Cytochalasin Support Studies. Macrocycle Synthesis via Enolate-Assisted, Intraannular 1,4-Fragmentation Reactions

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Abstract: The intramolecular reactions of the four possible diastereomers of cis- and trans-fused 6α- and β-benzenesulfonoxy-4,4-dimethylbicyclo[5.4.0]undecan-3-one were examined. Conversion of these substances to their enolates caused the cis-β and trans-β isomers to form cyclobutanes by intramolecular alkylation. The cis and trans α isomers underwent fragmentation reactions to produce *trans,cis*- and *trans,trans*-11,11-dimethylcycloundeca-2,8-dienone, respectively. These dienones could not be directly isolated from the simple fragmentation reaction (because of dimer formation); however, when the fragmentation reaction was carried out in the presence of diisobutylaluminum hydride, the corresponding dienols were isolated in >90% yield. The mechanisms of these reactions are discussed as well as their applicability to cytochalasin synthesis.

Introduction

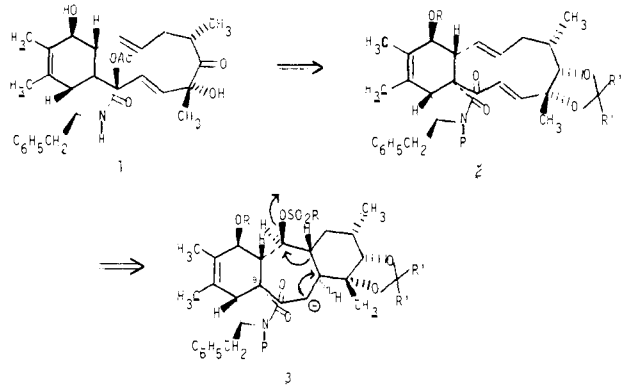
A conceptual approach for the construction of the macrocyclic ring of the [11]cytochalasins,[3,4] as illustrated for cytochalasin C (**1**), is via an enolate-assisted, endocyclic, intraannular 1,4-fragmentation reaction (**3** → **2**).

1,4-Fragmentation reactions of polycyclic systems can be conveniently classified according to the relationship of the assisting orbital and the leaving group terminus. Hence, a fragmentation in which the participating orbital and the leaving group are within the same ring can be termed *intraannular* (**4**); when the participating orbital is in a different ring from the leaving group, the arrangement is called *interannular* (**5**); when the participating orbital is external to the ring system, the fragmentation is designated as *extraannular* (**6**). As can readily be seen by examination of the three schematics, these examples represent structurally "frozen" conformations, formally generated by rotation of orbital 1 around the C-2, C-3 bond. The relationship of orbital 1 and the leaving group is given by the dihedral angle ϕ where $\phi \simeq 0°$ for an intraannular fragmentation (**4**), $\phi \simeq 180°$ for an interannular fragmentation (**5**), and $\phi \simeq 90°$ for an extraannular fragmentation (**6**).

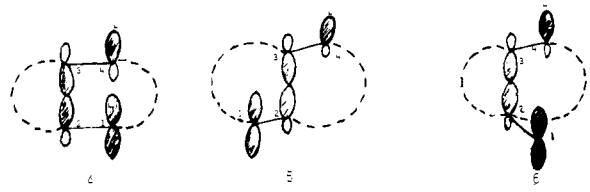
The formation of macrocyclic dienes via intraannular 1,4-fragmentation reactions involving boronate (**7a**) and organozinc (**7b**) assisting groups is well-known.[5-8] These and other similar 1,4-fragmentation reactions are highly stereospecific and proceed via a transition state where the leaving group, L (halide, sulfonate), breaking bond, and assisting orbital are aligned in an antiperiplanar fashion[9] (**7** → **8**).

At the outset of our investigation the prospects for an enolate-assisted fragmentation seemed especially bleak. The only reported example of an endocyclic (both sp^2 centers of the enolate within the ring), enolate-assisted fragmentation was

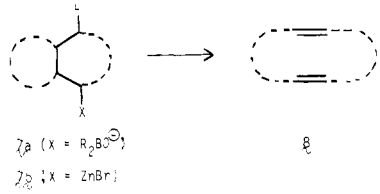
Scheme I



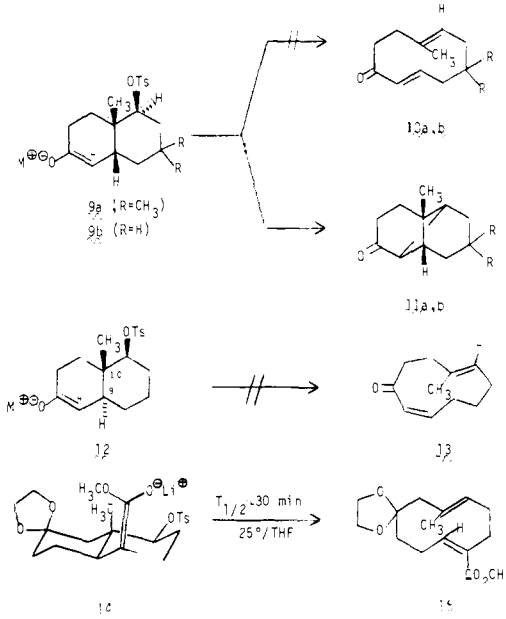
Scheme II



Scheme III



Scheme IV



of the interannular variety (**9a** → **10a**),[10] and had been disproven by Heathcock[11,12] (**9a,b** ↛ **10a,b**; **9a,b** → **11a,b**). Heathcock has similarly shown that keto tosylate **12**, which is incapable of forming a cyclobutane, also does not afford a fragmented dienone (**13** or **10b**).[13] Heathcock reasonably postulates that the failure of **12** to fragment is a consequence of poor orbital overlap between the "assisting" enolate sp^2 center (C-4) and the C-9, C-10 bond.[11,13]

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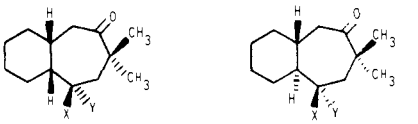
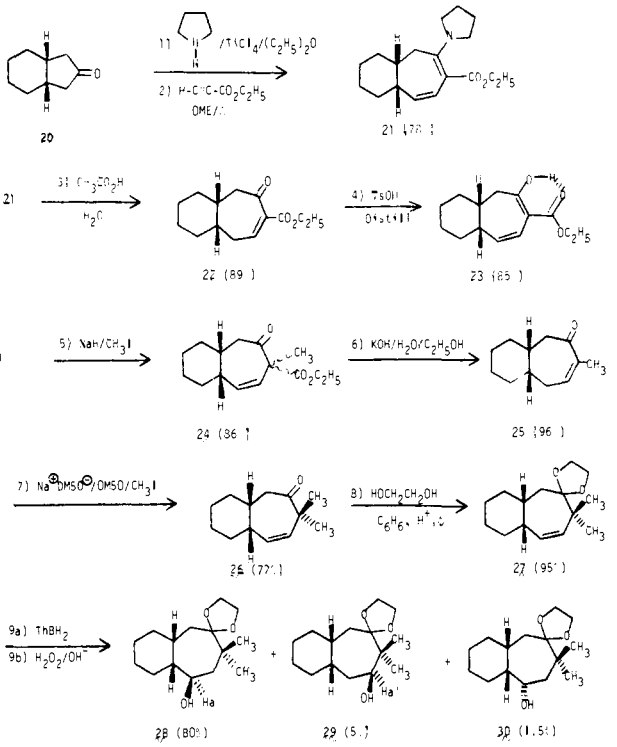
Scheme V



16 (X=OSO$_2$C$_6$H$_5$, Y=H)
17 (X=H, Y=OSO$_2$C$_6$H$_5$)
18 (X=OSO$_2$C$_6$H$_5$, Y=H)
19 (X=H, Y=OSO$_2$C$_6$H$_5$)

Scheme VI



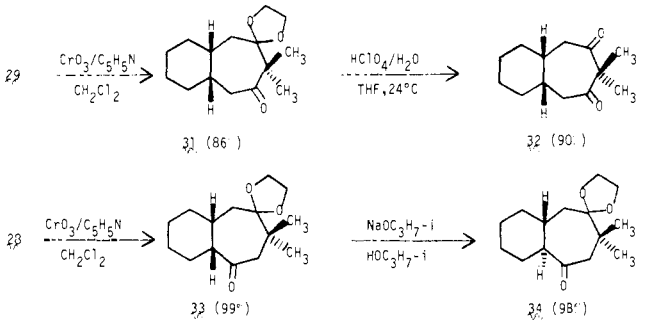
Very recently, Brown, Cresp, and Mander have provided the first example of an enolate-assisted fragmentation reaction. They showed that the tosyloxy ester **14**, in which the activating ester is exocyclic to the ring, cleanly undergoes intraannular fragmentation to yield **15**.[14]

The intraannular fragmentation necessary for the cytochalasin approach (**3** → **2**) requires *both* sp^2 centers of the enolate system to be endocyclic to the fragmenting ring, unlike the above example (**14** → **15**). While we felt that the greater conformational mobility enjoyed by the cycloheptyl system (cf. **9, 12**) would enable the enolate orbital to assume geometries reasonable to assist the fragmentation, it was deemed prudent to investigate this reaction on a simpler model system prior to construction of substrate **3**. Therefore, we elected to synthesize and investigate the enolate chemistry of the four possible diastereomers of cis- and trans-fused 6α- and β-benzenesulfonoxy-4,4-dimethylbicyclo[5.4.0]undecan-3-one (**16, 17, 18, 19**).[15]

Results and Discussion

Conversion of ketone **20** to its pyrrolidine enamine followed by Berchtold-Brannock ring expansion[16] provides the highly crystalline dienamine ester **21** in 78% overall yield. Hydrolysis of **21** with aqueous acid affords enone **22**, which may be easily transformed to enol **23** by distillation from a trace of toluenesulfonic acid. After distillation the **23**/**22** ratio is ca. 95/5. Methylation of **23** yields keto ester **24** as a mixture of epimers. Hydrolysis and decarboxylation of **24** produce **25**, which may be further methylated in Me_2SO to afford ketone **26**. Treatment of **26** with ethylene glycol in refluxing benzene affords ketal **27**. Reaction of ketal olefin **27** with thexylborane produced alcohol **28** in 66% yield by direct crystallization from the crude reaction mixture. Chromatography of the crystallization residues provided an additional 14% of **28**, as well as 5% of **29** and 1.5% of **30**.

Scheme VII



The regiochemical assignment of the isomers **28** and **29** was based on several observations. The NMR of minor isomer **29** has H_a' at δ 3.5 as a doublet of triplets (J = 9, 3 Hz) and the OH at δ 3.1 as a doublet (J = 9 Hz). Addition of D_2O causes the OH peak to disappear and H_a' collapses to an apparent triplet. Oxidation of alcohol **29** with chromium trioxide/pyridine[17] gave ketal ketone **31**, which exhibited the following partial NMR for the AB methylene group α to the carbonyl: δ 3.15 doublet of doublets (1 H, J = 12, 4 Hz), 2.4 doublet of doublets (1 H, J = 12, 7 Hz). Hydrolysis of the ketal of **31** (3.5% perchloric acid/tetrahydrofuran) afforded the symmetrical diketone **32**. The ^{13}C NMR of **32** showed only seven signals instead of the expected eight;[18] however, addition of Eu(fod)$_3$ (20 mol %) separated the overlapping methyl peaks.[19]

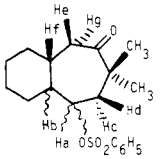
Major isomer **28** has H_a at δ 3.5 as a doublet of doublet of doublets (J = 11, 7, 2 Hz) and the OH as a singlet at δ 2.8. Oxidation of **28** (chromium trioxide/pyridine)[17] gave ketal ketone **33**, which exhibited the following partial NMR for the AB methylene α to the carbonyl: δ 3.10 doublet (1 H, J = 12 Hz), 2.0 doublet (1 H, J = 12 Hz). Finally, ketone **33** could be quantitatively isomerized in sodium isopropoxide/2-propanol to trans-fused ketone **34** (**34**/**33** > 99:1).

The requisite four keto benzenesulfonates **16–19** could all be prepared using **28** as a starting material. Hydrolysis of ketal **28** smoothly afforded keto alcohol **35**, which was, in turn, sulfonated to yield substrate **16**. The epimeric cis-fused keto benzenesulfonate **17** was easily synthesized in three steps from ketal ketone **33**. Lithium selectride[20] reduction of **33** cleanly produces the α alcohol **30** (**30**/**28** > 99:1), identical in all respects with the minor product from the hydroboration-oxidation reaction of olefin **27**. Sulfonation of **30** in the presence of dimethylaminopyridine[21] produces ketal benzenesulfonate **36**. Hydrolysis of **36** generates keto benzenesulfonate **17**.

