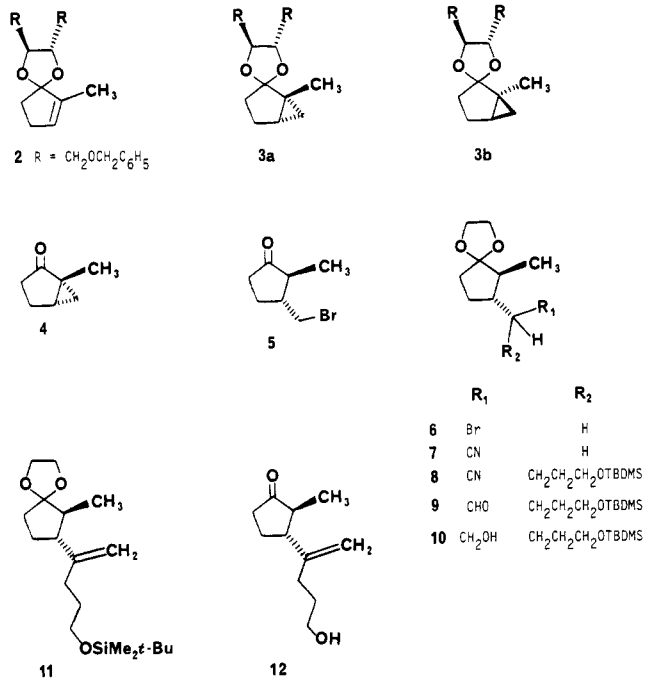
gave ketal **2** in 89% yield. Treatment of **2** with an excess of the Simmons-Smith reagent[6] in refluxing diethyl ether




gave, after 20 h and in 92% chemical yield, an inseparable 9:1 mixture of cyclopropane ketals **3a** and **3b** as determined by 62.9-MHz $^{13}C$ NMR spectroscopy.[7,8] Hydrolysis of the mixture of **3a** and **3b** (aqueous HCl, $CH_3OH$, room temperature, 1.5 h) gave enantiomerically enriched cyclopropyl ketone **4**, $bp_{26}$ 84-85 °C, $[\alpha]^{27}_D$ +33.4° (*c* 1.97, $CHCl_3$), in 73% yield. The chiral auxiliary, 1,4-di-*O*-benzyl-L-threitol, was recovered in 93% yield following chromatographic repurification.

Assignment of the 1*R*,5*S* absolute stereochemistry to **4** was based upon application of the "reversed octant rule"[9] in interpreting the CD spectrum of **4**.[10] This assignment was also in accord with all previously examined cyclopropyl ketones.[9,11]

Treatment of **4** with excess trimethylsilyl bromide (3 equiv, $CH_2Cl_2$, -25 °C to 0 °C, 9 h) produced (2*S*,3*S*)-2-methyl-3-(bromomethyl)cyclopentanone (**5**), along with lesser amounts of 2-methyl-4-bromocyclohexanone.[12] Ketalization of **5** (ethylene glycol, *p*-TsOH, $C_6H_6$, reflux, 20 h) provided ketal **6**. Exchange of cyanide for bromide (KCN, NaI, DMSO, room temperature, 72 h) gave nitrile **7**, $[\alpha]^{25}_D$ -31.1° (*c* 6.09, $CDCl_3$), in 59% yield from **4**. Alkylation of nitrile **7** (2 equiv of $LiN(SiMe_3)_2$, THF, -78 °C; $ICH_2CH_2CH_2OSiMe_2$-*t*-Bu, THF, -78 °C to -20 °C) provided in 83% yield nitrile **8** as an inseparable mixture of diastereoisomers. Treatment of **8** with DIBAL (1.1 equiv, $CH_2Cl_2$, -78 °C, 30 min; mild acid workup) gave aldehyde **9** which, when reduced ($NaBH_4$, EtOH, room temperature, 15 min), gave in 53% yield alcohol **10** as an inseparable mixture of diastereoisomers. Tosylation of **10** (TsCl, pyr, 0 °C, 48 h), displacement of the tosylate with sodium *o*-nitrophenyl selenide[14] (2.2 equiv, EtOH, room temperature, 72 h), and treatment with 30% hydrogen peroxide (7.5 equiv, 2:1 EtOH:THF, room temperature, 48 h) gave olefin **11**, $[\alpha]^{25}_D$ -25.9° (*c* 2.68, $CHCl_3$), in 77% yield. Hydrolysis (aqueous HCl, $CH_3OH$, room temperature, 8 h) gave keto alcohol **12**, $[\alpha]^{23}_D$ +45.1° (*c* 2.1, $CHCl_3$), in 96% yield. Treatment of **12** with an excess of methyl cerium dichloride[15] (5 equiv, THF, -78 °C, 2 h) provided in 80% yield chokol A (**1**), $[\alpha]^{23}_D$ -46.3° (*c* 1.07, EtOH), lit.[2] $[\alpha]^{22}_D$ -26.6° (*c* 1.0, EtOH), identified by comparison of the IR, $^1H$ NMR, and $^{13}C$ NMR spectra of the synthetic material with spectra of the natural material.[16] The yield of (-)-chokol A of approximately 80% ee from 2-methyl-2-cyclopenten-1-one was 9% over 13 steps.[17]

