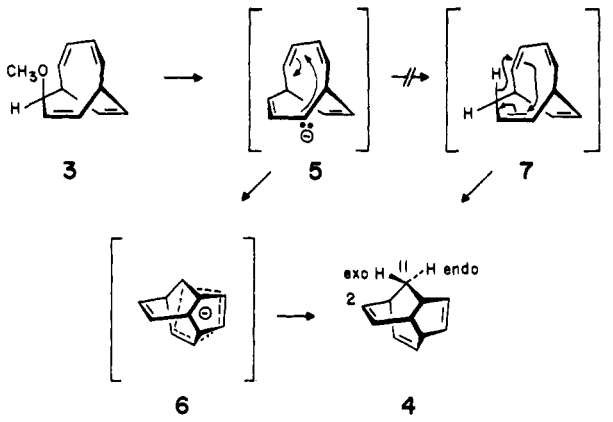
Scheme I



sistent with those reported for similar structures.[14] The critical assignment of C_{11} proton stereochemistry (vide infra) follows from the agreement of observed and calculated ^3J.[15] If the first set of observed ^3J (10.5, 4.5 Hz, Table I) is matched with those calculated for J_{ij} (9.5 Hz, $\theta = 27°$) and J_{hj} (4.1 Hz, $\theta = 54°$) and the second set (2.5, 2.0 Hz) matched with those calculated for J_{ik} (2.5 Hz, $\theta = 62°$) and J_{hk} (0.1 Hz, $\theta = 95°$), a significantly better fit is obtained than if the assignments were reversed.

The anionic mechanism of Scheme I is to be regarded as plausible rather than established.[16] Attack of the three- onto the four-carbon bridge of the longicyclic anion (**5**) generates the tricyclic isomer (**6**). All illustrated, **6** is assumed to possess some measure of trishomocyclopentadienyl pericyclic stabilization that may facilitate the rearrangement.[17]

We think it more significant, however, that **4** is *not* formed by a rapid thermal rearrangement of the still unknown bicyclo[4.3.2]undecatetraene (**7**). Methanol-*O-d* quenching of the anionic solution introduced 0.464 ± 0.009 deuterium atoms exclusively at the endo methylene position.[18] Such stereospecificity exactly matches that of the pericyclic bishomocyclopentadienyl bicyclo[3.2.1]octadienyl anion.[19] Had **7** been an intermediate, the isotopic label would have appeared at the exo position of C_{11} and/or at C_2.

Clearly, the preparative value of the longicyclic stabilization rule does not extend to the $C_{11}H_{11}$ bicyclo[4.3.2]undecatetraene skeleton. In a similar way, the preparative value of the pericyclic $[4n + 2]$ stabilization rule also falters when its homologation reaches $C_{10}H_{10}$.[20] Subsequent homologation, however (to $C_{12}H_{12}^{-2}$,[21a] $C_{14}H_{14}$,[21b] $C_{16}H_{16}^{+2}$,[21c] and $C_{17}H_{17}^{-}$ [21d]), recovers the preparative value of the pericyclic stabilization rule. It remains to be seen whether subsequent longicyclic homologation will behave similarly.

Acknowledgment. Financial support at Cornell was provided by U.S. Public Health Research Grant No. 10495 from the National Cancer Institute.

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(10) (a) Obtained by sodium hydride/methyl iodide treatment of the corresponding alcohol[10b] and characterized both spectroscopically and by elemental analysis. Calcd: C, 82.72; H, 8.10. Found: C, 83.04, 83.24; H, 8.16, 7.94. (b) M. J. Goldstein and S. A. Kline, *Tetrahedron Lett.*, 1089 (1973).
(11) *m/e* 144; IR (neat) 3080 (s), 2899 (s), 1093, 957, 910, 878, 837, 793, and 784 cm^{-1} (no absorption at 765, 895–885 cm^{-1}). Calcd: C, 91.61; H, 8.39. Found: C, 91.37; H, 8.37.
(12) Significantly lower yields (≤2%) were isolated with **3** was treated with sodium–potassium alloy in either 1,2-dimethoxyethane or tetrahydrofuran or when the correspondlng chloride was treated with either reducing agent in either solvent.
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(22) Japan Society for the Promotion of Science Visiting Professor at the University of Tokyo, 1977.
(23) Taken in part from the Ph.D. Thesis of Shuji Tomoda, Cornell University, 1975.

