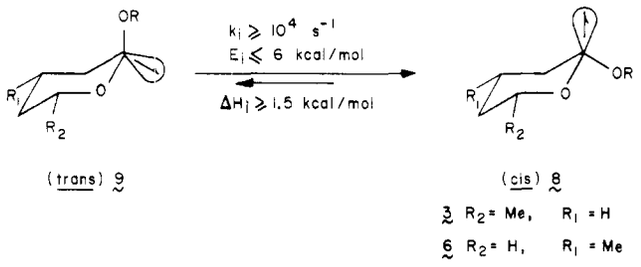
Table I. EPR Parameters for Methyl-2-alkoxytetrahydropyran-2-yl Radicals in Cyclopropane at −98 °C [a]

radical precursor	g	a^H(1 H)	a^H(1 H)	a^H(3 H)
1	2.0028_5	27.32	4.12	0.75
2	2.0028_7	27.44	4.14	0.74
4 [b]	2.0029_0	28.92	3.99	
5 [b]	2.0028_8	28.94	3.86	

[a] Hyperfine splittings are in gauss. The number of hydrogens producing each splitting are given in parentheses. [b] A trace of a second radical is also present which appears to have a^H(1 H) = 14.5 G, a^H(3 H) = 22.5 G, and g = 2.0029.

Similarly, our failure to detect a trans radical at the highest temperatures reached allows a lower limit of ~1.5 kcal/mol to be placed on ΔH_i for the cis–trans equilibrium. These ex-



perimentally derived conclusions are fully consistent with the results of a theoretical study of 2-alkoxytetrahydropyran-2-yl radicals.[23]

The preference of these radicals for the cis conformation is too large to be entirely attributed to steric factors since these factors probably amount to little more than 0.6 kcal/mol.[6,7] The conformational preference of the radicals stands in sharp contrast to that of their parent molecules for which the trans structure having the OR group axial is preferred by ca. 0.35–0.74 kcal/mol.[6,7] Since an equatorial preference is usually observed in monosubstituted cyclohexanes, an axial preference is anomalous and is commonly referred to as the "anomeric effect".[8,24,25] In the 2-alkoxytetrahydropyrans it arises because of interactions between the lone pairs of the ring oxygen and the exocyclic C_2–O and C_2–H bond orbitals.[26] In radicals 3 and 6 the alkoxy group adopts the equatorial position. This allows stabilization[27] of the radical center by conjugative delocalization to the p-type lone pair on the ring oxygen.[28] That is, in the cis conformation the radical will be stabilized by electron delocalization to the p-type lone pairs of both of the adjacent oxygen atoms, but in the trans conformation only the exocyclic oxygen can provide this stabilization.[28] We attribute the more rapid hydrogen abstraction from *cis*- than from *trans*-2-methoxy-4-methyltetrahydropyran[4] to the fact that the cis isomer is thermodynamically less stable than the trans *and* that it can *directly* yield the thermodynamically more stable cis radical.

Acknowledgment. We would like to thank Dr. A. R. Gregory for several helpful discussions.

Registry No.—1, 932-80-9; 2, 7429-28-9; 3, 69239-32-3; 4, 17230-09-0; 5, 17230-10-3; 6, 69239-33-4; di-*tert*-butyl peroxide, 110-05-4.

