Chair Topology of the Palladium Dichloride Catalyzed Cope Rearrangement of Acyclic 1,5-Dienes[1]

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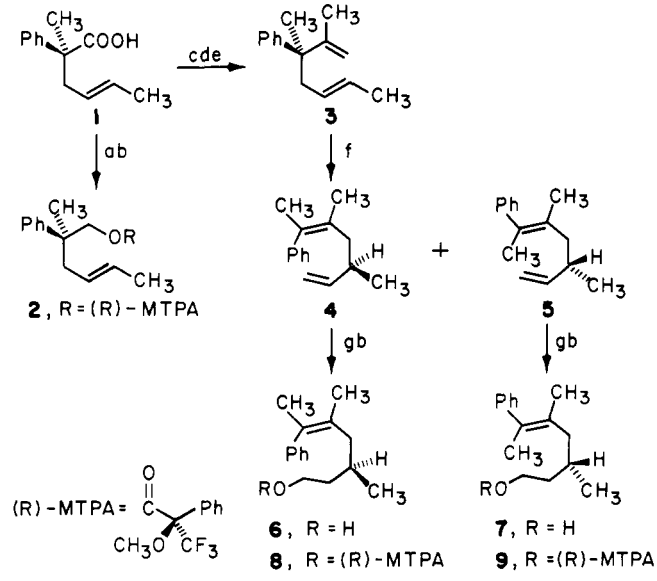
Abstract: The palladium dichloride catalyzed Cope rearrangement of (3*R*,5*E*)-2,3-dimethyl-3-phenyl-1,5-heptadiene (**3**) occurs at room temperature with virtually complete chirality transfer to afford (2*Z*,5*R*)-3,5-dimethyl-2-phenyl-2,6-heptadiene (**4**) and (2*E*,5*S*)-3,5-dimethyl-2-phenyl-2,6-heptadiene (**5**) in a 7:3 ratio and 86% yield. This is the same sense of asymmetric induction as observed in the thermal (240 °C) Cope rearrangement of **3** and demonstrates that the palladium dichloride catalyzed Cope rearrangment of **3** occurs preferentially ($\Delta\Delta G^{\ddagger} > 1.9$ kcal/mol at 25 °C) with a chair topology. Possible mechanisms for palladium(II)-catalyzed Cope rearrangements are considered in light of this stereochemical result.

That palladium dichloride could promote the Cope rearrangement of 1,5-dienes was first described in 1966.[2] In this report, Jonassen and co-workers described the treatment of excess *cis,trans*-1,5-cyclodecadiene with bis(benzonitrile)palladium dichloride at room temperature to give the crystalline palladium dichloride complex of *cis*-1,2-divinylcyclohexane.[2] The similar transformation of a series of substituted *cis,trans*-1,5-cyclodecadienes and a germacrene *trans,trans*-1,5-cyclodecadiene to palladium dichloride complexes of substituted divinylcyclohexanes has been described by Heimbach[3] and Sutherland.[4] Heimbach and co-workers have also reported a detailed study of the rearrangement of a series of *cis*-1,2-divinylcyclobutanes to give palladium dichloride complexes of 1,5-cyclooctadienes.[5] In 1980, we reported,[1] for the first time, that palladium(II)-promoted Cope rearrangements could be conducted in a *catalytic fashion* to produce the rearranged diene rather than the diene–palladium dichloride complex. The palladium dichloride catalyzed rearrangements of unstrained, acyclic 1,5-dienes occurred readily at room temperature, and a catalytic rate acceleration of 10^{10} (1 M $PdCl_2$) was estimated.[1]

Mechanistic aspects of palladium(II)-catalyzed Cope rearrangements have been virtually unexplored. Mechanisms involving cleavage of the allylic C–C bond to form,[2,6,7] for example, a bis(η^3-allyl)palladium(IV) intermediate[7] have been proposed, while we have noted that the alkyl substituent effects observed in our study[1] could be rationalized by a very different mechanism (a "cyclization-induced rearrangement")[8] involving the intervention of cyclohexyl intermediates. The palladium dichloride catalyzed Cope rearrangement of acyclic 1,5-dienes provides an ideal arena to explore the mechanism of these catalyzed reorganizations. In particular, the rearrangment in acyclic systems is not biased by ring stereochemistry,[9] and thus allows the intrinsic topology of the catalyzed transformation to be examined. In this paper, we report that the bis(acetonitrile)palladium dichloride catalyzed Cope rearrangment of (3*R*,5*E*)-2,3-dimethyl-3-phenyl-1,5-heptadiene occurs with complete 1,4 transfer of chirality. This transformation moreover occurs preferentially with a chair topology similar to that established for the thermal Cope rearrangement by the classic experiments of Doering and Roth[10] and the related experiments of Hill and Gilman.[11] The high stereospecificity demonstrated for this catalyzed conversion enhances the potential utility of this rearrangment in synthesis as well as significantly restricts the allowable mechanisms for palladium(II)-catalyzed Cope rearrangements.

Scheme I



[a] $LiAlH_4$, ether, reflux. [b] (+)-MTPA-Cl (1.5–10 equiv), pyridine (1.5–10 equiv), CH_2Cl_2, room temperature. [c] EtI, K_2CO_3, DMF, 50 °C. [d] MeLi (2.0 equiv), THF, -78 °C to room temperature. [e] $SOCl_2$, pyridine, 2 °C. [f] $(MeCN)_2PdCl_2$ (0.09 equiv), THF, room temperature. [g] 9-BBN, THF, room temperature; HOOH, NaOH, room temperature.

Results

Our investigation was identical in strategy with the earlier study of the thermal Cope rearrangement by Hill and Gilman.[11] Unfortunately, we could not use the diene employed by these authors, (3*R*,5*E*)-3-methyl-3-phenyl-1,5-heptadiene, since this diene failed to undergo palladium dichloride catalyzed Cope rearrangement.[1] We, therefore, utilized (3*R*,5*E*)-2,3-dimethyl-3-phenyl-1,5-heptadiene (**3**), which was prepared as shown in Scheme I. Enantiomer ratios and absolute configuration assignments were made by correlation of the Cope products to heptenols **6** and **7**, authentic samples of which were prepared from optically active (*R*)-citro-

(1) Catalyzed Sigmatropic Rearrangements. 6. For part 5, see: Overman, L. E.; Knoll, F. M. *J. Am. Chem. Soc.* **1980**, *102*, 865.
(2) Trebellas, J. C.; Olechowski, J. R.; Jonassen, H. B. *J. Organomet. Chem.* **1966**, *6*, 412.
(3) Heimbach, P.; Molin, M. *J. Organomet. Chem.* **1973**, *49*, 477.
(4) Brown, E. D.; Sam, T. W.; Sutherland, J. K.; Torre, A. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2326.
(5) Heimbach, P.; Molin, M. *J. Organomet. Chem.* **1973**, *49*, 483.
(6) Heck, R. F. "Organotransition Metal Chemistry. A Mechanistic Approach"; Academic Press: New York, 1974, p 114.
(7) Hamilton, R.; Mitchell, T. R. B.; Rooney, J. J. *J. Chem. Soc., Chem. Commun.* **1981**, 456.
(8) Cf. Overman, L. E.; Campbell, C. B.; Knoll, F. M. *J. Am. Chem. Soc.* **1978**, *100*, 4822.
(9) Because of ring-strain effects, thermal Cope rearrangment of *cis,trans*-1,5-cyclodecadienes and 1,2-*cis*-divinylcyclobutanes can occur in a concerted manner via only chair and boat transition states, respectively.
(10) Doering, W. von E.; Roth, W. R. *Tetrahedron* **1962**, *18*, 67.
(11) (a) Hill, R. K.; Gilman, N. W. *J. Chem. Soc., Chem. Commun.* **1967**, 619. (b) Gilman, N. W. Ph.D. Thesis, Princeton University, 1967; *Diss. Abstr. B* **1967**, *28* (8), 3220.

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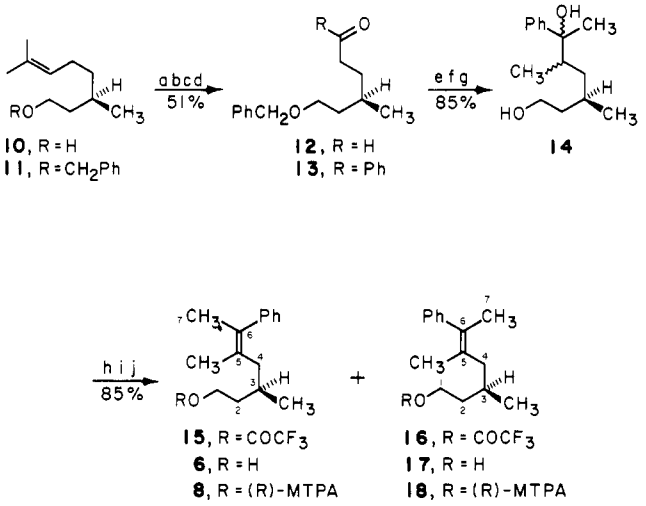
Scheme II



[a] NaH, $PhCH_2Br$. [b] O_3, MeOH, -78 °C; Me_2S. [c] PhLi, -78 °C to room temperature. [d] PCC, CH_2Cl_2. [e] LDA, -78 °C; MeI, -78 °C to room temperature. [f] MeMgBr. [g] H_2, Pd-C. [h] CF_3COOH, $(CF_3CO)_2O$, $CHCl_3$, 60 °C. [i] Na_2CO_3, MeOH. [j] (+)-MTPA-Cl, pyridine, room temperature.

nellol, as outlined in Scheme II.

