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Diels-Alder Reactions with *o*-Quinodimethanes: The Influence of Protective Groups and Substituents of Allyl Alcohols on the Stereochemical Course—— A New Access to 18-Trifluoroestrans

Hideo Nemoto, Atsushi Satoh, and Keiichiro Fukumoto*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-77, Japan

Abstract: The induced diastereoselectivity of the intramolecular Diels-Alder reaction of the trifluoromethyl substituted olefinic *o*-quinodimethanes **10**, **11**, and **21a** - **g**, generated *in situ* by the thermolysis of the corresponding benzocyclobutenes **6**, **7**, and **20a** - **g** respectively, was investigated experimentally and theoretically. The both *cis* (ring juncture) and *anti* selectivity [relative configuration of C_{13} and C_{17} (steroid numbering) substituents] were enhanced on comparing with that of the corresponding methyl analogs. Semi empirical PM3 calculations have been used to locate the transition structures of the intramolecular Diels-Alder reactions of **10**, **11**, and some of **21**. The obtained data were compared with the experimental results of the cycloadditions and showed a good agreement.

Introduction

Diels-Alder reactions[1] have continued to attract considerable interest mainly because of their importance in organic synthesis for the generation of six-membered rings with high regio- and stereoselectivity leading to the creation of four contiguous stereogenic centers in one synthetic operation. Especially, the diastereofacial selectivity of this reaction has recently recognized to be important in connection with asymmetric synthesis.[1a,d,f] Among the many ways to obtain good facial selectivity such as linking the diene[1g] or the dienophile[1e] to a chiral auxiliary or chelating the dienophile with a chiral Lewis acid,[1i] the incorporation of an allylic stereogenic center has been attracting way. In this case, when the starting diene or dienophile is enantiomerically pure, high diastereofacial selectivity in the cycloaddition means the formation of highly enantiomerically enriched cycloadducts. Along with this concept, numerous reports on the role[2] of a heteroatom substitution at the allylic position and the use[3] of protecting groups of allylic alcohol as a means of controlling π-facial selectivity have appeared. In contrast, very few investigations[4] have been made concerning the influence of protecting groups of allylic alcohols as dienophiles on the π-facial selectivity of the cycloaddition reaction with *o*-quinodimethanes.[5] During the course of our studies[6] directed toward the total synthesis of steroids *via* intramolecular cycloaddition reaction of olefinic *o*-quinodimethanes, our research interest has recently centered on the total synthesis of 18-trifluoroestrans **3**, which have attracted much attention expecting the separation[7] of estrogenicity and antifertility effects, *via* des A B-trienic steroids **2** prepared by intramolecular cycloaddition of olefinic *o*-quinodimethane **1** (Chart 1). This strategy has several advantages, such as the control of chirality of the final steroids **3** by controlling the chirality of starting allylic stereogenic center of **1**, the routine manipulation of hydroxyl protective groups in organic synthesis,[8] and the promising transformation of des A B-trienic steroids like **2** into the many types of biologically important steroids,[6] although the information about the influence of hydroxyl protective groups on the stereochemical course of cycloaddition reaction of **1** is crucial. Herein we describe the results.

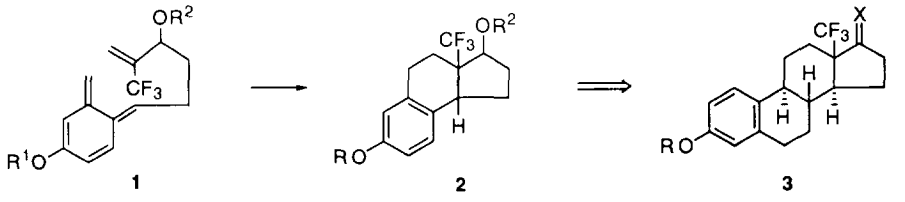
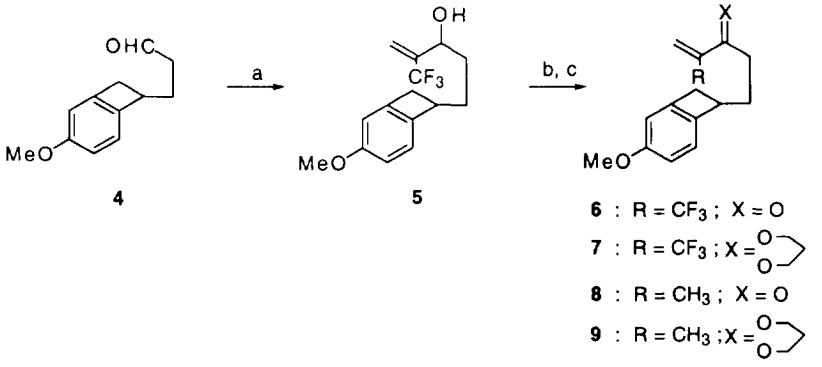


Chart 1

Results and Discussion

The Influence of Trifluoromethyl on [4+2] Cycloaddition Reaction of o-Quinodimethanes. Preliminary experiments for the influence of trifluoromethyl (vinyl substituent) on the stereochemical course of [4+2] cycloadditions of **1** were carried out. The ketone **6** and the acetal **7** emerged as candidates for this purpose since there is no stereogenic center in its transition states **10** and **11** of cycloaddition reactions. The synthesis of **6** and **7** was straightforward (Scheme 1).



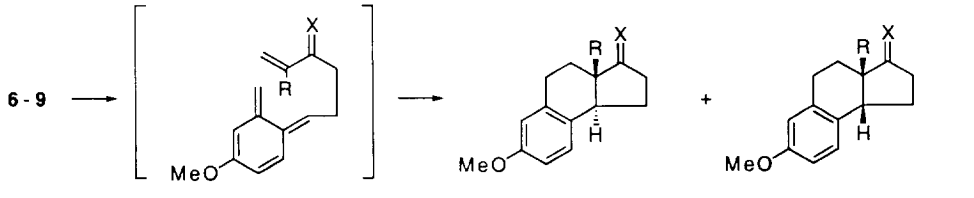
Scheme 1: Reagents and conditions; a CH_2=C(CF_3)Br, Zn, CuCl, THF-pyridine,))), rt, 10 h; b PCC, 4 Å MS, CH_2Cl_2, rt, 1 h; c $HOCH_2CH_2CH_2OH$, *p*-TsOH, benzene, reflux, 40 h.