This synthesis demonstrates the utility of the diastereoselective cyclopropanation process for establishing appendages enantioselectively at both $\alpha$ and $\beta$ carbons of cycloalkanones.[7,11] Since a number of important natural products possess such substructural elements, this methodology should prove to be a useful cornerstone in natural product synthesis in future years.[18]

**Supplementary Material Available:** Complete experimental details and spectral data for compounds **1-4**, **7**, **8**, **10**, **11**, and **12** (11 pages). Ordering information is given on any current masthead page.

(6) Shank, R. S.; Shechter, H. *J. Org. Chem.* **1959**, *24*, 1825-1826.
(7) For previous examples of the use of this diastereoselective Simmons-Smith cyclopropanation in synthesis, see: (a) Mash, E. A.; Fryling, J. A. *J. Org. Chem.* **1987**, *52*, 3000-3003. (b) Nelson, K. A.; Mash, E. A. *J. Org. Chem.* **1986**, *51*, 2721-2724. (c) Mash, E. A.; Nelson, K. A. *Tetrahedron Lett.* **1986**, *27*, 1441-1444. (d) Mash, E. A.; Nelson, K. A. *J. Am. Chem. Soc.* **1985**, *107*, 8256-8258. Also see: Arai, I.; Mori, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 8254-8256.
(8) An authentic diastereomeric mixture of cyclopropane ketals was prepared for spectral comparison by reketalization of **4** with 1,4-di-*O*-benzyl-DL-threitol. For previous examples of the use of $^{13}C$ NMR in the measurement of diastereomer ratios, see: Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, 2183-2186.
(9) Lightner, D. A.; Jackman, D. E. *Tetrahedron Lett.* **1975**, 3051-3054, and references cited therein.
(10) From the CD spectrum of **4**: $[\theta]_{305}$ +2750°, $[\theta]_{295}$ +4400°, $[\theta]_{286}$ +4125° (*c* 0.08, pentane).
(11) Mash, E. A.; Nelson, K. A. *Tetrahedron* **1987**, *43*, 679-692.
(12) For a related process involving trimethylsilyl iodide, see: Miller, R. D.; McKean, D. R. *J. Org. Chem.* **1981**, *46*, 2412-2414.
(13) Arseniyadis, S.; Kyler, K. S.; Watt, D. S. *Org. React.* (*N.Y.*) **1984**, *31*, 1-364.
(14) Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1975**, *40*, 947-949.
(15) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233-4236.
(16) We thank Professor T. Yoshihara, Faculty of Agriculture, Hokkaido University, Sapporo, Japan for copies of spectra of natural (-)-chokol A.
(17) This synthesis should provide (-)-chokol A of approximately 80% ee. The actual optical rotation for natural (-)-chokol A should therefore be approximately -58°. The 500-MHz proton NMR spectrum of natural chokol A supplied by Professor Yoshihara provides evidence that the sample of chokol A used for that spectrum was not homogeneous. This may help explain the discrepancy between the rotation of the synthetic material and the value reported for the natural product.
(18) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. Partial support of this research by the American Heart Association, Arizona Affiliate, is gratefully acknowledged.

