Allenyldiene Electrocyclization. A Stereospecific Tandem Center–Axis–Center Chirality Transfer: Synthesis of Drimatrienes and Related *trans*-Decalins[1]

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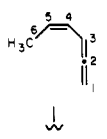
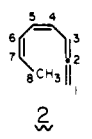
Abstract: In attempts to convert propargylic derivatives **3** to allenyldienes of the type **4**, electrocyclization products, drimatrienes **5**, were obtained. Reaction of *cis*-ethynyl alcohol **6a**, prepared by one-way photosensitized irradiation of **9a**, with phenylsulfenyl chloride afforded diastereomers **8** and **8′**. Diisobutylaluminum hydride reduction of **6a** afforded the parent triene **10e**. Attesting to the generality of this new decalin synthesis was the observation that the benzoate ester of **6a** reacted with higher order mixed cuprates of the type $R_2Cu(CN)Li_2$ to afford **10a–d**. Zinc–acetic acid reduction of **8** and **8′** afforded the sulfide **10f**, but $LiAlH_4$ reduction afforded in an unusual manner the *trans*-decalin **20**. The latter process is shown to be the result of a direct, highly stereoselective 1,6-reduction by deuterium-labeling studies. The trans ring fused stereochemistry assigned to **20** was established by its conversion to β-bicyclofarnesol **25** via the sequence **20** → **22** → **23** → **24** → **25**. Finally, a transformation of the type **3** → [**4**] → **5** was shown to occur completely stereospecifically. Reaction of optically active *cis*-propargyl alcohol **16** (84% enantiomeric excess, ee) with phenylsulfenyl chloride afforded sulfoxide **19** (and its sulfur diastereomer **19′**), which was shown to have retained its stereochemical integrity (84% ee by high pressure liquid chromatography) during its formation, presumably via a [2,3]-sigmatropic shift followed by electrocyclization. Conversion of optically active **19** and **19′** to the known ketone **32** established its absolute configuration. The stereospecific tandem center → axis → center chirality transfer process described in this study is unprecedented.

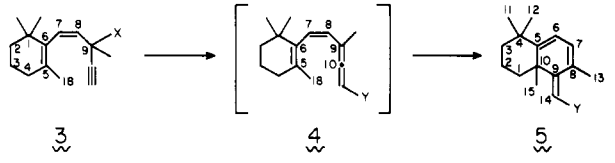
Whereas the prototype vinylallene[2,3] system **1** undergoes a thermal [1,5]-sigmatropic hydrogen shift ($C_6 \rightarrow C_2$ migration),[4,5] the vinylogous allenyldiene **2** rearranges via a six-electron electrocyclization (C_2–C_7 bonding)[6-8] rather than a [1,7]-sigmatropic hydrogen migration ($C_8 \rightarrow C_2$ shift).[4] In a preliminary communication,[1] we described various transformations of *cis*-dienyne **3** to drimatriene **5**, wherein **4**, containing the putative allenyldiene prototype **2**, is considered to be the likely intermediate. A transformation of one of the drimatrienes to *trans*-decalin derivatives was also disclosed.



1



2

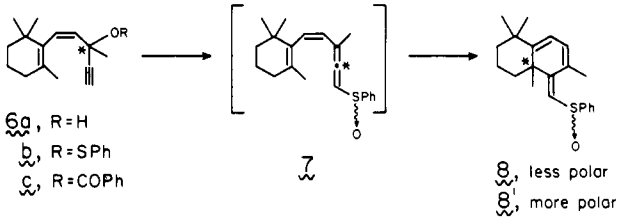


3 **4** **5**

This article provides a full account of the experimental details of the earlier communication and describes new results. In particular, we demonstrate in an optically active system related to **3** that the putative process **3** → [**4**] → **5** may be made to occur with essentially complete stereochemical integrity. More specifically, the reported transformation **6b** → [**7**] → **8** and **8′**, a [2,3]-sigmatropic shift[9] in tandem with six-electron electrocyclization,[6] is shown to be completely stereospecific.

Results

Electrocyclization of Allenyldienes. In order to synthesize allenyldienes of the type **4**, the plan was to react propargyl benzoate **6c** with organocuprates by analogy with already known transformations of *trans*-benzoate **9c**.[5p,r] The benzoate **6c** was prepared by esterification of **6a**,[10] which in turn was prepared by triplet-sensitized one-way photoisomerization[11] of readily available



6a, R=H
b, R=SPh
c, R=COPh

7

8, less polar
8′, more polar

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[‡] Fulbright Postdoctoral Fellow, 1981–1982.

(1) For a preliminary account of this study, see: Reischl, W.; Okamura, W. H. *J. Am. Chem. Soc.* **1982**, *104*, 6115.
(2) For reviews of vinylallenes (enallenes), see: (a) Okamura, W. H. *Acc. Chem. Res.* **1983**, *16*, 81. (b) Egenburg, I. Z. *Russ. Chem. Rev.* (*Engl. Transl.*) **1978**, *47*, 470.
(3) For recent comprehensive reviews of allene chemistry, see: (a) Landor, S. R., Ed. "The Chemistry of Allenes"; Academic Press: New York, 1982; Vol. 1–3. (b) Patai, S., Ed. "The Chemistry of Ketenes, Allenes and Related Compounds"; Wiley: New York, 1980; Parts 1–2.
(4) (a) Spangler, C. W. *Chem. Rev.* **1976**, *76*, 187. (b) Mironov, V. A.; Fedorovich, A. D.; Akhrem, A. A. *Russ. Chem. Rev.* (*Engl. Transl.*) **1981**, *50*, 666.
(5) For vinylallene variants of [1,5]-shifts, besides ref 2a, see: (a) Crowley, K. J. *Proc. Chem. Soc.* **1964**, 17. (b) Mikolajczak, K. L.; Bagby, M. O.; Bates, R. B.; Wolff, I. A. *J. Org. Chem.* **1965**, *30*, 2983. (c) Skattebøl, L. *Tetrahedron* **1969**, *25*, 4933. (d) Bakker, S. A.; Lugtenburg, J.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 1459. (e) Minter, D. E.; Fonken, G. J. *Tetrahedron Lett.* **1977**, 1717. (f) Minter, D. E.; Fonken, G. J. *Ibid.* **1977**, 4149. (g) Minter, D. E.; Fonken, G. J.; Cook, F. T. *Ibid.* **1979**, 711. (h) Hammond, M. L.; Mouriño, A.; Okamura, W. H. *J. Am. Chem. Soc.* **1978**, *100*, 4907. (i) Condran, P., Jr.; Hammond, M. L.; Mouriño, A.; Okamura, W. H. *Ibid.* **1980**, *102*, 6259. (j) Condran, P., Jr.; Okamura, W. H. *J. Org. Chem.* **1980**, *102*, 4011. (k) Mouriño, A.; Lewicka-Piekut, S.; Norman, A. W.; Okamura, W. H. *Ibid.* **1980**, *45*, 4015. (l) Gerdes, J. M.; Lewicka-Piekut, S.; Condran, P., Jr.; Okamura, W. H. *Ibid.* **1981**, *46*, 5197. (m) Leyes, G. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1982**, *104*, 6099. (n) Haces, A.; Okamura, W. H. *Ibid.* **1982**, *104*, 6105. (o) Sueiras, J.; Okamura, W. H. *J. Am. Chem. Soc.* **1980**, *102*, 6255. (p) Knudsen, G. C.; Carey, S. C.; Okamura, W. H. *Ibid.* **1980**, *102*, 6355. (q) Chandraratna, R. A. S.; Okamura, W. H. *Ibid.* **1982**, *104*, 6114. (r) Knudsen, C. G.; Chandraratna, R. A. S.; Walkeapää, L. P.; Chauhan, Y. S.; Carey, S. C.; Cooper, T. M.; Birge, R. R.; Okamura, W. H. *Ibid.* **1983**, *105*, 1626. (s) Chandraratna, R. A. S.; Bayerque, A. L.; Okamura, W. H. *Ibid.* **1983**, *105*, 3588. (t) Gerdes, J. M.; Okamura, W. H. *J. Org. Chem.* **1983**, *48*, 4030. (u) Jeganathan, S.; Johnston, A. D.; Kuenzel, E. A.; Norman, A. W.; Okamura, W. H. *Ibid.* **1984**, *49*, 2152.
(6) Marvell, E. N. "Thermal Electrocyclic Reactions"; Academic Press: New York, 1980.

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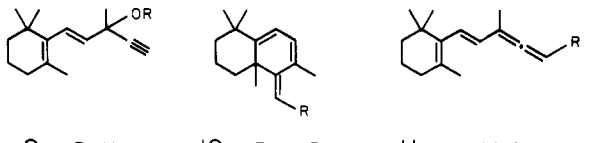
9a.[12] Reaction of **6c** with the higher order mixed cuprate[13]

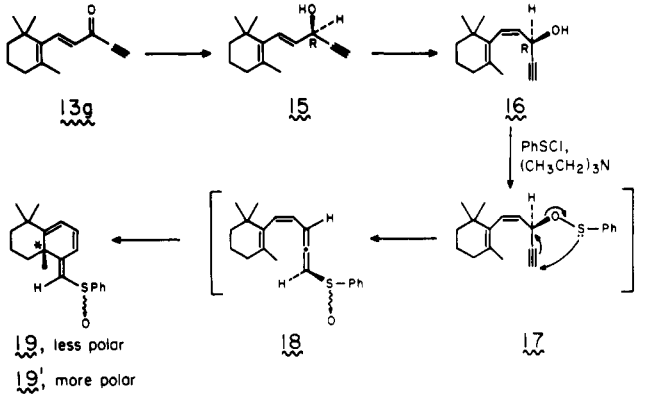


9a, R=H **10a**, R=n-Bu **11a**, R=S(O)Ph
b, R=SPh **b**, R=tert-Bu **b**, R=alkyl, vinyl
c, R=COPh **c**, R=CH_3
d, R=C_6H_5
e, R=H
f, R=SPh

$(t\text{-Bu})_2Cu(CN)Li_2$ in ether afforded not the anticipated allene but rather the electrocyclized product **10b** (79%). The analogous preparation of the *n*-butyl (**10a**, 77%), methyl (**10c**, 32%), and phenyl (**10d**, 60%) derivatives attests to the generality of this new decalin synthesis. After some trial, it was determined that the parent triene system **10e** could best be prepared by direct diisobutylaluminum hydride reduction (77%) of the alcohol **6a**.[14] Using the same procedure, the noralcohol **12a** (vide infra) was converted to the 13-desmethyl derivative of the parent triene **10e**.