The benzocyclobutenylaldehyde **4**,[9] easily obtainable in large quantities from 4-methoxybenzocyclobutene-1-carbonitrile,[10] was treated with trifluoroisopropenyl bromide in the presence of zinc and cuprous chloride[11] under irradiation of ultrasound to give the alcohol **5** (54%). The oxidation (PCC) of **5** afforded the enone **6** (72%) which on acetalization ($HOCH_2CH_2CH_2OH$, *p*-TsOH) furnished the acetal **7** (17%). The thermal reactions of these olefinic benzocyclobutenes **6** and **7** were conducted in boiling *o*-dichlorobenzene. The present (entries 1 and 3) and the reported[12] (entries 2 and 4) results, which are summarized in Table 1, show that the substitution of trifluoromethyl for methyl of vinyl substituents (**8**→**6** and **9**→**7**) causes the remarkable enhancement of *cis* selectivity.[13]

In order to understand these results by locating the transition structures and evaluating these energy differences, semiempirical calculation (PM3[14] Hamiltonian implemented in MOPAC 6.0[15]) were performed (Figure 1).

Table 1 [a]

Thermolysis of Olefinic Benzocyclobutenes 6 and 7, and 8 (methyl analog of 6) and 9 (methyl analog of 7)



10 : R = CF_3 ; X = O
11 : R = CF_3 ; X = 
12 : R = CH_3 ; X = O
13 : R = CH_3 ; X = 

14a : R = CF_3 ; X = O
15a : R = CF_3 ; X = 
16a : R = CH_3 ; X = O
17a : R = CH_3 ; X = 

14b : R = CF_3 ; X = O
15b : R = CF_3 ; X = 
16b : R = CH_3 ; X = O
17b : R = CH_3 ; X = 

entry	substrate	product ratio [c]		yield (%) [d]
1	**6**	**14a** : **14b**	1 : 6.5	99
2 [b]	**8**	**16a** : **16b**	1.4 : 1	99
3	**7**	**15a** : **15b**	2.1 : 1	94
4 [b]	**9**	**17a** : **17b**	6.7 : 1	90

[a] All reactions were run under argon in boiling *o*-dichlorobenzene.

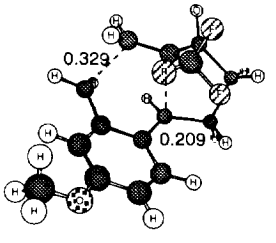
[b] ref. 12.

[c] The ratio of isomers was determined by ^{1}H NMR integration of C-7 hydrogen (steroid numbering) signals [7.08 ppm for **14a** and 7.15 ppm for **14b**] of the corresponding ketones derived by 10% HCl treatment of initial products in case of entry 3.

[d] All yields were based on products purified by passing through a short column (SiO_2).

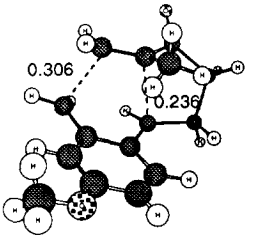
In the transition structures **10** of the thermolysis of **6**, the greater difference (0.202) of bond orders between terminal (0.384) and inner (0.182) forming bonds in **TS 10** *cis* leading to **14b** than that (0.12) of **TS 10** *trans* between terminal (0.329) and inner (0.209) leading to **14a** is in agreement with *asynchronous transition states of internally activated nonatriene favoring cis-fused cycloadduct.*[1h] This can be the same situation for the difference of bond orders between terminal and inner forming bonds of **TS 12** *cis* (0.123) and **TS 12** *trans* (0.07) of the thermolysis of **8**. The larger calculated ΔΔH value (1.59 kcal/mol) between **TS 10** *cis* (ΔH = -136.27 kcal/mol) and **TS 10** *trans* (ΔH = -134.68 kcal/mol) than that (0.21 kcal/mol) between **TS 12** *cis* (ΔH = 11.39 kcal/mol) and **TS 12** *trans* (ΔH = 11.60 kcal/mol) is in excellent agreement with the remarkable enhancement of *cis* selectivity in case of **6**. The same argument could be taken into account for the transition structures **11** and **13** in the thermolysis of **7** and **9** respectively (Figure 2). Namely, the greater differences (0.079 and 0.059) of bond orders between terminal and inner forming bonds in **TS 11** *cis* (0.292 and 0.213) and **TS 13** *cis* (0.297 and 0.238) leading to **15b** and **17b** respectively than that (0.067 and 0.042) of **TS 11** *trans* (0.293 and 0.226) and **TS 13** *trans* (0.284 and 0.242) leading to **15a** and **17a** respectively, are in agreement with asynchronous transition states. The larger calculated ΔΔH value (2.24 kcal/mol) between **TS**

11 *cis* (ΔH = -176.92 kcal/mol) and **TS 11** *trans* (ΔH = -174.68 kcal/mol) than that (0.46 kcal/mol) between **TS 13** *cis* (ΔH = -27.29 kcal/mol) and **TS 13** trans (ΔH = -27.75 kcal/mol) is in agreement with the decreased *trans* selectivity.