References and Notes

(1) Issued as N.R.C.C. No. 17411.
(2) N.R.C.C. Research Associate 1977–1978.
(3) (a) Department of Chemistry, The Institute of Paper Chemistry, Appleton, Wis. 54911. (b) Present address: Department of Chemistry, The University of Wisconsin, La Crosse, Wis. 54601.
(4) K. Hayday and R. D. McKelvey, *J. Org. Chem.*, **41**, 2222 (1976).
(5) C. Bernasconi and G. Descotes, *C. R. Hebd. Seances Acad. Sci. Ser. C*, **280**, 469 (1975).
(6) E. L. Eliel and C. A. Giza, *J. Org. Chem.*, **33**, 3754 (1968).
(7) E. L. Eliel and E. C. Gilbert, *J. Am. Chem. Soc.*, **91**, 5487 (1969).
(8) See also E. L. Eliel, *Acc. Chem. Res.*, **3**, 1 (1970).
(9) M. Anteunis, D. Tavernier, and F. Borremans, *Bull. Soc. Chim. Belg.*, **75**, 396 (1966).
(10) A pair of rapidly interconverting radicals would, of course, yield the same result.
(11) This conclusion arises from the fact that all of the radicals that could be formed by hydrogen abstraction are sterically unhindered. These radicals will therefore decay by radical–radical reactions which will all occur with the same rate constant since they will all be diffusion controlled.[12] Even if one or more of the radicals formed initially decays by a rapid unimolecular rearrangement, the "secondary" radical it produces will decay by a radical–radical reaction.
(12) K. U. Ingold, *Free Radicals 1973*, **1**, Chapter 2 (1973).
(13) Cyclohexyl in the slow exchange limit has $a^{H_{ax}}$ = 39.4 G and $a^{H_{eq}}$ = 5.3 G.[14]
(14) S. Ogawa and R. W. Fessenden, *J. Chem. Phys.*, **41**, 994 (1964).
(15) J. E. Bennett and L. H. Gale, *Trans. Faraday Soc.*, **64**, 1174 (1968).
(16) A. L. J. Beckwith and P. K. Tindal, *Aust. J. Chem.*, **24**, 2099 (1971).
(17) A. J. Dobbs, B. C. Gilbert, and R. O. C. Norman, *J. Chem. Soc., A*, 124 (1971).
(18) G. Brunton, K. U. Ingold, B. P. Roberts, A. L. J. Beckwith, and P. J. Krusic, *J. Am. Chem. Soc.*, **99**, 3177 (1977).
(19) J. K. Kochi, *Adv. Free-Radical Chem.*, **5**, 189 (1975).
(20) A. Hudson and K. D. J. Root, *Tetrahedron*, **25**, 5311 (1969).
(21) See ref 16 and references cited therein for a discussion on this point.
(22) It must be admitted that an inversion at the radical center which is rapid on the ESR time scale at all temperatures, though highly improbable, cannot be unambiguously ruled out by the present results. Chemical trapping experiments are planned which will, we believe, confirm that all radical-derived products arise entirely from the cis conformer.
(23) A. R. Gregory and V. Malatesta, to be submitted.
(24) R. U. Lemieux, K. B. Hendriks, R. V. Stick, and K. James, *J. Am. Chem. Soc.*, **97**, 4056 (1975), and references cited therein.
(25) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis", Interscience, New York, 1965, p 375.
(26) S. David, O. Eisenstein, W. J. Hehre, L. Salem, and R. Hoffmann, *J. Am. Chem. Soc.*, **95**, 3806 (1973).
(27) N. C. Baird, *J. Chem. Educ.*, **54**, 291 (1977).
(28) The role that such overlap plays in producing nonplanarity at the radical center has been discussed in ref 17 and 29.
(29) See, e.g., R. C. Bingham and M. J. S. Dewar, *J. Am. Chem. Soc.*, **95**, 7182 (1973); P. J. Krusic and R. C. Bingham, *ibid.*, **98**, 230 (1976); F. Bernardi, N. D. Epiotis, W. Cherry, H. B. Schlegel, M. H. Whangbo, and S. Wolfe, *ibid.*, **98**, 469 (1976). See also F. Bernardi, W. Cherry, S. Shaik, and N. D. Epiotis, *ibid.*, **100**, 1352 (1978).

Revised Structures of Pleniradin and Baileyin and Their Bearing on the Biogenesis of Helenanolides[1]

Werner Herz* and R. Murari

Department of Chemistry, The Florida State University, Tallahassee, Florida 32301

John F. Blount

Research Division, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

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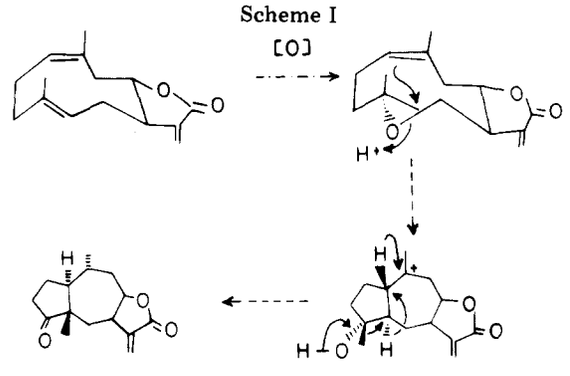
One of us has proposed[2] a biogenetic scheme for the class of sesquiterpene lactones known as helenanolides which is depicted in Scheme I. It was speculated that the formation of these compounds is initiated by enzyme-mediated anti-Markownikoff cyclization of a *cis*-1(10),*trans*-4,5-germacra-