M. J. Goldstein*[22]
Department of Chemistry, Cornell University
Ithaca, New York 14853

Yujiro Nomura, Yoshito Takeuchi, Shuji Tomoda[23]
Department of Chemistry, College of General Education,
The University of Tokyo
Komaba, Meguro-ku, Tokyo 153, Japan
Received November 28, 1977

A Novel Inhibitor of Steroid Biosynthesis

Sir:

During studies[1] of the oxidative demethylation at C-4 in the latter stages of steroid biosynthesis we have discovered that 4,4,10β-trimethyl-*trans*-decal-3β-ol[2] (**1**, TMD), first prepared in 1958,[3] has important biochemical properties. The evidence described herein demonstrates that TMD is a specific inhibitor of cholesterol biosynthesis in both rat liver enzyme preparations and cultured mammalian cells, and indicates that inhibition occurs at the cyclization of squalene oxide.

Initial experiments were run to determine whether TMD would act as a bicyclic analogue of 4,4-dimethyl steroids and be demethylated by a standard S_{10} rat liver homogenate[4] (S_{10}-RLH). However, when *dl*-TMD[5] labeled with tritium[6] was incubated with S_{10}-RLH, no demethylated product was detected. Instead, 4,4,10β-trimethyl-*trans*-decalin-3β,7β-diol (**2**) was isolated as the major product. This metabolite, iden-

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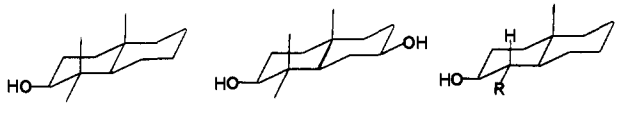
Table I. Relative Protein Content (Percent of Control) of CHO Cells Grown with Varying Concentrations of Added Inhibitor[a]

inhibitor	concn, μg/mL 1	3	7
25-Hydroxycholesterol[b]	38		10
l-TMD	74	26	20
d-TMD	95	81	38
dl-TMD	75	38	19
dl-**3**	92	83	39
dl-**4**	97	99	93

[a] Cells grown in F-12 + 10% fetal calf serum were trypsinized and replated at 0.1×10^6 cells per 25-cm^2 Corning flask in the same medium. After 2 days the cells were rinsed once with 4 mL of saline and the medium was replaced with 5 mL of F-12 + 10% delipidated bovine serum that contained the required amount of inhibitor in duplicate flasks. The medium was renewed every 2 days. After 5 days the cellular protein content was determined as described in ref 15a. The protein content of control cells was 1.0 ± 0.1 mg/flask. [b] Purchased from Steraloids, Inc., Wilton, N.H., and purified by TLC.

tified by comparison[7] with **2** synthesized from the known 4,4,10β-trimethyl-*trans*-decal-3β-ol-7-one,[8] was obtained in 15–32% yield.[9] Racemic TMD was resolved,[10] and the separated enantiomers were found *both* to be converted to the respective enantiomers of **2**.[11] However, *d*-TMD was almost twice as effectively hydroxylated as *l*-TMD.



1 2 3, R = CH_3 4, R = H

When TMD was incubated with S_{10}-RLH in the presence of [^{3}H]mevalonate, cholesterol biosynthesis was inhibited. At 2 mM (0.4 mg/mL) and 10 μM (2 μg/mL) concentrations of *dl*-TMD there was, respectively, 96 and 19% inhibition of cholesterol formation.[12] Both *d*- and *l*-TMD are inhibitors. Significant accumulations of [^{3}H]squalene 2,3-oxide (17%)[13] and [^{3}H]squalene 2,3:22,23-dioxide (14%)[13] were found[14] when *dl*-**1** (2 mM) was incubated with S_{10}-RLH.

