Application of the α,β-Epoxy Ketone Photorearrangement to Diterpene Construction. Stereoselective Synthesis of (±)-4aβ,10β-Doladiol Acetate

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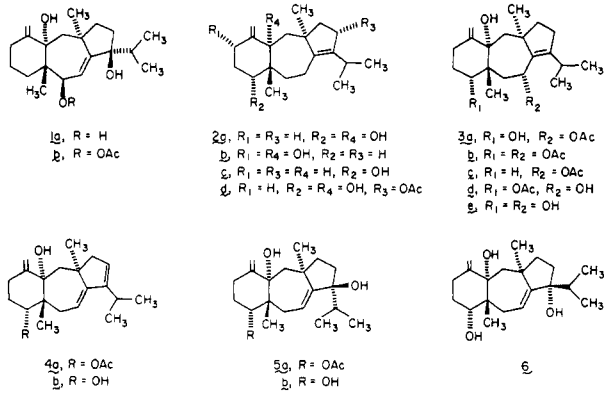
The feasibility of using anthracenone precursors for the synthesis of dolastanes has been examined. The *anti*-tricyclic dienone **11** was prepared as shown in Scheme II. Following conversion to α,β-epoxy ketone **12**, its photoisomerization with 3000-Å light was studied. Although the 6-7-5 fused β-diketone was produced with excellent stereocontrol as expected, this substance was labile to chromatography. For this reason, direct conversion to enol acetate **13** preceded its isolation. Regiospecific introduction of the isopropyl group was realized by transformation of **13** into the vinylogous thio ester **14** and cuprous cyanide catalyzed addition of isopropylmagnesium bromide to this intermediate as illustrated in Scheme III. The NMR spectrum and conformation of **15** were compared to those of the syn isomer prepared in an analogous manner (Scheme IV). Finally, **15** was converted into the title compound (**7**) by a three-step sequence involving singlet oxygenation, hydride reduction, and regiospecific acetylation.

The dolestanes are a group of more than 15 marine diterpenes that possess a uniquely distinctive linear 6-7-5 array of fused alicyclic rings. In 1976, dolatriol (**1a**) was characterized by Pettit and co-workers,[3] who also showed **1a** to be strinkingly cytotoxic. Although both substances were isolated from the digestive gland of the poisonous Indian Ocean sea hare *Dolabella auricularia*, they are actually produced by algae (family Dictyotaceae) and concentrated by *Dolabella* through its diet.[4] At a somewhat later date, amijiol (**2a**), isoamijiol (**2b**), 14-deoxyamijiol (**2c**), and amijidictyol (**2d**) were isolated by Ochi et al. from the brown seaweed *Dictyota linearis* and found to exhibit antimicrobial activity against *Bacillus subtilus* and *Penicillium crustosum*.[5] Sun and his group characterized **3a–c** and **4a** as being present in the Caribbean alga *Dictyota divaricata*.[6] Like 1,[7] the structures **2–4** were secured by a combination of X-ray crystallography, spectral data, and chemical interconversion. The indicated absolute stereochemistry has been assigned to isoamijiol (**2b**)[8] following application of Nakanishi's CD allylic chiroptical technique.[9,10]



1a, R = H
b, R = OAc

2a, $R_1 = R_3 = H$, $R_2 = R_4 = OH$
b, $R_1 = R_4 = OH$, $R_2 = R_3 = H$
c, $R_1 = R_3 = R_4 = H$, $R_2 = OH$
d, $R_1 = H$, $R_2 = R_4 = OH$, $R_3 = OAc$

3a, $R_1 = OH$, $R_2 = OAc$
b, $R_1 = R_2 = OAc$
c, $R_1 = H$, $R_2 = OAc$
d, $R_1 = OAc$, $R_2 = OH$
e, $R_1 = R_2 = OH$

4a, R = OAc
b, R = OH

5a, R = OAc
b, R = OH

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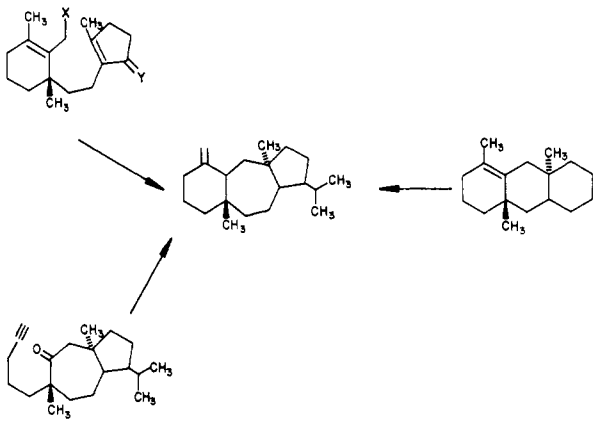
Scheme I



Still more recently, Crews and co-workers isolated **2a** and **4a** from the intertwined toxic algae *D. linearis* and *D. divaricata*.[11] Finally, a collection of *D. dichotoma* from the Canary Islands has yielded a number of dolastane metabolites (**3b, 3d, 3d, 4a,b, 5a,b, 6**).[12]

Conceptually, several broad strategies for construction of the dolastane framework appear possible (Scheme I). One approach involves assembly of the tricyclic nucleus by closure to form the seven-membered ring last. However, any dependence upon penultimate construction of the medium ring appears ill-fated.[13] A complementary protocol would be to fuse the methylenecyclohexane ring onto a preformed perhydroazulene nucleus. In actuality Pattenden and Robertson have recently deployed this scheme to prepare isoamijiol.[14] Finally, it should be possible to utilize a functionalized anthracene precursor, which is ultimately caused to undergo bond-switching of an intraannular link and concomitant ring expansion–ring con-

