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SYNTHESIS OF OPTICALLY ACTIVE (+)-19-NORTESTOSTERONE BY ASYMMETRIC BIS-ANNULATION REACTION

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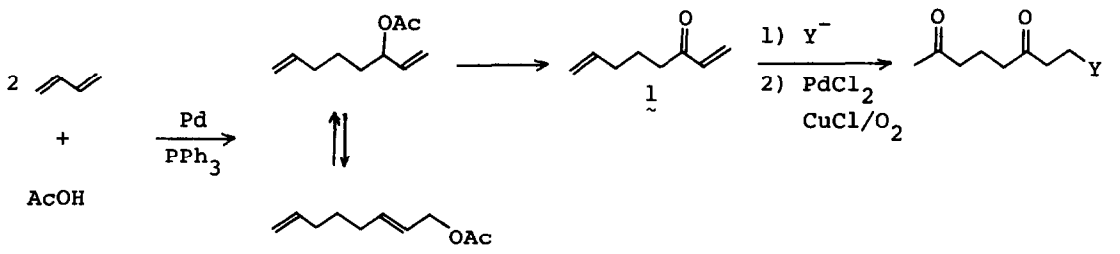
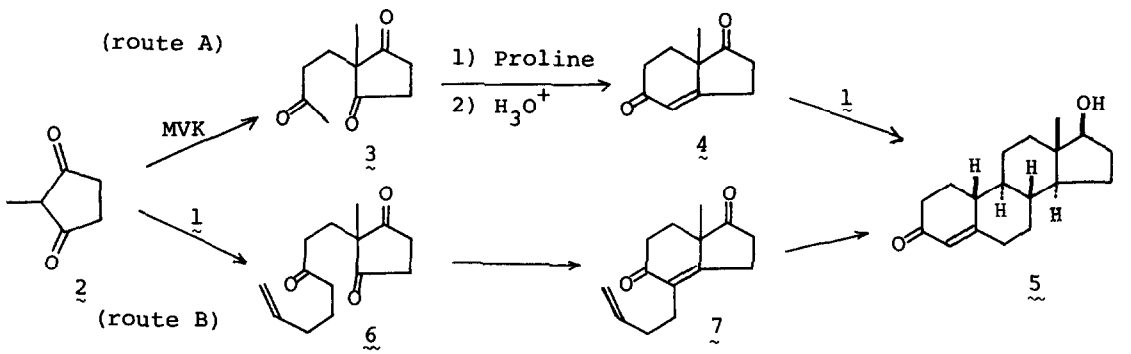
Summary: Michael reaction of 1,7-octadien-3-one with 2-methylcyclopentane-1,3-dione, followed by intramolecular aldol condensation promoted by L-amino acids produced the optically active (+)-4-(3-butenyl)-7a-methyl-5,6,7,7a-tetrahydro-indane-1,5-dione in high chemical and optical yields. The $PdCl_2$-catalyzed oxidation of the terminal double bond gave the methyl ketone, which had 76% optical purity and was made 100% optically pure by recrystallization. Then aldol condensation afforded the tricyclic ketone, which was alkylated with 3-butenyl iodide to afford (-)-3β-*t*-butoxy-2,3,3a,4,5,7,8,9,9aβ,9bα-decahydro-6-(3-butenyl)-3aβ-methyl-1H-benz[e]inden-7-one. The synthesis of this compound means the total synthesis of (+)-19-nortestosterone.

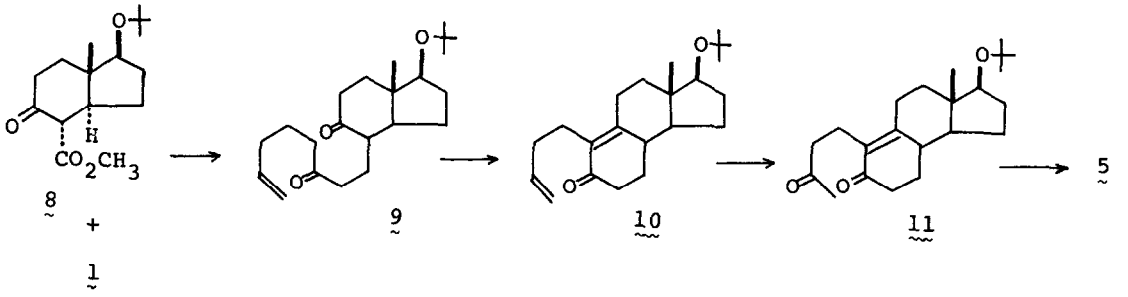
In a previous paper we have reported the preparation of 1,7-octadien-3-one (1) as a new and simple bis-annulation reagent from an easily available butadiene telomer.[1)] This reagent undergoes the addition to nucleophiles at the enone moiety and then the other terminal olefin is unmasked by the $PdCl_2$-catalyzed oxidation to give a 1,5-dione system.