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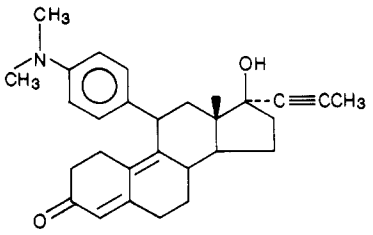
## New Steroids by Simmons-Smith Methylenation and Subsequent Rearrangement[1]

*Summary:* Product distribution and stereochemical outcome in the rearrangement of some new steroidal cyclopropyl carbinols were examined. Molecular conformation and nucleophilic assistance were shown to be key parameters for chemoselective formation of products.

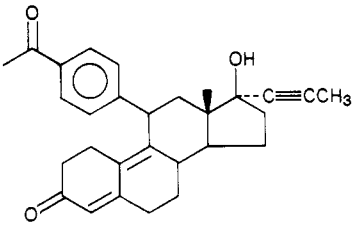
(1) Dedicated to Prof. Dr. Erich Gerhards on the occasion of his 60th birthday.

0022-3263/87/1952-4143$01.50/0 

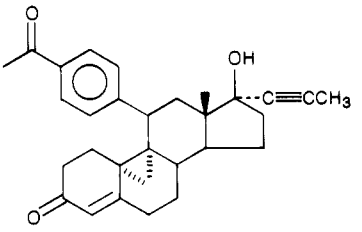
*Sir:* The discovery of the first competitive progesterone antagonist RU 38 486 (mifepristone)[2] has initiated an intense search for more potent and more selective antiprogestins.[3] The estrane and gonane derivatives currently under development have a 11$\beta$ 4-(dimethylamino)phenyl substituent in common, which is rather sensitive to oxidative attack and subsequent N-demethylation. This behavior creates problems for chemical and microbial modifications. Consequently, the aromatic substitution pattern was broadly varied in this series of compounds. The search resulted in the discovery of 11$\beta$ 4-acetylphenyl derivative ZK 112 993, which proved to be superior in antiprogestational activity compared with mifepristone.[4]



RU 38 486
(mifepristone)



ZK 112 993

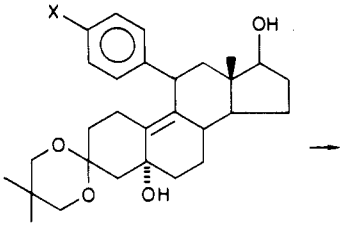


ZK 114 057

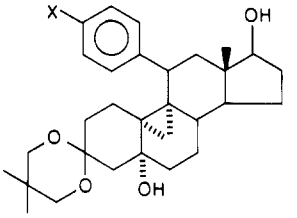
The chemical advantage of the 4-acetylphenyl substituent and its protected equivalent became apparent when the attempt was made to synthesize 9$\alpha$,10$\alpha$-methylene derivatives **2a,b** by employing the allylic alcohols **1a,b** as easily accessible starting materials.[5]

The anilide derivative **1a** could not be converted to cyclopropane **2a** under the conditions of a Simmons–Smith methylenation.[6] Due to nitrogen basicity carbene attack primarily occured at the aniline moiety resulting in a complex mixture of unidentified polar products.

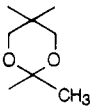
In contrast, precursor **1b** cleanly reacted with formation of cyclopropyl carbinol **2b** which was subsequently transformed to ZK 114 057 by a standard sequence described previously.[3] The observations and results described above prompted us to take a closer look at the chemistry of 9,10-methylene derivatives in the estrane series. As a first part of our study, we examined systems of type **5** unsubstituted at C-11.