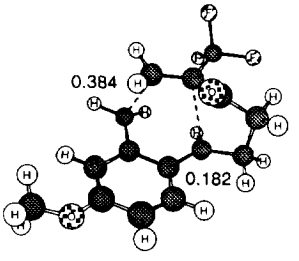
ΔH= -134.68 kcal/mol

TS10 *trans*



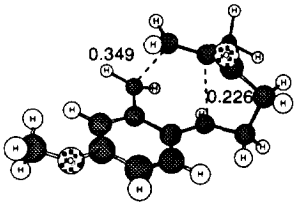
ΔH= 11.60 kcal/mol

TS12 *trans*



ΔH= -136.27 kcal/mol

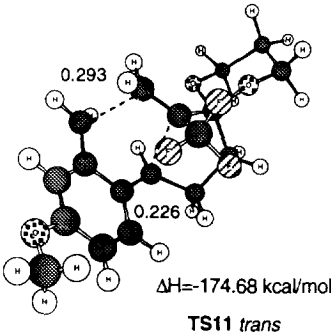
TS10 *cis*



ΔH= 11.39 kcal/mol

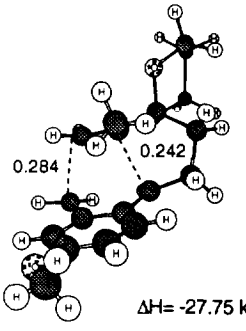
TS12 *cis*

Figure 1



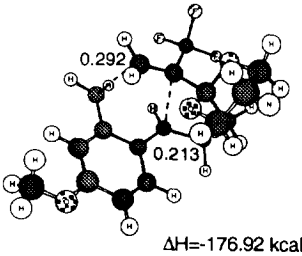
ΔH=-174.68 kcal/mol

TS11 *trans*



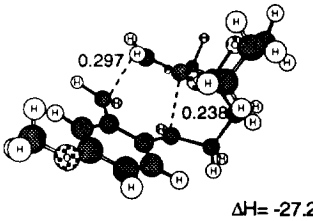
ΔH= -27.75 kcal/mol

TS13 *trans*



ΔH=-176.92 kcal/mol

TS11 *cis*



ΔH= -27.29 kcal/mol

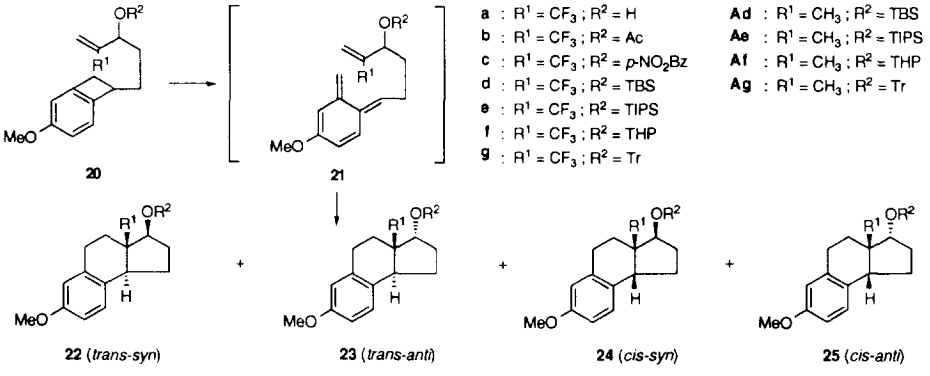
TS13 *cis*

Figure 2

The Influence of Hydroxyl Protective Groups on [4+2] Cycloaddition Reaction of o-Quinodimethanes. We are set out to examine the influence of hydroxy protective groups and also trifluoromethyl substituent of vinyl group on the stereochemical course of [4+2]cycloaddition reaction of *o*-quinodimethanes. The preparation of allyl alcoholic benzocyclobutenes **20** bearing various protective groups, substrates for the generation of *o*-quinodimethane **21**, was achieved by following the standard derivatisation procedure for **5** to furnish **20b** - **f** {**20b** (Ac_2O, pyridine, rt, 2 h); **20c** [*p*-nitrobenzoyl chloride (*p*-NO_2BzCl), pyridine, 0 °C, 5 h]; **20d** [*tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf), 2,6-lutidine, CH_2Cl_2, 0 °C, 14 h]; **20e** [triisopropylsilyl trifluoromethanesulfonate (TIPSOTf), 2,6-lutidine, CH_2Cl_2, 0 °C, 3 h]; **20f** [dihydropyran (DHP), pyridinium *p*-toluenesulfonate (PPTs), CH_2Cl_2, rt, 3 h]; **20g** [trityl chloride (TrCl), silver trifluoromethanesulfonate (AgOTf), 2,6-lutidine, 0.5 h]}. The thermolyses of these allyl alcoholic benzocyclobutenes were conducted in boiling *o*-dichlorobenzene. The present (**a** - **g** series) and the reported[4] (**Ad** - **Ag** series) results, which are summarized in Table 2, reveal that the trifluoromethyl substituent on vinyl dienophile enhances the *cis* selectivity and also *anti* selectivity[16] on comparison with methyl analogs for the most part.

Table 2 [a]

Thermolysis of Allyl Alcoholic Benzocyclobutenes



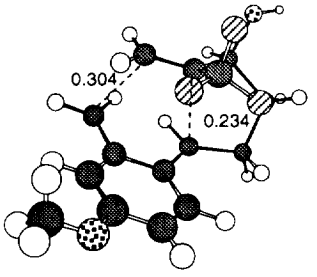
entry	substrate	product ratio [b] 22 : 23 : 24 : 25				yield (%) [c]
1	**20a** (**5**)	1	2.3	1.5	1.9	55
2	**20b**	1	1.1	0.9	2.5	97
3	**20c**	1	0.5	0.9	2.4	84
4	**20d**	1	5.2	1.7	1.4	46
5	(**20Ad**)	1	2.3	–	–	99
6	**20e**	1	8.9	2.9	4.1	65
7	(**20Ae**)	1	2.0	–	–	81
8	**20f**	1	2.9	1.6	2.7	74
9	(**20Af**)	1	1.2	–	–	72
10	**20g**	1	2.0	1.7	4.1	65
11	(**20Ag**)	1	1	–	–	90

a All reactions were run under argon in boiling *o*-dichlorobenzene for 6-12 h.

b The isomer (**22**, **23**, **24** and **25**) ratio was determined by ^1H NMR integration of C17-H (steroid numbering) signals [δ 5.13 (dd, J = 8.4 and 8.8 Hz) for **22b**, δ 5.43 (dd, J = 1.2 and 6.6 Hz) for **23b**, δ 5.56 (dd, J = 4.8 and 6.2 Hz) for **24b**, and δ 5.33 (dd, J = 9.5 and 7.3 Hz) for **25b**] of the corresponding acetates[17] which were prepared as follows: Initial products were treated with K_2CO_3 for entries 2 and 3, Bu_4NF for entries 4 and 6, and 10% HCl for entries 8 and 10, and then the resulting alcohols (the initial products for entry 1) were acetylated with Ac_2O in pyridine.

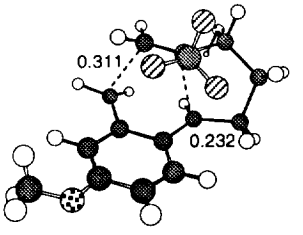
c All yields are based on purified products by passing through a short column (SiO_2).

These results could be understood by locating the transition structures **21** leading to these four isomers **22** - **25** and evaluating the energy differences of these possible transition structures, and these semiempirical calculations (PM3)[14] were performed [Figure 3 (**21a**, trifluoromethyl analog) and Figure 4 (**21Aa** methyl analog)].