The two trans-fused diastereomers were obtained from the epimerized ketone **34**. Lithium aluminum hydride reduction of **34** produces a mixture of ketal alcohols **37** and **38**. (L-Selectride[20] reduction of **34** very selectively yields **37**.) Hydrolysis of **37** (to **39**) followed by sulfonation affords keto benzenesulfonate **18**. The last substrate, **19**, is prepared via sulfonation of **38** (to **40**) followed by ketal hydrolysis.

Extensive 360-MHz ^{1}H NMR experiments were carried out in order to firmly establish the stereochemistry of the four keto benzenesulfonates as well as to attempt to secure information with respect to their preferred conformations in solution. The bicyclo[5.4.0] ring system is quite mobile and several conformations had to be considered. In each of the four cases a preferred conformation could be assigned which was in agreement with the ^{1}H NMR. It should be noted that predicted coupling constants from "frozen" conformers are slightly different from the observed values because of averaging due to conformational interconversions (see Table I).

Table I. 360-MHz NMR Data (C_6D_6)



	16 ($H_a = \alpha$, $H_b = \beta$)	**17** ($H_a = \beta$, $H_b = \beta$)	**18** ($H_a = \alpha$, $H_b = \alpha$)	**19** ($H_a = \beta$, $H_b = \alpha$)
		δ, ppm		
H_a	5.05 **m**	4.85 dd	4.85 dt	4.45 td
H_b	1.95 br d	2.70 br dd		2.10 d
H_c	2.20 d	2.60 dd	1.75 dd	2.10 dd
H_d	2.00 dd	2.05 d	2.30 dd	2.30 d
H_e	2.50 dd	2.30 d	2.40 dd	2.30 dd
H_f		2.20 br d		
H_g	2.30 dd	3.15 t	2.15 dd	2.45 t
		J, Hz		
ab	6.3	3.5	3.1	9.9
ac	~0	11.5	3.1	9.9
ad	9.4	~0	8.8	1.5
cd	15.1	14.5	15.0	14.4
ef	3.8	~0	4.4	2.5
eg	12.5	11.8	11.2	11.2
gf	8.8	11.8	8.1	11.2

In addition to being totally consistent with the detailed decoupling experiments, the configurations and conformations assigned also explain both anisotropic effects noted in this series. (1) The proton of the methylene (H_e or H_g) α to the carbonyl which is parallel to the π system always appears further downfield. A similar effect is known for cyclohexanones where the axial α protons absorb further downfield.[22] (2) In the two

Scheme VIII

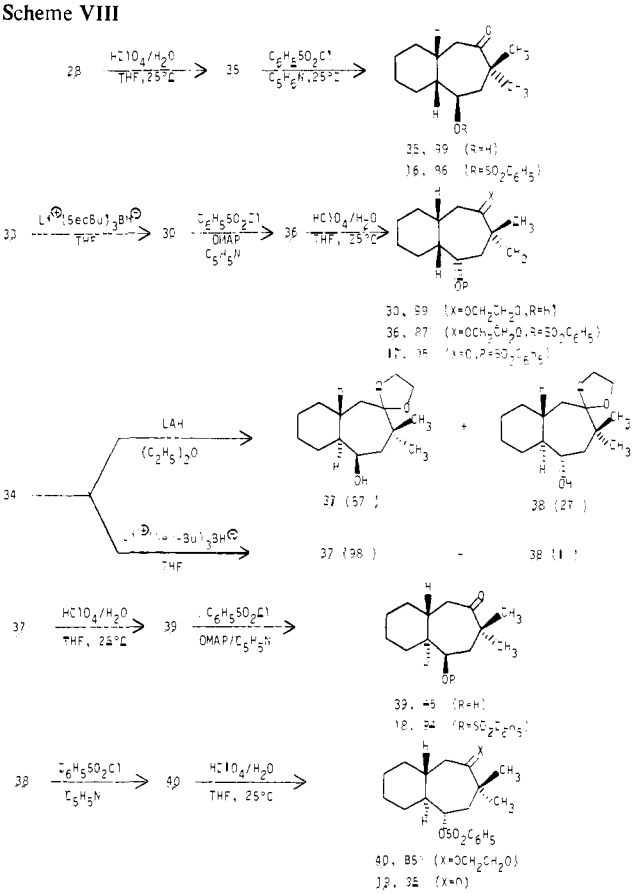


Table II. Chemical Shift of H_a in Four Isomeric Keto Benzenesulfonates

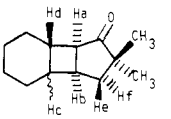
isomer	chemical shift of H_a ($CDCl_3$), δ	multiplicity
16	4.75	m
17	4.30	dd J = 11, 3.5 Hz
18	4.80	dd J = 8.5, 3 Hz
19	4.15	td J = 9.5, 2 Hz

Table III. Preferred Conformation for Four Isomeric Keto Benzenesulfonates

isomer	$CHOSO_2C_6H_5$[a]	cycloheptanone	δH_a (C_6D_6)[b]
16	equatorial	folded	5.05
17	equatorial	extended	4.85
18	equatorial	folded	4.85
19	equatorial	extended	4.45

[a] Orientation with respect to the cyclohexane ring. [b] Chemical shifts were determined using the benzene-d_5 H signal as the internal standard (δ 7.4).

Table IV. 360-MHz NMR Data (C_6D_6)



	δ, ppm	
	44 ($H_c = \beta$)	**55** ($H_c = \alpha$)
H_a	2.85 t (J = 7.25 Hz)	2.85 dd (J = 8.25, 6 Hz)
H_b	2.15 brdd ($W_{1/2}$ = 22.5 Hz)	2.65 m (J = 9, 8.25, 6.5, 6.5 Hz)
H_c		
H_d	2.60 m	1.90 m
H_e	1.65 dd (J = 13.5, 7.25 Hz)	
H_f	1.90 dd (J = 13.5, 9.0 Hz)	

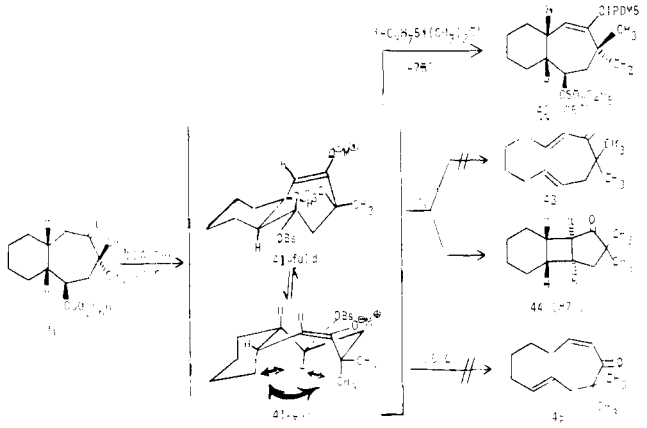
folded conformers (**16** and **18**) H_a is shifted downfield because it lies in the deshielding cone of the carbonyl. The positive solvent effect observed ($\delta_{CHCl_3} - \delta_{benzene\text{-}d_6} > 0$) is consistent with H_a located behind the carbonyl[23] (see Tables II and III).

Treatment of keto benzenesulfonate **16** at −78 °C with lithium diisopropylamide (LDA) produces a solution of enolate **41** as demonstrated by low-temperature quenching with dimethylisopropylchlorosilane to yield silyl enol ether **42**. Warming the solution of **41** to 25 °C for 4 h affords the tricyclic ketone **44**, the product of internal alkylation. No trace of fragmented dienones **43** or **45** could be detected.

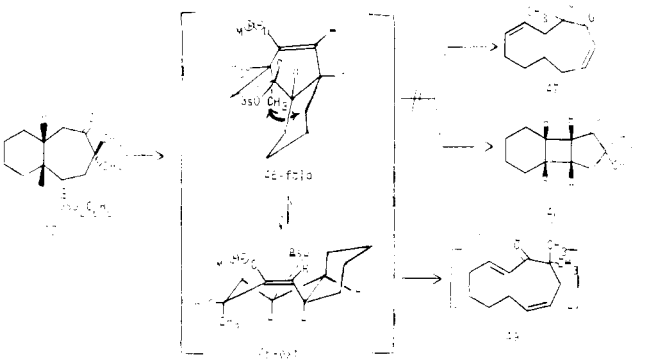
The stereochemistry (1β,2α,6α,7β) of ketone **44** is assigned by assuming a simple unimolecular displacement for the intramolecular alkylation. Evidence supportive of this view was obtained by 360-MHz NMR (see Table IV). Examination of molecular models of the ketone of opposite stereochemistry (**48**) predicts H_b to be coupled to a greater extent (width >28 Hz).

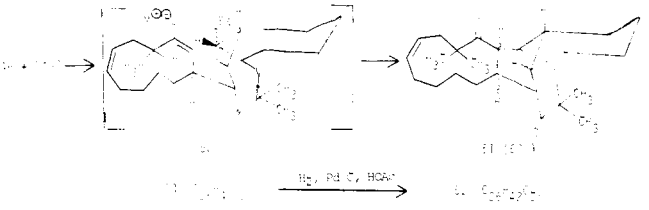
Treatment of the cis-fused α-benzenesulfonate **17** with LDA resulted in a fragmentation reaction to produce dienone **49** but this product suffered further reaction with enolate **46** to afford "dimer" **51** by way of a Michael addition-intramolecular alkylation sequence.[24] Hydrogenation of dimer **51** confirmed the presence of the single olefinic moiety.

Scheme IX

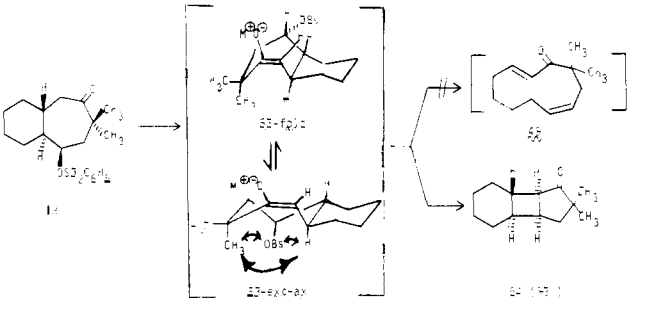


Scheme X





Scheme XI

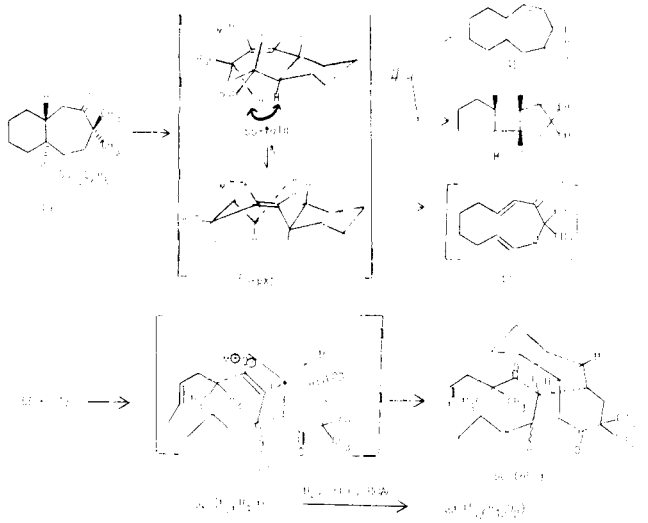


Attention was next turned to the trans-fused keto benzenesulfonate **18.** Treatment of **18** with LDA at −78 °C followed by warming to room temperature for 2.5 h again afforded a keto cyclobutane **54,** the product of internal alkylation.

