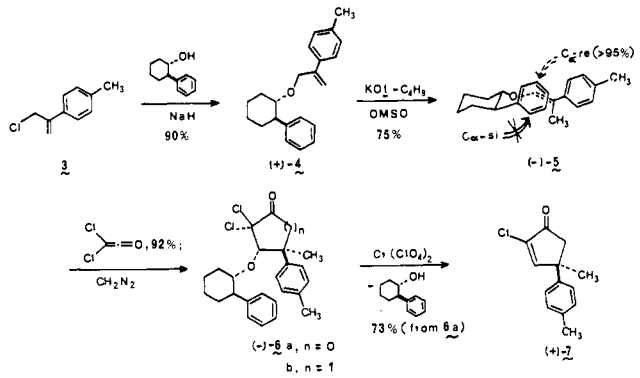
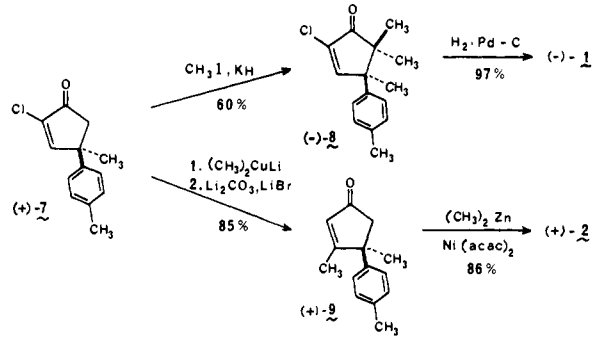
Scheme I



Scheme II



the C_α-re face of the enol ether to dichloroketene attack, while positioning the C_α-si face so as to be sterically shielded by the adjacent phenyl group. In reality, treatment of (−)-**5** with dichloroketene (3 equiv of CCl_3COCl, 5 equiv of Zn–Cu)[14] in ether at 20 °C produced in excellent yield the nicely crystalline cyclobutanone (−)-**6a**. Most pleasingly, an examination of the crude product by ^1H NMR (300 MHz) indicated that *a minimum level of induction of 95:5 had been achieved in this cycloaddition reaction.*[15] A single recrystallization of this material (pentane, −30 °C) efficiently provided pure (−)-**6a**.[11]

Ring expansion of cyclobutanone (−)-**6a** with excess diazomethane in 97:3 ether–methanol at room temperature proceeded, as expected,[8] highly regioselectively to generate the desired dichlorocyclopentanone, which on exposure to 3 equiv of chromous perchlorate in aqueous acetone[16] at 0 °C then cleanly furnished the key, optically pure[17] intermediate, α-chloroenone (+)-**7**[11] (73% from (−)-**6a**, $[\alpha]^{20}_D$ +71°).[18,19]

From this versatile α-chloroenone, both cuparenones could readily be secured by geminal dimethylation procedures (Scheme II). In the presence of excess methyl iodide and potassium hydride in tetrahydrofuran, (+)-**7** suffered α′, α′-dimethylation to give (−)-**8**[11] (60%), which on hydrogenation in ethyl acetate in the presence of sodium acetate, provided in 97% yield optically pure (−)-α-cuparenone[11] ($[\alpha]^{21}_D$ −170°, lit.[5c] $[\alpha]^{20}_D$ −170°). β,β-Dimethylation of (+)-**7** could easily be accomplished through sequential conjugate addition (1.5 equiv of $(CH_3)_2CuLi$, ether, −78 °C), dehydrochlorination (excess Li_2CO_3, LiBr, DMF, 80 °C → (+)-**9**,[11] 85% from (+)-**7**), and conjugate addition (5 equiv of $(CH_3)_2Zn$, catalytic $Ni(acac)_2$, ether, room temperature, 86%)[20] to furnish for the first time synthetically derived (+)-β-cuparenone[11] ($[\alpha]^{29}_D$ +45°, lit.[5a] $[\alpha]^{30}_D$ +48°).[21]

The successful realization of this approach demonstrates the feasibility of an entirely new, powerful stategy for enantioselective natural product synthesis. While this work is obviously most relevant to chiral cyclopentanone synthesis, there is also relevance to chiral lactam and lactone synthesis. These areas are currently being developed in our laboratory, and their potential will be demonstrated in forthcoming papers.

