1 PERKIN

Asymmetric total synthesis of (+)-equilenin utilizing two types of cascade ring expansion reactions of small ring systems

Masahiro Yoshida, Mohamed Abdel-Hamid Ismail, Hideo Nemoto † and Masataka Ihara *

Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University, Aobayama, Sendai 980-8578, Japan

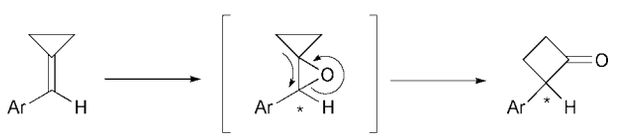
Received (in Cambridge, UK) 4th May 2000, Accepted 14th June 2000
Published on the Web 24th July 2000

Enantioselective synthesis of (+)-equilenin **1** utilizing two types of cascade ring expansion reactions of small ring systems is described. The first key step is an asymmetric epoxidation–ring expansion reaction of cyclopropylidene derivatives to afford chiral cyclobutanones. We found that both the fructose-derived chiral ketone and the chiral (salen)Mn(III) complex were effective catalysts for the asymmetric induction. The second key step is the palladium-promoted cascade ring expansion–intramolecular insertion reaction of the isopropenylcyclobutanol. Solvents were an important factor for the diastereoselective formation of hydrindanes. By utilizing these methodologies, the asymmetric total synthesis of (+)-equilenin **1** has been accomplished.

Introduction

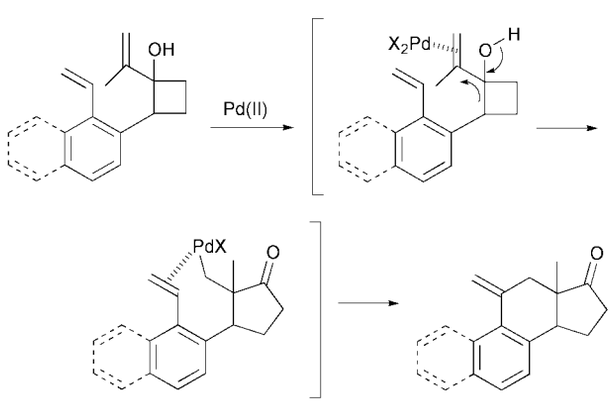
Steroids are one of the most widely distributed groups of natural products and display a variety of physiological activities.[1] Since the first total synthesis of equilenin was achieved by Bachmann *et al*. in 1939,[2] numerous synthetic strategies for steroids have been developed over the second half of the twentieth century.[3] Several elegant approaches have been developed which could construct the steroidal framework in a single step, such as cationic cyclisation,[4] transition metal promoted reaction,[5] radical cyclisation,[6] and the double Michael reaction.[7] These 'cascade' reactions are effective methods to synthesise steroids. However, the number of total syntheses of steroids is rather limited compared to the volume of literature dealing with the partial synthesis of steroids and selective functionalizations of the steroidal tetracycles.[8]

Here we describe a novel strategy for the enantioselective synthesis of the steroid (+)-equilenin **1**, using two types of cascade ring expansion reactions of small ring systems.[9] The first ring expansion reaction is the asymmetric epoxidation–ring expansion reaction, which involves the asymmetric epoxidation of an aryl-substituted cyclopropylidene derivative to form the chiral oxaspiropentane, followed by its enantiospecific rearrangement to the chiral cyclobutanone (Scheme 1).[10] For



Scheme 1 Cascade asymmetric epoxidation–ring expansion reaction.

methods of asymmetric induction, we have utilised Shi's fructose-derived chiral ketone with Oxone[11] or Jacobsen's chiral (salen)Mn(III) complex with NaClO,[12] which are excellent reagents for asymmetric epoxidation reactions. The second ring expansion reaction is the palladium-promoted ring expansion–insertion reaction of isopropenylcyclobutanols, the methodology of which has been previously reported by us (Scheme 2).[13,14] This reaction was initiated by coordination of the isopropenyl group to a palladium(II) complex, followed by ring expansion of the cyclobutanol ring, insertion of the olefin, and elimination of palladium to construct the desired steroidal framework in a single step.



Scheme 2 Pd(II)-promoted cascade ring expansion–insertion reaction.

Results and discussion

Synthetic plan

Scheme 3 shows our retrosynthetic analysis of (+)-equilenin **1**. The naphthalene-fused *trans*-hydrindane‡ **2**, which is the important intermediate for the synthesis of (+)-equilenin, could be constructed by the palladium-promoted cascade ring expansion and insertion process of the isopropenylcyclobutanol derivative **3**. It was anticipated that the desired fused hydrindane **2** could be stereoselectively obtained by the proper choice of reagents and reaction conditions. The chiral cyclobutanone **4**, a precursor of **3**, could be prepared *via* asymmetric epoxidation–ring expansion reaction from the cyclopropylidene derivative **5**, which would be derived from the 1-hydroxy-2-naphthaldehyde **6**.

Synthesis of chiral cyclobutanone

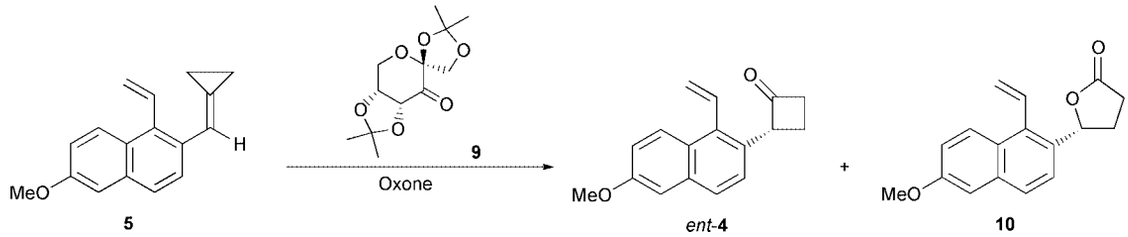
Our investigations began with the enantioselective synthesis

† Present address: Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Suginami 2630, Toyama 930-0194, Japan.

‡ IUPAC name for hydrindane is hexahydroindane.

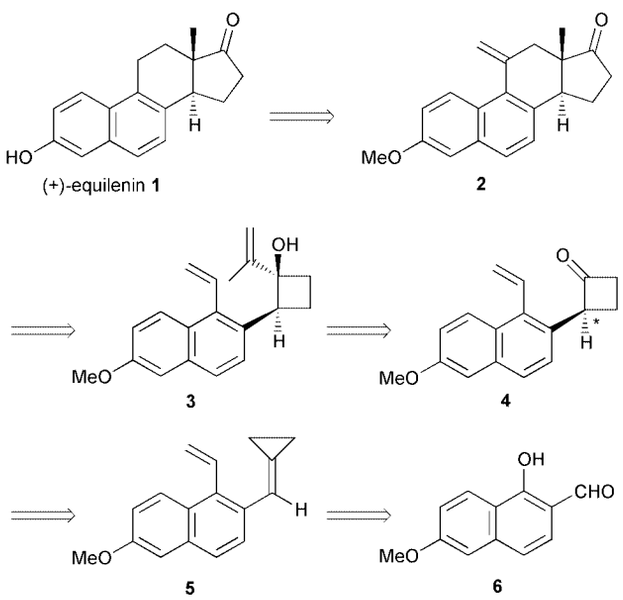
DOI: 10.1039/b003578p

Table 1 Asymmetric epoxidation–ring expansion reaction using chiral ketone **9**[a]



Entry	**9** (equiv.)	Oxone (equiv.)	Solvent	pH	Recovered **5** (%)	*ent*-**4** Yield (%)	*ent*-**4** Ee (%)[b]	**10** Yield (%)	**10** Ee (%)[b]
1	1.0	1.0	CH_3CN	10.5	24	33	50	19	57
2	1.0	1.0	DME	10.5	61	—	—	33	40
3	1.0	1.0	Dioxane	10.5	37	—	—	43	34
4	0.2	1.0	CH_3CN	10.5	43	—	—	22	53
5	2.0	1.0	CH_3CN	10.5	40	30	60	—	—
6[c]	2.0	1.0	CH_3CN	9.0	—	61	63	—	—
7	2.0	2.0	CH_3CN	10.5	—	—	—	60	72

