Tetrahedron Letters,Vol.29,No.11,pp 1251-1254,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

EXTREME TWISTING OF THE RETINOID SIDE-CHAIN: 11-TERT-BUTYL RETINOIDS BY CATALYZED ISOMERIZATION OF β-ALLENIC RETINALS

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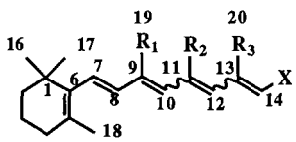
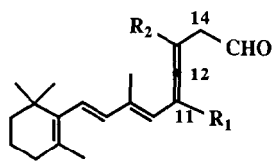
Abstract: The base-catalyzed isomerization of 11-tert-butyl-11,12-allenic retinal (7) afforded 11-tert-butylretinals with fixed 11-cis geometry. Similar treatment of the 13-tert-butyl-11,12-allenic retinal (8) provided the analogues with fixed 13-cis geometry. The extreme twisting of the retinal polyene chain in the 11-tert-butylretinals 6a,b is reflected by the observation of their dramatically blue shifted absorption maxima (~270 nm).

In order to further investigate the conformational and/or configurational requirements that the retinoids must possess for expressing their biological function,[1] and for developing insight into their spectroscopic and isomerization behavior, the synthesis and study of retinoid analogues having highly distorted side-chains such as 1-4 have become of some interest to this laboratory.[2] We have previously described the synthesis and spectroscopic properties of



1 R_1= t-Bu, R_2= H, R_3= Me, X= -CH_2OH
2 R_1= t-Bu, R_2= H, R_3= Me, X= -CHO
3 R_1= Me, R_2= H, R_3= t-Bu, X= -CH_2OH
4 R_1= Me, R_2= H, R_3= t-Bu, X= -CHO
5 R_1= Me, R_2= t-Bu, R_3= Me, X= -CH_2OH
6 R_1= Me, R_2= t-Bu, R_3= Me, X= -CHO



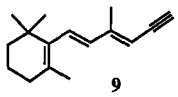
a, Δ^{11}=Z; Δ^{9}=Δ^{13}=E (11-cis)
b, Δ^{11}=Δ^{13}=Z; Δ^{9}=E (11,13-dicis)
c, Δ^{9}=Δ^{11}=Δ^{13}=Z (9,11,13-tricis)
d, Δ^{13}=Z; Δ^{9}=Δ^{11}=E (13-cis)

7 R_1= t-Bu, R_2= Me
8 R_1= H, R_2= t-Bu

retinals incorporating a bulky tert-butyl group at the branched positions of the polyene chain (C_9 and C_{13}) as in **2a-d** and **4b,d**, respectively.[2,3] We wish to report here on the chemical and spectral properties of the 11-tert-butylretinals **6a-b**, the most highly side chain twisted derivatives yet synthesized. The synthesis described herein is based on the prototropic rearrangement of 11,12-vinylallenals **7** and **8** (formally referred to as 12,14-retro-retinals[4]). We have already described the use of the thermal rearrangement of 11,12-vinylallenes to 11-cis-retinoids, both for the preparation of the parent retinoids[4a] and the 13-tert-butylretinoids **3b,d** and **4b,d**.[2a,b]

The incorporation of the tert-butyl group at the 11-position in the desired 11,12-allene was accomplished by the regioselective S_N2' displacement of a propargylic benzoate by a higher order heterocuprate.[2] Trienyne **9**[5] was condensed (n-BuLi, THF, -78 °C; room temp., 20 min)

with the silyl ether derivative 10 (0.66 mol equiv., -78 °C) of 4-hydroxy-2-butanone to give in 72% yield the propargyl alcohol 11.[7] The latter was benzoylated (n-BuLi, THF, -78 °C; PhCOCl; then room temp.) to give 12 (82%), which was reacted with $(t\text{-Bu})_2Cu(CN)Li_2$[6] in ether at 0 °C to afford the 11,12-vinylallenic silyl ether 13 (70%). Desilylation of 13 (Bu_4NF, THF) afforded the desired vinylallenol 14 (80%).[7a]



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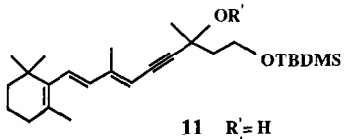
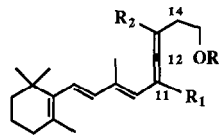
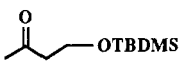


11 R'= H
12 R'= Bz



13 R_1= t-Bu, R_2= Me, R= TBDMS
14 R_1= t-Bu, R_2= Me, R= H
15 R_1= H, R_2= t-Bu, R= H



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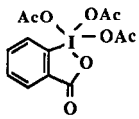

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The complex thermal behavior (a [1,5]-sigmatropic hydrogen shift followed by a [1,7]-sigmatropic hydrogen shift) of the 11,12-vinylallene in the parent system[4a] as well as the similarly complex thermal behavior of 13[8] led us to seek alternative methods for the rearrangement. One attractive possibility was the rearrangement of a β-allenic carbonyl compound,[9-12] but previous attempts to oxidize β-allenic primary alcohols such as 14 had failed. We now report that the Dess-Martin reagent 16[13] can be effective in oxidizing a vinylallenol such as 14 to the corresponding vinylallenal. A 30% excess of the Dess-Martin reagent in anhydrous methylene chloride effects complete transformation of vinylallenols to vinylallenals within ten minutes. A 77% yield was obtained for oxidation of the 11-tert-butyl allenol 14 and a 75% yield for the 13-tert-butyl allenol 15[2a] to afford the vinylallenals 7[7b] and 8,[7c] respectively.

