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PRACTICAL ASYMMETRIC SYNTHESIS OF AKLAVINONE[1]

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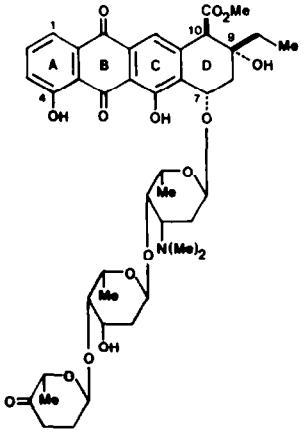
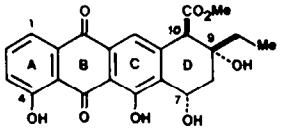
Abstract—A practical synthesis of (+)-aklavinone, the aglycone of antitumor antibiotic aclacinomycin A, is achieved by using the asymmetric aldol reaction of **6a** to **10a** as the key step.

The clinical efficacy of the anthracycline antibiotics adriamycin and daunomycin as agents for the treatment of human cancers has stimulated extensive synthetic work.[2] However, in spite of some promising aspects such as low cardiac toxicity, very little attention had been focused on the synthesis of aclacinomycin A (**1**)[3,4] until 1981, when three independent total syntheses of racemic aklavinone (**2**), the aglycone of aclacinomycin A, were reported by Kende, by Confalone, and by us.[5] It is important to note that the Kende synthesis is suited to obtain optically enriched aklavinone by using an asymmetric expoxidation reaction. Our route has also been extended to the asymmetric synthesis of aklavinone, 11-deoxydaunomycinone and related substances.[6] In this paper, we would like to describe the experimental details for an asymmetric synthesis of optically active aklavinone.



1 : Aclacinomycin A

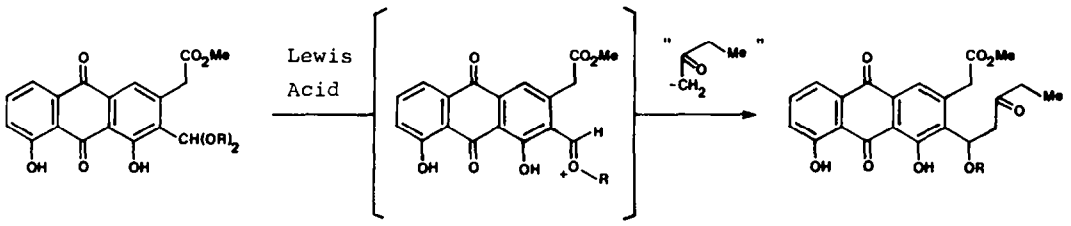


2 : Aklavinone

In planning an asymmetric synthesis of aklavinone, we naturally focused our attention on possible modifications of our route to racemic aklavinone. The first asymmetric center in our synthesis was introduced during the Lewis acid-promoted reaction of dimethyl acetal **3** with 1-(trimethylsilyl)-2-butanone (Scheme 1). An intermediate in this reaction is presumably the oxonium ion **4**. We felt that preparation of a chiral acetal **6** using an optically active alcohol, followed by Lewis acid treatment, would allow for generation of the chiral oxonium ion **7**. The oxonium ion **7** could, in turn, react with the nucleophile derived from 1-(trimethylsilyl)-2-butanone from either of its two diastereotopic faces, thereby producing potentially unequal amounts of the two possible diastereomeric aldols **8**.

In order to test this possibility, we decided to synthesize the optically active acetal **6a** from the aldehyde **9**[5c] and D-(−)-2,3-butanediol (*R,R* configuration)[7] (Scheme 2). We were encouraged by the successful asymmetric polyene cyclizations reported by Johnson using an optically active acetal derived from D-(−)-2,3-butanediol.[8] Since D-(−)-2,3-butanediol possesses C_2 symmetry, Lewis acid-promoted cleavage of either of the acetal C—O bonds in **6a** generates the same chiral oxonium ion. In addition, both enantiomers of 2,3-butanediol are available[7,9] so that it would be possible to synthesize either enantiomer at the crucial C7 stereocenter in **10a**. Thus, the aldehyde **9**[5c] was reacted with D-(−)-2,3-butanediol and a catalytic amount of pyridinium *p*-toluenesulfonate[10] in refluxing benzene for 24 hr. After aqueous workup and purification by column chromatography on silica gel, the acetal **6a** was obtained in 92% yield. The structure of **6a** was concluded from the spectroscopic data.

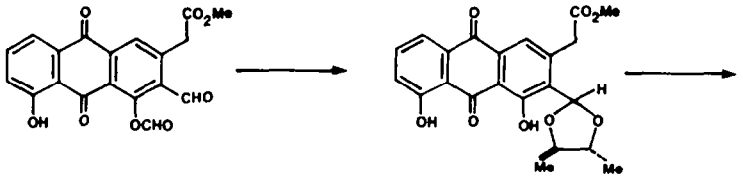
When the acetal **6a** was treated with excess 1-(trimethylsilyl)-2-butanone and two equivalents of stannic chloride in methylene chloride at −40°, the original conditions for effecting the aldol reaction of dimethyl acetal **3** with 1-(trimethylsilyl)-2-butanone,[5c] the starting material was recovered unchanged. Under more forcing conditions, i.e., allowing the reaction mixture to warm to room temperature, the acetal **6a** disappeared but many unidentified products were formed. Possibly, the acetal **6a** is less reactive than the dimethyl acetal **3** because of its cyclic nature, and we decided to investigate a non-cyclic chiral acetal.