Preparation of Chiral Diene 3. *trans*-2-Methyl-2-phenyl-4-hexenoic acid was prepared and resolved with dehydroabiethylamine by the procedure of Gilman.[11b] The (2*S*,4*E*)-(+)-acid **1** obtained in this manner had been previously correlated[11] with 2-methyl-2-phenylbutyric acid of known absolute configuration.[12] Our sample of **1** was shown to have a 99% enantiomeric excess by quantitative 250-MHz ^1H NMR analysis of the (*R*)-α-methoxy-α-((trifluoromethyl)phenyl)acetyl ester[13] **2** [(*R*)-MTPA ester]. Esterification of **1** gave the ethyl ester, which contained <2% of the corresponding *Z* isomer by gas chromatography (GC) analysis. Conversion to the tertiary alcohol, followed by dehydration, gave the (3*R*,5*E*)-(+)-diene **3** in 41% yield from **1**. Diene **3** showed a characteristic[14] signal for an *E* vinylic methyl group at 18.2 ppm in the ^{13}C NMR spectrum and was 98.2% pure by capillary GC analysis.[15]

Preparation of (*R*- and *S*-) and (*E*- and *Z*-)3,5-Dimethyl-6-phenylhepten-1-ols from (+)-Citronellol. The standard reaction sequence outlined in Scheme II was used to convert (*R*)-(+)-citronellol (29% enantiomeric excess)[16] to the (*R*)-keto ether **13**. The 2:1 mixture of *R* and *S* enantiomers was intentionally employed to facilitate NMR[13] assignments. Enolate methylation, methyl Grignard addition, and debenzylation converted **13** to the (3*R*)-heptanediols **14**, which were a complex mixture of diastereomers. Dehydration of the *tert*-benzylic alcohol functionality of **14** was accomplished at 60 °C with a mixture of trifluoroacetic acid and trifluoroacetic anhydride and gave in 85% yield a 2.5:1 mixture of heptenyl trifluoroacetates **15** and **16**. The in situ formation of the *prim*-trifluoroacetate was likely essential for the success of this dehydration, since attempts to deprotect benzyl ether derivatives of **6** and **17** under acidic conditions invariably resulted in cyclic ether formation. Separation by preparative high-performance liquid chromatography (HPLC) gave a pure sample of the major (3*R*,5*Z*)-ester **15** and an enriched sample of the minor (3*R*,5*E*)-ester **16**. The *Z* isomer **15** showed a triplet at δ 4.24 for the C_1 hydrogens, broadened singlets for the vinylic methyls at δ 1.95 (C_7–H) and 1.76 (C_5–CH_3), and a doublet for an unusually shielded secondary methyl group at δ 0.76 in the 250-MHz ^1H NMR spectrum. The minor *E* isomer **16** showed ^1H NMR signals for the C_1 hydrogens at δ 4.45, broadened singlets for the vinylic methyls at δ 1.95 (C_7–H) and 1.52 (C_5–CH_3), and a doublet for a secondary methyl at δ 1.10. Deacylation with sodium carbonate and methanol gave alcohols **6** and **17**, which showed similar characteristic differences in their 250-MHz ^1H NMR spectra. Thus, the C_1 hydrogens and the secondary methyl were upfield in the *Z* isomer **6** (3.54 and 0.73 ppm, respectively, vs. 3.72 and 0.97 ppm for **17**), while the C_5 vinylic methyl was downfield in the *Z* isomer (1.77 ppm vs. 1.53 ppm for **17**).

The stereochemical assignments for **15** and **16** are not easy to make, since the double bond in question is tetrasubstituted. However, two lines of evidence leave little doubt about the correctness of our assignments: (1) ^1H NMR assignments for the methyl groups in 2,3-dimethyl-1-phenylpropene have been made.[17] The β-methyl cis to the aromatic ring is upfield,[18] presumably reflecting shielding of this group by the aromatic ring that is twisted out of conjugation in these congested systems.[19] (2) The C_1 hydrogens and the secondary methyl group of **6** and **15** are observed in the ^1H NMR spectrum upfield by 0.2–0.25 ppm of corresponding hydrogens of the *E* isomers. Importantly, this difference reflects special magnetic shielding in the *Z* stereoisomer, since the "normal" position[20] for an allylic methyl is that observed for the *E* isomer. Shielding by the π electrons of the aromatic ring is possible only for the *Z* stereoisomer and nicely rationalizes this unusual NMR behavior. Aromatic shielding of this type is well-known, of course, in rigid systems and has been observed in flexible systems as well.[21]

Treatment of the (*Z*)-alcohol **6** with an excess of (+)-α-methoxy-α-((trifluoromethyl)phenyl)acetyl chloride[13] gave the diastereomeric (*R*)-MTPA esters **8**. Differences in the ^{19}F, ^{13}C, and ^1H NMR spectra were observed for the two diastereomers, and the ^1H NMR chemical shift differences of the secondary methyl groups were judged most useful for the analysis of small samples: major *R*,*R* diastereomer δ 0.715; minor *R*,*S* diastereomer δ 0.706. Careful integration of these signals at 500 MHz indicated a (1.6 ± 0.2):1.0 ratio of diastereomers, which when corrected for the optical purity of the (+)-MTPA chloride used (96% ee)[13] implied an enantiomeric excess of 23% for alcohol **6**, in reasonable agreement with the optical purity of the starting (+)-citronellol. Similar differences were observed for the secondary methyl groups of (*R*)-MTPA esters **18**: major *R*,*R* diastereomer δ 0.955; minor *R*,*S* diastereomer δ 0.946.

Cope Rearrangement of (3*R*,5*E*)-Diene 3. Treatment of diene **3** with 9 mol % of bis(acetonitrile)palladium dichloride in tetrahydrofuran at room temperature for 20 h gave, in 86% yield, a 7:3 mixture of the Cope products **4** and **5**. These isomers were very difficult to separate, but could be resolved by tedious preparative GC. The major *Z* isomer **4**[22] showed ^1H NMR signals for the vinylic methyls at δ 1.94 and 1.77 and a characteristic doublet for an unusually shielded (vide supra) secondary methyl group at δ 0.80. The minor *E* isomer **5** showed these ^1H NMR signals at δ 1.94, 1.54, and 1.06, respectively.

Hydroboration of **4** and **5** with 9-borabicyclo[3.3.1]nonane[23] gave the primary alcohols **6** and **7** in good yield. These alcohols

(12) Cram, D. J. *J. Am. Chem. Soc.* **1952**, *74*, 2149. Mitsui, S.; Imaizumi, S.; Senda, Y.; Konno, K. *Chem. Ind. (London)* **1964**, 233.

(13) (a) Dale, J. A.; Dull, D. A.; Mosher, H. *S. J. Org. Chem.* **1969**, *34*, 2543. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(14) Cf. de Haan, J. W.; van de Ven, L. J. M. *Org. Magn. Reson.* **1973**, *5*, 147.

(15) A 25-m SE-30 glass capillary column was used for this analysis.

(16) Klyne, W.; Buckingham, J. "Atlas of Stereochemistry. Absolute Configurations of Organic Molecules", 2nd ed.; Oxford Press: New York, 1974; Vol. 1, p 75.

(17) Barltrop, J. A.; Thomson, A. T. *J. Chem. Soc.* **1968**, 155.

(18) Chemical shifts[17] are 1-methyl (δ 1.92), 2(*Z*)-methyl (δ 1.56), and 2(*E*)-methyl (δ 1.78). These assignments were based on the observation of five-bound coupling between the methyl groups at δ 1.56 and 1.92. That ^5J (transoid) should be greater than ^5J (cisoid) is considered reliable; cf.: Gaudemer, A. In "Stereochemistry: Fundamentals and Methods"; Kagan, H. B., Ed.; Georg Thieme: Stuttgart, 1977; Vol. 1, p 47.

(19) This ^1H NMR behavior is also seen with trisubstituted β,β-dimethylstyrenes; Cf.: Rottendorf, H.; Sternhell, S.; Wilmshurst, J. R. *Aust. J. Chem.* **1965**, *18*, 1759.

(20) For example, the allylic methyl group of 3-methyl-1-hexene is observed at δ 0.98: Aldrich Library of NMR Spectra, *1*, 22c.

(21) Cf.: Bovey, F. A. "Nuclear Magnetic Resonance Spectroscopy"; Academic Press: New York; 1969; pp 64–71.

(22) This isomer was incorrectly assigned the *E* configuration in our original publication[1] describing this rearrangement in the achiral series.

