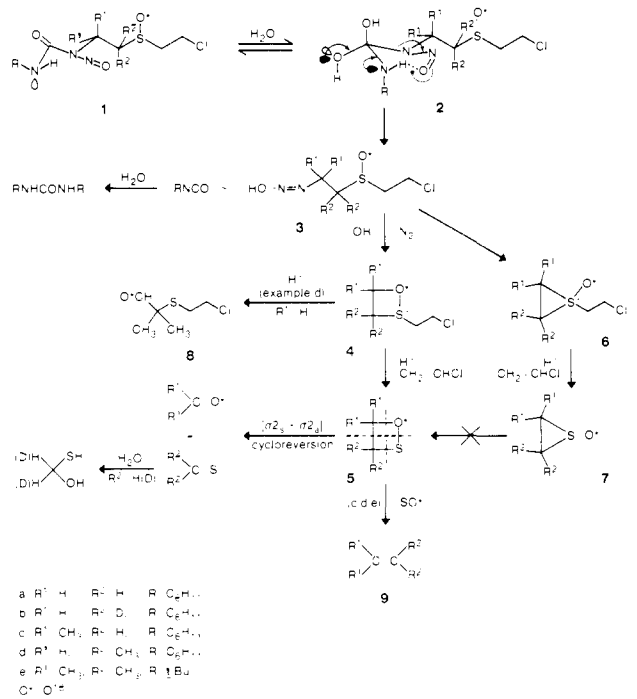
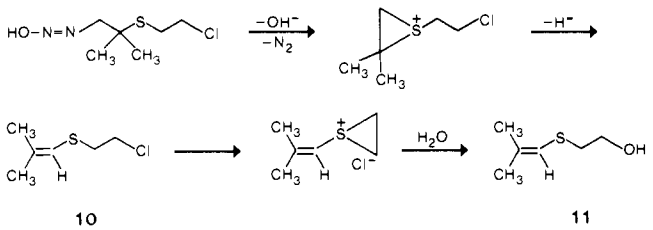
Scheme I



Scheme II



hydrate among the volatile products. Thus the reaction proceeds by intramolecular transfer of ^{18}O via a four-membered-ring intermediate.

The isomeric 1-[2-[(2-chloroethyl)sulfinyl]-2,2-dimethylethyl]-3-cyclohexyl-1-nitrosourea (**1d**)[12] decomposes in pH 7.0 buffer to give 2-[(2-chloroethyl)thio]-2-methylpropanal (**8**) and small amounts of 1-[(2-chloroethyl)thio]-2-methylpropene (**10**),[13] 1-[(2-hydroxyethyl)thio]-2-methylpropene (**11**),[13] cyclohexyl isocyanate, and dicyclohexylurea. Isolation of aldehyde **8** is in accord with the generation of the sulfoxide-substituted diazohydroxide **3d** and then formation from the latter of a 3,3-dimethyl-2-(2-chloroethyl)-1,2-oxathietanium (**4d**), which undergoes proton loss at position 4 and breakage of the O–S bond with formation of the propanal **8**. The corresponding reaction of 1-[2-[(2-chloroethyl)sulfinyl-^{18}O]-2,2-dimethylethyl]-3-cyclohexyl-1-nitrosourea (**1d**-^{18}O)[11] to afford 2-[(2-chloroethyl)-thio]-2-methylpropanal-^{18}O (**8**-^{18}O) is in accord with the suggested pathway.

Controlled aqueous decomposition of 1-[2-[2-chloroethyl)-sulfinyl]-1,1,2,2-tetramethylethyl]-3-*tert*-butyl-1-nitrosourea (**1e**)[14] at pH 7.0 and 38 °C afforded acetone, thioacetone, *tert*-butyl isocyanate, and di-*tert*-butylurea. GC analysis[5,15] of the reaction mixture permitted detection of the labile 3,3,4,4-tetramethyl-1,2-oxathietane (retention time 5.3 min), GC–MS analysis of which gave the corresponding correct *m/e* of 132.[16] The GC analysis also detected 2,3-dimethyl-2-butene (**9e**) from the extrusion of SO from the 1,2-oxathietane.[15] This alternative mode of cleavage has a counterpart in the fragmentation of the *m/e* 132 molecular ion of **5e**.[16]

Evidence for the existence of 1,2-oxathietane has not, to our knowledge, been hitherto reported. Only one report claiming the intermediacy of such a species in the pyrolysis of 1,2,3-oxadithiolane 2-oxide and thiirane 1-oxide at 1043–1404 K has been made;[17] however, no evidence was obtained for what now appears to be the characteristic (2 + 2) cycloreversion. The latter reaction is anticipated by analogy with the 1,2-dioxetanes.[18] Attempts to isolate 1,2-oxathietanes and to examine their possible chemiluminiscent behavior are in progress.