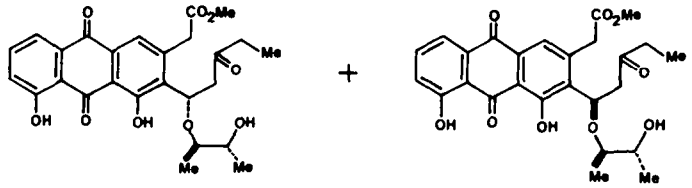
3 : R = Me 4 : R = Me 5 : R = Me

6 : R = chiral alcohol residue 7 : R = chiral alcohol residue 8 : chiral alcohol residue

Scheme 1.



9 6a



10a 11a

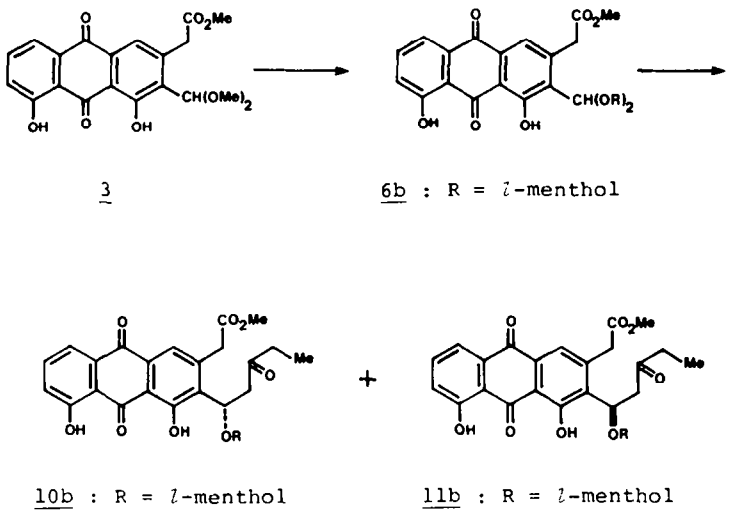
Scheme 2.

The acetal **6b** was synthesized by reaction of dimethyl acetal **3** with a large excess of **l**-menthol and a catalytic amount of pyridinium *p*-toluenesulfonate[10] in refluxing benzene for 94 hr (Scheme 3). After aqueous workup, Kugelrohr distillation to remove the relatively volatile **l**-menthol and purification of the residue by preparative TLC on silica gel, the acetal **6b** was obtained in 57% yield. Although the acetal **6b** was somewhat more reactive than the acetal **6a** when treated with excess 1-(trimethylsilyl)-2-butanone and stannic chloride in methylene chloride at $-20°$ to 0°, the reaction mixture still generated several unidentified products. Thus, we decided to investigate the effect of solvents on this reaction.

An important observation was then made when the acetal **6b** was reacted with excess 1-(trimethylsilyl)-2-butanone and stannic chloride (1.1 M in methylene chloride) in anhydrous *acetonitrile* at $-23°$ for 3 hr. After aqueous workup, TLC analysis showed that a very clean reaction had occurred in which only a trace of starting material remained and two major products were formed in a ratio of *ca* 3:2. After separation by preparative TLC on silica gel, the NMR spectrum of each product was found to be consistent with the desired aldol diastereomers **10b** and **11b**.[11] Although it appeared that the ratio of two diastereomers was only *ca* 3:2, we were nonetheless encouraged by this result. We were particularly pleased that changing the solvent from methylene chloride to acetonitrile had almost totally eliminated the formation of unidentified side-products.

In light of this observation, we decided to re-investigate the reaction of cyclic acetal **6a** with 1-(trimethylsilyl)-2-butanone. Thus, the acetal **6a** was treated with excess 1-(trimethylsilyl)-2-butanone and 1.5 equivalents of stannic chloride (1.1 M in methylene chloride) in anhydrous acetonitrile at $-23°$ to $-10°$ for 4.5 hr (Scheme 2). After aqueous workup, TLC and 270-MHz NMR analyses of the crude product revealed that a very clean reaction had occurred in which two products were formed in a *ca* 10:1 ratio (Fig. 1). These products were easily separated by preparative TLC on silica gel to give the desired aldol products **10a** (75% yield) and **11a** (7.5% yield).[12] The gross structure of **10a** and **11a** was assigned based on the spectroscopic data. The C7 configuration of the major aldol product **10a** was concluded from its conversion to (+)-aklavinone as described below.

