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STEREOCHEMICAL STUDIES—LVIII[1]

SYNTHESIS OF OPTICALLY ACTIVE COMPOUNDS BY THE NOVEL USE OF *MESO*-COMPOUND-2.[1] EFFICIENT SYNTHESIS OF AN OPTICALLY PURE STEROID INTERMEDIATE.[2]

M. NARA

Tokyo Research Laboratories, Kowa, Co. Ltd., 2-27-43, Noguchicho, Higashimurayama, Tokyo, 189, Japan

S. TERASHIMA

Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo, 113, Japan

and

S. YAMADA

Faculty of Pharmaceutical Sciences, Josai University, 1-1, Keyakidai, Sakado, Saitama, 350-02, Japan

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Abstract—In order to explore the general application of a novel method for preparing optically active compounds, synthesis of the optically pure steroid intermediate((−)-**1**) has been examined by employing the diol(**2**) as a *meso*-compound and N-mesyl-(S)-phenylalanyl chloride(**3**) as a source of the optically active functional group.

In the preceding paper,[1] the authors have developed a novel method to convert a total amount of starting material into an optically pure compound of the desired absolute configuration. While the method recommends utilization of a symmetrically functionalized *meso*-compound in place of a racemic modification, it has already been realized by the successful synthesis of two structural types of the prostaglandin intermediates.[1]

This report describes our successful synthesis of optically pure steroid intermediate ((−)-**1**)[3,4,7] from the *meso-diol*(**2**)[8] using N-mesyl-(S)-phenylalanyl chloride(**3**)[1] as an optically active reagent.

RESULTS AND DISCUSSION

Although compound **2**[8] was first synthesized by successive stereoselective reduction of the dione(**4**)[5a] (60% yield),[5a,9] acetylation of *dl*-**5** (99% yield),[5a] stereoselective reduction of the C-14 CO group of *dl*-**6** and alkaline hydrolysis (92% yield) according to a combination of the reported methods,[5a,8] we developed the new preparation method of **2** being simpler and more efficient than that described above.

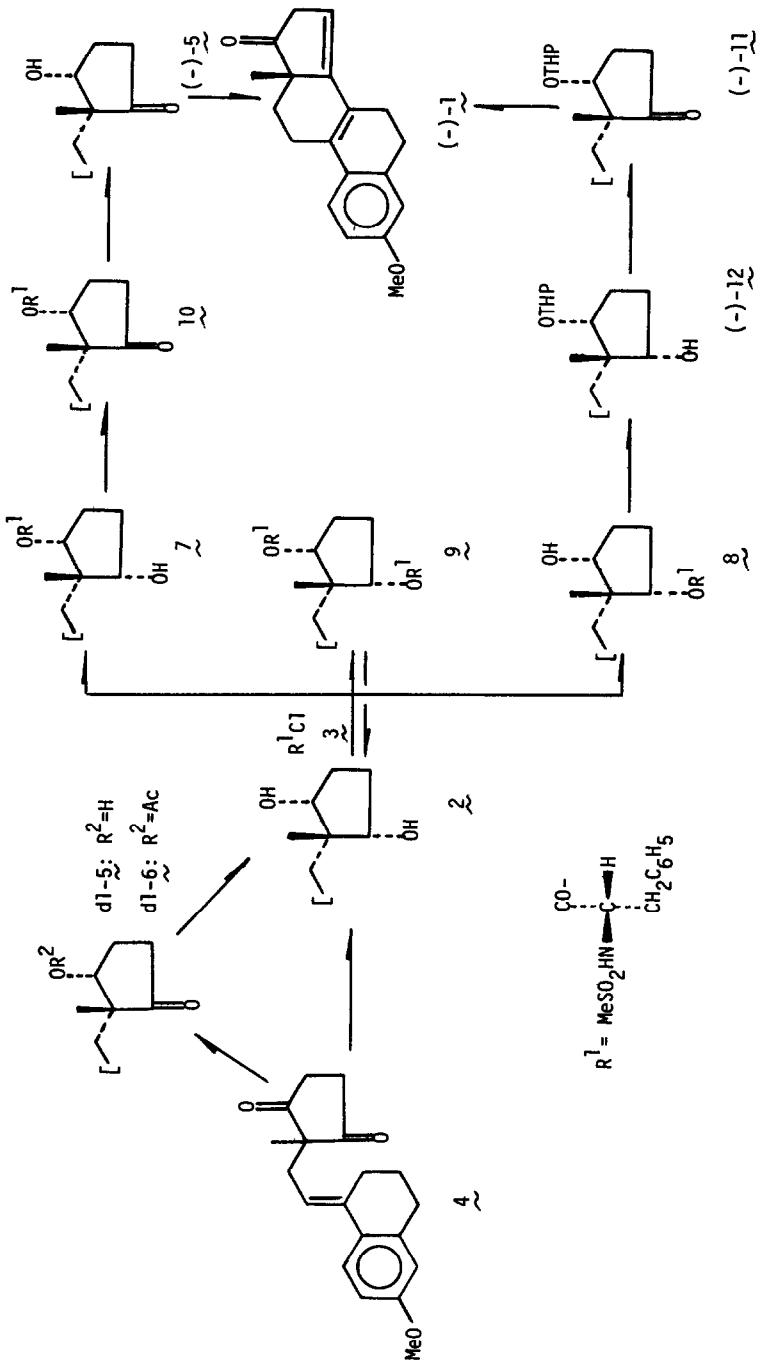
Thus, direct reduction of the metal complex, produced by the reduction of **4** with lithium tri-t-butoxyaluminum hydride,[9] with lithium aluminum hydride without isolation was found to proceed fairly stereoselectively under an influence of the large tri-t-butoxyaluminum group at the β-position, giving the desired **2** in 59% yield after recrystallization.