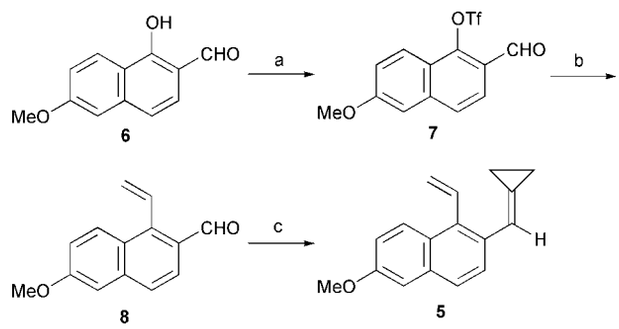
[a] The reaction was carried out using substrate **5**, chiral ketone **9**, Oxone, and K_2CO_3 in solvent–0.05 M $Na_2B_4O_7{\cdot}10H_2O$ of aqueous $Na_2(EDTA)$ (4×10^{-4} M) solution (1 : 1 v/v) at 0 °C for 1 h. [b] Enantiomeric excess was determined by HPLC chiral column (Chiralcel OA). [c] Instead of K_2CO_3, NaOH was used to maintain the reaction pH at 9.0.



Scheme 3 Retrosynthesis of (+)-equilenin.

of the cyclobutanone **4** by the asymmetric epoxidation–ring expansion reaction of cyclopropylidene derivative **5**. The substrate **5** was synthesised as follows (Scheme 4). The triflate **7**, prepared from 1-hydroxy-2-naphthaldehyde **6**[15] (61% yield), was subjected to the Stille reaction[16] with tri-*n*-butyl(vinyl)-stannane to give the vinylnaphthaldehyde **8** (98% yield). Subsequently, the Wittig cyclopropylidenation of **8** provided the cyclopropylidene derivative **5** in 70% yield.

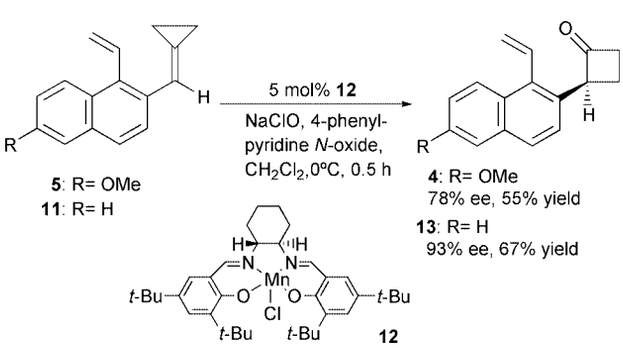
With the substrate **5** in hand, asymmetric epoxidation using the fructose-derived ketone **9** and Oxone[11] was first examined. The results are summarized in Table 1. When the reaction was carried out using 1 equiv. of **9** and Oxone in CH_3CN–H_2O (adjusted to pH 10.5), the expected reaction proceeded to give the chiral cyclobutanone *ent*-**4** in 33% yield with 50% ee (entry 1). The lactone **10**, which would be the product of further oxidation, was also obtained as a byproduct along with the recovered substrate **5**. When the reactions were performed in DME and dioxane, only the lactone **10** was obtained with low ee in poor yield (entries 2 and 3). An attempt to use a catalytic amount of chiral ketone **9** (0.2 equiv.) failed (entry 4). However, considerable improvements in the yield and enantiomeric excess



Scheme 4 *Reagents and conditions*: a, Tf_2O, DMAP, pyridine, 0 °C, 61%; b, tri-*n*-butyl(vinyl)stannane, $Pd(PPh_3)_4$, LiCl, THF, reflux, 98%; c, cyclopropylidenetriphenylphosphorane, NaH, THF, 62 °C, 70%.

were observed by using 2 equiv. of **9** (entry 5). Furthermore, when the reaction was carried out at pH 9.0, the substrate was completely consumed to give *ent*-**4** with 63% ee in 61% yield (entry 6). Interestingly, the lactone **10** was exclusively obtained with 72% ee in 60% yield by using 2 equiv. of Oxone at pH 10.5 (entry 7). This is a novel method to synthesise the chiral γ-butyrolactones from cyclopropylidene derivatives in a one-pot process.[17]

Next, the asymmetric epoxidation reaction was attempted using the chiral (salen)Mn(III) complex (Scheme 5). When a



Scheme 5 Asymmetric epoxidation–ring expansion reaction using chiral (salen)Mn complex **12**.

mixture of **5**, 5 mol% of (*R*,*R*)-(salen)Mn(III) complex **12** and 4-phenylpyridine *N*-oxide (4-PPNO) in CH_2Cl_2 was treated with NaClO as the oxidant at 0 °C, the reaction successfully

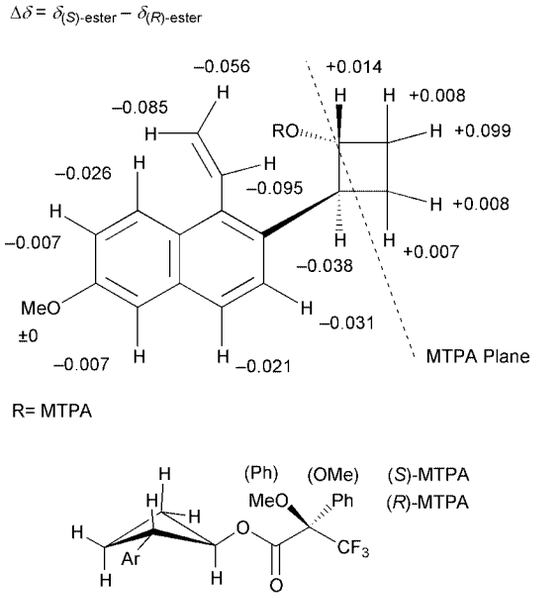
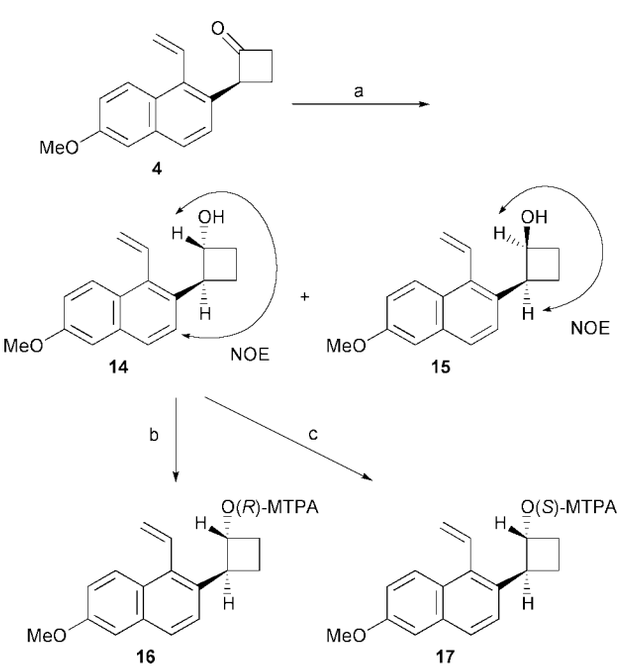


Fig. 1

proceeded to provide the desired chiral cyclobutanone **4** with a fair enantiomeric excess in a moderate yield (78% ee, 55% yield). Furthermore, when the reaction was carried out utilizing the demethoxylated substrate **11**, the corresponding cyclobutanone **13** was obtained with a high enantiomeric excess (93% ee, 67% yield).

