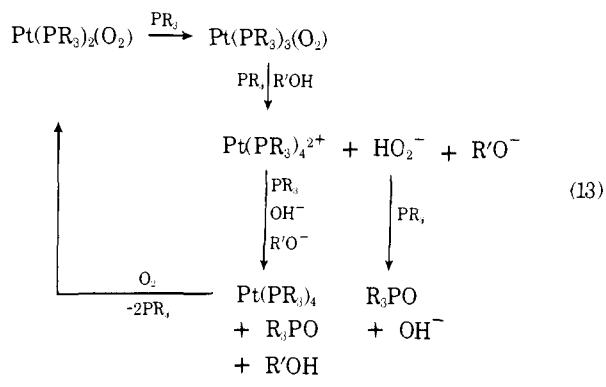
and 11 yields the overall reaction 12 which is the "PMe_2Ph analogue" of reaction 2.

$$Pt(PPh_3)_2(O_2) + 6PMe_2Ph \rightarrow Pt(PMe_2Ph)_4 + 2Me_2PhPO + 2PPh_3 \quad (12)$$

These results strongly suggest the detailed mechanism 13 for the $Pt(PR_3)_n(O_2)$-catalyzed oxidation of phosphines.[16]

Although the various steps and intermediates in this scheme (13) have been demonstrated for the modified systems in-



(13)

volving $PMePh_2$ and PMe_2Ph, the modification is sufficiently modest that it seems reasonable to extrapolate the mechanism also to the $Pt(PPh_3)_3$-catalyzed oxidation of PPh_3, as well as to the catalytic oxidation of phosphines by other metal complexes (e.g., $Rh(PPh_3)_3Cl$[5] and $Ru(NCS)(CO)(NO)(PPh_3)_2$[12]) which also form O_2 adducts. Furthermore, although the scheme (13) as depicted (and as demonstrated) uses protons derived from the solvent to generate the OH^- and HO_2^- intermediates, the steady-state concentrations of these intermediates, required to sustain a catalytic cycle, are sufficiently low that the same mechanism (using trace protic impurities) may also be invoked in nominally "aprotic" solvents such as benzene in which the catalytic reaction can occur.[8-10]

It is noteworthy that, in contrast to earlier suggestions,[9-13] the mechanism encompassed by scheme 13 does not involve direct oxygen transfer from the metal-dioxygen adduct to the substrate. Instead the role of the "substrate" (i.e., phosphine) is to effect the displacement of coordinated peroxide by nucleophilic attack on the metal. Not surprisingly, substrates such as olefins are not sufficiently strong nucleophiles to accomplish this and are not readily oxidized by O_2 adducts such as $Pt(PPh_3)_2O_2$. On the other hand, other *strong* nucleophiles such as carbanions are expected to exhibit reactions similar to phosphines and indeed steps analogous to 8 and 10 have been demonstrated for the reaction of LiBu with $Pt(PPh_3)_2(O_2)$, *even in an aprotic solvent.*[17]

The mechanistic conclusions derived from these studies suggest that the scope for oxidation of substrates via O_2 adducts such as $Pt(PR_3)_2(O_2)$ is rather limited. The effective oxidants in this system are really platinum(II) and free peroxide. Only strongly nucleophilic substrates such as phosphines are likely to effect the displacement of peroxide from the O_2 adduct and such substrates are almost certain to be themselves oxidized readily by the displaced peroxide. On the other hand, the reactivity patterns of platinum(II) complexes as oxidants (which we are presently investigating) are such that reduction by other substrates (for example reduction by olefins through Wacker-type mechanisms) may well compete with reduction by phosphines. Thus, *co-oxidation* of phosphines and other substrates may be possible through mechanisms related to those of scheme 13. The recently reported co-oxidation of olefins and PPh_3, catalyzed by $Rh(PPh_3)_3Cl$ under conditions where the latter forms O_2 adducts, may be an example of such a process.[5]

Acknowledgment. Support of this research through a grant from the National Science Foundation is gratefully acknowledged.

