Tetrahedron Vol. 40, No. 22, pp. 4701 to 4710, 1984
Printed in Great Britain.

0040-4020/84 $3.00+.00

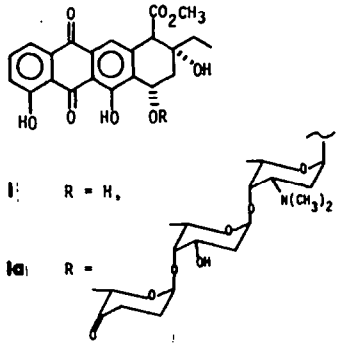
A FACILE TOTAL SYNTHESIS OF RACEMIC AKLAVINONE†

TSUNG-TEE LI,* YU LIN WU‡ and TIMOTHY C. WALSGROVE§
Institute of Organic Chemistry, Syntex Research, Palo Alto, California 94304.

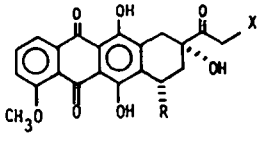
(*Received in USA* 15 *June* 1984)

Abstract—A convergent total synthesis of aklavinone, based on the annelation reaction of cyanophthalide addition to an enone as the key step, was accomplished.

Aclacinomycin A (**1a**)[1] belongs to the anthracyclinone family of antibiotics[2] which, in recent years, have emerged as important anti-cancer agents. The finding that it may possess improved therapeutic indices over adriamycin (**2a**) and daunomycin (**3a**)[3] had aroused much interest among synthetic chemists[4] in searching for an efficient pathway for the preparation of its aglycone, aklavinone (**1**).[5] In the quest for a practical synthesis of adriamycinone (**2**) and daunomycinone (**3**), many laboratories have made significant contributions[6] and a large variety of successful approaches has been adroitly explored. However, at the inception



1 R = H,
1a R =



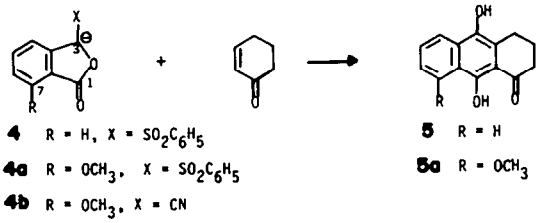
2 X = OH, R = OH
2a X = OH, R = L-daunosamine
3 X = H, R = OH
3a X = H, R = L-daunosamine

of our program,[7] there was not any published method that would lead to the aklavinone skeleton. The absence of a C-11 OH group and the presence of C-10 carbomethoxy group in aklavinone required a novel approach.[8]

RESULTS

A convergent strategy offers obvious advantages, and we settled on a scheme centered on a connective annelation reaction which forms the C-ring while assembling the tetracyclic skeleton. Thus, it was of interest to us to come across the publications of Hauser,[9] Kraus,[10] and van Heusen[11] that demonstrated the use of phthalide anion in a ring-forming reaction resulting in a p-hydroquinone moiety. Of particular relevance was the following example cited by Hauser where phthalide (**4**) reacted with the Michael acceptor cyclohexenone, and the product was the intriguing tricyclic ketone (**5**). The ketonic ring on further oxidation should be convertible into a phenol, the B-ring of aklavinone.

To serve as the aklavinone C-, D-ring precursor, 7-methoxy phthalide derivatives were needed. A four-step preparation of the 3-benzenesulfonyl phthalide (**4a**) was described in Hauser's publication; however, the 3-cyano derivative (**4b**) was not available. We, therefore, designed a synthesis of **4a** and **4b** based on the dialkylamido-directed aromatic ortho lithiation reaction of Snieckus and Beak[12] and reinvestigated the addition of their anions to cyclohexenone. Under the



4 R = H, X = $SO_2C_6H_5$
4a R = OCH_3, X = $SO_2C_6H_5$
4b R = OCH_3, X = CN

5 R = H
5a R = OCH_3

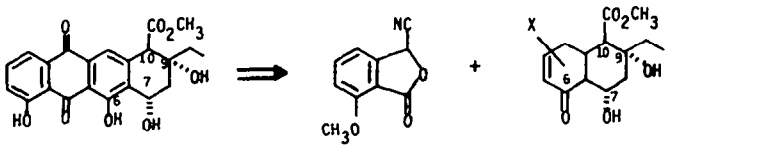
mild conditions we have chosen, the anion of benzenesulfonyl phthalide (**4a**) gave the tricyclic ketone (**5a**) in moderate yield; however, the anion of cyanophthalide (**4b**) gave ketone (**5a**) in over 80% yield in the form of crystals.

The above experiments clearly established that the cyanophthalide (**4b**) provides a facile entry into the fused BCD ring of our target molecule, and the missing A-ring may be delivered appended onto a cyclohexenone. The insertion of a heteroatom substitution onto the cyclohexenone ring would raise its oxidation state, and if eliminated during the annelation step, should lead to the phenolic B-ring. A molecule such as **6**, therefore, would be an ideal building block. However, we anticipate some difficulty with structure **6** since C-7 and C-9 OH groups, being β to CO functionalities,

† Contribution No. 676 from the Institute of Organic Chemistry, Syntex Research, Palo Alto, CA 94304.

‡ Shanghai Institute of Organic Chemistry, People's Republic of China. Syntex Postdoctoral Fellow, 1980–1982.

§ Syntex Postdoctoral Fellow, 1978–1980.

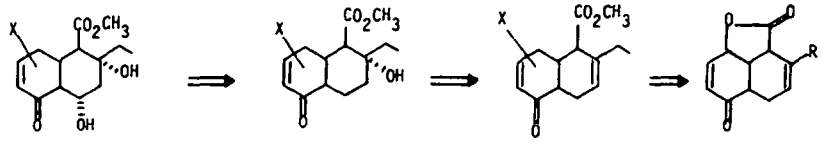


4b 6 X = hetero atom

could be subject to elimination under the basic annelation conditions. The Kende method[13] for the introduction of OH group to 7-deoxy adriamycinone offers a solution to the C-7 problem. Namely, 7-deoxy aklavinone can be expected to be convertible to aklavinone in a similar manner, and compound **6** did not need to carry the C-7 OH group. On the other hand, we chose to deal with the labile C-9 OH challenge by replacing it with a latent OH functionality, a double bond.

tetrahydrofuran provided a methyl ester, identified as the tetracyclic aromatic compound **13**.

Apparently, the anion of cyanophthalide underwent 1,4-conjugated addition to the enone system; this was followed by attack of the resulting enolate anion on the phthalide CO group and the subsequent loss of cyanide ion, establishing the tetracyclic skeleton in the form of a trione intermediate. Furthermore, the basic reaction media promoted the opening of the lactone ring as the consequence of a β-elimination reaction, induced a

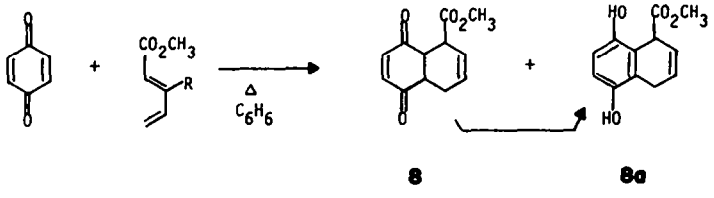


6 6a 6b 7 R = C_2H_5 7a R = H

Finally, a connective operation[14] linking the hetero atom X to the C-10 carbomethoxy functionality simplified compound **6b** to the tricyclic structure **7**. The molecule **7** was an unknown substance while the lower analog **7a** had been described in Woodward's reserpine synthesis.[15] We settled on the ketolactone (**7**) as a key building block and decided to use **7a** as a model compound to investigate the key annelation reaction.

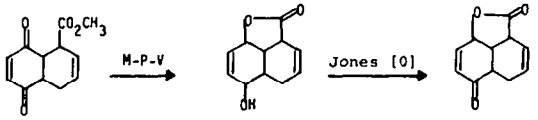
series of enolizations, and led finally to a hydroquinone which was oxidized during isolation. We postulated that the final oxidative aromatization step might have occurred during the aqueous base treatment. To our delight, we did obtain the desired product **12** when the base extraction isolation was omitted during workup of the annelation reaction.