Acylation of **2** with **3**[1] followed by separation with preparative tlc, afforded unreacted **2** in 26% recovery, and the oily diester(**9**), $[\alpha]_D^{20}$ − 89.5° ($CHCl_3$), the oily less polar monoester(**7**), $[\alpha]_D^{20}$ − 50.8° ($CHCl_3$), and the crystalline more polar monoester(**8**), $[\alpha]_D^{22}$ + 22.6° ($CHCl_3$), in 23%, 22%, and 19% yields, respectively. The structures of **7** and **8** were determined by the successful preparation of (−)-**1** from **7** and **8** as described later. The yields of **7** and **8** were found to be improved when **3**[1] was added to the mixture all at once (Experimental). Since alkaline hydolysis of useless **9** readily recovered **2** in 96% yield and N-mesyl-(S)-phenylalanine without racemization in 74% yield, the yields of **7** and **8** could be calculated as 42% and 36%, respectively, when corrected for the total amount of recovered **2**.

Separation of **7** and **8** could also be accomplished more simply by fractional recrystallization to afford crystalline **8**, $[\alpha]_D^{20}$ + 22.4° ($CHCl_3$), and an oily mixture of **7** and **8**, $[\alpha]_D^{20}$ − 34.5° ($CHCl_3$), in 20% and 70% yields (corrected for the recovery of **2**).[10] The ratio of **7** to **8** in the oily mixture was estimated as 3.5:1 by comparing its optical rotation with those of pure **7** and **8** separated by preparative tlc.

The Pfitzner–Moffatt oxidation[11] of oily pure **7** gave the ketone(**10**), $[\alpha]_D^{20}$ − 106° ($CHCl_3$), in 80% yield. When the same oxidation was examined using the mixture of **7** and **8** (**7**:**8** 3.5:1) and crude **10** thus obtained was twice recrystallized from MeOH, pure **10** could be also obtained in 32% yield. The acyl group of **10** was then cleaved by alkaline hydrolysis, giving known optically pure (−)-**5**,[5b] $[\alpha]_D^{20}$ − 89.6° ($CHCl_3$), in 86% yield. The hydroxy ketone ((−)-**5**) could be readily converted into optically pure (−)-**1**,[6a,c] $[\alpha]_D^{20}$ − 102° ($CHCl_3$), by successive acidic cyclization under the established condition[5] and the Pfitzner–Moffatt oxidation.[11]