Scheme I



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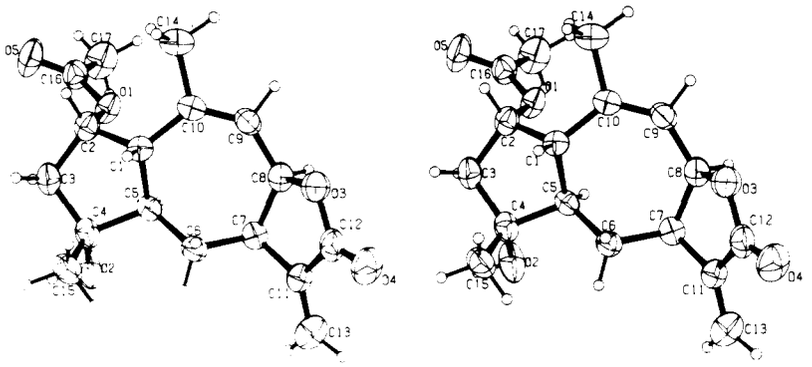


Figure 1. Stereoscopic view of pleniradin acetate.

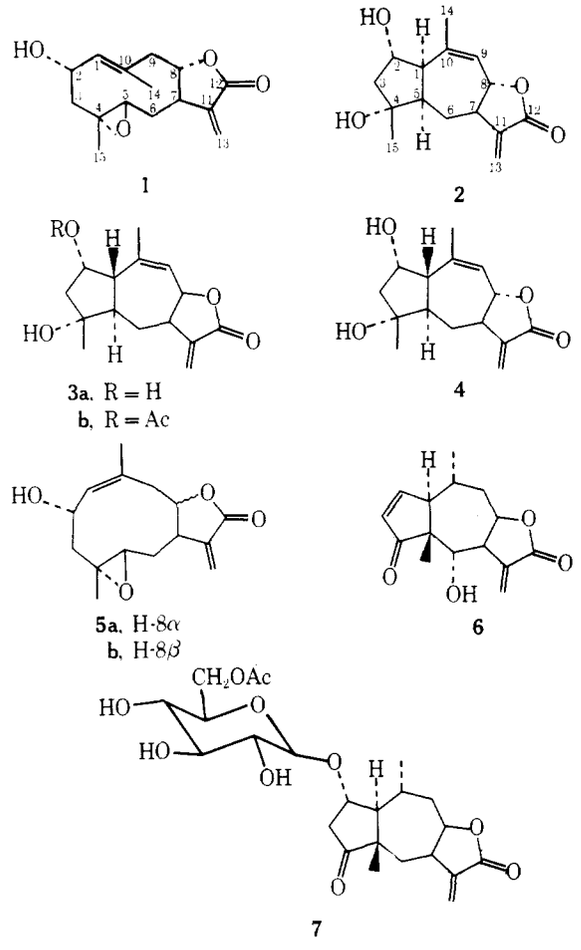
dienolide[3] or the equivalent 4,5-epoxide similar to the acid-catalyzed process shown. The resulting trans-fused guaianolide ion could stabilize itself by proton expulsion or reaction with a nucleophile; alternatively, it could undergo a series of rearrangements (arrows) to a helenanolide.[6]

Elaboration of the scheme was prompted by the observation that although trans-fused guaianolides are quite rare in nature, the few that have been found occur either in conjunction with helenanolides or are found in chemical races of species which normally contain helenanolides (for examples, see ref 2). The scheme was subsequently reinforced by the actual discovery in nature of the postulated *cis*-1(10),*trans*-4,5-germacradienolides and their 4,5-epoxides, the so-called melampolides.[8,9] To date, however, no single species has yielded representatives of all three lactone classes lying on the presumed biogenetic pathway. We now report that the structures of baileyin and pleniradin, two sesquiterpene lactones from *Baileya pleniradiata* Cav. and *B. multiradiata* Harv. and Gray, require revision and that in consequence these two species do in fact fulfil the conditions for the proposed biogenetic scheme.