(1) Kimberly Graduate Fellow, 1984–1985.
(2) Author to whom inquiries concerning X-ray analysis should be directed at the Merck Sharp and Dohme address.
(3) Pettit, G. R.; Ode, R. H.; Herald, C. L.; Von Dreele, R. B.; Michel, C. *J. Am. Chem. Soc.* **1976**, *98*, 4677.
(4) Fenical, W., private communication.
(5) (a) Ochi, M.; Watanabe, M.; Miura, I.; Taniguchi, M.; Tokoroyama, T. *Tetrahedron Lett.* **1980**, *21*, 1229. (b) Ochi, M.; Watanabe, M.; Kido, M.; Ichikawa, Y.; Miura, I.; Tokoroyama, T. *Ibid*, **1980**, 1234.
(6) Sun, H. H.; McConnell, O. J.; Fenical, W.; Hirotsu, K.; Clardy, J. *Tetrahedron* **1981**, *37*, 1237.
(7) Von Dreele, R. B. *Acta Crystallogr., Sect. B* **1977**, *B33*, 1047.
(8) Harada, N.; Yokota, Y.; Iwabuchi, J.; Uda, H.; Ochi, M. *J. Chem. Soc., Chem. Commun.* **1984**, 1220.
(9) (a) Harada, N.; Iwabuchi, J.; Yokoto, Y.; Uda, H.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 5590. (b) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy–Exciton Coupling in Organic Chemistry*; University Science Books: Mill Valley, CA, 1983.
(10) In much of the early work, only the correct *relative* stereochemistry of the available dolastanes was deduced. The more recent developments point to a consistent *absolute* stereochemical interrelationship. This notation is used herein, despite the fact that all necessary correlations have not yet been made.
(11) Crews, P.; Klein, T. E.; Hogue, E. R.; Myers, B. L. *J. Org. Chem.* **1982**, *47*, 811.
(12) Gonzalez, A. G.; Martin, J. D.; Norte, M.; Rivera, P.; Perales, A.; Fayos, J. *Tetrahedron* **1983**, *39*, 3355.
(13) Belmont, D. T.; Paquette, L. A. *J. Org. Chem.* **1985**, *50*, 4102.
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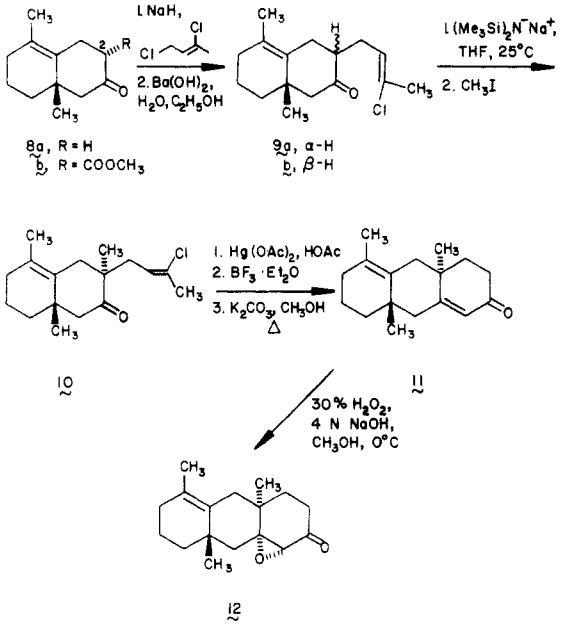
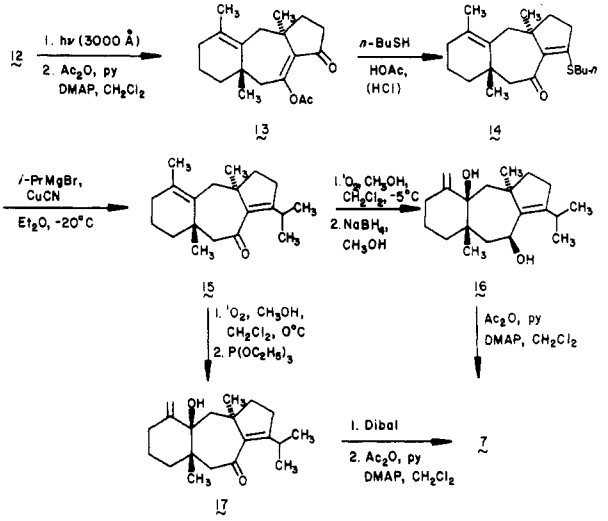
Scheme II

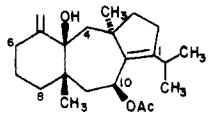


Scheme III



traction in the proper direction.

Since we had successfully employed an α,β-epoxy ketone photoisomerization route[15] to gain access to isoingenol derivatives,[16] we have now explored this strategy for the synthesis of dolastanes. Herein we report the results of



this investigation, which has resulted in a total synthesis of 4aβ,10β-doladiol acetate (**7**) and opened a direct avenue to a series of compounds stereoisomeric with **1**–**6** at C-4a.

The key transformation envisioned was the excited-state isomerization of **12**. Accordingly, we first prepared anthracenone **11** as illustrated in Scheme II. Previous studies have shown[17] that the readily available octahydronaphthal-8(9)-en-3-one **8a**[18] not only enolizes regiospecifically toward C-2 but also undergoes fully stereocontrolled α-alkylation or acylation at this site. The sodium salt of known β-keto ester **8b**[17] was alkylated with 1,3-dichloro-2-butene[19] in refluxing toluene. Without purification, the Wichterle product was subjected to base-promoted hydrolysis and decarboxylation.[20] This two-step transformation proceeds to give a chromatographically separable mixture of **9a** (62%) and **9b** (25%). This ratio appears to be near the point of thermodynamic equilibration, since independent treatment of **9b** under comparable alkaline conditions returned **9a** (71%) and **9b** (28%) after medium pressure chromatography.

In actuality, there exists no need to fractionate these stereoisomers since both undergo stereospecific conversion to **10** following generation of the enolate anion under thermodynamic conditions. Although use of potassium *tert*-butoxide in a refluxing solvent system comprised of benzene and *tert*-butyl alcohol (4:1)[21] proved satisfactory (67%), greatly improved yields were realized with sodium hexamethylidsilazide in tetrahydrofuran at room temperature (94%).[22] Hydrolysis of the vinyl chloride with mercuric acetate and boron trifluoride etherate in acetic acid[23] gave rise efficiently to the expected diketone whose ultimate cyclization furnished the desired enone **11**. While performance of the latter sequence at the 150-mg level provided tricyclic product in 65% yield, an increase in scale to 4–10 g was accompanied by halving of the overall efficiency (32–37%). We were not able to ascertain the cause of this unattractive facet of the synthesis.

Alkaline peroxidation of **11** proceeded slowly. When the reaction was carried out at 2–5 °C to guard against excessively rapid hydrogen peroxide decomposition, an 84% yield of **12** was realized after 2 days. This stereochemically homogeneous product is tentatively assigned as the α isomer on the basis of precedent.[17,24] Precise resolution of this question is not relevant to our goal, since both newly introduced stereogenic centers are destroyed in the next immediate chemical maneuver.

Based upon Jeger's use of the epoxy ketone photorearrangment in steroids,[15] it was expected that **12** would undergo conversion to a 6-7-5 tricyclic diketone *without loss of stereochemistry at either of its two methyl-substituted chiral centers*. Indeed, irradiation in tetrahydrofuran with 3000-Å light triggered the intended ring-switching transformation. Best results were obtained when the photoisomerization was halted at 40–50% conversion because of further deleterious excited-state reactions of the resulting 1,3-diketone during excessively long irradiation periods. Because the photoproduct proved unstable to chromatographic adsorbents, its enol acetate **13** was prepared in situ[25] prior to separation from unreacted **12**. These experimental conditions routinely led to the isolation of **13** in 33% overall yield alongside 52% recovery of **12** (Scheme III).

(15) (a) Jeger, O.; Schaffner, K.; Wehrli, H. *Pure Appl. Chem.* **1964**, *9*, 555. (b) Jeger, O.; Schaffner, K. *Ibid.* **1970**, *21*, 247.
(16) Paquette, L. A.; Nitz, T. J.; Ross, R. J.; Springer, J. P. *J. Am. Chem. Soc.* **1984**, *106*, 1446.
(17) Paquette, L. A.; Belmont, D. T.; Hsu, L.-Y. *J. Org. Chem.* **1985**, *50*, 4667.
(18) Marshall, J. A.; Cohen, N.; Hochstetler, A. R. *J. Am. Chem. Soc.* **1966**, *88*, 3408.
(19) (a) Dauben, W. G.; McFarland, J. W. *J. Am. Chem. Soc.* **1960**, *82*, 4245. (b) Marshall, J. A.; Schaeffer, D. J. *J. Org. Chem.* **1965**, *30*, 3642. (c) Caine, D.; Tuller, N. F. *Ibid.* **1969**, *34*, 222.
(20) Miller, R. B.; Nash, R. D. *Tetrahedron Lett.* **1974**, 2961.
(21) Mazur, Y.; Sondheimer, F. *J. Am. Chem. Soc.* **1958**, *80*, 5220.
(22) Ziegler, F. E.; Klein, S. I.; Pati, U. K.; Wang, T.-F. *J. Am. Chem. Soc.* **1985**, *107*, 2730.
(23) Martin, S. F.; Chou, T. *Tetrahedron Lett.* **1978**, 1943.
(24) See, for example: Jung, M. E.; Hatfield, G. L. *Tetrahedron Lett.* **1983**, *24*, 3175.
(25) Suginome, H.; Yabe, T.; Osawa, E. *J. Chem. Soc., Perkin Trans. 1* **1982**, 931.

