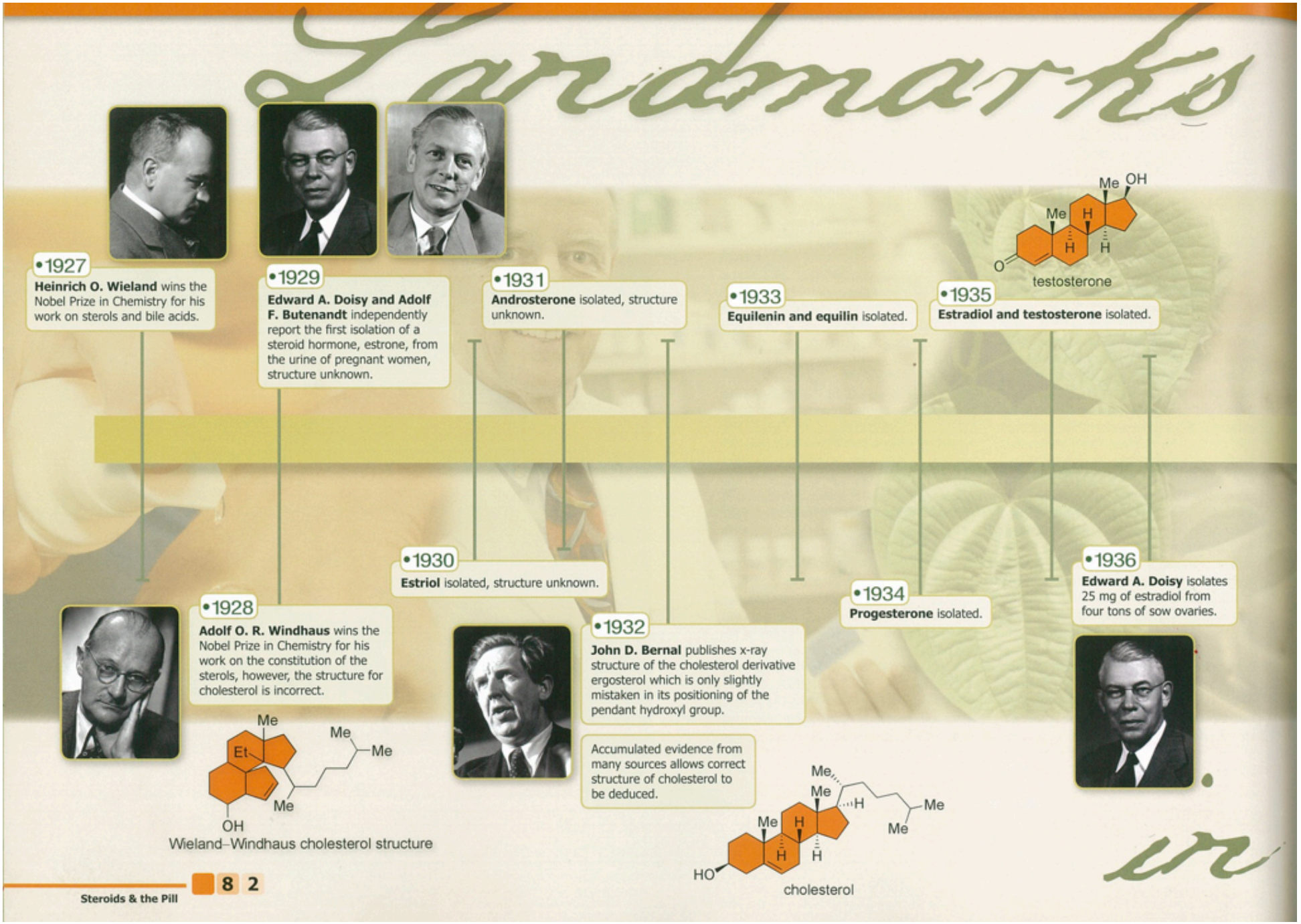
Professor Scott E. Denmark
University of Illinois, Urbana-Champaign

The Gleanings and Impact of Steroid Research on Chemistry and Society

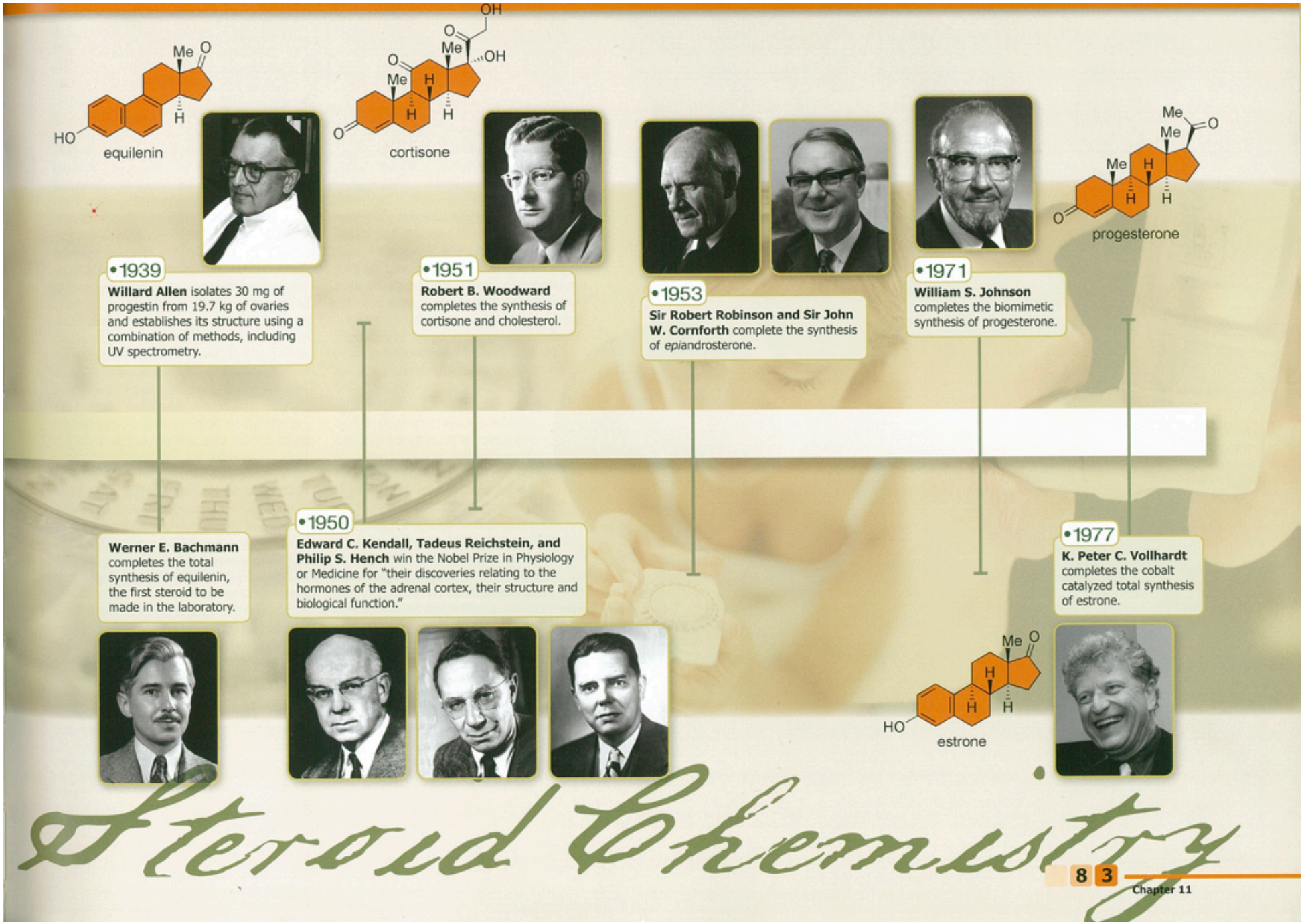
National Chemical Historical Landmark Dedication
Chemistry Symposium
Kalamazoo, Michigan

17 May 2019

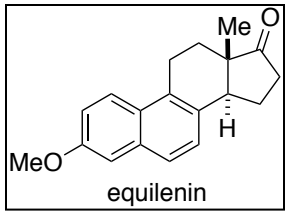
Landmarks in Steroid Chemistry



Landmarks in Steroid Chemistry

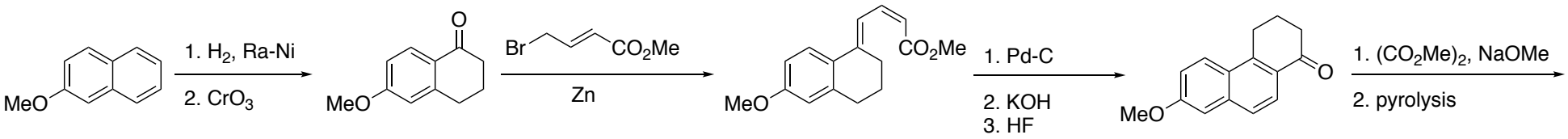


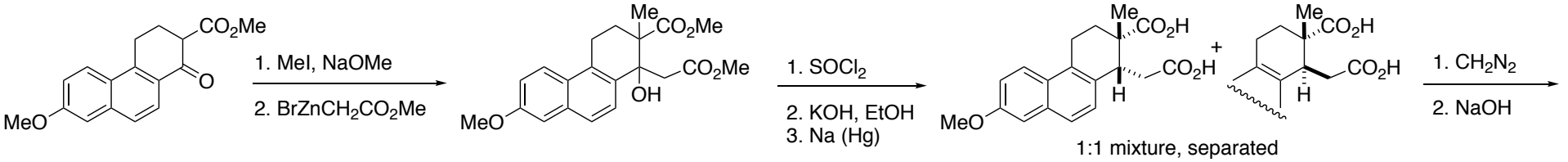
Impact on Chemistry: The Challenge of Total Synthesis



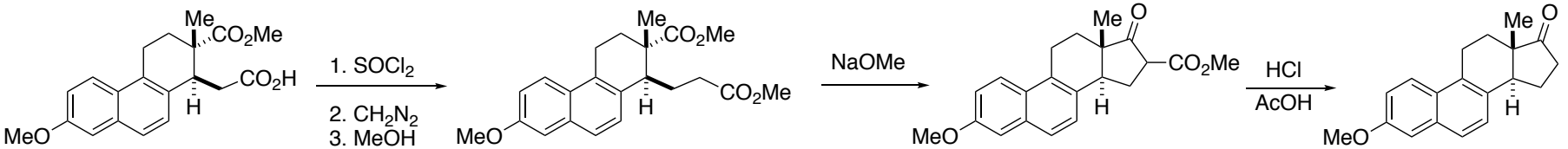
equilenin

Werner Bachmann
(1901-1951)





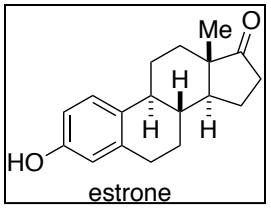
1:1 mixture, separated



equilenin

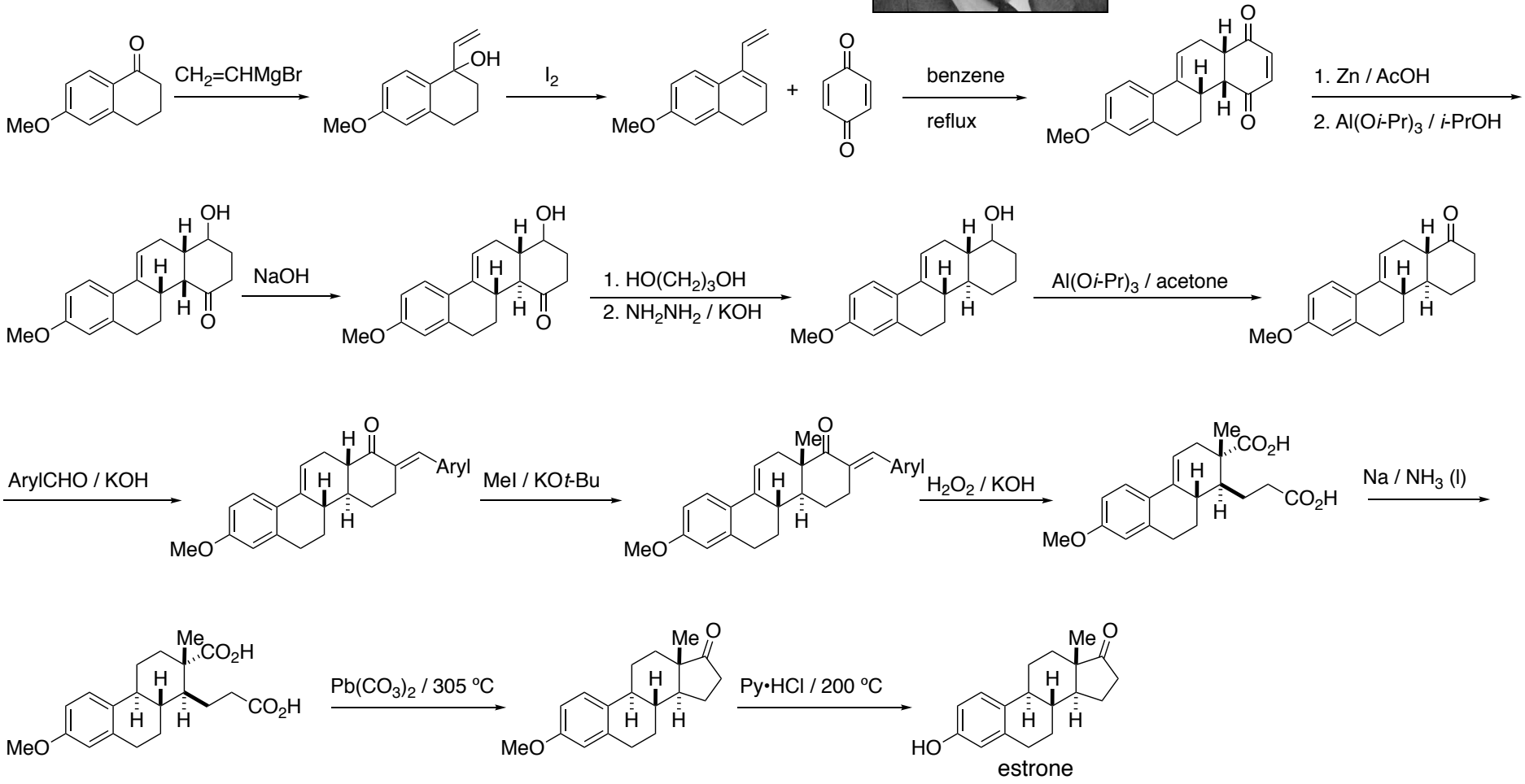
Bachmann, W. E.; Cole, W.; Wilds, A. I *J. Am. Chem. Soc.* **1939**, *61*, 974

Impact on Chemistry: The Challenge of Total Synthesis



estrone

William S. Johnson
(1913-1995)



Anner, G.; Miescher, K. *Helv. Chim. Acta,* **1948**, *31*, 2173

Cole, J. E.; Johnson, W. S.; Robins, P. A.; Walker, J. *Proc. Chem. Soc.* **1958**, 114

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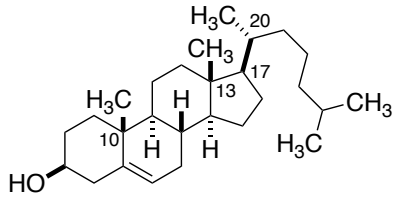

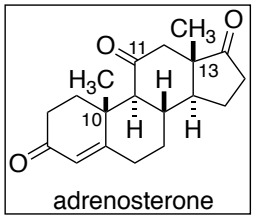

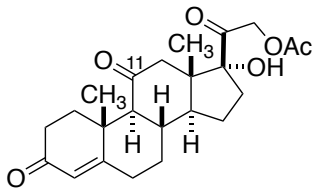

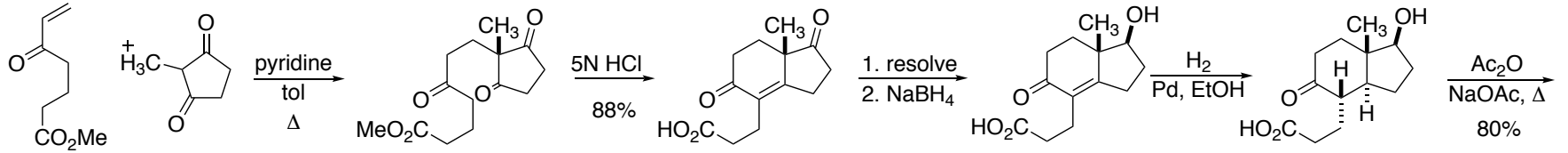

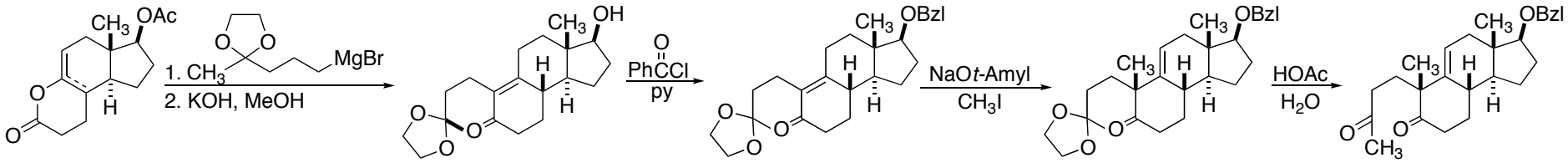

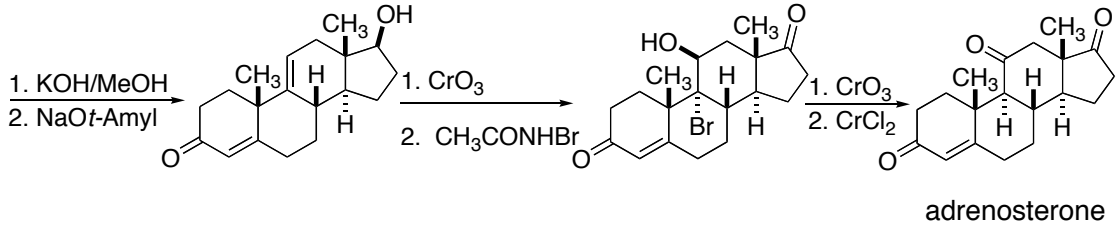

cholesterol/cortisone: Woodward, R. B. et al. *J. Am. Chem. Soc.* **1952**, *74*, 4223

adrenosterone: Velluz, L. et al. *Compt. Rend.* **1963**, *257,* 3086

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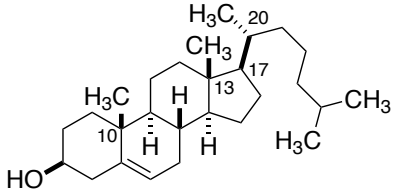
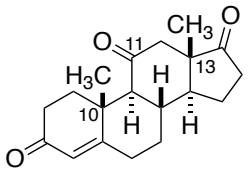
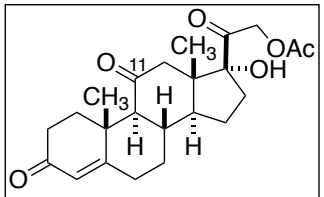


cholesterol

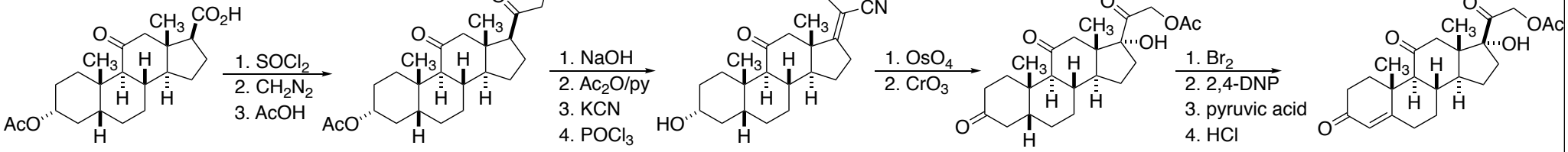


adrenosterone



cortisone acetate

Woodward et al.



