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AROMATIC RETINOIDS: A SHORT SYNTHESIS OF 7-HYDROXY-6-(5,6,7,8-TETRAHYDRO-5,5,8,8-TETRAMETHYL -2-NAPHTHYL)-2-NAPHTHOIC ACID, (7-HYDROXY-TTNN).

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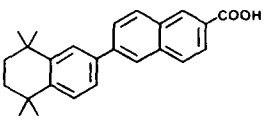
Abstract: *7-hydroxy-TTNN, a possible metabolite of the aromatic retinoid: 6-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2-naphthoic acid (TTNN) (2), was synthesized through a short route, the key step of which was a one pot oxidation / cyclisation / aromatisation of a 1,5 diol to afford the phenolic ring C (see scheme 1).*

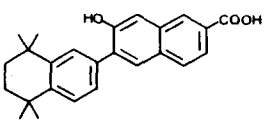
Retinoids have been known for many years to play a crucial role in epithelial cell growth and differentiation and as a consequence, trans-retinoic acid and some related compounds,(13-cis-retinoic acid, etretinate) have been used for the treatment of dermatological diseases such as acne or psoriasis and are being evaluated for their possible beneficial effect in several cancerous conditions.[1] Unfortunately, their severe biological side effects (hypervitaminosis A syndrome, etc.) and the chemical instability of retinoids render their extensive clinical use difficult.

In an effort to obviate these drawbacks, many new molecules, often structurally very different from standard retinoids, have been synthesized during the last few years [2,3,4]. Recently, Dawson et al. reported the synthesis of TTNN (1), the first fully aromatic molecule showing a strong retinoid-like activity.

In the course of our own research, we had independently prepared TTNN as well as structurally related molecules. We report here the synthesis of a possible metabolite of TTNN, 7-hydroxy-6-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2-naphthoic acid.



1

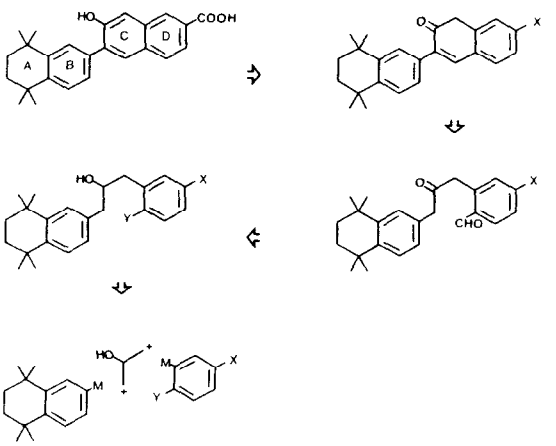


2

Fig 1

Inspection of the target structure (2), suggested that a regiospecific conversion of TTNN into its 7-hydroxy derivative would be difficult. In view of previous unpublished work in our laboratories, the transition metal catalysed coupling between the zincate derived from a 2-bromo-5,6,7,8-tetrahydro-5,5,8.8-tetramethylnaphthalene and a 7-alkoxy-2-naphthoic acid ester, (in a manner analogous to that used for the synthesis of TTNN itself) did not appear very promising. We then turned to a different approach in which the envisaged key step was the cyclisation / aromatization of a 1,5-dicarbonyl compound leading to the desired phenolic ring C. In turn, the former would result from the coupling of two suitable moieties.

The principle of this approach is shown in scheme 1



Scheme 1

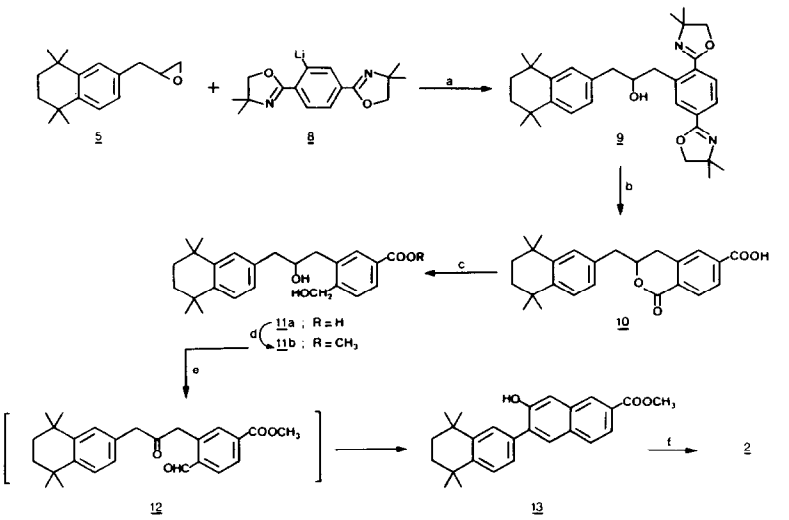
For this approach to be successful, the groups X and Y had to fulfil the following requirements:

* Allow the regiospecific metalation of the phenyl ring in the first step of the synthesis.
* Be easily convertible into carboxyl and formyl groups, respectively.