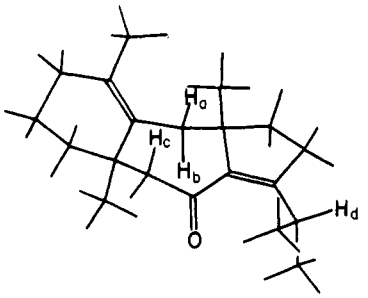
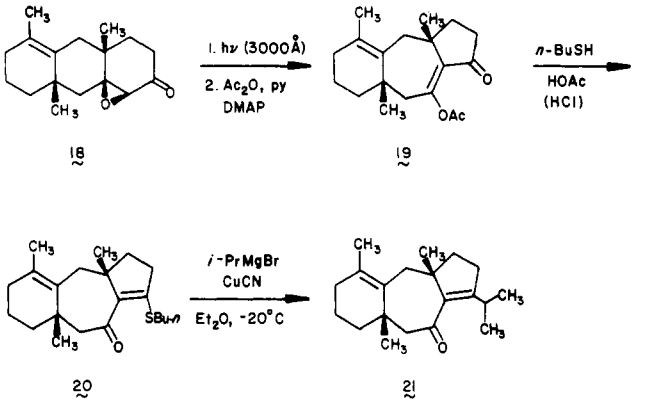


Figure 1.

Scheme IV



Addition of an isopropyl nucleophile to the carbonyl group of **13** was now required to arrive at the dolastane skeleton. Following relatively extensive preliminary chemical exploration, it was determined that acquisition of **15** could be accomplished most efficaciously by prior conversion to **14**. Thus, initial exposure to *n*-butyl mercaptan in acetic acid with concentrated hydrochloric acid as catalyst[25] provided **14** without proclivity for side reactions. Vinylogous thio esters of this type have proved receptive to substitution by Grignard reagents in the presence of cuprous cyanide.[26] Application of this methodology to **14** with appropriate temperature control gave **15** exclusively. Maximum efficiency was achieved with 2.3 equiv of isopropylmagnesium bromide and 0.14 equiv of CuCN in ether at −20 °C.

The ^{1}H NMR spectrum of **15** is characterized by several resonances that are downfield shifted to appreciable levels. These effects, likely arising as a consequence of the particular conformation adopted by this conjugated enone, held our curiosity and caused us to pursue a companion study. Specifically, the synthesis of **21** where the angular methyl groups now enjoy a cis relationship was undertaken. For this purpose, epoxy ketone **18**, available from an earlier investigation in these laboratories,[17] was subjected to an entirely comparable four-step sequence (Scheme IV). Since similar efficiencies were realized at each stage, the pathway appears to hold general applicability.

To assist in gaining information on the stereostructures of **15** and **21**, molecular mechanics calculations were carried out. Through use of Still's program MODEL[27] (an enhanced graphics interactive version of Allinger's MM2 program[28]), multiple energy minimizations were made and eventually refined through application of MMP2 (a π-enhanced version of MM2 for recalculation under the π-planar

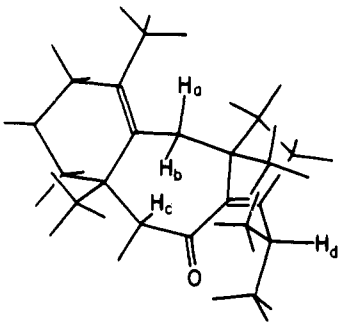


Figure 2.

nonrestriction mode). This resulted in arrival at a final global energy minimum in both instances and these conformations are illustrated in Figures 1 and 2, respectively.

Although the conformations of **15** and **21** differ in many respects and the syn isomer is more sterically strained by 4.4 kcal/mol,[29] certain spectroscopically observable parameters are rather similar. For example, the angular methyl groups in this pair of dienones have closely comparable chemical shifts. In **15**, the two relevant resonances appear at δ 1.08 and 1.02, while in **21** the corresponding signals are found at δ 1.16 and 1.03 (in $CDCl_3$ solution). Similarly, both compounds display an appreciably deshielded doublet of unit area (δ 2.85 and 2.82, respectively). The implicated proton is H_a as a direct result of its approximate position in the *xy* plane of the carbon–carbon double bond where strong deshielding is exerted because of near maximum π-bond anisotropy.[30] The geminal proton H_b, to which H_a is strongly coupled, resides well above or below this plane.

One α-carbonyl proton also experiences increased deshielding relative to its geminal partner (δ 2.57 in **15**; 2.70 in **21**) and these are labeled as H_c. Finally, the methine hydrogen of the isopropyl substituent (H_d) is the most strikingly affected proton of all, appearing well downfield of all other signals at δ 3.34 and 3.65, respectively. This effect is likely the result of relatively restricted rotation about the isopropyl group, with fixation of H_d in the plane of the C–O double bond 3.5–4 Å distant from the oxygen atom. Long-range deshielding effects operate effectively under these circumstances.[31]

Since the C_{3a}-methyl group in **15** is clearly seen to shield the proximal face of the cyclohexene double bond effectively, singlet oxygenation of this substrate (Scheme III) was certain to proceed with β introduction of the allylic hydroperoxy group. When the oxidation was followed immediately by sodium borohydride reduction[32] and acetylation, **7** was obtained in less than satisfactory overall yield (25%). On the other hand, treatment of the allylic hydroperoxide with triethyl phosphite[33] gave **17** in 66% yield. Subsequent Dibal reduction and acetylation of this intermediate proved to be essentially quantitative steps.

As noted above, the β stereodisposition of the angular hydroxyl group in ring A was anticipated on steric grounds. This conclusion received added support from the chemical shifts of the exo methylene protons in **7**, **16**, and **17** relative

(26) (a) Gammill, R. B.; Bryson, T. A. *Tetrahedron Lett.* **1975**, 3793. (b) Gammill, R. B.; Bryson, T. A. *Synth. Commun.* **1976**, *6*, 209.
(27) (a) Still, W. C.; MacPherson, L. J.; Harada, T.; Rheingold, A. *Tetrahedron* **1984**, *40*, 2275. (b) Still, W. C.; Galynker, I. *Ibid.* **1981**, *37*, 3981.
(28) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.
(29) More precisely, the computed steric energies are as follows: **15** = 34.25 kcal/mol and **21** = 38.63 kcal/mol.
(30) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed; Pergamon Press: Oxford, 1969; Chapters 2.2, 3.6.
(31) Pople, J. A. *J. Chem. Phys.* **1962**, *37*, 60.
(32) See, for example: Paquette, L. A.; Hertel, L. W.; Gleiter, R.; Bohm, M. C.; Beno, M. A.; Christoph, G. G. *J. Am. Chem. Soc.* **1981**, *103*, 7106.
(33) See, for example: Herz, W.; Juo, R.-R. *J. Org. Chem.* **1985**, *50*, 618.