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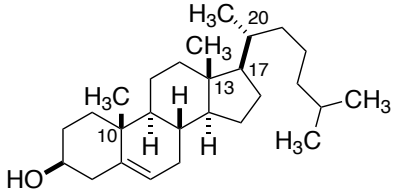
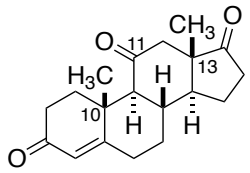
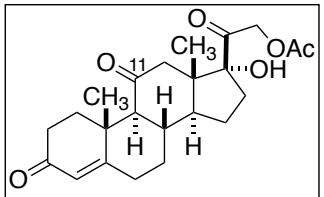


cholesterol



adrenosterone



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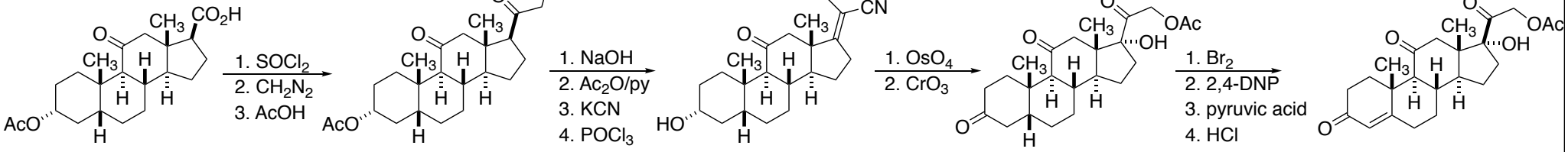

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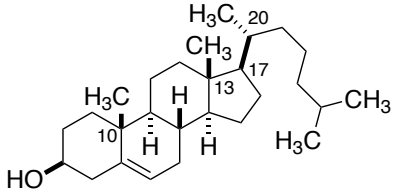
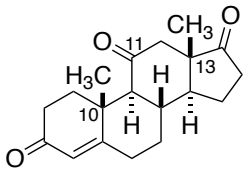
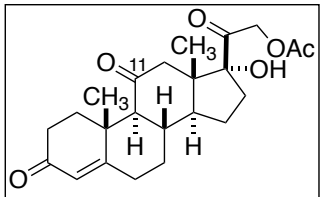


cholesterol



adrenosterone



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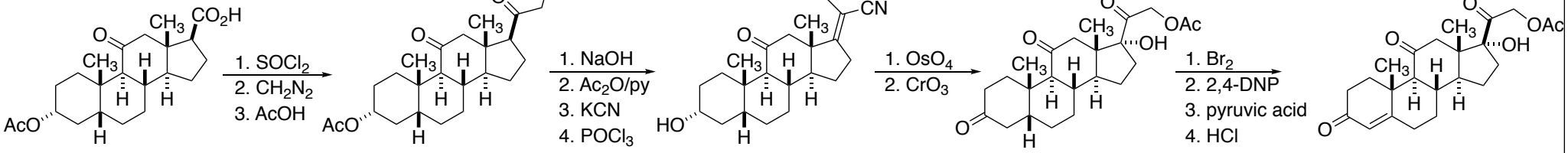
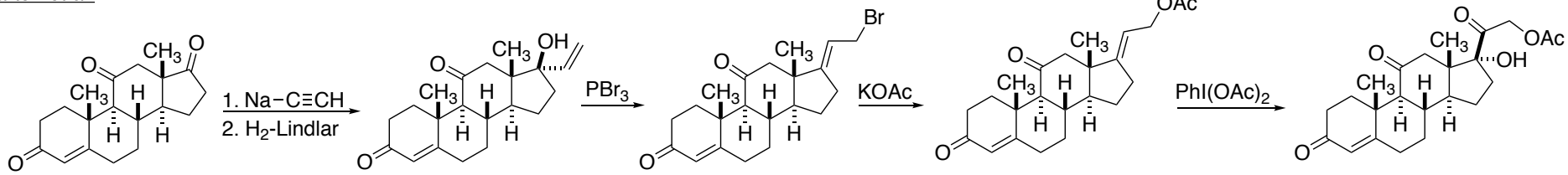
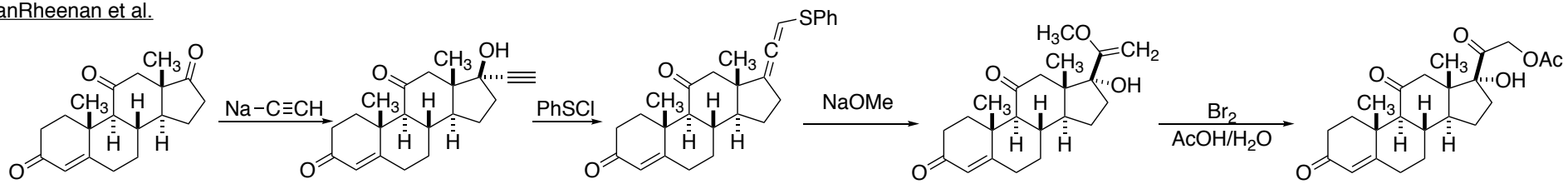
Woodward et al.



Barton et al.



VanRheenan et al.



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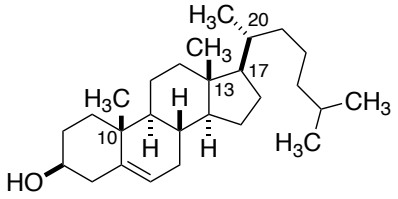
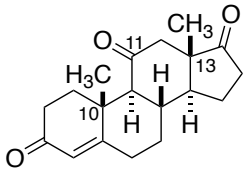
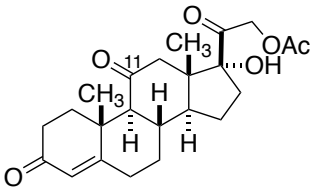
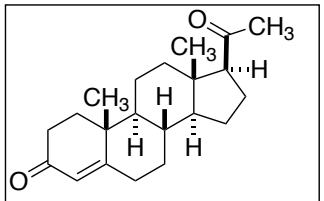

cholesterol

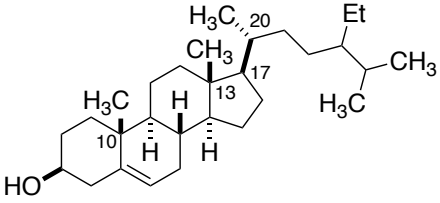

adrenosterone

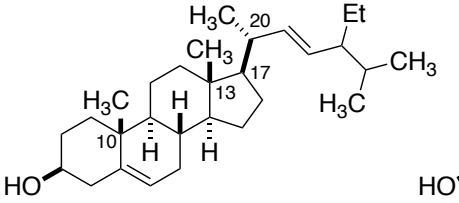

cortisone acetate

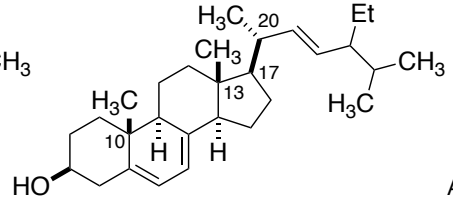

progesterone

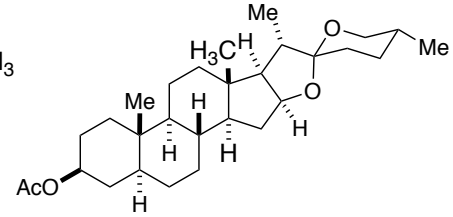
"leaching process"
Greiner and Fevig (1961)

soy bean sterols

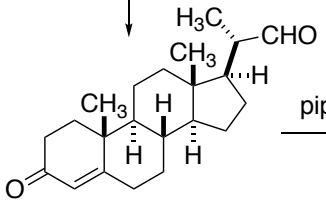

sitosterol


stigmasterol

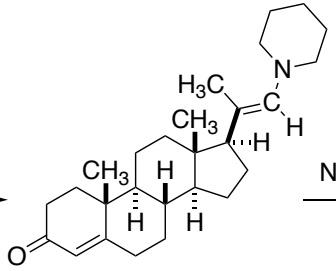

ergosterol


diosgenin

?

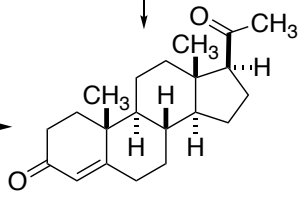


piperidine

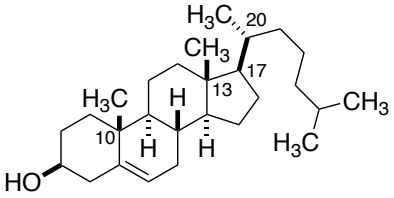


$Na_2Cr_2O_7$

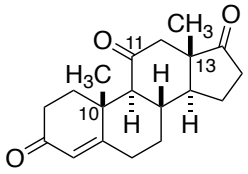
Marker
(Syntex)


progesterone

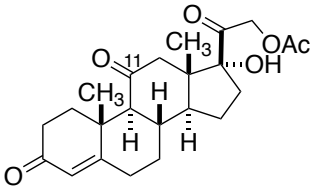
Impact on Chemistry: The Challenge of Semi Synthesis



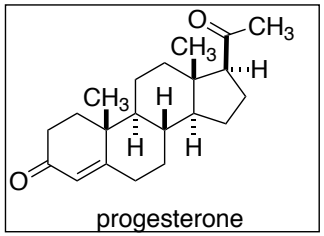
cholesterol



adrenosterone



cortisone acetate



progesterone

"Sitosterol Pile ca. 1990"

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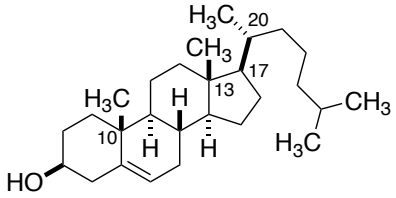
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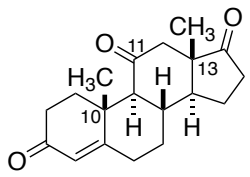
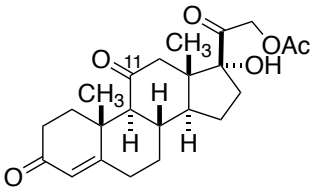
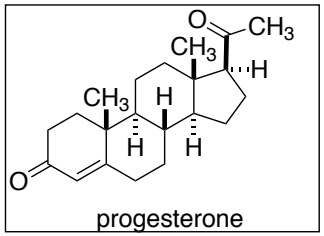

adrenosterone


cortisone acetate


progesterone

soy bean sterols

"leaching process"
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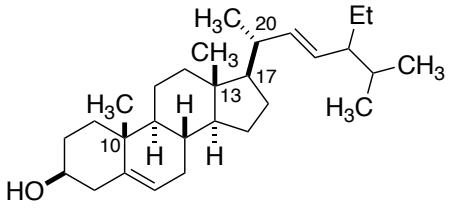
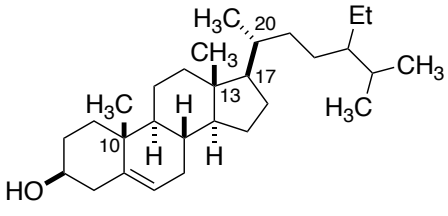
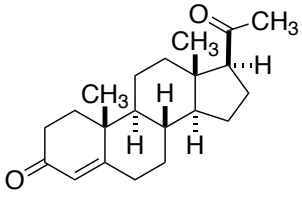
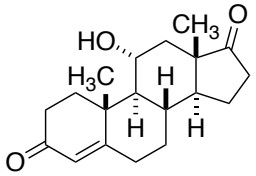

stigmasterol

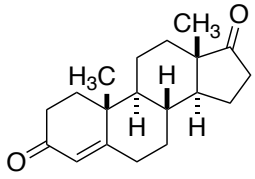

sitosterol

4 steps

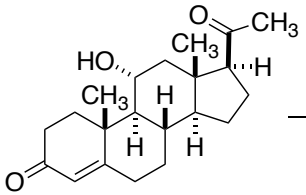
mycobacterium F (mutants)

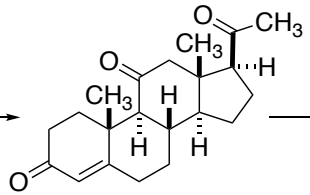


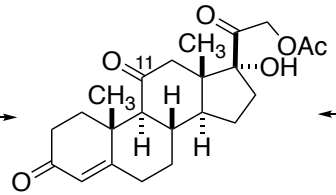


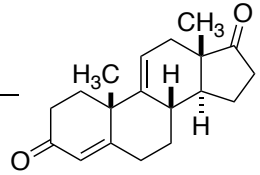


bugs

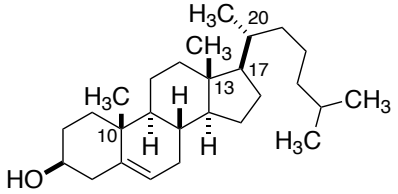

11a-hydroxyprogesterone



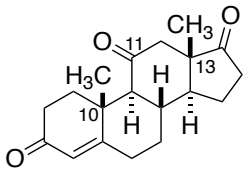

cortisone acetate



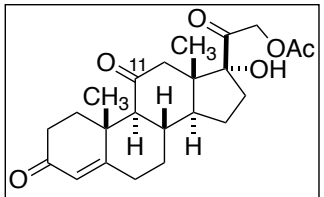
Impact on Chemistry: The Challenge of Semi Synthesis



cholesterol

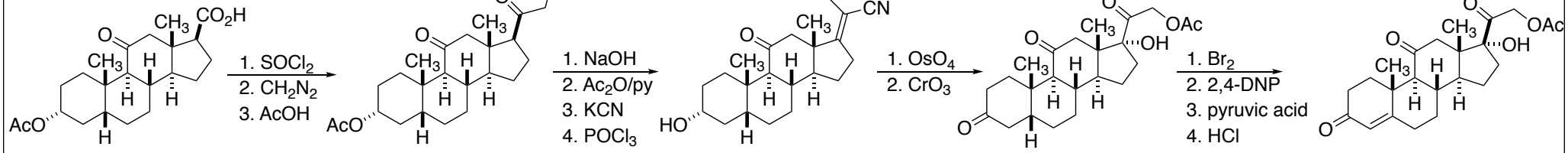


adrenosterone

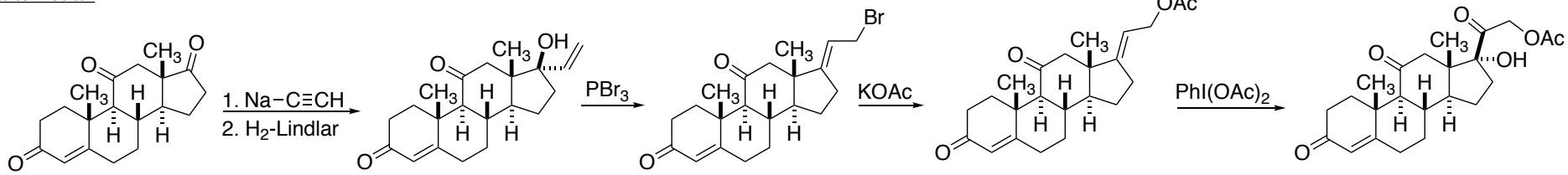


cortisone acetate

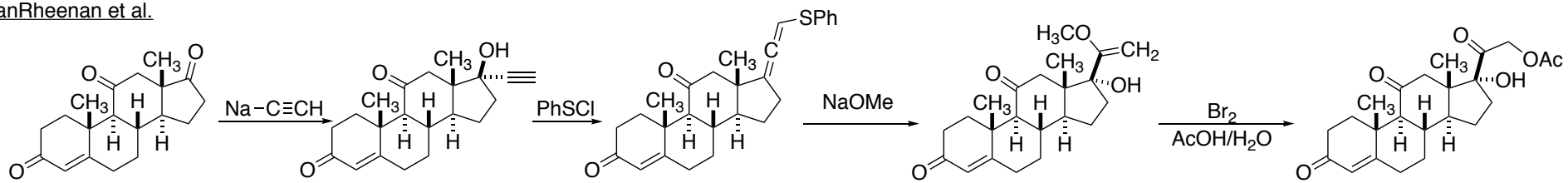
Woodward et al.



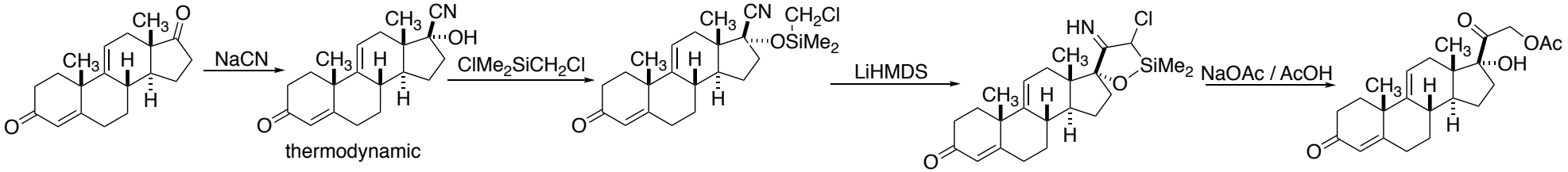
Barton et al.



VanRheenan et al.

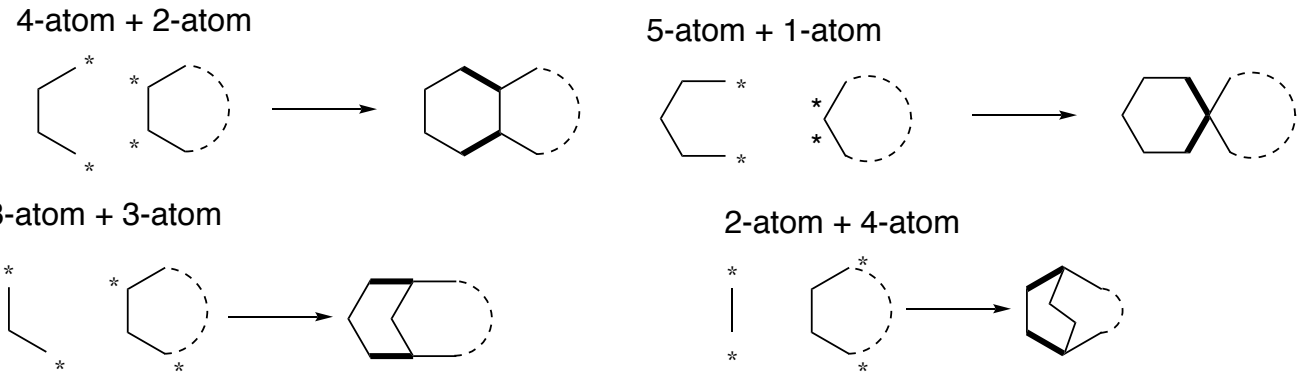


Denmark, Pearlman, Livingston et al.