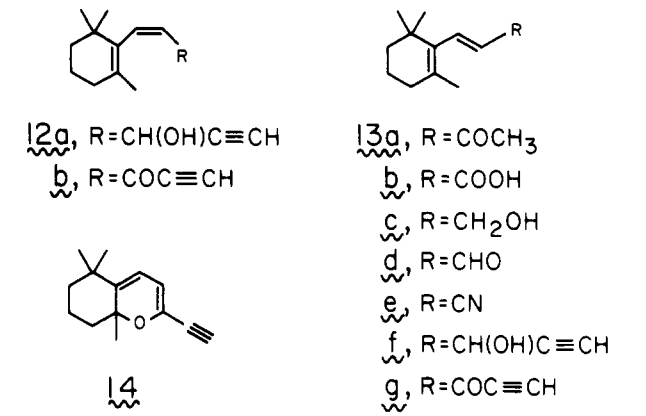
Since **10** possesses the skeleton of a rather large class of natural products, the *drimanes* (e.g., warburganal[15]), its preparation with a more useful functional group was sought. Thus, treatment of *cis*-propargyl alcohol **6a** with phenylsulfenyl chloride (PhSCl) in the presence of excess triethylamine (CH_2Cl_2) afforded a 75–80% yield of the separable diastereomeric mixture of the drimatriene sulfoxides **8** and **8'** (3:2 ratio).[9,16] Examination (IR, ^1H NMR) of crude reaction mixtures from this reaction maintained below room temperature revealed the absence of the putative allenyldiene intermediate **7**. However, it should be noted that the corresponding *trans*-allenyl sulfoxide **11a**[17] can be synthesized from **9b**, generated in situ by reacting **9a** with $PhSCl/Et_3N$. *trans*-Allenyldienes of the type **11b** have also already been reported.[5p-s]

Scheme I



Stereospecific Formation of the Drimatriene. The [2,3]-sigmatropic shifts of propargylic sulfenate esters to allenyl sulfoxides[18] as well as thermal electrocyclizations of (*Z*)-hexa-1,3,5-trienes[6,19] have been demonstrated to be stereospecific processes. Thus, it became of great interest to establish that the chiral center in **6** could be transferred in tandem to the axis in **7** and then to the bridgehead center in **8**. Not only would this provide a new route to optically active bicyclic molecules, potentially useful as intermediates in synthesis, but this would provide additional evidence for the mechanism of the production of **5** from **3**. The synthesis of an optically active variant of **6a**, namely one related to the secondary alcohol **12a**, became the objective.

The aldehyde **13d**, prepared by a known procedure [β-ionone (**13a**) → **13b** → **13c** → **13d**] or by a newer method [β-cyclocitral → **13e** → **13d**],[20] was reacted with lithium acetylide to afford **13f** (89%) and then the latter was one-way photoisomerized[11] to **12a** (94%) in the same manner as described for the preparation of **6a**.



12a, R=CH(OH)C≡CH
b, R=COC≡CH

13a, R=$COCH_3$
b, R=COOH
c, R=CH_2OH
d, R=CHO
e, R=CN
f, R=CH(OH)C≡CH
g, R=COC≡CH

14

Manganese dioxide oxidation of **12a** afforded the pyran tautomer **14** (45%), which is presumably in equilibrium with the *cis*-ketone **12b**.[21] Since pyran tautomers of the type **14** are known to react

(7) Besides in ref 1, allenyldienes (diene allenes) with a central cis double bond have been invoked as intermediates in various reactions: (a) Eglinton, G.; Raphael, R. A.; Willis, R. G. *Proc. Chem. Soc.* **1960**, 247. (b) Ben-Efraim, D. A.; Sondheimer, F. *Tetrahedron Lett.* **1963**, 313. (c) Eglinton, G.; Raphael, R. A.; Willis, R. G.; Zabkiewicz, J. A. *J. Chem. Soc.* **1964**, 2597. (d) Hopf, H. *Tetrahedron Lett.* **1970**, 1107; *Chem. Ber.* **1971**, *104*, 3087. (e) Scott, L. T.; Erden, I. *J. Am. Chem. Soc.* **1982**, *104*, 1147.

(8) The electrocyclization of hetero variants (dienyl ketones and dienylketenimines) of **2** are known. For example, see: (a) Quinkert, G. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 1072. (b) Quinkert, G. *Pure Appl. Chem.* **1973**, *33*, 285. (c) Dannenberg, W.; Lemmer, D.; Perst, H. *Tetrahedron Lett.* **1974**, 2133. (d) Dannenberg, W.; Perst, H.; Seifert, W. J. *Ibid.* **1975**, 3481. (e) Eckhardt, H. H.; Perst, H. *Angew Chem., Int. Ed. Engl.* **1978**, *17*, 465. (f) Eckhardt, H. H.; Perst, H. *Tetrahedron Lett.* **1979**, *23*, 2125.

(9) (a) Bickart, P.; Carson, F. W.; Jacobus, J.; Miller, E. G.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4869. (b) Tang, R.; Mislow, K. *Ibid.* **1970**, *92*, 2100. (c) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147. (d) Braverman, S.; Stabinsky, Y. *Israel J. Chem.* **1967**, *5*, 125. (e) Smith, G.; Stirling, C. J. M. *J. Chem. Soc. C* **1971**, 1530. (f) Horner, L.; Binder, V. *Liebigs Ann. Chem.* **1972**, *757*, 33. (g) Hoffmann, R. W.; *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 563.

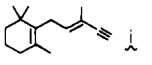
(10) Kaiser, E. M.; Woodruff, R. A. *J. Org. Chem.* **1970**, *35*, 1198.

(11) (a) Ramamurthy, V.; Butt; Y.; Yang, C.; Yang, P.; Liu, R. S. H. *J. Org. Chem.* **1973**, *38*, 1247. (b) Ramamurthy, V.; Tustin, G.; Yau, C. C.; Liu, R. S. H. *Tetrahedron* **1975**, *31*, 193.

(12) Oroshnik, W.; Mebane, A. D. *J. Am. Chem. Soc.* **1949**, *71*, 2062.

(13) (a) Lipshutz, B. H.; Wilhelm, R. S.; Floyd, D. M. *J. Am. Chem. Soc.* **1981**, *103*, 7672. (b) Lipshutz, B. H.; Kozlowski, J.; Wilhelm, R. S. *Ibid.* **1982**, *104*, 2305.

(14) A standard reagent for converting propargyl alcohols to allenes entails reduction with $LiAlH_4$–$AlCl_3$ (3:1 mole ratio in THF). Under these conditions, the allylic Δ^7 double bond was attacked to afford a hydrocarbon tentatively identified as **i** (^1H NMR; mass spectra).



i

(15) (a) Kubo, I.; Lee, Y.-W.; Pettei, M.; Pilkiewicz, F.; Nakanishi, K. *J. Chem. Soc., Chem. Commun.* **1976**, 1013. (b) Nakanishi, K.; Kubo, I. *Israel J. Chem.* **1977**, *16*, 28.

(16) For an application of the reagent to alkenynols, see: van Kruchten, E. M. G. A.; Okamura, W. H. *Tetrahedron Lett.* **1982**, *23*, 1019.

(17) The unstable allene sulfoxide **11a** was obtained in low (<30%) yield. After rapid chromatographic purification, it exhibited appropriate ^1H NMR, MS, and IR (e.g., ν 1940 cm^{-1}, weak) data.

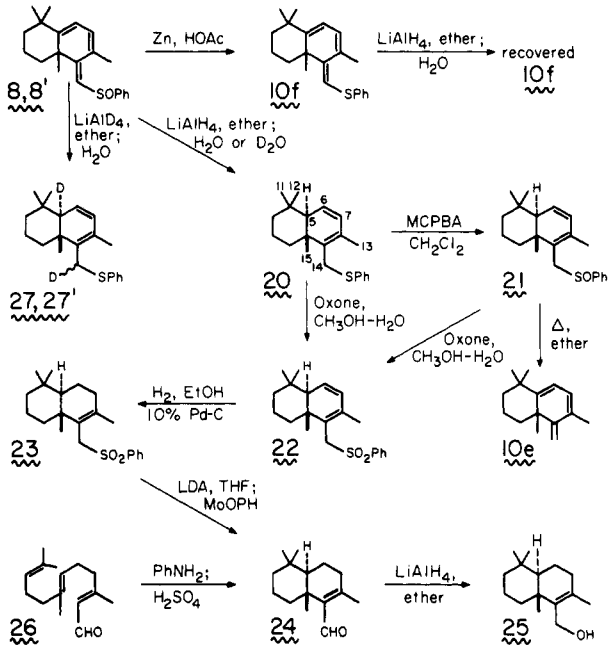
(18) Besides ref 9e, see: (a) Cinquini, M.; Colonna, S.; Stirling, C. J. M. *J. Chem. Soc., Chem. Commun.* **1975**, 256. (b) Cinquini, M.; Colonna, S.; Cozzi, F.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans 1* **1976**, 2061.

