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ON THE ABSOLUTE STEREOCHEMISTRY OF THE PHOTOCHEMICAL REARRANGEMENT OF 2,5-CYCLOHEXADIENONES TO LUMIKETONES[1]

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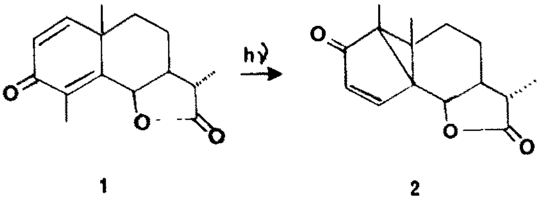
Abstract Specification of the absolute configurations of starting material and product in the photochemical rearrangement of a 2,5-cyclohexadienone to a bicyclo[3.1.0]hexen-2-one (lumiketone) permits unambiguous determination of the stereochemistry at two crucial stages in the generally accepted reaction mechanism, namely the electrocyclic ring closure to give a 3,5-bonded intermediate, and the subsequent [1,4]-sigmatropic shift. The stereochemical course of the latter process in turn allows specification of whether the rearrangement is occurring directly from an electronically excited intermediate or a ground state zwitterion. An unconstrained monocyclic chiral cyclohexadienone has been studied in which steric constraints are minimal, and in which the system should have free choice of available pathways. The absolute configuration of the resolved dienone was determined by X-ray crystallographic analysis of a derivative containing a chiral center of known configuration. The absolute configuration of the resultant optically active diastereomeric lumiketones has been assigned from the Cotton effects observed on the corresponding dihydrolumiketones, assuming these chiroptical effects are governed by a normal Octant Rule instead of the Inverse Octant Rule which empirically correlates such data for cyclopropyl ketones lacking polarizable substituents. The limitations on these assignments are discussed, as well as alternative efforts to obtain completely unambiguous stereochemical assignments for the lumiketones. On the basis of these assignments, it is concluded that the sigmatropic shift proceeds with inversion of configuration at the migrating carbon, consistent with reaction via a ground state zwitterion.

INTRODUCTION

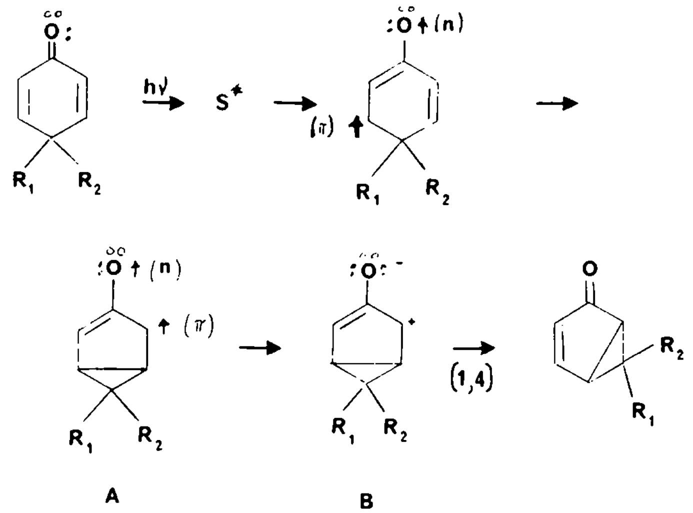
The photorearrangements of 2,5-cyclohexadienones have intrigued organic photochemists for many years.[2] The most characteristic photoisomerization of these molecules results in bicyclo[3.1.0]hexen-2-ones, so-called "lumiketones", as illustrated by the prototypical isomerization of α-santonin (**1**) to lumisantonin (**2**).[3] A detailed mechanism to describe this type of photoisomerization was put forth many years ago by Zimmerman and Schuster,[4] and is shown in Scheme 1. This mechanism has survived a number of experimental tests, as summarized in several reviews of research in this area,[2f,g] and seems generally to be accepted at the present time, although several of the proposed intermediates have been only indirectly characterized. For example, the intermediacy of bicyclic oxyallyl zwitterions of type B[4] is implied by the formation of products resulting from nucleophilic attack by the solvent or added nucleophiles,[2] which at least in the case of dienone **3** has been shown to compete directly with rearrangement to lumiketone,[5] i.e., a common intermediate (zwitterion) affords both types of products, as shown in Scheme 2. The observations supporting this conclusion are summarized elsewhere.[2f,6]



1 **2**

There are three factors which dictate the overall stereochemistry of the dienone-lumiketone photorearrangement:[7,8] (i) the stereochemistry of the initial electroyclic ring closure to give the 3,5-bonded intermediate A, i.e. the *exo-endo* preference in A of substituents originally located at C_4 of the dienone; (ii) the stereochemistry at the migrating carbon (originally C_4) in the [1,4]-sigmatropic shift which converts A or B into the lumiketone, since this step can occur *a priori* with either inversion or retention of configuration at C_6, i.e. in the former, *exo* and *endo* orientations of substituents in A or B are maintained during the rearrangement, while in the latter the *exo* substituent in A or B ends up *endo* in the lumiketone, and *vice versa*; (iii) the [1,4]-sigmatropic rearrangement can occur in either a clockwise or counterclockwise direction on the surface of the 5-membered ring, which can be differentiated only when the original cyclohexadienone is unsymmetrically substituted.

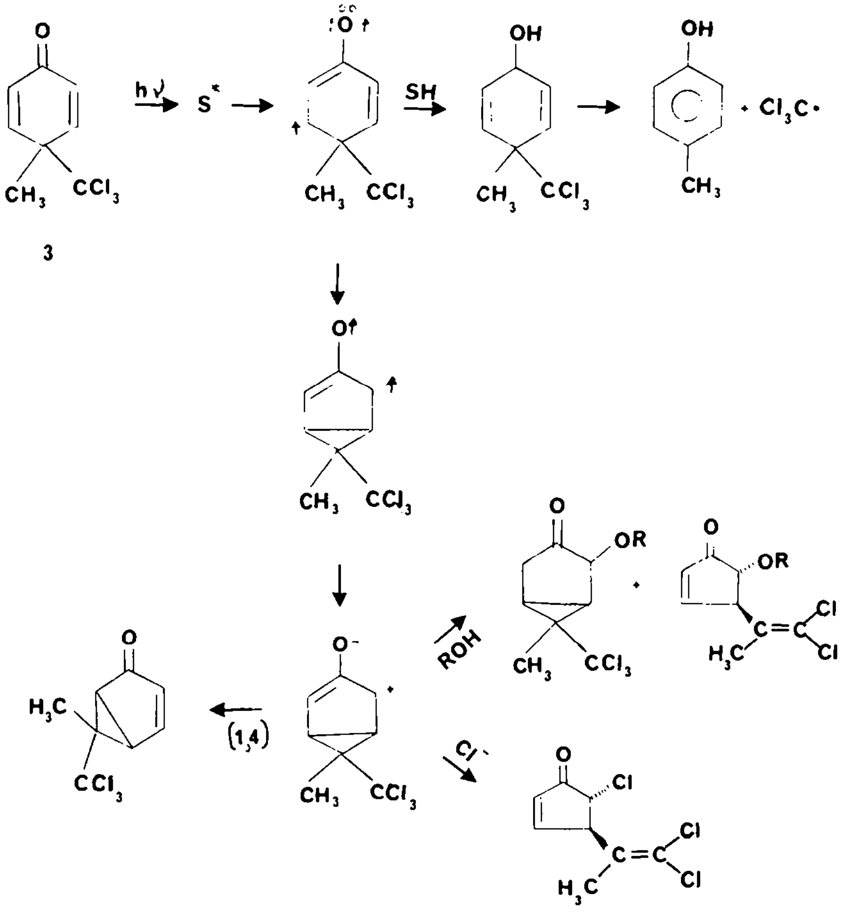
In the case of α-santonin and other A,B-ring fused cyclohexadienones, the stereochemical course of the photorearrangement is unambiguous.[8] The constraints of the A/B ring fusion require that in step i the angular Me group must assume an *endo* orientation