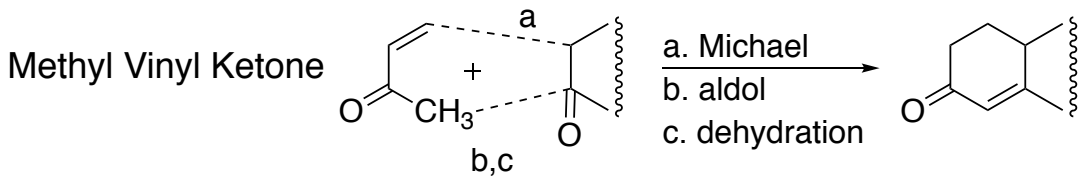


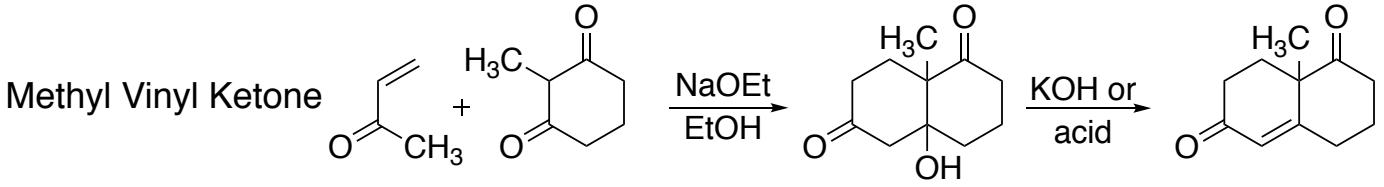
Impact on Chemistry: The Challenge Six-Ring Annulation

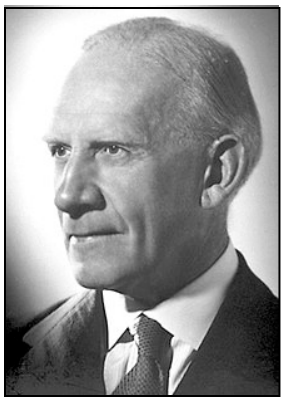
Annulation: The process of forming a ring from two separate partners



Robinson Annulation: 4-atom + 2-atom

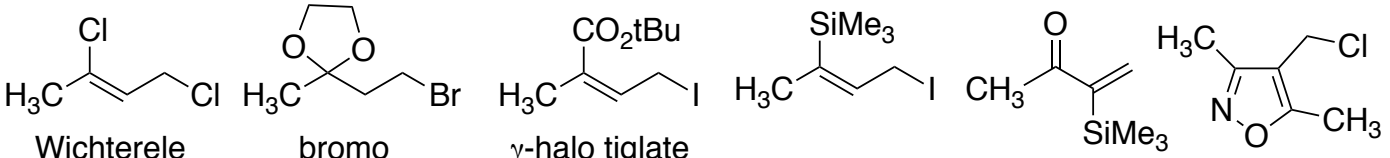






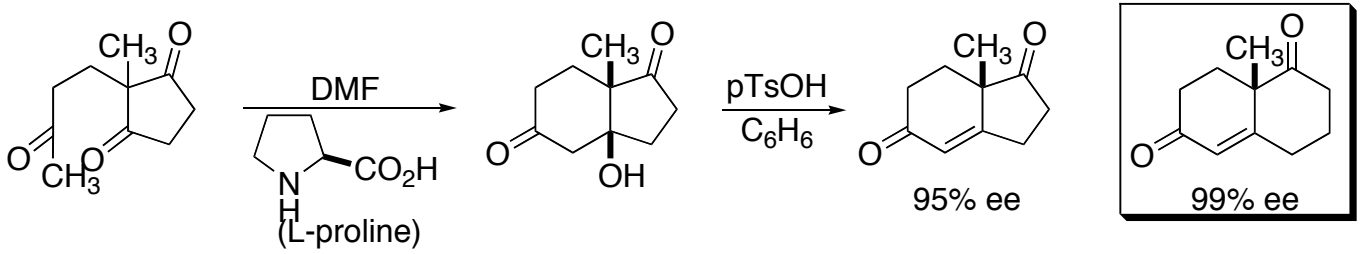
Sir Robert Robinson
Nobel Prize 1947

Methyl Vinyl Ketone Surrogates



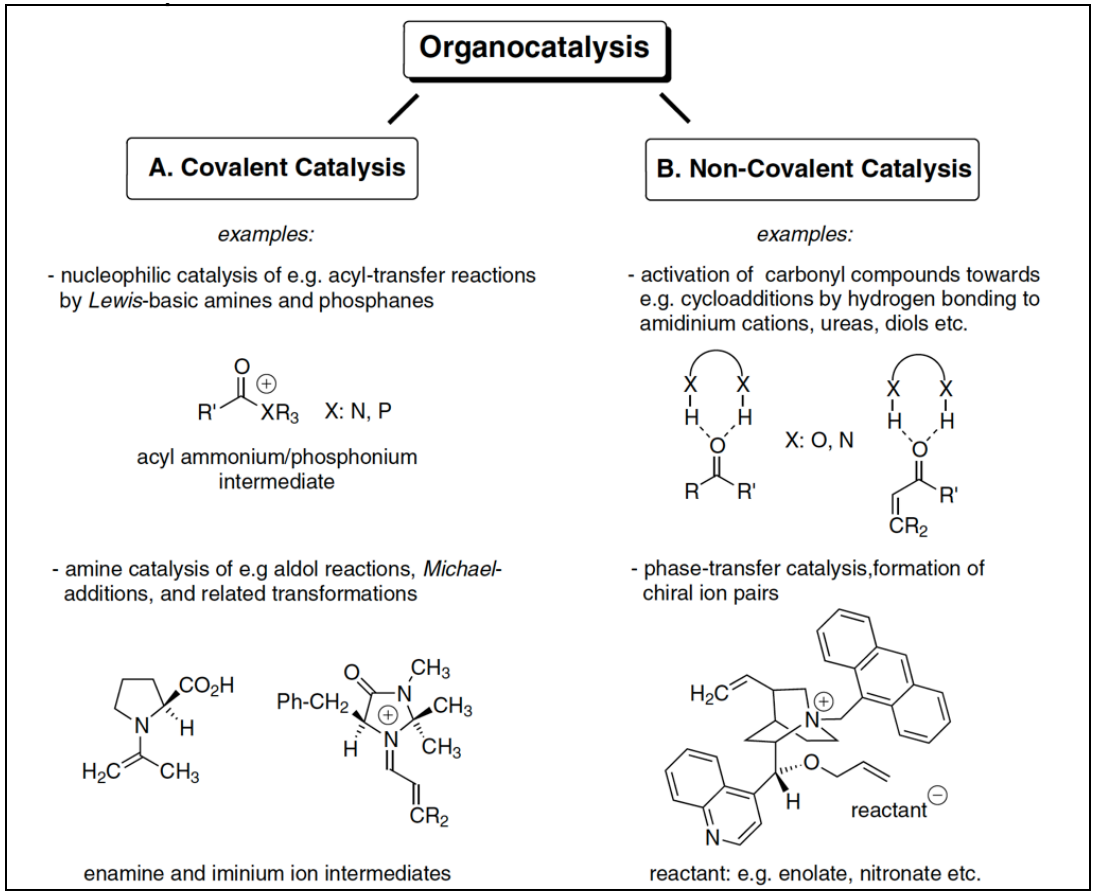
Impact on Chemistry: Organocatalysis

Hajos-Parrish; Eder-Sauer-Weichert, Enantioselective Robinson Annulation



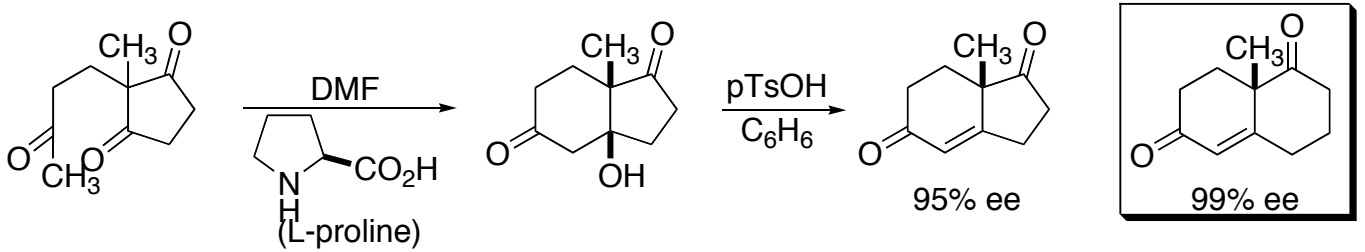
Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed.* **1971**, *10*, 496

Hajos, Z.; Parrish, D. R. *J. Org. Chem.* **1974**, *39,* 1615



Impact on Chemistry: Organocatalysis

Hajos-Parrish; Eder-Sauer-Weichert, Enantioselective Robinson Annulation



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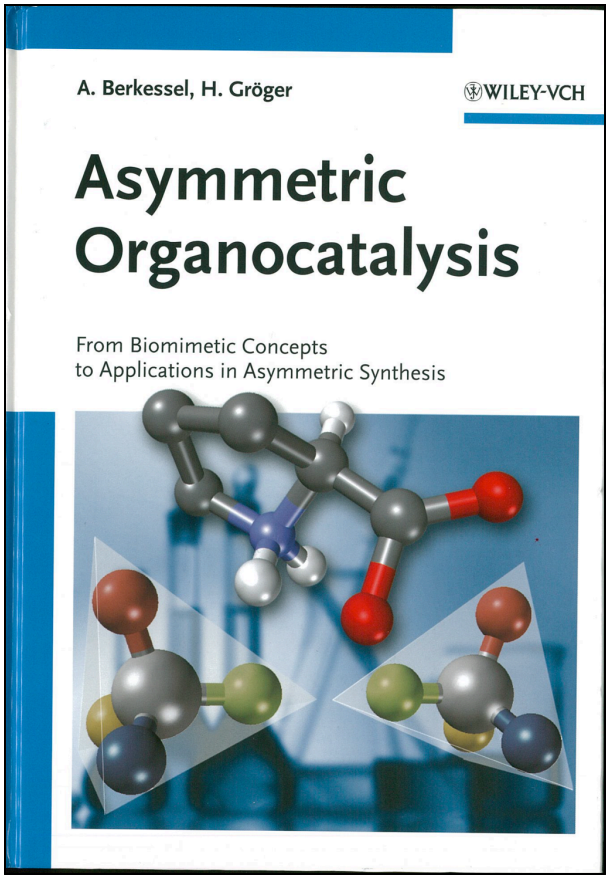
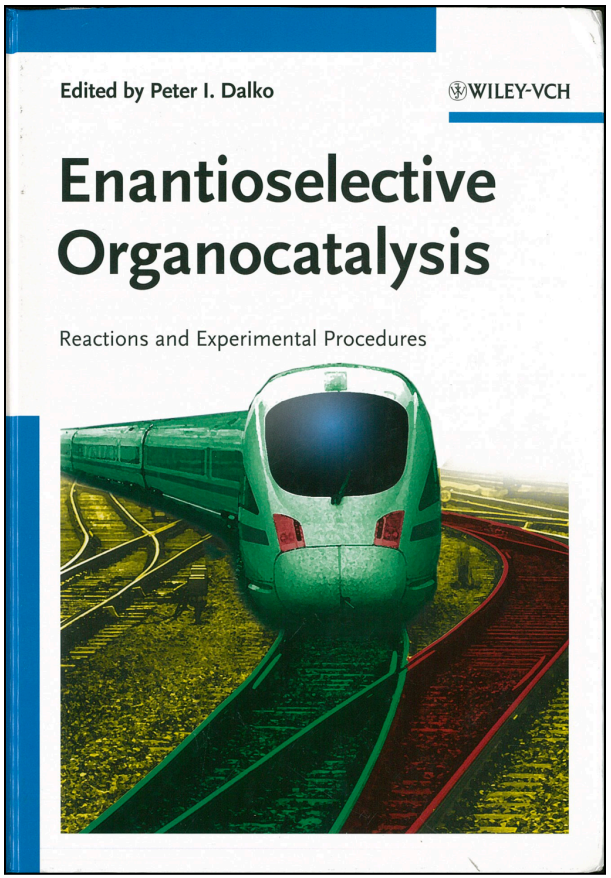
Hajos, Z.; Parrish, D. R. *J. Org. Chem.* **1974**, *39,* 1615

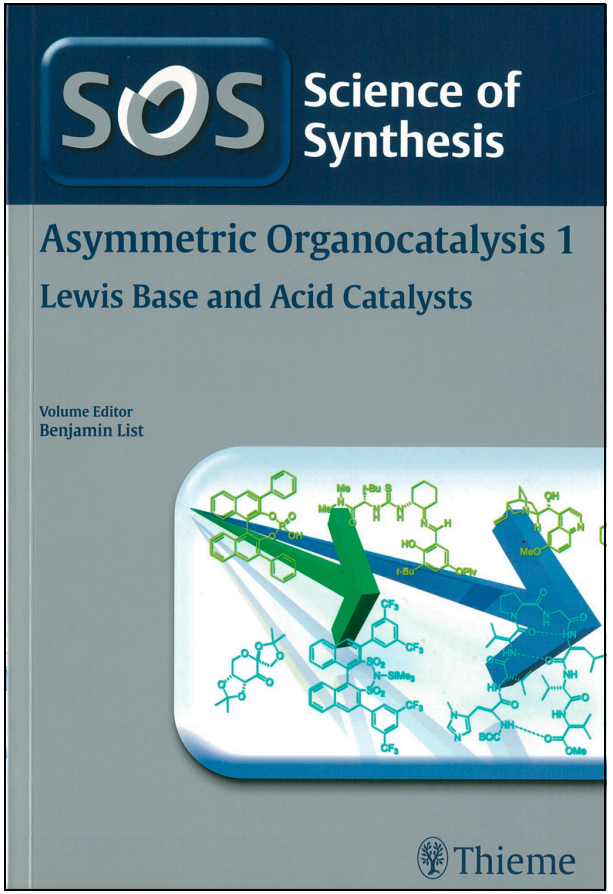
2005



2007



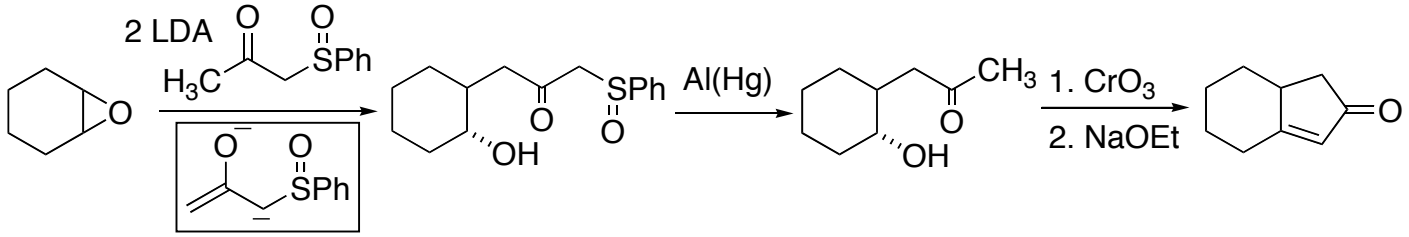
2012

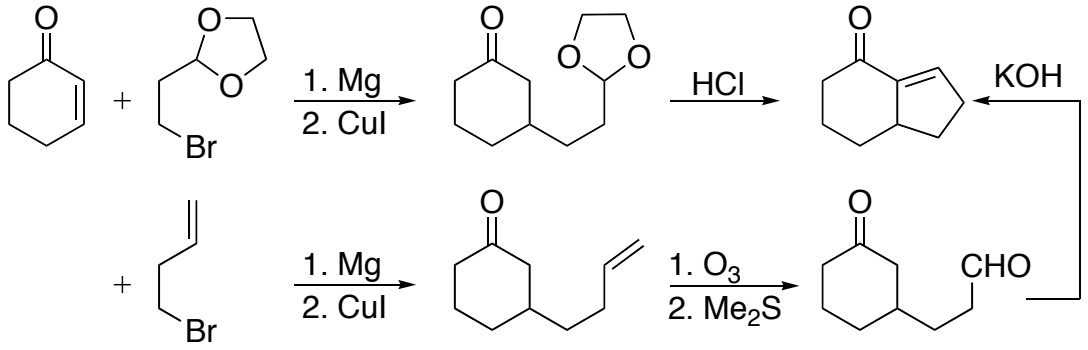


Impact on Chemistry: The Challenge Five-Ring Annulation

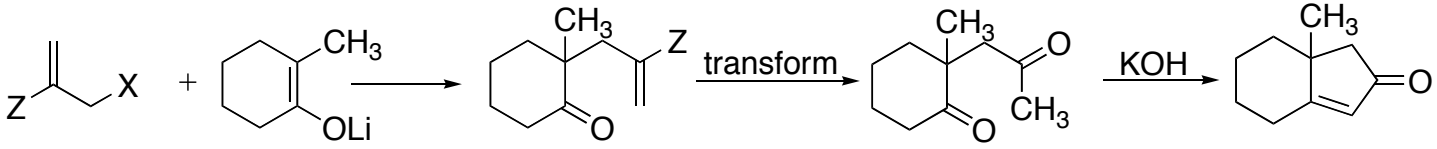
Annulation: The process of forming a ring from two separate partners

Nucleophilic Three Carbon Units

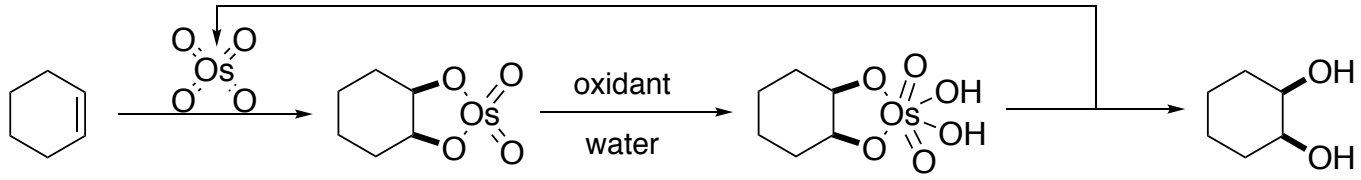




Electrophilic Three Carbon Units



Impact on Chemistry: The Challenge of Catalytic Dihydroxylation



Osmium Tetraoxide OsO_4

mp 40°C, bp 135°C, toxic, expensive $50-60/g

oxidants including chlorates and hydrogen peroxide often give overoxidation

Tetrahedron Letters No. 23, pp 1973 - 1976, 1976. Pergamon Press. Printed in Great Britain.

AN IMPROVED CATALYTIC OsO_4 OXIDATION OF OLEFINS TO CIS-1,2-GLYCOLS USING TERTIARY AMINE OXIDES AS THE OXIDANT

V. VanRheenen, R. C. Kelly and D. Y. Cha

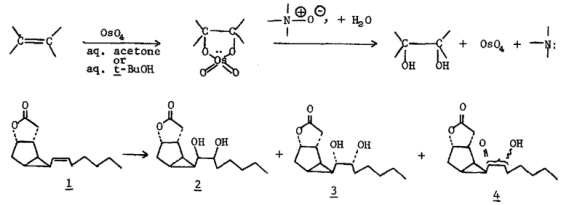
The Upjohn Company

Kalamazoo, Michigan 49001

(Received in USA 24 February 1976; received in UK for publication 27 April 1976)

The reaction of an olefin with osmium tetroxide is undoubtedly the most reliable method for cis-dihydroxylation of a double bond.[1] When used stoichiometrically, however, the high cost of OsO_4 can make a large scale glycolization prohibitively expensive, and the workup procedures can be cumbersome, particularly when pyridine is used. These considerations, coupled with the high toxicity of OsO_4, have provided the incentive to develop procedures using OsO_4 catalytically. Catalytic osmylation using chlorate[2] or hydrogen peroxide (Milas' reagent[3]) to regenerate OsO_4 can be useful, but further oxidation to an α-ketol is a commonly encountered problem, resulting in yield losses and separation problems.