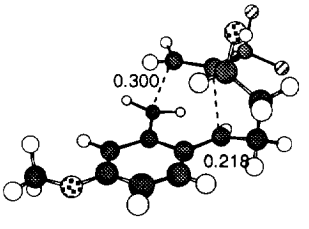
ΔH= -144.53 kcal/mol, 3.9D

21a *trans-syn*



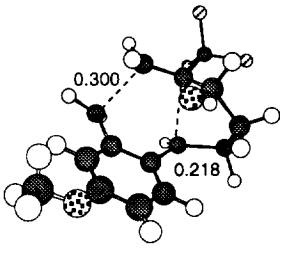
ΔH= -147.16 kcal/mol, 3.0D

21a *trans-anti*



ΔH= -147.40 kcal/mol, 3.9D

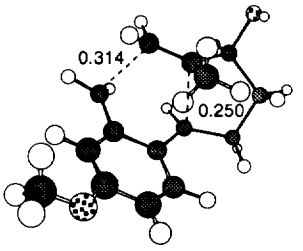
21a *cis-syn*



ΔH=-149.97 kcal/mol, 3.1D

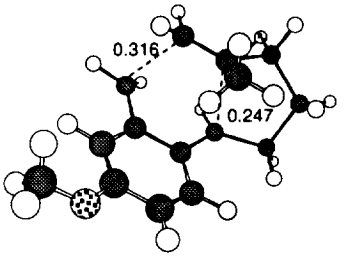
21a *cis-anti*

Figure 3



ΔH= -0.58 kcal/mol

21Aa *trans-syn*



ΔH= -0.57 kcal/mol

21Aa *trans-anti*

Figure 4

Although the product ratio of all possible isomers **22**, **23**, **24**, and **25** could not be understood by these calculations, the enthancement of *cis* and *anti* selectivity of **20a** compared with that of methyl analogue could be rationalized as follows.

The larger calculated ΔΔH values [2.87 kcal/mol for **21a** *cis-syn* (ΔH = -147.40 kcal/mol) and **21a** *trans-syn* (ΔH = -144.53 kcal/mol) (leading to **24** and **22** respectively) and 2.81 kcal/mol for **21a** *cis-anti* (ΔH = -149.97 kcal/mol) and **21a** *trans-anti* (ΔH = -147.16 kcal/mol) (leading to **25** and **23** respectively) of trifluoromethyl analogs] are in agreement with the enhancement of *cis* selectivity. The greater differences of the calculated ΔΔH values (2.63 kcal/mol for **21a** *trans-anti* and **21a** *trans-syn* and 2.57 kcal/mol for **21a** *cis-anti* and **21a** *cis-syn*) of trifluoromethyl analogs than that [0.01 kcal/mol for **21Aa** *trans-anti* (ΔH = -0.57 kcal/mol) and **21Aa** *trans-syn* (ΔH = -0.58 kcal/mol)] of methyl analogs are consistent with the enhancement of *anti* selectivity. The *cis* selectivity could be attributed to the greater differences of bond orders between terminal and inner forming bonds in **21a** *cis-syn* (0.082) and **21a** *cis-anti* (0.082) than that in **21a** *trans-syn* (0.070) and **21a** *trans-anti* (0.079) respectively, as described for **TS 10** *cis* and *trans*, and **TS 12** *cis* and *trans* before. The origins of the enhanced *anti* selectivity in trifluoromethyl analogs could be described in terms of dipole repulsion between trifluoromethyl and alkoxy groups. Thus, the dihedral angles of these groups and the dipole moments of these four transition structures were calculated to be 54 ° and 3.9 D for **21a** *trans-syn*, 54 ° and 3.9 D for **21a** *cis-syn*, 165 ° and 3.0 D for **21a** *trans-anti*, and 162 ° and 3.1 D for **21a** *cis-anti* showing **21a** *trans-anti* and **21a** *cis-anti* to be more favorable than **21a** *trans-syn* and **21a** *cis-syn* respectively. Thus, the calculations of "PM3 transition state" leading to the cycloadducts are in excellent agreement with the experimental data. Furthermore, the calculations support the concerted mechanism with a highly unsymmetric transition states for the cycloaddition mechanism of trifluoromethyl substituted *o*-quinodimethanes-*asynchronous transition states*[1h]—favoring the *cis* fused cycloadducts which is due to the difference in the bond length of the forming terminal and inner bonds. The enhanced *anti* selectivity for the cycloadditions of trifluoromethyl substituted allyl alcoholic *o*-quinodimethanes is also supported by the calculations showing the transition states leading to *anti* isomers to be more favoured in energy than that leading to *syn* isomers. It seems to be clear that this enhanced *anti* selectivity is due to the dipole repulsion between trifluoromethyl and alkoxy groups because the dihedral angles between trifluoromethyl and alkoxy groups in the transition states leading to *anti* isomers are larger than those of *syn* isomers and also the dipole moments of the formers are smaller than those of the latters.

Thus, we could demonstrate the influences of the trifluoromethyl substituents and the hydroxyl protective groups on the stereochemical course of the cycloaddition reactions of *o*-quinodimethanes and propose the transition structures of these reactions by using the semiempirical PM3 calculations poviding the informations valuable for the synthesis of 18-trifluoroestrans.

Experimental Section

General Procedure: All reactions were carried out under positive atmosphere of dry N_2 unless indicated otherwise. Solvents were freshly distilled prior to use: THF and Et_2O were distilled from sodium benzophenone, and DMSO, DMF, CH_2Cl_2 and Et_3N were distilled from CaH_2 and kept over 4 Å molecular sieves. The phrase "residue upon workup" refers to the residue obtained when the organic layer was separated and dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. Silica gel column chromatography was carried out with Wako gel C-200, while Merck Kiesegel 60 Art. 9385 was used for flash chromatography.

5-(1,2-Dihydro-4-methoxybenzocyclobuten-1-yl)-2-trifluoromethylpent-1-en-3-ol (5).

To a suspension of Zn (2.50 g, 38.2 mmol) and a catalytic amount of CuI in 21 mL of THF-pyridine (2:1 v/v) were added aldehyde **4** in 2 mL of THF and 2-bromo-3,3,3-trifluoropropene (3.0 mL, 30.0 mmol) at room temperature. After sonicating for 10 h at the same temperature, the reaction mixture was diluted with CH_2Cl_2 and filtered through Celite. The filtrate was extracted with Et_2O. 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 chromatographed with hexane-AcOEt (19 : 1 v/v) to give the alcohol **5** (471 mg, 54%) as a colorless oil. IR (neat) 3450 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.70-1.94 (5H, m), 2.66-2.72 (1H, m), 3.24-3.31 (1H, m), 3.37-3.41 (1H, m), 3.77 (3H, s), 4.37-4.45 (1H, m), 5.29, 5.75 (each 1H, each s), 6.68 (1H, s), 6.73 (1H, d, *J*=8.1 Hz), 6.97 (1H, d, *J* = 8.1 Hz); MS *m/z* 286 (M^+); HRMS calcd for $C_{15}H_{17}F_3O_2$ 286.1181 (M^+), found 286.1189.

5-(1,2-Dihydro-4-methoxybenzocyclobuten-1-yl)-2-trifluoromethylpent-1-en-3-one (6).