The original study of these species by Geissman and coworkers[13-15] yielded the germacranolide baileyin (**1**), the guaianolide pleniradin (**2**), and several helenanolides whose structures were either already known or established subsequently.[16-18] Pleniradin was assigned[15] the gross structure of formula **2** because of its NMR spectrum and some chemical transformations. Its lactone ring was assumed to be trans because of the positive Cotton effect associated with the n,π^* transition of the unsaturated lactone;[19] the C-2 hydroxyl group was assigned the α configuration by application of Horeau's method.[20] The stereochemistry ascribed to C-1, C-4, and C-5 was based on the assumption that pleniradin was biogenetically related to baileyin, whose properties seemed to be consonant with formula **1**, and to the helenanolides by a rearrangement involving the epoxide of pleniradin.

To accommodate the biogenetic scheme for the helenanolides, one of us has suggested[2a] that baileyin is actually a *cis*-1(10)-germacrenolide and that pleniradin is a trans-fused guaianolide with H-1β and H-5α, in which case the presumed series of shifts leading to the helenanolides of *Baileyea* species would operate unexceptionally. It was also pointed out that if pleniradin were indeed a trans-fused guaianolide, its stereochemistry at C-2 and/or C-8 would require revision as well since pleniradin acetate differs from gaillardin (**4**) of established relative and absolute configuration.[21]

Attempts to verify this suggestion were long frustrated by the unavailability of the two compounds. However, through the courtesy of Professor Pettit and Dr. Cherry L. Herald who have recently reinvestigated the constituents of *Baileya* extracts because of their antitumor properties,[18,22] we obtained a few milligrams each of baileyin and pleniradin acetate and were able to substantiate our guess as to the stereochemistry



of these substances at the relevant carbon atoms.

Analysis of the ^{1}H NMR spectrum of pleniradin acetate at 270 MHz (Table I) verified the carbon skeleton proposed previously, but was not very helpful in establishing the stereochemistry of the ring junction since both cis- and trans-fused guaianolides exhibit large values for $J_{1,5}$.[23] Consequently, a single crystal of pleniradin acetate was examined by X-ray crystallography. This resulted in formula **3b** with *a trans fusion of the two carbocyclic rings;* hence, pleniradin is **3a.**

Crystal data of **3b** are listed in the Experimental Section. Figure 1 is a stereoscopic drawing of the molecule which shows that H-1 and H-5 are trans, with the two hydroxyl groups cis to H-5 and trans to H-1, and that the lactone ring is cis fused.

While it was not possible to deduce the absolute configuration of pleniradin acetate from the X-ray data, one would normally infer that Figure 1 and formula **3b** also represent the absolute configuration since earlier[14] application of the Ho-

Table I. NMR Spectra (δ) of Baileyin and Pleniradin Acetate[a]

	3	4b
H-1	5.33 (br d, 10)	1.82 (br d, $J_{1,5}$ = 14 Hz)
H-2	4.69 (m 10, 10, 6)	5.22 (m)
H-3a	2.62 (dd 12, 6)	2.32 (dd, 15, 8)
H-3b	1.27 (t, 12, 10)	2.12 (br d, 15)
H-5	2.33 (d, 15)[b]	2.32 (m, $J_{5,6b} \approx$ 14 Hz)
H-6a	2.75 (dd, 15, 12)[c]	2.32 (m, $J_{6a,6b} \approx$ 15 Hz)
H-6b	1.4 (m)	1.34 (q, $J_{6b,7} \approx$ 13 Hz)
H-7	2.85 (m, $J_{7,8} \approx$ 9 Hz)	3.46 (m, $J_{7,8} \approx$ 9 Hz)
H-8	4.05 (dd, 9. 12)[d]	5.39 (dd, 9, 3)
H-9a	2.47 (t, 12)	5.46 (br)[f]
H-9b	1.3[e]	
H-13a	6.37 (d, 3.5)	6.22 (d, 3)
H-13b	5.67 (d, 2.7)	5.54 (d, 3)
H-14	1.85 (br, 1)	1.69 (br)
H-15	1.18	1.21
Ac		2.03

[a] Run in CDCl at 270 MHz. Registry no.: baileyin, 27875-37-2; pleniradin acetate, 25873-32-9. [a] $J_{5,6b}$ is very small. [c] $J_{6a,7}$ is very small. [d] $J_{8,9b}$ is very small. [e] Partially obscured. [f] Coupled to H-14; $J_{8,9}$ is very small.