The absolute configuration of **4** was determined by the improved Mosher's method developed by Kusumi *et al.*[18] Thus, reduction of **4** with $NaBH_4$ led to the cyclobutanol **14** and its diastereomer **15** in 61 and 35% yields (Scheme 6). The stereochemistries of **14** and **15** were determined by ^{1}H-NOESY. When the major isomer **14** was treated with (*R*)- and (*S*)-MTPA [α-methoxy-α-(trifluoromethyl)phenylacetic acid], the corresponding MTPA esters **16** and **17** were formed in quantitative yield. On the basis of the $\Delta\delta$ values ($\Delta\delta = \delta_{(S)\text{-ester}} - \delta_{(R)\text{-ester}}$), the absolute configuration of **4** was determined as *S* (Fig. 1).



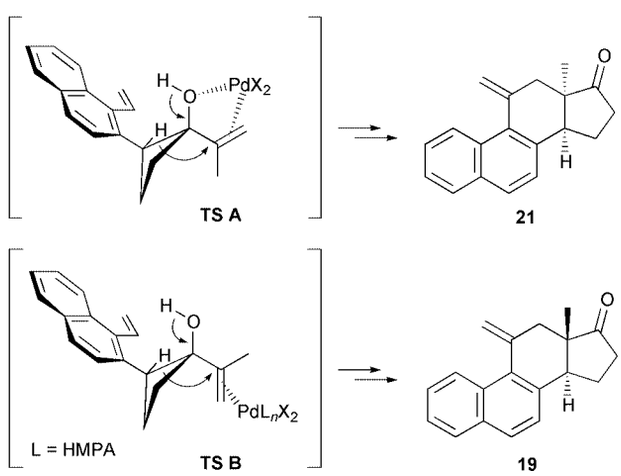
Scheme 6 *Reagents and conditions*: a, $NaBH_4$, MeOH, rt, 61% of **14** and 35% of **15**; b, (*R*)-MTPA, DCC, DMAP, CH_2Cl_2, rt, quant.; c, (*S*)-MTPA, DCC, DMAP, CH_2Cl_2, rt, quant.

It has been made clear that the method using chiral (salen)-Mn(III) catalyst **12** is more suitable for the production of the desired enantiomer **4**. Therefore, we decided to utilize this method for the synthesis of (+)-equilenin **1**.

Diastereoselective construction of a naphthalene-fused hydrindane

Next, our attention was focused on the diastereoselective construction of the naphthalene-fused *trans*-hydrindane. We have already developed the palladium-promoted ring expansion–insertion reaction, which can synthesize benzene- and naphthalene-fused hydrindanes in a one-pot process.[13] However, several issues need to be addressed before utilizing this reaction in the synthesis of (+)-equilenin; (1) the naphthalene–hydrindanes were not stereoselectively obtained from isopropenylcyclobutanol; (2) the olefin-isomerized products were obtained as the major products. To overcome these hurdles, we closely scrutinized the reaction conditions in order to construct the naphthalene-fused *trans*-hydrindane diastereoselectively from **18**[13] (Table 2). These studies revealed that the olefin isomerization could be effectively suppressed by using $Pd(OAc)_2$ (entry 2) instead of $PdCl_2(MeCN)_2$[13] (entry 1). Furthermore, we were delighted to find that the diastereoselectivity could be controlled by the proper choice of the solvent. Thus, in non-polar solvents such as toluene, the fused *cis*-product **21**[13] was predominantly produced (entry 3). In contrast, both the fused *trans*- and *cis*-products **19**[13] and **21** were formed in polar solvents such as DMF, THF, DMPU, NMP (entries 2, 4, 5 and 6). In particular, the *trans*-product **19** was selectively provided by using a mixture of HMPA and THF (entries 7 and 8).

Scheme 7 shows the proposed mechanisms for the diastereoselectivity observed in the above process. It is presumed that the selectivity of the products depends on the conformation of the isopropenyl group during the cascade reaction. Thus, the ring expansion reaction would proceed *via* the intermediate **TS A** in a non-polar solvent such as toluene to give the *cis*-product **21**, in which the palladium would be associated with both the olefin and the hydroxy group. In contrast, in the case of polar solvents such as HMPA, the reaction would take place *via* **TS B** to afford the *trans*-product **19**, in which the palladium would be associated with only the olefin because the solvent coordinates to palladium as a ligand.

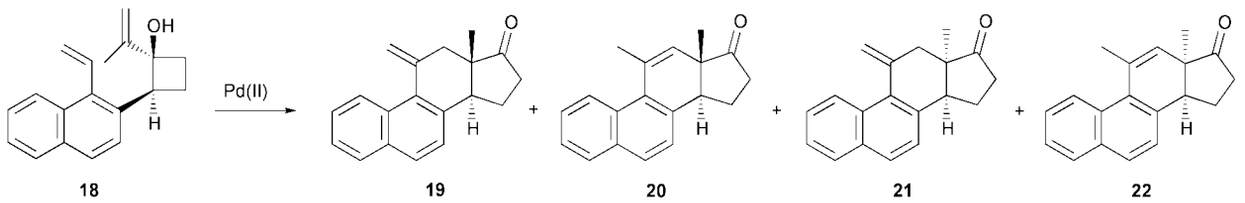


Scheme 7 Proposed mechanisms for diastereoselectivities observed.

Asymmetric total synthesis of (+)-equilenin

With an efficient method for the chiral synthesis of the naphthalene-fused hydrindane in hand, we investigated the asymmetric total synthesis of (+)-equilenin **1**. Thus, the chiral cyclobutanone **4**, which was obtained with 78% ee in 55% yield from **5**, was stereoselectively converted to

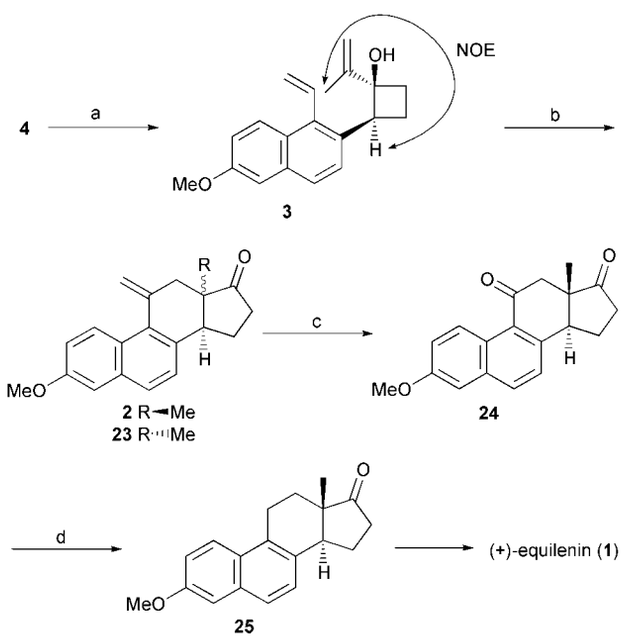
Table 2 Cascade ring expansion and insertion reactions of **18**[a]



Entry	Reagent	Solvent	Time/h	Product **19**:**20**:**21**:**22**[b]	*trans*:*cis*[c]	Yield (%)
1[d]	$PdCl_2(CH_3CN)_2$	DMF	10	4:48:15:33	52:48	56
2	$Pd(OAc)_2$	DMF	10	47:5:43:5	52:48	61
3	$Pd(OAc)_2$	Toluene	10	3:0:88:9	3:97	61
4	$Pd(OAc)_2$	THF	10	34:18:41:7	52:48	36
5	$Pd(OAc)_2$	DMPU	10	46:18:36:0	64:36	81
6	$Pd(OAc)_2$	NMP	10	52:8:36:4	60:40	52
7	$Pd(OAc)_2$	HMPA–THF = 9:1	10	58:15:25:2	73:27	47
8	$Pd(OAc)_2$	HMPA–THF = 4:1	10	61:14:24:1	75:25	61