Treatment of **10a** with excess potassium carbonate in methanol at room temperature for 2 hr, followed by aqueous workup,[5c] provided the cyclization products **12** and **13**, which were easily separated by preparative TLC on silica gel (Scheme 4). Cyclization products **12** and **13** were isolated in 53% yield and 42% yield,



3 6b : R = *l*-menthol

10b : R = *l*-menthol 11b : R = *l*-menthol

Scheme 3.

respectively. The structures of **12** and **13** were concluded on comparison of their spectroscopic data with those of the corresponding products in the racemic series.[5c] It is interesting to note that the ratio of **12** to **13** was significantly improved compared with that of the corresponding diastereomers in the racemic series.[5c]

As in the racemic series,[5c] hydrolysis of the C7 ether group was effected by boron trifluoride to yield exclusively aklavinone. However, the chemical yield by this procedure varied from 40% up to 80%. A much more reliable conversion was realized using a slight modification of Swenton's procedure;[13] the cyclization product **12** was treated with trifluoroacetic acid at −78° to room temperature, followed by workup with aqueous sodium bicarbonate in acetone, to give at least a 25:1 mixture of aklavinone and its C7 epimer. Preparative TLC allowed isolation of aklavinone in 84% yield, which showed $\alpha_D + 150°$ ($c = 0.21$, $CHCl_3$), while a sample of naturally occurring aklavinone which was purified by preparative TLC on silica gel showed $\alpha_D + 150°$ ($c = 0.32$, $CHCl_3$).[14] A sample of synthetic (+)-aklavinone, crystallized from benzene–hexane, showed m.p. 170–172°. The literature m.p. of naturally occurring aklavinone is 170°.[15]

Thus, the asymmetric synthesis of (+)-aklavinone was completed in seven steps in 23% overall yield from bromojuglone (Scheme 5). It is worth pointing out that this route should be applicable for the synthesis of the

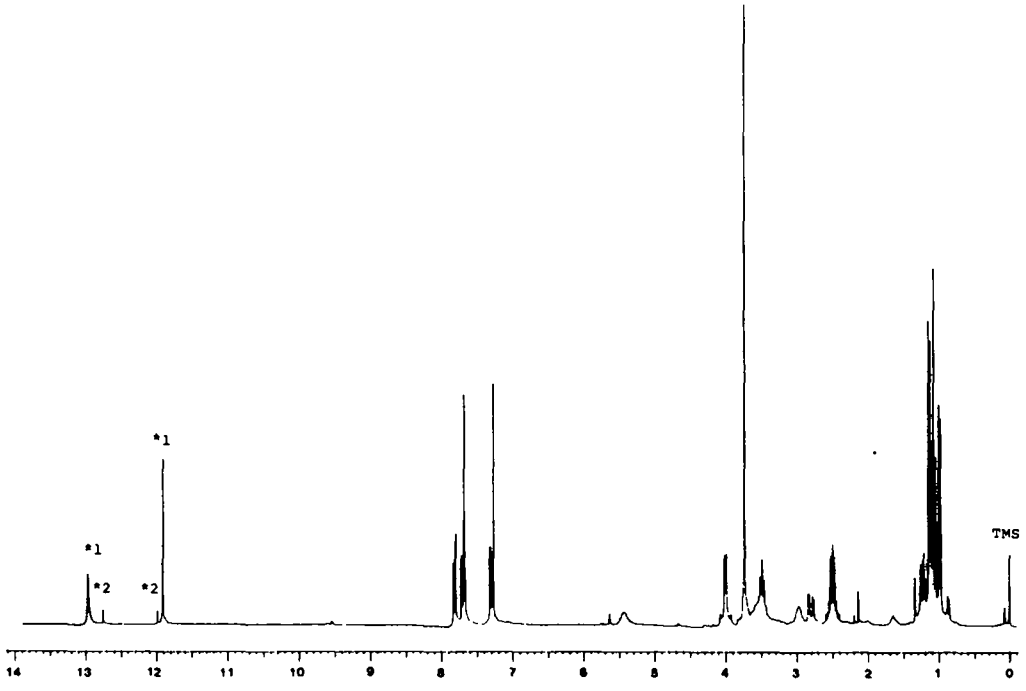
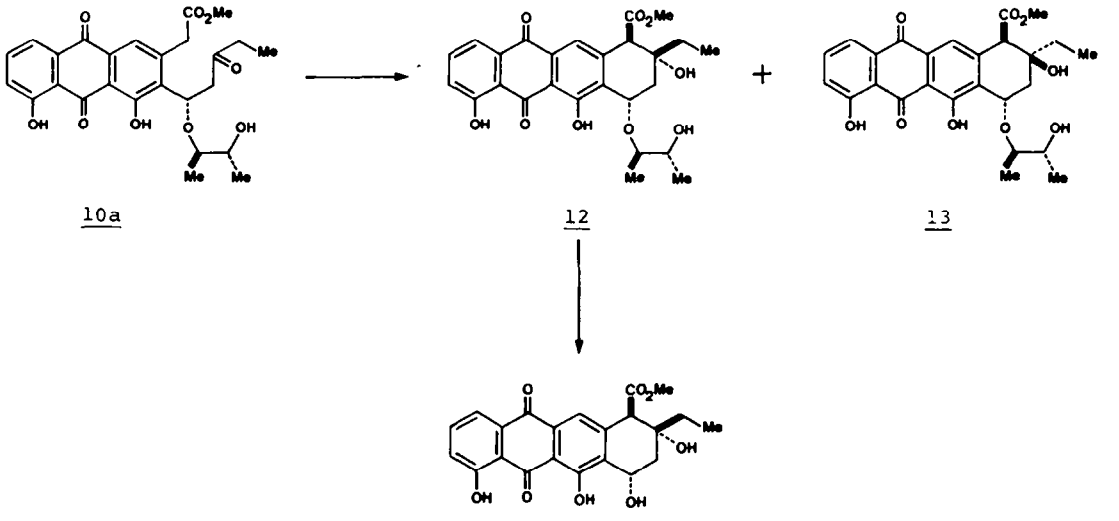