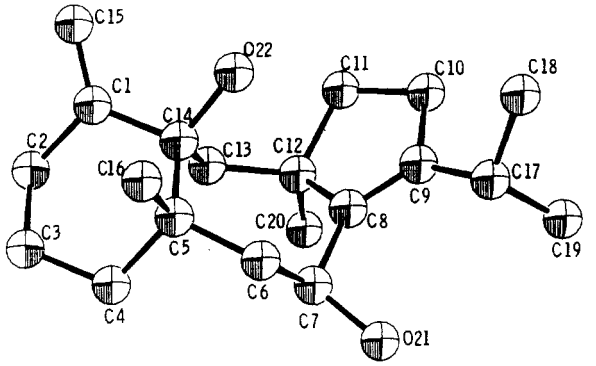
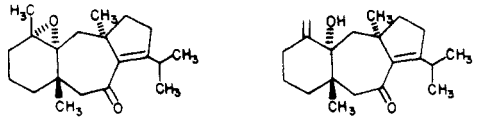


Figure 3. Computer-generated drawing of **16** derived from the X-ray coordinates with hydrogens omitted for clarity.

to those seen in **3c** and its relatives. Thus, in C_6D_6 solution the two olefinic protons in **3c** appear as two closely spaced singlets at δ 4.75 and 4.66. In **7**, the same protons are seen at δ 5.28 and 4.75. While a $\Delta\delta$ of 0.05–0.13 is characteristic of the natural 4aα-hydroxyl series ($CDCl_3$ or C_6D_6), β orientation of the angular hydroxyl invariably increases the magnitude of this gap to 0.21–0.53.

In contrast, the stereochemistry of hydride attack at the carbonyl group in **17** is less easily predicted. Although π-facial selectivity by sodium borohydride and Dibal proved to be unidirectional, it was not possible to establish the configuration of the secondary allylic hydoxyl center with certainty by spectroscopic means. For this reason, recourse was made to an X-ray crystal structure analysis of **16**. As can be seen from the final X-ray model illustrated in Figure 3, the newly introduced chiral center possesses a β hydroxyl group. Furthermore, an intermolecular hydrogen bond of length 2.80 Å links O21 (H21) to O22.

In an attempt to reverse the 4a-hydroxyl stereochemistry, **15** was treated with *N*-bromosuccinimide in buffered aqueous tetrahydrofuran. The expectation was that initial bromonium ion formation on the more open β face would permit subsequent base-promoted cyclization of the bromohydrin to α-epoxide **22**. The projected ring opening to give **23** is well precedented.[34] However, only the direct oxidation of **15** to **24** was observed in 70% yield. This transformation is not unknown, having been previously observed with a few triterpene and steroidal olefins possessing sterically hindered double bonds much as in **15**.[35]



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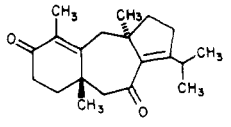

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In summary, we have explored the α,β-epoxy ketone photorearrangement[36] as a method for constructing the dolastane skeleton and found it to be well suited for this purpose. Although ready entry is gained to the relevant tricyclic array of differently sized fused rings, that conformation adopted by the anti isomer is such that introduction of the angular hydroxyl via singlet photooxygenation can only be realized from the β direction. Thus, substrates epimeric with the natural series at the tertiary alcohol site result. This stereochemical scenario is not reversed, even in part, if the allylic hydroperoxidation is implemented prior to photorearrangement.[37] Notwithstanding, the pathway developed herein makes practically available dolastane stereoisomers not attainable from natural sources.

Experimental Section

1,2,3,4,4a,5,6,7-Octahydro-2-(3-chloro-2-butenyl)-4a,8-dimethyl-3-naphthalenone (9). To a stirred suspension of sodium hydride (50% dispersion in oil, 933 mg, 20.3 mmol) in 30 mL of dry toluene under nitrogen was added dimethyl carbonate (2.85 mL, 33.8 mmol) followed by a solution of **8a** (3.01 g, 16.9 mmol) in 10 mL of the same solvent. The resulting mixture was heated at the reflux temperature for 2.25 h, at which point 2.73 mL (25.4 mmol) of 1,3-dichloro-2-butene was introduced in one portion. After an additional 4.25 h of heating, the slurry was cooled to room temperature, treated with solid ammonium chloride, stirred for 15 min, and filtered through a short pad of Florisil that was subsequently washed with 50% ethyl acetate in petroleum ether. After concentration of the filtrate in vacuo at 25 °C, 6.5 g of alkylation product was obtained.

The above material was dissolved in a mixture of water (80 mL) and 95% ethanol (160 mL). Following the addition of barium hydroxide (2.74 g, 16.0 mmol), the solution was heated to reflux for 9 h, cooled to room temperature, treated dropwise with 8 mL of 4 N hydrochloric acid, and diluted with brine (100 mL). The product was extracted in ether–petroleum ether (1:1, 3 × 250 mL) and the combined organic layers were dried and concentrated. Flash chromatographic purification on silica gel (elution with 2% ethyl acetate in petroleum ether) gave 2.82 g (62%) of **9a** and 1.12 g (25%) of **9b**.

For **9a**: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.55 (t, J = 7.7 Hz, 1 H), 2.92 (dd, J = 13.8 and 6.0 Hz, 1 H), 2.45 (m, 1 H), 2.35 (m, 2 H), 2.25 (m, 1 H), 2.14 (d, J = 12.7 Hz, 1 H), 2.09 (d, J = 1.1 Hz, 3 H), 2.0 (m, 3 H), 1.70 (s, 3 H), 1.65–4.40 (m, 4 H), 0.99 (s, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) ppm 211.67, 170.71, 131.73, 127.53, 123,57, 56.05, 49.93, 39.52, 32.87, 32.23, 28.63, 26.14, 19.57, 19.37 (two carbons not observed); MS, m/z (M^+) calcd 266.1437, obsd 266.1425.

For **9b**: colorless oil; IR (neat, cm^{-1}) 2915, 2855, 1700; ^{1}H NMR (300 MHz, $CCCl_3$) δ 5.38–5.27 (m, 1 H), 2.65 (d, J = 12.5 Hz, 1 H), 2.57–1.87 (series of m, 8 H), 2.06 (s, 3 H), 1.68 (s, 3 H), 1.75–1.38 (m, 4 H), 1.04 (s, 3 H); MS, m/z (M^+) calcd 266.1437, obsd 266.1436.

Equilibration of 9b. A magnetically stirred solution of **9b** (104.5 mg, 0.391 mmol) in 3 mL of 95% ethanol and 1 mL of water was treated with 10 mg of barium hydroxide and heated to the reflux temperature for 35 min. After cooling, the solution was diluted with brine (10 mL) and extracted with ether–petroleum ether (1:1, 3 × 20 mL). The combined organic phases were washed with brine, dried, and concentrated in vacuo. MPLC of the residue on silica gel (elution with 4% ethyl acetate in petroleum ether) furnished 73.6 mg (71%) of **9a** and 29.0 mg (28%) of **9b**.

1,2,3,4,4a,5,6,7-Octahydro-2-(3-chloro-2-butenyl)-2,4a,8-trimethyl-3-naphthalenone (10). A magnetically stirred solution of the **9a**/**9b** mixture (4.21 g, 15.8 mmol) in 60 mL of dry tetrahydrofuran was treated dropwise under nitrogen with 1.0 M sodium hexmethyldisilazide in the same solvent (16.6 mL, 16.6 mmol). The resulting mixture was stirred at room temperature for 10 min, methyl iodide (1.08 mL, 17.4 mmol) was added, and stirring was continued for an additional 20 min. The product was taken up in ether–petroleum ether (1:1, 500 mL), and this solution was washed with brine, dried, and concentrated. Flash chromatographic purification of the residue on silica gel (elution with 2% ethyl acetate in petroleum ether) furnished 4.17 g (94%) of

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(36) The first example of this process was reported by Bodforss, S. *Ber. Dtsch. Chem. Ges.* **1918**, *51*, 214.
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10 as a coloreless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.58 (t, J = 7.0 Hz, 1 H), 2.50 (d, J = 14.2 Hz, 2 H), 2.36 (t, J = 8.8 Hz, 2 H), 2.25 (m, 1 H), 2.10 (d, J = 0.7 Hz, 3 H), 2.05 (m, 3 H), 1.69 (s, 3 H), 1.65–1.40 (m, 4 H), 1.07 (s, 3 H), 0.98 (s, 3 H); MS, m/z (M^+) calcd 280.1594, obsd 280.1583.

