Pergamon

Tetrahedron 54 (1998) 5425–5464

TETRAHEDRON

Tetrahedron report number 451

Second Generation of Steroid Synthesis *via* *o*-Quinodimethane

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Received 17 December 1997

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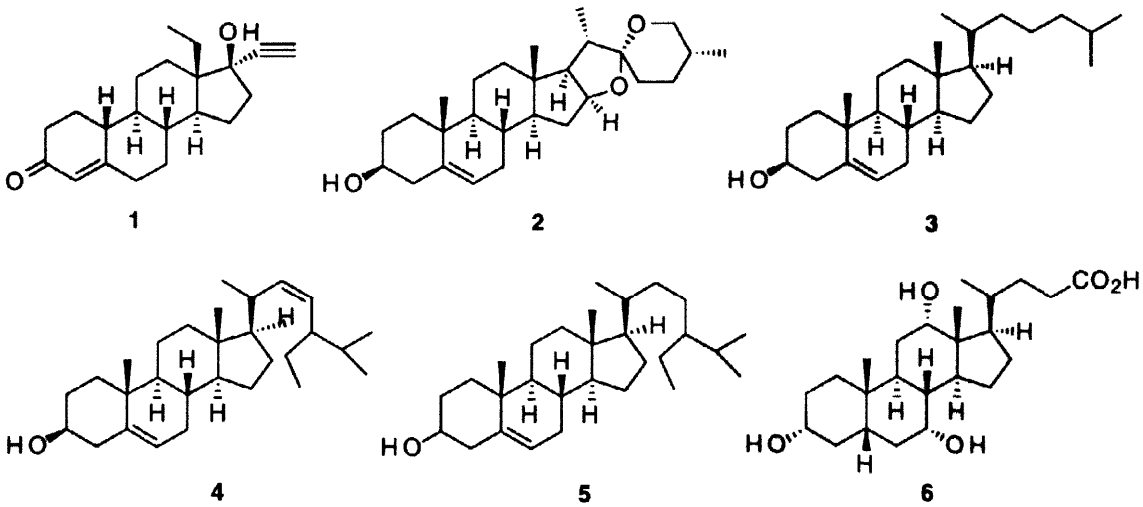
PII: S0040-4020(98)00017-9

1. Introduction

The total synthesis of steroids[1] has been recognized as an important field of research, mainly because of the pronounced physiological activity among members of this series. The need for total synthesis can be seen through the increased importance of modern ovulation inhibitors such as norgestrel (**1**), which can only be efficiently produced by total synthesis, and the possibile future scarcity of raw materials, such as diosgenin (**2**), cholesterol (**3**), stigmasterol (**4**), sitosterol (**5**), and cholic acid (**6**), for the semi-synthetic production of other steroids (Figure 1).

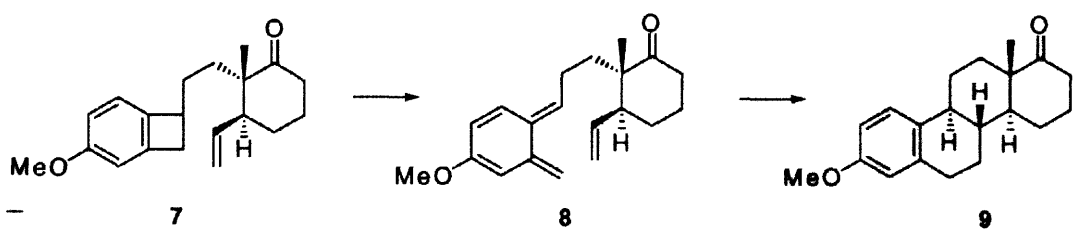
Figure 1



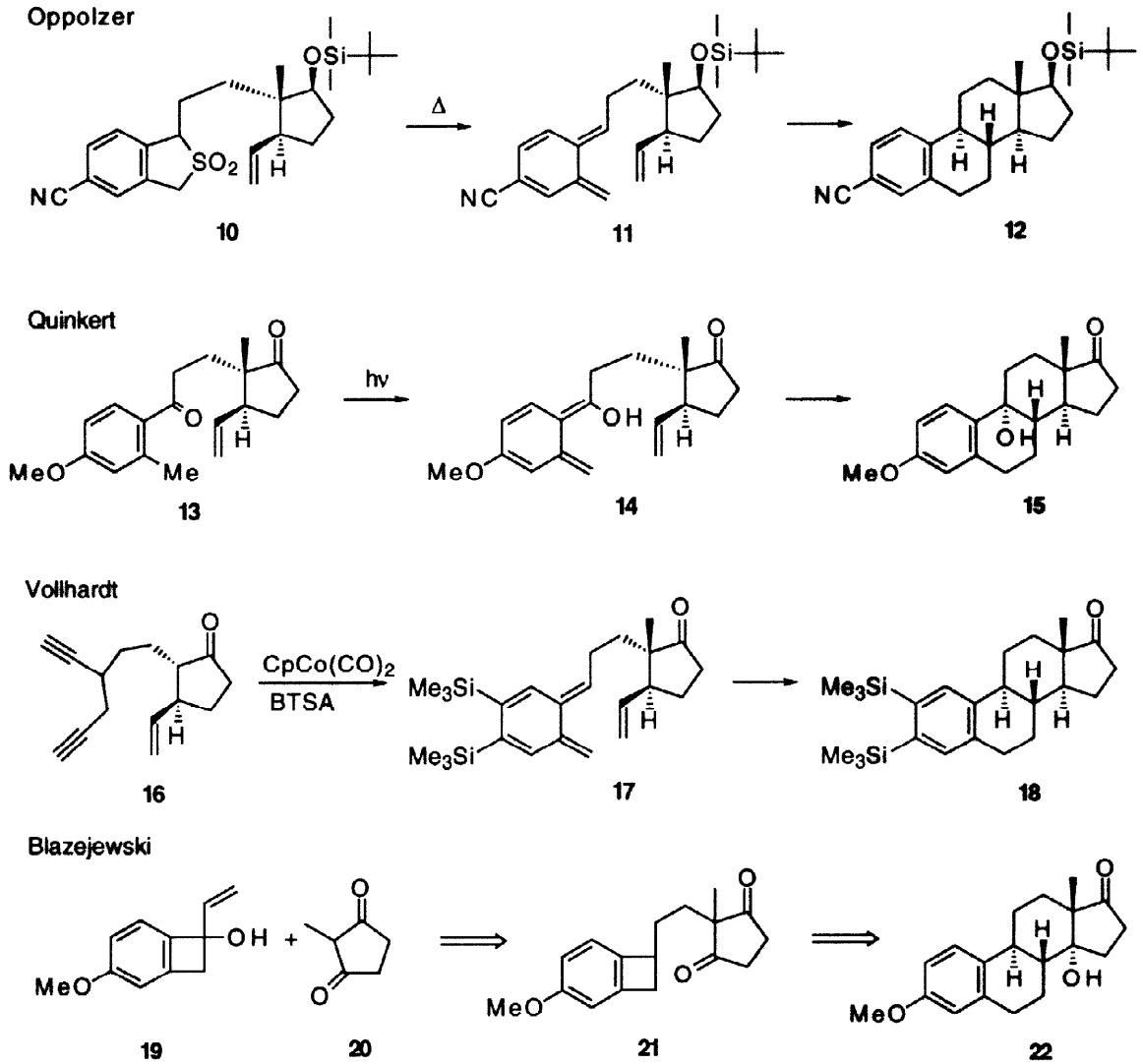
1 **2** **3** **4** **5** **6**

Since our introduction of intramolecular cycloadditions of *o*-quinodimethane **8**, generated *in situ* by thermolysis of the corresponding benzocyclobutene **7**, for the total synthesis of D-homoestrone methyl ether (**9**) in 1976,[2] this approach has been developed extensively by several groups for other steroids.[3] Some examples are: the thermoysis[3a] of the monosubstituted sulfone **10** to generate the *o*-quinodimethane **11** giving the polycyclic product **12**, which was converted into (+)-estradiol; the photoenolization[3b] of *o*-toluketone **13** to yield the 9α-hydroxyestrone methylether **15** *via* the *o*-quinodimethane **14**; and the cobalt-mediated co-cyclization[3c] of the diyne **16** with bis(trimethylsilyl)acetylene (BTSA) to generate the *o*-quinodimethane **17** affording the polycyclic product **18** which was then converted into (±)-estrone. Recently, a shorter route —the Torgov reaction of the benzocyclobutanol **19** and the cyclopentadione **20** followed by catalytic hydrogenation—to the key intermediate **21** in our synthesis[3d] of 14α-hydroxyestrone methylether (**22**) was developed,[3h] which makes this approach more efficient (Scheme 1).

Scheme 1

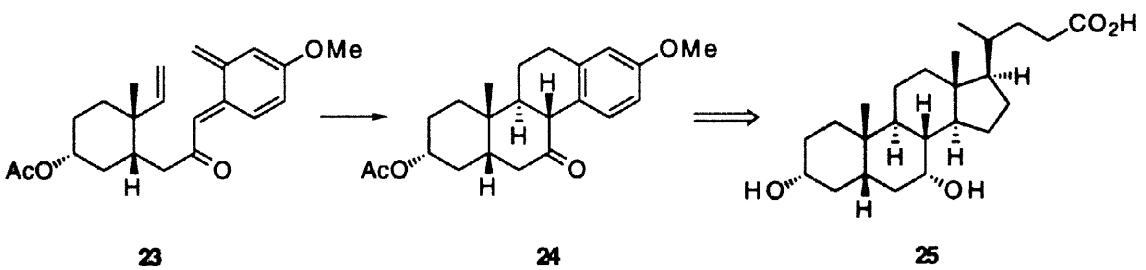


7 **8** **9**



While these routes are useful for preparing aromatic steroids, the physiologically important non-aromatic steroids are generally not directly accessible. An exception is our total synthesis[4] of (+)-chenodeoxycholic acid (**25**) *via* the D-aromatic steroid **24**, a result of intramolecular cycloaddition of the *o*-quinodimethane **23** (Scheme 2). However, the transformation of **24** into **25** was laborious and made this approach inefficient.

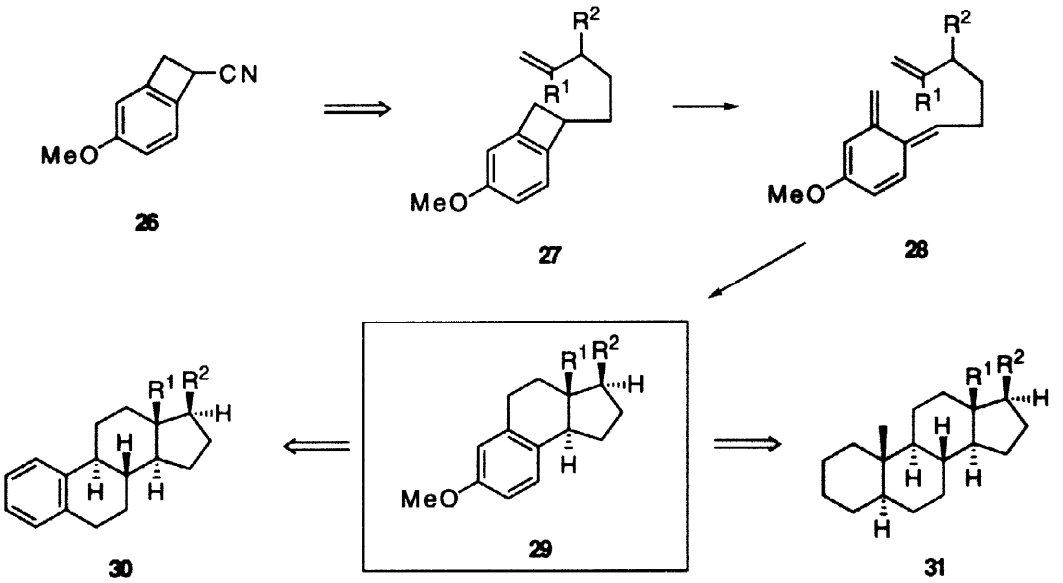
Scheme 2



In this context, we have been involved in developing more flexible and efficient routes to both aromatic and non-aromatic steroids than those of Schemes 1 and 2.[5] The present review highlights the events of the last

10 years that led to the successful development and application of a 'second generation of steroid synthesis *via* o-quinodimethane.' Thus, the route was planned on the basis of the reaction sequence outlined in Scheme 3.

Scheme 3

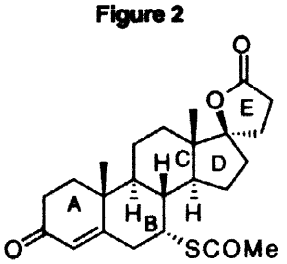


In this route, the *trans*-benzoperhydroindane **29** was set as a key compound for preparing either A-trienic or non-aromatic steroids (**30** or **31** respectively) by easy manipulation on its benzene ring. In turn, **29** could be accessed by intramolecular cycloaddition of the *o*-quinodimethane **28**, generated *in situ* by thermolysis of benzocyclobutene **27**. The source of benzocyclobutene ring[6-9] was chosen to be 1-cyano-4-methoxybenzocyclobutene (**26**),[10] which could be easily alkylated regioselectively at the cyclobutene ring with various substituents and produced on large scale.

2. Total Synthesis of (dl)-19-Norcanrenone – A Formal Total Synthesis of (dl)-19-Norspironolactone[11]

Since the first reports[12] on the synthesis and the antialdosterone activity of the steroidal spironolactone in the late 1950s, immense efforts have been devoted to the study of structurally diverse steroids, mainly because of the clinical importance of this type of steroids for the treatment of primary hyperaldosteronism, diseases related to secondary hyperaldosteronism (edema), and hypertension. Of those reported, spironolactone (**32**) has emerged as the most effective representative that is capable of eliciting this type of biological response and it has been, to date, the only orally active aldosterone antagonist on the market (Figure 2).

Figure 2



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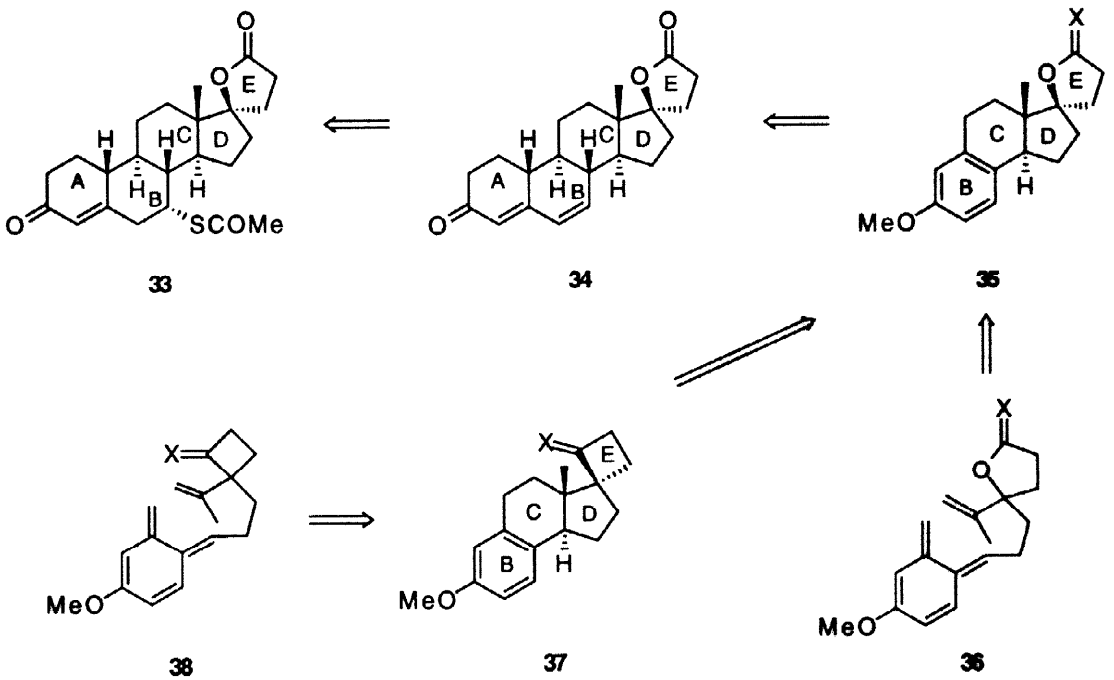
These facts stimulated us to explore an effective methodology for the synthesis of 19-norspironolactone (**33**), which is more difficult to prepare and is expected to be more effective than its normal analogue **32**.[13] Our synthetic strategy for **33** is characterized by the one step creation of B, C, D, and E rings (**35** or its precursor **37**) in a stereoselective manner *via* intramolecular [4+2] cycloaddition of the *o*-quinodimethanes **36** or **38**, and

then A-ring formation (**35**→**34**) followed by functionalization of C-7 position (**34**→**33**) (Scheme 4). This is contrast to the traditional methods[14] where the spirolactone ring is created by the manipulation on the preformed C-17 keto steroids.

