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THERMAL REARRANGEMENT OF TERT-BUTYL SUBSTITUTED 9,10- AND 11,12-ALLENIC RETINOIDS: 11-CIS-ISOMERS OF 19,19,19- AND 20,20,20-TRIMETHYLRETINOIDS

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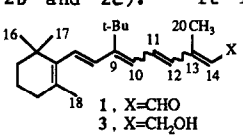
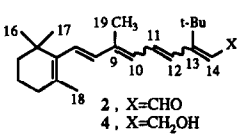
Abstract: The 9,10- and 11,12-allenic retinoids, **5a** and **6a**, respectively, were synthesized in high yield and specificity by t-butylation of the propargylic benzoates **9b** and **12b**, respectively. Thermal isomerization of the allenes afforded the 11-cis, the 11,13-dicis and the 9,11,13-tricis isomers of the 9-t-butyl retinol 3 and the 11,13-dicis isomer of the 13-t-butyl retinol 4.

There is continuing intense interest in the preparation of retinoid (vitamin A) analogues as biochemical research tools. Analogues of especial interest are those which probe the steric, electronic and conformational features of the retinoid side chain in terms of the selectivity of binding of the retinoid to an ubiquitous array of receptor proteins. Examples include opsin in the visual system, bacterioopsin in the light energy transduction system of Halobacterium halobium, and putative receptors which are undoubtedly pertinent in cell differentiation and proliferation systems.[1] As a means of gaining further insight into the sterically related topographical restrictions of the side chain, the availability of analogues possessing exceptionally bulky groups on the retinoid side chain could provide useful structure-function information. In this regard, a recent report by Hopf describes the preparation of several 9-cis, 13-cis and 9,13-dicis-retinals bearing side-chain tert-butyl groups (1a, 1b, 2b and 2c).[2] It is the purpose of this and the accompanying communication to

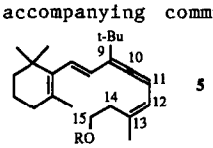


1, X=CHO
3, $X=CH_2OH$



2, X=CHO
4, $X=CH_2OH$

a, Δ^9=Z; Δ^{11}=Δ^{13}=E (9-cis)
b, Δ^9=Δ^{13}=Z; Δ^{11}=E (9,13-dicis)
c, Δ^{13}=Z; Δ^9=Δ^{11}=E (13-cis)
d, Δ^{11}=Δ^{13}=Z; Δ^9=E (11,13-dicis)
e, Δ^9=Δ^{11}=Δ^{13}=Z (9,11,13-tricis)
f, Δ^{11}=Z; Δ^9=Δ^{13}=E (11-cis)
g, Δ^9=Δ^{11}=Z; Δ^{13}=E (9,11-dicis)
h, Δ^9=Δ^{11}=Δ^{13}=E (all-trans)



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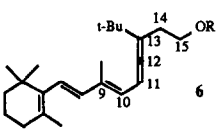
(a, R=TBDMS; b, R=H)



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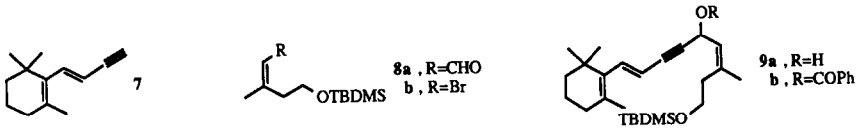
describe our complementary results concerning the preparation of several additional isomers in the series 1-4. Our syntheses are based on regiospecific tert-butylation of retinoid side chain propargylic benzoates to afford 9,10- and 11,12-allenic retinoids, 5 and 6, respectively, which are then subjected to thermal [1,5]-sigmatropic shifts. This thermal strategy,[3] although not normally selective with regard to Δ^9-cis or Δ^{13}-cis geometry, is specific for the

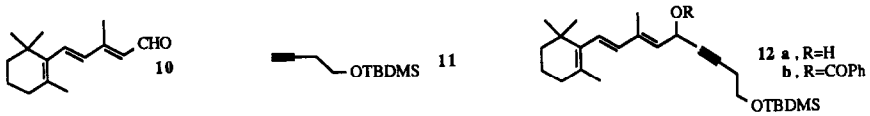
especially important and difficult to obtain Δ^{11}-cis geometry.