To a stirred solution of alcohol **5** (76.7 mg, 0.268 mmol) in 3 mL of CH_2Cl_2 were added 4Å-molecular sieves (84.3 mg) and PCC (91.4 mg, 0.424 mmol) at room temperature. After stirring for 1 h, the reaction mixture was diluted with Et_2O and filtered through Celite. The residue upon evaporation of the solvent was chromatographed with hexane-AcOEt (4 : 1 v/v) to give the ketone **6** (54.7 mg, 72%) as a colorless oil. IR (neat) 1700 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.93-2.14 (2H, m), 2.70 (1H, dd, *J* = 2.2, 13.9 Hz), 2.83-2.88 (2H, m), 3.28 (1H, dd, *J* = 5.1, 13.9 Hz), 3.38-3.45 (1H, m), 3.77 (3H, s), 6.44, 6.51 (each 1H, each s), 6.69 (1H, s), 6.73 (1H, d, *J* = 8.1 Hz), 6.96 (1H, d, *J* = 8.1 Hz). MS *m/z* 284 (M^+). HRMS calcd for $C_{15}H_{15}F_3O_2$ 284.1024 (M^+), found 284,1010.

2-[2-(1,2-Dihydro-4-methoxybenzocyclobuten-1-yl)ethyl]-2-(1-trifluoromethylethenyl)-1,3-dioxane (7).

To a stirred solution of ketone **6** (49.4 mg, 0.174 mmol) in 5 mL of benzene were added ethylene glycol (0.50 mL, 9.0 mmol) and a catalytic amount of CSA. The reaction mixture was refluxed in a flask with a Dean-Stark trap for 40 h. The reaction mixture was diluted with benzene, and the benzene solution was 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 ketal **7** (10.1 mg, 17%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 2.65 (1H, d, *J* = 13.9 Hz), 3.23 (1H, dd, *J* = 5.4, 13.9 Hz), 3.30-3.36v(1H, m), 3.76 (3H, s), 3.83-3.91 (4H, m), 5.78, 6.13 (each 1H, each s), 6.66 (1H, s), 6.71 (1H, d, *J* = 7.7 Hz), 6.96 (1H, d, *J* = 7.7 Hz). MS *m/z* 342 (M^+). HRMS calcd for $C_{18}H_{21}F_3O_3$ 342.1443 (M^+), found 342.1468.

***trans*- and *cis*-1,2,3a,4,5,9b-Hexahydro-7-methoxy-3a-trifluoromethyl-cyclopenta[*a*]-naphthalen-3-one (14a and 14b).**

From The Thermolysis of the ketone 6.

A solution of the benzocyclobutene **6** (46.5 mg, 0.164 mmol) in 8 mL of ODB was refluxed for 6 h and then evaporated. The residue was chromatographed with hexane-AcOEt (9 : 1 v/v) to give the mixture of the tricyclic ketones **14a** and **14b** (46.2 mg, 99%) as a colorless oil.

From the Thermolysis of the ketal 7.

A solution of the benzocyclobutene **7** (10.1 mg, 0.0295 mmol) in 5 mL of ODB was refluxed for 13 h and then evaporated. The residue was dissolved in 3 mL of acetone. To this stirred solution was added 1 mL of 10% HCl at room temperature. After stirring for 3 h at the same temperature, to the reaction mixture was added saturated aqueous $NaHCO_3$. The residue upon evaporation of solvent was diluted with water and was extracted with Et_2O. The combined extracts were washed with saturated aqueous NaCl and dried (Na_2SO_4). The residue upon evaporation of solvent was chromatographed with hexane-AcOEt (9 : 1 v/v) to give the mixture of the tricyclic ketones **14a** and **14b** (47.9 mg, 94%) as a colorless oil.

***cis*-2,3,3a,4,5,9b-Hexahydro-7-methoxy-3aβ-trifluoromethyl-1*H*-cyclopenta[*a*]naphthalen-3α-ol (18).**

To a stirred solution of the mixture of the ketone **14a** and **14b** from the thermolysis of **6** (48.3 mg, 0.170 mmol) in 4 mL of MeOH was added $NaBH_4$ (13.2 mg, 0.349 mmol) at room temperature. After stirring for 30 min, the residue upon evaporation of the solvent was diluted with water and extracted with CH_2Cl_2. 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 (3 : 17 v/v) to give the alcohol **18** (21.5 mg, 44%) as a colorless oil. IR (neat) 3450 (OH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.78 (3H, s), 4.19-4.22 (1H, m), 6.69 (1H, d, J = 3.1 Hz), 6.73 (1H, dd, J = 7.9, 3.1 Hz), 7.04 (1H, d, J = 7.9 Hz); MS *m/z* 286 (M^+); HRMS calcd for $C_{15}H_{17}F_3O_2$ 286.1181 (M^+) found 286.1163.

***cis*-1,2,3a,4,5,9b-Hexahydro-7-methoxy-3a-trifluoromethyl-cyclopenta[*a*]naphthalen-3-one (14b).**

To a stirred solution of alcohol **18** (6.9 mg, 0.024 mmol) in 2 mL of CH_2Cl_2 were added 4Å-molecular sieves (13 mg) and PCC (10.1 mg, 0.468 mmol) at room temperature. After stirring for 2 h at the same temperature, the reaction mixture was diluted with Et_2O and was filtered through silica gel. The residue upon evaporation of solvent was chromatographed with hexane-AcOEt (9 : 1 v/v) to give ketone (4.8 mg, 70%) as a colorless oil. IR (neat) 1755 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.67-3.71 (1H, m), 3.79 (3H, s), 6.65 (1H, d, J = 2.6 Hz), 6.79 (1H, dd, J = 2.6, 8.1 Hz), 7.15(1H, d, J = 8.1 Hz); MS *m/z* 284 (M^+); HRMS calcd for $C_{15}H_{15}F_3O_2$ 284.1024 (M^+), found 284.1005.

***trans*-2,3,3a,4,5,9b-Hexahydro-7-methoxy-3aβ-trifluoromethyl-1*H*-cyclopenta[*a*]napththalen-3β-ol (19).**

To a stirred solution of the mixture of the ketone **14a** and **14b** from the thermolysis of **7** (7.9 mg, 0.023 mmol) in 1 mL of MeOH was added $NaBH_4$ (4.8 mg, 0.13 mmol) at room temperature. After stirring for 30 min at the same temperature, the residue upon evaporation of solvent was diluted with water and extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous NaCl and dried (Na_2SO_4). The residue upon evaporation of solvent was chromatographed with hexane-AcOEt (17 : 3 v/v) to give the alcohol **19** (2.4 mg, 30%) as a colorless oil. IR (neat) 3450 (OH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.77 (3H, s), 4.11-4.15 (1H, m), 6.68 (1H, s), 6.69 (1H, d, J = 7.3 Hz), 6.93 (1H, d, J = 7.3 Hz); MS *m/z* 286 (M^+); Anal. Calcd for $C_{15}H_{17}F_3O_2$: C; 62.93, H; 5.99. Found: C; 62.75, H; 5.99.

trans-1,2,3a,4,5,9b-Hexahydro-7-methoxy-3a-trifluoromethyl-cyclopenta[_a_]naphthalen-3-one (14a).

