A Rapid Access to Both Enantiomers of 1,2,3,4-Tetranor B-Trienic 18,18,18-Trifluorosteroids. The First Enantiocontrolled Total Synthesis of 18,18,18-Trifluorosteroids

Hideo Nemoto,† Atsushi Satoh,† Keiichiro Fukumoto,*,† and Chizuko Kabuto‡

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-77, Japan and Instrumental Analysis Center for Chemistry, Faculty of Science, Tohoku University, Aobayama, Sendai 980-77, Japan

Received May 20, 1994®

Chiral A-tetranor B-trienic 18,18,18-trifluorosteroid **2a** and its enantiomer **1a** were synthesised by the thermolysis of chiral olefinic benzocyclobutenes **7b** and **7a** which were in turn prepared by the aldol reaction of chiral oxazolidinone **5** and **11** with 2-(4-methoxybenzocyclobutenyl-1)-acetaldehyde as a key step. The compound **1a** was then transformed into 18,18,18-trifluorosteroid **9** *via* the ketone **13** and the diketone **14**.

Introduction

Recently, there has been growing interest[1] in the synthesis of steroids bearing an angular trifluoromethyl group, expecting the reversible inhibition of the cytochrome P-450 enzyme aromatase in estrogen biosynthesis[2] for 19,19,19-trifluorosteroids[3] and the separation[4] of estrogenicity and antifertility effects for 18,18,18-trifluorosteroids.[5] The difficulty encountered in the synthesis of these trifluorosteroids in comparison with the synthesis of mono- or difluorosteroids[6] and the significant biological activity of some of (±)-18,18,18-trifluoro-17β-estradiol derivatives[5] prompted us to develop an efficient route for the enantioselective synthesis of these types of steroids. Consequently these enantiomerically pure steroids would be able to display accurate biological activities upon evaluation.

Our initial synthetic target was the tetracyclic A-tetranor B-trienic steroid **1a**, a potential intermediate for the synthesis of 18,18,18-trifluorosteroids. These A-tetranor B-trienic steroids (13-methyl analog of **1a**) have been known to lead to many types of biologically important steroids such as estradiol,[7] 19-nortestosterone,[7] adrenosterone,[7] 11-oxoprogesterone,[8] 19-nordeoxycorticosterone,[9] cortisone,[10] 19-norspironolactone,[11] and 25-hydroxy Grundmann's ketone[12] (C,D-ring fragment of active metabolite of vitamin D_3). We were also interested in the synthesis of the tetracyclic A-tetranor B-trienic steroid **2a**, an enantiomer of **1a**, as a potential precursor to enantiomers of the steroids described above. Our strategy was therefore a one-step creation of A-tetranor B-trienic steroid **1a** in an enantioselective manner *via* a chirality transfer from preformed stereogenic centers C-16 and C-17 to C-13 and C-14 (steroid numbering). This can be accomplished *via* an intramolecular [4 + 2] cycloaddition reaction of the olefinic *o*-quinodimethane **8a** (Scheme 1).

We wish to report herein the successful synthesis of A-tetranor B-trienic 18,18,18-trifluorosteroid **1a** and its enantiomer **2a**. Thus, the first enantiocontrolled total synthesis of 18,18,18-trifluorosteroid **9** was accomplished by incorporation of the A-ring into **1a**.

Results and Discussion

Stereochemical Outcome of Intramolecular [4 + 2] Cycloaddition of Olefinic *o*-Quinodimethanes. Our recent studies[7-12] have shown that stereoselective formation of A-tetranor B-trienic steroids having a *trans*-fused C,D-ring and *syn* relationship between the trifluoromethyl group and C-17 substituent (steroid numbering) can be achieved. This was accomplished by an intramolecular [4 + 2] cycloaddition of an olefinic *o*-quinodimethane bearing a bulky substituent at C-17. However, the stereochemical outcome of such a cycloaddition of the olefinic *o*-quinodimethane bearing a cyclic substituent between C-16 and C-17, such as **8a** or **8b**, has not been demonstrated. We therefore set out to examine

† Pharmaceutical Institute, Tohoku University.
‡ Instrumental Analysis Center of Chemistry, Tohoku University.
® Abstract published in *Advance ACS Abstracts*, January 15, 1995.

(1) (a) Marcotte, P. A.; Robinson, C. H. *Biochemistry* **1982**, *21*, 2773–2778. (b) Mann, J.; Pietrzak, B. *J. Chem. Soc., Perkin Trans. 1* **1987**, 385–388. (c) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123–3197. (d) Uneyama, K. *J. Synth. Org. Chem., Jpn.* **1991**, *49*, 612–623 and references cited therein.

(2) Cole, P. A.; Robinson, C. H. *J. Med. Chem.* **1990**, *33*, 2933–2942 and references cited therein.

(3) (a) Mukawa, F. *J. Synth. Org. Chem., Jpn.* **1988**, *46*, 742–752. (b) Hanzawa, Y.; Ito, H.; Kohara, N.; Sasaki, H.; Fukuda, H.; Morikawa, T.; Taguchi, T.; Iitaka, Y. *Tetrahedron Lett.* **1991**, *32*, 4143–4146. (c) Blazejewski, J.-C.; LeGuyader, F.; Wakselman, C. *Tetrahedron Lett.* **1992**, *33*, 499–502.

(4) (a) *Hormone Antagonists*, Agarwal, M. K., Eds.; Walter de Gruyter: New York, 1982. (b) Zeelen, F. J. In *Steroid Contraceptives*; Roberts, S. M., Price, B. J., Eds.; Academic Press: London, 1985; pp 189–208.

(5) (a) Blazejewski, J.-C.; Dorme, R.; Wakselman, C. *J. Chem. Soc., Chem. Commun.* **1983**, 1050–1051. *J. Chem. Soc., Perkin Trans. 1* **1986**, 337–341. (b) Blazejewski, J.-C.; Haddad, M.; Wakselman, C. *Tetrahedron Lett.* **1992**, *33*, 1269–1271.

(6) Fried, J.; Abraham, N. A. In *Organic Reactions in Steroid Chemistry* Fried, J.; Edwards, J. A., Eds.; van Nostrand-Reinhold: New York, **1972**; Vol. 1, pp 423–493.

(7) (a) Nemoto, H.; Nagai, M.; Moizumi, M.; Kohzuki, K.; Fukumoto, K.; Kametani, T. *Tetrahedron Lett.* **1988**, *29*, 4959–4962. (b) Nemoto, H.; Nagai, M.; Moizumi, M.; Kohzuki, K.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1639–1645.

(8) (a) Nemoto, H.; Nagai, M.; Fukumoto, K.; Kametani, T. *Tetrahedron Lett.* **1985**, *26*, 4613–4616. (b) Idem *J. Chem. Soc., Perkin Trans. 1* **1986**, 1621–1625.

(9) (a) Nemoto, H.; Satoh, A.; Ando, M.; Fukumoto, K. *J. Chem. Soc., Chem. Commun.* **1990**, 1001–1002. (b) *Idem. J. Chem. Soc., Perkin Trans. 1* **1991**, 1309–1314.

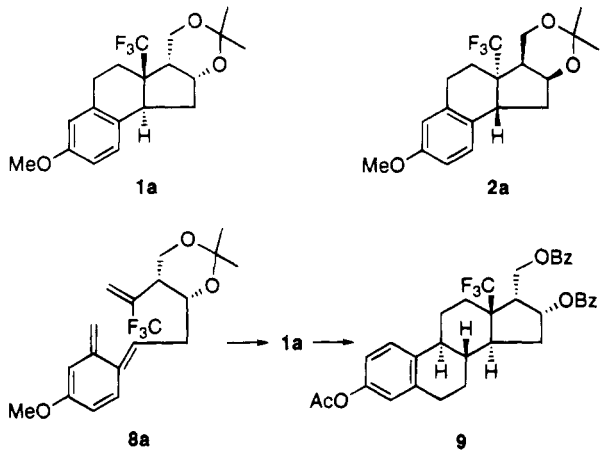
(10) (a) Nemoto, H.; Nagai, M.; Abe, Y.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Chem. Commun.* **1985**, 1316–1317. (b) Nemoto, H.; Nagai, M.; Abe, Y.; Moizumi, M.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1727–1733. (c) Nemoto, H.; Moizumi, M.; Nagai, M.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Perkin Trans. 1* **1988**, 885–887. (d) Nemoto, H.; Matsuhashi, N.; Imaizumi, M.; Nagai, M.; Fukumoto, K. *J. Org. Chem.* **1990**, *55*, 5625–5631.