Preparation of the 9,10-allene 5: The Negishi dienyne 7[4a] was transformed into its lithium salt (n-BuLi, THF, -78 °C) and then reacted with aldehyde 8a (prepared by reacting the lithium salt of bromide 8b[3b,4b] with N,N-dimethylformamide) to afford propargyl alcohol 9a in 85% yield.[5] Benzoylation (0.74 mmol PhCOCl, 2.5 mL pyridine, 9 mg N,N-dimethylaminopyridine)



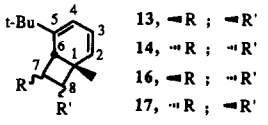
of 9a (0.71 mmol) afforded 9b in 95% yield. Addition of the benzoate 9b (0.23 mmol; 1 mL ether) to $(t\text{-Bu})_2Cu(CN)Li_2$ (1.0 mmol t-BuLi in pentane, 0.51 mmol CuCN, 2 mL ether) at -78 °C afforded after work-up, a 94% yield of TBDMS (t-butyldimethylsilyl) protected 9,10-allenic alcohol 5a. The latter was characterized as the alcohol 5b[6a] [prepared in 97% yield by treatment of 5a with 1 M tetrabutylammonium fluoride (TBAF) in THF for 2 h at room temperature].

Preparation of the 11,12-allene 6: The aldehyde 10[7] was reacted with the lithium salt of the TBDMS ether of 3-butyn-1-ol (11) to afford 12a (89%), which in turn was benzoylated as above to afford 12b (~ quantitative). Reaction of the latter with $(t\text{-Bu})_2Cu(CN)Li_2$ in ether as above afforded the TBDMS protected 11,12-allene 6a in 90% yield. The latter was also characterized as the corresponding vinylallenol 6b[6b] (91% yield from 6a).

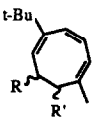


Thermolysis of the 9,10-allene: A solution of the 9,10-allene 5a (176 mg) in hexanes (~10^{-3} M) was refluxed (69 °C) for 22 h, cooled, and then concentrated to dryness. After exposing the residue to TBAF in THF (1-2 h) as above followed by conventional work-up, HPLC separation (Whatman Partisil M9 10/50 column, 3% iPrOH/Skellysolve B) afforded in order of elution the following: bicyclooctadiene A[6c] (13 or 14; 13.8 mg, 11%); bicyclooctadiene B[6d] (16 or 17; 26.3 mg, 20%); the 11,13-dicis-retinol 3d[6e] (25.0 mg, 19%); the 9,11,13-tricis-retinol 3e[6f] (9.6 mg, 7%); and the 11-cis-retinol 3f[6g] (13.4 mg, 10%) [67% total yield after separation based on 5a]. In control experiments, all five alcohol products were transformed back into their TBDMS ethers and individually subjected to the original reaction conditions (69 °C, 22h). The TBDMS ether of tricis-retinol 3e, besides apparent decomposition or transformation to minor olefinic material (^{1}H-NMR), afforded bicyclooctadiene A (70% 13 or 14) and recovered starting material (30%). The remaining four TBDMS ethers led mainly to recovered starting material. Thermolysis of 9,10-allenic retinoids of the type 5a was anticipated to afford one mono-cis-retinol (11-cis), two dicis-retinols (the 9,11- and 11,13-dicis isomers) and one tricis-retinol (the 9,11,13-tricis isomer).[3b,c] It was also expected that the 9,11-dicis isomer would not be isolable, but rather, its doubly electrocyclized bicyclo[4.2.0]octa-2,4-diene product would be obtained.[3b,c] Except for the one unexpected, but now reasonably explicable difference that 3e isomerizes to bicyclooctadiene A,

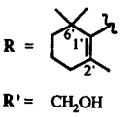
this is precisely the behavior exhibited by **5a** upon heating (TBDMS ethers were heated in all experiments). The bicyclooctadiene A (13 or 14) is considered to result from initial eight-electron conrotatory electrocyclization of the tricis isomer **3e** (to cyclooctatriene 15) followed by six-electron disrotatory electrocyclization.[3c-d,8] Similarly, bicyclooctadiene B (16 or 17) is considered to result from the putative 9,11-dicis isomer **3g** via **18**.[3c-d,8] Thus, besides the spectroscopic data used to assign stereostructures to the three retinols **3d-f** and the two bicyclooctadienes A and B, the mechanistic conjecture serves as a further basis for these assignments. Additional support for stereochemical assignments of the retinols accrues from their conversion to the corresponding retinals described in the accompanying communication



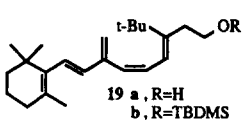
13, ⁃R ; ⁃R'
14, ⁻R ; ⁻R'
16, ⁃R ; ⁻R'
17, ⁻R ; ⁃R'



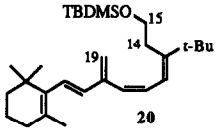
15, ⁃R ; ⁃R'
18, ⁃R ; ⁻R'