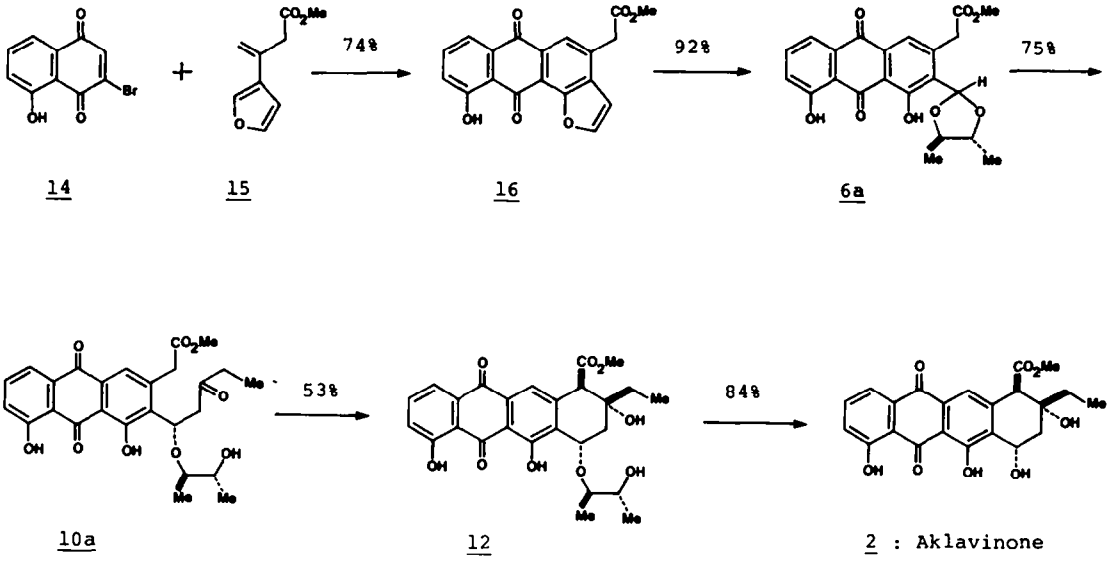
Fig. 1. ^{1}HNMR (270 MHz, $CDCl_3$) spectrum of the crude product obtained from the asymmetric aldol reaction, i.e. **6a** → **10a** + **11a**. Signals marked by *1 are the phenolic protons of **10a** whereas signals marked by *2 are the phenolic protons of **11a**.



10a 12 13

2 : Aklavinone

Scheme 4.



14 15 16 6a

10a 12 2 : Aklavinone

Scheme 5.

antipode of naturally occurring aklavinone simply by substituting L-(+)-2,3-butanediol (S,S configuration)[9] for D-(−)-2,3-butanediol in the acetalization step. Furthermore, this method has successfully been extended to the practical synthesis of optically active 11-deoxydaunomycinone and related substances.[6b]

EXPERIMENTAL

M.ps were taken on a Koffler hot stage apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 727 spectrophotometer and are reported in wave numbers (cm^{-1}). These spectra were calibrated with the 1601 cm^{-1} absorption of polysterene film. PMR were recorded using a Varian CFT-20 spectrometer at 80 MHz or a JEOL FX-270 spectrometer at 270 MHz. Spectra were recorded in $CDCl_3$, and chemical shifts are reported in ppm downfield from TMS (δ). NMR data are presented in the following form: chemical shift (number of protons, multiplicity, coupling constants in hertz). Mass spectra (MS) were determined on either an AEI MS-9 or Kratos MS-50L double focusing instrument at 70 eV using direct insertion at temps of 50–180°. UV spectra were measured on a Perkin–Elmer Model 124 double beam spectrophotometer. Absorption maxima are reported in nanometers (nm) in the form λ_{max} (log ε). The presence of a shoulder is reported in the form λ_{max} (sh, log ε). Optical rotations were measured on a Perkin–Elmer Model 241 polarimeter at ambient temperature. Elemental analyses were performed by Analytical Laboratories, Meijo University, Nagoya, Japan.