(11) Nemoto, H.; Fujita, S.; Nagai, M.; Fukumoto, K.; Kametani, T. *J. Am. Chem. Soc.* **1988**, *110*, 2931–2938.

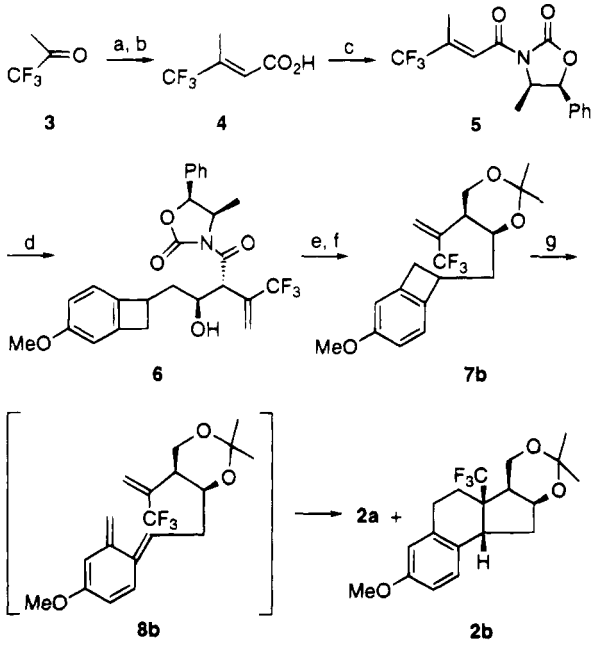
(12) Nemoto, H.; Ando, M.; Fukumoto, K. *Tetrahedron Lett.* **1990**, *31*, 6205–6208.

0022-3263/95/1960-0594$09.00/0

Scheme 1



Scheme 2



[a] steps: (a) $(MeO)_2P(O)CH_2CO_2Me$, NaH, benzene, 0 °C, 1 h; (b) LiOH, THF - H_2O, room temperature, 7 h; (c) pivaloyl chloride, Et_3N, THF, -78 °C, 15 min→0 °C, 1.5 h then *n*-BuLi, (4R,5S)-4-methyl-5-phenyl-2-oxazolidinone, THF, -78 °C, 15 min→room temperature, 1.5 h; (d) 2-(4-methoxybenzocyclobutenyl-1)-acetaldehyde, *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, -78 °C, 45 min→0 °C, 1 h; (e) $LiBH_4$, *n*-Bu_3B, AcOH, 0 °C, 1 h→room temperature, 1 h; (f) $(MeO)_2CMe_2$, CSA, CH_2Cl_2, room temperature, 3 h; (g) ODB, reflux, 7h.

the substituent effect of C-16 and C-17 on the cycloaddition of *o*-quinodimethane **8b**, the enantiomer of **8a**.

As shown in Scheme 2, the synthesis of benzocyclobutene **7b** was accomplished in a straightforward manner. The mixed anhydride of the acid **4**,[13] which was prepared by Horner–Emmons reaction of 1,1,1-trifluoroacetone followed by hydrolysis (34% overall yield based on 1,1,1-trifluoroacetone) and pivalic acid, was then coupled with the lithiated (4*R*,5*S*)-4-methyl-5-phenyl-2-oxazolidinone[14] to give the chiral unsaturated imide **5** (61%). The stereoselective aldol condensation of **5** with

(13) Poulter, C. D.; Satterwhite, D. M. *Biochemistry* **1977**, *16*, 5470–5478.

(14) Evans, D. A.; Mathre, D. J.; Scott, W. L. *J. Org. Chem.* **1985**, *50*, 1830–1835.

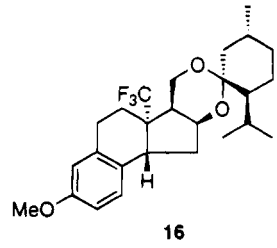
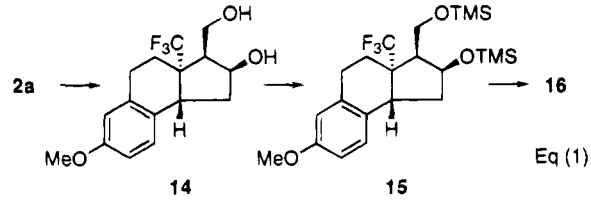


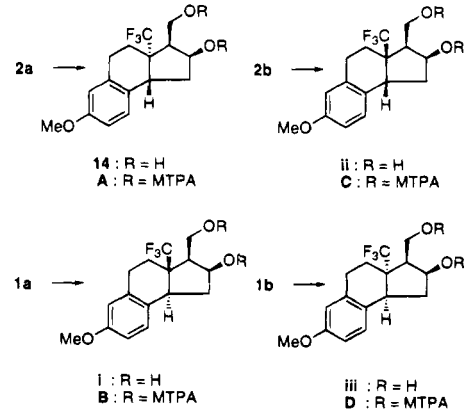
Figure 1.

2-(4-methoxybenzocyclobutenyl-1)acetaldehyde[10b] was performed *via* the boron enolate (di-*n*-butylboron triflate, Et_3N) to afford **6** (65%). Reduction with lithium borohydride followed by protection [$Me_2C(OMe)_2$, camphorsulfonic acid (CSA)] of the resulting diol provided the acetonide **7b** (63%). Thermolysis of **7b** in boiling *o*-dichlorobenzene afforded the A-tetranor B-trienic steroid **2a** (70%) and its isomer **2b**[15] (23%). The absolute configuration of **2a** and **2b** was established by X-ray analysis of the derivative **16** (Figure 1)[20] and also NMR analysis and chemical correlation of **2a** and **2b**. Thus, the *l*-menthone ketal **16** was prepared by deketalization [pyridinium *p*-toluenesulfonate (PPTs), MeOH, reflux, 2 h] (96%) of the acetonide **2a** followed by silylation (TMSCl, Et_3N, THF, room temperature, 2 h) (88%) of the diol **14** and ketalization (*l*-menthone, TMSOTf, CH_2Cl_2, −78 °C, 1 h) (84%) of the silyl ether **15** (eq 1). The

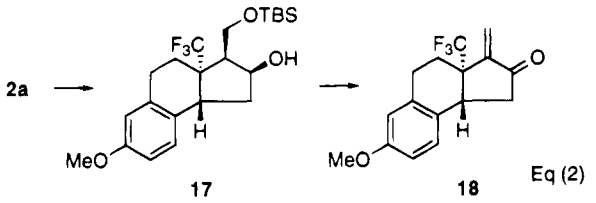


acetonide **2a** was converted into the enone **18** *via* the monosilyl ether **17** by successive reactions, namely deketalization (PPTs, MeOH, reflux, 2 h) (96%) of **2a** followed by silylation [*tert*-butyldimethylsilyl chloride (TBSCl), Et_3N, DMAP, CH_2Cl_2, room temperature, 1 h) (71%) of the resulting diol to give **17** and then oxidation

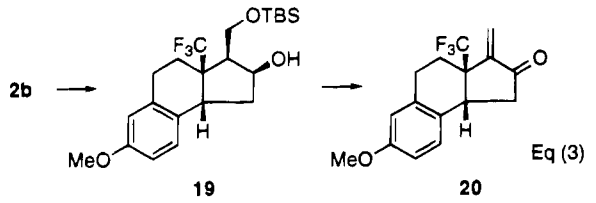
(15) All of the enantiomeric excess of **2a**, **2b**, **1a**, and **1b** were determined to be 100% by comparison of the ^1H NMR (300 MHz) spectra of the methoxy(trifluoromethyl)phenylacetyl (MTPA) esters **A**, **B**, **C**, and **D** derived [(S)-(−)-MTPA acid, dicyclohexylcarbodiimide (DCC), 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, room temp., 13 h] from the alcohols **14**, **i**, **ii**, and **iii** respectively. In turn, the alcohols **i**, **ii** and **iii** were prepared by following the same procedure described for **14**. The ^1H NMR analysis focused on C*H*OMTPA. These protons were typically observed at δ 5.69–5.74 (ddd) and δ 5.81–5.87 (ddd) for the enantiomeric pair of **A** and **B** and δ 5.35–5.38 (ddd) and δ 5.18–5.21 (ddd) for that of **C** and **D**, respectively.