**1a,b**



**2a,b**

**a**: X = $-N(CH_3)_2$, **b**: X = 

Scheme I describes a simple and stereospecific access to 9,10-methylene derivatives **5a,b**. Conjugate reduction of known epoxides **3a,b** turned out to be a crucial step. Although intermediates **4a,b** finally could be made available by lithium/ammonia reduction in isolated yields of 35%, the regioselectivity of this step remained unsatisfactory. A broad variation of reduction conditions did not result in the discovery of systems with a more favorable relation between hydride transfer to C-10 or to C-11. As allylic alcohols **4a,b** could easily be separated from the product mixture, we did not insist upon further improvement of the reduction step.

Simmons–Smith methylenation of **4a,b** proceeded cleanly with formation of cyclopropyl carbinols **5a,b**. As expected and previously demonstrated by others, the stereochemical outcome was perfectly determined by the orientation of the hydroxy group.[7]

The acid treatment of compounds **5a,b** resulted in the formation of several new steroidal skeletons and revealed remarkable differences in the behavior of both isomers (Scheme II). The resulting products are easily explained by initial formation of a cyclopropyl carbenium ion and subsequent rearrangement along the pathways previously described for such reactive intermediates.[8] However, product distribution and stereochemical outcome deserve further comment.

As another important aspect, chemoselectivity could be considerably influenced by modifying reaction conditions appropriately. In the absence of external nucleophiles (trace of $CF_3COOH$, $CH_2Cl_2$) 9$\beta$,10$\beta$-methylene compound **5a** exclusively reacted by formation of B-homo product **6**, which upon further treatment with 2 N sulfuric acid in acetone gave unsaturated ketones **7a,b** as a mixture of C-10 epimers.

(2) Teutsch, G.; Philibert, D. In *Adrenal Steroid Antagonism*; Agarwal, M. K., Ed.; Walter de Gruyter: Berlin-New York, 1984; pp 43, 77, and references cited therein.
(3) Neef, G.; Beier, S.; Elger, W.; Henderson, D.; Wiechert, R. *Steroids* **1984**, *44*, 349.
(4) Neef, G. Presented at the IXth International Symposium on Medicinal Chemistry, Berlin (West), Sept. 14–18, 1986.
(5) Teutsch, G. *Steroids* **1981**, *37*, 361.
(6) Simmons, H. E.; Cairns, T. L.; Vladucheck, S. A.; Hoiness, C. M. *Org. React. (N.Y.)* **1973**, *20*, 1.
(7) Maruoka, K.; Fukutami, Y.; Yamamoto, H. *J. Org. Chem.* **1985**, *50*, 4414 and references cited therein.
(8) Wiberg, K. B.; Andes Hess, B., Jr.; Ashe, A. J., III. *Carbonium Ions* **1972**, *3*, 1295.