Analytical TLC was performed on 0.25 mm pre-coated silica gel plates supplied by E. Merck or on 0.25 mm high performance pre-coated silica gel plates (HPTLC) supplied by E. Merck. Spots were visualized using one or more of the following techniques: (a) visible absorption; (b) UV illumination; (c) *p*-anisaldehyde stain; (d) phosphomolybdic acid stain. PLC separations were carried out on 0.50 mm pre-

coated silica gel plates or 2 mm silica gel plates prepared from silica gel PF_{254}. Compounds were eluted from the adsorbent with 10% MeOH in CH_2Cl_2 or ether. Column chromatography was performed on E. Merck Kieselgel 60.

All moisture- and/or oxygen-sensitive reactions were performed in oven-dried apparatus under a positive pressure of argon. Sensitive liquids and solns were transferred by syringe or cannula and introduced to reaction vessels through rubber serum caps. Reaction mixtures were stirred magnetically unless otherwise noted.

Reagents and solvents were commercial grades and were used as supplied with the following exceptions:

Acetonitrile (dry): distilled from calcium hydride and stored over 4A molecular sieves.
Benzene: distilled from sodium benzophenone ketyl.
Diisopropylamine: distilled from sodium hydride and stored over 4A molecular sieves.
Dimethylformamide: stored over 4A molecular sieves.
Ether: distilled from sodium benzophenone ketyl.
Methylene chloride: distilled from calcium chloride.
Tetrahydrofuran: distilled from sodium benzophenone ketyl.
Toluene: stored over 4A molecular sieves.

Benzofuran **16**: *The following procedure for the preparation of diene* **15** *is more practical and more convenient than the method originally reported in ref 5c*

3-Furoic acid (30.0 g, 0.268 mol) was dissolved in 1.2 l of dry ether in a dry 3-neck, 3-l flask under argon and cooled to 0°. MeLi (1.42 M in ether, 420 ml, 0.596 mol) was added dropwise with stirring over 1 hr. The cooling bath was removed and the mixture was stirred at room temp for 6 hr and then poured into cold 1 M HCl (1.3 l). The aqueous and organic layers were separated and the aqueous layer was extracted with ether (2 ×). The combined organic layers were washed with 1 M NaOH (1 l) and brine (1 l) and dried over $MgSO_4$. Solvent was carefully removed at reduced pressure, first with cooling in an ice-water bath and then briefly at room temp, to afford 26.0 g (0.236 mol, 88%) of crude 3-acetylfuran which was used in the next reaction without further purification. A pure sample was prepared by sublimation (40°, 20 mm), m.p. 51–51.5° [lit.[16]: m.p. 52–52.5°].

Sodium hydride (60% dispersion in mineral oil, 9.50 g, 0.237 mol) was placed in a dry 3-neck, 3-l flask under argon and washed with hexane (3 × 700 ml) in order to remove the oil. Dry tetrahydrofuran (THF) (350 ml) was added and trimethyl phosphonoacetate (43.1 g, 0.237 mol) dissolved in 350 ml of dry THF was added dropwise with stirring over 45 min at room temp. The mixture was stirred for an additional 30 min and dry DMF (210 ml) was added. After stirring for 1 hr, the crude 3-acetylfuran (12.6 g, 0.114 mol) dissolved in 350 ml of dry THF was added dropwise over 20 min. The mixture was heated to 50° for 5 hr during which time the thick white ppt dissolved to leave a gold soln. After cooling to room temp, the mixture was partitioned between satd NH_4Cl (800 ml) and ether (700 ml). The aqueous layer was extracted with ether (300 ml) and the combined organic extracts were washed with water (3 × 1 l) and dried over $MgSO_4$. Solvent was removed at reduced pressure to give the residue (18.6 g). The crude product was purified by silica gel column chromatography (280 g) with elution by hexane and then 10% ether in hexane to give 16.2 g (0.0975 mol, 86%) of the conjugated ester as a *ca* 1:1 mixture of *cis* and *trans* isomers. IR (neat): 3120, 1715, 1630, 1020, 865. NMR ($CDCl_3$): *ca* 1:1 mixture: 2.16 (3H, d, J = 1), 2.46 (3H, d, J = 1), 3.69 (3H, s), 3.73 (3H, s), 5.80 (1H, q, J = 1), 6.07 (1H, q, J = 1), 6.58 (1H, m), 6.72 (1H, m), 7.39 (1H, m), 7.39 (1H, m), 7.65 (1H, m), 7.92 (1H, m). MS: 166 (M^+, 100), 149(39), 137(23), 135(95), 134(41), 95(22), 81(25), 79(33), 77(55). Exact mass: Calc for $C_9H_{10}O_3$: 166.06299. Found: 166.06302.

