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NEW SYNTHESIS OF A CHIRAL STEROID CD-RING SYNTHON BY MEANS OF ENANTIOSELECTIVE DOUBLE MICHAEL ADDITION

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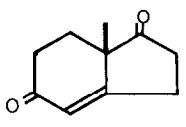
Summary: A new synthetic method of (+)-(1R)-acetyl-(7aR)-methyl-4-hydroinden-5-one (**2**) by highly enantioselective double Michael addition involving alkenylcopper-phosphine complex, 3-trimethylsilylbutenone and 2-methyl-2-cyclopentenone is presented.

The recent discovery of new steroids, such as vitamin D_3 metabolites and the plant growth regulator brassinolide, has spurred to search for the effective synthetic method for steroids. So far, two types of researches in steroid syntheses : (1) the development of synthetic strategy for the construction of steroid nucleus (A, B, C, and D rings)[1] and (2) the stereoselective introduction of side chain onto the basic nucleus,[2] have appeared. Most of previous syntheses of steroid nuclei are, however, racemic approaches and the optically active approach[3,4] is recent requisite for steroid syntheses. By now the optically active hydroindenone **1**,[3,4] prepared by the asymmetric aldol condensation, is a typical synthetic precursor for various steroids. In this communication we report the synthesis of the chiral (+)-diketone **2** as a new synthetic precursor for 20-ketosteroids.



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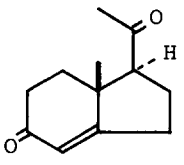
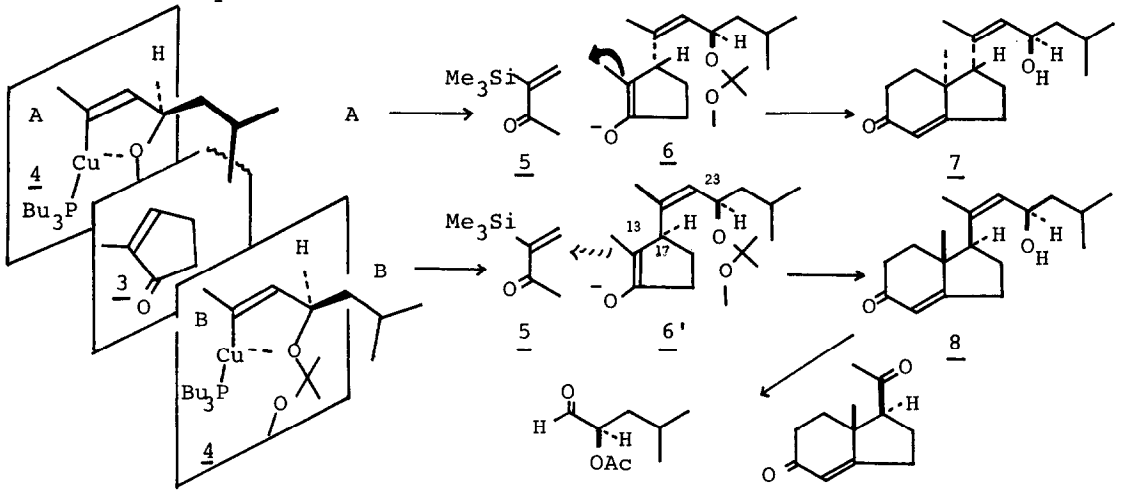


2

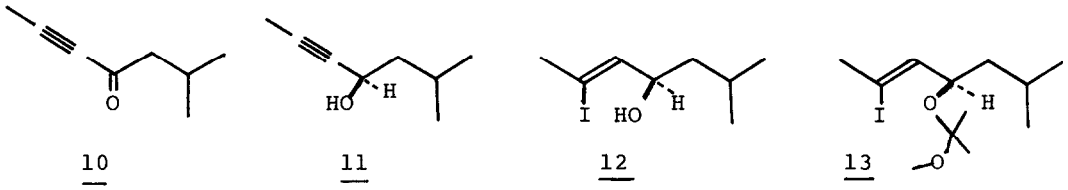
We have recently described[5] the synthesis of (±)-de-AB-isocholesta-8(14),22-dien-9-one by the stereoselective double Michael addition, and predicted that the cis-vinylcopper phosphine complex with (23R)-configuration (steroidal numbering) should provide the chiral steroid CD-rings. In our chiral approach (Scheme 1), key steps are the highly enantioselective Michael addtion of the alkenylcopper-phosphine complex **4**, derived from the (R)-vinyl iodide **13**, to 2-methyl-2-cyclopentenone (**3**) and the subsequent conjugate addition of the resultant enolate **6** to 3-trimethylsilylbutenone (**5**). Two transition states A and B are possible in the first Michael addition. The transition state A is less favorable than B owing to the interaction between the isobutyl group and cyclopentenone ring. Consequently, the first Michael addition