Thermolysis of the 11,12-allene: The 11,12-allene **6a** in iso-octane (~3 x 10^{-3} M) was refluxed (98 °C) for 64 h and then the reaction solution and the resulting residue was processed under the same conditions as described for **5a** above. HPLC separation (as above) of the deprotected alcohol residue afforded in order of elution the following: 11,13-dicis-retinol **4d**[6h] (32%) and then the 12-trans-19,14-retro-retinol[6i] (**19a**, 16%). The formation of these isomers is readily rationalized on the basis of the expected initial [1,5]-sigmatropic shift of **6a** to afford **19b** and **20** with the latter further isomerizing through an antarafacial [1,7]-sigmatropic shift (of the hydrogen at the C-14 to C-19 in **20**) to afford the observed 11,13-dicis isomer. The 11,12-allene in the parent series (t-Bu replaced by methyl)[3e] has been previously reported to afford besides a retro-retinol (corresponding to **19**) and the



19 a, R=H
b, R=TBDMS



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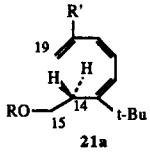
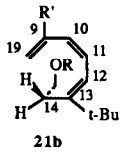


21a



21b

11,13-dicis-retinol, the 11-cis isomer. In the present case, none of the 11-cis isomer **4f** was detected and this may be a consequence of greater steric congestion between the C-15 methylene and the t-Bu group in **21a** (the conformer leading to the 11-cis isomer) than in **21b** (the conformer leading to the observed 11,13-dicis isomer **4d**).

Summary. The results of this study amply demonstrate that in propargylic systems as complex as **9b** and **12b**, where there exists the possibility of allylic as well as propargylic displacement, and where introduction of a bulky alkyl group such as a t-Bu cuprate is involved, complete specificity and high yield can be achieved. The route described herein for producing 9,10- and 11,12-allenes possessing bulky alkyl groups or other groups should be quite general. It should be further emphasized that despite the proclivity of the allene thermal isomerization route to afford certain undesirable isomers, the method allows easy access to several of the difficult to prepare hindered 11-cis-retinoid analogues in adequate quantities for further study.

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(5) All new compounds exhibited appropriate ^{1}H-NMR (200 or 300 MHz), ^{13}C-NMR, IR, UV and low resolution and exact mass MS data. See ref. (6) for selected ^{1}H-NMR data.