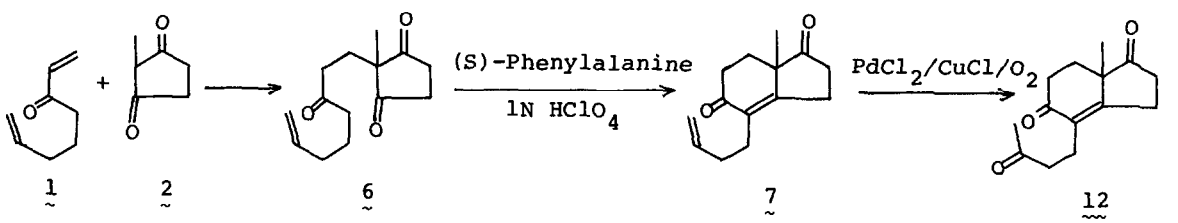
When we apply this reagent 1 to steroid synthesis, two approaches are possible. The first one is the route of D→CD→ABCD, and the AB rings are derived from the bis-annulation reagent; (route A). The other is D→ BCD→ ABCD, and the BC rings are derived from the reagent 1; (route B).

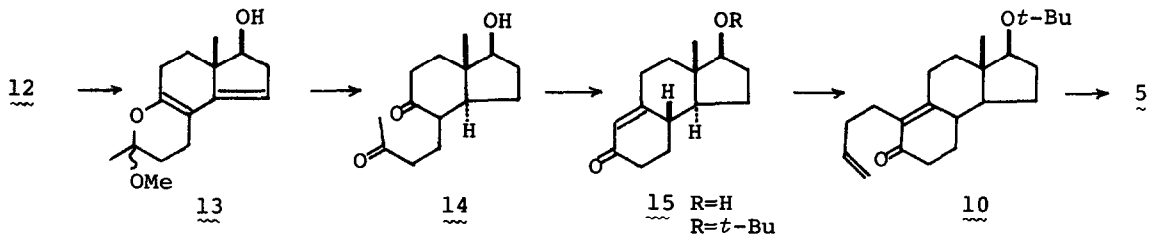


Based on the route A, we have already synthesized (+)-19-nortestosterone (5) from the optically active keto ester 8 by the following sequence of reactions.[1]



Recently Schering and Hoffmann La Roche groups developed an ingenious method of asymmetric aldol condensation of 3 using L-proline as a promoter to give 4 in nearly quantitative optical yields,[2-4] thus opening the way to synthesis of optically pure steroids.[2,5-9] In our former synthesis of 5 based on the route A, we have utilized the optically pure keto ester 8, which was derived from the optically active diketone 4. We now wish to report the synthesis of the optically pure steroid 5 based on the route B. In order to synthesize the optically pure steroid, we attempted the asymmetric aldol condensation of 6 to form 7. The synthesis was carried out by the following sequence of reactions.





The Michael addition of 2-methylcyclopentane-1,3-dione (2) to the enone 1 was carried out in ethyl acetate using triethylamine as a catalyst at room temperature to give the triketone 6 in 84% yield: NMR (CCl_4) δ 1.00 (3H, s, CH_3), 2.75 (4H, s, CH_2CH_2-), 4.72-6.20 (3H, m, vinyl); IR (film) 1723, 1641, and 918 cm^{-1}. Then the asymmetric aldol condensation was attempted by using several L-amino acids. As shown in table 1, (S)-(-)-phenylalanine with 1N-$HClO_4$ in acetonitrile showed the best results, which were comparable to those reported by Eder[3] and Danishefsky.[8] The optically active ketone 7 obtained under the conditions of entry 2 showed the following properties: $[\alpha]_D^{25}$ = +216° ($CHCl_3$); NMR (CCl_4) δ 1.02 (3H, s, CH_3); IR (film), 1720, 1640, and 918 cm^{-1}. The optical yield was determined after the oxidation of the terminal olefin to give the known compound 12 as crystals. Thus the oxidation of 7 using $PdCl_2/CuCl/O_2$ in aqueous DMF gave the triketone 12 in 77% yield: NMR (CCl_4) δ 1.23 (3H, s, angular CH_3), 2.03 (3H, s, $COCH_3$); IR (KBr) 1650, 1712, and 1740 cm^{-1}. Its optical rotation $[\alpha]_D^{23}$ = +186° (benzene) was compared with the reported one[10] and the optical purity was found to be 76% ee. The recrystallization of the product 12 from ether produced the racemic compound as the first crop (mp 92-94°C, lit.[11] 93.5-94.5°C) and the optically pure compound was obtained as the second crop: $[\alpha]_D^{23}$ = +254° (benzene), lit.[10] $[\alpha]_D^{23}$ = +249°; mp 72-73°C, lit.[10] 72-73.5°C.

