Reduction of Steroid 17-Ketones by Enantiomeric Chiral Reducing Agents

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The reduction of steroid 17-ketones by a chiral hydrosilane–rhodium–(−)(2*S*,3*S*)-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane reagent allows greater stereoselectivity of 17α-alcohol formation than is obtained by other methods.

Asymmetric hydrogenation of double bonds catalysed by soluble transition metal compounds bearing chiral ligands has been a subject of intense study,[1] and together with the studies on asymmetric reduction of prochiral ketones[2–6] has made available a number of well characterized chiral reducing agents in both enantiomeric forms.

Control of the direction of reduction of steroid ketones by achiral reagents has been the subject of many articles well reviewed by Fried and Edwards.[7] A direct reduction which has not yet been accomplished with stereoselectivity is that of 17-ketones to the 17α-alcohol; and, to a lesser extent, that of 20-ketones to the 20α-alcohol. It appeared to us that increased control of the direction of reduction might be obtained by the use of chiral reducing agents. Since different achiral reducing agents give different proportions of enantiomeric steroid alcohols, we confined this study to an enantiomeric pair of reducing agents, (+)- and (−)-diop,[3]† a bidentate ligand attached to a rhodium hydride species. The only reported use of chiral reducing agents (other than dehydrogenase systems) on steroid ketones is the reduction of a steroid side-chain 25-en-24-one to the allylic alcohols by a complex of lithium aluminium hydride and the chiral 2,2′-dihydroxy-1,1′-binaphthyls where good stereoselectivity was obtained.[8]

In a typical analytical procedure the steroid ketone (10 μmol) was allowed to react under argon with a hydrosilane (20 μmol) in the presence of the chiral rhodium complex [(+)- or (−)-diop]Rh(S)Cl (0.0305 or 0.061 μmol, S = solvent), generated *in situ* from [(cyclo-octa-1,5-diene)-RhCl]$_2$ and diop in benzene or other solvent. The reactions were carried out with varying time, temperature, and solvent. The resulting steroid silyl ethers were hydrolysed with 0.1% toluene-*p*-sulphonic acid in methanol to give the free alcohols. The starting materials and products were separated by high performance liquid chromatography (h.p.l.c.) on a Partisil PXS 10/25 column (Whatman) and detected by u.v. absorption at suitable wavelength, and by refractive index.

Reduction of estrone-3-methyl ether at 22 °C with diphenylhydrosilane and the Rh–(+)-diop complex in benzene gave the 17β:17α-alcohols in the ratio of 82:18, close to that obtained by reduction of the ketone with achiral reagents such as $NaBH_4$, Li–NH_3, or $LiAlH_4$.[7] The same proportions were obtained at 75 °C (83:17). Estrone in xylene at 22 °C gave essentially the same ratio (80:20). Substitution of Rh–(−)-diop for the (+)-enantiomer gave, with estrone methyl ether, a ratio of 58:42 (22 °C) and 63:37 (75 °C). Rh–(−)-diop is thus a useful mild reagent for reduction of a 17-ketone to the relatively inaccessible 17α-alcohol.

The aromatic hydrocarbons benzene, toluene, xylene, and 1,1-bis(3,4-dimethylphenyl)ethane (dixylylethane) were found to be good solvents for the reduction of estrone methyl ether. The steroid and reagents are sufficiently soluble, and there was a consistent difference in the direction of reduction, the (−)-diop reagent giving a larger proportion of the 17α-alcohol than the (+)-diop reagent. In methanol this distinction essentially disappeared; the Rh–(+)-diop reagent gave the 17-alcohols β:α 89:11 while the Rh–(−)-diop reagent gave β:α 80:20. The nature of the catalytic species in methanol is not clear. In tetrahydrofuran no reduction was seen.

Attempts were made to use other silanes in place of diphenylsilane. Using the standard analytical conditions, triethoxysilane and triphenylsilane with either enantiomer of Rh–diop (0.061 μmol) gave only traces of the 17β-alcohol after 168 h at 22 °C. With a larger excess of triphenylsilane (40 μmol) either enantiomer of Rh–diop gave exclusively the 17β-alcohol, though still in poor yield (12%). Diethylsilane gave predominantly the 17β-alcohol (β:α 8:2) with either enantiomer of Rh–diop. n-Pentylsilane behaved like diphenylsilane in giving, with Rh–(−)-diop, complete reduction to the 17-alcohols (β:α 53:57). However, with Rh–(+)-diop (80:20), the reaction was slower than with diphenylsilane.

On a preparative scale, estrone methyl ether (56.8 mg) was reduced by diphenylsilane (80 mg), [(cyclo-octa-1,3-diene)-RhCl]$_2$ (0.5 mg), and (−)-diop (1.5 mg) in xylene under argon at 22 °C for 24 h, followed by the acidic work up as described. The products were separated cleanly by h.p.l.c. with hexane–chloroform (2:1) as eluant giving, after recrystallization, the 17α-alcohol (20.7 mg, 36% yield), the 17β-alcohol (15.0 mg, 26% yield), and recovered ketone (2.4 mg, 4% yield).

The reduction of the 20-ketone group was studied using pregna-3,5-dien-20-one.[9] With diphenylsilane and either the Rh–(+)-diop or the Rh–(−)-diop reagent the 20-ketone gave the same 20β:20α-alcohol ratio of 7:3.

The reduction of 5β-pregnane-3,20-dione with (+)- and with (−)-diop took place at both 3- and 20-ketone groups showing little regioselectivity; the ratio of epimers at the

† (−)-diop = (2*S*,3*S*)-*O*-isopropylidene-2,3-dihydroxy-1,4-bis-(diphenylphosphino)butane.

3-position was 3β:3α-alcohol 67:33 [(+)-diop] and 64:36 [(−)-diop].

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