Acknowledgment. We thank Dr. J. L. Luche for his interest in our work, Professors J. K. Whitesell and C. Triantaphylides for helpful information, and the CNRS (UA 332) for financial support. A.M. is grateful to NATO for a postdoctoral fellowship.

Supplementary Material Available: Analytical data for compounds **1**, **2**, and **4–9** (2 pages). Ordering information is given on any current masthead page.

(13) *cis*-Alkenyl ethers adopt an s-trans or nearly s-trans conformation, see: Fischer, P. In *Chemistry of Ethers, Crown Ethers, Hydroxyl Groups, and Their Sulphur Analogues*; Patai, S., Ed.; John Wiley and Sons: New York, 1980; Vol. 2, Chapter 17. In addition to steric effects, π–π interaction may be important, see: Whitesell, J. K.; Lawrence, R. M.; Chen, H. H. *J. Org. Chem.* **1986**, *51*, 4779–4784.

(14) Krepski, L. R.; Hassner, A. *J. Org. Chem.* **1978**, *43*, 3173–3179.

(15) That the cycloaddition had, in fact, occurred as expected on the C_α-re face of enol ether **5** was confirmed by the obtention of (−)-α-cuparenone, the absolute configuration of which is known to be R.[5b,c] (The S designation given in references 6h,i for the absolute stereochemistry of the levo isomer is incorrect.)

(16) Kochi, J. K.; Singleton, D. M. *J. Am. Chem. Soc.* **1968**, *90*, 1582–1589. Wade, R. S.; Castro, C. E. *Org. Synth.* **1972**, *52*, 62–66.

(17) An optical purity of >99% was established for (+)-**7** through comparison of the ^{13}C NMR (75.4 MHz) spectra of the acetals of (±)-**7** and (+)-**7** formed with (*R,R*)-(−)-2,3-butanediol. (See: Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, 2183–2186.) The presence of 0.5% of the diastereomeric acetal would readily have been detected by this technique.

(18) The ejected chiral auxiliary is easily recovered in high yield at this stage.

(19) For recent alternative methods of preparing stereogenic quaternary carbon centers, see: Cram, D. J.; Sogah, G. D. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 625–628. Kogen, H.; Tomioka, K.; Hashimoto, S.; Koga, K. *Tetrahedron* **1981**, *37*, 3951–3956. Dolling, U. H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446–447. Meyers, A. I.; Harre, M.; Garland, R. *J. Am. Chem. Soc.* **1984**, *106*, 1146–1148. Tomioka, K.; Ando, K.; Takemasa, Y.; Koga, K. *J. Am. Chem. Soc.* **1984**, *106*, 2718–2719. Pfau, M.; Revial, G.; Guingant, A.; d'Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273–274. Meyers, A. I.; Wanner, K. Th. *Tetrahedron Lett.* **1985**, *26*, 2047–2050. Fuji, K.; Node, M.; Nagasawa, H.; Naniwa, Y.; Terada, S. *J. Am. Chem. Soc.* **1986**, *108*, 3855–3856. See, also: ref 6f-i.

(20) Petrier, C.; Barbosa, J. C. S.; Dupuy, C.; Luche, J. L. *J. Org. Chem.* **1985**, *50*, 5761–5765.

(21) ^{13}C NMR (75.4 MHz) analysis of the acetals of (±)-**2** and (+)-**2** formed with (*R,R*)-(−)-2,3-butanediol (quantitative yield) clearly indicated (+)-**2** to be, as expected,[17] >99% optically pure. We have no explanation for the (slight) discrepancy in the optical rotations.