Table I outlines the results for the catalyzed rearrangement of the 11-tert-butyl- and 13-tert-butyl-vinylallenals 7 and 8. Several aspects of the results deserve further comment.

Table I. Base catalyzed rearrangement of 11,12-vinylallenals

Entry	Substrate	Products	Yield[d]
1[a]	7	6a (28%), 6b (28%)	56%
2[a]	8	4b (27%), 4d (27%)	54%
3[b]	7	6a (50%), 6b (25%)	75%
4[c]	8	4b (20%), 4d (30%)	50%

[a] 1.0 M NaOEt, EtOH, 0 °C, 2h; quenching with HOAc; ref. 11b. [b] Activated Al_2O_3, C_6H_6, 80 °C, 6 hours; ref. 10c. [c] Activated Al_2O_3, C_6H_6, room temperature, 48 hours. [d] Yields refer to HPLC purified compounds and account for oxidation and rearrangement steps.

Firstly, the bulky tert-butyl group imparts cis stereoselectivity at the double bond to which it is attached. The products derived from the 11-tert-butyl vinylallenal 7 possess 11-cis geometry (6a,b),[7d,e] whereas the 13-tert-butyl-allenal 8 rearranges to give products with

13-cis geometry (**4b,d**).[2b] Secondly, the 11-cis isomer obtained in entry 3 can be accounted for by a competing thermal pathway,[4a] not by a base-catalyzed isomerization of the 11,13-dicis-retinal **6b** to the 11-cis-retinal **6a**. This was corroborated by the observation that thermal treatment of 11,13-dicis-retinal **6b** led to apparent decomposition and not to any of its isomers (**6a** or possibly even **6d**[2b]). The formation of **6d** by an electrocyclic pathway[2b] from **6b** was an anticipated result; we take the lack of formation of **6d** to be indicative of the bulky tert-butyl group preventing the formation of the α-pyran intermediate postulated for the interconversion of retinals containing 11,13-dicis and 13-cis geometries.[2b,c,14] The stereochemistries about the Δ^{11} and Δ^{13} double bonds in **6a** and **6b** accrue from analysis of their ^{1}H-NMR spectra[7d,e] and are supported by NOE experiments[15] and the following experiment: the oxidation of the retinols **5a,b** obtained by the thermal rearrangement sequence starting from **13**[8] gave the same aldehydes **6a,b** as described above. Since the thermal rearrangement of 11,12-allenes is known to afford 11-cis and 11,13-dicis retinoids,[2a,4a] this provides further evidence for the geometries assigned to **6a,b**.

The electronic spectral data for the 11-tert-butylretinals **6a,b** as well as the 11,13-dicis isomers of 9-tert-butyl- and 13-tert-butylretinals (**2b** and **4b**)[2b] appear for comparison in Table II. It has already been observed[2b] that the electronic spectra of the

Table II. – UV Absorption Data. For comparison purposes, the UV spectra of compounds **2b** and **4b** (ref. 2b) are included.

	95% EtOH λ_{max} nm (ε)	hexanes λ_{max} nm (ε)	CH_3CN λ_{max} nm (ε)
2b	234 (12,800), 278 (10,100) 344 sh (5,800)	216 (13,100), 234 sh (11,100) 278 (10,000), 338 sh (7,500)	236 (12,800), 278 (10,500) 346 sh (6,600)
4b	234 (19,600), 300 (25,000)	226 (18,500), 302 (24,900)	230 (19,700), 302 (25,400)
6a	274 (20,300)	272 (20,600)	274 (20,800)
6b	270 (18,600)	268 (17,700)	272 (19,500)

13-tert-butyl retinals **4b,c** resemble those observed for the conformationally similar 12-s-cis locked retinals[2d] while positioning a tert-butyl group at the 9-position causes a blue shift in the UV spectra.[2b] We have observed that the 11-tert-butylretinals **6a,b** exhibit a broad absorption centered at about 270 nm, which is the most blue shifted absorption maximum ever observed for a retinal analogue possessing the complete pentaenal chromophore. This clearly reflects the extremely distorted nature of the side chains of **6a,b**.

Acknowledgements. The National Institutes of Health (USPHS Grant DK-16595), NATO (Postdoctoral Fellowship to A.R. de Lera), UC Riverside (President's Undergraduate Fellowship to T.C. Norman) and Badische-Anilin und Soda Fabrik, Ludwigshafen (starting material) are acknowledged for support of this study.