[pyridinium chlorochromate (PCC), 4 Å-MS (molecular sieves), CH_2Cl_2, room temperature, 4 h] (84%) followed by base treatment {1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), CH_2Cl_2, room temperature, 3 h} (99%) to afford the enone **18** (eq 2). The acetonide **2b** was also converted



into the enone **20** *via* the monosilyl ether **19** by following the same reaction sequences (eq 3) in almost same yields described for **2a** → **18**. The spectral comparison of the



enones **18** and **20** indicated that these were not identical, showing the ring juncture of **20** and also **2b** to be *cis*. In turn, the low field shifts of the benzylic methine (3.69 ppm) and oxymethylene (3.97 and 4.09 ppm) of **2b** in comparison with the benzylic methine (3.56 ppm) and oxymethylene (3.63–3.71 ppm) of **2a** suggested the *syn* relationship of trifluoromethyl, benzylic methine, and oxymethylene groups. On the basis of these, the structure of **2b** was determined tentatively as indicated. From this result, it seems possible that the stereoselectivity favoring the *trans-anti* isomer **2a** rather than the *cis-syn* **2b**, *trans-syn* **2c**, and *cis-anti* **2d** isomers probably reflects the steric interactions present in the *endo* transition state T_2 and T_4 and the *exo* transition state T_3 relative to the *exo* transition state T_1 (Figure 2).

Total Synthesis of 18,18,18-Trifluorosteroid 9. Based on these preliminary studies demonstrated above, the chiral olefinic benzocyclobutene **7a** was emerged as an apparent precursor to our targeted acetonide **1b**. The synthesis of this compound was accomplished by following sequence (Scheme 3): Wittig reaction of the (triphenylphosphoranylidene)acetate derived from the chiral oxazolidinone bromoacetate **10**[16] with 1,1,1-trifluoroacetone (**3**) gave the unsaturated chiral imide **11** (66%). Alternatively, this was also prepared by the selective amidolysis of the mixed anhydride (**4**,[13] pivaloyl chloride, Et_3N) with the lithiated chiral oxazolidinone[17] (70%). The stereoselective aldol condensation of this chiral imide **11** with 2-(4-methoxybenzocyclobutenyl-1)acetaldehyde[10b] was accomplished *via* the boron enolate (n-Bu_2BOTf, Et_3N) to afford **12** (77%). Reduction with $LiBH_4$ followed by protection [$Me_2C(OMe)_2$, CSA] of the resulting diol provided the acetonide **7a** (71%). Thermolysis of **7a** in boiling *o*-dichlorobenzene afforded the desired acetonide **1a** (67%) along with its isomer **1b** (30%).[15,18]

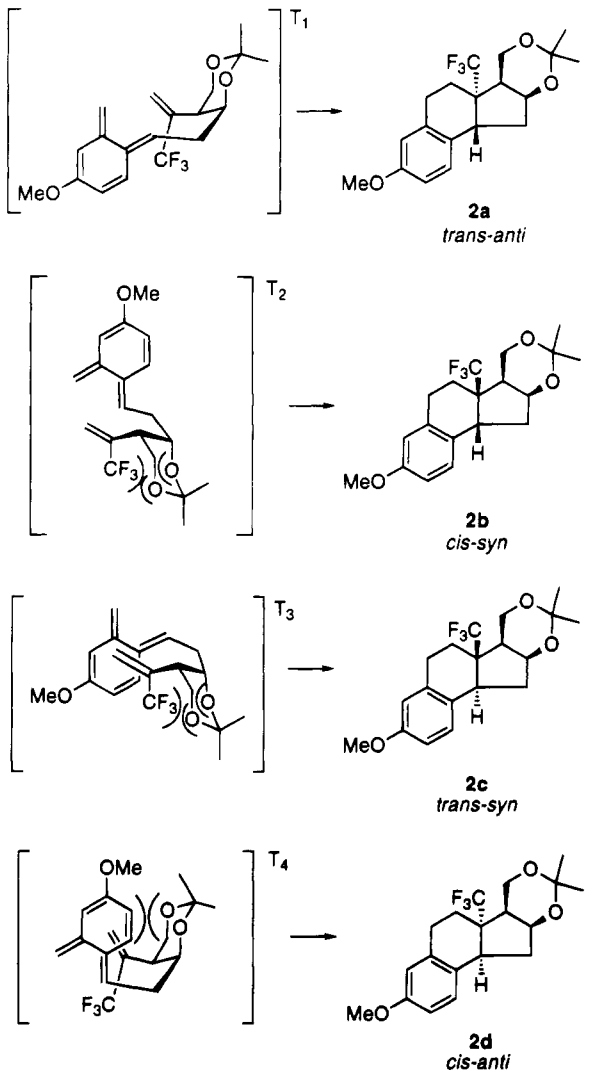


Figure 2.

Incorporation of A-ring into **1a** was easily accomplished *via* the following synthetic sequence: Birch reduction (Na, liquid NH_3, EtOH) of **1a** followed by acid [$(CO_2H)_2$] treatment gave the ketone **13** (74%). Enamine formation (pyrrolidine, TsOH) followed by alkylation (1,3-dichloro-2-butene, KI), reprotection (PhCOCl, pyridine), and hydrolysis [$Hg(OCOCF_3)_2$] of the vinyl chloride afforded the diketone **14** (42%). Finally, cyclization (pyrrolidine) of **14** followed by acetylative isomerization[19] (AcBr, Ac_2O) furnished the 18,18,18-trifluorosteroid **9** {$[\alpha]^{22}_D$ +25.0° (*c* 0.64, $CHCl_3$)} (24%). Thus, we have accomplished the total synthesis of 18,18,18-trifluorosteroid **9** *via* an enantioselective formation of its precursor, A-tetranor B-trienic 18,18,18-trifluorosteroid **1a**. This work has also demonstrated that the enantiomers of these biologically interesting steroids can also be synthesized.

Experimental Section

General Procedures. All reactions were carried out under dry nitrogen unless indicated otherwise. Solvents were distilled prior to use: THF, Et_2O, and benzene were freshly

(16) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 7151–7157.

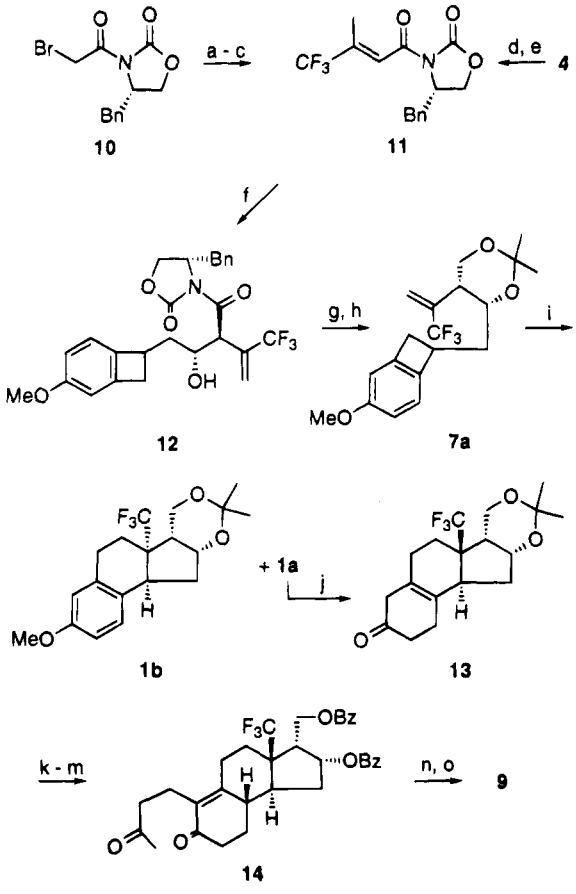
(17) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757–6761.

(18) The structures including absolute stereochemistry of **33** and **1** were determined unambiguously by direct comparison with its enantiomers **19** and **10**, respectively, with opposite sign of optical rotations.

(19) Danishefsky, S.; Cain, P.; Angel. A. *J. Am. Chem. Soc.* **1975**, *97*, 380–387.