On the other hand, successive protection of the alcoholic function of crystalline **8** as a tetrahydropyranyl (THP) ether,[12] hydrolytic removal of the acyl group under alkaline condition, and the Pfitzner–Moffatt oxidation,[11] yielded the protected ketone((−)-**11**), $[\alpha]_D^{20}$ − 27.3° ($CHCl_3$), in 88%



Scheme 1.

overall yield, by way of the alcohol((−)-12), $[\alpha]_D^{20}$ − 38.5° ($CHCl_3$). Simultaneous acidic cleavage of the protective THP group of (−)-11 and ring closure followed by oxidation under the Pfitzner–Moffatt condition,[11] furnished optically pure (−)-1,[6a,c] $[\alpha]_D^{20}$ − 102° ($CHCl_3$), in 65% overall yield.

Summarizing the above results, the preparation of optically pure (−)-1 could be accomplished in 41% or 25% yields (corrected for the recovery of 2) from 2, by separating 7 and 8 by preparative tlc or recrystallization.

Although many aspects, especially optimization of the chemical yield for each synthetic step, still remain to be improved, the successful preparation of optically pure (−)-1 outlined above, is considered to broaden the general applicability of our novel method.[1]

EXPERIMENTAL

All m.ps and b.ps are uncorrected. IR spectra measurements were carried out using a JASCO Spectrometer Model DS-403G and a JASCO IRA-1 Spectrometer. NMR spectra were measured with a Varian EM-360 Spectrometer. All signals are expressed by the ppm down field from TMS used as an internal standard. Following abbreviations are used: singlet(s), doublet(d), triplet(t), quartet(q), multiplet(m), broad(br). Measurements of optical rotations were carried out using a Yanagimoto OR-10 polarimeter. All reactions were performed using anhyd solvents, and purification with column chromatography was examined by the use of silica gel as an adsorbent except otherwise stated. The combined organic extracts obtained in each experiment, were dried over Na_2SO_4 before successive filtration and evaporation *in vacuo*.

3-*Methoxy*-8(14)*seco*-1,3,5(10),9(11)-*estratetraen*-14,17-*dione*(4)

This was prepared according to the reported procedure.[5a] Colorless needles, mp 76.5–78° (recrystallized from MeOH) (lit.,[5a] mp 77–79°).

dl-3-*Methoxy*-8(14)-*seco*-1,3,5(10),9(11)-*estratetraen*-17α-*ol*-14-*one*(dl-5)

Reduction of 4 with lithium tri-t-butoxyaluminum hydride[9] according to the reported procedure,[5a] followed by recrystallization from hexane-ether gave a 60% yield of *dl*-5 colorless needles, mp 74.5–76.5° (lit.,[5a] mp 74–76°; lit.,[5b] 72–73°).

3-*Methoxy*-8(14)-*seco*-1,3,5(10),9(11)-*estratetraen*-14α,17α-*diol*(2)

Compound (a) 2 *from* 4. A THF soln (180 ml) of lithium tri-t-butoxyaluminum hydride[9] (5.10 g, 20.1 mmole) was added over 30 min to a cooled(-68–−72°), stirred soln of 4 (5.45 g, 18.3 mmole) in THF (120 ml), and the mixture was stirred at the same temp for 30 min. A suspension of LAH (0.34 g, 9.0 mmole) in THF (150 ml) was further added over 30 min to the mixture, and the stirring was continued at the same temp for another 30 min. After sat Na_2SO_4 aq was added to quench the reaction a ppt was filtered off and the filtrate was extracted with ether. The combined extracts were washed with H_2O. Filtration and evaporation *in vacuo* gave a crystalline residue (6.20 g), which was recrystallized from hexane-EtOAc to give pure 2 as colorless prisms (3.23 g, 59%), mp 100–103° (lit.,[8] mp 99–105°). IR ν_{max}^{KBr} cm^{-1}: 3330 (OH). NMR (in $CDCl_3$): 0.80 (3 H, s, CCH_3), 3.74 (3 H, s, OCH_3), 3.8 (2 H, m, CHOH × 2), 5.97 (1 H, t, J = 8 Hz, C=CH).