We report here a catalytic OsO_4 cis-dihydroxylation which provides the high yields of the stoichiometric reaction without its expense and workup problems, and avoids the α-ketol byproducts encountered with presently available catalytic processes. In this process one mole of tertiary amine N-oxide is used to regenerate OsO_4, allowing the glycolization to proceed at room temperature using around one mole percent of OsO_4 as catalyst. The following scheme illustrates the reaction:



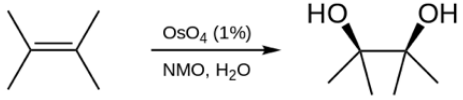
We first encountered this process for cis dihydroxylation while working out conditions for transformation of olefin 1 to cis-glycols 2 and 3 in our prostaglandin synthesis.[4] Catalytic osmylation of 1 with $NaClO_3$ in aqueous THF gave after optimization a 75% yield of glycols 2 and 3 and 25% of the four isomeric α-ketols 4. A similar result was obtained using a modification of the Milas' reaction in which hydrogen peroxide is introduced as a 1:1 complex with N-methylmorpholine-N-oxide (NMO).[5] When NMO is used without H_2O_2, however, the reaction proceeded to

Upjohn dihydroxylation

From Wikipedia, the free encyclopedia

Upjohn dihydroxylation	
Named after	The Upjohn Company
Reaction type	Addition reaction
Identifiers	
Organic Chemistry Portal	upjohn-dihydroxylation

The **Upjohn dihydroxylation** is an organic reaction which converts an alkene to a *cis* vicinal diol. It was developed by V. VanRheenen, R. C. Kelly and D. Y. Cha of the Upjohn Company in 1976.[1] It is a catalytic system using *N*-methylmorpholine *N*-oxide (NMO) as stoichiometric re-oxidant for the osmium tetroxide. It is superior to previous catalytic methods.



Prior to this method, use of stoichiometric amounts of the toxic and expensive reagent osmium tetroxide was often necessary. The Upjohn dihydroxylation is still often used for the formation of *cis*-vicinal diols; however, it can be slow and is prone to ketone byproduct formation. One of the peculiarities of the dihydroxylation of olefins is that the standard "racemic" method (the Upjohn dihydroxylation) is slower and often lower yielding than the asymmetric method (the Sharpless asymmetric dihydroxylation).

Improvements to Upjohn dihydroxylation [edit]

In response to these problems, Stuart Warren and co-workers[2] employed similar reaction conditions to the Sharpless asymmetric dihydroxylation, but replacing the chiral ligands with the achiral quinuclidine to give a racemic reaction product (assuming an achiral starting material is employed). This approach takes advantage of the fact that when using the Sharpless alkaloid ligands, the dihydroxylation of alkenes is faster and higher yielding than in their absence. This phenomenon became known as "ligand accelerated catalysis", a term coined by Barry Sharpless during the development of his asymmetric protocol.

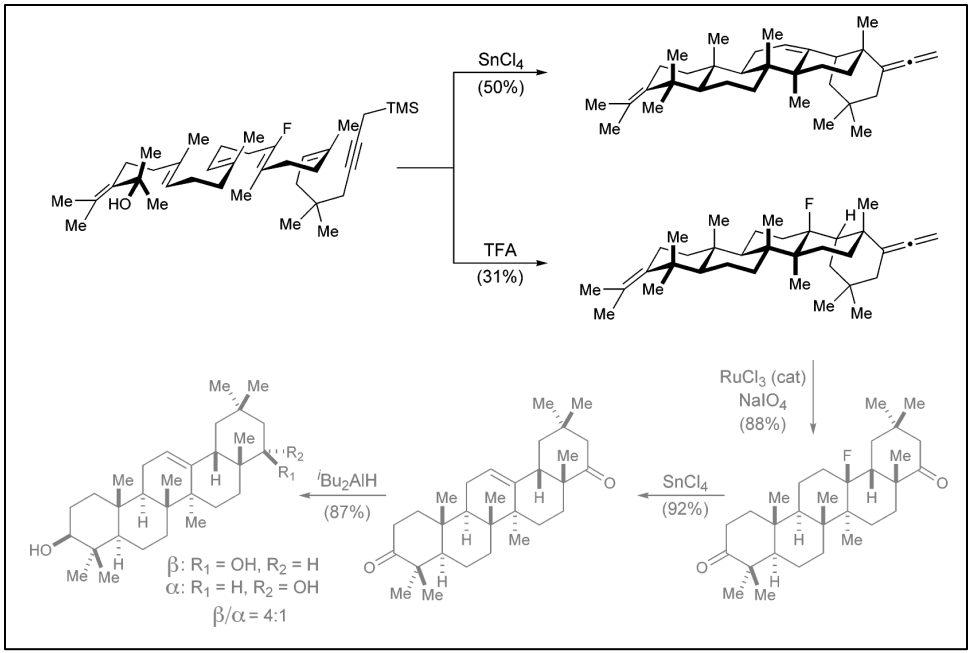
See also [edit]

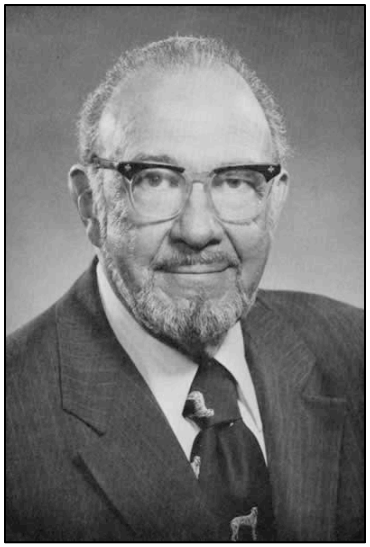
- Milas hydroxylation
- Sharpless asymmetric dihydroxylation

References [edit]

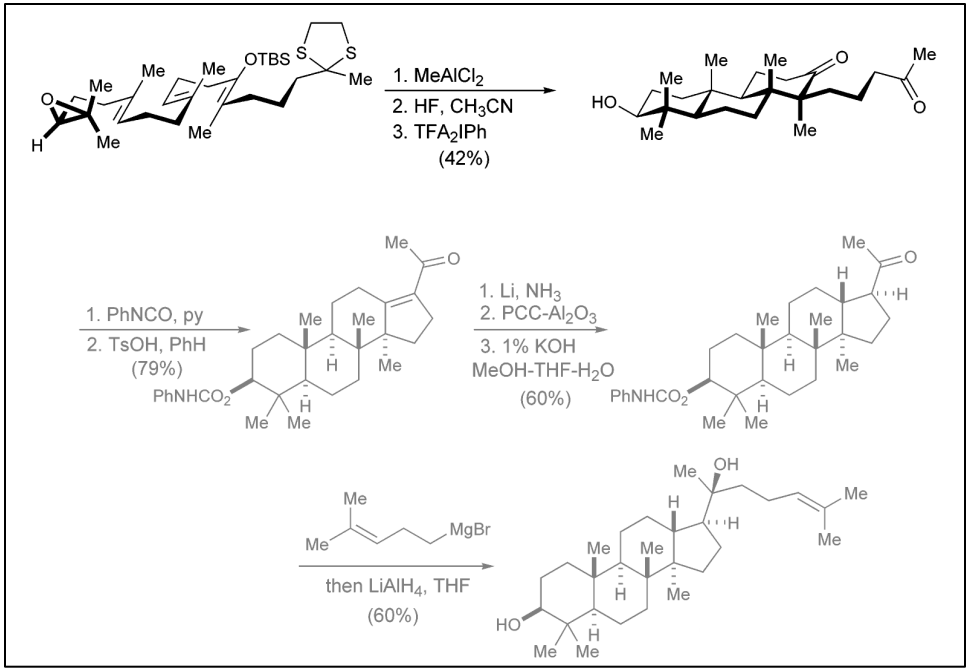
1. ^ Vanrheenen, V.; Kelly, R. C.; Cha, D. Y. (1976). "An improved catalytic OsO_4 oxidation of olefins to *cis*-1,2-glycols using tertiary amine oxides as the oxidant". *Tetrahedron Lett.* **17** (23): 1973–1976. doi:10.1016/S0040-4039(00)78093-2.
2. ^ Eames, Jason; Mitchell, Helen J.; Nelson, Adam; o'Brien, Peter; Warren, Stuart; Wyatt, Paul (1999). "An efficient protocol for Sharpless-style racemic dihydroxylation". *J. Chem. Soc., Perkin Trans. 1.* **1999** (8): 1095–1104. doi:10.1039/a900277d.

Impact on Chemistry: Biomimetic Polyene Cyclization





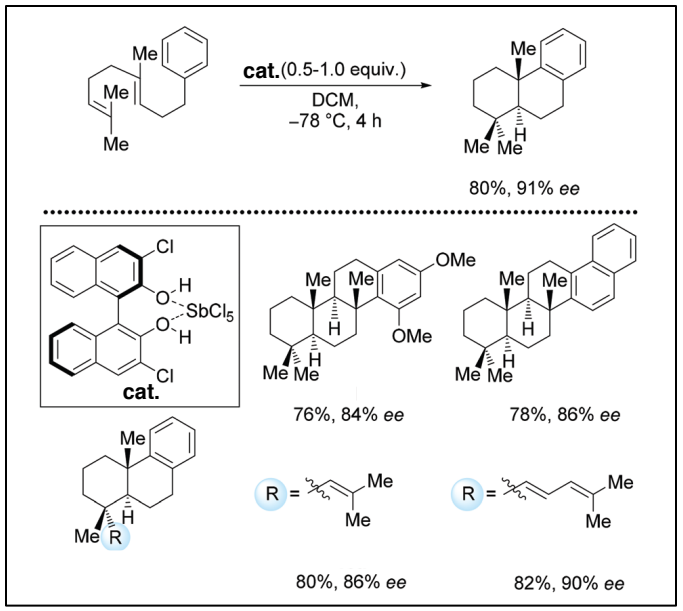
William S. Johnson



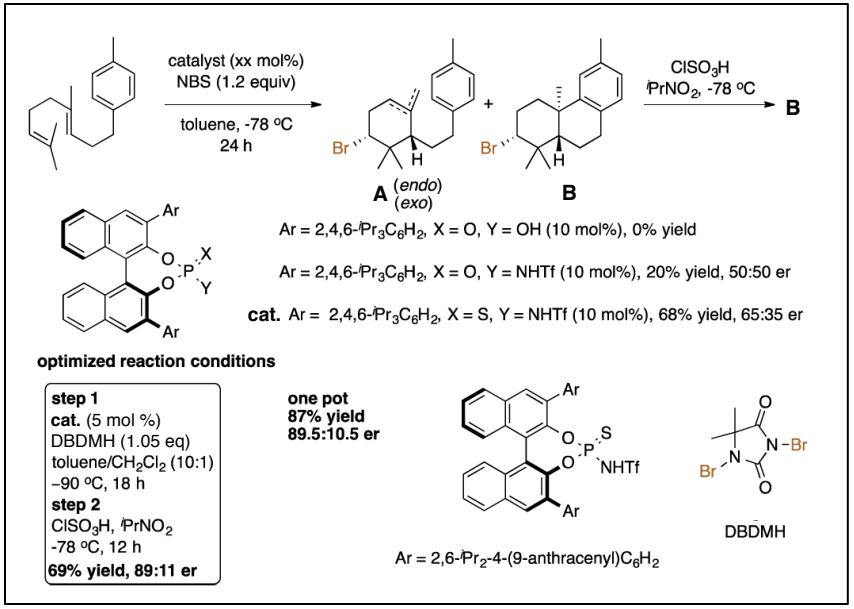
E. J. Corey

Impact on Chemistry: Biomimetic Polyene Cyclization

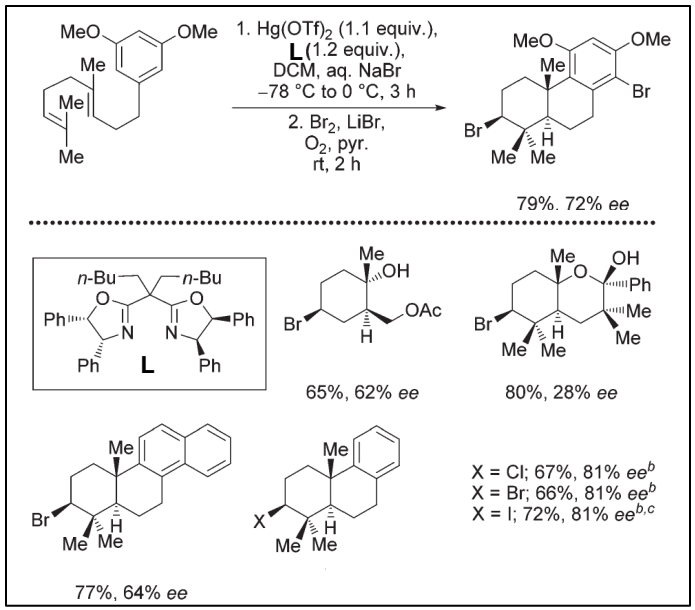
Yamamoto



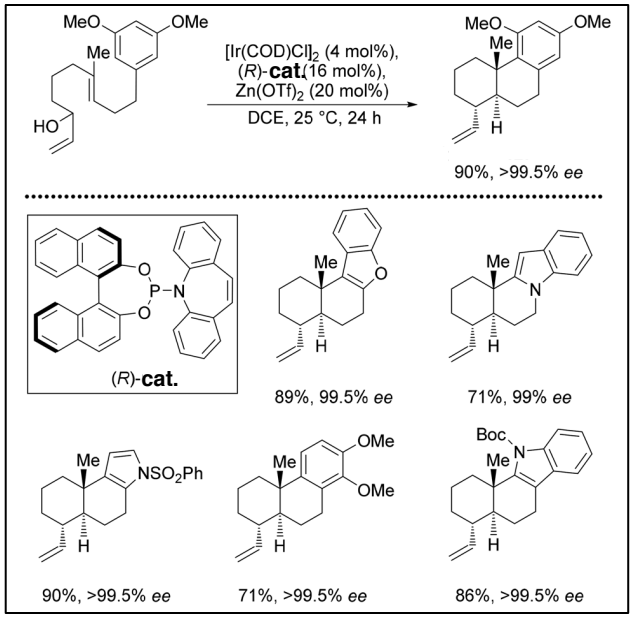
Yamamoto



Snyder

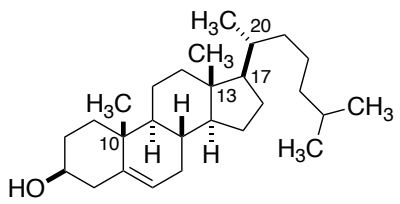


Carreira

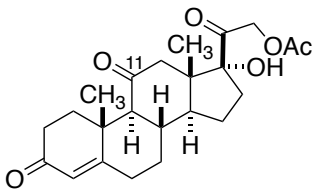


Also: Ishihara, Jacobsen, MacMillan, Toste, Gagné, Denmark

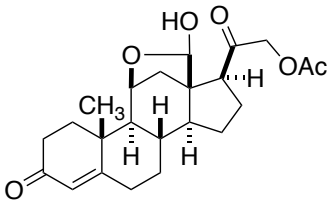
Impact on Chemistry: Radical Chemistry/CH-Activation



cholesterol

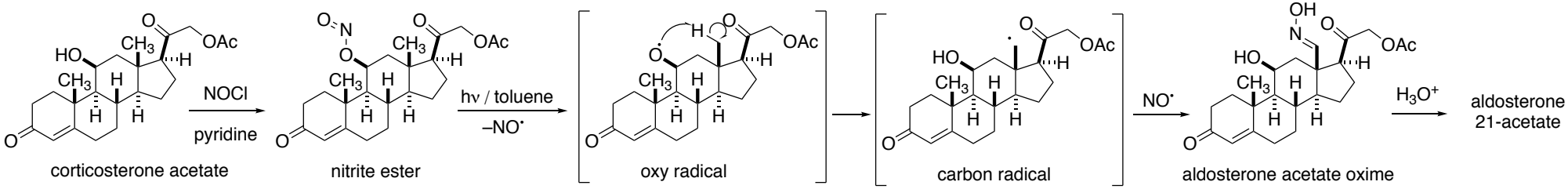


cortisone acetate



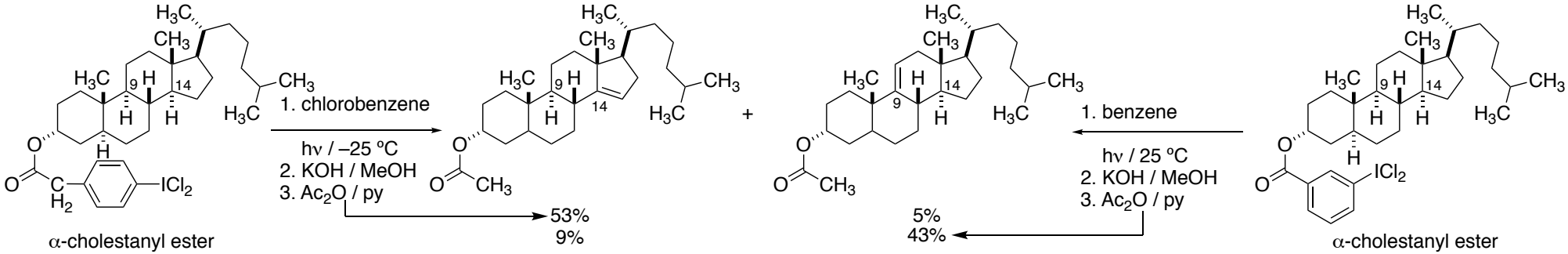
aldosterone 21-acetate

Barton *J. Am. Chem. Soc.* **1960**, *82*, 2641



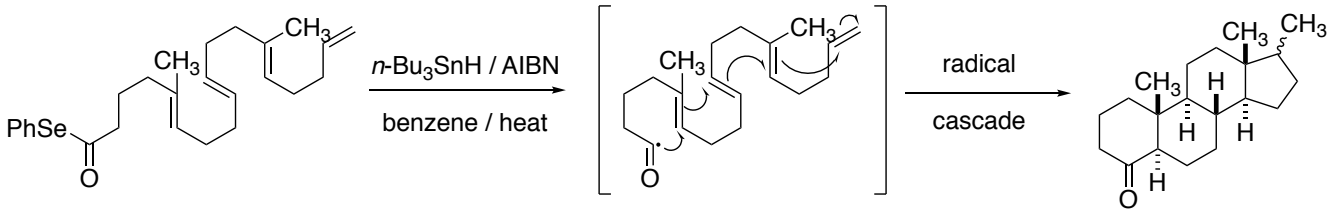
corticosterone acetate → nitrite ester → oxy radical → carbon radical → aldosterone acetate oxime

