Table I. Rate Constants for Reaction of *p*-G-Ph-OSO_2-Ph-Y with Halide Ion in Salt **2** at 100 °C

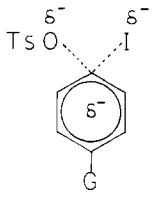
entry	substrate	G	Y	σ^a	σ^{-b}	salt	$k \times 10^7$, M^{-1} s^{-1} [c]	log k	ρ^d
1	**1a**	NO_2	*p*-CH_3	0.78	1.24	**2c**	18	-5.75	
2	**1b**	CO_2Et	*p*-CH_3	0.52	0.64	**2c**	1.8	-6.75	
3	**1c**	H	*p*-CH_3	0	0	**2c**	0.33	-7.27	
4	**1d**	OCH_3	*p*-CH_3	-0.27	-0.27	**2c**	0.41	-7.39	1.5 (1.1)[e]
5	**5**	NO_2	*p*-Br	+0.23		**2c**	20	-5.68	
6	**6**	NO_2	*m*-NO_2	0.71		**2c**	27	-5.52	0.22[f]
7	**1a**	NO_2	*p*-CH_3			**2a**	9 ± 1		
8	**1a**	NO_2	*p*-CH_3			**2b**	18 ± 3		

[a] Reference 12, p 28. [b] Reference 12, p 32. [c] Pseudo-first-order rate constant: $[substrate]_0 = 1-3\%$ $[\mathbf{2}]_0$. Measured to 10-30% conversion (5-8 aliquots). Standard deviations ±7-15%. [d] ρ determined from slope of the plot of log k vs. σ. [e] Data from first four entries: first values from σ (r = 0.95); second from σ^- (r = 0.98). [f] Data from entries 1, 5, and 6 using σ (r = 0.98).

complete retention of the C-O bond.[13] In the latter case the oxygen is bound to a carbon that changes from sp^2 in the starting material to sp^3 in the intermediate. We suggest that this change ought to be effected very little by Y since it is insulated by the SO_2 group.

Table I (entries 1, 7, 8) contains data from reactions of **1a** with **2** and represents relative halide reactivity. The similarity of the rates independent of anion is consistent with an early transition state (irrespective of the amount of C-O bond breakage) since most relative reactivity arguments for halides in aromatic substitution are based on their size.[11] The lack of selectivity in a reaction with an early transition state is also consistent with the reactivity-selectivity principle (Hammond postulate). In addition to supporting the notion that the incipient C-X bond is long in the transition state, these data rule out the intermediacy of a $S_{RN}1$ mechanism since the differences in halide redox properties would require a much more substantial rate difference.[14]

Figure 1 represents the projection of a three-dimensional potential energy surface, a More O'Ferrall diagram. Three mechanisms are represented: S_N1, dashed line; S_N2, solid line; S_NAr, x-dash. The transition state for the last one must lie very close to the lower left corner because of the large magnitude of the ρ value (C-I bond order close to 1). The transition state for the reactions reported herein must lie less than half the way along that axis. Using the same arguments for the C-O bond order places our reaction approximately one-quarter the distance along the C-O bond coordinate. The cross-hatched area represents the intersection of these two substituent studies. It appears to resemble the S_N2 more than the "pure" S_NAr and is represented by **4**. The



4

location of the early transition state does not preclude the possibility that the reaction proceeds from it to an intermediate similar to a Meisenheimer complex.

We conclude that the use of molten salts **2** as nucleophile sources has profound effect on aromatic substitution reactions: (1) the rates of reaction of substrates with nitro or methoxy substituents differ only by a factor of about 40; (2) the halides all react about the same; (3) the transition state is early with respect to carbon-halogen bond formation, while carbon-nucleofuge bond breakage is already beginning to occur. We suggest that these are manifestations of the interaction of the solvent, the molten salt. We postpone speculation on the specific nature of these phenomena pending further investigations.[15]