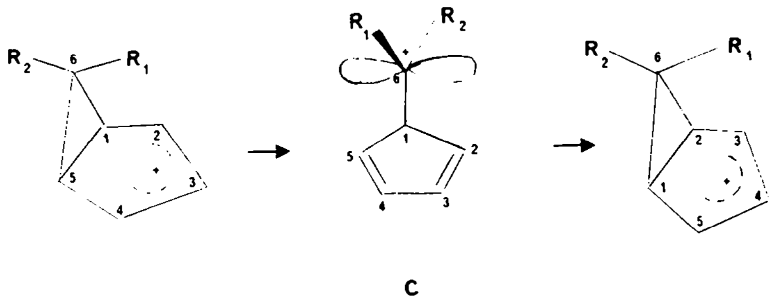
Scheme 1

relative to the original dienone chromophore, so as to preserve the *cis*-fusion of the 5- and 6-membered rings attached to the cyclopropane ring in intermediates A and B. In addition, the [1,4]-sigmatropic rearrangement *must* occur with inversion of configuration at the migrating carbon (the angular Me must remain *endo* in the lumiketone) so as to avoid a *trans* ring fusion of the 3- and 6-membered rings in the final product.

Knowledge of the absolute stereochemistry of the dienone-lumiketone photorearrangement in a sterically unconstrained system should provide considerable information about the nature of the intermediates

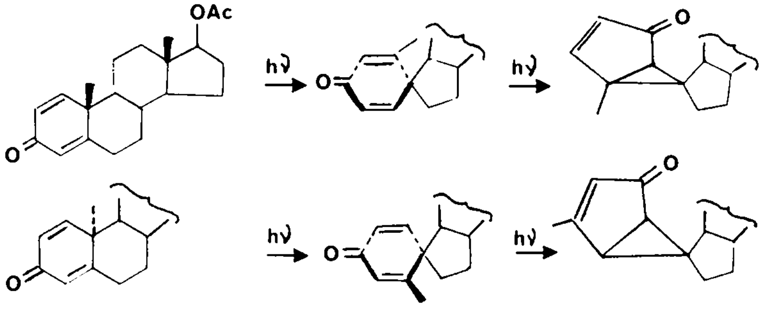


Scheme 2



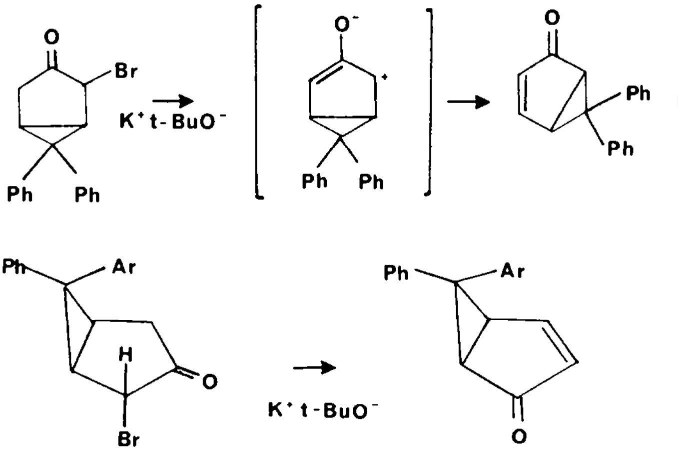
(1)

and the timing of the individual steps in this reaction. Suprafacial circumambulations of the cyclopropane moiety around the 5-membered ring in bicyclo-[3.1.0]hexenyl cations (eqn 1) occur stereospecifically with inversion of configuration at C_6 through bisected transition states C,[9,10] in complete accord with orbital symmetry[10] and related Hückel-Möbius predictions.[11] Zwitterions of type B can be considered 3-oxybicylo [3.1.0] hexenyl cations, and might be expected to rearrange similarly.[8] Indeed, ground state Favorskii-like rearrangements of bromoketones (eqn 2) which are presumed to take place via zwitterions analogous to those generated photochemically from cyclohexadienones[12] proceed stereospecifically with inversion at C_6. However, as argued elsewhere previously,[2f] this result does not rigorously *require* that the photochemical reaction follows the same course, since the charged intermediates produced photochemically from dienones and thermally from bromoketones may not be identical; the timing of bond breaking and bond formation could conceivably be different, and the counter ion involved in the latter reaction may play a role.

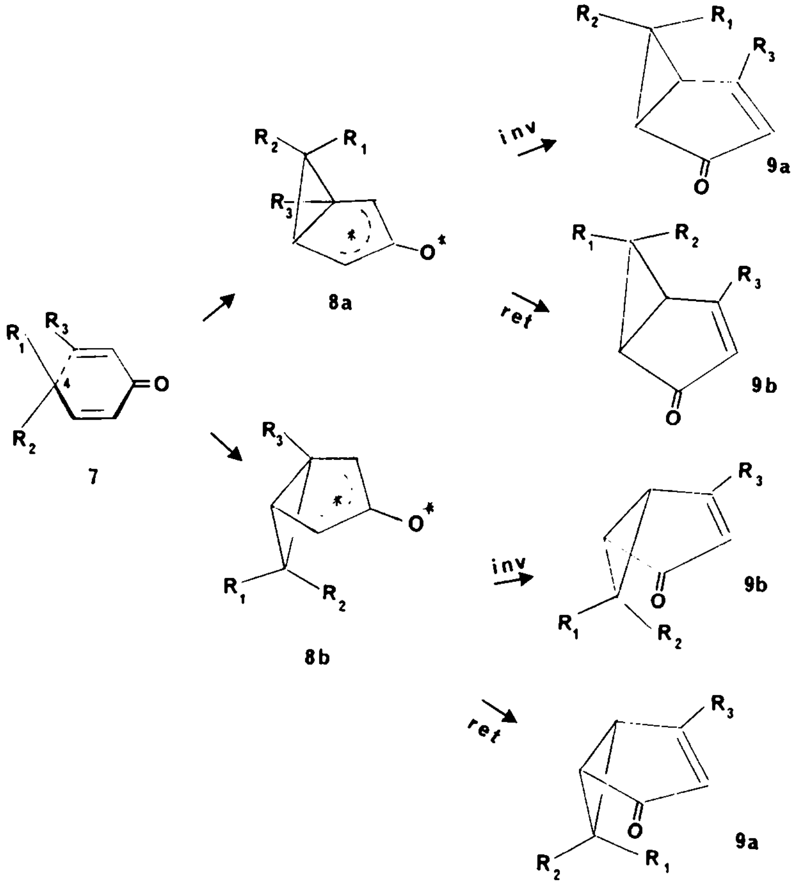


5 4 6

Jeger and Schaffner *et al.* have described the photochemical lumiketone rearrangements of spirodienones **4**, which are in turn derived photochemically from dehydrotestosterone acetates **5**.[13] There is no obvious structural constraint discriminating against rearrangement with retention of configuration at the migrating carbon in these systems, as there is in fused ring dienones typified by santonin. Based on the configurational assignments to the spiro carbons in the dienones **4** and lumiketones **6**,[2g,16] the lumiketone rearrangements in these systems must



(2)