(6) ^{1}H-NMR (200 or 300 MHz, CDCℓ$_3$). (a) **5b**: δ 0.99 (6H, $C_{16,17}$-2CH_3, s), 1.09 (9H, t-Bu, s), 1.70 (3H, C_{18}-CH_3, s), 1.82 (3H, C_{20}-CH_3, d, J~1.5 Hz), 2.46 (2H, $2H_{14}$, t, J~6.8 Hz), 3.73 (2H, $2H_{15}$, t, J~6.8 Hz), 5.72 (1H, H_7, dd, J~15.6 Hz, 1.0 Hz), 5.82 (1H, H_{12}, d, J~10.7 Hz), 6.19 (1H, H_8, d, J~15.6 Hz), 6.25 (1H, H_{11}, d, J~10.7 Hz). (b) **6b**: δ 1.03 (6H, $C_{16,17}$-2CH_3, s), 1.09 (9H, t-Bu, s), 1.71 (3H, C_{18}-CH_3, s), 1.90 (3H, C_{19}-CH_3, s), 2.30 (2H, $2H_{14}$, m), 3.70 (2H, $2H_{15}$, t, J~6.2 Hz), 5.80 (1H, H_{10}, d, J~11.1 Hz), 6.08 (2H, H_7 and H_8, s), 6.27 (1H, H_{11}, dt, J~11.1 Hz, 3.3 Hz). (c) **13 or 14** (Isomer A): δ 0.88 (3H, C_1-CH_3, s), 0.94 and 0.95 (6H, C_6'-2CH_3, two s), 0.97 (9H, t-Bu, s), 2.05 (3H, C_2'-CH_3, s), 2.51 (1H, H_8, ddd, J~8.8 Hz, 8.8 Hz, 7.8 Hz), 3.34 (1H, H_7, dd, J~11.2 Hz, 8.8 Hz), 3.48 (1H, H_6, d, J~11.2 Hz), 3.92 (1H, diastereotopic C_8-CH_2, dd, J~11.7 Hz, 7.8 Hz), 4.04 (1H, diastereotopic C_8-CH_2, J~11.7 Hz, 8.8 Hz), 5.40 (1H, H_2, d, J~9.3 Hz), 5.70 (1H, H_4, d, J~5.9 Hz), 5.84 (1H, H_3, dd, J~9.3 Hz, 5.9 Hz). (d) **16 or 17** (Isomer B): δ 0.82 and 0.84 (6H, C_6'-2CH_3, diastereotopic, two s), 0.97 (9H, t-Bu, s), 1.13 (3H, C_1-CH_3, s), 1.98 (3H, C_2'-CH_3, s), 2.8-2.9 (2H, H_8 and H_7, m), 3.19 (1H, H_6, d, J~9.8 Hz), 3.6-3.8 (2H, C_8-CH_2, m), 5.43 (1H, H_2, d, J~9.8 Hz), 5.66 (1H, H_4, d, J~5.9 Hz), 6.00 (1H, H_3, dd, J~9.8 Hz, 5.9 Hz). (e) **3d**: δ 1.00 (6H, $C_{16,17}$-2CH_3, s), 1.24 (9H, t-Bu, s), 1.68 (3H, C_{18}-CH_3, s), 1.87 (3H, C_{20}-CH_3, s), 4.05 (2H, $2H_{15}$, d, J~6.8 Hz), 5.58 (1H, H_{14}, t, J~6.8 Hz), 5.83 (1H, H_{12}, d, J~11.7 Hz), 6.08 (2H, H_7 and H_8, s), 6.11 (1H, H_{10}, d, J~11.7 Hz), 6.68 (1H, H_{11}, dd, J~11.7, 11.7 Hz). (f) **3e**: δ 1.04 (6H, $C_{16,17}$-2CH_3, s), 1.10 (9H, t-Bu, s), 1.77 (3H, C_{18}-CH_3, s), 1.89 (3H, C_{20}-CH_3, s), 4.08 (2H, $2H_{15}$, d, J~6.8 Hz), 5.55 (1H, H_{14}, t, J~6.8 Hz), 5.78 (1H, H_{12}, d, J~11.2 Hz), 5.89 (1H, H_7, d, J~16.6 Hz), 6.02 (1H, H_8, d, J~16.6 Hz), 6.06 (1H, H_{10}, d, J~10.7 Hz), 6.55 (1H, H_{11}, dd, J~11.2 Hz, 10.7 Hz). (g) **3f**: δ 1.01 (6H, $C_{16,17}$-2CH_3, s), 1.24 (9H, t-Bu, s), 1.69 (3H, C_{18}-CH_3, s), 1.89 (3H, C_{20}-CH_3, s), 4.27 (2H, $2H_{15}$, d, J~6.8 Hz), 5.73 (1H, H_{14}, t, J~6.8 Hz), 5.83 (1H, H_{12}, d, J~8.3 Hz), 6.10 (2H, H_7 and H_8, s), 6.56 (1H, H_{11}, dd, J~11.7 Hz, 8.3 Hz), 6.60 (1H, H_{10}, d, J~11.7 Hz). (h) **4d**: δ 1.02 (6H, $C_{16,17}$-2CH_3, s), 1.10 (9H, t-Bu, s), 1.70 (3H, C_{18}-CH_3, s), 1.95 (3H, C_{19}-CH_3, s), 4.02 (2H, $2H_{15}$, d, J~6.0 Hz), 5.60 (1H, H_{14}, t, J~6.6 Hz), 5.90 (1H, H_{10}, d, J~11.4 Hz), 5.99 (1H, H_{12}, d, J~11.4 Hz), 6.05 (1H, H_8, d, J~16.1 Hz), 6.18 (1H, H_7, d, J~16.1 Hz), 6.58 (1H, H_{11}, t, J~11.4 Hz). (i) **19a**: δ 1.01 (6H, $C_{16,17}$-2CH_3, s), 1.26 (9H, t-Bu, s), 1.71 (3H, C_{18}-CH_3, s), 2.39 (2H, $2H_{14}$, t, J~6.6 Hz), 3.67 (2H, $2H_{15}$, t, J~6.6 Hz), 5.01 (1H, H_{19}, t, J~2.1 Hz), 5.22 (1H, H_{19}, d, J~2.1 Hz), 6.07 (1H, H_{10}, d, J~11.4 Hz), 6.09 (2H, $H_{7,8}$, s), 6.14 (1H, H_{12}, dd, J~11.4 Hz, 0.8 Hz), 6.77 (1H, H_{11}, dd, J~11.4 Hz, 11.4 Hz).

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(8) The formation of only one bicyclooctadiene (13 or 14 from 15 and 16 or 17 from 18) may reflect a steric effect, but recent studies address the importance of electronic effects in competitive electrocyclizations. See Dolbier, W.R., Jr.; Koroniak, H.; Burton, D.J.; Heinze, P.L.; Bailey, A.R.; Shaw, G.S.; Hansen, S.W. J. Am. Chem. Soc. 1987, 109, 219 and references cited.

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