(13) Precedent for the former value is taken from data on limiting S_N1 reactions involving sulfonate leaving groups on bridgehead positions in aliphatic molecules: See: Lowry, T. H.; Richardson, K. S. "Mechanism and Theory in Organic Chemistry", 2nd ed.; Harper and Row: New York, 1981; p 340 and references cited therein. The argument of analogy to reactions of carboxylate esters leads one to the same limiting value: see ref 12, pp 21-24. Leaving group abilities are also dependent on solvent and thus changes in rate may reflect differential solvation of the anionic nucleofuge. For examples and discussion in aliphatic cases, see: (a) Hartshorn, S. R. "Aliphatic Nucleophile Substitution"; Cambridge University Press: London, 1973; pp 52-58. (b) Streitweiser, A. "Solvolytic Displacement Reactions"; McGraw-Hill: New York, 1962; pp 29-33, 81. Thus, measuring leaving group propensity for the same substrate in another solvent does not necessarily provide the appropriate answer.

(14) We rule out an elimination mechanism involving benzynes because of the absence of regioisomers in the products. After completion of a kinetic run the remaining salt solution was extracted with hexane and analyzed by gas chromatography under conditions where meta and para isomers could be discriminated. An S_N1 mechanism is ruled out by the sign of ρ unless the unlikely case of the nucleophile addition to the phenonium cation were the rate-determining step.

(15) Additional preliminary studies indicate that the transition state is even earlier in $(n\text{-}Bu)_4P^+I^-$ as evidenced by a smaller ρ value. An Arrhenius plot suggests that substantial rate enhancement is observed in **2c** especially for **1c** and **1d** when compared with traditional solvents. Other probes of the microscopic nature of these molten salts are being pursued. A reviewer kindly suggested that the traditional mechanism may be in force with the exception that the novel medium stabilizes the σ complex by electrostatic interaction and thereby lessens the ρ value. This is also consistent with the lower ρ value for the tetrabutylphosphonium salt but does not explain why the halides are virtually identical in reactivity. Solvation of the incipient cyclohexadienyl anion does not lessen the steric requirements for halide approach.

Organolithium Reagent Promoted Conversion of a Functionalized 7-Oxanorbornane to Annulated Fulvenes. An Expedient Route to 1,7-Cyclohexenonorbornadienes

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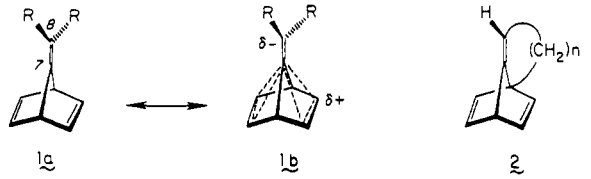
In simple undistorted methylenenorbornadienes, homoconjugative interaction is intense and substantial ground-state electronic drift as in **1b** takes hold. The phenomenon is perhaps best revealed



1a **1b** **2**

by ^{13}C NMR spectroscopy. For example, if the R groups in **1** are hydrogen, C-7 resonates at 177.1 ppm,[1,2] a record downfield shift for an olefinic carbon.[3] Annulation as in **2** must induce some

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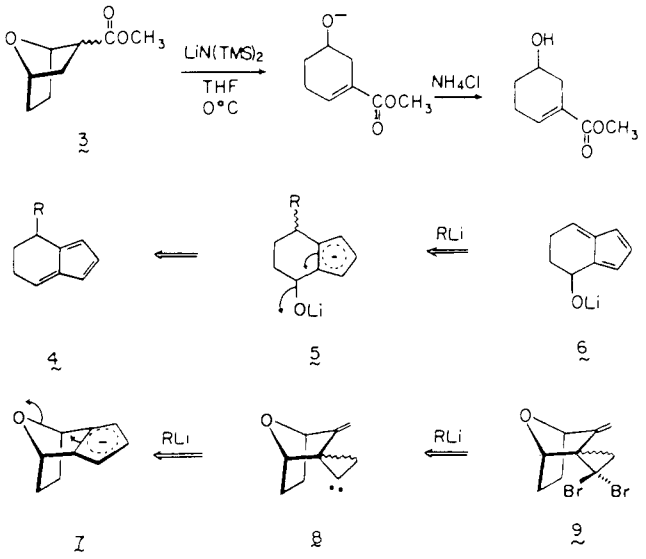
warping of the parent framework as the size of n is decreased. The extent to which incremental enhancement of the strain energy by this means would perturb electronic interaction within this particular π system is unknown. Additionally, a number of interesting mechanistic problems could be addressed if substrates possessing these structural features were available. Although saturated analogues of **2** have recently commanded attention,[4-7] the synthetic routes utilized to gain access to these examples are not extendable to the title system. Herein we describe an unprecedented rearrangement that leads to fulvenes capable of giving rise to the first known 1,7-cycloalkenonorbornadienes.