Table II. Lactone Ring Torsion Angles of 3b

C(8)–O(3)–C(12)–C(11)	ω_1 −9.6°
C(13)–C(11)–C(12)–O(4)	ω_2 −12.4°
C(11)–C(7)–C(8)–O(3)	ω_3 −29.6°
C(6)–C(7)–C(8)–C(9)	ω_4 −32.1°

reau method to pleniradin had shown C-2 to be α. As was to be expected, the absolute configuration of pleniradin acetate would then parallel the absolute stereochemistry of its congeners, dihydrohelenalin (plenolin, **6**) and paucin (**7**), whose absolute configuration is known.[14,17,24] However, in this case the sign of the -C=CCO torsion angle (ω_2 of Table II), which as usual is paired with the sign of ω_3,[25] would not correspond to the sign of the Cotton effect associated with the n,π* transition of the α,β-unsaturated lactone which we have verified as being positive ($[\theta]_{250}$ 5700).

Although violations of Horeau's rule are known,[26] the biosynthesis of sesquiterpene lactones with opposite absolute configuration in the same species would be without precedent; in fact, we know of no sesquiterpene lactone with H-7 authenticated as H-7β in higher plants. On the other hand, adherence to precedent would constitute pleniradin acetate, an exception to the rather hesitantly expressed generalization[27] that chirality in the cisoid α,β-unsaturated lactone system determines the sign of the Cotton effect. Resolution of this dilemma, which would require additional supplies of pleniradin, is obviously of importance in a far larger context.

Our study of the second lactone, baileyin, was perforce limited to an examination of the ^{1}H NMR spectrum at 270 MHz (Table I). Spin decoupling experiments established the sequence C-1 through C-3 and C-5 through C-9. Since the other terminus of the oxirane ring was a quaternary carbon and H-1 was allylically coupled to the vinylic methyl, the previously proposed gross structure follows. Irradiation at the frequency of the C-10 methyl group produced a 12.9% enhancement in the strength of the H-1 signal; *hence, baileyin was indeed a melampolide* rather than a *trans*-1(10)-germacrenolide.

The approximate coupling constants give in Table I were not sufficient to establish unambiguously the stereochemistry at C-2 and C-8. On balance, a *trans*-lactone fusion, as in **5a** (H-8β), with the C-2 hydroxyl group α, seems preferable, but this arrangement, in the *C* conformation, does not satisfactorily explain the displacement of the H-8 and H-15 signals to somewhat higher than normal field and would differ in mode of lactone ring closure from all other constituents of *Baileya* species.[28] Attempts to obtain more conclusive evidence for the stereochemistry of the two questionable centers by determining the presence or absence of transannular NOE's failed because of superposition of signals and gradual decomposition of the sample.

In conclusion, it has been shown that *Baileya* species elaborate a melampolide and a trans-fused guaianolide of the type previously postulated to lie on the biogenetic pathway to their major lactone constituents, the helenanolides. This of course does not constitute proof for the actual involvement of such intermediates, which must await the outcome of biosynthetic studies. That two frequently used generalizations lead to mutually contradictory conclusions concerning the absolute configuration of pleniradin acetate indicates the need for caution in this area and poses a problem for the future.

Experimental Section

Single crystals of pleniradin acetate as received from Professor G. R. Pettit were monoclinic, space group $I2$, with a = 16.743 (2), Å b = 5.408 (1) Å, c = 17.601 (3) Å, β = 95.31 (1)°, and d_{calcd} = 1.282 g cm^{-3} for Z = 4 ($C_{17}H_{22}O_5$, M_r = 306.36). The intensity data were measured on a Hilger-Watts diffractometer (Ni-filtered Cu Kα radiation, θ–2θ scans, pulse height discrimination). A crystal measuring approximately 0.10 × 0.10 × 0.5 mm was used for data collection; the data were not corrected for absorption (μ = 7.8 cm^{-1}). A total of 1197 reflections were measured for $\theta < 57°$, of which 1135 were considered to be observed [$I > 2.5\sigma(I)$]. The structure was solved by a multiple solution procedure[27] and was refined by full-matrix least squares. In the final refinement, anisotropic thermal parameters were used for the heavier atoms and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indices were R = 0.041 and wR = 0.050 for the 1135 observed reflections. The final difference map had no peaks greater than ±0.2 e Å^{-3}.