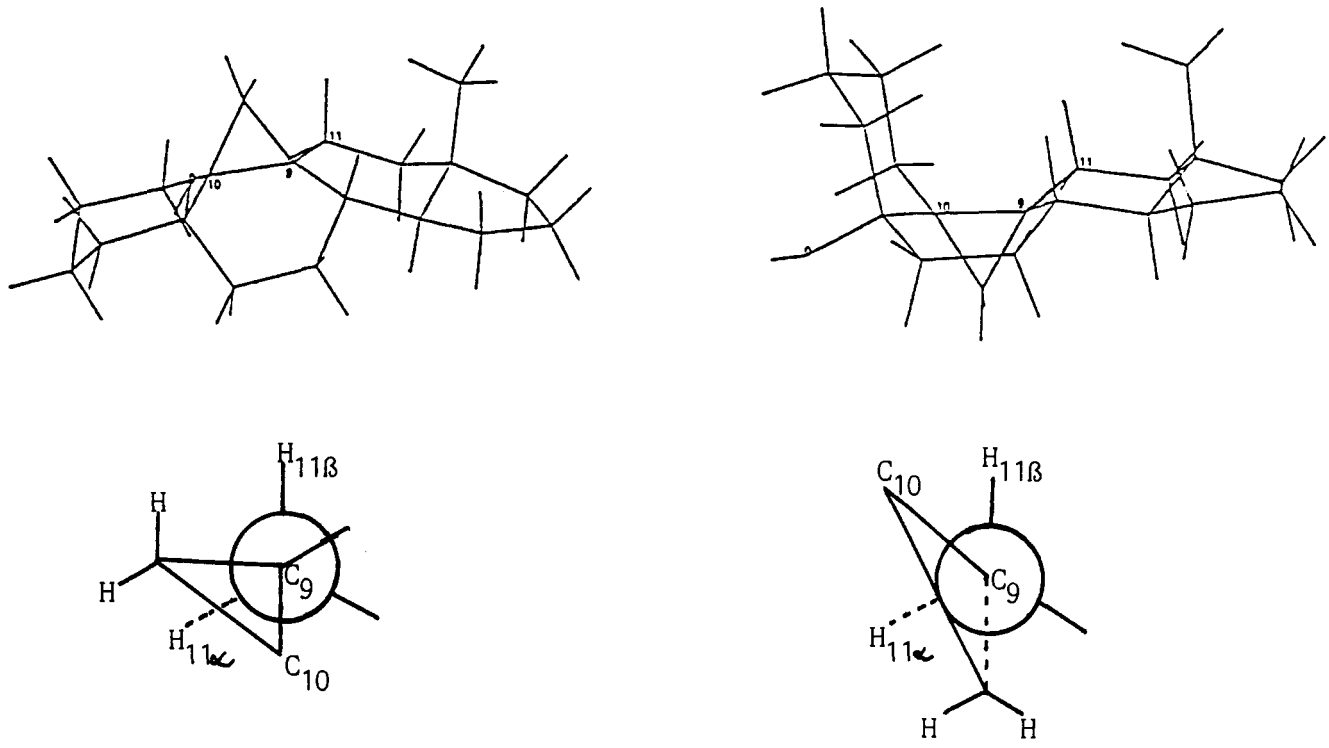
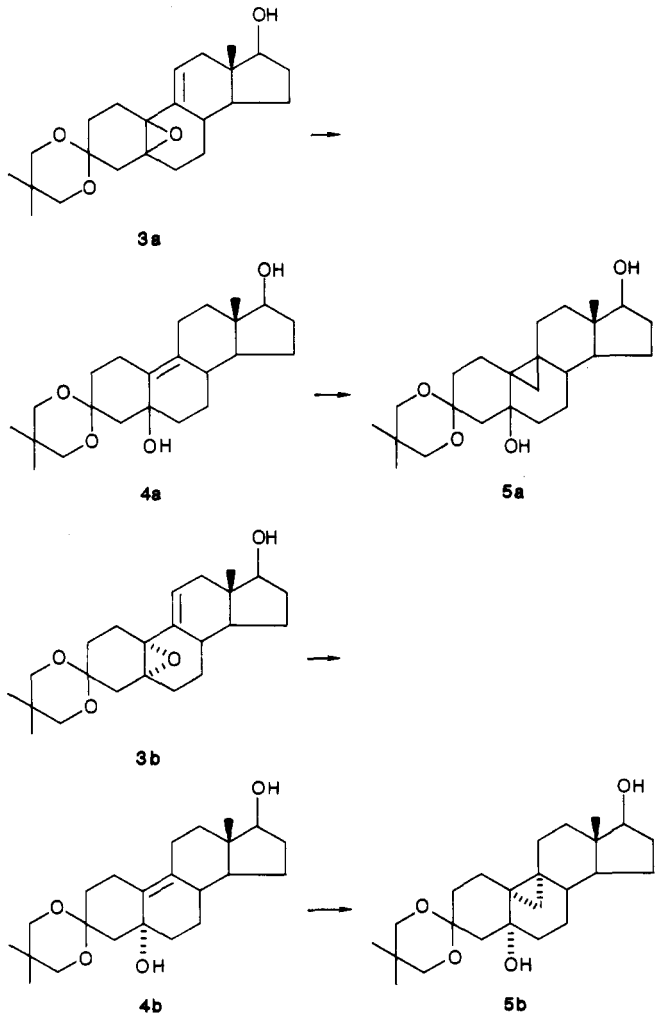



**Figure 1.** Conformations of **5a,b** constructed with the aid of SYBYL[9] and further optimized by using Allinger MM2 force field calculations.