(23) Brown, H. C.; Liotta, R.; Kramer, G. W. *J. Org. Chem.* **1978**, *43*, 1058.

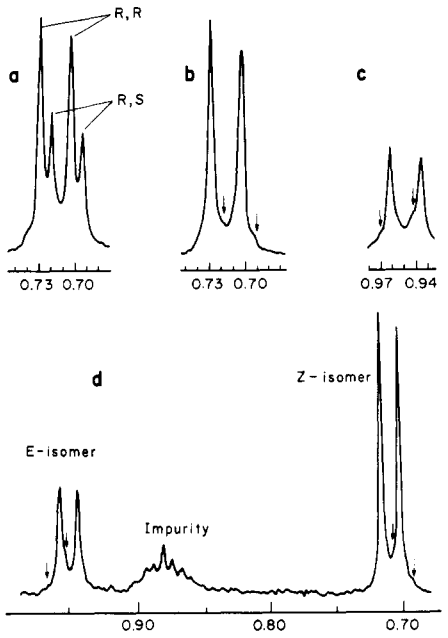


Figure 1. (a) 250-MHz ^{1}H NMR spectra of the 2:1 mixture of (*R,R*)- and (*R,S*)-MTPA esters **8** prepared from 29% ee (*R*)-citronellol. (b) 250-MHz ^{1}H NMR spectra of the (*R,R*)-MTPA ester derived from *Z* Cope product **4** produced by palladium dichloride catalysis. The arrows indicate the chemical shift of the corresponding *R,S* diastereomer. (c) 250-MHz ^{1}H NMR spectra of the (*R,S*)-MTPA ester derived from *E* Cope product **5** produced by palladium dichloride catalysis. The arrows indicate the chemical shift of the corresponding *R,R* diastereomer. The chemical shift scale is identical for spectra a–c. (d) 500-MHz ^{1}H NMR spectra of the (*R*)-MTPA esters prepared from the 7:3 mixture of **4** and **5** produced by palladium dichloride catalysis. The arrows indicate the chemical shift of the minor diastereomers. The impurity at δ 0.88 comes from 9-BBN.

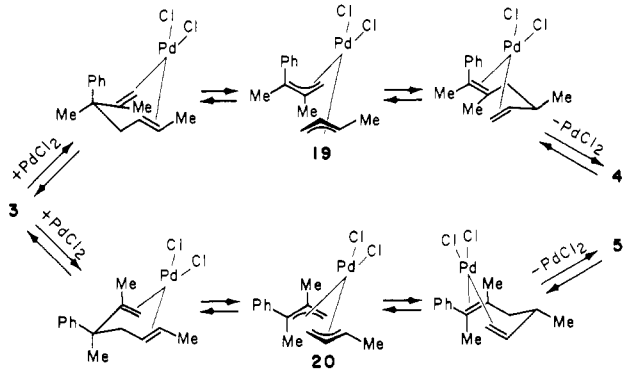
were identical with authentic samples prepared from citronellol. Esterification with (+)-MTPA chloride and ^{1}H NMR analysis of the corresponding (*R*)-MTPA esters as described in the previous section showed that the (*Z*)-alcohol **6** (and corresponding diene **4**) had the *R* configuration and an enantiomeric excess of 97 ± 5%, and the (*E*)-alcohol **7** (and corresponding diene **5**) had the *S* configuration and a similar (96 ± 6%) enantiomeric purity. Typical 250- and 500-MHz ^{1}H NMR spectra for the (*R*)-MPTA esters **8** and **9** are shown in Figure 1.

Diene **3** underwent thermal Cope rearrangement at 240 °C for 16 h to give, after filtration through silica gel, a 1:1 mixture of the Cope products **4** and **5** in 50% yield. Hydroboration and analysis as the (*R*)-MPTA esters showed that the same enantiomer of each diene was formed in the thermal Cope rearrangement as was produced in the palladium(II)-catalyzed rearrangement. The enantiomer excess of (*R*)-**4** and (*S*)-**5** produced in the thermal rearrangement was ~90%.

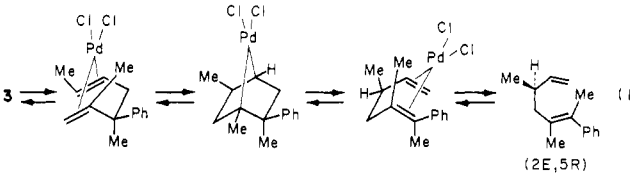
Discussion

The palladium dichloride catalyzed Cope rearrangement of (3*R*,5*E*)-2,3-dimethyl-3-phenyl-1,5-heptadiene (**3**) occurred with virtually complete chirality transfer to afford the 2*Z*,5*R* and 2*E*,5*S* Cope products **4** and **5**. This is the same sense of asymmetric induction as observed in the thermal Cope rearrangement[11] and unequivocally demonstrates that the palladium(II)-catalyzed reaction also occurs preferentially ($\Delta\Delta G^{\ddagger} > 1.9$ kcal/mol at 25 °C)[24] with a chair topology. The formation of the (*Z*)-alkene isomer as the major product from the catalyzed rearrangement of diene **3** is also nicely consistent with the chair topology of this transformation, since 1-methyl-1-phenylcyclohexane is known[25] to prefer a chair conformation with the phenyl group axial.

Scheme III



Several mechanistic possibilities for palladium(II)-catalyzed Cope rearrangements are excluded by this experiment. The observation of high chirality transfer effectively precludes mechanisms involving *separated* allyl fragments. Also ruled out are mechanisms that involve suprafacial formation and fragmentation of metallacyclopentane (specifically palladabicyclo[2.2.1]heptane) intermediates.[26,27] A mechanism of this type would have a boat topology and would produce Cope products enantiomeric with those observed (illustrated for the formation of the *E* Cope product in eq 1).



At least two mechanisms can be written that are consistent with the stereochemical results of this study. One such mechanism is illustrated in Scheme III.[28] In this mechanism, a palladium dichloride diene complex undergoes oxidative addition of the allylic C–C bond to form a bis(η^3-allyl)palladium(IV) intermediate.[2,6,7] These intermediates (**19** and **20**) can then reductively eliminate to give palladium(II) dichloride complexes of the starting diene or the Cope products. For a mechanism of this type to be consistent with the chirality transfer results, the bis(η^3-allyl)palladium(IV) intermediates must have several specific characteristics: (1) They must be formed and consumed in a conformation in which the two η^3-allyl groups are mutually trans.[29,30] If these intermediates were produced and reacted in conformations with the two η^3-allyl groups mutually cis, the overall conversion would have a boat topology and lead to the incorrect sense of asymmetric

(24) Using 92% ee as a lower limit for the enantiomeric purity of Cope product **4** and assuming that the starting diene was enantiomerically pure, it follows that $\Delta\Delta G^{\ddagger} = RT \ln (96/4)$. This analysis assumes that there are only two competing pathways, one of chair topology giving (5*R*)-**4** and one of boat topology giving (5*S*)-**4**.

(25) Cf.: Eliel, E. L.; Manoharan, M. *J. Org. Chem.* **1981**, *46*, 1959 and references therein.

(26) (a) Palladacyclopentanes are known for palladium(II), although to our knowledge they have not been produced from coordinated dienes. Cf.: Diversi, P.; Ingrosso, G.; Lucherini, A. *J. Chem. Soc., Chem. Commun.* **1978**, 735. (b) The reversible formation of nickel acyclopentanes from bis(olefin)–nickel(0) complexes is well established: Grubbs, R. H.; Miyashita, A. *J. Am. Chem. Soc.* **1978**, *100*, 1300.

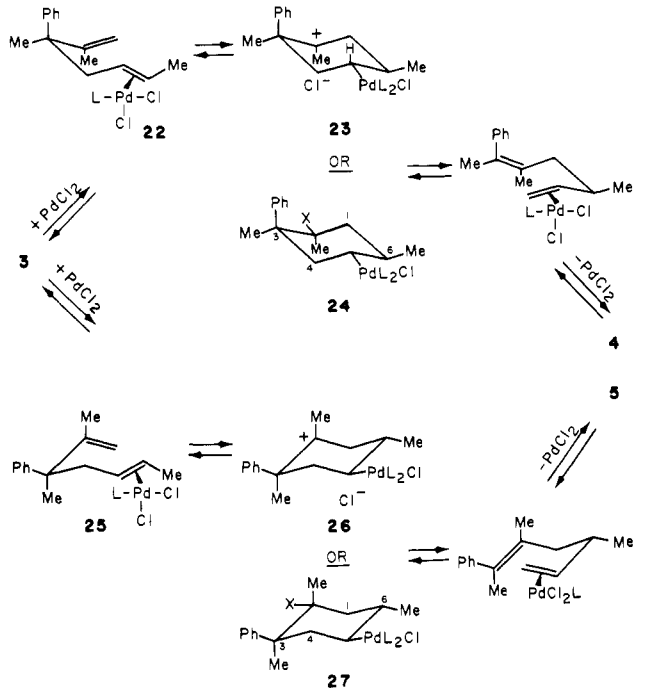
(27) A mechanism involving antarafacial addition to one of the π bonds and its reverse, antielimination, is not ruled out by this experiment.