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(7) All new compounds exhibited satisfactory ^{1}H-NMR (200 or 300 MHz), ^{13}C-NMR, IR, and UV spectra as well as low resolution and exact mass MS data. Selected ^{1}H-NMR data ($CDCl_3$) are as follows: (a) **14**: δ 1.02 (6H, $C_{16,17}$-$2CH_3$, s), 1.06 (9H, t-Bu, s), 1.70 (3H, C_{19}-CH_3, s), 1.77 (3H, C_{18}-CH_3, s), 1.86 (3H, C_{20}-CH_3, s), 2.00 (2H, $2H_4$, m), 2.25 (2H, $2H_{14}$, t, J~6.3 Hz), 3.71 (2H, $2H_{15}$, t, J~6.3 Hz), 5.77 (H, H_{10}, s), 6.08 (2H, $H_{7,8}$, s); (b) **7**: δ 1.03 (6H, $C_{16,17}$-$2CH_3$, s), 1.08 (9H, t-Bu, s), 1.4-1.6 (4H, $2H_2$ and $2H_3$, two m), 1.72 (3H, C_{19}-CH_3, s), 1.82 (3H, C_{18}-CH_3, s), 1.87 (3H, C_{20}-CH_3, s), 2.04 (2H, $2H_4$, t, J~6.0 Hz), 3.03 (2H, $2H_{14}$, AB geminal splitting pattern with further doublet splitting, J_{AB}~16.3 Hz and $J_{14,15}$~2.6 Hz), 5.78 (1H, H_{10}, s), 6.13 (2H, H_7 and H_8, s), 9.74 (1H, H_{15}, t, J~2.6 Hz); (c) **8**: δ 1.023 and 1.026 (6H, $C_{16,17}$-$2CH_3$, two s), 1.09 (9H, t-Bu, s), 1.71 (3H, C_{18}-CH_3, s), 1.89 (3H, C_{19}-CH_3, d, J~1.2 Hz), 2.02 (2H, $2H_4$, t, J~6.0 Hz), 3.03 (2H, $2H_{14}$, m), 5.80 (1H, H_{10}, dd, J~11.3 Hz, 1.0 Hz), 6.08 (1H, H_8, d, J~16.3 Hz), 6.12 (1H, H_7, d, J~16.3 Hz), 6.31 (1H, H_{11}, dt, J~11.2 Hz, 2.5 Hz), 9.61 (1H, H_{15}, t, J~2.8 Hz); (d) **6a**: δ 1.03 (6H, $C_{16,17}$-$2CH_3$, s), 1.13 (9H, t-Bu, s), 1.62 (3H, C_{19}-CH_3, s), 1.72 (3H, C_{18}-CH_3, s), 2.03 (2H, $2H_4$, t, J~6.0 Hz), 2.16 (3H, C_{20}-CH_3, s), 5.96 (1H, H_{14}, d, J~8.0 Hz), 6.10-6.15 (4H, $H_{7,8,10,12}$, m), 10.03 (1H, H_{15}, d, J~8.0 Hz); (e) **6b**: δ 1.02 (6H, $C_{16,17}$-$2CH_3$, s), 1.15 (9H, t-Bu, s), 1.61 (3H, C_{19}-CH_3, s), 1.70 (3H, C_{18}-CH_3, s), 1.98 (3H, C_{20}-CH_3, s), 2.01 (2H, $2H_4$, t, J~6.0 Hz), 5.75 (1H, H_{14}, d, J~8.3 Hz), 5.96 (1H, H_{10}, s), 6.07 (2H, $H_{7,8}$, s), 6.40 (1H, H_{12}, s), 9.82 (1H, H_{15}, d, J~8.3 Hz).

(8) Thermolysis of 13 (~10^{-3} M solution of allene, refluxing isooctane, 12 h) followed by deprotection afforded an inseparable mixture of 11-cis (**5a**) and 11,13-dicis (**5b**) retinols together with a 20,14-retro-retinol (see ref. 4 for a related retro-retinol). Separation was achieved after selective MnO_2 oxidation of the retinols to the retinals **6a** and **6b**. The retro-retinol, being a non-allylic alcohol, is not oxidized with MnO_2, rendering the resulting retinals **6a** and **6b** easily separable.

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(14) Such an interconversion was observed when **8** was treated under condition b of Table 1, the only isomer obtained being **4d** accompanied by unreacted **8**. Of mechanistic interest is the observation that treatment of **7** or **8** with activated silica gel for short periods of time afforded a single isomer, **6b** or **4b**, respectively, and unreacted starting material. This could indicate that a cyclic [1,5]-hydrogen shift of the Z-enol form of the vinylallenal **7,8** is taking place.

(15) In support of the Δ^{11} configurational assignment, saturation of the t-Bu signal of **6a** and **6b** caused strong enhancement of the H_{12} resonance (6.14 and 6.40 ppm, respectively) of both isomers. Strong enhancement of the aldehyde signal (10.03 ppm) of **6a** upon saturation of the C_{20}-CH_3 resonance (2.16 ppm) supports its 13-trans assignment. In support of the 13-cis geometry for **6b**, saturation of the C_{20}-CH_3 resonance (1.98 ppm) resulted in enhancement of the H_{14} resonance (5.75 ppm), but no enhancement of the aldehyde signal.

(Received in USA 1 December 1987)