[a] The reaction was carried out under argon at room temperature by using an equimolar amount of reagent. [b] The isomer ratios were determined by ^{1}H NMR integration of angular methyl signals (δ 0.55 for **19**, δ 0.67 for **20**, δ 1.19 for **21** and δ 1.15 for **22**). [c] *trans*:*cis* is equal to **19** + **20**:**21** + **22**. [d] This result has been previously reported by us (see ref. 13).

the isopropenylcyclobutanol **3** by Grignard reaction with isopropenylmagnesium bromide in the presence of cerium trichloride[19] (82% yield) (Scheme 8). The stereochemistry of **3** was determined by an NOE experiment. Next, the palladium-promoted cascade ring expansion–insertion reaction was examined. When **3** was treated with $Pd(OAc)_2$ in HMPA–THF (1:4), a 73:27 mixture of the *trans*- and *cis*-fused products **2** and **23** was obtained in 60% yield. To complete the synthesis of equilenin, the mixture of **2** and **23** was exposed to osmium tetraoxide and sodium periodate to furnish the diketone **24** in 59% yield, after separation of the diastereomer. Finally, the selective reduction of the benzylic ketone of **24** was performed by hydrogenolysis on Pt/C in the presence of $PdCl_2$[20] to afford equilenin methyl ether **25** (82% yield), which could be purified as in an optically pure form by recrystallization. Since **25** had been converted to **1** by treatment with boron tribromide,[21] our asymmetric synthesis of (+)-equilenin **1** was complete.



Scheme 8 *Reagents and conditions*: a, isopropenylmagnesium bromide, $CeCl_3$, THF, −78 °C, 82%; b, $Pd(OAc)_2$, HMPA–THF (1:4), rt, 60%, **2**:**23** = 73:27 and 7% of *endo*-olefin isomer; c, OsO_4, $NaIO_4$, acetone–H_2O, 59% from **2**; d, H_2, Pt/C, $PdCl_2$, EtOH, rt, 82%.

Conclusion

In summary, we have established a novel method for the enantioselective synthesis of steroidal frameworks utilizing two types of cascade ring expansion reactions of small ring systems, which has been successfully applied to the total synthesis of (+)-equilenin **1**. (+)-Equilenin **1** was synthesized from the readily available naphthaldehyde **6** in 9 steps. The key features of the synthetic strategy include (1) the chiral (salen)Mn(III) complex or fructose-derived chiral ketone catalysed cascade asymmetric epoxidation–ring expansion reaction of cyclopropylidene derivatives affording chiral cyclobutanones, and (2) the stereoselective formation of naphthalene-fused hydrindanes *via* a cascade ring expansion–olefin insertion reaction using palladium catalysts.

Experimental

All non-aqueous reactions were carried out under a positive atmosphere of argon or nitrogen in dried glassware unless otherwise indicated. Materials were obtained from commercial suppliers and used without further purification except when otherwise noted. Solvents were dried and distilled according to standard procedures. The phrase 'residue upon work-up' refers to the residue obtained when the organic layer was separated and dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. Column chromatography was performed on silica gel 60N (Merck, 100–210 mesh, 60 Å), and flash column chromatography was performed on silica gel 60 (Merck, 40–100 mesh, 60 Å) using the indicated solvent. A Shimazdu LC-10AD instrument was employed for HPLC, equipped with a Shimadzu SPD-10A as a UV detector at 254 nm. CHIRALCEL OA (0.46 × 25 cm, Daicel Chemical) was used as an HPLC chiral column. All melting points were determined on a Yanaco micro melting point apparatus and are uncorrected. Optical rotations were measured with a Horiba SEPA-300 high sensitive polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were measured on a JASCO IR Report-100 spectrometer. NMR spectra were recorded on a Hitachi R-300, Varian Gemini 2000, or JEOL JNM-GX 500 spectrometer with tetramethylsilane or chloroform as an internal standard. Mass spectra were recorded on a JEOL JMS-DX-303 or JMS-AX-500 spectrometer.

6-Methoxy-1-trifluoromethylsulfonyloxynaphthalene-2-carbaldehyde 7

To a stirred solution of the naphthaldehyde **6**[15] (5.0 g, 24.7 mmol) and a catalytic amount of DMAP in pyridine (200 mL) was added dropwise Tf_2O (4.6 mL, 24.7 mmol) at 0 °C; stirring was continued for 1 h at the same temperature. The resulting solution was diluted with water and extracted with AcOEt. The combined extracts were washed sequentially with 10% HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. The residue upon work-up was chromatographed on silica gel with hexane–AcOEt (9:1 v/v) as eluant to give the triflate **7** (5.03 g, 61%) as colourless needles, mp 79 °C (Et_2O) (Found: C, 46.70; H, 2.73. $C_{13}H_9O_5F_3S$ requires C, 46.71; H, 2.71%); $\nu_{max}(CHCl_3)$/cm^{-1} 1685; δ_H(300 MHz, $CDCl_3$) 3.98 (3H, s, OMe), 7.21 (1H, d, J = 2.5 Hz, ArH), 7.34 (1H, dd, J = 9.4 and 2.5 Hz, ArH), 7.81 (1H, d, J = 8.8 Hz, ArH), 7.97 (1H, d, J = 8.8 Hz, ArH), 8.12 (1H, d, J = 9.4 Hz, ArH) and 10.40 (1H, s, CHO); δ_C(75 MHz, $CDCl_3$) 55.4, 106.1, 116.6, 120.8, 121.2, 121.6, 123.8, 124.2, 127.6, 140.0, 147.3, 161.0 and 186.4; *m*/*z* 334 (M^+).

6-Methoxy-1-vinylnaphthalene-2-carbaldehyde 8

To a slurry of LiCl (5.50 g, 38.6 mmol) and $Pd(PPh_3)_4$ (884 mg, 0.765 mmol) in THF (200 mL) was added a solution of the triflate **7** (6.4 g, 19.2 mmol) and vinyltri-*n*-butyltin (7.31 mL, 24.9 mmol). The mixture was refluxed for 12 h with stirring, cooled to rt, and diluted with AcOEt. The resulting solution was washed sequentially with water, 10% NH_4OH, water, and saturated aqueous NaCl. The residue upon work-up was chromatographed on silica gel with hexane–AcOEt (9:1 v/v) as eluant to give the vinylnaphthaldehyde **8** (4.01 g, 98%) as colourless needles, mp 89 °C (Et_2O) (Found: C, 79.21; H, 5.70. $C_{14}H_{12}O_2$ requires C, 79.23; H, 5.70%); ν_{max}(neat)/cm^{-1} 1620 and 1685; δ_H(300 MHz, $CDCl_3$) 3.91 (3H, s, OMe), 5.48 (1H, dd, J = 17.4 and 1.8 Hz, CHCH*H*), 5.99 (1H, dd, J = 11.1 and 1.8 Hz, CHC*H*H), 7.17 (1H, d, J = 2.4 Hz, ArH), 7.23 (1H, dd, J = 9.0 and 2.4 Hz, ArH), 7.35 (1H, dd, J = 17.4 and 11.1 Hz, C*H*CHH), 7.73 (1H, d, J = 9.0 Hz, ArH), 7.98 (1H, d, J = 9.0 Hz, ArH), 8.12 (1H, d, J = 9.0 Hz, ArH) and 10.41 (1H, s, CHO); δ_C(75 MHz, $CDCl_3$) 55.4, 106.6, 119.4, 123.8, 125.6, 126.6, 126.9, 127.9, 129.7, 130.8, 137.8, 143.4, 160.1 and 192.5; *m*/*z* 212 (M^+).