(28) An exactly analogous mechanism proceeding via palladium(0) diene complexes and bis(η^3-allyl)palladium(II) intermediates could be written. Since the catalyzed Cope rearrangement has been described for palladium(II) salts only[1-6] and we have found $Pd(Ph_3P)_4$ to be an ineffectual catalyst,[1] we feel there is no reason, at this time, to consider a mechanism of this type.

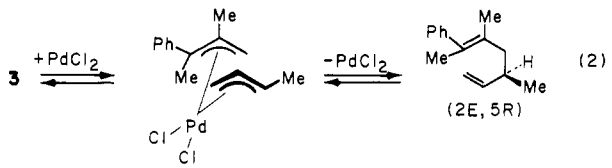
(29) (a) For a review of allyl–metal compounds which discusses conformational isomerism, syn–anti isomerism, and fluxional behavior of η^3-allyl ligands, see: Clarke, H. L. *J. Organomet. Chem.* **1974**, *80*, 155. (b) For a general discussion of (η^3-allyl)palladium compounds, see: Maitlis, P. M. "The Organic Chemistry of Palladium"; Academic Press: New York, 1971; Vols. 1 and 2.

(30) For a recent detailed structural study of bis(η^3-allyl)metal complexes of nickel, palladium, and platinum, see: Henc, B.; Jolly, P. W.; Saltz, R.; Wilke, G.; Benn, R.; Hoffman, E. G.; Mynott, R.; Schroth, G.; Seevogel, K.; Sekutowski, J. C.; Krüger, C. *J. Organomet. Chem.* **1980**, *191*, 425.

Scheme IV

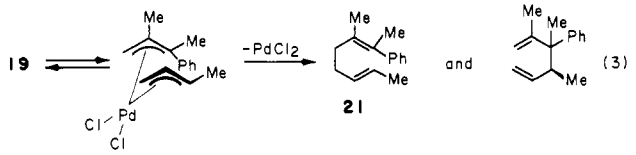


induction (illustrated for the formation of the *E* Cope product in eq 2). (2) Equilibration[29,30] of the initially formed trans-



(2)

bis(η^3-allyl) intermediates with the related cis conformers and reductive elimination of the latter could also not occur as this would lead to the formation of products of formal [1,3] sigmatropic rearrangement. This result is illustrated for intermediate **19** in eq 3; diene **21**, if formed, would have been observed since it should



(3)

be more stable than the observed Cope products. (3) Equilibration of the allyl ligands of the bis(η^3-allyl) intermediates by η3-allyl–η^1-allyl interconversions cannot occur on the time scale of the catalyzed Cope rearrangement. Such fluxional behavior could result[29,30] in inverting the stereochemistry of each allyl fragment (as well as interchanging syn and anti η^3-allyl substituents) and thus could lead to racemization.

Whether these properties are reasonable for bis(η^3-allyl)palladium(IV) intermediates is currently impossible to say, since palladium(IV) complexes of this type are not known. The related palladium(II) complexes are characterized, and in solution[31] two isomers of similar energy (believed to be the cis and trans conformers) have been observed for $(\eta^3\text{-allyl})_2$Pd.[29,30] These isomers are reported to interconvert readily below room temperature as well as undergo facile syn–anti equilibration of the η^3-allyl ligands.[29,30,32]

A second mechanism for the palladium(II)-catalyzed Cope rearrangement consistent with a chair topology is outlined in Scheme IV. Palladium dichloride complexation with the 5,6 double bond of the starting diene **3** could occur to give either the (5*R*,6*R*)-olefin complex **22** or the 5*S*,6*S* complex **25**. Attack of the noncoordinated 1,2 double bond from the face opposite the palladium could lead to the chair cyclohexyl cations **23** and **26**, or, perhaps more likely in tetrahydrofuran, the covalent cyclohexane intermediates **24** and **27** (where X is a tetrahydrofuran molecule). The spatial alignment of the C–Pd, C–X, and 3,4 or 1,6 σ bonds in these cyclohexyl intermediates is ideal for fragmentation[33] to give palladium(II)–olefin complexes of either the starting diene **3** or the Cope products **4** and **5**. The observed sense of asymmetric induction would be rationalized by this "cyclization-induced rearrangement" mechanism[8] if cyclization occurred preferentially to afford chair, rather than boat, cyclohexane intermediates.

That electrophile-promoted cyclizations of a 1,5-diene would occur preferentially to give a chair cyclohexane with equatorially oriented C–Pd and C–X bonds has ample precedent in the extensive investigations during the past 20 years of polyolefin cyclizations.[34] Fragmentations of cyclohexanes substituted at C_1 and C_4 with electrofugal and nucleofugal groups to give 1,5-dienes have considerable precedent also.[33,35,36] Less clear, however, is whether the fragmentation of cyclohexyl intermediates **23** (**26**) or **24** (**27**) would occur rapidly enough (a) for these species to be allowable intermediates in the catalyzed Cope transformation and (b) for fragmentation to completely dominate over cis-β-hydrogen elimination.[29b,42] (σ-Alkyl)cyclohexylpalladium(II) compounds with leaving groups at C_4 are not known; so again no definitive statement about these points can be made. The most closely related reaction of an alkylpalladium(II) compound of which we are aware is the fragmentation of (2-substituted-alkyl)palladium(II) complexes (2 substituent = OR, OCOR) to give alkenes and palladium(II) salts.[37] Elimination reactions of this type are believed to occur very rapidly during the course of palladium(II)-catalyzed vinylic and allylic exchange reactions.[37,38]

Although the data available at this time do not allow exclusion of either of the mechanisms outlined in Schemes III and IV,[39-41] we currently favor the "cyclization-induced rearrangement"

(31) An X-ray crystal structure of the more stable bis(η^3-2-methylallyl)-nickel complex shows the allyl groups to be mutually trans: Uttech, R.; Dietrich, H. *Z. Kristallogr.* **1965**, *122*, 60.

(32) The rate of syn–anti equilibration of a variety of (η^3-allyl)palladium-(II) complexes is known to be increased by the presence of complexing solvents or ligands, which presumably stabilize η^1-allyl intermediates.[30] Many examples of rapid exchange below room temperature have been reported.[30,45]

(33) (a) Becker, K. B.; Grob, C. A. In "Supplement A. The Chemistry of Double-Bonded Functional Groups,"; Patai, S., Ed.; Wiley: New York, 1977; Part 2, Chapter 8. (b) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535. (c) Grob, C. A.; Schiess, P. W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1.

(34) Cf.: Johnson, W. S. *Biorg. Chem.* **1976**, *5*, 51. Sutherland, J. K. *Chem. Soc. Rev.* **1980**, 265.

(35) The closest analogies of which we are aware are the fragmentation of *cis*- and *trans*-1,4-dibromocyclohexanes upon treatment with zinc in refluxing dioxane to give 1,5-hexadienes[36a] and the similar fragmentation,[36b] at or below room temperature, of a large variety of 4-(methansulfonyloxy)-cyclohexyl boranes upon treatment with base.

(36) Cf.: (a) Grob, C. A.; Baumann, W. *Helv. Chem. Acta* **1955**, *38*, 594. Wharton, P. S.; Sumi, Y.; Kretchmer, R. A. *J. Org. Chem.* **1965**, *30*, 234. (b) Marshall, J. A. *Synthesis* **1971**, 229. Marshall, J. A.; Babler, J. H. *Tetrahedron Lett.* **1970**, 3861.

(37) For a review which discusses transformations of this type, see: Henry, P. M. *Adv. Organomet. Chem.* **1975**, *13*, 363.

(38) For example, the palladium(II)-catalyzed exchange of ethyl propenyl ether with propanol to give propyl propenyl ether is rapid at temperatures below −30 °C: McKeon, J. E.; Fitton, P.; Griswold, A. A. *Tetrahedron* **1972**, *28*, 227.

(39) The little information which is available about the structure of palladium dichloride complexes of acyclic 1,5-dienes provides no help in choosing between the mechanisms of Schemes III and IV. Structural data[40] for crystalline (1,5-hexadiene)palladium dichloride are claimed to show that the two vinyl groups coordinated to palladium are eclipsed with respect to the central C_3–C_4 bond (C_S symmetry, rather than the C_2 symmetry of the "chairlike" diene complexes, illustrated in Scheme III).

