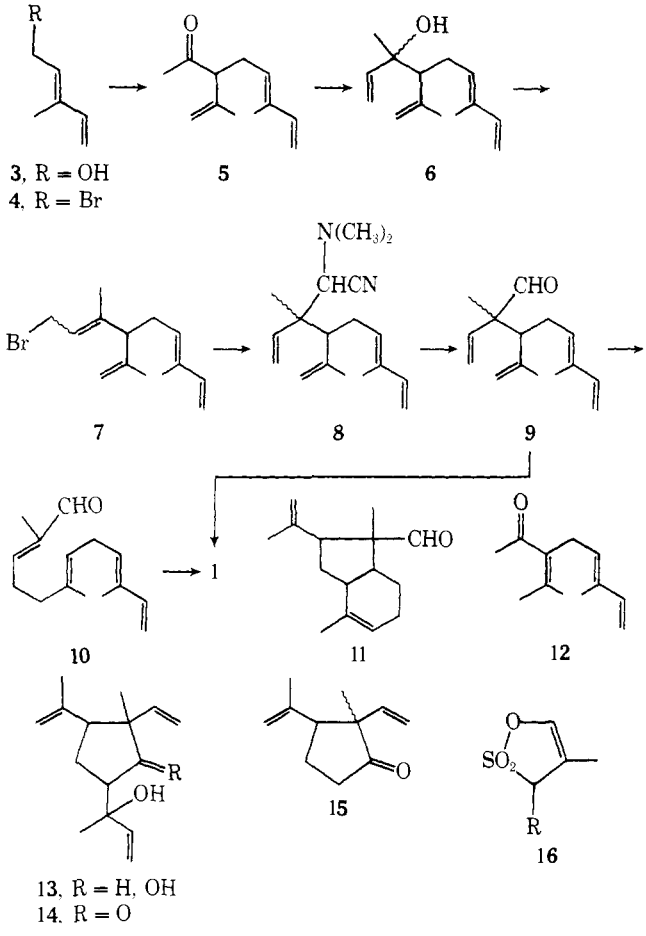
Scheme I



clopentaneous **15**, ir ($CHCl_3$) 1740 cm^{-1}. Hydrolysis of the nitrile **8** with 2 *N* ethanolic sodium hydroxide[11] (90 min, reflux) did afford aldehyde **9** but the propensity of α-disubstituted aldehydes to undergo the Cannizzaro reaction in alkali led us to search for a superior method. The aminonitrile **8** was hydrolyzed within 5 min when ethanol solutions were refluxed with slightly less than equimolar amounts of $FeSO_4 \cdot 7H_2O$ or preferably with the more soluble $CuSO_4 \cdot 5H_2O$. Filtration followed by distillation gave a 6:4 mixture of diastereomeric aldehydes **9** (nmr δ 9.35 (s) and 9.4 (s)), bp 65° (0.1 mm), in over 80% yield. Cupric and ferrous ions presumably remove cyanide from the aminonitrile–iminium cyanide equilibrium by precipitating insoluble $[Cu(CN)_4]^{3-}$ or $[Fe(CN)_6]^{4-}$ salts.

Cope rearrangement of **9** in refluxing xylene (40 min) produced a 4:6 mixture of the *E*-isomer **1** (nmr δ 9.3 (s)) and the *Z*-isomer **10** (nmr δ 10.1 (s)) (Scheme I).[14] Quantitative isomerization of the latter to the more stable *E*-isomer **1** was achieved by heating the mixture over anhydrous sodium carbonate (xylene–methanol 1:1, 18 hr, reflux) or more interestingly by storing xylene solutions containing 1% gaseous SO_2 at 20° for 20 hr. This seemingly novel isomerization may proceed *via* the intermediate **16.** Gas chromatography revealed crude synthetic α-sinensal (**1**) to contain 10% of the bicyclic aldehydes **11** resulting from intramolecular Diels–Alder reaction of **9** and approximately 5% of what may be the Δ^6-cis isomer formed in the Cope rearrangement.[15] Infrared, mass, ultraviolet, and proton spectra of distilled material, bp 82° (0.1 mm), were identical with those of natural α-sinensal (**1**) and a mixture of the synthetic 2,4-dinitrophenylhydrazone mp 98–100° and the "natural" derivative mp 100–102° melted at 98–101°. Preparative runs gave α-sinensal (**1**) in 44% yield from alcohol **6.**

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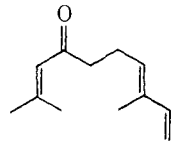

i

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Acid Homoketonization with Inversion of Configuration. A Dramatic Effect of Water in Control of Stereochemistry[1]

Sir:

Homoketonizations in deuterated media provide generally useful ways for site-selective and stereoselective placement of deuterium at β,[2-7] γ,[8-10] and δ[11,12] positions with respect to carbonyl groups. The stereochemistry of these ring openings can differ markedly in alkaline and acid media.

