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APPLICATION OF THE HECK REACTION IN THE SYNTHESIS OF TRUNCATED NAPHTHOIC ACID RETINOIDS

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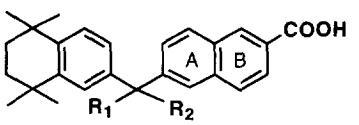
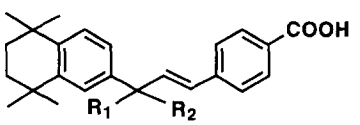
Abstract A series of truncated naphthoic acid retinoids have been prepared using the Heck reaction. These retinoids were evaluated in the RAR transactivation assay in vitro and in the utriculi reduction assay in vivo. It has been found that the naphthalene ring of the retinoids is crucial for their retinoid activity and receptor selectivity. Copyright © 1996 Elsevier Science Ltd

Over the last two decades there has been a great effort in the study of the regulation of retinoids (retinoic acid and its derivatives) in cell differentiation and cell proliferation.[1] This effort has resulted in several drugs of clinical use such as 13-cis-retinoic acid (Accutane) and etretinate (Tegison) for the treatment of cancers and dermatological diseases. However, there are still some major concerns regarding the adverse effects caused by these retinoids (e.g. irritation and teratogenecity). Recent evidence has shown that retinoic acid exerts its functions through at least two classes of nuclear receptors, RAR (α, β, γ) and RXR (α, β, γ), which are unevenly distributed in different tissues.[2] The current trend in retinoid research has been focused on developing receptor selective retinoids in attempts to define the functions of each receptor. It has been hoped that these receptor selective retinoids might exert their desired functions through a specific receptor, thus avoiding side effects.[3]

Pfahl and his colleagues have demonstrated that 6-substituted naphthalene-2-carboxylate derivatives **1** and **2** are RAR β, γ and RAR-γ selective, respectively.[3e] We also have reported that this type of retinoid with varied linkers between 1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene and 2-naphthoic acid are generally RAR β, γ selective.[3a] **Ch 80**,[4] a naphthoate derivative in which the A ring is truncated, has been found to be more potent than **1**, but lacks receptor selectivity. In contrast, the corresponding alcohol **3**[3b] is more potent than **2** and yet maintains RAR γ-selectivity. These findings prompted us to investigate the importance of the B ring of **1** for retinoid activity and receptor selectivity. Thus, compounds **4-12** with various truncated B ring structures were prepared (Chart 1).