Acknowledgment. This work was supported by Grant 1R01 CA21488-01 awarded by the National Cancer Institute, DHEW, to J.W.L. and by a grant from the Alberta Provincial Cancer Hospitals Board.

(11) Prepared by the methylene blue sensitized photooxidation of **1a**, **1d**, or **1e** in methanol in the presence of $^{18}O_2$ (99% isotopic enrichment), **1a**-^{18}O; *m/e* 312, 249 (100), $M^+ - CH_2CH_2Cl \equiv C_{11}H_{23}N_2OS\ ^{18}O$.

(12) Prepared as described in ref 8 from (2-hydroxy-2-methylpropyl)-amine.

(13) These products arise from a competing minor deoxygenation pathway of the parent sulfoxide giving rise, in each case, to traces of aqueous decomposition products characteristic of the corresponding thioether nitrosourea[8] (Scheme II).

(14) Prepared from tetramethylaziridine (Closs, G. L.; Brois, S. J. *J. Am. Chem. Soc.* **1960**, *82*, 6068) as described in footnote 9. The *tert*-butyl group ensures the desired regiochemistry in the nitrosation step.

(15) Integrated GC peak areas of components given as percent relative to the *tert*-butyl isocyanate peak: vinyl chloride (14.5); thioacetone (7.0); 2,3-dimethyl-2-butene (53); acetone (22); 3,3,4,4-tetramethyl-1,2-oxathietane (2.0).

(16) *m/e* (%) 132.15904 (10) M^+ (measured for $C_6H_{12}SO$), 117 (4) ($M^+ - CH_3$), 116 (17) ($M^+ - O$), 84 (100) ($M^+ - SO$), 74 (8) ($(CH_3)_2C{=}S^+$).

(17) Carlsen, L.; Egsgaard, H. *J. Chem. Soc., Perkin Trans. 2* **1982**, 279. Semiempirical CNDO/B calculations predict a planar configuration for 1,2-oxathietane at least in the gas phase (Snyder, J. N.; Carlsen, L. *J. Am. Chem. Soc.* **1977**, *99*, 2931.

(18) (a) Kopecky, K. R.; Filby, J. E., Mumford, C.; Lockwood, P. A.; Ding, J.-Y. *Can. J. Chem.* **1975**, *53*, 1103. (b) Richardson, W. H.; Montgomery, F. C.; Yelvington, H. E.; O'Neal, H. E. *J. Am. Chem. Soc.* **1974**, *96*, 7525. (c) Turro, N. J.; Lechtken, P. *Ibid.* **1972**, *94*, 2886. (d) White, E. H.; Wildes, P. D.; Weicko, J.; Doshan, H.; Wei, C. C. *Ibid.* **1973**, *95*, 7050 and references therein.

Stereocontrolled Osmylation of Medium-Ring Alkenes: Synthesis of a C_1–C_9 Erythronolide Fragment

E. Vedejs,* J. M. Dolphin, and H. Mastalerz

S. M. McElvain Laboratory of Organic Chemistry
Chemistry Department, University of Wisconsin
Madison, Wisconsin

Received July 15, 1982

We are interested in the stereochemistry of medium- and large-ring alkene addition reactions, many of which occur with high selectivity.[1] The goal is to identify dominant conformational factors that might have predictive value in synthesis. In this communication we report that osmylation of the nine-membered-ring alkene **1** can be used for stereocontrolled synthesis of an erythronolide fragment having the correct C_2–C_6 stereochemistry.[2] For comparison, two isomeric ten-membered-ring alkenes **2** and **3** have also been studied.

