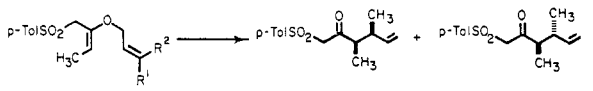
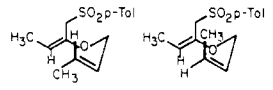
Table I. Carbanionic Claisen Rearrangements of 2 and 3[a]



2 or 3 4 5

entry	substrate	base (equiv)[b]	solvent	temp, °C	time, h	4:5 ratio[c]	yield,[d] %
1	2	none	Me_2SO	100	4	96:4	97
2	2	KH (2.2)	Me_2SO	20[e]	4	93:7	79[f]
3	2	NaH (2.2)	Me_2SO	20[e]	4	98:2	85
4	2	KH (2.2)/LiCl (4.2)	Me_2SO	20[e]	4	97:3	73
5	3	none	Me_2SO	100	8	4:96	89
6	3	KH (2.1)	Me_2SO	20[e]	6.75	14:86	7[f]
7	3	NaH (2.2)	Me_2SO	50	3	6:94	64[f]
8	3	KH (2.6)/LiCl (15)	Me_2SO	50	1.5	6:94	85
9	2	KH (2.2)	THF	20	24	89:11	78
10	2	KH (2.1)	HMPA	20	2	64:36	83
11	3	KH (1.9)	THF	20	23	7:93	19[f]
12	2	NaH (2.2)	Me_2SO	20	6	95:5	57
13	2	NaH (2.2)	Me_2SO	50	0.25	98:2	93

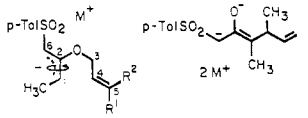
[a] All anionic reactions were done under rigorous exclusion of moisture and oxygen. The reaction were run at 0.09–0.12 M concentrations and were homogeneous throughout. Reaction progress was monitored by TLC until complete and then worked up by aqueous extraction in the usual way. The products were purified by flash chromatography on silica gel. [b] Potassium and lithium dimsylate were prepared freshly from hexane-washed KH at 20 °C (see ref 18). Sodium dimsylate was prepared freshly by warming hexane-washed NaH in Me_2SO to 65 °C for 40 min and cooling to 20 °C. [c] Ratios were determined by analytical HPLC (UV detection, 250 nm). [d] Yields of products after column chromatographic purification. [e] The completion of this run was difficult to discern due to an unknown side product that was coincident with starting material. Heating to 50 °C for 2–5 min assured complete conversion. [f] 9 was isolated in this run: entry 2, 13%; entry 6, 65%; entry 7, 24%; entry 11, 28%.



2 3

to pseudo-1,3-diaxial interactions between $CH_3C(5)$ and the sulfonylmethylene group. The *carbanionic* rearrangement of **3** is 12 times slower than that of **2**, suggesting a more serious interaction probably due to the strong association with the metal ion and its attendant solvent molecules.

The high stereoselectivity of these rearrangements is striking. Originally we perceived two pitfalls, either of which could destroy stereoselectivity. The first concerned the geometrical integrity of the stabilized allyl anion i



i ii

and the second an ex post facto epimerization requiring only equilibrium quantities of dianion ii. Unfortunately, very little information is available concerning structures and rotational barriers of sulfonyl-stabilized allyl anions.[21,22] Rotation about the C(1)–C(2) bond is stereochemically crucial and we must conclude that either (1) the barrier is extremely high or (2) the *E* geometry as shown is strongly favored at equilibrium. The relative orientation of the *p*-toluenesulfonyl group (C(2)–C(6) geometry) is unknown at present, as is its importance in cation chelation or its indirect influence on the C(1)–C(2) geometry. Finally, it is clear that species ii are not accessible in Me_2SO even in the presence of excess base.[23]

The results reported herein provide a firm foundation for the investigation of rearrangements employing chiral carbanions and studies on the structure of heteroatom-stabilized anions which will be the subject of future reports.

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Registry No. 2, 87039-98-3; 3, 87039-99-4; 4, 87040-00-4; 5, 87040-01-5;]-(*p*-toluenesulfonyl)-1,2-butadiene, 32140-55-9; lithium dimsylate, 57741-62-5; *trans*-crotyl alcohol, 504-61-0; *cis*-crotyl alcohol, 4088-60-2; KH, 7693-26-7; NaH, 7646-69-7; LiCl, 7447-41-8.