A soln of the conjugated ester (12.3 g, 74.0 mmol), dissolved in 110 ml of dry THF at room temp, was added dropwise by cannula over 15 min to a stirred soln of lithium diisopropylamide (prepared from n-BuLi (2.31 M in hexane, 48 ml, 111 mmol) and diisopropylamine (15.5 ml, 111 mmol)) in 200 ml of dry THF at −78° under argon. The mixture was stirred for an additional 20 min and phenol (12.3 g, 131 mmol) was added in one portion at −78°. After stirring for 20 min under argon, the cooling bath was removed and stirring was continued for an additional 10 min. Satd NH_4Cl (400 ml) was added and the mixture was extracted with ether (2 ×). The combined organic extracts were washed with 1 M NaOH (500 ml), water (2 × 500 ml), and brine (300 ml), and dried over $MgSO_4$. Solvent was removed at reduced pressure to give 12.4 g of the crude product (yellow oil) as a mixture of the deconjugated and conjugated esters (3.5:1.0 ratio by nmr). Column chromatography on silica gel (130 g) with elution by hexane and then 10% ether in hexane yielded 9.65 g (58.1 mmol, 78%) of a mixture of the deconjugated and conjugated esters (3.5:1.0 ratio), which was used directly in the Diels–Alder reaction.[17] If desired, the two compounds can be separated by silica gel column chromatography (TLC R_f of the conjugated ester: 0.34; R_f of **15**: 0.24; 10% ether in hexane).

Deconjugated esters **15**. IR (neat): 3120, 1735, 1635, 1020, 865. NMR ($CDCl_3$): 3.33 (2H, d, J = 1), 3.68 (3H, s), 5.09 (1H, br s), 5.42 (1H, br s), 6.53 (1H, br s), 7.35 (1H, t, J = 2), 7.47 (1H, br s). MS: 166 (M^+, 100), 149(13), 135(35), 134(13), 109(12), 108(53), 107(21), 95(30), 93(15), 79(35), 78(17), 77(62). Exact mass: Calc for $C_9H_{10}O_3$: 166.06299. Found: 166.06300.

The Diels–Alder reaction was carried out as follows. A 500-ml flask was charged with bromojuglone[18] (1.71 g, 6.75 mmol), a freshly prepared 3.5:1.0 mixture of the deconjugated and conjugated furan-dienes[17] (4.32 g, 26.0 mmol), $SrCO_3$ (3.00 g, 20.3 mmol), and 180 ml of dry benzene. The flask was fitted with a Dean–Stark trap (filled with benzene) and a reflux condenser with a $CaCl_2$ drying tube. The Dean–Stark trap was insulated with cotton and the mixture was heated to reflux (the temp of the oil bath was 115°) for 19 hr with stirring. After cooling to room temp, the mixture was filtered through a bed of Celite using CH_2Cl_2. Solvent was removed at reduced pressure and the crude product was purified by column chromatography on silica gel (240 g) with elution by CH_2Cl_2 and then 5% EtOAc in CH_2Cl_2. Elution with CH_2Cl_2 easily separated the remaining conjugated diene[19] (>90% recovery after Kugelrohr distillation). The Diels–Alder adduct (2.04 g, 6.03 mmol, 89%) was easily separated by elution with 5% ethyl acetate in CH_2Cl_2.

The adduct was dissolved in 180 ml of $CHCl_3$ under oxygen and Et_3N (1.68 ml, 12.0 mmol) was added with stirring and after 6 hr solvent was removed at reduced pressure. Column chromatography on silica gel (105 g) with elution by CH_2Cl_2 and then 20% EtOAc in CH_2Cl_2 afforded 1.68 g (5.01 mmol, 83%; 74% yield from bromojugulone) of the benzofuran **16**. An analytical sample (m.p. soften at 207–210° and then melt at 217–218°) was prepared by recrystallization from hot CH_2Cl_2-MeOH and then from hot benzene-EtOH (2 ×).

Purification of the Diels–Alder adduct by silica gel column chromatography was not necessary before the oxidation step. Thus, in a 50-mg scale experiment, bromojuglone was converted to the benzofuran **16** in 75% overall yield.

Dihydroanthraquinone. NMR ($CDCl_3$): 2.51 (1H, dd, J = 15, 7), 2.61 (1H, dd, J = 16, 7), 2.95 (1H, dd, J = 18, 8), 3.11 (1H, dd, J = 18, 8), 3.62 (1H, m), 3.70 (3H, s), 6.47 (1H, d, J = 2), 7.58 (1H, d, J = 2), 12.08 (1H, s). MS (CI): 339 ($M^+ + 1$, 100).

Benzofuran **16**. IR (KBr): 1735, 1665, 1635, 1590, 1570. NMR ($CDCl_3$): 3.72 (3H, s), 3.98 (2H, s), 6.97 (1H, d, J = 2), 7.28 (1H, dd, J = 8, 2), 7.63 (1H, t, J = 8), 7.81 (1H, dd, J = 8, 2), 8.01 (1H, d, J = 2), 8.11 (1H, s), 12.59 (1H, s). UV (MeOH): 391 (4.09), 295 (sh, 4.13), 273 (4.54), 226 (4.57). MS: 336 (M^+, 100), 278(18), 277(84), 249(36), 101(16), 97(13). (Found: C, 67.79; H, 3.40. Calc for $C_{19}H_{12}O_6$: C, 67.85; H, 3.60%).