Syntheses of alkenes **1–3** are outlined in Scheme I. The α-oxo dithioester Diels–Alder reaction occurs with normal regiochemistry[3] to give **4**, which is efficiently desulfenylated to **5**.[4] After

(1) (a) Still, W. C. *J. Am. Chem. Soc.* **1979**, *101*, 2493. (b) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981. (c) Still, W. C.; Galynker, I. *J. Am. Chem. Soc.* **1982**, *104*, 1774. (d) Doskotch, R. W.; Kelley, S. L., Jr.; Bufford, C. D. *J. Chem. Soc., Chem. Commun.* **1972**, 1137. (e) Corey, E. J.; Nicolaou, K. C.; Melvin, L. S., Jr. *J. Am. Chem. Soc.* **1975**, *97*, 654.

(2) For total synthesis of erythronolide A, see: Corey, E. J.; Hopkins, P. B.; Kim, S.; Yoo, S.; Nambiar, K. P.; Falck, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 7131.

(3) Vedejs, E.; Arnost, M. J.; Dolphin, J. M.; Eustache, J. *J. Org. Chem.* **1980**, *45*, 2601.

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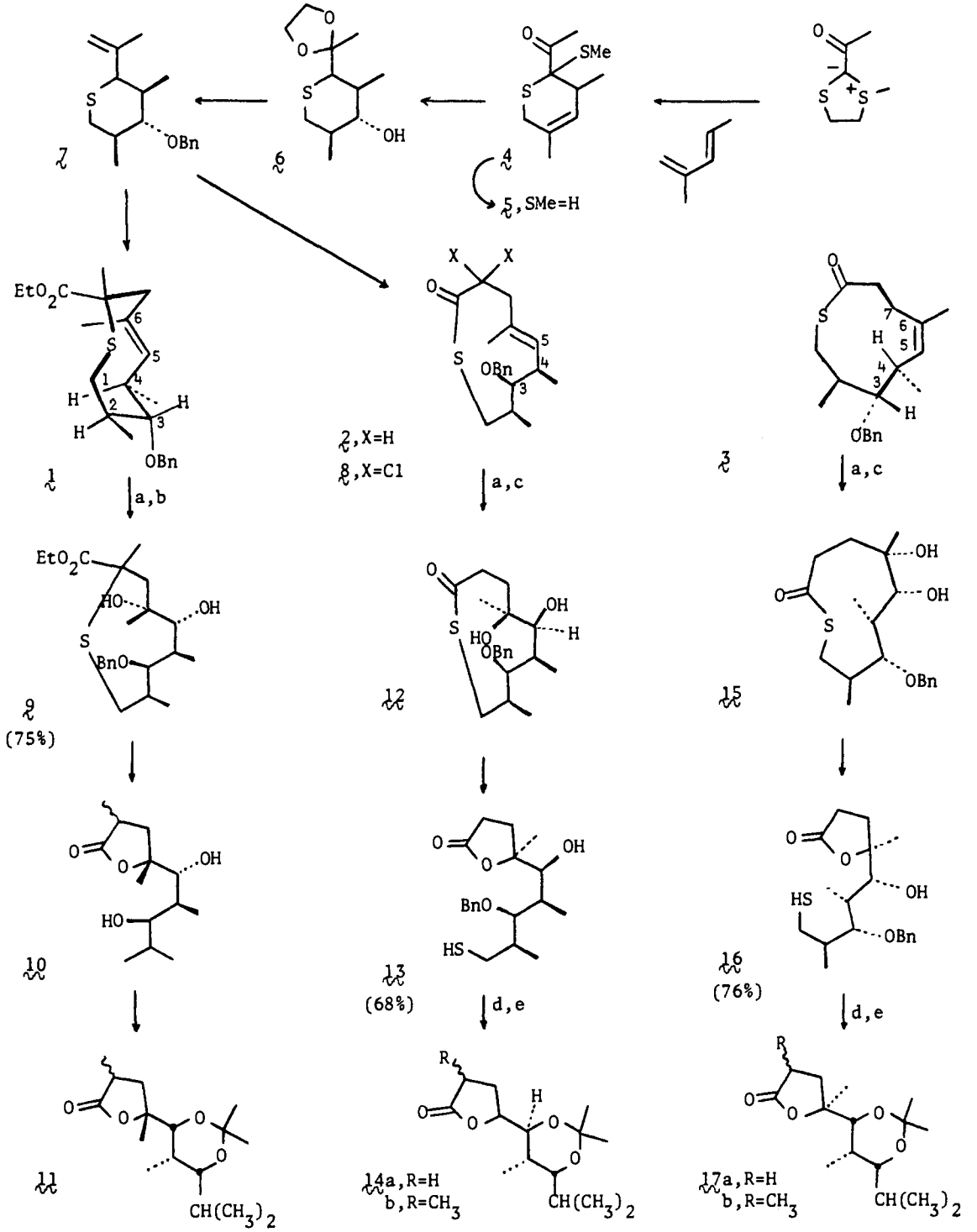
Scheme I