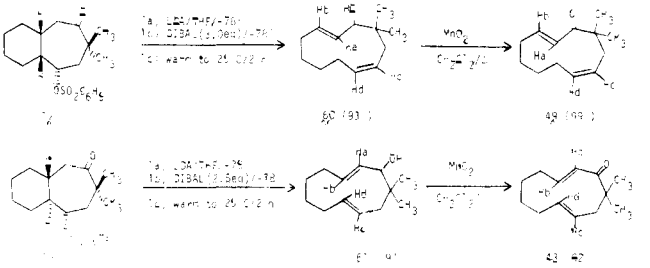
The 360-MHz NMR again provided supportive evidence for the assigned stereochemistry (see Table IV). Examination of molecular models shows that in the trans-fused ketone of the opposite stereochemistry H_b is perpendicular to H_e and would not be coupled. The difference in chemical shift of H_d in **44** and **54** is attributed to anisotropy of the ring system since in **44** H_d is equatorial and in **54** H_d is axial.[25,26]

The final substrate **19,** upon treatment with LDA and warming to room temperature, affords "dimer" **58,** presumably by way of intermediates **43** and **57.**

Scheme XII



Scheme XIII

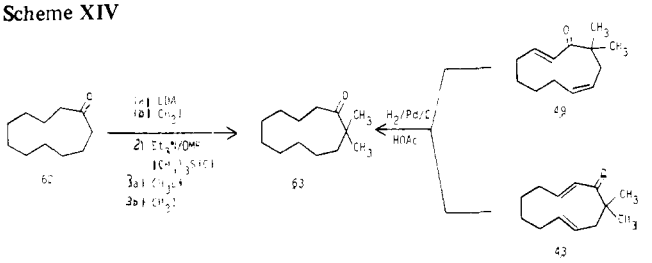


In an effort to avoid the dimerization reaction substrates **17** and **19** were converted to their enolates (**46, 55**) at −78 °C as before, and then treated with excess diisobutylaluminum hydride (2.5–3.0 equiv) prior to warming. Upon warming to room temperature (1–2 h) dienols **60** and **61** were obtained. Inasmuch as dienol functionality is required for the natural product, the combined fragmentation-reduction reaction is a pleasant bonus. Manganese dioxide oxidation of dienols **60** and **61** smoothly produced dienones **49** and **43,** respectively.

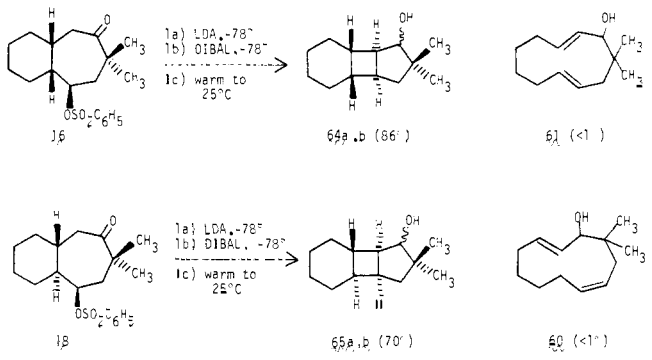
The stereochemistry of the dienone **49** was established from the NMR. H_a appeared as a doublet at δ 6.7 (J = 16 Hz) and H_b appeared as a doublet of triplets at δ 6.4 (J = 16, 6 Hz). The isolated olefin protons (H_c and H_d) were a multiplet at δ 5.3–5.6. Decoupling in the aliphatic region (δ 2.3) simplified H_b to a doublet (J = 16 Hz). The stereochemistry of the isolated olefin was deduced from a 25 mol % Eu(fod)$_3$ shift study. H_a and H_b were shifted to δ 8.2 and 8.8, respectively, and two olefin patterns appeared at δ 5.2 as a multiplet (25 Hz wide) and δ 5.85 as a quartet (J = 9 Hz). Europium shift studies of the dienol **60** also verified the trans-cis structure assigned (J_{trans} = 16, J_{cis} = 11 Hz). The stereochemistry of alcohol **61** and enone **43** was also established from NMR coupling constants. The olefins of dienol **61** appeared together as a complex multiplet at δ 5.2–5.7. Addition of Eu(fod)$_3$ shifted H_a to δ 8.5 as a doublet of doublets (J = 16, 7 Hz), H_b to δ 8.1 as a doublet of triplets (J = 16, 7 Hz), and H_c and H_d to δ 6.5 as a multiplet. The NMR pattern of enone **43** showed H_a and H_b at δ 6.3–6.5 and H_c and H_d at δ 5.1–5.6. Decoupling at δ 2.1 produced a singlet at δ 6.4 for H_a and H_b and caused H_c and H_d to collapse to two doublets at δ 5.2 (J = 16 Hz) and 5.4 (J = 16 Hz).

Although the structural assignments of the dienols and dienones were completely definitive, one further experiment was undertaken. Catalytic hydrogenation (10% Pd/C/acetic acid) of both dienones (**43, 49**) yielded a single ketone which was shown to be 2,2-dimethylcycloundecanone (**63**) by direct comparison with an authentic sample prepared from cycloundecanone (**62**).

Scheme XIV



Scheme XV



The two substrates which underwent intramolecular alkylation were also subjected to the LDA/DIBAL conditions. Keto benzenesulfonate **16** yielded an alcohol mixture (**64a,b**) which could be reoxidized with chromium trioxide/pyridine[17] to the previously characterized tricyclic ketone **44**. Similarly, keto benzenesulfonate **18** afforded alcohol mixture **65a,b** which could be oxidized to tricyclic ketone **54**. In both instances no trace of the fragmented products (**61, 60**) could be detected (TLC analysis). This places the preference for alkylation rather than fragmentation for these two substrates at ca. 100:1.

Conclusions

The enolate conformation appears to be all-important in determining the reaction products of the four diastereomeric keto benzenesulfonates. Whenever the enolate can easily assume a folded conformation (**41**-fold, **53**-fold), the cyclobutane product (**44, 54**) will result, *even when that same conformation could have also yielded the substantially less strained fragmented product* (**43, 49**). Formation of trans-fused cyclobutane **54** from enolate **53** is especially remarkable. It should be noted that this substrate *cannot* attain an extended conformation (**53**-ext-eq) where the leaving group is antiperiplanar to the central bond. The only extended conformation possible (**53**-ext-ax) has the leaving group in a nonreactive pseudoaxial conformation.

The observation that cyclobutane formation is preferred over fragmentation (by ca. 2.8 kcal) for substrates **16** and **18** requires a kinetic preference for direct bond formation (cyclobutane) rather than for polarization-bond formation (fragmentation); however, since all four substrates have a reaction rate within a factor of 2, the explanation of this kinetic preference will have to be found either in a difference in their ground-state energies or in some more fundamental effect.[27]

Models of the enolates (**46, 55**) for those substrates (**17, 19**) where intraannular fragmentation successfully occurred show that the folded conformations (**46**-fold, **55**-fold) are more strained than are the extended conformations (**46**-ext, **55**-ext) which, in turn, predict the correct diene stereochemistry (**49, 43**). The Mander substrate (**14**) also cannot assume a reasonable folded conformation for cyclobutane formation. In this case, the product would be even more strained than trans-fused cyclobutane **54** and presumably much of this strain information would be imparted to a cyclobutane-forming transition state.

Experimental Section

General Procedures. Melting points were taken on a Fisher-Johns melting point apparatus. All melting and boiling points are uncorrected. Infrared spectra were recorded neat or as KBr pellets on a Perkin-Elmer Infracord or 137 spectrophotometer. NMR spectra were determined in chloroform-d_1 solution with tetramethylsilane as a reference unless otherwise stated. NMR instrumentation included a Varian A-60A, Perkin-Elmer R-32, Varian XL-100, Varian CFT-20, and Nicolet 360.[28] Splitting patterns are designated as s, singlet; d, doublet, t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were recorded on CEC-21-110-B high-resolution mass spectrometer at an ionizing voltage of 70 eV and an ionizing current of 100 μA. Exact mass determinations were obtained on the CEC-21-110B instrument. Ultraviolet spectra were recorded on a Cary Model 15.

All experiments were carried out under a positive pressure of nitrogen in dry flasks equipped with rubber stopples for introduction of reagents via syringe. All solvents used for workup or recrystallization were distilled. Reactions were monitored by TLC on precoated thin-layer Sil G-25 UV_{254} plates obtained from Brinkmann Instruments, Inc. Thick-layer plates were made from silica gel PF-254 containing $CaSO_4$ from EM Reagents. Column chromatography was done on silica gel 60–200 mesh obtained from Sargent-Welch. Gas chromatographic analyses were performed on a Variah Aerograph Model 920. Solvents were evaporated on a Buchi Rotavapor R.

Normal reaction solvents were purified as follows. THF, DME, and ether were distilled from sodium/benzophenone; benzene, methylene chloride, ethyl acetate, Me_2SO, HMPA, and DMF were distilled from CaH_2. LDA was routinely prepared by adding *n*-butyllithium to a solution of diisopropylamine in THF at −78 °C and allowing the solution to stir for 0.5 h. 2,2′-Dipyridyl was used as an indicator for reactions involving alkyllithiums and LDA as bases.

TLC data for compounds in the synthesis section are reported as (solvent, R_f). The following solvent systems were used: (1) 10% THF/hexane; (2) 30% THF/hexane; (3) methylene chloride; (4) ether; (5) 20% ether/chloroform; (6) 10% ethyl acetate/chloroform. Mass spectral data is reported as *m/e* (rel intensity). IR data is reported in microns. ^{13}C NMR data is reported in parts per million with tetramethylsilane as the internal standard.

***cis*-2-β-Decalol.** A commercial mixture[29] of decalols (5 lb) was suspended in hexane (5 L) and the resultant white solid was collected by filtration. A total of 580 g was obtained: mp 105 °C (lit.[30] mp 105 °C); mass spectrum *m/e* 154 (M^+, calcd for $C_{10}H_{18}O$ 154.136, found 154.135, 40), 136 (100); IR (KBr) 3.1 μ (OH); ^1H NMR δ 1.0–2.0 (16 H), 2.2 s (1 H, exchanges with D_2O), 3.5 m (1 H); ^{13}C NMR 71.6 (CH), 35.6, 35.0, 34.8, 31.8, 30.5, 30.1, 26.8, 26.0, 21.1 ppm.

***cis*-2-Decalone.** *cis*-2-β-Decalol (0.39 mol, 60.0 g) was dissolved in ether (1200 mL) in a three-neck flask equipped with a thermometer, dropping funnel, reflux condenser, and mechanical stirrer. The ether solution was cooled to 0 °C and an oxidizing solution[31] consisting of sodium dichromate dihydrate (0.155 mol, 47.0 g), sulfuric acid (0.630 mol, 64.0 g), and water (140 mL) was added dropwise over 4 h. The solution was stirred for an additional 3 h and the layers were separated. The aqueous solution was extracted with ether (7 × 100 mL). The combined ether layers were washed with saturated NaCl (2 × 200 mL), dried ($MgSO_4$), and evaporated in vacuo leaving 58.3 g (98%) of *cis*-2-decalone. VPC analysis (20% DEGS on Chromosorb P, 10-ft × $^3/_8$ in., 150 °C) showed no *trans*-2-decalone (retention time: *cis*-2-decalone, 16 min; *trans*-2-decalone, 12 min): TLC (1, 0.39); mass spectrum *m/e* 152 (M^+, calcd for $C_{10}H_{16}O$ 152.120, found 152.121, 11), 83 (100); IR (neat) 5.83 μ (C=O); ^1H NMR δ 1.0–2.5 m; ^{13}C NMR 221 (C=O), 45.4 (CH_2), 39.3 (CH_2), 38.6 (CH_2), 34.9 (CH), 28.8, 28.4, 23.8, 23.0 ppm.

***cis*-1,2-Cyclohexanediacetic Acid and 2-Carboxycyclohexanepropionic Acid.** In a 2-L three-neck flask equipped with a thermometer, reflux condenser, dropping funnel, and mechanical stirrer were placed nitric acid (400 mL), water (200 mL), and ammonium metavanadate (0.5 g).[32] The contents was heated to 70 °C and then *cis*-2-decalone (0.66 mol, 100.0 g) was added over 4 h (*Caution*—add only a few milliliters of the ketone until the reaction has initiated—evolution of NO_2) at a rate such that the temperature is kept below 90 °C. The reaction mixture was heated to reflux for an additional 2 h, allowed to slowly cool, and finally cooled at 0 °C overnight. The product was collected by filtration to yield 79.5 g (60%) of a mixture of the diacids. The mixture was cyclized without separation of the isomers.