The above results demonstrated that two readily



8 8a

The three-step synthesis for lactone **7** as reported in Woodward's original paper turned out to be quite difficult to produce the needed intermediate **8**. This was mainly due to its ready conversion into the isomeric molecule **8a** which cocrystallizes with *p*-hydroquinone, an unavoidable side-product, and any attempt at chromatographic isolation induced further isomerization. It was discovered, after much ado, that an extremely concentrated hot ethanolic solution (1 g/ml) of the crude Diels–Alder product yielded essentially pure enedione (**8**) on crystallization quite suitable for further transformation. Meerwein–Ponndorf–Verley reduction[15] proceeded smoothly to give the lactone **9** and Jones oxidation gave the enone **10**.

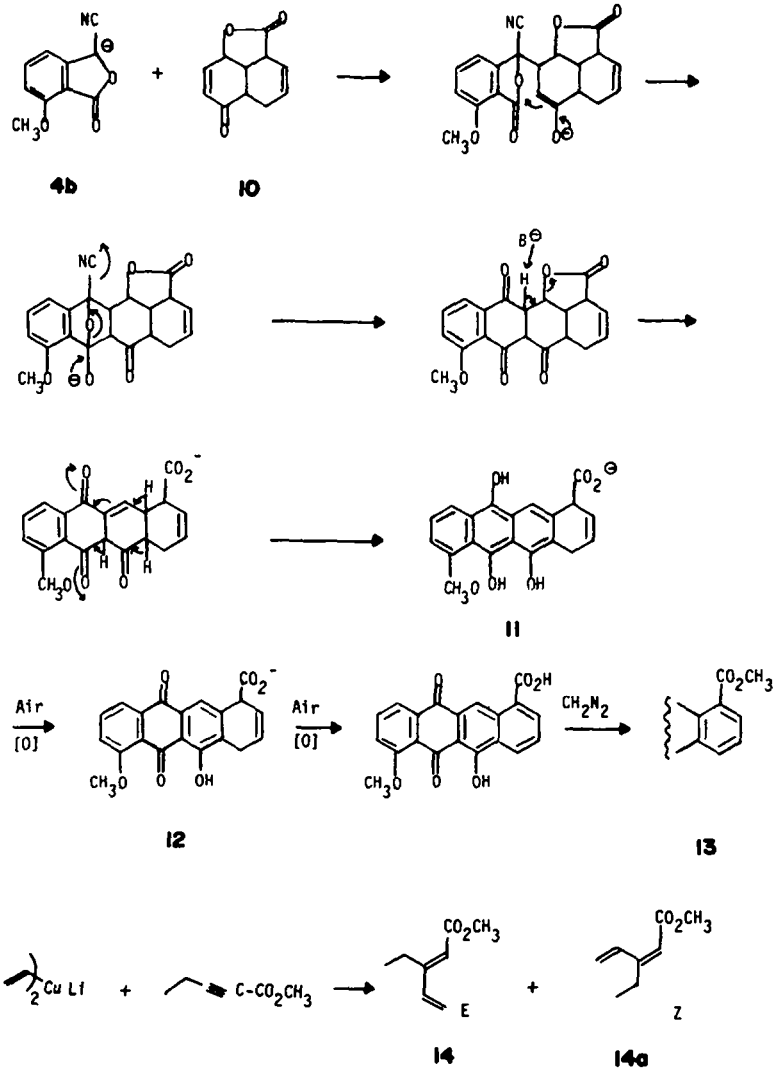


8 9 10

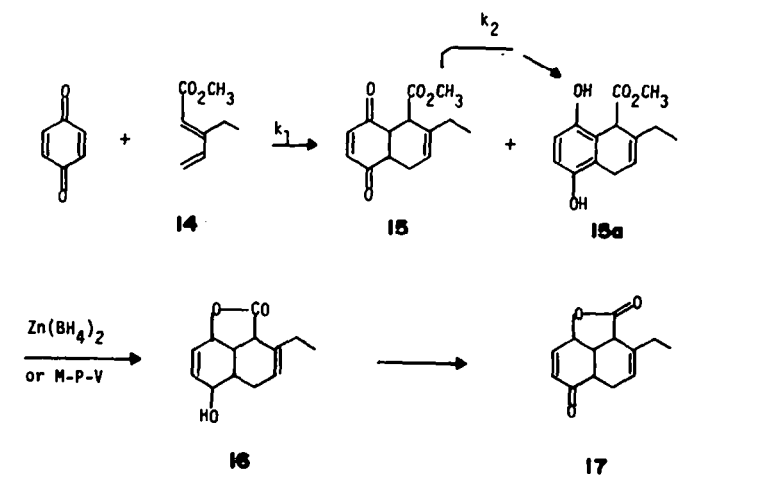
The stage is now set for the investigation of the key annelation reaction. Treatment of the lithio anion of the phthalide (**4b**) with enone (**10**) gave a sparingly soluble high melting solid which was dissolved in dilute sodium hydroxide. Acidification of the basic solution gave a yellow solid which on treatment with diazomethane in

available simple chemicals **4b** and **10** gave the tetracyclic skeleton **12** in a single reaction where all the needed functionalities, C-4 methoxy, C-5, C-12 dione, C-6 hydroxy, C-10 carbomethoxy groups, were delivered with complete regio specificity, and a latent C-9 OH group was strategically placed in the form of a double bond between C-8 and C-9. We then undertook the task of the construction of the aklavinone molecule using the above reaction as the key step.

Addition of vinyl cuprate (**14**) to methyl-2-pentynoate gave mainly the *E* form of methyl 3-ethylpenta-2,4-dienoate (**14**)[16] (b.p. 62.5–64°/32 mm),



which could be isolated from the 10% *Z* isomer **14a** (b.p. 64°/27 mm) by spinning band distillation.[17] The mixture of isomers could be used without isolation for the next step since the *Z* isomer was totally inert to the Diels–Alder reaction[18] and did not interfere with the isolation of its product. The additional Et group of dienic ester **14** rendered it much less reactive than the corresponding vinyl acrylate for the Diels–Alder reaction with *p*-benzoquinone. It required a three-day reflux to achieve an optimal result, and the enedione (**15**) was isolated in conjunction with the crystalline hydroquinone (**15a**), formed during the prolonged



reaction period as a major side product. The enedione (**15**), which readily isomerized to the side product (**15a**) under chromatographic conditions (silica gel, Florisil, and alumina), was not isolatable; and the crude product was directly reduced with zinc borohydride or aluminum isopropoxide[15] to give the lactone (**16**) isolated by chromatography as crystals. The overall yield from **15** was ~20%.

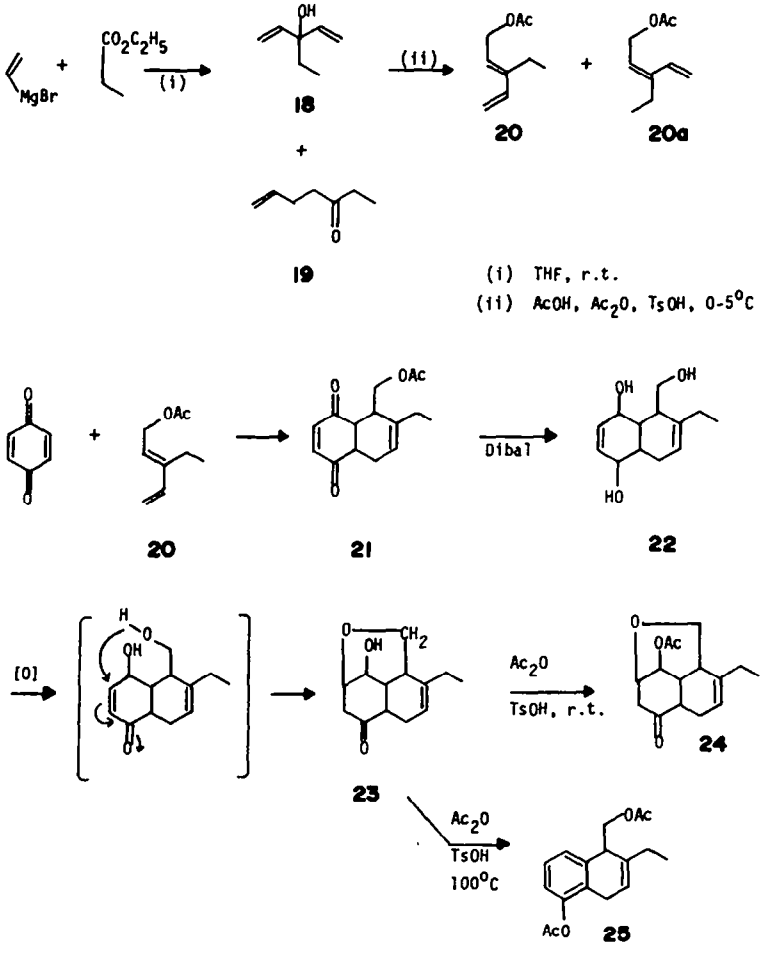
We sought to ameliorate the Diels–Alder reaction results by two approaches. Removal of the electron withdrawing functionality attached to the diene should enhance the rate of the Diels–Alder reaction k_1,[19] while the rate of the enolization process, k_2, leading to the side products could be expected not to be significantly altered (inductive effect). Another means of promoting k_1 without changing k_2 is to conduct the reaction under higher pressure (pressure effect).[19,20]