Intramolecular Carbametalations. A [2 + 2 + 2] Cycloaddition as Evidence for a Palladacyclopentene Intermediate

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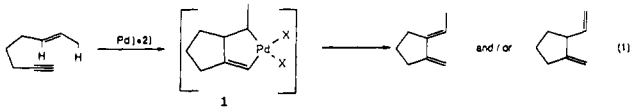
In our examination of the Pd^{2+}-catalyzed cyclization of 1,6-enynes according to eq 1, we suggested the feasibility of a palladacyclopentene intermediate such as **1**.[1] Attempts to intercept



such an intermediate utilizing our palladium acetate derived catalysts failed. Suspecting that the electron deficiency of the Pd in **1** with X being acetoxy made its rate of hydrogen shift so fast that we could not intercept **1**, we searched for a less electron deficient Pd^{2+} catalyst. We wish to report that tetracarbomethoxypalladacyclopentadiene (**2**, TCPC)[2] is a catalyst that effects the intramolecular carbametalation according to eq 1 that it also

(1) Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1985**, *107*, 1781. Trost, B. M.; Lautens, M. *Tetrahedron Lett.* **1985**, *26*, 4887.

(2) Moseley, K.; Maitlis, P. M. *J Chem. Soc., Dalton Trans.* **1974**, 169.

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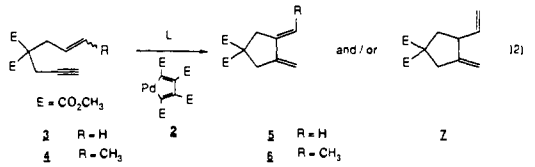
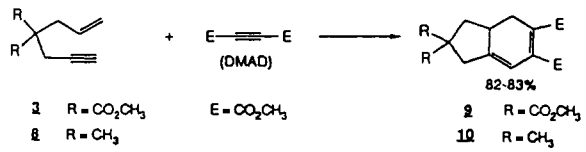
catalyzes a [2 + 2 + 2] cycloaddition.[3,4] These results may be taken as evidence in support of Pd^{2+}-catalyzing cyclization of 1,6-enynes to palladacyclopentenes.[5]

Activation of TCPC by addition of a trivalent phosphorus compound is required to break down the insoluble polymer to create a catalyst. The enynes **3** and **4** cyclize with 5 mol% TCPC

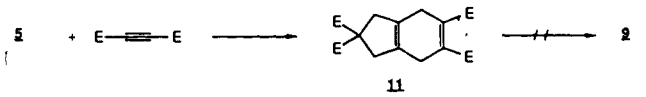


and 5 mol% of triphenylphosphine in benzene at 60 °C. For the parent enyne **3**, the diene **5**[6] is isolated in 54% yield, and the methyl substituted substrate **4** gives a 2:3 mixture of **6**[6] and **7**[6], respectively, in 59% yield.

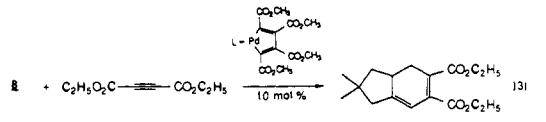
Having established the utility of TCPC as an enyne cyclization catalyst, we examined the question of trapping any intermeidates. Attempts to use CO[5] led to deposition of Pd black. On the other hand, adding 1.1 equiv of dimethyl acetylenedicarboxylate (DMAD) to 1 equiv of enyne **3** in benzene or 1,2-dichloroethane with use of 5 mol% of TCPC and 5 mol% of triphenylphosphine or tri-*o*-tolylphosphite leads to none of the diene **5** but only the 1:1 adduct **9**[6] in 52% and 83% yield, respectively. Tri-*o*-tolyphosphite invariably gave higher yields and, therefore, was the ligand of choice. To verify that the diene **5** is not a precursor



to **9**, we first established that the Diels–Alder adduct of **5** and DMAD, i.e., **11**,[6] which readily forms upon warming a mixture of these two, does not isomerize to **9**. Further, treating **5** with DMAD under the cyclization conditions leads only to the Diels–Alder adduct **11** not the isomeric **9**.