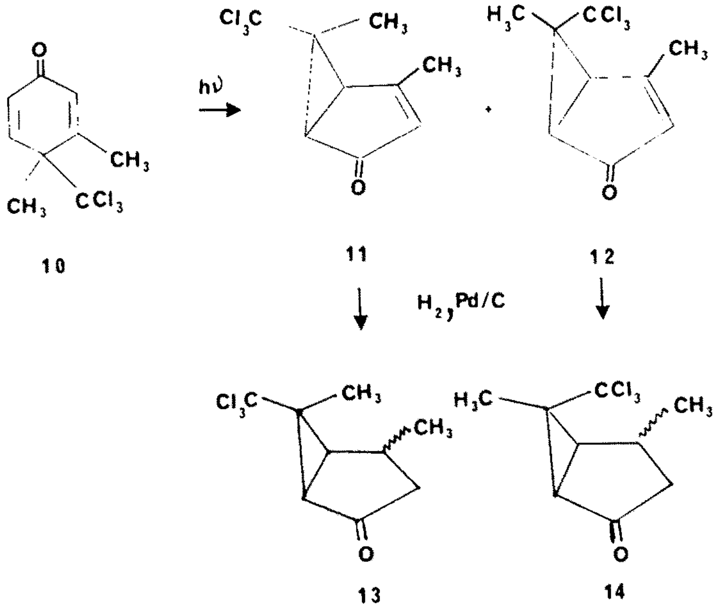
Scheme 3

have occurred with inversion at the migrating (spiro) carbon.

Nonetheless, upon consideration of the structural complexity of these tetracyclic and pentacyclic systems and the somewhat indirect stereochemical assignments to the dienones 4,[2g,13] an unequivocal determination of absolute stereochemistry on photorearrangement of a simple unconstrained monocyclic dienone seemed eminently desirable. The stereochemistry of both the initial electrocyclic ring closure (i) and the subsequent sigmatropic shift (ii) can be unambiguously assigned by relating the absolute configurations of the dienone and photochemically derived lumiketone, as shown in Scheme 3. Thus, optically active dienone **7** leads to two diastereomeric intermediates **8a** and **8b** by upward or downward motion, respectively, of C_4 relative to a given face of the cyclohexadienone ring. These intermediates, be they diradicals (excited state or ground state) or zwitterions, could *a priori* undergo [1,4]-sigmatropic rearrangement by either the inversion or retention modes, to give lumiketones **9a** and **9b**. It can be seen that the product of rearrangement of **8a** by inversion is the enantiomer of the product of rearrangement of **8b** by retention; the other two products are also related as enantiomers. Thus, knowledge of the absolute configurations of dienone and derived lumiketone permits assignment simultaneously of both the stereochemistry of the bicyclic intermediate and its mode of subsequent sigmatropic rearrangement.[8,14]

The steric and electronic factors which govern the direction of initial ring closure (step i) are discussed elsewhere.[15–19]

It only remained to choose a monocyclic dienone system to use in such a stereochemical study. Based on our success using dienone **3** to elucidate many mechanistic features of dienone phototransformations,[2f] it seemed appropriate to use a simple homolog of **3** as the chiral substrate, namely dienone **10**. The resolution of a closely related dienone had already been described in the literature,[20] which was an additional advantage. A description of the photochemical behavior of the racemic dienone **10** has been published.[19] In the present context, the most important result of that work is that both epimeric lumiketones **11** and **12** are formed on irradiation of **10**, which therefore permits determination of the absolute stereochemistry of two lumiketone photorearrangements simultaneously, which was not possible previously. The plan was to determine the configuration at C_4 of optically active dienone **10** by X-ray analysis of a derivative containing a chiral center of

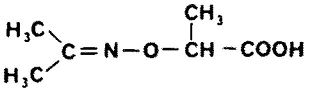


known configuration, while the absolute configuration of the lumiketones was to be assigned[21] from the sign of the long wavelength Cotton effect in the ORD or CD curves of bicyclo[3.1.0]-hexan-2-ones **13** and **14**.

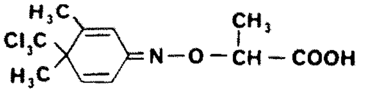
RESULTS

Preparation, optical purity and configuration of optically active dienone **10**

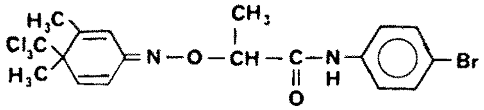
The tedious resolution of dienone **10** using α-(isopropylidenaminooxy)-propionic acid was carried out initially[22] using the procedure of Newman *et al.* utilized for 2,4,5-trimethyl-4-trichloromethyl-2-5-cyclohexadien-1-one.[20] Modifications detailed in the Experimental led to some improvement over the original procedure.[23] The purest samples of (−)-dienone adduct **16** prepared from the (+)-acid had m.p. 154–157° and specific rotation −194°, while the (−)-acid afforded (+)-adduct **16** with m.p. 153–155° and specific rotation +192°. Optically active dienone **10** could be obtained in poor yield from heating the respective adducts with levulinic acid at reflux.[20] The highest rotation for the (−)-dienone derived from the (−)-adduct was −31.7°.



$(H_3C)_2C{=}N{-}O{-}CH(CH_3){-}COOH$ **15**



16



17

PMR spectra of the adduct **16** showed single resonances for the Me's at C_3 and C_4 on the dienone ring in samples of highest rotation, and doublets for these Me's in samples of lower rotation, indicating that diastereotopic Me groups in optically impure samples of **16** are resolvable. Thus, the crystalline adduct **16** and the initial filtrate obtained during the above resolution of dienone **10** showed significant differences in the ratios of the C_4 Me resonances at δ 1.60 and 1.67 and of the C_3 Me doublets centered at δ 2.15 and 2.23 ppm, from which one could calculate that the crystalline material had a 94% excess of one diastereomer, while the filtrate was enriched in the other diastereomer to the extent of only 5%. These two samples were cleaved by treatment with levulinic acid to give dienones (−)-**10** and (−)-**10**, respectively, with rotations of −29° and −1.6° (*c* 0.92, benzene). From the direct correlation of optical rotations of several samples of adduct **16** with the ratios of the Me resonances in the PMR spectra, it was concluded that adducts **16**, with rotations of −194° or −194° were indeed optically pure, corresponding to rotations of 31.7° for optically pure dienone **10**.

Attempts to directly determine opticaly purities of dienone **10** and lumiketones **11** and **12** using chiral shift reagents were completely unsuccessful, utilizing ^1H as well as ^{13}C spectra.[23] Limited success was achieved using nickel optishift reagents on the oxime of dienone **10**, but peak resolution was not as good as obtained for the diastereomers of **16**.