The inhibitory effect of TMD is equally dramatic in whole cells. When Chinese hamster ovary (CHO) cells[15] were treated with 1 μg/mL (5 μM) of *l*-TMD, cells were killed within 72 h. The relative protein content of CHO cells treated for 5 days with various concentrations of *l*-TMD and *d*-TMD is shown in Table I. For comparison, the effect of 25-hydroxycholesterol,[16] a well-known, very potent cholesterol inhibitor, on CHO cell growth under the same conditions was also determined. The data in Table I show that 25-hydroxycholesterol is somewhat more effective than *l*-TMD at slowing cell growth.

The following preliminary results demonstrate that the cytotoxicity of TMD is caused specifically by inhibition of cholesterol biosynthesis. Analysis by GLC of CHO cells treated with 5 μg/mL of *l*-TMD for 5 days showed that they had about one fourth the cellular cholesterol content of control cells. If exogenous cholesterol is added to the growth medium, however, the cytotoxicity of *l*-TMD is prevented. This protective effect of added cholesterol is not due to its blocking entry of *l*-TMD into the cell. The incorporation of [^{3}H]-*l*-TMD into CHO cells was essentially identical in the absence and presence of 10 μg/mL of cholesterol.

Conversion of acetate to cholesterol in CHO cells is profoundly affected by *l*-TMD. Only 1% of added [^{14}C]acetate was incorporated into cholesterol in cells treated with 5 μg/mL of *l*-TMD, compared with 44% in control cells. In these same treated cells there were significant accumulations of [^{14}C]-squalene 2,3-oxide and [^{14}C]squalene 2,3:22,23-dioxide,[17] indicating that inhibition of cholesterol biosynthesis by *l*-TMD in whole cells also occurs at the squalene oxide cyclization stage.

TMD is of a structural type different from any of the vast number of compounds which have been previously reported[18] to inhibit cholesterol biosynthesis. A few preliminary experiments to elucidate the portions of the TMD structure required for inhibition have been conducted. The effect of *dl*-4α,10β-dimethyl-*trans*-decal-3β-ol (**3**)[19] and *dl*-10β-methyl-*trans*-decal-3β-ol (**4**)[3] on CHO cell growth was determined, and the results are compared with those for *dl*-TMD in Table I. It can be inferred that at least the 4α-methyl group plays a significant role in the inhibition.

The mechanism of inhibition by TMD remains to be determined. It would be tempting to suggest that *l*-TMD acts as an analogue of a conformationally rigid,[20] relatively advanced transition state between squalene oxide and cyclized product. However, such a speculation fails to take into account the fact that *d*-TMD is also an effective inhibitor.

Acknowledgment. This research was generously supported by USPHS Grants AM 12855 and HL 21246.

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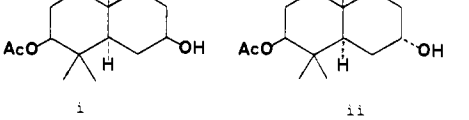
(7) The structure of metabolite [^{3}H]-**2** was established by (a) GC–MS molecular weight; (b) identity of GLC retention times with those of synthetic **2** on three columns; (c) isotopic dilution and recrystallization to constant specific activity of both [^{3}H]-**2** and its diacetate. Synthetic **2** and its diacetate were fully characterized by IR, NMR, MS, and combustion analysis. Proof that the C-7 OH of **2** has the β configuration was obtained by conversion of precursor 4,4,10β-trimethyl-*trans*-decal-3β-ol-7-one[6] to its acetate,[6] which was reduced with $NaBH_4$ to i and with K(*sec*-Bu)$_3$BH to ii. $LiAlH_4$ reduction



i ii

of i afforded **2**. The NMR spectra of i and ii showed the distinctive 7α axial H of i and 7β equatorial H of ii. Details are given in the Ph.D. Dissertation of M.R. Czarny, Dartmouth College, 1977.