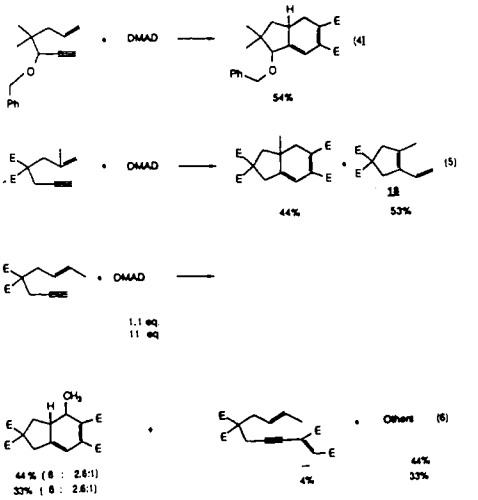
The integrity of TCPC under the reaction conditions was tested by a crossover experiment. The enyne **8** smoothly undergoes the [2 + 2 + 2] cycloaddition to **10**[6] in 82% yield under the above condition. Treating enyne **8** with 1.1 equiv of diethyl acetylenedicarboxylate, 10 mol% of TCPC, and 10 mol% of tri-*o*-tolylphosphite in 1,2-dichloroethane at 60 °C gave **12**,[6] *not* **10**.



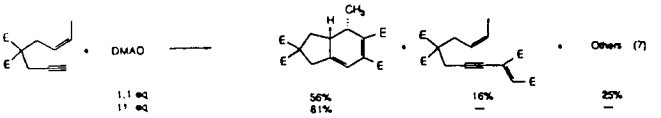
Capillary GC analysis establishes the ratio of **12**:**10** as >230:1.

If TCPC served as a source of the acetylene dicarboxylate fragment, the ratio of diethyl or dimethyl esters should have been up to 5:1, at least easily detected. The experimental ratio of >230:1 clearly suggests the integrity of TCPC is maintained. We also do not see formation of any mellitic esters during any of the above reactions.[3]

The reaction is general with respect to the enyne under the standard conditions with use of 5 mol% of catalyst and ligand as further illustrated by eq 4–6. In the example depicted in eq 5,

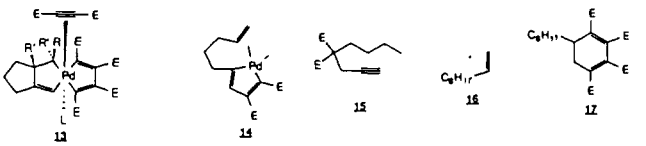


the normal [2 + 2 + 2] cycloadduct was accompanied by an unusual enyne cyclization product **18**[6] with a rearranged carbon skeleton. The sensitivity of the trapping to steric effects is shown in comparing the *E*–*Z* olefin pair in eq 6 and 7. An *E* enyne



provides the [2 + 2 + 2] cycloadduct much more poorly and with lower stereospecificity compared to a *Z* enyne. The presence of the methyl group on the olefin slows the trapping even with the latter case such that optimum trapping requires use of excess DMAD. Only the α-isomer of the product is observed in eq 7.

The formation of the trapped products in yields ranging from 40–83% is suggestive of palladacyclopentenes such as **13** as intermediates. To test the possibility that reaction might be initiated at the acetylene to form a palladacyclopentadiene such as **14**, we



treated **15** under our standard [2 + 2 + 2] cycloadition conditions to look for aromatic products. The acetylene **15** was recovered in 85% yield. The alternative possibility that reaction might have initiated at the olefin was examined by subjecting a simple olefin, **16**, to the normal conditions. Again, mostly starting material was recovered, and only a very small amount (<8%) of a trimer like **17**[3] was detected. These results suggest that the special juxtaposition of the olefin and acetylene in the 1,6-enynes are required for reactivity. Invoking the palladacycle **13** accommodates these facts. It also accounts for the sensitive steric effects. In an octahedral complex like **13**, making R, R′, or R″ alkyl will increase the steric congestion around Pd and therefore disfavor trapping. Assuming the acetylene preferably approaches the exo face since the endo face is blocked by the cyclopentyl ring, making R alkyl hinders this coordination. The difference between the *E* and *Z* enynes of eq 6 and 7 is then easily understood. By making R = CH_3 as in the *E* olefin, coordination to the exo face is disfavored. In contrast, by making R = H and R′ = CH_3 as in the *Z* olefin,