(19) (a) Marvell, E. N.; Caple, G.; Schatz, B. *Tetrahedron Lett.* **1965**, 385. (b) Vogel, E.; Grimme, W.; Dinnē, E. *Ibid.* **1965**, 391. (c) Marvell, E. N.; Caple, G.; Schatz, B.; Pippin, W. *Tetrahedron* **1973**, *29*, 3781. (d) Padwa, A.; Brodsky, L.; Clough, S. *J. Am. Chem. Soc.* **1972**, *94*, 6767.

(20) (a) van den Tempel, P. J.; Huisman, H. O. *Tetrahedron* **1966**, *22*, 293. (b) Byers, J. *J. Org. Chem.* **1983**, *48*, 1515.

(21) (a) Büchi, G.; Yang, N. C. *J. Am. Chem. Soc.* **1957**, *79*, 2318. (b) Marvell, E. N.; Caple, G.; Gosink, T. A.; Zimmer, G. *Ibid.* **1966**, *88*, 619. (c) Marvell, E. N.; Chadwick, T.; Caple, G.; Gosink, T.; Zimmer, G. *J. Org. Chem.* **1972**, *37*, 2992. (d) For a general review of α-pyran-*cis*-dienone equilibria, see ref 6, pp 305–319.

Scheme II



with nucleophilic reagents via the keto tautomer,[22] we anticipated asymmetric reduction of **14**. However, attempted reduction of **14** with either Alpine-borane[23] or $LiAlH_4$–Chirald,[24] reagents known to effectively reduce acetylenic ketones to secondary propargyl alcohols in an asymmetric sense, failed. The reaction appeared to be too slow, and only starting material **14** was recovered.

Anticipating that the *trans*-acetylenic ketone **13g** would be more readily reduced, the latter was prepared by MnO_2 oxidation of racemic **13f**. As shown in Scheme I, asymmetric reduction of ketone **13g** (Chirald–$LiAlH_4$,[24,25]) afforded (*R*)-**15** (84% ee), which upon sensitized photolysis[11] gave (*R*)-**16** (84% ee).[26] The optical purity (% ee) in each case was determined by the ^1H NMR–LIS method using $Eu(hfc)_3$ (see Experimental Section).[27] Reaction of (*R*)-**16** with PhSCl–triethylamine in the usual fashion afforded a separable 1:1 diastereomeric mixture of **19** (less polar) and **19′** (more polar). The enantiomeric purity of **19** was estimated to be 8:92 (84% ee) by high-pressure LC using a chiral stationary-phase column as described by Pirkle and co-workers.[28] It

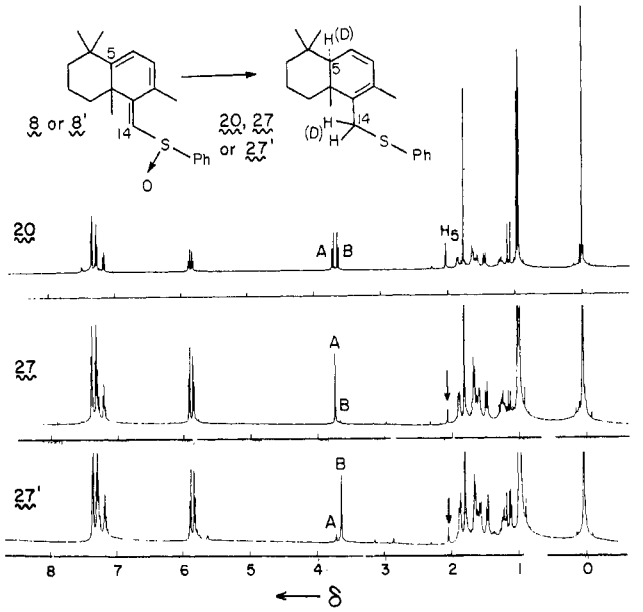


Figure 1. ^1H NMR spectra at 500 MHz: upper spectrum, 14-(phenylthio)drima-6,8-diene **20** from $LiAlH_4$ reduction of either diastereomeric sulfoxide **8** or **8′**; middle spectrum, 5,14-dideuterio-**27** from $LiAlD_4$ reduction of major (crystalline) sulfoxide **8**; lower spectrum, 5,14-dideuterio-**27′** from $LiAlD_4$ reduction of minor (liquid) sulfoxide **8′**. In the upper spectrum, the pertinent signals are those due to the two diastereotopic H_{14} protons (AB pattern) and the H_5 bridgehead proton (1:1:1 integration ratio). For the middle spectrum, this ratio is 1.0:0.03:0.2, indicating a 97% diastereoselective reduction at C_{14}. For the lower spectrum, the ratio of 1.0:0.1:0.2 is indicative of ~90% diastereoselective reduction at C_{14}. In either case, deuterium incorporation at C_5 is less complete (~80%).

should be noted that whereas **19** eluted more rapidly than **19′** on a standard silica column, their elution order was reversed on the chiral column. As described in detail in the Experimental Section, whereas the optical purity of **19** could be readily estimated, the diastereomer **19′** could not be chromatographically resolved into its antipodes. But presumably, **19′** is of the same optical purity as that of its simultaneously formed diastereomer **19**.[29] Absolute configurational assignments are discussed in a later section.

Synthetic Transformations of the Drimatriene Sulfoxides 8 and 8′. In order to confirm the general drimatriene structural assignment **5** and to develop some of the chemistry of this highly functionalized decalin system, one of the derivatives, the diastereomeric sulfoxides **8** and **8′**, was subjected to a series of reducing agents. While zinc reduction[30] of the sulfoxides afforded the expected vinyl sulfide **10f**, hydride reduction proceeded in a most unusual fashion (Scheme II). After some trial, it was established that a large excess of $LiAlH_4$ in ether transformed **8** and **8′** into the allylic sulfide **20** in excellent yield (90%).[31] The trans ring junction was established by the sequence **20** → **22** → **23** → **24** → **25** outlined in Scheme II.[32,33] The aldehyde **24** and alcohol **25** were independently synthesized for direct comparison purposes from farnesal by the acid-catalyzed route described previously by Commarmont and by Eschenmoser and Stork.[34] The at-

(22) Selected recent examples are given in ref 10b and 21c.

(23) Alpine-borane (a trademark of the Aldrich Chemical Co.) is *B*-3-pinanyl-9-borabicyclo[3.3.1]nonane. Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867.

(24) Chirald, a trademark of the Aldrich Chemical Co. and previously referred to as "Darvon alcohol", is (+)-(2*S*,3*R*)-4-(dimethylamino)-3-methyl-1,2-diphenyl-2-butanol. (a) Yamaguchi, S.; Mosher, H. S.; Pohland, A. *J. Am. Chem. Soc.* **1972**, *94* 9254. (b) Yamaguchi, S.; Mosher, H. S.; *J. Org. Chem.* **1973**, *38*, 1870. (c) Cohen, N.; Lopresti, R. J.; Neukom, C.; Saucy, G. *Ibid.* **1980**, *45*, 582. (d) Brinkmeyer, R. S.; Kapoor, V. M. *J. Am. Chem. Soc.* **1977**, *99*, 8339. (e) Johnson, W. S.; Brinkmeyer, R. S.; Kapoor, V. M. Yarnell, T. M. *Ibid.* **1977**, *99*, 8341.

(25) In one unoptimized attempt, Midland's reagent (for leading references see: Midland, M. M.; Tramontano, A.; Kazubski, A.; Graham, R. S.; Tsai, D. J. S.; Cardin, D. *Tetrahedron* **1984**, *40*, 1371) afforded mainly the same enantiomer as $LiAlH_4$–Chirald. Neat Alpine-borane (see: Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1982**, *47*, 1606) afforded *R*-**15** in 73% ee (56% yield) using 92% ee α-pinene.

(26) The *R* configuration for **15** (Scheme I) was initially assumed based on the generalization described in ref 24. This same absolute configuration for **16** is assumed on the basis of the method of synthesis. Finally, the absolute configurations as shown in Scheme I of the bridgehead carbon (C_{10}) of **19** and **19′** and that of the allene **18** are based on generalizations previously ascribed to electrocyclic (ref 19) and [2,3]-sigmatropic shift (ref 18) processes. The transformation of **19** and **19′** to optically active **32** with a (+) rotation (see Scheme III) further attests to these absolute configurational assignments.

(27) Kutal, C. In "Nuclear Magnetic Resonance Shift Reagents"; Sievers, R. E., Ed.; Academic Press: New York, 1973; pp 87–98.

(28) (a) Pirkle, W. H.; Finn, J. M.; Schreiner, J. L.; Hamper, B. C. *J. Am. Chem. Soc.* **1981**, *103*, 3964. (b) Pirkle, W. H.; Finn, J. M. *J. Org. Chem.* **1982**, *47*, 4037.

(29) An attempt to analyze **19** or **19′** with several different fluorinated chiral LIS reagents (ref 27) by ^1H NMR at 200 MHz was unsuccessful.

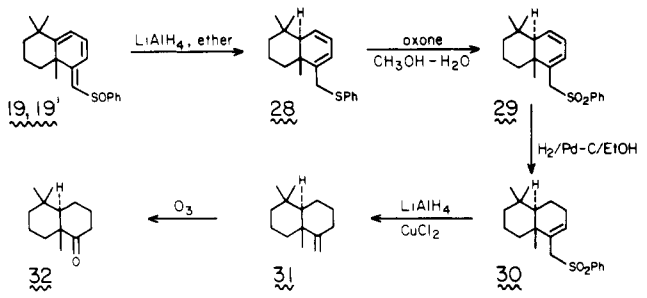
(30) Gazdar, M.; Smiles, S. *J. Chem. Soc.* **1910**, *97*, 2248.