Registry No.—**3a**, 25941-24-6.

Supplementary Material Available: Tables III–VII listing final atomic and anisotropic thermal parameters, bond lengths, bond angles, and selected torsion angles (5 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Work at The Florida State University was supported in part by a grant (CA-13121) from the U.S. Public Health Service through the National Cancer Institute.

(2) (a) W. Herz in "Pharmacognosy and Phytochemistry", H. Wagner and L. Hörhammer, Eds., Springer-Verlag, West Berlin and Heidelburg, 1971, p 64; (b) W. Herz, *Nobel Symp.*, **No. 25,** 73 (1974); (c) W. Herz. *Isr. J. Chem.*, **16,** 32 (1977).

(3) Such an intermediate was first suggested by Parker, Roberts, and Ramage[4] to explain the co-occurrence of the eudesmanolide microcephalin and the guaianolide pseudoivalin.[5] Depiction of lactone intermediates in Scheme I does not imply that lactone formation must necessarily precede cyclization.

(4) W. Parker, J. S. Roberts, and R. Ramage, *Q. Rev., Chem. Soc.*, **21,** 311 (1967).

(5) W. Herz, C. Högenauer, and A. Romo de Vivar, *J. Org. Chem.*, **29,** 1700 (1964); W. Herz, A. Romo de Vivar, and M. V. Lakshmikantham, *ibid.*, **30,** 118 (1965); G. D. Anderson, R. Gitany, R. S. McEwen, and W. Herz, *Tetrahedron Lett.* 2409 (1973).

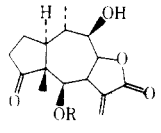
(6) Ambrosanolides, which differ from helenanolides in configuration at C-10, presumably arise by cyclization of *trans*-1(10),*trans*-4,5-germacradienolides (or the 4,5-epoxides) in the favored crown (or *C*[7]) conformation to cis-fused guaianes followed by an analogous series of cationic rearrangements.[2]

(7) J. K. Sutherland, *Tetrahedron*, **30,** 1651 (1974).

(8) N. H. Fischer, R. Wiley, and J. D. Wander, *J. Chem. Soc., Chem. Commun.*, 137 (1973); S. Neidle and D. Rogers, *ibid.*, 140 (1973); W. Herz and S. V. Bhat, *J. Org. Chem.*, **35,** 2605 (1970); *Phytochemistry*, **12,** 1737 (1973).

(9) Fischer[10] has modified the scheme by arguing that in a *T*-melampolide (i.e., a melampolide in which the conformation of carbon atoms 10 through 6 clockwise is such so as to lead to a boat or twist-boat on cyclization[7]) the center-to-center distance between the two double bonds is considerably greater than in a *C*-melampolide or in the *C* or *T* conformations of a *trans,-trans*-germacradienolide. It is suggested that the resulting inhibition of cyclization imposes alternate biosynthetic pathways on a *T*-melampolide such as the oxidation of the C-10 methyl group typical of melampolides.[11] He suggests that trans-fused guaianolides and helenanolides (in which the lactone ring is invariably closed to C-8) are formed by transannular cyclization of epoxides derived from the *T* conformers of *trans,trans*-germa-