Breslow *J. Am. Chem. Soc.* **1974**, *96*, 1973

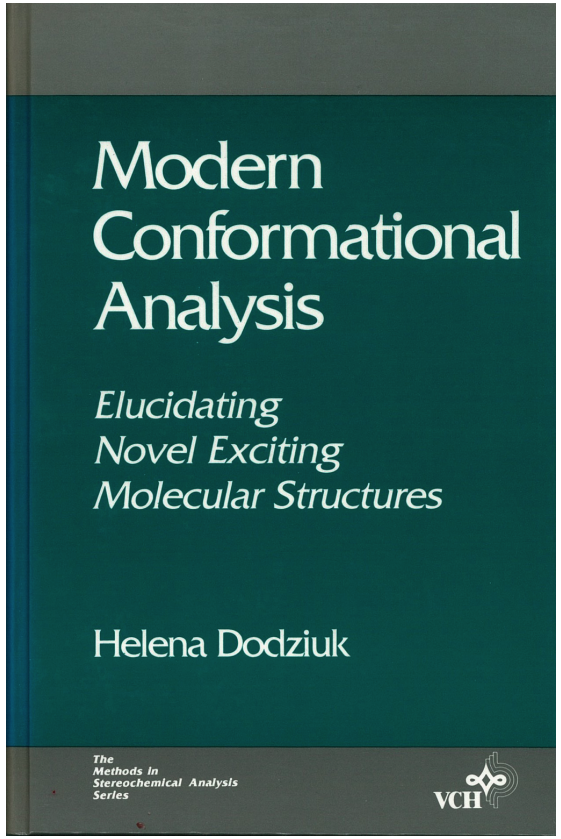


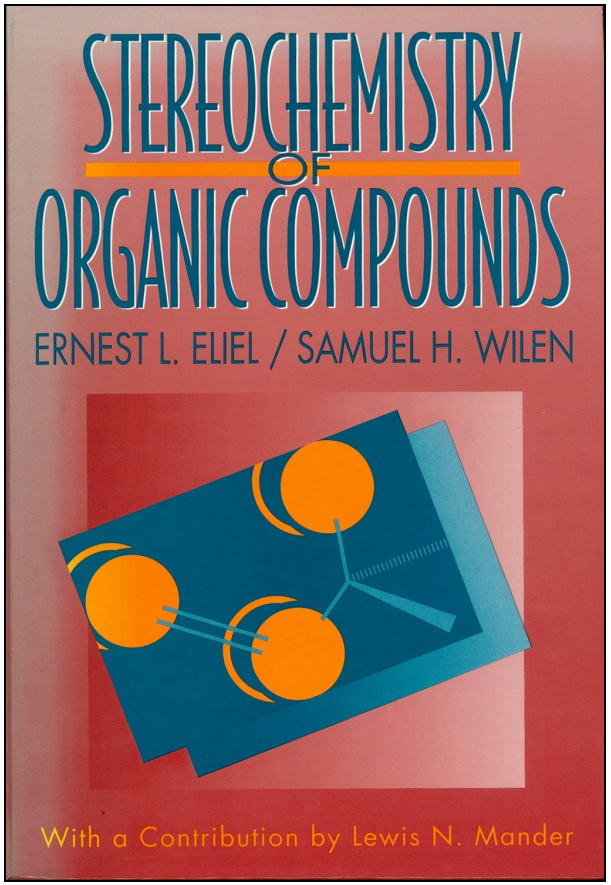
α-cholestanyl ester

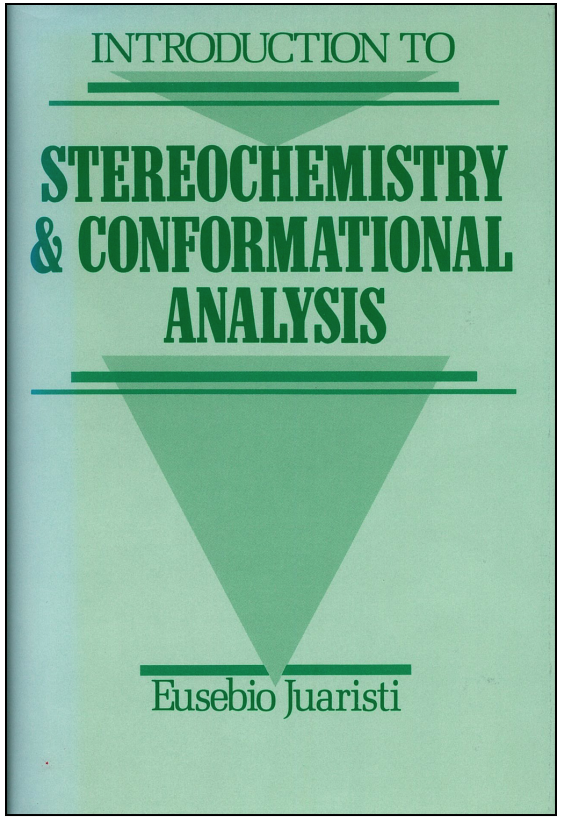
Pattenden *J. Chem. Soc. Perk 1* **1996**, 45



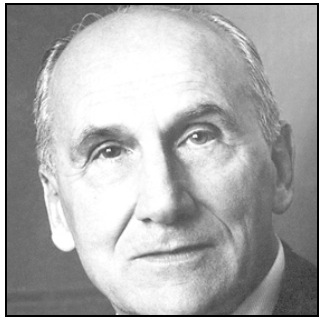
Impact on Chemistry: Stereochemistry - Conformational Analysis



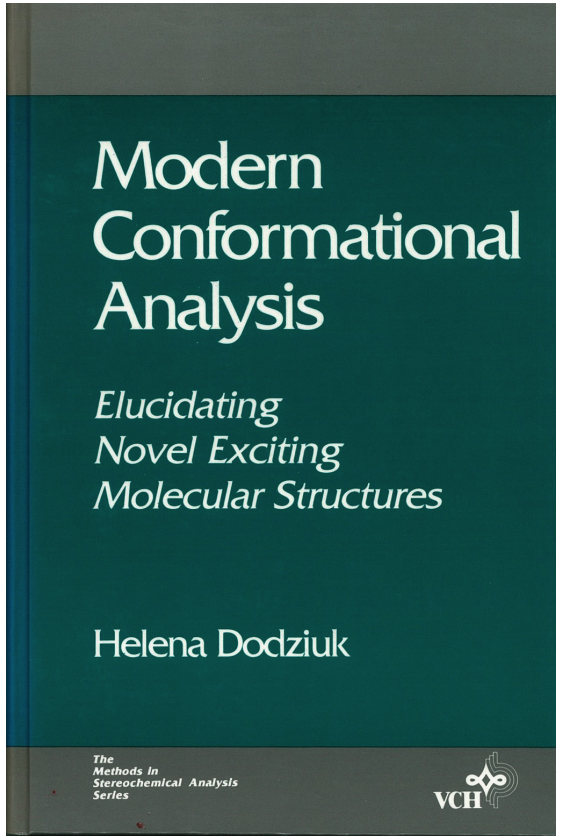


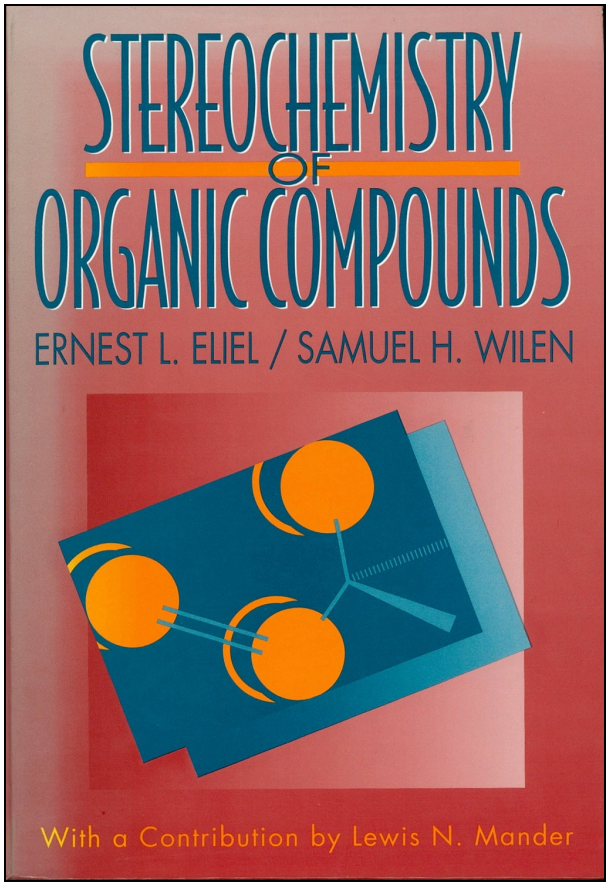


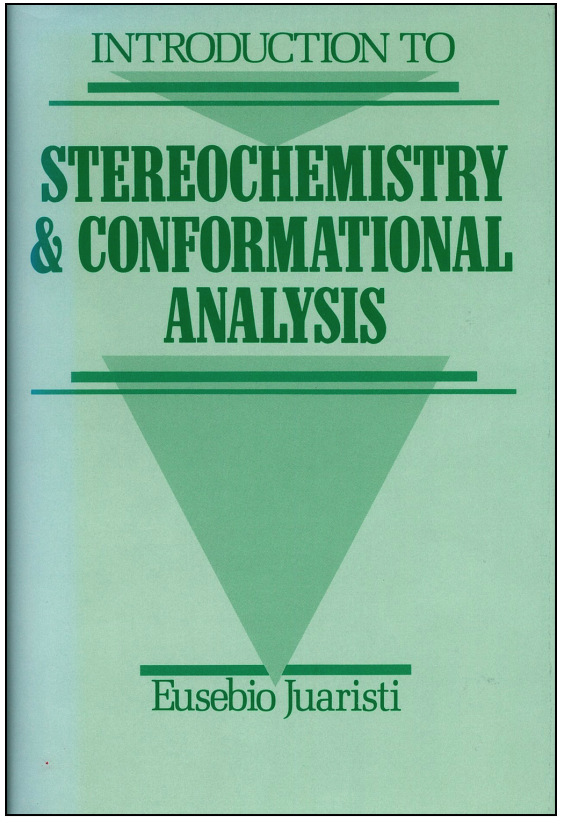
All of these people except one have Nobel Prizes related to stereochemistry



Impact on Chemistry: Stereochemistry - Conformational Analysis







All of these people except one have Nobel Prizes related to stereochemistry

L. Pasteur No Prize! Fundamentals of Molecular Dissymmetry	**J. H. van't Hoff** 1901 Theory of Bonding and Stereochemistry	**D. H. R. Barton** 1969 Conformational Analysis	**V. Prelog** 1975 Stereochemistry of Medium Rings	**J. W. Cornforth** 1975 Stereochemistry of Enzymatic Reactions

Impact on Chemistry: Stereochemistry - Conformational Analysis

D. H. R. Barton, "Conformation of the Steroid Nucleus" *Experientia* **1950**, *6(8)*, 316

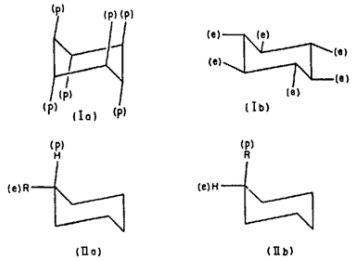
STUDIORUM PROGRESSUS

The Conformation[1] of the Steroid Nucleus

By D. H. R. BARTON[2], Cambridge, Mass.

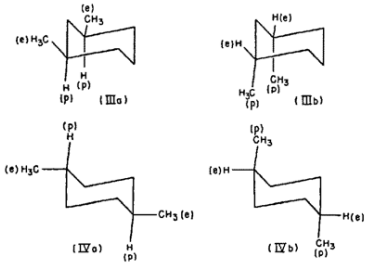
In recent years it has become generally accepted that the chair conformation of cyclohexane is appreciably more stable than the boat. In the chair conformation it is possible[3,4] to distinguish two types of carbon-hydrogen bonds; those which lie as in (Ia) perpendicular to a plane containing essentially the six carbon atoms and which are called[3] *polar* (p), and those which lie as in (Ib) approximately in this plane. The latter have been designated[3] *equatorial* (e).

The notable researches of HASSEL and his collaborators[5,6] on the electron diffraction of cyclohexane derivatives have thrown considerable light on these more subtle aspects of stereochemistry. Thus it has been shown[5] that monosubstituted cyclohexanes adopt the equatorial conformation (IIa) rather than the polar one (IIb). This is an observation of importance for it indicates that the equatorial conformations are thermodynamically more stable than the polar ones. It should perhaps be pointed out here that although one conformation of a molecule is more stable than other



possible conformations, this does *not* mean that the molecule is *compelled* to react as if it were in this conformation or that it is rigidly fixed in any way. So long as the energy *barriers* between conformations are small, separate conformations cannot be distinguished by the classical methods of stereochemistry. On the other hand a small difference in free energy content (about one kilocal. at room temperature) between two possible conformations will ensure that the molecule appears by physical methods of examination and by thermodynamic considerations to be substantially in only *one* conformation.

The equatorial conformations are also the more stable in both cis-1:3- and trans-1:4- disubstituted cyclohexanes[1]. Thus cis-1:3-dimethylcyclohexane adopts the diequatorial conformation (IIIa) rather than the dipolar one (IIIb), whilst trans-1:4-dimethylcyclohexane exists as (IVa) rather than (IVb).



Thermodynamic calculations[1] show that trans-1:2-dimethylcyclohexane takes up the diequatorial conformation (V; R=CH_3) rather than the dipolar one (VI; R=CH_3). For cis-1:2-disubstituted cyclohexanes there are two possible conformations. In both of these one of the substituents forms an equatorial bond, the other a polar one. Since these differences in thermodynamic stability between equatorial and polar conformations are presumably of steric origin[1], it would appear logical to make the larger substituent form the equatorial bond.

Considerations of the same type can be extended to 2-substituted cyclohexanols. Thus[2,3] the cis-alcohols (VII; R= alkyl), on equilibration by heating with sodium, furnish almost entirely the trans-isomers (VIII; R= alkyl). In the former one substituent is polar, one equatorial; in the latter both are equatorial. The same conclusion on relative stability is reached from a consideration of thermochemical data[4]. Similarly[5] the 2:6-disubstituted cyclohexanol (IX), with two equatorial and one polar substituents, is isomerized to (X) on equilibration. The situation is the same[3] with the bicyclic trans-α-decalol. Here the isomer (XI) is isomerized to (XII) on equilibration.

A consideration of the conformations[6] (XIII) and (XIV), assumed by the steroid nucleus when the A/B ring fusion is respectively trans- and cis-, provides a striking illustration of the usefulness of the concept of

[1] The word conformation is used to denote differing strainless arrangements in space of a set of bonded atoms. In accordance with the tenets of classical stereochemistry, these arrangements represent only one molecular species.

[2] Harvard University Visiting Lecturer, 1949–50, Harvard University, Cambridge 38, Mass.

[3] C. W. BECKETT, K. S. PITZER, and R. SPITZER, J. Amer. Chem. Soc. *69*, 2488 (1947).

[4] O. HASSEL's nomenclature[5] is different, but the distinction remains the same.

[5] O. HASSEL and H. VIERVOLL, Acta Chem. Scand. *1*, 149 (1947).

[6] See O. HASSEL and B. OTTAR, Acta chem. Scand. *1*, 929 (1947) for a summarizing paper and references to earlier work.

[1] C. W. BECKETT, K. S. PITZER, and R. SPITZER, J. Amer. Chem. Soc. *69*, 2488 (1947).

[2] G. VAVON, Bull. Soc. Chim. [4], *49*, 937 (1931).

[3] W. HÜCKEL, Ann. Chem. *533*, 1 (1937).

[4] A. SKITA and W. FAUST, Ber. Dtsch. Chem. Ges. *64*, 2878 (1931).

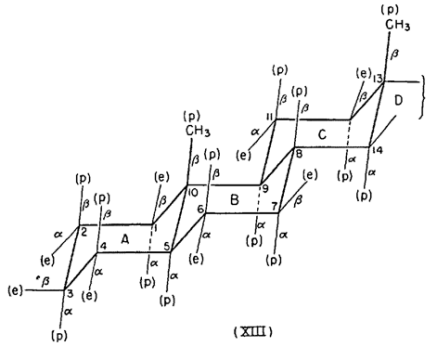
[5] G. VAVON and P. ANZIANI, Bull. Soc. Chim. [5], *4*, 1080 (1937). In connection with the conformations of poly-substituted cyclohexanes it should be mentioned that O. BASTIANSEN, O. ELLERSEN, and O. HASSEL, (Acta chem. Scand. *3*, 918 [1949]) have recently shown that the five stereoisomeric benzene hexachlorides assume, in agreement with our general argument, those conformations which have the maximum possible number of equatorial carbon-chlorine bonds.

[6] Conformations (XIII) and (XIV) are unambiguous representations of the steroid nucleus provided that rings A, B, and C are chairs. This is almost certainly true for a trans-A/B ring fusion (compare the X-ray evidence of C. H. CARLISLE and D. CROWFOOT (Proc. Roy. Soc. A *184*, 64 [1945]) on the conformation of cholesteryl iodide) and a similar situation, at least in solution, probably holds for a cis-A/B fusion. The justification for the latter has been more

This observation is adequately accommodated by the present theory if the rate determining step is attack upon the carbon-hydrogen bond rather than upon the carbon-hydroxyl linkage.

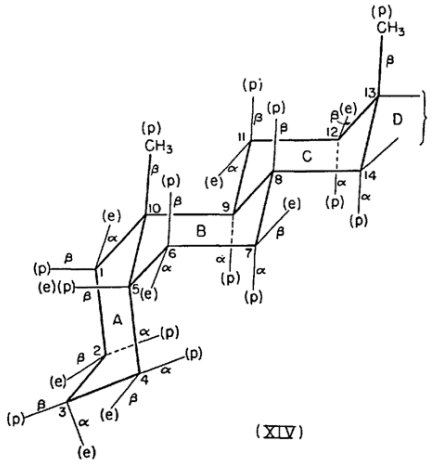
The situation in the steroid field is summarized in Table III. In every case the expected order of hindrance holds good. Also included are data for oxidations of alcohols by Br^+ to give the corresponding ketones. If such oxidations are assumed to involve attack upon the carbon-hydrogen bond then the results are in agreement with the other observations summarized in the Table.

Although the concept of polar and equatorial bonds is not, of course, applicable to cyclopentane, it is of interest to note that the 17α-bond in the steroid nucleus has, because of the ring fusion to a six-membered ring, the character of a polar bond with respect to that ring. Also the 17β-bond has in its relationship to ring C the aspect of an equatorial bond. These facts are in agreement with the greater thermodynamic stability of 17β-substituents and the greater degree of steric hindrance shown by 17α-substituents[1].

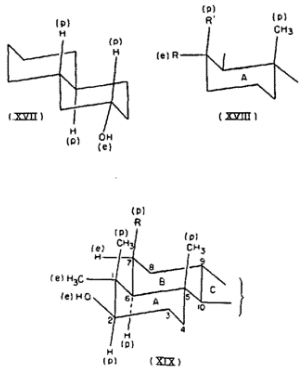


Use of the Concept. It will be clear that it is possible to assign configurations on the basis of the concept of polar and equatorial bonds. One such example has already been given in Table I. An additional illustration is provided by trans-β-decalol[2]. The more stable epimer m.p. 75° must have the hydroxyl in the equatorial conformation as in (XVII); this is in agreement with the fact that its esters are more rapidly hydrolysed than those of the epimeric (polar hydroxyl) alcohol. Other examples are mentioned below.

Extension to di- and tri-terpenoids. It would seem reasonable to extend the concept of equatorial and polar bonds to the correlation of the stereochemistry of other ring systems built up from fused cyclohexane units. Thus ring A of the diterpenoid abietic acid may be represented[3] by (XVIII; R=CO_2H, R′=CH_3) with the carboxyl occupying an equatorial conformation. It is understandable then that the esters of this acid should be more easily hydrolysed than those of (say) podocarpic acid where ring A is as shown in (XVIII; R—CH_3, R′=CO_2H), for in the latter the carboxyl occupies the more hindered polar conformation.



Now that it is recognised[1] that rings A and B of the α- and β-amyrin groups of triterpenoids and also[2] those of the lupeol group are trans-fused, it is possible to make a tentative representation of their stereochemistry



as shown in (XIX; R=H). Placing the hydroxyl in the equatorial conformation explains the more facile hydrolysis of β-amyrin acetate relative to epi-β-amyrin

[1] L. F. FIESER, Exper. *6*, 312 (1950).

[2] W. HÜCKEL, Ann. Chem. *533*, 1 (1937). – W. HÜCKEL *et al.*, Ann. Chem. *533*, 128 (1937).