Acetal **6a**. The benzofuran **16** (0.560 g, 1.66 mmol) was dissolved in 450 ml of CH_2Cl_2 in a 1-l flask fitted with a gas inlet tube and a $CaSO_4$ drying tube and cooled to −78°. O_3 was bubbled through the soln for 12 min with stirring. Excess O_3 was removed by bubbling argon through the soln for 45 min at −78°. Me_2S (30 ml) was added with stirring and the cooling bath was then removed. After 1 hr, the mixture was

concentrated at reduced pressure to give the crude **9** contamined with dimethylsulfoxide.

The crude **9** was dried by azeotropic evaporation with toluene and then suspended in 50 ml of dry benzene in a 200-ml flask. D-(−)-2,3-Butanediol (0.75 g, 8.3 mmol) and pyridinium *p*-toluene-sulfonate[10] (*ca* 20 mg, 0.08 mmol) were added and the mixture was heated to reflux under argon with azeotropic removal of water for 24 hr. After cooling to room temp, the mixture was partitioned between CH_2Cl_2 and 5% $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were washed with water (2 ×) and dried over Na_2SO_4. Solvent was removed at reduced pressure to give the crude product. It was purified by column chromatography on silica gel (100 g) with elution by CH_2Cl_2 and then 5% EtOAc in CH_2Cl_2 to give 0.632 g (1.53 mmol, 92%) of the acetal **6a**. An analytical sample (m.p. 192–194°) was prepared by recrystallization from hot MeOH (2 ×). IR (CH_2Cl_2): 1740, 1680, 1625, 1575, 1080. NMR ($CDCl_3$): 1.33 (3H, d, J = 6), 1.42 (3H, d, J = 6), 3.67 (3H, s), 3.85 (2H, m), 3.99 (2H, s), 6.53 (1H, s), 7.68 (1H, s), 11.95 (1H, s), 12.63 (1H, s). UV (MeOH): 432 (4.12), 287 (4.07), 278 (4.07), 253 (4.37), 228 (4.82). MS: 412 (M^+, 18), 340(22), 339(100), 312(15), 310(16), 309(16), 308(18), 307(35), 281(29), 280(45), 267(19). $[\alpha]_D$: −47.9° (*c* 0.192, $CHCl_3$). (Found: C, 64.02; H, 4.83. Calc. for $C_{22}H_{20}O_8$: C, 64.07; H, 4.89%).

Aldols **10a** *and* **11a**. The acetal **6a** (288 mg, 0.698 mmol), 1-(trimethylsilyl)-2-butanone (1.41 g, 9.78 mmol), and 105 ml of dry acetonitrile were placed in a dry 250-ml flask under argon. The mixture was cooled to *ca* −23° and $SnCl_4$ (1.1 M in CH_2Cl_2, 0.95 ml, 1.04 mmol) was added dropwise with stirring over 3 min. After 3 hr at *ca* −23°, the temp of the cooling bath was allowed to slowly rise to −10°. Satd $NaHCO_3$ aq (50 ml) was added (the total reaction time was 4.5 hr) and the mixture was partitioned between CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2 (3 ×) and the combined organic extracts were dried over Na_2SO_4. Solvent was removed at reduced pressure to give the crude product, which was dissolved in warm benzene. Hexane was added and after gradual cooling to −15°, the major product **10a** crystallized. The solid was collected by filtration, washed with hexane, and recrystallized from benzene-hexane to afford 157 mg (0.324 mmol) of pure **10a**. The combined mother liquors were purified by PLC on silica gel with 12% EtOAc in benzene as eluant to give an additional 98 mg (0.202 mmol, 75% total yield of **10a**) and 25.4 mg (0.0524 mmol, 7.5%) of **11a** (TLC R_f of **10a**: 0.36; R_f of **11a**: 0.27; 15% ethyl acetate in CH_2Cl_2). An analytical sample of **10a** (m.p. 120–124°) was prepared by recrystallization from benzene-hexane (2 ×).

Major aldol **10a**. IR (CH_2Cl_2): 1735, 1715, 1670, 1620, 1570, 1080. NMR ($CDCl_3$): 0.95 (3H, d, J = 6), 1.06 (3H, t, J = 7), 1.12 (3H, d, J = 6), 2.48 (2H, q, J = 7), 3.73 (3H, s), 4.00 (2H, s), 5.46 (1H, dd, J = 8, 4), 7.68 (1H, s), 11.89 (1H, s), 12.93 (1H, s). UV (MeOH): 432 (4.08), 288 (4.03), 277 (sh, 4.05), 257 (4.40), 228 (4.74). MS: 484 (M^+, <1), 396(24), 376(13), 365(21), 340(50), 339(100), 338(71), 337(59). $[\alpha]_D$: −155° (*c* 0.190, $CHCl_3$). (Found: C, 64.35; H, 5.83. Calc for $C_{26}H_{28}O_9$: C, 64.45; H, 5.83%).

