Our synthetic route focuses initially upon the preparation of the key tetracyclic ketone **7**, which is a common intermediate toward all target aglycones. Ketone **7** was obtained in four steps from dihydroresorcinol **8**[8] as shown in Scheme I. The mixture of tetracyclic ketones **7** and **9** was readily separable by fractional crystalization to provide pure **7** (mp 144–145 °C).[9-11]

Conversion of **7** to **1** and **2** was initiated by selective deprotection of the C-11 oxygen with SbF_5–HF in CH_2Cl_2 at −78 °C (93% yield) as shown in Scheme II.[12] Introduction of the C-6 oxygen was accomplished by treatment of the resulting phenol with $NO_2^+CF_3CO_2^-$ in CH_2Cl_2, which afforded a mixture of **10** (mp 190–193 °C) and the related nitro compound **11** (3:2) in 84% yield.[13] Nitro ketone **11** could be efficiently converted (75% overall yield) to **10** by reduction (H_2/Pd–C/EtOAc) and diazotization ($NaNO_2/H_2SO_4/H_2O$). Reduction of **10** by diborane in THF followed by protection of the C-6,7 hydroxyl groups (CH_3OCH_2Cl-$AgOSO_2CF_3/CH_2Cl_2$) afforded the ester **12** (mp 210–212 °C) as a single diastereomer (60–65%). Ester **12** was then oxidized (LDA/O_2/(EtO)$_3$P) to provide the C-9 hydroxylated esters **13** as a 1:1 mixture of diastereomers (75%).[14]

This mixture is of no consequence since subsequent equilibration of the C-7 hydroxyl establishes the required stereorelationship between C-7 and C-9. Hydroxy esters **13** can be directly converted to either **1** or **2** by ester hydrolysis, conversion to the thioester (1,1′-carbonyldiimidazole, EtSH, $Mg(OEt)_2$) and treatment with an excess of the appropriate lithium dialkylcuprate reagent ($(CH_3)_2CuLi$ or (p-$CH_3OPhCH_2OCH_2)_2CuLi$)[15] to provide the ketones **14** and **15** in 63% and 60% yield, respectively. Hydrolysis of the protecting groups in **14** and **15** with concomitant isomerization of C-7 (CF_3CO_2H) then affords **1** (mp 278–280 °C) and **2** (mp 284–287 °C) in good yield (86% and 84%, respectively) identical in all respects with authentic materials (NMR, MS, TLC).[16,17]

The C-6 deoxy systems **5** and **6** were prepared from **7** by a series of transformations analogous to those shown in Scheme II. In the case of the 6-deoxy series, the C-7 oxygen function was protected as a methoxy methyl ether.[9,18] Conversion of the 6-deoxy analogue of **12** to the two analogues of daunomycinone, **5** (mp 267–269 °C), and adriamycinone, **6** (mp 293–295 °C), was accomplished along the lines of the natural series including the stereochemical equilibration at C-7, which proceeded stereospecifically.[19,20]

Thus, the synthetic route to adriamycinone and daunomycinone presented above comprises 13 steps and proceeds in ~8% overall yield. Besides convergency, the route offers substantial flexibility for production of analogues by substitution in the naphthoquinone unit as well as analogues in the 6-deoxy series.

Acknowledgment. This investigation was generously supported by research grants (CA-28897 and CA-29108) from the National Cancer Institute of the National Institutes of Health, to whom we are grateful.

Supplementary Material Available: Scheme for preparation of **5** and **6** and partial NMR data for **7** and **9–15** (3 pages). Ordering information is given on any current masthead page.

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[8] Kuehne, M. E.; Lambert, B. F. *J. Am. Chem. Soc.* **1959**, *81*, 4278.

[9] All new compounds had satisfactory spectroscopic data (IR, NMR) and acceptable high-resolution mass spectroscopic or combustion analytical data. A listing of NMR spectral data can be found in the supplementary material.

[10] Prepared by Jones oxidation of 1,4,5-trimethoxynaphthalene in 70% yield. For the preparation of 1,4,5-trimethoxynaphthalene: Jackson, D. K.; Swenton, J. S. *Synth. Commun.* **1977**, 333.

[11] The mixture was crystallized from acetone–hexane to effect the separation of the majority of **7**. The residual material could be separated by chromatography.

[12] (a) Gesson, J. P.; Jacquesy, J. C.; Mondon, M. *Tetrahedron Lett.* **1980**, *21*, 3351. (b) Gesson, J. P.; Giusto, L. D.; Jacquesy, J. C. *Tetrahedron* **1978**, 1715.