To a stirred solution of alcohol **19** (2.8 mg, 0.0098 mmol) in 1 mL of CH_2Cl_2 were added 4Å-molecular sieves (5.2 mg) and PCC (5.0 mg, 0.023 mmol) at room temperature. After stirring for 2 h at the same temperature, the reaction mixture was diluted with Et_2O and was filtered through the short pad of silica gel. The residue upon evaporation of solvent was chromatographed with hexane-AcOEt (9 : 1 v/v) to give the ketone **14a** (2.1 mg, 75%) as a colorless oil. IR (neat) 1760 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.80 (3H, s), 6.71 (1H, d, J = 2.2 Hz), 6.77 (1H, dd, J = 2.2, 8.1 Hz), 7.08 (1H, d, J = 8.1 Hz); MS *m/z* 284 (M^+); HRMS calcd for $C_{15}H_{15}F_3O_2$ 284.1024 (M^+), found 284.1050.

5-(1,2-Dihydro-4-methoxybenzocyclobuten-1-yl)-2-trifluoromethylpent-1-en-3-yl acetate (20b).

To a stirred solution of the alcohol **5** (75.5 mg, 0.264 mmol) in 4 mL of pyridine was added Ac_2O (0.10 mL, 1.1 mmol) at 0 °C. After stirring for 2 h at room temperature, the reaction mixture was diluted with water and extracted with Et_2O. 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 chromatographed with hexane-AcOEt (1 : 9 v/v) to give the acetate **20b** (72.6 mg, 84%) as a colorless oil. IR (neat) 1740 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.67-1.75 (2H, m), 1.89-1.98 (2H, m), 2.08 (3H, s), 2.67 (1H, d, J = 13.9 Hz), 3.27 (1H, dd, J = 13.9, 4.8 Hz), 3.36-3.40 (1H, m), 3.77 (3H, s), 5.47-5.52 (1H, m), 5.66, 5.87 (each 1H, each s), 6.68 (1H, s), 6.73 (1H, d, J = 8.1 Hz), 6.97 (1H, d, J = 8.1 Hz); MS *m/z* 328 (M^+); HRMS calcd for $C_{17}H_{19}F_3O_3$ 328.1286 (M^+), found 328.1312.

5-(1,2-Dihydro-4-methoxybenzocyclobuten-1-yl)-2-trifluoromethylpent-1-en-3-yl 3-nitrobenzoate (20c).

To a stirred solution of the alcohol **5** (168 mg, 0.587 mmol) in 2 mL of pyridine was added *p*-nitrobenzoyl chloride (163 mg, 0.878 mmol) at 0°C. After stirring for 5 h at the same temperature, to the reaction mixture was 0.1 mL of MeOH and the solution was stirred for 30 min at 0°C. The mixture was diluted with AcOEt and 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-Et_2O (1 : 1 v/v) to give the ester **20c** (160 mg, 63%) as a colorless oil. IR (neat) 1730 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.76-1.83 (2H, m), 2.06-2.14 (2H, m), 2.69 (1H, d, J = 14.3 Hz), 3.29 (1H, dd, J = 4.1, 14.3 Hz), 3.40-3.45 (1H, m), 3.76, 3.77 (3H, each s), 5.74-5.80 (1H, m), 5.77, 5.96 (each 1H, each s), 6.68 (1H, s), 6.72, 6.74 (1H, each d, J = 8.1 Hz), 6.98 (1H, d, J = 8.1 Hz), 8.19-8.31 (4H, m). MS *m/z* 435 (M^+). Anal. Calcd for $C_{22}H_{20}F_3O_5N$: C, 60.69; H, 4.63; N, 3.22. Found: C, 60.43; H, 4.72; N, 3.31.

3-_tert_-Butyldimethylsilyloxy-5-(1,2-dihydro-4-methoxybenzocyclobuten-1-yl)-2-trifluoromethylpent-1-ene (20d)

To a stirred solution of alcohol **5** (52.5 mg, 0.183 mmol) in 2 mL of CH_2Cl_2 were added 2,6-lutidine (0.08 mL, 0.6 mmol) and TBSOTf (0.076 mL, 0.33 mmol) at 0 °C. After stirring for 14 h at room temperature, to the reaction mixture was added saturated aqueous NaCl and the mixture was extracted with CH_2Cl_2 and the extract was dried (Na_2SO_4). The residue upon evaporation of the solvent was chromatographed with hexane-

AcOEt (19 : 1 v/v) to give TBS ether **20d** (63.1mg, 86%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01, 0.02, 0.07, 0.08 (6H, each s), 0.91 (9H, s), 1.62-1.86 (4H, m), 2.66 (1H, d, *J* = 13.9 Hz), 3.26 (1H, dd, *J* = 4.8, 13.9 Hz), 3.33-3.37 (1H, m), 3.78 (3H, s), 4.37-4.42 (1H, m), 5.72, 5.79 (each 1H, each s), 6.69 (1H, s), 6.73 (1H, d, *J* = 8.0 Hz), 6.96 (1H, d, *J* = 8.0 Hz). MS *m/z* 400 (M^+). HRMS calcd for $C_{21}H_{31}F_3O_2Si$ 400.2046(M^+), found 400.2057.

5-(1,2-Dihydro-4-methoxybenzocyclobuten-1-yl)-2-trifluoromethyl-3-triisopropylsilyloxypent-1-ene (20e).

To a stirred solution of alcohol **5** (102 mg, 0.357 mmol) in 3 mL of CH_2Cl_2 were added 2,6-lutidine (0.16 mL, 1.4 mmol) and TIPSOTf (0.18 mL, 0.67 mmol) at 0°C. After stirring for 3 h at the same temperature, the reaction mixture was diluted with saturated aqueous NaCl and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4). The residue upon evaporation of solvent was chromatographed with hexane-AcOEt (49 : 1 v/v) to give the TIPS ether **20e** (131 mg, 83%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04-1.60 (18H, m), 3.77 (3H, s), 4.63-4.65 (1H, m), 5.74 and 5.75 (1H, each br s), 5.82 (1H, br s), 6.67 (1H, s), 6.71 (1H, d, *J* = 8.1 Hz), 6.94 and 6.95 (1H, each d, *J* = 8.1 Hz); MS *m/z* 442 (M^+). Anal. Calcd for $C_{24}H_{37}F_3O_2Si$: C, 65.12; H, 8.43. Found: C, 65.32; H, 8.42.