(31) (a) For a related example using $LiAlH_4$, see Cookson, R. C.; Parsons, P. J. *J. Chem. Soc., Chem. Commun.* **1978**, *822*. (b) Cutting, I.; Parsons, P. J. *Tetrahedron Lett.* **1983**, *24*, 4463. (c) A related reduction using $NaBH_4$–Co(II) salts was also recently reported: Chung, S-K.; Han, G. *Synth. Commun.* **1982**, *12*, 903.

(32) Oxone is potassium hydrogen persulfate or, more precisely, it is a 2:1:1 mixture of $KHSO_5$, K_2SO_4, and $KHSO_4$. See: Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *22*, 1287.

(33) MoOPH refers to the 1:1:1 complex of molybdenum pentoxide, pyridine, and hexamethylphosphoramide. See: (a) Little, R. D.; Myong, S. O. *Tetrahedron Lett.* **1980**, *21*, 3339. (b) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.

Scheme III



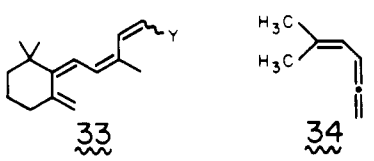
tractiveness of the allylic sulfoxide intermediate **21** for further synthetic transformations was negated by its propensity to undergo a facile elimination[35] to the parent drimatriene **10e**, a substance better obtained in one step from **6a** (vide supra).

That lithium aluminum hydride reduction of sulfoxides **8** and **8′** produces only **20** is *most unusual*. Accordingly, some mechanistic insight was sought through labeling experiments. That the sulfide **10f** was inert to $LiAlH_4$ and that $LiAlD_4$ reduction of **8** or **8′** followed by H_2O quench (but not $LiAlH_4$ reduction followed by D_2O quench) afforded the dideuterio derivatives **27** and **27′** indicate that the formal 1,6-reduction of the triene moiety in **8** and **8′** must be the result of the *direct action* of the hydride source. By separately reducing the diastereomeric **8** and **8′** with $LiAlD_4$, the production of **27** and **27′**, respectively, was shown to occur in a highly stereoselective fashion (>9:1, see Figure 1).

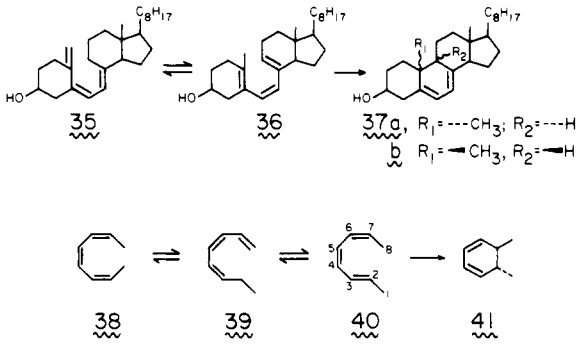
Synthetic Transformations of the Drimatriene Sulfoxides 19 and 19′. In order to delve into the matter of the absolute configuration of optically active **19** and **19′**, the latter was subjected to $LiAlH_4$ reduction. By analogy to the sequence applied to **8** and **8′**, **19** and **19′** afforded successively diene sulfide **28**, diene sulfone **29**, and ene sulfone **30** (Scheme III). Surprisingly, although the diene **29** was readily handled and purified, the monoene **30**, due to its poor solubility and amorphous nature, proved difficult to characterize. Accordingly, **30** was converted directly to the well-known ketone **32**[36] through the intermediacy of exocyclic olefin **31**, the latter being produced by an unusual S_N2' type displacement of a phenylsulfonyl residue.[37] The sign of the specific rotation of our substance **32** ($[\alpha]^{20}_D$ +30.8 ($CHCl_3$, *c* 0.05); $[\alpha]^{20}_D$ +35.9° (CH_3OH, *c* 0.05) was opposite to that reported for the enantiomer of **32** ($[\alpha]^{20}_D$ −35° (neat)) reported by Ohloff and co-workers.[36] It is concluded that the asymmetric sequence in terms of absolute configuration is that shown in Scheme I.

Discussion

A central question concerning the results described herein is related to the relative facility of the familiar duo of competing thermal pericyclic processes, [1,7]-sigmatropic hydrogen shift[4a] vs. electrocyclization.[6] The putative allenyldiene **4** was originally anticipated to undergo an *extraordinarily* facile [1,7]-shift to the tetraene **33**, a chromophoric arrangement once hypothesized as a component in the visual cycle.[38] Because **1** undergoes a



Scheme IV



[1,5]-sigmatropic hydrogen shift with a much smaller activation barrier (e.g., E_a ~24.6 kcal/mol for **34**)[5c] than related nonallenic cases (e.g., E_a ~32–35 kcal/mol)[4,39] *and* since topologically unconstrained [1,7]-sigmatropic shifts are significantly more facile (e.g., E_a ~15–21 kcal/mol)[4a,39] than [1,5]-shifts (e.g., E_a ~32–35 kcal/mol),[4,39] the propensity of **2** toward a [1,7]-shift was expected to be extraordinary. The complexion of the question has changed, of course, because of the observed rearrangement of **4** to **5** rather than **33**. It is well-known that in nonallenic cases, [1,7]-sigmatropic shifts are significantly more facile (E_a ~15–21 kcal/mol)[4a,39] than electrocyclizations (E_a ~29–33 kcal/mol).[6,39] In the classical case of vitamin D_3 (**35**),[40] its equilibrium conversion via a [1,7]-sigmatropic shift to precalciferol **36** (Scheme IV) occurs under very mild conditions (~60 °C)[41] compared to the irreversible electrocyclization of the latter to pyro- (**37a**) and isopyrocalciferol (**37b**) (≳150 °C).[42] Similarly, **38** and **40** may be equilibrated at ~100 °C via the presumed intermediacy of **39**, while irreversible rearrangement to **41** occurs only upon heating to ~180 °C.[19a,c] In the cases exemplified in Scheme IV, it is reasonable that the transition-state steric demands of a helical antarafacial [1,7]-sigmatropic hydrogen shift process[4a] are minimal compared to that of a boatlike disrotatory electrocyclization.[19b,6] In other words, the reacting termini for the [1,7]-shift (e.g., C_8 and C_2 in **40**) are sterically less encumbered than those for electrocyclization (e.g., C_2 and C_7 in **40**). It seems clear, however, that formation of the electrocyclization product is thermodynamically favored because a new carbon–carbon bond is ultimately formed; [1,7]-shifts, by contrast, lead to relatively thermoneutral products.

By replacing the C_1–C_2 single bond of **40** by a π bond, as in the analogous dienylallene **2**, it can be anticipated that electrocyclization should be accelerated because C_2 (sp carbon) is less crowded in **2** than that (sp^2 carbon) in **40**. On this basis, in order to rationalize why electrocyclization is faster than the [1,7]-shift in the allene case, it must be argued that from a steric standpoint, there is much less to be gained for the [1,7]-shift process on going from **40** to **2**.[43] An alternative possibility that **4** and **33** may be undergoing a rapid equilibrium (similar to those shown in Scheme IV) under conditions even milder than the electrocyclization of **4** to **5** is deemed unlikely for two reasons. First, the back reaction **33** → **4** seems energetically inaccessible since the rupture of a vinyl C–H bond would be required. Second, such a preequilibrium

(34) (a) Stadler, P. A.; Eschenmoser, A.; Schinz, H.; Stork, G. *Helv. Chim. Acta* **1957**, *40*, 2191. (b) Stoll, M.; Commarmont, A. *Ibid.* **1949**, *32*, 1836.

(35) Related α,ω-eliminations of allylic sulfoxide systems have been previously recorded: (a) Guittet, E.; Julia, S. *Tetrahedron Lett.* **1978**, 1155. (b) Corey, E. J.; Oh, H.; Barton, A. E. *Ibid.* **1982**, *23*, 3467.

(36) Ohloff, G.; Giersch, W.; Schulte-Elte, K. H.; Vial, C. *Helv. Chim. Acta* **1976**, *59*, 1140.

(37) (a) Pascali, V.; Umani-Ronchi, A. *J. Chem. Soc., Chem. Commun.* **1973**, 351. (b) Mukaiyama, T.; Narasaka, K.; Maekawa, K.; Furusato, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2285.

(38) (a) Fransen, M. R.; Luyten, W. C. M. M.; van Thuijl, J.; Lugtenburg, J.; Jansen, P. A. A.; van Breugel, P. J. G. M.; Daemen, F. J. M. *Nature (London)* **1976**, *260*, 727. (b) van der Meer, K.; Mulder, J. J. C.; Lugtenburg, J. *Photochem. Photobiol.* **1976**, *24*, 363. (c) Fransen, M. R.; Palings, I.; Lugtenburg, J.; Jansen, P. A. A.; Groenendijk, G. W. T. *Recl. Trav. Chim. Pays-Bas* **1980**, *99*, 384.

(39) For a comparative discussion, see: Crowley, K. J.; Traynor, S. G. *Tetrahedron* **1978**, *34*, 2783.

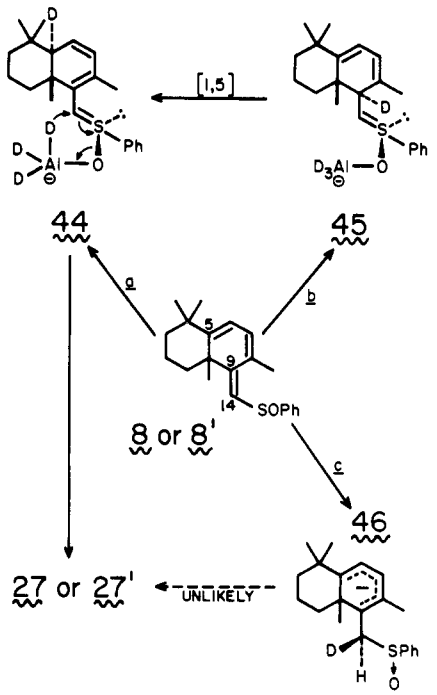
(40) Fieser, L. F.; Fieser, M. "Steroids"; Reinhold: New York, 1959; Chapter 4.