Scheme 4



2-1. Stereochemical Course of Intramolecular [4+2] Cycloaddition Reactions of Olefinic *o*-Quinodimethanes

As a preliminary investigation, the thermolysis of olefinic γ-lactone **39**, its thioacetal **40**, and disiloxane **41** (Figure 3), all of which had ring E of **33** or its equivalent, was carried out and the results are summarized in Table 1.[11]

Figure 3

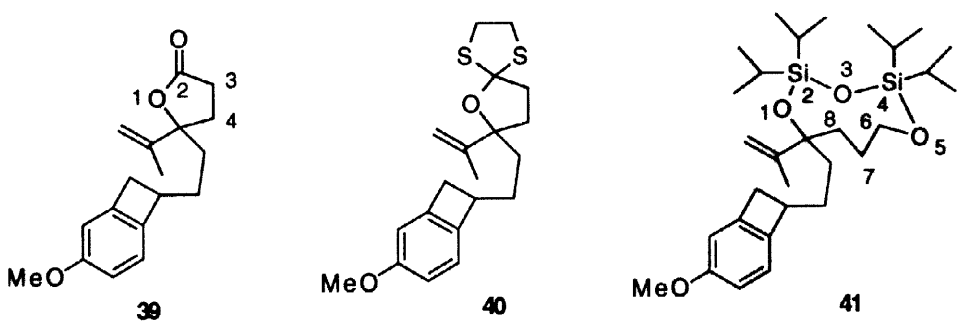
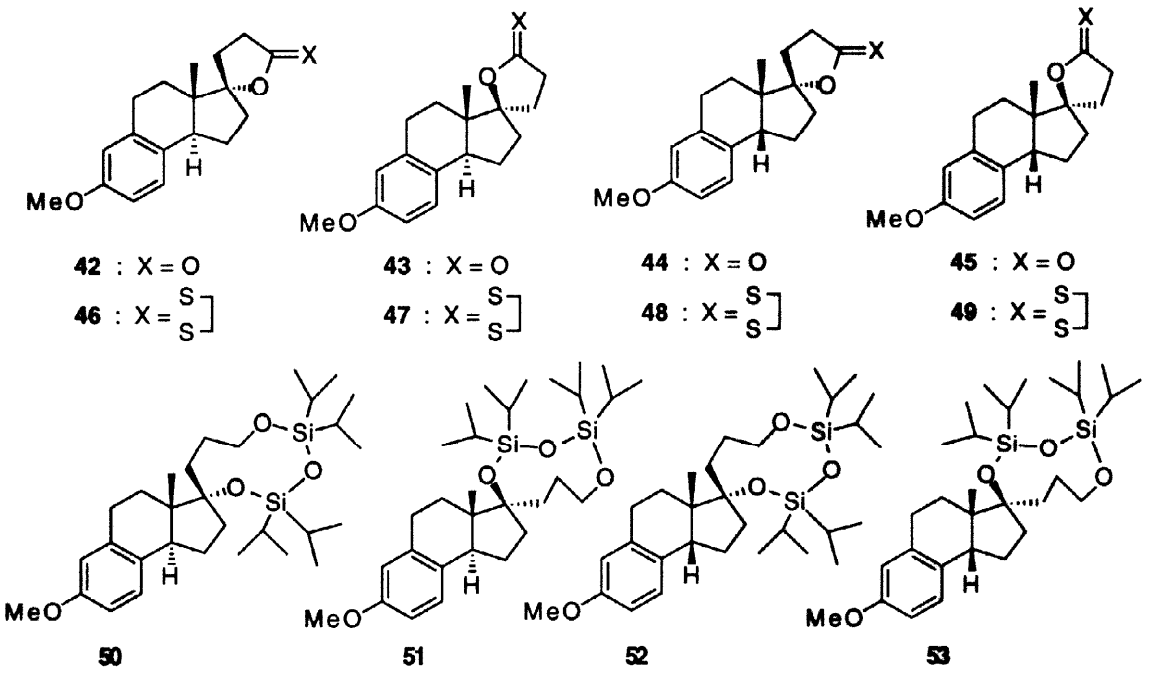


Table 1[a] Thermolysis of Olefinic Benzocyclobutenes 39, 40, and 41

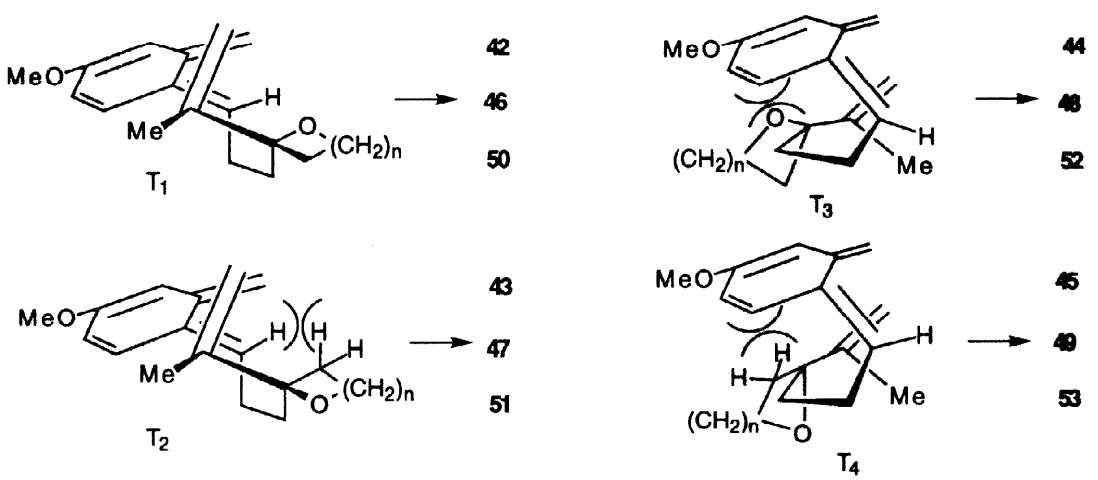


entry	substrate	time, h	product	ratio
1	**39**	11	**42 : 43**	(94 : 6)
2	**40**	1.5	**46 : 47**	(93 : 7)
3	**41**	5	**50 : 51**	(96 : 4)

[a] All reactions were run under an inert atmosphere (argon) in boiling *o*-dichlorobenzene.

These results showed that all of these reactions proceeded with high stereoselectivity, leading to the preferred formation of the *trans-anti*[15] isomers **42**, **46**, and **50** rather than the *trans-syn* isomers **43**, **47**, and **51**. None of the *cis-anti* isomers **44**, **48**, and **52**, and *cis-syn* isomers **45**, **49**, and **53** were detected. Thus, it seemed possible that the high stereoselectivity for *trans-anti* isomers might reflect the severe steric interactions present in the *endo* transition states T_3 and T_4 and the *exo* transition state T_2 relative to the *exo* transition state T_1 (Figure 4).

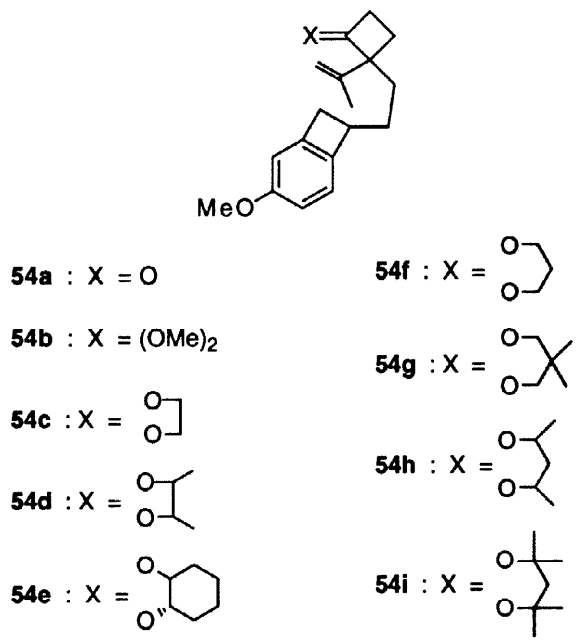
Figure 4



The *syn* or *anti* selectivity is strictly controlled by the bulk of position 1 or 4 (for **39** and **40**) and position 1 or 8 (for **41**) and not affected by the bulk at position 2 to a detectable degree, despite large steric bulk (1,2-dithiane ring for **40** and diisopropylsilyl group for **41**) (see Figure 3). Thus, we could obtain information about the stereochemical course of the cycloaddition reactions of the olefinic *o*-quinodimethanes **36** that have unsymmetrically substituted tertiary chiral centers.

On the basis of these resluts, our efforts were then directed toward the cycloaddition reaction of the olefinic *o*-quinodimethanes **38** that have a cyclobutane ring with various substituents (X). It was expected that the bond having a bulky substituent (X) on the cyclobutane ring in the product **37** would be *syn*. Thus, the cyclobutanone acetals were suitable candidates for this steric demand. Furthermore, the functional group is versatile and suitable for further synthetic transformation to spirolactones. Thermolyses of these cyclobutanone derivatives **54a–i** (Figure 5) were conducted in refluxing *o*-dichlorobenzene. Table 2 summarizes the distribution of the products for each substrates.

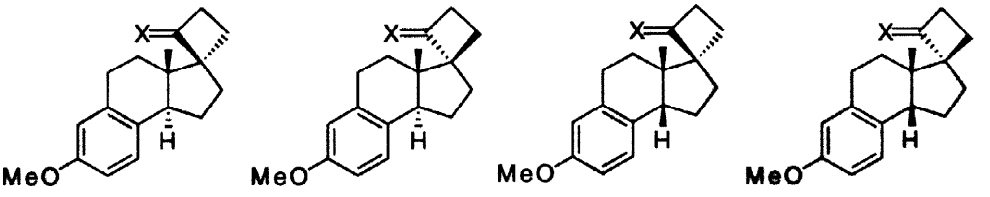
Figure 5



The observed *trans-anti*[16] (for entry 1) and *trans-syn* (for entries 2–9) selectivity could be most conveniently rationalized by invoking the same explanation of the stereoselectivity in the thermolytic reaction of **39**, **40**, and **41** (*vide supra*), although the selectivity was somewhat decreased with the decrease of ring size from five- and nine-member rings to a four-member ring in this case. In the most predominant isomers, the bulky substituents at the spiro position (methylene rather than ketone for entry 1 and acetals rather than methylenes for entries 2–9) were located in a *syn* mode in their preferred *trans* isomers.

The straightforward synthesis of 19-norcanrenone (**34**) illustrates the power of this methodology and constitutes a formal synthesis of 19-norspironolactone (**33**).

Table 2[a] Thermolysis of Olefinic Benzocyclobutenes 54a–i



37a–i **55a–i** **56a–i** **57a–i**

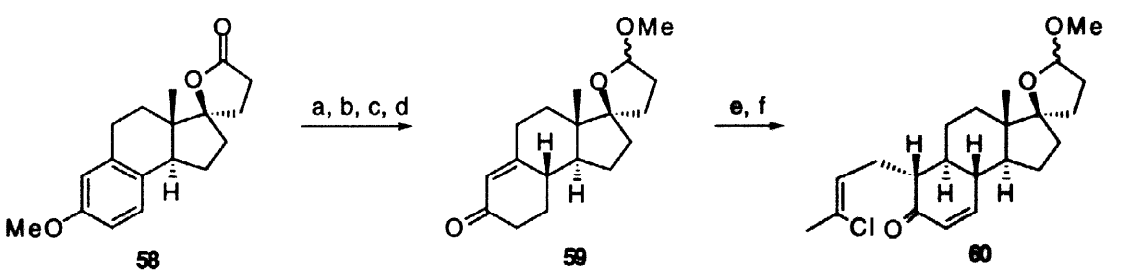
entry	substrate	product ratio **37a : 55a : 56a**	isolated yield[b] %
1	**54a**	28 : 60 : 12	97
2	**54b**	88 : 3 : 9	56
3	**54c**	60 : 21 : 19	73
4	**54d**	59 : 22 : 19	97
5	**54e**	59 : 23 : 18	97
6	**54f**	65 : 15 : 20	82
7	**54g**	62 : 13 : 25	75
8	**54h**	66 : 15 : 19	99
9	**54i**	61 : 20 : 19	90

[a] All reactions were run under an inert atmosphere (argon) in boiling *o*-dichlorobenzene for 9 h.
[b] For entries 2–9, the initial products were hydrolyzed and then purified.

2-2. Total Synthesis of (dl)-19-Norcanrenone

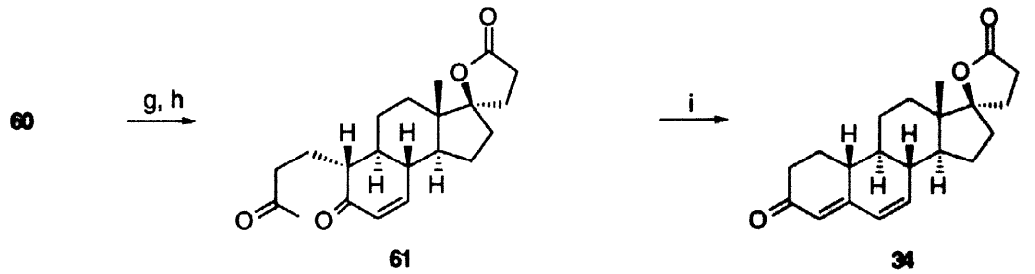
The tetracyclic cyclobutanone **37a** was prepared in a stereoselective manner by the thermolysis of the olefinic cyclobutanone acetals (the best yield for *trans-syn* isomer is shown in entry 8) followed by acid treatment. This cyclobutanone was subjected to the Baeyer Villiger oxidation to give the lactone **58**. The lactone **58** thus obtained was converted into the enone **59** (65%) whose reductive alkylation followed by dehydrogenation gave the enone **60** (45%). Acid treatment of **61**, which was prepared from **60** in two steps (82%), furnished the pentacyclic dienone, 19-norcanrenone (**34**) (54%). Since (dl)-19-norcanrenone (**34**) has already been converted[14k] into (dl)-19-norspironolactone (**33**), this work constitutes a formal total synthesis of (±)-19-norspironolactone (**33**) (Scheme 5).

Scheme 5



58 **59** **60**

Scheme 5 (continued)



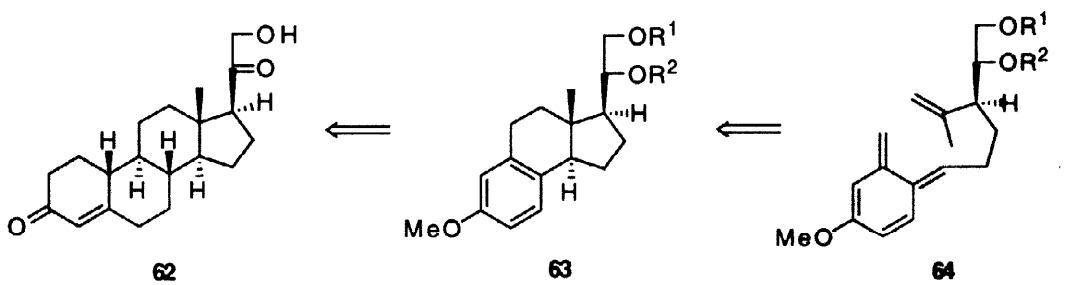
Steps: (a) DIBAL, toluene-THF, −78 °C, 1 h; (b) BF_3-Et_2O, MeOH, THF, r.t., 27 h; (c) Li, liq. NH_3, EtOH, THF, −78 °C, 1 h; (d) 10% HCl, MeOH, r.t., 3 h; (e) Li, liq. NH_3, THF, −78 °C→ −20 °C, 1 h; then $BrCH_2CH{=}CClMe$, THF, −20 °C, 2 h; (f) TMSCl, LDA, THF, −78 °C, 1 h; then $Pd(OAc)_2$, DDQ, MeCN, r.t., 36 h; (g) Jones reagent, acetone, 0 °C, 40 min; (h) $Hg(OCOCF_3)_2$, CH_2Cl_2, r.t., 1 h; (i) conc. HCl, AcOH, H_2O, r.t., 90 h.

Thus, we could develop a novel and efficient methodology for the stereoselective synthesis of 19-norspironolactone (**33**).

3. Total Synthesis of (+)-19-Nordeoxycorticosterone

Because of the increasing interest[17,18] in its physiological significance, much attention has been focused on the chemistry[19] of (+)-19-nordeoxycorticosterone (**62**) (a potent mineral corticoid with sodium-retaining activity comparable to that of aldosterone) with a view to developing synthetic routes capable of providing significant amounts of this compound. However, a practical and flexible synthetic methodology, affording satisfactory yields and providing a wide variety of compounds of this type for biological studies, still remains to be developed. Hence, we have undertaken the development of an efficient and flexible route for the production of 19-nordeoxycorticosterone derivatives *via* the benzoperhydroindane **63**, which could be accessed by intramolecular [4+2] cycloaddition of the *o*-quinodimethane **64**, as shown in Scheme 6.