(21) (a) Biellmann, J. F.; Ducep, J.-B. *Org. React. (N.Y.)* **1982**, *27*, 1. For studies on the structure of sulfenyl-stabilized anions, see: (b) Biellmann, J. F.; Ducep, J. B. *Tetrahedron* **1971**, *27*, 5861. (c) Hartmann, J.; Muthukrishnan, R.; Schlosser, M. *Helv. Chim. Acta* **1974**, *57*, 2261.

(22) (a) Block, E. "Reactions of Organosulfur Compounds"; Academic Press: New York, 1978; pp 36–90. (b) Bordwell, F. G.; Branca, J. C.; Johnson, C. R.; Vanier, N. R. *J. Org. Chem.* **1980**, *45*, 3884 and references cited therein.

(23) The low stereoselectivity of the rearrangement of K^+2^- in HMPA may well be due to the existence of ii in this solvent.

Scott E. Denmark,* Michael A. Harmata†

Roger Adams Laboratory
School of Chemical Sciences
University of Illinois, Urbana, Illinois 61801

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Synthesis of Dehydrooogoniol, a Female-Activating Hormone of *Achlya*

Summary: The structure of dehydrooogoniol (3β,11α,15β,29-tetrahydroxystigmasta-5,24(28)(*E*)-dien-7-one), a female-activating hormone of the water mold *Achlya*, has been confirmed by synthesis. The starting material was progesterone, which was converted to the 11α,15β-dihydroxy derivative by microbiological hydroxylation with *Aspergillus giganteus* (ATCC 10059). The side chain was constructed in a stepwise manner by

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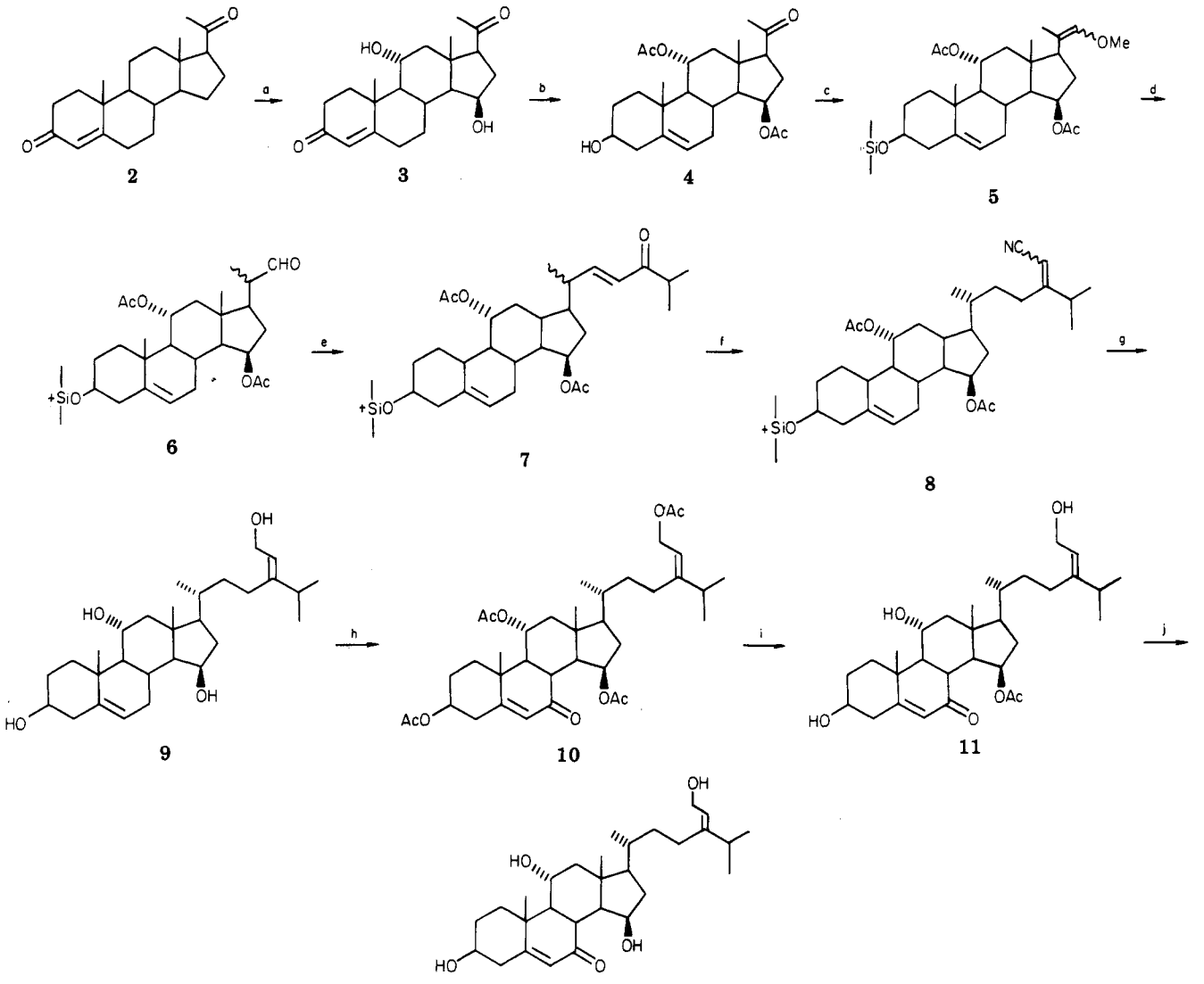
means of Wittig reactions, and the C-7 ketone was then introduced by allylic oxidation. The biological activity of the synthetic compound was similar to that of the natural hormone.