2-(Cyclopropylidenemethyl)-6-methoxy-1-vinylnaphthalene 5

To a stirred suspension of NaH (691 mg, 60% suspension in oil, 17.3 mmol) in THF (140 mL) was added cyclopropyltriphenylphosphonium bromide (6.93 g, 17.3 mmol) at rt. After the mixture had been stirred for 10 h at 62 °C, a solution of the vinylnaphthaldehyde **8** (1.83 g, 8.64 mmol) in THF (20 mL) was added dropwise, and stirring was continued for 1 h at the same temperature. The reaction mixture was diluted with water and extracted with AcOEt. The combined extracts were washed with saturated aqueous NaCl. The residue upon work-up was chromatographed on silica gel with hexane–AcOEt (99:1 v/v) as eluant to give the cyclopropylidene derivative **5** (1.40 g, 70%) as a colourless oil, ν_{max}(neat)/cm^{-1} 1620; δ_H(300 MHz, $CDCl_3$) 1.16–1.21 (2H, m, 2 × cyclopropyl H), 1.46–1.55 (2H, m, 2 × cyclopropyl H), 3.92 (3H, s, OMe), 5.44 (1H, dd, J = 18.0 and 2.2 Hz, CHCH*H*), 5.82 (1H, dd, J = 11.0 and 2.2 Hz, CHC*H*H), 7.07–7.23 (4H, m, 2 × ArH, CCHC and C*H*CH_2), 7.61 (1H, d, J = 8.8 Hz, ArH) and 8.00–8.04 (2H, m, 2 × ArH); δ_C(75 MHz, $CDCl_3$) 0.5, 4.1, 54.9, 106.3, 116.9, 118.2, 122.0, 123.9, 124.7, 126.1, 127.2, 128.3, 130.7, 133.6, 133.7, 133.8 and 157.3; *m*/*z* (EI) 236.1201 (M^+, $C_{17}H_{16}O$ requires 236.1200).

Asymmetric epoxidation–ring expansion reaction using fructose-derived ketone (entry 6, Table 1)

To a stirred solution of the cyclopropylidene derivative **5** (30 mg, 0.126 mmol) in acetonitrile (3 mL) were added the buffer (2 mL) [0.05 M $Na_2B_4O_7{\cdot}10H_2O$ in 4×10^{-4} M aqueous Na_2(EDTA), adjusting with 1.0 M aqueous KH_2PO_4 for pH 9.0], tetrabutylammonium hydrogen sulfate (4.4 mg, 0.013 mmol) and the ketone **9** (61.5 mg, 0.252 mmol). After the reaction mixture had been cooled to 0 °C, a solution of Oxone (78.0 mg, 0.126 mmol) in aqueous Na_2(EDTA) (4×10^{-4} M, 1.5 mL) was added dropwise over a period of 1.5 h, while the reaction pH was maintained at pH 9.0 by addition of 0.5 M aqueous NaOH. After the stirring had been continued for 1 h at the same temperature, the reaction mixture was diluted with water and extracted with AcOEt. The combined extracts were washed with saturated aqueous NaCl. The residue upon work-up was chromatographed on silica gel with hexane–AcOEt (95:5 v/v) as eluant to give the cyclobutanone *ent*-**4** (19.4 mg, 61% yield, 63% ee) as a colourless oil, $[\alpha]_D^{25}$ −28.5 (*c* 0.1 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 1780; δ_H(300 MHz, $CDCl_3$) 2.21–2.22 (1H, m, $COCH_2CHH$), 2.24–2.55 (1H, m, $COCH_2CHH$), 3.07–3.13 (1H, m, COCH*H*), 3.18–3.27 (1H, m, COC*H*H), 3.91 (3H, s, OMe), 4.95–5.05 (1H, m, COCH), 5.44 (1H, dd, J = 18.0 and 2.2 Hz, CHCH*H*), 5.76 (1H, dd, J = 12.0 and 2.2 Hz, CHC*H*H), 7.08 (1H, dd, J = 18.0 and 12.0 Hz, C*H*CH_2), 7.11–7.15 (2H, m, 2 × ArH), 7.35 (1H, d, J = 8.8 Hz, ArH), 7.65 (1H, d, J = 8.8 Hz, ArH) and 7.96 (1H, d, J = 8.8 Hz, ArH); δ_C(75 MHz, $CDCl_3$) 19.6, 44.9, 55.3, 63.3, 106.1, 118.8, 122.2, 125.3, 126.8, 127.3, 127.4, 129.4, 133.9, 134.1, 135.6, 157.6 and 209.5; *m*/*z* (EI) 252.1150 (M^+, $C_{17}H_{16}O_2$ requires 252.1149). Enantiomeric excess was determined by HPLC analysis (CHIRALCEL OA column, 10% propan-2-ol–hexane, 0.5 mL min^{-1}, λ = 254 nm, 23 °C, retention times 21.1 min (*R*) and 26.2 min (*S*)).

(*R*)-4-(6-Methoxy-1-vinyl-2-naphthyl)butan-4-olide 10

To a stirred solution of the cyclopropylidene derivative **5** (22.1 mg, 0.0936 mmol) in acetonitrile (3 mL) were added the buffer (2 mL) [0.05 M $Na_2B_4O_7{\cdot}10H_2O$ in 4×10^{-4} M aqueous Na_2(EDTA), adjusting with 1.0 M aqueous KH_2PO_4 for pH 10.5], tetrabutylammonium hydrogen sulfate (3.4 mg, 0.010 mmol) and the ketone **9** (45.6 mg, 0.187 mmol). After the reaction mixture had been cooled to 0 °C, a solution of Oxone (115.8 mg, 0.187 mmol) in aqueous Na_2(EDTA) (4×10^{-4} M, 1.5 mL) was added dropwise over a period of 1.5 h while the reaction pH was maintained at pH 10.5 by addition of K_2CO_3. After stirring had been continued for 1 h at the same temperature, the reaction mixture was diluted with water and extracted with AcOEt. The combined extracts were washed with saturated aqueous NaCl. The residue upon work-up was chromatographed on silica gel with hexane–AcOEt (80:20 v/v) as eluant to give the butyrolactone **10** (15.0 mg, 60% yield, 72% ee) as a colourless oil, $[\alpha]_D^{25}$ +43.1 (*c* 1.0 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 1770; δ_H(300 MHz, $CDCl_3$) 2.13–2.28 (1H, m, 3-H), 2.54–2.67 (1H, m, 3-H), 2.68–2.74 (2H, m, 2 × 2-H), 3.92 (3H, s, OMe), 5.40 (1H, dd, J = 17.4 and 1.8 Hz, CHCH*H*), 5.81 (1H, dd, J = 11.4 and 1.8 Hz, CHC*H*H), 5.93 (1H, dd, J = 9.3 and 6.3 Hz, 4-H), 7.07 (1H, dd, J = 17.4 and 11.4 Hz, C*H*CH_2), 7.11–7.19 (2H, m, 2 × ArH), 7.48 (1H, d, J = 8.8 Hz, ArH), 7.73 (1H, d, J = 8.8 Hz, ArH) and 7.97 (1H, d, J = 8.8 Hz, ArH); δ_C(75 MHz, $CDCl_3$) 29.5, 31.2, 55.4, 79.6, 106.3, 119.2, 122.8, 123.0, 126.9, 127.3, 127.5, 131.6, 133.2, 134.7, 134.8, 158.2 and 177.4; *m*/*z* (EI) 268.1095 (M^+, $C_{17}H_{16}O_3$ requires 268.1100). Enantiomeric excess was determined by HPLC analysis (CHIRALCEL OA column, ethanol, 0.5 mL min^{-1}, λ = 254 nm, 23 °C, retention times 12.7 min (*R*) and 15.8 min (*S*)).