Replacement of the ester functionality of the diene **14** with an acetoxy-Me group will result in a much less electron-poor diene (**20**) and yet provide a potentially useful moiety in our synthesis. We prepared the acetoxydiene (**20**) according to the following scheme.

Addition of vinyl Grignard reagent to ethyl propionate gave a mixture of the alcohol **18** and enone **19**.[21] Treatment of this mixture under the allylic rearrangement conditions[22] resulted in a mixture from which the 1 : 1 mixture of *E* and *Z* acetoxydienes (**20** and **20a**) (b.p. 74–76°/3 mm) could be readily isolated from the enone **21** (b.p. 32°/5 mm) by distillation. The overall yield of the mixture of dienes was 14%.[23] The mixture of *E* and *Z* dienes **20** and **20a** was reacted with *p*-benzoquinone at room temperature for three days to give the crystalline adduct **21** in 72% yield without meaningful amount of the aromatization side product. The *Z* isomer **20a** could be quantitatively recovered from the reaction mixture.[18] Dibal reduction of **21** gave the triol **22** which on oxidation (Jones, PCC.,[24a] Brown's two phase oxidation,[24b] O_2/Pt[24c]) gave the cyclic ether **23**, the product of an intramolecular Michael addition. The best result (97% yield) was achieved by using Fetizon's oxidant[25] (Ag_2CO_3/celite). In an attempt to induce a reverse-Michael reaction, the ether (**23**) was treated with acetic anhydride in the presence of *p*-toluenesulfonic acid at room temperature and an acetate **24** was obtained; however, a phenolic acetate **25** was produced at 100° overnight. Both compounds are potentially useful intermediates for the synthesis of anthracyclinones. but we proceeded to investigate the pressure effect in the Diels–Alder reaction.

Under high pressure,[26] (15 Kbar) the *E* isomer of dienic ester (**14**) reacted with *p*-benzoquinone to give the adduct **15** without meaningful amount of the aromatic side product **15a**. The crystalline product **15** was reduced under the Meerwein–Ponndorf–Verley conditions to give the lactone **16** which was smoothly converted into the enone **17** under Jones conditions.

The anion of cyanophthalide **4b** was formed at −78° with lithium diisopropylamide in tetrahydrofuran in the presence of hexamethylphosphoramide. Sub-



sequent addition of the enone **17**, warming to room temperature and stirring for 2 hr at ambient temperature, led to completion of the annelation reaction. The workup procedure consisted of the bubbling of a stream of air through the acidified aqueous suspension of the reaction mixture, and the brown gummy material gradually solidified to give a brownish yellow solid. The crude acid **26** was converted into the corresponding crystalline methyl ester with diazomethane. The overall yield for the two steps was 42% based on recrystallized analytically pure ester **27**.

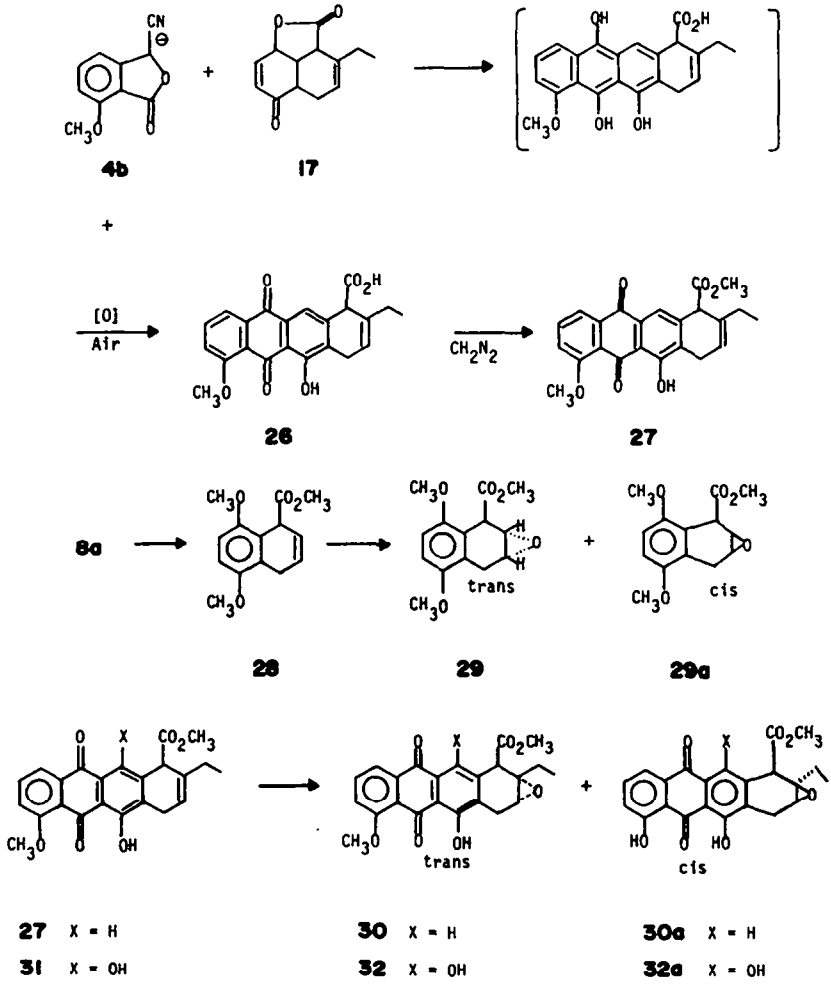
The latent C-10 OH functionality was revealed via a sequence of reactions in the manner described below, and the dimethyl ether **28**[27] of the by-product **8a** was used as a model compound to optimize the reaction conditions.

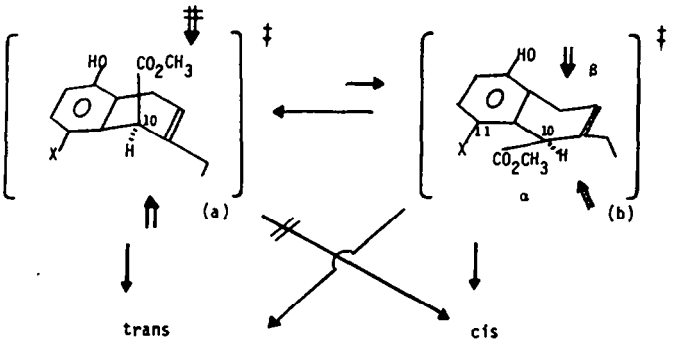
Thus, epoxidation of compound **28** with *m*-chloroperbenzoic acid gave a mixture of the *trans* and *cis* oxiranes **29** and **29a** separable by chromatography.

Epoxidation of ester **27** with *m*-chloroperbenzoic acid, however, gave the epoxide **30** in 85.8% yield and its isomer **30a** in ~2% yield. This result was in contrast with the report of Remers *et al.*[28] which described a product ratio of 6 : 4 for the isomers **32** and **32a** from the epoxidation of 8,9-dehydro-5-rhodomycinone (**31**).