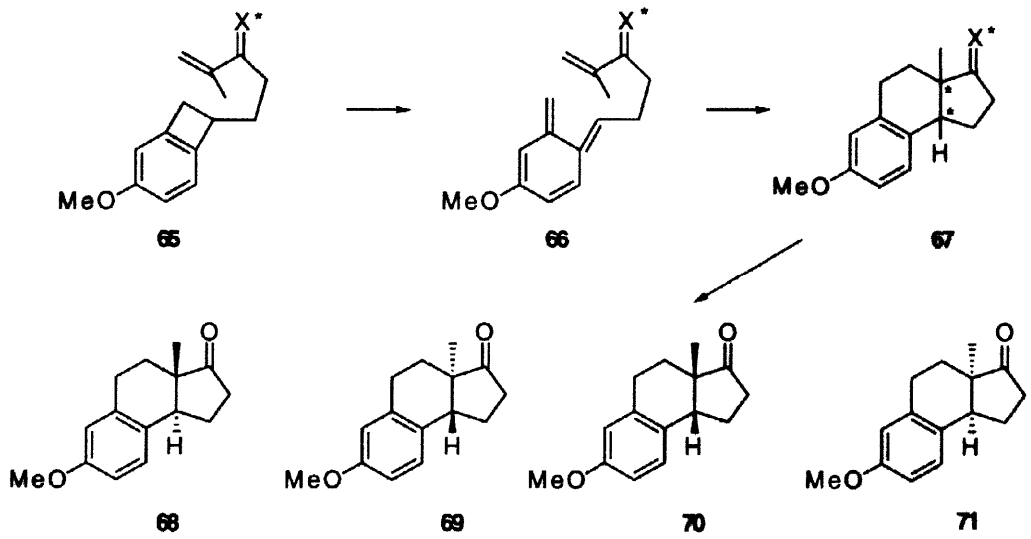
Scheme 6



3-1. Enantioselective Approach to Benzoperhydroindanes

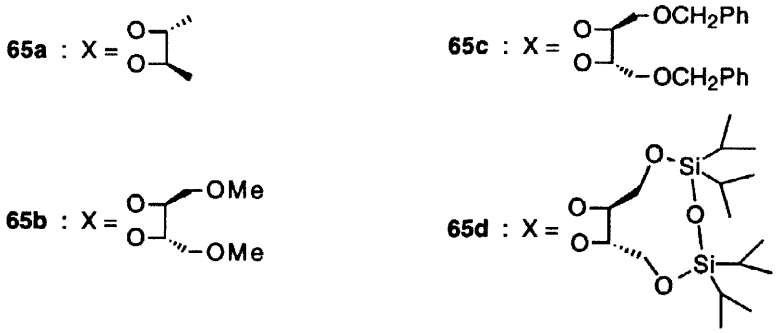
In order to make this novel methodology applicable to the enantioselective synthesis of steroids, we have explored efficient methods for the enantioselective synthesis of benzoperhydroindanes *via* intramolecular [4+2] cycloaddition of the olefinic *o*-quinodimethanes. First, we tried cycloaddition of the olefinic *o*-quinodimethane **66**, generated *in situ* by thermolysis of the benzocyclobutene **65** having a C_2-symmetric acetal moiety as a chiral auxiliary.[20] After hydrolytic removal of the chiral auxiliary (X) of the product **67**, the yields and ratios of the four possible products **68–71** were analyzed (Scheme 7) and the results are summarized in Table 3.

Scheme 7



The selectivity and predominant formation of **68** for **65b–d** could be well explained by proposing the preferred *exo* transition state T_1 rather than T_2, which leads to **69**, or the *endo* transition states which lead to **70** and **71** (Figure 6). Since the reactions have not proceeded in a sufficiently enantioselective manner, alternative routes to chiral benzoperhydroindanes were investigated. Thus,[21] the chiral isopropenyl alcohol **74** was easily prepared *via* reductive epoxide ring opening (100%) of the mesylate (100%) of the chiral epoxide **73**, which was obtained by Sharpless epoxidation (96%, 88% e.e.) of the allyl alcohol **72** as shown in Scheme 8.

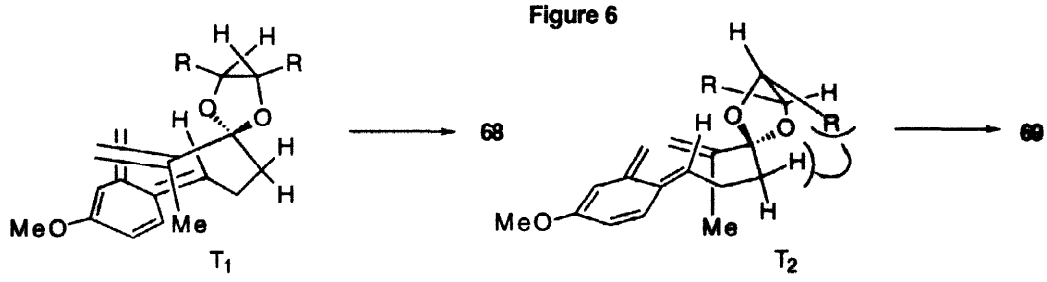
Table 3[a] Thermolysis of Chiral Acetals 65a–d



entry	substrate	product ratio and e.e.[b] **68 : 69 : 70 : 71**	isolated yield %[c]
1	**65a**	0 : 95 (36) : 0 : 5	90
2	**65b**	91 (12) : 0 : 9 : 0	95
3	**65c**	92 (14) : 0 : 8 : 0	57
4	**65d**	97 (29) : 0 : 3 : 0	82

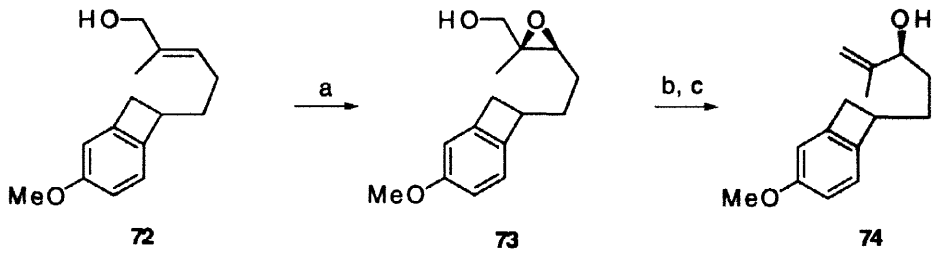
[a] All reactions were run under an inert atmosphere (argon) in boiling *o*-dichlorobenzene for 4 h and then the products were subjected to acid hydrolysis and analysis.
[b] Enantiomeric excess (e.e.) is shown in parenthesis.
[c] All yields correspond to overall yields.

Figure 6



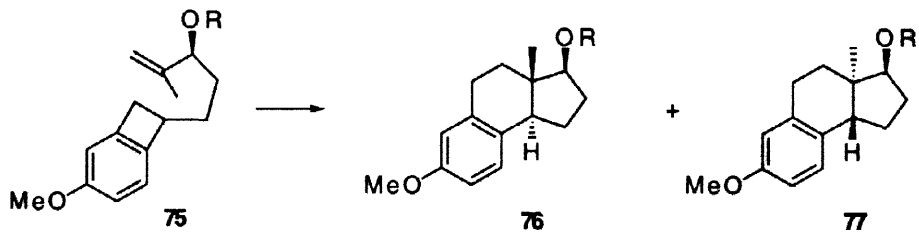
The thermolysis of the chiral isopropenyl alcohol derivatives **75a–f** prepared by standard derivatisation of the alcohol **74** was then examined and the results are summarized in Table 4.

Scheme 8



Steps: (a) ^{t}BuOOH, Ti(OPr^{i})$_4$, (+)-L-diisopropyl tartrate, 4 Å molecular sieves, CH_2Cl_2, –20 °C, 3 h; (b) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C, 1 h; (c) Zn, NaI, DMF, 100 °C, 30 min.

Table 4[a] Thermolysis of Chiral Alcohol Derivatives 75a–f



entry	substrate	product ratio and e.e.[b] 76 : 77	isolated yield %[c]
1	**75a** : R = Pr$^{i}_3$Si	2 : 1	81
2	**75b** : R = Bu^{t}Me$_2$Si	2.3 : 1	100
3	**75c** : R = Ph$_2$Bu^{t}Si	1.5 : 1	94
4	**75d** : R = PhCH$_2$OCH$_2$	1 : 1.3	89
5	**75e** : R = THP	1.2 : 1	72
6	**75f** : R = Ph$_3$C	1 : 1	90

[a] All reactions were run under an inert atmosphere (argon) in boiling *o*-dichlorobenzene for 3 h.
[b] The isomer ratio was determined for the corresponding alcohols derived by the hydrolysis of initial products.
[c] All yields are based on purified products by passing through a short column (SiO_2).

The stereoselectivity of this reaction could be also rationalized in terms of steric factors as shown in Figures 4 and 6. Since the diastereomers **76** (R=H) and **77** (R=H) were easily separated on silica gel column chromatography, the corresponding ketones **68** and **69** could be prepared in more pure states than was possible with the chiral acetal procedure described before. However, the diastereselectivity of this reaction was not high enough for practical synthesis of steroids and we continued to search for a more effective route[22] to chiral benzoperhydroindanes. It was found that the thermolysis of the chiral acetonide **78** proceeded stereoselectively to furnish the optically pure benzoperhydroindane **79** (98%) as a single product (Scheme 9).

Scheme 9

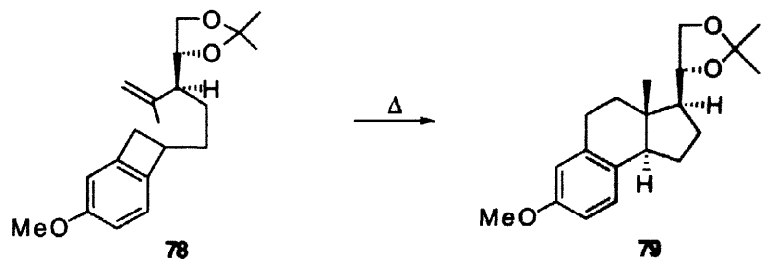
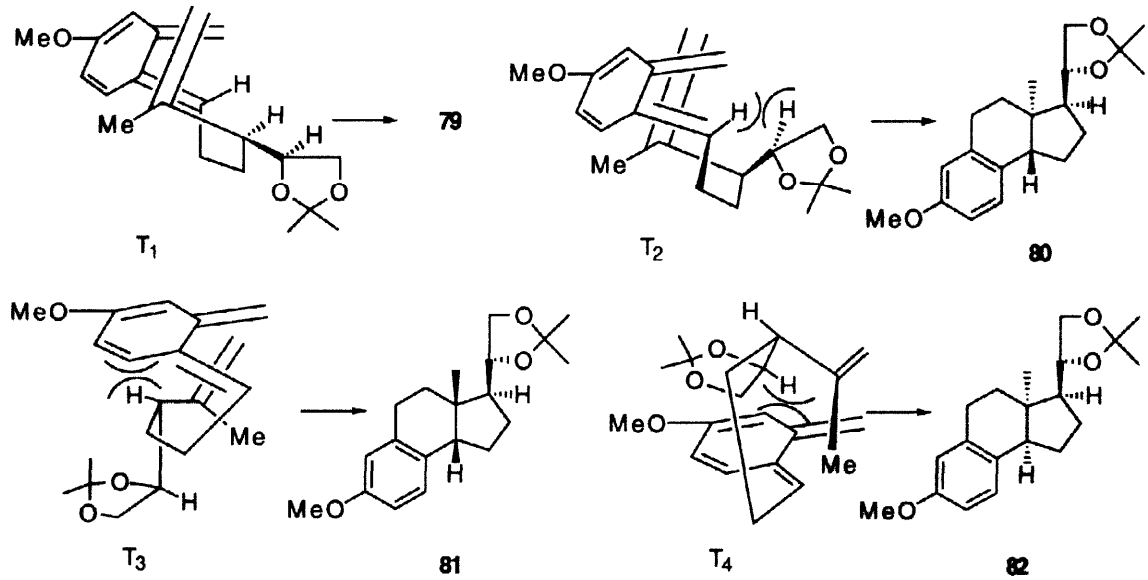


Figure 7



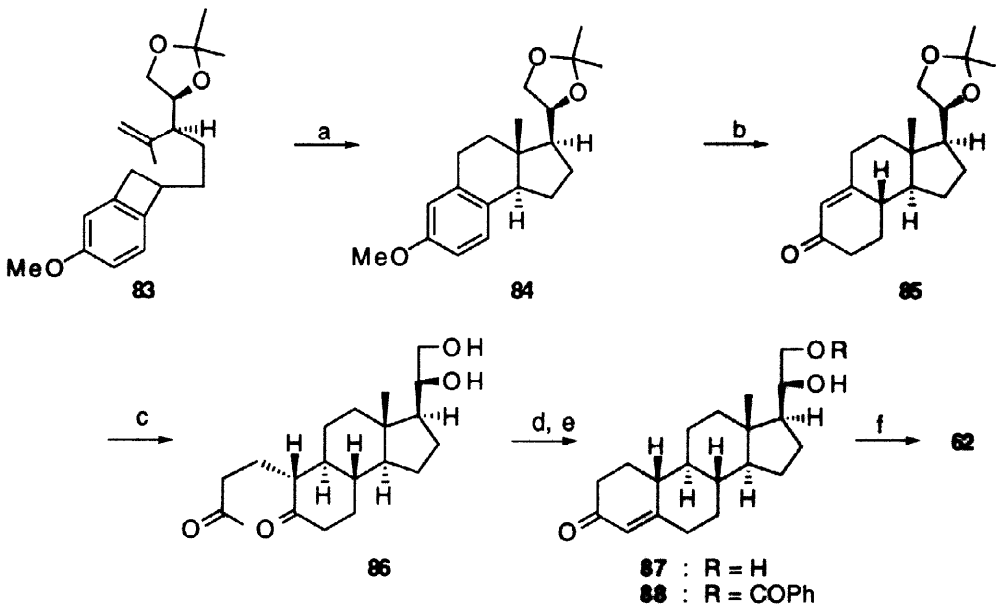
The complete stereoselectivity of this thermolysis reaction could also be attributed to the large steric bulkiness of acetonide moiety forcing [4+2] cycloaddition reaction to proceed *via* sterically more favorable transition state T_1 leading to **79** rather than T_2, T_3, and T_4 which have unfavorable steric congestion and lead to **80**, **81**, and **82**, respectively (Figure 7).

Thus, we could develop an efficient route to chiral benzoperhydroindanes.

3-2. Completion of the Total Synthesis of (+)-19-Nordeoxycorticosterone

Based on the preliminary studies for the synthesis of chiral benzoperhydroindanes described above, we have completed the total synthesis of (+)-19-nordeoxycorticosterone (**62**) as follows.[23] In this synthesis, glyceraldehyde acetonide, easily obtainable in large quantities from D-mannitol, was used as a chiral source.

Scheme 10



Steps: (a) *o*-dichlorobenzene,190 °C, 13 h; (b) Li, liq. NH_3, THF, EtOH, –78 °C, 45 min; 10% HCl, MeOH, r.t., 13 h; then $Me_2C(OMe)_2$, CSA, CH_2Cl_2, r.t., 1 h; (c) Li, liq. NH_3, THF, –78 °C, 45 min; then $MeCCl{=}CHCH_2Br$, 30 min; $Hg(OCOCF_3)_2$, $MeNO_2$, r.t., 3 h; then 10% HCl, r.t., 1 h; (d) 10% KOH, MeOH, r.t., 2 h; (e) PhCOCl, pyridine, CH_2Cl_2, r.t., 1 h; (f) PCC, Florisil, CH_2Cl_2, r.t., 5 h; K_2CO_3, MeOH, CH_2Cl_2, H_2O, r.t., 80 min.

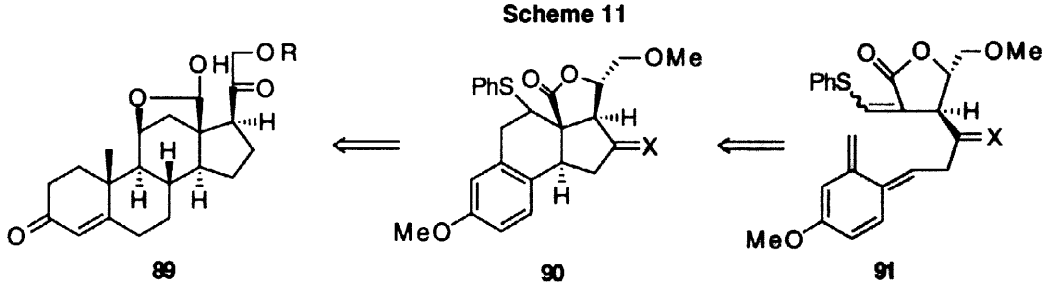
The thermolysis of **83** was effected at 190 °C to give stereoselectively the benzoperhydroindane **84** (98%) as a single product. Birch reduction of **84** followed by acid treatment and protection of the diol group afforded the thermodynamically predominant compound **85** (37.5% from **84**), which on reductive alkylation using 1-bromo-3-chlorobut-2-ene and successive hydrolysis yielded the diketone **86** (43%). The diol **87** obtained (81%) by cyclization of **86**, was selectively converted into the monobenzoate **88** (52%). Finally, oxidation of **88** followed by hydrolysis furnished (+)-19-nordeoxycorticosterone (**62**) (68.4% from **88**) (Scheme 10).