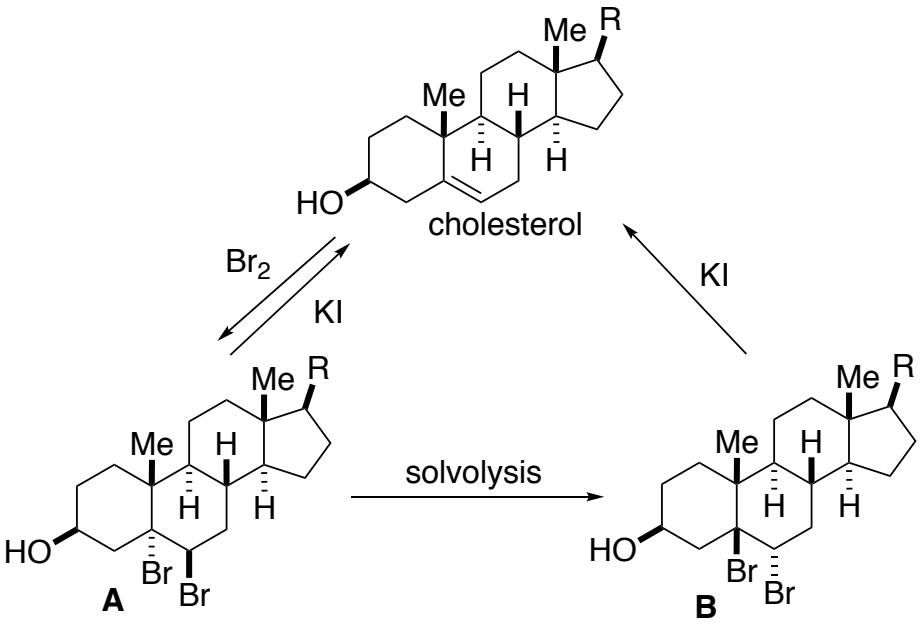
[3] D. H. R. BARTON, Quart. Rev. *3*, 36 (1949).

[1] D. H. R. BARTON, Quart. Rev. *3*, 36 (1949).

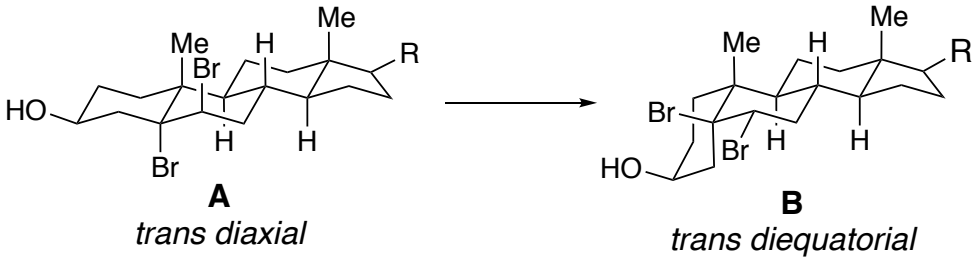
[2] T. R. AMES and E. R. H. JONES, Nature *164*, 1090 (1949).

Impact on Chemistry: Stereochemistry - Conformational Analysis

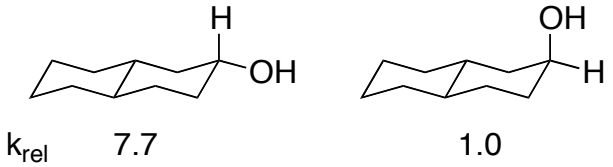
Barton (1950) First clear statement about relationship of conformation and reactivity in reactions of steroids.



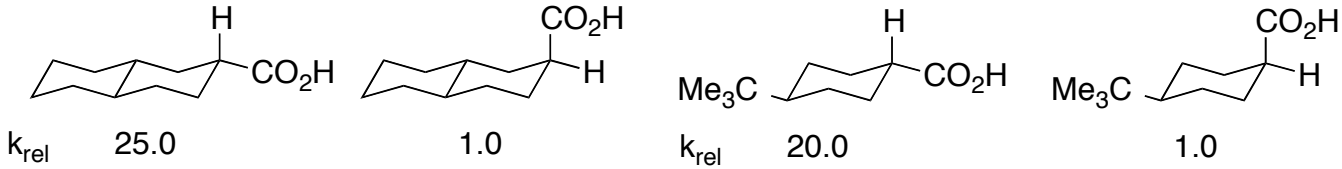
debromination rate: **A** >> **B**



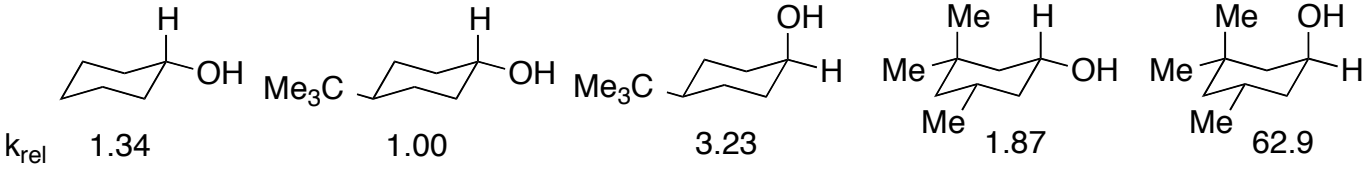
Rates of reaction with acetic anhydride/pyridine



Rates of Fischer esterification



Rates of oxidation with chromic acid



Impact on Chemistry: Stereochemical Course of Reactions

L. F. Fieser, "Steric Course of Reactions of Steroids" *Experientia* **1950**, *6(8)*, 312

Informations - Informationen - Informazioni - Notes

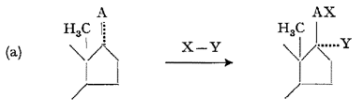
STUDIORUM PROGRESSUS

Steric Course of Reactions of Steroids

By LOUIS F. FIESER[1], Cambridge, Mass.

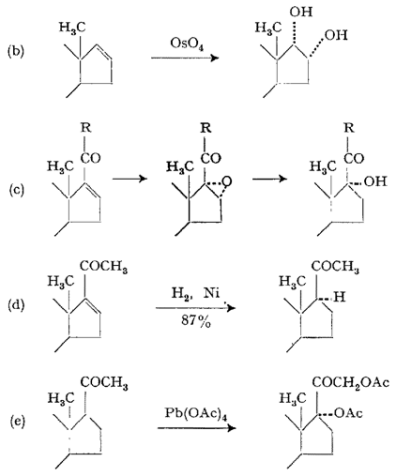
In previous reviews[2] attention was called to two types of hindrance effects that determine the steric course or rate of reactions involving functional groups at the 17-position of steroids. In this paper the concept will be defined more specifically and applied to other positions in the steroid structure.

Intra- and extraradial effects at C_{17}. One type of hindrance controls the direction of opening of a carbon-oxygen or carbon-carbon double bond extending from C_{17}; the relative disposition of atoms and groups in the immediate vicinity of the front and rear side of C_{17} appears to be such as to render C_{17} more accessible to attack from the rear than from the front, for the rear member of the double bond invariably opens preferentially or exclusively (a). Thus 17-ketones on hydro-

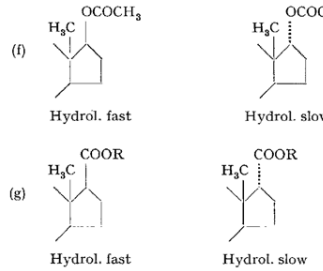


genation, reduction with lithium aluminum hydride, addition of Grignard reagents, or addition of potassium acetylide yield chiefly products in which the hydrogen atom attached to C_{17} is oriented to the rear (α-Y) and the hydroxyl group is oriented to the front (β-AX)[3]; 17,20-ethylenes add osmium tetroxide chiefly by rear-bond attack to give α-hydroxylated products with the normal β-side chain; 17,20-enol acetates react with perbenzoic acid in the same steric sense to give 17α-hydroxy-20-ketones of the normal series[4]. Other instances of preferential rear attack of C_{17} are: (b) formation of 17-epiestriol by osmium tetroxide hydroxylation of the Δ^{16}-ethylene; (c) reaction of a 16,17-ethylene with perbenzoic acid to give the 16,17-α-oxide convertible into a 17α-hydroxy compound[5]; (d) hydrogenation of a 16,17-unsaturated 20-ketone to a pregnanolone; (e) formation of a 17α,21-diacetoxy compound (rather than 17β,21-) as a by-product of acetoxylation of a 20-ketone.

The rule of rear attack at C_{17} thus seems to apply to a wide variety of structures and reagents. Whatever the source and nature of the spatial characteristics in the immediate vicinity of C_{17} that favor attack from the rear, the overall effect must be associated with atoms within the van der Waals radius of C_{17} and hence can be described as an intraradial effect.



That a hindrance effect of a second type determines the course of reactions involving functional groups attached to C_{17} can be recognized from the fact that attack from the front is favored over attack from the rear. Thus in the pairs of epimeric esters (f) and (g), the



17β-epimer is hydrolyzed more rapidly than the 17α-epimer. Here the attack is at carbonyl groups at some distance from C_{17}, and whatever hindrance effects determine the relative accessibility of groups oriented on the front and rear sides of the molecule these effects must operate outside the van der Waals radius of C_{17} and are therefore defined as extraradial with respect to the point of attachment to the nucleus. Other instances indicating greater availability of space on the front than on the rear side in the region extraradial to C_{17} are as

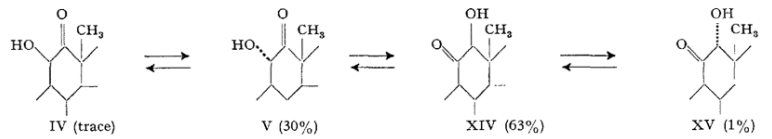
[1] Converse Memorial Laboratory, Harvard University, Cambridge 38, Massachusetts.

[2] L. F. FIESER and M. FIESER, Exper. *4*, 285 (1948); Natural Products Related to Phenanthrene, 3rd Ed., Reinhold, New York (1949).

[3] Unless otherwise indicated, references to the literature are to be found in the Monograph by FIESER and FIESER, loc. cit.

[4] B. A. KOECHLIN, D. L. GARMAISE, T. H. KRITCHEVSKY, and T. F. GALLAGHER, J. Amer. Chem. Soc. *71*, 2362 (1949).

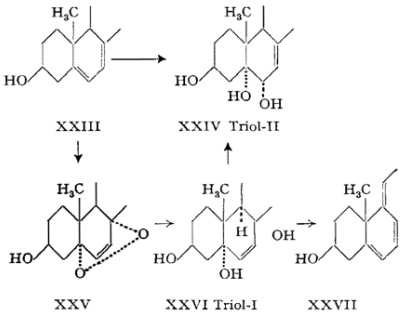
[5] PL. A. PLATTNER, H. HEUSSER, and M. FEUSER, Helv. chim. acta *31*, 2210 (1948). – P. L. JULIAN, E. W. MEYER, and I. RYDEN, J. Amer. Chem. Soc. *71*, 756 (1949).



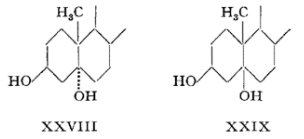
When either of the epimeric 11-hydroxy-12-keto acids IV or V or their bromo precursors is refluxed with alcoholic alkali an equilibrium mixture of isomers results in which the Marker-Lawson acid XIV predominates; the yields of components obtained after equilibration of pure XIV (GALLAGHER) are indicated under the formulas. GALLAGHER and KRITCHEVSKY have suggested an interpretation of the predominance of XIV based on the concept of a rear-attack by a proton of a common enediol ion, but this explanation seems inadmissible because the relative rates of enolization reactions cannot influence the final position of equilibrium. The phenomenon seems rather to be related to the isomerization of 17-ketones and etio esters discussed above; the position of equilibrium should be dependent upon the relative availability of space in the front and rear extraradial regions surrounding position 11 and 12. If accommodation of the hydroxyl group alone were involved, the relative abundance of the isomers expected from relative hindrance in the hydrolysis of esters would be: V>XIV>XV>IV; this corresponds to the actual order except for the reversal of V and XIV.

Positions 5 and 6. Many reactions involving the 5,6-double bond bear evidence that attack is predominately from the rear. Thus hydrogenation of cholesterol gives exclusively a cholestane derivative (XVI); hydroxylation with osmium tetroxide or permanganate gives the 3β,5α,6α-triol (XVII); reaction with perbenzoic acid gives chiefly the α-oxide (XVIII), which on hydrolysis yields the 3β,5α,6β-triol (XIX). Bromination of cholesterol has been shown by BARTON and MILLER[1] to yield the 5α,6β-dibromide (XXII); the reaction is here formulated as involving rear attack and fission of the α-bromonium ion XXI in the direction established for the α-oxide.

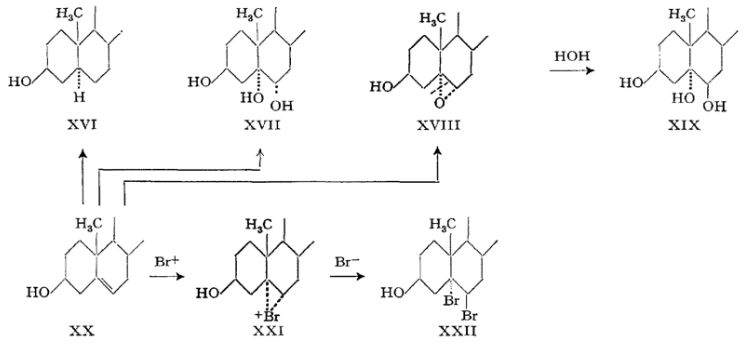
There is some reason to believe that both hydroxylation of ergosterol (XXIII) with lead tetraacetate or osmium tetroxide and reaction of the sterol with oxygen proceed by attack from the rear, as represented in formulas XXIV and XXV, since the ready dehydration of the triol-I (XXVI) on pyrolysis suggests that the hydroxyl group at C_8 is cis to the hydrogen atom at C_9.



Extraradial hindrance at C_5 operates to shield the front side of the molecule more than the rear side. Thus



the 5α-hydroxyl group of cholestane-3β,5α-diol (XXVIII) is acylable whereas the 5β-hydroxyl group present in many cardiac aglycones (XXIX) is not. The relation-



[1] D. H. R. BARTON and E. MILLER, J. Amer. Chem. Soc. *72*, 1066 (1950).

Impact on Chemistry: Stereoelectronic Effects

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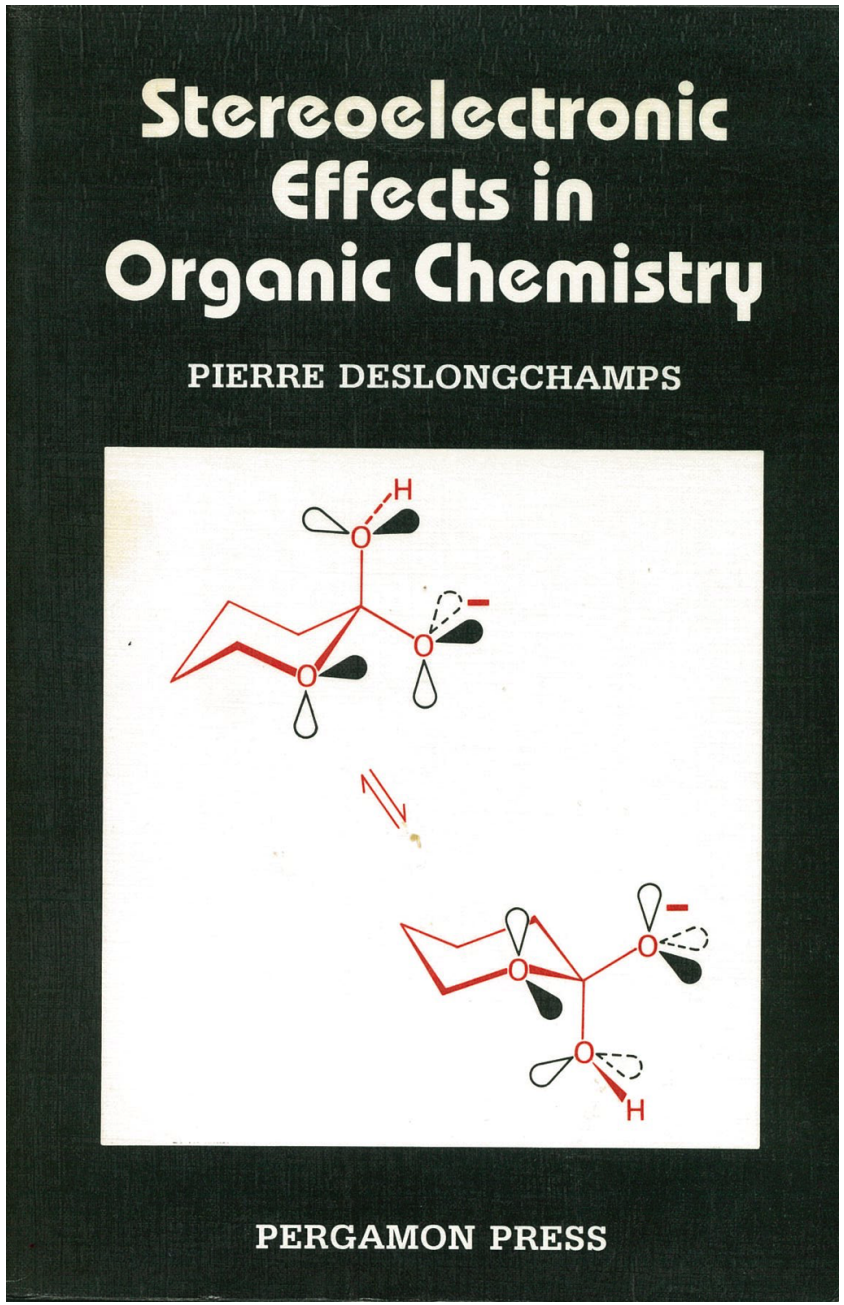

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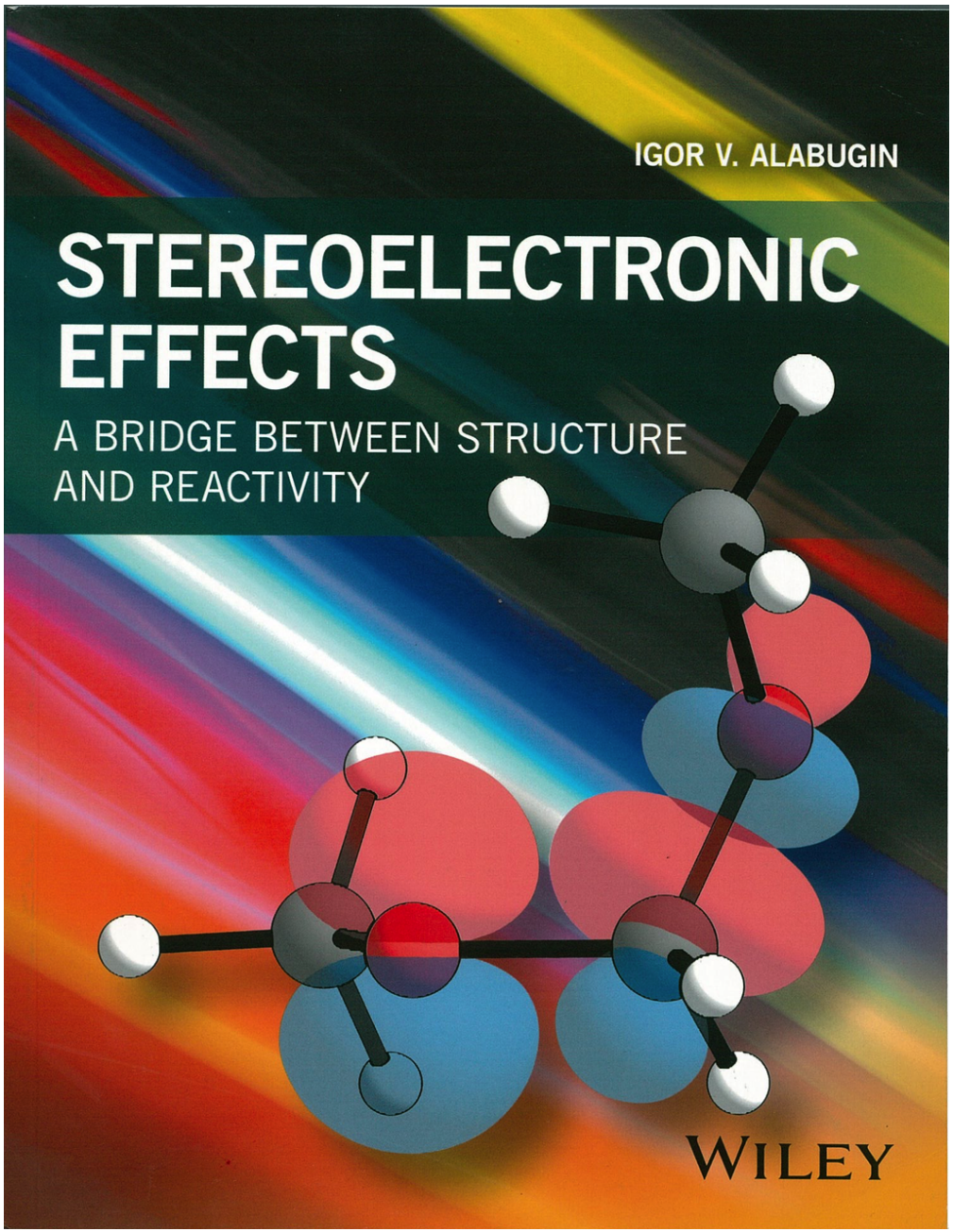

Impact on Chemistry: Stereoelectronic Effects

E. J. Corey, "..Stereochemistry of α-Brominated Ketosteroids" *Experientia* **1953**, *15(9)*, 329

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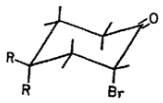
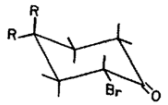
Prediction of the Stereochemistry of α-Brominated Ketosteroids

Previous work[1] has shown that the orientation of bromine in the most stable conformation of a monocyclic α-bromocyclohexanone is sometimes polar and sometimes equatorial. For example, the stable conformation of 2-bromocyclohexanone is that chair form in which the bromine is *polar* (I *A*), while the stable form of 2-bromo-4,4-dimethylcyclohexanone is that chair form in which bromine is *equatorial* (II *B*) (Table I). This dichotomy is due to the fact that both steric and electrical repulsions[2] between ring substituents are important in determining the preferred molecular configuration. When the bromine substituent in an α-bromocyclohexanone is equatorial electrical repulsions are at a maximum and steric repulsions are at a minimum; however, when the bromine is polar the reverse is true.