5-(1,2-Dihydro-4-methoxybenzocyclobuten-1-yl)-3-(tetrahydropyran-2-yloxy)-2-trifluoromethylpent-1-ene (20f).

To a stirred solution of alcohol **5** (92.6 mg, 0.323 mmol) and dihydropyran (0.10 mL, 1.1 mmol) in 3 mL of CH_2Cl_2 was added a catalytic amount of PPTS at room temperature. After stirring for 3 h, the reaction mixture was diluted with CH_2Cl_2 and 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 THP derivative **20f** (86.4 mg, 72%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77 (3H, s), 5.64, 5.78, 5.84, 5.84 (2H, each s), 6.68 (1H, s), 6.72 (1H, d, *J* = 8.1 Hz), 6.96, 6.97 (1H, each d, *J* = 8.1 Hz); MS *m/z* 370 (M^+); HRMS calcd for $C_{20}H_{25}F_3O_3$ 370.1756 (M^+), found 370.1756.

5-(1,2-Dihydro-4-methoxybenzocyclobuten-1-yl)-2-trifluoromethyl-3-triphenylmethoxypent-1-ene (20g).

To a stirred suspension of silver trifluoromethanesulfonate (84.4 mg, 0.328 mmol) in 2 mL of CH_2Cl_2 was added triphenylmethyl chloride (90.8 mg, 0.326 mmol) at 0°C. After stirring for 30 min at the same temperature, to this suspension were added alcohol **5** (38.1 mg, 0.133 mmol) in 2 mL of CH_2Cl_2 and 2,6-lutidine (0.10 mL, 0.86 mmol) at the same temperature. After stirring for 30 min at the same temperature, the reaction mixture was diluted with CH_2Cl_2 and filtered through Celite. The filtrate was 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 (97 : 3 v/v) to give ether **20g** (44.2 mg, 63%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76 (3H, s), 4.41-4.43 (1H, m), 5.50, 5.52, 5.53, and 5.55 (2H, each br s), 6.65 (1H, s), 6.69 and 6.71 (1H, each d, *J* = 8.1 Hz), 6.84 and 6.89 (1H, each d, *J* = 8.1 Hz), 7.20-7.51 (15H, m); MS *m/z* 285 (M^+-Tr); HRMS calcd for $C_{15}H_{16}F_3O_2$ 285.1103 (M^+-Tr), found 285.1129.

***trans*-2,3,3a,4,5,9b-Hexahydro-7-methoxy-3aβ-trifluoromethyl-1*H*-cyclopenta[*a*]naphthalen-3β-yl acetate (22b).**

To a stirred solution of alcohol **19** (7.4 mg, 0.026 mmol) in 1 mL of pyridine was added Ac_2O (0.10 mL, 1.1 mmol) at 0°C. After stirring for 8 h at room temperature, the reaction mixture was diluted with water and extracted with Et_2O. 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 solvent was chromatographed with hexane-AcOEt (17 : 3 v/v) to give acetate **22b** (8.4 mg, 99%) as colorless needles: mp 119-120 °C (Et_2O-hexane). IR (neat) 1730 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.10 (3H, s), 3.77 (3H, s), 5.13 (1H, dd, J = 8.4 and 8.8 Hz), 6.67 (1H, s), 6.69 (1H, d, J = 8.1 Hz), 6.94 (1H, d, J = 8.1 Hz); MS *m/z* 328 (M^+); Anal. Calcd for $C_{17}H_{19}F_3O_3$: C, 62.19; H, 5.83. Found: C, 61.91; H, 5.86.

***cis*-2,3,3a,4,5,9b-Hexahydro-7-methoxy-3aβ-methyl-1*H*-cyclopenta[*a*]naphthalen-3α-yl acetate (25b).**

To a stirred solution of alcohol **18** (21.5 mg, 0.0751 mmol) in 1 mL of pyridine was added Ac_2O (0.10 mL, 1.1 mmol) at 0 °C. After stirring for 10 h at room temperature, the reaction mixture was diluted with water and extracted with Et_2O. 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 chromatographed with hexane-AcOEt (9 : 1 v/v) to give the acetate **25b** (16.7 mg, 68%) as a colorless oil. IR (neat) 1730 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.11 (3H, s), 3.42 (1H, dd, J = 8.1, 10.6 Hz), 3.78 (3H, s), 5.33 (1H, dd, J=7.3, 9.5 Hz), 6.91 (1H, d, J=2.5 Hz), 6.73 (1H, dd, J = 2.5, 8.1 Hz), 7.04 (1H, d, J = 8.1 Hz); MS *m/z* 328 (M^+); *Anal.* Calcd for $C_{17}H_{19}F_3O_3$: C, 62.19; H, 5.83. Found: C, 62.16; H, 5.79.

Thermolysis of 20 and Derivatization to Acetate

From 20a.

A solution of the benzocyclobutene **20a** (31.2 mg, 0.109 mmol) in 10 mL of ODB was refluxed for 8 h and then evaporated. The residue was dissolved in 1 mL of pyridine. To this stirred solution was added Ac_2O (0.10 mL, 1.1 mmol) at 0°C. After stirring for 3 h at room temperature, the reaction mixture was diluted with water and extracted with Et_2O. The combined extracts were washed with 10% HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. The residue upon workup was passed through a short pad of silica gel with hexane-AcOEt (9 : 1 v/v) as an eluent to give the mixture of the acetates (19.8 mg, 55%) as a colorless oil.

From 20b.

A solution of the benzocyclobutene **20b** (48.7 mg, 0.148 mmol) in 5 mL of ODB was refluxed for 10 h and then evaporated. The residue was chromatographed with hexane-AcOEt (9 : 1 /v/v) to give the mixture of the acetates (47.0 mg, 97%) as a colorless oil.

From 20c.

A solution of the benzocyclobutene **20c** (16.6 mg, 0.038 mmol) in 4 mL of ODB was refluxed for 6 h and then evaporated. The residue was dissolved in 1 mL of MeOH. To this stirred solution was added K_2CO_3 (38.0 mg, 0.275 mmol) at room temperature. After stirring had been continued for 3 h at the same temperature, the

reaction mixture was extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous NaCl and dried (Na_2SO_4). The residue upon evaporation of solvent was dissolved in 1 mL of pyridine. To this stirred solution was added Ac_2O (0.20 mL, 2.1 mmol) at 0°C. After stirring for 16 h at room temperature, the reaction mixture was diluted with water and extracted with Et_2O. The combined extracts were washed with 10% HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. The residue upon workup was passed through the short pad of silica gel with hexane-AcOEt (9 : 1 v/v) as an eluent to give the mixture of the acetates (10.5 mg, 84%) as a colorless oil.