(41) Hanewald, K. H.; Rappoldt, M. P.; Roborgh, J. R. *Recl. Trav. Chim. Pays-Bas* **1961**, *80*, 1003 and the references cited.

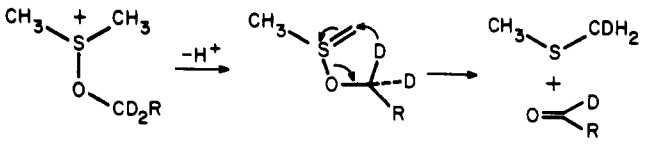
(42) For recent data and leading references: Pelc, B.; Marshall, D. H. *Steroids* **1978**, *31*, 23.

(43) However, by introducing two bulky substituents at the allene terminus in **4**, H. Elnagar of this laboratory has recently observed [1,7]-sigmatropic hydrogen-shifted products.

Scheme V

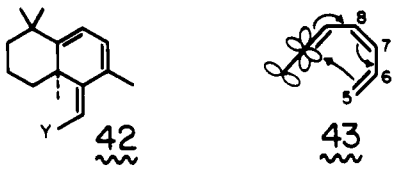


Scheme VI



would have led to racemic rather than the observed optically active products (**19** and **19′**) in the studies shown in Scheme I.

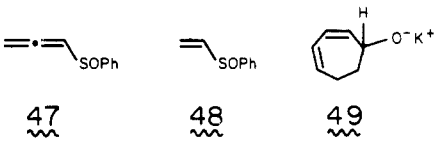
Up to this point, it has been assumed that the conversion of **4** to **5** is best viewed as a classical, concerted electrocyclic process proceeding in a stereospecific disrotatory manner.[19] Since there are two possible modes of disrotation, the other allowed geometric isomer of **5**, namely **42**, is presumably not observed for steric reasons. That **4** may be undergoing a pseudoelectrocyclic pro-



cess[44] as depicted in **43** is yet another possibility. This would entail formal bonding of the p orbital on C_5 with the *orthogonal* p orbital of the allenic sp carbon (C_{10}). The orthogonality of the terminal allenic π bond to the reacting π system (C_5 to C_{10}) would seemingly preclude stereospecificity for pseudoelectrocyclization[45] (**43**). Since in fact stereospecificity is experimentally indicated (Scheme I), the classical disrotatory, electrocyclic picture seems more reasonable. However, high stereoselectivity has been predicted by Pasto for the (2 + 2) cycloaddition of allenes with alkenes, wherein the orthogonal π bonds of the allene are both involved. The relationship of Pasto's system to the electrocyclic processes described herein awaits further analysis.[46]

The $LiAlH_4$ reduction of drimatriene sulfoxides **8** and **8′** is highly unusual[31] and thus deserves brief comment. In order to accommodate the labeling studies, the intermediacy of **44** (path a, Scheme V) formed via initial hydride attack at C_5, was proposed.[1] It was further envisaged that the oxygen coordinated aluminate complex **44** (shown for only one diastereomer)[47] was reduced through intramolecular delivery of deuteride to C_{14} in order to account for the stereoselective production of **27** or **27′**. Perhaps the best analogy for the deuteride delivery depicted in **44** is the intramolecular process shown in Scheme VI, a sequence reasonably convincingly established for the Pfitzner–Moffatt oxidation.[48] In point of fact, Scheme VI or **44** → **27,27′** can equally justifiably be referred to as a Pummerer reaction in which the nucleophile is a deuteride ion.[49] In as much as both deuteriums in **27** and **27′** must originate from $LiAlD_4$, initial deuteride attack to afford **46** (path c, Scheme IV) seems unreasonable. Further deuteride reduction at C_5 of the cyclohexadienyl anion **46** is highly unlikely.

An intriguingly reasonable alternative pathway entails initial deuteride attack at C_9 (path b, Scheme V) to produce **45**. The latter would require an α-carbanion accelerated [1,5]-sigmatropic hydrogen shift of **45** to **44**.[50] The formation of **45** rather than **44** as the initial product is attractive since although deuteride attack at C_5 or C_9 seems encumbered by serious steric factors, initial attack at C_9 may conceivably be assisted intramolecularly by association of the aluminum reagent with the sulfoxide oxygen. Related conjugate reduction of α,β-unsaturated sulfoxides is certainly well-known (**47** → allyl phenyl sulfide and **48** → ethyl phenyl sulfide).[31] Finally, regarding the intriguing possibility



of an accelerated conversion of **45** to **44**, Paquette has recently described the 10^5–10^6 rate acceleration of [1,5]-sigmatropic shifts in alkoxides **49** and related systems when compared to the corresponding alcohols.[51] For simple cyclohexadienes, temperatures of >300 °C are frequently required for effecting [1,5]-shifts.[4]

Summary

The formation of drimatrienes offers a new method for the stereospecific asymmetric synthesis of polycyclic ring systems. The tandem center → axis → center chirality transfer process demonstrated herein appears to be unprecedented. It was presumed that the stereospecifically produced intermediate (*R*)-allenyldiene **18** electrocyclizes in a disrotatory manner to afford the less hindered *E* isomers **19** and **19′** possessing the *R*-bridgehead carbon.

(44) The more general term pseudopericyclic process was coined by Lemal and co-workers for allylic rearrangements: (a) Ross, J. A.; Seiders, R. P.; Lemal, D. M. *J. Am. Chem. Soc.* **1976**, *98*, 4325. (b) Bushweller, C. H.; Ross, J. A.; Lemal, D. M. *Ibid.* **1977**, *99*, 629. (c) For a recent theoretical discussion, see Henriksen, U.; Snyder, J. P.; Halgren, T. A. *J. Org. Chem.* **1981**, *46*, 3767.

(45) Pseudoelectrocyclizations have also been discussed. (a) See ref 6, pp 311–312. (b) Burke, L. A.; Elguero, J.; Leroy, G.; Sana, M. *J. Am. Chem. Soc.* **1976**, *98*, 1685. (c) Schiess, P.; Scheller-Krattiger, V., unpublished data, University of Basel, Switzerland. We are grateful to Prof. Schiess for informative discussions.

(46) Strictly speaking, pseudopericyclizations have been discussed (ref 44) in terms of concerted transformations whose primary changes involve a cyclic array of atoms wherein the role of bonding and nonbonding (empty or filled) *atomic orbitals* change roles. In the pericyclization of **2**, the "nonbonding" orbital is replaced by the Δ^1 π-bond of the allene moiety. However, Pasto has examined the (2 + 2) cycloaddition of allenes and olefins in terms of a stereoselective process where all three π systems participate in a concerted fashion. See Pasto, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 37.

(47) Except as noted (Schemes I and III), all structures shown in this paper are racemic.

(48) (a) Fenselau, A. H.; Moffatt, J. G. *J. Am. Chem. Soc.* **1966**, *88*, 1762. (b) Pfitzner, K. E.; Moffatt, J. G. *Ibid.* **1963**, *85*, 3027. (c) Pfitzner, K. E.; Moffatt, J. G. *Ibid.* **1965**, *87*, 5661.

(49) Russell, G. A.; Mikol, G. J. In "Mechanisms of Molecular Migrations"; Thyagarajan, B. S., Ed.; Interscience: New York, 1968; Vol. I, pp 157–176.

(50) We are grateful to Prof. Robert K. Boeckman for this interesting suggestion. For leading references on neighboring charge accelerated pericyclic processes, see: (a) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765. (b) Carpenter, B. K. *Tetrahedron* **1978**, *34*, 1877.

(51) Paquette, L. A.; Crouse, G. D.; Sharma, A. K. *J. Am. Chem. Soc.* **1980**, *102*, 3972.

Had disrotation occurred in the opposite allowed sense, then the corresponding *Z,S* combination should have resulted. In other words, a novel situation emerges wherein *geometric* diastereomers correspond to optical antipodes. The results of this study further attest to the utility of vinylallenes in organic synthesis.

Experimental Section

(7*Z*)-9-Ethynyl-β-ionol (6a). A solution of (7*E*)-9-ethynyl-β-ionol (**9a**; 16.0 g, 73.3 mmol) and 2′-acetonaphthone (0.320 g) in benzene (80 mL) was irradiated with a Hanovia 450-W medium-pressure mercury lamp (standard, water-cooled Pyrex immersion well; nitrogen purging with a long syringe needle).[11,12] The reaction was found to be complete after 15 h (monitoring by ^{1}H NMR). Evaporation of the solvent and then distillation of the residue on a short vigreux column yielded 15 g (94%) of pure *cis*-alcohol **6a** with bp 79 °C, 0.4 mm.

(7*Z*)-9-Ethynyl-β-ionyl Benzoate (6c). A solution of *n*-butyllithium (20 mmol, 1.53 M hexane) was added dropwise to a cold (0 °C), stirred solution of ethynyl alcohol **6a** (4.36 g, 20 mmol) in dry ether (8 mL). After 20-min stirring at 0 °C, benzoyl chloride (20 mmol, 2.3 mL) was added dropwise and then the solution was warmed to room temperature and stirred for an additional 3 h.[10] The resulting mixture was extracted with saturated aqueous $NaHCO_3$ and saturated aqueous NH_4Cl and then dried over $MgSO_4$. Evaporation of the solvent (rotary evaporator and then a high vacuum pump) afforded the benzoate **6c** as a viscous oil, which was used without further purification. The ^{1}H NMR spectrum indicated the ester to be uncontaminated by starting materials. Attempts to purify the ester (distillation or chromatography) led to elimination of benzoic acid.

