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CIRCULAR DICHROISM OF SESQUITERPENE LACTONES (1)

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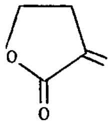
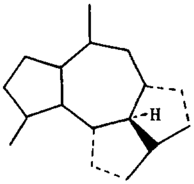
Optical rotatory dispersion (ORD) and circular dichroism (CD) have become valuable techniques for the solution of stereochemical problems (2), especially in the chemistry of natural products (3). In recent years the lactone chromophore has been studied to some extent in saturated lactones (4,5) and endocyclic α,β-unsaturated lactones (6,7), but there have been no systematic studies of the ORD or CD of α,β-unsaturated-γ-lactones with an exocyclic double bond. W report here our preliminary results on the CD of sesquiterpenes containing the α-methylene-γ-lactone element (I). These natural products occur most commonly in five different carbon skeletons, II-VI, illustrated below; the dotted lines indicate the possible positions of the lactone ring closure.

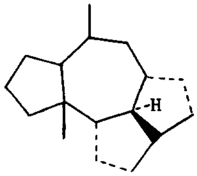


I



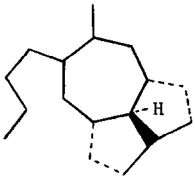
II

guaianolide



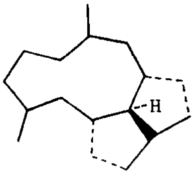
III

ambrosanolide



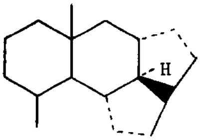
IV

xanthanolide



V

germacranolide



VI

santanolide

To determine whether ORD and CD could be applied to compounds of this type, we have undertaken a systematic study of sesquiterpene lactones, measuring the sign of the lactone Cotton effect (CE) from the CD curve of each compound. The table summarizes the results.

TABLE

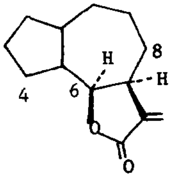
Compound	Structural Type	Lactone	CE Predicted by "Rule"	CE Found†	
				$\lambda_{(max)}$ (mμ)	[θ]
Neoambrosin (8)	III	cis,C-6	+	255	+320
Damsin (9)	III	cis,C-6	+	250	+496
Coronopilin (10)	III	cis,C-6	+	246	+1785
Deacetylconfertiflorin (11)	III	cis,C-6	+	250	+1620
Apoludin (12)	III	cis,C-6	+		-1080*
Ambrosiol (13)	III	cis,C-6	+		-1870*
Burrodin (12)	III	cis,C-8	-	254	-3400
Cumanin (14)	III	cis,C-8	-	256	-4360
Aromaticin (15)	III	trans,C-8	+		+1900*
Paucin (16)	III	cis,C-8	-	255	-4320
Baileyin III (17)	V	trans(?),C-8	+	255	+1550
Xanthumin (18)	IV	cis,C-8	-	256	-4730
Xanthinin (18)	IV	trans,C-8	+	255	+3280
Isoxanthanol (18)	IV	trans,C-8	+	255	+3340
Xanthanol (18)	IV	trans,C-8	+	255	+3150
Dihydrobigelovin (19)	III	trans,C-8	+		+274*
Costunolide (20)	V	trans,C-6	-	261	-5460
Parthenolide (21)	V	trans,C-6	-	250	-1400
Cumambrin B (22)	II	trans,C-6	-		-2920*
Douglanine (23)	VI	trans,C-6	-	250	-2780
Chamissonin diacetate (24)	V	?	?	248	-3630
Ambrosin (25)	III	cis,C-6	+		?
Helenalin (26)	III	cis,C-8	-		?

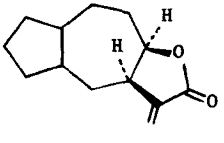
*Not a maximum, ellipticity taken at 255 mμ.

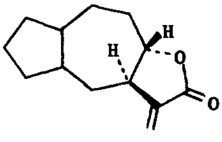
†CD spectra taken in methanol, 1 cm cell.

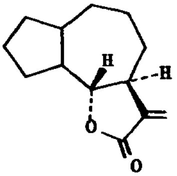
The $n \rightarrow \pi^*$ transition of the α-methylene-γ-lactone chromophore was observed in the range 246-261 mμ.