(b) *Compound* 2 from dl-5. According to the reported method,[5,8] successive acetylation of *dl*-5 with Ac_2O in pyridine (99%),[5a] reduction of *dl*-6 with $NaBH_4$ in MeOH followed by separation of the major isomer with column chromatography (Al_2O_3, hexane-$CHCl_3$ 2:1) (73%),[8] and usual alkaline hydrolysis of the acetyl group (92%), gave pure 2 as colorless prisms, mp 100.5–103° (recrystallized from hexane–EtOAc) (lit.,[8] mp 99–105°). Spectral (IR and NMR) and chromatographic (tlc) properties of this sample were identical with those of 2 obtained in (a).

(−)-3-*Methoxy*-14α-*hydroxy*-8(14)-*seco*-1,3,5(10),9(11)-*estratetraen*-17α-yl N-*Mesyl*-(S)-*phenylalaninate*(7), (+)-3-*methoxy*-17α-*hydroxy*-8(14)-*seco*-1,3,5(10),9(11)-*estratetraen*-14α-yl N-*mesyl*-(S)-*phenylalaninate*(8), *and* (−)-3-*methoxy*-8(14)-*seco*-1,3,5(10),9(11)-*estratetraen*-14α,17α-*diyl bis*-N-*mesyl*-(S)-*phenylalaninate*(9)

(a) To a stirred soln of 2 (2.00 g, 6.6 mmole) in pyridine (30 ml) was added a THF soln (10 ml) of 3[1] (2.77 g, 10.6 mmole) all at once at room temp. The mixture was stirred at room temp overnight, then diluted with H_2O. The aq mixture was extracted with EtOAc, and the combined extracts were washed successively with H_2O and sat $NaHCO_3$aq. Filtration and evaporation *in vacuo* gave an oily residue (2.8 g). This was subjected to preparative tlc (silica gel, hexane-EtOAc 1:1, 4 developments), giving three kinds of the reaction products (7, 8, and 9) and starting 2.

Compound 9: 1.14 g (23% yield), oil, R_f 0.60 (silica gel, hexane-EtOAc 1:1, 4 developments), $[\alpha]_D^{20}$ − 89.5° (*c* = 1.1, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725 (COO). NMR (in $CDCl_3$): 1.00 (3 H, s, CCH_3), 2.25, 2.43 (6 H, two s, CH_3SO_2x2), 3.70 (3 H, s, OCH_3), 5.2 (2 H, br s, CHOx2), 5.65 (1 H, t, J = 7 Hz, C=CH).

Compound 7. 0.76 g (22% yield), oil, R_f 0.45 (silica gel, hexane–EtOAc 1:1, 4 developments), $[\alpha]_D^{20}$ − 50.8° (*c* = 1.2, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (COO). NMR (in $CDCl_3$): 0.87 (3 H, s, CCH_3), 2.60 (3 H, s, CH_3SO_2), 3.78 (3 H, s, OCH_3), 5.0 (1 H, br s, CHOH), 5.52 (1 H, d, J = 10 Hz, CHOCO), 5.86 (1 H, t, J = 7 Hz, C=CH). (Found: C, 65.90; H, 7.00; N, 2.49. Calc for $C_{29}H_{37}O_6NS$: C, 66.02; H, 7.07; N, 2.65%).

Compound 8. 0.66 g (19% yield), colorless fine needles, mp 120–121.5° (recrystallized from hexane–EtOAc), R_f 0.35 (silica gel, hexane-EtOAc 1:1, 4 developments), $[\alpha]_D^{20}$ + 22.6° (*c* = 1.1, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3850 (OH), 1725 (COO). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (COO). NMR (in $CDCl_3$): 0.89 (3 H, s, CCH_3), 2.52 (3 H, s, CH_3SO_2), 3.77 (3 H, s, OCH_3), 5.0 (1 H, br s, CHOH), 5.36 (1 H, d, J = 10 Hz, CHOCO), 5.89 (1 H, t, J = 7 Hz, C=CH). (Found: C, 65.90; H, 7.00; N, 2.49. Calc for $C_{29}H_{37}O_6NS$: C, 66.02; H, 7.07; N, 2.65%).