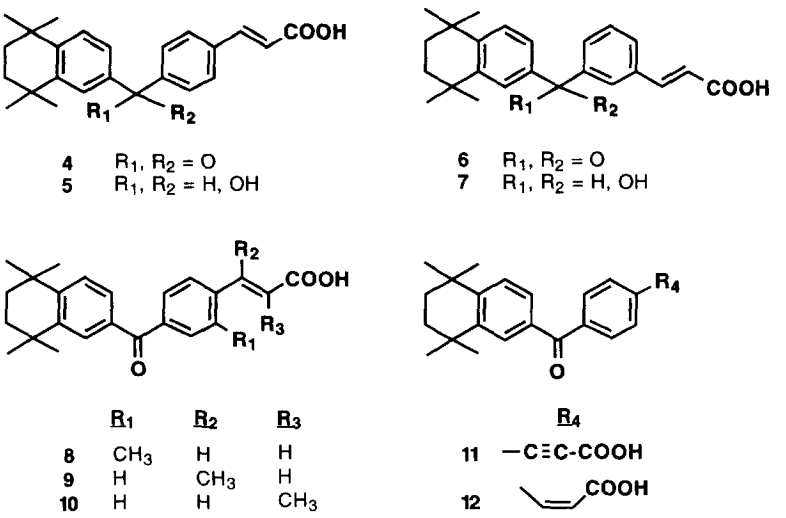


1 R_1, R_2 = O
2 R_1, R_2 = H, OH



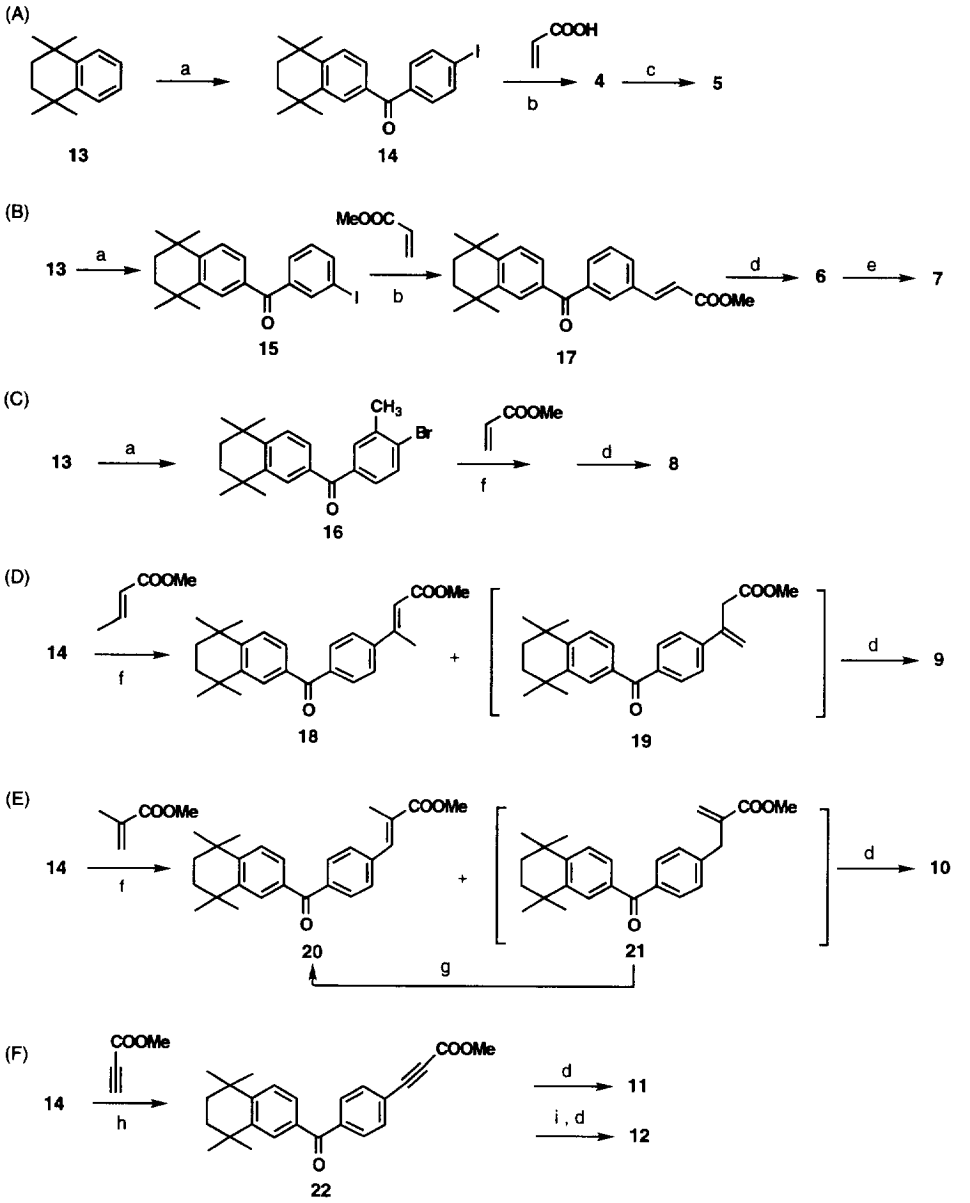
Ch 80 R_1, R_2 = O
3 R_1, R_2 = H, OH

Chart 1



All of the retinoids in the study were prepared using the Heck reaction and are shown in Scheme 1. Acylation of 1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene (**13**) with 4-iodo- or 3-iodobenzoyl chloride or 3-methyl-4-bromobenzoyl chloride provided intermediates **14-16**, respectively, in good yields (60-90%). Heck reaction of **14** with acrylic acid in the presence of $Pd(OAc)_2$-P(2-Tol)3 and Bu_3N,[5] followed by recrystallization of the product from THF-hexane, gave acid **4** in 19% yield (Scheme 1A). Reduction of ketone **4** using DIBAL in THF resulted in alcohol **5** in 20% yield. The low yield of the Heck reaction was improved when acrylic acid was replaced with methyl acrylate. Thus, **15** afforded ester **17** in 74% yield (Scheme 1B). Saponification of **17** gave ketone acid **6** which was further reduced using $NaBH_4$ to provide alcohol **7** (95%). Interestingly, the same Heck reaction conditions gave no reaction with less reactive aryl bromide **16**.[7] However, the reaction occurred in the presence of the phase transfer catalyst Bu_4NCl[6] (84% yield) (Scheme 1C). Using these reaction conditions, **14** reacted with methyl 3-methyl acrylate to provide **18** and a side product **19** that resulted from isomerization of ester **18** in the presence of the palladium catalyst[7] (Scheme 1D). Similarly, **14** reacted with methyl 2-methyl acrylate to yield a mixture of **20** and isomer **21** that could not be separated (Scheme 1E). Unconjugated olefin **21** was easily isomerized to the more thermodynamically stable **20**, with DBU in boiling toluene (72% for two steps). To obtain acetylene **11**, **14** was treated with methyl propiolate in the presence of $PdCl_2(PPh_3)_2$ and CuI[8] to afford **22** in 9% yield (Scheme 1F). Several attempts to improve the reaction yield were unsuccessful due to the polymerization of the acetylene. Hydrogenation of acetylene **22** using Lindlar's catalyst yielded the cis olefin ester of **12**. Saponification of the methyl esters of the retinoids described above yielded the corresponding acids in good yields.