Thus, when electrical repulsions due to equatorial bromine are much more important than steric repulsions due to polar bromine, the stable molecular configuration will be that in which bromine is polar. This is the situation with 2-bromocyclohexanone, as has been confirmed by calculations[1]. Electrical interaction between the C–O and C–Br dipoles destabilize form I *B* of 2-bromocyclohexanone by at least 2·7 kcal./mole relative to form I *A*, while steric interactions destabilize form I *A* by only *ca.* 0·4 kcal./mole relative to form I *B*. In the case of 2-bromo-4,4-dimethylcyclohexanone, however, the steric interaction in II *A* between polar bromine and a polar, *cis*-methyl group at C_4 completely overshadows the electrical interactions in II *B* involving equatorial bromine and, consequently, the stable form is II *B*.



I *A*, R = H
II *A*, R = CH_3



I *B*, R = H
II *B*, R = CH_3

From a knowledge of the stable molecular configuration of non-rigid α-bromocyclohexanones[3], which is easily obtained by infrared spectroscopy[4], one can evaluate the relative importance of the electrical and steric interactions between substituents in any type of cyclohexane ring systems, rigid or non-rigid. Consequently, the preferred molecular configurations of suitable non-rigid reference systems can be used to derive the preferred configuration at an asymmetric carbon atom in a rigid system.

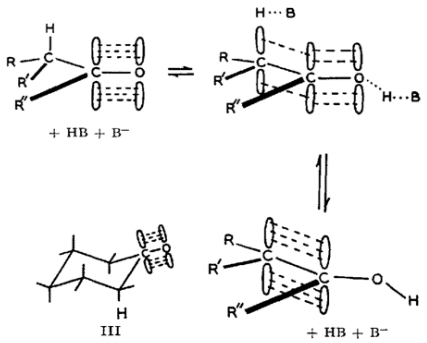
Table I

Relative stabilities of chair-formed conformations of α-bromocyclohexanones

Ketone	Approx. Keq., (Br polar)* / (Br equatorial)
2-bromocyclohexanone-1	> 50
2-bromo-3,3-dimethyl-cyclohexanone-1	> 40
2-bromo-4,4-dimethyl-cyclohexanone-1	< 0·01
2-bromo-6,6-dimethyl-cyclohexanone-1	~ 0·4
7-bromo-spiro[4·5]decane-6-one	~ 0·4
cis-2,6-dibromocyclohexanone-1	< 0·05

* In carbon tetrachloride solution at 25°. Data obtained by infrared spectroscopy [ref. 1; E. J. Corey and T. Topie, to be published].

Thus, from the data in Table I on preferred molecular configurations we have deduced the relative stabilities of the epimeric bromination products of any ketosteroid with ketone function in ring *A*, *B* or *C* and *A*/*B* *cis* or trans. The results are recorded in Table II. Since the stable epimer predominates when the product of bromination is *thermodynamically* (*equilibrium*) *controlled*, it is possible by means of these data to *predict* the configuration at $C_{(Br)}$ of any bromoketone thus formed.



+ HB + B^-

III

+ HB + B^-

We also have found a rule, which has a theoretical basis, for predicting the stereochemistry of the *kineti-*

[1] E. J. Corey, J. Amer. Chem. Soc. *75*, 2301 (1953).
[2] By electrical repulsions we mean the inverse-square field effect associated with the proximity of non-bonded atoms of like net charge; by steric repulsions we mean the inverse-exponential field effect due to interaction between the outer valence-shell electrons of non-bonded atoms.
[3] The term non-rigid is used to mean that both possible chair forms of the cyclohexane ring can exist. A rigid chair-formed six-membered ring is one which is prevented from assuming the other possible chair form.
[4] E. J. Corey, J. Amer. Chem. Soc. *75*, 2301 (1953). – R. N. Jones, D. A. Ramsay, F. Herling, and K. Dobriner, J. Amer. Chem. Soc. *74*, 2828 (1952).

We also have found a rule, which has a theoretical basis, for predicting the stereochemistry of the kinetically (rate) controlled bromination products of keto-steroids. This rule rule…leads invariably to the correct assignment of configuration: the epimer which is formed faster in the bromination of a keto-steroid is always that in which bromine is polar (axial). **The theoretical basis for this rule depends on the recognition of both the enolization of a ketone and the ketonization of an enol as stereoselective processes. In general, the energy of the transition state for enolization will be minimized when there is maximum overlap between the $sp^3 \rightarrow p$ orbital made available by the by the leaving α-hydrogen and the π orbital of the carbonyl carbon. In the case of a chair-formed, six-membered ring, such a favored transition state is possible only if the departing α-hydrogen is polar (see III). Consequently, enolization of a cyclohexanone should take place preferentially with a leaving polar hydrogen and, by the principle of microscopic reversibility, the reverse reaction, ketonization, should involve an entering electrophilic species (e.g. H^+ or Br^+) which preferentially adopts the polar orientation.**

Impact on Chemistry: Stereoelectronic Effects

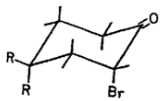
E. J. Corey, "..Stereochemistry of α-Brominated Ketosteroids" *Experientia* **1953**, *15(9)*, 329

Brèves communications - Kurze Mitteilungen
Brevi comunicazioni - Brief Reports

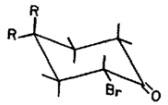
Prediction of the Stereochemistry of α-Brominated Ketosteroids

Previous work[1] has shown that the orientation of bromine in the most stable conformation of a monocyclic α-bromocyclohexanone is sometimes polar and sometimes equatorial. For example, the stable conformation of 2-bromocyclohexanone is that chair form in which the bromine is *polar* (I *A*), while the stable form of 2-bromo-4,4-dimethylcyclohexanone is that chair form in which bromine is *equatorial* (II *B*) (Table I). This dichotomy is due to the fact that both steric and electrical repulsions[2] between ring substituents are important in determining the preferred molecular configuration. When the bromine substituent in an α-bromocyclohexanone is equatorial electrical repulsions are at a maximum and steric repulsions are at a minimum; however, when the bromine is polar the reverse is true.

Thus, when electrical repulsions due to equatorial bromine are much more important than steric repulsions due to polar bromine, the stable molecular configuration will be that in which bromine is polar. This is the situation with 2-bromocyclohexanone, as has been confirmed by calculations[1]. Electrical interaction between the C–O and C–Br dipoles destabilize form I *B* of 2-bromocyclohexanone by at least 2·7 kcal./mole relative to form I *A*, while steric interactions destabilize form I *A* by only *ca.* 0·4 kcal./mole relative to form I *B*. In the case of 2-bromo-4,4-dimethylcyclohexanone, however, the steric interaction in II *A* between polar bromine and a polar, *cis*-methyl group at C_4 completely overshadows the electrical interactions in II *B* involving equatorial bromine and, consequently, the stable form is II *B*.



I *A*, R = H
II *A*, R = CH_3



I *B*, R = H
II *B*, R = CH_3

From a knowledge of the stable molecular configuration of non-rigid α-bromocyclohexanones[3], which is easily obtained by infrared spectroscopy[4], one can evaluate the relative importance of the electrical and steric interactions between substituents in any type of cyclohexane ring systems, rigid or non-rigid. Consequently, the preferred molecular configurations of suitable non-rigid reference systems can be used to derive the preferred configuration at an asymmetric carbon atom in a rigid system.

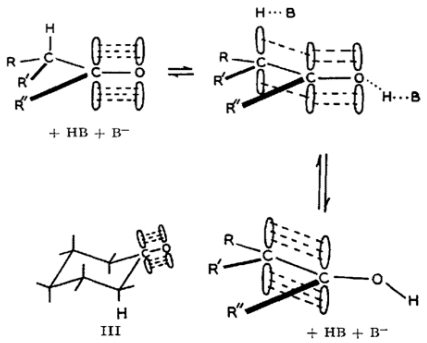
Table I

Relative stabilities of chair-formed conformations of α-bromocyclohexanones

Ketone	Approx. Keq., (Br polar)* / (Br equatorial)
2-bromocyclohexanone-1	> 50
2-bromo-3,3-dimethyl-cyclohexanone-1	> 40
2-bromo-4,4-dimethyl-cyclohexanone-1	< 0·01
2-bromo-6,6-dimethyl-cyclohexanone-1	~ 0·4
7-bromo-spiro[4·5]decane-6-one. . . .	~ 0·4
cis-2,6-dibromocyclohexanone-1 . . .	< 0·05

* In carbon tetrachloride solution at 25°. Data obtained by infrared spectroscopy [ref. 1; E. J. Corey and T. Topie, to be published].

Thus, from the data in Table I on preferred molecular configurations we have deduced the relative stabilities of the epimeric bromination products of any ketosteroid with ketone function in ring *A*, *B* or *C* and *A*/*B* *cis* or trans. The results are recorded in Table II. Since the stable epimer predominates when the product of bromination is *thermodynamically* (*equilibrium*) *controlled*, it is possible by means of these data to *predict* the configuration at $C_{(Br)}$ of any bromoketone thus formed.



+ HB + B^-

III

+ HB + B^-

We also have found a rule, which has a theoretical basis, for predicting the stereochemistry of the *kineti-*

[1] E. J. Corey, J. Amer. Chem. Soc. *75*, 2301 (1953).
[2] By electrical repulsions we mean the inverse-square field effect associated with the proximity of non-bonded atoms of like net charge; by steric repulsions we mean the inverse-exponential field effect due to interaction between the outer valence-shell electrons of non-bonded atoms.
[3] The term non-rigid is used to mean that both possible chair forms of the cyclohexane ring can exist. A rigid chair-formed six-membered ring is one which is prevented from assuming the other possible chair form.
[4] E. J. Corey, J. Amer. Chem. Soc. *75*, 2301 (1953). – R. N. Jones, D. A. Ramsay, F. Herling, and K. Dobriner, J. Amer. Chem. Soc. *74*, 2828 (1952).

Reaction of 1-Fluoro-2-methylnaphthalene with Sodium Amide and Piperidine.—The reaction was run as described[3] for the bromonaphthalenes, and the basic products were purified by fractional distillation at reduced pressure. A colorless liquid, b.p. 134° (2 mm.), $n^{18}D$ 1.6060, was obtained in 84.5% yield (reckoned as 1-piperidino-2-methylnaphthalene).

Anal. Calcd. for $C_{16}H_{19}N$: C, 85.28; H, 8.50. Found[23]: C, 85.38; H, 8.82.

1-Piperidino-2-methylnaphthalene from 1-Bromo-2-methylnaphthalene.—As a check on the identity of the above product, 22.1 g. of 1-bromo-2-methylnaphthalene and 35 cc. of piperidine were heated in a sealed tube 82 hours at 200°. The basic products were isolated by standard procedures including distillation at reduced pressure. The liquid so obtained was treated with *p*-toluenesulfonyl chloride in pyridine to remove primary and/or secondary amines apparently derived solely from the piperidine,[3] and the remaining basic product was finally purified by distillation at reduced pressure. A clear oil (2.1 g., 9%), b.p. 137–141° (3–4 mm.), $n^{25}D$ 1.6051, was so obtained. Its infrared spectrum was identical to that of the product described immediately above.

The products of the two reactions are identical, and the substance is almost surely 1-piperidino-2-methylnaphthalene. If the piperidino group is anywhere but the 1-position, an unprecedented rearrangement has occurred in two separate instances.

Attempted Reaction of α-Naphthyl Methyl Sulfone with Piperidine.—This experiment was run to check on the unlikely possibility that the production of III from this sulfone and the sodium amide–piperidine reagent might have been due solely to the action of the piperidine in the reagent. The sulfone and piperidine were combined just as in the earlier experiment except that sodium amide was omitted. The mixture was refluxed two hours. No III was obtained, and 86% of the sulfone was recovered in a state of high purity.

Chapel Hill, N. C.

[Contribution from the Noyes Chemical Laboratory, University of Illinois]

Stereoelectronic Control in Enolization–Ketonization Reactions[1]

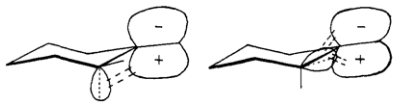
By E. J. Corey and R. A. Sneen

Received March 26, 1956

The stereochemistry of the enolization of 3β-acetoxycholestan-7-one to the Δ⁶-en-7-ol and of the ketonization of this enol have been studied using deuterium tracer. With hydrogen bromide as catalyst in chloroform solution the axial hydrogen at C_6 is lost in enolization 1.2 times as rapidly as the equatorial hydrogen (corrected for isotope effect); for the reverse reaction, ketonization, an axial hydrogen is gained *ca.* 1.5 times as rapidly as an equatorial hydrogen. These values, which in theory should be identical, are in reasonably good agreement and indicate that despite a strong steric retardation of the gain and loss of an axial hydrogen, axial attack is still at least as favorable as equatorial attack. Correction for this steric effect gives the result that stereoelectronic factors favor axial attack over equatorial attack by a factor of at least 12. The acetic acid catalyzed enolization–ketonization reaction is even more specific and axial attack is favored over equatorial attack by a total factor of at least 9 with a stereoelectronic component of at least 50. The kinetic isotope effect of deuterium in enolization of 7-ketosteroids has been found to be *ca.* 7.4, close to the theoretical maximum at 10°. A thermodynamic explanation is presented to explain the variation in degree of stereoelectronic control with reactivity of the reagent and supporting data are cited from a comparison of chlorination and bromination experiments. The occurrence of a high degree of stereoelectronic control is postulated to explain the exclusive axial attack observed in reactions of steroidal 4,5,6-allyl cations.

It has been shown previously[2] that the bromination of steroid ketones *via* the corresponding enols is characterized in several cases, and perhaps generally, by an effect which directs the incoming bromine substituent to the axial rather than the equatorial position. Opposing this effect is the classical steric effect, which directs a large substituent such as bromine to the less crowded equatorial orientation. The net result of these two effects, which influence the relative rates of formation of the epimers with axial and equatorial bromine, is clear in those cases where the bromoketone which is isolated is the unstable epimer, formed for kinetic rather than for steady-state reasons. In such instances the importance of the non-steric effect is apparent since the major product has invariably been found to be the epimer with axial bromine.[2]

It has been proposed that the orienting influence which is responsible for this stereochemical preference is stereochemical–electronic in nature and depends on the difference in degree of delocalization of electrons in perturbed axial and equatorial bonds which are alpha to an exocyclic π-orbital. Reference to Fig. 1 indicates the relationship between stereochemical orientation and the extent of delocalization of exocyclic σ-electrons to an adjacent exocyclic π-orbital. Since the transition state for enolization–ketonization type processes



axial interaction (bonding) equatorial interaction (non-bonding)

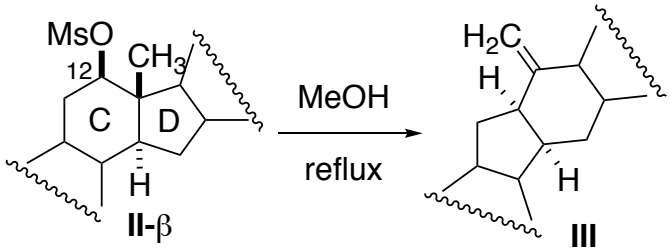
Fig. 1.

is stabilized by bonding between the alpha and carbonyl carbon atoms involving σ–π delocalization as shown in Fig. 1, there should be a preference for loss or gain of an axial α-substituent over an equatorial α-substituent. Or, in slightly different terms, there is better bonding in the transition state for enolization–ketonization when the entering or leaving α-substituent possesses the axial orientation than the alternative equatorial orientation. Because the structure of the transition state for such processes is intermediate between the structures of the enol and ketone or ketone conjugate acid, the bond being formed to or broken from C_α will not possess pure axial or equatorial character and the considerations expressed in Fig. 1 are extreme. However, as the transition

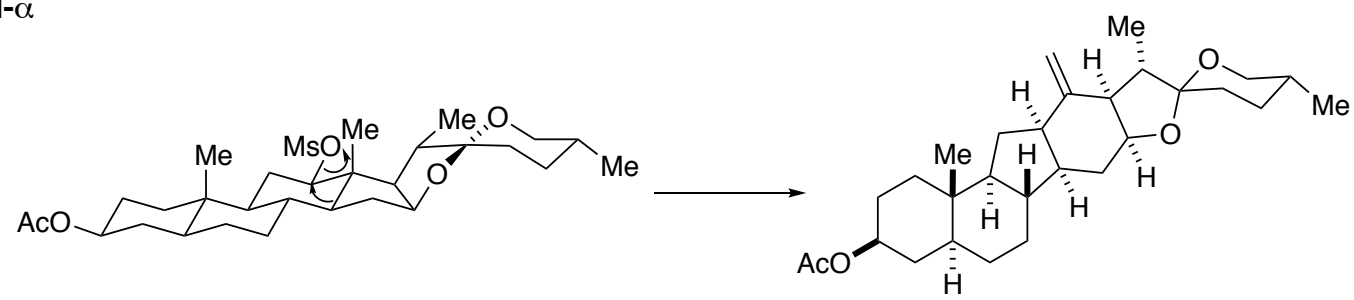
(1) Presented at the Fifth Conference on Organic Reaction Mechanisms, Durham, N. H., September, 1954. Taken from the Ph.D. thesis of Richard A. Sneen, University of Illinois, 1955.
(2) E. J. Corey, This Journal, **76**, 175 (1954).