[a] OsO_4/pyridine. [b] $NaHSO_3$. [c] $HSCH_2CH_2CO_2H$; $NaHCO_3/H_2O$. [d] W 2 Raney nickel. [e] $(CH_3O)_2C(CH_3)_2H^+$.

ketalization, highly selective hydroboration with thexylborane leads to **6** after oxidative workup with alkaline H_2O_2. The key olefin **7** can then be prepared by deketalization, Wittig reaction, and benzylation, 42% overall from acyclic precursors. Three-carbon ring expansion by alkylation with $C_2H_5O_2CCH(CH_3)OSO_2CF_3$ followed by DBU affords **1** in 86% yield. The *E*-olefin geometry is proved by NOE studies (see below) and is anticipated provided that S-alkylation occurs with normal equatorial selectivity.[5]

Synthesis of **2** is accomplished by an adaptation of the remarkable 3,3-rearrangement which is observed when dichloroketene is generated in the presence of allylic ethers or sulfides.[6] Thus, Cl_3CCOCl (1.5 equiv) is added to a refluxing mixture of Zn/Cu (5 equiv), ether, and thiane **7**. Dechlorination of the initial product **8** with Zn/HOAc affords **2** in 80% yield from **7**. The isomeric *Z*-olefin **3** is available from **2** by photosensitized isomerization of the double bond (33% of **3** recovered at 50% conversion of **2**).

An assignment of preferred conformation along the C_2–C_7 segment of **1** can be made from NMR data. The crownlike

(4) Desulfenylation with Ph_3P/CH_3CO_2H/EtOH: Oki, M.; Fukanishi, W.; Nakamura, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 828, 832.

(5) Vedejs, E.; Arco, M. J.; Powell, D. W.; Renga, J. M.; Singer, S. P. *J. Org. Chem.* **1978**, *43*, 4831. Cerē, V.; Paolucci, C.; Pollicino, S.; Sandri, E.; Fava, A. *Ibid.* **1981**, *46*, 3315.

(6) Malherbe, R.; Bellus, D. *Helv. Chim. Acta* **1978**, *61*, 3096. Rosini, G.; Spineti, G. G.; Foresti, E.; Pradella, G. *J. Org. Chem.* **1981**, *46*, 2228.

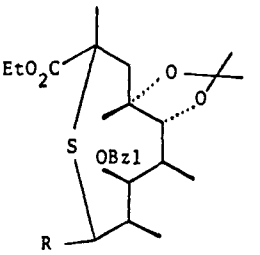
geometry drawn in Scheme I follows from uniformly large coupling constants ($J_{2,3} = J_{3,4} = 8.6$ Hz, $J_{4,5} = 11$ Hz) for adjacent proton pairs and from NOE effects suggesting eclipsed C-4 (H) and C-6 (CH_3) groups (irradiate C-6 (CH_3), 23% enhancement at C-4 (H), no enhancement at C-5 (H); irradiate C-5 (H), 13% enhancement at C-3 (H)). NOE experiments with the *E*-olefin **2** have proved inconclusive, and only two of the relevant coupling constants can be assigned securely: $J_{3,4} \cong J_{4,5} = 10$ Hz. The dihedral angles for H–C_5–C_4–H and H–C_4–C_3–H apparently are similar in both **1** and **2**. In the case of **3**, NOE enhancement at C-5 (H) is observed upon irradiation of C-6 (CH_3), and $J_{4,5} = 12$ Hz while $J_{3,4} \leq 1$ Hz. These results establish olefin geometry and suggest a preference for conformers in which the C-4 methyl avoids the C-7 methylene group and minimizes transannular interactions, as in **3** (Scheme I).