References and Notes

(1) For recent general reviews, see J. Valentine, *Chem. Rev.*, **73**, 235 (1973); V. J. Choy and C. J. O'Connor, *Coord. Chem. Rev.*, **9**, 145 (1972); G. Henrici-Olivé and S. Olivé, *Angew. Chem., Int. Ed. Engl.*, **13**, 29 (1974).
(2) J. P. Collman, M. Kubota, and J. W. Hosking, *J. Am. Chem. Soc.*, **89**, 4809 (1967).
(3) J. E. Lyons, *Adv. Chem. Ser.*, **No. 132**, 64 (1974), and references therein.
(4) A. Fusi, R. Ugo, F. Fox, A. Pasini, and S. Cenini, *J. Organomet. Chem.*, **26**, 417 (1971).
(5) C. W. Dudley, G. Read, and P. J. C. Walker, *J. Chem. Soc., Dalton Trans.*, 1926 (1974); G. Read and P. J. C. Walker, *ibid.* 883 (1977).
(6) J. Farrar, D. Holland and D. J. Milner, *J. Chem. Soc., Dalton Trans.*, 815 (1975).
(7) V. P. Kurkov, J. Z. Pasky, and J. B. Lavigne, *J. Am. Chem. Soc.*, **90**, 4743, (1968).
(8) G. Wilke, H. Schott, and P. Heimbach, *Angew. Chem., Int. Ed. Engl.*, **6**, 92 (1967).
(9) J. P. Birk, J. Halpern, and A. L. Pickard, *J. Am. Chem. Soc.*, **90**, 4491 (1968).
(10) J. Halpern and A. L. Pickard, *Inorg. Chem.*, **9**, 2798 (1970).
(11) R. Ugo, *Engelhard Tech. Bull.*, **XI**, 45 (1970).
(12) B. W. Graham, K. R. Laing, C. J. O'Connor, and W. R. Roper, *J. Chem. Soc., Dalton Trans.*, 1237 (1972).
(13) E. W. Stern in "Transition Metals in Honogeneous Catalysis", G. N. Schrauzer, Ed., Marcel Dekker, New York, N.Y., 1971, p 138.
(14) The choice of solvent for these studies, generally ethanol or ethanol–toluene mixtures, was dictated by solubility considerations, taking account of the relatively high concentrations ($\gtrsim 10^{-2}$ M) of reagents required for the NMR measurements and the low temperatures of the experiments.
(15) In every experiment where both PPh_3 and a more basic phosphine, notably $PMePh_2$ or PMe_2Ph, were present in the same solution containing a $Pt-O_2$ adduct, only the more basic phosphine was oxidized; i.e., no Ph_3PO was formed.
(16) Our proposed mechanism predicts that in the presence of added excess H_2O, 50% of the oxygen in the product Me_2PhPO should be derived from the H_2O and the other 50% from the O_2. The results of preliminary experiments using ^{18}O-labeled H_2O are at least qualitatively consistent with this.
(17) S. L. Regen and G. M. Whitesides, *J. Organomet. Chem.*, **59**, 293 (1973).

Ayusman Sen, Jack Halpern*
Department of Chemistry, The University of Chicago
Chicago, Illinois 60637
Received August 8, 1977

Asymmetric Reduction. Reduction of Acetylenic Ketones with Chiral Hydride Agent

Sir:

The production of optically active synthetic intermediates from achiral starting materials via asymmetric induction has been of increasing interest in recent years.[1] One of the most widely studied aspects of this field has been the synthesis of chiral carbinols from the reduction of achiral ketones with chiral hydride agents.[1-5] Thus far, however, this area has been of more theoretical than practical interest since only aryl ketones have been reduced in high enantiomeric ratios (ranging from 85:15 to 93:7). Indeed there has not yet been to our knowledge an example of an asymmetric reduction of an aliphatic ketone to give enantiomeric ratios of greater than 70:30. We now wish to disclose our finding that the reduction of acetylenic ketones (Scheme I) with the complex formed from

Scheme I

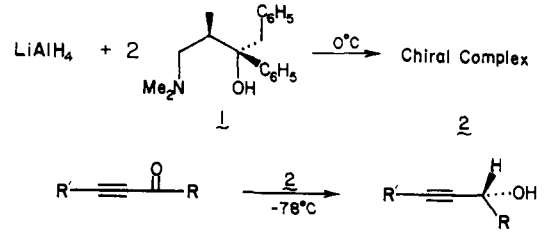
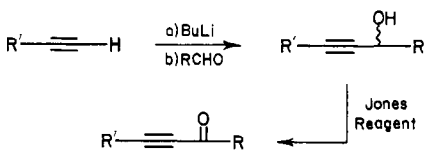