Optical rotatory dispersion curves for partially resolved dienone **10** are shown in Fig. 1. A portion of the purest samples of the (−)-adduct **16** prepared from (+)-acid **15** was converted into the *p*-bromoanilide **17**, and suitable crystals for X-ray crystallographic study were grown. The crystal structure of this material is shown in Fig. 2.[24] Structural parameters are given in Tables 1–6. Since the configuration at the chiral center in the (+)-acid **16** has been independently established to be **R**,[25] the X-ray analysis establishes that the

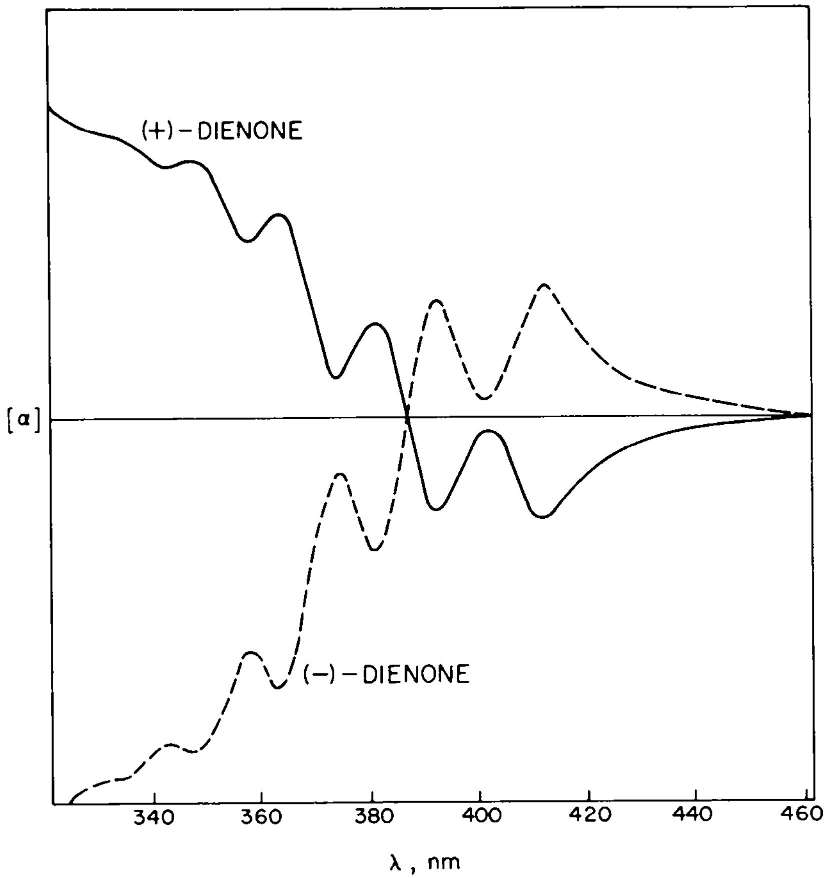


Fig. 1. Optical rotatory dispersion curves for (+) and (−) cyclohexadienone **10**.

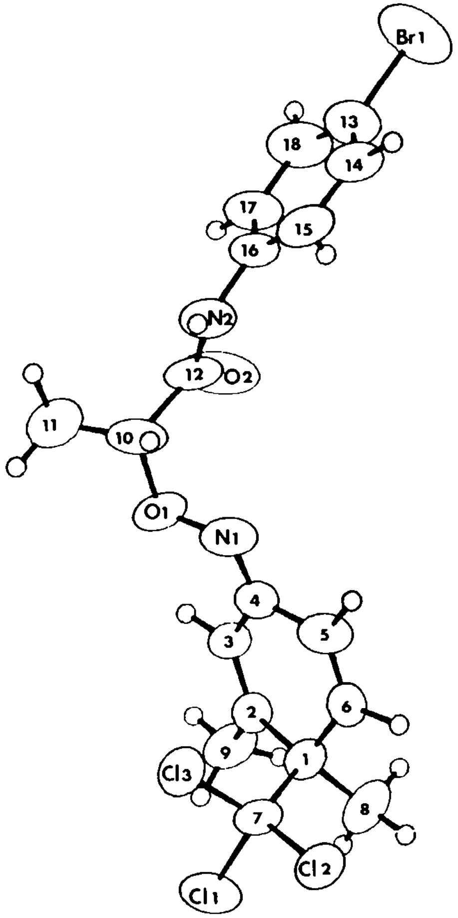
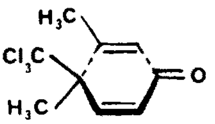


Fig. 2. ORTEP drawing of X-ray crystallographic structure for p-bromoanilide **17**

Table 1. Cell parameters for compound **17**

a = 6.027 (2)
b = 9.422 (7)
c = 18.322 (2)
α = 90.00
β = 90.03 (3)
γ = 90.00
Space Group $P2_1$

configuration at the chiral center on the cyclohexadienone ring in the (−)-adduct must be S. Thus, the absolute configuration of the S-(−)-dienone **10** is as depicted below.



S-(−)-**10**

Photochemical rearrangement of optically active dienone[22]

Due to the small quantities of optically active dienone **10** available with high specific activity, different batches of (+)-**R**-dienone **10** were mixed and then diluted with racemic dienone to give 4.0 g of dienone with α_D + 2.1° (t-BuOH). This material was dissolved in 100 ml t-BuOH, nitrogen was passed through the solution for 1/2 hr, and the material was irradiated for 6 hr at 254 nm with continuous passage of nitrogen through the solution. The residue after removal of the solvent was chromatographed on silica gel. A pure (by glpc) 70 mg sample of lumiketone **12** was obtained directly with α_D − 2.85° (hexane). Spectra of this material were compared directly with those of this compound previously characterized from irradiation of racemic **10**. A sample (734 mg) of the diastereomeric lumiketone **11**, also identified by spectral comparisons as above, was obtained in about 80% purity. This material was contaminated by a small amount of dienone and another photolysis product, and had α_D + 10.4° (EtOH). This material

Table 2. Fractional coordinates of the non-hydrogen atoms for compound 17

	x	y	z
Cl (1)	1.0365 (6)	0.2135 (5)	0.9865 (1)
Cl (2)	0.6481 (5)	0.0446 (4)	0.9626 (11)
Cl (3)	1.0319 (5)	0.0068 (4)	0.8735 (2)
N (1)	0.9300 (17)	0.0984 (11)	0.6556 (4)
C (1)	0.7734 (16)	0.2452 (13)	0.8632 (5)
C (2)	0.9566 (14)	0.3164 (10)	0.8196 (5)
C (3)	1.0030 (16)	0.2742 (12)	0.7524 (5)
C (4)	0.8770 (18)	0.1641 (13)	0.7144 (5)
C (5)	0.6628 (21)	0.1277 (19)	0.7459 (6)
C (6)	0.6175 (16)	0.1683 (16)	0.8131 (5)
C (7)	0.8647 (18)	0.1347 (14)	0.9173 (5)
C (8)	0.6419 (22)	0.3595 (17)	0.9074 (7)
C (9)	1.0753 (23)	0.4457 (14)	0.8503 (6)
Br (1)	0.4378 (4)	0.2500 (0)	0.1870 (9)
N (2)	0.9688 (18)	0.0579 (11)	0.4519 (4)
O (1)	1.1457 (14)	0.1409 (10)	0.6314 (4)
O (2)	1.0262 (27)	0.2730 (10)	0.5070 (5)
C (10)	1.1838 (24)	0.0725 (15)	0.5618 (5)
C (11)	1.4279 (30)	0.0859 (30)	0.5494 (8)
C (12)	1.0473 (26)	0.1439 (13)	0.5030 (6)
C (13)	0.5974 (24)	0.1863 (15)	0.2697 (6)
C (14)	0.7856 (29)	0.2647 (17)	0.2896 (6)
C (15)	0.9046 (23)	0.2246 (16)	0.3512 (5)
C (16)	0.8521 (20)	0.1036 (13)	0.3882 (5)
C (17)	0.6703 (22)	0.0253 (13)	0.3664 (6)
C (18)	0.5421 (23)	0.0704 (20)	0.3060 (6)

Table 3. Anisotropic thermal parameters (X100) of the non-hydrogen atoms in compound **17**

The thermal parameters are expressed in the form:

$$T = \exp[2\pi^2 (U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}l^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}hla^*c^* + 2U_{23}klb^*c^*)]$$