(20) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

Scheme 3



[a] steps: (a) Ph_3P, benzene, reflux, 1 h; (b) NaOH, H_2O-ether, 25 °C, 2 h; (c) **3**, benzene, 25 °C, 14 h; (d) pivaloyl chloride, Et_3N, 0 °C, 30 min; (e) *n*-BuLi, (4S)-4-benzyl-2-oxazolidinone, THF, 0 °C, 30 min; (f) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C, 45 min then 2-(4-methoxy-benzocyclobutenyl-1)acetaldehyde, CH_2Cl_2, -78 °C,12 h; (g) $LiBH_4$, THF, H_2O, 0 °C, 30 min; (h) $Me_2C(OMe)_2$, CSA, CH_2Cl_2, 25 °C, 10 h; (i) *o*-dichlorobenzene, reflux, 8 h; (j) Na, liquid NH_3, EtOH, THF, -78 °C, 10 min then $(CO_2H)_2$, EtOH, H_2O, 25 °C, 14 h; (k) pyrrolidine, TsOH, benzene, reflux, 3 h then 1,3-dichloro-2-butene, KI, DMF, 0 °C, 30 min; (l) PhCOCl, pyridine, 25 °C, 10 h; (m) $Hg(OCOCF_3)_2$, $MeNO_2$, 25 °C, 1 h; (n) pyrrolidine, benzene, reflux, 3 h; (o) AcBr, Ac_2O, CH_2Cl_2, 25 °C, 1 h.

distilled from Na benzophenone; CH_2Cl_2 was distilled from CaH_2 and kept over 4-Å molecular sieves. Column chromatography was carried out with silica gel (Wako gel C-200). All new compounds described in this Experimental Section were homogeneous on TLC.

(2*E*)-4-Trifluoro-3-methylbut-2-enoic Acid (4). A solution of 1,1,1-trifluoroacetone **3** (10 mL, 108 mmol) in 50 mL of benzene was added to a stirred suspension of the sodium salt of ethyl diethylphosphonoacetate [from NaH (3.90 g, 165 mmol) and ethyl diethylphosphonoacetate (33 mL, 165 mmol)] in 150 mL of benzene at 0 °C. Then the mixture was stirred for 1 h at same temperature and for 2 h at room temperature. The reaction mixture was washed with water and saturated aqueous NaCl and dried (Na_2SO_4). The residue obtained on evaporation of the solvent was dissolved in mixture of 100 mL of THF and 100 mL of water. To this stirred solution was added lithium hydroxide (8.46 g, 202 mmol) at room temperature. After stirring had been continued for 7 h at the same temperature, the reaction mixture was diluted with Et_2O and extracted with saturated aqueous $NaHCO_3$. The aqueous layer was acidified by the addition of 10% HCl and extracted with Et_2O. The combined extracts were dried (Na_2SO_4). Distillation (21 mmHg, 80–81 °C) of the residue on evaporation of the solvent gave the carboxylic acid (5.66 g, 34%) as colorless oil: IR (neat) 1710 (C=O) cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 2.28 (3H, s), 6.37 (1H, br s), 12.06 (1H, br s); MS *m/z* 154 (M^+); HRMS calcd for $C_5H_5F_3O_2$ 154.0241 (M^+), found 154.0237.

(2′*E*,4*R*,5*S*)-4-Methyl-5-phenyl-3-(4′,4′,4′-trifluoro-3′-methylbut-2-enoyl)oxazolidin-2-one (5). A solution of carboxylic acid **4** (2.88 g, 18.7 mmol) in 90 mL of THF was cooled to −78 °C, and triethylamine (3.4 mL, 24.4 mmol) followed by pivaloyl chloride (2.6 mL, 21.1 mmol) were added with stirring. The resulting slurry was stirred at the same temperature for 15 min and 0 °C for 1.5 h and then recooled to −78 °C. In a separate flask, (4*R*,5*S*)-4-methyl-5-phenyl-2-oxazolidinone was dissolved in 45 mL of THF and cooled to −78 °C. To this solution was added 18.0 mL (28.1 mmol) of 1.56 M *n*-butyllithium in hexane. The metalated oxazolidinone was added *via* cannula to the white slurry prepared as described above. The resulting slurry was stirred for 15 min at −78 °C and then warmed to room temperature over 1.5 h. The reaction was quenched by addition of 100 mL of saturated aqueous potassium bisulfate. The THF was removed *in vacuo*, and the remaining aqueous mixture was extracted with Et_2O. The combined extracts were washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl and dried (Na_2SO_4). The residue upon evaporation of the solvent was chromatographed with hexane–AcOEt (9:1 v/v) to give the imide **5** (3.54 g, 61%) as colorless prisms: mp 57–58 °C (hexane): IR ($CHCl_3$) 1780, 1690 (C=O) cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.95 (3H, d, J = 6.6 Hz), 2.22 (3H, d, J = 1.5 Hz), 4.82 (1H, dq, J = 6.6, 7.3 Hz), 5.71 (1H, d, J = 7.3 Hz), 7.30–7.53 (5H, m); MS *m/z* 313 (M^+); HRMS calcd for $C_{15}H_{14}F_3NO_2$ 313.0926 (M^+), found 313.0953; $[\alpha]^{22}_D$ +13.6° (*c* 0.56, $CHCl_3$). Anal. Calcd for $C_{15}H_{14}F_3NO_2$: C, 57.51; H, 4.50; N, 4.47. Found: C, 57.60; H, 4.50; N, 4.59.

(1″*S*,2′*R*,4*R*,5*S*)-3-{2′-[2″-(1,2-Dihydro-4-methoxybenzocyclobuten-1-yl)-1″-hydroxyethyl]-3′-(trifluoromethyl)but-3′-enoyl}-4-methyl-5-phenyloxazolidin-2-one (6). To a cooled (−78 °C) and stirred solution of imide **5** (1.52 g, 4.87 mmol) in 10 mL of CH_2Cl_2 was added 5.6 mL (5.60 mmol) of 1.0 M di-*n*-butylboron triflate in CH_2Cl_2. After 5 min, triethylamine (0.88 mL, 6.31 mmol) was added. The reaction temperature was maintained at −78 °C for 30 min and then allowed to slowly warm to 0 °C and held at this temperature for 1 h. The solution was recooled (−78 °C) and 2-(4-methoxybenzocyclobutenyl-1)acetaldehyde (1.16 g, 6.56 mmol) in 5 mL of CH_2Cl_2 was added in one portion. The reaction temperature was held at −78 °C for 45 min and then allowed to rise to 0 °C and maintained at this temperature for 1 h. The reaction mixture was quenched by the addition of 6 mL of phosphate buffer (pH 7), poured into 12 mL of MeOH, cooled to 0 °C, and treated with a solution of 6 mL of 30% aqueous H_2O_2 in 20 mL of MeOH for 1 h. The organic solvents were removed in vacuo, saturated aqueous $NaHCO_3$ was added, and the resultant solution was extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4). The residue upon evaporation of the solvent was chromatographed with hexane–AcOEt (4:1 v/v) to give the imide **6** (1.54 g, 65%) as colorless oil: IR (neat) 3500 (OH), 1780, 1690 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (3H, d, J = 6.2 Hz), 3.78 (3H, s), 4.75–4.86 (1H, m), 5.02 (1H, dd, J = 5.9, 8.8 Hz), 5.68 (1H, d, J = 7.3 Hz), 6.01, 6.02 (1H, each br s), 6.10 (1H, br s), 6.69 (1H, s), 6.73 (1H, d, J = 7.7 Hz), 7.02 (H, d, J = 7.7 Hz), 7.28–7.43 (5H, m); MS *m/z* 489 (M^+); HRMS calcd for $C_{26}H_{26}F_3NO_5$ 489.1763 (M^+), found 489.1753.