**Scheme I**




However, when the cleavage of **5a** was performed with sulfuric acid/acetone, cyclobutanol derivative 8 became the major product accompanied by a small amount of B-homo steroids **7a,b**.

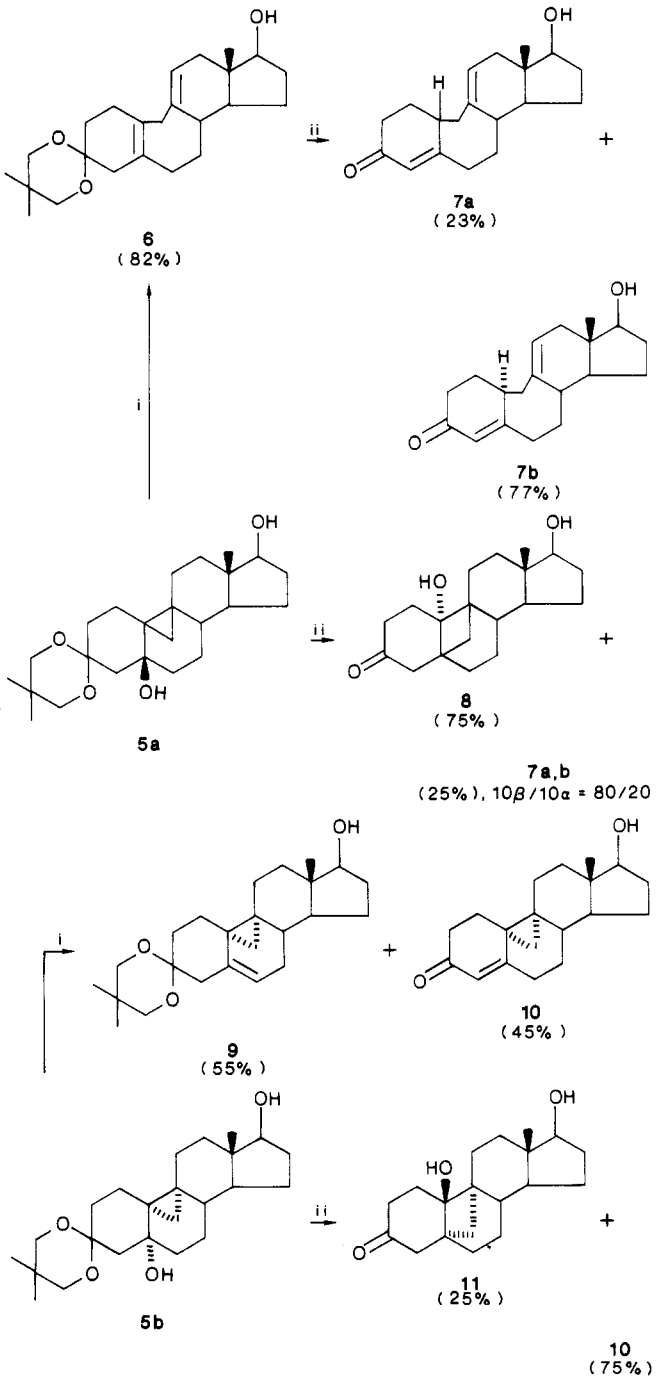
9α,10α-Methylene precursor **5b** behaved quite differently: trifluoroacetic acid treatment led to dehydration with concomitant partial deketalization, the cyclopropane ring being left intact. The nucleophilic system predominantly gave the trivial product of dehydration/deketalization (**10**), but now accompanied by a 25% amount of cyclobutanol **11**.

These experimental results become plausible when a closer look is taken at the conformations of cyclopropyl carbinols **5a,b** (Figure 1).

The molecular model for 9β,10β-methylene derivative **5a** clearly shows that the orbital C(11)–H(11β) and cyclopropane orbital (C9)–C(10) are well arranged for overlap so that carbenium ion formation at C-5 allows for a perfectly concerted process leading to B-homo product **6**. The Wagner–Meerwein-type rearrangement which accounts for cyclobutanol 8 formation becomes an alternative only when there is support by an external nucleophile to weaken the respective cyclopropane bond on its way to migration. The stereochemical result is in perfect agreement with such a view.