This led us to the synthetic route depicted in scheme 2

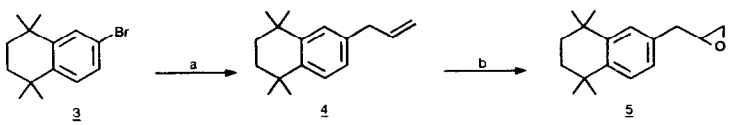
The precursor 5 (racemic) was obtained in 65% yield from the known bromo derivative 4 [6], conversion to the corresponding grignard, coupling with allyl bromide and peroxidation (MCPBA) (see scheme 3).

For our second requisite precursor, we chose the bis-oxazoline 7. This was easily prepared from the readily available 3-bromoterephthaloyl chloride, by successive treatment with 2-amino-2-methylpropanol, chlorination of the latter ($SOCl_2$), and potassium *tert*-butoxide induced cyclisation to form the two oxazolinyl rings (overall yield 79%), as shown in scheme 4.



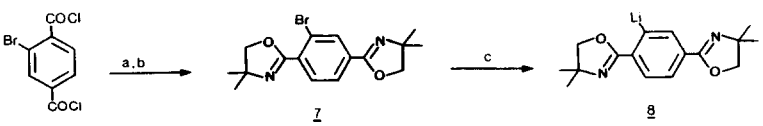
a) cat CuI, THF, -78°C→20°C, 8h, 67%. b) 5N HCl, reflux, 8h,98% . c) 1. $LiBH_4$,THF, reflux, 12h; 2. H^+,0°C, 98%. d) 1. NaH, DMF, 20°C, 1h; 2. CH_3I, 2h, 91%. e) 1. $(COCl_2)$, DMSO, DBU, CH_2Cl_2, -78°C, 2h; 2. -78°C →20°C, 1h, 25%, f) 2N NaOH, CH_3OH, reflux, 2h, .

Scheme 2



a) 1. Mg, THF,20°C,2h; 2. $BrCH_2$-CH=CH_2, 0°C→20°C, 4h, 79%. b) MCPBA, CH_2Cl_2, 20°C, 8h, 87%.

Scheme 3



a) 1. NH_2-$C(CH_3)_2$-CH_2OH, $N(C_2H_5)_3$, CH_2Cl_2, 20°C, 2h; 2. $SOCl_2$,20°C, 4h. b) KOtBu, ether,2h, 79%. c) tBuLi, THF, -78°C, 1h.

Scheme 4

Choosing for X and Y oxazolidine groups fulfilled the first of our initial requirements. We anticipated that differentiation between the two protected carboxyl groups would be possible at a later stage of the synthesis. Thus, conversion of 7 to the corresponding lithio derivative 8 (tBuLi, 2 eq, THF, -78°C, 1h) and coupling with epoxyde 5, (cat CuI, 20°C, 8h) afforded 9 in 67% yield. Hydrolysis of the oxazolinyl groups (5N HCl, 20°C, 8h, 98%) directly afforded the acid lactone 10, thus differentiating the two carboxyl groups. Selective reduction of the lactone moiety ($LiBH_4$, THF, reflux, 12h), gave the diol-acid 11 a which was then converted to the corresponding methyl ester 11 b (NaH, DMF, 20°C, then CH_3I). Oxidation of the 1,5-diol to the corresponding 1,5-dicarbonyl proved to be unexpectedly troublesome. Using Swern's conditions [7], formation of the very unstable keto aldehyde 12 was observed as evidenced by the ^1H NMR spectrum of the material partially purified by fast filtration through a plug of silica gel. However chromatographic purification proved to be impossible due to extensive decomposition. We then examined the possibility of going from 11 b to 13 in a "one pot" two step sequence of reactions involving low temperature oxidation of 11 b to 12, and base induced cyclisation to 13. Accordingly, treament of 11b under Swern's conditions ($(COCl)_2$/DMSO, -78°C, CH_2Cl_2, 2h), then addition of DBU (-78°C→20°C, 1h), afforded 13 in 25% yield, which was saponified to give 2.

Preliminary studies in our biological screening system showed that 2 is able to induce differentiation of F9 teratocarcinoma cells in culture[8] but, unlike TTNN or other potent retinoids, is a poor inhibitor of induced ornithine decarboxylase activity [9,10] in rat skin.

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