(4*S*,5*S*)-4-[(1,2-Dihydro-4-methoxybenzocyclobuten-1-yl)methyl]-2,2-dimethyl-5-[1-(trifluoromethyl)vinyl]-1,3-dioxane (7b). To a stirred solution of imide **6** (185 mg, 0.378 mmol) in 3 mL of THF were added 0.42 mL (0.42 mmol) of 1.0 M tri-*n*-butylborane in THF and acetic acid (0.032 mL, 0.60 mmol) at room temperature. After stirring for 1.5 h at same temperature, the solution was cooled to 0 °C and treated with lithium borohydride (16 mg, 0.73 mmol) in 1 mL of THF for 1 h at same temperature and for 1 h at room temperature. To the reaction mixture were added 3 mL of MeOH, 1.5 mL of 0.025 M aqueous Na_2HPO_4, and a solution of 1 mL of 30% aqueous H_2O_2 in 2 mL of MeOH at 0 °C. After stirring for 1.5 h at room temperature, the residue obtained on evaporation of the solvent was diluted with 10% aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined extracts were dried

(Na_2SO_4). The residue obtained on evaporation of the solvent was dissolved in 2 mL of CH_2Cl_2. To this stirred solution were added 2,2-dimethoxypropane (0.23 mL, 1.88 mmol) and a catalytic amount of camphorsulfonic acid at room temperature. After stirring had been continued for 3 h at the same temperature, the reaction mixture was diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, and dried (Na_2SO_4). The residue upon evaporation of the solvent was chromatographed with hexane–AcOEt (19:1 v/v) to give the acetonide **7b** (86 mg, 63%) as colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47, 1.49, 1.56, 1.57 (6H, each s), 3.49–3.56 (1H, m), 3.77 (3H, s), 5.92, 6.22 (2H, each s), 6.67, 6.69 (1H, each s), 6.74 (1H, d, J = 7.9 Hz), 6.95, 6.96 (1H, each d, J = 7.9 Hz); MS m/z 356 (M^+); HRMS calcd for $C_{19}H_{23}F_3O_3$ 356.1599 (M^+), found 356.1591. Anal. Calcd for $C_{19}H_{23}F_3O_3$: C, 64.03; H,6.51. Found: C, 64.18; H, 6.50.

(2*S*,3*S*,3a*R*,9b*S*)-*trans*-2,3,3a,4,5,9b-Hexahydro-2-hydroxy-3-(hydroxymethyl)-1′,2-*O*-isopropylidene-7-methoxy-3a-(trifluoromethyl)-1*H*-cyclopenta[*a*]naphthalene (2a) and (2*S*,3*S*,3a*S*,9b*S*)-*cis*-2,3,3a,4,5,9b-hexahydro-2-hydroxy-3-(hydroxymethyl)-1′,2-*O*-isopropylidene-7-methoxy-3a-(trifluoromethyl)-1*H*-cyclopenta[*a*]naphthalene (2b). A solution of the benzocyclobutene **7b** (184 mg, 0.516 mmol) in 60 mL of ODB was refluxed for 7 h and then evaporated. The residue was chromatographed with hexane–AcOEt (97:3 v/v) to give the *trans*-benzoperhydrindane **2a** (129 mg, 70%) as prisms: mp 134–135 °C (EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33, 1.42 (6H, each s), 1.89–1.96 (1H, m), 2.12 (1H, ddd, J = 3.7, 7.3, 14.0 Hz), 2.19–2.24, 2.26–2.33 (2H, each m), 2.75 (1H, ddd, J = 6.7, 7.3, 10.4 Hz), 2.91–3.02 (2H, m), 3.56 (1H, dd, J = 6.1, 12.8 Hz), 3.63–3.71 (2H, m), 3.77 (3H, s), 4.59 (1H, dd, J = 6.1, 6.7 Hz), 6.66 (1H, d, J = 2.4 Hz), 6.69 (1H, dd, J = 2.4, 7.9 Hz), 6.96(1H, d, J = 7.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.6, 23.9, 26.6, 27.3, 33.9, 44.0, 44.6, 52.1 (J_{CF} = 20.9 Hz), 55.3, 57.7, 72.3, 99.2, 111.0, 113.4, 125.1, 128.7, 129.2 (J_{CF} = 286.1 Hz), 137.9, 158.2; MS m/z 356 (M^+); HRMS calcd for $C_{19}H_{23}F_3O_3$ 356.1599 (M^+), found 356.1598; $[\alpha]^{21}_D$ −35.1° (c 0.70, $CHCl_3$). Anal. Calcd for $C_{19}H_{23}F_3O_3$: C, 64.03; H,6.51. Found: C, 63.91; H, 6.52. The second fraction afforded the *cis*-benzoperhydrindane **2b** (42.4 mg, 23%) as colorless prisms: mp 133–134 °C (EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40, 1.41 (6H, each s), 1.73–1.84 (2H, m), 1.99 (1H, ddd, J = 5.5, 7.9, 14.0 Hz), 2.25–2.29 (2H, m), 2.64–2.85 (2H, m), 3.69 (1H, dd, J = 7.9, 11.0 Hz), 3.78 (3H, s), 3.97 (1H, dd, J = 6.1, 12.2 Hz), 4.09 (1H, dd, J = 6.0 and 12.2 Hz), 4.33 (1H, dd, J = 5.5, 5.5 Hz), 6.66 (1H, d, J = 2.4 Hz), 6.73 (1H, dd, J = 2.4, 8.6 Hz), 7.07 1H, d, J = 8.6 Hz); MS m/z 356 (M^+); HRMS calcd for $C_{19}H_{23}F_3O_3$ 356.1599 (M^+), found 356.1581; $[\alpha]^{21}_D$ +75.4° (c 0.74, $CHCl_3$). Anal. Calcd for $C_{19}H_{23}F_3O_3$: C, 64.03; H, 6.51. Found: C, 63.83; H, 6.35.

(2*S*,3*S*,3a*R*,9b*S*)-*trans*-2,3,3a,4,5,9b-Hexahydro-2-hydroxy-3-(hydroxymethyl)-7-methoxy-3a-(trifluoromethyl)-1*H*-cyclopenta[*a*]naphthalene (14). A solution of the acetonide **2a** (35.0 mg, 0.0982 mmol) and a catalytic amount of PPTS in 4 mL of MeOH was refluxed for 2 h and then evaporated. The residue was chromatographed with hexane–AcOEt (7:3 v/v) to give the diol **14** (29.8 mg, 96%) as colorless oil: IR (neat) 3400 (OH) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56 (2H, br s), 3.77 (3H, s), 3.89–4.05 (2H, m), 4.87–4.92 (1H, m), 6.67–6.72 (2H, m), 6.94 (1H, d, J = 8.1 Hz); MS m/z 316 (M^+); HRMS calcd for $C_{16}H_{19}F_3O_3$ 316.1286 (M^+), found 316.1291; $[\alpha]^{24}_D$ +2.5° (c 1.00, $CHCl_3$).

(2*S*,3*S*,3a*R*,9b*S*)-*trans*-2,3,3a,4,5,9b-Hexahydro-7-methoxy-3a-(trifluoromethyl)-2-[(trimethylsilyl)oxy]-3-[[(trimethylsilyl)oxy]methyl]-1*H*-cyclopenta[*a*]naphthalene (15). To a stirred solution of the diol **14** (95.4 mg, 0.302 mmol) in 3 mL of THF was added TMSCl (0.2 mL, 1.57 mmol) and triethylamine (0.25 mL, 1.79 mmol) at room temperature. After stirring for 2 h at same temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with water and dried (Na_2SO_4). The residue upon evaporation of the solvent was chromatographed with hexane–AcOEt (19:1 v/v) to give the silyl ether **15** (112 mg, 88%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.12, 0.13 (18H, each s), 3.78 (3H, s), 4.60–4.65 (1H, m), 6.67–6.72 (2H, m), 6.94 (1H, d, J = 8.1 Hz); MS m/z 460 (M^+); HRMS calcd for $C_{22}H_{35}F_3O_3Si_2$ 460.2077 (M^+), found 460.2080; $[\alpha]^{21}_D$ −9.9° (c 1.29, $CHCl_3$). Anal. Calcd for $C_{22}H_{35}F_3O_3Si_2$: C, 57.36; H, 7.66. Found: C, 57.63; H, 7.64.