Thus, we could provide an efficient route for the enantioselective synthesis of (+)-19-nordeoxycorticosterone (**62**).

4. Synthetic Approach to (+)-Aldosterone and Its Relatives

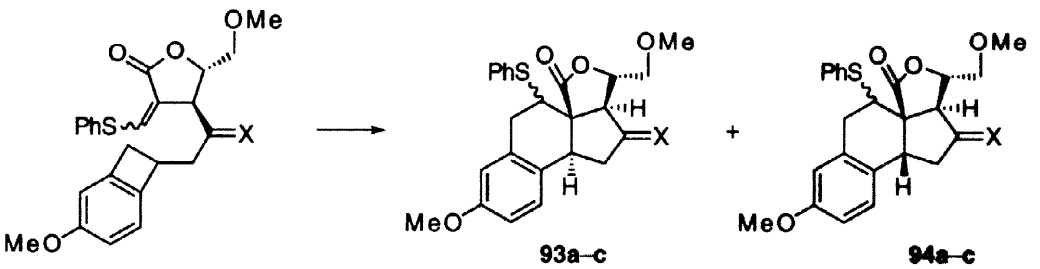
Because of the physiological importance as a mineral corticoid, much attention has been paid to the synthesis of (+)-aldosterone (**89**).[24] We planned an asymmetric total synthesis of **89** through the chiral benzoperhydroindane **90** *via* intramolecular [4+2] cycloaddition of the *o*-quinodimethane **91** as a key step[25] (Scheme 11).

Scheme 11

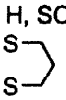


The thermolysis of the substrates **92a–c** was firstly carried out and the results are summarized in Table 5.

Table 5[a] Thermolysis of Chiral Butenolides 92a–c



92a : X = H, SO_2 Tol.

92b : X = 

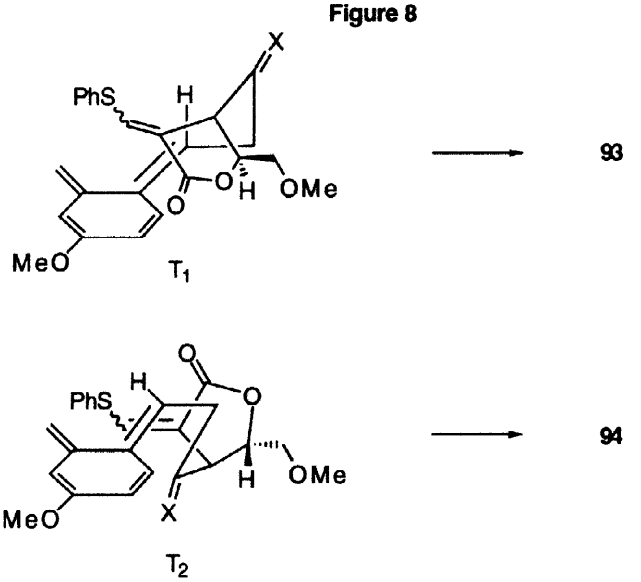
92c : X = H_2

entry	substrate	reaction time, h	product ratio **93 : 94**	isolated yield %[b]
1	**92a**	4	73 : 27	84
2	**92b**	14	100 : 0	76
3	**92c**	22	30 : 70	72

[a] All reactions were run under argon at 180 °C.
[b] All yields are based on purified products.

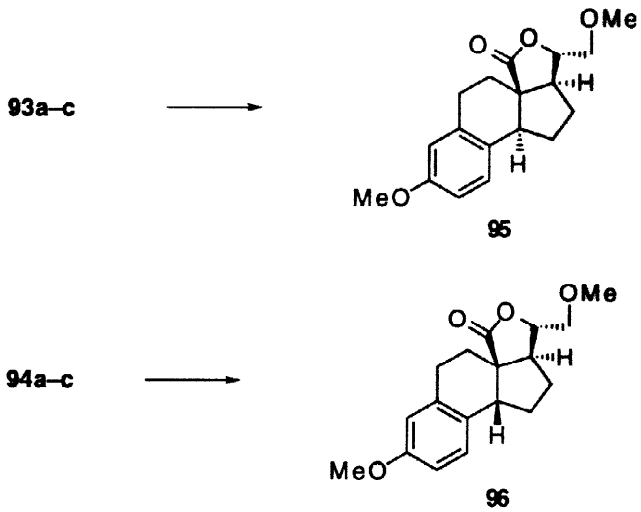
From these results, it became obvious that all of these reactions proceeded in moderate to high yield and the stereochemical course of these reactions was deeply dependent on the substituents, X. A rationalization of these stereochemical outcomes could be achieved by proposing the two possible transition states T_1 and T_2 as shown in Figure 8. In the case of **92c**, transition state T_2 (X=H_2) leading to **94c** might be favored rather than transition state T_1 (X=H_2), which has a steric repulsion between the *o*-quinodimethane moiety and the lactone ring and leads to **93c**. On the other hand, the transition state T_2 having bulky substituents (X=SO_2Tol, $SCH_2CH_2CH_2S$) in the substrates **92a** and **92b** might be disfavored with respect to T_1 because of the large steric congestion between *o*-quinodimethane moiety and X,thus resulting in *trans* fused compounds **93a** and **93b** as major or exclusive products.

Figure 8



Finally, these products **93a–c** and **94a–c** were converted into the compounds **95** and **96** respectively which might be potential intermediates for the synthesis of (+)-aldosterone (**89**) and its relatives (Scheme 12).

Scheme 12

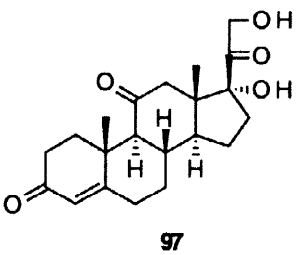


Thus, we have been able to develop an enantioselective route to C-18 functionalized steroids.

5. Total Synthesis of Corticosteroids

Corticosteroids that have an oxygen functionality at C-11 are important regulatory hormones.[26] Because of this physiological and also clinical importance, much effort has been devoted to solving the problems presented by this class of steroids,[27] especially developing efficient methods for introducing a hydroxyacetyl[28] and an oxygen substituent[29] at C-17 and C-11 positions, respectively; such functionality are important for steroidal physiological activity (e.g. cortisone **97** in Figure 9). These facts prompted our search for an effective methodology for the synthesis of this class of steroids.

Figure 9



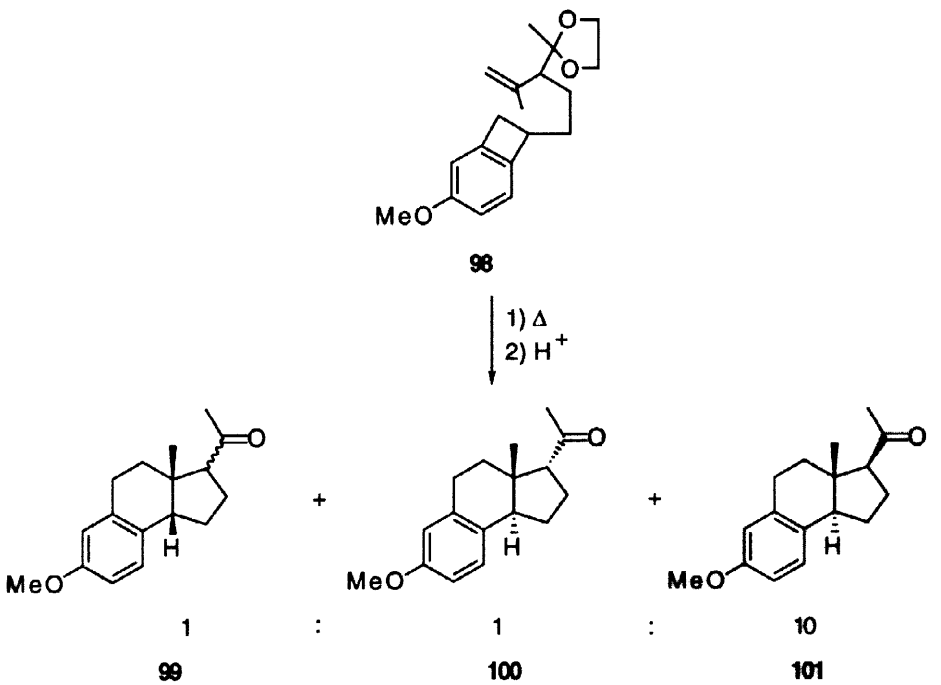
Preliminary studies dealt separately with the introduction of a C-11 oxygen and a C-17 hydroxyacetyl substituent and are discussed below.

5-1. Total Synthesis of C-11 Oxygenated Steroids

5-1-1. Total Synthesis of (dl)-11-Oxoprogesterone[30]

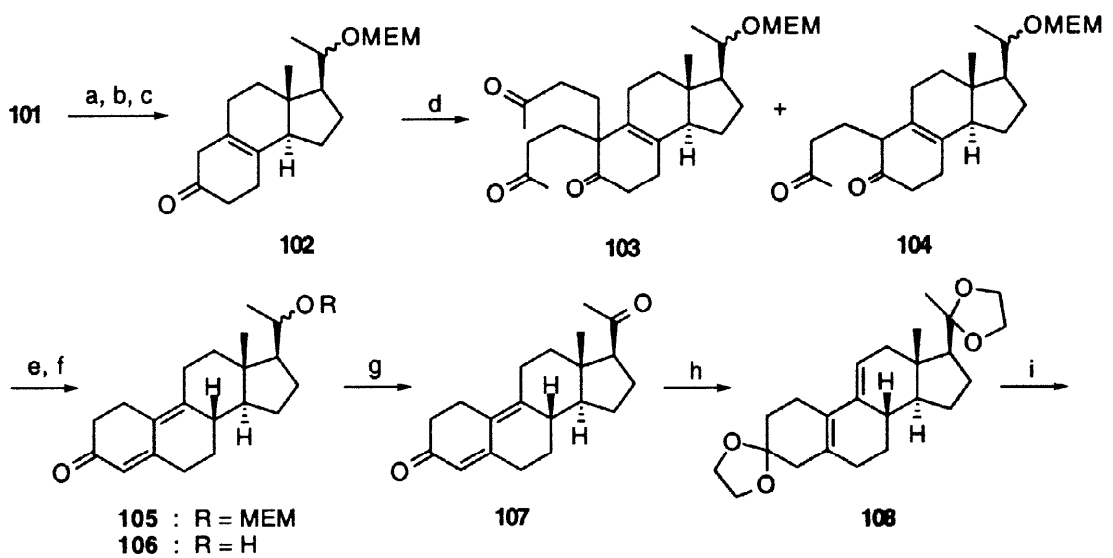
The thermolysis of the benzocyclobutene **98** proceeded quantitatively and the diastereomers **99**, **100**, and **101** were obtained in a ratio of 1:1:10 respectively after the hydrolysis of initial products (Scheme 13). The stereochemical course of this reaction could be rationalized in terms of steric demands as given in the previous sections. The conversion of **101** to (dl)-11-oxoprogesterone (**112**) was straightforward.

Scheme 13

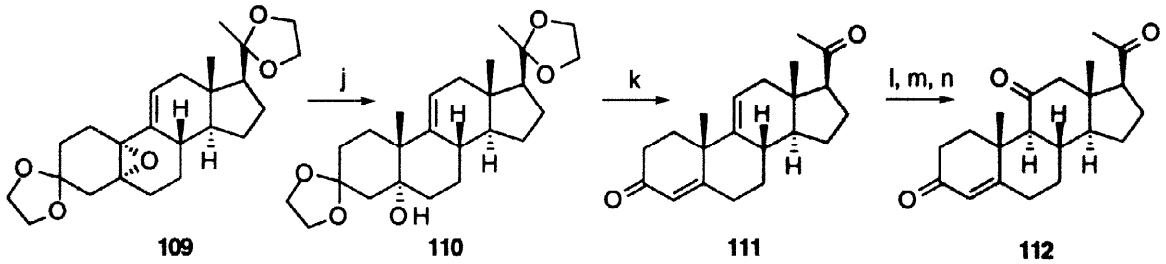


The alkylation of the enone **102**, which was obtained from **101** in three steps (80%), afforded a mixture of **103** and **104** (1:1, 63%). The monoalkylated compound **104** was cyclized to **105** and then hydrolyzed to give the tetracyclic compound **106** (27% from **104**), which was oxidized to give 19-nor-$\Delta^{9(10)}$-progesterone (**107**) (69%). Next, the diketal **108**, obtained (80%) by acetalization of **107**, was oxidized to give the monoepoxide **109** (40%) which was then successively treated with Grignard reagent and then acid to afford Δ^{9}-progesterone (**111**) *via* **110** (24% from **109**). Finally, the compound **111** was then converted into 11-oxoprogesterone (**112**) in three steps (Scheme 14).

Scheme 14



Scheme 14 (continued)

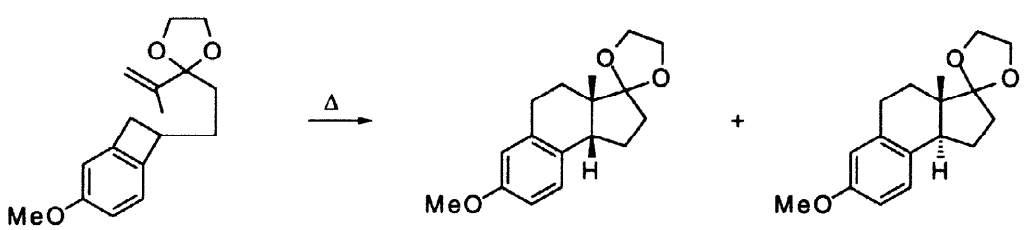


Steps: (a) $NaBH_4$, MeOH, r.t., 4 h; (b) $MeOCH_2CH_2OCH_2Cl$, $^iPr_2EtN$, CH_2Cl_2, 4 h; (c) Li, liq. NH_3, THF, EtOH, −78 °C, 20 min; then $(CO_2H)_2$, EtOH–H_2O, r.t., 3 h; (d) $KN(SiMe_3)_2$, Et_3B, THF, −78 °C, 1 h; then $^nBu_4NF$, THF, r.t., 14 h; (e) KOH, MeOH, reflux, 4 h; (f) 10% HCl, MeOH, reflux, 7 h; (g) Jones reagent, acetone, 0 °C, 5 min; (h) $HOCH_2CH_2OH$, CSA, benzene, reflux, 6 h; (i) MCPBA, $NaHCO_3$, H_2O, CH_2Cl_2, 0 °C, 10 min; (j) MeMgBr, Et_2O, 0 °C, 5 min; (k) 10% HCl, MeOH, reflux, 1 h; (l) *N*-bromoacetamide, 70 % $HClO_4$, dioxane, H_2O, r.t., 1 h; (m) PDC, CH_2Cl_2, r.t., 5 h; (n) Zn, AcOH, r.t., 30 min.

5-1-2. Total Synthesis of (dl)-Adrenosterone[31]

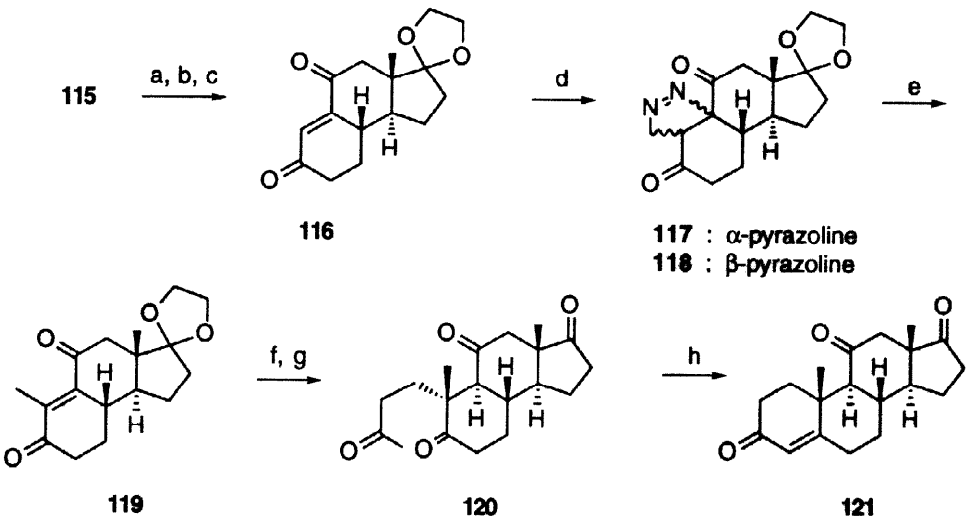
The thermolysis of **113** was conducted in boiling *o*-dichlorobenzene to give the mixture of the benzoperhydroindanes **114** and **115** (5:95, 96%) and it was found that just one crystallization of this mixture afforded *trans*-benzoperhydroindane **115** as a pure state (Scheme 15).