14-(Phenylsulfinyl)drima-5,7,9(14)-triene (8 and 8′). Benzenesulfenyl chloride was freshly prepared by addition of a stock solution of chlorine in CCl_4 (1.32 mL, 1.40 M, 1.85 mmol) to diphenyl disulfide (0.404 g, 1.85 mmol) with stirring at 0 °C. After addition was complete, the orange–red solution was stirred for another 30 min at room temperature. To a cold (−78 °C) solution of **6a** (0.800 g, 3.66 mmol) and triethylamine (1.02 mL, 0.742 g, 7.32 mmol) in dry dichloromethane (30 mL) was slowly added the freshly prepared solution of benzenesulfenyl chloride (0.37 mmol) in CCl_4. The colorless solution was stirred at −78 °C for 30 min before it was allowed to warm to room temperature. Aqueous $NaHCO_3$ was added, and the layers were separated. The aqueous phase was extracted twice with CH_2Cl_2, and the combined organic layers were washed with NH_4Cl solution. After drying ($MgSO_4$) and concentrating, the residue was flash chromatographed (silica gel; 1:1 lbpe ether) to afford a diastereomeric mixture of **8** and **8′** (0.891 g, 75%). The isomers can be separated by HPLC (Whatman Partisil, 30% EtOAc/SSB) or column chromatography (silica gel, 1:1 lbpe ether) to afford a ~60:40 ratio of **8** (mp 152–153 °C from lbpe ether; less polar) and **8′** (viscous oil; more polar), respectively.

14-*n*-Butyldrima-5,7,9(14)-triene (10a). A solution of *n*-butyllithium (1.49 M in hexane, 4.96 mL, 7.4 mmol) was added dropwise to a cold (~−5 °C), stirred suspension of cuprous cyanide (0.334 g, 3.70 mmol) in dry ether (6 mL). After 10 min at ~−5 °C and then cooling to −78 °C, *cis*-benzoate **6c** (0.568 g, 1.76 mmol) in ether (5 mL) was added dropwise. The mixture was allowed to warm to room temperature over ~2 h and was quenched (aqueous NH_4Cl), and the ether layer was then extracted 3 times with aqueous NH_4Cl. The ether layer was dried ($MgSO_4$), concentrated, and then chromatographed (silica gel, lbpe containing 1% pyridine). Concentration of appropriate fractions afforded 0.350 g (77%) of the *n*-butyl derivative **10a**.

14-*tert*-Butyldrima-5,7,9(14)-triene (10b). The procedure was similar to that used for preparing the *n*-butyl derivative **10a**. The following were used: *tert*-butyllithium solution (2.1 M in pentane, 2.31 mL, 4.85 mmol), CuCN (0.219 g, 2.43 mmol) suspended in ether (5 mL), and *cis*-benzoate **6c** (0.391 g, 1.21 mmol) in ether (5 mL). The chromatographically pure *tert*-butyl derivative **10b** was obtained in 79% yield (0.246 g).

14-Methyldrima-5,7,9(14)-triene (10c). To a suspension of cuprous cyanide (0.075 g, 0.84 mmol) in dry ether (5 mL) at −10 °C was added a solution of methyllithium (LiBr complex in ether; 1.2 mL, 1.4 M, 1.7 mmol). After the solution was cooled to −78 °C, *cis*-benzoate **6c** (0.269 g, 0.84 mmol) in ether (3 mL) was added with stirring and then the mixture was allowed to warm to room temperature over ~2 h. The reaction was quenched (aqueous NH_4Cl) and then the ether layer was extracted 3 times with aqueous NH_4Cl, dried ($MgSO_4$), concentrated, and then chromatographed (silica gel, lbpe containing 1% pyridine). Concentration of appropriate fractions afforded 0.065 g (32%) of the methyl compound **10c**. In other experiments, the utilization of a greater than ~1:1 ratio of $(CH_3)_2CuCNLi_2$ to benzoate **6c** was observed to give lower yields of **10c**.

14-Phenyldrima-5,7,9(14)-triene (10d). The cuprate, prepared from CuCN (0.218 g, 2.36 mmol) suspended in ether (5 mL) and phenyllithium (1.95 M in 7:3 cyclohexane ether, 2.42 mL, 4.72 mmol), was reacted with *cis*-benzoate **6c** (0.380 g, 1.18 mmol) in ether (5 mL) and then processed by the same procedure used for preparing the *n*-butyl derivative **10a**. The chromatographically pure phenyl derivative **10d** was obtained in 60% yield (0.197 g).

Drima-5,7,9(14)-triene (10e). After the diene sulfoxide **21** (0.052 g, 0.06 mmol) in ether (6 mL) had been refluxed for 6 h and was then allowed to stand at room temperature for 18 h, the mixture was concentrated. Passage of the residue through a short column (silica gel, lbpe) afforded after concentration of pooled fractions 0.032 g (94%) of the pure triene **10e** as an oil.

A more direct procedure involves reduction of (7*Z*)-9-ethynyl-β-ionol **6a**. To a solution of **6a** (0.130 g, 0.60 mmol) in dry THF (25 mL) was added dropwise diisobutylaluminum hydride (2.05 mL, 3.6 mmol; 1.75 M in toluene) and then the mixture was refluxed for 24 h. The cooled mixture was quenched with water and then worked up with ether in the usual fashion. The crude product was passed through silica gel (lbpe) to afford after vacuum drying 0.093 g (77%) of (>90% pure by ^{1}H NMR) **10e**. In a second experiment, 2 g of **21** afforded after flash chromatography (silica gel, lbpe) and vacuum drying 1.172 g (63%) of ^{1}H NMR pure **10e**.

13-Nordrima-5,7,9(14)-triene (13-Nor-10e). To a solution of **12a** (0.10 g, 0.49 mmol) in 20 mL THF was slowly added diisobutylaluminum hydride (3.0 mL, 3.6 mmol, 1.2 M in hexane), and the solution was refluxed for 22 h. The mixture was cooled in an ice bath, water was added, and the mixture was then extracted twice with lbpe. The combined organic layers were washed with NH_4Cl solution and dried over $MgSO_4$. Flash chromatography (silica gel, 20:1 lbpe ether) of the residue afforded 0.043 g (47%) of **13-nor-10e.**

14-(Phenylthio)drima-5,7,9(14)-triene (10f). A solution of the diastereomeric mixture of sulfoxides **8** and **8′** (0.249 g, 0.76 mmol) in acetic acid (5 mL) was treated with excess zinc dust and then the mixture was stirred overnight at room temperature. The reaction mixture was diluted with ether and neutralized with aqueous NaOH. TLC showed 50% conversion. The reduction product was separated easily by chromatography over silica gel in lbpe and yielded 0.115 g (49%) of sulfide **10f** as an oil. The starting material was eluted later from the column with ether. Longer reaction times or higher reaction temperature yielded a more polar side product.

A solution of sulfide **10f** (0.037 g, 0.12 mmol) and lithium aluminum hydride (0.10 g, 2.6 mmol) in ether (5 mL) was refluxed for 4 h. After standard workup, only starting material was recovered.

Racemic (7*Z*)-9-Ethynyl-9-demethyl-β-ionol (12a). The racemic *trans*-alcohol **13e** (1.0 g, 4.89 mmol) and the sensitizer 2′-acetonaphthone (0.10 g) in benzene (80 mL) was irradiated (9 h) as described above for preparing **6a**. Kugelrohr distillation (bp 85 °C, 0.2 mm) afforded 0.941 g (94%) of **12a**.

Racemic (7*E*)-9-Ethynyl-9-demethyl-β-ionol (13f). To a cold (−78 °C) THF solution of lithium acetylide [27.3 mmol; prepared by slowly adding *n*-butyllithium (27.3 mmol, 17.3 mL, 1.6 M in hexane) to excess acetylene (30 mmol) dissolved in dry THF (150 mL) under nitrogen at −78 °C] was slowly added a solution of aldehyde **13d** (4.917 g, 27.6 mmol) in THF (20 mL). After 20 min, the mixture was allowed to warm to room temperature and then worked up as previously described. Distillation (80 °C, 0.3 mm) afforded 5.0 g (89%) of **13f** as a yellow, viscous oil.

(7*E*)-9-Ethynyl-9-demethyl-β-ionone (13g). Freshly activated MnO_2 (40 g) was suspended in a solution of ethynyl alcohol **13f** (3.614 g, 17.7 mmol) in CCl_4 (150 mL). After 20-min magnetic stirring at room temperature, the conversion was complete (IR monitoring). The MnO_2 was removed by filtration (CCl_4 rinsings), the solvent was vacuum evaporated, and the residue was then distilled (Kugelrohr, bp 120 °C, 0.5 mm) to afford 2.452 g (68%) of **13g**.

Pyran Tautomer of (7*Z*)-9-Ethynyl-9-demethyl-β-ionone (14). The *cis*-alcohol **12a** (0.376 g, 1.85 mmol) was oxidized (2.5 h; monitored by IR) with freshly activated MnO_2 (5 g) in CCl_4 (150 mL) and then worked up as described above for the *trans*-ketone **13g**. Filtration (silica gel, lbpe) and then vacuum drying afforded 0.170 g (45%) of ^{1}H NMR pure **14**. Attempts to reduce this material with chiral reducing agents at −78 °C were too slow to be practical.