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(12) Percent cholesterol inhibition ≡ [(percent yield of cholesterol isolated by TLC in control − percent yield in run with inhibitor) ÷ percent yield in control] 10^2.

(13) Yields of squalene 2,3-oxide and squalene 2,3:22,23-dioxide are based on the percent of starting (*R*)-mevalonate radioactivity isolated in the TLC bands corresponding to these products. The yield of squalene 2,3-oxide was confirmed by constancy of specific activity throughout its chemical conversion, isotopically diluted, to squalene-2,3-diol and squalene-2,3-diol acetonide (cf. E. E. van Tamelen and T. J. Curphey, *Tetrahedron Lett.*, 121

(1962)). In analogous, separate incubations of mevalonate with d-1 and l-1 the yields of squalene 2,3-oxide were 16 and 14% and the yields of squalene 2,3:22,23-dioxide were 14 and 11%.
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(15) CHO cells possess intact cholesterol biosynthetic capacity: (a) T. Y. Chang and P. R. Vagelos, *Proc. Natl. Acad. Sci. U.S.A.*, **73**, 24 (1976); (b) T. Y. Chang, C. Telakowski, W. Vanden Heuvel, A. W. Alberts, and P. R. Vagelos, *ibid.*, **74**, 832 (1977).
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(17) TLC of the product obtained from this [^{14}C]acetate incorporation experiment yielded bands corresponding to [^{14}C]squalene 2,3-oxide and [^{14}C]squalene 2,3:22,23-dioxide which contained 30 and 10%, respectively, of the total radioactivity in the nonsaponifiable fraction.
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(19) Compound **3**, reported as an oil by M. Yanagita and R. Futaki, *J. Org. Chem.*, **21**, 949 (1956), was isolated as a solid, mp 47–50 °C (characterized by IR, NMR, and combustion analysis), from $NaBH_4$ reduction of 4α,10β-dimethyl-*trans*-decal-3-one, obtained via Li/NH_3 reduction of 4,10-dimethyl-Δ^4-decal-3-one, prepared by the method of N. C. Ross and R. Levine, *ibid.*, **29**, 2341 (1964).
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James A. Nelson,* Michael R. Czarny
Thomas A. Spencer*
Department of Chemistry, Dartmouth College
Hanover, New Hampshire 03755

James S. Limanek, Keith R. McCrae, Ta Yuan Chang*
Department of Biochemistry, Dartmouth Medical School
Hanover, New Hampshire 03755
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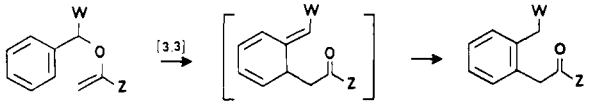
Regiospecific Synthesis of Substituted Arenes. [3,3] Sigmatropic Rearrangement of Benzyl Vinyl Ethers[1]

Sir:

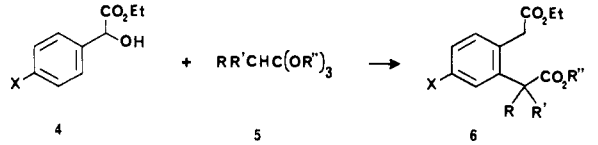
The [3,3] sigmatropic rearrangement of allyl vinyl ethers provides a versatile method for the construction of new carbon to carbon bonds with high regio- and stereospecificity under mild reaction conditions.[2] Although the [3,3] sigmatropic rearrangement of *allyl phenyl ethers* is well examplified in the classic Claisen rearrangement,[3] the [3,3] sigmatropic rearrangement of *benzyl vinyl ethers* **1** (W = H) is not generally



1 2 3

possible.[4] Inspection of the putative intermediate **2** suggested to us that the [3,3] sigmatropic rearrangement of **1** should be facilitated by an appropriately selected and suitably positioned substituent W.[5,6]