[13] Crivello, J. V. *J. Org. Chem.* **1981**, *46*, 3056.

[14] Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.

[15] Prepared from the lithium reagent in the usual way. The lithium reagent was prepared from the corresponding tributylstannane by transmetalation with n-BuLi. This particular dialkylcuprate reagent shows markedly higher thermal stability than other related cuprate reagents and alkyllithium reagents (cf.: Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481). A further description of the utility of this reagent as a methanol carbanion equivalent will be reported in due course.

[16] We thank Professor Andrew Kende for an authentic sample of racemic **1** and Dr. Daniel Lednicer of Adria Laboratories for an authentic sample of optically active **2**.

[17] Steric factors that favor attack from the pseudoaxial direction upon the half-chair cyclohexyl ring of the intermediate carbonium ion or protonated acetal in the precursors to **1** and **2** (the C-6 OH) are enhanced in the cyclic acetals **17** and **18**, leading exclusively to the natural C-7 configuration; cf. for a similar case: Kende, A. S.; Belletire, J.; Bentley, T. J.; Hume, E.; Airey, J. *J. Am. Chem. Soc.* **1975**, *97*, 4425.

[18] A scheme describing these transformations may be found in the Supplementary Material.

[19] ^1H NMR spectral data (400 MHz, $CDCl_3$). **5**: δ 12.95 (s, 1 H), 7.99 (d, J = 7.7 Hz, 1 H), 7.95 (s, 1 H), 7.74 (t, J = 8.0 Hz, 1 H), 7.37 (d, J = 8.3 Hz, 1 H), 4.93 (dd, J_1 = 10.0 Hz, J_2 = 3.6 Hz, 1 H), 4.45 (s, 1 H), 4.06 (s, 3 H), 4.02 (d, J = 10.0 Hz, 1H), 3.11 (d, J = 17.9 Hz, 1 H), 2.98 (d, J = 17.9 Hz, 1 H), 2.41 (s, 3 H), 2.37–2.26 (m, 2 H). **6**: δ 12.91 (s, 1 H), 8.00 (d, J = 7.7 Hz, 1 H), 7.84 (s, 1 H), 7.76 (t, J = 8.1 Hz, 1 H), 7.39 (d, J = 8.6 Hz, 1 H), 5.09 (m, 1 H), 4.80 (dd, J_1 = 20.6 Hz, J_2 = 5.2 Hz, 1 H), 4.71 (dd, J_1 = 20.6 Hz, J_2 = 5.2 Hz, 1 H), 4.46 (s, 1 H), 4.06 (s, 3 H), 3.27 (d, J = 18.0 Hz, 1 H), 3.02 (d, J = 18.0 Hz, 1 H), 2.39 (d, J = 14.6 Hz, 1 H), 2.24 (dd, J_1 = 14.6 Hz, J_2 = 4.3 Hz, 1 H).

[20] The unexpectedly high stereospecificity of the equilibration in the 6-deoxy series is apparently related to delivery of the nucleophile (H_2O) from the pseudoaxial direction with assistance of the C-9 axial hydroxyl group. Concurrent with our studies, an Italian group observed similar selectivity in the 4-demethoxy compound: Penco, S.; Angelucci, F.; Arcamone, F.; Ballabio, M.; Barchielli, G.; Francheschi, F.; Franchi, G.; Suarato, A.; Vanotti, E. *J. Org. Chem.* **1983**, *48*, 405.

Short, Stereocontrolled Synthesis of [4]Peristylane

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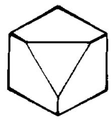
The peristylanes (**1–3**) are attracting growing interest because of their unusual hemispherical topology and their obvious relationship to highly symmetric $(CH)_{2n}$ polyhedral systems (e.g., **4–6**).[1] The original synthesis of [3]peristylane (**1**) by Nickon and Pandit[2] in 1968 has been followed by the design of two alternative routes in Garratt's laboratory.[1] Concurrently, the group headed by Eaton succeeded in devising an elegant pathway to [5]peristylane (**3**).[3] To date, however, the central compound of this series (**2**) has remained elusive. Our interest in [4]peristylane and select functionalized derivatives of this hydrocarbon was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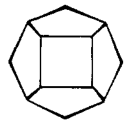
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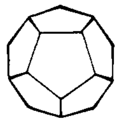
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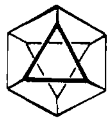
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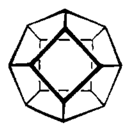
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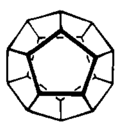
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[1] Garratt, P. J.; White, J. F. *J. Org. Chem.* **1977**, *42*, 1733.