(40) (a) Zakharova, I. A.; Leites, L. A.; Aleksanyan, V. T. *J. Organomet. Chem.* **1974**, *72*, 283. Zakharova, I. A.: Kukina, G. A.; Kuli-Zade, T. S.; Moissev, I. I.; Yu. Pek, G.; Porai-Koshits, M. A. *Russ. J. Inorg. Chem.* **1966**, *11*, 1364. (b) A similar structure with C_s symmetry is reported for (1,5-hexadiene)nickel tricyclohexylphosphine.[45]

(41) Of course, other mechanisms are certainly possible. For example, palladium(II) could in principle coordinate (and stabilize) a "chair pericyclic transition state" in a way structurally distinct from the process of Scheme III. We plan to investigate this possibility computationally.

mechanism (Scheme IV) for the palladium dichloride catalyzed Cope rearrangement for several reasons: (1) Probably the most characteristic reactions of palladium(II)–olefin complexes is the addition of nucleophiles to form alkylpalladium(II) intermediates.[29b,37,42] Many of these reactions have been shown to involve attack by an external nucleophile from the face opposite the palladium,[37,42,43] and thus the only thing "new" in the cyclization suggested in Scheme IV is that the nucleophile is an intramolecular alkene π bond. (2) No documented examples have been reported of the oxidative addition of a C–C bond to a coordinated palladium(II) intermediate. For that matter, we are not aware of examples of the more likely oxidative addition of C–C bonds to palladium(0) complexes.[44,45] The formation of acetone from the oxidation of 1,5-hexadiene under Wacker conditions ($PdCl_2$, CuCl, $CuCl_2$, O_2, 60 °C) has been interpreted[7] to imply the intermediacy of bis(η^3-allyl)palladium(IV) dichloride; however, other reasonable mechanisms for the formation of acetone can be written.[46] (3) The substituent effects observed in our original study are well rationalized[1] by a "cyclization-induced rearrangement" mechanism. (4) The cyclization of 1,5-dienes with bis(acetonitrile)-palladium dichloride at room temperature to afford cyclohexene products has recently been observed. For example, ethyl 3-methyl-3-cyclohexenylcarboxylate is formed in reasonable yield from ethyl 2-vinyl-4-methyl-4-pentenoate.[48]

Conclusion

The palladium dichloride catalyzed Cope rearrangement of the chiral acyclic 1,5-diene **3** proceeds at room temperature in high yeild with virtually complete transfer of chirality. The stereochemistry of the Cope products **4** and **5** is consistent with a chair topology for the catalyzed transformation similar to that observed for the thermal Cope rearrangement. This stereochemical observation significantly restricts the allowable mechanisms for palladium(II)-catalyzed Cope rearrangments. Moreover, the high chemical and enantiomeric yields of the catalyzed conversion suggest potential applications in organic synthesis.

Experimental Section[49]

(2*S*,4*E*)-2-Methyl-2-phenyl-4-hexenoic Acid (1). This material was prepared and resolved with dehydroabietylamine by the procedure of Gilman:[11b] $[\alpha]^{27}_D$ +39.4° (*c* 7.4, $CHCl_3$). For precise determination of the optical purity of **1**, a 50-mg sample was reduced with $LiAlH_4$ and the resulting alcohol treated in pyridine with 1.5 equiv of (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (95.7% ee) to give the corresponding (*R*)-MTPA ester **2**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.1–7.6 (m, PhH), 5.0–5.5 (m, CH=CH), 4.40 (AB q, J_{AB} = 10.8 Hz, $\Delta\nu_{AB}$ = 53.0 Hz, CH_2O), 3.38 (br s, OCH_3), 2.2–2.5, (d of AB q, *J* = 7.7 Hz, 13.9 Hz, CH_2C=C), 1.57 (br d, *J* = 6.3 Hz, CH_3CH), 1.34 (s, CH_3). The corresponding ester prepared from a sample of racemic alcohol showed characteristic signals for the other diastereomer at δ 4.39 (AB q, J_{AB} = 10.9 Hz, $\Delta\nu_{AB}$ = 36.5 Hz), 1.31 (s, CH_3). Careful integration at 250 MHz of the δ 4.26–4.36 region of the (*R*)-MTPA ester derived from the optically active alcohol showed a 36:1 mixture of diastereomers that, when corrected for the optical purity of the (+)-MTPA chloride employed, indicates that the enantiomeric excess of **1** was 99%.

(3*R*,5*E*)-2,3-Dimethyl-3-phenyl-1,5-heptadiene (3). A solution of 500 mg (2.45 mmol) of **1**, 500 mg (3.6 mmol) of K_2CO_3, 1.0 mL (13 mmol) of freshly distilled ethyl iodide, and 15 mL of dry DMF was stirred at 50 °C for 6 h under a nitrogen atmosphere. Aqueous workup (ether, Na_2SO_4) and chromatographic purification of the organic extract (silica gel, 9:1 hexane:ethyl acetate) gave 374 mg (1.61 mmol) of ethyl (2*S*,4*E*)-2-methyl-2-phenyl-4-hexenoate: >98% pure by GLC analysis[50] (<2% of the cis isomer); IR (film) 1730 (C=O) cm^{-1}.

A solution of this sample in 30 mL of dry THF was treated dropwise over 10 min at −74 °C with 4.0 mL of a 0.98 M solution of methyllithium in ether. After 30 min at −74 °C, the cooling bath was removed, and after 3 h, the reaction was quenched by addition of 10 mL of saturated NH_4Cl solution (pH 8 with NH_4OH). Isolation (ether, $MgSO_4$) gave 300 mg of crude (3*S*,5*E*)-2,3-dimethyl-3-phenyl-5-hepten-2-ol: IR (film) 3480 (OH) cm^{-1}. This sample was immediately dissolved in 25 mL of dry pyridine, treated dropwise over 5 min at 2 °C with 0.40 mL (5.5 mmol) of thionyl chloride, and stirred for an additional 2 h at 2 °C. Aqueous workup (ether, $MgSO_4$) and chromatographic purification of the organic extract (silica gel, 95:5 pentane:ether) by flash chromatography gave 201 mg (41% from **1**) of **3**: GC[15] 98.2% pure; $[\alpha]^{25}_D$ +40.0 ± 0.3° (*c* 0.62, $CHCl_3$);[51] IR (film) 1638, 1600, 1495 cm^{-1} (C=C); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.1–7.3 (m, PhH), 5.35–5.5 (m, *CH*=CH), 5.1–5.3 (, CH=C*H*), 4.9–5.0 (m, CH_2=C), 2.45–2.6 (m, CH_2CH=) 1.62 (dq, *J* = 6.3 and 1.3 Hz, =CHCH_3), 1.49 (br s, CH_3C=), 1.32 (s, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ 151.4 (s), 147.7 (s), 128.2 (2 C, d), 128.0 (d), 127.6 (d), 126,8 (2 C, d), 125.9 (d), 111.1 (t), 47.2 (s), 42.4 (t), 25.5 (q), 20.6 (q), 18.2 (q); mass spectrum, *m/z* (methane CI, relative percent) 201 (MH^+, 2), 145 (63), 131 (19), 123 (27), 119 (100), 105 (31); high-resolution mass spectrum, *m/z* (70 eV) 200.1559 (200.1565 calcd for $C_{15}H_{20}$).

(*R*)-(+)-6-(Benzyloxy)-4-methylhexanal (12). (*R*)-(+)-Citronellol (**10**, 4.97 g, 32 mmol; 28.6% ee; from mixing 1.42 g of 99.1% ee (*R*)-(+)-citronellol,[52] $[\alpha]^{25}_D$ 5.47° (neat), with 3.55 g of racemic citronellol) was added dropwise at 25 °C to a rapidly stirred mixture of 960 mg (40 mmol) of NaH and 18 mL of dry THF. After 1 h, 4.0 mL (34 mmol) of freshly distilled benzyl bromide was added and the resulting mixture was heated at reflux for 1 h. Aqueous workup (1:1 hexane:ethyl acetate, $MgSO_4$) and short-path distillation gave 7.55 g (96%) of pure **11**: bp 108 °C (0.25 mm); $[\alpha]^{25}_D$ +1.19 ± 0.05° (*c* 4.0, $CHCl_3$).

A solution of 16.0 g (65 mmol) of **11** and 30 mL of methanol was treated at −78 °C with 1 equiv of ozone (0.084 g/min; KI end point) following the general ozonolysis procedure of Pappas.[53] Concentration and short-path distillation gave 12.4 g (87%) of pure **12**: bp 112 °C (0.3 mm); $[\alpha]^{25}_D$ 0.51 ± 0.06° (*c* 3.4, $CHCl_3$); IR (CCl_4) 2925, 1724, 1454, 1094 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.8 Hz, CHO), 7.20–7.45 (m, PhH), 4.49 (s, PhCH_2O), 3.45–3.6 (m, CH_2O), 0.90 (d, *J* = 6.6 Hz, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ 202.7, 138.7, 128.5, 127.7, 127.6, 73.1, 68.4, 41.7, 36.6, 29.7, 29.0, 19.4; mass spectrum, *m/z* (isobutane CI, relative percent) 221 (MH^+, 3), 113 (42), 91 (100).

(*R*)-(+)-6-(Benzyloxy)-4-methyl-1-phenyl-1-hexanone (13). A solution of 5.15 g (23.4 mmol) of **12** and 6 mL of dry ether was added dropwise at −78 °C to 48 mmol of phenyllithium in a 7:3 mixture of ether and benzene, and the resulting solution was allowed to warm to room temperature. Aqueous workup (4:1 hexane:ethyl acetate, $MgSO_4$) and purification by flash chromatography (silica gel, 4:1 hexane:ethyl acetate) gave 5.58 g (80%) of 6-(benzyloxy)-4-methyl-1-phenylhexanol as a mixture of diastereomers: IR (CCl_4) 3620, 3465, 1452, 1202, 1097 cm^{-1}; mass spectrum, *m/z* (isobutane CI, relative percent) 281 ($MH^+ - H_2O$, 20), 263 (52), 203 (35), 179 (40), 91 (100).