4,4a,6,7,8,8a,9,10-Octahydro-4a,5,8a-trimethyl-2(3*H*)-anthracenone (11). To a stirred solution of **10** (9.80 g, 34.9 mmol) in 388 mL of glacial acetic acid at 25 °C was added mercuric acetate (12.2 g, 38.4 mmol) in small portions. After stirring for an additional 15 min, boron trifluoride etherate (4.72 mL, 38.4 mmol) was added dropwise. Two hours later, the mixture was diluted with water (800 mL) and ethyl acetate–petroleum ether (1:1, 800 mL), and the aqueous phase was reextracted with the same solvent combination (3 × 800 mL). The combined organic layers were washed with water (2 × 800 mL), dried, and concentrated. The residue was dissolved in ethyl acetate/petroleum ether (1:9, 500 mL), filtered, and concentrated at room temperature to give 14.5 g of the diketone as a colorless oil, which was used without further purification; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.55 (m, 4 H), 2.17 (s, 3 H), 2.05 (m, 4 H), 1.85–1.70 (m, 2 H), 1.68 (s, 3 H), 1.65–1.40 (m, 4 H), 1.06 (s, 3 H), 1.00 (s, 3 H).

The above material and potassium carbonate (28.9 g, 209 mmol) in methanol (500 mL) were heated at the reflux temperature for 11.5 h, at which time the solvent was evaporated. The residue was partitioned between water (350 mL) and ethyl acetate–petroleum ether (1:1, 600 mL). The organic phase was washed with brine (2 × 250 mL), dried, and concentrated. Purification of the residue by flash column chromatography on silica gel (elution with 15% ethyl acetate in petroleum ether) gave 3.17 g (37%) of **11** as a colorless solid, mp 59–60 °C; IR (neat, cm^{-1}) 2955, 2920, 2860, 1670, 1616, 1210; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77–5.71 (m, 1 H), 2.56–2.28 (m, 4 H), 2.12–1.74 (m, 6 H), 1.65 (s, 3 H), 1.70–1.50(m, 3 H), 1.50–1.34 (m, 1 H), 1.13 (s, 3 H), 0.97 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 199.25, 169.17, 130.94, 127.89, 124.99, 48.18, 40.32, 39.54, 37.89, 37.42, 37.32, 34.18, 32.87, 25.63, 22.43, 19.50, 19.24; MS, m/z (M^+) calcd 244.1827, obsd 244.1831. Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H., 9.90. Found: C, 83.42; H, 9.80.

1,9a-Epoxy-1,4,4a,6,7,8,8a,9,9a,10-decahydro-4a,5,8a-trimethyl-2(3*H*)-anthracenone (12). A magnetically stirred solution of **11** (215 mg, 0.881 mmol) in 12 mL of methanol cooled to 2 °C was treated with 2.0 mL (17.6 mmol) of 30% hydrogen peroxide. Sodium hydroxide solution (1.10 mL of 4 N) was added dropwise and the resulting mixture was stirred at 2–5 °C for 2 days. Following the addition of saturated sodium sulfite solution (2 mL), the reaction mixture was diluted with brine (20 mL) and extracted with ether (3 × 50 mL). The combined organic layers were dried and evaporated to leave a residue that was purified by MPLC on silica gel (elution with 12% ethyl acetate in petroleum ether). There was obtained 193 mg (84%) of **12** as a colorless solid, mp 97.2–97.7 °C (from ether–petroleum ether): IR (CH_2Cl_2, cm^{-1}) 2960, 2932, 2870, 1700, 1457, 1375; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.09 (s, 1 H), 2.52–1.86 (series of m, 8 H), 1.63 (s, 3 H), 1.74–1.50 (m, 3 H), 1.50–1.30 (m, 2 H), 1.07 (s, 3 H), 1.05 (s, 3 H), 0.95 (d, J = 13.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 206.11, 130.36, 128.95, 66.92, 63.46, 44.55, 39.72, 37.40, 35.53, 34.67, 33.42, 32.95, 30.81, 25.73, 22.36, 1966, 18.85; MS m/z (M^+) calcd 260.1776, obsd 260.1769. Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.40; H, 9.29.

***anti*-3,3a,4,6,7,8,8a,9-Octahydro-10-hydroxy-3a,5,8a-trimethylbenz[*f*]azulen-1(2*H*)-one Acetate (13).** Epoxy ketone **12** (424 mg, 1.63 mmol) was distributed into eight Pyrex test tubes (ca. 50 mg each), which were subsequently capped with a rubber septum and flushed with nitrogen. Dry tetrahydrofuran (8 mL) was introduced via syringe into each tube, which were then mounted on a merry-go-round apparatus housed inside a Rayonet reactor and irradiated with 300-nm light for 18 h. The combined solutions were concentrated and the residue was dissolved in 10 mL of dry dichloromethane. While this solution was stirred under nitrogen, anhydrous pyridine (2.64 mL, 32.6 mmol) and acetic anhydride (0.768 mL, 8.15 mmol) were added suquentially at room temperature. 4-(Dimethylamino)pyridine (20 mg) was introduced and the reaction mixture was stirred at room temperature for 4 h, diluted with ether, washed with water, and dried. Following solvent evaporation, the residue was subjected to MPLC on silica gel (elution with 15% ethyl acetate in petroleum ether). Subsequent to the recovery of unreacted **12** (219 mg, 52%), there was isolated 160 mg (33%) of **13** as a colorless crystalline solid, mp 122.6–123.5 °C (from ether–petroleum ether): IR (neat, cm^{-1}) 2950, 2920, 2860, 1763, 1714, 1630, 1212, 1200, 1146, 1036; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.99 (d, J = 15.8 Hz, 1 H), 2.59 (d, J = 13.9 Hz, 1 H), 2.52–2.25 (m, 3 H), 2.21 (s, 3 H), 2.09–1.95 (m, 2 H), 1.90–1.42 (m, 7 H), 1.68 (s, 3 H), 1.15 (s, 3 H), 1.10 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 203.81, 167. 86, 154.19, 132.74, 131.71, 129.75, 48.76, 42.63, 41.29, 38.40, 37.45, 36.39, 35.73, 33.38, 26.60, 21.82, 20.97, 20.71, 19.23; MS, m/z (M^+) calcd 259.1698, obsd 259.1665. Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.72; H, 8.74.

***anti*-3,3a,4,6,7,8,8a,9-Octahydro-1-(*n*-butylthio)-3a,5,8a-trimethylbenz[*f*]azulen-10(2*H*)-one (14).** To a magnetically stirred solution of **13** (191 mg, 0.632 mmol) in 10 mL of *n*-butyl mercaptan was added dropwise a solution of 4 drops of concentrated hydrochloric acid in 4 mL of glacial acetic acid. The reaction mixture was stirred at room temperature for 4 h, diluted with ethyl acetate-petroleum ether (1:1, 120 mL), and washed with brine (2 × 20 mL) and a solution of 2 mL of saturated sodium bicarbonate in 20 mL of brine prior to drying. Solvent evaporation left a residue that was taken up in dry dichloromethane (5 mL) and treated sequentially with dry pyridine (2 mL), acetic anhydride (1 mL), and 4-(dimethylamino)pyridine (20 mg) in order to reacetylate unreacted diketone. Workup in the predescribed manner was followed by MPLC on silica gel. Elution with 8% ethyl acetate in petroleum ether afforded 138 mg (66%) of **14** while an increase in polarity to 15% ethyl acetate returned 51.7 mg (27%) of **13**.