Table I. Asymmetric Reduction of Acetylenic Ketones with $LiAlH_4$ and Amino Alcohol **1**[a]

Run	Ketone	Synthetic yield, %[b]	Obsd $[\alpha]_D$ (c, solvent),	Reported $[\alpha]_D$ (c, solvent), deg	Enantiomeric ratios	Config[c]
1	**3**	94	+11.32 (4.0, $CHCl_3$)	+13.48 (4.9, $CHCl_3$)[d]	91:9[e]	*R*
2	**4**	96	+14.78 (2.0, Et_2O) +3.99 (2.0, $CHCl_3$)	+20.5 (Et_2O)[f] +5.5 ($CHCl_3$)	86:14	*R*
3	**5**	96	+13.6 (2.0, Et_2O)[g] +3.7 (2.0, $CHCl_3$)	+20.5 (Et_2O)[f] +5.5 ($CHCl_3$)	83:17	*R*
4	**6**	97	+2.93 (4.9, $CHCl_3$)		81:19[h,i]	*R*
5	**7**	70	+63.46 (2.01, $CHCl_3$)		91:9[h]	*R*
6	**8**	80	+49.05 (2.0, $CHCl_3$)[g]		89:11[h]	*R*
7	**9**	95	+39.00 (3.8, $CHCl_3$)		92:8[h]	*R*
8	**10**	92	+8.7 (2.0, $CHCl_3$)		62:37[h]	*R*

[a] Optically pure amino carbinol **1** was used, $[\alpha]_D$ +8.10° (*c* 9.6, EtOH). [b] All alcohols were purified by column chromatography on basic alumina and/or distillation. [c] Configuration assignments based on work of Pappo and Fried;[15] also see ref 16. [d] See ref 14; [e] This corresponds to an enantiomeric excess (% ee) of 82%. [f] See ref 15. [g] Trimethylsilyl group was hydrolyzed under basic conditions and the rotation of the terminal acetylene is given. [h] Determined by conversion of the optically active alcohol from reduction of ketone **4** to the alcohol from this reduction. [i] Determined by gas chromatographic analysis of the diastereomeric MTPA derivatives.

Scheme II



lithium aluminum hydride and "Darvon alcohol", (+)-(2*S*,3*R*)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol (**1**)[6] provides high enantiomeric ratios of the corresponding chiral propargylic carbinols (see Table I).

The $LiAlH_4$–Darvon alcohol complex, for which a structure has been proposed,[6] was formed in situ according to the procedure of Mosher et al.[6] For example, the chiral amino alcohol **1** (2.53 mol equiv) in dry diethyl ether was added to a suspension of lithium aluminum hydride (1.1 mol equiv) in dry ether at 0 °C. After the mixture was stirred for 2–3 min, the solution of the chiral complex was cooled to −78 °C[7] and the acetylenic ketone (1.0 mol equiv) in ether was added slowly over a period of 30–60 min;[7] then the mixture was stirred at −78 °C for 5–7 h. The excess hydride was destroyed by the addition of wet ether at −78 °C, and the solution was warmed to 20 °C and washed with cold, dilute hydrochloric acid to remove the chiral amino carbinol **1**. The product was then purified by column chromatography on basic alumina and/or distillation.

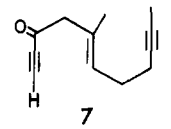
The enantiomeric ratios of the carbinols, listed in runs 1–3, Table I, were determined by comparison with published optical rotation values for the corresponding alcohol of known optical purity. In runs 4–8 the optical purity was established by VPC analysis of the methoxytrifluoromethylphenyl acetate (MTPA) derivatives.[8]

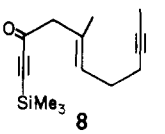
The ketones used in these experiments were synthesized in a straightforward manner by the reaction of lithium acetylides with the appropirate aldehydes.[9] These alcohols were then oxidized with Jones reagent (Scheme II) to give the ketones **3**–**9**.[10-12] Ketone **10** was prepared by Jones oxidation of the corresponding allylic alcohol.