General procedure for the asymmetric epoxidation–ring expansion reaction using the chiral (salen)Mn complex

To a stirred solution of the cyclopropylidene derivative **5** (700 mg, 2.96 mmol), the (*R*,*R*)-(salen)Mn complex **12** (31.8 mg, 0.148 mmol) and 4-phenylpyridine *N*-oxide (203 mg, 1.18 mmol) in CH_2Cl_2 (20 mL) was added dropwise a 0.55 M solution of NaClO in a phosphate buffer (3.94 mL, 3.55 mmol,

adjusted to pH 11.3) at 0 °C. After stirring had been continued for 0.5 h at the same temperature, the reaction mixture was diluted with water and extracted with AcOEt. The combined extracts were washed with saturated aqueous NaCl. The residue upon work-up was chromatographed on silica gel with hexane–AcOEt (95:5) as eluant to give the cyclobutanone **4** (412 mg, 55%, 78% ee) as a colourless oil, $[\alpha]_D^{25}$ +37.5 (*c* 0.2 in $CHCl_3$). Other spectral data were consistent with those of the *ent*-**4**.

(*S*)-2-(1-Vinyl-2-naphthyl)cyclobutanone 13

Yield 67%, 93% ee; $[\alpha]_D^{25}$ +79.7 (*c* 3.5 in $CHCl_3$). Enantiomeric excess was determined by HPLC analysis (CHIRALCEL OA column, 10% propan-2-ol–hexane, 0.5 mL min^{-1}, λ = 254 nm, 23 °C, retention times 13.9 min (*R*) and 16.2 min (*S*)). Other spectral data were consistent with those of the racemic cyclobutanone.[13]

(1*R*,2*S*)- and (1*S*,2*S*)-2-(6-Methoxy-1-vinyl-2-naphthyl)cyclobutanols 14 and 15

To a stirred solution of the cyclobutanone **4** (21.3 mg, 0.0805 mmol) in MeOH (5 mL) was added $NaBH_4$ (22.4 mg, 0.0864 mmol) at 0 °C. After stirring had been continued for 1 h at the same temperature, the reaction mixture was diluted with water and extracted with AcOEt. The combined extracts were washed with saturated aqueous NaCl. The residue upon work-up was chromatographed on silica gel with hexane–AcOEt (94:6 v/v) as eluant to give the cyclobutanol **14** (12.8 mg, 61%) as a colourless oil, ν_{max}(neat)/cm^{-1} 3400; δ_H(300 MHz, $CDCl_3$) 1.57–1.65 (1H, m, 3-H), 1.83–1.91 (1H, m, 4-H), 2.03 (1H, br s, OH), 2.08–2.15 (1H, m, 3-H), 2.28–2.36 (1H, m, 4-H), 3.69–3.77 (1H, m, 2-H), 3.92 (3H, s, OMe), 4.33 (1H, q, *J* = 8.0 Hz, 1-H), 5.41 (1H, dd, *J* = 18.0 and 2.0 Hz, CHCH*H*), 5.76 (1H, dd, *J* = 11.0 and 2.0 Hz, CHC*H*H), 7.06–7.13 (3H, m, 2 × ArH and C*H*CH_2), 7.47 (1H, d, *J* = 8.5 Hz, ArH), 7.67 (1H, d, *J* = 8.5 Hz, ArH) and 8.01 (1H, d, *J* = 9.0 Hz, ArH); δ_C(75 MHz, $CDCl_3$) 20.1, 29.6, 49.2, 55.4, 73.1, 106.1, 118.6, 121.7, 124.8, 126.4, 127.1, 127.5, 133.5, 134.4, 134.7, 134.8 and 157.2; *m*/*z* (EI) 254.1317 (M^+, $C_{17}H_{18}O_2$ requires 254.1307). Further elution gave the diastereomer **15** (8.5 mg, 35%) as a colourless oil, ν_{max}(neat)/cm^{-1} 3300; δ_H(300 MHz, $CDCl_3$) 1.34 (1H, br s, OH), 1.97–2.05 (1H, m, 4-H), 2.16–2.25 (1H, m, 3-H), 2.41–2.48 (1H, m, 4-H), 2.49–2.56 (1H, m, 3-H), 3.93 (3H, s, OMe), 4.12 (1H, q, *J* = 7.0 Hz, 2-H), 4.58 (1H, br s, 1-H), 5.41 (1H, dd, *J* = 18.0 and 2.0 Hz, CHCH*H*), 5.74 (1H, dd, *J* = 11.0 and 2.0 Hz, CHC*H*H), 7.01 (1H, dd, *J* = 18.0 and 11.0 Hz, C*H*CH_2), 7.11–7.17 (2H, m, 2 × ArH), 7.57 (1H, d, *J* = 8.5 Hz, ArH), 7.73 (1H, d, *J* = 8.5 Hz, ArH) and 8.05 (1H, m, ArH); δ_C(75 MHz, $CDCl_3$) 21.2, 30.2, 44.5, 55.4, 70.8, 106.0, 118.8, 121.6, 125.9, 126.4, 127.3, 127.4, 130.6, 133.9, 134.4, 136.2 and 157.4; *m*/*z* (EI) 254.1316 (M^+, $C_{17}H_{18}O_2$ requires 254.1307).

(*R*)-MTPA ester 16

To a stirred solution of the cyclobutanol **14** (8.1 mg, 0.0324 mmol) in CH_2Cl_2 (2 mL) were added (*R*)-MTPA (11.4 mg, 0.0481 mmol) and a catalytic amount of DMAP at rt. After stirring had been continued for 12 h at the same temperature, the reaction mixture was diluted with NH_4Cl and extracted with AcOEt. The combined extracts were washed with saturated aqueous NaCl. The residue upon work-up was chromatographed on silica gel with hexane–AcOEt (97:3 v/v) as eluant to give the (*R*)-MTPA ester **15** (16.3 mg, quant.) as a colourless oil, ν_{max}(neat)/cm^{-1} 1740; δ_H(300 MHz, $CDCl_3$) 1.75 (1H, dddd, *J* = 20.7, 9.9, 8.1 and 2.4 Hz, 3-H), 2.02 (1H, dddd, *J* = 20.1, 9.9, 8.1 and 1.2 Hz, 4-H), 2.29 (1H, dddd, *J* = 20.7, 8.1, 1.8 and 1.2 Hz, 3-H), 2.51 (1H, dddd, *J* = 20.1, 8.1, 2.4 and 1.8 Hz, 4-H), 3.48 (3H, s, MTPA OMe), 3.92 (3H, s, OMe), 4.09 (1H, q, *J* = 8.1 Hz, 2-H), 5.31 (1H, dd, *J* = 18.0 and 2.1 Hz, CHCH*H*), 5.50 (1H, q, *J* = 8.1 Hz, 1-H), 5.68 (1H, dd, *J* = 11.2 and 2.1 Hz, CHC*H*H), 6.96 (1H, dd, *J* = 18.0 and 11.2 Hz, C*H*CH_2), 7.12 (1H, s, ArH), 7.13 (1H, d, *J* = 10.2 Hz, ArH), 7.30–7.38 (3H, m, 3 × PhH), 7.43–7.47 (2H, m, 2 × PhH), 7.52 (1H, d, *J* = 9.0 Hz, ArH), 7.71 (1H, d, *J* = 9.0 Hz, ArH) and 7.98 (1H, d, *J* = 10.2 Hz, ArH); *m*/*z* (EI) 470.1685 (M^+, $C_{17}H_{18}O_2$ requires 470.1704).