Scheme 15



Thus, having an efficient procedure for **115** in hand, the total synthesis of (dl)-adrenosterone (**121**) was achieved as follows. Treatment of **116**, which was prepared from **115** in three steps (48%), with diazomethane afforded a separable mixture of the α- and β-pyrazolines **117** and **118** in the ratio of 3:2 (93%). The mixture of these pyrazolines was heated to give the methylated compound **119** (72%), which was then converted into the tetraketone **120** in two steps (50%). The cyclization of **120** furnished the target compound (dl)-adrenosterone (**121**) (80%) (Scheme 16).

Scheme 16



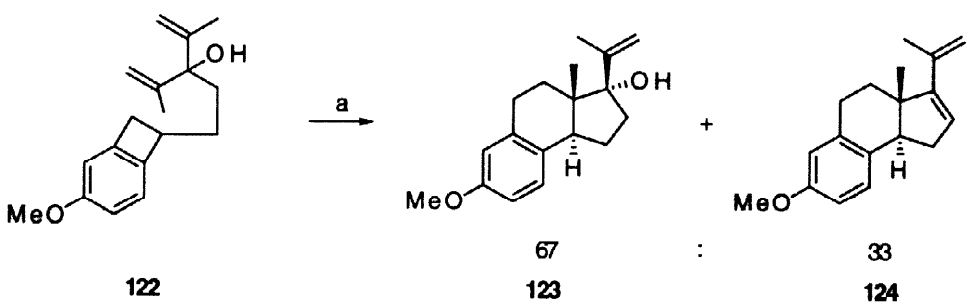
Steps: (a) Li, liq. NH_3, EtOH, THF, –78 °C, 30 min; then $(CO_2H)_2$, EtOH, H_2O, r.t., 2 h; (b) $Me_2NCH_2CH_2NH_2$, MeOH, reflux, 15 h; (c) 3,5-dimethylpyrazole–CrO_3, CH_2Cl_2, r.t., 20 h; (d) CH_2N_2, $CHCl_3$–Et_2O, 0 °C, 3.5 h; (e) *o*-dichlorobenzene, 180 °C, 5 min; (f) Li, liq. NH_3, THF, –20 °C, 1 h; then1-bromo-3-chloro-2-butene, 40 min; (g) H_2SO_4, AcOH, r.t., 45 min; (h) KOH, MeOH, H_2O, 50 °C, 1 h.

5-2. Synthetic Approach to C-17 Hydroxyacetyl Steroids[32]

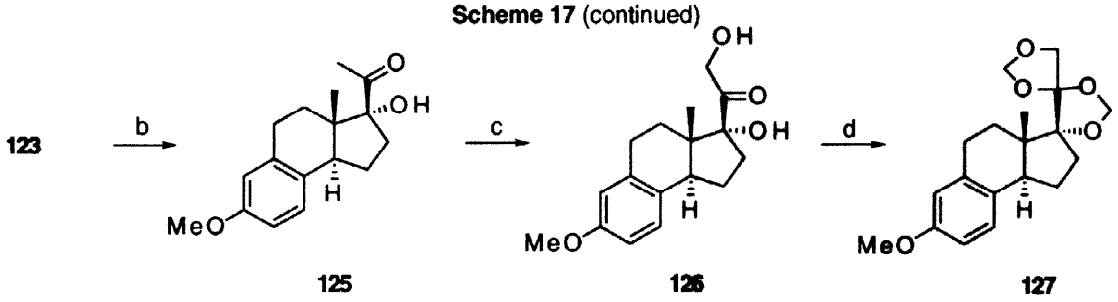
The thermolysis of the benzocyclobutene **122** was carried out to give stereoselectively a mixture of the *trans*-benzoperhydroindanes **123** and **124** (67:33, 90%). The stereoselectivity of this reaction could be rationalized again in terms of steric demands as discussed in the previous sections. The hydroxyketone **125** obtained (76%) by ozonolysis of **123** was converted into the dihydroxyketone **126** (47%) and then the didioxolane **127** (26%) (Scheme 17).

The synthesis of **127** was, however, too low yielding to be applied to the synthesis of steroids and a more efficient method was explored as follows. The thermolysis of the benzocyclobutene **128** afforded a mixture of *trans*-benzoperhydroindanes **129** and **130** (84:16, 98%), the former of which was subjected to Lemieux-Johnson oxidation to give the ketone **131** (99%). The oxidation of **131** with iodosylbenzene gave the alcohol **132** (17%) and the aldehyde **133** (14%) (Scheme 18).

Scheme 17

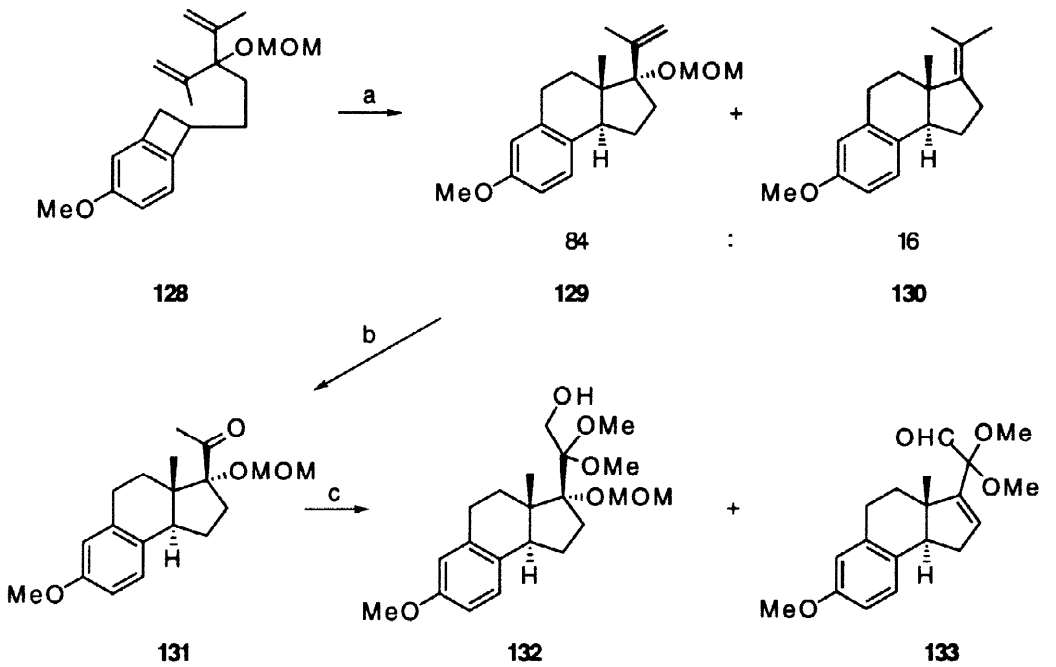


Scheme 17 (continued)



Steps: (a) *o*-dichlorobenzene, reflux, 40 h; (b) O_3, CH_2Cl_2–MeOH, –78 °C, 5 min; then Me_2S, –78 °C, 30 min; (c) LDA, MoO_5·Py·HMPA, THF, –78 °C, 1 h; (d) HCHO, conc. HCl, CH_2Cl_2, r.t., 50 h.

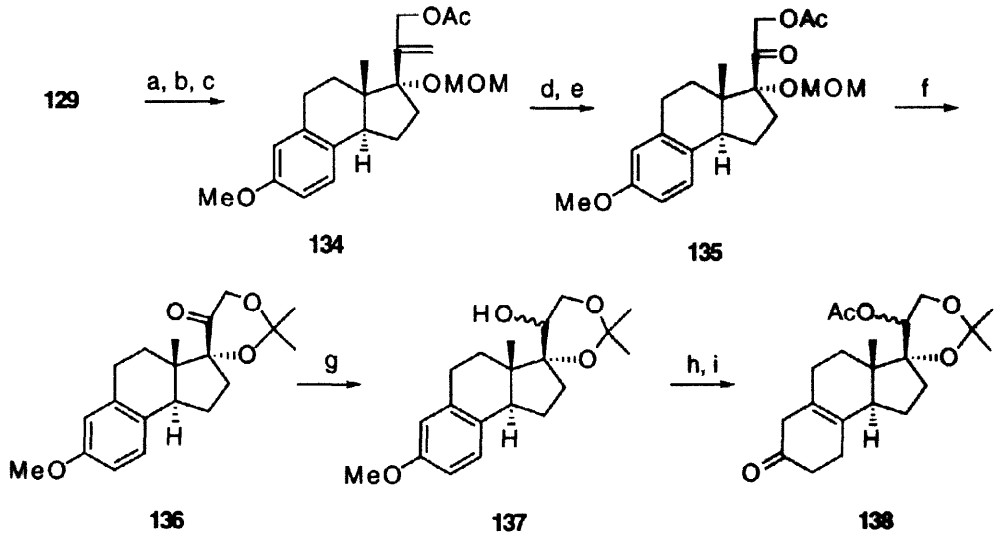
Scheme 18



Steps: (a) *o*-dichlorobenzene, reflux, 5 h; (b) $NaIO_4$, OsO_4, dioxane–H_2O, 35 °C, 24 h; (c) iodosylbenzene, KOH, MeOH, r.t., 48 h.

Alternatively, the benzoperhydroindane **129** was converted into the acetate **134** in three steps (56%) and then into the ketone **135** (56%). Direct deprotection of both hydroxyl groups of **135** was achieved by acid treatment to give the dihydroxyketone **126** (75%). The dioxolane **136**, prepared (73%) from **126**, was reduced to the alcohol **137** (94%) as a diastereoisomeric mixture at the C-20 position. Successive Birch reduction, acetylation and hydrolysis of **137** afforded the oxo acetate **138** (25%) (Scheme 19).

Scheme 19



Steps: (a) MCPBA, KF, NaF, CH_2Cl_2, r.t., 12 h; (b) $LiNEt_2$, Et_2O, reflux, 5 h; (c) Ac_2O, pyridine, r.t.,1 h; (d) OsO_4, NMO, THF, ^tBuOH, r.t., 12 h; then HIO_4, THF–Et_2O, r.t., 1 h; (e) CSA, THF–H_2O, reflux, 72 h; (f) $MeC(OMe)=CH_2$, CSA, CH_2Cl_2, 0 °C, 20 min; (g) $NaBH_4$, MeOH–THF, 0 °C, 1 h; (h) Li, liq. NH_3, THF, EtOH, –78 °C, 30 min; then Ac_2O, pyridine, r.t., 3 h; (i) PPTs, acetone–H_2O, r.t., 9 h.

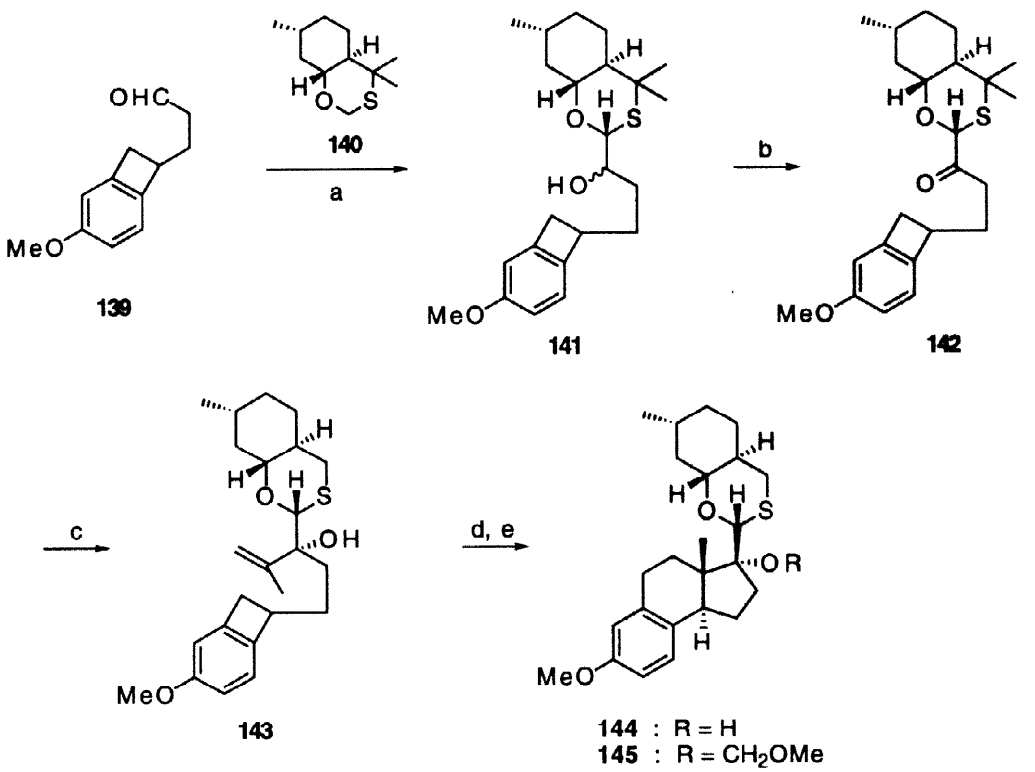
Thus, we could develop a route to potential precursors having substituents at C-17 suitably functionalized for the synthesis of corticosteroids.

5-3. Enantioselective Total Synthesis of (+)-Cortisone[33]

5-3-1. Intramolecular [4+2] Cycloaddition of Chiral Olefinic *o*-Quinodimethanes

Based on the preliminary studies discussed in the previous sections, we achieved the first enantioselective total synthesis of (+)-cortisone as follows. Firstly, the key intermediate **141** was synthesized using the oxathiane **140**[34] as a chiral auxiliary. Reaction of the aldehyde **139**[32b] with lithiated oxathiane **140** gave the alcohol **141** (96%) as a stereoisomeric mixture. Grignard reaction of the ketone **142**, obtained (86%) by Swern oxidation of **141**, afforded the isopropenyl alcohol **143** (90%) as a single stereoisomer with respect to the hydroxylated position but two diastereoisomers with respect to the benzocyclobutenylic position. The thermal reaction of **143** was carried out to give the benzoperhydroindane **144** (100%) with no detectable amount of any other isomers. The high stereoselectivity for **144** probably reflects the increased steric interactions in the transition states T_2–T_4 caused by the bulky oxathiane substituent and increased relative stability of T_1 (see Figure 7). Thus, the oxathiane group functioned not only as a chiral auxiliary but also as a stereodirecting factor in the thermal reaction. The corresponding MOM ether **145** was derived quantitatively from **144** (Scheme 20).

Scheme 20

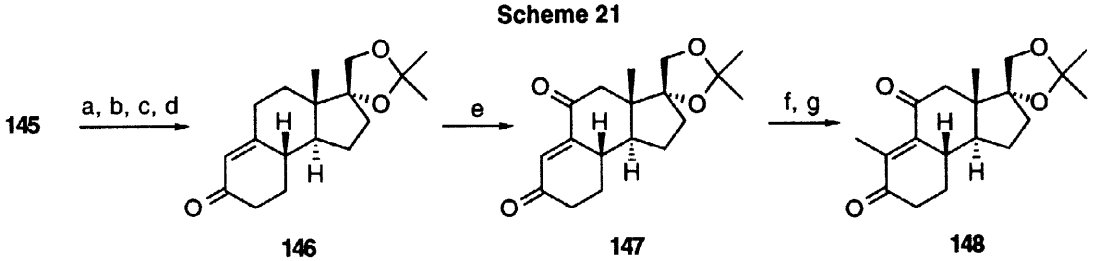


Steps: (a) ^{n}BuLi, THF, –78 °C, then **160**, –78 °C, 30 min; (b) DMSO, $(CF_3CO)_2O$, CH_2Cl_2, –78 °C, 30 min; then Et_3N, –78 °C, 1 h; (c) CH_2=CMeMgBr, THF, –78 °C, 1 h; (d) *o*-dichlorobenzene, reflux, 6.5 h; (e) $MeOCH_2Cl$, DMAP, $^{i}Pr_2NEt$, CH_2Cl_2, r.t., 72 h.