Osmylation of **1** occurs to give a single diol, **9** (75%).[7a] To prove which alkene face is attacked, we converted **9** into **11** by treatment with W2 Raney nickel (desulfurization and debenzylation to **10**) followed by acetonide formation with dimethoxypropane/TsOH. The values $J_{3,4} = J_{4,5} = 2.2$ Hz support a chairlike acetonide with an axial C_4–CH_3 group and equatorial isopropyl and lactone substituents. Similar (within 0.6 Hz) *J* values are reported for related erythronolide 3,5-acetonide segments.[8] Osmylation stereochemistry of **1** therefore corresponds to attack on the exposed olefin face of the conformer deduced from NMR data (Scheme I).

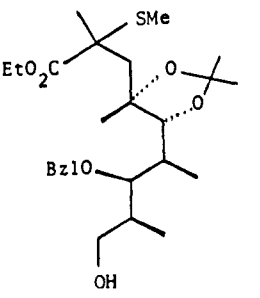
Diol intermediates have not been isolated from reaction of **2** or **3** with OsO_4/pyridine due to rapid S to O acyl transfer.[7b] Rearranged γ-lactones are formed in each case. Stereochemical correlation as before (Raney nickel desulfurization; acetonide formation) establishes the following events: **2** → **12** → **13** → **14** and **3** → **15** → **16** → **17**. The correlation compound **17a** has $J_{3,4} = 1.8$ Hz and $J_{4,5} = 2.2$ Hz, values nearly identical with those of **11**. Methylation of **17a** (LDA, CH_3I) affords **17b** (single major isomer), which is different from either methyl epimer of **11** but has similar $J_{3,4}$ and $J_{4,5}$ values. Therefore, **11** and **17** have the same stereochemistry at C_3, C_4, and C_5, but differ at C_6 as expected from the differing olefin geometry in precursors **1** and **3**. The correlation compound **14a** and the diastereomers **14b** obtained by methylation all have $J_{3,4} = 3.7$ Hz and $J_{4,5} = 6.4 \pm 0.2$ Hz. These coupling constants are in excellent agreement with the corresponding values from Heathcock's analogous structure.[8b] Therefore, **14** must have unnatural stereochemistry at both C_5 and C_6 relative to erythronolide, and osmylation of the *E*-olefin isomer **2** in the ten-membered ring series must occur with opposite olefin face selectivity compared with the nine-membered *E*-olefin **1**.

The correct diol **9** can be converted into an acyclic C_1–C_9 erythronolide fragment having differentiated oxygen substitution at each end of the chain. Acetonide **18** is easily prepared, and reaction with *N*-chlorosuccinimide affords α-chloro sulfide **19** (95%). Solvolysis ($H_2O/CH_3CN/CaCO_3$), borohydride reduction, and S-methylation afford the desired erythronolide segment **20** (73%). Related applications of this strategy to total synthesis will be described in due course.

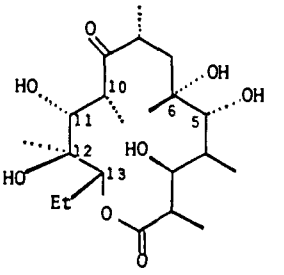
Our approach was based on the expectation that **1** would adopt a crownlike geometry in the vicinity of the *E* olefin as shown in Scheme I. This seemed likely because numerous naturally occurring medium- or large-ring *E* olefins have similar *local* geometries in the solid state, and alkyl branch points α to the double bond adopt the pseudoequatorial orientation whenever possible.[9]



18, R=H
19, R=Cl



20



Erythronolide A

An extrapolation of this geometry to olefin cis-addition reactions is plausible for reactant-like transition states, and least hindered approach ("peripheral attack"[1]) corresponds to the conversion of **1** into **9**.

We are aware of two examples in the literature where cyclic *E* olefins follow the same stereochemical pattern. Corey and Hopkins have recently shown that the C_{11}, C_{12} hydroxyls of erythronolide A 3,5-diacetonide can be introduced with natural stereochemistry by osmylation of the corresponding *E* olefin.[10a] If the alkene adopts a crownlike local geometry, both α-alkyl branch points can occupy pseudoequatorial orientations. Similar olefin face selectivity is observed in the epoxidation of an α-branched trisubstituted *E* olefin in the maytansinoid series.[10b] If these reactions are examples of a resonably general stereochemical phenomenon, it will be necessary to study simpler *E* olefins before the contrasting behavior of the ten-membered alkene **2** can be understood. At this point, speculations on the role of special features such as the transannular effect of a thiol ester π system would be premature.[11]