cradienolides closed toward C-8, which are conformationally more flexible than germacradienolides closed toward C-6.
(10) N. H. Fischer, R. A. Wiley, and D. L. Perry, *Rev. Latinoam. Quim.*, **7**, 87 (1976); N. H. Fischer, *ibid.*, **9**, 41 (1978).
(11) All melampolides reported to date contain a carbonyl group on C-14, which by deactivating the 10 double bond would seem to make them unlikely candidates for further cyclization. Those melampolides which have been studied by X-ray crystallography or analyzed by high-resolution NMR spectrometry are locked into a rigid highly distorted *C* conformation with antiorientation of the substituents on C-4 and C-10 as the result of containing a trans-fused lactone ring closed to C-6. By contrast, a Dreiding model of frutescin,[12] the only melampolide which contains a lactone ring closed to C-8, is very much more flexible.
(12) W. Herz, S. V. Bhat, and V. Sudarsanam, *Phytochemistry*, **11**, 1829 (1972).
(13) T. G. Waddell and T. A. Geissman, *Tetrahedron Lett.*, 515 (1969).
(14) T. G. Waddell and T. G. Geissman, *Phytochemistry*, **8**, 2371 (1969). A lactone which was named plenolin was subsequently recognized as 11,13-dihydrohelenalin (**6**): K. H. Lee, T. Ibuka, A. T. McPhail, K. G. Onan, T. A. Geissman, and T. G. Waddell, *Tetrahedron Lett.*, 1149 (1974).
(15) A. Yoshitake and T. A. Geissman, *Phytochemistry*, **8**, 1735 (1969).
(16) W. Herz, S. Rajappa, S. K. Roy, J. J. Schmid, and R. J. Mirrington, *Tetrahedron*, **22**, 1907 (1966); W. Herz, K. Aota, and A. L. Hall, *J. Org. Chem.*, **35**, 4117 (1970).
(17) W. Herz, K. Aota, M. Holub, and Z. Samek, *J. Org. Chem.*, **35**, 2611 (1970); P. J. Cox and G. A. Sim, *J. Chem. Soc., Perkin Trans. 2*, 259 (1977).
(18) G. R. Pettit, C. L. Herald, G. F. Judd, G. Bollinger, and P. S. Thayer, *J. Pharm. Sci.*, **64**, 2023 (1975); G. R. Pettit, C. L. Herald, D. Gust, D. L. Herald, and L. D. Vannell, *J. Org. Chem.*, **43**, 1092 (1978); J. J. Einck, C. L. Herald, G. R. Pettit, and R. B. van Dreele, *J. Am. Chem. Soc.*, **100**, 3544 (1978).
(19) W. Stöcklin, T. G. Waddell and T. A. Geissman, *Tetrahedron*, **26**, 2379 (1970). That this rule cannot be applied indiscriminately and that the chirality of the α,β-unsaturated lactone system is affected by factors not directly associated with lactone ring fusion or orientation have since been amply demonstrated.
(20) A. Horeau, *Tetrahedron Lett.*, 506 (1961); *ibid.*, 965 (1962); W. Herz and H. B. Kagan, *J. Org. Chem.*, **32**, 216 (1967).
(21) S. M. Kupchan, J. M. Cassidy, J. E. Kelsey, H. K. Schnoes, D. H. Smith, and A. L. Burlingame, *J. Am. Chem. Soc.*, **88**, 5292 (1966); T. A. Dullforce, G. A. Sim, D. N. J. White, J. E. Kelsey, and S. M. Kupchan, *Tetrahedron Lett.* 973 (1969). This constituent of a chemically and cytologically distinct race of *Gallardia pulchella* can be transformed on paper into pulchellin, the main sesquiterpene lactone of the coastal race of *G. pulchella*, by the usual series of shifts followed by a reduction step.
(22) All constituents, including some new helenanolides, were active in the cytotoxicity and PS-388 assay.
(23) $J_{1,5}$ of gaillardin is reported[20] as 12 Hz, whereas $J_{1,5}$ of the common cis-fused guaianolides, whether lactonized toward C-6 or C-8, hovers in the 9–11 Hz region.
(24) To these might be added three other congeners,[14,18] fastigilins A, B, and C (**8a, 8b,** and **8c**), on the basis of the Cotton effect associated with their cyclopentenone function.



8a, R = senecioyl, 11,13-dihydro
b, R = tigloyl, 11,13-dihydro
c, R = senecioyl

(25) A. T. McPhail and G. A. Sim, *Tetrahedron*, **29**, 1751 (1973).
(26) For an example, see R. W. Doskotch and F. S. El-Feraly, *J. Org. Chem.*, **35**, 1928 (1970).
(27) A. F. Beecham, *Tetrahedron*, **28**, 5543 (1972).
(28) The values of $J_{7,8}$ and $J_{8,9}$ in baileyin differ somewhat from those exhibited by the 4,5-epoxide of frutescin, another melampolide with a lactone ring closed to C-8, but presumed to be cis.[12] Chemical shifts in the two epoxides are not strictly comparable because of the presence in frutescin of an aldehyde function on C-10 which, for one, is closely responsible for paramagnetic displacement of H-9b. The presence of the α,β-unsaturated aldehyde in frutescin also beclouds interpretation of the lactone Cotton effect near 250 nm (negative for frutescin epoxide,[12] positive for baileyin[14]) which would normally be taken as evidence for opposite stereochemistry at C-8, i.e., **5a** for baileyin.
(29) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).