Compound 2. 0.52 g (26% recovery), colorless crystalline solid, mp 99–101.5°, R_f 0.2 (silica gel, hexane–EtOAc 1:1, 4 developments). This sample was identified by spectral (IR and NMR) and chromatographic (tlc) comparisons.

(b) A THF soln (10 ml) of 3[1] (2.40 g, 9.2 mmole) was added to a stirred, cooled (0°) mixture of 2 (2.80 g, 9.3 mmole) and pyridine (2.3 ml, 28 mmole) in THF (200 ml) over 1 hr. After the mixture was stirred at 0° for 3 hr, the cooling bath was removed, and the stirring was continued overnight. Work-up in the same way as for (a) gave a mixture of products (6.0 g) which was separated by column chromatography (Al_2O_3, $CHCl_3$) to afford 9 as an oil (2.2 g, 32%), $[\alpha]_D^{20}$ − 90.0° (*c* = 1.1, $CHCl_3$), a mixture of 7 and 8 as an oil (1.7 g, 35%), $[\alpha]_D^{20}$ − 24.0° (*c* = 0.8, $CHCl_3$), and 2 (0.90 g, 32% recovery).

A part of the mixture of 7 and 8 (1.00 g) was dissolved in a small amount of hexane–EtOAc and the soln was left in a refrigerator after pure crystalline 8 was seeded. Crystals which appeared were collected and twice recrystallized from hexane–EtOAc, giving pure 8 as colorless needles (0.21 g, 20% corrected for the recovery of 2[10]), mp 120–121°, $[\alpha]_D^{20}$ + 22.4° (*c* = 1.4, $CHCl_3$). Three lots of the mother liquors from the recrystallization were combined and evaporated *in vacuo* to afford crude 7 as an oil (0.75 g, 70% corrected for the recovery of 2[10]), $[\alpha]_D^{20}$ − 34.5° (*c* = 1.1, $CHCl_3$). The oily mixture was found to contain 7 and 8 in a ratio of 3.5:1 by comparing its optical rotation with those of pure 7 and 8 obtained in (a).

All products obtained here were identified by spectral (IR and NMR) and chromatographic (tlc) comparisons with the samples prepared in (a).

Recovery of **2** from **9** was carried out as follows. A mixture of **9** (0.75 g, 1.0 mmole) and KOH (0.22 g, 4.0 mmole) in aq MeOH (MeOH (10 ml)-H_2O(2 ml)) was kept at room temp for 2 days. After evaporation *in vacuo*, the usual extractive isolation of the neutral fraction with ether gave **2** (0.29 g, 96%) as a solid, mp 100–102.5°. N-Mesyl-(S)-phenylalanine was also recovered as colorless needles (0.36 g, 74%) from the acidic fraction without racemization, mp 105–106.5°, $[\alpha]_D^{20}$ − 16.3° (c = 4.3, $CHCl_3$) (lit.,[1] mp 105–107°, $[\alpha]_D^{20}$ − 16.7° (c = 4.2, $CHCl_3$)).

(−)-3-*Methoxy*-8(14)-*seco*-1,3,5(10),9(11)-*estratetraen*-14-*on*-17α-yl N-*mesyl*-(S)-*phenylalaninate*(**10**)

A mixture of **7** ($[\alpha]_D^{20}$ − 51.3° (c = 1.2, $CHCl_3$)) (0.61 g, 1.6 mmole), dicyclohexyl carbodiimide (1.20 g, 5.8 mmole), dimethyl sulfoxide (3 ml), pyridine (0.1 ml), and trifluoroacetic acid (0.05 ml) in benzene (10 ml) was stirred at room temp for 5 hr.[11] The reaction was quenched by adding an aq soln of oxalic acid. After being stirred for 5 min, the mixture was extracted with benzene. The combined extracts were filtered to remove insoluble materials, and washed with sat $NaHCO_3$aq. Filtration and evaporation *in vacuo* gave the residue, which was purified by column chromatography ($CHCl_3$) and recrystallization from MeOH to yield pure **10** as colorless needles (0.49 g, 80%), mp 116.5–118°, $[\alpha]_D^{20}$ − 106° (c = 1.4, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3210 (NH), 1730 (COO). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 (COO). NMR (in $CDCl_3$): 1.06 (3 H, s, CCH_3), 2.54 (3 H, s, CH_3SO_2), 3.78 (3 H, s, OCH_3), 4.1–4.6 (1 H, m, CH_2CHCO), 5.06 (1 H, d, J = 10 Hz, CHOH), 5.33 (1 H, m, CHOCO), 5.70 (1 H, t, J = 7 Hz, C=CH). (Found: C, 66.23; H, 6.81; N, 2.54. Calcd for $C_{29}H_{35}O_6NS$: C, 66.26; H, 6.71; N, 2.66%).