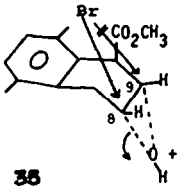
A plausible rationalization for these observations is that the preferred conformations for the epoxidation transition state are represented mainly by the following equilibrium. In case of 11-desoxy derivatives (X = H), transition state (a) is favored since the C-10 carbomethoxy group of (b) being in the pseudo-equatorial position is subject to the allylic strain.[29] Approach of the oxidant from the β-face of transition state (a) leading to the *cis* product **30a** is hindered and, as a consequence, the major product is the *trans* isomer. On the other hand, the 11-OH group of the rhodomycinone derivative is capable of stabilizing the conformation (b) by the formation of an H-bond with the CO group of the C-10 carbomethoxy functionality. Since the approach of oxidant from the β-face of transition state (b) does not result in steric repulsion, the yield of the *cis* product **32a** is increased. Absence of the vinyl ethyl group in structure **28** may lessen the difference between the conformations (a) and (b).

When a solution of the epoxide **29** in acetonitrile was treated with sodium bromide and *p*-toluenesulfonic acid at room temperature, a single bromohydrin **33** was obtained together with the tosylate **34** as a significant by-product. Fürst and Plattner's rule[30] requires that opening of the epoxide should lead to predominantly diaxial cleavage, and as indicated in the formula **35** for the epoxide opening transition state, approach of the nucleophile to the C-9 position would result in severe steric interference with the C-10 carbomethoxy group. As a consequence, the ring opening reaction proceeded regioselectively to give the C-8 bromohydrin (**33**). The





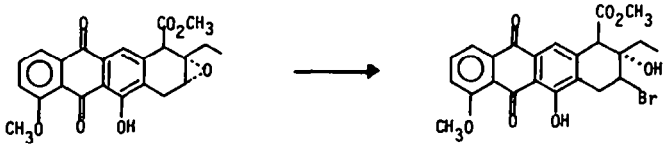
29 33 34



35

side product tosylate (**34**) could be avoided if *p*-toluenesulfonic acid was added in small portions to a solution of the epoxide and sodium bromide in acetonitrile. Indeed, when the improved reaction conditions were applied to the tetracyclic epoxide **30**, the bromohydrin **36** was obtained in 85.8% yield, and its regio isomer **36a** was not isolatable.

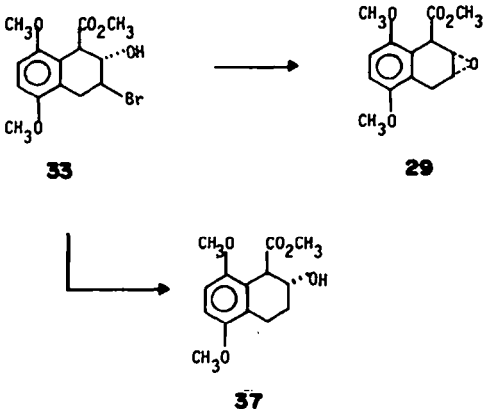
Demethylation of the 4-OMe group proceeded smoothly with aluminum chloride in methylene dichloride[32] at room temperature and 7-desoxy aklavinone (**39**) was obtained in 81% yield. Radical initiated bromination[13] gave the 7-bromo derivative which during preparative silica gel thick layer chromatography was solvolyzed, giving racemic aklavinone (**1**)[33] in 30% overall yield. When solvolysis reaction was carried out in aqueous dioxane in the presence of calcium carbonate,[24] the yield was improved to 54% for the two steps. The synthetic material was identical to a sample of the natural product[35] in terms of chromatographic properties and mass, infrared, ultraviolet, and nuclear magnetic resonance spectra. We have achieved a regio- and stereo-selective total synthesis of racemic aklavinone in



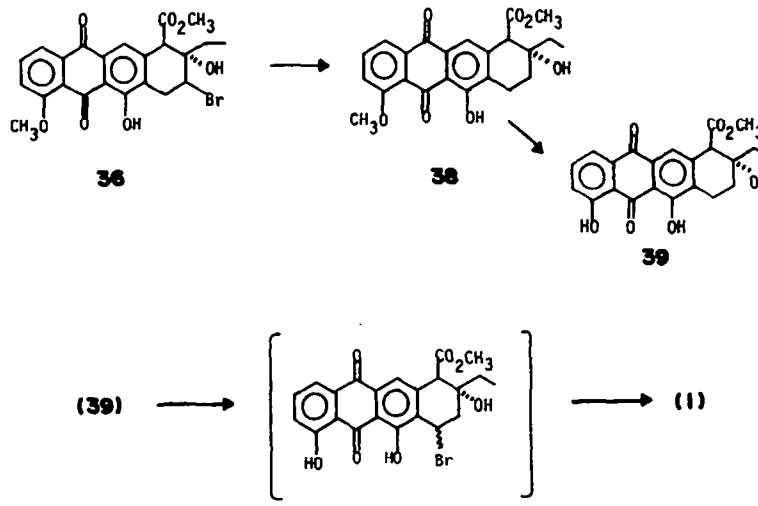
30 36

n-Butyltin hydride proved to be an unsuitable reagent for the removal of the extraneous bromide group of compound **36**, presumably because the quinonoid skeleton acted as a radical scavenger. The hydrogenolysis conditions of Ringold *et al.*[31] were used with bromohydrin **33** as a model compound. Thus, when compound **33** was shaken over Pd–C in methanol in the presence of ammonium acetate, the major product was the oxirane **29**, apparently the result of base-promoted cyclization. Addition of acetic acid to the above reaction mixture suppressed the cyclization side reaction and the desired 9-hydroxy compound **37** was obtained in excellent yield (~80%).

However, in our hands the best yield for 7-desoxy-aklavinone derivative **38** from the hydrogenolysis of bromide **36** was 53%.



33 29 37



12 steps in 1.7% yield from readily available starting materials.

EXPERIMENTAL

Preparation of cyanophthalide **4b**. s-BuLi (46 ml, 1.3 M in cyclohexane, 60 mmol) was added dropwise to a stirred soln of N,N-diethyl-*o*-anisylamide (10 g, 48 mmol) and tetramethylethylenediamine (8.12 g, 70 mmol) in dry tetrahydrofuran (THF) at −78° under N_2. After 2 hr stirring at −78°, dimethylformamide (DMF) (10 ml) was added dropwise, and the flask was warmed to room temp over 1 hr. The reaction was quenched by adding water (10 ml) at 0°, and the organic solvent was removed under reduced pressure. The product was extracted with EtOAc and washed with water and brine. Removal of solvent yielded the crude aldehyde[12] (9.2 g) which was suitable for the next step without further purification.

The aldehyde (5 g, 21 mmol) was dissolved in 50% aqueous THF and cooled to 0°. KCN (1.5 g, 23.1 mmol) was then added, and the soln was stirred until all the solid had dissolved. *p*-Toluenesulfonic acid (3.99 g, 21 mmol) in 50% aqueous THF was then added dropwise at 0°. After 5 min, the soln turned basic and was then allowed to warm up to 20°. More *p*-toluenesulfonic acid was added until the soln remained acidic, and the stirring continued for 15 min. The cyanohydrin was extracted with EtOAc, washed with bicarbonate soln, dried over $MgSO_4$ and evaporated. A white crystalline solid formed, m.p. 120–121° (5.30 g). The crude cyanohydrin was dissolved in 80:20 THF:H_2O with *p*-toluenesulfonic acid (3.99 g, 21 mmol) and heated under reflux for 4 hr. The pH was monitored to ensure constant acidity. The mixture was then diluted with water, extracted with methylene dichloride, washed with bicarbonate, dried over $MgSO_4$, and crystallized from EtOAc/hexane, m.p. 155° (3.56 g, 93% yield), m.p. 155°. IR δ_{max}^{KBr} cm^{-1} 1800, 1690, 1601, 1495, 1302, 1200. NMR (60 MC, $CDCl_3$) δ ppm, 4.02 (3H, S, OCH_3), 6.02 (1H, S, —CHCN—O—), 7.10 (1H, d, J = 8 Hz), 7.23 (1H, d, J = 7 Hz), 7.78 (1H, dxd, J = 7.5 Hz), MS (70 eV) *m/e* 189 (M^+), 171 ($M^+ - H_2O$), 159 ($M^+ - H_2CO$), 143 ($M^+ - H_2O$—CO). (Found: C, 63.78; H, 3.71; N, 7.45. Calc for $C_{10}H_7NO_3$: C, 63.49; H, 3.72; N, 7.41%).