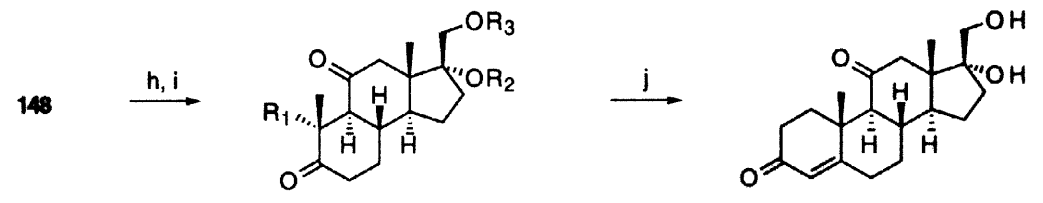
5-3-2. Construction of the Basic Skeleton of (+)-Cortisone

Allylic oxidation of **146**, which was prepared from **145** in four steps (66%), gave the enedione **147** (75%). 1,3-Dipolar cycloaddition of diazomethane to **147** followed by thermolysis of the adduct afforded the C-10 methylated compound **148** (73%). Thus, the functionalization at the C-11 position and the introduction of 19-methyl were achieved in moderate yield. Next, the enedione **148** was subjected to reductive alkylation with Wichterle's reagent to give the alkylated dione **149** (64%), which was then hydrolyzed to the triketone **150** (42%). Base-catalyzed cyclization of **150** furnished the tetracyclic compound **151** (86%) which has the basic skeleton of (+)-cortisone (Scheme 21).

Scheme 21



Scheme 21 (continued)



149 : $R_1 = CH_2CH{=}CClMe$; $R_2 + R_3 =$ 

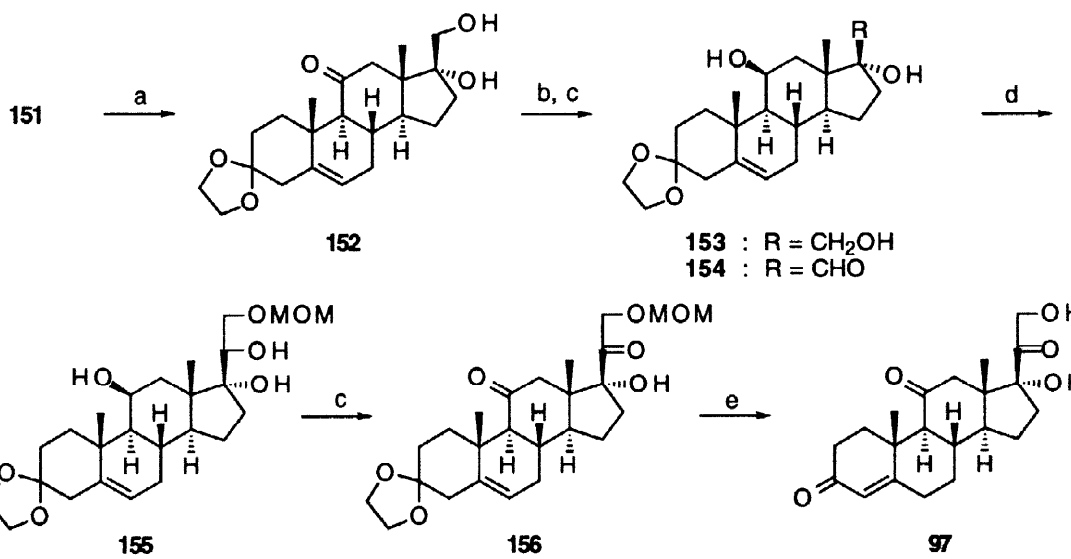
150 : $R_1 = CH_2CH_2COMe$; $R_2 = R_3 = H$

Steps: (a) NCS, $AgNO_3$, MeCN–H_2O, r.t., 30 min; (b) $NaBH_4$, MeOH, r.t., 10 min; (c) Li, liq. NH_3, THF–EtOH, –78 °C, 1 h; then 10% HCl, MeOH, r.t, 10 min; (d) $(MeO)_2CMe_2$, CSA, CH_2Cl_2, r.t., 10 min; (e) SeO_2, MeCN, reflux, 30 min; then PCC, CH_2Cl_2, r.t., 2 h; (f) CH_2N_2, $CHCl_3$, 0 °C, 1 h; (g) *o*-dichlorobenzene, reflux, 5 min; (h) liq. NH_3, THF, –78 °C, 45 min; then $BrCH_2CH{=}CClMe$, THF, –78 °C, 30 min; (i) $Hg(OCOCF_3)_2$, $MeNO_2$, r.t., 42 h; then 10% HCl, r.t., 1 h; (j) 10% KOH, MeOH, r.t., 90 min.

5.3.3. Total Synthesis of (+)-Cortisone

The monoacetal **152** obtained (54%) by the acetalization of the diol **151** was reduced to give the triol **153** (80%), which was then selectively oxidized to afford the aldehyde **154** (83%). The reaction of **154** with [(methoxymethoxy)methyl]lithium, generated *in situ* by the transmetalation of [(methoxymethoxy)methyl]-tributylstannane with *n*-butyllithium, gave the MOM ether adduct **155** (83%), which was then subjected to Swern oxidation to afford the diketone **156** (72%). Finally, the acid treatment of **156** furnished (+)-cortisone (**97**) (75%) (Scheme 22). Thus, we have completed the first enantioselective total synthesis of (+)-cortisone (**97**).

Scheme 22



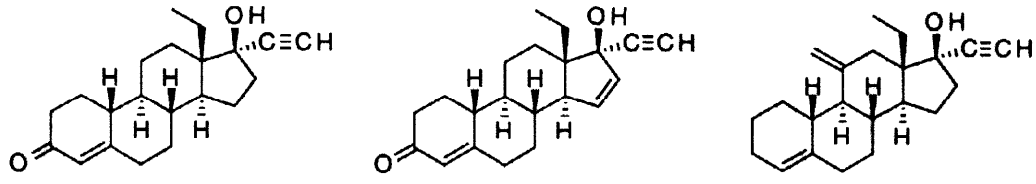
Steps: (a) $HOCH_2CH_2OH$, CSA, benzene, reflux, 3 h; (b) $LiAlH_4$, THF, 0 °C, 30 min; (c) DMSO, $(COCl)_2$, –78 °C, 1 h; then Et_3N, –78 °C→0 °C, 1 h; (d) $^nBu_3SnCH_2OCH_2OMe$, ^{n}BuLi, THF, –78 °C, 30 min; (e) 10% HCl, MeOH, r.t., 96 h.

6. Enantioselective Total Synthesis of Unnatural Steroids

6-1. Synthetic Approach to C-13 Ethyl Steroids[35]

The steroids possessing an angular C-13 ethyl substituent such as norgestrel (**1**),[36] its C-15-dehydro analogue **157**,[37] and desogestrel (**158**)[38] have recently attracted much attention as second and third generations of steroid oral contraceptives. They have been produced commercially by total synthesis,[39] because there are no naturally occurring steroid precursors having such a substituent at C-13 (Figure 10).

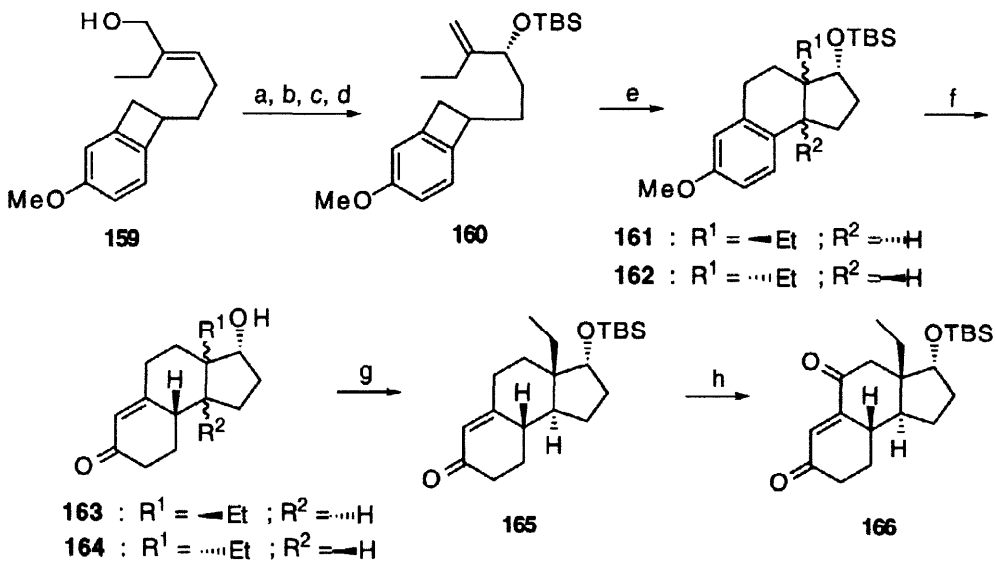
Figure 10



1 **157** **158**

Thus, we have explored an efficient way to these types of steroids and succeeded in developing a novel route to the optically active des-A steroids **165** and **166**. The chiral silyl ether **160**, which was prepared from the allyl alcohol **159** in four steps (88%), was subjected to thermolysis to afford the benzoperhydroindanes **161** and **162** selectively. Birch reduction of this mixture followed by acid treatment afforded a mixture of the enones **163** and **164** (3:1, 69% from **160**), easily separable on silica gel column chromatography. Finally, oxidation of the silyl ether **165**, derived (95%) from **163**, furnished the diketone **166** (43%) (Scheme 23).

Scheme 23



159 **160**

161 : R^1 = —Et ; R^2 = ····H

162 : R^1 = ····Et ; R^2 = —H

163 : R^1 = —Et ; R^2 = ····H

164 : R^1 = ····Et ; R^2 = —H

165 **166**

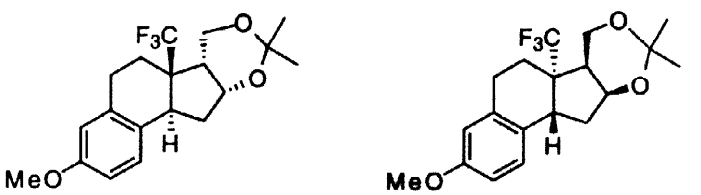
Steps: (a) ^{t}BuOOH, Ti(O^{i}Pr)$_4$, (–)-D-diisopropyl tartrate, 4 Å molecular sieves, CH_2Cl_2, –70 °C, 13 h; (b) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C, 1 h; (c) Zn, NaI, DMF, 100 °C, 1 h; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h; (e) *o*-dichlorobenzene, reflux, 8 h; (f) Li, liq. NH_3, EtOH, –78 °C, 1 h; then 10% HCl, MeOH, r.t., 10 h→reflux, 1 h; (g) TBSCl, imidazole, DMAP, r.t., 3.5 h; (h) SeO_2, MeCN, reflux, 2 h; then PCC, CH_2Cl_2, r.t., 1 h.

Des-A steroids **165** and **166** are potentially intermediates for the synthesis of the C-13 ethyl steroids **1**, **157** and **158**.

6-2. Total Synthesis of C-13 Trifluoromethyl Steroids[40]

Recently, there has been growing interest[41] in the synthesis of steroids bearing an angular trifluoromethyl group, expecting the reversible inhibition of the cytochrome P-450 enzyme aromatase in estrogen biosynthesis[42] for C-10 trifluoromethyl steroids[43] and the separation[44] of estrogenicity and antifertility effects for C-13 trifluoromethyl steroids.[45] The difficulty encountered in the synthesis of these trifluorosteroids in comparison with the synthesis of mono- or difluorosteroids[46] and the significant biological activity of some of (±)-18,18,18-trifluoro-17β-estradiol derivatives[45] prompted us to develop an efficient route for the enantioselective synthesis of these types of steroids. Our initial synthetic targets were the benzoperhydroindanes **167** and **168**, potential intermediates for the synthesis of both enantiomers of C-13 trifluoromethyl steroids (Figure 11).

Figure 11

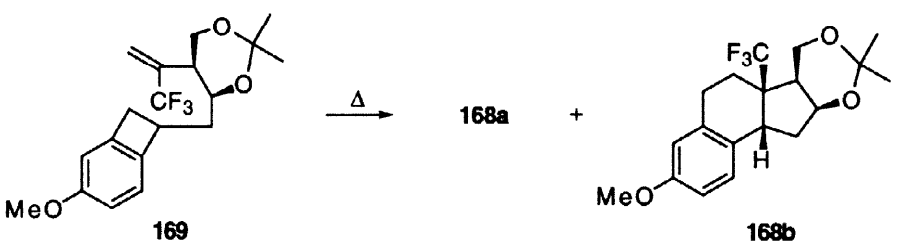


167a **168a**

6-2-1. Stereochemical Outcome of Intramolecular [4+2] Cycloaddition of Olefinic *o*-Quinodimethanes having Trifluoromethyl Group

At first, the thermolysis of the readily available chiral acetonide **169** was used to obtain the *trans*- and *cis*-benzoperhydroindanes **168a** (70%) and **168b** (23%) (Scheme 24).

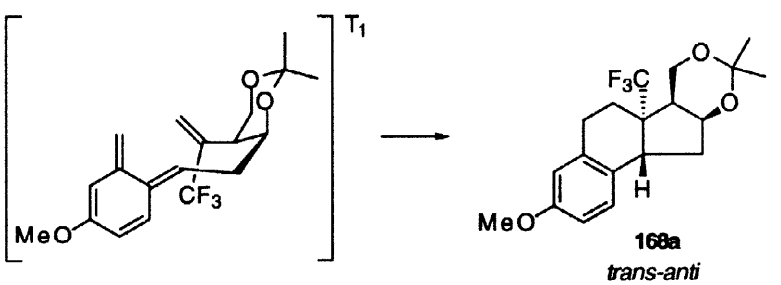
Scheme 24



169 **168b**

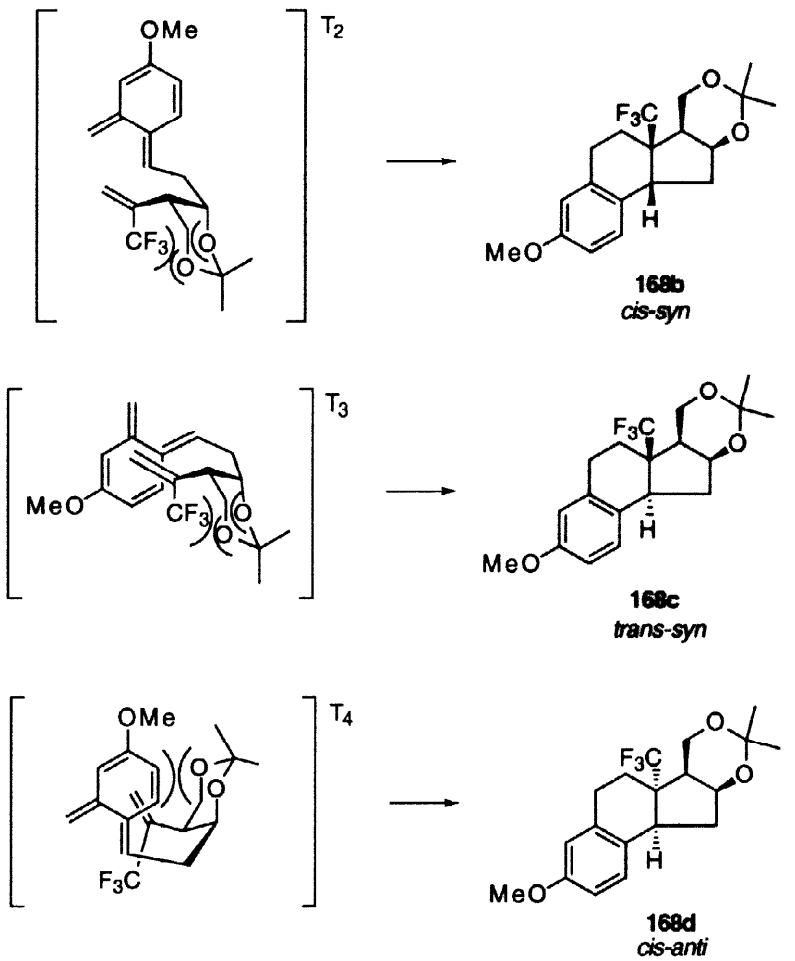
For the stereochemical outcome of this thermolysis, it seems possible that the stereoselectivity favouring the *trans-anti* isomer **168a** rather than the *cis-syn* **168b**, the *trans-syn* **168c**, and the *cis-anti* **168d** isomers probably reflects the steric interactions present in the *endo* transition states T_2 and T_4 and the *exo* transition state T_3 relative to the *exo* transition state T_1 (Figure 12).