Sir: The oogoniols are a group of steroids secreted by hermaphroditic strains of the water mold *Achlya* and also by the male strain *Achlya ambisexualis* E87 when the latter is stimulated by the steroid antheridiol.[1] These steroids induce the formation of oogonia or female sex organs in female strains of *A. ambisexualis*. The structure of dehydrooogoniol (3β,11α,15β,29-tetrahydroxystigmasta-5,24(28)(*E*)-dien-7-one, **1**) (Scheme I) was determined in 1978,[2] and we have now confirmed this structure by synthesis. We selected progesterone as our starting material and introduced hydroxyl groups at C-11 and C-15 by microbiological hydroxylation. The side chain was constructed in a stepwise manner by means of Wittig reactions, and the C-7 ketone was then introduced by allylic oxidation.

Aspergillus giganteus (ATCC 10059) metabolized progesterone (**2**) to 11α,15β-dihydroxyprogesterone (**3**) in ~40% yield and small amounts of several other hydroxylated derivatives.[3] Conversion of the dihydroxy steroid to 3β,11α,15β-trihydroxy-5-pregnen-20-one 11α,15β-diacetate (**4**) was readily accomplished by the following sequence: formation of the 3,5-diene triacetate by refluxing a solution with acetic anhydride–acetyl chloride, protection of the C-20 ketone as the ketal (ethylene glycol, *p*-toluenesulfonic acid), treatment with sodium borohydride in ethanol, and finally, removal of the ketal protecting group.[4] The C-3 hydroxyl was converted to the *tert*-butyldimethylsilyl

Scheme I



[a] (a) Microbiological hydroxylation with *Aspergillus giganteus*. (b) Ac_2O, AcCl; $HOCH_2CH_2OH$, H^+; $NaBH_4$, EtOH; pTsOH, EtOH. (c) *t*-$BuMe_2SiCl$, (dimethylamino)pyridine triethylamine; $Ph_3P{=}CHOMe$. (d) Me_3SiI. (e) $(EtO)_2P(O)\bar{C}HCOCH(CH_3)_2$. (f) Chromatography to isolate 20*R* isomer; H_2, Pd-$BaSO_4$; $(EtO)_2P(O)\bar{C}HCN$. (g) DIBAL-H; AcOH, H_2O; Ac_2O, pyridine; chromatography to isolate *E* isomer; DIBAL-H. (h) Ac_2O, pyridine; chromium trioxide/3,5-dimethylpyrazole. (i) K_2CO_3, H_2O, MeOH. (j) KOH, H_2O, MeOH (45 °C).