Reduction of the enone system of 12 to give the saturated diketone 14 with the trans-fused ring junction was carried out by the known hydrogenation method of the diene 13.[10] The aldol condensation of 14 afforded the tricyclic ketone 15 (R = H) in 43% yield from 12: $[\alpha]_D^{23}$ = -45.6° ($CHCl_3$), lit.[10] $[\alpha]_D^{23}$ = -44.5°; mp 109-113°C, lit.[10] 113-114°C.

In order to add the ring A, we used the butenylation and its oxidation,[12] instead of a common annulating reagent. The alcohol of 15 was protected as a *t*-butyl ether ($[\alpha]_D^{25}$ = -12.5° ($CHCl_3$), mp 128-130°C), and its sodium enolate was treated with an excess of 3-butenyl iodide in DMSO at room temperature to give the butenylated ketone 10 in 54% yield based on conversion. Some O-alkylated product and starting material were recovered. The optically pure 10, thus obtained, was identical with an authentic sample prepared before in this laboratory: $[\alpha]_D^{25}$ = -14.5° ($CHCl_3$), lit. $[\alpha]_D^{25}$ = -14.8°[1]

The synthesis of 10 means the total synthesis of (+)-19-nortestosterone (5), because the conversion of 10 to 5 has been accomplished already.

Table. Asymmetric Aldol Cyclization of 6 to 7

Entry	Amino acid (1-equiv.)	Solvent	1N $HClO_4$ (equiv.)	Reaction time (hr)	$[\alpha]_D^{25}$ ($CHCl_3$)	Chemical yield (%)[b]
1	(S)-Phenylalanine	CH_3CN	1.0	69	+142°	32
2			0.4	72	+216	85
3			0.25	63	+185	67
4		CH_3CO_2H	-	26	+48.2	77
5		Dioxane	0.5	18.5	+160	49
6		DME	0.5	63	+208	41
7		MeOH	0.5	69	+180	40
8		EtOH	0.5	35	+203	63
9		*t*-BuOH	0.5	37	+189	84
10		DMF (100°C)	0.5	24	+128	21
11		DMSO (90°C)	0.5	12	+183	33
12	(S)-Tryptophane	CH_3CN	0.5	65	+193	40
13	(S)-Tyrosine	CH_3CN	0.5	37	+67.8	65
14	(S)-Alanine	CH_3CN	0.5	74	0	22
15	(S)-Proline	CH_3CN	1.0	45	0	55
16			0.5	120	+57.3	22

a) The reactions were carried out under reflux except entries 10 and 11.

b) Isolated yields by chromatography (silica gel).

References:

1. J.Tsuji, I.Shimizu, H.Suzuki, and Y.Naito, J.Am.Chem.Soc., 101, 5070 (1979).
2. N.Cohen, Acc.Chem.Res., 9, 412 (1976).
3. U.Eder, G.Sauer, and R.Wiechert, Angew.Chem., 83, 492 (1971).
4. Z.G.Hajos and D.R.Parrish, J.Org.Chem., 39, 1615 (1974).
5. R.A.Micheli, Z.G.Hajos, N.Cohen, D.R.Parrish, L.A.Portland, W.Sciamanna, M. A.Scott, and P.A.Wehrli, J.Org.Chem., 40, 675 (1975).
6. N.Cohen, B.L.Banner, W.F.Eichel, D.R.Parrish, and G.Saucy, J.Org.Chem., 40, 681 (1975).
7. G.Sauer, U.Eder, G.Haffer, G.Neef, and R.Wiechert, Angew.Chem., 87, 413 (1975)
8. S.Danishefsky and P.Cain, J.Am.Chem.Soc., 98, 4975 (1976).
9. T.Kametani, H.Matsumoto, H.Nemoto, and K.Fukumoto, J.Am.Chem.Soc., 100, 6218 (1978).
10. U.Eder, G.Sauer, J.Ruppert, G.Haffer, and R.Wiechert, Chem.Ber., 108, 2673 (1975).
11. O.I.Fedorova, G.S.Grinenko, and V.I.Maksimov, Dokl.Akad.Nauk SSSr, 171, 880 (1966).
12. J.Tsuji, I.Shimizu, and K.Yamamoto, Tetrahedron Lett., 2975 (1976).

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