Preparation of E-methyl 3-ethylpenta-2,4-dienoate (**14**). A soln of 45.8 ml of vinyllithium (89.4 mmol) in THF was added to a soln of 8.51 g of CuI (44.7 mmol) in 10.2 ml of Me_2S (139 mmol) and 30 ml of THF at −50°. The dark soln was warmed to −15° over 15 min, then cooled to −78°. To this soln of divinyl copper lithium, 4.17 g of methyl α-pentynoate (3.9 mmol) in 10 ml of THF was added at −70°, followed by stirring at the same temp for 3 hr and then quenching with 5 ml of MeOH. The mixture was then poured into 200 ml of NH_4Cl aq and extracted with EtOAc. The combined extracts were washed with water, dried over $MgSO_4$ and evaporated *in vacuo*. Separation of the residue by silica gel chromatography afforded 3.96 g of product and some paraffin that came from the soln of vinyllithium. In large scale, they could be separated by fractional distillation.

GLC and NMR of this product showed that it consisted of about 85% desired diene, 10% *Z*-isomer and some starting material.

The *E*- and *Z*-isomers could be separated by distillation using a spinning band column, but some product polymerized during the distillation. *E*-isomer (**14**). B.p./32 mm 62.5–64°. UV (MeOH) 252 nm (ε 19,600). IR δ_{max}^{film} cm^{-1} 1710, 1625, 1600. NMR (100 MC, $CDCl_3$) δ ppm, 1.02 (3H, t, J = 8 Hz, $C\underline{H}_3CH_2^-$), 2.82 (2H, q, J = 8 Hz, $CH_3C\underline{H}_2^-$), 3.70 (3H, S, $OC\underline{H}_3$), 5.40 (1H, d, J = 10.5 Hz, C_5—H_B), 5.6 (1H, d, J = 17 Hz, C_5—H_A), 5.74 (1H, S, C_2—H), 6.3 (1H, dxd, J = 10.5, 17 Hz, C_4—H). GC-MS (70 eV) *m/e* 140 (M^+), 125 ($M^+ - CH_3$), 109 ($M^+ - CH_3O$), 81 ($M^+ - COOCH_3$). *Z*-isomer b.p. 27–64°. UV (MeOH) 251 nm (ε 17,600). NMR (60 MC, $CDCl_3$) 8 ppm, 1.13 (3H, t, J = 8 Hz, $C\underline{H}_3CH_2^-$), 2.42 (2H, q, J = 8 Hz, $CH_3C\underline{H}_2^-$), 3.70 (3H, S, $OC\underline{H}_3$), 5.3–5.75 (3H, m, C_5—H_A, H_B, C_2—H), 7.7 (1H, dxd, J = 11, 18 Hz, C_4—H). GC-MS (70 eV) *m/e* 140 (M^+), 125 ($M^+ - CH_3$), 109 ($M^+ - CH_3O$), 81 ($M^+ - COOCH_3$).

Preparation of hydroxy lactone (**16**). A soln of 1.86 g of **14** and 1.43 g of benzoquinone in 18 ml of benzene was refluxed under N_2 for 75 hr. The mixture was diluted with CH_2Cl_2, washed with 10% $NaHSO_3$ aq and water, and dried over Na_2SO_4. When the solvent was removed, 2.91 g of gum† remained.

0.425 g of such gum and 1.92 g of freshly distilled aluminum isopropoxide were dissolved in 10 ml of isopropanol. The mixture was heated to a gentle boil and acetone and isopropanol distilled slowly from the mixture. In the meantime, isopropanol was introduced at such a rate as to keep the mixture approximately at constant volume. After 5.5 hr, the mixture was concentrated under reduced pressure, treated with ice-cold 5% HCl and extracted with CH_2Cl_2. The organic phase was washed with a soln of Na_2CO_3 aq and water and taken to dryness *in vacuo*. The residue was crystallized from ether-hexane to give 86.5 mg of **16**. M.p. 148.5–149°. Elemental analytical sample, m.p. 149–150°. (Found: C, 70.91; H, 7.39. Calc for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32%). IR δ_{max}^{KBr} cm^{-1} 3400, 1760. NMR (100 MC, $CDCl_3$) δ ppm. 1.02 (3H, t, J =

† The major component was ester **15**, but it could not be purified. When the gum was purified by silica gel column chromatography, a crystal was isolated which was the aromatized **15a**, m.p. 154–155°.

7 Hz, —$CH_2C\underline{H}_3$),

3.42 (1H, d, J = 11 Hz, —C<u>H</u>—C(=O)—O—).

4.43 (1H, m, >C<u>H</u>OH), 4.77 (1H, m, >CH—C(=O)—C—).

5.7–5.9 (3H, m, olefinic protons). IR δ_{max}^{KBr} cm^{-1} 3350, 1700, 1610. NMR (300 MC, D^6-DMSO) 8 ppm. 1.04 (3H, t, J = 7.5, —$CH_2C\underline{H}_3$), 2.13 (2H, m, —$C\underline{H}_2$CH),

3.05 (1H, bd, J = 22)
3.27 (1H, bd, J = 22) >$C\underline{H}_2$. 3.53 (3H, S, —$COOCH_3$),

4.33 (1H, t, J = 3.5 Hz, >C<u>H</u>—COO—).

5.77 (1H, bs, olefinic proton), 6.47, 6.53 (2H, d and d, J = 8.5 Hz aromatic protons), 8.65, 8.79 (2H, bs, phenolic protons).

When the Diels–Alder reaction was performed under high pressure (15 Kbar), crystal of **15** could be isolated. M.p. 54–54.5°. UV (MeOH) 293 nm (ε404). 224 nm (ε 10,300). IR δ_{max}^{KBr} cm^{-1} 3300–3500, 1730, 1690, 1600. NMR (300 MC, $CDCl_3$) δ ppm. 1.02 (3H, t, J = 7.4, —$CH_2C\underline{H}_3$), 2.00–2.24 (2H, m, —$C\underline{H}_2CH_3$),

2.28–2.4 (1H, m) >CH_2
2.90, 2.97 (1H, bd)
3.11–3.19 (1H, m)
3.24–3.30 (1H, m) 2 × (—OH)
3.49 (1H, d, J = 5.3 —CH(H)—COOMe)
3.54 (3H, S, $COOC\underline{H}_3$),
5.56 (1H, m, olefinic proton)
6.67 (1H, d, J = 10.4) O=C(H)—C(H)=C=O

6.79 (1H, d, J = 10.4) MS (70 eV) *m/e* 248 (M^+), 216 ($M^+ - CH_3OH$), 188 ($M^+ - HCO_2CH_3$), 189 ($M^+ - COOCH_3$), 160 ($M^+ - HCO_2CH_3$—CO).

Preparation of enone lactone (**17**). Hydroxy lactone **16**, 0.65 g, was dissolved in acetone (20 ml) and cooled to 0–5°. 8 N chromic acid (1.5 ml) was added dropwise until the brown color persisted. After 3 min, isopropyl alcohol was added to destroy the excess oxidant. The mixture was diluted with water and extracted with CH_2Cl_2 (four times). The extract was washed with water and dried over $MgSO_4$. Removal of solvent gave 0.647 g of product, m.p. 130–131.5°. The analytical sample was recrystallized from acetone-hexane, m.p. 132–132.5°. UV (MeOH) 210 nm (ε 9510). IR δ_{max}^{KBr} cm^{-1} 1730, 1680, 1630. NMR (100 MC, $CDCl_3$) δ ppm. 1.05 (3H, t, J = 7 Hz, —$CH_2C\underline{H}_3$),

5.04 (1H, dxd, J = 4.65 Hz, >C<u>H</u>—O—)

5.77–5.93 (1H, m, >C=C(H)—)

6.20 (1H, d, J = 10 Hz, O=C(H)—<u>H</u>)

6.97 (1H, dxd, J = 4, 10 Hz, O=C(H)—C(H)=<u>H</u>)

MS (70 eV) *m/e* 218 (M^+), 203 ($M^+ - CH_3$), 173 ($M^+ - COOH$), 159 ($M^+ - CO_2$—CH_3), 145 ($M^+ - COOH$—CO). (Found: C, 71.61; H, 6.50. Calc for $C_{13}H_{14}O_3$: C, 71.54; H, 6.46%).