(1) McMorris, T. C.; Seshadri, R.; Weihe, G. R.; Arsenault, G. P.; Barksdale, A. W. *J. Am. Chem. Soc.* **1975**, *97*, 2544.
(2) Preus, M. W.; McMorris, T. C. *J. Am. Chem. Soc.* **1979**, *101*, 3066–3071.
(3) McMorris, T. C.; Baker, M. E.; Terry, L.; Barrow, S. E.; Villanueva, D. L; Le, P. H.; Greaves, A. W. *Steroids*, submitted for publication.
(4) The corresponding triol had earlier been prepared from 15α-hydroxy-11-oxoprogesterone. See: Weihe, G. R.; McMorris, T. C. *Steroids* **1981**, *37*, 291–301.

ether, and the latter was then subjected to a Wittig reaction with methoxymethyltriphenylphosphorane, giving the enol ether **5**.[5] The overall yield of **5** from **3** was 32%.

Cleavage of the enol ether **5** with trimethylsilyl iodide[6] afforded the aldehyde **6** a mixture of C-20 isomers with the isomer of natural configuration, 20*S*, in slightly greater amount as indicated by the NMR signal for the aldehyde proton. Attempts to separate the isomers were unsuccessful. The mixture was therefore reacted with the anion of diethyl (3-methyl-2-oxobutyl)phosphonate to give the enone **7** (80% from **5**, mixture of C-20 isomers). Separation of the isomers was accomplished by medium-pressure chromatography with silica gel (230–400 mesh) and dichloromethane. The configuration at C-20 in the less polar isomer (20*R*) was established by comparing its CD curve ([θ] +11 600 (227 nm)) with that of 3β-acetoxycholesta-5,22(*E*)-dien-24-one[7] ([θ] +3100 (230 nm)). The more polar isomer (20*S*) had quite a different CD curve ([θ] −18 000 (232 nm).[8]

Catalytic hydrogenation of the enone **7** (20*R* isomer) with 10% Pd on $BaSO_4$ afforded an almost quantitative yield of the ketone with the saturated side chain, and this derivative on reaction with the anion of diethyl(cyanomethyl)phosphonate gave the unsaturated nitrile **8** (85%) as a mixture of isomers (ratio of *E* to *Z*, 4:1). Reduction of the nitrile mixture with DIBAL-H followed by hydrolysis of the resulting imine with dilute acetic acid yielded the unsaturated aldehyde, which, after reacetylation, was separated into the pure *E* (50%) and *Z* isomers by chromatography with silica gel (230–400 mesh) and chloroform.

The *E* aldehyde was further reduced with DIBAL-H to give the alcohol **9** (69%). Acetylation of the latter and oxidation with chromium trioxide/3,5-dimethylpyrazole[7] gave a 50% yield of ketone **10**. Treatment of the ketone tetraacetate with dilute K_2CO_3 in aqueous methanol gave C-15 monoacetate **11**. This compound was therefore subjected to more forcing conditions (dilute KOH in methanol at 45 °C), which yielded dehydrooogoniol (**1**), unreacted monoacetate, and some 3,5-dienone. The three compounds were well separated by HPLC[9]. Synthetic dehydrooogoniol had the same retention time as the natural compound, and its spectral properties were in full accord with the structure. A similar sequence of reactions was employed for the synthesis of 3β,11α,29-trihydroxystigmasta-5,24(28)(*E*)-dien-7-one (15-deoxydehydrooogoniol) starting from commercially available 11α-hydroxyprogesterone.

Biological assays on the synthetic compounds were carried out according to the method of Barksdale and Lasure.[10] Synthetic dehydrooogoniol was active in inducing formation of oogonial initials in the female strain *A. ambisexualis* 734 at a concentration of ~2 μg/mL. A concentration of 0.2 μg/mL was slightly active. Natural dehydrooogoniol, assayed at the same time, showed similar activity. The activity found for synthetic dehydrooogoniol was confirmed in an independent assay carried out by Professor Paul Horgen, Erindale College, University of Toronto. The intermediate tetraol **9** and 15-deoxydehydrooogoniol were inactive when tested at a concentration of ~10 μg/mL for the former and at 4 μg/mL and 40 μg/mL for the latter compound. Thus, the 15β-hydroxy and 7-oxo substituents are important for biological activity.