For **14**: colorless solid, mp 45.5–46.7 °C; IR (neat, cm^{-1}) 2958, 2930, 2870, 1630, 1505; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.88 ($^1/_2$AB d, J = 13.9 Hz, 1 H), 2.84–2.71 (m, 4 H), 2.63 ($^1/_2$AB d, J = 14.0 Hz, 1 H), 2.24 ($^1/_2$AB d, J = 13.9 Hz, 1 H), 2.20 ($^1/_2$AB d, J = 14.0 Hz, 1 H), 2.02 (br t, J = 5.6 Hz, 2 H), 1.92–1.80 (m, 2 H), 1.67 (s, 3 H), 1.70–1.36 (m, 8 H), 1.10 (s, 3 H), 1.01 (s, 3 H), 0.92 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 198.46, 157.978, 139.14, 133.93, 128.95, 57.77, 48.29, 42.39, 41.37, 40.78, 36.18, 33.52, 31.71, 31.16, 25.77, 22.80, 22.05, 20.63, 19.27, 13.56 (one carbon resonance overlapping and not independently observed); MS, m/z (M^+) calcd 332.2174, obsd 332.2208.

***anti*-3,3a,4,6,7,8,8a,9-Octahydro-1-isopropyl-3a,5,8a-trimethylbenz[*f*]azulen-10(2*H*)-one (15).** To a cold (−20 °C), magnetically stirred suspension of dry cuprous cyanide (10.5 mg, 0.117 mmol) in 30 mL of anhydrous ether under argon was added dropwise 1.16 mL of ethereal isopropylmagneisum bromide (0.71 *M*, 0.823 mmol). Following an additional 15 min of stirring at −20 °C, a solution of **14** (275 mg, 0.828 mmol) in anhydrous ether (6 mL) was rapidly introduced and allowed to react at this temperature for 1 h. The reaction mixture was quenched with 4 mL of saturated ammonium chloride solution and 2 mL of ammonium hyroxide before warming to room temperature where it was stirred for 1 h. Following dilution with 100 mL of ethyl acetate–petroleum ether (1:1, 100 mL), the organic layer was separated, washed with brine (2 × 15 mL), and dried. The filtrate was concentrated and purified by MPLC on silica gel (elution with 3% ethyl acetate in petroleum ether) to give 184 mg (78%) of **15** as a colorless crystalline solid, mp 73.9–74.5 °C (from ethanol): IR (neat, cm^{-1}) 2960, 2933, 2870, 1660, 1655, 1600, 1455; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.34 (heptet, J = 6.9 Hz, 1 H), 2.85 ($^1/_2$AB d, J = 14.3 Hz, 1 H), 2.57 ($^1/_2$AB d, J = 14.1 Hz, 1 H), 2.40 (t, J = 7.2 Hz, 2 H), 2.22 ($^1/_2$AB d, J = 14.3 Hz, 1 H), 2.16 ($^1/_2$AB d, J = 14.2 Hz, 1 H), 2.01 (br t, J = 5.5 Hz, 2 H), 1.67 (s, 3 H), 1.75–1.44 (m, 6 H), 1.08 (s, 3 H), 1.02 (s, 3 H), 1.02 (d, J = 7.0 Hz, 3 H), 0.99 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 202.69, 161.69, 142.85, 133.71, 129.04, 57.98, 48.68, 41.98, 40.81, 39.60, 36.06, 33.35, 29.14, 27.94, 25.58, 23.03, 20.92, 20.73, 20.68, 19.10; MS, m/z (M^+) calcd 286.2297, obsd 286.2297. Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.93; H, 10.57.

Conversion of 15 to 7 via 16. A solution of **15** (10.4 mg, 0.0364 mmol) and rose bengal (2 mg) in methanol (1 mL) and dichloromethane (10 mL) was irradiated with a 500-W tungsten lamp while oxygen was bubbled through and cooling to −5 °C was maintained. After 40 min, the reaction mixture was concentrated in vacuo at room temperature and the residue was dissolved in methanol (4 mL). An excess of sodium borohydride was introduced and the progress of the reduction was followed by TLC analysis. Upon completion of the reaction, 5 mL of 1.2 N sodium

hydroxide was added and stirring was maintained for 20 min. After the usual workup, the crude diol was dissolved in dry dichloromethane (1 mL) and treated in turn with anhydrous pyridine (0.5 mL), acetic anhydride (0.2 mL), and 4-(dimethylamino)pyridine (1 mg). Processing of this reaction mixture as described above provided 3.2 mg (25% overall) of **7** as a colorless oil after MPLC purification on silica gel (elution with 5% ethyl acetate in petroleum ether); IR (neat, cm^{-1}) 3555, 2960, 2940, 2870, 1735, 1368, 1240, 1025; ^1H NMR (300 MHz, C_6D_6) δ 5.42 (br d, J = 11.9 Hz, 1 H), 5.28–5.27 (m, 1 H), 4.75 (br s, 1 H), 3.33 (heptet, J = 6.8 Hz, 1 H), 2.45–2.32 (m, 1 H), 2.09 ($^1/_2$AB d, J = 15.3 Hz, 1 H), 2.27–1.84 (m, 7 H), 1.71 (s, 3 H), 1.62 ($^1/_2$AB d, J = 15.3 Hz, 1 H), 1.75–1.42 (m, 3 H), 1.38–1.25 (m, 1 H), 1.18 (s, 3 H), 1.09–0.99 (m, 1 H), 0.98 (s, 3 H), 0.97 (d, J = 6.8 Hz, 3 H), 0.91 (d, J = 6.8 Hz, 3 H); MS, m/z (M^+) calcd 346.2509, obsd 346.2499.

Conversion of 15 to 7 via 17. A solution of **15** (70.3 mg, 0.246 mmol) and rose bengal (1.2 mg) in methanol–dichloromethane (13 mL, 1:9) was irradiated at −5 °C with a 500-W tungsten lamp while oxygen was bubbled through. After 40 min, the reaction mixture was treated with triethyl phosphite (0.3 mL) at room temperature for 1 h with vigorous stirring. After concentration, the residue was purified by MPLC on silica gel (elution with 12% ethyl acetate in petroleum ether) to give 49.3 mg (66%) of **17** as colorless crystals, mp 112.5–113.0 °C (from ether–petroleum ether): IR (CH_2Cl_2, cm^{-1}) 3600, 2945, 2875, 1660, 1592, 1332; ^1H NMR (300 MHz, $CDCl_3$) δ 4.96 (s, 1 H), 4.75 (t, J = 1.7 Hz, 1 H), 3.80 (heptet, J = 6.9 Hz, 1 H), 2.69 ($^1/_2$AB d, J = 11.7 Hz, 1 H), 2.34 ($^1/_2$AB d, J = 15.0 Hz, 1 H), 2.40–2.25 (m, 3 H), 2.15–2.05 (m, 1 H), 2.02 ($^1/_2$AB d, J = 11.7 Hz, 1 H), 1.88 (dd, J = 21.4, 10.1 Hz, 1 H), 1.80 ($^1/_2$AB d, J = 15.0 Hz, 1 H), 1.75–1.64 (m, 2 H), 1.64–1.38 (m, 4 H), 1.23 (s, 3 H), 1.04 (d, J = 6.9 Hz, 3 H), 0.96 (s, 3 H), 0.94 (d, J = 6.9 Hz, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 197.11, 160.64, 154.80, 141.73, 107.23, 79.35, 55.02, 46.68, 46.54, 43.99, 41.23, 34.22, 29.20, 27.99, 27.81, 23.09, 20.63, 20.54, 19.29; MS m/z (M^+) calcd 302.2246, obsd 302.2240. Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.55; H, 10.00.