Scheme 1[a]



[a] (a) $AlCl_3$, halogenated acyl chloride; (b) $Pd(OAc)_2$, $(2\text{-Tol})_3P$, Bu_3N or Et_3N; (c) DIBAL; (d) NaOH; (e) $NaBH_4$; (f) $Pd(OAc)_2$, Bu_4NCl, K_2CO_3; (g) DBU; (h) $PdCl_2(PPh_3)_2$, CuI, K_2CO_3; (i) Lindlar catalyst, H_2.

Retinoids **4-12** were evaluated in the *in* vitro RAR transactivation assays[9] using chimeric retinoic acid receptors to determine their potency and selectivity in regulating gene expression. The ability of each compound to activate gene expression of RAR α, β, and γ, respectively, is presented in Table 1 using EC_{50} and maximum activity that are normalized with those of retinoic acid (i.e. EC_{50} ratio and % maximum). The table clearly indicates that some these truncated derivatives are likely RAR β, γ selective, but less potent than the parent compound (**1**). Among these analogs, acrylate **4** demonstrated a profile very similar to that of **1**, but is less potent. Surprisingly, reduction of ketone **4** to alcohol **5** greatly reduced transactivation activity such that only very weak activity was observed at RAR γ and no activity at RAR α and RAR β. When the substitution position of the acrylate on the aromatic ring changed from para to meta (ketone **6**), the activity was drastically reduced as compared to ketone **4**. Conversion of the E-acrylate to a propiolate or a Z-acrylate (**11** and **12**, respectively) also caused a substantial loss in activity. These results suggest that the orientation and the distance between the carboxylic acid and the aromatic ring is crucial to the activity of these retinoids. In attempts to improve the activity of **4** through increased hydrophobic interactions, methyl groups were introduced at various positions around the acrylate or the aromatic ring, which resulted in analogs **8-10**. Methyl substitution at the α position of acrylate **4** gave **10**, which is slightly less active than **4**. Other methyl substituted compounds (**8** and **9**) also failed to produce improved activity. The weaker activity of all of these truncated retinoids could be due to a decrease in structural rigidity near the carboxylic acid group or loss of π–π interaction of the B ring with the receptors.