Figure 12



168a
trans-anti

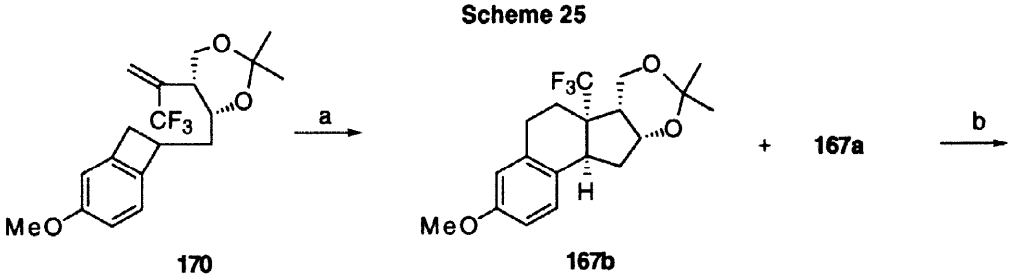
Figure 12 (continued)



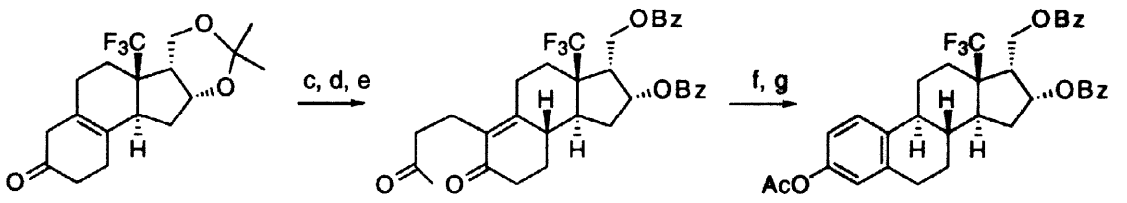
6-2-2. Total Synthesis of C-13 Trifluoromethyl Estrane

Based on these preliminary studies, the chiral olefinic benzocyclobutene **170** emerged as an apparent precursor to our target acetonide **167a**. Thus, thermolysis of **170** afforded the desired benzoperhydroindane **167a** (67%) along with its isomer **167b** (30%). Incorporation of A-ring into **167a** was easily accomplished *via* the following synthetic sequence: Birch reduction of **167a** followed by acid treatment gave the ketone **171** (74%). Enamine formation followed by alkylation, reprotection, and hydrolysis of the vinyl chloride afforded the diketone **172** (42% overall). Finally, cyclization of **172** followed by acetylative isomerization furnished the C-13 trifluoromethyl estrane **173** (Scheme 25).[40]

Scheme 25



Scheme 25 (continued)



171 172 173

Steps: (a) *o*-dichlorobenzene, reflux, 8 h; (b) Na, liq. NH_3, EtOH, THF, –78 °C, 10 min; then $(CO_2H)_2$, EtOH, H_2O, 25 °C, 14 h; (c) pyrrolidine, TsOH, benzene, reflux, 3 h; then $MeCCl{=}CHCH_2Cl$, KI, DMF, 0 °C, 30 min; (d) PhCOCl, pyridine, 25 °C, 10 h; (e) $Hg(OCOCF_3)_2$, $MeNO_2$, 25 °C, 1 h; (f) pyrrolidine, benzene, reflux, 3 h; (g) AcBr, Ac_2O, CH_2Cl_2, 25 °C, 1 h.

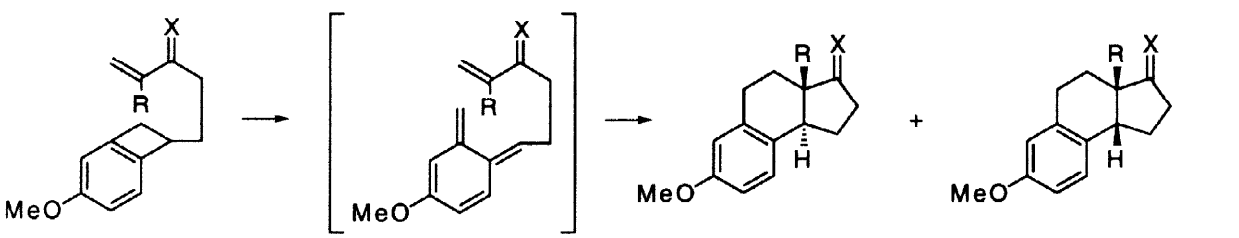
Thus, we have accomplished the total synthesis of the C-13 trifluoromethyl estrane **173** *via* an enantioselective formation of its precursor **167a**. This work has also demonstrated that the enantiomers of these biologically interesting steroids can also be synthesized.

6-2-3. Studies on the Stereochemical Course of Intramolecular [4+2] Cycloaddition of Olefinic *o*-Quinodimethanes having a Trifluoromethyl Group[47]

6-2-3-1. On the Influence of the Trifluoromethyl Group

The olefinic benzocyclobutenes **174–177** emerged as suitable candidates for estimating the influence of trifluoromethyl group on the stereochemical course of cycloaddition reaction of *o*-quinodimethanes since there was no stereogenic center in its transition states **178–181** and the results are summarized in Table 6.

Table 6[a] Thermolysis of Benzocyclobutenes 174–177



174 : R = CF_3; X = O
175 : R = CF_3; X = O,O-ethylene
176 : R = Me ; X = O
177 : R = Me ; X = O,O-ethylene

178 : R = CF_3; X = O
179 : R = CF_3; X = O,O-ethylene
180 : R = Me ; X = O
181 : R = Me ; X = O,O-ethylene

182a : R = CF_3; X = O
183a : R = CF_3; X = O,O-ethylene
184a : R = Me ; X = O
185a : R = Me ; X = O,O-ethylene

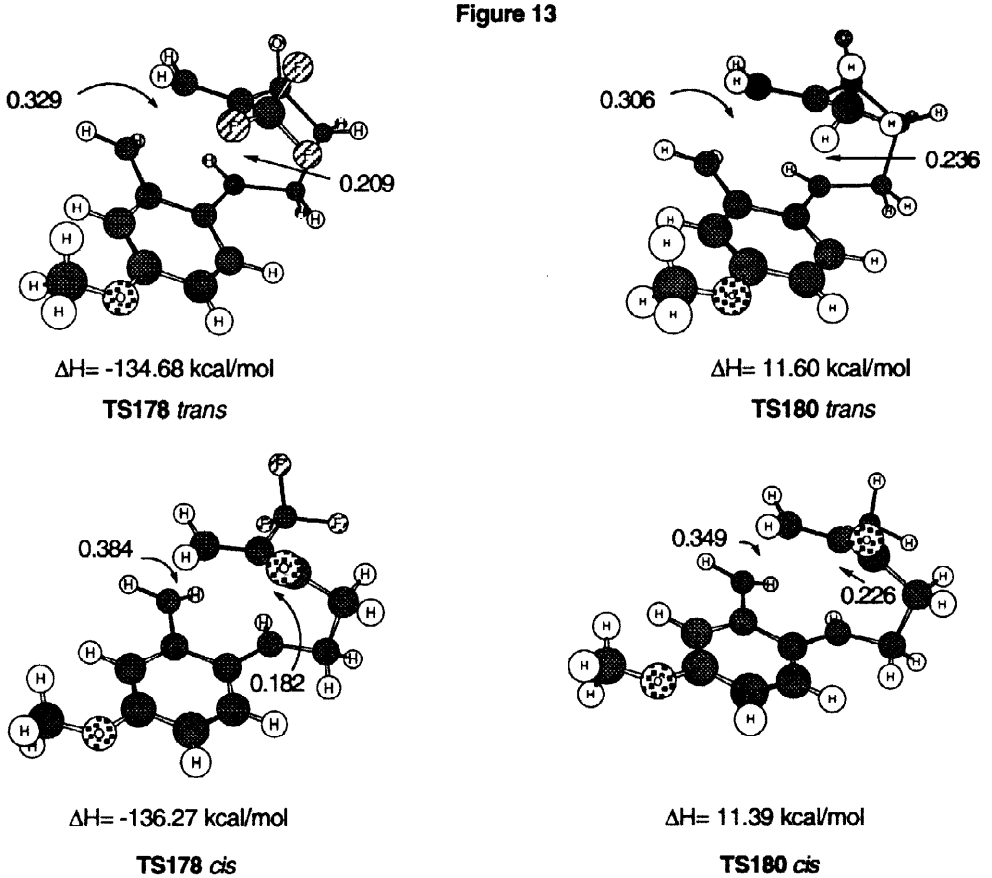
182b : R = CF_3; X = O
183b : R = CF_3; X = O,O-ethylene
184b : R = Me ; X = O
185b : R = Me ; X = O,O-ethylene

entry	substrate	product ratio	isolated yield %
1	**174**	**182a** : **182b** 1 : 6.5	99
2[b]	**176**	**184a** : **184b** 1.4 : 1	99
3	**175**	**183a** : **183b** 2.1 : 1	94
4[b]	**177**	**185a** : **185b** 6.7 : 1	90

[a] All reactions were run under argon in boiling *o*-dichlorobenzene.
[b] Reference 31b.

From these results, it became clear that the substitution of trifluoromethyl for methyl on the vinyl substituent (**176**→**174** and **177**→**175**) caused a remarkable enhancement of *cis* selectivity. In order to understand these results by locating transition structures and evaluating these energy differences, semiempirical calculations (PM3[48] Hamiltonian implemented in MOPAC 6.0[49]) were performed. The greater difference (0.202) of bond orders between terminal (0.384) and inner (0.182) forming bonds in **TS178** *cis* leading to **182b** than that (0.12) of **TS178** *trans* between terminal (0.329) and inner (0.209) leading to **182a** was in agreement with *asynchronous transition states of internally activated nonatrienes favouring cis-fused cycloadduct.*[50] The same situation could be the case for the difference of bond orders between terminal and inner forming bonds of **TS180** *cis* (0.123) and **TS180** *trans* (0.07) of the thermolysis of **176**. The remarkable enhancement of *cis* selectivity in case of **174** was in excellent agreement with the larger calculated ΔΔH value (1.59 kcal/mol) between **TS178** *cis* (ΔH = −136.27 kcal/mol) and **TS178** *trans* (ΔH = −134.68 kcal/mol) than that (0.21 kcal/mol) between **TS180** *cis* (ΔH = 11.39 kcal/mol) and **TS180** *trans* (ΔH = 11.60 kcal/mol) (Figure 13).

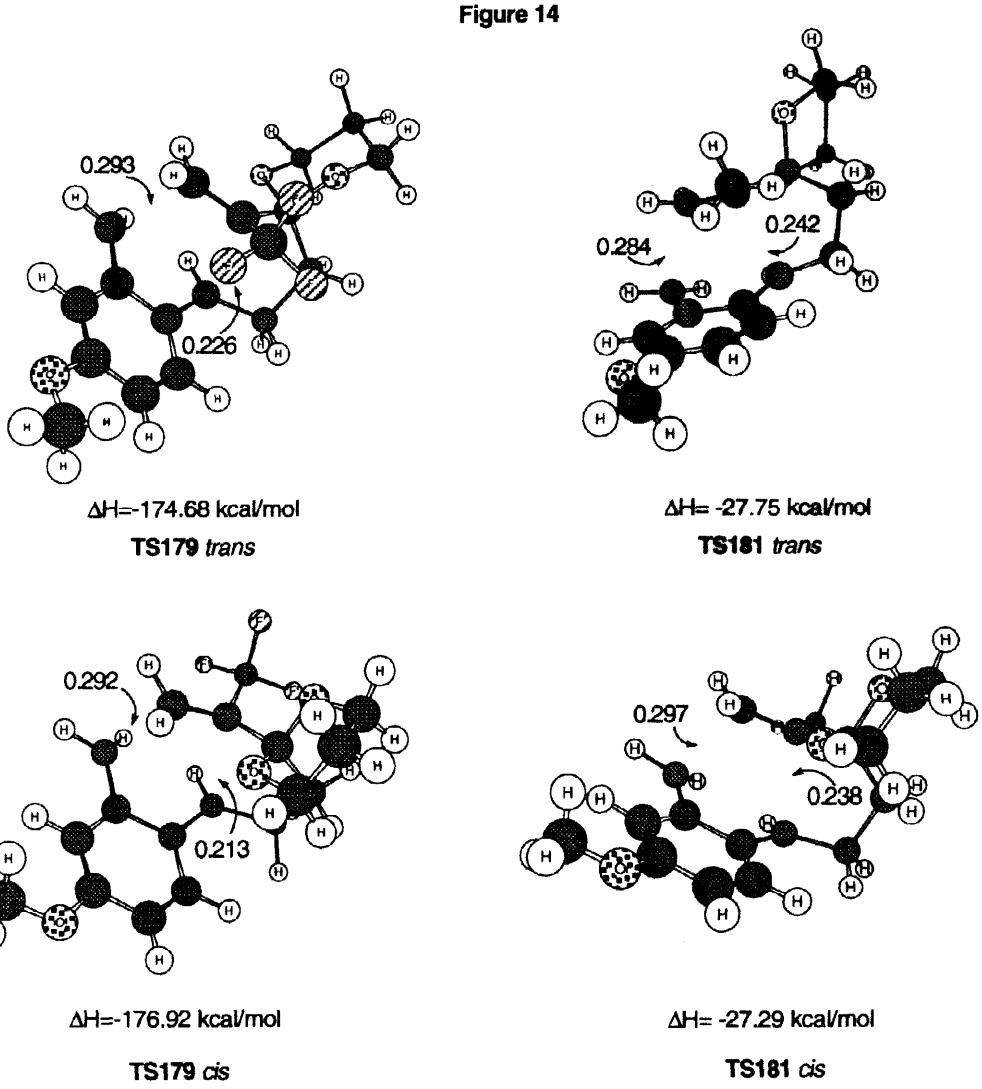
Figure 13



The same argument could be taken into account for **TS179** and **TS181** in the thermolysis of **175** and **177** respectively. Thus, asynchronous transition states could be agreement with the greater differences (0.079 and 0.059) of bond orders between terminal and inner forming bonds in **TS179** *cis* (0.292 and 0.213) and **TS181** *cis* (0.297 and 0.238) leading to **183b** and **185b** respectively than those (0.067 and 0.042) of **TS179** *trans* (0.293 and 0.226) and **TS181** *trans* (0.284 and 0.242) leading to **183a** and **185a** respectively. The decreased *trans* selectivity was in agreement with the larger calculated ΔΔH value (2.24 kcal/mol) between

TS179 *cis* (ΔH = −176.92 kcal/mol) and **TS179** *trans* (ΔH = −174.68 kcal/mol) than that (0.46 kcal/mol) between **TS181** *cis* (ΔH = −27.29 kcal/mol) and **TS181** *trans* (ΔH = −27.75 kcal/mol) (Figure 14).

Figure 14



6-2-3-2. On the Influence of Protective Groups

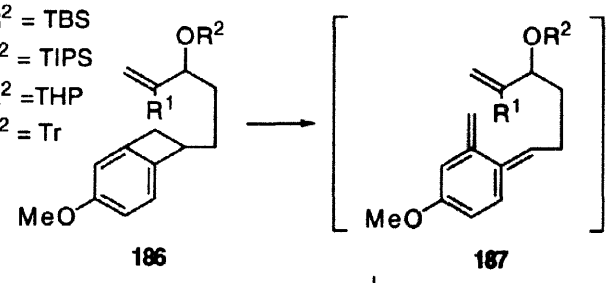
We also set out to examine the influence of hydroxyl protective groups in combination with a vinyltrifluoromethyl group on the stereochemical course of [4+2] cycloaddition reaction of *o*-quinodimethanes. The results of the thermolysis of various types of allyl alcoholic benzocyclobutenes **186a–g** and **186Ad–g**, which are summarized in Table 7, revealed that the trifluoromethyl substituent on vinyl dienophile enhanced the *cis* selectivity and also *anti* selectivity in comparison with methyl analogues for the most part (Table 7).

These results could be understood by locating the transition state **187** leading to these four isomers **188–191** and evaluating the energy difference of these possible transition structures, and thus these semiempirical calculations (PM3)[48] were performed [Figure 15 (**187a**, trifluoromethyl analog) and Figure 16 (**187Aa** methyl analog)]. Although the product ratio of all possible isomers **188**, **189**, **190**, and **191** could not be understood by these calculations, the enhancement of *cis* and *anti* selectivity of trifluoromethyl analogues compared with those of methyl analogues could be rationalized as follows.