[2] Nickon, A.; Pandit, G. D. *Tetrahedron Lett.* **1968**, 3663.

[3] Eaton, P. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 1014. Eaton, P. E.; Mueller, R. H.; Carlson, G. R.; Cullison, D. A.; Copper, G. F.; Chou, T.-C.; Krebs, E.-P. *Ibid.* **1977**, *99*, 2751.

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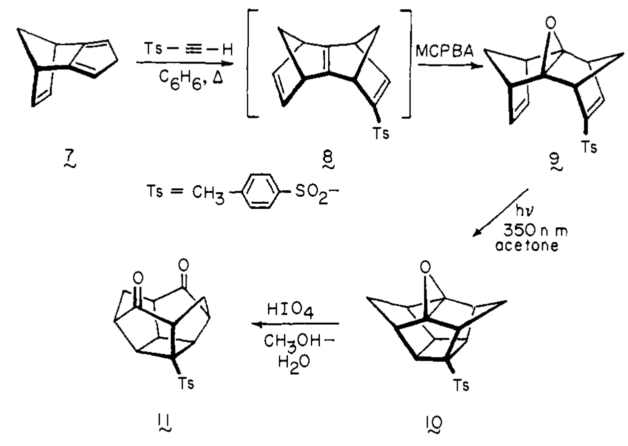
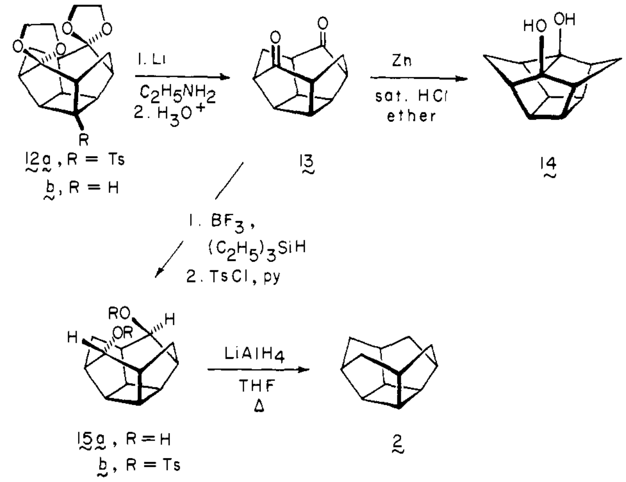
Scheme I



Scheme II



aroused by their possible role as precursors to *p*-[4^2:5^8]decahedrane (**5**).[4] In this communication, we showcase an approach to this heretofore unknown class of molecules that is notably brief and stereocontrolled.

From the retrosynthetic perspective, it appeared that brevity could be realized if three points would be accorded proper attention: (1) formation of the four-membered ring by photoactivation,[5] with due allowance for the high symmetry (C_{4v}) within **2**; (2) installation of the pair of double bonds intended for the [2 + 2] cycloaddition as parallel and spatially proximate syn-locked norbornenyl fragments; (3) facile central bond cleavage in the bishomopentaprismane photoproduct.

The synthesis was initiated by Diels–Alder addition of *p*-toluenesulfonylacetylene[6] to tricyclo[5.2.1.0^{2,6}]deca-2,5,8-triene (**7**)[7] with the full expectation that dienophile capture would occur with complete below-plane π-facial stereoselectivity (Scheme I).[8] Although **8** was not isolated due to its propensity for air oxidation,[9] the stereochemical course of the cycloaddition was revealed subsequent to controlled peracid oxidation. Epoxide **9** was obtained in 98% overall yield as a homogeneous, colorless crystalline solid, mp 150–151 °C.[10] Molecular models reveal clearly that installation of the oxirane ring from the exo surface has the anticipated effect of compressing the π systems in a face-to-face arrangement.[9,11] The activating influence of the arenesulfonyl substituent was deployed to advantage a second time by irradiating acetone solutions of **9** in a Rayonet apparatus with 350-nm light. The ensuing ready conversion to **10** (mp 138–139 °C; quantitative) confirmed that the initial [4 + 2] cycloaddition had indeed proceeded from the endo surface of **7**.