Acknowledgment. We thank D. L. Villanueva and B. D. Ruano for assistance in the biological assays. High-resolution mass spectral data were provided by the Bioorganic, Biomedical Mass spectrometric Resource (A. L. Burlingame, Director), supported by NIH Grant RR 00719. Our investigation was supported by NIH grants GM 27583 (GG/MS Shared Instrument Grant), GM 21350, and RR 08135.

Registry No. **1**, 82251-59-0; **2**, 57-83-0; **3**, 82538-36-1; **4**, 86846-34-6; **5**, 86846-35-7; **6** (isomer 1), 86835-69-0; **6** (isomer 2), 86835-70-3; **7** (isomer 1), 86835-71-4; **7** (isomer 2), 86853-01-2; (*E*)-**8**, 86846-36-8; (*Z*)-**8**, 86835-72-5; (*E*)-**8** aldehyde derivative, 86835-73-6; (*Z*)-**8** aldehyde derivative, 86835-74-7; **9**, 86835-75-8; **10**, 86835-76-9; **11**, 86835-77-0; Ph_3P=CHOMe, 20763-19-3; diethyl (3-methyl-2-oxobutyl)phosphonate, 7751-67-9; diethyl (cyanomethyl)phosphonate, 2537-48-6; 3β-acetoxycholesta-5,22(*E*)-dien-24-one, 32230-64-1; 3β,11α-diacetoxycholesta-5,22(*E*)-dien-24-one, 86846-37-9; (20*S*)-3β,11α-diacetoxycholesta-5,22(*E*)-dien-24-one, 86900-14-3.

(5) The conditions were similar to those reported earlier: Schow, S. R.; McMorris, T. C. *J. Org. Chem.* **1979**, *44*, 3760–3765. However, only 1.5 equiv of phosphorane were used. A larger excess caused extensive elimination of the C-15 acetoxy group.

(6) Kosarych, Z.; Cohen, T. *Tetrahedron Lett.* **1980**, *21*, 3959. Partial loss of the *tert*-butyldimethylsilyl group occurred in this step.

(7) Le, P. H.; Preus, M. W.; McMorris, T. C. *J. Org. Chem.* **1982**, *47*, 2163–2167.

(8) 3β,11α-diacetoxycholesta-5,22(*E*)-dien-24-one, prepared from 11α-hydroxyprogesterone by a method similar to that used for preparation of **7**, had [θ] +5800 (223 nm). The ^{1}H NMR spectrum had δ 2.00 (3-OAc + 11-OAc). Its C-20 epimer (more polar) had [θ] −18 000 (235 nm), and the ^{1}H NMR spectrum had δ 1.93 (11-OAc) and 2.00 (3-OAc). The corresponding resonances for (20*R*)-**7** were δ 2.02 (11-OAc + 15-OAc) and for (20*S*)-**7**, δ 1.93 (11-OAc) and 2.01 (15-OAc).

(9) The separation was performed on a Waters Associates Model 6000 A instrument, using a 30 cm × 4 mm i.d. prepacked μ-Bondapak C18 column. The mobile phase was 55% MeOH/H_2O and the flow rate was 2mL/min at 2000 psi. Three peaks with retention times 10, 18.8, and 28 min were observed. These corresponded to dehydrooogoniol, the C-15 monoacetate, and the 3,5-dienone (ratio 3:2:1). Dehydrooogoniol was isolated as a solid (noncrystalline): mp 125–130 °C; high-resolution MS, *m/z* (relative intensity) 456.3213 (5), 438.3128 (51), 420.3016 (8), 342.2175 (6), 299.1659 (84), 161.0961 (100); IR ν_{max} 3330, 2940, 1658, 1450, 1105, 1020 cm^{-1}; ^{1}H NMR (360 MHz) δ 0.99 (s, 18-H), 1.02 (d, J = 6.5 Hz, 26-H and 27-H), 1.34 (s, 19-H), 3.65 (m, 3-H), 4.15 (m, 11-H and 29-H), 4.69 (m, 15-H), 5.36 (m, 28-H), 5.82 (s, 6-H).

(10) Barksdale, A. W.; Lasure, L. L. *Appl. Microb.* **1974**, *28*, 544–546.

Trevor C. McMorris,* Phu Huu Le, Martin W. Preus Steven R. Schow, Gary R. Weihe

Department of Chemistry
University of California, San Diego
La Jolla, California 92093

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