In light of this interpretation, it becomes obvious that 9α,10α-methylene compound **5b** cannot react in an analogous manner. The molecular model shows for **5b** that neither of the C(11)–H(11) orbitals is suitably located for overlap with cyclopropane orbital C(9)–C(10). Consequently, no trace of B-homo steroid is observed when the reaction is run in a nonnucleophilic environment. As the cyclopropane ring is preserved to a major extent even under conditions of nucleophilic assistance, Wagner–Meerwein rearrangement (cyclobutanol **11**) does not seem to be a favorable alternative for **5b**. The explanation is straightforward after a look at the molecular model: a nucleophile approaching the cyclopropane ring of **5b** from

**Scheme II**[a]




[a] (i) $CF_3COOH$ (trace), $CH_2Cl_2$, 30 min reflux; (ii) 2 N $H_2SO_4$, acetone, 15 min, 50 °C.

the backside finds itself in a rather unfavorable steric environment.

Constitutions were confirmed by NMR and mass spectrometry and configurational assignments were based on CD spectra.[10]

**Acknowledgment.** We are much indebted to Prof. E. Winterfeldt for a discussion of the mechanistic aspects. We thank Dr. C. Herrmann and Dr. G.-A. Hoyer for conformational analysis, as well as H. Vierhufe and G. Ast for technical assistance.

(9) TRIPOS Ass. Inc., SYBYL Molecular Modeling System, Release 3.2, St. Louis, 1985.

(10) Snatzke, G.; Snatzke, F. In *Fundamental Aspects and Recent Developments in ORD and CD*; Giardelli, F., Salvadori, P., Ed.; Heyden & Son Ltd.: London, 1973, p 114.