Minor aldol **11a**. IR (CH_2Cl_2): 1735, 1715, 1670, 1620, 1570, 1080. NMR ($CDCl_3$): 0.86 (3H, d, J = 6), 1.08 (3H, t, J = 7), 1.09 (3H, d, J = 6), 2.48 (2H, q, J = 7), 3.72 (3H, s), 4.02 (1H, d, J = 15), 4.20 (1H, d, J = 15), 5.74 (1H, dd, J = 10, 3), 7.69 (1H, s), 11.97 (1H, s), 12.73 (1H, s). UV (MeOH): 432, 288, 277 (sh), 257, 228. MS: 484 (M^+, <1), 376(100). $[\alpha]_D$: −14.2° (*c* 0.445, $CHCl_3$). M.p.: 77–86° (ether-hexane).

Cyclization products **12** *and* **13**. To a stirred suspension of **10a** (179 mg, 0.369 mmol) in 60 ml of MeOH was added K_2CO_3 (124 mg, 0.897 mmol). After stirring the blood-red soln for 2.5 hr at room temp, 1 M HCl (2 ml) was added. The mixture was partitioned between CH_2Cl_2 and water and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with water and dried over Na_2SO_4. Solvent was removed at reduced pressure to give the crude product. It was purified by PLC on silica gel with 12% EtOAc in CH_2Cl_2 as eluant to give 95.6 mg (0.197 mmol, 53%) of **12** and 74.5 mg (0.154 mmol, 42%) of **13** (TLC R_f of **12**: 0.57; R_f of **13**: 0.25; 15% EtOAc in CH_2Cl_2 (2 developments)). An analytical sample of **12** (m.p. 116° and 163–165° (double m.ps)) was prepared by recrystallization from ether-hexane (2 ×). An analytical sample of **13** (m.p. 179–180°) was prepared by recrystallization from ether-hexane (2 ×).

Major cyclization product **12**. IR (CH_2Cl_2): 3480, 1730, 1675, 1620, 1570, 1380. NMR ($CDCl_3$): 1.10 (3H, t), 1.18 (3H, d, J = 6), 1.26 (3H, d, J = 6), 2.40 (2H, d, J = 3), 3.69 (3H, s), 4.15 (1H, s), 4.31 (1H, br s), 4.51 (1H, s), 5.33 (1H, t, J = 3), 7.72 (1H, s), 11.87 (1H, s), 13.26 (1H, s). UV (MeOH): 430 (4.02), 287 (sh, 3.97), 287 (sh, 4.00), 256 (4.35), 228 (4.66). MS: 484 (M^+, <1), 376(100). $[\alpha]_D$: +202° (*c* 0.384, $CHCl_3$). (Found: C, 64.04; H, 5.83. Calc for $C_{26}H_{28}O_9$: C, 64.45; H [illegible]

Minor cyclization product **13**. IR [illegible] 3480, 1725, 1575, 1620, 1570, 1380. NMR ($CDCl_3$): 1.02 (3H, t), 1.14 (3H, d, J = 6), 1.24 (3H, d, J = 6), 2.09 (1H, dd, J = 14, 4), 2.55 (1H, dd, J = 14, 6), 3.84 (3H, s), 4.11 (1H, s), 5.23 (1H, dd, J = 6, 4), 7.55 (1H, s), 11.91 (1H, s), 13.01 (1H, s). UV (MeOH): 431 (4.08), 287 (sh, 3.92), 278 (sh, 3.98), 258 (4.44), 228 (4.63). MS: 484 (M^+, 1), 376(86), 319(100). $[\alpha]_D$: +180° (*c* = 0.152, $CHCl_3$). (Found: C, 63.96; H, 5.80. Calc for $C_{26}H_{28}O_9$: C, 64.45; H, 5.83%).

(+)-*Aklavinone* (**2**). The cyclization product **12** (43.6 mg, 0.090 mmol) and a magnetic stirring bar were placed in a 50-ml flask under argon and cooled to −78°. Trifluoroacetic acid (3 ml) was added dropwise down the sides of the flask over 2 min. The temp of the cooling bath was allowed to slowly rise to 10° over 3 hr; stirring was begun when the trifluoroacetic acid began to melt at *ca* −15°. After the 3-hr period, the cooling bath was removed and stirring was continued for 1.7 hr. The mixture was thoroughly concentrated at reduced pressure and the crude adduct was dissolved in 7.2 ml of acetone. Freshly prepared 5% $NaHCO_3$ aq (3 ml) was added with stirring and after 1 hr water (16 ml) was added. The mixture was extracted with CH_2Cl_2 (3 ×) and the combined organic extracts were dried over $NaSO_4$ and concentrated at reduced pressure. The crude product was purified by PLC on silica gel with 12% EtOAc in benzene as eluant (two developments) to afford 31.3 mg (0.076 mmol, 84%) of (+)-aklavinone (**2**) ([α]$_D$ +150° (*c* 0.214, $CHCl_3$)) and 1.10 mg (0.003 mmol, 3%) of 7-epi-aklavinone. A sample of (+)-**2** was crystallized from hot benzene to give red-orange needles with m.p. 170–172° [lit.: m.p. 170°[14]].

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