***cis*-Bicyclo[4.3.0]nonan-8-one (20) and *cis*-Bicyclo[4.3.0]nonan-**

7-one. The mixture of above diacids (0.50 mol, 100.0 g) was placed in a 1-L round-bottom flask containing finely ground $Ba(OH)_2 \cdot 8H_2O$ (15 g).[32] A distillation column was attached and the contents were heated slowly with a Bunsen burner as CO_2 and H_2O distilled over at 100 °C followed by the ketones at 240 °C. The distillate was transferred to a separatory funnel with the aid of ether (400 mL) and the ether was washed with 10% $NaHCO_3$ (75 mL). The pot residue was stirred in 10% $NaHCO_3$ (100 mL) and ether (200 mL) and the layers were separated. The combined ether layers were washed with saturated NaCl (75 mL), dried ($MgSO_4$), and concentrated in vacuo to afford 59.5 g (86%) of the mixture of the ketones. VPC analysis (20 ft × ¼ in. 10% FFAP on Chromosorb P, 130 °C) showed a mixture of the 8-keto and 7-keto material (66% **20**) (retention time: 8-keto, 9 min; 7-keto, 8 min). The ketone mixture was dissolved in ethanol (200 mL) and sodium bisulfite (1.6 mol, 166 g) dissolved in water/ethanol (800 mL, 2:1) was added. The solution was stirred for 1 h and the solid bisulfite adduct of ketone **20** was collected by filtration. The solid was washed with ether (400 mL) and then dissolved in saturated Na_2CO_3 solution. The basic solution was extracted with ether (3 × 200 mL) and the combined ether layers were dried ($MgSO_4$) and concentrated in vacuo. Distillation (84 °C, 4 mmHg) gave 37 g of ketone **20** (>95% pure by VPC). The 7-ketone can be isolated by ether extraction of the initial bisulfite filtrate.

20: TLC (1, 0.33); mass spectrum *m/e* 138 (M^+, calcd for $C_9H_{14}O$ 138.104, found 138.106, 5), 83 (100); ^1H NMR δ 1.0–1.7 m (8 H), 2.0–2.5 m (6 H); ^{13}C NMR 227 (C=O), 43.4 (CH_2), 35.8 (CH), 27.8 (CH_2), 22.6 (CH_2) ppm.

***cis*-8-(1-Pyrrolidinyl)bicyclo[4.3.0]non-7-ene. A.** *cis*-2-Hydrindanone (**20**, 0.326 mol, 45.0 g) dissolved in ether (300 mL) was added to a 1-L flask containing 5 Å molecular sieves (200 g).[33] Pyrrolidine (0.365 mol, 26.0 g) was added along with hydroquinone (300 mg) and a trace of *p*-toluenesulfonic acid. The reaction mixture was allowed to stand at room temperature for 6 h, the solution was filtered, and the solvent was removed in vacuo. Distillation (84 °C, 1 mmHg) afforded 53.3 g (86%) of the enamine, IR (neat) 6.2 μ (C=C).

B. The ketone **20** (0.293 mol, 40.5 g) was dissolved in ether (500 mL) along with pyrrolidine (2.0 mol, 170 mL). The solution was cooled to 0 °C and titanium tetrachloride[34] (0.146 mol, 16.0 mL) dissolved in pentane (50 mL) was added slowly over 45 min (mechanical stirrer required). The solution was stirred for 5 h and then filtered and evaporated in vacuo. The crude enamine was used directly for the next step.

***cis*-Ethyl 3-(1-Pyrrolidinyl)bicyclo[5.4.0]undeca-3,5-diene-4-carboxylate (21). A.** Ethyl propiolate (0.295 mol, 29.0 g) and hydroquinone (250 mg) were dissolved in DME (850 mL) and heated to reflux.[35] The above enamine (0.278 mol, 53.0 g) dissolved in DME (500 mL) was added dropwise over 1 h and then the solution was heated at reflux for an additional 1 h. The solvent was evaporated in vacuo, replaced with warm hexane (150 mL), and allowed to slowly cool. The resultant yellow, crystalline needles (41 g) were collected by filtration. A second crop gave a total of 62.5 g (78%): mp 105–107 °C; ^1H NMR δ 1.2 t, J = 7 Hz (3 H), 1.3–2.5 m (12 H), 3.0–3.8 m (4 H), 4.15 "dq" J = 7, 3 Hz (2 H), 5.6 dd, J = 10, 6 Hz (1 H), 6.5 dd, J = 10, 2 Hz (1 H); ^{13}C NMR 165 (C=O), 131 (C=CH), 127 (C=CH), 97 (C=C), 59 (CH_2), 54 (CH), 52 (CH_2), 41 (CH_2), 38 (CH), 29 (CH_2), 28.5 (CH_2), 25.5 (CH_2), 25 (CH_2), 22 (CH_2), 14.5 (CH_3) ppm; mass spectrum *m/e* 289 (M^+, calcd for $C_{18}H_{27}NO_2$ 289.204, found 289.206).

B. A more efficient synthesis of **21** could be realized using a 9:1 mixture of cis- and trans-fused enamines (only the cis-fused dienamine ester crystallizes) prepared in two steps from 2-indanone as described in the following two experiments.

***cis*- and *trans*-α,β-8-Hydroxybicyclo[4.3.0]nonane.** 2-Indanone (0.200 mol, 26.4 g), ethanol (100 mL), triethylamine (10 mL, reactions in the absence of triethylamine produced large amounts of indan), and W-2 Raney nickel[36] (~6 g) were hydrogenated at room temperature (1800 lb of H_2) for 3 h and then at 100 °C for 40 h (repressurized to 1800 lb after 20 h). The catalyst was filtered and washed with ether (200 mL). The solvent was removed in vacuo, leaving 23 g (85%) of a mixture of the above alcohols, TLC (2, 0.44).

***cis*- and *trans*-Bicyclo[4.3.0]nonan-8-one.** The mixture of the above alcohols (160.0 mmol, 23.8 g) was dissolved in ether (250 mL) and cooled to 0 °C. An oxidizing solution[33] consisting of sodium dichromate (20.6 g), sulfuric acid (28.0 g), and water (61 mL) was added over 15 min and the solution was stirred at room temperature for 2 h. Saturated NaCl (200 mL) was added and the solution was extracted with hexane/ether (1:1, 3 × 150 mL). The combined organic layers were washed with saturated NaCl (50 mL), dried ($MgSO_4$), and evaporated in vacuo. Distillation (84 °C, 4.0 mmHg) gave 21.0 g (95%) of a mixture of ketones **20** and its trans-fused epimer; ^{13}C NMR showed the mixture to contain ~90% **20.**

***cis*-Ethyl Bicyclo[5.4.0]undec-4-en-3-one-4-carboxylate (22) and *cis*-Ethyl 3-Hydroxybicyclo[5.4.0]undeca-3,5-diene-4-carboxylate (23).** The dienamine ester **21** (62.5 mmol, 18.0 g) was dissolved in acetic acid (100 mL) and water (20 mL) along with sodium acetate (25 g). The solution was stirred at room temperature for 20 h. Water (100 mL) was added, and the solution was extracted with hexane (4 × 100 mL). The combined hexane was washed with saturated NaCl (50 mL), dried ($MgSO_4$), and evaporated in vacuo at 50 °C. The liquid was then placed under high vacuum for 2 h at 40 °C. Distillation (146 °C, 1 mmHg) gave 12.5 g (89%) of a mixture of **22** (13%) and **23** (87%). Distillation of this mixture in the presence of a trace of *p*-toluenesulfonic acid gave a mixture which consisted of 95% enol **23** (85% yield). Hydrolysis in the absence of sodium acetate and distillation in the absence of acid gave pure keto ester **22:** TLC (1, 0.28); IR (neat) 5.78 (C=O) and 5.9 μ (C=O); ^1H NMR δ 1.3 t, J = 7 Hz (3 H), 1.3–2.8 m (14 H), 4.2 q, J = 7 Hz (2 H), 7.4 dd, J = 8.5 Hz (1 H). **23:** TLC (1, 0.48); IR (neat) 5.84, 6.09, 6.24 μ; ^1H NMR δ 1.3 t, J = 7 Hz (3 H), 1.3–1.7 v br s (8 H), 2.2–2.6 v br s (4 H), 4.2 q, J = 7 Hz (2 H), 5.5 dd, J = 12, 4 Hz (1 H), 6.2 dd, J = 12, 1.5 Hz (1 H), 13.0 s (1 H); ^{13}C NMR 179 (s), 172.5 (s), 131 (d), 121 (d), 100 (s), 110 (t), 42, 39, 30, 24, 23, 13.5 (q) ppm; mass spectrum *m/e* 236 (M^+, calcd for $C_{14}H_{20}O_3$ 236.141, found 236.143, <1), 91 (50), 83 (100).

***cis*-Ethyl 4-Methylbicyclo[5.4.0]undec-5-en-3-one-4-carboxylate (24).** Sodium hydride (33.0 mmol, 800 mg) was suspended in DME (50 mL) and cooled to 0 °C. Enol **23** (30.0 mmol, 7.1 g) dissolved in DME (40 mL) was added to the sodium hydride suspension over 0.5 h and the solution was stirred for 15 min at room temperature. Methyl iodide (53.0 mmol, 3.3 mL) was added and the solution was stirred for 3 h. Water (100 mL) was added and the solution was extracted with ether (2 × 100 mL). The ether was dried ($MgSO_4$) and evaporated in vacuo. Distillation of the crude residue (142 °C, 2 mmHg) afforded 6.5 g (86%) of a colorless oil: TLC (1, 0.53); mass spectrum *m/e* 250 (M^+, calcd for $C_{15}H_{22}O_3$ 250.157, found 250.158, <1), 204 (30), 144 (100); IR (neat) 5.75 and 5.83 μ (C=O); ^1H NMR δ 1.2 t, J = 7 Hz (3 H), 1.4 s (3 H), 1.3–1.8 m (8 H), 2.0–3.0 m, 4 H, 4.2 q, J = 7 Hz (2 H), 5.4 dd, J = 11, 2 Hz (1 H), 5.8 dd, J = 11, 5 Hz (1 H); ^{13}C NMR 215 (C=O), 173 (C=O), 135.8 (CH), 128.6 (CH), 61.6 (CH_2), 44.7 (C), 38.5, 36.5, 30.1, 28.9, 24.4, 22.9, 22.5, 14.0 ppm.

***cis*-4-Methylbicyclo[5.4.0]undec-4-en-3-one (25).** The keto ester **24** (21.6 mmol, 5.4 g) was dissolved in a solution of potassium hydroxide (10 g), water (50 mL), and ethanol (50 mL). The homogeneous solution was stirred at room temperature for 3 h and extracted with hexane (4 × 50 mL). The combined hexane was washed with saturated NaCl (50 mL), dried ($MgSO_4$), and evaporated in vacuo. Distillation (87 °C, 3 mmHg) gave 3.7 g (96%) of enone **25:** TLC (1, 0.50); mass spectrum *m/e* 178 (M^+, calcd for $C_{12}H_{18}O$ 178.136, found 178.134, 1), 84 (100), 82 (100); IR (neat) 5.95 μ (C=O); ^1H NMR δ 1.1–1.8 m (14 H), 1.8 bs (3 H), 6.5 m (1 H); ^{13}C NMR 212 (C=O), 141.6 (CH), 139.2 (C), 48.7 (CH_2), 37.7 (CH), 33.9, 32.2, 30.4, 24.6, 23.0, 18.9 ppm.

***cis*-4,4-Dimethylbicyclo[5.4.0]undec-5-en-3-one (26).** Sodium hydride (0.126 mol, 3.02 g) and Me_2SO (300 mL) were heated at 70 °C for 1 h and then cooled to room temperature.[37] Ketone **25** (0.126 mol, 22.4 g) dissolved in Me_2SO (100 mL) was added over 15 min and the resulting homogeneous red solution was stirred for 0.5 h. Methyl iodide (0.157 mol, 9.8 mL) was added and the yellow solution was stirred for 1.5 h. Ice water (500 mL) was added and the mixture was extracted with hexane (4 × 250 mL). The combined hexane layers were washed with saturated NaCl (250 mL), dried ($MgSO_4$), and evaporated in vacuo. Distillation (90 °C, 1 mmHg) afforded 18.7 g (77%) of *gem*-dimethyl ketone **26:** TLC (1, 0.50); mass spectrum *m/e* 192 (M^+, calcd for $C_{13}H_{20}O$ 192.151, found 192.151, 9), 110 (100); IR (neat) 5.85 μ (C=O); ^1H NMR δ 1.15 s (6 H), 1.2–2.7 m (12 H), 5.5 m (2 H); ^{13}C NMR 175.3 (C=O), 136.5 (CH), 128.6 (CH), 75.4 (C), 50.8, 44.7, 41.0, 34.2, 29.9, 29.5, 27.4, 25.6, 22.6, 21.3 ppm.