proceeds through the transition state B as a major course and the C(23R) absolute configuration serves to control the C(17R) absolute configuration, while the transition state A as a minor course gives the C(17S) absolute configuration. The second Michael additions of the resultant enolates **6** and **6'** to methyl vinyl ketone **5** introduce the C(13S) and C(13R) absolute configuration, respectively, with the right cis stereochemistry between C(13)-methyl and the side chain at C(17), since the methyl vinyl ketone **5** reacts from sterically less hindered side of the enolates. This double Michael addition can be carried out in one pot. The removal of the silyl group and the simultaneous formation of the C ring by intramolecular aldol condensation with base and hydrolysis of 2-methoxypropyl ether with acid give predominantly the enone **8**. These overall transformations can be carried out without any purifications. The site-selective ozonolysis of the $\Delta^{20(22)}$-olefin in **8** gives the (+)-diketone **2** and the aldehyde **9**.



(Scheme 1)

Thus the (+)-(Z)-2-iodo-4-hydroxy-6-methyl-2-heptene (**12**) was our initial synthetic target and easily prepared from the 6-methyl-2-heptyn-4-one (**10**) in the following way (Scheme 2). The asymmetric reduction[7] of the acetylenic ketone **10** (19.7 mmol), prepared by the addition of propynylmagnesium bromide to 3-methylbutanal followed by the oxidation (88% overall yield), with lithium aluminum hydride (21.7 mmol) in the presence of Darvon alcohol (49.4 mmol) in dry ether at -78 °C gave the optically active alcohol **11** in 89% yield: $[\alpha]^{25}_{D}$=+11.42 (c 5.08, $CHCl_3$); 82% e.e. based on lit[8] $[\alpha]^{25}_{D}$=+13.48 (c 4.9, $CHCl_3$). The hydroalumination of the acetylenic alcohol **11** (11.9 mmol) with lithium aluminum hydride (11.9 mmol) in the presence of sodium methoxide (23.7 mmol) at THF reflux and quenching of the resultant alkenylaluminium complex with iodine (59.1 mmol) at -78 °C gave the (R)-vinyl iodide **12** in 58% overall yield: $[\alpha]^{25}_{D}$=+22.67 (c 1.95, benzene). Protection of the allyl alcohol **12** ($CH_2CHOMe/POCl_3/CH_2Cl_2$ at 0 °C) gave in quantative yield the 2-methoxypropyl ether **13** which was used for next reaction without purification.

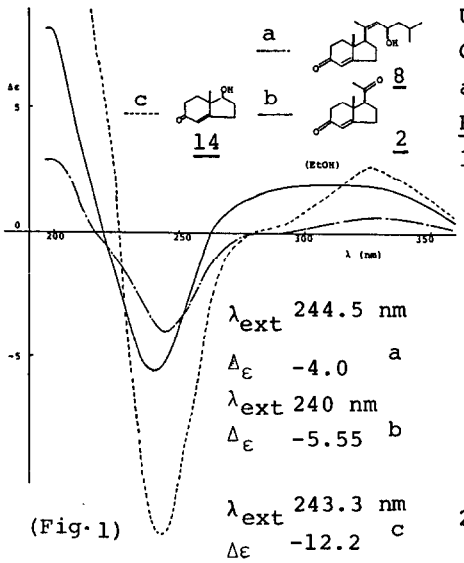


10 11 12 13

(Scheme 2)