When the same oxidation was carried out using **7** ($[\alpha]_D^{20}$ − 34.5° (c = 1.1, $CHCl_3$)) (7:8 3.5:1) (0.75 g, 1.4 mmole), crude **10** was obtained as a yellow viscous oil (0.71 g, 95%), $[\alpha]_D^{20}$ − 36.8° (c = 0.9, $CHCl_3$), after purification by column chromatography. Two recrystallizations of this sample from MeOH gave pure **10** as colorless needles (0.24 g, 32%), mp 116–118°, $[\alpha]_D^{20}$ − 106° (c = 1.6, $CHCl_3$). This sample showed identical spectral (IR and NMR) properties with those of **10** obtained from pure **7**.

(−)-3-*Methoxy*-8(14)-*seco*-1,3,5(10),9(11)-*estratetraen*-14-*on*-17α-*ol*((−)-**5**

A soln of **10** ($[\alpha]_D^{20}$ − 106° (c = 1.4, $CHCl_3$)) (0.49 g, 1.4 mmole) and KOH (0.20 g, 3.6 mmole) in a mixture of MeOH (2 ml), THF (5 ml), and H_2O (2 ml), was stirred at room temp overnight, and the mixture was evaporated *in vacuo*. From the residue, the neutral fraction was extracted with ether by the usual manner. Filtration and evaporation *in vacuo* of the combined extracts followed by recrystallization from MeOH, gave optically pure (−)-**5** as colorless fine needles (0.30 g, 86%), mp 103.5–104°, $[\alpha]_D^{20}$ − 89.6° (c = 1.2, $CHCl_3$) (lit.,[5b] mp 102–103° and $[\alpha]_D^{24}$ − 83.6° (c = 1, $CHCl_3$)).

(−)-3-*Methoxy*-17α-*tetrahydropyranoxy*-8(14)-*seco*-1,3,5(10),9(11)-*estratetraen*-14α-*ol*((−)-**12**)

(a) (−)-3-*Methoxy*-17α-*tetrahydropyranoxy*-8(14)-*seco*-1,3,5(10),9(11)-*estratetraen*-14α-*yl* N-*mesyl*-(S)-*phenylalaninate*. To a stirred mixture of **8** ($[\alpha]_D^{20}$ + 22.6° (c = 1.1, $CHCl_3$)) (0.46 g, 0.87 mmole) and dihydropyran (0.15 g, 1.8 mmole) in CH_2Cl_2 (5 ml) was added a THF soln (0.87 ml) of anhyd TsOH (5 mg, catalytic amount), and the whole was stirred at room temp for 2 hr. After adding pyridine (2 drops), extraction with $CHCl_3$ followed by successive washing with H_2O, filtration, and evaporation *in vacuo*, afforded the crude product as a pale yellow viscous oil (0.60 g, quantitative yield), $[\alpha]_D^{20}$ − 1.7° (c = 1.4, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1740 (COO). NMR (in $CDCl_3$): 1.00 (3 H, s, CCH_3), 2.45, 2.51 (3 H, two s, CH_3SO_2), 3.70, 3.73 (3 H, two s, OCH_3), 5.7 (1 H, m, C=CH). This sample was immediately subjected to the next hydrolysis.

