cis* and 13-*cis* double bond are locked in cyclohexene or thiophene and cyclopentene respectively.



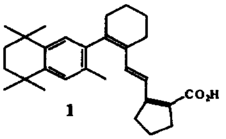
RA



9-cis RA



9,13-dicis RA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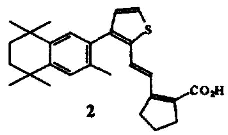
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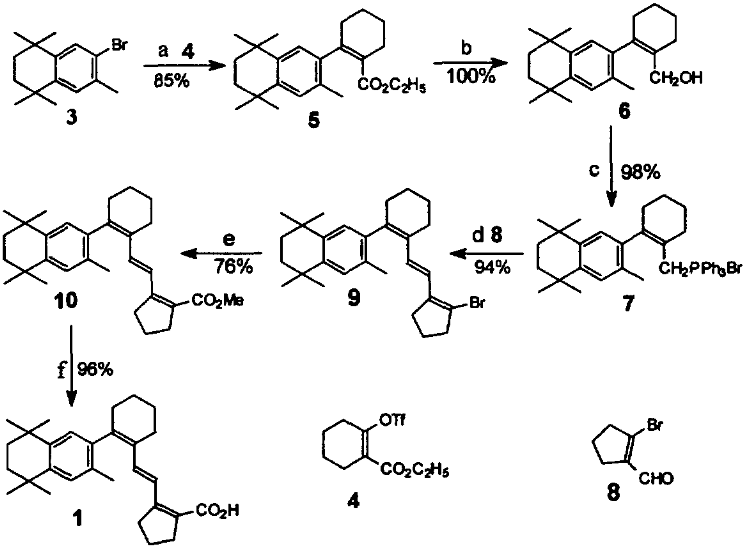
Bromide **3** (Scheme 1) , prepared in 85% yield by reaction of o-bromotoluene with 2,5-dichloro-2,5-dimethylhexane in the presence of aluminum chloride, was used as the starting material for the synthesis of **1**. Bromide **3** was treated with *tert*-butyl lithium at -78°C, followed by zinc chloride at room temperature to give the organozinc compound, which is in turn reacted with ethyl 2-trifluoromethanesulfonyloxycyclohexene-1-ylcarboxylate **4** [6] under palladium(0) catalysis [7] to give ester **5** in 85% yield. This is the first example of palladium-catalyzed cross-coupling of 2-carboethoxy enol triflate with an aryl zinc compound. Lithium aluminium hydride reduction of the ester **5** to the alcohol **6**, followed by reaction with triphenylphosphine hydrogen bromide in dried methanol afforded the phosphonium salt **7** quantitatively. Wittig olefination of phosphonium salt **7** with 2-bromocyclopentene-1-ylaldehyde **8** [8] in dried dichloromethane in the presence of potassium *tert*-butoxide gave the single *trans* isomer vinyl bromide **9** in 94% yield. The *trans* isomer was determinated by the coupling constant of two vinyl protons ($J_{H,H}$ =16.0 Hz). Carbonylation of the unstable vinyl bromide **9** with carbon monoxide in DMF under palladium(0) catalysis [9] at 85°C afforded methyl carboxylate **10** in 76% yield. The ester **10** was cleanly saponified to the 9,13-di*cis*-blocked acid **1**[10].

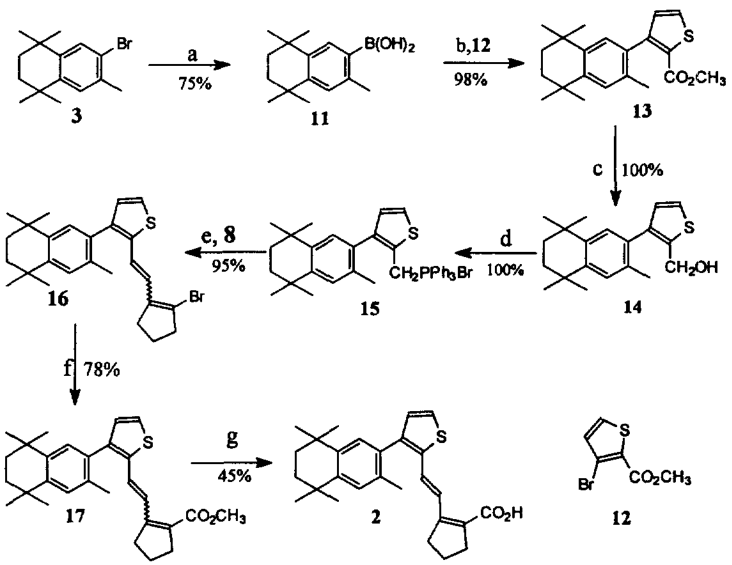
Scheme 1.