(9*R*,7*E*)-9-Ethynyl-9-demethyl-β-ionol (15). A solution of Chirald (Aldrich Chemical Co.; 3.0 g, 10.57 mmol) in dry ether (30 mL) was added dropwise to a stirred solution of $LiAlH_4$ (0.175 g, 4.60 mmol) in dry ether (100 mL) at 0 °C. After the addition was complete, the mixture was stirred for 2 min and then cooled to −78 °C. After a solution of ethynyl ketone **13g** (0.847 g, 4.18 mmol) in ether (20 mL) was added dropwise to the cold (−78 °C) reduction solution over a period of 50 min, the stirred mixture was maintained at this temperature for 9 h. Water was added, and the mixture was allowed to warm to room temperature and worked up conventionally. Column chromatography (silica gel; 9:1

lbpe ether) of the crude product afforded 0.619 g (73%) of **15** exhibiting excellent ^{1}H NMR purity.

An optical purity of 84% ee was determined by ^{1}H NMR using the chiral LIS reagent Eu(hfc)$_3$, tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III), sold by Aldrich Chemical Co. To a solution of optically enriched ethynyl alcohol **15** in $CDCl_3$ were added small increments of Eu(hfc)$_3$, and the ^{1}H NMR spectrum was recorded after dissolution of each incremental addition of shift reagent. When the terminal acetylenic proton peaks attributable to the individual enantiomers were resolved, the spectrum was expanded and the relative peak areas were integrated by the cut and weigh method. This procedure must be and was carried out on the racemic material as a control.

(9*R*,7*Z*)-9-Ethynyl-9-demethyl-β-ionol (16). The 84% ee (9*R*)-*trans*-alcohol **15** (1.0 g, 4.89 mmol) was photolyzed and worked up as described above for the racemic alcohol **12a**. Chromatographic purification (silica gel; 9:1 lbpe ether) followed by vacuum drying afforded 0.979 g (98%) of **16**. Analysis using the ^{1}H NMR chiral LIS reagent method described above for the optically enriched *trans*-alcohol **15** indicated an identical optical purity of 84% ee.

(15*R*)-14-(Phenylsulfinyl)-13-nordrima-5,7,9(14)-triene (19 and 19′). To a solution of 84% ee (9*R*)-7-*cis*-alcohol **16** (0.608 g, 2.98 mmol) and triethylamine (0.83 mL, 0.602 g, 5.96 mmol) in dry CH_2Cl_2 (50 mL) at −78 °C slowly added phenylsulfenyl chloride (0.431 g, 2.98 mmol). The reaction mixture was allowed to warm slowly to room temperature and was then quenched and worked up as described for **8** and **8′**. Chromatography (silica gel, 3:2 lbpe ether) afforded 0.891 g (96%) of a 1:1 diastereomeric mixture (by ^{1}H NMR or high-pressure LC analysis) of sulfoxides **19** and **19′** (yellow, viscous oil). Semipreparative high-pressure LC separation (Partisil column; 30% ethyl acetate in Skellysolve B) afforded diastereomers **19** ($[\alpha]^{20}_D$ +4.1° ($CHCl_3$, *c* 1.1)) and **19′** ($[\alpha]^{20}_D$ +6.3° ($CHCl_3$, *c* 1.2)). The enantiomeric purity was measured by high-pressure LC using a chiral stationary-phase column (Pirkle Type 1-A column, Regis Chemical Co.; 4% isopropyl alcohol in Skellysolve B, 0.7 mL/min flow rate, UV detection at 254 nm). Peak identification was made by coinjection with racemic material. On the Pirkle Type 1-A column, only the enantimorphs of diastereomer **19** could be resolved and the elution order was reversed from that observed on the Whatman partisil column. The results were as follows: the retention time on the Pirkle Type 1-A column for the unresolved enantiomers of **19′** was 42 min; those for the faster eluting and the more slowly eluting enantiomers of **19** were 75 and 79 min, respectively, with a peak ratio of 8:92 (which corresponds to an optical purity of 84% ee).

Racemic 14-(Phenylsulfinyl)-13-nordrima-5,7,9(14)-triene (*rac*-19,19′). Racemic 7-*cis*-alcohol **12a** (0.434 g, 2.10 mmol) was treated exactly as in the preceding experiment to afford 0.645 g (98%) of racemic diastereomers of **19** and **19′**. Analysis and separation of diastereomers were carried out as described in the preceding section.

14-(Phenylthio)drima-6,8-diene (20). To a suspension of lithium aluminum hydride (1.900 g, 50.1 mmol) in dry ether (180 mL) at −78 °C was slowly added a solution of the diastereomeric mixture of sulfoxides **8** and **8′** (1.362 g, 4.07 mmol) in dry THF (25 mL). The reaction mixture was allowed to warm and was then kept at room temperature overnight. The excess $LiAlH_4$ was destroyed with aqueous Na_2SO_4, the salts were removed by filtration, and the organic layer was then dried over $MgSO_4$. Concentration under vacuum afforded 1.178 g (90%) of diene sulfide **20** of excellent purity (^{1}H NMR). Further purification can be achieved by chromatography (silica gel, lbpe). In separate experiments, $LiAlH_4$ reduction of the individual diastereomers of sulfoxide **8** and **8′** followed by D_2O quenching afforded the same undeuterated drimadiene **20**.

The minor (liquid) sulfoxide **8′** (0.097 g, 0.31 mmol) was reduced as above with excess lithium aluminum deuteride to afford 0.074 g (80%) of dideuterated product **27′** [*m/z* 314.2054 (calcd for $C_{21}H_{26}D_2S$, 314.2039), rel intensities, 314 (100%), 313 (11%), 312 (0%)]. Similar reduction of the major (crystalline) sulfoxide **8** (0.080 g, 0.26 mmol) afforded 0.062 g (77%) of a different dideuterated product **27** [*m/z* 314.2039 (calcd for $C_{21}H_{26}D_2S$, 314.2039); no peaks at *m/z* 313 or 312]. The two dideuterated products **27** and **27′** differed in their ^{1}H NMR spectra as shown in Figure 1.

14-(Phenylsulfinyl)drima-6,8-diene (21). To a solution of **20** (0.254 g, 0.81 mmol) in CH_2Cl_2 (6 mL) at −5 °C was added slowly a solution of MCPBA (80% titer; 0.175 g, 0.81 mmol) in CH_2Cl_2 (6 mL). The reaction was monitored by TLC, and after ~7 h, the reaction was complete. The organic layer was extracted twice with aqueous Na_2CO_3 and once with aqueous NH_4Cl and was then dried over $MgSO_4$. Chromatography of the residue on silica gel (lbpe ether, 1:1) yielded 0.211 g (79%) of diene sulfoxide **21** as a diastereomeric mixture.

14-(Phenylsulfonyl)drima-6,8-diene (22). To a solution of diene sulfide **20** (0.286 g, 0.916 mmol) in 2 mL of CH_2Cl_2 and 25 mL of methanol was added a solution of 0.838 g of oxone[32] (0.72 molar equiv) in 5 mL of water. The resulting heterogeneous mixture was stirred at room temperature overnight, diluted with water, and then extracted 3 times with CH_2Cl_2. The organic layer was washed with saturated aqueous NH_4Cl and was then dried over $MgSO_4$. After concentration under reduced pressure, the residue was chromatographed over silica gel in 2:1 lbpe ether to give 0.231 g (73%) of sulfone **22**. Oxidation of sulfoxide **21** under similar conditions afforded sulfone **22** in 60% yield.

14-(Phenylsulfonyl)drim-8-ene (23). A solution of 0.249 g (0.72 mmol) of diene sulfone **22** in 15 mL of 95% ethanol was stirred with 0.2 g of 10% Pd/C for 30 min at room temperature. The catalyst was removed by filtration through a short dry column of silica gel and then the filtrate was concentrated under reduced pressure. The residue was subjected to hydrogenation (room temperature, 1 atm, 10% Pd/C, 95% ethanol), and after the uptake of 1 molar equiv of hydrogen, the reaction mixture was worked up in the same manner as above. Concentration afforded an amorphous solid (quantitative yield), which exhibited an excellent ^{1}H NMR spectrum. This material was carried on directly to the next step. Note that the pretreatment of diene sulfone with catalyst was necessary to remove an unknown inhibitor of the hydrogenation reaction.

β-Bicyclofarnesal (24). To a solution of 0.039 g (0.114 mmol) of sulfone **23** in 15 mL of dry THF at −40 °C was slowly added 0.38 mL of LDA/THF (0.3 M, 1.1 mmol). After 15 min, a solution of 0.247 g (5 mmol) of MoOPH[33] ($MoO_5 \cdot C_5H_5N \cdot HMPA$) in 10 mL of THF was added at once (double-ended needle); after another 15 min, the reaction mixture was quenched with ~5 mL of saturated aqueous Na_2SO_3. The organic layer was diluted with ether and washed successively with 1 M HCl, aqueous $NaHCO_3$, and aqueous NH_4Cl. Chromatography over silica gel (9:1 lbpe ether) and then concentration of the appropriate fractions afforded 0.011 g (44%; 68% based on recovered sulfone) of aldehyde **24** [mp 46–48 °C (lit.[34] mp 48–51 °C)] and 0.010 g (36%) of starting material. The spectroscopic data (^{1}H NMR, IR) were essentially identical with that of β-bicyclofarnesal synthesized according to the procedure of Stoll and Commarmont.[34b] The aldehyde **24** prepared by the literature method could not be crystallized, but the corresponding authentic alcohol was crystalline (see next section).

β-Bicyclofarnesol (25). The β-bicyclofarnesal **24** (8 mg, 0.036 mmol) prepared from sulfone **23** was reacted with excess $LiAlH_4$ in ether and then worked up in the usual fashion to afford 6 mg (~73%) of alcohol **25** [mp 86 °C (softens, ~80 °C) from pentane; lit.[35] mp 89 °C or 86–88 °C]. This same alcohol **25** (crystallized from pentane), prepared as above from authentic aldehyde **24**, exhibited mp 85–86 °C (softens, ~81 °C). The mixed mp was 84–85 °C (softens, 79–80 °C). The ^{1}H NMR spectroscopic data and TLC behavior for the two specimens were identical.