In alkaline solutions, studies on a variety of substrates have revealed that homoketonizations can proceed with high inversion,[2,3,6] with high retention,[4,5,8-12] or with low stereospecificity[4,5,7,11] depending on the structure of the substrate and on the reaction medium. Mechanistic interpretations have been proposed but have been of limited predictive value for new structural types, especially in constrained polycycles. Although high stereospecificity in alkaline homoketonizations can sometimes be diminished by solvent changes, no case has yet been found where it can be completely reversed by change in the alkaline solvent system.[13]

Table I. Stereochemistry in Acid Homoketonizations of 1-Acetoxynortricyclane at 27° ± 3

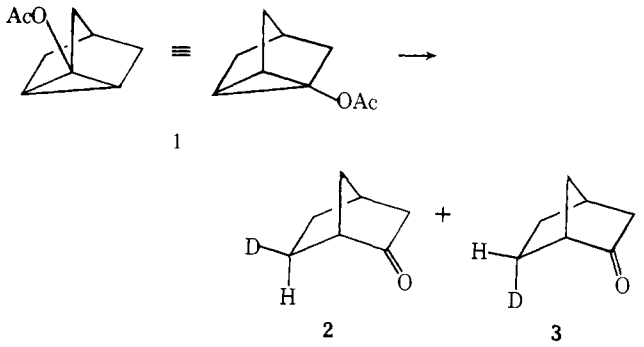
Run	Solvent (approx vol ratio)	Reagent	Concn (molal) Reagent	Concn (molal) Substrate	Mole ratio D_2O/substrate	*d* Assay (rel % ±1[a]) d_0	*d* Assay (rel % ±1[a]) d_1	Stereochemistry[b] % inversion	Stereochemistry[b] % retention
1[c]	CH_3CO_2D	D_2SO_4	0.52	0.52	0	20	80	94	6
2[c]	CH_3CO_2D	D_2SO_4	0.93	0.50	0	15	85	94	6
3	CH_3CO_2D–D_2O(85:1)	D_2SO_4	1.0	0.57	1.0	25	75	81	19
4	CH_3CO_2D–D_2O(28:1)	D_2SO_4	1.0	0.57	3.0	26	74	38	62
5[c]	CH_3CO_2D–D_2O(17:1)	D_2SO_4	0.88	0.40	7.1	22	78	31	69
6[c]	CH_3CO_2D–D_2O(12:1)	D_2SO_4	0.88	0.40	10.2	23	77	24	76
7[c]	CH_3CO_2D–D_2O(9:1)	D_2SO_4	1.2	0.54	10.0	19	81	13	87
8[d]	CH_3CO_2D–D_2O(2:1)	D_2SO_4	0.37	0.69	28			7[e]	93[e]
9[d]	CH_3CO_2D–D_2O(1:1)	D_2SO_4	0.29	0.60	39			7[e]	93[e]
10[d]	CH_3OD	D_2SO_4	2.6	0.53	0			5–10	90–95
11[c,f]	DCO_2D	None		0.59	0	9	91	82	18
12[c,g]	DCO_2D–D_2O(10:1)	None		0.35	13	8	92	15	85

[a] After enolizable deuterium was washed out with KOH–MeOH (see ref 3). [b] Corrected for configurational purity of the standards. Details of the ir assays are described in the Ph.D. Dissertation of J. J. Frank, The Johns Hopkins University, 1971. Natural abundance ketone does not interfere with the exo/endo *d* assay. [c] Values are averages from duplicate runs that agreed closely. [d] Reported earlier (ref 3). [e] Determined by dmr. Compare ref 3. [f] Run done at 50° for 6 days, then 65° for 14 days to ensure completion. [g] Run done at 27° for 84 hr, then 50° for 96 hr to ensure completion.

In acid media all known cleavages of homoenols and homoenol acetates have proceeded with high stereochemical retention (usually 90–100%) irrespective of substrate or of solvent.[2-6] The acids used have included sulfuric, hydrochloric, and trifluoroacetic, in solvents such as acetic acid, methanol, 1,2-dimethoxyethane, and dioxane, and appreciable water has been present in all instances except one (methanol–sulfuric acid[3]). Therefore, "retention in acid" seemed a reliable generalization.