(*S*)-MTPA ester 17

By following the same procedure described for **16**, (*S*)-MTPA ester **17** was prepared from (*S*)-MTPA in quantitative yield, colourless oil, ν_{max}(neat)/cm^{-1} 1740; δ_H(300 MHz, $CDCl_3$) 1.76 (1H, dddd, *J* = 21.0, 9.9, 8.1 and 2.1 Hz, 3-H), 2.12 (1H, dddd, *J* = 20.1, 9.9, 8.1 and 1.5 Hz, 4-H), 2.30 (1H, dddd, *J* = 21.0, 8.1, 1.8 and 1.5 Hz, 3-H), 2.52 (1H, dddd, *J* = 20.1, 8.1, 2.1 and 1.8 Hz, 4-H), 3.54 (3H, s, MTPA OMe), 3.92 (3H, s, OMe), 4.05 (1H, q, *J* = 8.1 Hz, 2-H), 5.23 (1H, dd, *J* = 18.0 and 2.1 Hz, CHCH*H*), 5.51 (1H, q, *J* = 8.1 Hz, 1-H), 5.63 (1H, dd, *J* = 11.2 and 2.1 Hz, CHC*H*H), 6.87 (1H, dd, *J* = 18.0 and 11.2 Hz, C*H*CH_2), 7.11 (1H, s, ArH), 7.12 (1H, d, *J* = 10.2 Hz, ArH), 7.28–7.37 (3H, m, 3 × PhH), 7.44–7.47 (2H, m, 2 × PhH), 7.49 (1H, d, *J* = 8.7 Hz, ArH), 7.69 (1H, d, *J* = 8.7 Hz, ArH) and 7.95 (1H, d, *J* = 10.2 Hz, ArH); *m*/*z* (EI) 470.1700 (M^+, $C_{17}H_{18}O_2$ requires 470.1704).

(+)-(1*S*,2*S*)-1-Isopropenyl-2-(6-methoxy-1-vinyl-2-naphthyl)-cyclobutanol 3

To a stirred suspension of $CeCl_3$ (1.83 g, 7.42 mmol) in THF (30 mL) was added a 1.0 M solution of isopropenylmagnesium bromide in THF (6.36 mmol) at −78 °C. After stirring had been continued for 1 h, a solution of the cyclobutanone **4** (536 mg, 2.12 mmol) in THF (5 mL) was added dropwise to this reaction mixture at the same temperature and the temperature was then raised to rt during 2 h. The reaction mixture was treated with saturated aqueous NH_4Cl and extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl. The residue upon work-up was chromatographed on silica gel with hexane–AcOEt (95:5 v/v) as eluant to give the isopropenylcyclobutanol **3** (512 mg, 82%) as a colourless oil (Found: C, 81.35; H, 7.70. $C_{20}H_{22}O_2$ requires C, 81.60; H, 7.53%); $[\alpha]_D^{25}$ +62.7 (*c* 3.5, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3400; δ_H(300 MHz, $CDCl_3$) 1.88 (3H, s, CMe), 2.01–2.09 (1H, m, 3-H), 2.13–2.20 (1H, m, 4-H), 2.42–2.58 (2H, m, 3-H and 4-H), 3.91 (3H, s OMe), 4.29 (1H, t, *J* = 7.5 Hz, 2-H), 4.81 (1H, s, CC*H*H), 4.98 (1H, s, CCH*H*), 5.32 (1H, dd, *J* = 18.0 and 2.2 Hz, CHCH*H*), 5.74 (1H, dd, *J* = 11.0 and 2.2 Hz, CHC*H*H), 6.97 (1H, dd, *J* = 18.0 and 11.0 Hz, C*H*CH_2), 7.10–7.16 (2H, m, 2 × ArH), 7.64 (2H, m, 2 × ArH) and 8.03 (1H, d, *J* = 8.8 Hz, ArH); δ_C(75 MHz, $CDCl_3$) 18.7, 21.6, 31.3, 44.5, 55.0, 81.2, 105.7, 109.7, 118.4, 121.7, 125.9, 126.9, 127.2, 127.5, 130.9, 133.6, 134.5, 136.5, 148.6 and 157.3; *m*/*z* 294 (M^+).

(−)-11-Oxoequilenin methyl ether 24

To a stirred solution of the isopropenylcyclobutanol **3** (80.2 mg, 0.273 mmol) in HMPA–THF (1:4) (5 mL) was added $Pd(OAc)_2$ (73.6 mg, 0.328 mmol) at rt; stirring was continued for 5 h at the same temperature. The resulting solution was diluted with water and extracted with AcOEt. The combined extracts were washed with saturated aqueous NaCl. The residue upon work-up was chromatographed on silica gel with hexane–AcOEt (98:2 v/v) as eluant to give the naphthalene–hydrindanes **2** and **23** (**2**:**23** = 73:27, 47.6 mg, 60%) and the *endo*-olefin isomer (5.6 mg, 7%) as a colourless oil, **2** + **23**: ν_{max}(neat)/cm^{-1} 1740; δ_H(300 MHz, $CDCl_3$) 0.55 (2.19H, s, 13-Me), 1.20 (0.81H, s, 13-Me), 1.82–1.94 (0.27H, m, 15-H), 2.11–2.26 (1.73H, m), 2.30–2.52 (3H, m), 2.63–2.72 (1H, m), 2.91–3.01 (0.73H, m, 14-H), 3.29 (0.27H, t, *J* = 9.2 Hz, 14-H), 3.92 (3H, s, OMe), 5.43–5.54 (0.73H, m, CCH*H*), 5.46 (0.54H, s, CCH_2), 5.51–5.52 (0.73H, m, CC*H*H), 7.11–7.19 (2H, m, 2 × ArH), 7.29 (1H, d, *J* = 8.4 Hz, ArH), 7.63 (0.27H, d, *J* = 8.4 Hz, ArH), 7.70 (0.73H, d,

J = 8.4 Hz, ArH), 8.31 (0.73H, d, J = 8.4 Hz, ArH) and 8.39 (0.27H, d, J = 8.4 Hz, ArH); *m/z* (EI) 292.1455 (M^+, $C_{20}H_{20}O_2$ requires 292.1462).

To a stirred solution of the mixture of **2** and **23** (**2**:**23** = 73:27, 23.0 mg, 0.079 mmol) in acetone–H_2O (1:1) (5 mL) was added to 2% w/v solution of OsO_4 in water (0.10 mL, 0.008 mmol) at rt. After stirring had been continued for 15 min, $NaIO_4$ (42.1 mg, 0.197 mmol) was added during 30 min, and stirring was continued for 2 h at the same temperature. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$, and extracted with AcOEt. The combined extracts were washed with saturated aqueous NaCl. The residue upon work-up was chromatographed on silica gel with hexane–AcOEt (9:1 v/v) as eluant to give the diketone **24** (13.7 mg, 59% from **2**) as colourless needles, mp 184 °C (decomp.) (MeOH); $[\alpha]_D^{25}$ −31.7 (*c* 0.1 dioxane); ν_{max}(neat)/cm^{-1} 1660 and 1740; δ_H(300 MHz, $CDCl_3$) 0.83 (3H, s, 13-Me), 2.08–2.22 (1H, m, 15-H), 2.35–2.52 (1H, m, 15-H), 2.58–2.77 (2H, m, 2 × 16-H), 2.70 (1H, d, J = 18.9 Hz, 12-H), 2.94 (1H, d, J = 18.9 Hz, 12-H), 3.34 (1H, dd, J = 12.5 and 6.3 Hz, 14-H), 3.94 (3H, s, OMe), 7.15 (1H, d, J = 2.8 Hz, ArH), 7.29–7.38 (2H, m, 2 × ArH), 7.98 (1H, d, J = 8.7 Hz, ArH) and 9.22 (1H, d, J = 8.7 Hz, ArH); δ_C(75 MHz, $CDCl_3$) 15.0, 21.9, 35.8, 46.0, 48.8, 48.9, 55.3, 106.6, 121.8, 123.7, 126.7, 127.0, 128.0, 134.1, 140.9, 157.6, 199.0 and 217.8; *m/z* (EI) 294.1246 (M^+, $C_{19}H_{18}O_3$ requires 294.1256).