$H_3CC{\equiv}CCOCH_2CHMe_2$ **3** $\quad HC{\equiv}CCOC_5H_{11}$ **4**

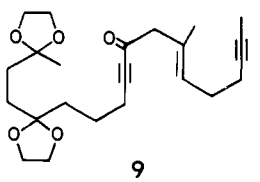
$Me_3SiC{\equiv}CCOC_5H_{11}$ **5** $\quad C_5H_{11}C{\equiv}CCOC_5H_{11}$ **6**

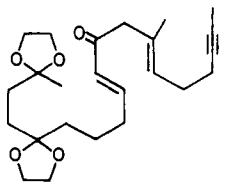
To a major degree the high enantioselectivity of these reductions is associated with the presence of the acetylenic function adjacent to the carbonyl group. The π-electron system of the acetylenic bond appears to have a similar effect to that of the aromatic moiety in the reduction of aryl ketones by Mosher et al.[6] Not only do the resulting carbinols from the reduction of both acetylenic and aryl ketones have enantiomeric ratios as high as 92:8 but also in both cases the absolute configuration of the carbinols is the *R* configuration.


7



8


9


10

In contrast to the acetylenic bond, the olefinic bond does not show the effect of enhancing the asymmetric reduction of an adjacent carbonyl group. Thus, in the reduction of ketone **10** (Table I) the enantiomeric ratio of the carbinol is only 62:38—a dramatic difference from the case of the corresponding acetylenic ketone **9** which gives a ratio of 92:8. Saturated, aliphatic ketones also show a small effect;[6] e.g., the enantiomeric ratio for the reduction of *tert*-butyl methyl ketone was 58:42. Although other structural features in these ketones, such as branching at the β' carbon (cf., for example, runs 1 and 2), may play a role in the degree of enantioselectivity, too few examples have been examined to establish any correlation.[13]

In conclusion, the present method represents the first reported example of high enantiomeric ratios (ranging from 80:20 to 92:8) obtained in the chiral reduction of nonaromatic ketones. Optically active carbinols obtained in the present study have already been shown to be useful intermediates in the total syntheses of natural products. Thus, the carbinol from ketone **3** has been used in the synthesis of tocopherol,[14] the carbinols from ketones **4** and **5** in the synthesis of prostaglandins,[15] and the carbinols from ketones **7**–**9** in the synthesis of 11α-hydroxyprogesterone.[16] This method also represents a potential source of a variety of types of optically active compounds (e.g., allenes, allylic alcohols, dialkylcarbinols, propargylic amines, hydroxy ketones, etc.) that are accessible from propargylic alcohols. Further investigations of the synthetic utility of this asymmetric reduction are underway.

Acknowledgment. The authors wish to thank Professor William S. Johnson for his encouragement and helpful discussions. Financial assistance was provided from grants to W.S.J. from the National Institutes of Health and the National Science Foundation. R.S.B. was also assisted by an NIH Postdoctoral Fellowship (National Cancer Institute Grant No.

1F32 CA 05575-01) and V.M.K. by the J. N. Tata Endowment, India. We also wish to thank Professor H. S. Mosher for providing the optically active amino carbinol **1**.

References and Notes

(1) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, N.J., 1970; Reprint Edition, American Chemical Society Book Department, Washington, D.C., 1976. J. W. Scott and D. Valentine, *Science*, **184**, 943 (1974).

(2) For a review see S. Yamada and K. Koga in "Selective Crganic Transformations", Vol. 1, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N.Y., 1970, pp 1–33.

(3) Chiral lithium aluminum hydride reagents not included in ref 1 and 2: A. S. Angeloni, R. Andrisano, and S. Marzocchi, *Tetrahedron*, **29**, 913 (1973); A. I. Meyers and P. M. Kendall, *Tetrahedron. Lett.*, 1337 (1974); T. A. Whitney and A. W. Langer, *Adv. Chem. Ser.*, **No. 130**, 270 (1974); M. F. Grundon, D. G. McCleery, and J. W. Wilson, *Tetrahedron Lett.*, 295 (1976); D. Seebach and H. Daum, *Chem. Ber.*, **107**, 1748 (1974); J. P. Vigneron and I. Jacquet, *Tetrahedron Lett.*, 2065 (1974); J. P. Vigneron and I. Jacquet, *Tetrahedron*, **32**, 939 (1976); H. J. Schneider and R. Haller, *Chem. Ber.*, **106**, 1312 (1973); G. M. Giongo, F. Di Gregorio, N. Palladino, and W. Marconi, *Tetrahedron Lett.*, 3195 (1973).