Catalytic Transfer Reduction: Scope and Utility

Gottfried Brieger,* Terry J. Nestrick, and Tzuu-Heng Fu

Department of Chemistry, Oakland University, Rochester, Michigan 48063

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Catalytic transfer reduction has been reviewed recently.[1] In an attempt to extend the scope and utility of this reaction, we have demonstrated its applicability to the complete reduction of aromatic aldehydes and ketones.[2] In this paper we wish to elaborate on this topic. Specifically, we have investigated the interception of the intermediate benzylic alcohol as the acetate, the reduction of some more complex carbonyl compounds, and the relative effectiveness of a variety of donor compounds.

Table I. Partial Reduction of Aromatic Aldehydes[a]

aldehyde	product (% yield)[b]
p-anisaldehyde	*p*-methoxybenzyl acetate (83)
2,6-dimethylbenzaldehyde	2,6-dimethylbenzyl acetate (77)
p-isopropylbenzaldehyde	*p*-isopropylbenzyl acetate (81)
α-naphthaldehyde	1-naphthalenemethanol acetate (68)
benzaldehyde	benzyl acetate (72)

[a] Reaction conditions: 0.5 g of starting material, 5 mL of cyclohexene donor, 100 mg of 10% Pd/C, 50 mg of anhydrous $FeCl_3$, 1.0 mL of acetic anhydride, reflux 12 h maximum. [b] Yield determined gas chromatographically.

Table II. Reduction of More Complex Aryl Ketones[a]

ketone	product (% yield)[b]
cyclopropyl phenyl ketone	*n*-butylbenzene (100)
4-benzoylbutyric acid	5-phenylpentanoic acid (60)
trans-1,2-dibenzoylethylene	1,4-diphenylbutane (68)
6-methoxytetralone	6-methoxytetralin (33) 2-methoxynaphthalene (20)
4-chloroacetophenone	ethylbenzene (100)

[a] Reaction conditions: 1.0 g of starting material, 10 mL of limonene donor, 400 mg of 10% Pd/C, 100 mg of anhydrous $FeCl_3$, reflux 4 h. [b] Yield determined by gas–liquid chromatography.

Trapping of Intermediate Benzylic Alcohols. During the reduction of *o*-acetylbenzoic acid and salicylaldehyde, it was noted that intermediate lactones were formed, which remained relatively stable to further reductions. Accordingly, reduction of aromatic aldehydes and ketones was carried out in the presence of acetic anhydride. This allowed the trapping of intermediate benzylic alcohols in the form of acetates, starting with a variety of aromatic aldehydes. The results are given in Table I. It was not possible to trap intermediates from aryl ketones. Presumably, the rate of hydrogenolysis of secondary benzylic acetates is competitive with the initial reduction. On the basis of these results, catalytic transfer reduction of aromatic aldehydes may be seen as a useful alternative to hydride reduction, provided other groups such as nitro or halo substituents are not present since these groups are readily reduced.

Reduction of More Complex Aryl Ketones. In a further effort to determine the structural limits for catalytic transfer reduction, a variety of aryl ketones were selected for study. The results are given in Table II. It was noted during the reduction of phenyl cyclopropyl ketone that the initial reaction was cleavage of the cyclopropyl ring to form phenyl *n*-propyl ketone. This was followed by quantitative reduction of the carbonyl group. 4-Benzoylbutyric acid and *trans*-1,2-dibenzoylethylene were reduced to the expected products without incident. During the reduction of 6-methoxytetralone, 2-methoxynaphthalene was also formed. Not unexpectedly, the initially formed 6-methoxytetralin partly dehydrogenates under the reaction conditions. Ethylbenzene was formed quantitatively during the reduction of 4-chloroacetophenone, indicating the ease of hydrogenolysis of aromatic halogen under the reaction conditions employed.

Comparison of Donor Compounds. In the course of these studies, the relative reducing capacities of a variety of donors

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