Reagents and Conditions: a) t-BuLi, -78°C, then $ZnCl_2$ room temperature, then $Pd(PPh_3)_4$ and 4 ; b) $LiAlH_4$; c) $Ph_3P.HBr$. MeOH; d) t-BuOK, CH_2Cl_2 then 8 e)CO, $Pd(PPh_3)_4$, MeOH, Et_3N, DMF, 85°C; f) aq.KOH, MeOH, reflux, then HCl

We then turned our attention to the synthesis of **2**(Scheme 2) . Our initial approach to the key intermediate **13** by the cross-coupling of the corresponding organozinc compound of aryl bromide **3** with methyl 3-bromo-2-thiophenecarboxylate **12**[11] under palladium (0) or nickel(0) catalysis [12] failed and the compound **12** was recovered. Therefore, an alternative route was adopted for preparation of **13**. Aryl bromide **3** was reacted with *t*-butyllithium, followed by the addition of triisopropylborate and then hydrolysis to a boronic acid **11** in 75% yield. The Suzuki cross-coupling [13] of boronic acid **11** with **12** in the presence of $Pd(PPh_3)_4$ gave the ester **13** in 98% yield. Then the methodology used in Scheme 1 was extented to the preparation of **2**. Thus, in an analogous manner, phosphonium salt **15** was prepared from **13**. However, Wittig-olefination of phosphonium salt **15** with **8** afforded the mixture of vinyl bromide **16** in a ratio of *trans*:*cis* of 8:5 (as determined by ^1H NMR). The mixed vinyl bromide **16** could not be separated by column chromatography and used directly in carbonylation. The mixed ester **17** was hydrolyzed to give a solid which after recrystallization from absolute ethyl alcohol to afford the desired acid **2**[14].

Scheme 2.



Reagents and Conditions: a)t-BuLi,-78°C, then $B(OPr\text{-}i)_3$, R.T., HCl
b) $Pd(PPh_3)_4$, $NaHCO_3$, DME, R.T.; c) $LiAlH_4$; d) $Ph_3P.HBr$, MeOH;
e) t-BuOK, CH_2Cl_2 ; f)CO, $Pd(PPh_3)_4$, MeOH, Et_3N, DMF, 85°C;
g) aq.KOH, MeOH, reflux, then HCl, Recrystallized from ethyl alcohol

The successful approach described herein, enabled us to synthesize a number of analogues related to **1** and **2** . The structure-activity relationships of these derivatives and their ability to transactivate RAR or RXR selectively will be reported in a future publication.

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10. Compound 1: m.p. 264-264.5°C; ^1H NMR(300 MHz, $CDCl_3$): δ: 1.22(s, 3H), 1.25(s,3H), 1.26(s, 3H), 1.28(s, 3H), 1.72(s, 4H), 1.73-1.79(m, 6H), 2.08(s, 3H), 2.33-2.40(m, 6H), 2.67(t, J=7.0Hz, 2H), 6.27(d, J=16.0Hz, 1H), 6.89(s,1H), 7.08(s, 1H), 7.37(d, J=16.0Hz, 1H)ppm; ^{13}C NMR(75 MHz,$CDCl_3$) : δ: 19.18, 21.38, 22.78, 23.02, 25.11, 31.89, 32.09, 32.27, 33.20, 34.16, 35.37, 120.61, 126.70, 126.84, 127.68, 131.31, 132.13, 137.35, 139.49, 141.98, 143.27, 144.26, 156.24, 171.34 ppm; IR(KBr): γ_{max} : 3069, 3015, 2925, 2589, 1666, 1655, 1568, 1495, 1446, 1391, 1361, 1282, 1263, 1247, 978, 894, 766 cm^{-1}. UV(in CH_2Cl_2): 330 nm; MS (EI): 418(M^+, 60), 385(84), 281(100), 195(55), 123(61), 111(75), 69(47), 57(49); HRMS: calcd for $C_{29}H_{35}O_2$ 418.2853, found 418.2834.

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14. Compound 2: m. p. 238-239°C; ^1H NMR(300 MHz,$CDCl_3$): δ: 1.27(s, 6H), 1.32(s,6H), 1.70(s, 4H), 1.85(pent, J= 7.0Hz, 2H), 2.17(s, 3H), 2.62(t, J=7.0Hz, 2H), 2.75(t, J=7.0Hz, 2H), 6.73(d, J=16.0Hz, 1H), 7.00(d, J=5.0Hz, 1H), 7.08(s, 1H), 7.19(s, 1H), 7.27(d, J=5.0Hz, 1H), 7.87(d, J=16.0Hz, 1H)ppm; ^{13}C NMR(75Hz, $CDCl_3$): δ: 20.13, 21.48, 31.93, 32.03, 34.14, 34.25, 34.49, 35.35, 123.35, 124.47, 128.30, 128.41, 128.96, 129.21, 130.73, 132.73, 133.43, 138.17, 142.25, 142.85, 144.49, 154.45, 170.20 ppm; IR(KBr): γ_{max}: 3053, 2927, 2615, 1719, 1668, 1600, 1492, 1391, 1272, 1094, 908, 733, 689, cm^{-1}. UV(in CH_2Cl_2): 340nm; MS(EI): 420(M^+, 100), 405(21), 387(45), 279(70), 3239(27). HRMS: calcd for $C_{27}H_{32}$ O_2S 420.2097, found 420.2071.

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