(2*S*,3*S*,3a*R*,9b*S*,1″*R*,2″*S*,5″*R*)-*trans*-2,3,3a,4,5,9b-Hexahydro-2-hydroxy-3-(hydroxymethyl)-1′,2-*O*-(2″-isopropyl-5″-methylcyclohexylidene)-7-methoxy-3a-(trifluoromethyl)-1*H*-cyclopenta[*a*]naphthalene (16). To a stirred solution of silyl ether **15** (29.5 mg, 0.064 mmol) and *l*-menthone (0.02 mL, 0.116 mmol) in 2 mL of CH_2Cl_2 was added TMSOTf (0.02 mL, 0.103 mmol) at −78 °C. After stirring for 11 h at same temperature, to the reaction mixture was added pyridine (0.2 mL) at same temperature, and the mixture was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$, and dried (Na_2SO_4). The residue upon evaporation of the solvent was chromatographed with hexane–AcOEt (19:1 v/v) to give the ketal **16** (24.2 mg, 84%) as needles: mp 119–120 °C (EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.86 (6H, d, J = 7.0 Hz), 0.92 (3H, d, J = 7.0 Hz), 3.78 (3H, s), 4.78–4.82 (1H, m), 6.91 (1H, s), 6.99 (1H, d, J = 8.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.5, 21.9, 22.4, 23.8, 23.9, 27.3, 29.4, 33.9, 34.8, 41.4, 42.7, 45.0, 51.3, 52.5 (J_{CF} = 21.0 Hz), 55.3, 58.9, 71.3, 100.1, 110.9, 113.4, 124.8, 128.9, 129.3 (J_{CF} = 286.1 Hz), 138.6, 158.3; MS m/z 452 (M^+); HRMS calcd for $C_{26}H_{35}F_3O_3$ 452.2538 (M^+), found 452.2526; $[\alpha]^{21}_D$ −35.8° (c 0.98, $CHCl_3$). Anal. Calcd for $C_{26}H_{35}F_3O_3$: C, 69.00; H, 7.80. Found: C, 68.98; H, 7.84.

(2*S*,3*S*,3a*R*,9b*S*)-*trans*-3-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-2,3,3a,4,5,9b-hexahydro-2-hydroxy-7-methoxy-3a-(trifluoromethyl)-1*H*-cyclopenta[*a*]naphthalene (17). To a stirred solution of diol **14** (35.6 mg, 0.112 mmol) in 2 mL of CH_2Cl_2 were added triethylamine (0.03 mL, 0.215 mmol), a catalytic amount of DMAP, and TBSCl (30.0 mg, 0.199 mmol) at room temperature. After stirring for 1 h at same temperature, the reaction mixture was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$ and saturated NaCl, and dried (Na_2SO_4). The residue upon evaporation of the solvent was chromatographed with hexane–AcOEt (19:1 v/v) to give the silyl ether **17** (34.4 mg, 71%) as colorless oil: IR (neat) 3500 (OH) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.12, 0.13 (6H, each s), 0.90 (9H, s), 3.77 (3H, s), 4.73–4.79 (1H, m), 6.66–6.70 (2H, m), 6.96 (1H, d, J = 8.1 Hz); MS m/z 430 (M^+); HRMS calcd for $C_{22}H_{33}F_3O_3Si$ 430.2151 (M^+), found 430.2170; $[\alpha]^{23}_D$ +10.1° (c 0.77, $CHCl_3$).

(3a*R*,9b*S*)-*trans*-3a,4,5,9b-Tetrahydro-2-methylene-7-methoxy-3a-(trifluoromethyl)-1*H*-cyclopenta[*a*]naphthalen-2-one (18). To a stirred solution of alcohol **17** (34.4 mg, 0.08 mmol) in 3 mL of CH_2Cl_2 were added 4 Å-MS (29.0 mg) and PCC (57.4 mg, 0.266 mmol) at room temperature. After stirred for 4 h at same temperature, the reaction mixture was diluted with Et_2O and filtered through Celite. The residue upon evaporation of the solvent was chromatographed with hexane–AcOEt (19:1 v/v) to give the ketone (28.7 mg, 84%) as colorless oil; IR (neat) 1760 (C=O) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03 (3H, s), 0.06 (3H, s), 0.83 (9H, s), 3.80 (3H, s), 3.93 (1H, dd, J = 2.4, 10.1 Hz), 4.19–4.25 (1H, m), 6.72–6.74 (2H, m), 6.92 (1H, d, J = 8.6 Hz); MS m/z 428 (M^+); HRMS calcd for $C_{22}H_{31}F_3O_3Si$ 428.1995 (M^+), found 428.1971; $[\alpha]^{23}_D$ +14.9° (c 1.28, $CHCl_3$). To a stirred solution of this ketone (8.4 mg, 0.0196 mmol) in 2 mL of CH_2Cl_2 was added one drop of DBU at room temperature. After stirred for 3 h at same temperature, the reaction mixture was diluted with CH_2Cl_2, washed with 10% HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, and dried (Na_2SO_4). The residue upon evaporation of the solvent was chromatographed with hexane–AcOEt (9:1 v/v) to give the enone **18** (5.8 mg, 99%) as colorless oil: IR (neat) 1730 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80 (3H, s), 5.59, 6.35 (1H, each s), 6.74–6.77 (2H, m), 6.97 (1H, d, J = 7.3 Hz); MS m/z 296 (M^+); HRMS calcd for $C_{16}H_{15}F_3O_2$ 296.1024 (M^+), found 296.1053; $[\alpha]^{23}_D$ +148.9° (c 0.76, $CHCl_3$).

(2*S*,3*S*,3a*S*,9b*S*)-*cis*-3-[[(*tert*-Butyldimethylsilyl)oxy]methyl]-2,3,3a,4,5,9b-hexahydro-2-hydroxy-7-methoxy-3a-(trifluoromethyl)-1*H*-cyclopenta[*a*]naphthalene (19). A stirred solution of the acetonide **2b** (137 mg, 0.385 mmol) and a catalytic amount of PPTS in 4 mL of MeOH was refluxed for 2 h and then evaporated. The residue was chromatographed with hexane–AcOEt (1:1 v/v) to give the diol (118 mg,

97%) as colorless oil: IR (neat) 3450 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.65 (1H, dd, J = 7.7, 12.1 Hz), 3.78 (3H, s), 3.98–4.16 (2H, m), 4.43–4.47 (1H, m), 6.71–6.75 (2H, m), 7.06 (1H, d, J = 8.1 Hz); MS m/z 316 (M^+); HRMS calcd for $C_{16}H_{19}F_3O_3$ 316.1286 (M^+), found 316.1283. $[\alpha]^{26}_D$ +74.5° (c 0.86, $CHCl_3$). To a stirred solution of this diol (118 mg, 0.372 mmol) in 4 mL of CH_2Cl_2 were added triethylamine (0.09 mL, 0.646 mmol), a catalytic amount of DMAP, and TBSCl (84.2 mg, 0.559 mmol) at room temperature. After stirring for 13 h at same temperature, the reaction mixture was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, and dried (Na_2SO_4). The residue upon evaporation of the solvent was chromatographed with hexane–AcOEt (19:1 v/v) to give the silyl ether **19** (132 mg, 82%) as colorless oil: IR (neat) 3500 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.11 (6H, s), 0.92 (9H, s), 3.68 (1H, dd, J = 7.7, 12.1 Hz), 3.79 (3H, s), 3.94–4.08 (2H, m), 4.40–4.46 (1H, m), 6.71–6.75 (2H, m), 7.07 (1H, d, J = 8.1 Hz); MS m/z 373(M^+ − 57); HRMS calcd for $C_{18}H_{24}F_3O_3Si$ 373.1447 (M^+ − 57), found 373.1438; $[\alpha]^{22}_D$ +75.8° (c 1.45, $CHCl_3$).

(3a*S*,9b*S*)-*cis*-3a,4,5,9b-Tetrahydro-2-methylene-7-methoxy-3a-(trifluoromethyl)-1*H*-cyclopenta[*a*]naphthalen-2-one (20). To a stirred solution of alcohol **19** (71.9 mg, 0.167 mmol) in 3 mL of CH_2Cl_2 were added 4 Å-MS (117 mg) and PCC (107 mg, 0.498 mmol) at room temperature. After stirred for 1 h at same temperature, the reaction mixture was diluted with Et_2O and filtered through Celite. The residue upon evaporation of the solvent was chromatographed with hexane–AcOEt (19:1 v/v) to give the ketone (62.7 mg, 88%) as colorless oil: IR (neat) 1740 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.90 (9H, s), 3.79 (3H, s), 4.15 (1H, dd, J = 3.7, 11.0 Hz), 6.64 (1H, d, J = 2.2 Hz), 6.80 (1H, dd, J = 2.2, 8.8 Hz), 7.04 (1H, d, J = 8.8 Hz); MS m/z 371 (M^+ − 57); HRMS calcd for $C_{18}H_{22}F_3O_3Si$ 371.1290 (M^+ − 57), found 371.1281; $[\alpha]^{23}_D$ +16.7° (c 1.06, $CHCl_3$). To a stirred solution of this ketone (24.7 mg, 0.0576 mmol) in 2 mL of CH_2Cl_2 was added one drop of DBU at room temperature. After stirred for 1 h at same temperature, the reaction mixture was diluted with CH_2Cl_2, washed with 10% HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, and dried (Na_2SO_4). The residue upon evaporation of the solvent was chromatographed with hexane–AcOEt (9:1 v/v) to give the enone **20** (11.2 mg, 66%) as colorless oil: IR (neat) 1720 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.12–2.22 (2H, m), 2.45 (1H, dd, J = 4.3, 18.2 Hz), 2.62–2.74 (2H, m), 3.13 (1H, dd, J = 9.2, 18.9 Hz), 3.77 (3H, s), 3.83 (1H, dd, J = 4.3, 9.2 Hz), 5.72, 6.45 (1H, each s), 6.58 (1H, d, J = 3.1 Hz), 6.78 (1H, dd, J = 3.1, 8.5 Hz), 7.06 (1H, d, J = 8.5 Hz); MS m/z 296 (M^+); HRMS calcd for $C_{16}H_{15}F_3O_2$ 296.1024 (M^+), found 296.1040; $[\alpha]^{24}_D$ +156.6° (c 1.02, $CHCl_3$).