***cis*-4,4-Dimethyl-3,3-ethylenedioxybicyclo[5.4.0]undec-5-ene (27).** In a 250-mL flask equipped with a Dean-Stark trap were placed the ketone **26** (26.5 mmol, 5.1 g), benzene (50 mL), ethylene glycol (10 mL), and *p*-toluenesulfonic acid (0.5 g). The contents was heated to reflux for 4 days and then poured into 10% $NaHCO_3$ (50 mL). The

layers were separated and the aqueous portion was extracted with hexane (2 × 50 mL). The combined organic layers were washed with saturated NaCl (50 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo. Distillation (100 °C, 1.4 mmHg) yielded 6.0 g (95%) of ketal **27:** TLC (1, 0.58); mass spectrum *m/e* 236 (M^+, calcd for $C_{15}H_{24}O_2$ 236.178, found 236.176, <1), 85 (80), 83 (100); ^1H NMR δ 1.1 s (6 H), 1.2–2.7 m (12 H), 3.9 bs (4 H), 5.3 AB (2 H); ^{13}C NMR 138 (d), 134 (d), 116 (s), 68 (t), 67.5 (t), 46 (s), 40, 38, 36, 33, 31, 27.5, 25 ppm.

(1β,7β)-4,4-Dimethyl-3,3-ethylenedioxy-6β-hydroxybicyclo[5.4.0]undecane (28), (1β,7β)-4,4-Dimethyl-3,3-ethylenedioxy-5β-hydroxybicyclo[5.4.0]undecane (29), and 1β,7β-4,4-Dimethyl-3,3-ethylenedioxy-6α-hydroxybicyclo[5.4.1]undecane (30). 2,3-Dimethyl-2-butene (90.0 mmol, 10.8 mL) was dissolved in THF (100 mL) and cooled to 0 °C. Borane methyl sulfide complex[38] (90.0 mmol, 9.0 mL) was added and the contents stirred at 0 °C for 1 h and room temperature for 1 h. The olefin **27** (85.0 mmol, 20.0 g) dissolved in THF (25 mL) was added and the solution was stirred for 2.5 h. The solution was cooled to 0 °C and ethanol (100 mL) was slowly added followed by cautious addition of 10% NaOH (45 mL) and 30% H_2O_2 (45 mL). The contents was heated to 50 °C for 1 h and poured into water (250 mL). The solution was extracted with hexane (3 × 250 mL) and the combined hexane was washed with saturated NaCl (100 mL), dried ($MgSO_4$), and evaporated in vacuo. Warm hexane (150 mL) was added and the contents allowed to cool slowly. The crystals were collected yielding 11.2 g. A second crop gave a total of 14.2 g (66%). Column chromatography on silica gel (100 g) using 20% ether/chloroform gave an additional 3.0 g (total 17.2 g, 80%) of **28** along with 1.1 g (5%) of **29** and 300 mg (1.5%) of **30. 28:** TLC (5, 0.28); mp 98–100 °C; mass spectrum *m/e* 254 (M^+, calcd for $C_{15}H_{26}O_3$ 254.188, found 254.188, 66), 157 (100); ^1H NMR δ 0.9 s (3 H), 1.05 s (3 H), 1.0–2.4 m (15 H), 3.6 m (1 H), 3.95 bs (4 H); ^{13}C NMR 114 (C), 74.3 (CH), 65.3 (CH_2), 64.3 (CH_2), 46.7, 44.4, 40.8, 35.1, 34.6, 29.1, 28.6, 26.5, 25.6, 24.6, 21.6 ppm. Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.57; H, 10.16. **29:** TLC (5, 0.45); mass spectrum *m/e* 254 (M^+, calcd for $C_{15}H_{26}O_3$ 254.188, found 254.189, 30), 125 (100), 114 (100), 99 (90); ^1H NMR δ 1.05 s (3 H), 1.1 s (3 H), 1.15–2.4 m (14 H), 3.15 d, *J* = 9 Hz (1 H, exchanges with D_2O), 3.55 dt, *J* = 9, 3 Hz (1 H, simplifies to t, *J* = 3 Hz, with D_2O addition), 3.95 m (4 H); ^{13}C NMR 115.0, 75.5, 66.0, 63.3, 46.1, 36.7, 33.5, 32.6, 31.5, 29.7, 24.6, 24.3, 23.7, 21.7 ppm.

For **30** see specific synthesis from **33.**

***cis*-4,4-Dimethyl-3,3-ethylenedioxybicyclo[5.4.0]undecan-5-one (31).** Pyridine (1.85 mmol, 150 mg) was dissolved in methylene chloride (15 mL) and chromium trioxide (0.95 mmol, 95 mg) was added.[17] The mixture was stirred for 15 min and the alcohol **29** (0.158 mmol, 40 mg) was added dissolved in methylene chloride (2 mL). The solution was stirred for 20 min and ether (40 mL) was added. The solution was filtered and the black precipitate was washed with ether (40 mL). The combined organics were washed with 5% NaOH (2 × 15 mL), 5% HCl (15 mL), and water (15 mL). The ether was dried ($MgSO_4$) and evaporated in vacuo, leaving 34 mg (86%) of ketone **31:** TLC (5, 0.51); IR (neat) 5.88 μ (C=O); ^1H NMR δ 1.0 s (3 H), 1.2 s (3 H), 1.3–2.3 m (12 H), 2.4 dd, *J* = 7, 12 Hz (1 H), 3.15 dd, *J* = 4, 12 Hz (1 H).

***cis*-4,4-Dimethylbicyclo[5.4.0]undecane-3,5-dione (32).** The ketal **31** (1.0 mmol, 252 mg) was dissolved in THF (20 mL) and 3.5% $HClO_4$ (12 mL). The solution was stirred for 4 h at room temperature and water (25 mL) was added. The mixture was extracted with ether (2 × 25 mL) and the ether dried ($MgSO_4$). Removal of the solvent in vacuo gave 175 mg (90%) of diketone **32:** ^1H NMR δ 1.2 s (6 H), 1.3–2.2 m (10 H), 2.3–2.8 m (4 H); ^{13}C NMR 219 (C=O), 61.3 (C), 44.3 (CH_2), 38.5 (CH), 29.9 (CH_2), 23.3 (CH_2), 20.9 (2 CH_3)[18,19] ppm.

***cis*-4,4-Dimethyl-3,3-ethylenedioxybicyclo[5.4.0]undecan-6-one (33).** Pyridine (0.192 mol, 15.2 g) was dissolved in methylene chloride (200 mL) and chromium trioxide (96.0 mmol, 9.6 g) was added over 5 min.[17] The mixture was stirred for 0.5 h and alcohol **28** (0.6.0 mmol, 4.07 g) dissolved in methylene chloride (75 mL) was added. The reaction mixture was stirred for 1 h and ether (250 mL) was added. The reaction mixture was filtered and the black precipitate was washed with ether (3 × 100 mL). The combined organics were washed with 5% NaOH (3 × 100 mL), 5% HCl (2 × 100 mL), and saturated NaCl (100 mL). The solvent was dried ($MgSO_4$) and evaporated in vacuo, leaving 4.0 g (99%) of ketone **33:** TLC (5, 0.62); mp 76–78 °C; mass spectrum *m/e* 252 (M^+, calcd for $C_{15}H_{24}O_3$ 252.173, found 252.174, 100); IR (KBr) 5.9 μ (C=O); ^1H NMR δ 0.9 s (3 H), 0.95 s (3 H), 1.1–2.2 m (12 H), 2.0 d, *J* = 12 Hz (1 H), 3.10 d, *J* = 12 Hz (1 H); ^{13}C NMR 222 (C=O), 113.6 (C), 65.5 (CH_2), 65.1 (CH_2), 51.3 (C), 41.9, 35.8, 35.0, 29.5, 26.4, 26.2, 25.0, 23.8, 23.4, 20.9 ppm.

***trans*-4,4-Dimethyl-3,3-ethylenedioxybicyclo[5.4.0]undecan-6-one (34).** The ketone **33** (8.0 mmol, 2.02 g) was dissolved in 2-propanol (40 mL) and sodium hydride (0.5 g) was slowly added. The contents was stirred for 2 h and water (100 mL) was added. The aqueous solution was extracted with hexane (3 × 50 mL) and the combined organics were washed with water (50 mL), dried ($MgSO_4$), and evaporated in vacuo to afford 1.98 g (98%) of trans ketone **34:** TLC (3, 0.28); mass spectrum *m/e* 252 (M^+, calcd for $C_{15}H_{24}O_3$ 252.173, found 252.170, 100); IR (neat) 5.9 μ (C=O); ^1H NMR δ 1.05 s (6 H), 1.1–2.0 m (12 H), 2.0 d, *J* = 12 Hz (1 H), 3.15 d, *J* = 12 Hz (1 H).

(1β,7β)-4,4-Dimethyl-6β-hydroxybicyclo[5.4.0]undecan-3-one (35). The alcohol **28** (12.0 mmol, 3.05 g) was stirred in THF (50 mL) and 3.5% $HClO_4$ (30 mL) for 3 h at room temperature. $NaHCO_3$ (10%, 50 mL) was added and the solution was extracted with hexane (2 × 50 mL). The combined organics were washed with saturated NaCl (50 mL), dried ($MgSO_4$), and evaporated in vacuo to afford 2.5 g (99%) of keto alcohol **35:** TLC (2, 0.33); mass spectrum *m/e* 210 (M^+, calcd for $C_{13}H_{22}O_2$ 210.162, found 210.161, 2), 192 (5), 85 (70), 83 (100); IR (neat) 2.95 (OH), 5.88 μ (C=O); ^1H NMR δ 1.05 s (3 H), 1.1 s (3 H), 1.2–2.85 m (15 H), 3.85 m (1 H); ^{13}C NMR 223 (C=O), 67.5 (CH), 47.7, 47.3, 45.1, 44.7, 35.1, 29.5, 28.6, 27.7, 25.7, 24.9, 21.8 ppm.

(1β,7β)-6β-Benzenesulfonoxy-4,4-dimethylbicyclo[5.4.0]undecan-3-one (16). The alcohol **35** (11.6 mmol, 2.45 g) and benzenesulfonyl chloride (25.0 mmol, 3.2 mL) were stirred in pyridine (25 mL) for 16 h.[39] Ether (200 mL) was added and the solution was washed with *cold* 5% HCl (2 × 50 mL) and saturated NaCl (50 mL). The ether was dried ($MgSO_4$) and evaporated in vacuo. Recrystallization of the crude solid from methylene chloride (10 mL) and hexane (70 mL) gave 3.5 g (86%) of crystalline benzenesulfonate **16:** TLC (4, 0.50); mp 68–69 °C; mass spectrum *m/e* 350 (M^+, calcd for $C_{19}H_{26}O_4S$ 350.155, found 350.153, 5), 192 (90), 111 (100); IR (KBr) 5.87 (C=O), 7.4 (S=O), 8.45 μ (SO); ^1H NMR δ 1.05 (3 H), 1.1 s (3 H), 1.1–2.5 m (13 H), 2.6 dd, *J* = 11, 3 Hz (1 H), 4.75 m (1 H), 7.6 m (3 H), 7.9 m (2 H).

(1β,7β)-4,4-Dimethyl-3,3-ethylenedioxy-6α-hydroxybicyclo[5.4.0]undecane (30). The ketone **33** (8.0 mmol, 2.02 g) was dissolved in THF (50 mL) and cooled to −78 °C. L-Selectride[20] (16.0 mmol, 16 mL of 1 M solution) was added over 5 min and the reaction mixture was stirred for 0.5 h. The solution was then warmed to 0 °C and 10% NaOH (6.4 mL) and 30% H_2O_2 (6.4 mL) were carefully added. The contents was then heated at 50 °C for 0.5 h. Water (100 mL) was added and the solution was extracted with hexane (2 × 75 mL). The hexane was washed with saturated NaCl (25 mL), dried ($MgSO_4$), and evaporated in vacuo, leaving 2.0 g (99%) of alcohol **30:** TLC (20% ether/chloroform) showed only a trace of **28. 30:** TLC (5, 0.40); mp 63–64 °C; mass spectrum *m/e* 254 (M^+, calcd for $C_{15}H_{26}O_3$ 254.188, found 254.191, 15), 158 (100); IR 3.0 μ (OH); ^1H NMR δ 1.0 s (3 H), 1.05 s (3 H), 1.1–2.3 m (15 H), 3.85–4.0 m (5 H).