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Cl (1)	9.6 (2)	9.3 (2)	4.6 (1)	-2.3 (2)	-1.2 (1)	0.5 (1)
Cl (2)	6.2 (1)	8.5 (2)	5.8 (1)	-1.3 (1)	1.8 (1)	2.3 (1)
Cl (3)	6.7 (2)	5.6 (1)	7.1 (1)	1.0 (1)	1.3 (1)	1.2 (1)
N (1)	8.7 (6)	5.8 (5)	4.3 (4)	-1.7 (5)	-0.2 (4)	-0.5 (4)
C (1)	5.2 (5)	5.2 (5)	4.7 (4)	0.1 (5)	1.2 (4)	1.5 (4)
C (2)	4.0 (4)	3.9 (4)	4.8 (4)	-1.1 (4)	0.2 (3)	0.8 (3)
C (3)	5.3 (5)	5.7 (6)	3.9 (4)	0.0 (5)	0.5 (4)	0.8 (4)
C (4)	5.7 (5)	5.9 (6)	4.0 (4)	0.5 (5)	-0.2 (4)	0.5 (4)
C (5)	6.5 (10)	10.6 (5)	4.7 (5)	-4.5 (7)	-0.3 (5)	1.0 (6)
C (6)	3.8 (5)	9.0 (9)	5.5 (5)	-0.9 (5)	-0.0 (4)	0.9 (5)
C (7)	6.5 (6)	6.9 (7)	3.7 (4)	-0.3 (5)	1.0 (4)	1.1 (4)
C (8)	6.7 (7)	8.2 (8)	8.5 (7)	0.0 (7)	3.3 (6)	-0.0 (7)
C (9)	8.5 (7)	5.5 (6)	6.3 (5)	0.2 (6)	1.9 (5)	-0.9 (5)
Br (1)	17.8 (1)	8.4 (1)	10.5 (1)	3.3 (1)	-6.1 (1)	0.0 (1)
N (2)	9.1 (6)	4.8 (5)	4.5 (4)	-0.3 (5)	0.1 (4)	-0.5 (4)
O (1)	7.6 (5)	7.2 (5)	4.3 (3)	-1.2 (4)	1.3 (3)	-1.8 (3)
O (2)	19. (1)	4.6 (5)	5.6 (4)	0.3 (6)	-2.2 (5)	-0.9 (4)
C (10)	10.3 (9)	7.1 (8)	3.6 (4)	-1.5 (7)	-0.6 (5)	-0.9 (5)
C (11)	10. (1)	18. (2)	7.0 (7)	3. (1)	0.9 (7)	-4.1 (1.1)
C (12)	9.9 (9)	5.7 (6)	3.1 (4)	-0.3 (6)	1.0 (5)	-0.5 (4)
C (13)	9.9 (9)	6.3 (7)	5.7 (6)	0.4 (7)	-.9 (6)	-0.0 (6)
C (14)	13. (1)	6.6 (8)	6.1 (6)	-0.2 (9)	0.3 (7)	1.8 (6)
C (15)	9.2 (8)	7.6 (8)	4.4 (4)	-2.1 (7)	-.1 (5)	0.7 (5)
C (16)	7.6 (7)	5.0 (6)	3.4 (4)	0.8 (5)	-.1 (4)	-.6 (4)
C (17)	9.6 (8)	4.6 (6)	5.2 (5)	-.5 (6)	1.9 (5)	-1.0 (5)
C (18)	9.0 (8)	10. (1)	4.5 (5)	-1.1 (8)	.4 (5)	-2.0 (6)

was rechromatographed on silica gel, to give a fraction (283 mg) which was >95% lumiketone, according to glpc analysis, and had α_D + 13.7° (EtOH). Finally, a 1.05 g sample of recovered dienone **10** containing only minor contaminants (according to glpc and NMR analysis) was obtained, which showed α_D + 1.52° (EtOH). A similar experiment was done using (−)-S-dienone **10**, 4.02 g, α_D − 0.80° (t-BuOH). From irradiation of this material there were obtained 106 mg of lumiketone **12**, α_D + 0.80° (hexane), 300 mg of lumiketone **11** with α_D − 4.6° (EtOH) and 1.07 g of dienone **10** (>95% pure by glpc) with α_D − 0.64°.

It should be noted that the rotations observed for lumiketone **11** from irradiation of the (+) and (−) dienones agree quite well, when correction is made for the difference in optical purities of the starting materials. The data for the epimeric lumiketone **12** are not in nearly as good agreement, but a larger error in handling and measurement may be involved since this is the minor lumiketone product. The data also suggest that the amount of photoracemization of the dienone is at most 20–25%, but is probably much less since the recovered dienone was impure.

Hydrogenation of lumiketones.[22] The stereoisomeric bicyclohexenones (lumiketones) **11** and **12** from (+)- and (−)-dienone **10** were hydrogenated in hexane solution using 10% Pd/C as catalyst. The hydrogenated ketones **13** and **14** were compared spectrally and by glpc with samples obtained previously from racemic lumiketones.[19] Hydrogenation on a microscale of (−)-lumiketone **11**, derived originally from (−)-dienone **10**, gave a saturated ketone **13** which showed α_D − 1.07 (EtOH). This material was combined with product of a second hydrogenation and purified by chromatography on silica gel, to give (−)-dihydrolumiketone **13** of 98–99% purity (glpc), which had α_D − 2.32 (EtOH). Similar procedures starting with the enantiomeric (+)

Table 4. Bond distances in **17** in A

C (1) - C (7)	1.53 (1)
C (1) - C (8)	1.57 (2)
C (1) - C (2)	1.52 (1)
C (1) - C (6)	1.50 (1)
C (7) - Cl (1)	1.81 (1)
C (7) - Cl (2)	1.77 (1)
C (7) - Cl (3)	1.75 (1)
C (2) - C (9)	1.52 (1)
C (2) - C (3)	1.33 (1)
C (3) - C (4)	1.46 (1)
C (4) - C (5)	1.46 (2)
C (4) - N (1)	1.28 (1)
C (5) - C (6)	1.31 (1)
N (1) - O (1)	1.43 (1)
O (1) - C (10)	1.45 (1)
C (10) - C (11)	1.51 (2)
C (10) - C (12)	1.51 (2)
C (12) - O (2)	1.22 (1)
C (12) - N (2)	1.32 (1)
N (2) - C (16)	1.43 (1)
C (16) - C (15)	1.37 (2)
C (16) - C (17)	1.38 (2)
C (15) - C (14)	1.39 (2)
C (14) - C (13)	1.40 (2)
C (13) - Br (1)	1.89 (1)
C (13) - C (18)	1.32 (2)
C (18) - C (17)	1.40 (2)
C (17) - C (16)	1.38 (2)

Table 5. Bond angle in **17** ( ).