(4) Chiral borohydrides: J. P. Masse and E. R. Parayre, *J. Chem. Soc., Chem. Commun.*, 438 (1976); S. Colonna and R. Fornasier, *Synthesis*, 531 (1975); and M. F. Grundon, J. A. Khan, D. R. Boyd, and W. R. Jackson, *J. Chem. Soc. C*, 2557 (1971).

(5) Chiral hydride reagents used in synthesis: M. J. Drabicky, P. C. Myhre, C. J. Reich, and E. R. Schmittou, *J. Org. Chem.*, **41**, 1472 (1976); D. Seebach and H. Meyer, *Angew, Chem., Int. Ed. Engl.*, **13**, 77 (1974); M. Lahav, F. Laub, E. Gati, L. Leiserowitz, and Z. Ludmer, *J. Am. Chem. Soc.*, **98**, 1620 (1976); and K. Kabuto and H. Ziffer, *J. Org. Chem.*, **40**, 3467 (1975).

(6) S. Yamaguchi, H. S. Mosher, and A. Pohland, *J. Am. Chem. Soc.*, **94**, 9254 (1972); and S. Yamaguchi and H. S. Mosher, *J. Org. Chem.*, **38**, 1870 (1973).

(7) When the reductions were performed at temperatures above −78 °C, significantly lower enantiomeric ratios were obtained. Moreover, when additions of the ketones were carried out in <5 min at −78 °C, low enantiomeric ratios also resulted.

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

(9) Cf. M. M. Midland, *J. Org. Chem.*, **40**, 2250 (1975).

(10) (a) K. Bowden, I. M. Heilborn, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946). (b) For the oxidation to ketone **4** see A. Nobuhara, *Agr. Biol. Chem.*, **33**, 1264 (1969); *Chem. Abstr.*, **72**, 89714† (1970).

(11) All new compounds demonstrate acceptable analysis and spectral data in accord with assigned structures.

(12) The synthesis of ketones **7–9** is described in detail in ref 16. For a description of the synthesis of the alcohol precursor to ketone **10**, see W. S. Johnson, S. Escher, and B. W. Metcalf, *J. Am. Chem. Soc.*, **98**, 1039 (1976). For alternate syntheses of the ketones used in runs 1 and 4, see E. S. Turbanova, Y. I. Porfir'eva, and A. A. Petrov, *Zh. Organ. Khim.*, **2**, 772 (1966), and L. S. Meriwether, E. C. Colthup, and G. W. Kennerly, *J. Org. Chem.*, **26**, 5163 (1961), respectively.

(13) We have learned in a private communication that N. Cohen and C. Neukom of Hoffmann-La Roche Inc., using the procedure described in the present paper, have effected asymmetric reductions of several acetylenic ketones and also have obtained generally high enantiomeric ratios.

(14) For example, see K. K. Chan, N. C. Cohen, J. P. DeNoble, A. C. Specian, Jr., and G. Saucy, *J. Org. Chem.*, **41**, 3497 (1976).

(15) For an example, see J. Fried, C. Lin, M. Mehra, W. Kao, and P. Dahren, *Ann. N.Y. Acad. Sci.*, **180**, 38 (1971); and R. Pappo, P. Collins, and C. Jung, *ibid.*, **180**, 64 (1971).