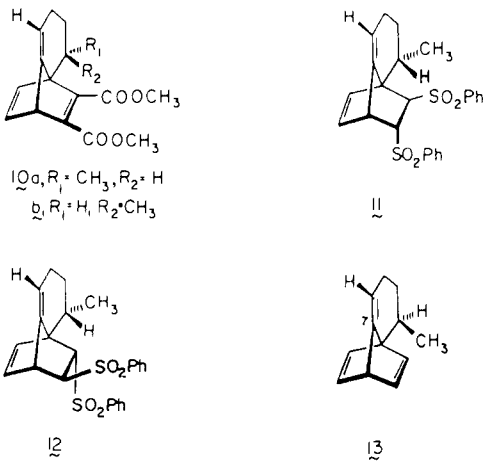
With the ready fragmentation earlier reported for several oxabicycloheptanes including **3** as precedent,[8] we were attracted to the possibility that cyclopentadienide anion **7** might behave analogously and serve as precursor to **6**. A straightforward route to **7** appeared to reside in the Skattebøl rearrangement,[9] notwithstanding its less than predictable serviceability in strained bicyclic systems.[10] Also, since organolithium reagents are required for the conversion of dibromide **9** to carbene **8**, the presence of these organometallics should trigger the facile conversion of **6** to **5**. Ejection of the oxygenated functionality in **5** would complete the conversion to **4**. This pivotal step could occur as shown or by dehydration during the workup process.



To arrive at **9**, furan was condensed with fumaryl chloride in the absence of solvent.[11a] Under these conditions, the Diels–Alder adduct was formed in essentially quantitative yield. Use of a solvent as previously directed[11b] led to equilibrium mixtures containing much less (~33%) of the desired product.[12] Immediate reduction of this diacid chloride with $LiAlH_4$ provided the diol whose hydrogenation and conversion to the known[13] 2,3-dimethylene derivative were accomplished by the method of Butler and Snow.[14] Dibromocarbene addition[15] gave the dibromocyclopropane as a mixture of stereoisomers.

Reaction of **9** with 4 equiv of methyllithium in ether at room temperature for 15 h delivered, after quenching with water and chromatogrphy on silica gel, **4** (R = CH_3), a bright yellow oil (8%), and small amounts of indene as the only high R_f components.[16] The ^1H NMR [($CDCl_3$, 300 MHz) δ 6.74 (m, 1 H), 6.46 (m, 1 H), 6.13–6.10 (m, 2 H), 2.70–2.60 (m, 1 H), 2.53–2.37 (m, 2 H), 1.93–1.85 (m, 1 H), 1.55–1.41 (m, 1 H), 1.25 (d, J = 3.9 Hz, 3 H)] and ^{13}C NMR spectra [(20 MHz, $CDCl_3$) 144.82 (s), 139.65 (s), 138.37 (d), 132.24 (d), 122.02 (d), 119.34 (d), 33.86 (t), 30.22 (d), 26.97 (t), 19.36 (q) ppm] of this hydrocarbon were fully consistent with the structural assignment. The generality of this process was demonstrated by exposure of **9** to n-butyllithium, phenyllithium, and cyclopropyllithium under analogous conditions. The resultant bright yellow substances **4** (R = n-C_4H_9, oil, 6%), **4** (R = C_6H_5, crystals, mp 165–166 °C, 9%), and **4** (R = c-C_3H_5, oil, 12%) were isolated with equal ease.[17,18] Although the absolute yields of these fulvenes are low, the reactions are readily amenable to scaleup and the preparation of relatively large amounts of **4** is consequently entirely feasible.