(11) Spectroscopic and physical properties. ZK 112 993: mp 151–154 °C; $[\alpha]^{20}_D$ +117.1° ($CHCl_3$, *c* 0.525); $^1H$ NMR ($CDCl_3$) δ 0.48 (s, 3 H, H-18), 1.91 (s, 3 H, 17α-C≡$CCH_3$), 2.59 (s, 3 H, $ArCOCH_3$), 4.47 (m, 1 H, H-11α), 5.80 (s, 1 H, H-4), 7.29/7.90 (d (*J* = 8.6 Hz), 4 H, Ar H). ZK 114 057: mp 233–235 °C; $[\alpha]^{20}_D$ +36.4° ($CHCl_3$, *c* 0.505); $^1H$ NMR ($CDCl_3$) δ 0.38 (s, 3 H, H-18), 1.93 (s, 3 H, 17α-C≡$CCH_3$), 2.60 (s, 3 H, $ArCOCH_3$), 2.96 (m, 1 H, H-11α), 5.99 (s, 1 H, H-4), 7.48/7.94 (d (*J* = 8.6 Hz), 4 H, Ar H). **4a**: mp 165–168 °C; $[\alpha]^{20}_D$ +54.2 ($CH_2Cl_2$, *c* 0.525); $^1H$ NMR (pyridine-$d_5$) δ 0.89 (s, 3 H, H-18), 3.90 (t (*J* = 8.5 Hz), 1 H, H-17α). **4b**: mp 114–118 °C; $[\alpha]^{20}_D$ −105.0° ($CH_2Cl_2$, *c* 0.5); $^1H$ NMR (pyridine-$d_5$) δ 0.89 (s, 3 H, H-18), 3.81 (t (*J* = 8.5 Hz), 1 H, H-17α). **5a**: oil; $[\alpha]^{20}_D$ +47.4° ($CH_2Cl_2$, *c* 0.54); $^1H$ NMR (pyridine-$d_5$) δ 0.08 (d (*J* = 5 Hz), 1 H, 9,10-$CH_2$), 0.87 (s, 3 H, H-18), 1.24 (d (*J* = 5 Hz), 1 H, 9,10-$CH_2$), 3.91 (t (*J* = 8.5 Hz), 1 H, H-17α). **5b**: mp 182–185 °C; $[\alpha]^{20}_D$ −42.5° ($CH_2Cl_2$, *c* 0.505); $^1H$ NMR ($CDCl_3$) δ −0.03 (d (*J* = 5 Hz, 1 H, 9,10-$CH_2$), 0.79 (s, 3 H, H-18), 0.90 (d (*J* = 5 Hz, 1 H, 9,10-$CH_2$), 3.67 (m, 1 H, H-17α), 4.32 (s, 1 H, 5α-OH). **6**: mp 157–159 °C; $[\alpha]^{20}_D$ −37.9° ($CH_2Cl_2$, *c* 0.58); $^1H$ NMR ($CDCl_3$) δ 0.74 (s, 3 H, H-18), 0.87 (s, 3 H, ketal-$CH_3$), 1.05 (s, 3 H, ketal-$CH_3$), 3.72 (t (*J* = 8.5 Hz), 1 H, H-17α), 5.80 (m, 1 H, H-11). **7a**: $^1H$ NMR ($CDCl_3$) δ 0.76 (s, 3 H, H-18), 3.76 (m, 1 H, H-17α), 5.50 (m, 1 H, H-11), 5.82 (s, 1 H, H-4); CD spectrum (dioxane) λ 230 nm (Δε −3.6), 324 (−0.96), 336 (−1.36), 350 (−1.32), 364 (−0.65). **7b**: $^1H$ NMR ($CDCl_3$) δ 0.74 (s, 3 H, H-18), 3.73 (m, 1 H, H-17α), 5.38 (m, 1 H, H-11), 5.82 (s, 1 H, H-4); CD spectrum (dioxane) λ 233 nm (Δε −13.9), 325 (+0.67), 338 (+0.93), 353 (+0.83), 370 (+0.35). **8**: mp 187–188 °C; $[\alpha]^{20}_D$ −53.4° ($CHCl_3$, *c* 0.5); $^1H$ NMR ($CDCl_3$) δ 0.84 (s, 3 H, H-18), 2.43 (d (*J* = 16 Hz), 1 H, 9β,5-$CH_2$), 2.62 (d (*J* = 16 Hz), 1 H, 9β,5-$CH_2$), 3.66 (m, 1 H, H-17α); CD spectrum (dioxane) λ 286 nm (Δε −1.25), 293 (−1.47), 302 (−1.26), 313 (−0.54), 323 (+0.03). **9**: mp 98–101 °C; $[\alpha]^{20}_D$ −25.4° ($CH_2Cl_2$, *c* 0.5); $^1H$ NMR (pyridine-$d_5$) δ 0.25 (d (*J* = 4 Hz), 1 H, 9,10-$CH_2$), 0.90 (d (*J* = 4 Hz), 1 H, 9,10-$CH_2$), 0.91, 0.95, 0.99 (3 s, 3 H each, H-18, ketal-$CH_3$), 3.92 (m, 1 H, H-17α), 5.24 (m, 1 H, H-6). **10**: mp 163–164 °C; $[\alpha]^{20}_D$ −69.0° ($CHCl_3$, *c* 0.51); $^1H$ NMR ($CDCl_3$) δ 0.58 (d (*J* = 5 Hz), 1 H, 9,10-$CH_2$), 0.86 (s, 3 H, H-18), 1.03 (d (*J* = 5 Hz), 1 H, 9,10-$CH_2$), 3.73 (m, 1 H, H-17α), 5.85 (s, 1 H, H-4); CD spectrum (dioxane) λ 264 nm (Δε −6.06), 327 (−1.17), 337 (−1.94), 350 (−2.01), 365 (−0.99). **11**: mp 181–185 °C; $[\alpha]^{20}_D$ +16.1° ($CHCl_3$, *c* 0.54); $^1H$ NMR ($CDCl_3$) δ 0.74 (s, 3 H, H-18), 2.40 (d (*J* = 16 Hz), 1 H, 9α,5-$CH_2$), 2.58 (d (*J* = 16 Hz), 1 H, 9α,5-$CH_2$), 3.74 (m, 1 H, H-17α); CD spectrum (dioxane) λ 287 nm (Δε +1.41), 293 (+1.65), 302 (+1.43), 312 (+0.64).

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