(3) (a) Suzuki, H.; Itoh, K.; Ishii, Y.; Simon, K.; Ibers, J. A. *J. Am. Chem. Soc.* **1976**, *98*, 8494. (b) Brown, L. D.; Itoh, K.; Suzuki, H.; Hirai, K.; Ibers, J. A. *J. Am. Chem. Soc.* **1978**, *100*, 8232. (c) Itoh, K. *Fundamental Research in Organometallic Chemistry—Proceedings of the China–Japan–United State Trilateral Seminar of Organometallic Chemistry*; Van Nostrand-Reinhold Co., Science Press: 1982; pp 149–174. (d) Itoh, K.; Hirari, K.; Sasaki, M. *Chem. Lett.* **1981**, 865.

(4) For an excellent overview of Co mediated [2 + 2 + 2] cycloadditions, see: Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *96*, 525.

(5) Cf. formation of cobaltocyclopentenes: Wakatsubi, Y.; Aoki, K.; Yamazaki, H. *J. Am. Chem. Soc.* **1979**, *101*, 1123. Khand, I. U.; Knox, G. R.; D. C.; Pauson, P. L.; Watts, W. E. *J. Chem. Soc., Perkin Trans. 1* **1973**, 977. Billington, D. C.; Pauson, P. L. *Organometallics* **1982**, *1*, 1560. Magnus, P.; Principe, L. M. *Tetrahedron Lett.* **1985**, *26*, 4851. For a review, see: Lindner, E. *Adv. Heterocycl. Chem.* **1986**, *39*, 237.

(6) All new compounds have been fully characterized spectrally and elemental composition established by high resolution mass spectroscopy and/or combustion analysis.

hindrance to approach of the DMAD is reduced. Furthermore, it is tempting to rationalize the formation of the simple cyclization product of rearranged skeleton in eq 5, i.e., **18**, as arising from a disrotatory opening of a cyclobutene **19** which may arise by a 1,1-elimination from **13**, R″ = CH_3.[7] This speculation must await futher experimental support.

19 **18**

Acknowledgment. We thank the National Science Foundation for their generous support of our programs.

Supplementary Material Available: Typical cocyclization procedure and ^1H NMR, ^{13}C NMR, and IR data (2 pages). Ordering information is given on any current masthead page.

(7) For 1,1-eliminations from Pd^{2+}, see: Gillie, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4933. Loar, M. K.; Stille, J. K. *J. Am. Chem. Soc.* **1981**, *103*, 4174. Moravskiy, A.; Stille, J. K. *J. Am. Chem. Soc.* **1981**, *103*, 4182. Numata, S.; Kurosawa, H. *J. Organomet. Chem.* **1977**, *131*, 301. For 1,1-eliminations fro Pd^{4+}, see: Ito, T.; Tsuchiya, H.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1319. Kurosawa, H.; Emoto, M.; Urabe, A. *Chem. Commun.* **1984**, 968. For conversion of platinacyclobutanes to cyclopropanes, see: Hall, P. W.; Puddephatt, R. J.; Tipper, C. F. H. *J. Organomet. Chem.* **1975**, *84*, 407. Casey, C. P.; Scheck, D. M.; Shusterman, A. J. *J. Am. Chem. Soc.* **1979**, *101*, 4233.