Arrival at the [4]peristylane framework materialized upon subjecting **10** to the action of periodic acid in refluxing 10% aqueous methanol.[12] To our delight, diketo sulfone **11** (mp 181.5–183 °C) was produced in 95% yield. Evidently, the high solvolytic reactivity present in **10**[13] results in conversion to the *cis*-1,2-diol, the cleavage of which is probably accelerated to achieve relief of ring strain.[9]

Of the various methods examined to arrive at **13** (Scheme II), the most expedient involved sequential ketalization, reductive desulfonylation with lithium in ethylamine,[14] and acidic hydrolysis (69% overall). Though examination of molecular models, we were well aware that a pouch-shaped ground-state conformation for **13** (mp >300 °C) was dictated by the need of the "inside" methylene hydrogens to move apart as far as possible.[15] The consequence of these prevailing nonbonded steric interactions is to compress the two carbonyl groups together. These considerations do not, of course, affect the C_{2v} symmetry of **13**, which is unmistakingly revealed by its four-line ^{13}C NMR spectrum (228.6, 53.7, 42.7, 41.8 ppm in CDCl$_3$). However, they do become apparent under certain reductive conditions. For example, the action of zinc in ether saturated with dry hydrogen chloride[16] on **13** results in pinacolization and conversion to diol **14** (74%, mp >300 °C).

To avoid this complication, **13** was reduced to diol **15a**.[17] Either the boron trifluoride–triethylsilane reagent system[18] or lithium tri-*tert*-butoxyaluminum hydride proved effective (90–95% yield) in avoiding transannular ether formation. Following conventional tosylation (71%), the functional groups in **15b** were removed by treatment with lithium aluminum hydride in refluxing ether for 8 h. Higher temperatures and longer reaction times led to the

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[4] In an effort to resolve the exasperating nomenclature problem associated with **4**, **5**, and their isomers, we advance the following system of colloquial terminology for consideration. The name is composed of three segments, the last of which refers to the number of faces present in the polycyclic system. The larger numbers within the brackets serve as descriptors of the ring sizes involved, and the superscripts pertain to their number in the carbocyclic framework. Finally, the ortho, meta, and para prefixes have the same connotation as they do in benzenoid chemistry and serve to locate the relative positioning of the *less numerous* smaller (or larger) rings. Thus, **4** is named simply as *p*-[3^2:5^6]octahedrane. If three or more identical rings happen to be present, it suffices to replace these latter prefixes with the proper symmetry designation for the molecule (e.g., C_2, C_{2v}, C_s, etc.). We note that the superscripts give the same information about the number of rings as the name and represent an additional point of reference. Also, for the symmetric molecules considered herein, the carbon number is readily obtained as

$$(A^b{:}C^d)\text{: carbons (vertices)} = (A \times b) + (C \times d)$$

Of course, this relationship breaks down for less symmetric species. The proposed nomenclature should prove widely applicable. For example, cubane is [4^6]hexahedrane and pentaprismane is *p*-[4^5:5^2]heptahedrane.

[5] Kricka, L. J.; Ledwith, A. *Synthesis* **1974**, 539.

[6] Bhattacharya, S. N.; Josiah, B. M.; Walton, D. R. M. *Organomet. Chem. Synth.* **1970**, *1*, 145.

[7] (a) Alder, K.; Flock, F. H.; Janssen, P. *Chem. Ber.* **1956**, *89*, 2689. (b) Sugimoto, T.; Kobuke, Y.; Furukawa, J. *J. Org. Chem.* **1976**, *41*, 1457. (c) Paquette, L. A.; Carr, R. V. C.; Böhm, M. C.; Gleiter, R. *J. Am. Chem. Soc.* **1980**, *102*, 1186. (d) Böhm, M. C.; Carr, R. V. C.; Gleiter, R.; Paquette, L. A. *Ibid.* **1980**, *102*, 7218.

[8] (a) Paquette, L. A. In "Stereochemistry and Reactivity of Pi Systems"; Watson, W. H., Ed.; Verlag Chemie, in press. (b) Gleiter, R.; Paquette, L. A. *Acc. Chem. Res.*, in press.

[9] Paquette, L. A.; Carr, R. V. C. *J. Am. Chem. Soc.* **1980**, *102*, 7553.

[10] All compounds described herein exhibited compatible infrared, proton magnetic resonance, and mass spectroscopic data. In addition, the elemental composition of all key intermediates has been substantiated by combustion analysis.