Cl (1) - C (7) - Cl (2)	106.6 (4)
Cl (1) - C (7) - Cl (3)	105.8 (5)
Cl (2) - C (7) - Cl (3)	108.3 (7)
Cl (1) - C (7) - C (1)	111.9 (8)
Cl (2) - C (7) - C (1)	111.4 (7)
Cl (3) - C (7) - C (1)	112.3 (6)
C (2) - C (1) - C (6)	110.5 (7)
C (2) - C (1) - C (7)	112.2 (8)
C (2) - C (1) - C (8)	110.0 (9)
C (6) - C (1) - C (8)	109.5 (8)
C (6) - C (1) - C (7)	106.5 (9)
C (3) - C (2) - C (1)	120.6 (8)
C (9) - C (2) - C (1)	120.2 (8)
C (3) - C (2) - C (19)	119.1 (8)
C (2) - C (3) - C (4)	123.2 (8)
C (3) - C (4) - C (5)	115.6 (9)
C (3) - C (4) - N (1)	128.3 (9)
N (1) - C (4) - C (5)	116.2 (9)
C (4) - C (5) - C (6)	119.8 (11)
C (5) - C (6) - C (1)	125.2 (9)
C (4) - N (1) - O (1)	110.2 (9)
O (1) - C (10) - C (11)	104.3 (11)
O (1) - C (10) - C (12)	110.3 (10)
N (2) - C (12) - O (2)	124.2 (11)
N (2) - C (12) - C (10)	115.2 (10)
C (12) - N (2) - C (16)	125.2 (10)
C (15) - C (16) - C (17)	118.9 (10)
C (16) - C (17) - C (18)	120.2 (11)
C (17) - C (18) - C (13)	120.4 (13)
C (18) - C (13) - C (14)	120.4 (11)
C (18) - C (13) - Br (1)	122.7 (10)
C (14) - C (13) - Br (1)	116.9 (9)
C (13) - C (14) - C (15)	119.0 (13)
C (14) - C (15) - C (16)	120.9 (12)

– **11** gave, after silica gel chromatography, ketone **13** which appeared to be at least 95% pure by glpc, but which had a smaller specific rotation than expected, α_D + 1.04 (EtOH).

Similar operations starting with the (+)- and (–)-lumiketones **12** obtained respectively from (–)- and (+)-dienone **10** afforded very small quantities of crystalline dihydrolumiketones **14**, m.p. 114–116 and 113–114, respectively (m.p. for racemic dihydrolumiketone **14** found earlier[19] was 115–116). Optical rotations were unfortunately not measured on these samples, which were submitted directly for CD measurements.

Circular dichroism data.[22] CD measurements were made in ether solution on a Cary Model 60 spectropolarimeter. The (+)-dihydrolumiketone **13** showed a strong negative Cotton effect with maxima at 310 and 322 nm. The enantiomeric (–)-dihydrolumiketone **13** had a much weaker effect which was nonetheless clearly positive, with a maximum near 322 nm. Similarly, the hydrogenation product from (–)-lumiketone **12** showed a positive Cotton effect with a maximum at 315 nm and intercept at 297 nm, while no measurable Cotton effect could be seen using the small amount (8 mg) available of the crystalline product from (+)-lumiketone **12**.

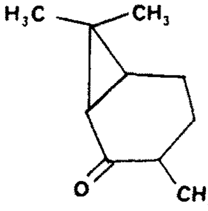
Table 6. Torsional angles in the dienone portion of **17**

C (1) - C (2) - C (3) - C (4)	3.29
C (2) - C (3) - C (4) - C (5)	15.56
C (3) - C (4) - C (5) - C (6)	-15.93
C (4) - C (5) - C (6) - C (1)	-2.40
C (5) - C (6) - C (1) - C (2)	19.89
C (6) - C (1) - C (2) - C (3)	-19.79

The purity of the dihydrolumiketones **13** was checked by glpc a few days following the CD measurements. The enantiomeric ketones **13** showed only trace impurities, and their purity was estimated at 97–99%. The samples of the ketones **14** which had been stored in EtOH for over a year had a purity of only 40–60%. However, samples of these ketones are known to deteriorate on standing over long periods of time. On the basis of their sharp melting points, it is likely that the (+)- and (−)-ketones **14** were of good quality at the time of the CD measurements.

DISCUSSION

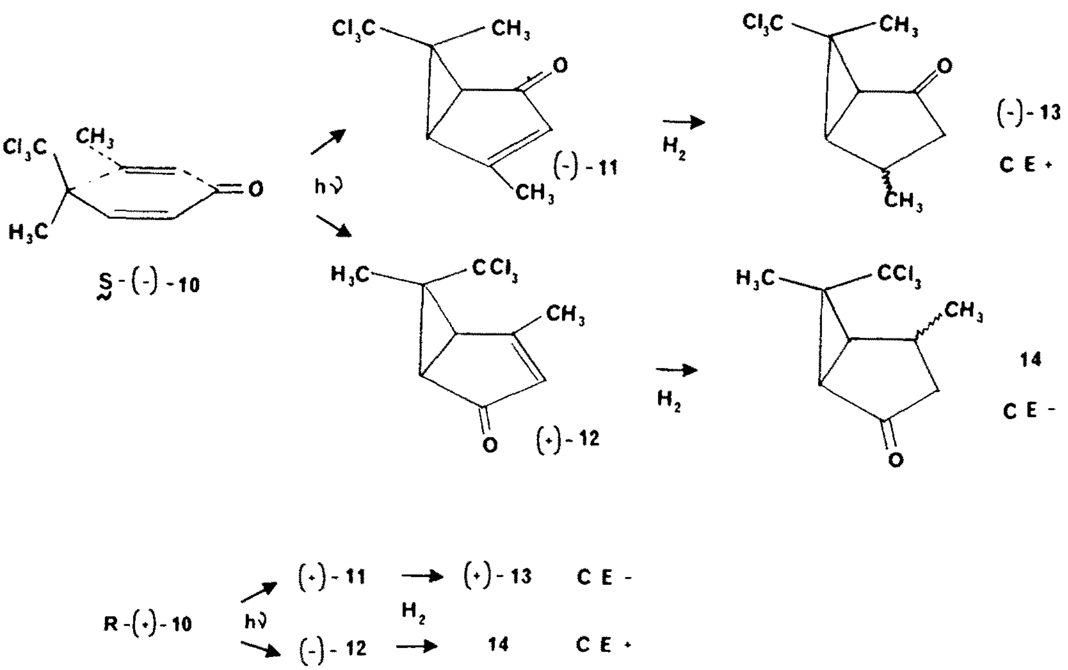
The sign of the long wavelength Cotton effect for a large number of bicyclo[3.1.0]hexan-2-ones and analogous epoxy ketones of known absolute configuration has been shown to be empirically correlated by an "inverse octant rule",[21,26] which however is lacking theoretical justification. Although dihydrolumisantonin (derived from **2**) obeys the "inverse" octant correlation, (+)-carone **18** demonstrates "normal" octant behavior.[21] Both of these compounds possess gem-dialkyl substitution on the apical carbon of the cyclopropane ring in the cyclopropyl ketone chromophore. Introduction of a highly polarizable trichloromethyl group at such a position should enhance the contribution of "normal" *vis a vis* "inverse" contributions to the observed Cotton effect.[21,26] The opposition of these two factors is supported by the fact that the sign of rotation of **3** and **14** changes without going through a maximum or minimum as the wavelength is decreased from the sodium D line at 589 nm. Based on these considerations, we hesitantly conclude that the absolute configurations of **13** and **14** are more likely to follow a "normal" rather than an "inverse" octant correlation with the experimentally observed Cotton effect.