The stereochemistry of osmylation of the *Z*-olefin **3** also corresponds to least hindered attack (away from ring carbons) on a local geometry having a pseudoequatorial methyl group. There are some examples of related conformational preferences in the work of Still et al.,[1] and X-ray data support the notion that *Z* alkenes prefer local geometries similar to **3**.[12]

(7) (a) Osmylation of **1**: 0.27 mol of OsO_4 + 0.182 mmol of **1**, pyridine (3 mL), room temperature, 10 min; $NaHSO_3$ (1 g) in 10 mL H_2O, 1 h. (b) Osmylation of **2** or **3**: 0.14 mmol of OsO_4, 0.094 mmol of **2** or **3**, 3 mL of pyridine, 30 min, room temperature. To cleave the osmate ester, 3-mercaptopropionic acid (0.8 mL) is added (0.5 h, 0 °C.) After standard aqueous bicarbonate workup, the crude product is stirred with silica gel (4 g) in CH_2Cl_2 overnight to complete conversion of diol into lactone.

(8) (a) Heathcock, C. H.; Hagen, J. P.; Jarvi, E. T.; Pirrung, M. C.; Young, S. D. *J. Am. Chem. Soc.* **1981**, *103*, 4972. Masamune, S.; Hirama, M.; Mori, S.; Ali, S. A.; Garvey, D. S. *Ibid.* **1981**, *103*, 1568. We thank Professors Heathcock and Masamune for comparison spectra. (b) Heathcock, C. H., Personal communication.

(9) Selected medium–large-ring α-alkyl *E* olefins. Dolabella diterpenes: Ireland, C.; Faulkner, D. J.; Finer, J.; Clardy, J. *J. Am. Chem. Soc.* **1976**, *98*, 4664. Kijanimycin: Mallams, A. K.; Puar, M. S.; Rossman, R. R.; McPhail, A. T.; Macfarlane, R. D. *Ibid.* **1981**, *103*, 3940. Avermectins: Springer, J. P.; Arison, B. H.; Hirshfield, J. M.; Hoogsteen, K. *Ibid.* **1981**, *103*, 4221. Kromycin: Tsai, C.; Stezowski, J. J.; Hughes, R. E. *Ibid.* **1971**, *93*, 7286. Whaley, H. A.; Chidester, C. G.; Mizsak, S. A. Wnuk, R. J. *Tetrahedron Lett.* **1980**, *21*, 3659. Obtusallene: Cox, P. J.; Imre, S.; Islimyeli, S.; Thomson, R. H. *Ibid.* **1982**, *23*, 579. Tetronolide: Hirayama, N.; Kasai, M.; Shirahata, K.; Ohashi, Y.; Sada, Y. *Ibid.* **1980**, *21*, 2559. Euphoscopins: Yamamura, S.; Kosemura, S.; Ohba, S.; Ito, M.; Saito, Y. *Ibid.* **1981**, *22*, 5315. Euglobal: Sawada, T.; Kozuka, M.; Komiya, T.; Amano, T.; Goto, M. *Chem. Pharm. Bull.* **1980**, *28*, 2546. Cytochalasin H: Beno, M. A.; Cox, R. H.; Wells, J. M.; Cole, R. J.; Kirksey, J. W.; Christoph, G. G. *J. Am. Chem. Soc.* **1977**, *99*, 4123. Chaetoglobosins: Springer, J. P.; Clardy, J.; Wells, J. M.; Cole, R. J.; Kirksey, J. W.; Macfarlane, R. D.; Togerson, D. F. *Tetrahedron Lett.* **1976**, 1355.

(10) (a) Corey, E. J.; Hopkins, P. B. *Tetrahedron Lett.* **1982**, *23*, 1979. (b) Corey, E. J.; Weigel, L. O.; Chamberlin, R.; Cho, H.; Hua, D. H. *J. Am. Chem. Soc.* **1980**, *102*, 6613.

(11) An acyclic derivative of **2** is osmylated with essentially no selectivity. Thus, thiol lactone cleavage (LiOEt) and S-acylation followed by OsO_4 affords a 1.5:1 mixture of γ-lactones that have been converted into **14a** and **11**, respectively.