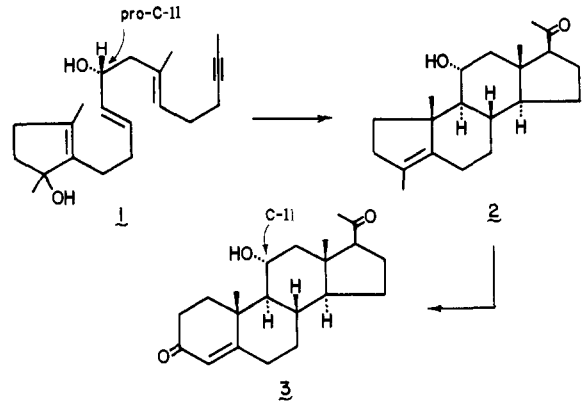
(16) W. S. Johnson, R. S. Brinkmeyer, V. M. Kapoor, and T. M. Yarnell, *J. Am. Chem. Soc.*, following paper in this issue.

Raymond S. Brinkmeyer,* Vijaya M. Kapoor
Department of Chemistry, Stanford University
Stanford, California 94305
Received August 10, 1977

Asymmetric Total Synthesis of 11α-Hydroxyprogesterone via a Biomimetic Polyene Cyclization[1]

Sir:

We have previously shown that the racemic form of substance **1** can be induced to undergo a stereoselective acid-catalyzed biomimetic cyclization so as to produce mainly a single tetracyclic product (**2** + enantio-**2**).[2] This latter material was readily converted, by ozonolysis followed by cyclodehydration of the resulting ring A seco diketone, into racemic 11α-hydroxyprogesterone (**3** + enantio-**3**). The failure to detect any racemic 11β isomer at this stage showed that the cyclization step was proceeding asymmetrically owing to the influence of the chiral center at pro-C-11 (see formula **1**). It, therefore, became of prime importance to ascertain whether cyclization of the optically active form of the substrate **1** (with the *R* configuration at pro-C-11) would occur faster than racemization to produce an optically active product **2.** The outcome of this finding has been the realization of an asymmetric total synthesis of 11α-hydroxyprogesterone (**3**) which is the key intermediate in the commercial production of hydrocortisone acetate.[3]



The reported synthesis[2] of the racemic form of the cyclization substrate **1** involved, as the convergent step, addition of the lithium acetylide of the diketal **13** to the aldehyde **5** to give the propargylic alcohol **12,** which was then submitted to the following steps: hydride reduction to the trans allylic alcohol; ketal hydrolysis; cyclodehydration of the resulting δ diketone giving the cyclopentenone system; and then, finally, reaction with methyllithium. Thus the pro-C-11 chiral center first appeared at the stage of the propargylic alcohol **12.** Preliminary attempts to resolve this substance were unpromising; therefore attention was turned to an alternative synthesis in which the chiral center was established at an earlier stage in a smaller molecule which promised to be more susceptible to resolution.

The new scheme was first examined in the racemic series. Thus the aldehyde **5** was treated with the lithium salt of trimethylsilylacetylene (**4**)[4] to give the trimethylsilylacetylenic alcohol **6**[5] (Scheme I) in 92% yield after distillation.[6] Treatment of **6** with aqueous methanolic potassium hydroxide effected desilylation and the product (**8** + enantio-**8**),[5] obtained in 100% yield after distillation,[6] was converted to the known diketal propargylic alcohol **12** as follows. Treatment of **8** + enantio-**8** with *tert*-butyldimethylsilyl chloride and imidazole in DMF gave a 92% yield of the *O*-silyl ether,[5] which was converted into the lithium salt with *n*-butyllithium in glyme containing 20% HMPA. Alkylation of this salt with the diketal bromide **9** (15 h at 25 °C), afforded the *tert*-butyldimethylsilyl ether[5] of **12** which was isolated in 71% yield after chromatography on silica gel. Desilylation of this ether with tetra-*n*-butylammonium fluoride in THF gave a quantitative yield of **12,** identical with authentic material by IR, NMR, and VPC comparison.

The racemic propargylic alcohol (**8** + enantio-**8**) could be partially resolved as the brucine salt of the half-acid phthalate. Hydrolysis of the fraction which crystallized from benzene/ether yielded the product **8**, $[\alpha]^{EtOH}_{D}$ + 14.8° (*c* 1.87)[7] corresponding to an enantiomeric ratio of ~90:10, as estimated by GC analysis of the methoxytrifluoromethylphenylacetic (MTPA) ester[8] on a 12-ft OV-3 column (baseline separation). The absolute configuration of the dextrorotatory product[9] was confirmed as **8** by relating it to 11α-hydroxyprogesterone (see