[11] Paquette, L. A.; Carr, R. V. C.; Charumilind, P.; Blount, J. F. *J. Org. Chem.* **1980**, *45*, 4922.

[12] Nagarkatti, J. P.; Ashley, K. R. *Tetrahedron Lett.* **1973**, 4599.

[13] Paquette, L. A.; Ohkata, K.; Carr, R. V. C. *J. Am. Chem. Soc.* **1980**, *102*, 3303.

[14] Grieco, P. A.; Masaki, Y *J. Org. Chem.* **1974**, *39*, 2135.

[15] For a more highly pronounced example of this behavior, see: Christoph, G. G.; Engel, P.; Usha, R.; Balogh, D. W.; Paquette, L. A. *J. Am. Chem. Soc.* **1982**, *104*, 784.

[16] Toda, M.; Hirata, Y.; Yamamura, S. *J. Chem. Soc., Chem. Commun.* **1969**, 919.

[17] The endo, endo configuration of the hydroxyl groups is reflected in the magnitude of spin coupling involving C*H*OH and its neighboring protons (J = 8 Hz)[3] and the simplified (four-line) ^{13}C NMR spectrum.

[18] Fry, J. L.; Orfanopoulos, M.; Adlington, M. G.; Dittman, W. R., Jr.; Silverman, S. B. *J. Org. Chem.* **1978**, *43*, 374.

destruction of **2** and had to be avoided. The highly volatile hydrocarbon so produced (mp >225 °C)[19] clearly has 4-fold symmetry: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.98–2.91 (m, 4 H), 2.65–2.54 (m, 4 H), 2.15 (d of t, J = 13.7, 9.9 Hz, 4 H), 1.65 (d, J = 13.7 Hz, 4 H); ^{13}C NMR ($CDCl_3$) 48.44, 46.85, 46.31 ppm.

Studies aimed at crafting **13** into **5** are currently in progress.[20]

Registry No. 2, 85850-64-2; **7**, 6675-71-4; **9**, 85850-65-3; **10**, 85850-66-4; **11**, 85850-67-5; **12a**, 85850-68-6; **12b**, 85850-69-7; **13**, 85850-70-0; **14**, 85864-53-5; **15a**, 85850-71-1; **15b**, 85850-72-2; TSC≡CH, 13894-21-8.

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(19) These conditions do not result in complete reduction of the tosylate. The amount of pure **2** obtained after chromatography and sublimation exceeded 10%.

(20) We express our warm appreciation to the National Institutes of Health for their generous support of this program (Grant AI-11490).

Electrostatic Control of Regioselectivity in Competing Bimolecular Eliminations

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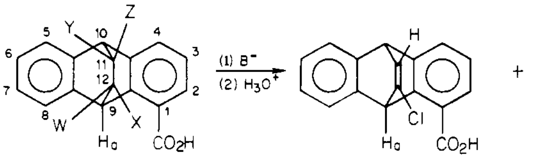
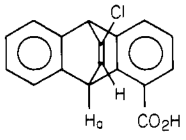
Previously we demonstrated substituent electrostatic field effects on various reactions of carboxyl groups at the 1- and 2-positions of geometrically isomeric 11,12-dichloro-9,10-dihydro-9,10-ethanoanthracenes.[1,2]

We now report preliminary results of a study of base-induced eliminations of HCl from the anions of the four isomeric 11,12-dichloro-9,10-dihydro-9,10-ethano-1-anthroic acids, **1–4**. In each case the ratio of vinyl halides, **5**/**6**, appears to be determined primarily by the relative electrostatic repulsive interactions between the carboxylate anion and the attacking base.



1, X = Z = Cl; W = Y = H
2, X = Z = H; W = Y = Cl
3, X = Y = H; W = Z = Cl
4, X = Y = Cl; W = Z = H

5



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The preparation, separation and characterization of acids **1** and **2** have been previously described.[2] Isomers **3** and **4** (via the corresponding methyl esters) were similarly prepared by the cycloaddition of methyl 1-anthroate and *trans*-1,2-dichloroethene followed by hydrolysis of the separated[3] esters. The geometric assignments for **3** and **4** are based upon the single-crystal X-ray analysis of the methyl ester of **3**.[4,5]