Following the procedure of Corey,[54] 5.13 g (17.2 mmol) of this sample

(42) Cf.: (a) Collman, J. P.; Hegedus, L. S. "Principles and Applications of Organotransition Metal Chemistry"; University Science Books: Mill Valley, CA, 1980; pp 585–591, 604–624. (b) Trost, B. M. *Tetrahedron* **1977**, *33*, 2615.

(43) For a recent example and references to other stereochemical studies, see: Bäckvall, J. E.; Åkermark, B.; Ljunggren, S. O. *J. Am. Chem. Soc.* **1979**, *101*, 2411.

(44) The reverse of this reaction, reductive elimination of M(0) and a 1,5-diene from bis(η^3-allyl)metal complexes is well-nown for Ni.[29,45]

(45) Henc, B.; Jolly, P. W.; Salz, R.; Stobbe, S.; Wilke, G.; Benn, R.; Mynott, R.; Seevogel, K.; Goddard, R.; Krüger, C. *J. Organomet. Chem.* **1980**, *191*, 449.

(46) For example, oxypalladation of 5-hexen-2-one should occur some of the time[47] to form a 6-hydroxy-5-pallada-2-hexanone intermediate that could fragment to acetone and allyl alcohol.

(47) Kitching, W.; Rappoport, Z.; Winstein, S.; Young, W. G. *J. Am. Chem. Soc.* **1966**, *88*, 2054. Yamamoto, S.; Konaka, T. *Kogyo Kagaku Zasshi* **1966**, *69*, 2137.

(48) Renaldo, A.; Overman, L. E., manuscript in preparation.

(49) General experimental details have been described recently; see: Overman, L. E.; Freerks, R. L.; Petty, C. B.; Clizbe, L. A.; Ono, R. K.; Taylor, G. F.; Jessup, P. J. *J. Am. Chem. Soc.* **1981**, *103*, 2816. In cases where reaction intermediates or products were isolated by "aqueous workup (organic solvent, drying agent)", the procedure was to quench the reaction mixture with H_2O, dilute with the indicated organic solvent, separate the organic layer, extract the aqueous layer several times with the organic solvent, dry the combined organic extracts over the indicated drying agent, and concentrate with a rotary evaporator at reduced pressure. (+)-(α)-Methoxy-α-((trifluoromethyl)phenyl)acetic acid was purchased from Aldrich and converted to the chloride as described by Mosher.[13a] The (*S*)-(+)-α-methoxy-α-((trifluoromethyl)phenyl)acetyl chloride so obtained showed $[\alpha]^{25}_D$ +128.3° (*c* 2.2, CCl_4), which corresponds[13b] to an optical purity of 95.7%.

(50) GLC conditions: 10 ft × $^1/_8$ in. glass column of 10% SP2330 on 100/120 Supelcoport; 140–180 °C at 2 °C/min.

(51) This sample had a purity of 97.5% by capillary GC analysis.[15]

(52) Overberger, C. G.; Kaye, H. *J. Am. Chem. Soc.* **1967**, *89*, 5640. Henrick, C. A.; Anderson, R. J.; Staal, G. B.; Ludvik, G. F. *J. Agric. Food Chem.* **1978**, *26*, 542.

(53) Pappas, J. J.; Keaveney, W. P.; Gancher, E.; Berger, M. *Tetrahedron Lett.* **1966**, 4273.

was oxidized with 9.1 g (42.2 mmol) of pyridinium chlorochromate in 95 mL of dichloromethane to give, after purification by flash chromatography (silica gel, 9:1 hexane:ethyl acetate), 3.93 g (77%) of pure ketone **13**: a colorless liquid; $[\alpha]^{25}_D$ +2.42 ± 0.21° (*c* 0.95), $CHCl_3$): IR (CCl_4) 1689, 1449, 1203, 1098 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.95 (two apparent d, *J* ~ 8.5 Hz, *o*-Ph*H*), 7.2–7.6 (m, PhH), 4.49 (s, $PhCH_2O$), 3.45–3.6 (m, CH_2O), 2.85–3.05 (m, $CH_2C{=}O$), 0.95 (d, *J* = 6.25 Hz, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$) δ 200.7, 138.8, 137.2, 133.0, 128.7, 128.5, 128.2, 127.8, 127.7, 73.1, 68.6, 36.7, 36.4, 31.5, 29.9, 19.7; mass spectrum, *m/z* (isobutane CI, relative percent) 297 (MH^+, 100), 256 (47), 189 (36), 133 (22), 91 (79); mass spectrum, *m/z* (EI, relative percent) 205.1223 (28%, 205.1228 calcd for $C_{13}H_{17}O_2$, $M^{+\cdot} - C_7H_7$).

(3*R*)-3,5-Dimethyl-6-phenyl-1,6-heptanediol (14). A solution of 1.23 g (4.15 mmol) of **13** and 2 mL of dry THF was added dropwise over 5 min at −78 °C to 8.0 mL of a 0.60 M solution of lithium diisopropylamide. After stirring at −78 °C for 30 min, a solution of 0.26 mL (4.2 mmol) of methyl iodide and 1 mL of THF was added dropwise, and the resulting pale yellow solution was stirred at −78 °C for 30 min and allowed to warm to room temperature. Aqueous workup (hexane, $MgSO_4$) gave 1.22 g (95%) of the monoalkylated ketone, a 1:1 mixture of diastereomers which was sufficiently pure for the next step; IR (CCl_4) 1689 cm^{-1}.

Addition of a 1.01-g (3.26 mmol) sample of this material to 5.58 mmol of methylmagnesium bromide in 10 mL of a 5:1 mixture of dry THF and hexane at room temperature followed by heating at reflux for 1 h and aqueous workup (4:1 hexane:ethyl acetate, $MgSO_4$) gave 1.04 g (98%) of (5*R*)-7-(benzyloxy)-3,5-dimethyl-2-phenyl-2-heptanol. This complex mixture of diastereomers was sufficiently pure for the next step; IR (CCl_4) 3612, 3504, 1447, 1368, 1101 cm^{-1}.

Catalytic debenzylation (1 atm of H_2, 10% Pd–C) of a 105-mg (0.322 mmol) sample of this material in 5 mL of ethyl acetate afforded 69.5 mg (91%) of **14** as a complex mixture of diastereomers: a gelatinous colorless solid; $[\alpha]^{25}_D$ +1.44 ± 0.12° (*c* 1.6, $CHCl_3$); IR (CCl_4) 3613, 3366, 1445, 1375, 1050 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.1–7.45 (m, PhH), 3.5–3.7 (m, CH_2O), 0.7–0.95 (at least five d, CH_3CH); mass spectrum, *m/z* (isobutane CI, relative precent) 219 ($MH^+ - H_2O$, 80), 201 (63), 173 (40), 145 (50), 131 (93), 121 (100), 105 (51).

(3*R*,5*Z*)-3,5-Dimethyl-6-phenyl-5-hepten-1-yl Trifluoroacetate (15) and (3*R*,5*E*)-3,5-Dimethyl-6-phenyl-5-hepten-1-yl Trifluoroacetate (16). Trifluoroacetic anhydride (0.34 mL, 2.4 mmol) was added at room temperature to a stirred solution of 290 mg (1.23 mmol) of diol **14** and 15 mL of $CHCl_3$. After 10 min, 0.093 mL (1.2 mmol) of trifluoroacetic acid was added and the resulting solution was heated at 60 °C for 18 h. After cooling to room temperature, the reaction mixture was concentrated and the resulting brown oil was filtered through a short plug of silica gel (20 g, 9:1 hexane:ethyl acetate) to yield 327 mg (85%) of a yellow oil, which 250-MHz ^1H NMR analysis showed to be a 2.5:1 mixture of *Z* and *E* isomers, respectively.

Separation by preparative HPLC (Zorbax PSM-60, 26:1 hexane:ethyl acetate) gave a pure sample of the faster eluting *Z* isomer **15**: a colorless oil; $[\alpha]^{25}_D$ +5.42 ± 1.02° (*c* 0.30, $CHCl_3$); IR (CCl_4) 1784, 1599, 1349, 1150 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.12–7.35 (m, PhH), 7.0–7.1 (m, PhH), 4.24 (t, *J* = 7.0 Hz, CH_2O), 1.95 (br s, $CH_3(Ph)C{=}$), 1.76 (br s, $CH_3(CH_2)C{=}$), 1.5–1.9 (m, 4 H), 1.2–1.4 (m, CH_3CH), 0.76 (d, *J* = 6.3 Hz, CH_3CH); ^{13}C NMR (63 MHz, $CDCl_3$) δ 157.7 (q, *J* = 41.3 Hz, $COCF_3$), 145.5, 133.1, 129.2, 128.7, 128.3, 126.1, 114.9 (q, *J* = 285.5 Hz, CF_3), 66.9, 42.3, 34.7, 28.3, 21.6, 19.5, 17.8; mass spectrum, *m/z* (isobutane CI, relative percent) 315 (MH^+, 21), 314 (30), 201 (43), 145 (80), 105 (100).