The construction of CD rings was carried out by the following way. The vinyl iodide **13** (1.2 mmol) was metalated in dry n-hexane with n-butyllithium (1.3 mmol) at -78 °C under argon atmosphere. To this solution was added, at -78°C over a period of 1 hour, a solution of copper phosphine complex [9] which was separately prepared from CuI (1.2 mmol) and P(n-Bu)$_3$ (3.2 mmol) in dry ether at room temperature under argon. The reaction mixture was slowly warmed to -55 °C over a period of 1 hour and cooled to -78 °C. Subsequently, a solution of 2-methyl-2-cyclopentenone (**3**) (1.0 mmol) in dry ether was added over a period of 50 min, and then the solution was allowed to warm to -20 °C over a period of 2 hours. To this solution was added dropwise a solution of -silylvinyl methyl ketone **5** [10] (1.0 mmol) in dry ether over a period of 50 min and the temperature was maintained for 2 hours at -20 °C. After usual work-up with aqueous NH_4Cl, the obtained crude mixture was dissolved in methanol, and sodium methoxide (5 mmol) was added. The mixture was refluxed for 3 hours under nitrogen atmosphere. Usual work up and treatment of the resultant aldol product with 3N HCl at 0 °C for 5 min gave an easily separable mixture of diastereomers **7** and **8** in a 1 : 10 ratio [**8**: 30% overall yield (six steps) based on **3**; high resolution mass spectrum, calcd for $C_{18}H_{28}O_2$, m/e=276.2089, found m/e=276.2081; NMR ($CDCl_3$) 1.00 (s, 3H, CH_3), 1.81 (d, J=2 Hz, 3H, CH_3), 4.51 (dt, J=4 and 9 Hz, 1H, CHOH), 5.51 (br d, J=9 Hz, 1H), 5.78-5.94 (m, 1H, olefinic); IR (neat) 3400, 1650, 1055, 737 cm^{-1}; $[\alpha]^{25}_D$=16.38 (c, 0.586, $CHCl_3$); **7**: 3% overall yield; NMR ($CDCl_3$) 0.96 (s, 3H, CH_3), 1.77 (d, J=2 Hz, 3H, CH_3), 3.83-4.34 (m, 1H, CHOH), 5.10-5.41 (m, 1H), 5.72-5.90 (m, 1H, olefinic)].

Conversion of the enone **8** to the diketone **2** was carried out in the following way. Acetylation of the allyl alcohol **8** [Ac_2O/pyridine, 87% yield] and its selective ozonolysis of $\Delta^{20(22)}$-olefin in CH_2Cl_2 at -78 °C and the reductive work up (Me_2S at -78 °C) gave the diketone **2** and the aldehyde **9** in 55 and 50% yields respectively [**2**: $[\alpha]^{25}_D$=+95.45 (c 0.88, $CHCl_3$); IR (neat) 1700, 1660 cm^{-1}; NMR ($CDCl_3$) 1.08 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 5.7-5,82 (m, 1H, olefinic)]. We determined here the absolute configuration of the enone **8** and the diketone **2** by CD spectra. The CD spectra of **8**, **2** and the optically active enone **14** were shown in Figure 1. The simple comparisons of CD spectra of **8** (curve a) and **2** (curve b) with that of **14** (curve c, the absolute configuration of **14** is known) [11] led to an (R)-configuration at C(13) of **8** and **2**. These results indicate that the initial Michael addition of the alkenylcopper phosphine complex **4** with (23R)-configuration to the cyclopentenone **3** led predominantly to the C(17R)-configuration in **8**.



(Fig. 1)

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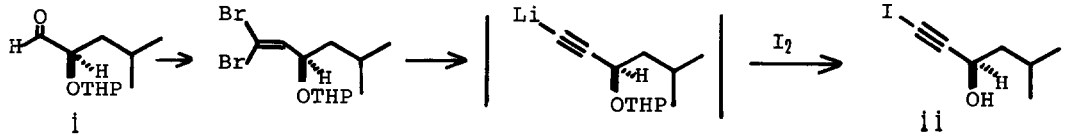

i ii

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