(1β,7β)-6α-Benzenesulfonoxy-4,4-dimethyl-3,3-ethylenedioxybicyclo[5.4.0]undecane (36). The alcohol **30** (8.0 mmol, 2.03 g), benzenesulfonyl chloride (16.0 mmol, 2.82 g), and 4-dimethylaminopyridine[21] (20 mg) were stirred in pyridine[39] (25 mL) for 24 h. Ether (200 mL) was added and the solution was washed with cold 5% HCl (2 × 50 mL) and saturated NaCl (25 mL). The ether was dried ($MgSO_4$) and evaporated in vacuo. Plug filtration through silica gel (methylene chloride) afforded 2.74 g (87%) of **36.** This material was routinely carried on to **17** without first removing the excess benzenesulfonyl chloride. **36:** TLC (3, 0.33); mass spectrum *m/e* 394 (M^+, calcd for $C_{21}H_{30}O_5S$ 394.181, found 394.178, <1); IR (neat) 7.5 (S=O), 8.5 μ (SO); ^1H NMR δ 0.68 s (3 H), 0.95 s (3 H), 1.05–2.35 m (14 H), 3.82 bs (4 H), 4.90 dm, *J* = 10 Hz (1 H), 7.55 m (3 H), 7.90 m (2 H).

(1β,7β)-6α-Benzenesulfonoxy-4,4-dimethylbicyclo[5.4.0]undecan-3-one (17). The crude benzenesulfonate **36** (7.0 mmol, 2.74 g) was stirred in THF (50 mL) and 3.5% $HClO_4$ (30 mL) for 6 h at room temperature. $NaHCO_3$ (10% 50 mL) was added and the solution was extracted with ether (3 × 50 mL). The ether was washed with saturated NaCl (25 mL), dried ($MgSO_4$), and evaporated in vacuo. The crude solid was recrystallized from hexane to afford 2.33 g (95%) of crystalline **17:** TLC (3, 0.36); mp 127–128 °C; mass spectrum *m/e* 350 (M^+, calcd for $C_{19}H_{26}O_4S$ 350.155, found 350.154, <1), 192 (20), 77 (100); IR (KBr) 5.88 (C=O), 7.4 (S=O), 8.4 μ (SO); ^1H

NMR δ 0.85 s (3 H), 1.0 s (3 H), 1.0–2.0 m (12 H), 2.3 dd, J = 12, 15 Hz (1 H), 3.1 t, J = 12 Hz (1 H), 4.30 dd, J = 11, 3.5 Hz (1 H), 7.6 m (3 H), 7.9 m (2 H).

(1β,7α)-4,4-Dimethyl-3,3-ethylenedioxy-6β-hydroxybicyclo[5.4.0]undecane (37) and (1β,7α)-4,4-Dimethyl-3,3-ethylenedioxy-6α-hydroxybicyclo[5.4.0]undecane (38). A. The trans ketone **34** (3.0 mmol, 747 mg) dissolved in ether (20 mL) was added at 0 °C to a suspension of $LiAlH_4$ (2.6 mmol, 100 mg) in ether (25 mL). The contents was stirred for 15 min and then water (0.10 mL), 10% NaOH (0.10 mL), and water (0.3 mL) were added. The solution was stirred for 0.5 h and filtered. The ether was washed with water (10 mL), dried ($MgSO_4$), and removed in vacuo. The residue was chromatographed on silica gel (20% ether/chloroform) to afford 434 mg of **37** (57%) and 197 mg of **38** (27%). **37:** TLC (5, 0.57); mp 73–74 °C; mass spectrum m/e 254 (M^+, calcd for $C_{15}H_{26}O_3$ 254.188, found 254.188, 100); IR (KBr) 2.85 μ (OH); ^1H NMR δ 1.0 s (6 H), 1.1–2.2 m (14 H), 3.7 m (2 H), 3.9 m (4 H). **38:** TLC (5, 0.45); mp 74–75 °C; mass spectrum m/e 254 (M^+, calcd for $C_{15}H_{26}O_3$ 254.188, found 254.189, 100); IR (neat) 3.0 μ (OH); ^1H NMR δ 0.95 s (3 H), 1.0 s (3 H), 1.0–2.2 m (15 H), 3.5 (1 H), 3.7–3.9 m (4 H).

B. The trans ketone **34** (3.74 mmol, 945 mg) was dissolved in THF (25 mL) and cooled to −78 °C. L-Selectride (7.5 mmol) was added and the contents stirred for 0.5 h. The solution was warmed to 0 °C and 10% NaOH (3.2 mL) and 30% H_2O_2 (3.2 mL) were cautiously added. The solution was then heated at 50 °C for 0.5 h and water was added (50 mL). The solution was extracted with hexane (2 × 50 mL) and evaporated in vacuo, leaving 925 mg (98%) of alcohol **37**, TLC shows only a trace of **38**.

(1β,7α)-4,4-Dimethyl-6β-hydroxybicyclo[5.4.0]undecan-3-one (39). The ketal alcohol **31** (3.0 mmol, 760 mg) was stirred in THF (25 mL) and 3.5% $HClO_4$ (15 mL) at room temperature for 0.5 h. $NaHCO_3$ (10% 25 mL) was added and the solution was extracted with hexane (2 × 25 mL). The combined hexane layers were washed with saturated NaCl (25 mL), dried ($MgSO_4$), and evaporated in vacuo, leaving 596 mg (95%) of keto alcohol **39:** TLC (5, 0.36); mp 94–95 °C; mass spectrum m/e 210 (M^+, calcd for $C_{13}H_{22}O_2$ 210.162, found 210.159); IR (KBr) 2.65 (OH), 5.85 μ (C=O); ^1H NMR δ 1.1 s (3 H), 1.2 s (3 H), 1.2–2.7 m (15 H), 3.9 m (1 H).

(1β,7α)-6β-Benzenesulfonoxy-4,4-dimethylbicyclo[5.4.0]undecan-3-one (18). The alcohol **39** (2.88 mmol, 603 mg), benzenesulfonyl chloride, DMAP (50 mg), and pyridine (10 mL) were stirred for 36 h at room temperature. Ether was added (150 mL) and the solution was washed with 10% HCl (2 × 25 mL) and water (25 mL) and dried ($MgSO_4$). The solvent was removed in vacuo and the residue was plug filtered through silica gel (CH_2Cl_2 followed by ether) to remove excess benzenesulfonyl chloride. Evaporation in vacuo of the ether afforded 950 mg 94% of solid **18:** TLC (5, 0.71); mp 133–134 °C; mass spectrum m/e 350 (M^+, calcd for $C_{19}H_{26}O_4S$ 350.155, found 350.153, 5), 192 (80), 77 (100); IR (KBr) 5.85 μ (C=O); ^1H NMR δ 1.05 s (6 H), 1.1–2.6 m (14 H), 4.80 dd, J = 8.5, 3 Hz (1 H), 7.6 (3 H), 7.90 m (2 H).

(1β,7α)-6α-Benzenesulfonoxy-4,4-dimethyl-3,3-ethylenedioxybicyclo[5.4.0]undecane (40). The alcohol **38** (0.675 mmol, 172 mg), benzenesulfonyl chloride (1.50 mmol, 0.195 mL), and pyridine (5 mL) were stirred at room temperature for 24 h. Ether (75 mL) was added and the solution was washed with 10% HCl (2 × 15 mL) and water (15 mL) and dried ($MgSO_4$). The ether was removed in vacuo. The residue was plug filtered through silica gel (methylene chloride/hexane, 1:1) to remove excess benzenesulfonyl chloride and the solvent was evaporated in vacuo, leaving 200 mg (85%) of ketal benzenesulfonate **40.** Alternatively the crude material was hydrolyzed directly to the ketone without removing the excess benzenesulfonyl chloride. **40:** TLC (3, 0.54); ^1H NMR δ 0.75 s (3 H), 0.90 s (3 H), 0.9–2.1 m (14 H), 3.8 m (4 H), 4.6 m (1 H), 7.5 m (3 H), 7.9 m (2 H).

(1β,7α)-6α-Benzenesulfonoxy-4,4-dimethylbicyclo[5.4.0]undecan-3-one (19). Ketal **40** (1.0 mmol, 394 mg) was stirred in THF (10 mL) and 3.5% $HClO_4$ (6 mL) for 6 h. $NaHCO_3$ (10%, 25 mL) was added and the solution was extracted with ether (2 × 50 mL). The ether was washed with water (25 mL), dried ($MgSO_4$), and evaporated in vacuo, leaving 333 mg (95%) of ketone **19:** TLC (5, 0.45); mp 90–92 °C; mass spectrum m/e 350 (M^+, calcd for $C_{19}H_{26}S_4$ 350.155, found 350.158, <1), 192 (15), 77 (100); IR (neat) 5.85 (C=O), 7.5 (S=O), 8.5 μ (SO); ^1H NMR δ 1.0 s (3 H), 1.05 s (3 H), 1.1–2.4 m (13 H), 2.8 t, J = 10 Hz (1 H), 4.15 td, J = 9.5, 2 Hz (1 H), 7.6 m (3 H), 7.85 m (2 H).

(1β,2α,6α,7β)-4,4-Dimethyltricyclo[5.4.0.0^{2,6}]undecan-3-one (44). A. The keto benzenesulfonate **16** (0.50 mmol, 175 mg) was dissolved in THF (5 mL) and cooled to −78 °C. LDA (1.5 equiv) was added and the solution was stirred at −78 °C for 15 min and then at room temperature for 4 h. Hexane (75 mL) was added and the solution was washed with 10% HCl (10 mL). The hexane was dried ($MgSO_4$) and removed in vacuo to afford 86 mg (89%) of tricyclic ketone **44:** TLC (2, 0.46); mass spectrum m/e 192 (M^+, calcd for $C_{13}H_{20}O$ 192.151, found 192.148, 35), 95 (100); IR (neat) 5.80 μ (C=O); ^1H NMR δ 0.95 s (3 H), 1.15 s (3 H), 1.1–2.1 m (11 H), 2.05 dd (1 H, J = 7, 15 Hz), 2.5 m (1 H), 2.9 t (1 H, J = 7 Hz); ^{13}C NMR 232 (C=O), 49.8 (C), 48.1, 42.0, 37.6, 36.3, 35.0, 29.0, 26.9, 25.8, 24.1, 24.0, 22.7, 21.9 ppm.

B. Chromium trioxide[17] (1.75 mmol, 175 mg) was added to pyridine (3.5 mmol, 278 mg) dissolved in methylene chloride (10 mL) and the solution was stirred for 15 min. The alcohol mixture **64a,b** (0.29 mmol, 56.5 mg) dissolved in methylene chloride (5 mL) was added and the solution was stirred for 0.5 h. Ether (50 mL) was added and the solution was filtered. The black precipitate was washed with ether (50 mL) and the combined organics were washed with 10% NaOH (3 × 20 mL), 10% HCl (2 × 20 mL), and saturated NaCl (20 mL). The ether was dried ($MgSO_4$) and evaporated in vacuo, leaving 50 mg (90%) of ketone **44.**

(1β,2α,6α,7β)-4,4-Dimethyl-3-hydroxytricyclo[5.4.0.0^{2,6}]undecane (64a,b). The keto benzenesulfonate **16** (1.0 mmol, 350 mg) was dissolved in THF (10 mL) and cooled to −78 °C. LDA (1.5 mmol) was added and the solution was stirred for 15 min. DIBAL (3.0 mmol) was added and the solution was stirred for 3 h at room temperature. Ether (25 mL) was added and then were added successively water (0.3 mL), 10% NaOH (0.3 mL), and water (0.9 mL). The solution was stirred for 0.5 h and filtered. The aluminum salts were washed with water (25 mL), dried ($MgSO_4$), and evaporated in vacuo, leaving 165 mg (86%) of a mixture of **64a,b** (~20:1): TLC (major 3, 0.39; minor 3, 0.25); mp 37–39 °C; mass spectrum m/e 194 (M^+, calcd for $C_{13}H_{22}O$ 194.167, found 194.168, 10), 93 (100); IR (neat) 2.85 μ (OH); ^1H NMR δ 0.80 s (3 H), 1.05 s (3 H), 1.2–2.8 m (15 H), 3.6 d, J = 6 Hz (1 H); ^{13}C NMR 80.7 (CH), 47.8, 47.6, 44.1, 41.7, 37.1, 27.9, 22.7, 21.8 ppm.