A pure sample of the minor *E* isomer **16** could not be obtained. The NMR spectra of **16** could be ascertained, however, from a HPLC fraction that was a 7:3 mixture of **16** and **15**. Spectral data for **16**: ^1H NMR (250 MHz, $CDCl_3$) δ 7.0–7.4 (m, PhH), 4.4–4.5 (m, CH_2O), 2.1–2.25 (m, $CH_2C{=}$), 1.95 (br s, $CH_3(Ph)C{=}$), 1.52 (br s, $CH_3(CH_2)C{=}$), 1.5–1.8 (m, 3 H), 1.2–1.4 (m, CH_3CH), 1.01 (d, *J* = 6.6 Hz, CH_3CH); ^{13}C NMR (63 MHz, $CDCl_3$) δ 155.1 (the only signal for CCF_3 which could be clearly assigned), 145.7, 132.9, 129.6, 128.4, 128.3, 126.1, 111.4 (the only signal for CF_3 which could be clearly assigned), 67.0, 41.6, 35.2, 29.0, 21.3, 20.3, 19.6; mass spectrum, *m/z* (isobutane CI, relative percent) 315 (MH^+, 21), 201 (21), 145 (49), 105 (100).

(3*R*,5*Z*)-3,5-Dimethyl-6-phenyl-5-hepten-1-ol (6) and the (*R*)-MTPA Ester 8. A mixture of 94.8 mg (0.302 mmol) of **15**, 50 mg (0.47 mmol) of Na_2CO_3, and 5 mL of methanol was stirred at room temperature for 1.5 h and concentrated, and the residue was triturated with 10 mL of 9:1 hexane:ethyl acetate to give, after concentration, 65.4 mg (99%) of **6**, a clear thick oil which was homogeneous by TLC: $[\alpha]_D^{25}$ +4.31 ± 0.24° (*c* 0.84, $CHCl_3$); IR (CCl_4) 3642, 3471, 1680, 1204 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.05–7.35 (m, PhH), 3.54 (t, *J* = 7.0 Hz, CH_2O), 1.95 (s, $CH_3(Ph)C{=}$), 1.77 s, $CH_3(CH_2)C{=}$), 1.65–1.9 (m, $=CCH_2$), 1.35–1.50 (m, CH_3CH), 1.1–1.3 (m, CH_2CH_2O), 0.73 (d, *J* = 6.3 Hz, CH_3CH); ^{13}C NMR (63 MHz, $CDCl_3$) δ 146.7, 133.4, 130.7, 129.5, 129.0, 126.7, 61.1, 43.6, 40.5, 29.1, 21.7, 19.8, 17.8; mass spectrum, *m/z* (EI, relative percent) 218.1670 (13, 218.1671 calcd for $C_{15}H_{22}O$), 145 (100), 129 (19) 117 (30), 105 (30), 91 (38).

Following the procedure of Mosher,[13a] an 11.9-mg (0.055 mmol) sample of **6** was treated at room temperature for 2 h with 20.0 mg (0.079 mmol) of (+)-α-methoxy-α-((trifluoromethyl)phenyl)acetyl chloride (95.7% ee) and 0.4 mL of dry pyridine to give 14 mg (59%) of the diastereomeric (*R*)-MTPA esters **8**. The yield was 70% on a 20-mg scale. The crude (*R*)-MTPA esters could be purified, without diastereomer resolution, by flash chromatography (silica gel, 9:1 hexane:ethyl acetate). This sample showed characteristic signals in the 250-MHz ^1H NMR spectrum for the major *R,R* diastereomer at δ 0.715 (d, *J* = 6.25 Hz, CH_3CH) and in the 63-MHz ^{13}C NMR spectrum at δ 28.6. These signals for the minor *R,S* diastereomer were observed at δ 0.706 (d, *J* = 6.25 Hz) and 28.2 in the ^1H and ^{13}C NMR spectra, respectively. A diastereomer ratio of 1.7:1 was obtained from the ^{13}C NMR peaks at 28.6 and 28.2 ppm. The ^1H NMR signals at δ 0.706 and 0.715 were not totally resolved at 250 or 500 MHz (see Figure 1) but could be graphically curve resolved to give a diastereomer ratio of 1.6 ± 0.2:1.

(3*R*,5*E*)-3,5-Dimethyl-6-phenyl-5-hepten-1-ol (17). A 50-mg (0.16 mmol) sample of **16** (containing 30% of **15**) was hydrolyzed as described for **15** to give 31 mg (90%) of **17** (contaminated with 30% of **6**). Spectral data for **17** obtained from this mixture were as follows: ^1H NMR (250 MHz, $CDCl_3$) δ 7.05–7.35 (m, PhH), 3.65–3.8 (m, CH_2O), 2.05–2.2 (m, $=CCH_2$), 1.95 (br s, $CH_3(Ph)C{=}$), 1.53 (br s, $CH_3(CH_2)C{=}$), 1.2–1.8 (m, 3 H), 0.97 (d, *J* = 6.6 Hz, CH_3CH); ^{13}C NMR (63 MHz, $CDCl_3$) δ 145.9, 132.3, 130.3, 128.5, 128.2, 126.0, 61.5, 42.0, 40.2, 29.0, 21.3, 20.4, 19.7; high-resolution mass spectrum, (70 eV) 218.1673 (13, 218.1671 calcd for $C_{15}H_{22}O$).

The (*R*)-MTPA ester (6.5 mg, 75%) was prepared[13a] from 5.0 mg (0.02 mmol) of this sample of alcohol and 15.0 mg (0.06 mmol) of (+)-α-methoxy-α-((trifluoromethyl)phenyl)acetyl chloride. The 250-MHz ^1H NMR spectrum of the (*R*)-MTPA esters **18** showed characteristic peaks for the major *R,R* diastereomer at δ 0.955 (*J* = 6.62 Hz) and for the minor *R,S* diastereomer at δ 0.946 (*J* = 6.60 Hz).

Palladium Dichloride Catalyzed Rearrangement of (3*R*,5*E*)-Diene 3. Preparation of (2*Z*,5*R*)-3,5-dimethyl-2-phenyl-2,6-heptadiene (4) and (2*E*,5*S*)-3,5-Dimethyl-2-phenyl-2,6-heptadiene (5). A solution of 90 mg (0.45 mmol) of chiral diene **3** (99% ee based on the enantiomeric purity of **1**), 10 mg (0.039 mmol) of bis(acetonitrile)palladium dichloride, and 5 mL of dry THF was stirred at room temperature for 20 h. Concentration and bulb-to-bulb distillation (bath temperature 70 °C, 0.10 mm) gave 77.8 mg (86%) of a 7:3 mixture[15] of **4** and **5**. Pure samples of **4** and **5** were obtained by very careful preparative GC.[55] (2*Z*,5*R*)-Diene **4**: 16 mg of a colorless liquid; >99% pure by capillary GLC analysis (retention time 6.7 min);[15] $[\alpha]^{25}_D$ +52.7 ± 0.9 (*c* 0.41, $CHCl_3$); IR (film) 1670, 1645, 1450, 995, 915 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.0–7.35 (m, PhH), 5.5–5.65 (m, $CH{=}CH_2$), 4.8–4.95 (m, $=CH_2$), 2.25–2.4 (m, $CHCH_3$), 1.94 (br s, $CH_3(Ph)C{=}$), 1.77 (br s, $CH_3(CH_2)C{=}$), 0.81 (d, *J* = 7.0, H_2, CH_3CH); ^{13}C NMR (22.6 MHz, C_6D_6) δ 144.6 (2 C), 132.6, 128.4 (2 C), 126.8, 126.0 (2 C), 112.1, 42.4, 36.6, 21.4, 19.7, 17.9; mass spectrum, *m/z* (isobutane CI, relative percent) 201 (MH^+, 7), 146 (11), 145 (100), 104 (24). (2*E*,5*S*)-Diene **5**: 6 mg of a colorless liquid; 91.2% pure by capillary GC analysis (retention time 7.8 min),[15] contaminated with 2.1% of **4** and 6.7% of an unknown material (retention time 8.0 min); this sample was dextrorotatory, but the sample size and purity precluded obtaining a meaningful rotation; ^1H NMR (250 MHz $CDCl_3$) δ 7.1–7.4 (m, PhH), 5.75–5.96 (m, $CH{=}CH_2$), 4.9–5.1 (m, $=CH_2$), 2.4–2.45 (m, $CHCH_3$), 2.1–2.2 (m, $=CCHH$) 1.94 (br s, $CH_3(Ph)C{=}$), 1.54 (br s, $CH_3(CH_2)C{=}$), 1.06 (d, *J* = 6.6 Hz, CH_3CH); mass spectrum, *m/z* (isobutane CI, relative percent) 201 (MH^+, 7), 146 (11), 145 (100), 104 (24).