We wish to report the first example of an acid homoketonization that goes by high inversion of configuration. More remarkably, it occurs in a system (1-acetoxynortricyclane) found earlier to open in D_2SO_4–CH_3CO_2D–D_2O with high retention,[3] and we find that the stereospecificity can be varied from high inversion to high retention simply by changing the amount of water in the solvent. Such complete reversal of stereochemical opening with change of solvent is unprecedented in acid or alkaline homoketonizations and has practical utility in preparation of *d*-labeled, bicyclo[2.2.1]heptyl compounds for mechanistic studies.[14]

Our substrate, 1-acetoxynortricyclane (**1**), was prepared directly from nortricyclane in 31% yield by action of lead tetraacetate in acetic acid.[15] Homoketonization of **1** in deuterium media produces, after work-up, 6-*exo*-*d*-norbornan-2-one (**2**) and 6-*endo*-*d*-norbornan-2-one (**3**) according to



1 2 3

whether the three-membered ring opens, respectively, with inversion or retention of configuration at carbon. Reference samples of the *d*-ketones **2** and **3** were available from earlier studies[3] where configurational purity (94.5–98% for the exo-*d* and 90–95% for the endo-*d*) was estimated by infrared correlations. Now by deuteron magnetic resonance spectroscopy,[16] we find that the exo-*d* signal occurs at δ 1.60 and the endo-*d* signal at δ 1.34; and relative area measurements indicated our reference exo-*d* ketone **2** is 98%, and our endo-*d* ketone **3** is 93%, configurationally pure. Mixtures of **2** and **3** were prepared as ir standards, and all assays were done by ir comparison of *d*-ketones derived from homoketonizations of **1** with these authentic mixtures. The results of several openings promoted by acid (usually D_2SO_4) are summarized in Table I.

Runs 8, 9, and 10 are taken from earlier work[3] that revealed high retention (*ca.* 93%) in aqueous acetic acid and also in neat methanol. We now find that omission of the water from the acetic acid (runs 1 and 2) completely reverses the stereochemistry and gives 94% inversion. In fact, by increasing the proportion of added water (runs 3–7), we observed progressive increase in the per cent retention, so that virtually any desired combination of inversion to retention could be realized.

To learn if D_2SO_4–CH_3CO_2D is unique in promoting inversion and in this dramatic effect of water, we homoketonized **1** in DCO_2D, with and without added D_2O (runs 11 and 12). No D_2SO_4 was used in these runs, so the ring openings were slower, but again we found largely inversion of configuration (82%) without added D_2O and largely retention (85%) when *ca.* 10% by volume of D_2O was included. Although the stereospecificity is not as high as in the sulfuric–acetic system, the complete turnabout in stereochemistry by the water is just as dramatic.

Whether this unusual behavior has any generality or is peculiar to 1-acetoxynortricyclane remains to be determined. Possibly in acetic acid the homoketonization involves direct ring cleavage in the *homoenol acetate*,[17] whereas with water the ester first undergoes hydrolysis (or methanolysis in methanol) and the ring cleavage then takes place in the *homoenol*. If so, the behavior would be just as surprising because it implies fundamentally different stereochemical pathways for two very similar cyclopropyl substrates. Current mechanistic interpretations[18] of cyclopropane cleavages with protonic acids assign no stereo-influential role to oxygenated groups on the ring, a tacit view that may deserve closer examination. To gain further insight, we hope to find other substrates that can undergo acid homoketonizations by inversion and to learn if they experience "reversals" of the type found here.

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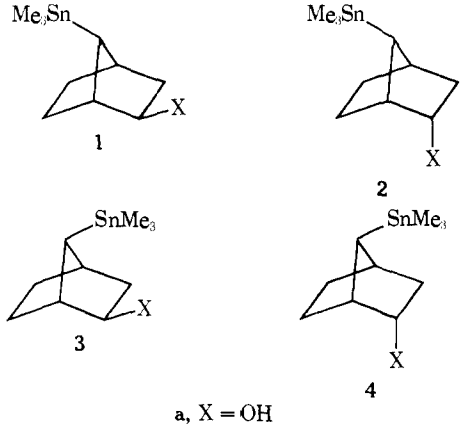
Stereospecific Cyclopropane-Ring Formation by 1,3-Deoxymetalation of Trimethyltin-Substituted Norbornyl Mesylates

Sir:

γ-Trimethyltin-substituted alcohols and sulfonates have been shown to undergo facile cyclopropane ring-forming reactions.[1] A study of the stereoelectronic effects in the reaction of conformationally rigid 7-(2-mesyloxynorbornyl)trimethyltins has provided some interesting insights into the mechanism of this reaction.