14-(Phenylthio)-13-nordrima-6,8-diene (28). To a suspension of lithium aluminum hydride (0.975 g, 25.7 mmol) in 30 mL of ether at −78 °C was slowly added a solution of the diastereomeric mixture of sulfoxides **19** and **19′** (0.656 g, 2.1 mmol) in 3 mL of THF. After 30 min at −78 °C, the green-grey mixture was allowed to warm to room-temperature overnight. The flask was cooled in an ice bath, and the excess of $LiAlH_4$ was destroyed with aqueous Na_2SO_4. After dilution with water and phase separation, the aqueous layer was extracted twice with ether. The combined organic layers were washed with NH_4Cl solution and dried over $MgSO_4$. Removal of solvent followed by flash chromatography (silica gel, 30:1 lbpe ether) afforded 0.422 g (67%) of diene sulfide **28**.

14-(Phenylsulfonyl)-13-nordrima-6,8-diene (29). Diene sulfide **28** (0.524 g, 1.76 mmol) was dissolved in 2 mL of dichloromethane and 50 mL of methanol. Oxone[32] (1.61 g, 1.4 molar equiv) in 5 mL of water was added at 0 °C. After addition was complete, the heterogeneous mixture was stirred at room temperature for 15 h. Water (50 mL) was added, and the organic layer was extracted 3 times with CH_2Cl_2. The combined organic phases were washed with water and brine and dried over $MgSO_4$. Flash chromatography (silica gel, 2:1 lbpe ether) afforded 0.486 g (84%) of diene sulfone **29** as a white solid (mp 89 °C, crystallized from 4:1 SSB EtOAc).

14-(Phenylsulfonyl)-13-nordrim-8-ene (30). A solution of diene sulfone **29** (0.160 g, 0.48 mmol) in 20 mL of 95% EtOH was hydrogenated in the presence of 0.20 g of 5% Pd/C at room temperature (1 atm). After the uptake of 1 molar equiv of hydrogen, the mixture was stirred under hydrogen for an additional hour. The catalyst was filtered off under slight vacuum through a short silica gel column. After evaporation of solvent, the sulfone **30** (0.149 g, 93%) was obtained as a white amorphous solid, which showed very limited solubility in a variety of solvents (hexane, toluene, ether, THF, ethyl acetate, and ethanol). Its ^{1}H NMR spectrum exhibited the following data: δ ($CDCl_3$) 0.82, 0.88, 0.92 (3 H each, $C_{11,12,15}$–$3CH_3$, three s), 3.72 (2 H, 2 H_{14}, br s), 5.70 (1 H, H_8, t, J ~ 3.6 Hz), 7.5–7.7 (3 H, Ar, m), 7.9–8.1 (2 H, Ar). Due to the difficulty in further purifying this amorphous material of limited

solubility, the crude product was carried on to the next step.

13-Nordrim-9(14)-ene (31). Oven-dried $CuCl_2$ (0.478 g, 3.56 mmol) was added slowly with ice-cooling to a suspension of $LiAlH_4$ (0.270 g, 7.12 mmol) in 20 mL of THF. The resulting black heterogeneous mixture was stirred at room temperature for 45 min before a suspension of crude sulfone **30** (0.296 g, 0.89 mmol) in 5 mL of THF (plus three more THF rinses) was added. The mixture was refluxed for 8.5 h. After the solution was cooled to room temperature, 30 mL of a NaCl solution was added, followed by phase separation and three ether extractions. The combined organic layers were washed with brine and water and dried ($MgSO_4$). Flash chromatography (silica gel, lbpe) afforded after vacuum drying an olefinic mixture (0.143 g of an oil, 83% based on $C_{14}H_{24}$) with **31** as the major product. The details of the ^1H NMR spectra (90 and 200 MHz) were as follows: δ ($CDCl_3$) 0.84, 0.86, 1.06 (3 H each, $C_{11,12,15}$-$3CH_3$, three s), 4.49 (2 H, 2 H_{14}, br s with fine structure, $W \sim 3$ Hz). Most notably, the δ 4.49 signal is characteristic of the exocyclic olefinic linkage. The hydrocarbon **31** could not be resolved by HPLC, and, accordingly, the material was ozonized directly to the known ketone as described in the next section.

5,5,8aβ-Trimethyl-3,4,4aα,5,6,7,8,8a-octahydronaphthalen-1(2*H*)-one (32). The crude olefinic mixture (preceding experiment; 0.143 g, 0.74 mmol based on $C_{14}H_{24}$) was dissolved in 2 mL of dichloromethane and 20 mL of methanol. The ozonolysis was carried out at -78 °C until the appearance of the blue color. Excess ozone was flushed out with N_2, a mixture of 5 mL of 30% H_2O_2 and 5 mL of acetic acid was added, and the dry ice bath was removed. After reaching room temperature the mixture was refluxed for 1 h, water was added, and the aqueous layer was extracted 3 times with CH_2Cl_2. The combined organic phases were washed successively with water, KI, $Na_2S_2O_3$, $NaHCO_3$, and NaCl solutions and dried over $MgSO_4$. Flash chromatography (silica gel, 12:1 lbpe ether) afforded **32** (0.071 g, 50%). The product proved pure by ^1H (90 and 200 MHz) and ^{13}C NMR (50.4 MHz): ^1H NMR δ ($CDCl_3$) 0.89, 0.92, 1.14 (3 H each, $C_{9,10,11}$-$3CH_3$, three s), 0.8-2.7 (13 H, ring protons, m); ^{13}C NMR δ ($CDCl_3$) 18.1, 18.6, 20.9, 22.0, 26.3, 33.1, 34.1, 37.5, 41.6, 49.0, 53.5, 215.8. The ^1H NMR spectrum (90 MHz) of this specimen was identical with the spectrum kindly provided by Dr. G. Ohloff (Firmenich, Geneva, Switzerland). The ketone **32** showed the following optical data: $[\alpha]^{20}_D$ +30.8° ($CHCl_3$, *c* 0.05) and $[\alpha]^{20}_D$ +35.9° (CH_3OH, *c* 0.05); Ohloff reported $[\alpha]^{20}_D$ -35° (neat).[36]

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Supplementary Material Available: Spectral (^1H and ^{13}C NMR, UV, IR, and mass spectra) and analytical data (11 pages). Ordering information is given on any current masthead page.

Divalent Metal Ion Catalysis in the Hydrolysis of Esters of Picolinic Acid. Metal Ion Promoted Hydroxide Ion and Water Catalyzed Reactions

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Abstract: Rate constants have been determined for hydrolysis of a series of phenolic and aliphatic esters of picolinic acid in H_2O. Hydroxide ion, hydronium ion, and water catalyzed reactions were observed in hydrolysis of the phenolic esters. Catalysis by low concentrations of Ni^{2+} and Cu^{2+} occurs even though binding of the metal ions is weak (saturation effects were not observed). Both metal ion promoted water and OH^- catalyzed reactions were observed with the esters having leaving groups with pK_a values of 12.4 or less. Rate enhancements produced by 0.01 M Ni^{2+} and 0.001 M Cu^{2+} range from 10- to near 200-fold in the pH-independent water reactions and from 10^2- to over 10^5-fold in the OH^- catalyzed reactions. Significant metal ion catalysis was not observed in the hydrolysis of 4-nitrophenyl isonicotinate or 8-(5-nitroquinolyl) isonicotinate; therefore, metal ion catalysis in the hydrolysis of the esters with the pyridine nitrogen ortho to the ester function must be associated with a chelation effect. The rate constants k_0 and k_{OH} for hydrolysis of the picolinate esters in the metal ion promoted water and OH^- catalyzed reactions are little affected by the leaving group ($\beta_{lg} \sim 0$) for leaving groups with pK_a values ranging from 4.1 with 2,4-dinitrophenol to 12.4 with trifluoroethanol, and ratios of k_{OH}/k_0 are nearly constant. This indicates that there is little or no C–O bond breaking in the critical transition state, i.e., in both reactions the nucleophilic attack step is rate determining. When the leaving group is ethanol, then k_{OH} is markedly less than in the case of the trifluoroethyl ester, and a metal ion promoted water reaction is not detected even at pH values as low as 4. Thus, a change in rate-determining step has occurred with the change in the leaving group. Likewise only metal ion promoted OH^- catalysis is observed with ethyl 6-carboxypicolinate. Rate enhancements produced by saturating concentrations of Ni^{2+} and Cu^{2+} are in that case 2.7×10^4- and 1.3×10^5- fold, respectively. Intramolecular general base catalysis does not occur in the metal ion promoted water reaction of 8-quinolyl picolinate or 8-(5-nitroquinolyl) picolinate. With the nitro substituted esters of picolinic acid a metal ion promoted formate and acetate ion catalyzed reaction takes place which is quite dependent on leaving group ability. It is likely that formate and acetate ions are attacking the metal ion complexes as nucleophiles.

Carboxypeptidase A is a Zn(II) metalloenzyme that catalyzes the hydrolysis of peptides and O-acyl derivatives of α-hydroxy carboxylic acids.[2] The metal ion presumably complexes the carbonyl oxygen of peptide substrates.[2-4] X-ray crystallographic analysis at 2-Å resolution also revealed the presence of the carboxyl group of glutamic acid-270 in the active site.[2-4] Both nucleophilic and general base mechanisms have been suggested for the enzyme involving Glu-270[3-5] as well as nucleophilic attack by Zn(II)-

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