Hydroboration of the Palladium Dichloride Catalyzed Cope Products and Determination of the Absolute Configuration and Optical Purity of the (*Z*)- and (*E*)-3,5-Dimethyl-6-phenyl-5-hepten-1-ol Products. A. Analysis of Cope Product 4. A 3.0-mg (0.015 mmol) sample of the pure (*Z*)-diene **4** described in the previous experiment was added to 0.3 mL of a 0.50 M solution of 9-borabicyclo[3.3.1]nonanane (9-BBN, 0.15 mmol) in dry THF. The resulting solution was stirred at room temperature for 4.5 h and then treated sequentially with 0.060 mL of 3 M NaOH and 0.060 mL of 30% H_2O_2. Dilution with brine and extraction with ether gave 3 mg of (*Z*)-3,5-dimethyl-6-phenyl-5-hepten-1-ol, con-

(54) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

(55) A 0.25 in. × 10 ft glass column of 3% SP2100 on 100/120 Supelcoport was used for this analysis or separation.

taminated with some oxidation residues derived from 9-BBN.

This alcohol sample was treated[13a] with 20 mg (0.08 mmol, ~10 equiv) of (+)-α-methoxy-α-((trifluoromethyl)phenyl)acetyl chloride (95.7% ee), to give ~2 mg of the (*R*)-MTPA esters. The 250-MHz ^{1}H NMR spectra showed a characteristic doublet at δ 0.715 (J = 6.25 Hz) for the *R,R* diastereomer. Graphical curve resolution of the very small shoulder due to the upfield signal of the δ 0.706 doublet (which is due to the *R,S* diastereomer) was done in several different fashions at both 250 and 500 MHz to estimate a (93 ± 5):1 ratio for the *R,R* and *R,S* diastereomers (see Figure 1). Correction for the optical purity of the (+)-MTPA chloride implies an enantiomeric excess of 97 ± 5% for the (2*Z*,5*R*)-diene product **4**.

For confirmation of the correctness of the ^{1}H NMR assignments, this sample of the (*R*)-MTPA ester was spiked with an authentic sample of (*R*)-**8** (23% ee). The 250-MHz ^{1}H NMR spectrum of this mixture showed a major doublet at δ 0.716 and a minor doublet at δ 0.706.

B. Analysis of Cope Product 5. The amount of enriched (*E*)-diene **5** on hand proved insufficient for hydroboration and Mosher ester analysis. As a result, the absolute configuration and optical purity of **5** were determined by hydroboration and esterification of a mixture of **4** and **5**. A 9-mg (0.045 mmol) sample of the Cope products **4** and **5**, which had been somewhat enriched in **5** by preparative GC (**4**:**5** = 1.6:1), was hydroborated with 0.063 mmol of 9-BBN exactly as described in part A to give 4.7 mg (48%) of a 1.55:1 ratio of (*Z*)- and (*E*)-3,5-dimethyl-6-phenyl-5-hepten-1-ols, respectively.

This alcohol sample was treated[13a] with 20 mg of (+)-α-methoxy-α-((trifluoromethyl)phenyl)acetyl chloride (95.7% ee) to give 8.1 mg (85%) of the corresponding (*R*)-MTPA esters. The 250-MHz ^{1}H NMR spectrum showed a doublet at δ 0.715 for the *R,R* diastereomer of the *Z* isomer and a doublet at δ 0.947 (J = 6.26 Hz) for the *R,S* diastereomer of the *E* isomer. A small shoulder for the *R,R* diastereomer of the *E* isomer could be seen,for which graphical curve resolution at 250 MHz allowed a (92 ± 6):1 ratio of diastereomers to be estimated. Correction for the purity of the (+)-MTPA chloride used indicates an enantiomeric excess of 96 ± 6% for the diene product **5**.

For confirmation of the ^{1}H NMR assignments, this sample of (*R*)-MTPA esters was spiked with an authentic sample of the *E* ester prepared from (*R*)-**17** (23% ee). The 250-MHz ^{1}H NMR spectra showed retention of the doublet at δ 0.948 and the buildup of a doublet at δ 0.958 (J = 6.60 Hz).

Thermal Rearrangement of (*R*)-Diene 3. Preparation of (2*Z*,5*R*)-3,5-Dimethyl-2-phenyl-2,6-heptadiene (4) and (2*E*,5*S*)-3,5-Dimethyl-2-phenyl-2,6-heptadiene (5) and Determination of Absolute Configurations and Optical Purities. A 22-mg (0.11 mmol) sample of (*R*)-**3** (99% ee based on the enantiomeric purity of **1**) was sealed in an evacuated Pyrex ampule and heated at 240 °C for 16 h. The brown residue was purified by filtration through a short plug of silica gel (hexane) to give 11 mg (50%) of a 1:1 mixture of dienes **4** and **5**.

Hydroboration with 9-BBN and esterification[13a] with (+)α-methoxy-α-((trifluoromethyl)phenyl)acetyl chloride (95.7% ee) gave a mixture of diastereomeric (*R*)-MTPA esters. The 250-MHz ^{1}H NMR spectrum showed a doublet for the *R,R,Z* diastereomer **8** at δ 0.716 (J = 6.63 Hz) and a doublet for the corresponding *R,S,E* diastereomer at δ 0.948 (J = 6.60 Hz). Because of the small quantity of this sample available, accurate isomer ratios could not be determined. As with the product from the $PdCl_2$-catalyzed reaction, the *R,S,Z* diastereomer and the *R,R,E*-diastereomer were detectable only as small shoulders and are clearly minor (<15%) components.

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Registry No. 1, 83541-10-0; **1**·Et ester, 83478-46-0; (*R,R*)-**2**, 83478-45-9; (*R,S*)-**2**, 83478-32-4; **3**, 83541-11-1; **4**, 83478-33-5; **5**, 83478-34-6; **6**, 83478-35-7; **7**, 83478-36-8; (*R,R*)-**8**, 83478-37-9; (*R,S*)-**8**, 83478-38-0; **9**, 83478-54-0; **10**, 1117-61-9; **11**, 83541-12-2; **12**, 83541-13-3; **13**, 83478-39-1; **14**, 83478-40-4; **15**, 83478-41-5; **16**, 83478-42-6; **17**, 83478-43-7; **18**, 83478-53-9; (2*S*,4*E*)-2-methyl-2-phenyl-4-hexen-1-ol, 83478-44-8; (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, 20445-33-4; (±)-(*E*)-2-methyl-2-phenyl-4-hexen-1-ol, 83541-14-4; ethyl iodide, 75-03-6; (3*S*,5*E*)-2,3-dimethyl-3-phenyl-5-hepten-2-ol, 83478-47-1; (1*R*,4*R*)-6-(benzyloxy)-4-methyl-1-phenylhexanol, 83478-48-2; (1*S*,4*R*)-l-(benzyloxy)-4-methyl-1-phenylhexanol, 83478-49-3; (2*R*,4*R*)-6-(benzyloxy)-2,4-dimethyl-1-phenyl-1-hexanone, 83478-50-6; (2*S*,4*R*)-6-(benzyloxy)-2,4-dimethyl-1-phenyl-1-hexanone, 83478-51-7; 7-(benzyloxy)-3,5-dimethyl-2-phenyl-2-heptanol, 83478-52-8; bis(acetonitrile)palladium dichloride, 14592-56-4; (±)-(*Z*)-3,5-dimethyl-6-phenyl-5-hepten-1-ol, 83541-15-5; (±)-(*E*)-3,5-dimethyl-6-phenyl-5-hepten-1-ol, 83541-16-6.

Hydrolysis of Adenosine 5′-Triphosphate: An Isotope-Labeling Study[1]

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Abstract: We have used a combination of ^{18}O-labeling experiments and kinetic studies to clarify the nonenzymatic hydrolytic pathways of adenosine 5′-triphosphate (ATP) at pH values ranging from 0 to 8.3. In 1 N and 0.1 N HCl, the data are consistent with the hypothesis that hydrolysis occurs by addition–elimination, with initial attack 93% γ and 7% β; both lead only to ADP + P_i. In the subsequent hydrolysis of the ADP to AMP + P_i, attack is 83% β and 17% α. At pH 8.3, the data are consistent with the hypothesis that hydrolysis occurs by elimination–addition. Over the entire pH range studied, we detected no oxygen exchange between water and ATP, ADP, or P_i. Nonenzymatic hydrolysis and isotopic analysis of the resultant P_i comprise a preferred means of assaying the isotopic enrichment of [γ-^{18}O]ATP to be used in studies of enzymatic processes.

A clear picture of the mosaic of events at the molecular level that together constitute the enzymatic hydrolysis of adenosine 5′-triphosphate (ATP),[3] as, for example, in muscle contraction, remains an unattained objective. Among the many modern experimental tools that today loom large in biochemical research, the use of stable isotope labeling as a mechanistic probe[4] has

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(3) Appreviations used: ATP, ADP, and AMP = adenosine 5′-tri-, -di-, and -monosphosphate; P_i and PP_i = inorganic phosphate and pyrophosphate. O with no superscript mass specification denotes unlabeled oxygen and, in particular, the ^{16}O isotope.

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