Impact on Chemistry: Stereoelectronic Effects

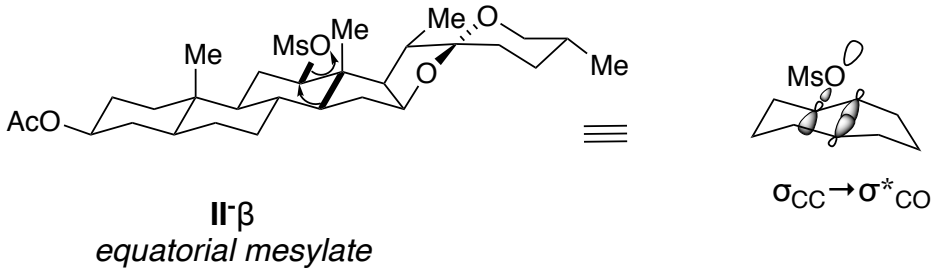
R. Hirschmann "Rearrangement of the Steroid C/D Rings" *J. Am. Chem. Soc.* **1952**, *74*, 2693



The formation of **III** from rockogenin by C/D ring contraction and expansion represents a rearrangement path wherein the **stereoelectronic** requirements are fulfilled only in the case of the natural C_{12}-β-configuration **II-**β. The significance of this geometrical factor is reflected in the extraordinary ease with which this rearrangement occurs.



Stereoelectronic mandate: antiperiplanarity of bonding orbitals



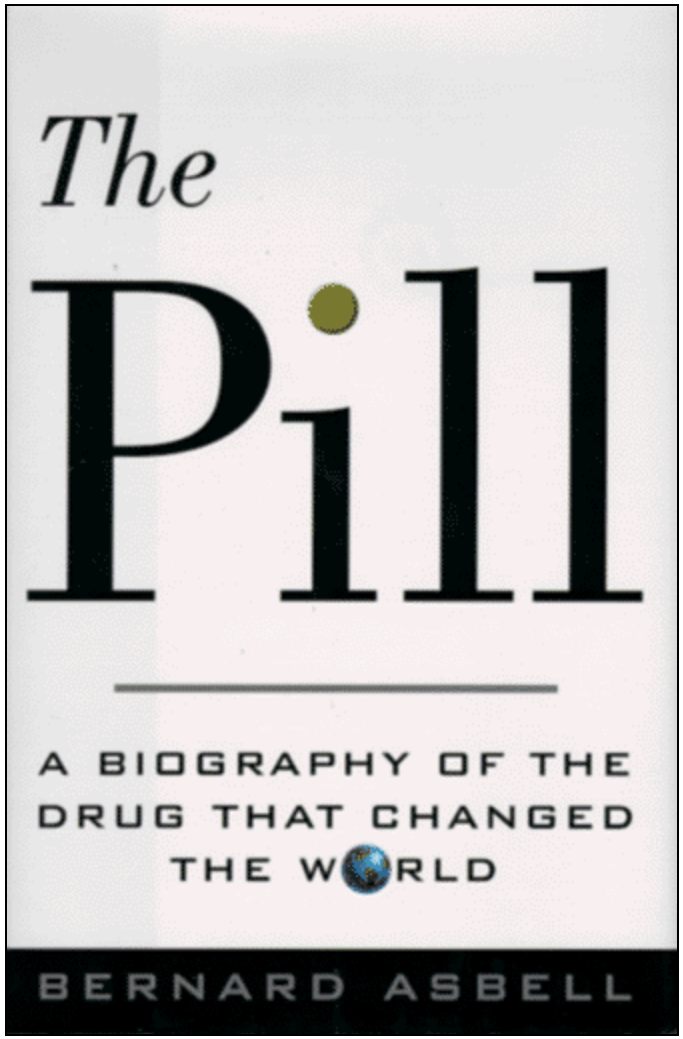
Impact on Society: "The Pill"

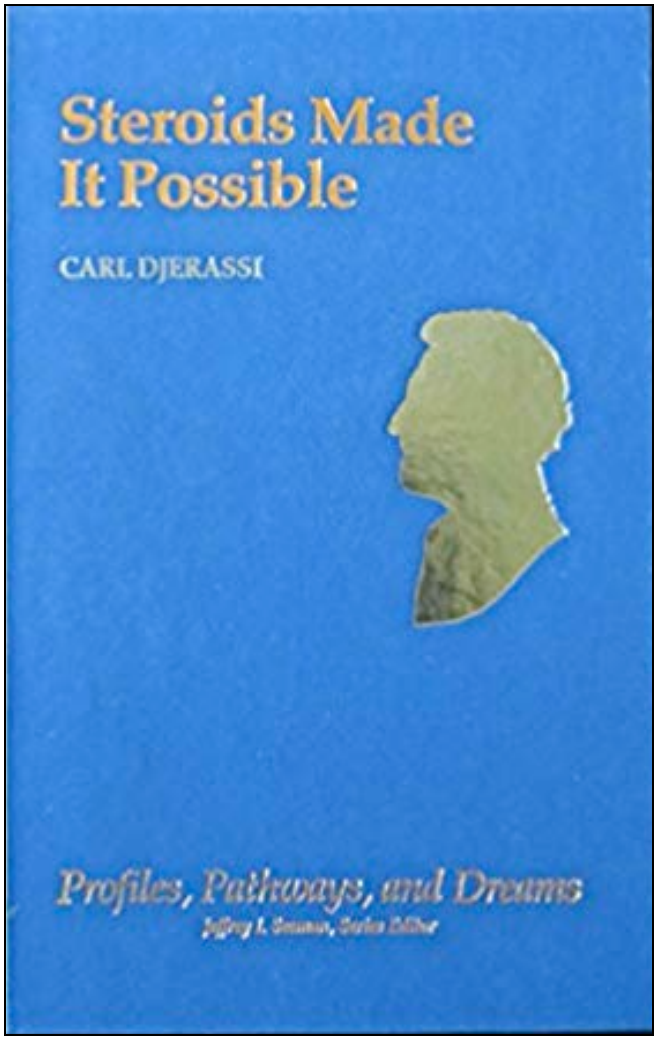
In 2015–2017, 64.9% of the 72.2 million women aged 15–49 in the United States were currently using contraception. The most common contraceptive methods currently used were female sterilization (18.6%), **oral contraceptive pill (12.6%)**, **long-acting reversible contraceptives (LARCs) (10.3%)**, and male condom (8.7%).

Center for Disease Control, *Data Brief No. 327,* December 2018

Modern contraceptive methods constitute most contraceptive use. Globally in 2015, 57% of married or in-union women of reproductive age used a modern method of family planning, constituting 90 per cent of contraceptive users.

United Nations, *Trends in Contraceptive Use Worldwide,* 2015

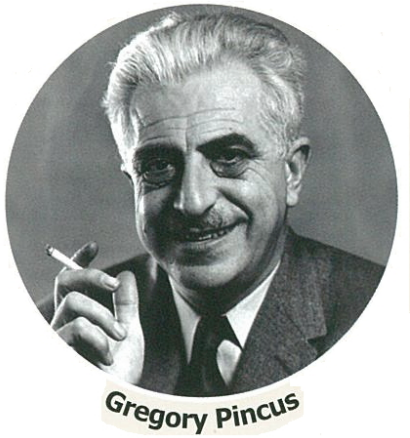




Impact on Society: "The Pill"


Margaret Sanger

In 1951, Margaret Sanger, a veteran birth control campaigner was introduced to a physiologist, Dr. Gregory Pincus in New York. Sanger described her lifelong dream of a "magic pill" which would prevent unwanted pregnancies and give working-class women more control over their lives. Pincus told her of recent investigations into fertility that suggested the use of steroid hormones might result in such a treatment. She decided to fund Pincus through her charitable foundation (Planned Parenthood).


Gregory Pincus

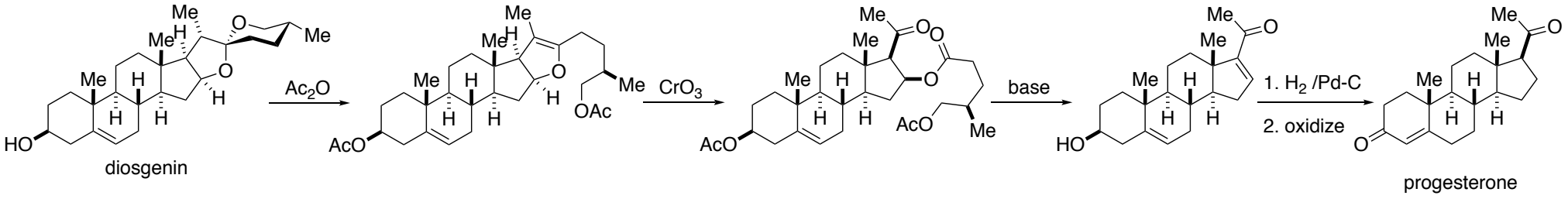
Pincus knew of research in the 1930's and 1940's that established a woman cannot become pregnant a second time during pregnancy because her ovaries secrete estrogen and progesterone. Together these steroids inhibit ovulation by acting on the pituitary gland and by suppressing the production of leutenizing hormone. Thus, administering these steroids during the estrus cycle could prevent pregnancy. Unfortunately, only 20 mg of progesterone could be isolated from 625 kg of sow ovaries, making its use economically infeasable.


Carl Djerassi

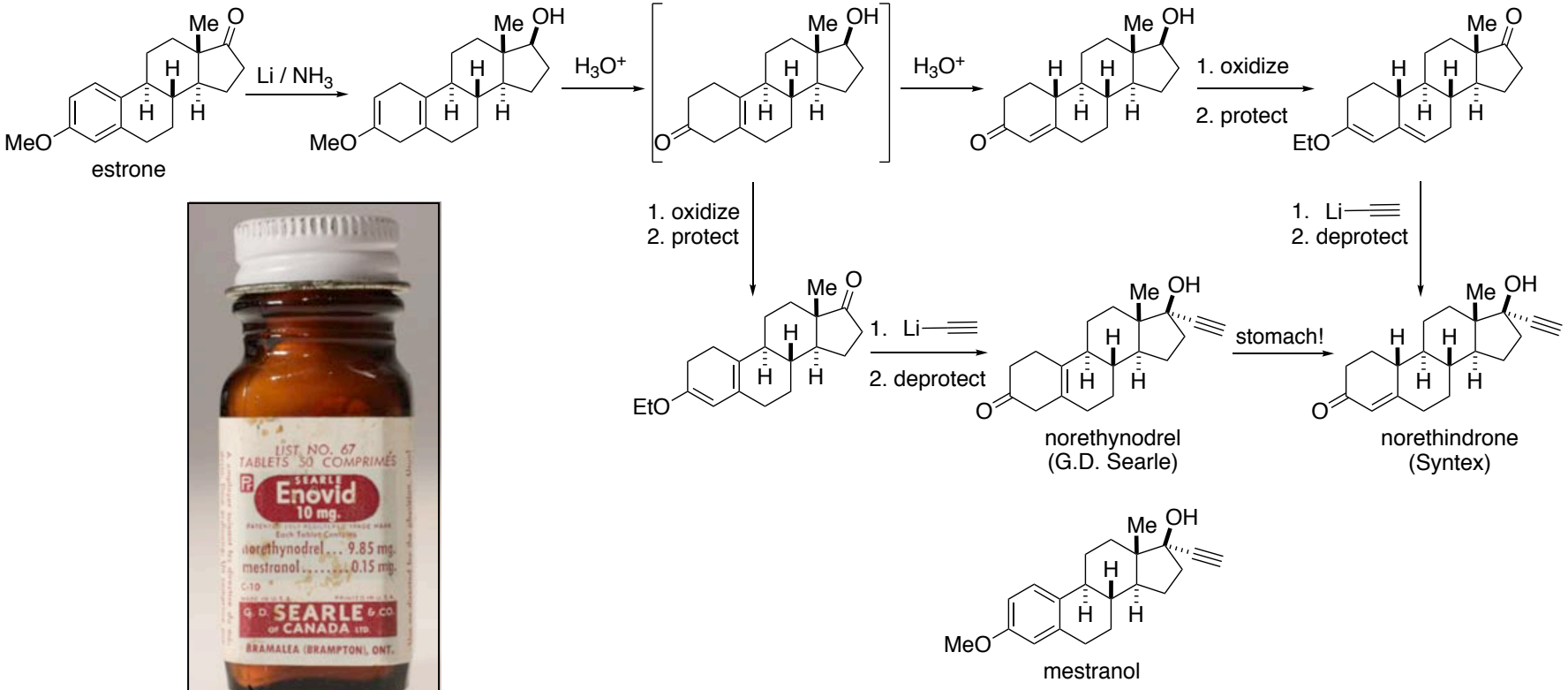
The successful syntheses of cortisone and progesterone from sapogenins from Mexican Yams thrust Syntex and Djerassi into the limelight. However, progesterone was weakly active taken orally. By combining earlier observations about the enhancement of progestational activity of 19-nor steroids and the surprising progestational activity of 17-ethynyltestosterone, Djerassi prepared 19-nor-17-α-ethynyltestosterone (norethindrone). The synthesis was completed on 15 October 1951, patent applied for on 22 November 1951, entered in the National Inventors Hall of Fame in the U.S. Patent Office.

Impact on Society: "The Pill"

Syntex Synthesis of Progesterone from Diosgenin



Syntex Synthesis of Norethindrone from Estrone Methyl Ether

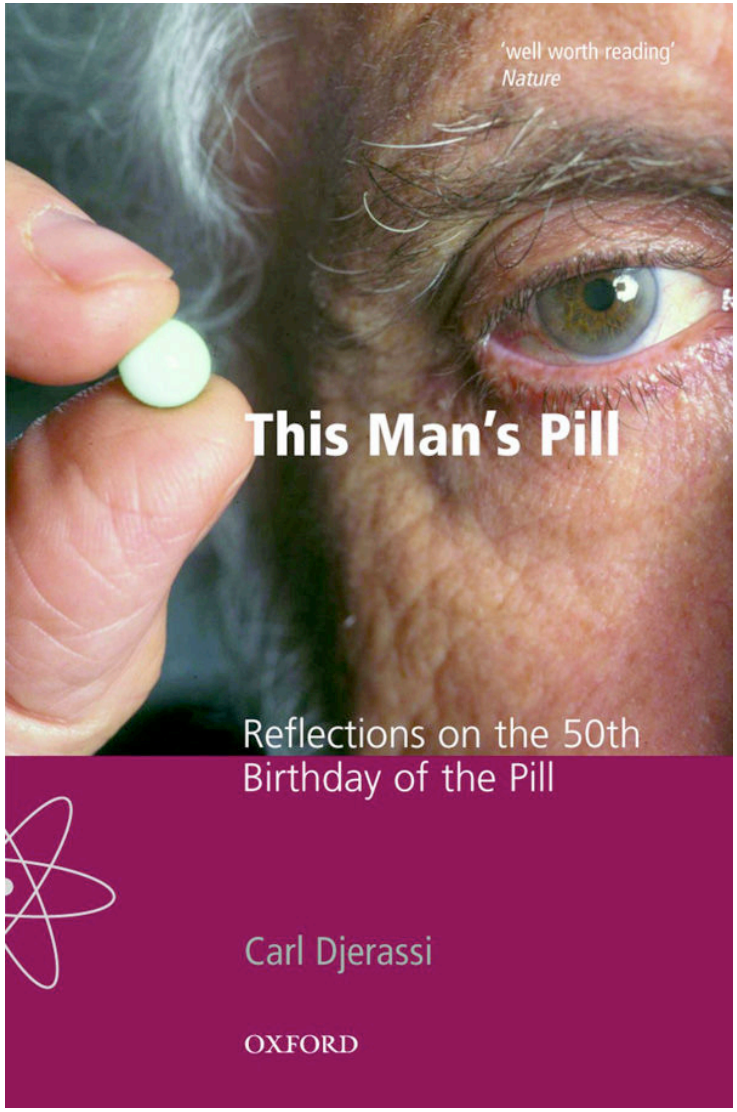


Impact on Society: "The Pill"

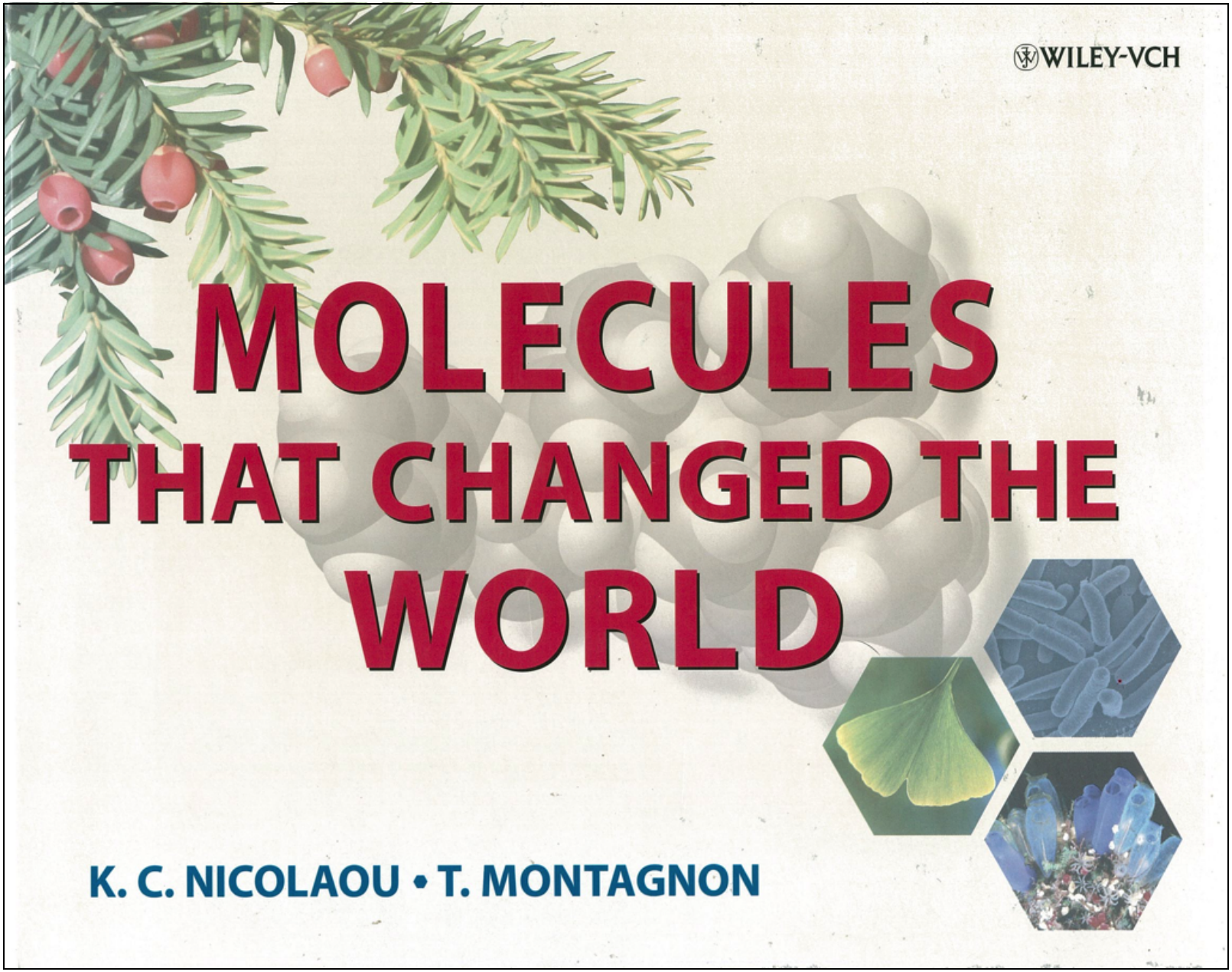
In the opinion of this author, the successful development of orally available, synthetic steroids to modulate the estrus cycle, is the single greatest gift of organic synthesis to mankind. The fact that an contribution of this significance has never been recognized by a Nobel Prize in either Chemistry or in Physiology or Medicine is clearly an egregious oversight or an accomplishment too fraught with complexities to award.

S. E. Denmark, *Isr. J. Chem.* **2018**, *58*, 61

Djerassi receiving the National Medal of Science at the White House from President Nixon in 1973. Two weeks later, Djerassi's name appeared on the President's "Enemies List".



Acknowledgements



Dedication

Jerry Walker (1948-2015)

Edwin Vedejs (1941-2017)