A Chemodirected, Triply Convergent Total Synthesis of *d*-(+)-Carbacyclin[1]

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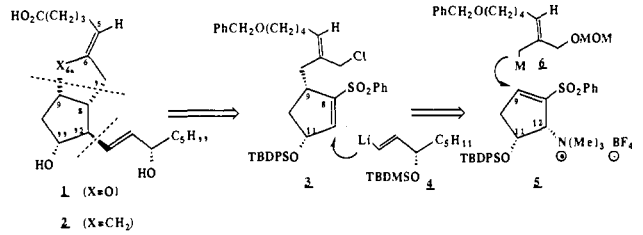
Received September 2, 1986

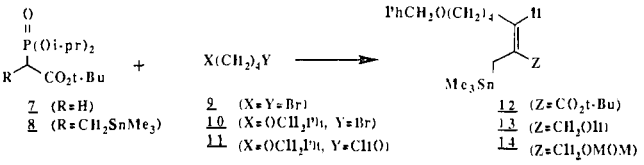
Prostaglandin I_2 (prostacyclin **1**) is well-recognized to be the prototype of a new generation of antithrombotic drugs.[2] Unfortunately, the demonstrated hydrolytic instability imparted by the enol ether moiety of **1** under physiological conditions precludes the use of this material for the inhibition of platelet aggregation.[2] A number of analogues of **1** have been prepared and among the best pharmaceutical candidates is carbacyclin (**2**).[2-4]

Previous syntheses of carbacyclin (**2**)[3] have, with two exceptions,[4] failed to stereoselectively effect either the geometry of the trisubstituted olefin or the C-15 stereocenter. Moreover, the best reported overall yield for a synthesis of chiral **2** is only ca. 0.95%.[3d]

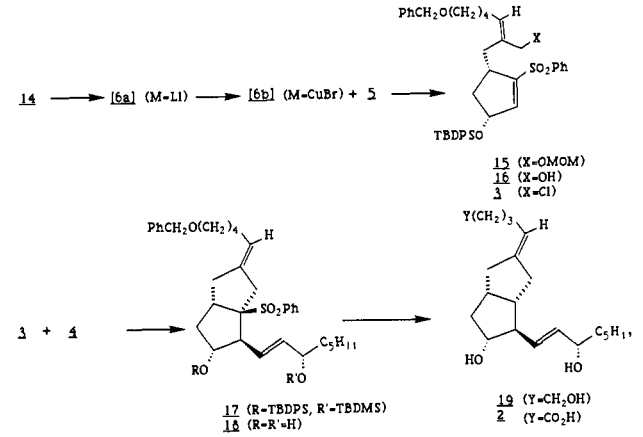
Scheme I



Scheme II



Scheme III



In conjunction with our vinyl sulfone program,[1] we wished to provide a synthesis of **2** which would remedy these difficulties. The basic plan involved a triply-convergent approach reminiscent of our earlier synthesis of 1-PGE_2[5] in that the allylic alcohol side chain was to be affixed via conjugate addition of the chiral reagent **4**[5] to vinyl sulfone **3**, a process that was expected to be highly stereocontrolled at C-12. Construction of **3** was, in turn, projected to be via S_N2' addition of the allylic organometallic reagent **6** to chiral ammonium salt **5**.[6,7] As can be readily seen from Scheme I, successful union of **5** and **6** requires control of two stereochemistries (C5,6 and C9,11) as well as two regiochemistries (C5 vs. C6a and C9 vs. C12).

Synthesis of reagent **6** was accomplished as follows: (1) Treatment of *tert*-butyl bromoacetate with triisopropyl phosphite at 90–215 °C affords a 95% yield of phosphonate ester **7**[8] which is subsequently deprotonated with sodium hydride in THF followed by reaction with trimethyliodomethylstannane[9] to provide **8**[8] in 95% yield. (2) Reaction of excess (3 equiv) 1,4-dibromobutane

(1) Syntheses via vinyl sulfones. 22. For the previous paper in this series, see: Toth, J. E.; Fuchs, P. L. *J. Org. Chem.* **1987**, *52*, 473.

(2) (a) Bartmann, W.; Beck, G. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 751–764. (b) Newton, R. F.; Roberts, S. M.; Taylor, R. J. K. *Synthesis* **1984**, 449–478.