The results indicate that a generalization can be made. Regardless of structural type, cis-fused lactones closed at C-8 give negative Cotton effects; for trans-fused lactones at the same position, the sign of the CE is positive. On the other hand, cis-fused lactones closed at C-6 show positive Cotton effects; C-6 trans-fused lactones show negative values. Of twenty sesquiterpene lactones studied, which showed clear Cotton effects for the lactone, only one exception to the generalization was observed. Apoludin and ambrosiol can be regarded as one exception since they differ only in the position of a hydroxyl group. This deviation might be explained by the presence in each compound of a 4α-hydroxyl group, close to the lactone chromophore. Two other compounds, ambrosin and helenalin, both containing a cyclopentenone ring, showed no clear CE for the $n \rightarrow \pi^*$ transition of the lactone.









Sign of CE	+	-	+	-
	VII	VIII	IX	X

Structures VII-X illustrate the data and the conclusions. They also provide a rationalization for the results obtained. VII and VIII are enantiomeric with respect to the asymmetry immediately surrounding the *cis* lactone and should give Cotton effects of opposite sign. This is observed. Likewise, IX and X are enantiomeric about the trans lactone and show opposite Cotton effects, as expected. Thus, the sign of the CE for the $n \rightarrow \pi^*$ transition of the α-methylene-γ-lactone chromophore is dependent only on the asymmetry at C-7 and C-6 or C-8, and not on the structural type of the sesquiterpene lactone. This fact allows the rule formulated through structures VII-X to be used generally in determining the stereochemistry of the lactone ring fusion in sesquiterpene lactones of this type. Experiments to further test this rule are in progress.

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References

1. Contribution No. 2367 from the Department of Chemistry, U.C.L.A.
2. G. Snatzke, *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*. Heyden & Son, London (1967).
3. G. Snatzke, *Angew. Chem.*, **80**, 15 (1968); *Angew. Chem. internat. Edit.*, **7**, 14 (1968).
4. W. Klyne, P. M. Scopes, R. C. Sheppard, and S. Turner, *J. Chem. Soc., (London) (C)*, **1968**, 1954 and earlier references cited therein.

5. A. F. Beecham, *Tetrahedron Letters*, **1968**, 2355, 3591.
6. G. Snatzke, H. Schwang, and P. Welzel in R. Bonnett and J. G. Davin, *Some Newer Physical Methods in Structural Chemistry*, p. 159, United Trade Press, London (1967).
7. F. Burkhardt, W. Meier, A. Fürst, and T. Reichstein, *Helv. Chim. Acta*, **50**, 607 (1967).
8. T. A. Geissman and F. P. Toribio, *Phytochemistry*, **6**, 1563 (1967).
9. M. Suchý, V. Herout, and F. Šorm, *Collect. Czech. Chem. Comm.*, **28**, 2257 (1963).
10. W. Herz and G. Högenauer, *J. Org. Chem.*, **26**, 5011 (1961).
11. N. H. Fischer and T. J. Mabry, *Tetrahedron*, **23**, 2529 (1967).
12. T. A. Geissman and S. Matsueda, *Phytochemistry*, **7**, 1613 (1968).
13. T. J. Mabry, W. Renold, H. E. Miller, and H. B. Kagan, *J. Org. Chem.*, **31**, 681 (1966).
14. J. Romo, P. Joseph-Nathan, and G. Siade, *Tetrahedron*, **22**, 1499 (1966).
15. J. Romo, P. Joseph-Nathan, and F. Díaz A., *Tetrahedron*, **20**, 79 (1964).
16. T. G. Waddell and T. A. Geissman, *Tetrahedron Letters*, in press.
17. T. G. Waddell and T. A. Geissman, unpublished results.
18. T. E. Winters, T. A. Geissman, and David Safir, *Phytochemistry*, in press.
19. B. A. Parker and T. A. Geissman, *J. Org. Chem.*, **27**, 4127 (1962); W. Herz and M. V. Lakshmikantham, *Tetrahedron*, **21**, 1711 (1965).
20. M. Suchý, V. Herout, and F. Šorm, *Collect. Czech. Chem. Comm.*, **31**, 2899 (1966).
21. A. S. Bawdekar, G. R. Kelkar, and S. C. Bhattacharyya, *Tetrahedron Letters*, **1966**, 1225.
22. J. Romo, A. Romo De Vivar, and E. Diaz, *Tetrahedron*, **24**, 5635 (1968).
23. S. Matsueda and T. A. Geissman, *Tetrahedron Letters*, **1967**, 2159.
24. T. A. Geissman, R. J. Turley, and S. Murayama, *J. Org. Chem.*, **31**, 2269 (1966).
25. M. T. Emerson, W. Herz, C. N. Caughlan, and R. W. Witters, *Tetrahedron Letters*, **1966**, 6151.
26. M. T. Emerson, C. N. Caughlan, and W. Herz, *Tetrahedron Letters*, **1964**, 621.