Preparation of $\Delta^{8,9}$*-tetracycline* (**27**). A sample of 0.500 g (2.65 mmol) of **4a** in 15 ml of THF was added over 5 min to a soln of LDA prepared from 0.426 ml (3.06 mmol) of diisopropylamine, 2.92 mmol of n-BuLi and 1.0 ml of hexamethylphosphoramide in 10 ml THF at −78°. After stirring at −78° for 10 min, enone **17** (0.55 g, 252 mmol) in 15 ml of THF was added to the yellow soln over 10 min. The mixture was allowed to warm to room temp and stirred for another 2 hr at room temp. AcOH (3 ml) was added. The color of the mixture turned yellow again. The mixture was poured into 300 ml of 2.5% HCl, stirred, and a stream of air was bubbled through the soln. At first, a brown gum floated on the surface, which turned into a brown-yellow solid. The solid was filtered and washed with water and ether; 0.709 g of crude acid was obtained, m.p. 165–167°.

The crude acid was suspended in 50 ml of CH_2Cl_2 at 0–5°. After addition of CH_2N_2 in ether, the soln turned clear. After 3.5 hr, some AcOH was added. Removal of solvent gave 0.8 g of an orange gum. Trituration with ether and filtration gave 0.544 g of crystal (m.p. 175–185°). Recrystallization from $CHCl_3$-ether yielded 0.416 g of $\Delta^{8,9}$-tetracycline **27**, m.p. 189.5–194.5°. The m.p. of the analytical sample was 197.5–198.5°. UV (MeOH) 415 nm (ε 10,400), 262 nm (ε 25,200), 253 nm (Sh ε 21,700), 224 nm (ε 36,800). IR δ_{max}^{KBr} cm^{-1} 3430, 1730, 1665, 1625, 1585. NMR (100 MC, $CDCl_3$) δ ppm. 1.09 (3H, t, J = 7 Hz, —$CH_2C\underline{H}_3$). 2.0–2.4 (2H, m, —$C\underline{H}_2CH_3$), 3.3–3.6 (2H, m, —C_7—H_2), 3.63 (3H, S, —$COOCH_3$), 4.02 (3H, S, —OCH_3), 4.38 (1H, m, —C_{10}—H), 5.89 (1H, m, C_8—H), 7.30 (1H, dxd, J = 8, 1.5 Hz, C_3—H), 7.62 (1H, S, C_{11}—H), 7.67 (1H, t, J = 8 Hz, C_2—H), 7.90 (1H, dxd, J = 8, 1.5 Hz, C_1—H). MS 70 eV *m/e* 392 (M^+), 363 ($M^+ - C_2H_5$), 333 ($M^+ - COOCH_3$). (Found: C, 70.63; H, 5.13. Calc for $C_{23}H_{20}O_6$: C, 70.4; H, 5.13%).

Preparation of 8,9-α*-epoxide* (**30**). A sample of 0.204 g of **27** was treated with *m*-chloroperbenzoic acid in 30 ml of CH_2Cl_2 at room temp for 17 hr. The mixture was diluted with CH_2Cl_2 and washed with 10% soln of $NaHSO_3$ aq, 5% soln of $NaHCO_3$ aq and water. The organic phase was dried over $MgSO_4$. When the solvent was removed, 0.211 g of orange solid remained. Recrystallization from EtOAc/$CHCl_3$ gave 0.176 g of **30**. M.p. 228–231°. Elemental analysis sample—m.p. 233.5–234.5°. UV (MeOH) 416 nm (ε 11,000), 285 nm (ε 9590), 260 nm (ε 26,000), 228 nm (ε 38,500). IR δ_{max}^{KBr} cm^{-1} 3450, 1735, 1665, 1630, 1585. NMR (100 MC, $CDCl_3$) δ ppm. 1.04 (3H, t, J = 7 Hz, —$CH_2C\underline{H}_3$),

3.13 (1H, 6d, J = 18.5)
3.50 (1H, 6s,) } C_7—H_2, C_8—H)
3.74 (1H, 6d, J = 18.5)

3.76 (3H, S, —$COOC\underline{H}_3$), 4.03 (3H, S, —$OC\underline{H}_3$), 4.34 (1H, 6S, C_{10}—H), 7.30 (1H, dxd, J = 8, 1.5 Hz, C_3—H), 7.59 (1H, S, C_{11}—H), 7.68 (1H, t, J = 8 Hz, C_2—H), 7.90 (1H, dxd, J = 8 Hz, 15 Hz, C_1—H). MS 70 eV *m/e* 408 (M^+), 390 ($M^+ - H_2O$), 379 ($M^+ - C_2H_5$), 349 ($M^+ - COOCH_3$). (Found: C, 67.54; H, 4.75. Calc for $C_{23}H_{20}O_7$: C, 67.64; H, 4.94%).

Preparation of bromohydrin (**36**). *p*-Toluenesulfonic acid (0.082 g, 0.43 mmol) in 5 ml of acetonitrile was added to a suspension of NaBr (0.50 g) and **30** (0.176 g, 0.43 mmol) in 25 ml of acetonitrile at room temp over 45 min. The mixture was stirred overnight. Some CH_2Cl_2 was added, the mixture was washed with water, and the organic phase was dried over $MgSO_4$. When the solvent was removed *in vacuo*, 0.200 g of orange solid remained. Recrystallization from $CHCl_3$/ether gave 0.1505 g of orange crystal of **36**. M.p. 165–170° (dec). The analytical sample melted at 192–194° (dec). NMR (300 MC, $CDCl_3$). 1.02 (3H, t, J = 7.5 Hz, —$CH_2C\underline{H}_3$), 2.01 (2H, m, —$C\underline{H}_2CH_3$),

3.32 (1H, dxd, J = 9, 19 Hz,
3.68 (1H, dxd, J = 6, 19 Hz, } C_7—H_2),
3.83 (3H, S, —COOC$\underline{H}_3$), 4.02 (1H, S, C_{10}—H), 4.08 (3H, S, —OC$\underline{H}_3$), 4.49 (1H, dxd, J = 6.9 Hz, C_8—H), 7.37 (1H, d, J = 8 Hz, C_3—H), 7.46 (1H, S, C_{11}—H), 7.76 (1H, t, J = 8 Hz, C_2—H), 7.95 (1H, d, J = 8 Hz, C_1—H), 2.63 (1H, S, —O$\underline{H}$), 13.39 (1H, S, Ar—O$\underline{H}$). MS 70 eV *m/e* 408 ($M^+ - HBr$), 390 ($M^+ - HBr - H_2O$), 379 ($M^+ - HBr - C_2H_5$), 349 ($M^+ - HBr - CO_2CH_3$), 82.80 (HBr^+).