(+)-Equilenin methyl ether 25

To a stirred solution of the diketone **24** (7.5 mg, 0.0255 mmol) in EtOH (2 mL) was added a catalytic amount of Pt/C and $PdCl_2$ under an atmospheric pressure of hydrogen at rt, and stirring was continued for 30 min. The reaction mixture was filtered through Celite. The residue upon work-up was chromatographed on silica gel with hexane–AcOEt (97:3 v/v) as eluant to give equilenin methyl ether (**25**) (5.9 mg, 82%). The product was recrystallized from MeOH to give the optically pure **25** as colourless needles, mp 198 °C (decomp.) [lit.,[21] mp 197 °C (decomp.)]; $[\alpha]_D^{25}$ +78.9 (*c* 0.4 dioxane) [lit.,[21] $[\alpha]_D^{25}$ +82.8 (*c* 1.0 dioxane)]; ν_{max}(neat)/cm^{-1} 1730; δ_H(300 MHz, $CDCl_3$) 0.81 (3H, s, 13-Me), 1.83–2.09 (2H, m, 2 × 15-H), 2.17–2.26 (1H, m, 16-H), 2.40 (1H, dt, J = 8.6 and 19.3 Hz, 12-H), 2.50–2.61 (1H, m, 16-H), 2.70 (1H, dd, J = 18.9 and 8.6 Hz, 12-H), 3.15–3.22 (1H, m, 11-H), 3.26–3.35 (2H, m, 11-H and 14-H), 3.94 (3H, s, 13-Me), 7.14 (1H, d, J = 2.7 Hz, ArH), 7.19 (1H, dd, J = 9.5 and 2.7 Hz, ArH), 7.28 (1H, d, J = 8.5 Hz, ArH), 7.64 (1H, d, J = 8.5 Hz, ArH) and 7.88 (1H, d, J = 9.5 Hz, ArH); *m/z* 280 (M^+). The ^{1}H NMR spectrum of **25** was in complete agreement with that of an authentic sample.[21]

Acknowledgements

We thank Professor Ogasawara, Pharmaceutical Institute, Tohoku University, Sendai, for providing the ^{1}H NMR spectrum of **25**. M. Y. acknowledges support by a Research Fellowship from the Japan Society for the Promotion of Science (JSPS) for Young Scientists.

References

1 G. M. Anstead, K. E. Carlson and J. A. Katzenellenbogen, *Steroids*, 1997, **62**, 268.
2 W. E. Bachmann, W. Cole and A. L. Wilds, *J. Am. Chem. Soc.*, 1939, **61**, 974.
3 For reviews, see (*a*) R. Pappo, *Annu. Rep. Med. Chem.*, 1967, 307; (*b*) A. A. Akhrem and Y. A. Titov, *Total Steroid Synthesis*, Plenum Press, New York, 1970; (*c*) *Steroids*, *Vol. 8*, ed. W. F. Johns, *M. T. P. International Review of Science*, *Organic Chemistry*, Butterworths, London, 1973; (*d*) *The Total Synthesis of Natural Products Vol. 2*, ed. J. W. ApSimon, Wiley-Interscience, New York, 1973; (*e*) W. S. Johnson, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 9; (*f*) T. Kametani and H. Nemoto, *Heterocycles*, 1978, **10**, 349; (*g*) T. Kametani and H. Nemoto, *Tetrahedron*, 1981, **37**, 3; (*h*) M. B. Groen and F. Zeelen, *Recl. Trav. Chim. Pays-Bas*, 1986, **105**, 465; (*i*) M. B. Groen and F. Zeelen, *Nat. Prod. Rep.*, 1994, **11**, 607; (*j*) H. Nemoto and K. Fukumoto, *Tetrahedron*, 1998, **54**, 5425.
4 (*a*) W. S. Johnson, V. R. Fletcher, B. Chenera, W. R. Bartlett, F. S. Tham and R. K. Kullnig, *J. Am. Chem. Soc.*, 1993, **115**, 497; (*b*) E. J. Corey, S. C. Virgil, H. Cheng, C. H. Baker, S. P. T. Matsuda, V. Singh and S. Sarshar, *J. Am. Chem. Soc.*, 1995, **117**, 11819.
5 (*a*) R. L. Funk and K. P. C. Vollhardt, *J. Am. Chem. Soc.*, 1980, **102**, 5253; (*b*) Y. Zhang, G. Wu, G. Agnel and E. Negishi, *J. Am. Chem. Soc.*, 1990, **112**, 8590; (*c*) V. Gauthier, B. Cazes and J. Gore, *Tetrahedron Lett.*, 1991, **32**, 915; (*d*) J. Bao, V. Dragisich, S. Wenglowsky and W. D. Wulff, *J. Am. Chem. Soc.*, 1991, **113**, 9873; (*e*) R. Grigg, R. Rasul and V. Savic, *Tetrahedron Lett.*, 1997, **38**, 1825; (*f*) L. F. Tietze, T. Nöbel and M. Spescha, *J. Am. Chem. Soc.*, 1998, **120**, 8971.
6 (*a*) Y. W. Andemichael, Y. Huang and K. K. Wang, *J. Org. Chem.*, 1993, **58**, 1651; (*b*) T. Takahashi, S. Tomida, Y. Sakamoto and H. Yamada, *J. Org. Chem.*, 1997, **62**, 1912.
7 M. Ihara, T. Takahashi, N. Shimizu, Y. Ishida, I. Sudow and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 1989, 529.
8 J. R. Hanson, *Steroids*, 1996, **13**, 373.
9 Part of the present work has been published as a preliminary communication: H. Nemoto, M. Yoshida, K. Fukumoto and M. Ihara, *Tetrahedron Lett.*, 1999, **40**, 907.
10 Syntheses of the chiral cyclobutanones by other methods: H. Nemoto and K. Fukumoto, *Synlett*, 1997, 863, and references cited therein.
11 Z.-X. Wang, Y. Tu, M. Frohn, J.-R. Zhang and Y. Shi, *J. Am. Chem. Soc.*, 1997, **119**, 11224.
12 (*a*) W. Zhang and E. N. Jacobsen, *J. Org. Chem.*, 1991, **56**, 2296; (*b*) E. N. Jacobsen, W. Zhang, A. R. Muci, J. R. Ecker and L. Deng, *J. Am. Chem. Soc.*, 1991, **113**, 7063.
13 H. Nemoto, J. Miyata, M. Yoshida, N. Raku and K. Fukumoto, *J. Org. Chem.*, 1997, **62**, 7850.
14 For our recent work on the palladium-catalysed ring expansion reactions of cyclobutanols: (*a*) H. Nemoto, M. Nagamochi and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2329; (*b*) H. Nemoto, M. Nagamochi, H. Ishibashi and K. Fukumoto, *J. Org. Chem.*, 1994, **59**, 74; (*c*) H. Nemoto, M. Shiraki and K. Fukumoto, *Synlett*, 1994, 599; (*d*) H. Nemoto, J. Miyata and K. Fukumoto, *Tetrahedron*, 1996, **52**, 10363; (*e*) H. Nemoto, M. Yoshida and K. Fukumoto, *J. Org. Chem.*, 1997, **62**, 6450; (*f*) H. Nemoto, J. Miyata and M. Ihara, *Tetrahedron Lett.*, 1999, **40**, 1933; (*g*) H. Nemoto, E. Takahashi and M. Ihara, *Org. Lett.*, 1999, **1**, 517.
15 C. Bilger, P. Demerseman and R. Royer, *Eur. J. Med. Chem.*, 1987, **22**, 363.
16 W. J. Scott and J. K. Stille, *J. Am. Chem. Soc.*, 1986, **108**, 3033.
17 M. Yoshida, M. A.-H. Ismail, H. Nemoto and M. Ihara, *Heterocycles*, 1999, **50**, 673.
18 I. Ohtani, T. Kusumi, Y. Kashman and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, **113**, 4092.
19 T. Imamoto, N. Takiyama, K. Nakamura, T. Hatajima and Y. Kamiya, *J. Am. Chem. Soc.*, 1989, **111**, 4392.
20 A. J. Birch and G. S. R. Subba Rao, *Tetrahedron Lett.*, 1967, **23**, 2763.
21 S. Takano, K. Inomata and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1990, 1544.