The four epimeric *syn*- and *anti*-7-(2-hydroxynorbornyl)trimethyltins were synthesized from the corresponding 7-norbornenyltrimethyltins.[2]



a, X = OH
b, X = OSO_2CH_3

Table I. Acetolysis[a] of 7-(2-Mesyloxynorbornyl)trimethyltins

Compound	k, sec^{-1} (25.0°)[b]	k_{rel}	k_{exo}/k_{endo}	ΔH^*, kcal/mol	ΔS^*, eu
1b	$(3.37 \pm 0.21) \times 10^{-4}$	5.5	2.6	20.2	−6.7
3b	$(1.18 \pm 0.05) \times 10^{-3}$	19	2960		
5b	$(6.09 \pm 0.28) \times 10^{-5}$	1.0	495	20.5	−8.9
2b	1.30×10^{-4} [c]	(1050)		16.2	−21.9
4b	3.98×10^{-7} [c]	(3.2)		23.5	−8.3
6b	1.23×10^{-7} [c]	(1.0)		25.5	−4.6

[a] Conductometric rates in HOAc (0.5 *M* H_2O). [b] Determined by least-squares computer fit. Error values are for the mean of at least three kinetic runs. [c] Extrapolated from higher temperatures by means of the Eyring equation, k_{obs}, 75°, $(7.64 \pm 0.34) \times 10^{-3}$, $(1.34 \pm 0.02) \times 10^{-4}$, $(6.80 \pm 0.09) \times 10^{-5}$ sec^{-1}, respectively.

Hydroboration–oxidation of *anti*-7-norbornenyltrimethyltin yields **1a** while **2a** is obtained by chromic oxidation–hydride reduction of **1a**. Hydroboration–oxidation[3a] of *syn*-7-norbornenyltrimethyltin gives a 55/45 mixture of **3a** and **4a** easily separable by chromatography on silica gel. Stereochemical assignments, discussed in detail elsewhere,[3b] are made on the basis of chemical evidence, nmr spectra, including lanthanide shift reagent studies, and mass spectral fragmentation patterns. Mesylates of the alcohols were prepared in the standard manner[4] and solvolyzed in acetic acid containing 0.5 *M* water. Rate data for **1b–4b** and the parent *exo*- and *endo*-2-norbornyl mesylates, (**5b, 6b,** respectively) are given in Table I.

Substitution of the inductively donating Me_3Sn group ($\sigma_I = -0.05$)[5] gives rise to a modest rate enhancement and an exalted exo/endo ratio for the **3b–4b** pair, consistent with data for other 7-substituted norbornyl sulfonates.[6] However, the anti–endo isomer, **2b,** solvolyses with a greatly accelerated rate resulting in an exo/endo ratio which is the smallest reported value that we are aware of for pairs in which the exo isomer is not retarded.[6]

These reactions are unusual in the sense that no products are observed which still retain the Me_3Sn group. **1b** and **3b** give only norbornene and Me_3SnOAc at 25°. The syn–endo isomer **4b** yields a mixture (100°) composed of 65% *exo*-2-norbornyl acetate (**7**), 3.4% *exo*-2-norbornanol (**8**), 16% *endo*-2-norbornyl acetate (**9**), 16% 7-norbornyl acetate (**10**), and an equivalent of Me_3SnOAc. For comparison, *exo*-2-norbornyl mesylate (**5b**) gives (25°) 94.5% **7**, 4.2% **8**, and 1.3% nortricyclene, whereas only **7** was observed from the solvolysis of **6b** at 100°. Because of the rate acceleration, it was possible to determine the products from reaction of **2b** at 25°. In addition to 22% **7**, 14% **9**, and 13% **10**, a 50% yield of tricyclo[3.2.0.$0^{2,7}$]heptane (pseudonortricyclene) **11**, was obtained. In buffered (NaOAc) HOAc at 25°, **11** and Me_3SnOAc are the sole products. The identity of **11** was verified by spectral and chromatographic comparisons with material prepared here and in other laboratories.[7] Control experiments show **11** to be stable in HOAc at 25° but the addition of methanesulfonic acid results in a slow (15 hr) protolytic cleavage to yield nearly equal amounts of the norbornyl acetates, **7**, **9**, and **10**. The 1:1 ratio of **9** and **10** which also occurs in the product distribution for **4b** is suggestive of **11** as an initial product which is subsequently destroyed under the more rigorous conditions (100°, unbuffered). Norbornene and nortricyclene are determined as such at 25° but primarily as **7** in unbuffered systems at 100°.

That both exo isomers, **1b** and **3b,** produce only norbornene with a small rate acceleration relative to the unsubstituted norbornyl mesylate supports a scheme in which solvol-