Debromination of the bromohydrin (**36**), *7-desoxy-4-O-methyl-aklavinone* (**38**). A sample of 100 mg of **36** dissolved in 15 ml of MeOH was stirred under H_2 in the presence of 100 mg of 5% Pd–C and 54 mg of ammonium acetate and 0.07 ml of AcOH. In 4 hr, 14 ml of H_2 was absorbed. The residue, after removal of catalyst and concentration *in vacuo*, was separated by preparative silica gel TLC and gave 13.2 mg of **30** and 22.7 mg of debromination product **38**. M.p. 238–239° (corrected), 234–235° (uncorrected) for elemental analysis. UV (MeOH). 418 nm (ε 8060, 347 nm (Sh) (ε 4740), 284 nm (9920) (Sh), 260 nm (ε 22,600), 226 nm (ε 30,600). IR δ_{max}^{KBr} cm^{-1} 3450, 1734, 1675, 1630, 1590. NMR (300 MC, $CDCl_3$) δ ppm. 1.09 (3H, t, J = 7 Hz, —CH_2CH_3), 1.85–2.05 (2H, m, —C$\underline{H}_2$CH$_3$),
2.0–2.3 (2H, m, C_8-H_2)
2.8–2.95 (1H, m, C_7-αH)
3.0–3.15 (1H, m, C_7-βH)
3.72 (3H, S, —COOC$\underline{H}_3$), 3.94 (1H, S, C_{10}—H), 4.08 (3H, S, —OCH_3), 7.37 (1H, d, J = 9.5 Hz, C_3—H), 7.60 (1H, S, C_{11}—H), 7.74 (1H, t, J = 8.5 Hz, C_2—H), 7.95 (1H, d, ~7.5 Hz, C_1—H), 12.78 (1H, S, Ar—OH). MS 70 eV *m/e* 410 (M^+), 392 ($M^+ - H_2O$), 363 ($M^+ - H_2O - C_2H_5$), 360 ($M^+ - H_2O - CH_3OH$), 333 ($M^+ - H_2O - COOCH_3$). (Found: MW 410.1415. Calc for $C_{23}H_{22}O_7$: MW 410.1366).

Demethylation of (**38**), *7-desoxyaklavinone* (**39**). Methyl ether **38** (22 mg) and 108 mg of $AlCl_3$ in 5 ml of CH_2Cl_2 were stirred under N_2 at room temp for 19 hr. HCl (1 ml 10%) was added. The mixture was extracted with CH_2Cl_2, and the extract was washed with water. The residue, after concentration *in vacuo*, was purified by preparative silica gel TLC and 17.3 mg of **39**. For analysis, this product was recrystallized from EtOAc. M.p. 214–216° uncorrected, 218–220° corrected. UV (MeOH) 432 nm (ε 12,400), 290 nm (ε 9230), 278 nm (Sh, ε 12,600), 259 nm (ε 27,300), 229 nm (ε 34,400). IR δ_{max}^{KBr} cm^{-1} 3560, 3440, 1730, 1675, 1625, 1580. NMR (300 MC, D^6-acetone). 1.08 (3H, t, J = 7.4 Hz, —CH_2C$\underline{H}_3$), 1.5–1.8 (2H, m, —C$\underline{H}_2$CH$_3$), 1.98, 2.25 (2H, m, C_8—H_2), 2.8–3.05 (2H, m, C_7—H_2), 3.71 (3H, S, —COOC$\underline{H}_3$), 4.00 (1H, S, C_{10}—H), 7.34 (1H, dxd, J = 1.8, 8 Hz, C_3—H), 7.57 (1H, S, C_{11}—H), 7.75–7.83 (2H, m, C_2—H and C_1—H). MS 70 eV *m/e* 396 (M^+), 378 ($M^+ - H_2O$), 364 ($M^+ - CH_3OH$), 346 ($M^+ - CH_3OH - H_2O$), 340 ($M^+ - CH_3CH{=}CHO$), 319 ($M^+ - COOCH_3$). (Found: M.W. 396.1237. Calc for $C_{22}H_{20}O_7$: M.W. 396.1209).

D-Aklavinone (**1**). N_2 was bubbled through a soln of 3.6 mg of **39** in 10 ml of CCl_4. A soln of Br_2 in CCl_4 (0.75 ml, 0.05 M) was slowly added while the mixture was stirred and irradiated with a 150 W lamp. After 0.5 hr concentration *in vacuo*, it gave a yellow-orange solid.

Separation and solvolysis with a hydrated silica gel plate, which was pretreated with elution of 2% MeOH in CH_2Cl_2 and air dried at room temp for 15 min, gave 1.6 mg of *d,l*-aklavinone. Recrystallization from EtOAc-hexane (twice) raised the m.p. to 177–179° (uncorrected) and recrystallization from MeOH–$CHCl_3$ gave a needlelike crystal m.p. 207–209°. Comparison with an authentic sample of aklavinone showed that they had the same R_f value in TLC and coincidental mass and NMR spectra. MS 70 eV *m/e* 412 (M^+), 394 ($M^+ - H_2O$), 376 ($M^+ - 2H_2O$), 361 ($M^+ - 2H_2O - CH_3$). UV (MeOH) 289 nm (ε 7110), 277 nm (Sh, ε 7290), 258 nm (ε 18,000), 228 nm (ε 30,500), 211 nm (Sh, ε 12,700). IR δ_{max}^{KBr} cm^{-1} 3440, 1730, 1680, 1625, 1575.

Acknowledgements—We thank Dr. L. Tőkés, Dr. I. Massey, D. Cho, J. Smith, Dr. M. Maddox, J. Nelson, L. Kurz, and the Syntex Analytical Department for their expert help in obtaining the analytical data and Drs. J. Edwards, J. G. Moffatt, J. Múchowski, and M. Marx for their encouragement throughout the course of this research effort.

REFERENCES

[1] [a]T. Oki, Y. Matsuzawa, A. Yoshimoto, K. Numata, I. Kitamura, S. Hori, A. Takamatsu, H. Umezawa, M. Ishizuka, H. Naganawa, H. Suda, M. Hamada and T. Takeucyi, *J. Antibiotics* **28**, 830 (1975); [b]T. Oki, N. Shibamoto, Y. Matsuzawa, T. Ogasawara, A. Yoshimoto, I. Kitamura, T. Inui, H. Naganawa, T. Takeuchi and H. Umezawa, *Ibid.* **30**, 683 (1977); [c]T. W. Doyle, D. E. Nettleton, R. E. Grulich, D. M. Balitz, D. L. Johnson and A. L. Vulcano, *J. Am. Chem. Soc.* **101**, 7041 (1979).

[2] [a]T. R. Kelly, *Ann. Reports in Med. Chem.* **14**, 288 (1979); [b]H. S. El Khadem, Ed., *Anthracycline Antibiotics*. Academic Press, New York (1982); [c]F. Arcamone, *Med. Chem. Academic* 17 (1981); [d]T. Kametani and K. Fukumoto, *Med. Res. Rev.* **1**, 23 (1981).

[3] [a]S. Hori, M. Shirai, S. Hirano, T. Oki, T. Inui, S. Tsukagoshi, M. Ishizuka, T. Takeuchi and H. Umezawa, *Gann* **68**, 685 (1977); [b]J. A. Will, G. A. Splitter, J. J. Lalich, S. R. K. Dennis and W. Dennis, *Gov. Rep. Announce. Index (U.S.)* **79**(21), 87 (1979); [c]D. Dantchev, V. Silioussartzhouk, M. Paintraud, M. Hayat, C. Bourut and G. Mathe, *Cancer Treat. Rep.* **63**(5), 875 (1979), *C. R. Seances Soc. Biol. Ses. Fil.* **173**(2), 394 (1979); [d]M. Ogawa, J. Inagaki, N. Horikoshi, K. Inoue, T. Chinen, H. Ueoka and E. Nagura, *Cancer Treat. Rep.* **63**, 931 (1979) and refs cited.

[4] [a]Y. Tamura, S. Akai, M. Sasho and Y. Kita, *Tetrahedron Letters* 1167 (1984); [b]F. M. Hauser, S. Prasanna and D. W. Combs, *J. Org. Chem.* **48**, 1328 (1983); [c]A. V. R. Rao, A. R. Mehendale and K. B. Reddy, *Tetrahedron Letters* 2415 (1982); [d]A. V. R. Rao, V. H. Deshpande and N. L. Reddy, *Ibid.* 775 (1982); [e]M. E. Jung, M. Node, R. W. Pflunger, M. A. Lyster and J. A. Lowe III, *J. Org. Chem.* **47**, 1150 (1982); [f]J. P. Gesson and M. Modon, *J. Chem. Soc.* Chem. Commun. 421 (1982); [g]J. Alexander, D. L. Flynn, L. A. Mitscher and T. Veysoglu, *Tetrahedron Letters* 3711 (1981); [h]S. D. Kimball, P. R. Walt and F. Johnson, *J. Am. Chem. Soc.* **103**, 1561 (1981); [i]J. Yadan, P. Corey, C. T. Hsu, K. Perlman and C. Sih, *Tetrahedron Letters* 811 (1981); [j]T. t. Li and T. C. Walsgrove, *Ibid.* 3741 (1981).