A magnetically stirred solution of **17** (38.5 mg, 0.127 mmol) in dry dichloromethane (4 mL) under argon at −78 °C was treated dropwise with diisobutylaluminum hydride (0.32 mL of 1.0 M in hexane). The resulting mixture was stirred at −78 °C for 1 h, treated at this temperature with methanol (2 mL) and half-saturated Rochelle's salt solution (8 mL),[38] and allowed to warm to 25 °C where it was stirred for an additional hour. Following dilution with 50 mL of ethyl acetate–petroleum ether (1:1), the organic phase was separated, washed with brine, and dried. The concentrated residue was purified by MPLC on silica gel (elution with 8.5% ethyl acetate in petroleum ether). There was isolated 37.1 mg (96%) of the diol, mp 129.5–130.2 °C (from ether–petroleum ether): IR (CH_2Cl_2, cm^{-1}) 3600, 3550, 2940, 2880, 1450, 1040, 1010; ^1H NMR (300 MHz, C_6D_6) δ 5.30–5.29 (m, 1 H), 4.77–4.76 7m, 1 H), 4.17 (br d, J = 11.2 Hz, 1 H), 3.66 (heptet, J = 6.9 Hz, 1 H), 2.41–2.29 (m, 1 H, 1.96 ($^1/_2$AB d, J = 15.1 Hz, 1 H), 2.23–1.95 (m, 6 H), 1.80–1.70 (m, 1 H), 1.58 ($^1/_2$AB d, J = 15.1 Hz, 1 H), 1.67–1.46 (m, 3 H), 1.40–1.25 (m, 1 H), 1.28 (br s, 1 H), 1.10–1.00 (m, 1 H), 1.01 (d, J = 6.9 Hz, 3 H), 1.00 (s 3 H), 0.96 (d, J = 6.9 Hz, 3 H), 0.95 (s, 3 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 153.40, 143.33, 143.03, 105.19, 80.20, 66.36, 51.72, 48.26, 45.14, 41.17, 38.17, 35.75, 32.70, 28.33, 27.61, 26.89, 23.84, 21.45, 21.38; MS, m/z (M^+) calcd 304.2402, obsd 304.2405. Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found: C, 78.87; H, 10.49.

To a magnetically stirred solution of the diol (20.3 mg, 0.0668 mmol) and dry pyridine (0.5 mL) in 1.5 mL of anhydrous dichloromethane was added 0.3 mL of acetic anhydride and a catalytic quantity (~2 mg) of 4-(dimethylamino)pyridine. After 3 h, the usual workup was implemented and the product was purified by MPLC on silica gel (elution with 2% ethyl acetate in petroleum ether). There was obtained 22.3 mg (96%) of **7**, identical in all respects with the material obtained earlier.

***syn*-3,3a,4,6,7,8,8a,9-Octahydro-10-hydroxy-3a,5,8a-trimethylbenz[*f*]azulen-1(2*H*)-one Acetate (19).** A solution of 50 mg (0.19 mmol) of **18** in 25 mL of dry dioxane was irradiated at 300 nm through quartz in a Rayonet reactor under nitrogen for 24 h. Removal of the solvent under reduced pressure gave a clear, colorless oil that was taken up in 3 mL of acetic anhydride, 3 mL of dry pyridine, and 4-(dimethylamino)pyridine (5 mg) and stirred at 25 °C for 3 h. The mixture was cooled (0 °C) and saturated aqueous sodium bicarbonate solution was slowly added. After 2 h, the reaction mixture was diluted with ether (50 mL), washed with 10% aqueous hydrochloric acid (0 °C, 20 mL) and brine (20 mL), and evaporated. The residual yellow oil was purified by MPLC on silica gel (elution with 18% ethyl acetate in petroleum ether) to give 20 mg (40% recovery) of **18** and 29 mg (78% based on recovered **18**) of **19**: IR ($CDCl_3$, cm^{-1}) 2940, 2840, 1765, 1712, 1640, 1365, 1215; ^1H NMR (300 MHz, $CDCl_3$) δ 2.82 (d, J = 14.2 H, 1 H), 2.60 (d, J = 14.4 Hz, 1 H), 2.10 (m, 6 H), 2.02 (s, 3 H), 1.70 (m, 5 H), 1.65 (s, 3 H), 1.38 (m, 1 H), 1.24 (s, 3 H), 1.05 (s, 3 H); MS, m/z ($M^+ - CH_3CO_2$) calcd 243.1749, obsd 243.1704.

Hydrolysis of 19. Potassium hydroxide (10% in ethanol) was added to a solution of **19** (40 mg, 0.13 mmol) in 5 mL of ethanol until the starting material was consumed (TLC analysis). The mixture was diluted with ether (40 mL) and washed with 10% aqueous hydrochloric acid (20 mL) and brine (20 mL) prior to drying. The solvent was evaporated to leave 30 mg (75%) of 1,3-diketone as a colorless oil: IR ($CDCl_3$, cm^{-1}) 2940, 1660, 1605, 1370; ^1H NMR (300 MHz, $CDCl_3$) δ 2.62 (m, 2 H), 2.45 (m, 1 H), 2.20 (m, 1 H), 1.95 (m, 7 H), 1.64 (m, s at 1.64, 6 H), 1.17 (s, 3 H), 1.08 (s, 3 H), enolic proton not observed; ^{13}C NMR (75 MHz, $CDCl_3$) ppm 205.61, 175.49, 192.28, 129.36, 116.83, 45.41, 43.99, 39.96, 37.16, 36.11, 35.27, 35.05, 31.26, 27.18, 27.14, 21.04, 18.74.

***syn*-3,3a,4,6,7,8,8a,9-Octahydro-1-(*n*-butylthio)-3a,5,8a-trimethylbenz[*f*]azulen-10(2*H*)-one (20).** A solution of the 1,3-diketone (35 mg, 0.13 mmol), *n*-butanethiol (35 mg, 0.4 mmol), and 5 drops of concentrated hydrochloric acid in 3 mL of glacial acetic acid was stirred at 25 °C for 4 days. The green solution was diluted with ether (50 mL) and washed in turn with water (30 mL), saturated aqueous bicarbonate solution (30 mL), 10% aqueous potassium hydroxide (30 mL), and brine (30 mL). After drying and removal of the solvent, the residue was purified by MPLC on silica gel (elution with 8% ethyl acetate in petroleum ether) to provide 33 mg (77%) of **20** as a faint yellow oil: IR ($CDCl_3$, cm^{-1}) 2945, 2890, 1640, 1520, 1544; ^1H NMR (300 MHz, $CDCl_3$) δ 2.84 ($^1/_2$AB d, J = 12.4 Hz, 1 H), 2.82–2.61 (m, 4 H), 2.25–1.95 (m, 2 H), 2.04 ($^1/_2$AB d, J = 12.5 Hz, 1 H), 1.75 (m, 2 H), 1.65 (s, 3 H), 1.57 (m, 4 H), 1.44 (m, 6 H), 1.18 (s, 3 H), 1.06 (s, 3 H), 0.95 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (20 MHz, $CDCl_3$) ppm 196.50, 158.17, 137.60, 132.62, 128.40, 54.30, 50.02, 39.80, 38.46, 38.07, 34.56, 33.47, 31.62, 31.30, 31.11, 27.72, 26.70, 22.10, 21.14, 18.65, 13.61; MS, m/z (M^+) calcd 332.2174, obsd 332.2161.