Work is underway to determine the scope of local conformational control in medium-ring alkene addition reactions.

Acknowledgment. This work was supported by a grant from the National Science Foundation (CHE-8113026).

Supplementary Material Available: Spectral characterization of **1-3**, **9**, and **20** (2 pages). Ordering information is given on any current masthead page.

(12) Selected medium-large-ring α-alkyl *Z* olefins. Dictiodiol: Finer, J.; Clardy, J.; Fenical, W.; Minale, L.; Riccio, R.; Battaile, J.; Kirkup, M.; More, R. E. *J. Org. Chem.* **1979**, *44*, 2044. Neolemnanes: Izac, R. R.; Fenical, W.; Tagle, B.; Clardy, J. *Tetrahedron* **1981**, *37*, 2569. Rubradirin: Hoeksema, H.; Mizsak, S. A.; Baczynski, L. *J. Antibiot.* **1979**, *32*, 773. Macbecins: Muroi, M.; Haibara, K.; Asai. M.; Kamiya, K.; Kishi, T. *Tetrahedron* **1981**, *37*, 1123. Latrunculine A: Kashman, Y.; Groweiss, A.; Shmueli, U. *Tetrahedron Lett.* **1980**, *21*, 3629.

Additivity Relation in the Amplitudes of Exciton-Split Circular Dichroism Curves Arising from Interactions between Different Chromophores and Its Application in Structural Studies

Richard J. Stonard, Diane A. Trainor, Munehiro Nakatani, and Koji Nakanishi*

Department of Chemistry, Columbia University New York, New York 10027

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Interaction of the electric transition moments of two or more chromophores within a chiral molecule constitutes a coupled oscillator.[1] This condition gives rise to Davydov split CD curves.[2] The closer the λ_{max} of the interacting chromophores, the more efficient the coupling.[3] However, a split CD is observed when the λ_{max} values differ by as much as 100 nm.[3,4] Valid analyses can also be obtained when only one of the Cotton effect extrema is discernable.[4,5]

The results of over 40 pyranose *p*-bromobenzoates showed that the amplitudes of split CD curves ("*A* values") can be approximated by the sum of dibenzoate interactions which are constants.[6] Herein we show that this additivity relation can be generalized as illustrated (Scheme I) by the interaction between enone (e.g., **1** λ_{max} 244 nm (ϵ 12400), and **2** λ_{max} 243 nm (ϵ 10300), in MeOH) and unsubstituted benzoate (λ_{max} 229.5 nm (ϵ 15300), in MeOH) chromophores. These results are then applied to a configurational problem involving complex natural product derivatives having benzoate and furan chromophores.

The phytocdysteroids ponasterone A (PN-A, **1**)[7] and ajugasterone C (AJG-C, **2**)[8] can be converted into the 2,3-dibenzoate **3** and 2,3,11-tribenzoate **4** of the respective 6-hydroxy-20,22-acetonides, by acid hydrolysis of the 2,3,20,22-diacetonide to the 20,22-acetonide, benzoylation, and $NaBH_4$ reduction.[9] Dibenzoate **3** displays a split CD (all data in MeOH) with negative/positive Cotton effects at 237 nm/219 nm, *A* −33, arising from the negatively coupled oscillator (see conformational structure I). In tribenzoate **4** the *A* value is −59. In view of the additivity relation,[6] the 2,3-dibenzoate and 11-benzoate interaction can then be assigned an *A* value of −26* (calculated values indicated by