(4*S*)-4-Benzyl-3-(4,4,4-trifluoro-3-methylbut-2-enoyl)-oxazolidin-2-one (11). To a stirred solution of 1,1,1-trifluoroacetone **3** (1.0 mL, 11.2 mmol) in 50 mL of $CHCl_3$ were added phosphonium salt of **10** (9.52 g, 17.0 mmol) and DMAP (2.83 g, 23.2 mmol) at room temperature. After stirring for 3 h at the same temperature, the reaction mixture was diluted with CH_2Cl_2, washed with saturated aqueous potassium bisulfate and saturated aqueous NaCl, and dried (Na_2SO_4). The residue upon evaporation of the solvent was chromatographed with hexane–AcOEt (4:1 v/v) to give the imide **11** (2.77 g, 79%) as plates: mp 60–61 °C (Et_2O–hexane); IR ($CHCl_3$) 1780, 1685 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.25 (3H, d, J = 1.5 Hz), 2.80 (1H, dd, J = 9.7, 13.2 Hz), 3.36 (1H, dd, J = 3.3, 13.2 Hz), 4.19–4.28 (2H, m), 4.70–4.78 (1H, m), 7.72–7.38 (5H, m), 7.50 (1H, d, J = 1.5 Hz); MS m/z 313 (M^+); HRMS calcd for $C_{15}H_{14}F_3NO_3$ 313.0926 (M^+), found 313.0914; $[\alpha]^{24}_D$ +43.7° (c 0.99, $CHCl_3$). Anal. Calcd for $C_{15}H_{14}F_3NO_3$: C, 57.51; H, 4.50; N, 4.47. Found: C, 57.57; H, 4.46; N, 4.59.

(1″*R*,2′*S*,4*S*)-4-Benzyl-3-{2′-[2″-(1,2-dihydro-4-methoxybenzocyclobuten-1-yl)-1″-hydroxyethyl]-3′-(trifluoromethyl)but-3′-enoyl}oxazolidin-2-one (12). To a solution of the imide **11** (4.05 g, 12.9 mmol) in 30 mL of CH_2Cl_2 were added 14.2 mL (14.2 mmol) of 1.0 M di-*n*-butylboron triflate in CH_2Cl_2 and triethylamine (2.5 mL, 17.9 mmol) at 0 °C, and stirring was continued for 45 min at the same temperature. To this reaction mixture was added a solution of the aldehyde (2.62 g, 14.9 mmol) in 8 mL of CH_2Cl_2 at −78 °C, and stirring was continued for 12 h at the same temperature and for 1.5 h at 0 °C. The reaction mixture was quenched by addition of pH 7 phosphate buffer (20 mL) and MeOH (30 mL) at 0 °C. A solution of MeOH–30% aqueous H_2O_2 (2:1, 60 mL) was added dropwise to the mixture and the solution was stirred at 0 °C for 1 h. The residue upon evaporation of the solvent was extracted with AcOEt. The combined extracts were washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl and dried (Na_2SO_4). The residue upon evaporation of solvent was chromatographed with hexane–AcOEt (7:3 v/v) to give the aldol adduct **12** (4.90 g, 78%) as an oil. IR (neat) 1780, 1690 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.56 (3H, br s), 3.77 (3H, s), 6.10, 6.11 (1H, each br s), 6.14 (1H, br s), 6.68 (1H, s), 7.16–7.36 (5H, m); MS m/z 489 (M^+); HRMS calcd for $C_{26}H_{26}F_3NO_5$ 489.1763 (M^+), found 489.1780.

(4*R*,5*R*)-4-[(1,2-Dihydro-4-methoxybenzocyclobuten-1-yl)methyl]-2,2-dimethyl-5-[1-(trifluoromethyl)vinyl]-1,3-dioxane (7a). To a stirred solution of the imide **12** (1.99 g, 4.06 mmol) in 90 mL of Et_2O were added water (0.08 mL, 4.44 mmol) and lithium borohydride (97 mg, 4.47 mmol) in THF (3 mL) at 0 °C, and the solution was stirred for 30 min at the same temperature and then 1 h at room temperature. The reaction was then quenched with 10% NaOH (1 mL), and the mixture was stirred for 30 min at room temperature. The mixture was poured into water and extracted with AcOEt. The combined extracts were washed with saturated aqueous NaCl, and the solvent was evaporated. To a stirred solution of the residue in 3 mL of CH_2Cl_2 at room temperature were added a catalytic amount of camphorsulfonic acid and 2,2-dimethoxypropane (1.0 mL, 8.18 mmol). After stirring was continued for 10 h at the same temperature, the reaction mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The residue upon evaporation of the solvent was chromatographed with benzene to give the acetonide **7a** (1.03 g, 71%) as colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 1.47, 1.50, 1.56, 1.58 (6H, each s), 3.77 (3H, s), 4.22–4.37 (3H, m), 5.95, 6.22 (2H, each s), 6.67, 6.69 (1H, each s), 6.73 (1H, d, J = 8.1 Hz), 6.95, 6.97 (1H, each d, J = 8.1 Hz); MS m/z 356 (M^+); HRMS calcd for $C_{19}H_{23}F_3O_3$ 356.1599 (M^+), found 356.1602. Anal. Calcd for $C_{19}H_{23}F_3O_3$: C, 64.03; H, 6.51. Found: C, 63.96; H, 6.63.

(2*R*,3*R*,3a*S*,9b*R*)-*trans*-2,3,3a,4,5,9b-Hexahydro-2-hydroxy-3-(hydroxymethyl)-1′,2-*O*-isopropylidene-7-methoxy-3a-(trifluoromethyl)-1*H*-cyclopenta[*a*]naphthalene (1a) and (2*R*,3*R*,3a*R*,9b*R*)-*cis*-2,3,3a,4,5,9b-Hexahydro-2-hydroxy-3-(hydroxymethyl)-1′,2-*O*-isopropylidene-7-methoxy-3a-(trifluoromethyl)-1*H*-cyclopenta[*a*]naphthalene (1b). A solution of the benzocyclobutene **7a** (3.37 g, 9.46 mmol) in 600 mL of *o*-dichlorobenzene (ODB) was refluxed for 8 h and then evaporated. The residue was chromatographed with hexane–AcOEt (19:1 v/v) to give the *trans*-benzoperhydrindane **1a** (2.20 g, 65%) as colorless prisms: mp 106–107 °C (EtOH); ^1H NMR (300 MHz, $CDCl_3$) δ 1.33, 1.42 (6H, each s), 3.77 (3H, s), 6.67 (1H, s), 6.68 (1H, d, J = 8.1 Hz), 6.96 (1H, d, J = 8.1 Hz); MS m/z 356 (M^+); HRMS calcd for $C_{19}H_{23}F_3O_3$ 356.1599 (M^+), found 356.1601; $[\alpha]^{21}_D$ +37.6° (c 1.13, $CHCl_3$). Anal. Calcd for $C_{19}H_{23}F_3O_3$: C, 64.03; H,6.51. Found: C, 63.75; H, 6.78. The second fraction afforded the *cis*-benzoperhydrindane **1b** (42.4 mg, 23%) as colorless prisms: mp 133–134 °C (EtOH); ^1H NMR (500 MHz, $CDCl_3$) δ 1.40 and 1.41 (6H, each s), 1.73–1.84 (2H, m), 1.99 (1H, ddd, J = 5.5, 7.9, 14.0 Hz), 2.25–2.29 (2H, m), 2.64–2.85 (2H, m), 3.69 (1H, dd, J = 7.9, 11.0 Hz), 3.78 (3H, s), 3.97 (1H, dd, J = 6.1, 12.2 Hz), 4.09 (1H, dd, J = 6.0, 12.2 Hz), 4.33 (1H, dd, J = 5.5, 5.5 Hz), 6.66 (1H, d, J = 2.4 Hz), 6.73 (1H, dd, J = 2.4, 8.6 Hz), 7.07 (1H, d, J = 8.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ :21.7, 26.3, 27.2, 29.5, 41.8, 43.2, 49.4, 51.4 (J_{CF} = 24.2 Hz), 55.3, 57.4, 70.7, 98.8, 112.5, 113.8, 129.1 (J_{CF} = 283.3Hz), 129.5, 130.3, 136.3, 158.2; MS m/z 356 (M^+); HRMS calcd for $C_{19}H_{23}F_3O_3$ 356.1599 (M^+), found 356.1581; $[\alpha]^{21}_D$ −93.2° (c 0.83, $CHCl_3$). Anal. Calcd for $C_{19}H_{23}F_3O_3$: C, 64.03; H, 6.51. Found: C, 63.82; H, 6.77.