(3) (a) Konishi, Y.; Kawamura, M.; Iguchi, Y.; Arai, Y.; Hayashi, M. *Tetrahedron* **1981**, *37*, 4391. (b) Skuballa, W.; Vorbruggen, H. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1046. (c) Aristoff, P. A. *J. Org. Chem.* **1981**, *46*, 1954. (d) Shibasaki, M.; Sodeoka, M.; Ogawa, Y. *J. Org. Chem.* **1984**, *49*, 4096. (e) Shibasaki, M.; Iseki, K.; Ikegami, S. *Chem. Lett.* **1979**, 1299. (f) Yamazaki, M.; Shibasaki, M.; Ikegami, S. *Chem. Lett.* **1981**, 1245. (g) Amemiya, S.; Kojima, K.; Sakai, K. *Chem. Pharm. Bull.* **1984**, *32*, 1349. (h) Nicolaou, K. C.; Spiro, W. J.; Magolda, R. L.; Seitz, S.; Barnette, W. E. *J. Chem. Soc., Chem. Commun.* **1978**, 1067. (i) Shibasaki, M.; Veda, J.-I.; Ikegami, S. *Tetrahedron Lett.* **1979**, *20*, 433. (j) Morton, D. R., Jr., Brokaw, F. C. *J. Org. Chem.* **1979**, *44*, 2880. (k) Sugie, A.; Shimomura, H.; Katsube, J.; Yamamoto, H. *Tetrahedron Lett.* **1979**, *20*, 2607. (l) Kojima, K.; Sakai, K. *Tetrahedron Lett.* **1978**, *19*, 3743. (m) Barco, A.; Benetti, S.; Pollini, G. P.; Baraldi, P. G.; Gandolfi, C. *J. Org. Chem.* **1980**, *45*, 4776.

(4) Control of the reduction of an enone at C-15 has been reported to afford a 94:6 ratio of the (*S*)- and (*R*)-alcohols,[3a] and the stereochemistry of the trisubstituted olefin has been shown to be stereospecifically effected by 1,4-hydrogenation of a diene.[3d] In neither of these papers were *both* of these stereochemical problems solved.

(5) (a) Donaldson, R. E.; Fuchs, P. L. *J. Am. Chem. Soc.* **1981**, *103*, 2108. (b) Donaldson, R. E.; Saddler, J. C.; McKenzie, A. T.; Byrn, S.; Fuchs, P. L. *J. Org. Chem.* **1983**, *48*, 2167.

(6) Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1985**, *107*, 6137.

(7) Chiral **5** is available in 19.9% overall yield from cyclopentadiene via an enantioconvergent process (see: ref 6 and Donaldson, R. E.; Saddler, J. C.; Fuchs, P. L. *J. Am. Chem. Soc.* **1981**, *103*, 2110.).

(8) This compound exhibited satisfactory spectral and analytical properties. Yields refer to material of >95% purity. $[\alpha]_D^{25}$ values are recorded in the following form (compound number; rotation; concentration; solvent): **15**: +20.8°, (*c* 0.680, CH_2Cl_2); **16**: +23.7°, (*c* 0.720, $CHCl_3$); **3**: +5.5°, (*c* 0.780, $CHCl_3$); **17**: +4.4°, (*c* 0.770, $CHCl_3$); **18**: +62.4°, (*c* 1.610, $CHCl_3$); **19**: +72.4°, (*c* 1.230, $CHCl_3$).

(9) Trimethyliodomethylstannane was prepared by a modification of the method of Seyferth (Seyferth, D.; Andrews, S. B. *J. Organomet. Chem.* **1971**, *30*, 151.). We find this to be an economically preferable solution to the more recent preparation proposed by Seitz (Seitz, D. E.; Carroll, J. J.; Cartaya, M. C. P.; Lee, S.-H.; Zapata, A. *Synth. Commun.* **1983**, *13*, 129.).

0002-7863/87/1509-4755$01.50/0