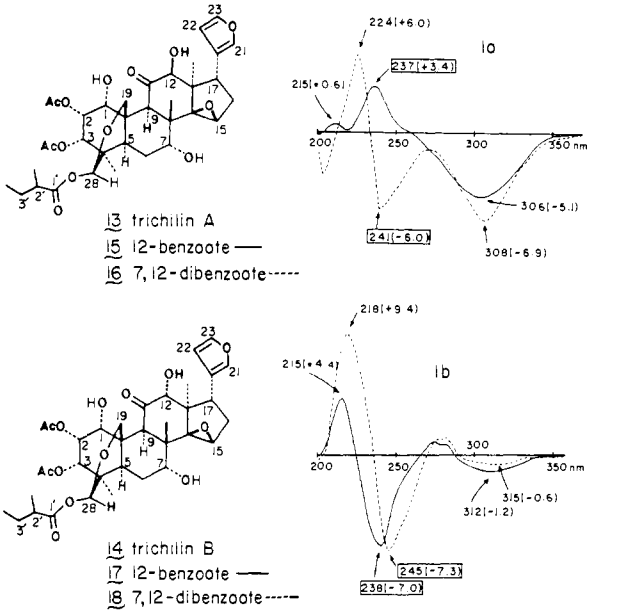
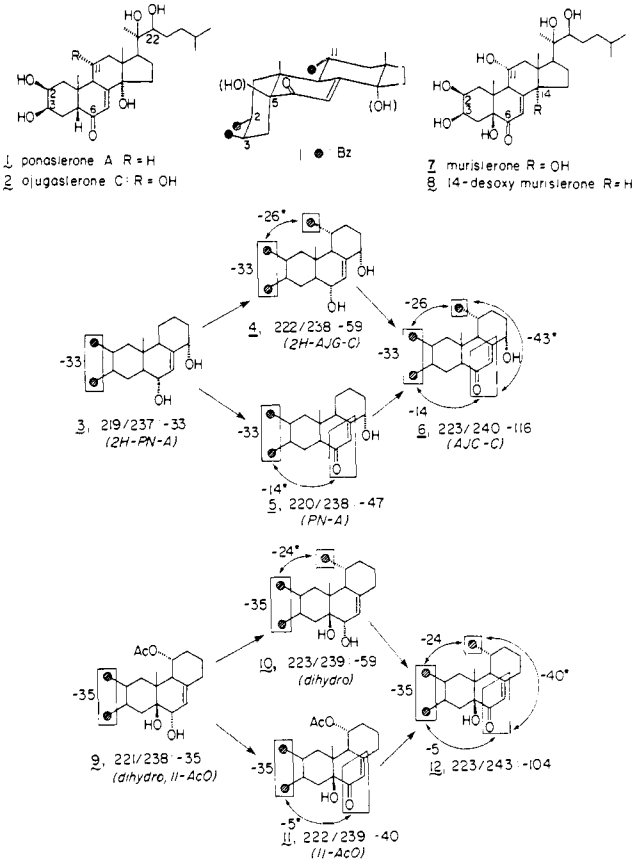


Figure 1. CD of 12-benzoates and 7,12-dibenzoates of trichilins A and B, in MeOH.

Scheme I



(1) Kuhn, W. *Trans. Faraday Soc.* **1930**, *2B*, 293. (b) Kirkwood, J. G. *J. Chem. Phys.* **1937**, *5*, 479.

(2) (a) Moffitt, W. *J. Chem. Phys.* **1956**, *25*, 467. (b) Schellman, J. A.; Oriel, P. *Ibid.* **1962**, *37*, 2114. (c) Mason, S. F. *Proc. Chem. Soc.* **1962**, 362. (d) Schellmann, J. A. *Acc. Chem. Res.* **1968**, *1*, 144. (e) Bosnich, B. *Ibid.* **1969**, *2*, 266. (f) Johnson, W. C.; Tinoco, I., Jr. *Biopolymers* **1969**, *8*, 715. (g) Buckingham, A. D.; Stiles, P. J. *Acc. Chem. Res.* **1974**, *7*, 258.

(3) (a) Harada, N.; Nakanishi, K. *Acc. Chem. Res.* **1972**, *5*, 257; (b) "Circular Dichroic Spectroscopy—Exciton Coupling in Organic Stereochemistry"; University Science Books: Mill Valley, CA, 1983; p 550.

(4) Harada, N.; Iwabuchi, J.; Yokota, Y.; Uda, H.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 5590.

(5) Gonnella, N. C.; Nakanishi, K.; Martin, V. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1982**, *104*, 3775.

(6) Liu, H. W.; Nakanishi, K. *J. Am. Chem. Soc.* **1982**, *104*, 1178.

(7) Nakanishi, K.; Koreeda, S.; Sasaki, S.; Chang, M. L.; Hsu, H. Y. *J. Chem. Soc., Chem. Commun.* **1966**, 915.

(8) Imai, S.; Murata, E.; Fujioka, S.; Koreeda, M.; Nakanishi, K. *J. Chem. Soc., Chem. Commun.* **1969**, 546.

(9) All derivatives were purified by HPLC and fully characterized by spectroscopic methods.

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