(*E*,*Z*)-11,11-Dimethylcycloundeca-2,8-dienol (60). A. The ketone **17** (1.0 mmol, 350 mg) was dissolved in THF (10 mL) and cooled to −78 °C. LDA (1.5 mmol) was added and the solution was stirred for 15 min. DIBAL (3.0 mmol) was added and the solution was stirred at room temperature for 2 h. Ether (25 mL) was added followed by sequential addition of water (0.3 mL), 10% NaOH (0.3 mL), and water (0.9 mL). The solution was stirred for 0.5 h and filtered. The aluminum salts were rinsed with ether (100 mL) and the combined ether was washed with saturated NaCl (25 mL), dried ($MgSO_4$), and removed in vacuo. The residue was passed through silica gel (5% THF/hexane) to afford 181 mg (93%) of allylic alcohol **60:** TLC (1, 0.25); mp 37–39 °C; mass spectrum m/e 194 (M^+, calcd for $C_{13}H_{22}O$ 194.167, found 194.168, 30), 95 (100); IR (neat) 2.9 (OH), 10.3 (C=C), 14.3 μ (C=C); ^1H NMR δ 1.0 s (3 H), 1.05 s (3 H), 1.4–2.3 m (11 H), 3.65 d, J = 7 Hz (1 H), 5.1–6.0 m (4 H); ^{13}C NMR 135.4 (CH), 130.6 (CH), 128.5 (CH), 126.3 (CH), 82.1 (CH), 38.4, 37.1, 30.5, 29.3, 26.3, 25.4, 21.5 ppm.

Dimer **51** obtained without the use of DIBAL had the following properties: TLC (3, 0.25); mass spectrum m/e 384 (M^+, calcd for $C_{26}H_{40}O_2$ 384.302, found 384.303); IR (neat) 5.85 μ (C=O); ^1H NMR δ 1.05 s (3 H), 1.15 s (6 H), 1.25 s (3 H), 1.2–2.4 m (23 H), 2.55 dd (1 H, J = 9, 14 Hz), 3.4 d (1 H, J = 6 Hz), 4.2 m (1 H), 5.2–5.6 m (2 H).

Dihydro Dimer 52. The dimer **51** (10 mg) was placed in a Paar hydrogenation bottle along with acetic acid (10 mL) and 10% Pd/C (100 mg). The solution was hydrogenated at 3–4 atm for 1 h. The solution was filtered, hexane (30 mL) was added, and the acetic acid was neutralized with solid $NaHCO_3$. The hexane was washed with water (2 × 25 mL), dried ($MgSO_4$), and removed in vacuo, leaving 10 mg of dihydro dimer **52:** TLC (3, 0.32); mass spectrum m/e 386 (M^+, calcd for $C_{26}H_{42}O_2$ 386.318, found 386.320).

(*E*,*Z*)-11,11-Dimethylcycloundeca-2,8-dienone (49). The alcohol (0.44 mmol, 86 mg), manganese dioxide (1 g), and methylene chloride (15 mL) were heated to reflux for 18 h. The solution was filtered and the solvent was removed in vacuo, leaving 84 mg (99%) of enone **49:** TLC (3, 0.52); mp 45–47 °C; mass spectrum m/e 192 (M^+, calcd for $C_{13}H_{20}O$ 192.151, found 192.151); IR (neat) 5.9 (C=O), 6.1 μ (C=C); ^1H NMR δ 1.2 s (6 H), 1.5–2.5 m (10 H), 5.4 m (2 H), 6.4 dt (1 H, J = 16, 6 Hz), 6.7 d (1 H, J = 16 Hz); ^{13}C NMR 186.5 (C=O), 145.7 (CH), 132.5 (CH), 128.2 (CH), 125.3 (CH), 46.8, 37.7, 31.0, 29.2, 24.6, 23.4 ppm.

(1β,2α,6α,7α)-4,4-Dimethyltricyclo[5.4.0.0^{2,6}]undecan-3-one (54). The keto benzenesulfonate **18** (1.0 mmol, 350 mg) dissolved in THF (10 mL) was cooled to −78 °C and LDA (1.5 mmol) was added. The solution was stirred for 15 min and then warmed to room temperature and stirred for 2.5 h. Ether (75 mL) was added and the solution was washed with 10% HCl (10 mL) and water (10 mL) and dried ($MgSO_4$). The ether was evaporated in vacuo, leaving 178 mg of ketone **54:** TLC (1, 0.60); mass spectrum *m/e* 192 (M^+, calcd for $C_{13}H_{20}O$ 192.151, found 192.148); ^1H NMR δ 0.95 s (3 H), 1.15 s (3 H), 1.2–2.2 m (12 H), 2.75–2.95 m (2 H).

B. Chromium trioxide (3.0 mmol, 300 mg) was added to a solution of pyridine (5.95 mmol, 470 mg) in methylene chloride (10 mL). The solution was stirred for 15 min and the alcohol mixture **65a,b** (0.495 mmol, 96 mg) dissolved in methylene chloride (5 mL) was added. The solution was stirred for 2 h and ether (50 mL) was added. The solution was filtered and the black precipitate was washed with ether (50 mL). The combined organic layers were washed with 10% NaOH (3 × 20 mL), 10% HCl (20 mL), and saturated NaCl (20 mL). The ether was dried ($MgSO_4$) and evaporated in vacuo to afford 85 mg (89%) of ketone **54.**

(1β,2α,6α,7α)-4,4-Dimethyl-3-hydroxytricyclo[5.4.0.0^{2,6}]undecane (65a,b). The ketone **18** was dissolved in THF (10 mL) and cooled to −78 °C. LDA (1.5 mmol) was added and the solution was stirred for 15 min. DIBAL (3.0 mmol) was added and the reaction mixture was stirred for 6 h at room temperature. Ether (25 mL) was added and water (0.3 mL), 10% NaOH (0.3 mL), and water (0.9 mL) were successively added. The solution was stirred for 0.5 h and then filtered. The aluminum salts were washed with ether (50 mL) and the combined ether was washed with saturated NaCl (20 mL), dried ($MgSO_4$), and removed in vacuo. The residue was passed through silica gel (10% THF/hexane) to afford 134 mg (70%) of a mixture of alcohols **65a,b** (~5:1): TLC (major 1, 0.23; minor 1, 0.114); IR (neat) 2.9 μ (OH); ^1H NMR δ 0.85 s (3 H), 1.1 s (3 H), 1.1–2.2 m (13 H), 2.4–2.9 m (2 H), 3.7 m (1 H).

(*E,E*)-11,11-Dimethylcycloundeca-2,8-dienol (61). The keto benzenesulfonate **19** (0.82 mmol, 288 mg) was dissolved in THF (10 mL) and cooled to −78 °C. LDA (1.2 mmol) was added and the contents stirred for 15 min. DIBAL (2.5 mmol) was added and the solution was stirred at room temperature for 2 h. Ether (25 mL) was added and water (0.25 mL), 10% NaOH (0.25 mL), and water (0.75 mL) were successively added. The solution was stirred for 0.5 h and filtered, and the aluminum salts were rinsed with ether (50 mL). The combined ether was washed with saturated NaCl (10 mL), dried ($MgSO_4$), and evaporated in vacuo. The residue was passed through silica gel (methylene chloride) to afford 145 mg (91%) of alcohol **61:** TLC (3, 0.3); mass spectrum *m/e* 194 (M^+, calcd for $C_{13}H_{22}O$ 194.167, found 194.169); IR (neat) 2.85 (OH), 10.3 μ (C=C); ^1H NMR δ 1.0 s (3 H), 1.05 s (3 H), 1.3–2.4 m (10 H), 3.95 d (1 H, *J* = 7 Hz), 5.2–5.8 m (2 H); ^{13}C NMR 135.0, 132.1, 128.8, 81.2, 44.3, 37.3, 33.1, 33.0, 29.3, 29.1, 28.7, 27.8, 21.5 ppm.

Reaction without DIBAL produced dimer **58:** TLC (3, 0.24); mass spectrum *m/e* 384 (M^+, calcd for $C_{26}H_{40}O_2$ 384.303, found 384.302); IR (neat) 5.9 μ (C = O); ^1H NMR δ 0.95 s (3 H), 1.1 s (6 H), 1.1–2.4 m (23 H), 2.6 dd (1 H, *J* = 10, 12 Hz), 3.15 d (1 H, *J* = 7 Hz), 3.75 bd (1 H, *J* = 8 Hz), 5.1–5.6 m (2 H).

Hydrogenation of this material using the same conditions as for **51** gave dihydro dimer **59:** TLC (3, 0.29); mass spectrum *m/e* 386 (M^+, calcd for $C_{26}H_{42}O_2$ 386.318, found 386.319).

(*E,E*)-11,11-Dimethylcycloundeca-2,8-dienone (43). The alcohol **61** (0.34 mmol, 66 mg) and MnO_2 were heated to reflux in methylene chloride (15 mL) for 12 h. The solution was filtered and the solvent evaporated in vacuo to afford 60 mg (92%) of enone **43:** TLC (3, 0.51); mass spectrum *m/e* 192 (M^+, calcd for $C_{13}H_{20}O$ 192.151, found 192.149); IR (neat) 5.98 (C=O), 6.2 (C=C), 10.3 μ (C=C); ^1H NMR δ 1.2 s (6 H), 1.4–2.3 m (10 H), 5.1–5.6 m (2 H), 6.2–6.5 m (2 H).

2,2-Dimethylcycloundecanone (63). Cycloundecanone (**62**, 4.0 mmol, 670 mg) was dissolved in THF (20 mL) and cooled to −78 °C. LDA (5.0 mmol) was added and the solution was stirred for 15 min. Methyl iodide (5.0 mmol, 0.31 mL) was added and the solution was stirred at room temperature for 2 h. Hexane (75 mL) was added and the solution was washed with 10% HCl (20 mL) and saturated NaCl (20 mL), dried ($MgSO_4$), and removed in vacuo. The residue was passed through silica gel (methylene chloride) to afford 661 mg (91%) of 2-methylcycloundecanone: TLC (3, 0.54); ^1H NMR δ 1.1 d (3 H), 1.1–3.0 (19 H).

2-Methylcycloundecanone (3.0 mmol, 546 mg), chlorotrimethylsilane (4.0 mmol, 0.375 mL), and triethylamine (8.0 mmol, 1.1 mL) were heated to reflux in DMF (10 mL) for 4 days. The solution was cooled and hexane (75 mL) was added. The hexane was washed quickly with *cold* 5% HCl (10 mL), 10% $NaHCO_3$ (10 mL), 5% HCl (10 mL), 10% $NaHCO_3$ (10 mL), and saturated NaCl (10 mL). The solvent was dried ($MgSO_4$) and evaporated in vacuo. The residue was a mixture of the trisubstituted olefin (3% THF/hexane, R_f 0.65), tetrasubstituted olefin (3% THF/hexane, R_f 0.57), and unreacted starting material. A small sample of the tetrasubstituted olefin was isolated by column chromatography: ^1H NMR δ 0.15 s (9 H), 1.1–1.6 m (14 H), 1.5 s (3 H), 2.0–2.4 m (4 H).

The tetrasubstituted silyl enol ether (50 mg) was dissolved in THF (10 mL) and cooled to 0 °C. Excess methyllithium was added (bpy, red) and the solution was stirred for 2 h at room temperature. TLC still showed 50% of silyl enol ether remaining. Methyl iodide (0.1 mL) was added and the solution was stirred for 2 h. Hexane (50 mL) was added and the solution was washed with water (10 mL), dried ($MgSO_4$), and evaporated in vacuo. The residue was chromatographed on silica gel (3% THF/hexane) to yield unreacted silyl enol ether and 25 mg of **63:** TLC (3, 0.63); mass spectrum *m/e* 196 (M^+, calcd for $C_{13}H_{24}O$ 196.182, found 196.185); IR (neat) 5.88 μ (C=O); ^1H NMR δ 1.05 s (6 H), 1.2–1.9 m (16 H), 3.55 m (2 H).

Hydrogenation of enones **49** and **43** with 10% Pd/C in acetic acid using the conditions described for dimers **51** and **58** gave quantitative yields of **63.** Comparison by NMR, IR, TLC, and GC (2% SE-30 on Chromosorb P) of these samples with the authentic sample showed them to be identical.