***syn*-3,3a,4,6,7,8,8a,9-Octahydro-1-isopropyl-3a,5,8a-trimethylbenz[*f*]azulen-10(2*H*)-one (21).** To a stirred suspension of cuprous cyanide (9.6 mg, 0.11 mmol) in 3 mL of tetrahydrofuran at −20 °C was added isopropylmagnesium bromide (0.12 mL of 2.0 M in ether). After 0.5 h of stirring, **20** (33 mg, 0.10 mmol) dissolved in 1 mL of tetrahydrofuran was rapidly injected and stirring was continued for 1 h. Saturated aqueous ammonium chloride/ammonium hydroxide (3 mL, pH 8) and ether (8 mL) were introduced and the mixture was stirred for 1 h at 25 °C. The organic phase was separated, washed with brine (10 mL), and dried. Evaporation of the solvent and isolation of the product of MPLC on silica gel (elution with 8% ethyl acetate in petroleum ether) afforded 18 mg (65%) of **21** as a colorless oil: IR ($CDCl_3$, cm^{-1}) 2950, 1670, 1595, 1460; ^1H NMR (300 MHz, $CDCl_3$) δ 3.65 (heptet, J = 6.9 Hz, 1 H), 2.82 ($^1/_2$AB d, J = 13.2 Hz, 1 H), 2.70 ($^1/_2$AB d, J = 14.2 Hz, 1 H), 2.31 (m, 2 H) 2.19 ($^1/_2$AB d, J = 14.2 Hz, 1 H), 2.02 ($^1/_2$AB d, J = 13.2 Hz, 1 H), 1.90 (m, 2 H), 1.85–1.55 (m, 4 H), 1.66 (s, 3 H), 1.40–1.20 (m, 2 H), 1.16 (s, 3 H), 1.03 (s, 3 H), 0.97 (d, J = 6.8 Hz, 3 H), 0.95 (d, J = 6.8 Hz, 3 H); MS, fragmentation at 70 eV prevented accurate mass measurement of the molecular ion.

***anti*-2,3,3a,4,7,8,8a,9-Octahydro-1-isopropyl-3a,5,8a-trimethylbenz[*f*]azulene-6,10-dione (24).** To a magnetically stirred solution of **15** (82.9 mg, 0.290 mmol) in 13 mL of tetrahydrofuran–water (9:1) at 0 °C was added powdered calcium carbonate (87 mg, 0.87 mmol) and in turn a solution of *N*-bromosuccinimide (129 mg, 0.725 mmol) in tetrahydrofuran (5 mL). The reaction mixture was stirred at 0 °C for 1 h and at room temperature for 1 h before cyclopentene was introduced. The major portion of the organic solvent was removed in vacuo without

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heating. The residue was diluted with 50 mL of 1:1 ethyl acetate/petroleum ether and this solution was washed with water (2 × 10 mL), dried, and concentrated. The resulting viscous material was purified by MPLC on silica gel (elution with 24% ethyl acetate in petroleum ether) to give 60.6 mg (70%) of **24** as colorless crystals, mp 86.5–87.5 °C (from petroleum ether): IR (CH_2Cl_2 8 Cm^{-1}) 2967, 2937, 2870, 1658, 1598, 1338; ^1H NMR (300 MHz, $CDCl_3$) δ 3.30 (heptet, J = 6.8 Hz, 1 H), 2.91 ($^1/_2$AB d, J = 14.6 Hz, 1 H), 2.81 ($^1/_2$AB d, J = 13.4 Hz, 1 H), 2.55 ($^1/_2$AB d, J = 13.4 Hz, 1 H), 2.51–2.43 (m, 4 H), 2.42 ($^1/_2$AB d, J = 14.6 Hz, 1 H), 1.85 (s, 3 H), 1.97–1.75 (m, 4 H), 1.18 (s, 3 H), 1.08 (s, 3 H), 1.02 (d, J = 6.8 Hz, 3 H), 1.01 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 200.67, 198.25, 162.44, 159.77, 141.97, 132.13, 54.92, 49.28, 41.76, 40.85, 38.60, 37.28, 33.83, 29.20, 28.02, 25.50, 23.53, 20.97, 20.68, 12.46; MS, m/z (M^+) calcd 300.2089, obsd 300.2071. Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 80.34; H, 9.34.

X-ray Crystal Structure Analysis of 16. Suitable crystals of **16** ($C_{20}H_{32}O_2$) for X-ray diffraction studies formed with space group symmetry of $P2_1/c$ and cell constants of a = 19.409 (5) Å, b = 7.627 (2) Å, c = 12.267 (1) Å, and β = 91.92 (1)° for Z = 4 and a calculated density of 1.114 g/cm^3. Of the 2443 reflections measured with an automatic four-circle diffractometer equipped with Cu radiation, 2047 were observed ($I > 3\sigma I$). The structure was solved with a multisolution tangent formula approach and difference Fourier analysis and refined by using full-matrix least-squares techniques.[39] Hydrogen were assigned isotropic temperature factors corresponding to their attached atoms. The function $\sum w(|F_o| - |F_c|)^2$ with $w = 1/(\sigma F_o)^2$ was minimized to give an unweighted residual of 0.069. Tables I, II, and III containing the final fractional coordinates, temperature parameters, bond distances, and bond angles are available as supplementary material. Figure 3 is a computer-generated perspective drawing of **16** from the final X-ray coordinates showing the relative stereochemistry.

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Supplementary Material Available: Tables of the atomic positional and thermal parameters, bond distances, and bond angles for **16** (3 pages). Ordering information is given on any current masthead page.

(39) The following library of crystallographic programs was used: MULTAN 80, Main, P. et al., University of York, York, England (1980); ORTEP-II, Johnson, C. K., Oak Ridge National Laboratory, Oak Ridge, TN (1970); SDP PLUS V1.1, Okaya, Y. et al., Frenz, B. A. and associates, College Station Texas (1984).

Total Syntheses of Atrovenetin and Scleroderodione

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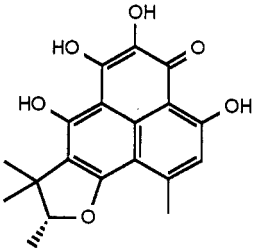
Total syntheses of (±)-atrovenetin (**1**) and (±)-scleroderodione (**26**) in 11 steps are described. The novel regioselective Claisen rearrangement–cyclization of the dianion **11** to the dihydrobenzofuran **7** and the regioselective, acid-catalyzed cyclization of **15** to the naphthalenes **16** and **17** constitute the critical phases of the syntheses.

Atrovenetin (**1**), a fungal metabolite of *Penicillium atrovenetum*,[1] belongs to the class of naturally occurring phenalenones. It is also produced by *Penicillium herquei*[2]



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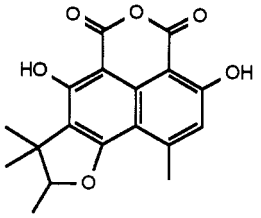

2

and was found to be responsible for the antibiotic activity displayed by extracts of this fungus.[3] The metabolite **1** and related phenalenones have been the subject of many chemical and biosynthetic studies.[1,4] An unambiguous structural assignment emerged from an X-ray analysis of atrovenetin trimethyl ether ferrichloride.[4b] By chemical correlation with (−)-(*S*)-ethyl lactate, **1** was shown to have the *R* configuration at its single chiral center.[4i] Atrovenetin has been synthesized.[5] A second, more efficient, synthesis that also allowed the preparation of its cometabolite **2**[6] is presented in this paper.

Alkylation of dimethyl 3,5-dihydroxyhomophthalate (**3**)[7]

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