When **4** (R = CH_3) was allowed to stand with dimethyl acetylenedicarboxylate (DMAD) in chloroform solution for 6 days, [4 + 2] cycloaddition occured (>95% efficiency) to give an 85:15 mixture of **10a** and **10b**. As expected, the spectral properties of



these diesters show considerable similarity to those of the structurally related azulene–DMAD adduct.[19]

To arrive at the unadorned carbocyclic network, **4** (R = CH_3) was stirred with (*E*)-1,2-bis(phenylsulfonyl)ethylene[20] in CH_2Cl_2 at 20 °C for 48 h. The product was predominatly a 70:30 mixture of **11** and **12** (71%). Very minor quantities of the remaining two isomeric possibilities were also detected. Reduction of the combined disulfones with 1–2% sodium amalgam in methanol buffered with disodium hydrogen phosphate[3] led efficiently (73%) to **13**.

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(16) The structure assigned to each new compound was in accord with its infrared, 300-MHz ^1H NMR, ^{13}C NMR, and high-resolution mass spectra. All recorded yields are based upon isolated material of >97% purity.
(17) The unidentified byproducts of these reactions exhibit much higher polarity and possess hydroxyl substitution. Several attempts to achieve the conversion of these substances to **4** by dehydration were to no avail.
(18) Following completion of this study, we learned of an independent preparation of **4** (R = H) by totally different method: Sugimura, T. Ph.D. Dissertation, Osaka University, 1984.
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Its ^1H NMR spectrum reflects the dissymmetry introduced by the methyl substituent. Compared to **1** (R = H), the C-7 signal for **13** at 171.3 ppm is shifted upfield by 5.8 ppm. The shielding is fully accommodated by the monoalkyl substitution plan at C-8, since C-7 in **1** (R = CH_3) is seen at 165.7 ppm.[1c] In fact, the incremental Δppm values of 5.6–5.8 indicate that **13** is strain-free as suggested by molecular models.

In summary, a convenient synthesis of annulated fulvenes and their conversion to previously unknown 1,7-cyclohexenonorbornadienes has been demonstrated. We believe the pathway from **9** to **4** to be as illustrated. This protocol and both classes of product molecules are expected to play useful roles in future synthetic and mechanistic investigations.

Acknowledgment. We are grateful to the National Institutes of Health for the financial support of this work (Grant CA-12115) and to Dr. Pana Charumilind for an early preliminary experiment.

Biosynthesis of Aristeromycin. Elucidation of the Origin of the Adenine and Cyclopentane Rings

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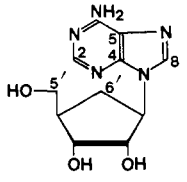
Received May 13, 1985

Aristeromycin (**1**) is a novel, carbocyclic analogue of adenosine obtained from the fermentation broth of *Streptomyces citricolor*.[1] The compound exhibits a number of interesting biological properties[2,3] including inhibition of AMP synthesis in mammalian cells, inhibition of cell division and elongation in rice plants, and inhibition of the enzyme *S*-adenosylhomocysteine hydrolase.[4] The unusual structure of aristeromycin and its important biological activity have prompted us to carry out the biosynthetic investigations that are reported here.



1

The initial phase of our studies was concerned with the origin of the cyclopentane ring in **1**. Since a carbohydrate origin appeared likely, both [U-^{14}C]-D-glucose and [1-^{14}C]-D-ribose were evaluated as precursors (Table I, experiments 1 and 2). Very low incorporations were observed in each instance. These experiments were carried out using the fermentation medium reported in the literature.[1] Since this medium contains glucose, soluble starch, and cornsteep liquor, it seemed likely that the low incorporation of glucose observed in experiment 1 could be attributed to dilution of the labeled precursor. Accordingly, a series of experiments were carried out to measure aristeromycin production in replacement cultures. After many trials, it was discovered that excellent production of the antibiotic could be obtained by fermentation in the "normal" medium for 48 h followed by fermentation in a replacement medium lacking both glucose and soluble starch. When [1-^{14}C]glucose was administered to *S. citricolor* growing in replacement culture, there was a sixfold increase in the specific incorporation figure (experiment 3). This observation was followed up by administration of (1-^{13}C)-D-glucose to *S. citricolor* under the same conditions. Examination of the noise-decoupled ^{13}C NMR spectrum of the resulting aristeromycin revealed a fourfold enrichment of the signal due to C-5′ of aristeromycin (experiment 4).