(b) *Compound* (−)-**12**. The crude THP ether (0.60 g) obtained in (a) was added to aq MeOH(MeOH (5 ml)-H_2O(2 ml)) containing KOH (0.24 g, 4.3 mmole), and the mixture was stirred at room temp for 16 hr. After evaporation *in vacuo*, the residue was extracted with EtOAc, and the combined extracts were washed with H_2O. Filtration and evaporation *in vacuo*, followed by purification with column chromatography (Al_2O_3, $CHCl_3$), gave (−)-**12** as a colorless viscous oil (0.16 g, 88% corrected for the recovery of the starting material), $[\alpha]_D^{20}$ − 38.5° (c = 0.2, $CHCl_3$), and the starting THP ether as an oil (0.28 g, 47%). The following spectra were recorded on (−)-**12**. IR ν_{max}^{film} cm^{-1}: 3520 (OH). NMR (in $CDCl_3$): 0.80 (3 H, s, CCH_3), 3.74 (3 H, s, OCH_3), 3.95 (1 H, s, CHOH), 4.70 (1 H, s, OCHO), 6.08 (1 H, t, J = 7 Hz, C=CH).

(−)-3-*Methoxy*-17α-*tetrahydropyranoxy*-8(14)-*seco*-1,3,5(10),9(11)-*estratetraen*-14-*one*(−)-**11**.

A benzene soln (5 ml) containing (−)-**12** ($[\alpha]_D^{20}$ − 38.5° (c = 0.2, $CHCl_3$)) (0.19 g, 0.49 mmole), dicyclohexyl carbodiimide (0.40 g, 1.9 mmole), dimethyl sulfoxide (3 ml), pyridine (0.1 ml), and trifluoroacetic acid (0.05 ml) was stirred at room temp for 5 hr.[11] Treatments of the mixture in the same way as for the oxidation of **7** gave pure (−)-**11** as a colorless oil (0.19 g, 100%), $[\alpha]_D^{20}$ − 27.3° (c = 1.0, $CHCl_3$), after purification by column chromatography (Al_2O_3, benzene). IR ν_{max}^{film} cm^{-1}: 1740 (CO). NMR (in $CDCl_3$): 1.03 (3 H, s, CCH_3), 3.76 (3 H, s, OCH_3), 4.8 (1 H, m, OCHO), 5.7–6.3 (1 H, m, C=CH).

(−)-3-*Methoxy*-1,3,5(10),8,14-*estrapentaen*-17-*one*((−)-**1**)

(a) *Compound* (−)-**1** *from* (−)-**5**. To a methanolic soln (6 ml) of (−)-**5** ($[\alpha]_D^{20}$ − 89.6° (c = 1.2, $CHCl_3$)) (0.20 g, 0.67 mmole) was added conc HCl (0.6 ml), and the acidic mixture was heated at reflux for 2 hr. Similar work-up of the mixture to that reported[5b] gave the crude cyclization product as a foam (0.19 g).

Oxidation of the crude sample (0.19 g) by the same procedure as for the preparation of **10** from **7**, followed by purification with column chromatography (hexane-benzene 1:1), afforded (−)-**1** as almost colorless plates (0.13 g, 70%), mp 141.5–142.5° (recrystallized from EtOH) and $[\alpha]_D^{20}$ − 102° (c = 1.0, $CHCl_3$) (lit.,[6a] mp 143° and $[\alpha]_D$ − 103° (c = 0.6, $CHCl_3$); lit.,[6c] mp 141–142° and $[\alpha]_D$ − 102° (c = 1, $CHCl_3$)).

(b) *Compound* (−)-**1** *from* (−)-**11**. In a similar manner as the preparation of (−)-**1** from (−)-**5**, acidic treatment of (−)-**11** ($[\alpha]_D^{20}$ − 27.3° (c = 1.0, $CHCl_3$)) (0.19 g, 0.49 mmole) followed by oxidation[11] gave pure (−)-**1** as colorless plates (0.09 g, 65%), mp 141–142.5° (recrystallized from EtOH), $[\alpha]_D^{20}$ − 102° (c = 0.9, $CHCl_3$). IR and NMR spectra of this sample were superimposable on those of (−)-**1** obtained in (a).

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