18

On the basis of the unambiguous assignment of stereochemistry to the (+)- and (−)-dienone **10** based on the X-ray structure of the *p*-bromoanilide **17** and the more questionable assignment to **13** and **14** discussed above, the stereochemical course of the photochemical rearrangement of dienone **10** is as depicted in Scheme 4. It is clear that these structural assignments require that the [1,4]-sigmatropic shift which converts the bicyclic intermediate of type A or B (Scheme 1) into the lumiketone occurs with inversion of configuration at the migrating C atom, by reference to Scheme 3. This result is consistent with the stereochemistry of the model [1,4]-sigmatropic rearrangements of bicyclo[3.1.0]hexenyl cations discussed earlier, and is compatible with the mechanistic description of this photochemical rearrangement involving a ground state zwitterionic intermediate.[2,4,6]

The force of this conclusion is mitigated somewhat by the uncertainty regarding the applicability of the octant rule to the assignment of absolute configuration to **13** and **14**, which is a critical factor in this study. The lack of reliability of these correlations has been further demonstrated by β, γ-cyclopropyl ketones which as a group follow neither normal nor inverse octant correlations.[27] Crabbé[26c] has warned that caution must be exercised in applying such rules to ketones



Scheme 4

containing functional groups in the vicinity of the CO. It would therefore be nice to be able to report additional data to support these configurational assignments, such as the conversion of **11**, **12**, **13** or **14** to suitable derivatives containing chiral centers of known configuration together with an X-ray analysis of the structure. However, all attempts to prepare such derivatives using chiral amines or reagents such as **15** failed. The failure to prepare such derivatives also precluded determination of the optical purity of lumiketones **11** and **12** using the NMR method that was applied to dienone **10**. Thus, it is not possible to say at this time how much, if any, racemization occurs on photorearrangement of dienone **10**. However, any such racemization would have to occur by a concomitance of pathways involving fundamentally different rearrangement modes, as depicted schematically in Scheme 3, and therefore appears to us highly improbable.

EXPERIMENTAL

General. NMR spectra were taken on Varian Associates Models A-60 and XL-100 and Hitachi Perkin-Elmer Models R-24 and R-20B Spectrometers. Infrared spectra were recorded on Perkin-Elmer Model 735 and 337 spectrophotometers. Mass spectra were recorded on a Varian M-66 Double Focusing Cycloidal Path Mass Spectrometer and later on a DuPont Model 21-492B Mass Spectrometer by Mr. Charles Strom. Optical rotations were measured at the sodium D line (589 nm) initially on a Rudolph Photoelectric Polarimeter Model 200-A with an Oscillating Polarizer and later on a Perkin-Elmer Model 141 Digital Recording Polarimeter using 10 cm cells. Analytical glpc analysis were carried out on an F and M Model 5750 Research Chromatograph with dual column flame ionization and disc chart integrator, and a Hewlett-Packard Model 5710A Chromatograph equipped with oven temperature programmer, electronic integrator and strip chart recorders. The columns used are indicated in the individual experiments.

Racemic 3,4-dimethyl-4-trichloromethyl-2,5-cyclohexadien-1-one (**10**) was prepared according to the procedure of Newman and Wood[28] as described previously.[19]

Resolution of dienone **10** was performed initially[22] according to the procedure of Newman *et al.*,[20] but an improved procedure was later devised by Smith.[23] Racemic α-**15** was prepared a number of times by the procedure of Newman and Lutz,[20] m.p. 56.5–58.5° (lit[20] 57.8–60.8°). The racemic acid (IPA) was resolved using (−)-ephedrine essentially by the literature procedure.[20] Repeated recrystallization gave the (−) salt, m.p. 121–124° (lit.[20] 121–123°) which had α_D − 24.1° (*c* 1, H_2O) (lit.[20] − 25.5°). Hydrolysis of this salt in aq HCl and appropriate extractions and separations gave an oily acidic material which could only be made to crystallize on standing in the refrigerator for up to 2 weeks in an acetone-petroleum ether mixture (1:5 or 1:6) while the solvent was allowed to slowly evaporate. This material, m.p. 82–86° (lit.[20] 81–85°) had α_D (+)-31.3–31.4° (*c* 1.0, H_2O) (lit.[20] 30.4 ± 0.6°). Workup of the filtrate obtained after separation of the (−)-salt (above) gave the (+)-salt of IPA and ephedrine, which was either recrystallized to give maximal optical rotations or hydrolyzed directly to (−)-IPA. The purest sample of (−)-IPA so obtained had m.p. 83–86° and α_D −31.7°, while the material obtained directly by hydrolysis had α_D − 29.3° (*c* 1.0, H_2O) (lit[20] −29.8°).

The adducts **16** were prepared as described previously[20] by heating **10** with either (+)- or (−)-IPA in glacial AcOH containing a small amount of *p*-toluenesulfonic acid with N_2 passing through the soln until there was no further evolution of acetone (tested by passing the exit gases through 2,4-dinitrophenylhydrazine soln). Workup and extraction as described previously[20] gave a dark brown viscous mixture of adducts **16**, which could only be made to crystalline with difficulty, and which gave low yields of the pure diastereomers upon repeated recrystallization from benzene-cyclohexane mixtures. The best sample of the adduct obtained by this tedious method using (+)-IPA had m.p. 154–157° and α_D − 194° (*c* 0.1, dioxane), and did not afford any of the other diasteromer in pure form. An improved procedure was developed in which the mixture of diastereomers was treated with an equimolar amount of (−)-ephedrine, and the resulting mixture of diastereomeric salts (i.e. derived from the two enantiomeric dienones, the enantiomer of IPA utilized and (−)-ephedrine) could be readily recrystallized from benzene containing a small amount of cyclohexane. The second recrystallization gave a salt which could be hydrolyzed to (−)-**16** with the same rotations as obtained above, while the filtrate was highly enriched in the diastereomeric salt, which could be hydrolyzed to (+)-**16** of high optical purity. The recrystallizations of the salts were nearly quantitative in contrast to the poor yields realized on recrystallization of **16** directly, affording both diastereomeric adducts in about 25% yield each.

Hydrolysis of adducts **16** to generate optically active **10** was done according to the published procedure[20] by heating with levulinic acid and HCl at reflux. Workup gave **10** in different states of optical purity, and crystallization of the material always proceeded with difficulty. The sample of (−)-**10** obtained from (−)-**16** of highest specific rotation had α_D − 31.7° (*c* 1.0, benzene).

Several other procedures for resolution of **10** were attempted, and all were unsuccessful. One of these involved resolution of the dienone oxime using resolved α-bromopropionic acid, and another involved direct resolution of **10** using (−)-ephedrine, a method employed successfully by Eaton in the case of trishomocubanone.[29] The *p*-bromoanilides **17** of the diastereomeric adducts **16** prepared from racemic **10** and (+)-**15** were prepared (see procedure below) in the hopes that these diastereomeric amides might be readily separable by crystallization or chromatography. A partial separation was achieved, as indicated by differing ratios of PMR resonances for the vinyl Me's (δ 2.16 vs 2.26 ppm) and the quaternary Me's (1.62 vs 1.65 ppm) in crystals *vis à vis* filtrates, but a clean separation could not be achieved.