(2*R*,3*R*,3a*S*,9b*R*)-*trans*-1,2,3,3a,4,5,6,8,9,9b-Decahydro-2-hydroxy-3-(hydroxymethyl)-1′,2-*O*-isopropylidene-3a-(trifluoromethyl)cyclopenta[*a*]naphthalen-7-one (13). To

a stirred solution of the *trans*-benzoperhydrindane **1a** (230 mg, 0.645 mmol) in a mixture of 40 mL of THF, 80 mL of liquid ammonia, and 2.0 mL of EtOH was added sodium (178 mg, 7.74 mmol) at −78 °C. After stirring had been continued for 20 min at the same temperature, the solvent was concentrated. The residue was diluted with saturated aqueous NH_4Cl and extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl and dried (Na_2SO_4). The residue obtained on evaporation of the solvent was dissolved in a mixture of 8 mL of EtOH and 0.8 mL of water. To this stirred solution was added oxalic acid dihydrate (98.0 mg, 0.777 mmol) at room temperature. After stirring had been continued for 14 h at the same temperature, the solvent was neutralized by addition of saturated aqueous $NaHCO_3$ and concentrated. The residue was diluted with water and extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl and dried (Na_2SO_4). The residue upon evaporation of the solvent was chromatographed with hexane−AcOEt (17:3) to give the ketone **13** (165 mg, 74%) as colorless oil; IR (neat) 1710 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.32, 1.38 (6H, each s), 2.45−2.55 (2H, m), 2.66−2.80 (2H, m), 4.43−4.52 (1H, m); MS *m/z* 344 (M^+); HRMS calcd for $C_{18}H_{23}F_3O_3$ 344.1599(M^+), found 344.1570. $[\alpha]^{26}_D$ −3.61° (*c* 3.15, $CHCl_3$).

(2*R*,3a*S*,9a*S*,9b*R*)-*trans*-2-(Benzoyloxy)-3-[(benzoyloxy)methyl]-1,2,3,3a,4,5,8,9,9a,9b-decahydro-6-(3-oxobutyl)-3a-(trifluoromethyl)cyclopenta[*a*]naphthalen-7-one (14). To a solution of ketone **13** (221 mg, 0.642 mmol) in 20 mL of benzene were added pyrrolidine (0.5 mL, 5.99 mmol) and a catalytic amount of *p*-toluenesulfonic acid at room temperature. The reaction mixture was then refluxed in a flask fitted with a Dean−Stark trap for 3 h. The residue upon evaporation of the solvent was dissolved in 6 mL of DMF. To this stirred solution were added potassium iodide (221 mg, 1.33 mmol) and 1,3-dichloro-2-butene (0.20 mL, 1.89 mmol) at 0 °C. After stirring had been continued for 30 min at same temperature and for 1 h at room temperature, to the reaction mixture was added 10% HCl and the solution was refluxed for 1 h. The reaction mixture was diluted with water and extracted with $CHCl_3$. The combined extracts were washed with saturated aqueous NaCl and dried (Na_2SO_4). The residue upon evaporation of the solvent was dissolved in 5 mL of pyridine. To this stirred solution was added benzoyl chloride (0.5 mL, 4.31 mmol) at 0 °C. After stirring had been continued for 10 h at room temperature, to the reaction mixture was added 0.5 mL of MeOH and the solution was stirred for 30 min. Then the reaction mixture was diluted with AcOEt, washed with 10% HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, and dried (Na_2SO_4). The residue upon evaporation of the solvent was dissolved in 6 mL of nitromethane. To this stirred solution was added mercuric trifluoroacetate (410 mg, 0.962 mmol) at room temperature. After stirring had been continued for 1 h at the same temperature, the reaction mixture was treated with 10% HCl for 1 h and extracted with AcOEt. The combined extracts were washed with saturated aqueous NaCl and dried (Na_2SO_4). The residue upon evaporation of the solvent was chromatographed with hexane−AcOEt (4:1 v/v) to give the diketone **14** (157 mg, 42%) as an oil: IR (neat) 1715, 1660 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.11 (3H, s), 4.47−4.58 (2H, m), 5.88−5.92 (1H, m), 7.36−7.94 (10H, m); MS *m/z* 582 (M^+); HRMS calcd for $C_{33}H_{33}F_3O_2$ 582.2230 (M^+), found 582.2227. $[\alpha]^{21}_D$ −2.3° (*c* 0.86, $CHCl_3$).

(16*R*,17*R*)-3-(Acetyloxy)-2-(benzoyloxy)-3-[(benzoyloxy)methyl]-18-trifluoro-1,3,5(10)-estratriene (9). To a solution of diketone **14** (26.1 mg, 0.0448 mmol) in 5 mL of benzene was added pyrrolidine (0.5 mL, 5.99 mmol) at room temperature. The reaction mixture was then refluxed in a flask fitted with a Dean−Stark trap for 16 h. The residue, upon evaporation of the solvent, was dissolved in 10 mL of benzene. To this solution were added acetic acid (0.5 mL), sodium acetate (0.25 g), and water (0.5 mL) at room temperature. After the reaction mixture was refluxed for 3 h, the reaction mixture was diluted with water and extracted with AcOEt. The combined extracts were washed with 10% HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl and dried (Na_2SO_4). The residue upon evaporation of the solvent was dissolved in 1 mL of CH_2Cl_2. To this stirred solution were added acetyl bromide (0.05 mL, 0.67 mmol) and acetic anhydride (0.05 mL, 0.53 mmol) at room temperature. After stirring for 1 h at the same temperature, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl and dried (Na_2SO_4). The residue upon evaporation of the solvent was chromatographed with hexane−AcOEt (4:1 v/v) to give the estran **9** (6.4 mg, 24%) as colorless oil: IR (neat) 1715 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.41−1.51 (1H, m), 1.76−2.25 (7H, m), 2.28 (3H, s), 2.41−2.43 (3H, m), 2.65−2.96 (2H, m), 3.22 (1H, dd, J = 8.9 14.7 Hz), 4.53−4.59 (2H, m), 5.93 (1H, dd, J = 7.3, 7.3 Hz), 6.81 (1H, s), 6.85 (1H, d, J = 8.5 Hz), 7.22 (1H, d, J = 8.5 Hz), 7.35−7.43 (4H, m), 7.50−7.56 (2H, m), 7.94 (4H, d, J = 8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 21.2, 26.2, 28.4, 29.3, 35.0, 37.1, 43.8, 45.5, 50.4, 52.8 (J_{CF} = 24.2 Hz), 61.4, 74.9, 118.9, 121.7, 126.1, 128.5, 128.5, 129.5, 129.6, 129.7, 129.9, 133.3, 136.9, 137.9, 139.7 (J_{CF} = 286.1 Hz), 148.9, 165.9, 166.3, 169.9; MS *m/z* 606 (M^+); HRMS calcd for $C_{35}H_{33}F_3O_6$ 606.2230 (M^+), found 606.2217. $[\alpha]^{22}_D$ +25.0° (*c* 0.64, $CHCl_3$).

Supplementary Material Available: Copies of ^1H NMR spectra of compounds **11**, **16**, **20**, **23-26**, **31**, **34** and **35** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO940830T