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References and Notes

(1) Graduate Research Associate. David Ross Fellow (1975–1977), Phillips Petroleum Fellow (1977–1978); for additional discussion and experimental data see Ph.D. Thesis, Purdue University, 1978.
(2) Alfred P. Sloan Fellow, 1977–1979.
(3) For a review on the cytochalasin family, see M. Binder and C. Tamm, *Angew. Chem., Int. Ed. Engl.*, **12**, 370 (1973).
(4) For other synthetic studies in the cytochalasin area see (a) J. Auerbach and S. M. Weinreb, *J. Org. Chem.*, **40**, 3311 (1975); (b) G. E. Stork, 5th Annual Lehrmakers Symposium, Wesleyan University, Middletown, Conn., May 5, 1977; (c) R. Brettle and D. P. Cummings, *J. Chem. Soc., Perkin Trans. 1*, 2385 (1977); (d) S. Masamune, Y. Hayase, W. Schilling, W. K. Chan, and G. S. Bates, *J. Am. Chem. Soc.*, **99**, 6756 (1977); (e) E. Vedejs and R. C. Gadwood, *J. Org. Chem.*, **43**, 376 (1978); (f) S. J. Bailey, E. J. Thomas, W. B. Turner, and J. A. J. Jarvis, *J. Chem. Soc., Chem. Commun.*, 474 (1978); (g) T. Schmidlin and Ch. Tamm, *Helv. Chim. Acta*, **61**, 2096 (1978); (h) G. Stork, Y. Nakahara, Y. Nakahara, and W. J. Greenlee, *J. Am. Chem. Soc.*, **100**, 7775 (1978).
(5) For general reviews of fragmentation reactions see (a) C. A. Grob and P. W. Schiess, *Angew. Chem., Int. Ed. Engl.*, **6**, 1 (1967); (b) C. A. Grob, *ibid.*, **8**, 535 (1969); (c) J. A. Marshall, *Synthesis*, 229 (1971).
(6) Boronate fragmentations: (a) J. A. Marshall and G. L. Bundy, *J. Chem. Soc. D*, 855 (1967); (b) M. Mitashita, T. Yanami, and A. Yoshikoshi, *J. Chem. Soc., Chem. Commun.*, 846 (1972); see also ref 5c.
(7) Organozinc fragmentations: P. S. Wharton, Y. Sumi, and R. A. Kretchmer, *J. Org. Chem.*, **30**, 234 (1965); see also C. A. Grob and W. Baumann, *Helv. Chim. Acta*, **38**, 594 (1955); J. H. Babler and A. E. Moormann, *J. Org. Chem.*, **41**, 1477 (1976).
(8) An intraannular fragmentation in which a nitrogen lone pair served as the assisting orbital affords the product which appears to be a result of peripheral, rather than central, bond cleavage: C. A. Grob, H. R. Kiefer, H. Lutz, and H. Wilkens, *Tetrahedron Lett.*, 2901 (1964). Marshall and Babler have demonstrated, however, that the product arose via internal cleavage followed by a facile aza-Cope arrangement [J. A. Marshall and J. H. Babler, *J. Org. Chem.*, **34**, 4186 (1969)].
(9) Stereochemical control has been particularly well documented in the case of the extraannular fragmentation reactions of bridgehead hydroxy tosylates: (a) P. S. Wharton, *J. Org. Chem.*, **26**, 4781 (1961); (b) E. J. Corey, R. B. Mitra, and H. Uda, *J. Am. Chem. Soc.*, **85**, 362 (1963); (c) H. H. Weston, *Helv. Chim. Acta*, **47**, 575 (1964); (d) M. Tanabe and D. F. Crowe, *Tetrahedron Lett.*, 2955 (1964); (e) P. S. Wharton and G. A. Hiegel, *J. Org. Chem.*, **30**, 3254 (1965); (f) C. H. Heathcock and R. A. Badger, *ibid.*, **37**, 234 (1972).
(10) (a) P. C. Mukharji and T. K. Das Gupta, *Tetrahedron*, **25**, 5275 (1969); (b) P. C. Mukharji, T. K. Das Gupta, and D. P. Ghosh, *Tetrahedron Lett.*, 2309 (1970).
(11) C. H. Heathcock and D. Gray, *Tetrahedron*, **27**, 1239 (1971).
(12) The cyclization of **9b** to **11b** is the key step in the synthesis of copaene and ylangene: C. H. Heathcock, R. A. Badger, and J. W. Patterson, Jr., *J. Am. Chem. Soc.*, **89**, 4133 (1967).
(13) C. H. Heathcock, personal communication.
(14) J. M. Brown, T. M. Cresp, and L. N. Mander, *J. Org. Chem.*, **42**, 3984 (1977).
(15) The *gem*-dimethyl moiety is used as a surrogate for the quaternary spiro

linkage at C-9 in the real substrate (**3**).
(16) (a) G. A. Berchtold and G. F. Uhlig, *J. Org. Chem.*, **28,** 1459 (1963); (b) K. C. Brannock, R. D. Burpitt, and J. G. Thweatt, *ibid.*, **28,** 1462 (1963); (c) C. F. Huebner, L. Dorfmann, M. M. Robinson, E. Donoghue, W. G. Pierson, and P. Strachan, *ibid.*, **28,** 3134 (1963); (d) K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *ibid.*, **29,** 818 (1964).
(17) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35,** 4000 (1970).
(18) The trans-fused symmetrical ketone analogous to **32** has a C-2 axis. Therefore, the methyl groups are equivalent and the trans ketone would only exhibit seven signals. The cis-fused diketone **32,** on the other hand, has no C-2 axis and thus the methyl groups are diastereotopic.
(19) The methyl peaks of **32** also overlapped in the ^{1}H NMR. The Eu(fod)$_3$ spectrum shifted them from δ 1.0 to two singlets at δ 3.0 and 3.05.
(20) H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, **94,** 7159 (1972).
(21) G. Hofle and W. Steglich, *Synthesis*, 619 (1972), and references cited therein.
(22) N. S. Bhacca, J. E. Gurst, and D. H. Williams, *J. Am. Chem. Soc.*, **87,** 302 (1965).
(23) If one assumes that isomers **17** and **19** are "normal", then the characteristic shift for H_a in $CDCl_3$ should be $(4.30 + 4.15)/2 \simeq \delta$ 4.22. The deshielding caused by the carbonyl group is therefore $\delta \sim 0.53$ for isomer **16** and $\delta \sim 0.58$ for isomer **18.** In C_6D_6 the "normal" position for H_a is at $(4.45 + 4.85)/2 \simeq \delta$ 4.65. The deshielding for isomer **16** is therefore $\delta \sim 0.4$ and 0.2 for isomer **18.** The positive solvent shift is thereby seen, in that the deshielding of H_a caused by the carbonyl group is less in C_6D_6 than in $CDCl_3$ for each isomer. The gross C_6D_6 deshielding of all isomers is probably a consequence of the polar benzenesulfonate substituent. See D. H. Williams and N. S. Bhacca, *Tetrahedron*, **21,** 2021 (1965)) for an extended discussion of benzene solvent shifts with carbonyl compounds.
(24) Dienone **49** could be isolated from several of the **17** → **51** reaction mixtures, but the major component was always dimer **51.**
(25) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Oxford, 1969, p 185.
(26) (a) See ref 25, p 225; (b) H. B. Kagan, Ed., "Determination of Configurations by Spectrometric Methods," Vol. I. Georg Thieme Verlag, Stuttgart, 1977, p 59.
(27) Hoffmann has done a molecular orbital analysis of fragmentation reactions [R. Gleiter, W. D. Stohrer, and R. Hoffmann, *Helv. Chim. Acta*, **55,** 893 (1972)] and finds that, for those cases where the dihedral angle $\phi = 0°$, cyclobutane formation can be preferred. The cases in point (**41**-fold, **53**-fold) have $\phi \simeq 60°$, but the Hoffmann calculations do not give results other than for $\phi \simeq 0, 90, 180°$.
(28) Technical assistance for some of the 360-MHz NMR experiments by R. E. Santini, J. Dallas, and N. Nowicki is greatly appreciated.
(29) International Flavors and Fragrances, sold as *trans*-decahydro-β-naphthol.
(30) W. G. Dauben, R. C. Tweit, and C. Mannerskantz, *J. Am. Chem. Soc.*, **76,** 4420 (1954).
(31) H. C. Brown, C. P. Garg, and K. T. Liu, *J. Org. Chem.*, **36,** 387 (1971).
(32) A. Kandiah, *J. Chem. Soc.*, 922 (1931).
(33) (a) K. Taguchi and F. H. Westheimer, *J. Org. Chem.*, **36,** 1571 (1971); (b) H. Weingarten and W. A. White, *ibid.*, **32,** 213 (1967); (c) I. Moretti and G. Torre, *Synthesis*, 141 (1970).
(34) (a) H. Weingarten and W. A. White, *J. Org. Chem.*, **32,** 213 (1967); (b) I. Moretti and G. Torre, *Synthesis*, 141 (1970).
(35) (a) A. K. Bose, G. Mina, M. S. Manhas, and E. Rzucidlo, *Tetrahedron Lett.*, 1467 (1963); (b) K. L. Brannock, R. D. Burpitt, U. W. Goodlett, and J. G. Thweatt, *J. Org. Chem.*, **29,** 818 (1964); (c) C. F. Huebner, L. Dorfman, M. M. Robison, E. Donoghue, W. G. Pierson, and P. Strachan, *ibid.*, **28,** 3134 (1963); (d) J. A. Hirsch and F. J. Cross, *ibid.*, **36,** 955 (1971); (e) A. J. Birch and E. G. Hutchinson, *J. Chem. Soc. C*, 3671 (1971); (f) E. Yoshi and S. Kimoto, *Chem. Pharm. Bull.*, **17,** 629 (1969); (g) G. A. Berchtold and G. F. Uhlig, *J. Org. Chem.*, **28,** 1459 (1963); (h) D. W. Boerth and F. A. Van-Catledge, *ibid.*, **40,** 3319 (1975).
(36) R. Mozing, "Organic Syntheses", Collect. Vol. III, Wiley, New York, 1955, p 181.
(37) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87,** 1345, 1353 (1965).
(38) (a) H. C. Brown, "Organic Synthesis via Boranes", Wiley-Interscience, New York, 1975; (b) H. C. Brown, A. K. Mandal, and S. U. Kulkarni, *J. Org. Chem.*, **42,** 1392 (1977); (c) H. C. Brown and N. Ravindran, *ibid.*, **42,** 2533 (1977).
(39) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, Wiley, New York, 1967, p 1180.

Mechanism of the Cannizzaro Reaction[1-4]

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Abstract: An ultimate technique for disqualifying compounds suspected of being intermediates is illustrated by the use of isotope dilution to prove that benzyl benzoate is not an intermediate in the Cannizzaro reaction of 0.5 M benzaldehyde-*p*-*t* (tritium labeled) with 0.25 M sodium hydroxide in 74% methanol–26% water at 100 °C. The adduct from hydroxide ion and two molecules of benzaldehyde that was thought to rearrange to benzyl benzoate could alternatively rearrange directly to the products, benzoate ion and benzyl alcohol. However, this mechanism also is disproved because methoxide ion acting instead of hydroxide ion should lead to benzyl methyl ether, but less than 1% is found. Two other mechanisms involving a proton transfer concerted with the hydride transfer are disproved by the k_{D_2O}/k_{H_2O} isotope effect of 1.9. The rate-determining steps can be represented by two hydride transfer reactions to C_6H_5CHO, from the adduct from HO^- + C_6H_5CHO and from the adduct from CH_3O^- + C_6H_5CHO, or, equivalently, by two termolecular reactions, HO^- + $2C_6H_5CHO$ and CH_3O^- + $2C_6H_5CHO$.

The Cannizzaro reaction[6] is the disproportionation of an aldehyde to an equimolar mixture of primary alcohol and carboxylic salt. It is characteristic of aldehydes that have no α hydrogens, and therefore cannot undergo aldol condensation. The reaction is usually brought about in a homogeneous, strongly basic solution or in a heterogeneous system consisting of an organic phase and a strongly basic aqueous phase. A typical example is reaction of benzaldehyde (I) with concentrated sodium hydroxide in hot aqueous methanol to yield benzyl alcohol (II) and sodium benzoate (III). Formaldehyde disproportionates in acid solution also.[7] The Cannizzaro reaction was considered one of the most important synthetic reactions of organic chemistry prior to the discovery of $LiAlH_4$ in 1946, but has now been totally supplanted by metal hydrides for laboratory syntheses.

$$\underset{\text{I}}{2C_6H_5CHO} + NaOH \xrightarrow{CH_3OH} \underset{\text{II}}{C_6H_5CH_2OH} + \underset{\text{III}}{C_6H_5CO_2Na}$$

Benzyl benzoate (VI) was isolated from the reaction of I with NaOH in water or in homogeneous aqueous methanol solution when heating and excess NaOH were avoided.[8] In heavy water (D_2O), the alcohol produced from the reaction of I or formaldehyde contains no carbon-bound D;[9] this excludes all mechanisms involving a hydride transfer from or to oxygen atoms, for example, eq A or B.

The kinetic order with I and several derivatives in water, methanol, aqueous methanol, or aqueous dioxane is third:

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