We are now pleased to report that the reaction of ethyl mandelate derivatives **4** in the Claisen ortho ester rearrangement[7,8] with **5** provides an extremely convenient method for



4 5 6

the regiospecific synthesis of substituted arenes **6**.[9] The results of these studies are summarized in Table I.[10]

Several noteworthy features of the above transformation follow: (1) a large assortment of substituted ethyl mandelates **4**[11] and ortho esters **5**[12] are readily available; (2) the reaction occurs for ethyl mandelates with either electron-donating or electron-withdrawing groups; (3) the reaction conditions are compatible with a wide array of functionality;[13] (4) the reaction provides a method for the regiospecific synthesis of substituted arenes[14] that would be difficulty accessible by alternative methods; and (5) the carboethoxy groups are convenient handles for subsequent synthetic transformations.

Table I. Claisen Ortho Ester Rearrangement of Ethyl Mandelates (**4**)

entry	mandelate (**4**), X	ortho ester (**5**) R	R′	R″	reaction[a] conditions	% yield[b] of **6**
a	H	H	H	Et	A	84
b	H	Me	H	Et	B	50
c	H	Me	Me	Et	A	41
d	Me	H	H	Et	B	65
e	Me	Me	H	Et	B	47
f	MeO	H	H	Et	C	50
g	Cl	H	H	Et	A	30
h	Cl	Me	H	Et	B	21
i	EtO_2C	H	H	Et	A	33
j	EtO_2C	Me	H	Et	B	18

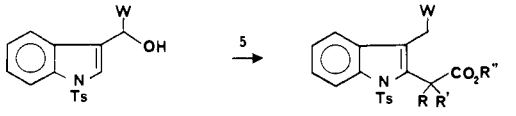
[a] All reactions use 6 to 8 equiv of **5** and 0.1 equiv of hexanoic acid/equiv of **4**. The reaction flask is fitted with a 15-cm Vigreux column during the first time period and a short-path distillation head during the second time period (see sample experimental procedure). Reaction conditions: A, 12 h at 220 °C, 8 h at 185 °C; B, 12 h at 220 °C, 12 h at 185 °C; C, 5 h at 220 °C, 7 h at 185 °C. [b] See ref 10.

Table II. Claisen Ortho Ester Rearrangement with 3-Indoleglycolates

entry	indole 7, W	ortho ester **5**[a] R	R′	R″	% yield[b] of **8**
a	CO_2Et	H	H	Et	79
b	CO_2Et	H	H	Me	48[c]
c	CO_2Et	Me	H	Et	40
d	$CONMe_2$	H	H	Me	59
e	H	H	H	Me	*d*

[a] All reactions use 30 equiv of **5** and 0.1 equiv of hexanoic acid/equiv of **4**. The reaction flask was filtered with a 15-cm Vigreux column topped with a short-path distillation head and was heated at reflux for 12 h, the Vigreux column was removed, and heating was continued at 185 °C for 8 h. [b] See ref 10. [c] No ester exchange was detected. [d] The corresponding mixed ortho ester was isolated (90%).[18]

We have also extended this procedure to the Claisen ortho ester rearrangement of **5** with the 3-indoleglycolic acid derivatives **7** (W = CO_2Et or $CONMe_2$)[15,16] to give 2,3-disubstituted indoles **8**[17] (Table II).[10] The crucial influence of the



7 8

carboxy derivative at the benzylic position in facilitating the [3,3] sigmatropic rearrangement is again illustrated by experiments in which 1-tosyl-3-indolemethanol (**7**, W = H) failed to undergo any detectable rearrangement with trimethyl orthoacetate under comparable reaction conditions, but led only to the corresponding mixed ortho ester.[18]

It is notable that the 2,3-disubstituted indoles **8** contain both a two-carbon functionalized chain at the 3 position and an α-substituted carboxy group at the 2 position. These features are present in a number of indole alkaloids such as vincadine, vindoline, carbomethoxyvelbanamine, and catharanthine. We are currently investigating the application of the [3,3] sig-

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