[5] [a]A. S. Kende and J. P. Rizzi, *J. Am. Chem. Soc.* **103**, 4247 (1981); [b]B. A. Pearlman, J. M. McNamara, I. Hasan, S. Hatakeyama, H. Sekizaki and Y. Kishi, *Ibid.* **103**, 4248 (1981); [c]P. N. Confalone and G. Pizzolato, *Ibid.* **103**, 4251 (1981); [d]T.-t. Li and Y. L. Wu, *Ibid.* **103**, 7007 (1981); [e]R. K. Boeckman Jr. and F. W. Sum, *Ibid.* **104**, 4604 (1982); [f]K. Maruyama, H. Uno and Y. Naruta, *Chem. Lett. Japan* 1767 (1983); [g]K. Krohn, *Liebigs Ann. Der Chemie* **12**, 2151 (1983).

[6] For more recent approaches, see [a]W. D. Wulff and P.-C. Tang, *J. Am. Chem. Soc.* **106**, 434 (1984); [b]J. Tamariz, L. Schwager, J. H. A. Stibbard and P. Vogel, *Tetrahedron Letters* 1497 (1983); [c]A. V. R. Rao, K. B. Reddy and A. R. Mehendale, *J. Chem. Soc.* Chem. Commun. 564 (1983); [d]M. J. Broadhurst and C. H. Hassal, *Ibid.* Perkins Trans. 2227 (1982); [e]S. D. Kimball, K. S. Kim, D. K. Mohanty, E. Vanotti and F. Johnson, *Tetrahedron Letters* 3871 (1982); [f]J. S. Swenton, D. K. Anderson, D. K. Jackson and L. Narasimhan, *J. Org. Chem.* **46**, 4825 (1981); [g]F. M. Hauser and S. Prasanna, *J. Am. Chem. Soc.* **103**, 6378 (1981); [h]M. G. Dolson, B. L. Chenard and J. S. Swenton, *Ibid.* **103**, 5263 (1981).

[7] Preliminary results of this study were reported at the 179th National Meeting, American Chemical Society, Las Vegas, Nevada, August 25–29, 1980; Abstract No. 23, Division of Organic Chemistry.

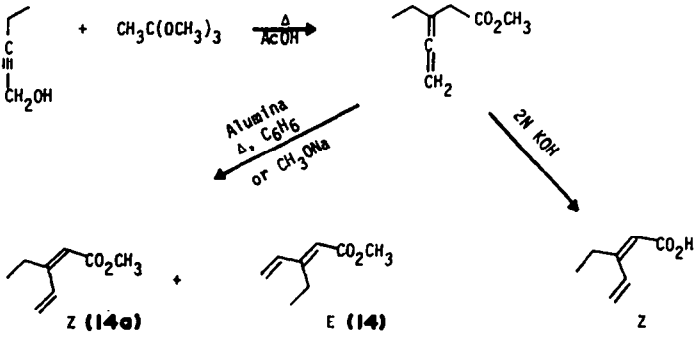
[8] J. L. Fox, *Chemical & Engin. News* 31 (1981).

[9] [a]F. M. Hauser and R. P. Rhee, *J. Org. Chem.* **43**, 178 (1978); [b]F. M. Hauser and J. Prasanna, *Ibid.* **44**, 2596 (1979).

[10] G. A. Kraus and H. Sugimoto, *Tetrahedron Letters* 2263 (1978).

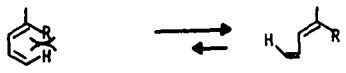
[11] J. Wildeman, P. C. Borgen, H. Plium, P. H. F. M. Rouwette and A. M. van Heusen, *Tetrahedron Letters* 2213 (1978).

[12a] S. O. DeSilva, J. N. Reed and V. Snieckus, *Tetrahedron Letters* 5099 (1978); [b] P. Beak and V. Snieckus, *Acc. Chem. Res.* **15**, 306 (1982) and refs cited.
[13] A. S. Kende, Y. G. Tsay and J. E. Mills, *J. Am. Chem. Soc.* **98**, 1967 (1976).
[14] E. J. Corey and W. L. Jorgensen, *J. Am. Chem. Soc.* **98**, 189 (1976).
[15] R. B. Woodward, F. Baker, H. Bickel, A. Frey and R. Kierstead, *Tetrahedron* **2**, 1 (1958).
[16] E. J. Corey, C. U. Kim, R. H. K. Chen and M. Takeda, *J. Am. Chem. Soc.* **94**, 4395 (1972).
[17] An alternative route to the dienic ester (**14**) was investigated as follows:



Thus, in the presence of acetic acid, pent-2-yn-1-ol and trimethylorthoacetate under reflux gave the allenic ester which, when heated with alumina in benzene or treated with NaOMe in MeOH, gave predominantly the *Z*-isomer (**14a**) and a minute amount of the desired *E*-isomer (**14**). Treatment of the allenic ester with aqueous 2N KOH under reflux gave the undesired 2-*Z*-4 dienic acid in 62% yield. We do not have an explanation for the apparent selectivity of the reaction.

[18] This is apparently due to the Diels–Alder reaction requirement that the diene needs to be in the cisoid conformation. As R becomes more bulky, steric repulsion prevents the cisoid conformer to remain in a planar configuration and thus favors the transoid conformation. See ref. 19.



[19] J. Sauer, *Angew Chemie.* Int. Ed. **6**, 16 (1967).
[20a] W. G. Dauben and A. P. Kozinkowski, *J. Am. Chem. Soc.* **96**, 3664 (1974); [b] W. G. Dauben and H. O. Krabbenhoft, *J. Org. Chem.* **42**, 282 (1974); [c] W. G. Dauben, C. R. Kessel and K. H. Takemura, *J. Am. Chem. Soc.* **102**, 6893 (1980).
[21] N. Boccara and P. Maitte, *Bull. Soc. Chim. Franc.* 1448 (1972).
[22] J. H. Babler and D. O. Olsen, *Tetrahedron Letters* 351 (1974).
[23] No attempt has been made to optimize the yield.
[24a] E. J. Corey and W. Suggs, *Tetrahedron Letters* 2647 (1975); [b] H. C. Brown, C. P. Garg and K.-T. Liu, *J. Org. Chem.* **36**, 387 (1971); [c] J. Fried and J. C. Sik, *Tetrahedron Lett.* 3899 (1973).
[25] M. Fetizon and M. Golfier, *C. R. Acad. Sci. Paris rend.* **267**, 900 (1968).
[26] This experiment was carried out in Professor Dauben's laboratories. [a] W. G. Dauben and A. P. Kozikowski, *J. Am. Chem. Soc.* **96**, 3664 (1974); [b] W. G. Dauben and H. O. Krabbenhoft, *J. Org. Chem.* **42**, 282 (1977); [c] W. G. Dauben, C. R. Kessel and K. H. Takemura, *J. Am. Chem. Soc.* **102**, 6893 (1980).
[27] Prepared from base catalyzed alkylation of the side-product quinol (**8a**) with dimethyl sulfate.
[28] H.-J. Lin, V. Kumar and W. A. Remers, *J. Med. Chem.* **23**, 1242 (1980).
[29] F. Johnson, *Chem. Rev.* **68**, 375 (1968).
[30] A. Fürst and P. A. Plattner, *Abstr. of Papers 12th Intern. Congr. Pure Appl. Chem.* 409 (1951).
[31] H. J. Ringold, B. Löken, G. Rosenkranz and F. Sondheimer, *J. Am. Chem. Soc.* **78**, 816 (1956).
[32a] T.-t. Li and R. H. Ellison, *J. Am. Chem. Soc.* 100 (1978); [b] A. S. Kende and J. P. Rizzi, *Tetrahedron Letters* 1779 (1981).
[33] We are grateful to Dr. T. Oki of Sanraku-Ocean Co. and Dr. T. Takita of Tokyo Microbial Institute for a generous gift of an authentic sample of this natural product.