Table I. Administration of Labeled Precursors to *S. citricolor*

expt	precursor ($^3H/^{14}C$)	fermentation conditns	spec incorpn, % ($^3H/^{14}C$)	labeling pattern
1	[U-^{14}C]-D-glucose	normal	0.01	
2	[1-^{14}C]-D-ribose	normal	0.0003	
3	[1-^{14}C]-D-glucose	replmnt	0.06	
4	(1-^{13}C)-D-glucose	replmnt	4	C-5′
5	(6-^{13}C)-D-glucose	replmnt	2	C-6′
6	sodium [^{14}C]formate	normal	0.04	
7	[1-^{14}C]glycine	normal	0.24	
8	sodium (^{13}C)formate	normal	0	
9	(1,2-$^{13}C_2$)glycine	normal	7 at C-4, C-5	C-4, C-5 $^1J_{CC}$ = 65 Hz
			13 at C-2, C-8	C-2, C-8
10	(^{15}N,2-^{13}C)glycine	normal	10 at C-5	C-2, C-5, C-8
			9 at C-2, C-8	
11	[2-^3H,8-^{14}C]-adenosine (5.98)	normal	0.39 (4.90)	

If D-glucose is incorporated intact into the cyclopentane moiety of aristeromycin, the discovery that C-1 of glucose corresponds to C-5′ of the antibiotic indicates that C-6 of D-glucose should reside at either C-3′ or C-6′ of aristeromycin. In order to differentiate between these two possibilities, (6-^{13}C)-D-glucose was synthesized[5] and administered to replacement cultures of *S. citricolor*. Examination of the ^{13}C NMR spectrum of the antibiotic isolated in this experment showed a twofold enhancement in the signal due to C-6′ of aristeromycin (experiment 5). From this result, one can conclude that the formation of the cyclopentane moiety of aristeromycin proceeds with formation of a carbon–carbon bond between C-2 and C-6 of glucose. The details of this cyclization process remain to be elucidated.

The second phase of our investigation focused upon the origin of the adenine ring in **1**. The biosynthesis of the adenine ring of purine nucleosides has been extensively studied in both avian liver and bacterial systems.[6] As a result of these studies, it is generally accepted that C-2 and C-8 of the adenine moiety are derived from formate, while C-4 and C-5 are derived from C-1 and C-2 of glycine, respectively. The C-7 nitrogen atom is also derived from the nitrogen atom of glycine. A preliminary evaluation of this pathway in *S. citricolor* was carried out by administration of [^{14}C]formate and [1-^{14}C]glycine. Radioactive aristeromycin was obtained in both experiments (experiments 6 and 7) and glycine was clearly the more efficient precursor. Experiments 6 and 7 were followed by evaluation of (^{13}C)formate and (1,2-$^{13}C_2$)glycine as aristeromycin precursors. The results from these studies were surprising. No visible enrichment was apparent in the ^{13}C NMR spectrum of aristeromycin derived from (^{13}C)formate (experiment 8). On the other hand, (1,2-$^{13}C_2$)glycine yielded aristeromycin that was highly enriched at C-2 and C-8 as well as having lower enrichment at C-4 and C-5 (experiment 9). The coupling between C-4 and C-5 observed in this experiment confirms the expected intact incorporation of glycine into this position of the purine nucleus.[7] The derivation of C_1 units from glycine observed in the experiment is unusual, but not without precedent. Some 37 years ago, Karlsson and Barker[8] reported that C-2 and C-8 of uric acid were labeled by both [^{14}C]formate and [2-^{14}C]glycine

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