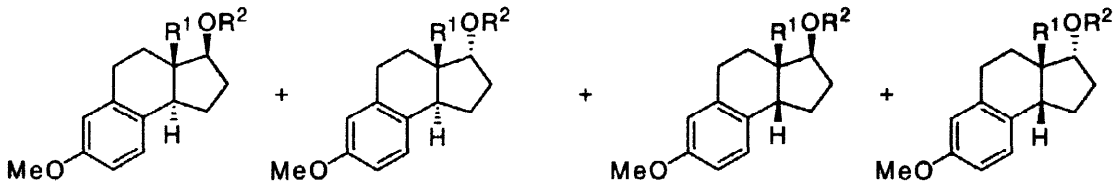
Table 7[a] Thermolysis of Allyl Alcoholic Benzocyclobutenes 186a–g and Ad–g

a : $R^1 = CF_3$; R^2 = H
b : $R^1 = CF_3$; R^2 = Ac
c : $R^1 = CF_3$; R^2 = *p*-NO_2Bz
d : $R^1 = CF_3$; R^2 = TBS
e : $R^1 = CF_3$; R^2 = TIPS
f : $R^1 = CF_3$; R^2 = THP
g : $R^1 = CF_3$; R^2 = Tr

Ad : R^1 = Me; R^2 = TBS
Ae : R^1 = Me; R^2 = TIPS
Af : R^1 = Me; R^2 = THP
Ag : R^1 = Me; R^2 = Tr



186 **187**



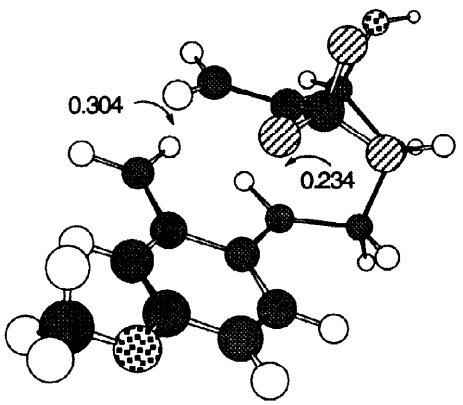
188 (*trans-syn*) **189** (*trans-anti*) **190** (*cis-syn*) **191** (*cis-anti*)

entry	substrate	product ratio **188 : 189 : 190 : 191**	isolated yield %
1	**186a**	1 : 2.3 : 1.5 : 1.9	55
2	**186b**	1 : 1.1 : 0.9 : 2.5	97
3	**186c**	1 : 0.5 : 0.9 : .2.4	84
4	**186d**	1 : 5.2 : 1.7 : 1.4	46
5	**(186Ad)**	1 : 2.3 — —	99
6	**186e**	1 : 8.9 : 2.9 : 4.1	65
7	**(186Ae)**	1 : 2.0 — —	81
8	**186f**	1 : 2.9 : 1.6 : 2.7	74
9	**(186Af)**	1 : 1.2 — —	72
10	**186g**	1 : 2.0 : 1.7 : 4.1	65
11	**(186Ag)**	1 : 1 — —	90

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

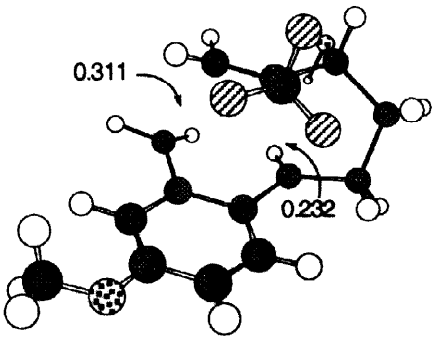
The enhancement of *cis* selectivity was in agreement with the larger calculated ΔΔH values [2.87 kcal/mol for **187a** *cis-syn* (ΔH = −147.40 kcal/mol) and **187a** *trans-syn* (ΔH = −144.53 kcal/mol) (leading to **190** and **188** respectively) and 2.81 kcal/mol for **187a** *cis-anti* (ΔH = −149.97 kcal/mol) and **187a** *trans-anti* (ΔH = −147.16 kcal/mol) (leading to **191** and **189** respectively) of trifluoromethyl analogues].

Figure 15



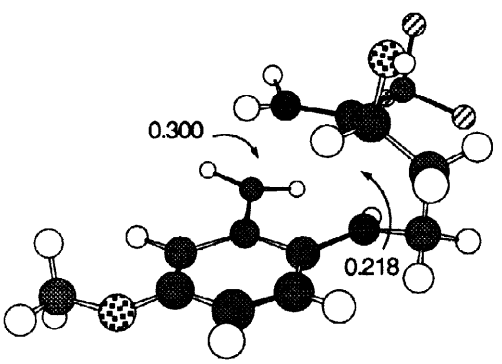
ΔH= -144.53 kcal/mol, 3.9D

187a *trans-syn*



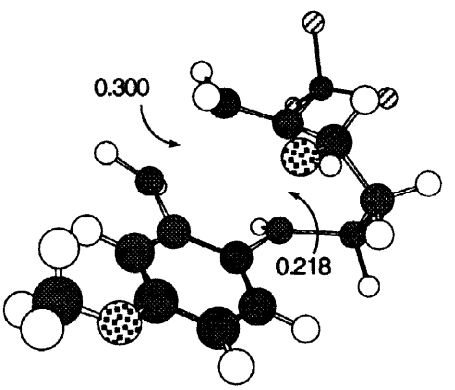
ΔH= -147.16 kcal/mol, 3.0D

187a *trans-anti*



ΔH= -147.40 kcal/mol, 3.9D

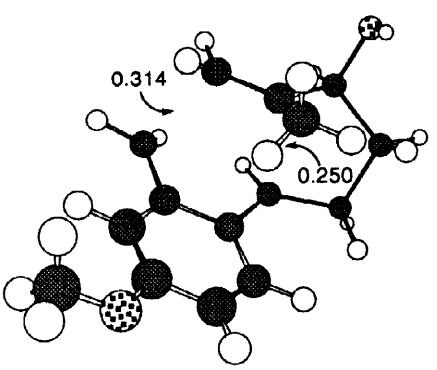
187a *cis-syn*



ΔH=-149.97 kcal/mol, 3.1D

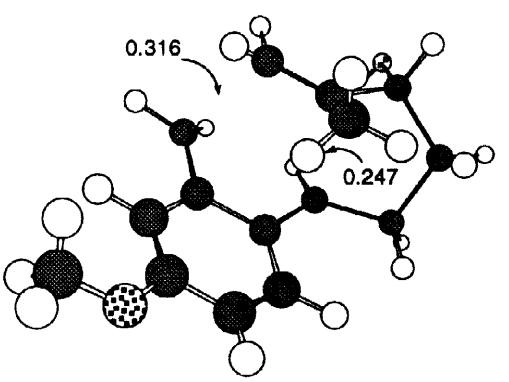
187a *cis-anti*

Figure 16



ΔH= -0.58 kcal/mol

187Aa *trans-syn*



ΔH= -0.57 kcal/mol

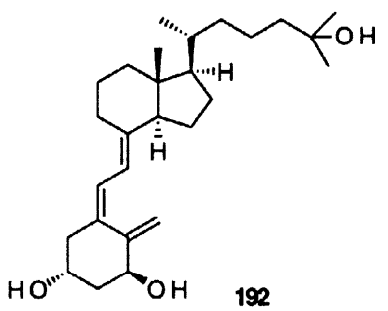
187Aa *trans-anti*

The enhancement of *anti* selectivity was consistent with the greater differences of the calculated ΔΔH values (2.63 kcal/mol for **187a** *trans-anti* and **187a** *trans-syn* and 2.57 kcal/mol for **187a** *cis-anti* and **187a** *cis-syn*) of trifluoromethyl analogues than those [0.01 kcal/mol for **187Aa** *trans-anti* (ΔH = –0.57 kcal/mol) and **187Aa** *trans-syn* (ΔH = –0.58 kcal/mol)] of methyl analogues. The *cis* selectivity could be attributed to the greater differences of bond orders between terminal and inner forming bonds in **187a** *cis-syn* (0.082) and **187a** *cis-anti* (0.082) than in **187a** *trans-syn* (0.070) and **187a** *trans-anti* (0.079) respectively, as described for **TS178** *cis* and *trans*, and **TS180** *cis* and *trans* before. The dipole repulsion between trifluoromethyl and alkoxy groups could be the origins of the enhanced *anti* selectivity in trifluoromethyl analogs. Thus, these dihedral angles and the dipole moments were calculated to be 54 ° and 3.9D for **187a** *trans-syn* 54° and 3.9D for **187a** *cis-syn* 165° and 3.0D for **187a** *trans-anti*, and 162 ° and 3.1D for **187a** *cis-anti*, which showed that **187a** *trans-anti* and **187a** *cis-anti* were more favourable than **187a** *trans-syn* and **187a** *cis-syn* respectively. From these data, the calculations of "PM3 transition state" were in excellent agreement with the experimental data. Furthermore, the calculations supported the concerted mechanism with a highly unsymmetric transition state for the cycloaddition of trifluoromethyl substituted *o*-quinodimethanes—*asynchronous transition states*[50]— thereby favouring the *cis* cycloadducts through the difference in the bond length of the forming terminal and inner bonds. The calculations showing the transition states leading to *anti* isomers to be more favoured in energy than those leading to *syn* isomers and supported the enhanced *anti* selectivity for the cycloadditions of trifluoromethyl substituted allyl alcohol *o*-quinodimethanes. Since 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 former are smaller than those of the latter, it might be clear that this enhanced *anti* selectivity is due to the dipole repulsion between trifluoromethyl and alkoxy groups. Thus, we could propose the transition structures of these reactions by using the semiempirical PM3 calculations which provided the information valuable for the synthesis of 13-trifluoromethyl estranes.

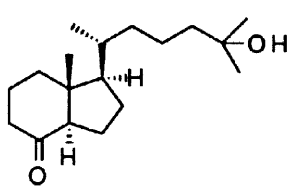
7. Total Synthesis of (+)-25-Hydroxy Windaus-Grundmann's Ketone[51]

Of many types of vitamin D_3 metabolites, 1α,25-dihydroxyvitamin D_3 (**192**) has emerged at present time as one of the most important compounds because of its increasing biological importance.[52] On the basis of Lythgoe's methodology[52] for the synthesis of calciferols *via* convergent routes, 25-hydroxy Windaus-Grundmann's ketone (**193**) has proven useful in the synthesis of **192** (Figure 17).

Figure 17



192

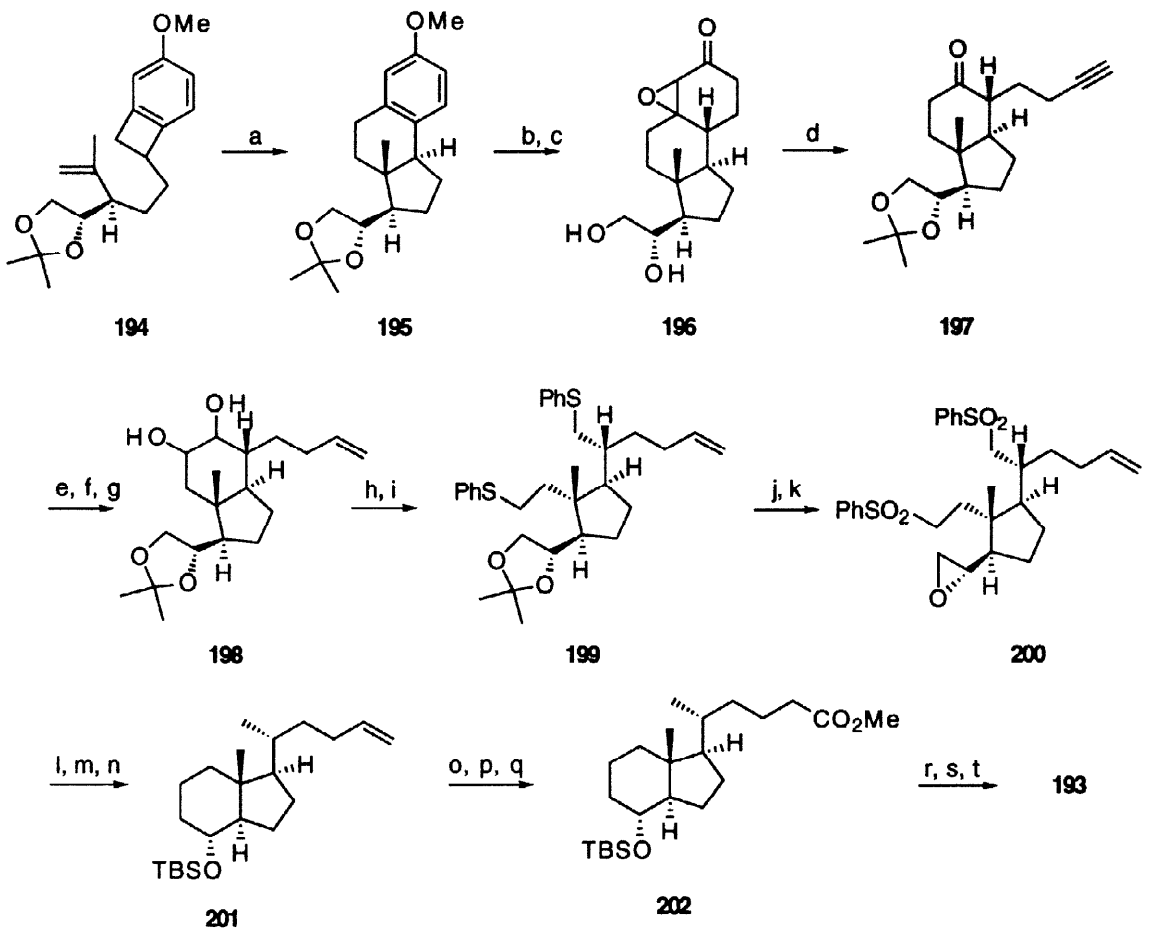


193

Thus, the synthesis of the optically active **193** was initiated by the stereoselective intramolecular cycloaddition reaction of the olefinic *o*-quinodimethane generated *in situ* by the thermolysis of the chiral

benzocyclobutene **194** to give the benzoperhydroindane **195** (90%). Birch reduction of **195** followed by acid treatment afforded the epoxide **196**, whose Eschenmoser ring opening followed by acetonide formation gave the acetylenic ketone **197** (40% from **195**). Catalytic semihydrogenation of **197**, followed by regioselective oxidation, and reduction gave the diol **198** (71%from **197**).

Scheme 26



Steps: (a) *o*-dichlorobenzene, 190 °C, 12 h; (b) Li, liq. NH_3, THF, –78 °C, 1 h; then 10% HCl, MeOH, 25 °C, 10 h→reflux, 1 h; (c) 30% H_2O_2, 10% NaOH, MeOH, 0 °C, 1 h; (d) $TsNHNH_2$, AcOH, –20 °C, 20 h→25 °C, 4 h; then $Me_2C(OMe)_2$, CSA, CH_2Cl_2, 25 °C, 2 h; (e) H_2, Lindlar cat., AcOEt, 25 °C, 30 min; (f) $PhSO_2N$(O)$CHPh$, $KN(SiMe_3)_2$, –78 °C, 20 min; (g) $NaBH_4$, MeOH, CH_2Cl_2, 25 °C, 30 min; (h) $NaIO_4$, MeOH, 25 °C, 12 h; then (g); (i) $(PhS)_2$, $^nBu_3P$, pyridine, 25 °C, 48 h; (j) TsOH, MeOH, 25 °C, 15 h; MsCl, Et_3N, CH_2Cl_2, 25 °C, 10 min; then NaH, EtOH, 25 °C, 10 min; (k) MCPBA, CH_2Cl_2, 25 °C, 1 h; (l) LDA, THF, –78 °C, 30 min→0 °C, 1 h; (m) Na–Hg, Na_2HPO_4, MeOH, 25 °C, 1 h; (n) TBSCl, DMAP, Et_3N, CH_2Cl_2, 25 °C, 5 h; (o) BH_3·Me_2S, THF, 0 °C, 30 min; then 30% H_2O_2, 10% NaOH, MeOH, 0 °C, 30 min; (p) PDC, DMF, 25 °C, 20 h; (g) CH_2N_2, Et_2O, 0 °C, 10 min; (r) MeMgBr, THF, 25 °C, 1 h; (s) $^nBu_4NF$, THF, 25 °C, 20 h; (t) PCC, 4 Å molecular sieves, CH_2Cl_2, 25 °C, 1 h.

Oxidative cleavage of **198**, followed by reduction and substitution afforded the diphenylsulfide **199** (58%). Transformation of **199** into the epoxide followed by oxidation gave the epoxy sulfone **200** (78%). A complete regiocontrolled cyclization of **200** was effected by the base treatment to give the bicyclic alcohol which was then

subjected to reductive removal of the phenylsulfonyl groups and protection to give the silyl ether **201** (36%). The compound **201** was then subjected to hydroboration-oxidation to afford the alcohol whose oxidation and esterification gave the ester **202** (73%). Finally, the ester **202** was subjected to Grignard reaction, deprotection and oxidation to furnish the 25-hydroxy Windaus-Grundmann's ketone **203** (90%), in an optically pure state (Scheme 26).

The synthetic design described above could make possible use of *o*-quinodimethane chemistry for the synthesis of vitamin D analogs as well.

8. Conclusions

A novel development of *o*-quinodimethane chemistry for the synthesis of steroids using benzoperhydroindanes as key intermediates has been achieved and exemplified through the total synthesis of various types of biologically important steroids such as 19-norspironolactone, 19-nordeoxycorticosterone, aldosterone analogs, 11-oxoprogesterone, adrenosterone, cortisone, and vitamin D_3 related compounds. The synthesis of unnatural types of steroids having 13-ethyl or 13-trifluoromethyl substituent may be even more noteworthy because the traditional semisynthetic process using natural steroids could not be applied in these cases.

Acknowledgment

We would like to express our deep gratitude to our co-workers. This research was supported in part by grants from a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Culture and Sports, Japan.

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Biographical sketch

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