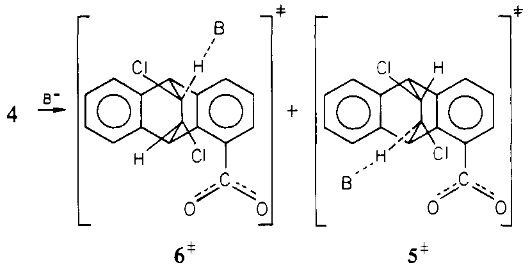
Table I. Observed and Calculated Ratios of 6/5 from Dehydrochlorinations[a] at 80 °C

compd	obsd ratio[b]	calcd ratio[c]
1	2.4 (71/29)	3.0 (75/25)
2	13.3 (93/7)	9.7 (91/9)
3	24 (96/4)	19 (95/5)
4	1.70 (63/37)	1.53 (61/40)

[a] A 0.50 M solution of KO-*t*-Bu in *t*-BuOH was used as the base. The substrate concentration in the basic solution was 0.095 M. A 1.1 mole ratio of 18-crown-6/total K$^+$ was employed. [b] Average of two runs. Estimated uncertainty is ±3%. [c] See discussion.

Dehydrochlorinations of degassed solutions of **1–4** (KO-*t*-Bu/*t*-BuOH) were conducted in the presence of crown ether (18-crown-6).[6] Combined yields of **5** plus **6** exceeded 90%. The ratios **6**/**5** were determined by area integrations for H_a. The results are shown in Table I.

We propose that the ratio of products formed in each dehydrochlorination is primarily determined by transition-state potential-energy differences arising from variable repulsive energies generated between the charge on the carboxylate anion and the charge on the attacking base (possibly distributed in part onto the β-carbon).[9] Calculations of these repulsive energies assume certain constant features for the transition states (see illustrations for transition states from **4**). Direct through-space distances between the carboxylate anionic center and either C_β or the oxygen of the attacking base were estimated by using Dreiding models. Differences in total repulsive potential energies for each pair of competing transition states were computed from Coulomb's law, with variables being the effective dielectric constant[10] and the fractions of charge on the oxygen of the attacking base and on C_β. Differences in repulsive potential energies were converted to



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(1) Grubbs, E. J.; Fitzgerald, R.; Phillips, R. E.; Petty, R. *Tetrahedron* **1971**, *27*, 935.

(2) Wang, C. T.; Grubbs, E. J. *J. Org. Chem.* **1977**, *42*, 534.

(3) The methyl esters of **3** and **4** were separated by repeated fractional crystallizations from hexane. All new compounds including pure samples of **5** and **6** afforded proper elemental analyses as well as reasonable NMR spectra.

(4) Full details of the crystal structure determination will be reported (Noordik, J. *Acta Crystallogr., Sect. C.*, in press). We thank Dr. Noordik for his assistance with the X-ray crystallography. Questions regarding this aspect of our work should be addressed to him at the University of Nijmegen, The Netherlands.

(5) Additional studies involving pK_a determinations of the isomeric acids confirm these assignments and will be presented in the full report of this work.

(6) Under conditions promoting aggregation (tetrahydrofuran, no crown ether) regioselectivity is diminished. For example, under these conditions, the KO-*t*-Bu-induced elimination from **1** gives a ratio, **6**/**5**, of only 1.3 (compared with 2.4 in *t*-BuOH and crown ether).

(7) The basic oxygen was assumed to be linearly extended along the C_β–H axis at 2.7 Å from C_β.[8]

(8) This is a typical distance between oxygen atoms in hydrogen-bonded alcohols (Pimentel, G. C.; McClelland, A. L. "The Hydrogen Bond"; W. H. Freeman: San Francisco, 1960).

(9) Evidence for the bimolecular nature of eliminations (possessing some carbanion character) in systems that are similarly conformationally constrained has been reported. See: (a) Bartsch, R. A.; Mintz, E. A.; Parlman, R. M. *J. Am. Chem. Soc.* **1974**, *96*, 4249. (b) LeBel, N. A.; Beirne, P. D.; Subramanian, P. M. *Ibid.* **1964**, *86*, 4144. (c) Cristol, S. J.; Hause, N. L. *Ibid.* **1952**, *74*, 2193 and references therein.

(10) This is an "empirical effective dielectric constant" as defined earlier[11,12] (a number that allows one to fit an observed substituent effect to an equation such as the Bjerrum or Eucken equation, representing Coulombic interactions).

(11) Hoefnagel, A. J.; Wepster, B. M. *J. Org. Chem.* **1982**, *47*, 2318.

0002-7863/83/1505-4115$01.50/0