From 20d.

A solution of benzocyclobutene **20d** (102 mg, 0.255 mmol) in 25 mL of ODB was refluxed for 12 h and then evaporated. The residue was dissolved in 2 mL of THF. To this stirred solution was added 0.5 mL (0.5 mmol) of 1.0 M n-Bu_4NF in THF at room temperature and stirring was continued for 2 h at the same temperature. The mixture was diluted with water and extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous NaCl and dried (Na_2SO_4). The residue upon evaporation of the solvent was dissolved in 1 mL of pyridine. To this stirred solution was added Ac_2O (0.10 mL, 1.1 mmol) at 0°C. After stirring had been continued for 3 h at the same temperature, the reaction mixture was diluted with water and extracted with Et_2O. 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 passed through the short pad of silica gel with hexane-AcOEt (9 : 1 v/v) to give the mixture of the acetate (38.7 mg, 46%) as a colorless oil.

From 20e.

A solution of the benzocyclobutene **20e** (71.3 mg, 0.161 mmol) in 16 mL of ODB was refluxed for 12 h and then evaporated. The residue was dissolved in 2 mL of THF. To this stirred solution was added 0.40 mL (0.40 mmol) of 1.0 M *n*-Bu_4NF in THF at room temperature. After stirring had been continued for 2 h at the same temperature, the reaction mixture was diluted with water and was extracted with CH_2Cl_2. The combined extracts were washed with saturated aqueous NaCl and dried (Na_2SO_4). The residue upon evaporation of solvent was dissolved in 2 mL of pyridine. To this stirred solution was added Ac_2O (0.50 mL, 5.3 mmol) at 0°C. After stirring for 3 h at room temperature, the reaction mixture was diluted with water and extracted with Et_2O. The combined extracts were washed with 10% HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl and dried (Na_2SO_4). The residue upon workup was passed through the short pad of silica gel with hexane-AcOEt (9 : 1 v/v) as an eluent to give the mixture of the acetates (38.4 mg, 65%) as a colorless oil.

From 20f.

A solution of the benzocyclobutene **20f** (86.2 mg, 0.233 mmol) in 23 mL of ODB was refluxed for 6 h and then evaporated. The residue was dissolved in 2 mL of MeOH. To this stirred solution was added 0.5 mL of 10% HCl at room temperature. After stirring had been continued for 30 min at the same temperature, the reaction mixture was extracted with CH_2Cl_2. 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 dissolved in 2 mL of pyridine. To this stirred solution was added Ac_2O (0.50 mL, 5.3 mmol) at 0°C. After stirring for 18 h at the room temperature, the reaction mixture was diluted with water and extracted with Et_2O. The combined extracts were washed with 10% HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl.

The residue upon workup was passed through the short pad of silica gel with hexane-AcOEt (9 : 1 v/v) as an eluent to give the mixture of the acetates (56.5 mg, 74%) as a colorless oil.

From 20g.

A solution of the benzocyclobutene **20g** (44.2 mg, 0.0836 mmol) in 8 mL of ODB was refluxed for 12 h and then evaporated. The residue was dissolved in 1 mL of MeOH. To this stirred solution was added a catalytic amount of TsOH at room temperature. After stirring had been continued for 10 h at the same temperature, the residue upon evaporation of solvent was dissolved in 1 mL of pyridine. To this stirred solution was added Ac_2O (0.10 mL, 1.1 mmol) at 0°C. After stirring for 11 h at room temperature, the reaction mixture was diluted with water and extracted with Et_2O. The combined extracts were washed with 10% HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. The residue upon workup was passed through the short pad of silica gel with hexane-AcOEt (9 : 1 v/v) as an eluent to give the mixture of the acetates (38.4 mg, 65%) as a colorless oil.

References and Notes

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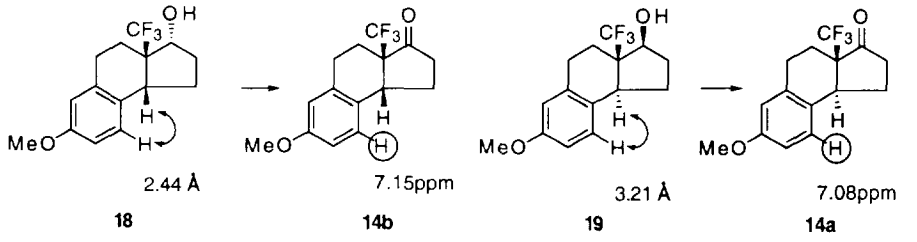

Chart 2

In the optimized conformations of **18** and **19** obtained by the MM2 calculation (PCMODEL Serena Software, Bloomingston, IN 47402-3076), the distances between C-7 and C-14 (steroid numbering) hydrogens of **18** and **19** were calculated to be 2.44 Å and 3.21 Å, respectively. The observed NOE

enhancement (7.5%) between these hydrogens of **18** suggested the ring juncture of **18** to be *cis*, and hence that of **19** to be *trans*. Then the pure **18** and **19** were oxidized (PCC) to give the pure sample of **14b** and **14a** respectively, in which the C-7 hydrogens were observed at 7.15 and 7.08 ppm respectively.

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(17) The stereochemical assignment of these isomers were based on spectroscopic data and as follows. At first, the MM2 calculations of the acetates **23b**, **24b**, and **25b** were carried out to obtain the optimized structures and then Karplus rule (Haasnoot, C. A. G.; de Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783) was applied to predict the stereochemistry of these isomers. The coupling constants of C-17 hydrogen (steroid numbering) of **23b**, **24b** and **25b** were calculated to be 1.6 and 8.6 Hz, 6.9 and 10.2 Hz, and 7.2 and 8.9 Hz, respectively. The authentic acetates **22b** and **25b** were prepared by acetylation of the alcohols **19** and **18** respectively. The C-17 hydrogens of **22b** and **25b** thus obtained were observed at 5.13 ppm (dd, J = 8.4 and 8.8 Hz) and 5.33 ppm (dd, J = 7.3 and 9.5 Hz) respectively. So, the signals observed at 5.43 ppm (dd, J = 1.2 and 6.6 Hz) were reasonably assigned to C-17 hydrogens of **23b** (predicted to be J = 1.6 and 8.6 Hz) rather than that of **24b** (predicted to be J = 6.9 and 10.2 Hz). Thus, the signals observed at 5.56 ppm (dd, J = 4.8 and 6.2 Hz) could be assigned to C-17 hydrogen of **24b**.

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