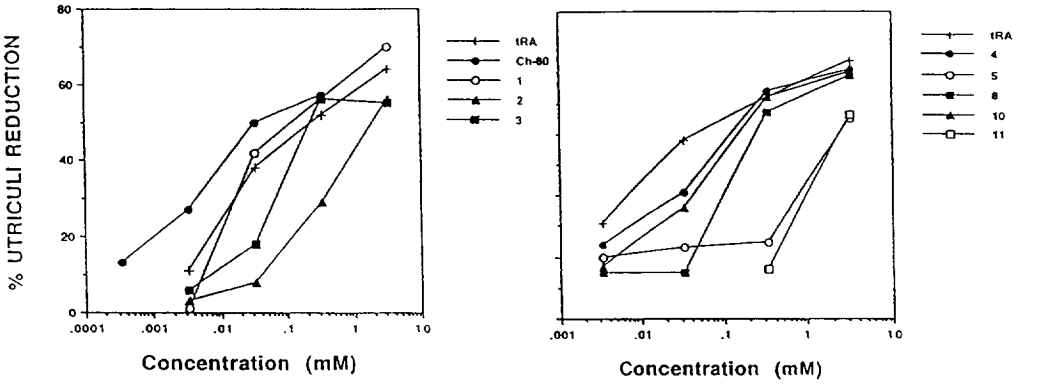
Table 1: RAR Transactivation[a] And Utriculi Reduction Assays of the Truncated Retinoids

comp'd	EC_{50} Ratio [b]			% Max[c]			ED_{30} (mM)
	RAR α	RAR β	RAR γ	RAR α	RAR β	RAR γ	
1	13	3	1.4	65	82	93	0.029
2	NA	133	14	0	77	95	0.223
Ch 80	0.7	1.2	1.0	100	91	98	0.0034
3	20	80	6	89	100	103	0.065
4	63	100	67	63	78	86	0.054
5	NA	NA	NA	0	0	28	1.74
6	NA	NA	167	0	0	41	ND
7	NA	NA	NA	0	0	0	ND
8	NA	100	17	0	66	66	0.184
9	NA	100	17	0	47	51	ND
10	14	10	1	37	70	65	0.092
11	NA	75	10	0	47	39	1.0 [d]
12	NA	100	20	0	41	46	ND

(a) Compounds were evaluated at concentrations ranging from 10^{-10} to 10^{-6} M. NA: not active. ND: not determined due to low activity. (b) The EC_{50} ratio of each compound was obtained by dividing the concentration required to obtain 50% of the maximum transactivation activity of each compound with that of retinoic acid. (c) % Max is the maximum transactivtion activity of the tested compound relative to that of retinoic acid at 10^{-6} M. (d) estimated value.

Compounds that showed significant RAR transactivation activity in vitro were evaluated in a rhino mouse utriculi reduction assay[10] to determine their in vivo efficacy (Figure 1). In this study, retinoids were applied on the skin of rhino mice, and the efficacy of the retinoids was measured by the reduction of the diameter of the utriculi in the skin. Sixty percent utriculi reduction is the maximal efficacy observed in the assay. The ED_{30} is, therefore, defined as the concentration that induces 30% utriculi reduction. The results shown in Table 1 and Figure 1 indicate that in vivo activity of these retinoids correlates well with their in vitro activity described above.

Figure 1. In Vivo Utriculi Reduction Assay of the Retinoids



In conclusion, the Heck reaction has been applied to prepare a series of truncated naphthoic acid retinoids. The SAR of these retinoids indicates that the B ring of **1** has no influence on the RAR receptor selectivity. However, the ring is important to direct the orientation of the carboxylic acid to the receptor, which is essential for the retinoid activity. In contrast, **Ch80** which has a truncated A ring is not receptor selective, indicating that the A ring of **1** is crucial for the RAR β, γ selectivity of the naphthoates.

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