Attempted resolution of lumiketone **11**. Several attempts were made to resolve **11** with (+)-**15** by the procedures used successfully for **10** (see above). However, there was no evidence (IR, PMR, Mass spectra) for adduct formation on heating **11** with (+)-**15** in refluxing acetic acid or in benzene containing *p*-toluenesulfonic acid. In addition, allowing **11** to react with (−)-ephedrine in hopes of formation of oxazolidines,[29] and also with several chiral amines in hopes of formation of diastereomeric Schiff's bases, also met with failure. In some runs, **11** could be quantitatively recovered, while in others (generally at higher temps) **11** decomposed. Again, spectra gave no indication of adduct formation in any of these reactions.

p-*Bromoanilide* **17** *of* (−)-*adduct* **16**. A 100 mg sample of pure (−)-adduct **16** with α_D − 191° (dioxane), prepared from **10** and (+)-acid **15**, was heated at reflux for 0.5 hr with 1 ml of freshly distilled $SOCl_2$. The excess $SOCl_2$ was removed using a steam bath to give a yellowish tacky material, which was dissolved in 5 ml benzene and added to a soln of 50 mg of freshly crystallized (from EtOH) *p*-bromoaniline in 5 ml benzene. The resulting soln was then washed successively with 5 ml 5% HCl aq, 5 ml of 5% NaOH aq and twice with 10 ml water. The organic layer was dried over $NaSO_4$ and the solvent was removed using a Rotovap. The resulting white solid was recrystallized from EtOH–water to give 70 mg of *p*-bromoanilide **17**, m.p. 148–152° with decomposition. This material had *m/e* 478 (M^+), 408, 361 (base peak, $M^+ - CCl_3$), 279, 259, 226, 198, 171, 164, 155, 147, 136, 132, 119, 106, 91, 77, 63, 45 and 43. IR ($CHCl_3$): 3410, 3020, 2980, 2940, 1695, 1615, 1590, 1510, 1480, 1390, 1290, 1245, 1180, 1100, 1080, 1040, 1010 and 970 cm^{-1}. The pmr spectrum in $CDCl_3$ showed a broad resonance at δ 7.85 (1 H) for the amide proton, and resonances at 7.4 (s, 4 H, aromatic), 6.85 (m, 3 H, vinyl protons), 4.78 (q, 1 H, J = 7, methylene), 2.28 (d, 3 H, J ~ 1, vinylic Me), 1.69 (s, 3 H, quaternary Me) and 1.63 ppm (d, 3 H, J = 7, Me on aliphatic chain).

A single crystal of this material suitable for X-ray analysis was prepared as follows. A 10 mg sample of the anilide was dissolved in 1 ml of abs EtOH in a 3 ml beaker. This beaker and a second 3 ml beaker containing 2 ml water were placed inside an inverted 100 ml beaker, and were allowed to stand for 2 days at room temp. A slow equilibration process was initiated, which resulted in the gradual appearance of white crystals in the first beaker. These plate-like crystals were carefully removed from the beaker after the solvent had been removed by suction, and were dried *in vacuo*.

X-Ray analysis of p-*bromoanilide of* (–)-**16**. Compound **16** yielded prismatic crystals upon evaporation of an acetone soln. The space group was found to be $P2_1$ from Weissenberg and Precession photographs (OKO, k = 2n + 1 absent). Cell parameters which are reported in Table 1 were determined from ten carefully centered reflections measured on a Picker FACS I diffractometer. Integrated intensity data were collected from a crystal measuring 0.05 × 0.15 × 0.05 mm mounted along b using θ–2θ scans and Cu-K_α radiation and a scan rate of 1 degree/min. Background was measured on both sides of each peak for a total time equal to the time spent scanning the peak. Reflections were classified as observed when $I > 2\sigma$. A total of 1877 observed reflections and 189 unobserved were collected.

The structure was solved by heavy atom methods using the X-ray 72 programs.[30] Most of the rest of the structure was evident in a difference Fourier map phased on bromine alone. After all the non H-atoms were located, the structure was refined isotropically. Hydrogen positions were calculated for all position except for the two Me groups. The methyl H-atoms were located in a difference map. Anisotropic refinement with a weighting scheme of the non H positions with H positions fixed reduced R to 0.065. Tables 2 and 3 list the final positional and thermal parameters, respectively. Tables 4 and 5 show the bond distances and angles, respectively, and Table 6 shows the torsional angles for the cyclohexadienone ring. The final structure is shown in Fig. 2.

Irradiation of (+)-*dienone* **10**. Different batches of (+)-**10** were combined and diluted with 4 g of racemic dienone in 100 ml of t-BuOH. The resulting soln showed α_D + 2.1°. The soln was deoxygenated by passing N_2 through it for 0.5 hr, and was then irradiated at 254 nm in a quartz vessel in a Rayonet reactor for 6 hr. The solvent was removed using a Rotovap to give a dark brown viscous liquid which was chromatographed on silica gel, as described previously[19] in the case of the photolysate from racemic **10**. The various fractions from the column chromatographic separation were compared spectrally and by coinjection on the gas chromatograph with racemic photoproducts available from the earlier study.[19] Purity of products was established by glpc analysis (6 in × 1/8 in column of 5% or 15% SE-30 on chromosorb G, AW/DMCS, column 150–155°, injection port 195°). Impure fractions were subjected to repeated fractionation of silica gel. Rotations are given in the Results section. In this study, no attempt was made to achieve a mass balance (see the study of racemic **10**),[19] but rather the goal was to isolate the lumiketones **11** and **12** and unreacted **10** in as pure form as possible for polarimetric measurements and hydrogenation, as described below.

Irradiation of (–)-*dienone* **10**. The experiment was carried out much as described above using 4.02 g of **10**, comprising 3.3 g of racemic material and 0.72 g of different samples of (–)-**10** of varying optical purity. This material was again dissolved in 100 ml of t-BuOH, deoxygenated using N_2, and irradiated for 6 hr at 254 nm. The column chromatographic separation and analysis for products were as described above. The results are given in the Results section.

Hydrogenation of optically active lumiketones. The procedure described below starting with (–)-**11** is typical of that used for each of the four stereoisomers of **11** and **12**. Several chromatographic fractions derived from irradiation of (–)-**10** which had been shown by glpc analysis (see above) to contain predominantly **11** and only trace contaminants were combined to give a total of 300 mg. PMR analysis confirmed that this material was of very high purity. About half of this material (152 mg) was added to 50 ml of spectral grade hexane, to which a few drops of ethanol were added to dissolve the entire sample. Analysis by glpc confirmed that the material (isolated several months previously) was mainly **11** containing only trace impurities. To the soln was added 15 mg of fresh 10% Pd–C, and the soln was then attached to a standard atmospheric pressure hydrogenation apparatus. The progress of reaction was checked by glpc on the SE-30 column. After 3 hr only one major peak was observed, with retention time slightly longer than that of the starting material, which was coinjected along with the hydrogenation product. The catalyst was removed by filtration, and the solvent was removed from the filtrate on a Rotovap. The residue (168 mg) was dissolved in 10 ml abs EtOH and the rotation of the soln was measured on the Perkin–Elmer polarimeter, as indicated in the Results section. The EtOH was then removed on the Rotovap, and the PMR spectrum of the residue in CCl_4 soln compared exactly with the spectrum of racemic dihydrolumiketone **13** obtained previously,[19,22] except for tiny blips due to minor impurities. Hydrogenation of the unused portion of (–)-**11** (see above) was carried out using the same procedure. The products of the two runs were combined and chromatographed on a 22 cm column (1.5 cm diameter) of Davison 950 silica gel, 60–200 mesh, with elution by hexane–ether mixtures. The fractions were analyzed by glpc on the SE-30 column. The purest fractions of **13** were combined (151 mg), and this material was at least 98–99% pure according to glpc analysis. The optical rotation of this material was as indicated in the Results section. The circular dichrograph of this sample was measured on the Cary 60 spectropolarimeter, and the purity of the sample was then rechecked by glpc after the CD measurement.

The same procedure was used on (+)-**11** derived from irradiation of (+)-**10** and on (+) and (–)-**12** derived from (–)- and (+)-**10**, respectively. In the latter cases, the reactions were necessarily carried out on a much smaller scale. Fortunately, however, the hydrogenation products crystallized after removal of the catalyst and solvent after being stored in the refrigerator overnight in a small volume of hexane. The m.ps agreed well with that of racemic **14** (see Results). The amount of material was too small to allow spectral comparison with racemic **14** prepared previously.[19,22] At a later time, when such a comparison might have been possible, the samples were found to have decomposed on storage in the refrigerator, according to glpc analysis.

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